

AMERICAN ACADEMY OF PEDIATRICS

# Textbook of Pediatric Care

2nd EDITION



**McInerny**

**ADAM \* CAMPBELL \* DEWITT \* FOY \* KAMAT**

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®



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# **Textbook of Pediatric Care**

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# Textbook of Pediatric Care

2ND EDITION



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Every effort is made to keep this publication consistent with the most recent advice and information available from the American Academy of Pediatrics.

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## DEDICATION

**W**e dedicate this edition to Robert Hoekelman, MD, whose legacy of excellence, commitment to quality health care for children, and dedication to education in pediatrics are reflected in these pages.

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# Foreword

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**T**he American Academy of Pediatrics (AAP) and our member pediatricians dedicate ourselves to promoting the optimal physical, mental, and social health and well-being of infants, children, adolescents, and young adults. An important aspect of our work is creating the educational materials necessary to provide appropriate, equitable, and high-quality pediatric care. I am proud to announce the second edition of the *AAP Textbook of Pediatric Care*.

The AAP is the leading publisher in the field of pediatrics, offering more than 500 publications, both print and electronic, for pediatricians and other health professionals who care for children. This kind of leadership saves lives, improves children's health, and supports the high quality of the profession of pediatrics.

The second edition of the *AAP Textbook of Pediatric Care* was created by a distinguished editorial team led by Thomas K. McInerney, MD, FAAP. Featuring contributions from experienced clinicians worldwide, this textbook addresses clinical issues faced by physicians who care for children: screening, diagnosis, treatment, and management for both common and uncommon diseases. The second edition contains more than 75 new chapters on specific diseases, conditions, signs, symptoms, and

more. Priorities for the 21st century, including the practice of evidence-based medicine, electronic health records, and continuous quality improvement, are also addressed. There is fully integrated coverage of mental health topics, in keeping with the Academy's mission, and enhanced discussion of the family-centered medical home, including important topics such as health literacy.

Because the practice of pediatrics is constantly changing and because we need information to be accessible in multiple ways, we also offer this textbook as part of *Pediatric Care Online*, our Web-based point-of-care resource. *Pediatric Care Online* was brand new when the first edition of this textbook was published. It has since grown into an indispensable and comprehensive resource for the practicing pediatrician. It features the complete text of this book and the *Red Book*, an extensive library of patient education handouts in English and Spanish, quick reference topics based on this book, interactive clinical tools, and much more. Please see [pediatriccare.solutions.aap.org](http://pediatriccare.solutions.aap.org) for updates to the *Textbook* and the latest news in pediatric health care.

Benard P. Dreyer, MD, FAAP  
President, American Academy of Pediatrics, 2016

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# Introduction

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**I**n 2008, the American Academy of Pediatrics (AAP) revised and updated Dr. Robert Hoekelman's venerable *Primary Pediatric Care* to create a new, comprehensive resource centered around the concept of the medical home. The first edition of the *AAP Textbook of Pediatric Care* applied the principles of evidence-based medicine to a diverse range of practice settings, including community health clinics, solo and private group practices, and hospitals, and to pediatricians practicing in urban, suburban, and rural areas.

The nearly eight years since that first publication have seen enormous changes in the practice of pediatric medicine; in our understanding of the relationships between mental and physiologic health and between early childhood adversity and long-term health outcomes; and, not the least, in the ways in which medical information can be organized, distributed, and accessed. This new, fully revised second edition has been created in response to these important challenges.

Reflecting the importance of incorporating mental health care into routine primary pediatric care, we have reorganized the book's content so that mental health screening, surveillance, promotion, symptoms, and conditions are now fully integrated throughout, rather than being divided into a separate section. New chapters have been added, including several based directly on the work of the AAP Task Force on Mental Health.

In addition to the enhanced coverage of mental health topics, new chapters have been developed that cover more than 25 new diseases and conditions and more than a dozen new signs and symptoms. Furthermore, each chapter's selection of Tools for Practice has been fully updated. Two dedicated tools editors have undertaken the task of reviewing and curating these tools for patient engagement, medical decision support, community advocacy, and practice management throughout the book.

The AAP recognizes that physicians need not only in-depth educational and resource materials for learning but also point-of-care decision support and tools to engage patients. To meet these needs, the *Textbook* is now seamlessly integrated within *Pediatric Care Online*, the essential AAP resource

for trusted pediatric information. The *Textbook*, linked with the other components of *Pediatric Care Online*—namely, *Red Book Online* and *Pediatric Patient Education*—provides a single point-of-care resource for child health professionals as we continue to move into an increasingly digital world. In addition, *Pediatric Care Online* provides a more-than-complete version of the *Textbook*, including full reference lists, interactive tools and forms, new and updated Point-of-Care Quick Reference topics, and exclusive online-only chapters, beginning with an important chapter on Disaster Preparedness and Response, which is available now.

In addition to these exciting electronic developments, we think you will find the core content of the *Textbook* more valuable and relevant than ever.

Part 1, **Delivering Pediatric Health Care**, discusses health care delivery and organizational issues for pediatric practices, including the use of electronic health records, digital resources, evidence-based medicine, and methodologies for quality improvement. This new edition highlights the importance of patient- and family-centered care.

Part 2, **Principles of Care**, has been reorganized to encompass the full range of traditional pediatric practice as well as emerging issues that pediatricians now deal with day to day. Section One covers physical, behavioral, and social assessment. Section Two features a greatly expanded discussion of health promotion based on the *Bright Futures* guidelines, including environmental health, community pediatrics, surveillance and screening, and, crucially, emerging issues such as obesity, physical activity, healthy use of media, and violence prevention. Section Three covers the general management of children with health and behavioral problems, including communication strategies, the provision of culturally effective care, pain management, psychosocial and psychopharmacologic therapies, transitions to adulthood, and palliative, end-of-life, and bereavement care. Section Four highlights the unique challenges to the pediatrician in caring for special populations, such as children exposed to adverse childhood experiences, in foster or kinship care, in the juvenile justice system, and in military families, as well as lesbian, gay, and bisexual youth.

Part 3, **Maternal and Fetal Health: Effect on Pregnancy Outcomes and Perinatal Health**, discusses the developing opportunities in prenatal diagnosis and fetal interventions as well as perinatal preventive care, assisted reproductive technologies, and the effects of maternal depression.

Part 4, **Care of Healthy and High-Risk Infants**, covers the primary care pediatrician's role in neonatal care. Section One addresses routine care issues, such as breastfeeding, the circumcision decision, hospital discharge, and follow-up care, as well as medical-legal considerations. Section Two deals with assessment and physical examination of the newborn, including maternal medical history, common congenital anomalies, and postnatal evaluation of prenatal findings. Section Three covers the most common neonatal medical conditions, including jaundice, abnormalities of growth, breathing disorders, heart murmur, cyanosis, metabolic conditions, and neurologic findings. Section Four provides guidance in caring for the high-risk infant, including surgical emergencies of the chest and abdomen. Section Five encompasses health and developmental outcomes of medically complex neonates, including very preterm and very low-birth-weight infants as well as those with significant congenital heart disease and those treated with therapeutic hypothermia. This section also discusses palliative and supportive care needs. Section Six provides guidance on supporting families whose infant is sick or dying.

Part 5, **Adolescence**, discusses issues specific to teenagers, such as interviewing and counseling, as well as adolescent sexuality, including contraception, pregnancy, and abortion.

Part 6, **Presenting Signs and Symptoms**, provides alphabetized, easy-to-use guidance on 85 of the most common physiologic and behavioral signs

and symptoms encountered by the pediatrician. These chapters include the physical and laboratory evaluation necessary to formulate a differential diagnosis, followed by approaches to initial management and guidance on when to refer and when to admit.

Part 7, **Specific Clinical Problems**, details the common physical and mental health issues seen in pediatric primary care settings. The latest evidence-based medicine information is used to enable the pediatrician to follow the recommended guidelines for diagnosis and treatment.

Part 8, **Critical Situations**, guides the pediatrician in responding to life-threatening illnesses and injuries seen in children, including psychiatric emergencies such as suicidality and psychosis, enabling rapid diagnosis and treatment.

As always, this textbook marshals the full resources and expertise of the AAP. The contributing authors include more than 500 top clinicians and experts across the scope of pediatrics and children's health. Each chapter has been reviewed by experts representing the relevant AAP committees, sections, and councils to ensure that the best evidence and AAP policy are reflected. Finally, chapters are cross-referenced to relevant AAP policy statements, clinical and technical reports, and clinical practice guidelines.

We would like to gratefully acknowledge the work of the AAP editorial team, including senior developmental editor Chris Wiberg and assistant editor Carrie Peters, along with the many other staff members from AAP Publishing who have made this new edition possible. We hope you will find this textbook to be a valuable addition to your library—in print, digital, or both formats—and an indispensable resource as you care for your patients.

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Albert Einstein College of Medicine  
Bronx, New York  
**86:** *Prenatal Pediatric Visit*  
**90:** *Care of the Late Preterm Infant*  
**92:** *Follow-up Care of the Healthy Newborn*  
**93:** *Maternal Medical History*  
**94:** *Physical Examination of the Newborn*  
**97:** *Postnatal Assessment of Common Prenatal Sonographic Findings*  
**112:** *Continuing Care of the Infant After Transfer From Neonatal Intensive Care*  
**113:** *Discharge Planning for the High-Risk Newborn Requiring Intensive Care*  
**115:** *Health and Developmental Outcomes of Very Preterm and Very Low-Birth-Weight Infants*  
**116:** *Health and Developmental Outcomes of Selected Medically Complex Neonates*  
**117:** *Support for Families Whose Infant Is Sick or Dying*

**John Campo, MD**

Professor and Chair  
Department of Psychiatry and Behavioral Health  
The Ohio State University Wexner Medical Center  
Columbus, Ohio  
**177:** *Medically Unexplained Symptoms*

**Mary T. Caserta, MD**

Professor of Pediatrics  
Division of Pediatric Infectious Diseases  
University of Rochester Medical Center  
Rochester, New York  
**366:** *Meningococemia*

**Jared Cash, BS, PharmD, BCPS**

Director, Pharmacy  
Primary Children's Hospital  
Intermountain Healthcare  
Salt Lake City, Utah  
**246:** *Drug Interactions and Adverse Effects*

**Heidi Castillo, MD, FAAP**

Assistant Professor of Pediatrics  
Baylor College of Medicine  
The Meyer Center for Developmental Pediatrics  
Texas Children's Hospital  
Houston, Texas  
**296:** *Neural Tube Defects*

**Sarah Chambers, MD**

Director, Fetal Heart Program  
Assistant Professor of Pediatrics  
Division of Pediatric Cardiology  
The Children's Hospital at Montefiore  
Bronx, New York  
**116:** *Health and Developmental Outcomes of Selected Medically Complex Neonates*

**Jayanthi Chandar, MD**

Associate Professor of Clinical Pediatrics  
University of Miami Miller School of Medicine  
Medical Director, Pediatric Kidney Transplant Program  
Miami Transplant Institute  
Miami, Florida

**163:** *High Blood Pressure*

**Pimpanada Chearskul, MD, FAAP**

Children's Hospital of Michigan  
Department of Pediatrics  
Wayne State University School of Medicine  
Detroit, Michigan

**308:** *Parasitic Infections*

**Amy Yuntzu-Yen Chen, MD, FAAD**

Assistant Professor of Dermatology  
Department of Dermatology  
University of Connecticut School of Medicine  
Farmington, Connecticut

**95:** *Neonatal Skin*

**Catherine Chen, MD**

Division of Dermatology  
Scripps Clinic Medical Group  
San Diego, California

**209:** *Acne*

**345:** *Verrucae (Warts)*

**Meera Chitlur, MD**

Barnhart Lusher Hemostasis Research Endowed  
Chair

Director, Hemophilia Treatment Center and  
Hemostasis Program  
Associate Professor of Pediatrics  
Wayne State University School of Medicine  
Children's Hospital of Michigan  
Detroit, Michigan

**262:** *Hemoglobinopathies and Sickle Cell Disease*

**Emma Ciafaloni, MD, FAAN, FANA**

Professor of Neurology and Pediatrics  
University of Rochester Medical Center  
Rochester, New York

**293:** *Muscular Dystrophy*

**Melinda B. Clark, MD, FAAP**

Associate Professor of Pediatrics  
Division of General Pediatrics  
Albany Medical College  
Albany, New York

**240:** *Dental Problems*

**Garfield Clunie, MD**

Assistant Professor of Obstetrics and Gynecology  
Division of Maternal-Fetal Medicine  
Icahn School of Medicine at Mount Sinai  
New York, New York

**82:** *Prenatal Diagnosis*

**83:** *Fetal Interventions*

**Chanelle A. Coble, MD, FAAP**

Assistant Professor of Pediatrics  
Division of General Pediatrics/Adolescent  
Medicine  
New York University School of Medicine  
New York, New York

**121:** *Adolescent Sexuality*

**Bruce H. Cohen, MD**

Director of the NeuroDevelopmental Science  
Center

Professor of Pediatrics  
Akron Children's Hospital  
Northeast Ohio Medical University  
Akron, Ohio

**223:** *Brain Tumors*

**Judith A. Cohen, MD**

Professor of Psychiatry  
Allegheny General Hospital  
Drexel University College of Medicine  
Pittsburgh, Pennsylvania

**317:** *Post-traumatic Stress Disorder*

**William I. Cohen, MD†**

**278:** *Intellectual Disability*

**Molly Cole**

Director, CT Council on Developmental Disabilities  
Past President, Family Voices Inc.  
Albuquerque, New Mexico

**9:** *Partnering With Families in Hospital and  
Community Settings*

**Blaise Congeni, MD**

Director, Division of Infectious Diseases  
Akron Children's Hospital  
Akron, Ohio

**60:** *Antimicrobial Therapy*

**Elizabeth Alvarez Connelly, MD**

Assistant Professor of Dermatology  
Department of Dermatology and Cutaneous  
Surgery

Assistant Professor  
Department of Pediatrics  
Co-Director of the Division of Pediatric  
Dermatology

University of Miami Miller School of Medicine  
Miami, Florida

**326:** *Seborrheic Dermatitis*

**Carol Conrad, MD**

Director, Pediatric Lung Transplant Program  
Associate Professor of Pediatrics  
Stanford University  
Palo Alto, California

**348:** *Airway Obstruction*

**W. Carl Cooley, MD, FAAP**

Chief Medical Officer, Crotched Mountain  
Foundation

Clinical Professor of Pediatrics  
Geisel School of Medicine at Dartmouth College  
Hanover, New Hampshire

**6:** *Medical Home Collaborative Care*

**7:** *Planned Coordinated Care to Support the  
Medical Home*

**Lynzee A. Cornell, PhD, F-AAA, CCC-A**

Clinic Director and Assistant Professor  
Division of Audiology  
University of Louisville School of Medicine  
Louisville, Kentucky

**26:** *Auditory Screening*

†Deceased

**Timothy Cornell, MD**

Associate Professor  
 Director, Pediatric Critical Care Fellowship  
 Department of Pediatrics and Communicable Diseases  
 University of Michigan  
 Ann Arbor, Michigan  
**373: Shock**  
**Appendix B: Outpatient Procedures**

**David N. Cornfield, MD, FAAP**

Anne T. and Robert M. Bass Professor of Pulmonary Medicine  
 Director, Center for Excellence in Pulmonary Biology  
 Department of Pediatric and (by courtesy) Surgery  
 Stanford University School of Medicine  
 Chief, Pulmonary, Asthma, and Sleep Medicine and Medical Director, Respiratory Therapy  
 Lucile Salter Packard Children's Hospital at Stanford  
 Palo Alto, California  
**348: Airway Obstruction**  
**372: Severe Acute Asthma (Status Asthmaticus)**

**Josef Misael Cortez, MD, FAAP**

Assistant Professor  
 Division of Neonatal Perinatal Medicine  
 Department of Pediatrics  
 Wayne State University School of Medicine  
 Detroit, Michigan  
**104: Prenatal Drug Use: Neonatal Effects and the Drug Withdrawal Syndrome**

**Susan M. Coupey, MD, FAAP**

Professor of Pediatrics  
 Chief, Division of Adolescent Medicine  
 Albert Einstein College of Medicine  
 The Children's Hospital at Montefiore  
 Bronx, New York  
**121: Adolescent Sexuality**

**Mario Cruz, MD**

Assistant Professor of Pediatrics  
 Drexel University College of Medicine  
 Associate Residency Program Director  
 St. Christopher's Hospital for Children  
 Philadelphia, Pennsylvania  
**41: Healthy Sexual Development and Sexuality**

**Timothy P. Culbert, MD, FAAP**

Medical Director: Integrative Medicine  
 PrairieCare Medical Group  
 Chaska, Minnesota  
**57: Complementary and Integrative Medical Therapies**

**David R. Cunningham, PhD**

Professor Emeritas  
 Department of Surgery  
 School of Medicine  
 University of Louisville  
 Louisville, Kentucky  
**26: Auditory Screening**

**Dennis Cunningham, MD**

Section of Infectious Diseases  
 Nationwide Children's Hospital  
 The Ohio State University School of Medicine  
 Columbus, Ohio  
**248: Enterovirus and Evolving Infections**

**Joseph R. Custer, MD**

Pediatric Critical Care Medicine  
 Professor of Pediatrics and Communicable Diseases  
 Associate Director for Fellowship Programs  
 Medical Director, Respiratory Therapy Services  
 C.S. Mott Children's Hospital  
 University of Michigan Health System  
 Ann Arbor, Michigan  
**373: Shock**  
**Appendix B: Outpatient Procedures**

**Lara Danziger-Isakov, MD, MPH, FAAP**

Professor of Pediatrics  
 Director, Immunocompromised Host Infectious Disease  
 Cincinnati Children's Hospital Medical Center  
 University of Cincinnati College of Medicine  
 Cincinnati, Ohio  
**325: Rocky Mountain Spotted Fever**

**Viral A. Dave, MD, FAAP**

Assistant Professor of Pediatrics  
 Section of Neonatology  
 Department of Pediatrics  
 Texas Children's Hospital and Baylor College of Medicine  
 Houston, Texas  
**90: Care of the Late Preterm Infant**

**Lynn F. Davidson, MD, FAAP**

Assistant Professor of Pediatrics  
 Department of Pediatrics  
 Albert Einstein College of Medicine  
 The Children's Hospital at Montefiore  
 Bronx, New York  
**51: Care of Children With Special Health Care Needs**

**Philip W. Davidson, PhD**

Professor Emeritus of Pediatrics, Environmental Medicine, and Psychiatry  
 University of Rochester Medical Center  
 School of Medicine and Dentistry  
 Rochester, New York  
**49: Discussing Serious Symptoms, Results, and Diagnoses With the Patient and Family**

**Beth Ellen Davis, MD, MPH, FAAP (COL, MC, USA, Retired)**

Clinical Professor of Pediatrics  
 Division of Developmental Medicine  
 University of Washington  
 Seattle, Washington  
**77: Children in Military Families**

**Adekunle Dawodu, MBBS**

Professor and Director of International Education and Patient Care  
 Global Health Center  
 Cincinnati Children's Hospital Medical Center  
 University of Cincinnati College of Medicine  
 Cincinnati, Ohio  
**346: Vitamin D Inadequacy**

**Lilia C. De Jesus, MD, FAAP**

Clinical Assistant Professor of Pediatrics  
 Department of Pediatrics/Neonatology Division  
 UCSF Benioff Children's Hospital  
 San Francisco, California  
**104: Prenatal Drug Use: Neonatal Effects and the Drug Withdrawal Syndrome**

**Sonia Dela Cruz-Rivera, MD**

Attending Pediatrician and Assistant Clinical Professor  
The Children's Hospital at Montefiore  
Albert Einstein College of Medicine  
Division of Pediatrics  
Bronx, New York

**91:** *Hospital Discharge of the Healthy Term and Late Preterm Infant*

**Marcela Del Rio, MD, FAAP**

Assistant Professor of Pediatrics  
Division of Pediatric Nephrology  
Medical Director, Renal Transplantation  
The Children's Hospital at Montefiore  
Albert Einstein College of Medicine  
Bronx, New York

**160:** *Hematuria*

**David R. DeMaso, MD**

Psychiatrist-in-Chief and Chairman of Psychiatry, Boston  
Children's Hospital  
George P. Gardner and Olga E. Monks Professor of Child  
Psychiatry and Professor of Pediatrics  
Harvard Medical School  
Boston, Massachusetts

**370:** *Psychiatric Emergencies: Suicidality, Agitation, Psychosis, and Disaster Exposure*

**Jayant K. Deshpande, MD, MPH, FAAP**

SVP/Chief Medical Officer  
Arkansas Children's Hospital  
Professor of Pediatrics and Anesthesiology  
University of Arkansas for Medical Sciences  
Little Rock, Arkansas

**63:** *Preoperative Assessment*

**64:** *Postoperative Care*

**Leena Shrivastava Dev, MD, FAAP**

Child Abuse Pediatrician  
General Pediatrician  
The Pediatric Center  
Frederick, Maryland

**41:** *Healthy Sexual Development and Sexuality*

**Chitra Dinakar, MD, FAAP, FAAAAI, FAAAAI**

Professor of Pediatrics  
University of Missouri-Kansas City School of Medicine  
Division of Allergy, Asthma, and Immunology  
Children's Mercy Hospital  
Kansas City, Missouri

**218:** *Asthma*

**Linda M. Dinerman, MD, PC**

Adolescent and Young Adult Medicine  
Private Practice  
Huntsville, Alabama

**141:** *Dysmenorrhea*

**205:** *Vaginal Discharge*

**Elaine A. Dinolfo, MD, MS, FAAP**

Assistant Clinical Professor of Pediatrics  
Columbia University  
Attending Physician  
Department of Pediatrics  
Harlem Hospital Center  
New York, New York

**87:** *Care of the Newborn After Delivery*

**207:** *Weight Loss*

**Cecilia Di Pentima, MD, MPH, FAAP**

Department of Pediatrics  
Vanderbilt University School of Medicine  
Nashville, Tennessee

**60:** *Antimicrobial Therapy*

**Aleksandra Djukic, MD, PhD**

Professor of Clinical Neurology  
Director, Tri State Rett Syndrome Center  
Albert Einstein College of Medicine  
Bronx, New York

**107:** *The Newborn With Neurologic Findings*

**Mary Iftner Dobbins, MD, FAAP**

Department of Family and Community Medicine  
Southern Illinois University School of Medicine  
Carbondale, Illinois

**150:** *Family Dysfunction*

**Eileen Dolan, MD**

Department of Pediatrics  
Hackensack University Medical Center  
Hackensack, New Jersey

**318:** *Prader-Willi Syndrome*

**Nienke P. Dosa, MD, MPH**

Upstate Foundation Professor of Child Health Policy  
Center for Development Behavior and Genetics  
Department of Pediatrics  
SUNY Upstate Medical University  
Syracuse, New York

**52:** *School-Related Issues for Children With Special Health Care Needs*

**Susan dosReis, PhD**

Associate Professor of Pharmacy  
Department of Pharmaceutical Health Services  
Research  
University of Maryland School of Pharmacy  
Baltimore, Maryland

**62:** *Psychotropic Medications in Primary Care Pediatrics*

**Dwayne E. Dove, MD**

**297:** *Neurocutaneous Syndromes*

**M. Catherine Driscoll, MD**

Professor of Clinical Pediatrics  
Department of Pediatrics  
Division of Hematology-Oncology  
Albert Einstein College of Medicine  
The Children's Hospital at Montefiore  
Bronx, New York

**103:** *The Newborn With Hematologic Abnormalities*

**George T. Drugas, MD, FACS, FAAP**

Director of Surgical Quality Improvement  
Pediatric General and Thoracic Surgery  
Seattle Children's Hospital  
University of Washington  
Seattle, Washington

**359:** *Esophageal Caustic Injury*

**Howard Dubowitz, MD, MS, FAAP**

Professor of Pediatrics  
University of Maryland School of Medicine  
Baltimore, Maryland

**367:** *Physical Abuse and Neglect*



**Paula M. Duncan, MD, FAAP**

Professor of Pediatrics  
University of Vermont College of Medicine  
Burlington, Vermont

**24:** *Promoting the Health of Adolescents*

**45:** *Conducting the Health Supervision Visit*

**Paul H. Dworkin, MD, FAAP**

Executive Vice President for Community Child Health  
Connecticut Children's Medical Center

Professor of Pediatrics  
University of Connecticut School of Medicine  
Hartford, Connecticut

**25:** *Screening: General Considerations*

**Dana Michelle Hines Dykes, MD**

Assistant Professor of Pediatrics  
Division of Pediatric Gastroenterology, Hepatology,  
and Nutrition

Cincinnati Children's Hospital Medical Center  
University of Cincinnati College of Medicine  
Cincinnati, Ohio

**276:** *Inflammatory Bowel Disease*

**Marian Earls, MD, FAAP**

Clinical Professor of Pediatrics  
University of North Carolina Medical School

Chapel Hill, North Carolina  
Director of Pediatric Programs  
Community Care of North Carolina

Raleigh, North Carolina

**33:** *Healthy Child Development*

**84:** *Maternal Depression*

**Sarah Edwards, DO**

Assistant Professor  
Director of Training, Child and Adolescent Psychiatry  
Fellowship

Medical Director of Child and Adolescent Psychiatry  
Hospital Services

Division of Child and Adolescent Psychiatry  
University of Maryland School of Medicine

Baltimore, Maryland

**192:** *Self-stimulating Behaviors*

**Jerrold M. Eichner, MD, FAAP**

Clinical Professor of Pediatrics  
University of Washington

School of Medicine  
Seattle, Washington

**10:** *Family-Centered Care of Hospitalized Children*

**Mohammad F. El-Baba, MD**

Division Chief, Pediatric Gastroenterology  
Fellowship Program Director

Children's Hospital of Michigan  
Wayne State University School of Medicine  
Detroit, Michigan

**142:** *Dysphagia*

**Dianne S. Elfenbein, MD, FAAP**

Division Director, Adolescent Medicine  
Professor of Pediatrics

St. Louis University School of Medicine  
St. Louis, Missouri

**122:** *Adolescent Pregnancy and Parenthood*

**Robin S. Everhart, PhD**

Assistant Professor  
Department of Psychology

Virginia Commonwealth University  
Richmond, Virginia

**47:** *Adherence to Pediatric Health Care  
Recommendations*

**Jonathan M. Fanaroff, MD, JD, FAAP, FCLM**

Associate Professor of Pediatrics  
Case Western Reserve University School  
of Medicine

Director, Rainbow Center for Pediatric Ethics  
Co-Medical Director, Neonatal Intensive Care Unit  
Rainbow Babies and Children's Hospital  
Cleveland, Ohio

**85:** *Medical-Legal Considerations in the Care of  
Newborns*

**Marianne E. Felice, MD, FAAP**

Professor of Pediatrics and Obstetrics/Gynecology  
Division of Adolescent Medicine

University of Massachusetts Medical School  
Worcester, Massachusetts

**122:** *Adolescent Pregnancy and Parenthood*

**371:** *Rape*

**Jon R. Felt, MD**

Fellow, Pediatric Emergency Medicine  
Carman and Ann Adams Department of Pediatrics

Wayne State University School of Medicine  
Children's Hospital of Michigan

Detroit, Michigan

**58:** *Fluids, Electrolytes, and Acid-Base Composition*

**Evan S. Fieldston, MD, MBA, MS, FAAP**

Assistant Professor of Pediatrics  
Perelman School of Medicine at the University of  
Pennsylvania

Medical Director of Clinical Operations  
The Children's Hospital of Philadelphia

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**1:** *Health Care Delivery System*

**Barbara H. Fiese, PhD**

Professor and Director of the Family Resiliency  
Center

University of Illinois at Urbana-Champaign  
Urbana, Illinois

**47:** *Adherence to Pediatric Health Care  
Recommendations*

**Lisa Figueiredo, MD**

Division of Pediatric Hematology/Oncology  
The Children's Hospital at Montefiore

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**181:** *Petechiae and Purpura*

**Jeffrey S. Fine, MD, FACMT**

Assistant Professor  
Ronald O. Perelman Department of Emergency Medicine  
and the Department of Pediatrics

New York University School of Medicine  
New York, New York

**369:** *Poisoning*

**Martin A. Finkel, DO, FACOP, FAAP**

Professor of Pediatrics

Medical Director, Institute Co-Director  
Child Abuse Research Education Services (CARES)  
Institute

Rowan University School of Osteopathic Medicine  
Stratford, New Jersey

**367:** *Physical Abuse and Neglect*

**Howard Fischer, MD\***

**233:** *Common Cold*

\*Retired

**Martin Fisher, MD, FAAP**

Chief, Division of Adolescent Medicine  
Cohen Children's Medical Center  
Northwell Health  
Professor of Pediatrics  
Hofstra Northwell School of Medicine at Hofstra  
University

Hempstead, New York

**216:** *Anorexia Nervosa, Bulimia Nervosa, and Other Eating Disorders*

**Leigh Anne Flore, MD, MS**

Assistant Professor of Pediatrics  
Division of Genetic, Genomic, and Metabolic Disorders  
Detroit Medical Center  
Wayne State University School of Medicine  
Detroit, Michigan

**250:** *Fetal Alcohol Spectrum Disorders*

**Glenn Flores, MD, FAAP**

Distinguished Chair of Health Policy Research  
Medical Research Institute  
Minneapolis, Minnesota

**69:** *Caring for Families New to the United States*

**Christopher B. Forrest, MD, PhD**

Director, Center for Child Health Development  
The Children's Hospital of Philadelphia  
Philadelphia, Pennsylvania

**1:** *Health Care Delivery System*

**Rene J. Forti, MD**

Assistant Professor of Clinical Pediatrics  
Albert Einstein College of Medicine  
Attending Physician, Pediatric Emergency Medicine  
The Children's Hospital at Montefiore  
Bronx, New York

**349:** *Altered Mental Status*

**Jane Meschan Foy, MD, FAAP**

Professor of Pediatrics  
Wake Forest School of Medicine  
Winston-Salem, North Carolina

**34:** *Mental Health*

**50:** *Care of Children With Mental Health Problems*

**62:** *Psychotropic Medications in Primary Care Pediatrics*

**Lorry R. Frankel, MD, FCCM**

Chair, Department of Pediatrics  
California Pacific Medical Center  
Emeritus Professor of Pediatrics  
Stanford University School of Medicine  
San Francisco, California

**356:** *Drowning and Near Drowning (Submersion Injuries)*

**Barbara L. Frankowski, MD, MPH, FAAP**

Professor of Pediatrics  
Division of Primary Care  
University of Vermont Children's Hospital  
Burlington, Vermont

**23:** *Promoting the Health of School-aged Children*

**172:** *Learning Difficulty*

**Andrew L. Freedman, MD**

Director, Pediatric Urology  
Professor of Surgery  
Cedars-Sinai Medical Center  
Los Angeles, California

**89:** *The Circumcision Decision*

**Karen S. Frush, MD**

Professor of Pediatrics  
Chief Patient Safety Officer  
Duke University Health System  
Durham, North Carolina

**12:** *Emergency Care*

**Mamta Fuloria, MD, FAAP**

Assistant Professor of Pediatrics  
Director, Neonatology Fellowship Program  
Department of Pediatrics  
Division of Neonatology  
The Children's Hospital at Montefiore  
Albert Einstein College of Medicine  
Bronx, New York

**108:** *Surgical Emergencies of the Chest and Abdomen in the Newborn*

**Sheila Gahagan, MD, MPH, FAAP**

Professor and Chief  
Division of Academic General Pediatrics  
University of California, San Diego  
San Diego, California

**298:** *Obesity and Metabolic Syndrome*

**Robert J. Gajarski, MD, MHSA, FACC**

Professor of Pediatrics  
Director, Cardiac Critical Care and Transplantation  
C.S. Mott Children's Hospital  
University of Michigan  
Ann Arbor, Michigan

**234:** *Congenital and Acquired Heart Disease*

**Mariam Gangat, MD**

Department of Pediatrics  
Division of Pediatric Endocrinology  
Rutgers Robert Wood Johnson Medical School  
New Brunswick, New Jersey

**164:** *Hirsutism, Hypertrichosis, and Precocious Sexual Hair Development*

**Anna Christina Ganster, MD, FAAP**

Assistant Professor of Clinical Pediatrics  
Division of Neonatology at LAC/USC  
Children's Hospital Los Angeles  
Keck School of Medicine  
University of Southern California  
Los Angeles, California

**108:** *Surgical Emergencies of the Chest and Abdomen in the Newborn*

**Andrew Garner, MD, PhD, FAAP**

Clinical Professor of Pediatrics  
Case Western Reserve University School of Medicine  
Cleveland, Ohio

**68:** *Children Exposed to Adverse Childhood Experiences*

**Jose M. Garza, MD**

Director, Neurogastroenterology and Motility Program  
Children's Healthcare of Atlanta  
Children's Center for Digestive Healthcare  
Atlanta, Georgia

**232:** *Colorectal Disorders*

**John P. Gearhart, MD, FAAP, FACS, FRCS**

Professor and Director of Pediatric Urology  
The James Buchanan Brady Urological Institute  
The Johns Hopkins Hospital  
Baltimore, Maryland

**272:** *Hypospadias, Epispadias, and Cryptorchidism*

**Gina Marie Geis, MD, FAAP**

Attending Neonatologist  
Associate Medical Director of the Neonatal Intensive  
Care Unit Floating Hospital for Children at Tufts  
Medical Center  
Co-Chair of the Hospital Ethics Committee at Tufts  
Medical Center  
Assistant Professor of Pediatrics  
Tufts University School of Medicine  
Boston, Massachusetts  
**111:** *Care of the Sick or Premature Infant Before  
Transport*

**Paul L. Geltman, MD, MPH, FAAP**

Assistant Professor of Pediatrics  
Harvard Medical School  
Medical Director for Refugee and Immigrant Health  
Division of Global Populations and Infectious Disease  
Prevention  
Massachusetts Department of Public Health  
Boston, Massachusetts  
**69:** *Caring for Families New to the United States*

**Welton M. Gersony, MD**

Alexander S. Nadas Emeritus Professor of Pediatrics  
College of Physicians and Surgeons of Columbia  
University  
New York, New York  
**323:** *Rheumatic Fever*

**Harry L. Gewanter, MD, FAAP, FACP**

Pediatric Rheumatologist  
Pediatric and Adolescent Health Partners  
Midlothian, Virginia  
**324:** *Rheumatologic Diseases*

**Mirko S. Gilardino, MD, MSc, FRCSC, FACS**

Director, Plastic Surgery Residency Program  
Associate Professor of Surgery  
Division of Plastic Surgery  
McGill University Health Centre  
Director, Craniofacial Surgery  
Montreal Children's Hospital  
Montreal, Quebec, Canada  
**261:** *Hemangiomas*

**Jack Gladstein, MD, FAAP**

Professor of Pediatrics and Neurology  
University of Maryland School of Medicine  
Baltimore, Maryland  
**157:** *Headache*

**Mary Margaret Gleason, MD, FAAP**

Associate Professor  
Child Psychiatry and Pediatrics  
Tulane University School of Medicine  
New Orleans, Louisiana  
**199:** *Symptoms of Emotional Disturbance in Young  
Children*

**Beatrice Gollav, MD**

Assistant Professor of Pediatrics  
Director, Pediatric Nephrology Training  
Program  
Division of Pediatric Nephrology  
The Children's Hospital at Montefiore  
Albert Einstein College of Medicine  
Bronx, New York  
**144:** *Dysuria*

**Melanie A. Gold, DO, DABMA, MQT, FAAP, FACOP**

Professor of Pediatrics  
Columbia University Medical Center (CUMC)  
Professor of Population and Family Health  
Mailman School of Public Health, CUMC  
Medical Director, School Based Health Centers  
New York–Presbyterian Hospital  
New York, New York  
**75:** *Gay- and Lesbian-parented Families*  
**119:** *Interviewing Adolescents*

**Johanna Goldfarb, MD, FAAP**

Pediatric Infectious Diseases  
Cleveland Clinic Children's Hospital  
Cleveland, Ohio  
**304:** *Osteomyelitis*  
**328:** *Septic Arthritis*

**David L. Goldman, MD**

Associate Professor of Pediatrics  
Assistant Professor of Microbiology  
The Children's Hospital at Montefiore  
Albert Einstein College of Medicine  
Bronx, New York  
**187:** *Recurrent Infections*

**Stuart L. Goldstein, MD, FAAP, FNKF**

Director, Center for Acute Care Nephrology  
Cincinnati Children's Hospital Medical Center  
Professor of Pediatrics  
University of Cincinnati College of Medicine  
Cincinnati, Ohio  
**365:** *Acute Kidney Injury*

**Meggan Goodpasture, MD, FAAP**

Assistant Professor of Pediatrics and Adolescent Medicine  
Wake Forest Baptist Medical Center  
Winston-Salem, North Carolina  
**292:** *Munchausen Syndrome by Proxy: Medical Child  
Abuse*

**Carol Lynn Greene, MD, FAAP, FACMG**

Professor of Pediatrics  
Director of Clinical Genetics  
University of Maryland School of Medicine  
Baltimore, Maryland  
**291:** *Metabolic Disorders Beyond the Newborn Period*

**Frank R. Greer, MD, FAAP**

Professor of Pediatrics  
University of Wisconsin School of Medicine and  
Public Health  
Madison, Wisconsin  
**36:** *Healthy Nutrition: Infants*  
**37:** *Healthy Nutrition: Children*  
**38:** *Healthy Nutrition: Adolescents*

**D. Gary Griffin, MD, MPH, FAAP**

Associate Clinical Professor  
Florida State University College of Medicine  
Tallahassee, Florida  
**339:** *Tonsillectomy and Adenoidectomy*

**James A. Grifo, MD, PhD**

Professor of Obstetrics and Gynecology  
New York University Langone Medical Center  
New York, New York  
**81:** *Assisted Reproductive Technologies, Multiple Births,  
and Pregnancy Outcomes*



**Lindsey K. Grossman, MD, FAAP**

Chair Emerita, Department of Pediatrics  
 Baystate Children's Hospital  
 Tufts University School of Medicine  
 Springfield, Massachusetts  
**266: Herpes Infections**

**James Guevara, MD, MPH, FAAP**

Associate Professor of Pediatrics and Epidemiology  
 Perelman School of Medicine at the University of  
 Pennsylvania  
 Attending Physician  
 The Children's Hospital of Philadelphia  
 Philadelphia, Pennsylvania  
**220: Attention-deficit/Hyperactivity Disorder**

**Lisa Hackney, MD**

Clinical Assistant Professor of Pediatrics  
 Division of Pediatric Hematology/Oncology  
 Rainbow Babies and Children's Hospital  
 Cleveland, Ohio  
**225: Cancers in Childhood**

**Waseem Hafeez, MBBS, FAAP**

Associate Professor of Clinical Pediatrics  
 Albert Einstein College of Medicine  
 Attending Physician  
 Division of Pediatric Emergency Medicine  
 The Children's Hospital at Montefiore  
 Bronx, New York  
**169: Irritability and Fussiness**

**Joseph F. Hagan, Jr, MD, FAAP**

Clinical Professor in Pediatrics  
 University of Vermont College of Medicine  
 Burlington, Vermont  
**45: Conducting the Health Supervision Visit**

**David Hains, MD**

Associate Professor of Pediatrics  
 Division of Pediatric Nephrology  
 University of Tennessee Health Science Center  
 Memphis, Tennessee  
**30: Use of Urinalysis and Urine Culture in Screening**

**Caroline Breese Hall, MD†**

**175: Lymphadenopathy**  
**224: Bronchiolitis**  
**352: Croup (Acute Laryngotracheobronchitis)**

**William J. Hall, MD, MACP**

Director, Center for Healthy Aging  
 Professor of Medicine  
 University of Rochester Medical Center  
 Rochester, New York  
**352: Croup (Acute Laryngotracheobronchitis)**

**David C. Hanson, MD**

Assistant Professor  
 Division of General Pediatrics  
 Department of Pediatrics  
 University of Minnesota Masonic Children's Hospital  
 Minneapolis, Minnesota  
**147: Extremity Pain**

**Winita Hardikar, MBBS, FRACP, PhD, FAASLD**

Associate Professor  
 Director of the Department of Gastroenterology  
 Royal Children's Hospital  
 Melbourne, Australia  
**265: Hepatitis**

**William Harmon, MD**

Associate Professor of Pediatrics  
 Medical Director, Pediatric Critical Care  
 Services  
 University of Virginia School of Medicine  
 Charlottesville, Virginia  
**361: Heart Failure**

**J. Peter Harris, MD**

Professor Emeritus  
 Department of Pediatrics  
 University of Rochester Medical Center  
 Rochester, New York  
**132: Cardiac Arrhythmias**

**Sandra G. Hassink, MD, MS, FAAP**

Director, American Academy of Pediatrics  
 Institute for Healthy Childhood Weight  
 Elk Grove Village, Illinois  
**35: Healthy Weight**

**Jessica Hawkins, MS**

**1: Health Care Delivery System**

**Nicole Hayde, MD, MS**

Assistant Professor of Pediatrics  
 Albert Einstein College of Medicine  
 Bronx, New York  
**264: Henoch-Schönlein Purpura**

**Nancy Heath, PhD**

Department of Educational and Counseling  
 Psychology  
 McGill University  
 Montreal, Quebec, Canada  
**191: Self-harm**

**Elizabeth Baltus Hebert, PhD, OTR/L**

Assistant Clinical Professor  
 Occupational Therapy  
 Nazareth College of Rochester  
 Rochester, New York  
**49: Discussing Serious Symptoms, Results, and  
 Diagnoses With the Patient and Family**

**Sebastian Heersink, MD, FACS**

Eye Center South  
 Dothan, Alabama  
**188: Red Eye/Pink Eye**

**Lauren Henderson, MD**

Resident Physician  
 Department of Dermatology  
 Eastern Virginia Medical School  
 Norfolk, Virginia  
**245: Drug Eruptions, Erythema Multiforme, Stevens-  
 Johnson Syndrome**

**Neil E. Herendeen, MD, FAAP**

Associate Professor of Pediatrics  
 University of Rochester Medical Center  
 Rochester, New York  
**215: Animal and Human Bites**  
**238: Cystic and Solid Masses of the Face and Neck**

**Ginette A. Hinds, MD**

Assistant Professor of Dermatology  
 Johns Hopkins School of Medicine  
 Baltimore, Maryland  
**320: Psoriasis**

†Deceased

**Breena Welch Holmes, MD, FAAP**

Maternal and Child Health Director  
Vermont Department of Health  
Burlington, Vermont

*24: Promoting the Health of Adolescents*

**Charles J. Homer, MD, MPH, FAAP**

Deputy Assistant Secretary for Human Services Policy  
U.S. Department of Health and Human Services  
Office of the Assistant Secretary for Planning and  
Evaluation  
Washington, DC

*5: Quality Improvement in Practice*

**Douglas N. Homnick, MD, MPH, FAAP**

Medical Director  
Kalamazoo County Health and Community Services  
Kalamazoo, Michigan  
Professor of Pediatrics and Human Development  
Division of Pediatric Pulmonology  
Michigan State University College of Human Medicine  
East Lansing, Michigan

*16: Pediatric Physical Examination: Interpretation of Findings*

**Robert J. Hopkin, MD, FAAP**

Associate Professor of Clinical Pediatrics  
Division of Human Genetics  
Cincinnati Children's Hospital Medical Center  
University of Cincinnati College of Medicine  
Cincinnati, Ohio

*313: Pierre Robin Sequence*

**Evalyn Horowitz, MD**

Former Director, Juvenile Justice  
Former Chief of Public Health  
California Department of Corrections and Rehabilitation  
Sacramento, California

*73: Children in the Juvenile Justice System*

**Amy Houtrow, MD, PhD, MPH, FAAP**

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and Rehabilitation  
Division of Pediatric Rehabilitation Medicine  
Department of Physical Medicine and Rehabilitation  
School of Medicine  
University of Pittsburgh  
Pittsburgh, Pennsylvania

*332: Spina Bifida*

**Jonathan C. Howell, MD, PhD**

Assistant Professor of Pediatrics  
Division of Endocrinology  
Cincinnati Children's Hospital Medical Center  
University of Cincinnati College of Medicine  
Cincinnati, Ohio

*342: Turner Syndrome and Noonan Syndrome*

**Sharon G. Humiston, MD, MPH, FAAP**

Professor of Pediatrics  
Children's Mercy Hospital  
University of Missouri-Kansas City School of Medicine  
Kansas City, Missouri

*20: Immunizations*

**Norman T. Ilowite, MD**

Professor of Pediatrics  
Albert Einstein College of Medicine  
Chief, Division of Pediatric Rheumatology  
The Children's Hospital at Montefiore  
Bronx, New York

*173: Limp*

**Sonia O. Imaizumi, MD, FAAP**

Medical Director  
Amerihealth New Jersey  
Cranbury, New Jersey  
Independence Blue Cross  
Philadelphia, Pennsylvania

*51: Care of Children With Special Health Care Needs*  
*115: Health and Developmental Outcomes of Very Preterm and Very Low-Birth-Weight Infants*

**Lilly Cheng Immergluck, MD, MS**

Associate Professor  
Departments of Microbiology/Biochemistry/Immunology  
and Pediatrics  
Morehouse School of Medicine  
Associate Professor of Clinical Pediatrics  
Division of Pediatric Infectious Diseases  
Emory University  
Atlanta, Georgia

*236: Contagious Exanthematous Diseases*

**Sean Indra, MD**

Pediatric Emergency Medicine Fellow  
Children's Hospital of Michigan  
Detroit, Michigan

*360: Head Injuries*

**Brian Inouye, MD**

Resident, Urology  
Duke University Medical Center  
Durham, North Carolina

*272: Hypospadias, Epispadias, and Cryptorchidism*

**Franca M. Iorember, MD, MPH**

Associate Professor of Pediatrics  
Division of Pediatric Nephrology  
Louisiana State University Health Sciences Center  
New Orleans, Louisiana

*249: Enuresis*

**Yaron Ivan, MD, FAAP**

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Children's Hospital of Pittsburgh of UPMC  
Pittsburgh, Pennsylvania

*266: Herpes Infections*

**Abieyuwa Iyare, MD**

General Academic Pediatrician  
The Children's Hospital at Montefiore  
Bronx, New York

*97: Postnatal Assessment of Common Prenatal Sonographic Findings*

**Mary Anne Jackson, MD, FAAP**

Professor of Pediatrics  
University of Missouri-Kansas City School  
of Medicine  
Division Director, Infectious Diseases  
Children's Mercy Hospital  
Kansas City, Missouri

*280: Kawasaki Disease*

**Timo Jahnukainen, MD, PhD**

Assistant Professor of Pediatrics  
Department of Pediatric Nephrology and  
Transplantation  
University of Helsinki  
Helsinki, Finland

*344: Urinary Tract Infections*

**Amrish Jain, MD**

Assistant Professor of Pediatrics  
Division of Pediatric Nephrology and Hypertension  
Wayne State University School of Medicine  
Detroit, Michigan  
**301: Oliguria and Anuria**

**Ginger Janow, MD**

Department of Pediatrics  
Division of Rheumatology  
Joseph M. Sanzari Children's Hospital  
Hackensack, New Jersey  
**173: Limp**

**Asma Javed, MBBS, FAAP**

Assistant Professor of Pediatrics  
Mayo Clinic  
Rochester, Minnesota  
**241: Diabetes Mellitus**

**Parul Jayakar, MD, FACMG**

Director, Division of Genetics and Metabolism  
Director, Neurogenetics/Metabolic Program  
Director, Miami Genetic Laboratories  
Nicklaus Children's Hospital  
Miami, Florida  
**281: Klinefelter Syndrome**

**Sandra H. Jee, MD, MPH, FAAP**

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Division of General Pediatrics  
University of Rochester Medical Center  
Rochester, New York  
**72: Children in Foster or Kinship Care**

**Michael S. Jellinek, MD, FAAP**

Professor of Psychiatry and of Pediatrics  
Harvard Medical School  
Chief Executive Officer and Executive Vice President  
Lahey Health, Community Network  
Burlington, Massachusetts  
**15: Pediatric History: Assessing Functioning and Mental Health**

**Renée R. Jenkins, MD, FAAP**

Professor and Chair Emerita  
Department of Pediatrics and Child Health  
Howard University College of Medicine  
Washington, DC  
**79: Children in Poverty**

**Alain Joffe, MD, MPH, FAAP**

Director, Student Health and Wellness Center  
Johns Hopkins University  
Associate Professor of Pediatrics  
Johns Hopkins University School of Medicine  
Baltimore, Maryland  
**127: Amenorrhea**  
**204: Vaginal Bleeding**  
**205: Vaginal Discharge**  
**330: Sexually Transmitted Infections**

**Brandon Johnson, MD**

Assistant Professor of Ophthalmology and Visual Sciences  
Albert Einstein College of Medicine  
Bronx, New York  
**214: Amblyopia and Strabismus**

**Nicholas Jospe, MD**

Professor of Pediatrics  
Chief, Division of Pediatric Endocrinology  
Golisano Children's Hospital  
Department of Pediatrics  
University of Rochester Medical Center  
Rochester, New York  
**270: Hyperthyroidism**

**Stephen G. Kahler, MD**

Professor of Pediatrics  
Section of Genetics and Metabolism  
University of Arkansas for Medical Sciences  
Little Rock, Arkansas  
**29: Screening for Genetic-Metabolic Diseases**

**Ronald Kallen, MD**

Associate Professor of Clinical Pediatrics  
Feinberg School of Medicine  
Northwestern University  
Chicago, Illinois  
**322: Renal Tubular Acidosis**

**Deepak M. Kamat, MD, PhD, FAAP**

Professor of Pediatrics  
Vice Chair for Education  
Department of Pediatrics  
Wayne State University School of Medicine  
Designated Institutional Official  
Children's Hospital of Michigan  
Detroit, Michigan  
**316: Positional Deformational Plagiocephaly**  
**321: Pyloric Stenosis**

**Nirupama Kannikeswaran, MBBS**

Associate Professor of Pediatrics and Emergency Medicine  
Children's Hospital of Michigan  
Wayne State University School of Medicine  
Detroit, Michigan  
**334: Sports Musculoskeletal Injuries**

**Vikramjit Kanwar, MRCP(UK), MBA, FAAP**

Chief and Professor of Pediatrics  
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Director, Melodies Center for Childhood Cancer and Blood Disorders  
Albany Medical Center  
Albany, New York  
**59: Blood Products and Their Uses**

**Vishal Subodhbhai Kapadia, MD, FAAP**

Assistant Professor of Pediatrics  
Department of Pediatrics  
Division of Neonatal Perinatal Medicine  
University of Texas Southwestern Medical Center  
Dallas, Texas  
**99: Neonatal Jaundice**

**Sebastian G. Kaplan, PhD**

Associate Professor of Psychiatry  
Department of Psychiatry and Behavioral Medicine  
Child and Adolescent Psychiatry Section  
Wake Forest School of Medicine  
Winston-Salem, North Carolina  
**31: Applying Behavior Change Science**

**Paul Kaplowitz, MD, PhD, FAAP**

Division of Endocrinology  
Children's National Medical Center  
School of Medicine and Health Sciences  
George Washington University  
Washington, DC

**193:** *Short Stature*

**Frederick J. Kaskel, MD, PhD, FAAP**

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Director, Division and Training Program in Pediatric  
Nephrology  
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Bronx, New York

**144:** *Dysuria*

**Dona Rani Kathirithamby, MD**

Pediatric Physiatrist  
Children's Evaluation and Rehabilitation Center  
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Associate Professor of Rehabilitation Medicine  
Assistant Professor of Pediatrics  
Albert Einstein College of Medicine  
Bronx, New York

**65:** *Pediatric Rehabilitation*

**Harpreet Kaur, MD**

Attending Neonatology  
Department of Pediatrics  
Saint Peter's University Hospital  
New Brunswick, New Jersey

**93:** *Maternal Medical History*

**94:** *Physical Examination of the Newborn*

**Martha Ann Keels, DDS, PhD**

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Duke University Medical Center  
Durham, North Carolina

**240:** *Dental Problems*

**Alex R. Kemper, MD, MPH, MS, FAAP**

Professor of Pediatrics  
Division of Children's Primary Care  
Duke University  
Durham, North Carolina

**28:** *Vision Screening*

**Kathi J. Kemper, MD, MPH, FAAP**

Director, Integrative Health and Wellness  
The Ohio State University School of Medicine  
Columbus, Ohio

**57:** *Complementary and Integrative Medical Therapies*

**Jonette E. Keri, MD, PhD**

Associate Professor of Dermatology and Cutaneous  
Surgery  
University of Miami Miller School of Medicine  
Miami, Florida

**219:** *Atopic Dermatitis*

**235:** *Contact Dermatitis*

**Bryce A. Kerlin, MD**

Associate Professor of Pediatrics  
The Ohio State University School of Medicine  
Principal Investigator, Center for Clinical and Translational  
Research  
The Research Institute at Nationwide Children's Hospital  
Director, The Joan Fellowship in Pediatric Hemostasis-  
Thrombosis  
Division of Hematology/Oncology/BMT  
Nationwide Children's Hospital  
Columbus, Ohio

**27:** *Screening for Anemia*

**John A. Kerner, Jr, MD, FAAP**

Professor of Pediatrics and Director of Nutrition  
Director of Pediatric Gastroenterology Fellowship  
Pediatric GI, Hepatology and Nutrition  
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Stanford, California  
Medical Director, Children's Home Pharmacy and the  
Nutrition Support Team  
Lucile Packard Children's Hospital Stanford  
Palo Alto, California

**256:** *Gastrointestinal Allergy*

**259:** *Gluten-Sensitive Enteropathy (Celiac Sprue)*

**Jill Kerr, DNP, MPH**

Family Nurse Practitioner (Retired)  
Chapel Hill Carrboro City Schools Head Start  
Carrboro, North Carolina

**22:** *Promoting the Health of Young Children*

**Unab I. Khan, MD, MS**

Director of Health Sciences  
Associate Professor of Pediatrics  
Warren Alpert School of Medicine  
Brown University  
Providence, Rhode Island

**121:** *Adolescent Sexuality*

**David W. Kimberlin, MD, FAAP**

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Co-Director, Division of Pediatric Infectious Diseases  
Department of Pediatrics  
The University of Alabama at Birmingham  
Birmingham, Alabama

**227:** *Chickenpox*

**Diana King, MD, FAAP**

Assistant Professor of Clinical Pediatrics  
Albert Einstein College of Medicine  
Attending Physician  
Division of Pediatric Emergency Medicine  
The Children's Hospital at Montefiore  
Bronx, New York

**169:** *Irritability and Fussiness*

**Robert A. King, MD**

Professor of Child Psychiatry  
Yale Child Study Center  
Yale University School of Medicine  
New Haven, Connecticut

**202:** *Tics*

**Genna W. Klein, MD**

Division of Pediatric Endocrinology  
Joseph M. Sanzari Children's Hospital  
Hackensack University Medical Center  
Hackensack, New Jersey

**164:** *Hirsutism, Hypertrichosis, and Precocious Sexual  
Hair Development*

**Jonathan D. Klein, MD, MPH, FAAP**

Associate Executive Director  
American Academy of Pediatrics  
Elk Grove Village, Illinois

**120:** *Counseling Parents of Adolescents*

**Michael D. Klein, MD, FACS, FAAP**

Philippart Chair and Professor of Surgery  
Wayne State University School of Medicine  
Children's Hospital of Michigan  
Detroit, Michigan

**347:** *Acute Surgical Abdomen*

**Evelyn A. Kluka, MD, FAAP**

Division Chief, Pediatric Otolaryngology  
Nemours Children's Specialty Care  
Pensacola, Florida

**339: Tonsillectomy and Adenoidectomy**

**Penelope Knapp, MD, FAAP**

Professor Emeritus of Psychiatry and Pediatrics  
Department of Psychiatry and Behavioral Sciences  
University of California, Davis  
Davis, California

**14: Pediatric History: Assessing the Social Environment**

**Samuel A. Kocoshis, MD**

Professor of Pediatrics  
University of Cincinnati College of Medicine  
Medical Director, Intestinal Care Center and Intestinal  
Transplantation  
Cincinnati Children's Hospital Medical Center  
Cincinnati, Ohio

**306: Pancreatitis**

**Tsoline Kojaoghlanian, MD**

Assistant Professor  
Department of Pediatrics  
Division of Infectious Diseases  
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Bronx, New York

**102: The Newborn at Risk for Infection**

**Faye Kokotos, MD, FAAP**

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Division of General Pediatrics  
The Children's Hospital at Montefiore  
Bronx, New York

**87: Care of the Newborn After Delivery**

**E. Anders Kolb, MD**

Vice Chairman for Research, Department of Pediatrics  
Nemours Alfred I. DuPont  
Hospital for Children  
Associate Professor  
Thomas Jefferson University, Jefferson Medical College  
Adjunct Professor  
University of Delaware, Center for Bioinformatics and  
Computational Biology  
Wilmington, Delaware

**285: Leukemias**

**David J. Kolko, PhD, ABPP**

Professor of Psychiatry, Psychology, Pediatrics, and  
Clinical and Translational Science  
University of Pittsburgh School of Medicine  
Director, Special Services Unit  
Western Psychiatric Institute and Clinic  
Pittsburgh, Pennsylvania

**317: Post-traumatic Stress Disorder**

**Sabine Kost-Byerly, MD, FAAP**

Associate Professor of Anesthesiology and Critical Care  
Medicine  
Director, Pediatric Pain Service  
Johns Hopkins Charlotte R. Bloomberg Children's Center  
Baltimore, Maryland

**55: Managing Chronic Pain in Children**

**Jonathan B. Kotch, MD, MPH, FAAP**

Research Professor  
University of North Carolina Gillings School of Global  
Public Health  
Chapel Hill, North Carolina

**22: Promoting the Health of Young Children**

**Richard E. Kreipe, MD, FAAP**

Dr. Elizabeth McAnarney Professor of Pediatrics  
Division of Adolescent Medicine  
Department of Pediatrics  
Golisano Children's Hospital  
University of Rochester Medical Center  
Rochester, New York

**118: Challenges of Health Care Delivery to Adolescents**

**Leonard R. Krilov, MD, FAAP**

Chief, Pediatric Infectious Disease  
Vice Chairman, Department of Pediatrics  
Children's Medical Center  
Winthrop University Hospital  
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Professor of Pediatrics  
State University of New York Stony Brook School of  
Medicine  
Stony Brook, New York

**228: Chronic Fatigue Syndrome**

**275: Infectious Mononucleosis and Other Epstein-Barr  
Viral Infections**

**Lakshmanan Krishnamurti, MD**

Professor of Pediatrics  
Emory University  
Joseph Kuchenmeister/Aflac Field Force Chair  
Director BMT  
Aflac Cancer and Blood Disorders Center  
Children's Healthcare of Atlanta  
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**279: Iron-Deficiency Anemia**

**Robert K. Kritzler, MD**

Deputy Chief Medical Officer  
Johns Hopkins Healthcare LLC  
Assistant Professor  
Johns Hopkins University  
Glen Burnie, Maryland

**185: Puberty: Normal and Abnormal**

**Daniel Krowchuk, MD, FAAP**

Department of Pediatrics  
Wake Forest School of Medicine  
Winston-Salem, North Carolina

**186: Rash**

**242: Diaper Rash**

**Elizabeth M. Kryszak, PhD**

Psychologist  
Child Development Center at Nationwide Children's  
Hospital  
Clinical Assistant Professor  
Departments of Pediatrics and Psychology  
The Ohio State University School of Medicine  
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**221: Autism Spectrum Disorder**

**Shobana Kubendran, MBBS, MS, CGC**

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Assistant Professor  
Kansas University School of Medicine  
Wichita, Kansas

**29: Screening for Genetic-Metabolic Diseases**

**Zuzanna Kubicka, MD**

Department of Newborn Medicine  
Boston Children's Hospital  
Boston, Massachusetts

**105: Transient Metabolic Disturbances in  
the Newborn**



**Erik Langenau, DO, MS, FAAP**

Chief Academic Technology Officer  
Philadelphia College of Osteopathic Medicine  
Philadelphia, Pennsylvania  
**180:** *Odor (Unusual Urine and Body)*

**John D. Lantos, MD**

Professor of Pediatrics  
University of Missouri-Kansas City School of Medicine  
Director, Children's Mercy Bioethics Center  
Children's Mercy Hospital  
Kansas City, Missouri  
**11:** *Ethical and Legal Issues for Primary Care Physicians*

**Danielle Laraque, MD, FAAP**

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Vice President, Maimonides Infants and Children's Hospital of Brooklyn  
Professor of Pediatrics  
Albert Einstein College of Medicine  
Yeshiva University  
Brooklyn, New York  
**210:** *Adjustment Disorder in Children and Adolescents*

**Gitte Larsen, MD, MPH, FAAP**

Professor of Pediatrics  
Associate Director, Quality Improvement and Patient Safety  
Primary Children's Hospital  
Division of Pediatric Critical Care  
University of Utah Medical Center  
Salt Lake City, Utah  
**246:** *Drug Interactions and Adverse Effects*

**Judith B. Lavrich, MD**

Associate Surgeon  
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Wills Eye Hospital  
Clinical Instructor  
Sidney Kimmel Medical College  
Thomas Jefferson University  
Philadelphia, Pennsylvania  
**188:** *Red Eye/Pink Eye*

**Taiwo Lawal, MD**

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Division of Pediatric Surgery  
University of Ibadan and University College Hospital  
Ibadan, Nigeria  
**232:** *Colorectal Disorders*

**Claire M.A. LeBlanc, MD, FAAP**

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Division of Rheumatology  
McGill University  
Montreal, Quebec, Canada  
**39:** *Physical Activity*

**Minou Le-Carlson, MD**

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Oakland, California  
**256:** *Gastrointestinal Allergy*

**Lori Legano, MD, FAAP**

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**71:** *Children of Divorce*

**Laurel K. Leslie, MD, MPH, FAAP**

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Tufts University School of Medicine  
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**220:** *Attention-deficit/Hyperactivity Disorder*

**John M. Leventhal, MD, FAAP**

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Yale University School of Medicine  
Director of the Child Abuse Programs and Child Abuse Prevention Programs  
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New Haven, Connecticut  
**329:** *Sexual Abuse of Children*

**Rebecca Levin, MPH**

Strategic Director, Injury Prevention and Research Center  
Ann and Robert H. Lurie Children's Hospital of Chicago  
Chicago, Illinois  
**42:** *Safety and Injury Prevention*

**Terry L. Levin, MD**

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Bronx, New York  
**18:** *Pediatric Imaging*

**Michael A. Levine, MD, FAAP, MACE, FACP**

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Professor of Pediatrics and Medicine  
University of Pennsylvania Perelman School of Medicine  
Philadelphia, Pennsylvania  
**271:** *Hypocalcemia, Hypercalcemia, and Hypercalciuria*

**Marc A. Levitt, MD, FAAP**

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Professor of Surgery  
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**232:** *Colorectal Disorders*

**Adam S. Levy, MD**

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Albert Einstein College of Medicine  
Bronx, New York  
**128:** *Anemia and Pallor*  
**181:** *Petechiae and Purpura*

**Paul A. Levy, MD, FAAP**

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Bronx, New York  
**145:** *Edema*

**Sharon Levy, MD, MPH, FAAP**

Director, Adolescent Substance Abuse Program  
Boston Children's Hospital  
Assistant Professor of Pediatrics  
Harvard Medical School  
Boston, Massachusetts  
**198:** *Substance Use: Initial Approach in Primary Care*  
**336:** *Substance Use Disorders*

**Samuel M. Libber, MD**

Department of Pediatrics  
Johns Hopkins University School of Medicine  
Baltimore, Maryland  
**182: Polyuria**

**Michael Light, MD, FAAP**

Pediatric Pulmonologist  
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Gainesville, Florida  
**315: Pneumonia**

**Jenifer R. Lightdale, MD, MPH, FAAP**

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UMass Memorial Children's Medical Center  
Professor of Pediatrics  
University of Massachusetts Medical School  
Worcester, Massachusetts  
**255: Gastroesophageal Reflux Disease**

**Meghan McAuliffe Lines, PhD**

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Nemours Al DuPont Hospital for Children  
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Sidney Kimmel Medical College  
Thomas Jefferson University  
Wilmington, Delaware  
**61: Psychosocial Therapies**

**Steven E. Lipshultz, MD, FAAP, FAHA**

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Carman and Ann Adams Endowed Chair in Pediatric Research  
Professor and Chair, Carman and Ann Adams Department of Pediatrics  
Professor of Medicine (Cardiology), Oncology, Obstetrics/Gynecology, Molecular Biology/Genetics, Family Medicine/Public Health Sciences, and Pharmacology  
Member, Center for Urban Responses to Environmental Stressors  
Wayne State University School of Medicine  
President, University Pediatricians  
Interim Director, Children's Research Center of Michigan  
Pediatrician-in-Chief, Children's Hospital of Michigan  
Specialist-in-Chief, Department of Pediatrics, Detroit Medical Center  
Scientific Member, Karmanos Cancer Institute, an NCI-designated Comprehensive Cancer Center  
Detroit, Michigan  
**163: High Blood Pressure**  
**286: Lipid Abnormalities**  
**361: Heart Failure**

**George A. Little, MD, FAAP**

Active Emeritus Professor of Pediatrics and Obstetrics and Gynecology  
Geisel School of Medicine at Dartmouth College  
Hanover, New Hampshire  
**80: Perinatal Preventive Care: Fetal Assessment**  
**105: Transient Metabolic Disturbances in the Newborn**  
**117: Support for Families Whose Infant Is Sick or Dying**

**Mark N. Lobato, MD**

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National Center for HIV, Hepatitis, STD, and TB Prevention  
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**341: Tuberculosis**

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**269: Hydrocephalus**

**Ann M. Loeffler, MD**

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**341: Tuberculosis**

**Anthony M. Loizides, MD**

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**125: Abdominal Pain**

**Christina Long, DO**

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Uniformed Services University of the Health Sciences  
Bethesda, Maryland  
**100: Respiratory Distress and Breathing Disorders in the Newborn**  
**113: Discharge Planning for the High-Risk Newborn Requiring Intensive Care**

**Dominique Long, MD**

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**185: Puberty: Normal and Abnormal**

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**243: Disorders of Sex Development**

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**213: Altitude Sickness**

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**357: Drug Overdose**

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**69: Caring for Families New to the United States**

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**58:** *Fluids, Electrolytes, and Acid-Base Composition*

**353:** *Dehydration*

**360:** *Head Injuries*

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**271:** *Hypocalcemia, Hypercalcemia, and Hypercalciuria*

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**222:** *Bacterial Skin Infections*

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**135:** *Cough*

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**189:** *School Absenteeism and School Refusal*

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**96:** *Common Congenital Anomalies*

**148:** *Facial Dysmorphism*

**343:** *Umbilical Anomalies*

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**239:** *Cystic Fibrosis*

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**171:** *Joint Pain*

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**301:** *Oliguria and Anuria*

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**97:** *Postnatal Assessment of Common Prenatal  
 Sonographic Findings*

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**302:** *Oppositional Defiant Disorder*

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**194:** *Sleep Disturbances (Nonspecific)*

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**143:** *Dyspnea*

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**6:** *Medical Home Collaborative Care*  
**7:** *Planned Coordinated Care to Support the Medical Home*

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**327:** *Seizure Disorders*  
**374:** *Status Epilepticus*

**Edith A. McCarthy, MD**

**81:** *Assisted Reproductive Technologies, Multiple Births,  
 and Pregnancy Outcomes*

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**234:** *Congenital and Acquired Heart Disease*

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**128:** *Anemia and Pallor*



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**174:** *Loss of Appetite*  
**206:** *Vomiting*

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**2:** *Practice Organization*

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**78:** *Homeless Children*

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**287:** *Lyme Disease*

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**267:** *Human Herpesvirus-6 and Human Herpesvirus-7 Infections*

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**163:** *High Blood Pressure*  
**286:** *Lipid Abnormalities*

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**182:** *Polyuria*

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**286:** *Lipid Abnormalities*

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**257:** *Gastrointestinal Obstruction*  
**309:** *Pectus Excavatum and Pectus Carinatum*

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**257:** *Gastrointestinal Obstruction*  
**309:** *Pectus Excavatum and Pectus Carinatum*

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**337:** *Sudden Unexpected Infant Death*

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**191:** *Self-harm*

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**73:** *Children in the Juvenile Justice System*

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**268:** *Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome*

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**293:** *Muscular Dystrophy*

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**49:** *Discussing Serious Symptoms, Results, and Diagnoses With the Patient and Family*

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**221:** *Autism Spectrum Disorder*

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**110:** *Identifying the Newborn Who Requires Specialized Care*

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**226:** *Cerebral Palsy*

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**236:** *Contagious Exanthematous Diseases*

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**98:** *Abnormalities of Fetal Growth*  
**100:** *Respiratory Distress and Breathing Disorders in the Newborn*

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**344:** *Urinary Tract Infections*

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**208:** *Wheezing*

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**74:** *Children in Self-care*

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**214:** *Amblyopia and Strabismus*

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**90:** *Care of the Late Preterm Infant*  
**97:** *Postnatal Assessment of Common Prenatal Sonographic Findings*

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**288:** *Medical Errors, Adverse Events, and Patient Safety*

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**299:** *Obstructive Uropathy and Vesicoureteral Reflux*

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**219:** *Atopic Dermatitis*  
**235:** *Contact Dermatitis*  
**282:** *Labial Adhesions*  
**335:** *Stomatitis*

**Michelle L. Niescierenko, MD**

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**248:** *Enterovirus and Evolving Infections*

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**312:** *Phimosis*

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**214:** *Amblyopia and Strabismus*

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**67:** *Palliative, End-of-Life, and Bereavement Care*

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**48:** *Providing Culturally Effective Care*  
**56:** *Self-regulation Therapies: Hypnosis and Biofeedback*

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**125:** *Abdominal Pain*

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**273:** *Hypothyroidism*

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**104:** *Prenatal Drug Use: Neonatal Effects and the Drug Withdrawal Syndrome*

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**130:** *Ataxia*

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*151: Fatigue and Weakness*  
*162: Hepatomegaly*  
*196: Splenomegaly*  
*203: Torticollis*

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*303: Osteochondroses*

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*190: Scrotal Swelling and Pain*

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*170: Jaundice*

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*165: Hoarseness*  
*251: Foreign Bodies of the Ear, Nose, Airway, and Esophagus*

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*269: Hydrocephalus*

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*232: Colorectal Disorders*

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*32: Family Support*

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*268: Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome*

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*278: Intellectual Disability*

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*109: Assessment and Stabilization at Delivery*

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*355: Disseminated Intravascular Coagulation*

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*32: Family Support*

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*182: Polyuria*  
*185: Puberty: Normal and Abnormal*

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*57: Complementary and Integrative Medical Therapies*

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*285: Leukemias*

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*201: Temper Tantrums and Breath-holding Spells*  
*237: Conversion Reactions and Hysteria*

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*227: Chickenpox*

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**62:** *Psychotropic Medications in Primary Care Pediatrics*

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**80:** *Perinatal Preventive Care: Fetal Assessment*

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**176:** *Macrocephaly*

**178:** *Microcephaly*

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**254:** *Fungal Infections (Systemic)*

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**149:** *Failure to Thrive: Pediatric Undernutrition*

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**308:** *Parasitic Infections*

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**217:** *Apparent Life-Threatening Events*

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**78:** *Homeless Children*

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**59:** *Blood Products and Their Uses*

**230:** *Coagulation Disorders*

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**200:** *Syncope*

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**20:** *Immunizations*

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**300:** *Ocular Trauma*

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**274:** *Immune (Idiopathic) Thrombocytopenia Purpura*

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**321:** *Pyloric Stenosis*

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**320:** *Psoriasis*

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**62:** *Psychotropic Medications in Primary Care Pediatrics*

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**160:** *Hematuria*

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**151:** *Fatigue and Weakness*

**162:** *Hepatomegaly*

**196:** *Splenomegaly*

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**359:** *Esophageal Caustic Injury*

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**62: Psychotropic Medications in Primary Care Pediatrics**

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**106: Specific Congenital Metabolic Diseases**

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**170: Jaundice**

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**140: Dizziness and Vertigo**

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**300: Ocular Trauma**

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**4: Evidence-based Medicine**

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**179: Nonconvulsive Periodic Disorders**  
**327: Seizure Disorders**  
**374: Status Epilepticus**

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**5: Quality Improvement in Practice**

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**248: Enterovirus and Evolving Infections**  
**340: Toxic Shock Syndrome**

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**96: Common Congenital Anomalies**

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**65: Pediatric Rehabilitation**  
**195: Speech and Language Concerns**

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**11: Ethical and Legal Issues for the Primary Care Physician**

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**285: Leukemias**

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**158: Hearing Loss**

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**229: Cleft Lip and Cleft Palate**

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**361: Heart Failure**

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**223: Brain Tumors**



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**21:** *The Essential Role of the Primary Care Pediatrician*

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**310:** *Pertussis (Whooping Cough)*

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**276:** *Inflammatory Bowel Disease*

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**259:** *Gluten-Sensitive Enteropathy (Celiac Sprue)*

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**66:** *Transitions to Adulthood*

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**324:** *Rheumatologic Diseases*

**Joy Samanich, MD**

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Division of Genetics  
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Bronx, New York  
**96:** *Common Congenital Anomalies*  
**148:** *Facial Dysmorphism*  
**343:** *Umbilical Anomalies*

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**107:** *The Newborn With Neurologic Findings*

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Madras Medical College  
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**363:** *Hypoglycemia*

**Richard M. Sarles, MD**

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**192:** *Self-stimulating Behaviors*

**Sharada A. Sarnaik, MD**

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Children's Hospital of Michigan  
Professor of Pediatrics  
Wayne State University School of Medicine  
Detroit, Michigan  
**262:** *Hemoglobinopathies and Sickle Cell Disease*

**Anirudh Saronwala, MD, MS, FAAP**

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**29:** *Screening for Genetic-Metabolic Diseases*

**Robert A. Saul, MD, FAAP, FACMG**

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Children's Hospital, Greenville Health System  
Greenville, South Carolina  
**253:** *Fragile X Syndrome*

**Lawrence A. Schachner, MD**

Senior Associate Dean and Executive Director for Development  
Professor and Chair Emeritus and Stiefel Laboratories Chair  
Director of the Division of Pediatric Dermatology  
Department of Dermatology and Cutaneous Surgery  
Professor, Department of Pediatrics  
University of Miami Miller School of Medicine  
Miami, Florida  
**326:** *Seborrheic Dermatitis*

**Eric Schaff, MD, FAAP**

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Cherry Tree Pediatrics  
Uniontown, Pennsylvania  
**123:** *Contraception and Abortion*

**Richard J. Schanler, MD, FAAP**

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Hofstra Northwell School of Medicine at Hofstra University  
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**88:** *Breastfeeding the Newborn*

**Miriam Schechter, MD, FAAP**

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Bronx, New York  
**146:** *Epistaxis*

**Steven C. Schlozman, MD**

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The Clay Center for Young Healthy Minds  
Massachusetts General Hospital  
Boston, Massachusetts  
**15:** *Pediatric History: Assessing Functioning and Mental Health*

**John P. Schmidt, MD, FAAP**

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*Appendix B: Outpatient Procedures*

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 University of Colorado School of Medicine  
 Aurora, Colorado  
*247: Encopresis*

**Marcie Schneider, MD, FAAP, FSAHM**

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 Greenwich, Connecticut  
*216: Anorexia Nervosa, Bulimia Nervosa, and Other Eating Disorders*

**Cindy Schorzman, MD, FAAFP**

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 University of California, Davis  
 Davis, California  
*75: Gay- and Lesbian-parented Families*

**Alan R. Schroeder, MD, FAAP**

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 San Jose, California  
 Clinical Associate Professor of Pediatrics (Affiliate)  
 Stanford University School of Medicine  
 Stanford, California  
*372: Severe Acute Asthma (Status Asthmaticus)*

**Scott A. Schroeder, MD, FCCP, FAAP**

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 The Floating Hospital for Children at Tufts Medical Center  
 Boston, Massachusetts  
*133: Chest Pain*  
*161: Hemoptysis*

**Cindy L. Schwartz, MD, MPH**

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 The Curtis Distinguished Professor of Pediatric Cancer  
 Professor, Departments of Pediatrics and Investigational Cancer Therapeutics  
 The University of Texas M.D. Anderson Cancer Center  
 Children's Cancer Hospital  
 Houston, Texas  
*225: Cancers in Childhood*

**Robert P. Schwartz, MD, FAAP**

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 Wake Forest School of Medicine  
 Winston-Salem, North Carolina  
*31: Applying Behavior Change Science*

**Kathleen B. Schwarz, MD**

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 Professor of Pediatrics  
 Johns Hopkins University School of Medicine  
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*265: Hepatitis*

**Richard M. Schwend, MD, FAAP**

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 University of Missouri-Kansas City School of Medicine  
 Director of Research  
 Children's Mercy Hospital  
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*97: Postnatal Assessment of Common Prenatal Sonographic Findings*

**W. Frederick Schwenk II, MD**

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*241: Diabetes Mellitus*  
*354: Diabetic Ketoacidosis*

**Elizabeth Secord, MD**

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*350: Anaphylaxis*

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*325: Rocky Mountain Spotted Fever*

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 Health Resources in Action  
 Boston, Massachusetts  
*44: Violence Prevention*

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 Emeritus Professor of Pediatrics  
 University of Rochester School of Medicine  
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*175: Lymphadenopathy*

**Elizabeth A. Sellars, MD, FAAP**

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*313: Pierre Robin Sequence*

**Catherine R. Sellinger, MD, FAAP**

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 Department of Pediatrics  
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 Bronx, New York  
*140: Dizziness and Vertigo*

**Aimee E. Seningen, MD**

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*119: Interviewing Adolescents*

**Usha Sethuraman, MD**

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Carman and Ann Adams Department  
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**362: Hypertensive Emergencies**

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Director of Neurotrauma and Neurocritical Care  
Orange County Global Medical Center  
Santa Ana, California  
**364: Increased Intracranial Pressure**

**Anjali A. Sharathkumar, MBBS, MD, MS**

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Carver College of Medicine  
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Director, Iowa Hemophilia and Thrombosis Centre  
Stead Family Department of Pediatrics, University of Iowa  
Children's Hospital  
Iowa City, Iowa  
**355: Disseminated Intravascular Coagulation**

**Ruchika Sharma, MD**

Joan Pediatric Hemostasis-Thrombosis Fellow  
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Nationwide Children's Hospital  
The Ohio State University School of Medicine  
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**27: Screening for Anemia**

**Judith S. Shaw, EdD, MPH, RN, FAAP**

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Executive Director, Vermont Child Health Improvement  
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Burlington, Vermont  
**45: Conducting the Health Supervision Visit**

**Katherine M. Shea, MD, MPH**

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Chapel Hill, North Carolina  
**19: Environmental Health: The Role of the Primary Care Physician**

**Robert L. Sheridan, MD, FACS**

Burn Service Medical Director, Boston Shriners Hospital  
for Children  
Division of Burns, Massachusetts General Hospital  
Department of Surgery  
Harvard Medical School  
Boston, Massachusetts  
**375: Thermal Injuries**

**Rashmi Shetgiri, MD, MSHS**

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David Geffen School of Medicine at UCLA  
Los Angeles Biomedical Research Institute at Harbor-  
UCLA Medical Center  
Torrance, California  
**69: Caring for Families New to the United States**

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**8: Health Literacy**

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**65: Pediatric Rehabilitation**

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**171: Joint Pain**  
**324: Rheumatologic Diseases**

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Royal Oak, Michigan  
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Oakland University William Beaumont School of Medicine  
Rochester, Michigan  
President  
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Ann Arbor, Michigan  
**350: Anaphylaxis**

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**292: Münchhausen Syndrome by Proxy: Medical Child Abuse**

**Pamela S. Singer, MD**

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**183: Proteinuria**

**Michelle Sirak, MD**

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**65: Pediatric Rehabilitation**

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Detroit, Michigan  
**260: Guillain-Barré Syndrome**



**Catherine C. Skae, MD**

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 Associate Dean for Graduate Medical Education  
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**203:** *Torticollis*

**251:** *Foreign Bodies of the Ear, Nose, Airway, and Esophagus*

**Douglas P. Sladen, PhD, CCC-A**

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**158:** *Hearing Loss*

**Stephanie Slagle, MD, MPH, MS**

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 University of Florida Pediatric Residency  
 Assistant Professor of Pediatrics  
 Pensacola, Florida

**339:** *Tonsillectomy and Adenoidectomy*

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 University of Washington School of Dentistry  
 Seattle, Washington

**40:** *Oral Health*

**David V. Smith, MD, FAAP**

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 Department of Pediatrics  
 Children's Hospital of The King's Daughters  
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**131:** *Back Pain*

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 Dimon R. McFerson Endowed Chair in Injury Research  
 Professor of Pediatrics  
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**42:** *Safety and Injury Prevention*

**Michael L. Smith, MD, FAAP**

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 Vanderbilt University School of Medicine  
 Nashville, Tennessee

**297:** *Neurocutaneous Syndromes*

**Tara Smith, PharmD**

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**339:** *Tonsillectomy and Adenoidectomy*

**Matthew D. Smyth, MD, FACS**

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 St. Louis Children's Hospital  
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**364:** *Increased Intracranial Pressure*

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**Appendix C:** *Formulas and Reference Range Values*

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 Steven and Alexandra Cohen Children's Medical Center of  
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 University

Hempstead, New York

**211:** *Adrenal Dysfunction*

**John David Spencer, MD**

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 Division of Nephrology  
 Nationwide Children's Hospital  
 The Ohio State University School of Medicine  
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**30:** *Use of Urinalysis and Urine Culture in Screening*

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 Georgetown University Hospital/Washington Hospital  
 Center  
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**281:** *Klinefelter Syndrome*

**Alfred J. Spiro, MD, FAAP**

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 Albert Einstein College of Medicine  
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 Bronx, New York

**167:** *Hypotonia*

**Mark L. Splaingard, MD**

Nationwide Children's Hospital  
 Professor of Pediatrics  
 The Ohio State University School of Medicine  
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**194:** *Sleep Disturbances (Nonspecific)*

**S. Andrew Spooner, MD, MS, FAAP**

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 Professor, Biomedical Informatics  
 Cincinnati Children's Hospital Medical Center  
 University of Cincinnati College of Medicine  
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**3:** *Information Systems in Pediatric Practice*

**Sarah H. Springer, MD, FAAP**

Kids Plus Pediatrics  
 Pittsburgh, Pennsylvania

**70:** *Adoption*

**James E. Squires, MD, MS**

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 and Nutrition  
 Cincinnati Children's Hospital Medical Center  
 University of Cincinnati College of Medicine  
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**306:** *Pancreatitis*

**Anthony Stallion, MD, FACS, FAAP**

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 Chief of Pediatric Surgery  
 Levine Children's Hospital  
 Jeff Gordon Children's Hospital  
 Carolinas HealthCare System  
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**257:** *Gastrointestinal Obstruction*

**309:** *Pectus Excavatum and Pectus Carinatum*

**Thomas J. Starc, MD, MPH**

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**323: Rheumatic Fever**

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St. Lucia, Australia  
Clinical Professor  
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**311: Pharyngitis and Tonsillitis**

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**22: Promoting the Health of Young Children**

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**277: Insect Bites and Infestations**

**Ruth E. K. Stein, MD**

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**51: Care of Children With Special Health Care Needs**

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**88: Breastfeeding the Newborn**

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**146: Epistaxis**

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**252: Fractures and Dislocations**  
**351: Appendicitis**

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**43: Healthy Use of Media**

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**243: Disorders of Sex Development**

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**91: Hospital Discharge of the Healthy Term and Late  
Preterm Infant**

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**334: Sports Musculoskeletal Injuries**  
**362: Hypertensive Emergencies**  
**363: Hypoglycemia**

**Nicole J. Sutton, MD, FAAP**

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Bronx, New York  
**101: The Newborn With a Heart Murmur  
or Cyanosis**

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**34: Mental Health**

**Sarah A. Sydlowski, AuD, PhD**

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**26: Auditory Screening**

**Frank Symons, PhD**

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**191: Self-harm**

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**72: Children in Foster or Kinship Care**

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**20: Immunizations**  
**215: Animal and Human Bites**  
**238: Cystic and Solid Masses of the Face  
and Neck**

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**305:** *Otitis Media and Otitis Externa*  
**331:** *Sinusitis*

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Children's Hospital at Dartmouth-Hitchcock Medical Center  
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**338:** *Tobacco and Nicotine Use*

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**23:** *Promoting the Health of School-aged Children*

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**63:** *Preoperative Assessment*

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**195:** *Speech and Language Concerns*

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**241:** *Diabetes Mellitus*  
**354:** *Diabetic Ketoacidosis*

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**52:** *School-Related Issues for Children With Special Health Care Needs*

**Anne Marie Tharpe, PhD**

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**158:** *Hearing Loss*

**John F. Thompson, MD**

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**125:** *Abdominal Pain*

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**54:** *Managing Acute Pain in Children*

**Kristine Torjesen, MD, MPH, FAAP**

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**48:** *Providing Culturally Effective Care*

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**191:** *Self-harm*

**Ali Tourchi, MD**

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**272:** *Hypospadias, Epispadias, and Cryptorchidism*

**Christine Tracy, MD, FACC**

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**159:** *Heart Murmurs*

**Mark S. Tremblay, PhD, FACSM**

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**39:** *Physical Activity*

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**127:** *Amenorrhea*  
**204:** *Vaginal Bleeding*

**Julian Trevino, MD**

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**95:** *Neonatal Skin*

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Department of Risk, Quality, and Safety-Central Coast Service Area  
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**85:** *Medical-Legal Considerations in the Care of Newborns*

**W. Douglas Tynan, PhD, ABPP**

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Thomas Jefferson University  
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**61:** *Psychosocial Therapies*

**Kanagasabai Udhayashankar, MD, MPH**

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**248:** *Enterovirus and Evolving Infections*

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**95:** *Neonatal Skin*

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Durham, North Carolina  
**138:** *Diarrhea and Steatorrhea*  
**174:** *Loss of Appetite*  
**206:** *Vomiting*

**H. Michael Ushay, MD, PhD, FAAP**

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**136:** *Cyanosis*

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University of Rochester School of Medicine/Dentistry  
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**152:** *Fever*  
**153:** *Fever of Unknown Origin*  
**Appendix A:** *Pediatric Cardiopulmonary Resuscitation*

**William S. Varade, MD**

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**294:** *Nephritis*  
**295:** *Nephrotic Syndrome*

**Abhay Vats, MD**

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**344:** *Urinary Tract Infections*

**Sandra Vicari, PhD, LCPC**

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**150:** *Family Dysfunction*

**Alfin G. Vicencio, MD**

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**197:** *Stridor*  
**208:** *Wheezing*

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Allergy Division Chief, Seattle Children's Hospital  
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**212:** *Allergic Rhinitis*

**Joseph A. Vitterito II, MD**

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**117:** *Support for Families Whose Infant Is Sick or Dying*

**Jennifer Vodzak, MD, FAAP**

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**236:** *Contagious Exanthematous Diseases*

**Carol L. Wagner, MD, FAAP**

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**346:** *Vitamin D Inadequacy*

**Ellen R. Wald, MD, FAAP**

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**319:** *Preseptal and Orbital Cellulitis*

**Ruth R. Walden, MSW**

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**9:** *Partnering With Families in Hospital and Community  
Settings*

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## Chapter 1

# HEALTH CARE DELIVERY SYSTEM

Christopher B. Forrest, MD, PhD; Jessica Hawkins, MS;  
Evan S. Fieldston, MD, MBA, MS

Health care services accessibility, the content and quality provided, and outcomes occur within the context of the health care delivery system. Findings from child health services research provide pediatricians with an increasingly accurate and complete picture of how health care affects child health, development, and well-being. Understanding how pediatric services improve child health should begin with examining the structure of the delivery system and processes that occur once health professionals and patients interact.

This chapter uses a structure-process-outcome framework to describe the health care delivery system and to analyze its effects on children. *Structure* refers to the organizational and financial arrangements that are present before health professionals and patients interact. Structural elements include the pediatric workforce, delivery sites (including the medical home), information technology, and financing of services. The delivery, or *process*, of care occurs when patients come into contact with providers or suppliers. The number and content of visits (utilization), the costs of these services, patients' evaluations of and satisfaction with these services, and the volume and types of surgical procedures are all examples of processes of care. The end results of the health care delivery process are patient *outcomes*: changes in health, functional status, and well-being. The degree to which health care is consistent with the best available medical evidence and linked to positive and desired health outcomes determines the level of quality of care.

## HEALTH CARE DELIVERY SYSTEM

### Overview and Financing

Health care services in the United States are delivered within a complex system. In 2013, the United States spent \$2.9 trillion on health care, amounting to 17.4% of total economic output for the nation, and equal to \$9,255 per person. The ultimate source of all funding for health care is from a portion of workers' total compensation directed to health benefits or from taxes collected. Health care services are consumed by individuals but paid for through a combination of private and public insurance coverage, out-of-pocket spending, and public health programs. Over one-half (55%) of all health care is directly paid for by the private sector, but indirect financing via tax deductions means that the federal, state, and local governments actually contribute more than half of all spending (54% if the federal tax deduction for health insurance premiums is moved from the private side to the public side of the ledger). Growth in health care spending in the United States has been a significant concern during the past

several decades. These concerns culminated most recently in the 2010 passage of the Patient Protection and Affordable Care Act of 2010 (ACA), which is viewed as the most comprehensive package of changes and reforms to the US health system in decades.

Although most children have health insurance coverage through their parents' employer-based health insurance or another private source (54%), many children (37%) have publicly sponsored coverage through Medicaid and the Children's Health Insurance Program (CHIP). On average, children younger than 18 years receive one-fifth of the public spending on health services. Despite their representing one-third of the population, just 15% of personal health care spending (\$285 billion, 2010 data) was on children. This equates to \$3,628 per child, which is 60% of the spending on 19- to 64-year-olds and one-fifth of the spending on those older than 65 years. As with adults, the largest category of spending for children's health care was on hospital services (\$121 billion) followed by physician and clinical services (\$76 billion). Increasing numbers of children are taking prescription medications, with rising expenditures in that area over time (\$18 billion in 2010), which is also similar to adults. Also, like adults, a small percentage of children consume a disproportionate share of health spending. For example, in the Medicaid and CHIP programs, the top 10% of enrollees consumed 72% of total spending. Two-thirds of these children have chronic conditions.

### Child Health Care Delivery Sites

Children receive health care services in a wide variety of inpatient and outpatient settings. Although home visits and home-based care were once commonplace in the United States, most pediatric professionals no longer make house calls. Select populations of higher-risk families (eg, teen mothers) or higher-risk infants (eg, those with poor weight gain, borderline elevated bilirubin in newborns) may receive home care visits, but most formal medical care is not provided at home. In other countries, however, nurse home visitation, particularly for families of newborn and infant children, is a routine part of pediatric primary care.

### Inpatient Care Facilities

Hospitals have changed dramatically during the past 20 years in response to financial pressures to reduce lengths of stay and rates of admission. Many hospitals now offer a wide range of services across multiple sites integrated in a network, including inpatient care, outpatient diagnostic procedures, surgery, and outpatient physician visits. Up to 28% of hospitals are part of systems, defined by the American Hospital Association (AHA) as "a group of hospitals, physicians, other providers, insurers and/or community agencies that work together to coordinate and deliver a broad spectrum of services to their community." Whereas all inpatient care occurs in hospitals, hospital care can no longer be equated with inpatient care. Many hospitals have become integrated delivery systems that provide primary care, specialty care, ancillary services, and inpatient care.

There are 5,686 registered hospitals in the United States, including 4,986 nonfederal, short-term general and specialty hospitals. The remaining hospitals are psychiatric (406), federal (213), long-term care (81), and parts of institutions, such as prisons or college infirmaries. Among the nonfederal short-term hospitals, 2,904 are private not-for-profit hospitals (58%), 1,010 (20%) are state- or local-government-owned hospitals, and 1,060 (20%) are for-profit (investor-owned) hospitals. Not-for-profit status exempts institutions from paying taxes and allows them to borrow money in the tax-exempt bond market. In return, nonprofit hospitals are expected to provide community benefit, such as unreimbursed care to patients without insurance or community health programs. Twenty percent of hospitals are teaching hospitals affiliated with one of the nation's 134 allopathic medical schools. Most teaching hospitals are urban, whereas most of the nation's rural hospitals are small institutions with fewer than 100 beds.

Approximately 250 (5%) of US hospitals are considered children's hospitals. There are approximately 50 freestanding acute care children's hospitals, nearly all of which are teaching hospitals. There are approximately 100 joint children's hospitals, which are large pediatric programs in larger medical centers. Approximately 40 freestanding children's rehabilitation, specialty, and convalescent hospitals provide care to children in 16 short-term facilities and 24 long-term facilities. Finally, approximately 50 freestanding children's psychiatric hospitals provide mental health services to children and adolescents at 10 short-term and 40 long-term care facilities. The remaining majority of inpatient pediatric admissions occur at general hospitals.

In 2010, there were 35.1 million hospital discharges in the United States, including 3.8 million newborns. Excluding newborn admissions, there are approximately 2.0 million hospitalizations per year for infants and children younger than 16 years old. Children's hospitals account for 40% of pediatric inpatient days and 50% of the costs of childhood hospitalization in the United States (\$10 billion each year). The remaining majority of children, therefore, are hospitalized in general hospitals with and without pediatric units. Many smaller, rural hospitals are no longer operating pediatric units because of insufficient demand.

According to data from the Children's Hospital Association (formerly National Association of Children's Hospitals and Related Institutions), children's hospitals care for the sickest pediatric patients. Children's hospitals have diverse patient populations, with acute illness or acute exacerbation of illness accounting for many short admissions and complex illness or complex chronic conditions accounting for longer stays among fewer admissions. The median length of stay at children's hospital is in the 2- to 3-day range, but the mean is in the 5- to 7-day range. Children residing in low-income communities are more likely to be admitted to the hospital via the emergency department compared with those from higher-income residences.

Coordination of care for hospitalized children is a complex task that involves many health professionals. Because most pediatric inpatient care is infrequent and brief, it is important that it be managed and linked to the

child's primary medical home. This requires communication between the hospital physicians and the primary care pediatrician, as well as involvement of the family, meticulous and seamless hand-offs, and clear delineation of responsibilities at each stage in the care process.

Methods of payment for hospital services continue to evolve in the United States. Changes occurred in the early 1980s when the prospective payment system was instituted in the Medicare program. Hospital payment shifted from a cost basis (payment for each service billed) to a fixed fee based on the principal problem managed during the hospitalization (known as the diagnosis-related group [DRG]). This DRG-based payment system paid hospitals the same amount of money for all patients with the same diagnosis and severity, regardless of how long they stayed or what services were provided. DRGs provided financial incentives to shorten lengths of stay. The introduction of the DRG-based hospital payment system stimulated the proliferation of large outpatient specialty and surgical centers. Today the United States has one of the lowest hospital admission rates and among the lowest average hospital occupancy rates throughout all developed nations. Another hospital payment model is per diem, whereby hospitals are paid a set amount for each day a patient is hospitalized, again regardless of what services are provided. Contracts may have higher payments for days in intensive care units but may also have blended rates that pay the same amount for any location or level of service. Per diem contracting is typically linked to utilization review, in which case insurers review the level of care provided and need for hospital services. Children's hospitals face an array of payment methods, unlike adult hospitals, which primarily encounter Medicare DRG payments, or private insurance contracts that echo the DRG structure from Medicare. DRG or case-based payment is a growing trend in pediatric hospitals and is expected to increase the need for hospitals to operate efficiently.

### Outpatient Care Facilities

Outpatient visits for children occur in a large variety of publicly and privately owned facilities. Approximately 88% of primary care visits among children occur at physician's offices, 8% in hospital primary care clinics, and 4% in community health centers. Children may also receive care in school-based health centers, emergency departments, urgent-care centers, and, most recently, retail-based clinics located in drug stores and stores such as CVS, Wal-Mart, and Target. Unfortunately, services that occur in these varied settings are challenging to coordinate with services for the same patient that occur in the medical home.

### Practice Organizations and Locations

Pediatric physician organizations can be categorized into solo practice, group practice (single-specialty practices with general pediatricians only and multispecialty groups, which include general pediatrics and other types of specialties), health maintenance organizations, hospital-based practices, and freestanding emergency departments. The practice locations for office-based pediatricians in 2013 are shown in Table 1-1.



**Table 1-1**  
**Practice Settings**  
**for Office-Based**  
**Pediatricians, 2013**

TYPE OF PRACTICE SETTING	PERCENTAGE OF PRACTICE TYPE
Solo/2-physician group	12
Pediatric group, 3-10 physicians	26
Pediatric group, >10 physicians	6
Multiple-specialty group	12
Health maintenance organization (staff/group model)	2
Hospital/clinic	14
Medical school	18
Community health center	3
Other (eg, freestanding emergency department)	5

From American Academy of Pediatrics Periodic Survey of Fellows. Pediatrician's Practice and Personal Characteristics: US only, 2013. Percent of Pediatricians by Primary Employment Setting (Table 3). Available at: [www.aap.org/en-us/professional-resources/Research/pediatrician-surveys/Pages/Personal-and-Practice-Characteristics-of-Pediatricians-US-only.aspx](http://www.aap.org/en-us/professional-resources/Research/pediatrician-surveys/Pages/Personal-and-Practice-Characteristics-of-Pediatricians-US-only.aspx). Accessed September 8, 2015.

Once common, solo practice is now in decline. During the interval between 1996 and 2005, the proportion of visits to physicians who were in solo = 2-physician practices decreased 8.2%, whereas visits to physicians who were part of a group practice with at least 6 physicians increased by 4.5%. Historically, a single physician could provide high continuity of care for patients. Although this autonomy and continuity appeal to some physicians, they also require an individual facility with the operational and financial aspects of health care delivery, which have grown increasingly complex. Solo physicians also have a more difficult time arranging for after-hours, weekend, and vacation coverage than their group practice peers. Pediatricians entering the medical marketplace are increasingly concerned not only with their incomes but also with such quality-of-life factors as time spent in the office, vacation, and coverage flexibility. Other benefits of group practice include administrative economies of scale, more stable cash flow, stronger negotiating position with health plans, greater financial reserves that may facilitate investments in practice improvements such as health information technology, and the possibility of physicians developing areas of special expertise, which is useful for both primary care and specialty practices.

Private pediatric providers may be paid through fee-for-service payments for each office visit or outpatient service provided. This is the predominant form of payment for non-managed care private insurance primary care and nearly all specialty care. Capitated payments consist of fixed dollar payments to physicians on a per-member per-month basis, regardless of actual use by patients. This form of contracting is most common for Medicaid managed care programs and commercial health maintenance organizations. To gain efficiencies of scale for administrative expenses and greater leverage for negotiations with payers, practices may organize into Independent Practice

Associations (IPAs) or Group Practice Without Walls (GPWW). An IPA is a third-party physician-directed joint venture that allows contract negotiations and collaborative activities by practices that maintain separate tax identifications. It is the loosest form of multiple-practice organization, primarily formed to gain contracting leverage for physician services with managed care organizations. A GPWW is formed when private physicians form a new legal entity to develop and control a professional corporation but maintain separate office locations and direct operational control of their support staffs, equipment, records, and patient relationships. The GPWW has more centralized control, with a board and management structure, than does an IPA. In recent years, hospitals and health systems have also increased their purchase of physician practices, an activity seen in both adult and pediatric ambulatory practices.

Community health centers are one component of the federal government's consolidated Health Center Program that also includes homeless health centers, centers in public housing, and migrant health centers. For more than 35 years, the Bureau of Primary Health-care within the US Department of Health and Human Services, the Health Resources and Services Administration, has provided federal support for health center programs. These resources are used to fund services for medically underserved populations, particularly uninsured children and their families, immigrant and seasonal farm workers and their families, homeless persons, public housing residents, and those needing school-based health care. Community health centers focus on providing comprehensive primary health care to persons in medically underserved areas. The proportions of visits made to community health clinics and hospital clinics are much higher for the uninsured and minority racial and ethnic groups because of poorer access to physician practices for these groups. There are 1,250 community health centers that care for 20 million Americans with limited financial resources. It is estimated that they save the nation up to \$17.6 billion through preventive care and decreased use of emergency departments. Community health centers have received significant increases in funding during the past decade, and several provisions in the ACA provided funds and demonstration projects that include them.

Several other public sector *safety-net* provider systems offer health care services for uninsured and underinsured pediatric patients. These entities include local public health departments, community and migrant health centers, public hospital systems, and school-based clinic systems. In addition, many not-for-profit organizations assist in meeting the health care needs of uninsured and underinsured children.

### Access to and Utilization of Outpatient Services

More than three-quarters of children have at least 1 visit to a physician's office each year, 6% visit physicians in a hospital clinic, and 18% have 1 or more emergency department visits. Many studies have documented that children make fewer than the number of health assessment visits recommended by the American



Academy of Pediatrics (AAP). Barriers to accessing outpatient services are a chief cause of this underuse. A most important barrier to accessing care is limited availability of pediatric providers in some geographic regions, which has at its root decreased financing of pediatric care. A shortage of pediatricians in rural areas is linked to the maldistribution of pediatricians nationally, in part because of challenges of financial viability in rural areas. The effects of payment levels are also seen in all parts of the country for other services, including pediatric specialty care, mental health services, and dentistry. For example, use of dentists in the United States remains low, with just 40% of children seeing a dentist annually, a consequence of lack of adequate financing for these services. For other types of services, children's insurance may not fully cover the office visit. (Lack of coverage among insured persons for needed services is a problem that has been labeled *underinsurance*.) Additional access barriers to seeking outpatient care include geographic access problems (lack of pediatricians in the community or difficulty traveling to the practice site) and organizational access problems (eg, for non-native English speakers, a lack of interpreters, limited after-hours care, or long appointment waits).

One-parent families and those with 2 working parents make up most of the families in the United States. To maintain access to services with these logistical barriers in mind, practices have extended their office hours to provide coverage during evenings and on weekends, in addition to on-call coverage at night. This trend is a departure from the office hours that pediatricians traditionally provided. After-hours coverage is provided in settings that are convenient, such as using the pediatrician's own office or an examination suite at the local community hospital. Many pediatricians join with their colleagues in sharing after-hours or weekend coverage. They take turns covering the telephone and meeting patients' needs, with prompt referral back to the patient's designated physician. This approach provides efficient off-hours medical care and affords each physician more time for other activities.

### **Distribution, Practice Locations, and Access to Pediatric Care**

Pediatrics is widely viewed as the principal specialty responsible for setting child health care policy and ensuring the health of the nation's children. Between 1996 and 2006, the percentage of visits to general pediatricians by children and adolescents aged 17 and younger increased from 61% to 71%, whereas the percentage of visits to nonpediatric generalists (eg, family physicians) decreased from 28% to 22%. Notably, between 2000 and 2006, the proportion of visits for adolescents changed most, with 53% of visits to general pediatricians in 2006, up from 38% in 2000. The percentage of visits to pediatric specialists for these patients increased from 2% to 5%, whereas the percentage of visits to nonpediatric specialists declined from 22% to 12%. These data suggest that more children, especially adolescents, are receiving care from general and specialized pediatricians. These data, however, must be interpreted with caution as they represent proportions,

rather than rates per child. Although certain conditions may be better suited to care of pediatric specialists, there are limited data on improved outcomes for children cared for by pediatric specialists versus adult specialists, especially among older children and youth. One exception, among several, is the field of cardiology, where adult cardiologists are generally not trained to care for patients with congenital heart disease. As pediatric care increases survival of patients such as these, new demand will emerge for specialists who can transition children into adolescence and adulthood, with knowledge of the physiology and pathology of diseases and their adult sequelae, for example, physicians trained in both internal medicine and pediatrics (med-peds physicians).

On average, 1 certified general pediatrician can be found for every 1,300 children throughout the United States. This ratio is generally deemed to be an adequate supply of pediatricians overall, particularly given the higher growth in the number of pediatricians compared with the rate of growth of children. However, the statistic does not reflect important regional variation in the supply of pediatricians, with many rural and inner-city areas experiencing child health professional shortages. Approximately 1 in 10 children live in an area without a pediatrician. As of 2006, 1 million children lived in areas with no local pediatrician. Eighteen states had ABP-certified physician-to-child ratios of less than 0.1 per 100,000 children (which is rounded to 0 by the American Board of Pediatrics [ABP]) in 1 of 13 fields: adolescent medicine (8), cardiology (1), child abuse pediatrics (7), critical care medicine (1), development-behavioral medicine (4), emergency medicine (4), endocrinology (1), gastroenterology (1), hematology-oncology (1), infectious diseases (3), nephrology (3), pulmonology (3), and rheumatology (12). Although not considered a pediatric subspecialty, there are also shortages for child neurology and child and adolescent psychiatry.

Only 8% of pediatricians in the United States practice in rural communities to care for the 19% of the childhood population that lives there. By contrast, the 30% of children who live in large metropolitan areas are cared for by almost 54% of practicing pediatricians. The remaining 37% of pediatricians practice in suburban settings, serving 34% of the nation's children. Several factors have led to this maldistribution of pediatricians, but financial viability of practice in rural areas is one challenge. Except for pediatricians practicing in sparsely populated areas, which have limited hospital and technical support services and few pediatric specialists, pediatricians generally practice similarly throughout the United States. These professionals, like those in other specialties, tend to settle in areas that have a higher per capita income.

### **Medical Home**

The pediatric primary care patient-centered medical home (PCMH) is important for all children, not simply those who have long-term special health care needs. In addition to providing routine preventive services, anticipatory guidance, and acute care, the medical home adds several components to the conventional

examination room–based model of primary care: registries of patients with specific diseases to better facilitate ongoing chronic care management; care coordination processes that link children and families to appropriate medical, social, and community services; active and integrated comanagement between primary and specialty care; and patient education, particularly for patients with chronic and psychological disorders. The medical home should be easily accessible for patients, promote continuity of care, provide a wide range of services to meet most of the needs of children, and coordinate care received in all locations. These functions—access, continuity, comprehensiveness, and coordination—are the core attributes of primary care as defined by the Institute of Medicine. Research evidence demonstrates that when these functions are attained at a high level, children are less likely to be hospitalized for health problems that might be managed in outpatient settings, families report greater satisfaction with care, and health care costs are reduced. Widespread adoption of the PCMH model, however, calls for a more rational and enhanced payment for primary care services to replace the current episodic and volume-driven payment mode. (For a comprehensive discussion regarding the medical home, see Chapter 6, Medical Home Collaborative Care.)

### Patient Call Centers or After-Hours Programs

Pediatric call centers or after-hours programs (AHPs) have been established in all areas of the United States. Patients greatly value ready access to medical advice outside of office hours, a trend that has grown with the rise of families with 2 parents in the workforce. AHPs are staffed by trained personnel on nights, weekends, and holidays. They give advice for symptomatic care and appropriate prescription refills, make referrals to an emergency facility or to an after-hours pediatric office, or advise seeing the patient's own pediatrician during office hours. AHPs operate under professional oversight, using standardized protocols provided by pediatricians who use their services. In many instances, health care systems subsidize AHPs on behalf of their network of pediatricians because of the efficiency and cost savings attributed to them. In a large, multicenter study, 65% of parents reported no preference about speaking with a physician or nonphysician for after-hours care, but 28% indicated a preference to speak with a physician. More than 80% of parents follow through with recommendations made by the call center professionals.

## PEDIATRIC WORKFORCE

Pediatrics and children's health care are not synonymous. A pluralistic mix of pediatricians, internal medicine, family medicine, pediatric specialists, and nonphysician clinicians provide services to the nation's children. Key trends in the pediatric workforce include: sustained interest in the field among graduating medical students; more rapid growth in pediatricians than the population of children in the United States; the dominance of women in the field; the importance of international medical graduates to the

pediatric workforce, especially the subspecialty workforce; and a geographic maldistribution of physicians, particularly subspecialists but also primary care physicians.

### Physicians, Pediatricians, and Pediatric Specialists

In 2013 the total number of licensed physicians in the United States was approximately 829,962, with 56,282 (7%) self-designating as pediatricians. Approximately 70% of self-designated pediatricians obtain board certification from the ABP, and 53,697 were board certified in 2007 according to the American Medical Association. Among certified general pediatricians, 20,138 (38%) have an additional certificate in a pediatric subspecialty.

Across all medical specialties, women constitute 33% of all physicians, but they represent 60% of pediatricians. Currently, 73% of pediatric resident trainees are women compared with only 30% in 1975. Historically, more men entered pediatric subspecialties, but this is changing. The rise in the number of female pediatricians is one of the more impressive and important trends shaping the pediatric workforce. Women are more likely than men to work part-time, and they spend fewer hours in direct patient care over their work lives. To maintain the same number of full-time equivalent physicians, more pediatricians may need to be trained each year in the future if the proportion of women in pediatrics remains as high as it is now or even increases.

Between 1993 and 2009 the proportion of pediatricians working part-time increased from 11% to 24%. On average, however, the way in which pediatricians spent their time was constant between these years. In 2010 office-based pediatricians worked 48 hours per week, spending approximately 34 of these hours in direct patient care, 6 in administration, 3 in academic medicine, 2 in research, and 2 in fellowship training. The allocation of time, however, is heterogeneous. Those in predominantly clinical roles may spend all their time on patient care and related administration, whereas those in academic settings may spend 50% to 80% of their time on research and/or teaching. For example, only 59% of certified pediatric subspecialists' time is spent in direct patient care. The remainder is spent in research, teaching, and administration. This is because 60% practice in academic health centers, contrasting with fewer than 33% of internal medicine subspecialists who do so. The perceived or required need to practice subspecialties in pediatrics at academic medical centers has implications for geographic distribution of these physicians, the clinical work hours they offer, and incentives for choosing the field as a career. Increasing numbers of pediatricians practice part-time, with those physicians reporting an average of 25 hours per week of direct clinical care.

### Physician Training for Pediatrics

The traditional path to medical practice in pediatrics includes completion of 4 years of undergraduate studies, 4 years of medical school (or more if in a dual-degree program), and 3 years of residency training in

pediatrics. The current structure and processes of medical education are rooted in early 20th-century “reforms” following the Flexner report. In the past 2 decades, questions have been raised about the relevance of the training model given the current and future nature of medical science and health care delivery. Medical students and physicians also do not receive training in the economics or business of health care delivery of medical practice.

Consumers and providers of health services differ in the priorities they place on the 3 main challenges of the health care delivery system: ensuring *access* to care, controlling *costs*, and improving the *quality* of care. Costs of and access to medical care are of prime importance to consumers, who tend to assume that quality of care will always be good. In contrast, neither access nor cost has been an important component of medical school training, which focuses almost exclusively on how to make a diagnosis; how to support this diagnosis with appropriate information from the history, physical examination, and laboratory findings; and how to institute treatment that is appropriate to the diagnosis. The nature of most educational settings (university based, research oriented, with generally a highly specialized faculty) is responsible for a medical educational process that focuses largely on the biological bases of disease. In contrast, relatively little attention is devoted to understanding the social, occupational, and environmental causes of ill health, although issues such as these are major determinants of disease and dysfunction or patients’ subjective assessment of their own health.

### Residency Training

After medical school (referred to as undergraduate medical education), approximately 14% of medical school seniors select a pediatric training program (graduate medical education, or GME). There are 123,310 on-duty residents in the United States, among whom 7% are training in pediatrics. In academic year 2014–2015, there were 199 programs accredited according to the Accreditation Council for Graduate Medical Education, or ACGME for general pediatric residency training in the United States and another 17 in Canada. There were 8,979 on-duty pediatric residents in academic year 2014–2015 according to the ACGME; according to the ABP, there were 9810 residents in training in 2014. These differences are the result of trainees in combined programs, such as child neurology, as well as special tracks, such as research. When compared with 1999 figures, this growth is a 23% increase in the absolute number of pediatric residents, a rate of rise that far exceeds the proportional increase in the number of children in the country. Interest in pediatrics as a career choice continues to be strong.

In 1967 the ABP and the American Board of Internal Medicine (ABIM) agreed that individuals who had 2 years of general internal medicine and 2 years of general pediatrics were eligible for board certification in both specialties. In 2014–2015, there were 79 accredited for combined med-peds residency in the United States; these programs have 1,477 on-duty residents.

The percentage of women enrolled is less than in categorical pediatrics and has been stable over the last few years at about 58%. In rural communities or small towns, the med-peds physician may play a role as a consultant in the care of high-risk newborns and children who have a chronic illness or as a hospitalist for children and adults. These physicians may subspecialize in fields with larger numbers of children with chronic illnesses of childhood who are surviving into adulthood. In other markets, internal medicine and pediatric practices can use the med-peds physician to attract new patients, especially adolescents and families desiring health care for everyone in the same practice. Because med-peds physicians can alter their practice according to patient demand, the amount of pediatric care that these health professionals will provide will likely decrease with the aging of the population and the growing cohort of adult survivors of congenital and chronic childhood illness. Upon completion of residency, trainees are eligible to sit for the pediatric certifying exam (“board eligible”). They may enter practice in general pediatrics on an inpatient or outpatient basis or continue training in a fellowship program for further specialization.

### Pediatric Specialization

In 2014, 59% of first-time general pediatrics test-takers selected a career as a general pediatrician, 30% a career in a pediatric subspecialty, and 5% a career in another nonpediatric specialty. In addition to general pediatrics, 20 areas of pediatric subspecialization are certifiable by the ABP (Table 1-2). The absolute number of subspecialty trainees has nearly doubled since 1999. 1996 and 2003. In 2014–2015, there were 1,541 first-year, 1,386 second-year, and 1,293 third-year fellows in pediatric subspecialty training. By comparison, in 1999–2000, there were 796 first-year fellows (in fewer specialty training programs). The top 5 career choices among pediatric subspecialty fields are neonatal-perinatal medicine, critical care medicine, hematology-oncology, cardiology, and emergency medicine. Women graduating from medical schools more recently are more likely than their older female counterparts to choose a subspecialty career, although male physicians still predominate within most subspecialties.

In general, primary care salaries are lower than those for specialists, although the differences are not as stark in pediatrics as in adult medicine. For the first 3 to 5 years after residency, primary care physicians can be expected to have expenses that exceed earnings.

### International Medical Graduates

International medical graduates (IMGs) constitute an important share of the pediatric workforce. IMGs receive their undergraduate medical education abroad but complete their residency in the United States. In 2014, IMGs accounted for 25% of all general pediatricians (vs 24% of all US physicians). Nearly 1 in 3 board-certified pediatric subspecialists are IMGs. Pediatrics is the third-highest specialty among IMGs (8.5%), representing growth from 1980 when it was fifth highest (6.8%). The subspecialties with the greatest proportions of IMGs are geriatric medicine (50%), nephrology (45%), and international cardiology (43%).



**Table 1-2**      **Number of Board-Certified Pediatric Subspecialists Through 2014**

<b>PEDIATRIC SUBSPECIALTY*</b>	<b>NUMBER CERTIFIED</b>
Adolescent medicine (1994) <sup>s</sup>	650
Cardiology (1961) <sup>s</sup>	2,947
Child abuse and pediatrics (2009) <sup>s</sup>	324
Critical care medicine (1987) <sup>s</sup>	2,377
Developmental-behavioral pediatrics (2002) <sup>s</sup>	720
Emergency medicine (1992) <sup>s</sup>	2,046
Endocrinology (1978) <sup>s</sup>	1,635
Gastroenterology (1990) <sup>s</sup>	1,469
Hematology-oncology (1974) <sup>s</sup>	2,780
Hospice and palliative care (2008) <sup>^</sup>	234
Infectious disease (1994) <sup>s</sup>	1,432
Medical toxicology (1994) <sup>s</sup>	42
Neonatology-perinatal medicine (1975) <sup>s</sup>	5,930
Nephrology (1974) <sup>s</sup>	932
Neurodevelopmental disabilities (2001) <sup>^</sup>	255
Pulmonology (1986) <sup>s</sup>	1,203
Rheumatology (1992) <sup>s</sup>	364
Sleep medicine (2007) <sup>^</sup>	251
Sports medicine (1993) <sup>^</sup>	247
Transplant hepatology (2006) <sup>^</sup>	103

\*Year in parentheses indicates when subspecialty board was established.

<sup>s</sup> = certificate of special qualifications

<sup>^</sup> = certificate of added qualifications

From American Board of Pediatrics 2014 Workforce Data: Pediatric subspecialty Diplomates Certified Through December 31, 2014.

Available at: [www.abp.org/sites/abp/files/pdf/workforcebook.pdf](http://www.abp.org/sites/abp/files/pdf/workforcebook.pdf).

Accessed September 8, 2015.

The most common countries of citizenship for IMGs are (in rank order, 2007 data): United States (US citizens trained abroad), India, Philippines, Mexico, Pakistan, and the Dominican Republic. Resident and fellowship training of IMGs continues, although the percentage of first-year pediatric residents who were IMGs declined from 33% to 20% from 1991 to 2014. For fellowship, however, large numbers of subspecialty trainees are IMGs, notably in pulmonary disease (92%), nephrology (68%), and geriatric medicine (63%).

### Hospitalists

The traditional American system in which primary care physicians have cared for their hospitalized patients is undergoing a dramatic change. The field of hospital medicine and the role of hospitalists have grown rapidly in the past decade, and hospital medicine has been the fastest growing field in pediatrics. Hospitalists replace primary care physicians in managing patients while in the hospital. Factors contributing to the growth of hospitalists' role include greater complexity of hospital care, need for greater efficiency in both outpatient and inpatient settings limiting the ability to do both, reduced work hours for trainees, and demand for attention to high-quality outcomes

for hospitalized children. A 2009 survey by the Society of Hospital Medicine found that there are nearly 30,000 hospitalists in the United States, with an estimated 2,500 who focus exclusively on pediatrics. This represents rapid growth from 2002, when there were an estimated 600 pediatric hospitalists. In 2003, 40% of pediatricians were affiliated with a hospital that employed a hospitalist. This proportion is expected to continue to grow over the next several years.

Hospitalists are physicians whose main responsibility is the general medical care of hospitalized patients and whose responsibilities may also include teaching, research, and administrative duties. Pediatric hospitalists spend most of their clinical time on inpatient units, but not in the nursery, subspecialty units, or outpatient clinics. However, as with adult counterparts, pediatric hospitalists are taking on additional roles, including provision of newborn services, comanagement of surgical patients, and additional training and work in sedation and procedural roles. Hospitalists also seem to be effective teachers in academic centers. Patients are referred by primary care physicians and are referred back at the time of hospital discharge. The disadvantages of this arrangement include a loss of continuity of care between the primary care physician and the patient and a decreased scope of practice among general pediatricians. This requires careful attention to coordination of care and communication across the inpatient and outpatient domains. The use of hospitalists allows for increased productivity by the office-based pediatrician. During office hours, leaving the office with waiting patients to see a hospitalized patient is difficult for a physician. Other reported advantages of hospitalists include their competency in technical skills (skills easily lost to the physician who visits the hospital only occasionally), shorter patient hospital stays because of constant in-hospital supervision, and the immediate availability of urgent care. (See Chapter 9, Partnering With Families in Hospital and Community Settings, and Chapter 10, Family-Centered Care of Hospitalized Children.)

### Nonphysician Clinicians

A large body of research evidence indicates that appropriately trained nonphysician clinicians—nurse practitioners and physician assistants—provide health care for many health conditions that is of equal quality to that provided by physicians. Because they can be trained at lower costs to society and their salaries are lower than those of physicians, many physician organizations and health maintenance organizations employ these professionals as primary care physicians and physician extenders in specialty settings. States are giving more independence to nonphysician clinicians. Restrictions on the work hours of resident physicians enacted in 2003 and updated in 2010 by the ACGME are another driver of the increasing role of nonphysician clinicians. In its official policy statement on nonphysicians in clinical care, the AAP states, "Pediatricians should respect the contributions of other health care professionals but also acknowledge the appropriate limitations and roles of these professionals." Further, "The AAP realizes that nurse practitioners, physician assistants, and other nonphysician

pediatric clinicians may care for children in underserved areas where patients have limited or no access to a physician. However, a pediatrician should oversee these clinicians.”

Pediatric nurse practitioners (PNPs) are usually prepared at the master’s degree level after training in nursing. Approximately 90% practice in primary care settings. A small share may be certified in a specialty, and recently there have been increases in those practicing in hospital settings. Outpatient PNPs conduct physical examinations, track medical histories, make diagnoses, treat minor illnesses and injuries, monitor chronic disease maintenance therapy, and provide an array of counseling and educational services. Inpatient PNPs are often found in intensive care units and emergency departments, although also in general medical and surgical units, and provide front-line care similar to resident physicians or hospitalists. In many states, PNPs prescribe medications independently, admit patients to hospitals, and make hospital rounds. As of 2008, there were 13,384 PNPs in the United States. Most PNPs worked in private practice (39%) or an academic medical center (25%). The remainder worked in community hospitals (14%), community clinics (10%), school-based health clinics (7%), managed care organizations (3%), retail-based or urgent care sites (1%), and nurse-managed centers (1%).

Physician assistants (PAs) are health care professionals licensed to practice medicine with physician supervision. Similar to nurse practitioners, PAs conduct physical examinations, diagnose and treat illnesses, order and interpret tests, write prescriptions, and counsel on preventive health care; they may also assist in surgery and in other procedures. Because of the close working relationship they have with physicians, PAs are educated in the medical model designed to complement physician training. The number of pediatric PAs is smaller but growing. In 2009, 2,144 pediatric PAs self-identified.

## PROCESSES OF HEALTH CARE

The process of health care consists of the interactions between patients and professionals. From the physician’s perspective, key processes include identification of and screening for new problems; patient education; matching appropriate services to a patient’s needs; diagnosis using cognitive processes, laboratory testing, and imaging studies; treatment with watchful waiting, information giving and guidance, prescribing, and therapeutic procedures; follow-up of ongoing problems; referral to specialists and community resources; and admission to the hospital. From the patient and family’s perspectives, the key processes of health care are seeking health care and choosing to use services, disclosing health-related information and asking questions, self-management for ongoing problems, participating in the recommended care plan, and assessing treatment effectiveness.

### Scope of Pediatric Practice

The time a pediatrician spends in office practice remains challenging and interesting, although it is channeled differently than it was in the past. Through much of the early and middle 20th century, the practicing

general pediatrician was the daily expert, always on call in the office for families in need or making frequent house calls and hospital rounds. General pediatricians dealt with all minor and most major illnesses. Pediatric subspecialists were few, usually found only in academic medical centers. Concepts such as *primary* and *tertiary* pediatric care were less known, and pediatric intensivists, neonatologists, and other subspecialists did not exist in community hospitals.

Today, the office-based primary care pediatrician practices differently, although still as the specialist providing medical care for children. The patient is almost always seen in the office, rarely in the hospital, and almost never in the home. The illnesses treated by the primary care pediatrician today do not resemble those of the past when serious infections and their sequelae were more common. Today, upper respiratory tract infections, moderate lower respiratory tract problems, feeding problems, gastrointestinal upsets, and minor trauma account for upward of 85% of illness care. Pediatricians evaluate and diagnose more serious conditions, coordinate and manage chronic illnesses, and collaborate with specialists on the care of children receiving such services. The primary care pediatrician spends more time on anticipatory guidance, including the promotion of health and well-being in children. A large portion of practice time is spent giving well-child care, dealing with family dynamics, and managing the new morbidities of mental illness, obesity, and school failure. Practices in urban areas deal with many of these issues with greater frequency and intensity. The new scope of contemporary pediatric primary care is summarized in Box 1-1.

Changes in how acute infections are managed or prevented will have important and perhaps even dramatic effects on the future scope of pediatric practice. National policy recommendations to decrease use of antibiotics for upper respiratory infections and otitis media have led to fewer prescriptions and visits for these conditions. New vaccines will further reduce the burden of acute illnesses in pediatric practice and could allow pediatricians to provide more comprehensive services to enhance child health and development; promote healthy transitions into school, adolescence, and adulthood; reduce the suffering associated with psychosocial problems; and collaborate with families to maximize the chances that all children become flourishing adults.

### Referrals: Linking Primary Care With Specialty Care

Physicians providing primary pediatric health care assume responsibility for a broad spectrum of preventive and curative care and for coordinating the care their patients receive from other physicians. When primary care physicians need assistance in diagnosing and managing difficult cases, desire a specialized test or procedure (eg, endoscopy or surgery), or believe that management of their patients’ health problems falls outside their scope of practice, they seek consultation and referral (See Chapter 6, Medical Home Collaborative Care). Approximately 2% of all general pediatric visits lead to a referral, and pediatricians make approximately 1 referral a day. Referrals are also



**BOX 1-1 Scope of Pediatric Primary Care Practice**

- Prenatal counseling to families preparing for the birth of their child
- Immunization for all age groups in the practice, with prior educational advice as to the benefit, risk, and alternatives
- Acute illness management, including watchful waiting, appropriate prescribing, education, and follow-up
- Injury prevention by giving advice about seat belts, smoke alarms, water safety, home safety, poison control, and bicycle helmets
- Minor injury treatment
- Coordinating services for children with complex medical needs
- Structuring the practice consistent with the principles of the medical home
- Collaborating with families to support the achievement of educational goals from infancy through adolescence
- Becoming an expert on violence prevention and abuse avoidance
- Providing advice and support during divorce, marital crises, or a loss of a family member
- Counseling families on lifestyle goals, such as the need for family time and for an understanding of work-related time constraints and stresses and how the family copes with them
- Promoting good health habits through advice about a prudent diet and nutrition, exercise, and dental hygiene
- Promoting avoidance of bad health habits such as sedentary activity, excessive television watching and video game playing, and parental smoking
- Identification and management of developmental and psychosocial problems, which is composed of screening, talk therapy, medication management, referral to and comanagement with behavioral health specialists, and linkage with appropriate community resources
- Encouraging community activism through knowledge and use of common resources and involvement with school boards, religious groups, school athletic programs, and community facilities
- Care of adolescents and young adults, with the twin goals of providing guidance and anticipating problems in areas such as sexuality, sexually transmitted infection avoidance, drug and alcohol abuse and teenage pregnancy prevention, and education and career goals advice
- Supporting families to ensure that all children become flourishing adults

made in telephone conversations with parents, which account for 25% of all referrals. For 75% of referrals, pediatricians anticipate sharing care with, not delegating care entirely to, the specialist; unfortunately, this practice is not often achieved, although delivery systems are finding ways to promote comanagement using an information technology platform or by locating generalists in specialty offices to evaluate and manage lower-acuity referrals.

The 15 most common health problems that general pediatricians refer to specialists and the types of specialists referred to for each problem are shown in Table 1-3. Most referrals are not for chronic diseases or for children with special health care needs but rather are made for time-limited musculoskeletal, skin, eye, or ear, nose, and throat problems. An important caveat is the large share of referrals for psychosocial and developmental problems, which, if combined, would be the most common reason for referral. Many specialties have overlapping scopes of practice, which is reflected in Table 1-3; for example, pediatricians send patients with hernias and hydroceles to both general surgeons and urologists. Why one type of specialist is selected rather than another is related to a pediatrician's personal preference and the relationships the primary care physician may have with specialist colleagues.

Among young children, an equal proportion of visits are made to pediatric subspecialists and non-pediatric-trained specialists. By adolescence, however, a greater share of visits occurs with specialists who

are not trained as pediatricians. Pediatric societies have championed the notion that the specialty care of children and adolescents should be provided by pediatric-trained medical and surgical specialists. For example, the Surgical Advisory Panel of the AAP in 2002 asserted that all children 5 years or younger who require surgical care should be referred to a pediatric surgeon.

**OUTCOMES OF CARE**

The purpose of health care is not merely to build delivery systems or produce medical services. A society establishes a child health care system to improve children's health and well-being. Thus, the most important measures of pediatric health care effectiveness are related to the effect of services on child health and well-being. The claim that *children are healthy* is a myth that originates in the anachronistic notion of children as little adults. Pediatrics is clearly different from adult medicine, as articulated by the 4 unique characteristics of childhood: developmental change; dependency on parents and other adults for receiving health care; differential epidemiology of health, illness and disability; and demographic patterns that include high rates of poverty and single-parent families. Focusing on the word *healthy* in this context, if children are considered *little adults*, then their lower disease burden is certainly an indicator of better health. Only 10% of children have one of the long-term disorders—diabetes, cardiovascular disease, or asthma—that are typically included in disease-specific

**Table 1-3****The 15 Most Common Health Problems General Pediatricians Refer to Specialists and Nonphysician Clinicians With Specialized Skills**

HEALTH PROBLEM REFERRED	PERCENTAGE OF ALL REFERRALS MADE BY GENERAL PEDIATRICIANS	MOST COMMON TYPES OF SPECIALISTS REFERRED TO (PERCENTAGE OF TOTAL)
Otitis media	9.2	Otolaryngologist (95.3) Audiologist (3.5)
Refractive errors	5.6	Ophthalmologist (67.3) Optometrist (32.7)
Musculoskeletal signs and symptoms	5.0	Orthopedic surgeon (71.0) Physical therapist (11.8)
Benign skin lesions	4.5	Dermatologist (80.7) Plastic surgeon (10.8)
Behavioral problems	3.5	Psychologist (58.5) Psychiatrist (18.5)
Fractures (excluding hips and digits)	2.9	Orthopedic surgeon (92.5) Otolaryngologist (7.5)
Joint disorders, trauma related	2.7	Orthopedic surgeon (87.8) Physical therapist (12.2)
Developmental delay	2.6	Neurologist (20.8) Orthopedic surgeon (12.5)
Hearing loss	2.5	Audiologist (71.3) Otolaryngologist (28.3)
Strabismus, amblyopia	2.5	Ophthalmologist (97.8) Optometrist (2.2)
Viral warts and molluscum contagiosum	2.5	Dermatologist (87.0) Podiatrist (8.7)
External abdominal hernia and hydrocele	2.3	Pediatric or general surgeon (90.7) Urologist (9.3)
Depression and anxiety	2.3	Psychiatrist (52.4) Psychologist (40.4)
Allergies	2.1	Allergist (89.5) Ophthalmologist (5.3)
Chronic pharyngitis and tonsillitis	2.0	Otolaryngologist (94.6)

studies. Likewise, no more than 20% of children have a chronic physical, developmental, behavioral, or emotional condition that requires health and related services of a type or amount beyond that required by children generally. Less than half of these have conditions that affect a child's activities of daily living. The low prevalence of medical disorders calls into question the appropriateness for children of the conventional disease-oriented model of health. Certainly, a focus on children with chronic conditions merits continued attention. However, if improvement in the health and well-being of all children is the goal, then pediatrics must maintain an expanded conceptualization of child outcomes.

The developmental trajectories of childhood, which result from dynamic person-environment interactions, and the importance of the family to child outcomes are additional reasons that a child-specific outcomes framework is needed. Perspectives of health that incorporate a time dimension and the need to consider factors that threaten or promote future health are now encompassed in accepted definitions of health. Using this comprehensive concept of health, more than 50% of children have a significant need in terms of their

well-being, symptom burden, risk behaviors, or psychosocial resilience. The time dimension of health suggests the need to focus attention on risks—health states and behaviors that are precursors to future morbidity, injury, and illness—as well as health promotive factors. Although the consequences of risks may not manifest until adulthood, antecedents to risk behaviors and states are molded during childhood, and many risk behaviors make their debut in adolescence. The weight-activity-nutrition complex illustrates this life course perspective. In childhood, the antecedents to obesity—eating and activity behaviors—are formed. By late middle childhood and early adolescence, approximately 1 in 6 individuals is overweight, with a heightened risk for future disease. For most individuals, the consequences of obesity—diabetes, asthma, low back pain, hypertension, and heart disease—do not become a problem until adulthood, although they occasionally appear in adolescence and even in childhood.

Promoting child health has intrinsic merit and has benefits for adulthood. Viewing health across the life span has been called the *life course model of health*. The model suggests that health is produced across the

life span, but childhood is a critical period. Unique person–environment interactions exist at each stage of development, some of which can have profound effects on future health. In addition, health care delivery must be considered in the framework of broader societal needs, such as improving the health of the whole population, enhancing patient experiences, and reducing (or at least controlling) per capita costs of care—aims the Institute for Healthcare Improvement calls the Triple Aim.

In summary, a framework for assessing the effects of health delivery systems on child outcomes must be specific to the unique needs and experiences of children, be developmentally sensitive, incorporate a time dimension, and be rooted in a life course model of health production. Table 1-4 provides such a framework, showing the key child outcome concepts and examples of specific metrics. Each of the 8 child outcome domains from Table 1-4 is discussed here, with special emphasis given to linkages with medical services.

### Survival

The significant declines in mortality during the past century can be attributed more to improvements in public health than to specific technological advances applied to individual patients. The discovery of antibiotics was the most important scientific advance applied to individual patients that has had an impact on improving life span. The marked improvement in life expectancy over the last century has resulted primarily from lowered infant mortality. Infant mortality began to decline long before specific medical interventions were imposed, and the decline resulted from general improvements in sanitation, maternal nutrition, hygiene, and infant feeding. Immunizations are an important, although not singular, determinant of this decline. After infancy, deaths in childhood are so relatively infrequent that they are an insensitive indicator of the value of medical interventions. Some researchers have argued that disease-specific mortality statistics, such as 5-year cancer survival, are the most

**Table 1-4**

**Child Outcomes Framework for Assessing the Effects of Health Care Delivery Systems, Organized by 8 Domains**

OUTCOME	MEASURES (EXAMPLES)
<b>SURVIVAL</b>	<ul style="list-style-type: none"> <li>• Infant mortality</li> <li>• Life expectancy</li> <li>• Five-year survival rates for specific diseases, such as cancer</li> <li>• Cause-specific mortality rate, such as mortality caused by asthma</li> </ul>
<b>INJURY AND DISEASE</b>	
Injury	<ul style="list-style-type: none"> <li>• Unintentional injuries</li> <li>• Intentional injuries</li> <li>• Child abuse and neglect rates</li> <li>• Suicide rates among youth</li> </ul>
Development of disease	<ul style="list-style-type: none"> <li>• Vaccine-preventable infections, such as measles, hepatitis B, pertussis</li> <li>• New cases of specific disorders, such as asthma, depression, attention deficit disorder, type 2 diabetes, seizure disorder, allergies, acne, metabolic syndrome, anxiety</li> </ul>
Disease complications	<ul style="list-style-type: none"> <li>• Severe dehydration</li> <li>• Suicide associated with depression</li> <li>• Iatrogenic complications associated with surgical interventions</li> <li>• Iatrogenic complications associated with medications</li> <li>• Consequences of untreated or inadequately treated infections, such as post-streptococcal glomerulonephritis, Lyme arthritis, pelvic inflammatory disease</li> </ul>
Disease severity	<ul style="list-style-type: none"> <li>• School days lost resulting from illness</li> <li>• Among patients with diabetes, glycated hemoglobin level</li> <li>• Among patients with asthma, forced expiratory volume in 1 second</li> <li>• Among children with hypertension, systolic and diastolic blood pressure levels</li> <li>• Cancer stage at diagnosis</li> </ul>
<b>GROWTH</b>	<ul style="list-style-type: none"> <li>• Birth weight</li> <li>• Underweight and failure to thrive</li> <li>• Overweight and obesity</li> </ul>
<b>FUNCTIONING AND DEVELOPMENT</b>	
Mobility	<ul style="list-style-type: none"> <li>• Attainment of age-appropriate mobility developmental milestones (eg, age child walked)</li> <li>• Days of restricted activity</li> <li>• Amount and frequency of physical activity</li> </ul>

*Continued*

**Table 1-4****Child Outcomes Framework for Assessing the Effects of Health Care Delivery Systems, Organized by 8 Domains—cont'd**

OUTCOME	MEASURES (EXAMPLES)
Self-management	<ul style="list-style-type: none"> <li>• Attainment of age-appropriate self-care developmental milestones (eg, getting dressed independently)</li> <li>• Sleep habits</li> <li>• Nutritional intake behaviors</li> <li>• Dental hygiene</li> <li>• Adherence to medication regimens</li> </ul>
Communication	<ul style="list-style-type: none"> <li>• Attainment of age-specific receptive language capacities</li> <li>• Attainment of age-specific expressive language capacities</li> </ul>
Interpersonal interactions	<ul style="list-style-type: none"> <li>• Developing satisfying and fulfilling friendships</li> <li>• For youth and young adults, developing intimate relationships</li> </ul>
Intellectual performance	<ul style="list-style-type: none"> <li>• School readiness</li> <li>• Academic performance, such as grades and grade completion</li> <li>• Graduation from secondary school</li> </ul>
<b>FAMILY</b>	
Family impact	<ul style="list-style-type: none"> <li>• Parental work days lost resulting from a child's illness</li> <li>• Parental worry about child's health</li> </ul>
Family connectedness	<ul style="list-style-type: none"> <li>• Parental time spent with children in activities such as play, recreation, meals</li> <li>• Quality and frequency of child–parent discussions about the child's life</li> <li>• Parental monitoring of children's activities within and outside the home</li> <li>• Parental monitoring of children's use of the media (TV, Internet, social networking)</li> </ul>
<b>RISKS</b>	
Risk behaviors	<ul style="list-style-type: none"> <li>• Tobacco smoking</li> <li>• Alcohol use</li> <li>• Drug use</li> <li>• Early sexual debut; unsafe sex practices</li> <li>• Not wearing a seat belt while riding in a motor vehicle</li> <li>• Not using a helmet while riding a bicycle</li> </ul>
<b>SYMPTOMS AND COMFORT</b>	
Symptoms	<ul style="list-style-type: none"> <li>• Physically experienced sensations, feelings, and perceptions that are the result of a disease process</li> <li>• Emotionally experienced sensations, feelings, and perceptions that are the result of a disease process</li> </ul>
Comfort	<ul style="list-style-type: none"> <li>• Physically experienced body sensations, feelings, and perceptions that are not associated with a known disease process</li> <li>• Emotionally experienced body sensations, feelings, and perceptions that are not associated with a known disease process</li> </ul>
<b>WELL-BEING</b>	<ul style="list-style-type: none"> <li>• Happiness</li> <li>• Self-worth</li> <li>• Life satisfaction</li> <li>• Meaning and purpose</li> </ul>

compelling mortality statistics to use to assess system effectiveness because they are directly related to the adequacy of treatment.

### Disease and Injury Prevention

Even though pediatricians may not be able to prevent the occurrence of most disorders, they should be expert at recognizing these problems when they occur. The application of diagnostic or therapeutic strategies requires first that problems, or potential problems, be recognized. Evidence indicates that the existence of many types of health problems is often overlooked. For example, physicians are consistently poorer at

recognizing the existence of behavior problems and social factors related to illness than they are at recognizing problems that have obvious biophysiologic or anatomic manifestations, even though these factors have profound influences on health and well-being. However, even organic problems may be neglected. Problem recognition also extends to prevention of disease.

One type of prevention, *primary prevention*, is traditional to pediatricians. It consists of recognizing susceptibility to disease and applying interventions to prevent disease from occurring. Although immunizations are the most obvious example of primary

prevention, prevention goes far beyond this measure. In some instances, only certain people are at risk for acquiring disease later in life; pediatricians must direct efforts at discovering who these people are, keeping them under surveillance, and trying to eliminate the situations that allow the illness to develop. This approach is known as *secondary prevention*, which is aimed at identifying disease in early stages before it causes significant morbidity. Secondary prevention occurs at the physician–patient level, as well as through the initiatives of government and social agencies. Examples of such efforts include hearing and vision screening in schools, screening programs for specific disease in special populations (eg, sickle cell anemia), and state-mandated neonatal screening for inherited metabolic disorders (eg, phenylketonuria). Newer prevention challenges for pediatricians concern recognizing and dealing with occupational hazards that result in parents unknowingly exposing their children to toxic materials invisibly carried home from the workplace. As social, occupational, environmental, and behavioral factors become recognized as important antecedents of many chronic illnesses, pediatricians will become more involved in activities directed toward preventing them.

Much of health care is devoted to minimizing the effect of diseases on health, which is *tertiary prevention*. Reducing the impact of injury by limiting the duration of disability is an outcome that health care delivery systems can affect, although the provision of health services is not the only determinant of functional recovery. Similarly, health care attempts to prevent or mitigate the effects of disease complications and to stabilize the disease itself so as to reduce its severity. Because managing the complexity, stability, and complications of disease is a common and effective part of pediatric practice, indicators of the adequacy of disease control are obvious candidates for outcomes for which the health care delivery system should be accountable.

### Growth

Monitoring children's growth is one of the cornerstones of pediatric primary care. Assessing growth requires pediatricians to examine both tails of the distribution, underweight and overweight, and linear growth. The ability of pediatricians to identify growth problems is well established. Whether pediatric professionals have an important effect on preventing growth problems is less clear. Today, approximately 17% of children are obese. Interventions that pediatricians can apply to prevent the problem of obesity are lacking. Problems with inadequate weight are more easily addressed by health care; however, the degree to which a health care delivery system can affect the healthy growth of an entire population remains to be demonstrated. (See Chapter 298, Obesity and Metabolic Syndrome.)

### Functioning and Development

Children's functional capacities in the areas of self-management, mobility, communication, interpersonal

interactions, and intellectual capacity rapidly change, and acquisition of new abilities characterizes stages of development; they are also targets of health services. Monitoring age-appropriate development of new capacities and intervening with children who have problems in each dimension are a fundamental part of well-child care. Increasing attention to early brain and child development, as well as reducing toxic stress, in the first 3 years of life holds great promise for reducing learning and behavior problems in school-aged children and adolescents.

Reducing the number of days of restricted activity, for example, because of acute illness or asthma is often a primary treatment outcome. When asked about the meaning of *being healthy*, children and youth talk about "being able to do what I want to do, play what I want to play, or see my friends." Similarly, children know that healthful self-management habits are an important part of their health status, and counseling on these topics is part of virtually every routine health visit. One of the new morbidities with which pediatricians have become more concerned is learning and intellectual development. For young children, pediatricians counsel parents about the importance of reading to brain development, enjoyment, and being prepared to learn once the child starts school. Programs such as Reach Out and Read ([www.reachoutandread.org](http://www.reachoutandread.org)) have been developed to provide office-based physicians with tools for promoting early childhood literacy.

As children get older, pediatricians work with them and their families in setting educational goals, monitoring children's performance in school, and, with youth, setting goals for their young adult professional lives. Perhaps the single best indicator of the health of a population of children and youth is the rate of graduation from secondary school. Healthy children finish high school and successfully transition into adulthood.

### Family

Children's health outcomes are inextricably bound with their family. The family and home life are the most important contexts in the production of children's health and for promoting their development. Parenting and family involvement in a child's life are especially critical. A variety of studies have shown that accumulated childhood exposures to different types of abuse or household dysfunction directly increase the risk for psychiatric disorder and several chronic diseases that emerge later in life. Abuse appears to alter the structures and functions of a child's brain and the body's reactivity to stress. Unstable (especially rejecting) parent–child relationships produce biological changes that interact with future environmental stimuli to produce adult disease.

Child health can affect the family by influencing parental emotions and mood (eg, excessive worry about a sick child, a depressed mood in a parent who devotes a large share of time to the care of a child with a special health care need) and parents' work productivity. These family outcomes can then affect children's health in a reciprocal dynamic relationship.



### Risks

When a child or youth engages in high-risk behavior, the chances of future injury or disease are increased. Not wearing a helmet while riding a bike enhances the likelihood that if the child is in a bike accident, a head injury will occur. Tobacco smoking in adolescence negatively affects pulmonary function and begins a cascade of negative effects on future cardiovascular and pulmonary structure and function. Early sexual debut heightens the chances for acquiring sexually transmitted infections and teen pregnancy. Inappropriate exposures to smoking, sex, and violence in the media, on the Internet, and via social networking all increase the likelihood of risky behavior in adolescents.

Routine health visits for adolescents should always address risk avoidance. Significant effects of these interventions, primarily information giving and counseling, on the incidence and frequency of risk behaviors have not been shown in research studies. This type of evidence is needed to guide risk avoidance interventions better. Until these data are made available, most professionals would not want to be held accountable for the levels of risk behavior in the population for whom they care.

### Symptoms and Comfort

Feelings of discomfort can be experienced physically and emotionally, and they may or may not be linked to a disease. Almost one-half of all office-based visits involve some degree of symptom management. Children who feel uncomfortable are less involved in desired activities, more likely to miss school, and more unhappy than others without the same feelings. Relieving the suffering associated with illness is a core function of health services delivery. Thus the level of comfort of a patient population or the symptom burden of a diseased subgroup is a clear outcome indicator that can be linked to health services.

### Well-Being

Well-being has 2 components. The first component, simply stated, is happiness—the degree to which life experiences match the individual's expectations. Health care delivery systems add to the happiness of children by ensuring that the risk of injury and disease is as low as possible and the impact of disorders when injury or disease occurs is minimized by preventing unwanted symptoms and ensuring the highest level of comfort possible, by promoting growth and development, by counseling on behavior (both ways to improve health directly and ways to avoid harm), and by supporting families in the care of their children.

The second component is meaning, predictability, and flourishing. Healthy children see and plan for their future. Children who have led healthy lives are more likely to become flourishing adults.

### Outcomes and Health Services

Some outcomes Table 1-4 are more amenable to health care services than others. The knowledge base linking services to outcomes is largest for the biological outcomes of survival, disease, and growth. The fact that many commonly applied therapeutic maneuvers are of unproved usefulness and may even

be dangerous is well known. For example, several studies demonstrate that surgical rates in the United States are much higher than those in other developed countries, without any demonstrable difference in the need for surgery as defined by prevalence of disease or illness. Even within the United States, the number of hospital admissions, the length of stay in the hospital, and the rate of surgical procedures vary markedly from area to area, unrelated to differences in medical need—although socioeconomic circumstances may be a component of this variation. This potential overuse of specialized services might actually result in poorer outcomes, with more patients than necessary experiencing iatrogenic complications of interventions. Another problem is the misuse of drug therapy. Outcomes data will be helpful in determining the usefulness of various therapeutic maneuvers and will guide the appropriate use of drugs. In a related way, prescribing medications or home-based management strategies that are not adhered to by patients or families is an important challenge to the ongoing care of illness. Nonadherence is costly and can result in unnecessary escalation of therapy or hospitalization for exacerbation that could have been prevented (eg, asthma). As the demand to connect outcomes to process grows, the likely scenario is that physicians will be encouraged, and perhaps even required, to keep certain types of data about children in their practices. A data set for hospitals to use for each patient admitted and a similar set for ambulatory care have been accepted by the National Center for Health Statistics and recommended for wide use. This information includes registration data (patient identification number, name, address, birth date, gender, race, and marital status) and encounter data (facility identification number, provider identification number, patient identification number, source of payment, date of encounter, patient's purpose for visit, physician's diagnosis, diagnostic and management procedures, and disposition). Adoption of this or a similar system for collecting and standardizing information will facilitate the understanding of health and disease processes and the role medical care plays in influencing them. (For more details, see Chapter 5, Quality Improvement in Practice.)

To ensure that diagnostic procedures and instituted therapy are adequate and that problems are being resolved as expected, patients must be monitored; this approach is known as *outcomes assessment*. Medical textbooks and teaching rarely include information that helps the physician define appropriate intervals for reassessing particular health problems. Such information has to come from careful studies of the natural history of patients' problems, with and without intervention, and such studies are rare. Moreover, little is known about the extent to which physicians follow up with problems they treat. When the issue has been examined, research shows that failure to follow up on treated patients results in unresolved health problems; at the very least, it produces a highly inefficient health care system: Care is paid for, but no benefit is gained. At the most, outcomes assessment will ultimately lead to societal demands for greater

accountability of the profession. Fortunately, careful review and analysis of publications on the diagnosis and treatment of illness has led to the development of evidence-based guidelines, which, when used, are expected to improve health outcomes. Yet, no consensus exists on the specific outcome metrics by which the effectiveness of health care delivery systems should be evaluated. For which outcomes should health care delivery systems be held fully accountable, partially accountable, or not at all accountable? This question remains largely unanswered, which severely limits the profession's ability to use outcomes assessment to improve health care services. Future health care delivery systems for children must become more outcomes oriented. Deciding on which outcomes to base these new delivery systems is an urgent task facing all child health care professionals and managers.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *The AAP Child Health Mapping Project* (interactive tool), American Academy of Pediatrics and Dartmouth Medical School, Center for Evaluative Clinical Sciences ([www.aap.org/mapping](http://www.aap.org/mapping))

### Engaging Patient and Family

- *Pediatric Specialists* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/default.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/default.aspx))

### Practice Management and Care Coordination

- *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* (CD-ROM), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *American Telemedicine Association* (Web site), ([www.americantelemed.org/home](http://www.americantelemed.org/home))
- *Pediatric Call Centers and the Practice of Telephone Triage and Advice: Critical Success Factors* (report), American Academy of Pediatrics ([www.aap.org/sections/telecare/11\\_98.pdf](http://www.aap.org/sections/telecare/11_98.pdf))
- *Pediatric Telehealth Care* (Web page), American Academy of Pediatrics ([www2.aap.org/sections/telecare/default.cfm](http://www2.aap.org/sections/telecare/default.cfm))
- *Pediatric Telephone Protocols*, 14th ed (book), American Academy of Pediatrics, Schmitt BD ([shop.aap.org](http://shop.aap.org))
- *Practice Transformation* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/professional-resources/practice-support/Pages/Practice-Support.aspx](http://www.aap.org/en-us/professional-resources/practice-support/Pages/Practice-Support.aspx))

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## Chapter 2

# PRACTICE ORGANIZATION

Thomas K. McInerney, MD

The organization of the practice is critical for the primary care physician's success in providing high-quality care within a medical home and implementing and maintaining sound business principles. A study of 44 private pediatric and family medicine practices in North Carolina shows that low levels of preventive service performance and a significant percentage of bankruptcies were largely a result of poor organizational characteristics. A well-organized practice can meet the demands of patients, families, and payers for high-quality, cost-effective care by developing positive attributes in 4 major areas: (1) culture, (2) recruitment and retention, (3) defining and achieving goals, and (4) planning.

## CULTURE OF A PRACTICE

The culture of a practice is the subjective feeling of the physicians, staff, and patients and their families about what it is like to work in and visit the practice. Is the atmosphere pleasant, friendly, caring, and supportive? Is it just the opposite? Or is it somewhere in between? The culture of the practice is set by the physicians, the natural leaders of the practice. Their attitudes and beliefs are often mirrored by the practice staff. Projecting a positive image is the responsibility of all staff, including nurses, receptionists, and administrators, but the physicians set the tone for providing

compassionate, family-centered care. First and foremost, physicians in well-organized practices believe that caring for children and working with their parents/guardians to achieve the best possible health outcomes for their children is a special privilege. Acknowledging and respecting the patient's and family's individual beliefs and customs are essential in providing comprehensive, culturally effective care. Pre-visit and follow-up patient communication and comprehensive office visits are seen as welcome opportunities to achieve these goals. Admittedly, sometimes on particularly busy days, maintaining this positive attitude can be difficult, but doing so is most important, lest a negative attitude be projected toward patients and parents by the physicians or staff. Increasingly, physicians recognize that patient- and family-centered care leads to optimal care and patient, family, physician, and staff satisfaction. By forming true partnerships with patients and families and practicing shared decision making between families and physicians and the care team, pediatricians develop a better understanding of the patient's/family's goals and increase the likelihood of a mutually agreed-upon management plan and better compliance with that plan.

Mutual respect is a fundamental characteristic of a well-organized practice. All members of the practice must treat each other with courtesy and dignity at all times, avoiding negative remarks or comments. If someone in the practice shows a need for improvement, then this need should be discussed with the individual privately in a positive fashion. Creating a respectful atmosphere in the practice is highly beneficial for staff performance and families' perception of the practice.

Teamwork provides the basis for a high-functioning medical home. Delivering high-quality care is a complex process requiring the coordinated efforts of physicians, nurses, receptionists, and administrative personnel. All activities must be coordinated to develop a well-functioning team with clearly defined roles and responsibilities and a seamless system of transition among the staff. This is particularly important when patients are transferred from one physician to another at the end of a session or day. One way of ensuring that all the pertinent information about the patient is appropriately communicated is to use the acronym DATAS:

- Descriptive identification of the patient
- Active patient issues
- To do—follow-up issues
- Anticipate potential problems and interventions
- Special instructions

Finally, notably, a well-organized practice functions in a democratic fashion rather than an authoritarian one. It is important to define practice governance so each individual knows to whom they directly report and who should hear their ideas or concerns. Decisions regarding practice policies, goals, and activities are reached by a thorough discussion with all members of the practice, hopefully leading to consensus so that all staff members are invested in the decisions that are made. This process requires physicians and staff to listen respectfully and with an open mind to everyone's opinions and to encourage frank discussion regarding potential solutions to problems and challenges. Patients and families should also be able to

contribute their ideas for practice improvement, whether through a suggestion box, family advisory group, or other venue. Ultimately, the practice needs an identified individual physician or group who is empowered to make final decisions in the best interest of its patients, families, employees, and fiscal viability. The pediatrician managing partner has the ultimate responsibility for making decisions about the conduct of the practice. Often, she or he may be assisted by a planning or executive committee of physicians, nurses, staff, and parents.

A mission statement that reflects the individual values of the care team can be a useful tool to clearly define priorities of the practice and establish a positive culture within the family-centered medical home.

## RECRUITMENT AND RETENTION

Recruitment of high-quality physicians, nurses, and medical assistants, nonclinical staff, and administrators into the pediatric practice is an important goal for a well-organized practice. However, recruitment is only one half of the equation, with retention of valued employees forming the other half. Given that orientation of new staff members to their functions within the practice can be disruptive, time-consuming, and expensive, high turnover rates are to be avoided. Furthermore, patients and families greatly appreciate hearing a familiar voice or seeing a familiar face in their interactions with the practice. Additionally, long-term staff members gain an understanding of patient and family characteristics that can be particularly helpful in providing care for those patients and families. Finally, physicians and staff develop efficient patterns of interaction with each other over time, and regular staff meetings where opinions are addressed and valued greatly improve the overall functioning of the practice. Thus taking the appropriate measures necessary to retain a high-quality staff is in the pediatrician's best interests.

Developing positions of responsibility within the care team can be beneficial in providing a high-quality medical home. It is important to establish a designated care coordinator whose role goes beyond coordinating a patient's medical care, and includes engaging other resources in the community to support the growth and development of the child. Assigning tasks and responsibilities to other staff members such as asthma coordinator, newborn-screening coordinator, and lab coordinator, as well as bringing in ancillary staff such as nutritionists, psychologists, therapists, and lactation consultants, helps to round out the comprehensive-care team. Designating clear roles and responsibilities to members of the care team acknowledges their importance and improves efficiency, satisfaction, and clinical outcomes.

Continuing education is a critical component to staff retention and satisfaction and can be incorporated into practice routines. Clinical education can be done while in the process of care or in more didactic sessions. A "lunch and learn" program encourages staff collegiality and increases their knowledge base.

Competitive salaries and benefits (health, life, and disability insurance and retirement plans) are essential to recruiting and retaining high-quality physicians and employees. Appropriate salaries and benefits should



be regarded as investments in high-performing individuals that will provide a substantial return on investment to the practice.

Financial rewards are obviously effective, but other techniques can be quite helpful as well. For example, frequent (daily) praise and appreciation provides employees with a sense of well-being and value. In addition, letting the staff know the outcomes of patients of concern with whom they have interacted will give them a sense of true investment in the care of the patient. Other methods of rewarding staff include occasional gifts to thank them for exemplary service during particularly stressful times. Finally, including all staff members in celebrations of such events as the achievement of major practice goals, the arrival of any new physician or staff member, 25th anniversaries, holiday parties, or retirements will let staff members know their value in the practice.

## DEFINING AND ACHIEVING GOALS

The 2 major goals of a well-organized practice are providing high-quality care for its patients and families and implementing and maintaining sound business principles for financial success. Providing high-quality care requires more than well-trained physicians and staff. The practice needs to develop systems of care and daily work-flow processes designed to achieve the best practice results. Both the Institute of Medicine and the Institute for Healthcare Improvement have called for the implementation of appropriate systems of care at all levels in the medical-care spectrum. The systems-of-care principles are taken from those developed by the manufacturing industry and have been demonstrated to reduce variation and improve product quality. Many of these principles are applicable to medical practice and have been shown to improve outcomes significantly. One of the most important systems-of-care principles is measurement. Randolph and his colleagues show that some practices that measured immunization rates found that these rates were significantly lower than the physicians' estimates. The common business saying, "you can't manage what you don't measure" is applicable to pediatric practices. Pediatric practices should institute a host of measurement processes such as immunization registries, appointments-kept ratios, waiting time for appointments, and time taken to answer telephone calls, among other processes. See Chapter 5, Quality Improvement in Pediatric Primary Care, for detailed information on small cycles of improvement necessary for quality improvement.

Dedication to practicing evidence-based medicine for patients promotes safety and ensures a practice's commitment to lifelong learning and continuous quality improvement. As part of this process, physicians need to be aware of the latest guidelines for care as published by the American Academy of Pediatrics (AAP) and other organizations and to work to institute these guidelines as a regular part of their practice. Essential to the quality improvement process are regular meetings of the physicians and staff to determine best how to put in place systems of care necessary to ensure high-quality outcomes. Finally, a well-organized pediatric practice must assess patient and family

satisfaction and work toward improving staff members' performance in this area that will become increasingly important as patients and families have more incentive to seek out high-quality care with newer health insurance products. Thus listening to and acting on patient concerns and complaints, and surveying patients regularly to assess their satisfaction, are important activities. In addition, the practice should solicit patient and family feedback periodically in the form of patient surveys or a family advisory council. Such a council can consist of patients and parents who meet regularly (eg, 4 to 6 times per year) with physicians, nurses, and staff members to discuss ways to improve services for patients and families. The one constant in life is change. Defining and engaging in a continuous quality improvement process is essential in allowing a practice to meet the ever changing needs of its patients and families.

Given that the primary care practice of pediatrics is a business, sound business principles are required for practices to perform well financially. Because providing direct patient care is the primary revenue stream for most practices, the physicians themselves must maximize their time in clinical care; business management may be better handled by specifically trained employees. Practice policy development, adherence to legal regulations of governing bodies (OSHA, HIPAA, CLIA), and contract negotiations with insurers are critical areas where physicians should seek the advice or help of high-quality professional consultants. Practice clinical policy manuals, telephone advice instructions, and employee manuals should be used regularly and updated frequently. Experts in medical legal matters should be employed to assist with contracts and negotiation and to provide suggestions to reduce the risk of medical malpractice suits. Accountants with specific knowledge of medical economics should review the practice's financial accounts regularly and provide advice to improve financial performance. Similarly, management consultants with experience in medical-practice management should be consulted for advice in the structure of the practice. For practices of 3 to 5 physicians, an office manager with expertise in the business aspects of running a medical practice should be employed. In many cases, someone with a master's degree in business administration will be more effective than someone with less training. For practices of 6 or more physicians, a well-qualified and experienced practice administrator should be hired to oversee the complex operations of large practices. Although well-trained individuals may be expensive, they will usually return their salary many times over and should therefore be considered as an investment rather than an expense. In addition to an office manager, one or more of the physicians in the practice need to serve as managing partners, often overseeing a particular aspect of practice management such as personnel, financial performance, or quality improvement. Practices also should benchmark their performance financially by comparing their revenues and expenses to the performances of the best practices of similar size. Finally, attention to detail is absolutely required to ensure that the services provided are appropriately coded and billed for, all charges are captured, and collections are tracked carefully and maximized.

The AAP Section on Administration and Practice Management (SOAPM) has used the services of the Medical Group Management Association to survey pediatric practices and provides the results of these surveys on its Web site ([www.aap.org/practicesupport](http://www.aap.org/practicesupport)). At least one pediatrician in the practice, preferably the managing partner, should be a member of SOAPM, keep up with the SOAPM list serve, utilize Practice Support frequently, and review the work of the AAP Private Payer Advocacy Advisory Committee (PPAAC) recommendations to learn the latest developments in the business of pediatrics and for helpful discussions on practice management. SOAPM, Practice Support, and the PPAAC are valuable benefits of AAP membership.

The use of computers in the well-organized pediatric practice is increasingly essential. Computerized billing systems have long been the norm for pediatric practices, and their hardware and software systems should be periodically upgraded to meet the demands imposed by an increasingly complex health-insurance system. Consultants are available either locally or nationally who can be of great assistance in purchasing the right computerized system for the practice. Beyond this effort, computerized or electronic medical records (EMRs) are becoming essential to provide high-quality care in the framework of a medical home (see Chapter 3, Information Systems in Pediatric Practice). The benefits of electronic medical records in providing reminder recall systems, improving immunization rates, and notifying patients and families of the recommended frequency of health assessment visits to care for children with chronic illnesses, to alert physicians regarding patients' allergic reactions to drugs, and to prevent drug-drug interactions have been well documented. Although these systems are quite expensive in terms of actual cost and the expense entailed in converting from paper records to EMRs, the benefits to patients and families and the reduction in personnel expenses for filing and transcribing justify the investment. Of course, installing an EMR system is essential to being able to provide patients and their families with a personal health record (PHR). For the latest information regarding EMRs, physicians should visit the AAP Council on Clinical Information Technology (COCIT) Web site ([www2.aap.org/informatics/COCIT.html](http://www2.aap.org/informatics/COCIT.html)).

## PLANNING

Another key element in determining the success of a business is planning for the future. Thus a well-organized practice will hold annual retreats to assess past progress, survey the local and national medical environmental trends, and develop a set of goals and measurable objectives for the next year. Preparation for this retreat should include a strengths, weaknesses, opportunities, and threats (SWOT) analysis, with particular attention paid to anticipated changes in health care financing (eg, new payment models or an increase in the number of patients moving to consumer-driven health plans), emerging changes in the structure of delivering primary care from privately operated pediatric practices to multi-site organizations to larger integrated health systems and accountable care organizations, birth rates, child health disparities, population changes, and physician supply

changes. The practice should formulate a strategic plan for the coming year and review the plan every quarter to determine progress toward the goals and objectives. Hiring a professional facilitator to assist in the retreat activities may be worth the investment.

## CONCLUSION

Developing and maintaining a well-organized pediatric practice requires hard work, constant attention, and skills that are not usually taught in medical school or residency. However, physicians must devote the time and effort and acquire the necessary skills if they are to provide high-quality care in the context of the medical home model for patients and families and to be successful financially. A practice must have a commitment to quality improvement and be open to transformation in order to respond to the changing health care landscape and provide the highest-quality care to patients and families. The AAP and other professional societies offer courses in practice management. In addition, the AAP offers practice-management resources and tools on its Web site ([www.aap.org/practicesupport](http://www.aap.org/practicesupport)). Running a successful practice can be challenging, but the rewards are well worth the effort.

## TOOLS FOR PRACTICE

### Community Coordination and Advocacy

- *A Checklist for Attitudes About Patients and Families as Advisors* (questionnaire), Institute for Patient- and Family-centered Care ([www.ipfcc.org/advance/Checklist\\_for\\_Attitudes.pdf](http://www.ipfcc.org/advance/Checklist_for_Attitudes.pdf))
- *Creating Patient and Family Advisory Councils* (booklet), Institute for Patient- and Family-centered Care ([www.ipfcc.org/advance/Advisory\\_Councils.pdf](http://www.ipfcc.org/advance/Advisory_Councils.pdf))
- *Culturally Effective Care Toolkit: What Is Culturally Effective Pediatric Care?* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/professional-resources/practice-support/Patient-Management/Pages/Culturally-Effective-Care-Toolkit.aspx](http://www.aap.org/en-us/professional-resources/practice-support/Patient-Management/Pages/Culturally-Effective-Care-Toolkit.aspx))
- *Healthy People 2020 Program Planning* (Web page), US Department of Health and Human Services ([www.healthypeople.gov/2020/tools-and-resources/Program-Planning](http://www.healthypeople.gov/2020/tools-and-resources/Program-Planning))

### Medical Decision Support

- *EQIPP* (online program), American Academy of Pediatrics ([eqipp.aap.org](http://eqipp.aap.org))

### Practice Management and Care Coordination

- *Family Centered Care Self-Assessment Tool*, Family Voices ([www.familyvoices.org/admin/work\\_family\\_centered/files/fcca\\_FamilyTool.pdf](http://www.familyvoices.org/admin/work_family_centered/files/fcca_FamilyTool.pdf))
- *Measuring Medical Homes: Tools to Evaluate the Pediatric Patient- and Family-Centered Medical Home* (monograph), National Center for Medical Home Implementation ([medicalhomeinfo.aap.org/tools-resources/Documents/Monograph\\_FINAL\\_Sept2010.pdf](http://medicalhomeinfo.aap.org/tools-resources/Documents/Monograph_FINAL_Sept2010.pdf))
- *Patient- and Family-Centered Ambulatory Care: a Checklist* (fact sheet), Institute for Patient- and Family-Centered Care ([www.ipfcc.org/advance/topics/Ambulatory-Care-Key-Concepts.pdf](http://www.ipfcc.org/advance/topics/Ambulatory-Care-Key-Concepts.pdf))
- *Practice Transformation* (Web page), American Academy of Pediatrics ([www.aap.org/practicesupport](http://www.aap.org/practicesupport))



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## Chapter 3

# INFORMATION SYSTEMS IN PEDIATRIC PRACTICE

S. Andrew Spooner, MD, MS

### INTRODUCTION

Fundamental to a functional medical home for children is an information system that supports a comprehensive, longitudinal record for each child and the ability to manage patient populations. The growing popularity of the Patient-Centered Medical Home (PCMH) program from the National Council for Quality Assurance formalizes one definition of the medical home and outlines the information management activities that a recognized practice should master. Although the PCMH program does not, strictly speaking, require an electronic health record (EHR), many of the activities specified in the program would be difficult to perform on paper. Table 3-1 outlines the main areas of functionality for the 2014 PCMH recognition program, along with examples of EHR functions that could help perform these activities efficiently.

During the past decade, physician practices and hospitals have spent an increasing amount of time and money on EHR systems. The rapid rise in the use of EHRs has been partly a response to the American public's long-standing call for better information management in health care, echoed by US presidents and

codified in federal regulations as the Meaningful Use (MU) program and supported by patient perceptions of care quality. Adoption has been rapid, at least for basic EHR systems, but the barriers of complexity and cost mean that it will be many years before health care is completely paperless. Fortunately, the EHR market is responding to the need for systems that work for child health care, allowing pediatricians to adopt these systems, albeit at a slower pace. Only a minority of pediatric physicians use EHR systems that possess the full range of functionality. Although MU incentive payments reduce the net cost of implementation, questions remain about how to select a system, manage the change, and bear the total expense.

### DEFINITIONS

#### Electronic Health Record Versus Electronic Medical Record

The Institute of Medicine defines an EHR system:

An EHR system includes (1) longitudinal collection of electronic health information for and about persons, where health information is defined as information pertaining to the health of an individual or health care provided to an individual; (2) immediate electronic access to person- and population-level information by authorized, and only authorized, users; (3) provision of knowledge and decision-support that enhance the quality, safety, and efficiency of patient care; and (4) support of efficient processes for health care delivery. Critical building blocks of an EHR system are the electronic health records (EHR) maintained by providers . . . and by individuals (also called personal health records).

In this chapter, the term *EHR* refers to the system a physician would use in an ambulatory or inpatient setting to implement the primary and specialty care of infants, children, and adolescents. There is an older term, electronic medical record (EMR), that is often also used to describe these systems. The US Office of the National Coordinator for Health Information Technology makes the distinction that an EHR contains information aggregated from *all* physicians involved in a patient's care—not just from the physician who purchased the computer system. Although this may be a useful distinction, the reality in the marketplace today is that all vendors who sell EMRs call them EHRs, so that term will be used in this chapter.

**Table 3-1**

#### Patient-Centered Medical Home Standard (2014) and Examples of Supportive Electronic Health Record Functionality

Patient-centered access	Provide online access to medical record information. Support secure electronic messaging with patients.
Team-based care	Calculate proportion of encounters held with patient's personal physician. Maintain a written transition plan from pediatric to adult care.
Population health management	Record family history as structured data. Record social or cultural needs in health assessment. Create lists of patients who need preventive care.
Care management and support	Identify children and adolescents with special health care needs or high-cost utilization. Identify patients based on social determinants of health. Maintain individual care plans.
Care coordination and care transitions	Record laboratory and radiology orders. Track overdue laboratory results. Report on percentage of patients identified as needing care management.
Performance measurement and quality improvement	Report on 2 measures related to care coordination. Exchange data bidirectionally with a health information exchange.

### Meaningful Use

The major driver of EHR design in the United States since 2009 has been the MU incentive program, a part of the Health Information Technology for Economic and Clinical Health (HITECH) Act of the American Recovery and Reinvestment Act of 2009. HITECH was intended to stimulate the adoption of EHR software, but the legislation was careful to define what sort of system could be called an EHR and what sort of uses of the system would qualify as *meaningful*. The motivation for creation of a definition of MU was to ensure that physicians would implement systems that had some benefits for patients and would enhance their ability to study care, to empower individuals, and to improve health outcomes. To ensure that EHR systems met the definition, a certification program was established in which software was required to demonstrate certain functions to become certified for the purpose of the MU incentive program. There was never any intent in the certification criteria to ensure that every EHR was appropriate for child health, but there are a few criteria that do help in this regard. For example, the criteria require that the system have growth charts and be able to communicate with immunization registries. Although promising, these requirements fall short of what most pediatricians would consider adequate. For instance, the growth chart requirement omits head circumference charts. Other gaps include omission of head circumference from the vital signs criterion, omission of a requirement for weight-based

dose calculations in prescribing, and omission of passive smoking (or other forms of tobacco exposure important in pediatrics) in the tobacco history criterion. There are some other criteria that do meet some needs in child health, but a system that adheres to all the criteria for certification would not necessarily be rich in child health functionality as specified by the literature.

### ELECTRONIC HEALTH RECORD SYSTEM AND CHILD HEALTH

Not all certified EHRs support all the published child health functions, and not all EHR systems are designed for pediatric care, so the pediatrician should examine carefully the capabilities of any system intended for use in a practice serving infants, children, and adolescents. In advocating for the inclusion of EHR functionality that supports important pediatric work flows, pediatricians should point out that most functions important in pediatric care are also useful outside of pediatric care. For example, drug dosing by body weight is critical in pediatrics, but has enough usefulness in geriatric care that it would also be desirable in nonpediatric systems. Likewise, weight and height monitoring have application in adult care. The ability to record guardianship status and accommodate proxy access is important in the care of adults with diminished capacity. Table 3-2 lists questions one might ask in the evaluation of the suitability of a system for a child health environment.

**Table 3-2**

**Pediatric Functions of an Electronic Health Record With Questions to Ask About Electronic Health Record Functionality**

FUNCTIONAL AREA	QUESTIONS TO ASK
Growth monitoring	<p>Can the system plot growth data (height, weight, head circumference) over time and allow simultaneous comparison to normative curves? Does it include normative curves for special populations seen by the practice?</p> <p>Does the system plot BMI against appropriate normative curves of percentiles?</p> <p>Does the system indicate abnormalities in growth parameters (eg, flagging any weight below a certain percentile value or a BMI above a certain percentile)?</p> <p>Does the display of growth data allow magnification (<i>zooming</i>) of the display when examining densely packed data points?</p> <p>Does the system indicate corrections for prematurity on growth charts? Can the pediatrician note events such as Tanner staging, bone age determinations, or growth-arresting therapeutic episodes on the growth chart?</p> <p>Does the system allow printouts of the growth curves for parents? Is the growth chart viewable in the patient portal?</p>
Immunization management	<p>Does the system have active interfaces to any state immunization registries? If so, what is required to bring those interfaces live in the current practice?</p> <p>Can the system analyze a record of immunizations and recommend what immunizations are due at the time of the current encounter? At a designated future encounter?</p> <p>Can the system analyze a record of immunizations and indicate when the next immunizations are due? Are physicians alerted to this fact when the patient presents for care?</p> <p>Can the system store lot numbers and the versions of vaccine information provided for new immunizations?</p> <p>Can the system incorporate data indicating that a given series of immunizations is complete without having to manually enter the data on individual immunizations administered in the past? If so, is this information on series completion incorporated appropriately into decision support functions?</p> <p>Can the system print paper immunization forms for school entry based on data in the patient's record?</p>

Table 3-2

### Pediatric Functions of an Electronic Health Record With Questions to Ask About Electronic Health Record Functionality—cont'd

FUNCTIONAL AREA	QUESTIONS TO ASK
Medication prescribing	<p>Does the system suggest a drug dose based on actual body weight? On age? On gestational age?</p> <p>Does the system allow dosing based on a <i>dosing weight</i> rather than actual body weight?</p> <p>Does the system display current body weight in the same view in which the user is expected to create prescriptions?</p> <p>If a non-weight-based dose is entered, does the system check drug doses for appropriateness based on body weight?</p> <p>Does the system support indication-specific dose ranges for a given medication?</p> <p>Does the system round the dose to a dose that is easily measured by parents (eg, 3 mL vs 2.8 mL, or ½ tablet vs 0.45 tablet)?</p> <p>Does the system alert the user regarding allergies to medications and possible adverse drug-drug interactions?</p> <p>In the case of controlled substances for behavioral disorders, does the system allow the user to authorize recurrent monthly prescriptions in accordance with applicable laws on controlled substances?</p>
Breast milk management	<p>In appropriate environments (eg, nurseries), does the system store data needed to administer breast milk (patient and mother identifiers, expiration dates)?</p> <p>At the time of delivery of the breast milk to the patient, does the system capture data that validate the correct matching of patient to milk aliquot?</p>
Data norms	<p>Does the system display the percentile value of each height, weight, and head circumference in every place where such data are displayed?</p> <p>Does the system indicate abnormal blood pressure based on age and height?</p> <p>Does the system store and display age-dependent normative ranges as supplied by the clinical laboratory?</p> <p>Does the system allow graphical plotting of laboratory values over time, with age-based normative ranges that change over the life span?</p> <p>In cases in which documentation by exception is used, are physical examination findings that normally change with age (eg, Babinski sign, unsteady gait) shown as normal at appropriate ages?</p>
Privacy	<p>Does the system store and display clear guidance to the user about who can access the record in cases of adoption of foster care?</p> <p>In the case of systems that allow parental access to the record (eg, a Web-based portal), can the system limit this access to match the level of assent of an adolescent?</p> <p>Does a way exist to represent multiple guardians or health care agent relationships in the system?</p>
Terminology	<p>In the portion of the EHR in which diagnoses are recorded, can the user specify rare congenital syndromes without resorting to free text?</p> <p>Can the problem list include items that are not typically considered specific diseases (eg, <i>high-risk social situations</i>, <i>developmental delay</i>, <i>immunizations up to date</i>, <i>vaccine refusal</i>, or <i>school avoidance</i>)?</p> <p>In recording birth history, can the system distinguish specific terms that apply to the mother from those that apply to the baby (eg, diabetes of the mother that affected the baby as a fetus)?</p> <p>Does the system allow retrieval of all patients with a particular diagnosis, symptom, or physical finding?</p>
Granularity	<p>Are ages displayed in units that are appropriate to the patient's age (eg, 3 weeks of age is not shown as 0 months of age)?</p> <p>Can the user enter weight to the nearest gram or other suitable precision?</p>
Pediatric decision support	<p>In the case in which guidelines are supported, can the system omit guidelines that are appropriate only for adults?</p> <p>Can the system filter reminders by age to reduce the number of inappropriate alerts?</p> <p>Can the system trigger reminders based on age combined with other data such as diagnosis or time since last encounter?</p>
Adolescent privacy	<p>Can the system's Web-based patient portal features match practice policy about who can access the adolescent's record?</p> <p>Are there ways to flag certain types of information as confidential?</p> <p>Can printouts or data displays accessible to parents be tailored to adolescents' privacy requests, within the boundaries of practice policy and applicable law?</p>

BMI, body mass index; CDC, Centers for Disease Control and Prevention; EHR, electronic health record; FDA, US Food and Drug Administration.

## NECESSARY FUNCTIONS OF AN ELECTRONIC HEALTH RECORD IN THE PEDIATRIC SETTING

### Growth Monitoring

Fundamental to the practice of pediatrics is the analysis of growth, as documented by height, weight, and head circumference. In the United States, curves showing the distribution of these measurements at each age are published by the Centers for Disease Control and Prevention and the World Health Organization; special curves for premature infants and populations of children with specific congenital conditions such as achondroplasia, Down syndrome, Turner syndrome, or Williams syndrome are also available. Caution must be used in applying these special charts to a given patient because, in some cases, the data on which they are based were collected before the availability of treatments that may improve growth rates. Standard practice is to plot these values on the appropriate curve at each encounter. Although the use of growth charts in this way has not been expressly validated, it is a practically universal practice in pediatrics. Manually plotting these points is laborious and prone to error. Computer systems into which these data are entered can easily display a plot of growth data over time, just as they can produce a temporal plot of other clinical data. Pediatricians expect that these plots will behave in much the same way as paper plots; with careful attention to design, computer-based growth charts can retain the analytic usefulness of the paper curves while adding functions that no paper system can hope to offer. The evaluation of any EHR intended for use in the pediatric setting should include a careful examination of growth chart functions, including calculation of body mass index and body mass index percentiles by age and gender. (See Table 3-2 for specific questions to ask.)

### Immunization Management

A common yet complex task in pediatric practice is determining which immunizations are due and when they are to be administered. The rules for indications and dosing intervals change at least every year and often more frequently as new vaccines come to market and as the epidemiologic factors of preventable diseases change. Many EHR systems sold today do not offer the pediatrician any decision support for this task, and a significant minority will not record immunizations. Immunization management is one of the more obvious functional areas in which a computer can improve the pediatrician's efficiency, yet the large difference in complexity between child and adult immunization management poses an often insurmountable implementation challenge to vendors of EHR systems. The ideal system will alert physicians regarding overdue immunizations whenever the patient's EHR is accessed, or at some future date when an encounter is planned (see Table 3-2 for appropriate questions to ask).

As EHRs are used more for population health (the management of groups of patients outside the context

of individual patient encounters), these systems will become powerful tools for improvements in vaccine coverage. Population health tools in EHRs can facilitate outreach interventions that have been shown to improve immunization coverage.

### Medication Prescribing

To a much greater degree than in adult care, pediatric prescribers compute doses of medications based on a recommended dosage of drug to be used per unit of body weight. Although body surface area and ideal body weight are sometimes used in pediatrics, actual body weight is the most common basis for dose calculations in general pediatric practice. Although most EHR systems offer prescribing, not all offer weight-based dosing support for many reasons, including lack of standardization of dosages; although the US Food and Drug Administration (FDA)-approved labeling of drugs includes weight-based dosages for products approved for use in children, many products used in children are not FDA approved, and many have recommended dosages in drug handbooks that differ from the approved product labeling. Another barrier to computerized weight-based dosing decision support is the practice of rounding to convenient doses (eg, whole milliliters are multiples of a 5-mL amount), which makes calculating doses even more complex. In addition to providing weight-based dosing support, the best systems will also alert pediatricians regarding allergies to medications and possible adverse drug-drug interactions.

### Data Norms

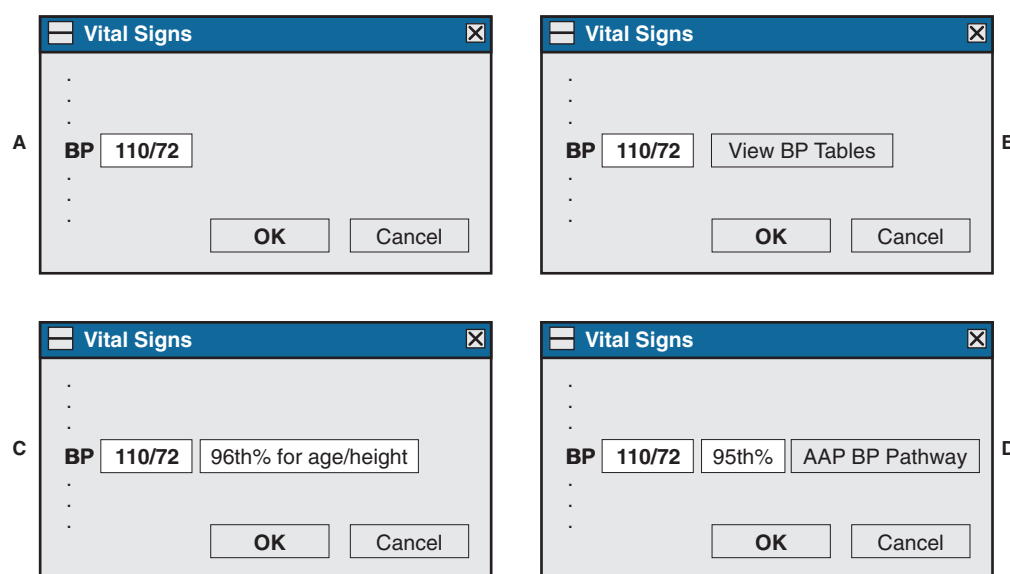
When interpreting data from children—especially numerical data—age (and sometimes gestational age, body measurements, or stage of sexual maturity) must be taken into account. For example, blood pressure in adults is easy to interpret without referring to any of these factors; if it is above 120/80 mm Hg, then it is abnormal. In child health care, interpreting blood pressure requires either time-consuming references to tables or the assistance of an electronic information system that incorporates pediatric norms. Assistance with interpretation using gender-, height-, and age-based norms is technically easy but often not implemented in EHRs. Pediatricians who are evaluating any clinical information system should pay particular attention to how the system assists the user with normative data (see Table 3-2). Figure 3-1 illustrates one of the more complex examples of what it means to have a rich pediatric context—the display of blood pressure and the accompanying percentiles to allow decision making.

Population health tools in the EHR should be able to identify those in need of care coordination based on age-related abnormalities, like body mass index, body-weight percentile, and stages of hypertension.

### Terminology

To be useful in decision support, terms used to describe clinical data (eg, symptoms, signs, diagnoses, tests) need to be stored as a member of a defined terminology set, rather than as free text. Although free-text storage of clinical concepts provides maximum





**Figure 3-1** The pediatric context. The degree to which an electronic health record system understands cases in which pediatric care differs from adult care is a measure of its ability to present the pediatric context. Four fragments from a hypothetical user interface illustrate the different levels of pediatric context that a system can provide. **A**, Level 0: No recognition of pediatric factors. The system displays the patient's blood pressure. This behavior is expected, but it fails to reflect the pediatric complexities of blood pressure display. **B**, Level 1: Recognition of pediatric factors but no automation of special functions. The system begins to offer some pediatric context by offering the user the opportunity to look up norms for blood pressure in the same portion of the user interface that displays the blood pressure. **C**, Level 2: Recognition and basic automation. The system goes one step further by calculating the percentile value for the blood pressure (perhaps the higher of systolic or diastolic percentile values). **D**, Level 3: Recognition, automation, and integration with pediatric-specific evidence. The system calculates the percentile and offers to take the user to a pediatric-specific guideline pathway of some sort.

flexibility (and often speed) to the user at the point of care, free-text data entry is subject to typographic errors, redundancy, and the use of nonstandard terms. There are some emerging techniques that allow analysis of free-text clinical entries, but physicians cannot realize the full value of an EHR without some amount of encoded data.

The most readily available encoded data from clinical information systems has been claims data because these tend to be generated reliably. The biggest drawback of the use of claims data in pediatrics is that the terminology system used to encode diagnoses, the *International Classification of Diseases, ninth edition, Clinical Modification (ICD-9-CM)* is often not detailed enough to adequately express important diagnostic concepts. Although *International Classification of Diseases, tenth edition, Clinical Modification (ICD-10-CM)*, mandated for implementation by the US Center for Medicare and Medicaid Services by October 1, 2015, offers slightly more granularity, the extra detail it includes has little clinical importance. There will always be a need for clinical terminology sets that are detailed enough to meet the requirements of physicians at the point of care. Terminology as displayed in the user interface should employ terms physicians use to describe concepts. SNOMED-CT (Systematized Nomenclature of Medicine—Clinical Terms) offers some promise in this area, but EHR vendors more commonly offer proprietary terminology systems like IMO (Intelligent Medical Objects, Northbrook, IL, e-imo.

com) or Medcin (Medicomp Systems, Chantilly, VA, [www.medicomp.com](http://www.medicomp.com)).

### Granularity

Pediatrics involves smaller units of time, weight, and distance than adult health care. The scale of these measurements varies with age and with care setting. For example, age to the nearest minute is important in the delivery room, but in the newborn nursery, age to the nearest hour is usually sufficient (eg, for evaluating newborn screening laboratory results). In the first few months of life, the patient's age should be expressed initially in days, but later in weeks and then months. Body weight to the nearest gram is required in the neonatal intensive care unit setting, but is not usually necessary in the outpatient follow-up of older infants. Doses measured in fractions of a milliliter are necessary for some medications. EHRs intended for use with young infants should be able to adjust units of measure to the appropriate scale for the situation at hand. The evaluation of any EHR system should encompass its capacity to manage basic data on very small and very young infants.

### Aliases

Name changes are more common in children than in adults because of naming conventions at birth. Names associated with laboratory values obtained for a newborn may not match the name of the patient when the infant is brought to the pediatrician's office for primary



care. Name changes may also occur for children as a result of divorce, remarriage, or adoption. EHRs should be able to store and allow searching for results based on multiple aliases.

### Patient and Parent Education

Most EHR systems, and many stand-alone systems, offer electronic sources of information for parents and patients. For these sources to be effective in pediatrics, this educational information needs to be available in versions that are appropriate—in both wording and reading level—for variable parental reading levels. Many authorities recommend that these informational materials be written at a fourth-grade level. Materials for infants should refer to the patient in the third person, and material for adolescents should be written in the second person.

### Data Source

Information in adult care comes from the patient in most cases. In pediatrics, a parent provides most information, but schools, other family members, and a potentially complex system of guardians and representatives may also contribute to data on a child. EHR systems should support an indication of the source of medical history.

### Adolescent Privacy

An ideal for care held out by adolescent medicine specialists is that adolescents should be able to seek care without being forced to reveal certain information to their parent or guardian. This need for confidential care becomes accentuated when clinical information systems share information with guardians and when state laws dictate policy along these lines. To offer this ideal of confidential care, therefore, an EHR must accommodate an array of functions aimed at limiting dissemination of information, or at least being able to comply with practice policies and laws aimed at who is allowed to see adolescents' health information. Examples of these functions are listed in Table 3-2.

## MANAGING CHILDREN WITH CHRONIC ILLNESSES AND POPULATION HEALTH MANAGEMENT

For a physician caring for children with chronic illness, the quantity and complexity of information make the EHR a necessity. By simply storing and organizing this clinical information, the EHR facilitates the maintenance of an effective medical home for children with chronic or complex disease. But the EHR can do more than just store the information; it can provide decision support to increase the likelihood that the right care is given at the right time. Although this decision support can take the form of automated alerts, there are simpler, less obtrusive forms as well, such as order sets, documentation templates that incorporate care guidelines, and care plans that may be specific to a particular diagnosis or risk.

A population health tool within the EHR that will be of increasing importance to those who care for children with chronic illness is the *registry*. A registry in

an EHR is fundamentally a list of patients. Membership in this list can be determined automatically (through a diagnosis-based inclusion rule) or manually by clinical users. Registries in an EHR typically present selected data points for each patient that are relevant to the monitoring of disease state, such as viral load laboratory data for HIV patients or last hemoglobin concentration for children with sickle cell disease. Registries also typically support the display of severity scores, which, in turn, can be used to drive prioritization of outreach efforts.

Of course, population management tools such as registries can be used to target areas of health needs outside chronic care. A registry that identifies patients who are due for (or behind in) immunizations can boost immunization rates. The same can apply to well child care or other forms of health supervision. This kind of data-driven outreach is fundamental to the modern concept of the medical home.

As more physicians adopt EHRs, there are more opportunities to provide patients and families with direct access to their own records and to allow them to contribute data directly through personal health record portals. The ubiquity of smart phones and other Internet-connected devices makes it possible for families of children with chronic disease to view the medical record, complete surveys online, and even file data directly to the EHR. This data entry has the potential to get families more engaged in care while moving the data collection process closer to the patient. As EHRs make it more possible to perform care management activities outside the context of the office visit, direct interaction of the family and patient with the record will become more important. Patient portals should support appropriate features to protect adolescent privacy according to practice policy. For example, if it is the policy of the practice to restrict parents' online access without the adolescent's assent, the system should allow management of that assent.

## DECIDING TO IMPLEMENT AN ELECTRONIC HEALTH RECORD

In a small practice, the decision to implement an EHR system, the choice of vendor, and the responsibility to fund it fall to the physician. In larger practices or in an academic medical center, these decisions take place in the hands of a committee, which must try to accommodate the needs of diverse physician groups with a solution from a single vendor. These decisions are complex, time-consuming, and momentous. Despite the widely touted assumption that the use of EHRs improves the quality of care, this claim has never been validated for an EHR system as a whole. Although individual pieces of an EHR have been shown to improve adherence to health supervision guidelines, documentation completeness, and incidence of medication errors, the sparse results on health outcomes have been mixed. The best reason to implement an EHR in pediatric practice is to automate and control processes that serve the larger goal of providing excellent care. The EHR should give pediatricians the opportunity to spend less time on mundane tasks, such as following documentation

guidelines, and more time on important tasks, such as talking to families and proactively managing their patient population within the medical home in a team environment.

Several methods can be used for approaching the first step, which is choosing a list of EHR systems to consider implementing.

- *Integration:* The most important predictor of success in an EHR implementation is how well the system works with existing information systems in the environment, especially systems that are critical to the financial success of the clinical operation. Most physician groups and hospitals begin their EHR project by looking at what systems work with their practice management and administrative systems.
- *Peer recommendations:* Another powerful influence over the product-selection process is word-of-mouth recommendations from professional peers. The American Academy of Pediatrics (AAP) Council on Clinical Information Technology supports these communications through its meetings, electronic mailing list, and Web site ([aap.org/informatics/cocit.html](http://aap.org/informatics/cocit.html)). Although there have been efforts to create descriptions of what functions are needed in child health, there is no certification process that a physician can use to gain assurance that a given product works in pediatric settings. Demonstrated usefulness in setting similar to a physician's own setting is still the best way to know how well the EHR can work. Of course, variations in what version is implemented and decisions made as to how it should be implemented make each EHR installation different from the next.
- *Purchasing consortia:* Children's hospitals, physician practice organizations, medical societies, and health data exchange organizations often organize group purchasing arrangements or subsidies to allow practices to purchase EHRs and support services at a lower cost. Although these business arrangements do not necessarily ensure greater usability of the software, larger consortia of purchasers carry more clout in driving the decisions about how the product is designed and implemented. Furthermore, such consortia often have experience installing systems in similar practices, have learned what works in the community, and can provide an instant group of experienced peers to help a practice through the transition.

After candidate systems have been selected, most physicians attempt to evaluate them systematically by interviewing vendors and attending demonstrations. Professional meetings, including those sponsored by the AAP, offer an efficient way of beginning this process through exhibit halls or public competitions between systems. Site visits to practices that are similar to the physician's own are expensive, but offer the most realistic information on how the system performs. The value of site visits is limited by the fact that no 2 practices are alike and that current users may offer a biased opinion about a system purchased and implemented at great cost.

The cost of EHR systems is the most frequent barrier cited by physicians to EHR implementation. No easy answer exists to the question of how much an EHR

costs. Pricing plans vary greatly from vendor to vendor, and no vendor offers a pricing plan that a physician can apply without a lengthy interaction with a sales representative. Old published data from the American Academy of Family Physicians suggest that an EHR system costs approximately \$5,500 per physician per year, with the cost rising to \$7,200 per physician per year for a combined EHR and practice management system that includes billing, patient scheduling, accounts receivable, and similar nonclinical functions. Open-source EHR software, in which the software itself is included in the price, may not be any cheaper than commercially sold software, given that the bulk of an EHR system's cost comprises installation, setup, and ongoing support. EHR software vendors are creating pricing plans at all points along the spectrum, hoping to capitalize on tradeoffs that physicians are willing to make to keep the price low.

A recognized factor in the success of any EHR system implementation is support among the physicians who will be using the system. Implementing an EHR system is disruptive to a practice because it changes almost all established work patterns. EHR implementation also requires physicians and staff to agree on the best procedures for a given task because computerization tends to require uniform procedures. An essential component is to have a *physician champion* who has major responsibility for the EHR implementation in the practice. This person should be a genuine leader in the practice. In addition to the physician leader (and, perhaps, leaders in other job roles), the practice needs to decide on a process for introducing the system into its work. The 2 general implementation approaches are the *big bang*, in which a given system is brought up to full operation over a very short period (eg, a week), or the gentler, but slower, incremental approach, whereby pieces of the system are put into place gradually and used more and more over a longer period. Another technique for introducing an EHR system in a manageable fashion is to either reduce the number of patients to be seen during the rollout (not an economic possibility for most pediatricians) or to use the system on only a small number of patients per day at first. The incremental approach with graduated numbers of patients is feasible but extends the period in which the practice must operate in an environment in which some information is on paper and some is in the EHR.

The full transition to an EHR system, in which no paper charts are used at all, is another challenge to EHR implementation. Information in the paper chart is useful and necessary for a long time (years, in some cases). Manually entering data from the old charts should be done only for the most complex patients, whose charts might benefit from manual sifting of old data. For most patients, scanning of selected pieces of paper (growth charts, immunization records, latest clinic visit, latest consultant reports) may be sufficient. Alternatively, the physician can simply continue to pull paper charts for the visits and enter new data in the EHR as needed. This task can continue until enough time has passed that the paper charts are no longer worth having for most patients. As long as a data source is of sufficient quality (ie, has reliable

patient identifiers), some data may be worth loading into the new EHR electronically. For example, even basic data like encounter dates or claims data can give useful context for patterns of care. Most pediatricians will continue to maintain physical storage facilities for old paper charts because of statutory requirements, but the cost of maintaining this storage will eventually shrink because of the declining need to access archival data.

The question of whether the cost of an EHR system has a financial return is legitimate. Although savings can be demonstrated from electronic order entry because of avoidance of errors in hospitalized adults or from reductions in redundant imaging because of access to exchanged data, research on the return-on-investment question is not extensive for a wide variety of practice scenarios. Some of the benefits of an EHR system accrue to people and organizations other than the physician. For example, if physicians are asked to provide immunization data from their EHR to update the state immunization registry, in all likelihood the entire cost of this project will fall to the practice.

For the pediatrician's practice, EHRs can significantly reduce personnel costs by eliminating the pulling, filing, and locating (often extremely time-consuming) of paper charts for office visits, telephone calls, and prescription refills, among other duties. EHRs can also dramatically reduce the labor required to gather data for quality reporting purposes, provided the system is set up to capture the appropriate data elements. Other cost savings from EHRs are listed in Box 3-1.

Whether time is saved documenting care depends on the state of the user's paper-based documentation in the first place. If the most common Medicare and Medicaid guidelines are followed when coding for evaluation and management services, then the EHR will undoubtedly perform this task faster and more accurately than any paper system. Often in pediatric practices, the paper chart system does not comply with these guidelines. Implementation of an EHR can raise the bar dramatically for documentation detail, given that Medicare compliance is a major selling point for these systems in adult care. Because the

trend suggests that documentation compliance guidelines from all payers will be getting stricter, a system by which an EHR is the only way a physician can be expected to generate the detail necessary to justify payment may be a foregone conclusion, regardless of efficiency considerations.

## DIAGNOSTIC DECISION SUPPORT

The use of a computer to aid in the diagnosis of children with challenging presentations has been a tantalizing possibility since the dawn of the computer age. Diagnostic decision support systems (ie, systems that can take a list of signs and symptoms and suggest possible diagnoses) with pediatric clinical domains have been available for years, yet few physicians use these systems, and demand for such systems has been so low that few vendors of commercial EHR systems have attempted to integrate an automated diagnostic decision support program into their products. It is more common instead to offer links to medical texts from the EHR. Perhaps when EHRs become more widespread, resurgence in interest in the use of these diagnostic aids will take place, if they can be integrated into new patterns of work. More practical means of decision support exist commonly in EHRs, like order sets that suggest standard treatments or documentation templates that remind the physician about ideal care.

## AAP POLICY

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### BOX 3-1 Cost Savings of Electronic Health Records to Practice

- Reduction or elimination of transcription costs
- Elimination of missing charges
- Reduction of medical records staff time and storage space
- Elimination of time spent waiting for chart pulls or finding paper charts
- Reduction of rework attributable to illegible or off-formulary prescriptions
- More efficient tracking of laboratory results and referrals
- Reduction of resources spent managing phone calls (if secure messaging is used)



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## Chapter 4 EVIDENCE-BASED MEDICINE

Brett W. Robbins, MD

Evidence-based medicine (EBM) is the conscientious, explicit, and judicious use of current best evidence to solve clinical problems. It requires integration of individual clinical expertise and patient preferences with the best available external clinical evidence from systematic research and consideration of available resources. EBM provides the pediatrician with an explicit process to locate, appraise, and apply clinical research reports to patient care. The 4-part process of EBM (ask, acquire, appraise, apply) provides an organized framework to facilitate bringing evidence to the point of patient care.

### WHY BOTHER?

The proliferation of medical literature is rapid. A large number of new randomized trials are published each month. To keep abreast of advances in health care requires an organized approach that includes methods to

verify the validity of the information. Another reason for using an organized approach to examine the medical literature is that clinical practice is rich with questions. On average, for every 3 outpatients seen, physicians have 2 questions that are pivotal to the care of these patients. A similar number of questions arise during the care of inpatients. EBM is therefore worth the effort because it allows physicians to remain current with best practices and improve patient outcomes.

### Step 1: Ask

Formulating an answerable and searchable clinical question is the first step of the EBM process. It focuses the busy physician on exactly what is needed to provide patient care. Spending a few minutes to formulate and format a good clinical question is well worth the investment because this effort saves time later in the searching process.

The 2 types of questions in clinical medicine are background and foreground. Background questions deal with disease-specific information and the basics of a condition. An example of a background question is, “What is ondansetron and how does it work?” The answers to background questions are most often found in standard textbooks and review articles. Foreground questions deal with patient-specific information regarding the diagnosis, prognosis, or therapy of a condition. Unlike background questions, the answers to these questions are best found in the medical literature. Time is saved searching for answers to foreground questions if they are first expressed in the format known as PICOTT: **p**atient, **i**ntervention, **c**omparison, **o**utcome, **t**ype of question, and **t**ype of study format. An example of a foreground question is, “In children with acute viral gastroenteritis, does ondansetron reduce symptoms and prevent admission?” Putting this question into the PICOTT format focuses busy physicians on exactly the answer they are interested in finding and begins the search process (Box 4-1).

### Step 2: Acquire

Physicians acquire information from the medical literature in 2 ways: passively (gathering) and actively (hunting). Physicians gather information when they peruse articles that come to them, either through subscription or happenstance. Acquiring the article takes little effort, but the author of the article, not the physician, defines the question. This process is further limited by a lack of context for the article because other data that may exist on this same question are not

### BOX 4-1 Example of a Foreground Question

**Patient:** Child with acute viral gastroenteritis  
**Intervention:** ondansetron  
**Comparison:** Placebo  
**Outcome(s):** Reduction of symptoms, prevention of admission  
**Type of question:** Therapy  
**Type of study needed:** Randomized controlled trial

**Table 4-1** Schema for Ranking Sources of Evidence

SOURCE	SUMMATIVE	VALID	PREAPPRAISED	SYSTEMATICALLY SEARCHED
<i>Cochrane Database of Systematic Reviews</i> (www.cochrane.org)	+	+	+	+
<i>Evidence-Based Clinical Practice Guidelines</i> (www.guidelines.gov)	+	+	+	+
<i>Clinical Evidence</i> (www.clinicalevidence.com)	+	+	+	+
<i>Essential Evidence Plus</i> (www.essentialevidenceplus.com)	+	+	+	+
<i>ACP Journal Club</i> (www.acpjcl.org)	–	+	+	+
<i>InfoPOEMs/InfoRetriever</i> (www.infopoems.com)	–	+	+	+
<i>Textbooks/Up-to-Date</i> (www.uptodate.com)	+	–	–	–
<i>AAP Grand Rounds</i> (aapgrandrounds.aapublications.org/)	–	–	–	+/–
<i>PubMed</i> (www.pubmedcentral.nih.gov/)	–	–	–	–

+ = yes, – = no; +/- = somewhat.

known. Thus, although gathering requires little energy, it also leaves little under the direct control of the physician.

Hunting is actively pursuing an answer to a physician-generated PICOTT question. In general, the search terms are drawn directly from the PICOTT question itself. Time is best spent hunting in grounds known to have valid, preappraised, and summative evidence (Table 5-1). The best databases will have done most of the work already. Physicians should search in a database where they know that all the information has been systematically searched to include everything that exists on the topic. The gold-standard database in this regard is the *Cochrane Database of Systematic Reviews*, which is a database that is systematically searched, preappraised, and up to date. The reviews are updated about every 2 to 3 years. *Evidence-Based Clinical Practice Guidelines* and *Clinical Evidence* are also systematically searched and preappraised. These sources are also updated periodically. A clearinghouse database of all high-level databases is *Essential Evidence Plus* (www.essential-evidenceplus.com), where busy physicians can search all of the high-tier and rigorously searched databases at one site. Second-tier databases include summaries of individual articles such as the *ACP Journal Club* and *InfoPOEMs*, both of which contain some pediatric literature. If these sources are unrevealing, the physician can search in databases that are unfiltered for validity such as PubMed (see Table 4-1 for links to these databases). Early in a physician's career is the best time to form a strong working relationship with the medical librarian, who can assist with questions and assist in accessing these databases.

### Step 3: Appraise

Once an article is located, the next step is to determine its validity. The *Users' Guides to the Medical Literature*, published by JAMA, is an excellent resource. The relevant types of study designs are described using principles of epidemiology, from randomized controlled trials to cost-effectiveness analyses. A clinical example is used to lead the reader through 3 tasks: assessing

validity, quantifying results, and applying the evidence to patients. Table 4-2 is an example of some of the common study types and the information that is found in the User's Guide. It also includes the most efficient method of finding each type of article in PubMed.

### Assessing Validity

Each study type in the *Users' Guide to the Medical Literature* has a list of criteria to determine if a study is valid. These criteria are based on epidemiologic principles and are explained in detail using a clinical example. The criteria appear roughly in their order of importance, but they are not intended to lead to a dichotomous decision of being valid or not valid for a study. Rather, they are intended to assist the physician in determining the relative validity of the study and thus the relative strength of its results. If a study is not valid, then its results are in question and should not be used in the clinical decision-making process. An example of the validity criteria for therapy (randomized-controlled trial) is found in Box 4-2.

### Quantifying Results

The *Users' Guide to the Medical Literature* provides methods to determine the magnitude of effect of an intervention in a more clinically meaningful way than is offered by *P* values. Each type of article has its own methods and terms, such as number needed to treat (NNT) for therapy, likelihood ratios (LR) for diagnosis, and relative risk (RR) for prognosis. For example, the NNT is calculated by dividing 100 by the absolute difference between the outcome rates of the intervention and placebo groups. The result is the number of patients that need to be treated to prevent one bad outcome or to cause a good outcome. For example, in a study of 215 children presenting to the emergency department with mild to moderate dehydration from viral gastroenteritis, of those randomized to treatment with ondansetron, 14% vomited in the next 1-hour oral rehydration period after medication administration. Of the patients randomized to placebo, 35% vomited in this hour. This result was statistically significant ( $P < 0.001$ ), with an NNT of 100/(35–14) or



**Table 4-2** Commonly Confused Terminology in Evidence-Based Medicine

STUDY TYPE	TIMELINE	LOGISTICS	STATISTICS USED	COMMENTS	HOW TO FIND ON OVID MEDLINE
Randomized controlled trial (therapy or prevention)	Prospective	Single group of patients randomized to 2 or more therapeutic or screening methods	Relative risk reduction; absolute risk reduction; number needed to treat	Gold standard; most powerful information	Limit to randomized control trial publication type
Cohort (prognosis)	Prospective or retrospective	Single group of patients gathered at a common point in their diseases and followed forward in time	Relative risk— <i>predicts</i> outcomes	A comparison cohort may or may not exist Framingham study is good example of retrospective cohort	Combine the following MeSH heading with subject search—expand cohort studies
Case control (harm)	Retrospective	Group of patients with the disease compared with group of patients without the disease Look backward for exposure(s)	Odds ratios— <i>predicts</i> exposure(s)	The most difficult to control for bias when conducting	Combine the following MeSH heading with subject search—expand case-control studies
Diagnostic test (diagnosis)	Prospective (optimally)	Single group of patients at risk for a disease; All get tested	Sensitivity Specificity Likelihood ratios Odds ratio	This point is where physicians use pretest and posttest probabilities along with thresholds	Combine the following MeSH heading with subject search—expand “sensitivity and specificity”
Meta-analysis (overview)	Retrospective look at multiple studies	All relevant studies addressing the same question combined mathematically as if they were one large trial	Effect size	Can combine any of the study types, most commonly therapy and diagnosis	Limit to meta-analysis publication type

**BOX 4-2 Validity Criteria for a Randomized Controlled Trial**

Did experimental and control groups begin the study with a similar prognosis?

- Were patients randomized?
- Was randomization concealed?
- Were patients analyzed in the groups to which they were randomized? That is, did an intention to treat exist?
- Were patients in the treatment and control groups similar with respect to known prognostic factors? That is, were baseline characteristics equal?

Did experimental and control groups retain a similar prognosis after the study started?

- Were patients aware of group allocation?
- Were physicians aware of group allocation?
- Were outcome assessors aware of group allocation?

Was follow-up complete?

about 5. Thus the physician would need to treat 5 children with mild to moderate dehydration with ondansetron rather than placebo to prevent 1 from vomiting in the next hour. In addition, at the end of the hour-long oral rehydration period 14% of the ondansetron-treated children and 33% of those receiving placebo needed intravenous (IV) rehydration. (NNT ~ 6), but hospital admission rates were no different (4% vs 5%). Other outcomes that are nondichotomous, such as length and volume of IV fluid needed and time in the emergency department, were in favor of ondansetron as well. An NNT cannot be calculated from this type of continuous data unless an arbitrary cutoff is set to make the outcome dichotomous (eg, the percentage of children who spent more than 4 hours in the emergency department). The NNT is more clinically meaningful than a simple *P* value and helps the physician balance risk and benefit more explicitly. Not only is a low NNT important, it is also necessary to understand the risks and benefits of the treatment and underlying disorder to

make an informed decision regarding the proposed therapy. In this example, children in the ondansetron group on average had 1.4 episodes of diarrhea in the oral rehydration hour vs 0.5 episodes on average for the placebo group ( $P < 0.001$ ). Again, an NNT cannot be calculated from this continuous outcome. The only other adverse event would be cost of the medication, but one needs to look at overall costs of IV hydration as well when comparing costs.

The NNT is difficult to interpret without its precision, or 95% confidence interval. For our ondansetron example, given that the study population is of moderate size ( $N = 215$ ), the confidence intervals around our NNT of 6 for intravenous rehydration are moderately wide (3-17). Thus we are 95% certain that our true NNT falls somewhere between 3 and 17.

#### Step 4: Apply

After determining that an article is valid and quantifying its results, the final step is to decide whether it applies to the patient. This process has less to do with the inclusion and exclusion criteria than with the patient's underlying physiologic condition. Inclusion and exclusion criteria are written for logistic purposes of the study itself rather than for the person to whom the information can be applied. Patients who may not have met inclusion criteria for the study may still benefit from the study results. However, if something in the patient's underlying physiologic condition is very different from the patients in the study, then the findings from the study may not apply to this particular patient. In the case of the ondansetron study, the physician might be appropriately hesitant to apply this evidence to children presenting for vomiting from other etiologies such as increased intracranial pressure.

In making the decision whether to use valid evidence for a particular patient, the physician must balance 4 factors: the evidence, her or his own clinical judgment, the patient's values and preferences, and the clinical state and circumstances at the time the decision needs to be made (Figure 4-1). The physician must decide how much weight to give each of

these 4 factors in making the decision. The process of EBM provides the validity and thus strength of the evidence. In doing so, it does not replace clinical judgment, but rather informs it. Patients have the right to refuse an effective intervention with valid evidence behind it, even if the intervention is judged to be worthwhile. Furthermore, even if an intervention is proven to be effective by valid evidence and the physician and patient agree to use it, the intervention may not be readily available or financially viable. This fluidity of interaction of these 4 issues results in different decisions on different days with the same evidence, and perhaps even with the same patient.

#### TIME

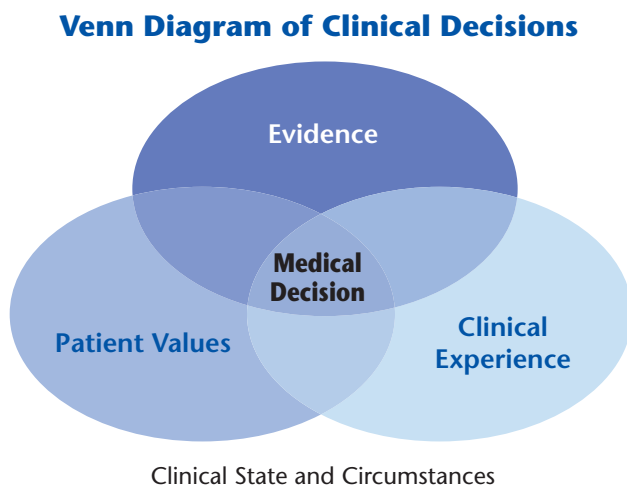
For EBM to be useful to the busy pediatrician, it has to be time efficient. Three suggestions might make EBM efficient in a busy practice. First, the more physicians use the process, the more efficient they become. Learning the EBM process mimics learning how to perform a history and a physical examination; efficiency comes with time and practice. Second, hunt and gather in databases that are known to be fertile. Focus on databases such as *Essential Evidence Plus*, the *Cochrane Database*, *Clinical Evidence*, and [www.guideline.gov](http://www.guideline.gov). In doing so, clinicians can be assured that the information obtained has been thoroughly searched, assessed, and summarized. Third, hunt and gather only those questions that are common to actual practice, are critical to an individual patient's care, or involve subjects about which physicians are intensely curious.

#### GETTING STARTED

The *Users' Guides to the Medical Literature* is the best resource on how to learn, practice, and teach EBM because it is complete, easy to read, and well organized; it also comes with a CD-ROM and on-line version with all the mathematics distilled to simple calculators. When an article from the literature is read, the *correlate chapter* feature should be used to guide the assessment of the article. Over one-half of the foreground questions asked in practice deal with therapy, diagnosis, and disease management. Thus, if physicians are adept at critically appraising these types of articles, then they are well prepared to answer most of their clinical questions. The next time a clinical question is worth the time to research, the physician should start with one of the fertile databases. If the inquiry is a common question or about a common disorder, then in all likelihood relevant evidence that is preappraised, presearched, and pre-summarized will exist.

#### CONCLUSION

Patients deserve to have physicians who make decisions regarding their care based on sound evidence. EBM provides an explicit, transparent process to track down information, assess its validity, and apply it to individual patients. It does not replace sound, seasoned clinical judgment, but rather informs it. A growing



**Figure 4-1** Venn diagram of clinical decisions.

array of resources is now available that makes the process timely and thus useful to the busy primary care pediatrician.

### TOOLS FOR PRACTICE

#### Medical Decision Support

- *BMJ Clinical Evidence* (book), British Medical Journal ([www.clinicalevidence.com/ceweb/index.jsp](http://www.clinicalevidence.com/ceweb/index.jsp))
- *Essential Evidence Plus* (Web site), ([www.essential-evidenceplus.com](http://www.essential-evidenceplus.com))

### AAP POLICY

American Academy of Pediatrics Steering Committee on Quality Improvement and Management. Classifying recommendations for clinical practice guidelines. *Pediatrics*. 2004;114(3):874–877 ([pediatrics.aappublications.org/content/114/3/874](http://pediatrics.aappublications.org/content/114/3/874))

### SUGGESTED READING

Guyatt GH, Rennie D. *Users' Guides to the Medical Literature. A Manual for Evidence-Based Clinical Practice*. Chicago, IL: JAMA Press; 2001

## Chapter 5

# QUALITY IMPROVEMENT IN PRACTICE

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## INTRODUCTION

Quality of care has become a central theme in the delivery and management of health care. The focus on quality results from consistent data indicating that health care in the United States has a “serious and pervasive . . . overall quality problem,” and that “the burden of harm conveyed by the collective impact of all of our health care quality problems is staggering.”

Data from both inpatient and outpatient settings in pediatrics show widespread gaps in care. A recent, detailed analysis of ambulatory health care for children found that children receive recommended care less than one-half of the time, and the performance of children's health care was 10 percentage points lower than a comparable assessment of adult care.

Fortunately, methods and tools that enhance the quality of care are increasingly available and can be applied in primary care settings. Programs to enhance care have been successful in improving preventive services and the care of children with both acute and chronic conditions. This chapter reviews these methods and provides practical guidance for applying them in practice.

## DEFINITIONS

The Institute of Medicine (IOM) defined *quality* as “the degree to which health services for individuals and populations increase the likelihood of desired health

outcomes and are consistent with current professional knowledge.” This definition, which provides a foundation for current thinking, acknowledges the importance of outcomes, the key roles of individuals and the public in determining which outcomes matter, the essential role of probability (doing the right thing even if the right result does not always occur), and the constraint placed on current quality of care by the current state of knowledge.

The IOM refined its definition in the report, *Crossing the Quality Chasm*, which outlined 6 specific aims for the health care system, now widely viewed as the critical dimensions of quality. These aims, provided here along with explanations behind them, are that health care be

- **Safe:** Safety (defined here as protection from harm as a consequence of health care) is a system property rather than a reflection of individual shortcomings; system redesign is the necessary strategy to address shortcomings in this area.
- **Effective:** Effective care refers to the reliable delivery of care that is known to be more likely to achieve desired results; that is, care that is consistent with evidence when available with appropriate consideration of individual patient characteristics and preferences.
- **Efficient:** Efficient care refers to the judicious and appropriate use of resources or, more specifically, not delivering care known to be ineffective (eliminating overuse).
- **Patient centered:** Patient centeredness is the core, central aim of health services. The fundamental definition of quality refers to outcomes desired by patients as the key aim of care. The experience of care is one dimension of patient centeredness, and satisfaction with care is one component—a subjective assessment of how these experiences compare with expectations. In child health, this is better framed as patient and family centeredness.
- **Timely:** Timeliness refers to eliminating the delays that are omnipresent in health care; it is a dimension that clearly affects efficiency and patient centeredness, and it affects safety (eg, delay in providing a needed immunization as a result of scheduling) and effectiveness (delays in appointments for appropriate medical tests and therapies).
- **Equitable:** Quality applies to the care of all patients, not simply subsets of patients in the care of the physician. The IOM report *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care* demonstrates that disparities of care exist throughout the health care system and calls for widespread educational and improvement efforts to eliminate them.

Until recently, quality improvement efforts in primary care focused on 1 or, at most, 2 aspects of quality—such as effectiveness (eg, use of appropriate medications for asthma or rates of immunization) or patient centeredness (typically measured in terms of patient satisfaction). Nonetheless, the IOM concept of quality suggests that high-quality programs that meet the needs of children and families are characterized by excellence in all 6 areas. Practices that provide the best care deliver the right care—based on evidence and

associated with the best outcomes—in a manner that is respectful of family needs and values, that wastes neither resources nor time, that does not cause preventable harm, and that is delivered without bias and designed to achieve equitable results across different patient populations. Timeliness of access is an attribute of the practice's delivery system; geographic and financial access are attributes of the larger health care finance and policy system rather than attributes of the practice system itself.

Because of the nature of primary care, care must be designed to address the full spectrum of child health needs—preventive care, acute care, and the care of children with chronic or special health care needs. In most cases, care should also address community needs, including both societal health needs (eg, high immunization rates) and the particular public health concerns of the community served by a practice. This latter emphasis is consistent with the pursuit of the “Triple Aim”—simultaneously improving health, improving the experience of care (framed as the 6 IOM dimensions discussed previously) and reducing per capita costs. The Triple Aim is the most recent reframing of quality, initially developed by the Institute for Healthcare Improvement and now incorporated into the US Federal National Quality Strategy. From this perspective, practices need to help address the broader social needs of their patients, and must also be aware of the impact of earlier life experiences on long-term health and well-being.

The fundamental requirement for addressing all of these issues in a practice is to view the primary care practice as a system or, in some cases, as one component of a larger system such as a medical group, hospital network, or accountable care organization. When viewed as a system, the methods and tools of improving system performance can be applied to practices.

### Establishing Priorities

Given the breadth and scope of quality, as well as the substantial gaps in performance across the spectrum of quality dimensions, choosing where to begin is daunting. One strategy to inform the choice of priorities is the use of a monitoring tool such as a quality compass, balanced scorecard, or family of measures. Although such dashboards or scorecards are often viewed only in the context of corporate management, the concept here is to develop a set of indicators that reflect practice performance across the 6 dimensions of quality for a practice, as well as across other dimensions that practices already likely monitor, such as financial performance and staff satisfaction. Such a management tool can assist practice leadership in setting priorities. Often, external organizations, such as managed care plans, require measures in 1 or more of the quality dimensions, and national quality award programs, such as the Baldrige Award, look for such a systematic approach to priority setting and performance monitoring.

In choosing to develop and apply a monitoring tool, practices should first consider their overall purpose in establishing a measurement system. Although these tools can be used to comply with insurance requirements and identify priorities for mandated projects, a

more appropriate purpose is to enable practices to provide appropriate, timely care for the child and the child's family, with the overall goal being to promote better health outcomes for children, families, and the community. Because practices need to stay organizationally vital to provide this care, a reasonable additional aim is to sustain the organization over the long term.

What should a monitoring tool measure? Individual practices or practice networks may choose different measures, but an ongoing commitment to quality includes monitoring across the full spectrum of care.

In the area of safety, practices can measure several dimensions. One critical aspect of safety in primary care is reporting and responding to critical test results. This can be assessed by identifying abnormal values from laboratory results and tracking the proportion of patients with these results who were notified appropriately or had appropriate follow-up actions documented.

The measure of timeliness in primary care is increasingly standardized. The most widely used measure is the time to the third available appointment in a practice (regardless of visit type). Another measure of timeliness that assesses the performance of the broader health system is the wait for a subspecialty appointment (using the same third-available construct).

Measuring the effectiveness of care should include all 3 aspects of care—acute, chronic, and preventive.

Acute care is a major component of pediatric primary care. Fewer firm measures of care exist in this field. Among the most widely used measures of the quality of acute care is the appropriate use of antibiotics, a measure now widely in use through the Healthcare Effectiveness Data and Information Set (HEDIS), a standard set of measures used to assess quality of managed care plans developed by the National Committee for Quality Assurance. This measure tracks the rate of antibiotic prescriptions for children between 3 months and 18 years of age who were diagnosed with upper respiratory tract infections.

Numerous metrics are available to assess the effectiveness of care for children with chronic conditions. The most widely used metrics relate to care for children with asthma, the most common chronic medical condition. These metrics include measures of care processes, such as whether severity is assessed or whether appropriate medications are prescribed, and measures of patient outcomes, such as hospitalization, emergency department visits, and days without symptoms over a specified period. Measures also exist for the care of children with attention-deficit/hyperactivity disorder (ADHD) that are broadly consistent with the guidelines of the American Academy of Pediatrics (AAP). These measures include the use of criteria established in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* in making the diagnosis and undertaking appropriate follow-up after the prescription of a stimulant or other medication. Measures of symptoms and function can also be collected to provide a more comprehensive assessment of care quality. More rigorous measures of effectiveness combine, or bundle, multiple measures into a single *raise-the-bar* indicator, requiring that all



appropriate processes be undertaken for a specific patient (eg, assessing severity, using a written management plan, and prescribing appropriate medication for a child with asthma).

Because the needs and concerns of families with children with special health care needs are quite similar regardless of the specific condition, broad measures assessing the degree to which practices fulfill these needs are available. These measures assess, among other items, how well practices coordinate care and link families to available resources. Such measures can be obtained from the “Children With Chronic Conditions” item set of the Consumer Assessment of Healthcare Providers and Systems (CAHPS) survey. These measures rely on the most appropriate source of information—the parent or caretaker.

Preventive care is the most commonly assessed aspect of primary care for children. Typical measures of effectiveness of preventive services include immunization rates, the performance of screening tests (eg, developmental assessments), and the provision of anticipatory guidance consistent with recommendations. The recent dramatic increase in childhood obesity has led to specific emphasis on the quality of preventive care related to this condition. These measures typically include performing the body mass index percentile calculation, categorizing the obesity risk status, and providing counseling about appropriate health behaviors.

A more sophisticated approach to assessing the quality of preventive services might entail assessing whether a patient-specific health risk assessment was undertaken and whether appropriate follow-up assessments and plans were developed depending on these risks. Parent-reported measures of preventive care—particularly related to promoting appropriate development—are also available (see Tools for Practice).

Measures of efficiency in primary care pediatrics are often monitored by practices themselves or by third-party payers; these measures might include provider productivity, use of high-cost pharmaceuticals or radiologic tests, and hospitalization or emergency department use.

Patient and family centeredness can only truly be assessed by patients and families themselves. The dimensions of these measures are typically included in patient experience-of-care surveys and usually consist of

- Perceived access
- Courtesy and respect
- Provision of information
- Involvement in decision making
- Care coordination
- The physical environment of the practice
- Overall assessment

These dimensions have been assessed on a widely available plan-level measure, the CAHPS. A medical group and practice-level CAHPS for child health has recently become available.

The measurement of equity of care is relatively simple in concept, but has often been controversial in implementation. To assess equity, practices need a reliable indicator of membership in a particular group (eg, racial group, income or insurance category, language spoken). Then, all the other measures in the

scorecard can be stratified by the different categories (examining, for example, whether rates of prescribing appropriate medication for patients with persistent asthma vary by race or whether critical test follow-up rates differ according to language).

If practices identify improving community health as one of their aims, then tracking broader community-based measures of health will also be appropriate, such as rates of injury caused by intentional or unintentional trauma and population-based indicators of obesity and diabetes. These data might lead to specific practice-based initiatives or might prompt more active engagement in advocacy and program development within the broader community. Such data are often available through local and state health departments or may be found online at the state, county, or city level. See, for example, County Health Rankings & Roadmaps ([www.countyhealthrankings.org/rankings/data](http://www.countyhealthrankings.org/rankings/data)).

A comprehensive practice measurement set combines these clinical metrics with additional performance metrics, such as financial performance and measures of staff satisfaction. Practice leaders developing such scorecards for a single practice within a larger system must also realize that maximizing performance on a single unit is typically not the goal of an overall institution, so care must be taken to avoid policies that negatively affect performance elsewhere. For example, maximizing productivity in a practice by referring all complex patients to specialists may decrease access to those specialists for other practices.

Primary care practices do not typically undertake comprehensive monitoring and assessment. The burden on an individual practice of compiling these measures regularly in the absence of an effective clinical information system, such as an electronic health record and effective practice registries, is substantial. On the other hand, the ability to generate such performance data and then use the data to manage and improve quality within a system is a clear advantage of electronic health information systems and one of many arguments for the potential benefit of such systems. Making such measures transparent (ie, sharing them publicly with staff, patients, and the community) may also serve to deepen widespread engagement and generate ideas for improvement.

Measurement does not result in improvement in quality; rather, it is necessary to identify opportunities for improvement and for tracking progress towards a goal. For quality to improve, measurement must be linked to purpose, better ideas for how to practice, and a process that reliably produces change and enhanced results.

## UNDERTAKING AN IMPROVEMENT PROJECT

Regardless of the priority chosen, the fundamental approaches used in improving quality at the practice level are similar. The first step is chartering a team to undertake improvement. In a small practice, the team might consist of the entire practice—physician, nurse, and manager. In a larger practice, improvement teams typically include part of the practice, but must maintain ongoing communication with the rest of practice



so that improvements can subsequently spread. If the practice has a senior partner or some other form of formal leadership, then the leadership should develop the charge for the team. The team should be multidisciplinary and, in almost all cases, should involve patients and families as team members.

### Establishing Aims

The first task of an improvement team is establishing an aim, which may need to be refined by leadership (See Figure 5-1). Aims for improvement programs should be based on data and should be sufficiently bold to engage the energies of the project team. Similar to any research hypothesis, aims should be directional and specify magnitude. Aims should be closely aligned with the mission and vision of the organization and, whenever possible, reflect the priorities of patients and families. A hypothetical aim statement might be, “Our project aim is to increase the function of children with ADHD cared for in our practice; we will do so by improving the care of children with ADHD so that more than 95% receive perfect care, without disparities”; in this case, *perfect care* is precisely defined (eg, use of *DSM-5* criteria for diagnosis, development of shared goals, use of evidence-based treatment, and follow-up consistent with AAP guidelines). This example clearly indicates the interrelatedness of the 6 quality aims. Although ostensibly

focused on effectiveness of care (giving evidence-based treatment for ADHD), the project will also necessarily involve issues of safety (monitoring for side effects and complications), efficiency (use of mental health specialists), timeliness (wait times for assessment and treatment), patient and family engagement, and, given the current lower level of use of evidence-based treatments among black children who meet criteria for this diagnosis, equity.

### Selecting Performance Measures

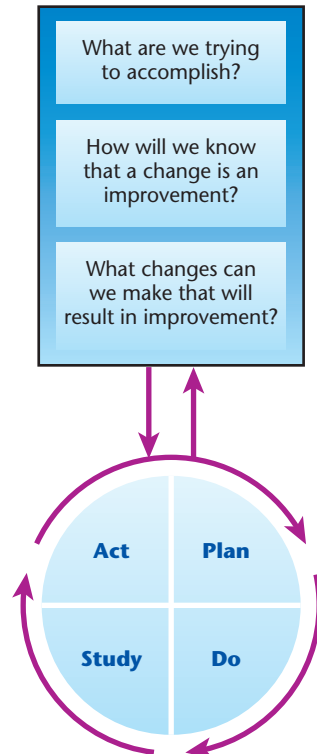
The second step in an improvement program is establishing measures to assess performance and track gains. Measuring for improvement generally should focus only on the most important elements of the work. Ideally, measures should be derived from data collected routinely in the course of care, such as through an electronic health record or patient registry or through ongoing patient survey activity, but in most cases this must be supplemented by project-specific data collection and analysis. Importantly, data should be plotted and tracked over time using simple tools, such as run charts, or more sophisticated tools, such as control charts, rather than aggregated for evaluation-oriented before-and-after studies. A typical improvement project will include between 4 and 8 measures, including measures of the processes of care (was the right thing done?), of the outcomes of care (did the right result occur?), and of potential adverse outcomes (balancing measures; did unintended harm occur?). In the example, ADHD measures of process would include whether information about child symptoms and function was collected from a parent and 1 other source (eg, a teacher) and whether *DSM-5* criteria were used. Outcome measures might include symptom scales and measures of function. Balancing measures might include patient satisfaction and physician productivity.

### Identifying Good Ideas

The third step for an improvement initiative is identifying changes or innovations that are likely to lead to accomplishing the desired aims. Ideas for such changes can often be found in the medical literature, with recognition that medical innovations often take between 1 and 2 decades to enter widespread use after being proved effective. Changes can also be found outside of health care; safety innovations, for example, are typically imported from high-reliability industries such as aviation, nuclear power, and high-speed transport. Patients, families, and health care staff are additional valuable sources of innovation. Generic change concepts from industry are another useful source of innovation that can be customized to the health care setting.

### Example of a Good Idea: Care Model for Child Health in a Medical Home

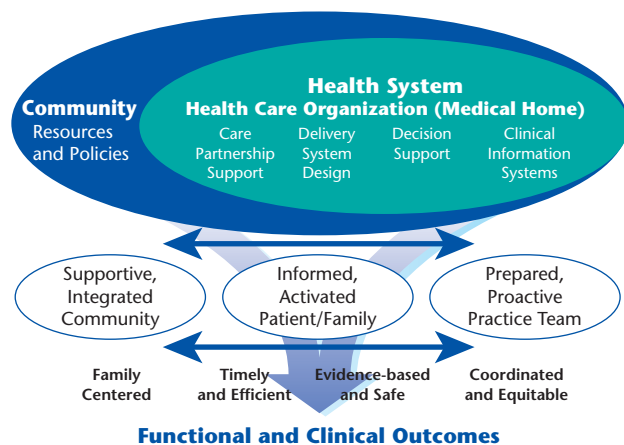
An idea that is widely applicable to improving the quality of primary care—particularly preventive care and the care of children with special health care needs—is the care model for child health in a medical home, a modest modification of the chronic care model



**Figure 5-1** Model for Improvement. (From Langley GL, Moen R, Nolan KM, Nolan TW, Norman CL, Provost LP. *The Improvement Guide: A Practical Approach to Enhancing Organizational Performance*. 2nd ed. San Francisco, CA: Jossey-Bass Publishers; 2009. Reprinted with permission.)

developed by Wagner and colleagues (Figure 5-2). The care model asserts that primary care is best delivered not by an individual provider, but rather by a health care team, and that the team will best serve the patient if it can anticipate patient needs and act accordingly. The team can function most effectively when supportive clinical information, decision support, care delivery, and self-management support systems are in place within a practice or clinic and when larger organizational systems are also aligned in support of the overall approach. The care model further asserts that patients must participate in their own care as members of the care team. To accomplish this task, patients need sufficient knowledge, skills, and abilities to monitor and manage their well-being. For younger children, a parent or caregiver often serves as the patient's voice and agent. The care model advises that health care practices and systems draw on community resources to help patients achieve better outcomes.

Practices with appropriate clinical information systems are able to list which of their patients have specific clinical conditions (eg, asthma), the severity or complexity of these conditions (eg, severe persistent asthma), and other bits of information relevant to the patient management question at hand (eg, are all eligible children with asthma using the proper dose of anti-inflammatory medication?). Information systems can also indicate which patients have received specific preventive services (eg, immunization, screenings, and assessment of healthy weight) and provide reminders when they are due.



**Figure 5-2** The care model for child health in a medical home. This diagram indicates the desired outcomes of excellent care for children; the shared contribution of the health care system and community resources to improved results; the key role of organizational policies and leadership; and the four specific elements of an effective medical home—information system, decision support, delivery system design, and care partnership support. (From Homer CJ, Cooley WC. *Creating a medical home for children with special health care needs*. In: Sobo EJ, Kurtin PS, eds. *Optimizing Care for Young Children with Special Health Care Needs*. Baltimore, MD: Paul H. Brookes; 2007, with permission.)

Two aspects of the design of the delivery system merit particular attention. Interactions among physicians, other health care providers, patients, and families should be designed to address issues of importance to patients and their families and to anticipate future needs. The most effective settings for such interactions are planned visits. Planned visits are routine in preventive care (well-child visits) but are less common—although essential—in the care of children with special health care needs. Because of the fragmentation of services for children, the care model for child health also emphasizes care coordination. A designated office staff member may provide care coordination, or care coordination functions may be distributed in clearly defined ways among several individuals. Finally, because children are ethnically and culturally diverse, capturing ethnic information in patient registries is important to ensure that practices can examine their care and outcomes by patient subgroups. Trained interpreters in the care partnership enable appropriate goal setting and care planning.

Chronic care must be based on evidence when evidence is available and on expert guidance when evidence is not available or needs interpretation. Basing care on evidence requires mechanisms for determining what type and degree of evidence is required to drive change, for obtaining and reviewing evidence-based recommendations, for sharing such information with patients and families, for entering the evidence in medical record systems so that faulty memory does not impede care, and for maintaining ready access to subspecialty expertise.

The most critical component of the care model is providing care in a way that promotes patients' ability to provide self-care and manage their own care. This framing acknowledges that pediatricians and other health care professionals are facilitators and that the actions of patients are the final determinants of outcomes. The core aspect of self-management support is the development of shared goals between patients and physicians and the subsequent development of specific, mutually agreed-on plans to achieve these goals.

Because care for children includes supporting both the family's ability to provide care and the child's ability to assume self-care, practices should provide both self-management support (supporting the ability of the child to manage their own health and health care) and family-management support (that is, promoting the ability of the family to manage that care). For example, children with diabetes or asthma need to take increasing responsibility for monitoring their own condition and for adjusting their medical regimen as they approach adolescence. The medical home, where the care model is implemented, needs to support the child's increasing competence in managing her well-being and to counsel and support the family in monitoring the success of that effort while also maintaining the child's safety.

The care model highlights 2 additional areas critical to providing preventive care and care that meets the needs of persons with chronic conditions. The first area is alignment of health care provider activities with organizational aims. The second is that practices must draw on the resources of the larger community

to meet patient needs. This includes obtaining access to not only formal supports and entitlements such as housing services or special education, but also informal supports provided by resources such as churches and libraries.

Although not simple, the care model for child health is a powerful framework for the organization (and reorganization) of pediatric primary care. Combined with evidence-based guidelines as well as an effective strategy to undertake small changes that will ultimately effect large changes in practice systems, it results in better care for children and families. This model provides the detail that is needed to make the medical home concept a reality.

### Implementing Change

In primary care practices, fully implementing a new approach, such as the care model described previously, in a way that anticipates all the challenges that such change will bring is not typically possible. A more effective approach to introducing change is through the use of repeated small tests of change, sometimes referred to as the Shewhart cycle after the industrial engineer who first developed the approach, or more commonly, the plan-do-study-act (PDSA) cycle.

The PDSA cycle starts with the question, “What is the largest meaningful test of change that we can conduct by next Tuesday?” The priority for a PDSA cycle is to expeditiously try something out (do) in a way that is planned and that allows learning (study) and revision (act). A typical health care PDSA cycle involves the care of one patient at one point in time by one health care provider, such as the use of a new dehydration assessment form or patient instruction diagram. A full cycle involves planning what will be done (including the questions of who, what, where, and when, if not why), performing the test, reflecting on what happened during the test, and modifying the test for the next cycle. Effective improvement programs conduct numerous cycles, building one on the other and addressing different dimensions of the care system with different series of tests.

This approach to improvement—the combination of aims, measures, changes, and the PDSA cycle—is known as the Model for Improvement. Developed by Associates in Process Improvement, the Model for Improvement is among the most widespread improvement frameworks in health care. Different approaches use different terminology and have somewhat different emphases but in general they share the use of aims, measures, and repeated tests of change.

### COLLABORATIVE LEARNING

Sharing data allows individual organizations both to set priorities better and to identify practice settings that have better performance for learning (also known as *benchmarking*). The benefits of collaborative learning have formed the basis for numerous collaborative improvement programs in children’s health care. Many networks initially established for clinical and health services research, including the AAP Pediatric Research in Office Settings and the Continuity Research Network for academic primary care, have the potential to serve this purpose. Topic-specific

learning collaboratives conducted by the National Institute for Children’s Health Quality and other organizations can also serve this function. Many regional improvement programs have also been established, often involving state professional association chapters working together with public health officials, academic institutions, and public and private health insurance agencies. Participation in such external efforts typically accelerates learning and improvement and facilitates the pediatricians’ efforts in quality improvement, which are often difficult to accomplish without external resources.

### SUMMARY

Widespread deficiencies abound in health care across all 6 dimensions of quality (safety, timeliness, effectiveness, efficiency, equity, and patient centeredness). A systematic approach to monitoring quality can help set priorities for improvement, although the specific topics and initiatives to be undertaken must also be customized to the specific institutional environment. Use of a quality improvement approach such as the Model for Improvement increases the likelihood of making positive changes in care and outcomes. The care model for child health is one powerful idea that can be used to organize and improve the quality of primary care practices, particularly when combined with evidence-based recommendations such as Bright Futures. Collaboration across organizations can accelerate improvement efforts as well.

### TOOLS FOR PRACTICE

#### Community Advocacy and Coordination

- *Be Our Voice: Obesity Prevention Advocacy Training* (online course), National Institute for Children’s Health Quality ([obesity.nichq.org/resources/obesity%20prevention%20advocacy%20training](http://obesity.nichq.org/resources/obesity%20prevention%20advocacy%20training))
- *Bright Futures, Theme 10: Promoting Community Resources and Relationships* (guidelines), American Academy of Pediatrics ([brightfutures.aap.org/Bright%20Futures%20Documents/11-Promoting\\_Community\\_Relationships.pdf](http://brightfutures.aap.org/Bright%20Futures%20Documents/11-Promoting_Community_Relationships.pdf))
- *Community Toolbox* (Web site), Work Group for Community Health and Development, University of Kansas ([ctb.ku.edu/en](http://ctb.ku.edu/en))
- *Tools and Resources* (Web page), National Center for Medical Home Implementation ([medicalhomeinfo.aap.org/tools-resources/Pages/default.aspx](http://medicalhomeinfo.aap.org/tools-resources/Pages/default.aspx))

#### Practice Management and Care Coordination

- *Care Coordination Task Force Key Elements Framework (report)*, Massachusetts Child Health Quality Coalition ([www.masschildhealthquality.org/wp-content/uploads/2014/06/care-coordination-framework.pdf](http://www.masschildhealthquality.org/wp-content/uploads/2014/06/care-coordination-framework.pdf))
- *Child Clinician and Group CAHPS Survey* (Web page), Agency for Healthcare Research and Quality ([cahps.ahrq.gov/Surveys-Guidance/CG/index.html](http://cahps.ahrq.gov/Surveys-Guidance/CG/index.html))
- *Creating a Patient and Family Advisory Council: A Toolkit for Pediatric Practices (booklet)*, National Institute for Children’s Health Quality ([medicalhome.nichq.org/resources/pfac-toolkit](http://medicalhome.nichq.org/resources/pfac-toolkit))
- *For Practices: Getting Started* (Web page), National Center for Medical Home Implementation ([medicalhomeinfo.aap.org](http://medicalhomeinfo.aap.org))



homeinfo.aap.org/tools-resources/Pages/For-Practices.aspx)

- *Medical Home Change Package*, National Institute for Children's Health Quality (medicalhome.nichq.org/resources/medical%20home%20change%20package)
- *Putting Theory Into Practice: A Practical Guide to Medical Home Transformation Resources* (Web page), Patient-Centered Primary Care Collaborative (www.pcpcc.org/guide/putting-theory-practice)

### AAP POLICY

American Academy of Pediatrics Council on Community Pediatrics. Community pediatrics: navigating the intersection of medicine, public health, and social determinants of children's health. *Pediatrics*. 2013; 131(3):623–628 (pediatrics.aappublications.org/content/131/3/623)

American Academy of Pediatrics Council on Children With Disabilities. Care coordination in the medical home: integrating health and related systems of care for children with special health care needs. *Pediatrics*. 2005;116(5):1238–1244 (pediatrics.aappublications.org/content/116/5/1238)

American Academy of Pediatrics Steering Committee on Quality Improvement and Management. Toward transparent clinical policies. *Pediatrics*. 2008;121(3): 643–646. Reaffirmed February 2014 (pediatrics.aappublications.org/content/121/3/643)

### SUGGESTED READINGS

AAP Professional Resources on Practice Support: Quality Improvement (www.aap.org/en-us/professional-resources/practice-support/quality-improvement/Pages/Quality-Improvement.aspx)

Center for Medical Home Improvement (www.medicalhomeimprovement.org)

National Institute for Children's Healthcare Quality (www.nichq.org)

The Institute for Healthcare Improvement (www.ihl.org)

of specialists as well as other health and non-health community resources. Well children may also require referral to specialists for troubling signs or symptoms of disease or when screening in the medical home raises suspicion of a problem. Health maintenance for all children suggests a broad population approach. Depending on the risk patterns of children in a practice's population, this approach may require communication with and linkage to public health resources. All of these interactions involve collaboration both within and beyond the walls of the medical home.

### FIVE LEVELS OF COLLABORATION

The primary care family-centered medical home occupies a crucial intersection within the community-based system of supports and services on which families, children, and youth depend (Figure 6-1). The medical home is positioned to collaborate and coordinate care vertically within the health care system as well as horizontally among community-based organizations. As a result, much depends on a proactive approach to collaborative care. To realize a fully integrated, family-centered, community-based system of care and services, collaborative care must manifest itself in 5 domains. First, and central to the provision of family-centered care (see Chapter 9, Partnering With Families in Hospital and Community Settings), pediatricians and other providers of pediatric care promote a true partnership with families. This is the relationship around which all other collaborations revolve. Second, the staff of the primary care medical home functions as a team with explicit roles for all members aimed at providing the most effective, efficient care and the best possible experience for families. Third, the primary care medical home team collaborates with specialists around initial consultations and ongoing chronic condition care to ensure seamless comanagement and clarity about diagnostic impressions and treatment plans. Fourth, the medical home team needs to work with insurers (private and public) and accountable care organizations to ensure appropriate

## Chapter 6 MEDICAL HOME COLLABORATIVE CARE

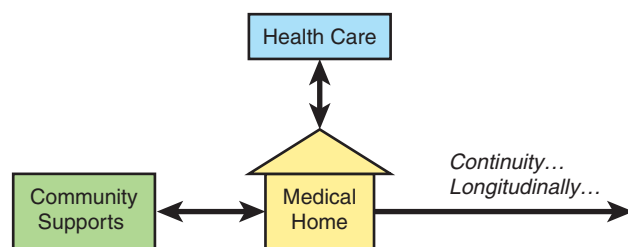
Jeanne W. McAllister, BSN, MS, MHA; W. Carl Cooley, MD

### BACKGROUND

The complexity of health maintenance, acute illness care, and chronic condition management no longer permits the simple model of a single practitioner meeting all of the health care needs of every child in every family. The primary care family-centered medical home requires an organized team of providers and staff working together to ensure the safest, most effective, and most efficient delivery of care. At least 15% of children have 1 or more special health care needs, and their care often requires the involvement

### The Primary Care Medical Home Coordinates Care...

- Vertically – within the health care system
- Horizontally – among community agencies
- Longitudinally – with continuity over time



**Figure 6-1** Medical home responsibilities.

access to and payment for their patients' care. Finally, the primary care medical home collaborates with other community-based organizations such as schools, early intervention programs, mental health agencies, home health agencies, and family support organizations to ensure that a child's health care needs are fully understood and considered in the context of the whole range of community services that impact the child and family.

### **Family-Centered Care: Collaboration With Patients and Families**

Family-centered care was defined by an expert panel of health care professionals, family leaders, and maternal and child health policy makers in the following manner:

Family-Centered Care assures the health and well being of children and their families through a respectful family-professional partnership. It honors the strengths, cultures, traditions and expertise that everyone brings to this relationship. Family-Centered Care is the standard of practice, which results in high quality services.

A growing evidence base demonstrates improved outcomes for children and families receiving family-centered care. In particular, studies have demonstrated lower hospitalization rates, reduced rates of unmet needs, and increased use of community services. Furthermore, family-centered care has been associated with improved physical and mental health and fewer missed school days for children with chronic conditions. Families receiving family-centered care are more satisfied with care to which they have easier access and about which they have better communication.

Family-centered care has evolved over the past 30 years to become integral to all pediatric health care whether in the hospital, the outpatient department, the emergency department, or the primary care medical home. It is grounded in the understanding that the family, however it may be configured, is the constant in the child's life and crucial to health, development, and general well-being. In the provision of all aspects of primary care (preventive, acute, and chronic), the medical home team must regard the family as a full partner in the health care of each child with a shared stake in both decision making and outcomes. Chapter 9, *Partnering With Families in Hospital and Community Settings*, addresses family-centered care in more depth.

### **Team-Based Care: Collaboration Within the Medical Home**

In the late 20th century, the pediatric primary care office consisted of individual physician providers of care supported by a variety of staff members, depending on the size of the practice. The staff might have included a receptionist at the front desk, a nurse or medical assistant to escort patients to examination rooms and assist the physician with procedures, and someone to handle billing and financial matters. Larger practices might have more physicians, an office manager, a medical records manager, and additional front desk staff and nurses. However, to a large

extent, everyone's role was to support individual office encounters between patients and their families and the primary care physician. Surveys of families described high levels of satisfaction with their primary care physicians. However, as the health care system and the health care needs of children and youth have become more complex, the traditional model of care proved to be less efficient, effective, and accessible, and even less safe than it needed to be.

In the past 20 years, new members of the typical pediatric office staff have materialized, including nonphysician providers such as advanced practice registered nurses (nurse practitioners), child health associates, and physician assistants and medical assistants to handle patient flow in the office. Some primary care practices have added the role of a care coordinator who may work with families, particularly those with children with special health care needs, to ensure timely planning, access, and follow-through with needed services. More importantly, the delivery of care in a primary care medical home has required that office staff members collaborate in more defined ways as care delivery teams. The growth of team-based care has paralleled the adoption and spread of the medical home model as a means of ensuring comprehensive, coordinated, easily accessible care. In the medical home, the pediatrician leads a team that is concerned not only about caring for individual patients, but also about promoting the overall health of the population it serves. The members of such a team have specific roles to play that are clearly articulated and understood by everyone and that ensure that each team member functions at the top of their training, expertise, and licensure. The expectation for expanded access to the primary care medical home with evening, weekend, and holiday office hours, as well as interactive Web sites and patient portals, requires that teams can cross-cover for one another and still retain knowledge of a panel of patients. As more of the pediatric workforce serves in part-time positions, team-based care in the medical home provides necessary continuity while also providing enhanced access to care. Such expanded access with continuity of care has demonstrated cost savings in emergency department utilization and admissions.

A large pediatric primary care medical home may include several teams delivering care to a specific panel of patients. This team might include a lead pediatrician, 2 or 3 nonphysician providers, several medical assistants, and a care coordinator. This primary care team would meet each morning in a brief "huddle" to examine the list of patients scheduled for the day, determine if there are any special or unanticipated needs, and identify who may need help with care coordination or, among patients of the nonphysician providers, who will require physician consultation. Such meetings have been shown to improve patient flow, reduce waiting times, and reduce the risk of overlooking a problem. In the course of a busy day, the care coordinator will make contact with specialty clinics, hospitals, schools, and community agencies on behalf of patients with special or complex needs, freeing the direct care providers (physician and nonphysician) to see patients with fewer interruptions.



The medical home team not only needs to perform as a collaborative team, but also shares a responsibility for the quality and cost of the care it delivers. In a medical home, teams may create and receive reports about the clinical outcomes they are achieving, about the satisfaction of the patients and families they serve, and about costs of care incurred by those patients and families. Armed with such data, the medical home team also functions as a quality improvement team as it reflects upon its performance and then discusses, tests, and evaluates ways to improve the care that is delivered. Wherever possible, this process of continuous improvement solicits the input and suggestions of patients and families as consumers of medical home services. Further discussion of quality improvement in the medical home can be found in Chapter 7, Planned Coordinated Care to Support the Medical Home.

### **Comanagement of Chronic Conditions: Collaboration With Specialists**

Pediatric specialists provide critical, often lifesaving evaluation and care for children and youth with chronic conditions and can be an important source of decision-making support for primary care pediatricians and other professionals. Patients with suspicious symptoms or screening results are referred to specialists for diagnostic confirmation, and those found to have chronic conditions may require ongoing management from specialists. The presence of a chronic health condition requiring specialty care poses the risk of care being fragmented into the chronic condition management provided by specialists and the routine preventive and minor acute illness management provided by the primary care pediatrician. With the advent of the medical home model, the role of the primary care team in the management and coordination of care of chronic conditions has become better defined and valued. An ample body of evidence supports better outcomes for children with chronic conditions who receive care in a medical home. Clear communication between the primary care pediatrician and specialist is essential to ensure that they both understand what roles they will be playing in caring for the patient.

On the other hand, beyond a few conditions like asthma and attention-deficit/hyperactivity disorder (ADHD), many chronic conditions affecting children are uncommon, and a growing number of children have combinations of conditions that complicate their care. Specialists in the diagnosis and management of these conditions may believe that only they are equipped with the knowledge, experience, and technological resources needed to produce the best results. Some specialists may regard primary care physicians as too uncomfortable, too ill-informed, or even too disinterested to participate in the management of rare or complex conditions. However, the primary care medical home is the only entity in the health care system that is positioned to both communicate and coordinate within the system (eg, with specialists) and with community-based organizations that may be important for a child with a complex, chronic condition. The key is a process of explicit,

coordinated comanagement in which the role of the specialist and that of the primary care medical home team are clearly defined and reliably communicated in a bidirectional manner. Such planned comanagement ensures that the specialist makes critical care decisions while the primary care medical home has clear information about the treatment plan, a role in monitoring the patient's status, and the ability to triage new symptoms or problems. Some chronic conditions may stabilize enough to allow for an expanded primary care role in management with a reduction in specialty care involvement over time, and other conditions may fluctuate between periods of routine management and periods of high specialty-care needs.

Effective collaboration between the primary care medical home and specialists involves planning and communication. The electronic medical record—particularly with electronically interoperable interfaces with specialists, imaging, and laboratories—helps facilitate the necessary explicit, bidirectional communication for comanagement of children with chronic or complex conditions. The collaborative care roles of subspecialists and primary care pediatricians must be planned, explicitly defined, and understood by all involved. That planning manifests itself in a written care plan. Ideally, the care plan becomes the instrument of communication as it is shared among the specialists, the primary care medical home, and the patient or family. These 3 could be regarded as the core collaborative care team, because each of them must understand and accept his or her role in the comanagement process. To do so, each must work from the same proposed care plan. This is often best addressed by using a patient portal that is available to primary care pediatricians, subspecialists, and patients' families alike.

In some situations, particularly within large integrated systems of care, the relationship between certain specialists or specialty groups and primary care pediatricians for relatively common conditions and/or situations may have clearly articulated parameters and expectations that apply to all shared patients and clinical situations. Such comanagement or service agreements spell out the expected actions of the primary care team alongside the expected availability and actions of specialists. For example, for children with seizures, the neurologists may agree to see new patients for evaluation in a timely manner and communicate their findings and plans rapidly, and the primary care team may agree to provide some of the seizure follow-up, obtain anticonvulsant blood levels, and share the findings with the neurologist. By sharing some of the follow-up management with the primary care team, the neurologist will have better access for new patients on her schedule.

In some situations, the specialists may have a team that is very capable of providing comprehensive care to patients with chronic illnesses, thereby functioning as a medical home for those patients. This can be an appropriate alternative model to the primary care medical home as long as there is clear communication about the roles of the specialist teams and the primary care medical home so that there is no confusion regarding who provides the various aspects of care.

### Community Outreach: Collaboration With Community-Based Organizations

Children and their families are high utilizers of community-based services. Child care, preschool services, early intervention programs for infants and toddlers, public and private schools, and community mental health services provide supports to children and families. In many instances, particularly in settings like child care and school where children spend many hours each day, important health issues arise frequently and collaboration is important. Children with chronic conditions like asthma, diabetes, and ADHD may require the administration of medication at school, and school health officials will need up-to-date information about overall management. Children affected by rare conditions may manifest symptoms at school that need accurate assessment, and children with some complex health care needs may receive enteral feedings or require respiratory care while at school. Early intervention programs conduct ongoing assessments of developmental progress in children with developmental delays that should be integrated with medical information in those children's health records. The work culture in a busy primary care office practice is different than that of an elementary school, often making direct communication difficult. However, a care coordinator serving as a member of the primary care medical home team may communicate regularly with counterparts in various community-based organizations, creating a better flow of information and establishing a more personal relationship between the medical home and the community agencies.

Because the medical home can be regarded as providing an interface between personal, individual health and public health in the community, the medical home team will also need to collaborate with public health agencies and officials. From the reporting of communicable diseases to immunization registries to the follow-up of newborn screening tests, the effective and timely exchange of information can be critical. State Title V programs are responsible for ensuring access to appropriate care and treatment for all children with special health care needs and often have information and personnel to assist the primary care medical home in serving this population. An active, collaborative relationship with Title V agencies can help connect patients and families with resources that they need.

### COLLABORATIVE CARE AND THE CULTURE OF THE MEDICAL HOME

The medical home model has helped operationalize new primary care functions or improve existing ones such as family-centered care, care coordination, access, and population-based care. However, the medical home transformation of primary care has also brought new cultural values that underlie all of the structures and processes of care. Chief among those new values is the commitment to quality and to continuous improvement, but a collaborative approach to care ranks as another important value. Intrinsic to collaboration is a respect for

others involved in the common endeavor of good health, including the patient, the family, colleagues in the medical home, specialists, and local community service professionals.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Building Your Care Notebook* (Web page), American Academy of Pediatrics ([medicalhomeinfo.aap.org/tools-resources/Pages/For-Families.aspx](http://medicalhomeinfo.aap.org/tools-resources/Pages/For-Families.aspx))
- *Emergency Information Form for Children with Special Needs* (template), American Academy of Pediatrics ([www.aap.org/advocacy/blankform.pdf](http://www.aap.org/advocacy/blankform.pdf))
- *Hospital Stay Tracking Forms* (file archive), National Center for Medical Home Implementation ([medicalhomeinfo.aap.org/tools-resources/Documents/Hospital%20Stay%20Tracking%20Forms.zip](http://medicalhomeinfo.aap.org/tools-resources/Documents/Hospital%20Stay%20Tracking%20Forms.zip))
- *Medical Summary Part I* (handout), American Academy of Pediatrics ([medicalhomes.aap.org/Documents/PediatricCarePlan.pdf](http://medicalhomes.aap.org/Documents/PediatricCarePlan.pdf))
- *Pediatric Specialists* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/default.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/default.aspx))
- *Positioning the Family and Patient at the Center: A Guide to Family and Patient Partnerships in the Medical Home* (monograph), National Center for Medical Home Implementation ([medicalhomeinfo.aap.org/tools-resources/Documents/Positioning\\_FINAL\\_May24.pdf](http://medicalhomeinfo.aap.org/tools-resources/Documents/Positioning_FINAL_May24.pdf))

#### Practice Management and Care Coordination

- *APEX Digital Navigator* (practice transformation tool), American Academy of Pediatrics ([www.aap.org/en-us/professional-resources/practice-support/APEX/Pages/Digital-Navigator.aspx](http://www.aap.org/en-us/professional-resources/practice-support/APEX/Pages/Digital-Navigator.aspx))
- *Family-Centered Care Self-Assessment Tool* (self-assessment), Family Voices ([www.familyvoices.org/admin/work\\_family\\_centered/files/fcca\\_FamilyTool.pdf](http://www.familyvoices.org/admin/work_family_centered/files/fcca_FamilyTool.pdf))
- *Measuring Medical Homes: Tools to Evaluate the Pediatric Patient- and Family-Centered Medical Home* (monograph), National Center for Medical Home Implementation ([medicalhomeinfo.aap.org/tools-resources/Documents/Monograph\\_FINAL\\_Sept2010.pdf](http://medicalhomeinfo.aap.org/tools-resources/Documents/Monograph_FINAL_Sept2010.pdf))

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- American Academy of Pediatrics Medical Home Initiative for Children With Special Needs Project Advisory Committee. The medical home. *Pediatrics*. 2002; 113(5):1545–1547. Reaffirmed May 2008 ([pediatrics.aappublications.org/content/110/1/184](http://pediatrics.aappublications.org/content/110/1/184))

American Academy of Pediatrics Council on Children With Disabilities and Medical Home Implementation Project Advisory Committee. Patient- and family-centered care coordination: a framework for integrating care for children and youth across multiple systems. *Pediatrics*. 2014;133(5):e1451–e1460 ([pediatrics.aappublications.org/content/133/5/e1451](http://pediatrics.aappublications.org/content/133/5/e1451))

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## Chapter 7

# PLANNED COORDINATED CARE TO SUPPORT THE MEDICAL HOME

Jeanne W. McAllister, BSN, MS, MHA; W. Carl Cooley, MD

### BACKGROUND

A family-centered pediatric medical home provides proactive, planned, coordinated care. This is very much like the patient-centered medical home, but with a greater emphasis on the whole family. Primary care practices that achieve this standard are able to make 4 key claims: first, they can demonstrate how they enter into partnerships with families and work together to help families meet the needs of their children; second, the practice has chosen a model of family-centered, team-based care coordination; third, this model is expressly shared with families and delivered through a partnership that is jointly and continuously evaluated for improvement; and finally, the physicians and their teams find this partnership professionally gratifying.

Chapter 9, Partnering With Families in Hospital and Community Settings and Chapter 10, Family-centered Care of Hospitalized Children address collaboration across the continuum of health and community care. The purpose of this chapter is to define and describe care coordination in the medical home—its characteristics, processes, tools, and core functions. Care coordination is needed because fragmentation continues to plague our health care delivery systems. The medical home, family partnerships, and coordinated care are true counterparts; one cannot exist without the others. Highly functioning health care teams provide reliable and flexible options for full access to the medical home. Care in this environment uses proactive, planned, coordinated approaches, and does so with the help of family-centered, team-based care.

### TEAM-BASED CARE COORDINATION

Bodenheimer defines a team as “a group with a specific task or tasks, the accomplishment of which requires the interdependent and collaborative efforts of its members.” Effective teamwork is also described in terms of relational coordination, which requires shared goals, shared knowledge, problem solving, and frequent and timely communication, salted with mutual respect—blending the management of people and of their care tasks.

### THE COORDINATION OF CARE

A key care process in the medical home is the provision of care coordination; often all or most team members provide some coordination functions. Care coordination is defined as a patient- and family-centered, assessment-driven, continuous, team-based activity designed to meet the bio-psychosocial needs of children and youth while enhancing personal and family caregiving skills and capabilities. Care coordination in the medical home provides for communication linkages with people within other health and community agencies. To be effective, care coordination functions should be centralized and implemented in a partnership with the patient and his or her family. A key result of team-based care coordination is a family supported in their own primary caregiving and coordinating role, and children and youth who are appropriately prepared to gain responsibility and confidence caring for themselves. Reliable, explicit, and systematic processes are needed to ensure timely, optimal, and consensual exchange of relevant information.

### INTEGRATION OF CARE

Practice-based care coordination also emphasizes communication with nonmedical professionals at schools and within community agencies in order to advocate for children and families and establish shared care or service goals. There is a strong need for care continuity and for the integration of primary care efforts with other services and supports that children and families use. This is particularly true when circumstances include pediatric conditions requiring the input of multiple specialized physicians and therapists. The pediatric primary care medical home is ideally suited to centralize care and integrate the input of other physicians and professionals across the care and community continua (eg, home/school, clinic, hospital). Coordinating care and facilitating communication in this way is often referred to as “the warm handshake” of the medical home. Box 7-1 provides an example.

Care coordination in a highly functioning pediatric medical home meets the following criteria:

1. Patient and family centered
2. Community based
3. Proactive with planned, comprehensive care
4. Promotes the development of self-management skills among children, youth, and their families
5. Facilitates cross-organizational linkages, relationships, and multidirectional communication (including medical specialists and consultants and nonmedical providers such as schools and community agencies).



**BOX 7-1 Case Example**

Whitney is a 15-year-old who on her best days dreams of getting her driver's license. She has longstanding uncontrolled type 1 diabetes. Compounding social factors contribute to her school absences and even to truancy charges. In the 6 months prior to her switch to a new medical home with care coordination, Whitney had 9 emergency room visits and 7 hospitalizations resulting from ketoacidosis.

**CARE COORDINATION OVERALL AIMS**

- Effective management of type 1 diabetes
- Improved communication, collaboration, and coordination among teen, family, physicians, and school team

**SHARED PLAN OF CARE GOALS**

- Transition to insulin pump (pending her diabetes control)
- Obtain driver's license
- Improve school performance

**SHARED PLAN OF CARE—NEGOTIATED ACTIONS (PERIOD OF 10 MONTHS)**

- Enroll in a quality medical home
- Engage with care coordinator
- Support teen and family
- Hold/attend care conferences
- Update and detail the goal-related strategies within the shared plan of care
- Align partners
- Develop an emergency plan
- Increase contact, communication, and collaboration with medical home and school
- Overcome (persistent) communication and transportation barriers to counseling
- Work with diabetes educator 2 times per month
- Work with dietitian 2 times per month

**RESULTS**

- Access to a high-quality medical home with care coordination
- Use of the strategies and approaches within the shared plan of care
- Multiple collaborative contacts with medical home "neighborhood" or collaborating partners
- Counseling in place

**UTILIZATION**

Ten months after onset of care coordination with a plan of care, Whitney had 2 emergency department visits, no hospitalizations, improved A1C test results, and improved school attendance. Her insulin pump is pending.

family benefits from linkages to needed services and resources. Children and families with temporary or long-standing psychosocial concerns may also need help with the coordination of relevant care and services. Care coordination may be a short, time-limited process or part of a long-term continuous care relationship, or somewhere in between. An outcome of care coordination is an increasingly empowered family that knows where to look for assistance when needed. This means a primary care medical home must offer a clear message about all available care coordination supports.

The medical home team (with senior leadership, if appropriate), should decide whether care coordination will be available for every patient in the practice or delivered in some defined manner based on need. The team may target a specific patient population for available care coordination services. For example, they may decide that services will be directed towards a population of children/youth with special health care needs (CYSHCN). Such children have, or are at increased risk for, chronic physical, developmental, behavioral, or emotional conditions that require health and related services of a type or an amount beyond that required by children generally. The team may determine levels of care coordination service based upon care complexity. Care complexity will vary with changes in a child's condition and over time. The Child and Adolescent Health Measurement Initiative offers a screening tool readily available to every medical home at no cost to help with the identification of the population of CYSHCN in each practice. Care coordination has been shown to meet child and family needs and to have a positive effect upon health and cost outcomes.

Care coordination is meant by design to foster a strong relationship between families and the medical home and to link families to needed services and resources. Beginning with an identified population, the team can either reach out to targeted families or identify patients and families prospectively at the time of an office visit. These patients are typically enrolled in a registry (spreadsheet, database, or electronic tool) that stores health information in a way that supports proactive, planned, and coordinated care. A registry should include critical items for tracking and monitoring patients along with items necessary to help demonstrate best available known pediatric practice (eg, annual flu vaccine reminders) for purposes of program evaluation. Once a population is identified and enrolled in a registry it may be useful to stratify this grouping by applying a complexity score or sorting by level of concern. (To learn more, go to [www.medicalhomeinfo.org](http://www.medicalhomeinfo.org) to access the Building Your Medical Home Toolkit.) Organizing patients by levels helps the team to prioritize patient and family needs and apply limited care coordination resources in the most efficient and effective manner.

**PROVISION OF CARE COORDINATION: STRUCTURES AND PROCESSES**

When asked what they need to help them care for their children, families often request a team approach to care along with help coordinating efforts across

**WHO NEEDS CARE COORDINATION?**

A variety of patient and family needs and circumstances warrant strong care coordination. Examples include a child who has recently been diagnosed with a chronic condition, a family navigating the multiple agencies involved in the care of their child, a child who requires multiple interventions or hospitalizations that may interfere with his or her school attendance or daily activities, and a child in foster or kinship care. Each child and



multiple services and settings. Families need to know that they have professional partners who will back them and a team that facilitates cross-organizational communication and collaboration. Care tools, such as portable care plans, help to pull these multiple pieces together into a coherent description of goals, assets, and needs with action steps to address them. Trusting relationships are therefore cultivated between and among children, families, and the medical home team.

Historically, the family experience of care has been one of fragmentation—the opposite of coordination. When care is disjointed, families encounter a confusing matrix of people, services, and systems instead of the synergy of supports that they need. Effective care coordination integrates these people, services, and systems, thereby increasing the value of care. Care coordination demonstrates this integration through timely, clear communication with patients and families, team members in the medical home, other health care providers across other settings, and community-based organizations.

A set of care coordination services should be defined and made available to families; such services or functions are outlined in the report *Making Care Coordination a Critical Component of the Pediatric Health System: A Multidisciplinary Framework*, published by the Commonwealth Fund. Families need to know that these care coordination supports are available and how to access them. Awareness of practice-based care coordination can be achieved with descriptive brochures, posters, flyers, and information on the practice's Web site.

## A CARE COORDINATION MODEL

Essential, continuous cycles of coordination include the use of assessments, care planning with mutual goal setting, care plan implementation, and monitoring with evaluation. (See Figure 7-1.)

- 1. Assessment:** Identification of child and family needs is the first step in the care coordination process. Accordingly, medical home team members collect and review medical, educational, and other information and concerns. They also obtain information about family strengths, goals, needs, and available resources. This assessment might be broad or narrow, depending upon the family circumstances, and it should be repeated at predetermined intervals. Many primary care practices use a social worker, nurse, or family advocate to support these activities. (See Figure 7-2.)
- 2. Care Planning/Goal Setting:** Child, youth, and family assessment results inform the creation of a comprehensive shared plan of care. Family and medical home team goals should guide this plan. While every child benefits from a plan of care, comprehensive care planning is critical for children with more complex needs or circumstances. Comprehensive care planning involves using intake information and assessment results to create a medical summary, an emergency plan (if needed), and an action plan. The medical summary includes relevant history, diagnostic concerns, medications and treatments, allergies, information about subspecialists and other key physicians involved, and



**Figure 7-1** Shared plan of care: implementation with families.

any information the family wants each professional to understand about their child. The emergency plan supplements this with clear actions to take in response to an adverse event. Engaged patients and families, together with the physician and team, set goals for the management of care, self-care, and resource utilization. An action plan is developed with specific goals, objectives, and interventions to address specific concerns. The action plan component of comprehensive care planning clearly identifies who will be responsible for each action, documents when each process occurs, and provides for continuous updating. (See Figure 7-3.)

- 3. Implementation/Use:** When the action plan is put in motion, all team members know each other's roles and actions. The family and the team have access to an electronic copy or (as necessary) a paper copy of their plan. The medical home team initiates and facilitates specific activities and interventions that lead to accomplishing the set goals. For example, they may convene a community team to establish a common intervention strategy, or a team member may reach out to a pediatric subspecialist to learn more about a condition in order to support comanagement efforts at the community practice level. Patients may participate in care skills building, and families may use relationships or links provided to connect to community resources and supports. Each action item in the plan includes goal-oriented time targets. Care and action plans serve as guides or scripts for the team's coordinating efforts, interactions, and monitoring. Planned follow-up visits provide the opportunity for measuring progress and keeping the plan current.
- 4. Monitoring:** The medical home team gathers information about the activities, interventions, and services outlined in the action plan. Was the specialist referral appointment made and kept? What are the results? What subsequent tests were completed? What about other recommendations and needed resources? The team and family determine the effectiveness of care and services in reaching desired goals and outcomes, and what further steps are

Patient Name \_\_\_\_\_ Date \_\_\_\_\_

- 1) What would you like us to know about your child?  
What does he/she do well? Like? Dislike? What matters to them?
- 2) What would you like us to know about you/your family? What matters to your family?  
\_\_\_\_\_
- 3) Do you have any concerns or worries for your child? (Some examples below)
 

<input type="checkbox"/> Their growth/development	<input type="checkbox"/> Doing things for themselves
<input type="checkbox"/> Learning	<input type="checkbox"/> Falling behind in school
<input type="checkbox"/> Sleeping	<input type="checkbox"/> Behavior
<input type="checkbox"/> Self-care	<input type="checkbox"/> The future
<input type="checkbox"/> Making and keeping friends	<input type="checkbox"/> Playing with friends
<input type="checkbox"/> Other (fill in): _____	
- 4) Have there been any changes since we saw you last, such as a:
 

<input type="checkbox"/> Brother or sister leaving home?	<input type="checkbox"/> New job or job change?
<input type="checkbox"/> Move to a new town?	<input type="checkbox"/> Separation or divorce?
<input type="checkbox"/> Sickness or death of a loved one?	<input type="checkbox"/> Other (fill in below)?

  
\_\_\_\_\_
- 5) Can we help you with any of the following needs?
  - ☐ **Medical** (For example, help finding or understanding medical information; help finding health care for yourself or your family)?
  - ☐ **Social** (For example, having someone to talk to when you need to; getting support at home; finding supports for the rest of your family)?
  - ☐ **Educational** (For example, explaining your child's needs to teachers; help reading or understanding medical information)?
  - ☐ **Financial** (For example, understanding insurance or finding help paying for needs that insurance does not cover-such as medications, formulas, or equipment)?
  - ☐ **Legal** (For example, discussing laws and legal rights about your child's health care or their school needs )?
  - ☐ **General.** Please let us know what else you need help with (if we don't know, we will work with you to find the answer)?

Notes: \_\_\_\_\_

**Figure 7-2** Pediatric care coordination assessment tool.

needed. Periodic check-in opportunities help the family-centered team maintain positive momentum. Assessments are refreshed, and changes are made to the plan with new needs and ideas incorporated. The action plan is the dynamic portion of comprehensive care planning and serves to provide proactive, preventive, and planned population care.

### ACHIEVING THE FUNCTIONS OF CARE COORDINATION IN THE MEDICAL HOME

Many pediatricians have questioned how they can possibly provide all that comprehensive care coordination is meant to be within their medical home. Care coordination is a time- and resource-intensive service.

A key strategy used by practices to help them coordinate care involves creating a designated practice role filled by someone who acts as a care coordinator. This staff person shares responsibility for coordination of care with the rest of the medical home team and family. The time required to redesign a system of reactive coordination of care into a more planned, proactive approach is time well spent. For example, a physician might see 2 or 3 more urgent patients during time realized through the use of a team member who is designated to perform cross-organizational communication and patient education. Many practices have redirected registered nurses from triage roles to provide population care, registry management, proactive patient and family assessments, education, and

Child's name:	DOB:	Parents/Guardians:
Primary diagnosis:	Secondary diagnosis:	Secondary diagnosis(s):
Original date of plan:	Last Updated:     /     /     /     /     /	

<b>1) Patient/Family Goal(s)</b>	(1)		
<b>2) Clinical Goals</b>	(2)		
<b>Main Concerns/Priorities</b>	<b>Current Plans/Actions</b>	<b>Person(s) Responsible</b>	<b>Progress Date or Date Complete?</b>

Parent/Caregiver Signature:	Clinician Signature:	Care Coordinator:
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**Figure 7-3** Share plan of care: negotiated actions.

outreach. Others have used a social worker, family member, or other layperson familiar with community resources to help link families with needed supports and services.

Some practices are too small to afford a dedicated care coordinator position. In those settings, someone with at least partial responsibility can ensure that the practice is managing care coordination functions effectively. They might achieve this by distributing care coordination functions across various staff or by better utilizing any outside care coordination resources. In such situations it is important to articulate the intent to enhance the coordination of care and put a plan in motion to achieve team-based coordination. Links to resources to aid practices in this development, such as care coordination models, role descriptions, and related competencies, can be found in Tools for Practice at the end of this chapter.

A designated care coordinator fosters the delivery of family-centered services through a continuous cycle of assessment, goal setting, care planning, and follow-up. Someone in this role can help the team know families better, facilitate access to the team by being the point person in between visits, become an expert in community resources and government program eligibility, encourage family-to-family connections and supports, and build the team's capacity and ability to achieve its goals. A professional in this unique role must possess an array of key competencies and attributes. Smart hiring is important, as it takes a special person, passionate about the success of children and families, to provide excellent coordination of care. Fortunately, we now have new knowledge and tested tools to support these needs and

indeed the development of care coordination as a standard of care.

### DEMONSTRATING THE BENEFITS OF CARE COORDINATION

Measurement of ongoing progress can be achieved with activities like tracking the number of action plans in place or monitoring how care plan goals are addressed and met. Gaining direct family feedback about experiences and benefits is invaluable. Outcome measures can assess families' satisfaction with their use of care coordination. Many practices engage families as partners in their medical home improvement efforts. These families can guide and evaluate the developing role of the care coordinator. Families can also assist by speaking to the critical role care coordination holds in supporting them to raise, care for, and achieve optimal health for their children and youth.

A medical home team approach with fully developed care coordination services will also improve health and cost outcomes for children, youth, and families, and will increase the satisfaction of those receiving care. A number of studies have shown significant benefits related to implementation of care coordination models. These benefits include

- Achieved patient/family goals
- Reduced unmet needs
- Increased parent/caregiver social connectivity
- Improved patient/family satisfaction
- Improved communication among all stakeholders

Examples of cost outcomes include reduced hospital admissions, length of hospital stay, inpatient charges, and emergency department visits.

Creating patient-friendly experiences in the medical home also helps to create a favorable work environment that can lead to increased physician and staff satisfaction. Early adopters have addressed achieving care coordination with grants, collaborations, participation in demonstrations, data collection, and negotiation with health plans. While costly, developed care coordination activities align practices for health care reform activities and opportunities.

## SUMMARY

Highly functioning pediatric medical homes, providing family-centered care and including flexible access, population approaches, and comprehensive team-based coordination, are emerging as a new standard of pediatric quality. A model of care coordination needs to be explicitly identified and shared—what, how, and for whom. Coordination tools such as assessments and goal-oriented care plans provide mechanisms for measurement and demonstration of quality. This is the future of pediatrics: the medical home, family partnerships, and well-coordinated team-based care.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Building Your Care Notebook* (Web page), American Academy of Pediatrics ([www.medicalhomeinfo.org/for\\_families/care\\_notebook](http://www.medicalhomeinfo.org/for_families/care_notebook))
- *Emergency Information Form for Children With Special Needs* (template), American Academy of Pediatrics ([www.aap.org/advocacy/blankform.pdf](http://www.aap.org/advocacy/blankform.pdf))
- *Hospital Stay Tracking Forms* (file archive), National Center for Medical Home Implementation ([medicalhomeinfo.aap.org/tools-resources/Documents/Hospital%20Stay%20Tracking%20Forms.zip](http://medicalhomeinfo.aap.org/tools-resources/Documents/Hospital%20Stay%20Tracking%20Forms.zip))
- *Partnering in Self-Management Support: A Toolkit for Clinicians* (Web page), National Center for Medical Home Implementation ([www.medicalhomeinfo.org/how/care\\_partnership\\_support.aspx#self](http://www.medicalhomeinfo.org/how/care_partnership_support.aspx#self))
- *Pediatric Care Plan* (template), National Center for Medical Home Implementation ([medicalhomes.aap.org/Documents/PediatricCarePlan.pdf](http://medicalhomes.aap.org/Documents/PediatricCarePlan.pdf))
- *Pediatric Specialists* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/default.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/default.aspx))

### Practice Management and Care Coordination

- *APEX Digital Navigator* (practice transformation tool), American Academy of Pediatrics ([www.aap.org/apex](http://www.aap.org/apex))
- *Improving Systems of Care for Children With Special Health Care Needs* (Web page), Lucile Packard Foundation for Children's Health ([www.lpfch.org/programs/cshcn](http://www.lpfch.org/programs/cshcn))
- *Measuring Medical Homes: Tools to Evaluate the Pediatric Patient- and Family-Centered Medical Home* (monograph), National Center for Medical Home Implementation ([medicalhomeinfo.aap.org/tools-resources/Documents/Monograph\\_FINAL\\_Sept2010.pdf](http://medicalhomeinfo.aap.org/tools-resources/Documents/Monograph_FINAL_Sept2010.pdf))

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## Chapter 8 HEALTH LITERACY

Laura Shone, DrPH, MSW

## INTRODUCTION

### Definition of Health Literacy

Health literacy is defined by Nielsen-Bohlman and colleagues and Berkman, respectively, as the set of skills that “allow an individual to *obtain, process, understand, and communicate information about health; function in*



the health system, and make informed decisions during different phases of life.” Health literacy is distinct from—yet often confused with—general (reading) literacy; this distinction hinges on context. General literacy describes the ability to “use printed and written information to function in society, to achieve one’s goals, and develop one’s knowledge and potential.” In contrast, health literacy addresses these skills specifically in the context of navigating the health care and health insurance systems; using and understanding health information; managing health conditions, treatment and medicine use; and making health decisions—both individually and on behalf of others.

Health literacy problems interfere with an individual’s ability to access and pay for medical care, understand health care advice, weigh the risks and benefits of health decisions, follow recommendations for treatment, use medicines safely and correctly, and understand rights and responsibilities in health care. People with limited health literacy face great difficulty in managing basic demands of the health system. However, health literacy is increasingly understood as a shared challenge and opportunity to balance the needs and skills of individuals with the complex demands of modern health care. However, health literacy problems extend beyond the health system itself. “People confront a complex and potentially overwhelming set of health messages every day,” through health experiences and interactions, friends and family, the news and advertising media, and the virtual world of email and Web-based information from sources that range from reliable

to dangerous. To manage disease, promote health, and prevent harm, patients need to make sense of the health information they hear, read, see, and experience in all of these contexts. An example of an encounter in which the health literacy level of the parent affects the health of a child is in Box 8-1.

### Levels of Health Literacy

The 2003 National Assessment of Adult Literacy categorized 4 levels of health literacy: below basic, basic, adequate, and proficient (Figure 8-1). At the below basic level (14% of the US English-speaking population), individuals cannot use a bus or television schedule, understand an appointment slip, or complete medical paperwork—meaning that they have great difficulty just making or getting to a medical appointment. Although most US adults have basic (24%) or adequate (50%) health literacy, the demands of the US health care system more often require proficient skills. Everyday health behavior and decisions, use of the health system, and response to public health warnings increasingly require proficiency, yet only 12% of US English-speaking adults function at this level, with the skills necessary to understand and use medicolegal documents such as a consent form, medical release, or health care proxy.

Susan’s case exemplifies one of many ways in which health literacy can affect pediatric care. Nationally, 30% of English-speaking parents have health literacy problems, yet this overall estimate can under-represent the scope and magnitude of specific challenges in pediatric care. When faced with scenarios in a national

### BOX 8-1 A Case Study in Health Literacy

Susan’s daughter had been ill for several days when she took her to the pediatrician. The doctor examined her daughter and diagnosed mild otitis media. He explained that this was probably caused by a virus, for which antibiotics are ineffective. Because parents are so used to receiving antibiotics for otitis, he was especially careful to explain why antibiotics were not necessary, assuring Susan that the baby would gradually get better over the next several days without them. He prescribed ear drops, and also recommended an over-the-counter analgesic to reduce fever and relieve pain. Finally, he reminded Susan to push fluids, reassured her that her daughter would be fine, and sent her to the drugstore. Several days later, the doctor received a call from the emergency department: Susan was there with her daughter, who was febrile, hyponatremic, and in obvious pain.

**What happened?** During the visit, the pediatrician recommended 2 liquid medicines, both to be administered as drops. At the drugstore, Susan filled the prescription and purchased acetaminophen liquid. Over the next several days, she gave the 2 medicines exactly on schedule; 1 by mouth and 1 in the baby’s ears. She also forced her daughter to drink as much as she possibly could.

**What went wrong?** When Susan got home with the 2 medications, she knew that one was meant to be swallowed and one was meant to go in the baby’s ears. With both medications in the same bag, she wasn’t sure which was which, so she thought back to what the doctor had said. She knew that her daughter had an ear infection, and remembered that the doctor spent a lot of time talking about antibiotics. That made sense, because that’s what you get for ear infections—antibiotics. She also knew that one medication was a prescription and the other was a “regular” medicine, that anybody could buy, to help with the pain in her daughter’s ears. Well, that made it easier, she thought: the one for pain goes in the baby’s ears, because that’s where the pain is; and the prescription must go into her mouth because that’s how you take antibiotics—you swallow them. Over the next few days, 3 things combined to send Susan and her daughter to the emergency department: she gave the ear drops by mouth and placed acetaminophen drops in her daughter’s ears. In addition, because the doctor said to “push fluids,” she wound up overhydrating her daughter to the point of hyponatremia.

**What can be done?** This case involves health literacy—but it is not just about Susan, it is about the health system as a whole and Susan’s experiences within it, and it is about unfamiliar situations, multiple interactions, and the many places within the process where communication and understanding can break down.

### National Assessment of Adult Literacy

#### Proficient (≈14%):

- Can** Calculate annual health costs from price table
- Can** Search document to define medical term (use context)
- Can** Use legal health documents (consent, release, proxy)

#### Intermediate (≈50%):

- Can identify drug interactions from OTC medicine label**
- Can** choose correct age for vaccine from immunization chart

#### Basic (22%):

- Can** understand *chronologic*: Mammogram every year after age 40
- Cannot** understand *conditional*: OR if you have a lump or feel pain

#### Below Basic (14%):

- Cannot** Use schedules (bus, TV)
- Cannot** Understand medical appointment slip
- Cannot** Fill out medical or insurance forms

**Figure 8-1** The 4 levels of health literacy from the National Assessment of Adult Literacy.

study, nearly 70% of parents could not correctly record basic information such as names or dates of birth on a health insurance form; 66% were unable to calculate the annual cost of a health insurance policy based on family size; and 46% were unable to perform 1 or more medication-related tasks.

It is impossible to gauge a parent's health literacy. Health literacy problems affect millions of people of all ages, races, income levels, and education levels, yet these problems are often hidden because adults with limited health literacy may feel ashamed of or conceal their struggles to read or understand material. These limitations have direct consequences for children, whose health care these parents are responsible for, as well as for the pediatricians who provide their medical care.

## MEASUREMENT AND MANAGEMENT OF HEALTH LITERACY

Measurement science has been at the root of health literacy research: first, to describe the nature and prevalence of the problem, and then to monitor trends in prevalence and disparities over time and across subgroups. However, measurement of health literacy during routine clinical practice is seldom recommended. Instead, accumulated evidence provides strong rationale for the use of universal precautions for clear communication. Universal precautions will be discussed further throughout the chapter. However, because an understanding of measurement in the context of health literacy offers both context and rationale for the tools and strategies available to physicians, this section will provide an overview of measurement, including historically dominant tools, evolution of approaches to measurement, and emerging tools.

One way to better understand this otherwise invisible problem is to measure health literacy. The most common health literacy measurement tools have been developed and validated for adults, whereas few tools exist to measure health literacy in children. Most common measures assess 1 or more of the following: word pronunciation, reading comprehension (prose literacy), ability to understand numbers and perform basic arithmetic calculations (numeracy), and ability to derive meaning from context (document literacy). Newer tools have expanded to assess the performance of basic health tasks among parents, adolescents, and young adults. Examples of commonly used tools include:

- The Rapid Estimate of Adult Literacy in Medicine (REALM) and REALM-Teen: Both are 66-item word pronunciation tests, without context. Both take 2 to 3 minutes to administer 3 lists of words, and are scored by the number of words the participant is able to pronounce correctly. The cutoff scores are high because the test is meant to give all participants a positive experience: there are many easy words and a smaller number of words that are difficult. By design, most respondents can get more than half correct even if literacy is very limited (REALM scoring accounts for this). Because it is a word pronunciation test using English-language words, there is no equivalent in non-English languages. The Teen REALM has been validated for use in middle- and high-school-aged students (some "mature" words were replaced with word content more appropriate for children).
- The Short Test of Functional Health Literacy in Adults (S-TOFHLA) involves both reading and numeric calculation. Reading comprehension questions ask participants to choose from a list of words to complete the missing part of a sentence. For some, they look at a prompt and then respond. For others, they must choose from among multiple-choice options the word that makes the most sense. This measures ability to determine meaning from context. For the example, "your doctor has sent you to have a [blank] x-ray," the choice that makes the most sense is "stomach." This tool has a time limit of 7 minutes—most participants finish quickly, but all participants must stop at 7 minutes, whether or not they are done. There are different variations of this tool: the original TOFHLA (or "long" TOFHLA) takes approximately 22 minutes. The S-TOFHLA is limited to 7 minutes as described above. This tool is available in English and Spanish.
- The Newest Vital Sign (NVS) involves 6 questions about a nutrition facts label from a package of ice cream. Participants view a prop card containing the label and then answer 6 questions that are read by an interviewer. Examples of the questions include the following:
  - "If you eat the entire container, how many calories will you eat?"
  - "If you are allowed to eat 60 grams of carbohydrates as a snack, how much ice cream can you have?"
  - "If you are allergic to penicillin, peanuts, latex, and bee stings, is it safe for you to eat this ice cream?"

A score of 4 to 6 indicates adequate literacy; 2 to 3 indicates that literacy problems are possible; 1 to 2 indicates that literacy problems are likely. The NVS is also available in Spanish.

### Evolution of Measurement and Emerging Tools

Measurement has continued to evolve toward more skills-based tools that address literacy and numeracy in simulated real-world task scenarios. Specific examples in pediatric health literacy include the Parent Health Literacy Activities Test (PHLAT). The PHLAT asks parents to act out or demonstrate what they do (or would do) in several scenarios common to child health, such as dispensing and administering a dose of liquid medicine using label instructions and dosing instruments. This evolution toward more pragmatic and comprehensive measurement approaches is particularly important for underserved parent, adolescent, and young adult populations because more reading-focused instruments can produce high scores that miss the chance to identify low numeracy.

There has been some concern that use of screening tools in clinical settings could cause embarrassment for children, particularly for those who have literacy problems. At the same time, most participants in one study reported no shame (99%) from screening with the NVS. Measurement among a sample of patients within a practice can provide practice-level estimates of health literacy to inform decisions about practice-level strategies and to become a more health-literate practice; however, routine measurement of health literacy for individual patients at visits is not recommended.

### A Universal Precautions Approach

One alternative to measurement in clinical settings is the use of strategies for clear communication in clinical practice. The Agency for Healthcare Research and Quality (AHRQ) encourages physicians to use universal precautions for health literacy—to employ evidence-based techniques to communicate, clarify, and confirm information in clinical care. Because it is impossible to tell which patients have problems with health literacy (and because only those who have proficient skills can manage most health situations), the universal precautions approach encourages use of the clearest communication possible *with everyone* at all times.

In Susan's case, the stress of parenthood, sleeplessness, and having a sick baby may have been factors, yet other life stresses can also play a role. This phenomenon extends to staff and others in the practice; if only 12% of adults have proficient health literacy, that leaves 9 of every 10 English-speaking adults with some degree of health literacy problem. Furthermore, stress can compete with the ability to focus and therefore interferes with the ability to understand medical information that may otherwise seem routine or simple. Stress does not discriminate: those who work in the practice are as likely as patients to be included in this group. Some individuals may struggle routinely, whereas others who function well under normal circumstances may become confused when dealing with a stressful, traumatic, or unexpected medical event. Pediatricians may not always know what other

stresses a family, staff member, or colleague may be facing; therefore, practicing universal precautions for clear communication with everyone can minimize confusion and enhance patient–physician experiences.

Universal precautions can include the use of pictograms to represent information visually as well as verbally; the use of techniques like teachback, whereby the pediatrician or nurse asks a patient to teach back to the physician the information or action just described; or Ask Me 3, which involves teaching new communication skills to empower patients.

### Teachback

One of the most useful and important universal precautions techniques is *teachback*. In teachback, the physician literally asks patients to teach back, or walk through, the treatment or process the physician just described. Teachback is iterative, with each participant confirming and clarifying points of confusion or misunderstanding, until the physician and the patient are able to describe the information to one another in the same way. For example, when a new medicine is prescribed, pediatricians can enhance patient and parent understanding by demonstrating how the medicine should be used and then asking the patient or parent to teach back the process or steps as they understood them.

The purpose of teachback is twofold: it is confirmatory for the physician and identifies when information should be clarified or repeated; and, for the patient, the experience of teaching new information or a new process back to the physician helps to move information from working memory to long-term memory and thus enhance comprehension. Demonstration and teachback can be particularly useful in ensuring patient adherence and safety with new treatments or medicines, particularly if dosing instruments or equipment such as a spacer or inhaler are required. Teachback can also be used to confirm that patients understand the risk and benefits of different treatments or health choices.

### Ask Me 3

Pediatricians can also empower parents and patients to facilitate their own understanding. The Ask Me 3 method teaches patients to ask 3 questions at every health visit:

1. What is my main problem?
2. What do I need to do?
3. Why is it important for me to do this?

Along with routine use of teachback, pediatricians can teach parents and patients together to use these questions, and—over time—can model and reinforce patients' growth in their use of Ask Me 3 until it becomes second nature. Teachback and Ask Me 3 are highly complementary, with patients and physicians teaming together to enhance communication, understanding, adherence, and safety.

## HEALTH LITERACY IN PEDIATRIC PRACTICE

Pediatricians are becoming more aware of health literacy and the importance of responding to communication challenges in health care, yet their use of evidence-based techniques in office practice is limited.

To help encourage the practice-based use of evidence-based techniques, AHRQ has produced a comprehensive toolkit, which is available on the Internet at no cost (see Tools for Practice at the end of this chapter). It includes video case examples like Susan's; examples of patient materials such as pictograms for medicine use and asthma action plans that can be adapted for specific needs of an individual practice; and quality improvement tools to assess the practice and identify opportunities for practice change.

Links to these and other resources, including toolkits of patient materials to support practices in implementing these methods, are included in Tools for Practice at the end of this chapter.

During the past decade, a wide range of interventions have demonstrated some success in improving medication adherence, management of chronic illness, understanding of specific health information, and ability to safely complete specific health tasks. Although most of these interventions have been conducted in adults, evidence for the importance of parent health literacy in caring for children is mounting. There is also increasing interest in exploring potential developmental links between parent or caregiver health literacy and child health literacy. As the field of health literacy expands beyond its original exploration of age-related cognitive decline to encompass parents, children, and adolescents, it is beginning to incorporate health literacy *development* in addition to health literacy *decline*. Health literacy in pediatric care therefore becomes an opportunity for learning and growth for parents, children, and pediatricians.

### Health Literacy and Parents

As Susan's case illustrates, a parent or caregiver's health literacy skills affect that individual's ability to make health decisions for a child. Studies have linked health literacy problems among parents with poorer health outcomes among their children, finding the most dramatic effects among young children. Parents who have health literacy problems may be unable to correctly administer medicines to children using dosing instruments and consumer medication information (ie, package inserts or label instructions); may struggle to understand written material, including medical forms and schedules for recommended visits, immunizations, or preventive screening; and may have difficulty managing a child's chronic health conditions such as asthma or diabetes.

Medicine packages routinely contain confusing, incomplete, or incorrect information about how to administer a dose of medicine for a child. One study of measuring devices and label instructions for the top-selling liquid medicines for children found that in 98.6% of cases, the dosing instruments and label instructions were inconsistent, particularly for units of measure and recommended dose. Such problems include missing markings, extraneous markings, atypical units of measurement, and use of different units of measurement on the device and on the label instructions (eg, label indicates teaspoons, whereas measuring device is labeled in milliliters). Although this example comes from a study of labels on 148 liquid

medicines for children, labels on all prescription drugs can be equally unclear, inconsistent, and confusing for patients. As the Safe Use Initiative of the US Department of Health and Human Services and the Food and Drug Administration undertake efforts to address labeling issues, efforts to support and enhance parents' skills continue to advance. In a small but growing body of evidence, interventions to address health literacy of caregivers, or of children themselves, have shown promise in helping caregivers learn to better understand written materials such as consent forms and vaccine information, improved management of asthma, and reduced errors in administration of liquid medicines to children.

### Health Literacy and Children

Pediatricians should recognize the health literacy needs of parents but should also consider the development of health literacy in children. Developmental theories support the ability of children and adolescents to develop health literacy skills through age-appropriate information and experiences. One conceptual model frames health literacy in a developmental context as *health learning capacity*. This framework synthesizes evidence from the fields of education, cognitive science, and psychology into a constellation of cognitive and psychosocial skills that can be learned and are needed to "promote, protect, and manage one's own or a child's health."

Ideally, health learning builds cumulatively. Health awareness develops throughout childhood and early adolescence; knowledge, experience, and independence in making decisions build during middle and late adolescence; and increasing autonomy and responsibility culminate in self-management of health among young adults. Evidence about cognitive development supports this progression: from basic or functional skills (concrete operational), to the development of interactive skills (formal operational), and finally to the maturation of executive function (the ability to plan, reason, apply logic, problem-solve, generalize, and apply information in new situations).

Framing health literacy in this developmental context allows delineation of potential roles for the pediatrician to enhance health learning through experiences for both parents and patients. Physicians can teach, model, role-play, rehearse, and reinforce key health concepts, skills, and processes during regular health care encounters. In turn, both parents and pediatricians can do the same to encourage health learning in children and adolescents. At the end of this chapter are resources that pediatricians can use to address and ameliorate health literacy problems in pediatric practice.

### SUMMARY

Every interaction between patients and physicians or individuals and health systems shapes the health literacy of parents, their children, and ultimately society. Using the techniques and resources described in this chapter, pediatricians can take tangible steps to alter these interactions. Health literacy problems compromise every aspect of individual health, medical care, and health outcomes and influence health-related interactions within and outside of a practice. Health



literacy is a clinical, public health, ethical, and disparities issue; for this reason, the US Department of Health and Human Services has highlighted health literacy as national health priority. As highlighted by Dr. Rima Rudd, although providers “can do little to improve literacy skills of the public, they can re-examine their own activities, assumptions, and [practice] environments to remove literacy-related barriers.” The pediatric community is a critical constituent in these and other efforts to improve communication, enhance patient safety, simplify health systems when possible, and foster the development of health literacy skills in parents and patients.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Ask Me 3* (Web site), National Patient Safety Foundation ([www.npsf.org/?page=askme3](http://www.npsf.org/?page=askme3))
- *What Is Health Literacy?* (fact sheet), Pfizer ([www.pfizer.com/health/literacy/patients\\_and\\_families](http://www.pfizer.com/health/literacy/patients_and_families))
- *What to Do for Health* (books), Institute for Healthcare Advancement ([www.ih4health.org/our-products](http://www.ih4health.org/our-products))

### Medical Decision Support

- *Attributes of a Health Literate Organization* (booklet), Brach C, et al; Institute of Medicine ([www.iom.edu/~media/Files/Perspectives-Files/2012/Discussion-Papers/BPH\\_HLit\\_Attributes.pdf](http://www.iom.edu/~media/Files/Perspectives-Files/2012/Discussion-Papers/BPH_HLit_Attributes.pdf))
- *FDA Safe Use Initiative: Collaborating to Reduce Preventable Harm from Medications* (booklet), US Food and Drug Administration ([www.fda.gov/downloads/Drugs/DrugSafety/UCM188961.pdf](http://www.fda.gov/downloads/Drugs/DrugSafety/UCM188961.pdf))
- *Health Literacy: A Prescription to End Confusion* (book), National Academies Press ([www.nap.edu/catalog.php?record\\_id=10883](http://www.nap.edu/catalog.php?record_id=10883))
- *Health Literacy Resources* (Web page), Centers for Disease Control and Prevention. ([www.cdc.gov/healthliteracy/Learn/Resources.html](http://www.cdc.gov/healthliteracy/Learn/Resources.html))
- *Health Literacy* (Web page), American Medical Association ([www.ama-assn.org/ama/pub/about-ama/ama-foundation/our-programs/public-health/health-literacy-program.page](http://www.ama-assn.org/ama/pub/about-ama/ama-foundation/our-programs/public-health/health-literacy-program.page))
- *Health Literacy Universal Precautions Toolkit* (toolkit), Agency for Healthcare Research and Quality ([www.ahrq.gov/professionals/quality-patient-safety/quality-resources/tools/literacy-toolkit/index.html](http://www.ahrq.gov/professionals/quality-patient-safety/quality-resources/tools/literacy-toolkit/index.html))
- *The Medical Library Association Guide to Health Literacy at the Library* (book), the Medical Library Association ([www.alastore.ala.org](http://www.alastore.ala.org))
- *National Action Plan to Improve Health Literacy* (booklet), US Department of Health and Human Services Office of Disease Prevention and Health Promotion ([www.health.gov/communication/HLActionPlan/pdf/Health\\_Literacy\\_Action\\_Plan.pdf](http://www.health.gov/communication/HLActionPlan/pdf/Health_Literacy_Action_Plan.pdf))
- *Plain Language Pediatrics: Health Literacy Strategies and Communication Resources for Common Pediatric Topics* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Plain Language Principles and Thesaurus for Making HIPAA Privacy Notices More Readable* (booklet), US Department of Health and Human Services ([www.aspiruslibrary.org/literacy/MakingHIPAAPrivacyNoticesMoreReadable.pdf](http://www.aspiruslibrary.org/literacy/MakingHIPAAPrivacyNoticesMoreReadable.pdf))

- *Proceedings of the Surgeon General's Workshop on Improving Health Literacy* (booklet), Office of the US Surgeon General ([www.ncbi.nlm.nih.gov/books/NBK44257/](http://www.ncbi.nlm.nih.gov/books/NBK44257/))
- *What Is Clear Health Communication?* (Web page), Pfizer Inc. ([www.pfizer.com/health/literacy/health\\_care\\_professionals/overview\\_of\\_health\\_literacy\\_health\\_communication/what\\_is\\_clear\\_health\\_communication](http://www.pfizer.com/health/literacy/health_care_professionals/overview_of_health_literacy_health_communication/what_is_clear_health_communication))

## SUGGESTED READINGS

- Berkman ND, Davis TC, McCormack L. Health literacy: what is it? *J Health Commun.* 2010;15(Suppl 2):9
- Borzekowski DL. Considering children and health literacy: a theoretical approach. *Pediatrics* 2009;124(Suppl 3):S282
- Nutbeam D. Health literacy as a public health goal: a challenge for contemporary health education and communication strategies into the 21st century. *Health Promot Int.* 2000;15(3):259–267
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- Yin HS, Johnson M, Mendelsohn AL, et al. The health literacy of parents in the United States: a nationally representative study. *Pediatrics* 124(Suppl 3):S289, 2009

## Chapter 9

# PARTNERING WITH FAMILIES IN HOSPITAL AND COMMUNITY SETTINGS

Ruth R. Walden, MSW; Molly Cole

During Nick's childhood he was seen by a series of orthopedic surgeons; neurologists; other pediatric specialists; nurses and nurse practitioners; and physical, speech, and occupational therapists. This rotation of health professionals is the norm for kids like Nick. But we have always been there, bringing him home from the hospital in a full-body cast, hosting birthday parties, learning to deal with his seizures, trying out new wheelchairs or computers, modifying our work schedules, teaching him to swim, remembering medicines, helping with homework, finding an accessible summer camp.

When our family moved . . . our pediatrician offered to continue to follow Nick and his siblings. But he also encouraged us to visit a nearby rural primary care clinic. [Our doctor] and his clinic staff grew to know and understand Nick and his changing diagnoses. We became comfortable at the clinic, dropping in before dinner for a quick consultation or to check blood levels. For 12 years Nick's schools trusted [his] experience and routinely followed his guidance about therapy and nutrition routines.

Knowing that Nick's primary providers were nearby supported our determination to care for him at home—a determination inspired by a pediatric movement called family-centered care

*that probably prolonged his life. In family-centered care, professionals . . . and families like ours build a partnership of trust that helps us make joint decisions. Together we connect the science of medicine with the evidence of daily life. This kind of care returned to my husband and me a sense of control over Nick's fragile health.*

—POLLY ARANGO, "A PEDIATRIC REVOLUTION AT HOME." FROM *HEALTH AFFAIRS*, SEPTEMBER 2004

Parenting a child with special health care needs and disabilities can be challenging and rewarding. Parents are faced with accessing care and services from multiple health care specialists; allied health services such as occupational, speech, and physical therapy; multiple public and private payment sources; and early intervention school programs and family support programs. Success hinges on the critical ability of parents to partner with their primary care physician (PCP) in developing and implementing a care plan that addresses the unique needs of their children. The collaboration of the physician and the family promotes optimal health for the child. The chief tenets of collaborating well with families are outlined in Box 9-1.

### FIRST CONTACT: SHARING UNEXPECTED NEWS

For a pediatrician, sharing the news with parents that their child has a special health care need may be a difficult and complex process. (For detailed guidance, please see Chapter 49, Discussing Serious Symptoms, Results, and Diagnoses With the Patient and Family.) Physicians' choice of words, willingness to listen and answer questions, and empathy and support at this time are a critical foundation to building a lasting and trusting relationship with families who may need ongoing and more specialized care within the practice. Just as the job of the PCP for this child's unique needs is only beginning,

when the parents receive this information, their job is only beginning as well. A parent's first challenge is sharing the information with other family members, including other siblings, the spouse, extended family, and friends in the community. Having complete information in a way that family members can understand it and share it becomes critical for them. Even more challenging, parents must then incorporate their child's unique health care needs into the context of their family's hopes, dreams, strengths, and challenges. They must make tough decisions based on their family's priorities and goals. Providing the family with adequate information to make these decisions and respecting choices that families make are important factors, provided the child's life is not at risk.

To assist parents through the journey of caring for their child, the pediatrician's focus needs to be on building a strong partnership with the family. Creating a trusting relationship, built on mutual respect, and valuing the parents' knowledge about their child, takes time and requires an initial meeting that is calm, focused, and free from distractions in a safe and supportive environment. Interruptions should be limited, and the PCP must make sure that the location is private and comfortable. The family should be given some warning of difficult news so that they have time to bring in other family members or other supports. Many parents will state that the most difficult experience for them is not hearing the news, but rather being faced with the task of sharing it with their children and other family members and trying to answer their questions. If only a single caregiver is present, then a time should be arranged to speak by telephone to the other family members. The PCP should help both parents think about ways to explain this situation to other children and, if possible, should talk to these other siblings as well. Brothers and sisters of a child with special health care needs often report that they felt left out of the care of their sibling. Their questions should be answered and suggestions should be given on how to be involved.

In many instances, when difficult news is shared with families, they hear only the first few words, becoming

#### BOX 9-1 Guide to Collaborating With Families

1. Respect parents for their knowledge and understanding about their child and their ability to relate to their child.
2. Accept the parents, and later the youth, as full and equal partners in the child's care. The primary care physician and both parents, and, later, the older child, all working together, will be powerful champions to obtain the best results.
3. Always take the time to listen to parents and the child. Their words and actions will reflect their emotional status and provide an opportunity to learn what their wants, desires, and hopes are for their child.
4. Learning about the meaning of the child's illness or condition is important to the parents because this information will explain their actions, reactions, and goals for their child and responses to changes in their child's condition or treatment recommendations. Give the family as much information in as understandable a format as possible. Families need this information in order to partner effectively with physicians; they also need to be able to communicate about their child's condition with their own support network of families and friends.
5. Keep the child as the center of focus.
6. If care coordination cannot be provided in the primary care physician's practice, then the parents should be referred to outside sources of support.
7. Early in the relationship with the family, discuss the fact that disagreements will occur. Make an arrangement to respect each other's judgment and to agree to disagree.

so distracted or anxious that they miss much of what is said. For the health professional, listening is a critical part of this exchange. The PCP must ensure that the family members' questions are answered, and maintain enough patience to answer them repeatedly. The ability of the PCP to be available to answer calls from the family, and to check back with family members to see how they are doing is important. Parents may seem to be in denial because they have not fully absorbed the complexity of their child's health condition.

Once a family has had time to absorb the information, share it with other family members, and ask questions, the time comes to make referrals for other community supports, such as early intervention programs, family support groups, or other evaluations and treatments. These referrals should be part of a care coordination plan, developed with the family, to ensure that the plan addresses the family's concerns and answers all questions. In this partnership, the care coordination plan will be the tool to ensure that the pediatrician's and the family's priorities are addressed. The referrals outlined in this plan are a mechanism to make sure that all the needs of this parent-professional partnership are addressed. During follow-up visits, parents can report what is happening in the early intervention program, school program, or family support program, and they hear results of the pediatrician's examinations, tests, and other medical referrals. Thus, the basis of the partnership—mutual respect for the knowledge, skills, and experience of both the parent and the physician—is in place.

Supporting the family through even relatively simple decisions may be necessary. Specialist referrals are a decision point that should be reached in partnership with the family. The PCP should listen carefully to the parents as they explain their needs or concerns and address them in a sensitive and caring manner. Although parents may be overwhelmed, their concern for their child drives all that they do. Unless the family's choices will have a negative outcome, pediatricians must try to empathize, putting themselves in the family's place before responding.

## OFFICE VISIT

Scheduling an office visit for a child with special health care needs can be a positive experience if a few accommodations are made. The child's record should be flagged to indicate if the child needs extended time for the appointment or if the child may need to be seen immediately on arrival to accommodate any special needs. The appointment should be scheduled at a time of day that will be easiest on the child, such as the first thing in the morning, at the end of the day, or right before or after lunch. Although many patients request these times, legitimate reasons exist for a child with special health care needs to be seen at a time that is best for him or her. Family centeredness is important. (See Chapter 6, Medical Home Collaborative Care.) Allowing for cultural differences is essential to ensure an optimal visit. (See Chapter 48, Providing Culturally Effective Care.)

The office visit should not consist only of milestones and physical examination, but also allow for dialogue to learn about the child. Getting to know the child and observing how the child interacts are important tasks.

Having the family report on how the child plays and relates to the environment and how the child is doing socially is important, because these interactions may be different from those of the typical child. The parents should be engaged in full partnership because they are the experts on their child. They know the child's likes, dislikes, behaviors, and abilities. Family members may need additional time for questions to be answered and concerns to be addressed. If possible, the child should be engaged in the discussion about his or her own health and asked about any concerns or questions. Writing out instructions for changes in routine or new medications and how they are to be taken is helpful. If an electronic medical record is used in the pediatrician's office, it is helpful to provide the parent with an electronic personal health record for their child, which can be shared with specialists and other allied health care providers and updated frequently. There should be a standardized, routine process for communication among the PCP, specialists, mental health professionals, therapists, teachers, and anyone else, in order for the medical home team to function well. The PCP should check to be sure that the family understands the recommendations and that questions are answered before leaving the office. The nurse, social worker, or health educator may be able to provide the explanations for the families. Translation may be needed for family members who speak a different language. The need to assess the emotional status of the family, including the siblings, should be emphasized during the visit. Parents should be referred to the directory of State Title V Programs at their state's department of health, to Family Voices, Inc. ([www.familyvoices.org](http://www.familyvoices.org)), and to the local MUMS National Parent-to-Parent Network ([www.netnet.net/mums](http://www.netnet.net/mums)) to provide avenues for exploring funding of services and sources of emotional support and advocacy. These programs can also provide matching with families whose children have the same diagnosis.

The child with special health care needs often requires emergency services from the office or the hospital. The PCP should check with the family to see if they have an emergency plan in place. The American Academy of Pediatrics and the American College of Emergency Physicians have developed an emergency form that can be completed and updated by the physician. Copies should be kept with the parents, with pediatricians, with the child's car seat or diaper bag, and in school. This document will prepare the emergency physicians and hospital staff to best meet the needs of the child because it will provide baseline information. This sheet is used in collaboration with a MedicAlert bracelet or tag. Parents should be urged to contact their local ambulance company to introduce their child and to help avoid misunderstandings when an emergency arises. Also important is knowing if the local community hospital is equipped to handle an emergency for the child or if the tertiary care hospital is best suited to deal with the child's condition. The parents should also be advised whether they should contact the office in an emergency or on arrival at the hospital. The parents, if they choose, should be permitted to stay with their child during emergency procedures, including resuscitation. The PCP may be able



to influence the hospital staff to support the family's choice. Parents may need support and care coordination during and after the emergency situation.

Many children with special needs require home care. Discharge planners may initially plan for the home care, but the PCP must follow up, complete the paperwork, and direct and coordinate the care. Families should be assisted throughout the process. The PCP should periodically check with the family to ensure consistency and quality of care. Home care agencies are often understaffed and cannot provide consistent care for the child. Parents should be trained to care for their children at home but should be advised to also care for their own mental health. The PCP should note that having outsiders who come into the home and intrude on family life is a burden on the entire family. Supporting the family members through this process and referring them for training on how to deal with the home health caregiver can be helpful. If the parents need financial assistance to access the home care, then referral to the Katie Beckett Medicaid waiver program or other public financing programs in their state should be made. Parents can contact the Title V Program in their state, which is prepared to direct them to the agency directing the waiver program for their state.

Early intervention, preschool, and school services are significant milestones for any child but particularly for the child with special health care needs. Parents often know the type of setting they want for their child; they understand their child's learning style and have a feeling for the type of experience that will work to make the child's formative years most productive. The physician may be asked to partner with the family to find the most appropriate placement. School placement decisions should include benefits for the child and the class as a whole. Modifications and the services of a special education teacher can lead to positive outcomes not just for the child with special health care needs, but also for the other children in the class who learn to accept people who are different. However, if parents choose a less inclusive setting in a special class, then their decision should be honored.

Information about the child's clinical needs will help in the development of the best program for the child, regardless of the placement choice. Forms for specific services (occupational, physical, and speech therapies among others) will be required. If possible, attending or participating by telephone in the school placement process is desired. Parents should be asked to envision what they see their child doing in 18 years. Transition to adult living, earning, and learning should take place from birth through adulthood, understanding that the child may go through many changes within that time. The physician is a role model for the family for advocating and championing the needs of the child. As an equal partner with the family, the PCP may be required to advocate with other physicians, insurance companies, and the educational system.

## **SUPPORT DURING HOSPITALIZATION**

Hospitalizations, whether planned or resulting from an emergency, are stressful times for families who have a child with special health care needs. In the

emergency department (ED), the hospital staff must engage the parents as partners in addressing the crisis at hand. The emergency plan developed with the family will assist the hospital staff in providing a smooth ED experience. When contacted by the ED physician, the child's health professional can assist in this process by providing the staff with insight into the parents' ability to report on their child's needs accurately and encouraging the staff to use the parents' input during their ED stay.

For a planned hospital admission, the parents must have a clear understanding of the usual information: the purpose of the admission and what is expected to happen during the time the child is hospitalized, potential challenges, and anticipated discharge. However, for a child with special health care needs, other considerations must also be addressed: special beds, seating, diets and feeding needs, specialized activities with the child life department or volunteers, communication problems, and behavior concerns. Parents should be encouraged to develop a list of their child's unique care needs and bring the list with them so that these points can be easily incorporated into the care plan with hospital staff.

Many parents who have a child with special health care needs prefer to stay in the hospital to ensure that their child's unique needs can be met. Some parents cannot be available for long periods because of other commitments. In either case, the PCP is critical to the development of a strong working partnership between the family and the hospital staff. Parents have unique insight and understanding about their child's care needs, and the staff should be encouraged to seek their input during the hospital stay. The PCP should encourage the staff to schedule times to meet with caregivers, whether they stay at the hospital or not. Parents must be allowed to be present during procedures. The staff should be encouraged to work with the parents and to incorporate the parents' knowledge about their child's unique care needs into the hospital care plan.

Teaching hospitals pose opportunities and challenges. Parents should be encouraged to be present during rounds ("family-centered rounds") and should be treated as a critical component of the child's hospital care team. Not only will this practice enhance outcomes for the child, but it can also be a good teaching tool for residents and other students in teaching hospitals. The PCP should model this partnership.

One of the usual learning opportunities in a teaching hospital is the practice of taking the child's history. Parents who have a child with frequent hospitalizations may find that this process of medical history taking, although a valuable teaching tool, is painful and stressful. Recalling traumatic and difficult events in their child's medical history at a time when their child is again being hospitalized is something that some parents will resist, and they may need support when they decline to participate in this process, if it is not critical to the treatment.

Parents often anxiously await the arrival of the PCP at the hospital each day. The PCP is their partner in their child's care, and they look for daily insight, support, and information. PCPs should let family members



know when they will be in the hospital and available to talk. If the physician and parents fail to connect, the PCP should check in with the parents by telephone later in the day so that any of their questions can be answered and so they can be updated on their child's status.

Parents must be involved in discharge planning—from a discussion of wellness and stability to the types of supports they may need at discharge. If their child's care needs have changed as a result of this hospitalization, then the team needs to ensure that the parents are trained on any new treatment methods or equipment, and that they have adequate support at home. The PCP should assist the team, including the family members, in the discharge process. Issues such as school, accessibility, nursing, equipment, medications, and follow-up with the PCP and other specialists are part of the process. Additionally, the care coordination plan developed by the PCP and the family may need to be modified.

On the day of discharge, the discharge planner or other hospital staff members usually meet with the family to review the discharge plan. The PCP should review the discharge plan either on the day of discharge or at an office visit after discharge. The parents should be comfortable with the treatments, needs, and follow-up appointments, especially if any changes in care have occurred as a result of this hospitalization.

## TRANSITIONS

Early intervention programs provide a nurturing and supportive staff and an environment for the child with special health care needs and the family. Services are focused on the child and are family centered. Programs are much less supportive when the child moves to the early childhood program within the child's school district. Services may be fewer than they were in the early intervention program; family supports may end completely or become less family centered. For many children, this move will also mean the transition from home-based to center-based services. Parents should be made aware of these differences and be supported during this potentially difficult transition. Referrals for other services through the Title V Program in their state and community agencies may become necessary to supplement the Individuals with Disabilities Education Act, Part B, Preschool Grants Program. The PCP may need to check with the parents to ascertain their needs more often than usual during this transition.

The transition from the smaller setting of the early childhood program to the elementary school program can be frightening for the family and child. How will the child be accepted? How will the staff meet the child's needs? Are the allied services going to continue to support progress? Is the child placed with the best teacher to meet the child's learning style? These questions are a few that the parents may have as they approach the beginning of school. During the school physical, the PCP may need to reassure the family. The PCP may agree or disagree with the placement, but the support will help the family approach the beginning or continuation of the program with less apprehension. Understanding and empathy will help the family.

Transition from elementary to middle and then from middle to high school may bring placement changes and insecurity to the child and family. Friends who have surrounded the child up to this point may not be available to support the child; teachers and staff will be new and perhaps less supportive and understanding of the child's needs. Providing clinical information, and clearly and concisely explaining the needs of the child may be necessary. The PCP should check with the parents to determine their needs and to see how smoothly the transition is proceeding.

Transitions occur at other junctures as well. An illness may result in changes in the child's ability to attend school. A child with a terminal illness may deteriorate for long periods, and the school personnel may not understand the need to adjust their demands of the student. This circumstance may be more characteristic of middle and high schools because of the more rigorous nature of the curricula. The physician's support of the family and staff within school will help increase understanding, reduce demands and expectations, and support the child or young adult through the illness. If the illness is one that results in physical or cognitive deterioration, then preparing the family and, if the parents wish, the educational program, for the changes is important. These transitions can be sources of great stress not only for the parents, but also the siblings and extended family members. Helplessly watching as the child's ability diminishes over time is difficult. Gently providing support and referrals for emotional and family support and services is critical.

The transition to adult health care takes planning and time for the PCP, the adolescent, and the family. Preparing the adolescent for an adult health care physician who may be less family centered requires advocating, sharing of information, mentoring the adolescent, and relying on the trust of the family. This preparation is a lifelong process of focusing on a vision for the future and developing the skills to achieve that vision. Choosing an adult health care physician should be an informed decision of the partnership: adolescent, parents, and PCP. Often a med-peds trained physician has the knowledge and experience to care for an adult with special health care needs originating during childhood. Preparing the new physician is the responsibility of the physician and parents. Adolescents should be empowered to speak on their own behalf, to describe their condition, to share how it affects them daily, and to seek care for themselves. The mentoring should begin early and continue until such time as the PCP discharges the adolescent from care.

## FINANCIAL CONSIDERATION

The parents may face significant unpaid bills, difficulties with getting insurance to pay for services, insurance companies reversing decisions, and the need to seek services that may be difficult to find locally. Referrals to the state insurance program, Medicaid for children, or Medicaid waiver programs if the family does not have insurance may assist families. If the physician's office does not accept these sources of payment, then helping the family identify a practice that does will also be helpful if the parents are not able

to afford the associated out-of-pocket expenses. Displaying brochures about the state insurance program and Medicaid within the physician's office will draw the attention of parents needing these services.

## END-OF-LIFE PLANNING

When caring for a child who has a terminal diagnosis, the PCP must have discussions with the family at a time other than when the child is in crisis. Included in this meeting should be a frank discussion of the family's wishes regarding do-not-resuscitate orders. (See Chapter 67, Palliative, End-of-Life, and Bereavement Care.)

## CONCLUSION

Parents seek physicians who are able to treat them as equal partners in the care of their children. They are looking for someone who will be nonjudgmental as long as the child is safe, well cared for, and treated with respect. The PCP needs to coordinate the care provided to the child with special health care needs by collaborating effectively with the various professionals involved in the child's care. Parents will respect the PCP who admits to not knowing but who will seek out the answer or the specialist who does know. Parents will respect the PCP who can provide sensitive, nurturing, and supportive care.

*"... Families are visionaries. Their dreams are not tied to bureaucratic limitations. Their ideas and hopes for their children, their families, and their communities provide challenge, inspiration, and guidance."*

(ELIZABETH S. JEPSON AND JOSIE THOMAS,  
ESSENTIAL ALLIES: FAMILIES AS ADVISORS,  
INSTITUTE FOR FAMILY CENTERED CARE, 1995)

## TOOLS FOR PRACTICE

### Community Advocacy and Care Coordination

- *A Patient and Family Advisory Council Work Plan: Getting Started* (form), Institute for Family-Centered Care ([www.ipfcc.org/pdf/PDF/advCouncil\\_workplan.pdf](http://www.ipfcc.org/pdf/PDF/advCouncil_workplan.pdf))
- *Creating Patient and Family Advisory Councils* (booklet), Institute for Patient- and Family-Centered Care ([www.ipfcc.org/advance/Advisory\\_Councils.pdf](http://www.ipfcc.org/advance/Advisory_Councils.pdf))

### Engaging Patient and Family

- *Pediatric Care Plan* (form), American Academy of Pediatrics ([medicalhomes.aap.org/Documents/PediatricCarePlan.pdf](http://medicalhomes.aap.org/Documents/PediatricCarePlan.pdf))

### Practice Management and Care Coordination

- *Coding for Medical Home Visits* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/professional-resources/practice-support/Coding-at-the-AAP/Pages/Coding-for-Medical-Home-Visits.aspx](http://www.aap.org/en-us/professional-resources/practice-support/Coding-at-the-AAP/Pages/Coding-for-Medical-Home-Visits.aspx))
- *Measuring Medical Homes: Tools to Evaluate the Pediatric Patient- and Family-Centered Medical*

*Home* (monograph), National Center for Medical Home Implementation ([medicalhomeinfo.aap.org/tools-resources/Documents/Monograph\\_FINAL\\_Sept2010.pdf](http://medicalhomeinfo.aap.org/tools-resources/Documents/Monograph_FINAL_Sept2010.pdf))

- *Patient- and Family-Centered Ambulatory Care: A Checklist* (handout), Institute for Family-Centered Care ([www.ipfcc.org/advance/topics/Ambulatory-Care-Key-Concepts.pdf](http://www.ipfcc.org/advance/topics/Ambulatory-Care-Key-Concepts.pdf))

## AAP POLICY

American Academy of Pediatrics Council on Children With Disabilities. Role of the medical home in family-centered early intervention services. *Pediatrics*. 2007;120(5):1153–1158 ([pediatrics.aappublications.org/content/120/5/1153](http://pediatrics.aappublications.org/content/120/5/1153))

American Academy of Pediatrics Committee on Hospital Care, Institute for Patient- and Family-Centered Care. Patient and family-centered care and the pediatrician's role. *Pediatrics*. 2012;129(2):394–404 ([pediatrics.aappublications.org/content/129/2/394](http://pediatrics.aappublications.org/content/129/2/394))

## SUGGESTED READINGS

Federation of Families for Children's Mental Health.

Helping children with mental health needs and their families achieve a better quality of life. Available at: [www.ffcmh.org](http://www.ffcmh.org)

Institute for Family-Centered Care. Resources. Available at: [www.familycenteredcare.org/resources/index.html](http://www.familycenteredcare.org/resources/index.html)

Kids As Self Advocates (KASA): Teens and young adults with special health care needs speaking on our own behalf. [www.fvkasa.org](http://www.fvkasa.org)

The Family Village. A Global Community of Disability-Related Resources. Available at: [www.familyvillage.wisc.edu](http://www.familyvillage.wisc.edu)

## Chapter 10

# FAMILY-CENTERED CARE OF HOSPITALIZED CHILDREN

Jerrold M. Eichner, MD

With the growth of the hospitalist movement has come a change in the organization of inpatient services. The patient- and family-centered medical home, or simply medical home (MH), is an approach to providing comprehensive primary care to children, youth, and adults. The primary care physician (PCP) is responsible for meeting the child's health care needs or appropriately arranging care with other qualified professionals. This may include hospitalists to meet the care needs of the child while in the hospital, although many times the PCP may not be able to choose the hospitalist because admissions to hospital are often through an emergency department or other urgent care setting. In the hospitalist model, the shift of responsibility for the patient during the inpatient stay from the MH and the PCP to the hospitalist has placed on both parties a burden of responsibility to ensure the continuity of care for the

patient. Research indicates that ineffective communication between the 2 types of providers on many levels can adversely affect patient care and safety. Differences in the attitudes of community pediatricians toward hospitalist programs vary widely and include significant concerns about communication. Successful communication between hospitalists and PCPs is an essential component of effective hospitalist medicine and a necessary way of avoiding interruptions in patient care. The collaborative relationship between these physicians ensures a smooth transition of patient care from the inpatient to the outpatient service, and vice versa. Support for the continuity of care facilitates a global understanding of the patient and assists in appropriate diagnosis and initiation of inpatient therapy and effective outpatient follow-up. This deeper understanding allows each physician to consider more effectively the effect of social, financial, and other factors that are unique to each patient's personal history.

Patient- and family-centered care recognizes that important role of the family in the patient's life. Most of the time, the child and family have established a working relationship with the PCP and the MH for the care of the child. They play an integral role in the health care team and participate in health care decision making. Temporarily transferring that relationship, even for a short time as an inpatient, is important in the continuity of family-centered care while the child is hospitalized. Including families in decision making and keeping them informed of their child's progress are as important in the hospital as they are in the outpatient setting. Family-centered hospital rounds enhance the exchange of information and encourage families in decision sharing.

### COMMUNICATION BETWEEN PRIMARY CARE PHYSICIAN AND HOSPITALIST

The PCP's knowledge and insight are critical in providing the best care for the patient. The hospitalist has the skills to provide care for the hospitalized child that the PCP does not and is the one to make appropriate use of diagnostic tests, consultations, and treatments in the hospital. The communication between the PCP and the hospitalist at the time of admission should include the pertinent medical information (past history, prior investigations, consultations, prior therapeutic interventions, etc) as well as the wishes and plans of the family. This information often can be provided only by the patient's PCP. This is particularly important in the care of children with chronic disease and special health care needs. These factors are instrumental in preventing interruptions in care, making critical decisions such as end-of-life care, suggesting social service interventions, and recognizing the value of specialty services for patients with special health care needs. Similarly, hospitalists may have knowledge of repeat hospitalizations and access to information available in inpatient medical records. Hospitalists have the opportunity to use the services of many ancillary providers within the hospital system. For example, hospitalists caring for children may have access to information about social services and community

resources not readily available to the PCP. Communication between the PCP and hospitalist prevents unnecessary duplication of diagnostic tests and facilitates consultation and a smooth transition between outpatient and inpatient care.

Successful interaction among different physicians and other professionals promotes an atmosphere of collegiality and mutual learning, and creates an open and supportive professional and educational medical community. Communication fosters a culture of safety and may reduce medication errors and unnecessary medication use. It supports patient education, has the potential to improve the use of chronic and preventive medicines, addresses the needs of patients with limited resources or without an MH, helps coordinate the care of chronically ill and vulnerable patients, and provides greater insight in family conferences.

Box 10-1 provides guidance for communication between PCPs and hospitalists. A partnership in patient and family education may help prevent unnecessary hospitalizations and may promote patient and family knowledge about chronic diseases, medications, and disease triggers. Many concerns regarding patient safety, such as medication reconciliation, follow-up of outstanding laboratory results, or the need for additional outpatient clinical tests or procedures, can be addressed by establishing effective and collegial communication among physicians. Both the PCP and the hospitalist are advocates for the patient. Differences in approach to diagnosis and treatment should be discussed in an open and mutually respectful manner. An optimal plan is a collaborative one; however, ultimately, the attending physician of record, the hospitalist, will be responsible for making decisions about the hospital stay. Any differences should be settled before discussion with the family. Involving the patient and family in these care decisions is an important and necessary part of the care collaboration. Effective communication and handoff also increases physicians' efficiency and satisfaction in their own practices.

Transitions in patient care when a hospitalist assumes the care of a PCP's patient and vice versa, such as inpatient hospitalization and discharge, carry the risk of losing patient information and decreasing communication. Similarly, subspecialty consultations, procedures, and therapeutic suggestions can be lost to the PCP if not adequately communicated by the hospitalist. Thus, in addition to collegial communication, continuing education for hospitalists, subspecialists, and PCPs in physician-physician communication and physician-patient communication improves rapport, a necessary component of the therapeutic relationship between the members of this triad.

Methods of communication are varied and often tailored to a particular service and patient population, although most PCPs prefer to communicate with hospitalists by telephone at admission and discharge. Other options include faxes, transcribed dictation, and e-mail. It would be optimal to agree on a method of communication prior to or during the hospitalization, but this may not be practical, so a standard method of communication for that hospital program should be known and adhered to.

### BOX 10-1 Guidance for Communication Between Primary Care Physicians, Hospitalists, and Families

- Communication should, above all, promote quality of care and patient safety.
- Communication between the hospitalist and primary care physician (PCP) should always occur at the time of admission, at discharge or transfer to a different institution, and during the hospitalization at the time of significant events and procedures (depending on physician preferences).
- During hospitalization, the child's family should participate in major decisions such as those regarding major procedures, transfers to other institutions, and changes in level of care. Family-centered hospital rounds are an effective method of encouraging this communication.
- Hospitalists, PCPs, and subspecialists should be easily accessible to each other by a mutually agreed upon method of communication or based on the model for that institution, be it by phone, e-mail, sharing electronic medical record notes, or another method.
- PCPs should maintain communication with patients and their families who are on a hospitalist service and are encouraged to visit the child in the hospital, especially a child with a chronic condition or special health care needs. The PCP should discuss any medical advice with the hospital team before discussion with the family.
- The treatment plan and follow-up suggestions are an essential part of the communication about transfer of care at discharge. The patient and family should participate in the generation of the health care plan, have ownership of it, and document their understanding of it. The use of care coordinators can be extremely helpful in that process.
- Hospitalists, subspecialists, PCPs, and families share in the responsibility to ensure adequate follow-up after discharge, including establishing follow-up appointments, informing patients of outstanding clinical test results, and educating patients about the necessity for follow-up care.

Derived from Eichner JM, Cooley WC. Coordinating the medical home with hospitalist care. *Hosp Pediatr*. 2012;2(2):105–108.

## TRANSITION OF CARE AT DISCHARGE

Interventions that increase patient satisfaction and improve safety after discharge are essential for hospitalist services. These interventions may include identifying a specific individual from the hospitalist team (a care coordinator) to contact patients after discharge, identify patients who have missed follow-up appointments, and track pending clinical results. For some services, providing follow-up telephone calls from a pharmacist has helped answer questions and resolve medication-related problems. First and foremost, communication should promote patient safety. The treatment plan must include preparations for follow-up after discharge and a method of communicating outstanding test results.

The importance of a controlled transfer of patient information after discharge cannot be overemphasized. The hospitalist and the PCP share responsibility and liability for patient care. A practice that focuses first on the best interests of the patient will ultimately benefit the physicians involved and help improve the quality of care after discharge from the hospital. The physician's legal duty to provide follow-up care is well established. In the case of hospitalists and PCPs, this responsibility is shared. The patient and family must leave the hospital with the following necessary tools: an understanding of the diagnosis and inpatient treatment, what tests results are still pending, a recognition of the need for any ongoing medical therapy or routine follow-up care, and a follow-up care plan with an identified PCP who has timely, adequate, and accurate information about the hospitalization, including any pending laboratory or other clinical test results. There also should be a clear understanding by the patient and family, hospitalist, and PCP regarding

who should be contacted and by what method during that critical period between discharge and the follow-up appointment. This can be provided by a care coordinator as part of the hospital team.

The failure to relay information about clinical test results that are outstanding at the time of discharge is a problem documented in the medical literature and identifies an important patient safety issue. By definition, hospitalist services have a large volume of potentially actionable test results pending at the time of discharge and may not have an established system for tracking these results or providing follow-up information to PCPs or patients. Fortunately, an inherent strength of hospitalist services is their ready access to patient information through integrated hospital information systems and their ability to coordinate care for patients with other specialists. These systems need to be used to enable and promote collaboration and communication between hospitalists and community physicians. Thus, there needs to be a system in place to ensure prompt, reliable, and confidential transfer of patient information between the hospital and PCP's medical record systems.

## CONCLUSION

The presence of a skilled pediatric hospitalist on an inpatient service provides a unique opportunity for teaching many members of the medical team. It is an ideal arrangement for direct evidence-based clinical teaching of medical students and residents, as well as providing immediate interaction with nursing staff and other ancillary staff. There are many benefits to including the family in these efforts. A pediatric hospitalist presence in the hospital promotes the consideration of pediatric concerns at many levels and



provides a pediatric focus during administrative and peer-review hospital committee activities. In addition, the pediatric hospitalist has the opportunity to improve the quality of care provided to hospitalized children by implementing and overseeing the use of evidence-based diagnosis and treatment guidelines published by the American Academy of Pediatrics and other professional organizations. They may also conduct other quality improvement activities, such as reducing nosocomial infections and adverse reactions to medications.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Building Your Care Notebook* (Web page), American Academy of Pediatrics ([medicalhomeinfo.aap.org/tools-resources/Pages/For-Families.aspx](http://medicalhomeinfo.aap.org/tools-resources/Pages/For-Families.aspx))
- *Emergency Information Form for Children with Special Needs* (template), American Academy of Pediatrics ([www.aap.org/advocacy/blankform.pdf](http://www.aap.org/advocacy/blankform.pdf))
- *Hospital Stay Tracking Form* (file archive), National Center for Medical Home Implementation ([medicalhomeinfo.aap.org/tools-resources/Documents/Hospital%20Stay%20Tracking%20Forms.zip](http://medicalhomeinfo.aap.org/tools-resources/Documents/Hospital%20Stay%20Tracking%20Forms.zip))
- *Pediatric Care Plan* (template), American Academy of Pediatrics ([medicalhomes.aap.org/Documents/PediatricCarePlan.pdf](http://medicalhomes.aap.org/Documents/PediatricCarePlan.pdf))

#### Practice Management and Care Coordination

- *Coding for Medical Home Visits* (fact sheet), American Academy of Pediatrics ([www.aap.org/en-us/professional-resources/practice-support/Coding-at-the-AAP/Pages/Coding-for-Medical-Home-Visits.aspx](http://www.aap.org/en-us/professional-resources/practice-support/Coding-at-the-AAP/Pages/Coding-for-Medical-Home-Visits.aspx))

### AAP POLICY

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- American Academy of Family Physicians, American Academy of Pediatrics, American College of Physicians, American Osteopathic Association. *Guidelines for Patient-Centered Medical Home (PCMH) Recognition and Accreditation Program*. 2011. [www.acponline.org/running\\_practice/delivery\\_and\\_payment\\_models/pcmh/understanding/guidelines\\_pcmh.pdf](http://www.acponline.org/running_practice/delivery_and_payment_models/pcmh/understanding/guidelines_pcmh.pdf). Accessed May 27, 2015
- American Academy of Pediatrics Committee on Hospital Care, Institute for Patient- and Family-Centered Care. Patient- and family-centered care and the pediatrician's role. *Pediatrics*. 2012;129:394–404
- Eichner JM, Cooley WC. Coordinating the medical home with hospitalist care. *Hosp Pediatr*. 2012;2:105–108
- Percelay JM; American Academy of Pediatrics Committee on Hospital Care. Physicians' roles in coordinating care of hospitalized children. *Pediatrics*. 2003;111(3):707–709
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## Chapter 11

# ETHICAL AND LEGAL ISSUES FOR THE PRIMARY CARE PHYSICIAN

Lainie Friedman Ross, MD, PhD; John D. Lantos, MD

The hallmark of clinical ethics in the setting of general internal medicine is its focus on the competent adult patient. In the physician–patient dyad, the patient is the decision maker, and the focus is patient autonomy. If the patient becomes incompetent, the focus remains on patient autonomy because the surrogate is supposed to be guided by the principle of substituted judgment; that is, to make decisions based on what the patient would have chosen if able to do so. In contrast, the foundation of pediatric clinical ethics is a triad that includes the physician, the child, and his or her parent or parents or guardians. In the triad, the legally entitled decision maker is not the patient. Historically, parents were legally empowered to make virtually all decisions for their children. All children were presumed to be incompetent, and their opinions were not sought. The guiding principle was the *best interest of the child* standard. However, in the past 2 decades, sociopolitical developments around the world have increased the child's legal authority and given the child, particularly the older child, his or her own voice (autonomy). Some people argue that mature children (specifically adolescents) should be allowed to make their own decisions without their parents' permission, even without their parents' awareness. This issue is an area of tension and controversy because reasonable people disagree about the degree to which children's values and choices should direct their health care.

Much of the literature of pediatric ethics focuses on the extreme cases: the premature infant who weighs 600 g, the child who has leukemia whose parents refuse chemotherapy, or the child whose sibling needs a kidney transplant. The unique issues that pediatricians in primary care practice face have not received comparable adequate scholarly attention or rigorous analysis. This circumstance may be because the ethical issues that arise in the daily practice of primary care pediatrics are usually not concerned with decisions about illnesses that are immediately life threatening. Nevertheless, pediatricians in primary care practice often face decisions that may have profound effects on a child's physical and mental health and on many emotional, spiritual, and economic elements of family life.

Societal standards about difficult moral choices in medicine have evolved through a dialogue among patients, patient advocacy groups, pediatricians and other physicians, bioethicists, professional societies, and the various branches of government. Legal disputes have been especially important for issues such as do-not-resuscitate orders, brain death, and treatment withdrawal. The controversies and disputes that arise in primary care seldom lead to legal actions. When they do, lower courts, rather than appeals courts, often decide these disputes. Lower-court

decisions are seldom published and do not establish precedent. As a result, in many cases, neither statutory law nor case law is directly applicable to the issues at hand.

This chapter presents common scenarios that arise in primary care pediatrics and that raise thorny ethical issues. Some of these issues are procedural—that is, they require a decision about who should decide. Others are substantive—that is, they require consideration of what the right decision is and what constraints should apply to any decision maker. In some cases, legal constraints exist on decision making; in others, the law allows the physician wide latitude. The focus is on situations in which the law is less clear because many applicable laws vary from state to state and because these situations require that pediatricians make their own moral judgments.

## CASE STUDIES AND ANALYSIS

### Case 1

Alan, an 8-year-old boy, comes to your office because he has multiple warts on his hands. The school is concerned that he is contagious, and he is not allowed to participate in contact sports until his condition is treated or, at a minimum, is under treatment. You explain to Ms A, his mother, and to Alan that many therapeutic options are available, including cryotherapy in the physician's office, a salicylate-based therapy or duct tape that is to be applied nightly, and watchful waiting. Ms A requests that you give Alan the in-office treatment. Alan says that he does not want any painful treatment and will apply the ointment nightly. What do you do?

### Discussion

On the surface, the case does not appear to involve an ethical issue because Alan, his mother, and the pediatrician all agree that Alan needs treatment. However, many very different treatments are available. Each approach has different benefits and burdens, and the evidence for the superiority of any one treatment is not strong. The child prefers one balance of the benefits and burdens, and the parent prefers another. Their different values, when brought to play on the therapeutic options, have created a conflict between the parent and child. The pediatrician may not have a strong opinion about which option is best.

The first step in any such conflict is further discussion. Understanding why Ms A prefers the liquid nitrogen therapy would be valuable. Issues to be weighed include efficacy, cost, convenience, attendant risks, and compliance. Ms A's choice is pragmatic; she sees the liquid nitrogen as being more reliable than other treatments. Ms A is afraid, based on experience, that her child will be poorly compliant with the nightly salicylate-based treatment. She does not want to have a nightly battle. Alan has had liquid nitrogen therapy before and finds it quite painful. He promises his mother that he will comply with the nightly ointment applications.

In many such discussions, parents and children will come to an acceptable compromise. For example, Ms A may agree to a trial of home therapy during

which Alan will agree to apply salicylate without parental reminders at home. If he fails to do so, then they will return for cryotherapy. In some cases, however, their positions are intractable, and the question remains, "Who should have the final word?" The American Academy of Pediatrics (AAP) Committee on Bioethics published recommendations regarding the roles of parents and children in decision-making for children. The committee recommends that the resolution of conflicts between parents and children depends, in part, on the child's decision-making capacity. For the child whose decision-making capacity is developed, the committee recommends that the child's decision be final. For the child whose capacity is developing, such as Alan, the committee urges the physician to try to achieve consensus. If the child and parent cannot reach consensus, then the AAP supports third-party intervention. Although some people may find this approach reasonable, others might find it hopelessly cumbersome. What third party would be available in a busy pediatric office? Furthermore, some parents may be intolerant of third-party scrutiny. These parents may find even the physician's scrutiny an inappropriate threat to their legitimate parental authority.

What are the pediatrician's options if consensus is not achieved? If the pediatrician sides with the parent, then the protesting child will receive a painful treatment. What if the child resists? Such actions convey to children the problematic message that their opinions do not matter. On the other hand, to side with children on the grounds of developing maturity places parents in an awkward position because they must now buy the medication and apply it to their child's hands nightly. What if Ms A resists and says, "OK, doctor, at what time will you come by to place the medicine on Alan's hands?" Her response demonstrates the bind that physicians have in their relationships with their patients. The challenge for professionals is to be caring without taking unnecessary control of the life of the child for whom they do not and cannot take full responsibility.

In a case such as this one, it appears reasonable that parents should have ultimate decision-making authority. The risks of either treatment are low, as are the burdens of therapy, and the child is at an age at which it is unlikely that he would be capable of taking responsibility for his own medication regimen. Still, physicians have the right, and the obligation, to involve children in the decision-making process and to explain to them why their wishes and requests are being overridden, even if their parents complain that this action threatens their autonomy and authority.

### Case 2

Betty, a 15-year-old girl, comes into the physician's office for a yearly physical. Her examination is normal. She attends St. Mary's High School, where she is on the honor roll. She is popular with her friends and tells you that she has recently fallen in love with Bob. She says that she is not sexually active yet, but she asks for birth control pills. She also asks that you not tell her parents because she knows that her sexual activity is

against their moral and religious beliefs, and she fears they will prohibit her from seeing Bob.

### Case 3

Vicky, a 15-year-old girl, is brought to your office by her mother, Ms V, who states that she knows that her daughter is sexually active, and she wants her to get long-term contraception to avoid pregnancy. Ms V is a single mother who became pregnant with Vicky when she was 14, and she wants to protect her daughter from the hardships she faced. Vicky acknowledges that she has a boyfriend, Tom, and is sexually active. She states that he wants her to get pregnant, although she is ambivalent. She does not want contraception because she fears her boyfriend will leave her.

### Discussion

Current data indicate that more than 51% of high school girls and 61% of high school boys have had sexual intercourse. Almost 850,000 American adolescents become pregnant every year. Many teens do not seek medical or gynecologic care or contraception for months or even years after they initiate sexual activity. Most teens who become pregnant are unmarried, and most of their pregnancies are unplanned. More than 60% of these girls will decide to take the pregnancy to term, and virtually all of these teenagers will take on the responsibilities of parenthood. Pregnant adolescents and their fetuses have a higher incidence of medical complications than older women. Their children do not fare as well psychosocially as do children of adult mothers. Thus, one can say both that Betty is acting unusually responsibly for a 15-year-old and that Ms V's concerns are well founded.

Both these requests should be interpreted as an opportunity for dialogue. The first step may be to assess the voluntariness of Betty and Vicky's sexual (or potential) sexual activity. The pediatrician should ascertain whether Bob and Tom are classmates and of similar age, or whether they are much older than Betty and Vicky, with the latter possibility raising concerns of sexual predators. Even if they are of similar age, different states have different laws about when minors can legally consent to sexual activity and different laws regarding abuse, statutory rape, and state reporting requirements. Assuming that the pediatrician is convinced that Betty and Vicky are not in abusive or non-voluntary relationships, the pediatrician should discuss with each teenager the consequences of her decision. Betty should be commended for seeking to be sexually responsible, but she must also be made aware of the risks of sexual activity, the efficacy of the various methods of contraception, and the fact that abstinence is the only 100% effective way to avoid pregnancy. The pediatrician should discuss with Betty what she might do if she were to get pregnant even though she has been taking the pill. Other questions that the pediatrician should ask are whether Betty has discussed with Bob what they would do if she were to get pregnant, and how her deception will affect her relationship with her family. Vicky's physician may want to address the issue of whether Vicky finds this three-way conversation embarrassing, perhaps suggesting to Ms V that the best way to protect Vicky from an unwanted pregnancy

might be to encourage her to talk with the pediatrician confidentially. Ms V and Vicky may be receptive to this idea. This approach does not resolve whether Vicky should receive the treatment that her mother requests but that Vicky rejects. However, it may give the pediatrician an opportunity to discuss with Vicky the most likely outcome of adolescent pregnancy: single parenthood and its attendant responsibilities. The pediatrician may try to help her see that pregnancy should be a positive decision (ie, I want to be a parent) and not a passive decision (ie, it will make my partner happy). The pediatrician may want to encourage Vicky to get counseling to help her sort out the complicated issues that she is facing.

Although parents generally have the legal right and responsibility to make medical decisions for their adolescent children, treatment related to reproductive health is an exception under the special consent statutes. These statutes vary by state and in their scope, and may apply differently to physicians in different practice settings, but they all give adolescents the legal autonomy to seek and consent to the diagnosis and treatment of drug and alcohol abuse, contraceptive counseling, and the procurement of contraceptives.

Some states even allow minors to consent to abortions without disclosure or consent from their parents. The statutes were designed to encourage adolescents to seek health care for problems they might deny or ignore or for which they might delay seeking treatment if they had to get parental permission. Pediatricians should know the specifics of laws in their state. Although such statutes allow physicians to provide this care, they do not compel them to do so. Thus, a pediatrician facing a patient such as Betty has the legal latitude to make a moral decision. However, even a pediatrician who thinks that prescribing contraception is inappropriate for Betty should inform her that she has a right to obtain contraception and should refer her to another provider.

The purported purpose of the specialized consent statutes is laudable: to encourage early, responsible sexual health care for adolescents. The pragmatic justification is compelling: Given that adolescents can be and frequently are sexually active even when birth control and other sexual health services are relatively inaccessible, they should be given the opportunity to be responsible for their sexual activity. However, whether the pragmatic justification is sufficient to justify empowering all adolescents to consent to or refuse all types of reproductive health care is unclear. Rather, both moral and pragmatic considerations might lead one to empower Betty and to disempower Vicky. In both cases, the goal would be to minimize the chances that either girl would get pregnant.

Three moral arguments can be made in these situations that would lead to 3 different decisions. First, we might base these decisions on a pure best-interest standard. That is, we might simply judge that it is not in either Betty or Vicky's best interest to get pregnant. Thus, we would make the decision that best advances these interests and prescribe contraceptives for both. This decision can be framed as a way of preserving their future autonomy; that is, granting autonomy to adolescents regarding their sexual activity when they



are 15 may be autonomy-restricting over a lifetime. As with many decisions that children make, we might justify restricting a child's autonomy now to give her greater lifetime autonomy. Second, one might argue that these teens have the right to make decisions for themselves in these matters. Following this view, we would confidentially prescribe contraceptives for Betty but not for Vicky. Third, one might argue that parents have a valid third-party interest in their children's development and activities, even when the children become teens and achieve a significant level of competency. To act on these interests and to participate in their children's moral development, they need to have the opportunity to try to inculcate their beliefs through rational discourse. They can accomplish this task only if they are aware of what their teens are doing. This argument acknowledges the child's decisional capacity, but it also asserts that decision-making capacity is necessary but may not be sufficient to grant an adolescent health care autonomy. In this case, one might prescribe contraception as requested by Vicky's mother but not for Betty, whose parents are not aware of their daughter's intentions.

This range of responses is consistent with both the specialized consent statutes and the AAP position on consent, permission, and assent. Teens are empowered to obtain contraception, but pediatricians are not required to provide such treatment. Parents are empowered to request medical treatment that they deem to be beneficial to their child, but pediatricians are not required to provide it. Thus, pediatricians must make a personal moral decision about how they will respond with one major caveat: When a pediatrician is not willing to provide a treatment that is a valid medical option (eg, contraception to minors), the pediatrician does have an obligation to refer the patient and family to another physician who is willing to do so.

#### Case 4

Ms C calls you the day before she is scheduled to bring in her 14-year-old son Charles for his yearly physical examination. She tells you that Charles was previously an A student but now is getting Cs and Ds. The family is going through turmoil because Mr C moved out of the house 3 months ago to live with his pregnant girlfriend. Ms C admits to being depressed and cries easily but has not sought outside help. Charles has been withdrawn and often comes home late and refuses to tell his mother where he has been. She fears that Charles is using drugs and would like you to screen him without telling him what you are doing.

#### Discussion

Ms C's request is a call for help. Ms C and Charles need counseling regardless of whether Charles is using drugs. Ideally, both of his parents need to realize how their actions and emotions are affecting their son's behavior. Charles needs parental supervision at a time when both parents are disengaged for different reasons. Each year, more than 1 million children experience the divorce of their parents. The parental conflict

that is associated with the separation is often expressed as behavioral problems in the child, and the pediatrician should be prepared to provide support or to refer for appropriate counseling.

A crucial question for Ms C is, "How will the surreptitious drug testing help?" A test that comes back negative does not prove that Charles is not using drugs. False-negative tests can occur because the half-life of many drugs is less than 24 hours and because urine drug testing applies to only some of the substances more commonly abused. Serum testing is more sensitive but can only be used for specific drugs, so you would need a list of the drugs that are suspected. If the test is positive, it indicates recent use but is not diagnostic of substance abuse. If the screen comes back positive, then Ms C will need to decide how she will approach Charles. Charles is presently not trusting of adults who have betrayed him. Surreptitious testing will increase his distrust.

The preferable course of action would be to ask Ms C to give you permission to establish a confidential relationship with Charles. You might explain that this approach is likely to be much better for Charles in the long run. Most parents will likely be willing to accept this advice. If Ms C gives you such permission, then you should arrange to meet with Charles privately and explain the confidential nature of the relationship. You should be honest about when confidentiality would be broken—specifically, in cases in which you believe that Charles is a danger to himself or others.

The opportunity to speak confidentially to his physician may be what Charles needs to help him cope with the turmoil at home. Charles may be willing to discuss whether he is abusing drugs and may be willing to be tested for drugs as well. However, many other issues need to be addressed with Charles that are even more compelling. Is he suicidal? Is he engaging in any other risky behaviors (of which drug use is but one dimension)? Is he depressed? Is he willing to seek counseling or begin antidepressant medication, if recommended? Are there any adults whom he trusts?

Despite your suggestion, Ms C may still demand that you test Charles for drugs. In fact, situations occur in which the grounds for suspecting drug abuse are compelling, and teens who are using drugs may not be in a position to assess the risks and benefits of testing or treatment. Pragmatically, however, testing Charles would be difficult without his cooperation unless he was deceived about the purpose of specimen collection. Pediatricians (similar to other physicians) should not deceive their patients. Thus, if Charles's mother insists on testing, then the pediatrician should insist on informing Charles of the nature of the test. Ideally, Charles should voluntarily agree to testing. In fact, some states prohibit testing a minor for drugs without the minor's consent. There are exceptions for urgent and emergent care, but they would not apply in the case presented. Even where legally permissible, involuntary testing should be performed only if reason exists to doubt his competency or if information exists that strongly suggests Charles is at high risk for imminent danger from his substance abuse. Even if testing is not voluntary, the disclosure that testing



will be performed will help maintain trust and keep the door open for future communication. Ms C has a moral obligation to care for her son and to determine what medical information she needs to do so. However, this obligation does not give her the right to demand that you lie to him about what you are doing or to violate his right to privacy without compelling evidence that it is in his medical best interest.

The physician also should use this appointment and the discussion about drug testing as an opportunity to encourage Charles and Ms C to seek counseling and to give Charles anticipatory guidance about any and all risky behaviors in which he is involved. Pediatricians should be aware that in recent years, a number of companies have begun to market home drug-testing products directly to parents. If Ms C cannot get you to test Charles, she may test him at home without having full capacity to interpret the results. As such, it behooves the pediatrician to work with Ms C to get her to agree with the plan of action.

### Case 5

Mr and Mrs D are the proud parents of David, a well-appearing 6-week-old boy. During their first well-baby visit, you learn that Mr D had retinoblastoma as a child and had his left eye removed. You recommend genetic testing to determine whether the child is at risk. Mrs D states that they were offered such testing in utero and that they refused and still refuse genetic testing.

### Discussion

Retinoblastoma may be inherited as an autosomal dominant gene, or it may develop spontaneously. Given that Mr D had retinoblastoma, David has a 50% risk for developing retinoblastoma. Before the discovery of the gene for retinoblastoma, children born into families that had a positive history for retinoblastoma underwent ophthalmologic surveillance every 3 months. The value of the genetic information is that if David tests negative for the gene, then he can avoid frequent eye examinations. If he tests positive, then he will need to undergo frequent screening to enhance the likelihood of early detection. If detected early, then the prognosis for survival and vision is improved.

Testing young children for early-onset conditions encompasses 2 very different categories: conditions such as Duchenne muscular dystrophy, for which early (presymptomatic) diagnosis and treatment do not affect the course of the disease; and conditions such as retinoblastoma, for which early diagnosis and treatment may improve treatment or even save lives.

In the first category of early-onset conditions, the value of presymptomatic diagnosis is to help avoid delay in diagnosis when early symptoms are nonspecific, to target surveillance screening more accurately, to allow parents to prepare for a child who will have special needs, and to give parents information to use in their reproductive planning. On the other hand, early diagnosis may be detrimental in a number of ways. The *vulnerable child syndrome* has been shown to cause morbidity that may be even greater than that

associated with the disease that is diagnosed. Early diagnosis may affect parent-child bonding adversely if the parents hold back on emotional investment because they fear their child will die. In older children, it may adversely affect the child's self-image and self-esteem. Finally, in the United States, obtaining appropriate health insurance for the child and even for healthy siblings was complicated by insurance discrimination against families in which a preexisting condition was documented. However, the passage and implementation of the Genetic Information Nondiscrimination Act (GINA) in 2008 ought to make such concerns obsolete. Parental expectations for the future may also be limited unnecessarily. For conditions in the first category in which early testing has not been shown to improve morbidity or mortality, the risk-benefit balance of presymptomatic testing will depend on the values and needs of each family. In such situations, parental choices should be respected. For conditions in the second category for which clear evidence exists that early testing might reduce morbidity and mortality, parental discretion may be limited by medical neglect statutes. In these cases, a pediatrician might choose to report a case to child protective services. Then, a judge would decide whether to order testing.

The value of presymptomatic testing in the second category is to prevent serious morbidity and mortality. Because articulating a compelling argument to explain why children should not be tested in these circumstances is difficult, wide consensus exists that children in families known to carry such genes should be tested. Also assumed is that parents are the child's appropriate decision makers. The question is whether, if parents refuse testing or diagnostic workups, physicians should feel compelled to seek state permission to override their refusal.

In such a case, the pediatrician needs to engage Mr and Mrs D in dialogue to try to determine why they are refusing testing. They may have refused genetic testing in utero because amniocentesis entails risks for morbidity and mortality and, assuming that a positive test would not have led them to terminate the pregnancy, would not have offered any tangible benefits. However, genetic testing for the gene for retinoblastoma in a 6-week-old child is a simple blood test, and the result clarifies whether the child needs frequent ophthalmologic follow-up. Mr and Mrs D may continue to refuse testing because of lack of knowledge, fear of stigma or discrimination, or fear that this procedure may interfere with obtaining insurance, particularly if either parent is looking for a new job, which may include a change in insurance.

What should be done if Mr and Mrs D continue to refuse testing? Ideally, knowing David's genetic status would be valuable, but as long as Mr and Mrs D are compliant with frequent surveillance, their decision is neither abusive nor neglectful. The eye examinations themselves are minimally invasive, although young children may require sedation. Physicians should respect this decision but realize that it adds the additional responsibility that they ensure that David does get appropriate quarterly examinations. If Mr and Mrs D refuse or fail to comply with quarterly ophthalmologic

examinations, then this failure is neglectful, and they should be reported to the appropriate child protection authorities.

### Case 6

Ms F delivered Frances, a healthy full-term infant, 24 hours ago. Ms F is a very well-informed parent, and she requests that Frances not receive either vitamin K or hepatitis B vaccine because she does not want to put Frances through any more discomfort than the birth process. You come to draw the newborn screen for phenylketonuria and other metabolic conditions before discharge, but she refuses. She agrees to reconsider and will take the card to her private pediatrician, whom she plans to see in 2 days. You suspect that she will again refuse newborn metabolic screening. How should you respond?

### Discussion

Traditionally, the conditions screened for with the Guthrie card were rare diseases for which early treatment would reduce morbidity and mortality. In 1968, the World Health Organization enumerated 10 criteria for evaluating screening programs, including that the disease must represent an important health problem for which an accepted treatment exists that can prevent most or all of the morbidity or mortality associated with the condition; that the screening test be simple and inexpensive and the follow-up confirmatory testing highly accurate; that a system be in place to ensure quick communication of results to relevant parties; and that the cost of case finding, diagnosis, and treatment be economically balanced in relation to expenditures on medical care as a whole. More recently, newborn screening programs are expanding, in part as a result of the development of tandem mass spectrometry and advances in gene chip technology, which allow for the detection of numerous conditions, not all of which meet all of the World Health Organization criteria.

Historically, there was wide variability in the number of conditions included in newborn screening panels. In 2005, the American College of Medical Genetics and Genomics (ACMG) and the Human Resources and Services Administration (HRSA) recommended a uniform panel including 29 primary and 25 secondary targets. This panel was endorsed by the Secretary Advisory Committee on Heritable Disorders in Newborns and Children. Today all states in the United States offer the uniform panel and some offer additional conditions as well. In the United States, 48 of the 50 states have mandatory universal newborn screening programs. Although screening is characterized as *mandatory*, in actual practice, parents can and occasionally do refuse testing. However, they generally are not asked for permission, and therefore, to refuse, they must be informed and proactive. Most parents (and physicians) are unaware of the parents' right to refuse.

Mandated medical interventions, whether diagnostic or therapeutic, override important parental rights. Generally, the state should not interfere in the medical decisions that parents make for their children. To do so undermines the family unit. The only exceptions to this rule are situations in which parental decisions expose the child to serious morbidity or mortality,

although wide interpretation may exist as to what degree of urgency, likelihood of harm, or magnitude of harm may justify overriding parental rights. Thus, parents whose religious beliefs lead them to oppose blood transfusions should not be permitted to refuse blood for their child in a life-threatening situation. They may, however, refuse in situations that are less directly life threatening. Newborn screening does not meet the criteria of an imminent risk for immediate danger because the probability of harm is remote. Each of the conditions included in the newborn screen occurs in fewer than 1 in 1,000 children. Some of these conditions may be diagnosable clinically; some may never manifest clinically. A parent who refuses newborn screening is taking a very small, albeit serious, risk. Their refusal should be respected.

Nevertheless, physicians should educate parents who refuse screening so that they understand why physicians believe that the benefits greatly outweigh the risks. Most parents will then accede to screening. In Maryland, where testing is voluntary, fewer than 1 parent in 1,000 refuses testing for newborns which is less than the number of children not tested because of lost and improperly obtained specimens.

Given the experience in Maryland, one might ask whether parental permission should be required for newborn screening. The arguments for seeking parental consent for newborn screening are twofold. First, procuring parental permission for newborn screening is a symbol of respect for the family—respect that is well placed, given that families are the primary source of childrearing and given that families, and not the state, will bear the greatest costs if diagnosis is delayed. Second, by requiring consent, parents must be educated about the purpose and limitations of screening, which may give them incentive to follow up on abnormal screening results. Knowledge of negative test results can be reassuring to parents, particularly those who have personal knowledge of any of the conditions for which their infant is being tested.

The major benefit of not requiring consent is to simplify the process of screening. Obtaining parental permission for newborn screening can be time-consuming. In this day and age, physicians are more and more pressed for time. In some cases, they may not have time to seek parental consent, and newborns may suffer as a result. A related argument is that the consent process for newborn screening is perfunctory. Neither argument morally justifies circumventing the consent process, although the practicalities may make true informed consent impossible. If each condition would only require a minute of explanation, consent might take more than an hour with expanded screening panels. Given the public health value of many of the conditions screened for, the goal of the consent process for newborn screening should not be to fully inform parents of each condition, but rather to inform parents of the general purpose of population health screening, which is to find individuals at risk for conditions for which early intervention reduces morbidity and mortality. For most parents, this explanation will be adequate. For parents who want additional information, pamphlets should be available, and referrals for more extensive counseling should be possible. In rare cases, parents will choose to opt out.

Given the low probability of a positive test, these parents should be counseled, but their refusals should be respected unless prohibited by state law (eg, Nebraska).

### Case 7

Tina is a 4-year-old new patient. Her parents are seeking to enroll her in school for the first time. You ask for Tina's immunization records, and her parents state that she has received no immunizations. They request that you write a school note excusing their daughter from vaccination based on religious beliefs. On further questioning, you discover that the parents do not really have a religious objection to immunizations but have refused immunizations because they have heard that these vaccines may cause seizures or autism.

### Discussion

Childhood immunization rates are among the 10 leading health indicators used to assess the health of the nation as part of the *Healthy People 2010* initiative, reflecting the high value placed on childhood immunizations. In the United States, childhood vaccinations for numerous infectious diseases are mandatory for entry into public schools and licensed child care facilities, although some private religious schools do not require them. Despite the success, the mandatory nature of immunizations represents a tension between individual autonomy and public health. Most states recognize a religious or philosophical exemption, although the courts have found that evaluating the sincerity, strength, and religious or philosophical nature of the refusals can be legitimate.

Parents refuse vaccinations for many reasons. For some parents, refusal is based on religious or philosophical beliefs; for others, it is based on fear of vaccine safety. In the 1970s, a report in *Archives of Disease of Childhood* suggested a connection between the whole-cell pertussis vaccine and neurologic damage in children. This finding was a major impetus to developing a safer acellular pertussis vaccine. In the late 1990s, fears arose over the measles-mumps-rubella (MMR) vaccine and its relationship to autism after the *Lancet* published a report of severe developmental regression in children by Wakefield and colleagues. The research team noted that the onset of symptoms occurred after MMR immunization, although they had not proved a causal link. In 2003, Simon Murch, one of Wakefield's collaborators, denounced assertions of a link between MMR and autism and declared the existence of "unequivocal evidence that MMR is not a risk factor for autism." In 2004, evidence revealed that Wakefield had concealed the fact that his research had been funded in part by the legal team seeking redress for parents who believed that their children had been injured by the MMR vaccine, and many of the original collaborators retracted their support for a link between autism and the MMR vaccine. However, it was not until 2010 that the *Lancet* fully retracted the manuscript, 1 week after the General Medical Council (UK) found Wakefield guilty of dishonesty and flouting ethics protocols. In addition, numerous medical studies, including a large Institute of Medicine review, have confirmed the lack of association between autism and the MMR vaccine.

In the United States, children who are undervaccinated are demographically different from children who

receive no vaccinations. Risk factors for being underimmunized include minority status, poverty, living in an urban area, living in a household with more than 3 children, and low maternal education. In contrast, children who have no vaccinations tend to be white children whose parents are married, older, and wealthier or children in religious communities whose parents have a religious objection to immunization. They often live in communities of like-minded families. The clustering of these families decreases herd immunity and makes these communities more susceptible to outbreaks. In September 2005, 4 children in an Amish community in Minnesota were found to have polio, a disease that had not been seen in the United States since 1979.

What should a pediatrician do when parents refuse recommended immunizations? Some pediatricians will discontinue care for such families. They claim that they cannot care for patients who do not trust their medical recommendations. In contrast to this approach, the AAP Committee on Bioethics recommends that the pediatrician should listen carefully and respectfully to the parents' concerns and to share honestly what is known about the risks and benefits of the vaccine in question and to correct any misconceptions and misinformation. They should explore the possibility that cost is a reason for refusal. Rather than dismiss the family, the AAP recommends that pediatricians take advantage of their ongoing relationship with the family and revisit the immunization discussion on subsequent visits. The AAP has also developed a form to document the parents' refusal.

If parents refuse immunizations for their children, then the pediatrician should document this refusal on the school form. In some states, this documentation is adequate for school entrance. In other states, parents may have to provide additional evidence as to the philosophical or religious nature of their objection.

### Case 8

Mr and Ms G come to the clinic with Gary, their 5-year-old son. Gary was adopted as a newborn. Mr and Ms G have told you they plan to tell Gary about his origins, but each time you ask, they give reasons why they have not yet done so. They have kept the adoption secret from all but their immediate family.

### Case 9

Mr and Ms S bring their 5-year-old child, Sam, for a well-child visit. The family has just moved from California. As you try to take a full medical history, the parents become visibly uncomfortable. Finally, Mr S takes Sam out of the room to play in the waiting room, at which time Ms S explains that they had infertility problems and used donor sperm and that Mr S is not Sam's genetic father. They have only sketchy information about the sperm donor, who was a 25-year-old healthy white medical student. They have chosen not to tell Sam about his genetic parentage.

### Discussion

Adoption is a legal procedure through which a permanent family is created for a child whose birth parents are unable, are unwilling, or are legally prohibited

from caring for their child. Adoption has existed throughout history, although the focus has changed. Historically, “adoption served the needs of adults . . . for the purpose of kinship, religion or the community,” in contrast to our current focus on the needs and well-being of the child.

In the United States, formal adoptions peaked in 1970 when about 175,000 adoptions occurred. Adoptions have decreased because of many social factors, including the decrease in the stigma of single mothers and the increased availability of abortion. Since 1987, the number of adoptions annually has remained relatively constant, ranging from 118,000 to 127,000. Despite the large number of children and families who are directly affected by adoption, the medical literature on adoption is scant.

Before World War II, professional adoption workers advised, if not insisted, that children be told of their adopted status for the pragmatic reason that learning of adoption from parents in a loving environment rather than by well-meaning or even malicious neighbors, schoolmates, or relatives was better for the child. After World War II, the professional community argued against disclosing. By the mid-1970s, the pendulum returned in favor not only of disclosing adoption but also of openness in all aspects of adoption. Nevertheless, some families still try to keep the adoption a secret.

Assisted reproductive technologies (ARTs) offer individuals another possible means to achieve parenthood (Chapter 81, Assisted Reproductive Technologies, Multiple Births, and Pregnancy Outcomes). ARTs have offered some new twists. Whereas adoption separated genetic and social parenthood, ARTs allow individuals to separate genetic, gestational, and social parenthood. For example, through in vitro fertilization, a woman can gestate a fetus who is the product of her husband’s sperm and a genetically unrelated egg donor whose identity is often unknown. More common are children born by the use of sperm donors, such as in the case of Sam. In the early days of donor insemination, the husband’s sperm was mixed with the donor’s sperm to leave open the possibility that the child was the genetic heir. Now, determination of paternity is widely available and accessible and makes this pretense obsolete. Although there was a lot of secrecy surrounding gamete donation, there has been a movement to encourage disclosure of gamete donors. Recently, the American Society for Reproductive Medicine has issued a statement encouraging the disclosure of gamete donation, and this trend is even greater in some other countries where openness is required by legislation. In most of the empirical studies to date, nondisclosure is common, but some studies are showing greater disclosure.

For Gary and Sam, the clinical value of knowing their correct genetic family history is that it may allow their health care providers to perform particular diagnostic measures or to counsel them about ways to minimize their genetic susceptibilities through particular lifestyle choices. As our understanding of genetics improves, emphasis on collecting family history information increases, and yet data suggest it may be highly inaccurate. Family history is growing

in importance because we understand that many illnesses have a genetic component; and yet, we are also learning that genotype frequently does not correlate with phenotype and that family history may or may not provide additional data.

Questions also arise as to whether children have a right to know their genetic inheritance, whether parents have a right to maintain secrecy, or both. The literature about the psychological risks of disclosure and nondisclosure is limited and inconclusive. Nevertheless, today most psychologists and psychiatrists support disclosure because of its role in health care screening, diagnosis, and treatment and the importance of genetic identity to one’s self-identity. Reasons to respect nondisclosure include the potential threat that such knowledge may pose to the parent–child relationship and the integrity of the family. Which reasons are stronger depends on how one weighs the advantages and disadvantages.

Although it might be argued that knowing their biologic identity is better for children, the physician’s right to interfere in interpersonal family dynamics is and should be limited to situations of clear-cut abuse or neglect; nondisclosure of biologic relationships does not rise to this level. Pediatricians should encourage disclosure in a developmentally appropriate manner and should discourage parents from *waiting until the right moment*. Parents can be referred to one study from the United Kingdom that queried adolescents and adults conceived through gamete donation and found that it was “less detrimental for children to be told about their donor conception at an early age.” The physician should encourage disclosure on the grounds that (1) secrecy may be detrimental to a trusting relationship between parents and children; (2) later discovery by the child may have an adverse effect on self-esteem; and (3) the child otherwise may learn of the genetic discrepancy in a less secure setting (eg, accidentally overhearing a relative). Nevertheless, physicians should not disclose this information to children without the parents’ permission.

### Case 10

Ms H brings her 17-year-old son Harold to the clinic for a preparticipation high school basketball physical examination. On taking the history, you learn that Harold’s father died from a heart condition last year at the age of 40 years. Harold’s uncle died in his late 20s when playing competitive tennis. You are concerned about the possibility of a familial cause of sudden death caused by a cardiac condition known as hypertrophic obstructive cardiomyopathy (HCM). You recommend either an echocardiogram or genetic testing to see whether Harold has HCM. Harold and his mother refuse. You then write on his school physical form that he is at risk for HCM and should not participate in school sports without a cardiac workup. Harold and his mother are quite angry. Harold is an all-state player and is being recruited heavily by many universities. The mother plans to take Harold to another physician and demands that you not inform his school or anyone else of your concerns. Harold and his mother do not disclose the family history to a



colleague in a practice across town, who approves him for interscholastic athletics.

### Discussion

HCM is an autosomal dominant condition that is usually asymptomatic in preadolescents. It is an idiopathic cause of cardiomyopathy, and the risk for sudden death, particularly during intense athletic activity, increases with age.

Harold is at risk for a life-threatening event that is exacerbated by physical activity. This diagnosis would make him ineligible for sports and take away his opportunity for a college sports scholarship. Of course, failure to diagnose this condition may result in premature death in a high school gymnasium. Competitive sports participation is clearly risky for Harold.

You try to convince Harold and his mother to have the echocardiogram. They acknowledge that he is at risk, but Harold states that basketball is his life, and he is willing to risk his life to play.

Harold and Ms H view the issue as one of autonomy. They understand the risks and benefits of playing, given Harold's possible cardiac condition, and they believe that playing basketball is better for Harold despite the risk for sudden death. They also view the issue as one of confidentiality. They ask that you not disclose to the school the family history that you discovered when interviewing Harold and his mother.

This case is one in which the parent and child are in consensus but in disagreement with the physician. The family's position for confidentiality and nondisclosure must be weighed against the physician's belief that he or she needs to protect this child from his mother and himself. Consensus guidelines state that adolescents with HCM should not participate in sports such as basketball. As a moral agent, the physician has an obligation to prevent a serious imminent risk for sudden death to a minor. Harold and his mother cannot relieve the physician of this obligation. The physician also has an obligation to protect the community. Imagine the reaction if Harold were allowed to play and he did die on the basketball court in front of many classmates and their families. Such an event might cause serious psychological trauma to the observers. How would the community respond if they knew that the physician might have prevented this event? The physician has an obligation to protect Harold and the community from such unnecessary trauma.

Harold's mother is correct that the physician must not breach confidentiality without the permission of the patient or parent. Instead, the physician should notify child protection about this unusual form of medical neglect, although whether child protective services would find the parent medically neglectful is not clear-cut given that the chance Harold has the gene is only 50%. They could require Harold to undergo testing if he wants to play sports. However, even if he has the gene, he is currently asymptomatic and his risk of having sudden cardiac death in the short term is low, but increases with age. Thus, the state will need to decide whether there is an imminent risk of death.

If the school were to be made aware (eg disclosure by child protective services), the school, in *loco parentis*, should prohibit Harold from playing basketball or other sports that may lead to his sudden death. This is true even after Harold turns 18 years of age.

### Case 11

Mr K brings Kevin for his prekindergarten examination, during which you notice some linear ecchymoses on his back. You ask Kevin how he got them, and he answers that his father beat him for talking back at dinner last night. Kevin's father confirms this explanation, explaining that he believes that corporal punishment is effective. He admits to using a belt because his hand "did not produce the desired effect." You inform the family that corporal punishment that leaves marks is abusive and that you plan to report your suspicions of child abuse to the department of family services. The father is irate, arguing that discipline is a family matter and that his religious faith supports his convictions of *spare the rod and spoil the child*.

### Discussion

An AAP policy statement on guidance for effective discipline begins by noting that "parents often ask pediatricians for advice about the provision of appropriate and effective discipline." The most controversial aspect of this issue is the role, if any, for corporal punishment. Although a recent survey of AAP members found that about 85% of respondents generally or completely opposed the use of corporal punishment, more than 90% of American families report having used spanking as a means of discipline at some time. And data show that children learn what they live: adults who reported corporal punishment as a child were more likely to use it with their own children. In contrast, corporal punishment is being abolished in many countries by statute on the basis that it violates the rights of the child.

Kevin's father raises the point that his actions are based on his religious beliefs. Some religious groups take a strong position in support of corporal punishment. Currently, religious exemptions to most of the child abuse and neglect statutes can be found, but the exemptions do not apply to corporal punishment, nor should they. The religious exemptions were written to protect parents who sought prayer-based therapy for their child rather than allopathic medical care; they were not meant to protect a parent from being charged with abuse for beating a child.

To examine the benefits and burdens of corporal punishment, the AAP cosponsored a consensus conference on this topic in February 1996. The conference concluded with 13 consensus statements that addressed the role of spanking and corporal punishment in parental discipline. Statement No. 6 comments on the lack of data on the effectiveness of spanking in general, and Statement No. 8 comments that the data show corporal punishment to be ineffective in older children and adolescents and "associated with increased risk for dysfunction and aggression later in life." The strongest statement against corporal punishment was Statement No. 12, which states that

“concerning forms of corporal punishment more severe than spanking, the data suggest that the risk for psychological or physical harm outweigh any potential benefits.” More recent data show that even nonabusive corporal punishment is associated with increased aggressive behavior and delinquency in children.

Despite common use and acceptance of corporal punishment, the data show that, over time, spanking is a less effective strategy than noncorporal methods for reducing undesired behavior. Furthermore, this type of punishment becomes less effective with continued use. The AAP recommends that parents “be encouraged and assisted in developing methods other than spanking in response to undesired behavior.” The AAP mentions both the *time-out* method and the removal of privileges as “two common discipline approaches that have been associated with reducing undesired behavior.” The AAP statement noted further that many parents go beyond spanking and use an object or other forms of unacceptable corporal punishment: “When punishment fails, parents who rely on it tend to increase the intensity of its use rather than to change strategies.” This action is no longer discipline but child abuse.

Pediatricians should help parents understand the facts about corporal punishment and to realize that any such punishment (beyond an occasional mild spanking) is unacceptable and will be reported. No morally justifiable reason exists for a parent to inflict physical harm on a child. Although physical manifestations of violence are an imperfect measure of the severity of punishment, they at least define an unacceptable threshold. The marks on Kevin are a sign that his father used more physical force than is morally acceptable. Reporting to child protective services may be necessary. The physician must work with this family to modify their discipline strategy.

### Case 12

Mr and Mrs R call you to arrange a prenatal visit. They have a healthy 2-year-old daughter who was born by cesarean delivery weighing 8 pounds 5 ounces. The couple explains that they were very dissatisfied with their care because they had wanted a natural childbirth. They tell you that their nurse midwife “panicked” after 18 hours of labor and that they were forced into having an unwanted cesarean delivery. They have decided to have their second child at home with a lay midwife. They ask if you would be willing to be “on call” for the home birth, in case any complications arise. On further questioning, Mrs R is clearly well versed in the risks and benefits of vaginal birth after cesarean delivery (VBAC). She states that she lives within a 10-minute drive of a major hospital and will go there if things are “not going well.” You argue that the additional time may risk her health and the health of the fetus. You tell her that VBAC is associated with uterine rupture and that this event might lead to death for both Mrs R and her baby. She says she understands but is determined to proceed with the home birth.

### Discussion

In 2006, there were 38,568 out-of-hospital births in the United States, including 24,970 home births and

10,781 births occurring in a freestanding birthing center. A review article in 2010 noted that the benefits of home birth are fewer cesarean or operative vaginal deliveries, episiotomies, infections, and third- and fourth-degree lacerations. The major concern about home deliveries is that they may be associated with excess perinatal and neonatal mortality, particularly among nonanomalous term infants. The American College of Obstetricians and Gynecologists (ACOG) strongly opposes the practice. In many other countries, however, professional obstetric societies have endorsed home birth for low-risk pregnancies.

VBAC is a more risky event than a typical vaginal delivery and is associated with more risks than a repeat cesarean delivery. The risk for uterine rupture is 0.7%, and the risk for hypoxic-ischemic encephalopathy is also increased (absolute risk, 0.46 per 1,000 women at term undergoing a trial of labor). An ACOG practice bulletin states that good and consistent scientific evidence indicates that most women with 1 previous cesarean delivery are candidates for attempting VBAC. However, because uterine rupture may be catastrophic, ACOG recommended that VBAC be attempted only in institutions equipped to respond to emergencies.

Clearly, Mrs R’s decision to attempt a VBAC at home is against the ACOG recommendations and is risky for both Mrs R and her fetus. It is not what you would recommend. Informing the parents that you believe that their action is placing Mrs R and the fetus at risk for harm is morally obligatory. The pediatrician should recommend in-hospital delivery for the sake of both the child and the pregnant woman. In the end, however, Mrs R has and should have broad autonomy with respect to her obstetric decisions, and many of these are beyond the purview of the pediatrician.

At the same time, physicians have a right to refuse to participate in treatment that goes against their moral conscience. Refusing to participate in home births would be morally acceptable for physicians. The parents should be given as much information as possible about the risks of uterine rupture and the danger signs. They should be informed about appropriate medical interventions for the newborn, including vitamin K, newborn screening, and hepatitis immunizations. Alternatively, the pediatrician may decide to participate out of concern for the best interest of the newborn. Needless to say, pediatricians should carefully document all discussions about risks and their strong recommendations against home birth. Physicians may want to discuss their decisions with legal or risk-management personnel before participating.

Whether you participate in the home birth or not, Mr and Mrs R may still ask if you are willing to be the pediatrician of their children. The authors of this chapter encourage pediatricians to accept such families into their practices so as to be in a position to advocate for the medical needs of these children. The children will suffer if the medical community abandons them because of their parents’ beliefs and

lifestyles. Whether pediatricians agree or do not agree with their parents' obstetric decision, the live newborn and siblings need a medical home.

## CONCLUSION

In the medical care of children, ethical conflicts can develop within the family and between the pediatrician and the family, or the pediatrician and family may be in conflict with the state. The preceding cases represent different health care scenarios that will be familiar to everyone who is involved in the primary health care of children. In each case, we consider the range of morally permissible resolutions and propose a stepwise ethical approach to resolve the conflict. The first and most important step is in-depth discussion among physicians, parents, and children to try to understand why people hold the beliefs that they do. Physicians should be open-minded and willing to compromise, up to a point. The second important consideration is some assessment of the benefits and the burdens of the proposed treatment or action and of the available alternatives. Generally, parents have both the legal responsibility and the moral authority to make medical decisions for their children. The pediatrician's respect for the child's opinion should increase as the child grows older, acquires increased capacity to understand and make decisions, and approaches the age of legal majority. In all of the previously mentioned situations, pediatricians must balance their own assessments of what is best for the child with an understanding that children benefit from interacting with their families in an environment that is safe from third-party intrusion. Pediatricians also must remember that their expertise is in deciding what is medically best for a child, whereas parental decisions need to reflect what is best for the child overall, balanced by the parents' right, privilege, and responsibility to preserve their cultural, social, and moral values.

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## Chapter 12

# EMERGENCY CARE

Karen S. Frush, MD

### INTRODUCTION

Pediatricians and other physicians who care for children deliver a variety of services to children and their families, including preventive care, such as immunizations and anticipatory guidance; acute or urgent care at the time of mild or moderate illness or trauma; and, occasionally, emergent care and stabilization of children with possibly life-threatening illnesses or injuries. When a true emergency happens (Box 12-1), pediatricians as well as nonphysician clinicians must be prepared to stabilize the child, rapidly access the emergency medical services (EMS) system for transport to a higher level of care, support the parents and family, communicate with the receiving team in the emergency department (ED), and continue to care for the other children and families in the office at the same time. To perform all these tasks successfully, pediatric office teams must have current training and skills, appropriate equipment and medications, and protocols that help guide each team member with a specific role at the time of the emergency.

### PEDIATRIC EMERGENCIES IN THE OFFICE

A number of studies describe the frequency and types of pediatric emergencies that occur in office-based practices. Office-based emergencies involving children have been reported to occur between 2 and 22 times per office per month. Klig and O'Malley suggest that the actual number of emergencies depends on the location and characteristics of the practice. Nearly 65% of pediatricians and family physicians who practice in urban settings reported that they care for at least 1 child who requires hospitalization or urgent care each week, and 80% had cared for at least 1 severely ill patient in the past 3 months. In another study, 51 pediatric offices in a suburban county in the Northeast reported more than 2,400 life-threatening emergencies per year, and 16% of office practices reported 1 to 2 incidents of cardiac arrests per year.

#### BOX 12-1 Office Emergency

A 9-month-old infant has had a fever, vomiting, and diarrhea for 2 days. The infant was brought to the office today because the mother was having difficulty waking her up. The mother reports that the infant has been sleeping all morning and would not take a bottle. The mother appears very concerned and frightened as she gives this information to the receptionist.

The types of emergency seen in an office vary as well, depending on factors such as the number of children in the practice with chronic illness and special needs, the location of the practice (eg, urban, rural), and the proximity of the practice to the nearest ED. The most common types of office emergency are respiratory emergencies (asthma and obstructed airway), seizures, infections in young infants (including meningitis), shock due to diabetic ketoacidosis (DKA) and dehydration, and head trauma. Pediatricians and other physicians may be required to stabilize children with these conditions in the office and to provide urgent or emergent care at least until the arrival of EMS or local emergency care personnel. The consequences of being unprepared can be devastating; therefore, adequate stabilization and timely transfer to an appropriate facility for definitive care are important responsibilities of every pediatrician and other physician caring for children.

### Emergency Response in the Office Setting

Optimal responses to office emergencies require consideration of a range of issues, including the knowledge and skills of the office team, effectiveness of office triage practices and documentation, availability of emergency equipment and medications, and accessibility of resources outside the office, such as the local EMS and ED or pediatric care center. Completion of an office-based self assessment survey is a good first step toward enhancing overall preparedness for pediatric emergencies. One example of such an assessment is shown in Box 12-2.

### Preparing the Office and the Team

Good resuscitation knowledge and skills are essential to the delivery of safe, high-quality emergency care to children, but no individual physician or nonphysician clinician can provide adequate care alone. A high-functioning team is required, and each member of the team must be familiar with his or her role at the time of an emergency. For example, the first person to assess children arriving in the office is often the least medically trained employee—the secretary or receptionist. Because the outcomes of children requiring stabilization depend on early recognition of shock and respiratory distress, it is imperative that the front-line team members know what signs and symptoms to look for and how to summon help when they encounter an emergent situation. Nonclinical office staff can be taught about findings that may signal an emergency in a child, such as labored breathing, cyanosis, audible stridor or wheezing, grunting or flaring, depressed mental status, and uncontrolled bleeding.

When an emergency is recognized, a clear response plan should be in place that facilitates notification of the whole team and clarifies the role of each member of the office staff. For example, one individual should be designated to access EMS, and this person should be knowledgeable about the capabilities and level of response provided by the local EMS agency. Cue cards can be posted by the telephone to assist staff in accessing emergency help and providing appropriate information.

Physicians, nurses, and other clinicians in the office should have preassigned roles on the resuscitation



### BOX 12-2 Questions to Guide Office Preparedness

1. Have you ever experienced emergencies in your office setting? What were they, and how often have they occurred?
2. What is your office setting (freestanding office, clinic based, health center based, hospital based, other)? Are there resources on site but outside of your office that you could call on during an office emergency (security, other medical or dental professionals in the same building, hospital code team)?
3. What is the emergency readiness of the staff present during those times? Include any training in:
  - First aid and cardiopulmonary resuscitation (CPR)
  - Basic life support (BLS) or advanced life support (ALS)
  - Pediatric advanced life support (PALS)
  - Advanced pediatric life support (APLS)
  - Emergency nurse pediatric course (ENPC)
  - Other continuing medical education (CME)
4. Have nonclinical staff been trained to recognize a potential or actual emergency?
5. Do all staff know how to access the EMS system? Are staff able to give the location of and directions to the office, level of clinical staff present, age and condition of the child (including vital signs if appropriate), desired transport location, and the level of emergency response required (eg, first response, BLS, or ALS)?
6. Have your local EMS providers ever been to visit your office for a nonemergency call or to receive experience in evaluating pediatric patients?
7. What level of provider comes when you call 911: first responder (ie, police or fire department), BLS (basic level EMTs), ALS (paramedics)? Does your local EMS have the necessary equipment and expertise to manage children?

From Massachusetts EMSC Task Force. *Office Preparedness for Pediatric Emergencies*. O'Malley P, ed. 2nd ed. Boston, MA: Massachusetts Department of Public Health; 2002.

team. The physician is usually the leader of the team (runs the code), providing medical direction. The office nurse may assist with procedures and draw up and administer medications or fluids. A clinical aide may assist the care providers, perform chest compressions, help gather equipment and supplies, and comfort the parents and family. The office secretary or receptionist may activate EMS, provide information to patients and families in the waiting room, and record events, as directed, during the stabilization event. To fulfill these roles, each office employee must be adequately trained and have an opportunity to practice his or her roles before an emergency occurs (see Maintaining Readiness/Mock Codes).

The American Academy of Pediatrics (AAP) recommends that all certified pediatric providers (including physicians, nurses, and physician assistants) have basic life support (BLS) training, and a more advanced level of training is encouraged for physicians who practice in settings without ready access to local EMS advanced life support (ALS) services. BLS, Pediatric

Advanced Life Support (PALS), and Advanced Pediatric Life Support (APLS) courses are available through many hospitals, EMS systems, and state and local professional organizations. Additionally, online certification and recertification courses are available for physicians and other nonphysician clinicians, and many of these offer continuing education credits along with course certification.

## EQUIPMENT AND MEDICATIONS

The clinical team must have immediate access to appropriate equipment and medications to use at the time of an emergency. A child struggling to breathe should have the necessary adjuncts immediately available (ie, a suction catheter when a child vomits and begins to aspirate, or an appropriate-sized mask and self-inflating bag when positive pressure ventilation is required). Equipment and medications can be stored in a resuscitation room where the child is taken to be stabilized; alternatively, the equipment and drugs can be stored in a bag or mobile storage system that can be quickly and easily transported to the site of the stabilization event. Whatever the system in a particular office, all office staff members need to know where resuscitation equipment and medications are located so that no time is wasted in finding them during an emergency.

Pediatricians and other physicians sometimes ask what equipment is required in the office setting. To answer this question, one should consider the population of children being cared for in the office (eg, a large number of children with special needs who might require replacement of a tracheostomy tube or gastrostomy tube) and the proximity to a higher level of care. As an example, for clinicians who practice in an office located in or near a hospital, basic airway equipment may be all that is needed. However, for practices and offices that have prolonged emergency response times, stabilization efforts may need to be maintained for up to 30 minutes before EMS personnel arrive with equipment and stabilization skills. In these offices, more equipment is required to manage an airway and to initiate treatment of shock.

The use of a clinical tool or system to help physicians rapidly determine the appropriate size of equipment and the correct dose of medication is encouraged in the office setting. One such tool, the Broselow pediatric resuscitation tape, has been used in many EDs, EMS services, and offices across the country. Studies have shown that the proper use of the Broselow tape can help decrease the frequency of medication dosing errors and the time it takes to administer medications during an emergency.

Charts or manuals with equipment size and medication dosing (including dose in mg/kg, drug formulation, and volume to administer) organized by patient weight are sometimes available through local hospital EDs, pediatric departments, or pediatric centers, and these resources may be useful to physicians in an office or clinic setting. The AAP Committee on Pediatric Emergency Medicine has provided lists of recommended equipment (Table 12-1) and medications (Table 12-2) for office emergencies.

**Table 12-1** Recommended Equipment for Pediatric Office Emergencies

OFFICE EMERGENCY EQUIPMENT AND SUPPLIES	PRIORITY
<b>AIRWAY MANAGEMENT</b>	
Oxygen delivery system	E
Bag-valve-mask (450 and 1,000 mL)	E
Clear oxygen masks, breather and nonrebreather, with reservoirs (infant, child, adult)	E
Suction device, tonsil tip, bulb syringe	E
Nebulizer (or metered-dose inhaler with spacer/mask)	E
Oropharyngeal airways (sizes 00–5)	E
Pulse oximeter	E
Nasopharyngeal airways (sizes 12–30F)	S
Magill forceps (pediatric, adult)	S
Suction catheters (sizes 5–16F) and Yankauer suction tip	S
Nasogastric tubes (sizes 6–14F)	S
Laryngoscope handle (pediatric, adult) with extra batteries, bulbs	S
Laryngoscope blades (0–2 straight and 2–3 curved)	S
Endotracheal tubes (uncuffed, 2.5–5.5; cuffed, 6.0–8.0)	S
Stylets (pediatric, adult)	S
Esophageal intubation detector or end-tidal carbon dioxide detector	S
<b>VASCULAR ACCESS AND FLUID MANAGEMENT</b>	
Butterfly needles (19–25 gauge)	S
Catheter-over-needle device (14–24 gauge)	S
Arm boards, tape, tourniquet	S
Intraosseous needles (16 and 18 gauge)	S
Intravenous tubing, microdrip	S
<b>MISCELLANEOUS EQUIPMENT AND SUPPLIES</b>	
Color-coded tape or preprinted drug doses	E
Cardiac arrest board/backboard	E
Sphygmomanometer (infant, child, adult, thigh cuffs)	E
Splints, sterile dressings	E
Automated external defibrillator with pediatric capabilities	S
Spot glucose test	S
Stiff neck collars (small/large)	S
Heating source (overhead warmer/infrared lamp)	S

E, essential; S, strongly suggested (essential if EMS response time is more than 10 minutes).

Adapted from American Academy of Pediatrics Committee on Pediatric Emergency Medicine. *Emergency Medical Services for Children: The Role of the Primary Care Provider*. Singer J, Ludwig S, eds. Elk Grove Village, IL: American Academy of Pediatrics; 1992.

### Documentation

Complete and accurate documentation of stabilization efforts in the office is vital for ongoing care, especially at the time of transfer to the ED.

Emergency situations are often difficult to document properly for numerous reasons: stress levels are high, many times there are not enough employees in the office to manage all the tasks, and children and families in the waiting room cannot be ignored. However, every effort should be made to document the date and time of treatment, the estimated or actual weight of the child, medications given with dosages and response noted, fluid types and volumes given, information or explanations given to the family, and the condition of the child at the time of departure from the office. A resuscitation log can serve as a checklist for office staff, and one copy can be sent with the transport team while another copy is kept in the office to refer to during review and debriefing of the event. Sending information about the patient's medical history, including a problem list and a medication list, is also helpful to ED staff.

### Emergency Medical Services for Children

Based on military experiences that demonstrated improved survival rates of soldiers stabilized in the field and transported to a well-equipped emergency facility, the EMS system in the United States was formally established in the early 1970s through the EMS Systems Act of 1973. Focused primarily on the needs of adults with life-threatening injuries and medical conditions, the EMS system lacked specific protocols, equipment, and training for providing optimal care in pediatric emergencies. In 1984, the EMS for Children (EMS-C) program was established to ensure that all children and adolescents receive appropriate care at the time of an emergency. The AAP has worked closely with the EMS-C program since its inception to support pediatric emergency care efforts and establish a close collaboration among pediatricians and nonphysician clinicians caring for children.

When a child is brought to the pediatrician's office with a serious illness or injury, the office becomes the entry point to the EMS-C system. The pediatrician and office staff, no matter how well prepared, often need

**Table 12-2** Office Emergency Drugs

MEDICATIONS	PRIORITY
<b>DRUGS</b>	
Oxygen	E
Albuterol for inhalation*	E
Epinephrine (1:1,000)	E
Epinephrine autoinjectors	E
Activated charcoal	S
Antibiotics	S
Anticonvulsant agents (diazepam, lorazepam)	S
Corticosteroids (parenteral/oral)	S
Dextrose (25%)	S
Diazepam, rectal	E
Diphenhydramine (parenteral, 50 mg/mL)	S
Epinephrine (1:10,000)	S
Atropine sulfate (0.1 mg/mL)	E
Midazolam, nasal	E
Naloxone (0.4 mg/mL)	S
Sodium bicarbonate (4.2%)	S
Supplies for reconstituting parenteral antibiotics	E
<b>FLUIDS</b>	
Normal saline solution or lactated Ringer solution (500-mL bags)	S
5% Dextrose, 0.45 normal saline (500-mL bags)	S

E, essential; S, strongly suggested (essential if EMS response time is more than 10 minutes).

\*Metered-dose inhaler with spacer or mask may be substituted.

Adapted from American Academy of Pediatrics Committee on Pediatric Emergency Medicine. *Emergency Medical Services for Children: The Role of the Primary Care Provider*. Singer J, Ludwig S, eds. Elk Grove Village, IL: American Academy of Pediatrics; 1992.

help from community members of the emergency care team. EMS personnel can provide vital support and assistance to the office team during stabilization in the office and ongoing care during transport to the ED. EMS personnel who respond to pediatric emergencies may include professionals with BLS or ALS training. First responders can offer essential BLS skills and transport, whereas ALS emergency medical technicians, acting under medical control and advanced protocols, can perform advanced airway management techniques, including positive pressure ventilation and placing airway adjuncts. They can also establish intravenous or intraosseous access, administer intravenous or nebulized medications, defibrillate, and perform other advanced techniques in accordance with local protocols. In most cases, EMS response to an office emergency will require the deployment of an ALS unit.

Pediatricians should educate patients and families about the emergency response system and teach parents how to recognize an emergency, respond appropriately in terms of first aid, and access the EMS system. Children with serious medical conditions or injuries should not be taken by the family car, taxi cab, or bus to the pediatrician's office, or even to the ED,

although parents may sometimes feel this would be faster than waiting for an ambulance. Safe transport requires the presence of trained emergency personnel with the skills and equipment needed to initiate appropriate care at the scene. Similarly, critically ill or injured children should not be sent from the pediatric office to the ED by any form of transport other than EMS. Optimal transport requires trained personnel who can maintain stabilization efforts that were begun in the office.

Deterioration or death of the child during transport without adequate equipment and personnel is the responsibility of the sending physician when nonmedical means of transportation are used, and the benefit of trained personnel and proper equipment during transport outweighs the risk of waiting for EMS personnel to arrive.

### Maintaining Readiness/Mock Codes

Full pediatric cardiopulmonary arrest is, fortunately, an extremely rare event in the office setting. Most office emergencies are severe presentations of common pediatric illnesses and diseases, such as asthma, bronchiolitis, DKA, dehydration, head injury, poisoning, or seizures. All of these disorders can become life threatening if not managed appropriately and swiftly in the office.

In any emergency, the ABCs (airway, breathing, circulation) must be addressed immediately. The sooner BLS and ALS maneuvers are initiated, the greater the chance for complete recovery. However, the knowledge and skills required at the time of an emergency are not among those that the pediatrician uses often. The best way to ensure readiness is to practice regularly in the office setting, with as many staff members as possible participating. Simulated exercises, or mock codes, provide a good opportunity for office staff to rehearse for an emergency. High-fidelity simulation with expensive mannequins is not required; indeed, a plastic baby doll can suffice for low-fidelity scenarios. To make the practice sessions more realistic, the scenario should be familiar to office staff (perhaps based on a real event that occurred in the office), and participants should be encouraged to act out each step of the resuscitation. For example, a "parent" comes to the reception area, holding an "infant" (mannequin) and complaining that the infant will not wake up. The receptionist would then need to activate the emergency response system designed for the office, and the nurse would respond as he or she would in a real emergency, perhaps by taking the infant to a treatment room.

Clinical staff should be required to locate specific pieces of equipment that might be needed and demonstrate use of devices (eg, connecting tubing from the oxygen tank to the bag-valve-mask device and demonstrating proper bagging technique). The physical act of locating and handling equipment can help prepare staff to perform these tasks when a true emergency occurs. Team members can offer observations of their own and others' performances, and specific improvement plans can be developed. Studies of mock codes in the office setting have demonstrated that these exercises can lead to enhanced readiness for pediatric

emergencies. It is also important to check the expiration dates of the drugs used for emergencies during the simulation exercises and replace those that have expired.

## SUMMARY

Pediatricians provide the services and support necessary for comprehensive health care, ranging from prevention of illness and injury to acute care services and management of chronic disease to critical care and rehabilitation following serious illness or injury. When a child is brought to the office with potentially life-threatening illness or injuries, the office staff must be prepared to provide swift, effective care to ensure the best possible outcome. Delivering optimal care requires coordination and collaboration with emergency care providers in the community and facilitating a safe transition from the office to a higher level of care. By considering these strategies and implementing a plan to improve office preparedness, pediatricians can greatly influence the outcome of an emergency and offer the best chance of intact survival to each child and family.

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## TOOLS FOR PRACTICE

### Medical Decision Support

- *APLS: The Pediatric Emergency Medicine Resource* (Web site), American Academy of Pediatrics, American College of Emergency Physicians, Jones & Bartlett Learning ([www.aplsonline.com](http://www.aplsonline.com))
- *Pediatric Office Emergencies* (article), *Pediatric Clinics of North America*, Vol 60, Issue 5, 2013

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## PART 2

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# Principles of Care

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## SECTION ONE

# Pediatric Assessment

### Chapter 13

## PEDIATRIC HISTORY: ASSESSING THE CHILD

William E. Boyle, MD

*“A good history carefully obtained from an intelligent mother puts the physician in possession of a fund of information about the patient which is of greatest value, not only in arriving at a diagnosis in the illness for which he is consulted, but is exceedingly helpful in the future management of the child.”*

L. EMMETT HOLT, 1908

*Note: Histories may be taken by a variety of persons, including students, residents, nonphysician clinicians (PNPs and PAs), and physicians. For the sake of clarity and brevity, the term “physician” will be used throughout this chapter.*

This chapter covers the general interview of a child or family. Specific history taking for adolescents is covered in Chapter 119, Interviewing Adolescents. Specific assessment of the social environment and taking a mental health history are covered in Chapter 14, Pediatric History: Assessing the Social Environment, and Chapter 15, Pediatric History: Assessing Functioning and Mental Health, respectively.

A history is a story told by the patient or the patient’s family. It is a unique and personal story in which are embedded the words, phrases, and clues that direct the physician to the general or specific medical concern or problem. The patient or family brings complaints of illness, which the pediatrician must translate into medical theories of disease. Care must be taken so that nothing is lost in translating this personal story into a precise disease entity. It requires the physician to listen to this detailed sequence of events and, through careful direct questioning, to formulate a differential diagnosis. Parents and patients hope the physician will hear their story and interpret it correctly. This task is not easy.

Perhaps in no other medical field is a history as important as it is in pediatrics. Early detection of problems related to health—including growth, development, and nutrition—and prevention of future difficulties relies on the pediatrician’s thorough knowledge of the child and the family, including their lifestyle, cultural beliefs, and environment. Unlike most other areas of medicine, the pediatric history may be

given by someone other than the patient. Thus, a certain amount of subjectivity and objectivity are lost. Signs and symptoms are filtered through parental perspectives before emerging as historical data, and these perspectives are influenced by parental hopes and fears. A pediatric history is a compilation of information gathered in a variety of ways through interviews, direct observations, questionnaires, and medical records that usually provides a concise record of the child and the family.

In the past, training in interviewing and history taking took place for an acute problem in which the concern or complaint was readily stated or easily seen. Today, however, children and adolescents are seen for an increasing number of problems outside of the hospital. These may include learning difficulties, chronic or disabling conditions, or behavioral or developmental concerns, all of which require sensitive, insightful listening. The pediatrician must have a thorough knowledge of the child’s health status, developmental stage, and cognitive level, as well as the family’s functional characteristics, belief systems, and socioeconomic circumstances. Much of pediatrics deals with vague questions or concerns such as “Why does she cry so much?” “Why is he so thin?” or “Is that cough serious?” These concerns must be answered and expectations managed if the encounter is to be fruitful. If the parent or patient and physician have different perceptions of the problem, then the physician must attempt to tease out and understand the patient’s or the parent’s concerns. The parent or patient may be worried about something tangential to the chief complaint; this situation is sometimes referred to as the *second diagnosis*.

Children and their families are diverse, and they bring with them a wide variety of cultural beliefs and customs. Physicians must be aware that their own belief systems may differ from those of the patient and family and try to make accommodations. Questions should be asked about what the family thinks caused the illness or condition and what treatments were attempted before seeing the physician. By understanding the patient and family’s perception of the illness or condition, the physician can develop expectations of treatment and outcomes.

Much transpires during the initial interview between a pediatrician and a family other than the gathering of a history. The tone of all future encounters is established, and, ideally, the family begins to develop a trusting, confident relationship with the pediatrician. Just as the pediatrician is trying to assess the problem at hand, so too are the parents (and child) *sizing up* the clinician. A warm, friendly, nonjudgmental, courteous manner facilitates a good relationship. Taking a history requires some degree of decision-making on the part of the interviewer as

to what is relevant. Taking a history is not merely gathering a list of all symptoms and pertinent historical *negatives*; it involves the synthesis of various facts, attitudes, and observations. To perform this task well requires experience, tact, and a degree of intuition. The task is difficult. A history is compiled best if, for each visit, the pediatrician can obtain the answers to 3 questions:

1. “Why did you come today?”
2. “What are you worried about most?”
3. “Why does that worry you?”

Answers to these questions not only direct further inquiry, but also provide clues to parent and patient concerns that need to be allayed or dealt with directly during the visit and, perhaps, thereafter. For example, a parent who brings a child to a physician because of swollen cervical lymph nodes may be worried that they have a malignancy because an aunt who died of Hodgkin disease had the same problem. Parents, older children, and adolescents need to be told what symptoms and signs do *not* represent, as well as what they do represent, especially if they are worried that the symptoms and signs indicate a serious or fatal illness.

## SETTING AND AMBIANCE

Pediatric histories are taken in a variety of locations, and a comfortable environment enhances communication. If the physician is courteous, interested, and helpful, then a trusting, positive relationship is likely to develop. Patients and parents are acutely aware of what the physician thinks of them or what they perceive the physician’s opinion of them to be; this perception is termed the *reflexive self-concept*. (“The doctor thinks I’m a good parent.”) If the reflexive self-concept is high, then parent (or patient) satisfaction and compliance with recommendations for management are more likely to be high. Some questions to consider are:

- Does the pediatrician imply disinterest in the patient by cutting short the parent’s description or allowing constant interruptions during the history taking?
- Is privacy ensured?
- Are children made comfortable?
- Is there a place for clothing and belongings (other than a lap)?

Obviously, seating should be available for all, and the history taker should remain seated for the session. The pediatrician should strive to maintain eye contact and not constantly view a computer screen or notes. Parents or guardians should be called by their formal names (Mrs. Williams, Mr. Adams), unless a personal relationship has been established that enables the use of first names. Children should be referred to by their first names rather than *he*, *she*, or *the infant*. Notes can be taken as long as doing so does not distract from the continuity or spontaneity of the interview. Most parents find that coping with more than one child is disruptive and distracting; therefore, seeing more than one child at a time should be discouraged. Toys or books should be available to help occupy infants and toddlers, if necessary.

Clothing and appearance may affect the ease with which a relationship is established. Parents and children view a visit to the pediatrician as a special occasion and frequently dress accordingly. They hope their physician will view the visit in the same manner. The

physician’s dress should be appropriate and consistent with local norms. Most pediatricians do not wear a white coat because it may evoke fearful memories for the child, although this notion has never been substantiated. Whatever the attire, a sense of competence must be conveyed.

## TYPES OF INTERVIEWS

The initial history may be taken during an interview with the parents before their infant’s birth, in the hospital after the birth, in the physician’s office during the visit for whatever reason, in an emergency department at the time of an acute illness, or in a hospital room after admission for a specific illness or elective surgery. The time devoted to the initial interview and the amount of information gathered depend on the circumstances. Similarly, subsequent history taking will vary in depth and breadth, depending on the reason for the visit and the amount of time that has elapsed since the last visit.

This chapter focuses on the information to be gathered and the techniques used in obtaining the comprehensive pediatric history. Circumstances may preclude completion of this exercise during the initial visit. For example, the initial history obtained for a child who has acute otitis media and who is squeezed in during fully scheduled office hours will be brief and relate primarily to the chief complaint. The rest of the history can be obtained during a scheduled follow-up visit.

### Prenatal Interview

Ideally, the parents should have their first encounter with a pediatrician before their infant is born. To many people, the idea of bringing an infant in utero to the pediatrician seems strange, but much information can be gathered at this time, and a strong, understanding relationship between the parents and the pediatrician can be fostered. Furthermore, some issues can be addressed before the postpartum period. For example, a pregnant woman with little psychosocial support may be identified and appropriate aid offered. In addition, society in the United States is mobile; most young couples live alone and are often far removed from parents and siblings, and they often turn to professionals for support and assistance.

Obstetricians traditionally care for women only throughout pregnancy and the immediate postpartum period. Pediatricians traditionally assume care of the infant at birth. Many women find difficulty in leaving someone who has supported them through a difficult psychobiologic change and developing a new relationship while they learn the new role of motherhood. A prenatal interview can greatly assist in this transition.

Prenatal interviews do not need to be long or detailed; 20 to 30 minutes should suffice. In addition to gathering facts, the pediatrician should set a tone for future encounters. Prospective parents should be interviewed together, if possible, so that parental concerns can be aired, and they can be helped to support each other. Parents are anxious about their adequacy and the health of their unborn infant, and a supportive attitude and tacit acknowledgment that these fears are understandable can be helpful.



A thorough family history is a way of showing concern, not just for the child but also for the entire family. Parents should understand the physician's interest in them as individuals and not merely as Teddy's or Sarah Jane's mother and father. The prenatal interview provides an excellent opportunity to inquire about belief systems and cultural values.

During a typical prenatal interview, plans for labor and delivery should be discussed, as well as a program of childbirth education and the type of infant feeding that is contemplated, indicating the many advantages of breastfeeding. Pointing out certain safety issues to which the parents should attend is wise at this time, before their infant comes home, such as obtaining a child safety seat and a smoke detector and setting the hot water heater at a safe temperature (see Chapter 42, Safety and Injury Prevention). Also, the pediatrician should ask about the age of the home and if there may be a risk for exposure to lead, which should be eliminated. Many couples will already know the sex of their unborn child through prenatal ultrasound. Circumcision should be discussed, if they know they are having a boy. If blood tests (newborn screening), immunizations (for hepatitis B virus), or vitamin K administration will be performed, then these subjects should be described and discussed.

The mother's blood type, medications taken, and rubella and HIV status (if known) should be elicited. Genetic information should be gathered about both sets of grandparents. In addition to inherited disorders and birth defects, familial tendencies such as obesity, hypertension, and short stature should be investigated. Asking what the couple's own parents were like is also wise because parenting techniques and cultural beliefs are frequently passed from one generation to the next. Parents should also be encouraged to update their Tdap and influenza immunizations as appropriate.

After dealing with the family history, the physician needs to gather some information about other supportive individuals. Who will help out when the infant comes home? Who will be the main caregiver? Will the father have a paternity leave of some sort? Will the mother be returning to work? if so, when? Who will be caring for their infant? Grandparents traditionally visit shortly after delivery, and the pediatrician should point this out and ask if they will be helpful or a burden. The pediatrician should also inquire if transportation and a telephone are readily available. The physician should be alert at all times for evidence of undue stress, isolation, and prior psychosocial issues such as maternal depression or drug abuse because these factors are known to be predictors of poor parenting. The parents will want to know when the pediatrician will see the infant in the hospital, what the appointment schedule will be, and how the pediatrician can be reached. Fees and payment options for visits can also be discussed at this time.

The parents should be allowed to ask questions about their concerns. Cultural beliefs and values should be explored. Supporting their instincts, rather than directing and showing the pediatrician's own personal bias, is best. The pediatrician should anticipate certain normal variations such as sleepy infants,

the postpartum "blues," and the physiologic slump that lasts from 6 to 8 weeks after birth. Parental questions may seem trivial (skin care, type of diapers), but they all revolve around the question, "Will we be good parents?" Strong reassurance that their instincts are good serves to reinforce and strengthen the couple's tendencies toward good parenting and leads to a confident beginning as parents.

At the conclusion of the interview, the physician should have an idea of the parents' lifestyle and coping mechanisms, and the parents should feel reassured that they have a supportive person who will help them enter parenthood.

As prenatal interviewing has become more widespread, interview requests for second or subsequent pregnancies have become more common. These sessions are generally not quite so formal and can take place during the routine health maintenance visits of an older child. Parental concerns deal not only with the health and soundness of the unborn but also with coping with another child. "Will I be able to divide myself and still survive?" The mother may find herself torn between her infant in utero and her older infant. Parental or caregiver efforts to push the older child into relinquishing diapers, crib, stroller, or high chair should be discouraged. Separation at the time of delivery can be a problem for a child, who must be told that his or her mother will leave for a while and then return. This separation should occur shortly before the expected delivery. The separation will also stress the supports that the family has developed, and the physician should review these at this time. Recounting any previous birth experience is similarly important so that conflicts or problems may be identified and thus prevented.

### Comprehensive Pediatric History Interview

Traditionally, history taking has been a stepwise delineation of the events that led to the physician-patient encounter. Most clinicians learn this technique while dealing with hospitalized or acutely ill children, in a location where the problem frequently is visible or obvious. Fortunately, a great deal of history taking now occurs in settings other than the hospital and frequently does not involve illness; this is termed the *pediatric history interview*. History taking is merely a part of the interview, which should include observation of behavior and family interactions. Essentially, a history is a story about an encounter between physician and parent and child that includes subjective and objective data and omits some details considered irrelevant.

Box 13-1 is a suggested outline for components of a comprehensive pediatric history. In certain settings, some of the data will have already been gathered, but a thorough knowledge of each component of the history is essential.

Usually, the interview begins with the parents stating the concerns that led to the present encounter—the *chief complaint*. The parents should be allowed, with as little interruption as possible, to relate their story as they recall it. Certain areas may be amplified and clarified, but direct or challenging questions should be avoided. After eliciting the chief complaint,

**BOX 13-1 Comprehensive Pediatric History**

The following comprehensive pediatric history is exhaustive and not meant to be used in its entirety with all patients. However, depending on the patient's age and gender and the nature of the chief complaint and the present illness, the interviewer will need to explore in depth some or all of the subjects listed. In most instances, common sense must be used in deciding how much information should be gathered.

**Date of interview**

**Identifying data:** Record the date and place of birth, gender, race, ethnicity, parent living arrangements, religious preference, nickname (particularly for children 2 to 10 years of age), parents' first names (and last names, if different), and where the parents can be reached during work hours.

**Source of and reason for referral**

**Source of the history:** This source may be the parents, the patient, or sometimes a relative or friend. The physician should use judgment of the validity of the source's reporting. Other possible sources of the history are the patient's medical record or a letter from a referring physician or the school nurse.

**Chief complaints:** When possible, quote the parents or the patient. Clarify whether these complaints are the concerns of the parents, the patient, or both. In some instances, they are the concerns of a third party, such as a teacher.

**Present illness:** This condition should be a clear, chronologic narrative of the problems for which the patient is seeking care. Include the onset of the problem, the setting in which it developed, its manifestations and treatments, its impact on the patient's life, and its meaning to the patient or the parents, or both. Describe the principal symptoms in terms of location, quality, quantity or severity, timing (ie, onset, duration, frequency), setting, factors that have aggravated or relieved these symptoms, and associated manifestations. Relevant data from the patient's chart, such as laboratory reports, also belong in the *present illness* section, as do significant negatives (ie, the absence of certain symptoms that will aid in differential diagnosis). Include how each member of the family responds to the patient's symptoms, their concerns about them, and whether the patient achieves any secondary gains from them.

**Medical history:** General state of health as the parents or patient perceives it. Other medical and dental providers of the child (names and contact info).

**Birth history:** This information is particularly important during the first 2 years of life and when dealing with neurologic and developmental problems. Review the hospital records if preliminary information from the parents indicates significant difficulties before, during, or after delivery.

**Prenatal history:** Determine the mother's health before and during the pregnancy, including nutritional patterns and specific illnesses related to or complicated by the pregnancy; doses and duration of all legal and illegal drugs taken during the pregnancy, including alcohol ingestion and cigarette smoking; weight gain; vaginal bleeding; duration of the pregnancy; and the parents' attitudes toward the pregnancy and parenthood in general and toward this child in particular.

**Natal history:** Determine the nature of the mother's labor and delivery, including degree of difficulty, analgesia used, and complications encountered; birth order, if a multiple birth; and birth weight.

**Neonatal history:** Determine the onset of respiration; resuscitation efforts; Apgar scores and estimation of gestational age; specific problems with feeding, respiratory distress, cyanosis, jaundice, anemia, convulsions, congenital anomalies, or infection; the mother's health after delivery; separation of the mother and infant and the reasons for the separation; the mother's initial reactions to her baby and the nature of bonding; and patterns of crying and sleeping and of urination and defecation.

**Feeding history:** This information is particularly important during the first 2 years of life and in dealing with problems of undernutrition and overnutrition. Document access to and volume of intake of fluoridated water. The history may require an environmental assessment including lead screening (see Chapter 19, Environmental Health: The Role of the Primary Care Physician).

**Infancy:**

*Breastfeeding:* frequency and duration of feedings, use of complementary or supplementary artificial (formula) feedings, difficulties encountered, and time and method of weaning. Family and work support for breastfeeding.

*Artificial (formula) feeding:* type, concentration, amount, and frequency of feeds; difficulties encountered (regurgitation, colic, diarrhea); and timing and method of weaning.

*Vitamin, iron, and fluoride supplements:* type, amount given, frequency, and duration.

*Solid foods:* types and amounts of baby foods given, when introduced and infant's response, introduction of junior and table foods, start of self-foods, start of self-feeding, and the parents' and child's responses to the feeding process.

**Childhood:**

*Eating habits:* likes and dislikes, specific types and amounts of food eaten, parents' attitudes toward eating in general and toward this child's undereating or overeating, and parents' response to any feeding problems. Does the child and family eat in front of the TV? With childhood feeding problems, the parents may need to keep a diet diary for 7 to 14 days to allow accurate assessment of the child's food intake.

**Growth and development history:** This history is particularly important during infancy and childhood and in dealing with problems such as delayed physical growth, psychomotor and intellectual retardation, and behavioral disturbances.

**Physical growth:** Determine the actual (or approximate) weight and height at birth and at 1, 2, 5, and 10 years; record any history of slow or rapid gains or losses; and note the tooth eruption and loss pattern.

**Developmental milestones:** Determine the ages at which the patient held head up while prone; rolled over from front to back and back to front; sat with support and alone; stood with support and alone; walked with support and alone; said first word, combinations of words, and sentences; tied own shoes; and dressed without help.

**Social development:**

*Sleep:* amount and patterns during the day and at night; bedtime routines; type and location of bed; and nightmares, terrors, and somnambulism.

**BOX 13-1 Comprehensive Pediatric History—cont'd**

**Toileting:** methods of training used, when bladder and bowel control were attained, occurrence of accidents or of enuresis or encopresis, parents' attitudes, and terms used in the family for urination and defecation (important to know when a young child is admitted to the hospital).

**Speech:** hesitation, stuttering, baby talk, lisping, and estimate of the number of words in the child's vocabulary.

**Habits:** bed rocking; head banging; tics; thumb sucking; nail biting; pica; ritualistic behavior; media usage or consumption; and use of tobacco, alcohol, or drugs.

**Hygiene:** Frequency of toothbrushing. Use and amount of fluoridated toothpaste.

**Discipline:** parents' assessment of child's temperament and response to discipline; methods used and their success or failure; negativism; temper tantrums; withdrawal episodes; and aggressive behavior.

**Schooling:** experience with child care, nursery school, and kindergarten; age and adjustment on entry; current level of parents' and child's satisfaction; academic achievement; and school's concerns.

**Sexuality:** relationships with members of the opposite gender; inquisitiveness about conception, pregnancy, and girl-boy differences; parents' responses to child's questions and what they have taught the child about masturbation, menstruation, nocturnal emissions, the development of secondary sexual characteristics, and sexual urges; and dating patterns.

**Personality:** degree of independence; relationships with parents, siblings, and peers; group and independent activities and interests; congeniality; special friends (real or imaginary); major assets and skills; and self-image.

**Childhood illness:** Determine the specific illnesses the child has had, as well as any recent exposures to communicable diseases.

**Immunizations:** Record the specific dates of administration of each vaccine so that a booster program can be maintained throughout childhood and adolescence; also record any untoward reactions to a vaccine. The parents should have their own written record of the child's immunizations. This may be supplemented by obtaining information from the state immunization registry, if available.

**Screening procedures:** Record the dates and results of any screening tests. Refer to the AAP Periodicity Schedule or the Bright Futures guidelines to determine which tests to perform at each health assessment visit.

**Operations, injuries, and hospitalizations:** Elicit the details of these events and the child's and the parents' reactions to them. If the child is old enough, then ask age-appropriate questions about safety and prevention of injuries.

**Allergies:** Pay particular attention to the allergic diseases that are more prevalent during infancy and childhood: eczema, urticaria, perennial allergic rhinitis, asthma, food intolerance, and insect venom hypersensitivity.

**Current medications:** Include home remedies, alternative medicines, nonprescription drugs, and medicines borrowed from family members or friends. If the patient appears to be taking one or more medications, then survey one 24-hour period in detail: "Take yesterday, for example. Starting from when he woke up, what

was the first medicine Thomas took? How much? How often during the day did he take it? What is he taking it for? What other medications?"

**Family history:** Record the education attained, job history, emotional health, and family background of each parent or parent substitute; the family's socioeconomic circumstances, including income, type of dwelling, and neighborhood; parents' work schedules; family cohesiveness and interdependence; history of domestic violence; support available from relatives, friends, and neighbors; ethnic and cultural milieu in which the family lives; and parents' expectations of the patient and attitudes toward the child in relation to siblings. (All or part of this information can be recorded in the *present illness* section, if pertinent to it, or under *psychosocial history*.)

Also record the age and health or age and cause of death of each immediate family member, including the parents and siblings (Figure 13-1). Ascertain consanguinity of the parents by inquiring if they are related by blood.

Note the occurrence in the family of any of the following conditions: diabetes, tuberculosis, heart disease, high blood pressure, stroke, kidney disease, cancer, arthritis, anemia, headaches, mental illness, dental disease (decay or periodontal disease), or symptoms resembling those of the patient.

**Psychosocial history:** This information is an outline or narrative description that captures the important and relevant information about the patient as a person: the patient's lifestyle, home situation, and significant others.

**Typical day:** How does the patient spend time between arising and going to bed? Parents' marital status, visitation arrangements, support; delineate caregivers for child during day.

**Religious and health beliefs of the family:** What beliefs of the family are relevant to the perceptions of wellness, illness, and treatment?

What is the patient's outlook on the future?

For more on the psychosocial history, see Chapter 14, Pediatric History: Assessing the Social Environment. For adolescent patients, see Chapter 119, Interviewing Adolescents.

**Review of systems:**

**General:** Usual weight, recent weight change, weakness, fatigue, fever, pallor.

**Skin:** Rashes, lumps, itching, dryness, color change, changes in hair or nails.

**Head:** Headache, head injury.

**Eyes:** Vision, glasses or contact lenses, last eye examination, pain, redness, excessive tearing, double vision.

**Ears:** Hearing, tinnitus, vertigo, earaches, infection, discharge.

**Nose and sinuses:** Frequent colds, nasal stuffiness, hay fever, nosebleeds, sinus trouble.

**Mouth and throat:** Condition of teeth and gums, bleeding gums, last dental examination, frequent sore throats, hoarseness.

**Neck:** Lumps in the neck, swollen glands, goiter, pain in the neck.

**Breasts:** Lumps, pain, nipple discharge.

**Respiratory system:** Cough, sputum (color, quantity), hemoptysis, wheezing, asthma, bronchitis, pneumonia, tuberculosis, pleurisy; results of last chest roentgenogram.

*Continued*

**BOX 13-1 Comprehensive Pediatric History—cont'd**

**Cardiac system:** High blood pressure, rheumatic fever, heart murmurs; dyspnea, cyanosis, edema; chest pain, palpitations; results of past electrocardiograms or other heart tests.

**Gastrointestinal tract:** Trouble swallowing, loss of appetite, nausea, vomiting, hematemesis, indigestion; frequency of bowel movements, change in bowel habits, rectal bleeding or black, tarry stools, constipation, diarrhea; abdominal pain, food intolerance, excessive passing of gas; jaundice, hepatitis.

**Urinary tract:** Frequency of urination, polyuria, nocturia, dysuria, hematuria, urgency, hesitancy, incontinence, urinary tract infections.

**Genitoreproductive system—male patients:** Discharge from or sore on penis, history of sexually transmitted infection and its treatment, hernias, testicular pain or masses, birth control method, any children, frequency of intercourse, libido, sexual difficulties, sexual preference, sexual practices. (Use HEADSSS Assessment in Chapter 119, Interviewing Adolescents.)

**Genitoreproductive system—female patients:** Age at menarche; regularity, frequency, and duration of periods; amount of bleeding, bleeding between periods, last

menstrual period; dysmenorrhea; discharge, itching, venereal disease, and its treatment; number of pregnancies, number of deliveries, number of abortions (spontaneous and induced); complications of pregnancy; birth control methods; frequency of intercourse; libido; sexual difficulties; sexual preference; sexual practices (see HEADSSS Assessment in Chapter 119, Interviewing Adolescents).

**Musculoskeletal system:** Joint pains or stiffness, arthritis, backache; if these conditions are present, then describe location and symptoms (eg, swelling, redness, pain, stiffness, weakness, limitation of motion or activity), muscle pains, or cramps.

**Neurologic system:** Fainting, blackouts, seizures, paralysis, local weakness, numbness, tingling, tremors, memory loss.

**Psychiatric issues:** Nervousness, tension, anxiety, moodiness, depression, emotional stressors.

**Endocrinologic issues:** Thyroid trouble, heat or cold intolerance, excessive sweating, diabetes, and excessive thirst, hunger, or urination.

**Hematologic issues:** Anemia, easy bruising or bleeding, past transfusions and possible reactions to them.

Modified from Bickley LS, Hoekelman RA. Interviewing and the health history. In: Bickley LS, Hoekelman RA, eds. *Bates' Guide to Physical Examination and History Taking*. 7th ed. Philadelphia, PA: JB Lippincott; 1999. Used with permission.

the physician should enumerate the events associated with it in an orderly sequence (*present illness*). In addition to facts, parental concerns and feelings about these symptoms should be elicited. The parents should be asked to speculate on what they think is causing the complaint or symptom. This information can be valuable in several respects. First, it demonstrates the level of parental concern, which may influence subsequent care and treatment. Thus parents who equate nosebleeds with leukemia, for instance, will need more than simple reassurance. Second, parental concerns about causation may color the history a great deal; for example, their concern about developmental delay can influence the information they supply about achievement of early milestones. Third, cultural bias or guilt as to causation may exist and should be addressed. Discovering how the present illness affects the rest of the family is always important. Who misses work? Who loses sleep? This information will help the physician better understand the family's concerns about and responses to a given symptom or illness and what, if any, secondary gain exists for the child.

Although the chief complaint must remain the central focus of the interview, it is frequently obvious that this complaint is not the main problem. This circumstance is especially true when dealing with very young children. Tired, anxious, or frightened parents often perceive their reactions to an infant as being abnormal in some way; they then project this perception as something being wrong with the infant, which makes seeking help acceptable. Once the physician recognizes this perception, an attempt should be made to

create an atmosphere that allows the parents to express all their concerns. Questions such as, "Are there any other problems with Kathy you would like to discuss?" or "Is there anything else bothering you about Connor?" might facilitate communication.

After the present illness has been defined and elaborated, certain significant events should be enumerated (*medical history*). Much of this material is factual and can be obtained by using a direct question-and-answer format. Significant events such as operations, serious injuries, and hospitalizations should be verified by obtaining and reviewing appropriate hospital records.

When obtaining the patient's early history, the physician should elicit medically significant facts from conception to the onset of the present illness. All areas delineated in Box 13-1 should be touched on to some degree. The amount of information obtained may vary, but prenatal problems such as bleeding, eclampsia, or infection should be noted, and birth weight, type of delivery, and neonatal problems, if any, should be described. Information about nutrition can reveal a great deal about family dynamics and parental perceptions and expectations. "Tell me how Jennifer eats" frequently brings forth a torrent of information; but its value, nutritionally speaking, may be limited. "Good eaters" and "picky eaters" frequently weigh the same, and children who "hardly eat a thing" are often overweight.

In dealing with issues of development, asking an indirect question such as, "Tell me what Ann did during her first (or second) year" is frequently best. This inquiry usually elicits much more information



than do direct questions about motor milestones. The physician should seek information concerning the level of skill rather than the age of achievement; for example, knowing that the child might make simple wants known at 2 years of age is more important than the age when the first word was uttered. Some information about social adaptability and temperament should be obtained (see Chapter 14, Pediatric History: Assessing the Social Environment, and Chapter 119, Interviewing Adolescents).

Previous health care is important, and the child's immunization status is a significant part of the early history. The physician should record all immunizations, skin tests, and pertinent screening information on a separate sheet that is readily accessible and retrievable. Filling out a few history forms later for camp or entry into preschool will prove the value of this record. A list of current and past medications used, including prescription, nonprescription, and homeopathic remedies, should be obtained.

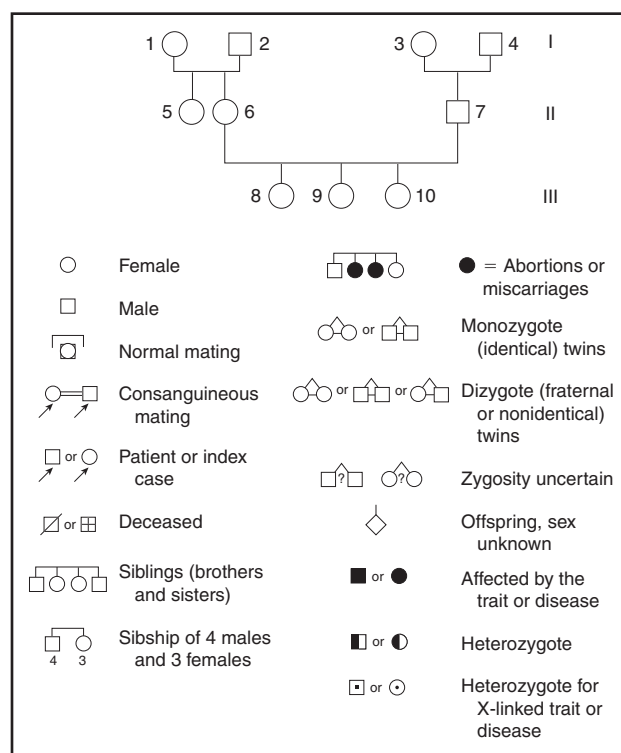
Allergies and allergic reactions to medications are also an important part of the early history. Specific allergic reactions should be described in as much detail as possible. Medications that cause vomiting or diarrhea are numerous but not usually allergenic. Idiosyncratic reactions to drugs such as amoxicillin and phenothiazides should also be described.

The *family history* contains variable information but is often difficult to construct. An attempt should be made to trace back at least 2 generations on each side of the family. Figure 13-1 shows one method of recording such data. The names, birth dates, and health of the 3 generations concerned are usually listed below the pedigree (although not shown here), using a number indicating each person. As more data such as births, deaths, and disease become available, they can be added easily.

Consanguinity of parents should be investigated specifically by asking if the parents are related by blood. In addition to seeking known inherited diseases such as diabetes, hemophilia, or neuromuscular disorders, the clinician should note familial tendencies such as obesity, short stature, early heart disease, and hypertension. Inquiring about the parenting techniques of forebears is sometimes appropriate. Research has shown that abusive parents were frequently deprived or abused themselves as children. Asking specifically about the health of the parents' brothers or sisters is also important because these individuals are often overlooked during an interview.

The *psychosocial history* describes the child's present milieu and relationships with family, peers, school, and community. This history should include information about the physical setting (eg, housing), environment, media use, and degree of isolation. Important points to determine include how children spend the day, who cares for them, what they like to do, and what their hobbies are. Inquiry should be made about the support system within the family, for example, the nature of an extended family, supportive or conflicting roles, the elements of stress that exist for this child, and how the child and family cope with them.

The psychosocial history should also touch on the parents' attitudes toward discipline and expectations



**Figure 13-1** Chart and symbols used to construct a family history, or family pedigree. The Roman numerals indicate generations; the Arabic numerals indicate specific persons.

about achievement. When appropriate, the physician should determine how the parents compare this child to the child's siblings or to other children. Asking the parents to describe the child's temperament (eg, "mellow," "feisty," "lazy"), as well as what they see as the child's strengths, is also helpful.

The *review of systems* should be detailed to obtain a baseline evaluation of all systems and their level of function. Children change over time, and various systems may be the target of stress or disease processes. Therefore, the clinician should reassess all organ systems periodically and record their apparent level of function.

## INTERVIEWING TECHNIQUES

Clarifying certain terms is essential. For example, *diarrhea* and *flu* mean different things to different people, and no true communication can occur until such terms are defined. *Tired* may mean sleepiness, fatigue, or true lethargy. The temporal nature of complaints must also be assessed carefully. Children who are "always sick" may have recurrent infections that clear in 5 to 7 days, or they may have a perpetually runny nose, which is seen in some children who have allergies.

If the patient has been seen before, then the physician should review the child's medical record before the visit to refresh the memory on past health and illnesses that may relate to the reason for the current

visit. Consultants should review the letter of referral and the reason for and goals of the visit before interviewing the parents and patient.

Many parents see their skills as parents being challenged during the pediatric interview: “After all, if we did things right, we wouldn’t need to see the doctor.” They become defensive and may answer questions *ideally*. At the same time, they want to share fears and worries with someone who is caring and empathetic. The pediatrician must strive to develop this trusting relationship. By being facilitative, the physician enables the parents to express fears and frustrations. Statements such as “That must have worried you” or “I bet that’s upsetting” let parents know that the physician is concerned with much more than the facts in the interview. On the other hand, statements or questions suggesting that the parents have not managed their child’s illness properly such as “You should have brought Gretchen in sooner,” or “It would have been better not to have fed Stephanie,” or “Why did you do *that*?” should always be avoided.

The techniques used to obtain a complete and accurate history vary with the situation and the person being interviewed.

### Types of Questions

In emergencies, the physician should ask only direct (not open-ended) questions that quickly elicit the important facts needed to make decisions regarding treatment. In nonemergencies in which time is not a factor, direct questions should be used to obtain identifying data and concerns. In nonemergency situations, having the parent or child tell the story without interruption is best. Time will dictate how much additional information is obtained.

Direct questions should be asked one at a time. Rapid-order direct questions such as “Has Karl ever had eczema, hay fever, asthma, or allergic reactions to drugs?” are logical to the questioner but are likely to confuse the respondent and lead to an overall “no” answer when a “yes” would be appropriate for one or more of the elements of the question.

Indirect (open-ended) questions are extremely useful in eliciting the present illness and psychosocial history. The answers to open-ended questions such as “How does Bonnie spend a typical day?” often provide clues to underlying, unstated problems and cues for pursuing specific elements of the patient’s illness.

Direct questions are also important in eliciting the details of the present illness and the psychosocial history. For example, if a cough is mentioned as a symptom in the patient’s illness, then the following sequence of direct questions is appropriate: “How long has Kathy had the cough?” “When does she have it?” “Does it wake her up at night?” “What does it sound like?” “Does she cough up any phlegm?” “How much?” and “What does it look like?” Thus, open-ended questions identify the direction for further inquiry, and direct questions help determine the importance of the symptoms or signs identified.

Leading, direct questions such as “Does Jane do well in school?” should be avoided because they are more likely to result in *expected*, affirmative answers than are nonleading, direct questions such as “What kinds of grades does Jane get in school?”

### Helping the Parent or Patient Communicate

Throughout the interview, the parents or patient should be assisted in several ways to relate all necessary information fully. The pediatrician should use medical terminology the parents or the patient understands. Words such as *tinnitus*, *palpitation*, and *incontinence* may have little meaning to the parents or patient, who will often be too embarrassed to ask for a definition and may simply answer “no” when asked if these signs and symptoms are present.

The interview process is one of interaction between the physician and the parents or patient. The person providing information should do most of the talking, and the physician should do most of the listening. However, the physician can encourage the parents or patient to communicate the story by using the following 7 techniques:

1. **Facilitation.** This technique is designed to convey interest in what the parent or patient is saying. Maintaining eye contact, leaning forward, nodding in affirmation, and saying “yes,” “uh huh,” “I see,” and similar responses all convey interest and encourage the parent or patient to continue. Additional information might be gained by giving an example, such as “In other situations like this, some parents have thought of alternative medicines. Have you thought so too?”
2. **Reflection.** Repetition of words the parent or patient has said encourages the provision of more detail, as is demonstrated in the following example:  
*Parent:* “Kara woke up in the middle of the night breathing hard.”  
*Interviewer:* “Breathing hard?”  
*Parent:* “Yes. She seemed to be breathing fast and making a wheezing noise.”  
*Interviewer:* “A wheezing noise?”  
*Parent:* “Yes, in and out—a musical wheezing sound.”  
 By using reflection, the interviewer was able to elicit the nature of the child’s breathing difficulty without influencing its description or diverting the parent’s thoughts.
3. **Clarification.** The interviewer must often clarify what the parent or patient has said, for example, “What do you mean by ‘Rob wasn’t acting right?’”
4. **Empathy.** Recognizing and responding to a parent’s or a patient’s feelings of concern, fear, or embarrassment shows understanding and acceptance and encourages continued expression of the emotion. “I can understand why that upset you” or “That must have been difficult to deal with” is an empathetic expression that tells the parent or patient that the physician appreciates what the parent or patient has been experiencing and is sympathetic. The physician can also ask how the parent or patient feels or felt about a particular situation that has been related. This question displays an interest in the parent’s or the patient’s feelings, as well as an interest in the medical facts.
5. **Confrontation.** This technique is used to clarify what seems to be a contradiction between the parent’s or the patient’s feelings and actions: “You say that Alison loves school but misses a lot because she has an upset stomach most mornings.” Although confrontation is used to seek clarification, it may also

lead to interpretation of the meaning of the contradiction.

6. *Interpretation.* This technique is used to move beyond clarification to an inference to be made from the circumstances presented. Thus, the previous example might lead to the following statement and questions by the physician: “Maybe there is some relationship between Alison’s upset stomach and her wanting or not wanting to go to school. Do you think that’s possible?”
7. *Recapitulation.* This technique is especially useful when a long and complicated history or an unusual history is presented. The physician summarizes to the parent or patient the history as the physician understands it. This task may be done at more than one point during the interview and serves to confirm the validity of the history; it also allows for possible changes.

Toward the end of the interview, asking the question, “Is there anything else you think I should know?” is sometimes helpful. This open-ended inquiry leaves parents with the sense that things were not rushed and that room still exists for discussion.

### Hindrances to Communication

Although a calm, reserved, interested demeanor is important to enhance communication, the physician must guard against appearing casual. Constant eye contact with the parent, interrupted by glances at the child (if present), should be maintained. Evidence of boredom or impatience—looking away from the parents or patient, tapping the fingers or a pencil on a tabletop, or rushing through the interview—must be avoided. Laptop computer records of the patient should be reviewed beforehand and not during the interview. Inappropriate smiling or laughter also hinders good communication. The parents or patient always should believe that they have the physician’s undivided attention. If time is short, then the parents or patient should be informed and another appointment made for completing the interview.

### Interviewing the Child

A great deal of information can be gained by interviewing the child directly. Many children interact spontaneously with the pediatrician and answer direct questions readily. In many instances, only the child can reveal the severity of the pain or the extent of the symptoms. Approaching children indirectly, encouraging them to talk about their symptoms, is sometimes better than seeking direct answers. For example, “Tell me about your cold, Gordon” is preferable to “Do you cough?” The pediatrician should always support the child’s *own story*. It should be taken seriously, and confidences should not be violated except in unusual circumstances.

With chronic problems, such as constipation or enuresis, reviewing with patients their knowledge of the complaint is helpful. A child can be asked what was discussed before coming to the physician’s office, how the child feels about the visit, how the child’s symptoms affect the daily routine and alter the child’s lifestyle, and whether the child is able to attend school

and carry out all regular activities. Asking children what they think is causing their symptoms, what they are worried about, and why it worries them is also important.

Interviewing the child provides another opportunity to assess parent–child interaction. Many parents cannot let their child speak without addition, interruption, or correction. A school-aged child who clings to a parent and cannot be coaxed to make eye contact with the pediatrician or interact in any way is a concern. As adolescence approaches, parent–child conflicts become more intense. Given the chance, many adolescents will make this distressing situation obvious. Under these circumstances, separate interviews are preferable (see Chapter 119, Interviewing Adolescents). It should be the expectation that teenagers are interviewed alone, for at least a portion of the time.

### Typical Day Technique

In many situations, information about a child’s typical day can be helpful and informative. Most parents can relate this information readily. In addition to concrete material (eg, sleep patterns, feeding activities), much can be learned about areas of stress and harmony within a family. Parents frequently find difficulty in discussing situations without seeking approval, even if tacit, of their own actions. Parents or caregivers who are confused or unsure of themselves may frequently ask advice on a particular aspect of their child’s behavior as it is presented in the description of the child’s typical day; however, deferring answers until the entire day has been described is best.

Discussion can begin with an introduction, such as, “To find out more about Kim, I am going to ask you to tell me how she spends a typical day.” The physician should then begin by asking what time the child arises and what happens. Some parents will launch into vivid descriptions and will require little direction, whereas others must be encouraged. Details can be elicited by asking some simple questions such as, “What is her mood on awakening?” “Who takes care of her?” and “What does she usually eat for breakfast?” Discussion can include food likes and dislikes, skill in eating, and conduct at the table. The physician can also learn about the child’s activities, habits, media use including computer/Internet, social networking, and television viewing practices. The subject of discipline might come up during this discussion, and the parents’ beliefs about prohibitions and punishments can be ascertained.

Lunchtime, afternoon rest periods, and activities are reviewed in much the same way. Descriptions of trips to the market or to other stores can provide information about behavior with others and reactions to new experiences. School, daycare, and after-school activities can be explored. What about homework and family chores?

The evening meal is often stressful in many families, and how it proceeds can provide many clues to family dynamics. For example, the physician should find out when the parents arrive home, if the child and/or family eat in front of the TV, whether the child eats with the parents, and, if so, the types of interactions that occur. Information about the events surrounding



preparation for sleep, bedtime rituals, and sleeping patterns are also important.

At the end of such an interview, assessing not only the child's style and temperament but also the family's strengths and weaknesses should be possible. This information is essential for advising parents of children who are having developmental and maturation problems.

## QUESTIONNAIRES

In certain instances, parental questionnaires may be used to supplement the history. Some questionnaires may be used as part of a general health appraisal; others are more applicable to a specific problem. Questionnaires are especially helpful for assessing developmental issues, emotional problems, and school problems. The American Academy of Pediatrics (AAP) policy statement on developmental screening includes developmental screening tools that may be incorporated into health maintenance visits. The wise physician will be thoroughly familiar with the questionnaire format and its pitfalls before using it; all such instruments may supply additional information, but all may also be subject to observer bias and should be interpreted accordingly. In addition, the AAP toolkit entitled *Addressing Mental Health Concerns in Primary Care* contains several mental health screening questionnaires.

## RECORDING HISTORICAL INFORMATION

Two main goals exist in recording the historical data gained in an interview: documenting the patient's symptoms and medical history, which will help in formulating a diagnosis and therapeutic plan, serve as a legal record of the physician-patient encounter, and provide information for billing purposes; and making a reasonable accounting of the patient's medical status. In doing so, a complaint is transformed into an *illness* or *disease*, and a child becomes a patient. Much can be lost in translation.

The medical record should contain all the medically significant facts of the child's life. The recorded history is a synthesis of material and observations gained during the interview, compiled in a legible, retrievable form.

The present illness must be recorded clearly and concisely. Consistency is paramount, especially when dealing with time. Events must be recorded by using either of these methods: "Dick developed a cough on March 17" or "Dick developed a cough 5 days before our interview on March 23." Using terms such as *Tuesdays* and *Fridays* are difficult to identify 2 weeks after an interview.

Ideally, conditions or concerns should be recorded on a problem list with date of identification and resolution (if possible) included. This allows for quick review and facilitates revisiting ongoing problems.

Data obtained during an interview can be recorded in a variety of ways, such as audio-recording the entire session, a method often used by psychiatrists. Merely noting *Dx-acute otitis media; Rx amoxicillin x*

*10 days* on an index card is inappropriate. Electronic Medical Records (EMRs) are essential in providing a high-quality medical home. Records should be legible, and much of the data should be retrievable without having to pore over volumes of paper. This process requires some foresight and planning so that different parts of the history can be separated for later use. Ideally, the historical database should be standard and uniform. However, certain problems change with time (hip clicks, birthmarks) and vary by age and gender (menstrual irregularities), by type of population served, and by geographic locale.

Careful documentation of medications (both prescription and over the counter) currently in use is important; this is often referred to as *medication reconciliation*.

Questionnaires facilitate record keeping and are designed to be age appropriate. They can be filled out by the parent or by a nurse, physician assistant, or other office personnel. However, they also present several drawbacks. First, questions tend to be answered in an idealized way because parents usually have a skewed opinion of their children. Second, all logical sequencing of information gathering is lost, and degrees of concern are not readily expressed. Third, unless the chart is updated frequently by subsequent questionnaires, much of the information soon becomes irrelevant.

The skills involved in gathering and recording a history and communicating compassionately and courteously with patients and their families are difficult to master. Describing a true vignette of the child's condition to professional colleagues and consultants is invaluable. These skills are not innate but rather require work, insight, perseverance, and practice. The work is hard, but the rewards are great.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *1 to 4 Years, From (Part 1): Framingham Safety Survey* (questionnaire), American Academy of Pediatrics (patiented.solutions.aap.org)
- *1 to 4 Years, From (Part 2): Framingham Safety Survey* (questionnaire), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Child Health and Development Inventory System (CHADIS)* (questionnaire), Barbara J. Howard, MD (www.childhealthcare.org)
- *You and Your Pediatrician* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Your Child's Health Record* (booklet), American Academy of Pediatrics (shop.aap.org)

### Medical Decision Support

- *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* (toolkit), American Academy of Pediatrics (shop.aap.org)
- *Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents* (book), American Academy of Pediatrics (shop.aap.org)

### Practice Management and Care Coordination

- *EQIPP: Medical Home* (online course), American Academy of Pediatrics (eqipp.aap.org)



- National Center for Medical Home Implementation (Web site), American Academy of Pediatrics ([www.medicalhomeinfo.org](http://www.medicalhomeinfo.org))

### AAP POLICY

American Academy of Pediatrics Council on Children With Disabilities, Section on Developmental and Behavioral Pediatrics, Bright Futures Steering Committee, Medical Home Initiatives for Children With Special Needs Project Advisory Committee. Identifying infants and young children with developmental disorders in the medical home: an algorithm for developmental surveillance and screening. *Pediatrics*. 2006;118(1):405-420. Reaffirmed August 2014 ([pediatrics.aappublications.org/content/118/1/405](http://pediatrics.aappublications.org/content/118/1/405))

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## Chapter 14

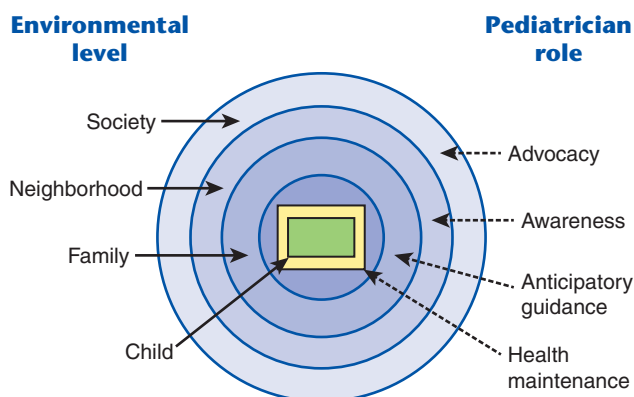
# PEDIATRIC HISTORY: ASSESSING THE SOCIAL ENVIRONMENT

Penelope Knapp, MD

## INTRODUCTION

The child's environment may nurture or hinder development from the level of the single cell to the broadest social surround. The pediatrician must be able to appraise environmental threats and assets, particularly in the social environment, to foster the child's healthy development, support resilient adaptation, and maximize social determinants of the child's health.

Figure 14-1 sketches the outline of environmental circles of influence on development. The family is surrounded by the extended family, peers, and other adults with direct influence on the child's experiences.



**Figure 14-1** Environmental circles of influence on development.

They are in turn influenced by the neighborhood, including school, which lies within a broader social environment that impinges on the child's world.

Broadly, the social environment may be considered as intrafamilial or extrafamilial. The intrafamilial social environment is the personal world of relationships with intimates; the extrafamilial social environment is the world in which the family lives and raises the child. The external environment influences how parents' and children's intimate relationships flourish or falter inside the family environment. The pediatrician's capacity to optimize children's health goes beyond well child care and treatment of illness to inquiring about the child's social environment in order to provide preventive interventions.

## Biologic Needs and Vulnerabilities

Social development has both a biologic basis and neurobiologic consequences. Normative theories of child development describe the progression from the newborn's complete dependence on parents through the acquisition of strengths, knowledge, and skills, and pursuit of independence and relationships outside the family during childhood and adolescence. This progression, propelled by physical and neurologic maturation, is well known to the pediatrician, and the pediatrician's role in helping the parent to understand and facilitate the child's development has been well established. To optimize biologically driven maturation, a fuller understanding of the critical influence of the child's interpersonal and social environment is also necessary, because psychological and social development is necessarily interpersonal and mediated by experience. The pediatrician should routinely and systematically assess the parents' and caregivers' understanding of the child's developmental capacity.

Knowledge of genetic influences on health and development is increasing rapidly. In parallel, awareness of genetic influences on social-emotional development and environmental influences on genetic expression is growing. Shared and nonshared idiosyncratic environmental factors contribute to individual differences in siblings in the same family, as shown by studies of adoptive and biologically related same-sex sibling pairs from the Sibling Interaction and Behavior Study

(SIBS), although genetic influences continue to be expressed even into adolescence. The importance of early and middle childhood is a new emphasis for Healthy People 2020, in recognition that positive social development has a biologic effect.

Relationships will determine how any child develops as a social being, beginning with the earliest reciprocal interactions of the infant with the parent, which influence gene expression and shape or reinforce neural architecture. Brain development proceeds according to the quality of relationships with siblings, teachers, and peers.

The younger the child, the more vulnerable he or she will be to family mental health problems or violence. Because the quality of the child's relationship to parents or caregivers will influence the child's ongoing physical and emotional response to stress, these relationships must be supported. The pediatrician's encouragement of strong early relationships is a powerful preventive intervention, not only during infancy, but throughout childhood and adolescence as the child and parent develop.

The pediatrician should assess the parent-child relationship, the child's social-emotional and developmental status, the degree to which the parent can protect the child from stress and injuries, and whether the parents can provide predictable routines to establish the child's sense of security. Early recognition and screening for emerging mental health problems has been facilitated by the work of the American Academy of Pediatrics (AAP) Task Force on Mental Health, including a summary of mental health screening and assessment tools for primary care (see Tools for Practice at the end of this chapter).

### **Environmental Threats to Family's Functioning**

Environmental threats to the developing child may begin in utero. Exposure to toxic environmental agents such as lead, allergens, and pesticides, is ubiquitous, but disproportionately affect minority, vulnerable, and underserved populations. In addition, secondhand smoke exposure is higher among children at 185% of the Federal Poverty level and below. Almost all parents strive to do their best for their children, but many work against daunting odds. Children and single mothers are increasingly overrepresented among the poor. Children comprise 43% of people in poverty, and 70% of children who live with a single parent, usually their mother, live in low-income families (defined as those whose household income is less than twice the federal poverty level), as compared to 48% of children with married parents. The likelihood that a child is growing up in poverty is higher if the family lies in a poor area (identifiable by ZIP code) and if the parents have less education, are recent immigrants, and have part-time or no employment. Direct effects of material impoverishment, such as inadequate nutrition leading to developmental delay, are compounded by the increased likelihood that poor children will be exposed to other hazards such as substandard housing, lead poisoning, parental psychological distress, inadequate child care arrangements, or neglect and abuse.

Children of color are disproportionately affected: in 2011, children in single-parent households varied by ethnicity; 67% were in black non-Hispanic families, 53% in Native American families, 47% in Hispanic families, 25% in white non-Hispanic families, and 17% in Asian American and Pacific Islander families. It follows that very young children of color are overrepresented in child welfare, comprise the largest proportion expelled from early care and learning settings, and are likelier to require specialty mental health care. They are also likelier to be victims of abuse, sexual abuse, or neglect in the home or neighborhood, and at best are more subject to experience factors placing them at risk for poor behavioral and social-emotional development.

Furthermore, it is more difficult for low-income parents without social supports to meet the basic needs of very young children and those with special health care needs. Parents of any economic level who have experienced adverse child experiences (ACEs) in early years may be at risk for poor or maladaptive parenting, may have diminished capacity to respond to stress in a healthy way, and also have a higher risk of health, mental health, or substance abuse problems. In addition, if a parent is working multiple jobs or is too depressed, tired, or detached to engage with children in challenging settings, they may resort to allowing excessive screen time or substituting media for parent-child interaction. The pediatrician should inquire about the family's ability to provide adequate nutrition, the safety of their housing, whether the parents are distressed, whether child care is of adequate quality, and whether there is neglect or abuse.

## **THE FAMILY ENVIRONMENT: RELATIONSHIPS AND CULTURE FOR THE DEVELOPING CHILD INSIDE THE FAMILY**

### **Family Composition**

The child's neurologic maturation, psychological growth, and development of social self are shaped by his or her intimate relationships. It is helpful to know how many people are in the child's family and how they influence the social environment. Optimal child development is linked to parent and family characteristics. Children whose parents are more educated, have higher incomes, have lower psychological distress, and provide emotionally supportive and cognitively rich environments show more cognitive, language, and social competence and more harmonious relationships with their parents. Grandparents may have a large direct role in child rearing, especially if the parent is an adolescent; but they are also involved indirectly, by transmitting family culture. Increasing numbers of same-gender parents raise children, but there is no causal relationship between parental sexual orientation and the child's healthy emotional development.

The family member bringing the child for pediatric care may be a grandparent or step-parent. Grandparents may be the child's primary caregivers because the extended family lives under a single roof, or for reasons involving tragedy, illness, substance abuse,

incarceration, deportation, or young age or military deployment of the biologic parent. Grandparents, undertaking the vigorous tasks involved with raising young children, may themselves have physical limitations or health problems. They may also be contending with role confusion, financial difficulties, or involvement in problematic custody disputes, which strain their capacity to provide a secure relationship base. Step-parents face a challenge to develop secure and robust attachments with the children they have undertaken to help raise—children who have adapted to earlier troubling experiences, whose loyalties may be unsettled, and whose emotions may be difficult for them or their parents to endure. Children in stepfamilies experience higher rates of unintentional injuries, and overall do not do better than children raised by single parents. However, step-parents may also enrich a child's upbringing economically and emotionally, offering the presence of an additional loving figure. Pediatricians should be aware of strengths and risks in the family composition.

A social genogram, similar to those used for identifying heritable diseases, but also depicting the child's relationships and who is in the home, is a useful tool for understanding the child's social world. Genogram software is available that describes standard symbols, including those for medical conditions and for describing social relationships. See Figure 14-2 for a simple example.

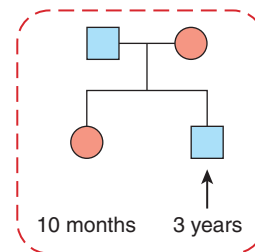
### Attachment

Attachment theory provides an important lens for viewing social development. Children of any age actively adapt to their relationship environment, and within the constellation of that interpersonal environment, they develop self-regulation and automatic expectations about others. Original studies of attachment indicate that most infants and toddlers have secure attachments with their primary caregiver. Children with insecure attachment styles fall into 3 groups, termed insecure/avoidant, resistant/ambivalent, and disorganized/disoriented. Attachment types are specific between an infant and a particular caregiver, are predictable from normal caregiving behavior in the first year of life, and remain stable to at least 6 years of age. Sensitive, responsive care leads to secure attachment. Rejecting caregiving leads to insecure/avoidant attachment. Inconsistent caregiving leads to resistant/ambivalent attachment.

If the constellation of intimate parent-child interactions is troubled, or disturbed enough to be characterized as attachment disorder, the child is at high risk for developing self-perpetuating troubled patterns of interactions with other children and adults. The pediatrician must recognize disordered attachment, not only because the child's development is contingent upon reciprocal interactions in an attached relationship, but also because without early intervention, disordered attachment may jeopardize or distort later close relationships. The *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (*DSM-5*) recognizes 2 types of attachment disorders: reactive attachment disorder and disinhibited social engagement; these have previously been described as nonattachment and indiscriminate

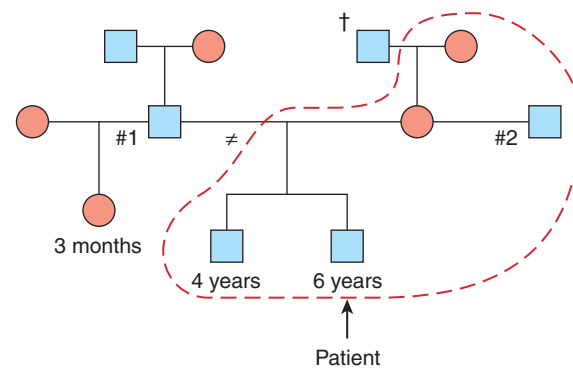
#### Example 1

The patient, a 3-year-old child, is the oldest of 2, living with both parents.



#### Example 2

The patient, a 5-year-old child, is the oldest of 2 boys, living with mother and stepfather. The child's father has remarried and has an infant daughter. The maternal grandmother lives in the home; the maternal grandfather is deceased.



□, male; ●, female; #, number of partner(s);  
 [dashed red line], persons living in household; ≠, divorced; †, deceased.

**Figure 14-2** Example social genograms.

sociability. This pattern of shallow, friendly, engaging behavior may result from cycling through multiple caretakers before removal from the parent, and multiple foster placements thereafter. Reactive attachment disorder may resemble internalizing disorders, with a lack of or incompletely formed preferred attachments to caregiving adults and a dampened expression of joy or happiness. Disinhibited social engagement disorder more closely resembles attention-deficit/hyperactivity disorder and may occur in children who do not lack attachments or who have established or even secure attachments. Children with disordered attachment may exhibit symptoms ranging from withdrawn behavior to angry, aggressive behavior.

Children with both patterns of attachment disorder are very challenging to parent, as they have difficulties with self-regulation along with disruptive or disturbing behavior, and they cannot return the love and trust that their parents try to give them, leaving the parents feeling ineffective and distressed.

Measures of attachment are available for both adults and children. If the pediatrician is concerned about the quality of the child-parent attachment, a

fuller history or use of a screening tool is indicated, followed by referral to a mental health professional for further assessment.

Another lens through which to view the infant's earliest relationships is the transactional model, which provides a comprehensive view of the interaction between nature and nurture, focusing on relations between the genotype (ie, the individual's biologic organization), the phenotype (ie, the individual's personal organization), and the environment (ie, the organization of experience). The child's behavior is seen as a product of transactions among the genotype, phenotype, and environment. The transactional model provides a framework for early intervention that can emphasize, depending on the nature of the relationship problem, remediation of the child's behavior, redefinition of the parents' interpretation of the child's behavior, or re-education of the parents to change their behavior to the child.

### Parenting Style

The culture within the family will shape the relationship and learning environment for the child. Families have individually distinct beliefs, rituals, and routines related to health and discipline. Baumrind's classical description of 4 parenting styles is widely used: Authoritative parents are comfortably consistent in providing limits and guidance to shape children's behavior and support their learning; they both demand that children adhere to developmentally appropriate clear standards and respond warmly to children's needs. Authoritarian parents, by contrast, demand but do not respond; they impose noncontingent or punitive discipline that children may experience as arbitrary, unfair or confusing. Permissive parents are responsive but not demanding; these parents fail to provide their children with consistent rules or discipline, so the child struggles with their own impulses without predictable controls. Uninvolved parents, also termed rejecting-neglecting parents, neither demanding nor responsive, do not provide emotional scaffolding to help children understand the effects of their emotions and feelings.

Children depend on their parents' control of the family emotional environment and on their engagement and stimulation for basic learning. This has measurable effects upon learning: young children whose parents have low responsiveness to their developmental activities have delayed vocabulary. Numerous instruments are available for assessing parenting style. In the Suggested Readings at the end of this chapter, see Johnson et al for a review, and Kemper & Kelleher for approaches to family psychosocial screening.

The pediatrician should observe parenting style in the office and ask about parenting stresses and challenges, and if concerns are noted, consider referral to a mental health professional for fuller assessment.

### Parental Mental Health: Maternal Depression, Intimate Partner Violence, and Substance Abuse

For infants and young children, the environment is created and embodied by the parents, particularly the mother. Parental mental illness powerfully affects the emotional and possibly the physical environment in

the home. The 12-month prevalence of mental illness in adults in the United States is estimated at 32.4% (National Comorbidity Survey replication, [www.hcp.med.harvard.edu/ncs/index.php](http://www.hcp.med.harvard.edu/ncs/index.php)), and Nicholson and colleagues note that two-thirds of these individuals are parents. A child whose parent has a mental illness is more likely to have developmental delay, difficulty regulating emotions, and/or problems with relationships. One-fifth of children in the general population have a psychiatric diagnosis, but 30% to 50% of children with mentally ill parents have a psychiatric diagnosis, so recognition of parental mental disorder is necessary to prevent or minimize childhood psychiatric disorders.

Depression has a prevalence of 16.6% in the population. According to the AAP, 400,000 infants are born each year to mothers who are depressed. Despite easy availability of depression screening, such as the Edinburgh Postnatal Depression Scale, a 10-item screening tool available in the public domain, depression in most mothers is either unidentified or untreated. Only about 10% of women experiencing postpartum depression discuss their symptoms with their physician. Because babies are wholly dependent on a caregiving adult for survival, they are therefore at greatest risk for abuse, neglect, and inadequate medical care. Babies' earliest reciprocal experiences shape the developing brain. Many depressed mothers work hard to meet their children's needs, but some infants of depressed mothers are at risk for developmental delay, impaired social interaction, attachment problems, behavior problems, and later problems with cognitive and social-emotional development.

Growing up in the environment created by a depressed mother may also affect children before and beyond infancy. Riley and colleagues, evaluating combined reports (mother, father, teacher) about children whose mothers were depressed, found that their adaptive skills were significantly poorer than those of sociodemographically similar children whose mothers were not depressed. Parents reported more emotional and behavioral problems among these children. Measured family stressors did not mediate the association with children's psychosocial problems, but the quality of mothers' parenting did.

Maternal depression is a cumulative risk factor because it sets in motion multiple risk processes. This process has been described and explained by the "launch-and-grow" cascade model through which the earlier risk factor, exposure to maternal depression before age 12, was demonstrated to predict other risk processes—stress, altered family relationships, and reduced self-worth—that set the course for children to develop depressive symptoms over time.

It is difficult to estimate the prevalence of intimate partner violence (IPV) between parents and children's witnessing domestic violence (DV) among others in the home, but its powerful toxicity to the child's emotional environment is obvious. Families with physical abuse between parents are likelier to be families with child maltreatment, and psychological abuse between parents is also strongly related to maltreatment of children. Even when only the husband perpetrates physical abuse toward the wife, the odds of child



neglect were found to be 5.29 times as great as in families with no psychological abuse. A pediatrician who uncovers a situation involving violence in the home should question whether the child has witnessed it, if the child's safety is jeopardized, and if the mother feels safe or has a plan if she does not feel safe.

Childhood exposure to IPV is a toxic stress associated with poor social-emotional child health outcomes and significantly more externalizing, internalizing, and total behavior problems. Both the age at which a child is first exposed to violence at home and the amount of violence the child witnesses in their lifetime have been found to be significantly related to behavioral problems. Cumulative violence exposure has been shown to have a greater effect, and also to mediate the relationship between early exposure and later externalizing behavior problems. This may include excessive exposure to violence through media. In addition, McFarlane and colleagues found children aged 6 to 18 years to be at greatest risk following psychological abuse in the home.

Thus, exposure to physical and psychological abuse between parents is an example of environmental stress that is both formative at an early age and cumulative during childhood. This presents an opportunity for prevention: identifying and intervening in families with abused mothers may prevent the development of problems for their children, as well as ensure the safety and well-being of the child and mother.

The prevalence of substance and alcohol abuse among adults who are parenting children is also difficult to estimate, but the likelihood of child maltreatment leading to out-of-home placement is higher in these families. From the child's perspective, the parent who is using substances inevitably provides a fluctuating interpersonal environment, depending on whether they are under the influence or experiencing withdrawal.

Children exposed to maternal substance abuse suffer both nonspecific risk and, in the case of alcohol exposure leading to fetal alcohol spectrum disorder, specific neurodevelopmental harm. Parental substance abuse is part of a cluster of risks: it is often associated with a chaotic, harsh, and stressed environment, exposure to interpersonal violence, and dysregulating experiences that prevent minimally adequate or consistent care for the child. Also, alcohol and substance abuse are related to parental depression or trauma, so even if the situation does not lead to active maltreatment, the home environment poses a threat to the child's adjustment.

The child is therefore intermittently or continuously deprived of a safe and solid relationship with a special adult who puts the child's needs first and is emotionally available to respond in all the ways that allow the child to build neuronal connections in an organized way within a secure attachment. Such kinds of toxic early experiences present an unfortunate "natural" experiment. Because normal language and cognitive development are contingent on environmental stimulation through earliest relationships, most young children coming into foster care show speech and language delays, and almost half show cognitive delays. However, these risks do not apply exclusively to foster children. Early recognition of parental

problems is an important preventive measure. The pediatrician should observe for or ask about maternal depression, interpersonal or domestic violence, and substance use. Screening tools may be useful.

### Discipline

Child rearing is challenging. The pediatrician will support positive parenting strategies; nonetheless, parents must at times set limits and provide consequences to guide their child to safe and prosocial behaviors. In what ways and how often parents set limits and provide discipline for their children depends on characteristics of the parents, the behaviors or predilections of the child, and the social context. Among these, parental characteristics such as warmth, protectiveness, or authoritarianism may be the most influential in determining the type of discipline used.

Limit setting and discipline are necessary elements of rearing most children. Each parent and each family develops a style for these, with a range from non-verbal demonstration of disapproval to scolding, to spanking. The AAP recommends against corporal punishment, yet it is endorsed or used at some times by most parents in the United States. Frequent corporal punishment is associated with other parenting risk factors, including whether parents considered abortion and whether there is neglect, physical and psychological maltreatment, IPV, maternal stress, substance use, and depression. In a large birth cohort study of children in 20 large US cities, frequent use of corporal punishment (defined as spanking more than twice in a month) with 3-year-old children was found to be associated with higher levels of child aggression when the child was 5 years of age, even controlling for key demographic features and potential confounding factors noted earlier.

The style of discipline of children is influenced by culture. In a study of low-income white, African American, and Mexican American families of toddlers, both spanking and verbal punishment were found to vary by maternal race/ethnicity. The interaction between harsh discipline and child temperament and behavior is complex and iterative, but overall, punishment does not improve behavior. Specifically, child fussiness at age 1 year predicted verbal punishment and spanking at ages 1, 2, and 3 years, but neither aggressive behavior problems in the child nor the child's development scores on a standardized measure predicted later spanking or verbal punishment. On the other hand, spanking at age 1 year predicted higher child aggressive behavior at age 2 years and lower scores at age 3 years. The effects of spanking and verbal punishment were moderated in some cases by mothers' race and ethnicity and her emotional responsiveness.

Mothers who did not endorse physical discipline, and who nonetheless spanked their children, were found likelier to be suffering from maternal distress, and in these families there was a stronger relationship between frequency of spanking and depressive symptoms reported by their children. The pediatrician should ask about parents' views on discipline, specifically for what behaviors, how, and how often they discipline their children.

### Family Disruption, Dissolution, and Variation: Cohabitation, Divorce, Blended Families

When the family shatters or scatters, the child is threatened and challenged to adapt. Disputes and tension may precede family disruption, and children, even very young ones, are affected.

About 50% of marriages end in divorce, and about half of school-age children spend time living with a single parent or in a stepfamily. Divorce, even when both parents love their child, presents a challenge to children's adjustment. Troubled and contentious marriage is a frightening emotional environment for the child, and one-third of divorced parents continue to contest child custody and visitation arrangements. Boys are more vulnerable to developing adjustment problems in such emotional environments, and girls are more vulnerable to depression if their mothers are depressed. Added to the effect on the emotional environment within the family is the fact that following divorce, most children spend most of their time with their mother, who almost always suffers reduction of economic stability.

Economic uncertainty may influence whether cohabiting couples raising children are able to maintain stability. Mother-child files from the National Longitudinal Survey of Youth indicate that in 1997 about one-fourth of children lived for some time during childhood in a family headed by a cohabiting couple; in 2011, 7% of children did. Subsequent, sometimes rapid, changes in family status may occur, posing adjustment challenges or threat of loss of important relationships for the child. The pediatrician should ask about the economic effect and time course of family changes and help the parent to understand and alleviate their effects on the child, considering the child's developmental level.

### Children in Foster or Kinship Care

Half a million children in the United States are in the child welfare system, having been removed from their parents' care because of neglect or maltreatment. The adults parenting children in out-of-home placement may be extended family members, foster parents, or residential care providers. Removal is typically preceded by toxic or troubled attachments, so the separation from the parent or parents is a loss for an already stressed child, as described by Szilagyi. The pediatrician caring for a child in foster or dependent care should expect complex issues. Knowledge of foster care agencies and familiarity with consent and confidentiality issues is necessary. Often, the child's full medical and developmental record is difficult to obtain, yet the pediatrician must take on the responsibility for health care case management and for promoting regular comprehensive preventive health care. The pediatric medical home should ensure that these children have access to all necessary services, and should maintain communication with their social services agency. Optimizing the physical, emotional, developmental, and mental health status of children in dependent care requires extra attention to screening and documentation. Guidelines found in the second edition of the AAP publication *Fostering Health: Health Care for Children and Adolescents in Foster Care* provide further detail. (See also Chapter 72, Children in Foster or Kinship Care.)

Younger children and infants in out-of-home placement are most vulnerable. In 2006, 169,500 children ages 5 and younger were in foster care (34% of the 510,000 children in the child welfare system). In the United States, maltreatment presents the highest risk of morbidity and mortality for infants and toddlers. These young children have usually suffered experiences that put the development of robust foundations for relationships at grave risk. Early recognition will enable early intervention, but often the pediatrician is appealed to for pharmacologic intervention to reduce children's troubled and troubling behaviors. However, evidence-based interventions to support foster parents can help avert the socially destructive process of multiple foster home placements for children with troubled attachments.

Child Protective Services is a necessary ally for the primary care physician, who is mandated to report abuse or neglect. As a mandated reporter of abuse, the pediatrician must recognize the threshold for reporting, but also as a physician who knows the child in the medical home, the pediatrician will put together the child's story to understand the effect of timing of stress in relation to the child's developmental stage.

## THE FAMILY'S ENVIRONMENT AND CULTURE: FACTORS OUTSIDE THE FAMILY

### Risks, Assets, Resilience

When the environment around the family is strained or threatening, parents' capacity to buffer stress for their children may suffer. Environmental risk rises as income and socioeconomic status fall. A salient fact of poverty is exposure to multiple environmental risk factors that threaten health and well-being for adults and children. Quality health care, child care, and education are harder to access. The neighborhood may lack resources or be unsafe. It may be more difficult for poor families to supervise their children and protect them from the physical and social dangers in their environment.

Risk factors (abuse, neglect, witnessing violence in the home, family discord or divorce, parents with poor health habits, unsafe schools, and unsafe neighborhoods) may be counterbalanced with assets (stable relationships with caring adults, anchor in a faith or spiritual belief or community, involvement in school, available recreational opportunities). Children continuously adapt, and their adaptive repertoire increases with age if they have a solid base upon which to build. It is beyond the power of the pediatrician to prevent the family's misfortune, but noting potential risk factors is important, and the more important question is how the family and child are coping.

Resilience is defined as good adaptation in relation to risk. No matter how resilient the child, more risk is a negative factor. It has long been known that cumulative risk factors increase the threat to healthy development. For example, children with numerous environmental risks, such as having a mother whose capacities are compromised, or living in a chaotic or violent family environment or in poverty, are more than 24 times likelier to have IQs below 85 than are low-risk children.

US Department of Education data show that young children living with multiple risk factors are less likely to achieve benchmarks for early school success. Young children from low-income neighborhoods have a higher incidence of behavioral problems with a negative effect on their development than children growing up in moderate-income or wealthier areas. Children of mothers with mental health conditions or substance abuse problems, or those exposed to domestic violence, are 2 to 3 times more likely to manifest aggression (19% vs 7%), anxiety and depression (27% vs 9%), and hyperactivity (19% vs 7%).

In evaluating the child's environmental risks, the pediatrician also weighs the child's resilience. Supporting parents' coping will directly benefit the child. Recognizing assets and areas of strength and helping parents to build children's resilience will counter the effect of environmental stress on the child.

### **Unemployment, Underemployment, Poverty, Homelessness**

Job loss, with associated financial strain and hardship, affects families greatly and is more common during economic recession. Stressors in the aftermath of job loss include depression and decline in the quality of the parents' relationship. For 2-parent families, both the parent seeking employment and his or her partner may experience depression and reduced relationship satisfaction. The economic environment may affect the child, even if parents are capable and affectionate. Increasing numbers of American households, including 16.7 million children, experienced food insecurity in 2011. Unemployment, rather than poverty, is the strongest predictor of food insecurity.

Households headed by women with limited education and those with teen births are especially vulnerable to economic catastrophe. In a labor market that has shifted away from manufacturing jobs, options for work for women with limited education and job skills are often limited to service-sector jobs with low pay, inadequate benefits, and inflexible hours. This presents a relentless challenge for single mothers, who bear sole responsibility for wage earning, child care, and homemaking. In addition to these pressures, they also must negotiate eligibility for Temporary Assistance to Needy Families (TANF) and Supplemental Nutrition Assistance Program (SNAP, also known as food stamps), and face long waiting lists for affordable housing.

Single mothers in low-wage jobs have been found to exhibit increased symptoms of depression, which directly and negatively affect their psychological functioning and the quality of their parenting, with measurable effects on their children's behavioral and academic outcomes. This is compensated for if mothers have higher educational attainment and capacity to provide emotional support for their children.

Extreme poverty, defined as household income at or less than 50% of the Federal Poverty Level (FPL), is the strongest predictor of family homelessness. Of the 2.3 to 3.5 million Americans who are homeless each year, 34% are families. The number of homeless children is increasing: currently 1.5 million children, or 1 child in

50, experience homelessness. Two-thirds of homeless children worry they will not have enough to eat, and overall they are twice as likely as middle-class children to actually experience hunger and to have moderate to severe health problems, both acute and chronic.

Very low birth weight, poor general health, malnutrition, exposure to lead and other toxins, maltreatment, and victimization are all endemic correlates of poverty. Thus, at a biologic level, poverty interferes with children's capacity to benefit from education. At a social level, the education available to the child may be compromised. In low-income districts, schools may be inadequately funded and their academic resources limited. Child care is likely to be of lower quality, schooling poorer, and some administrators and teachers may have low expectations of their students. Scarcity of books in the home may further impede children's cognitive development. Lack of parental engagement, reading, and family play, and too much screen time can do so as well.

Educational readiness requires good child mental health, which in turn depends upon parents' mental health. Compromised parental mental health, particularly maternal distress and depression, is more common in low-income families. This may disrupt the parent-child relationship upon which a child's social, emotional, and cognitive development is founded. Not surprisingly, children in low-income neighborhoods, with poor housing conditions, high unemployment, and high crime rates, have higher rates of behavior problems that affect their school readiness and performance.

For homeless children, disruption of schooling means they are twice as likely to be expelled or suspended from school, or to repeat a grade. Their estimated graduation rate from high school is below 25%, and at the end of high school, few are proficient in reading and math. It is important to recognize that a child's developmental or mental health "symptoms" may be reasonable adaptations to the stresses of his emotional environment, and that these should be understood and addressed before a psychiatric diagnosis is made.

### **Parental Employment: The Working Mother**

Increasingly, mothers must work for financial reasons. Pediatricians can support working parents by assessing how they balance demands of work and home, determining whether they have adequate child care options, and providing advice about finding quality child care. This may lessen the extent to which parents' work may draw away their available energy and the emotional resources needed for parenting. One-half of women with infants and 64% of women with children are in the workforce, most in full-time jobs. Although overall, research does not support the concern that family relationships, attachment to children, or children's development is harmed by the fact of a mother's work alone, some fatigue and strain inevitably accompanies working, and if the quality of child care is inadequate, children's developmental opportunities will be compromised.

The question of whether children suffer if their mothers work full time has been much debated. The NICHD



Study of Early Child Care and Youth Development showed that in a sample of more than 1,000 demographically and ethnically diverse children, the average child spent 27 hours a week over the first 4½ years of life in nonmaternal care. During children's first 2 years of life, most child care took place in family homes with relatives or in child care homes. As children aged, more were in center-based (formal) care. According to the NICHD report, family and parenting experiences were as important to the well-being of children who had extensive child care experience as they were for children with little or no child care experience.

The pediatrician should ask about hours of parental work, strain associated with work, and how the parent and child are dealing with it, particularly if the parent resorts to letting the child have screen exposure to occupy the time required to prepare meals and manage household chores.

### Child Care

The child's experiences outside the home open opportunities for social-emotional development. Children who attend preschool may be more ready to learn when they enter school, but the proportion of children enrolled in preschool and the quality of care they receive differs according to ethnicity and race. Black and Hispanic children are more likely than white children to participate in Head Start programs. Hispanic children are less likely and black children are more likely to attend preschool than are white children, but the quality of care received may be lower for black children.

Quality of child care is an important factor for preschool children. High-quality care attenuates negative effects of economic disadvantage on children's early academic trajectory. For children whose mothers had low levels of education, formal child care led to higher receptive vocabulary, reading and math achievement scores, and school readiness than for those cared for by their parents. Although children experiencing higher-quality child care have better language and cognitive development, and are more cooperative than those in low-quality care, long hours in child care, even of high quality, may take a toll. Children with higher combined numbers of hours in nonmaternal care showed relatively more behavior problems in both child care and kindergarten classrooms than did those who had spent fewer hours away from their mothers. Cognitive and language development was found to be somewhat better for children who attended child care centers, but also they showed more behavior problems in child care and kindergarten classrooms than children who were placed in other nonmaternal child care arrangements.

Child care is an early watershed for children with social and emotional problems, and may either add to the child's positive experience or exacerbate risks. Young children in preschool have 3 times the expulsion rate of children and youth in K-12 grades. Expulsion rates of 4-year-olds are 50% higher than for 3-year-olds, and boys are 4 times likelier to be expelled than girls.

The pediatrician should ask if the child care setting is formal or informal, how confident the parent feels in the child care providers, how many hours per week

the child spends there, and what happens during the child's day (eg, if much of the time is spent in front of a television set).

### School

School-age children spend most of their days in an educational environment that may be safe, supportive, and stimulating or that may threaten them, leave them feeling confused or unsure, and fail to engage their minds. Racial and ethnic gaps in school readiness carry over from early childhood care and education to affect the child's opportunities in school. The parent and the pediatrician need to know about the quality and environment of the school and whether the school has academic and social resources to optimize students' learning. It is important for the pediatrician to learn about the child's school as well as to know how the child experiences school. Does the child feel that the teacher and the other children like him or her? Does the child feel able to do the work? Has he or she experienced bullying?

School administrators and staff should be aware of bullying if it occurs, because 85% of the time other children witness bullying. Bullying is not a random event; individual child characteristics and family factors may be predictive. Children who are bullied show signs of distress and problems adjusting; these may be the cause or the effect of being bullied. Bullying persists and can be stable across ages, and the mental health effects of childhood bullying may persist until late adolescence. It is associated with internalizing mental health symptoms including self-harm, as well as violent behavior and trauma-associated psychotic symptoms. The pediatrician should inquire about the quality of school and the child's experience, including bullying and, especially for adolescents, cyberbullying.

### The Neighborhood

The child's neighborhood provides contact with other adults and children, as well as opportunities for play, learning, and community experiences. Impoverished and unsafe neighborhoods obviously limit those experiences. Disorganized neighborhoods with large numbers of youth in trouble pose actual danger. Children growing up in dangerous neighborhoods may be denied opportunities for exploration because their parents seek to protect them from harm. The same factors that jeopardize children's readiness for school or success in school may pose risk for gang activity in neighborhoods. Disorganized neighborhoods with large numbers of children who have poor relationships with their parents, who have a low attachment to school, and who have associations among peers involved in delinquent activities such as violence and drug use, are neighborhoods vulnerable to gang presence. According to a recent biennial School Crime Supplement to the Bureau of Justice Statistics (BJS) National Crime Victimization Survey, the proportion of urban students reporting gangs present at school (24%) is increasing.

This may not be a problem only for inner-city neighborhoods. According to the same BJS Survey, an increasing percentage of suburban and rural students ages 12 to 18 years report that gangs were present at their school during the previous 6 months. The rise in



gang activity at schools is partly because gangs use the venues of middle schools and high schools for recruitment and drug distribution. Gangs may direct their members who have dropped out of school to reenroll in order to recruit new members and sell drugs.

The pediatrician should be informed of or inquire about the quality of the neighborhood and how parents cope with potential dangers. Bright Futures provides information and resources on promoting community relationships. It also guides pediatricians to resources for vulnerable families who are recent immigrants or who have limited English proficiency.

### **Military Deployment; Military Culture**

Approximately 1.76 million children and youth grow up in military families, and they are younger than the national average: in the overall population 66% of children are under age 11, but in families on active duty, 78% of children are under 11. Frequent moves, multiple deployments, and injury/loss of a parent are facts of military life that inflict psychological stress on children and their parents. Stress related to deployment is associated with increased incidence of marital problems (44% among active duty and 39% among reserve), and military families' rates of mental health disorders and trauma are higher than national rates. In families of enlisted Army soldiers, child maltreatment was found to be 42% higher during deployment than during nondeployment.

In particular, the wartime deployment of a parent is highly stressful for a child. One-fourth of children with deployed parents experience depression; one-fifth exhibit academic problems. Parents remaining behind experience stress, of which even young children are aware. Children's difficulties are proportional to the mental health difficulties and coping problems of the parent; their mental health symptoms include externalizing and internalizing problems. For veteran spouses returning with PTSD, interpersonal violence rates are higher, and their partners experience higher caregiver burden and manifest poorer psychological adjustment. Mental health resources available to military families, including reserve and National Guard families, are often insufficient to meet families' needs.

Pediatricians who care for patients in military families, whether active duty, veteran, or reserve, or who practice in groups that contract with programs serving veterans or reserve families, will need to recognize and respond to child and family stress associated with the military environment. (See also Chapter 77, Children in Military Families.)

### **The Virtual Environment: Media, Video Games, and Television**

The AAP recommends no television for children under 2 years of age and limiting exposure to screens, including TV, smart phones, and video consoles, to 2 hours a day for older children. Regardless of the home environment and the school and neighborhood environment, children may be exposed to the virtual environment of media by exposure to television, video games, and the Internet. The positive or negative effects on the child depend on the timing, quantity, and quality of this exposure.

For very young children, even apparently benign exposure presents some risk. For infants 8 to 16 months old, each hour per day of viewing baby DVDs and videos was associated with a 16.99 point decrease in MacArthur-Bates Communicative Development Inventory, whereas among toddlers 17 to 24 months old, no statistically significant association was seen. For very young children whose language development is progressing most rapidly, exposure to baby DVDs and videos cannot substitute for reciprocal language interaction with adults and other children.

For older children, screen media exposure (television and video games) has been found to be significantly associated with teacher-reported attention problems, controlling for gender and earlier attention problems. This finding held across media type (TV, video games) and age (middle childhood to early adult). Over time, the negative effects are cumulative: every additional hour of television exposure at 29 months corresponded to a 7% decrease in classroom engagement, a 6% decrease in math achievement, a 10% increase in victimization by classmates, a 13% decrease in time spent engaging in weekend physical activity, a 9% decrease in activities involving physical effort, higher (9%) consumption of soft drinks and snacks (10%), and a 5% increase in body mass index.

For children and adolescents with good adjustment, online activity may be an asset. In a longitudinal sample of youth, the patterns of their peer relationships, the quality of their friendships, and their behavioral adjustment predicted the qualities of both interaction and problem behavior on their social networking Websites at ages 20 to 22 years. Thus, consistent with developmental theory, there is cross-situational continuity in youths' social behaviors, and this extends to the online domain. However, risk of victimization by pedophiles via online contact is also present, and may be higher for youth whose family support and adjustment are compromised.

The online environment also enables cyberbullying. In a large, diverse sample of urban middle- and high-school students, half (49.5%) indicated they had been bullied online, and 33.7% reported that they had bullied others online. Most bullying was by and toward friends, and generally youngsters did not tell anyone about the bullying. After being bullied online, they reported feeling sad, angry, and depressed. Those who bullied others online reported that they did so to feel popular, powerful, or funny, but many reported feeling guilty afterward.

The pediatrician should discuss with the family and the child what type of media exposure the child has, and how it influences him or her. Specific questions about media use should explore whether the media diet is healthy, and whether the child or adolescent turns to media because of loneliness, lack of interaction in the home, or difficulties with peer relationships. (See also Chapter 43, Healthy Use of Media.)

## **CONCLUSION**

The developing child is constantly trying to balance the physical environment, the intimate relationships of the family, and the direct and virtual social environment. To interview parents about the list of

environmental and risk factors presented in this chapter may seem daunting, because the focus of the pediatrician is the child patient, and the pediatrician's capacity to address environmental risk is necessarily limited. Thus, it is crucial to work collaboratively with the family who embody the child's intimate personal environment, and who live in a larger neighborhood and social environment that affects their capacity to optimize their child's experiences. The general area of anticipatory guidance, safety, and health promotion is a broad topic well covered by Bright Futures and in other chapters in this textbook. The AAP Task Force on Mental Health

and American Academy of Child and Adolescent Psychiatry Mental Health Task Force have developed guidelines for recognizing mental health problems in children and guiding them or their troubled family members to specialty services.

This chapter presents a recent literature review of the effects of the environment on the child. It links this information to developmental and psychological effects on the child, and offers guides to questioning and intervening. Table 14-1 summarizes areas for interviewing the parent. The interview about the social environment will empower parents and help them to address risks and optimize their child's environment.

**Table 14-1** Domains of Inquiry About Social-Emotional Environment

	FACTOR IN SOCIAL-EMOTIONAL ENVIRONMENT	EVALUATE
Overall factors influencing biologic basis of social-emotional development	Developmental progression	Parent's understanding of child's developmental capacity.
	Quality of mother-child relationship	Parent-child relationship: can parent protect child from stress and injuries and provide predictable, secure routines?
	Environmental pressures on family functioning	Can family provide adequate nutrition, safe housing, adequate child care/school; are parents under environmental strain?
Factors inside the family	1. Family composition	Social genogram
	2. Attachment	Assess attachment
	3. Parenting style	Inquire about and observe parenting style.
	4. Family member risks	Inquire about or screen for maternal depression or mental illness.
	a. Mental disorder	Inquire about violence or verbal abuse in the home.
	b. Intimate partner violence/ domestic violence	Inquire about substance abuse in the home.
	c. Substance use/abuse	Inquire about how the parent disciplines the child.
	5. Discipline	Inquire about time, course, emotional tone, and economic effect of family dissolution.
	6. Dissolution, disruption, divorce	If child is involved with Child Welfare Services, reconstruct the timeline of events to evaluate risk in relation to the child's developmental level.
	7. Foster children and families	Inquire about current financial stability and whether this affects parenting.
Factors outside the family	Economic hardship and financial stress	Inquire about strengths, resources, resilience. Evaluate if child's "symptoms" are a response to family strain in difficult social environment.
	1. Risks/assets/resilience	Inquire about hours of work, work strain.
	2. Unemployment, underemployment, poverty, homelessness	Is child care formal or informal? How many hours/week?
	3. Working mother	Inquire about the quality of school and the child's experience. Bullying?
	4. Child care	Be informed about or ask about neighborhood quality and how parents cope with potential dangers.
	5. School	If parents are in military or National Guard, inquire about positive or negative aspects.
	6. The neighborhood	Inquire about hours/day of media exposure.
	7. Military deployment	
	8. Media: the virtual environment—DVDs, TV, video games, Internet	

## TOOLS FOR PRACTICE

### Medical Decision Support

- *The CRAFFT Screening Tool* (questionnaire), Center for Adolescent Substance Abuse Research ([www.ceasar-boston.org/CRAFFT/index.php](http://www.ceasar-boston.org/CRAFFT/index.php))
- *Edinburgh Postnatal Depression Scale (EPDS)* (screen), ([www2.aap.org/sections/scan/practicingsafety/toolkit\\_resources/module2/epds.pdf](http://www2.aap.org/sections/scan/practicingsafety/toolkit_resources/module2/epds.pdf))
- *Mental Health Screening and Assessment Tools for Primary Care* (chart), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH\\_ScreeningChart.pdf](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH_ScreeningChart.pdf))
- *Pediatric Intake Form* (form), Bright Futures ([www.brightfutures.org/mentalhealth/pdf/professionals/ped\\_intake\\_form.pdf](http://www.brightfutures.org/mentalhealth/pdf/professionals/ped_intake_form.pdf))
- *A Safe Environment for Every Kid* (questionnaire), SEEK Project ([www.uspreventiveservicestaskforce.org/Home/GetFileByID/859](http://www.uspreventiveservicestaskforce.org/Home/GetFileByID/859))

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## Chapter 15

# PEDIATRIC HISTORY: ASSESSING FUNCTIONING AND MENTAL HEALTH

Steven C. Schlozman, MD; Michael S. Jellinek, MD

## NEED FOR PSYCHOSOCIAL SCREENING

### Prevalence of Psychosocial Dysfunction

Between 5% and 20% of American children experience psychosocial difficulties that include significant functional impairments and psychiatric disorders defined by the fourth edition of the *Diagnostic Statistical Manual of Mental Disorders (DSM-IV)* and the text revision edition (*DSM-IV-TR*). In addition, a significant number of children and adolescents consider suicide. Childhood psychiatric disorders are estimated to increase by 50% by the year 2020. It's also important to

note that with the advent of the fifth edition of the *DSM (DSM-5)*, these numbers might change slightly. Still, the overall burden of psychiatric symptomatology among children and adolescents is predicted to increase regardless of the nosology used.

Psychiatric diagnoses do not always take into account important developmental and functional assessments. For example, family discord may lead to school phobia or oppositionality in young children and to depression and substance abuse in adolescents. A more holistic nosologic discussion is available through the *Diagnostic and Statistical Manual of Mental Disorders, Primary Care Version (DSM-IV-PC)*, a manual defining psychosocial issues within a developmental context.

The *DSM-IV-PC* discusses a broad range of problems, some of which are consistent with formal psychiatric diagnoses and many issues that are clinically relevant despite not meeting full *DSM-IV* criteria. Dysfunction is grouped into 3 main categories: normal variation, problems, and disorders. Normal variation allows for different temperaments, personalities, and developmental paths among healthy children. Problems refer to a broad range of issues that may not meet formal criteria for a discrete psychiatric disorder. For example, the *DSM-IV-PC* recognizes that although a child's anxious reaction to divorce may be a normal and expected developmental response, the child might still be in need of support and services during this difficult time. Finally, disorders refer to specific conditions that meet the *DSM-IV* criteria for a psychiatric disorder. Additionally, the American Academy of Pediatrics (AAP) Task Force on Mental Health has quite appropriately noted that the longitudinal relationship characteristic of primary care allows physicians to recognize psychologic and psychiatric challenges early in the course of the presentation. To this end, primary care pediatricians are ideally suited to engage in secondary and even primary prevention. The long-term relationship with patients ensures a trusting alliance that is necessary for the different kinds of engagement that can be called for in mental health care.

### Secondary Consequences of Psychosocial Issues

Beyond mental health concerns, psychosocial issues in primary care have multiple secondary consequences. Psychosocial dysfunction is a major risk factor for unintentional injuries, the most common cause of death in children. Fires, falls from windows, drowning, and motor vehicle accidents are more common among children who have higher rates of psychosocial stressors. Detection of these broader stressors is challenging, given that *DSM-IV* diagnoses generally do not take into account developmental expectations and corresponding functional assessments. Thus, the pediatrician is served best by broadly screening for psychosocial dysfunction rather than focusing exclusively on psychiatric diagnoses. Additionally, specific populations of children have differential risk factors. Foster children, for example, are at a higher risk for teenage pregnancy, school failure, and incarceration. Familiarity with the risk factors that are particular to

special populations allows the physician to ask more pointed and targeted questions during general evaluations.

### Barriers to Detecting Psychosocial Difficulties

Despite a high prevalence of psychosocial difficulties encountered by children and adolescents, most of these problems are not detected by primary care physicians. Possible reasons for this lack of recognition include time limitations, hesitancy among physicians to attach possibly stigmatizing labels to children, the absence of widely available and easily implemented screening procedures, lack of adequate training regarding psychosocial issues, and limited resources for referral and treatment. In the absence of a medical home, different physicians might not communicate adequately so that problems can be adequately recognized. Further, migrant families change physicians often, adding again to the burden of knowing a given child well enough to recognize the onset of psychiatric difficulties. Additionally, some evidence suggests that primary care physicians may offer discouraging reactions to the presentation of psychosocial difficulties in their practice. The theoretical benefits of managed care, with its preventive focus and consistent quality assurance activities to improve care processes are being overshadowed by pressures of productivity that have decreased the number of minutes physicians spend with each patient and by barriers to referral. In many communities, the medical referral relationship between primary care and pediatric subspecialists does not extend to psychiatrists because of insurance barriers. However, in principle, managed care should encourage referral by emphasizing screening and quality and, perhaps, lower costs over time. Finally, the negative effect of family psychosocial problems and the resultant childhood toxic stress may be mitigated by strengthening critical socioemotional skills and building resiliency early in life.

### Reasons to Screen for Psychosocial Dysfunction

The clear epidemiologic burden of psychosocial challenges facing children and adolescents in the context of limited specialty care demands that primary care physicians play an active role in the detection and treatment of this multidimensional issue. The nature of pediatric practice has changed with the decreasing burden of infectious diseases and the growing need to address psychosocial issues ranging from psychiatric disorders to the psychosocial effects of chronic illnesses to injury prevention. As primary care providers, pediatricians have a unique opportunity to detect and address emerging mental health problems in a non-stigmatizing and supportive medical home, while coordinating with mental health specialty services, schools, child care providers, and social services. Primary care physicians also have the opportunity to both identify psychosocial problems and promote social-emotional health and resilience in children and families. Because psychosocial challenges are heterogeneous, and because the average primary care visit includes limited time and increasing psychosocial demands, screening routinely with structured instruments holds the most

promise for accurate detection of significant difficulties in the primary care setting.

### Goals of Psychosocial Screening

Obtaining a comprehensive psychosocial history is time consuming and inefficient. Practices should develop a structured process that ensures that the families' priorities are addressed, but also that tools for assessing the functioning of the child and family are included in routine health supervision visits. Use of screening tools, such as previsit questionnaires, enable the physician to focus on positive responses as a springboard to further discussion and clarification. Some children's psychosocial issues are recognized because of parental complaints of overt behavioral problems or because of school referral. Less obvious problems, such as dysfunction stemming from divorce or depression, are often identified in the primary care setting. The goal of psychosocial screening is to provide screening methods in harmony with pediatric primary care for early, efficient, and effective recognition of developing psychosocial problems.

## STRATEGIES TO INCREASE RECOGNITION OF PSYCHOSOCIAL DYSFUNCTION

### Interviewing

Careful attention to developmental aspects of the child's life, such as the child's family, friends, school, play, and mood, will help the pediatrician assess the child's overall function. Additionally, special attention must be paid to "out of home care." Many children, sometimes but not always as a result of poverty or marginalized living situations, are at extreme risk for psychosocial challenges in the absence of secure and stable households. Despite the obvious time involved, face-to-face interviewing, in which high-risk issues are discussed with the patient and parents, offers many advantages. The physician can address key issues directly, communicating to the family the importance of psychosocial issues, thus increasing the likelihood that the family will consider these issues appropriate to bring to the physician's attention.

Raising questions face to face builds trust; examples of clinically relevant questions are available through the AAP *Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents* and are easily accessible online at [brightfutures.aap.org](http://brightfutures.aap.org). Topics mentioned in both sources include instructions such as the following:

- Assessment of financial resources.
- At intake, ask all parents for a family history of psychiatric disorder (eg, depression, substance use). A family history of depression, anxiety, substance use, and attention-deficit/hyperactivity disorder (ADHD) places the child at high risk.
- Assessment of caretaker skills and reliability.
- At annual visits, ask about parental discord and marital stability.
- Assessment of academic issues.
- Assessment of high-risk behaviors (oppositiousness, drug use, etc).



- For newborns, assess parental coping, family support, and maternal depression. A depressed mother has a profound emotional and cognitive effect on an infant; because of the very good response to treatment, the pediatrician can do a real service to the family and the baby through early intervention.
- For toddlers, ask about the child's autonomy and the ability to *separate*.
- For early school-aged children, ask about social functioning.
- For adolescents, ask parents about their child's autonomy, and ask the adolescent about mood and substance use.

Additionally, physicians may refer to the algorithms found in the article "Enhancing Pediatric Mental Health Care: Algorithms for Primary Care through the AAP Task Force on Mental Health" ([pediatrics.aappublications.org/content/125/Supplement\\_3/S109](http://pediatrics.aappublications.org/content/125/Supplement_3/S109)). These algorithms provide a framework for promoting social-emotional health and identifying and responding to new mental health concerns, whether raised by parents in scheduling the visit or suggested by the data collection and assessment activities from routine screening.

### Screening Tools

#### Parent Questionnaires

Because of the time constraints inherent in a face-to-face approach, alternative strategies have been developed to screen more efficiently for psychosocial difficulties. Ideally, these tools are used to supplement face-to-face time. The Achenbach Child Behavior Checklist (CBCL) is the most studied and best validated behavioral screening device available for children aged 4 to 16 years. The Achenbach CBCL is completed by the child's parents and is divided into 2 distinct item groups (behavior problems and school competency). Although the results of the Achenbach CBCL are reliable and valid, the main drawbacks to the use of this instrument include length of administration (more than 100 items requiring approximately 20 minutes of the parents' time) and some complexity in methods for scoring and interpreting the results of the questionnaire.

A less cumbersome alternative to the Achenbach CBCL is the Pediatric Symptom Checklist (PSC), a 35-item survey also given to the parents and requiring only a few minutes to complete. In addition, the results of the PSC can be scored quickly, with 2 points assigned to each question answered "often," 1 point assigned to each answered "sometimes," and 0 points assigned to each answered "never." Administration and scoring commonly take 3 to 5 minutes. A score greater than 28 suggests a 70% likelihood that the child has significant psychosocial difficulties; scores less than 28 suggest a greater than 95% likelihood that the child has no substantial psychosocial problems. Thus, if the parents complete the PSC in the waiting room and have it scored by a receptionist or clinical assistant, then the pediatrician can quickly recognize and more closely evaluate significant psychosocial issues.

However, although the PSC works well in adolescent populations, it is somewhat hampered in this age group by the parents' limitations in correctly assessing, through a questionnaire, their child's intrapsychic

state. Specifically, some parents will not know that their child is depressed because the child seems to be in reasonable spirits and functioning well; thus, the PSC will, in this circumstance, yield a false-negative result. Despite this difficulty, because the PSC primarily assesses function, it still yields efficient and important information that can direct further inquiry.

A relatively new screening device is the Strengths & Difficulties Questionnaire. This instrument includes 25 items that assess specifically for emotional difficulties; problems with conduct, hyperactivity, and inattention; peer relationship indicators; and prosocial behavior. This screening tool is completed by parents and teachers of children aged 4 to 16 years, and additional versions exist for assessing younger children. The Strengths & Difficulties Questionnaire is similar to the PSC, but is perhaps slightly more complicated to score.

Finally, physicians who suspect specific psychiatric syndromes such as anxiety or depression can utilize specialized screening tools. For depression, the Patient Health Questionnaire-9 (PHQ-9) can be useful, and, for anxiety, the Generalized Anxiety Disorder-7 (GAD-7) can be of benefit. These are both short and easy to administer in the office or waiting area.

#### Patient Questionnaires

For young children, the Human Figure Drawing Screening Device has been found useful in elucidating occult anxiety and depression.

The issue of identifying the adequately functioning, but depressed, teenager can be addressed in several ways. Columbia University has started a nationwide program called TeenScreen. This program helps schools and physicians construct different means by which adolescents can be screened for depression and suicidality. Interestingly, some political opposition exists to this program, with several political groups suggesting that not all Americans are in favor of screening children for psychiatric difficulties. A more traditional approach involves use of the Beck Depression Inventory, completed by the adolescent at the time of the primary care visit. Twenty percent or more of teenagers have scores that raise concerns using this screening instrument.

#### Specific Screening

Some pediatric practices have gone beyond general psychosocial and depression screening to help identify children with autism, using the Modified Checklist for Autism in Toddlers (M-CHAT) and the Parents' Evaluation of Developmental Status (PEDS), and screening for adolescent substance use. Offering critiques or endorsements of every screening device available is not the goal of this chapter. All of the methods discussed have utility, and physicians must choose an instrument that best addresses their practice, level of interest, and patient population.

#### Assessing Severity of Psychosocial Dysfunction

When psychosocial issues are identified through screening or a clinical interview, patients should be assessed for the severity of the impairment in functioning. Although conditions such as psychosis or

serious suicidal ideation are clearly severe, other problems, such as depression or anxiety, are quite variable in their severity. Not all cases of depression, for example, need specialized treatment, although some depressed children require an aggressive and multimodal approach and even hospitalization.

An assessment of severity includes the following:

1. *Symptoms*: number, frequency, and duration of symptoms, and places where the symptoms are experienced
2. *Functioning*: developmental effect on functioning in key areas such as family, friends, school, activities, and self-esteem
3. *Burden of suffering*: intensity of suffering, duration, limitations on family activities, danger to self and others, and intrusion into developmental tasks or daily activities

## FACTORS AFFECTING PSYCHOSOCIAL HEALTH

In the process of screening and assessment for psychosocial health, understanding risk factors that may be associated with future problems is also important. Several biologic and environmental factors may be protective against the risk of adversity leading to serious psychosocial problems. Table 15-1 outlines both protective and risk factors for psychosocial difficulties. The number of moderate risk factors can have a cumulative effect on a child's dysfunction that is greater than the effect of any single severe risk factor. Children facing 3 or more risk factors have a very high likelihood of psychosocial problems. Individual risk factors that have special significance include single-parent households and poverty.

The issue of poverty deserves special mention. Although numerous studies have connected low socioeconomic status with increased risk of psychosocial dysfunction, research suggests that pediatricians tend

to address a larger proportion of psychosocial concerns in highly educated families than in less-educated families. A potential explanation for this discrepancy is that more highly educated parents might feel more comfortable bringing psychosocial issues to their pediatrician's attention, whereas less-educated parents might not realize that the pediatrician's office is appropriate for psychosocial inquiries. In addition, some studies have shown that middle- to upper-class parents tend to over-report their children's psychosocial problems, whereas lower-class parents tend to under-report. A recently posited alternative explanation for why poverty is a risk factor includes the possibility that some mothers are more likely to ask the community for support with their child's psychosocial difficulties. This practice may be more prevalent in lower-income families. All of these findings demonstrate the need for a thorough and systematic review of psychosocial issues in all patients within a pediatric practice.

## BRIEF EVALUATION

Many psychosocial problems will be elucidated through focused interviewing or using different screening instruments. For best results, physicians should be relatively consistent with their screening instruments, familiarizing themselves with one instrument with which they and their colleagues are most comfortable. In addition, patients might have a definite psychosocial complaint, often mentioned by parents or school personnel. At this point, the physician should attempt to elaborate the symptoms, further defining the nature of the complaint. Risk factors and developmental concerns should be considered, and the child's daily functioning should be examined. The SEEK (Safe Environment for Every Kid) model of pediatric care is an example of a program that was developed to help primary care physicians identify and address psychosocial problems that impair parental and family functioning and jeopardize children's

**Table 15-1**

**Children's Well-Being: Protective and Risk Factors**

HEALTH	GOOD HEALTH	CHRONIC DISEASE, ILL HEALTH
Temperament	Example: pleasant mood	Example: negative mood, irritable
Cognitive status	Normal intelligence quotient (IQ) (particularly verbal)	Learning disability or low IQ
Emotional health	Good mental health function	Pre-existing emotional disorder
Sociability	Good peer relations	Poor peer relations
Child reaction to stress	Perceives stress as limited; does not blame self	Perceives continued threat; blames self
Quality of attachment	High quality, high continuity; securely attached	Low quality, discontinuous; ambivalent, insecurely attached
Parent competence	Competent	Incompetent
Family resources	Adequate economic resources	Poverty or discrimination
Quality, stability, safety of environment	Adequate, stable, safe	Inadequate, unstable, unsafe
Family relationships	Good communication; little conflict	Poor communication; excessive conflict
Emotional and physical health of caregivers	Caregivers in good emotional and physical health	Mental illness or physical illness in caregivers
Availability of or access to community resources	High access	Low access

physical and mental health. (Dubowitz) Several guidelines will be helpful in this process.

1. For younger children, observe them while directing questions to the parents.
2. For school-aged children, use confirmatory questions, if possible, without parents being present.
3. For adolescents, perform a separate interview with the patient alone. Assess important issues such as substance use and depression. Inquire about sexual activity. Consider parental functioning, especially abuse, depression, and substance use.
4. Review relevant risk factors and potentially protective factors.
5. Assess safety, paying special attention to potential accidents, suicidal ideation, and risk-taking behaviors.
6. Complete a severity estimate using the Achenbach CBCL and the PSC formats, ranking the current issue as mild, moderate, or severe.

Once information is gathered, the presenting complaint should be categorized as either a normal variation that requires no further action or a problem that requires special consideration. Many issues can be addressed at the primary care level, often with comanagement by mental health professionals or school personnel. Other, more serious problems require outside referral for evaluation by a specialist and, possibly, ongoing treatment. The most severe cases often require emergency referral.

## THE FUTURE IS NOT QUITE HERE

The future of psychosocial screening is ripe with promise. Perhaps the most exciting aspect concerns the possible use of genetic screening to subtype risk factors for psychosocial difficulties and to predict treatment response. For example, Caspi and colleagues reported an autosomal recessive genotype of the serotonin transporter gene that is strongly correlated with the propensity to develop depression after a negative life event. Patients who were heterozygous or autosomal dominant seemed significantly less at risk for psychosocial difficulties after difficult events. Importantly, however, the technology and the understanding of these and similar findings are not yet applicable to routine practice; rather, they represent important directions of future inquiries. Similarly, numerous organizations suggest that sophisticated neuroimaging assays and the use of electroencephalographic evaluations have the capacity to predict the onset of psychosocial problems. The current standard of care and the state of the research concerning these techniques suggest that the information gleaned from these evaluations is no better than a careful clinical evaluation. For this reason, at this point, little practical stock can be placed in these tests, but they do hold great promise for the future.

## CHANGING PRACTICE ENVIRONMENT AND NEXT STEPS

Although the epidemiology of pediatric practice has shifted dramatically from infectious disease to immunologic and psychosocial concerns, the changes in reimbursement secondary to managed care constraints

have made psychosocial screening and referral for appropriate treatment increasingly difficult. For most children in the United States, mental health services are carved out of pediatric care, with financial incentives that discourage referral and comprehensive treatment. These carved-out companies limit the role of psychiatrists primarily to medication management, creating an environment increasingly overemphasizing psychotropic medication at the expense of both comprehensive and alternative treatments. Furthermore, capitation may be an additional disincentive to referral to specialty services.

However, innovative practices may be able to provide more children with adequate treatment in spite of the current health care insurance climate.

General psychosocial screening usually results in a substantial increase in recognition and an increase in referral rate from the 1% to 2% range to 4%. Many practices have made use of new technologies to set up electronic questionnaires on tablets in the waiting room or from home through the Internet. Built-in screening tests can be determined by the child's age and risk factors. For example, a family history of ADHD or a cluster of positive answers to school dysfunction questions may elicit, through internal logic, an ADHD screening questionnaire. Given the prevalence of disorders, some pediatricians already have mental health professionals in their practices to provide follow-up to screening, consultation, and ongoing services. The idea of the office social worker being at the hub of referral services, providing individual, family, and group treatment in the pediatric office setting, can be easily imagined. These groups might include preventive efforts regarding recent divorce, ongoing support for parents raising children with ADHD, or treatment for adolescents using substances or dealing with depression. Depending on the local reimbursement climate, screening, evaluation, and in-office services may be covered and self-sustaining.

Addressing a child's psychosocial development and dysfunction is among the highest priorities for parents who experience their child's emotional suffering on a daily basis. Parents are important partners in supporting the health and well-being of children, but they sometimes need help building their own capacity to effectively support their children. The Strengthening Families Protective Factors Framework ([www.cssp.org/reform/strengtheningfamilies](http://www.cssp.org/reform/strengtheningfamilies)) identifies the protective factors that all families need as parental resilience, knowledge of parenting and child development, social connections, concrete supports in the time of need, and social-emotional competence of children. To this end, the primary care pediatric office, with adequate reimbursement, is in an ideal setting to provide crucial screening and to initiate important treatments.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *Trauma Guide* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/healthy-foster-care-america/Pages/Trauma-Guide.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/healthy-foster-care-america/Pages/Trauma-Guide.aspx))



**Medical Decision Support**

- *Ages & Stages Questionnaires* (screen) (agesandstages.com)
- *The ASEBA Approach* (checklist), Achenbach System of Empirically Based Assessment ([www.aseba.org](http://www.aseba.org))
- *The CRAFFT Screening Tool* (screen), Center for Adolescent Substance Abuse Research ([www.ceasar-boston.org/CRAFFT/index.php](http://www.ceasar-boston.org/CRAFFT/index.php))
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- *Generalized Anxiety Disorder 7 Item (GAD-7) Scale* (questionnaire), Substance Abuse and Mental Health Services Administration ([www.integration.samhsa.gov/clinical-practice/GAD708.19.08Cartwright.pdf](http://www.integration.samhsa.gov/clinical-practice/GAD708.19.08Cartwright.pdf))
- *Mental Health Screening and Assessment Tools for Primary Care* (chart), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH\\_ScreeningChart.pdf](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH_ScreeningChart.pdf))
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- *PEDS* (screen), PEDStest.com ([www.pedstest.com](http://www.pedstest.com))
- *Screen for Child Anxiety Related Disorders (SCARED): Child Version* (questionnaire), University of Pittsburgh ([www.psychiatry.pitt.edu/sites/default/files/Documents/assessments/SCARED%20Child.pdf](http://www.psychiatry.pitt.edu/sites/default/files/Documents/assessments/SCARED%20Child.pdf))
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- *SEEK Parent Questionnaire* (screen), University of Maryland School of Social Work ([theinstitute.umaryland.edu/seek/seek\\_pq.cfm](http://theinstitute.umaryland.edu/seek/seek_pq.cfm))
- *Strengths and Difficulties Questionnaires* (screen), Youth in Mind ([www.sdqinfo.com](http://www.sdqinfo.com))

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**Chapter 16****PEDIATRIC PHYSICAL EXAMINATION: INTERPRETATION OF FINDINGS**

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It is assumed that the pediatrician has learned from training and practice to perform the physical examination specific to the age of the child encountered and consistent with the tried and true formula of general and close visual inspection, olfaction, manipulation, palpation, percussion, and auscultation. This chapter is dedicated to the physical examination and its findings, defined as what the physician discovers during the examination and his or her knowledge of conditions commonly encountered in pediatric practice. It is also convenient to relate these findings to specific age groups in order to enhance the efficiency of the development of differential diagnoses. Tables of common diagnoses associated with specific examination findings are provided. As is often the case, a single finding may produce a differential diagnosis spanning multiple organ systems, and the specifics of that finding as it relates to a particular organ or system can be found in the appropriate chapters of this book. Also, the order in which these findings are presented is based generally on a "head to toe" examination, which is by no means adaptable to every situation. While many textbooks are available on the subjects of pediatric and adult physical diagnosis, this chapter is meant to be a quick and convenient resource for those encountering a specific finding or multiple findings during a comprehensive physical examination.

**VITAL SIGNS AND ANTHROPOMETRICS****Temperature**

The definition of fever is a core temperature of 100.4°F (38°C) or higher. Any condition that affects hypothalamic regulation can affect temperature. The most common cause of fevers overall in pediatrics is infection from the release of exogenous or endogenous pyrogens. Causes of fever by age group are listed in Table 16-1.

Special conditions causing elevation in temperature include hyperthermia from exposure to ambient heat with insufficient heat elimination mechanisms (eg,



**Table 16-1** Common Findings in the Office Examination

VITAL SIGN	FINDING	NEWBORN AND INFANT	CHILD	ADOLESCENT
<b>Fever, hyperthermia</b>	Temperature $\geq 100.4^{\circ}\text{F}$ ( $38^{\circ}\text{C}$ )	Infection, overwrapping, excessive environmental heat	Infection, malignant hyperthermia, increased environmental heat (heat exhaustion, heat stroke), rheumatic disease, hyperthyroidism, inflammatory bowel disease, malignancy	Same as child
<b>Hypothermia</b>	Temperature $\leq 95.9^{\circ}\text{F}$ ( $35.5^{\circ}\text{C}$ )	Infection, underwrapping, insufficient environmental heat	Cold exposure, hypothyroidism, hypoglycemia, CNS neoplasms and other dysfunction (including stroke), chronic malnutrition	Same as child
<b>Heart rate and rhythm</b>	Varies with respiration (sinus arrhythmia)	Normal	Normal	Normal but less common
	Rapid heart rate (tachycardia)	Fever, fear, pain, infection, activity, anemia, drug toxicity (eg, adrenergics, anticholinergics), cardiac disease	Same as infant, but also psychostimulants, antihistamines, early shock, hyperthyroidism	Same as child and infant, but also other illicit substances, eg, cocaine
	Slow heart rate (bradycardia)	Cardiac conduction defects, drug toxicity, malnutrition	Same as infant, but also consider toxic ingestion, hypothyroidism	Same as infant and child, but also consider illicit drug use or toxic ingestion
	Heart rate lability	Drug toxicity, severe malnutrition	Same as infant, but also consider toxic ingestion	Same as infant and child, but also consider illicit drug use
<b>Respiratory rate</b>	Cessation of breathing (apnea)	Prematurity, gastroesophageal reflux disease, tracheoesophageal fistula, choanal atresia, Pierre Robin syndrome, sepsis, metabolic (electrolyte, acid-base disorders), drug toxicity, suffocation, positional asphyxia, sudden infant death syndrome, central hypoventilation syndrome	Tonsillar hypertrophy (significant), severe pneumonia or asthma, epiglottitis, bacterial tracheitis, retropharyngeal abscess, CNS lesion/infection/trauma, toxic ingestion	Obesity, CNS lesion/infection/trauma, severe pneumonia or asthma, toxic ingestion
	Rapid respirations (tachypnea)	Transient tachypnea of the newborn, infection, cardiac disease, fever	Fear/anxiety, infection, asthma, acidosis, CNS lesion, toxic ingestion	Same as child, but anxiety more common
	Slow respirations (bradypnea)	CNS lesions, hydrocephalus, drug toxicity, respiratory muscle fatigue	CNS lesions, drug toxicity, respiratory muscle fatigue	Same as child
	Deep and or labored respirations (dyspnea)	CNS lesions, infection, drug toxicity, cardiac dysfunction, pulmonary dysfunction, metabolic disease	CNS lesions, drug toxicity, fear/anxiety, pulmonary dysfunction, cardiac dysfunction	Same as child, but anxiety more common
<b>Blood pressure</b>	High (hypertension)	Renal artery stenosis, renal vein thrombosis, renal parenchymal disease, increased intracranial pressure, intracranial hematoma (trauma), congenital adrenal hyperplasia, tumor, drugs, hypercalcemia, fluid overload, hyperthyroidism, coarctation of the aorta, steroid toxicity	Hereditary, renal parenchymal disease, hyperthyroidism, Cushing disease, hyperaldosteronism, increased intracranial pressure, tumor, pain/anxiety, drugs	Same as child, but substance abuse is more common, stress/anxiety

Continued

**Table 16-1** Common Findings in the Office Examination—cont'd

VITAL SIGN	FINDING	NEWBORN AND INFANT	CHILD	ADOLESCENT
	Low (hypotension)	Hypovolemia, adrenal insufficiency, dehydration, sepsis, drugs, heart disease	Same as newborn, but also consider heart disease, steroid withdrawal (Addisonian crisis), CNS lesion, diabetes, heat stress	Same as child, but consider toxic ingestion, eating disorder
	Changes with position (orthostatic changes)	Rare	Prolonged bed rest, hypovolemia, autonomic dysfunction, malnutrition.	Same as child, but consider anorexia nervosa and bulimia

CNS, central nervous system.

sweating), malignant hyperthermia, heat cramps, heat exhaustion, and heat stroke. Malignant hyperthermia, an inherited disorder, may follow administration of inhalation anesthetics or succinylcholine. Heat cramps are painful, forceful contractions of large muscle groups usually later in exercise. Heat exhaustion includes fatigue, malaise, headache, dizziness, hypotension, tachycardia, nausea, and vomiting from intravascular volume depletion. Heat stroke includes elevation of temperature with mental status changes. These findings are also listed in Table 16-1.

Hypothermia results from hypothalamic dysregulation, exposure to cold with reduced ability to retain heat (increased surface area in a young infant), insufficient thermal protection (coverings), and inability to shiver. The definition of hypothermia is a core temperature of less than 96.0°F (35.5°C). Conditions associated with hypothermia are listed in Table 16-1.

### Heart Rate and Rhythm

Examination through auscultation and palpation gives a great deal of information about heart rate and rhythm. Commonly encountered findings include sinus arrhythmia, increased rate during inspiration and decreased rate during expiration (normal), tachycardia, rate above the normal rate for age, bradycardia, heart rate below normal range for age, heart rate lability, changes in rate and rhythm at rest, and irregular rhythms that may be caused by conduction abnormalities. Normal heart rate for age is found in Table 16-2, and diagnostic possibilities from these findings are found in Table 16-1.

### Respiratory Rate

Knowledge of normal respiratory rates by age group is useful to further define the presence or absence of cardiopulmonary and metabolic disease (Figure 16-1). Findings encountered during the pediatric physical examination include apnea (cessation of breathing for more than 20 seconds); tachypnea (respiratory rate above normal); bradypnea (respiratory rate below normal); dyspnea (shortness of breath); deep respirations with use of accessory muscles of respiration; Kussmaul respirations (rapid, heavy, deep breathing); and Cheyne-Stokes respiration (alternating periods of rapid and slow breathing). Retractions from greater

**Table 16-2** Average Heart Rate for Infants and Children at Rest

AGE	HEART RATE AT REST (BEATS/MIN)
Birth–1 mo	100–180
1–12 mo	100–180
1–3 y	70–110
4–6 y	70–110
7–12 y	70–110
13–19 y	55–90

Adapted from Monaghan A. Detecting and managing deterioration in children. *Paediatric Nursing*. 2005;17:32–35.

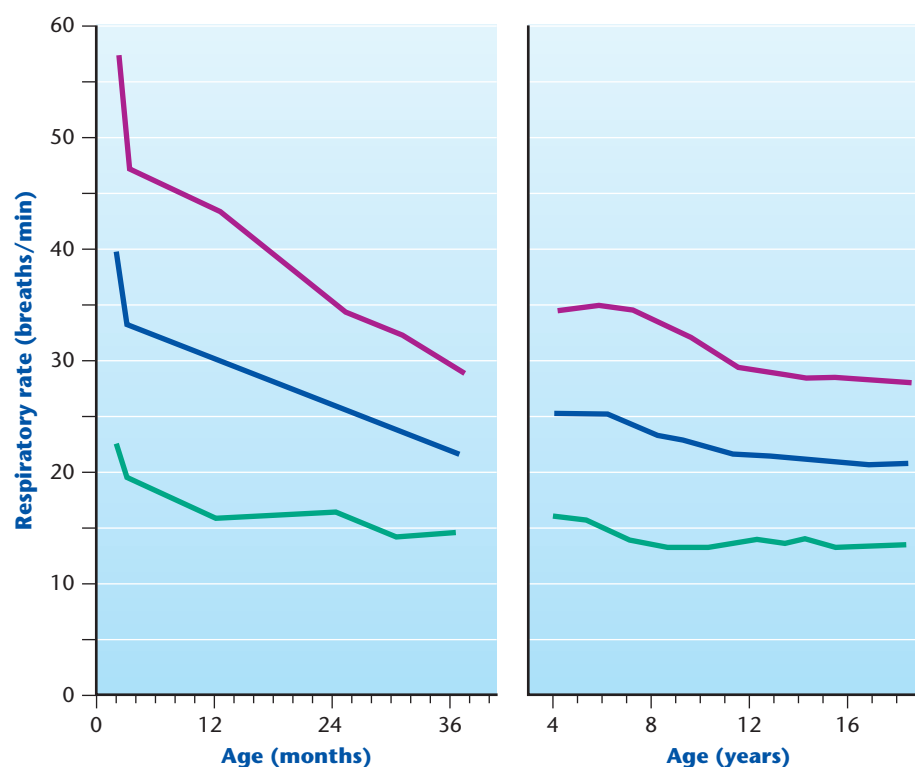
chest wall compliance and grunting are signs of significant lower respiratory disease in infants. Use of accessory muscles of respiration (sternocleidomastoids, scalenes) is associated with increased respiratory effort in older children and adolescents. Conditions associated with these findings are also found in Table 16-1 and Table 16-3.

### Blood Pressure

Knowledge of normal pediatric blood pressures at different ages assists in the interpretation of blood pressure measurements. These are found in Table 16-4 and Table 16-5. Most blood pressure measurements are necessarily peripheral measurements, most commonly obtained with a sphygmomanometer. Automated blood pressure relies on oscillometry and is less examiner dependent than manual cuff measurements. Findings, based on a knowledge of normal values, include hypertension, high blood pressure, hypotension, low blood pressure, shock, initial tachycardia and later perfusion abnormalities in children, and orthostatic changes, change of blood pressure (and pulse) with position. Orthostatic hypotension is the most commonly encountered finding. Findings related to abnormalities in blood pressure are shown in Table 16-1.

### Anthropometrics

Anthropometrics consists of height, weight, head circumference, and the calculated value of body



**Figure 16-1** Normal respiratory rate for children. (Adapted from Pasterkamp H. *The history and physical examination*. In: Chernick V, Boat TF, Wilmott RW, Bush A, eds. *Kendig's Disorders of the Respiratory Tract in Children*. 7th ed. Philadelphia, PA: Elsevier Saunders; 2006: 77, with permission from Elsevier.)

Table 16-3

Common Findings in the Chest Wall and Lungs

SITE	FINDING	NEWBORN AND INFANT	CHILD	ADOLESCENT
Chest wall	Asymmetry of anatomy	Poland syndrome, rib or thoracic vertebral anomaly	Pectus deformity, rib or vertebral anomaly, scoliosis, Poland syndrome	Pectus deformity, scoliosis, Poland syndrome
	Asymmetry of chest motion	Unilateral diaphragmatic paresis/paralysis, pneumothorax	Neuromuscular disease, diaphragmatic paresis, paralysis, pneumothorax, foreign body	Neuromuscular disease, pneumothorax, foreign body
	Large thorax	Masses including abdominal contents, bronchiolitis	Asthma, cystic fibrosis	Asthma, cystic fibrosis
	Small thorax	Neuromuscular disease, bony dysplasias	Costochondritis, xyphoiditis, Tietze's syndrome, bony dysplasias, trauma, infection	Costochondritis, xyphoiditis, slipping rib syndrome, Tietze's syndrome, bony dysplasias, trauma, infection, gynecomastia
	Dullness to percussion	Fluid in thorax, mass in thorax (bowel, tumor), hypoplastic lung	Fluid in thorax, tumor, consolidation	Same as child
	Retractions	Increased work of breathing from any cause	Same as infant	Same as child
	Accessory muscle use	Increased work of breathing from any cause	Same as infant	Same as child, includes panic/hyperventilation

Continued

**Table 16-3** Common Findings in the Chest Wall and Lungs—cont'd

SITE	FINDING	NEWBORN AND INFANT	CHILD	ADOLESCENT
<b>Lung</b>	Stridor	Vocal cord paresis/paralysis, vocal cord or laryngeal lesion/anomaly, GERD, vascular ring, mediastinal mass, chronic aspiration syndromes, tetany, airway trauma, subglottic stenosis	Vocal cord paresis/paralysis, infection (including laryngotracheobronchitis and epiglottitis), vocal cord or laryngeal lesion/anomaly, GERD, vascular ring, chronic aspiration syndromes, mediastinal mass, foreign body, airway trauma	Vocal cord paresis/paralysis, vocal cord dysfunction, infection including epiglottitis, GERD, mediastinal mass, toxins, foreign body, airway trauma, laryngeal lesions (including neoplasm)
	Decreased vocal fremitus/dullness to percussion, decreased breath sounds	Consolidation, intrathoracic fluid or air, atelectasis, bowel or liver in chest, masses	Consolidation, intrathoracic fluid or air, masses, atelectasis, pulmonary malformations	Same as child
	Coarse, wet crackles and snaps (rhonchi)	Aspiration syndromes, ineffective cough, pneumonia, GERD	Aspiration syndromes, pneumonia, tracheitis, bronchitis, asthma, cystic fibrosis, GERD	Aspiration syndromes, pneumonia, tracheitis, bronchitis, asthma, cystic fibrosis, GERD, primary smoking
	Fine crackles (also termed rales and crepitations)	Consolidation, heart failure, aspiration syndromes, bronchiolitis, pneumonia (viral, bacterial)	Consolidation, heart failure, asthma, pneumonia (viral, bacterial), aspiration syndromes	Consolidation, heart failure, asthma, pneumonia (viral, bacterial), aspiration syndromes
	Monophonic wheeze (fixed)	Tracheomalacia, airway compression because of vascular/GI/lung anomalies, mediastinal masses	Focal tracheomalacia, foreign body, airway compression because of vascular/GI/lung anomalies, mediastinal masses	Foreign body, masses, lung and vascular anomalies
	Polyphonic wheeze (dynamic)	Aspiration syndromes, bronchiolitis, heart failure, asthma	Aspiration syndromes, heart failure, asthma	Same as child
	Pleural rub	Pleuritis secondary to infection, neoplasm, rheumatic vasculitic disease, and trauma; with early pleural effusion of any etiology	Same as infant	Same as child
<b>Cyanosis</b>	Blue tinge to mucus membranes	Cardiac disease, infection/sepsis, aspiration syndromes, apnea, hypoventilation, atelectasis, methemoglobinemia	Cardiac disease, infection, atelectasis, intrathoracic fluid or air, toxin, methemoglobinemia	Same as child
<b>Clubbing</b>	Increased subungual tissue	Rare	Chronic cardiac, respiratory, or hepatic disease; familial	Same as child

GERD, gastroesophageal reflux disease; GI, gastrointestinal

mass index (BMI =  $\text{wt}/\text{ht}^2$ ), all of which may be displayed as absolute numbers or percentiles for age and gender. Knowledge of normal anthropometrics, including head circumference, is essential to the pediatrician, and these are found in Figure 16-2, Figure 16-3, Figure 16-4, and Figure 16-5. Charts of head circumference and growth are useful for serial

measurement and monitoring during regular office visits, and deviation from these curves may be the first sign of chronic disease or caregiver neglect. Abnormal findings related to height, weight, and head circumference are addressed in this chapter's discussion of Head, Eyes, Ears, Nose, and Throat and Endocrinology.



Table 16-4

Blood Pressure Levels for Boys by Age and Height Percentile<sup>a</sup>

AGE (YEAR)	BP (PERCENTILE)	SYSTOLIC BP (mm HG)							DIASTOLIC BP (mm HG)						
		PERCENTILE OF HEIGHT							PERCENTILE OF HEIGHT						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	85	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	110	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	117	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	76	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	78	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91

Continued

**Table 16-4** Blood Pressure Levels for Boys by Age and Height Percentile—cont'd

AGE (YEAR)	BP (PERCENTILE)	SYSTOLIC BP (mm HG)							DIASTOLIC BP (mm HG)						
		PERCENTILE OF HEIGHT							PERCENTILE OF HEIGHT						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP, blood pressure; SD, standard deviations.

<sup>a</sup>The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

From US Dept of Health and Human Services, National Institutes of Health, and National Heart, Lung and Blood Institute. *The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents*. National Institutes of Health publication 05-5267. Bethesda, MD: US Dept of Health and Human Services, National Institute of Health; 2005.

**Table 16-5** Blood Pressure Levels for Girls by Age and Height Percentile<sup>a</sup>

AGE (YEAR)	BP (PERCENTILE)	SYSTOLIC BP (mm HG)							DIASTOLIC BP (mm HG)						
		PERCENTILE OF HEIGHT							PERCENTILE OF HEIGHT						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81

Table 16-5

Blood Pressure Levels for Girls by Age and Height Percentile—cont'd

AGE (YEAR)	BP (PERCENTILE)	SYSTOLIC BP (mm HG)							DIASTOLIC BP (mm HG)						
		PERCENTILE OF HEIGHT							PERCENTILE OF HEIGHT						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	64	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

BP, blood pressure; SD, standard deviations.

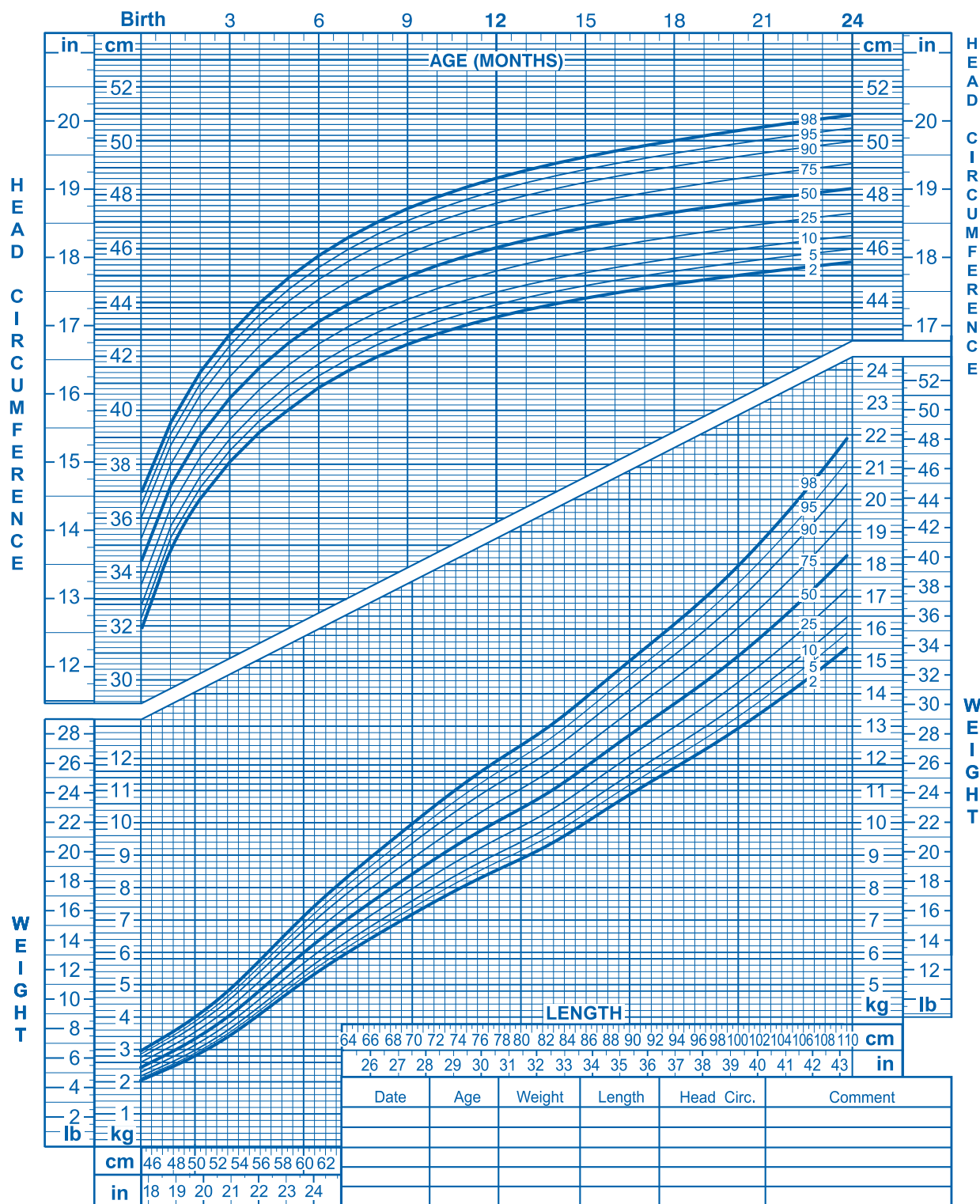
\*The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

From US Dept of Health and Human Services, National Institutes of Health, and National Heart, Lung and Blood Institute. *The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents*. National Institutes of Health publication 05-5267. Bethesda, MD: US Dept of Health and Human Services, National Institute of Health; 2005.

## Birth to 24 months: Boys Head circumference-for-age and Weight-for-length percentiles

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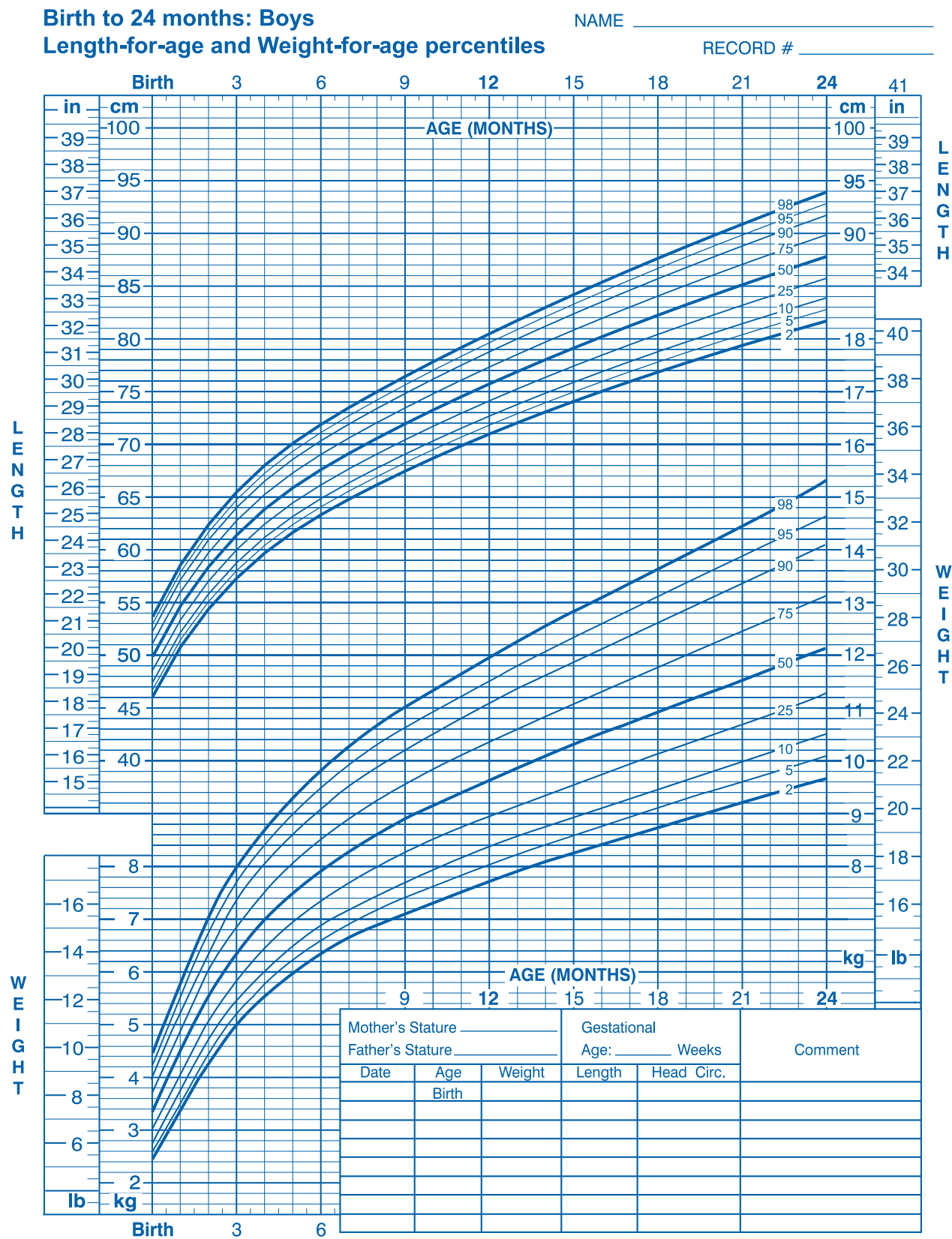


Published by the Centers for Disease Control and Prevention, November 1, 2009  
SOURCE: WHO Child Growth Standards (<http://www.who.int/childgrowth/en>)



**Figure 16-2** Head circumference and weight-for-length: boys.





Published by the Centers for Disease Control and Prevention, November 1, 2009  
 SOURCE: WHO Child Growth Standards (<http://www.who.int/childgrowth/en>)

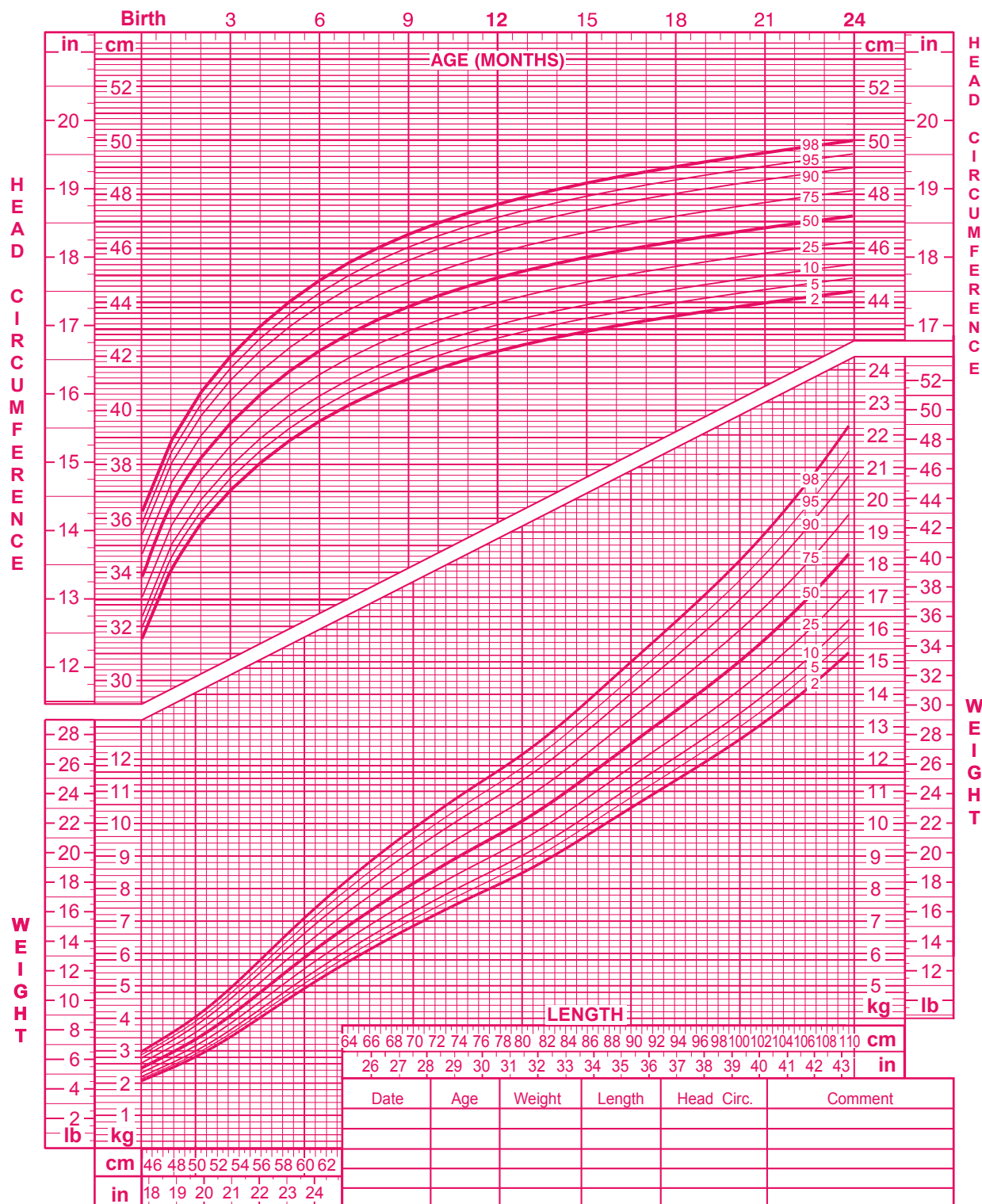


**Figure 16-3** Length-for-age, weight-for-age: boys.

### Birth to 24 months: Girls Head circumference-for-age and Weight-for-length percentiles

NAME \_\_\_\_\_

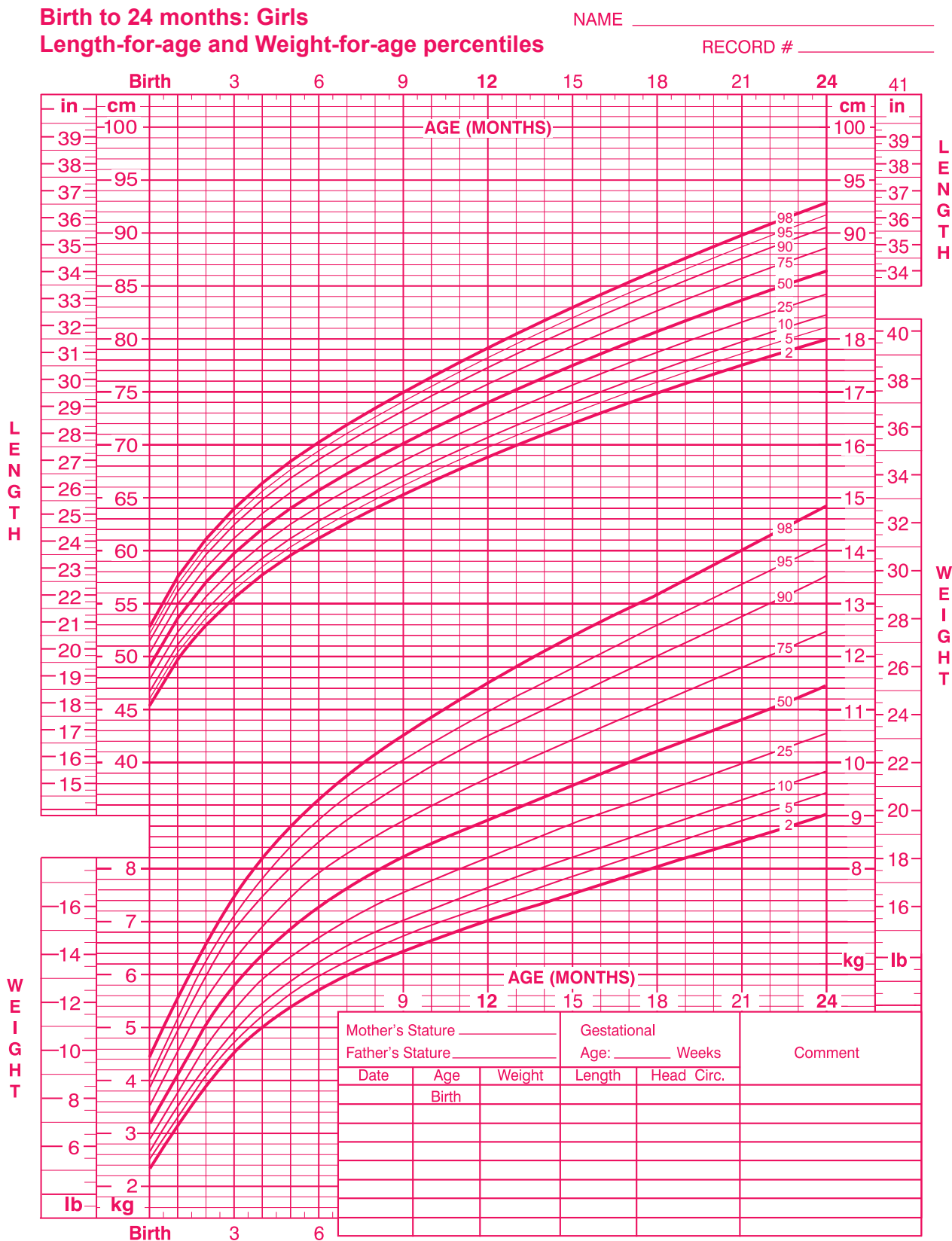
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Published by the Centers for Disease Control and Prevention, November 1, 2009  
SOURCE: WHO Child Growth Standards (<http://www.who.int/childgrowth/en>)



**Figure 16-4** Head circumference and weight-for-length: girls.



Published by the Centers for Disease Control and Prevention, November 1, 2009  
 SOURCE: WHO Child Growth Standards (<http://www.who.int/childgrowth/en>)



**Figure 16-5** Length-for-age, weight-for-age: girls.

## HEAD, EYES, EARS, NOSE, AND THROAT

### Head

Examination of the head is important at all ages, but even more so in the newborn and young infant. Occipitofrontal head circumference, configuration, fontanels, and sutures are all important to evaluate. Head circumference should be related to standard charts for age (see Figure 16-2, Figure 16-4). Macrocephaly (large head) is associated with a prominent or wide forehead and large fontanels. Microcephaly (small head) is associated with a short, posterior recessed forehead and small fontanels. Frontal plagiocephaly presents as unilateral flattening of the forehead caused by premature closure of a coronal and sphenofrontal suture while occipital plagiocephaly is most often caused by prolonged positioning on the back in infancy. Scaphocephaly presents as a long skull with narrowing in the bitemporal diameter, and brachycephaly is a short skull in the anteroposterior dimension. The skull may be also flattened in the occiput; this most commonly occurs in infants with profound developmental delay or severe neuromuscular disease who cannot move their heads from side to side.

Fontanels reveal not only possible genetic and other disorders but give information about the internal cranial environment. A bulging fontanel indicates increased intracranial pressure. Normal closure of the posterior fontanel occurs between 1 and 3 months of age, and the anterior fontanel closes at approximately 18 months. Delayed closure may cause Down syndrome, hypothyroidism, or intrauterine growth restriction, and is also seen in the premature infant. Less commonly it may result from rickets, osteogenesis imperfecta, achondroplasia, and familial macrocephaly.

Abnormal skull configuration may be caused by premature closure of specific sutures. A sunken fontanel indicates reduced intracranial contents, whether tissue or fluid, and is most often associated with dehydration. The conditions associated with findings on the examination of the head are listed in Table 16-6.

### Eyes

Findings during the eye examination include drooping eyelid, eyelid swelling, tearing, ocular misalignment, red eye, corneal clouding, “white pupil,” papillary size difference, cataract, ocular swelling, and orbital swelling (allergy, infection, or trauma). A red reflex should always be evaluated during a neonatal and infant examination to rule out retinal lesions such as retinoblastoma.

Poor vision may be evaluated objectively in older children and adolescents in the office (see Chapter 28, Vision Screening, for specific vision screening tools and techniques for various age groups), but other than noting absent or reduced tracking, poor vision in an infant will need to be evaluated by a pediatric ophthalmologist. Conditions associated with these findings are listed in Table 16-6.

### Ears

Common findings include those associated with examination of the auricle, ear canal, and middle ear. Low-set auricles are often associated with genetic syndromes. Inflammation of the auricle, including

perichondritis involving the cartilaginous portion, is often associated with visible inflammation and pain on palpation. Trauma presents as ecchymoses or hematomas (occasionally with obvious bite marks). Displacement of the auricle away from the side of the head suggests mastoiditis. Otitis externa (“swimmer’s ear”) occurs because of infection resulting from persistent moisture with maceration or trauma from inserted objects. Canal edema, inflammation, and discharge are also common findings.

In the child with otitis externa with discharge, a foreign body should be suspected. Acute otitis media from eustacean tube dysfunction is also associated with pain. With spontaneous perforation of the tympanic membrane, pain resolves but discharge appears. Bloody discharge may be associated with basilar skull fracture. Hearing loss is both a sign and an elicited finding, defined as conductive or sensorineural. Congenital causes are usually sensorineural but may result from congenital malformation. Sensorineural hearing loss, often caused by genetic factors, can be quantified in the newborn period with the increasing use of otoacoustic emissions analysis. Acquired sensorineural hearing loss usually occurs over time from sonic trauma or drug toxicity. The cause of conductive hearing loss can often be found during the physical examination and includes canal atresia, foreign body, excessive cerumen, otitis externa, middle ear effusion, perforation of the tympanic membrane, cholesteotoma, and otosclerosis. Helpful tests include tympanography and pneumatoscopy. Since inserted ventilation tubes may affect these tests, the presence of tubes should be investigated during the examination of the tympanic membrane.

### Nose

Findings commonly encountered during the physical examination of the nose include nasal obstruction, discharge, epistaxis, and nasal masses. Acute sinusitis is best diagnosed clinically, but when antibiotic treatment does not produce improvement, worsening of symptoms occurs, or there is suspected orbital involvement, imaging may be appropriate. Imaging may also be useful prior to referral to an ear, nose, and throat specialist for suspicion of chronic sinusitis as a cause of symptoms in conditions such as cystic fibrosis and others producing difficulty in mucus clearance. Acute nasal congestion is most often caused by allergy or viral infection. In the neonate, obstruction may be because of choanal atresia, leading to immediate feeding difficulty. Nasal foreign body should always be suspected in a child with unilateral, malodorous nasal discharge. Nasal polyps, although most commonly associated with chronic rhinitis, should always trigger a suspicion of cystic fibrosis, and epistaxis a consideration of clotting disorder. Common findings from the nose examination are summarized in Table 16-6.

### Oropharynx and Throat

The most common findings in the oral examination include those associated with bacterial, viral, or fungal infection, although oral ulcers can be found in systemic diseases including Crohn disease, systemic lupus erythematosus, erythema multiforme, Behcet syndrome,



**Table 16-6** Common Findings in the Head, Ears, Eyes, Nose, and Throat

SITE	FINDING	NEWBORN AND INFANT	CHILD	ADOLESCENT
<b>Head</b>	Large head (macrocephaly)	Familial, hydrocephalus, Beckwith-Weideman syndrome, Soto syndrome, Dandy-Walker syndrome, Arnold-Chiari malformation, cystic malformations, chromosomal disorders, chronic subdural hematoma, benign external hydrocephalus	Familial, hydrocephalus	Familial, hydrocephalus
	Small head (microcephaly)	Familial Intrauterine infection, maternal substance abuse, intrauterine CVA, chromosomal disorders	Familial, chromosomal disorders	Familial, chromosomal disorders
	Asymmetric head (plagiocephaly)	Prolonged back positioning, Intrauterine position, syndromic and nonsyndromic craniosynostosis	—	—
	Long head (scaphocephaly)	Premature sagittal suture fusion (syndromic and nonsyndromic craniosynostosis)	—	—
	Short head (brachycephaly)	Premature coronal suture fusion (syndromic and nonsyndromic craniosynostosis)	—	—
	Large fontanel	Macrocephaly because of hydrocephalus, craniosynostosis, osteogenesis imperfecta, achondroplasia, or hypothyroidism	—	—
	Small fontanel	Microcephaly, hyperthyroidism, malformation syndromes	—	—
	Bulging fontanel	Increased intracranial pressure	—	—
<b>Eyes</b>	Depressed fontanel	Dehydration, evolving cerebral atrophy	—	—
	Drooping eyelid (lid ptosis)	Congenital, Marcus-Gunn jaw winking, Horner syndrome, infant botulism	Congenital, myotonia, muscular dystrophy, myasthenia gravis, Horner syndrome, botulism	Same as child
	Lid swelling/erythema	Hemangioma, infection, trauma	Trauma, infection, tumor, edema	Same as child
	Red eye	Infection, trauma (corneal injury), glaucoma	Infection, trauma, toxin, allergy, Kawasaki disease	Infection, trauma, toxin, allergy
	Irregular pupil, iritis, trauma	Infection, colobomata, Horner syndrome, CHARGE syndrome	Infection, head trauma, colobomata, trauma, iritis, Horner syndrome, tumor	Same as child
	White pupil (leukocoria)	Retinoblastoma, dystrophies, toxoplasmosis, cataract	Retinoblastoma, infection, retinal disease, cataract	Infection, retinal disease, cataract
	Cloudy cornea	Congenital glaucoma, trauma, congenital corneal dystrophy, Peters anomaly, keratitis	Glaucoma, trauma, corneal dystrophy, Peters anomaly, keratitis, metabolic disease, storage disease	Keratitis, chemical and infectious conjunctivitis
	Ocular misalignment	Strabismus	Strabismus, amblyopia	Same as child
	Tearing	Congenital nasolacrimal duct obstruction, congenital glaucoma, infection, corneal injury	Infectious or allergic conjunctivitis, foreign body, trauma, corneal injury	Same as child

Continued

**Table 16-6** Common Findings in the Head, Ears, Eyes, Nose, and Throat—cont'd

SITE	FINDING	NEWBORN AND INFANT	CHILD	ADOLESCENT
<b>Ears</b>	<b>Auricle</b>			
	Low set	Genetic syndrome	Same	Same
	Swelling/erythema	Cellulitis, perichondritis, insect bite, trauma, eczema, malformation	Cellulitis, perichondritis, impetigo, eczema, insect bite, trauma	Cellulitis, perichondritis, insect bite, trauma, infection
	<b>Canal</b>			
	Swelling/erythema	Furunculosis, trauma, foreign body	Furunculosis, trauma, infection, otitis externa, foreign body, CNS leak with head trauma (may occur with inserted ventilation tubes)	Same as child
	Discharge	Otitis externa		
	<b>Middle ear</b>			
	Swelling/erythema	Otitis media, bullous myringitis	Otitis media, cholesteatoma, bullous myringitis	Same as child
	Discharge	Otitis media with perforation of the tympanic membrane	Same as infant	Same as child
<b>Nose</b>	Mass	Hemangioma, nasolacrimal duct obstruction, trauma	Polyps, infection, foreign body, tumor	Same as child
	Discharge	Infection	Foreign body, infection, allergy, toxin	Infection, allergy, vasomotor rhinitis, toxin including drug abuse
	Bleeding (epistaxis)	Hemangioma, trauma, congenital vascular abnormality, local skin infection	Trauma, clotting disorder, thrombocytopenia, local skin infection, nasal perforation	Trauma, clotting disorder, thrombocytopenia, toxin including drug abuse (snorting), hypertension
	Obstruction	Mass, atresia, trauma	Trauma, mass, allergy	Trauma, mass, allergy, toxin
<b>Oropharynx and throat</b>	Eythema/ulcer/exudate	Trauma, infection	Trauma, aphthous ulcer, infection, erythema multiforme, peritonsillar abscess, Ludwig angina, retropharyngeal abscess, Kawasaki disease	Trauma, infection, Behcet syndrome, Crohn disease, erythema multiforme, systemic lupus erythematosus, peritonsillar abscess, Ludwig angina, GERD

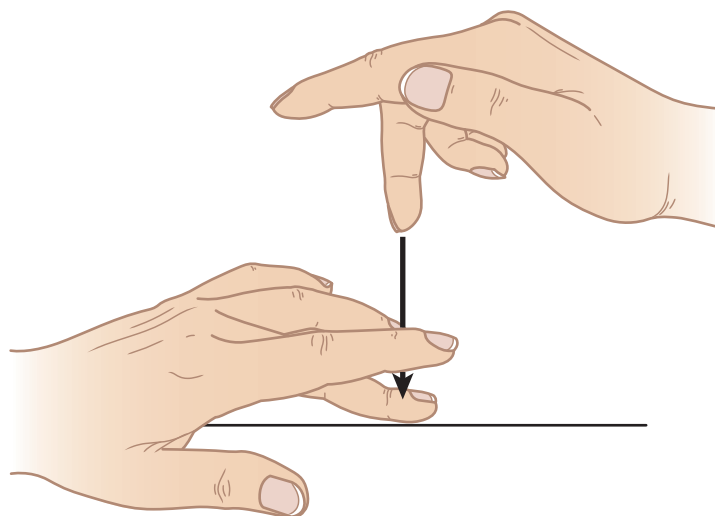
CNS, central nervous system; GERD, gastroesophageal reflux disease.

and others. Pharyngitis, with or without tonsillar hypertrophy, is the most common abnormal finding. If throat pain is associated with stridor, dysphagia, or systemic toxicity, then severe infectious conditions should be suspected including epiglottitis, peritonsillar abscess, and retropharyngeal abscess. These conditions are best evaluated in an emergency department with full respiratory support capabilities. Evaluation and referral for tooth and gum disease should also accompany the oral examination (specifically reviewed in

Chapter 40, Oral Health). These findings are outlined in Table 16-6.

## CHEST WALL AND LUNGS

Assessing respiratory rate and respiratory effort, and following the sequence of inspection, palpation, and auscultation, will reveal findings associated with chest wall and lung dysfunction. Abnormalities of chest wall configuration include asymmetry, enlarged or diminished thoracic cage, and a prominent or inwardly displaced



**Figure 16-6** Technique of chest percussion.

sternum. Palpation of the chest wall may reveal masses or tenderness. Chest pain is not always of pulmonary origin. Findings are summarized in Table 16-3.

Palpation of the chest wall, along with percussion (Figure 16-6) can reveal much about the internal environment of the lung. Decreased vocal fremitus (vibrations) can be felt by placing the hands on the chest wall. Auscultation of the chest and upper airway yields respiratory sounds associated with various respiratory conditions. Wheezing is common and can be defined as monophonic and fixed, or polyphonic and dynamic. Stridor can be defined as inspiratory, expiratory, or both (biphasic). Cough can be described as wet (productive) or dry (nonproductive), paroxysmal and intermittent, or persistent, but is a sign and symptom, not specifically a finding. Other findings upon auscultation include rhonchi (coarse wet snaps and crackles) and rales (fine crackles). A summary of findings associated with abnormal lung sounds is found in Table 16-3.

Central cyanosis (best seen in the oral pharynx and nail beds) is a sign of serious disease representing significant desaturation of hemoglobin. Cyanosis and digital clubbing (Figure 16-7) are findings most often associated with cardiorespiratory disease but may also originate from other systems. Conditions associated with these findings are also listed in Table 16-3.

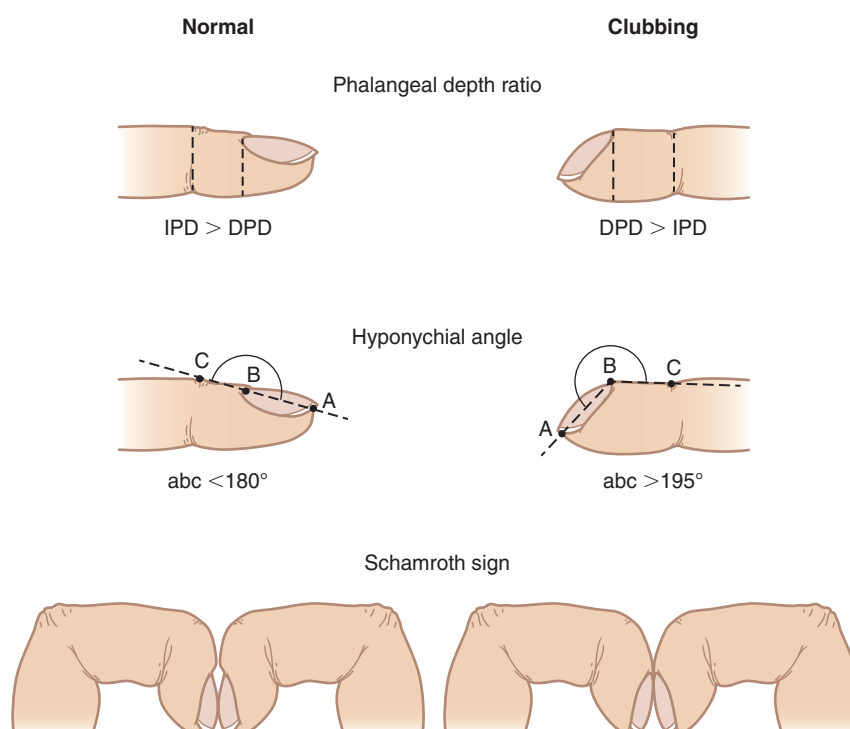
## HEART AND PULSES

Inspection, palpation, and auscultation are the mainstays of eliciting findings related to the cardiovascular system. Most physicians begin with observation of the dynamic nature of the heart through examination of the chest wall and palpation at the left sternal border. The examination then progresses to auscultatory evaluation of the first and second heart sounds (S1 and S2) and the 4 valve sites (aortic, pulmonic, tricuspid, and bicuspid [mitral] areas) (Figure 16-8). Other heart sounds may also be documented during this examination. Findings of central cyanosis and digital clubbing

(with chronic heart disease) should always place cardiovascular conditions in the differential diagnosis. Heart rate and rhythm are evaluated by auscultation and palpation of pulses. Pulses also indicate pathologic systemic and cardiovascular states. Decreased peripheral pulses are found in hypovolemia with hypotension, and in hypotension from other causes such as drugs, shock (thready pulse [ie, decreased pulse intensity with increased rate]), and aortic stenosis. Specifically, decreased leg pulses are found in coarctation of the aorta. Increased pulses are primarily found in hypertension but can also be associated with hyperthyroidism.

Pulsus paradoxicus is an exaggerated variation in the pulse rate with inspiration that is found in conditions involving airway obstruction (croup, bronchiolitis, asthma) but also with pericarditis, cardiac tamponade, and chronic sleep apnea.

The auscultatory examination is also essential to evaluate the heart sounds and timing, as well as the location, quality, and pitch of a murmur. A thrill felt over the precordium usually indicates a murmur with grading of at least 3/6 on the Levine scale. Systolic murmurs are described as holosystolic, systolic ejection, early systolic, midsystolic, or late systolic, whereas diastolic murmurs are described as protodiastolic, mid-diastolic, or late diastolic. Continuous murmurs are usually extracardiac. Pathologic murmurs require further evaluation through specialized testing and subspecialty evaluation to distinguish from functional (innocent) murmurs, especially with normal rhythms and lack of cyanosis. Functional or innocent murmurs are usually systolic ejection, virtually never holosystolic, and alter with change in position. They often have a musical or vibratory quality (Still murmur) and usually are noted between 6 months and 8 years of age. Common findings related to the heart and peripheral circulation are found in Table 16-7.



**Figure 16-7** Clubbing and Schamroth sign. Clubbing can be measured by comparing the distal phalangeal diameter (DPD) to the interphalangeal diameter (IPD), which is less than 1 in normal subjects. The hyponychial angle is increased in clubbing, and the normal diamond-shaped opening when opposite fingers are opposed disappears with clubbing (Schamroth sign). (Adapted from Pasterkamp H. *The history and physical examination*. In: Wilmott RW, Boat TF, Bush A, et al, eds. *Kendig and Chernick's Disorders of the Respiratory Tract in Children*. 8th ed. Philadelphia, PA: Elsevier Saunders; 2012: 127, with permission from Elsevier.)

## GASTROINTESTINAL

Inspection, auscultation, percussion, and palpation (usually in that order) elicit findings in the gastrointestinal tract. Findings on inspection include abdominal distention, scaphoid abdomen, and occasionally abdominal mass. In a newborn, a scaphoid abdomen associated with respiratory distress indicates congenital diaphragmatic hernia, but in an older child can occur as a result of abdominal trauma with diaphragmatic rupture. A flat or scaphoid abdomen may also occur in malnutrition (without ascites) and protuberant abdomen with neuromuscular disease. Abdominal distention may be caused by air, fluid, or masses.

Auscultation for bowel sounds may reveal their absence, hypoactivity, or hyperactivity.

Bowel sounds can be absent in peritonitis or with bowel obstruction. Hypoactive sounds occur with local ileus and obstruction, as may occur in distal intestinal obstruction syndrome (DIOS) in children and adolescents with cystic fibrosis. Hyperactive bowel sounds are most often found with gastroenteritis, but also with malabsorption. Current medication use must also be considered when evaluating bowel sounds.

Percussion may elicit tympany, which indicates gas accumulation (intra- or extraintestinal) and may be a clue as to the location of underlying fluid in ascites. Percussion with palpation will define the location and degree of ascites by evaluating the patient for shifting dullness and a fluid wave (Figure 16-9). Dullness on

percussion, as in the thoracic examination, is caused by fluid or a solid mass.

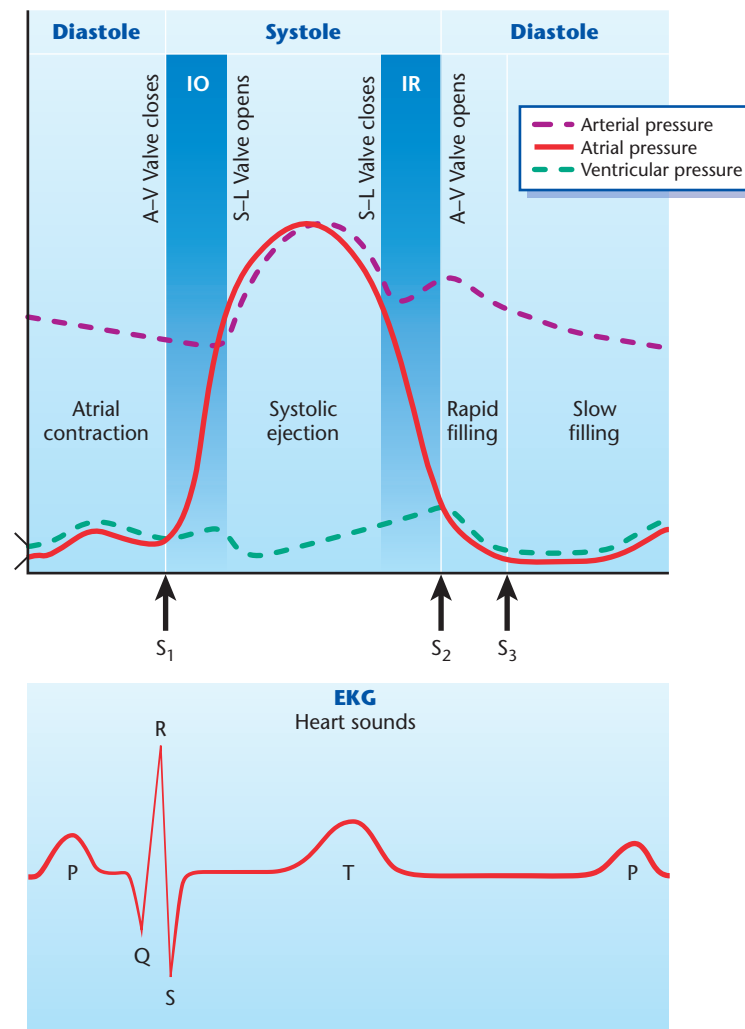
Palpation will specifically elicit pain as well as abnormal abdominal contents. Rebound tenderness (pain on sudden release of palpating fingers) is found with underlying peritoneal irritation. Pain elicited in a specific location gives clues as to the underlying diagnosis (Figure 16-10). Masses can often be localized through 1- or 2-handed ballottement, which will also distinguish enlarged intra-abdominal organs (Figure 16-11). Localizing a mass through palpation and ballottement and taking into account a child's age and sex gives clues as to its cause (Figure 16-12). Conditions associated with specific findings on the abdominal examination are found in Table 16-8.

## MUSCULOSKELETAL

Inspection and palpation with manipulation are the prime methods of eliciting findings related to the musculoskeletal system. Observation of gait and use of limbs, measuring strength, and establishing range of motion are also essential to the physical examination of this system. This part of the examination overlaps with neurology, which is discussed in full in the following section.

Findings associated with musculoskeletal dysfunction include not moving a limb, limb abnormality, limp, abnormal head shape or size (covered in the head, eyes, ears, nose, and throat section and





**Figure 16-8** The cardiac cycle and heart sounds.

**Table 16-7** Common Findings in the Heart and Circulation

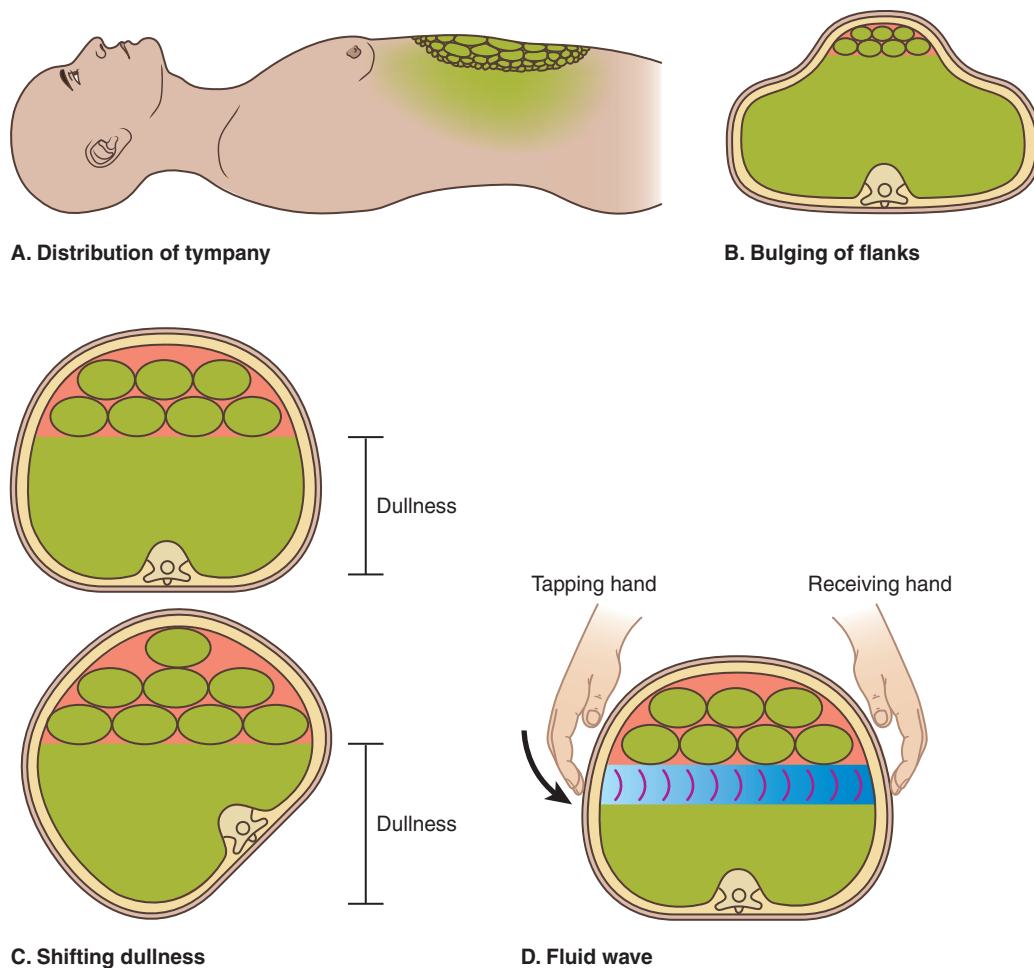
SITE	FINDING	NEWBORN AND INFANT	CHILD	ADOLESCENT
Heart	Thrill	>3/6 on the Levine scale	Same as infant	Same as child
	S2 fixed wide split	ASD	ASD	ASD
	S3 gallop	CHF	Same as infant	Same as child
	Systolic murmurs	Normal (functional, transition), Ejection: ventricular outflow abnormalities, aortic/pulmonic valve stenosis, VSD, A-V canal	Same as infant, but also consider mitral regurgitation, coarctation	Same as child, but functional murmurs rare
	Diastolic murmurs	A-V valve insufficiency	Same as infant, but also consider mitral stenosis	Same as child
	Continuous murmurs	Patent ductus arteriosus	Venous hum	Supraclavicular innocent murmur
	Systolic ejection clicks	Aortic/pulmonic valve stenosis, mitral/tricuspid prolapse (midsystolic), coarctation of the aorta	Same as infant	Same as child

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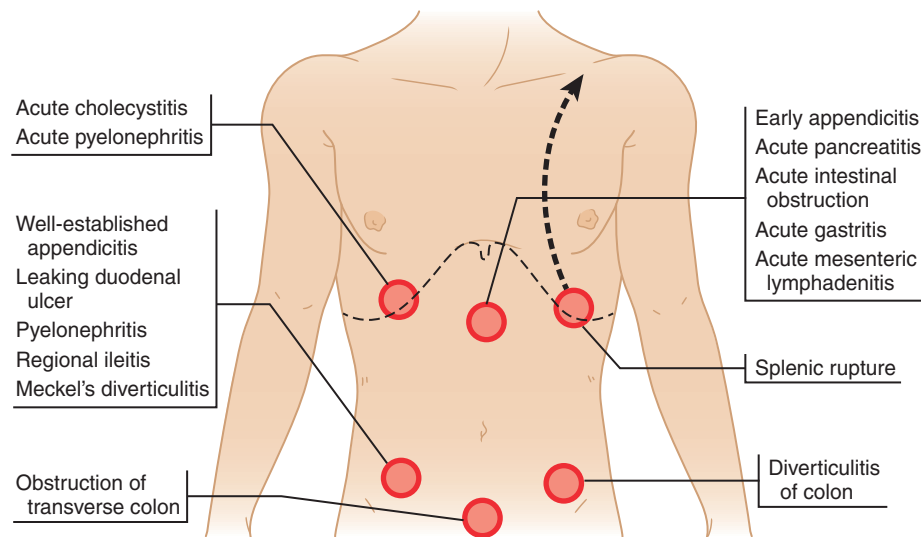
**Table 16-7** Common Findings in the Heart and Circulation—cont'd

SITE	FINDING	NEWBORN AND INFANT	CHILD	ADOLESCENT
<b>Pulses</b>	Diminished leg pulses	Coarctation of the aorta, hypoplastic left heart syndrome, decreased cardiac output, hypotension	Coarctation of the aorta, vascular obstruction (eg, embolus), decreased cardiac output, hypotension	Same as child
	Diminished peripheral intensity	Hypovolemia/hypotension, shock (thready), aortic stenosis, cardiac tamponade, drugs	Same as infant	Same as child
	Increased peripheral intensity	Hypertension, hyperthyroidism, drugs	Same as infant	Same as child
	Pulsus paradoxus	Asthma, bronchiolitis, croup (airway obstruction)	Asthma, pericarditis, cardiac tamponade, sleep apnea	Same as child

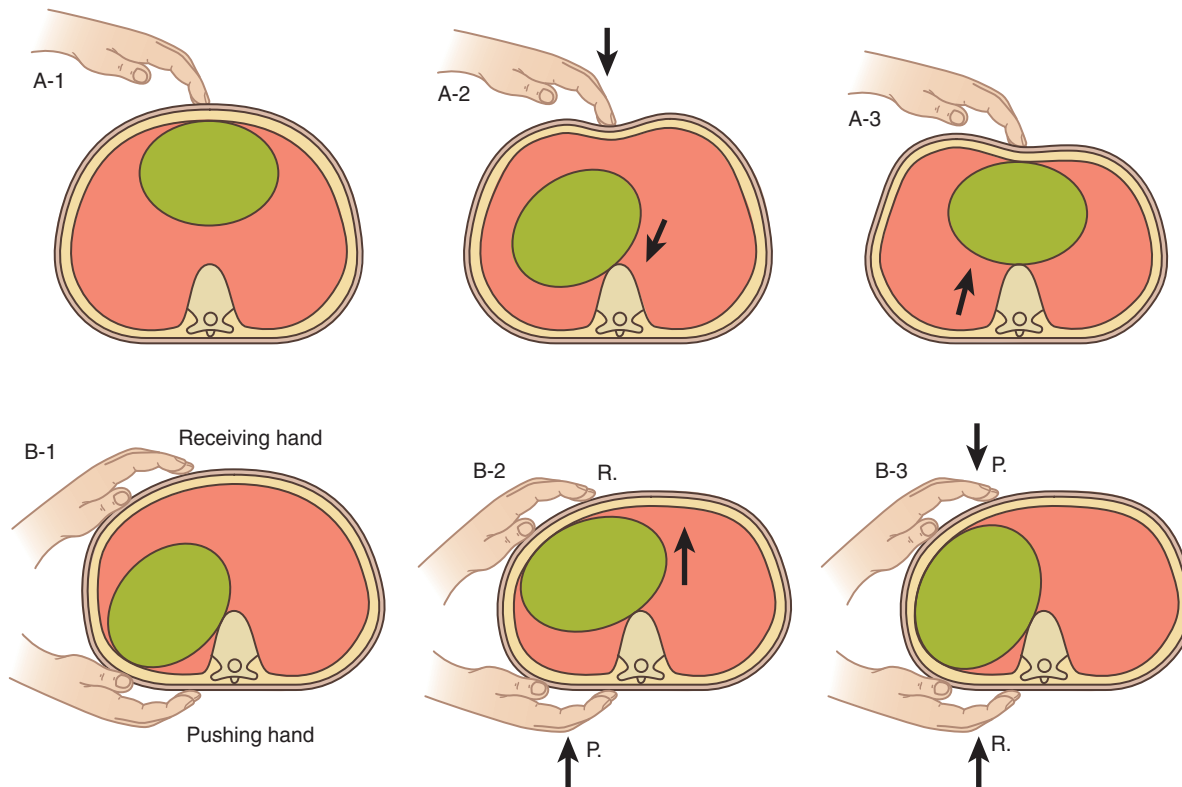
ASD, atrial septal defect; A-V, atrioventricular; CHF, congestive heart failure; VSD, ventricular septal defect.



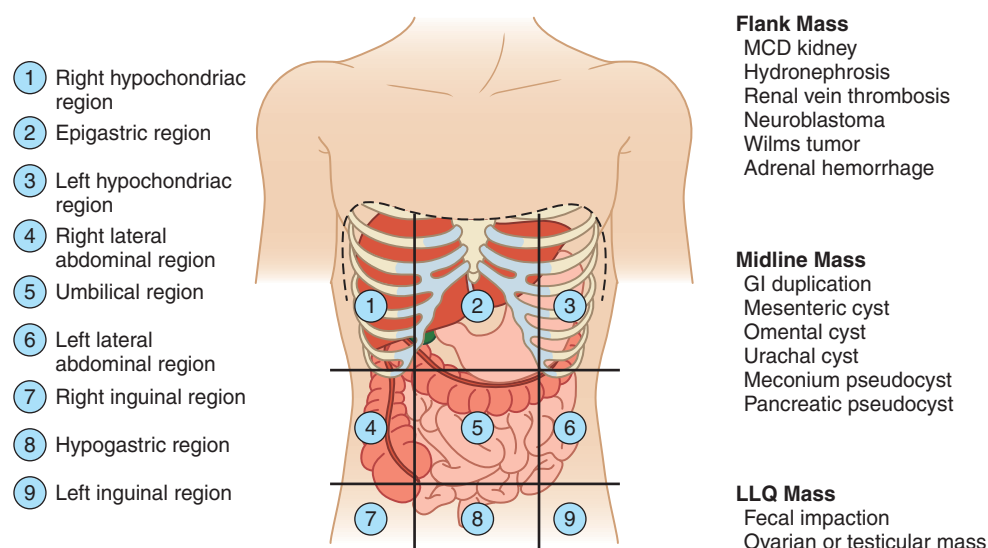
**Figure 16-9** Signs of ascites. (Adapted from LeBlond RF, DeGowin RL, Brown DD. *The abdomen*. In: DeGowin's Diagnostic Examination. 8th ed. New York, NY: McGraw-Hill; 2004.)



**Figure 16-10** Common location of acute abdominal pain. (Adapted from LeBlond RF, DeGowin RL, Brown DD. *The abdomen*. In: DeGowin's Diagnostic Examination. 8th ed. New York, NY: McGraw-Hill; 2004.)



**Figure 16-11** Ballottement of abdominal masses. **A.** One-hand ballottement. The fingers are plunged into the abdomen and held there; a freely moveable mass will rebound upward and be felt with the fingers. **B.** Bimanual ballottement. Used to determine the size of a large abdominal mass. One hand (P) pushes the posterior abdominal wall, while the other (R) palpates the anterior abdomen. The thickness of the mass may be determined between the two hands. (Adapted from LeBlond RF, DeGowin RL, Brown DD. *The abdomen*. In: DeGowin's Diagnostic Examination. 8th ed. New York, NY: McGraw-Hill; 2004.)



**Figure 16-12** Location of abdominal masses by anatomic regions.

**Table 16-8**

**Common Findings in the Gastrointestinal Tract**

SITE	FINDING	NEWBORN AND INFANT	CHILD	ADOLESCENT
Abdomen	Flat or scaphoid	Congenital diaphragmatic hernia, diaphragmatic paresis, paralysis, malnutrition	Traumatic diaphragmatic hernia, malnutrition	Same as child
	Distended	Intestinal obstruction (volvulus, intussusception, meconium ileus, rectal or anal stenosis, etc), ascites (hypoproteinemia from liver disease, renal disease, malabsorption), urinary retention, hepatosplenomegaly, tumor, and constipation	Intestinal obstruction (tumor, intussusception, polyps, DIOS), ascites from liver disease, renal disease, malabsorption, peritonitis, tumor, hepatosplenomegaly, and constipation	Same as child, consider pregnancy
	Pain	Pain is difficult to elicit in an infant; consider peritonitis, malrotation/volvulus, appendicitis, sickle cell disease, incarcerated hernia, Hirschsprung disease, gastroenteritis, UTI, pneumonia, trauma	Constipation, Hirschsprung disease, sickle cell disease, incarcerated hernia, peritonitis, appendicitis, GERD, UTI, pneumonia, trauma, abscess	Same as child but consider pregnancy (including tubal) and irritable bowel syndrome
	Mass	Enlarged liver or spleen, hydronephrosis, tumor, intussusception, pyloric stenosis, fecal impaction, cysts, incarcerated hernia	Enlarged liver or spleen, hydronephrosis, fecal impaction, DIOS, tumor, incarcerated hernia, cysts, renal vein thrombosis, adrenal hemorrhage	Same as child but consider pregnancy and ovarian masses
	Hypoactive bowel sounds	Peritonitis/sepsis, gastroenteritis with local ileus, drugs, hypokalemia	Peritonitis, obstruction, ileus, trauma, drugs, hypokalemia, fecal impaction	Same as child
	Hyperactive bowel sounds	Manual manipulation of the abdomen, malabsorption, gastroenteritis, diarrhea, drugs	Same as infant but consider Crohn disease and ulcerative colitis, enterocolitis, drugs	Same as child

DIOS, distal intestinal obstruction syndrome; GERD, gastrointestinal reflux disease; UTI, urinary tract infection.



Table 16-6), joint pain or swelling, curved spine, chest wall abnormalities (covered in the chest wall and lungs section and Table 16-3), stiffness of muscles and joints, hip instability, and foot abnormalities. An observation of symmetry is an important part of the musculoskeletal evaluation.

When an infant will not move a limb, the physician should always suspect trauma (accidental or intentional), any painful condition of the bones or joints, or muscle weakness. Fracture of the clavicle (with swelling and tenderness and sometimes crepitus), humeral fracture, or brachial plexus injury can occur with birth trauma, and results in the limited use of an arm. Increased muscle tone in a child after 1 year of age may suggest cerebral palsy (CP). Osteomyelitis of any bone, including the humerus, and septic arthritis of a joint will lead to reduced use of the corresponding limb (pseudoparalysis). Clavicular fracture and upper and lower extremity fractures with pain, swelling, and decreased use of the affected limb are also common sports injuries in children and adolescents. Atraumatic swelling of a joint, with or without systemic symptoms, always requires further investigation and is a finding with both infectious and collagen vascular disease etiologies. These occur most often in older children and teens. Developmental dysplasia of the hip occurs in infants and limits leg motion, as does aseptic necrosis of the head of the femur in older children (Legg-Calvé-Perthes disease). Likewise, atraumatic, localized swelling and tenderness of a lower extremity in an older child or adolescent should prompt a workup for infection (including osteomyelitis) and neoplasm (including osteogenic sarcoma and Ewing sarcoma). Swelling and tenderness over the tibial tuberosity is a finding in Osgood-Schlatter disease.

Scoliosis is common in children with neuromuscular disease but does occur progressively in otherwise normal children and adolescents. The back examination is an essential part of the physical examination at all ages, and scoliosis or kyphosis should be further monitored or evaluated. Other congenital anomalies may accompany scoliosis, including those of the bladder, kidneys, or heart, as well as hearing disorders. Kyphosis may be progressive and can result in paraplegia.

By age 7, most children have lost the wide-based, short-step gait of the younger child and have adopted the typical adult gait. Atypical gaits include reduced time in the stance phase of the gait cycle (limp) because of pain, lurching and a wide-based gait because of muscle weakness from any cause, circumduction (Trendelenburg gait) caused by neuromuscular disease, and the scissors gait of diplegic or quadriplegic CP. Genu varum (foot inturning) is not uncommon at all ages, but when severe it may lead to gait disturbance.

Examination of the hands and feet may reveal abnormalities sometimes associated with other congenital anomalies. Polydactyly and syndactyly are associated with multiple genetic syndromes. Joint contractures occur in arthrogryposis multiplex congenita. Foot findings in infants include metatarsus adductus and talipes equinovarus (clubfoot) among others. Finding of a rigid cavus (exaggerated medial longitudinal arch) suggests CP, myelomeningocele, or hereditary sensorimotor neuropathies.

Findings in the feet of older children and adolescents include pes planus or pes cavus deformities, bunions, ingrown nail, and a variety of toe deformities. Musculoskeletal findings are summarized in Table 16-9, but are also addressed in Table 16-6 and Table 16-10.

**Table 16-9** Common Findings in the Musculoskeletal System

SITE	FINDING	NEWBORN AND INFANT	CHILD	ADOLESCENT
<b>Upper limb</b>	Not moving	Clavicular fracture, brachial plexus injury, Erb or Klumpke palsy, limb fracture or contusion, septic joint, contractures, osteomyelitis, spinal cord injury, pain (consider child abuse)	Clavicular fracture, contusion, fracture, joint swelling (infection, arthritis), osteomyelitis, contractures, dislocation, subluxation, tumor, pain (consider child abuse)	Same as child, but also consider cystic fibrosis osteoarthritis
	Swelling	Contusion, fracture, septic joint, osteomyelitis, edema, lymphoma, hemangioma, infection	Same as infant, but consider rheumatic disease, Lyme arthritis, synovitis, sickle cell arthropathy, tumor	Same as child
	Erythema	Septic arthritis, osteomyelitis, cellulitis, ecchymoses, infection, fat necrosis	Same as infant, but also consider rheumatic disease	Same as child, but also consider muscle injury
<b>Lower limb</b>	Not moving	Hip dysplasia, septic joint, contractures, osteomyelitis, meningomyelocele	Aseptic necrosis, septic joint, osteomyelitis, viral synovitis, contusion, fracture, arthritis	Contusion, fracture, septic joint, viral synovitis, osteomyelitis, arthritis
	Swelling	Septic joint, osteomyelitis, contusion, fracture, edema, lymphoma, hemangioma, skin and tissue infection	Same as infant, but also consider collagen vascular disease and tumor, Osgood-Schlatter disease	Same as child but also consider deep vein thrombosis, ruptured Baker cyst (pseudothrombosis)

*Continued*

**Table 16-9** Common Findings in the Musculoskeletal System—cont'd

SITE	FINDING	NEWBORN AND INFANT	CHILD	ADOLESCENT
<b>Back</b>	Erythema	Septic arthritis, osteomyelitis, cellulitis, ecchymoses, skin and tissue infection	Same as infant, but also consider collagen vascular disease, Lyme arthritis, synovitis, sickle cell arthropathy, tumor	Same as child
	Scoliosis—lateral curve	Congenital, vertebral anomaly, neuromuscular disease, pain, tumor	Same as infant, congenital, idiopathic, neuromuscular disease, Scheuermann kyphoscoliosis	Same as child
	Kyphosis—anterior-posterior curve	Congenital, neuromuscular disease	Congenital, idiopathic, postural, neuromuscular disease, Scheuermann's kyphosis/kyphoscoliosis, osteogenesis imperfecta, bone dysplasias	Same as child
<b>Gait</b>	Wide-based	Normal	Neuromuscular disease, ataxia	Same as child
	Limp, antalgic	Pain in lower extremity from any cause, hip dysplasia	Pain in lower extremity from any cause, aseptic necrosis of the femur, vertebral abnormality with neuropathy	Same as child, but also consider slipped femoral capital epiphysis
	Hip drop, circumducting gait, Trendelenburg gait	Rare	Neuromuscular disease, rheumatic disease, hip disease	Same as child
<b>Hand</b>	Scissoring	Cerebral palsy	Cerebral palsy	Cerebral palsy
	Web fingers, syndactyly	Incidental anomaly, genetic syndrome (Apert, Carpenter, de Lange, Laurence-Moon-Biedl, etc)	Same as infant	Same as infant
	Multiple digits, polydactyly	Incidental anomaly, genetic syndrome (Carpenter, Ellis-van Creveld, Meckel-Gruber, Orofacial digital syndrome, etc)	Same as infant	Same as infant
<b>Feet</b>	Syndactyly, polydactyly	May have similar hand anomalies, occurs in genetic and chromosomal syndromes	Same as infant	Same as infant
	Foot turns in	Congenital metatarsus adductus, contracture, tibial torsion, femoral anteversion, club foot (talipes equinovarus)	Congenital metatarsus adductus, contracture, tibial torsion, femoral anteversion	Same as child
	Foot turns out	Physiologic until age 18 months, congenital, contracture	Congenital (external tibial torsion), flat foot	Same as child
	Flat foot (pes planus)	Congenital (may be normal)	Same as infant	Same as infant
	High arch (pes cavus)	Congenital, exaggerated and rigid in cerebral palsy, myelomeningocele, hereditary sensorimotor neuropathies	Same as infant	Same as infant
	Round bottom, rocker bottom foot, congenital vertical talus	Congenital, genetic and chromosomal syndromes	Same as infant	Same as infant

**Table 16-10** Common Neurologic Findings

SITE	FINDING	NEWBORN AND INFANT	CHILD	ADOLESCENT
<b>Systemic</b>	Altered consciousness, agitation, disorientation, lethargy, coma	CNS malformations, hydrocephalus, infection, glucose, calcium, and electrolyte abnormalities, inborn errors of metabolism, hypothyroidism, hypoadrenalism, trauma, hypoxia, hypercarbia, ingestion	Ingestion, toxins, infection, hypoglycemia, ketoacidosis, Reye syndrome, Lyme disease, encephalopathy, hypertension, electrolyte abnormality, trauma, tumor, hypoxia	Same as child; toxic ingestion or other self-administration, syncope, and hyperventilation become more common
	Developmental delay, regression	Genetic or chromosomal syndrome, hypothyroidism, infection, prenatal or neonatal hypoxia, trauma, hydrocephalus, metabolic disease, sensory deprivation	Same as infant, but also consider neurofibromatosis, tuberous sclerosis, tumor, heavy metal poisoning	Same as child
	Generalized decreased tone (hypotonia)	Genetic or chromosomal syndrome, oculocerebral renal syndrome, renal tubular acidosis, familial dysautonomia, metabolic myopathies, storage diseases, mitochondrial disorders, spinal muscular atrophy, infection, botulism, congenital myasthenia gravis	Genetic or chromosomal syndrome, spinal muscular atrophy, muscular dystrophies, storage disease, infection, Guillain-Barré syndrome, tumor, heavy metal exposure, uremia, drugs, spinal cord injury, myopathies, myasthenia gravis	Same as child, but also consider intentional toxic ingestion and psychosomatic disorder
	Generalized increased tone (hypertonia)	Genetic or chromosomal syndrome, prenatal or perinatal hypoxia leading to cerebral palsy, seizure disorder	Genetic or chromosomal syndrome, cerebral palsy, seizure disorder	Same as child
	Clumsiness (ataxia) See also gait disturbance (Table 16-9)	Hereditary, cerebellar aplasia, Chiari malformation, Dandy-Walker malformation, infection, postinfection, heavy metal toxicity, inborn errors of metabolism, mitochondrial disorders, trauma, tumor, AVM, stroke	Same as infant, but consider toxic ingestion vasculitis, and metastases from a primary tumor, rheumatic/vasculitic disorders, cerebellar disorders	Same as child, but trauma and toxic ingestion become more likely
	Seizures	See Chapter 327, Seizure Disorders	See Chapter 327, Seizure Disorders	See Chapter 327, Seizure Disorders
	Facial asymmetry	Facial nerve or muscle aplasia (Möbius syndrome), tumor	Congenital, Bell palsy, herpes zoster, tumor, Lyme disease	Same as child
<b>Focal</b>	Weakness on 1 side (hemiplegia)	AVM, arachnoid cyst, Chiari malformation, trauma, tumor, stroke (hemorrhagic or hypercoagulable states)	Same as infant, but consider cerebral abscess, viral myelitis, osteomyelitis, sarcoidosis, stroke	Same as child
	Weakness of both legs (paraplegia)	AVM, spina bifida, myelomeningocele arachnoid cyst, Chiari malformation, trauma, tumor, stroke (hemorrhagic or hypercoagulable states), osteopetrosis, mitochondrial disorders	Same as infant, but also consider cerebral abscess, viral myelitis, vertebral fracture, vertebral osteomyelitis, spinal TB, sarcoidosis, muscular dystrophy, demyelinating disease, primary tumor metastases	Same as child, but trauma becomes more likely

Continued

**Table 16-10** Common Neurologic Findings—cont'd

SITE	FINDING	NEWBORN AND INFANT	CHILD	ADOLESCENT
	Weakness of all 4 extremities (quadriplegia)	AVM, spina bifida, tethered cord, arachnoid cyst, Chiari malformation, trauma, tumor, stroke (hemorrhagic or hypercoagulable states), osteopetrosis, atlantoaxial dislocation, mitochondrial disorders, spinal muscular atrophy type 1, botulism, hypokalemia, congenital myasthenia gravis	Same as infant, but also consider viral myelitis, vertebral fracture, vertebral osteomyelitis, sarcoidosis, muscular dystrophy, spinal muscular atrophy type 2 and type 3, demyelinating disease, primary tumor metastases	Same as child, but trauma becomes more likely
	Not moving a limb	See Table 16-9	See Table 16-9	See Table 16-9

AVM, arteriovenous malformation; CNS, central nervous system; TB, tuberculosis.

## NEUROLOGY

As mentioned above, findings on the musculoskeletal examination may indicate neurologic disorders. Therefore, the musculoskeletal and neurologic examinations complement each other in the search for the primary cause of a specific finding. In addition, knowledge of appropriate developmental milestones in relation to musculoskeletal and neurologic maturity will help the physician determine whether a child is experiencing developmental delay or regression, which may have many causes, including degenerative muscle or neurologic disease and even social deprivation. Occasionally a child will present to the physician with a seizure, and multiple etiologies must be considered with this finding.

Common findings encountered on the neurologic examination include altered consciousness, developmental delay/regression, focal weakness, generalized weakness, hypotonia, ataxia, hypertonia (spasticity), hypo- and hyperreflexia, decreased and increased sensation, movement disorders, and, rarely, seizures (although a history of suspected or known seizures may be the reason for the evaluation).

Altered levels of consciousness can vary from disorientation to lethargy to unconsciousness. In an infant, secondary effects of drugs, disorders of electrolyte metabolism, inborn errors of metabolism, hypoglycemia, infection, and trauma should be considered. Intracranial or brainstem tumors must also be considered, especially with focal findings such as weakness. The Glasgow Coma Scale (Table 16-11) is useful to quantify and communicate the level of consciousness.

The finding of developmental delay can be the result of many causes including environmental (such as birth injury), infection, toxic exposure, and genetic etiologies.

However, social deprivation, malnutrition, chromosomal syndromes, and hypothyroidism must also be considered. Regression from previous milestones is always cause for concern and should suggest a genetic or metabolic syndrome. Sudden social deprivation may also lead to regression. The finding of focal weakness may be caused by a musculoskeletal

condition but may also be a result of a neurologic disorder, either of the peripheral or central nervous system. Hand preference in children younger than 2 years of age or a change in hand preference in older children should always prompt an investigation for musculoskeletal or neurologic causes. A general knowledge of specific innervations of body regions is helpful when categorizing this finding. Generalized weakness, if chronic, is most likely because of neuromuscular disease, but when acute, it may be attributed to many causes (eg, infant botulism, Guillain-Barré). Hypertonia and hypotonia have many causes, which, if chronic, need to be evaluated by a pediatric neurologist. Acute causes include drug ingestion, electrolyte disturbance, and trauma, among others. The finding of ataxia has multiple acute and chronic causes, and usually presents as gait disturbance. As with problems of muscle tone, drug ingestion, acute metabolic disturbance, and infection may be immediate issues, whereas cerebella dysfunction because of tumor, malformation, or bleeding may lead to more chronic problems. Hypo- and hyperreflexia are findings in both acute and chronic neurologic and metabolic disease, although a great deal of variability in deep tendon reflexes is seen in normal individuals. Asymmetry in tone, reflexes, strength, and sensation suggests a focal abnormality. Involuntary movement disorders stem from a variety of causes that include toxic, metabolic, infectious, vascular, and traumatic. Recognizing the pattern of the disorder can often help in determining the cause. The pattern of a seizure disorder is also important to recognize. True seizures, although always neurologic in origin, may be triggered by non-neurologic disorders, such as hypoglycemia or hyponatremia. A comprehensive discussion of seizure patterns and etiologies appears in Chapter 327, Seizure Disorders. Other than simple febrile seizures, seizure disorders should be evaluated by a child neurologist.

Findings from the neurologic examination are found in Table 16-10.



**Table 16-11** Glasgow Coma Scale**EYE-OPENING RESPONSE**

SCORE	>1 YEAR	<1 YEAR
4	Spontaneous	Spontaneous
3	To verbal command	To shout
2	To pain	To pain
1	None	None

**MOTOR RESPONSE**

SCORE	>1 YEAR	<1 YEAR
6	Obeys commands	Spontaneous response
5	Localizes pain	Localizes pain
4	Withdraws from pain	Withdraws from pain
3	Displays abnormal flexion to pain (decorticate rigidity)	Displays abnormal flexion to pain (decorticate rigidity)
2	Displays abnormal extension to pain (decerebrate rigidity)	Displays abnormal extension to pain (decerebrate rigidity)
1	None	None

**VERBAL RESPONSE**

SCORE	>5 YEARS	2–5 YEARS	0–23 MONTHS
5	Is oriented and converses	Uses appropriate words and phrases	Babbles, coos appropriately
4	Conversation is confused	Use inappropriate words	Cries but is consolable
3	Words are inappropriate	Cries or screams persistently to pain	Cries or screams persistently to pain
2	Sounds are incomprehensible	Grunts or moans to pain	Grunts or moans to pain
1	None	None	None

The Glasgow Coma Scale score is the sum of best eye-opening, motor, and verbal responses. Scores range from 3 to 15. Severe indicates a score of <9; moderate, 9–12; and mild, 13–15.

## INTEGUMENT

The integumentary system consists of skin, hair, and nails. Conditions associated with this system may be limited to a specific structure or may be a manifestation of a systemic disease. Therefore, knowledge of the findings associated with systemic disease is important, and a complete review of systems, history, and physical examination should be performed as indicated. Observation and palpation are the most useful components of the specific integument examination. Common findings of skin lesions are listed in Box 16-1. Any of these lesions may be associated with erythema depending on the etiology. The color of macules (red, blue, purple, hypo- or hyperpigmented, depigmented) will often indicate the likely cause (Table 16-12).

Common findings associated with examination of the hair include hair loss (alopecia), excess hair (hypertrichosis, hirsutism), and abnormalities of the hair shaft. Occasionally, coloration of the hair may be an indication of systemic disease such as the dried, rusty brown hair of kwashiorkor or the white patch of Waardenberg syndrome. Important considerations in evaluating findings of alopecia and hypertrichosis include pattern and distribution and the condition of the underlying skin.

Common findings associated with nails also include those associated with systemic disease (eg, clubbing with chronic respiratory, cardiovascular, or hepatic disease) and problems specific to the nails. These

### BOX 16-1 Common Skin Lesions

- Macules (flat, circumscribed lesions without palpable edges)
- Papules (raised lesions <1 cm)
- Cysts (sharply circumscribed)
- Movable lesions (below the epidermis)
- Nodules (elevated, circumscribed)
- Firm lesions (larger than papules)
- Tumors (large nodules)
- Vesicles (circumscribed, superficial collections of fluid in the epidermis <1 cm)
- Bullae (large vesicles, >1 cm)
- Scales (dried fragments of dead skin that often peel off spontaneously)
- Pustules (papules containing pus),
- Erosions (loss of superficial epidermis)
- Crusts (dried exudates)
- Lichenification (thick, dried plaques)
- Ulcers (deep erosions through the epidermis into the dermis)
- Indurations (hardening of the skin)
- Fissures (painful cracks)
- Scars

**Table 16-12** Common Integumentary Findings

SITE	FINDING	NEWBORN AND INFANT	CHILD	ADOLESCENT
Skin	Red macules	Measles (maculopapular), roseola, Fifth disease, mononucleosis (less common in infants), ehrlichiosis, urticaria, drug eruption, urticaria pigmentosa, JIA, infection (cellulitis, erysipelas), first degree burns	Same as infant, but also consider measles, cytomegalovirus, Rocky Mountain spotted fever, mononucleosis (more common), JIA, SLE (malar rash), dermatomyositis, toxic shock, intertrigo, Kawasaki disease and expanding lesion of Lyme disease	Same as child
	Purple or blue macules	Blue nevus, purpura, petechiae, telangiectasia, trauma (ecchymosis)	Same as infant	Same as child
	Brown to black macules (hyperpigmentation)	Nevi, lentigo syndromes, post-inflammatory (eczema, excoriations), fungal infection	Same as infant, but also consider café-au-lait spots (neurofibromatosis) Becker nevus, acanthosis nigrans	Same as child
	White macules (hypopigmentation)	Piebaldism, incontinentia pigmentosa (postvascular lesions), vitiligo	Same as infant, but also consider tuberous pityriasis alba, tuberous sclerosis, halo nevus, tinea versicolor, postinflammatory hypopigmentation (eg, eczema, topical anti-inflammatory agents).	Same as child
	Red papules	Urticaria, insect bites, eczema, contact dermatitis, milia, Kawasaki disease, drug eruption	Same as infant (except milia), but also consider acne, granuloma annulare, folliculitis, scarlet fever, Lyme disease, warts, scabies, fungal infection, JIA	Same as child (except Kawasaki disease), acne becomes more common
	Cysts	Dermoid	Dermoid, epidermoid, steatocystoma, trichoepithelioma, vellus hair cyst, synovial (subdermal), cystic hygroma, lymphangioma	Same as child, cystic acne becomes more common.
	Noninflamed nodules	Neurofibroma	Dermatofibroma, angiofibroma, neurofibroma, neuroma, Cowden disease, rheumatoid arthritis, rheumatic fever	Same as child
	Inflamed nodules	Carbuncle, panniculitis	Same as infant, but also consider erythema nodosum, hydradenitis suppurativa	Same as child, but acne becomes more common
	Vesicles	Miliaria crystallina, dyshydrosis, contact dermatitis, hand-foot-mouth, varicella, primary HSV	Same as infant, but also consider recurrent HSV and herpes zoster	Same as child, but also consider HSV II
	Bullae	Burns, impetigo, scalded skin ( <i>Staphylococcus</i> ), epidermolysis bullosa	Same as infant, but also consider pemphigus vulgaris, bullous pemphigoid, Stevens-Johnson syndrome, toxic epidermal necrolysis	Same as child (except epidermolysis bullosa)
	Scales	Ichthyoses, hyperkeratosis, syndromes (Netherton, Sjögren-Larsson, KID, CHILD, Conradi)	Same as infant	Same as child, but also consider Refsum disease

**Table 16-12** Common Integumentary Findings—cont'd

SITE	FINDING	NEWBORN AND INFANT	CHILD	ADOLESCENT
	Induration and sclerosis	Insect bites, infection	Infection, insect bites, scleroderma (post- <i>Streptococcus</i> ), scleroderma	Same as child
	Atrophy	Scarring, progeria, Lawrence-Seip syndrome (rare), cutis aplasia	Same as infant, but also consider morphea, Ehlers-Danlos syndrome, striae, trauma, scarring	Same as child, but also consider necrobiosis lipoidica diabetorum, Werner syndrome (rare)
	Ulcers	Neuropathic (toxic metal ingestion, spina bifida, diabetes), vasculitis, decubitus, trauma, infection	Same as infant, but also consider granulomas (inflammatory bowel disease, tuberculosis), cat scratch fever, balanitis ( <i>Streptococcus</i> ), HSV, other infection (eg, <i>Pseudomonas</i> )	Same as child, but also consider gonorrhea, genital warts, self-mutilation
<b>Hair</b>	Hair loss (alopecia) with underlying skin abnormality	Nevus, hemangioma, hamartoma, incontinentia pigmenti and cutis aplasia (scarring), ectodermal dysplasia	Same as infant, but also consider chemical and thermal burns, tinea capitis, trichotillomania	Same as child
	Hair loss (alopecia) without underlying skin abnormality	Local rubbing (bed position), alopecia areata, local infection	Trauma, infection, alopecia areata (local), alopecia totalis and universalis (generalized), metabolic disorders (hyperthyroidism, homocystinuria), heavy metal intoxication	Same as child, but also consider self-mutilation (trichotillomania) and toxic reaction to use of chemical agents on hair
	Excess hair (hypertrichosis, hirsutism)	Nevi, hamartoma (local), porphyria, drugs (eg, phenytoin), syndromes (mucopolysaccharidoses, leprechaunism, trisomy 18, Coffin-Siris, Marshall-Smith)	Same as infant, but also consider Cushing, adrenogenital, and polycystic ovary syndromes	Same as child
<b>Nails</b>	Underdeveloped (hypoplasia, aplastic)	In utero exposure to anticonvulsants, alcohol, and warfarin, congenital, Turner-Noonan syndrome, nail-patella syndrome, Lesch-Nyhan syndrome, chromosomal abnormalities	Same as infant	Same as child
	Pitting	Rare, usually a normal variant	Infection, psoriasis, normal variant after psoriasis	Same as child
	Abnormal shape (dystrophy)	Acrodermatitis enteropathica (zinc deficiency), ectodermal dysplasia, trauma	Same as infant, trauma self-inflicted or otherwise	Same as child
	Discoloration	Tetracycline exposure, subungual hematoma, trauma, Addison disease, jaundice, carotenemia, Wilson disease	Same as infant, but also consider chlorine phenothiazine exposure, endocarditis, melanoma, Peutz-Jeghers syndrome, uremia	Same as child, but also consider chronic tobacco use, fungal infection
	Spoon shape	Congenital (benign), Turner or Noonan syndrome, incontinentia pigmenti, iron deficiency	Same as infant, but also consider hemochromatosis	Same as child
	Brittle, dry	Malnutrition, ectodermal dysplasia, Plummer-Vinson syndrome, fungal infection, progeria, vitamin A deficiency (may be found in cystic fibrosis as presenting finding)	Same as infant, but also consider selenium poisoning, chronic disease, Reiter syndrome, thyroid disease, zinc deficiency	Same as child

CHILD, congenital hemidysplasia with ichthyosiform erythroderma and limb defects; HSV, herpes simplex virus; JIA, juvenile idiopathic arthritis; KID, keratitis with ichthyosis and deafness; SLE, systemic lupus erythematosus.

include absence, atrophy, dysplasia, hypertrophy of the nail bed, spoon shape, pitting, brittleness, separation, discoloration, ridging, and lines. Nail disorders are generally broadly classified as congenital or acquired.

Conditions associated with findings on the integument examination are found in Table 16-12.

## ENDOCRINOLOGY

Endocrinologic and renal disease, by their very natures, stem from or produce systemic disease and findings. Many of these findings (eg, failure to thrive, short stature, hyperpigmentation, edema) could also occur from dysfunction in other organ systems. With a high index of suspicion derived from a thorough history and physical examination, and appropriate laboratory tests, a reasonable differential diagnosis and ultimately a diagnosis will be made. Because hormones can't be seen, and laboratory tests are not physical examination findings, this section and the section covering the renal system will discuss specific common physical findings that often must be further substantiated by testing. General observation, palpation, and measurement are the primary diagnostic tools used during a complete physical examination for endocrine problems.

Observation of the infant and child may lead to specific endocrine diagnoses such as lymphedema of the hands and feet, neck webbing, a shield-shaped chest, or the low hairline of Turner syndrome. If the infant has poor tone, suck, or feeding, or exhibits lethargy or fussiness, endocrine diagnoses that should be considered include hypoglycemia, hypocalcemia, and hypothyroidism. In an older child, fatigue and lethargy can be associated with hypothyroidism, hypoglycemia, and adrenal insufficiency. A rachitic rosary (prominent knobs along the sternal costochondral junctions) is associated with rickets. Infants who are small for their age may have intrauterine growth restriction (IUGR) from Turner syndrome or hypopituitarism, and large infants may have mothers with gestational diabetes or have Beckwith-Wiedemann syndrome. Underweight infants with normal length usually result from malnutrition, including underfeeding or malabsorption, as in cystic fibrosis. Adolescents with growth delay may have delay in attaining puberty because of constitution (familial growth pattern), but also because of hypogonadism or chronic disease (eg, severe cystic fibrosis). An open posterior fontanel after 1 to 2 months of age suggests hypothyroidism. Weight loss and dehydration can be presenting symptoms of type 1 diabetes mellitus at any age. Slow growth in an older child can occur with any chronic disease, but with the finding of poor growth velocity, growth hormone deficiency should be suspected. Agitation and tremors can arise from multiple causes, but hyperthyroidism should be included in the differential diagnosis. Hypocalcemia can cause muscles to be prone to irritation at any age.

Findings from the integument examination can suggest endocrine disorders. Acanthosis nigrans associated with insulin resistance is often found in obese adolescents. Obese children and adolescents may also have stretch striae on the abdomen, but when associated

with cutaneous atrophy these suggest Cushing syndrome. The finding of hirsutism, particularly among females, suggests androgen excess, but can also be associated with hyperinsulinism. Dry or breaking hair and nonpitting edema suggest hypothyroidism. Bronzing of the skin (with no tan line) is associated with both Addison disease and congenital adrenal hyperplasia. Graves disease has associated exophthalmos and onycholytic (separation) nail changes. A mass in the neck may represent a goiter and, if painful, thyroiditis. Undescended testes may be because of prematurity or chromosomal and nonchromosomal syndromes usually associated with primary dysgenetic hypogonadism in males, but may also represent female virilization in congenital adrenal hyperplasia.

Microphallus suggests hypopituitarism, androgen insensitivity, or premature testicular failure. Early breast development can indicate exogenous exposure to estrogen or precocious puberty, especially if associated with premature development of pubic hair and accelerated growth.

Common findings associated with endocrine disorders are presented in Table 16-13.

## RENAL

As with the endocrine system, suspected renal diagnosis is typically made through laboratory evaluation. In addition, renal disease is often a secondary problem related to other systemic disease or drugs. Measurement, observation, and palpation are the most commonly utilized aspects of the physical examination when evaluating children for renal disease. Common findings include hypertension, edema, bruising, heart murmur, fever, purpura, flank mass, flank tenderness, and abdominal tenderness. As with other chronic disease, children with chronic renal disease may present with growth failure, and a workup for this condition should include a renal evaluation.

Hypertension in the newborn and infant may be a finding in renal diseases including renal vein thrombosis, renal tumor, adrenal tumor, and polycystic kidneys. In the older child or adolescent, it can be an intermittent manifestation of acute or chronic glomerulonephritis or may be secondarily associated with volume overload from hypoproteinemia. Edema as a finding in renal disease is associated with nephrotic syndrome, glomerulonephritis, membranous nephropathy, and focal sclerosis. Bruising can occur with coagulopathies and collagen-vascular disease; frank purpura with systemic infection and Henoch-Schönlein purpura. A flank mass may represent a polycystic kidney, urinary obstruction, tumor, or multicystic dysplasia. Flank tenderness is most often caused by pyelonephritis but may also represent trauma or urolithiasis. Abdominal tenderness can be a manifestation of renal colic because of urolithiasis, tumors, infection, or other urinary obstruction.

More common conditions associated with the renal findings in this section are summarized in Table 16-14.

## HEMATOLOGY/ONCOLOGY

Like findings associated with endocrine and renal disorders, hematologic and oncologic problems usually present with manifestations in other systems and a



**Table 16-13** Common Endocrine Findings

SITE	FINDING	NEWBORN AND INFANT	CHILD	ADOLESCENT
<b>General</b>	Short stature	IUGR, Turner syndrome, Russell-Silver syndrome, social deprivation, hypothyroidism	Constitution (familial growth pattern), Turner syndrome, growth hormone deficiency, Cushing syndrome, Prader-Willi syndrome, chronic inflammatory diseases, chronic oral steroid therapy, hypothyroidism	Same as child, but consider delayed puberty
	Tall stature	Beckwith-Wiedemann syndrome	Growth hormone–producing tumors, acromegaly, obesity, precocious puberty	Same as child, but also consider Klinefelter and Marfan syndromes
	Underweight (failure to thrive or gain weight)	Hyperthyroidism, diabetes mellitus, social deprivation	Same as infant	Same as child, but also consider anorexia and bulimia
	Overweight	Hyperinsulinism, overnutrition	Prader-Willi syndrome, Cushing syndrome, metabolic syndrome, overeating, reduced physical activity	Same as child
	Hyperreflexia Chvostek, Trousseau signs	Hyperthyroidism Hypocalcemia	Same as infant Same as infant	Same as infant Same as infant
<b>Head</b>	Hyporeflexia Open posterior fontanel	Hypothyroidism Hypothyroidism	Same as infant NA	Same as infant NA
<b>Neck</b>	Thyroid gland enlargement (painless goiter)	Iodine deficiency, enzymatic defects	Same as infant, but also consider Graves disease, Hashimoto thyroiditis, subacute hypothyroidism, malignancy	Same as child
	Painful goiter	NA	Subacute thyroiditis	Same as child
	Cystic mass in the midline anteriorly	Thyroglossal duct cyst, ectopic thyroid gland	Same as infant	Same as child
<b>Chest wall</b>	Webbing with low hair line	Turner syndrome, Noonan syndrome	Same as infant	Same as infant
	Pectus excavatum and rachitic rosary (see text)	Rickets	Same as infant	Same as infant
<b>Skin</b>	Dry, thickened, waxy	Hypothyroidism	Same as infant	Same as infant
	Thin with purple striae	Cushing syndrome	Same as infant	Same as infant
	Café-au-lait spots	NA	McCune-Albright syndrome, neurofibromatosis	Same as child
	Generalized bronzing (with-out tan line)	Addison disease	Same as infant	Same as infant
<b>Nails</b>	Spoon-like	Noonan syndrome	Same as infant	Same as infant
	Onycholysis	Rare	Graves disease, fungal infection, psoriasis	Same as child
<b>Cardiovascular</b>	Hypotension	Addison disease, salt wasting congenital adrenal hyperplasia, diabetes insipidus	Same as infant	Same as infant

Continued

**Table 16-13 Common Endocrine Findings—cont'd**

SITE	FINDING	NEWBORN AND INFANT	CHILD	ADOLESCENT
<b>Breast</b>	Hypertension	Rarely caused by endocrine problems	Cushing syndrome, metabolic syndrome, pheochromocytoma, Turner syndrome, Graves disease, chronic oral steroid therapy	Same as child
	Widened pulse pressure	Graves disease	Same as infant	Same as infant
	Murmur	Graves disease, Turner syndrome with coarctation of the aorta	Same as infant	Same as infant
	Early development	May be physiologically normal in early infancy	Precocious puberty, benign follicular cyst, exposure to estrogens	NA
	Painful breast bud Galactorrhea	Rare May be physiologically normal in early infancy	Normal in early puberty Drugs, prolactinoma, local infection	NA Same as child, but also consider pregnancy
<b>Male genitalia</b>	Breast development in males (gynecomastia)	May be physiologically normal in early infancy	Estrogen-producing tumor, drugs	Physiologic, Klinefelter syndrome, anorchia, defects in testosterone metabolism, feminizing adrenal tumors, drugs, exogenous estrogens
	Undescended testes	Prematurity, hereditary, genetic syndromes, androgen insensitivity	Same as infant except prematurity	Same as child
	Asymmetric testicular enlargement	Testicular tumors, hydrocele	Same as infant	Same as infant
	Painful testicular enlargement	Testicular torsion	Same as infant	Same as infant
	Micropenis	Hypopituitarism, androgen insensitivity	Same as infant	Same as infant
	Hypospadias	Disorder of sexual differentiation, Opitz syndrome, androgen receptor abnormalities	Same as infant	Same as infant
<b>Pubic hair</b>	Premature appearance	Idiopathic premature adrenarche, virilizing congenital adrenal hyperplasia, androgen-producing tumors	Same as infant	NA

IUGR, intrauterine growth restriction.

high index of suspicion as a result of a thorough history. Physical examination and judicious laboratory evaluation are necessary to make a diagnosis. The only specific system involved is the hematopoietic system, and oncologic disease can occur in any system, including the bone marrow. Table 16-15 lists general findings that could relate to hematology/oncology problems, but in most cases these findings cross

organ systems with other etiologies. These general findings include jaundice, pallor, mucus membrane bleeding, epistaxis, gastrointestinal bleeding, other spontaneous bleeding, petechiae, purpura, bruising, tissue and bone swelling, joint pain, and lymphadenopathy because of disturbance in the hematopoietic system. Oncologic findings, other than those related to the hematopoietic system, most often present with

**Table 16-14** Common Renal Findings

SITE	FINDING	NEWBORN AND INFANT	CHILD	ADOLESCENT
<b>General</b>	Hypertension	Renal vein thrombosis, renal artery stenosis, tumor (renal, adrenal), polycystic kidneys, fluid (volume) overload	Fluid overload, acute renal failure, chronic renal failure, tumor, renal vein thrombosis, acute glomerulonephritis, vasculitic disorders, chronic oral steroid therapy	Same as child
<b>Skin</b>	Edema	Fluid overload, nephrotic syndrome, proteinuria secondary to glomerulonephritis, membranous nephropathy, focal sclerosis, protein malnutrition	Same as infant, but also consider nephrotoxins and nephrotoxic drugs, SLE	Same as child
	Bruising	Coagulopathy, renal vein or artery thrombosis, tumor, drugs, vasculitis secondary to vasculitic disorders, HSP, hemolytic uremic syndrome	Same as infant	Same as infant
	Purpura	HSP, infection with shock and acute renal failure, hematologic and oncologic problems	Same as infant, also HSP	Same as child
<b>Flank</b>	Mass	Polycystic kidney, urinary obstruction, tumor, multicystic dysplasia, trauma, acute pyelonephritis, Beckwith-Wiedemann syndrome	Same as infant	Same as infant
	Tenderness	Rare finding (examination is difficult)	Acute pyelonephritis, urolithiasis, trauma, tumor	Same as child, but also consider sexually transmitted infection
<b>Abdomen</b>	Tenderness	Rare finding (examination is difficult)	Obstructive uropathy, urolithiasis, urinary tract infection, tumor, trauma	Same as child

HSP, Henoch-Schönlein purpura; SLE, systemic lupus erythematosus.

**Table 16-15** Common Hematologic Findings

SITE	FINDING	NEWBORN AND INFANT	CHILD	ADOLESCENT
<b>Skin</b>	Petechiae, ecchymoses, purpura	Inherited disorders of coagulation, acquired disorders of coagulation because of infection, toxins, trauma, autoimmune disease, HSP, platelet dysfunction, thrombocytopenia from any cause, rheumatic and vasculitic disorders	Same as infant, but also consider acquired immunodeficiency	Same as child
	Pallor	Anemia (iron deficiency, hemolytic, occult blood loss), blood loss from any site, suppressed bone marrow from drugs or toxins, inherited anemias (sickle cell disease, Diamond-Blackfan syndrome, TEC, anemia of chronic disease, malabsorption syndromes, hemolytic-uremic syndrome)	Same as infant, but TEC rare	Same as child (except TEC)
	Jaundice	Hemolytic anemias, liver or biliary tumor	Same as infant	Same as infant
	Enlarged lymph nodes	Infection, tumor (lymphoma, leukemia), rheumatic and vasculitic disorders	Same as infant	Same as infant
<b>Abdomen</b>	Enlarged liver and spleen (hepatosplenomegaly)	Infection, tumor, hemolytic anemias (sickle cell disease), spherocytosis, rheumatic and vasculitic disorders	Same as infant	Same as infant

HSP, Henoch-Schönlein purpura; TEC, transient erythroblastopenia of childhood.

masses that may obstruct organs and cause secondary symptoms. Discovery of an abdominal mass should prompt the physician to consider lymphoma, Wilms tumor, neuroblastoma, hepatoblastoma, teratoma, and germ cell tumors.

Spontaneous bleeding and easy bruising are always cause for concern in a infant, child, or adolescent, and are most often caused by coagulation and clotting disorders, platelet disorders, vitamin K deficiency, infection, malignancy, or vasculitic disorders. Pallor with normal cardiovascular status usually indicates anemia, which could have many causes, including bone marrow malignancies. Jaundice from hematologic causes results from rapid breakdown of red blood cells. Petechiae and bruising (ecchymoses) should always lead the physician to consider trauma (accidental or nonaccidental) but again are a manifestation of platelet deficiency or dysfunction. Purpura may be caused by autoimmune disease or infection, but could also be a consequence of extensive intradermal bleeding from other causes. Swelling, especially in a joint, should cause the physician to consider hemarthrosis.

## SUMMARY

The physician who thinks broadly and logically about a specific finding after performing a complete history, review of systems, and a physical examination is ahead of the game in forming a sound differential diagnosis and, ultimately, coming to a diagnostic conclusion. Findings usually span multiple organ systems and usually are consistent from one examination period to another (but not always if exacerbations and remissions occur spontaneously). Age-appropriate differential diagnoses must always be considered. Like symptoms, findings are, in the words of Jean-Martin Charcot (1825–1893), “in reality nothing but the cry from suffering organs.”

## TOOLS FOR PRACTICE

### Medical Decision Support

- Age-based Pediatric Blood Pressure Reference Charts (calculator), Baylor College of Medicine ([www.bcm.edu/bodycomplab/Flashapps/BPVAgeChartpage.html](http://www.bcm.edu/bodycomplab/Flashapps/BPVAgeChartpage.html))

## AAP POLICY

American Academy of Pediatrics Section on Ophthalmology and Committee on Practice and Ambulatory Medicine, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus, American Association of Certified Orthoptists. Instrument-based pediatric vision screening policy statement. *Pediatrics*. 2012;130(5):983–986 ([pediatrics.aappublications.org/content/130/5/983](http://pediatrics.aappublications.org/content/130/5/983))

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## Chapter 17

# SPORTS PREPARTICIPATION PHYSICAL EVALUATION

David T. Bernhardt, MD

More than 7 million high school students participate in sports each year, making the preparticipation physical evaluation (PPE) one of the most commonly performed examinations. Over the last decade, the PPE has evolved to allow physicians to provide consistent, high-quality examinations nationwide. In the early 1990s, the American Academy of Family Physicians, the American Academy of Pediatrics (AAP), the American Medical Society for Sports Medicine, the American Orthopaedic Society for Sports Medicine, and the American Osteopathic Academy of Sports Medicine formed the Preparticipation Examination Task Force to standardize the conduct and content of these examinations. In 1992, the Task Force published recommendations for the PPE based on the consensus of the current literature. These guidelines were updated in 1997, 2002, 2004, and 2010 and serve as the basis for the current PPE.

## GOALS OF THE PREPARTICIPATION PHYSICAL EVALUATION

The purpose of the PPE is to promote the health and safety of the young athlete in training and competition. Because pediatricians should counsel all patients to be physically active, the definition of athlete should include all pediatric patients.

The primary goals of the PPE are to detect conditions that might be life threatening, predispose the athlete to injury, or be disabling; and to meet legal or insurance requirements. The secondary goals are to determine general health, counsel athletes on health-related issues, update medications and immunizations, and establish a medical home. The secondary goals are part of the health supervision visit performed in the office as a routine part of the child or adolescent's health care.

Parents sometimes expect the PPE to be a comprehensive evaluation of the athlete's health, including areas that may be considered unrelated to sports participation, such as sexuality, substance abuse, and immunizations. Parents often use the PPE as the only medical evaluation for their child or adolescent. In contrast, many physicians view the PPE as a cursory examination that is only intended to detect conditions that might limit or impair athletic endeavors. Answers



### BOX 17-1 Common Questions Parents Have About the Preparticipation Physical Evaluation (PPE)

*My son had a physical examination for participation in football last year. Does he still need to see his physician this year?*

Although the PPE is comprehensive, it was never designed to take the place of a regular physician visit. The setting or time allocation for the PPE is often not conducive to discussions of health issues that are of primary importance during the adolescent years, such as drug and alcohol use, smoking, sexual activity education, safety issues, and diagnosis of depression. Therefore, the PPE should really be a small portion of a standard health supervision visit for all active patients.

*When should my child have a PPE relative to the beginning of an athletic season?*

The best time for the PPE is approximately 4 to 6 weeks before the beginning of the athletic season. This period allows enough time for thorough evaluations, consultations, and rehabilitation of any identified musculoskeletal injuries.

*Do I need to attend the PPE with my child?*

Although you may not be asked to attend the PPE with your child, you should review the accuracy and completeness of the medical history and family history provided. Your child may not know or remember some of the history. Most of the important information obtained in the PPE is obtained from the history.

*How often will my son or daughter need a PPE?*

The frequency of required evaluations varies by state. Most commonly, a PPE is required every other year. To determine the requirements of your state, check with the school district or the state high school athletic association.

*Will my child need to undergo any laboratory or radiographic studies at the PPE?*

Routine laboratory studies and radiographs are not generally performed. Based on information obtained during the history and physical examination, however, your physician may think that further studies are indicated.

to common questions parents have about the PPE are provided in Box 17-1.

Because parents and physicians view the evaluation differently, parents must be advised about the intent of the PPE, and the PPE's scope and purpose must be made clear to them. The most recent PPE guidelines suggest creating a medical home for all athletes (see Chapter 6, Medical Home Collaborative Care).

## CONDUCTING THE PREPARTICIPATION PHYSICAL EVALUATION

### Methods

The PPE is typically conducted using either the station-based method or the office-based method.

The station-based method divides the examination into several components, with physicians, nurses, athletic trainers, and coaches each assigned to a single task. This method is ideally suited for screening large numbers of athletes. Two benefits of this method are that it is relatively efficient and provides timely access to complete the PPE. However, this method affords less rapport with athletes, and privacy may be lacking. In addition, lack of access to parents and medical records may hinder the accuracy of the history. Without medical records being available, athletes and parents may hide crucial medical information in an attempt to get the athlete cleared for participation. Athletes have little opportunity to ask questions of the physicians regarding their own health or other medical or personal issues. Stations usually utilized in this situation include, but are not limited to, vital signs, vision screening, medical history and examination, orthopedic history and examination, an immunization station, and a checkout station.

The individual office-based method has the advantage of the screening examination being performed in the medical home or office with an established physician-patient relationship in which the medical history is known and continuity of care is fostered. Disadvantages may include a lack of consistency among physicians and their potential unfamiliarity with the sport and its disqualifying conditions.

### Timing

Ideally, the PPE is performed early enough before the sport's season begins to ensure that athletes who have medical problems can be thoroughly evaluated and treated, but not so early that intervening injuries are likely to occur. The best time for the evaluation to take place is 6 weeks prior to the first scheduled practice.

Although the current AAP guidelines suggest that the PPE should be performed every year, other sources suggest that the PPE be conducted before the beginning of each new level of competition (ie, middle school or junior high, high school, college), with annual updates of the history and targeted physical examinations of areas of concern. However, most state high school athletic associations require evaluations every other year.

## EVALUATION

### History

As in any health evaluation, the history identifies most potential problems for young athletes. Most experts agree that, despite the best screening of athletes to prevent sudden death, it is a rare occurrence to actually detect a condition that would possibly place the athlete at risk for sudden cardiac death. The key to identifying these problems is a questionnaire that systematically screens for conditions that often cause problems in athletes or that might lead to sudden death during athletic activity. Table 17-1 lists some of the most important questions to ask during the examination. PPE forms provided by state high school athletic associations may not incorporate all of the screening questions recommended by the Preparticipation

**Table 17-1** Medical History Questions

QUESTION	REASON
1. Injury or illness since last checkup?	Targets potential physical examination concerns
2. Chronic illnesses, hospitalizations, or surgeries?	Identifies potential counseling or rehabilitation issues
3. Any medications or supplements of any type?	Identifies drugs that may inhibit or interfere with sports participation
4. Allergies to medications, insects, or food?	Alerts physicians and trainers for potential allergic reactions
5. Dizziness, passing out, chest pain with exercise? History of sudden death in a close relative?	Identifies potential causes of sudden death caused by cardiovascular problems
6. Have you ever passed out or nearly passed out during exercise? Have you ever passed out or nearly passed out after exercise? Have you ever had discomfort, pain, or pressure in your chest during exercise? Does your heart race or skip beats during exercise? Does anyone in your family have Marfan syndrome?	Targets cardiovascular concerns
7. Ever been restricted from sports by physician?	Identifies potential disqualifying problems
8. Any skin problems?	Identifies potential transmittable disease during contact
9. Concussion, knocked out, unconsciousness, memory loss, seizure, or severe or frequent headache?	Targets neurologic concerns
10. Stinger, burner, pinched nerve, numbness or tingling in extremities?	Targets neurologic concerns
11. Problems while exercising in the heat?	Targets heat illness concerns
12. Asthma, allergies, wheezing, difficulty breathing, or chest pain?	Identifies potential for exercise-induced asthma
13. Special equipment or devices not usually used in your sport?	Identifies potential concerns for physician follow-up
14. Glasses, contacts, or vision or eye problems?	Identifies ophthalmologic concerns
15. Strain, sprain, fracture, joint pain, or swelling?	Identifies potential musculoskeletal problems
16. Concerns about weight: Do you lose weight regularly for your sport?	Identifies potential disordered eating
17. Feel stressed out?	Clue to ask follow-up questions regarding drug use, eating problems, sexuality, and home and school problems
18. Recent immunizations (tetanus, measles, hepatitis B, chicken pox)?	Health maintenance issues
19. Girls only: menstrual history?	Identifies oligomenorrhea and amenorrhea and potential risk for poor nutrition, stress fractures
20. Do you wear protective braces, splints?	Identifies injuries that have not been fully rehabilitated

Examination Task Force. The AAP provides a recommended standardized form (see Tools for Practice at the end of this chapter.)

One study showed that only 40% of PPE forms matched when filled out independently by parent and child. The athlete and the parents should, therefore, complete the form together to obtain a thorough and accurate history. Although the PPE forms should be completed by parent and patient, some issues may arise (particularly for those patients for whom the practice is the medical home) in which adolescent privacy on certain topics, such as sexuality and substance abuse, should be respected. A confidential form, such as the Guidelines for Adolescent Preventive Services (GAPS) form, should be completed by the adolescent when addressing these issues.

### Physical Examination

Two key components of the physical examination—cardiovascular and musculoskeletal—identify most athletes who warrant further evaluation or disqualification. The updated medical evaluation form recommended by the Preparticipation Examination Task Force can be accessed on the AAP Web site (see Tools for Practice at the end of this chapter).

### Cardiovascular Examination

The cardiovascular examination should include evaluation of peripheral pulses, murmurs, and blood pressure. Table 17-2 summarizes important aspects of the cardiovascular examination screening. All diastolic murmurs and grade 3/6 systolic murmurs warrant further evaluation. Hypertrophic cardiomyopathy, one

**Table 17-2** Cardiovascular Screening in Athletes

CONDITION	CARDIOVASCULAR EXAMINATION	ABNORMALITY
Hypertension	Blood pressure	Varies with age; general guideline is >135/85 mm Hg in adolescents
Coarctation of aorta	Femoral pulses	Decreased intensity of pulse
Hypertrophic cardiomyopathy	Auscultation with provocative maneuvers (standing, supine, Valsalva maneuver)	Systolic ejection murmur that intensifies with standing or Valsalva maneuver
Marfan syndrome	Auscultation	Aortic (decrecendo diastolic murmur) or mitral insufficiency (holosystolic murmur)

Derived from Maron BJ, Thompson PO, Puffer JC. Cardiovascular preparticipation screening of competitive athletes: a statement from the Sudden Death Committee [clinical cardiology] and Congenital Cardiac Defects Committee [cardiovascular disease in the young] American Heart Association. *Circulation*. 1996;94:850–856.

of the most important conditions to detect, may produce a systolic murmur that cannot be distinguished from an innocent murmur. The murmur of hypertrophic cardiomyopathy increases in intensity with a Valsalva maneuver (decreased ventricular filling, increased obstruction) and decreases with squatting (increased ventricular filling, decreased obstruction); it will also increase in intensity when the athlete moves from a squatting to standing position.

Blood pressures obtained during the PPE are often high. These readings are sometimes the result of using a blood pressure cuff that is too small, particularly in large adolescents. However, sometimes the athlete's blood pressure is truly high when an age-based table of norms is consulted. Hypertension is rarely severe enough to disqualify an athlete from participation, but it needs to be identified and monitored by the athlete's regular physician. Weight-training activities should be restricted in patients who have severe hypertension. Diagnostic tests, such as electrocardiograms, are still not universally accepted as a standard of care at this time. A low positive predictive value, a lack of trained or expert clinicians adept at interpreting electrocardiograms in athletes, and cost are most often cited as the reasons for this. Continued investigation into the cost-effectiveness and standardization of electrocardiogram interpretation in athletes may change this recommendation in the future.

Although sudden cardiac death in young athletes is rare, a positive response to the cardiac history questions detailed in the PPE monograph and history form warrants further, more detailed evaluation.

### Musculoskeletal Examination

The musculoskeletal examination is particularly important because it typically accounts for 50% of the abnormal physical findings identified on the PPE. The examination should focus on previously injured or symptomatic areas. Ninety-two percent of orthopedic injuries are detected by history alone.

Some authorities suggest a sport-specific approach to the physical examination. This method emphasizes the areas that are most commonly affected or injured in each specific sport. For example, a swimmer's examination would focus on the shoulders, whereas a

### BOX 17-2 Special Considerations for the Examination of Injured or Symptomatic Joints

- Inspect for visual deformity, muscle mass, asymmetry, and swelling.
- Palpate for localized areas of tenderness, warmth, and effusion.
- Assess range of motion (eg, an athlete with hip pain should be tested for loss of internal rotation and abduction, which can be seen in slipped capital femoral epiphysis and Legg-Calvé-Perthes disease).
- Test neurovascular status by evaluating muscle strength, sensation, reflexes, and pulses of the involved limb (eg, an athlete with a history of burners should undergo complete neurovascular testing of the neck and upper extremities).
- Test joint stability (eg, an athlete with knee pain should undergo tests for valgus and varus stress, Lachman test, and posterior drawer test).

football player's examination would include evaluation of neurologic conditions and musculoskeletal injuries.

Box 17-2 lists special considerations for the examination of injured or symptomatic joints.

### Laboratory Studies

Laboratory studies have not been shown to be cost-effective or warranted in young, asymptomatic athletes. Routine urinalysis and hematocrit for all athletes have been largely abandoned because these tests do not identify athletes who require disqualification, and they have a high rate of false-positive results. Similarly, electrocardiography, echocardiography, and stress testing are not suggested as screening tests in asymptomatic individuals because of the high rate of false-positive findings and high cost.

### SPORTS CLASSIFICATION

Sports are classified based on the likelihood of collision injury and the strenuousness of the exercise. These classifications are used to guide physicians on the risk

**BOX 17-3 Sport Classification by Contact****CONTACT OR COLLISION**

- Basketball
- Boxing
- Crew rowing
- Diving
- Field hockey
- Football (flag, tackle)
- Ice hockey
- Lacrosse
- Martial arts
- Rodeo
- Rugby
- Ski jumping
- Soccer
- Team handball
- Water polo
- Wrestling

**LIMITED CONTACT**

- Baseball
- Bicycling
- Cheerleading
- Canoeing and kayaking (white water)
- Fencing
- Field events (high jump, pole vault)
- Floor hockey
- Gymnastics
- Handball
- Horseback riding
- Racquetball
- Skating (ice, in-line, roller)

- Skiing (downhill, water)
- Softball
- Squash
- Ultimate frisbee
- Volleyball
- Windsurfing and surfing

**NONCONTACT**

- Archery
- Badminton
- Bodybuilding
- Canoeing and kayaking (flat water)
- Crew rowing
- Curling
- Dancing
- Field events (discus, javelin, shot put)
- Golf
- Orienteering
- Power lifting
- Race walking
- Riflery
- Rope jumping
- Running
- Sailing
- Scuba diving
- Strength training
- Swimming
- Table tennis
- Tennis
- Track
- Weight lifting

Adapted from American Academy of Pediatrics Committee on Sports Medicine and Fitness. Medical conditions affecting sports participation. *Pediatrics*. 2008; 121(4):841–848.

of injury and the degree of cardiopulmonary fitness required to engage in the sport successfully. The AAP has established classification guidelines by the level of contact and intensity (see Box 17-3 and Table 17-3).

**CLEARANCE TO PLAY**

Few athletes are disqualified from activity based on conditions identified during the PPE. Table 17-4, which is designed to be understood by both medical and nonmedical personnel, lists the most current recommendations regarding medical conditions and contraindications to participation. Working with athletes to find safe, enjoyable sports in which they can participate is important. If possible, and depending on the condition that is detected, sports participation should not be eliminated altogether. Figure 17-1 provides a sample of a form used for clearance for return to play.

Occasionally, an athlete or parent will disagree with a physician's recommendation for restricting participation in a particular sport. In these cases, the important steps are to explain fully the reasons for the recommendation and to consider having the athlete and parent sign a document acknowledging that this discussion occurred and that they were informed of the risks. Athletes may request a second opinion, and this is often reasonable when making important decisions related to clearance. Ultimately, the team physician is responsible for ensuring that athletes are able to participate safely and without undue risk of injury.

**SPECIAL CONSIDERATIONS****Nutritional Supplements**

Sports supplements have become a billion-dollar industry. Athletes as young as age 11 years are taking



**Table 17-3** Sports Classification by Intensity

<b>HIGH-TO-MODERATE INTENSITY; HIGH-TO-MODERATE DYNAMIC; HIGH-TO-MODERATE STATIC DEMANDS</b>	<b>HIGH-TO-MODERATE INTENSITY; HIGH-TO-MODERATE DYNAMIC; LOW STATIC DEMANDS</b>	<b>HIGH-TO-MODERATE INTENSITY; HIGH-TO-MODERATE STATIC; LOW DYNAMIC DEMANDS</b>	<b>LOW INTENSITY; LOW DYNAMIC; LOW STATIC DEMANDS</b>
<ul style="list-style-type: none"> <li>• Boxing</li> <li>• Cross-country skiing</li> <li>• Cycling</li> <li>• Downhill skiing</li> <li>• Fencing</li> <li>• Football</li> <li>• Ice hockey</li> <li>• Rugby</li> <li>• Running (sprint)</li> <li>• Speed skating</li> <li>• Water polo</li> <li>• Wrestling</li> </ul>	<ul style="list-style-type: none"> <li>• Badminton</li> <li>• Baseball</li> <li>• Basketball</li> <li>• Field hockey</li> <li>• Lacrosse</li> <li>• Orienteering</li> <li>• Table tennis</li> <li>• Race walking</li> <li>• Racquetball</li> <li>• Soccer</li> <li>• Squash</li> <li>• Swimming</li> <li>• Tennis</li> <li>• Volleyball</li> </ul>	<ul style="list-style-type: none"> <li>• Archery</li> <li>• Auto racing</li> <li>• Diving</li> <li>• Equestrian</li> <li>• Field events (jumping, throwing)</li> <li>• Gymnastics</li> <li>• Karate or judo</li> <li>• Motorcycling</li> <li>• Rodeo</li> <li>• Sailing</li> <li>• Ski jumping</li> <li>• Waterskiing</li> <li>• Weight lifting</li> </ul>	<ul style="list-style-type: none"> <li>• Bowling</li> <li>• Cricket</li> <li>• Curling</li> <li>• Golf</li> <li>• Rifle shooting</li> </ul>

Adapted with permission from Mitchell JR, Haskell W, Snell P, Van Camp SP. Task Force 8: classification of sports. *J Am Coll Cardiol.* 2005;45(8):1364–1367.

**Table 17-4** Medical Conditions and Sports Participation

<b>CONDITION</b>	<b>PARTICIPATE?</b>	<b>EXPLANATION</b>
Atlantoaxial instability (instability of the joint between cervical vertebrae 1 and 2)	Qualified yes	Athlete needs evaluation <sup>a</sup> to assess risk of spinal cord injury during sports participation.
Bleeding disorder	Qualified yes	Athlete needs evaluation.
Carditis (inflammation of the heart)	No	Carditis may result in sudden death with exertion.
Hypertension (high blood pressure)	Qualified yes	Persons with significant essential (unexplained) hypertension should avoid weight lifting and power lifting, bodybuilding, and strength training. Those with secondary hypertension (hypertension caused by a previously identified disease) or severe essential hypertension need evaluation.
Congenital heart disease (structural heart defects present at birth)	Qualified yes	Persons with mild forms may participate fully; those with moderate or severe forms or who have undergone surgery need evaluation.
Dysrhythmia (irregular heart rhythm)	Qualified yes	Athlete needs evaluation because some types require therapy or make certain sports dangerous, or both.
Mitral valve prolapse (abnormal heart valve)	Qualified yes	Persons with symptoms (chest pain, symptoms of possible dysrhythmia) or evidence of mitral regurgitation (leaking) on physical examination need evaluation. All others may participate fully.
Heart murmur	Qualified yes	If the murmur is innocent (does not indicate heart disease), then full participation is permitted; otherwise the athlete needs evaluation (see “Congenital heart disease” and “Mitral valve prolapse” above).
Cerebral palsy	Qualified yes	Athlete needs evaluation.
Diabetes mellitus	Yes	All sports can be played with proper attention to diet, hydration, and insulin therapy. Particular attention is needed for activities that last 30 minutes or more.
Diarrhea	Qualified no	Unless disease is mild, no participation is permitted, because diarrhea may increase the risk of dehydration and heat illness. See “Fever” below.

Continued

**Table 17-4** Medical Conditions and Sports Participation—cont'd

CONDITION	PARTICIPATE?	EXPLANATION
Eating disorders, anorexia nervosa, bulimia nervosa	Qualified yes	These patients need both medical and psychiatric assessment before participation.
Eyes: functionally one-eyed athlete, loss of an eye, detached retina, previous eye surgery or serious eye injury	Qualified yes	A functionally one-eyed athlete has a best-corrected visual acuity of <20/40 in the worse eye. These athletes would experience significant disability if the better eye were seriously injured, as would those with loss of an eye. Some athletes who have previously undergone eye surgery or had a serious eye injury may have an increased risk of injury because of weakened eye tissue. Availability of eye guards approved by the American Society for Testing Materials and other protective equipment may allow participation in most sports, but this determination must be made on an individual basis.
Fever	No	Fever can increase cardiopulmonary effort, reduce maximal exercise capacity, make heat illness more likely, and increase orthostatic hypotension during exercise. Fever may rarely accompany myocarditis or other infections that may make exercise dangerous.
History of heat illness	Qualified yes	Because of the increased likelihood of recurrence, the athlete needs individual assessment to determine the presence of predisposing conditions and to arrange a prevention strategy.
Human immunodeficiency virus infection	Yes	Because of the apparent minimal risk to others, all sports may be played that the state of health allows. In all athletes, skin lesions should be properly covered, and athletic personnel should use universal precautions when handling blood or body fluids with visible blood.
Kidney: absence of one	Qualified yes	Athlete needs individual assessment for contact or collision and limited contact sports.
Liver: enlarged	Qualified yes	If the liver is acutely enlarged, then participation should be avoided because of risk of rupture. If the liver is chronically enlarged, then individual assessment is needed before collision or contact or limited contact sports are played.
Malignancy	Qualified yes	Athlete needs individual assessment.
Musculoskeletal disorders	Qualified yes	Athlete needs individual assessment.
History of serious head or spine trauma, severe or repeated, concussions, or craniotomy	Qualified yes	Athlete needs individual assessment for collision or contact or limited contact sports and for noncontact sports if deficits exist in judgment or cognition. Recent research supports a conservative approach to management of concussions.
Convulsive disorder (well controlled)	Yes	Risk of convulsion during participation is minimal.
Convulsive disorder (poorly controlled)	Qualified yes	Athlete needs individual assessment for collision or contact or limited-contact sports. Avoid the following noncontact sports: archery, rifle shooting, swimming, weight lifting or power lifting, strength training, or sports involving heights. In these sports, occurrence of a convulsion may be a risk to self or others.
Obesity	Qualified yes	Because of the risk of heat illness, obese persons need careful acclimatization and hydration.
Organ transplant recipient	Qualified yes	Athlete needs individual assessment.
Ovary: absence	Yes	Risk of severe injury to the remaining ovary is minimal.
Respiratory, pulmonary compromise (including cystic fibrosis)	Qualified yes	Athlete needs individual assessment but generally all sports may be played if oxygenation remains satisfactory during a graded exercise test. Patients with cystic fibrosis need acclimatization and good hydration to reduce the risk of heat illness.
Asthma	Yes	With proper medication and education, only athletes with the most severe asthma will have to modify their participation.

**Table 17-4** Medical Conditions and Sports Participation—cont'd

CONDITION	PARTICIPATE?	EXPLANATION
Acute upper respiratory infection	Qualified yes	Upper respiratory obstruction may affect pulmonary function. Athlete needs individual assessment for all but mild diseases. See "Fever."
Sickle cell disease	Qualified yes	Athlete needs individual assessment. In general, if status of the illness permits, then all but high-exertion, collision, or contact sports may be played. Overheating, dehydration, and chilling must be prevented.
Sickle cell trait	Yes	Individuals with sickle cell trait do not likely have an increased risk of sudden death or other medical problems during athletic participation except under the most extreme conditions of heat and humidity and possibly high altitude. These individuals, as with all athletes, should be carefully conditioned, acclimatized, and hydrated to reduce any possible risk.
Skin: boils, herpes simplex, impetigo, scabies, molluscum contagiosum	Qualified yes	Because the patient is contagious, participation in gymnastics with mats, martial arts, wrestling, or other collision or contact or limited-contact sports is not allowed. Herpes simplex virus is probably not transmitted via mats.
Spleen: enlarged	Qualified yes	Persons with acutely enlarged spleens should avoid all sports because of risk of rupture. Those with chronically enlarged spleens need individual assessment before playing collision or contact or limited contact sports.
Testicle: absent or undescended	Yes	Certain sports may require a protective cup.

<sup>a</sup>*Needs evaluation* means that a physician with appropriate knowledge and experience should assess the safety of a given sport for an athlete with the listed medical condition. Unless otherwise noted, this term is used because of the variability of the severity of the disease, the risk of injury among the specific sport, or both.

Adapted from American Academy of Pediatrics Committee on Sports Medicine and Fitness. Medical conditions affecting sports participation. *Pediatrics*. 2008;121(4):841–848.

performance-enhancing supplements. Sports supplements contain impurities, and when taken inappropriately, they may result in adverse side effects, which can include muscle cramps, dehydration, abdominal bloating, tachycardia, arrhythmia, and even death. Supplement use should be discouraged in most scenarios. The PPE is an ideal time to question athletes briefly about supplement use.

### Obesity

Childhood obesity has reached epidemic proportions. Up to 30% of children are obese, and many of these youngsters are seeking to participate in sports. Obesity is not a contraindication to sports participation unless a comorbid finding such as severe hypertension is found. Obese children are at increased risk of heat injury and should be counseled accordingly. Sports participation with emphasis on activities that improve fitness should be encouraged for the obese child.

### Concussion

A history of previous concussions should be addressed during the PPE. Consensus related to concussion management continues to evolve with more evidence to help guide management. Concussions that require a long time for recovery, or that involve significant amnesia, prolonged loss of consciousness, or seizure, should be thoroughly evaluated by either a sports medicine professional or neurologist. Neuropsychologic testing is suggested with repeat concussions or

complicated concussion. Patients must meet 3 criteria to return to play: they must be asymptomatic at rest, be asymptomatic with exercise, and have no neurocognitive deficits (memory loss, concentration problems, fatigue, foggy, confusion).

### Medical Home

The most underserved population in health care today is adolescents. In many instances, their only contact with the medical system is the PPE. Ideally, the PPE would be performed in the medical home to provide the comprehensive care required for this population relating to a myriad of risk factors that affect more than their lives as athletes.

### SUMMARY

- A PPE should be performed on all patients with the goal of promoting overall wellness through physical exercise; it is not performed primarily to disqualify an athlete.
- Ideally, an entire PPE should be performed by a single physician in the office setting.
- Sudden cardiac death in young athletes is a rare event, but a positive cardiac history should be thoroughly evaluated.
- The musculoskeletal history and physical examination are the best ways to discover orthopedic problems.
- Concussion, heat injury, and use of nutritional supplements are topics that need to be discussed and emphasized during the PPE.

Clearance for Return to Play			
Name _____	Sex _____	Age _____	DOB _____
<input type="checkbox"/>	Cleared without restriction		
<input type="checkbox"/>	Cleared with recommendations for further evaluation or treatment:		
_____			
_____			
_____			
<input type="checkbox"/>	Not cleared for:		
<input type="checkbox"/>	All sports. Reason _____		
<input type="checkbox"/>	Certain sports. Reason _____		
Recommendations: _____			
_____			
<b>EMERGENCY INFORMATION</b>			
Allergies: _____			
Other information: _____			
Immunizations (eg, tetanus/diphtheria; measles, mumps, rubella; hepatitis A, B; influenza; poliomyelitis; pneumococcal; meningococcal; varicella)			
<input type="checkbox"/>	Up to date ( <i>see attachment documentation</i> )		
<input type="checkbox"/>	Not up to date. Specify: _____		
_____			
Name of physician ( <i>print or type</i> ) _____ Date _____			

**Figure 17-1** Sample clearance for return to play.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Sports and Your Child* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Sports Success Rx! Your Child's Prescription for the Best Experience: How to Maximize Potential and Minimize Pressure* (book), American Academy of Pediatrics (shop.aap.org)

#### Medical Decision Support

- *Preparticipation Physical Evaluation Forms* (forms), American Academy of Family Physicians, American Academy of Pediatrics, American College of Sports Medicine, American Medical Society for Sports Medicine, American Orthopaedic Society for Sports Medicine, and American Osteopathic Academy of Sports Medicine (www.aap.org/en-us/about-the-aap/



Committees-Councils-Sections/Council-on-sports-medicine-and-fitness/Documents/PPE-4-forms.pdf)

### AAP POLICY

Halstead ME, Walter KD; American Academy of Pediatrics Council on Sports Medicine and Fitness. Sport-related concussion in children and adolescents. *Pediatrics*. 2010;126(3):597–615. Reaffirmed August 2014 ([pediatrics.aappublications.org/content/126/3/597](http://pediatrics.aappublications.org/content/126/3/597))

Rice SG; American Academy of Pediatrics Committee on Sports Medicine. Medical conditions affecting sports participation. *Pediatrics*. 2008;121(4):841–848. Reaffirmed June 2014 ([pediatrics.aappublications.org/content/121/4/841](http://pediatrics.aappublications.org/content/121/4/841))

### SUGGESTED READINGS

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are better managed in the department. Findings on the plain radiograph will often indicate whether further imaging is needed and in many cases will dictate the choice of imaging modality, whether fluoroscopy, ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), or nuclear scintigraphy.

Newer, more efficient generations of CT scanners have resulted in a significant increase in the use of CT imaging in the United States. CT imaging accounts for most medically related exposures to ionizing radiation. The Society of Pediatric Radiology has instituted the ALARA (as low as reasonably achievable) principle, by which participating institutions agree to modify CT imaging parameters, modify protocols, and improve patient shielding to reduce patient exposure to ionizing radiation. Additional innovations already adopted by some institutions include the radiation dose passport, a document carried by the parent that records a child's radiation exposure much like a vaccination record.

### Fluoroscopy

Fluoroscopy provides real-time evaluation of the airway and of the gastrointestinal (GI) and genitourinary (GU) tracts. In patients with possible tracheomalacia, dynamic changes in airway diameter can be identified with fluoroscopic technique. The upper GI series, with or without small bowel follow-through, allows assessment of swallowing function, esophageal and GI motility, gastroesophageal reflux, and position of the duodenojejunal junction. The small bowel follow-through can evaluate small bowel abnormalities, particularly in children with inflammatory bowel disease. Similarly, the colon is well evaluated by fluoroscopy-guided contrast enemas. Fluoroscopic voiding cystourethrography is useful in evaluating the bladder and urethra and in assessing for vesicoureteral reflux in children with urinary tract infections. Videofluoroscopy allows studies to be replayed and analyzed at a later time. The length of the fluoroscopic procedure determines the radiation dose. Use of pulse fluoroscopy, rather than continuous fluoroscopy, limits dose exposure.

### Ultrasound

US is the initial imaging modality of choice when evaluating a child because it imparts no radiation. Additionally, US requires no patient sedation and can be performed at the patient's bedside if necessary. US is limited by body habitus and overlying bowel gas or air. Because the quality of the images depends on the skill of the US operator, the operator must be trained and experienced in working with children. In the GI tract, US is particularly useful in diagnosing pyloric stenosis, appendicitis, and intussusception. It may also be used to assess bowel wall thickening in cases of inflammatory bowel disease and is far superior to CT in determining whether pleural fluid contains debris or loculations in cases of empyema. US is effective in evaluating the GU system and biliary system as well as the neonatal brain and spine. Doppler US has proved useful in evaluating the renal arteries in children with hypertension, in evaluating vascular

## Chapter 18 PEDIATRIC IMAGING

Terry L. Levin, MD

### IMAGING MODALITIES

With the advent of new technologies in radiology, the choices of imaging modalities available to the physician have become increasingly complex. Selecting the best imaging modality depends on the clinical question at hand. The more focused the question, the clearer the choice of imaging technique.

The initial evaluation of a child often begins with a plain radiograph. Whenever possible, this should be performed in the radiology department rather than by portable units because patient positioning and technique, which affect the quality of the final radiograph,

and nonvascular lesions, in assessing for ovarian and testicular flow abnormalities, and in determining vessel position and patency. In patients with liver or renal transplants, Doppler US is essential in evaluating flow within the transplanted organ. Contrast agents for US, which consist of microbubbles and have been used in the evaluation of vesicoureteral reflux, have not yet gained wide acceptance.

### Computed Tomography

CT is based on a volumetric acquisition of information derived from differential tissue absorption of ionizing radiation. Helical CT significantly shortens image time, and coronal and sagittal reconstructed images are possible. Three-dimensional reconstructions can be obtained with multidetector CT and are effective in cardiac imaging and in evaluating the airway and skeletal system. The newer-generation CT scanners allow increased speed of scanning so that motion artifact is reduced, and a single breath-hold may be sufficient to image large areas. This feature is particularly helpful in young children. CT is not limited by overlying gas and provides a larger field of view than US. It is the imaging modality of choice in evaluating the lungs and is far more sensitive in detecting small lung lesions than plain chest radiography. CT is also the initial imaging modality of choice in cases of trauma, because it may detect organ injury not identified on ultrasound. Newer uses of CT include CT renal angiography for evaluating for renovascular hypertension and CT urography to evaluate renal function and anatomy. Neutral oral contrast agents, which distend the small bowel and provide excellent assessment of the bowel lumen and the bowel wall, are useful in patients with inflammatory bowel disease, particularly Crohn disease.

CT has several limitations. Patients must be cooperative, and sedation may be required in young children. Because it is based on gray-scale analysis, intravenous or oral contrast is often required, particularly in children who have very little body fat. With the advent of newer intravenous contrast agents, the risk for adverse contrast reactions has decreased. However, such reactions may still occur, and informed consent is necessary.

Because of its ready availability and its ability to rapidly acquire images, there has been a significant rise in the use of CT in the past decade in the United States and a trend to use CT scanning as a screening rather than a diagnostic technique. The risk for overuse of CT is significant, however, because CT delivers ionizing radiation, a known carcinogen, to our patients. A single abdominal CT scan may be equivalent to 250 to 500 plain chest radiographs. As a response to the rising use of CT imaging in children, the Alliance of Safety in Pediatric Imaging and the Image Gently campaign were created. As a result, awareness of medical radiation safety has improved. From the referring physician's perspective, CT scans should be obtained when specifically indicated and not used as screening examinations. "The procedure should be restricted to cases where it is specifically indicated, and promises to convey a commensurate benefit in terms of a diagnosis that is difficult to obtain by any other means." Children should be referred to institutions abiding by the ALARA principle for CT scanning.

### Magnetic Resonance Imaging

MRI requires no ionizing radiation and has the advantage of providing multiplanar imaging. The patient must be cooperative, and sedation may be necessary. Examination time is longer than that with a CT scan. Noniodinated contrast agents may be used in select cases and have a low incidence of adverse reactions. MRI provides excellent evaluation of vessels, solid organs, bone marrow, and soft tissues, but it cannot assess lung disease. Cardiac MRI evaluates both cardiac anatomy and cardiac function. MRI provides excellent evaluation of the central nervous system and is the imaging modality of choice to assess the spine, spinal cord, and spinal canal. Magnetic resonance (MR) urography displays urograms of nondilated and dilated collecting systems, and it provides information on both anatomy and function by determining renal transit time. As such, MRI has replaced conventional intravenous pyelograms. MR cholangiography is useful as a noninvasive method of assessing the biliary and pancreatic ducts and is superior to all other modalities in evaluating bony and soft tissue lesions.

MR venography and MR arteriography provide information about venous and arterial flow, including assessment of vessel patency, stenoses, lymphovascular malformations, and other abnormalities of both small and large vessels.

### Nuclear Scintigraphy

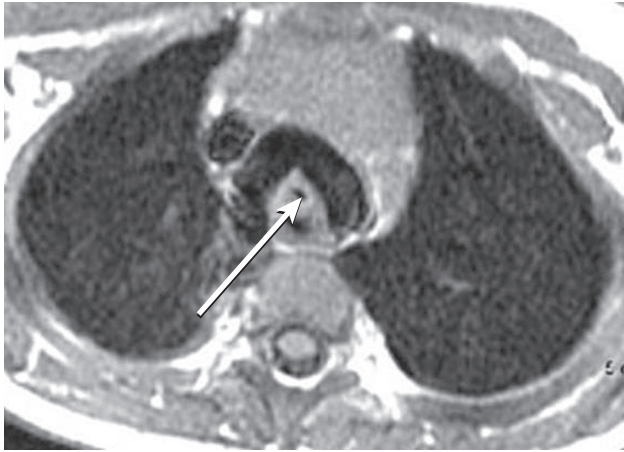
Nuclear scintigraphy has many uses in children. The diisopropyl iminodiacetic acid (DISIDA) scan can assess biliary excretion and gallbladder function and is a useful adjunct to US, which provides only anatomic information. The scintigraphic renogram shows differential renal function that can provide information on the degree of renal parenchymal damage. Additionally, when performed after intravenous furosemide administration, it is helpful in confirming the presence or absence of renal obstruction.

Scintigraphy has many applications in pediatric oncology. Positron emission tomography (PET) is useful in assessing tumor activity, particularly in cases of lymphoma. PET-CT combines both modalities in a fusion image. This combination provides anatomic and functional information and plays an important role in tumor staging, assessing of therapeutic response, and monitoring disease after completion of therapy. Unfortunately, PET-CT delivers a high dose of ionizing radiation. In patients with neuroblastoma, meta-iodobenzylguanidine (MIBG) scanning is sensitive in detecting tumor activity in primary and metastatic foci and is effective in evaluating patients for tumor recurrence. Thallium (Tl-201) scanning has been used to assess therapeutic response in patients with osteogenic sarcoma and Ewing sarcoma. Decreased tumor uptake of thallium after chemotherapy indicates a favorable response to therapy.

## SYSTEMS APPROACH

### Chest

The initial evaluation of the chest begins with a plain radiograph. Pneumonia, atelectasis, cardiac enlargement, pleural effusion, chest wall and ribs, and



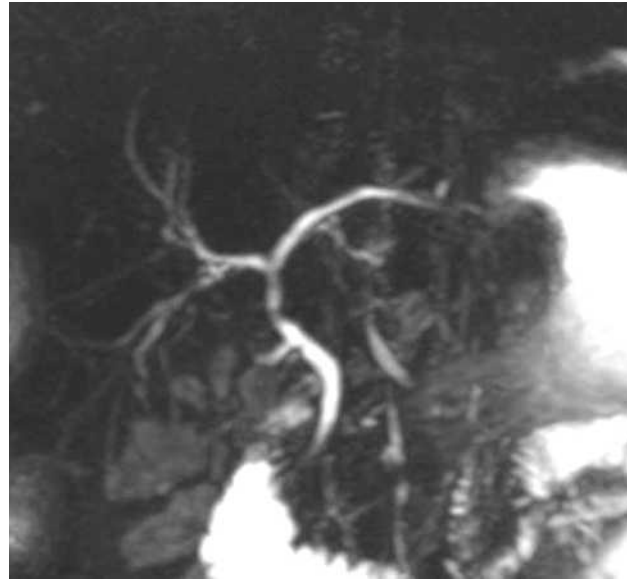
**Figure 18-1** T1-weighted axial magnetic resonance image clearly demonstrates a double aortic arch. Note the narrowed trachea (arrow).

adenopathy can be assessed by plain radiograph. Assessment for an aspirated foreign body is best performed with inspiratory and expiratory films of the chest or bilateral decubitus views of the chest. Evaluation for rib fractures should include dedicated oblique views of the ribs. Parenchymal and airway diseases, including congenital, neoplastic, infectious, or inflammatory conditions of the lung, are best evaluated by noncontrast CT. With current software, 3-dimensional endoscopic reconstructions of the airway may be obtained. Intravenous contrast-enhanced CT scans of the chest provide further information on pleural enhancement, loculation, or thickening in the setting of empyema, extent of hilar and mediastinal adenopathy in patients with neoplastic disease, and presence of vascular anomalies. Congenital abnormalities of the aorta and its branch vessels can be evaluated by either contrast-enhanced CT or MRI (Figure 18-1). Cardiac disease is best assessed by echocardiogram or MRI.

### Abdomen

The initial evaluation of the liver, spleen, and pancreas is best performed by US. Masses, vascular abnormalities, and diffuse parenchymal abnormalities may be identified on US. Infectious processes such as abscesses may also be identified. Although liver and splenic laceration may be imaged by US, contrast-enhanced CT is the study of choice when assessing for injury after abdominal trauma.

US is also the best method of assessing the gallbladder and biliary ductal anatomy. Gallstones not visualized on CT will be evident on US, and biliary duct dilation, stones, or masses can be identified. Findings of cholecystitis, including gallbladder distention, wall thickening, and edema, will be identified. Biliary function, however, is best evaluated with nuclear scintigraphy. Additionally, nuclear scintigraphy is the study of choice in diagnosing biliary atresia. MR cholangiography is a noninvasive method that provides excellent visualization of the biliary ducts (Figure 18-2).



**Figure 18-2** Heavily T2-weighted maximal image projection from a magnetic resonance cholangiogram demonstrates the normal biliary tree.

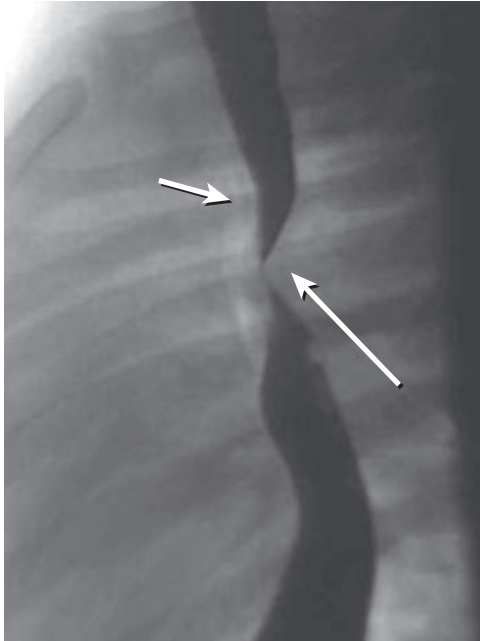
### Gastrointestinal Tract

Contrast studies are the first choice in evaluating the bowel after a plain radiograph has been taken to assess the abdominal bowel gas pattern. Barium or water-soluble contrast agents are administered orally or by feeding tube. In the esophagus, intrinsic lesions such as stenoses, fistulas, rings, foreign bodies, and esophagitis are well defined. Extrinsic lesions such as vascular rings or slings have a characteristic appearance (Figure 18-3). Motility disorders and gastroesophageal reflux may also be diagnosed. Contrast studies also provide information on intrinsic or extrinsic abnormalities of the stomach, including masses and ulcer disease, and are useful in evaluating the integrity of the gastroesophageal junction in children after fundoplication.

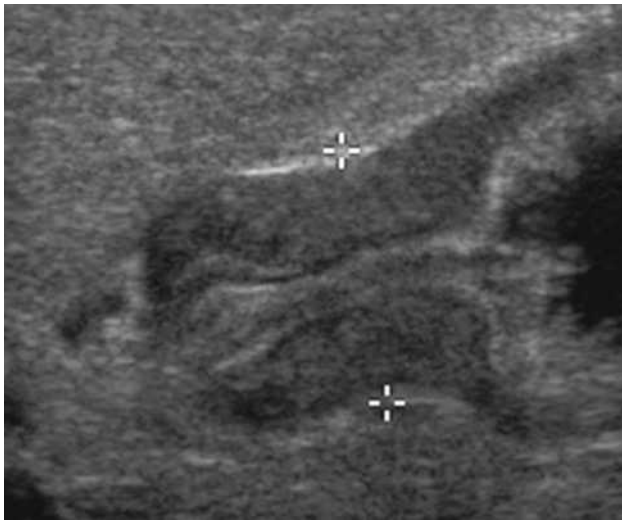
In children with suspected possible malrotation, an upper GI series will define the location of the duodenojejunal junction and confirm or exclude proximal small bowel distention. Contrast enema may be performed at the same time to define the position of the cecum in unclear cases. The relationship of the superior mesenteric artery and vein on US has been used to diagnose malrotation; however, because of false-positive and false-negative results, the upper GI series is the study of choice. Midgut volvulus can be diagnosed by US as a *whirlpool sign*, indicating that the torsed bowel will be demonstrated on color Doppler scanning. US has replaced the upper GI series for the evaluation of the pylorus in cases of suspected pyloric stenosis. The elongated and thickened pyloric muscle characteristic of pyloric stenosis is readily identifiable by US (Figure 18-4).

Small bowel disease, particularly inflammatory bowel disease, is best evaluated by upper GI series and small bowel follow-through or CT enterography. Terminal ileal strictures, fistulas, and mesenteric



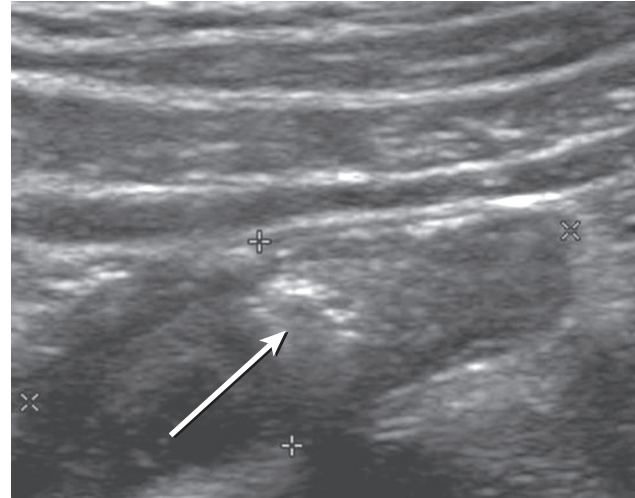


**Figure 18-3** Lateral view from a barium esophagram demonstrates an extrinsic impression on the posterior aspect of the esophagus (*long arrow*) and the anterior aspect of the esophagus (*short arrow*). The finding is consistent with a vascular ring.



**Figure 18-4** Longitudinal US image demonstrates the characteristic thickened and elongated pyloric muscle of pyloric stenosis. Calipers delineate the diameter of the pylorus.

infiltration can be clearly diagnosed on delayed images focused on the right lower quadrant. CT is helpful in evaluating for associated abscesses. The small bowel follow-through also is effective in evaluating for small bowel polyps, although with the introduction of newer neutral oral contrast agents, the role of CT will likely increase. Nuclear scintigraphy is the method of choice in diagnosing Meckel diverticulum. In cases of

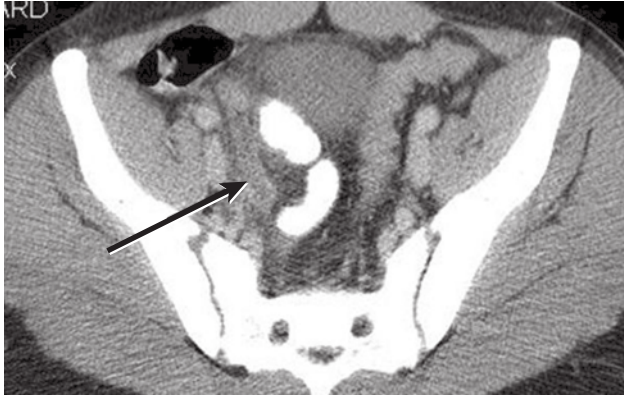


**Figure 18-5** US image of an inflamed appendix. Note the appendicolith (*arrow*). Calipers delineate the inflamed appendix.

possible intussusception, the imaging evaluation should begin with supine, prone, and decubitus views of the abdomen in an attempt to identify a filling defect in the transverse or ascending colon. If intussusception is suspected on plain radiograph, then US confirmation may be obtained. In cases in which an intussusception is present, a multilayered, masslike structure will be located in the abdomen. US has the advantage of providing further information, such as the presence or absence of ascites or a lead point and the presence or absence of vascularity within the intussusciptum and intussusceptum. Air-reduction enema has replaced contrast enema reduction of intussusception. Air is insufflated in a retrograde fashion into the rectum under fluoroscopic guidance. A pressure valve may be used to ensure that the insufflated pressure does not exceed 120 mm Hg.

The diagnosis of appendicitis can be difficult. Several imaging choices are available to aid in the diagnosis, and many opinions have been given on which modality is best. In a thin, cooperative child, US is an effective method of identifying the inflamed appendix, which will appear as a thick-walled, noncompressible structure with increased vascularity on Doppler US (Figure 18-5). US may also demonstrate the presence of an abscess or appendicolith. Lack of visualization of the appendix does not exclude appendicitis. Recent studies have found that US provides a high degree of diagnostic accuracy in patients with clinical findings suggestive of appendicitis, with a sensitivity of 86%, a specificity of 95%, a positive predictive value of 91%, a negative predictive value of 92%, and a diagnostic accuracy of 92%. Many authors suggest that US be used as the primary imaging modality in evaluating for appendicitis. In cases in which US is not diagnostic, CT with both oral and intravenous contrast can be used. Other authors support the use of contrast-enhanced CT, with reported sensitivity and specificity of 96.5% and 98%, respectively, as the initial imaging





**Figure 18-6** Transverse contrast-enhanced CT scan of a thickened, nonruptured inflamed appendix. A blind-ending, thickened loop of enhancing bowel is present (arrow).

technique to diagnose appendicitis. Some authors advocate a focused CT scan to reduce radiation exposure, whereas others avoid oral contrast and perform a CT scan after rectal contrast. Contrast-enhanced CT imaging characteristics of acute appendicitis include an enhancing blind-ending structure near the cecum (Figure 18-6). Associated abscesses, periappendiceal stranding, appendicolith, and free air can also be readily identified. Visualizing a normal appendix reliably excludes appendicitis.

Recent articles in the surgical literature note that more than half of patients with suggested appendicitis undergo imaging. In many cases, imaging findings provide little increase in diagnostic accuracy compared with a treating surgeon's clinical examination. Even though imaging may aid in difficult cases, appendicitis remains a clinical diagnosis, and imaging may contribute to delay in treatment and subsequent appendiceal rupture.

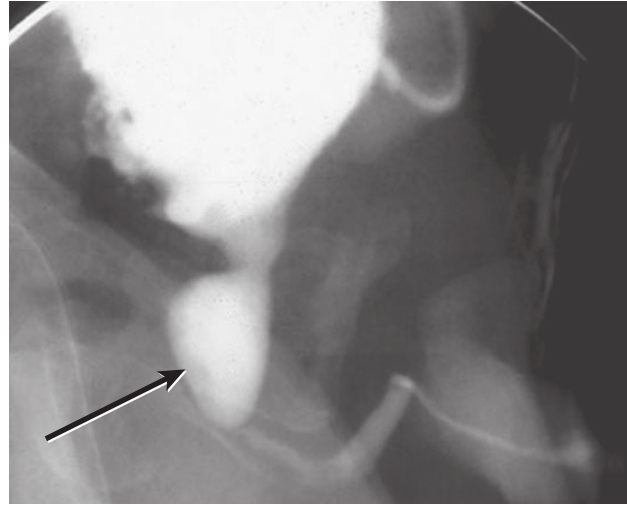
Patients with ruptured appendicitis, recurrent fever, and possible interloop abscesses are best assessed by CT. Ultrasound may also be helpful, although air-filled loops may obscure underlying pathologic anomalies or underestimate extent of abscess or phlegmon formation. In cases of perforated appendicitis, CT-guided abscess drainage may avoid surgery.

The colon may be evaluated by contrast enema. This approach is effective in determining the cause of abdominal distention in a neonate with a distal bowel obstruction and is also useful in identifying a transition zone in older patients with Hirschsprung disease.

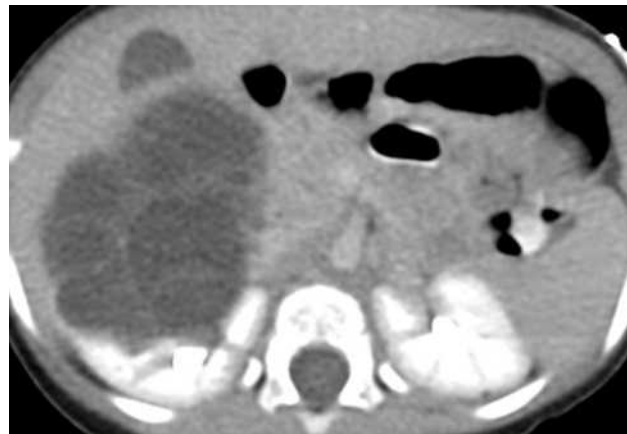
### Genitourinary Tract

The initial assessment of the pediatric GU tract begins with US. The kidneys and bladder are well assessed for hydronephrosis, infectious processes, masses, stones, and anatomic abnormalities. Further evaluation for vesicoureteral reflux and structural anomalies of the urethra and upper tracts may be performed by voiding cystourethrography (Figure 18-7).

In the case of a renal mass identified on US, US may assess for the presence of tumor thrombus within the ipsilateral renal vein and the presence of tumor in the



**Figure 18-7** Voiding cystourethrogram reveals a trabeculated bladder and a dilated posterior urethra (arrow). Findings are consistent with posterior urethral valves.



**Figure 18-8** Contrast-enhanced CT scan of a Wilms tumor.

contralateral kidney. CT is the study of choice to evaluate for lung metastases. Additionally, contrast-enhanced CT will provide information on tumor extent and vascularity and will also evaluate the contralateral kidney (Figure 18-8). MRI will provide similar information on tumor extent and vascularity and the status of the contralateral kidney. MRI provides superior evaluation of vascular invasion into the inferior vena cava or renal veins but is not effective in assessing for the presence of lung metastases. In the case of neuroblastoma, MRI provides superior evaluation of intraspinal extension and bone marrow involvement.

In patients with renovascular hypertension, Doppler US can detect anatomic abnormalities and provide information on flow velocities and resistive indices in the renal arteries and their branch vessels. However, the examination requires breath-holding and is difficult to perform in small children. A normal result



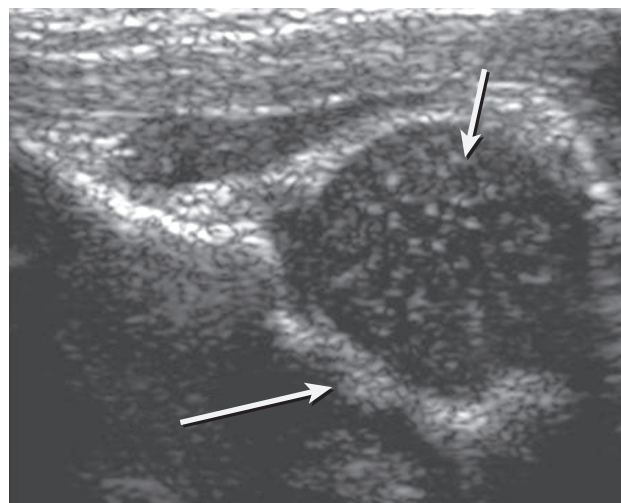
**Figure 18-9** Coronal computed tomography (CT) scan from a CT renal angiogram. Note normal renal arteries.

in young children and infants does not exclude renal artery stenosis. CT renal angiography provides excellent anatomic detail of renal artery abnormalities, particularly when images are reconstructed in multiple planes (Figure 18-9). The renal arteries can also be well evaluated by MR angiography, which avoids ionizing radiation.

US may be used to evaluate for pyelonephritis. However, contrast-enhanced CT clearly demonstrates areas of decreased renal perfusion secondary to edema in patients with pyelonephritis in whom US is equivocal. Dimercaptosuccinic acid (DMSA) nuclear scintigraphy is also effective in diagnosing the parenchymal defects characteristic of pyelonephritis. Although CT will demonstrate the extension of an inflammatory process into the perirenal space, nuclear scintigraphic information is limited to abnormalities within the renal parenchyma. Upper tract stone disease is best assessed by US. Noncontrast CT imaging has the advantage of identifying ureteral stones that may not be detected on US because of overlying bowel gas. Renal function may be evaluated by nuclear scintigraphy, although MR urography has the advantage of providing information on both anatomic features and renal function.

### Bone

Evaluation of the skeletal system begins with a plain radiograph. This method is effective in defining fractures, joint effusions, gross marrow infiltration, extent of scoliosis, and healing areas of bone infarction. In children who are suspected of having nonaccidental trauma, skeletal surveys are indicated and include the evaluation of the skull, spine, ribs, pelvis, long bones, hands, and feet by focused, high-detail images of individual bones. These images are evaluated for the presence of classic metaphyseal injuries highly



**Figure 18-10** Longitudinal image from a hip ultrasound. The cartilaginous femoral head (*short arrow*) is well seated in the acetabulum (*long arrow*).

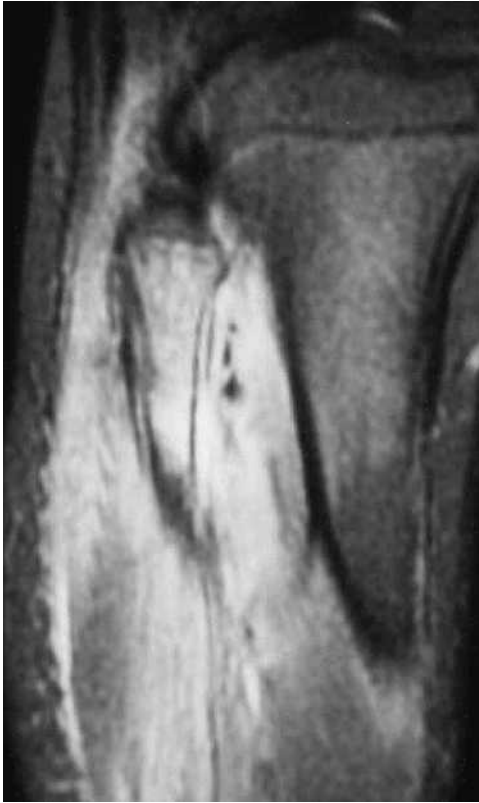
suggestive of abuse, fractures at different stages of healing, and unusual fractures. Skeletal surveys are also useful in evaluating patients with bone dysplasias.

Musculoskeletal US is useful in evaluating infants with developmental dysplasia of the hip (Figure 18-10), in assessing for joint effusions, and in directing the aspiration of the effusions under US guidance. US may also be used to evaluate for subperiosteal collections in cases of osteomyelitis. Ultrasound can image fractures of nonossified cartilage and epiphyses, such as salter fractures of the toddler elbow. It may also be useful in evaluating joints for hyperemia and joint effusions in cases of juvenile inflammatory arthritis.

MRI has the advantage of being able to define marrow, cortical, and soft tissue involvement and has become the imaging modality of choice in evaluating for skeletal lesions and osteomyelitis (Figure 18-11). MRI also has the ability to evaluate cartilage and is particularly useful in the skeletally immature child.

The use of CT in assessing the pediatric musculoskeletal system is limited. In the setting of trauma, CT reconstructions may be used to determine the degree of malalignment and displacement of fracture fragments at an articular surface. Additionally, in children with developmental dysplasia of the hip after varus derotational osteotomy and casting, CT best determines the position of the femoral head relative to the acetabulum. Scanograms to evaluate for leg-length discrepancy can now be performed with a CT scout view, rather than plain radiographs. The chest CT with 3-dimensional reconstruction can vividly identify rib fractures, which may be missed on plain film imaging.

Bone scintigraphy is useful in cases of possible osteomyelitis but can be limited by the normally increased radiotracer uptake seen in the metaphyses of growing bones, which may obscure areas of abnormally increased uptake in sites of metaphyseal osteomyelitis, a problem not encountered with MRI. Nuclear scintigraphy may be useful in cases of possible



**Figure 18-11** T2-weighted magnetic resonance image of the leg demonstrates high signal within the fibular marrow with adjacent soft tissue changes. The findings are consistent with osteomyelitis.

child abuse and may detect rib fractures not evident on plain radiographs; however, it is less effective in identifying classic metaphyseal injuries and skull fractures. Nuclear scintigraphy is also helpful when multifocal bone disease is suggested, such as with malignancy or multifocal osteomyelitis.

### Nervous System

Central nervous system imaging is performed by US, CT, or MRI. In the neonate or infant with an open fontanelle, US is an excellent method of imaging the brain. Repeat US studies can be performed to follow intracranial hemorrhage and ventricular size. Areas of the brain not well visualized by US and better evaluated by CT or MRI include the extra-axial spaces, the brain surface, and the frontal and occipital poles. In neonates, assessment of the spinal cord can be performed with US, provided that the posterior elements have not fused and an acoustic window is present. US is effective in determining the position of the conus in an infant with a sacral dimple. It may also identify intraspinal abnormalities such as lipomas. Findings may be confirmed with MRI.

The neonatal brain also may be assessed by CT or MRI. Both modalities demonstrate similar findings, with greater interobserver agreement with MRI. Additionally, MRI provides no ionizing radiation to the patient. In older children, MRI has the same advantages over CT and more clearly demonstrates myelination abnormalities,

edema, subdural hemorrhage, and infarcts. MRI is the study of choice in evaluating the spine, spinal cord, and spinal canal in children because the posterior elements have fused. Newer uses of MRI include diffusion-perfusion imaging and MR spectroscopy.

Although CT imaging of the brain has been largely replaced by MRI, it remains the most sensitive modality to detect subarachnoid blood and calcifications, which may be present in congenital lesions such as TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex virus) infections and tuberous sclerosis. It remains the imaging modality of choice in children with acute, unstable head trauma. In addition, CT is the study of choice in evaluating the temporal bone and in assessing for fractures of the face and spine. Three-dimensional reconstruction can greatly enhance the recognition of skull injuries compared with routine bone windows.

### CONCLUSION

Although newer imaging modalities now offer more detailed anatomic and functional information, the many imaging choices available to the physician can be overwhelming. The choice of examination depends on the question that the physician hopes to answer. The more focused the question, the clearer the choice of imaging modality. Radiation dose and risk for sedation, if required, and the ability of the child to undergo the examination must be considered. Ultimately, the pediatric radiologist should be consulted to help guide the physician through the myriad imaging options.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Pediatric Abdominal Ultrasound*, (fact sheet), Radiology Info ([www.radiologyinfo.org/en/info.cfm?PG=abdomus-pdi&bhcp=1](http://www.radiologyinfo.org/en/info.cfm?PG=abdomus-pdi&bhcp=1))
- *Pediatric Computed Tomography (CT)* (fact sheet), Radiology Info ([www.radiologyinfo.org/en/info.cfm?PG=pedia-ct](http://www.radiologyinfo.org/en/info.cfm?PG=pedia-ct))
- *Pediatric Nuclear Medicine* (fact sheet), Radiology Info ([www.radiologyinfo.org/en/info.cfm?PG=nuclear-pdi](http://www.radiologyinfo.org/en/info.cfm?PG=nuclear-pdi))
- *Radiology and Medical Imaging* (Web site), Cincinnati Children's Hospital Medical Center ([www.cincinnatichildrens.org/service/r/radiology/default/](http://www.cincinnatichildrens.org/service/r/radiology/default/))
- *What Is a Pediatric Radiologist?* (fact sheet), American Academy of Pediatrics ([healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Radiologist.aspx](http://healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Radiologist.aspx))

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## SECTION TWO

# Preventive Pediatrics

### Chapter 19

## ENVIRONMENTAL HEALTH: THE ROLE OF THE PRIMARY CARE PHYSICIAN

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### INTRODUCTION

Health is determined by complex and ongoing interactions between genes and the environment—the classic nature/nurture dialog in pediatrics. Throughout history, the most dramatic advances in population health have been associated with improving the environment—safe drinking water, safe and abundant food, adequate shelter, clean indoor and outdoor air. In the 20th century, progress in microbiology, biochemistry, and genomics produced advances in combating many diseases, simultaneously causing an overemphasis on the “nature” of disease and a neglect of the “nurture” of health in the form of safe and healthy environments. Since the maturation of a robust movement of pediatric environmental health (PEH) in the 1990s, attention is returning to environmental components of children’s health and disease. Genes, proteins, and microbes operate within the context of not just the human body, but also the greater environment. For children, that environment includes air, water, food, shelter, and consumer goods, as well as the maternal environment of the womb, breast milk, and even the preconception environment of each parent (see Box 19-1). The conditions

and integrity of these environments affect the expression and success of genes and are, therefore, within the purview of all pediatricians.

In the field of environmental health, the environment is typically categorized and studied according to the specific types of media that carry environmental hazards (eg, air, water, soil, and food), or by settings where exposures occur (eg, places children live, learn, play, and work). At the level of population health, the environment includes ecosystems (from pristine forests to urban landscapes) and natural biogeochemical cycles (from the nitrogen cycle to the climate system). No matter how the physical environment is defined, it is clear that humans are powerful in our ability to affect the integrity of the environment and how it interacts with genes.

PEH is a specialty area because children and adolescents are growing and changing, as are their settings and vulnerabilities, and they are often more severely affected by unhealthy environmental conditions compared to other age groups (see Box 19-2).

A life-stage approach to risk and prevention considers environmental exposures from preconception through completion of development (in the mid-twenties) and lends itself to preventive practice. Each life stage has distinct parameters of exposure, physiology, and susceptibility that affect health outcomes resulting from interaction with environmental hazards. In some cases, disease occurs shortly after the exposure and causality is obvious (as with acute chemical poisonings or radiation burns). After other environmental exposures (as with radon or asbestos), expression of adverse health outcomes is delayed, sometimes for years or even decades. Some exposures

### BOX 19-1 Prenatal Influences: Maternal Exposures and Body Burden, Paternal Exposures, Epigenetic Phenomena

Unique to pediatric environmental health is the need to consider the effect of maternal and paternal exposures on the preconception environment, and of previous and concurrent maternal exposures on the prenatal environment. Maternal exposures to certain pollutants before and during pregnancy can adversely affect fetal growth and development. Some toxicants are stored in the body over time, creating a high maternal body burden presented to a growing fetus. In general, the higher the body burden, the higher the prenatal exposure. Well-documented examples include the neurotoxicants polychlorinated biphenyls (PCBs), lead, and mercury.

Paternal preconception exposures are also linked to an increased risk of harm to children. One mechanism of exposure under intense investigation is related to epigenetic changes that affect gene expression but not nucleotide sequence. Some epigenetic changes can become transgenerational. Environmental hazards suspected of causing epigenetic changes in the zygote include ionizing radiation, organic solvents, and pesticides.

Derived from American Academy of Pediatrics Council on Environmental Health. Individual susceptibility to environmental toxicants. In: Etzel RA, Balk SJ, eds. *Pediatric Environmental Health*. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012:27–38

### BOX 19-2 Children Are Uniquely Vulnerable to Environmental Hazards

- Children are constantly growing and changing physically and metabolically.
- Their organs and systems are immature and susceptible to disruption.
- Their natural behaviors, curiosity, and location in the world often increase their exposures to environmental hazards.
- They have long lifetimes in which to express and experience environmental disease.
- They do not have political power with which to protect themselves from environmental harms and must rely on adults for protection.

that occur early in life lead to changes in structure and function of body systems; these may cause permanent deficits or predispose to adult-onset illness. Environmental conditions also play a causal role in epidemics seen in children: obesity, diabetes, asthma, allergies, and neurodevelopmental disorders. The pediatric traditions of prevention and anticipatory guidance provide natural approaches to integrating environmental disease prevention into practice. Furthermore, the emphasis in pediatrics on optimizing social, behavioral, and educational environments can be extended easily to counseling parents and communities on optimizing and protecting all aspects of the physical environment (see the Environmental Health Challenges section).

This chapter addresses approaches to prevention, recognition, and treatment of environmental illness in children, from the traditional exposure-disease model to the more universal primary prevention and precaution model. The examples chosen are a few of many possible. Physicians are encouraged to explore the tools, resources, and references provided for more comprehensive descriptions and details.

## ENVIRONMENTAL HAZARD APPROACH TO PEDIATRIC ENVIRONMENTAL HEALTH

Environmental hazards or threats can be categorized by type (eg, heavy metals, manmade chemicals, physical hazards, biological hazards, social/behavioral hazards) (Table 19-1). While some hazards cause distinct diseases or syndromes, others form part of the risk profile for arrays of illnesses and conditions. The more low-dose, chronic, or intermittent the exposure, the more difficult it is to link definitively an exposure to an adverse health outcome. Exposure can occur via many routes (eg, ingestion, inhalation, or dermal) and media (eg, air, water, or soil). Some of these can be controlled at the individual level and others only at the societal level. A few well-studied examples of hazards and health outcomes are described briefly in the following text.

### Heavy Metals

Lead poisoning is the classic heavy metal hazard. An understanding of children's special vulnerabilities to

lead evolved through the 20th century as knowledge accumulated about the many harms suffered by exposed children. Health effects range from catastrophic brain injury and death resulting from acute high-dose exposure to decreased intellectual capacity, attention-deficit/hyperactivity disorder (ADHD), lower academic achievement, and other effects from lower-dose exposure. Lead also illustrates the range of sources (in the United States, primarily paint chips and dust, but also imported jewelry, spices, and historically leaded gasoline); routes of exposure (in utero, inhalation, ingestion); the increased risk of exposure through normal childhood behaviors (hand-mouth/object-mouth behavior, nonnutritive ingestion); and vulnerability because of immature physiology. These behavioral and physiologic characteristics result in children having higher internal doses, as well as different and permanent harms compared to adults. Eliminating sources can prevent exposures and can thus prevent lead poisoning. See Chapter 283, Lead Poisoning, for more information.

An understanding of *mercury*, (the "new lead") has followed a similar but more rapid evolution. In Minamata Bay in Japan in the 1950s, prenatal exposure to high doses of methylmercury, an organo-metallic compound, in contaminated fish resulted in death or severe neurologic disability. In developed countries today, consumption of fish containing lower amounts of methylmercury (compared with Minamata Bay's contamination levels) by mothers before and during pregnancy, leading to subtle brain damage in the fetus, is now the major concern about mercury. Prevention is possible if heavily mercury-contaminated fish is limited in the diets of women of childbearing age and young children.

### Manmade Chemicals

More than 80,000 industrial and commercial chemicals have been synthesized globally in the latter half of the 20th century, and that number increases daily. However, their toxicities are largely unstudied. With the rapid advances in analytical chemistry over past decades, it is possible to measure very low levels of chemical pollutants in water, air, soil, food, animals, and people. Contamination of all media by a wide variety of chemicals is documented, but, for most chemicals, we have little knowledge of the effect of exposure on human health. For example, despite incomplete scientific information in humans, including children, there is increasing concern about health effects of the class of plasticizers known as *phthalates*, and a plastic building block, *bisphenol A* (BPA) (see Box 19-3).

When there is abundant scientific information, it is found that children are among the most susceptible to harm. For example, pesticides are among the most studied of industrial chemicals. A few have been quite thoroughly evaluated for harm to human health in general and children in particular. Chlorpyrifos, an organophosphate insecticide, was withdrawn voluntarily from all household use in the United States in 2001 because of concern raised by numerous studies. Research documented ubiquitous pediatric exposure; epidemiologic data and studies in animals identified chlorpyrifos as a neurotoxicant to the developing brain. Other pesticides (both restricted and

**Table 19-1** Examples of Specific Environmental Hazards

HAZARD CATEGORY WITH SPECIFIC EXAMPLES	MAJOR SOURCES	MAJOR ROUTES OF EXPOSURE	TARGET ORGAN/ SYSTEM
<b>METALS</b>			
Arsenic	Drinking well water, soil (especially around old structures made from wood treated with Chromated Copper Arsenate [CCA])	Ingestion, inhalation	Known carcinogen, also affects GI tract, cardiovascular, hematologic, neurologic systems, skin, and liver
Lead	Leaded paint and dust, ceramic glazes, imported jewelry, leaded gasoline (as of 2015, sold only in Algeria, Iraq, and Yemen), <sup>a</sup> drinking water	Ingestion, inhalation, transplacental	CNS, hematologic, GI tract, cardiovascular, kidney
Methylmercury	Long-lived, predatory fish, marine and fresh water	Ingestion, transplacental	Known teratogen at high doses, also affects CNS
<b>SYNTHETIC CHEMICALS</b>			
Bisphenol A (BPA)	Consumer products, including certain hard plastic bottles	Ingestion	Endocrine system
Pesticides	Food, air from drift, drinking water, home and yard use	Ingestion, inhalation, dermal absorption, transplacental	CNS, endocrine, acute poisoning, carcinogens (depending upon chemical and exposure)
Polychlorinated biphenyls (PCBs)	Environmentally persistent, found in food, plants, and soil	Ingestion, transplacental	CNS, endocrine
<b>PHYSICAL</b>			
Heat	Ambient temperatures, inadequate climate control in enclosed spaces	Direct, whole body	Water/electrolyte homeostasis
Ionizing radiation—radon	Poorly sealed basements, drinking water	Inhalation, ingestion	Known carcinogen
Nonionizing radiation—ultraviolet	Sun exposure, tanning beds	Direct dermal, eyes	Skin, eyes, immune system, known carcinogen
Noise	Traffic, airplanes, music, machinery, medical equipment in intensive care units	Direct to hearing apparatus	Otologic, CNS, cardiovascular
<b>BIOLOGIC</b>			
Aflatoxin	Wheat, corn, nuts, nut butters	Ingestion	Liver, known carcinogen, acute poisoning
Vector-borne	Outdoor activities	Dermal	Variable
<b>SOCIAL/BEHAVIORAL</b>			
Carbon monoxide	Poorly maintained or ventilated fuel-burning appliances	Inhalation	Hematologic, CNS
Secondhand tobacco smoke (SHS)	Maternal and household smoking	Inhalation, transplacental	Pulmonary, immune, cardiovascular, SIDS, known carcinogen, adverse pregnancy outcomes

CNS, central nervous system; GI, gastrointestinal; SIDS, sudden infant death syndrome.

<sup>a</sup>United Nations Environment Programme. *Leaded Petrol Phase-out: Global Status as of January 2015*. Available at [www.unep.org/Transport/new/PCFV/pdf/Maps\\_Matrices/world/lead/MapWorldLead\\_January2015.pdf](http://www.unep.org/Transport/new/PCFV/pdf/Maps_Matrices/world/lead/MapWorldLead_January2015.pdf). Accessed November 1, 2015.

This table contains representative examples in each category and only the major sources, routes of exposure, and adverse effects. For more comprehensive information readers should explore additional resources including the AAP Pediatric Environmental Health Handbook; Etzel RA, Balk SJ, eds. American Academy of Pediatrics. *Pediatric Environmental Health*. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012.

still in use) have been associated with adverse neurodevelopmental effects, increased cancer risk, birth defects, pregnancy loss, disruption of endocrine and immune systems, and adult-onset neurodegenerative illness (perhaps beginning with childhood exposures). As with lead, our understanding of the effects

of chemicals has improved through studying individual classes of chemicals, such as the organophosphates. The more we learn, the more we understand that there is often not a “safe” level of exposure for children. Eliminating or minimizing exposures is the best way to protect children’s health.

**BOX 19-3 Phthalates and Bisphenol A**

*Phthalates* are chemicals added to plastics and other products to impart flexibility and durability; *bisphenol A* (BPA) is a fundamental building block of plastic. Phthalates are found in consumer products such as children's toys, food packaging, vinyl flooring, wall coverings, and personal care products. Phthalates also are used in medical devices such as intravenous tubing. BPA is found in linings of food cans, including those for ready-to-feed infant formulas, and in hard plastics made of polycarbonate (found in sports water bottles, water dispensers, and baby bottles). Phthalates are not covalently bound to the plastics and can leach out of products. This may result in exposure through ingestion of foods found in packaging, mouthing of products, or inhalation of dust generated from these products. Young children are likely to have higher exposures because they often mouth toys and other plastic products. Newborns treated in intensive care units may be highly exposed to phthalates when they receive multiple medical therapies. Studies in humans have shown associations of phthalate exposure with endocrine and other outcomes. Studies in animals have shown an association between BPA exposure and adverse reproductive and neurobehavioral effects. Studies in people, although limited, have shown associations between high BPA exposure and heart disease, type 2 diabetes, and abnormal liver tests<sup>a</sup>. The US Centers for Disease Control and Prevention recently measured phthalate and BPA metabolite

levels in urine specimens from a nationally representative sample of people aged 6 to 85 years. Results showed that nearly everyone had measurable concentrations of these chemicals in their bodies; children and adolescents had higher levels compared to adults<sup>b</sup>. Because of rising concern about possible adverse health effects, parents can be advised to take the following precautionary measures to limit their children's exposures to potentially harmful plastics<sup>a</sup>:

- Avoid placing plastics in the dishwasher and microwave, since high temperatures may promote leaching.
- Look to recycling labels in the absence of mandatory labeling—#3 plastics *may* contain lead and phthalates, and #7 plastics *may* contain BPA. Choose plastics that are labeled #1, 2, 4, and 5.
- If formula is used, choose powdered rather than prepared canned infant formula.
- Choose unlined stainless steel water bottles over plastic. Consult bottle manufacturers' Web sites to obtain descriptions of the bottles, including whether they contain BPA.
- Consider using glass baby bottles and glass containers for food storage, being mindful of the slight increased risk of injury from breakage.
- Advocate for verifiable and enforceable right-to-know labeling for phthalates and BPA in consumer products and food packaging.

<sup>a</sup>Galvez MP, Forman JA, Graber NM, Sheffield PE, Balk SJ. Hot topics in environmental health. *Contemp Pediatr*. 2009;26:34–47. Available at: contemporary.pediatrics.modernmedicine.com. Accessed October 31, 2015.

<sup>b</sup>Centers for Disease Control and Prevention, National Center for Health Statistics. National Health and Nutrition Examination Survey. Available at: www.cdc.gov/nchs/nhanes.htm. Accessed November 1, 2015.

**Physical Hazards**

The health effects of physical hazards are as variable as the hazards themselves. Noise at very high levels can cause immediate temporary or permanent hearing loss and, at moderate levels, is implicated in poor school performance and information retention. Acute exposure to ionizing radiation, as occurred after atomic bomb exposure, can cause acute radiation poisoning. Increased rates of thyroid cancers were seen in children and adolescents after the Chernobyl disaster. Excessive exposure to ultraviolet rays from the sun or artificial sources, such as tanning beds, increases the risk of skin cancers; exposure occurring during childhood, adolescence, and young adulthood is thought to confer increased risk. Excessive ambient heat can be fatal for a baby left unattended in a closed car or apartment, because babies are less able to regulate body temperature and have no ability to remove themselves from danger. Older children are at increased risk of developing heat exhaustion or heat stroke during heavy exercise or sports activities that are often scheduled during hours of maximum temperatures in the late afternoon. Attention to these and other physical environmental health hazards is within the realm of pediatric practice.

**Biological Hazards**

This category includes envenomations, toxins, and allergens. In the developed world, cockroach, rodent, and dust mite allergens are major triggers for asthma. This phenomenon exemplifies an environmental aspect of a complex, epidemic disease. Especially in the developing world, aflatoxin exposure from contaminated grains and nuts puts billions of people at increased risk for hepatic cancer after exposures beginning in early childhood.

**Behavioral and Social Hazards**

Environmental diseases also may arise from habits and activities of others who bring hazards into a child's world. Tobacco use at home by parents, caregivers, and household members places children at risk for hazards, including pregnancy complications, decreased prenatal growth, SIDS, increased acute respiratory infections, and chronic respiratory diseases such as asthma. "Take-home" exposures are chemicals or metals that contaminate a child's environment when brought home on the person or clothing of a parent or household member. The complex mechanisms whereby children come into contact with environmental hazards are entry points for prevention strategies.



**BOX 19-4 Examples of Major Environmental Laws****ADMINISTERED BY US FOOD AND DRUG ADMINISTRATION (FDA) (WWW.FDA.GOV/REGULATORYINFORMATION/LEGISLATION/DEFAULT.HTM)*****Federal Food, Drug and Cosmetics Act (1938)***

Among other provisions, the law authorized the FDA to demand evidence of safety for new drugs, issue standards for food, and conduct factory inspections.

**ADMINISTERED BY US ENVIRONMENTAL PROTECTION AGENCY (EPA) (WWW2.EPA.GOV/LAWS-REGULATIONS/LAWS-AND-EXECUTIVE-ORDERS).*****Clean Air Act (1970)*** Amended in 1977 and 1990

The Clean Air Act is the comprehensive federal law that regulates air emissions from stationary and mobile sources. Among other things, this law authorizes the EPA to establish National Ambient Air Quality Standards (NAAQS) to protect public health and welfare, and to regulate emissions of hazardous air pollutants.

***Clean Water Act (1972)*** Amended in 1977

The Clean Water Act establishes the basic structure for regulating discharges of pollutants into the waters of the United States and regulating quality standards for surface waters.

***Safe Drinking Water Act (1974)*** Amended 1996

This law focuses on all waters actually or potentially designated for drinking use, whether from above-ground

or underground sources. The act authorizes the EPA to establish minimum standards to protect tap water and requires all owners or operators of public water systems to comply with these primary (health-related) standards.

***Resource Conservation and Recovery Act (1976)*** Amended in 1984 and 1986

The Resource Conservation and Recovery Act gives the EPA the authority to control hazardous waste from “cradle-to-grave.” This includes the generation, transportation, treatment, storage, and disposal of hazardous waste.

***Toxic Substances Control Act (1976)***

The Toxic Substances Control Act (TSCA) of 1976 provides the EPA with authority to establish reporting, record keeping, and testing requirements, and to issue restrictions relating to chemical substances or mixtures. Certain substances are generally excluded from TSCA, including food, drugs, cosmetics, and pesticides.

***Food Quality Protection Act (1996)***

Some of the major requirements of this act include stricter safety standards, especially for infants and children, and a complete reassessment of all existing pesticide tolerances (the maximum amounts of pesticide residues allowed in foods).

## MEDIA AND SETTINGS APPROACHES TO PEDIATRIC ENVIRONMENTAL HEALTH

While the *individual hazards* approach parallels the infectious disease paradigm of agent-susceptible host, the *media* and *settings approaches* define environmental hazards by opportunities or mechanisms of exposure. The *media approach* focuses on environmental media such as water or air. It parallels major environmental laws and regulations (Box 19-4) by categorizing exposures based on the medium carrying a particular pollutant or category of pollutants; (eg, outdoor air, drinking water, recreational water, food, soil, and consumer goods). This approach is particularly useful when exposures are dominated by a single medium (eg, ozone exposure from outdoor air or chlorination byproducts occurring in treated drinking water). Most exposures, however, are from multiple sources and media. Therefore, an integrated approach to protecting children is needed, taking into account all sources and routes, particularly because children’s behavior, settings, physiology, and vulnerabilities change over time. The Food Quality Protection Act of 1996 is a landmark law that requires pesticide regulations to be based on a comprehensive evaluation of all children’s exposure sources.

A *settings approach* (eg, home, school, play area, public parks, and work sites) offers another way to organize exposures and preventive strategies. Initiatives

are underway that seek to prevent unnecessary exposures, emphasizing precaution and prevention. Healthy homes programs aim to minimize as many toxic (or potentially toxic) environmental health hazards as possible, rather than establish “safe” exposure limits usually set by more traditional environmental laws.

## A PHYSICIAN’S ROLE IN PREVENTION, DIAGNOSIS, AND TREATMENT

Fortunately, the structure for protecting children from environmental hazards is built into pediatric care. Pediatric primary care already contains the elements needed to address environmental antecedents of disease—a focus on prevention, anticipatory guidance, and family orientation. The challenge for physicians is to integrate the environmental determinants of health more consistently into this pre-existing structure.

### Prevention

Because harm from environmental hazards can be severe and lifelong, prevention is the main goal. Many environmental consequences or illnesses are preventable by eliminating exposure. When an environmental hazard is well understood and effective interventions are available, as with lead, mercury, pesticides and secondhand smoke, giving routine anticipatory guidance should be second nature for pediatricians.

**BOX 19-5 The Precautionary Principle**

The Precautionary Principle as a policy tool was first codified in environmental law in Germany as *Vorsorgeprinzip* (foresight or precautionary principle) in the German Clean Air Act of 1974. It was also included as a key principle in the United Nations Rio Declaration on Environment and Development of 1992. In legal and policy realms, the Precautionary Principle allows for taking protective actions in the face of incomplete scientific information if there is sufficient reason to suspect that a substance is harmful to human health and/or the environment. The European Environment Agency proposed the following definition: “The Precautionary Principle provides justification for public policy actions in situations of scientific complexity, uncertainty, and ignorance, where there may be a need to act to avoid, or reduce, potentially serious or irreversible threats to health or the environment, using an appropriate level of scientific evidence, and taking into account the likely pros and cons of action or inaction.”<sup>a</sup> In the clinical setting, this concept is consistent with primary prevention and the avoidance of unnecessary exposures to potentially toxic substances or other environmental hazards. Common-sense applications of the Precautionary Principle in daily activities include using nonchemical pest control strategies (integrated pest management), using glass or crockery instead of plastic containers for storing and microwaving foods, and avoiding chemical air fresheners in homes, child care settings, and schools. Because so many chemicals have not been tested for toxicity, the Precautionary Principle suggests that avoiding exposure and using safe substitutes when available are the best ways to protect individual and public health.

<sup>a</sup>Gee D. Late lessons from early warnings: toward realism and precaution with endocrine-disrupting substances. *Environ Health Perspect.* 2006; 114(suppl 1):152–160.

Straightforward examples of interventions include recommending integrated pest management for homes and child care settings to avoid toxic pesticide exposures, and designating homes and child care settings as “tobacco-free zones” to prevent exposure to secondhand tobacco smoke (SHS). A more complex example is recommending that children with asthma avoid late afternoon exposure to outdoor air when ozone levels are elevated; for young athletes who have sports practice after school, it may be difficult to follow medical advice to stay indoors in air-conditioned spaces on ozone alert days.

When scientific information about other hazards is not complete, caution and common-sense avoidance of exposure should be advised (see Box 19-5). If an exposure is unnecessary and potentially harmful, it should be eliminated. Simply raising questions with parents often results in behavior changes that improve a child’s environment.

**Environmental History**

While taking an environmental history may seem like a time-consuming endeavor for busy physicians, it is indeed part of a complete pediatric history. Most

environmental hazards can be discovered by asking about social and occupational factors, including questions about where children spend time. Practices can integrate environmental questions into new patient questionnaires and review positive responses, similar to other reviews already taking place. For well-child visits, factors such as interval history, age of the child, season, and known hazards in the community can determine which hazards to ask about. Questions may be incorporated into electronic medical records, or be part of paper or electronic checklists for anticipatory guidance often used by pediatric practices. Key questions such as tobacco use in the home can be incorporated into “vital signs.” Medical assistants and nurses can take much of this initial history and give age-appropriate anticipatory guidance, leaving the physician to handle complex issues. Incorporating environmental histories should become as routine as dietary, immunization, and developmental histories taken at well visits.

A targeted environmental history should be incorporated into sick visits. For example, tobacco use should be reviewed when a child has asthma, otitis media, or respiratory symptoms. This represents a therapeutic opportunity to reduce exposure and speed up return to health, and also a “teachable moment” about the effect of the physical environment on health. Interventions at the time of illness can include brief counseling about smoking cessation if family members smoke, and referral to quit-smoking resources. Because many illnesses have an environmental component, any acute, chronic, or recurrent illness should trigger a discussion of potential environmental contributors to onset, severity, and duration.

**Diagnosis and Treatment of Environmental Illness**

Depending on the complaint, the environmental contributors to illness may be more or less obvious and more or less amenable to intervention.

Especially difficult is a situation in which a parent suspects that an environmental chemical has caused a chronic disease and requests laboratory tests to document specific exposures. Because our knowledge of the health consequences of many exposures is incomplete or even absent, it can be frustrating for parents and physicians to have such discussions. In addition, laboratory testing is almost never indicated. As with all other situations in medicine, tests should *not* be ordered unless the outcome will change management. If laboratory tests are ordered, it is imperative that the correct tests are performed on appropriate specimens, that tests are done by credible laboratories, and that well-established reference values are available. Since some exposures are far removed in time from the visit, testing may not be an option. In particular, large panels of tests run on random blood, urine, or hair specimens are useless. Consulting with environmental health specialists is often the most efficient way to address parental concerns. This strategy may avoid generating information of unknown value that may further confuse or alarm an already worried parent (see Box 19-6).

**BOX 19-6 Seven Cardinal Rules of Risk Communication**

1. Involve the patient and parent in identifying and solving the problem.
2. Have a communication plan and a clear message.
3. Listen to the patient and parent's story.
4. Be honest, open, and frank.
5. Work with credible sources.
6. Provide access to information.
7. Speak clearly and with compassion.

Adapted from American Academy of Pediatrics Committee on Environmental Health. Risk assessment, risk management, and risk communication. In: Etzel RA, Balk SJ, eds. *Pediatric Environmental Health*. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012:847–858.

**EXPANDED ROLES FOR PRIMARY CARE PHYSICIANS**

Primary care physicians can improve PEH through direct patient care, by running our offices in environmentally conscious ways, and by influencing the larger community. In addition to taking environmental histories and incorporating environmental health anticipatory guidance into practice, we can begin to write “prescriptions” for environmental health interventions (see Tools for Practice). Each practice can develop a list of “top 10 ways” to encourage healthy environments for children and to protect them from relevant environmental hazards (Box 19-7). We can find opportunities to counsel children and families on larger issues, such as the importance to health of spending time in natural environments and the effect of climate change. Discussions may be framed in the context of “win-win” behaviors that improve health and the environment simultaneously. For example, choosing walking over travel in motor vehicles reduces greenhouse gas emissions, cleans the air, and increases physical activity. We can actively “green” offices in visible and educational ways such as switching to low-energy lighting, improving energy efficiency, using nontoxic cleaners, reducing use of disposable items, and supporting carpooling or bus transport. Finally, we can work in our communities for environmental changes that improve and sustain children's health. Local projects could include developing organic community gardens, organizing walking school buses to promote physical activity, or renovating old housing to eliminate lead paint, mold, and other hazards. In addition, physicians have a powerful political voice that can be used to educate and advocate with elected officials and rule makers to improve child health. This voice should be used wisely and often on behalf of current and future generations.

**ENVIRONMENTAL HEALTH CHALLENGES**

Despite major advances made in PEH over the past 2 to 3 decades, much remains unknown about environmental exposures and toxicities. The sheer number of

**BOX 19-7 Example of a “Top 10 Ways to Promote Healthy Environments for Children”**

1. Serve a variety of fresh fruits and vegetables, 5 to 9 portions daily; choose local, organic, and in-season foods when possible.
2. Encourage vigorous, daily outdoor play, in natural environments if possible; abide by heat advisories, air quality reports, and pollen counts for sensitive individuals.
3. Encourage tap water as the default beverage instead of juice or soda; test well water, use stainless steel drink containers, and filter tap water if there are questions about possible contaminants.
4. Make your child's environment(s) tobacco free—do not smoke or allow smoking around your child, including in motor vehicles. If you are a smoker, quit.
5. Use nonchemical pest control and integrated pest management; do not use chemical pesticides unless pests are dangerous and other alternatives are not available or are ineffective.
6. Be sun safe; avoid prolonged direct exposures during peak sun hours, seek shade, use protective clothing, apply sunscreen, wear sunglasses, and do not allow your teenager to tan in a tanning salon.
7. Microwave and store food in glass containers; never microwave in plastic.
8. Use simple, nontoxic cleaning supplies; avoid aerosols and air fresheners.
9. Have your home and child care setting/school tested for known hazards, such as lead and radon; remediate appropriately.
10. Model sustainable living; teach your child that “enough is plenty.”

Each practice may develop its own Top 10 list depending on the local environment. For example, a practice in an inner city neighborhood with old housing stock, heavy traffic, and excessive noise might emphasize lead paint, use of public transport, and advocacy on noise abatement, whereas a suburban neighborhood in the sun belt might emphasize sun safety, attention to ozone alerts, and bike safety. Regardless, the emphasis should be on positive behaviors that are preventive in nature.

manmade chemicals, for example, makes it impossible to study comprehensively the health consequences of exposure to all individual chemicals or to mixtures and their breakdown products. Interactions among multiple classes of environmental hazards, nutrition, social circumstances, and genetic makeup have effects on major childhood and adult epidemics. It is difficult to explore these interactions for individuals and populations. Exponential population growth, resource depletion, loss of biodiversity, and climate change pose major health challenges to future generations. Researchers and policy makers who grapple with



these large issues require input from professionals who care for children. Physicians who are knowledgeable about the effects of the environment on children's health can be valuable resources for improving the health of individual children and for helping to design a future that sustains health and the environment for future generations.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Rx for Prevention Prescription Slips (English)* (handouts), Physicians for Social Responsibility ([www.psr.org/assets/pdfs/toolkit-rxpads-4up.pdf](http://www.psr.org/assets/pdfs/toolkit-rxpads-4up.pdf))
- *Rx for Prevention Prescription Slips (Spanish)* (handouts), Physicians for Social Responsibility ([www.psr.org/assets/pdfs/toolkit-rxpads-span-4up.pdf](http://www.psr.org/assets/pdfs/toolkit-rxpads-span-4up.pdf))

#### Medical Decision Support

- *American Academy of Pediatrics Council on Environmental Health* (Web site) ([www.aap.org/en-us/about-the-aap/Committees-Councils-Sections/Council-on-Environmental-Health](http://www.aap.org/en-us/about-the-aap/Committees-Councils-Sections/Council-on-Environmental-Health))
- *Case Studies in Environmental Medicine* (continuing education), Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention ([www.atsdr.cdc.gov/csem/csem.html](http://www.atsdr.cdc.gov/csem/csem.html))
- *Children's Environmental Health* (Web site), World Health Organization ([www.who.int/ceh/en](http://www.who.int/ceh/en))
- *National Center for Environmental Health* (Web site), Centers for Disease Control and Prevention ([www.cdc.gov/nceh](http://www.cdc.gov/nceh))
- *Protecting Children's Environmental Health* (Web site), US Environmental Protection Agency ([www2.epa.gov/children](http://www2.epa.gov/children))
- *Pediatric Environmental Health Specialty Units* (Web page), ([www.pehsu.net](http://www.pehsu.net))

#### Practice Management and Care Coordination

- *Pediatric Environmental Health Toolkit* (toolkit), Physicians for Social Responsibility ([www.psr.org/resources/pediatric-toolkit.html](http://www.psr.org/resources/pediatric-toolkit.html))

### SUGGESTED READINGS

- American Academy of Pediatrics Council on Pediatric Environmental Health. Chemical-Management Policy: Prioritizing Children's Health. *Pediatrics*. 2011;127:983–990
- Etzel RA, Balk SJ, eds. *Pediatric Environmental Health*. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics, Elk Grove Village IL; 2012
- Galvez M, Peters R, Graber N, Forman J. Effective risk communication in children's environmental health: lessons learned from 9/11. *Pediatr Clin North Am*. 2007;54(1):33–46
- US Centers for Disease Control and Prevention. *Healthy Homes*. Available at: [www.cdc.gov/healthyplaces/newhealthyhomes.htm](http://www.cdc.gov/healthyplaces/newhealthyhomes.htm). Accessed October 31, 2015
- US Centers for Disease Control and Prevention. *National Report on Human Exposure to Environmental Chemicals*. Available at: [www.cdc.gov/exposurereport](http://www.cdc.gov/exposurereport). Accessed November 1, 2015

## Chapter 20 IMMUNIZATIONS

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### INTRODUCTION

Vaccine-preventable diseases have left a legacy of suffering that must not be forgotten. Although considerable progress has been marked in recent years, children in the United States and many children elsewhere die when they lose their very personal battles with vaccine-preventable diseases.

Vaccination was one of the most important achievements in public health in the 20th century. The most salient feature of this achievement is decreased disease levels. Compared with pre vaccination era disease levels, the current US disease levels are 92% to 100% lower. Recent immunization successes include the first-ever interruption of indigenous measles and rubella transmission in the United States and the interruption of wild-type polio transmission in the Western hemisphere. Routine childhood vaccination is one of the few health care interventions that saves both lives and dollars: compared with a no-vaccination program, routine vaccination saves from \$2 (for hepatitis B vaccination) to \$29 (for measles-mumps-rubella [MMR] vaccination) for every dollar spent.

The primary reason for the low vaccine-preventable disease incidence is high immunization coverage levels, an achievement by the health care system that was accomplished during a period of increasing complexity in the immunization schedule. These successes resulted largely from major efforts by private and public health care providers. Sustaining success will require even greater effort, because the process of vaccinating children and adolescents is becoming increasingly complicated as the number of vaccines and vaccine combination choices increases.

The current US recommended childhood and adolescent immunization schedule is updated annually; the most current version is available on the Centers for Disease Control and Prevention (CDC) Web site.

### PRINCIPLES OF VACCINATION

#### Live versus Inactivated Vaccines

Currently available vaccines are either live, which replicate in the body, or inactivated. Live injected vaccines usually induce immunity through a single dose and, unlike inactivated vaccines, are susceptible to vaccine failure caused by circulating antibodies, including residual maternal antibodies in infants. Live vaccines include:

- Those that protect against viruses (eg, MMR, varicella, rotavirus, live attenuated influenza intranasal vaccine [LAIV], yellow fever, vaccinia, oral polio vaccine [OPV])



- Those that protect against bacteria (eg, *Bacillus Calmette–Guérin*, oral typhoid vaccine)

Inactivated vaccines do not contain infectious particles that can replicate in the body; they generally require several doses to immunize patients completely. Inactivated vaccines include:

- Inactivated viruses (eg, inactivated polio vaccine [IPV], hepatitis A, rabies)
- Inactivated subunits (eg, acellular pertussis, hepatitis B, human papillomavirus [HPV], split virus influenza, typhoid Vi)
- Toxoid (diphtheria, tetanus) agents
- Polysaccharides—either unconjugated (pneumococcal, meningococcal) or conjugated (*Haemophilus influenzae* type b [Hib], pneumococcal, meningococcal)

## Spacing and Timing

### Routine Schedule

The routine vaccination schedules are harmonized among the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AAFP), and the CDC Advisory Committee on Immunization Practices (ACIP). The harmonized schedules are not simple, but they do allow for office preferences by indicating acceptable ranges for routine on-time vaccination scheduling. The ranges were created so that offices might more easily accommodate routine vaccination into their well-child care schedule. To ensure timely immunizations, vaccinating early within the acceptable age range is important. The current version of the vaccination schedules can be found on the CDC Web site ([www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html](http://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html)).

### Intervals Between Different Vaccines Not Administered Simultaneously

Using all routine vaccines simultaneously is safe and effective, provided that vaccines are not combined within a single syringe (with the exception of combination vaccines). No contraindications exist to giving any 2 or more different routine childhood vaccines at the same visit.

Vaccines that are not administered simultaneously may be given without regard to intervals, with the exception that live vaccines not given by the oral route (eg, MMR, varicella, LAIV) that are not administered simultaneously should be separated by at least 4 weeks. This *4-week separation rule* is intended to reduce the theoretical risk of interference from the first vaccine on the subsequent vaccine. If, for example, varicella vaccine is given only 1 week after MMR, then the varicella vaccine should be repeated or serologic testing should be used to confirm seroconversion.

Physicians, parents, and, no doubt, children prefer fewer injections. As a consequence of the increasing number of diseases that can be prevented through vaccination, the number of required injections is continually increasing. The number of combination vaccines available has also increased. Combination vaccines reduce the number of injections and are preferred, when available, by ACIP, the AAFP, and the

AAP. All vaccines for which the child is eligible should be offered whenever possible. This strategy not only keeps the child on schedule, but also prevents an additional, unnecessary office visit.

### Minimal Age and Intervals Between Different Doses of a Multidose Vaccine

Vaccine doses that are given too early in life or too soon after a previous dose may be less effective. Table 20-1 shows the earliest acceptable ages for administration of the routinely recommended childhood vaccines and the minimal spacing between their doses. The most current version of this table can be found at [www.cdc.gov/vaccines/pubs/pinkbook](http://www.cdc.gov/vaccines/pubs/pinkbook).

Physicians often ask whether to count a vaccine dose given at an interval shorter than the minimal interval. For example, should a child who received doses 3 and 4 of diphtheria-tetanus-acellular pertussis (DTaP) vaccines within less than 6 months be revaccinated? Was the dose valid if a child received an MMR vaccination before 12 months of age? Though state requirements for school entry vary, ACIP considers a vaccination valid if the vaccine dose was within 4 days of the minimal interval. Vaccine doses, of course, are considered invalid if an incorrectly small amount was used, and there may be a higher risk of side effects if an incorrectly large amount was used. Steps should be taken to prevent these errors from occurring, and the physician should remember that vaccination is a safe procedure, even if the child is given more than the recommended number of doses. Overvaccination (ie, vaccination with more doses than recommended) with live vaccines does not have adverse biologic consequences because the extra vaccine virus will not infect an already immune person. Overvaccination with inactivated vaccines might cause an increase in local reactions if antibody levels are high.

Prolonged intervals between doses of a multidose vaccination series do not diminish vaccine effectiveness, although the benefit of vaccination may be delayed by prolonged intervals. Series never need to be restarted because of prolonged intervals (with the exception of the oral typhoid vaccine).

### Late-Start or Interrupted Schedule

Some children start routine vaccination late. The recommended compressed, catch-up, or accelerated immunization schedule for such children is derived from the minimal intervals for the routine vaccinations. A catch-up schedule is published annually with the routine schedule.

The presentation of a new patient whose vaccination status is unknown presents a challenge. In this situation, the physician must determine if any immunization record exists for the child and, if so, must obtain a copy of the record or a report from the previous physician. If no record can be found, then the child should be presumed to be unvaccinated, and the vaccination series should be given using the accelerated schedule. Serologic testing can be considered for some antigens (eg, MMR, hepatitis B).

**Table 20-1** Recommended and Minimum Ages and Intervals Between Doses of Routinely Recommended Vaccines<sup>a,b,c,d</sup>

VACCINE AND DOSE NUMBER	RECOMMENDED AGE FOR THIS DOSE	MINIMUM AGE FOR THIS DOSE	RECOMMENDED INTERVAL TO NEXT DOSE	MINIMUM INTERVAL TO NEXT DOSE
Diphtheria-tetanus-acellular pertussis (DTaP)-1 <sup>e</sup>	2 months	6 weeks	8 weeks	4 weeks
DTaP-2	4 months	10 weeks	8 weeks	4 weeks
DTaP-3	6 months	14 weeks	6–12 months	6 months <sup>f</sup>
DTaP-4	15–18 months	15 months <sup>g</sup>	3 years	6 months
DTaP-5	4–6 years	4 years	—	—
<i>Haemophilus influenzae</i> type b (Hib)-1 <sup>f, h</sup>	2 months	6 weeks	8 weeks	4 weeks
Hib-2	4 months	10 weeks	8 weeks	4 weeks
Hib-3 <sup>i</sup>	6 months	14 weeks	6–9 months	8 weeks
Hib-4	12–15 months	12 months	—	—
Hepatitis A (HepA)-1	12–23 months	12 months	6–18 months	6 months
HepA-2	≥18 months	18 months	—	—
Hepatitis B (HepB)-1 <sup>e</sup>	Birth	Birth	4 weeks–4 months	4 weeks
HepB-2	1–2 months	4 weeks	8 weeks–17 months	8 weeks
HepB-3 <sup>i</sup>	6–18 months	24 weeks	—	—
Herpes zoster (HZV) <sup>k</sup>	≥60 years	60 years	—	—
Human papillomavirus (HPV)-1 <sup>l</sup>	11–12 years	9 years	8 weeks	4 weeks
HPV-2	11–12 years	9 years	4 months	12 weeks <sup>m</sup>
	(+ 2 months)	(+ 4 weeks)		
HPV-3 <sup>m</sup>	11–12 years	9 years	—	—
	(+ 6 months)	(+24 weeks)		
Influenza, inactivated (IIV) <sup>n</sup>	≥6 months	6 months <sup>o</sup>	4 weeks	4 weeks
Influenza, live attenuated (LAIV) <sup>n</sup>	2–49 years	2 years	4 weeks	4 weeks
Measles-mumps-rubella (MMR)-1 <sup>p</sup>	12–15 months	12 months	3–5 years	4 weeks
MMR-2 <sup>p</sup>	4–6 years	13 months	—	—
Meningococcal conjugate (MCV)-1 <sup>q</sup>	11–12 years	6 weeks <sup>r</sup>	4–5 years	8 weeks
MCV-2	16 years	11 years	—	—
		(+ 8 weeks)		
Meningococcal polysaccharide (MPSV4)-1 <sup>q</sup>	—	2 years	5 years	5 years
MPSV4-2	—	7 years	—	—
Pneumococcal conjugate (PCV)-1 <sup>h</sup>	2 months	6 weeks	8 weeks	4 weeks
PCV-2	4 months	10 weeks	8 weeks	4 weeks
PCV-3	6 months	14 weeks	6 months	8 weeks
PCV-4	12–15 months	12 months	—	—
Pneumococcal polysaccharide (PPSV)-1	—	2 years	5 years	5 years
PPSV-2 <sup>s</sup>	—	7 years	—	—
Poliovirus, Inactivated (IPV)-1 <sup>e</sup>	2 months	6 weeks	8 weeks	4 weeks
IPV-2	4 months	10 weeks	8 weeks–14 months	4 weeks
IPV-3	6–18 months	14 weeks	3–5 years	6 months
IPV-4 <sup>t</sup>	4–6 years	4 years	—	—
Rotavirus (RV)-1 <sup>u</sup>	2 months	6 weeks	8 weeks	4 weeks
RV-2	4 months	10 weeks	8 weeks	4 weeks
RV-3 <sup>v</sup>	6 months	14 weeks	—	—
Tetanus-diphtheria (Td)	11–12 years	7 years	10 years	5 years

Table 20-1

### Recommended and Minimum Ages and Intervals Between Doses of Routinely Recommended Vaccines<sup>a,b,c,d</sup>—cont'd

VACCINE AND DOSE NUMBER	RECOMMENDED AGE FOR THIS DOSE	MINIMUM AGE FOR THIS DOSE	RECOMMENDED INTERVAL TO NEXT DOSE	MINIMUM INTERVAL TO NEXT DOSE
Tetanus-diphtheria-acellular pertussis (Tdap) <sup>w</sup>	≥11 years	7 years	—	—
Varicella (Var)-1 <sup>p</sup>	12–15 months	12 months	3–5 years	12 weeks <sup>x</sup>
Var-2 <sup>p</sup>	4–6 years	15 months <sup>y</sup>	—	—

<sup>a</sup>Combination vaccines are available. Use of licensed combination vaccines is generally preferred to separate injections of their equivalent component vaccines. When administering combination vaccines, the minimum age for administration is the oldest age for any of the individual components (*exception*: the minimum age for the first dose of MenHibrix is 6 weeks); the minimum interval between doses is equal to the greatest interval of any of the individual components.

<sup>b</sup>Information on travel vaccines including typhoid, Japanese encephalitis, and yellow fever, is available at [www.cdc.gov/travel](http://www.cdc.gov/travel). Information on other vaccines that are licensed in the United States but not distributed, including anthrax and smallpox, is available at [www.bt.cdc.gov](http://www.bt.cdc.gov).

<sup>c</sup>Ages and intervals less than 4 months may be expressed in weeks. When the term “months” is used to express an age or interval, it means calendar months.

<sup>d</sup>A dash used to express a range (as in “12–15 months”) means “through.”

<sup>e</sup>Combination vaccines containing a hepatitis B component (Comvax, Pediarix, and Twinrix) are available. These vaccines should not be administered to infants younger than 6 weeks because of the other components (ie, Hib, DTaP, HepA, and IPV).

<sup>f</sup>A special grace period of 3 months, based on expert opinion, can be applied to the minimum age of 15 months when evaluating records retrospectively, which will result in an acceptable minimum age of 12 months. An additional 4 days should not be added to this grace period.

<sup>g</sup>The minimum recommended interval between DTaP-3 and DTaP-4 is 6 months. However, DTaP-4 need not be repeated if administered at least 4 months after DTaP-3. This is a special grace period (2 months long) that can be used while evaluating records retrospectively. An additional 4 days should not be added to this grace period.

<sup>h</sup>Children receiving the first dose of Hib or pneumococcal conjugate vaccine at age 7 months or older require fewer doses to complete the series.

<sup>i</sup>If PRP-OMP (Pedvax-Hib) was administered at ages 2 and 4 months, a dose at age 6 months is not required.

<sup>j</sup>HepB-3 should be administered at least 8 weeks after HepB-2 and at least 16 weeks after HepB-1, and should not be administered before age 24 weeks.

<sup>k</sup>Herpes zoster vaccine is recommended as a single dose for persons 60 years of age and older.

<sup>l</sup>Bivalent HPV vaccine (Cervarix) is approved for females 9 through 25 years of age. Quadrivalent HPV vaccine (Gardasil) is approved for males and females 9 through 26 years of age.

<sup>m</sup>The minimum age for HPV-3 is based on the baseline minimum age for the first dose (9 years) and the minimum interval of 24 weeks between the first and third doses. Dose 3 need not be repeated if it is given at least 16 weeks after the first dose (and if the intervals between doses 1 and 2 and doses 2 and 3 are maintained at 4 weeks and 12 weeks, respectively).

<sup>n</sup>One dose of influenza vaccine per season is recommended for most people. Children younger than 9 years of age who are receiving influenza vaccine for the first time should receive 2 doses this season. See current influenza recommendations for other factors affecting the decision to administer 1 vs 2 doses to children younger than 9 years.

<sup>o</sup>The minimum age for inactivated influenza vaccine varies by vaccine manufacturer and formulation. See package inserts for vaccine-specific minimum ages.

<sup>p</sup>Combination measles-mumps-rubella-varicella (MMRV) vaccine can be used for children aged 12 months through 12 years. (See CDC. General recommendations on immunization: recommendations of the ACIP. *MMWR* 2011;60[No. RR-2],7.)

<sup>q</sup>Revaccination with meningococcal vaccine is recommended for previously vaccinated persons who remain at high risk for meningococcal disease. (See CDC. Updated recommendations from the ACIP for vaccination of persons at prolonged increased risk for meningococcal disease. *MMWR* 2009;58[1042-3].)

<sup>r</sup>Menactra can be given as young as 9 months for high-risk children. Menveo can be given as young as 2 months for high-risk children. MenHibrix can be given as young as 6 weeks for high-risk children. MenHibrix is given as a 4-dose series at 2 months, 4 months, 6 months, and 12–18 months.

<sup>s</sup>A second dose of PPSV 5 years after the first dose is recommended for persons <65 years of age at highest risk for serious pneumococcal infection, and for those who are likely to have a rapid decline in pneumococcal antibody concentration. (See CDC. Prevention of pneumococcal disease: recommendations of the ACIP. *MMWR* 1997;46[No. RR-8].)

<sup>t</sup>A fourth dose is not needed if the third dose was administered on or after the 4th birthday and at least 6 months after the previous dose.

<sup>u</sup>The first dose of rotavirus must be administered between 6 weeks 0 days and 14 weeks 6 days. The vaccine series should not be started after age 15 weeks 0 days. Rotavirus vaccine should not be administered to children older than 8 months 0 days, regardless of the number of doses received before that age.

<sup>v</sup>If 2 doses of Rotarix are administered as age appropriate, a third dose is not necessary.

<sup>w</sup>Only 1 dose of Tdap is recommended. Subsequent doses should be given as Td. For management of a tetanus-prone wound in a person who has received a primary series of a tetanus-toxoid containing vaccine, the minimum interval after a previous dose of any tetanus-containing vaccine is 5 years.

<sup>x</sup>For persons beginning the series on or after the 13th birthday, the minimum interval from varicella-1 to varicella-2 is 4 weeks. While it is not recommended if a child younger than 13 years receives varicella-2 at an interval of 4 weeks or longer from varicella-1, the dose does not need to be repeated.

<sup>y</sup>A special grace period of 2 months, based on expert opinion, can be applied to the minimum age of 15 months when evaluating records retrospectively, which will result in an acceptable minimum age of 13 months. An additional 4 days should not be added to this grace period.

### Intervals Between Live Injected Vaccines and Antibody-Containing Blood Products

Live injected vaccines (eg, MMR and varicella vaccines) have to replicate in the body to induce immunity and may be compromised by circulating antibodies against the vaccine virus. Live vaccines not administered by injection (eg, LAIV, oral typhoid, OPV) are thought to be unaffected by circulating antibodies. Generally, inactivated vaccines are not significantly affected by circulating antibodies and can be administered without regard to the relative timing of the administration of immune globulin-containing products.

MMR and varicella vaccine doses given more than 14 days before immune globulin-containing products are administered have time to replicate and are effective. When live injected vaccines are given after antibody-containing blood products, the situation is more complex. The specific immune globulin-containing product and its dose dictate the waiting period necessary before a valid dose of a live injected vaccine is given. MMR and varicella vaccination should be delayed from 3 months to 11 months, depending on the specific immune globulin preparation administered. Details of the appropriate waiting period can be found in the *AAP Red Book* and on the CDC Web site.

### Vaccinations Administered in Foreign Countries

Determining the immunization status of foreign-born children or other children who have been partially or completely vaccinated in another country can be difficult. Vaccines, their abbreviations, and vaccination age criteria often differ among countries. The immunization status needs to be determined for all children and special attention paid to the rest of the family in the case of recent immigration.

The first assumption to make is that the vaccines administered in other countries were as potent as those available in the United States. Then, it becomes a matter of determining which vaccines were administered and whether the doses qualify as valid doses when considering the minimal ages of administration and the minimal intervals between doses. Determining which vaccines were administered can be difficult because the standard abbreviations recorded in handheld vaccination records may be different from those used in the United States. Translation of foreign-language terms can be facilitated with materials from the CDC. Assistance with specific questions can be obtained from state immunization programs or from the CDC National Center for Immunization and Respiratory Diseases ([www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/foreign-products-tables.pdf](http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/foreign-products-tables.pdf)) or via telephone (800-CDC-INFO, ie, 800-232-4636) or e-mail ([nipinfo@cdc.gov](mailto:nipinfo@cdc.gov)). Once the vaccine types are determined, the CDC schedule for catch-up immunizations can be used to determine which doses are valid and which, if any, need to be repeated. The most current version of this table can be found at [www.cdc.gov/vaccines/schedules](http://www.cdc.gov/vaccines/schedules). As with vaccines administered in the United States, the CDC recommends that vaccine doses given 4 or fewer days before the minimum interval be counted as valid (except the rabies vaccine), unless state or local requirements specify otherwise.

Variation in vaccination strategies creates a problem for physicians caring for internationally adopted children and recent immigrants. Although evidence suggests that the documented vaccination status of foreign adopted children is not always accurate, the CDC's Advisory Committee on Immunization Practices (ACIP) recommends when interpreting the vaccination status of international adoptees is that documented vaccinations (that include the doses and dates of administration) are acceptable proof of vaccination.

### Contraindications and Precautions

The reader is encouraged to visit the *General Recommendations* and the CDC's detailed *Recommendations and Guidelines: Vaccine Contraindications and Precautions* ([www.cdc.gov/vaccines/recs/vac-admin/contraindications.htm](http://www.cdc.gov/vaccines/recs/vac-admin/contraindications.htm)). Contraindications and precautions are also outlined in the invaluable table, *Summary of Recommendations for Child/Teen Immunization*, which is available at [www.immunize.org/catg.d/p2010.pdf](http://www.immunize.org/catg.d/p2010.pdf).

### Anaphylactic Allergy

Anaphylactic-type allergy to a vaccine or a vaccine component, which includes even mild urticarial reactions, is

a contraindication to further vaccination with the vaccine in question unless the recipient has been desensitized.

### Encephalopathy

Encephalopathy within 7 days after a previous dose of a pertussis-containing vaccine (eg, DTaP, tetanus-diphtheria-acellular pertussis [Tdap]), not attributable to another identifiable cause, is a contraindication to further vaccination with pertussis-containing vaccines.

### Minor, Acute Illnesses

Some children will be ill at the time of a well-child visit or will be in need of a vaccination at an illness visit. In these situations, the pediatrician must decide whether to recommend vaccination based on 2 questions: Will vaccination be safe for this ill child? And, if not vaccinated at this visit, will the child be brought back for vaccination?

Minor illnesses, including upper respiratory tract infections, otitis media, and diarrheal illnesses, whether the individual is febrile or not, are not valid contraindications to vaccination. A second, perhaps more difficult, consideration is whether minor vaccine side effects, such as fever, will cause diagnostic confusion during the follow-up period for the illness—a problem that may be especially difficult when caring for very young infants.

Pediatricians often struggle to determine the likelihood that any given child will return for a scheduled vaccination visit. Although past appointment-keeping behavior will help in the judgment, it is not completely reliable. Because vaccinating children who have minor illnesses is safe and effective, and because it may be unclear whether a child will be brought back for an appointment, vaccinating the ill child is best, especially if he or she has missed previous preventive care visits.

Persons with moderate or severe acute illness should be vaccinated as soon as the acute illness has improved.

### Immunocompromise

There are many possibilities regarding vaccinations for persons with immunocompromising conditions. For example, persons with altered immunocompetence might be at increased risk for an adverse reaction after administration of live, attenuated vaccines because of uninhibited replication, so these vaccines may need to be deferred until immune function has improved; these patients may need to be revaccinated with inactivated vaccines after immune function has improved if vaccination during the period of altered immunocompetence was less effective; or these patients may need certain vaccines (eg, inactivated influenza and pneumococcal vaccines) because of specific disease vulnerabilities. Because of the variety of immunocompromising conditions and their degree of severity, as well as the variety of vaccine-preventable diseases, vaccination of immunocompromised children often is best managed in consultation with a pediatric infectious disease specialist.

**WHO IS IMMUNOCOMPROMISED?** Children who have congenital immunodeficiency, leukemia, lymphoma, or generalized malignancy should not receive live vaccines. Persons receiving immunosuppressive



treatments (eg, alkylating agents, antimetabolites, and radiation therapy) also should not receive live vaccines. Persons receiving daily large doses of corticosteroids (the equivalent of 2 mg/kg of prednisone per day) for 14 days or longer should not receive live virus vaccines; live vaccines should be deferred for at least 30 days after treatment cessation or dose reduction. Live vaccine use is not contraindicated if the corticosteroid is aerosolized (as in asthma inhalers) or topical, nor if it is given on an alternate-day short course (<14 days), or if the child is on a physiologic replacement schedule.

**LIVE VACCINES.** In general, live vaccines cannot be used in immunocompromised individuals because of the potential for severe or fatal reactions from uncontrolled replication of the vaccinating agent. Exceptions to this rule include the following:

- HIV infection: Limited data among human immunodeficiency virus (HIV)-infected children (specifically CDC class N, A, or B with age-specific CD4<sup>+</sup> T-lymphocyte percentages of  $\geq 15\%$ ) indicate that varicella vaccine is immunogenic, effective, and safe. When indicated, the ACIP recommends MMR vaccination for all asymptomatic and mildly symptomatic HIV-infected persons who do not have evidence of severe immunosuppression. The MMR with varicella (MMRV) vaccine should not be administered to persons with HIV infection.
- Immunocompromised people with limited humoral immunodeficiency (eg, hypogammaglobulinemia, immunoglobulin A deficiency) may be routinely vaccinated with varicella vaccine.
- Healthy persons with anatomic or functional asplenia can receive intranasal influenza vaccine (LAIV).
- Children with deficiencies in complement or with asplenia can receive both live, attenuated viral and bacterial vaccines.
- Children with defects in phagocyte function (eg, chronic granulomatous disease or myeloperoxidase deficiency) can receive live, attenuated viral—but not bacterial—vaccines.
- Immunocompromise is a precaution but not a contraindication to the live, oral pentavalent rotavirus vaccine.

**INACTIVATED VACCINES.** Persons with altered immunocompetence generally are advised to receive injectable influenza vaccine and age-appropriate polysaccharide-based vaccines (PCV, PPSV, MCV4, MPSV4, and Hib) on the basis of demonstrated effectiveness or an increased risk for disease if the vaccine is withheld. However, during chemotherapy or radiation therapy, vaccination should be avoided if possible (except with inactivated influenza vaccine) because antibody responses might be suboptimal. Patients vaccinated within 14 days before starting immunosuppressive therapy or while receiving immunosuppressive therapy should be considered unimmunized and should be revaccinated at least 3 months after therapy is discontinued if immune competence has been restored.

**BONE MARROW TRANSPLANT.** For vaccination of bone marrow transplant recipients, the physician should consult the *Red Book* or the *General Recommendations*.

**HOUSEHOLD CONTACTS.** Household and other close contacts of persons with altered immunocompetence should be vaccinated as indicated; in particular, they should receive annual influenza vaccination (intranasal or injectable). MMR and varicella vaccines—which are live vaccines contraindicated for use in most immunocompromised people—should be given to susceptible contacts of immunocompromised people. If the varicella vaccine recipient has a rash after vaccination, direct contact with susceptible household contacts should be avoided until the rash resolves. OPV, which is used outside the United States, should not be given to people who are immunocompromised or to their close contacts. Of course, all members of the household should wash their hands after changing the diaper of an infant, in particular to minimize rotavirus transmission.

### Pregnancy

Guidelines on vaccination of pregnant women can be found in the *General Recommendations* and on the CDC Web site. The following briefly summarizes key points on routine vaccines (but not travel vaccines).

**LIVE VACCINES.** Because of the theoretical risk to the fetus, women known to be pregnant generally should not receive live, attenuated virus vaccines (eg, MMR, varicella, intranasal influenza) or live bacterial vaccines. However, potential risks of vaccinating pregnant women are usually outweighed by the benefits when the likelihood of disease exposure is high, infection would pose a risk to the mother or fetus, and the vaccine is unlikely to cause harm. Routine pregnancy testing of women of childbearing age before administering a live-virus vaccine is not recommended. Women should avoid pregnancy for 4 weeks after vaccination with MMR, MMRV, or varicella vaccines. If a pregnant woman is inadvertently vaccinated or becomes pregnant within 4 weeks after receiving these vaccines, she should be counseled about the theoretical basis of concern for the fetus; however, MMR or varicella vaccination during pregnancy should not be considered a reason to terminate the pregnancy.

**INACTIVATED VACCINES.** Pregnant women generally may receive inactivated vaccines and toxoids. Routine influenza vaccination is recommended for all women who are or will be in any trimester of pregnancy during influenza season—usually early October through late March in the United States. The adult tetanus-diphtheria-acellular pertussis (Tdap) should be given to pregnant women during each pregnancy, preferably between 27 and 36 weeks' gestation, regardless of prior vaccination with the tetanus-diphtheria (Td) or Tdap. The CDC recommends that hepatitis B vaccine should be given to a pregnant woman for whom it is indicated. Vaccines against hepatitis A and meningococcal disease should be considered for women at increased risk for those infections. Similarly, IPV can be administered to pregnant women at risk for exposure to wild-type poliovirus infection. HPV vaccines are not recommended for use in pregnant women.

### Prematurity

Preterm infants should be vaccinated using the routine schedule based on their chronologic age (ie, time

since birth, regardless of gestational age or birth weight) and the standard doses of vaccine, with 2 exceptions:

**HEPATITIS B VACCINE.** Preterm infants born to mothers who are hepatitis B surface antigen (HBsAg)-positive or with unknown HBsAg status must receive hepatitis B vaccine within 12 hours after birth; then 3 additional doses of hepatitis B vaccine should be administered, beginning when the infant is 1 month of age. The infant also must be given hepatitis B immune globulin within 12 hours of birth unless postnatal serology shows the mother to be HBsAg-negative. Infants weighing less than 2,000 g born to HBsAg-negative mothers should receive the first dose of the hepatitis B series at chronologic age 1 month or at hospital discharge.

**ROTAVIRUS VACCINE.** If a child of at least 6 weeks of age has been hospitalized since birth, deferral of rotavirus vaccine is recommended until discharge. The rotavirus vaccine series should not be initiated for infants 15 weeks or older.

### Vaccine Safety

Vaccine safety concerns have been borne out in studies (eg, RotaShield and intussusception), a biologically plausible but unsubstantiated association (eg, thimerosal in the birth dose of hepatitis B vaccine and autism), or speculation (MMR vaccine and autism). New concerns are likely to arise. A few reliable, regularly updated sources of vaccine safety information include:

- American Academy of Pediatrics ([www.healthychildren.org/English/safety-prevention/immunizations/Pages/How-Safe-are-Vaccines.aspx](http://www.healthychildren.org/English/safety-prevention/immunizations/Pages/How-Safe-are-Vaccines.aspx))
- Centers for Disease Control and Prevention ([www.cdc.gov/vaccinesafety/index.html](http://www.cdc.gov/vaccinesafety/index.html))
- Immunization Action Coalition ([www.immunize.org/safety](http://www.immunize.org/safety))
- Vaccine Education Center ([www.chop.edu/service/vaccine-education-center/vaccine-safety](http://www.chop.edu/service/vaccine-education-center/vaccine-safety))
- Vaccine Safety Institute ([www.vaccinesafety.edu](http://www.vaccinesafety.edu))

## GREAT EXPECTATIONS FOR THE FUTURE OF VACCINATION

Until the late 1980s, routine childhood vaccination had been a field marked by slow but steady progress. Since then, routine vaccination has been anything but routine. Driven by major advances in biotechnology, the performance of childhood immunization, in terms of disease prevention, has been remarkable. However, this increased performance has come at the cost of increased complexity, including more choices among vaccines and combinations of vaccines and a more complex and rapidly changing immunization schedule. For example, combination vaccines allow prevention of diseases with fewer injections; however, the presence of nonoverlapping, noncomplementary vaccines (eg, DTaP–Haemophilus influenzae type B [Hib], Hib–HBV) makes the choice of which vaccines to purchase difficult.

Advances in biotechnology will continue to bring new combination vaccines, vaccines against additional

diseases, improvements in existing vaccines, and more changes in the routine vaccination schedule. At this time, more than 20 vaccines are at various stages of development and testing. More combination vaccines will lead to greater complexity in the short term, but these combinations will eventually provide protection from disease with fewer injections; they will also facilitate vaccination against newly preventable diseases by “piggybacking” new vaccines onto accepted and fully implemented vaccines.

Just as vaccine technology is changing, so is the US immunization delivery system. For example, a greater proportion of immunizations are now given in the primary care setting than a decade ago. Continued changes in immunization delivery will be driven by changes in the financing of vaccines, changes in the health care industry, and parental preferences.

Much has been accomplished since 1796 when Edward Jenner inoculated James Phipps with cowpox, terming the procedure *vaccination* (after the word *vacca* for cow). The future is bright for children to live free of many vaccine-preventable diseases. By combining technologic advances of vaccines with aggressive delivery of immunizations by primary care physicians and public health practitioners, the present health care system will ensure healthier lives for children.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

#### Answers to Frequently Asked Questions

- *Ask the Expert: Combination Vaccines* (Web page), Immunization Action Coalition ([www.immunize.org/askexperts/experts\\_combo.asp](http://www.immunize.org/askexperts/experts_combo.asp))
- *Basics and Common Questions: 10 Things You Need to Know About Immunizations* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/vaccines/vac-gen/10-shouldknow.htm](http://www.cdc.gov/vaccines/vac-gen/10-shouldknow.htm))
- *Parents' Guide to Childhood Immunization* (booklet), Centers for Disease Control and Prevention ([www.cdc.gov/VACCINES/PUBS/parents-guide/default.htm](http://www.cdc.gov/VACCINES/PUBS/parents-guide/default.htm))
- *Vaccinate Your Baby* (Web page), Every Child By Two ([www.vaccinateyourbaby.org/faq/index.cfm](http://www.vaccinateyourbaby.org/faq/index.cfm))

### Immunization Schedules

- *Catch-Up Scheduler for Children 6 Years and Younger* (Web site), Vacscheduler.org ([www.vacscheduler.org](http://www.vacscheduler.org))
- *Immunizations for Babies: A Schedule for Parents* (fact sheet), Immunization Action Coalition ([www.immunize.org/catg.d/p4010.pdf](http://www.immunize.org/catg.d/p4010.pdf))
- *Immunization Schedules* (Web page), American Academy of Pediatrics ([www2.aap.org/immunization/IZSchedule.html](http://www2.aap.org/immunization/IZSchedule.html))

### Childhood and Adolescent Immunizations

- *A Look at Each Vaccine* (Web page), Vaccine Education Center of Children's Hospital of Philadelphia ([www.chop.edu/service/vaccine-education-center/a-look-at-each-vaccine](http://www.chop.edu/service/vaccine-education-center/a-look-at-each-vaccine))
- *Books and Periodicals* (Web page), Immunization Action Coalition ([www.immunize.org/resources/books\\_refer.asp](http://www.immunize.org/resources/books_refer.asp))

- *Parent Handouts* (Web page), Immunization Action Coalition ([www.immunize.org/handouts/discussing-vaccines-parents.asp](http://www.immunize.org/handouts/discussing-vaccines-parents.asp))
- *Vaccinations for Preteens and Teens, Age 11–19 Years* (fact sheet), Immunization Action Coalition ([www.immunize.org/catg.d/p4020.pdf](http://www.immunize.org/catg.d/p4020.pdf))
- *Vaccine Preventable Diseases* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/vaccine-preventable-diseases/Pages/default.aspx](http://www.healthychildren.org/English/health-issues/vaccine-preventable-diseases/Pages/default.aspx))
- *What Vaccines Do You Need? Adolescent and Adult* (questionnaire), Centers for Disease Control and Prevention ([www2.cdc.gov/nip/adultimmsched](http://www2.cdc.gov/nip/adultimmsched))

#### Vaccine Safety

- *Immunizations* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/safety-prevention/immunizations/Pages/default.aspx](http://www.healthychildren.org/English/safety-prevention/immunizations/Pages/default.aspx))
- *Talking About Vaccines: Vaccine Safety* (Web page), Immunization Action Coalition ([www.immunize.org/safety](http://www.immunize.org/safety))
- *Vaccine Information Statements* (Web page), Immunization Action Coalition ([www.immunize.org/vis](http://www.immunize.org/vis))
- *Vaccine Safety* (Web page), American Academy of Pediatrics ([www2.aap.org/immunization/families/safety.html](http://www2.aap.org/immunization/families/safety.html))
- *Vaccine Safety* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/vaccinesafety/index.html](http://www.cdc.gov/vaccinesafety/index.html))
- *Vaccine Safety* (Web page), Vaccine Education Center of Children's Hospital of Philadelphia ([www.chop.edu/service/vaccine-education-center/vaccine-safety/vaccine-safety.html](http://www.chop.edu/service/vaccine-education-center/vaccine-safety/vaccine-safety.html))

#### Medical Decision Support

- *AAP Immunization Initiatives Newsletter*, American Academy of Pediatrics ([www.aap.org/en-us/Documents/immunization\\_newsletter.pdf](http://www.aap.org/en-us/Documents/immunization_newsletter.pdf))
- *ACIP Vaccine Recommendations* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/vaccines/hcp/acip-recs/index.html](http://www.cdc.gov/vaccines/hcp/acip-recs/index.html))
- *Basics and Common Questions: Some Common Misconceptions About Vaccination* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/vaccines/pubs/parents-guide/parents-guide-part4.html](http://www.cdc.gov/vaccines/pubs/parents-guide/parents-guide-part4.html))
- *Epidemiology and Prevention of Vaccine-Preventable Diseases (The Pink Book)* (e-book), Centers for Disease Control and Prevention ([www.cdc.gov/vaccines/pubs/pinkbook/index.html](http://www.cdc.gov/vaccines/pubs/pinkbook/index.html))
- *Immunization Training Guide* (booklet), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/immunization/Pages/training-guide.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/immunization/Pages/training-guide.aspx))
- *List of Vaccines Used in United States* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/vaccines/vpd-vac/vaccines-list.htm](http://www.cdc.gov/vaccines/vpd-vac/vaccines-list.htm))
- *Red Book: 2015 Report of the Committee on Infectious Diseases*, 30th ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Reporting Adverse Events* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/vaccines/programs/vfc/providers/reports.html](http://www.cdc.gov/vaccines/programs/vfc/providers/reports.html))
- *Screening Checklist for Contraindications to Vaccines for Children and Teens* (screen), Centers for

Disease Control and Prevention ([www.immunize.org/catg.d/p4060scr.pdf](http://www.immunize.org/catg.d/p4060scr.pdf))

- *Summary of Recommendations for Childhood and Adolescent Immunization* (chart), Immunization Action Coalition ([www.immunize.org/catg.d/rules1.pdf](http://www.immunize.org/catg.d/rules1.pdf))
- *Vaccine Storage and Handling* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/VACCINES/RECS/storage/default.htm](http://www.cdc.gov/VACCINES/RECS/storage/default.htm))
- *Yellow Book Homepage* (Web page), Centers for Disease Control and Prevention ([wwwnc.cdc.gov/travel/page/yellowbook-home](http://wwwnc.cdc.gov/travel/page/yellowbook-home))

#### Practice Management and Care Coordination

- *Business Case for Pricing New Vaccines* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/professional-resources/practice-support/Pages/Practice-Support.aspx](http://www.aap.org/en-us/professional-resources/practice-support/Pages/Practice-Support.aspx))
- *Clinic Resources* (Web page), Immunization Action Coalition ([www.immunize.org/clinic](http://www.immunize.org/clinic))
- *Immunization* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/immunization/Pages/default.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/immunization/Pages/default.aspx))
- *Standing Orders for Administering Vaccines* (Web page), Immunization Action Coalition ([www.immunize.org/standing-orders](http://www.immunize.org/standing-orders))
- *State Information* (Web page), Immunization Action Coalition ([www.immunize.org/stateinfo](http://www.immunize.org/stateinfo))
- *Vaccine Coding* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/professional-resources/practice-support/Coding-at-the-AAP/Pages/Vaccine-Coding.aspx](http://www.aap.org/en-us/professional-resources/practice-support/Coding-at-the-AAP/Pages/Vaccine-Coding.aspx))

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- American Academy of Pediatrics Committee on Infectious Diseases. Immunization for *Streptococcus pneumoniae* infections in high-risk children. *Pediatrics*. 2015;136(4):792–808 ([pediatrics.aappublications.org/content/136/4/792](http://pediatrics.aappublications.org/content/136/4/792))
- American Academy of Pediatrics Committee on Infectious Diseases. Prevention of rotavirus disease: updated guidelines for use of rotavirus vaccine. *Pediatrics*. 2009;123(5):1412–1420 ([pediatrics.aappublications.org/content/123/5/1412](http://pediatrics.aappublications.org/content/123/5/1412))
- American Academy of Pediatrics Committee on Practice and Ambulatory Medicine and Council on Community Pediatrics. Increasing immunization coverage. *Pediatrics*. 2010;125(6):1295–1304 ([pediatrics.aappublications.org/content/125/6/1295](http://pediatrics.aappublications.org/content/125/6/1295))
- American Academy of Pediatrics Committee on Practice and Ambulatory Medicine. Immunization information systems. *Pediatrics*. 2006;118(3):1293–1295. Reaffirmed October 2011 ([pediatrics.aappublications.org/content/118/3/1293](http://pediatrics.aappublications.org/content/118/3/1293))
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# Community Health

## Chapter 21

## THE ESSENTIAL ROLE OF THE PRIMARY CARE PEDIATRICIAN

Francis E. Rushton, MD

Community pediatrics has been described as the intersection between what individual physicians do on behalf of children and the other surrounding factors and services that affect child health. In 1968, Robert J. Haggerty, MD, defined community pediatrics as “Taking responsibility for all children in a community, providing preventive and curative services, and understanding the determinants and consequences of child health and illness.” The Council on Community Pediatrics of the American Academy of Pediatrics (AAP) expands on this definition and states that community pediatrics is

- A perspective that enlarges the pediatrician’s focus from one child to all children in the community
- A recognition that family, educational, social, cultural, spiritual, economic, environmental, and political forces act favorably or unfavorably, but always significantly, on the health and functioning of children
- A synthesis of clinical practice and public health principles directed toward providing health care to a given child and promoting the health of all children within the context of the family, school, and community
- A commitment to use a community’s resources in collaboration with other professionals, agencies, and parents to achieve optimal accessibility, appropriateness, and quality of services for all children and to advocate especially for those who lack access to care because of social, cultural, geographic, or economic conditions or special health care needs
- An integral part of the professional role and duty of the pediatrician

## A FOCUS ON ALL CHILDREN IN THE COMMUNITY

In part because of the successes of our predecessors, communities today are different from those of the past. Immunizations and improved living conditions have dramatically changed the types of health challenges that are seen. New legislation has made the world safer in

some ways, with seat belt laws and child seats mandatory in many developed countries. Antibiotic coverage, in spite of resistance, has improved the outcome of most infectious diseases in the industrialized world. More sophisticated treatments are now available for premature infants and seriously ill children. The resulting effect on communities includes dramatically lower perinatal mortality and child death rates.

However, communities today are not necessarily healthier than in previous decades. Obesity is pandemic. Asthma has dramatically increased, partially in response to environmental changes.

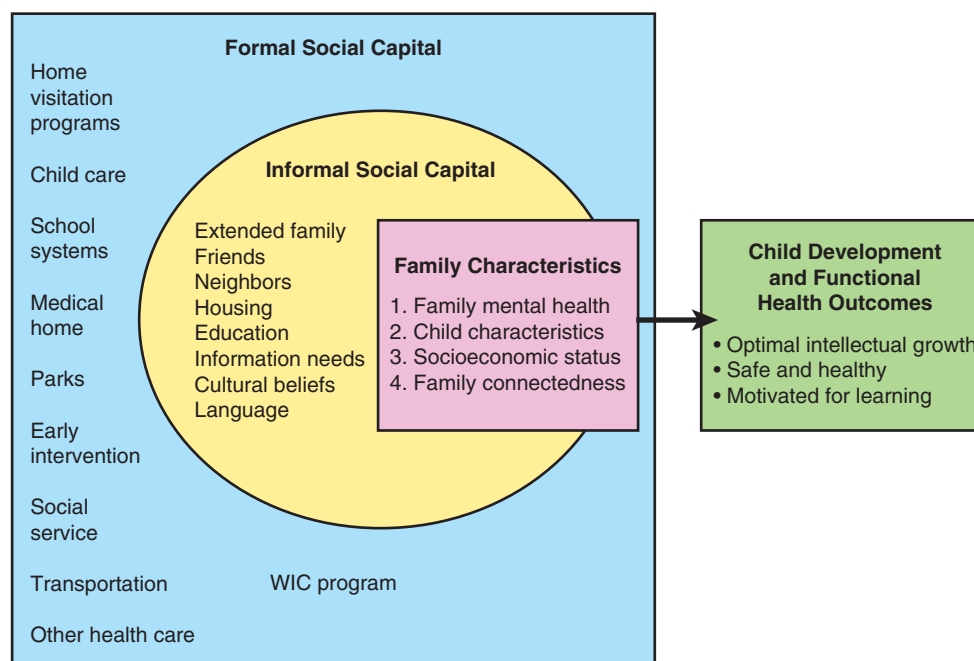
Social trends in communities affect optimal child development. Two-parent working families may have less face-to-face time, but programs such as adequate child care and family leave help support parental involvement. Fathers are now much more often involved in the birth of their babies and care of their children.

Much of the effectiveness of pediatric care has been based on the individual clinical encounter, the opportunity for physicians to promote health one by one with children in their practices. But as the problems and morbidities that affect children change over time, the individual clinical encounter by itself has become less adequate in promoting optimal functional health in children. Community pediatrics reflects this changing spectrum of pediatric practice. New morbidities include increasing numbers of children with chronic health care needs, obesity, children’s mental health conditions, exposure to environmental hazards, substance abuse, lack of school readiness, and family dysfunction. Facing these new challenges requires pediatricians to broaden their focus. While pediatricians have always cared for children within the context of their families and their practices, now there is the need to incorporate a perspective that charges pediatricians with considering all children in the community.

## A RECOGNITION THAT MANY FAMILY AND COMMUNITY FACTORS AFFECT CHILDREN’S HEALTH AND FUNCTION

A leading child advocate and one of the founders of pediatrics, Abraham Jacobi, MD (1830–1919) recognized that children are best understood within the





**Figure 21-1** Community context in which children grow and develop.

interlinking contexts of biology, family, and community. Children and their families are surrounded by a milieu of factors that negatively and positively affect functional outcome. The religious and cultural beliefs of the family lay a foundation on which childhood develops. Social isolation, the built environment, adequate child care, schools, and playgrounds all affect health. Children in poor communities experience the well-documented deleterious effect of poverty on their well-being. Certain populations, such as farm workers, immigrants, and foster children, are at increased risk for poor health. Substantial disparities exist in access to health care among populations within communities and provide a special challenge to pediatricians. Because legislative and social policies affect child health, pediatricians should advocate for universal access to quality health care for all children.

Positive physical and emotional development depends on the health of families and communities. These positive supports are referred to as social capital, both formal and informal, that impart a sense of health, safety, and well-being, and promote a supportive environment for families of all backgrounds. The pediatric medical home is part of a broad range of social supports that comprise a family's social capital (Figure 21-1).

### A SYNTHESIS OF CLINICAL PRACTICE AND PUBLIC HEALTH WITHIN THE CONTEXT OF FAMILY, SCHOOL, AND COMMUNITY

Essential to the concept of community pediatrics is the incorporation of public health methodology into clinical medicine. The US Surgeon General develops a

#### BOX 21-1 2020 Leading Health Indicators

- Access to health services
- Clinical preventive services
- Environmental quality
- Injury and violence
- Maternal, infant, and child health
- Mental health
- Nutrition, physical activity, and obesity
- Oral health
- Reproductive and sexual health
- Social determinants
- Substance abuse
- Tobacco

framework for prevention known as the Healthy People program every 10 years. Goals and objectives provide targets for positive change for many health indicators in the United States, including focused goals on maternal and child health issues (see Box 21-1). Using a public health approach, states, communities, professional organizations, and community pediatricians are instrumental in ensuring that these goals can be met. A public health approach is driven by the use of community data (epidemiologic, demographic, and economic) as the basis of understanding child health. Data help identify particular community-based strategies that improve child health potential and guide further activities. Data systems also instruct health care systems in quality improvement activities that promote efficiency and efficacy in the delivery of child health.

School health is often a component of community pediatric initiatives, and schools work interactively with public as well as private physicians. School nurses can be useful in assisting community pediatricians with the management of chronic health conditions. Schools themselves often provide access to health care services for disadvantaged populations, thereby reducing disparities in access to health care, and provide a unique opportunity for the provision of mental health services. Schools can be effective in spreading public health messages that lead to population-based changes in health behavior.

### **A COMMITMENT TO USE COMMUNITY RESOURCES TO PROMOTE OPTIMAL CHILD HEALTH**

Community pediatricians collaborate with professionals in other disciplines on child health and development issues. Opportunities for collaboration can take place in a variety of formats, such as colocation of services with providers from other disciplines, formal project relationships, or the development of community resource guides to assist care coordination and management. Informal ways of getting to know other service providers in the community, such as professional social gatherings, visits to service sites, or preparation of resource directories have assisted the identification of valuable adjunct services. Regardless of methodology, pediatricians and their staffs should educate themselves regarding the availability of community resources that augment their own efforts to improve the health and well-being of their patients.

Collaborative care has the potential to help families through greater knowledge transfer on health topics, improved access to formal and informal sources of social support, and access to other community-based services. Collaborative initiatives work best when implemented using a strength-based approach. Pediatric collaborative efforts should reflect the importance of the medical home in children's and families' lives and not undermine the therapeutic physician-patient relationship. Collaborative services with other professionals should not be viewed as a substitute for the important role of physicians in their patients' lives, but as a means to augment services.

Increasingly, collaborative arrangements take the form of a team of caring professionals providing a wide range of services for children. In addition to nurse practitioners, many pediatric offices now include on-site mental health providers, social workers, care coordinators, lactation consultants, healthy development specialists, and even home visitors. In some practices, designated case managers or care coordinators facilitate a team approach, as they often become experts on the nature of community services and can assist with linkages for appropriate care. Care coordination services are often cost efficient for practices and helpful in ensuring good outcomes. In some communities, care coordination services are pooled among several practices, often with public health or managed care support.

### **ADVOCATE FOR THOSE WHO LACK ACCESS TO CARE**

Advocacy can mean working with legislators, policy makers, the media, not-for-profit organizations, community programs, and others to improve child well-being, or working to address the needs and issues that affect a particular patient. Examples of successful pediatric legislative efforts include the Child Health Insurance Program Reauthorization Act (CHIPRA), laws requiring seat belt and car safety-seat use, and public funding for important child health programs such as immunizations. Media advocacy involves ensuring that the pediatric perspective is portrayed favorably in various news outlets (eg, community outreach programs). Pediatricians should advocate for neighborhood structures that support optimal health, safety, and development in children and their families. Consulting with school systems, child care facilities, and other local organizations concerned with child well-being provides opportunities for assisting children. Personal advocacy involves making contacts on behalf of a child with schools, insurance companies, home health nurses, and others who can benefit the child. Various organizations of which the pediatrician is a member can be helpful in developing meaningful advocacy activities. For example, state chapters of the AAP often provide leadership and support in the development of advocacy efforts at the state and local level. The Community Access to Child Health (CATCH) program of the AAP is a resource for pediatricians considering advocacy at the local level.

### **AN INTEGRAL PART OF THE PROFESSIONAL ROLE AND DUTY OF THE PEDIATRICIAN**

Caring pediatricians understand the importance of incorporating the community within the scope of their professional responsibility. Unfortunately, funding mechanisms underlying care often don't appreciate the importance of any activity outside of the individual clinical encounter. As patient-centered medical homes are being established, changes in the way traditional primary care is reimbursed are being evaluated. The provision of care management fees or pay-for-performance incentives could help cover extended services. Pediatricians often complain of being inadequately trained in community pediatric techniques. Younger pediatricians report more training in community child health during and before residency than in the past, but still report that their current level of involvement in community approaches to care is inadequate. Regardless of payment and training, however, community pediatrics has become and will continue to be an integral part of the professional role and duty of the pediatrician.

One example of a child health problem amenable to a community approach is the prevention and treatment of obesity. The current approach, based on the individual clinical encounter, has been less than satisfactory because it is not time-efficient for physicians to work one-on-one with children at risk for obesity. Even motivated families and children have difficulty

cooperating with treatment regimens. Recent studies suggest that a community approach has great potential for success in dealing with this issue. Collaboration with nutritionists, home visitors, public health officials, and parenting specialists can provide the basis for a successful support system for children at risk. An understanding of community factors that lead to weight problems, such as advertisements during children's TV programs, lack of opportunities for exercise, and easy availability of high-calorie food with poor nutritional value, opens the door to potential strategies. Advocacy using the media has the potential to promote healthier lifestyles through such means as public service announcements concerning the effect of TV, the caloric value of foods, and the importance of regular exercise in the maintenance of optimal body weight. Working with school health services to counsel students and school administrators may ensure that all children have the opportunity for regular physical activity and appropriate nutrition in school.

Community pediatrics has been an integral part of child health services since the very beginning of the specialty of pediatrics. But, with changing morbidities and the social, economic, and psychologic problems facing children, it has taken on a renewed importance in the daily routines of pediatricians. Only by recognizing the contextual nature of pediatrics within a variety of factors affecting health, and only by working with the broader community, can we achieve satisfactory results.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *Adolescent & School Health* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/healthyyouth/schoolhealth/index.htm](http://www.cdc.gov/healthyyouth/schoolhealth/index.htm))
- *Building the Legacy: IDEA 2004* (Web page), US Department of Education ([idea.ed.gov](http://idea.ed.gov))
- *Connected Kids Clinical Guide* (booklet), American Academy of Pediatrics ([www2.aap.org/connectedkids/ClinicalGuide.pdf](http://www2.aap.org/connectedkids/ClinicalGuide.pdf))
- *Healthy People 2020 Count Data Resources* (Web page), US Department of Health and Human Services ([www.healthypeople.gov/2020/county-data-resources](http://www.healthypeople.gov/2020/county-data-resources))
- *Healthy People 2020 Evidence-Based Resources* (Web page), US Department of Health and Human Services ([www.healthypeople.gov/2020/tools-resources/Evidence-Based-Resources](http://www.healthypeople.gov/2020/tools-resources/Evidence-Based-Resources))
- *Healthy People 2020 Program Planning Guide* (Web page), US Department of Health and Human Services ([www.healthypeople.gov/2020/tools-and-resources/Program-Planning](http://www.healthypeople.gov/2020/tools-and-resources/Program-Planning))
- *NACCHO Toolbox* (Web page), National Association of County and City Health Officials ([www.naccho.org/toolbox](http://www.naccho.org/toolbox))
- *The National School Lunch Program* (NSLP) (Web page), US Department of Agriculture ([www.fns.usda.gov/nslp/national-school-lunch-program-nslp](http://www.fns.usda.gov/nslp/national-school-lunch-program-nslp))
- *State School and Health Resources* (Web page), American Academy of Pediatrics ([www2.aap.org/sections/schoolhealth/contactmap/section\\_contacts.cfm.htm](http://www2.aap.org/sections/schoolhealth/contactmap/section_contacts.cfm.htm))

### Engaging Patient and Family

- *Child Care Aware Parent and Family Resources* (Web page), Child Care Aware America ([childcare-aware.org/parents-and-guardians/resources](http://childcare-aware.org/parents-and-guardians/resources))
- *Community Health Online Resource Center* (directory), Centers for Disease Control and Prevention ([nccd.cdc.gov/DCH\\_CHORC](http://nccd.cdc.gov/DCH_CHORC))
- *Data Tools* (Web page), National Center for Children in Poverty ([nccp.org/tools](http://nccp.org/tools))
- *Frequently Asked Questions About Section 504 and the Education of Children With Disabilities* (fact sheet), US Department of Education ([www.ed.gov/about/offices/list/ocr/504faq.html](http://www.ed.gov/about/offices/list/ocr/504faq.html))

### Practice Management and Care Coordination

- *Care Coordination Toolkit* (booklet), National Center for Medical Home Implementation ([www.medical-homeinfo.org/downloads/pdfs/CareCoordination-Toolkit06.pdf](http://www.medical-homeinfo.org/downloads/pdfs/CareCoordination-Toolkit06.pdf))

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## Chapter 22

# PROMOTING THE HEALTH OF YOUNG CHILDREN

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## INTRODUCTION: WHAT TODAY'S YOUNG CHILDREN FACE

The demographics of young children in the United States have changed dramatically during the past 15 years, and these changes are not slowing. According to the Pew Research Center, since 2000 more than 90% of population growth has been among racial and ethnic minorities, many of whom are immigrants. Most of this growth (56%) is from Hispanic births. Hispanics represent the largest population of minority infants (26.1%), followed by African Americans (13.7%) and Asians (4.4%). The US minority population is younger than the white population and has a large proportion of 20- to 34-year-old women who are at the height of their childbearing years. The prime childbearing age for whites and Asians is the late 20s

and early 30s. For African Americans and Hispanics, the peak is the early 20s. Hispanics have the highest total fertility rate of any group at 2.4, followed by African Americans at 2.1. Whites and Asians have the same rate, 1.8.

This growth in the minority population of the United States is important to child health trends because a large proportion of young racial and ethnic minority children live in low-income families. Although only 29% of Asian children and 35% of whites fall into the low-income category, 70% of blacks and 66% of Hispanics are living in low-income families. This effect of poverty is exacerbated by the fact that blacks and Hispanics are slightly more likely than Asians or non-Hispanic whites to be living in areas of concentrated poverty, making opportunity hard to find and magnifying the effects of the social determinants of health.

## POVERTY AND TOXIC STRESS

Toxic stress is strongly associated with income level. Nearly 67% of children with family incomes less than 100% of poverty have had an adverse childhood experience, as opposed to 27% of children with family incomes above 400% of poverty.

Toxic stressors may include child abuse or neglect, parental substance abuse, maternal depression, witness to domestic violence, and separation from loved ones. Many children exposed to these stressors go on to develop physical and mental health problems, even into adulthood. Some will be counted among the 11% to 20% of children in the United States who have a behavioral or emotional disorder. Emergency department (ED) visits increased by more than 20% for children 1 to 4 years of age between 2006 and 2011. This increase was likely related to an almost 61% increase in ED use for behavioral disorders, accounting for more than 75% of the patient visit increases for 1- to 4-year-olds.

According to the National Center for Children in Poverty, there are 7 risk factors associated with poverty that contribute most to young children's adversity:

- Being born to a teen mother
- Being born to a single parent
- Being born to a parent with low education
- Living in a large family
- Experiencing residential mobility
- Living in a household without an employed parent
- Living in a household without English speakers

Of the 37 million children younger than 6 years, 39% do not have any of the risk factors; 41% have 1 or 2; and 20% have 3 or more. The Annie E. Casey annual *Kids Count Data Book* tracks a total of 16 child health indicators with 4 subindicators in each of 4 categories: economic well-being, education, health, and family and community.

Trends in these categories from 2005 through 2012 were highlighted with the release of the 2014 *Data Book*, which marked 25 years of publication. Between 2005 and 2012 there were a number of encouraging trends: preschool attendance went up, as did high school graduation rates; there were small drops in child and teen mortality and in very low birth weight; the teen birth rates hit historical lows; and health

insurance coverage increased slightly. However, there were discouraging trends as well. Economic well-being has not recovered from the recession, with 22% of children still living in poverty and more concentrated pockets of low income. The economic recovery is not trickling down to provide jobs for heads of poor households. The fraction of children living in households with a solo parent increased. The most distressing trend was the continued chokehold that poverty has on almost one-fourth of US children's families. Notably, the indicators do vary significantly by state; these differences can be followed on individual state data reports.

## RATIONALE FOR INTERVENTION DURING EARLY CHILDHOOD

A strong rationale exists for the very earliest of interventions in the development and growth of children—the proverbial “first 1,000 days”—as the marginal effect on child health of therapeutic interventions diminishes over time. The “loss aversion” argument is also compelling: namely, we as a society cannot tolerate the great loss that would result from failure to implement relatively simple interventions early in life.

A new index has been developed to address the social determinants of health—the “The Child Opportunity Index.” It is designed to improve collaboration between community development agencies and public health in the 100 largest US metropolitan areas. In various neighborhoods, the researchers measured the extent of opportunity, ethnic mix, and income mix. They found that the lowest opportunity neighborhoods were most often populated with people of color—40% of black and 32% of Hispanic children—as opposed to less than 10% of white children. This is even more sharply felt in cities with high levels of segregated housing. The measures they used included the categories of social and economic opportunities (6 indicators), health and environmental opportunities (6 indicators), and educational opportunities (8 indicators). The authors think that this may be useful for health care institutions and accountable care organizations who desire to move into a metropolitan area but want to know how difficult it will be to meet their community benefit obligation in that community. A similar sort of investigation was performed on communities with Health Legacy Foundations to ascertain whether they were situated in communities that were relatively well-off in order to justify spending their funds elsewhere. The researchers found that Health Legacy Foundations by and large are in poorer resourced communities, so redistribution is not a likely source of money.

## PROMOTING THE HEALTH OF YOUNG CHILDREN

There are many different educational, medical, and social service settings with a variety of professionals, paraprofessionals, and laypersons involved in trying to promote positive responses and resilience, prevent or ameliorate adverse stress, or rehabilitate those young children who have suffered from toxic stress.



Some of these are embedded in clinical pediatrics; some are community-wide programs.

Chapters 31 through 45 describe strategies to promote health through the medical home, including early literacy promotion (talking, singing, and reading; Reach Out and Read); evidence-based programs to foster positive parenting (eg, Triple P, Incredible Years); and counseling around sleep, special time with parents, healthy weight, physical activity, sexuality, and limiting the use of electronic media. Chapter 79, Children in Poverty, describes a number of public programs designed to ameliorate the effects of poverty, including Temporary Assistance for Needy Families, the Earned Income Tax Credit, Child Support, Child Care Subsidies, Supplemental Nutrition Assistance Program (Food Stamps), and the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC). Other chapters describe the care of other special populations: Chapter 68, Children Exposed to Adverse Childhood Experiences; Chapter 69, Caring for Families New to the United States; Chapter 70, Adoption; Chapter 71, Children of Divorce; Chapter 72, Children in Foster or Kinship Care; Chapter 77, Children in Military Families; and Chapter 78, Homeless Children. Part 3 of this book addresses prenatal care, and Part 4 addresses assessment and stabilization at delivery and care of high-risk infants, including those with depressed mothers. These are critical strategies to protect and promote the health of young children.

This chapter focuses on early home visiting programs, medical-legal partnerships, initiatives to improve the health and safety of out-of-home care, Early Intervention programs, and Head Start. It also outlines the role of pediatricians in addressing the needs of young children at a community level.

## MATERNAL, INFANT, AND EARLY CHILDHOOD HOME VISITING PROGRAMS

As evidence of the critical importance of intervening early in vulnerable children's lives has mounted, so has interest in early home visitation programs. These programs were initially funded predominantly by small private and public sources, but early home visiting that meets certain outcome criteria has now gained Affordable Care Act (ACA) support and other public and private financing, indicative of the confidence that funders have developed in family-focused health interventions. The Maternal, Infant, and Early Childhood Home Visiting Program (MIECHV), administered by the Health Resources and Services Administration (HRSA) and the Administration for Children and Families, funds states, territories, and tribal entities to develop and implement evidence-based home visiting programs. These programs use models proved to improve maternal and child health and produce other positive outcomes, such as decreases in child abuse and neglect; decreased injuries; better speech development and readiness for school; reductions in behavioral problems, depression, and substance abuse; and, for mothers, fewer incidents of substance abuse, increased maternal employment, better spacing of births, and decreased necessity of public support.

Programmatic goals, target populations, and interventions may vary, but all programs are delivered in homes, by staff trained to improve knowledge, beliefs, and behaviors. By seeing the young child interacting in the home environment with family, the home visitor can better assess and respond to real needs, develop tailored strategies, and coordinate services for individual families. This is far superior to standardized, "one-size-fits-all" institutional treatment and appointment scheduling. One major opportunity from visiting is education regarding online health-related messages and websites, including those of the American Academy of Pediatrics (AAP). Many adolescents are used to communicating by cell phone, and the home visitor can introduce the many "apps" that give opportunities for health-related reminders and information, such as Text4Baby, Zero to Three, Bright Futures, the Incredible Years, Triple P-Positive Parenting Program, FamiliasUnidas, Autism Navigator, and many other information sheets and resources developed by the AAP and Centers for Disease Control and Prevention (CDC).

### Variation in Programs

The implementation of home visiting programs varies widely. Some programs begin during pregnancy, such as Nurse Family Partnership (NFP) and Early Head Start, whereas others begin when a child is born or even later. The length of most programs is 2 to 4 years, which ensures there will be adequate time to develop a strong relationship between mother, child, and home visitor. The background for home visitors' educational preparation ranges from professionals with bachelor's or master's degrees in nursing to paraprofessionals who live in the communities being served, many of whom possess language and cross-cultural skills that match those of the clients being served. Paraprofessionals have not been proved to be as effective as professional nurses in general home visiting. However, home visitation by community health workers has recently been shown to be cost-effective in some specialized areas for intervention, such as reducing asthma-related hospital care in children.

The varying structure of programs is based on disparate levels of resources and differing goals. Some programs, such as Healthy Families America (HFA), attempt to prevent child abuse and neglect by improving parenting skills and promoting healthy child development. Other programs focus on improving mothers' lives by supporting their efforts to return to school, to postpone subsequent pregnancies, and to earn a living. Programs emphasizing the personal relationship between parents and home visitors, such as Parents as Teachers (PAT), Home Instruction of Parents of Preschool Youngsters (HIPPIY), and Parent-Child Home Program (PCHP), can bridge the isolation between families and their communities. By providing social support and practical assistance, home visitors attempt to stimulate and nurture changes in parents' attitudes, knowledge, and behavior.

### Home Visitation Program Examples

In 2005, the federal government reauthorized MIECHV funding for 17 home visitation models they deemed "evidence based." The Colorado-based nonprofit

Nurse Family Partnership model of home visitation, the Nurse Home Visitation Program, is the most rigorously evaluated and widely replicated visitation model. The model is constantly being refined and re-evaluated under the guidance of pediatric researcher David Olds. It supports Eckenrode and colleagues' argument that altering a mother's life course has important implications for her children. A mother's ability to assume responsibilities associated with a steady job and postpone a second pregnancy may make it possible for her to emerge from poverty and focus her efforts on her child. A 19-year follow-up of a randomized trial showed that girls born to high-risk mothers who had Nurse Home Visitation Program model prenatal and infancy home visitation had fewer subsequent pregnancies, were more likely to defer second births, spent fewer months on welfare or receiving food stamps, and had fewer problems with arrests and substance abuse than the mothers who did not receive nurse home visits.

The Healthy Steps Program is a medical home visitation project. There are 70 such programs across the country in which young at-risk children are required to be seen in their pediatric home by a specially mandated additional staff person, the Healthy Steps Specialist. The specialist has advanced training in one or more pediatric fields and ensures that children receive appropriate development screening and other services designed to assure emotional health, in particular.

### Involvement of Fathers

Until recently the primary focus of home visiting had been almost exclusively on the mother-child relationship. During the past decade, however, there has been outreach to fathers and other family members. The NFP found that nurse home visitation had significantly more fathers in attendance than did paraprofessional home visitation. Recently Holmberg and Olds reported that father attendance in home visiting was associated with factors such as the number of completed maternal home visits, maternal cohabitation with the partner, being married, and white, non-Hispanic race.

Because the presence of the father is a positive influence on the child's and mother's life (except when he is abusive), it is important to engage him in the family parenting and family functioning process. Paternal presence has generally been low—between 2% and 32% of visits in the Nurse Home Visitation Program. Reports indicate that some success in engaging men has come from having more "male" types of activities, such as sporting events, outdoor events such as cookouts and picnics, coaching, and martial arts; fathers have been drawn in and then been integrated into healthy parenting topics and principles of successful fatherhood.

In their study of the differences in father's frequency of attendance, Holmberg and Olds reported that more of the difference was attributable to intangible clinic and nurse visitor characteristics, most likely the skill of the home visitor. This brings attention to the vital importance of the quality of interaction between visitor and family, particularly the visitor's ability to bring in and involve the father in the conversation. Holmberg and Olds conclude that

"the ability to remain interpersonally available to the mother and father in the same visit, attitudes about the role of fathers in the program, skill in advocating for father involvement, comfort and working with fathers will be important next steps for research in this area" and further research is needed on father participation and "organizational, team, and nurse factors . . . promising targets of intervention increasing safe, nurturing father involvement and home visits." Dr. Olds is increasing efforts to retain nurses: continuity of personnel enhances technical implementation of the program and strengthens the relationship of the nurse with parents. Mothers are reportedly 7 to 8 times more likely to drop out if they lose their current nurse visitor.

### Attaining Other Outcomes

Results from a variety of programs' evaluations document some change in parents' attitudes as a result of the home visiting programs, and often in their behaviors. Despite promoting the importance of prenatal care and the use of preventive health visits, none of the 6 evaluation studies found improvements in immunization rates or number of well-child visits. Results for assessments of children's development and behavior similarly suggested only modest improvement.

All home visiting programs depend on changes in parents' behavior to nurture children's health and development. However, the complexity and variety of the family situations affect the consistency with which a home visiting program can be implemented. To expand and develop home visitation, improved methods are needed to evaluate programs. This includes examining context, service intensity and "units," family engagement, and training and characteristics of home visitors. There needs to be an accurate understanding and measurement of risk. Assessment of the involvement of family members in addition to the mother and child requires further exploration. Strengthening home visitation programs to produce better outcomes for the children and families requires ensuring that the programs are an integrated component of a system of support rather than a separate intervention model. The results from evaluations of home visiting programs to date suggest that expectations for home visiting without clear standards of technical fidelity and clear, faithful commitment to clients can only be modest and, most important, that home visiting cannot be the only strategy for serving families with young children at risk for poor health and development.

### Universal Home Visiting

Buoyed by the predominantly positive findings and the experiences of other countries, some advocates in the United States have proposed universal nurse home visiting of families with newborns. The main reason for this is that even the most experienced and educated parents have difficulty with and questions regarding parenting their children, each of whom may have a different temperament. Universal home visiting has the potential to remove the stigma of being "high risk," provide a common experience for all mothers in the region, and foster open dialogue about parenting and the care of children.

## MEDICAL-LEGAL PARTNERSHIPS

Medical-legal partnerships have been developing since 1993. According to the National Center for Medical Legal Partnerships, there are currently 125 hospitals, 123 health centers, 26 medical schools, 36 residency programs, and 34 law schools in the United States that have adopted the model. O'Toole and colleagues demonstrated that residents who worked in clinics with social and legal resources had confidence to screen for social determinants of health.

Partnerships are being formed between pediatricians and legal aid, law school students, and *pro bono* lawyers in the community. Some are colocated in the clinical setting. They may provide direct legal aid or align strategies with health care services. The model can help improve young children's health by dealing with legal needs that affect well-being. Some examples of legal needs that affect health are government entitlements, housing (including mitigation of lead exposure), legal status, domestic violence, and custody issues.

## INITIATIVES TO IMPROVE HEALTH AND SAFETY IN CHILD CARE

Nonparental child care comes in various types, and any given child may participate in more than one type of nonparental care. According to the US National Household Education Survey, approximately 60% of US children 0 to 5 years who are not in kindergarten are in some form of regular, nonparental care every week. (Of course, older children may be in group child care before and after school, but their care is outside the scope of this chapter.)

In most states, nonparental care of 3 or more unrelated children for 4 or more hours per day at least once a week is considered to be the kind of child care falling under state regulatory authority. A facility providing group care for fewer than 6 children 0 to 5 years of age is considered a child care home, whereas a facility providing group care for 6 or more such children constitutes a child care center, regardless of the shape of the building in which the care is given. It is important, however, to recognize that these definitions may vary by state. Community-based pediatricians should be aware of the number, location, and variety of early care and education programs operating in their service areas.

All states have some way of measuring child care quality (quality rating and improvement systems, or QRIS), and in some cases states may attach benefits to higher quality ratings, such as higher rates for children who are eligible for public subsidy. Pediatricians should be aware of how child care centers and homes are rated in order to be better positioned to help families choose the best child care experiences for their children. Information about the availability and quality ratings of local child care facilities can be obtained from Child Care Resource and Referral Agencies (CCR&Rs). (See [www.childcareaware.org](http://www.childcareaware.org) for your state and local CCR&R.) More active involvement in the QRIS process at the local or state level is an option for pediatricians who are willing to contribute their

time to improving the quality of early care and education overall. Children's health and safety in child care is an important component and an essential basis of quality because physical, cognitive, and social-emotional development are inextricably linked and contribute to children's readiness for school. The pediatrician can be a powerful advocate for health and safety in child care in the QRIS and state regulatory processes.

## OPPORTUNITIES FOR HEALTH PROMOTION IN EARLY CARE AND EDUCATION PROGRAMS

For 60% of American children, early care and education programs are the best places to reach groups of children and their families between birth and kindergarten entry. The opportunities for promoting health, safety, and psychosocial development are enormous. All pediatricians are urged to discuss child care as part of the AAP recommended schedule of anticipatory guidance. In addition, the community-based pediatrician or designee can support individual child care facilities or the early care and education community in many ways.

### Infectious Disease Prevention

Infectious diseases (primarily upper respiratory and gastrointestinal infections) are more prevalent among young children cared for in group out-of-home care settings than in those cared for in their homes, but there are proven ways of reducing the transmission of infectious disease. Pediatricians can participate in planning and providing trainings for child care providers on how to prevent infectious disease transmission and how to control an outbreak in the child care facility should one occur. For children in child care who become sick, pediatricians and their designated mid-level providers should understand state child care regulations about exclusion from care in order to advise parents when it is recommended that children stay home and when they can return to group child care.

### Allergies and Asthma

Controlling exposure to allergens and asthma triggers is just as important in child care as it is in family homes. The pediatrician or designee can work with child care providers to reduce dust, dander, mold, and other allergens in the facility. This includes familiarity with Integrated Pest Management techniques for controlling vermin using a minimal amount (if any) of pesticides in or near facilities where children are cared for. In the cases of children with asthma or allergies, child care providers must be comfortable with the use of inhalers and epinephrine autoinjector (EpiPen). Written orders from a pediatrician are usually necessary; a well-written care plan is essential. In most states, training child care providers in the administration of both prescribed and over-the-counter medications is regulated by the state's nurse practice act, which pediatricians working with child care facilities should understand.



## Injury

It is not necessarily the case that children are at greater risk for medically attended injuries in out-of-home child care than they are in their own homes. It is true, however, that injuries in both settings can be reduced further. Most states mandate that injuries requiring medical attention be reported by the child care provider to a designated agency. Using data from such reports, investigators were able to show that strengthened playground safety regulations significantly reduced such medically reported injuries in one state. The pediatrician or designee can play an active role in developing state policies that mandate that child care facilities subscribe to stringent safety requirements. At the facility level, child care safety advocates can help providers identify and mitigate injury risks. The pediatrician can also counsel parents to discuss safe sleep practices with child care facilities.

## Immunizations

Immunization requirements for admission to out-of-home child care are regulated in most states, just as they are for school entry. Thus, children in regulated child care tend to be better immunized than children in family care. Nevertheless, many child care providers lack information about the importance of and the necessity for immunization. Pediatricians or their designees can play a role in raising the awareness of prevention of infectious disease through immunization by participating in the training of child care providers. At the same time, pediatricians need to be aware that state immunization requirements for child care may differ from the recommendations of the Advisory Committee on Immunization Practices.

## Nutrition and Physical Activity

In addition to the home and the neighborhood, out-of-home child care is a setting in which childhood overweight and obesity should be addressed. At the policy level, pediatricians and their designees can advocate for regulations to promote breast feeding, control the amount of sweetened beverages and juices and full-fat milk offered to children, establish a minimal level of physical activity, and limit screen time. At the facility level the pediatrician or designee can offer guidance with respect to healthy foods and beverages; encourage safe, active play; and discourage the overuse or abuse of television, computers, tablets, hand-held devices, and the like.

## Social-Emotional Health

Expulsion rates from early childhood programs are extremely high, and most of these are because of challenging behaviors. Child care is an ideal setting in which to address children's social, emotional, and behavioral needs before school authorities label them as "children with special needs." Evidence-based classroom teacher training in promoting mental health and responding to challenging behaviors is available (eg, Incredible Years, [incredibleyears.com](http://incredibleyears.com); and the Center on the Social and Emotional Foundations of Early

Learning, [csefel.vanderbilt.edu](http://csefel.vanderbilt.edu)), and the pediatrician or designee can encourage child care providers to avail themselves of these programs. Child care can also be a focus around which to organize parenting training. Finally, child care mental health consultants can work with teachers and parents in the child care setting through education, training, and coaching to address the social-emotional needs of young children to improve mental health outcomes and reduce expulsions.

## Oral Health

Tooth decay is the most common chronic disease in American children. Child health and child dental health providers can work together to take advantage of oral health care and educational opportunities in child care. The same dental hygiene that pediatricians and designees recommend to parents of infants and young children should be taught to child care providers and teachers. Children old enough to do so should brush their teeth with fluoridated toothpaste after meals and snacks just as they would at home. The nutrition recommendations that address overweight and obesity by eliminating sweets and empty calories from children's diets will also help prevent tooth decay. Finally, dental screening and fluoride sealants may be possible in the facility for children who are old enough.

## Child Care Health Consultants

Most states are served by child care health consultants (CCHCs). A CCHC is a child health professional who has "interest in and experience with children, . . . knowledge of resources and regulations and is comfortable linking health resources with facilities that provide primarily education and social services." A fully trained and qualified CCHC can assess the health and safety status of child care facilities; consult collaboratively with child care providers on-site or by telephone or electronic media; help develop or update health policies and procedures; provide referrals for health, mental health, and social needs, including medical homes, children's health insurance programs (CHIPs), and services for special health care needs; consult with a child's primary physician about medications as needed, in collaboration with parents or guardians; interpret standards, regulations, and accreditation requirements related to health and safety; and provide technical advice, separate and apart from the enforcement role of a regulatory inspector. Community-based pediatricians may receive referrals from CCHCs and in turn work with CCHCs, most of whom are nurses, to facilitate the implementation of medical care plans for their patients in out-of-home care. Working together, pediatricians, their designees, and CCHCs can promote quality, health, and safety for child care in their communities.

## EARLY INTERVENTION

In 2012, 8% of young children born in the United States weighed less than 2,500 grams or 5½ pounds. In 2011, 6.1 infants per 1,000 live births died before their first birthday. More than one-fourth of children younger than 6 years have a disability.



Pediatricians are specialists in the complex care of children with special health care needs. There is enormous potential and need for the pediatrician to take a central leadership role in care coordination for young children who receive services under the Individuals with Disabilities Education Improvement Act (IDEA).

IDEA is a federal law that dictates how states provide early intervention services and special education to children with special needs. Part C covers infants and toddlers from birth until 3 years old. Services are outlined in an Individualized Family Service Plan (IFSP). Part B covers children after their third birthday until age 21 years with an Individualized Education Plan (IEP), administered by the local education agency.

A child who demonstrates a delay in development, speech, language, or gross or fine-motor skills may be referred for evaluation by the pediatrician, parent, child care center, or hospital. If the child is younger than 3 years, the public health department or other coordinating agency does the initial screening. Between 3 and 5 years of age, the early intervention team of the public school system evaluates the child. If the child's delay was not identified until after kindergarten entry, the K-12 intervention team begins the process.

The evaluation is by a multidisciplinary team (not necessarily including a physician). With parent permission, the child is screened and, if found to have significant delays, referred for a full evaluation. If the child is eligible for Early Intervention (EI) or special education services, the team, in collaboration with the parent, determines which services to recommend (occupational therapy, physical therapy, speech-language therapy, special education) and with what frequency. The IFSP determines whether the services will be in home or at an office. Some states provide services recommended by the IFSP free of charge; others apply fees. The IEP will determine whether the services will be in either a school or child care setting or an EI office. These services are free of charge. IDEA regulations require that all services take place in the "least restrictive environment."

There are many professionals and paraprofessionals involved in developing and implementing the IFSPs and IEPs, including but not limited to social workers, occupational therapists, physical therapists, speech-language pathologists, nurses, psychologists, early childhood special educators, and pediatric specialists. Many pediatricians have a low level of involvement in these processes, and some think that an established diagnosis is necessary before making an EI referral. This perception is associated with decreased referral for children with speech delay, particularly among English language learners, despite parental concern for inappropriate development. Parents may or may not perceive the pediatrician as part of the care team. Without specific parental authorization through the Health Insurance Portability and Accountability Act (HIPAA) or the Family Educational Rights and Privacy Act (FERPA), the pediatrician of a child receiving EI services may be unaware of goals and progress. However, pediatricians can make significant contributions to communication (parents,

therapists, and agencies), information exchange, and service delivery coordination. The pediatrician has the ability to request a meeting of the EI team or to visit providers in their workplaces. Attendance at an IFSP or IEP meeting could be done virtually or by phone. At a minimum, parents should be instructed to bring copies of the plans and updates to be part of the child's medical record. If the pediatrician is unaware of the EI system or process, the local Area Health Education Center (AHEC) may be available to provide training.

## HEAD START

Head Start is an evidence-based program of the US Department of Health and Human Services, providing comprehensive early childhood education, health, nutrition, and parent involvement services to low-income children and their families. Head Start has personnel to ensure program fidelity: health services coordinators, parent services coordinators, and consultants as needed—nurse health consultants, nutrition professionals, mental health consultants, oral health consultants, home visitors, and social workers.

Head Start's major goal is to ensure that enrolled children enter elementary school with an educational foundation at least equivalent to that of their more economically advantaged peers. In the mid-1990s, in response to the emerging research about the critical importance of development in very early childhood, Early Head Start was developed to serve pregnant women, infants, and toddlers. Eligibility for services is determined by federal poverty level, but factors such as homelessness, child disabilities, foster care, or Supplemental Security Income allow the program to accept some over-income families. Currently, 80% of enrolled children are 3- to 4-year-olds served in preschool classrooms designed to nurture their social-emotional-behavioral development.

Head Start encourages parental involvement as classroom volunteers and requires staff to make home visits. In these ways the program aims to preserve each family's ethnic, cultural, and linguistic heritage. Each Head Start program has a designated staff member, usually with a health-related background, serving as the Head Start Health Services Coordinator. This person systematically evaluates enrolled children's health histories and ensures that each child receives screenings and referrals for preventive medical, dental, vision, nutrition, and mental health services; early intervention; and service coordination. This involves coordinating with other program staff who screen the children to ensure age-appropriate developmental, sensory, behavioral, motor, language, social, cognitive, and emotional skills. These screenings are mandated to be conducted by the 40th day of enrollment. Successful follow-up of findings involves partnering with the child's medical home. If the child does not have a medical home, the coordinator links the child's family to a pediatrician and works to ensure that the child continues to receive comprehensive health care, even after graduating from Head Start.

One-tenth of Head Start enrollment is reserved for children with disabilities, most of whom have hearing

or speech and language impairments. Children with low-incidence, severe disabilities such as blindness, deafness, and intellectual disability are enrolled in the Head Start population in approximately the same proportion as in the IDEA, Part B program for 3- and 4-year-olds. Head Start also enrolls children with feeding tubes and children served by full-time health care aids. For low-income areas and neighborhoods, Head Start is often the only program serving families who have children with severe disabilities.

During the past 50 years, Head Start has served 30 million children and their families. Head Start outcomes have been extensively evaluated, with mixed results. Lee and colleagues looked at data from the Early Childhood Longitudinal Study–Birth Cohort (about 6,950 children) and examined kindergarten readiness (academic skills and socioemotional well-being) in children who had attended Head Start compared with those who had experienced other types of child care (prekindergarten, other center-based care, other nonparental care, or parental care). Head Start participants had higher early reading and math scores than children who had not been in center-based care; however, they demonstrated higher levels of conduct problems than those in parental care. The benefits of Head Start were more pronounced for children who had low initial cognitive ability, children of parents with low levels of education, and children who attended Head Start for more than 20 hours per week. Puma and colleagues found positive comparative health effects; however, they were not retained after the end of third grade.

Many low-income parents with young children have shifted from public assistance to regular employment often requiring longer days and distances. These increased time and travel requirements have resulted in many parents either not getting their child to Head Start at all because of transportation and time issues; or, if they are able to enroll, they and their parents have trouble meeting the Head Start child and parent participation requirements. These factors, in addition to low staff wages, high staff turnover, and lack of training, threaten to jeopardize program quality and participant impact.

Pediatricians can serve as referral agents for Head Start and can connect with local Head Start programs in a variety of ways:

- Designate a staff person to be the coordinator of interactions with Head Start.
- Arrange a meeting early in each school year between the office coordinator and the Head Start Health Services Coordinator.
- Have the designated staff member link the practice to Head Start with business cards and educational pamphlets. Consider formalizing a partnership.
- Become a member of the Health Services Advisory Committee, which is designed to improve services by connecting with the health community.
- Participate in the quarterly, mandated meeting of the Health Services Advisory Committee.
- Participate in the development of IFSPs or IEPs for children from the practice in Head Start.
- Consider arranging a field trip to different types of classrooms (regular education, blended, or

self-contained) for pediatric residents, medical students, and office staff.

- Volunteer to accept Head Start patients who do not have a medical home.

## THE PEDIATRICIAN'S ROLE

In addition to their critical role as health care providers to young children, pediatricians can participate in (and, in many instances, lead) community health improvement processes. The CDC is a good source for several resources that form the foundation for these processes. The June 2011 version of *Principles of Community Engagement* provides an excellent chart of the continuum of levels of respectively engaging with communities and a series of strategies for becoming involved ([www.atsdr.cdc.gov/communityengagement/pce\\_what.html](http://www.atsdr.cdc.gov/communityengagement/pce_what.html)). The *CDC Guide to Clinical Preventive Services* and *Guide to Community Preventive Services* provide evidence-based strategies vetted by the US Preventive Health Services Task Force that can be used competently both in the clinical and community settings.

The pediatrician can also be a leader in identifying the many evidence-based programs that, when invested in sufficiently and run effectively, are successful in removing roadblocks to children's health. Given the myriad of programs and interventions available, success is highly contingent on quality of implementation, evaluation, and accountability. When vetted interventions are managed well, scaled correctly, and held accountable for results, health effects can be maximized.

Pediatricians can serve as medical advisers to individual child care centers or members of state child care regulatory bodies. Pediatricians can also serve as child advocates, working with other stakeholders to develop and implement policies that promote the health of young children and their families and to protect them against adverse stressors. Most states have a pediatrician member of the AAP chapter serving as the state Chapter Child Care Contact (CCCC). Each CCCC is charged with mobilizing and sustaining efforts to improve the health and safety of children in child care and engage parents in discussions about quality care and their options. The CCCC also serves as a liaison between his or her state chapter and the national AAP regarding early care and education topics and initiatives. Pediatricians are encouraged to work with their CCCCCs to increase their involvement in child care activities. See [www.healthychildcare.org/cccc.html](http://www.healthychildcare.org/cccc.html) for more information.

## SUMMARY

A growing number of young children in the United States live in poverty—the most powerful social determinant of health. Pediatricians should be aware of public programs to mitigate the effects of poverty and its many associated toxic stressors that contribute to poor health outcomes. Chapter 79, *Children in Poverty* describes a number of these programs: Temporary Assistance for Needy Families, the Earned Income Tax Credit, Child Support, Child Care Subsidies, Supplemental Nutrition Assistance Program (Food

Stamps), and the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC). Other chapters of this text describe the critical strategies of prenatal care, safe birthing, care of depressed mothers, and care of special populations (children exposed to adverse childhood experiences, children new to the United States, adopted children, children of divorce, children in foster or kinship care, children in military families, and homeless children. Still other chapters focus on promoting the health of young children in the context of primary care. The current chapter expands on several community-based approaches to improving the health of young children: maternal, infant, and early childhood home visiting programs; medical-legal partnerships; initiatives to improve the health and safety of out-of-home child care; the Early Intervention program; and Head Start. Pediatricians can improve the health of young children by ensuring that children and families who can benefit from these programs receive them. Pediatricians can also be effective leaders of and participants in processes to improve the health of young children at the community, state, and national levels.

### TOOLS FOR PRACTICE

#### Community Advocacy and Coordination

- *Caring For Our Children: National Health and Safety Performance Standards; Guidelines for Early Care and Education Programs*, 3rd ed (e-book), American Academy of Pediatrics, American Public Health Association, National Resource Center for Health and Safety in Child Care and Early Education (cfoc.nrkids.org)
- *Center on the Social and Emotional Foundations of Early Learning* (Web site), Center on the Social and Emotional Foundations of Early Learning (csefel.vanderbilt.edu)
- *Healthy People 2020 Evidence Based Resources* (Web site), Healthy People ([www.healthypeople.gov/2020/tools-resources/Evidence-Based-Resources](http://www.healthypeople.gov/2020/tools-resources/Evidence-Based-Resources))
- *Healthy People 2020 Program Planning Guide* (Web page) Healthy People ([www.healthypeople.gov/2020/tools-and-resources/Program-Planning](http://www.healthypeople.gov/2020/tools-and-resources/Program-Planning))
- *Healthy People 2020 Count Data Resources* (Web page) Healthy People ([www.healthypeople.gov/2020/county-data-resources](http://www.healthypeople.gov/2020/county-data-resources))
- *State Licensing and Regulation Information* (Web page), National Resource Center for Health and Safety in Child Care and Early Education (nrkids.org/index.cfm/resources/state-licensing-and-regulation-information)

#### Engaging Patient and Family

- *Child Care Aware Parent and Family Resources* (Web page), Child Care Aware ([childcareaware.org/parents-and-guardians/resources](http://childcareaware.org/parents-and-guardians/resources))
- *Community Health Online Resource Center* (handouts), Centers for Disease Control and Prevention (nccd.cdc.gov/DCH\_CHORC)
- *Head Start and Early Head Start* (Web page), US Department of Health and Human Services (eclkc.ohs.acf.hhs.gov/hs/hs/about)

- *National Center for Children in Poverty Data Tools* (fact sheet), National Center for Children in Poverty ([nccp.org/tools](http://nccp.org/tools))

### AAP POLICY

- American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health, Committee on Early Childhood, Adoption, and Dependent Care, and Section on Developmental and Behavioral Pediatrics. Early childhood adversity, toxic stress, and the role of the pediatrician: translating developmental science into lifelong health. *Pediatrics*. 2012;129(1):e224–e231 ([pediatrics.aappublications.org/content/129/1/e224](http://pediatrics.aappublications.org/content/129/1/e224))
- American Academy of Pediatrics Council on Community Pediatrics. Community pediatrics: navigating the intersection of medicine, public health, and social determinants of children's health. *Pediatrics*. 2013;131(3):623–628 ([pediatrics.aappublications.org/content/131/3/623](http://pediatrics.aappublications.org/content/131/3/623))

### SUGGESTED READINGS

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## Chapter 23

# PROMOTING THE HEALTH OF SCHOOL-AGED CHILDREN

Barbara L. Frankowski, MD, MPH; Howard Taras, MD

*It takes a village to raise a child.*

AFRICAN PROVERB

In 1996, then–First Lady Hillary Rodham Clinton published a book titled *It Takes a Village: And Other Lessons Children Teach Us*, thus popularizing this proverb. In this book, Clinton presents her vision for the children of America, focusing on the effect individuals and groups outside the family have, for better or worse, on a child's well-being, and advocating for a society that meets all of a child's needs. In 1997, America's Promise Alliance ([www.americaspromise.org](http://www.americaspromise.org)) was founded, with Retired General Colin L. Powell as the Chairman. The Alliance is committed to seeing that all children have access to the fundamental resources they need to succeed—the Five Promises: *Caring adults* in their lives, as parents, mentors, tutors, and coaches; *safe places* with structured activities in



which to learn and grow; a *healthy start* and healthy future; an *effective education* that equips them with marketable skills; and an *opportunity to give back* to their communities through their own service. Children who receive at least 4 of the Five Promises are much more likely than those who experience none or only one Promise to succeed academically, socially, and civically. They are more likely to avoid violence, contribute to their communities, and achieve high grades in school. Receiving at least 4 of the Five Promises also seems to mitigate gaps across racial and economic boundaries. To experience the full power of the Promises, young people must experience these critical supports throughout their lives—in their families, at schools, and out in their communities.

Pediatricians support children and families in achieving these goals. *Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents*, 3rd edition, gives priority to the discussion of school, development and mental health, nutrition and physical activity, oral health, and safety at every visit. For the school-age child, all these discussions need to include the community in which the child is growing. How does the community contribute to a child's physical health and safety? Are there sidewalks, playgrounds with safe equipment, after-school programs, and easy access to healthy food? How does the community contribute to a child's development and social/emotional health? Are there opportunities for social interactions (sports, boys and girls clubs, faith-based organizations, social services)? Pediatricians need to be aware of the context beyond the family that is supporting the child. They can also be advocates for improvement of their communities. For school-aged children, the most influential community setting is the school. Since 98% of school-aged children attend public, charter, or private school, it is not surprising that schools have an enormous influence, both positive and negative, on the health and well-being of our nation's children. The nature and quality of school health programs are germane to primary care physicians' success with disease management as well as illness and injury prevention. Moreover, pediatricians can influence the nature and quality of school health programs. Pediatricians need familiarity with how schools work, knowledge of how to work with schools on behalf of their patients, and knowledge of advocacy techniques that help improve school health programs for all students in a community to influence the health of their own school-aged patients and of all youth in a community.

## UNDERSTANDING COMPREHENSIVE SCHOOL HEALTH

One of the most widely used models for school health goals in the United States is the Coordinated School Health Program, a model originating in and endorsed by the Division of Adolescent and School Health at the Centers for Disease Control and Prevention (CDC). The model recognizes 8 major components to any coordinated school health program. One example of the logic that makes the term "coordinated" applicable to a school health program is this—it is counterproductive

to teach students about proper nutrition in the classroom if they are offered few healthy choices in the cafeteria. It is equally nonsensical to encourage school counselors and other staff to help students with emotional issues reach appropriate mental health services if staff members themselves do not feel supported by school personnel policies for their own mental health needs. Coordination among all 8 components of a school health program strengthens each of them. The 8 components of a coordinated school health program are described below in terms of what is recommended for schools and how a primary care physician can relate to each component. Further details of each component are available in 2 publications of the American Academy of Pediatrics (AAP)—*Health, Mental Health and Safety Guidelines for Schools*, and the sixth edition of *School Health Policy & Practice*.

### 1. Health and Safety Education

Under ideal circumstances, health education would be part of any school district's core academic curriculum and have the same budgetary and scheduling priority as literacy, mathematics, and other traditional subjects. Not surprisingly, such a situation is highly atypical. Among physicians and other providers of primary care for school-aged children who recognize this predicament, there are some who try to correct the situation by volunteering to teach a health class (eg, a nutrition class or a class on prevention of drug abuse). While this is well-intended, often enjoyed by students and lecturers, and possibly successful at increasing short-term knowledge of healthful practices, such interventions are unlikely to change student health behaviors. Schools must be encouraged to adopt health and safety curricula that have demonstrated effectiveness in changing student behavior. Research has shown that, to be effective, a curriculum should be planned and sequential (ie, each class builds upon skills and knowledge taught in a previous class), be interactive, have skills-based instruction, optimally involve the family, and be consistent with established health education standards. While classroom teachers may appropriately teach health education in elementary schools, certified health education teachers are necessary in secondary schools because of the complexity of teaching methodology required at this stage, as well as the complexity of the content. Ideally, health education is integrated with other content areas.

Content areas over the course of the 12 years should include prevention of tobacco, alcohol, and other drug use; growth, development, sexuality, and family life; personal and oral health; injury prevention and safety; violence prevention; nutrition; physical activity; Internet safety; and use of social media. The emphasis on some aspects of health over others should vary with a community's unique needs (eg, local injury rates, pregnancy rates, or nature of drug abuse). Pediatricians should consider ways of supporting and encouraging schools to enhance their health education programs and services. Collaboration and integration with community-wide health promotion efforts are helpful, because schools cannot do the job alone. Within the school, attempts should be made to relate all aspects of school life with the health program. Health education



needs to be sequential and developmentally appropriate. Physicians should advocate that schools have health educators credentialed with the National Commission on Health Education (CHES) who can guide them on current methods of teaching various health content areas.

## 2. Physical Education and Activity

Physical education should be provided daily, with no substitutions allowed for participation in other courses or activities, and should meet national standards. There should be ample resources for the entire class in physical education so that skill building and aerobic fitness are optimized. Physical educators should be appropriately trained. Experiences should be designed to help students acquire skills and knowledge that will help them adopt and maintain physically active lifestyles and enjoy the numerous benefits of being physically active. Recess, active play during and after school, sports, and other activities should be provided as well. Emphasis should be placed on participation, not on winning. Safety should be among the educational goals of the program, with safety gear provided as appropriate.

Most pediatricians interact with physical education programs through their role in preparticipation physical examinations for sports and by providing medical cause for exemption from, and resumption of, physical activity in school. Accordingly, it is important for physicians to recognize that schools must make physical education available to all children, including those with special needs (eg, severe asthma, physical or emotional disabilities, and developmental delays), either through modifications of a regular physical education class or through an adaptive physical education program. Written excuses from medical offices that exempt children from physical education should be reserved for severe and temporary conditions, such as children on chemotherapy. When possible, pediatricians should work with the school to find an appropriate physical education curriculum for patients with chronic health conditions. If pediatricians find that school athletic departments are unwittingly discouraging some students from participating in a sport because of an overemphasis on winning as opposed to gaining physical and team-building skills, this is an opportunity to advocate for change.

## 3. Health and Mental Health Services

Historically, school health was initiated to improve health and sanitary conditions in urban schools. A recent example of school involvement in public health is the 2009 H1N1 influenza outbreak, where several school nurses played key roles in identifying the outbreak in their communities, and many public health departments used schools as sites to efficiently deliver vaccines to large numbers of children.

Today, each school district must provide students with basic first aid services, mandated health screens (eg, vision and hearing screening), immunization monitoring, and medical services that are necessary to safely accommodate a student with special medical needs in a school setting (eg, gastric tube feeding; observation and suctioning for a student with a

tracheostomy; administration of medications during the school day). The school health service must also be prepared to offer immediate medical attention in crisis situations (eg, episodes of asthma or seizures, life-threatening situations affecting medically fragile children, eruption of violence, suicide, and community disasters). Trained personnel, standing policies and procedures, and key decision makers need to be identified. Most schools have ready access to emergency 911 systems.

Beyond these basic services, students often require a much broader range of health and mental health services to succeed in school. The recent proliferation of school-based and school-linked health services is a direct outgrowth of educational, health, and welfare reform movements. School-based and school-linked health services develop most often in urban settings and target disadvantaged populations. Typically, private-public partnerships coordinate a wide range of human services for the children and, often, their families.

The most important health service a school can provide is to identify student health problems and make appropriate referrals. The completeness and effectiveness of problem identification and solutions depend to a large degree on the numbers and quality of school health personnel. The more trained and sophisticated the personnel are, the more they can be expected to achieve. Differentiated staffing with appropriate use of aides, nurses, nurse practitioners, and physician consultant backup is likely to be the most cost-effective way of responding to the identified needs of a population. Students who make frequent visits to the school health room, underachieving students, or students with frequent problem behaviors are among those who may need attention.

For school health programs to be effective, linkages must be formed between the school and the source of primary health care for the child. All pediatricians can potentially benefit from the ability to link their primary care services to schools for treatment of minor conditions, follow-up and screening, medication administration, immunization delivery systems, monitoring of school absenteeism, and monitoring of achievement for selected patients. Major difficulties arise when no regular source of care or insurance coverage exists. Primary care physicians should examine ways to use school-based personnel to provide cost-effective services at school sites when it is deemed desirable for a given community. Although a school-based clinic could become a medical home for a family without other resources in a community, it is preferable to develop additional resources so that each family has an ongoing medical home that would be available over the long term. All school-based services should be linked to 24-hour, 7-days-per-week backup resources that extend beyond the school day and the school year. Providers of managed care need to examine the potential benefits of linking health services and education to families through schools. Public schools are obliged to meet the health needs of students in school if they have chronic health conditions and when health accommodations are necessary to allow these students to fully access their education. (This is outlined in Section 504 of the Rehabilitation Act of 1973.)

#### 4. Nutrition and Food Services

Schools should provide foods prepared according to specifications that guarantee its safety, composed of competitively priced selections that are low in fat and simple sugars, and served in an appetizing way that appeals to their ethnic student populations. Foods should never be used as a reward or punishment in school. This does occur, with staff providing a pizza party for a classroom that completed an assignment, for example. The National School Meal Program, sponsored by the United States Department of Agriculture (USDA), provides free or reduced-cost lunches to low-income students and is available in most public schools. In some schools, breakfasts and snacks are also provided under the program. Some districts, recognizing that many families rely on these programs to prevent child hunger, should be encouraged to arrange for summer meal programs or collaborate with food banks and other community-based organizations during weekends and holidays. The standards for foods that fall under the national lunch program are clearly delineated. Unfortunately, many students who are eligible for these meals do not eat them for various reasons (eg, long cafeteria lines, stigmatization, and preference for items sold at schools to compete with subsidized foods). Foods sold in school canteens, vending machines, and other venues can constitute healthy nutritional choices, but many schools earn a profit from sales of high-fat snacks and carbonated high-sugar soft drinks. Colorful packaging and prominent displays of unhealthy foods can distract students from healthier choices.

In addition to educating patients and their parents, pediatricians can advocate on behalf of school-aged children. In 2004, when the federal government reauthorized the child nutrition program (which covers the national school lunch program, the Special Supplemental Nutrition Program for Women, Infants, and Children [WIC], and others), the revised public law included a clause requiring each school or school district with these programs to develop a local wellness policy that addresses childhood obesity. Schools must comply with this law if they participate in these federal school lunch or breakfast programs. They must set goals (and take action to meet goals) for nutrition education, physical activity, and other school-based activities that promote student wellness. Schools must involve a broad group of community members to set goals and oversee efforts to meet these goals, often in the form of a school health council (also referred to as a school wellness council). Pediatricians can make excellent reference sources and enthusiastic advocates for these councils. Policies of the AAP (for example, on soft drinks in schools) can provide helpful guidance.

#### 5. Physical Environment and Transportation

Heating, ventilation, and air conditioning systems can easily fall into disrepair when funds are not set aside for adequate maintenance personnel or supplies. Health ramifications occur, but are not always obvious to students or their parents. Accumulation of mold and dust, attraction of vermin (cockroaches, rodents), and decaying organic materials can be causes of health hazards that first affect those with specific allergies,

but eventually cause health problems for a broad population of students and staff. To protect the school environment, schools should use integrated pest management strategies when they remediate pest problems. These are well described by the US Environmental Protection Agency. It is important for pediatricians to be aware of the general condition of schools in their area and to look for patterns of avoidable illness or symptoms. Also related to the physical environment are those safety precautions that schools must take in designated play areas (eg, for recess) and in classes for science, physical education, and industrial arts. Traffic safety around schools (sidewalks, crosswalks, traffic lights, and monitored intersections), availability of racks to lock bicycles, and places at school to store helmets and other safety gear might seem on the surface to be important primarily for student safety; however, these factors are equally important for encouraging children to be more physically active, because they remove barriers to students' walking and riding to and from school.

#### 6. Social Environment

Physicians must realize that patients who experience home or community violence, poverty, and hunger not only have difficulty with their own focus on education, but may change the social climate of their schools because of their experiences. Schools must have violence prevention strategies, suicide prevention strategies, actions against bullying, and policies on student discipline. Clearly written and well-known rules can contribute to a social environment that makes staff and students feel safe. Teaching staff must learn to recognize signs of student distress and know how to direct affected children to staff resources within the school (eg, a school counselor, psychologist, nurse, or site administrator trained for that purpose), who, in turn, must feel comfortable with initial assessment and working with pediatricians. Teachers should be as knowledgeable as possible about principles of child development. Teaching strategies need to be matched to the developmental and cognitive capabilities of children. Research has shown that systems that espouse noncoercive discipline and high academic expectations have the best educational outcomes.

There is always potential for spillover of neighborhood violence onto school campuses. Students who carry a weapon, possess an illicit drug, or threaten violence typically fall under a school's "zero-tolerance" rule, and are promptly suspended or expelled. If schools do not routinely involve or inform students' physicians about their suspensions or expulsions, members of the health community cannot advocate for change. Often, aberrant behaviors have health ramifications and/or health etiologies. However, many of these students with behavioral issues have unrecognized health, mental health, or family-dynamic problems that not only underlie their school behavior but are amenable to therapeutic interventions. School policies must be geared towards correcting problems, not solely towards punishing students.

Drug screening for students who want to enroll in extracurricular activities (eg, chess club, football team) became legal with a US Supreme Court decision in

2002. Although screening policies may be well intended, school districts and pediatricians must consider the ramifications of such screening. Will screening discourage students from joining extracurricular activities if they have experimented with illicit substances? Can this lead to fewer healthy connections to school and thus exacerbate rather than ameliorate substance abuse? Is there a physician with expertise in limitations of drug testing supervising any school drug testing program? Has any research found screening to be a deterrent? Has screening changed the social atmosphere of a school, and if so, for better or worse? Are false-positive results possible, and if so, what will the effect of a false-positive result be on the student and family until it is demonstrated to be false? As with any proposed screening program performed in the school setting (eg, vision screening, cholesterol screening), clear benefits of the screen must be established, and most importantly, potential harm must be known and measured against potential benefits.

### 7. Health Promotion for Staff

Employees' mental health and physical health are integrated with student health. School employees who exercise often and eat well are more likely to enthusiastically encourage others to do so, including their students. Employees who have taken advantage of wellness programs offered through their school district's insurance or a workplace program (eg, smoking cessation, stress management) may be more likely to recognize the importance of a healthy lifestyle for students.

### 8. Family and Community Involvement

Success in achieving school health goals depends largely on how well these goals are communicated with and endorsed by parents, physicians, and health and social agencies in the school's communities.

Pediatric primary and secondary care providers need to take an active role in the development and implementation of school policies. Busy pediatricians can do so by annually asking the school-aged patient (and then documenting in the patient's record) the name of the child's school. This allows for interaction, should it become necessary. Eliciting patient histories from parents and patients, as well as from school personnel, is essential particularly when there is a behavioral problem or a learning problem. This is important because children may act differently at home and at school (itself an important piece of diagnostic information), because parents may have a perspective different from other adults in the child's life, and because schools often need to become part of a management plan. Pediatricians and specialists often need to interact with schools on behalf of children with special health care or learning needs. The pediatrician may be effective not only as an advocate for a particular patient, but also for better school policies and practices that affect all students in that community.

Integrated service systems are essentially "one-stop shopping" for resources. They are also known in some communities as "family resource centers." Successful models in many communities have streamlined services and made social, health, and family support

services more cost effective and user friendly. Often these services are placed in or near a school and include multiple human services in a single, easily accessible place. Health services often rank high among perceived needs in these systems.

## KNOWLEDGE REQUIRED FOR PATIENT ADVOCACY AND CONSULTATION TO SCHOOLS

Many large school districts have district physicians. These are typically pediatricians, family doctors, and specialists in adolescent medicine. Districts may also employ nurse practitioners to work with these physicians. In some states, such as Maine, school districts are mandated to have such consultants. It takes time for physicians to acquire experience that is pertinent to schools. It takes repeated interaction before physicians learn to perform these tasks well and attain a consistently high quality of service delivery. In the best of these arrangements, physicians provide numerous services that, over time, become indispensable and cost-saving to schools.

The role of the school physician includes communicating on behalf of the school or school district to students' own physicians when the schools need information and assistance to address complex health and safety problems. School physicians should help schools facilitate ongoing communication between the school health office and physicians, assist schools with development and interpretation of school health-related policies (eg, exclusion policies for illness, nutrition policies), be on call for school nurses who have questions, and design and update protocols for medical procedures delivered in school (eg, gastric-tube feeding, administration of rectal diazepam).

Pediatricians may also serve as directors of comprehensive school-based or school-linked health programs. In these roles, they should have experience in planning, managing, and evaluating systems of care; be knowledgeable about funding and programmatic requirements in both health and education; and be able to establish quality assurance programs. These skills will build on a solid clinical expertise in child and youth health issues, as will firsthand knowledge and expertise with schools and educational systems. Guidelines for physicians as school consultants have been suggested (Table 23-1). Box 23-1, Box 23-2, and Box 23-3 illustrate examples of activities and suggested guidelines and approaches to be used by primary or secondary health care providers interested in working with local schools.

To assume any role in a school, a physician requires knowledge of the educational system and laws that protect students' rights in the health system. In the United States, the Individuals with Disabilities Education Act (IDEA) addresses children with special educational needs. Often, there are health needs associated with special education (eg, children with cerebral palsy often have severe developmental delay). A girl with a chronic illness, such as cancer, may not be able to learn to the extent of her full ability if she is expected to learn within the schedule of regular classroom instruction. These are examples of how

**Table 23-1** Examples of a Physician's Role in Schools

CLINICAL ISSUE OR PROBLEM	EXAMPLES OF PHYSICIAN'S ACTIVITIES AS CHILD'S PRIMARY CARE PROVIDER	EXAMPLES OF PHYSICIAN'S ACTIVITIES AS CONSULTANT TO SCHOOL OR SCHOOL SYSTEM
Learning disability	<ol style="list-style-type: none"> <li>1. Requests teacher's account of child's learning and behavior, as well as results of individualized testing</li> <li>2. Shares results of medical evaluation of child with the school</li> <li>3. Works cooperatively with school personnel and parents to develop educational and behavioral management plan for child (may include school visit)</li> <li>4. Sets up mechanism for follow-up on behavioral and educational progress of child</li> </ol>	<ol style="list-style-type: none"> <li>1. Serves on district committee to accomplish biannual review of progress of students with disabilities</li> <li>2. Assists in setting up mechanism for providing follow-up behavioral and academic information to physicians who have placed students on psychoactive medication</li> <li>3. Provides in-service session for classroom teachers on new concepts in attention-deficit/hyperactivity disorder</li> <li>4. Advises school board on need for movement training for children who have learning disabilities</li> </ol>
Asthma (school-age)	<ol style="list-style-type: none"> <li>1. Requests school information on absenteeism, communicates with school nurse; obtains evidence of nonparticipation in physical education activities</li> <li>2. Sets up mechanism for regular administration of bronchodilator at school</li> <li>3. Sets up follow-up mechanism for continued monitoring of school attendance, medication-taking compliance, and participation in appropriate physical activities</li> </ol>	<ol style="list-style-type: none"> <li>1. Reviews absenteeism data to identify groups of students who have excessive absences that might be amenable to some intervention</li> <li>2. Assists curriculum director and nurse in developing educational programs for children who have asthma</li> <li>3. Helps publicize program and communicates directly with students; solicits primary care physicians' input and support for the educational program by reinforcing concepts in their patient visits</li> </ol>

Adapted from Nader P. A pediatrician's primer for school health activities. *Pediatr Rev.* 1982;4:82-92.

### **BOX 23-1** Guidelines for the Physician as Child's Primary Care Provider

1. Always obtain permission from the parents to communicate with the school, and keep them informed of their child's progress.
2. Approach all school personnel as co-professionals who have skills and interests that complement your expertise and who can provide you with information you do not have. Recognize their interest in helping the children in their charge.
3. When contacting a school for the first time, contact the principal initially.
4. When calling a teacher, find out the best time for the teacher to talk.
5. Encourage direct school-parent and parent-school communication.
6. Be willing to attend a school meeting, if necessary, to share information and develop treatment plans.
7. Listen carefully to ascertain the school personnel's main concerns and questions, and attempt to respond to them.

### **BOX 23-2** Guidelines for the Physician as School Health Consultant

1. Distinguish between the roles of a primary care provider and those of a school consultant.
2. Become aware of laws and regulations affecting schools, including those related to school finance, education for children with disabilities, bilingual education, and other educational mandates.
3. Become knowledgeable about the formal and informal decision-making processes in schools regarding regular and special education of children (including health education).
4. Be a liaison to the rest of the medical community.
5. Establish a contract with the school that defines mutually agreed-on expectations and objectives.
6. Provide a regular report on your consultation to the school district.
7. Attempt to establish relationships at all levels and departments of the school system to permit access from the board and superintendent level to that of the classroom teacher.
8. Become aware of group process dynamics and decision making in groups.



### BOX 23-3 A Checklist for Working With Schools

#### STATE POLICIES AND PROGRAMS

- Have you familiarized yourself with state policies and programs related to comprehensive school health programs?
- Have you checked to see whether health outcome objectives exist, and, if so, how they are assessed?

#### LOCAL POLICIES AND PROGRAMS

- Have you familiarized yourself with district policies and programs related to comprehensive school health programs?
- Have you determined what health curriculum, textbooks, and materials are actually being used in the schools?
- Have you ascertained the following parameters?
  - Policies and programs that need strengthening
  - Serious gaps or deficits
  - Opportunities for health professionals to contribute meaningfully

#### INFLUENCING LOCAL POLICIES AND PROGRAMS

- Do you know how the local education system works? Who makes decisions? Who has authority? Who actually does the work?
- Do you know who supports (and who is concerned with) various aspects of comprehensive school health programs and their reasons for doing so?
- Have you contacted appropriate officials about your ideas and obtained their support for working with schools?
- Have you refined your ideas in consultation with key parties—teachers, administrators, school health professionals, public health professionals, school board members, and parents?
- Have you provided for periodic progress reports and changed direction or emphasis based on their results?

From National Association of State Boards of Education. *How Schools Work and How to Work With Schools*. Alexandria, VA: The Association; 1989.

health problems may affect the need for special education services. The school must address both the educational and the health needs in the child's written individualized education program (IEP). Laws require schools to place students in the least restrictive environment. Sometimes this means bringing in 1:1 nurse coverage in the classroom for a student (eg, when the child is tracheostomy dependent and requires frequent suctioning and continuous observation). In other circumstances, a child's specialized health needs require training of non-health staff who are already in the school or classroom. It is important for physicians to describe the child's health need (eg, "my patient needs someone trained to recognize a seizure, record the incident, and administer rectal diazepam if the seizure lasts longer than 5 minutes") and refrain from prescribing how the school should meet this need (eg, avoid saying "my patient needs a full-time 5-day-a-week nurse" or "my patient needs

a 1:1 aid"). Schools need to be able to choose from an assortment of safe solutions. Working with the school in a cooperative manner is the best way to meet the student's needs without compromising the student's safety and without unnecessarily compromising the school's budget.

Section 504 of the Rehabilitation Act of 1973 is another law with which physicians must be familiar. To receive special services under Section 504, a student does not need to have any special learning need. Schools must provide any service within reason if that service is required to safely accommodate a student's disabling condition. When there is more than 1 possible way to accommodate a student's educational needs, schools are permitted to make that choice. Unlike IDEA laws addressing special education, disabling conditions under Section 504 can be purely medical or physical, and are not required to include a problem that affects learning. However, the condition must be severe enough to "substantially limit a major life activity." A concrete example of an accommodation that a school must make is to build a ramp if necessary to accommodate a student with muscular dystrophy who is confined to a wheelchair. But Section 504 also applies to less concrete forms of access to education. Consider the example of a young student with type 1 diabetes who requires someone trained to assist him in testing and interpreting his serum glucose levels during the school day. Without this service, the student could not safely access his education. A "504 plan" is an individualized plan that describes what the school will do for a specific student to ensure access to the student's education. It describes the actions a school will take to override the substantial limitation in a student's major life activity. In this example, the district may relocate this child to a nearby school that has a 5-day-a-week nurse. Alternatively, the district may choose to keep the child in the originally assigned school and teach lay staff members to recognize hypoglycemia and respond to it (ie, test blood sugar, administer oral sucrose, and even inject glucagon). The district can arrange for a licensed nurse to come to the school each day at lunch hour to administer insulin. Many students may require medications, including psychoactive drugs, to keep them in school and "on task," but most will not require a 504 plan. The physician must master ways to ensure medication compliance in school. Standardized procedures for medication administration in schools are available.

It is advisable for a pediatrician to refrain from prescribing special services for a patient after having communicated with only the student and parent. Too often, parents encourage doctors to write notes to schools, often scribbled on prescription pads, that demand that a school provide a student with "door-to-door transportation," or an "air-conditioned classroom for heat intolerance," when these services are convenient but not medically necessary. Interaction with a school representative (eg, a school nurse or principal) can help the physician find an appropriate intervention without unnecessarily taxing the school budget and jeopardizing other worthwhile school programs. For more information on these laws, the US Department of Education Web site provides

continuously updated resources. For IDEA, go to [www.ed.gov/offices/OSERS/Policy/IDEA/index.html](http://www.ed.gov/offices/OSERS/Policy/IDEA/index.html). For Section 504, go to [www.ed.gov/about/offices/list/ocr/504faq.html](http://www.ed.gov/about/offices/list/ocr/504faq.html).

## NEIGHBORHOODS: WHATEVER IT TAKES

Schools need to work together with other neighborhood groups and institutions to support the optimal growth of children. In the early 1990s, Geoffrey Canada started the Harlem Children's Zone, a nonprofit organization for poverty-stricken children and families living in Harlem, NY. The 2 fundamental principles of the organization were to help children as early in their lives as possible and to create a critical mass of adults around them who understand what it takes to help children succeed. Described in the book *Whatever It Takes*, by Paul Tough, the Harlem Children's Zone provides free support for the children and families in the form of parenting workshops; a preschool program; public charter schools; health clinics and community centers for children and adults during after-school, weekend, and summer hours; youth violence prevention efforts; and social services, such as a foster-care prevention service. The organization's goal is to break the cycle of generational poverty for the thousands of children and families it serves, and to keep children on track through college and into the job market.

In 2010, the Obama administration authorized the establishment of 20 "Promise Neighborhoods" to be modeled after the Harlem Children's Zone, aimed at providing this full network of services to entire neighborhoods from birth to college to career. Promise Neighborhoods, established under the legislative authority of the Fund for the Improvement of Education Program, will provide funding to support eligible entities, including nonprofit organizations, which may include faith-based nonprofit organizations and institutions of higher education.

## CONCLUSION

It is important for pediatricians to be aware of and involved in all aspects of the community in which children are growing. Most importantly, pediatricians can help school health programs ensure a safe, healthy, and nurturing environment for the children they serve. Schools are a logical place to identify children in need of health and mental health referrals, as well as a good environment in which to provide preventive health care and education. Pediatricians who become integral parts of these systems can play a major role in improving health and educational outcomes for children in their communities.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *Adolescent & School Health* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/healthyyouth/schoolhealth/index.htm](http://www.cdc.gov/healthyyouth/schoolhealth/index.htm))
- *Building the Legacy: IDEA 2004* (Web page), US Department of Education ([idea.ed.gov](http://idea.ed.gov))

- *Connected Kids Clinical Guide* (booklet), American Academy of Pediatrics ([www2.aap.org/connectedkids/ClinicalGuide.pdf](http://www2.aap.org/connectedkids/ClinicalGuide.pdf))
- *Health, Mental Health and Safety Guidelines for Schools* (Web site), American Academy of Pediatrics ([www.nationalguidelines.org](http://www.nationalguidelines.org))
- *NACCHO Toolbox* (Web page), National Association of County and City Health Officials ([www.naccho.org/toolbox](http://www.naccho.org/toolbox))
- *The National School Lunch Program (NSLP)* (Web page), US Department of Agriculture ([www.fns.usda.gov/nslp/national-school-lunch-program-nslp](http://www.fns.usda.gov/nslp/national-school-lunch-program-nslp))
- *State School and Health Resources* (Web page), American Academy of Pediatrics ([www2.aap.org/sections/schoolhealth/contactmap/section\\_contacts.cfm.htm](http://www2.aap.org/sections/schoolhealth/contactmap/section_contacts.cfm.htm))

### Engaging Patient and Family

- *Frequently Asked Questions About Section 504 and the Education of Children With Disabilities* (fact sheet), US Department of Education ([www.ed.gov/about/offices/list/ocr/504faq.html](http://www.ed.gov/about/offices/list/ocr/504faq.html))

### Practice Management

- *Frequently Asked Questions About Section 504 and the Education of Children with Disabilities* (fact sheet), US Department of Education ([www.ed.gov/about/offices/list/ocr/504faq.html](http://www.ed.gov/about/offices/list/ocr/504faq.html))
- *Building the Legacy: IDEA 2004* (Web page), US Department of Education ([idea.ed.gov](http://idea.ed.gov))

## AAP POLICY

- American Academy of Pediatrics Committee on Children With Disabilities. The pediatrician's role in development and implementation of an individual education plan (IEP) and/or an individual family service plan (IFSP). *Pediatrics*. 1999;104(1):124–127 ([pediatrics.aappublications.org/content/104/1/124](http://pediatrics.aappublications.org/content/104/1/124))
- American Academy of Pediatrics Committee on Injury, Violence, and Poison Prevention and Council on School Health. School transportation safety. *Pediatrics*. 2007;120(1):213–220. Reaffirmed October 2011 ([pediatrics.aappublications.org/content/120/1/213](http://pediatrics.aappublications.org/content/120/1/213))
- American Academy of Pediatrics Committee on School Health. Policy Statement—Guidance for the administration of medication in school. *Pediatrics*. 2009;124(4):1244–1251. Reaffirmed February 2013 ([pediatrics.aappublications.org/content/124/4/1244](http://pediatrics.aappublications.org/content/124/4/1244))
- American Academy of Pediatrics Council on School Health. Out-of-school suspension and expulsion. *Pediatrics*. 2013;131(3):e1000–e1007 ([pediatrics.aappublications.org/content/131/3/e1000](http://pediatrics.aappublications.org/content/131/3/e1000))
- American Academy of Pediatrics Committee on School Health. School-based mental health services. *Pediatrics*. 2004;113(6):1839–1845. Reaffirmed May 2009 ([pediatrics.aappublications.org/content/113/6/1839](http://pediatrics.aappublications.org/content/113/6/1839))
- American Academy of Pediatrics Council on School Health. School-based health centers and pediatric practice. *Pediatrics*. 2012;129(2):387–393 ([pediatrics.aappublications.org/content/129/2/387](http://pediatrics.aappublications.org/content/129/2/387))
- American Academy of Pediatrics Council on School Health and Committee on Nutrition. Snacks, sweetened beverages, added sugars, and schools. *Pediatrics*. 2015;135(3):575–583 ([pediatrics.aappublications.org/content/135/3/575](http://pediatrics.aappublications.org/content/135/3/575))
- American Academy of Pediatrics Council on School Health. Medical emergencies occurring at school. *Pediatrics*.

2008;122(4):887–894. Reaffirmed September 2011 ([pediatrics.aappublications.org/content/122/4/887](http://pediatrics.aappublications.org/content/122/4/887))

American Academy of Pediatrics Council on School Health. Role of the school nurse in providing school health services. *Pediatrics*. 2008;121(50):1052–1056 ([pediatrics.aappublications.org/content/121/5/1052](http://pediatrics.aappublications.org/content/121/5/1052))

American Academy of Pediatrics Council on School Health. The crucial role of recess in school. *Pediatrics*. 2013;131(1):183–188 ([pediatrics.aappublications.org/content/131/1/183](http://pediatrics.aappublications.org/content/131/1/183))

American Academy of Pediatrics Council on School Health. Role of the school physician. *Pediatrics*. 2013;131(1):178–182 ([pediatrics.aappublications.org/content/131/1/178](http://pediatrics.aappublications.org/content/131/1/178))

American Academy of Pediatrics Council on School Health and Committee on Substance Abuse. The role of schools in combating illicit substance abuse. *Pediatrics*. 2007;120(6):1379–1384 ([pediatrics.aappublications.org/content/120/6/1379](http://pediatrics.aappublications.org/content/120/6/1379))

## Chapter 24

# PROMOTING THE HEALTH OF ADOLESCENTS

Breana Welch Holmes, MD; Paula M. Duncan, MD

## INTRODUCTION

Adolescence presents unique challenges for health promotion in communities. To promote healthy outcomes for youth and deliver high-quality preventive and treatment services for adolescents, pediatricians must work with community organizations and service providers in a community-based system of care. The role of families and schools as the primary community of children is discussed in Chapter 14, Pediatric History: Assessing the Social Environment. As adolescents develop autonomy and explore new behaviors, they become involved in the larger community.

## FRAMEWORKS FOR HEALTHY ADOLESCENT DEVELOPMENT

Protective factors are individual or environmental characteristics, conditions, or behaviors that reduce the effects of stressful life events, increase an individual's ability to avoid risks or hazards, and promote social and emotional competence to thrive in all aspects of life now and in the future. One of these factors is resilience, the ability to cope with and adapt to change. Being resilient allows children and youth to overcome difficulties in their lives.

In the 1990s, researchers developed a framework of developmental assets—the strengths and resources that promote positive development in adolescents as they transition from childhood. The Search Institute, a social science research group, identified 40 positive factors that promote healthy development in young people. A greater number of assets in the lives of adolescents correlates with fewer risk-taking behaviors.

Pediatricians can have a positive effect on youth development by helping to create opportunities for all

youth to feel connected, learn to make good decisions, help others, and develop skills such as managing stress and taking responsibility for their own behaviors. The components of healthy adolescent development can be characterized according to 3 prominent frameworks: developmental tasks, Circle of Courage, and the Seven Cs.

## Developmental Tasks

*Bright Futures*, the 2008 Preventive Services Guidelines, adopted the Association of Maternal and Child Health Programs framework to describe the 7 developmental tasks of adolescence (Box 24-1).

## Circle of Courage

Another way to describe the opportunities youth need to thrive is the Circle of Courage, a framework used by Brendtro and colleagues, who identified generosity, independent decision making, mastery, and belonging as essential to a healthy adolescence. Ideally, the activities adolescents pursue at the community level would provide opportunities to develop these qualities.

## Seven Cs

Lerner and Pittman's work has identified 5 Cs (competence, connection, contribution, character, and confidence) as key components of a positive youth development framework, and Lerner tested them through his 4H study work. Based on his work with youth, Ginsburg has added coping and control to the original five.

In his book *Reaching Teens*, Ginsburg describes a strengths-based approach and core principle. He also describes “wisdom from model” strengths-based programs that work with youth who are traditionally labeled “at risk.”

## Approaches for Assessing the Adolescent Environment

Youth need opportunities to grow in each of the areas outlined above (eg, opportunities to help others, practice independent decision making, and establish

### BOX 24-1 Seven Developmental Tasks of Adolescence

- Healthy behaviors
- Caring and supportive relationships
- Physical, cognitive, emotional, social, and moral competencies
- Self-confidence, hopefulness, and well-being
- Resilience when confronted with life stressors
- Responsible and independent decision making
- Positive engagement in the life of the community

From Hagan JF, Shaw JS, Duncan P. *Bright Futures Guidelines for Health Supervision of Infants, Children, and Adolescents*. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2008 and Fine A, Large R. *A Conceptual Framework for Adolescent Health: A Collaborative Project of the Association of Maternal and Child Health Programs and the State Adolescent Health Coordinators Network*. Washington, DC: Association of Maternal and Child Health Programs; 2005.

relationships with peers). Families often provide a setting for this growth and development, but by adolescence, school activities, community organizations, faith-based groups, and sports teams often supply youth with development opportunities. The inventory in Box 24-2 can help pediatricians assess their community's programs and services for adolescents.

Pediatricians who work toward positive youth development in their communities should also be familiar with the information in Table 24-1.

Klein and colleagues have identified and tested an inventory tool for use by community organizations for assessment and implementation of the positive youth development approach.

Kretzmann and McKnight have also developed a framework for use at the community level.

### BOX 24-2 Strengths-Based Practices Inventory

- Does the program help adolescents feel respected, valued, and treated as if they are knowledgeable and capable?
- Does the program help adolescents and families to acquire knowledge, skills, and self-confidence to do things for themselves?
- Does the program focus on helping adolescents and families develop positive relationships within their own lives?

Derived from Green BL, McAllister CL, Tarte JM. The Strengths-Based Practices Inventory: a tool for measuring strengths-based service delivery in early childhood and family support programs. *Families in Society: The Journal of Contemporary Social Services*. 2004;85(3):326–334.

**Table 24-1** Features of Community-Based Positive Developmental Settings

FEATURE	DESCRIPTORS	OPPOSITE POLES
Physical and psychological safety	Safe and health-promoting facilities and practices that increase safe peer group interaction and decrease unsafe or confrontational peer interactions.	Physical and health dangers; fear; feelings of insecurity; sexual and physical harassment; verbal abuse.
Appropriate structure	Limit setting; clear and consistent rules and expectations; firm enough control; continuity and predictability; clear boundaries; age-appropriate monitoring.	Chaotic; disorganized; laissez-faire; rigid; overcontrolled; autocratic.
Supportive relationships	Warmth; closeness; connectedness; good communication; caring; support; guidance; secure attachment; responsiveness.	Cold; distant; overcontrolling; ambiguous support; untrustworthy; focused on winning; inattentive; unresponsive; rejecting.
Opportunities to belong	Opportunities for meaningful inclusion, regardless of one's gender, ethnicity, sexual orientation, or disabilities; social inclusion, social engagement, and integration; opportunities for sociocultural identity formation; support for cultural and bicultural competence.	Exclusion; marginalization; intergroup conflict.
Positive social norms	Rules of behavior; expectations; injunctions; ways of doing things; values and morals; obligations for service.	Normlessness; anomie; laissez-faire practices; antisocial and amoral norms; norms that encourage violence; reckless behavior; consumerism; poor health practices; conformity.
Support for efficacy and mattering	Youth based; empowerment practices that support autonomy; making a real difference in one's community; being taken seriously. Practices that include enabling, responsibility granting, and meaningful challenge. Practices that focus on improvement rather than on relative current performance levels.	Unchallenging; overcontrolling; disempowering; disabling. Practices that undermine motivation and desire to learn, such as excessive focus on current relative performance level rather than improvement.
Opportunities for skill building	Opportunities to learn physical, intellectual, psychological, emotional, and social skills; exposure to intentional learning experiences; opportunities to learn cultural literacies, media literacy, communication skills, and good habits of mind; preparation for adult employment; opportunities to develop social and cultural capital.	Communities that promote bad physical habits and habits of mind; practices that undermine school and learning.
Integration of family, school, and community efforts	Concordance; coordination; synergy among family, school, and community.	Discordance; lack of communication; conflict.

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## POSITIVE YOUTH DEVELOPMENT FOCUS

As part of their preventive services visits with adolescents, pediatricians identify individual patient strengths through developmental surveillance, give feedback about progress on the developmental tasks to youth and (if appropriate) their parents, and practice shared decision making when a change needs to be made. As community pediatricians, they play an additional role. Based on their roles as board members, team physicians, volunteer coaches, community health leaders, and parents, pediatricians provide consultation about using the positive youth development approach and advocating for this approach with funders. Pediatricians understand the importance of community partners in the lives of adolescents. These partners may include state and national organizations of the American Academy of Pediatrics (AAP), state health departments, schools, faith-based organizations, and community organizations like 4H and Boys and Girls Clubs of America. Pediatricians can advocate for programs that have demonstrated effectiveness by being aware of what programs work for promoting healthy adolescent development. For example, Lerner has reported that participants in 4H, when compared to youth in other out-of-school programs, had better outcomes in healthy behaviors, academic competence, school engagement, and community contribution. The Big Brother/Big Sister mentoring programs evaluation in 2013 has found improved social acceptance among participants compared with those youth who have not yet been matched with a mentor. When followed over time, participants also showed improvement or maintenance of scholastic competence, educational expectations, attitudes toward risky behavior, and parental trust. Opportunities for community service are also associated with risk reduction in youth, and for this reason the Community Preventive Services Task Force of the Substance Abuse and Mental Health Services Administration recommends youth development-focused behavioral interventions coordinated with community service.

In recent years, many youth advocacy organizations have become more aware of, and focused on, positive youth development strategies.

In addition, pediatric practices often have a staff person who is in charge of knowledge about and links to community resources. Among these resources are programs with a youth development focus or proven efficacy for easy referral of patients seen for preventive services and acute visits in the medical home.

## RISK REDUCTION FOCUS

Health promotion activities at the community level also focus on the prevention of the 6 risk behaviors that result in the greatest morbidity and mortality for adolescents and adults: unhealthy nutrition, inadequate physical activity, unhealthy sexual behaviors, substance use and abuse, unintentional injury-related behavior, and intentional injury-related behaviors.

In some situations, physicians provide health promotion consultation and advocacy about specific risk areas. This can result from personal interest or expertise on the part of the physician or in response to a

critical need identified among the patient population or in the community (eg, prescription drug abuse or teen suicide).

Recent research has identified several community-based strategies for adolescent risk reduction. Safe, supervised recreational activities and physical activity promote healthy development. Neighborhoods and communities can work together with pediatricians to improve the built environment. Researchers have shown that increasing the percentage of park space in a neighborhood increases the percentage of non-overweight 8- to 12-year-olds.

Schools and retail environments that support healthy choices are especially important to adolescents' decision making regarding nutrition, tobacco, and alcohol. Pediatricians can advocate for laws to regulate the marketing and sale of non-nutritious food, tobacco, and alcohol to adolescents. They can also advocate at the community level for oral health initiatives like water fluoridation, access to dental homes, and school-based programs for screening and referral. Pediatricians can partner with communities and public health departments to call attention to the importance of adolescent vaccines in promoting healthy communities, and can conduct information campaigns to improve awareness. This is becoming more important with increasing rates of vaccine refusal.

Communities can also promote healthy attitudes about sexuality. Accepting one's changing body and exploring sexual feelings and identity are among the developmental tasks of adolescence. Pediatricians should advocate for medically accurate sexuality education in schools, and for an emotionally and physically safe environment for youth who are gay, lesbian, bisexual, or transgender. The Centers for Disease Control and Prevention Task Force on Community Preventive Services has identified competence, improved decision making, self-determination, and improved communication skills as critical components in a recommended sexuality risk reduction program.

Community-based substance abuse prevention is most effective when it involves programs to help individuals develop skills along with policies that support healthy behaviors. Communities must make enforcement of these policies a high priority.

An emotionally and physically safe environment is also critical to healthy adolescent development. School programs about bullying and Internet safety can contribute to a community-wide effort to promote a positive climate. Injury prevention at the community level might include safe driving legislation and enforcement, seatbelt and bike helmet legislation, and gun violence prevention.

Pediatricians are ideal advocates for wellness and mental health support for adolescents and should encourage opportunities for strength-building activities. Nutrition, exercise, sleep, sunshine, reading, music, sports, and spirituality all contribute to an adolescent's sense of well-being. These factors are essential components of a strategy to promote mental health. Communities also need ongoing resource development to help adolescents in crisis, those experiencing problems in school, and those in need of mental health treatment.

Schools continue to play a vital role in adolescents' community connections. As discussed in Chapter 23, Promoting the Health of School-Aged Children, coordinated school health has 8 essential components: health education and services, counseling, psychological and social services, physical education, nutrition services, healthy school environment (which includes emotional safety), health promotion for staff, and family/community involvement. Pediatricians should be a part of a coordinated school health program and, ideally, participate in school activities related to this approach.

Media can have significant effects on adolescent health behavior choices. Opportunities for education about safe, effective, and healthy media use should be promoted by families, schools, physicians, and community organizations.

Finally, pediatricians are a valuable source of support for parents and guardians, who may benefit from an understanding of strengths and positive youth development. Building on relationships often forged when children were much younger, the medical home provides adolescents and their families a supportive extension of the community. A helpful resource for parents is the AAP publication *Building Resilience in Children and Teens*.

Kenneth R. Ginsburg's book *Reaching Teens* is an excellent guide to implementation of the strengths-based approach for health care professionals, social workers, educators, and all professionals who work in youth-serving organizations.

## ADOLESCENTS IN DIFFICULT CIRCUMSTANCES

Pediatricians should recognize the special needs of certain groups within a community and strive to create opportunities for these vulnerable young people. Adolescents with special health care needs and vulnerable families who, because of income level or geography, lack access to social, cultural, and economic resources should be supported by pediatricians, public health professionals, and community organizations. Additional special populations include youth in foster care (see Chapter 72, Children in Foster or Kinship Care), youth in the judicial system (see Chapter 73, Children in the Juvenile Justice System), youth with previous loss or trauma (see Chapter 68, Children Exposed to Adverse Childhood Experiences), youth whose parents are in the military (see Chapter 77, Children in Military Families), youth with special educational needs, adolescents who are parents, and youth with substance abuse problems.

## CONCLUSION

Pediatricians play a vital role in ensuring that their communities support the developmental tasks of adolescence. *Bright Futures* provides specific guidance to assist health care professionals in this area: Box 24-3 identifies specific recommendations.

A comprehensive, coordinated approach promotes healthy outcomes in adolescents. Pediatricians are an essential component of this cooperative effort. Health promotion for adolescents involves the medical home,

### BOX 24-3 Recommendations for Promoting Community Relationships and Resources

- Learn about the community and collaborate with community partners (know your local resources, schools, and public health officials)
- Recognize the special needs of certain groups and collaborate with social services
- Encourage informal support: parent support networks
- Consult and advocate: opportunities to become agents for health-promoting community change

Derived from Hagan JF, Shaw JS, Duncan P. *Bright Futures Guidelines for Health Supervision of Infants, Children, and Adolescents*. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2008.

community-based organizations, schools, parents and guardians, and the youth themselves. By helping to develop strengths-based programs and foster the growth of developmental assets, pediatricians can encourage positive adolescent development.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *Building the Legacy: IDEA 2004* (Web page), US Department of Education ([idea.ed.gov](http://idea.ed.gov))
- *Adolescent and School Health* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/healthyyouth/schoolhealth/index.htm](http://www.cdc.gov/healthyyouth/schoolhealth/index.htm))
- *State School and Health Resources* (Web page), American Academy of Pediatrics ([www2.aap.org/sections/schoolhealth/contactmap/section\\_contacts.cfm.htm](http://www2.aap.org/sections/schoolhealth/contactmap/section_contacts.cfm.htm))
- *Healthy People 2020 Evidence-Based Resources* (Web page), Office of Disease Prevention and Health Promotion ([www.healthypeople.gov/2020/tools-resources/Evidence-Based-Resources](http://www.healthypeople.gov/2020/tools-resources/Evidence-Based-Resources))
- *Healthy People 2020 Program Planning* (Web page), Office of Disease Prevention and Health Promotion ([www.healthypeople.gov/2020/tools-and-resources/Program-Planning](http://www.healthypeople.gov/2020/tools-and-resources/Program-Planning))
- *Healthy People 2020 Count Data Resources* (Web page), Office of Disease Prevention and Health Promotion ([www.healthypeople.gov/2020/county-data-resources](http://www.healthypeople.gov/2020/county-data-resources))
- *National School Lunch Program (NSLP)* (Web page), US Department of Agriculture ([www.fns.usda.gov/nslp/national-school-lunch-program-nslp](http://www.fns.usda.gov/nslp/national-school-lunch-program-nslp))
- *Health, Mental Health, and Safety Guidelines for Schools* (Web site), American Academy of Pediatrics ([www.nationalguidelines.org](http://www.nationalguidelines.org))

### Engaging Patient and Family

- *Frequently Asked Questions About Section 504 and the Education of Children With Disabilities* (fact sheet), US Department of Education ([www.ed.gov/about/offices/list/ocr/504faq.html](http://www.ed.gov/about/offices/list/ocr/504faq.html))
- *National Center for Children in Poverty Data Tools* (Web page), National Center for Children in Poverty ([nccp.org/tools](http://nccp.org/tools))

**AAP POLICY**

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American Academy of Pediatrics Committee on Environmental Health. The built environment: designing communities to promote physical activity in children. *Pediatrics*. 2009;123(6):1591–1598. Reaffirmed January 2013 ([pediatrics.aappublications.org/content/123/6/1591](http://pediatrics.aappublications.org/content/123/6/1591))

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media. *Pediatrics*. 2013;132(5):958–961 ([pediatrics.aapublications.org/content/132/5/958](http://pediatrics.aapublications.org/content/132/5/958))

**SUGGESTED READINGS**

Duncan PM, Garcia AC, Frankowski BL, et al. Inspiring healthy adolescent choices: a rationale for and guide to strength promotion in primary care. *J Adolesc Health*. 2007;41(6):525–535

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# Screening

**Chapter 25****SCREENING: GENERAL CONSIDERATIONS**

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Primary care physicians are well positioned to participate in the early detection of childhood problems and conditions because of their access to young children and families. Universal screening refers to the process of testing all children at certain appropriate ages to detect those at high risk for significant deviations from normal. The emphasis is on distinguishing between children at high and low risk for certain problems, rather than on diagnosing such conditions. Screening typically involves the application of rapidly administered tests, examinations, or other procedures. Screening tools or instruments may also be used for validating history or physical findings after concerns are raised.

The number of conditions for which screening is currently recommended or mandated continues to increase. Research has better delineated the adverse effects of certain childhood conditions, such as the neurobehavioral and intellectual deficits associated with low-level lead exposure and iron-deficiency anemia. The Human Genome Project and improving technologies have identified many genes that may carry mutations that cause disorders and that can be identified by simple tests. The expansion of diverse technologies that rapidly measure multiple analytes from a single blood spot allow for more effective newborn screening. Changing morbidity within pediatric practice has led to emphasis on early identification of behavioral, developmental, and psychosocial problems, along with the need for updating screening policies for certain conditions such as autism spectrum disorders.

Societal changes have influenced the scope and content of screening programs. These changes include demands for confidentiality of test results, concerns with the stigma associated with certain diagnoses, and legislative mandates requiring early intervention for children who have developmental

disabilities and other chronic conditions. Remarkable advances in understanding of genetics and epigenetics have raised concerns that the ability to diagnose a genetic disorder for which no treatment is available may create undue anxiety and frustration. Health care reform, with its emphasis on population health, primary prevention, and cost containment, has contributed to an increased scrutiny of screening practices. Despite the time-honored tradition of performing screening tests during child health supervision visits, the effectiveness of many such practices is uncertain. For example, the US Preventive Services Task Force (USPSTF) issued recommendations for clinical preventive services in 2014 that endorsed universal screening for a limited number of conditions during childhood and adolescence. The Task Force recommended universal newborn screening for congenital hypothyroidism, phenylketonuria, sickle cell disease, and hearing loss; for major depressive disorder in adolescents; for obesity among 6- to 18-year-olds; and for childhood visual impairment. In contrast, they cited insufficient evidence to support universal screening for iron-deficiency anemia, blood lead levels, and lipid disorders. Because recommendations for screening practices are typically determined by a combination of limited scientific data, empiricism, and good intentions, they often provoke considerable debate.

The 2006 recommendations of the American Academy of Pediatrics (AAP) Council on Children with Disabilities endorse the administration of formal developmental screening tools at 9, 18, and 24 to 30 months of age. The statement emphasizes the importance of using such tools in the context of a comprehensive, longitudinal process of surveillance and screening that also engages parents as partners in the process of early detection, interprets the results of screening tools in the context of all that is known about the child and family, and ensures that positive screening results lead to further assessment and, if indicated, intervention.

This chapter reviews the criteria by which conditions are judged appropriate for screening and tests are selected for use in screening programs. In addition,



screening is compared with other approaches to early detection during the provision of child health supervision services.

### TRADITIONAL CRITERIA FOR CONDITIONS TO BE SCREENED

Historically, disease conditions have been judged appropriate for screening if they fulfill certain well-accepted and still relevant criteria that evolved during the last century.

1. The condition must be an important health problem and have significant morbidity or mortality, with serious consequences if not detected and remediated early. For example, the adverse effects of early sensorineural hearing loss on language development and subsequent academic achievement and on social and emotional development are cited to support recommendations for universal screening for hearing impairment of all newborns.
2. The condition must be sufficiently prevalent to justify the cost of screening programs. Determining the true prevalence of certain conditions is difficult. Furthermore, rates of conditions often vary widely across different geographic regions. For example, the Centers for Disease Control and Prevention (CDC) has recommended that state or local governments formulate their own recommendations for lead screening based on local data. Such data is important in determining cost versus benefit to society. The AAP has similarly encouraged physicians to follow local screening guidelines when available.
3. The screening program should include the entire population, especially those at particular risk for the condition. Screening programs are optimally implemented within a comprehensive system of preventive child health care directed at the entire population. The lack of access of some young children and families to child health supervision services and a medical home is well recognized. Disadvantaged children at increased risk for conditions such as iron-deficiency anemia, lead poisoning, and developmental delay may be less likely to receive recommended screening tests because of their limited access to health care.
4. Adequate resources must be available for the definitive diagnosis and treatment of disorders identified by screening. The lack of adequate diagnostic and therapeutic resources for developmental, behavioral, and psychosocial problems hampers efforts at early detection and intervention. While autism screening promotes early detection of at-risk children, insufficient evaluation capacity often delays diagnosis. Universal screening for hearing impairment in infants is problematic for some individuals because follow-up diagnostic testing and treatment of hearing loss may be difficult to carry out in rural or remote areas. Screening results should inform advocacy efforts to address gaps and capacity issues.
5. The condition, after detection, must be treatable or controllable. Developmental screening is based on the premise that positive screening will result in an intervention that will benefit the child. The benefits of early intervention for children who have developmental

disabilities (eg, Down syndrome, cerebral palsy) are well established. Furthermore, evidence increasingly supports the benefits of early identification and intervention for vulnerable young children who are at risk of adverse developmental and behavioral outcomes.

6. Detection and treatment during the asymptomatic phase can improve prognosis, and early treatment is advantageous. Newborn screening for inborn errors of metabolism (eg, congenital hypothyroidism, phenylketonuria) is clearly beneficial because early treatment prevents later brain damage and neurologic impairment. Similarly, prophylactic penicillin and pneumococcal conjugate vaccine have been clearly shown to reduce both morbidity and mortality from pneumococcal infections in young children who have sickle cell anemia. Screening for cystic fibrosis is supported by evidence that treatment before the development of severe pulmonary disease will increase well-being and the duration of survival.
7. The cost of screening should be outweighed by the savings in suffering and alternative expenditure that would occur if the condition were not diagnosed until the symptomatic stage. Costs of screening programs must include not only the direct cost of the procedures themselves, but also the cost of diagnostic evaluation, monitoring, and intervention as a consequence of screening, as well as the costs of false-positive and false-negative results. For example, one study found the total costs for initiating and establishing a universal newborn hearing screening program, including post-discharge screening and diagnostic evaluation costs, was \$46 per infant screened when utilizing automated auditory brainstem response (AABR) and \$58 when using transient evoked otoacoustic emissions (TEOAE). However, few studies have examined the long-term cost effectiveness of universal newborn hearing screening in relation to such other approaches as risk factor screening.

### CRITERIA FOR SCREENING TESTS

Once the decision has been made to screen for a particular disorder, judging which tests are appropriate to use in screening programs is based on widely accepted criteria.

1. Tests must be simple, practical, convenient, and safe. The relative ease and simplicity of performing TEOAE testing facilitates universal screening for hearing impairment in infants. However, the decrease in specificity of this test during the first 24 hours of life poses logistical problems in that early discharge may necessitate a second screening on an outpatient basis. Computer scoring software is available for several developmental screening tests to assist in administration within the busy practice setting.
2. Tests must be acceptable to patients and families, with assurance of informed parental consent and confidentiality of findings. Informed parental consent includes access to information on such issues as potential false-positive and false-negative findings, the possible need for time-consuming and often expensive follow-up evaluations, and the anxiety



generated by positive screening results. Confidentiality of screening results must be maintained because positive findings for disorders such as HIV infection and sickle cell disease may be socially stigmatizing and result in discrimination by insurance companies and potential employers.

3. Tests must be accurate and reliable. The validity of screening tests consists of 2 components: sensitivity—the proportion of individuals who have a disorder whose test result is positive; and specificity—the proportion of individuals who do not have the disorder whose test is negative. Of particular clinical importance is the probability of an individual having the disorder when the test is positive—the test's positive predictive value—as well as the probability of not having the disorder when the test is negative—negative predictive value. The predictive value of a test depends greatly on the prevalence of the disorder in the population being tested. The low prevalence of hearing impairment (approximately 1 to 3 of every 1,000 otherwise healthy newborns) contributes to the relatively low specificity of TEOAE testing alone, and suggests the potential benefit of a 2-step screening approach with positive TEOAE results confirmed by AABR testing.
4. Tests should be economical. The costs of newborn screening for metabolic disorders such as congenital hypothyroidism, galactosemia, and maple syrup urine disease are minimal because such tests are incorporated within established screening programs for phenylketonuria. The cost of screening for such rare disorders in isolation would be prohibitive.
5. Appropriate specialists should be available to assist in the interpretation of screening results, as well as to facilitate diagnostic assessment and treatment. The screening program must ensure the availability of appropriate education and genetic counseling for parents.

## SCREENING AS A PUBLIC HEALTH SERVICE

In recent years, the criteria for screening have evolved to include a broader definition of benefits to the affected child and the child's family, including the prevention of negative consequences or optimization of all outcomes. A greater emphasis on more moderate and family-centered benefits, including a reduction in recurrence risks through genetic counseling and the avoidance of diagnostic odysseys associated with unrecognized conditions such as uncommon inborn errors of metabolism, have implications for policy deliberations. For example, newborn screening for cystic fibrosis is justified based on such outcomes as nutritional benefits and improved growth, cognitive benefits for children at nutritional risk, reduction in diagnostic delays, the avoidance of hospitalization, and the recognition of carriers.

## EVIDENCE-BASED ASSESSMENTS

Recommendations for selecting disorders for population-based screening should include the systematic assessment of evidence of effectiveness and benefits

using standardized methods. The USPSTF develops recommendations for screening based on systematic reviews of research on the certainty of the evidence and on the balance of benefits and harms of the proposed screening process. The USPSTF currently grades its recommendations according to both the certainty and the magnitude of net benefit, judging each as either Substantial, Moderate, Small, or Zero/negative. For example, if screening for a given condition is found to have both high certainty and substantial magnitude of net benefit, it is assigned a grade of A, while a finding of the same degree of certainty with a moderate benefit is assigned a grade of B, that with a small benefit is assigned a C, and zero/negative benefit, a D. Definitions of grades are as follows:

- A. There is high certainty that the net benefit is substantial.
- B. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.
- C. There is at least moderate certainty that the net benefit is small.
- D. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.

In the absence of a grade, an I (Insufficient) statement indicates that current evidence is insufficient to assess the balance of benefits and harms of the service and that evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

## EVIDENCE-BASED RECOMMENDATIONS

The USPSTF publishes its recommendations for pediatric prevention and screening in its *Guide to Clinical Preventive Services*. Grade definitions now include recommendations for practice.

- A. The USPSTF recommends the service and suggests that physicians offer or provide this service.
- B. The USPSTF recommends the service and suggests that physicians offer or provide this service.
- C. The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences and that physicians offer or provide this service for selected patients depending on individual circumstances.
- D. The USPSTF recommends against the service and urges physicians to discourage the use of this service.

In the absence of a grade, an I (Insufficient) statement indicates that the USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. If the physician opts to offer the service, patients should understand the uncertainty about the balance of benefits and harms.

Examples of USPSTF recommendations for childhood screening and their grade classification include the following:

- Evidence is insufficient to make a recommendation for blood lead screening in asymptomatic children aged 1 to 5 years who are at increased risk (I). No screening is recommended for same-aged children at average risk (D).

- Screening for hearing loss is recommended in all newborn infants (B).
- Evidence is insufficient to make a recommendation for iron deficiency anemia screening in asymptomatic children aged 6 to 12 months (I).
- Evidence is insufficient to make a recommendation for screening for lipid disorders in asymptomatic infants, children, and adolescents (I).
- Screening is recommended for major depressive disorder in children and adolescents when systems for diagnosis, treatment, and follow-up are in place (B).
- Screening children aged 6 years and older for obesity is recommended (B).
- Screening children aged 3 to 5 years for vision impairment is recommended (B).
- Screening for congenital hypothyroidism, phenylketonuria, and sickle cell disease is recommended in all newborn infants (A).

In addition to the USPSTF, other organizations provide evidence-based recommendations for screening procedures. Examples include the AAP ([www.aap.org/publications.org/policy](http://www.aap.org/publications.org/policy)), the Canadian Task Force on Preventive Care ([canadiantaskforce.ca](http://canadiantaskforce.ca)), and the American College of Medical Genetics ([www.acmg.net](http://www.acmg.net)). The AAP, in collaboration with the Maternal and Child Health Bureau, has incorporated its recommendations for screening within preventive care in *Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents*, 3rd ed.

## SELECTIVE SCREENING OPTIONS

Selective, as opposed to universal, screening may be preferred for certain conditions to enable targeting of select subpopulations deemed to be at greater risk. For example, reported differences in blood lead levels between children living in urban and suburban areas have been cited to support a strategy of geographic targeting. In recognition of the greater risk of exposure among children of families of lower socioeconomic status, Medicaid requires blood lead screening of all children at 12 and 24 months of age. Selective screening programs may target a specific racial or ethnic group that has an increased prevalence of a particular disorder. For example, screening programs for Tay-Sachs disease target Ashkenazi Jews. However, selective screening may fail to identify certain affected individuals. For example, selective screening programs targeting a specific racial or ethnic group are unlikely to identify all infants who have sickle cell disease because defining an individual's racial or ethnic background reliably by surname, self-report, or physical characteristics is often not possible. Because prophylactic administration of penicillin and pneumococcal conjugate vaccine have been demonstrated to reduce morbidity and mortality in young children who have sickle cell anemia, universal screening of all newborns is recommended, regardless of race or ethnic background.

## HIGH-RISK REGISTER

Before 1994, the Joint Committee on Infant Hearing, composed of representatives from audiology, otolaryngology, pediatrics, and nursing, favored the use of a

register instead of screening to identify infants at risk for hearing impairment. The registry listed specific conditions that place a newborn at increased risk for hearing loss (eg, a family history of hearing loss, anomalies of the head and neck, and a birth weight less than 1,500 grams). Listing these high-risk factors in the form of a screening questionnaire and asking parents to complete the form after delivery was followed by selective AABR testing for infants considered at risk. Because risk-factor screening identifies only 50% of infants who have significant hearing loss, the Joint Committee now recommends the universal screening of all infants before discharge from the newborn nursery. The AAP has also endorsed the implementation of universal newborn hearing screening. In general, experts do not recommend such strategies as high-risk registers as alternatives to screening.

## PARENT-COMPLETED QUESTIONNAIRES AND PROFESSIONALLY ADMINISTERED TOOLS

Standardized and validated screening tools for developmental delays include both parent-completed questionnaires and professionally administered tests. Parent-report measures involve the child's caregiver completing a screening tool that typically includes parents' concerns, developmental-behavioral milestones, and both protective and risk factors. Professionally administered tests require a trained clinician to observe the child or demonstrate developmental-behavioral skills and milestones. Time constraints, logistics, and training contribute to the preference of many physicians and their practices for parent-completed questionnaires. Select examples of parent-completed questionnaires designed for use in developmental screening include the Ages and Stages Questionnaires, Third Edition (ASQ-3); the Child Development Inventories (CDI); and the Parents' Evaluation of Developmental Status (PEDS). Examples of professionally administered tools include the Bayley Infant Neurodevelopmental Screener (BINS), the BRIGANCE II Screens, and the Denver II. Screening requirements of many states and Medicaid, as well as the availability of reimbursement for developmental screening activities, have increased the use of developmental screening tools in practice settings.

## AN INTEGRATED APPROACH TO EARLY DETECTION AND INTERVENTION

Screening is most effective when viewed as a component in an integrated approach to early detection and intervention. For example, the Advisory Committee on Childhood Lead Poisoning Prevention of the CDC recommends that all children and their families receive a combination of screening questions, outreach, and education to minimize exposures prior to blood lead testing. The AAP recommends that early detection of developmental problems is best performed through the process of developmental surveillance and screening. Surveillance is a flexible, longitudinal, continuous, and cumulative process whereby knowledgeable professionals repeatedly observe children

during the provision of child health supervision over time. The components of surveillance include eliciting and attending to parents' concerns; documenting and maintaining a developmental history; making accurate observations of children; identifying risk and protective factors; maintaining an accurate record and documenting the process and findings; and, especially when concerns arise, soliciting input from others who know the child (eg, child care provider, home visitor, preschool teacher). In addition to these longitudinal activities, screening using valid parent-completed questionnaires or professionally administered tools is recommended at 9, 18, and 24 to 30 months of age. The AAP also recommends the use of an autism-specific screening tool (eg, Modified Checklist for Autism in Toddlers [M-CHAT]) for condition-specific screening at 18 and 24 months of age. Surveillance and screening enables the physician to interpret the results of screening in the context of all that is known about the child and family.

Screening processes should ensure the proper interpretation of screening results, as well as assessment and intervention for children identified as at increased risk through the screening process. Screening should be viewed as one component in an integrated approach to connecting children with services. Federal and state agencies are increasingly encouraging the role of screening in a systems approach that includes screening, early identification, referral, intake, evaluation and eligibility, and services. Despite increases in the use of screening tools in the practice setting, children with positive screens are not consistently referred for assessment, and those found to be in need of intervention may not be linked to services. Comprehensive systems must support each step in this critical process to ensure that screening is beneficial for children and their families.

### APP POLICY

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American Academy of Pediatrics Council on Children With Disabilities, Section on Developmental Behavioral Pediatrics, Bright Futures Steering Committee, Medical Home Initiatives for Children With Special Needs Project Advisory Committee. Identifying infants and young children with developmental disorders in the medical home: an algorithm for developmental surveillance and screening. *Pediatrics*. 2006;118:405–420. Reaffirmed August 2014 ([pediatrics.aappublications.org/content/134/5/e1520](http://pediatrics.aappublications.org/content/134/5/e1520))

### SUGGESTED READINGS

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## Chapter 26

## AUDITORY SCREENING

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### JUSTIFICATION FOR SCREENING

Hearing loss is a common congenital condition in newborns. It is 20 times more prevalent than phenylketonuria and occurs twice as often as hypothyroidism, galactosemia, phenylketonuria, and sickle cell disease combined. Routine screening for hearing loss is a justifiable procedure based on the prevalence of the disorder in the general pediatric population and at-risk groups along with the availability of effective interventions. Between 1 and 6 per 1,000 babies without risk factors and approximately 13.3 per 1,000 babies with high-risk factors are born with hearing loss greater than 40 dB. However, these estimates fail to account for babies who have mild (<40 dB) sensorineural hearing losses. Add to this number children with progressive hearing losses and acquired childhood hearing losses, and the importance of infant and childhood hearing screening is undeniable.

Approximately 14.9% of all children in the United States have a hearing loss with thresholds of at least 16 dB HL. Any hearing loss, including a minimal degree of loss (15–25 dB), may cause speech and language delay and difficulty in social and educational environments (see Chapter 195, Speech and Language Concerns). The consequences are profound: approximately 37% of children with a mild sensorineural hearing loss will fail at least 1 grade in school. Late-identified children with bilateral, permanent hearing loss leave the educational system at the age of 18 years having achieved, on average, a sixth-grade reading level and a language-age equivalent of 12 years. These developmental delays have been found to result in reduced educational and employment levels in adulthood.

To maximize communicative competence and literacy in children who are hard of hearing or deaf, the Joint Committee on Infant Hearing (JCIH) published a position statement (endorsed by the National Institutes of Health [NIH] and the American Academy of Pediatrics [AAP]) recommending an agenda of early hearing detection and intervention. The Committee endorsed the goal of testing children by 1 month of age, identifying those with hearing loss by 3 months



of age, and initiating intervention for children who are deaf or hard of hearing by 6 months of age, as suggested in the landmark 1998 study by Yoshinaga-Itano and colleagues. Despite the evidence that early identification and intervention are critical to the overall communicative, cognitive, educational, and emotional development of children with hearing loss, the average age of identifying early-onset hearing loss in the United States was between 12 and 25 months before implementation of Universal Newborn Hearing Screening (UNHS). However, it may be improving. Recent studies have reported the average age of diagnosis of hearing loss to be as young as 3.7 months after implementation of UNHS. Early intervention in the form of audiologic management, otologic treatment, amplification, parental counseling, and special education is important not only because of the seriousness of the medical sequelae of active otopathologic conditions, but also because of the negative consequences that even a mild hearing loss has for language growth, academic success, and behavioral development.

## GOALS OF SCREENING

The goal of hearing screening programs in general is to identify children with hearing loss as early as possible to prevent the detrimental effects that late diagnosis has on language and speech development. Approximately 40% to 50% of infants with hearing loss would remain unidentified if high-risk indicators were used as a screening method instead of direct testing of all children. In 1993, the NIH Consensus Development Conference recommended that all

babies be screened for hearing loss before being discharged from the hospital. As of 2005, all 50 states and the District of Columbia had Early Hearing Detection and Intervention (EHDI) programs in place. The primary responsibilities of the EHDI staff are to manage a system of services that ensures children born with permanent hearing loss are identified by 3 months of age and provided with intervention services before 6 months of age. However, at the time of this publication, only 43 states have legislation in place requiring mandatory UNHS, the goal of which is to detect moderate to severe hearing loss. (State-specific information is available through the National Center for Hearing Assessment and Management [NCHAM], Utah State University [[www.infanthearing.org/index.html](http://www.infanthearing.org/index.html)].)

## NEONATAL AND EARLY INFANT PERIOD

Empirical evidence suggests that the best method for the detection of and subsequent intervention for hearing loss in the neonatal and early infant period is the implementation of a UNHS program (Box 26-1 and Figure 26-1). Regardless of prior screening outcomes, all infants who are at risk for delayed-onset or progressive hearing loss should receive audiologic monitoring every 6 months for the first 3 years of life. (Box 26-2 summarizes the risk factors for hearing loss.) Additionally, all infants with or without risk factors should receive ongoing surveillance of communicative development beginning at 2 months of age during well-child visits.

Based on data suggesting the long-term developmental consequences of hearing loss in infants, the

### BOX 26-1 Principles That Provide the Foundation for Effective Early Hearing Detection and Intervention (EHDI) Systems

1. All infants should have access to hearing screening using a physiologic measure no later than 1 month of age.
2. All infants who do not pass the initial hearing screening and the subsequent screening should have appropriate audiologic and medical evaluations to confirm the presence of hearing loss no later than 3 months of age.
3. All infants with confirmed permanent hearing loss should receive early intervention services as soon as possible after diagnosis, but no later than 6 months of age. A simplified, single point of entry into an intervention system appropriate for children with hearing loss is optimal.
4. The EHDI system should be family centered with infant and family rights and privacy guaranteed through informed choice, shared decision making, and parental consent in accordance with state and federal guidelines. Families should have access to information about all intervention and treatment options and counseling regarding hearing loss.
5. The child and family should have immediate access to high-quality technology, including hearing aids, cochlear implants, and other assistive devices when appropriate.
6. All infants and children should be monitored for hearing loss in the medical home. Continued assessment of communication development should be provided by appropriate professionals to all children with or without risk indicators for hearing loss.
7. Appropriate interdisciplinary intervention programs for infants with hearing loss and their families should be provided by professionals knowledgeable about childhood hearing loss. Intervention programs should recognize and build on strengths, informed choices, traditions, and cultural beliefs of the families.
8. Information systems should be designed and implemented to interface with electronic health records and should be used to measure outcomes and report the effectiveness of EHDI services at the patient, practice, community, state, and federal levels.

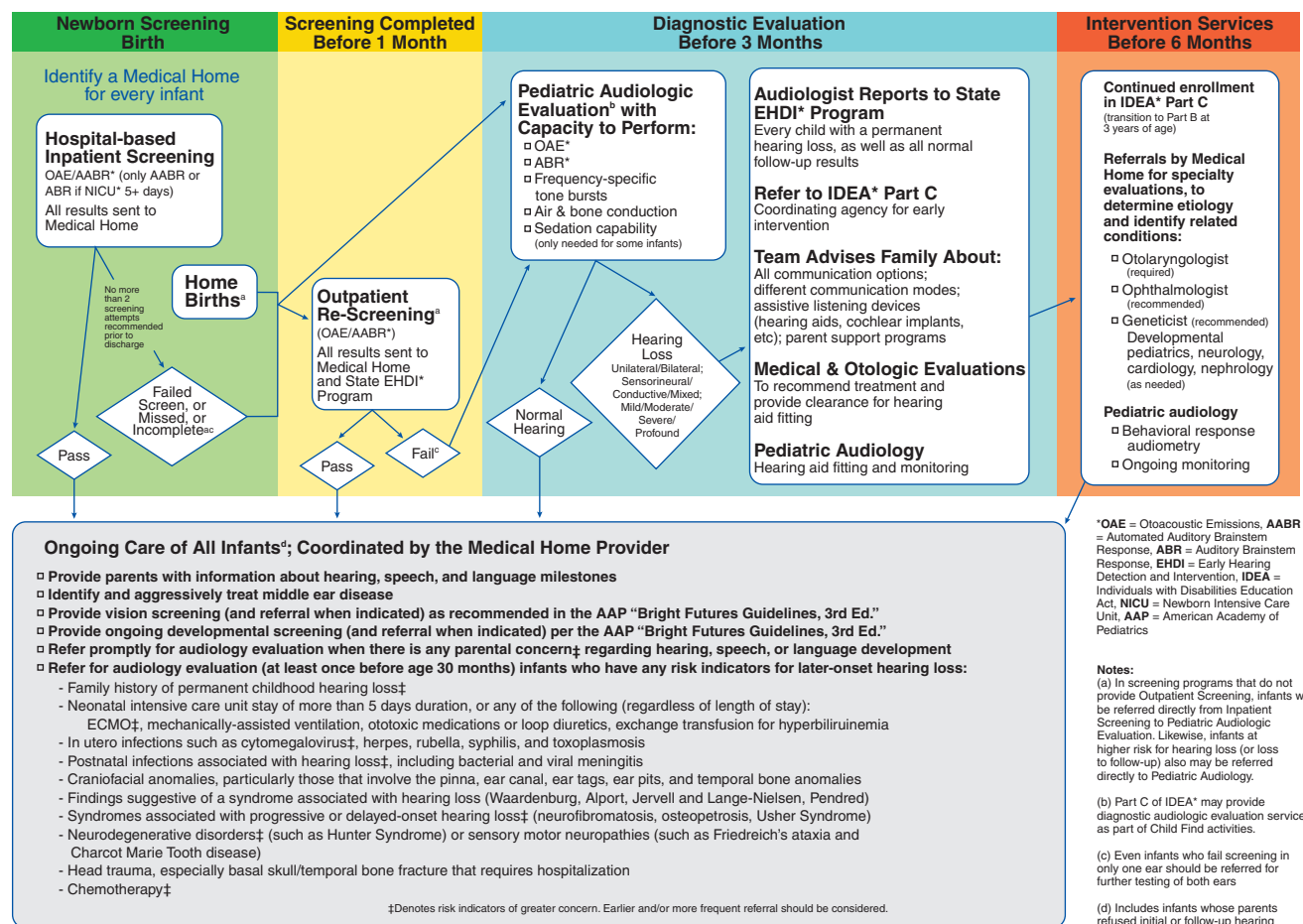
From Joint Committee on Infant Hearing, American Academy of Audiology, American Academy of Pediatrics, American Speech-Language-Hearing Association, Directors of Speech and Hearing Programs in State and Welfare Agencies. Year 2007 position statement: principles and guidelines for early hearing detection and intervention programs. *Pediatrics*. 2007;120:898–921.



JCIH defines the targeted hearing loss for UNHS programs as permanent bilateral or unilateral, sensory, or conductive hearing loss averaging 40 dB in the frequency region that is important for speech recognition (approximately 500–4,000 Hz). This guideline generally eliminates from identification children with transient conductive hearing losses and mild sensory or conductive hearing loss, as well as those with hearing loss related to auditory neuropathy or neural conduction disorders, which makes audiologic monitoring and routine screening later in life even more important. This issue will be discussed in more detail in later sections of this chapter. Objective physiologic measures must be used to identify newborns and young infants with hearing loss. Although different programs use different screening criteria and a conclusive recommendation has yet to be reached, the literature suggests that otoacoustic emissions (OAEs) and auditory brainstem response (ABR) measures used together provide much more accurate information than either test alone and that both are necessary for a comprehensive screening

program. Northern and Hayes report that using a 2-stage OAE-ABR screening protocol will result in only 1.7 infants with normal hearing being referred for a complete diagnostic evaluation for every baby who has hearing loss (based on a prevalence rate of 2 to 3 hearing-impaired infants per 1,000 births). In other words, the 2 screening technologies are complementary when used in a 2-stage screening protocol. Regardless of the protocol used, studies indicate that the best time frame for UNHS programs is approximately 3 to 4 days after birth. Korres and colleagues reported that the highest referral rates occur within the first 24 hours of life. Hall and colleagues (2010) reported the average length of stay after delivery is approximately 2.6 days; thus, testing is often completed prior to an ideal time frame, which may increase referral rates. The 2007 JCIH position statement recommends different protocols for the neonatal intensive care unit and well-baby nurseries. Screening of babies in the neonatal intensive care unit admitted for more than 5 days should always include ABR testing because of their increased risk for

### Early Hearing Detection and Intervention (EHDI) Guidelines for Pediatric Medical Home Providers



February 2010 - American Academy of Pediatrics Task Force for Improving Newborn Hearing Screening, Diagnosis and Intervention ([www.medicalhomeinfo.org](http://www.medicalhomeinfo.org))

**Figure 26-1** Early Hearing Detection and Intervention (EHDI) Guidelines for Pediatric Medical Home Providers.

### BOX 26-2 Risk Indicators Associated With Permanent Congenital, Delayed-Onset, or Progressive Hearing Loss in Childhood<sup>a</sup>

1. Caregiver concern<sup>b</sup> regarding hearing, speech, language, or developmental delay
2. Family history<sup>b</sup> of permanent childhood hearing loss
3. Neonatal intensive care of more than 5 days or any of the following regardless of length of stay: ECMO,<sup>b</sup> assisted ventilation, exposure to ototoxic medications (gentamycin and tobramycin) or loop diuretics (furosemide, lasix), and hyperbilirubinemia requiring exchange transfusion
4. In utero infections, such as CMV,<sup>b</sup> herpes, rubella, syphilis, and toxoplasmosis
5. Craniofacial anomalies, including those involving the pinna, ear canal, ear tags, ear pits, and temporal bone anomalies
6. Physical findings, such as white forelock, associated with a syndrome known to include a sensorineural or permanent conductive hearing loss
7. Syndromes associated with hearing loss or progressive or late-onset hearing loss,<sup>b</sup> such as neurofibromatosis, osteopetrosis, and Usher syndrome; other commonly identified syndromes such as Waardenburg, Alport, Pendred, and Jervell and Lange-Nielson
8. Neurodegenerative disorders,<sup>b</sup> such as Hunter syndrome, or sensorimotor neuropathies, such as Friedreich ataxia and Charcot-Marie-Tooth syndrome
9. Culture-positive postnatal infections associated with sensorineural hearing loss,<sup>b</sup> including confirmed bacterial and viral (especially herpesvirus and varicella) meningitis
10. Head trauma, especially basal skull or temporal bone fracture<sup>b</sup> requiring hospitalization
11. Chemotherapy<sup>b</sup>

CMV, cytomegalovirus; ECMO, extracorporeal membrane oxygenation.

<sup>a</sup>Any infant with a risk indicator for hearing loss should be referred for an audiologic assessment at least once by 24 to 30 months of age. Children with risk indicators highly associated with delayed-onset hearing loss, such as having received ECMO or having CMV infection, should have more frequent audiologic assessments.

<sup>b</sup>Risk indicators that are of greater concern for delayed-onset hearing loss.

From Committee on Infant Hearing, American Academy of Audiology, American Academy of Pediatrics, American Speech-Language-Hearing Association, Directors of Speech and Hearing Programs in State and Welfare Agencies. Year 2007 position statement: principles and guidelines for early hearing detection and intervention programs. *Pediatrics*. 2007;120:898-921.

neural hearing loss, including auditory neuropathy. Additionally, any baby readmitted to the hospital within the first month of life who also has risk factors for hearing loss should have a repeat hearing screening before discharge.

Both OAEs and ABRs are noninvasive recordings of the physiologic activity that underlies normal auditory function. Both tests are easily recorded in neonates, although environmental noise and the presence of birth fluids in the ear canal may influence test results. OAEs and ABR testing examine different levels of audition. OAEs provide information regarding the integrity of the outer hair cells. They are rapidly recorded and provide information regarding the presence or absence of hearing loss, but cannot distinguish the degree or type of hearing loss. OAEs are also generally absent in the presence of sensory hearing loss greater than or equal to a 40-dB hearing level. However, OAEs are also sensitive to ear canal obstruction and middle ear effusion and may, therefore, cause a failed test result in the presence of normal cochlear function. Because OAEs examine the integrity of the cochlea, neural dysfunction such as auditory neuropathy or neural conduction disorders without overlaying sensory loss will not be detected. In comparison, ABR testing reflects the activity of the cochlea, the auditory nerve, and the central auditory pathway up to the level of the brainstem. For this reason, the inclusion of ABR as a screening tool is particularly important for neonatal intensive care unit graduates. The test may also be affected by the presence of environmental noise or fluid in the

external auditory canal. ABR reflects conductive hearing loss, sensory hearing loss, and neural conduction disorders such as auditory dyssynchrony and neuropathy.

Despite the sensitivity of a 2-step screening protocol, some infants with hearing loss will still be missed. According to the JCIH, some examples of hearing loss types and configurations that are typically missed by current standards include isolated low-frequency (<1,000 Hz) hearing loss or steeply sloping high-frequency (>2,000 Hz) hearing loss. ABR testing can also suggest normal hearing in the presence of mid-frequency (500–2,000 Hz) hearing loss. Acquired or progressive hearing loss will also be unidentified in the neonatal population. Other factors that may result in a false-negative outcome include the performance and recording characteristics of the test technology, the pass-refer criteria, and excessive retesting using the same technology. Even if a child passes the newborn hearing screen, any time there is parental concern of speech language delay, comprehensive diagnostic evaluation by a licensed audiologist should be completed. In 2000, the JCIH and the AAP revised their goals for UNHS protocols to achieve a screening population capture rate of 95%, follow-up rate of 95%, referral rate of less than 4%, and false-positive rate less than 3%, all confirmed by 3 months of age and with intervention occurring by 6 months of age. If 95% of babies born are screened for hearing loss, as the JCIH recommends, then technology and protocols to screen for hearing loss at birth can detect approximately 90% of those with hearing loss. The primary

factor contributing to the effectiveness of hearing screening is appropriate follow-up. This critical issue is further explored in later sections of this chapter.

### TODDLER AND PRESCHOOL PERIOD (2–5 YEARS)

In the toddler and preschool periods, the screening protocol is modified to include the identification of otopathologic abnormalities (especially otitis media with effusion), mild conductive hearing loss, and previously undiagnosed, acquired, or progressive sensorineural hearing loss. Routine periodic screening of school-aged children is recommended to ensure hearing that is optimal for educational participation. Although the method of screening children in these age groups has not changed significantly, awareness of and sensitivity to the effects of hearing loss on skill development and educational achievement is far greater.

The primary goal of screening in the 2- to 5-year-old period is the detection of medically remediable otopathologic abnormalities, progressive hearing loss, or late-onset acquired hearing loss. Furthermore, parents and pediatricians should recognize that children with mild hearing loss are typically missed by UNHS programs. Screening procedures for young children are performed with the assumption that the more severe sensorineural hearing losses will have been identified by age 2 years. However, 20% to 30% of hearing loss in children up to age 18 years is acquired or progressive, and 75% of children will have at least one episode of otitis media by their third birthday. Even though this age group is particularly difficult to screen, obtaining accurate results is nonetheless important in this population. The principal cause of hearing loss in this age range is otitis media, a pathologic abnormality capable of producing subtle but significant auditory learning disorders and permanent middle-ear damage. Additionally, many conditions place children at risk for late-onset or progressive hearing loss (see Box 26-2); thus, these conditions also must be considered when screening this population.

Children in this age group are usually screened for hearing loss at well-baby clinics, pediatricians' offices, Head Start programs, and preschool programs. Although the screening procedures may differ from site to site depending on the availability of equipment and trained personnel and on the level of background noise in the screening environment, the ideal protocol would include the following elements:

1. Physical examination.
2. A detailed family history.
3. Acoustic immittance testing (tympanometry).
4. Otoscopic inspection of the ear canal.
5. Pure tone sweep at 1,000, 2,000, and 4,000 Hz at 20 dB HL for children aged 3 years and older (or OAEs, only for children who cannot condition to behavioral testing) completed by trained professionals.
6. An elicitation of parental or caregiver concern about the child's hearing and speech and language development. The importance of this element should not be underestimated. According to the NIH, 70% of children with acquired hearing loss are initially identified by parents. Parents are typically as much

as 12 months ahead of physicians in identifying their child's hearing loss. Thus, the NIH stresses that parental concern regarding hearing is sufficient reason to initiate prompt, formal, comprehensive hearing evaluation.

7. Failure to attain appropriate language milestones should result in prompt referral for further hearing evaluation by a licensed pediatric audiologist.

Although behavioral, ear-specific responses are the gold standard of hearing screening for this age group, for children who are unable to participate in behavioral procedures, screening with OAEs is acceptable, although even a mild conductive component may obscure results. Screening stimuli that lack frequency-specificity or behavioral observation techniques based on noncalibrated signals, such as rattles, music boxes, noisemakers, whisper tests, and finger-rub tests, among others, are neither recommended nor acceptable. Behavioral testing for children up to 36 months old can be conducted using visual reinforcement audiometry, whereas children older than 36 months should be able to participate in conditioned play audiometry. Both tests should be performed at a level of 20 dB in a sound booth. Any child who does not respond at this level at any one frequency should be referred for a comprehensive evaluation by a licensed audiologist. A more in-depth discussion of appropriate screening procedures for this age group can be found in the American Academy of Audiology's *Childhood Hearing Screening Guidelines*. Parents, particularly those with a child who is at risk for progressive or acquired hearing loss, should also be counseled regarding auditory and communicative milestones for their child (Box 26-3) so that they may monitor their child's development. All children should receive systematic developmental screening with an objective tool. Any children screening positive for concerns in the language domain should complete an audiologic evaluation.

### SCHOOL-AGE PERIOD (5–18 YEARS)

The primary goal of hearing screenings in this age group is identical to that of the toddler-preschool period, with the addition of the maintenance of educationally optimal hearing. Typically, these children are screened in the school setting by trained professionals and are referred to the physician only if they fail the screening. School-aged children should be screened on initial entry into school, annually in kindergarten through third grade, in seventh and eleventh grades, and as needed, requested, or mandated by regulation. In this age group, the most likely cause of hearing abnormality is an otopathologic abnormality; however, some children are still at risk for acquired or progressive hearing loss. At-risk children should be routinely monitored for hearing loss (see Box 26-2). Additionally, during this period, central auditory processing disorders typically become apparent. Children as young as 7 years may be evaluated for central auditory processing disorder by an audiologist. Parent and teacher reports are particularly important during this period and should be regarded seriously. Pediatricians should be aware of local resources for the evaluation and management of central auditory processing disorder.

### BOX 26-3 Checklist of Selected Speech-Language-Auditory Milestones Achieved by Infants and Children Who Have Intact Cognition and Hearing

#### BIRTH TO 3 MONTHS

- Startles to loud noise
- Awakens to sounds
- Blinks or widens eyes in response to new sounds

#### 3 TO 4 MONTHS

- Quiets to mother's voice
- Stops playing; listens to new sounds
- Looks for source of new sounds not in sight

#### 6 TO 9 MONTHS

- Enjoys musical toys
- Coos and gurgles with inflection
- Says, "mama"

#### 12 TO 15 MONTHS

- Responds to the baby's own name and "no"
- Follows simple requests

- Uses expressive vocabulary of 3 to 5 words
- Imitates some sounds

#### 18 TO 24 MONTHS

- Knows body parts
- Uses expressive vocabulary (2-word phrases, minimum of 20 to 50 words)
- Fifty percent of speech intelligible to strangers

#### BY 36 MONTHS

- Uses expressive vocabulary of 4- to 5-word sentences (approximately 500 words)
- Uses speech that is 80% intelligible to strangers
- Understands some verbs

Failure to achieve these milestones by expected age ranges might relate to hearing loss that necessitates audiologic testing.

Derived from Northern J, Downs M. *Hearing in Children*. 4th ed. Baltimore, MD: Williams & Wilkins; 1991.

The ideal protocol would include the following elements:

1. Otoscopic inspection of the ear canal
2. Acoustic immittance testing (tympanometry)
3. Behavioral testing under calibrated headphones or with insert phones including pure tone sweep at 1,000, 2,000 and 4,000 Hz at 20 dB HL
4. Elicitation of parental or caregiver concern about the child's hearing, speech and language development, and educational performance

Behavioral testing should be performed in the traditional method of hand raising in response to frequency-specific tones (1,000, 2,000, and 4,000 Hz) presented under headphones at 20 dB. Failure to respond at even 1 frequency in 1 ear should result in referral for complete audiometric evaluation by a licensed audiologist. Should failure of acoustic immittance testing occur at both initial testing and retesting 6 weeks later, then referral will be made to the primary care physician for evaluation of middle-ear disorder. A more in-depth discussion of appropriate screening procedures for this age group can be found in the American Academy of Audiology *Childhood Hearing Screening Guidelines*

### FOLLOW-UP CARE AND BENEFITS OF TREATMENT

The most critical aspect of an effective screening program is the subsequent follow-up care and treatment of children identified with hearing loss; those who fail their newborn hearing screening; or those labeled as at risk for progressive, late-onset, or acquired hearing loss. If no meaningful intervention and management occurs after hearing screening, or if children with a proclivity to acquired hearing loss are not screened frequently and appropriately, then the program has

failed in its primary purpose: initiating a process of timely habilitation. Timely, consistent follow-up is among the greatest challenges to hearing screening programs. In 2009, approximately 45% of children who were referred for a follow-up examination failed to return for it. A combination of administrative error and lack of parental education seem to be to blame. Inadequate data systems, inconsistent reporting requirements, and lack of communication among medical professionals have all been cited as reasons for the poor follow-up rate. In a 2004 study of medical care after school hearing screening, one of the most common barriers to follow-up was that 33% of parents surveyed did not suspect a hearing problem or doubted the screening test accuracy, or both. The importance of parental education cannot be overemphasized. A study conducted by Wittman-Price and Pope in 2002 found that although 97% of parents rated UNHS programs as "very important" on a survey and left the hospital with a scheduled follow-up appointment, only 77% returned their infant for follow-up testing. However, in an intervention group that received a 20-minute educational session on UNHS programs at a prenatal class and received educational literature, 100% of parents of referred infants returned for follow-up testing. Consistent, coordinated medical reporting and management combined with parental education are critical to the success of UNHS and early hearing detection and intervention programs. The AAP developed a checklist and flow chart to assist in the tracking of patients by their medical team (Figure 26-2; see also Figure 26-1). Simple systems such as these are an asset to primary care physicians and other members of the team.

The initial follow-up evaluation for an infant or child who fails a hearing screen or who is at risk for acquired or progressive hearing loss must include a comprehensive audiologic evaluation by a licensed audiologist, the



Early Hearing Detection and Intervention (EHDI)

Patient Checklist for Pediatric Medical Home Providers

Birth

Hospital-based Inpatient Screening Results (OAE/AABR)  
(also Home Births)

DATE: \_\_\_\_/\_\_\_\_/\_\_\_\_

Left ear: ☐ Missed ☐ Incomplete ☐ Failed Screen<sup>a, c</sup> ☐ Pass  
Right ear: ☐ Missed ☐ Incomplete ☐ Failed Screen<sup>a, c</sup> ☐ Pass

Before 1 month

Outpatient Screening Results (OAE/AABR)

\_\_\_\_/\_\_\_\_/\_\_\_\_

Left ear: ☐ Incomplete ☐ Failed Re-Screen<sup>a, c</sup> ☐ Pass  
Right ear: ☐ Incomplete ☐ Failed Re-Screen<sup>a, c</sup> ☐ Pass

Before 3 months

☐ Pediatric Audiology Evaluation<sup>b</sup>

\_\_\_\_/\_\_\_\_/\_\_\_\_

☐ Hearing Loss ☐ Normal Hearing

☐ Document child and family auditory history  
☐ Report to State EHDI Program results of diagnostic evaluation  
☐ Refer to Early Intervention (IDEA, Part C)  
☐ Advise family about communication options and assistive listening devices  
(hearing aids, cochlear implants, etc.)  
☐ Medical & Otologic Evaluations to recommend treatment and provide  
clearance for hearing aid fitting  
☐ Pediatric Audiology for hearing aid fitting and monitoring

\_\_\_\_/\_\_\_\_/\_\_\_\_  
\_\_\_\_/\_\_\_\_/\_\_\_\_  
\_\_\_\_/\_\_\_\_/\_\_\_\_  
\_\_\_\_/\_\_\_\_/\_\_\_\_

Before 6 months

☐ Enrollment in Early Intervention (IDEA, Part C)  
(transition to Part B at 3 years of age)

\_\_\_\_/\_\_\_\_/\_\_\_\_

☐ Medical Evaluations to determine etiology and identify related conditions  
☐ Otolaryngology (required)  
☐ Ophthalmologist (recommended)  
☐ Geneticist (recommended)  
☐ Developmental pediatrics, neurology, cardiology, and nephrology (as needed)

\_\_\_\_/\_\_\_\_/\_\_\_\_  
\_\_\_\_/\_\_\_\_/\_\_\_\_  
\_\_\_\_/\_\_\_\_/\_\_\_\_  
\_\_\_\_/\_\_\_\_/\_\_\_\_

☐ Ongoing Pediatric Audiology Services

\_\_\_\_/\_\_\_\_/\_\_\_\_

Patient Name: \_\_\_\_\_

Date of Birth: \_\_\_\_/\_\_\_\_/\_\_\_\_

Ongoing Care of All Infants<sup>d</sup>

☐ Provide parents with information about hearing, speech, and language milestones  
☐ Identify and aggressively treat middle ear disease  
☐ Vision screening and referral as needed  
☐ Ongoing developmental surveillance/referral  
☐ Risk indicators for delayed-onset hearing loss:

\_\_\_\_\_  
(If risk factors are present, refer for audiology evaluation at least once prior to age 30 months)

Service Provider Contact Information

Pediatric Audiologist:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Early Intervention Service Coordinator:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Other:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Other:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Other:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

(a) In screening programs that do not provide Outpatient Screening, infants will be referred directly from Inpatient Screening to Pediatric Audiology Evaluation. Likewise, infants at higher risk for hearing loss (or loss to follow-up) also may be referred directly to Pediatric Audiology.

(b) Part C of IDEA\* may provide diagnostic audiologic evaluation services as part of Child Find activities.

(c) Even infants who fail screening in only one ear should be referred for further testing of both ears.

(d) Includes infants whose parents refused initial or follow-up hearing screening.

OAE = Otoacoustic Emissions  
AABR = Automated Auditory Brainstem Response  
ABR = Auditory Brainstem Response  
IDEA = Individuals with Disabilities Education Act  
EHDI = Early Hearing Detection & Intervention

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NCHAM  
National Center for Hearing Assessment and Management  
Utah State University™

Pediatric Nurse Practitioners

February 2010 - American Academy of Pediatrics Task Force for Improving Newborn Hearing Screening, Diagnosis and Intervention  
(www.medicalhomeinfo.org)

Figure 26-2 Early Hearing Detection and Intervention (EHDI) Patient Checklist for Pediatric Medical Home Providers.

purposes of which are to assess the integrity of the auditory system, to estimate hearing sensitivity, and to identify all intervention options. At least 1 ABR test is also recommended as part of the complete diagnostic assessment of children younger than 3 years old before a permanent hearing loss can be confirmed. Once a hearing loss or the presence of middle-ear dysfunction has been confirmed by the audiologist, the child should be referred for otologic and medical consultation to determine the cause of the hearing loss, to identify related physical conditions, and to provide recommendations for medical treatment, if appropriate, as well as referrals for other services. Approximately 40% of children with hearing loss have other disabilities.

Evaluations after a failed screening should typically include the following elements for all children to help identify coexisting conditions that may affect learning and development:

1. Complete patient and family history to identify risk factors for hearing loss
2. Physical examination, and possibly laboratory and radiologic tests, to identify malformations or abnormalities of anatomic structures
3. Monitoring of developmental milestones

4. Referral for genetic evaluation and counseling by a medical geneticist
5. Referral to an ophthalmologist to test for visual acuity
6. Speech and language evaluation

In coordination with these comprehensive evaluations, audiologic intervention is usually recommended. Many treatment options are available, depending on the type and degree of the child's hearing loss. Kemper and colleagues noted that specific treatment was recommended for 51% of children who had follow-up appointments after a failed school screening. This number is even higher for those identified after UNHS evaluation. For children with conductive hearing loss, medical and surgical options are often available. In the case of a child with atresia or a similar anatomic condition that precludes medical or surgical treatment, the fitting of a bone-conduction sound processor on a softband or on a surgically implanted abutment (for children older than 5 years) is typically the treatment of choice. Amplification or the use of assistive listening devices is typically recommended for children with sensorineural hearing loss. Children as young as 4 weeks old may be fit with hearing aids

### BOX 26-4 Generalized Candidacy Criteria for Cochlear Implantation in Children

#### 12 TO 24 MONTHS

- Profound sensorineural hearing loss in both ears
- Lack of progress in development of auditory skills with appropriate binaural hearing aids
- High motivation and realistic expectations from the family
- Other medical conditions, if present, do not interfere with cochlear implant procedure

#### 25 MONTHS TO 17 YEARS, 11 MONTHS

- Severe-to-profound sensorineural hearing loss in both ears
- Receives limited benefit from hearing aids (speech scores of 30% or less in best-aided condition)
- Lack of progress in development of auditory skills
- High motivation and realistic expectations from family
- No medical contraindications

Derived from Sampaio AL, Araújo MF, Oliveira CA. New criteria of indication and selection of patients to cochlear implant. *Int J Otolaryngol*. 2011;2011:573968; and Russell JL, Pine HS, Young DL. Pediatric cochlear implantation: expanding applications and outcomes. *Pediatr Clin North Am*. 2013;60(4):841–863.

if appropriate physiologic test results have been obtained. Once diagnosed with a permanent hearing loss, children should be fit with hearing aids within 1 month of identification. Cochlear implantation is often considered for a child with severe to profound hearing loss when the child demonstrates limited benefit from hearing aids (Box 26-4 summarizes the candidacy criteria of the US Food and Drug Administration, which has approved cochlear implantation in children as young as 12 months of age). Audiologic management should be supervised by a licensed audiologist. For all of these children, speech and language assessment and therapy are essential to development and to the attainment of the goal of intelligible speech and adequate receptive language abilities by the time the child enters kindergarten.

Financial concerns should not limit a child's access to intervention services for hearing loss, although it can be challenging to identify viable sources of funding. The Individuals with Disabilities Education Act (IDEA) ensures that children who have hearing loss receive appropriate, family-centered, multidisciplinary intervention services at no charge to the family from birth through the school years. In addition, a variety of options are available to cover the cost of amplification for a child with permanent hearing loss, including private insurance, Medicaid, and the early intervention services provided by IDEA. Specifics vary by state; however, assisting patients in familiarizing themselves with the options they have available is worthwhile. (State-specific information is available at [www.infantheating.org](http://www.infantheating.org).)

## ROLE OF THE PRIMARY CARE PHYSICIAN

According to the JCIH, the AAP, and the NIH, all infants, regardless of newborn hearing screening outcome, should receive ongoing monitoring for the development of age-appropriate auditory behaviors and communication skills. Any infant who demonstrates an auditory or communicative delay should undergo comprehensive audiologic evaluation by a licensed audiologist. Additionally, any child who is at risk for hearing loss should undergo a complete audiologic evaluation at least once by 24 to 30 months of age. Being coordinator, caretaker, and advocate for the patient is the responsibility of the primary care physician. Additionally, because 30% to 40% of children with confirmed hearing loss will demonstrate developmental delays or other disabilities, the pediatrician should monitor developmental milestones and initiate referrals related to suspected disabilities. The pediatrician should strive for consistent medical management of all patients with hearing loss. Most importantly, the primary care physician should be a part of a medical team who, in collaboration with parents, the audiologist, and other health professionals, provides accessible, family-centered, continuous, comprehensive, coordinated, compassionate, and culturally appropriate health care.

## CONCLUSION

Hearing is crucial for the development of speech and language skills in children, and the presence of hearing loss can have a negative effect on social, emotional, and educational development. For this reason, hearing screening is a critical component of medical care for infants and children. Efficient screening methods combined with appropriate and timely follow-up and intervention are necessary to achieve the goals of testing by 1 month of age, identifying hearing loss by 3 months of age, and intervening by 6 months of age, all of which are important to provide optimal access to sounds during the most critical periods of development. The implementation of UNHS programs has decreased the average age of identification dramatically. However, taking the lead in the management and coordination of their patients' care is the responsibility of pediatricians and primary care physicians. Routinely referring children who fail their hearing screenings to a licensed audiologist for appropriate follow-up and management of their hearing is particularly important. Without adequate tracking and follow-up, coordinated by a team approach, maximal benefit cannot be achieved.

## ACKNOWLEDGMENT

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## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- 50 State Summary of Newborn Hearing Screening Laws (Web page), National Conference of State Legislatures ([www.ncsl.org/programs/health/hear50.htm](http://www.ncsl.org/programs/health/hear50.htm))

- *Funding Resources Through Local Agencies/Programs* (Web page), American Speech Language Hearing Association ([www.ncsl.org/research/health/newborn-hearing-screening-state-laws.aspx](http://www.ncsl.org/research/health/newborn-hearing-screening-state-laws.aspx))

### Engaging Patient and Family

- *Causes of Hearing Loss in Children* (fact sheet), American Speech-Language Hearing Association ([www.asha.org/public/hearing/disorders/causes.htm?print=1](http://www.asha.org/public/hearing/disorders/causes.htm?print=1))
- *Children and Hearing Aids* (fact sheet), American Speech-Language Hearing Association ([www.asha.org/uploadedFiles/AIS-Hearing-Aids-Children.pdf#search=%22children%22](http://www.asha.org/uploadedFiles/AIS-Hearing-Aids-Children.pdf#search=%22children%22))
- *Early Hearing Detection and Intervention - Pediatric Audiology Links to Services* (Web page), University of Maine ([www.ehdi-pals.org](http://www.ehdi-pals.org))
- *It's Important to Have Your Baby's Hearing Screened* (Web site), National Institute on Deafness and Other Communication Disorders ([www.nidcd.nih.gov/health/hearing/pages/screened.aspx](http://www.nidcd.nih.gov/health/hearing/pages/screened.aspx))
- *Just in Time So Your Baby's Care Is Right on Time: Early Hearing Detection and Intervention* (handout), Centers for Disease Control and Prevention ([www.cdc.gov/ncbddd/ehdi/documents/justintime/136poster.pdf](http://www.cdc.gov/ncbddd/ehdi/documents/justintime/136poster.pdf))
- *Parent's Guide to Hearing Loss* (Web site), Centers for Disease Control and Prevention ([www.cdc.gov/ncbddd/hearingloss/parentsguide](http://www.cdc.gov/ncbddd/hearingloss/parentsguide))

### Medical Decision Support

- *Childhood Hearing: A Sound Foundation in the Medical Home* (online course), American Academy of Pediatrics ([pedialink.aap.org](http://pedialink.aap.org))
- *Childhood Hearing Screening Guidelines*, American Academy of Audiology ([www.cdc.gov/ncbddd/hearingloss/documents/aaa\\_childhood-hearing-guidelines\\_2011.pdf](http://www.cdc.gov/ncbddd/hearingloss/documents/aaa_childhood-hearing-guidelines_2011.pdf))
- *Early Hearing Detection and Intervention* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/PEHDIC/Pages/Early-Hearing-Detection-and-Intervention.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/PEHDIC/Pages/Early-Hearing-Detection-and-Intervention.aspx))
- *The "State" of Early Hearing Detection and Intervention in the United States* (Web page), National Center for Hearing Assessment and Management, Utah State University ([www.infanthearing.org/states](http://www.infanthearing.org/states))
- *Universal Newborn Hearing Screening: Current Testing Techniques* (fact sheet), Gorga M, Eiten L, Boys Town National Research Hospital ([www.infanthearing.org/physicianeducation/UNHSFactSheet\\_Boystown.pdf](http://www.infanthearing.org/physicianeducation/UNHSFactSheet_Boystown.pdf))
- *Universal Newborn Hearing, Screening, Diagnosis, and Intervention: Guidelines for Pediatric Medical Home Providers* (guideline), American Academy of Pediatrics ([www.infanthearing.org/statelguidelines/Maine/Medical%20Guidelines.pdf](http://www.infanthearing.org/statelguidelines/Maine/Medical%20Guidelines.pdf))

### AAP POLICY

Harlor ADB Jr, Bower C; American Academy of Pediatrics Committee on Practice and Ambulatory Medicine and Section on Otolaryngology-Head and Neck Surgery. Hearing assessment in infants and children: recommendations beyond neonatal screening. *Pediatrics*. 2009;124(4):1252-1263 ([pediatrics.aapublications.org/content/124/4/1252](http://pediatrics.aapublications.org/content/124/4/1252))

Joint Committee on Infant Hearing, American Academy of Audiology, American Academy of Pediatrics, American Speech-Language-Hearing Association, Directors of Speech and Hearing Programs in State Health and Welfare Agencies. Year 2007 position statement: principles and guidelines for early hearing detection and intervention programs. *Pediatrics*. 2007;120(4):898-921 ([pediatrics.aapublications.org/content/120/4/898](http://pediatrics.aapublications.org/content/120/4/898))

### SUGGESTED READINGS

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- Ross DS, Visser AN. Pediatric primary care physicians' practices regarding newborn hearing screening. *J Prim Care Community Health*. 2012;3(4):256-63

## Chapter 27

## SCREENING FOR ANEMIA

Ruchika Sharma, MD; Bryce A. Kerlin, MD

Anemia may be defined by laboratory values (low hemoglobin) or by physiologic consequences (inadequate oxygen-carrying capacity); both are equally important. The World Health Organization (WHO) defines anemia as a hemoglobin (Hb) concentration  $\geq 2$  standard deviations (SD) below the mean Hb concentration for a normal population of the same gender and age range. Two commonly encountered pediatric conditions that may be associated with anemia and also meet criteria for screening programs (as outlined in Chapter 25, Screening: General Considerations), are sickle cell disease and iron deficiency.

### SCREENING PROGRAMS AND METHODS

Screening for anemia in infants and young children begins shortly after birth via the universal newborn screening programs, which are intended to identify cases of sickle cell disease as early as possible to enable early institution of penicillin prophylaxis. Screening continues in the office practice, emphasizing early detection of iron deficiency and appropriate implementation of nutritional counseling and iron supplementation. The latter is generally accomplished by determining the whole-blood Hb concentration, using blood obtained by finger or heel stick. The sample may be analyzed in the primary care office setting using a small portable spectrophotometer or one of the many bench-top particle counters now available. By either method, the procedure is quick and reliable, with minimal quality control and maintenance required. The Hb concentration is then compared with reference values for age- and gender-matched normal children. Hemoglobin levels that are less than the lower reference limit are defined as anemic.



Positive screening tests for anemia must be confirmed and correlated with the clinical presentation. Patients with anemia may present with signs and symptoms such as fatigue, decreased work or school performance, slow cognitive and social development during childhood, headaches, dizziness, pica, glossitis, stomatitis, pallor, or koilonychia (spooning of nails). Additional information that is relevant to the anemic patient is a history of neonatal jaundice, ethnicity, dietary intake, and family history of splenectomy, cholecystectomy, iron therapy, or blood transfusions. Information about the morphologic characteristics of the patient's red blood cells should also be obtained to guide further diagnostic evaluation. Confirmation usually is performed by submitting a venous blood sample anticoagulated with ethylenediaminetetraacetic acid (EDTA) to the hematology laboratory for a complete blood count (CBC) and microscopic examination of a Wright-stained peripheral blood smear. When abnormal hemoglobins are detected on the newborn screen, confirmatory Hb electrophoresis should be performed between 6 and 12 months of age.

For a complete discussion of the differential diagnosis, evaluation, and management of anemic children, see Chapter 128, Anemia and Pallor.

## SCREENING FOR SICKLE CELL DISEASE

### Epidemiology and Clinical Importance

Sickle cell disease is a common hereditary blood disorder in the United States, affecting an estimated 100,000 Americans. Identifying sickle cell disease early through newborn screening helps to prevent deaths and complications of the disease, such as fatal infections (eg, pneumococcal sepsis), splenic sequestration, and acute chest syndrome. The early detection of sickle cell disease through newborn screening, coupled with rapid institution of penicillin prophylaxis, has helped prevent death and other complications, including a dramatic decrease in the incidence of fatal pneumococcal sepsis in this population. Although sickle cell disease is the driving force behind these screening programs, other less common conditions that may be identified through this procedure include  $\alpha$ -thalassemia and severe forms of  $\beta$ -thalassemia.

### Benefits of Screening

With the advancement of newborn screening programs, there is now universal screening for sickle cell disease in the United States. These programs evolved from the basic tenets of newborn screening, inexpensive screening assays for common diseases for which an early intervention (penicillin) has been proved to improve overall outcomes. Therefore, the Hb screening program is focused on the early identification of infants afflicted with sickle cell disease. Box 27-1 summarizes the benefits of screening and early identification in these conditions.

### Managing a Positive Screen

All 50 US states and the District of Columbia now require screening for sickle cell disease through their respective newborn screening programs; many states also report variant hemoglobins identified incidentally

### BOX 27-1 Benefits of Screening for Sickle Cell Disease

- Screening can be accomplished using small quantities of blood and minimal risk to patients.
- Incorporation of Hb screening into existing newborn screening infrastructure allows cost efficiencies.
- Newborn Hb screening uses sensitive methods.
- Without screening, sickle cell disease may go undetected until the child presents with a life-threatening complication.
- Measures are available to prevent life-threatening complications in children identified early. These include:
  - Penicillin prophylaxis (125 mg orally twice daily)
  - Education (including parental ability to correctly palpate splenic size)
  - Referral to a pediatric hematology program for appropriate health surveillance under the guidance of hemoglobinopathy experts.
  - Timely immunization.
- Early identification also provides an opportunity for genetic counseling before a subsequent pregnancy.

during the screening process. Many of the variant hemoglobins are benign, particularly when heterozygous; a search engine provided by the Globin Gene Server (see Tools for Practice) is a useful tool for both the pediatrician and the pediatric hematologist when determining their clinical relevance. Although newborn screening improves the sensitivity of detection for  $\alpha$ -thalassemia, some forms of  $\beta$ -thalassemia may not be detectable until after Hb switching from fetal forms (at the  $\gamma\delta\beta$ -globin gene locus) has been completed, usually by 6 to 12 months of age. Consultation with a pediatric hematologist who is knowledgeable in hemoglobinopathies and thalassemic conditions may facilitate the interpretation of the potential clinical significance of variant hemoglobins and potential thalassemia cases.

Hemoglobins detected on newborn screening are typically presented in descending order of concentration within the specimen. Hb F ( $\alpha_2\gamma_2$ ) is almost always the most prevalent hemoglobin in an untransfused newborn and thus is usually the first, followed by additional species in order of prevalence when reading from left to right. Table 27-1 presents typical newborn screening results and their appropriate interpretation.

Based on these results, pediatricians should provide education and counseling to the family or refer them to a pediatric hematologist. The parents of children with an FAS pattern (sickle cell trait) should be referred to a genetic counselor from whom they can gain additional education regarding their risk for having a child with sickle cell disease and become informed regarding the effect of carriership for their children's children. These patients typically do not need to see a hematologist, although many pediatric sickle cell programs have a genetic counselor on staff who may provide the above services.



Table 27-1 Newborn Screening Hemoglobin Results and Interpretation	
HEMOGLOBINS	INTERPRETATION
FA	Normal (predominantly Hb F [ $\alpha_2\gamma_2$ ], some Hb A [ $\alpha_2\beta_2$ ])
FAS	Sickle cell trait (predominantly Hb F, some Hb A, with less Hb S [ $\alpha_2\beta^S_2$ ])
FS	Sickle cell disease (predominantly Hb F, some Hb S)
FSC	Sickle cell disease (predominantly Hb F, some Hb S, with less Hb C [ $\alpha_2\beta^C_2$ ])
FSA	Sickle cell disease with $\beta^+$ -thalassemia (predominantly Hb F, some Hb S, with less Hb A)
+ Barts	$\alpha$ -Thalassemia (Barts Hb [ $\gamma_4$ ])

Children with an FS, FSC, or FSA pattern have some form of sickle cell disease and should be prescribed penicillin prophylaxis (125 mg orally twice daily) as early as possible—optimally by 8 weeks of age—and be referred to a pediatric sickle cell program on discovery. Children with an FS pattern will likely have 1 of 2 forms of severe sickle cell disease, either Hb SS (homozygous  $\beta^S$ ) or Hb S $\beta^0$ -thalassemia (compound heterozygote for  $\beta^S$  and a  $\beta$ -thalassemia major mutation). Children with an FSC pattern also will have a severe form of sickle cell disease, Hb SC, caused by compound heterozygosity for both  $\beta^S$  and  $\beta^C$ . In contrast, children with an FSA pattern, who still express some normal adult Hb A (usually owing to compound heterozygosity for  $\beta^S$  and a  $\beta$ -thalassemia minor mutation) can be expected to have a milder course of disease.

Counseling should include education on the importance of adherence to the penicillin prophylaxis regimen, emphasizing the dramatic role that this simple intervention has played in reducing early sickle-related mortality, and guidance to seek medical attention immediately for any febrile illness, which may include admission for empirical parenteral antibiotic therapy, while excluding systemic infection. Moreover, the parents should receive instruction on how to appropriately palpate spleen size and be told to do so if their child is ill or appears pale. Whenever the spleen is enlarged beyond baseline, medical attention should be sought immediately for evaluation and treatment of a potential splenic sequestration crisis, which may include an emergent blood transfusion to reverse the process.

Children with Barts Hb should be followed closely and a careful family history taken to determine whether either or both parents have a history of anemia or have been diagnosed with  $\alpha$ -thalassemia. There are 4  $\alpha$ -globin genes, 2 paternal and 2 maternal. Often these children have either a single or double gene mutation. Single gene mutations result in a “silent carrier” state in which there are usually no detectable, clinically meaningful changes in their blood count profile, although they may have a slightly lower mean corpuscular volume (MCV). Children with 2 mutated genes have  $\alpha$ -thalassemia trait. These patients usually have a mild microcytic-hypochromic anemia (low MCV and mean corpuscular hemoglobin concentration [MCHC]) but rarely require therapy. Iron supplementation should be avoided because of a risk for eventual iron overload with long-term therapy, which will not correct the anemia. Some children, usually of Asian descent, have 3 deleted genes, leading to a

**BOX 27-2 Benefits of Screening for Iron-Deficiency Anemia**

- Iron deficiency is the most common nutritional deficiency.
- Iron deficiency has clinically significant consequences.
- Iron deficiency may go undetected without screening.
- Measurement of Hb is the most cost-effective method to screen for iron deficiency.
- Screening is convenient in the context of routine health supervision in the primary care setting.
- More sensitive and specific markers for iron deficiency may be used to confirm the diagnosis.
- Effective treatment for iron deficiency is available.

severe form of transfusion-dependent anemia called Hb H ( $\beta_4$ ) disease. These children will become progressively anemic and should be referred to a hematologist for evaluation and long-term management. Four gene deletions result in hydrops fetalis; thus, these fetuses rarely survive pregnancy.

Additional information on the care and management of children with sickle cell and thalassemia disorders can be found in Chapter 262, Hemoglobinopathies and Sickle Cell Disease.

**SCREENING FOR IRON DEFICIENCY**

**Epidemiology and Clinical Importance**

As the most commonly encountered nutritional deficiency in the world, iron deficiency is a significant public health issue. According to the National Health and Nutrition Examination 1999–2000 survey, the estimated prevalence of iron-deficiency anemia in the United States among young toddlers aged 1 to 2 years is 7%, increasing to 9% to 16% among adolescents and adult women of childbearing age, respectively ([www.cdc.gov/mmwr/preview/mmwrhtml/mm5140a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5140a1.htm)).

**Benefits of Screening**

Screening for anemia is the most reliable and cost-effective method for detecting occult iron deficiency (Box 27-2). Iron deficiency is associated with fatigue, neurocognitive delay, reduced physical capacity, and

exercise intolerance. For these reasons, inadequate iron levels should be detected and treated as early as possible. Thus, iron deficiency is the major impetus behind public health recommendations for office-based anemia screening programs as a part of health maintenance visits.

The overall incidence of iron-deficiency anemia in the United States has been decreasing over the past several decades. This decline has been attributed to use of iron-fortified formulas and iron-fortified infant foods provided by the Special Supplemental Program for Women, Infants, and Children (WIC) beginning in the early 1970s and the decrease in use of whole cow milk for infants. Thus encouragement of these dietary practices should be included in routine health counseling. Iron requirements are highest for infants and adolescents because of the increased growth velocity at these stages of development. Therefore, these children are at greatest risk for occult iron deficiency, and particular attention to appropriate dietary recommendations and indications for iron supplementation is essential. A comprehensive discussion of suitable dietary and supplementation recommendations is maintained by the Centers for Disease Control and Prevention *Morbidity and Mortality Weekly Report Recommendations and Reports* ([www.cdc.gov/mmwr/preview/mmwrhtml/00051880.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/00051880.htm)).

### Bright Futures Recommendations

Among children, iron deficiency is seen most often between 6 months and 3 years of age, owing to rapid growth and inadequate intake of dietary iron. Early detection of iron deficiency is important because occult iron deficiency may be associated with neurocognitive delay and impaired immune function. The American Academy of Pediatrics (AAP) recommends initial measurement of Hb or hematocrit for all full-term infants between 9 and 12 months of age. Preterm and low-birth-weight infants who are fed non-iron-fortified formula should be screened before 6 months of age. Children with underlying risk factors (Box 27-3) should be screened again at 15 to

18 months of age. Starting in adolescence, all non-pregnant women should be screened for anemia every 5 to 10 years throughout their childbearing years during routine health examinations, and those with risk factors for iron deficiency (eg, extensive menstrual or other blood loss, low iron intake, or a previous diagnosis of iron-deficiency anemia) should be screened annually. Adolescent males need to be screened for anemia only in the presence of risk factors.

### Managing a Positive Screening Result

When a low Hb is detected during routine screening in the office practice, a definitive diagnosis should be sought. The first step is to confirm the presence of anemia by requesting a complete blood count (see Screening Programs and Methods). Iron-deficiency anemia will typically have microcytic-hypochromic indices (low MCV and MCHC), with a high red-cell distribution width. An associated thrombocytosis is commonly observed, although thrombocytopenia may also be seen in severe cases. Other types of anemia that should be included in the differential diagnosis of microcytic anemia include thalassemia, sickle-thalassemia diseases, some hemoglobinopathies (eg, C and E), hereditary pyropoikilocytosis, severe lead intoxication, and the anemia of chronic disease. The differential diagnosis, evaluation, and management of normocytic (normal MCV) and macrocytic (elevated MCV) anemias are considered in Chapter 128, Anemia and Pallor.

For mild microcytic anemia (ie, Hb 8 to 10 g/dL), empirical treatment with iron supplementation (3 to 4 mg elemental iron/kg of body weight/day) is appropriate. Iron therapy, in combination with dietary strategies to increase iron and vitamin C intake (to enhance iron absorption), effectively treats iron-deficiency anemia by raising the Hb level and replacing iron stores. The reticulocyte count should increase within 1 week of beginning iron therapy, and the Hb should rise by at least 1 g/dL within 1 month. Treatment should continue, in patients who respond, for an additional 2 months to ensure adequate replacement of iron stores. Appropriate dietary counseling is important to prevent recurrence. Importantly, although “multivitamin with iron” formulations may be adequate to meet the recommended daily allowance, these products are not appropriate for treatment of iron deficiency.

For patients who fail to respond or who have recurrent iron deficiency, additional laboratory evaluation is indicated, and referral to a hematologist should be considered. Inadequate response may be related to continued blood loss (eg, heavy menses or occult gastrointestinal bleeding), inflammation, ineffective absorption, or poor adherence to treatment.

In patients with moderate to severe anemia (Hb <8g/dL), immediate referral to a pediatric hematologist may be appropriate, especially for children who are symptomatically anemic (eg, elevated heart or respiratory rate, failure to thrive, fatigue), and hospitalization for further evaluation and management may

#### BOX 27-3 Children at Risk for Iron-Deficiency Anemia

- Preterm and low-birth-weight infants
- Infants fed with cow milk before age 12 months
- Breastfed infants not receiving iron supplementation after age 6 months
- Formula-fed infants who do not receive iron-fortified formulas
- Children aged 1 to 5 years who ingest more than 24 ounces of cow's milk per day
- Children with special health care needs
- Children with low socioeconomic status

be indicated (especially for severe anemia, Hb <5 to 6 g/dL). For those who are clinically stable while awaiting a hematology appointment, simultaneous laboratory evaluation should be obtained at the time empirical iron therapy is begun (4 to 6 mg elemental iron/kg of body weight per day).

It is desirable to use the fewest tests that will accurately reflect iron status. Serum ferritin is a sensitive parameter for the assessment of iron stores in healthy subjects. A low serum ferritin (<15 ng/mL) confirms the diagnosis of iron deficiency. However, because serum ferritin is an acute-phase reactant, it may be elevated in the presence of chronic inflammation, infection, malignancy, or liver disease. Other studies that may be helpful in determining iron status include serum transferrin, serum iron, and iron-binding capacity; however, these assays may be misleading if the patient has recently partaken in an iron-rich meal and are, thus, best obtained in the fasting state. A lead level should be considered, particularly for younger children with iron deficiency because they may be more prone to lead intoxication secondary to the pica associated with iron deficiency.

Additional information on the care and management of children with iron-deficiency anemia can be found in Chapter 279, Iron-Deficiency Anemia.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Anemia and Your Child* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/chronic/Pages/Anemia-and-Your-Child.aspx](http://www.healthychildren.org/English/health-issues/conditions/chronic/Pages/Anemia-and-Your-Child.aspx))
- *Anemia and Your Young Child* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

#### Medical Decision Support

- *Globin Gene Server* (Web site), Penn State University ([globin.cse.psu.edu](http://globin.cse.psu.edu))

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## Chapter 28

# VISION SCREENING

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## BURDEN OF ILLNESS

Amblyopia, a permanent uncorrectable vision loss, is a major threat to vision that is preventable when detected in early childhood. During development, the visual cortex must receive focused images from both eyes to learn how to see. Conditions that interfere with the normal visual image during this time, such as strabismus, certain refractive errors, or cataracts, can lead to amblyopia if not identified and corrected. Approximately 3% of preschool-aged children have amblyopia, and up to 10% have vision problems, such as refractive error. The prevalence of refractive error increases with age and affects more than 20% of high school-aged children.

## BENEFITS OF SCREENING AND EARLY IDENTIFICATION

The likelihood of successfully treating amblyopia decreases with age. The goal is to detect amblyogenic conditions before 5 years of age. The earlier these conditions are identified and treated, the more likely and the more easily amblyopia can be prevented.

From a public health standpoint, screening for vision problems is readily justified on the following counts:

- Vision problems are common.
- Vision problems pose a threat to children's current and future well-being.
- Vision problems are likely to go undetected without screening.
- Screening tests are available that can identify children who have or are at risk for vision problems.
- Effective treatments for vision problems are readily available, and earlier treatment of amblyopia or conditions that lead to amblyopia is associated with improved treatment outcome.
- Many adolescents have refractive error that is easily correctable but unrecognized. Uncorrected refractive error could interfere with school or other activities that rely on sight.

## TOOLS

The goals of vision screening are to identify deficits in vision or conditions that might ultimately threaten vision before they otherwise would be discovered, and to ensure that appropriate diagnostic and therapeutic referrals are made so that conditions threatening vision are ameliorated. To achieve the first goal, the physician and staff must learn the appropriate vision screening techniques and procedures and then apply them systematically in their practice. To achieve the second goal, the physician must structure the primary care encounter so that screening results are



communicated accurately to parents, appropriate referrals are made (when indicated), and proper follow-up is achieved.

Appropriate vision screening techniques and procedures vary to some degree for infants and toddlers (younger than 3 years), preschool children (3 to 5 years), and school-aged children and adolescents. Instrument-based vision screening tests (eg, autorefractors) can be useful in young children who cannot cooperate with traditional vision screening tests. However, neither the American Academy of Pediatrics (AAP) nor the United States Preventive Services Task Force recommends routinely using instrument-based tests for children younger than 3 years of age.

The physician's physical examination provides some of the elements of vision screening, especially in infants and toddlers, but vision is tested more efficiently by ancillary personnel and apart from the physical examination. Children who have developmental disabilities are often at increased risk for vision problems and may require special expertise for assessment. Approaches to screening are discussed in the following sections.

## INFANTS AND TODDLERS

### Physical Examination

The eyes are first examined as part of the newborn examination and should be assessed subsequently at each health supervision visit. As part of the examination, the eyes should be inspected for any structural abnormalities. The red reflex is evaluated for abnormality or asymmetrical appearance through an ophthalmoscope. After an infant can fixate on an object, generally by 3 months of age, the corneal light reflections should be tested by using a penlight held in midline 12 inches in front of the eye (Hirschberg test). Asymmetry of the light's reflection on the 2 corneas suggests strabismus. The examiner should assess ocular motility by having the child follow a brightly colored object or toy. Information from the cover-uncover test is sometimes difficult for the unskilled person to interpret. This test detects movement of each eye when the other eye is covered and then uncovered. Such movement can suggest either a unilateral visual defect or an ocular muscle weakness in the eye that moves. (See Chapter 214, Amblyopia and Strabismus, for more detailed discussions of the physical examination of the eyes.)

### Formal Screening

Formal screening tests are not recommended for children younger than 3 years of age because of lack of data regarding screening in infants and toddlers. Any concern by parents or physicians should prompt referral.

### Special Circumstances

Infants whose circumstances or family history place them at special risk for visual problems, such as preterm infants at risk for retinopathy of prematurity, those who have a family history of congenital eye problems, or those who have genetic (eg, trisomy 21) or acquired (eg, cerebral palsy) problems that place their vision at risk, should be referred.

Parents sometimes give a history of asymmetry of the child's eyes when none can be demonstrated at the visit. Because some problems of muscle imbalance occur only when the child is fatigued, the examiner would be wise to pay attention to such a history and refer the patient to a specialist if these complaints are persistent. A family history of amblyopia, a *lazy eye*, or *crossed eyes* confers a higher risk of problems and should prompt consideration of referral.

## PRESCHOOL CHILDREN

### Physical Examination

Eyes should be inspected and the bilateral red reflex, corneal light reflex, and ocular motility tests should be performed at each health supervision visit.

### Formal Screening

Testing for visual acuity should be attempted beginning at age 3 years, and an interpretable result should be achieved by age 4 years. Having a child who is uncooperative or inconsistent in responses return for a repeat test is reasonable. Repeated failure to achieve an interpretable test result may be an indication of a visual problem.

In children 3 to 5 years old, the simpler tests of acuity that do not rely on knowledge of letters are the most acceptable. The Lea chart has become popular because children may have an easier time identifying the 4 symbols (apple, circle, square, and house) on this test than on some of the other tests. In general, these tests are available for testing from a distance of 10 and of 20 feet. At 10 feet, children are less likely to become distracted by other activities in the immediate environment.

Testing for binocular vision (stereoacuity) is not a substitute for assessing visual acuity, but it is a useful adjunct and will sometimes identify a child whose vision problems have been missed on physical examination and acuity testing. Acceptable tests for this age group include the Random Dot E Test and the Stereo Fly Test.

Instrument-based testing is an acceptable alternative to assessing visual acuity.

### Special Circumstances

Children at high risk for poor vision, as discussed previously, should be referred if satisfactory results cannot be obtained on screening.

## SCHOOL-AGED CHILDREN AND ADOLESCENTS

### Physical Examination

Eyes should be inspected and the bilateral red reflex, corneal light reflex, and ocular motility tests should be performed at each health supervision visit.

### Formal Screening

Once a child knows the alphabet, the Snellen letters on a wall chart are appropriate for visual acuity screening. For school-aged children and adolescents, vision testing machines that combine acuity testing with



tests of binocular vision are readily accepted and require less office space.

### Special Circumstances

School difficulties may be a presenting symptom of visual problems, and all children who have such troubles should have their vision evaluated if this has not been done recently. Although the prevention of amblyopia becomes less of a concern with increasing age, the overall prevalence of vision problems increases steadily over time; therefore, children should continue to be tested at health supervision visits.

## PERSONNEL AND EQUIPMENT

Nonprofessional personnel who have a high school education can be trained to administer all of these formal tests. The equipment necessary for most of these tests is readily available from medical supply houses and is inexpensive.

## REFERRAL

When strabismus or amblyopia is suspected, the child should be referred to an eye care specialist who is skilled in working with young children.

A child who has a structural abnormality of the eye or its movements, any asymmetry or abnormality of the red reflex, any asymmetry of the corneal reflections, aversion to the occlusion of one eye, or any movement of the eyes on the cover-uncover test should be referred.

Preschool children failing to pass a visual acuity test in either or both eyes at the 20/40 level or who display a 2-line discrepancy between the eyes (eg, 20/20 and 20/40), or who fail a test of binocular vision should be referred. In addition, any child who cannot be tested successfully by age 4 years after repeated attempts should be referred. School-aged children and adolescents who fail to pass at the 20/30 level in either or both eyes should be referred. In addition, children who have developmental disabilities who cannot be tested successfully should be referred.

## IMPROVING VISION SCREENING AND ITS OUTCOMES

The primary care practice and clinic settings, because they provide continuity of care, remain ideal places to carry out vision screening. Pediatricians need to screen systematically all of the children whom they see for health supervision visits. They should record and communicate the results of the screening to parents and make sure that follow-up and referral appointments are made and kept. Rates of screening are sub-optimal, and many children whose visual testing is abnormal never receive evaluation by an eye care specialist.

Few data are available about the accuracy of vision screening in the primary care setting. As in any screening program, a proportion of children will fail vision screening but have a normal eye evaluation. False-positive tests are a feature of all screening programs and should not discourage practitioners from screening. Vision screening examinations will

detect the overwhelming proportion of children who have treatable vision problems; practitioners must ensure that these cases are detected and treated properly.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Vision Screenings* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/eyes/Pages/Vision-Screenings.aspx](http://www.healthychildren.org/English/health-issues/conditions/eyes/Pages/Vision-Screenings.aspx))
- *Warning Signs of Vision Problems in Children* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/eyes/Pages/Warning-Signs-of-Vision-Problems-in-Children.aspx](http://www.healthychildren.org/English/health-issues/conditions/eyes/Pages/Warning-Signs-of-Vision-Problems-in-Children.aspx))

### Medical Decision Support

- *Screening for Visual Impairment in Children Ages 1-5 Years: Update for the USPSTF* (article), *Pediatrics*, Vol 127, Issue 2; 2011 ([pediatrics.aappublications.org/content/127/2/e442](http://pediatrics.aappublications.org/content/127/2/e442))
- *Vision Screening Recommendations* (Web page), American Association for Pediatric Ophthalmology and Strabismus ([www.aapos.org/terms/conditions/131](http://www.aapos.org/terms/conditions/131))

## AAP POLICY

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## Chapter 29

## SCREENING FOR GENETIC-METABOLIC DISEASES

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## INTRODUCTION

The aim of newborn screening is to screen for disorders for which early detection and treatment will improve outcome. Newborn screening began in the 1960s, when dried blood spots were first used to identify infants with a high phenylalanine level who might have phenylketonuria (PKU). Over the subsequent decades, tests for hypothyroidism, hemoglobinopathies, galactosemia, biotinidase deficiency, and other conditions were added. In 2006, a “uniform screening panel” of 29 conditions was recommended, as a minimal list to which all states and programs could aspire. This list includes hypothyroidism; hemoglobinopathies; congenital adrenal hyperplasia; cystic fibrosis; galactosemia; biotinidase deficiency; 22 disorders of amino acid, fatty acid, and organic acid metabolism; and hearing loss (not a blood test). More recent additions include severe combined immune deficiency, critical congenital heart disease (not a blood test), and Pompe disease (approved in 2015). This chapter addresses the metabolic disorders of galactosemia, biotinidase deficiency, and the 22 disorders of intermediary metabolism.

## OVERVIEW OF NEWBORN SCREENING

Newborn screening is a public health program run by states. The Association of Public Health Laboratories (APHL) maintains current information on those conditions for which the states conduct screening and contact information for the newborn screening coordinators in each state. This information can be accessed at [www.newsteps.org](http://www.newsteps.org). Because states differ in the conditions included in their newborn screening panel, health care providers must familiarize themselves with their state’s newborn screening panel. It is important to note that even though the newborn screening program is for the conditions, the screening itself is for analytes (see “Screening Methods” section later in this chapter). Therefore, this review is structured according to the analytes, and includes a discussion of the conditions screened for using a given analyte.

## Screening and Follow-Up

Newborn screening starts with a heel prick to collect blood on a blood spot card. Current guidelines from the Advisory Committee on Heritable Disorders in Newborns and Children state that the sample should be collected after 24 hours of age, and no later than 48 hours of age. Timing of sample collection can be modified for infants who received a transfusion or total parenteral nutrition, or were born outside a hospital (eg, home birth). Hospitals have standardized protocols for sample collection. Extensive guidelines are available through the Clinical and Laboratory Standards Institute and through local state newborn screening laboratories. The American Academy of

Pediatrics (AAP) has guidelines for efficiently integrating newborn screening follow-up into the clinic workflow. This includes confirmation of whether newborn screening was done, tracking results, communicating results, and coordinating care with subspecialists.

## Rescreening

Results of newborn screening are stratified based on the level and ratio of analytes. In general, the results fall into 3 categories: negative screening result, no follow-up required; positive screening result, repeat newborn screening recommended; positive screening result, urgent evaluation, diagnostic testing, and treatment initiation recommended. Each state newborn screening program has guidelines for stratifying and following up results in each of these categories.

All infants who screen positive should be examined by the primary care provider and the screening result explained to the parents. Box 29-1 is a list of resources that can be given to parents to explain the newborn screening report. Unacceptable specimens include those collected before 24 hours of age and those collected incorrectly; these should be re-collected.

## Screening Methods

Newborn screening for metabolic conditions uses measurement of either enzyme activity or analytes. Screening for biotinidase deficiency and galactosemia is performed using enzyme assays. The modern era of newborn screening (the expanded newborn screening panel) for metabolic errors began with the development of methods to analyze many amino acids and acylcarnitines in material extracted from dried blood spots on filter-paper Guthrie cards using tandem mass spectrometry (MS/MS). Work by an advisory panel and expert surveys led to the formulation of a list of 13 amino acids, representing 23 disorders, and 38 acylcarnitines, representing 42 disorders of fatty acid and organic acid metabolism. Although the tests are sometimes described as screens for disorders, they are actually screens for metabolites whose abnormal levels may be caused by a specific metabolic disorder. In addition to the primary metabolites, there are many secondary metabolites whose levels and ratios make the testing more precise; there are also many disorders, not part of the main list of 22, whose presence might be recognized by abnormalities of amino acids, acylcarnitines, or both. Tables detailing the metabolites and their associated disorders can be found in the paper by McHugh and colleagues published in *Genetics in Medicine* in 2011.

## BOX 29-1 Resources for Families

- Baby’s First Test ([www.babysfirsttest.org](http://www.babysfirsttest.org))
- American College of Obstetricians and Gynecologists newborn screening patient fact sheets ([www.acog.org/Patients/FAQs/These-Tests-Could-Save-Your-Babys-Life-Newborn-Screening-Tests](http://www.acog.org/Patients/FAQs/These-Tests-Could-Save-Your-Babys-Life-Newborn-Screening-Tests))
- American College of Obstetricians and Gynecologists seven things parents want to know about newborn screening ([www.acog.org/~media/Department%20Publications/nbs7Things.pdf](http://www.acog.org/~media/Department%20Publications/nbs7Things.pdf))

## Diagnostic Testing

Newborn screening is not diagnostic for any condition. The American College of Medical Genetics has published open-access newborn screening action (ACT; ACTION) sheets to guide primary care providers on initial management and follow-up testing. Expertise from the local or regional genetics/metabolic team should always be available. The team will be invaluable for confirming the suspected metabolic problem. Genetic counseling can help families understand the disorder, its causes, and the implications for other family members. False-negative results do occur with newborn screening, as with any other test, for various reasons. When a patient presents with features that suggest one of the inborn errors for which newborn screening has already been performed, it is prudent to conduct the appropriate diagnostic test for that disorder.

## Breastfeeding and Special Nutritional Needs

Infants with *most* inborn errors of metabolism, except for severe galactosemia, will tolerate some breastfeeding. Most inborn errors of metabolism will require lifelong dietary limitation of the toxic amino acid intake. This is accomplished by means of restriction of natural proteins, supplementation with special formula devoid of the toxic amino acids, and provision of adequate calories. Patients on special diets typically need regular assessment of intake and nutritional status, which includes serial laboratory testing. When needed, dietary guidance will be provided by a metabolic nutritionist. Laboratory samples for monitoring metabolic status may be obtained at home, at the primary care physician's office, or through the local hospital or pathologist, saving time and trouble for the family.

## SPECIFIC SCREENING RESULTS

### Low or Absent Biotinidase

#### Clinical Characteristics

Most infants are asymptomatic at birth. Even untreated infants usually do not become symptomatic until 4 to 5 months of age. However, presentation as early as 2 weeks of age can be seen, usually as a result of stresses such as infection. The delay in onset is caused by transfer of sufficient biotin from the mother to the infant. Symptoms, when present, typically involve the skin, brain, and immune systems. Skin manifestations commonly seen are alopecia, eczema, and dermatitis. Neurologic manifestations include hypotonia, seizures, developmental delays, sensorineural hearing loss, and progressive optic atrophy. Immune dysfunction can present as frequent infections. Associated metabolic acidosis can cause vomiting and hyperpnea. With newborn screening and early treatment initiation, biotinidase-deficient patients should remain asymptomatic for life. Newborn screening for biotinidase deficiency is not universal outside the United States and must be considered in the differential diagnosis for intractable dermatitis or a seizure disorder with associated dermatologic involvement. (For further information on biotinidase deficiency, see Chapter 106, Specific Congenital Metabolic Diseases.)

## Pathophysiology

Biotin is a B-complex vitamin (B7) that functions as a prosthetic group in all 5 human carboxylase enzymes: pyruvate carboxylase, propionyl-coenzyme A (CoA) carboxylase, 3-methylcrotonyl-CoA carboxylase, and acetyl-CoA carboxylase 1 and 2. These 5 carboxylases play important roles in gluconeogenesis, odd chain fatty acid and gluconeogenic amino acid catabolism, leucine catabolism, and fatty acid synthesis. Major sources of biotin are dietary intake and recycled biotin from endogenous proteins. Liberation of biotin from either of these sources requires the biotinidase enzyme. In biotinidase deficiency, the body is unable to recycle adequate biotin, leading to a functional deficiency of 1 or more of the carboxylases.

## Newborn Screening and Diagnostic Testing

Newborn screening uses a semiquantitative colorimetric assay to measure biotinidase enzyme activity. If low or absent, diagnostic testing involves a quantitative serum biotinidase enzyme assay, plasma acylcarnitine profile, and urine organic acid analysis. Some symptomatic infants do not exhibit urinary metabolites when they initially become symptomatic, probably because the effects of the enzyme deficiency are first manifested in the brain before they are evident in the periphery. Genetic analysis of the biotinidase (*BTD*) gene is usually conducted to understand the basis of the biotinidase deficiency and estimate its severity. Serum biotin measurement is not a sensitive indicator of biotin deficiency.

## Disease Management

Screening-positive infants should be started empirically on 10 mg of oral free biotin daily, while confirmatory tests are being performed. Relying solely on dietary sources of biotin is not recommended as a treatment option. Families should be advised to avoid raw egg white because it contains avidin, a protein that binds strongly to biotin, reducing its free bioavailable form. Cooked eggs are safe, because cooking inactivates avidin. If biotinidase deficiency is not diagnosed until symptoms develop, sensorineural hearing loss, optic atrophy, and developmental delays may not be reversible.

## Low Galactose-1-Phosphate Uridyltransferase

### Clinical Characteristics

Onset and severity depend on the degree of galactose-1-phosphate uridyltransferase (GALT, sometimes called *Gal-1-PUT* or *UDPGT*) enzyme deficiency. Classic galactosemia, seen with a GALT activity of 0 to 5% of normal, typically manifests 1 to 2 weeks after milk is introduced. Symptoms include poor feeding, poor weight gain, vomiting, diarrhea, and lethargy. Sepsis (especially *Escherichia coli* sepsis) is a common association and can be the presenting feature. Catabolism can develop within a few weeks, or later. Physical examination may reveal jaundice, hepatomegaly, signs of coagulation abnormalities, hypotonia, and bulging fontanelles. Abnormality of liver (mixed conjugated and unconjugated hyperbilirubinemia, elevated aspartate aminotransferase and alanine aminotransferase levels, coagulation abnormalities) and renal (renal tubular acidosis, galactosuria, glucosuria,



aminoaciduria, proteinuria) function may be present. Late manifestations include developmental delays, especially in speech and language development, ataxia, and premature ovarian insufficiency. These late manifestations have no correlation with the degree of dietary control.

Duarte variant galactosemia is seen when the GALT activity is around 25% of normal. This level of enzyme activity is sufficient to prevent the acute catastrophic consequences of severe GALT deficiency. (For further discussion of galactosemia, see Chapter 106, Specific Congenital Metabolic Diseases.)

### Pathophysiology

Lactose, the carbohydrate source in essentially all mammalian milk, is a disaccharide of glucose and galactose. Lactose is broken down into glucose and galactose by the intestinal enzyme lactase. The conversion of galactose to glucose requires 3 enzymes, 1 of them being GALT. Galactokinase deficiency, a rare cause of cataracts, will not be identified on GALT screening, nor will epimerase deficiency.

### Newborn Screening and Diagnostic Testing

Newborn screening for galactosemia typically uses the Beutler fluorometric assay to measure the GALT enzyme activity in the dried blood spot on filter paper. If low, diagnostic testing involves measuring the level of galactose-1-phosphate (substrate for GALT) in erythrocytes, and the level of GALT activity. Molecular DNA assay is the next step. Some states use a total galactose assay for newborn screening in an effort to better screen for other disorders of galactose metabolism besides classic galactosemia.

### Disease Management

The mainstay of management is a galactose-free diet. This is achieved by replacing human and cow milk

with soy milk. If there is significant liver disease at the time of diagnosis, an elemental formula with medium-chain triglycerides may be used transiently. Liver biopsy is rarely needed.

Infants with classic galactosemia can become symptomatic before results of the newborn screening test are reported. Therefore, galactose should be excluded from the diet immediately if clinically suspected, and if the newborn screening result is positive. Dietary treatment typically leads to rapid and complete recovery. Liver and renal dysfunction usually resolve in 1 to 2 weeks. Cataracts, if present, may resolve slowly. Unfortunately, dietary treatment does not alter the course of the late manifestations mentioned earlier in the Clinical Characteristics section. Girls need to be monitored closely in late childhood and adolescence for signs of primary/secondary amenorrhea, because those with ovarian insufficiency can benefit from hormone replacement therapy.

There is no universal agreement on dietary management for infants with Duarte variant galactosemia because the data on long-term neurodevelopmental outcomes are currently conflicting. Some authorities advocate a galactose-free diet in the first year after birth, followed by a galactose challenge with measurement of erythrocyte galactose-1-phosphate level. If this level is higher than 1 mg/dL, galactose restriction is continued. The challenge is repeated every 6 months until galactose-1-phosphate level stabilize at less than 1 mg/dL (.06 mmol/L), at which point galactose restriction is permanently lifted. Other authorities advocate no dietary restrictions from the start. Duarte variant galactosemia does not cause premature ovarian insufficiency.

### Results Suggesting Amino Acid Disorders

Table 29-1 summarizes the analytes screened for and the follow-up diagnostic testing for the amino acid disorders covered by newborn screening.

**Table 29-1** Amino Acid Disorders

ELEVATED ANALYTE ON NEWBORN SCREEN	POSSIBLE DISORDERS	DIAGNOSTIC TESTING
Phenylalanine, phenylalanine-tyrosine ratio Leucine, isoleucine (and hydroxyproline, which shares the same atomic mass) Methionine	<b>PKU</b> , hyperphenylalaninemia, BH4 deficiency, DHPR deficiency <b>MSUD</b> , hydroxyprolinemia  <b>Homocysteinuria (CBS deficiency)</b> , MAT I/III deficiency, GNMT deficiency, AdoHcy hydrolase deficiency, tyrosinemia, liver disease/injury	Plasma amino acid profile, PAH genotyping, urine pterin testing Plasma amino acid profile, urine organic acid analysis  Plasma amino acid profile, plasma total homocysteine, plasma vitamin B <sub>12</sub> level, urine organic acid analysis
Tyrosine, succinylacetone Succinylacetone Citrulline	Tyrosinemia (TAT deficiency, 4-HPPD deficiency), liver disease/injury <b>Tyrosinemia type I (FAH deficiency)</b> <b>Citrullinemia type I</b> , citrulinemia type II (citrin deficiency) <b>argininosuccinic acidemia</b>	Plasma amino acid profile, urine organic acid analysis  Plasma ammonia level, plasma amino acid profile, urine organic acid analysis

AdoHcy, S-adenosylhomocysteine; BH4, tetrahydrobiopterin; CBS, cystathionine beta-synthase; DHPR, dihydropteridine reductase; FAH, fumarylacetoacetate hydrolase; GNMT, glycine N-methyl transferase; 4-HPPD, 4-hydroxyphenylpyruvate dioxygenase; MAT I/III, methionine adenosyl transferase isoenzymes I/III; MSUD, maple syrup urine disease; PAH, phenylalanine hydroxylase; PKU, phenylketonuria; TAT, tyrosine aminotransferase.  
Disorders targeted in the uniform screening panel are in **bold**.



### **Elevated Phenylalanine With Low Tyrosine on Newborn Screening**

#### **PHENYLKETONURIA**

**Clinical Characteristics.** Based on the severity of enzyme deficiency, PKU is classified as classic PKU in infants with complete deficiency, or hyperphenylalaninemia in infants with partial deficiency. Untreated classic PKU results in global developmental delays, intellectual disability, and seizures. But with treatment, classic PKU can be clinically silent or manifest only subtle neuropsychiatric features (slowing of executive functioning, attention-deficit/hyperactivity disorder, depression, and anxiety).

**Pathophysiology.** Phenylketonuria is caused by deficiency of the enzyme phenylalanine hydroxylase (PAH). PAH oxidizes phenylalanine into tyrosine. Phenylalanine is an essential amino acid. In infants, one-third to one-half of dietary phenylalanine is used directly for incorporation into growing proteins. In adults, only 5% to 10% of dietary phenylalanine is incorporated into protein. The rest is converted to tyrosine. Tyrosine in turn acts as the substrate for the synthesis of the monoamine neurotransmitters (dopamine, epinephrine, and norepinephrine) and melanin. PAH deficiency leads to toxic accumulation of phenylalanine and relative tyrosine deficiency. High phenylalanine levels are directly neurotoxic. In addition, relative tyrosine deficiency leads to reduced synthesis of monoamine neurotransmitters. Excess phenylalanine is metabolized through minor pathways, producing phenylacetate, phenylpyruvate, phenethylamine, and phenylacetylglutamate which are excreted in the urine. Phenylpyruvate is a phenylketone.

**Newborn Screening and Diagnostic Testing.** An elevated phenylalanine and phenylalanine-tyrosine ratio on the newborn screen using MS/MS is reported as positive. Elevations are categorized as either mild to moderate or severe. Mild to moderate elevations require repeat newborn screening before diagnostic testing is considered. Diagnostic testing involves plasma amino acid profile. Molecular DNA assay is the next step, because direct enzyme assay requires a liver biopsy.

**Disease Management.** The normal blood phenylalanine level is 1–2 mg/dL (60–120 mcmo/L). No treatment is needed if the blood level is less than 6 mg/dL (363 mcmo/L). Restriction of dietary phenylalanine is the mainstay of treatment if phenylalanine levels are higher than. The goal is to achieve a plasma phenylalanine level of 2–6 mg/dL (120–263 mcmo/L). Restricting phenylalanine intake to the amount tolerated severely restricts total protein intake, so special metabolic formulas and foods that provide extra tyrosine without phenylalanine must be used. Infants with severe PAH deficiency may tolerate only 250 to 300 mg/d. Nutritional guidelines and recommendations were recently published by a collaborative of the Genetics Metabolic Dieticians International, Southeast Regional Genetics, and National Institutes of Health PKU scientific review committee and by the American College of Medical Genetics and Genomics.

Tetrahydrobiopterin (BH4) is a natural cofactor for PAH. Sapropterin dihydrochloride (synthetic tetrahydrobiopterin, BH4) is an adjunct to diet modifications. Any residual enzyme activity can boost the PAH

enzyme activity and increase phenylalanine tolerance. Most responders welcome this addition because it allows them to eat more regular popular protein foods. The brain's exposure to excess phenylalanine (or a high ratio of phenylalanine to tyrosine) is the basis of damage. Because several amino acids share the same transport system across the blood-brain barrier, supplementation with a group of large neutral amino acids may offer some protection by competing for transport. Experimental therapies being investigated include the oral use of an enzyme to convert dietary phenylalanine to a less toxic product (polyethyleneglycol-conjugated phenylalanine ammonia lyase [PEG-PAL]; ClinicalTrials.gov Identifier:NCT01819727).

Phenylketonuria and several other problems can occur together if there is a problem with BH4 metabolism. In addition to PAH, tyrosine hydroxylase and tryptophan hydroxylase also require BH4. These enzymes are necessary for the production of dopamine, norepinephrine, and serotonin. Infants with “malignant hyperphenylalaninemia” are identified by increased phenylalanine on newborn screening, but treating only the PKU component will not prevent brain damage. So after the newborn screening result (high phenylalanine) is confirmed, blood testing is performed for the enzyme dihydropteridine reductase and analysis of urine for pterin derivatives. Treatment of malignant hyperphenylalaninemia involves restriction of phenylalanine, supplementation with sapropterin dihydrochloride, tyrosine, the neurotransmitter precursors L-dopa and 5-hydroxytryptophan, and frequent monitoring. (For further discussion of PKU, see Chapter 106, Specific Congenital Metabolic Diseases.)

**MATERNAL PHENYLKETONURIA.** The severity of PKU has been greatly reduced with diet modifications and other therapies, so girls with PKU now grow up and wish to start families of their own. This poses a challenge for pediatricians working with adolescents, and physicians in family medicine/internal medicine/obstetrics and gynecology working with adult women with PKU. Poorly controlled maternal PKU is teratogenic, and will result in a spectrum of developmental anomalies called the *maternal PKU (MPKU) syndrome*. The features include microcephaly, intrauterine growth restriction, congenital heart defects, and severe intellectual disability. To avoid this outcome, the mother's phenylalanine level should be less than 6 mg/dL (363 mcmo/L) before conception and during the pregnancy. Frequent monitoring is required. Fetal echocardiography should be considered at 20 to 22 weeks of gestation. Breastfeeding by mothers with PKU is safe, unless the infant also has PAH deficiency.

### **Elevated Leucine Plus Isoleucine (Xle) on Newborn Screening**

#### **MAPLE SYRUP URINE DISEASE**

**Clinical Characteristics.** The age at onset and severity depend on the degree of branched-chain ketoacid dehydrogenase (BCKD) enzyme complex deficiency. Clinical groups include neonatal “classic,” intermediate, intermittent, thiamine-responsive, and E3-deficient forms. Encephalopathy is the main clinical manifestation, with elevated leucine thought to be the primary neurotoxin. The neonate with the classic form of maple syrup

urine disease (MSUD) will present with encephalopathy that can progress to cerebral edema and herniation. Most infants with severe MSUD will have some degree of permanent intellectual disability. Prompt newborn screening is followed by a very narrow window of only a few days to confirm the diagnosis and initiate treatment. This rapid course demands prompt action for follow-up evaluation and testing by the metabolic specialist in partnership with the primary care physician.

**Pathophysiology.** Maple syrup urine disease is caused by a deficiency of the BCKD enzyme complex. BCKD complex is a heteropentamer of 3 catalytic (E1, E2, and E3) and 2 regulatory (kinase and phosphorylase) subunits. BCKD complex plays a central role in the catabolism of branched-chain amino acids (BCAAs)—leucine, isoleucine, and valine. BCAA catabolism provides substrates for multiple pathways, including gluconeogenesis, lipogenesis, and ketogenesis. Deficiency of this multienzyme complex secondary to a deficiency of any of its subunits leads to accumulation of BCAAs and their derivative branched-chain ketoacids.

The BCKD enzyme complex has several subunits that are assembled together. Defects in all subunits are recessively determined. BCKD complex shares some of its components with pyruvate and  $\alpha$ -ketoglutarate dehydrogenase complexes. Thiamine as thiamine pyrophosphate (thiamine diphosphate) is a cofactor in all of them.

The intermediate and intermittent forms are less severe and often involve mutations in the E2 subunit, which may be responsive to thiamine supplementation. Mutations in E3 subunit are always severe; this is because E3 is a part of not only the BCKD complex, but also the pyruvate dehydrogenase and  $\alpha$ -ketoglutarate enzyme complexes and the glycine cleavage system. One would thus expect more severe metabolic derangements.

**Newborn Screening and Diagnostic Testing.** An elevated total level of leucine and isoleucine (which have the same molecular weight, so are sometimes listed as Xle) on the newborn screen is reported as positive. Diagnostic testing involves plasma amino acid profile and urine organic acid analysis. The BCAAs and their ketoacids are seen to be elevated. The markers with the highest sensitivity for the diagnosis of MSUD are elevated amino acid allo-isoleucine levels and an increased leucine-alanine ratio.

**Disease Management.** The mainstay of management is dietary restriction of BCAA, while providing adequate amounts of the other amino acids and other nutrients for normal growth and development. This typically involves a high-calorie BCAA-free formula, in addition to a dietary source of whole protein (ie, standard infant formula or breast milk). Because leucine is the most toxic amino acid of the 3, its intake must be rigorously restricted. Sometimes it is necessary to supplement with isoleucine and/or valine, in addition to what is present in the (restricted) natural protein source, to provide enough of those nutrients. Recommendations from the Genetic Metabolic Dietitians International are now available.

Metabolic decompensations are typically triggered by infection, fasting, and dietary indiscretions. It is essential to recognize an impending acute crisis early.

Early symptoms include poor feeding, vomiting, and fever. Dinitrophenylhydrazine testing of urine allows home detection of increasing BCAAs, which in turn, allows early initiation of a “sick day” management protocol. Altered level of consciousness and cerebral edema are a significant risk during episodes of illness with MSUD, so careful monitoring is essential. Rapid treatment of increased intracranial pressure may prevent herniation.

Early intervention significantly reduces neuropsychological deterioration over the long term. If the disease is poorly controlled despite good dietary management, liver transplantation is an option. Transplantation cannot reverse existing brain damage, but it will prevent overwhelming metabolic decompensation and further damage.

Successful management of MSUD has been reported during pregnancy and lactation. The metabolic shifts that occur during pregnancy may be rapid, and may be complicated by the nausea, vomiting, and poor intake that occur in many pregnancies. These principles apply to many inborn metabolic errors. (For further discussion of MSUD, see Chapter 106, Specific Congenital Metabolic Diseases.)

### **Elevated Methionine on Newborn Screening**

#### **HOMOCYSTINURIA AND OTHER DISORDERS OF TRANSULFURATION AND TRANSMETHYLATION.**

Methionine is the screening marker for cystathionine  $\beta$ -synthase (CBS) deficiency, the most prominent cause of homocystinuria. However, elevated methionine can be associated with other conditions listed in Table 29-1.

**Clinical Characteristics.** Four major organ systems are involved in CBS deficiency: eye (dislocated lens, myopia, glaucoma), bones (osteoporosis, lengthening of the long bones, scoliosis, high arched palate, pes cavus, widened metaphyses with spicules, long slender fingers, pectus deformities), central nervous system (intellectual disability, psychiatric disorders, seizures, dystonia), and vascular (thrombus formation and thromboembolism). Some infants respond to supplementation with pyridoxine (the precursor of pyridoxal-5'-phosphate, the cofactor for CBS). Those who do respond to pyridoxine supplementation typically are older at onset of symptoms and have a less severe phenotype. Age at onset and severity are variable, even within the same family. Thromboembolism has been reported as early as infancy, but most clinical features develop during later infancy to adolescence.

**Pathophysiology.** Homocysteine is an intermediate in the transulfuration pathway and the closely linked transmethylation pathway. In the transulfuration pathway, homocysteine condenses with serine to form cystathionine, using the enzyme CBS.  $\alpha$ -ketoglutarate is then cleaved away, leaving cysteine, containing the transferred sulfur. CBS deficiency is the basis of the best-known form of homocystinuria.

Homocysteine can be methylated to methionine by 2 separate processes. One process uses 5-methyltetrahydrofolate and a vitamin B<sub>12</sub> cofactor, methylcobalamin. After giving up its methyl group, the folate must be regenerated using methylene tetrahydrofolate reductase (MTHFR). Defects in the first steps of the vitamin B<sub>12</sub> pathway will lead to impaired synthesis of methionine

and accumulation of methylmalonic acid (“combined deficiency”). The second process of methionine synthesis involves using betaine as a donor, acting through betaine-homocysteine methyltransferase.

Methionine accepts the adenosine moiety from adenosine triphosphate to form S-adenosylmethionine (SAM), a reaction catalyzed by methionine adenosyltransferase isoenzymes I and III (MAT I/III) in the liver. SAM is a versatile methyl donor, taking part in many different reactions. Upon losing its methyl group, SAM becomes S-adenosylhomocysteine (SAH), which is hydrolyzed to form adenosine and homocysteine. Homocysteine can be remethylated to regenerate methionine, completing the methionine cycle.

The risk for thrombus formation and thromboembolism with homocystinuria is thought to be secondary to its effects on vascular endothelial wall and platelet function.

**Newborn Screening and Diagnostic Testing.** Elevation of methionine on the newborn screen is reported as positive. (Methionine may also be elevated in patients with tyrosinemia or other forms of liver disease.) Homocysteine is not directly measured because most of it is bound to protein. If newborn screening result is positive for hypermethioninemia, diagnostic testing includes plasma amino acid profile, plasma total homocysteine, vitamin B<sub>12</sub> levels, and urine organic acid analysis. (Amino acid analysis measures only *free* homocysteine; *total* homocysteine is measured using a different technique, and must be specifically requested. Total homocysteine is commonly measured in patients with coronary artery disease or thrombosis.) CBS deficiency will have both hypermethioninemia and hyperhomocystinemia. Enzyme or molecular DNA assay is the next step. It is important to note that newborn screening will miss most pyridoxine-responsive infants who have CBS deficiency. Therefore, clinical manifestations suggestive of CBS deficiency should trigger an evaluation even if the newborn screening result is normal. Low methionine with elevated homocysteine should direct the physician toward disorders of transmethylation (MTHFR and cobalamin complementation groups C-G deficiencies).

(A word about names: Homocysteine and cysteine have a terminal sulfhydryl group [-SH]. If a dimer is formed, with a bond between the 2 sulfurs [disulfide bond], the result is homocystine, cystine, or a mixed disulfide. The disorder is called *homocystinuria*; homocysteine is the amino acid measured.)

**Disease Management.** The first step in the management of CBS deficiency is to ascertain if the infant is responsive to pyridoxine supplementation. Pyridoxine responsiveness is best ascertained by a trial. There is no standard dosing or duration for a pyridoxine trial, which will probably be done by the geneticist. If responsive, pyridoxine supplementation alone is sufficient treatment. If the patient is not responsive to pyridoxine, however, dietary methionine restriction and supplementation with L-cystine and betaine are recommended. Methionine restriction and L-cystine supplementation have been shown to prevent intellectual disability, lens dislocation, and bony changes. Betaine has been shown to reduce the incidence of thromboembolic events. Anticoagulant therapy has

mixed results. If an infant with CBS deficiency needs to undergo surgery, the risk of thromboembolic events can be reduced by good metabolic control and hydration perioperatively.

**MATERNAL CBS DEFICIENCY.** Hyperhomocystinemia, resulting from any cause, is associated with an increased risk of preeclampsia. Women with CBS deficiency have an increased risk of thromboembolic events at baseline, which is further increased during the postpartum period. Successful pregnancy outcomes have been reported with good metabolic control, which includes dietary methionine restriction, folate supplementation, and betaine for homocysteine reduction.

### **Elevated Tyrosine with Normal Phenylalanine on Newborn Screening**

**TYROSINEMIA.** Three separate conditions may be identified: fumarylacetoacetate hydrolase (FAH) deficiency, tyrosine aminotransferase (TAT) deficiency, and transient tyrosinemia of the newborn.

**Clinical Characteristics.** Fumarylacetoacetate hydrolase deficiency is also called *tyrosinemia type I* or *hepatorenal tyrosinemia*. The onset of biochemical changes typically occurs in the neonatal period or infancy. It can be lethal if untreated. This disorder involves hepatic, renal, and peripheral nerve pathologies. Hepatic involvement is initially biochemical in nature, with elevated transaminases, and coagulation abnormalities (elevated prothrombin time/partial thromboplastin time) that are unresponsive to vitamin K administration. The infants can subsequently develop bleeding, hepatomegaly, and cirrhosis. Renal manifestations include glomerular and tubular injury, with excessive renal loss of glucose, phosphate, amino acids, and bicarbonate (renal Fanconi syndrome). This can lead to vitamin D-unresponsive rickets, nephromegaly, and failure to thrive. The hepatic disease can lead to hepatocellular carcinoma in childhood. (Tyrosinemia type I is one of the rare metabolic disorders that can cause malignancy.)

The mechanism behind the hepatic and renal involvement is not known. Peripheral neuropathy is thought to result from a direct toxic effect of elevated  $\delta$ -aminolevalonic acid (ALA), secondary to competitive inhibition of ALA dehydratase by succinylacetone. Patients with this condition present with an acute neuropathic pain. This condition is discussed in the section on sick day management principles. Infants with FAH deficiency may have a secondary deficiency of 4-hydroxyphenylpyruvate dioxygenase (4-HPPD), hypothesized to be protective because it reduces the production of toxic downstream metabolites like SUAC. This is the basis of nitisinone (2-[2-nitro-4-trifluoromethylbenzoyl]-1,3-cyclohexanedione; NTBC) therapy discussed in Disease Management in this section. Hypertrophic cardiomyopathy, albeit rare, has been described in this disorder.

Tyrosine aminotransferase deficiency is also called *tyrosinemia type II* or *oculocutaneous tyrosinemia*. Its onset is typically in infancy. Infants can present with painful corneal erosions, circumcorneal injection, lacrimation, and photophobia. These can mimic keratitis resulting from herpes simplex infection, but the lesions



do not take up fluorescein dye. Cutaneous lesions are painful, nonpruritic, hyperkeratotic scaly patches, typically localized to the palmoplantar regions. These lesions are not hyperpigmented, distinguishing them from inflammatory skin conditions. Half the infants have intellectual disability.

Transient tyrosinemia of newborn is caused by immaturity of the 4-HPPD enzyme (and of liver metabolism in general), and therefore, is more prevalent in premature infants or infants receiving high protein formula/intake ( $>5$  g/kg per day). Transient tyrosinemia is principally a biochemical abnormality in an otherwise asymptomatic neonate. The tyrosine level typically peaks by 2 weeks of age and resolves by 1 month or later in premature infants. Before widespread availability of infant formulas to families of limited means, evaporated milk was used as a substitute, leading to excessively high protein intake. Changing to a standard infant formula and vitamin C supplementation would rapidly lower the plasma tyrosine level.

There are some other very rare causes of tyrosine elevation that will not be discussed further in this chapter.

**Pathophysiology.** Tyrosine is a semiessential amino acid obtained from dietary protein and phenylalanine catabolism. Tyrosine contributes to gluconeogenesis, ketogenesis, synthesis of the monoamine neurotransmitters (dopamine, epinephrine, and norepinephrine), and melanin. Tyrosinemia or elevation of plasma tyrosine is a biochemical finding seen in various conditions. The most common causes are acquired and not inborn errors of metabolism. Transient tyrosinemia of the newborn and tyrosinemia secondary to severe hepatocellular injury are the usual causes. Tyrosinemia from inborn errors of metabolism include deficiencies of any of the 3 enzymes in the main tyrosine catabolic pathway: TAT, 4-HPPD, and FAH.

**Newborn Screening and Diagnostic Testing.** An elevated tyrosine level on newborn screen is reported as positive. Succinylacetone (SA) is being added to state newborn screening programs to identify infants with tyrosinemia type I (FAH deficiency), because tyrosine alone is unreliable to assess FAH deficiency. Many US state newborn screening laboratories have added succinylacetone to the mass spectrometry target list. Diagnostic testing includes plasma amino acid profile and urine organic acid analysis. In all 3 enzyme deficiencies, tyrosine and its metabolites are elevated in both plasma amino acid profile and urine organic acid analysis. SA is also elevated in FAH deficiency.

**Disease Management** The first steps are to check the urine organic acids for SA, and to look for acquired causes of hepatocellular injury. The mainstay of treatment for inborn errors of tyrosine metabolism is dietary restriction of tyrosine and phenylalanine by limiting natural protein, and supplementation with a special formula and later medical foods devoid of tyrosine and phenylalanine.

For FAH deficiency, NTBC, which inhibits the enzymatic step before the formation of fumarylacetoacetate is used. This prevents the formation of the most toxic metabolites, including succinylacetone. NTBC has altered the natural course of this disease. It significantly reduces both acute crises and chronic

hepatic, renal, and peripheral neuropathic manifestations, and dramatically lowers the risk for hepatocellular carcinoma and neurocognitive delays. Hepatic or combined hepatorenal transplantation can be curative. (See also Chapter 106, Specific Congenital Metabolic Diseases.)

For TAT deficiency, dietary intervention typically resolves the ocular and cutaneous symptoms. A trial of pyridoxine, the cofactor for TAT, can be considered.

**MATERNAL TYROSINEMIA TYPE I.** Successful pregnancy outcomes, with normal infant growth and development, have been reported in women with tyrosinemia type I. NTBC is not teratogenic and its continued use during the pregnancy is recommended. The newborn screening result in neonates born to mothers with tyrosinemia type I will be positive for elevated tyrosine, secondary to maternal tyrosinemia and NTBC treatment. However, this spontaneously resolves. A urine organic acid analysis will be negative for SA in these infants.

### **Elevated Citrulline on Newborn Screening**

**UREA CYCLE DISORDERS.** Screening for citrulline, a marker of 2 urea cycle disorders (citrullinemia and argininosuccinic aciduria), is included in the core panel.

**Clinical Characteristics.** Both conditions affect the urea cycle and share a similar clinical picture. The onset varies from the early neonatal period to late adulthood, depending on the degree of enzyme deficiency. Both conditions lead to hyperammonemia. Hyperammonemia is a respiratory center stimulant, causing tachypnea (and associated respiratory alkalosis), and later, respiratory depression and apnea (and acidosis). Glutamine accumulates as a temporary storage metabolite for excess ammonia. Ammonia may not leave the brain as rapidly as needed, so glutamine can accumulate intracellularly, including in the neurons. This can create an osmotic gradient, leading to diffuse cerebral edema, a bulging fontanelle, rapid increase in head circumference (in neonates), vomiting, lethargy, hypothermia, poor feeding, and eventually coma and death. Hyperammonemia is often confused with sepsis, cerebral trauma, or intracranial bleeding. Some degree of intellectual disability may occur even with good treatment. Infants with argininosuccinic aciduria also may have hair that breaks easily and has a characteristic appearance (on microscopy), with periodic bulging of the hair shafts and rupture of the cortical sheath, called *trichorexis nodosa* or *bamboo hair*. The hair becomes normal with appropriate metabolic treatment.

Neonatal onset seen with severe enzyme deficiency typically occurs after at least 24 hours after birth. Hyperammonemia occurring earlier may be the result of transient hyperammonemia of newborn, pyruvate dehydrogenase deficiency, glutaric acidemia (GA) type II, or sepsis.

Late onset seen in infants with a less severe enzyme deficiency may be triggered by an increase in protein intake. This can occur when an infant is weaned off breast milk or infant formula to cow milk or other nourishment with higher protein content, or later in life during times of increased protein intake. Infection



or other catabolic stressors can also precipitate an episode. The clinical features are similar to those with neonatal onset, but milder and intermittent.

Infants with hyperammonemia or other forms of protein intolerance who are not identified with newborn screening or clinical illness may self-select a low protein diet. This can be an important cue in the history.

**Pathophysiology.** Urea cycle is the primary pathway for nitrogen waste excretion. It also serves as the major pathway for arginine synthesis and metabolism. Five of the 6 urea cycle enzymes (N-acetylglutamate synthase, carbamoyl phosphate synthetase [CPS], ornithine transcarbamylase [OTC], argininosuccinate synthetase [AS], and argininosuccinate lyase [AL]) are commonly associated with hyperammonemia. The core newborn screening test targets AS deficiency (citrullinemia type I), and AL deficiency (argininosuccinic acidemia). With urea cycle impairment, the body is unable to synthesize sufficient arginine, which then becomes a semiessential amino acid. All 5 urea cycle deficiencies associated with hyperammonemia can be lethal in the neonatal age group, and must be considered in the differential diagnosis of any infant presenting with an encephalopathy after 24 to 48 hours of age. The first test in this situation is to measure the blood ammonia level.

**Newborn Screening and Diagnostic Testing.** An elevated citrulline on newborn screening is reported as positive. Further testing is required to define the cause of this elevation. Diagnostic testing includes plasma ammonia, plasma amino acid profile, and urine organic acid analysis. Ammonia (and if possible the other 2 tests) must be obtained at the earliest possible opportunity, preferably when the infant is seen again by the primary care physician for urgent evaluation after a positive newborn screening result. Hyperammonemia and plasma amino acid profile with increased glutamine and alanine, and relatively low arginine and ornithine, are present in all 4 urea cycle defects (CPS, OTC, and AS and AL deficiencies). Increased citrulline is only seen in AS and AL deficiencies. When citrulline is significantly elevated, and argininosuccinic acid is

not, AS deficiency (citrullinemia type I) is diagnosed. If argininosuccinic acid is also increased, then AL deficiency (argininosuccinic acidemia) is diagnosed.

**Disease Management.** The mainstay of management is dietary protein restriction, without compromising normal growth and development, by providing a calculated amount of natural protein based on age requirements, and supplementation with a protein-free caloric powder (containing carbohydrates, lipids, minerals, trace elements, and vitamins), and arginine. In addition, infants with AS deficiency are given phenylbutyrate (a precursor of phenylacetate), which acts to enhance excretion of excess nitrogen as phenylacetylglutamine. Phenylbutyrate is not usually required for infants with AL deficiency because they can synthesize argininosuccinate, which removes more waste nitrogen per molecule than citrulline. (Phenylacetate was used before phenylbutyrate, but it has an unpleasant odor and thus not as well tolerated.) Sodium benzoate, which can conjugate with glycine (forming hippurate) to remove excess nitrogen, is sometimes also used. Long-term treatment control and compliance is best assessed by monitoring plasma glutamine (which may be elevated even when ammonia is normal) in the plasma amino acids. Liver transplantation may be considered for severe cases in which metabolic control is difficult to achieve, or if there is a high risk for a catastrophic hyperammonemic event.

Results Suggesting Mitochondrial Fatty Acid Oxidation Disorders

The core newborn screening test is designed to target deficiencies of 4 mitochondrial fatty acid oxidation enzymes: carnitine uptake defect (CUD), medium-chain acyl-CoA dehydrogenase (MCAD), very-long-chain acyl-CoA dehydrogenase (VLCAD), long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), and trifunctional protein (TFP). (See also Chapter 106, Specific Congenital Metabolic Diseases.)

Table 29-2 summarizes the analytes screened for and the follow-up diagnostic testing for the mitochondrial

Table 29-2 Mitochondrial Fatty Acid Oxidation Disorders		
ABNORMAL LEVELS OF CARNITINE AND ACYLCARNITINES ON NEWBORN SCREENING	POSSIBLE DISORDERS	DIAGNOSTIC TESTING
Low/absent free carnitine	<b>CUD</b> , also called carnitine transporter	Plasma and urine total and free carnitine (and plasma creatinine, for determining the fractional excretion of carnitine)
Elevated C8 +/- C6 and C10	<b>MCAD</b>	Plasma acylcarnitine profile, urine organic acid analysis, urine acylglycine analysis
Elevated C14:1	<b>VLCAD</b>	Plasma acylcarnitine profile, urine organic acid analysis
Elevated C16-OH +/- C18-OH	<b>LCHAD, TFP deficiency</b>	Plasma acylcarnitine profile, urine organic acid analysis

:1, presence of 1 double bond; C, carbon length; CUD, carnitine uptake defect; LCHAD, long-chain 3-hydroxyacyl-CoA dehydrogenase; MCAD, medium-chain acyl-CoA dehydrogenase; OH, hydroxy fatty acid; TFP, trifunctional protein; VLCAD, very-long-chain acyl-CoA dehydrogenase. Disorders targeted in the uniform screening panel are in **bold**.

fatty acid oxidation disorders covered by newborn screening.

### Clinical Characteristics

**COMMON CLINICAL CHARACTERISTICS.** Onset can vary from day 1 of life into adulthood, presenting as episodes of altered mental status, lethargy, seizures, vomiting, dyspnea, tachypnea, apnea, and coma, triggered by catabolic stressors. This presentation is often confused with sepsis. If these episodes are severe, they can cause significant neurodevelopmental delays. Fatty infiltration of the liver can occur, leading to hepatomegaly, liver dysfunction, and the associated complications. This cerebrophepatic involvement is often confused with Reye syndrome. Families can have a history of loss of previous children from unknown causes or sudden infant death syndrome. These are recessive conditions, therefore unscreened siblings of affected children should be tested for the same condition.

Carnitine uptake defect, VLCAD, LCHAD, and TFP deficiencies can present with cardiomyopathy and skeletal myopathy causing exercise intolerance, weakness, soreness, fatigue, or rhabdomyolysis. These are rare in MCAD deficiency.

### ADDITIONAL DISEASE-SPECIFIC CLINICAL INFORMATION

**CUD.** The first peak is between 3 months and 2.5 years of age, presenting with episodes of hypoketotic hypoglycemia. If recurrent, fatty infiltration of major organs can be seen. The second peak is between 1 and 7 years of age, presenting as a cardiomyopathy.

**MCAD Deficiency.** This is the most common mitochondrial fatty acid oxidation disorder, with wide clinical variability ranging from neonatal death to absence of symptoms into adulthood, even in a family with severe symptoms. Rarely, a parent of a child with MCAD deficiency is also detected to have MCAD deficiency.

**VLCAD Deficiency.** VLCAD is categorized as 2 distinct phenotypes based on the predominant feature—the early-onset, more severe VLCAD cardiomyopathy (VLCAD-C) and later-onset, less severe VLCAD hypoglycemia/hepatic (VLCAD-H) type. They can be distinguished by enzyme activity and/or mutation analysis.

**LCHAD/TFP Deficiency.** In addition to the common manifestations discussed before, infants with LCHAD deficiency may have a pigmentary retinopathy and a mixed neuropathy. Hemolytic anemia and thrombocytopenia have also been reported. Women carrying a fetus affected with LCHAD/TFP deficiency may have an acute fatty liver of pregnancy or HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome.

### Pathophysiology

$\beta$ -Oxidation of fatty acids takes place in the mitochondria. This pathway is very active in the liver, heart, and skeletal muscles. Fatty acid oxidation is a crucial energy source in times of fasting. This pathway has at least 20 enzymatic steps to carry out the  $\beta$ -oxidation spiral of 4 recurring reactions, with the primary end-product being acetyl-CoA. Acetyl-CoA is used for gluconeogenesis and ketogenesis, and many other

processes. In disorders of fatty acid oxidation, paucity of acetyl-CoA leads to hypoketotic hypoglycemia (negative or inappropriately low urine ketones despite hypoglycemia), metabolic acidosis, and hyperammonemia. The unused fatty acids are redirected toward synthesis of triglycerides, phospholipids, and cholesterol esters, which progressively accumulate in different organs including the liver, heart, and skeletal muscles. They may also be conjugated with carnitine.

**CUD.** As the name suggests, cells are unable to take up carnitine because of a defect in the carnitine transporter protein, OCTN2. Carnitine is required for fatty acid oxidation. In its absence, the cells cannot use fatty acids for energy production despite normal mitochondrial  $\beta$ -oxidation enzymes.

**MCAD.** This enzyme plays an essential role in the  $\beta$ -oxidation of medium chain fatty acids, 4- to 10-carbon long.

**VLCAD.** This enzyme plays an essential role in the  $\beta$ -oxidation of long-chain fatty acids, 12- to 22-carbon long.

**LCHAD/TFP.** These enzymes play an essential role in the  $\beta$ -oxidation of long-chain hydroxy fatty acids, 12- to 16-carbon long. TFP is an enzyme complex made of 2 proteins, one with LCHAD and hydratase activity, the other with thiolase activity. Only LCHAD or all 3 enzyme activities may be impaired.

Note regarding names: Mitochondrial oxidation of long-chain fats, 12- to 22-carbon long, requires an enzyme that, for historical reasons, is called very-long-chain acyl-CoA dehydrogenase (VLCAD). This mitochondrial enzyme is NOT related to the metabolism of very-long-chain fatty acids (>22 carbons), that occurs in the peroxisomes.

### Newborn Screening and Diagnostic Testing

The newborn screening tests use MS/MS to evaluate for free carnitine and acylcarnitine species. Each of these 4 screened disorders has a specific pattern of acylcarnitine abnormalities. The patterns flagged positive are as follows:

CUD: Low/absent free carnitine  $\pm$  low levels of all acylcarnitine species

MCAD deficiency: Elevated C8  $\pm$  elevated C6 and C10 acylcarnitine species

VLCAD deficiency: Elevated C14:1  $\pm$  other long-chain acylcarnitine species

LCHAD/TFP deficiency: Elevated C16-OH  $\pm$  C18-OH and other long-chain acylcarnitine species

Diagnostic testing includes a plasma acylcarnitine profile and urine organic acid analysis (plus urine acylglycine analysis if screening is positive for C8  $\pm$  C6 and C10). The diagnosis is based on the pattern noted in these tests. Common mutation analysis (MCAD, LCHAD) or gene sequencing assays are the next steps.

Maternal CUD and other mitochondrial fatty acid oxidation disorders: If diagnostic testing for CUD in a screening-positive infant is normal, one must rule out a primary or secondary carnitine deficiency in the mother, including CUD or deficiencies of MCAD, 3-methylcrotonyl-CoA (3-MCC) carboxylase, or glutaryl-CoA dehydrogenase. Mothers in such cases are usually asymptomatic.

### Disease Management

The mainstay of daily management is to avoid fasting and to provide adequate calories intravenously during episodes of diminished oral intake.

**CUD.** Carnitine supplementation is the mainstay of treatment. Very large amounts of carnitine may be required. Carnitine supplementation is very safe. The 2 most common side effects are loose stools and a fishy odor resulting from the production of trimethylamine from carnitine by the gut flora. (There are several strategies to cope with the odor if it occurs.)

**MCAD DEFICIENCY.** Moderate restriction of dietary fat “heart-healthy diet” and carnitine supplementation is usually used.

**LCHAD AND VLCAD DEFICIENCY.** Restrict long-chain fat intake, providing adequate amounts of essential long-chain fatty acids. Medium-chain triglyceride formula or supplement will provide fatty acids of medium-chain length, which can be oxidized for energy. In older children, uncooked cornstarch can provide a gradual steady source of complex carbohydrates overnight, thus avoiding the fasting state associated with overnight sleep. Patients with LCHAD/TFP deficiency should undergo regular ophthalmology evaluations because of the risk of retinopathy.

### Results Suggesting Organic Acid Disorders

Many clinical and biochemical features of organic acidemias can be explained by the toxic organic acid intermediates that accumulate and the changes they trigger in other biochemical pathways. Hypoglycemia seen in most organic acidemias is caused by disruption of fatty acid oxidation and substrate production for gluconeogenesis because of the sequestration of CoA. Metabolic acidosis is secondary to accumulating organic acid intermediates, especially lactate and ketone bodies. Failure of gluconeogenesis leads the body to shift metabolism toward mitochondrial  $\beta$ -oxidation of fatty acids and ketogenesis for energy generation, resulting in worsening metabolic acidosis and ketosis. In nearly all these disorders, the metabolic block is at a step involving a substrate coupled to coenzyme A; free CoASH may be deficient in other reactions, including production of acetyl-CoA. Deficiency of acetyl-CoA impairs the urea cycle enzyme-N-acetylglutamate synthetase, leading to hyperammonemia. Thus, the majority of the organic acidemias discussed in this chapter will have hyperketotic hypoglycemia, metabolic acidosis, and hyperammonemia presenting as an encephalopathy (poor feeding, vomiting, lethargy, seizures, coma) with signs of metabolic acidosis (hyperpnea).

The primary goal of therapy is to minimize use of the pathway with the deficient enzyme. This is achieved by limiting dietary intake of its precursor, suppressing the production of the substrate from endogenous sources, and enhancing alternative pathways of utilization and detoxification. Dietary limitation must maintain a “balanced” caloric intake for normal growth and development with “substrate-free” formula supplementation. Despite this, the body will still generate some of the targeted substrate endogenously.

This will be exacerbated in times of catabolic stress (poor intake, infection, illness, fever, or trauma). Provision of adequate calories suppresses lipolysis, ketogenesis, and gluconeogenesis. Free CoA is recovered from the substrate at the metabolic block using alternative pathways. Carnitine, which is a carrier molecule for fatty acid transfer into the mitochondria, is especially helpful for conjugation with many other substances that have CoA intermediates. Occasionally, a vitamin cofactor for the deficient enzyme can boost its catalytic ability.

Mild, brief illnesses are generally treated by removing the specific substrate from the daily oral intake for 1 to 2 days and providing adequate calories to arrest catabolism. This is often called *sick day formula*. Supplemental carnitine or other detoxifying agents may be given.

If oral treatment is precluded, intravenous glucose (with appropriate electrolytes) and lipids are used. In times of acute crisis when the patient is in a state of hyperketotic hypoglycemia, metabolic acidosis, and hyperammonemia, additional measures must be taken to correct these metabolic derangements. Adequate caloric support is essential. Intravenous L-carnitine can enhance detoxification. Severe hyperammonemia can be treated using hemodialysis or hemofiltration. Patients must be appropriately monitored for blood glucose, ketones, ammonia, and other metabolites, and cerebral perfusion and edema. As with mild illnesses, prolonged complete avoidance of an essential nutrient will lead to ongoing catabolism, so the restricted amino acid(s) must be reintroduced relatively quickly, but gradually. Critically ill patients are usually best treated in an intensive care unit by an experienced team, and with rapid metabolic analysis available on site. (For additional discussion of organic acidemias, see Chapter 106, Specific Congenital Metabolic Diseases.)

Table 29-3 summarizes the analytes screened for and the follow-up diagnostic testing for the organic acid disorders covered by newborn screening.

### Elevated C3 (Propionylcarnitine) Species on Newborn Screening

#### PROPIONIC ACIDEMIA/METHYLMALONIC ACIDEMIA/SOME DISORDERS OF VITAMIN B<sub>12</sub> METABOLISM

**Clinical Characteristics.** These disorders share a common metabolic pathway and have overlapping clinical features. The onset of symptoms can range from infancy to adulthood, based on the severity of the enzyme deficiency. Common clinical manifestations include vomiting, poor feeding, lethargy, and tachypnea. In milder cases, self-selected protein avoidance may be seen. Late complications include cognitive delays, seizures, dystonia, and poor growth. Cardiomyopathy can be seen later in life with propionic acidemia and can be the presenting feature. Chronic renal disease and failure frequently occur in methylmalonic acidemia. Some disorders of vitamin B<sub>12</sub> metabolism present similar to methylmalonic acidemia. In addition, infants with some vitamin B<sub>12</sub> metabolism disorders have homocysteinuria, which puts them at an increased risk for thrombosis and retinopathy.

**Table 29-3**      **Organic Acid Disorders**

<b>ELEVATED ACYLCARNITINE ANALYTES ON NEWBORN SCREENING</b>	<b>POSSIBLE DISORDERS</b>	<b>DIAGNOSTIC TESTING</b>
C3 (propionylcarnitine)	<b>Propionyl-CoA carboxylase deficiency (propionic acidemia), methylmalonyl-CoA mutase deficiency (methylmalonic acidemia), cobalamin metabolism disorders</b> , maternal vitamin B <sub>12</sub> deficiency	Plasma acylcarnitine, profile, total plasma homocysteine, urine organic acid analysis
C5	<b>Isovaleryl-CoA dehydrogenase deficiency (isovaleric acidemia)</b> , antibiotics containing pivalic acid	Plasma acylcarnitine profile, urine organic acid analysis, urine acylglycine analysis
C5-DC (glutarylacarnitine)	<b>Glutaryl-CoA dehydrogenase deficiency (glutaric acidemia type I)</b>	Plasma acylcarnitine profile, urine organic acid analysis, urine acylglycine analysis
C5-OH	<b>3-MCCC deficiency, HMG-CoA lyase deficiency, multiple carboxylase (holocarboxylase synthetase) deficiency</b> , biotinidase deficiency, <b>mitochondrial acetoacetyl-CoA carboxylase (branched chain keto-thiolase) deficiency</b>	Plasma acylcarnitine profile, urine organic acid analysis

3-MCCC, 3-methylcrotonyl-CoA carboxylase; C, carbon length; CoA, coenzyme A; DC, dicarboxylic; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA lyase; OH, hydroxy.

Disorders targeted in the uniform screening panel are in **bold**.

secondary to a yet unidentified mechanism. These disorders were called *forms of ketotic hyperglycinemia* caused by significant elevation of plasma and urine glycine, until the individual enzyme defects were discovered. These disorders are unrelated to nonketotic hyperglycinemia, a disorder of glycine cleavage.

**Pathophysiology.** Propionyl-CoA is the main source of methylmalonyl-CoA. Their disorders share a common metabolic pathway and overlapping clinical features. (The CoA forms are intracellular. The free acids, propionic and methylmalonic, are found in body fluids and urine.) Roughly half the total body propionate is generated during catabolism of 4 essential amino acids (isoleucine, valine, methionine, and threonine), 25% from odd-chain fatty acid and cholesterol metabolism, and the remaining 25% from gut microbial metabolism. Propionyl-CoA is metabolized to D-methylmalonyl-CoA by propionyl-CoA-carboxylase, a biotin-dependent enzyme. D-methylmalonyl-CoA is racemized to L-methylmalonyl-CoA. Methylmalonyl-CoA is rearranged by methylmalonyl-CoA mutase, an adenosylcobalamin-dependent enzyme, to succinyl-CoA, a Krebs cycle intermediate. Propionyl-CoA is a 3-carbon compound. Therefore, elevation of the C3 acylcarnitine species on newborn screening indicates a possible problem in this metabolic pathway.

Propionic and methylmalonic acidemias have multiple causes. Propionic acidemia can be secondary to a deficiency of either propionyl CoA carboxylase, or its cofactor, biotin, which is made available by the enzyme biotinidase and enzymatically incorporated into the enzyme by holocarboxylase synthase. Similarly, methylmalonic acidemia is a biochemical diagnosis

and can be either from a primary deficiency of methylmalonyl-CoA mutase (complete deficiency: mut0; partial deficiency: mut–), or a deficiency of its cofactor, adenosylcobalamin.

Two forms of vitamin B<sub>12</sub> (cobalamin or Cbl) are used by humans, adenosylcobalamin and methylcobalamin. Vitamin B<sub>12</sub> is present in the diet. Several specialized proteins are required for digestion, absorption, and transport in the plasma. After being taken up into the cells, the cobalt moiety undergoes several enzymatic reductions. Separate pathways then lead to the 2 final products, adenosylcobalamin and methylcobalamin. Defects in the first shared steps lead to methylmalonic acidemia with homocysteinuria. Defects in the unshared steps of B<sub>12</sub> metabolism lead to just 1 of these problems. (Defects specific to the methylcobalamin pathway will not elevate propionylcarnitine.) An important cause of cobalamin problems in newborns is primary deficiency of vitamin B<sub>12</sub> arising from maternal B<sub>12</sub> deficiency.

**Newborn Screening and Diagnostic Testing.** Elevation of C3 acylcarnitine species (propionylcarnitine) on newborn screening can indicate propionic or methylmalonic acidemia. Diagnostic testing includes plasma acylcarnitine profile, total homocysteine, and urine organic acid analysis to help differentiate among propionic acidemia, methylmalonic acidemia (mut0, mut–, CblA, CblB deficiency), cobalamin transport, metabolism disorders (CblC, CblD, CblF deficiency), and vitamin B<sub>12</sub> deficiency (caused by maternal deficiency). All have an elevated C3 species in the acylcarnitine profile. Methylmalonic acidemia will have elevated urinary methylmalonic acid, a metabolite not seen in propionic acidemia. An elevated total



plasma homocysteine strongly suggests a disorder of cobalamin availability, transport, or metabolism. Complementation group analysis, enzyme assays, or mutation analysis are the next steps.

**Disease Management.** Management of cases of propionic and methylmalonic acidemia involves limiting natural protein to the amount required/tolerated of the toxic amino acids, supplementing with special formula devoid of the toxic amino acids, and providing adequate calories. Carnitine supplementation to replace that lost as propionylcarnitine is essential in propionic acidemia. In methylmalonic acidemia, relatively little carnitine is lost because methylmalonic acid itself is excreted very readily. Chronic alkali therapy is sometimes needed. The gut production of propionate can be reduced with pulsed oral administration of broad-spectrum antibiotics and early treatment of constipation. In addition, infants with cobalamin transport and metabolic defects (CblA and B), usually respond to hydroxycobalamin given by daily injection. Betaine (to enhance production of methionine by the alternative pathway), carnitine, folic acid, and pyridoxine are also used. In infants with frequent metabolic decompensations despite medical management, hepatic or combined hepatorenal transplantation significantly reduces the frequency of metabolic decompensation. Valproate should be avoided because its intermediate, valproyl-CoA, can combine with carnitine and deplete carnitine stores. In addition, all nephrotoxic drugs should be used cautiously in infants with methylmalonic acidemia, because these infants are susceptible to renal failure as a late complication.

### **Elevated C5 Acylcarnitine Species on Newborn Screening**

#### **ISOVALERIC ACIDEMIA**

**Clinical Characteristics.** Onset is typically in the neonatal period with episodes of vomiting, poor feeding, lethargy, metabolic stroke, and coma (encephalopathy), triggered by catabolic stressors. The infant may also have a peculiar odor reminiscent of “sweaty feet” because of the sweat and cerumen during these episodes. Transient pancytopenia caused by bone marrow suppression has been described. Long-term complications include neurocognitive delays and failure to thrive, if untreated. A good neurocognitive outcome is possible for milder cases. Pancreatitis, although rare, has also been reported.

**Pathophysiology.** Isovaleryl-CoA is the product of the reaction catalyzed by the BCKD complex, the deficiency of which leads to MSUD, as discussed earlier. This in turn acts as a substrate for isovaleryl-CoA dehydrogenase (IVD), which catalyzes its irreversible conversion to 3-methylcrotonyl-CoA. Deficiency of IVD leads to toxic accumulation of isovaleryl-CoA and its organic acid derivatives, leading to isovaleric acidemia. As mentioned under MSUD, BCAA catabolism provides substrates for multiple metabolic pathways, including gluconeogenesis, lipogenesis, and synthesis of nitrogen buffers alanine and glutamine. Interruption of these pathways will have consequences in

times of catabolic stress. Unlike MSUD, in which catabolism of all 3 BCAAs is disrupted, IVD deficiency only disrupts leucine catabolism.

**Newborn Screening and Diagnostic Testing.** An elevated C5 acylcarnitine finding on newborn screening is reported as positive. Newborn screening can detect C5 acylcarnitine species using MS/MS, but cannot distinguish the different C5 isomers seen in other organic acidemias and with certain antibiotic use. Diagnostic testing involves a quantitative plasma acylcarnitine profile, urine organic acid, and urine acylglycine analysis. Enzyme or DNA molecular assays are the next steps. In isovaleric acidemia, a specific mutation, 932C>T, has been described with a milder biochemical phenotype. Infants with at least 1 copy of this mutation tend to be either asymptomatic or have a milder clinical picture.

**Disease Management.** The mainstay of management is limitation of dietary leucine, which is achieved by restricting natural protein to the amount required/tolerated, supplementation with special formula devoid of leucine, and provision of adequate calories. In addition, carnitine and/or glycine supplementation enhances the excretion of the toxic organic acid intermediates by conjugating them into less toxic compounds. A good neurocognitive outcome is possible in many cases.

**MATERNAL ISOVALERIC ACIDEMIA.** With good metabolic control using the usual management as during nonpregnant states, successful pregnancy outcomes can be expected.

### **Elevated C5-DC (Glutaryl-carnitine) Acylcarnitine Species on Newborn Screening**

#### **GLUTARIC ACIDEMIA TYPE I**

**Clinical Characteristics.** Most infants are normal at birth, except for macrocephaly and occasional non-specific findings of jitteriness and irritability. Brain magnetic resonance imaging may show macrocephaly, increased fluid over the cerebral hemispheres. The Sylvian fissure may be widely open. Onset of symptoms (provoked by catabolic stressors) is typically between 6 and 18 months of age with vomiting, hypotonia, developmental regression, seizures, dystonia, dyskinesia (facial grimacing, tongue thrusting, fisting, opisthotonus), and coma (encephalopathy). Hepatomegaly might be present. Most infants do not fully recover from these acute episodes. Neurodegenerative changes accumulate over time with each new episode, revealing a pattern of frontotemporal atrophy and striatal degeneration. Despite the progressive neurodegeneration, cognition and intellect are not affected. Acute pancreatitis has also been reported in association with GA I.

**Pathophysiology.** GA I is caused by a deficiency of glutaryl-CoA dehydrogenase, a mitochondrial enzyme involved in the catabolism of 3 amino acids, lysine, hydroxylysine, and tryptophan. It catalyzes the conversion of glutaryl-CoA to crotonyl-CoA.

**Newborn Screening and Diagnostic Testing.** An elevated C5-DC (glutaryl-carnitine) acylcarnitine on newborn screening using MS/MS is reported as positive. Diagnostic testing involves a quantitative plasma amino

acid profile, urine organic acid, and urine acylglycine analysis, with elevated glutaric and hydroxyglutaric species in infants with this enzyme deficiency. Enzyme and molecular DNA assays are the next steps.

**Disease Management.** The possibility of neurodegeneration can be reduced with dietary limitation of lysine intake achieved by natural/tolerated level of the toxic amino acids, supplementation with special formula devoid of the toxic amino acids, provision of adequate calories, carnitine supplementation, and aggressive intervention during catabolic stresses (see Sick Day Management section in this chapter).

### **ISOLATED 3-METHYLCROTONYL-CoA CARBOXYLASE DEFICIENCY**

**Clinical Characteristics.** The onset typically includes an illness in the neonatal period with episodes of vomiting, lethargy, hypotonia, seizures, metabolic stroke, and coma (encephalopathy) triggered by catabolic stressors. Cardiomyopathy has been reported as a presenting feature in some infants. During these episodes, the infant may have a peculiar odor reminiscent of cat urine. Long-term complications include failure to thrive and neurocognitive delays. However, emerging data suggest that less than 10% of infants diagnosed with 3-MCC deficiency actually develop these symptoms.

**Pathophysiology.** 3-Methylcrotonyl-CoA carboxylase catalyzes the next step in leucine catabolism after dehydrogenation of isovaleryl-CoA to 3-methylcrotonyl-CoA by IVD. 3-MCC converts 3-methylcrotonyl-CoA into 3-methylglutaconyl-CoA. Deficiency of 3-MCC leads to accumulation of 3-MCC-CoA and its related organic acids. 3-MCC is initially synthesized as an apoenzyme requiring incorporation of biotin, catalyzed by the enzyme holocarboxylase synthetase. Thus, isolated 3-MCC deficiency shares biochemical and clinical features with infants with biotinidase and holocarboxylase synthetase (multiple carboxylase) deficiencies.

**Newborn Screening and Diagnostic Testing.** Elevated 3-hydroxyisovaleryl/2-methyl-3-hydroxybutyrylcarnitine (C5-OH) acylcarnitine is reported as positive. MS/MS detects the C5-OH acylcarnitine species, but cannot distinguish the different C5-OH isomers. Diagnostic/confirmatory testing involves a quantitative plasma acylcarnitine and urine organic acid analysis. Enzyme or molecular DNA analysis is the next step.

**Disease Management.** Most infants are asymptomatic except during times of stress; therefore, life long dietary protein (leucine) restriction and carnitine and/or glycine supplementation are usually not necessary.

**MATERNAL 3-METHYLCROTONYL-CoA CARBOXYLASE DEFICIENCY.** A positive newborn screening result for 3-MCC deficiency is sometimes caused by maternal enzyme deficiency; mothers with this condition often are asymptomatic.

### **3-HYDROXY-3-METHYLGLUTARYL-CoA LYASE DEFICIENCY**

**Clinical Characteristics.** Onset can be in the neonatal period to late childhood with episodes of vomiting, lethargy, hypotonia, seizures, and coma (acute encephalopathy), triggered by catabolic stressors. Unlike in IVD and 3-MCC deficiencies, ketosis is not prominent

in this condition. In fact, deficiency of this enzyme impairs 1 of the sources of acetoacetate used for ketogenesis. The differential diagnosis for nonketotic or hypoketotic hypoglycemia includes HMG-CoA lyase deficiency, acetoacetyl-CoA thiolase deficiency (discussed later in this chapter) and mitochondrial fatty acid oxidation disorders (discussed before). Long-term complications include neurocognitive delays and seizures secondary to leukodystrophic insults during acute episodes. Isolated cases of cardiomyopathy and pancreatitis have been reported.

**Pathophysiology.** 3-hydroxy-3-methylglutaryl-CoA lyase (HMG-CoA lyase) catalyzes the next step in leucine catabolism after carboxylation by 3-MCC. HMG-CoA lyase converts 3-methylglutaconyl-CoA into acetoacetate and acetyl-CoA, which then feed into ketogenesis and gluconeogenesis via the Krebs cycle. Deficiency of this enzyme leads to accumulation of 3-methylglutaconyl-CoA and its organic acid products, in addition to reduced ketogenesis and gluconeogenesis. As with 3-MCC deficiency, this condition does not present with elevation of leucine and its keto-acid, because the upstream reaction catalyzed by BCKD complex is irreversible.

**Newborn Screening and Diagnostic Testing.** An elevated C5-OH acylcarnitine on newborn screening is reported as positive. Newborn screening can detect C5-OH acylcarnitine species using MS/MS, but cannot distinguish the different C5-OH isomers. Diagnostic/confirmatory testing involves a quantitative plasma acylcarnitine profile and urine organic acid analysis. Enzyme or molecular DNA analysis is the next step.

**Disease Management.** The mainstay of management is avoidance of fasting. Dietary restriction of protein but not fat intake is recommended. Carnitine supplementation can be considered. A ketogenic diet is contraindicated.

### **MULTIPLE CARBOXYLASE DEFICIENCY**

**Clinical Characteristics.** Onset is typically in the first 3 months of age, with poor feeding, hypotonia, lethargy, seizures, and developmental delays. Dermatitis, alopecia, and immune dysfunction with frequent infections can be present.

**Pathophysiology.** Multiple carboxylase deficiency should be considered in the differential diagnosis for intractable dermatitis or a seizure disorder poorly responsive to anticonvulsants with associated dermatologic involvement. Multiple carboxylase deficiency is actually the deficiency of a single enzyme, holocarboxylase synthetase. The condition is termed *multiple carboxylase deficiency* because holocarboxylase synthetase is essential for the activation of all 5 human carboxylase enzymes: pyruvate carboxylase, propionyl-CoA carboxylase, 3-methylcrotonyl-CoA carboxylase, and acetyl-CoA carboxylase 1 and 2. All these enzymes are initially translated as inactive apoenzymes. Their activation to holoenzymes requires addition of biotin as a prosthetic group, a step facilitated by holocarboxylase synthetase. Therefore, deficiency of holocarboxylase synthetase can lead to deficiency of 1 or more carboxylases, presenting as a multiple carboxylase deficiency.

**Newborn Screening and Diagnostic Testing.** Elevation of C5-OH acylcarnitine is reported as positive. Newborn screening using MS/MS will detect C5-OH acylcarnitine species, but cannot distinguish among the different C5-OH isomers. Diagnostic testing involves a quantitative plasma acylcarnitine profile and urine organic acid analysis. Gene sequencing for the holocarboxylase synthetase (*HLCS*) gene is typically not required, except in infants who do not respond to standard treatment, including supplemental biotin. These infants might have mutations that affect the enzyme structure in a way that supplementation with biotin, this enzyme's prosthetic group, will not increase the activity of the enzyme.

**Disease Management.** Infants who are positive on newborn screening or symptomatic must be seen immediately by the pediatrician. All infants with positive results on newborn screening should be started empirically on 10 mg of oral biotin (free, not bound) daily. Although most infants respond to biotin supplementation, occasionally some infants do not. No other treatment is currently available.

#### **MITOCHONDRIAL ACETOACETYL-CoA THIOLASE (BRANCHED-CHAIN KETO-THIOLASE) DEFICIENCY**

**Clinical Characteristics.** Onset is typically in the first 2 years of age, with episodes of vomiting, lethargy, and coma (encephalopathy), triggered by catabolic stressors.

**Pathophysiology.** Acetoacetyl-CoA thiolase (branched-chain or  $\beta$ -ketothiolase) is involved in the catabolism of the BCAAs isoleucine and ketolysis. It facilitates the conversion of 2-methyl-acetoacetyl-CoA, an intermediate in isoleucine catabolism, into acetyl-CoA and propionyl-CoA, which then feed into gluconeogenesis via the Krebs cycle and ketolysis. Deficiency of this enzyme leads to accumulation of upstream organic acid intermediates and their derivatives. As with 3-MCC and HMG-CoA lyase deficiencies, this condition also does not present with elevation of isoleucine and its derivatives, because the upstream reaction catalyzed by BCKD complex is irreversible.

**Newborn Screening and Diagnostic Testing.** Elevation of C5-OH acylcarnitine on newborn screening is reported as positive. Newborn screening can detect C5-OH acylcarnitine species using MS/MS, but cannot distinguish the different C5-OH isomers. Diagnostic testing involves a quantitative plasma acylcarnitine profile and urine organic acid analysis. Enzyme or mutation analysis can confirm the diagnosis.

**Disease Management.** The mainstay of management is to avoid fasting. Dietary restriction of protein, but not fat intake is recommended. Carnitine supplementation can be considered. A ketogenic diet is contraindicated.

### **SICK DAY MANAGEMENT PRINCIPLES (GENERAL STATEMENTS)**

Metabolic decompensations are typically triggered by infection, fasting, and dietary indiscretions. It is essential to recognize an impending acute crisis early. Early symptoms include poor feeding, vomiting, and fever. This brief guide is to familiarize the primary care physician with the general principles. The

management usually requires the involvement of a metabolic geneticist and nutritionist.

#### **Phenylketonuria**

Anticipate an increase in plasma phenylalanine level during illness. Brief periods of elevated phenylalanine do not have long-term consequences. No urgent dietary changes are necessary.

#### **Maple Syrup Urine Disease**

Management includes rapid elimination of accumulating leucine, providing adequate calories to arrest protein breakdown, and controlling brain edema/herniation.

#### **Tyrosinemia Type I**

Acute hepatic crisis and acute peripheral neuropathy crisis are the 2 most common presentations. The first step is to limit catabolism by providing nutrition—preferably oral if tolerated, else lavage—in addition to supplemental intravenous glucose and treating the infection. Acute hepatic crisis, as the name implies, is worsening of liver functions and can present as jaundice, ascites, and/or a bleeding disorder, with hepatic encephalopathy as a late sign. Evaluate with liver enzyme studies, coagulation profile, serum  $\alpha$ -fetoprotein, and ammonia levels. Elevated  $\alpha$ -fetoprotein, bilirubin, and ammonia are markers of severe liver dysfunction, suggesting an increased risk of impending liver failure and hepatic encephalopathy. Management is otherwise supportive. A peripheral neuropathic crisis can present primarily as a painful peripheral neuropathy lasting for up to a week. Occasionally, this is accompanied by autonomic dysfunction (hypertension, tachycardia) and paralysis requiring mechanical ventilation. If abdominal imaging studies are needed, avoid barbiturates for sedation because they can induce/worsen a peripheral neuropathic crisis. Management involves pain control with analgesics and narcotics. Glucose also helps by inhibiting ALA synthetase. These crises can exacerbate the underlying renal syndrome, and therefore close monitoring of electrolytes and their replacement as needed is recommended.

#### **Citrullinemia Type I and Argininosuccinic Acidemia**

If the infant is symptomatic (respiratory symptoms and/or encephalopathy), obtain plasma ammonia measurements to assess the degree of hyperammonemia. If significantly elevated, discontinue all protein intake to reduce nitrogen load and initiate intravenous 10% glucose at maintenance. Urgent hemodialysis is the best way to lower the plasma ammonia level, but high-flow hemofiltration has also been used. Hemodialysis should be repeated until plasma ammonia level is down to 3 times the upper reference range. Once ammonia is down to 3-fold normal, treatment with intravenous sodium benzoate and sodium phenylacetate (in patients with citrullinemia) and 10% arginine (in patients with either citrullinemia or argininosuccinic acidemia) in 10% dextrose is the next step. Intravenous ondansetron 0.15 mg/kg during the first 15 minutes of the initial infusion can help with



vomiting. Increased intracranial pressure can be managed with mannitol. Once ammonia levels are near normal, intravenous medications are switched to oral.

### Mitochondrial Fatty Acid Oxidation Disorders

The goal is to divert the metabolism away from the affected mitochondrial fatty acid oxidation pathway and provide carnitine as a carrier for excreting accumulating toxic metabolic intermediates. Anticipatory treatment with D10 1/4NS at 1.5 to 2 times maintenance along with carnitine supplementation helps achieve this goal and should be started at the first sign of an illness. The degree of metabolic derangement can be ascertained by checking a basic metabolic panel (glucose, electrolytes, urea), ammonia, uric acid, creatine phosphokinase, lactate, liver function tests, complete blood count, urinalysis (for myoglobinuria), in addition to plasma total and free carnitine, acylcarnitine profile, and urine organic acid analysis (plus urine acylglycine analysis in infants with MCAD deficiency).

### Propionic Acidemia/Methylmalonic Acidemia

Plasma electrolytes, blood gases, and ammonia are the most sensitive tests to confirm a state of acute metabolic decompensation. In addition, lactate and a complete blood count will show lactic acidosis and cytopenia (neutropenia or pancytopenia). If abnormal, plasma acylcarnitine profile and urine organic acid analysis and orotic acid should be obtained, but results need not be awaited for initiating treatment. Additional laboratory tests including amylase, lipase, blood culture, and C-reactive protein should be considered, given reports of pancreatitis and neutropenia. Treatment includes discontinuing all protein intake for the first 24 to 48 hours, initiating intravenous fluids with dextrose 10% or higher to prevent catabolism, doubling the daily dose of carnitine, and lastly for hyperammonemia, initiating sodium benzoate and carbamylglutamate or, if severe, continuous hemofiltration. Do not use phenylbutyrate or phenylacetate. Intravenous sodium bicarbonate might be required if the acidosis is not controlled with the aforementioned measures. Consensus management guidelines published in 2014 by Baumgartner and colleagues provide detailed dosing recommendations for glucose, hydroxocobalamin, biotin, sodium benzoate, and sodium phenylbutyrate, L-arginine-HCL, and N-carbamyl-glutamate therapies.

### Isovaleric Acidemia

Management includes removing leucine from the diet and increasing total caloric intake by taking simple sugars and leucine-free formula. If the infant is unable to tolerate oral intake, intravenous glucose should be started at 8 mg/kg per minute (with insulin as needed) to maintain euglycemia. Leucine and other amino acids must be reintroduced after 24 hours to avoid protein catabolism. In addition, carnitine and glycine supplementation should be continued to enhance excretion of the accumulating toxic organic acids.

### Glutaric Acidemia Type I

Management includes increasing fluid and caloric intake to reverse the catabolic state with glucose (plus

insulin if needed to maintain euglycemia), complete removal of all natural protein for 24 to 48 hours, and carnitine supplementation to help excrete accumulating toxic organic acids. Kolker and colleagues have published detailed management guidelines.

### 3-Methylcrotonyl-CoA Carboxylase Deficiency

Most infants with 3-MCC deficiency do not need long-term dietary modifications. For the few patients who do become asymptomatic during times of catabolic stress, acute management includes increasing total caloric intake, either enterally with simple sugars or parenterally with intravenous glucose to stop further protein catabolism, in addition to carnitine and glycine supplementation to enhance excretion of the accumulating toxic organic acids.

### 3-Hydroxy-3-Methylglutaryl Coenzyme A Deficiency

Management includes increasing total caloric intake, either enterally with simple sugars or parenterally with intravenous glucose to stop further protein catabolism, in addition to carnitine supplementation.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *7 Things Parents Want to Know About Newborn Screening From Their Child's Health Professional* (booklet), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/PEHDIC/Documents/Newborn\\_screeningdisorders.pdf](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/PEHDIC/Documents/Newborn_screeningdisorders.pdf))
- *Baby's First Test* (Web site), ([www.babysfirsttest.org](http://www.babysfirsttest.org))
- *Educational Materials* (handouts), California Department of Public Health ([www.cdph.ca.gov/programs/nbs/Pages/NBSEducationMaterial.aspx](http://www.cdph.ca.gov/programs/nbs/Pages/NBSEducationMaterial.aspx))
- *Newborn Screening* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/PEHDIC/pages/newborn-screening.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/PEHDIC/pages/newborn-screening.aspx))
- *Newborn Screening Information* (Web page), National Newborn Screening & Global Resource Center ([genes-r-us.uthscsa.edu](http://genes-r-us.uthscsa.edu))

### Medical Decision Support

- *Genetics Home Reference* (Web site), National Institutes of Health ([ghr.nlm.nih.gov](http://ghr.nlm.nih.gov))
- *Newborn Screening Coding and Terminology Guide* (Web site), National Institutes of Health ([newborn-screeningcodes.nlm.nih.gov](http://newborn-screeningcodes.nlm.nih.gov))
- *Newborn Screening Technical Assistance and Evaluation Program (NewSTEPS)* (Web page), Association of Public Health Laboratories ([www.aphl.org/aphlprograms/newborn-screening-and-genetics/Pages/NewSTEPS.aspx](http://www.aphl.org/aphlprograms/newborn-screening-and-genetics/Pages/NewSTEPS.aspx))

## AAP POLICY

American Academy of Pediatrics Committee on Bioethics, Committee on Genetics; American College of Medical Genetics and Genomics Social, Ethical, and Legal Issues



Committee. Ethical and policy issues in genetic testing and screening of children. *Pediatrics*. 2013;131(3):620–622 ([pediatrics.aappublications.org/content/131/3/620](http://pediatrics.aappublications.org/content/131/3/620))

American Academy of Pediatrics Newborn Screening Authoring Committee. Newborn screening expands: recommendations for pediatricians and medical homes—implications for the system. *Pediatrics*. 2008;121(1):192–218 ([pediatrics.aappublications.org/content/121/1/192](http://pediatrics.aappublications.org/content/121/1/192))

### SUGGESTED READINGS

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Baumgartner MR, Hörster F, Dionisi-Vici C, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. *Orphanet J Rare Dis*. 2014;9:130

Kemper AR, Uren RL, Moseley KL, Clark SJ. Primary care physicians' attitudes regarding follow-up care for children with positive newborn screening results. *Pediatrics*. 2006;118:1836–1841

King TM, Tandon SD, Macias MM, et al. Implementing developmental screening and referrals: lessons learned from a national project. *Pediatrics*. 2010;125(2):350–360

Mercier CE, Barry SE, Paul K, et al. Improving newborn preventive services at the birth hospitalization: a collaborative, hospital-based quality-improvement project. *Pediatrics*. 2007;120(3):481–488

van Dyck PC, Edwards ES. A look at newborn screening: today and tomorrow. *Pediatrics*. 2006;117(suppl)

orthostatic proteinuria) results in additional tests that generate increased costs and anxiety for patients and families. However, the decision to perform routine dipstick urinalysis ultimately rests with the primary care physician.

Dipstick urinalysis clearly is warranted in symptomatic children. The presence of heavy proteinuria (nephrosis or other renal disease), hematuria (glomerulonephritis), glucosuria (diabetes mellitus), or nitrite/leukocyte esterase (urinary tract infection [UTI]) can help the pediatrician diagnose and manage pathologic conditions. Urinalysis may also be valuable in patients who have vague complaints, such as failure to thrive or malaise, because some renal diseases may present with nonspecific symptoms. This chapter outlines the importance of appropriate urine collection for screening dipstick urinalysis, highlights some of the common anomalies detected by dipstick urinalysis, and outlines select patient populations that may benefit from screening dipstick urinalysis.

### SAMPLE COLLECTION

The results of any urinalysis depend on proper collection, preservation, and careful examination. Urine should be collected in a clean, dry container. A first morning, midstream, clean-catch specimen is most reliable for this purpose. First morning voided specimens yield the most concentrated urine and are more likely to show formed elements and allow detection of bacteria because of overnight incubation in the bladder. When obtaining a first morning urine sample, it is important that the child empty his bladder the night before the collection is obtained. Upon awakening the following morning, the urine specimen needs to be collected before other daily activities are performed. Ideally, the voided sample should be tested upon waking to ensure sensitivity and specificity of the urinalysis. Preservation methods, such as refrigeration or the use of chemicals, are necessary if the urine is not tested within 1 hour of collection.

If a UTI is suspected, a urine culture should be obtained. In older children, a clean-catch midstream specimen collected in a sterile, covered container is sufficient. The area around the urethral meatus should be cleaned with an antiseptic solution and the first few milliliters of the voided specimen should be discarded before the clean-catch sample is obtained. For infants and small children, suprapubic aspiration or transurethral bladder catheterization is the preferred specimen for documenting a UTI. Cultures of urine specimens collected in a bag applied to the perineum have an unacceptably high false-positive rate (85%). In 2011, the AAP released updated guidelines for the detection and evaluation of UTIs in febrile infants and young children. These guidelines state that the diagnosis of a UTI cannot be established by a culture of urine collected in a bag.

### PROTEINURIA

Urine contains small amounts of protein, normally 100 mg/m<sup>2</sup>/24 hr. In children, two-thirds of the physiologic urine protein consists of albumin and one-third

## Chapter 30

# USE OF URINALYSIS AND URINE CULTURE IN SCREENING

David Hains, MD; John David Spencer, MD

### INTRODUCTION

Examination of the urine is a simple and efficient office procedure that may diagnose renal, urinary tract, or systemic disorders. Pediatricians should be comfortable performing and interpreting a urinalysis.

Until 2007, the American Academy of Pediatrics (AAP) recommended that all children undergo a dipstick urinalysis at 5 years of age and during adolescence if sexually active. The AAP no longer recommends that children undergo screening dipstick urinalysis. Because multiple large-scale studies of healthy school-aged children have demonstrated the low incidence of chronic kidney disease (CKD) in children, the AAP recommends that a dipstick urinalysis be performed only in patients at higher risk for chronic kidney disease (see following text). Further, the early detection of CKD in asymptomatic children does not seem to alter ultimate disease outcome. In addition, the high rate of false-positive and true-positive results for benign conditions (eg,

represents a mixture of globulin and Tamm-Horsfall protein. Proteinuria is detected readily by the dipstick method. The presence of protein causes a change in the dipstick's reagent indicators that use buffered bromophenol blue or tetrachlorophenol. The binding of protein to the reagent results in changing colors from yellow to blue-green that is proportional to the amount of protein present (from 300 to >1,000 mg/dL). The reagent strips are much more sensitive to albumin than globulins, hemoglobin, or Bence-Jones protein. The small quantity of protein that a healthy individual excretes is not usually detected by this method. The sensitivity of detecting proteinuria with a urine dipstick ranges from 83.9% to 95.1%, and the specificity ranges from 93.8% to 95.5%. False-positive findings can occur in alkaline urine (pH >7.5), in concentrated urine (specific gravity  $\geq 1.015$ ), or in urine contaminated by skin antiseptics such as chlorhexidine or benzalkonium chloride.

Proteinuria can best be categorized as transient, postural, or persistent. Transient proteinuria is defined by the disappearance of urinary protein following 1 or more positive tests. Transient proteinuria accounts for most cases of isolated proteinuria and can result from a mild illness, fever, heavy exercise, stress, or significant heat/cold exposure. It is commonly seen in the setting of evaluation for sports participation, especially if the evaluation occurs directly following practice or heavy exercise.

If a child has evidence of proteinuria on dipstick urinalysis, a first morning urine specimen should be collected to evaluate for postural proteinuria. A urine protein-to-creatinine ratio can be measured from this sample. A ratio greater than 0.2 mg protein/mg creatinine is considered abnormal for children older than 2 years. Up to 60% of children who have evidence of proteinuria on dipstick urinalysis will have postural proteinuria. Postural or orthostatic proteinuria is a benign condition occurring only when a child is in the upright position. Recumbent urine specimens do not have protein, while upright samples contain protein. Postural proteinuria is typically associated with normal blood pressure and normal kidney function.

In a 20-year follow-up study of young men who had persistent orthostatic proteinuria, none developed renal insufficiency, including those who had nonspecific glomerular abnormalities on renal biopsy. Regular follow-up, however, remains important for these children so that changes in the pattern of protein excretion can be evaluated. More than 40% of cases spontaneously resolve within 4 years, and the incidence of identifiable renal disease is 1 child per 1,000 children screened.

Persistent nonpostural proteinuria indicates an underlying renal disease and should be more thoroughly evaluated. Signs and symptoms such as edema, hematuria, polyuria, hypertension, poor weight gain, growth delay, recurrent UTI, or a past history of renal disease may help uncover the cause of proteinuria. A meticulous examination of fresh urinary sediment should precede any additional laboratory evaluation. Please refer to Chapter 183, Proteinuria, for more information on examining urinary

sediment and on an approach to the patient with proteinuria.

Yoshikawa and colleagues reported on 53 children who were examined retrospectively after being biopsied for asymptomatic, fixed isolated proteinuria. They found that 47% had significant glomerular changes (focal segmental glomerulosclerosis, IgA nephropathy, mesangial proliferative glomerulonephritis, and membranous glomerulonephritis), which seemed to progress with time to chronic renal impairment. In Silverberg's studies, approximately 9% of children with isolated proteinuria had evidence of scarring. While some children who have proteinuria may have an abnormality that requires no additional management (eg, a hypoplastic kidney), others may have diseases that may improve with treatment (eg, focal glomerulosclerosis or IgA nephropathy). However, most children who have significant renal disease do have other signs and symptoms (eg, hematuria, edema, poor weight gain, or hypertension) that cause them to seek medical care, and thus they can be identified even in the absence of screening programs.

## HEMATURIA

Persistent hematuria occurs in about 2% of children and adults in the community. Often, hematuria in children is benign, with unknown etiology and prognosis. Nonetheless, it can be distressing for patients, parents, and physicians. Red blood cells (RBCs) in the urine may originate from any site in the urinary tract. Bleeding may be microscopic or gross. It may be painless or painful. The differential diagnosis for hematuria includes glomerular disorders, UTIs, urethralgia, nephrolithiasis, hypercalciuria/crystalluria, hematologic disorders, drugs, and anatomic anomalies.

Not all discolored urine indicates hematuria. Urine can be discolored by a number of substances. Therefore, the presence of gross blood should be confirmed by dipstick analysis. The urinary dipstick is highly sensitive, reacting to hemoglobin levels as low as 0.015 to 0.062 mg/dL. Depending on the degree of hematuria, the sensitivity of the dipstick for blood is 85% to 100% and the specificity is 86.3% to 99.3%. False-positive test results for blood in the urine may result from the presence of contaminating oxidizing cleansing agents (eg, povidone-iodine or hypochlorite) or microbial peroxidases. False-negative results are caused by the presence of large amounts of a reducing agent, such as ascorbic acid.

A positive dipstick analysis for blood does not discriminate between hemoglobin and myoglobin. Myoglobin can be differentiated from hemoglobin because the plasma remains colorless with increased myoglobin and remains pink-red with hemoglobinemia. Additional tests, such as elevated serum creatinine kinase levels to detect muscle injury, electrophoresis, or ammonium sulphate tests (precipitates hemoglobin but not myoglobin), may also aid in differentiation.

The urine dipstick does not differentiate hemoglobinuria from hematuria or whether the blood originates from the upper or lower urinary tracts. Localizing the source of bleeding facilitates the diagnosis.

Glomerular bleeding (upper tract) is suggested by the presence of RBC casts, proteinuria, brown or tea-colored urine, and dysmorphic RBCs. Conversely, red or pink urine or clots usually indicate lower urinary tract bleeding.

Few children diagnosed with hematuria by large-scale screening programs are found to have significant renal or urologic disease. However, a positive dipstick reaction for blood should be confirmed by the presence of RBCs on microscopic analysis. If there are more than 5 RBCs per high-powered field, then a repeat dipstick for blood should be done in 2 to 3 weeks. Two-thirds of these children will have no hematuria on repeat testing. A positive reaction for blood by dipstick analysis in the absence of proteinuria is typically not associated with renal disease. Asymptomatic children and adolescents with both blood and protein on dipstick analysis are more likely to have renal disease than those with just 1 positive reactant. They may require further evaluation and referral to a nephrologist.

Hematuria persisting for longer than 6 months is likely to be associated with renal disease if the patient has had at least 1 episode of gross hematuria or proteinuria, or has a family history of hematuria in a first-degree relative. The most likely diagnoses in these cases are Alport syndrome (hereditary nephritis), thin basement membrane disease, and IgA nephropathy. In a review of studies of screened symptomless microscopic hematuria, IgA nephropathy was found in 2% to 21% of biopsies, and other glomerular lesions were much less common. The most common nonglomerular finding was asymptomatic UTI (4.8%–6.0%). In other follow-up studies of children referred for isolated hematuria, the most common underlying diagnosis found was hypercalciuria (11%–16%). The presence of hematuria with proteinuria is strongly suggestive of glomerular disease.

In the case of persistent microscopic hematuria, a careful examination of fresh urinary sediment and microscopic analysis should precede any additional laboratory evaluation for asymptomatic children. Most of these children will not have clinically significant disease. Please refer to Chapter 160, Hematuria for further workup and diagnostic evaluation of persistent hematuria.

## GLUCOSURIA

Urinary glucose can be detected by glucose oxidase-impregnated dipsticks. Normally, all of the filtered glucose is reabsorbed by the proximal tubules, and glucose is not detectable in the urine when the plasma glucose is less than 180 mg/dL. Glucosuria is seen most commonly when the filtered load of glucose is increased as a result of hyperglycemia in patients with diabetes mellitus. Less often there is a defect in proximal tubular reabsorption that may be selective, as in renal glucosuria, or may be part of a more generalized proximal tubular dysfunction, as in Fanconi syndrome. Measurement of blood glucose differentiates among these conditions. Glucosuria also is seen in the latter stages of tubular destruction of focal segmental

glomerulosclerosis. In this condition, the urinalysis usually also shows proteinuria and the urinary sediment may contain renal tubular cells and casts.

Screening for glucosuria reveals a prevalence that is less than 0.1%. Although between 10 and 50 previously undetected cases of diabetes mellitus per 100,000 children could be identified, new-onset diabetes mellitus is much more likely to present with classic symptoms of polyuria, polyphagia, and polydipsia. Cases of renal glucosuria, Fanconi syndrome, and other tubular dysfunction may be rarely identified. Therefore, the cost effectiveness of screening asymptomatic patients for glucosuria is extremely low, and such screening is not recommended.

## BACTERIURIA

When evaluating a febrile child with no apparent source for the fever, the physician should assess for the likelihood of a UTI. The overall prevalence of UTI in febrile infants who have no source for their fever is approximately 5%, but it is possible to identify patient populations with a higher or lower likelihood to develop a UTI. The prevalence of UTI among febrile infant girls is more than twice that among febrile boys (relative risk 2.27). The rate of UTI for uncircumcised boys is 4 to 20 times higher than that for circumcised boys, whose rate of UTI is only 0.2% to 0.4%.

As previously mentioned, the method of collection of a urine specimen in children is important for the diagnosis of a UTI. When obtaining a urine specimen, the criteria that are taken into consideration are contamination, technical feasibility of obtaining urine, and invasiveness. Overall, catheterization is the preferred method for urine collection for children who cannot void upon request. Suprapubic bladder aspiration, which is the method that is least likely to be contaminated, may be impractical in some settings. For children who are older than 2 years and who are toilet trained, a midstream urine sample is recommended.

When diagnosing a UTI, physicians should require *both* dipstick urinalysis results that suggest infection (pyuria and/or bacteriuria) and the presence of at least 50,000 colony-forming units per mL of a cultured uropathogen. A dipstick urinalysis cannot substitute for a urine culture but needs to be used in conjunction with a culture. Moreover, an appropriately collected urine specimen is critical, and bagged urine specimens have little clinical value.

The dipstick urinalysis tests that have received the most attention are the biochemical analysis of leukocyte esterase and nitrite. The nitrite test is not a sensitive marker in children, particularly infants, who empty their bladders frequently. Nitrites are extremely specific to bacteriuria with a specificity of 98%, but a sensitivity of only 50%. Leukocyte esterase is much more sensitive (84%), but has a lower specificity of only 78%. When either leukocyte esterase or nitrite is positive, the sensitivity is 88% with a specificity of 93%. When both leukocyte esterase and nitrites are positive, the sensitivity is 72% and the specificity is 96%.



A positive leukocyte esterase test result without the presence of nitrites should be interpreted with caution. Numerous conditions other than UTI can cause a positive leukocyte esterase, including febrile illnesses and inflammatory kidney disease (ie, nephritis). Therefore, the finding of pyuria (white blood cells) by no means confirms that an infection of the urinary tract is present. However, the absence of pyuria in children with true UTIs is rare.

If bacteria are detected in the urine in the absence of pyuria, the physician should consider the diagnosis of asymptomatic bacteriuria. Asymptomatic bacteriuria is often present in school-aged and older girls. The prevalence of asymptomatic bacteriuria in school-aged children is 1% to 2% in girls and 0% to 0.1% in boys. Asymptomatic bacteriuria is defined as growth of more than  $10^5$  cfu/mL of a single uropathogen in at least 2 consecutive urine specimens in a child who is asymptomatic. Asymptomatic bacteriuria can easily be confused with a true UTI in a febrile infant, but needs to be distinguished because studies suggest that antimicrobial treatment may do more harm than good. The key to distinguishing a true UTI from asymptomatic bacteriuria is the presence of pyuria and active inflammation.

Treatment of asymptomatic bacteriuria may be associated with a greater risk for pyelonephritis, because it may promote the development of more pathogenic and resistant organisms. Furthermore, antibiotic treatment does not prevent further renal scarring once it has occurred, nor does it restore poor renal growth.

Extensive investigations of asymptomatic bacteriuria in schoolgirls have shown that observation does not influence the episodes of symptomatic UTI, renal growth, or glomerular filtration rate in normal or scarred kidneys.

Screening of asymptomatic patients for asymptomatic bacteriuria is not recommended. If asymptomatic bacteriuria is discovered, it should not be treated. Persistent bacteriuria should be pursued with a careful history for renal and urinary tract symptomatology, examination of growth and blood pressure, and possibly a renal ultrasound to determine risk for progressive renal disease (see Chapter 344, Urinary Tract Infections).

## TESTING HIGH-RISK PATIENTS

The AAP recommends that a dipstick urinalysis should be performed only in patients at high risk for chronic kidney disease. Many pediatric nephrologists recommend that children with certain medical conditions, including diabetes mellitus, a history of postinfectious glomerulonephritis, acute kidney injury, or a history of hemolytic uremic syndrome or Henoch-Schönlein purpura have a dipstick urinalysis done at every health maintenance visit until several urines are negative. Children with sickle cell disease or trait or a strong family history of renal disease should have a dipstick urinalysis done at each or every other health maintenance visit. An occasional dipstick urinalysis may also be indicated for children with a body mass

index greater than 97%, a history of prenatal (or postnatal) hydronephrosis, prematurity (<32 weeks), or a strong family history of kidney stones.

## WHEN TO REFER

- Persistent proteinuria (first morning void)
- Gross hematuria of unknown cause
- Persistent hematuria associated with proteinuria or hypertension
- Elevated serum creatinine or proteinuria with glucosuria or history of diabetes
- Recurrent UTIs or history of recurrent pyelonephritis

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Urinalysis and Kidney Disease: What You Need to Know* (handout), National Kidney Foundation ([www.kidney.org/sites/default/files/11-10-1815\\_HBE\\_PatBro\\_Urinalysis\\_v6.pdf](http://www.kidney.org/sites/default/files/11-10-1815_HBE_PatBro_Urinalysis_v6.pdf))
- *Urinary tract infections* (fact sheet), National Kidney Foundation ([www.kidney.org/atoz/content/uti](http://www.kidney.org/atoz/content/uti))

### Medical Decision Support

- *Pathologic Proteinuria Calculator* (interactive tool), Metro Health ([www.metrohealthresearch.org/schelling](http://www.metrohealthresearch.org/schelling))
- *Periodicity Schedule* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/professional-resources/practice-support/Pages/PeriodicitySchedule.aspx](http://www.aap.org/en-us/professional-resources/practice-support/Pages/PeriodicitySchedule.aspx))
- *Screening for Albuminuria in Patients with Diabetes* (app), National Kidney Foundation ([www.kidney.org/apps/screening-albuminaria-patients-diabetes](http://www.kidney.org/apps/screening-albuminaria-patients-diabetes))

## AAP POLICY

American Academy of Pediatrics Committee on Practice and Ambulatory Medicine and Bright Futures Steering Committee. Recommendations for preventive pediatric health care. *Pediatrics*. 2007;120(6):1376. Reaffirmed January 2011 ([pediatrics.aappublications.org/content/120/6/1376](http://pediatrics.aappublications.org/content/120/6/1376))

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# Health Promotion in Practice

## Chapter 31

## APPLYING BEHAVIOR CHANGE SCIENCE

Sebastian G. Kaplan, PhD; Robert P. Schwartz, MD

Diseases cannot be managed with medication alone. In many instances, prognosis depends largely on whether the patient's caregivers adopt health behavior changes designed to prevent or effectively treat the child's condition.

As a result, effective communication is a crucial skill for any physician. Often the behavioral component of treatment is a complex set of lifestyle changes, such as new exercise regimens, adoption of behavior management strategies by parents, or frequent finger sticks to assess blood glucose levels. However, even when treating seemingly routine ailments, such as group A streptococcal pharyngitis, the pediatrician engages in communication about patient and caregiver behavior, in this case adherence to antibiotics. How can a pediatrician most effectively engage patients and caregivers in changing health behaviors?

### RELATIONSHIP BETWEEN PATIENT-CENTERED CARE AND HEALTH PROMOTION

In 2001, the Institute of Medicine (IOM) published a report titled *Crossing the Quality Chasm: A New Health System for the 21st Century*. To address growing concerns with the US health care system, the IOM proposed 6 aims for improvement, one of which was patient-centered care. The IOM defines *patient-centered care* as “respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions.” A similar term used by researchers is *relationship-centered care*, which advocates similar principles as the patient-centered approach but with more emphasis on the collaboration between the patient and physician. The American Academy of Pediatrics (AAP) has also recommended the use of patient-centered communication strategies (eg, motivational interviewing, described in more detail later) for challenging conditions such as pediatric obesity.

Implementing a patient-centered model of health care is easier said than done, in part because of the stark contrast between patient-centeredness and the authoritarian role traditionally found in physician-centered doctor–patient relationships. However, the empirical evidence supporting physician adherence to a patient-centered approach is expanding.

Safran et al found that the variables most predictive of patient adherence to physician advice were the physician's comprehensive or whole-person knowledge of the patient, as well as the patient's trust in his or

her physician. Stewart et al examined the effect of patient-centeredness during office visits using a cohort of 39 family physicians and 315 of their patients. Patient-centered communication was correlated with improved patient outcomes (eg, improvements with discomfort, pain, and emotional health), as well as reduced need for diagnostic tests and referrals. Finally, Stewart conducted a review of 21 studies on the effect of physician–patient communication on health outcomes and concluded that most published findings support a direct relationship between effective communication and a number of positive patient health outcomes, including emotional health, symptom resolution, function, physiologic measures, and pain control.

### SELF-DETERMINATION THEORY

Why might patient-centered care lead to such robust patient health outcomes? A number of possible theories and models exist. One theory of human motivation, called *self-determination theory* (SDT), differentiates among several types of human motivation rather than focusing on how much motivation a person may have. SDT also considers how each type of motivation predicts certain outcomes, including those pertaining to health and well-being.

A central tenet in SDT is the distinction between autonomous motivation and controlled motivation. Autonomous motivation includes a range of motivation types, from intrinsic, whereby a person experiences a natural inclination toward a particular behavior purely for its inherent satisfactions, to some forms of extrinsic motivation, whereby the person has largely internalized the value of a particular choice as a result of external forces. Controlled motivation, on the other hand, consists of 2 types of extrinsic motivation whereby the primary forces governing a person's actions are either completely external (ie, contingent rewards or punishments) or partially internalized (ie, internal gratification associated with approval from others or avoidance of shame).

The distinction between autonomous and controlled motivation is important in that each type predicts different outcomes. Research has demonstrated that the more an individual is intrinsically motivated, the more likely he or she is to experience improved performance, creativity, self-esteem, and general well-being. Regarding health outcomes, the application of SDT in health care settings has grown as the research supporting the link between autonomously motivated health behavior and positive health outcomes has strengthened.

Williams et al emphasized the importance of physicians being “autonomy supportive” rather than “controlling” in their interactions with patients and patients' families. They reviewed research on the relationship between intrinsic patient motivation, autonomy-supportive physician interaction, and a host of health-related benefits, including engagement in alcoholism treatment, adherence to long-term medication regimens, successful participation in a

weight management program, improved glucose control, and smoking cessation. A relevant caveat to these studies is that they all involved adult populations. Can SDT be applied to the practice of pediatrics, and if so, what strategies can be useful in pediatric settings?

## DEVELOPMENTAL PERSPECTIVES ON HEALTH PROMOTION

The practice of pediatrics poses unique challenges that are often absent in other areas of medicine. Beyond analyzing clinical data to arrive at a diagnosis and resulting treatment plan, the pediatrician must use vastly different approaches when working with infants, preteens, or adolescents. Furthermore, engaging the patient's caregivers is frequently a crucial element in both the diagnostic process and communication about treatments. How can physicians apply behavior change science to the range of pediatric clinical situations?

Most research on health behavior change has been conducted with adult populations. As is often the case, a theory first gains empirical support using adult samples, followed by attempts to test the theory with pediatric cohorts. Much of the initial evidence supporting the application of SDT with children and adolescents comes from research in educational settings, in which studies have demonstrated positive relationships between autonomous academic motivation and enhancements in behavioral, cognitive, and affective domains. Furthermore, research has shown that both parents and teachers can effectively support autonomous academic motivation in children and adolescents, which often results in positive educational outcomes. Support for SDT as a model for pediatric health promotion has emerged, primarily in the areas of increasing physical activity.

A school-based intervention using SDT principles was more effective in increasing high school students' intention to exercise and self-reported leisure time physical activity than the control condition. The authors designed the SDT-based intervention to include 4 important components of autonomy-supportive relationships: (1) providing a rationale for exercise; (2) feedback; (3) choice; and (4) acknowledging barriers to becoming more physically active. The control condition included only (1) providing a rationale and (2) feedback. Another study that tested a model grounded in SDT found that adolescents whose motivation to exercise was primarily intrinsic (eg, fitness, enjoyment) positively predicted improved quality of life and exercise behavior compared with adolescents whose motivation was primarily extrinsic (eg, pressure from others, weight control). Other studies explicitly testing SDT-based models with younger patient cohorts have found similarly positive outcomes, such as reduced dropout from an eating disorder inpatient program and increased engagement in substance abuse treatment.

## MOTIVATIONAL INTERVIEWING

Given the call to adopt patient-centered care and the science supporting its efficacy, how might a pediatrician engage with patients and caregivers to promote health

behavior change? Motivational interviewing (MI), a counseling method that originated as an intervention for alcohol abuse, has gained empirical support for its effectiveness in adults and children. From a relational foundation that is empathic, autonomy supportive, and nonconfrontational, MI seeks to enhance a patient's intrinsic motivation to adopt health behavior changes.

An MI practitioner uses a variety of engagement strategies with patients and caregivers, such as reflective listening, open-ended questions, and affirmations, which establish a collaborative relationship that honors a patient's autonomy. In addition to the patient-centered style, often referred to as the "MI spirit," MI practitioners strategically elicit and reinforce patient "change talk." For instance, if a patient expresses ambivalence about change ("sustain talk"), citing barriers to implementing a specific plan while also mentioning the desire or need to make lifestyle changes, an MI practitioner intentionally chooses to reflect on the desire and need for change expressed in the patient's statements rather than confronting the patient for a lack of progress. The MI practitioner would engage with the patient in such a way that increases the likelihood that the patient makes the necessary argument for and commitment to health behavior change.

Rollnick et al described 3 communication styles evident in health care settings: directing, guiding, and following. The authors distinguish the 3 styles based on how much a physician makes use of 3 communication skills: listening, asking, and informing. A *directing* style would rely heavily on informing, with less asking and even less listening. The *following* style is an opposite approach whereby the physician primarily listens to the patient's questions, concerns, or ideas about a particular issue, with some asking and very little informing. Although the authors acknowledge that both the directing and following styles are important in certain clinical situations, they describe MI as most consistent with the *guiding* style, which uses a balance of listening, asking, and informing, and which they argue is most effective for health behavior change interventions.

Much of the emphasis in MI is on the listening and asking skills that Rollnick described. The dual processes of the interpersonal "MI spirit" and the focus on eliciting "change talk" have been described as the main components of the proposed theory of MI. Maintaining a patient-centered, MI-adherent approach when informing patients and caregivers about an illness or its resulting treatment options is quite a challenge for pediatricians.

The provision of information from physician to patient or caregiver may seem at odds with a patient-centered model designed to make the patient's goals and values central to the decision-making process. Rollnick et al outlined a simple and useful strategy, the Elicit-Provide-Elicit (E-P-E) sequence, to help guide physicians in providing information that maintains the autonomy and collaborative emphasis in MI. The first Elicit step is an effort by the physician to evoke ideas from the patient or caregiver about a condition or its treatment.

The Provide step in the sequence is the point at which the physician shares information or recommendations about the clinical issue at hand. Often the

information provided follows a specific request for ideas or recommendations from the patient or caregiver. An MI-adherent strategy often used in the Provide step if the patient or caregiver does not make such a request is to ask for permission before giving advice. Although patients or caregivers rarely will turn down this request, the action of asking permission reinforces the collaboration between physician and patient or caregiver.

The final Elicit step occurs when the physician offers the patient or caregiver an opportunity to comment on the information provided. This step is crucial in helping to ensure that the patient or caregiver understands the information or recommendation being shared. It also allows the patient or caregiver a chance to respond, share concerns, or modify the recommendations in a manner that fits better with the patient and caregiver lifestyle. Box 31-1 contains an example of the E-P-E sequence in the context of smoking cessation.

The E-P-E sequence, asking permission to give advice, and other MI-consistent strategies are quite different from a traditional authoritarian or prescriptive clinical approach. When a pediatrician encounters patient or caregiver ambivalence about adopting health behavior strategies, confrontation will likely lead to increased resistance. Consistent with patient-centered strategies such as MI, pediatricians will be more effective if they avoid statements such as “you must,” “you should,” and “you need to,” which are more controlling and minimize a patient or caregiver’s autonomy and responsibility for change. MI is a shared process of decision making, and the reasons for change should come from the patient’s own goals and values. See Table 31-1 for a brief transcript of an MI session in the context of pediatric obesity.

MOTIVATIONAL INTERVIEWING IN PEDIATRICS—EMPIRICAL SUPPORT

Suarez and Mullins reviewed the research on MI and pediatric health behavior interventions. The authors described findings from 15 published studies (9 of which were randomized clinical trials) on the feasibility

BOX 31-1 Example of the Elicit-Provide-Elicit Sequence in the Context of Smoking Cessation

ELICIT

Physician: We’ve been talking a lot today about your smoking. What thoughts do you have at this point regarding your smoking?

Patient: It’s not that I think it’s good for me. I know about the risks. It’s just that I’ve tried to quit before, and I never stick with it. It’s so hard!

PROVIDE

Physician: It has been tough to quit on your own, and you are still concerned about the risks to your health. Could I share some information with you about quitting strategies that might help?

Patient: Sure.

Physician: Some strategies that have been very effective for other people that are trying to quit smoking are nicotine replacements, like the patch, as well as a support group.

ELICIT

Physician: What are your thoughts about those options?

Table 31-1 Transcript of Motivational Interview (MI) Session With an Adolescent Patient (Pt), Her Mother (Pt Mother), and a Dietitian (RD)

DISCUSSION

RD: Tell me what you have noticed since we saw you last.  
Pt: I have to be honest. I have not done the lunch thing at all. There is no good excuse. I just haven’t done it. I’ve done okay with the other goals, just not lunch.  
RD: You’re feeling pretty good about 2 of the 3 goals you identified.  
Pt: Yeah, I’ve been good about my stretches. That’s been easier than I thought it would be. I’m also doing pretty good at not overeating at home. Sometimes I overdo it, but not as much as before.  
RD: You are persistent and you’ve found quite a bit of success so far.  
Pt: I guess so, except with the whole lunch thing.  
RD: I appreciate your honesty. Tell me more about lunch at school. What kind of things have gotten in the way?  
Pt: I am just lazy. I haven’t wanted to pack, and really, I just don’t like to eat at school. The girls at lunch are all so skinny and complain about getting so full eating just an apple.  
RD: It’s hard seeing the other girls eating just an apple. It makes you not want to eat at school.

MI PRINCIPLES

Brief mention of success embedded in sustain talk  
Selectively reflecting change talk  
Pt expanding on several areas of success  
Affirmation  
Sustain talk regarding lunch goal  
Open-ended question  
Sustain talk: Pt. not interested in packing lunch, struggling with other “skinny” girls  
Reflection: Expressing empathy and rolling with resistance

Continued

**Table 31-1****Transcript of Motivational Interview (MI) Session With an Adolescent Patient (Pt), Her Mother (Pt Mother), and a Dietitian (RD)—cont'd****DISCUSSION**

Pt: Yes, exactly. I mean, later on I kick myself for not eating lunch because I know that leads to me getting really hungry, and then I overeat. And I notice my energy is really low at practice. I just can't decide what I could pack that I like and is easy. I know my mom would pack it for me.

RD: So on a scale from 1 to 10, how important is it for you to eat lunch at school?

Pt: Usually a 2. Except on game days, then it's more like a 4 or 5. I have started to buy a slice of pizza on game days, but that is no good. Pizza is a bad choice.

RD: What is it about game days that make it more important for you?

Pt: I know I need my energy to play well, and I usually can't get home before the game. So I have to eat at school. It's just that my choices could be better.

RD: So, you choose not to skip lunch on game days and typically order a slice of pizza. Even though this is a step in the right direction, you are thinking about making different choices.

Pt mother: Well, you only ate one slice of pizza, not a whole box. It is great that you are eating on game days.

Pt: Actually, I use more energy on practice days because we have to run 2 miles at the start of practice and do all kinds of intense drills. I really should just take something for lunch, but I can't get myself to pack anything. And if my mom were to pack it, I can't even think about what I would want to tell her to give me.

Pt mother: I would be happy to pack your lunch for you, and I have asked what I could get at the grocery store for your lunches.

RD: Tina, you are interested in taking your lunch to help with your energy and your performance during soccer, you have your mom's support, and you are willing to take lunch if you can find the right thing to take.

Pt: Peanut butter sandwiches would be easy and the perfect choice but we cannot have peanut butter in the house because I always eat too much of it.

RD: You know this is a trigger food that you overeat at home, yet eating peanut butter would be a good option for you at lunch.

Pt mother: We could get the little individual containers of peanut butter, or I could keep it with me and make your sandwiches.

Pt: Yes, and we could buy the presliced apples that I can eat with my braces.

RD: So, on a scale of 1 to 10, how confident are you about your new lunch plan?

Pt: 10/10. I know this is going to work.

RD: When do you think you can start?

Pt: Mom, can we stop at the store on the way home?

Pt mother: Absolutely.

RD: Looks like you guys have a plan that you are excited about.

**MI PRINCIPLES**

Increasing change talk. Listing cons of not eating lunch. Identifying barriers for success with possible solution involving mother.

Assessing importance of lunch goal  
Sustain talk and change talk

Open-ended question focusing on change talk

Reason for eating lunch Acknowledging possibility of better choices  
Reflection about changes made  
Affirming the effort

Mother expressing support for Tina

More change talk, eliciting help from mother

Supporting change talk

Summary

Pt developing change plan, identifies another barrier  
Double-sided reflection ending with change talk  
Family generating change plan

Strengthening plan  
Assessing confidence of change plan  
Change plan  
Seeking commitment with start date  
Seeking help from mother  
Support  
Reflection

From Irby M, Kaplan S, Garner-Edwards D, et al. Motivational interviewing in a family-based pediatric obesity program: a case study. *Fam Syst Health* 2010;28:236–246.

and efficacy of MI for a range of pediatric conditions and caregiver interventions: diabetes, obesity and diet, dental care, reproductive health, reducing second-hand smoke, and child behavior management interventions. The authors concluded that the emerging evidence is promising and worthy of further study.

For example, Channon et al conducted a pilot study and follow-up randomized controlled trial examining the feasibility and efficacy of MI for type 1 diabetes in adolescents. Results from both pilot and randomized controlled trial phases demonstrated the utility of MI in reducing A1C levels through a 2-year follow-up period, as well as positive outcomes on a number of psychosocial measures, such as well-being, quality of life, anxiety, and perceived impact of diabetes on the adolescents' lives. Another example was an MI intervention for

caregivers designed to reduce children's ( $\leq 3$  years of age) exposure to second-hand smoke. Results at 6-month follow-up showed reduced mean nicotine levels in homes of MI participants relative to controls.

**CONCLUSION**

The complexities of pediatric care require pediatricians to engage with patients and caregivers across a broad developmental spectrum. A major challenge in producing positive clinical outcomes is health promotion for patients and their caregivers. Early evidence supports the application of models such as SDT and motivational strategies such as MI in pediatric settings. Although more research is needed to better understand causal pathways of patient-centered strategies, the IOM and AAP have both



placed an increased focus on the use of patient-centered medicine in the promotion of health behavior changes in pediatrics.

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## Chapter 32 FAMILY SUPPORT

James M. Perrin, MD; Amy Pirretti, MS

### BACKGROUND

The definition of family can be complex. The following is a definition shared by the late family advocate Polly Arango to the *Bright Futures* guidelines.

*We all come from families. Families are big, small, extended, nuclear, multi-generational, with 1 parent, 2 parents, and grandparents. We live under one roof or many. A family can be as temporary as a few weeks, as permanent as forever. We become part of a family by birth, adoption, marriage, or from a desire for mutual support. As family members, we nurture, protect, and influence each other. Families are dynamic and are cultures unto themselves, with different values and unique ways of realizing dreams. Together, our families become the source of our rich cultural heritage and spiritual diversity. Each family has strengths and qualities that flow from individual members and from the family as a unit. Our families create neighborhoods, communities, states, and nations.*

DEVELOPED AND ADOPTED BY THE NEW MEXICO  
LEGISLATIVE YOUNG CHILDREN'S CONTINUUM AND  
NEW MEXICO COALITION FOR CHILDREN, JUNE 1990

The American Academy of Family Physicians defines the family as “a group of individuals with a continuing legal, genetic, or emotional relationship,” indicating the varied nature of families, the complexities of assessing each family constellation, and the

importance of recognizing diversity. Every family is an individual system with beliefs and attitudes of its own.

### Family Trends

The number of children living with 2 married parents has decreased during the past 40 years (see Figure 32-1). In 1970, 85% of children were living with married parents, whereas 67% of children in 2010 did so. During this same period, the number of children being raised by single mothers grew from 11% to 23%. The proportion of children being raised by single fathers has fluctuated from 1% to 5% and was 3% as of 2010. The number of children living without either parent has remained constant at about 4% across the past 4 decades. Other notable family structure trends include nearly 7% of children living with a grandparent, with a parent also present in more than half of these families (data from 2010). Families have become much more diverse in the past few decades. Increasing numbers of same-sex couples have children. Children and young families have increasing racial and ethnic diversity, with larger numbers of mixed-race families. Family structure also differs significantly when stratified by race (see Figure 32-2). Almost 85% of Asian children live in families with 2 married parents, compared with 71% of whites, 61% of Hispanics, and 35% of blacks, again indicating the diversity among families and the need to inquire about household structure with all families.

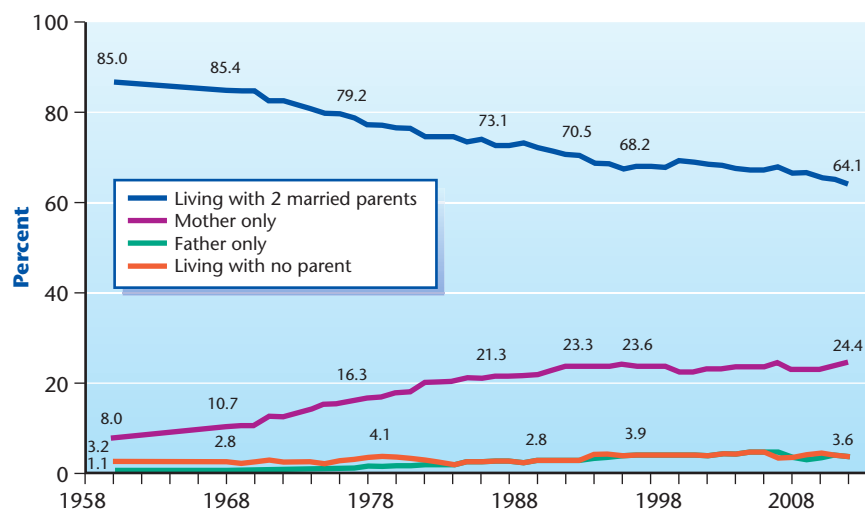
### Family Culture and Behaviors

The growing racial, ethnic, cultural, and gender diversity among US children and their families reflects diverse beliefs about family roles and activities, including childrearing and discipline. Cultural variations may include rituals and activities that help to ground a developing child in her community and its stories and beliefs, including those regarding health and living healthy lives. Cultural differences can influence eating behaviors and foods offered, definitions of appropriate and inappropriate behaviors, parental efforts at control, time together and activities, and views of medications and other treatments. The family's culture is an intrinsic part of the child's social environment, and pediatricians should develop cultural awareness while learning individual family preferences.

Understanding the cultural context of the family in concert with the internal family dynamics helps the pediatrician in providing quality care and ensuring good communication within the medical home. Pediatricians can become familiar with the major cultural groups in their community and develop ways to elicit cultural beliefs that may affect a child's health or medical treatments and can implement the culturally competent tools to enhance effective understanding and communication. Guidance for providing culturally effective care can be found in Chapter 48, Providing Culturally Effective Care.

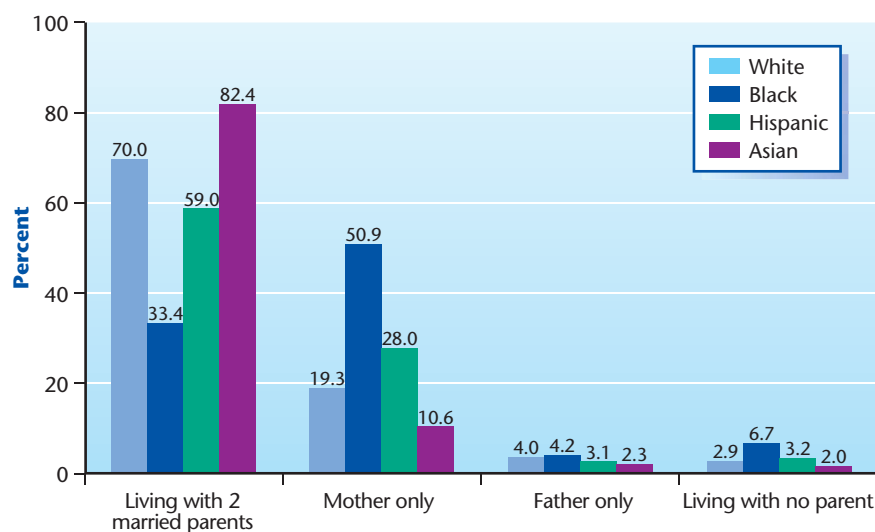
### Family and Community Environments

The communities where children live influence their health and development. Communities provide



Note: Children living with 2 married parents may be living with biological, adoptive, or non-biological parents. Children living with mother only or father only may also be living with the parent's unmarried partner.

**Figure 32-1** Living arrangements of children younger than 18 years, 1970–2012. (Reproduced with permission from Child Trends Databank. Family Structure. <http://www.childtrends.org/?indicators=family-structure>. Updated March 2015. Accessed October 28, 2015.)



**Figure 32-2** Living arrangements of children, by race and Hispanic origin, 2012. (Reproduced with permission from Child Trends Databank. Family Structure. <http://www.childtrends.org/?indicators=family-structure>. Updated March 2015. Accessed October 28, 2015.)

different levels of cohesiveness, safety, support, and beliefs, all of which have effects on the child and family. Families with children interact with a large number of community agencies and services, especially schools, which play a major role in child development and family support. Communities provide variation in opportunities for children, such as areas to play and exercise, access to nutritious foods, and exposure to potential toxins (including poor housing with mold or other antigens).

For an in-depth discussion of promoting the health of children at the community level, see Chapter 22, Promoting the Health of Young Children; Chapter 23, Promoting the Health of School-aged Children; and Chapter 24, Promoting the Health of Adolescents. Part 2, Section 4 of this textbook discusses promoting the health of specific populations of high-risk children. The discussion that follows focuses broadly on the role a child's medical home can play in enhancing families' capacity to support their children.

## ENHANCING FAMILY SUPPORT IN THE PRIMARY CARE SETTING

Change, stress, and happiness that affect one family member will have reciprocal effects on all family members. The pediatrician's role in promoting families' support of their children may include surveillance of family members' health, strengths, and challenges; formal screening of caregivers for health and social problems and signs of family dysfunction; evaluation of families' social and financial resources; and anticipatory guidance to enhance the family's resilience and address the challenges parents face in nurturing their child. Medical home principles emphasize partnership with families and providing them with the tools and education to participate actively in health care.

### Surveillance

To identify strength and needs of a child's family, the pediatrician might explore the following topic areas in the context of children's health supervision.

### Parental Strengths and Challenges

It is important for pediatricians to identify and reinforce a parent's strengths. These may include the parent's commitment to the child's health care, relationship with the other parent, extended family connections, patience, understanding of the child's developmental needs, use of helping services, or other ways in which a parent demonstrates his or her capacities as a caregiver. By recognizing and nurturing these strengths, the pediatrician can benefit the child and build trust with the family.

It is also important to recognize the parents' health needs and socioeconomic challenges, which may affect the child's well-being. Among people aged 20 to 40 years, the main use of health care is for mental health issues and obstetric care, and large numbers of people in this age group do not seek medical care on any regular basis. Thus, key issues that parents may face in their families may go unidentified and untreated. Among the most important are parental depression, substance use, domestic violence, poverty, and separation and divorce. The pediatric encounter may play a role in identifying important parental health and social issues, especially as they pertain to the family's ability to care for the child. The following sections provide further guidance on addressing these issues when they are identified.

### Family Configuration

In working with children, pediatricians should inquire about the whole family—who is in it, how they are doing, and how well their activities fit the needs of the developing child.

In general, having 2 parents, whether in heterosexual or same-sex households, involved in a child's care is associated with a number of improved outcomes. Ideally, parents share care and care decisions and recognize the value of collaborating with different adult caregivers in a child's environment. Both parents should be encouraged to share actively in child care and development; their involvement in the clinical encounter can also be encouraged.

Although many children do well in single-parent households, children in these circumstances have higher rates of school failure and developmental problems, partly reflecting much higher likelihood of poverty than in 2-parent households, as well as the additional parenting stress that accompanies parenting alone. Close connection with extended family members or other sources of support can significantly enhance the well-being of children in single-parent households.

Children whose parents divorce may have experienced much family discord and conflict and will need to adjust to the intermittent absence of 1 or both parents. Persistent conflict may also affect the child's health and behavior. Divorce may lead to new economic hardship for the child.

Parents involved in adoption or foster care face the relatively sudden inclusion of new children in a household and may know relatively little about the child's previous health or development. The children may have difficulties in new settings because of previous losses or inconsistent parenting, attachment, or bonding. Pediatricians can help parents gather more information, gain helpful skills, learn about resources, access support, and learn strategies to parent and care for a new child who may have had very different parenting experiences in the past. Identifying support and resources in the extended family may help grandparents (or others) play supportive roles. Adolescent parents may need support in developing their parenting skills, and referrals to parenting education programs that focus on young parents can help in this regard.

**CAREGIVER ROLES AND INTERACTIONS.** In modern families, parent roles and responsibilities vary widely, with many ways of distributing tasks, including child care, discipline, and daily activities such as supervision of homework, entertainment, eating, or sleep. Pediatricians should seek information about the role of a noncustodial parent in the household and encourage the parent's participation in various care and health areas.

A parent who is out of the home or working may feel too busy or otherwise excluded from interactions with a child's health care providers; encouraging the parent's interaction either in person or through other means of communication can help support these roles and provide broader understanding about the family.

### Children With Special Health Care Needs

Children and youth with special health care needs substantially increase the time (and often physical work) of parenting. Children with diabetes need attention to diet, blood testing, and insulin treatment. Families need to understand how various life issues (illness, stress) may influence blood sugar. Children with mental health and emotional problems require behavioral management and educational guidance. Children with developmental conditions also require family support and accommodation. Asthma, arthritis, epilepsy, leukemia, and other childhood chronic health conditions create demands specific to those conditions. The child's symptoms, absences from school or child care, health care appointments, hospitalizations, and medication management may require that caregivers

interface with schools and agencies, miss work, and deplete their emotional and financial resources, compounding the stress on the child and caregivers, individually, and on the family as a unit, including siblings. Primary care pediatricians can support the family by identifying and attending to these stressors, making appropriate referrals for both the child and caregivers, and connecting them to sources of peer support and respite care.

### **Change and Family Stress**

Families face many changes that are stressful, and their responses and adjustment to them may affect children's health. Obvious stresses include transitions—a new (parent) job, a new house, illness or death of a parent, and separation and divorce. Other transitions that the child may experience include discharge from hospital to home as a newborn or after care for a serious chronic or acute condition, entering school, or entering adolescence. Economic stresses, such as a parent's job loss or chronic unemployment, may have a powerful effect on the family's capacity to attend, physically and emotionally, to the child's needs. Indeed, family stressors, large and small, are very common. Chronic, toxic stress may have immediate and long-term negative health consequences for the child. (See Chapter 68, *Children Exposed to Adverse Childhood Experiences*.)

Pediatricians can help by querying about recent changes in the household or new stresses that the family may be experiencing. A brief mental health update can be adapted for this purpose.

When the pediatrician finds stresses that may affect family well-being, she can use common factors techniques (see Chapter 46, *Effective Communication Strategies*) to strengthen the therapeutic alliance with the family and develop a family-centered plan of action. The plan may include general steps to improve the family's health and resilience (eg, physical activity, sleep, help from friends or extended family, connection with spiritual resources) and specific referrals for mental health care, marital or financial counseling, social services, or peer support. The pediatrician's demonstrated empathy, hopefulness, and commitment will likely have their own therapeutic value.

### **Screening**

Parents may hesitate to bring up their stresses or personal health problems during pediatric visits, despite their importance in affecting child care and health. Brief screening tools exist to help pediatricians identify these concerns in a family.

### **Anticipatory Guidance**

To nurture a family's capacity to support its children, the pediatrician will need a relationship of trust with the family. The 2008 American Academy of Pediatrics Task Force on Mental Health report provides guidance on making a primary care practice a friendly environment for the discussion of family issues that may affect the child's health and well-being. Understanding and supporting the family in a family-centered medical home will, in turn, enhance the child's health and development.

Any clinical encounter offers opportunities for reinforcing the family's strengths and enhancing the family's capacity to support the child with challenges that lie ahead. This guidance may take many forms, depending on the family's readiness to accept help and the needs of the child. For example, the pediatrician may have an opportunity to advise new parents on the importance of their communication with the pediatrician, particularly emphasizing that child care providers should not use TV screens as babysitters; to encourage the parent of an adolescent to stay involved in the child's daily activities; to recommend a counselor for parents undergoing separation or divorce; or to involve extended family in supporting a parent facing military deployment.

Families needing additional support can be referred to helping agencies or peer support programs. Evidence-based programs such as the Nurse Family Partnership and early literacy promotion can assist caregivers in strengthening bonds with their children. For children and youth with special health care needs, legislative efforts have led to development of Family-to-Family Health Information Centers (F2F HICs) in each state. Staffed by parents of children with special health needs, the F2F HICs assist families and pediatricians in locating community resources.

## **SUMMARY AND RECOMMENDATIONS**

In many ways, pediatricians are physicians for the whole family. Thus, much clinical interaction relates to learning about family strengths and capabilities, understanding circumstances in which family health issues and stressors may affect a child's health, and determining with the family best strategies to identify and address a child's health needs in the family context. Pediatricians should know about community resources and refer appropriately.

In developing therapeutic relationships with children and families, pediatricians should take into consideration the diversity of families and family structures, the involvement of various adults in the relationship, variations in household and community culture and language, parental health and socioeconomic status, and the effect of the child's health condition on the family. Providing effective preventive care and anticipatory guidance builds on an understanding of the family and its characteristics, strengths, and challenges.

## **TOOLS FOR PRACTICE**

### **Community Advocacy and Coordination**

- *Adolescent and School Health* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/healthyyouth/schoolhealth/index.htm](http://www.cdc.gov/healthyyouth/schoolhealth/index.htm))
- *Building the Legacy: IDEA 2004* (Web page), US Department of Education ([idea.ed.gov](http://idea.ed.gov))
- *Connected Kids Clinical Guide* (handout), American Academy of Pediatrics ([www2.aap.org/connectedkids/ClinicalGuide.pdf](http://www2.aap.org/connectedkids/ClinicalGuide.pdf))
- *Culturally Effective Care Toolkit* (toolkit), American Academy of Pediatrics ([www.aap.org/en-us/professional-resources/practice-support/Patient-Management/Pages/Culturally-Effective-Care-Toolkit.aspx](http://www.aap.org/en-us/professional-resources/practice-support/Patient-Management/Pages/Culturally-Effective-Care-Toolkit.aspx))



- *Health, Mental Health, and Safety Guidelines for Schools* (Web site), American Academy of Pediatrics ([www.nationalguidelines.org](http://www.nationalguidelines.org))
- *National Association of County and City Health Officials Toolbox* (handouts), National Association of County and City Health Officials ([www.naccho.org/toolbox](http://www.naccho.org/toolbox))
- *The National School Lunch Program* (Web page), US Department of Agriculture ([www.fns.usda.gov/nslp/national-school-lunch-program-nslp](http://www.fns.usda.gov/nslp/national-school-lunch-program-nslp))
- *State School and Health Resources* (Web page), American Academy of Pediatrics ([www2.aap.org/sections/schoolhealth/contactmap/section\\_contacts.cfm.htm](http://www2.aap.org/sections/schoolhealth/contactmap/section_contacts.cfm.htm))
- *USDA Food and Nutrition Services* (Web site), US Department of Agriculture ([www.fns.usda.gov](http://www.fns.usda.gov))

### Engaging Patient and Family

- *Child Care Aware Resources* (Web page), Child Care Aware ([childcareaware.org/parents-and-guardians/resources](http://childcareaware.org/parents-and-guardians/resources))
- *Community Health Online Resource Center* (handouts), Centers for Disease Control and Prevention ([nccd.cdc.gov/DCH\\_CHORC](http://nccd.cdc.gov/DCH_CHORC))
- *Frequently Asked Questions About Section 504 and the Education of Children With Disabilities* (fact sheet), US Department of Education ([www.ed.gov/about/offices/list/ocr/504faq.html](http://www.ed.gov/about/offices/list/ocr/504faq.html))
- *Head Start: About Us* (Web page), Office of Head Start ([eclkc.ohs.acf.hhs.gov/hslc/hs/about](http://eclkc.ohs.acf.hhs.gov/hslc/hs/about))
- *National Center for Children in Poverty Data Tools* (Web page), National Center for Children in Poverty ([nccp.org/tools](http://nccp.org/tools))
- *Office of Child Support Enforcement* (Web site), Office of Child Support Enforcement ([www.acf.hhs.gov/programs/css](http://www.acf.hhs.gov/programs/css))
- *Rental Assistance* (Web page), US Department of Housing and Urban Development ([portal.hud.gov/hudportal/HUD?src=/topics/rental\\_assistance](http://portal.hud.gov/hudportal/HUD?src=/topics/rental_assistance))
- *Social Security* (Web site), Social Security Administration ([www.ssa.gov](http://www.ssa.gov))
- *Supplemental Nutrition Assistance Program* (Web site), US Department of Agriculture ([www.fns.usda.gov/snap](http://www.fns.usda.gov/snap))

### AAP POLICY

- American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health. Coparent or second-parent adoption by same-sex parents. *Pediatrics*. 2002;109(2):339–340. Reaffirmed May 2009 ([pediatrics.aappublications.org/content/109/2/339](http://pediatrics.aappublications.org/content/109/2/339))
- Coleman WL, Garfield C; American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health. Fathers and pediatricians: enhancing men's roles in the care and development of their children. *Pediatrics*. 2004;113(1):1406–1411. Reaffirmed August 2013 ([pediatrics.aappublications.org/content/113/5/1406](http://pediatrics.aappublications.org/content/113/5/1406))

### SUGGESTED READINGS

- Hagan, JH, Shaw JS, Duncan, PD. *Bright Futures: Guidelines for Health Supervision of Infants, Children and Adolescents*. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2008

- Kuhlthau KA, Bloom S, Van Cleave J, et al. Evidence for family-centered care for children with special health care needs: a systematic review. *Acad Pediatr*. 2011;11(2):136–143
- Radecki L, Olson LM, Frintner MP, Tanner JL, Stein MT. What do families want from well-child care? Including parents in the rethinking discussion. *Pediatrics*. 2009;124(3):858–865
- Stille C, Turchi RM, Antonelli R, et al. The family-centered medical home: specific considerations for child health research and policy. *Acad Pediatr*. 2010;10(4):211–217

## Chapter 33

# HEALTHY CHILD DEVELOPMENT

Marian Earls, MD

Primary care physicians (PCPs) who care for children and youth have the opportunity at every encounter with the family to promote healthy development—motor, language, cognitive, and social-emotional. Recent understanding of brain development highlights the importance of social-emotional development. Pediatricians know from brain research that experience affects brain development, both prenatally and postnatally. The implications for prevention and intervention are profound because growth, development, and behavior are inextricably linked. This chapter describes the PCP's role in promoting healthy child development, identifying developmental problems, and involving other professionals in the child's care when needed.

## BACKGROUND

Approximately 15% of children have developmental or behavioral disabilities, including speech and language delays, attention-deficit/hyperactivity disorder, intellectual disability, learning disabilities, cerebral palsy, autism, hearing loss, blindness, and emotional problems. Even at preschool age, 13% of children have mental health problems. In 2005 the Centers for Disease Control and Prevention reported that 5% of 4- to 17-year-olds in the United States (2.7 million children) were described by their parents as having severe emotional or behavioral difficulties in the National Health Interview Survey. These rates increase with the co-occurrence of risk factors such as poverty, maternal depression, substance abuse, domestic violence, and foster care placement. According to the National Center for Children in Poverty, in 2015 approximately 44% of children in the United States lived in low-income families. This number has been increasing since 2000, after a decade of decline. These children have an increased risk for language, learning, and behavioral problems. An infant living with a depressed mother can show disordered attachment as early as 2 months of age and is at risk for failure to thrive, impaired social interaction, and delays in language and cognitive development. For the older child or adolescent, there is increased likelihood of depression, anxiety, behavior problems, or conduct disorder. Many premature infants, especially those of extremely low birth weight (<1000 g), are at risk for

visual and hearing impairment, language delays and learning problems, and problems with motor development. In addition, for an infant who has had a prolonged neonatal intensive care unit course, bonding can be a challenge, particularly if ongoing medical or feeding issues exist.

Despite the medical community's knowledge of prevalence and risk, detection of developmental and behavioral problems before school age is very poor (<50%). This circumstance limits the possibility of early intervention. By contrast, 70% to 80% of children with developmental disabilities are correctly identified when standardized screening tests are used.

Screening rates for development and behavior, maternal depression, and family risk or protective factors have been poor in primary care practice. The American Academy of Pediatrics (AAP) Survey of Fellows No. 53 in 2002 revealed that 71% of fellows used only clinical observation without a screening instrument to identify children with a developmental delay. Only 23% reported using a standardized tool. Reasons given for not screening include that screening takes too long, tools are difficult to administer, children may not cooperate (an understatement with a screaming 2-year-old), and reimbursement is limited. Perceived barriers are time, cost, and staff required.

Despite these perceived barriers, during the past several years, national efforts such as the Commonwealth Fund's ABCD (Assuring Better Child Health and Development) Project have increased developmental and behavioral screening, referral, and coordination of care in practices across many states. Since 2000 there have been many successful models of screening in primary care practices, including developmental and behavioral screening, maternal depression screening, and psychosocial screening. In these projects, strategies have been implemented to integrate screening into office flow, to improve reimbursement, and to assist practices in identifying and collaborating with community resources, including mental health resources. The ABCD Project, funded by the Commonwealth Fund and administered by the National Academy for State Health Policy, has involved 28 states and their AAP chapters. The AAP, in addition to its screening policy statements, promotes screening through outreach, continuing education, and quality improvement activities. According to the National Survey of Children's Health 2011, the use of standardized, parent-completed developmental screening in primary care has been increasing (parents reported completing a standardized developmental screening tool in the past 12 months at a health care visit for a child between 10 months to 5 years of age 30.8% of the time in 2011, up from 19.5% of the time in 2007). Likewise, in 2009 the Survey of Fellows No. 74 revealed that 47.7% of pediatricians reported using a standardized tool (which had doubled since 2002). Those using only clinical observation decreased to 60.5%.

Early identification allows for referral and early intervention, even for children with significant developmental diagnoses that cannot be cured or completely remediated. Early intervention improves function for the child and family and allows for linking families with community supports. Early intervention can also save up to \$100,000 per student in special

education costs over the course of the child's education. However, although 15% have a developmental disability in childhood, only 2% to 3% receive public early intervention services by 3 years of age.

In the care of the child or adolescent, then, it is necessary to consider the whole child, including social and emotional development, in the context of family, school, and community. Routinely assessing risk allows for early implementation of preventive strategies.

## OFFICE-BASED HEALTH PROMOTION

The primary medical home provides the perfect setting for screening and surveillance, improving prevention, and early identification. The promotion of healthy development using a strengths-based approach is a central emphasis of the Bright Futures health supervision guidelines. Bright Futures health promotion themes include family support, child development, and mental health. The PCP's longitudinal relationship with the child and family is a key component of the "primary care advantage" described in the AAP statement regarding mental health competencies in primary care. Discussing assets and promoting connections for support are part of early and ongoing conversations with families, along with open discussion regarding risk factors.

Promotion of healthy development begins with the prenatal visit. At that visit, the longitudinal relationship begins, and the discussion of family assets and supports as well as stressors occurs. Early identification of risk factors, such as maternal depression, allows for early strategies to support the mother and family so that the infant is born into a nurturing environment. Reach Out and Read is an excellent example of health promotion. By reading to the infant, toddler, or preschooler, in a single activity the parent encourages healthy social-emotional (cuddling to read), language (imitating and pointing), and fine motor (reaching and turning pages) development. Encouraging the sharing of age-appropriate books together from an early age has benefits for the relationship, developing language skills, and success with early reading skills.

Asking the child or adolescent about his or her best and favorite subjects at school is as important as discussing where he or she has difficulty. PCPs partner with parents in encouraging the child about school (participation in class and completing homework) as well as in advocating for assessment and intervention for students who may have learning or attention difficulties. Showing interest in and encouraging prosocial activities for children and adolescents are powerful tools for the PCP; such activities help young people explore their talents and promote belonging. Examples include clubs, sports teams, dance, band, and choir. Particularly for adolescents, encouraging volunteerism and community activities is positive for building self-esteem and reducing risk behaviors. For adolescents, a useful model to promote such protective factors is the Circle of Courage mnemonic GIMB: generosity, independence, mastery, and belonging.

As part of routine care, the PCP should engage the family in discussion regarding parental well-being, family supports, and information about child care or school. To this end, the PCP would routinely perform developmental and behavioral surveillance and standardized

screening. PCPs who provide care for children and adolescents have long recognized the importance of developmental and behavioral screening and surveillance in helping families optimize their children's acquisition of skills, understand behavior, and facilitate learning. For children who may have developmental differences or delays, regular periodic screening provides the opportunity for early identification and referral for intervention. Screening not only has the benefit of early identification but also is an excellent promotional strategy in that a screen provides a discussion template for anticipatory guidance and asset building.

A strengths-based approach is of central importance. It is the PCP's role to elicit both strengths and concerns. From an early age the child should participate in reporting his or her strengths and concerns. This builds the relationship with the child and helps prepare for communication between the PCP and adolescent. The Search Institute documented the protective effect of assets when a child or adolescent is exposed to risk. The asset categories include external assets (support, empowerment, boundaries, and expectations, and constructive use of time) and internal assets (commitment to learning, positive values, social competencies, and positive identity).

When social-emotional, behavioral, or mental health concerns are voiced, the AAP Task Force on Mental Health recommends a "common factors" approach, applying motivational interviewing and other communication skills to engage the family in developing a plan for addressing the issue together and considering follow-up and referral if necessary. (See Chapter 46, Effective Communication Strategies.)

## IMPLICATIONS FOR PRACTICE

The PCP does not need to become an expert at diagnosing and managing developmental and behavioral disorders, nor a mental health professional. However, the PCP has the "primary care advantage" noted earlier, with the opportunity for surveillance and

screening, discussion of findings with the family (and child or adolescent), referral for further assessment and intervention, and monitoring of the child and family's progress over time. The PCP has multiple roles: a partner with the family in finding information and community resources, a sounding board, a facilitator in negotiating the system, and comanager of care with other specialists.

Promotion and early identification involve both surveillance and screening. Surveillance is the routine elicitation of family and patient concerns about development, behavior, or learning; it is generally accomplished by conversation and observation. It is part of the longitudinal relationship and occurs at every visit (Table 33-1). Formal screens are used at important intervals to understand and document development and to detect problems that are not observable through surveillance alone.

Primary developmental and behavioral screens and psychosocial screens can be interwoven into the schedule of well-child visits and into the growing relationship with the family. Screening may involve the family social environment and caregivers as well as the child. Screens are included in the routine health supervision schedule in anticipation of critical turning points. However, these screens are meant to be flexible to respond to individual family concerns.

Family psychosocial surveillance begins with the first visit with the family and is really part of the history-taking process. It can then take place with any updating of history at later visits. Specific psychosocial screens can be interwoven into registration material when a family first comes to the practice, at visits when developmental screening questionnaires are not being used, and into the conversations between the physician and parents at any visit. Screening should be routine for all families, not targeted because of assumptions about risk. Psychosocial screening includes asking about family relationships, maternal depression, domestic violence, substance abuse, and finances. Other important

**Table 33-1** Development: Possible Areas of Concern by Domain and Age

	<b>GROSS-MOTOR</b>	<b>FINE-MOTOR</b>	<b>LANGUAGE AND COMMUNICATION</b>	<b>PROBLEM SOLVING</b>	<b>SOCIAL-EMOTIONAL</b>
Infancy (0–1 yr)	Milestones: crawling, sitting, walking	Early: visual tracking, reaching Later: pointing, pincer grasp	Early: responsive vocalizing Later: gestures, first words, responses to name	Transferring object hand to hand, poking with index finger	Social smile, state regulation, temperament, play
Early childhood (1–5 yr)	Mastery of walking, coordination, ability to jump, running	Stacking, pencil grasp; fine motor control	Joint attention, pointing, expansion of vocabulary, forming sentences, ability to tell a story in sequence	Imaginary play; functional use of objects, cooperative play	Tantrums, problems in child care, ability to share
School age (6–10 yr) and adolescent (11–20 yr)	Coordination, control; difficulty with physical education class	Handwriting, completion of written work, note taking	Reading, phonics, written language; language organization; getting thoughts on paper	Homework organization; attention, concentration	Peer relationships, family relationships, participation, motivation, affect



questions regarding stable housing, financial resources, and insurance coverage are also pertinent.

Routine standardized screening, appropriate to the developmental age of the child, is a recommended part of the well-child schedule from infancy through adolescence. Informal checklists, in use by many primary care physicians, have no validated criteria for referral and result in missed referral opportunities. If a problem is already observable, then a screen is unnecessary and the pediatrician can proceed directly to discussion and referral, optimizing time for intervention.

### Discussion of Findings

Developmental and behavioral screening allows early identification of potential problems or delays. Of equal importance, screening also reviews appropriate expectations at a given developmental age, facilitating understanding regarding the child's behavior and potentially facilitating appropriate use of discipline by parents. A conversation about the screening identifies the child's strengths and weaknesses, gives a template for anticipatory guidance, and elicits and respects parental concerns. In this way, parental self-efficacy and confidence are promoted. The physician should review and discuss the screen—whether negative or positive—with the parents (and child or adolescent) at the time of the visit. The screen provides a template for anticipatory guidance, facilitates patient flow (by reducing “doorknob concerns”—those expressed as the physician leaves the examination room), and improves patient and physician satisfaction.

If surveillance or screening suggests that a developmental problem may be present, the PCP's role is to explain the findings and seek agreement with the child or adolescent and family on next steps, which may include further assessment, intervention, or both. Families are in varied stages of readiness for this conversation. Common factors for communication skills, discussed in Chapter 46, Effective Communication Strategies, are applicable to engage the family and address barriers such as denial, resistance, and conflict that may impede follow-through with referral.

### Referral

If a screen has an at-risk score, then the PCP initiates a more detailed assessment. For the young child, this assessment is generally performed outside the practice (eg, by a developmental and behavioral pediatrician, geneticist, neurologist, infant-toddler specialist, psychologist, speech and language pathologist, or physical therapist). When screenings reveal risk, the office is the source for initial discussion and referral to community resources. This role assumes previous networking by the practice with community partners and a working knowledge of and connection to community providers such as counselors, agencies, early intervention programs, child care, Head Start, and schools. For children aged 0 to 5 years with at-risk scores, referral to early intervention services occurs. Early intervention for 0- to 3-year-olds is covered under Part C of the federal Individuals With Disabilities Education Act (IDEA); early intervention for 3- to 5-year-olds is covered by Part B of IDEA and is provided by the school system. A school-aged child or adolescent

may need assessment through the school's exceptional children program or through other specialists, as with the young child. For a parent whose child has a medical condition or developmental problem, a connection to a family support network can provide parent-to-parent support. Early empowerment for parenting has implications for long-term outcomes, including readiness to learn, school success, and social success. In a family-centered medical home, financial issues need to be considered for each family for a plan of care to be realistic and practical (eg, for cost of medication or transportation to a referral).

### Office Process

Integrating surveillance and screening into the office process and flow is crucial for successful implementation of screening programs. Once integrated, the process is routine and occurs reliably. Prompts at appropriate ages can be made part of an electronic health record. Parent-completed (and child- or adolescent-completed) screens can be performed in the examination room while waiting for the physician or in the waiting room. With the advent of electronic health records and their associated secure patient portals, parents and patients may be able to complete the screens from home before the visit. For those who do not have access to the Internet at home, a kiosk can be made available at the practice for screen completion just before the visit. Use of a portal also eliminates the need to scan a paper screen into the record.

Steps include the following:

1. Assess protocols for developmental and behavioral screening already in use in the practice.
2. Map the workflow. This process needs to include the physician, nursing staff, and office manager and should be tailored to the practice. For example, the nurse can give the screening tool to the parent at intake to be completed in the examination room so as to be ready for the physician to review and score after coming into the room.
3. Select tool or tools. See the following section for further discussion of this step.
4. Identify system supports for parent education, referral, and community services.
  1. Meet with key partners. Inviting community partners to a lunch meeting at the practice to share screening plans and align goals is a good idea.
  2. Establish a process for referral and communication.
5. Orient all staff members to new procedures.

Billing issues are an important aspect of screening. For general developmental and behavioral screening tools (eg, Ages and Stages Questionnaire [ASQ], Parents' Evaluation of Developmental Status [PEDS], Modified Checklist for Autism in Toddlers, Revised With Follow-Up [MCHAT-R/F]), the American Medical Association Current Procedural Terminology code is 96110. The code 96127 is for behavioral and emotional screening tools (eg, Vanderbilt, Pediatric Symptom Checklist [PSC], Patient Health Questionnaire-9 [PHQ-9] Modified for Adolescents). These codes can be billed with a well-visit code or an evaluation and management code and have 0.36 relative value units.



## DEVELOPMENTAL AND BEHAVIORAL SCREENING TOOLS

Parents generally give accurate and high-quality information, and they are good reporters of what their child can do. Parents' concerns are accurate indicators of true problems, particularly for speech and language, fine-motor, hearing, and general function. When asked how old their child acts compared with other children, parent estimations correlate well with developmental quotients for cognitive, motor, self-help, and academic skills. Recall (eg, milestones) is unreliable, however. For tools completed by a parent, an inclusive reading level must also be considered, although the best tools have been developed with an eye to readability. If parental reading skills are a concern, then parents can be asked if they would like to complete the screen independently or have someone go through it with them. Language availability is an important consideration in some practices. Several advantages exist to using a parent questionnaire, not the least of which is that it is a family-centered process, recognizing the parent as the expert on the child. The parent is engaged as a partner in the care of the child. A parent-completed tool can address concerns about time and efficiency. A parent tool does not require administration by staff and can be completed while the parent is in the waiting room or examination room so that it does not impinge on visit time or office flow. In the case of young children, it also removes the problem of trying to elicit skills from a toddler or preschooler by a virtual stranger and in a setting that is not the child's natural environment.

Developmental and behavioral screening tools are of different types and include direct elicitation, interview, and questionnaires completed by parents and the child or adolescent. Effective screens have sensitivity and specificity of at least 70% to 80%. The tools referred to next do not reflect an exhaustive list but are conducive to use, and commonly used, in primary care practice.

### Surveillance

- Routine elicitation of family and patient concerns about development, behavior, or learning
- Generally accomplished by conversation and observation

### Primary Screening

- Formal screening done with the *total* population to identify those who are at risk
- Examples include ASQ, PEDS, Survey of Well-Being of Young Children (SWYC), PSC, Strengths and Difficulties Questionnaire (SDQ), Bright Futures Adolescent Supplemental Questionnaires, Edinburgh, and PHQ-2
- These are tools with validation and cutoff scores, except for the adolescent screens that ask about specific risks and strengths but do not have a numeric score

### Secondary Screening

- More specific screening done when risk is identified on a primary screen
- Examples include the ASQ Social-Emotional (ASQ-SE), Screen for Child Anxiety Related Disorders (SCARED), Children's Depression Inventory (CDI),

Center for Epidemiological Studies Depression Scale for Children (CES-DC), PHQ-9 Modified for Adolescents, Vanderbilt, Conners

- Note that a specific screen may be used as a primary screen if there is known risk in a given population. Examples include MCHAT-R/F, CRAFFT (tool to screen adolescents for high risk of substance abuse)
- Evaluation and Assessment**
- Goes beyond screening to ascertain diagnosis and develop recommendations for intervention or treatment
  - This is generally not done by the primary care medical home, unless colocated or integrated professionals are in the practice. For example, evaluation is done by Part C (Early Intervention Services for children 0 to 3 years of age), in the schools, by a developmental and behavioral pediatrician, psychologist, psychiatrist, geneticist, or other physician or specialist

## Primary Screens

Primary screens cover several areas of development, including gross and fine-motor, language, learning and problem-solving, social-emotional, and behavioral development.

For young children, commonly used (practical in a busy primary care practice) screens included in this group are the ASQ-3, PEDS, PEDS Developmental Milestones (PEDS DM), SWYC, and the Infant Developmental Inventory (IDI). For children born prematurely, screens should be used according to adjusted age until 2 years of age. The MCHAT-R/F screens for risk for autism spectrum disorders and is recommended routinely by the AAP at the 18- and 24-month visits. The follow-up questions for the MCHAT-R/F are used to clarify parental responses on the MCHAT tool and increase the tool's positive predictive value. For a complete description of tools with information on forms, content, sensitivity, and specificity, and for ordering, refer to the AAP Section on Developmental and Behavioral Pediatrics Web page on screening and assessment ([www2.aap.org/sections/dbpeds/screening.asp](http://www2.aap.org/sections/dbpeds/screening.asp)). Excluded tests, as a result of poor validation or sensitivity and specificity, are the Prescreening Developmental Questionnaire, the Denver Developmental Screening Test II, Developmental Indicators for the Assessment of Learning III, and Gesell Developmental Observation Test.

For older children and adolescents, the domains of development are reflected in learning skills (reading, written language, organization, attention, academics) and social skills. Primary screening tools include the PSC, SDQ, and Bright Futures Adolescent Supplemental Questionnaires for ages 11 through 20 years. These have tools for the child and adolescent as well as for the parent to complete. For adolescents there is also the HEADSSS (Home and Environment, Education and Employment, Activities, Drugs, Sexuality, Suicide/Depression, and Safety) interview that assesses strengths and risks.

A comparison of primary screening tools by time, staff, reading level, and language availability is shown in Table 33-2.

Table 33-2 Primary Developmental and Behavioral Screening Tools

	ASQ-3	PEDS	PEDS DM & PEDS	IDI	BRIGANCE	SWYC	MCHAT R/F	PSC	SDQ	BRIGHT FUTURES
TYPE	Parent Questionnaire	Parent Questionnaire	Parent Questionnaire	Parent Questionnaire	Direct Elicitation	Parent Questionnaire	Parent Questionnaire	Parent/Youth Questionnaire	Parent/Youth Questionnaire	Parent/Youth Questionnaire
AGES	1 mo–5 yrs	0–8 yrs	0–7 yrs, 11 mos	3–18 mos	0–35 mos	2 mos–5 yrs	16–30 mos	4–18 yrs	3–16 yrs	11–21 yrs
STAFF REQUIRED (to admin and or score)	Paraprofessional (to score)	Paraprofessional (to score)	Paraprofessional (to score)	Paraprofessional (to score)	Professional (to admin & score)	Paraprofessional (to score)	Paraprofessional (to score), and ask follow-up questions (if needed)	Paraprofessional (to score)	Paraprofessional (to score)	Paraprofessional (to score)
COST	Purchase kit	Purchase starter kit	Purchase starter kit and family books for exam rooms	Purchase kit	Each age range: purchase manual and data sheets	Public domain freely downloadable	Public domain freely downloadable	Public domain freely downloadable	Public domain freely downloadable	Purchase BF Toolkit
REFILLS/COPIES	OK to copy after purchase of kit(s)	Purchase refills	Purchase refills for scoring sheets	Purchase refills	Purchase refills	Copy	Copy	Copy	Copy	OK to copy
TIME	3 min to score	5 min to score	5–10 min to score	10 min to score	10–15 min to admin	5–10 min to score	3–5 min to score	3–5 min to score	10 min to score on-line scoring available	Review by PCC
LANGUAGES	English Spanish	English Spanish Vietnamese	English Spanish	English Spanish	English Spanish	English, Spanish, Burmese, Nepali, Portuguese	English, Spanish plus 27 languages	English Spanish Chinese	71 languages	English
READING LEVEL	4th–6th grade	5th grade	3rd–4th grade	Not specified	NA	Not specified	Not specified	Not specified	Not specified	Not specified

### Secondary Screens

For children who screen at risk for social-emotional problems, on a general screen or because of known risk factors, effective social-emotional screens are available to help the PCP in the medical home make decisions about referrals and types of interventions. A secondary screen can be performed at a follow-up visit with the PCP, by an integrated mental health provider in the practice, or by a care manager. Alternately, the primary care practice may opt not to do secondary screening and to refer for further assessment when the primary screen indicates an at-risk area. As an example, the ASQ-SE is an appropriate tool to be used if an ASQ or a parent or provider concern indicates risk. Practical tools for the very young child include the ASQ-SE and the Early Childhood Screening Assessment (ECSA). The SWYC (for 0- to 5-year-olds) actually incorporates the Baby Pediatric Symptom Checklist and the Preschool Pediatric Symptom Checklist. Therefore, for practices using the SWYC as a general tool, a social-emotional screen is also included. For older children, tools include the CDI, CES-DC, SCARED, PHQ-9 Modified for Adolescents, and CRAFFT (substance abuse). Bright Futures recommends screening for depression at every well visit from age 11 through 21 years. The US Preventive Services Task Force recommends routine screening for depression in adolescents. Routine screening for depression from age 12 years and up is a Meaningful Use measure (National Quality Forum #418).

### Family Psychosocial Screening

For family psychosocial screening, a variety of tools are available, ranging from brief to general, that incorporate a range of topics. Most of these tools screen for maternal depression, domestic violence, and substance abuse. These can identify both parental ACEs and risk for ACEs and toxic stress for the child. These psychosocial factors have significant impact on

healthy development. Examples of such screens include the following:

- Kemper-Kelleher: includes questions about parent's childhood experiences (substance use and abuse, discipline, abuse and neglect, foster care), depression, substance use, support
- SWYC: includes questions about smoking, substance use, food availability, depression, domestic violence
- SEEK (A Safe Environment for Every Kid): includes questions about smoking, guns, food availability, depression, substance use, discipline, domestic violence
- Parents' Assessment of Protective Factors, from Strengthening Families, Center for the Study of Social Policy
- Edinburgh: postpartum depression

Bright Futures highlights the importance of addressing these risk areas and identifying family protective factors to promote the healthy development of the child. (See Chapter 34, Mental Health.)

For an overview of how these various tools may be integrated into the well-child schedule, see Table 33-3, which incorporates the screenings based on current recommendations. See Chapter 32, Family Support, for more information about use of these tools.

### SUMMARY

Promotion of healthy development begins as early as the prenatal visit and continues through the longitudinal relationship of the PCP with the child and family. Routine discussion of assets and risks is an essential health promotion and preventive strategy. Opportunities for promoting healthy development and identifying developmental problems include prenatal visits, surveillance, psychosocial screening of both the child and family, developmental and behavioral screening of the child, and secondary social-emotional and mental health screening of children and adolescents at

**Table 33-3**

**Healthy Child and Adolescent Development: Promotion and Screening for Risk**

VISIT	PRIMARY SCREEN/ SURVEILLANCE	CONCERN	FOLLOW-UP SCREEN	REFERRAL CONSULTATION	INTERVENTION
<b>AGE 0-5 YR</b>					
1, 2, 4 mo	Edinburgh/PHQ-2	Postpartum depression	ASQ-SE	MHP	E-B therapy EI Part C
9, 18, 24, or 30 mo	ASQ/PEDS/SWYC, etc.	Motor, language Social-emotional	ASQ-SE	MHP	EI Part C E-B therapy
36, 48, 60 mo		Motor, language Social-emotional	ASQ-SE	MHP	EI Part B E-B therapy
Any	At-risk psychosocial situation	Maternal depression, DV, SA	ASQ-SE	MHP	E-B therapy
Any	Parent concern	Motor, language Social-emotional	ASQ-SE	MHP	EI E-B therapy, EI
18 and 24 mo	MCHAT-R/F	ASD			EI Part C

*Continued*

**Table 33-3** Healthy Child and Adolescent Development: Promotion and Screening for Risk—cont'd

VISIT	PRIMARY SCREEN/ SURVEILLANCE	CONCERN	FOLLOW-UP SCREEN	REFERRAL CONSULTATION	INTERVENTION
<b>AGE 6–10 YR</b> Every well visit	PSC/SDQ	Depressive symptoms Anxiety Learning, school behavior problems	CDI, CES-DC SCARED Vanderbilt and school records	MHP MHP School evaluation	CBT CBT IEP for OHI/LD
<b>AGE 11–20 YR</b> Every well visit	Bright Futures Supplemental	Function Depressive symptoms	SDQPHQ-9 Modified for Adolescents	MHP	CBT
	HEADSSS	Anxiety Learning, school behavior problems	SCARED Vanderbilt and school records	MHP School evaluation	CBT IEP for OHI/LD
	CRAFFT	Substance use, abuse		MHP	E-B therapy

CBT, Cognitive behavioral therapy; E-B, evidence-based; EI, early intervention; IEP, Individualized Education Plan; LD, learning disability; MHP, mental health professional (integrated in practice or in community); OHI, other health impaired.

risk. The use of routine standardized screening tools at recommended intervals enhances surveillance and the ability to identify risk early. The roles of the medical home include the following:

- Develop a reliable system for integration of surveillance, screening, referral, follow-up, and linkage to resources into the office workflow.
- Develop relationships with specialists and community agencies to include standardized referral and feedback processes.
- Follow criteria for referral after a positive screen. There is *no rationale* for a “wait and see” approach because it delays early intervention.

When developmental problems are identified, the PCP uses the “primary care advantage” to engage the child or adolescent and family in developing a plan for further assessment and care. The PCP refers, if necessary, and communicates and collaborates with specialists, schools, and other providers in the monitoring and ongoing care of the child or adolescent.

### AAP POLICY

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### SUGGESTED READINGS

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## Chapter 34 MENTAL HEALTH

Jack T. Swanson, MD; Jane Meschan Foy, MD

### BACKGROUND: THE PEDIATRICIAN'S ROLE IN PROMOTING CHILDREN'S MENTAL HEALTH

Children's mental health—including all its psychosocial and emotional aspects—is an intrinsic part of their overall health and well-being. The pediatrician has an important role to play in influencing the intentional pursuit of optimal mental health as part of each child's development. Good mental health has been described as “the reasonable, regular experience and effective practice of

- Confidence and courage
- Adaptability
- Cheerfulness
- Attention/concentration
- Harmony
- Hardiness
- Social connectedness”

The foundation of mental health begins before birth, with the parents' and caregivers' own well-being and with preparations they make for the physical and emotional care of the child. Caregivers continue to build on this foundation after the child's birth by providing their attention and love in a safe and nurturing environment. This environment expands from the child's home to include the child care setting, school, and community. Box 34-1 provides examples of the skills needed by caregivers in all settings to nurture social and emotional competence in a young child.

While fostering mental health is, in practice, intertwined with fostering healthy development generally, Chapter 33, Healthy Child Development, provides context for the present chapter.

Each stage of childhood provides pediatricians with unique opportunities to promote children's mental health during regular contacts with the child and his or her caregivers. These unique opportunities, described by the American Academy of Pediatrics (AAP) Task Force on Mental Health (TFOMH) as the “primary care advantage,” include:

- A longitudinal, trusting, and empowering therapeutic relationship with children and family members
- A family-centered medical home
- Regular contacts in which to promote healthy lifestyles; foster the skills caregivers need to promote children's social and emotional competence; reinforce child and family strengths; recognize adverse

### BOX 34-1 Examples of Caregiver Skills to Promote Social and Emotional Competence

- Engage infants in frequent face-to-face social interactions each day (verbal and nonverbal behaviors).
- Quickly respond to infants' and toddlers' cries or other signs of distress by providing physical comfort and needed care.
- Support children's development of friendships and provide opportunities for children to play with and learn from each other.
- Help children practice social skills and build friendships by helping them enter into, sustain, and enhance play.
- Help children resolve conflicts by helping them identify feelings, describe problems, and try alternative solutions.
- Help children talk about their own and others' emotions; provide opportunities for them to explore a wide range of feelings and the different ways to express them.
- Actively teach children social communication and emotional regulation.
- Help children manage their behavior by guiding and supporting them to: (1) persist when frustrated; (2) play cooperatively with other children; (3) use language to communicate needs; (4) learn turn-taking; (5) gain control of physical impulses; (6) express negative emotions in ways that do not harm others or themselves; (7) use problem-solving techniques; and (8) learn about themselves and others.

From National Association for the Education of Young Children (NAEYC). NAEYC Early Childhood Program Standards and Accreditation Criteria & Guidance for Assessment. Updated October 1, 2015. [www.naeyc.org/academy/torch-resource/naeyc-early-childhood-program-standards-and-accreditation-criteria-guidance-assessment](http://www.naeyc.org/academy/torch-resource/naeyc-early-childhood-program-standards-and-accreditation-criteria-guidance-assessment). Copyright © 2015 National Association for the Education of Young Children.

childhood experiences and stressors (see Chapter 68, Children Exposed to Adverse Childhood Experiences, for a discussion of the importance of this); offer anticipatory guidance, including strategies for self-soothing and stress management; and provide timely intervention for common problems

- Understanding of common social, emotional, and educational problems in the context of a child's development and environment
- Knowledge of community resources to assist children and families in building resilience and addressing the mental health challenges they encounter.

Mental health problems occur often during childhood and adolescence. In the United States, between 9.5% and 14.2% of children from birth to 5 years experience social-emotional problems that cause suffering to the child and family and interfere with functioning. More than 20% of children ages 9 to 17 have a diagnosable mental health disorder, and another 16%

or more of children have impaired mental health functioning without a diagnosable mental health disorder. Furthermore, half of adults with mental health disorders experienced the onset of symptoms by age 14. Parents' misperceptions about their children's behavior may also be an issue: 10% to 13% of children have parents who think their child has a behavioral problem when the child is, in fact, functioning normally for his or her age. Mental health problems are more common among children with chronic medical or developmental conditions and among those who have experienced abuse or neglect, foster care, poverty, separation or divorce of parents, domestic violence, school failure, parental or family mental health or substance abuse issues, natural disasters, military deployment of a family member, and grief accompanying the illness or death of a family member.

Unfortunately, youth and parents may be reluctant to discuss their mental health or substance abuse concerns with their pediatrician because of embarrassment, because they do not understand that their concern may be a mental health issue, or because they do not see the physician as a mental health resource. Pediatricians can address these barriers by posting information about mental health–related topics and events and offering mental health brochures and handouts in the physical practice, and by including mental health content on the practice Web site and in newsletters. They can ensure that all members

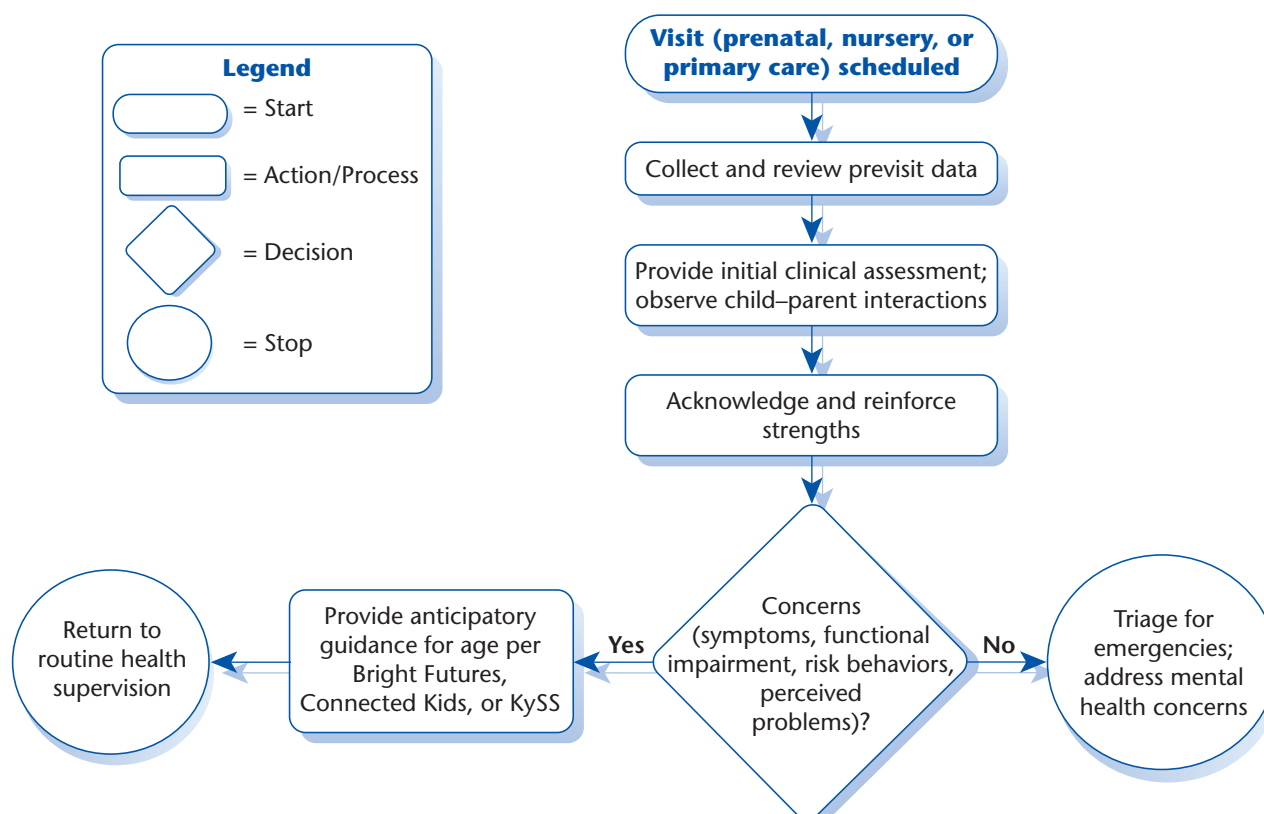
of the practice respect the privacy of children and families and that their language and attitudes reflect the fact that mental illnesses are treatable, that they are no one's fault, and that they do not define the person (eg, a child has schizophrenia, he or she is not a schizophrenic). Pediatricians can also promote mental health through the choice of topics discussed at each visit, whether providing routine health supervision, acute care, or management of a chronic illness. By integrating mental health care into all contacts with the child and family, the physician and office staff demonstrate the importance of mental health, normalize the process of providing mental health care in the medical home, and help to reduce the stigma of mental illness.

### PREVENTIVE MENTAL HEALTH CARE AT ROUTINE HEALTH SUPERVISION VISITS

The TFOMH describes a process for incorporating preventive mental health services into routine well-child visits. This process is summarized in an excerpt from the TFOMH Algorithm A (Figure 34-1).

#### A1a. Visit (prenatal, nursery, or primary care) scheduled.

Scheduling of any visit at any age can trigger data-gathering in advance of the visit, as described in step A2a.



**Figure 34-1** Promoting Social-Emotional Health, Identifying Mental Health and Substance Concerns, Engaging the Family, and Providing Early Intervention in Primary Care.

**A2a. Collect and review pre-visit data.**

To create efficiency during scheduled visits, pediatricians can adopt the use of a pre-visit questionnaire, either paper or electronic, filled out at home or in the waiting room. Such an approach enables the physician to focus on building rapport and on exploring findings, rather than on rote data-gathering, while still being systematic in obtaining information. *Bright Futures Tool and Resource Kit* includes pre-visit questionnaires to elicit a psychosocial history and concerns of parents, and information about changes that have occurred in the family and home, particularly family and environmental stressors. *Bright Futures* also recommends incorporating mental health and substance abuse questions into the adolescent pre-visit questionnaire.

Validated screening tools may be part of pre-visit data collection. Table 34-1 lists a number of those available for use in primary care. Studies demonstrate the feasibility of using brief, psychometrically sound mental health screening tools in the primary care setting. American Academy of Pediatrics recommendations address the type and timing of tools to screen for developmental delays, autism, and behavioral and emotional problems during early childhood. The *AAP Periodicity Schedule* now includes the recommendation to screen all adolescents for depression at health supervision visits. The TFOMH also makes a strong case for periodic mental health screening of children and their families. This includes instruments to assess psychosocial functioning (at home, with peers, at childcare, at school, and in the community) and instruments to identify symptoms associated with mental health disorders. A number of these instruments include parent, teacher, and youth reporting formats. Electronic tools have the advantage of greater acceptability to adolescents. Furthermore, electronic questionnaires provide an opportunity for the use of “item responses.” For example, the computer asks the respondent 2 or 3 basic questions. If the answer is “no” to those, the respondent moves on; if the answer is “yes,” the computer asks more questions.

Box 34-2 summarizes AAP guidance on psychosocial screening of the child, and Box 34-3 of the family, as published by the TFOMH in June 2010 and affirmed in February 2015 in the clinical report *Promoting Optimal Development: Screening for Behavioral and Emotional Problems*.

Examples of screening tools useful in primary care settings are included in Table 34-1. The use of screening tools does not replace the clinical interview needed to confirm findings and expand on identified problems.

Pediatricians may encounter some limitations to the use of screening tools, including their use in populations for which English is a second language and those for which the cultural context of a child's behavior or family's parenting may vary from that of the population in which the screening tool was validated.

Whatever questionnaires and screening instruments are used, a structured process, developed by

the practice in advance, should ensure that the following content is covered:

- Family's priorities for the visit
- Family/social history (including stresses, support system, environmental risk assessment, trauma, separation, and loss)
- Identification of the child's and family's strengths
- Functional assessment of the child and family
- Temperament and risk behaviors
- School or child care reports, if school or child care personnel have expressed concerns
- Symptoms of psychosocial problems

If pre-visit data collection is not feasible, the pediatrician will need to incorporate data collection into the clinical encounter, step A3a.

**A3a. Provide initial clinical assessment; observe child-parent interactions.**

During the face-to-face encounter, the PCP can complete the following steps:

- Identify, elicit, or review the child's and family's priorities for the visit.
- Review pre-visit questionnaire, screening tools, and other data collected (or complete data collection as described in A2a), review progress on any previous concerns, and update information about adjustment and progress in child care, preschool, or school.
- Broaden the agenda by indicating openness to mental health issues. For example, elicit further information about any current concerns, the child's or family's past or current sources of care for the concerns, and progress on previous concerns; if screening tools have been completed, use any positive responses as a springboard to further discussion and clarification. Ask broad, open-ended questions such as, “What has been the hardest part about taking care of Jonah?,” followed by, “What has been the best part?” Such questions convey the doctor's interest in family functioning and invite vexing questions that may have been posed to relatives and friends but may have not felt appropriate for this medical setting. Whatever methods are used to gather information, include inquiry about parental well-being (looking particularly for problems with parental mood, affect, or attachment to the child) and the child's developmentally-specific symptoms of emotional disturbance. Also consider the family's cultural context.
- Observe parent-child interaction. Pediatricians can gain additional insights from examining their own reaction to the parent and child.
- Interact with the child.
- Complete the interview and physical examination (including vision and hearing screen, because a sensory deficit may cause academic or behavioral difficulties).

The increasing independence of adolescents—and the likelihood that parents and guardians may not be fully aware of their adolescents' activities or feelings—reinforce the need for private, confidential discussions between pediatricians and their adolescent patients. These discussions should augment, not replace, discussions with parents. Youth and parents differ in their ability to report on various mental health

**Table 34-1 Behavioral and Emotional Screening Measures for Use in Primary Care in the Public Domain<sup>a</sup>**

Young children (0–5 yr)	Baby Pediatric Symptom Checklist	2–17 mo	12	Parent completed	Retest reliability and internal reliability >0.7	sites.google.com/site/swycreen
	Preschool Pediatric Symptom Checklist	18–60 mo	18	Parent completed		sites.google.com/site/swycreen
	Strengths and Difficulties Questionnaire	3–17 yr	25 items	Parent/teacher 3(4)-yr-old; parent/teacher 4–10-yr-old; parent/teacher follow-up forms available	Variable across cultural groups; sensitivity: 63%–94%, specificity: 88%–96%; available in >70 languages	www.sdqinfo.org
School-age and adolescent children	Strengths and Difficulties Questionnaire	3–17 yr	25 items	Parent/teacher 4–10-yr-old; parent/teacher 11–17-yr-old; youth self-report 11–17-yr-old; parent/teacher/self follow-up forms available	Variable across cultural groups; sensitivity: 63%–94%, specificity: 88%–96%; available in >70 languages	www.sdqinfo.org
	Pediatric Symptom Checklist—17	4–16 yr	17 items	Parent completed; youth self-report >10 yr; pictorial version available	Variable psychometrics for detection of psychiatric problems; available in multiple languages	www.massgeneral.org/psychiatry/services/psc_home.aspx
	Pediatric Symptom Checklist—35	4–16 yr	35 items	Parent completed; youth self-report >10 yr; pictorial version available	Sensitivity: 80%–95%, specificity: 68%–100%; available in multiple languages	www.massgeneral.org/psychiatry/services/psc_home.aspx
<b>PSYCHOSOCIAL SCREENS</b>						
	WE-CARE (Well-Child Care Visit, Evaluation, Community Resources, Advocacy, Referral, Education)	Parent	10 items	Parent completed		pediatrics.aappublications.org/content/120/3/547
	Family Psychosocial Screen	Parent	50 items	Parent completed	Variable psychometrics for detection of specific psychosocial problems; cut points for various domains recommended	depts.washington.edu/dbpeds/Screening%20Tools/FamPsychoSocQaire.pdf



**Table 34-1 Behavioral and Emotional Screening Measures for Use in Primary Care in the Public Domain<sup>a</sup>—cont'd**

Survey of Wellbeing in Young Children	Parent	9 items	Parent completed	Preliminary findings show promise	<a href="http://sites.google.com/site/swycscreen/parts-of-the-swyc/family-questions">sites.google.com/site/swycscreen/parts-of-the-swyc/family-questions</a>
Adverse Childhood Experience Score	Parent	10 items	Parent completed	Increasing score associated with many adverse physical and mental health outcomes	<a href="http://acestoohigh.com/got-your-ace-score">acestoohigh.com/got-your-ace-score</a>
<b>SCREENS FOR SPECIFIC DISORDERS</b>					
Parental or adolescent depression					
Edinburgh Maternal Depression	Parent (mother)	10 items	Parent self-report	Sensitivity 86%; specificity 78%	<a href="http://www.fresno.ucsf.edu/pediatrics/downloads/edinburghscale.pdf">www.fresno.ucsf.edu/pediatrics/downloads/edinburghscale.pdf</a>
2 Question Screen (modification of the Patient Health Questionnaire—2 Patient Health Questionnaire (PHQ)—9	Parent, adolescent	2 items	Parent or adolescent self-report	Sensitivity: 83%–87%; specificity: 78%–92%	<a href="http://www.cqaimh.org/pdf/tool_phq2.pdf">www.cqaimh.org/pdf/tool_phq2.pdf</a>
Center for Epidemiologic Studies Depression Scale	Parent	9 items	Parent or adolescent self-report	Sensitivity: 88% for major depression; specificity: 88% for major depression	<a href="http://www.integration.samhsa.gov/images/res/PHQ%20-%20Questions.pdf">www.integration.samhsa.gov/images/res/PHQ%20-%20Questions.pdf</a>
	Parent; adolescents >14 yr (modified version for children as young as 6 available)	20 items	Parent completed; youth self-report	Coefficient $\alpha > .9$ ; sensitivity: 91%; specificity: 81%. Psychometrics for children <14 indicate measure may not discriminate well between depressed and nondepressed youth	<a href="http://cesd-r.com">cesd-r.com</a>
Mood and Feelings Questionnaire	Has been used with children as young as 7	Short version: 9 items; long version: 34 items	Parent completed; youth self-report	Parent report version: sensitivity 75%–86%; specificity 73%–87%	<a href="http://devepi.mc.duke.edu/mfq.html">devepi.mc.duke.edu/mfq.html</a>

*Continued*

Table 34-1		Behavioral and Emotional Screening Measures for Use in Primary Care in the Public Domain <sup>a</sup> —cont'd				
Substance abuse	CRAFT (Car, Relax, Alone, Forget, Friends, Trouble) CAGE-AID	11–21 yr Adolescents	3 screener questions, then 6 items 4 items	Interview of youth; youth self-report version available Youth self-report	Sensitivity: 76%–93%; specificity: 76% to 94%; available in multiple languages One or more positive answers is associated with a sensitivity of 79% and specificity of 77%; $\geq 2$ answers, 70% sensitivity and 85% specificity Coefficient $\alpha$ : .9	www.ceasar-boston.org/CRAFT  www.integration.samhsa.gov/images/res/CAGEAID.pdf  www.psychiatry.pitt.edu/research/tools-research/assessment-instruments www.scaswebsite.com
Anxiety	Screen for Child Anxiety Related Disorders (SCARED) Spence Children's Anxiety Scale (SCAS) Vanderbilt ADHD Diagnostic Rating Scales	$\geq 8$ yr  2.5–6.5 yr and 8–12 yr 4–18 yr	41 items  45 items 55-items parent scale; 43-items teacher scale	Parent completed; youth self-report  Parent completed 2.5–6.5 yr; youth self-report 8–12 yr Parent, teacher completed; follow-up forms available  Parent, teacher completed	High internal consistency and adequate test-retest reliability in adolescents Sensitivity: 80%; specificity: 75%; retest reliability $>0.80$	www.brightfutures.org/mentalhealth/pdf/professionals/bridges/adhd.pdf www.attentionpoint.com/x_upload/media/images/swan-description-questions.pdf www.myadhd.com/snap-iv-6160-18saml.html
ADHD	Strengths and Weaknesses of ADHD Symptoms (SWAN) SNAP-IV	6–18 yr 6–18 yr	30 items (18-item version available) 90 items (18-item version available)	Parent, teacher completed Parent, teacher completed	Coefficient $\alpha > .90$ ; available in multiple languages	

CAGE-AID, CAGE Questions (Cut Down, Annoyed, Guilty and Eye Opener) adapted to include drug use; Swanson, Nolan and Pelham Questionnaire, Version IV (SNAP-IV).

<sup>a</sup>This list is not meant to be exhaustive but is representative of a range of screening instruments suitable for primary care that are in the public domain. Psychometrics may vary based on the findings of different studies, and there is considerable variability in the strength of psychometric reliability among measures.

### BOX 34-2 Guidance on Mental Health Screening of Children and Adolescents in Primary Care Settings

1. Use validated instruments to screen for socioemotional problems in children 0 to 5 years old with abnormal developmental screening test results (typically performed at 9, 18, and 24 or 30 months) or abnormal autism screening test results (typically performed at 18 and 24 months); at any time the pediatrician observes poor growth or attachment or symptoms, such as excessive crying, clinginess, or fearfulness for developmental stage, or regression to earlier behavior; and at any time the family identifies psychosocial concerns.
2. Use validated instruments to screen all school-aged children (ages 5 through adolescence) for symptoms of mental illness and impaired psychosocial functioning at health maintenance visits; at any time of family disruption, poor school performance, reported behavioral difficulties, recurrent somatic complaints, or involvement of a social service or juvenile justice agency; or when the child or family identifies psychosocial concerns.<sup>a</sup>
3. In addition to #2 above, screen all adolescents for substance use (including tobacco) at each health maintenance visit and whenever circumstances such as an injury, car crash, or decrease in school performance suggest the possibility of substance abuse. If adolescent reports using substance(s), assess for extent of use.

<sup>a</sup>The US Preventive Services Task Force recommends screening adolescents (12–18 years old) for major depressive disorder [specifically] when systems are in place to ensure accurate diagnosis, psychotherapy (cognitive-behavioral or interpersonal), and follow-up.

### BOX 34-3 Proposed Screening and Surveillance of Family and Social Environment for Risk Factors

1. Obtain a history of trauma exposure and update child's and family's psychosocial history (eg, parental distress or discord, domestic violence, parental substance abuse or mental illness, youth and family social support, grief and loss issues) at each health maintenance visit and as dictated by clinical need.
2. Screen for maternal depression in the child's first year of life and when psychosocial history indicates. The incidence of postpartum maternal depression peaks when infants are between 2 and 6 months of age.

conditions: a parent may have a more accurate picture of the effect of externalizing symptoms (eg, hyperactivity, inattention, oppositionality), while youth may be better able to articulate the toll of internalizing symptoms or conditions (eg, anxiety, depression); or the youth and parents may disagree about the nature or

importance of symptoms. As part of these discussions, pediatricians are obliged to address confidentiality and its limits with both adolescents and their parents. (See Chapter 11, Ethical and Legal Issues for the Primary Care Physician.)

#### A4a. Acknowledge and reinforce strengths.

Effective mental health care requires that pediatricians move from a medical model focused on problems to a more comprehensive view of the child's and family's capacities. There are 8 empirically-determined independent "intelligences": linguistic, logical-mathematical, spatial, bodily-kinesthetic, musical, interpersonal, intrapersonal, and naturalistic. Acknowledging strengths—one or more of these intelligences; talents; qualities such as resilience, generosity, courage, tenacity, goal-orientation, focus; social supports such as strong family bonds, extended family support, or good peer relations; healthy behaviors such as regular exercise/sleep routines, participation in extra-curricular or spiritual/religious activities; or attitudes such as hope, optimism, motivation to seek help—can build rapport, provide groundwork for an intervention plan, and facilitate accomplishment of subsequent steps. Diagnosing strengths may also stimulate the family to provide further opportunities for the child's development of competence, serving as a buffer for the challenges and peer pressures of adolescence and offering alternatives to risky activities.

#### A5a. Concerns (symptoms, functional impairment, risk behaviors, perceived problems)?

At this point in the algorithm, the pediatrician need not feel pressed to make a diagnosis, but simply to determine whether or not there may be a mental health concern in the child or family. Box 34-4 outlines symptoms of emotional disturbance by age group. Physical symptoms and signs may, in some instances, point to mental health and substance abuse problems. Box 34-5 outlines physical symptoms and signs suggestive of mental health and substance abuse concerns.

#### No, there are no concerns.

If the child and family show no signs of functional impairment or distress and if no risk behaviors are identified and no mental health concerns are raised by the family, derived from screening, or perceived by the pediatrician, the pediatrician can move to step A6a.

#### Yes, there are concerns.

Any findings—functional impairment; symptoms concerning to the child, family, or pediatrician; family distress; exposure to trauma or to significant environmental risks, such as a weapon in the home or family member with mental illness; risky behaviors; or perceived problems—necessitate further attention from the pediatrician. Chapter 370, Psychiatric Emergencies: Suicidality, Agitation, Psychosis, and Disaster Exposure, discusses the process of triaging for psychiatric emergencies. Chapter 50, Care of Children With Mental Health Problems, discusses a primary care process for addressing mental health and substance abuse concerns identified at routine health supervision visits.

#### A6a. Provide anticipatory guidance for age per *Bright Futures*, *Connected Kids*, or *KySS: Keep your Children/Yourself Safe and Secure*.

Strategies to promote mental health and provide anticipatory guidance appropriate to the child's age are

**BOX 34-4 Behavioral or Emotional Symptoms of Mental Health Concerns by Age Group****INFANTS AND YOUNG CHILDREN**

- Excessive crying
- Feeding problems or poor weight gain
- Dysregulation (difficulty organizing feelings and emotions, difficulty being soothed or comforted, difficulty falling or staying asleep)
- Irritability
- Excessive clinginess for developmental stage
- Excessive fearfulness for developmental stage
- Poor eye contact or engagement with caregiver

**SCHOOL-AGED CHILDREN**

- Anger
- Bullying
- Fighting
- Irritability
- Fear of separation
- Fluctuating moods
- Sleep disturbance
- Academic decline
- Sadness
- Isolation

**ADOLESCENTS**

- Numbness or avoidance of feelings
- Anger
- Fearfulness
- Aggression, fighting, rule- or lawbreaking
- Self-injury
- Poor school attendance; disciplinary problems; suspension or expulsion
- Appetite change, weight loss or gain
- Difficulty sleeping or excessive sleeping
- Exaggerated mood swings
- Academic decline
- Isolation, withdrawal from friends, loss of interest in usual activities
- Substance use, sexual promiscuity, or other risky behaviors

**ALL AGE GROUPS**

- Chronic, recurrent, or unexplained physical symptoms
- Very disruptive or persistent nightmares
- Regression to earlier behavior
- Change in sleep pattern
- Exacerbation of chronic mental condition

From Appendix S13: symptoms and signs suggestive of mental health and substance abuse concerns. *Pediatrics*. 2010;125(Suppl 3):S193–S194.

**BOX 34-5 Physical Symptoms and Signs Suggestive of Mental Health and Substance Abuse Concerns****SLEEP PROBLEMS**

- Excessive sleep
- Significant change in sleep pattern
- Difficulty falling or staying asleep
- Nightmares
- Chronic, recurrent, or unexplained physical symptoms
- Abdominal pain
- Joint pain
- Headache
- Fatigue or low energy
- Loss of appetite
- Epigastric pain or gastritis (alcohol use)
- Chest pain or difficulty breathing (panic/anxiety attacks)
- Oligomenorrhea or amenorrhea, especially in women of low weight (anorexia, teen pregnancy)
- Irregular menses (anorexia, bulimia)

**NEUROLOGIC SYMPTOMS**

- Leg weakness
- Limb paralysis (conversion reaction)

- Pseudoseizures
- Nonphysiologic neurologic symptoms
- Difficulty concentrating, inattention in school
- Irritability, restlessness

**PHYSICAL FINDINGS**

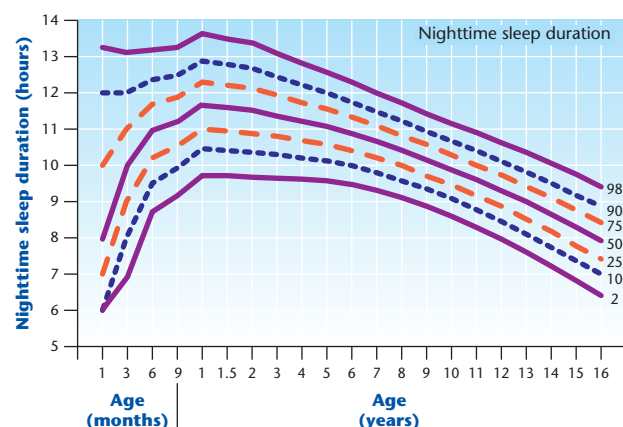
- Excess weight gain or loss
- Parotid gland enlargement, dental enamel erosion, calluses or erosions on knuckles (purging)
- Cigarette burns, multiple linear cuts or patterns (self-harm, maltreatment)
- Metabolic abnormalities such as hypochloremic metabolic alkalosis, low potassium, or elevated amylase (purging)
- Recurrent injuries (maltreatment, self-harm)
- Isolated systolic hypertension (alcohol use)
- Chronic nasal congestion (cocaine use)
- Chronic red eyes (marijuana use)

**OTHER**

- Worsening symptoms of previously well-managed chronic illness
- School absences

From Appendix S13: symptoms and signs suggestive of mental health and substance abuse concerns. *Pediatrics*. 2010;125(Suppl 3):S193–S194.





**Figure 34-2** Percentiles for nighttime sleep duration per 24 hours from infancy to adolescence. (From Iglowstein I, Jenni OG, Molinari L, Largo RH. Sleep duration from infancy to adolescence: reference values and generational trends. *Pediatrics*. 2003;111(2):302-307.)

provided in *Bright Futures 3<sup>rd</sup> Edition*, *Connected Kids*, and *KySS* (Keep Your Children/Yourself Safe and Secure). Mental health is, in fact, one of the core themes identified by *Bright Futures*. Psychosocial topics are a recommended component of every health supervision contact, from the prenatal visit through adolescence. Table 34-2 summarizes mental health anticipatory guidance topics by age.

Several natural strategies for promoting mentally healthy lifestyles have been identified by the AAP Section on Complementary, Holistic, and Integrative Medicine and the TFOMH (toolkit):

- Outdoor time (with appropriate skin protection)
- Special one-on-one time for child with caregiver
- Sufficient sleep (see Figure 34-2 for percentiles of nighttime sleep by age)
- Social connections
- Good nutrition
- Expressions of appreciation and kindness
- Physical activity
- Limited screen time
- Stress management through relaxation techniques

Programs such as *Reach Out and Read* and *Purposeful Parenting* are also helpful for the primary prevention of mental health problems. For a comprehensive listing of resources to promote early brain and child development see [www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/EBCD/Pages/Resource-Library.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/EBCD/Pages/Resource-Library.aspx).

## PREVENTIVE MENTAL HEALTH CARE AT ACUTE CARE VISITS

Because families sometimes miss routine health supervision visits, and because stress and other mental health issues may be the cause of symptoms presenting as acute problems—eg, fatigue, headache, gastrointestinal symptoms, recurrent somatic complaints—acute care visits present an opportunity to elicit mental health

concerns. The TFOMH drew from the expertise of its professional members, opinions of its youth and family members, and informal trials in primary care practices to develop a brief mental health update. (See Table 34-3.)

Responses to these questions provide information that can alert pediatricians to the need for more extensive assessment. In the absence of any concern, 3 to 5 general questions can be completed in a brief time.

Alternatively, pediatricians can use the context of the acute care visit—for example, an injury—to lead naturally into mental health topics—eg, “Had you or your friends been drinking when this happened?”, or “Has this person (the perpetrator of the injury) ever threatened you or injured you before?”

Because of the association between sleep difficulties and mental health conditions, questions regarding sleep are helpful throughout childhood. The wording of such questions is important to adolescents, who may have conflict with their parents around sleep issues. The TFOMH recommends that pediatricians avoid questions requiring only yes/no answers and phrasing such as, “Are you getting enough sleep?” Instead they might ask, for example, “How hard is it for you to fall asleep when you want to?”

Adolescents caution that questions on substance abuse and other sensitive topics may seem intrusive and unlikely to yield a candid response during a brief mental health update. A framing statement, such as, “Many young people I’m seeing feel lots of stress this time of year” or “. . . lots of pressure to use drugs . . .,” or a circular question, such as “Do any of your friends smoke, drink, or use other drugs?” may be better received than direct questions about the adolescent’s behaviors. If the pediatrician has cause for concern, such as deteriorating school performance or injuries, or if this is an issue he or she is already following, more specificity is warranted. Many adolescents do not disclose sensitive information because of confidentiality concerns; therefore, appropriate assurances about conditional confidentiality are a critical part of providing mental health care to adolescents. The Adolescent Health Working Group’s *Behavioral Health: An Adolescent Provider Toolkit* provides tools to aid in conversing with adolescents.

If mental health or substance abuse concerns are raised by parents, children, youth, or the pediatrician as a result of a brief mental health update, the process moves on to triaging for emergencies and addressing the concerns. See Chapter 50, Care of Children With Mental Health Problems.

## PREVENTIVE MENTAL HEALTH CARE OF CHILDREN AND YOUTH WITH SPECIAL HEALTH CARE NEEDS

A chronic medical problem or disability places a child or adolescent at greater risk for mental health problems. Unidentified mental health problems in children and youth with special health care needs may contribute to poor adherence to prescribed therapy, somatization, and overutilization of medical services by both

Table 34-2

## Anticipatory Guidance by Age

## INFANCY (BIRTH TO 11 MONTHS)

## MENTAL HEALTH CONCERN

## POSSIBLE PROMPTS

Poor attachment

[Observe parent-child interactions.] Since the baby was born, have you been feeling down, depressed, irritable, or hopeless? Who is helping/supporting you? Are you able to comfort and care for your baby? Do you have people to call if you feel frustrated?

Difficult temperament (irritable, hard to console, unpredictable needs, difficulty feeding)  
Child abuse/domestic violence or substance abuse

Do you feel safe in your home? Has your partner ever hurt you or your baby? Have you ever experienced abuse? Have you ever been afraid you might hurt your baby?

## ANTICIPATORY GUIDANCE

Hold, cuddle, talk to, and sing to your baby often. Respond promptly to your baby's needs. Ask for help from family, friends, and your pediatrician.

Take time for yourself and your partner. Ask for help from family, friends, and your pediatrician.

Your pediatrician and community resources are available to help your family.

## EARLY CHILDHOOD (1–4 YEARS)

## MENTAL HEALTH CONCERN

## POSSIBLE PROMPTS

Delayed development

Do you have any concerns about your child's development, learning, or behavior?

Poor attachment

Do you have any difficulty understanding or responding to your child's needs? What kinds of activities do you do with your child and as a family?

Difficulty forming relationships

How comfortable is your child around other people?

Behavior problem (impulsivity/temper tantrums/aggression)

Do you reward your child for good behavior? What circumstances tend to lead to your child's misbehavior? How do you correct your child for misbehavior? Has your child ever had a very frightening or painful experience or an extended separation from you or another loved one?

## ANTICIPATORY GUIDANCE

Read to your child often. Enroll your child in preschool or Head Start. Discuss your concerns with your pediatrician.

Be alert for your child's spoken and unspoken messages and feelings; respond promptly to needs. Set aside "special time" one-on-one with your child. Play and eat together as a family. Discuss your concerns with your pediatrician.

Make sure your child has the chance to play with other children. Model kindness to others, taking turns, sharing, and empathy. Discuss your concerns with your pediatrician.

Notice and praise your child's good behavior. Do not hit, spank, or yell at your child. Set age-appropriate limits on your child's behavior, and ensure all caregivers use the same rules. Help your child develop vocabulary to describe his or her feelings. Use positive messages whenever possible; eg, "Please use your inside voice" instead of "Don't yell." Consider a parenting class. Encourage healthy habits: good diet, sufficient sleep, physical activity, limited screen time, outdoor play. Discuss your concerns with your pediatrician.

**Table 34-2** Anticipatory Guidance by Age—cont'd**MIDDLE CHILDHOOD (5–10 YEARS)****MENTAL HEALTH CONCERN****POSSIBLE PROMPTS****ANTICIPATORY GUIDANCE**

Poor success at school, learning difficulties, inattention	How is your child learning and doing in school?	Attend parent–teacher meetings and school events. Limit screen time. Show interest in your child's school experiences and homework. If your child is struggling academically, request testing by the school psychologist. Avoid battles over homework.
Bullying/violence at school	Does your child feel safe and happy at school?	Talk with your child about bullies and bullying. Discuss bullying concerns with school personnel.
Anxiety, worries	How does your child sleep? Does your child have more fears or worries than most children his or her age? Has your child ever had a very frightening or painful experience or an extended separation from you or another loved one?	Talk about what worries your child. Show your child techniques for relaxing. Reward small steps toward managing fears/brave behavior. If your child's worries began after a frightening or painful experience, let your pediatrician know.
Behavior problems (impulsivity/temper tantrums/aggression/oppositionality)	Do you reward your child for good behavior? What circumstances tend to lead to your child's misbehavior? How do you correct your child for misbehavior? Has your child ever had a very frightening or painful experience or an extended separation from you or another loved one?	Notice and praise your child's good behavior. Do not hit, spank, or yell at your child. Set age-appropriate limits on your child's behavior and ensure all caregivers use the same rules. Help your child talk about his or her feelings. Consider a parenting class. Encourage healthy habits: good diet, sufficient sleep, physical activity, limited screen time, outdoor play. Discuss your concerns with your child's teacher and pediatrician.
Depression	Does your child often seem irritable, sad, or depressed?	Help your child talk about his or her feelings. Encourage activities that make your child feel happy, confident, and generous. Encourage healthy habits: good diet, sufficient sleep, physical activity, limited screen time, outdoor play. Discuss your concerns with your pediatrician.

**ADOLESCENCE (11–21 YEARS)****MENTAL HEALTH CONCERN****POSSIBLE PROMPTS****ANTICIPATORY GUIDANCE**

School problems	How are you doing in school? What do you plan to do after high school?	Praise your child's positive accomplishments in school and involvement in extracurricular activities. Check in with your child's teacher about academic progress and relationships with peers. Attend teacher conferences. If your child is struggling academically, request testing by the school psychologist. Avoid battles over homework. Monitor and limit screen time and use of social media.
Depression/suicide	During the past 2 weeks, how often have you felt down, depressed, irritable, or hopeless? How often have you felt little interest or pleasure in doing things? Have you had trouble falling asleep, staying asleep, or sleeping too much? Have you ever tried to kill yourself or thought about trying to kill yourself?	Listen to your adolescent's hopes and concerns. Encourage activities that make your child feel happy, confident, and generous. Encourage healthy habits: good diet, sleep, physical activity, limited screen time. If you are concerned that your teen is often irritable or depressed, speak to your pediatrician. Be sure your child does not have access to weapons or medications.

*Continued*

Table 34-2 Anticipatory Guidance by Age—cont’d	
ADOLESCENCE (11–21 YEARS)	
MENTAL HEALTH CONCERN	POSSIBLE PROMPTS
	ANTICIPATORY GUIDANCE
Anxiety	Do you worry a lot or feel overly stressed? How do you sleep?  Set aside time to listen to your teen’s hopes and concerns. Encourage healthy habits: good diet, sleep, physical activity, limited screen time. Support your adolescent as he or she figures out healthy ways to relax and deal with stress. Monitor and limit screen time and use of social media.
Substance use or abuse	During the past 12 months, have you drunk any alcohol (more than a few sips), smoked any marijuana or hashish, or used anything else to get high? Have you ever ridden in a car driven by someone (including yourself) who was high or had been using alcohol or drugs? Have you talked with your child about alcohol, drugs, and misuse of medications?  Make sure your child knows how you feel about alcohol and drugs. Know your child’s friends and whereabouts. Be a positive role model. Have a safety plan in case your child finds him or herself in a car driven by someone who is high.
Sexual abuse/dating violence	Have you ever felt forced to touch someone or be touched by someone in ways that made you uncomfortable?  Know your child’s friends and whereabouts. Model and talk with your child about healthy, respectful relationships.



Table 34-3

## Using an Acute Care Visit for a Brief Mental Health Update: Suggested Questions by Age

AGES 0–5 YEARS	AGES 5–12 YEARS	AGES 12–21 YEARS (PARENT/CHILD SEPARATELY)
<ul style="list-style-type: none"> <li>• How have things been going since our last visit?</li> <li>• How are you coping with [the presenting acute illness]?</li> <li>• How is [the illness] affecting your child, other than primary symptoms? (If an injury) How did it happen?</li> <li>• How is your child sleeping, in general and in light of the condition?</li> <li>• How are things going at home in general?</li> <li>• Is there anything else that's worrying you about parenting your child?</li> </ul>	<ul style="list-style-type: none"> <li>• How have things been going since our last visit?</li> <li>• How are you coping with [the presenting acute illness]?</li> <li>• How is [the illness] affecting your child, other than primary symptoms? (If an injury) How did it happen?</li> <li>• How is your child sleeping, in general and in light of the condition?</li> <li>• How is everyone getting along at home?</li> <li>• Has your child been enjoying school? (To the child) How's school going?</li> <li>• What is the best part of parenting this child? What is the most difficult part?</li> <li>• Do you have any worries or concerns about your child's mental health, emotions, or behaviors?</li> </ul>	<ul style="list-style-type: none"> <li>• How have things been going since our last visit?</li> <li>• How are you/how is your child coping with [the acute presenting illness]?</li> <li>• How is [the illness] affecting you/your child, other than primary symptoms? (If an injury) How did it happen? Had anyone been drinking or using drugs?</li> <li>• How are you/how is your child sleeping, in general and in light of the condition?</li> <li>• How are you/how is your child getting along at home? At school?</li> <li>• [Parents of] teenagers often mention that they are having difficulties with stress, worries, or changes in mood—has this been a problem for you/your child?</li> </ul>

Select questions as appropriate to the clinical circumstances and time available.

From American Academy of Pediatrics Task Force on Mental Health algorithm teams, group discussion, fall 2005; and Appendix S8: brief mental health update. *Pediatrics*. 2010;125(Suppl 3):S159–S160.

the child and parents. Efforts to identify mental health concerns are important at each contact with a chronically ill child—especially if the child has experienced frequent emergency department visits or hospitalizations. Parents and siblings may also experience stress and need support, respite, or mental health care. See Chapter 32, Family Support, for resources to address these issues.

## SUMMARY

Pediatricians have unique opportunities to promote mental health in children and their families and to identify emerging mental health and substance abuse problems. These opportunities may present themselves in the course of routine health supervision visits, acute care visits, or the monitoring of children with special health care needs. Tools developed by the AAP and other resources may be helpful in implementing a systematic approach to promotion of mental health and early identification of mental health and substance abuse problems.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *Connected Kids Clinical Guide* (booklet), American Academy of Pediatrics ([www2.aap.org/connectedkids/ClinicalGuide.pdf](http://www2.aap.org/connectedkids/ClinicalGuide.pdf))
- *Trauma Guide* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/healthy-foster-care-america/Pages/Trauma-Guide.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/healthy-foster-care-america/Pages/Trauma-Guide.aspx))

### Engaging Patient and Family

- *Partnering With Parents: Apps for Raising Happy, Healthy Children* (booklet), Institute for Safe Families ([www.instituteforsafefamilies.org/sites/default/files/isffiles/20130324-Partnering-With-Parents-Brochure-WEB.pdf](http://www.instituteforsafefamilies.org/sites/default/files/isffiles/20130324-Partnering-With-Parents-Brochure-WEB.pdf))
- *The First 1,000 Days: Bright Futures Examples for Promoting EB CD* (booklet), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/EB CD/Documents/EB CD\\_Well\\_Child\\_Grid.pdf](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/EB CD/Documents/EB CD_Well_Child_Grid.pdf))

### Medical Decision Support

- *A Safe Environment for Every Kid* (questionnaire), SEEK Project ([www.uspreventiveservicestaskforce.org/Home/GetFileByID/859](http://www.uspreventiveservicestaskforce.org/Home/GetFileByID/859))
- *Ages & Stages Questionnaires* (assessment) ([www.agesandstages.com](http://www.agesandstages.com))
- *Center for Epidemiologic Depression Scale for Children (CES-DC)* (assessment), Bright Futures ([www.brightfutures.org/mentalhealth/pdf/professionals/bridges/ces\\_dc.pdf](http://www.brightfutures.org/mentalhealth/pdf/professionals/bridges/ces_dc.pdf))
- *Columbia Impairment Scale* (assessment), American Academy of Pediatrics, in *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* ([shop.aap.org](http://shop.aap.org))
- *Edinburgh Postnatal Depression Scale (EPDS)* (assessment), American Academy of Pediatrics ([www2.aap.org/sections/scan/practicingsafety/toolkit\\_resources/module2/epds.pdf](http://www2.aap.org/sections/scan/practicingsafety/toolkit_resources/module2/epds.pdf))
- *Feelings Need Checkups Too* (booklet), American Academy of Pediatrics ([www.aap.org/en-us/](http://www.aap.org/en-us/))

advocacy-and-policy/aap-health-initiatives/children-and-disasters/Documents/Feelings-Need-Checkups-Toolkit\_0823.pdf)

- *Mental Health Screening and Assessment Tools for Primary Care* (chart), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH\\_ScreeningChart.pdf](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH_ScreeningChart.pdf))
- *Modified Checklist for Autism in Toddlers* (assessment), M-CHAT ([www.m-chat.org](http://www.m-chat.org))
- *Patient Health Questionnaire-9 Modified for Teens* (assessment), American Academy of Pediatrics, in *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* ([shop.aap.org](http://shop.aap.org))
- *Pediatric Intake Form*, Bright Futures ([www.brightfutures.org/mentalhealth/pdf/professionals/ped\\_intake\\_form.pdf](http://www.brightfutures.org/mentalhealth/pdf/professionals/ped_intake_form.pdf))
- *Pediatric Symptom Checklist* (assessment), Bright Futures ([www.brightfutures.org/mentalhealth/pdf/professionals/ped\\_symptom\\_chklst.pdf](http://www.brightfutures.org/mentalhealth/pdf/professionals/ped_symptom_chklst.pdf))
- *PEDS Tools* (Web site), Parents' Evaluation of Developmental Status ([www.pedstest.com](http://www.pedstest.com))
- *Strengths & Difficulties Questionnaires* (assessment) ([www.sdqinfo.org](http://www.sdqinfo.org))
- *The CRAFFT Screening Tool* (assessment), Center for Adolescent Substance Abuse Research ([www.ceasar-boston.org/CRAFFT/index.php](http://www.ceasar-boston.org/CRAFFT/index.php))
- *The Resilience Project: Clinical Assessment Tools* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/resilience/Pages/Clinical-Assessment-Tools.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/resilience/Pages/Clinical-Assessment-Tools.aspx))

### AAP POLICY

- Shonkoff JP, Garner AS; American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health, Committee on Early Childhood, Adoption, and Dependent Care, and Section on Developmental and Behavioral Pediatrics. The lifelong effects of early childhood adversity and toxic stress. *Pediatrics*. 2012;129(1):e232–e246 ([pediatrics.aappublications.org/content/129/1/e232](http://pediatrics.aappublications.org/content/129/1/e232))
- Weitzman C, Wegner L; American Academy of Pediatrics Section on Developmental and Behavioral Pediatrics, Committee on Psychosocial Aspects of Child and Family Health, Council on Early Childhood; Society for Developmental and Behavioral Pediatrics. Promoting optimal development: screening for behavioral and emotional problems. *Pediatrics*. 2015;135(2):384–395 ([pediatrics.aappublications.org/content/135/2/384](http://pediatrics.aappublications.org/content/135/2/384))

### SUGGESTED READINGS

- Enhancing Pediatric Mental Health Care: Report From the American Academy of Pediatrics Task Force on Mental Health. *Pediatrics*. 2010;125(Suppl 3):S69–S195
- Hagan JF, Shaw JS, Duncan PM, eds. *Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents*. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2008
- Kemper KJ. *Mental Health, Naturally: The Family Guide to Holistic Care for a Healthy Mind and Body*. Elk Grove Village, IL: American Academy of Pediatrics; 2010
- Shonkoff JP, Phillips DA, eds. *From Neurons to Neighborhoods: The Science of Early Childhood Development*. Washington, DC: National Academies Press; 2000

## Chapter 35

# HEALTHY WEIGHT

Sandra G. Hassink, MD, MS

Childhood obesity has emerged as a major health problem that increases the risk for chronic illnesses in children. Obesity comorbidities include dyslipidemia, hypertension, type 2 diabetes, nonalcoholic steatohepatitis, gallbladder disease, polycystic ovarian syndrome, slipped capital femoral epiphysis, Blount disease, pseudotumor cerebri, and sleep apnea. These illnesses, along with depression and low self-esteem, are occurring in children with increasing frequency and mandate that obesity prevention, intervention, and treatment become part of the pediatrician's repertoire.

## INCIDENCE OF OBESITY

The incidence of obesity has increased dramatically in the United States and the world in the last 2 decades (Figure 35-1). In 2011 to 2012, 34.9% of adults had obesity (defined as a body mass index [BMI] >30), 16.9% of 2- to 19-year-olds had obesity (defined as a BMI >95% for age and gender), and 8.1% of infants and toddlers had obesity (defined as weight/length >95% for age and gender). Obesity prevalence increases with age, affecting 8.4% of 2- to 5-year-olds, 17.7% of 6- to 11-year-olds, and 20.5% of 12- to 19-year-olds. Prevalence of obesity decreased among children 2 to 5 years of age from 13.9% in 2003 to 2004, to 8.4% in 2011 to 2012, which is encouraging, but significant racial disparities persist. In 2011 to 2012, 22.4% Hispanic, 20.2% non-Hispanic black, 14.1% non-Hispanic white, and 8.6% of Asian youth had obesity.

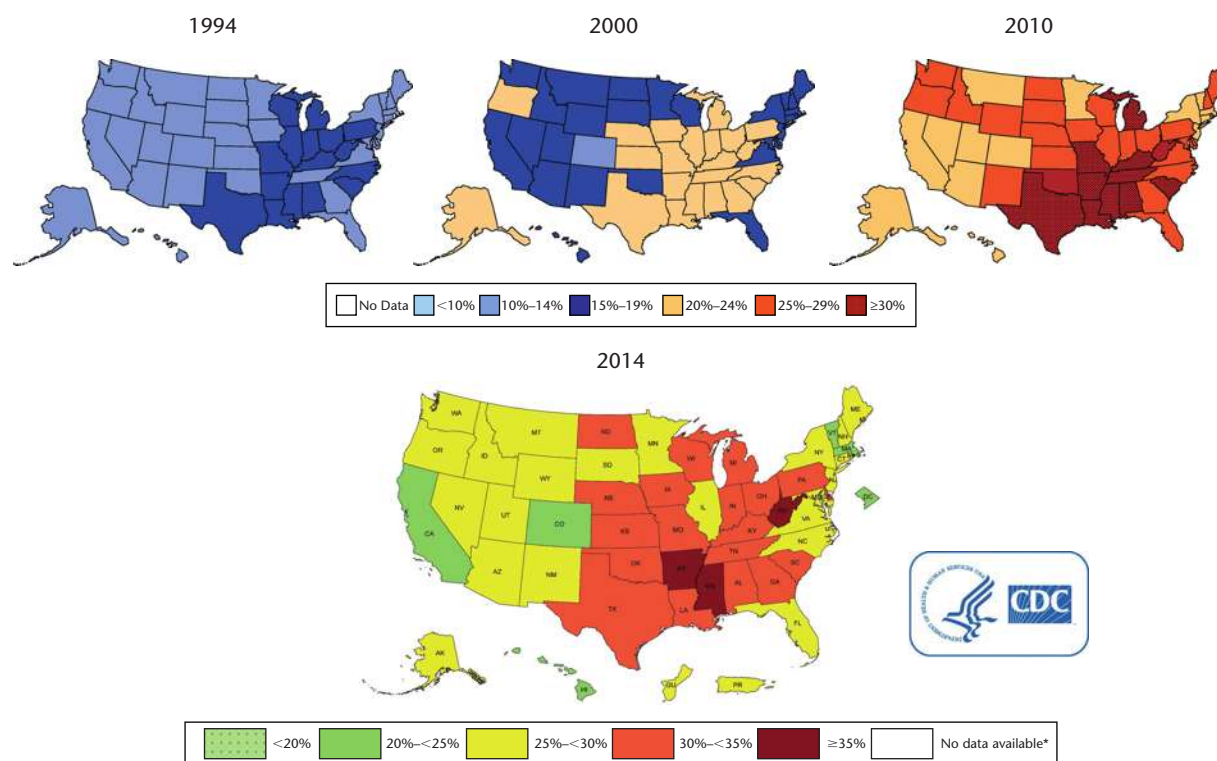
Body mass index (calculated as  $\text{wt}/\text{ht}^2$ ) correlates with body fat. This index is used to screen populations for obesity and is the most clinically feasible measure to categorize individuals to target obesity prevention, intervention, and treatment.

In children, body fat changes throughout development, and, therefore, BMI percentile must be used. (See BMI charts in Chapter 16, Pediatric Physical Examination: Interpretation of Findings.) The recommendations of the American Medical Association Expert Committee for children classify BMI between 85% and 94% as overweight and BMI greater than the 95% as obesity (Box 35-1).

Calculation of BMI and classification of weight status at least once a year are considered essential parts of pediatric well care.

## EFFECTS OF OBESITY

Increased BMI in adults is correlated with increases in obesity-related comorbidities, and BMI greater than 99% in children is associated with a very high risk of cardiovascular disorders (high blood pressure, elevated insulin, and lipid abnormalities) and severe adult obesity. Obesity is on its way to becoming the largest preventable cause of disease in the United States. It has the potential to make the current generation of US



**Figure 35-1** Progression of adult obesity in the United States. (From *Maps of diagnosed diabetes and obesity in 1994, 2000, and 2013*. Centers for Disease Control and Prevention Web site. January 2, 2015. [www.cdc.gov/diabetes/statistics/slides/maps\\_diabetesobesity94.pdf](http://www.cdc.gov/diabetes/statistics/slides/maps_diabetesobesity94.pdf); *Prevalence of self-reported obesity among U.S. adults by race/ethnicity, state, and territory, BRFSS, 2012–2014*. Centers for Disease Control and Prevention Web site. September 11, 2015. [www.cdc.gov/obesity/data/prevalence-maps.html](http://www.cdc.gov/obesity/data/prevalence-maps.html).)

### BOX 35-1 Classification of Children by Body Mass Index (BMI) Percentage

- BMI <5%: underweight
- BMI 5%–84%: healthy or normal weight
- BMI 85%–95%: overweight
- BMI >95%: obese

children the first to have a shorter life expectancy than their parents.

Pediatricians must be prepared to prevent, identify, and treat obesity and obesity-related comorbidities. These comorbidities include diseases that were traditionally considered adult diseases—sleep apnea, type 2 diabetes, hypertension, dyslipidemia, polycystic ovarian syndrome, and nonalcoholic steatohepatitis. The uniquely pediatric comorbidities of slipped capital femoral epiphysis and Blount disease occur as a result of injury to open growth plates in the hip and knee. Depression and low self-esteem are also associated with childhood obesity. Box 35-2 provides a summary of screening and treatment measures for obesity-related comorbid diseases. Pediatricians also need to be prepared to deal with obesity-related emergencies,

such as hyperosmolar hyperglycemia, pseudotumor cerebri, pulmonary emboli, and cardiomyopathy. These comorbidities of obesity add to the burden of chronic disease in children.

Total direct health care costs for children with obesity are estimated to be \$14 billion annually, with increased individual costs of \$194 for outpatient visits, \$114 for prescription drugs, and \$25 for emergency department visits. Three billion dollars of this amount is accounted for by children covered by Medicaid.

- Childhood obesity-related hospital costs doubled between 2001 and 2005 to \$238 billion.
- A recent study showed that a 10-year-old child with obesity will have an excess lifetime medical cost of \$19,000 compared with a normal-weight 10-year-old.

### FACTORS ASSOCIATED WITH OBESITY

The cause of the obesity epidemic is multifactorial and complex. Genetic predisposition, the environment, nutrition, and physical activity each play a role in the development of obesity. These factors play out at the individual, family, community, and population levels, accounting for the global shift in obesity demographics.

#### Genetic Effects

The contribution of genetics to obesity has been studied in twins and shows that BMI is highly correlated

**BOX 35-2 Summary of Screening and Treatment Measures****TYPE 2 DIABETES**

- *History:* maternal diabetes during pregnancy, small for gestational age, intrauterine growth restriction, family history of diabetes, polycystic ovarian syndrome, obesity.
- *Review of systems:* polyuria; polydipsia, nocturia; recurrent vaginal, bladder, or other infections; recent weight loss. Screen for other obesity related comorbidities.
- *Physical examination:* acanthosis nigricans.
- *Laboratory assessments:* elevated fasting glucose ( $\geq 126$  mg/dL), positive glucose tolerance test (2-hr glucose  $\geq 200$  mg/dL). Hemoglobin A1c (HgbA1c)  $\geq 6.5$ , symptoms of diabetes plus a random glucose  $\geq 200$  mg/dL. Screen for dyslipidemia, nonalcoholic steatohepatitis.
- *Treatment:* tailored nutrition and exercise plan. Metformin. Insulin if severe or uncontrolled on oral medication.
- *Monitoring:* self-monitoring of blood glucose. Follow HgbA1C, lipids and blood pressure, annual screening for nephropathy, retinopathy, and neuropathy.

**NONALCOHOLIC STEATOHEPATITIS**

- *History:* no specific history; some cases have other family members affected.
- *Review of systems:* possible nausea and right upper quadrant discomfort. Screen for other obesity related comorbidities.
- *Physical examination:* hepatomegaly.
- *Laboratory and imaging assessments:* elevated serum aminotransferases with absence of other causes of liver disease, echogenicity of liver on ultrasound. Screen for diabetes and dyslipidemia.
- *Treatment:* referral to pediatric gastroenterologist for evaluation, definitive diagnosis (liver biopsy), and treatment; weight loss.

**HYPERTENSION**

- *History:* family history of hypertension or other obesity-related comorbidity.
- *Review of systems:* usually asymptomatic. Screen for other obesity related comorbidities.
- *Physical examination:* elevated systolic or diastolic blood pressure.
- *Laboratory assessments:* evaluation for other causes of hypertension as indicated and for end organ damage; blood urea nitrogen/creatinine, lipids. Screen for diabetes and other obesity related comorbidities.
- *Treatment:* referral to pediatric hypertension specialist, dietary treatment, pharmacologic treatment.

**DYSLIPIDEMIA**

- *History:* family history of lipid disorders, cardiovascular disease.
- *Review of systems:* asymptomatic; other obesity comorbidities, particularly signs of metabolic syndrome.
- *Physical examination:* no specific signs; acanthosis nigricans may indicate metabolic syndrome.
- *Laboratory assessment:* lipid panel. Screen for other obesity related comorbidities.
- *Treatment:* referral to lipid specialist; dietary management.

**SLEEP APNEA**

- *History:* family history of sleep apnea.
- *Review of systems:* snoring, snoring with apnea, daytime tiredness, napping, poor concentration in school, enuresis.
- *Physical examination:* large tonsils or adenoids.
- *Imaging assessment:* night-time polysomnography.
- *Treatment:* referral to pediatric pulmonologist, weight loss, continuous positive airway pressure.

**SLIPPED CAPITAL FEMORAL EPIPHYSIS**

- *History:* knee or hip pain.
- *Review of systems:* knee, thigh, or hip pain, limp.
- *Physical examination:* limp, pain in knee, hip, or thigh.
- *Imaging:* Anteroposterior view of the pelvis and frog leg lateral that includes both hips
- *Treatment:* immediate referral to pediatric orthopedist.

**BLOUNT DISEASE**

- *History:* bowing.
- *Review of systems:* bowing (tibia vera), knee pain, limp.
- *Physical examination:* bowing, knee pain, limp.
- *Imaging:* Anteroposterior lateral and tunnel view of the knee.
- *Treatment:* referral to pediatric orthopedist.

**DEPRESSION**

- *History:* family history of depression, history of abuse, psychological trauma, teasing, low self-esteem.
- *Review of systems:* loss of interest, anger, irritability, sadness, suicidal ideation.
- *Physical examination:* no signs or may have sad, irritable appearance with lack of self-care, flat affect.
- *Laboratory or imaging assessments:* none.
- *Treatment:* mental health referral for counseling or pharmacologic treatment.

From Hassink S, ed. *Pediatric Obesity Prevention, Intervention and Treatment Strategies for Primary Care*. Elk Grove Village, IL: American Academy of Pediatrics; 2007; International Expert Committee. International Expert Committee report on the role of the A1c assay in the diagnosis of diabetes. *Diabetes Care*. 2009; 32(2):1327–1334; and American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2012;35(Suppl 1):S64–S71.



with genetic factors. Body mass index measures of identical twins reared apart correlate strongly with the BMI of their biological parents rather than their adoptive parents, indicating a strong genetic predisposition toward weight gain. Parental obesity also increases the risk of a child becoming an adult with obesity, allowing for early identification of obesity risk in families.

Newborns of mothers who have obesity or diabetes during pregnancy have an increased risk for childhood and adult obesity, as do newborns who are small or large for gestational age. Maternal gestational weight gain and maternal cigarette smoking have also been implicated in increasing the risk of childhood obesity. The explanation of gene–environment interaction involves epigenetic mechanisms. *Epigenetics* refers to “a set of reversible heritable changes that occur without a change in DNA sequence”. The 2 most common epigenetic changes are DNA methylation and histone modification. Studies show that epigenetic changes in monozygotic twins cause increasing genetic divergence over time. Environmental factors can act during intrauterine development, possibly via epigenetic modification of gene expression without altering DNA sequences, to increase the risk of obesity, type 2 diabetes, and cardiovascular disease.

### Environmental Effects

Early infant weight gain is independently associated with being overweight in childhood. Infants who gain excess weight in the first 4 months of life are likely to be overweight at the age of 7 years. In addition, the ratio of a child’s weight increase between birth and 12 months to birth weight is independently associated with becoming overweight by 6 years of age. When combined with protein intake at 9 to 12 months of age, this early weight gain was able to explain 50% of the variance in boys’ BMIs at 6 years.

Prolonged breastfeeding (6 to 12 months) is associated with a reduced risk of becoming overweight among non-Hispanic white children. In an evidence-based review of breastfeeding studies, breastfeeding was associated with a reduced risk of obesity and type 2 diabetes in the children, and type 2 diabetes in mothers.

Minority and disadvantaged children are disproportionately affected by obesity, possibly reflecting a greater exposure to obesity-promoting environments. For example, children from low-income groups, blacks, and Hispanics watch more television than white children. Lower physical activity levels are associated with low family income, time spent indoors, higher crime areas, and maternal education level, factors that differentially affect disadvantaged populations.

Changes in the secular environment have increased calories available to children and families. Portion sizes of commercially available foods began to increase above recommended dietary guidelines in the 1970s and have increased steadily since, with the average chocolate chip cookie more than 700% larger than its counterpart at the onset of the obesity epidemic. Studies in adults and children show that people eat more as portion sizes increase.

Eating out is cited among the factors important in the development of the obesity epidemic. Between 1977 and 1996, the proportion of foods that children consumed from restaurants and fast-food outlets increased by nearly 300%. Fast-food consumption is a significant risk factor for obesity. In one study, children who consumed fast food took in an average of 187 kcal/day more than children who did not consume fast food. In the same study, 30% of children ate fast food on any given day.

Obesity correlates with the number of hours of television viewing. After-school time is a particularly vulnerable time for children in terms of television exposure. Food advertising may play a role in increases in high-energy food consumption. Children are the targets of significant advertising of foods with high caloric density. They see an average of 1 food commercial per 5 minutes of television time and may see 3 hours of food commercials per week. Food advertising ranges from product placement in movies and television shows to vending machines in schools and includes the use of sports heroes to sell soda and highly advertised collectible toys to sell fast-food meals. Exposure to such advertisements affects children’s food choices, even in preschool.

Consumption of more than 1 soda per day by children as young as 2 years of age was correlated with obesity. Soda consumption was also associated with excess weight gain in children studied from age 7 years through preadolescence.

Inactivity is also associated with obesity. In a 30-year longitudinal twin study, the twin in the pair who was inactive over the course of the study had significantly more weight gain and waist circumference than the active twin. In a review of obesity prevention trials, moderate to vigorous physical activity was significantly correlated with obesity prevention in children. Nutrition- and activity-related behaviors act at the interface between the individual and family and the environment. The primary care physician can counsel parents and patients on lifestyle issues that affect children’s nutrition and activity. Table 35-1 provides age-appropriate obesity prevention information.

Obesity prevention and treatment are family based. Children’s eating habits and preferences can be predicted by their mother’s behaviors. Maternal preferences predict child preferences for milk type and amount and predict the intake of calcium and cholesterol in the child’s diet. Early parental behavior influences a child’s eating behavior through at least 5 mechanisms—availability and accessibility of foods, meal structure, adult food modeling, food socialization practices, and food-related parenting styles.

Parental modeling seems to be consistently correlated with child eating behaviors and attitudes. Attempts by parents to control what their children eat or to use food to control other behaviors has much less consistent effects, sometimes having the opposite effect from what is desired. The authoritative parenting style that sets limits in a supportive rather than punitive way is linked with improved health outcomes, including preventing obesity.

**Table 35-1** Age-Appropriate Obesity-Prevention Guidance

AGE OF CHILD	NUTRITION INFORMATION	APPROPRIATE ACTIVITY
Newborn or infant	Promote breastfeeding. Teach parents to recognize hunger and satiety cues. Assess family's eating habits and nutrition environment. No juice.	Encourage face-to-face playtime with newborn or infant to lay groundwork for shared activity. Tummy time in a safe, supervised environment. Take daily walk in stroller to establish outdoor time. Use safe toys. No television viewing.
Toddler	Remind parents of appropriate portion sizes. "Parents provide (correct portions), child decides (what to eat)." Encourage structured meals and snack time with family. Model desired eating behavior. Address picky eating, food refusal, and grazing, if problematic. Discuss safe eating to prevent choking. No sugar-sweetened beverages. Limit juice to 4–6 oz/day.	Encourage <i>free play</i> in safe indoor and outdoor environments. Spare use of strollers. Limit screen time to <2 hours/day. No screens in the bedroom. Do not mix screen time and eating. Review age-appropriate motor-skill development. Encourage adequate sleep.
Preschool	Parents, not children, should be making food choices. Limit eating out. Review growth charts with goal to <i>keep on the chart</i> . Help parents identify and assess all the different nutritional environments in their child's day (ie, child care, school, extended family, friends). No sugar-sweetened beverages or sports drinks. Limit juice to 4–6 oz/day. Be aware of food marketing that targets children. Help parents maintain structured meals and snacks. Help parents address child's behavior around demands for food if a problem.	Encourage free play. Encourage outdoor play. Encourage participation, not competition. Limit screen time to <2 hours/day. No screens in the bedroom. Do not mix screen time and eating. Encourage family time that is physically active. Encourage adequate sleep.
School age	Check nutritional choices at school, after-school care, extracurricular activities; may need to pack food from home. Advocate for change, if necessary. Address weekend, vacation, and summer nutritional challenges. Minimize junk food. No sugared beverages. Limit juice. Lowfat milk and water should be the primary drinks. Nutrition decisions are health decisions. Do not bring food into the house that you do not want your child to eat. Monitor after-school eating.	Balance free play and entry-level sports participation (fundamental skill development with minimal competition and flexible rules). Focus on fun activities. Limit screen time to <2 hours/day. No screens in the bedroom. Do not mix screen time and eating. Help child find other indoor activity options.
Early adolescent	Encourage family meals. Discuss the importance of breakfast (breakfast skipping is common at this age). Help child and family with healthy after-school snack. Help child make decisions around social eating. No sugar-sweetened beverages. Limit juice. Lowfat milk and water should be the primary drinks. Limit eating out and fast food.	Help schedule physical activity around homework and social demands. Encourage extracurricular activities to avoid sedentary time after school. Limit screen time to <2 hours/day. No screens in bedroom. Do not mix eating and screen time. Social-skill building, if needed, can help encourage participation in peer activities.

**Table 35-1** Age-Appropriate Obesity-Prevention Guidance—cont'd

AGE OF CHILD	NUTRITION INFORMATION	APPROPRIATE ACTIVITY
Middle adolescent	Review growth chart with adolescent. Help teen with self-assessment of eating and nutritional choices. Encourage breakfast. Discourage meal skipping. Discuss social eating, healthy choices. Limit fast food. No sugared beverages. Limit juice. Lowfat milk and water should be the primary drinks. Limit eating out and fast food.	Find ways to help teen keep participating in physical activity. Encourage lifestyle activities. Limit screen time to <2 hours/day (find alternatives such as volunteering, hobbies, clubs). No screens in the bedroom. Do not mix eating and screen time.
Late adolescent and young adult	Encourage self-monitoring. Discuss structure and time management of meals, activity, and sleep. Go over health priorities. Provide nutrition information on fast food. Screen for binge eating. No sugared beverages.	Maintain activity of daily living. Limit screen time to 2 hours/day. No screens in bedroom. Do not mix eating and screen time. Encourage lifestyle sports and activities. Take advantage of community and school recreation facilities.

Engaging parents and families to partner in obesity prevention and treatment is a core skill for pediatricians. Techniques such as motivational interviewing show promise as feasible office-based interventions. (See Chapter 46, Effective Communication Strategies, for a description of motivational interviewing and other techniques for communicating with children and families.)

## OBESITY ASSESSMENT, PREVENTION, AND TREATMENT

The most current methods for preventing childhood obesity are recommended by an expert panel and endorsed by the American Academy of Pediatrics (AAP). The AAP published the *5210 Pediatric Obesity Clinical Decision Support Chart* as a resource for pediatricians.

### Assessment

All children 2 years of age and older should have BMI measured at least yearly and have their weight status classified (see Box 35-1). Children younger than 2 years of age should have weight and length measured and weight for length plotted on World Health Organization (WHO) growth charts.

### Well Visit

At each well child visit for all children, the physician should

1. Measure height and weight, and calculate and classify BMI, for children 2 years of age and older using the Centers for Disease Control and Prevention growth chart.
2. Plot weight for length for children younger than 2 years of age, using the WHO growth chart.

3. Assess self-efficacy and readiness to change lifestyle behaviors.
4. Assess diet, including attention to the following behaviors that may be targets for change:
  - 1 Frequency of eating outside the home
  - 2 Excessive consumption of sweetened beverages, including juice
  - 3 Consumption of excess portion sizes
  - 4 Frequency of breakfast
  - 5 Excessive snack-food consumption
  - 6 Low fruit and vegetable consumption
  - 7 Meal frequency and snack patterns and portions
  - 8 Frequency of family meals
5. Assess activity, including the following:
  - 1 Environmental support and barriers to physical activity
  - 2 Whether the child is meeting a recommendation of 60 minutes of moderate exercise every day
  - 3 Evaluate the child's screen time per day and recommend no screen time for children under 2 years of age and that screen time be limited to 2 hours a day or less in children older than 2 years of age.
  - 4 Assess location of meals—are meals being consumed in front of a television or computer?
6. Take a focused family history for obesity, type 2 diabetes, liver disease, and cardiovascular disease, including hypertension and early deaths from cardiovascular disease or stroke.
7. Take a pregnancy history for presence of gestational diabetes, obesity, gestational weight gain, and smoking during pregnancy.
8. Assess risk for current or future obesity-related comorbidities.
9. Perform a complete physical examination that includes pulse and blood pressure, as well as signs of obesity-related comorbidities.

10. Order the following laboratory tests:
  - 1 Lipid profile for all children between 9 and 11 years of age and again between 17 and 21 years of age and all children older than 2 years of age who have a BMI of 85% to 94%.
  - 2 Every 2 years, aspartate aminotransferase, alanine aminotransferase, fasting glucose or hemoglobin A1c for children with BMI of 85% to 94% with risk factors for obesity-related conditions.
  - 3 Fasting lipid profile, aspartate aminotransferase, alanine aminotransferase, fasting glucose or hemoglobin A1c, blood urea and nitrogen with creatinine for children with BMI greater than 95% and follow as clinically indicated.
  - 4 Other studies as clinically indicated.

### Prevention of Obesity

For children 2 to 18 years of age with a BMI greater than 5% and less than 84%, the physician should counsel as follows:

- 5 or more servings of fruits and vegetables per day
- 2 or fewer hours of screen time per day, and no television in the room where the child sleeps
- 1 hour or more of daily physical activity
- 0 sugar-sweetened beverages

The physician can also address age-appropriate portion size, structured meals and snacks, and limiting energy-dense snack foods and eating out.

### Treatment of Obesity

Children who have a BMI greater than 85% should be treated appropriately. Treatment consists of 4 stages depending on the status of the child and includes all guidance found in the prevention section presented previously and the following points.

#### Stage 1: Prevention Plus

Stage 1 is also known as *prevention plus*. Messages should build on prevention messages and involve the following areas:

- Establish healthy lifestyle goals with the family using motivational interviewing.
- Focus on evidence-based behavior change.
- Limit consumption of sugar-sweetened beverages.
- Limit television (0 hours before 2 years of age, less than 2 hours for children 2 years of age and older).
- Remove television from primary sleeping area.
- Eat breakfast daily.
- Build on prevention messages in the following areas:
  - Limit eating out.
  - Encourage family meals.
  - Limit portion size.
  - Ensure adequate sleep.
  - May also focus on behaviors where there is suggestive evidence of efficacy.
  - Eat a diet rich in calcium.
  - Eat a diet high in fiber.
  - Eat a diet with balanced macronutrients (food groups).
  - Encourage breastfeeding.

- Promote moderate to vigorous activity 60 minutes per day.
- Limit consumption energy-dense foods.

The goal of prevention plus is weight maintenance, and this stage should include monthly follow-up appointments with review of lifestyle goals. If no improvement is seen after 3 to 6 months, then the physician should move to the next stage, as follows.

#### Stage 2: Structured Weight Management Protocol

In Stage 2, the primary care physician should stress the following areas in addition to developing targeted goals with the family based on evidence as in Stage 1:

1. Develop a plan for a low-energy, dense, balanced macronutrient diet. This may be best done with the help of a dietician.
2. Increase structured daily meals and snacks.
3. Supervise active play at least 60 minutes a day.
4. Limit screen time to less than 1 hour per day.
5. Increase monitoring of these behaviors and encourage parents to follow guidelines as well.

The goal of Stage 2, the structured weight management protocol, is weight maintenance that results in decreasing BMI as height increases. Weight loss is not to exceed 1 pound per month in children 2 to 11 years of age or 2 pounds per week in children older than 11 years of age.

If no improvement is seen in BMI or weight after 3 to 6 months, then the primary care physician should advance to Stage 3.

See the AAP resource *Next Steps: A Practitioner's Guide for Themed Follow-up Visits for Patients to Achieve a Healthy Weight* to target follow up around specific lifestyle goals.

#### Stage 3

Stage 3 is a multidisciplinary intervention by an obesity care team. If this stage is not successful, then the patient is referred to Stage 4, a tertiary care intervention.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *Action for Healthy Kids* (Web site), ([www.actionforhealthykids.org](http://www.actionforhealthykids.org))
- *Institute for Healthy Childhood Weight* (Web site), American Academy of Pediatrics ([ihcw.aap.org](http://ihcw.aap.org))

### Engaging Patient and Family

- *A Parent's Guide to Childhood Obesity: A Road Map to Health* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *About Child & Teen BMI* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/healthyweight/assessing/bmi/childrens\\_bmi/about\\_childrens\\_bmi.html](http://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html))
- *BAM! Body and Mind* (Web site), Centers for Disease Control and Prevention ([www.cdc.gov/bam](http://www.cdc.gov/bam))
- *Encourage Your Child to Be Physically Active* (hand-out), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))



- *Feeding Guide for Children* (chart), American Academy of Pediatrics ([www.healthychildren.org/Documents/tables/Feeding-Guide-for-Children.html](http://www.healthychildren.org/Documents/tables/Feeding-Guide-for-Children.html))
- *Feeding Kids Right Isn't Always Easy: Tips for Preventing Food Hassles* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Get Fit, Stay Healthy* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Growing Up Healthy: Fat, Cholesterol and More* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Choose My Plate* (Web site), US Department of Agriculture ([www.choosemyplate.gov](http://www.choosemyplate.gov))
- *Right From the Start: ABCs of Good Nutrition for Young Children* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Sports and Your Child* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *What's to Eat? Healthy Foods for Hungry Children* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *VERB: CDC Youth Campaign* (Web site), Centers for Disease Control and Prevention ([www.cdc.gov/youthcampaign](http://www.cdc.gov/youthcampaign))

### Medical Decision Support

- *Care of Children and Adolescents With Type 1 Diabetes* (policy statement), American Diabetes Association ([care.diabetesjournals.org/cgi/content/full/28/1/186](http://care.diabetesjournals.org/cgi/content/full/28/1/186))
- *Appendix A.4: Patient Worksheets and Self-assessment Forms*. In: Hassink SG. *Pediatric Obesity: Prevention, Intervention, and Treatment Strategies for Primary Care*, 2nd ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Growth Charts* (chart), Centers for Disease Control and Prevention ([www.cdc.gov/growthcharts](http://www.cdc.gov/growthcharts))
- *Obesity Prevention in Pediatrics* (online course), American Academy of Pediatrics ([pedialink.aap.org](http://pedialink.aap.org))
- *5210 Pediatric Obesity Clinical Decision Support Chart* (chart), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

### AAP POLICY

- American Academy of Pediatrics Committee on Communication. Children, adolescents, and advertising. *Pediatrics*. 2006;118(6):2563–2569. Reaffirmed March 2010 ([pediatrics.aappublications.org/content/118/6/2563](http://pediatrics.aappublications.org/content/118/6/2563))
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## Chapter 36

## HEALTHY NUTRITION: INFANTS

Frank R. Greer, MD

Nutrition of the infant is an important topic for the practice of pediatrics. During the first half of the twentieth century, before pediatrics was recognized as a subspecialty, the feeding of infants was an even larger part of the practice of physicians who cared for children, given the high infant mortality rate. The

interaction between the pediatrician and the family over infant nutritional issues helps to establish an ongoing doctor–patient/family relationship that extends into childhood and adolescence. At no other point does the pediatrician have more influence on the nutrition of the pediatric patient. A rapid period of growth and physical development occurs during the first 12 months of life, and with a relatively high level of specific nutrient requirements. It includes the critical period when breast milk or infant formula is the sole source of nutrition, as well as the transition period to a mixed diet that follows the introduction of complementary foods. The nutritional choices made in the first 12 months of life are the basis for future good nutritional practices that are essential for present and future health and well-being. For the best health outcomes, the American Academy of Pediatrics (AAP) recommends exclusive breastfeeding for approximately 6 months followed by continued breastfeeding with complementary foods for at least 1 year and beyond as mutually desired.

## OFFICE-BASED HEALTH PROMOTION STRATEGIES

### Prenatal Visit

Nutritional guidance for the infant begins ideally with the prenatal office visit, where plans for feeding the infant after birth are discussed with the expectant mother and father. The importance of good maternal nutrition, including folate, prenatal vitamins, and iron for the fetus, is emphasized at this time. If parents are unsure about the benefits of breastfeeding or the mother's ability to breastfeed, this is the ideal time to address these issues and to promote breastfeeding. This would include advice on the initiation of breastfeeding as soon as possible after birth and plans for continuing exclusive breastfeeding for approximately 6 months in accordance with AAP guidelines. If the mother has elected not to breastfeed for any reason, then the pediatrician should also be supportive of this decision and recommend that the infant be placed on an iron-fortified infant formula. The formula choices available can be discussed, as well as the importance of preparing formulas according to the directions on the containers using clean bottles and nipples. Parents should be informed of the availability of supplemental food programs if appropriate, including the Supplemental Nutrition Assistance Program and the availability of the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) food packages for pregnant and lactating women. This is also the time to assess the family for a history of food allergy or sensitivity, to ask about special dietary preferences, including vegetarianism, and to inquire about the maternal intake of medications (including prenatal vitamins) or herbal preparations that may be passed into breast milk. Maternal intake of illicit drugs and alcohol, as well as smoking, should also be determined and discussed as appropriate. If breastfeeding is planned, then the mother should also be assessed for conditions that may make breastfeeding difficult, such as breast reduction or bariatric surgery.

Referral to a lactation consultant may be indicated at this time. In recognition of the present pediatric obesity epidemic, parents who are clearly overweight should be identified as at risk for having children who are also overweight. It is not too early for the pediatrician to begin discussing changes in lifestyle that decrease the risk of obesity, including breastfeeding.

### Newborn Hospital Visit

Nutritional guidance should be continued at the time of the newborn hospital visit, which should occur within 24 hours of birth. If a prenatal visit did not occur, this visit should include the prenatal nutritional assessment as described earlier, especially if this is a first child and the pediatrician is unfamiliar with this family. If the delivery of the newborn occurs in a planned home birth by a licensed midwife, the newborn should be evaluated within 24 hours by a health care professional experienced in pediatrics.

The hospital visit should include an assessment of infant feeding and an observation of an actual breastfeeding or formula feeding if possible, particularly if this is a first-time mother or a breastfeeding mother who has not been successful with the breastfeeding of previous children. Any newborn or maternal barriers to successful feeding can be assessed at this visit, including complications of labor and delivery and peripartum maternal drug exposure. For concerns about breastfeeding technique, referral to a lactation consultant or other pediatric health care provider is appropriate to ensure a supportive environment for the mother who is breastfeeding. Stool and urine output, as well as degree of jaundice, should be evaluated to identify potential problems with inadequate intake. Newborns initially lose up to 10 percent of their body weight, largely because of fluid loss after birth. How to recognize hunger cues should be discussed, and feeding the infant only when hungry should be emphasized. Expected frequency of breastfeeding is 8 to 12 times in 24 hours in the early days of life, though clustered feeding followed by longer intervals of sleeping often occur. Intake of iron-fortified formula is approximately 20 oz per day after the first few days, which should result in feedings of 2 to 3 oz every 2 to 3 hours. This amount should be increased as the newborn's appetite increases.

The importance of the newborn metabolic screen can be discussed: if positive, this screen may lead to identification of medical disorders that can significantly affect infant nutrition choices as well. In accordance with AAP guidelines, mothers who are breastfeeding should be encouraged to start supplements of 400 IU per day of vitamin D to their infants within the first few days of life. Otherwise, infant formula (as required by federal laws) as well as breast milk contain all the basic nutrients for the sole means of nutritional support for the infant. No additional juice or water is needed.

### First Office Visit, 3 to 5 Days of Age (or 2–3 Days After Hospital Discharge)

Careful nutritional assessment is needed in the first week of life, especially if breastfeeding is not well established prior to hospital discharge. The AAP

recommends that newborns discharged at 48 hours of age be seen at a follow-up visit 3 to 5 days after birth, or 48 to 72 hours after hospital discharge. The assessment at this time includes measurements of weight, length, and head circumference that are plotted on the 2006 World Health Organization (WHO) growth charts to include anthropometric measurements made at the time of birth. It would also include a plot of weight for length. Newborns should have gained some weight since hospital discharge, but it is unlikely that birth weight will have been regained at this early visit, especially if the newborn is breastfeeding. Most newborns should have regained their birth weight by 7 to 10 days of life. Physical examination includes an assessment of jaundice and overall hydration status with special attention to the exclusively breastfed newborn. Infants should be feeding 8 to 12 times in a 24-hour period and have 5 to 8 wet diapers and 3 to 4 stools per day. Again, no supplements of water or juice are necessary for either breastfed or formula-fed infants. Parents should be reassured that their infant is getting enough breast milk or formula. If there are problems with breastfeeding and questions about adequate milk intake, the pediatrician should observe a feeding and refer to a lactation consultant if necessary. Formula-fed infants should be receiving iron-fortified formula. Breastfed infants should be receiving an oral supplement of 400 IU of vitamin D each day at this time. Parents should be encouraged not to introduce solid foods before about age 6 months. A discussion of the recognition of the infant's hunger cues as well as the potential for overfeeding of formula-fed infants should be discussed.

### Well Baby Visits, 1 to 4 Months

For the 1-, 2- and 4-month well baby visits, anthropometric measurements are again made and plotted on appropriate growth curves with documentation that the infant is growing appropriately for weight, length, and head circumference. Babies should gain about one-half pound per week (1 oz/day) or 2 lbs per month. Breastfed infants will grow more rapidly during the first 6 months of life, but then slow down in the second 6 months of life compared to the more rapid growth of formula-fed infants during this later time period. This information can be used to assure parents that their infant is getting an adequate intake of nutrients. Exclusive breastfeeding (with a vitamin D supplement of 400 IU day) or iron-fortified formula feeding should be continued without water or juice supplements. If the mother is returning to work, then plans for continuing or discontinuing breastfeeding should be discussed, along with options for breast pumps, breast milk storage, or introduction of bottle feeding. Mothers should be asked about conditions in the workplace that support breastfeeding, as present federal regulations require provision of a satisfactory place as well as break time for expressing breast milk. Formula intake should increase from 24 oz at 1 month of age to 30 to 32 oz by 4 months of age. Breastfed infants continue to need 8 to 12 feedings per 24 hours. Growth spurts may occur during this period, which may result in the baby's breastfeeding more often at times. Most infants will double their birth weight

between 4 and 5 months of age. Infants will gain approximately one inch per month in length during this period.

The AAP and the Centers for Disease Control and Prevention (CDC) have recommended use of the 2006 WHO growth charts for all US children between 0 and 23 months of age. These can be downloaded readily from the CDC Web site ([www.cdc.gov/growthcharts/who\\_charts.htm](http://www.cdc.gov/growthcharts/who_charts.htm)). These charts are based on 882 infants who were exclusively or predominantly breastfed for at least 4 months and who continued breastfeeding for at least 12 months. Complementary foods were introduced between the ages of 3 and 6 months. Cohorts of infants and children were from the United States (Davis, CA), Brazil, Norway, India, Oman, and Ghana. Each infant was weighed and measured 21 times in 24 months. Thus, the charts show how predominantly breastfed infants "should grow" under ideal conditions and are considered a "growth standard." This is in contrast to the CDC 2000 curves, which represent a "growth reference," showing how a large cross-section of US infants actually grew between 1970 and the early 1990s, regardless of economic status. These charts used data from infants whose feeding approximated the mix of feedings infants received in the 1970s and 1980s. During this period, 50% of US infants were ever breastfed, and 33% were at least partially breastfed up to 3 months.

Using the WHO charts in an office setting will require a different mindset on the part of physicians and parents. It is recommended for the WHO growth charts that the cutoff percentiles of 2.3% and 97.7%, or 2 standard deviations above and below the mean, be used, rather than the customary 5th and 95th percentiles on the CDC 2000 growth curves. In comparing the WHO and the CDC 2000 growth charts, the WHO charts show a somewhat faster initial weight gain in breastfed infants compared to the mixed-fed infants in the CDC 2000 curves during the first 3 months. After this time, the weight gain of breastfed infants in the WHO charts lags behind the growth rate of the infants in the CDC 2000 charts.

For many years, the CDC charts have been thought to over-identify children who are underweight, the prevalence of low weight for age being 7% to 11% of children aged 6 to 23 months. In comparison, the WHO standard shows a prevalence of less than 3% of low weight for age beginning at 6 months. This should lead to fewer infants being referred for expensive workups for inadequate weight for age, and may be reassuring to concerned parents and physicians. On the other hand, infants and children identified as having low weight for age on the WHO charts will be more likely to have a significant deficiency that will require some intervention.

At the present time, most infants (80%) begin complementary foods between 4 and 6 months of age. There is no evidence that earlier introduction of complementary foods helps infants to sleep through the night. Though there may be some advantages to exclusive breastfeeding for 6 months, the well-documented benefits of exclusive breastfeeding have occurred by 4 to 5 months, including decreasing the risks for infection and atopic disease.



The current AAP policy is exclusive breastfeeding for about 6 months. Mothers should be encouraged to partially breastfeed for about 12 months after the introduction of complementary foods, or as long as it is mutually convenient for both parties.

Infants vary greatly in their readiness for solid foods. They are developmentally ready when they can sit with support with good head control and begin putting things into their mouth. Introduction of solids should be done slowly with small amounts of pureed food. The typical infant will respond favorably over a short period of time with resolution of tongue thrusting, more coordinated swallowing efforts, and an increasing awareness of and interest in the foods offered. There is little evidence supporting the timing or the order of introduction of any solid food, but a gradual introduction of a variety of foods, flavors, and textures is recommended.

If breastfed infants are exclusively breastfed beyond 4 months of age without the introduction of iron-rich complementary foods, including fortified whole grain cereals, then, according to AAP recommendations, these infants should be supplemented with 1 mg/kg per day of oral iron beginning at 4 months of age. Partially breastfed infants (defined as those taking more than one-half of their daily feedings as human milk) who are also not receiving iron-rich complementary foods should also be supplemented with 1 mg/kg per day of medicinal iron. Breastfed infants should continue with a supplement of 400 IU of vitamin D per day. Iron supplements are generally not needed for infants receiving iron-fortified formula. As complementary foods are added, it is recommended to gradually introduce well-cooked, strained, or pureed meats with iron (eg, lean beef, pork, chicken, turkey), as these offer the best source of bioavailable iron. For families with vegetarian preferences who are not using iron-fortified formulas, supplements of medicinal iron should be provided for infants.

### Well Baby Visits, 6 to 12 Months

Between 6 and 12 months, the pediatrician should continue to monitor the anthropometric measures of growth as described previously. Growth slows down during this period, and infants will regulate their energy intake according to their needs. Infants of this age typically need about 850 calories per day. Most infants will triple their birth weight before 12 months and will grow about one-half inch in length each month. Breastfeeding or formula feeding should be continued. Cow milk, low-iron formulas, reduced-fat milk, goat milk, and soy drinks should not be used at any time during the first year of life. Breastfed infants should continue to receive a vitamin D supplement of 400 IU per day and medicinal iron if the intake of iron-rich complementary foods is limited. Unless a vegetarian diet is a family preference, there are no indications for soy formula. An increasing variety of complementary foods will become a larger part of the infant's diet as the first year of life progresses. At 12 months of age, switching to whole milk is recommended for formula-fed infants, but breastfeeding may continue for as long as is mutually convenient. "Follow-up" formulas are not recommended. However, if the infant is

overweight or at risk for overweight, reduced-fat (2% or 1%) milk may be used. Skim milk should not be used. Also at 12 months of age, babies should be screened for both iron deficiency and iron-deficiency anemia. This includes a hemoglobin determination and additional laboratory tests according to the child's risk factors for iron-deficiency anemia (see the following section).

Cup feeding can be introduced after 6 months of age. Fruit juices should not be introduced before 1 year of age, and should be limited to 4 to 6 oz per day with cup feeding. Sweetened beverages or fruit drinks should not be offered. Families should drink fluoridated water.

At approximately 6 months of age, the infant will typically develop her first tooth and, even as additional teeth erupt, mostly pureed foods should be continued because infants largely gum their food even if they have front teeth. Finger foods can also be introduced after 6 months of age. In general, infants should be offered small amounts of a wide variety of foods with different tastes and textures. It is well documented that repeated attempts at offering the same food may be required before the infant accepts the food. There is no scientific evidence to support the introduction of specific food groups at any defined interval. The ultimate goal is a wide selection of foods from every food group (though not necessarily at every meal) so that the intakes of all essential nutrients can be achieved. Similarly, there is little evidence to support the delayed introduction of "allergic foods," including eggs, fish, and peanut butter, which are a rich source of nutrients. Introducing "allergic foods" while still breastfeeding may be protective against the development of allergy. It is important that parents understand to feed the infant only when hungry with appropriately sized infant portions (no more than a few tablespoons) and to progress toward a schedule that corresponds with family meal times as the second 6 months of life progress. Every authority on the subject concurs that feeding should *never* be forced and meal times should never become a battle zone.

## NUTRITIONAL IMPLICATIONS FOR PRACTICE

Given the large number of physician/infant contacts that occur during this period, advice for nutritional practice is summarized in Box 36-1.

### Nutritional Questionnaire

Pediatricians can assess dietary intake selectively, asking questions about the infant's nutritional status at office visits. This can include asking parents to fill out a questionnaire before the office visit. Suggested questions can be found in Tool A: Nutrition Questionnaire for Infants found in the AAP publication *Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents: Nutrition*.

### Growth Curves—WHO

The AAP recommends the new WHO growth curves for infants and children up to 2 years of age. The



**BOX 36-1 Synopsis of Nutrition Guidance: First Year of Life****PRENATAL VISIT**

Discuss feeding options—breastfeeding vs bottle feeding with iron-fortified formula; promote breastfeeding, identify barriers to breastfeeding, discuss optimal breastfeeding environment; assess maternal health, use of prenatal vitamins, and exposure to drugs, alcohol and tobacco; assess family history for food allergy, food preferences, and risk for obesity.

**NEWBORN HOSPITAL VISIT**

Assess breastfeeding mechanics, stool and urine output; infant physical examination; encourage infant vitamin D supplement of 400 IU/day; discuss newborn screen.

If the newborn was born by a planned home delivery, this assessment should occur by a pediatrician within 24 hours of birth.

**OUTPATIENT VISIT IN FIRST WEEK OF LIFE**

Physical examination; anthropometric measurements, using World Health Organization (WHO) growth curves 0 to 2 years; assess breastfeeding adequacy and/or formula intake; continue vitamin D 400 IU/day.

**1-MONTH AND 2-MONTH VISITS**

Physical examination; anthropometric measurements, using WHO growth curves for 0 to 2 years; assess adequacy of breastfeeding/formula intake; continue vitamin D at 400 IU/day; discourage introduction of complementary foods.

**4-MONTH VISIT**

Physical examination; anthropometric measurements, using WHO growth curves for 0 to 2 years; assess adequacy of breastfeeding/formula intake; continue vitamin D at 400 IU/day; begin iron supplement (1 mg/kg/day) for exclusively breastfed infants; continue iron-fortified formula for formula-fed infants and discuss use of complementary foods beginning at about 6 months of age; juices should not be offered.

**6-MONTH VISIT**

Physical examination; anthropometric measurements, using WHO growth curves for 0 to 2 years; assess adequacy of breastfeeding/formula intake; infants should be making progress towards eating complementary foods from all food groups, emphasizing those that are good sources of iron; continue vitamin D at 400 IU/day; if iron intake is inadequate, especially for breastfeeding infants, then supplements of iron should be continued (1 mg/kg/day).

**9-MONTH VISIT**

Physical examination; anthropometric measurements, using WHO growth curves for 0 to 2 years; assess adequacy of breastfeeding/formula and complementary food intake; continue vitamin D 400 IU/day; infants should be taking complementary foods from all food groups, and these should contain adequate amounts of iron; if iron intake is inadequate in breastfed infants, then iron supplements should be continued; discourage use of whole milk and continue iron-fortified formula or breast milk.

**12-MONTH VISIT**

Physical examination; anthropometric measurements, using WHO growth curves for 0 to 2 years; assess adequacy of breastfeeding/formula intake, which should be continued until at least 12 months; continue vitamin D 400 IU/day; babies should be taking complementary foods from all food groups that contain adequate amounts of iron; screen for iron deficiency and iron deficiency anemia—babies may need additional iron if screening for iron deficiency is positive and if iron intake is inadequate in babies breastfeeding beyond 1 year of age; begin whole cow milk for babies receiving formula at this time; 2% milk, but not skim milk, may be used in babies who are overweight at 12 months of age.

WHO growth charts are available in pounds/ounces for weight and inches for length. The charts also include head circumference and weight for length. They can be downloaded from [www.cdc.gov/growthcharts/who\\_charts.htm](http://www.cdc.gov/growthcharts/who_charts.htm).

It is recommended that pediatric health care providers use the customary WHO cutoff percentiles, 2.3% and 97.7%, or 2 standard deviations below and above the mean.

During the first 3 months of life, the WHO charts show a somewhat faster weight gain than the CDC 2000 charts, the slower growth rate being in the formula-fed infants of the CDC 2000 charts compared with the breastfed infant cohort used in the WHO charts. However, as the rate of weight gain in breastfed infants slows down after 3 months compared with the mostly formula-fed infants in the CDC charts, use

of the WHO charts will identify fewer infants during the first year of life with inadequate weight for age.

**TOOLS FOR PRACTICE****Engaging Patient and Family**

- *Feeding & Nutrition: Baby* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/baby/feeding-nutrition/Pages/default.aspx](http://www.healthychildren.org/English/ages-stages/baby/feeding-nutrition/Pages/default.aspx))

**Medical Decision Support**

- *Growth Charts* (Web page), World Health Organization ([www.cdc.gov/growthcharts/who\\_charts.htm](http://www.cdc.gov/growthcharts/who_charts.htm))
- *Nutritional Questionnaire for Infants* (questionnaire), American Academy of Pediatrics, in *Bright Futures: Guidelines for Health Supervision of Infants*,

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### Chapter 37

## HEALTHY NUTRITION: CHILDREN

Frank R. Greer, MD

### BACKGROUND

This chapter covers nutritional guidance for a broad age range of children. It includes toddlers (13–35 months), preschoolers (36–60 months) and middle childhood (5–10 years). It also includes what is often referred to as the preadolescent period (9–11 years).

After the period of rapid growth and increased appetite of infancy, both the toddler and the preschool-aged child undergo a relative decrease in the rate of growth. Toddlers gain on average 0.5 pounds (0.23 kg) per month and 0.4 inches (1 cm) of height/length per month. The preschool child gains only 4.4 pounds (2 kg) and 2.75 inches (7 cm) per year. Accompanying this decreasing growth rate is a dramatic decrease in appetite and a decreased interest in food. In the parents' eyes, the child may become a "picky" eater.

School-aged children gain an average of 7 pounds (3–3.5 kg) in weight and 2.5 inches (6–7 cm) in height per year. For both weight and height, growth is not continuous, but occurs with irregular spurts lasting on average about 8 weeks. After increasing 0.8 inches (2 cm) during the second year, head circumference increases only by about 2 additional inches (5 cm) between 3 and 18 years. Myelination of the CNS is completed by age 10 years.

During middle childhood and the preadolescent years, the percentage of body fat reaches a nadir of 16% in females and 13% in males, before increasing again in preparation for the adolescent growth spurt. This normal increase in body fat is known as the "adiposity rebound" and can be a cause of concern for children and their parents as well.

### NUTRITIONAL REQUIREMENTS OF CHILDREN AGED 13 MONTHS TO 11 YEARS

The Dietary Guidelines for Americans are readily available ([www.health.gov/dietaryguidelines](http://www.health.gov/dietaryguidelines)) for checking the targeted nutrient intakes in children after 2 years of age. An average child's diet will generally meet or even exceed these recommendations if healthy food choices are available, as young children have a unique ability to regulate dietary intake when appropriate food choices are made available. On the other hand, regarding the availability of healthy food choices, children between the ages of 2 and 9 years generally do not consume the recommended number of servings of whole grains (6), fruits (2–3), vegetables (3–5), lean meats (2–3) and dairy products (2–3), according to the 2010 dietary guideline report. Thus, an increasing number of children may not be getting the recommended dietary intakes, particularly of vitamins and minerals.

Key nutrients likely to be deficient in the diet include iron, vitamin D, and calcium. The American Academy of Pediatrics (AAP) recommends an iron intake of 7 mg/day for children aged 1 to 3 years; the Institute of Medicine (IOM) recommends 10 mg a day for children 4 to 8 years old and 8 mg a day for children 9 to 11 years old. A 2011 report from the IOM recommends a daily vitamin D intake for children after 1 year of age to be 600 IU per day, which is higher than the 400 IU recommended by the AAP in its 2008 report. (These recommendations assume no sunshine exposure.) It is unlikely that this amount of vitamin D intake can be achieved in this age group without vitamin supplements, which typically contain 400 IU per dose. The 2011 IOM report and the AAP recommend a calcium intake of 700 mg per day for children between the ages of 1 and 3 years, which can be met by a diet that includes at least 2 servings of dairy products per day. The calcium requirement increases to 1,000 mg per day from 4 to 8 years of age, and rises to 1,300 mg per day between the ages of 9 and 11 years; these levels of intake require up to 3 servings of dairy products a day. Some soy milks are also fortified with calcium and vitamin D, if a vegetarian diet is preferred.

In 2011 and 2012, almost 8.4% of children aged 2 to 5 years were obese, and 17.4 % of children aged 6 to 11 years were obese. Childhood obesity tracks into adulthood, and studies show that the risk for obesity is even greater in the lower-income population. For children aged 2 to 3 years, the American Heart Association and the AAP have recommended that total energy from fat not exceed 30% to 35% of the total energy intake, and this is reduced to 25% to 35% after 4 years. Anticipation and prevention of overweight and obesity have become critical parts of health supervision visits in all age groups. For a full discussion of prevention and treatment of obesity and its related comorbidities, see Chapter 35, Healthy Weight.

## OFFICE-BASED HEALTH PROMOTION STRATEGIES

### Screening and Surveillance

Routine health supervision visits up to 2 years of age should include an accurate measurement of head circumference, length, and weight; for toddlers whose measurements fall outside of expected percentiles, a weight-for-length percentile may provide additional information for the assessment of adiposity; from 2 to 9 years of age, visits should include measurement of weight and height and calculation of body mass index (BMI). In addition to documenting these measurements in the health record, the physician should plot them on growth charts to identify those children whose rate of growth falls outside expected percentiles.

The AAP and the Centers for Disease Control and Prevention (CDC) have recommended use of the 2006 World Health Organization (WHO) growth charts for all US children between 0 and 23 months old. (See Chapter 16, Pediatric Physical Examination: Interpretation of Findings.) Although the WHO curves include BMI, the use of BMI before 2 years of age is not

recommended because there is limited information on its predictive value in children.

After 23 months, it is recommended that the 2000 CDC growth curves (2–20 years), including BMI percentiles, be used for all children and adolescents (see Box 37-1). The BMI percentile is predictive of body fat for this age group. Typically, the BMI-for-age reaches a nadir between 4 and 6 years of age, before increasing again into adulthood. If adiposity rebound occurs before 4 to 6 years of age, there is increased risk of obesity. A BMI above the 85th percentile and below the 95th percentile indicates that the child is overweight; a BMI above the 95th percentile indicates that the child is obese.

At each visit, the physician should also take a family history and a dietary history with special emphasis on intake of foods rich in iron, vitamin D, and calcium.

The AAP recommends that obese children, as well as children from families with a history of hyperlipidemia or early onset of heart disease, should undergo lipid screening after 2 years, but no later than 10 years of age, because they are at significant risk for developing cardiovascular disease later in life. Children who are obese with abnormal lipid profiles and family history of early onset heart disease are at risk for the metabolic syndrome and other medical and mental health conditions. See Chapter 298, Obesity and Metabolic Syndrome, for a full discussion of prevention

### BOX 37-1 Recommendations for Use of World Health Organization and Centers for Disease Control and Prevention Growth Charts

In using the World Health Organization (WHO) growth charts (0–23 months), it is recommended that the cutoff percentiles of 2.3 and 97.7, or 2 standard deviations above and below the mean, be used rather than the customary 5th and 95th percentiles on the Centers for Disease Control and Prevention (CDC) 2000 growth curves. The CDC charts overidentify low length for age in 7% to 11% of children between 6 and 23 months of age, compared with only 3% using the WHO charts (see Chapter 36, Healthy Nutrition: Infants). At 2 years of age, when switching from measuring recumbent length to standing height, there is typically a loss in height of 1 cm, resulting in a disjunction between the 2 curves. When switching from the newer WHO/0 to 2 years to the CDC 2000/2 to 20 years, a disjunction in both height and weight will be exaggerated and should not be cause for alarm. The WHO charts show a slower and more appropriate rate of growth during the first 2 years of life, and the percentile lines are not the same as the CDC 2000 curves. Looking at the child's overall growth pattern over time with multiple data points both before and after the time of "disjunction," as well as the medical and family history, should aid in the assessment of appropriate growth during the transition period. This information can be used to reassure the parents that the child's growth is normal.

and management of obesity and its associated comorbidities.

The AAP recommends that infants and toddlers be screened for iron deficiency and anemia at 12 months with follow-up in later years, if necessary.

### Anticipatory Guidance

The physician can advise parents that they have a great deal of influence on establishing good dietary habits that will have a positive impact on their child's health later in life. However, parents should not attempt to control intake by coercive practices, such as rewarding children with favored foods for eating more vegetables. Nearly all studies have shown that authoritarian controls over children's eating habits, including the restriction of caloric intake by parents concerned about weight gain, have a negative impact and actually increase adiposity and the risk for overweight. More over, a total restriction of the intake of junk foods high in fat, sugar, and sodium, has been shown to make these foods even more desirable to the child, and increase the risk for obesity.

In general, children should never be forced to eat anything. Influence of a child's dietary habits is largely accomplished by setting a good example and making available, for both meals and snacks, healthy food choices from the 5 food groupings in MyPlate.

By toddlerhood, the child should become a participatory member in family meals. Parents should be reminded that eating meals together as a family is very important in establishing healthy eating habits. At family meals, the dietary intake is improved with higher intakes of essential nutrients such as calcium, iron, and vitamins. The intake of fruits and vegetables is also increased. Meals should be eaten without television, given the influence of the media on unhealthy food choices and the fact that an excess of screen time contributes to obesity.

The child should be eating the same foods as the rest of the family at meal times, with the emphasis on foods with high nutritional value, rather than nutrient-poor foods high in fat, sugar, and salt. Children should be encouraged to make selections from all food groupings from MyPlate, but not necessarily from all the groups at each meal. Parents should provide for 3 meals a day and make available healthy snack foods (low in fat, sugar and salt) at scheduled intervals between meals, especially for younger children with limited intake capacity.

Physicians will need to reassure parents of toddlers and preschoolers that "picky" eating is normal and typical behavior for children of this age; in most cases, children will continue to have adequate intake of calories and nutrients and continue to grow appropriately.

BMI in the middle years (4–6 years) bottoms out before adiposity rebound occurs in preparation for the adolescent growth spurt. The subsequent increase in body fat (increasing BMI) may be cause for concern in children and their parents, and inappropriate dieting may occur. The physician should reassure parents and patients that this is part of normal growth, and changes are not likely to be permanent

unless the child is greatly overweight or obese. An earlier onset of adiposity rebound (before 6 years of age) is a cause for concern. As the child progresses through the middle years, more meals are eaten outside the home and there is less parental guidance of food choices. Parents and older siblings have an effect on the child's eating behavior, but, as the child approaches preadolescence, peer influence becomes more important. The frequency of family meals may decrease as the child approaches the adolescent period. This coincides with a tendency toward skipping meals, most frequently breakfast. Parents should be advised that eating breakfast has been shown to have a positive effect on school performance, though this maybe more related to encouraging school attendance than a direct effect on cognitive ability. Skipping breakfast has been thought to adversely affect dietary intake, because it promotes snacking on less healthy food throughout the day to make up for the loss of energy intake, though this has been controversial. An alternative is to send children off to school with healthy breakfast bars and pieces of fruit to eat along the way.

Children also continue to increase their total screen time—time spent in front of TV, computers, and smart phones—during the middle years. A media history with media questions should occur at every well-child visit and should include an assessment of the child's access to electronic devices. Parents should be encouraged to limit recreational screen time to no more than 2 hours per day. The media and the Internet have a negative effect on dietary intake, because they advertise foods with low nutrient density and increased amounts of fat, sugar, and salt. Increasing screen time also has a negative impact on physical activity. Chapter 39, Physical Activity, discusses limits on screen time and presents a variety of strategies for enhancing physical activity to the recommended 60 minutes per day.

### IMPLICATIONS FOR PRACTICE

At every office visit from ages 1 to 11 years, a complete physical examination should be done. The visit should also include an accurate measurement of weight, length, and head circumference for children up to 2 years; and height, weight, and calculation of BMI and percentile in children 2 years and older. The WHO growth charts and CDC growth curves provide guidelines for assessing both underweight and overweight. A dietary history should be obtained with particular concern for intake of calcium, iron and vitamin D. (See Tools for Practice.) Family history is important in assessing risks for obesity and obesity-related comorbidities.

Routine health supervision visits also provide opportunities for offering guidance to children and their families about making healthy choices to prevent nutrition-related problems and to address any identified risks, including media exposure. If there are concerns about the child's nutritional status, the tools listed in the following section will help with nutritional counseling in the office.



## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *BAM!* (Web page), Centers for Disease Control and Prevention ([www.bam.gov](http://www.bam.gov))
- *Let's Move!* (Web site), ([www.letsmove.gov](http://www.letsmove.gov))
- *Mindless Eating* (Web site), Brian Wansink ([www.mindlesseating.org](http://www.mindlesseating.org))
- *We Can!* (Web page), National Heart, Lung, and Blood Institute ([wecan.nhlbi.nih.gov](http://wecan.nhlbi.nih.gov))

### Engaging Patient and Family

- *Choose My Plate* (Web site), US Department of Agriculture ([www.choosemyplate.gov](http://www.choosemyplate.gov))
- *Healthy Active Living for Families Implementation Guide* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/HALF-Implementation-Guide/Pages/HALF-Interactive-Tools.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/HALF-Implementation-Guide/Pages/HALF-Interactive-Tools.aspx))

### Medical Decision Support

- *Growth Charts* (charts), Centers for Disease Control and Prevention ([www.cdc.gov/growthcharts](http://www.cdc.gov/growthcharts))
- *In Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents: Nutrition*, 3rd ed (book), American Academy of Pediatrics
  - Tool B: Nutrition Questionnaire for Children Ages 1 to 10 (pp 227–232)
  - Tool D: Key Indicators of Nutrition Risk for Children and Adolescents (pp 239–244)
  - Tool F: Stages of Change—A Model for Nutrition Counseling (pp 249–250)
  - Tool G: Strategies for Health Professionals to Promote Healthy Eating Behaviors (pp 251–254)
  - Tool I: Tips for Fostering a Positive Body Image Among Children and Adolescents (pp 257–258)

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## Chapter 38

# HEALTHY NUTRITION: ADOLESCENTS

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## BACKGROUND

Adolescence (11–21 years of age) is a time of physical and emotional change that affects nutrition and physical activity. There is a dramatic increase in physical growth and development that requires the adolescent to adjust to a new body size with new physiologic requirements. The nutritional needs for all major nutrients are increased. The pregnant adolescent undergoes even more dramatic changes with additional nutrient requirements, but these will be discussed in Chapter 122, Adolescent Pregnancy and Parenthood.

As adolescents assert their independence and interact with peers, they may develop nutritionally undesirable eating behaviors, including excessive dieting, increased consumption of foods and beverages high in fats and carbohydrates, skipping meals, use of nutritional and non-nutritional supplements, and reliance on fad diets. At the same time, the period of adolescence is an important time for anticipatory guidance to further develop healthy eating practices and promote ongoing participation in competitive or non-competitive physical activities essential to developing a healthy lifestyle that will extend into adulthood.

In comparison with other age groups, the nutritional needs of the adolescent are determined by the degree of sexual maturation and biological maturity, rather than the chronologic age. The increases in lean body mass, skeletal mass, and body fat during puberty are greater than those at any other time in the life cycle. Between the ages of 11 and 21, nutritional needs may change dramatically from one office visit to the next. Thus, a 15-year-old boy who has experienced rapid linear growth and muscle development will have nutritional needs that differ from the 11-year-old girl who has not yet entered puberty. Health professionals can refer to the sexual maturation rating (SMR), or Tanner stages, to assess the degree of pubertal maturation in the adolescent at each office visit (see Table 38-1). Of the 5 Tanner stages, stage 1 corresponds with prepubertal growth and development, while stages 2 through 5 denote the period of puberty. In adolescent females, menarche occurs  $2.3 \pm 1.1$  years after the development of breast buds and pubic hair (stage 2), most commonly during SMR stage 4. Only 10% of females are menstruating at 11.11 years of age and 90% are menstruating by 13.75 years. There are racial differences in the development of secondary sexual characteristics in females, with non-Hispanic black females developing pubic hair on average a year earlier than Mexican American or non-Hispanic white females. Similarly, the onset of menarche is earlier in non-Hispanic black females (12.06 yrs) than in Hispanic (12.25 yrs) and non-Hispanic white females

**Table 38-1 Sexual Maturity Rating for Girls and Boys**

<b>GIRLS STAGE</b>	<b>BREAST DEVELOPMENT</b>	<b>PUBIC HAIR GROWTH</b>
1	Prepubertal; nipple elevation only	Prepubertal; no pubic hair
2	Small, raised breast bud	Sparse growth of hair along labia
3	General enlargement of raising of breast and areola	Pigmentation, coarsening, and curling with an increase in amount
4	Further enlargement with projection of areola and nipple as secondary mound	Hair resembles adult type, but not spread to medial thighs
5	Mature, adult contour, with areola in same contour as breast, and only nipple projecting	Adult type and quantity, spread to medial thighs

<b>BOYS STAGE</b>	<b>GENITAL DEVELOPMENT</b>	<b>PUBIC HAIR GROWTH</b>
1	Prepubertal; no change in size or proportion of testes, scrotum, and penis from early childhood	Prepubertal; no pubic hair
2	Enlargement of scrotum and testes; reddening and change in texture in skin of scrotum; little or no penis enlargement	Sparse growth of hair at base of penis
3	Increase first in length, then width of penis; growth of testes and scrotum	Darkening, coarsening, and curling with an increase in amount
4	Enlargement of penis with growth in breadth and development of glands; further growth of testes and scrotum, darkening of scrotal skin	Hair resembles adult type, but not spread to medial thighs
5	Adult size and shape of genitalia	Adult type and quantity, spread to medial thighs

(12.55 yrs). The median age of menarche for all girls is 12.43 years.

Good nutritional intake is very important during adolescence. In females, 15% to 25% of final adult height will be gained during puberty, with an average increase in height of 9.8 inches or 25 cm. During the peak adolescent growth spurt, females gain 3 to 5 inches (8–9 cm) per year. This growth spurt lasts 24 to 26 months, ending by 16 years of age in most females. In males, the peak velocity of linear growth occurs at 13.5 years of age on average, coinciding with testicular development and the first appearance of facial hair. At its peak, the growth spurt will increase height at a rate of 4.3 inches (9.5 cm) per year. Linear growth continues throughout adolescence, though at a slower rate, ending by 18 years of age. In the end, boys on average are 5 inches (12.5 cm) taller than girls.

As much as 50% of the ideal adult body weight is gained during adolescence. In females, peak weight gain follows 3 to 6 months after the peak linear growth spurt. Females will gain about 18.4 pounds (8.3 kg) per year at peak weight gain, typically at 12.5 years of age. Though weight gain slows after this, females will gain up to 14 additional pounds (6.3 kg) during the latter half of adolescence. Among males, peak weight gain coincides with the timing of peak linear growth and peak muscle mass accumulation. During the peak, males may gain 20 pounds (9 kg) per year.

Body composition changes dramatically in females during puberty, with the average lean body mass falling from 80% to 74% of body weight and average body fat increasing from 16% to 27% of body weight at full maturity. Females gain about 2.5 pounds (1.14 kg) of body fat mass per year. In contrast, males' lean body mass increases from 80% to 90% of total

body weight, and body fat in adolescent males decreases to 10% of body weight by the end of puberty.

Nearly half of adult peak bone mass is accrued during adolescence. By age 18, more than 90% of adult skeletal mass has been formed, largely determined by genetics, physical activity, and intakes of vitamin D and calcium.

## **NUTRITIONAL REQUIREMENTS DURING ADOLESCENCE**

Physical activity in both males and females declines during adolescence. It is recommended that adolescents engage in 60 minutes or more of physical activity per day. The energy and nutrient needs of these activities vary widely. Average caloric intake for moderately active adolescents is about 2,800 cal for males and 2,000 for females. Individual energy needs vary greatly, depending on body size, degree of physical maturation, rate of growth, and level of physical activity. The assessment of growth rate is key to determining adequate energy intake, as noted above.

Adolescents need large amounts of protein, up to one-half gram per pound of body weight per day. Thus, a 124-pound adolescent male needs 55 g of daily protein intake. The recommended daily allowance (RDA) for iron is 15 mg/day for females and 11 mg/day for males, the difference relating to menstrual losses of blood in females. Other key nutrients for adolescents are calcium and vitamin D for bone growth. The Institute of Medicine and the American Academy of Pediatrics (AAP) recommend daily calcium intake of 1,300 mg and daily vitamin D intake of 600 IU for adolescents.

Relatively few adolescents meet the dietary guidelines for intake of fruits, vegetables, whole grains, and

dairy products. However, adolescents often exceed their daily energy requirement, boys more so than girls. Adolescent females, in particular, fail to achieve the recommended intakes of not only calcium and vitamin D, but many other nutrients as well. The median intake of calcium in adolescent females 14 to 18 years of age is only about 60% of the RDA of 1,300 mg. Male adolescents do considerably better with calcium intake.

Obesity in adolescents is a real concern for the physician. Of adolescents ages 12 to 19 years, 20.5% were considered obese in 2011 and 2012. See Chapter 298, Obesity and Metabolic Syndrome, for a full discussion of the epidemiology of obesity and related comorbidities, as well as their prevention and treatment. See also the AAP policy on obesity prevention.

It is estimated that 0.5% of adolescent girls in the United States have anorexia nervosa, and 1% to 2% meet the criteria of bulimia nervosa. While prevalence among boys is much lower, 5% to 10% of all eating disorders do occur in males. Adolescents with eating disorders may benefit from dietary supplements. For a discussion of eating disorders, see Chapter 216, Anorexia Nervosa, Bulimia Nervosa, and Other Eating Disorders.

Adolescent eating behavior is influenced by many factors, including peers' eating choices, parental modeling, personal (cultural) food preferences, food availability, convenience, costs, mass media, and body image. Adolescents typically lack the ability to relate their current dietary patterns to long-term effects on their health, whether positive or negative.

## OFFICE-BASED HEALTH PROMOTION STRATEGIES

### Screening and Surveillance

Routine health supervision of adolescents should begin with an annual screening for indicators of nutritional risk (see the Tools for Practice section at the end of this chapter). These include overweight and underweight, eating disorders, hyperlipidemia, hypertension, iron deficiency anemia, amount of physical activity, and amount of screen time. Unhealthy eating practices that should be screened for include frequent dieting, meal skipping, purging, food fads, and increased consumption of foods and beverages high in fat and sugar, such as fast foods and soft drinks. Adolescents should also be screened for use of dietary supplements including high-energy sports drinks. Nutrition screening should include a physical examination with measurement of blood pressure, an assessment of SMR, an accurate measurement of height and weight, calculation of body mass index (BMI), and determination of BMI percentile. Nutrition screening should also include a broader dietary assessment for adolescents who are at increased nutritional risk, with a food frequency questionnaire, 24-hour dietary recall, or a food diary to further define nutritional problems (see the Tools for Practice section at the end of this chapter). Adolescents should be screened for iron deficiency and anemia if they are at risk for iron deficiency.

Anthropometric measures should be plotted on the NCHS 2000 growth charts accessible at [www.cdc.gov/growthcharts/data/set1clinical/set1color.pdf](http://www.cdc.gov/growthcharts/data/set1clinical/set1color.pdf). Adolescents

below the fifth percentile in weight or BMI are underweight and should undergo additional screening. Those above the 85th and below the 95th BMI percentile are considered at risk for overweight and should also undergo additional screening.

Adolescents whose BMI is above the 95th percentile are obese and should receive a full-scale medical evaluation and a weight management program designed to meet the needs of adolescents and their families. This should include evaluation of screen time and physical activity. Referrals to specialists, including a nutritionist, may be necessary (see Chapter 298, Obesity and Metabolic Syndrome). Adolescents with a BMI less than 5% should also receive full medical evaluation including a risk assessment for eating disorders (see Chapter 216, Anorexia Nervosa, Bulimia Nervosa, and Other Eating Disorders).

The AAP and the American Heart Association have recommended that obese children and adolescents, as well as children and adolescents from families with familial hyperlipidemia and early onset of heart disease, should undergo lipid screening, because they are at significant risk for developing cardiovascular disease later in life. If lipid screening reveals an abnormality, adolescents will need close follow-up and ongoing dietary management. These adolescents are also at risk for a number of physical and mental health comorbidities. See Chapter 35, Healthy Weight, for screening and treatment measures related to these comorbidities.

### Anticipatory Guidance

Throughout childhood and adolescence, parents are the gatekeepers of foods and serve as important role models for eating behavior. They should be advised to keep a variety of healthy foods in the home, provide fruits and vegetables at every meal, and use whole grain breads and cereals. The diet should avoid high intakes of saturated fats and trans-fats, as well as cholesterol, sweetened beverages, and fast foods low in nutrient density. For adolescents, the American Heart Association and the AAP have recommended that total energy from fat not exceed 25% to 35% of energy intake. Lean meats, including chicken and fish, should be served.

Adolescents require 4 servings per day of low-fat (1%) or nonfat milk, or other low-fat dairy products, to provide adequate amounts of calcium and vitamin D for strong bones. Fortified milk (1,500 mL) will also supply the daily 600 IU of vitamin D recommended for adolescents. Weight-conscious adolescents should be assured that reduced-fat or skim milk contains just as much calcium and vitamin D as whole milk. Alternative sources of calcium are tofu, fortified soy milk, and dark green leafy vegetables, though very large quantities of vegetables will have to be eaten to match the iron intake from meat. Heme iron from meat (including shellfish) is the best source of iron, given its relatively high absorption rate.

It is important for the adolescent to eat with the family as often as possible. Parents should be encouraged to insist on some minimum number of meals with the family every week. Eating meals as a family has been shown to improve dietary intake with higher intakes of essential nutrients such as calcium, iron, and vitamins. The intake



of fruits and vegetables is also increased with family meals.

The tendency for meal skipping increases during adolescence. The most frequently skipped meal is breakfast. Adolescents should be advised that eating breakfast has been shown to have a positive effect on school performance, though this may be more related to encouraging school attendance than a direct effect on cognitive ability. Skipping breakfast has been thought to adversely affect dietary intake, because it promotes snacking on less healthy food throughout the day to make up for the loss of energy intake, though this assertion is controversial. Parents should be encouraged to keep healthy snacks around the home and to encourage adolescents to take breakfast bars or fruit with them to school rather than skip breakfast.

Adolescents experience significant amounts of screen time—time spent in front of TV, smartphones, and computers. The media and the Internet have a negative influence on diet because they advertise foods with low nutrient density and increased amounts of fat, sugar, and salt. Electronic social networking is also greatly increased during adolescence. These sedentary activities replace physical activity and are significant factors contributing to the epidemic of obesity. Parents should be encouraged to limit screen time (TV, video, cell phone, computer) to 2 hours per day and never allow television watching in the bedroom. See Chapter 35, Healthy Weight, and Chapter 39, Physical Activity, for further discussion of the role of physical activity in obesity prevention and treatment.

## IMPLICATIONS FOR PRACTICE

In addition to the measures described in the Screening and Surveillance Section, routine health supervision visits also provide opportunities for offering guidance to adolescents and their families about making healthy choices to prevent nutrition-related problems and to address any identified risks. If there are serious concerns about the adolescent's nutritional status, the resources listed in Tools for Practice will help with the nutritional counseling of the adolescent patient in the office.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Choose My Plate* (Web site), US Department of Agriculture ([www.choosemyplate.gov](http://www.choosemyplate.gov))
- *Healthy Active Living for Families Implementation Guide* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/HALF-Implementation-Guide/Pages/HALF-Interactive-Tools.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/HALF-Implementation-Guide/Pages/HALF-Interactive-Tools.aspx))
- *Office of Child Support Enforcement* (Web site), US Department of Health and Human Services ([www.acf.hhs.gov/programs/css](http://www.acf.hhs.gov/programs/css))
- *Supplemental Nutrition Assistance Program (SNAP)* (Web site), US Department of Agriculture ([www.fns.usda.gov/snap](http://www.fns.usda.gov/snap))

- *Teen—Nutrition* (Web page), American Academy of Pediatrics ([www.healthychildren.org/english/ages-stages/teen/nutrition/Pages/default.aspx](http://www.healthychildren.org/english/ages-stages/teen/nutrition/Pages/default.aspx))

#### Community Advocacy and Coordination

- *CDC Healthy Schools* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/healthyyouth/schoolhealth/index.htm](http://www.cdc.gov/healthyyouth/schoolhealth/index.htm))
- *National School Lunch Program (NSLP)* (Web page), US Department of Agriculture ([www.fns.usda.gov/nslp/national-school-lunch-program-nslp](http://www.fns.usda.gov/nslp/national-school-lunch-program-nslp))
- *State School Health Resources* (Web page), American Academy of Pediatrics ([www2.aap.org/sections/schoolhealth/contactmap/section\\_contacts.cfm.htm](http://www2.aap.org/sections/schoolhealth/contactmap/section_contacts.cfm.htm))
- *USDA Food and Nutrition Services* (Web page), US Department of Agriculture ([www.fns.usda.gov](http://www.fns.usda.gov))

#### Medical Decision Support

- *Bright Futures Nutrition*, 3rd ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
  - Tool B: Nutrition Questionnaire for Adolescents Ages 11 to 21 (pp 233–238)
  - Tool D: Key Indicators of Nutrition Risk for Children and Adolescents (pp 239–244)
  - Tool F: Stages of Change—A Model for Nutrition Counseling (pp 249–250)
  - Tool G: Strategies for Health Professionals to Promote Healthy Eating Behaviors (pp 251–254)
  - Tool I: Tips for Fostering a Positive Body Image Among Children and Adolescents (pp 257–258)
- *Growth Charts* (charts), Centers for Disease Control and Prevention ([www.cdc.gov/growthcharts](http://www.cdc.gov/growthcharts))
- *The SCOFF Questionnaire: Assessment of a New Screening Tool for Eating Disorders* (article), *BMJ*, Vol 319, Issue 7223, 1999

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## Chapter 39 PHYSICAL ACTIVITY

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## BACKGROUND

The World Health Organization defines *health* as a state of complete physical, mental, and social well-being. Thus, pediatricians should not only address disease, but also promote healthy lifestyles. Unfortunately, poor nutrition, increasing sedentary behavior, and declining physical activity (PA) have resulted in rising pediatric obesity rates and a decline in physical fitness, with adverse health consequences that extend into adulthood. This chapter focuses on the promotion of regular PA to achieve lifelong healthy active living.

## Definitions

Physical activity can be defined as any body movement produced by skeletal muscle that results in an increase in energy expenditure above rest. Exercise is planned, structured, and repetitive PA to condition any part of the body and can include the following:

- **Aerobic** activity, which improves cardiovascular endurance. Moderately intense aerobic activities include brisk walking, slow bicycling, dancing, and light weight lifting. Vigorous activities include jogging, running, intense cycling, and most competitive sports.
- **Flexibility** exercises (eg, yoga), which increase muscle and joint range of motion.
- **Anaerobic** exercises, like weight lifting, which improve muscle strength.
- **High-impact** activities (like skipping and jumping), which promote good bone health.

Physical activities and exercise are typically described and prescribed using the FITT formula: *frequency*, *intensity*, *time* (duration), and *type*. In a similar fashion, sedentary behaviors can be described using the SITT formula: *sedentary* behavior frequency (number of bouts of a certain duration); *interruptions* (eg, getting up from the couch while watching television); *time* (the duration of sedentary behaviors); and *type* (mode of sedentary behavior, such as television viewing, sitting in a car, or using a computer).

## Sedentary Behavior

Children and adolescents are increasingly sedentary with behaviors promoted by widespread exposure to electronic entertainment technologies, automobile transport, and mechanized living. The average 8- to 10-year-old American child spends about 8 hours/day and the average American adolescent more than 11 hours/day on a variety of screen-based media. Although television is the most common screen-based activity, more than 30% of TV programming is viewed on computers, tablets, or cell phones. Infants and preschoolers watch 2 to 3 hours/day of TV at home and 1.5 hours/day in center-based child care. In 2009, almost 33% of grade 9 to 12 students watched at least 3 hours/day of TV. Highest viewing times are associated with the greatest prevalence of obesity. Lower resting metabolism, consumption of low-nutritive value foods prompted by TV advertisements, and displacement of PA may explain this relationship. Screen time behaviors are higher in older teens, minorities, and those with bedroom TV sets.

## Inadequate Physical Activity

Most young children accumulate insufficient unstructured free play at home and in family- or center-based child care. Research shows an inverse relationship between time spent in child care and time engaged in PA. Few states have policies and standards to ensure child care centers achieve national PA guidelines for this age group and national standards for safe outdoor play areas and equipment.

School-aged children are also not sufficiently active, and fitness scores have dropped over the past 30 years. Less than 33% of Americans 2 to 19 years of age meet recommended aerobic fitness levels. Older girls, youth with a high body mass index (BMI), and those with greater sedentary behaviors and lower PA levels are most affected. Physical education (PE) recommendations from Healthy People 2010 include 150 minutes/week for elementary students and 225 minutes/week for middle and high school students; however, implementation of these guidelines is inconsistent. “No Child Left Behind” elementary schools devote more daily instructional time to reading (47%) and mathematics (37%), and less time to PE (35%) and recess (28%). School boards often justify such reductions on the grounds that more PE time will detract from academic achievement, but research suggests otherwise.

In the United States from 1969 to 2001, there was a 68% reduction in the number of children who walked or biked to school. Barriers to active transportation include harsh climate; lack of sidewalks, bike trails, and crosswalks; traffic and safety dangers; and geographical separation of living, working, education, shopping, and leisure activities. Since the 1970s, children have lost about 12 hours/week of free time, which includes a 25% decrease in play and 50% reduction in unstructured outdoor activities. Time spent outdoors increases PA levels, yet many children have poor access to parks and open spaces. Accessible parks may be underused because they lack playgrounds or sport fields or because they have poor aesthetics, inadequate maintenance, and other safety issues.

Participation in organized sport and recreation programs also increases PA. In 2009, only 58% of students nationwide joined at least one school or community-based sports team, and participation was lower among older students and females. Cost, sport availability and variety, peer support, peer pressure, and parental time commitments may influence participation. Free recreation facilities are often lacking in low-income communities. Children who are overscheduled and those who are not involved in or dislike sports may be less engaged. Disabled children may have poor access to affordable quality recreational facilities.

### Health Benefits of Physical Activity

The health benefits of regular aerobic activity include weight reduction or maintenance, improved body composition, lower blood pressure, improved dyslipidemia, reduced biomarkers of inflammation and atherosclerosis, and enhanced self-concept and mental wellness. Other benefits include reduction in insulin resistance, risk for type 2 diabetes, nonalcoholic fatty liver disease, and sleep-disordered breathing. Experts suggest that exergaming (active computer games) may be a suitable replacement for sedentary activities if the whole body is moved; but evidence is mixed on whether cardiorespiratory fitness improves. These indoor screen-based activities should not replace outdoor active play, PE, or sports.

Strength, anaerobic, high-impact, skill-based, and flexibility exercises provide many other health benefits. Although bone mass is largely determined by genotype, weight-bearing PA can affect bone mass acquisition and structural adaptation during youth. Weight training improves neuromuscular learning and muscle and bone strength in both genders during puberty. Team sports can lead to new skills, increased self-confidence, and better problem solving and conflict resolution. Growing children and those with neuromuscular disabilities require stretching programs to improve flexibility and avoid injury. Most children with chronic disease benefit from a variety of exercises and habitual physical activities.

## PHYSICAL ACTIVITY RECOMMENDATIONS

Aerobic activities provide numerous, diverse health benefits in a dose-response fashion, suggesting that the more time spent being active the better. According to the Centers for Disease Control and Prevention, children and adolescents should be active at least 1 hour/day. Most activity should be of moderate or vigorous intensity. Vigorous activity and muscle- and bone-strengthening exercises should occur at least 3 days a week.

The World Health Organization recently released Global Recommendations on Physical Activity for Health for children aged 5 to 17 years. For children and adolescents, physical activity includes play, games, sports, transportation, recreation, and PE or planned exercise, in the context of family, school, and community activities. To improve cardiorespiratory and muscular fitness, bone health, and cardiovascular and metabolic health biomarkers and to reduce symptoms

of anxiety and depression, the following are recommended:

1. Accumulate at least 60 minutes of moderate- to vigorous-intensity PA daily.
2. PA in amounts greater than 60 minutes daily will provide additional health benefits.
3. Most of the daily physical activity should be aerobic. Vigorous-intensity activities should be incorporated, including those that strengthen muscle and bone, at least 3 times per week.

The American Academy of Pediatrics (AAP) recommends children and adolescents limit recreational screen time to less than 1 to 2 hours/day and accumulate (in small increments) at least 60 minutes of moderate to vigorous PA per day. Ideally, PA would include enjoyable group and individual activities through sport, recreation, transportation, chores, and planned exercise. Activities should be structured (games, organized sports) and unstructured (free play). Safety should be a priority through the use of appropriate protective equipment and the promotion of fair play. Specific recommendations (Table 39-1) should be age and developmentally appropriate.

## ACTIVE HEALTHY LIVING STRATEGIES: IMPLICATIONS FOR PRACTICE

Pediatricians can assess children's and adolescents' lifestyle risks for chronic disease by identifying unhealthy eating patterns, sedentary habits, and PA habits and by calculating and plotting BMI. Active healthy living promotion begins with a baseline individual and family history, which can be obtained through administering a waiting room survey, estimating current sedentary behavior and PA levels, discovering existing barriers to healthy active living, and assessing the individual's self-efficacy to make change. (Table 39-2, Table 39-3) (See also Chapter 31, Applying Behavior Change Science.)

### Family-Based Strategies

Families may require concrete medical reasons to begin a PA program, such as illness in their child (high blood pressure, insulin resistance, fatty liver, musculoskeletal conditions like Blount disease and slipped capital femoral epiphysis and fractures) or a family history of cardiovascular disease or diabetes. Identifying family stressors (limited finances, separation or divorce, and physical or mental abuse) before embarking on healthy active living counseling allows appropriate referral to a mental health professional and a greater likelihood of behavior change. Determining existing family strengths and supports helps families meet these goals.

Tabulating all family members' current sedentary behaviors and physical activity through work and play provides a good base from which to start. Sedentary behaviors can be characterized using the SITT formula to get a true estimate of total inactivity. Counseling can begin by helping parents learn how to set limits on screen time (Table 39-2). Activity promotion can start by identifying all barriers the family may have to becoming more active and developing strategies to overcome these obstacles. Subsequent action

**Table 39-1** Physical Activity Recommendations

AGE	SCREEN TIME	PHYSICAL ACTIVITY	SKILLS	SPORTS
<b>Infant and toddler</b>	Discourage all screen media exposure	Toddlers accumulate structured (30 min/day) and unstructured ( $\geq 60$ min/day) exercise by show-and-tell instruction.	Gross motor play. <i>Fun</i> games. Safe exploration and experimentation under adult supervision.	Walking tolerable distances with family members. <i>Fun</i> games focused on gross motor development.
<b>Child (2–5 yr)</b>	<1–2 hr/day total entertainment screen time RECOMMEND quality TV programming. Reduce stroller and car transport.	Accumulate 60 min/day structured and $\geq 60$ min/day unstructured physical activity.	<i>Fun</i> , active play to develop basic fundamental skills. Short, show and tell instruction. No competition.	Running, swimming lessons ( $\geq 4$ yr), tumbling, throwing, and catching. <i>Fun</i> games promoting basic fundamental skills.
<b>Child (6–9 yr)</b>	<1–2 hr/day total entertainment screen time RECOMMEND quality TV programming. Reduce car transportation.	At least 60 min/day moderate to vigorous structured or unstructured PA. Vigorous PA plus muscle and bone strengthening 3 days/wk.	Better motor skills, visual tracking, and balance. Begin transitional skills (fundamental skill in combinations). Short instructions. Little competition.	<i>Fun</i> organized coeducational sports. Flexible rules. Running, swimming, skating, entry-level soccer, skiing, tennis, baseball, martial arts, gymnastics.
<b>Child (10–12 yr)</b>	<1–2 hr/day total entertainment screen time RECOMMEND quality TV programming. Reduce car transportation.	At least 60 min/day moderate to vigorous structured or unstructured PA. Vigorous PA plus muscle and bone strengthening 3 days/wk. Regular flexibility exercises.	Fully developed visual tracking, balance, and motor skills. Improved transitional skills. <i>Fun</i> participation and skills. Some sport tactics and strategy.	<i>Fun</i> team sports by maturity, not age. Basketball, volleyball, hockey, football. Weight training using <i>small</i> free weights; high repetitions, proper technique, and supervision.
<b>Adolescent (13–18 yr)</b>	<1–2 hr/day total entertainment screen time RECOMMEND quality TV programming. Reduce car transportation.	At least 60 min/day moderate to vigorous structured or unstructured PA. Vigorous PA plus muscle and bone strengthening 3 days/wk. Regular flexibility exercises.	<i>Fun</i> preferred variety of activities including friends. Lifelong PA. Weight training: longer sets using heavier weights; fewer repetitions; proper technique and supervision.	Personal fitness, active transport, household chores, workplace-related activity, and competitive and noncompetitive sports. Contact and collision sports based on size and ability, not age. Keep it <i>fun</i> .

Derived from Harris SS, Anderson SJ, eds. *Care of the Young Athlete*. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009; and Hagan JF, Shaw JS, Duncan PM, eds. *Bright Futures Guidelines for Health Supervision of Infants, Children and Adolescents*. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2008.

**Table 39-2** Office-Based Strategies to Reduce Sedentary Activity

SEDENTARY ACTIVITIES	STRATEGIES TO IMPROVE
Establish baseline inventory of televisions (TVs) and computers in bedrooms. Establish baseline level of total daily TV time.	Eliminate TVs, computers, and other screen-related activity from child's bedroom. Children <2 years old should be discouraged from watching all screen-based media.
Take a baseline inventory of other screen-related activity (computer games, interactive cell phones, Internet browsing, chat lines, and related Web sites).	Older children should limit total recreational screen time to <1–2 hr/day.
Make a baseline assessment of meals taken in front of the TV.	Families should avoid eating in front of the TV.

Derived from Perrin EM, Finkle JP, Benjamin JT. Obesity prevention and the primary care pediatrician's office. *Curr Opin Pediatr*. 2007;19(3):354–361; and Harris SS, Anderson SJ, eds. *Care of the Young Athlete*. 2nd Ed. Elk Grove Village, IL: American Academy of Pediatrics; 2010.

**Table 39-3** Office-Based Strategies to Increase Physical Activity

PHYSICAL ACTIVITIES	STRATEGIES TO IMPROVE
<p>Ask about existing family physical activity (PA) routines and other lifestyle-related activities.</p> <p>Tabulate daily PA at home, school, or child care; through work, transportation, recreation, dance, outside play, and organized and unorganized sports.</p> <p>Determine whether adequate parental role modeling is occurring.</p> <p>Determine access to free play, parks, and green spaces.</p> <p>Determine access to sport and recreation programs.</p> <p>Determine child/adolescent access to high-quality school physical education.</p> <p>Establish family and child/adolescent levels of active transportation.</p> <p>Determine whether time barriers exist to PA participation.</p> <p>Determine whether safety barriers exist to PA participation.</p> <p>Determine child/adolescent preferred recreation or sport.</p> <p>Determine whether sport enjoyment and ability are barriers to participation.</p> <p>Determine whether overweight and low fitness are barriers to participation.</p>	<p>Place active living posters and educational information in waiting rooms.</p> <p>Exercise prescription: At least 60 min/day of moderate to vigorous PA plus vigorous PA and bone and muscle strengthening 3 days/wk. Promote outside free play.</p> <p>Post photos or posters in office demonstrating active families.</p> <p>Suggest family-based activities.</p> <p>Identify and promote nearby open spaces and recreation centers. Increase school PA.</p> <p>Promote affordable recreation centers. Increase PA at school.</p> <p>Advocate for compulsory quality daily PE (kindergarten through grade 12) taught by qualified, trained educators.</p> <p>Promote walking and biking, especially to and from school daily.</p> <p>Encourage increasing incidental movement, taking breaks from inactivity, avoiding sitting for long periods, walking throughout the day and taking the stairs.</p> <p>Suggest working out or dancing in the home, a community recreation facility, or school recreation programs—before, during, or after school. Recommend neighborhood supervision for outdoor activities.</p> <p>Recommend preferred sport or recreational activity.</p> <p>Promote enjoyable activities with friend or older buddy (walking, dancing, swimming). Pedometers and exergaming may be motivational.</p> <p>Decrease inactivity. Start slow with 10-minute bouts.</p> <p>Encourage enrolling in an after-school or community program to learn a new skill. Suggest considering water-based sports or strength training, with less focus on competition.</p>

Derived from EM, Finkle JP, Benjamin JT. Obesity prevention and the primary care pediatrician's office. *Curr Opin Pediatr.* 2007;19(3):354–361; and Harris SS, Anderson SJ, eds. *Care of the Young Athlete*. 2nd Ed. Elk Grove Village, IL: American Academy of Pediatrics; 2010.

plans might include encouraging parents to become good role models by becoming more active themselves and including all members of the family—especially with infants, toddlers, or preschoolers in the home; ensuring children play more outside; and supporting children in developmentally and age-appropriate sports and recreational activities using standard safety measures (Table 39-3).

### Child- and Adolescent-Based Strategies

Inactive youth may not be ready to adopt an active lifestyle and may resist change. Addressing underlying bullying, anxiety, depression, and low self-esteem is important before developing an action plan. Motivational interviewing may elicit and strengthen the patient's intrinsic incentive to identify reasons to change behavior and move toward agreed-on goals. (See Chapter 31, Applying Behavior Change Science.) Youth have little concern for any future health benefits of regular PA; hence, emphasis should be placed on the immediate and short-term rewards. These might include having fun, spending time with friends, increasing energy levels and endurance for sports and hobbies, feeling stronger and getting more muscular, and improving self-image.

After a youth is engaged, individual sedentary behavior and PA prescriptions can be written to reflect

agreements reached with the youth and family on incremental steps. Sedentary behaviors can be reduced using the SITT formula—reducing the most common sedentary activity duration and frequency and increasing the number of interruptions during sedentary time. Physical activity and exercise prescriptions can employ the FITT formula described previously. PA prescriptions can specify the frequency (daily), intensity (moderate to vigorous), time (accumulate  $\geq 60$  minutes), and type of activity (variety of primarily aerobic activities with some strengthening and vigorous intensity exercise). Should a pediatrician require assistance with patient evaluation or prescription, consultation with an exercise specialist or certified exercise physiologist may be useful. Specific prescriptions ideally promote the child's favorite type of PA; activities that are integrated into daily activities in ways that make them fun, easy, natural, and desirable; activities with family and friends; unstructured and structured play; and sports that promote equal participation, enjoyment, safety, and nonviolence.

### Physician-Specific Strategies

Physicians can use motivational interviewing techniques to praise all patients and families for positive changes, no matter how small, and to promote PA for patients with underlying chronic illnesses. Consultation



with a sports medicine physician or specialist may be needed to determine what types of activities are appropriate. Most overweight children can be encouraged to partake in activities that take advantage of their muscle strength, such as water-based sports and strength training, rather than those that require weight bearing (eg, jumping, jogging). Physicians and their professional organizations can advocate for comprehensive school health programs; quality daily PE in schools; the protection of children's recess time, extra-curricular PA programs, and unstructured PA before, during, and after school hours; safe parks and playgrounds; affordable recreation center programs; urban planning promoting active transportation; and reasonable screen-time limits for children of all ages.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *5210 Pediatric Obesity Clinical Decision Support Chart* (flip chart), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *ACSM's Behavioral Aspects of Physical Activity and Exercise* (book), American College of Sports Medicine ([www.acsmstore.org](http://www.acsmstore.org))
- *Active Healthy Kids Canada* (Web site), ([www.activehealthykids.ca](http://www.activehealthykids.ca))
- *The AHA's Recommendations for Physical Activity in Children* (Web page), American Heart Association ([www.heart.org/HEARTORG/GettingHealthy/Physical-Activity-and-Children\\_UCM\\_304053\\_Article.jsp](http://www.heart.org/HEARTORG/GettingHealthy/Physical-Activity-and-Children_UCM_304053_Article.jsp))
- *Caring for Kids* (Web page), Canadian Paediatric Society ([www.caringforkids.cps.ca](http://www.caringforkids.cps.ca))
- *Effectiveness of Exercise-Referral Schemes to Promote Physical Activity in Adults: Systematic Review* (article), *British Journal of General Practice*, Vol 57, Issue 545, 2007
- *Fitness* (Web page), American Academy of Pediatrics ([www.healthychildren.org/english/healthy-living/fitness/Pages/default.aspx](http://www.healthychildren.org/english/healthy-living/fitness/Pages/default.aspx))
- *Global Recommendations on Physical Activity for Health* (Web page), World Health Organization ([www.who.int/dietphysicalactivity/factsheet\\_recommendations/en](http://www.who.int/dietphysicalactivity/factsheet_recommendations/en))
- *Let's Get Moving: A Systematic Pathway For the Promotion of Physical Activity In a Primary Care Setting* (article), *Global Health Promotion*, Vol 18, Issue 1, 2011
- *Let's Move!* (Web site), ([www.letsmove.gov](http://www.letsmove.gov))
- *Physical Activity: How Much Physical Activity Do Children Need?* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/physicalactivity/everyone/guidelines/children.html](http://www.cdc.gov/physicalactivity/everyone/guidelines/children.html))

## AAP POLICY

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American Academy of Pediatrics Council on Sports Medicine and Fitness and Council on School Health. Active healthy living: prevention of childhood obesity through increased physical activity. *Pediatrics*. 2006;117(5):1834–1842. Reaffirmed May 2009 ([pediatrics.aappublications.org/content/117/5/1834](http://pediatrics.aappublications.org/content/117/5/1834))

## SUGGESTED READINGS

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## Chapter 40 ORAL HEALTH

Rebecca L. Slayton, DDS, PhD

## BACKGROUND

Oral health is a vital component of overall health. In 2000, at the first Surgeon General's Conference on Oral Health, the participants concluded that "dental caries is the single most common chronic disease of childhood" and that there are significant demographic disparities in dental disease, with poor children and ethnic minorities being twice as likely to be affected and much more likely to have untreated disease. A recent follow-up to the Surgeon General's report stated that although there have been significant advances in the science and technology related

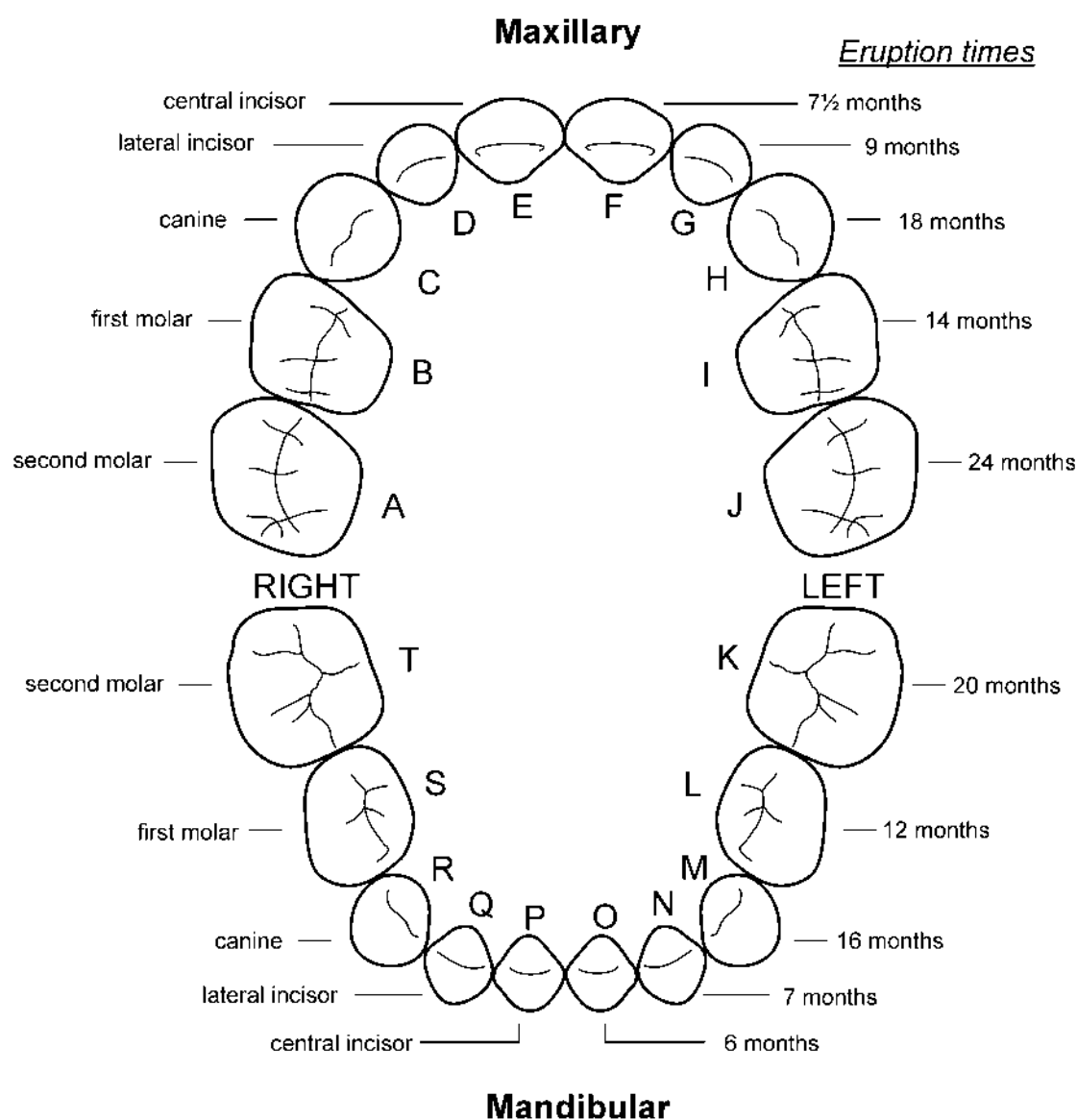
to caries prevention, very little progress has been made in dental disease prevalence in young children. At the National Oral Health Summit in 2008, and in the subsequent Special Issue on Children's Oral Health published in *Academic Pediatrics*, there was a recommendation for a mandate to prevent dental disease in the nation's children and to develop a shared responsibility for children's oral health among dentists, physicians, and other health professionals. The goal of this chapter is to provide pediatricians and other health professionals with the necessary tools to educate families regarding the prevention of dental caries, dental trauma, and other diseases of the oral cavity.

## DENTAL DEVELOPMENT

Oral health refers to the health of soft tissues such as oral mucosa and gingiva, as well as hard tissues such as teeth and supporting bone. The most common

diseases that affect children's oral health are dental caries and gingivitis. Oral structures are constantly changing throughout development until the child's growth is complete as a young adult. Teeth begin to erupt into the mouth at approximately 6 months of age, with the completion of the primary dentition (10 teeth in each arch) between 2 and 3 years of age. The primary teeth are replaced by permanent teeth between the ages of 6 and 12 years. A complete permanent dentition consists of 32 teeth. Eruption times and names of primary and permanent teeth are summarized in Figure 40-1 and Figure 40-2. There is some variability in these times, with females tending to be ahead of males and some racial groups being ahead of others.

The crown of the tooth is composed of enamel, dentin, and pulp tissue (containing blood vessels and nerves), whereas the root of the tooth is composed of cementum, dentin, and pulp tissue. The periodontal



**Figure 40-1** Primary tooth names and timing of tooth eruption.

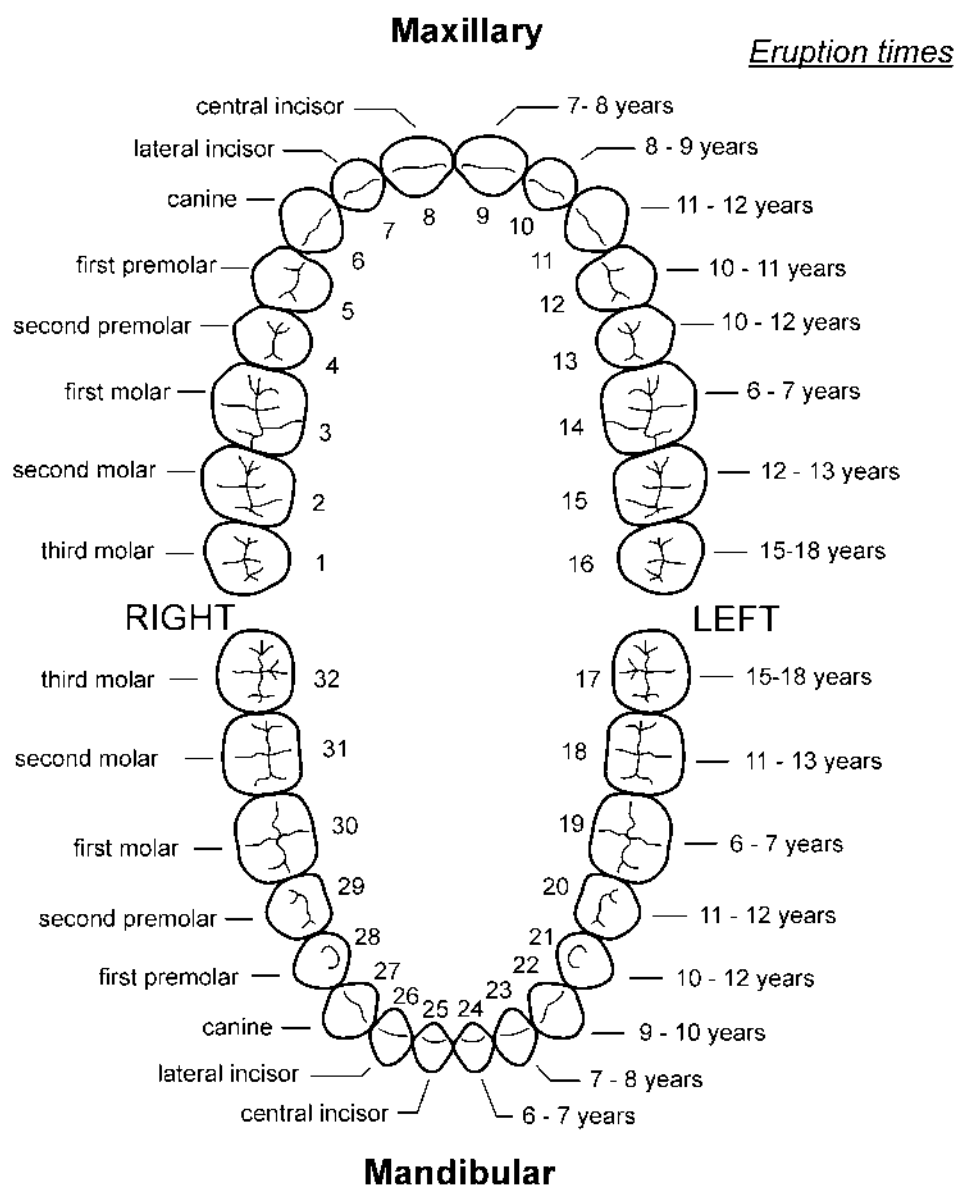
ligament (a group of connective tissue fibers) connects the root of the tooth to the alveolar bone in the socket. Figure 40-3 illustrates the structures present in a fully developed tooth.

### Diseases of the Oral Cavity

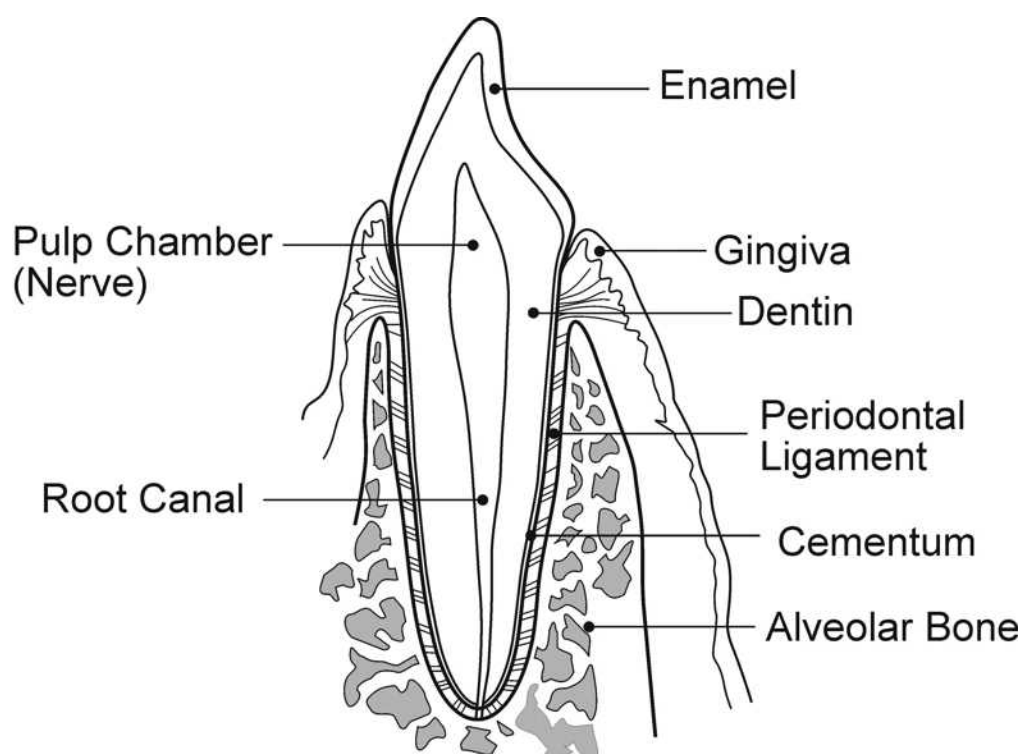
#### Dental Caries—Etiology and Prevalence

Dental caries is one of the most common chronic diseases of childhood. It occurs in children and adults of all socioeconomic classes and in every country around the world. In the United States, disparities in oral health have led to substantially higher average disease prevalence among children in poverty and people of color. The essential components needed to initiate the caries process include a tooth, cariogenic (acid-producing) bacteria such as the mutans streptococci, fermentable carbohydrates, and time. These factors are moderated

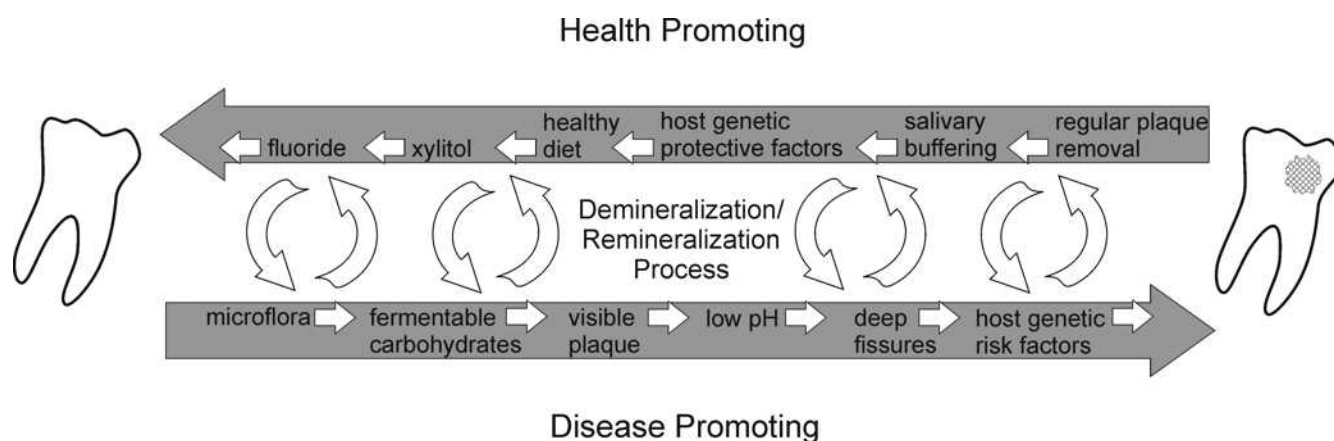
by exposure to fluoride and regular oral hygiene procedures to remove food and plaque from the oral cavity as well as the individual's genetic makeup (which can either increase or decrease susceptibility) (Figure 40-4). Cariogenic bacteria are generally transmitted from parent or caregiver to the infant before tooth eruption. Because in most cases the mother is the primary caregiver, she is usually the source of this bacteria. The mutans streptococci colonize tooth surfaces and form a complex biofilm. This group of bacteria include *Streptococcus mutans*, *S. sobrinus*, *S. sanguinis*, *S. salivarius*, and *S. milleri*. These bacteria convert dietary sugars into acid, which over time cause demineralization and cavitation of the tooth surface, creating a cavity. Once the cavity progresses through the enamel, it destroys the dentin and then infects the pulp tissue, resulting in abscess formation. In primary teeth, this process can



**Figure 40-2** Permanent tooth names and timing of tooth eruption.



**Figure 40-3** Anatomy of a tooth.



**Figure 40-4** Diagram of caries process.

occur relatively quickly, necessitating the extraction of abscessed teeth in children as young as 1 year of age.

When cavities occur in children younger than 6 years, the disease process is referred to as *early childhood caries* (ECC). This term is used in place of “nursing caries,” “baby bottle tooth decay,” and “bottle rot” because there are multiple factors that contribute to ECC and the former names implied one etiology. ECC interferes with a child’s ability to eat, sleep, and learn. It is expensive to treat because it frequently requires treatment under general anesthesia in a hospital setting because of a young child’s inability to cooperate

for care in the traditional dental setting. Although caries is decreasing in some age groups, in the most recent National Health and Nutrition Examination Survey (NHANES), the prevalence of caries in 2- to 5-year-olds had increased. This is a disease in which early detection and risk assessment have the potential to prevent significant morbidity in young children.

#### **Gingivitis and Periodontal Disease—Etiology and Prevalence**

Gingivitis is an inflammation of the gums caused by both local and systemic factors. The most common



### BOX 40-1 Systemic Conditions Associated With Gingivitis or Premature Loss of Primary Teeth in Children

Localized or generalized periodontitis  
Fibrous dysplasia  
Papillon-Lefèvre syndrome  
Hypophosphatasia  
Leukemia  
Chédiak-Higashi syndrome  
Cyclic neutropenia  
Leukocyte adhesion deficiency  
Langerhans cell histiocytosis  
Letterer-Siwe disease  
Hand-Schüller-Christian disease  
Eosinophilic granuloma

local factor is dental plaque. Dental plaque forms on tooth surfaces as a result of the metabolic by-products of oral bacteria. It can be removed by tooth brushing and flossing but begins forming again almost immediately. There are more than 700 microbial species that inhabit the oral cavity, and together they form a complex biofilm. In the mouth of children with good oral health, there is a microbial homeostasis that maintains stability within the composition of the plaque. When this homeostasis is disrupted, oral diseases are the result (both caries and gingivitis). Plaque that is left in place for some length of time causes gingival inflammation. When combined with salivary proteins, the plaque becomes mineralized and turns into calculus (tartar) and cannot be removed with tooth brushing. Once calculus forms on the teeth, it must be removed by a dentist or dental hygienist. Calculus causes additional inflammation of the gingival tissue, may cause gingival recession, and eventually may lead to loss of the alveolar bone supporting the tooth. Periodontal disease is described as loss of bone between and around the teeth. Bone loss leads to mobility of the teeth and eventually to tooth loss.

The etiology of periodontal disease is multifactorial and includes local factors and systemic factors. Local factors include plaque and calculus that lead to inflammation of the gums and supporting tissues, as well as susceptibility to microbes, primarily *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis*. Systemic factors include variations in specific genes involved with inflammatory response to pathogens and genetic syndromes affecting systemic immunity and metabolism. Periodontal disease is a relatively uncommon finding in children. Children who present with severe inflammation of the gingival tissues, premature loss of primary teeth, gingival recession, or alveolar bone loss should be evaluated for possible systemic conditions to explain these findings. Systemic conditions that are associated with periodontal disease in young children are summarized in Box 40-1.

### Traumatic Injuries—Prevalence, Causes

Thirty percent to 40% of children suffer trauma to the primary dentition. Most injuries to primary teeth occur between 18 and 30 months of age when toddlers are learning to walk. Because more than 70% of the injuries to abused children occur in the head and neck region, health care providers should be attentive to injuries in which the family's description of the injury's cause does not fit its appearance.

Twenty-five percent of children suffer trauma to permanent teeth. Most of these injuries involve the maxillary central incisors. When incisors have excessive flaring (overjet >2 mm), there is an increased risk for trauma. In school-aged children, dental trauma is 2 times more common in boys than in girls.

Dental injuries include concussion (or bruising) of the teeth, fracture of the crown, fracture of the root, luxation of the tooth (lateral or intrusive), and avulsion of the tooth from the socket. Adept initial management and referral by the primary care physician may prevent complications and tooth loss. A description of each injury and treatment recommendation for primary and permanent teeth are provided in Table 40-1.

## PEDIATRICIANS AND ORAL HEALTH PROMOTION

Surveys of practicing pediatricians indicate that a small percentage recognize and adhere to the American Academy of Pediatrics (AAP) recommendation of a first dental visit at 12 months of age. In these studies, an even smaller percentage thought that fluoride varnish application should be part of a well-child visit. Lack of oral health training is routinely cited as a barrier to performing caries risk assessment and applying fluoride varnish. Perceived barriers to referring patients to a dental home include finding dentists who are willing to treat young children or children who are uninsured or have Medicaid or State Children's Health Insurance Program (SCHIP). Among pediatric residents, most were dissatisfied with the quantity of oral health training they received during their residency and were not confident in their ability to identify enamel demineralization. These studies point to the need for increased oral health training in residency programs as well as continuing education focused on oral health promotion for practicing pediatricians.

## OFFICE-BASED HEALTH PROMOTION STRATEGIES

Dental caries prevention should start before eruption of the first tooth and ideally before the child is born by addressing maternal oral health. Pediatricians are in an ideal position to counsel families on good oral health and caries prevention because they see infants for at least 5 well-child visits before any of the child's teeth have erupted. Anticipatory guidance during this time period should be focused on nutrition and on educating families about the importance of healthy primary teeth to prevent cavities and the resulting pain and infection. During this time, it is also important to counsel parents about the importance of their

**Table 40-1** Traumatic Dental Injuries—Description and Treatment

PRIMARY DENTITION	DESCRIPTION	TREATMENT
Concussion	Slight mobility, bleeding around gums	Observe, soft foods for 1 week, radiograph to rule out root fracture
Luxation	Displacement of tooth laterally or incisally, mobility	Reposition tooth or extract, do not splint
Intrusion	Displacement of tooth apically, may appear to be missing	Make occlusal radiograph, observe and allow to reerupt, extract if alveolar plate is compromised
Simple crown fracture	Fracture of tooth leaving either enamel or dentin exposed, may or may not be mobile	Restore tooth, smooth sharp edges, radiograph to rule out root fracture
Complicated crown fracture	Fracture of tooth leaving pulp tissue exposed	Pulp treatment, restore or extract tooth, observe for infection
Root fracture	Tooth is fractured below the gum line, moderate to severe mobility	Occlusal radiograph, extract if root fracture is in middle or cervical third of root
Avulsion	Tooth is out of the socket	Do not replant, make radiograph to rule out intrusion

PERMANENT DENTITION	DESCRIPTION	TREATMENT
Concussion	Slight mobility, bleeding around gums	Observe, soft foods for 1 week, radiograph to rule out root fracture
Luxation	Displacement of tooth laterally or incisally, mobility	Radiograph, reposition tooth, splint for 2 weeks
Intrusion	Displacement of tooth apically, may appear to be missing	Make occlusal radiograph, observe and allow to reerupt, surgical or orthodontic repositioning, root canal treatment
Simple crown fracture	Fracture of tooth leaving either enamel or dentin exposed, may or may not be mobile	Restore tooth, smooth sharp edges, radiograph to rule out root fracture
Complicated crown fracture	Fracture of tooth leaving pulp tissue exposed	Pulp treatment, restore tooth, observe for infection, may require root canal treatment
Root fracture	Tooth is fractured below the gum line, moderate to severe mobility	Occlusal radiograph, splint, may require root canal treatment, if in cervical third, may need to extract
Avulsion	Tooth is out of the socket	Replant within 30 minutes or place in recommended transport medium: Hank's balanced saline, cold milk, saline. Radiograph, replant and splint ASAP. Systemic antibiotics, soft diet, chlorhexidine, close follow-up

own oral health to minimize transmission of cariogenic bacteria to their child.

Caries risk assessment, performed early, informs recommendations that are individualized for each child. Many of the risk factors for caries are present at birth and can be ascertained by asking a few focused questions of the parents or caregivers. Before eruption of the teeth, the best predictors of dental caries in children are a family history of caries (parent or sibling) and being in a family with low socioeconomic status.

As soon as teeth erupt, they become susceptible to colonization by oral bacteria. Prevention of cavities requires regular disruption of the plaque biofilm by

brushing teeth and regular exposure of teeth to topical fluoride from toothpaste or, optimally fluoridated water. Because the saliva is capable of buffering acid in the oral cavity, the damaging effects of acid are minimized by reducing the frequency of intake of dietary sugars, not just the quantity. This is why caregivers should be discouraged from putting a child to bed with a bottle or sippy cup and why sugary snacks are best consumed as part of a meal rather than distributed throughout the day. Currently, the most accurate predictor of a child's risk for caries once teeth have erupted is past caries experience. Oral health promotion, especially in the area of dental caries prevention, is most successful if it is initiated before the occurrence of cavities. Early

clinical signs of caries risk, once teeth have erupted, are visible plaque on primary incisors and white spot lesions (demineralized areas) on maxillary primary incisors.

### Use of Fluoride Varnish

Fluoride varnish is a topical agent containing 5% sodium fluoride in a base that adheres to teeth. It is applied to teeth with a small, disposable brush. This form of fluoride is more easily tolerated by young children than the gels and foams that are applied in a tray. Although it is more concentrated, the risk for ingestion is low because of its adhesion to the tooth surface. As of August 2012, 44 state Medicaid programs reimburse primary care providers for preventive oral health services. This almost always includes the application of fluoride varnish and in some states also includes reimbursement for oral health education.

### Referral Criteria—When and to Whom

Children identified to be at high risk for dental caries and children with obvious cavities should be referred to a pediatric or general dentist for management of the disease process or restoration of tooth structure. In addition, it is recommended that all children have a dental home—a regular source of dental care—by 1 year of age.

Gingivitis is a fairly common finding in children and becomes even more common in adolescents. In most studies, about 50% of preschool-aged children and 100% of adolescents are found to have gingivitis. Inflammation of the gingival tissues is associated with plaque on the tooth surface, calculus, or hormonal changes that occur during adolescence and pregnancy. There is also increased risk for gingivitis during orthodontic treatment because the brackets and appliances make oral hygiene more challenging. Gingivitis may also be associated with systemic factors as discussed above and listed in Box 40-1.

Gingivitis can be improved within a few days by regular tooth brushing to remove plaque, scaling by a dentist or dental hygienist to remove calculus, flossing to remove plaque and food particles between teeth, or antimicrobial mouth rinses containing chlorhexidine. When gingivitis is present with no obvious cause, other systemic causes should be investigated.

Periodontal disease is fairly uncommon in children and is seen more commonly in adolescents and adults. In periodontal disease, there is loss of attachment of the periodontal tissues to the tooth at 1 or more sites. This may occur in about 20% of adolescents between 14 and 17 years of age. Early signs of periodontal disease can be reversed with good oral hygiene (brushing, flossing, scaling, antibacterial rinses), as with gingivitis. Smoking is a major risk factor for periodontal disease, so smoking cessation should be recommended for this as well as other health reasons. Diabetes is also a significant risk factor for periodontal disease, so in patients with diabetes, early signs of periodontal involvement should be addressed with aggressive preventive regimens. Periodontal disease may be localized, affecting a few teeth, or generalized, affecting all

teeth. For aggressive forms of periodontal disease, systemic antibiotics are frequently indicated, as is local débridement. In young children, symptoms of periodontal disease are rare and should be thoroughly investigated and diagnosed to rule out other systemic diseases as mentioned above.

### Differential Diagnosis

A common instrument used to diagnose gingivitis or periodontal disease is the periodontal probe. This is a blunt-ended, narrow metal tool with marks every few millimeters along its length to measure the depth of the pocket formed between the gums and the tooth. A normal pocket depth is less than 3 mm. The specific diagnosis of gingivitis or periodontal disease is made based on clinical findings such as bleeding on probing, probing depth ( $>3$  mm), extent of clinical attachment of the gingival tissues, and bone loss. Other findings include medical and dental history and presence of signs and symptoms such as plaque, calculus, pain, ulceration, or edema. In children, premature loss of primary teeth warrants further investigation to rule out systemic diseases as the cause. In both children and adolescents, significant gingival inflammation or gingival enlargement should also be investigated.

### Referral Criteria

Children and adolescents with significant gingival inflammation or premature tooth loss should be evaluated by their physician for possible systemic diseases (described in Box 40-1). In cases in which there is obvious plaque and poor oral hygiene, referral to a pediatric or general dentist is recommended.

### Anticipatory Guidance

Guidance for oral health promotion in each pediatric age group is summarized in Table 40-2 and can be found in the guidelines of the American Academy of Pediatric Dentistry (AAPD).

## IMPLICATIONS FOR PRACTICE

### Caries Risk Assessment Protocol

The caries risk in a child changes as new teeth erupt into the mouth, as the child starts selecting the foods and beverages he or she consumes, and as the child enters school where eating behaviors are not monitored as closely by parents. An assessment of a child's caries risk should be completed at each visit to take these changing risk factors into account. There is always a balance of risk and protective factors that must be considered. Disease results when the balance shifts in favor of the caries risk factors. Factors that contribute to caries can be determined from an interview with the parent combined with a clinical examination of the child. The caries risk assessment form developed by the AAPD and available as part of their guidelines (Figure 40-5) is a tool that can be used to assess a child's caries risk. Once the caries risk is determined, a management plan can be developed. This should ideally be a collaboration between the child's pediatrician and dentist so that the family is receiving the same message from both health care providers.

**Table 40-2** Oral Health Anticipatory Guidance

ACTION	ASSESSMENT
<b>4 MONTHS</b>	
Assess maternal oral health	Encourage regular dental care. Recommend use of xylitol products to reduce oral bacteria
Perform caries risk assessment	Siblings or parents with history of caries
Discuss dental home	First dental visit by 1 year
Feeding habits	No bottle to bed
Oral hygiene	Wipe gums with clean cloth. Parents brush own teeth with fluoride toothpaste
<b>6–12 MONTHS</b>	
Assess maternal oral health	Encourage regular dental care. Recommend use of xylitol products to reduce oral bacteria
Caries risk assessment	Is there visible plaque on teeth? Are there white spots on teeth? Is there a familial history of caries?
Assess fluoride exposure	Evaluate all sources of fluoride in the diet including water, formula, toothpaste
Recommend fluoride toothpaste	Use a smear of toothpaste 2 times daily; parents assist with brushing
Establish dental home	Refer to pediatric or general dentist
Counsel on injury prevention	Protect from stairs, coffee tables, sharp objects
Feeding habits	Limit juice, no bottle to bed
<b>12–36 MONTHS</b>	
Assess maternal oral health	Encourage regular dental care. Recommend use of xylitol products to reduce oral bacteria
Repeat caries risk assessment	Is there visible plaque on teeth? Are there white spots on teeth? Is there a familial history of caries?
Assess fluoride exposure	Evaluate all sources of fluoride in the diet including water, formula, toothpaste
Recommend fluoride toothpaste	Use a smear of toothpaste 2 times daily; parents assist with brushing
Apply fluoride varnish	2–3 times annually for moderate-risk to high-risk children
Verify dental home	Refer to pediatric or general dentist if not already established
Counsel on injury prevention	Protect from stairs, coffee tables, sharp objects
Feeding habits	Transition from bottle to cup, limit juice, no bottle to bed, encourage healthy snacks
Oral habits	Discuss weaning from pacifier or stopping digit habit
<b>3–6 YEARS</b>	
Assess maternal oral health	Encourage regular dental care. Recommend use of xylitol products to reduce oral bacteria
Repeat caries risk assessment	Is there visible plaque on teeth? Are there white spots on teeth? Is there a familial history of caries? Are there cavities or fillings present?
Assess fluoride exposure	Evaluate all sources of fluoride in the diet including water, formula, toothpaste
Recommend fluoride toothpaste	Use a pea-sized amount of toothpaste 2 times daily; parents assist with or supervise brushing
Apply fluoride varnish	2–3 times annually for moderate-risk to high-risk children
Verify dental home	Refer to pediatric or general dentist if not already established
Counsel on injury prevention	Encourage bike helmets, mouth guard for sports
Feeding habits	Limit juice, avoid soda pop, no bottle to bed, encourage healthy snacks, avoid sweetened between meal snacks
Oral habits	Recommend weaning from pacifier or stopping digit habit
Cavity prevention	Recommend xylitol products for high-risk children
<b>6–12 YEARS</b>	
Repeat caries risk assessment	Is there visible plaque on teeth? Are there white spots on teeth? Is there a familial history of caries? Are there cavities or fillings present?
Assess fluoride exposure	Evaluate all sources of fluoride in the diet including water, formula, toothpaste
Recommend fluoride toothpaste	Use a pea-sized amount of toothpaste 2 times daily; parents supervise brushing; flossing once daily
Apply fluoride varnish	2–3 times annually for moderate-risk to high-risk children
Verify dental home	Refer to pediatric or general dentist if not already established
Counsel on injury prevention	Encourage bike helmets, mouth guard for sports
Eating habits	Limit juice and sports drinks, avoid soda pop, encourage healthy snacks, avoid sweetened between meal snacks
Intraoral/perioral piercing	Provide counseling on risks associated with piercing
Substance abuse	Provide counseling on oral health and smoking/smokeless tobacco
Cavity prevention	Recommend xylitol products for high-risk children. Recommend chlorhexidine rinse for gingivitis



Table 40-2

Oral Health Anticipatory Guidance—cont'd

ACTION	ASSESSMENT
<b>12 YEARS AND OLDER</b>	
Repeat caries risk assessment	Additional risk if in orthodontic treatment
Recommend fluoride toothpaste	Use a pea-sized amount of toothpaste 2 times daily. Flossing once daily. For high-risk patients, recommend 5,000 ppm toothpaste
Apply fluoride varnish	2–3 times annually for moderate-risk to high-risk children
Verify dental home	Refer to pediatric or general dentist if not already established
Counsel on injury prevention	Encourage bike helmets, mouth guard for sports
Eating habits	Limit juice and sports drinks, avoid soda pop, encourage healthy snacks, avoid sweetened between-meal snacks
Intraoral/perioral piercing	Provide counseling on risks associated with intraoral piercing
Substance abuse	Provide counseling on oral health and smoking/smokeless tobacco
Cavity prevention	Recommend xylitol products for high-risk children. Recommend chlorhexidine rinse for gingivitis
<b>CHILDREN AND YOUTH WITH SPECIAL HEALTH CARE NEEDS</b>	
Establish dental home	Refer to pediatric or general dentist as soon as possible
Medication use	Counsel regarding oral side effects of medications—caries risk with high sucrose medications or xerostomia
Apply fluoride varnish	2–3 times annually for moderate-risk to high-risk children
Eating habits	Limit juice and sports drinks, avoid soda pop, encourage healthy snacks, avoid sweetened between-meal snacks
Oral hygiene	Often dependent on caregiver. Use a pea-sized amount of toothpaste 2 times daily. Flossing once daily
Injury prevention	Increased risk for children with poor coordination or limited ambulation

Factors	High Risk	Low Risk
<b>Biological</b>		
Mother/primary caregiver has active cavities	Yes	
Parent/caregiver has low socioeconomic status	Yes	
Child has >3 between meal sugar-containing snacks or beverages per day	Yes	
Child is put to bed with a bottle containing natural or added sugar	Yes	
Child has special health care needs	Yes	
Child is a recent immigrant	Yes	
<b>Protective</b>		
Child receives optimally-fluoridated drinking water or fluoride supplements		Yes
Child has teeth brushed daily with fluoridated toothpaste		Yes
Child receives topical fluoride from health professional		Yes
Child has dental home/regular dental care		Yes
<b>Clinical Findings</b>		
Child has white spot lesions or enamel defects	Yes	
Child has visible cavities or fillings	Yes	
Child has plaque on teeth	Yes	

Circling those conditions that apply to a specific patient helps the health care worker and parent understand the factors that contribute to or protect from caries. Risk assessment categorization of low or high is based on preponderance of factors for the individual. However, clinical judgment may justify the use of one factor (eg, frequent exposure to sugar containing snacks or beverages, visible cavities) in determining overall risk.

Overall assessment of the child's dental caries risk: High ☐ Low ☐

**Figure 40-5** Caries-risk assessment form for 0-3 year olds (for physicians and other non-dental health care providers). (Reprinted with permission from American Academy of Pediatric Dentistry. Guideline on caries-risk assessment and management for infants, children, and adolescents. *Pediatr Dent*. 2013;35(5):E157–E164.)

### Anticipatory Guidance for Oral Health

The *Bright Futures Guidelines for Health Supervision of Infants, Children, and Adolescents* includes extensive anticipatory guidance recommendations that coincide with regular well-child visits from birth through late adolescence. At most visits, there is an oral health component to the physical assessment. At each visit, it is important to reassess the child's risk for caries and to address the oral health of the parent. In addition to the recommendations for oral health in the *Bright Futures Guidelines*, health care professionals should make every attempt to include the topics listed in Table 40-2 at each visit.

### Motivational Interviewing Focused on Oral Health

Motivational interviewing is a behavior modification technique that has been used successfully to change habits and behaviors that are detrimental to health, such as smoking, drinking, and illicit drug use (see Chapter 46, Effective Communication Strategies). Recently, this technique has been shown to be effective at changing oral health behaviors, particularly as they relate to the oral health of children. Studies using motivational interviewing for the improvement of oral health in children focus on attitudes and behaviors of parents or caregivers such as putting water in the baby's bottle instead of juice or using a smear of toothpaste when brushing their baby's teeth. Studies using motivational interviewing to improve the oral health of high-risk children have shown significant improvements in caries incidence compared with children in a control group who received education through printed materials without motivational interviewing. This technique holds great promise for the promotion of oral health in young children.

### SUMMARY

The promotion of oral health in children and the prevention of chronic, transmissible diseases such as dental caries are the responsibility of all health care professionals who interact with children and should be incorporated into the pediatric well-child visit whenever possible.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *First Steps to a Healthy Smiles* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *A Guide to Children's Dental Health* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *How to Prevent Tooth Decay in Your Baby* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Mouth Healthy* (Web page), American Dental Association (www.mouthhealthy.org/en)
- *Oral Health* (Web page), American Academy of Pediatrics (www.healthychildren.org/English/healthy-living/oral-health/Pages/default.aspx)

- *Oral Health Fact Sheets* (Web page), California Dental Association (www.cda.org/public-resources/patient-fact-sheets)
- *Oral Health Practice Tools* (Web page), American Academy of Pediatrics (www2.aap.org/compmpeds/doch/oralhealth/PracticeTools.html)
- *Patients with Special Needs* (Web page), University of Washington School of Dentistry (dental.washington.edu/departments/omed/decod/special\_needs\_facts.php)
- *What is a Pediatric Dentist?* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)

### Medical Decision Support

- *Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents*, 3rd ed (book), American Academy of Pediatrics (brightfutures.aap.org)
- *Oral Health Risk Assessment Tool* (tool), American Academy of Pediatrics (www2.aap.org/oralhealth/RiskAssessmentTool.html)
- *Pediatric Guide to Children's Oral Health Flip Chart and Reference Guide* (Web page), American Academy of Pediatrics (www2.aap.org/compmpeds/doch/oralhealth/PediatricGuides.html)
- *Protecting All Children's Teeth (PACT): A Pediatric Oral Health Training Program for Physicians* (online program), American Academy of Pediatrics (www2.aap.org/ORALHEALTH/pact/index.cfm)

### Practice Management and Care Coordination

- *Fluoride Varnish Resource Guide* (manual), National Maternal and Child Oral Health Resource Center (www.mchoralhealth.org/PDFs/ResGuideFlVarnish.pdf)
- *Oral Health Practice Tools* (Web page), American Academy of Pediatrics (www2.aap.org/compmpeds/doch/oralhealth/PracticeTools.html)
- *State Information and Resource Map* (Web page), American Academy of Pediatrics (www2.aap.org/compmpeds/doch/oralhealth/State.html)

### AAP POLICY

- American Academy of Pediatrics Section on Pediatric Dentistry and Oral Health. Preventive oral health intervention for pediatricians. *Pediatrics*. 2008;122(6):1387-1394 (pediatrics.aappublications.org/content/122/6/1387)
- American Academy of Pediatrics Section on Pediatric Dentistry. Oral health risk assessment timing and establishment of a dental home. *Pediatrics*. 2003;111(5):1113-1116. Reaffirmed May 2009 (pediatrics.aappublications.org/content/111/5/1113)
- Norwood KW, Slayton RL; American Academy of Pediatrics Council on Children with Disabilities, Section on Oral Health. Oral health care for children with developmental disabilities. *Pediatrics*. 2013;131(3):614-619 (pediatrics.aappublications.org/content/131/3/614)

### SUGGESTED READINGS

- Berg JH, Slayton RL, eds. *Early Childhood Oral Health*. Ames, IA: Wiley-Blackwell; 2008
- Mouradian WE, Slayton RL, eds. *Children's Oral Health*. *Acad Pediatr*. 2009;9(6, theme issue):371-476. Available

at: [www2.aap.org/oralhealth/SummitOralHealth.html](http://www2.aap.org/oralhealth/SummitOralHealth.html). Accessed September 8, 2015

*Topical Fluoride Recommendations for High Risk Children: Development of a Decision Support Matrix. Recommendations from MCHB Expert Panel, 2007.* Washington DC: Altarum Institute; 2007. Available at: [www.mchoralhealth.org/PDFs/opicalFluorideRpt.pdf](http://www.mchoralhealth.org/PDFs/opicalFluorideRpt.pdf). Accessed September 8, 2015

**Chapter 41**  
**HEALTHY SEXUAL  
DEVELOPMENT AND  
SEXUALITY**

Leena Shrivastava Dev, MD; Mario Cruz, MD

Anticipatory guidance offers pediatricians the opportunity to address educational needs and areas of concern for patients and their families. One area that often is not

routinely covered is sexuality and sexual health. This chapter focuses on the importance of addressing sexual health issues and concerns during well-child and adolescent visits, and of encouraging parents and patients to learn how to discuss this topic with their physician and with each other. Throughout this chapter there are examples of various questions that may come up during a pediatric visit. Some of these issues are addressed in this chapter, whereas others are discussed in more detail in other chapters in this textbook. Issues specific to lesbian, gay, bisexual, and transgender youth are addressed elsewhere (see Chapter 76, Lesbian, Gay, and Bisexual Youth, and Chapter 156, Gender Expression and Identity Issues).

The concepts of sexuality and sexual health refer not only to the sexual organs and their functions but also to a child's identity, gender roles, sexual orientation, emotional health, and physical safety. Children ideally learn about themselves and their sexuality and sexual health from infancy through adolescence, at the appropriate developmental level. It is the physician's role to assist them in achieving this understanding. Table 41-1 describes developmental theories and their application to child and adolescent sexuality.

Table 41-1 Developmental Theories and Their Application to Sexuality		
ERICKSON	PIAGET	APPLICATION
<b>Trust vs Mistrust (Infancy)</b> Basic trust learned by having needs met	<b>Sensorimotor (Birth–2 years)</b> Coordinating sensations and perceptions with own actions	Learning to trust people because basic needs are satisfied Learning to trust oneself and own body as control over body movements is developed Beginning understanding of relationship between actions and consequences, eg, pleasure sensations elicited when genitals are touched Intense curiosity about own body
<b>Autonomy vs Shame (Toddler)</b> Gaining independent control over own body	<b>Preoperational (2–7 years)</b> Symbolic system enlarges Here-and-now reasoning only Egocentric—see only own perspective	Knowing and interested in genital differences between boys and girls Developing love–hate feelings for parent of opposite sex with fear of fulfilling sexual fantasies Imitating behavior strengthens sense of male or female
<b>Initiative vs Guilt (Preschool)</b> Initiating actions to overcome feelings of powerlessness Oedipal conflict	<b>Concrete Operations (7–11 years)</b> Increasing intellectual capacity Able to think from different perspectives and about 2 or more aspects of a problem, but relies on concrete events to think in this way	Curious, with some ideas and questions about where babies come from Period of expanding factual knowledge about oneself, including physical aspects, and the world around.
<b>Industry vs Inferiority (Middle Childhood)</b> Developing feelings of competency in intellectual and physical skills	<b>Formal Operations (11–14 years)</b> Develops abstract thinking Able to conceptualize Able to use symbols and logic	Compares accomplishment to peers Discovering one's identity through experimentation with ideas, behavior, and relationships, including the same and opposite sex, without having to commit oneself Moving toward acceptance of consequences for behavior and fitting into society Peer groups and youthful romances serve as mechanism for identity development Being able to identify sexual needs and establish healthy intimate relationships
<b>Identity vs Role Confusion (Puberty and Adolescence)</b> Establishing one's personal identity through socially accepted vocational decisions		
<b>Intimacy vs Isolation (Young Adulthood)</b> Ability to establish close, intimate relationships with the opposite sex that include openness, sharing, trust, self-abandon, and commitment		

Adapted with permission from Smith M. Pediatric sexuality: promoting normal sexual development in children. *Nurse Practitioner*. 1993;18(8):37–44.

Sexuality and sexual health are generally perceived as sensitive and private issues. It is essential for the pediatrician to create a sense of trust with the family and patient. Communication about this topic can be effective only after families have developed confidence in their physician. Pediatricians should be honest with the family and themselves about their comfort and expertise in the realm of sexual health. Furthermore, the pediatrician needs to be capable of discussing sexuality and sexual health without bias. This can include but is not limited to homosexuality, masturbation, gender identity, and adolescent sexual behavior. Pediatricians who are managing a sexuality or sexual health issue that is beyond their comfort level or expertise can seek assistance from a colleague or make referrals to an appropriate physician, therapist, or agency.

In addition to discussing sexual health and sexuality, the genital examination is essential during routine well-child examinations and the adolescent physical examination. Not only is the genital examination essential for a proper complete physical, but it also demystifies the genital area and possibly offers opportunities to discuss concerns the parent, child, or adolescent may have with regard to the genital organs, sexual health, sexuality, or reproduction. Many primary care physicians tend to avoid or defer the genital examination, only for it to be done on an as-needed basis should there be a particular concern regarding the genitourinary system, but this only accounts for problem-focused examination and does not lend itself to assessing the general health of the patient or the anticipatory guidance needs of the parent, child, or adolescent.

Children observe other people's attitudes towards sexuality and affection. These can include their parents' or caregivers' reactions to each other, to the child, and to others in their environment. Children also observe actions, including gender roles, nudity, and displays of affection toward a spouse, a child, and adult friends. These observations, from infancy through adolescence, affect a child's own perception of his or her sexuality and his or her body. Behaviors that involve touch, such as hugging, kissing, and cuddling, are all ways of expressing affection that may or may not be sexual in nature, and children process this information from an early age.

## INFANTS

Infants learn and derive a sense of security from their environment, from physical and emotional stimulation, and from having their basic needs met. Caregivers, in the process of caring for an infant, teach the infant about his or her own body. In the process of caring for an infant during feeding, changing, playing, cuddling, and giving positive reinforcement, the infant learns about security in a comforting way. Caregivers also teach the infant that caring, love, and affection should not be intrusive or cause discomfort in any way. Nonsexual contact with the infant such as kissing and cuddling gives the infant a feeling of security, enhances the infant's emotional health, and teaches the infant empirically about physical boundaries.

During infancy, children begin to form patterns of trust in their caregivers. Parents should realize that

### BOX 41-1 Questions and Concerns Parents of Infants May Have

1. Why does my newborn look as if she is having a period?
2. How do I clean my newborn's genital area? How far in do I need to go to clean my daughter's genital area?
3. How do I care for my son's circumcision?
4. How do I care for my son's uncircumcised penis?
5. Why does my son/daughter put his/her hands in his/her diaper or touch his/her genitals during diaper changes?
6. Why does it seem that my baby boy has an erection when he is urinating or when I am changing his diaper?

hugging, kissing, loving, and caring for their infant contributes to a trusting relationship. When parents make appropriate arrangements for child care, this contributes to the creation of trust between parent and child, including monitoring the care the babysitter or daycare provider gives the infant.

Older infants begin to explore their bodies and occasionally elicit the pleasurable sensation that can come from touching their own genitals. It is not uncommon for older infants to reach for their genitals when their diaper comes off during diaper changes. Parents can be counseled that this exploratory behavior is normal at this age and not a cause for concern. Box 41-1 contains questions that parents of infants may have, directly or indirectly pertaining to their child's sexual organs, sexual health, or establishment of appropriate boundaries. Physicians can prepare themselves to answer them with patience and understanding.

## TODDLERS

Toddlers, by nature, are curious about everything around them, including their bodies and the bodies of others. It is also during toddlerhood that voluntary sphincter control and toilet training begin. At this stage, toddlers are also curious about differentiating between males and females, and gender identity begins to emerge (see Table 41-1).

At well-child visits, parents of toddlers may need advice on a variety of topics with regard to sexuality and sexual health. First and foremost, they will need guidance in addressing children's questions about the body parts of females versus males. Physicians can urge parents to use correct terms for the male and female anatomy because this practice promotes open communication with the child and allows the child to accurately describe any pain or problems he or she may have with his or her genitals.

Gender identity becomes more established at this age, and a toddler will typically identify with his or her same-gender caregivers and other children. Parents should not, however, be alarmed if a toddler is interested in traditional opposite or other-gender activities or roles, such as boys wanting to wear dresses or



**Table 41-2** Examples of Sexual Behaviors in Children 2 to 6 Years of Age

<b>NORMAL, COMMON BEHAVIORS</b>	<b>LESS COMMON, NORMAL BEHAVIORS</b>	<b>UNCOMMON BEHAVIORS IN NORMAL CHILDREN</b>	<b>RARELY NORMAL BEHAVIORS</b>
Touching/masturbating genitals in public/private	Rubbing body against others	Asking peer/adult to engage in specific sexual act(s)	Any sexual behaviors that involve children who are 4 or more years apart
Viewing/touching peer or new sibling genitals	Trying to insert tongue in mouth while kissing	Inserting objects into genitals	A variety of sexual behaviors displayed on a daily basis
Showing genitals to peers	Touching peer/adult genitals	Explicitly imitating intercourse	Sexual behavior that results in emotional distress or physical pain
Standing/sitting too close	Crude mimicking of movements associated with sexual acts	Touching animal genitals	Sexual behaviors associated with other physically aggressive behaviors
Trying to view peer/adult nudity	Sexual behaviors that are occasionally, but persistently, disruptive to others	Sexual behaviors that are often disruptive to others	Sexual behaviors that involve coercion
Behaviors are transient, few, and responsive to distraction	Behaviors are transient and moderately responsive to distraction	Behaviors are persistent and resistant to parental distraction	Behaviors are persistent and child becomes angry if distracted

Adapted from Kellogg ND; American Academy of Pediatrics Committee on Child Abuse and Neglect. Clinical report—the evaluation of sexual behaviors in children. *Pediatrics*. 2009;124:992–998. Reaffirmed March 2013. Available at: [pediatrics.aappublications.org/content/124/3/992](http://pediatrics.aappublications.org/content/124/3/992). Accessed November 23, 2015.

makeup, or girls wanting to wear boys' clothes or underwear. These behaviors manifest the natural curiosity of the toddler. A separate chapter discusses in further detail issues surrounding gender identity and offers guidance in addressing issues that pose a concern for the family (Chapter 156, Gender Expression and Identity Issues). Parents need to be advised that there are a number of behaviors that may be alarming or perceived as improper, yet are within the range of normal behavior for a toddler. Examples include masturbation, curiosity about their own genitals or those of their peers, and curiosity about the nude adult body. Table 41-2 provides examples of common, less common, uncommon, and rarely seen behaviors in children aged 2 to 6 years. This information may be valuable in discussing parents' concerns and in deciding which behaviors are normal and which behaviors are concerning, requiring further assessment. Box 41-2 lists several questions common among parents of toddlers.

Parents of toddlers who masturbate can be reassured that this is a normal behavior. They can be guided as to when the behavior is concerning, such as chronic, repetitive masturbation that the child is not able to control or behavior that causes injury to the genitalia. Parents can instruct their toddlers that masturbation, although not wrong, should be done in private and not in public places. Often the toddler learns that masturbating is a way to self-soothe during stressful situations, relieve boredom, or relax at naptime or bedtime.

Trust that is established during infancy continues developing into the toddler years. These years are a good time to bring up ideas of body safety, "private" parts of the body, and modesty. Children should know that only certain caregivers are allowed to assist them with their bodily needs and that no one should make

### **BOX 41-2** Questions and Concerns Parents of Toddlers May Have

1. How do I potty-train my son? How do I potty-train my daughter?
2. They want to know about boy and girl parts . . . what do I tell them?
3. I am having a baby, and my toddler is curious. What do I tell him/her?
4. My daughter is playing with her clitoris with her fingers. What do I do?
5. My son lies on his tummy and puts his hands in his diaper and "humps" in the bed. Is that normal?
6. My toddler is curious about the new baby's genitals. What should I tell him/her?
7. How much should I say to my child about good touch/bad touch? I do not want to scare him/her.

them feel uncomfortable when it comes to touching their bodies. This should include actions that come in the form of play, such as games that result in discomfort (including excessive tickling), or showing or touching private parts of the body.

The pediatrician and parents can tell toddlers that no one should ask children to keep any secrets from a parent. Pediatricians may want to guide parents into discussing with their older toddler that any games or interactions that result in a secret should be revealed to the parent to make sure the child is safe. Toddlers can begin learning that they should always tell someone they trust (parent, grandparent, teacher, police, doctor) if someone has touched them or made them feel uncomfortable in any manner. Other topics

the pediatrician may want to discuss during the well-child visits include co-bathing, co-sleeping, parental nudity, and access to sexually explicit materials.

Toddlers may become curious about reproduction and where babies come from. This may arise from a mother who is pregnant, a friend who is about to become a big brother or sister, or a family pet that has given birth. Such occurrences create the opportunity for parents to discuss the topic of birth and the birthing process. The pediatrician can advise parents to answer the child's question in a clear and concise manner that is appropriate to the child's age and level of understanding. In addition, there are many child-oriented books relating to new babies in the family that may help a parent discuss the topic with their child.

Finally, the pediatrician can raise the issue of the effect of media on the toddler's perception of sexuality and sexual behaviors. This topic will be further discussed in the next sections.

### **PRESCHOOL-AGED CHILD**

As the curious toddler grows into the more inquisitive and assertive preschool-aged child, parents and pediatricians may revisit sexuality topics from the past, as well as begin new conversations. Toilet training and sphincter control are maturing at this stage. Masturbation continues at this age, and this topic is an important lead-in to discussion of parental values regarding sexual pleasure in the preschool-aged child. The pediatrician can assess the parents' perceptions and responses to this behavior, reassuring them that in most cases masturbation is a normal act. Parents can reinforce to the child who masturbates that masturbation is to be done in private. This is also an important time to discuss with the parent and child issues of personal safety, including (if this is an issue for the child) the discovery of body orifices and refraining from inserting foreign objects into the body, including vaginal, urethral, rectal, nasal, oral, and aural orifices. Preschool-aged children should also be told that their bodies are their own property and should be kept private. The concept of body safety—safe touch versus unsafe touch, and not keeping secrets—can be reinforced.

Preschool-aged children have a desire to know how things work, including the human body. Thus they may want to see how other people are made and what is under their clothes. It is also during this stage that children may be interested in playing “doctor” with others. As long as this type of play is with peers, parents can be reassured that this play is not sexual in nature but rather a natural extension of the child's curiosity and need to explore.

Preschool-aged children are also becoming more aware of gender identity and gender roles. In fact, some preschool-aged children may go through a period in which they express the desire to marry one of their parents and seem to be in competition with the other. In families where this occurs and seems to be a concern, parents can be advised that this is a normal part of the preschool-aged child's development. Parents can explain in a nonjudgmental manner that the parent already has a partner or that the child needs to be much older to marry someone. Gender role play is

#### **BOX 41-3 Guide for Parents When Children Ask About Sex**

1. Do not make your child feel ashamed for being curious.
2. Be honest and use appropriate terms for all body parts.
3. Determine whether your child's question has been answered or if he/she has more questions.
4. Listen to your child's responses and reactions.
5. Be prepared to repeat yourself.

Adapted from American Academy of Pediatrics. Talking to Your Young Child About Sex. [www.healthychildren.org/English/ages-stages/preschool/Pages/Talking-to-Your-Young-Child-About-Sex.aspx](http://www.healthychildren.org/English/ages-stages/preschool/Pages/Talking-to-Your-Young-Child-About-Sex.aspx). Updated August 20, 2015. Accessed October 7, 2015.

also common at this stage, as is cross-gender role play.

As mentioned in the previous section, the toddler and preschool-aged child may become curious about where babies come from. It is important for the parent to address this in terms the child understands, using appropriate terminology about parts of the body, but to remember that the child may just want basic facts rather than an entire discussion about sex education. The parent can be guided to give simple answers appropriate to the child's level of understanding (eg, when parents love each other, they can make a baby) and allow the child to maintain control of the conversation, initiating his or her own questions. Parents should be clear that they understand the child's questions and give the child the sense that they are available for future questions. Box 41-3 is a guide for parents whose children ask about sex. There are many age-appropriate books and Web resources available to help parents talk to young children about sex, reproduction, and anatomy.

As during all other stages of development, the pediatrician will find it helpful to inquire about the child's exposure to media. In the preschool years, children begin to access television, video games, and computers more independently. Well-child visits provide an opportunity to address exposure to media and limitations parents should place on “screen time” for their child. Exposure to sexually explicit and violent media may influence some children's behaviors and decrease their sensitivity to sexual violence and behaviors such as premarital sex and infidelity. Parents should monitor their child's viewing and never allow young children to access the computer or television without adult supervision.

Topics of modesty, privacy, co-sleeping or co-bathing with a parent or sibling, and parental nudity around the child are other important topics for discussion (see Box 41-4).

### **SCHOOL-AGED AND PREADOLESCENT CHILD**

The early school-age years are a time when children are less interested in their bodies and those of others and are more focused on school, friends, and activities.

### **BOX 41-4 Questions and Concerns Parents of a Preschool-Aged Child May Have**

1. My child is asking questions about body parts when taking a bath with a sibling. What should I tell him/her?
2. My child masturbates at preschool at naptime, and the teachers are worried. What should I tell my child? What should I tell the teachers?
3. My daughter tries to put the beak of her bathtub duck in her genital area. What should I do?
4. How do I get my daughter who used to breastfeed to stop grabbing my breasts?
5. We have a babysitter coming to watch the kids. What should I tell my children about safe touch?
6. I turned on the television with my child present. There was a nude scene, and now she is asking questions. What should I tell her?

Sexual behaviors generally peak at 5 years of age and then begin to diminish. During this time parents will find that their child has fewer questions that are sexual in nature. However, it is important for parents to continue to communicate with their child about sexuality and sexual health.

In assessing sexual behaviors of school-aged children, the pediatrician should pay attention to both child and family variables, including the developmental level of the child, presence of family violence in the home, and nonfamily influences such as child care. If behavior falls out of the typical range, or a parent is concerned about the child's behavior, a referral to a therapist may be necessary. The Child Sexual Behavior Inventory (CSBI), a 38-item scale that assesses a broad range of sexual behaviors as a means to clarify concerning behavior, may be administered. Other referral options include a pediatrician or physician specializing in child abuse or maltreatment. Of course, if at any time there is a suspicion of child abuse or neglect, a referral to children's protective services is mandatory.

Because the school-aged child's body is changing and preparing for puberty, the pediatrician should encourage parents to discuss topics of body cleanliness, body safety, and changes the body will go through (Chapter 185, Puberty: Normal and Abnormal). Physiologic changes such as erections and ejaculations in boys, development of pubic hair, and development of breast buds and physiologic vaginal discharge in girls should all be discussed. It is important to speak in clear, concise, and concrete terms because preadolescents may not understand abstract terms at this stage in development. Parents need to be skilled in maintaining open communication with their school-aged child and preteen. Parents who are prepared to handle questions and situations that may arise with their school-aged child are better equipped to communicate confidently regarding matters that are of a sexual nature. That said, many parents feel uncomfortable talking about sexuality. Their fears may have to

### **BOX 41-5 Questions and Concerns Parents of a School-Aged Child May Have**

1. I found my child masturbating in his/her bed the other night. Is this normal?
2. What is your opinion about overnight summer camps? Sleepovers? I am worried about what other children know about sex and what they will share with my child.
3. My child is beginning to develop pubic hair. Should I tell him/her about puberty now?
4. Should both parents sit together to talk to my child about puberty? How much do I tell my child?
5. In school the kids are talking about same-sex relationships. What should I tell my child about this?

do with the idea that if one talks about these issues to children, this is giving permission to be sexually active. Thus, the pediatrician should explore how parents feel about talking with their children, and if they are uncomfortable, should empower them to talk with their children.

Generally speaking, mothers seem to be the primary educator for their school-aged daughters regarding sexual health, whereas fathers were found to be the primary educator for their sons. However, both parents' involvement in their child's sexual health education is important. Cooperation among both parents allows the child to go to either one if questions regarding sexuality arise (Box 41-5). Effective communication about sexual health is best achieved through early and repeated conversations.

Parental monitoring of a child's recreational activities before adolescence has been found to create a strong foundation for healthy sexual attitudes of adolescents. When it comes to sexual behaviors and attitudes, children are influenced by a variety of factors, including peer groups, dating partners (as children enter adolescence), media exposure, and their community; however, it is parental monitoring that has been found to be the most influential of societal factors in creating healthy sexual attitudes in adolescents.

Parents are seen as "nonreplaceable significant others" who are responsible for the socialization of children and adolescents. Parental monitoring, control, supervision, closeness, and support all influence sexual attitudes and behaviors; this groundwork is begun in the school-age and preteen years. By adolescence, the groundwork is nearly complete.

In the prepubertal years, patients should be given the opportunity to speak alone with their physician to discuss subjects they would rather not address in front of a parent. During the physical examination of a school-aged child and preadolescent, the pediatrician should be aware of and emphasize the patient's right to privacy and modesty. The examiner should always have a chaperone present, and the entire examination—especially the genital examination—

**Table 41-3****Percentage of Adolescents Who Have Had Sexual Intercourse With at Least One Person in the Past 3 Months**

GRADE	WHITE		BLACK		HISPANIC/LATINO		ASIAN	
	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE
<b>All grades</b>	36	30	38	47	35	35	18	14
<b>9</b>	20	15	21	34	20	21	N/A	N/A
<b>10</b>	31	22	40	47	30	29	N/A	N/A
<b>11</b>	43	37	36	52	41	42	N/A	N/A
<b>12</b>	50	44	57	61	53	54	N/A	N/A

N/A, not available because of insufficient sample size (&lt;100).

Adapted from Centers for Disease Control and Prevention. 2013 Youth risk behavior surveillance system. Available at [www.cdc.gov/yrbss](http://www.cdc.gov/yrbss). Accessed on January 6, 2016.

should be explained to the patient in concrete terms. While examining the patient, the pediatrician may want to continue to inquire about concerns or questions the patient or parent may have, including pubertal changes in the body. It is also a good idea to address the importance of body safety at the onset of the examination, clarifying that it is okay for a physician to examine the patient's genital area because of the nature of the visit *and* because the parent and patient have both given permission to do so. If during the examination the patient seems uncomfortable, the examiner must stop examining the patient and address the discomfort. The physician should then discuss with the patient the possibility of another appointment when the patient is more comfortable.

As in all previous sections, the concept of safe and unsafe touch should also be discussed in an age-appropriate and nonthreatening manner. Topics of co-bathing and co-sleeping with siblings (and parents, if this is still occurring) and family nudity should be addressed on a case-by-case basis.

## ADOLESCENCE

Interest in sexuality peaks during adolescence because of pubertal changes, the need for independence, and the increased role of societal and peer influences. At this stage, sexual curiosity can manifest in several ways, from thoughts and questions about sexuality to masturbation and sexual behaviors with other adolescents.

The cognitive immaturity of adolescents increases their risk for participation in unsafe sexual practices and adverse sexual consequences such as a sexually transmitted infection (STI), unintended pregnancy, sexual abuse, social stigma, and bullying. These issues can be especially challenging for lesbian, gay, bisexual, and transgender youth. (See Chapter 76, Lesbian, Gay, and Bisexual Youth, and Chapter 156, Gender Expression and Identity Issues.) Although there are no firm guidelines about how much sexual behavior is appropriate, the general goals of pediatricians and adolescent caregivers are to delay sexual initiation, minimize unsafe sexual practices, prevent STI acquisition, avoid unintended pregnancy, and behave in accordance with parental value systems.

Sexual behaviors are extremely common in adolescence. The average age of sexual initiation is 16 years for males and 17 years for females. In 2013, 20% of teenagers had heterosexual vaginal intercourse by

ninth grade, 29% by tenth grade, 40% by eleventh grade, and 49% by twelfth grade (see Table 41-3). Among middle-school children in Mississippi, 19.9% of sixth graders, 25.4% percent of seventh graders, and 40.6% of eighth graders had already participated in vaginal intercourse (Table 41-4). These numbers are concerning because children who have had vaginal intercourse at an early age are at great risk for coercion. In fact, 60% of girls who had sex before the age of 15 years reported that at least 1 episode was involuntary. Rates of sexual activity vary by gender and race, with blacks and males reporting earlier sexual initiation and a greater number of sexual partners (Table 41-3 and Table 41-4).

Given the cognitive immaturity of adolescents and the high prevalence of vaginal intercourse, it is not surprising that unintended pregnancy and STIs are also common. In one study, nearly 4 in 10 sexually active adolescents did not use a condom with their last intercourse, and almost 80% did not use a hormonal contraceptive method. In another, one-third of adolescent females became pregnant at least once by the age of 20 years, and approximately 90% of these pregnancies were unintended. In 2003, approximately 1 in 4 adolescent females had a confirmed STI, with human papillomavirus being the most commonly identified organism.

## Development of Adolescent Sexual Behaviors

Eighty-nine percent of adolescents reported that they were very or somewhat concerned about sexual health issues (Table 41-5), particularly questions about the symptoms and diagnosis of STIs and about contraceptive options. The social and societal pressures to have sex can be difficult for adolescents to manage. Sixty percent had felt pressured to have sex "by a certain age," and most agreed that abstinence is "a nice idea" but not realistic. Adolescents get most of their sexual health information from peers, the media, and their parents. Importantly, the influence of parents on adolescent sexual behavior is strong and seems to be at least equal to that of peers and the media.

Adolescents generally think that sexual behaviors should progress incrementally with age from less invasive public displays of affection (like holding hands, hugging, and kissing) to more private activities (like touching of the breasts, touching of the genitals, oral sex, and vaginal intercourse) (Table 41-6).



**Table 41-4** Percentage of Mississippi Middle-School Children Who Have Had Vaginal Intercourse at Least Once

GRADE	TOTAL			WHITE			BLACK		
	ALL	FEMALE	MALE	ALL	FEMALE	MALE	ALL	FEMALE	MALE
All grades	28.4	21.4	35.7	20.6	16.8	24.5	36.1	26.9	46.4
6	19	13.3	26.5	11.5	N/A	N/A	30.2	N/A	N/A
7	25.4	18.8	32.7	19.2	15.1	23.8	31.4	23.4	41.1
8	40.6	32.4	49.3	32.9	26.5	N/A	46.6	37.5	57.7

Adapted from Centers for Disease Control and Prevention. Youth risk behavior surveillance system 2011. Available at [www.cdc.gov/yrbss](http://www.cdc.gov/yrbss). Accessed on January 6, 2016

**Table 41-5** Percentage of Young (13–14 Years) and Older (15–17 Years) Adolescents Who Want to Know More About Each of the Following

	13- TO 14-YEAR-OLDS	15- TO 17-YEAR-OLDS
How to know if you have an STI	70	67
How to protect yourself from STIs	69	66
Where to get tested for STIs	59	59
What is involved in STI testing	56	62
Birth control options	55	63
How to deal with pressure to have sex	54	46
How to bring up sexual health issues with a doctor	52	51
How to talk to a partner about sexual health issues	46	50
How to use condoms	33	29

Adapted from Hoff T, Greene L, Davis J. *National Survey of Adolescents and Young Adults: Sexual Health Knowledge, Attitudes and Experiences*. Menlo Park, CA: Henry J Kaiser Family Foundation; 2003:38,41. Available at: [kff.org/hiv/aids/report/national-survey-of-adolescents-and-young-adults](http://kff.org/hiv/aids/report/national-survey-of-adolescents-and-young-adults). Accessed November 23, 2015.

**Table 41-6** Percentage of Adolescent Boys and Girls Indicating the Ages at Which It Is Okay to *Begin* Engaging in a Range of Sexual Behaviors

	GIRLS			BOYS		
	12–14 YEARS	15–17 YEARS	18–20 YEARS	12–14 YEARS	15–17 YEARS	18–20 YEARS
<b>AT WHICH AGE IS IT OKAY FOR A GIRL TO ENGAGE IN THE FOLLOWING WITH A BOY?</b>						
Briefly kiss him on the mouth	96.5	2.7	0.8	92.6	6.9	0.5
Tongue kiss him	68.9	30.4	0.8	55.8	41.9	2.3
Have him touch her breast underneath clothes	22.6	70	6.2	16.6	74.7	7.8
Have him touch her between the legs underneath clothes	12.5	68.5	16	10.1	75.6	11.5
Touch his genitals underneath his clothes	12.1	70.4	14.0	9.2	74.7	13.8
Have sexual intercourse with him	1.9	58.8	32.3	3.2	64.5	28.6
Have oral sex with him	6.6	57.2	27.6	5.1	65.9	23.5
<b>AT WHICH AGE IS IT OKAY FOR A BOY TO ENGAGE IN THE FOLLOWING WITH A GIRL?</b>						
Briefly kiss her on the mouth	96.1	3.1	0.8	94	5.5	0.5
Tongue kiss her	69.3	30	0.8	59	39.2	1.8
Touch her breast underneath her clothes	22.2	70.8	6.2	25.3	65.9	7.8
Touch her between the legs underneath her clothes	13.2	67.3	16.7	16.6	69.6	11.5
Have her touch his genitals underneath his clothes	12.8	68.9	15.6	15.2	69.1	13.4
Have sexual intercourse with her	2.3	59.1	32.7	5.5	65.4	25.3
Have oral sex with her	6.2	57.2	29.2	8.8	63.1	23

Adapted with permission from Rosenthal D, Smith AMA. Adolescent sexual timetables. *J Youth Adolesc*. 1997;26(5):619–663.

**BOX 41-6 Questions and Concerns Parents of an Adolescent May Have**

1. I found my child masturbating in his/her bed the other night. Is this normal?
2. When should I let my child have a boyfriend/girlfriend?
3. Do I need to talk with my child about sex? He already learns about it in school.
4. How can I tell if my daughter is still a virgin?
5. How can I keep my daughter/son from having sex?

Oral sex and mutual masturbation are 2 sexual behaviors that often precede vaginal intercourse. Nearly half of all adolescents have engaged in oral sex before engaging in vaginal intercourse. In fact, among young adolescents, oral sex is more common than vaginal sex. Teens generally view oral sex as safer and less immoral compared with vaginal intercourse. Similarly, mutual masturbation is a well-accepted behavior among adolescents. By the age of 15 years, most adolescents think that this activity is acceptable (see Table 41-6). Self-masturbation is another common sexual behavior of adolescents. By the age of 15 years, nearly 70% of boys had masturbated weekly and 30% of girls had masturbated monthly. There is no evidence to suggest that masturbation has any effect on sexual initiation or the frequency of vaginal intercourse.

**Role of Parents and Physicians in Guiding Sexuality in Adolescence**

Parents must recognize the tremendous effect that they have in guiding adolescent attitudes about sexuality and sexual behavior. Parents who have effective discussions with their adolescents about sexuality can delay sexual initiation, increase the use of condoms and contraceptives during vaginal intercourse, and improve the ability of their teens to discuss sexual health issues with their partners. Physicians can guide parents who are struggling with how and when to discuss these issues with their children. Box 41-6 lists common questions from parents of adolescents. In particular they can steer them away from some very common mistakes (see Table 41-7). Some of these include avoiding or curtailing the discussion because of discomfort or embarrassment; assuming that the child has already learned about this from other sources; and trying to have a single, comprehensive “birds and bees” conversation. One of the major principles of effective parental discussions about sexuality is repetition. Sexuality and sexual health cannot be discussed in a single conversation; rather, the principles should be reiterated and reviewed over and over again. Conversations about this topic should be longitudinal, open, reciprocal, and honest. Such conversations can result in improved connectedness between parent and child, increased adolescent adoption of parental value systems, and decreased risk for unsafe sexual practices.

Parents can apply several other techniques to assist them in curbing the sexual risk-taking behavior of their children. These include monitoring the whereabouts of their children (ie, knowing where the child is at all times), relating to their children with an authoritative (firm yet supportive) parenting style, minimizing exposure to sexual content in social media, participating in religious activities (if applicable), and involving their children in adult-supervised after-school activities. When combined, these activities can modify an adolescent's attitudes about sexual behavior. When virginal adolescents are asked why they haven't had sex, parental influence and morals are among the 2 most common reasons provided (see Table 41-8). Parental monitoring is important because it eliminates the perception of privacy required for sexual activity to take place and reminds the adolescent to behave in accordance with parental values. Minimizing exposure to sexual media content is also extremely important. Adolescents spend more than 7 hours daily exposed to music, movies, television, the Internet, and video games. These forums often glamorize sexual behavior and minimize its potential consequences. In fact, adolescents with unlimited and unmonitored exposure to the media are more likely to participate in unsafe sexual practices and initiate sex at a younger age. Parents should also consider monitoring their child's access to social networking Web sites, as well as reviewing the content of their cell phone text messages. Parents should know who their children's friends are and should have a relationship with their friends' parents. Parents must recognize that most adolescents have sex after school in their own home or the home of their partner while parents are away at work. This underscores the importance of organized, adult-supervised, after-school activities for adolescents.

The role of the pediatrician is to support parents in these efforts; to ensure the sexual health of the adolescent by performing routine, opt-out screening of adolescents for STIs and pregnancy; and to provide adolescents with confidential counseling about sexual health and sexual abuse prevention.

**CHILDREN WITH SPECIAL HEALTH CARE NEEDS**

Taking time to discuss sexual health with families of children with special health care needs is important but has often been overlooked while addressing general health concerns. In addition, these children are often erroneously thought to be childlike and asexual. Barriers to discussing sexuality include these factors, as well as the fact that the amount of time allotted for a special needs visit may not lend itself to a discussion of a topic that can be both sensitive and extensive. Box 41-7 lists some of the physician and parental barriers to discussing sexual health in the special needs population.

Physicians can foster open discussion by calling attention to pubertal changes in the body and mind of the child. These changes may affect the child's self-image, self-esteem, and interaction with peers. The special needs population can present some additional challenges; for example, patients with neurodevelopmental disabilities may experience pubertal changes

**Table 41-7****Mistakes That Parents Commonly Make in Discussing Sexuality and Sexual Health With Adolescents****COMMON PITFALLS BY PARENTS IN DISCUSSING SEXUALITY WITH TEENS****HOW THE PEDIATRICIAN SHOULD RESPOND**

Not discussing it because of their personal discomfort	Prepare for discussions about sexuality and sexual health by first asking your friends and neighbors, "How did you discuss this with your children?" Next, read books and Web sites about the topic. Several books on this topic exist (see Engaging Patient and Family in the Tools for Practice section).
Not wanting to embarrass the child or adolescent	Even if your child is embarrassed by the discussion, this does not mean that he/she does not want your input. Most adolescents want more information from their parents, but they are often too ashamed to ask for it.
Not discussing it because they assume that someone else (eg, school, the other parent) will discuss it with their teen	Discussing sexuality is a great opportunity for parents to give their adolescent children accurate information and reinforce their own values and expectations. Nobody else can do that. Fathers, in particular, have experiences and opinions that can be very helpful to their adolescents' emerging sexuality. It's surprising how much teenagers can value their fathers' input.
Talking about it too late (eg, after the child has already formed strong attitudes about sexuality and/or has already engaged in vaginal intercourse)	Sexuality and sexual health conversations should not wait until adolescence. Discuss these issues early and often with your children. In the school-aged years they will be influenced by the media and peers, who often glamorize sex without discussing consequences. Your children need you to help provide a counterpoint.
Not setting clear expectations about sexual behavior	Be clear but leave the door open for future conversations. Try, "I want to be clear about this. I don't want you to have sex until you . . . (are ready/have completed high school/are married, etc.). I would not be happy if you had sex before then, but if you are even beginning to think about it I need you to speak with me first."
Talking about sex in a single "birds and bees" conversation	Sexuality is a complex issue and cannot possibly be covered in a single conversation. Talk about sex with your children early and often. Repeated conversations will reinforce the lessons you taught earlier.
Assuming that abstinence is not an option	Children who choose to abstain from sex often do so because of the influence of their parents. If you assume that abstinence is not an option, then so will they. Keep in mind that it is possible to abstain from sex even after losing one's virginity. The most common reason for having sex the first time is curiosity. Once they have explored sex, it is realistic that they may not want to do it again for quite some time.
Not supporting their children with alternatives to sex	Keep your children busy, especially during after-school hours, with organized adult-supervised activities like athletics and interest clubs.
Inadvertently promoting sexual behavior by allowing their children to have unlimited and unmonitored exposure to sexual media, particularly the Internet	Limit your child to less than 2 hours of screen time per day and be sure that he/she is watching age-appropriate media. Become familiar with content labels that come with music, movies, video games, and television programming.
Discussing sex at a cognitive level beyond the adolescent's understanding	Adolescents are concrete thinkers and often cannot think 2, 3, or 4 steps ahead. For example, making abstract comments like, "having sex as a teenager will destroy your life" is incomprehensible for many teenagers. They cannot connect the 2 dots. Try talking about some of the more short-term consequences of unsafe sex.
Making the teenager afraid to ask them questions	Avoid threatening your child for engaging in sexual behavior, eg, "If you have sex, I'll make you very sorry you did." Clearly this will close off any future communication about this topic. Be clear about your expectations but leave the door open for future conversations.
Not practicing what they preach	Discuss your mistakes with your children. This type of reciprocal conversation is vital to effective adolescent communication. If you or another family member has made mistakes regarding sexuality, you should discuss them with your children. For example, let's say you had an unintended pregnancy at a time when you were not ready for it. Discuss with your child how you got into that situation and what you wish you had done differently.

Adapted from Rosenthal DA, Feldman SS. The importance of importance: adolescents' perceptions of parental communication about sexuality. *J Adolesc*. 1999;22(6):835–885; and Martino SC, Elliott MN, Corona R, Kanouse DE, Schuster MA. Beyond the "big talk": the roles of breadth and repetition in parent-adolescent communication about sexual topics. *Pediatrics*. 2008;121(3):e612–618.

**Table 41-8****Factors That Influence Adolescents' Decisions About Whether or Not to Have Sex****FACTORS THAT HAVE INFLUENCED VIRGINAL TEENS 15–17 YEARS OLD NOT TO HAVE SEX**

Concern about pregnancy (94%)  
 Concern about sexually transmitted infections (92%)  
 Feel you are too young (92%)  
 Because of what your parents taught you about sex (91%)  
 Because of what you learned in sex education (89%)  
 Because of your religious or moral values (84%)  
 Haven't met the right person yet (83%)  
 Concern for your reputation (77%)  
 Your partner is not ready (66%)  
 You don't have access to birth control or condoms (59%)  
 You have not had the opportunity (54%)  
 None of your friends are doing it (54%)

**FACTORS THAT HAVE INFLUENCED NONVIRGINAL TEENS 15–17 YEARS OLD TO HAVE SEX**

Curiosity (85%)  
 Partner wanted to (84%)  
 Feel like it was the right time (82%)  
 You were ready to lose your virginity (80%)  
 You met the right person (76%)  
 You had been with the partner for a long time 74%)  
 You hoped it would make the relationship closer (70%)  
 You were in love with the partner (69%)  
 Many of your friends were already doing it (62%)  
 You wanted to get it over with (58%)  
 You are going to marry the partner (53%)  
 You were drinking or using drugs at the time (18%)

Adapted from Virginity and the First Time. Copyright © The Henry J. Kaiser Family Foundation. Available at: [kaiserfamilyfoundation.files.wordpress.com/2013/01/virginity-and-the-first-time-summary-of-findings.pdf](http://kaiserfamilyfoundation.files.wordpress.com/2013/01/virginity-and-the-first-time-summary-of-findings.pdf). Accessed November 23, 2015.

**BOX 41-7 Barriers to Discussing Sexual Health of Children With Special Health Care Needs****PHYSICIAN BARRIERS**

1. Child possibly perceived as asexual
2. Paternalistic attitude on the part of the physician
3. Time limitation during the visit
4. Parental concerns about other health issues
5. Child unable to communicate concerns to physician

**PARENTAL BARRIERS**

1. Parental desire to keep child innocent
2. Parental desire to discuss sexuality in his/her own way
3. Parent may be too preoccupied with medical concerns to raise issues of sexual health
4. Parent perceives child as asexual

Derived from Murphy NA, Elias ER; American Academy of Pediatrics Council on Children With Disabilities. Sexuality of children and adolescents with developmental disabilities. *Pediatrics*. 2006;118:398–403.

earlier than their peers. Early maturation requires the parent(s) to begin learning about and accepting these changes sooner than planned.

A number of sexual health topics are appropriate for well-child visits with children with special needs, including the child's level of understanding regarding sexuality and sexual health, understanding of his/her body and changes to it, and his/her ability to self-protect. These topics are important to discuss not only with the parent but also with the adolescent while the parent is not present. The pediatrician can provide education while performing the genital examination and pelvic examination. These can be done in a modified position for patients with orthopedic or neuromuscular disorders. Physicians

can supply the parent and patient information on abstinence. They can also supply information on pregnancy and contraception and how each would interfere with the patients' physical health and medication regimens. Some parents of children with special health care needs may bring up the possibility of permanent sterilization as a way to prevent pregnancy. The American Academy of Pediatrics (AAP) Committee on Bioethics recommends that pediatricians discuss such an option if the parent expresses concern, but also discuss less permanent contraceptive options with the parent and the patient. It is also recommended that the pediatrician become familiar with the applicable laws regarding sterilization of persons who have developmental disabilities.

The pediatrician's role includes assessing the expectations of the patient and parents with regard to dating, sexual intercourse, and contraception. The pediatrician can serve as a source of information and assist in finding information regarding sexuality in patients with similar disabilities. The pediatrician can recommend that the Individualized Education Plan (IEP) developed by the child's school include the provision of sexuality education to children with disabilities, including a discussion of body parts, pubertal changes, hygiene, personal care, social skills, sexual expression, the medical examination, contraception, and rights and responsibilities of sexual behavior.

When it comes to cautioning parents and children with special health care needs on sexual abuse, the pediatrician's role is crucial. Such children are at an especially higher risk for being victimized for a number of reasons (see Box 41-8).

Masturbation in this population should not be seen as a concerning behavior unless it is done in public, is obsessive, or is causing injury to the patient. It is important to note that a patient's developmental age is a critical factor in considering masturbation behaviors; for example, if a patient has a chronological age of 9 years but is developmentally a preschooler, the child's



### **BOX 41-8 Why Special Needs Patients May be at Increased Risk for Sexual Abuse or Exploitation**

1. May be vulnerable because of disability
2. May be more trusting
3. May have increased number of care providers
4. May have reliance on assistance for toileting
5. May not be able to communicate or describe what has happened to them
6. May have limited capacity for self-defense

Derived from Murphy NA, Elias ER; American Academy of Pediatrics Council on Children With Disabilities. Sexuality of children and adolescents with developmental disabilities. *Pediatrics*. 2006;118:398–403.

### **BOX 41-9 Guide for Discussions With the Special Needs Patient and Parent**

1. Discuss on a regular basis issues of physical development, maturity, and sexuality, starting early in childhood and continuing through the adolescent years.
2. Ensure the privacy of each child and adolescent.
3. Assist parents in understanding how the cognitive abilities of their children affect behavior and socialization.
4. Encourage children with disabilities and their parents to optimize independence, particularly as related to self-care and social skills.
5. Be aware of special medical needs, such as modified gynecologic examinations, latex-free protection from STIs, unplanned pregnancies, and genetic counseling when appropriate.
6. Recognize that children with disabilities are at an increased risk for sexual abuse and monitor for early indications of abuse.
7. Advocate for developmentally appropriate sexuality education in home, community, and school settings.
8. Encourage parents to be the principal source of developmentally appropriate sexuality education for their children, incorporating family values, cultural traditions, and religious beliefs.
9. Provide families with information regarding appropriate community programs that address issues of sexuality for children and adolescents with disabilities.

Derived from Murphy NA, Elias ER; American Academy of Pediatrics Council on Children With Disabilities. Sexuality of children and adolescents with developmental disabilities. *Pediatrics*. 2006;118:398–403.

sexual curiosity and masturbation should be seen within the context of a preschooler's development.

In the special needs population, as in any other pediatric population, the physician's role includes discussion of sexual health and sexuality with the child and parents, especially the increased vulnerability to abuse in this population. Box 41-9 summarizes important discussion points.

### **BOX 41-10 Guidance from the AAP to Minimize a Child's Risk for Molestation**

1. Teach your child about privacy of body parts and that no one has the right to touch them.
2. Teach your child to be able to differentiate between appropriate and inappropriate touching (loving hug vs. touching private areas, but be aware that if a loving hug is unwanted or undesired then this is also considered inappropriate).
3. Teach your child and empower him/her that he/she has the right to say no to any unwanted touching.
4. Teach your child about potentially dangerous situations in which a stranger may lure him/her into being alone or separated from his/her parent or group of friends.
5. Teach your child about the dangers of being offered drugs or mind-altering substances by friends, familiar adults, or strangers.
6. Teach your child that threats from a molester are against the law and not to keep secrets regardless of what the threat may be.
7. Teach your child never to go door to door without an adult, and never to go into someone else's home without parental/adult permission or supervision.
8. Spend time with your child and give him/her a sense of love and attention so that he/she does not seek it elsewhere and become an easy target.
9. Know whom your child spends time with and where your child is when with friends, at parties, etc.
10. At the community level, know the abuse prevention programs offered at local libraries, schools, and police or fire departments.
11. Monitor activities at your child's child care programs, daycare, summer camp, etc.

Adapted from American Academy of Pediatrics. Sexual abuse. [www.healthychildren.org/English/safety-prevention/at-home/Pages/SexualAbuse.aspx](http://www.healthychildren.org/English/safety-prevention/at-home/Pages/SexualAbuse.aspx). Updated August 20, 2015. Accessed October 7, 2015.

## **MINIMIZING RISK OF EXPLOITATION AND TALKING ABOUT SAFE AND UNSAFE TOUCH WITH CHILDREN**

Much has been said about talking to children about safe and unsafe touch, yet information on what to discuss with children, at what age to start such discussions, and how much to tell them is a source of much controversy. Psychology and interpersonal violence literature debates the methods used to teach about safe and unsafe touch, how much information to provide, retention of information, and negative effects of discussing the potential for sexual abuse (eg, confusing nonsexual affection for sexual abuse).

There is general agreement on the need for age-appropriate discussions of sexuality and sexual health; use of correct names for body parts; differentiation between appropriate and inappropriate touch, realizing that inappropriate touch may sometimes feel good too; empowering children to say no; and making sure they know to whom they can go for help. Box 41-10

outlines the AAP recommendations to minimize a child's risk for sexual molestation.

## SUMMARY

In addition to their role in performing a sensitive, age-appropriate genital examination on children and youth during well-child care, physicians play an important role in discussing sexual health, sexuality, and safety with both typical and special needs children in a developmentally appropriate manner, beginning in the child's infancy and continuing through adolescence. Physicians' role also includes discussing these topics with parents, encouraging them to discuss these topics with their child regularly, and promoting open communication about sexual issues between the child and parents. Sexual curiosity and exploration can be normal behavior at each stage of childhood. Children whose sexual behavior falls outside the range of normal or common sexual behaviors may require the assistance of a specialist.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Dating & Sex* (Web page), American Academy of Pediatrics ([www.healthychildren.org/english/ages-stages/teen/dating-sex/Pages/default.aspx](http://www.healthychildren.org/english/ages-stages/teen/dating-sex/Pages/default.aspx))
- *Masturbation* (Web page), University of Michigan Health System ([www.med.umich.edu/yourchild/topics/masturb.htm](http://www.med.umich.edu/yourchild/topics/masturb.htm))
- *Questions and Answers About Sex* (Web page), The Nemours Foundation ([kidshealth.org/parent/emotions/feelings/questions\\_sex.html](http://kidshealth.org/parent/emotions/feelings/questions_sex.html))
- *Sexuality Education for Youth With Disabilities or Chronic Illness* (Web page), University of Michigan Health System ([www.med.umich.edu/yourchild/topics/disabsex.htm](http://www.med.umich.edu/yourchild/topics/disabsex.htm))
- *Talking to Your Child About Sex* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/preschool/Pages/Talking-to-Your-Young-Child-About-Sex.aspx](http://www.healthychildren.org/English/ages-stages/preschool/Pages/Talking-to-Your-Young-Child-About-Sex.aspx))

### Medical Decision Support

- *Youth Risk Behavior Surveillance System* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/HealthyYouth/yrbs/index.htm](http://www.cdc.gov/HealthyYouth/yrbs/index.htm))

## AAP POLICY

- American Academy of Pediatrics Committee on Adolescence. Condom use by adolescents. *Pediatrics*. 2013;132(5):973–981 ([pediatrics.aappublications.org/content/132/5/973](http://pediatrics.aappublications.org/content/132/5/973))
- American Academy of Pediatrics Committee on Adolescence. Contraception for adolescents. *Pediatrics*. 2014;134(4):e1244–e1256 ([pediatrics.aappublications.org/content/134/4/e1244](http://pediatrics.aappublications.org/content/134/4/e1244))
- American Academy of Pediatrics Committee on Adolescence. Emergency contraception. *Pediatrics*. 2012;130(6):1174–1182 ([pediatrics.aappublications.org/content/130/6/1174](http://pediatrics.aappublications.org/content/130/6/1174))
- American Academy of Pediatrics Committee on Bioethics. Sterilization of minors with developmental disabilities. *Pediatrics*. 1999;104(2):337–340. Reaffirmed May 2009 ([pediatrics.aappublications.org/content/104/2/337](http://pediatrics.aappublications.org/content/104/2/337))

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Strasburger VC; American Academy of Pediatrics Council on Communications and Media. Sexuality, contraception, and the media. *Pediatrics*. 2010;126(3):576–582 ([pediatrics.aappublications.org/content/126/3/576](http://pediatrics.aappublications.org/content/126/3/576))

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## Chapter 42

# SAFETY AND INJURY PREVENTION

Rebecca Levin, MPH; Gary A. Smith, MD, DrPH

## INTRODUCTION

By many measures, injury is the most significant health problem of childhood and adolescence. Injury control includes preventing events that might cause injury; diminishing the likelihood or severity of injury, even though events with injury-causing potential occur; and minimizing the effects of the injury, after it occurs, through state-of-the-art emergency response, medical care, and rehabilitation. This section concentrates on the first 2 parts of injury control, those classically considered as primary injury prevention, and describes the role of the pediatrician in the primary care setting in ensuring injury prevention. It highlights the critical opportunity to prevent injury by providing counseling about injury and injury prevention to children and families. Pediatricians can assume

Table 42-1

**Numbers and Rates of Injury Deaths by Age and Event and Percentage of All Deaths Caused by Injury, United States Children and Adolescents (2013)**

EVENT	AGE IN YEARS											
	<1		1–4		5–9		10–14		15–19		0–19	
	N	R	N	R	N	R	N	R	N	R	N	R
All injuries	1,541	39.09	1,718	10.79	897	4.36	1,345	6.51	6,937	32.79	12,438	15.12
Unintentional injuries	1,156	29.33	1,316	8.26	746	3.63	775	3.75	3,652	17.26	7,645	9.30
Motor vehicle traffic	66	1.67	327	2.05	342	1.66	414	2.00	2,338	11.05	3,487	4.24
Suffocation	979	24.84	161	1.01	44	0.21	37	0.18	47	0.22	1,268	1.54
Drowning	23	0.58	393	2.47	116	0.56	93	0.45	241	1.14	866	1.05
Poisoning	6	*	29	0.18	9	*	21	0.10	587	2.77	652	0.79
Fires, burns	17	*	129	0.81	87	0.42	48	0.23	53	0.25	334	0.41
Homicide	282	7.15	337	2.12	125	0.61	152	0.74	1,407	6.65	2,303	2.80
Suicide	0	*	0	*	9	*	386	1.87	1,748	8.26	2,143	2.61
Firearms (all intents)	15	*	67	0.42	65	0.32	262	1.27	2,056	9.72	2,465	3.00
Percentage of all deaths caused by injury	7%		42%		37%		46%		73%		29%†	

Data from Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Web-based Injury Statistics Query and Reporting System [database]. [www.cdc.gov/injury/wisqars](http://www.cdc.gov/injury/wisqars). Accessed October 21, 2015.

N, number of deaths; R, deaths per 100,000 population.

\*Rates based on 20 or fewer deaths may be unstable and are omitted.

†Fifty-eight percent of deaths of persons aged 1 to 19 years are a result of injury.

effective roles for injury prevention at many additional levels (eg, with schools, communities, local health departments, and state and national agencies and legislatures). Successful injury control demands active advocacy outside the pediatrician's office.

## INCIDENCE

The number of unintentional injury deaths during childhood has been decreasing as a result, in part, of the hard work of pediatricians and public health professionals. However, injuries still cause the majority of deaths of children and adolescents aged 1 to 19 years. Although the leading causes of injury death vary by age group (Table 42-1), events involving motor vehicles, firearms, drowning, suffocation, and fires are important in every age group.

Although deaths may be the most often noted injury statistic, injury results in acute morbidity, short- and long-term disability, and high medical care costs. The causes of nonfatal injury encompass those that produce fatal injury, but falls, burns, poisonings, fights, sports, and recreational activities (including play) are more prominent causes of nonfatal injury than they are of fatalities. For almost all types of injury, boys are at greater risk than girls. This increased risk has yet to be explained fully, but may stem from several factors, including innate behavioral differences, societal expectations, and exposure. Children living in poverty are more likely to suffer serious and fatal injury of many types; children subjected to abuse and neglect and those with special health care needs are at higher risk for injury; and injury risk varies by geographic factors as well.

Successful injury prevention in the primary care setting is based on a clear understanding of the principles of injury prevention and on sound counseling skills.

## PRINCIPLES OF INJURY CONTROL

Events leading to injury are, for the most part, predictable and preventable. They should not be considered as *accidents* because this term implies a sense of randomness and lack of preventability. In some instances, prevention is achieved through eliminating injury-producing events (eg, building divided highways to reduce motor vehicle crashes). Prevention is sometimes achieved by eliminating injury even though the event takes place (eg, protecting child passengers by restraining them in car safety seats).

When energy affects the body acutely at a damaging level, injury results. For most pediatric injuries, the energy is mechanical. However, thermal, chemical, radiation, and electrical energy are also agents of injury. To prevent injury, energy must be kept away from the child, or the energy transfer to tissue must be diffused over time or space (or both) so that it does not reach damaging levels. The former is well illustrated by building a bicycle path as an alternative to riding on streets with motor vehicles. The latter is illustrated by the protection provided by a helmet in a fall from a bicycle. The helmet absorbs and dissipates the forces of the impact over a larger area of the head so that the brain is exposed to a lower level of energy over a longer period, even though the fall has occurred.

Injury control strategies may be categorized in several ways. Haddon's matrix places strategies in a

Table 42-2

## Haddon's Matrix and Examples of Variables and Injury Prevention Interventions

PHASE	EPIDEMIOLOGIC DIMENSION			
	HUMAN	VECTOR OR VEHICLE	PHYSICAL ENVIRONMENT	SOCIOECONOMIC ENVIRONMENT
Pre-event	Judgment Coordination	Safe storage of firearms Infant walker ban	Bicycle paths Swimming pool barriers	Speed limits Graduated driver licensing
Event	Car safety seat use Use of protective equipment	Airbags Energy-absorbing surfacing on playgrounds	Smoke alarms Highway guardrails	Helmet laws Enforcement of seat belt laws
Postevent	Age Physical condition	Activated charcoal Fuel system integrity	Time to emergency treatment Availability of rehabilitation programs	Training of emergency medical system personnel Cardiopulmonary resuscitation training

Adapted from American Academy of Pediatrics Committee on Injury and Poison Prevention. *Injury Prevention and Control for Children and Youth*. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 1997.

framework according to phase (before the event, during the event, or after the event) and factor (human, vector or vehicle, physical environment, and socioeconomic environment). Comprehensive injury prevention efforts incorporate interventions from multiple matrix cells. Table 42-2 lists examples of variables and injury prevention interventions stratified according to Haddon's matrix.

### Active and Passive Injury Prevention

Prevention strategies can be active or passive. Active strategies require involvement of the child or parent every time protection is needed. Seat belts in automobiles are a good example of an active strategy. Passive (or automatic) strategies protect the individual whether the person needing protection is mindful of the need and takes appropriate action or not. Airbags are a good example. Both active and passive strategies can be quite successful when used, but passive strategies, when they exist, are usually favored over active strategies. Active strategies require compliance, and a risk always exists that they will not be fully used. Active strategies are often least likely to be adopted by the persons at greatest risk.

### Education, Engineering, and Enforcement

Another framework for categorizing injury prevention measures is the 3 Es. *Education* is the approach that is most familiar to health professionals; examples include counseling during health supervision visits and public education campaigns. *Engineering* involves modifying a hazard or the environment to prevent injuries or reduce the severity of injuries. *Enactment and enforcement* of legislation and regulation can motivate people to adopt safety-promoting behaviors, require environmental modifications to reduce hazards, and facilitate changes in social norms. Injury prevention is usually most effective when all 3 approaches are incorporated. For example, bicycle helmet use can be

promoted through education in schools, design of more comfortable or attractive helmets, and local laws or ordinances requiring helmet use.

### Intentional Versus Unintentional Injuries

Injuries are often classified as unintentional or intentional. This dichotomy is useful in many ways; however, the intent of human behavior is not always clear-cut and is better described as a continuum. For example, should injuries that result in part from inadequate parental supervision be considered unintentional or intentional resulting from child neglect? Additionally, strategies that prevent unintentional injury (eg, locking up firearms, turning down the water heater temperature) may also prevent some intentional injuries. For these reasons, and because injuries result from both, injury control efforts often address both intentional and unintentional injury. Nevertheless, some forms of intentional injury (eg, child abuse and child and adolescent suicide and homicide) are so important as causes of pediatric morbidity and mortality that they demand focused attention. Furthermore, the causes of intentional injury are extremely complex, and violence prevention efforts must take a multifaceted approach that includes the pediatrician. The pediatrician's important role in violence prevention is discussed in Chapter 44, Violence Prevention.

### Pediatrician Roles

Pediatricians can attempt to persuade individuals to decrease their risk for injury through educational efforts with individuals or groups. Injury control advocates have additional strategies at their disposal. Pediatricians can be involved in many of these activities, including media campaigns, legislation, regulation, litigation, environmental design, and cultural change. For most causes of injury, multiple strategies will need to be applied. The pediatrician can also become involved in research to identify risk and protective factors for injury and to



### BOX 42-1 Topics Recommended by the American Academy of Pediatrics for Office-Based Unintentional Injury Prevention Counseling

#### INFANTS

- Traffic safety: Appropriate use of rear-facing car safety seats in the back seat
- Burn prevention: Smoke alarms, hot water temperature no higher than 120°F
- Fall prevention: Window and stairway guards and gates, avoiding walker use
- Choking and strangulation prevention: Keeping small objects and balloons or plastic bags away from infants, blind and drapery cord safety
- Drowning prevention: Supervising baths, emptying buckets
- Safe sleep environment: “Back to sleep” in a crib that meets current safety standards
- CPR training: Parent knowledge of infant or child CPR and local emergency medical services (911)

#### PRESCHOOLERS

- Traffic safety: Appropriate use of car safety seats, not leaving children unsupervised in or around cars
- Burn prevention: Smoke alarm batteries; keeping children away from hot objects
- Fall prevention: Window and stairway guards and gates; preventing furniture tip-overs
- Poison prevention: Storage of poisons; poison control phone number (1-800-222-1222)
- Drowning prevention: Pool fencing; touch supervision
- Firearm safety: Preferably keeping firearms out of the home or at least keeping firearms unloaded and locked separately from locked ammunition

#### SCHOOL-AGED CHILDREN

- Traffic safety: Booster seat and seat belt use, avoiding riding on ATVs and in the beds of pickup trucks; safe pedestrian practices; helmets for biking
- Water safety: Swimming lessons, but no swimming alone; personal flotation devices for boating
- Sports safety: Safety equipment, physical conditioning, and protective equipment for rollerblading and skateboarding
- Firearm safety: Preferably keeping firearms out of the home or at least keeping firearms unloaded and locked separately from locked ammunition; asking about firearms in other homes the child visits

#### ADOLESCENTS

- Traffic safety: Seat belt use, role of alcohol in motor vehicle crashes, and minimizing distracted driving; graduated driver licensing; rules for teenage drivers; helmets for biking, motorcycling, and riding an ATV
- Water safety: Role of alcohol and other drugs in water-related injuries; personal flotation devices for boating
- Sports safety: Safety equipment; physical conditioning
- Firearm safety: Preferably keeping any firearms out of the home or at least unloaded and locked separately from locked ammunition

ATV, all-terrain vehicle; CPR, cardiopulmonary resuscitation.

Modified from American Academy of Pediatrics Committee on Injury, Violence, and Poison Prevention. Office-based counseling for unintentional injury prevention. *Pediatrics*. 2007;119:202–206.

evaluate prevention interventions. For a complete list of all policy statements from the American Academy of Pediatrics Committee on Injury, Violence, and Poison Prevention visit: [pediatrics.aappublications.org/collection/injury-violence-poison-prevention](http://pediatrics.aappublications.org/collection/injury-violence-poison-prevention).

## ANTICIPATORY GUIDANCE

Evidence of positive outcomes after injury prevention counseling in clinical practice was identified by a structured review of the literature. The evidence for the effectiveness of injury prevention counseling is stronger in some areas than it is in others, prompting continual calls for additional research, improvements in counseling, and investment in more passive injury-control strategies. For example, the redesign of baby walkers resulted in a dramatic decrease in injuries associated with falls down stairs with this product, demonstrating the effectiveness of the passive prevention approach after years of unsuccessful anticipatory guidance and the use of warning labels.

Even though injury prevention counseling has become a cornerstone of pediatric practice, it can be

daunting not only because of the time and expertise it requires, but also because of its breadth. Injury risk is so universal and the sources of possible injury so diverse that a pediatrician cannot counsel on all possible risks. Injury prevention topics can be prioritized based on severity of the injury, frequency with which the injury occurs, and availability of effective preventive strategies. Pediatricians will want to be sensitive to the individual circumstances of patients and families as well. For instance, farm families may need advice that city families do not, and vice versa. Knowing that a family has a boat or a backyard swimming pool prompts a special discussion of drowning risk. In another example of the need to customize anticipatory guidance, counseling a family that has 2 automobiles about car safety seats poses a different set of issues than does counseling a family that relies on taxis for transportation, yet child passenger safety is a high priority for both.

The American Academy of Pediatrics (AAP) recommends that parents be given advice by the pediatrician about various injury issues, depending on the age of the child (Box 42-1). The AAP also provides several tools to facilitate counseling, including age-specific survey instruments to assess risk and handouts for families, as

part of TIPP—The Injury Prevention Program. (The counterpart AAP program for intentional injury prevention is Connected Kids: Safe, Strong, Secure, as described in Chapter 44, Violence Prevention.)

Counseling about any injury prevention topic requires both knowledge and counseling skill. In addition to TIPP materials, several resources are listed at the end of this chapter that can provide a pediatrician with the knowledge for advising parents (and communities) about injury prevention. Counseling technique is not specific to injury prevention, but can be adapted from existing methods for prompting and supporting healthy behavior change (eg, motivational interviewing). Counseling techniques that include motivational interviewing are addressed in Chapter 31, Applying Behavior Change Science, and Chapter 46, Effective Communication Strategies.

### Traffic Safety

#### Car Safety Seats

Because motor vehicle crashes are the leading cause of death of children and adolescents, the topic warrants frequent discussion during well child care. Use of car safety seats is a complex issue that pediatricians should not expect to master fully. Rather, pediatricians should know how to counsel parents on appropriate car safety seat selection based on developmental milestones (age, height, weight, and behavior) and where to refer parents for more information. When counseling on car safety seat selection, pediatricians should be familiar with state laws. However, recognizing that state laws often do not reflect best practice in car safety seat use is important. Table 42-3 provides information about car safety seat selection. Parents should be encouraged to read the instruction manuals for their car safety seats and vehicles to learn how to install and use car safety seats. For more

information, parents can be referred to local *child passenger safety technicians*; a pediatric practice may even choose to have a staff member complete the 3- to 4-day training course to become a certified technician.

#### Counseling Teen Drivers

Counseling on motor vehicle safety remains important even after children have outgrown car safety seats. In fact, such counseling may be more important because motor vehicle–related death rates increase dramatically in adolescence, and novice teen drivers and their passengers are at particularly high risk. The pediatrician can play a key role in helping parents and teens negotiate their changing relationship, balancing the need to ensure the teen's safety with the teen's growing independence and increasing mobility. A state's graduated driver licensing (GDL) system may provide a good starting point for counseling, and pediatricians should be familiar with their state's laws. Under GDL, teen drivers graduate from a learner's permit to an intermediate or provisional license to a regular driver's license after spending a required amount of time and demonstrating proficiency in a lower stage; each stage has its own restrictions. Although all states have a 3-tiered GDL system, few states' systems meet all recommendations from the AAP and other safety organizations. Therefore, parents should be counseled about additional restrictions (eg, limits on the number of teenage passengers, limits on nighttime driving) that they should place on novice teen drivers. Parents and teens both should be counseled on seat belt use and the dangers of impaired driving. They should also be encouraged to have a safe ride agreement, whereby the teen promises to call the parent rather than driving while impaired or with another impaired driver and the parent agrees to provide a ride home in a nonjudgmental way. Pediatricians can consider

**Table 42-3**

**Appropriate Car Safety Seat Selection Based on Child's Age, Height, and Weight**

IF THE CHILD IS	USE THE FOLLOWING TYPE OF CAR SAFETY SEAT	AND REMEMBER THE FOLLOWING
Younger than 2 years AND below the height and weight limits of his rear-facing car safety seat	Rear-facing car safety seat (infant-only or convertible)	NEVER place a rear-facing car safety seat in the front seat with an airbag.
Older than 2 years OR above the height or weight limit of her rear-facing car safety seat	Forward-facing car safety seat (convertible, combination, or forward-facing only) to seat's height or weight limit.	When switching a convertible seat from rear-facing to forward-facing, adjustments are usually needed to the harness, the angle of the seat, and the seat belt.
Too tall or heavy for a forward-facing seat with a harness	Belt-positioning booster seat	Booster seats must be used with lap and shoulder belts.
Big enough to fit in the adult seat belt (usually about 4'9" tall and between 8 and 12 years of age)	None. Use the vehicle's seat belt if it fits properly (shoulder belt across chest and shoulder, lap belt low and snug on thighs, child's back against vehicle seat back, and knees bent at edge of vehicle seat).	Children should sit in the back seat until they turn 13 years of age.

Adapted from American Academy of Pediatrics Committee on Injury, Violence, and Poison Prevention. Child passenger safety. *Pediatrics*. 2011;127:788–793.

having a family develop a parent-teen driving contract that specifies restrictions on teen drivers, when the restrictions will be relaxed, and the consequences for violating the restrictions.

### Firearms

Because firearms-related injuries (unintentional and intentional) are the second leading cause of death of children and adolescents, firearms are an important topic on which to provide anticipatory guidance. Pediatricians are often reluctant to counsel on this topic, and parents may view such counseling as intrusive or outside the purview of pediatrics. Fortunately, strategies are available that can make counseling on firearms more palatable to both parents and pediatricians. For families with infants and toddlers, firearms can be discussed in the context of childproofing and children's natural curiosity. For parents of depressed adolescents, the association between presence of firearms in the home and higher risk for teen suicide can be discussed. Especially for parents who are receptive to firearm injury prevention counseling, the pediatrician can introduce the concept of asking about the presence of guns in other homes where their children spend time.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *Injury Free Coalition for Kids* (Web site), ([www.injuryfree.org](http://www.injuryfree.org))
- *Insurance Institute for Highway Safety* (Web site), ([www.iihs.org](http://www.iihs.org))
- *National Center for Injury Prevention and Control* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/injury](http://www.cdc.gov/injury))
- *National Highway Traffic Safety Administration* (hotline), 1-888-327-4236 ([www.nhtsa.gov](http://www.nhtsa.gov))
- *National Poison Control Number* (hotline), 1-800-222-1222 ([poisonhelp.hrsa.gov](http://poisonhelp.hrsa.gov))
- *Safe Kids Worldwide* (Web site), ([www.safekids.org](http://www.safekids.org))
- *Teen Driving* (fact sheet), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/state-advocacy/Documents/GDL.pdf](http://www.aap.org/en-us/advocacy-and-policy/state-advocacy/Documents/GDL.pdf))
- *US Consumer Product Safety Commission* (Web site), ([www.cpsc.gov](http://www.cpsc.gov))
- *WISQARS*, Web-based Injury Statistics Query and Reporting System (database), Centers for Disease Control and Prevention ([www.cdc.gov/injury/wisqars](http://www.cdc.gov/injury/wisqars))

### Engaging Patient and Family

- *Pediatric Patient Education* (handouts), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *The Injury Prevention Program (TIPP)* (handouts), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

### Medical Decision Support

- *TIPP—A Guide to Safety Counseling in Office Practice* (booklet), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

## AAP POLICY

- American Academy of Pediatrics Committee on Injury, Violence, and Poison Prevention, Committee on Adolescence. The teen driver. *Pediatrics*. 2006;118:2570–2581. Reaffirmed June 2010 ([pediatrics.aappublications.org/content/118/6/2570](http://pediatrics.aappublications.org/content/118/6/2570))
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## Chapter 43

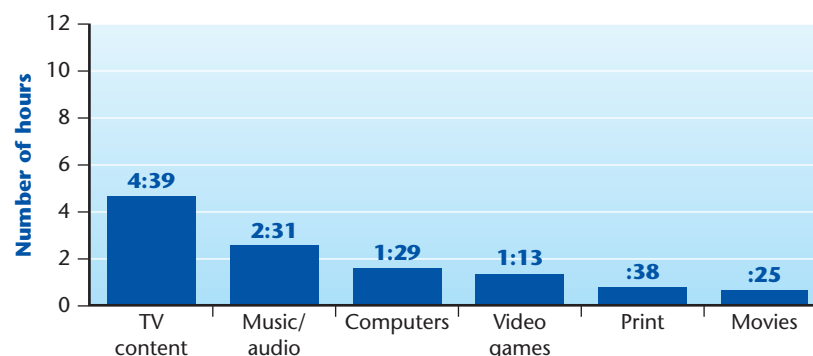
# HEALTHY USE OF MEDIA

Victor C. Strasburger, MD

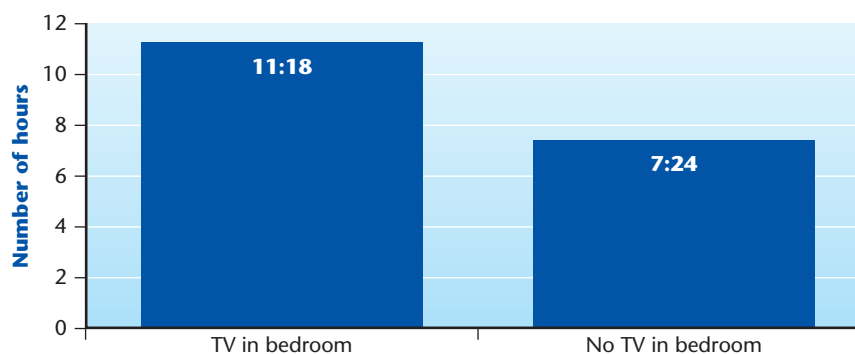
The media can potentially affect almost every area of concern that pediatricians and parents have about children and adolescents, including sex, drugs, violence, suicide, obesity, eating disorders, and school problems. Although newer media (eg, the Internet, social networking sites, tablets, and smart phones) seem to be causing the most concern, there are very few studies on their actual influence. In contrast, several thousand studies attest to the behavioral effects of traditional media (eg, TV, movies, and videos). Pediatricians can help protect young people from harmful media influence, regardless of the medium involved, and can advise parents on how to maximize positive media influences.

## TYPES OF MEDIA

By the time today's children and teens reach age 70, they will have spent 7 to 10 years of their lives watching television and using a variety of other media. Television remains the predominant medium used by children and teens of all ages, although it is now often accessed on alternative newer platforms—the Internet, smart phones, tablets, and so on. A nationwide 2009 sample of more than 2,000 children in grades 3 through 12 found that young people spend an average



**Figure 43-1** Media use according to platform. (Derived from Rideout VJ, Foehr UG, Roberts DF. Generation M<sup>2</sup>: Media in the Lives of 8- to 18-Year-Olds. Menlo Park, CA: Henry J. Kaiser Family Foundation; 2010: 2.)



**Figure 43-2** Media use according to television environment and rules. (Derived from Rideout VJ, Foehr UG, Roberts DF. Generation M<sup>2</sup>: Media in the Lives of 8- to 18-Year-Olds. Menlo Park, CA: Henry J. Kaiser Family Foundation; 2010: 2.)

of more than 7 hours a day with a variety of different media (Figure 43-1). In a 2009 poll, 22% of teenagers reported logging on to their favorite social media site more than 10 times a day, and more than half of adolescents logged on to a social media site more than once per day. Nearly all (93%) American teenagers use the Internet, with an average of nearly 40 hours per week online; 70% of 12- to 17-year-olds own a cell phone; one-third of texting teens send an average of 3,364 texts per month; and 80% own a digital music player and a game console. Despite the American Academy of Pediatrics (AAP) recommendation that children under the age of 2 should not watch TV, a study of 0- to 2-year-olds found that two-thirds of them watch TV for an average of 75 minutes per day and one-third watch nearly as much video. A more significant finding is that nearly three-fourths of American children and teens have a TV set or DVD player in their own bedroom, one-half have a video game console, and more than one-third have a computer. The presence of a bedroom TV increases time spent with media considerably (Figure 43-2).

## CONTENT ANALYSES

Content analyses are studies of exactly what children and teens view in different media. Although the studies do not address the issue of causality, they do give an

accurate snapshot of what content is potentially being viewed. Virtually all of these content studies contain worrisome data about the amount of sex, drugs, and violence to which young people are exposed.

## Newer Media

Newer media are worrisome in that they provide uninterrupted access to media content without parental oversight. Cyberbullying, “sexting,” and access to pornography represent 3 significant health threats, but there are other risks as well. At the same time, newer media allow instant communication with peers and near-instantaneous access to an amazing amount of information; so pediatricians should recognize both the benefits and the potential risks.

Estimates of cyberbullying vary, but most studies find that 20% to 40% of teenagers report being bullied online at least once. Cyberbullying may have significantly more detrimental effect than in-person bullying because the home is no longer a safe haven, the bullying may be anonymous, and the harassing material remains online indefinitely. Estimates of sexting (sending or posting nude or seminude photos or videos via cell phone or the Internet) have varied and have been as high as 20% of all teens, but a recent study puts the figure closer to 1% of teens having sent a sexually graphic message and 5% having received one. In an



older study, two-thirds of teenagers have accidentally stumbled across pornography online. In a newer study, 54% of boys and 17% of girls reported lifetime intentional pornography exposure. Children and teens also see considerable alcohol and drug content in online videos, and more than half of social networking profiles contain references to substance abuse.

The behavioral effects of newer media remain to be determined. Currently, there are only a handful of studies, but that will undoubtedly change. At the same time, pediatricians and parents need to recognize that there are thousands of studies that already document the positive and negative effects of traditional media and that storytelling media (eg, TV, movies) may have the greatest behavioral effect.

Among college freshmen, displaying sexual references is positively correlated with intention to begin having sexual intercourse. Similarly, adolescents who meet their sexual partners online are more likely to report a higher number of sex partners and a lower age at first intercourse, although not more sexually transmitted infections. As might be expected, young people who view sexually suggestive photos on social media estimate that more of their peers are having unprotected sex and sex with strangers than actually are.

Pornography use and its effects on adolescents are obviously difficult to study, but a few studies have been done. Use of pornography seems to foster beliefs about women as sex objects and decrease attractiveness of actual partners, and may even be associated with earlier sexual activity. Exposure to violent pornography has been associated with coercive sex in 2 recent studies.

Only 3 studies to date have examined the behavioral effects of new media on substance use: a correlational study from Columbia University found that compared with teens who spend no time on social networking sites, those who do were 5 times likelier to use tobacco, 3 times likelier to use alcohol, and twice as likely to use marijuana. A 6-month longitudinal study of 1,563 tenth-grade students in 5 Southern California high schools found that exposure to friends' online pictures of partying or drinking was significantly associated with both smoking and alcohol use. An even larger study of 1,787 California students in grades 6 through 8 over 2 years examined all media use (Internet videos, social networking sites, movies, television, magazine ads, songs, and video games) and found that greater alcohol-related media exposure in grade 7 was significantly associated with a higher probability of alcohol use in grade 8.

### **Problematic Internet Use**

Problematic Internet use (PIU) refers to use that is, in Moreno and colleagues' definition, "risky, excessive or impulsive in nature leading to adverse life consequences, specifically physical, emotional, social, or functional impairment." The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* lists it as a disorder needing further study. It can include Internet addiction, increased social anxiety or depression, a change in offline relationships, or loss of sleep. Pediatricians are in a unique position to counsel parents and patients about PIU, given that

Internet use usually begins at a young age. Estimates of prevalence vary, but 4% to 6% of adolescents and college-age students seem to be affected according to several recent studies.

### **Traditional Media**

#### **Violence**

The average American child sees an estimated 10,000 acts of violence per year on TV alone. Of the 10,000 acts, 500 or more are considered high risk: the perpetrator is an attractive role model; the violence is portrayed as being realistic, justified, or unpunished; or the consequences of the violence are not shown. (See also Chapter 44, Violence Prevention, and Chapter 139, Disruptive Behavior and Aggression.)

#### **Sex**

According to the most comprehensive analysis of American television ever performed, more than 75% of all prime-time shows contain sexual content, 1 of every 7 shows includes a portrayal of sexual intercourse or implied intercourse, and only 15% of shows with sexual content mention any of the risks or responsibilities that go with having sex (Figure 43-3). In addition, movies, music videos, and advertising have all become increasingly suggestive. At the same time, the media far outrank parents or schools as a source of information about birth control.

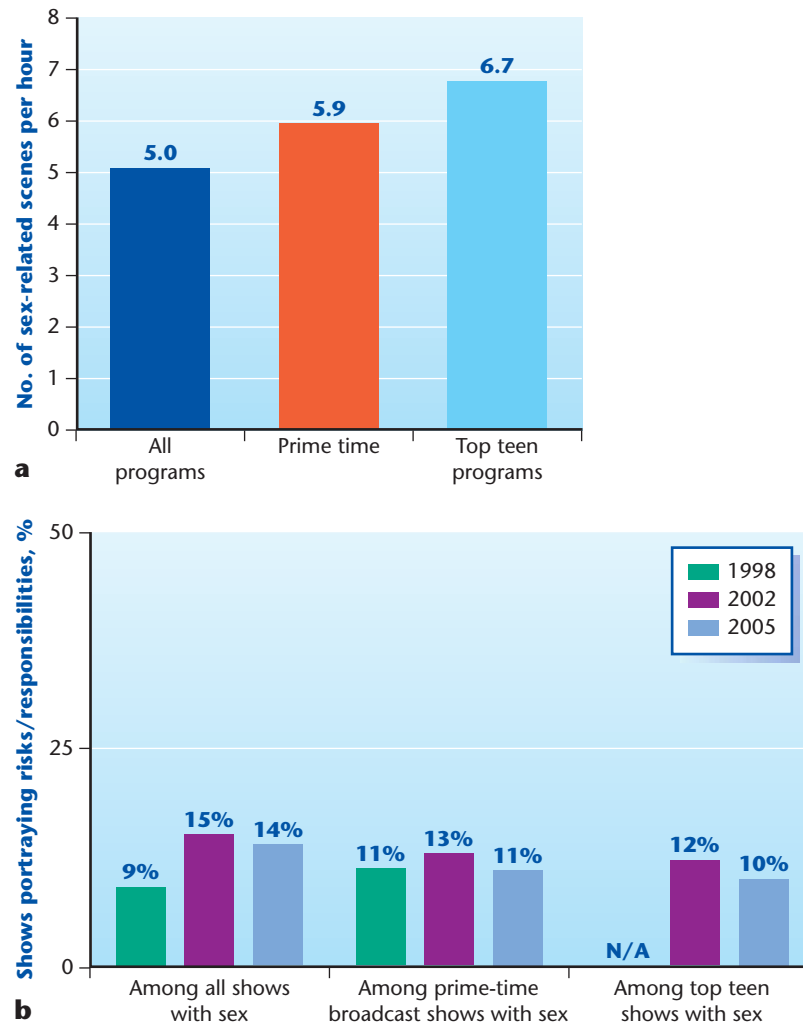
#### **Drugs**

Alcohol, tobacco, or illicit drugs are present in 70% of prime-time TV programming, 95% of top-grossing movies, and 50% of music videos. Despite the federal government's policy and enforcement priorities, it is 2 legal drugs—alcohol and tobacco—that pose the greatest threat to youth, not illicit drugs; and alcohol and tobacco are far more prevalent in mainstream media than are illicit drugs (Figure 43-4). Cigarette smoking, in particular, remains common in Hollywood movies: although the number of smoking scenes has decreased significantly from the late 1990s, more than half of all PG-13 movies still contain smoking. Even many G-rated animated children's movies contain high levels of tobacco and alcohol use.

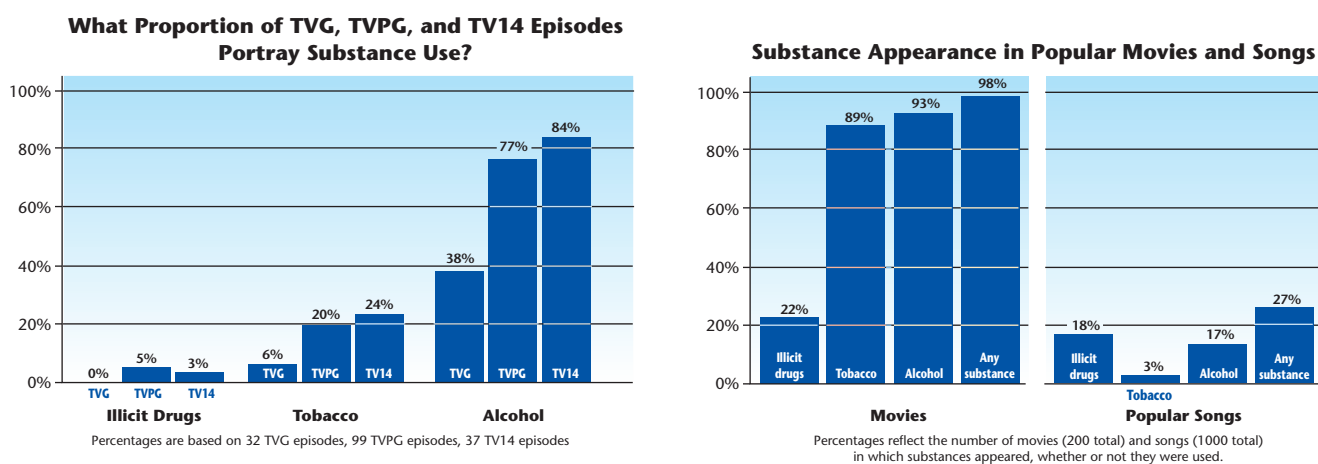
## **HOW MEDIA AFFECT CHILDREN AND ADOLESCENTS**

By sheer numbers, the media are a powerful influence on young people. The 7 hours a day spent with media are 7 hours not spent reading, exercising, or playing with friends. This phenomenon is known as the *displacement effect*. Most young people spend more time watching screen media than in any other activity except for sleeping. Television alone accounts for 15,000 hours by the time teens graduate from high school, compared with only 12,000 hours spent in formal classroom instruction.

There are many theories about how media affect youngsters. According to the social modeling theory, the media expose young people to a variety of different role models who demonstrate potential behaviors—both negative and positive—to young and sometimes impressionable viewers. Role modeling may be a crucial factor in whether preteens or teens begin smoking



**Figure 43-3** A, Programs for teenagers actually contain more sexual content scenes per hour than adult-oriented programs. B, Despite the prevalence of sexual content on television, fewer than 14% of shows contain any mention of the risks and responsibility of sexual activity. (Reproduced with permission from Kaiser Family Foundation. Sex on TV 4, Executive Summary 2005. <http://kff.org/other/sex-on-tv-4-exec-summary>. October 30, 2005. Accessed October 27, 2015.)



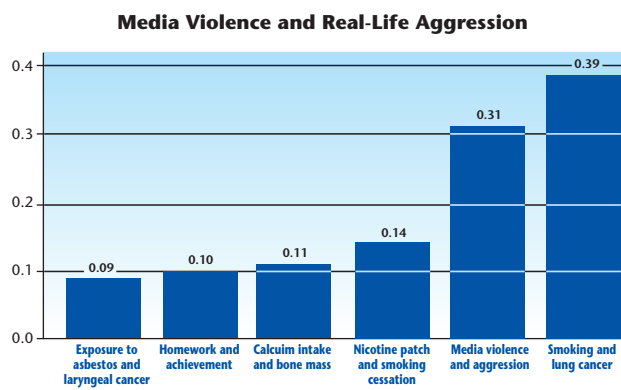
**Figure 43-4** Although marijuana and cocaine are targets of federal antidrug advertisements, the 2 most significant drugs for teenagers are tobacco and alcohol; they are the drugs most often portrayed in mainstream media. (From Christenson PG, Henriksen L, Roberts DF. Substance Use in Popular Prime-Time Television. Washington, DC: Office of National Drug Control Policy; 2000, and Roberts DF, Henriksen L, Christenson PG. Substance Use in Popular Movies and Music. Washington, DC: Office of National Drug Policy Control Policy; 2000.)

cigarettes, drinking alcohol, or having sex. In that sense, the media function as a kind of super-peer, making unhealthy behavior seem like normative behavior (“everyone’s doing it”). According to the cultivation hypothesis, people who view a lot of television and other media tend to think that media depict real behavior in the real world or that the real world should conform to media rules. Clearly, the media represent a powerful teacher of children and adolescents. The only question is, what are the media teaching them? One group of researchers worries about the media’s ability to influence young people’s attitudes and perceptions about the world and the media’s “stalagmite effects”—cognitive deposits built up almost imperceptibly from the constant drip of television’s electronic limewater.”

## MEDIA VIOLENCE

According to many researchers, the controversy about whether media violence influences aggressive behavior should be over. More than 1,000 studies and 2,500 reviews document the effect of media violence on children’s and adolescents’ behavior. By contrast, fewer than 30 studies have found no relationship. Given the difficulty of undertaking social science research and of pinpointing influences on human behavior, these 2 statistics seem rather remarkable.

The research demonstrates that high levels of television viewing are related causally to aggressive behavior in some children and teens and to the acceptance of aggressive attitudes (desensitization) in nearly everyone. In several longitudinal studies, exposure to media violence at young ages has been found to be a highly significant risk factor for adolescent or young adult aggressive behavior and criminal violence. Children seem to learn their attitudes about violence at a very young age, and these attitudes apparently persist throughout their lives. American media are uniquely problematic in 2 important ways: First, screen media are rife with portrayals of “justified” violence (the “good guy” beats up or kills the “bad guy”); portraying interpersonal violence as being justified is the strongest positive reinforcement known. Second, guns are glorified in the media, at the same time that they contribute heavily to the second and third leading causes of death among teenagers, homicide and suicide. On TV alone, 25% of all violent episodes involve gun play. First-person shooter video games are used by the military and by law enforcement agencies to teach new recruits how to shoot. In one of the school shootings during the 1990s, a teenager walked into his school in Paducah, Kentucky, and opened fire on a prayer group. In spite of never having fired a gun in his life, Michael Carneal hit 8 different teens with 8 shots, all in the head and upper torso, resulting in 3 deaths and 1 case of paralysis. He had learned to fire a gun from playing first-person shooter video games. Overall, the research suggests that media violence may contribute to between 5% and 15% of all violence in the United States. The connection between media violence and real-life aggression is nearly as strong as the connection between smoking and lung cancer (Figure 43-5).



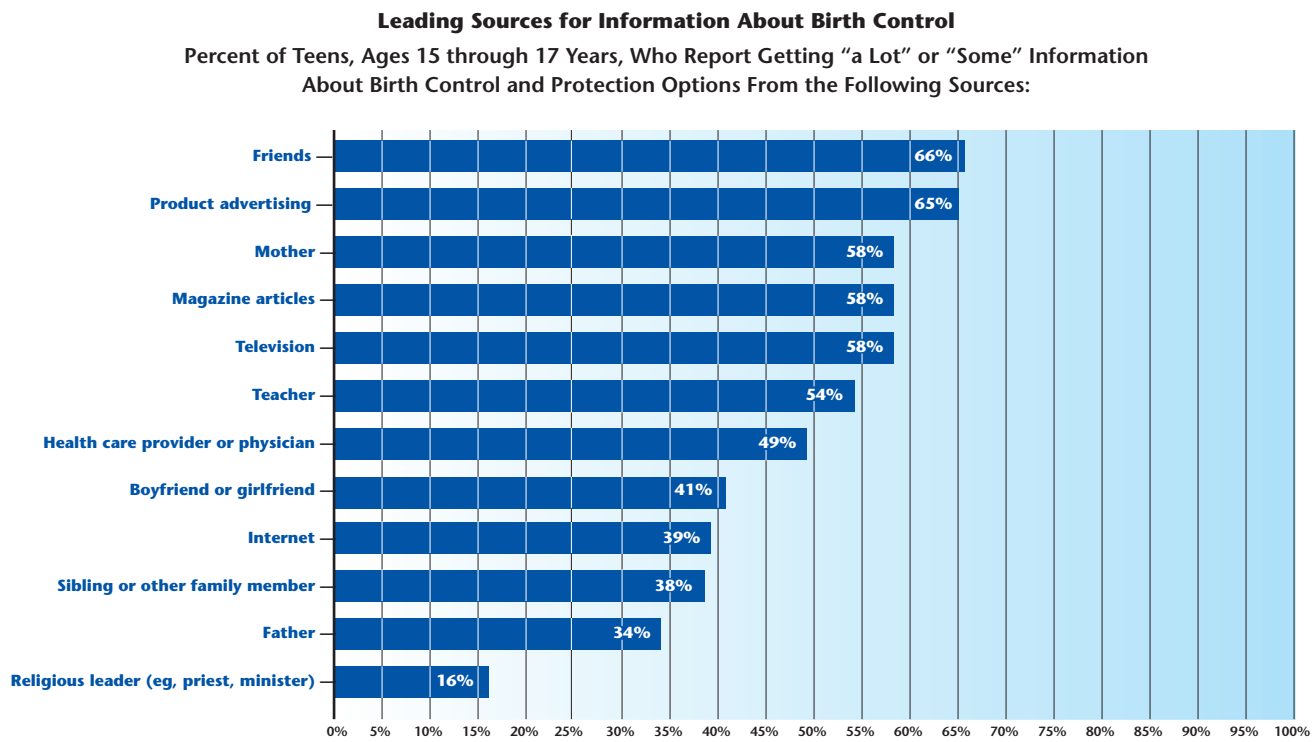
**Figure 43-5** The impact of media violence on real-life aggressive behavior is stronger than many commonly accepted public health risks and nearly as strong as the link between smoking and lung cancer. (Adapted with permission from Bushman BJ, Huesmann LR. *Effects of televised violence on aggression*. In: Singer DG, Singer JL, eds. *Handbook of Children and the Media*. Thousand Oaks, CA: Sage, 2001.)

## SEX AND THE MEDIA

American media have arguably become the leading sex educator of teenagers today in the United States. With parents traditionally reluctant to discuss sexual matters in detail with their teens, and after a decade of abstinence-only sex education, teenagers who want more information about sex, sexuality, and contraception increasingly look to the media for information. A 2004 national survey of teenagers ages 15 to 17 found that the media far outrank parents or schools as a source of information about birth control, for example (Figure 43-6). Unfortunately, teenagers are much more likely to find sexually suggestive material in the media than factual information or portrayals of sexual responsibility.

Unlike the thousands of studies about media violence, there are only a handful of studies on media portrayal of sex and sexuality. There are now 20 longitudinal studies that find that teens exposed to sexual content at a young age are more likely to begin having sexual intercourse earlier than their peers who did not have this exposure. The most comprehensive study—a 2006 survey of more than 1,000 North Carolina 12- to 14-year olds—found that exposure to sexual content in a wide variety of media (TV, movies, music, magazines) accelerates white adolescents’ sexual activity and doubles their risk of early intercourse.

Despite the suggestiveness of American media, and the fact that 2 national surveys have documented that most American adults (even Catholics, whose religious doctrines oppose most birth control methods) favor the advertising of birth control products on television, 3 of the major TV networks refuse to air advertisements for oral contraceptives, and 3 refuse to air advertisements for condoms. Nevertheless, drug companies advertising Viagra, Levitra, and Cialis spent \$343 million in 2004 to advertise their products—probably 10 times the amount spent on TV advertisements for birth control products.



**Figure 43-6** The media represent a leading source of information about birth control for teens. (From Sex Smarts: Birth Control and Protection. Copyright © 2004, The Henry J. Kaiser Family Foundation. Available at: [kaiserfamilyfoundation.files.wordpress.com/2013/01/sex-smarts-birth-control-and-protection-brchure.pdf](http://kaiserfamilyfoundation.files.wordpress.com/2013/01/sex-smarts-birth-control-and-protection-brchure.pdf). Accessed November 24, 2015.)

## OBESITY AND EATING DISORDERS

The media play a crucial role in the development of young girls' body self-image. For example, a large study of nearly 7,000 9- to 14-year-olds found that girls who want to look like TV or movie stars were twice as likely to be concerned about their weight, to be constant dieters, or to engage in purging behavior. A study of nearly 3,000 Spanish 12- to 21-year-olds over a 19-month period found that those who read girls' magazines had a doubled risk of developing an eating disorder. The Pacific isle of Fiji had virtually no problems with eating disorders until American television shows were introduced. In a survey 2 years later, 75% of the teen girls reported feeling “too big or fat.” Social network exposure in Fiji has also been shown to be associated with the development of eating disorders.

At the opposite end of the spectrum, there seems to be an important connection between TV viewing and obesity, although the exact nature of it remains to be determined. Children and adolescents see more than 5,000 food ads per year, and most of the ads are now for fast food. Several longitudinal studies and many cross-sectional studies have found a significant association between TV viewing and obesity. Children with a television set in their own bedroom have a 30% increased risk of being overweight. A simple 6-month curriculum that reduced media use resulted in significant decreases in body mass index in children in grades 3 and 4. It is unknown whether the connection exists because of food advertising, snacking while

watching television, displacement of exercise, or interference with sleep.

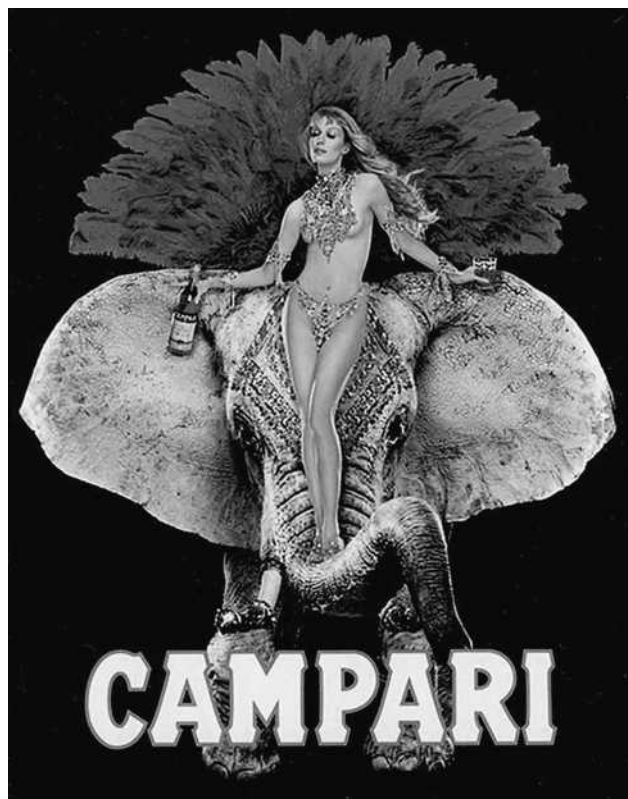
## DRUGS AND THE MEDIA

Although American society wants children and teens to “just say no” to drugs, nearly \$20 billion is spent on cigarette, alcohol, and prescription drug marketing and advertising. Frequently, alcohol and tobacco advertisers use sex to sell their products (Figure 43-7).

United States tobacco manufacturers spend more than \$10 billion per year on advertising and promotion. Several large longitudinal and cross-sectional studies have found that approximately one-third of all adolescent smoking can be attributed to tobacco advertising and promotions. In addition, cigarette smoking remains unacceptably high on prime-time TV and especially in movies. Similarly, many studies have found that a child or teen who sees a lot of smoking scenes—especially in R-rated movies—has double the risk of beginning smoking. A child or teen who views more than 4 hours of TV per day is 5 times more likely to begin smoking than a child or teen who watches fewer than 2 hours per day. Seeing scenes of tobacco use in movies may, in fact, exceed the influence of family members and peers on a teenager's decision to smoke.

Beer and wine manufacturers spend nearly \$6 billion per year on advertising. The average American teen sees 2,000 beer and wine commercials per year, with





**Figure 43-7** Alcohol manufacturers routinely use sexual images to sell their products.

most of them concentrated during sports programming. On prime-time television, 71% of programs depict alcohol use. As with cigarette advertising and program content, the research suggests that adolescents exposed to alcohol advertising and depictions are more likely to become drinkers.

Relatively new to media is advertising for prescription drugs. Currently, \$4 billion is spent on it, and this figure is likely to increase. Prescription drug advertising gives young people the message that a drug is available to cure all ills, and for every occasion (including sexual intercourse, “when the time is right”). The United States is one of only 2 countries in the world that even allow advertising of prescription drugs (New Zealand is the other).

## OTHER EFFECTS

In 1971, the average age for the onset of TV viewing was 4 years; now it is 5 months. Currently, there are no studies showing beneficial effects of allowing babies under the age of 2 years to watch TV or videos, and there are nearly a dozen studies showing potential language delays.

Researchers have also found associations between increased screen time and the development of attention-deficit disorder, depression, poorer school performance, and sleep deficits. “Internet depression” may also be a side effect of newer technology.

## BEDROOM MEDIA

Media effects are increased significantly when a TV is present in the bedroom. Viewing increases by 1 to 2 hours per day, risk of overweight increases by 31%, and the likelihood of smoking doubles. Parents are less able to monitor viewing habits, children participate in fewer activities such as reading and hobbies, and sleep is shortened. As an increasing number of homes are now wired for Internet use, the presence of computers, smartphones, or tablets in the bedroom can be just as problematic.

## THE ROLE OF THE PEDIATRICIAN

Although they sometimes may feel overwhelmed by the amount of counseling they need to do, by addressing media use pediatricians can play a significant role in nearly every health issue about which they and parents are concerned. Consequently, a minute or 2 of counseling about media and its effects may pay rich dividends.

### Counseling Parents

Asking 2 short questions may give an important glimpse into a child or teenager’s risk:

1. How much media such as television and video games does he or she consume in an average day?
2. Does he or she have a television set or Internet access in the bedroom?

The current AAP recommendation is that parents be counseled to limit their child’s total entertainment media time to no more than 2 hours per day, that children under the age of 2 should not view television, and that television sets should not be present in children’s bedrooms. Nonetheless, a recent survey of 365 pediatricians found that only one-half recommended limitations on total screen time, and nearly one-half were not interested in learning about media effects on young people through continuing medical education programs.

Some critics have assailed the AAP for its 2-hour recommendation and for not having suggestions about infants’ use of new technology. The 2-hour rule was derived from several large longitudinal studies that found that excessive screen time for young children was a major risk factor for obesity in adolescence and even adulthood. Unfortunately, the AAP does not yet have recommendations about cell phone or tablet usage, either for older children and adolescents or for infants, simply because no data are yet available. Many questions are unanswered, including how total media use should be assessed, if time spent doing homework online should “count,” if tablet use by infants predisposes them to more media use when older, and if reading online or on a tablet is fundamentally different from reading a book. One researcher has suggested that tablets with specific programs for infants may be useful since they are interactive, but others strongly disagree.

### Media Education

A hundred years ago, to be literate meant that you could read and write. In 2015, to be “literate” means

that you can decipher and decode a bewildering array of media and media messages. Media education programs can teach young people how to use media properly, how to understand media, and how to avoid harmful media influences. In particular, media education programs have been successful in reducing violence, obesity, and drug use. The United States is one of the few Western nations lacking a comprehensive, school-based media education program for children.

### Advocacy

Since it formed its Task Force on Children and Television in 1983, the AAP has been a leader in trying to create a healthy media environment for children and adolescents. Pediatricians can become involved at the local, state, or national level. Specific public health proposals that physicians might support include:

- A mandate for media education for all school children from kindergarten through grade 12
- Development of more effective monitoring tools and filters for children's and teens' use of the Internet and social networking sites
- Creation of parent education programs that would help them teach their children media literacy
- A mandate for a media education component for all sex education and drug education programs
- Greater dialogue between public health organizations and the creative community in Hollywood, including topics such as cigarette smoking, use of profanity, violence, and sexual suggestiveness in movies and on television
- Greater restrictions on cigarette and alcohol advertising, including the creation of more aggressive counter-advertisements
- Support for the television industry to air contraceptive advertisements during prime-time programming
- Creation of voluntary standards for the advertising industry regarding the use and depiction of severely underweight models
- Greater pressure on Congress to restrict fast-food advertising on television
- Creation of a universal ratings system. Currently, each medium has its own idiosyncratic ratings system, which is confusing to parents. A universal system would provide actual content information to parents, not just age-based categories (eg, PG-13, TV-Y7).
- More funding for a variety of much-needed media research

A half century ago, no one could have anticipated that limitations would be placed on tobacco advertising; that workplaces, restaurants, and airplanes would be smoke free; that a multimillion-dollar settlement against the tobacco industry would occur; or that public opinion would be solidly mobilized against the unhealthy practice of cigarette smoking. Public health activism has created all of these circumstances. Media can, at times, be a powerful positive tool. Nevertheless, the negative effects are widespread and have been well documented. Despite the power of the new multinational media conglomerates and the reluctance of the entertainment industry, pediatricians *can* make a difference in the future.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Common Sense Media* (Web site), ([www.common sense media.org](http://www.common sense media.org))
- *How to Make a Family Media Use Plan* (fact sheet), American Academy of Pediatrics ([www.healthy children.org/English/family-life/Media/Pages/How-to-Make-a-Family-Media-Use-Plan.aspx](http://www.healthy children.org/English/family-life/Media/Pages/How-to-Make-a-Family-Media-Use-Plan.aspx))
- *The Internet and Your Family* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Media* (Web page), American Academy of Pediatrics ([www.healthy children.org/English/family-life/Media/Pages/default.aspx](http://www.healthy children.org/English/family-life/Media/Pages/default.aspx))
- *Media and Your Family: Television and Other Screens* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Pulling the Plug on TV Violence* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Ratings: Making Healthy Media Choices* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *SafetyNet* (Web site), American Academy of Pediatrics ([safetynet.aap.org](http://safetynet.aap.org))
- *Set the Rules for Internet Use* (fact sheet), American Academy of Pediatrics ([www.healthy children.org/English/family-life/Media/Pages/Set-the-Rules-for-Internet-Use.aspx](http://www.healthy children.org/English/family-life/Media/Pages/Set-the-Rules-for-Internet-Use.aspx))

### Medical Decision Support

- *Media and Children* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Pages/Media-and-Children.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Pages/Media-and-Children.aspx))

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## Chapter 44 VIOLENCE PREVENTION

Robert Sege, MD, PhD

### UNDERSTANDING VIOLENCE

Most peer violence in the United States results from conflicts among friends, acquaintances, or intimate partners. Estimates of the incidence of stranger violence range from 6% to 40% of new cases among all instances of personal violence. In addition to direct effects, violence may interfere with the education of children and adolescents; according to the Centers for Disease Control and Prevention, 7% of US high school students reported staying home from school at least 1 day in the past out of fear of violence.

Aside from physical violence between bullies and their targets, the distinction between victim and perpetrator is often fluid. From a public health perspective, the conclusion from years of research is dramatically simple: Young people who fight get hurt, whether in their families or in their communities.

Primary prevention in pediatrics includes helping children learn nonviolent problem-solving skills and attitudes. Developing these skills and attitudes begins in infancy. Effective, nonviolent discipline throughout childhood and adolescence is among the keys to developing resilient children who can resist being drawn into violence. In addition, parents can help reduce the risk of serious violence through attention to the child's environment—both decreasing exposure to media and domestic violence and decreasing access to firearms effectively reduce serious violence. Parents can encourage a nonviolent attitude by resisting toys that promote violence, such as toy guns, violent video games, and toys that encourage racial or ethnic stereotypes. Physician counseling around violence-related issues has been demonstrated to be effective.

### Violence Is Learned

In the 1980s, Patterson proposed a model based on an extensive review of the literature that accounted for the developmental progression of antisocial behavior. These results have been confirmed by more recent longitudinal studies. Aggression naturally increases during early childhood; parents serve to temper and redirect these impulses before school entry. Thus, the foundations of antisocial behavior begin with coercive or inadequate parenting in early childhood. Children whose parents are unable to set effective limits, particularly in households where corporal punishment is extensively used, develop dysfunctional behavior patterns in interactions with their peers and with adult authorities, including teachers. These children then have behavioral problems even before they enter school. In school, they are rejected by peers and have difficulties academically. In later childhood and adolescence, these ostracized children find each other and form peer groups that reward violence and antisocial behavior. The result of this cycle is juvenile delinquency.

Children growing up in violent urban settings have reiterated the importance of peer relationships but stressed the central role that being willing to fight plays in establishing social hierarchy. Boys, in particular, fear that if they do not establish themselves as courageous fighters early in life, they will be harassed by others. Nevertheless, most young men growing up in these communities learn how to avoid participating in violence; they repeatedly state that they are able to walk away from potential fights. Their resilience begins early in life.

This overall trajectory model provides a focus for interventions in the pediatric office. The 2009 American Academy of Pediatrics (AAP) policy statement on the role of pediatricians in youth violence prevention describes the clinical implications of a far-reaching model that traces the origins of violent behavior to earliest childhood. This policy suggests that pediatricians should adopt the *Connected Kids: Safe, Strong, Secure* anticipatory guidance program, which includes parent and patient education materials that encourage the development of resilience as a means of preventing child abuse and youth violence. Much of this material is incorporated in the third edition of *Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents*.

Although many social and environmental factors place children at high risk for violence, countervailing resilience factors, many beginning in early childhood, help reduce the risk.

### Witnessing Domestic Violence

The greatest risks of violence for infants and toddlers originate in the family through domestic violence and child abuse. In fact, witnessing violence in the home may lead to long-term health consequences as a result of the influence of toxic stress on the growing brain.

One of the goals of the pediatrician in speaking to families with new babies should be to assess family functioning, including the risk for domestic violence. Pediatricians who are concerned that a patient's parent has been the victim of spousal abuse should ask directly, but confidentially. The physician should have



information available in the office concerning battered women's advocates or shelters, legal aid resources, and safety plans. Many offices place small cards with relevant telephone numbers in the restroom so this information can be obtained discreetly.

### Witnessing Television Violence

Children in the United States spend more time watching television than in any other activity except sleep. While watching television, they observe an enormous amount of violence: the average child will see, on television, more than 10,000 deaths resulting from violence before completing high school. New media, including interactive games and mobile platforms, contribute to the high levels of violence exposure in children. However, many Americans resist the idea that exposure to violence in the media may be associated with subsequent violent behavior. Television violence differs from real-life violence in quality and quantity. On television, violence is used by both heroes and villains. As a result, young viewers generally view violence as socially acceptable behavior. Although adults feel competent to separate fiction from reality, research suggests that even adults who are exposed to television violence have a more negative view of society and feel more hopeless and alienated than do less frequent viewers. Adults who rely on television as their major news source, for example, feel less safe in their homes and neighborhoods than do other adults.

Children, because they have more difficulty separating facts from fantasy, are even more likely to be affected by television violence. The American Psychological Association, in reviewing hundreds of research studies, has concluded that exposure to television violence is a major risk for children. Children who view violent television are more likely to experience violence as victims or aggressors and are much less likely to intervene in tense situations, as bystanders, to reduce the likelihood of violence.

The AAP Council on Communications and Media recommends that pediatricians counsel families to reduce the amount of television viewed by young children. Television and its influence on children are discussed further in Chapter 43, Healthy Use of Media.

## VIOLENCE COUNSELING FOR FAMILIES IN HIGH-RISK URBAN COMMUNITIES

Neighborhood effects profoundly influence rates of violence, as youth develop strategies for living in violent neighborhoods and adopt behaviors that conform to their perceived social norms. Ethnographic research conducted in poor urban neighborhoods has identified another pattern of violence in which fighting and the willingness to fight are key components of a broader protective strategy for coping with extremely dangerous environments. Young people have observed that individuals who are unable to defend themselves are likely to fall prey to multiple and repeated attacks. Parents also understand this phenomenon and encourage their children to *stand up for themselves* by becoming able fighters. This pattern of violence is known as the *code of the streets* or the

*sucker* phenomenon. Other parents adopt protective strategies that keep their children out of harm's way in the first place, often by enrolling them in supervised after-school programs or keeping them safely in the house, watching television, rather than risking participation in the street culture.

In counseling patients in these communities, physicians need to be aware of this logic and refrain from offering unrealistic or counterproductive advice. Nevertheless, in discussions with most young people, it is important to remember that these same communities also contain nonviolent problem solvers who are well known to their classmates. Thus, the reality of the code of the streets need not prevent individual children and adolescents from avoiding violent injuries through avoiding the culture of violence. Although it is outside the scope of clinical practice, it should be noted that increasing attention to these neighborhood factors has led to a decrease in violence in many US cities.

## YOUNG CHILDREN

### Primary Prevention: Anticipatory Guidance

During infancy and early childhood, patterns of behavior and family interactions are established. The proper role of the pediatrician is to ameliorate risk factors and reinforce factors that protect the child from harm. In this age group, the following topics should be addressed when providing anticipatory guidance to parents: reduction in exposure to violence, including both domestic violence and television violence; and teaching appropriate, nonviolent methods of discipline (violence-free parenting). Because patients and families see their physicians often during this period, opportunities for brief, focused interventions are numerous. Research has demonstrated the effectiveness of focused guidance in encouraging parental use of alternatives to corporal punishment and awareness of the effects of television violence during early childhood.

### Violence-Free Parenting: Effective Parenting Without Corporal Punishment

As children enter the second year of life, patterns of discipline become established in families. Developmentally, this is the age when children are typically separating emotionally and cognitively from their parents—a time of potential stress in the family. Several lines of research evidence suggest a link between the use of corporal punishment and the subsequent use of violence by children as they grow. The AAP issued a policy statement in 1998 advocating that pediatricians counsel families in the use of alternatives to corporal punishment, a recommendation that has subsequently been incorporated into *Bright Futures*.

Many families, however, think that corporal punishment is necessary. A direct challenge to family beliefs is unlikely to lead to successful behavior change. Instead, the pediatrician may incorporate several salient observations about families who use corporal punishment. First, most of the parents who use corporal punishment do not like to hit their children. Instead, they use corporal punishment when all other methods



of correcting their child's behavior seem to have failed. This approach results in an erratic pattern of punishment because parents end up using threats and cajoling to avoid spanking. Second, these same parents often think that some children "don't need to be spanked." An appropriate goal for guiding these families is to teach them effective techniques for discipline that will allow their children to be among those who do not "need" to be spanked.

Most importantly, many parents have little knowledge of other effective alternatives to corporal punishment. Faced with a choice of spanking a child or letting him or her "run wild," many parents will opt for corporal punishment. The goal for anticipatory guidance at this age is to describe and endorse specific effective behavioral techniques to help discipline children. Maintaining toddler discipline is understood best from the child's perspective: toddlers gain power over their world by being able to understand what is happening and predict what will happen next. Maintaining a schedule for children—for example, bedtimes, naptimes, mealtimes, bath time, and playtime—helps give children this feeling of mastery.

Toddlers crave parental attention. The best kind of attention, of course, is parental praise for good behavior. In the absence of this positive reinforcement, toddlers may feel ignored and misbehave simply to grab the attention of their parents. The parental misperception that children who are praised will become self-centered and egotistical blocks the effective use of parenting and parental attention to encourage good behavior. Parents can be told very simply to tell their child, "I love it when you. . ."

Of course, times will occur when a child's misbehavior necessitates negative consequences. The most effective yet simple negative reinforcement technique for parents to use is *time-out* from positive reinforcement. Parents can be taught that time-out periods can be used judiciously, in the background of positive reinforcement, and consistently whenever the child has certain behavior patterns that need to be corrected. Children should be placed in time-out for approximately 1 minute per year of age. Parents should explain clearly to the child why the time-out was deserved and ignore the child during the time-out. Longer explanations and discussions should be deferred until things have calmed down.

## SCHOOL-AGED CHILDREN

As children get older, the external influences of their behavior become more important. Television has an enormous effect at this age, and children also begin dealing with playground fights and bullying.

### Bullying

Bullying prevention is an important task for school administrators. Bullying—the repeated infliction of harm on younger, smaller, or less powerful peers—is a nearly universal problem for school-aged children. Severe and even lethal bullying has been described in the United Kingdom, Japan, and Scandinavia, as well as in the United States. Bullies are usually larger and stronger (among boys) or more socially powerful

(among girls) than are their victims. Typically, bullies will begin the school year by trying to pick on several children. Children who become singled out as targets are weaker, physically and emotionally, and are unable to strike back, either physically or verbally. Although bullying is a problem of school-aged children, the negative behaviors often happen outside of school supervision: before school, after school, or at recess. Thus, classroom teachers are often unaware of the problem and are almost always unable to solve it without significant support from their administrators.

Bullying has severe adverse consequences for both bully and victim. Victims may be hurt physically, often cannot concentrate on their studies, and develop poor self-esteem. Recent news reports suggest that several perpetrators in school shootings in the United States were victims of bullies, and their lethal outbursts may have resulted from the effects of being bullied. Bullying may lead to a variety of behavioral presentations in the doctor's office.

Children who are bullies, in contrast, often feel powerful and effective. They typically come from chaotic households, and their parents feel ineffective in controlling their children's behavior. In many instances, bullies do not experience effective limit-setting at home. In the long term, the outcome for bullies is poor: by age 30, they are more likely to be incarcerated and less likely to be employed, married, or in other stable adult relationships than their peers.

Olweus has developed an effective antibullying program in Scandinavia that has led to a dramatic reduction in bullying. Based on this prototype, current antibullying programs begin with information gathering. Students who are asked to complete anonymous surveys are quite willing to report to school administrators where and when bullying usually occurs. Active efforts to control bullying occur on 3 levels: in the school building and grounds, in the classroom, and with individual students.

Schoolwide interventions focus on 2 issues: ensuring a safe physical environment and endorsing and coordinating classroom activities. To ensure a safe physical environment, staff monitoring is improved before and after school and at lunch, and any architectural or landscaping changes needed to improve supervision are made. A schoolwide assembly is convened in which the announcement is made that bullying will not be tolerated anywhere in the school environment and that all necessary steps will be taken to control it.

Classroom teachers lead discussions with their students. These discussions identify roles of bullies, victims, and bystanders and establish that bullying behavior will not be tolerated. The students themselves are helped to generate rules to prevent bullying and to prevent the social isolation of victims. The students agree to report bullying behavior, and resist attempts by the bullies to ostracize their victims. Successful antibullying programs work, in part, by mobilizing the large number of bystanders. In so doing, they make bullies less respected and accepted by their peers and thereby reduce the allure of bullying.

Individual measures reinforce the antibullying messages. When a bully is identified, the child receives

a stern message from the principal, and the principal also speaks with the child's parents. Parents are told of the possible short- and long-term consequences for their child, and a social worker or guidance counselor is assigned to work with them on setting appropriate and enforceable behavioral limits at home.

Bullying has also been identified as an important precursor to other forms of violence. The federal government has launched Stop Bullying Now, a comprehensive set of resources for parents, schools, and communities (see [www.stopbullying.gov](http://www.stopbullying.gov)). This approach implements the approach of Olweus in the American context.

Federal incentives have led to the adoption of school policies on bullying and bullying prevention in all 50 states. When bullying is identified as a problem, pediatricians may be able to refer parents to their child's school district for assistance.

## ADOLESCENTS

Violence among adolescents has long been a major concern of urban teens and their parents. Recent outbreaks of school violence have led to the same concerns among many other groups. Pediatricians have several clear roles to play in working with their adolescent patients to reduce the risk of violence: screening all adolescents to identify those at high risk, preventing reinjury to injured adolescents, and referring high-risk or traumatized adolescents for appropriate treatment. (See also Chapter 317, Post-traumatic Stress Disorder.) Recent research strongly supports identifying and reinforcing teen resilience factors in addition to screening for risk. Attachment to school, family, community, and prosocial peer groups all exert strong protective effects, even in the face of risk factors. Programs that provide opportunities for teenagers to belong to prosocial groups and develop mastery of particular activities—ranging from academics to dance—protect young adults from health-risk behaviors, including fighting. Increasingly, programs for youth are based on the positive youth development model, which has been demonstrated to reduce high-risk behaviors. A focused social history might include questions about engagement in after-school activities, arts programs, athletics, faith-based youth programs, or other activities that engage adolescents and young adults in prosocial activities.

## SCREENING

Screening for violence risk can take the form of either a specific violence history or a general screen for related risk factors.

### Violence History

Teenagers can be asked directly about their experiences with violence, using the acronym FISTS and asking the screening questions listed in Box 44-1.

### Fighting

Teens who have been in more than 1 physical fight in the preceding 12 months are at increased risk of violence-related injury.

### BOX 44-1 Taking a Violence History—Adolescents and Young Adults (FISTS)

- **Fighting:** When was your last pushing or shoving fight? How many fights have you been in over the last month? In the last year?
- **Injuries:** Have you ever been injured in a fight? Has anyone you know been injured in a fight? Has anyone you know been injured or killed?
- **Sexual violence:** What happens when you and your boyfriend or girlfriend have an argument? Have you ever been forced to have sex against your will?
- **Threats:** Have you ever been threatened with a knife? With a gun?
- **Self-defense:** How do you avoid getting in fights? Do you carry a weapon for self-defense?

Adapted from Alpert EJ, Sege RD, Bradshaw YS. Interpersonal violence and the education of physicians. *Acad Med.* 1997;72(Suppl 1):S41–S50.

### Injuries

A review of medical records of teens who were seriously injured or killed through violence usually reveals previous episodes of injuries that required medical attention. Multiple or serious previous injuries may indicate an increased risk of future injury.

### Sexual Violence

Teen dating violence is both a serious problem in itself and a harbinger of future domestic violence.

### Threats

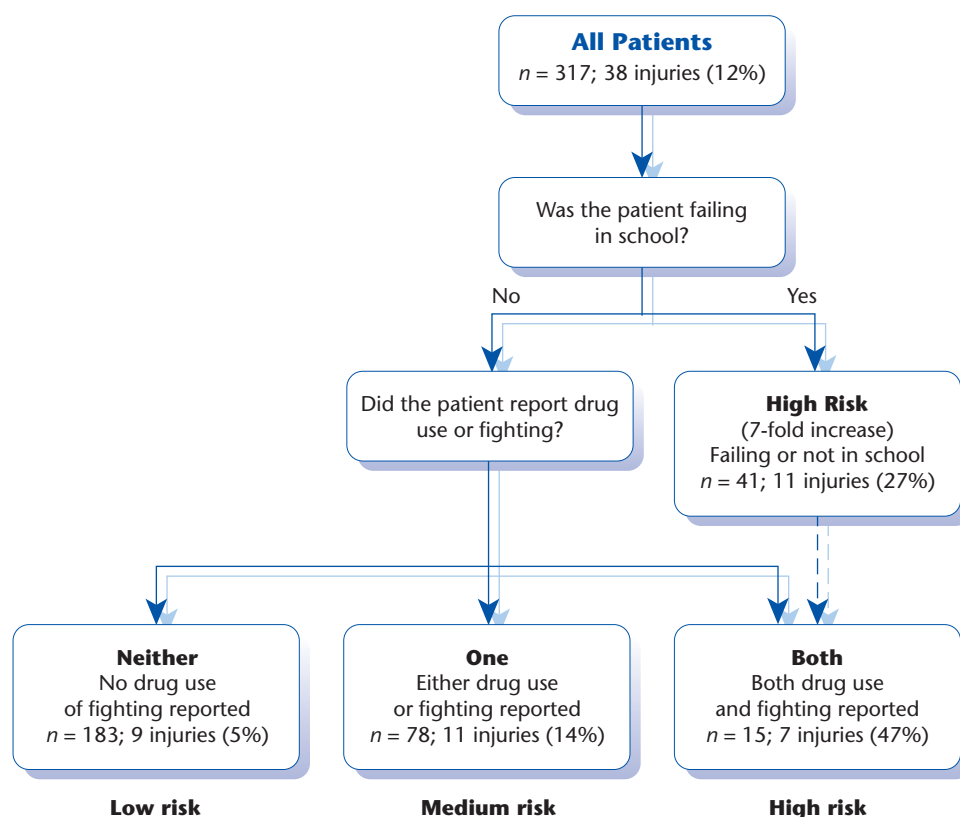
Previous threats with a weapon indicate that the patient is at future risk of weapons-related injury, either through the circumstances that led to the original threat or because these young people are far more likely to arm themselves than are those who have never been threatened directly.

### Self-Defense

Young people who have learned to de-escalate situations of conflict (or to avoid them altogether) deserve praise and encouragement. On the other hand, teens who arm themselves in self-defense are at extremely high risk, as discussed previously.

### Violence-Related Risk Factor Screening

A second, broader set of risk factors influences the likelihood of serious violence-related injury (see Figure 44-1). Problem teen behaviors tend to cluster as a result of both intrapersonal and social factors. Analysis of office-based risk factor screening results has identified 3 classes of risk. Young people in school who report neither drug use nor fighting to their primary care physician are at low risk of violence-related injuries. Teens who are in school and are passing their courses but who report either fighting or drug use are at medium risk—approximately 3 times that of low-risk students. Adolescents who are failing school, have already dropped out of school, or report both fighting and drug use are at approximately 7 times the



**Figure 44-1** Classification of patients into high, medium, and low risk for future violence-related injury. (Modified from Sege RD, Stringham P, Short S, et al. Ten years after: examination of adolescent screening questions that predict future violence-related injury. *J Adolesc Health*. 1999;24:395–402. Used with permission from the Society for Adolescent Medicine.)

risk for future violence-related injury as low-risk students. In the clinical setting, most practitioners already inquire about school performance and drug use as part of the adolescent risk behavior screening (eg, HEADSS); the addition of a single question, “How many fights have you been in over the past 12 months?” completes the screening. Patients who are in school and deny fighting or drug use are at low risk. Patients who are in school but report either drug use or fighting are at intermediate risk. Patients who have either dropped out of school or report both drug use and fighting are at high risk and should be referred to appropriate community-based intervention services.

Finally, physicians should be aware of the strong clustering of health risk behaviors among teens. For example, male teenagers who smoke are at increased risk for carrying weapons.

### COUNSELING AND REFERRAL FOR ADOLESCENTS AT INCREASED RISK

Intervention for patients who are identified as being at increased risk for violence-related injuries through either screening approach must be tailored to fit both the degree of risk and the individual circumstances of each child. Teens at low risk deserve acknowledgment of their success at avoiding this problem, particularly noting that courage is often needed to walk away from

a fight. Teens at moderate risk need to hear that the risks are real and individual: “You are strong and healthy. However, I am worried about your telling me that you have been in several fights this year.” Basic information concerning techniques for defusing particularly tense situations should be discussed. Teens who carry weapons, have left school, or are otherwise at high risk deserve intense social service or mental health intervention. Adolescent health providers need to maintain a roster of appropriate community-based referral agencies or individual counselors for these children and emphasize the importance of follow-up to both the patient and parents.

### AFTER A FIGHT (SECONDARY PREVENTION)

Patients who have been hurt in a fight are at high risk for further violence, either as the victim of another violence-related injury or by attempting to exact revenge on the assailants. The immediate need after an injury is for crisis intervention. Ask the patient: “Is the fight over? Do you feel safe leaving here? If the fight is ongoing, is there someone who can mediate?” If the situation is volatile, then the patient and family should be referred to social services or, if necessary, the police. Police intervention is warranted whenever the patient is in danger or reveals specific plans

to harm another person. At a minimum, parents and patients should be advised of the risk of serious injury and that successful injury prevention involves learning how to de-escalate conflicts.

After a serious injury, the following steps are recommended:

- Ask the parents to remove any handguns from the home, or, if that is not possible, to store them locked and unloaded with ammunition stored separately. Teen homicide and suicide are increased when firearms are available at home, and physician counseling in this setting seems to be effective.
- Have the child tell you about the problem. Allow the narrative to flow freely, avoiding judgments. This approach allows feelings of revenge to be expressed and offers an opportunity to learn the patient's perspective before offering advice.
- Evaluate the youth's other risks: Does he or she carry a weapon? Does he or she use alcohol or other drugs? Is he or she involved in a gang?
- Discuss with the patient the known risk factors for violence, including the fact that most violent injuries occur between friends or acquaintances and often involve alcohol or drugs. Carrying weapons *increases* the risk of serious injury by encouraging the patient to take unnecessary risks and by encouraging his or her opponent to *draw first*.
- Develop a plan to stay safe after leaving the hospital or clinic. Does the patient have a relative with whom to stay who lives outside of the neighborhood? Do the police need to be involved?
- Discuss conflict avoidance strategies. This discussion can start with the particular incident involved and may need to be continued on subsequent visits. Health care professionals need to respect the patient's need not to be labeled as a *sucker* by peers.
- Refer to others, including a psychologist or social worker. For many patients, this referral may involve reaching out to church members, recreation departments, or mentoring programs.

## ADVOCACY

Youth violence, although a serious health risk, is a complex social problem that requires broad-based public action. Pediatricians, in addition to caring for their own patients, are often able to influence public debate in areas that affect child health. The AAP and other organizations advocate for social policies that benefit children.

Pediatricians who serve as school consultants have a critical role. School boards and principals should be advised of the importance of age-appropriate violence prevention programs. School districts have antibullying programs as required by state laws. Pediatricians may review these policies and their implementation. In addition, pediatricians may assist in locating high-quality mental health and parenting resources for affected children.

Pediatricians and child psychologists continue to call attention to the dangers of excess exposure to media violence. In addition to counseling individual families, many pediatricians provide testimony at public hearings or endorse community television *tune-out* weeks.

Despite a general reduction in traumatic injury and death, child and adolescent deaths caused by firearms continue. Individual families can be counseled that the safest home for children is a home without handguns, and that any guns present in the home should be locked and unloaded. Physician testimony and endorsement by medical professional organizations may help support stronger legislation and regulation to reduce minors' access to firearms.

## SUMMARY

Violence is a major cause of death and disability for children in the United States. Although the problem has complex social roots and requires multifaceted solutions, pediatricians have important roles to play. Primary prevention of violence begins with anticipatory guidance for parents of infants and toddlers. Secondary prevention involves the identification, counseling, and referral of high-risk patients and should be a part of standard care for older children and adolescents. Finally, pediatricians can advocate for school policies and state and federal legislation to reduce the risk of violence for children.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Crime, Violence, and Your Child* (Web page), American Academy of Pediatrics ([healthychildren.org/English/safety-prevention/at-home/Pages/Crime-Violence-and-Your-Child.aspx](http://healthychildren.org/English/safety-prevention/at-home/Pages/Crime-Violence-and-Your-Child.aspx))
- *Discipline and Your Child* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Guidelines for Special Time* (handout), Bright Futures ([www.brightfutures.org/mentalhealth/pdf/families/ec/special\\_time.pdf](http://www.brightfutures.org/mentalhealth/pdf/families/ec/special_time.pdf))
- *How to Handle Anger* (handout), Bright Futures ([www.brightfutures.org/mentalhealth/pdf/families/mc/handle\\_anger.pdf](http://www.brightfutures.org/mentalhealth/pdf/families/mc/handle_anger.pdf))
- *Parents' Guide: A Strengths-Based Approach* (fact sheet), American Academy of Pediatrics, in *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* ([shop.aap.org](http://shop.aap.org))
- *Stopbullying.gov* (Web site), US Department of Health and Human Services ([www.stopbullying.gov](http://www.stopbullying.gov))
- *Teaching Good Behavior: Tips on How to Discipline* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

### Medical Decision Support

- *Feelings Need Check Ups Too* (toolkit), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/children-and-disasters/Documents/Feelings-Need-Checkups-Toolkit\\_0823.pdf](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/children-and-disasters/Documents/Feelings-Need-Checkups-Toolkit_0823.pdf))
- *Mental Health Screening and Assessment Tools for Primary Care* (chart), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH\\_ScreeningChart.pdf](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH_ScreeningChart.pdf))
- *A Safe Environment for Every Kid (SEEK)* (questionnaire), US Preventive Services Task Force ([www.uspreventiveservicestaskforce.org/Home/GetFileByID/859](http://www.uspreventiveservicestaskforce.org/Home/GetFileByID/859))



**Community Advocacy and Coordination**

- *Connected Kids Clinical Guide* (booklet), American Academy of Pediatrics ([www2.aap.org/connected-kids/ClinicalGuide.pdf](http://www2.aap.org/connected-kids/ClinicalGuide.pdf))
- *Trauma Guide* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/healthy-foster-care-america/Pages/Trauma-Guide.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/healthy-foster-care-america/Pages/Trauma-Guide.aspx))

**AAP POLICY**

American Academy of Pediatrics Committee on Injury, Violence, and Poison Prevention. Role of the pediatrician in youth violence prevention. *Pediatrics*. 2009;124(1):393–402 ([pediatrics.aappublications.org/content/124/1/393](http://pediatrics.aappublications.org/content/124/1/393))

American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health, Committee on Early Childhood, Adoption, and Dependent Care, and Section on Developmental and Behavioral Pediatrics. Early childhood adversity, toxic stress, and the role of the pediatrician: translating developmental science into lifelong health. *Pediatrics*. 2012;129(1):e224–e231 ([pediatrics.aappublications.org/content/129/1/e224](http://pediatrics.aappublications.org/content/129/1/e224))

American Academy of Pediatrics Council on Injury, Violence, and Poison Prevention Executive Committee. Firearm-related injuries affecting the pediatric population. *Pediatrics*. 2012;130(5):e1416–e1423 ([pediatrics.aappublications.org/content/130/5/e1416](http://pediatrics.aappublications.org/content/130/5/e1416))

**SUGGESTED READINGS**

- Barkin SL, Finch SA, Ip EH, et al. Is office-based counseling about media use, timeouts, and firearm storage effective? Results from a cluster-randomized, controlled trial. *Pediatrics*. 2008;122(1):e15–25
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- Strasburger VC, Jordan AB, Donnerstein E. Health effects of media on children and adolescents. *Pediatrics*. 2010;125(4):756–767
- Zatzick D, Russo J, Lord SP, et al. Collaborative care intervention targeting violence risk behaviors, substance use, and posttraumatic stress and depressive symptoms in injured adolescents: a randomized clinical trial. *JAMA Pediatr*. 2014;168(6):532–539

**Chapter 45****CONDUCTING THE HEALTH SUPERVISION VISIT**

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**INTRODUCTION**

According to the World Health Organization, “Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.” This text’s preceding section on Preventive Pediatrics includes 26 individual chapters, representing 26 broad topics with recommended interventions

important to child and adolescent health. Each chapter builds the physician’s fund of knowledge in a particular area and deepens the reader’s understanding of essential aspects of the preventive care of children and adolescents. This depth of understanding is required for the pediatrician to be able to address the questions posed by parents, the health concerns uncovered in the preventive visit, and health issues essential to the family’s unique culture, community, or circumstances.

The current chapter answers the following questions: How can this knowledge base best be applied to practice? How can pediatricians providing preventive care know which interventions are best for an individual child or family? How can preventive services be offered efficiently and effectively?

**EVIDENCE FOR PEDIATRIC PREVENTIVE SERVICES**

Of the many potential interventions in a health supervision visit, those elements for which there is evidence of effectiveness ideally receive priority. Pediatrician and family time is limited, and proven interventions are of the highest value. Thus, immunizations and evidence-based screenings are core elements of pediatric health supervision. Studies on the benefits of preventive health care are sparse. *Absent evidence commonly indicates lack of study, not lack of value.* For example, strong evidence supporting the utility of a health supervision physical examination does not exist. However, the physical examination, including measurements of growth, body mass index, and blood pressure, together with appropriate screening tests, may facilitate the detection of health problems or health risk behaviors; when results are normal, these actions may also have the benefit of reassuring the child and family.

Evidence for management of problems detected may be available and more definitive. When evidence exists, the pediatrician ideally practices in a manner consistent with that evidence. Lacking evidence from randomized and controlled trials, select recommendations are derived from a review of existing scientific studies, available data supporting or refuting the proposed recommendation and experience, to build a rationale in support of the preventive service under consideration. This evidence-informed approach is founded on the principle of *do no harm* and judiciously combines science and experience.

**The Bright Futures Guidelines**

Under the leadership of the Maternal Child Health Bureau, the American Academy of Pediatrics (AAP) joined with representatives of the American Medical Association, the National Association of Pediatric Nurse Practitioners, the American Academy of Family Physicians, and other organizations in the development of *Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents*, third and fourth editions. The expert contributors to the third edition believed that the Bright Futures guidelines are “a set of principles, strategies, and tools that are theory based, evidence driven, and systems oriented that

can be used to improve the health and well-being of all children through culturally appropriate interventions that address the current and emerging health-promotion needs at the family, clinical practice, community, health systems, and policy levels.” Consistent with the AAP Periodicity Schedule (see the following section), the Bright Futures guidelines detail the content of each age-based health supervision visit and recommend interventions. Bright Futures comprises the primary and authoritative guidelines for the preventive health care of American children.

### The Periodicity Schedule

The AAP *Recommendations for Preventive Pediatric Health Care*, referred to as the Periodicity Schedule, is a compilation of screenings, services, and interventions that are recommended for each health supervision visit, from birth to age 21 years. The Periodicity Schedule is derived from recommendations of the United States Preventive Services Task Force, AAP guidelines, other authoritative sources, and expert opinion. It represents a consensus of the AAP and its collaborators. New content is added based on a rigorous evidence assessment process. The Periodicity Schedule recommends what is to be done in a specific visit. The Patient Protection and Affordable Care Act of 2010 stipulates that services listed in the Periodicity Schedule are to be covered benefits in non-grandfathered insurance plans.

## CONTENT AREAS

Components of the health supervision visit can be categorized as follows:

- Disease detection
- Disease prevention
- Health promotion
- Anticipatory guidance

### Disease Detection

Disease detection is often cited as the impetus for health supervision activities. Its components are surveillance and screening activities, which aim to detect disease states or signs and symptoms that may indicate or lead to medical or psychosocial problems.

*Surveillance* is the longitudinal monitoring of growth, development, or other health parameters by an experienced observer in partnership with the parent. Facets of surveillance occur in every health encounter and are enhanced by the opportunity for repeated visits and observations over time. Surveillance of a child’s growth and development (including school performance) and an initial or interval history (including both the social and physical environment) are essential components of each pediatric preventive health care visit. Other elements are tailored to the particular risks of the child and family, the child’s age and stage of development, and findings of previous visits. For example, a child in foster care will require special attention to the child’s social-emotional health and adjustment, the biologic parents’ involvement and progress, and the reunification or adoption plan. A child with asthma will require monitoring of pulmonary functioning, symptom control, adherence to the asthma action plan, and school attendance. An adolescent

with attention-deficit/hyperactivity disorder (ADHD) will require monitoring of functioning at home, at school, and with peers; symptoms; adherence to the treatment regimen; risk behaviors; and mental health comorbidities. A teenaged mother will require special attention to her educational progress, living arrangements, and support system, as well as the baby’s health and well-being. Effective surveillance relies on the experience and intuition of a skilled pediatrician. Nonetheless, clinical surveillance alone may have insufficient sensitivity to detect the full range of problems affecting a child’s physical and psychosocial well-being.

*Screening* is the more formal process of applying a specific screening tool to detection of the preclinical phase of a disease or condition, when symptoms or signs are not obvious. Screening is appropriate when preclinical detection is possible; when a tool with high sensitivity, specificity, and predictive value is available; when the cost of screening is reasonable; when treatments are available; and when early detection offers more of a treatment benefit than later detection.

The Bright Futures guidelines recommend that some screening tests be performed universally (eg, autism screening at ages 18 and 24 months). Other screens are recommended selectively at a particular age, with additional screening if a risk assessment is positive: For example, anemia screening with a hemoglobin or hematocrit is a universal screen for all infants at 12 months of age; at other visits, if a risk assessment for anemia is positive (eg, early introduction of cow’s milk, prematurity), the screen is indicated. Other screens are recommended only if risks are present (eg, screening for sexually transmitted infections in sexually active adolescent girls).

Positive results at primary screening may lead to secondary screening or in-depth medical evaluation. For example, a child found to have no spoken words at the 15-month visit might appropriately receive secondary screening for hearing impairment or autism spectrum disorders; a child whose mother has a positive screen for depression may need further assessment for social-emotional problems; and a youth who screens positive for use of substances may require assessment for psychosocial problems and learning difficulties.

### Disease Prevention

Disease prevention may involve interventions targeting all children or interventions targeting groups that have an identified higher risk for a condition. Examples of preventive counseling appropriate to all children are immunizations to prevent infectious diseases, “Back to Sleep” advice to reduce the incidence of sudden unexplained infant death, counseling about healthy nutrition and the importance of physical activity to prevent obesity, and resources for education about positive parenting to enhance the child–parent relationship and build resilience against life’s stressors.

More specific and intensive counseling can target children with additional risks, such as those who have been exposed to adverse childhood experiences (eg, trauma, neglect, parental separation, or military deployment), children with weight greater than the 85th percentile for age or overweight family members, and children living in poverty.

## Health Promotion

Health promotion activities focus on helping children, adolescents, and families make lifestyle choices that enhance their health or, in some instances, change unhealthy lifestyles, such as reducing screen time, increasing physical activity, and improving nutrition.

## Anticipatory Guidance

Anticipatory guidance recognizes the unique relationship of the child health professional with a child and family over time. Knowledge of child and family development allows the pediatrician to anticipate information that will be important to the child over the upcoming months or years. Screening for social determinants of health, such as parental depression, intimate partner violence, and other risks as well as protective factors, provides valuable insight into the family environment. Applying this knowledge to a particular child's situation allows the pediatrician to give family-specific advice that is cogent, coherent, and relevant to the child's developmental progress for the immediate future.

In addition, children with special health care needs require care planning and coordination, monitoring of their functioning over time, secondary preventive services (eg, efforts to prevent school failure and behavior problems in the child with ADHD or a learning disability), and tertiary preventive services (eg, efforts to maximize global functioning and minimize disability in children with cystic fibrosis or sickle cell anemia). For in-depth discussion of the care of children and youth with special health care needs, see Chapter 50, Care of Children With Mental Health Problems and Chapter 51, Care of Children With Special Health Care Needs.

## STRATEGIES FOR PREPARING THE PRACTICE

Prior decision making, establishment of daily scheduling parameters, identification of referral sources, skills in performing the elements of a health supervision visit, office routines, assignment of roles, a documentation plan, and continuous quality improvement are key elements in preparing the practice.

*Prior decision making* begins with gathering all relevant expert guidance, requirements (and limits) of major insurers, and quality measures. From these, pediatricians can make decisions about the ideal visit content for each age group. Because the child and family's concerns, the screening and surveillance results, and the realities of a particular clinic day (eg, staffing shortage, backup because of an emergency, approaching school deadline) will create variation in the time available for a particular activity or service, the practice will benefit from prior decisions about options to complete each necessary component. For example, the pediatrician may be the only team member who can provide a service; a delegated staff member may provide the service, routinely or under special circumstances; or the family may be provided reading material and Web resources that inform about a topic or fill a particular need, with plans to address the topic more completely at the next scheduled visit.

*Establishment of daily scheduling parameters* for the practice will depend on the needs of the child and family and the pace and business requirements of the practice. Children with mental health problems or parental concerns may require a longer appointment or multiple appointments. Children with special medical needs may also require additional time. Pediatricians will need to establish parameters for the practice, and staff members who schedule patients must understand how to apply the established parameters to the various scenarios that may present to them (eg, pre-school physical examination, sports preparticipation physical examination, parent with behavioral concern, child with special health care needs). Increasing availability and utility of electronic health records allow the creation of patient registries, which can be useful for tracking, follow-up, and recall.

Sometimes, the extra time requirements of a visit cannot be anticipated in advance. A positive screening result or parental concern, for example, may require additional time of the physician and cannot be postponed to a return visit. Some types of scheduling absorb unanticipated time variations better than others. Wave scheduling, for example, clusters several appointments at the beginning of each hour, rather than spacing them equally over the hour.

With experience, pediatricians gain insight regarding their own practice style and rate of practice. Attention to the scheduling strengths and weaknesses of the practice and the pediatrician can allow the absorption of unanticipated time demands. When patients have been required to wait, an apology is indicated, and most families accept the explanation that "each problem takes as long as it takes."

Group well-child visits hold promise and have been demonstrated to address the current and emerging need of parents for more detailed parenting education.

*Identification of referral sources* deserves particular consideration in preparing the practice. Pediatricians need relationships with pediatric subspecialists, mental health professionals, and community resources to complement and support the practice in virtually all clinical areas not covered within the practice. Patients' insurers may dictate referral patterns and require prior authorization. Office staff will need to become familiar with these requirements, identify contacts within each insurance plan, and prepare to assist families in overcoming any barriers such as payment, copayment, and transportation. Practices require a procedure for overcoming initial insurance company refusals. Tracking mechanisms can be put in place to ensure timely consultation, exchange of information about the consultation, and appropriate follow-up in the medical home.

The availability of services varies across communities. Mental health services may be particularly challenging to access. The pediatrician and practice may need to adapt the treatment and referral plan based on adequacy of and access to resources.

Practices must also be prepared to help with myriad social concerns that may be elicited in the visit, including, but not limited to, food insecurity, housing problems and homelessness, inadequate health insurance, and substance abuse. A medical home will not remedy



these problems, but rather will help the family address them through programs and services in the community. A practice registry or compendium of community services is an important asset. Some practice models use a care coordinator or a social worker to facilitate the identification, choice, and completion of a community service referral.

*Skills in performing the elements of a health supervision visit* are critical to preparation. Importantly, these include handling positive findings when they occur. Although pediatricians often receive training in giving bad news, such training typically focuses on the inpatient setting—life-and-death scenarios in which the patient is hospitalized and a multidisciplinary conference with the child and family can be quickly improvised. A primary care finding, such as a heart murmur, developmental delay, sexually transmitted infection, or substance use may have heavy emotional impact and require both time and expertise of the pediatrician. This important clinical relationship is facilitated by an empathetic approach, emphasizing the ongoing nature of the physician–patient bond in dealing with this new problem. As information becomes available, it is important to share data in language that can be understood and interpreted, with information about both risks and expectations for the clinical course and recovery. Identifying key support personnel both in and out of the practice can be helpful to families. Skills developed in the inpatient setting may be adapted for this purpose, but conveying bad news about primary care findings requires thought and attention in advance of a presenting need, as well as time to address the family's response, which may include denial, anger, and grief. See Chapter 49, *Discussing Serious Symptoms, Results, and Diagnoses With the Patient and Family*, for discussion of these skills.

Decisions about *office routines* require participation of all staff members. Following the principles of the patient-centered medical home, the team together determines what steps happen at each point in the visit—previsit contact, sign-in station, waiting room, nurses' station, laboratory, examining room, conference room, and sign-out station. Equally important are decisions about how and when to make health supervision appointments (initial and follow-up of positive findings or concerns), relay office policies to families (eg, the need for time with the adolescent alone during his health supervision visits; conditions of confidentiality for information shared by adolescents; completion of school, athletic participation, and college forms), remind patients of appointments, follow up on missed appointments, track referrals, disseminate educational materials, provide immunizations and counseling, and document each element.

*Assignment of roles* is integral to smooth practice flow. Some level of flexibility and cross-training will ensure that flow continues smoothly during periods of staff shortage and time constraints. Pediatricians can examine each element of the visit to determine whether they are critical to that element or whether others (eg, nurse, social worker, referral coordinator, other staff member trained in that function) might perform

that element effectively. A system for intrastaff communication will ensure that other team members know what elements have been completed and by whom. Particularly critical is prior understanding about reporting abnormal laboratory or screening results to the child and family and making the adjustments necessary to allow that child and family additional time with the pediatrician.

A *documentation plan* is critical to monitoring the services offered (and not offered) to the child, accurately completing claims, meeting auditing requirements of payers and administrators, and measuring quality. Electronic recording stimulated by prompts or a drop-down menu ideally provides a full array of options to record both the service and the person or mechanism providing it. In paper records, a menu with check boxes may serve a similar purpose (although without the benefit of automatic reporting). The *Bright Futures Tool and Resource Kit* provides previsit tools, patient and parent handouts, and documentation tools in paper format that are adaptable as electronic health record templates. Documentation should also include use of a problem list for the individual child and entry of children with an identified condition or positive screen into a registry of children with that condition, triggering office protocols for tracking and monitoring that condition.

*Continuous quality improvement* is the process whereby a clinical team regularly assesses its effectiveness and efficiency in meeting established goals. In the case of routine health supervision, such goals might include consistency of service delivery and patient satisfaction with the services provided. Several studies have demonstrated that office-based quality improvement strategies were associated with more consistent delivery of preventive services and decreased variability within and between practices on important measures.

Efforts were designed to ensure that the services with the strongest evidence (eg, immunizations, lead screening, vision screening in children younger than 5 years, Chlamydia screening in sexually active female adolescents, and other services needed in unique practice settings) were delivered.

The American Board of Pediatrics has endorsed several quality improvement programs targeting preventive services in its Maintenance of Certification activities, including certain AAP EQIPP courses. These may be a convenient starting point for physicians who wish to improve the quality of their routine health supervision activities.

## SETTING THE AGENDA FOR THE HEALTH SUPERVISION VISIT

A successful preventive visit can be accomplished within typically time-limited schedules; yet every topic will not be covered at every visit. Experienced pediatricians develop routines and systems to improve efficiency. Successful visits will accomplish the following:

- Build on the Bright Futures guidelines and Periodicity Schedule, which reflect available evidence and expert opinion on the efficacy of preventive services.



- Use previsit screening tools such as the *Bright Futures Tool and Resource Kit* to increase efficiency.
- Customize health promotion and anticipatory guidance topics for the particular child and family, addressing concerns of the child and the parent as the top priority for the visit.

### Previsit Screening

To complete the health supervision visit in the time allowed, the pediatrician will ideally collect in advance historical information regarding child and family health, interval use of specialty or emergency care, family strengths and needs, and the family's and youth's own priorities for the visit. Use of a previsit questionnaire and screening tools, either paper and pencil or electronic, creates efficiency and allows the pediatrician to use the face-to-face visit to focus on identified needs rather than rote collection of information. Previsit questionnaires are available in the *Bright Futures Tool and Resource Kit*. Online tools have also been developed.

### Customizing the Agenda for the Visit

The pediatrician can begin the visit by recapping the findings of the previsit questionnaire and screening. Using the child and family's own words, rather than clinical jargon, pediatricians can reflect these findings and test their assumptions about the implications of these findings for the visit. They can then elicit other concerns of the child or family and further information about identified concerns. In the case of adolescents, the pediatrician will need a private conversation with the adolescent, including a discussion of confidentiality and its limits (see Chapter 8, Health Literacy, and Chapter 9, Partnering With Families in Hospital and Community Settings) before settling on the visit content.

The first priority of the visit is to attend to the immediate concerns of the parent and child. At times, disagreement will be apparent—either disagreement between parent and child, disagreement among parents, or (tacit) disagreement between the pediatrician and one or more members of the family—about what constitutes the most serious health risk to the child or what deserves priority at the visit. In these instances, common factors techniques may be helpful in finding common ground for the visit agenda. (See Chapter 46, Effective Communication Strategies.)

If concerns and needs are complex, it may be necessary to develop mutual understanding of what can and cannot be accomplished that day and what may require a return visit, “homework,” or referral resources. The pediatrician can apply common factors techniques to bringing the visit to a supportive close. If a customized visit lacks elements critical to the child's needs, quality measurement, or payment, the practice will need a strategy for adapting coding and billing to the circumstances (eg, coding and billing using an alternative Evaluation and Management code and scheduling for another visit to meet health supervision requirements) or completing missing elements in another way that is cost-effective and convenient for the family.

## CONDUCTING THE HEALTH SUPERVISION VISIT

Pediatricians who consult the Bright Futures guidelines and the Periodicity Schedule and attend to the concerns of the child and family, as described earlier, will learn *what* to do at a specific visit. However, the question remains *how* to provide those services.

### The Medical Home

The AAP holds that every child deserves a medical home. The *medical home* is a practice that is “accessible, continuous, comprehensive, family centered, coordinated, compassionate, and culturally effective.” With this standard of care, every child and family enjoys a relationship with the physician. This relationship may be with an individual or a group. Value, depth, and breadth are added to this relationship by experienced nurses and dedicated support staff. The medical home may also include mental health services by mental health professionals on staff or in collaborative practices. Community support personnel can assist in connecting families with additional nonmedical community services. Each team member plays an appropriate, complementary role in the health supervision visit, planned in advance by the team as a whole and ideally assessed and reassessed through quality improvement cycles.

There are providers of pediatric preventive services in settings that do not meet this definition of medical home. Examples include retail-based clinics and some urgent care centers. They may provide a service such as sports participation physical examinations, pre-kindergarten or camp physical examinations, or immunizations, without the comprehensive elements of health supervision as envisioned by Bright Futures and without a longitudinal relationship with the family. Although such services may have intrinsic value, the absence of a longitudinal relationship with a physician and lack of awareness of the child's history, social setting, and other medical and psychosocial needs may result in neglect of other health supervision needs (eg, psychosocial problems and chronic medical conditions).

For more discussion of the medical home, see Chapter 6, Medical Home Collaborative Care.

### Family

Preventive health care for infants, children, and adolescents occurs in the context of family. Partnering with families enhances the relevance of services offered to the child or adolescent and family. To do this effectively, pediatricians will need an understanding of the family's strengths and assets as well as its needs.

Because children and families are in various stages of readiness to accept advice, change their behavior, or seek help for an identified problem, pediatricians can benefit from skills such as motivational interviewing and shared decision making that identify and address barriers to changing behavior. Chapter 31, Applying Behavior Change Science, and Chapter 46, Effective Communication Strategies, provide guidance in acquiring and applying these skills.

## Community

The medical home may not itself be able to provide the broad range of services that a family requires. Collaboration with community providers of health and social services will be necessary, including school-based health centers where they are available. The pediatrician's familiarity with the community's strengths, challenges, and cultural characteristics provides important context for the services offered in and through the medical home. Partnership between the medical home and local public health professionals helps provide population-based data and links to necessary community resources. See Chapter 9, Partnering With Families in Hospital and Community Settings, for further discussion of community resources.

## SUMMARY

The AAP Bright Futures guidelines and Periodicity Schedule are authoritative guidelines for planning and implementing preventive services in pediatric practice. These services involve disease detection, disease prevention, health promotion, and anticipatory guidance. Services offered to an individual child and family will necessarily depend on their particular strengths, needs, and concerns, as well as findings on previsit screening and the pediatrician's knowledge of the child's health and developmental trajectory.

Pediatricians can take a number of steps to prepare their practice in advance for health supervision activities. Concepts of medical home and family-centeredness are central to effective preventive care, as are relationships with community health and human service providers. Skills such as motivational interviewing and delivering bad news can be helpful in addressing problems identified in the health supervision visit. Quality improvement initiatives have been successful in improving the delivery of preventive services.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *The Paper Chase: Managing Your Child's Documents* (article), Wrightslaw ([www.wrightslaw.com/info/advo.paperchase.crabtree.htm](http://www.wrightslaw.com/info/advo.paperchase.crabtree.htm))

## Engaging Patient and Family

- *Building Your Care Notebook* (Web page), American Academy of Pediatrics ([www.medicalhomeinfo.org/for\\_families/care\\_notebook](http://www.medicalhomeinfo.org/for_families/care_notebook))
- *Pediatric Care Plan* (template), National Center for Medical Home Implementation ([medicalhomes.aap.org/Documents/PediatricCarePlan.pdf](http://medicalhomes.aap.org/Documents/PediatricCarePlan.pdf))

## Medical Decision Support

- *Bright Futures Tool and Resource Kit* (CD-ROM), Bright Futures ([shop.aap.org](http://shop.aap.org))
- *WHO Growth Charts* (charts), Centers for Disease Control and Prevention ([www.cdc.gov/growthcharts/who\\_charts.htm](http://www.cdc.gov/growthcharts/who_charts.htm))

## Practice Management and Care Coordination

- *Family-Centered Care Self-Assessment Tool* (self-assessment), Family Voices ([www.familyvoices.org/admin/work\\_family\\_centered/files/fcca\\_FamilyTool.pdf](http://www.familyvoices.org/admin/work_family_centered/files/fcca_FamilyTool.pdf))
- *Measuring Medical Homes: Tools to Evaluate the Pediatric Patient- and Family-Centered Medical Home* (monograph), National Center for Medical Home Implementation ([medicalhomeinfo.aap.org/tools-resources/Documents/Monograph\\_FINAL\\_Sept2010.pdf](http://medicalhomeinfo.aap.org/tools-resources/Documents/Monograph_FINAL_Sept2010.pdf))
- *Patient- and Family-Centered Ambulatory Care: A Checklist*, Institute for Patient- and Family-Centered Care ([www.ipfcc.org/advance/topics/Ambulatory-Care-Key-Concepts.pdf](http://www.ipfcc.org/advance/topics/Ambulatory-Care-Key-Concepts.pdf))

## AAP POLICY

American Academy of Pediatrics Medical Home Initiatives for Children With Special Needs Project Advisory Committee. The medical home. *Pediatrics*. 2002; 110(1):184–186. Reaffirmed May 2008 ([pediatrics.aappublications.org/content/110/1/184](http://pediatrics.aappublications.org/content/110/1/184))

## SUGGESTED READINGS

- Barkin SL, Scheindlin B, Brown C, et al. Anticipatory guidance topics: are more better? *Ambul Pediatr*. 2005;5:372–376
- Schor EL. Rethinking well-child care. *Pediatrics*. 2004; 114:210–216

## SECTION THREE

# General Management of Children With Health and Behavioral Problems

### Chapter 46 EFFECTIVE COMMUNICATION STRATEGIES

Lawrence S. Wissow, MD, MPH

Approximately 15% of school-aged children and adolescents in the United States are thought to have an emotional or behavioral disorder. Nearly two-thirds of those who are depressed receive no formal mental health care, and only one-half receive counseling or some other form of assistance at school. Providing adequate care for this group of young people requires several strategies, including reducing stigma and financial barriers, educating young people and their families about the benefits of seeking care, and increasing the availability of effective services in accessible settings.

One way of broadening access and reducing both financial and psychological barriers involves promoting the detection—and in some cases treatment—of mental health problems by primary care physicians. Primary care visits offer many potential advantages for helping families with mental health problems. Primary care's philosophy of promoting and tracking healthy development fits well with the task of preventing and monitoring for emerging mental health issues. Longitudinal relationships have the potential to build trust and willingness to share sensitive information. Long-term relationships also mean that mental health care can be delivered episodically as needed, in a familiar setting, and in the context of care for medical issues.

However, many young people (and their parents) do not disclose their emotional problems to their primary care physicians. Parent and physician assessments of child mental health often do not agree, and estimates suggest that families follow through with only approximately 40% of the mental health referrals made by primary care physicians. These challenges are not surprising when considering how pediatric primary care is structured. Visits are relatively short, and many competing concerns need to be addressed. If problems are found, referral sources may be limited, and primary care physicians report low levels of confidence in managing mental health problems themselves.

The skills presented in this chapter were chosen to help primary care physicians efficiently uncover and clarify mental health needs, have therapeutic encounters

with people who are demoralized or angry, and give advice about mental health problems, including making referrals, that will be accepted and followed. The skills offer an approach to clinical interaction that contrasts with the style of most routine encounters. The traditional pediatric style is energetic and directive. It assumes that patients and their families come with questions and needs, and that the physicians should respond with a straightforward diagnosis and plan for treatment. This approach works much of the time, especially for situations in which few emotional overlays exist. However, it can fail when people are ambivalent, ashamed, or anxious, or if they believe that their freedom is being challenged. In these situations, patients do not always admit what really concerns them, and they may resist advice that is offered.

An alternative style is what has been called *patient centered* or *quiet and curious*. In this approach, the physician provides a setting in which patient concerns can be expressed, patients take the lead in developing goals and the strategies to attain them, and information is offered when patients say they are ready to hear it. This approach can be an efficient method for helping people institute change in their lives, and it helps physicians and patients work together during times when change is not yet possible. The techniques described here are framed in the context of emotional and behavioral concerns, but their use is not limited to visits with an explicit mental health agenda. They have wide application to situations in which families and physicians are trying to understand each other's attitudes and develop mutually acceptable plans of action. Many of the skills will seem intuitive or already part of common practice, such as motivational interviewing; others may seem new. The results of many studies suggest that these sorts of skills can be learned fairly quickly; however, not surprisingly, opportunities for practice, feedback, and self-assessment lead to greater clinical effectiveness.

The patient-centered style discussed in this chapter draws heavily from the "common factors" literature in mental health care. "Common" refers to aspects of patients, physicians, and their interaction that are shared across successful treatments for a wide variety of mental health problems, including the use of medication. Though there are many formulations of these factors, they can be summarized as attitudes and interactions that promote both the patient's and provider's engagement in care (individually and as a

team), their optimism that care will lead to mutually desired outcomes, and their agreement on how to attain those outcomes. Physician behaviors that promote common factors seem to have a dual influence on outcomes—they seem to be directly therapeutic and they potentiate the effect of specific treatments. Recognizing the potential of common factors skills to assist primary care pediatric physicians in addressing a broad array of mental health concerns, the American Academy of Pediatrics (AAP) Task Force on Mental Health incorporated them into their conceptualization of pediatricians' mental health competencies and clinical process algorithms.

Some physicians may not be able to imagine themselves using the exact phrases described below or taking this approach in every visit. Approaches can be tailored to each physician's own style, selectively used by different physicians sharing a practice, and, of course, applied to the needs and desires of particular patients and their families. Effective practices structure their approach to care around the talents and interests of their staff members. Helping patients with difficult emotional and behavioral problems is rarely a solo effort, and can include front desk staff, medical assistants, nursing staff, and colocated mental health professionals.

### **EFFICIENTLY ELICITING AN AGENDA AND SETTLING ON A TOPIC FOR THE VISIT**

Many, if not most, patients never tell their physician their full list of concerns. Physicians, especially when pressed for time, may cut short disclosures by prematurely taking over discussions, and, consciously or not, disregarding patients' comments that seem off topic but that might in fact be hints that there is something else to bring up. Why might patients be so hesitant to speak up? People can be ambivalent about disclosing distressing situations. One aspect they may fear in particular is losing control of the situation—if they admit they have a problem, then someone will tell them what to do about it or do something themselves before the patient can object. Evidence suggests, for example, that some patients do not tell physicians about depression because they are afraid that the physician will pressure them or their child into taking medication.

Many methods can be used to elicit a full range of concerns. Despite being busy, the physician can show interest and attention through closing the door, sitting down before speaking, and making good eye contact. If there is a need to consult a paper chart or fill in an electronic record during the visit, the physician can ask the parent and child for their permission to take a minute to do so, rather than trying to listen and simultaneously look. These efforts suggest that the physician has time to listen (even if the physician believes time is limited). Initial greetings can be open ended: "How have things been since the last time?", "How can I be of help?", or "What is most important for you today?" rather than, "So I see we are here for shots today." Introductions, when needed, or comments suggesting that the physician remembers the patient and is glad to see them again, help establish a commitment to a

personal relationship. Children may appreciate a brief period of informal talk that gives them a chance to relax in what may still be frightening surroundings.

Once patients have begun to speak, the physician can show interest by nodding, allowing a brief pause that encourages them to continue, or summing up what has been said and asking for more detail. Perhaps the most important techniques include not jumping in prematurely with a focused question and not ignoring hints about bigger problems. Patients can interpret focused questions asked too early as a sign of what they *should* be discussing, decreasing the chance they will spontaneously disclose key concerns or information. Similarly, hints often represent patients' desire to go beyond what they believe is the primary care physician's agenda for the visit. If the practice is using previsit screening for mental health, development, or somatic concerns, this can be a good time to scan the results. One can note that the parent or child has indicated some concerns and ask if they should be discussed at this visit; if no concerns have been raised, this can be briefly confirmed with the door left open for any future related issues.

Of course, the main reason physicians do not always ask open-ended questions to elicit concerns or follow up on hints is the fear that they will lose control of time. Families may disclose far more concerns than can be discussed in a short visit, or they may ramble about things that seem only tangentially related. Sometimes it seems obvious that the multiple concerns all relate to a single underlying issue. The physician can speculate on this possibility, check for the patient's agreement, and then ask about which aspect is the most troubling or ask which the patient would like to start with.

You've raised several things related to how he is doing in school—paying attention in class, sitting still, doing his homework. Is there one of these that you see as most important at this point? Perhaps we should start by thinking about that.

If several concerns are elicited and their relationship is not clear, the physician can play back the list and the impression of what seems to be the most important.

You've mentioned several things, but it seems that your worry about his staying out late is what concerns you the most, is that right? Maybe that is what we should focus on today. [Conversely, if a priority is not clear] You've mentioned several concerns—which ones did you want to make sure we talked about today?

When patients seem to be having trouble organizing their thoughts, or if the physician genuinely needs to move the visit along more quickly, it is possible to gently interrupt, summarize what has been heard so far, and ask for additional concerns.

I'm sorry to interrupt, but so that we don't run out of time, let me see if I understand your concern(s). [The physician can recite the list and get confirmation.] OK, good. Now, was there anything else that concerned you?

Visits often involve both adults and children. Children may be reluctant participants; they rarely initiate visits in which emotional or behavioral topics are likely to be brought up. Connecting with them, however, is likely to be crucial to ensuring their collaboration with



any treatment that results. Parents are more satisfied, children learn more, and outcomes may be improved when physicians give information to both parents and children. In addition, children and parents provide contrasting information about many problems—parents report more overt behavior problems than children, but they tend to lack knowledge of children's mood problems and underestimate the extent to which children have been exposed to stresses outside the home. Thus the physician needs to make an effort to engage everyone who is present and make a connection with each person: a specific greeting for each and a handshake, if appropriate. While talking, the physician should shift eye contact and body position to address everyone; the physician should also get everyone's name if unclear and use their names when addressing them. The visit agenda should be developed from talking to all parties, not just the parent. Each person (including the child) should be invited to add to the list or validate the priorities. New patients or those who have not had a visit for a long time can benefit from a review of standards for confidentiality and participatory decision making. Depending on the child's age, the child and parents' desires, and prevailing practices in the community, either the parents or child may be invited to speak first, or given opportunities to speak with the physician alone.

### TIMING AND DELIVERY OF ADVICE

Even when people seem to be clearly stating a concern or directly asking for advice, they may not always accept suggestions given in response. Both patients and physicians can create problems at this stage in a visit. Patients may not be ready to take action, even when they are quite concerned about something. They may not see the problem as the most important concern that they face, they may see equally strong reasons not to act, or they may have little confidence in their ability to make a change. Even patients who are ready to change may feel cornered, challenged, shamed, or otherwise disempowered by well-intentioned physicians whose advice seems, to them, formulaic or comes with a label that patients are not ready to assume. People are generally more likely to act when they develop their own motivation to do so, rather than when they believe that they are being pushed or actively persuaded.

Thus, advice has to be tailored to where individuals are in their readiness to make a change, to their confidence that they can do it, and to their particular goals and values. Although providing advice this way is not nearly as complicated as it sounds (and is not necessarily any more time consuming than straightforward offering of advice), it does require a few steps.

First, time should be taken to understand why something is a problem for the family, what they think is causing it, what they see as the relative importance of addressing it now, and how confident they are that they can make a change.

I know that this is something that you want to act on, but tell me first a little bit about what has brought you to want to act on it now. How confident do you feel that you can do something about it now? Is there anything that

makes you worry that this might not be the time to act (or that you shouldn't do anything about this problem)?

Second, the physician should find out the issues about which patients have been thinking. Most people come to a physician for advice after already having tried various things or asking family members or friends for help. Ideally, the physician should have an opportunity to validate and reinforce something that the patient has already decided to do. In addition, learning about the patient's opinion may help avoid or be more tactful about suggesting something the patient already thinks is not likely to work or about which they have strong feelings.

I am happy to give you some ideas, but first I wonder what sorts of things you have been thinking about or have heard about? Is there anything that you have already tried or anything that you feel has or hasn't worked for this?

This can be a good place to seek agreement with the family about things they have already tried but that might not have worked: Might they be willing to try it again if the physician can give them some advice on modifications, or are they willing to move on to a different intervention?

Third, the physician should try to present ideas as a range of choices. Even if the choices overlap or appear to be variants on the same thing, patients feel more in control if they perceive that room is available to choose. Even if they reply by asking what the physician thinks is best, patients still have the knowledge that alternatives exist and that the physician believes in the importance of their preferences.

Fourth, the physician should ask about potential barriers to carrying out the advice. Often, people agree to things that they know will be difficult or impossible for them to do. The physician can help families find telephone numbers or plan how they will get to a referral. It can be worthwhile to go back over the rationale for interventions, so that family members present at the visit can feel comfortable about explaining them to important people in their lives.

Finally, the physician should engage children as much as possible in developing and troubleshooting treatment plans. Language that children can understand should be used while filling in more details for the parent as needed. When developing a treatment plan, the physician can ask children to walk through it to determine what part they want to play. Feedback on specific parts should be elicited, making a note of specific aspects to follow up with the child at subsequent visits. For example:

So, it seems that you and your mom agree that we should try medicine to see if it can help you do better in school. That's going to mean taking a pill every morning. How are you at taking pills? Are you good at remembering things? Do you have any ideas about how we should do that? Next time, can you tell me how that plan you had for remembering worked out?

### WHEN PEOPLE SEEM AMBIVALENT ABOUT ACTING ON A PROBLEM

In some instances, ambivalence is obvious: people tell the physician that they cannot make up their mind about how they feel or what they want to do. Sometimes

the physician can only read it in their expression. These situations present 3 challenges: avoiding turning ambivalence into resistance, getting permission to provide information that may help resolve the ambivalence, and turning ambivalence into a decision to act. Throughout the process, the physician hopefully communicates empathy, a willingness to provide information and support, and patience during a decision-making process that may span more than 1 visit.

One approach at this point is to circle back and ask for a restatement of the parent or child's initial concerns. "OK, let's make sure we understand things clearly..." That can give everyone involved a chance to rethink their priorities and not feel rushed into a decision.

The *elicit-provide-elic* model is another way of getting permission to give information that might help people decide, thus avoiding a lecture that can result in further ambivalence or even resistance. First, the physician elicits a request for information.

You mentioned that you were worried about his mood but that you were not a real fan of counselors or of medicines. Would you like to hear some thoughts about those things?

Next, the physician provides information in a neutral way, keeping it simple and slow paced. Finally, the physician elicits a response: "What do you make of that? Does any of that make sense to you?" The physician should be ready to hear the response and initiate another cycle if doing so seems helpful.

Also helpful is to quantify both the patient's feeling that taking action is important and the patient's confidence in his or her ability to act. Patients can be asked to rate, on a scale of 0 to 10, the importance of an issue and their confidence in their ability to address it. These exercises have 3 goals: they help elicit self-affirming statements about resolve and confidence, they help people define for themselves factors that would motivate them to act, and they generate numbers that can be used as benchmarks for further discussion. If the number is low but not zero (that is, low importance or confidence), the physician should ask, "That is not a lot, but what are the things that make it not zero?" "What would have to happen to increase the importance [or confidence] by a couple of points?" If the number is relatively high (that is, high importance or confidence), then the physician should ask, "Why is it so high?" "How could you move it up even higher?" "What stops you from moving up higher?"

Next, the physician can examine the pros and cons. In this exercise, which may develop information similar to the information generated by quantifying, people are asked to consider the pros and cons (or potential benefits and costs) of leaving a problem as it is and the pros and cons of making an effort to change. The physician can jot down a  $2 \times 2$  chart as patients talk. An important point to remember is that this exercise is not meant to induce some simple weighing of the good and bad and coming up with a decision. For example, the goal is not to have someone say that, on the whole, smoking looks good because it makes her social interactions go better, and therefore he or she will not attempt to quit. Rather, the goal is for the

physician to be able to empathize with the dilemma that the patient faces and at the same time to help the patient focus on what the decision really involves.

I can see why this is a difficult decision for you. Smoking makes it easier to socialize, and you are afraid that if you stop you will gain weight; but at the same time you recognize that it is not good for your health. That's a tough place to be. Does thinking about it leave you with any new ideas or questions?

## WHEN PEOPLE SEEM UNAWARE OF A PROBLEM

In some instances, the physician may think that someone has a problem, but the patient does not agree. An example might be a parent who uses physical punishment to an extent that the physician thinks is unproductive. The goal is to help the parents identify for themselves the reasons why they might want to recognize the issue as a problem. However, the advice is likely to be heard politely and ignored, or rejected outright, if the physician approaches it head on with a *prescription*.

One way to start a discussion is to use the *elicit-provide-elic* model described previously.

You mentioned that sometimes you use spanking to get her to behave. That's an area that people have a lot of thoughts about—would you like to hear some more about it?

Another way is to ask how the issue has caused a problem for the patient, the parent, or the family. The question is deliberately phrased as "how" rather than "if," with the tacit assumption that problems exist. If the patient answers, then the physician should amplify it with, "What else have you noticed?"

So that's probably been a mixed blessing for you. It gets her to behave but everyone feels badly afterwards ...

Answers to either of these approaches can be an opening into helping people focus on both dilemmas and discrepancies posed by their behavior. How current behaviors contrast with stated goals and values is gently and respectfully pointed out. Notably, this approach is different from warnings and negative predictions. Instead, the physician's comments are always framed as empathetic speculations.

I remember you telling me that you would like to be a lawyer when you grow up. I was wondering how that fits with the kind of grades you are getting now? [or] You have talked about how important it is to feel respected; it seems like your friends might not respect you when they see how you behave when you drink. Can you tell me a little more about how respect works among your friends?

Contrast these comments with

See, even you acknowledge that your drinking isn't consistent with your career plans or how you want your friends to see you.

## WHEN ADVICE SEEMS TO BE REJECTED OVERTLY OR SUBTLY

The physician's goal is, of course, to avoid resistance by eliciting patients' concerns and attitudes, giving advice when people are ready, and working to avoid barriers to action. However, none of these approaches

works all the time. How does the physician know that the advice is being rejected? Patients may overtly argue, become defensive, deny or minimize problems, or simply ignore what the physician is saying. Why might this circumstance happen? The traditional view of resistance is that it reflects lack of motivation, personality issues, or a lack of insight and intelligence. Although all of these factors may play some role, physicians' behaviors also play a part. In particular, individuals may become resistant

- As a defense against feeling ashamed of their current or past behavior
- If they believe that they are being coerced, cornered, or rushed
- If they are being urged to do something before they are ready to do it
- If they do not want to lose face in front of another family member who is in the room

A variety of ways can be used to *roll with resistance*. One alternative is to reflect the thought back: "So you have heard some bad things about this medication." In many instances, people will then come back to the physician with a statement that offers some kind of opening. They may go into detail about their concern, providing an opportunity to show respect for their position, provide information, and understand parameters that might form an alternative plan. They may become more conciliatory, revealing that they do, in fact, see both sides of the issue. This action also opens a possible path to a workable solution. As a second alternative, the physician can also apologize and back up.

I am sorry if I got ahead of where you were thinking. It is perfectly fine to put this issue aside until you feel that you have all the information that you need. Where do you think we should start?

As a third alternative, the physician can agree, but "with a twist"

You are right—medicines certainly can be a problem if they are not used carefully. Those cases you have heard about where children had problems with medicine—do you know anything about the dose they were using or how they were checking for side effects?

## WHEN PARENTS OR CHILDREN BELIEVE THEY HAVE BEEN COERCED INTO COMING

Children and teens often say that coming to the physician for a particular problem was not their idea. Parents sometimes have been told by an agency, school, or court that they must see the physician for counseling or medication. The physician can often empathize with patients and families in this situation, and doing so in a way that puts down the referring source is sometimes tempting.

The school people think every kid needs medication.  
or The social services people seem to refer everyone whether they need it or not.

Although these statements may contain a grain of truth from the physician's perspective, they can undermine the legitimacy of the whole therapeutic system, including the physician's part in it. Perhaps worse, they reinforce the patient or family's role as a

victim, which ultimately is not helpful. An alternative goal is to start a process through which the patient or family can regain a sense of control. This process can be seen as having 3 stages: acknowledging anger, distancing tactfully from the coercive referral, and offering choice.

I would be angry too if I felt that someone was telling me what to do that way. I know that I can't make anyone do anything they don't want to do. The schools know a lot about kids and classroom behavior, so I respect their concern; but I am your physician, and my first responsibility to you is to figure out what is right for you. Let's first take a good, broad look at the situation and decide what you think is best to do. I will be glad to talk to the school and explain to them whatever we decide.

A variant for a child or teen might be

I realize that it wasn't your idea to come, but I am really interested in hearing how you feel about this issue. Would you want to talk to me alone now or with your mother here? I guess it is doubly hard getting told you have to talk to someone and then not even having the choice of who that is. Do you think you might feel more comfortable with someone else? I can help you set that up if you would like.

## HELPING PEOPLE WHO SAY THEY ARE STUCK OR HOPELESS, OR HAVE TRIED EVERYTHING

Anger, low mood, and anxiety cause tunnel vision that makes seeing a way out of problems difficult; hopelessness and demoralization become vicious cycles. Focusing on goals for the future and how to get there can initially be more productive than a detailed analysis of how problems came about; focusing on goals is sometimes all that is needed. Solution-focused therapy grew out of a need for ways to help people in the course of brief interactions.

Asking specifically about just how bad patients are feeling and specifically if patients feel in danger of being hurt, hurting themselves, or hurting someone else is always important. These problems need to be addressed immediately. If people report a major fall in their mood, energy, self-esteem, or interest in daily affairs, then they may be depressed, and further treatment may be warranted. For many individuals, however, more transient periods of low mood and discouragement can be helped by identifying and building on strengths and past successes, by reframing events and feelings so that negative attributions about the patient can be made positive or at least neutral, and by breaking down distant and diffuse goals into small, concrete steps that are more readily accomplished.

At least 2 key elements exist to solution-focused interactions. First, the patient is considered to be the expert on both desired goals and on ways to get there; the physician is a facilitator and coach. Following from this point, the patient—often through telling the story of the problem—provides the outlines of the solution. Second, solution-focused interactions look at observable behavior that either leads to or is part of a desired goal. This element is in comparison to focusing on stopping an undesired behavior or focusing on having poorly observable things such as *attitude* as goals.



Solution-focused interactions often start by asking someone to tell the story of the person's problem. *Story* means the patient's understanding of how he or she came to be in a particular situation. Although many people will initially say that they do not know, the physician can prompt the parent or patient to simply describe when the problem started and how it has evolved: "I know that we could probably talk about this for hours, but in a few minutes, starting at the beginning, tell me how you got to this point."

The first, and often the only, response necessary is your ability to play the story back in a way that provides validation and empathy. To change, people need to feel understood and supported. The physician need not agree with everything the patient did, but the difficulty of the situation and the strengths that the person has demonstrated can be supported, and how the problems make sense, given the circumstances, can be pointed out.

So, here you are, a single parent trying to hold down 2 jobs, with a child who you've told me is not the easiest in the world to manage. Then on top of that, your own mother gets sick and needs you. What a tough situation.

A related technique is to look for situations that seem important to the physician but that seem to be glossed over in the family's or patient's account. For example, a parent tells the story of progressive difficulties with a child's behavior and quickly mentions in the middle of the account the fact that the parent's own parent died during that time. In the physician's playing back of the story, this factor is noted with the thought that it must have had an effect: "So in the middle of all these difficulties with the school, you lose your own mother. That must have made things particularly hard." Patients or parents who offer corrections or provide more information that changes the physician's interpretation do not present a problem; this is part of the conversation. What matters in this exchange is that the patient has a chance to clarify the story in their own mind.

A third technique when listening to stories is to observe and comment on "shoulds." "Shoulds" can be stated explicitly, as in "whenever he does X, I have to do Y"; as regrets, as in "I should have done ..."; or implicitly, through a pattern of behavior that recurs in a story.

So you are saying that every time he gets into trouble it is your job to bail him out. That sounds like an important rule that you are following—where did it come from?

In using this comment, the physician is not suggesting that the rule is bad or even suggesting an alternative point of view. However, by asking someone if this procedure really is a rule that is followed and asking the patient to comment on its origin, the physician presents an opportunity and grants permission to make a modification.

Eliciting stories usually segues into "So where do we go from here?" or "So what do you want to have happen next?" The physician can help families set concrete, observable goals. In general, useful goals have the following characteristics:

- People develop goals for themselves.
- Goals are framed in terms of positive behaviors that are observable.

- Goals are often framed in very small steps. "What is the first change in that direction that you would like to see?"
- Goals can be counted or documented objectively; thus, progress can be assessed.

When people say that they are at a loss for a goal, the physician can ask them what they believe would be the first, small sign that things were beginning to improve—preferably so small that they feel confident they could achieve it. For example, if a father's lack of participation in a child's bedtime is the focus of disagreement between parents, then a first achievable step might be seeing if the father would be the one to get the child a cup of water while the mother is reading the bedtime story. The physician can also ask for a highly detailed account of the problem, look at the sequence of events that leads up to it, and identify places where a behavior or response might be changed. People can also be asked to recall exceptions—a time when the desired outcome or state actually occurred, even if only briefly. The discussion can then move on to what might have been happening then and whether these circumstances might be recreated.

## WHEN PARENTS AND CHILDREN ARGUE DURING THE VISIT

Parent-child arguments during a visit can derail plans for diagnosis and treatment, and they often leave everyone involved feeling impotent and in a bad mood. In some instances, arguments can be avoided by taking steps at the outset of the visit to ensure that everyone gets a chance to speak. Physicians can provide this opportunity informally by shifting their gaze and body position from parent to child and back, implying that the physician is both listening to and expecting to hear from everyone. If the parent interrupts the child or vice versa, then they can be asked to wait briefly while the other finishes.

One way to break up arguments is to interrupt them to point out areas of agreement.

I hear you both saying that relationships in the family are important, but you [the teen] are concerned about being respected by your parents and you [the parent] are concerned about how much time he spends at home. Do you think there is a common thread to those things that we could talk about?

Arguments can also be normalized to take some of the emotion out of them.

It's pretty common for parents and children to disagree about curfews and calling to say where you are. It's part of the whole process of learning how to be independent and responsible. How has your family been handling that?

If one or both parties seem particularly angry or are saying things that seem hurtful, several methods can be used to appeal for a calmer approach. One technique is to suggest that the argument is happening in the context of a caring relationship.

This must be hard—it's difficult when 2 people care a lot about each other but really disagree. Is there a way you could tell X how you feel but also let him know how much you care about him?



Another technique is to point out the use of polarizing or black-and-white words and thinking. These terms tend to promote escalating insults; they also obscure concerns that might be the focus of a plan. Examples include: “He is always late—he never picks up after himself.” “He is lazy—he doesn’t care about anyone else in the family.” Responses on your part can be

Ever, never, always—those words have a way of putting people on the defensive. Can you try telling her those concerns again but without using those words? [or] People often get upset if they feel you are labeling them—and it can really stick with kids even if they tell you they don’t care. Can you tell him what he does that upsets you without using that label to explain why he does it?

## CONCLUSION

Building communication skills is an endeavor that spans a career. Endless variations in clinical situations and patient and family personalities offer the opportunity to learn new skills and analyze new experiences. As physicians mature, they develop new insights and new relational preferences that change the way they interact with their patients and families. They grow older; but, on the whole, their patients and parents stay relatively young. The growing gap both enriches the patient–physician relationship and creates hurdles to be overcome. Continuing to work on communication skills remains an important component of clinical practice.

Many of the communication techniques described in this chapter are described in detail in the books *The Family Is the Patient: Using Family Interviews in Children’s Medical Care*, and *Health Behavior Change: A Guide for Practitioners* (see Suggested Readings).

Detailed suggestions about general approaches to mental health issues in primary care and information about diagnosis and treatment for a range of commonly occurring behavioral and developmental problems may be found in *Bright Futures in Practice: Mental Health*. A blueprint for interacting with schools, including sharing responsibility for diagnosis and follow-up, was developed by Drs Foy and Earls and is helpful in caring for children with behavioral or developmental disorders. Conferences and training courses in effective communication and motivational enhancement techniques are available (see Tools for Practice).

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## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Tips for Parents of Adolescents* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

### Medical Decision Support

- *Addiction Technology Transfer Center Network* (Web site), ([www.attcnetwork.org](http://www.attcnetwork.org))
- *American Academy on Communication in Healthcare* (Web site), ([www.aachonline.org](http://www.aachonline.org))
- *Generic or Common Factors Interventions: HELP* (mnemonic), American Academy of Pediatrics ([pediatriccare.solutions.aap.org](http://pediatriccare.solutions.aap.org))

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## Chapter 47

# ADHERENCE TO PEDIATRIC HEALTH CARE RECOMMENDATIONS

Robin S. Everhart, PhD; Barbara H. Fiese, PhD

In pediatric chronic illnesses, adherence is defined as the extent to which a child’s health-related behaviors coincide with agreed recommendations from a physician. Adherence refers to not only taking medications as prescribed, but also adhering to other aspects of health care recommendations such as exercise, nutrition, and sleep. Because many underlying factors contribute to a family’s ability to effectively manage child conditions, adherence in pediatrics is complex. Behaviors from both the parent and child must be considered. Nonadherence may result from delayed or forgotten doses, child oppositional behaviors, child anxiety, difficulty with pill swallowing, lack of knowledge, and parents feeling overwhelmed or stressed. This chapter focuses primarily on adherence with medication use to illustrate the extent and consequences of nonadherence in pediatrics; factors associated with nonadherence, especially within families; and strategies to improve adherence within a pediatric population.

## RATES OF ADHERENCE

Adherence rates in pediatric populations are estimated to be about 50%. Rates of adherence, however, vary across pediatric conditions, with adherence to acute treatments, which show immediate effects, typically higher than adherence to chronic treatments. For example, rates of adherence to airway clearance and diet recommendations for children with cystic fibrosis (CF) are often between 20% and 40%. Rates of nonadherence to dietary aspects of HIV treatment regimens have been reported at over 90%. Rates of medication nonadherence for transplant recipients are estimated at 43%. In pediatric asthma, rates of adherence to daily controller medications have been reported to range from 34% to 71%. Rates of adherence vary within conditions for a variety of reasons, including

measurement of adherence and which component of the treatment regimen is being reported (eg, diet, medication). Self-reported measures of adherence, although cost effective and easy to administer, often lead to higher estimates of adherence because of social desirability bias. Thus, rates of adherence reported to physicians by children and parents may actually be lower than reported. Reports of adherence are often more accurate when patients are asked to recall the last 24 hours (eg, cued recall) or when electronic monitoring devices (eg, metered-dose inhalers) are used.

### CONSEQUENCES OF POOR ADHERENCE

Depending on pediatric condition, the consequences of poor adherence may include disease complications, disease progression, increased symptoms, higher rates of health care utilization, and even mortality. For instance, in both CF and asthma, increased health care use has been associated with lower rates of adherence. In fact, estimates of the cost to the health care system are close to \$300 billion. For infectious diseases, problems with nonadherence may cause relapses of infections or the emergence of resistant microbial strains.

Nonadherence can also compromise the efficacy of the medical regimen. Certain children who have diabetes mellitus are hospitalized repeatedly for ketoacidosis and demonstrate highly elevated hemoglobin A<sub>1c</sub> levels related to nonadherence to the prescribed regimen for insulin therapy. Furthermore, nonadherence can adversely affect medical decisions and evaluation of treatment efficacy, leading to inappropriate increases in dose, changes in the scheduling regimen, or additional medical tests or procedures. Although poor adherence affects both current and future disease-related outcomes, poor adherence can also affect other areas of the child's daily life, including school attendance and overall quality of life.

### FACTORS CONTRIBUTING TO ADHERENCE

Adherence in pediatric populations is complex and determined by multiple factors, including child and caregiver characteristics and family factors, including cultural beliefs, communication with physicians, health literacy, and factors specific to the disease and its treatment. Moreover, rates of adherence have been found to decline in adolescence. A description of several central factors that may affect pediatric adherence and that may serve as discussion points for physicians working with pediatric patients is presented in Table 47-1.

#### Child and Caregiver Characteristics

Because pediatric conditions are typically managed by the child's parent or caregiver (and more so by children as they enter adolescence), emotional difficulties in either caregiver or child can contribute to lower rates of adherence. For instance, in pediatric asthma, maternal depressive symptoms have been associated with incorrect usage of inhalers and forgetting doses. Oppositional child behaviors, such as tantrums, can also make it difficult for caregivers to administer child medications and adhere to nutritional components of the treatment regimen. Caregiver and child knowledge and disease-related skills can also affect adherence. Poor aerosol delivery or misunderstandings about the use of preventative medications have been linked to lower rates of adherence. Caregivers may also have difficulty with instructions involving medication dosing and mistakenly choose the incorrect dosing device for liquid medications.

As children mature, adherence rates often decline as adolescents struggle for independence and autonomy in their medical care. When parents cannot directly monitor treatment behaviors, adherence declines. A strategy may be to include children early on in disease management behaviors so that the transition

**Table 47-1**

**Risk Factors for Lower Rates of Pediatric Adherence**

LEVEL	FACTOR
Child and caregiver	Emotional difficulties (eg, depressive symptoms) Oppositional child behaviors Limited disease-related knowledge or skills Adolescence (eg, denial, autonomy seeking, peer influence)
Family	Insufficient parental monitoring Disorganized family environment Conflict, disengagement, criticism Difficulty integrating adherence into routines
Physician communication	Cultural beliefs related to medication necessity Mistrust from family Unclear communication about therapies
Disease related	Short-term relationship with physician Chronic therapies Complicated regimens with several components Unpleasant-tasting medications Uncomfortable treatments (eg, airway clearance)

to independence in management behaviors is easier when children reach adolescence. Denial and rebelliousness among adolescents with chronic conditions further complicate adherence. For instance, teenagers with cystic fibrosis may smoke or impose weight-loss regimens, which contradict medical advice. Negative attitudes about physicians, reluctance to adhere to treatments in front of peers, and denial of the consequences of nonadherence can also contribute to lower adherence rates in adolescence.

### Family Factors

A cohesive family climate (ie, a family that works together well) and supportive family interactions have been found to promote adherence in pediatric conditions such as diabetes and CF. Family conflict, disengagement, criticism, and high levels of stress can hinder adherence. Families that have clear, daily management practices that allow them to effectively incorporate a child's treatment regimen into existing family routines will likely have greater success in adhering to treatments.

The family's perception of the illness and treatment and its sense of control over the illness influence its adherence to a therapeutic regimen. Among parents of children with asthma, fears and misconceptions about preventive medications can negatively affect patient adherence. Cultural beliefs related to medication necessity have been found to predict adherence; lower rates of adherence have also been linked to the use of alternative medications. In line with the Health Belief Model, caregivers who show concern about their child's illness, perceive the illness as a threat, and believe in the accuracy of the diagnosis and the benefits of treatment are more likely to comply with a therapeutic regimen.

### Communication With Physician

Effective communication between a child's family and physician can enhance patient adherence significantly. Parents and physicians have been found to disagree on up to 17% of the medications prescribed. Adherence tends to be higher when patients have access to a consistent physician, as well as a physician that the family views as empathetic and with whom they have established rapport. Improved patient-physician communication has also been found to decrease health care utilization and missed school days for children with asthma. For adolescents, it is important that the physician also establish rapport directly with the patient and spend time speaking with her individually without parents present. Prior to such discussions, the physician should ask for assent in the treatment from children and adolescents. Other factors that can improve adherence in patient-physician communication include treatment plans that are discussed verbally and sent home in written form.

### Disease-Related Factors

Lower rates of adherence are associated with treatments that require long-term medications, multiple medications and components of the regimen, and frequent medication administration. Other important

issues include the ease and comfort of administration, volume of medication, and palatability.

## STRATEGIES FOR IMPROVING ADHERENCE

Physicians treating pediatric patients may find it useful to frame their recommendations regarding treatment adherence within the context of the child and family. This may require that the physician tailor his or her recommendations based on how the family can succeed at adherence. Some families may be able to handle multiple components of the treatment regimen reasonably well, whereas others may need considerable encouragement and support to succeed at one particular aspect of the pediatric treatment regimen. Strategies for improving adherence to pediatric health care recommendations are provided in Box 47-1.

Because physicians have limited time with each patient and family, physicians may find it useful to begin the conversation by asking about nonadherence. The physician might ask, "What has gotten in the way of helping your child take all of his medications this week?" or "What has been the area of your child's treatment regimen that you've had the hardest time

### BOX 47-1 Strategies for Improving Adherence

#### CHILD, CAREGIVER, AND FAMILY FOCUSED

- Assess and provide appropriate referrals for oppositional behaviors, risk-taking behaviors, and psychological difficulties.
- Focus on how the family can succeed; what can they accomplish that will build efficacy related to adherence?
- Ask about family beliefs, fears, and misconceptions about disease and treatment.
- Assess how well the family is balancing adolescent autonomy and parental supervision in adherence.
- Provide written information that addresses family concerns.
- Enlist other family members as support.
- Focus on incorporating adherence in daily family routines.

#### PHYSICIAN COMMUNICATION AND TREATMENT

- Establish rapport early by normalizing nonadherence and asking what makes adherence difficult.
- Spend time speaking with adolescents without parents present.
- Practice techniques with the child and caregiver in the clinic.
- Be aware of palatability of different medications and possibility of prescribing generic medications.
- Increase continuity of care.
- Keep treatments as simple as possible.
- Provide written treatment plans.



with this week?" By doing so, the physician is normalizing adherence, building rapport with the family, and diving right into issues that the caregiver might be hesitant to bring up. The physician should then follow up on that particular area with concrete, written strategies folded into daily routines that the family can take with them, refer to, and work to improve.

Physicians should also be prepared to address family beliefs, fears, and misconceptions concerning the child's disease and treatment. Physicians can ask specific questions about medication concerns and worries, including side effects, dependency, and long-term usage. Some families may benefit from individualized, written information that is focused on the family's understanding of disease, medication and other needs, and the importance of treatments. Other strategies might include providing additional sources of information or enlisting support from other family members with sensitivity toward their cultural beliefs. For some caregivers, practicing techniques (eg, aerosol delivery) in the office with the physician or nursing staff may improve their confidence and ability to use the device, which may improve adherence at home.

Another strategy to improve adherence is recognizing depressive symptoms, oppositional child behaviors, adolescent risk-taking behaviors, and families that may not be supportive of each other. Physicians may need to provide referrals for adult or child psychological services, as well as family-focused therapy. Physicians may also want to focus on the family structure and how the family has integrated treatment behaviors into its daily routine. Is there a set time for treatments every day? If not, how can the family go about altering a daily routine to include medical adherence? Physicians may find it necessary to consult a caseworker or psychologist for families that seem extremely overwhelmed by the child's treatment regimen. The physician should also consider how the family is balancing an adolescent's desire for independence with parental monitoring of adherence behaviors. Some adolescents will require little monitoring and will easily assume responsibility for treatment behaviors; for others, it will be a gradual process that slowly allows the parent to assume less of the day-to-day responsibilities.

Patient-physician interactions can be improved by increasing continuity of care and physician awareness of family concerns. Treatment goals should be set in collaboration with the child and family. The physician should explain likely side effects and suggest ways that these effects can be minimized. Routine supervision with adherence monitoring may be necessary to ensure continuation of therapies for chronic disease. This monitoring may involve follow-up appointments, telephone calls, home visits, blood level monitoring, or counting unused pills. Other members of the health care team, including nurses and social workers, can help provide support for families to improve adherence and can assist with contracts, monitoring, and education.

Finally, a treatment should be as simple as possible to maximize the likelihood of patient adherence. Medications should be prescribed by using the shortest regimen that is reasonable, and dosing should be

tailored to the patient's daily routine. Furthermore, being aware of the palatability of different medications when there is a choice in medication can also be helpful in improving adherence. In some cases, generic drugs may be preferable to reduce the cost of the treatment. Issues of access to prescribed therapies should be addressed during the original encounter; the physician should prescribe the medication entailing the least out-of-pocket expense for the patient whenever possible.

## SUMMARY

Nonadherence is a common challenge that physicians face in treating pediatric patients. Increased rates of nonadherence can contribute to a range of consequences, including increased symptoms, disease progression, the emergence of resistant microbial strains, and even mortality. Nonadherence can also adversely affect medical decisions and the evaluation of treatment efficacy. Barriers at the child, caregiver, family, and physician levels, as well as the disease itself, can contribute to lower rates of adherence. The role of youth in partnership with families and physicians is important to emphasize and cultivate to increase adherence. Physicians who recognize barriers specific to an individual family and work with the family to address those barriers through a tailored approach may have greater success at promoting adherence. Adherence is a complicated issue that requires a multifactorial approach that includes providing accurate, concise, and easy-to-understand information to families; addressing health-related beliefs; improving communication between physicians and families; and simplifying and individualizing the treatment. Ideally, patients will receive adherence monitoring, with consistent follow-up and support from the health care team. Barriers to adherence should be identified early in the course of therapy to allow for timely intervention and to minimize negative consequences.

## ACKNOWLEDGMENT

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## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Patient Education Online* (Web site), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

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## Chapter 48

# PROVIDING CULTURALLY EFFECTIVE CARE

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Cultural competency is recognized as an important component of high-quality pediatric practice and essential to provide safe, effective, and equitable care to the increasingly diverse patient population found in the United States. Providing culturally and linguistically appropriate health care services has emerged as a critical intervention in efforts to address racial, ethnic, and socioeconomic disparities in health care, including recommendations for improving cultural diversity of the health care team, physician training, interpreter services for Limited English Proficiency (LEP) patients, and other strategies. Physicians encounter different types of cross-cultural situations in everyday practice. Whether overtly demonstrated or not, children and families carry a cultural framework with them into each patient-physician encounter. Similarly, pediatricians bring and apply their own cultural frame of reference into patient care, which may be further influenced by the culture of the medical, social, political, and economic communities in which they practice. Generational cultural differences (eg, around communication, social media, and ethnic identity) add further complexity as pediatricians seek to meet diverse patient needs. Cultures vary for children growing up in different states, in urban or rural settings, in immigrant or nonimmigrant families, in single or married or same-sex parent households, in resource-poor or resource-rich settings, and in many other variations. Strengthening the awareness, understanding, and ability of pediatricians to communicate and solve problems effectively across cultural perspectives has gained increasing attention within pediatric education. From medical student clerkships to residency training to future pediatric workforce planning, cultural competency training modules and approaches abound.

The American Academy of Pediatrics (AAP) provides a Web-based resource, the Culturally Effective Care Toolkit, as a practice management tool to help practitioners learn more about providing culturally effective care to their patients and families. Additional resources for effective communication, cultural competence, and patient- and family-centered care are available through the Joint Commission Web site, as

well as the Web site for the National Standards for Culturally and Linguistically Appropriate Services (CLAS) in Health and Health Care. In keeping with the nature of medical education, cultural competency requires a lifelong process of self-learning, that is, using each patient-physician encounter to broaden one's perspective and understanding of both the cultural regularity and variation observed.

Rogoff writes eloquently in her book *The Cultural Nature of Human Development* about reframing the traditional ethnocentric view of culture to one in which children and families are understood to develop within cultural communities, and about how this is a dynamic process that shapes perspective and shifts over time. A large component of primary care practice involves well-child care with a focus on behavior and development; pediatricians may be dogmatic in asserting the timing of developmental milestones or in giving advice on co-sleeping, eating, and parental discipline. Rogoff provides a lens for viewing how children develop in a myriad of cultural communities that invites the questions: How much of North American pediatric “anticipatory guidance” is a reflection of cultural perspective rather than scientific fact? How much of our approach to pain, or childhood disability, or palliative care, or mental health, or gender identity is influenced by the dominant North American culture?

The goal of cultural competency in pediatrics is to help pediatricians set aside their own cultural lens for a moment and understand how high-quality patient care might be accomplished in the context of the child and family's cultural community. Ignoring cultural context can result in poor adherence, misinterpretation of diagnosis and treatment, adverse events, health care disparities, and frustration for the patient and pediatrician. The goal of this chapter is to sensitize pediatricians to some of the cultural beliefs that may affect families' views of diseases and treatments, as well as their expectations of the pediatrician's role.

## DEFINITIONS

Americans encounter cultural differences every day. The individual's perceptions of social self and of culture and cultural norms play a part in the way reality is defined. *Social self* refers to the way individuals perceive or present themselves to others. It includes the degree of acceptance of the cultural community in which the individuals live and how they project this acceptance or rejection to those around them. *Culture* is defined as a way of life for a group of people—how they work; how they relax; their values, prejudices, and biases; and the way they interact with one another. *Cultural norms* are the ethical, moral, or traditional principles of a given society and include unwritten definitions of health, sickness, and abnormality. Social self, culture, and cultural norms change over generations of families. Persons of the same ethnic group may have very different cultures or cultural norms. Consider, for example, the different cultures of a Chinese farmer living in a rural area of Shanxi province and a fourth-generation American who is ethnically Chinese, has a doctorate in economics, and lives in a mostly white suburb of Minneapolis. Focusing on

individual families as unique cultural units rather than on the cultural origins or ethnic background of the family is preferable because what is typical of a group does not necessarily predict the beliefs of an individual. Although medical training traditionally defines competency in terms of mastery of a body of knowledge, *cultural competency* requires a more qualitative definition that emphasizes commitment to a lifelong process of self-reflection that demonstrates a physician's willingness to listen, learn, and value the cultures of their patients and families. To this end, cultural competency may be better described in terms of cultural humility as physicians move beyond factual knowledge to a change in self-awareness, attitudes, and behavior toward diverse populations.

### EXPLANATIONS OF DISEASE: CULTURAL VARIATIONS

Namboze notes that cultural beliefs about disease causation in Ugandan society fall under the categories of magical, supernatural, infectious, and hereditary. She notes that some of these beliefs are beneficial and can be included in health teaching; other beliefs are harmless and best left alone by pediatricians. Some cultural practices, however, are harmful. In general, these types of cultural beliefs and practices are common to all societies.

Many ethnic groups within the United States bring their ill children to both pediatricians and traditional healers within the community. Special ceremonies, herbal remedies, chanting, and prayer are often prescribed by the latter. Sharing this information with the pediatrician is unusual for the family unless the pediatrician is of the same ethnic group, speaks the same language, or has a long-standing, trusting relationship with the family. Notably, families from many different cultural backgrounds may purchase vitamins, minerals, and food supplements or consult chiropractors for their children and may not inform their pediatricians about all treatments being used. A recent survey of American adults found that 34% reported using at least 1 unconventional therapy in the last year. One-third of these adults saw practitioners of unconventional therapy, making an average of 19 visits in 1 year. The types of therapy included relaxation and imagery techniques, chiropractic and spiritual healing, commercial weight-loss programs, megavitamin therapy, homeopathy, acupuncture, and massage.

### CULTURAL ASSESSMENT

Appraising a family's cultural beliefs, values, and customs is as important as a physical or psychological assessment and can help explain behavior that might otherwise be interpreted as negative or noncompliant. Cultural assessments are multilayered. They may involve linkages with local community groups or a narrative approach through which physicians read and reflect on literature and stories from the communities they serve. At an individual level, a cultural assessment involves creating a safe environment for the patient and family to share their experiences, asking open-ended questions about the family's cultural

background and beliefs, and listening to the responses in a nonjudgmental way (eg, does the family consult any traditional healers or use any traditional medicines or herbs? What does the family believe caused the illness?).

The ability to be interculturally sensitive is desirable but can be difficult to achieve. Teufel notes that ethnocentricity counteracts the ability to be interculturally sensitive and describes 6 stages of development toward the ideal. Initially, the other culture is denied, and cultural differences go unrecognized. The second stage is defensive, and a person may either denigrate the other culture or claim the person's own to be superior. In the third stage, differences between cultures are trivialized; such a perspective does not recognize the different social, physical, and spiritual environments in which worldviews are constructed. In the fourth stage, the individual moves toward accepting that a cultural difference exists and that another culture is worthy of understanding. In the fifth stage, the person adapts to the difference and shifts from an ethnocentric worldview to one that is ethnorelative. Finally, the ideal is that the difference is integrated. The individual attains the ability to analyze and evaluate situations from one or more cultural perspectives and is neither totally a part of nor totally apart from the person's own culture, but lives within comfortable boundaries.

It is essential to avoid stereotypical assumptions and remain sensitive to individual differences within cultural groups while gathering information concerning a particular family. For example, although many Native American adolescents enjoy traditional dancing and powwows, assuming that any Native American adolescent enjoys these activities would be erroneous. A tendency exists to assume that all members of a similar cultural background share commonalities, such as language, religion, and viewpoints. Developing a false sense of cultural knowledge can impede the physician from learning specific aspects about a particular family.

An accurate understanding of several cultures would take an anthropologist years of study. For pediatricians, a starting point can be to review available literature and interview colleagues who are members of a specific cultural group. Training in narrative medicine and active listening skills can enrich this process. Observation and interviews are useful tools when assessing cultural background. When possible, home visiting can provide a wealth of insight into a patient's cultural community. Adding a few questions to the medical history can provide insight into cultural context. Although gathering information about a patient's ethnic group affiliation, preferred language, and dietary practices may take a relatively short time, knowing about the values and beliefs, including health beliefs, of a given family in the context of the family's unique community may take a long time. The AAP Culturally Effective Care Toolkit provides additional online resources for strengthening cultural competency in practice. The American Medical Association also distributes a manual on providing culturally competent care to adolescents. This guide lists open-ended questions to facilitate understanding of how an

adolescent from another culture perceives personal health problems (eg, “Apart from me, who do you think can help you get better?”).

### Racial and Ethnic Identities

The racial and ethnic diversity of the United States is increasing, with minority (not single-race white and not Hispanic) births now constituting most births. Although race has historically been viewed as a biologic construct based on physical characteristics, it is now better understood to have both biologic and social dimensions that change over time and vary across societies and cultures. Ethnicity is typically understood as a social construct reflecting a shared nationality, ancestry, religion, language, or other cultural and folk traditions. Although there is much discussion about race in the United States, other societies may place more emphasis on class, tribal affiliation, or other characteristics. Within the boundaries of one country, such as Uganda or Laos, there may live scores of different tribes varying with respect to physical characteristics, genetically transmitted diseases, and health beliefs. The categorization of race and ethnicity has developed and changed as geographic, social, and cultural forces have shifted. Although the use of race as a proxy for genotype is controversial, there are higher rates of specific genetic diseases among racial and ethnic groups, such as sickle cell disease in African American individuals or Tay-Sachs disease in families of Ashkenazi Jewish origin. The AAP acknowledges that race and ethnicity influence health through social, physical, behavioral, and biologic mechanisms as fundamental causes, mediators, and moderators of child health and predictors of adult health status. Their influences are evident in the extensive and persistent racial and ethnic disparities in children’s health documented in the literature.

Within the United States, racial and ethnic identities vary both in terms of importance and use by different individuals and communities. The effects of racial and ethnic identification may be perceived as positive, negative, or neutral. For example, immersion in a cultural tradition or value system linked to racial or ethnic identity may be perceived as a positive source of strength and confidence for an individual or community, or, in turn, may result in stigmatization of those perceived to be different. Alternatively, racial or ethnic identity may seem unconscious or invisible to some, particularly those whose culture matches that of mainstream society, but may nevertheless manifest in an individual’s attitudes and behavior. As demographics shift, younger people increasingly embrace and express multiracial or multiethnic identities. Although racial or ethnic background is an important variable to assess for clinical risk factors, it is also important to assess the patient and family’s individual perceptions around race and ethnicity, as well as how these constructs may facilitate or impede effective communication and access to care or contribute to health disparities.

### Health Beliefs and Practices

Viewpoints on health and healing vary from group to group. The basic definition of illness in North America

stems from the dominant culture and is based on Western scientific thought, which views illness as a breakdown in a body part because of an infectious organism or injury. Extreme effort is necessary to see illness and healing from a different perspective. The issue of pain is discussed in Zborowski’s classic study. Although the dominant American culture values stoicism and nonemotional expressions of pain, other cultures may express pain through screaming, moaning, and verbal complaining. An understanding of these differences is important in assessing and treating pain in children. Zatzick and Dimsdale reviewed 13 studies in which subjects were exposed to various noxious stimuli, and pain responses of different cultural groups were compared. None of the studies demonstrated cultural differences in the ability to discriminate painful stimuli. This finding suggests that differences in expression of pain among cultural groups do not have a neurosensory origin.

Beliefs and perceptions regarding disabilities relate to culture. Many Asian societies are concerned about the spiritual cause of a disability (eg, failure to follow a tradition). A child born with a disability may be thought to be the recipient of punishment assigned to a parent or relative. These beliefs are present among Americans from Asian cultures and may affect a family’s perception about the importance of rehabilitation.

### Religious Influences or Special Rituals

The dominant North American culture has separated church and state for so many years that separating these specific entities in health care is quite common as well. However, for many cultures, religion strongly influences beliefs concerning health and illness, death, and treatment. Assessing these beliefs and the role of significant religious leaders is important, especially during times of life-threatening illness. Special religious ceremonies may be comforting to the ill child and family members. These beliefs can be integrated into the treatment plan.

### Language Barriers and Communication Styles

Determining which language is spoken at home and assessing a family’s ability to read and write in English are parts of a cultural assessment. Although the family and child may speak English, their words and understanding, especially related to abstract concepts, may be limited. Providing linguistically appropriate services is essential for patient safety and effective care. Relying on informal translators, such as family members, friends, or multilingual colleagues, can result in inaccurate or incomplete information being conveyed and can significantly compromise patient safety. Common translation pitfalls include underestimating the language barriers when patients speak some English; having difficulty translating certain concepts from one language to another; inadequate training or supervision of translators; use of the wrong language or dialect for some ethnic minority groups (eg, speaking Lao to a Hmong patient); and unrecognized sociocultural, political, or hierarchical differences between the interpreter and patient or family that limit open communication. In addition to needing translation services during a medical visit, LEP patients may also need



help filling out forms and navigating the health system to access specialty care or community services. Significant problems may also occur when translations are made of standard research consent forms. In addition to verbal language, physicians should be attentive to cultural variation in nonverbal communication, which may have different meanings in different cultures. Many Americans of East Asian descent nod out of respect, not necessarily out of understanding. Some nonverbal behaviors can lead to alienation and eventually withdrawal; thus, their meanings are essential in keeping communication open. For example, crossing the legs in such a way as to point the sole of the foot toward a person from Southeast Asia is interpreted as an insult. In Bulgaria, a person nods the head to mean “no” and moves the head back and forth to denote “yes.” It is important to identify communication needs for each patient and family and to provide interpreters or translation services that are culturally, as well as linguistically, competent to address questions and misunderstandings. Many clinics and hospitals have translation services available on site; others use telephone-based medical translation services. Many resources for physician and care team training on how to provide linguistically appropriate care are now available online.

### Parenting Styles and Role of Family

Understanding that parenting is neither good nor bad in any culture, simply different, is the basis of acknowledging differing cultural attitudes toward the family. Assuming that the dominant American culture has all the answers is inaccurate when parenting is considered. Although the dominant American culture may value independence in children, another culture may value submissiveness. Attitudes toward family members vary with each culture. Culture will address how different members’ advice is regarded and whether these members are involved in decisions. Culture will also affect the values held about children, family structure, and gender. Parental attitudes regarding infant development and sleeping arrangements often reflect cultural values.

### Dietary Practices

Diet is an integral part of a person’s culture and may be tied to religious beliefs. Dietary practices can include not only preferences and dislikes of particular foods, but also food preparation, consumption, frequency, time of eating, and utensils used. When a prescribed diet is part of a patient’s treatment, assessing the cultural influences involved is essential. Consulting a nutritionist, a cultural informant, or colleagues of various ethnic backgrounds can be helpful. In the United States, children from underserved, ethnically diverse population groups are at increased risk for obesity, increased serum lipid levels, and dietary consumption patterns that do not meet the standards in the *Dietary Guidelines for Americans*. However, the overall diet and eating styles in the United States represent a unique culture in the world, generally different from that of the countries of origin, and result in more than 80% of US children consuming more than recommended amounts of total fat and saturated fat. This

circumstance is a good example of how facets of culture can change dramatically over a few generations.

### HOW PEOPLE INTERACT: EXPECTATIONS FOR APPROPRIATE BEHAVIOR

Perhaps in a century, all people of the world will share a common culture with respect to appropriate interactions. The US population has scores of views regarding appropriate interpersonal interactions. More than a common language is required to develop consensus regarding, for example, eye contact, touching, personal space or territory, appearance, gestures, use of the voice, greetings, partings, and facial expressions. Most humans tend to use the rules regarding these interactions developed from childhood cultural experiences. Complicating this tendency within the United States is that chaotic living situations for children may not provide models for appropriate interpersonal interactions. Young children who watch television a great deal may be unable to distinguish what is real from what is acting and may imitate unusual or inappropriate interpersonal interactions. An explosion in the use of technology and social media has dramatically changed social norms around communication, particularly for young people and often with a resulting generational gap in expectations around appropriate behavior.

In diplomatic circles, norms can be found, some of them written, with respect to communication. Diplomats are encouraged to learn about cultural norms within their host country (eg, who can shake hands, how close to another one stands at a reception, and how much eye contact is allowed). Nonetheless, diplomats make mistakes and are, therefore, misinterpreted. Pediatricians who interact with peers from other cultures should study cultural norms when working with foreign colleagues, whether in this country or their own. Visitors from East Africa and Southeast Asia often complain that they find American friendliness superficial. In their cultures, the immediate pleasant friendliness of Americans represents a more advanced stage of personal intimacy and friendship, and they are offended when they discover that it does not necessarily reflect depth. They also find difficulty in accepting gifts from Americans because, in many cultures, gifts are given only in exchange for something or to acquire an advantage. Direct expression of feelings is inappropriate and considered bizarre in many cultures. In Thailand, for example, a person turns anger toward another object, either animate or inanimate, called *prachot*. This practice is performed consciously to alert the person (who is the object of the person’s displeasure and annoyance) as to how the injured party feels. In Southeast Asia, avoiding confrontation is considered positive, and expressing anger, hatred, and annoyance overtly is considered negative.

In terms of generational cultural gaps around appropriate behavior, physicians must be aware of their own assumptions as well as those of the family and patient. Generation gaps may be compounded by other cultural influences within a given family, such



that texting at the dinner table or exploration of gender identity are perceived as much more challenging or stigmatizing within a given family's cultural environment. The AAP provides resources on how to assess and respond to changing norms around the use of social media, including how to talk to children and adolescents about social media use and sexting.

Several training programs are available to increase sensitivity among people toward varying cultural norms and values. Pediatricians who plan to work in other cultures may benefit from a game (*BaFá BaFá*) in which participants are divided into 2 groups and provided with values, expectations, and customs of a new culture. Training programs that raise awareness of varying cultural norms should be incorporated into standard training of pediatric residents in the United States.

## PERCEPTUAL DIFFERENCES AMONG CULTURES

Perceptual differences among various groups of humans relate not only to group beliefs, customs, and experiences but also to differences in sensory systems that may have evolved in response to the need for individual survival or in response to that society's needs. These differences in auditory, visual, musical, and tactile skills are well documented and may relate to differences in eye-hand coordination, information processing, and language and spatial perceptions.

Some of the differences may be genetic, but others reflect the emphasis, focus, and practice of a skill within a culture. For example, an infant's perceptual abilities are modified by listening to a particular language. Syllables, words, and sentences used in all human languages are formed from a set of speech sounds called *phones*. Only a portion of the phones is used in any particular language. Young infants can discriminate nearly every phonetic contrast, but this broad-based sensitivity declines by 1 year of age. Adults have difficulty discriminating phonemes that do not connote meaning in their own native language and are thus handicapped when learning a new language. English-speaking natives have difficulty in perceiving the difference between 2 *k* phonemes (sounds) used in Thai. Japanese-speaking adults have difficulty distinguishing between the English /*ra*/ and /*la*/. Adults who learn another language early, but who do not practice the language as they mature, may lose their ability to differentiate among its sounds.

Learning the language of another culture helps in understanding that culture. Dependency on translators is fraught with the likelihood of misunderstanding, especially in medicine. In some cultures, the status of the translator affects what information is provided by the patient and how it is prepared for the ears of the foreign physician. If the patient is of higher social status than the translator, then an awkward situation can result such that personal questions may be answered to preserve social standing and result in changed meaning. Furthermore, abstract concepts may not translate well from English to other languages. For example, expressing abstract concepts in Norwegian or in Russian is much more difficult than

in English. Many words from Western languages do not exist in Asian languages; therefore, certain concepts may be difficult to convey, even with a translator. Similarly, some Asian concepts are difficult to express in English. The Lao language, for example, is richer in words related to family relationships than is the English language.

## ETHICAL ISSUES IN CROSS-CULTURAL MEDICINE

Many ethical issues operate in making transcultural diagnostic and treatment decisions. These issues relate to communication barriers, varying explanations for disease, and different expectations regarding what is honest or valuable. Can an American pediatrician truly explain a surgical consent form to newly arrived parents of a Southeast Asian baby? When newly arrived refugees fear that they will be returned and, therefore, sign anything or do anything to gain favor, then is asking them to sign a consent form to have blood drawn for clinical research ethical? Mental illness is defined very differently among cultures. Is using psychotherapy considered ethical when therapist and patient are unmatched culturally?

Oppenheim and Sprung have reviewed cross-cultural differences in ethical decisions related to critical care. They compare Chinese and Israeli cultures with respect to informed consent in intensive care units. For Chinese, giving all information regarding grave decisions directly and openly to the patient or to the parent of the patient is considered callous and inconsiderate. Therefore, informed consent, as a Western physician understands it, may not be achieved. Recognizing that physicians' attitudes may differ from those of the patient is important in considering ethical decisions in the intensive care unit, even when the physician and patient are from the same ethnic group.

## EDUCATION FOR HEALTH CARE PROFESSIONALS

Megatrends, such as increasing flow of refugees and immigrants, will make all pediatric practices more multicultural and multiethnic. The AAP has issued policy statements defining culturally effective health care and its importance for pediatrics. *Culturally effective pediatric health care* is defined as the delivery of care within the context of appropriate physician knowledge, understanding, and appreciation of cultural distinctions leading to optimal health outcomes. Such understanding takes into account the beliefs, values, actions, customs, and unique health care needs of distinct population groups. The AAP affirms that such knowledge and skills can be taught and acquired through educational courses. It recommends that the pediatric community develop and evaluate curricular programs in medical schools and residency programs to enhance the provision of culturally effective health care and to develop continuing medical education materials for pediatricians and other physicians, with the goal of increasing culturally effective health care. Examples of such curricula include the Society for Developmental and Behavioral Pediatrics guidelines for

residency training, which emphasize the need for pediatric residents to develop skills in working with diversity in cultural beliefs. Similarly, Ohio State University, University of California San Francisco, and Maimonides Medical Center have all published examples of programs to help pediatric residents communicate in culturally diverse environments.

## SUMMARY

Cross-cultural issues in pediatrics affect communication, expectations, medical explanations, patient safety, quality, and access to care. Pediatricians, although enculturated by their specialty training, also have individual cultural experiences that affect their beliefs and values. A commitment to lifelong learning about the varying beliefs and cultural frames of reference that exist among colleagues and patients will strengthen the ability of pediatricians to provide culturally competent and effective care. Wherever a strong belief exists in a folk explanation for the cause of an illness, pediatricians are most likely to succeed if they acknowledge the belief and attempt to work with it. When simultaneous use of a traditional and biomedical regimen is possible and will do no harm, it is likely to enhance long-term, trusting relationships. Awareness of cultural evolution, perceptual differences related to cultural background, and implications for decision making with respect to children is essential for pediatricians.

## TOOLS FOR PRACTICE

### Medical Decision Support

- *Culturally Effective Care Toolkit* (toolkit), American Academy of Pediatrics ([www.aap.org/en-us/professional-resources/practice-support/Patient-Management/Pages/Culturally-Effective-Care-Toolkit.aspx](http://www.aap.org/en-us/professional-resources/practice-support/Patient-Management/Pages/Culturally-Effective-Care-Toolkit.aspx))
- *Patients with Limited English Proficiency* (toolkit), Agency for Healthcare Research and Quality ([www.ahrq.gov/professionals/education/curriculum-tools/teamstepps/lep](http://www.ahrq.gov/professionals/education/curriculum-tools/teamstepps/lep))

## AAP POLICY

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## Chapter 49

# DISCUSSING SERIOUS SYMPTOMS, RESULTS, AND DIAGNOSES WITH THE PATIENT AND FAMILY

Daniel W. Mruzek, PhD; Elizabeth Baltus Hebert, PhD;  
Philip W. Davidson, PhD

Simplifying treatment choices and clarifying prognoses are critical goals in the disclosure of any diagnosis to parents. An important step in this process is the sharing of pertinent information with the child or with the child's family. In most circumstances in which the illness is minor or carries an excellent prognosis, the diagnostician presents such information straightforwardly to the patient and family. However, in cases that involve children who are gravely ill, severely disabled, learning disabled, or emotionally disturbed or those who have an intellectual disability or an autism spectrum disorder, the situation becomes far more complex. Parents, years after the fact, vividly remember how and when the "bad news" was related. The interpretive presentation, often with the primary care physician (PCP) and involving 1 or more specialists, can become part of a broader counseling session that deals with feelings and emotions, as well as facts, to ensure understanding of the information being shared.

This chapter focuses on the process of information sharing with families or patients as an extension of the diagnostic process. The goal of interpreting diagnostic findings is more than merely announcing technical information. The real objective in providing this information is to establish a partnership between the PCP or specialist and the family that will enhance the family's capacity to respond appropriately to their child's condition, to adhere to the treatment plan, and to become a partner with the rest of the treatment team. This partnership between families and professionals is even more crucial when considering that federal legislation mandates participation by parents in decisions about their children who have special needs (eg, autism, intellectual disability) and chronic conditions (eg, ventilator dependency). The Reauthorization of

the Individuals With Disabilities Education Act (Public Law No. 108-446), for example, emphasizes family-centered, coordinated, case-managed care and parent-driven planning of service provision to their offspring ages 0 to 2 years who have disabilities.

No blueprint exists for building the crucial relationship between physician and families; however, interpretation of the physician's findings to the family without unnecessary delay is essential in case management, as is the need to attend to the family's expectations and questions initially and over time. Moreover, negative attitudes, disrespect for the family's knowledge and beliefs, and the physician's own biases and anxieties interfere with constructive communication about a child's diagnosis and treatment. This dialogue may be complicated further when physicians become frustrated by their inability to cure or save the child, when they know that no local resources are available to deal with the child's condition, or when the family members ask questions that the physician cannot answer.

Relationships with families and children based on the posture, "I have the information, and I know what's best," represent a misinterpretation of the kind of relationship between family and physician that is necessary when information about a complex and threatening illness or disability has to be shared. Diagnosis is typically derived from biomedical or behavioral considerations; however, treatment decisions require consideration of nonmedical variables as well (eg, family resources, values, educational matters) and respect for families' strengths, beliefs, and preferences. Assuming that simply having information or knowledge about *what is best* for the child is sufficient for communicating diagnostic, therapeutic, and prognostic information to the family is inappropriate. Family members usually know their child better than anyone else and are central as nurturers, caregivers, and guardians of their child.

To communicate effectively, physicians must maintain a flow of information between families and themselves; simply telling family members the facts of an evaluation does not guarantee that they will hear or understand. This is true for the general pediatrician who finds an unexpected concern during a routine visit and must discuss next steps in the diagnostic process (eg, lab results suggestive of leukemia), as well as for the specialists confirming a suspected diagnosis or elucidating functional ramifications (eg, traumatic brain injury). Considering this circumstance, disclosure should be an interactional process that is conversational in nature and demonstrates respect for the equality and individual needs of the families. Such communication can be described in general terms, but its effective implementation depends on careful individual planning and a reasonable investment of time. Box 49-1 outlines a method for conducting an *interpretive conference*. The format outlines 4 equally important steps that are essential for effective communication when the child is evaluated by the physician (physician, nurse, psychologist, social worker, or educational specialist) alone or when several professionals have been involved as members of an interdisciplinary team in the diagnostic evaluation.

### BOX 49-1 Interpretive Conference Format Outline

1. Entry pattern
  - A. Review of evaluation procedures conducted
  - B. Parents' and child's perceptions
  - C. Restatement of parental concerns
    - (1) Main worry
    - (2) Additional concerns
2. Presentation of findings
  - A. Encapsulation: brief overview
  - B. Reaction by parents and patient
  - C. Detailed findings
    - (1) Reactions to normal test results
    - (2) Reactions to abnormal test results
3. Recommendations—only after time has been allowed for reactions
  - A. Restatement of concerns with both parents
  - B. Recommendations—1 at a time
  - C. Reactions after each recommendation
  - D. Sharing with the child
4. Summary
  - A. Repetition of findings, in varied wording if possible
  - B. Restatement by parents or patient
  - C. Planning for future contacts

## PREPARATION FOR AN INTERPRETIVE CONFERENCE

The interpretive conference must be planned beforehand to ensure that the conference will achieve its purpose. The first important step in preparation is choosing which parents/guardians to have the discussion with. This decision may be significantly affected when issues of potential abuse or neglect are raised, including those instances in which a child is injured while not adequately supervised by a custodial adult (eg, brain injury following a drowning accident). In these cases, decisions about whom to include are contingent on a variety of interpersonal and incident-specific factors; however, the best interest of the child and family is paramount. Also, in consultation with family members, physicians must weigh whether to have the child present during the meeting, taking into consideration the child's age and maturity. The conference should occur as soon as possible after the examination and testing of the patient. The physician who conducts the conference is best prepared, emotionally and cognitively, immediately after the last visit or staffing conference, and parents are anxious to hear about the outcome of the evaluation as soon as possible. Consideration of the family's health literacy, cultural background, and support network before the conference will increase the probability that objectives are met, both in terms of conveying information and connecting the family with helpful supports. Collaboration between specialists and the child's PCP at this stage is very important. The child's PCP most likely



has a knowledge of family background, capabilities, values, and priorities that other physicians do not possess. Also, the PCP may very well continue providing support and guidance in the immediate absence of specialists; therefore, the PCP's participation in the interpretive conference (if possible) or collaboration before the conference is a critical consideration. Likewise, for children who receive services through mental health or developmental disability agencies, careful consideration should be given to information that case managers, advocates, physicians, or other service providers from these agencies might provide.

If other professionals besides the PCP are involved in the conference, then the basic aim should be to establish maximal communication between families and professionals while this expertise is available, thus ensuring that most of the family members' questions can be answered effectively. With certain conditions, such as intellectual disability, autism, and learning or emotional disorders, the physician may not be included in the conference or may not be the primary spokesperson. In these circumstances, the psychologist, special educator, or social worker might serve this role.

Families sometimes view the physician as the ultimate authority figure, and in these cases the credibility of a team that does not include the physician may be impaired. On the other hand, the physician need not automatically be cast in the role of leader at an interpretive conference unless the bulk of the information to be discussed is biomedical. Typically, only professionals who participated in the diagnostic workup should reveal the information, unless serious practical limitations (eg, family's limited availability for follow-up visit with geographically distant specialists) preclude this arrangement. In no case should the interpretation of technical material to families be left in the hands of nonprofessionals or professionals whose lack of expertise might lead to confusion for the family.

After the team members have been selected, they should meet long enough to organize the conference, following the outline in Box 49-1. This planning session should allow enough time to ensure that all the team members agree on the major information to be shared with the family and that all terminology is understood. Because organization of the conference is the key to satisfactory communication, team members should also select a leader who will structure the conference. This selection is of paramount importance. The leader's responsibility is to control the flow of information from professionals to the family and vice versa to ensure 2-way communication. *Control* implies not only organization but also a certain empathic sensitivity for the family members' feelings and reactions so that emotional highs and lows can be adequately recognized, permitted, and dealt with in ways that respect the families' cultural proscriptions and without undermining the purpose of the conference. These preparations are especially important when only one physician is to be present at the conference. During disclosure, the lone physician will not have the colleagues present to add omitted

points or rephrase statements that remain unclear to parents.

## CONDUCTING THE CONFERENCE

### Entry Pattern

The beginning of the interview often sets the tone for what follows. The first important step in preparation is choosing which parents/guardians to have the discussion with. In all cases, the assumption is that planning has included specific physical and interpersonal requirements that create an empathic climate, privacy, and freedom from interruption and that the physician has arranged to arrive on time. Diagnostic results should be shared with a minimum of technical jargon so that parents are not intimidated when asked to discuss their main worry. During such a discussion, a hidden agenda often surfaces, related either to the cause of the problem or to the problem itself. Therefore, before the information is presented to the parents, the parents' perception of the child and the child's current situation should be sought. For example, the physician might ask both parents, "How do you see Mary's problems and strengths today?" Even if both parents have accompanied their child throughout the evaluation, each may have different knowledge about and reactions to what is happening. This time also is appropriate to ask what others have told them of their child's condition. If family members are coping adequately with the news and are prepared to support the child emotionally, this may be an appropriate time to invite the child to participate in the conference.

### Presentation of Findings

Dwelling on technical data that do little to enhance the family member's or child's understanding of their disorder accomplishes nothing and may interfere with establishing good communication with the family and child. Such data only serve to confuse, rather than clarify, the concerns. When several different tests have been performed in a lengthy, technical evaluation, understanding that the data presented summarize the results of all those tests is especially helpful for families. Some parents/caregivers need a name for their child's illness or problem. If labels have not already been used by others, then they may well be in the future. Most individuals want honest appraisals and will resent ambiguous assurances that border on deception. *Honesty with tact is vital.* For example, if an infant has been born with fetal alcohol syndrome, the family should be clearly and directly informed of the diagnosis rather than given vague or technical terms such as *multiple craniofacial and other anomalies* to explain their child's condition. Similarly, if the determination has been made that a school-aged child has an intellectual disability, then this finding should be presented gently but directly, with avoidance of euphemisms or inaccurate terms (eg, *slow learner*, *learning disabled*). In cases of suspected child abuse or neglect, physicians should relate in a nonjudgmental manner their concerns, as well as their decision to report suspected maltreatment as required by law.



The physician or physicians should focus on the parents' own perceptions of their child when explaining findings, particularly as these may relate to the parent's experiences with other children. Age or grade equivalents rather than ratio scores are useful when conveying the presence of developmental delay or immaturity. For example, the physician might say, "Susan's language development is delayed. You tell me that she, at age 2, babbles but has no words. Babbling is the typical way a 6-month-old communicates." And, rather than, "Your son's test scores show 'scatter,' and he has a learning disability," a clearer statement would be, "Joey reads and understands written information more like a third grader than a ninth grader."

It often is said that after the parents hear the bad news, they hear very little else. For this reason the actual presentation should begin with areas of strength or normality. In fact, this presentation is as much a part of the physician's responsibility as describing weaknesses, and doing so provides parents with the opportunity to see more clearly current ability and establish new hopes for their child's future. Abnormal findings stated honestly but gently should be restated more than once and using different words to convey the same findings.

Families should be encouraged to react to the diagnosis of the condition and to accept their feelings, including the anger that is often directed at the physician. Physicians need to learn how to cope with parent anger, not expect gratitude, and listen with empathy and without undue interruption. Kaminer and Cohen emphasize the relationship between empathy and honesty: "The literature documents that communication skills can be taught or at least improved. Acquiring an understanding heart seems to be more difficult." Indeed, one of the physician's most important tasks is gently facilitating the family's response to the diagnostic information and providing an initial opportunity for family members to process the information in light of their own values, spirituality, personal experience, and world view. Responses that reflect shock, guilt, bereavement, and inadequacy often are seen in various intensities and combinations. Family members need to be assured of the normalcy of those responses. Communication at this level is also influenced by sociocultural and educational differences between the professionals and the parents. A physician who demonstrates great care in listening, has a nonjudgmental and supportive interpersonal style, and is responsive to the specific questions and concerns of the family and child will provide much more than simply the diagnostic information. In these instances, the physician will provide an opportunity for the family and child to begin the process of coming to terms with the diagnosis, a prerequisite for planning productive next steps.

### Recommendations

Specific information should be shared at a pace that can be handled emotionally and cognitively. Parents seldom feel comfortable asking for clarification; however, if they are asked to restate their main worry and other concerns, the physician's recommendations can

become meaningful and relevant. Parents often welcome clearly written take-home materials that provide current and accurate information on the relevant diagnosis, including general descriptions of treatment and intervention options. In fact, Brogan and Knussen found that the provision of written materials by physicians was a key factor in promoting parent satisfaction with their disclosure experience. Information regarding additional resources, such as family resource rooms at some medical libraries and local family support groups, as well as reputable Internet sites, give parents options for educating themselves about their child's diagnosis. Questions about complementary and alternative treatments (eg, specialized diets for autism) should be treated with compassion, respect, and honesty. Family members may be referred to reputable online resources; however, they should be warned about the presence of inaccurate information and costly, ineffective and potentially dangerous "treatments" promoted to some Internet sites. Finally, parents usually find it helpful to receive recommendations that include opportunities to communicate with other parents who have a child with a similar problem and referral elsewhere for help. Parents' wishes and the cognitive and emotional development of the child are important considerations.

After recommendations have been shared and before the session is terminated, findings, once again, should be highlighted. One successful method for obtaining feedback is to ask parents to restate what they heard and what decisions were made. This approach provides the physician with the parents' perception and understanding of the problem and allows for further clarification, if necessary.

In many instances, a second interpretive session is indicated. This session can be planned by arranging for parents to contact the physician by telephone (at a specific time) after they have had time to think about and react to the information that was shared or when further questions and concerns arise. The session should be terminated only after the physician has stated a willingness and an ability to participate in a therapeutic alliance with the parents.

### SUMMARY

A family conference to disclose diagnostic findings is a dynamic process that serves as an initial step in building a therapeutic milieu. Key elements of the model outlined here are advance preparation; presentation of clinical findings, diagnosis, and prognosis in a way that is appropriate to the family's health literacy level and cultural background and that reinforces their strengths; response to the child and family's questions, perceptions, and emotions; education about the condition and available resources; and shared decision making about next steps. Organized and conducted in this way, the conference enables the family to process the information in the context of their own values, spirituality, personal experience, and world view. In turn, it enhances the physician's relationships with the family and child and encourages immediate and future communication and adherence to recommendations.

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## Chapter 50

# CARE OF CHILDREN WITH MENTAL HEALTH PROBLEMS

Jane Meschan Foy, MD

### BACKGROUND

Increasingly, families and communities across the United States are looking to pediatric primary care clinicians (PCCs)—pediatricians, family physicians, nurse practitioners, and physician assistants—as a source of mental health (MH) care, a gateway to specialty MH care, and a source of primary care that is coordinated with specialty MH care. The opportunity and urgency for PCCs to fulfill these roles were articulated in the *President's New Freedom Commission Report, Mental Health: A Report of the Surgeon General*, and the *Future of Pediatric Education II* (FOPE II) Project. In 2004, in response to these reports and requests from its members, the American Academy of Pediatrics (AAP) formed the Task Force on Mental Health (TFMH) to assist pediatric PCCs in meeting these challenges. The TFMH recognized “the primary care advantage”—the unique skills and experience of PCCs and their opportunity for longitudinal, trusting relationships with families. Building on this advantage, the TFMH issued guidance for the care of children with MH problems in the pediatric medical home. This chapter and a number of other chapters in this textbook draw from the publications of the TFMH.

This chapter describes an approach to the primary care of children with identified MH problems. In this chapter, the term *mental health* incorporates the full range of social-emotional, substance use, behavioral, and psychosocial issues. This is not to suggest that the PCC is solely responsible for this full spectrum of care, but rather that children with the full range of MH conditions need a medical home, as do other children with special health care needs. The PCC plays a critical role in identifying their needs, engaging them in care, coordinating their care with other professionals, and monitoring their progress in care.

The chapter builds on others in this book—Chapter 13, Pediatric History: Assessing the Child; Chapter 14, Pediatric History: Assessing the Social Environment; Chapter 15, Pediatric History: Assessing Functioning and Mental Health; Chapter 16, Pediatric Physical Examination;

Interpretation of Findings; and Chapter 33, Healthy Child Development. Chapter 34, Mental Health, describes opportunities for anticipatory guidance, preventive MH care, surveillance, and screening during both routine health supervision and acute care visits. By applying the strategies outlined, PCCs may prevent or minimize later MH concerns.

### THE PEDIATRICIAN'S ROLE IN ADDRESSING MENTAL HEALTH PROBLEMS

Mental health problems may come to the attention of a PCC in a variety of ways—referral by school or child care personnel; expression of concern by the youth or parent directly to the PCC; or findings by the PCC through surveillance or formal psychosocial screening. Frequently, children and families have not framed these visits as MH related. They may be seeking routine health supervision, acute care for a physical complaint, help with a challenging behavior, or simply reassurance. Often, the child's problem is undifferentiated (eg, a child who is not functioning well at child care or school, parents who are frustrated and angry with an adolescent's rebelliousness, or a youth who is not fitting in well with peers).

Thus, the role of the PCC often begins with eliciting psychosocial and MH concerns and differentiating normal developmental variations from MH problems that adversely affect the child's functioning. The PCC's priority is to recognize those emergent situations that compel an immediate intervention. In their absence, the PCC's role may be providing reassurance when that is appropriate, engaging the child and family to seek care for significant problems, addressing any barriers to their seeking and receiving care, assessing and managing the child in the primary care setting (in a role similar to that of an MH specialist), or guiding the family toward appropriate referral sources and comanaging the child's care with any involved MH professionals.

Whether providing MH services alone or collaboratively, the PCC's role also includes monitoring the child and family's functioning and progress in care, applying chronic care principles as for other children and youth with special health care needs, and providing and coordinating the care of the child's comorbid medical conditions. PCCs have the added challenge of fulfilling these roles within the constraints of a busy practice without compromising the efficiency and financial viability of the practice.

The TFMH has issued a policy statement describing the MH competencies requisite to these roles.

### GENERAL PRINCIPLES OF MENTAL HEALTH CARE IN THE PRIMARY CARE SETTING

Certain principles apply universally to the MH care of children in primary care settings.

- PCCs can be effective in reducing the child and family's distress and improving the child's functioning, even in the absence of a specific diagnosis.
- All children with MH problems should be triaged for psychiatric emergencies, including the potential to do harm to self or others.

- Mental health problems often coexist with developmental and physical health problems.
- Although physical health conditions can cause MH symptoms and should always be considered as a possible source, the PCC need not exclude physical health problems before considering and caring for a child's MH problems.
- Mental health problems can impair a child's functioning, even in the absence of a diagnosable disorder; thus, the assessment and monitoring of MH functioning are basic to caring for a child with MH problems.
- Children and families may not be ready to take action on an MH problem once it is identified; ensuring the child and family's engagement in care is a fundamental role of the PCC. This involves assessing the child and family's state of readiness to take action and identifying any barriers to moving forward, such as conflict within the family, a sense of hopelessness, or prior adverse experiences with seeking help, and then addressing barriers and moving the child and family toward a greater state of readiness.
- A therapeutic alliance—a bond of trust between the PCC and the child and family—is the most effective of all MH interventions; using communication techniques that convey hopefulness and loyalty, the PCC can enhance the likelihood of good outcomes.
- The child and family's strengths, perceived needs, and preferences are central to developing a plan for the child's care.
- The decision to involve an MH specialist does not end the PCC's role; effective MH care requires comanagement with specialists.
- The chronic care model, used in organizing the care of children with medical conditions such as asthma and diabetes, is applicable to the care of children with MH problems.

Mental health care is not confined to the traditional pediatric primary care visit. Care begins when the family schedules an appointment for an MH concern. The practice ideally establishes routines for completion of parent and youth psychosocial questionnaires and behavior checklists in advance of the visit, either electronically or by paper and pencil; completion of behavior checklists from other key adults, such as teachers, child care providers, or a noncustodial parent; transfer of records of prior psychological assessment or previous MH care; and acquisition of report cards or other school records. During a single extended visit or multiple brief visits that fit the pace of primary care, the PCC can observe the child and family, as well as their interactions, explore significant responses in the data previously gathered (separate conversations with parents and youth), and perform a psychosocial and physical assessment. Each contact with the child and family incorporates engagement techniques that express the clinician's commitment to the child and family, addresses any barriers to care, and finds common ground for future action steps. Intervisit activities may include phone calls from the PCC or a designated staff member, e-mail, or text contacts; further assessment by an MH professional; trial of evidence-based psychosocial therapy (or common elements of evidence-based therapies); trial of medication in a child who has a diagnosed disorder and specific indications for that medication; consultation with an

MH professional, either through a traditional referral and visits to that professional or a consultation directly between professionals; exchange of information with child care or school personnel and any involved MH professionals; and periodic reassessment of the child's functioning.

The Mental Health Practice Readiness Inventory (see Tools for Practice at the end of this chapter) developed by the TFMH enables PCCs to assess their practice's strengths and needs in providing and managing the care of children with MH problems and to focus quality improvement efforts on strategies to enhance their office systems in support of that care.

## ELEMENTS OF MENTAL HEALTH CARE IN THE PRIMARY CARE SETTING

### Triage for Emergency

The presence of an MH concern triggers the triage process. Psychiatric and social emergencies include sexual or physical abuse, suicidality, threat of violence to or by the child, psychosis, addiction to or withdrawal from substances, acute intoxication, and family dysfunction or social circumstances that threaten the safety of the child (eg, domestic violence). Inadequate family resources (eg, homelessness or hunger) may also pose urgent health and safety risks.

PCCs should ask key questions regarding suicidal or homicidal thoughts, presence of a plan, access to lethal weapons such as firearms, and support systems. PCCs will need a system in place to ensure immediate psychiatric evaluation of children at risk for suicide. The SAD PERSONS tool assists in identifying the level of suicide risk. Chapter 137, Depression, and Chapter 370, Psychiatric Emergencies: Suicidality, Agitation, Psychosis, and Disaster Exposure, provide additional guidance on triaging for psychiatric emergencies.

### Referral for Emergency Services

The presence of certain psychiatric or social emergencies (eg, suspicion of abuse or neglect, risk for homicide) may require immediate action mandated by state law (eg, reporting to social services or legal authorities) and steps to protect the safety of anyone threatened by the emergency, as well as referral for psychiatric care. Ideally, the practice would have procedures in place and a community-wide understanding of optimal care for children and youth experiencing a psychiatric or social emergency. The PCC's role is to provide medical care as indicated, follow procedures for notification of authorities, ensure that the child receives needed emergency psychiatric services, provide reassurance to the child and family about the PCC's ongoing interest in them, and put in place a plan to follow up and provide other medical home services.

The PCC can facilitate sharing of information with MH specialty or social service providers by obtaining written permission from the family for exchange of information about the child's or family's progress in MH specialty treatment or social services. This exchange is critical to primary care follow-up.

### Mental Health Assessment: Key Points

For the child presenting with a positive psychosocial screen or MH symptoms, without a psychiatric



emergency, further assessment may be a single, formal process or may take place over time by gathering data from the child, family, and collateral sources and by observing the child's response to primary care interventions. Several aspects of the assessment warrant highlighting here.

### **Global Functional Assessment**

It is important to determine the effect of the child's problem on her functioning at home, at school or child care, and with peers. This global functional assessment can serve as a baseline for monitoring the effect of the child's problem over time and contribute to decision making about the resources the child will require—children whose functioning is severely impaired will require care in the MH specialty system; for those with lesser degrees of dysfunction, the PCC and family can decide together whether to involve an MH specialist in the assessment, treatment, or both, based on their preferences and other factors, discussed later. Primary care-friendly tools, such as the Impact Scale of the Strengths and Difficulties Questionnaire and the Columbia Impairment Scale, are available to measure functional impairment and can become a routine element in assessing and monitoring children with MH problems, much like a vital sign. (See Tools for Practice at the end of this chapter.)

### **History of Trauma**

It is also important to inquire of the child and parent, separately, about any traumatic events or losses in the life of the child and family that may have triggered the child's symptoms or may be contributing to the child's or family's problems in coping. Examples of such events or losses include the death of a loved one or pet; a move; homelessness; conflict, separation, or divorce of parents; military deployment of a parent or other loved one; incarceration (or juvenile detention) of the child or a loved one; breakup of a relationship; abuse or bullying by the child or targeting the child; child abuse; foster care; exposure to violence (either directly or emotionally, through death or injury of a loved one or through exposure to violent media); or a natural disaster. The finding of trauma exposure may indicate the need for specialized trauma-focused interventions. See Chapter 129, Anxiety; Chapter 210, Adjustment Disorder in Children and Adolescents; and Chapter 317, Post-traumatic Stress Disorder for more discussion about eliciting and addressing a history of trauma.

### **Sleep Pattern**

Poor sleep can cause MH symptoms; it can also result from mental illness, treatments for mental illness, or the breakdown in routine sleep patterns when families are disrupted by mental illness. Parents of youth presenting with MH problems often observe (or complain) that the youth gets insufficient sleep. The PCC should determine whether the youth is unable to sleep *even when she wants to sleep* (potentially a presenting sign of serious mental illness, such as bipolar disorder, depression, or schizophrenia); whether the youth is missing sleep because of a physiologic sleep problem such as obstructive sleep apnea; or whether the youth is communicating with peers at all hours,

doing homework, or losing sleep for other reasons associated with unclear boundaries, youth-parent conflict, procrastination, learning difficulties, or other factors. These are important distinctions that influence care. Sleep deprivation can exacerbate symptoms, increase irritability, and decrease resilience of the child (and the parents, if their sleep is also disrupted); as such, addressing it appropriately is an important component of management. For a discussion of sleep disturbances and resources to assist in addressing them, see Chapter 194, Sleep Disturbances, Nonspecific.

### **Use of Complementary and Integrative Medicine Therapies**

Because parents (and adolescents) commonly try complementary and integrative medicine approaches before or while seeking help from the PCC for psychosocial problems, and because some medicinal therapies may interact with prescription medications, it is important to inquire about them as part of the psychosocial assessment. See Chapter 56, Self-regulation Therapies: Hypnosis and Biofeedback, and Chapter 57, Complementary and Integrative Medical Therapies, for discussion of hypnosis, biofeedback, and other therapies; if asked directly, adolescents and parents may report experience with or interest in complementary and integrative medicine therapies.

### **Common Factors Intervention**

If there are no findings that suggest a psychiatric or social emergency, if the child's problem is undifferentiated (eg, sibling conflict, poor school performance, adolescent rebellion against family rules), or if the child is awaiting further assessment or specialty referral, the PCC can apply "common factors" skills, represented by the HELP mnemonic in Box 50-1.

These skills are drawn from evidence-based therapeutic approaches, including motivational interviewing, cognitive behavioral therapy, and family therapy. Application of these skills has been effective in decreasing parents' distress and improving children's functioning across a range of MH problems. They can be applied in brief visits of 15 minutes, allowing for the rapid pace of pediatric practice. They include techniques helpful in managing conflict between family members during the visit (eg, avoiding taking sides, acknowledging the legitimacy of feelings, reminding that strong feelings often occur when people care about each other, and offering to have separate conversations with youth and parents to give both a chance to be fully heard). Importantly, they can also be applied to bringing the visit to a supportive close. See Chapter 46, Effective Communication Strategies, for a more complete discussion of these skills, which are core competencies in the primary care of children with MH problems.

The purposes of this initial "generic" primary care intervention are to develop a therapeutic alliance with the child and family, to involve the child and family in developing a plan for addressing the problem, and to identify and address any barriers to carrying out that plan. At times, especially if symptoms are just emerging and dysfunction is minimal, primary care



### BOX 50-1 HELP Build a Therapeutic Alliance

#### H = HOPE

Increase the family's hopefulness by describing your realistic expectations for improvement and reinforcing the strengths and assets you see in the child and family.

#### E = EMPATHY

Communicate empathy by listening attentively.

#### L<sup>2</sup> = LANGUAGE, LOYALTY

Use the child or family's own language to reflect your understanding of the problem as they see it and to give the child and family an opportunity to correct any misperceptions.

Communicate loyalty to the family by expressing your support and your commitment to help.

#### P<sup>3</sup> = PERMISSION, PARTNERSHIP, PLAN

Ask the family's permission for you to ask more in-depth questions or make suggestions for further evaluation or management.

Partner with the child and family to identify any barriers or resistance to addressing the problem, find strategies to bypass or overcome barriers, and find agreement on achievable steps aligned with the family's motivation.

Establish a plan (or incremental first step) through which the child and family will take some action(s), work toward greater readiness to take action, or monitor the problem, then follow up with you, based on the child and family's preferences and sense of urgency. (The plan might include, for example, gathering information from other sources such as the child's school, making lifestyle changes, applying parenting strategies or self-management techniques, reviewing educational resources about the problem or condition, initiating specific treatment, seeking referral for further assessment or treatment, or returning for further family discussion.)

From American Academy of Pediatrics. *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit*. Elk Grove Village, IL: American Academy of Pediatrics; 2010.

intervention may be all that is needed. When referring to a specialist, common factors methods can be applied to readying the child and family for referral and increasing their sense of hopefulness about receiving help.

The PCC and family may decide to have a single primary care session or additional visits. The PCC can incorporate any of the following elements into primary care MH visit, in accordance with the family's wishes and the child's needs.

**Offer to provide advice, if wanted**, on parenting techniques to address acute problems (eg, sibling conflicts, anger outbursts, family rules) **or specific evidence-based approaches** in which the PCC has been trained, such as relaxation techniques, brief problem-oriented cognitive behavioral therapy, or mindfulness interventions. The PCC can suggest ways the family can, at least temporarily, avoid the interactions

and precipitating events that are contributing to the child and family's stress, such as arguments about homework. The PCC can also offer guidance on general steps that will enhance the child and family's MH naturally—ensuring sufficient sleep (critically important because of the role sleep deficits can play in exacerbating symptoms and decreasing resilience), reducing time spent watching television or using electronic media, increasing outdoor time, increasing physical activity, learning stress management techniques, and scheduling a special time each day (not subject to withdrawal as punishment) for the parent to give one-on-one attention to each child.

**Offer intervisit activities.** Examples of intervisit activities include the following:

- Screening, behavior checklists (youth, parent, teacher)
- Functional assessment
- Diary
- Reading (Internet or print)
- Behavioral “homework” assignment (ideally just 1 or 2 targeted changes)
- Stress and conflict reduction
- Evidence-based electronic treatment programs (Internet or software applications)

If the history or functional assessment of a school-aged child points to academic or behavioral problems in school, PCCs will need information directly from the child's school about the child's academic performance. In addition to the teachers' behavioral observations, the PCC is looking for discrepancy between the child's cognitive ability and academic achievement. Such a discrepancy could suggest the possibility of a learning disability and require further psychological testing; it could also suggest psychosocial or emotional barriers to learning, such as bullying or anxiety. To facilitate communication between PCCs and school personnel, it is helpful to develop a community understanding about the role of school personnel in collecting data for PCCs and the role of PCCs in informing school personnel about students' medical and MH needs.

The PCC can also request information about pre-school-aged children from their child care provider. Use of a tool such as the ABLE will facilitate this communication.

Practice procedures should ensure that parents complete a form authorizing the PCC to exchange information with other professionals, as appropriate to the child's situation. In addition to school and child care personnel, this might include agencies and other health professionals who have been involved with the child or family.

**Make plans to include other adults.** If parents are separated, divorced, or in conflict, it is important to gather information from the parent who is not represented at the visit. In some family circumstances other adults, such as a grandparent, step-parent, or other relative, may have important perspectives to consider and opportunities to help the child. Several tools have parent versions that can be used more broadly to gather behavioral data from these individuals (eg, Strengths and Difficulties Questionnaire, Pediatric Symptom Checklist). Use of a tool is not a substitute for

including these other significant adult figures in future discussions about the child and plans for care.

For children in foster care, it is critically important to obtain authorization for exchange of information from the assigned social service agency and involve case workers in collecting information from biologic and foster parents, particularly if adults who are unfamiliar with the child's history accompanied the child to the visit.

**Offer community resources and educational materials** that may aid the child or parents in understanding the MH problems being addressed. These resources can include reliable Web sites. It may also be appropriate at this point to mention that the PCC can be a bridge to MH specialists who can provide further assessment and treatment, as needed.

**If a family member has medical, MH, or social needs that contribute to the child's problem or to family stress, explore this person's readiness to seek and accept help** and initiate referrals as appropriate, taking care to avoid "blaming" language.

At the close of each visit, the PCC can revisit the HELP mnemonic to reinforce the therapeutic alliance, enlist the parents to observe for persistence or worsening of symptoms, and bring the visit to a supportive close. The PCC can also plan telephone contact with the family at appropriate intervals and an appropriate return for follow-up.

### Care of Children With Common Symptoms

If screening results, behavior checklists, clinical assessment, or observations over the course of primary care visits suggest that the child's problem falls into one of the commonly presenting symptom clusters bulleted below, other chapters in this book offer evidence-informed guidance for further assessment of the child and primary care management. This guidance can be applied even when a child's symptoms do not reach the threshold for a disorder.

- Anxiety, Chapter 129
- Depression, Chapter 137
- Disruptive Behavior and Aggression, Chapter 139
- Inattention and Impulsivity, Chapter 168
- Learning Difficulty, Chapter 172
- Substance Use, Chapter 198
- Symptoms of Emotional Disturbance in Young Children, Chapter 199

### Prescription of Psychotropic Medications in Primary Care

A number of childhood MH disorders are responsive to psychotropic medications. Chapter 62, *Psychotropic Medications in Primary Care Pediatrics*, describes these medications and provides a rationale the PCC can apply in determining which medications they can safely and effectively prescribe. *Any child who is diagnosed with an MH disorder and who is a candidate for psychotropic medication should be offered concomitant, evidence-based psychosocial therapy.*

For children with attention-deficit/hyperactivity disorder, major depressive disorder, or generalized anxiety disorder, PCCs may choose to prescribe and monitor a psychotropic medication themselves. For children with multiple conditions or other conditions, a child psychiatrist, developmental-behavioral

pediatrician, neurologist, adolescent specialist, or other licensed PCC with specialized MH training would ideally participate in the child's care, either by prescribing the psychotropic medication or by consulting with the PCC in the use of medication.

Whichever physician prescribes the psychotropic medication, responsibility falls to the PCC to ensure that the child is monitored for adverse effects, either by the prescribing physician or the PCC, and that care of the child's medical conditions is coordinated with the MH care.

## COMANAGEMENT OF CHILDREN WITH MENTAL HEALTH AND SUBSTANCE ABUSE PROBLEMS

### Integration of a Mental Health Professional

In some parts of the United States, payment structures have the potential to support an MH professional on site in the primary care practice. Ideally, this professional is fully integrated within the primary care team, accepting "warm handoffs" from the PCC (ie, face-to-face introductions), participating in real-time decision making with the family and PCC, providing MH care, using a common health record, expediting consultation with school- and other community-based MH specialists when indicated, and enhancing communication among the PCC, family, and involved MH specialists. Such an arrangement has many advantages, including convenience and destigmatization for the child and family, increased adherence to treatment, high PCC and patient satisfaction, and cross-fertilization and mutual support of the professionals involved. Lacking such an arrangement, PCCs can build relationships with community-based MH and substance abuse (SA) professionals to collaborate in the treatment of children with MH and SA problems.

### The Decision to Involve a Specialist

The decision about whether and when to involve a specialist is pivotal. Multiple factors must be taken into account, including the family's preferences; the PCC's comfort; and the availability, accessibility, and appropriateness of MH, SA, and developmental specialty resources. PCCs should consider specialty involvement for any child whose functioning does not improve with primary care interventions, a child whose symptoms worsened or persisted despite initial interventions, and a parent or child who manifests distress out of proportion to findings.

General guidance for involving a subspecialist can be summarized by age group.

### Children From Birth to Age 5 Years

Children from birth to 5 years of age with significant symptoms of social-emotional problems (see Chapter 199, *Symptoms of Emotional Disturbance in Young Children*) should receive evaluation and management by specialists. Examples of problems requiring specialty care of young children include disordered parent-child relationship, parental mental illness, language or communication delay (often associated with social-emotional concerns), disruptive behavior

with aggression, abuse or neglect of the child, and self-injury.

For this age group, the PCC can consider referring the child for assessment by a developmental-behavioral pediatrician, MH specialist with expertise in early childhood, therapist for the parent or the parent-child dyad, or specific professional (eg, speech pathologist, developmental evaluation team, or other community resource).

The federal law known as the Individuals with Disabilities Education Act (IDEA) mandates that states have an Early Intervention (EI) agency to identify children 0 to 3 years of age with developmental delays. Those states receiving certain categories of federal funding must provide assessment (not necessarily including general or subspecialty pediatric assessment) and an Individual Family Services Plan (IFSP) to all 0- to 3-year-olds who are substantiated as abused or neglected or who are identified as affected by illegal SA or withdrawal symptoms that result from prenatal drug exposure. Children 0 to 3 years of age who qualify for services (occupational, physical, or speech therapy; education) must receive them in the least restrictive environment (usually their home) on the basis of their documented delay in language, motor, personal social, or adaptive domains. Some states provide EI services free of charge or charge on a sliding fee scale according to families' income; others do not provide financial assistance. Some states go beyond the IDEA mandates to screen for developmental risk factors and social and emotional problems and extend EI services to these children. PCCs will need specific knowledge about the range of EI services provided in their own state and the process for gaining access to them.

Developmental and educational services for children aged 3 to 5 years are also mandated and regulated by the IDEA. In most states, the public school system is responsible for developmental assessment and education of children with significant delays,

whereas in other states, the EI programs continue to provide assessment and services for this age group.

See Table 50-1 and Tools for Practice at the end of this chapter for examples of evidence-based interventions for infants and young children, their parents, or caregivers. High-quality child care and preschool have a long-lasting protective benefit, especially for children at high developmental and behavioral risk; PCCs may also refer to these programs.

### Children Aged 5 to 21 Years

For children aged 5 to 21 years, one or more of the following circumstances constitute an indication for referral:

- Suicidal or homicidal intent
- Severe functional impairment, regardless of symptoms or diagnosis
- Rapid cycling mood
- Depressive symptoms in a preadolescent
- Extreme outbursts and problems with conduct
- Severe eating problems
- Psychotic thoughts or behavior
- Self-injury
- Comorbidity of SA and MH problems
- A score of 2 or more on the CRAFFT (car, relax, alone, forget, friends, trouble) SA screening tool
- Attention-deficit/hyperactivity disorder with comorbidities
- Behavioral or emotional symptoms in a child with a history of abuse or neglect
- Behavioral or emotional symptoms in a child with a developmental disability or physical condition
- Any other problem that the PCC does not feel prepared to address

PCCs in a wide range of disciplines can provide diagnostic and therapeutic assistance in these situations, including developmental-behavioral pediatricians, neurodevelopmental pediatricians, adolescent medicine specialists, pediatric neurologists, psychiatrists, clinical psychologists, school psychologists,

**Table 50-1** Evidence-Based Programs for Young Children

PROGRAM	AGE RANGE	TREATMENT AREA/GOALS
The Incredible Years ( <a href="http://www.incredibleyears.com">www.incredibleyears.com</a> )	3–12 yr	Conduct problems
Triple P Positive Parenting Program ( <a href="http://www.triplep.net">www.triplep.net</a> )	—	Social and behavioral problems
Parent–Child Interaction Therapy	2–8 yr	Conduct problems
Help the Noncompliant Child Parent Training Program	3–8 yr	Noncompliance
Nurse–Family Partnership ( <a href="http://www.nursefamilypartnership.org">www.nursefamilypartnership.org</a> )	Infants	Improved health, education, and self-sufficiency
Infant Caregiver Project ( <a href="http://icp.psych.udel.edu">icp.psych.udel.edu</a> )	Infants	Children who experience disruptions in care at an early age
Circle of Security ( <a href="http://www.circleofsecurity.org">www.circleofsecurity.org</a> )	—	Parents' caregiving capacity
Partners in Parenting Education ( <a href="http://www.howtoreadyourbaby.org/pipe.html">www.howtoreadyourbaby.org/pipe.html</a> )	Babies and toddlers	Parents' emotional availability and relationship-building skills
Parents as Teachers ( <a href="http://www.parentsasteachers.org">www.parentsasteachers.org</a> )	—	Early detection of developmental delays and health issues; prevention of child abuse and neglect; school readiness and success

Adapted from Appendix S7: references for evidence-based programs for young children. *Pediatrics*. 2010;125(Suppl 3):S155–S158. For full program details, see [pediatrics.aappublications.org/content/125/Supplement\\_3/S155](http://pediatrics.aappublications.org/content/125/Supplement_3/S155).



clinical social workers, licensed professional counselors, licensed marriage and family therapists, advanced practice nurses with specialized psychiatric training, and SA specialists. These professionals may practice in public MH or developmental clinics, in schools, in private practice, or in university settings. If an MH referral will require authorization by the family's health insurance plan, entry into a carved-out or parallel private behavioral health insurance plan, or entry into the public MH system, the family will likely need guidance and time to research the options. The Mental Health Parity and Addiction Equity Act of 2008 may ultimately have the effect of diminishing administrative and financial barriers that have historically impeded access to MH services.

### Evidence-Based Psychosocial Treatments

There are many effective, evidence-based psychosocial treatments (often called simply "therapy" in the MH community) for school-aged children with MH and SA disorders, including a growing number of electronic, interactive programs to address specific concerns. See Chapter 61, *Psychosocial Therapies*, for a synopsis of evidence-based psychosocial treatments.

### Key Services

Table 50-2 offers a listing of key MH services and the professionals who provide them. A PCC whose community does not offer the full array of key services will need to partner with others, including developmental-behavioral pediatricians, local school systems, early childhood educators, parent educators, MH providers, and advocates, to address gaps. Given the necessity for child psychiatry consultation and shortage of child psychiatrists, many regions in the United States are piloting new models of psychiatry consultation by video and telephone. One of the earliest of these, the Massachusetts Child Psychiatry Access Project (MCPAP), has demonstrated an increase in participating PCCs' comfort in managing common childhood disorders and improvement in the outcomes of children in their care.

### Tracking Referrals

Because stigma and administrative, financial, and logistical barriers often prevent children from seeking or receiving MH specialty care, it is important that PCCs track the children they refer. If the family is unsuccessful in acquiring timely assessment or treatment for the child, the PCC can offer generic interventions as described earlier, further primary care assessment and management strategies, or periodic telephone contacts to monitor for worsening or emergent problems. Unfortunately, it may be necessary in some instances to use emergency procedures to obtain needed services.

### Communication

The decision to involve a specialist does not end the PCC's role in the care of the child. It does mean that the PCC's role will include communicating with the specialist. As with any other specialty referral, the process is enhanced by conveying to the specialist the nature of the concern and the PCC's specific

questions, results of previous assessment and intervention efforts, and openness to discussion with the professional. Although the Health Insurance Portability and Accountability Act (HIPAA) allows exchange of information among professionals who are involved in the care of a mutual patient, many MH professionals are reluctant to share information without express consent of the child and family. By obtaining written consent and sending it to the MH professional, the PCC can convey interest and facilitate communication.

For children in the foster care system, the assigned social service agency must authorize exchange of information. It is important to collect information from case workers and to convey information back to the worker. If the child changes placement and the caregivers are unaware of previous health assessment, plan of care, and sources of care, the child suffers discontinuity of health care as well as placement. In some situations, the PCC may need to be the primary advocate for the MH of a child in the foster system, expressing concerns and recommendations clearly and repeatedly to the appropriate social service agency.

Forms for exchange of information may facilitate the comanagement process (see *Tools for Practice* at the end of this chapter). Telephone and e-mail contacts may be helpful in some instances.

### Development of a Family-Centered Care Plan

The purpose of a family-centered care plan is to seek improvement in the child's overall emotional health and functioning. It articulates the child's and the family's goals; child and family strengths; service and educational needs; roles of involved service providers, family members, and other caregivers; schedule of follow-up and routine health supervision visits; steps to take in an emergency, if one should occur; and, ultimately, the route to self-care or family care, transition to adult primary care and specialty health services, and the other services and care coordination needed to support the young person's achievement of his educational, social, and vocational goals in adulthood.

A care planning conference is a very helpful (some would say, essential) mechanism to develop and coordinate a plan of care for a child with an MH or SA disorder. Ideally the family, other caregivers, school personnel, case workers, and service providers all participate in the plan's development. If the child has a comorbid medical condition that involves medical specialty care, inclusion of medical specialists is also important. For children in the foster care system, it is essential to include the case worker.

The family should not be placed in the position of transmitting information between professionals who are involved in their child's care; if the inclusion of involved specialists in the care planning conference is not feasible, the PCC needs information from them in advance of the conference to ensure understanding of the child's problems and the options available for further care. Together, the family, PCCs, and other partners can set the timetable of care, determine need for involvement of additional or alternative specialists, and select interventions. They can also establish a plan



**Table 50-2****Sources of Specialty Services for Children With Mental Health Problems and Their Families**

<b>SPECIALTY SERVICES</b>	<b>SOURCES</b>
Psychiatric emergency services	<ul style="list-style-type: none"> <li>• Local mental health screening, triage, and referral service or other intake point for public specialty system</li> <li>• Mobile crisis unit, if available</li> <li>• Child psychiatrist</li> <li>• General psychiatrist with pediatric expertise (or consultation with child psychiatrist)</li> <li>• Emergency department</li> </ul>
Medication consultation or management of patients with problems of high severity (MD or DO required)	<ul style="list-style-type: none"> <li>• Child psychiatrist</li> <li>• General psychiatrist with child expertise or child psychiatry consultation</li> <li>• Neurodevelopmental/developmental-behavioral pediatrician (NDP/DBP)</li> <li>• Adolescent medicine specialist</li> <li>• Pediatric neurologist</li> </ul>
Early Intervention (EI) services	<ul style="list-style-type: none"> <li>• Local public mental health agency</li> <li>• Developmental evaluation agency</li> <li>• NDP/DBP</li> <li>• Child psychiatrist with expertise in young children</li> <li>• EI specialist</li> </ul>
Child protective services	<ul style="list-style-type: none"> <li>• Department of Social Services</li> </ul>
Grief counseling	<ul style="list-style-type: none"> <li>• Licensed mental health professional (LMHP)</li> <li>• Hospice agency</li> </ul>
Substance abuse counseling	<ul style="list-style-type: none"> <li>• Licensed substance abuse counselor</li> <li>• Agency specializing in substance abuse</li> </ul>
Psychosocial assessment	<ul style="list-style-type: none"> <li>• LMHP with expertise</li> </ul>
Educational assessment	<ul style="list-style-type: none"> <li>• School psychologist</li> <li>• Other licensed psychologist</li> <li>• Developmental-behavioral pediatrician</li> <li>• Educational specialist</li> </ul>
Psychosocial treatment	<ul style="list-style-type: none"> <li>• LMHP trained in the specific intervention (eg, cognitive behavioral therapy specific to the condition, exposure, behavior therapy, intensive communication training, parent management training, family therapy)</li> </ul>
Specialized counseling programs (eg, domestic violence, family reunification, children of alcoholics, juvenile sex offender, divorce, stress management, smoking cessation)	<ul style="list-style-type: none"> <li>• LMHP with expertise</li> <li>• Agency specializing in that area</li> </ul>
Parenting education	<ul style="list-style-type: none"> <li>• Parent educator trained in evaluated curriculum</li> <li>• Family services agency</li> <li>• LMHP</li> <li>• School system's social work services (some have parenting education programs)</li> <li>• Agricultural extension service (some have parenting education programs)</li> </ul>
Care coordination/case management	<ul style="list-style-type: none"> <li>• LMHP with expertise</li> <li>• Local public mental health agency</li> <li>• Peer support program</li> </ul>
Peer support	<ul style="list-style-type: none"> <li>• Local organization of National Alliance on Mental Illness, National Federation of Families for Children's Mental Health, Family Support Network, Children and Adults With Attention-Deficit/Hyperactivity Disorder</li> <li>• Local public mental health agency</li> <li>• Al-Anon</li> </ul>

From Appendix S1: sources of specialty services for children with mental health problems and their families. *Pediatrics*. 2010;125 (Suppl 3):S126–S127.

for monitoring treatment response and safety and create a common understanding of limits of confidentiality. For adolescents, direct input to the plan is critical for engagement and success of treatment; and their transition to adulthood and to adult care deserves specific attention in the plan. (See Chapter 66, Transitions to Adulthood.)

For children previously involved in MH specialty care, a care plan may already be in place and may omit primary care issues, such as healthy lifestyle (eg, nutrition, exercise, sleep, stress management, social support), routine health supervision, or care of chronic medical conditions. In this instance, rather than developing a new or alternative plan of care, the PCC can augment the existing plan by pointing to the roles that she can play in coordinating and complementing the care of the MH specialists.

Some children with severely impairing emotional disturbance may have an MH or EI care manager involved in their care; if so, the participation of this care manager is central to the process. The care manager may organize periodic meetings of teachers, social workers, and agency representatives involved with the child and family. In the MH specialty system, such processes are sometimes called a system-of-care approach—a coordination system built around the family's strengths and priorities. If such a system exists, the PCC (or his staff representative), often inadvertently omitted, can join in that process as an alternative to convening a primary care conference.

Participation in care planning is time consuming. A primary care-integrated MH specialist can be a tremendous asset to the PCC in the care planning process, representing primary care perspectives and ensuring coordination of medical and MH specialty care. In the absence of an integrated MH specialist, participation by the PCC or other members of the primary care team is valuable to the child and family and may ultimately produce efficiencies in the care of children and adolescents with complex conditions. In the future, secure electronic methods may be developed to house care plans that are accessible to the family and to all those participating in the child's care.

See the Tools for Practice section of this chapter for sample care plans.

## MONITORING CHILDREN WITH MENTAL HEALTH AND SUBSTANCE ABUSE PROBLEMS

Office systems used to organize and monitor the care of children with chronic medical conditions such as asthma and diabetes can be applied to the care of children with MH and SA conditions. Elements particularly important for the care of children with MH and SA problems include the following:

- *Registries* (lists of children with MH problems that require monitoring): Registries can be developed within the practice for children and youth with positive psychosocial screens, children with concerns that do not rise to the level of a diagnosis, those who are not yet ready to seek or accept care for MH problems, those with social concerns that pose a risk to the child (eg, infants whose

mothers have a positive screen for postpartum depression, children exposed to trauma), children with disorders, and children prescribed psychotropic medication.

- *Assignment of staff roles* in care of children on the MH/SA registry. Examples might include the following:
  - Obtaining parental permission for information exchange with the MH or SA professional and school or child care
  - Tracking referral completion
  - Scheduling return to the PCC's office
  - Gathering collateral data (eg, school or child care progress reports, functional assessment scale)
  - Reaching out to child and family between visits
  - Monitoring medication effects and side effects
- *Forms and tools* to facilitate these office processes
- *Educational tools and resources* for youth and families (see Box 50-2)
- *Directory of community resources*, including providers of evidence-based psychosocial treatments and parenting programs (see Table 50-2 for a listing of key services)
- *Resources to support PCCs* in decision making
- *Coding and billing strategies* to optimize payment

The interval between primary care contacts will be determined by the acuity and severity of the child's condition; the child's and family's strengths, needs, and preferences; adverse effects and monitoring requirements of any treatments; the role of other professionals in monitoring the child; and the level of the child's impairment. Just as spirometry measures pulmonary function and assists the PCC in monitoring children with asthma, global functional assessment scales assist the PCC in monitoring children with mental illness.

When children are being followed by specialists, the PCC and specialists will need a coordinated follow-up plan, developed with the family. To assess the child's current status, they may rely on progress

### BOX 50-2 Helpful Web Sites for Families of Children With Behavioral Problems

- Healthy Children ([www.healthychildren.org](http://www.healthychildren.org))
- Zero to Three ([www.zerotothree.org](http://www.zerotothree.org))
- National Alliance on Mental Illness ([www.nami.org](http://www.nami.org))
- American Psychological Association ([www.apa.org](http://www.apa.org))
- Children and Adults With Attention-Deficit/Hyperactivity Disorder ([www.chadd.org](http://www.chadd.org))
- National Federation of Families for Children's Mental Health ([www.ffcmh.org](http://www.ffcmh.org))
- Substance Abuse and Mental Health Services Administration ([www.samhsa.gov](http://www.samhsa.gov))
- American Academy of Child & Adolescent Psychiatry ([www.aacap.org](http://www.aacap.org))
- The Compassionate Friends ([www.compassionatefriends.org](http://www.compassionatefriends.org))

reports from other professionals involved in the child's care; functional assessment scales completed by the parent, teacher, and youth; and their own clinical assessment. When pharmacologic agents are part of the treatment plan, laboratory tests may be necessary to monitor levels and adverse effects. Responsibility for each of these roles should be clearly assigned. Responsibility for routine health supervision and monitoring of the child's comorbid medical conditions falls to the PCC.

Applying chronic care principles to the child's care does not mean that the child's condition is permanent. Children and families can and do recover from mental illnesses. The PCC can periodically reconvene a conference with the family (and youth) to determine whether further assessment or a change of plan is indicated.

## CODING AND BILLING FOR MENTAL HEALTH SERVICES IN PRIMARY CARE

Many PCCs are reluctant to elicit and address MH concerns because of inadequate payment for the additional time required. The coding guidance that follows may assist in overcoming this barrier.

### Evaluation and Management (E and M) Codes

The following *Current Procedural Terminology (CPT)* codes may be used for primary care visits involving MH services:

- Office or other outpatient services (new patient): **99201–99205**
- Office or other outpatient services (established patient): **99211–99215**
- Office or other outpatient consultations (new or established patient): **99241–99245**
- Preventive medicine services (new patient): **99381–99385**
- Preventive medicine services (established patient): **99391–99395**
- Brief emotional behavioral assessment (new or established patient): **96127**

### The Primary Care Clinician as Mental Health Consultant

Under specific circumstances, a PCC may serve as a consultant in addressing children's MH concerns (as well as other concerns). Because consultation codes have higher relative value units (RVUs) than office or other outpatient service codes, they are usually paid at a higher rate. The following criteria, known as the 3 Rs, must be met for a service to qualify as a consultation:

- A *request* for consultation must be made by an appropriate source (not a patient or family member) and documented in the chart.
- The consulting PCC must *render* an opinion or advice back to the requesting source.
- The consulting PCC must provide a written *report* back to the requesting source.

If these criteria are met, a PCC can report consultation codes **99241–99245** for services provided. The request for consultation may come from any appropriate source, such as school personnel, another colleague in the same practice, a therapist, a nurse

practitioner, or an attorney. The PCC cannot use consultation codes for return visits related to the initial consultation.

The consulting PCC can be a physician or nonphysician practitioner (NPP) with expertise in the relevant clinical area. If an NPP is performing the MH consultation, code **90791** (psychiatric diagnostic evaluation) could be more appropriate for describing the service.

### The “Greater Than 50 Percent” Rule

Frequently, MH visits require considerable time spent in counseling or care coordination. When these aspects take up more than 50% of the face-to-face time spent with a patient, the PCC can use time as the key or controlling factor for a particular evaluation and management service rather than the history, physical examination, or medical decision-making elements that would otherwise be necessary to support that code. To code these encounters, the PCC must carefully document the total time spent with the patient and the amount of that time spent in counseling or care coordination. Suppose, for example, the physician spends 25 minutes face-to-face with an established patient and 15 of those minutes are spent in counseling or care coordination. The typical duration of code **99214** is 25 minutes. Because more than 50% of that time was spent in counseling or care coordination, the PCC could use **99214** regardless of the history, physical examination, or medical decision making provided during that encounter.

### Prolonged Services

If the PCC spends at least 30 minutes longer, face-to-face, than the time typical for a particular visit, the PCC may additionally report prolonged service codes **99354–99355**. Time must be spent on the same day as the visit, but does not need to be continuous. The prolonged service codes are add-on codes, meaning they are reported separately in addition to the appropriate code for the service provided (eg, office or other outpatient service codes). It is essential to document the time and services provided to substantiate the use of these prolonged service codes.

Even correct coding and documentation in the medical record may not result in payment for prolonged services because of a payer's policy not to cover them. If the patient is on a capitated plan, the PCC may request authorization to bill the family directly for these noncovered services.

Few payers pay PCCs for non-face-to-face prolonged services codes **99358–99359**, care plan oversight codes **99339–99340**, and telephone care codes **99441–99443**.

## SUMMARY

Increasingly, pediatric PCCs are expected to be a source of MH care, a gateway to specialty MH care, and a source of primary care that is coordinated with specialty MH care. With the requisite competencies and with office systems in place to organize and monitor the care of children with MH problems, PCCs are positioned to fulfill these roles. They can recognize those emergent situations that compel an immediate intervention; find ways to support and help the family

that is resistant to seeking psychosocial care; assess and manage the child in the primary care setting—in a role similar to that of an MH specialist—or co-manage the child's care with MH professionals. By applying evidence-based methods, the PCC can reduce distress of the child and family and improve the child's functioning across a variety of MH problems, even in the absence of a diagnosis and while awaiting MH specialty assessment and treatment.

Factors determining the role of the PCC in a particular child's care include the type and severity of problem the child is experiencing, the family's preferences, the PCC's comfort, and accessibility of MH specialists with pediatric expertise. The PCC has a critical role to play in facilitating development of a family-centered plan that coordinates the child's care and defines roles for the family members and professionals involved.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Family Care Plans* (templates), American Academy of Pediatrics, in *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* (shop.aap.org)
- *Medication Guides* (Web page), US Food and Drug Administration ([www.fda.gov/Drugs/DrugSafety/ucm085729.htm](http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm))

#### Medical Decision Support

- *Adapted SAD PERSONS* (screen), American Academy of Pediatrics, in *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* (shop.aap.org)
- *Enhancing Pediatric Mental Health Care: Algorithms for Primary Care* (article), *Pediatrics*, Vol 125, Supplement 3, 2010
- *Evidence-Based Child and Adolescent Psychosocial Interventions* (chart), PracticeWise, American Academy of Pediatrics ([www.aap.org/en-us/Documents/CRPsychosocialInterventions.pdf](http://www.aap.org/en-us/Documents/CRPsychosocialInterventions.pdf))
- *Feelings Need Checkups Too* (booklet), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/children-and-disasters/Documents/Feelings-Need-Checkups-Toolkit\\_0823.pdf](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/children-and-disasters/Documents/Feelings-Need-Checkups-Toolkit_0823.pdf))
- *Generic or Common Factors Intervention: HELP* (mnemonic), American Academy of Pediatrics, in *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* (shop.aap.org)
- *Mental Health Screening and Assessment Tools for Primary Care* (chart), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH\\_ScreeningChart.pdf](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH_ScreeningChart.pdf))
- *Sources of Specialty Services for Children With Mental Health Problems and Their Families* (chart), American Academy of Pediatrics, in *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* (shop.aap.org)

#### Practice Management and Care Coordination

- *Coding for the Mental Health Algorithm Steps* (fact sheet), American Academy of Pediatrics, in *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* (shop.aap.org)

- *HIPPA Privacy Rule and Provider to Provider Communication* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/HIPAA-Privacy-Rule-and-Provider-to-Provider-Communication.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/HIPAA-Privacy-Rule-and-Provider-to-Provider-Communication.aspx))
- *Mental Health Practice Readiness Inventory* (self-assessment), American Academy of Pediatrics ([pediatrics.aappublications.org/content/125/Supplement\\_3/S129](http://pediatrics.aappublications.org/content/125/Supplement_3/S129))
- *Primary Care Referral and Feedback Form* (template), American Academy of Pediatrics, in *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* (shop.aap.org)

### AAP POLICY

American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health and Task Force on Mental Health. The future of pediatrics: mental health competencies for pediatric primary care. *Pediatrics*. 2009;124(1):410–421. Reaffirmed August 2013 ([pediatrics.aappublications.org/content/124/1/410](http://pediatrics.aappublications.org/content/124/1/410))

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## Chapter 51

# CARE OF CHILDREN WITH SPECIAL HEALTH CARE NEEDS

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All children experience minor illnesses and injuries. Although most children have no ongoing consequences from these episodes, some children have more serious or recurrent impairments or disruptions



of their health with which they live for prolonged periods. These conditions, and the children who have them, have been given many names over the past decades. Some authorities have referred to them as having chronic illness, but some of these children are not ill. Other authors have referred to them as having disabilities or handicaps, but many children do not exhibit these features. The trend recently has been to refer to these children and youth as having special health care needs (CSHCN or CYSHCN). In addition, the subgroup of more severely affected children whose conditions involve more than one body system have been referred to as children with medical complexity. The term *children with special health care needs* was originally introduced as a euphemism for the other terms used earlier to describe these children with ongoing conditions. More recently, the Maternal and Child Health Bureau has used CYSHCN to include children who do not currently have any condition or impairment but who are at risk for one, such as foster children. Because no agreement exists on which children to include in the at-risk category, CYSHCN are referred to in this chapter as children with ongoing or chronic conditions.

## DEFINITION

Identifying children with ongoing or chronic conditions requires a definition. In fact, many current definitions are quite similar. One useful definition has 3 key components: the presence of a condition, a duration or expected duration of at least 1 year, and a consequence for the child. This definition recognizes 3 main types of consequences: having a functional limitation (something that prevents the child from participating in the normal range of age-appropriate activities), increased use of health care services beyond those used by age mates, and reliance on compensatory mechanisms (medication, special treatments, assistive devices, or personal assistance) to function.

The definition adopted by the Maternal and Child Health Bureau combines the latter 2 categories of consequences and considers *at-risk* children as well: “Those children who have or are at increased risk for a chronic physical, developmental, behavioral, or emotional condition and who also require health and related services of a type or amount beyond that required by children generally.” Because no validated method currently exists for fully operationalizing the Maternal and Child Health Bureau definition that includes those at risk, and because the concept of compensatory mechanisms is conceptually and critically distinct from receipt of services, the definition with 3 key components is used here. Compensatory mechanisms are especially important as medical care finds new ways to minimize functional limitations and allows children to carry on with their normal activities. For example, a child with a pacemaker or one who is on insulin, inhaled steroids, or overnight infusions may only be able to *pass* and function as a healthy child because of those treatments and may have few, if any, other consequences of his underlying condition. Unless these special aspects of care are

considered, children whose compensatory mechanisms are successful may be counted as healthy children, and thus the success of treatments and the need to sustain them will be underappreciated, undercounted, and underfunded.

The use of an umbrella definition that includes children regardless of their diagnosis is important because the epidemiology of ongoing conditions in children and adolescents includes a few common conditions, such as asthma, developmental delay, or diabetes, and far more uncommon conditions, such as congenital malformations and inborn errors of metabolism, malignancies, and a wide range of acquired injuries and illnesses. Even though the names of many of these conditions are known, an all-inclusive list would be extremely long, and many children would still not find their diagnoses on the list. Because of this circumstance, thinking of CYSHCN as sharing some common characteristics of duration and consequences without necessarily naming the condition is far more convenient for many purposes other than biomedical treatment. However, the specific diagnosis is extremely important when providing the appropriate specific treatments for the condition. Many specific conditions and their treatment are described elsewhere in this text.

## PREVALENCE

Estimates suggest that between 15% and 20% of children have some impairment or underlying condition that qualifies them as CYSHCN, depending on how the definition is applied. Some experience only minor, if any, difficulties from their conditions, but others are severely affected. Between one-half and two-thirds of the children who meet the definition experience a functional limitation, either with or without other types of consequences. Approximately 10% of all children who have ongoing conditions experience consequences in all 3 categories, (functional limitations, increased use of services, and need for compensatory mechanisms) and these are often the children with the most severe conditions.

Three factors will likely lead to an increase in the numbers of children with ongoing conditions. The first factor is improvements in early detection and diagnosis as a result of molecular genetics. Second is the use of preventive interventions that postpone the onset of the full manifestations of some conditions to which children are genetically vulnerable, thus increasing the number of children receiving care. Finally, medical advances increase the numbers of children who survive their conditions, sometimes with prolonged dependence on technology.

## EFFECT OF THE CONDITIONS

Ongoing conditions vary in their severity from very mild, requiring little health care, to extremely debilitating affecting every aspect of life and requiring intensive health care services. However, all ongoing conditions have some implications for children’s long-range health and service needs and in many cases for their longevity as well. Additionally, all conditions

affect how families view their children and their vulnerability. Research has demonstrated that there is not always a correlation between the pediatrician's sense of the severity of the condition and the family's perception of its effect or influence on their child and their lives.

Children with functional limitations tend to experience fewer of the usual activities and opportunities for socialization that are important for normal development. Depending on the age of the child and the level of functional limitations, these effects vary considerably. Motor or sensory impairments may limit exploratory opportunities to varying degrees and therefore can influence the child's developmental trajectory. Even children who do not have limitations are sometimes overprotected by their parents, which can result in unnecessary restrictions of opportunity for developing important social skills and psychological well-being. This is referred to as *the vulnerable child syndrome*.

Parents face a great deal of physical, emotional, and financial strain, and in many cases the entire family experiences significant social isolation. All of these stresses place additional burdens and demands on family members. Some studies suggest that parents who assume major caregiving responsibilities for children with severe conditions are at increased risk for physical and mental health problems and divorce, while others contest these findings.

Siblings and the children themselves are often stigmatized when conditions are visible. In addition, many siblings are forced to function more independently than usual because parental attention may be focused on the child with a condition. They may feel jealous, abandoned, and sad, or they may assume increased adult responsibilities. Sometimes these children become caregivers for the sibling with an ongoing condition or take on the care of younger, healthy siblings.

Conditions that are not obvious can also be particularly challenging emotionally, because children and families face issues regarding if and when to disclose the condition and must navigate between the world of the well and the world of their conditions. The lack of visibility creates uncertainty, and any type of uncertainty is particularly challenging. Most people seem to have the greatest difficulty with conditions that fluctuate in their severity, even when most of the time the children are relatively well. The emotional toll of these conditions is sometimes worse than when there is a stable level of greater dysfunction.

Transition times are especially stressful. Transition times include stages and events such as becoming ambulatory, entering school or child care, moving from one school or community to another, or moving into latency, adolescence, or adulthood. When healthy age-mates move from one major stage to another, the family of a child with an ongoing condition is often confronted with the ways in which their own child is different or with the need to make special accommodations to ensure that medical safety or special needs are managed. Primary care professionals can anticipate that these are times when families may need extra help and support.

## SPECIAL CARE CONSIDERATIONS

The primary care physician (PCP) needs to be aware of multiple special aspects of care of a child with an ongoing health condition and how usual practices may need to be modified. These aspects of care include the provision of health care maintenance and management of acute illness.

### Health Care Supervision

Because many children with ongoing conditions have more contact with the health care system than other children, their parents often assume that they are receiving a full package of services, but often this assumption is not true. The actual number of visits that focus on issues of health care supervision for children with ongoing conditions is much lower than for the general population. Many subspecialists assume that these services are being provided elsewhere. However, studies show that many children with ongoing conditions do not receive the routine screenings that are a part of recommended health care supervision for all children. Many are underimmunized as well. In most cases, this situation represents a failure of care rather than a reflection of recommendations for modification of the immunization schedule because of the child's condition or its treatment. Physicians should be aware of special recommendations concerning live vaccines, especially for immunocompromised patients, and document when vaccines are being modified for that reason. If vaccination is postponed, then the PCP should have a mechanism for remembering to provide appropriate alternate protection or later immunization if possible.

The usual anticipatory guidance should also be provided, although in the case of children with developmental impairments, the guidance should be adjusted to the appropriate developmental stage. This process may be complex, because children with ongoing conditions may develop normally or even be precocious in some areas while lagging in others.

In addition to following the usual health care supervision schedule for age-appropriate screening, specific recommendations exist for many children with ongoing conditions to have additional screening for specific vulnerabilities caused by their primary diseases or by the medications that they take. When sharing responsibility for the care of such patients with subspecialists, the PCP must establish who is providing the routine screening, immunizations, and anticipatory guidance, and who is monitoring these special risks to prevent failures or duplications of care. If a division of services exists, then the family must know this and the reasons that they need to make regular visits to both providers.

### Management of Acute Illness or Injury

Children with ongoing conditions experience the same minor illnesses that affect others in the community. However, every evaluation of a seemingly minor chief complaint requires the treating physician to consider whether the symptoms are complications of the underlying disease process, side effects related to medication taken to treat the condition, or a normal intercurrent event. Even when the child has a

minor illness or injury, physicians also should consider whether the condition or its treatment requires the child to receive any special care or medication adjustment. For example, a child with diabetes who experiences an episode of gastroenteritis is likely to need adjustment to the insulin regimen. A child who is being weaned from steroids or who is on permanent physiologic levels of exogenous steroid may need extra coverage during the illness. A child with vomiting caused by gastroenteritis might require an alternate mode of administration of an essential medication or special monitoring or titration of the dose.

In evaluating the patient and the management plan for the acute minor illness, the physician must check with the parents and older child about whether they have any special concerns or questions. This responsibility is most essential in an encounter in which the treating physician does not know the family, given that the family is often able to distinguish between the child's current and baseline condition in ways that may not be immediately obvious to someone who does not know the patient well. In many instances, the patient or parents will raise practical issues in daily management that may not have occurred to the physician. This circumstance is particularly true when they have experienced similar circumstances in the past. Box 51-1 lists some of the questions to consider in the management of acute illness or injury.

Technology-dependent children comprise a unique group among children and youth with special health care needs. These are children who require both a medical device to compensate for the loss of a vital bodily function and substantial, ongoing care to avoid further disability or death. It is estimated that between 0.1% to 0.25% of children in the United States are technology dependent. Common technologies include: enteral feeding tubes (nasogastric/gastrostomy), medium- to longterm central venous access (for parenteral nutrition, intravenous antibiotics, clotting factor, dialysis), clean intermittent catheterization, ventriculoperitoneal (VP) shunts and respiratory therapies (oxygen, cardiorespiratory [apnea] monitoring, pulse oximetry, tracheostomy care, respiratory support [home mechanical ventilation or positive airway pressure equipment, etc], and nasal cannulae).

## MANAGEMENT OF THE CHILD WITH SPECIAL HEALTH CARE NEEDS

Each health condition requires special biomedical treatment and monitoring to prevent secondary complications and to ensure optimal health and functioning. Regardless of the specific type of condition, there are many aspects of management, goals of treatment, and family challenges that are similar across the full range of physical, developmental, and behavioral conditions. Ideally, the child will receive family-centered care that is accessible, compassionate, comprehensive, continuous, and coordinated at the medical home. Such care should involve all the necessary team members. (See Chapter 6, Medical Home Collaborative Care.)

### BOX 51-1 Assessing Acute Conditions in Children With Ongoing Health Conditions

- Can the chief complaint and associated symptoms be explained by the child's underlying condition?
- Can the chief complaint and associated symptoms be explained by the current or recent medications or other treatments?
- Might the chief complaint and associated symptoms represent a complication of the child's underlying condition or a special vulnerability caused by the underlying condition?
- If so, what special evaluations should be performed?
- How do the child's current physical and laboratory findings differ from the child's baseline?
- Has the child skipped, vomited, or failed to absorb recent medications, and might this circumstance be causing a problem?
- What features of the child's condition are of most concern to the family or patient?
- What do they think the problem is?
- Can these features be explained by the presumptive diagnosis of the acute condition?
- What events or circumstances worry the family or patient most? Is this worry a realistic concern, and can something be done to reassure the family?
- In light of the acute diagnosis, does the child need a modification of usual care or medication? Can this modification be handled at home? If the situation can be handled at home, then what is the plan for follow-up, and should it be modified in light of the child's underlying condition?

## Diagnosis

The detection and confirmation of a condition herald the first stage of management. The care of children with ongoing conditions differs from the care of those with acute conditions in the degree to which the family must be involved actively in care decisions. This is because there are likely to be more care options, decisions to make, and adherence over long periods of time. Moreover, many need longterm treatments that require the physician and the parents to figure out how they can best be implemented in the home. Making choices that fit best into the family's routines and preferences has been shown to enhance adherence. The treatment plan may be developed by the PCP and, where appropriate, the subspecialists in partnership with the family. The clinical care responsibilities may be shared with a subspecialist or the staff of a referral hospital, but the PCP must work out a pattern of communication in which the various responsibilities of each of the parties are delineated. The PCP needs to determine regular mechanisms for communication, ascertain key issues that need to be monitored, and determine how these responsibilities are to be divided amongst all providers. In the case of children with



very rare conditions, especially when the primary expertise is far from the patient's home, the PCP should make sure that the delegated responsibilities are clearly understood and that the expert has reviewed the special issues to monitor and the indications for further consultation in order to ensure the best possible care.

Confirming a diagnosis and discussing its implications with parents and the child are ongoing processes that are never accomplished in a single conference. Parents should be encouraged to ask questions regularly, because they are usually unable to absorb a great deal of information at the time of confirmation of the diagnosis. The PCP should suggest that parents write down their questions and other people's questions and advice and discuss them at each subsequent visit. Providing this mechanism and a socially acceptable way to ask naive or awkward questions can enable family members to address issues they may find embarrassing or difficult. In cases in which the condition is life threatening, it may be appropriate to involve a palliative care specialist to talk about quality of life issues early in the care of the child and family.

Some physicians are uncomfortable sharing uncertainty about answers to questions posed by family members. In most instances the key questions that the parents want answered are related to what will happen to their child. Even the most expert physicians cannot answer such questions except in a probabilistic way. Parents repeatedly state that a cornerstone to working well with pediatricians over time is honesty, including sharing uncertainty or seeking additional information when the physician does not have ready answers.

When the information provided is especially distressing, many parents want to seek a second opinion (see Chapter 49, *Discussing Serious Symptoms, Results, and Diagnoses With the Patient and Family*). In these situations, the PCP should recommend places where this can be accomplished responsibly and offer to make study results available. For some families, the offer of opening the results to scrutiny is reassuring. For others who wish to follow through on the offer, it avoids the need for repeated tests and the awkwardness of their worrying about raising the issue with the physician or finding a way to discuss and reconcile conflicting recommendations.

Grief is a normal reaction to the confirmation of a diagnosis and to the loss of the idealized perfect child. Parents normally go through a series of reactions at the time of diagnosis. These reactions may include shock, denial, anger, sadness, and anxiety. Dealing with denial and anger can be challenging even for a pediatrician skilled in caring for children with complex or serious conditions, especially when the anger is directed at the pediatrician. Care must be taken to recognize the displaced anger and to avoid letting it negatively affect the physician-patient relationship. All parents feel guilty about real or imagined things that might have prevented the condition or led to its earlier recognition. Addressing this guilt as universal is important. When parents are encouraged to share their worries, they often can be reassured that the thing that is the source of their guilty feelings is often unrelated to the child's ongoing condition.

Eventually, reorganization (a normalization of emotional well-being) occurs, but any condition-related event or exacerbation may lead to a resurfacing of a cascade of emotional reactions. Parents may go through these reactions at different rates, and this circumstance can affect their communication with and relationship with the physician. The physician should avoid overreacting to parents' behavior and maintain a professional relationship.

### Developing and Promoting Partnerships With Families

Unlike acute conditions, in which life quickly returns to normal, the disruption caused by ongoing conditions continues or ameliorates slowly. In the long term, families bear the brunt of the care responsibilities, and they need to be full partners in care. (See Chapter 9, *Partnering With Families in Hospital and Community Settings*.)

At times, the traditional medical approach becomes a central barrier to the formation of partnerships with families. Two aspects are particularly problematic. The first problem is the paternalistic and hierarchical nature of medicine, which is often associated with entirely prescriptive decision making. Effective management of a chronic condition or impairment requires the physician to understand that the parents are the experts in raising their child and they assume most of the day-to-day care. Within a short time, some parents will know more, especially about rare conditions, than the average pediatrician, and their expertise should be valued and respected. Even at the beginning, the importance of the parents' role with and knowledge about their own child necessitates active involvement and sharing of responsibility that may run counter to the traditional hierarchical paternalism of the health care system. This shared decision-making process leads to better health outcomes for the child.

The second problem with a traditional medical approach is the emphasis on the deficit model, which focuses entirely on what is *wrong* with the patient, rather than seeing the strengths and assets. Physicians are trained to focus on the problem and fix it. For the most part, chronic conditions cannot be cured entirely, and the challenge for both the family and the PCP is to live with this reality and to minimize the disruption in the child's life as much as possible while still maximizing the child's longer-term future health and potential. To accomplish this task, focus must be placed on the whole child, while assets and impairments must be actively recognized and assessed.

When communication and mutual respect are established among the partners, a care plan can be developed that includes the priorities of all parties, is medically and culturally acceptable, and has a far better chance of being implemented and being successful than a plan that does not recognize the parents' role.

### Goals of Care

Regardless of the nature of the child's condition, the primary goal of care is to contain or minimize its effect



and to provide maximal opportunity for the child to function and develop physically, socially, cognitively, and emotionally. This process involves providing optimal biomedical treatment of the condition and helping the family *normalize* the entire family's life experiences as much as possible. To accomplish this, PCPs should place as few restrictions on the child's activities as possible, limiting only these activities that are absolutely necessary to avoid. Additionally, the care plan should be implemented in a way that minimizes the burden on the family as much as possible. This may require gathering information about the child and family that is sometimes beyond the usual inquiry. As a result, the PCP may be perceived by families as intrusive; however, most families are able to understand this exploration of their family life once it is explained to them. For example, information about the family's routines and preferences may help in suggesting minor modifications in the type or timing of medication administration or procedures that will make the child's care less disruptive. Family members may not know on their own whether or not they can safely modify schedules. Tailoring care to the individual family also requires a longitudinal and developmental framework in which the management strategies and responsibilities shift over time as the parents become increasingly comfortable with the management of the condition and with the child's developmental progress.

### Involving and Preparing the Child

The PCP must provide developmentally appropriate information to the child about his or her treatment. The child should also be involved in the timing, nature of, and assent for special procedures, especially when real choices exist. As the child matures, communicating directly with the child, rather than exclusively through the parents, is important. Explanations that may have been given to a young child require expansion and revision as the child matures. Daily care routines are optimally shifted to the child as early as possible, and well before adolescence, to prepare the child to become independent and responsible for self-care and self-management. This emphasis on the child promotes individualized goal-setting processes and ensures the child's inclusion. Just as with other responsibilities, special care for the condition starts out as the parents' duty and must become the child's responsibility to the fullest extent possible. As the child ages, the PCP must also start preparing adolescents with ongoing health conditions for transitioning their care to physicians trained to care for adults.

### Coordination of Care

Families often need assistance with learning how to use different parts of the health care system and health-related services. Dealing with multiple systems, each of which has its own requirements and regulations, can be daunting. The PCP often knows about other resources in the community that can be helpful.

Coordination of care includes 2 major aspects: coordination within the parts of the health care system and coordination with other community agencies and

resources in the educational, recreational, and human services sectors. Family coalitions that range from disease-specific organizations to more general groups of parents of children with ongoing conditions, such as Family Voices ([www.familyvoices.org](http://www.familyvoices.org)) or the Federation of Children with Special Health Care Needs ([www.fcsn.org](http://www.fcsn.org)), may provide critical advice and networking. Other families in the practice who have struggled with finding resources may be willing to partner with parents of a child with the same or another condition. These arrangements vary from informal networking to formal parent-to-parent programs. In some instances, opportunities for care coordination can be found through private agencies, insurance companies, or Title V programs. However, for these care coordination efforts to be successful they must be family-centered. Familiarity with these programs and resources can be extremely helpful.

### Family-Centered Care

Family-centered care is based on *mutual beneficial partnerships between families and health care providers*, a philosophy first articulated by Shelton, Jeppson, and Johnson. It recognizes each family's strengths, regardless of the family's circumstances, and how these strengths can add positively to the family's health care experiences. The principles of family-centered care are listed in Box 51-2.

### Periodic Reassessment

At each stage in the care of a child with an ongoing condition, it is important to ensure that the family (including all the primary caregivers, whenever possible, and the older patient) and the PCP agree on the priorities and on the plan. Many programs use a written plan that outlines the next phase of care and builds on the mutual priorities. Although this step may be time consuming initially, it saves time in the long run. An agreed-upon plan may encourage adherence to therapy better than presumptive decisions that are made quickly and unilaterally. It is also important to remember that things change over time and that the plan will need to be revised as the goals and priorities for care evolve.

Children with ongoing conditions and their family members often experience more stress and difficulty in adjusting to the demands of their lives than other families. As a result, families with children with ongoing conditions are more likely than others in a physician's practice to need assistance from mental health services. It can be helpful for parents to understand that most families of children with ongoing conditions face extra stresses and may feel isolated. Knowing that they are not alone in their feelings can relieve some of that stress. Additionally, providing an opportunity for parents to talk about their challenges and find respite when needed may help prevent serious mental health concerns.

### THE ROLE OF HOME HEALTH CARE

Medical advances in treatments and technologies permit children with complex medical conditions to be cared for at home, where their social and developmental needs are better met. Children who benefit

**BOX 51-2 Principles of Family-Centered Care**

- Respecting child and family regardless of the family's social circumstances.
- Identifying and building on family strengths and identifying areas in which a given family may need support, taking into account their goals, priorities, and values.
- Exploring choices. In this era of cost cutting by insurers (private or public), the dialogue between the family and the health care team becomes even more important when parents decide that the best place for their child is at home.
- Coordinating care. The availability of a case manager to work with the family varies by payer and specific health insurance policy. The primary care physician is the most important link between the family and the case manager. Good communication among all health care providers is crucial to ensure that unnecessary barriers are not added to the care of the child at home.
- Providing flexible service. Home health care providers and agencies need to be aware and willing to accommodate the potential problems of interrupting normal family routines, loss of privacy, and the family's perceived loss of control of their daily lives.
- Communicating. Families need to be informed so they can collaborate and plan their child's care. Home health care providers need to recognize the importance of this relationship-based care and that sharing information is an essential part of it. This process includes documentation that takes into account the principles of family-centered care and the family's literacy level and language. This documentation will enhance the child's care by facilitating handoff procedures and overall communication among all the involved care providers, thus contributing to improved continuity of care.
- Providing ongoing emotional and practical support for families. This support is needed to help the family come to terms with the responsibility they have acquired, which may grow beyond the skills that they successfully learned when the child arrived at home, and to ensure that the child's developmental and educational needs are completely met.
- Providing family-to-family support. To prevent a family from feeling isolated and alone, opportunities for families to network with others whose child is at home under similar circumstances must be facilitated. This model can also serve as a source of potential respite.
- Providing respite care, which is needed to prevent burnout and child neglect.

Source: Johnson BH, Schluter J. Family-centered care. In: McConnell MS, Imaizumi SO, eds. *Guidelines for Pediatric Home Health Care*. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2002; Ahmann E. *Home for the High Risk Infant: A Family Centered Approach*. Gaithersburg, MD: Aspen Publishers; 1996.

from home health care vary widely in their need for assistive technology, and the intensity and duration of the health care needs. Variability in illness trajectory and the inability to identify a definitive prognosis present additional challenges. In addition to the increasing complexity in child illness, parents find themselves increasingly in the role of care providers in the home and community. To care for their child at home, parents must develop specialized skills and knowledge to manage the child's condition and the technology on which their child depends. High-acuity care in the home may include tracheostomy care, long-term ventilation, enteral and parenteral feeding, and the use of intravenous drugs (the latter via central lines). Thus the child's care requirements can significantly affect daily family functioning, leaving parents and caregivers physically and emotionally exhausted and isolated, with little personal time and limited financial resources.

The rapid growth of pediatric home health services since the 1980s has been attributed not only to increased survival of children with complex medical conditions, but also to pressures from payers to decrease lengths of stay and reduce the high costs associated with care. Current home health services include a wide array of services, from a single home visit for family support to the ongoing care of the ventilator-dependent child.

The exact number of children receiving home health care services is unknown, because they are a widely

diverse group, although dependence on technology is a common situation among patients discharged from a children's hospital. Despite this, home health care services are planned for only a small percentage of cases. A lack of consistency in discharge planning and few evidence-based clinical guidelines for children needing home health care services are further challenges. The groups of children who often receive in-home care services are children with cerebral palsy, technology dependent children (ie, home ventilator), and children with multiple chronic conditions.

Family-centered care should be the hallmark of care for children with ongoing conditions, but it is especially critical for children needing home care. These principles offer an opportunity for families and home health care providers to negotiate their respective roles and responsibilities. This fosters open communication and respect, thus decreasing the stress generated by the loss of privacy for the families and the lack of direct professional and supervisory guidance for the home health care providers, which is always available in an inpatient setting. The plan of care should take into consideration an open, honest dialogue with the parents so that they can truly understand the issues that they will encounter once the child is home, including arrangements for respite care and ways to incorporate the child's care into the family's activities with minimal interruptions. Transition planning for the discontinuation of home services needs to be an ongoing process as the child's condition progresses

and medical needs evolve. This termination of home health care services typically occurs because of insurer coverage limits or when such services are no longer clinically necessary. However, in some cases, the child's needs never lessen to the extent that home care can be discontinued. Issues relevant to the delivery of home health services are reviewed in the following sections, but specific clinical guidelines relevant to a particular disease process or condition are outside the scope of this chapter.

### Who Are Pediatric Home Health Care Providers?

Pediatric home health care providers encompass a wide range of licensed professionals whose skills and expertise support the child's health and developmental care needs and the needs of the family. Among these professionals are nurses, physical and occupational therapists, speech-language pathologists, social workers, child life specialists, and physicians. Nursing care may be provided by registered or licensed practical nurses. They may serve as direct care providers in the home and also participate in care coordination for the child and family.

Home-based physical therapy is indicated for homebound patients with rehabilitative or habilitative therapy needs or for children who qualify for early intervention. The physiatry team (which may include physical, occupational, or speech therapists) is responsible for developing short- and long-term goals, for periodically assessing the child, and for providing the family with an individualized home therapy program. The goals of the program need to be reviewed regularly with the health care team and the family. Speech therapy is indicated for children with speech and hearing impairment, who have undergone tracheostomy, or who have feeding issues. Feeding therapy can also be provided by occupational therapists with specialized knowledge and skills in facilitating feeding and swallowing using guidelines for occupational therapy practice. Medical social workers can help the parents navigate through fragmented and complicated health care and educational systems and can also connect the parents with community resources. The medical social worker should communicate regularly with the PCP. Unfortunately, many payers do not reimburse families for medical social work services.

The PCP monitors the quality of care provided in the home, coordinates the child's medical care, and makes referrals to subspecialists and early intervention programs, in addition to being responsible for the development of an individualized health care plan. Conversations with the family and the medical professionals involved in planning and providing the child's care should encompass both health and developmental care needs. The PCP should communicate the child's health care and developmental needs to local early intervention (under IDEA), and both the child's regular and special education programs (504 plans) as part of providing high-quality health care.

Subspecialist physicians involved in the child's care should also be active members of the child's home health care team, as needed. The many professionals

involved in the provision of home health care highlight the critical importance of collaboration among the family and the providers, and the need for strong interprofessional coordination. Clear delineation of the medical professional responsible for each specific aspect of a child's home health care treatment plan (eg, changes in the child's feeding tolerance or respiratory status) is necessary to avoid confusion and to ensure that issues can be addressed appropriately and in a timely fashion.

### Family-Directed Home Health Care

An alternative for parents of some of these children is family-directed home health care. Instead of a nurse being the child's primary caregiver at home, the family takes on this responsibility after proper medical training. The child's PCP, specialists, family, and local support services work together as a team to keep the child at home. Churches, schools, and social service agencies often help out by providing trained caregivers. Family-directed home health care can provide a child with a chronic condition with the benefit of a loving home environment. However, crucial to its success is consistent, ongoing communication between doctors and parents.

Several factors contribute to the growing importance of family-directed health care. In an attempt to control costs, payers frequently reduce or limit benefits. This is further compounded by a shortage of nurses and other personnel trained to work with children in a community- or hospital-based home health care program. As many state Medicaid programs are engaging in health system redesign to reduce health care expenditures, families are being offered a choice between family-directed services and traditional home health care service delivery. As an example, family-directed services for a child with developmental disabilities in Idaho allows families to use their child's individualized Medicaid budget (based on the child's strengths and assessed needs) to purchase and direct the services and supports the child receives ([www.familydirected.dhw.idaho.gov](http://www.familydirected.dhw.idaho.gov)).

In the family-directed model of home health care, the parent or other primary caregiver assumes responsibility for selecting and determining the roles of professional health care and support providers. For family-directed home health to succeed, a detailed home health care plan must be developed, with the parents, physicians, health care team, and home health care providers all working together. This type of home health care must provide some ancillary services and ongoing maintenance, just as in nurse-directed home health care programs. In this model, one of the essential roles of the PCP is to address the caregiver's needs and abilities. The physician must work with the family to ensure that the home health care plan is being followed and the established goals and resource needs are being met. A definitive respite care plan should be determined before a crisis or emergency arises. These arrangements can include other family members, community-based respite care, personal care attendants, and out-of-home medical day care. In some instances, and as a last resort, the child may have to be rehospitalized. The latter should occur only when the

family can no longer safely care for the child. For this model to succeed, a true parent-payer-pediatrician relationship should be developed, with the identification of a willing PCP being a crucial first step. Other issues that need to be addressed include defining roles and responsibilities, creating an ongoing communication plan, evaluating available community resources, identifying educational resources, and obtaining reimbursements by payers.

### **Paying for Pediatric Home Health Care**

#### **Public Funding**

Children and youth with special health care needs require health care coverage that is universal, continuous, adequate, and affordable. However, there are major gaps in the current system of health care coverage and financing that cause significant problems in accessing care for CYSHCN and financial hardship for their families. According to the National Survey of Children with Special Health Care Needs, over one-third of insured families report that their child's coverage is inadequate to pay for the services they need, and 18% say their child's health condition has caused their family financial problems.

Private insurance varies greatly in type and amount of coverage. For children who need long-term care, insurance benefits are quickly exhausted, and parents must seek other resources. One such resource is Medicaid. Eligibility for Medicaid is determined by each state and is based on family income levels. Physicians need to familiarize themselves with the eligibility criteria of the state in which they practice. In 1981, certain Medicaid eligibility requirements were waived so that every technologically dependent child could be cared for at home. This became known as the *Katie Beckett Waiver*. Physicians should also be familiar with their local and state waiver programs.

#### **Supplemental Security Income**

Supplemental security income is a cash benefit for people with disabilities and is administered by the Social Security Administration. Determination of eligibility takes into consideration finances of the family of a child younger than 18 years and disability criteria related to the child's condition. For a child, the criteria are based on the child's ability to engage in age-appropriate activities. Supplemental security income is another way of becoming eligible for Medicaid, depending on the family's circumstances and income.

#### **Early and Periodic Screening, Diagnosis, and Treatment**

The EPSDT program is a mandated Medicaid service limited to individuals younger than 21, and it ensures comprehensive pediatric health services, with an emphasis on prevention. It requires that all diagnostic and treatment services be available to an EPSDT recipient, which means that under this program, even specific services not included under a state's Medicaid plan must be made available to an EPSDT recipient.

Under the Affordable Care Act (ACA), enacted in 2010, states are encouraged or required to adjust benefits in numerous ways. Significantly, early periodic

screening, diagnosis, and treatment (EPSDT) became available to more children in 20 states beginning in 2014, because Medicaid eligibility for children ages 6 to 21 increased in those states to 250% of the federal poverty level, shifting children from Children's Health Insurance Program (CHIP) to Medicaid. Two states, Arkansas and Iowa, received waivers allowing them to enroll 19- and 20-year-olds into adult programs, although EPSDT requirements must be fulfilled. The remaining states already covered these older children under Medicaid. Depending on the benefits covered by their state's CHIP program, these children may also become newly eligible for assistance with nonemergency transportation for medical appointments. Another important service change under the ACA is that families of terminally ill children enrolled in Medicaid or CHIP may elect to receive hospice care without having to forgo potentially curative care.

Medicaid benefits are described in each state's plan, which must be approved by the Centers for Medicare and Medicaid Services. Home health care is among the mandatory services covered by Medicaid. However, private-duty nursing is an optional service that is not mandated, and its availability may vary from state to state.

#### **Medicaid Managed Care Organizations**

Managed care organizations receive contracts from Medicaid. To obtain these contracts, organizations must demonstrate an adequate network of health care providers and offer a vast array of services. This system is based on providing primary care for the beneficiaries. The child's PCP coordinates the necessary care and makes all the needed referrals, including referral for home health care services. While these organizations may have incentives to restrict services, it should be noted that fee-for-service reimbursement systems have incentives to increase services. Neither system is perfect for children with ongoing conditions. An important new concern with the insurance exchanges created under the Affordable Care Act is that some plans may not have adequate levels of specialized care providers in network to provide for children with rare conditions, and therefore families may need to obtain services at high out-of-pocket cost outside of their networks.

This system has built-in disincentives and barriers, and the requirements vary from state to state. Patients may be moved automatically from one plan to another without being aware of it, necessitating a change in PCPs. This movement among plans may interrupt the continuity of care for these patients.

#### **Medical Day Treatment Programs**

Parents of children who have complex medical needs face a myriad of challenges. They must provide direct, around-the-clock care and coordinate multiple therapies and medical appointments while managing their other family, personal, and work-related responsibilities. Demands on families such as administering medications and therapies, maintaining equipment, and providing transportation to appointments may require that parents cut down their work hours or give up a job. As reported in the 2009–2010 National



Survey of Children With Special Health Care Needs Chartbook, families of 37.2% of children with special health care needs devote 1 to 4 hours per week providing and coordinating care for their children. Thirteen percent of families spend 11 hours a week or more managing these tasks. Medical day treatment programs offer many clinical and personal advantages for these families.

As more children with medically complex health conditions and varied technology support needs survive to school-age and young adulthood, interdisciplinary programs are evolving and adapting into hybrid settings that provide educational placement alternatives for children whose needs are too complicated to allow them to attend regular school. Children are able to continue to meet school expectations in an environment that provides the required medical and emotional interventions. Comprehensive programs integrate disease management and self-care in conjunction with therapeutic activities in an outpatient setting that provides the intensity of inpatient medical care. This approach provides children and their families an increased sense of independence, confidence, and control over the illness. High-quality, cost-effective pediatric medical day treatment can facilitate faster rehabilitation, reduce rehospitalizations, reduce homebound isolation, and supply a cost-effective alternative to traditional home health care.

As in all home health care programs, a written individual health plan needs to be developed, and the communication between all members of the health care team is an essential ingredient.

## EMERGENCY AND DISASTER PREPAREDNESS

Electrotechnology-dependent children and young adults comprise a unique, extremely high-risk group during an emergency or disaster. These children and youth may be technology dependent for life support or maintenance of activities of daily living. The inability to use required devices because of an electrical failure and lack of back-up generator power could jeopardize a patient's life. Electrical devices can fail for a variety of reasons aside from those associated with a natural or man-made disaster. Studies have demonstrated the unrealistic expectations of families in responding to such an event, as well as the benefits of a parent-focused preparedness intervention. It is important for physicians to recognize that electricity is often taken for granted, so families should be drilled in how to prepare for and respond to a power failure.

## TRANSITION TO ADULT CARE

Transition from pediatric to adult-centered health care should be carefully planned. In youth with a chronic condition this planning is complicated and time consuming; fortunately, there are guidelines and algorithms available to assist the PCP (Figure 51-1) (see Chapter 66, Transitions to Adulthood).

### Definition

The goal of transition is “to maximize lifelong functioning and potential through the provision of high

quality, developmentally appropriate health care services that continue uninterrupted as an individual moves from adolescence to adulthood.” The process of transition also encompasses the consideration of future education/training, vocation, housing, medical insurance, and legal planning. Although nonmedical issues may seem beyond the realm of the PCP, families and the patient often value the PCP's advice, especially when these issues are not being addressed elsewhere.

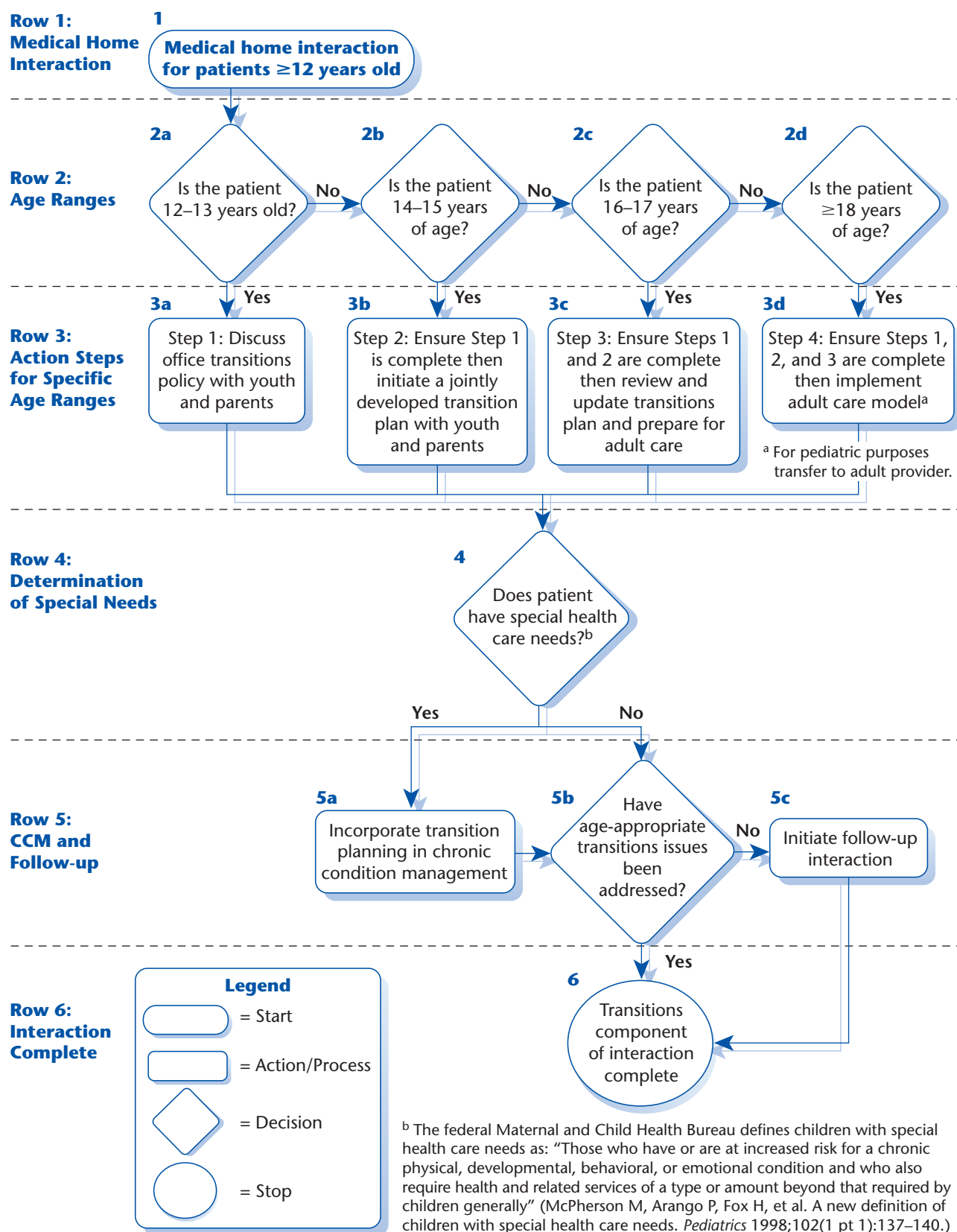
## The Scope and Complexity of Transition

Ninety percent of youth with chronic conditions survive into their adult years, making the transition to the adult medical world a reality for most. This process requires thoughtful, coordinated planning among the PCP, the family, and the youth. Finding a physician and maintaining medical insurance are 2 major hurdles youth with chronic conditions face. Adjustment to the differences between the pediatric and adult models of care is often difficult, but is easier if the adolescent is able to begin taking a more active part in care prior to the formal transition. Dependency, cognitive impairment, psychosocial immaturity, and conditions that affect mental health may present additional challenges.

Youth with chronic conditions are at risk for dependency on their families because of their ongoing medical needs and the tendency for families to overprotect them. Some have intellectual delays or lower cognitive levels inherent to their conditions or experience learning problems because of lost school time during prolonged or frequent hospitalizations. Medical treatments and severe complications of a disease may additionally lower cognitive levels compared to typical teens. Complications or treatment of youth with sickle cell disease, youth who are liver transplant recipients, youth who have had cardiac and kidney transplants, and survivors of childhood cancer are examples of conditions associated with lower IQs. Delays in psychological and social development may also be present, because of frequent hospitalizations and functional limitations that have prevented extracurricular, social, and work-related experiences. Associated mental health issues secondary to having a chronic condition can include problems with attention, anxiety, and depression. This has been described in youth with seizure disorders, sickle cell disease, and recipients of cardiac transplants.

## Management of the Transition Process

Ideally, a transition should start with the PCP who knows the patient's history well and will oversee the process, coordinating with the subspecialty medical providers and assisting the patient and family. Transition planning should start much earlier than the transfer process (when the patient actually moves to adult care). Current recommendations suggest starting the planning at age 12 or 13 and involving the teen in his or her own care more actively over time. Reasons for starting early include encouraging development of maximal independence during the ensuing years, involving the youth before the social pulls of middle adolescence, and recognizing that transition planning takes many years.



**Figure 51-1** Health care transition-planning algorithm for all youth and young adults within a medical home interaction. (From American Academy of Pediatrics, American Academy of Family Physicians, and American College of Physicians, Transitions Clinical Report Authoring Group. Supporting the health care transition from adolescence to adulthood in the medical home. *Pediatrics*. 2011;128(1):182–200.)

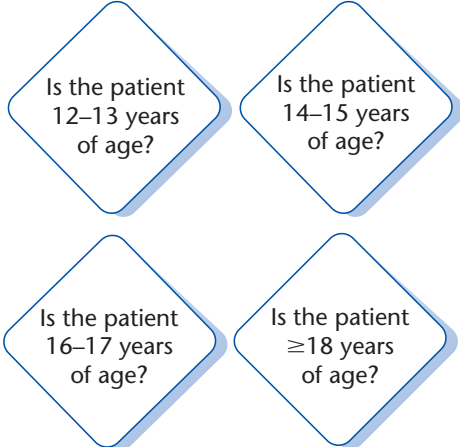
ALGORITHM COMPONENT	DESCRIPTIVE TEXT
<b>Medical home interaction for patients <math>\geq 12</math> years old</b>	<b>1.</b> Initiate first step in the health care transition planning process at age 12.
	<b>2a, 2b, 2c, 2d. Age Ranges.</b> By age 12, conduct surveillance to assess any special health care needs. Start actual transition planning by age 14. By ages 16–17, transition planning should be well established. At age 18, initiate an adult model of care for most youth, even if there is no transfer of care. If transition planning does not occur on the schedule described by the algorithm, a concentrated effort is required (eg, special visits) to successfully complete the process.
<b>Step 1:</b> Discuss office transitions policy with youth and parents	<b>3a.</b> Every practice should have a written transition policy that is prominently displayed and discussed with youth and families. The policy should explicitly state the practice's expectations and care process for the health care transition of their adolescent patients to an adult model of care.
<b>Step 2:</b> Ensure Step 1 is complete then initiate a jointly developed transition plan with youth and parents	<b>3b.</b> The practice should use a standard transition plan that can be adapted for each patient's needs. This tool should include components to obtain an accurate assessment of the patient's ability to successfully transition. Providers should interview youth and family members to identify needs and to assess the intentions and motivations for youth independence.
<b>Step 3:</b> Ensure Steps 1 and 2 are complete then review and update transitions plan and prepare for adult care	<b>3c.</b> Transitions plans must be reviewed regularly and updated as necessary. The provider must also perform surveillance for changes in the youth's medical status and address youth and family concerns that may warrant changes in transition goals. Failure to achieve transition readiness goals warrants reevaluation of the existing plan, and increased frequency of medical home interventions/visits. A "pretransfer" visit to the adult medical home could be conducted during the year before the transfer.
<b>Step 4:</b> Ensure Steps 1, 2, and 3 are complete then implement adult care model <sup>a</sup>	<b>3d.</b> Transition to an adult model of care occurs appropriate for youth's developmental level. This is followed as appropriate by transfer to an adult medical home. Complete medical records should be delivered to the adult provider, along with a portable summary, which is also provided to the patient or guardian. For children and youth with special health care needs, direct communication between pediatric and adult providers is essential, as adult medical personnel may be unfamiliar with certain pediatric conditions.

Figure 51-1, Cont'd

Continued


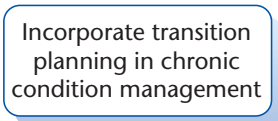

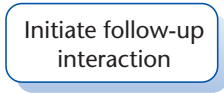
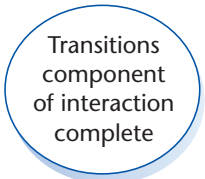
ALGORITHM COMPONENT	DESCRIPTIVE TEXT
 <p>Does patient have special health care needs?<sup>b</sup></p>	<p><b>4.</b> Transition planning for children and youth with special health care needs should include specific chronic condition management (CCM) activities such as: use of registries; care plans; care coordination; CCM office visits; and comanagement with medical subspecialists. Transition goals must be individualized to account for variations in the complexity of a youth's condition and in the youth's intellectual ability and guardianship status.</p>
 <p>Incorporate transition planning in chronic condition management</p>	<p><b>5a.</b> Youth with special health care needs require an expanded transition planning process. Transition planning in CCM includes addressing the exchange of complex health information; competencies for self-care; transfers of specialty care; and issues related to insurance entitlements, guardianship, and eligibility for adult services. In a medical home, such youth may have a written care plan as part of the medical record. At age 14, this plan should include a section titled "transition plan," which should be expanded and developed as the youth approaches age 18 and beyond.</p>
 <p>Have age-appropriate transitions issues been addressed?</p>	<p><b>5b.</b> Use of transition planning tools and readiness checklists facilitate the provider's ability to ensure that all age-appropriate transition issues have been addressed. Each action step must be completed in order, even if it means the provider has to schedule specific visits to initiate and complete steps missed earlier in the process in order to catch up before the next visit.</p>
 <p>Initiate follow-up interaction</p>	<p><b>5c.</b> Focused tasks involving little detail or complexity can be addressed by the medical home care coordinator, medical provider, or other appropriate staff through telephone or electronic media. More complex issues may necessitate face-to-face office visits.</p>
 <p>Transitions component of interaction complete</p>	<p><b>6.</b> The provider is finished with the transition tasks for that specific interaction or visit; transition planning is an ongoing activity that occurs at every interaction.</p>

Figure 51-1, Cont'd

A transition policy should be established at each practice site to provide a uniform understanding for medical providers and families. It should include the expected age of patient transfer and the responsibilities of the patient, caregivers, and medical providers before transfer. This policy should be available to patients and families to review and can be posted or provided in the form of a brochure. Examples are available at [www.gottransition.org](http://www.gottransition.org).

Assessing a patient's readiness skills and core knowledge of medical problems allows the PCP to plan steps that maximize independence and facilitate the ultimate transfer. The process should be

individualized to the patient's intellectual level and overall functioning. Various examples of readiness checklists are available. Most assess the patient's knowledge of the chronic medical condition and of medications; current level of independence in daily living activities; and individual skills, strengths, and weaknesses.

A portable medical summary and an emergency information form are helpful transition tools. An emergency information form should be filled out soon after the initial diagnosis of a chronic condition and updated regularly. It should be readily accessible in the event that a youth needs to be taken to an emergency room.



It allows efficient communication of information to providers who are not familiar with the details of a patient's chronic condition. A medical summary that can be updated regularly is an additional source of information and can be expanded into a medical transfer summary at the time of transfer to adult care. A variety of templates are available for the medical summary, and the American Academy of Pediatrics has a downloadable emergency information form at [www.aap.org/advocacy/blankform.pdf](http://www.aap.org/advocacy/blankform.pdf). Both the emergency form and medical summary should be updated in collaboration with the subspecialists who provide ongoing care, depending on the youth's condition, and can be kept on a flash drive or computer. Including these forms in the electronic medical record and updating them regularly can provide accurate communication between providers during the transition process and during transfer.

A transition plan, similar to a care plan, should discuss who provides, and who pays for, ongoing care, including education, transportation, and upkeep of equipment, if applicable. Ongoing routine medical care up until the actual transfer is also essential for the health and well-being of youth with chronic conditions and should include ensuring that immunizations are up to date and monitoring nutritional needs, exercise, sexual activity, mental health, and the use of illegal drugs, alcohol, and cigarettes. There is a tendency to avoid these routine adolescent topics in the care of patient with chronic conditions, in particular in patients with intellectual disabilities and those who are physically challenged. Youth with chronic conditions attempt to "normalize" their adolescent experience as much as possible. By ignoring inquiry about sexual activity, drugs, cigarettes, alcohol, and mental health issues (eg, suicidal ideation, depression, anger, and anxiety) the PCP will miss opportunities to provide safety advice and appropriate adolescent counseling. In many states, minors are able to provide consent for treatment for mental health problems, substance use, contraception, and sexually transmitted infections and can be seen without a parent or guardian for these issues.

Appropriate medical insurance is imperative to ongoing medical care. With current insurance regulations, youth who have medical insurance under their parents' insurance plan are able to continue until 26 years old. Many youth with chronic conditions receive Supplemental Security Income (SSI), which provides Medicaid in most states. SSI rules change dramatically when a youth turns 18 years old and may affect ongoing coverage. Before age 18, youth qualify by their physical or medical impairments and a financial assessment based on the resources of the patient's parents/guardians. At 18, qualification is determined by the youth's ability to work and by the patient's own financial resources, rather than his or her parents or guardians. One-third of youth who receive SSI lose their coverage at age 18 years, based on either disability or financial criteria. Alternately, some youth who previously were financially ineligible because of their parent's income become eligible for SSI at 18 because of the adult financial criteria applies only to their own income.

Youth with chronic conditions who qualify for special education services should have an Individualized Educational Plan (IEP). These youth will age out of special education at 21 years. Beginning at age 16 or younger, the youth should be included at a yearly IEP meeting, and a transition plan individualized to that youth's abilities should be established. Included in the transition plan should be a plan for future education, vocation or training programs, and housing. A transition linkage coordinator from the school should attend these meetings to facilitate planning (IDEA regulations guarantee transition planning, but how it is implemented may vary state to state). Making a family aware of this aspect of the school process and reviewing the plan provides the PCP with insight about the youth's level of functioning and ability to participate in the planning process. Many colleges across the United States have special programs for the inclusion of intellectually disabled youth and have offices to assist youth with learning disabilities.

Legal advice is well beyond the PCP's capability; however, it is important to understand the terminology and the importance of decision making for those youth with chronic conditions. Under HIPAA, a child's medical information is protected and thus not available to parents once that person turns 18 years. It is therefore extremely important to discuss in advance and legally determine who will be available to participate in the young adult's care after the 18th birthday. This is especially important for those individuals whose capacity (cognitive or emotional) is intermittently or continuously impaired or who have conditions that are particularly likely to cause them to be temporarily impaired and unable to make decisions for themselves. Legal documents must be prepared to deal with these issues before the actual birthday in order to clarify who can act on behalf of the youth. While it is usually clear that arrangements are necessary for someone who cannot live independently, situations in which health issues are more episodic and the level of impairment is intermittent can be more complicated. Issues such as who will take on the responsibility for the disabled youth are best decided in advance, especially as their parents are also aging. There are various degrees of legal supervision that a parent can obtain, with guardianship being the most restrictive. A less restrictive set of supports often can be put in place. Divided decision making between the youth and his or her parent(s) can be specific to health decisions or financial decisions, or tailored to that youth's needs. Examples include: conservatorship, a health surrogate, health guardianship, or powers of attorney (health and financial). In addition most hospitals expect adults (those over 18 years old) to have advanced directives. It is important to discuss advance care planning with youth who are capable of participating in such discussions. Because each state and county has different rulings related to these legal decisions, a legal consultation is important to guide a family properly.

The transition of youth with chronic conditions generally has not been a well-organized process. Unnecessary hospitalizations, medical procedures, and visits to the emergency department result from lack of coordinated transition to adult care providers.

**BOX 51-3 Transition Resources**

- Center for Health Care Transition Improvement (Got Transition): Tools for the pediatrician including templates for transition policy, transition plan, readiness assessment, medical summary, emergency plan, transfer letter ([www.gottransition.org](http://www.gottransition.org)).
- Hospital for Sick Kids Transition Tools: Resources for patients and families ([www.sickkids.ca/good2go/for-youth-and-families/transition-tools](http://www.sickkids.ca/good2go/for-youth-and-families/transition-tools))
- National Center of Medical Home Initiatives for Children with Special Needs: AAP clinical report on supporting transition, video resources, and more ([www.medicalhomeinfo.org/how/care\\_delivery/transitions.aspx](http://www.medicalhomeinfo.org/how/care_delivery/transitions.aspx)).
- Family Voices: Information on family health information centers ([www.familyvoices.org/page?id=0034](http://www.familyvoices.org/page?id=0034))
- The Parent Advocacy Coalition for Educational Rights (PACER): A parent training and information center for families of children and youth with all disabilities from birth through 21 years old. Parents can find publications, workshops, and other resources about a number of topics including sexuality and disabilities ([www.pacer.org](http://www.pacer.org)).
- Catalyst Center: A national center dedicated to improving health care coverage and financing for children and youth with special health care needs. ([www.hdwg.org/catalyst](http://www.hdwg.org/catalyst))
- The Affordable Care Act: A Working Guide for MCH Professionals ("ACA 101") ([www.hdwg.org/catalyst/publications/ACA-101-for-Title-V](http://www.hdwg.org/catalyst/publications/ACA-101-for-Title-V))

Fortunately, beginning early and referring to pre-existing guidelines and other tools (see Box 51-3) can smooth the transitions, provide better medical care, and help ensure long-term functioning for youth with chronic conditions. The ultimate goal is to have young adults who are as independent as possible and are able advocates for their medical care.

**CONCLUSION**

Pediatric home health care has been the fastest-growing expenditure of health care in the United States, motivated by the increased survival of fragile infants and children and by managed care pressures. Despite this trend, research and studies about pediatric home health care from the PCP's perspective have lagged. More outcome studies are needed not only to develop evidence-based clinical guidelines, but also to learn how to address family issues such as barriers, access, stress levels, psychological problems, financial consequences, job absenteeism, and family satisfaction.

**TOOLS FOR PRACTICE****Community Advocacy and Coordination**

- *Building the Legacy: IDEA 2004* (Web page), US Department of Education ([idea.ed.gov](http://idea.ed.gov))
- *Caring for Our Children: National Health and Safety Performance Standards for Out-of-Home Child Care* (book), American Public Health Association and American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

**Engaging Patient and Family**

- *Building Your Care Notebook* (Web page), National Center for Medical Home Implementation ([www.medicalhomeinfo.org/for\\_families/care\\_notebook](http://www.medicalhomeinfo.org/for_families/care_notebook))
- *Developing Your Child's IEP* (Web page), National Dissemination Center for Children With Disabilities ([www.parentcenterhub.org/repository/pa12](http://www.parentcenterhub.org/repository/pa12))
- *Emergency Information Form for Children With Special Needs* (template), American Academy of Pediatrics ([www.aap.org/advocacy/blankform.pdf](http://www.aap.org/advocacy/blankform.pdf))
- *Frequently Asked Questions About Section 504 and the Education of Children With Disabilities* (fact sheet), US Department of Education ([www.ed.gov/about/offices/list/ocr/504faq.html](http://www.ed.gov/about/offices/list/ocr/504faq.html))
- *Hospital Stay Tracking Forms* (file archive), National Center for Medical Home Implementation ([medicalhomeinfo.aap.org/tools-resources/Documents/Hospital%20Stay%20Tracking%20Forms.zip](http://medicalhomeinfo.aap.org/tools-resources/Documents/Hospital%20Stay%20Tracking%20Forms.zip))
- *Pediatric Care Plan* (form), American Academy of Pediatrics ([medicalhomes.aap.org/Documents/PediatricCarePlan.pdf](http://medicalhomes.aap.org/Documents/PediatricCarePlan.pdf))
- *Pediatric Specialists* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/default.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/default.aspx))

**Practice Management and Care Coordination**

- *Family-Centered Care Self-Assessment Tool* (booklet), Family Voices ([www.familyvoices.org/admin/work\\_family\\_centered/files/fcca\\_FamilyTool.pdf](http://www.familyvoices.org/admin/work_family_centered/files/fcca_FamilyTool.pdf))
- *Measuring Medical Homes: Tools to Evaluate the Pediatric Patient- and Family-Centered Medical Home* (monograph), National Center for Medical Home Implementation ([medicalhomeinfo.aap.org/tools-resources/Documents/Monograph\\_FINAL\\_Sept2010.pdf](http://medicalhomeinfo.aap.org/tools-resources/Documents/Monograph_FINAL_Sept2010.pdf))
- *Patient- and Family-Centered Ambulatory Care: A Checklist* (form), Institute for Patient- and Family-Centered Care ([www.ipfcc.org/advance/topics/Ambulatory-Care-Key-Concepts.pdf](http://www.ipfcc.org/advance/topics/Ambulatory-Care-Key-Concepts.pdf))

**AAP POLICY**

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health care need. This likelihood may be related to the higher proportion of boys who are diagnosed with Attention Deficit Hyperactivity Disorder and other behavioral disorders. Although children with special health care needs have the same basic educational and developmental needs as their healthy peers, many have a range of problems that may interfere with their academic performance or require special medical services in school. Collaborative efforts among school personnel, health professionals, and families enhance the health, education, and development of these children and should be the basis for addressing their needs in school.

In the past, children with special health care needs were often isolated from healthy children in schools or were taught at home; they were thus deprived of crucial social contacts and a broad educational experience. Several laws now ensure that all children have access to education in the least restrictive environment.

Public Law 94-142, the Education for All Children Act of 1975, ensures a free and appropriate public education for preschool (ages 3–5 years) and school-aged children who have disabilities. The law was amended in 1990 by Public Law 101-476 and renamed the Individuals with Disabilities Education Act (IDEA). Under IDEA, children and parents are entitled to therapeutic and related services such as occupational, physical, vision, and hearing therapy; family support; social services; mental health services; educational intervention; and case management services, even if the child is not receiving special education, as long as these services relate to a child's education. Changes made to IDEA with the Individuals with Disabilities Education Improvement Act (IDEIA) of 2004 and subsequent regulations and judicial rulings have altered IDEA. Children may now be identified as having a learning disability by their response to instruction (RTI). Establishing a discrepancy between a child's ability and achievement (ie, "wait to fail") is no longer necessary to initiate psychoeducational evaluation and services. However, when conflict exists regarding what constitutes a *free and appropriate education*, the burden of proof lies with the party bringing suit (usually the parents) rather than the school district.

Section 504 of the Rehabilitation Act of 1973, appended through 1998, requires school districts to eliminate barriers that exclude children with special needs from full participation. These barriers can be either physical (buildings that are not wheelchair accessible) or programmatic (keeping children with hepatitis segregated from other children). Section 504 is, in essence, an antidiscrimination law. The definition of disability is broader under Section 504 than it is under IDEA, but fewer services are provided under 504 plans than under IDEIA. Section 504 gives students access to programs such as adaptive physical education and accommodations such as extra time for test taking. However, federal funding for remediation and school-based services such as physical therapy is only made available if a student is in special education (IDEIA). Another important distinction is that federal funding is not provided to schools under Section 504.

Under both laws, children are required to have a written plan with educational goals. This plan is called

## Chapter 52

# SCHOOL-RELATED ISSUES FOR CHILDREN WITH SPECIAL HEALTH CARE NEEDS

Karen L. Teelin, MD, MEd; Nienke P. Dosa, MD, MPH

Approximately 15% of children in the United States have a chronic physical, developmental, behavioral, or emotional condition that requires health and related services of a type or amount beyond that generally required by other children. At all grade levels, boys are 1.5 times more likely than girls to have a special



an Individual Education Plan (IEP) under IDEA and a 504 Plan under Section 504. When a child turns 16, but ideally by age 14, the IEP must include transition goals. These are appropriate, measurable postsecondary goals related to training, education, employment, and independent living skills, where appropriate. Involvement in formulating these goals is an opportunity for the pediatrician to coordinate a child's educational program with a medical treatment plan and to help families and children review beneficial services to which they are entitled. Transition planning may also include planning for a new medical provider, changes in insurance coverage, and increasing responsibility for self-care (eg, taking medications, scheduling appointments).

An up-to-date overview of relevant public laws is available on the Wright's Law Web site ([www.wrightslaw.com](http://www.wrightslaw.com)).

## SCHOOL ISSUES FOR CHILDREN WITH SPECIAL HEALTH CARE NEEDS

School provides a child with academic skills and multiple experiences critical to emotional and social development. The school-related problems and concerns that all children have can be exacerbated for a child who has special health care needs. The child's chronic condition may require frequent and, occasionally, long absences. Illness and medications may affect cognitive functioning, and physical limitations may restrict participation in school activities. These obstacles, when combined with inappropriate expectations of teachers and parents and altered interactions with peers, can provide formidable impediments to academic achievement, psychosocial development, and vocational placement.

### Medical Issues

The primary school-related goal for the pediatrician who cares for children who have chronic conditions is to ensure a safe environment. Specific issues such as transportation, special equipment, backup, and emergency plans need to be identified. Additional issues such as notification of the parents if the child's health status changes in school, responsibility for monitoring the child's health in school, and the role of the physician need to be addressed. For children who have severe or complex conditions, especially those who require technology-assisted care, a formal process of entry into school should be followed, including early notification of the school and discussion with school administrators of the child's condition and needs. The physician helps develop and approve a formal health care plan, created in collaboration with the family and child, school administration, and other health care personnel. The physician can also make recommendations regarding the program, placement, and staffing, and can participate in the training of school personnel. Excellent guides for the training of school personnel who care for children who have chronic conditions are available (see Tools for Practice at the end of this chapter). Box 52-1 lists the components of an emergency plan; Box 52-2 lists specific guidance for a child who has a chronic condition in school.

### BOX 52-1 Components of an Emergency Plan for a School Child Who Has a Chronic Condition

- Names, addresses, and telephone numbers of family and caretakers
- Emergency telephone numbers:
  - Ambulance
  - Home care company
  - Utility companies
  - Hospital
  - Emergency department
  - Primary care physician
  - Specialists
- Child-specific emergency plan
- Other school personnel to contact

### BOX 52-2 Components of Child-Specific Guidance For Care Providers

- Important personnel, including specialists and primary care provider
- Background information:
  - Conditions
  - Medical history
  - Special health care needs
  - Baseline status
  - Medications
  - Diet
  - Technological aids
  - Transportation needs
- Procedures required
- Equipment
- Child-specific techniques
- Special considerations and precautions (eg, latex allergy)
- List of possible problems for observation, reason, action
- Daily log

### School Achievement

Approximately 10% to 15% of school-aged children repeat or fail a grade in school. Children with special health care needs are nearly 3 times as likely to repeat at least 1 grade as children who have no disabilities.

The risk of school failure may be present in the earliest school years; children with special needs are significantly more likely than their healthy peers to repeat kindergarten or first grade. The pediatrician can help prevent school failure by promoting school readiness at health supervision visits, advocating for psychoeducational support, and identifying health behaviors or psychosocial factors that negatively affect school performance. Developmental concerns should be



addressed at each preventive health visit during at least the first 5 years of life. Developmental surveillance includes eliciting parents' concerns, documenting a developmental history, accurate observations of the child, and identifying risks and protective factors (eg, low birth weight or demographics). If this surveillance indicates risk, developmental screening should be conducted. In addition, screening should be conducted at all 9-, 18-, and 30-month preventive visits, using a validated, standardized tool (eg, the Parents' Evaluation of Status, or PEDS). The screening may indicate areas in which further evaluation is needed, and if so, a developmental evaluation may be indicated. Pediatricians can also promote school readiness by promoting the 5 Rs of early childhood education: reading together as a family, rhyming, routines, rewards (praise), and reciprocal and nurturing relationships. If screening tools are positive, physicians may refer appropriately. Referrals may include Early Intervention (for ages 0-3 years) or the local school system for further evaluation. Note that parents may also refer their child.

In some cases, school difficulties are caused by neurocognitive, visual, or auditory impairments. Medical treatment, such as intrathecal chemotherapy and cranial irradiation, and certain medications, such as anticonvulsants, may impair cognitive functioning. Fatigue, caused by medication or underlying conditions, should also be considered. Physicians can help identify the cause of fatigue and may be able to treat the problem by adjusting medication schedules, such as with anticonvulsants, by treating the underlying condition (eg, depression, obstructive sleep apnea), or by suggesting that a rest period be incorporated into the school day.

For most children who have chronic health conditions, however, these concerns are not significant. Many children face academic adversity because of the social and psychological consequences of their condition. "Chains of adversity" can occur when the individual's physical impairments initiate a sequence of disadvantageous outcomes. Diminished expectations, lower self-esteem, fatigue, pain, and preoccupation with symptoms that often accompany chronic conditions can be associated with a decreased self-efficacy that may develop into a learned helplessness resulting in diminished expectations and efforts. This situation may be complicated by altered parental expectations that involve many aspects of the *vulnerable child syndrome* (see Chapter 189, School Absenteeism and School Refusal). Failure to understand these psychosocial complications can lead to expectations that are unreasonably high or detrimentally low. Furthermore, there is evidence now that some behavioral and developmental problems of children with chronic conditions (eg, congenital heart disease, sickle cell disease, renal failure) are rooted in associated neurologic differences.

Children who have special health care needs often have increased school absences, which may lead to significant educational disadvantage (see Chapter 189, School Absenteeism and School Refusal). Homebound teaching often becomes available only when a child misses at least 5 consecutive days of school (varies by

school system), yet most children who have chronic conditions have frequent, intermittent absences. Pediatricians can encourage parents and teachers to help keep children who are disadvantaged by absences from falling behind in school work and can advocate that a child be made eligible for homebound teaching without the usual waiting period. Homebound teaching has significant limitations, including fewer hours of instruction and lack of social contact. School attendance should be encouraged whenever possible. Medical appointments should be scheduled during nonschool hours whenever possible.

### Job Achievement and Independent Living

For most children who have special health care needs, expectations for participation in the work force as adults should be no different from the expectations for their healthy peers. Nonetheless, many children, particularly those with developmental disabilities, fail to participate fully in society once they become young adults. High school graduation rates for students who have disabilities are lower than for those who have no disabilities, and of those who graduate, fewer go on to college. Vocational rehabilitation, a federally funded, state-operated program, is an important funding stream for adolescents with disabilities seeking post-secondary education, adaptive driving skills, or employment. Because most vocational services do not become available until candidates are 18 years old, prevocational skills, including social skills training and independent living planning, should be included in a child's IEP or 504 plan during the high school years.

Schools must provide opportunities for youths to be active participants in pre-employment and employment activities from the earliest stages of the child's academic experience. Unfortunately, many youths with special health care needs enter the workforce later than their nondisabled peers. Participation in peer-appropriate activities at every stage of schooling is essential to successful transition to adulthood. Parental support and adult role models are also important.

### COLLABORATION OF SCHOOL STAFF AND HEALTH PROFESSIONALS

Collaboration among school-based educational and health personnel, community-based providers, and parents is essential in caring for the chronically ill child in school. Only through well-coordinated efforts do educators become aware of the child's medical needs and health care providers become aware of the child's learning needs.

Primary care physicians provide direct medical care and guidance about medical issues and play a vital role as advocates for their patients who have chronic conditions. As the professional who knows the child medically and psychosocially, the pediatrician can encourage academic achievement and socialization and help anticipate major transitions in a child's educational career. Not all medical diagnoses meet eligibility requirements under IDEA for special education services. The determination of eligibility may be made at the discretion of state and local education authorities. Physicians are often asked to provide notes

for home tutoring, and it is usually best to contact the school system before providing these notes. Familiarity with a child's IEP is a prerequisite for effective primary care of the child who has a chronic health condition. One example of the primary care physician's role is physician guidance in the development of an adaptive physical education program for children with special needs. The National Center on Physical Activity and Disability is a clearinghouse for guidelines for physical activity that can be used for planning an adaptive physical education program for a wide variety of pediatric conditions, such as autism and spina bifida.

Teachers and parents need to know the implications of the child's medical condition for school performance. Lack of such information can result in misunderstanding the child's medical condition, which can lead to denial of services, misinterpretation of behaviors, unnecessary restrictions, or unrealistic expectations. With adequate information, teachers and parents can foster not only academic achievement, but also social competence. Teachers can implement recommendations and provide ongoing evaluation of a child's progress. Their input is central to the IEP and invaluable to comprehensive medical management.

The school nurse usually coordinates health services in the school. In most school districts the nurse is responsible for contacting physicians and parents about a child's medical needs. Nurses also often develop and implement care plans and emergency plans in collaboration with the school pediatrician, the primary care pediatrician, or pediatric subspecialists. Federal standards for school nurses set forth in the Healthy People 2020 initiative include a nurse-to-student ratio of 1:750. Many school districts fall short of this goal, and some schools do not have a nurse on site. School nurse practice acts currently define the scope of nursing service on a state-by-state basis. School nurses are increasingly involved with public health measures such as obesity prevention and mental health screening. In addition, the number of school-based health care clinics is growing rapidly, especially in medically underserved areas. Most of these clinics have a multidisciplinary staff (eg, a physician, nurse practitioner, social worker, or health educator); their potential contribution to the care of children with special health care needs should not be overlooked.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *Building the Legacy: IDEA 2004* (Web page), US Department of Education ([idea.ed.gov](http://idea.ed.gov))
- *The Paper Chase: Managing Your Child's Documents* (article), Wrightslaw ([www.wrightslaw.com/info/advo.paperchase.crabtree.htm](http://www.wrightslaw.com/info/advo.paperchase.crabtree.htm))

### Engaging Patient and Family

- *Building Your Care Notebook* (Web page), American Academy of Pediatrics ([medicalhomeinfo.aap.org/tools-resources/Pages/For-Families.aspx](http://medicalhomeinfo.aap.org/tools-resources/Pages/For-Families.aspx))
- *Council of Parent Attorneys and Advocates* (Web page), ([www.copaa.org](http://www.copaa.org))
- *Developing Your Child's IEP* (booklet), National Dissemination Center for Children With Disabilities ([www.parentcenterhub.org/repository/pa12](http://www.parentcenterhub.org/repository/pa12))

- *Emergency Information Form for Children With Special Needs* (form), American Academy of Pediatrics ([www.aap.org/advocacy/blankform.pdf](http://www.aap.org/advocacy/blankform.pdf))
- *Frequently Asked Questions About Section 504 and the Education of Children With Disabilities* (fact sheet), US Department of Education ([www.ed.gov/about/offices/list/ocr/504faq.html](http://www.ed.gov/about/offices/list/ocr/504faq.html))
- *Hospital Stay Tracking Forms* (file archive), National Center for Medical Home Implementation ([medicalhomeinfo.aap.org/tools-resources/Documents/Hospital%20Stay%20Tracking%20Forms.zip](http://medicalhomeinfo.aap.org/tools-resources/Documents/Hospital%20Stay%20Tracking%20Forms.zip))
- *National Disabilities Rights Network* (Web page), ([www.ndrn.org](http://www.ndrn.org))
- *Pediatric Care Plan* (handout), American Academy of Pediatrics ([medicalhomes.aap.org/Documents/PediatricCarePlan.pdf](http://medicalhomes.aap.org/Documents/PediatricCarePlan.pdf))
- *Pediatric Specialists* (Web page) Healthy Children ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/default.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/default.aspx))
- *State Parent Information Center* (Web page), ([www.parentcenterhub.org](http://www.parentcenterhub.org))

### Practice Management and Care Coordination

- *Family-Centered Care Self-Assessment Tool* (questionnaire), Family Voices ([www.familyvoices.org/admin/work\\_family\\_centered/files/fcca\\_FamilyTool.pdf](http://www.familyvoices.org/admin/work_family_centered/files/fcca_FamilyTool.pdf))
- *Measuring Medical Homes: Tools to Evaluate the Pediatric Patient- and Family-Centered Medical Home* (monograph), National Center for Medical Home Implementation ([medicalhomeinfo.aap.org/tools-resources/Documents/Monograph\\_FINAL\\_Sept2010.pdf](http://medicalhomeinfo.aap.org/tools-resources/Documents/Monograph_FINAL_Sept2010.pdf))
- *Patient- and Family-Centered Ambulatory Care: A Checklist* (form), Institute for Family-Centered Care ([www.ipfcc.org/advance/topics/Ambulatory-Care-Key-Concepts.pdf](http://www.ipfcc.org/advance/topics/Ambulatory-Care-Key-Concepts.pdf))

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## Chapter 53

# PHYSIOLOGY AND MANAGEMENT OF FEVER

Henry M. Adam, MD

Viewing fever as both a response to illness and a disease has a long history in Western cultures. Hippocrates perceived fever as a defense mounted by the body against an underlying disorder; the Galenic and medieval traditions understood fever to be a means of restoring balance among the humors by burning off an excess of phlegm (water) with yellow bile (fire). On the other hand, the writers of the Gospels saw fever as

the disease that Jesus “rebuked,” miraculously curing Simon’s mother-in-law.

This *double vision* regarding fever has persisted despite our relatively sophisticated understanding of the physiologic mechanisms of temperature control, blurring how we as physicians and as parents see the child who is febrile. Although our science teaches us that fever, as part of the inflammatory response, is only a sign or symptom of the real pathologic process, we have the need to *treat* fever with a drug and a sponge, as if it were the noxious culprit. Fever, as opposed to hyperthermia, rarely poses a threat to a child’s well-being; in fact, the argument has been made that as an energy-expensive phenomenon, fever is not likely to have weathered evolution without conferring some survival benefit. Considering that fever is the most common signal of illness in children, serving as the chief complaint for as many as one-third of all pediatric office visits, we would do well to clarify our approach to its management, which is distinct from management of the illnesses that cause it.

## FEVER AND THERMOREGULATION

Fever is a regulated elevation of body temperature, mediated by the anterior hypothalamus, that occurs in response to an insult that stimulates the body’s inflammatory defenses. Similar to a thermostat, the hypothalamic set point controls the temperature that the body tries to maintain. Some provocation, most commonly a viral infection in children, induces macrophages to release low-molecular-weight proteins called cytokines, among them interleukin-1 and interleukin-6 and probably tumor necrosis factor, that function as endogenous pyrogens. They circulate to the anterior hypothalamus, where by increasing local levels of prostaglandin E<sub>2</sub>, they induce a rise in the set point. With the body’s thermostat now up-regulated, several mechanisms come into play to bring the core temperature (defined as the temperature of blood within the pulmonary artery) up to the new set point. Because the core temperature, even as it begins to elevate, is lower than the thermostat setting, a person developing fever feels chilled. Physiologically, the body’s response is to generate more internal heat, setting skeletal muscles to shivering and stimulating cellular metabolism while minimizing heat loss to the environment by vasoconstricting the skin and turning off sweat glands. The one phenomenon is analogous to heating up the furnace, the other to closing the windows.

Hyperthermia, on the contrary, is an unregulated rise in core temperature to a level above the hypothalamic set point, either from overproduction of heat (thyroid storm) or a reduced ability to dissipate heat (a bundled-up baby), or as with heat stroke from overexertion on a hot and humid day, which is a combination of the two. The body’s response to hyperthermia is the opposite of its response when a fever is induced; instead of an initial chill, intense flushing ensues as blood vessels in the skin vasodilate and sweat glands activate in an attempt to lose as much heat as possible to the outside. The furnace is burning out of control; the only strategy is to try to open the windows wide.



Whereas hyperthermia may raise body temperature to dangerous, even deadly, levels, fever seems to be a homeostatic process, physiologically regulated within benign limits. DuBois first noted how unusual it was, even for patients who had an untreated serious infection, to have a body temperature exceeding 106°F (41.1°C). Two studies, one retrospective and the other prospective, that examined large numbers of children who came to emergency departments were consistent in finding that in only 0.05% of visits did the child have a temperature of 106°F or higher. Although the pediatric literature conflicts about whether a temperature greater than 106°F (frequently called hyperpyrexia) is a marker of particular risk for serious underlying infection, no study suggests that the elevated temperature itself poses a threat to an otherwise healthy child except in the extraordinarily rare event that body temperature exceeds 107°F (41.7°C). A child who has a temperature greater than 106°F is likely to have an element of hyperthermia, such as dehydration, in addition to fever. Evidence is accumulating that as an intrinsic feature of the febrile response, the body releases *endogenous cryogens*, peptides that counterbalance pyrogens and modulate how high the hypothalamus sets its thermostat. Vasopressin and melanocyte-stimulating hormone, as well as some of the cytokines that also may act as pyrogens, seem to help limit the height fever can reach.

As a centrally regulated response to an inflammatory insult, fever may well serve as a helpful component of the body's acute phase reaction and is an adaptive response widely present in the animal kingdom among cold-blooded and warm-blooded species. At least some species of fish and lizards, when infected, move to a warmer part of their environment, thus raising their body temperatures. This behaviorally induced fever has demonstrable survival benefit, which can be negated with antipyretic agents that lower temperature and increase mortality. Fever can retard the growth and reproduction of many invasive pathogenic microorganisms, both bacterial and viral, and it seems to lower the amount of iron that is available to invading bacteria, many of which have a greater iron requirement at higher temperatures. Among its other effects on human physiology, fever enhances neutrophil migration and the production of superoxides; it promotes T-cell proliferation and increases the release and activity of interferon. Interestingly, some of fever's apparently beneficial stimulation of immunologic function may be reversed at very high temperatures, in the hyperpyretic range.

Unfortunately, no conclusive experimental information is available to prove that fever benefits humans clinically in the course of an infection, and some data suggest that, at least within the context of endotoxemia, the metabolic cost of fever contributes to mortality. However, in a teleologic sense, its metabolic cost argues for fever playing some protective role in the infected host. A process that results in a 7% to 10% increase in energy expenditure for every 1°C rise in temperature is not likely to have persisted so widely in nature, among invertebrates, fish, amphibians, and reptiles, as well as among birds and mammals, for millions of years without conferring some survival advantage.

## FEVER PHOBIA

If, then, fever only rarely poses a threat to a child and may even be of benefit, why are parents and pediatricians so generally aggressive about treating it? Schmitt coined the phrase *fever phobia* when he described the prevalence of misunderstanding about fever among parents bringing their children to an inner-city clinic. He found that 58% of parents defined temperatures below 102°F (39°C) as *high*, and 16% actually believed that, if left untreated, body temperature might rise to 110°F (43.3°C) or higher. Almost every parent thought fever could cause harmful side effects, with 46% fearing permanent brain damage. Given these responses, not surprisingly, 63% of all the parents worried "lots" about the harm fever might cause their children, and 56% gave an antipyretic agent for a temperature within the normal range. For temperatures below 102°F (38.9°C), 85% of parents treated with a drug and 62% with sponging. Twenty years later, a study in Baltimore revisiting fever phobia in 2 urban hospital-based clinics documented the enduring persistence of the misconceptions and fears Schmitt had first identified.

The population Schmitt described consisted mainly of medically indigent, poorly educated families. Kramer, Naimark, and Leduc essentially repeated Schmitt's study in a private practice with middle-class parents. Almost 50% defined temperatures in the normal range as fever; 43% thought that temperatures below 104°F (40°C) could be dangerous, and 15% believed that untreated fevers could rise above 107.6°F (42°C). Death, brain damage, and stroke were among the complications of fever these educated parents feared, with 20% believing that such complications might occur at temperatures below 104°F and 95% believing that they might occur at levels below 107.6°F. One in 5 of these parents would treat normal temperatures, and virtually all (97%) would treat a temperature below 104°F.

The fact that the use of medication to treat fever is so widespread is not surprising. The English, for example, administer antipyretic drugs for an estimated 68 million child-days each year. Fifty percent of the parents in Schmitt's study stated that physicians or nurses were their most important source of information about fever. This claim was given credence by a survey of members of the American Academy of Pediatrics in Massachusetts, in which 2 of 3 believed fever itself can pose a danger to children, and 25% of the responding physicians cited death and brain damage as potential complications of temperatures as low as 104°F (40°C). Almost three-fourths of the pediatricians always or often recommended treatment for fever, two-thirds of them for temperatures under 102°F (38.9°C). The children may be the ones who swallow the medicine, but the therapy seems aimed more at the anxiety of their parents and physicians than at any real danger that fever holds for them.

## DEFINITION AND MEASUREMENT

As would be expected with any physiologic parameter, no single normal value represents the gold standard for body temperature. Rather, a range of normal



values must take into account variations from person to person, fluctuations that reflect both a circadian pattern and age-related differences and disparities arising from the method and site of temperature measurement. A reading of 98.6°F (37.0°C) has traditionally been considered the *norm*; however, the average mean daily oral temperature, measured every 6 hours for 41 to 108 days, of 9 healthy young adult volunteers was 97.9°F (36.6°C), with a range of 97.5°F to 98.4°F (36.4°C to 36.9°C). Young children tend to have higher normal body temperatures than older children or adults; yet infants in the first 1 or 2 months of life are less likely than older children to develop fever with an infectious illness. Normally, body temperature is higher in the late afternoon and early evening than it is late at night or early in the morning, with a swing of as much as 3.0°F (1.7°C). Probably the temperature cited most frequently as defining fever is 100.4°F (38.0°C), measured rectally. However, given all the variables that affect a particular person's body temperature, any specific number used to define fever is arbitrary. The measurement of fever is discussed fully in Chapter 152, Fever.

## MANAGEMENT

The management of fever rightly begins well before a child becomes febrile. As a first step, pediatricians must recognize the part we have played in creating fever phobia in our patients' parents. The almost ritualistic dependence on measuring a child's temperature, even at routine encounters in which illness is not an issue, as well as readiness to recommend antipyretic therapy for any elevation of temperature, must certainly confuse parents when physicians tell them not to worry about fever itself. Offering counseling about fever when a child is already ill is not as likely to be as effective as introducing the subject routinely in the course of a health maintenance visit. The pediatrician should explain that fever is one of the body's natural responses and is not a threat in itself and that temperature will not spiral out of control to dangerous heights without treatment other than sensible care (eg, maintaining hydration and not overbundling). In identifying the underlying illness as the possible danger to the child, the pediatrician would do well to educate parents about the symptoms and behaviors that should alert them to trouble and signal the need for medical attention.

Treating fever is a question of judgment. If the source of the fever poses a threat, then obviously it must be addressed specifically. However, intervening against fever *per se* should be a decision that is individualized to each child who is febrile. By far the most common reason for treating fever is that it makes the child uncomfortable. Although on an evolutionary scale, fever surely must be beneficial, its benefit during the course of an acute illness is not so well proved as to override concern for the child's comfort. The decision to treat for comfort's sake should not be based on any particular temperature threshold, but rather on how the child looks and behaves; many children tolerate fevers to 104.0°F (40.0°C) without apparent ill effect, whereas others become cranky and restless

with a temperature barely above 100.4°F (38.0°C). In some cases, concern for a child's comfort may have to be balanced against the usefulness of a fever's pattern or persistence when making a diagnosis. At least one study has even suggested that acetaminophen's efficacy in improving a febrile child's comfort is more presumption than fact. In a randomized, double-blind, placebo-controlled trial of 225 children aged 6 months to 6 years who had acute fever, those treated with acetaminophen were somewhat more active and alert than the control group but were no different in mood, comfort, appetite, or fluid intake. The acetaminophen group's fever and other symptoms lasted as long, and at the end of the trial, parents were unable to tell with any reliability whether their child had received the drug or the placebo.

Some researchers also believe that reducing fever with a dose of antipyretic can distinguish children who appear ill only because they are febrile from children who have a seriously threatening infection. In fact, neither the magnitude of fever reduction nor a child's clinical appearance after receiving antipyretic medication can reliably distinguish serious from trivial infectious disease.

## Hyperthermia

Hyperthermia is different from fever, posing a real and immediate threat to any child suffering from heat illness. Successful treatment depends on restoring the core temperature to normal as rapidly as possible. Antipyretic agents, which work by lowering the hypothalamic set point, are not helpful because the set point is already below a rising body temperature that has escaped regulation. Physical cooling along with fluid resuscitation is the mainstay of therapy. Although a number of relatively unusual pediatric conditions can lead to hyperthermia (eg, malignant hyperthermia, autonomic neuropathies, encephalopathies, thyrotoxic crisis, toxin or drug exposures, pheochromocytoma, hypohidrotic ectodermal dysplasia), far more commonly dehydration, overbundling, and overexertion, particularly in a hot environment, are the underlying culprits in children.

## Treating the Infant

Particularly when comfort is the issue for an infant in the first few months of life, 2 factors weigh against routine use of medication for fever. The half-lives of all available antipyretics are prolonged early in infancy, making inadvertent overdose more of a problem. With their larger surface area relative to volume, infants are also more responsive to physical interventions that reduce body heat, such as removing clothing and blankets, keeping the room temperature moderate, and improving air circulation.

## Treating the Compromised Child

Although fever itself is benign in an otherwise healthy child who has a self-limited viral illness, the metabolic stress it entails may be more than an already compromised child can tolerate. Increased oxygen consumption and insensible water loss, along with tachycardia and tachypnea, can further threaten a child who is significantly anemic, septic, or in shock, as well as

a child rendered vulnerable by cardiac, pulmonary, renal, or any other systemic disease that strains homeostasis. Fever may also exacerbate an acute brain injury, either infectious or traumatic, and its effect on the sensorium may be confounding in a child who has a neurologic disorder.

### Seizures

More troublesome is defining the role of antipyretic medication in preventing febrile seizures. Children who are most at risk for febrile seizures (those 6 months to 6 years of age) are also the children who most frequently have self-limited viral illnesses. Urging parents to treat their young children's fever with an antipyretic agent will likely promote fever phobia, as well as an unwarranted fear of the risk that a febrile seizure poses. Undeniably, a convulsive episode in a young child is terribly frightening, but only very rarely is it dangerous. Aggressive attention to the possibility of a seizure with any fever will only magnify the anxiety parents already feel about both—and without any convincing evidence the strategy will work. The relationship between fever and seizures is neither clear nor predictable. The convulsive activity in a febrile seizure can, in fact, precede the fever, making causality at best uncertain. Parents are often not aware that their child has a fever until after the seizure has occurred. Some children seize with low-grade fever and not again when their temperature is high. The lower the child's temperature is with the first seizure, the greater the risk; this circumstance makes having a sense of control more difficult for parents because lower-grade fevers are hard to detect. Parents overcall fever when they use palpation, which may lead either to excessive dosing with an antipyretic drug or confirmatory rectal probes that become part of too many children's routine. Last, it is doubtful that even around-the-clock administration of acetaminophen or ibuprofen can prevent recurrence of febrile seizures. Parents deserve reassurance that another seizure is neither their fault nor a real threat to their child's well-being. In fact, the threat may come from the treatment if prophylaxis becomes too aggressive.

### Medical Management

If a fever is to be treated beyond routine attention to hydration and ambient conditions, the most sensible approach follows from understanding how the brain controls the body's temperature. When the hypothalamic set point rises, fever follows. Nonsteroidal anti-inflammatory drugs (NSAIDs), particularly aspirin and ibuprofen, are effective antipyretic agents because they lower the hypothalamic set point back toward normal by inhibiting the synthesis of prostaglandin  $E_2$ ; acetaminophen, which is a para-aminophenol derivative, indirectly does the same by inhibiting cyclooxygenase.

In most circumstances, aspirin should not be the drug of choice for children because of its reported association with Reye syndrome. When reducing fever is the principal concern, acetaminophen has the advantage of a long record of safety; it has almost no side effects, other than allergic reactions, unless ingested in toxic amounts greater than 140 mg/kg,

which is at least 10-fold greater than its therapeutic dose (10 to 15 mg/kg). Children younger than 6 years, the group most frequently febrile, are less susceptible than older children and adults to liver destruction, the major toxicity of acetaminophen poisoning. However, over the past decade growing epidemiologic evidence has implicated the use of acetaminophen as a contributing factor to the rising prevalence of asthma in children, and it has been recommended that children who have asthma or are at risk for asthma be advised to avoid acetaminophen. Concern has also been raised that using acetaminophen as prophylaxis against fever at the time of vaccination blunts the antibody response, which has important implications not only for individual children but also for public health: in particular, higher levels of antibody are needed to interrupt the asymptomatic carriage and transmission of *Haemophilus influenzae* and *Streptococcus pneumoniae*.

At its optimal dose (10 mg/kg), ibuprofen reduces fever as effectively as acetaminophen, and because its duration of action is moderately longer, it can be given every 6 hours rather than every 4 hours. However, ibuprofen's less frequent dosing has a cost. Typical of anti-inflammatory agents, ibuprofen can cause gastritis and gastrointestinal bleeding, and it inhibits platelet function; with chronic use, and most likely even acutely, it can cause nephropathy. The clinical situation determines whether ibuprofen's suppression of inflammation is a benefit or potentially an undesirable side effect. In a child who is febrile with rheumatoid disease, ibuprofen offers relief that acetaminophen cannot; a child whose fever arises from infection may well do better with the inflammatory response left intact. Other NSAIDs, with properties and side effects similar to those of ibuprofen, are coming on the market. Naproxen is available in a pediatric suspension; with its relatively long half-life, it can be given twice daily, at a dose of 5 mg/kg. Indomethacin and meloxicam are other NSAIDs available as suspensions but are not approved by the US Food and Drug Administration for the indication of fever control.

Using acetaminophen and ibuprofen in combination, either simultaneously or alternately, has become a common practice. Although the 2 together may be more effective at maintaining a lower body temperature than either drug alone, no evidence supports any clinical benefit to the combination, and the risk for toxicity may well be increased.

### Physical Cooling

As an alternative to medication, physical cooling can lower the body temperature of a child who is febrile, but the physiologic mechanism of fever explains why the result may paradoxically make the child feel worse. With fever, the hypothalamic thermostat is set above normal, dictating that the body will generate heat. Whereas acetaminophen or NSAIDs push the thermostat back down, damping the impulse to produce heat, physical measures such as sponging work the opposite way; in effect, they open the windows to let heat escape without adjusting the thermostat at all. As cooling begins, the hypothalamus senses

wider divergence between its own set point and the body's actual temperature; to close the gap, it sends out the directive to generate still more heat, with muscular shivering and a rise in the general metabolic rate. Aside from how uncomfortable the child may feel, with the set point remaining high after the sponging is finished, the temperature is likely to renew its climb.

Of course, under some circumstances, physical cooling has a place. Some fevers that warrant intervention clinically may not respond to antipyretic drugs, as in a neurologically impaired child whose temperature control is aberrant. If an underlying illness gives special urgency to reducing the metabolic stress that comes with a fever, then the combination of an antipyretic medication and cooling not only works more quickly than either alone but also makes physiologic sense; while cooling physically draws heat off, the drug lowers the set point to avert a rebound temperature rise. The same holds for the rare fever high enough to be a concern itself or for a fever that is complicated by some element of hyperthermia. When sponging a child, tepid water (approximately 90°F [32°C]) is probably best. It sets a moderate but effective gradient down from body temperature, rather than the precipitous decline colder water would induce, and it is less likely to distress the child who has a shivering response. Alcohol solutions have no place at all in the management of a febrile child because alcohol can be absorbed through the skin.

Hippocrates saw it right when, without the insights of our science, he somehow appreciated fever as part of the body's natural defense. We often do best to let nature have its way.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Febrile Seizures* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/fever/pages/Febrile-Seizures.aspx](http://www.healthychildren.org/English/health-issues/conditions/fever/pages/Febrile-Seizures.aspx))
- *Fever and Your Child* (handout), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *How to Take Your Child's Temperature* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/fever/pages/How-to-Take-a-Childs-Temperature.aspx](http://www.healthychildren.org/English/health-issues/conditions/fever/pages/How-to-Take-a-Childs-Temperature.aspx))

## AAP POLICY

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## Chapter 54

# MANAGING ACUTE PAIN IN CHILDREN

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## INTRODUCTION

A transformation in pediatric pain management began with the rejection of previously held misconceptions that neonates, infants, and children do not feel, experience, or react to pain as adults do because of the immaturity of their peripheral and central nervous systems. These misconceptions, compounded by fears of addiction and adverse effects, led to the undertreatment of pain in both the outpatient and the hospital settings. Clinical studies have demonstrated that infants and children experience a similar severity of postoperative pain as adults and that even preterm infants demonstrate alterations in physiologic and biochemical markers of stress after painful stimuli. In fact, preterm infants respond more dramatically to nociceptive input. Although the ability to sense pain develops during the first trimester in utero, the descending inhibitory pathways that regulate the transmission of pain in the dorsal horn of the spinal cord are the last to develop. As such, this descending inhibition may be absent or underdeveloped in preterm infants.

Aside from the obvious humanitarian concerns, the inadequate treatment of pain during infancy may have long-lasting consequences, including the development of chronic pain syndromes or a heightened sensitivity to subsequent painful stimuli that may persist throughout childhood. Despite the ongoing emphasis on the need to treat acute pain, pain management in the hospital, emergency department, and outpatient setting is in many circumstances less than optimum. This reflects the need for ongoing education and scientific evaluations to determine the optimal methods of acute pain management.

Barriers to the effective treatment of acute pain in infants and children are multifactorial. In addition to wide variations in ages of the pediatric patient, several variables exist in the acute pain process that may affect treatment options and decisions. Causes of acute pain include trauma, acute medical illnesses, and surgical procedures. Pain treatment may occur in the hospital or the outpatient setting, in a tertiary care center, or in a community hospital. The child's underlying status may range from a healthy child free of systemic disease to a compromised child with several comorbid features.

## MEASURING ACUTE PAIN

The first steps in treating acute pain are to assess its severity, which may be used to guide therapy, and then assess the response to therapy. Although older children can identify when they hurt and how bad the pain is, the evaluation of preverbal children or those with cognitive impairment is difficult and can complicate the issues of pain assessment and management.

Although generalized irritability and agitation may be related to the pain, they may also be related to other factors, including parental absence or hunger. There are various pain scales and assessment tools created to overcome the problems with assessing pain. These tools range from simple, bedside checklists with 4 to 5 components that require only 5 to 10 seconds to lengthy surveys that are cumbersome and time consuming. Regardless of the clinical scenario, the child's response to the analgesic therapy must be evaluated. Pain cannot be identified if it is not assessed.

One method to evaluate children for pain is to consider the pain score to be the fifth vital sign and encourage the nursing staff to assign a pain score for all hospitalized children whenever the other vital signs are assessed. Pain is assessed to identify untreated pain even if the child is not receiving analgesics. Pain is a frequent accompaniment of many of the diseases that lead to the hospitalization of infants and children. Compliance with the use of pain scales is mandated by various hospital credentialing boards and by auditing agencies that frequently evaluate pain management protocols as a benchmark criterion.

Pain assessment tools can be categorized into self-report, observational, and physiologic scales. Many of the more involved scoring systems use components from 2 or all 3 of these types of scales. Pain assessment in the verbal child is relatively straightforward using a self-reported, visual analog score such as asking the child to identify where the pain falls on a straight line from 0 (no pain) to 10 (worst imaginable pain). These techniques rely on children's ability to assess and report their own pain. Variations of the scales aimed at being more user friendly and applicable in younger children (5 to 7 years of age) include the use of poker chips, a ladder, colored crayons, or pictures of children in varying degrees of distress. With the poker chip scale, the child expresses pain as a certain number of red poker chips (1 to 4). Mild pain would be 1 poker chip, whereas 4 poker chips would be the worst pain the child could have. The pain ladder is a picture of a ladder with 9 steps or rungs. At the bottom of the ladder is "no hurt," and at the top of the ladder is "hurt as bad as it could be." The children are then asked to point at the appropriate place on the ladder that may indicate the amount of pain they are experiencing. The severity of pain can also be expressed by selecting a colored crayon, with red indicating severe pain and blue indicating little or no pain. However, the use of colors to express pain has some variability among various ethnic groups. The association of blue with calm or no pain and red with pain does not cross all ethnic groups.

Alternatively, the child can use a *faces* scale. This self-report uses simple drawings of 6 faces with the eyes, nose, and a mouth in various positions from a smile to a frown. These faces are placed beside a corresponding 100-point vertical scale. Another scale known as the Oucher uses actual photographs of children in various degrees of distress. This scale is available with photographs of children from various ethnic groups. Both the faces and the Oucher scales are generally meant to be used as a self-report type of scoring system. However, they are sometimes modified and

the faces scale has been used as an observational tool. Pediatricians can assess the child and select the face and hence the degree of pain they think the child is feeling. A more involved assessment tool that combines both observational and self-report tools is the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS). Given its complexity, CHEOPS is more commonly used for clinical research than in actual clinical practice. The scale assigns a score of 0 to 2 for 6 categories, including cry, facial expression, verbal complaints of pain, position of the torso, whether the child is touching the wound, and position of the legs.

The assessment of pain in preverbal children or those with cognitive impairment is more difficult because these patients are unable to express the severity of the pain. The tools used in these scenarios are limited to those using observational scoring, physiologic factors, or a combination of both. Observational tools may include an assessment of the child's facial features, body positioning, and the presence or absence of crying. Physiologic parameters commonly used in pain scales include heart rate, blood pressure, respiratory rate, and oxygen saturation. Although not practical for everyday bedside use, clinical research of pediatric pain may also include physiologic parameters, including neurohumoral changes such as the alterations in the plasma concentration of stress hormones.

When a child's conditions or age preclude the use of self-report scales, several observational tools have been described and validated for neonates, preterm infants, and patients with cognitive impairment. For children with cognitive impairment, different options can be used that may be helpful in assessing their pain, including the noncommunicative children's pain checklist—postoperative version (NCCPC-PV). The NCCPC-PV includes the grading of several specific behaviors such as vocalization, socialization, facial expression, activity, body and limb positioning, and physiologic signs that have been shown to indicate pain in children with cognitive impairment. Alternatively, scales such as the face, legs, activity, cry, and consolability (FLACC) scoring system, which is used for preverbal children, can be modified for cognitively impaired children by adding specific descriptors and parent-identified behaviors for each individual child. These tools have excellent interobserver reliability and are quick and easy to use even in a busy clinical practice.

Effective pain management first identifies children in pain and includes an ongoing assessment of the response to the therapy. The tool chosen for use is not as crucial as its standard use in all hospitalized children.

## PHARMACOLOGIC MANAGEMENT OF ACUTE PAIN

Treatment regimens should incorporate a graded approach (Box 54-1) similar to what has been used for the treatment of cancer-related pain, regardless of the cause of pain. Although a primary assessment of the severity of pain is made to guide initial therapy, if



**BOX 54-1 Analgesic Ladder for Managing Acute Pain****MILD PAIN**

NSAIDs, acetaminophen, or salicylates

**MODERATE PAIN**

1. NSAIDs or acetaminophen with weak opioid (oxycodone, hydrocodone)
2. Intravenous opioids (with addition of fixed-interval NSAID or acetaminophen)
  - a. Intravenous opioid by PCA
  - b. Continuous infusion of opioid with as-needed rescue doses of opioid
  - c. Fixed, interval dosing of opioid
3. Regional anesthetic techniques

**SEVERE PAIN**

1. Continue fixed interval dosing of NSAID or acetaminophen
2. Intravenous opioid by PCA
3. Regional anesthetic techniques

NSAID, Nonsteroidal anti-inflammatory drug; PCA, patient-controlled analgesia.

effective analgesia is not achieved with the approach rung of the ladder, then the pediatrician must consider moving up to the next step. Selecting an analgesic also depends on the setting in which the pain is treated. Outpatient management requires nonintravenous routes, including oral administration, whereas the inpatient setting provides an appropriate scenario for the administration of parenteral opioids. Treatment with a nonopioid analgesic agent such as a prostaglandin synthesis inhibitor (acetaminophen, acetylsalicylic acid, or a nonsteroidal anti-inflammatory drug [NSAID] such as ibuprofen) is used for mild pain such as that after a soft tissue surgical procedure or that caused by a mild medical illness such as pharyngitis or otitis media. Moderate pain such as that after a bony orthopedic procedure or a fracture can usually be controlled with a combination of a prostaglandin synthesis inhibitor and a weak opioid (eg, an acetaminophen with oxycodone or hydrocodone). Although codeine was previously a commonly used agent, genetic variation in its metabolism to morphine results in significant variations in its effects. It is poorly metabolized in up to 30% of children, resulting in inadequate pain relief. Of even more concern, in up to 10% of some African and Middle Eastern populations, ultrarapid metabolism can lead to respiratory depression and death from increased serum concentrations of morphine. The US Food and Drug Administration (FDA) released a warning regarding its use in August 2012 and it is no longer recommended for use in children. More severe pain such as sickle cell vaso-occlusive crisis, major burns, or the pain after a major surgical procedure (thoracotomy or an exploratory laparotomy) generally requires either a regional anesthetic technique or parenteral opioids.

**Mild to Moderate Pain in the Outpatient Setting (Prostaglandin Synthesis Inhibitors and Weak Opioids)**

With tissue disruption, fatty acids are released from cell membranes and are metabolized to prostaglandins. This results in local inflammation and pain by stimulating the free nerve endings of C and A fibers. NSAIDs, acetaminophen, and salicylates inhibit the enzyme cyclooxygenase, thereby blocking prostaglandin formation. In contrast to opioids, the prostaglandin synthesis inhibitors demonstrate a ceiling effect such that, after a specific plasma concentration is achieved, increasing the dose provides no further analgesia. Although most of these agents are available as over-the-counter medications, they represent an effective and relatively safe means of controlling mild to moderate pain. The prostaglandin synthesis inhibitors include para-aminophenol derivatives (acetaminophen), NSAIDs (ibuprofen), and salicylates (acetylsalicylic acid and choline magnesium trisalicylate).

**Role of Prostaglandin Synthesis Inhibitors**

The role of the prostaglandin synthesis inhibitors to treat acute pain includes their use as the sole agent for minor pain, their combination with weak opioids for oral administration to control moderate pain, and their addition to parenteral opioids and regional anesthetic techniques for severe pain. In the last situation, their use does not replace opioids but rather provides adjunctive analgesia, thereby lowering the total amount of opioid required. Because most of opioid-related adverse effects are dose related, decreasing total opioid consumption plays a significant role in decreasing or preventing opioid-associated adverse effects.

**Route of Administration of Prostaglandin Synthesis Inhibitors**

Although prostaglandin synthesis inhibitors are most frequently administered orally, obstacles to effective analgesia may exist with this route, including a delay in the onset of analgesia, decreased bioavailability when compared with parenteral administration, refusal to take the medication, vomiting, and an inability to give enteral medications because of an ileus or abdominal complaints. Acetaminophen and ibuprofen are the most commonly prescribed medications of this class. Both medications are available in several preparations, including chewable tablets and elixirs. Acetaminophen is also available in suppository form and sustained-release tablets. An intravenous preparation of acetaminophen has recently received approval by the FDA and is available in the United States.

**Specific Uses of Prostaglandin Synthesis Inhibitors**

Acetaminophen, a para-aminophenol derivative, has a significant role in managing acute pain. Phenacetin is no longer used because of its toxicity profile and the risk for renal papillary necrosis. The association of Reye syndrome with salicylates, combined with the diverse array of NSAIDs on the market, has markedly

reduced the use of aspirin products. Despite the limited use of salicylates, the role for choline magnesium trisalicylate remains, which combines the analgesic advantages of a salicylate with limited effects on platelet function. It is an effective choice in children with qualitative and quantitative platelet issues. Table 54-1 outlines the more commonly prescribed prostaglandin synthesis inhibitors for children. In the perioperative setting, the oral premedication (midazolam) can be combined with either acetaminophen (10 to 15 mg/kg) or ibuprofen elixir (10 mg/kg). This technique provides the child analgesia on awakening and masks the taste of the midazolam premedication. If preoperative administration is not chosen, then an acetaminophen suppository (40 mg/kg) can be placed after anesthetic induction. Rectal administration means a larger dose of acetaminophen is required to achieve analgesic plasma concentrations of 10 to 20 mcg/mL. Suggested doses for acetaminophen in neonates and infants were derived from 6 pediatric acetaminophen dosing studies.

Another possibility for perioperative pain management is the postoperative administration of either ibuprofen or acetaminophen when the child complains of pain in the recovery room. This approach is valued in the outpatient setting when the physician is confronted with a child in acute pain. Waiting until the child complains is less desirable in the perioperative setting because the onset activity of any of these agents after oral or rectal administration is 20 to 30 minutes. If intravenous access is established, then small, incremental doses of an intravenous opioid (fentanyl 0.5 mcg/kg, morphine 0.02 mg/kg, or nalbuphine 0.02 to 0.04 mg/kg) are titrated every 3 to 5 minutes to provide immediate analgesia while waiting for the onset of the oral or rectal acetaminophen or ibuprofen. These doses can be repeated incrementally until the desired level of analgesia is achieved. Although dosing guidelines may list the dose of morphine as 0.1 mg/kg, it makes sense to use small, incremental doses and administer the dose at 3 to 5 minute intervals until effective analgesia is achieved. When the child is ready for discharge home, ongoing analgesia can be provided

with either acetaminophen or ibuprofen. Although administering these agents on an as-needed basis is common, fixed-interval dosing may provide more effective analgesia. Fixed-interval dosing is the administration of the medication around the clock for the first 24 to 48 hours without waiting for the child to complain of pain. For this purpose, acetaminophen (10 to 15 mg/kg) every 4 hours or ibuprofen (10 mg/kg) every 6 hours can be used. If the child is receiving acetaminophen as a fixed-interval dose and has breakthrough pain, then a supplemental dose of ibuprofen can be administered, and vice versa. Fixed-interval dosing is also recommended when opioids are used in the treatment of severe pain (see discussion later in this chapter). By maintaining a plasma concentration of the prostaglandin synthesis inhibitor, a synergistic effect is achieved, and pain can be managed with a decreased total dose of opioid.

When fixed-interval acetaminophen is administered, the pediatrician must ensure that the infant or child is not receiving acetaminophen in other forms, such as cold medicines. Additionally, given that several different acetaminophen preparations are available from numerous manufacturers, ensuring that the parents and the pediatrician know the concentration of acetaminophen or ibuprofen in the specific product is equally important. The most common cause of acetaminophen toxicity in children younger than 10 years remains inadvertent overdosing by parents.

### Role of Weak Opioids

Aspirin or acetaminophen can be combined with a weak opioid such as tramadol, oxycodone, or hydrocodone for the outpatient treatment of moderate pain or when NSAIDs alone fail to control mild pain. Although it was frequently used in the past, codeine should not be administered to children. As noted earlier, there is genetic variation in its metabolism. A hepatic microsomal enzyme metabolizes codeine to morphine for a significant part of its analgesic effect. In a cohort of 96 children, 47% had genotypes associated with low activity of the enzymes necessary for the conversion of codeine to morphine, and in 36% of

**Table 54-1** Potency and Half-Life of Opioids

OPIOID AGONISTS	POTENCY (RATIO COMPARED WITH MORPHINE)	HALF-LIFE	ACTIVE METABOLITES
Morphine	1	2–3 hr	Yes
Meperidine	0.1	2–3 hr	Yes
Hydromorphone	5–8	2–3 hr	No
Oxymorphone	10	1–4 hr	No
Methadone	1	12–24 hr	No
Fentanyl	100	20–30 min	No
Sufentanil	1000	20–30 min	No
Alfentanil	20	10–15 min	No
Remifentanyl	100	5–8 min	No
<b>AGONIST-ANTAGONISTS</b>			
Butorphanol	5	2–4 hr	No
Nalbuphine	1	4–5 hr	No
Pentazocine	0.3–0.4	2–3 hr	No

the patients, neither morphine nor its metabolites were detected. The authors concluded that the reduced ability to metabolize codeine may be more common than previously reported and that codeine analgesia is less reliable than morphine. More important, excessive amounts of morphine may be produced in those children who are ultrarapid metabolizers. This has resulted in deaths with codeine use. Given these concerns, there is no role for the use of codeine for any indication in the pediatric population.

Several of these weak opioid preparations are available in both liquid and tablet formulations. The use of a liquid or tablet is determined by the child's age and preference. For younger children, acetaminophen with oxycodone elixir (Roxicodone) is a frequently chosen option, with dosing based on the oxycodone component (0.1 to 0.15 mg/kg every 4 to 6 hours). Alternatively, if the child has recently received acetaminophen, an oxycodone elixir can be used. For older children, oxycodone and hydrocodone can also be administered as a tablet in combination with either acetaminophen or acetylsalicylic acid. Hydrocodone (7.5 mg) is also available as a tablet combined with 200 mg ibuprofen (Vicoprofen). As noted previously, the dose should be based on the oxycodone or hydrocodone component, starting at 0.1 to 0.15 mg/kg (maximal starting dose 5 mg) every 4 to 6 hours. Regardless of the preparation used, with dose escalation, the amount of acetaminophen may exceed the maximal recommended dose of 60 to 90 mg/kg/day. When higher doses of the opioid component are needed, switching to preparations that contain oxycodone or hydrocodone without the acetaminophen or aspirin is best to prevent the possibility of acetaminophen toxicity. A sustained-release formulation of oxycodone (OxyContin) is also available, which allows an analgesic plasma concentration to be maintained with a dosing interval of every 8 to 12 hours. Although used occasionally to achieve a baseline steady-state plasma concentration of opioid to provide analgesia after major operative procedures, given its abuse, diversion potential for illegal use, and a lack of data regarding its pharmacokinetics in children, the risk-to-benefit ratio of such regimens must be considered.

Tramadol (Ultram) is a unique analgesic agent with a dual mechanism of action, including agonism at the  $\mu$ -opioid receptor and inhibition of norepinephrine and serotonin reuptake in the central nervous system. Although initially thought to have limited abuse potential, clinical experience has demonstrated an abuse potential that may be similar to that of other weak opioids. Tramadol's potency is roughly equivalent to that of meperidine. An intravenous intraoperative dose of tramadol (2 mg/kg) decreases the need for rescue opioid analgesia in the recovery room in children receiving tramadol. Tramadol is well tolerated and provides effective pain relief. Tramadol analgesia is rated as very good or excellent by 69% of parents and 70% of children. Adverse events are mild or moderate and similar in incidence to that seen with other oral opioids. Tramadol has a longer half-life (6 to 7 hours) than other oral agents and an active metabolite with a half-life of 10 to 11 hours. The active metabolite is renally excreted and can accumulate in

children with renal insufficiency or failure, making it a poor choice in this setting. Despite its longer half-life, tramadol fails to decrease analgesic needs after discharge when compared with placebo. The adverse effect profile of tramadol is similar to that of other opioids (see later discussion); however, as with meperidine, a unique adverse effect generally seen only with large doses or in children with renal failure is seizure activity. Respiratory depression may be less with equipotent doses of tramadol when compared with other weak opioids.

Throughout the world, tramadol is available in injectable solution, suppository, liquid, and tablet formulations. A tablet containing 50 mg of tramadol and the combination of 37.5 mg of tramadol with 325 mg of acetaminophen in a tablet (Ultracet) are the only 2 preparations available in the United States. The 50 mg tablet is scored and can be cut in half, allowing its administration to smaller children. The manufacturer's recommendations for dosing include 0.5 to 1.0 mg/kg (initial maximal dose of 50 mg) every 4 to 6 hours as needed. However, doses up to 2 mg/kg have been used in some pediatric trials.

### Moderate to Severe Pain, Inpatient Setting (Prostaglandin Synthesis Inhibitors)

In the inpatient setting, the options for controlling acute pain are more diverse, including the option for the use of parenteral prostaglandin synthesis inhibitors and opioids. Even when the choice is made to use parenteral opioids, the prostaglandin synthesis inhibitors have a role in controlling pain because they can be used to decrease the total postoperative opioid requirements and thereby opioid-related adverse effects.

Although a significant amount of literature exists regarding the use of the parenteral agent ketorolac (Toradol), less expensive alternatives, including oral ibuprofen and acetaminophen, may also be beneficial. In patients receiving opioids, the addition of either ibuprofen (10 mg/kg orally every 6 hours) or acetaminophen (10 to 15 mg/kg orally or rectally every 4 hours) on a fixed-interval schedule is suggested. Children receiving rectal ibuprofen (40 mg/kg/day) after inpatient surgery have lower pain scores and decreased opioid requirements in the recovery room during the day of operation and the first 72 hours after the procedure. Additionally, the incidence of opioid-related adverse effects is lower in children receiving ibuprofen. Although rectal preparations of ibuprofen are not available in the United States, similar results have been reported in both children and adults with the use of rectal indomethacin or acetaminophen.

When oral or rectal administration is not feasible, intravenous administration is possible using the parenteral NSAID ketorolac. Although preliminary clinical trials suggested that ketorolac was as effective as opioids in treating acute pain, its more applicable clinical role is similar to that of other NSAIDs as an adjunct to opioid analgesia during the postoperative period. Ketorolac may also be effective in acute pain of other causes, including inflammatory and musculoskeletal pain, such as in children with pleuritic pain or vaso-occlusive crisis caused by sickle cell disease.

Ketorolac (0.5 mg/kg) demonstrated similar pharmacokinetic properties in children ranging from 1 to 16 years as in adults. A plasma concentration in the adult therapeutic range is maintained for 6 hours in most patients. More recent work has demonstrated similar clearance in infants and toddlers ranging from 6 to 18 months and those from 2 to 6 months of age.

After its initial release (recommendations for ketorolac dosing included 1 mg/kg up to 60 mg), many physicians have decreased the maximum dose to 15 or 30 mg.

To date, data regarding the analgesic efficacy of ketorolac in children younger than 1 year of age are limited. In one study, daily morphine requirements ( $0.04 \pm 0.05$  versus  $0.15 \pm 0.06$  mg/kg/day,  $P < .01$ ) were significantly decreased in 10 infants who received ketorolac. No differences in pain scores were noted between the 2 groups, and no adverse effects related to ketorolac were noted. Another study reported no adverse renal or hematologic effects in a retrospective review of ketorolac use in 53 children younger than 6 months of age who received at least 1 dose of ketorolac after cardiac surgery. The greatest increase in serum creatinine from baseline was 0.3 mg/dL. Four patients had minor episodes of bleeding while receiving ketorolac. However, safety concerns have been anecdotally reported by others. In a retrospective review of 57 children ranging in age from 0 to 3 months who received ketorolac, 10 (17.2%) had a bleeding event. Those who experienced a bleeding event received ketorolac at a mean of 20.7 days of life, with 70% receiving the medication at less than 14 days of age. Those without a bleeding event received ketorolac at a mean of 31.9 days ( $P = .04$ ). Bleeding events correlated with glomerular filtration rate of less than 30 mL/minute per  $1.73 \text{ m}^2$  or concomitant medications in all but 1 child. The authors concluded that infants younger than 21 days and less than 37 weeks' gestational age are at significantly increased risk for bleeding events and should not be candidates for ketorolac therapy.

Other specific contraindications to the use of ketorolac include children with bleeding dyscrasias or settings in which acute hemorrhage is a concern (ie, children with abnormal coagulation function, children after trauma, children after intracranial or otolaryngologic surgery). Foster and Williams reported 2 children who developed bradycardia that was temporally related to the administration of ketorolac. Adverse effects of NSAIDs and acetylsalicylic acid generally result from the inhibition of prostaglandins distant from the sites of inflammation (Box 54-2). Acetaminophen or magnesium choline trisalicylate should be considered instead of NSAIDs in children with qualitative or quantitative platelet disorders because neither agent alters platelet function. Alterations in glomerular filtration rate with NSAIDs are uncommon, except in children with pre-existing renal dysfunction, with the concomitant administration of other nephrotoxic agents, in the presence of hypovolemia, or with prolonged administration. An additional concern with NSAIDs is the inhibition of new bone formation, and in some centers, use of these agents is restricted in children undergoing spinal fusion and other procedures in which bone grafts are used.

### BOX 54-2 Adverse Effects of Nonsteroidal Anti-inflammatory Drugs

Central nervous system effects, including headache, dizziness, drowsiness  
Nausea and vomiting  
Peptic ulcer formation  
Gastrointestinal bleeding  
Decreased glomerular filtration rate, renal insufficiency or failure  
Platelet dysfunction  
Bronchospasm  
Interaction with other medications (this effect varies from one NSAID to another)

NSAID, Nonsteroidal anti-inflammatory drug.

Recent efforts to maintain analgesia while diminishing the incidence of adverse effects of NSAIDs have focused on the use of specific isomers of the NSAIDs or agents that selectively inhibit cyclooxygenase (COX) type 2 versus type 1. Although NSAID isomers are still in the investigational phase, experience with other medications has demonstrated the potential for decreasing adverse effects while maintaining efficacy by separating the 2 enantiomers of a chiral compound. Ibuprofen is a chiral mixture of its 2 optical isomers, and animal data suggest that the S(+)-isomer may provide analgesia while having limited effects on the homeostatic COX (see discussion later in this chapter), thereby limiting its adverse effect profile.

COX type 1, referred to as the homeostatic COX, controls renal blood flow, protects the gastric mucosa, and maintains normal platelet function. COX type 2, referred to as inducible COX, is responsible for the inflammatory process. Celecoxib (Celebrex), valdecoxib (Bextra), and rofecoxib (Vioxx) were the first COX-2 inhibitors introduced into clinical use. As with nonspecific NSAIDs and acetaminophen, when used as an adjunct to opioid analgesia, these medications were effective in decreasing opioid requirements and opioid-related adverse effects. However, the enthusiasm for these agents and their clinical use have decreased dramatically after several investigations demonstrated their association with an increased risk for cardiovascular events, including myocardial infarctions.

### Strong Opioids

Several options are available when considering the use of strong opioids for treating moderate to severe pain in infants and children. The most clinically relevant differences between the opioids are their potency, duration of action, and their metabolic fate, including the presence or absence of active metabolites (Table 54-2). The opioids exhibit their end-organ effects through the interaction with specific opioid receptors ( $\mu$  or  $\kappa$ ) in the peripheral and central nervous system. Opioids may act as either pure agonists (bind and activate  $\mu$ - and  $\kappa$ -receptors) or agonist-antagonists (bind and activate  $\kappa$ -receptors while binding to, but not activating,  $\mu$ -receptors). The agonist-antagonists, including nalbuphine (Nubain),



**Table 54-2****Salicylate and Nonsteroidal Anti-inflammatory Drug Preparations Commonly Used in Acute Pain Management**

MEDICATION	PREPARATION	DOSE FORMS
Ibuprofen	Oral suspension Infant drops Chewable tablets Children's caplets Tablets	100 mg/5 mL 50 mg/1.25 mL 50 and 100 mg 100 mg 200, 400, 600, and 800 mg
Choline magnesium trisalicylate	Liquid Tablets	500 mg/5 mL 500, 750, and 1,000 mg
Naproxen	Suspension Delayed-release tablets Tablets	125 mg/5 mL 275 and 500 mg 250, 275, 375, 500, and 550 mg
Tolmetin	Tablets	200 and 600 mg
Acetylsalicylic acid	Capsules Several different preparations available	400 mg —

butorphanol (Stadol), and pentazocine (Talwin), should not be administered to children who have been chronically receiving opioids because they can precipitate withdrawal symptoms. Although these agents have a decreased potential to cause repression depression, a ceiling effect also exists for their analgesia. When escalating doses for increasing or persistent pain, a limit or ceiling exists to the analgesia. Although the potency and efficacy of agonist-antagonists for severe pain is less than that of pure agonists, they are useful for mild to moderate pain when the oral administration of other agents, such as acetaminophen with codeine, is not feasible or when a more rapid onset of action is desired. One option to treating moderate pain postanesthesia is to administer a single intravenous dose of an agonist-antagonist opioid followed by a switch to an oral agent when the child is discharged home. For this purpose, nalbuphine is a good option. An additional benefit of nalbuphine is that it clinically provides more sedation than other opioids because of its effects on the  $\kappa$ -opioid receptor and therefore, in addition to providing analgesia, may provide sedation for the agitated postoperative child. The agonist-antagonists should also be considered when supplemental intravenous analgesia is required in children who are receiving or have received neuraxial (epidural or intrathecal) opioids within the previous 24 hours. The potential for respiratory depression that can occur with the combination of intravenous and neuraxial opioids is less if an agonist-antagonist is used rather than a pure agonist such as morphine.

When opioids are chosen for postoperative analgesia, three choices must be made, including the opioid to be used, the mode of administration, and the route of administration. Information to help decide which opioid is best for postoperative analgesia is relatively limited. Several acceptable alternatives are available, any of which will provide equivalent analgesia provided that equipotent doses are administered. The potential for respiratory depression is present with all of the pure opioid agonists and is not more likely with any specific opioid, provided that equipotent doses are administered.

### Choosing the Appropriate Opioid

In the acutely ill child with comorbid diseases, such as a compromised cardiovascular status, or when a risk for pulmonary hypertension exists, the synthetic opioids (fentanyl, sufentanil, alfentanil, remifentanyl) with their cardiovascular stability, beneficial effects on pulmonary vascular resistance, and their ability to blunt the sympathetic stress response may be advantageous. Because the synthetic opioids have short plasma half-lives (less than 30 minutes), they are generally administered by a continuous infusion to maintain a plasma concentration adequate to provide analgesia. No inherent advantage seems to exist in regard to any of the currently available synthetic opioids, except that fentanyl is the least expensive. Remifentanyl, metabolized by plasma esterases, has the shortest half-life of any of the synthetic opioids (approximately 10 minutes). Unlike the other opioids that depend on hepatic metabolism, no difference exists in the clearance of remifentanyl across the age ranges; thus its half-life is consistent even in neonates. Given these properties, remifentanyl has become a popular agent for intraoperative use with limited applications outside of the operating room. The synthetic opioids are also used in critically ill infants and children in the intensive care unit to provide sedation and analgesia during mechanical ventilation.

Although the synthetic opioids maintain a stable hemodynamic pattern in children with compromised cardiovascular function, alternatives such as morphine are acceptable in children with normal cardiovascular function. For most children, morphine is generally the first-line agent. The dose depends on the mode of administration chosen (Box 54-3). Because of decreased hepatic metabolism and increased permeability of the blood-brain barrier with an increased risk for respiratory depression, dosing with any opioid should start at 50% of the listed dose in infants younger than 6 months. Furthermore, the monitoring of respiratory function with continuous pulse oximetry is recommended when opioids are used in this age group or in children with compromised cardiorespiratory status. Morphine can cause venodilation and

**BOX 54-3 Morphine Dosing<sup>a</sup>**

Initial intravenous titration for acute, moderate to severe pain:

0.01–0.02 mg/kg every 5 min; titrate to effective analgesia

As-needed or fixed-interval dosing:

0.05 mg/kg every 3 hr

Continuous infusion:

0.01–0.03 mg/kg/hr

Patient-controlled analgesia:

Bolus: 0.02 mg/kg every 10 min

Infusion: 0.004–0.005 mg/kg/hr

<sup>a</sup>The doses listed are for initial doses in patients who have not previously been receiving opioids. These doses should be adjusted up or down as necessary to achieve the desired level of analgesia while limiting adverse effects. When opioids are used in infants younger than 6 months or in patients with severe systemic illnesses or other comorbid diseases that place them at risk for opioid-related adverse effects, the starting dose should be 50% of the previously listed doses. Cardiorespiratory function monitoring is suggested.

may decrease blood pressure, especially in children with hypovolemia. Additionally, morphine can cause histamine release that leads to pruritus, an adverse effect particularly common in adolescents and young adults. Morphine is metabolized in the liver to morphine-6-glucuronide (M6G), which is significantly more potent than the parent compound. Because it is water soluble, M6G penetrates the central nervous system poorly and, in most circumstances, is of little consequence. However, because M6G is cleared by the kidneys and can accumulate in children with renal failure or insufficiency and lead to respiratory depression, alternative opioids such as hydromorphone (see discussion later in this chapter), which has no active metabolites, should be considered.

Other opioids that have been used to treat acute pain include hydromorphone (Dilaudid), meperidine (Demerol), and methadone (Dolobid). Hydromorphone may be advantageous when adverse effects related to histamine release such as pruritus occur with morphine. Given that pruritus tends to be more common in adolescents and young adults, hydromorphone may be considered the opioid of choice for the control of severe pain in this population. Hydromorphone's potency is 5 to 8 times that of morphine, and therefore one-fifth to one-eighth of the morphine dose is used. Patient-controlled analgesia (PCA) solutions can be prepared such that an equipotent amount of the opioid is present in each milliliter of the solution (1 mg/mL for morphine, 1 mg/mL for nalbuphine, 0.15 mg/mL for hydromorphone, and 10 mg/mL for meperidine).

Meperidine (pethidine in Europe and the United Kingdom) is approximately one-tenth as potent as morphine and is associated with a relatively high incidence of adverse central nervous system effects, including dysphoria, agitation, and seizures. Meperidine's central nervous system toxicity, including its epileptogenic potential, results from the accumulation of normeperidine, a metabolite produced by the hepatic *N*-methylation of the parent compound. Normeperidine has a long half-life (15 to 20 hours)

and is dependent on renal clearance. High or toxic levels occur more commonly in the setting of renal failure or insufficiency with the coadministration of drugs such as phenobarbital that stimulate hepatic microsomal enzymes and with large doses (greater than 2 g/day in an adult). Because meperidine offers no particular advantage over other opioids and may in fact be less efficacious than morphine in controlling acute pain, morphine or hydromorphone is preferred.

Methadone has a potency similar to that of morphine; however, the plasma half-life is 12 to 24 hours. Its long plasma half-life provides a continuous steady-state serum concentration after a single-bolus administration, thereby providing prolonged analgesia without the need for a continuous infusion or the use of a PCA device. Intraoperatively, a single intravenous dose of 0.2 mg/kg has been shown to result in lower pain scores and a decreased need for supplemental opioid analgesic agents during the initial 36 postoperative hours. The longer duration of action offers analgesic advantages over the intermittent administration of agents with shorter half-lives and may be useful in situations in which PCA devices or continuous infusions are not available. However, the use of intravenous methadone in the acute pain setting remains somewhat investigational and is therefore limited to institutions involved in ongoing clinical trials or in the hands of investigators with significant experience with its use. Additionally, the intravenous preparation may not be readily available in many institutions.

### Deciding Mode of Administration

**INTRAVENOUS ADMINISTRATION.** After deciding which opioid to prescribe, the second decision is the mode of administration. Intravenous options include on-demand (as-needed) dosing, fixed-interval administration, continuous infusion, or PCA. To provide optimal analgesia, opioids should be administered in a manner that maintains a steady-state serum concentration. For moderate to severe pain, as-needed or on-demand administration generally does not provide adequate analgesia. A significant delay can occur from the time that the child is recognized as being in pain until the medication is drawn up, administered, and has time to take effect. The optimal mode for the delivery of opioids to provide analgesia remains PCA, which allows the patient to administer a preset amount of opioid at specific intervals. These devices may be used in children as young as 5 to 6 years.

Appropriate education is required before instituting a pediatric PCA program to avoid potential adverse effects and the ineffective use of this technique. Decisions regarding PCA include the opioid to be used, the bolus dose, the lockout interval (the time that must elapse between doses), whether a continuous or basal infusion will be used in addition to the intermittent bolus doses, and the maximal total hourly dose. Although any opioid can be used with PCA, most of the reported experience is with morphine. A common starting point for the bolus dose is 0.02 mg/kg every 10 minutes as needed; however, this level may need to be adjusted based on the child's previous exposure to opioids or comorbid disease processes.

Before initiating PCA for acute pain, effective analgesia must be obtained. To accomplish this task, an opioid is titrated in incremental intravenous bolus doses (morphine 0.02 mg/kg every 5 minutes) until the desired level of analgesia is obtained. After this level is reached, the PCA device is started. A frequent problem is that children are provided adequate analgesia in the recovery room after a surgical procedure and are then discharged to the floor only to have a significant amount of time expire until the PCA pump arrives. When this circumstance happens, the child will need to repeatedly push the PCA button to re-establish an analgesic plasma concentration of the opioid. Making arrangements for the PCA pump to be delivered to the recovery room and started before the child is discharged to the floor is ideal.

One of the relatively controversial issues regarding PCA is whether to include a low basal infusion rate in addition to the patient-administered bolus doses. The use of a basal infusion rate is thought by some experts to contradict the inherent safety factor of PCA; with the basal infusion rate, opioid is infused regardless of the patient's demands. Different results have been reported in children depending on the dose used for the basal infusion rate. When comparing PCA with and without a basal infusion rate of 0.02 mg/kg per hour, the pain scores showed no difference, and adverse effects were increased, including nausea, sedation, and hypoxemia in the patients who received the basal infusion rate. In a follow-up study, a low basal infusion of 0.004 mg/kg per hour (4 mcg/kg per hour) improved the sleep pattern compared with no basal infusion rate.

When used in its classic sense, PCA requires an awake, cooperative child who is able to comprehend its purpose and is able to push the button. Therefore its use may be limited in certain children because of underlying illness or diminished cognitive capabilities. An additional controversy regarding PCA is whether to allow the use of nurse- or family-controlled analgesia in these patient populations. When used in this fashion, the PCA device eliminates the delay in opioid administration that may occur as the nurse signs out the medication and draws it up. Equivalent levels of analgesia and equivalent opioid consumption are observed when comparing PCA with nurse-controlled analgesia, although the inherent safety factor of PCA is lost.

#### **NONINTRAVENOUS ADMINISTRATION OF OPIOIDS.**

Although most moderate to severe acute pain is treated with intravenous opioids, certain situations limit or preclude intravenous administration. Nonintravenous routes include subcutaneous, oral, transdermal, and transmucosal (sublingual, buccal, intranasal, rectal, and inhaled) administration. Many of these techniques are considered investigational and are therefore likely to have a limited role in the day-to-day management of acute pain in children. Given its rapid absorption and the ability to achieve a quick clinical effect without intravenous access, the use of intranasal fentanyl has been a popular agent and route of administration in the management of acute pain in the emergency department. The intramuscular route is strictly avoided because variability in uptake and absorption leads to

erratic serum levels and ineffective analgesia. Additionally, children often deny pain to avoid a shot.

The simplest and cheapest of the nonintravenous routes remains oral administration. Although this route is frequently chosen for outpatients, its use remains limited in hospitalized patients. The oral administration of the weak opioids, including codeine and oxycodone, is a viable option even in hospitalized children provided that the pain is considered mild to moderate. Other opioids such as morphine, hydromorphone, and methadone can be administered orally. Decreased oral bioavailability necessitates the use of larger doses. Regardless of the opioid chosen, problems that arise with oral administration include a delay in the onset of action, the need for larger doses because of decreased bioavailability, and underlying medical or surgical problems that preclude the use of the gastrointestinal tract. Although the use of these opioids through the oral route is common practice for controlling cancer-related pain in the outpatient setting, information regarding this technique for controlling moderate to severe pain in the inpatient setting is limited. A novel technique termed *oral PCA* (hydromorphone or morphine) has been used to treat acute pain related to medical illnesses.

Subcutaneous administration has generally been reserved for children with terminal cancer. However, studies suggest its efficacy for controlling acute postoperative pain. Subcutaneous administration is associated with significantly fewer hypoxemic events (oxygen saturation less than 90%) than intravenous administration. When compared with intermittent intramuscular administration of opioids, 95% of nurses preferred the subcutaneous route and 74% stated that they would give morphine more readily through the subcutaneous route compared with intramuscular administration. For subcutaneous administration, a butterfly needle or a standard intravenous catheter is inserted into the subcutaneous tissue of the thigh, abdominal wall, subclavicular area, or deltoid. Dosing regimens such as basal infusions, continuous infusions, and boluses are the same as for intravenous administration. Although the plasma concentration of the opioid during subcutaneous administration are equivalent to those achieved with intravenous administration, the peak plasma concentration is not achieved as rapidly after subcutaneous administration compared with intravenous bolus dosing. The fluid volume used to deliver the opioid should be restricted to a maximum of 1 to 3 mL/hour. The site should be changed at 7-day intervals or sooner if erythema or local tissue reaction is noted. Several different opioids can be administered subcutaneously, including morphine, hydromorphone, and fentanyl. Methadone can cause significant tissue reaction with erythema and is not recommended for subcutaneous administration.

#### **Adverse Effects of Opioids**

Several adverse effects may occur with opioids that interfere with the delivery of effective analgesia (Table 54-3). Respiratory depression is directly related to potency and occurs with all opioids; equi-analgesic doses of opioids produce equivalent degrees of respiratory depression. Factors that may predispose children to

**Table 54-3** Adverse Effects of Opioids and Treatment Strategies<sup>a</sup>

ADVERSE EFFECT	TREATMENT STRATEGY
Respiratory depression	Stop opioid Airway management as needed Naloxone 1 mcg/kg every 3 min up to 10 mcg/kg; consider use of infusion for longer acting opioids
Constipation or ileus	Stool softeners Cathartic agents Motility agent (metoclopramide)
Nausea or vomiting	Phenothiazine (promethazine 0.25 mg/kg up to 12.5 mg) 5-HT <sub>3</sub> antagonist: ondansetron (0.15 mg/kg up to 4 mg)
Pruritus	Diphenhydramine (0.5 mg/kg up to 12.5 mg) Change opioid

<sup>a</sup>Monitoring respiratory status is suggested when opioids are used with phenothiazines because of the possible potentiation of opioid-induced respiratory depression.

#### **BOX 54-4** Patients at Risk for Opioid-Related Adverse Effects

1. Infants younger than 6 months
2. Patients with severe underlying systemic illness:
  - a. Cardiorespiratory dysfunction
  - b. Hepatic insufficiency
  - c. Renal insufficiency
  - d. Altered mental status
  - e. Airway obstruction
  - f. Central or obstructive apnea
3. Concomitant use of other medications:
  - a. Barbiturates
  - b. Phenothiazines
  - c. Benzodiazepines

The presence of the problems mentioned does not preclude opioid administration. When opioids are used in these patients, 50% of the usual dose is recommended in addition to continuous monitoring of cardiorespiratory function.

respiratory depression include extremes of age, severe underlying systemic diseases, pre-existing altered mental status, and the addition of other medications that potentiate the central respiratory depressant effects of opioids (Box 54-4). The presence of these comorbid problems does not preclude the use of opioids; however, initial doses should start at approximately 50% of the usual regimens, and the monitoring of cardiorespiratory function is suggested to help provide the early identification of cardiovascular and respiratory compromise.

Respiratory depression may also occur in the setting of renal failure in children receiving morphine. Whereas morphine undergoes primarily hepatic metabolism, the metabolite M6G is dependent on renal excretion. M6G possesses respiratory depressant activity and analgesic activity several times that of the parent compound. In children with altered renal function, an opioid such as hydromorphone, which does not have active metabolites, may be a safer alternative.

In children who develop respiratory depression, the first priority remains airway management with provision of supplemental oxygen or bag-mask ventilation as needed followed by the incremental administration of naloxone. Because several different dilutions of naloxone are available, particular attention must be paid to the individual ampule. Standard pediatric ampules contain either 0.4 or 1.0 mg/mL. Naloxone should be administered in incremental doses of 1 to 2 mcg/kg, repeated every 3 minutes as needed, up to a total dose of 10 mcg/kg. The administration of small incremental doses is suggested because reversing respiratory depression is possible without reversing analgesia. Using the doses recommended in many reference texts (10 to 15 mcg/kg) will result in a precipitous reversal of all analgesia, which may lead to agonizing consequences for the patient. These large doses are used only for reversing opioid effects in the setting of an acute overdose. After respiratory depression is reversed, continued monitoring of the patient is important because the half-life of naloxone is only 20 to 30 minutes compared with 2 to 3 hours or longer for many opioids, including morphine, meperidine, or hydromorphone. Although 2 longer-acting opioid antagonists (naltrexone and nalmefene) are available, information regarding their use in children is limited.

Although the life-threatening effects of opioids such as respiratory depression are most worrisome, more commonly, the non-life-threatening problems interfere with the delivery of effective analgesia. Inadequate analgesia may occur in younger children and infants because of physicians' unfounded fears of addiction. The incidence of addiction in children receiving opioids for acute pain management is exceedingly rare. Physical dependence follows the prolonged administration (more than 5 to 7 days) of opioids and sedative agents. These problems should not limit the use of opioids but rather emphasize the need to have protocols in place that outline the options for preventing and treating such problems.

Additional adverse effects of opioids include sedation, constipation, pruritus, nausea, and vomiting. Stool softeners given concurrently with opioid therapy may help prevent constipation. Although



tolerance to some of the other adverse effects of opioids such as sedation may develop, tolerance to the opioids' effects on gastrointestinal motility does not occur. Cathartic or osmotic agents (Milk of Magnesia, 70% sorbitol) may be needed for refractory cases or when constipation has already developed. Preventing constipation with a daily dose of Milk of Magnesia during outpatient opioid therapy is easier than treating the problem after it has occurred. Children receiving opioids for acute pain are frequently inactive and may have less than normal fluid intake, which only serves to aggravate the problem of constipation. New opioid antagonists that do not cross the blood-brain barrier may soon be available. These agents may be effective in eliminating the effects of opioids on gastrointestinal motility while preserving their analgesic activity. These agents may be available in the near future for both oral and intravenous administration.

Nausea and vomiting are probably the most bothersome of the non-life-threatening adverse effects of opioids. There are 3 different mechanisms that may be involved: a direct stimulation of the central chemoreceptor trigger zone of the medulla, decreased gastrointestinal motility and increased pyloric tone, and sensitization of the vestibular apparatus. Regardless of the mechanisms involved, treatment is primarily symptomatic and may include phenothiazines, metoclopramide, 5-HT<sub>3</sub> antagonists such as ondansetron, or a new class of drug, the neurokinin-1 receptor antagonists, aprepitant, which has recently been introduced for clinical use. Phenothiazines such as promethazine are available in a preparation for rectal administration, and ondansetron has recently been released in a wafer that dissolves in the mouth. Although most experience is with the phenothiazines, adverse effects may occur with these agents, including dystonic reactions, lowering of the seizure threshold, alteration of cardiac repolarization, and potentiation of opioid-induced respiratory depression. When the phenothiazines are used to treat nausea in children receiving PCA, stopping the PCA for 30 minutes before and after the dose may be appropriate because phenothiazines potentiate opioid-induced respiratory depression. Other options to treat nausea and vomiting include metoclopramide (0.1 mg/kg up to 10 mg) or 1 of the serotonin antagonists (ondansetron, dolasetron, or granisetron). Ondansetron is administered intravenously in a dose of 0.15 mg/kg (maximum of 4 mg) intravenously every 6 hours as needed. Unlike the phenothiazines, ondansetron, dolasetron, and granisetron do not cause sedation or potentiate the respiratory depressant effects of opioids. If nausea or vomiting persists despite symptomatic treatment, then changing opioids may be helpful. No particular opioid seems to cause a higher incidence of nausea and vomiting.

Pruritus may occur as an isolated symptom or in association with urticaria. The mechanisms of opioid-induced pruritus are multifactorial and include a direct central effect as well as histamine release. Strategies to control pruritus include administering antihistamines such as diphenhydramine (0.5 mg/kg up to 12.5 mg, preferably PO to avoid excessive drowsiness) or changing to another opioid. The sedative properties

of diphenhydramine may also potentiate opioid-induced sedation. When pruritus is not controlled with antihistamines, changing to another opioid with less histamine-releasing properties may be helpful. For intravenous use, these substances include hydromorphone, oxycodone, and the synthetic agent fentanyl. Given the higher incidence of pruritus in some patient populations (adolescents, patients with sickle cell disease), initiating PCA with hydromorphone in these patients is suggested. Children with severe skin diseases such as cutaneous involvement of graft-versus-host disease may be particularly likely to develop opioid-induced pruritus. In this group of children, using fentanyl may be necessary to provide analgesia and prevent pruritus. In such circumstances, the physician should consult with the anesthesiology department or pain service for dosing guidance.

### Regional Anesthetic Techniques

Regional anesthetic techniques such as neuraxial blockade (epidural or spinal-intrathecal analgesia) or peripheral nerve blockade can be continued into the postoperative period to provide effective analgesia while preventing the potential adverse effects associated with parenteral opioid therapy. The administration of local anesthetic agents into the epidural or intrathecal space provides profound analgesia; however, undesirable side effects of the use of high concentrations of local anesthetics include blockade of the sympathetic nervous system with hypotension, urinary retention, and blockade of motor function. Epidural and intrathecal opioids can provide intense, segmental, localized analgesia without sensory, motor, or sympathetic nervous system effects. However, adverse effects of neuraxial opioids may include respiratory depression, nausea, pruritus, sedation, and urinary retention. As a result, a combination of low-dose epidural local anesthetics and opioids is commonly used to take advantage of their synergistic effects and limit the side effects of each. Fentanyl, hydromorphone, and morphine are commonly used neuraxial opioids, whereas bupivacaine and ropivacaine are the most commonly used local anesthetic agents.

The lipid solubility of the opioid predicts its clinical behavior. Fentanyl is very lipid soluble, penetrating the dura and rapidly binding to spinal cord opioid receptors, producing a fast onset of action but a short duration of action. Significant vascular absorption of fentanyl also occurs, decreasing its epidural effect and reducing its advantage over parenteral administration. Morphine is lipid insoluble and has a slower onset of action but a much longer duration of action. However, given its hydrophilic nature, morphine remains in the cerebrospinal fluid for a longer period with cephalad spread and the risks for delayed respiratory depression for up to 24 hours after neuraxial administration, thereby mandating ongoing monitoring of respiratory function during this time. Other methods of postoperative analgesia include the use of long-acting local anesthetic agents for either wound infiltration or peripheral nerve blockade. Examples of peripheral nerve blockade include brachial plexus blocks for upper extremity pain, femoral nerve blocks for femur and knee surgeries, sciatic nerve blocks for

analgesia below the knee, and intercostal nerve blocks for thoracic and abdominal surgeries. Options include the placement of a catheter to allow for continuous infusion during the postoperative period and to provide long-term analgesia for up to 3 to 5 days. Although these regional anesthetic techniques are used most commonly for the control of acute postoperative pain, they may also have applications in the treatment of acute pain of other causes. Regardless of their site of administration, attention must be paid to the dosing strategies of the local anesthetic agents to limit the potential for systemic toxicity. As such, these techniques should only be practiced by pediatric anesthesiologists with training and experience in regional anesthesia in children.

## SUMMARY

Ongoing evidence continues to demonstrate the deleterious physiologic effects of pain and the beneficial results of effective postoperative analgesia. A graded, 3-step approach is recommended with the initial therapy based on an assessment of the severity of pain. This strategy uses a combination of NSAIDs or acetaminophen, the weak opioids (codeine, oxycodone, hydrocodone), and intravenous opioids. In the setting of moderate to severe pain, acetaminophen or an NSAID should be continued on a fixed-interval basis as a means of decreasing total opioid consumption and thereby opioid-related adverse effects. Decisions regarding opioid use include the choice of opioid, route of administration, and mode of administration. For severe pain in the hospitalized child, PCA is the preferred mode of administration. Although the intravenous administration of opioids remains the primary route of administration for moderate and severe pain in the hospital setting, future formulations and developments may allow for the increased use of nonparenteral routes. Regional anesthetic techniques are frequently used to control acute postoperative pain, although these techniques may also be applicable to treat acute pain of other causes. In addition to the appropriate choice of medications, an integral aspect of pain management is the assessment of the child's pain, of the response to therapy, and of the need to increase or decrease the level of analgesia.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Anesthesia and Your Child* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)

### Medical Decision Support

- *Children's Hospital Eastern Ontario Pain Scale (CHEOPS)*, Children's Hospital Eastern Ontario (www.anes.ucla.edu/pain/assessment\_tool-cheops.htm)
- *Pediatric Pain Management for Primary Care, 2nd ed* (book), American Academy of Pediatrics (shop.aap.org)
- *Self-Report Scales for Children* (Web page), American Medical Association (www.ama-cmeonline.com/pain\_mgmt/module06/03pain/03\_01.htm)

- *The Revised FLACC Observational Pain Tool: Improved Reliability and Validity for Pain Assessment in Children with Cognitive Impairment* (article), *Pediatric Anaesthesia*, Vol 16, Issue 3, 2006
- *Visual Analog Scale* (scale), Agency for Healthcare Research and Quality and Texas Cancer Council (www.partnersagainstpain.com/printouts/A7012AS1.pdf)
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## Chapter 55

# MANAGING CHRONIC PAIN IN CHILDREN

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## DEFINITIONS AND PATHOPHYSIOLOGIC MECHANISMS

The International Association for the Study of Pain defines pain as an “unpleasant and emotional experience with actual or potential tissue damage, or described in terms of such damage.” The experience requires a complex interaction of multiple processes of the nervous system: *transduction*, *transmission*, *modulation*, and *perception*. The conversion of a noxious

stimulus (mechanical, chemical, or thermal) into electrical energy by a peripheral nociceptor (free afferent nerve ending) is called *transduction*. Tissue inflammation with the release of prostaglandins, bradykinin, and a variety of other mediators can augment the receptiveness of the peripheral nerve endings. Nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and local anesthetics can reduce or inhibit the response of the nervous system at this level. The next phase of nociception is characterized by the *transmission* of information to the cell bodies of the nociceptors, the dorsal root ganglia, and to the dorsal horn of the spinal cord. Initial sharp pain is propagated through faster A- $\delta$  fibers, whereas a second, more delayed, dull, throbbing pain is transmitted through slower C fibers. Local anesthetics and  $\alpha_2$  agonists can effectively interrupt transmission. From the dorsal horn of the spinal cord and along the spinothalamic tract, excitatory neuropeptides such as glutamate (at the N-methyl-D-aspartate [NMDA] receptor) and substance P (at the neurokinin-1 receptor) can modulate the message such that it is facilitated or augmented.

Simultaneously, endogenous descending analgesic systems dampen or completely obliterate the nociceptive response. Local anesthetics,  $\alpha_2$  agonists, opioids, NSAIDs, tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and NMDA receptor antagonists can interfere with the nociceptive response at the level of modulation. Finally, when reaching the central nervous system, pain is *perceived* as an individualized unpleasant and emotional experience.

Psychological factors, such as attention, anticipation of pain, and the individual's emotional state, can influence the experience. Cognitive behavioral therapy, hypnotics, sedatives, anxiolytics, opioids, and  $\alpha_2$  agonists can ameliorate or interrupt perception.

The duration of the pain at which it should be considered chronic varies, but in general, any pain that persists for longer than 3 months is considered chronic pain. Advanced neuroimaging studies in patients with chronic pain suggest that, compared with healthy individuals, their pain processing is amplified with more intense and widespread activation of brain regions. Chronic pain can be continuous or episodic and recurrent, as in migraine headaches. Pain may last for hours, days, or even weeks but then resolve completely, only to recur at a later date. Many patients with chronic pain can have adequate pain relief with their daily management but may still experience breakthrough pain. Episodes of breakthrough pain should be assessed to identify certain patterns (eg, during physical therapy, before the next dose is due). Appropriate interventions and adjustments in therapy will prevent patient frustration and noncompliance.

## TYPES OF PAIN

Two types of pain have been identified: nociceptive and neuropathic. Nociceptive pain is most commonly associated with tissue injury or inflammation. After an injury, the painful stimulus is transmitted through the normal physiologic pathways, from the peripheral nerve ending to the central nervous system. It can originate in the musculoskeletal system as somatic

pain or in the internal organs as visceral pain. Somatic pain, such as that with osteoarthritis and rheumatoid arthritis, is often described as constant and aching. Pain caused by pancreatitis or bladder spasms is typical of visceral pain. Patients likely complain of cramping and sharp pain in these conditions.

Neuropathic pain is initiated by a primary lesion or dysfunction in the nervous system. It has a central origin when it results from an injury to the central nervous system at the level of the spinal cord or above. A typical example is pain developing after a stroke. Neuropathic pain of peripheral origin involves neural structures distal to the spinal cord. These neuropathies are caused by a multitude of conditions, such as metabolic derangements (diabetes mellitus, vitamin deficiencies), viral illnesses (herpes zoster), or toxins (chemotherapeutic agents). Independent of the origin, patients typically complain of persistent, deep aching pain, constant burning sensations, and paroxysmal cramping or lancinating pain.

Nociceptive and neuropathic pain can be associated with peripheral and central sensitization. Peripheral sensitization refers to tissue inflammation augmenting the receptiveness of the nociceptor (primary hyperalgesia). Involvement of previously unaffected afferent nerve fibers in the vicinity of the original injury (secondary hyperalgesia) may be caused by central sensitization. The combination of peripheral and central sensitization leads to an increase in the magnitude and duration of pain. In the affected area, patients might experience pain caused by a normally innocuous stimulus (allodynia), an exaggerated response to a mildly noxious stimulus (hyperesthesia), and pain in neighboring areas not originally affected by injury (secondary hyperalgesia). Proposed mechanisms to explain the characteristics of neuropathic pain include a decreased threshold of the peripheral nociceptor caused by an abnormal accumulation of sodium channels, neurogenic inflammation, and ectopic discharges in C and A- $\beta$  nerve fibers. An increased responsiveness to norepinephrine might contribute to the localized autonomic dysregulation observed in some chronic pain syndromes. In the central nervous system, hyperexcitability mediated by the NMDA receptor in the dorsal horn of the spinal cord, altered modulatory responses to a stimulus, and changes in the somatosensory cortical map of the affected body area are believed to contribute to the neuropathic pain experience.

In children, the primary care physician will encounter neuropathic pain after trauma or surgery resulting in neurologic injury. Symptoms range from continued sensitivity at the site of an incision to phantom pain after amputation. In children with cancer, peripheral neuropathic pain is common, although not always persistent, after treatment with chemotherapeutic agents such as vincristine. Neuropathic pain can also be caused by direct nerve compression by a tumor or extensive lymphadenopathy. Complex regional pain syndrome (CRPS) types 1 and 2 (formerly known as *reflex sympathetic dystrophy* and *causalgia*, respectively), once thought to be rare in children, have been described in more than 1,000 children in the literature. Particularly challenging to treat is neuropathic pain



caused by a neurodegenerative disorder or after central nervous system injury because communication with the patient and therefore assessment are often limited.

## PREVALENCE

Chronic or frequent recurrent pain disproportionately affects adolescent girls. In the United States, almost 30% of adolescent girls have reported headaches, 21% stomachaches, and 24% back pain occurring more than once a week, with 53% of these girls experiencing pain in more than 1 location. Heavy abuse of nicotine, caffeine, and alcohol was associated with these symptoms, whereas parent and teacher support was found to be protective. The prevalence of migraine headaches has been estimated to be 10% in children and up to 28% in adolescents. Children with chronic pain are more often overweight and obese than their peers, a finding associated with limitations in vigorous activities. Obese children with chronic pain experience a greater reduction in health-related quality of life than those with either one of these afflictions alone.

Daily pain in children and adolescents with life-threatening oncologic or infectious diseases such as HIV is common. Prevalence of pain is also high in patients with congenital diseases such as cystic fibrosis and Marfan syndrome, and in chronic neuromuscular or neurodegenerative processes. Intense focus on treatment of the primary disease process can result in a neglect of the illness-associated pain.

Health care use is variable: approximately 50% of children and adolescents with back pain, limb pain, and abdominal pain seek medical advice, whereas only 30% do so for headaches. Medication use, on the other hand, is much more common for headaches than for other pains. Increasing age and greater intensity and longer duration of pain, but not the frequency of pain, will bring the patient in contact with health care providers.

## EFFECT ON PATIENT AND FAMILY

Chronic pain affects the child, the child's daily life, other members of the family, and the social environment. Following the World Health Organization's model of impact of disease, the experience of chronic pain can be divided into 4 areas: *disease* or *disorder*, *impairment*, *disability*, and *handicap*. *Impairment* is assessed by taking a history and performing a physical examination. Reported symptoms such as pain, edema, or joint tenderness are a measure of the severity of the impairment. The disability caused by the disease can be evaluated by asking how the child's activities in home, school, and community are affected. Restricted involvement or inability to participate in sports or to attend school is a sign of the degree of disability. School absence has been found to be a common indicator of disability in children with a variety of conditions associated with chronic pain. Disability is influenced not only by the child's severity of pain and emotional status but also by parental coping style and expectations of teachers and school administrators. Protective parents who discourage active coping behavior in their children can unwittingly promote

withdrawal from life at school. Large schools with several thousand children can be difficult to navigate for children on crutches or in wheelchairs. Hearing from parents that school administrators advise home teaching is not unusual because accommodating the child is too time consuming. Unfortunately, removal from school can lead to *handicap*, the restriction of social roles and interactions available to the child. Children who attend school, even on a part-time basis for as little as 1 class a week, are generally easier to rehabilitate than those who have completely withdrawn from school. In these cases, the pediatrician or other physician might have to become an advocate for the child.

## EVALUATION

Pain is a subjective experience. Only patients know where, when, and how much pain they are experiencing. In infants, toddlers, and children with significant cognitive impairments, pain and discomfort after a painful stimulus are assessed indirectly by measuring changes in physiologic parameters, such as facial expressions, body movement, and intensity of crying. The Face Legs Activity Cry Consolability (FLACC) scale, although initially intended for scoring postoperative pain, is now commonly used in all clinical settings for patients between the ages of 2 months and 7 years. An adaptation of the FLACC scale is available for children with cognitive impairments. Self-report measures are appropriate for children with normal cognition who are older than 3 years of age. These tools use numbers, pictures, or words to assess pain in a graded fashion from mild to severe. The most commonly used scale for preschool-aged children is the Wong-Baker faces scale, in which a cartoon smiling face gradually changes in 5 steps to a crying face. Because of their limited vocabulary, younger children are unable to describe the particular qualities associated with chronic pain. Comparative expressions such as *crushing*, *burning*, *stabbing*, or *dull* are beyond the comprehension and lifetime experiences of younger children. For older children, in addition to numerical or visual analog scales, the pediatrician can offer a list of descriptive adjectives associated with pain and ask the child to pick several terms most representative of the pain. Location of the pain can be pointed out by the child with the help of a doll, an action figure, or the drawing of an outline of the body. Because chronic pain varies from day to day and with different activities, asking the older child to keep a pain journal is also useful. Entries into the journal should be as timely as possible because recall of intensity and frequency of pain at a later date is unreliable.

## History and Physical Examination

A thorough history and physical examination are helpful in establishing the correct diagnosis and appropriate treatment plan. A complete pain history should address the following questions:

- When was pain first noted?
- Was the onset sudden or gradual?
- Did an injury precede the pain?



- Has the pain been limited to 1 area of the body, or has it migrated?
- How often is the child in pain?
- Is the pain worse in the morning or at night?
- Is sleep affected by pain?
- How is the child's mood?

Exacerbating factors should be explored because they can point to activities to be modulated or avoided. Alleviating factors are just as important because these can be integrated into a treatment protocol. Children whose pain improves when taking a hot bath might be amenable to exploring aqua therapy as a complementary therapy.

If the child has seen other health care providers with the same concerns in the past, every effort should be made to document the quality and efficacy of previous interventions used. Medications tried should be closely evaluated for adequate dosing. It is not unusual to find that adjuvant medications such as antidepressants or anticonvulsants were stopped at too low a dose to represent an adequate trial of the medication. This circumstance only contributes to long lists of medications that the patient deems to be *not* working. On the other hand, reintroducing a previously unsuccessful treatment not only is time consuming and costly but also increases the family's frustration with the health care system.

In addition to the pain history, it is important to assess the child's functioning within his or her daily surrounding. How much assistance does the child require for taking care of personal hygiene, getting dressed, attending school, or participating in extracurricular activities? Regression to a state of dependence appropriate for an earlier developmental age is common and can lead to psychological distress and heightened family conflict.

A detailed past surgical and medical history exploring for medical and psychological comorbidities should be included. The behavioral and physical development of the child in comparison to siblings and peers might provide clues to the diagnoses of chronic pain conditions. Children with diffuse musculoskeletal pain, eventually diagnosed as benign hypermobility syndrome, may have a history of significant motor development issues in early childhood, including poor coordination, general clumsiness, and difficulties with handwriting.

Family history and social history need to be reviewed. Parents of children with chronic pain have a higher incidence of anxiety, depressive symptoms, and somatoform disorders. Certain pain syndromes, such as migraines, have long been known to aggregate in families. Children with disabilities can be at increased risk for abuse and neglect.

A thorough physical examination from head to toe is invaluable in reaching a diagnosis and designing a treatment plan. Facial expressions, body position, protective behaviors, movement, and gait can provide important information. Palpation of the head in patients with chronic or recurrent headaches might reveal tender areas. Most pediatricians are familiar with facial headaches caused by chronic or recurrent sinusitis. These headaches can have a neuropathic component because of irritation of the superior and inferior orbital nerves. Tenderness at the facial foramina of the nerves can be exquisite. A similar irritation of the

occipital nerves may be seen after posterior fossa surgeries such as a cervicomedullary decompression. Patients may suffer from headaches preoperatively and may be concerned that the procedure was unsuccessful. Tenderness at the foramen opening should be sought. Treating neuropathic pain with TCAs or anticonvulsants and referring to a pain specialist for injection of the area with local anesthetics and steroids should be considered. A patient exhibiting intolerable pain a few days after an injury such as a sprained ankle might also have hypersensitivity of the skin to even the lightest touch and an erythematous, edematous, and warm extremity. Although the pediatrician will have to consider cellulitis, the pain might also be a presentation of CRPS. On the other hand, the same syndrome may be present if the patient instead had a painful, cold, and lividly discolored extremity—with deep vein thrombosis as the differential diagnosis. The findings on the physical examination will guide further studies. A patient whose pain is initially confined to the hand or elbow may protect the arm by positioning it close to the body; the shoulder is slightly elevated, the trapezius muscle is tightened, and the head might be cocked to the side. This unnatural position leads to secondary musculoskeletal pain in the shoulder and neck region, potentially requiring a different intervention than the primary pain. Children with cognitive impairments are especially difficult to evaluate but are at risk for chronic pain syndromes caused by spasticity, scoliosis, or chronic hip dislocations. A gentle, nonthreatening examination paying close attention to changes in facial expressions or muscle tone might bring the physician closer to a diagnosis. For children who have supportive equipment such as splints and wheelchairs, the physician should take a look at the child while using the equipment. A growth spurt may turn the perfectly fitting wheelchair with chest wall supports into a compression device. Chest wall pain, back pain, or even femoral nerve and brachial plexus compression syndromes may be found on examination.

### Laboratory Evaluation

Laboratory, radiographic, and scintigraphic studies are used in children with chronic pain of unclear origin to further define a differential diagnosis (see Box 55-1). Laboratory screening tests might suggest an inflammatory or infectious process, which can help in the decision-making process and determine which specialists, if any, should be consulted. Nonspecific tests (eg, antinuclear antibodies [ANAs]) can only lead to anxiety because ANAs are found in many healthy children, particularly those with viral illnesses within the previous 3 months, and are best used as confirmatory tests for a likely diagnosis of systemic lupus erythematosus or a test to indicate the frequency of ophthalmologic exams in children with juvenile idiopathic arthritis. Three-phase bone scans can show increased or decreased uptake of the radioactive tracer. Unfortunately, these findings are only of limited diagnostic value. No consistent pattern of tracer uptake has been found to be diagnostic of a specific chronic pain condition. Nerve conduction studies and electromyography can help distinguish more diffuse cases of neuropathic

### BOX 55-1 Laboratory Evaluations to Rule Out Causes of Chronic Pain

#### LABORATORY TESTS

- Complete blood count with differential, erythrocyte sedimentation rate
- Urinalysis and urine culture

#### LABORATORY TESTS INDIVIDUALIZED ACCORDING TO INDICATION

- Stool testing and culture for polymorphonuclear leukocytes, parasites, *Giardia* species antigen
- Serum chemistry profile, amylase level
- Pregnancy test, cultures for sexually transmitted diseases
- Breath hydrogen test: lactose, fructose
- Serologic testing for amoebae, *Helicobacter pylori*

#### IMAGING STUDIES INDIVIDUALIZED ACCORDING TO INDICATION

- Abdominal and pelvic sonography
- Upper gastrointestinal contrast study with small bowel testing, abdominal computed tomography
- Upper endoscopy, colonoscopy, laparoscopy

pain from a localized nerve injury or a nerve entrapment. Quantitative sensory testing and autonomic testing are offered by a variety of pain centers. The sensitivity and specificity of the results of these studies are unclear at this point. Frequently, the main purpose of laboratory evaluation is to reassure the patient, parent, and physician of the absence of organic disease.

### Consultation

For patients with significant disability caused by their painful condition and prolonged or recurrent school absences, the pediatrician should consult with a psychologist or psychiatrist and a physiatrist. The child's functional limitations and disabilities can be better assessed and documented, a possible learning disability and school avoidance might become apparent, or presence of comorbid depression interfering with successful pain management might be diagnosed.

Once the assessment is complete, an individualized treatment plan is implemented. Age-appropriate short-term goals should be combined with long-term ones, such as walking along the shallow end of a pool without a brace, participating in a summer day camp, or obtaining a driver's license.

Dependent on a patient's individual presentation, comorbidities, or family needs, referral to other specialists should be considered early, not just for further diagnostic evaluations but also for ongoing consultation such as with an adolescent medicine specialist for a teenager or a palliative care medicine specialist for a child with cancer.

## MANAGEMENT

The goal for effective chronic pain management is a reduction of the child's pain, improvement in daily functioning, and return to age-appropriate activities.

Before initiation of any therapy, it is recommended that the pediatrician explore the child's and family's expectations. Complete pain relief may not be a realistic goal, leading to disappointment and frustration in the presence of residual pain even if the child's condition significantly improves. Instead of a simple pharmacologic intervention, multimodal therapy is usually required. Multimodal therapy can include referrals to a physical therapist, psychologist, orthopedist, rheumatologist, or other health care specialist. The pediatrician has a vital role in the process of care coordination, in concert with the family. Care coordination has been shown to improve family satisfaction and reduce health care costs. As medical home professionals, pediatricians should also assess each child's specific needs for special educational and early intervention services. Awareness of local resources and of federal, state, and local requirements is essential.

All therapies need to be weighed for their risks and benefits, particularly more aggressive interventional and surgical modalities. Many pharmacologic therapies have not been evaluated in children but have instead been extrapolated from adult management. Level 1 evidence for chronic pain therapy is virtually nonexistent in children. Benefits and potential adverse effects should be discussed in detail with the parents and child, taking the child's developmental stage into consideration.

In general, the approach to treatment of chronic pain in children is more conservative. Far fewer interventional procedures are performed in children than adults. The need for sedation or anesthesia to safely perform interventions such as a sympathetic nerve block is at least partly responsible for the more conservative treatment. Pediatricians can successfully integrate many of the therapies into their practice.

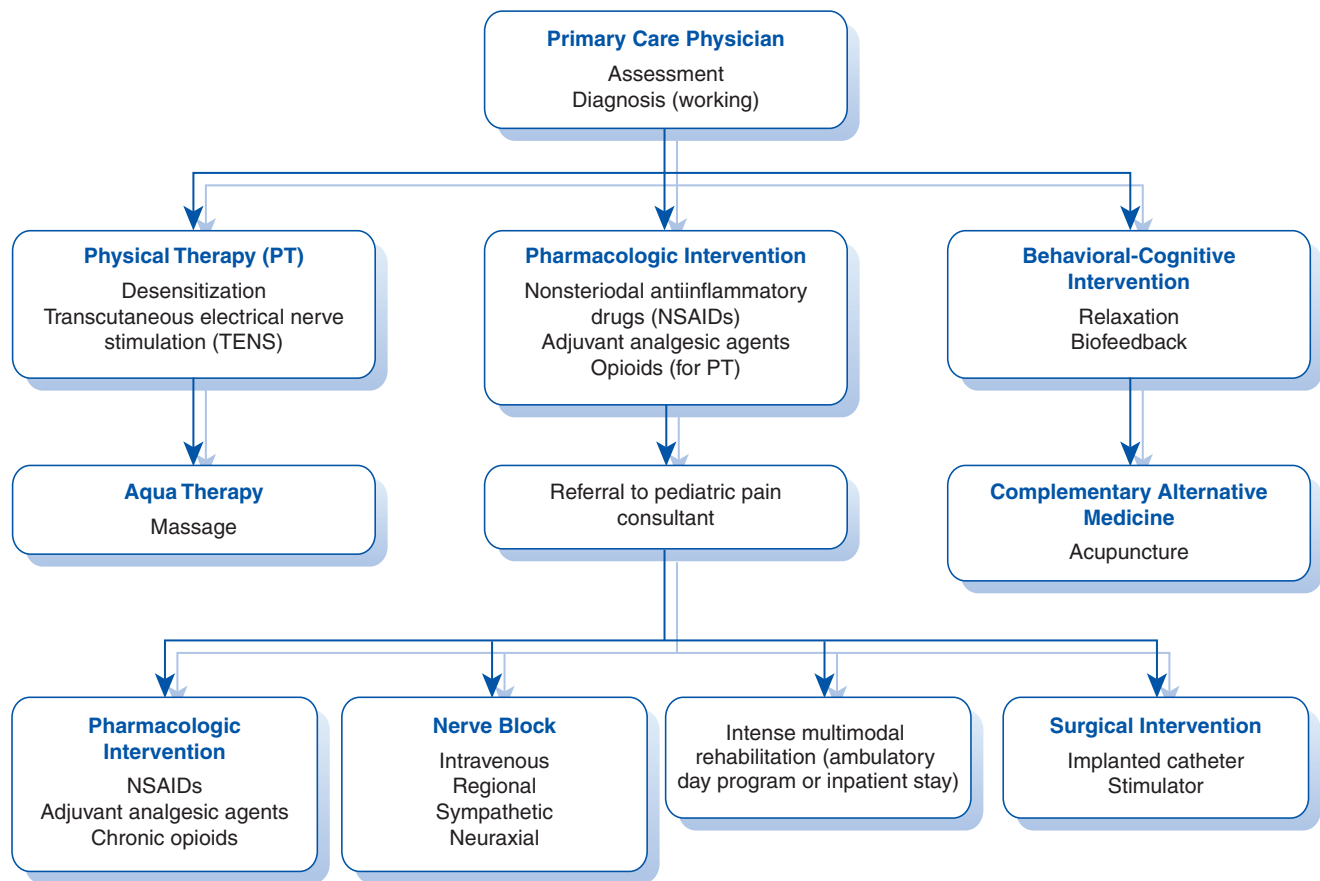
Once treatment has been initiated, continually assessing and documenting pain control and changes in function is important. Because many patients experience fluctuations in pain intensity from day to day, it is advisable to continue assessments over a longer period of time. Any positive patient and family behavior and contributions should be welcome and reinforced. Figure 55-1 highlights a possible algorithm for managing chronic pain.

### Nonpharmacologic Therapies

Ideally, nonpharmacologic therapies are fully integrated into a multimodal approach to chronic pain management in children. They should be viewed as neither something to try before "we have to get the heavy guns out" nor the last resort because "everything else we've tried has failed." Many nonpharmacologic therapies emphasize self-management skills and can improve patients' confidence in their abilities. Pediatricians can familiarize themselves with these therapies during introductory workshops or seminars offered at many professional meetings.

### Cognitive Behavioral Interventions

Cognitive behavioral interventions rely on providing age-appropriate information to the child and on the child's natural interest in imaginative play. Simple comfort measures such as swaddling, massage, and soft



**Figure 55-1** Algorithm for approach to chronic (neuropathic) pain. The pediatrician can initiate therapy. If no improvement is noted, then the patient may be referred to the pediatric pain specialist, who will continue effective modalities and add more aggressive therapy.

music are commonly used for infants, but even older children like to have their favorite stuffed animal or blanket with them in times of distress. Distraction with kaleidoscopes, bubbles, movies, or videos is appropriate for many children, even those with limited communication skills. Suggestion requires greater participation by the child. A magic item, such as a blanket, is used to lessen the pain in one area or of one procedure. The child has to be willing to be enveloped into this magic story.

Relaxation exercises offer relief to the child with chronic pain who experiences acute exacerbation of pain. Breathing techniques with deep-chest, rhythmic, or patterned breathing can be learned without professional help. Trained child-life specialists, occupational therapists, or psychologists are usually needed to explore guided imagery, progressive muscle relaxation, biofeedback, and hypnosis. Hypnosis has been found to be more effective than distraction and breathing for procedural distress in children undergoing oncologic procedures. Hypnosis and guided imagery can improve analgesia and shorten length of stay after surgery in children. Web-based cognitive behavioral interventions for patients and their families may offer an alternative to office visits in the future, potentially increasing mental health resources in areas with limited access otherwise.

### Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) consists of a battery-powered unit delivering electrical impulses to skin electrodes placed in the vicinity of the painful area. There are several theories explaining the efficacy of TENS. The gate-control theory stipulates that non-noxious impulses from TENS are transmitted through large-diameter afferent fibers. Simultaneous painful stimuli, traveling along small-diameter afferent fibers, will be suppressed at various *gates* within the spinal cord. TENS has also been suggested to activate inhibitory, descending pathways in the central nervous system because it has been associated with an increase in endogenous opioids in the serum and spinal fluid.

A variety of amplitudes, frequencies, and stimulation patterns can be programmed: low-intensity stimulation remains sensory; higher intensity will result in muscle contraction. Research evaluating the efficacy of TENS for acute and chronic pain management has been hampered by the large variety of frequencies and stimulation patterns used in studies, which makes comparisons difficult. Patients should try different patterns and intensities of stimulation to find one with which they are most comfortable. TENS appears to be most effectively used at times when pain is temporarily increased.

Adverse effects are usually limited to skin irritation, which may resolve with a switch to hypoallergenic electrode pads. TENS units should not be used together with other programmable or implantable devices (eg, pacemakers) without first contacting the manufacturers and inquiring about the safety of the combination.

### Complementary and Integrative Medicine

The use of complementary and integrative medicine (CIM) to treat chronic illness or disability is increasing in the United States. Pain was cited as the most common reason for the use of CIM in children in a recent survey. In children, the most common therapies include dietary supplements such as fish oil/omega-3 supplements, body-mind practices such as deep breathing and yoga, or body-based interventions such as massage and manipulations. The pediatrician may be asked to provide balanced advice concerning therapeutic options, although at this point only limited recommendations have been published regarding the use of CIM in the care of children with chronic illness or disability.

Acupuncture has been part of traditional Chinese medicine for more than 5,000 years. Interest in acupuncture has gradually increased during the past 30 years despite the fact that the underlying theory is different from the teachings of Western medicine: Energy (*Chi*) flows through various channels (*meridians*) in the body. Interrupting the flow leads to pathologic conditions, pain, or both. Inserting needles at particular points along the meridians can re-establish the flow of energy, thus improving or resolving the pathologic condition or pain. Acupuncture is often presumed as acceptable only to a small group of children because of the common presence of needle phobia. However, combining acupuncture and hypnosis in patients with chronic pain has been found to be highly acceptable, with a decline in anticipatory anxiety and significant improvements in pain after treatment. Further studies are necessary to assess the efficacy of acupuncture in different painful conditions.

### Pharmacotherapy

Pharmacotherapy for chronic pain includes nonopioid, opioid, and adjuvant medications. Instead of a gradual progression from nonopioids to weak opioids (disregarding the fact that at equianalgesic doses, all opioids have the same potency) and finally to strong opioids, multimodal analgesic therapy is generally preferable. The goal of such therapy is an augmentation of analgesia and a simultaneous reduction in adverse effects. Continuation of nonopioid analgesia with opioids may decrease the required dose of opioids and the incidence of opioid-related adverse effects.

Some adverse effects, such as sedation or dizziness, may be more apparent at the beginning of therapy. Initiating therapy at a low dose and titrating the dose carefully is therefore prudent. For children who attend school, weekends may be a good time to begin or augment therapy. Occasionally, an otherwise effective analgesic may require the addition of another medication to treat adverse effects such as nausea or pruritus.

Readers are referred to a more in-depth discussion of some of the listed analgesics in Chapter 54, Managing Acute Pain in Children.

### Nonopioid Analgesics

Acetaminophen has been a safe and effective analgesic for the treatment of mild to moderate pain. Administration in normal doses is well tolerated. Continuous use over many months may require lower doses. Acetaminophen is frequently an ingredient in commercially available analgesic compounds. Patients taking 1 or more acetaminophen preparations simultaneously are at risk for severe liver toxic effects.

The NSAIDs provide pain relief primarily by peripheral and central inhibition of the cyclooxygenase (COX) enzyme. Administered by the oral route, these agents are considered to be equipotent, although efficacy in individual patients may vary. The NSAIDs are particularly useful for inflammatory, bony, or rheumatic pain. Long-term administration must take the risk for gastrointestinal and renal side effects into consideration. Patients with a history of gastritis and those taking corticosteroids are generally not candidates for long-term therapy. NSAIDs that selectively inhibit one of the isoforms of COX (COX-2 inhibitors) are thought to have a lower risk for gastrointestinal adverse effects and no effect on thromboxane-induced platelet activity. In December 2004 the US Food and Drug Administration (FDA) issued a public health advisory indicating that some COX-2 inhibitors may be associated with an increased risk for thromboembolic phenomena (myocardial infarction, stroke). It remains unclear how this risk would affect children.

Whereas aspirin has largely been abandoned in pediatric practice because of its association with Reye syndrome, one aspirin-like compound with no effect on platelet function, choline-magnesium trisalicylate, continues to be prescribed in chronic pain management. The main treatment group includes patients with cancer who are experiencing bony pain and decreased platelet function. The drug is available in both liquid and tablet form and is administered twice a day. As in acute pain management, the most commonly used NSAID is ibuprofen. The limited duration of action of this drug with a required administration of 3 to 4 times a day may necessitate a switch to the longer-acting naproxen, which is administered twice a day. Dosing strategies for the most commonly prescribed nonopioid analgesics are listed in Table 55-1.

### Opioid Analgesics

Opioid analgesics are neurotransmitters that interact with several distinct receptors in the peripheral and central nervous system. The 4 major receptors are designated *mu*, *delta*, *kappa*, and *sigma*. Most currently used opioid analgesics primarily attach to the *mu* receptor. Morphine is 50 to 100 times stronger at this receptor than at the *delta* receptor. The *mu* receptor and its subspecies and the *delta* receptor are known as being related to analgesia, respiratory depression, euphoria, and physical dependence. Butorphanol attaches at a ratio of 1:4:25 at the *mu* to *delta* to *kappa* receptors.



**Table 55-1** Dosing Strategies for Frequently Used Oral Nonsteroidal Anti-inflammatory Drugs

GENERIC NAME	PEDIATRIC ORAL DOSE AND FREQUENCY	MAXIMUM ADULT ORAL DAILY DOSE	INDICATIONS	COMMENTS
Acetaminophen	10–15 mg/kg q4h	4,000 mg	Mild to moderate pain, fever	Lacks antiinflammatory activity; hepatotoxic effects at higher doses
Ibuprofen	6–10 mg/kg q6-8h	2,400 mg	Mild to moderate pain, fever, RA, OA	Oral suspension available
Naproxen	5–10 mg/kg q12h	1,000 mg	OA, RA, other rheumatic or bony pain	Oral suspension available
Salicylates (aspirin)	10–15 mg/kg q4h	4,000 mg	Mild to moderate pain, fever	Inhibits platelet aggregation, causes gastrointestinal irritability, Reye syndrome
Choline magnesium trisalicylate	8–10 mg/kg q6h	3,000 mg	Mild to moderate pain, fever	Aspirin compound that does not affect platelets

OA, osteoarthritis; RA, rheumatoid arthritis.

All opioid analgesics can be classed into agonist, antagonist, and mixed agonist-antagonist based on their receptor-binding capacities. Agonist attachment to a receptor leads to a cascade of intracellular activity, whereas antagonist attachment at the receptor does not have this response. Antagonists, such as naloxone, can competitively remove an agonist from the receptor and stop the action of the agonist. Butorphanol, a mixed agonist-antagonist, functions as an antagonist at the mu receptor and as an agonist at the kappa receptor. Therefore butorphanol, as with naloxone, can lead to withdrawal symptoms when it is used indiscriminately in patients taking mu opioids for a longer time. The most commonly used drugs are listed in Table 55-2.

Opioids are titrated to effect because response to specific opioids will vary. Tolerance with chronic administration is common, making upward dose adjustments necessary. Although mu receptor opioids are known to produce similar degrees of adverse effects, such as respiratory depression, sedation, euphoria, nausea, biliary tract spasm, and constipation, the response of particular patients will vary. If the need for dose escalation is rapid or adverse effects begin outweighing the benefits of an opioid, then the patient may be prescribed a different one, a process known as *opioid rotation*. To avoid an overdose, it is recommended to subtract 20% to 50% from the calculated equianalgesic dose when switching from one opioid to another because cross-tolerance is not completely predictable.

Most opioids for chronic pain management are administered orally. They are available as liquids of various concentrations, immediate-release tablets, and sustained-release preparations. Even for chronic pain, opioids do not always have to be administered around the clock. Providing the patient with a single dose of an opioid before physical therapy might be sufficient and might result in much better therapy. When

multiple doses of a short-acting opioid are needed throughout the day, switching to sustained-release opioids is more effective—and more convenient—because they prevent peaks and troughs in the serum and provide a better steady state. The patient's daily opioid requirement should be well known before initiating any long-acting opioids. Asking the patient and the parents to keep a journal in which they document how often a short-acting opioid was required can be helpful. This information can then be evaluated with the following questions in mind:

- Do they wake up in the middle of the night because of pain?
- Do they need medication in the middle of the school day?

Many manufacturers of sustained-release opioids provide conversion tables, but starting at lower doses than suggested and gradually titrating over several days is advisable. Immediate-release opioids can be supplemented during this period, which will avoid oversedation and drowsiness.

Methadone is currently the only long-acting opioid in liquid form. The analgesic is commonly prescribed in gradually diminishing doses for infants and children after intensive care stays with prolonged analgesic and sedative needs. Clinical guidelines for QTc monitoring during treatment with methadone have been proposed for adults but have not been formulated for children. Opioids in pill form need to be swallowed whole because chewing the pill can lead to a rapid release of the active drug and a potential overdose. Transdermal administration of the opioid is another possibility if the oral route is not available. Studies in children assessing the efficacy and safety of oral opioids lasting for up to 24 hours are lacking. Currently available long-acting opioids are listed in Table 55-3.

A child who is receiving opioids on a daily basis with generally good results might still experience an occasional escalation of pain or even daily short-lived

**Table 55-2** Dosing Strategies for Frequently Used Oral Immediate-Release Opioid Analgesics

GENERIC NAME	PEDIATRIC ORAL DOSE AND FREQUENCY	INITIAL ADULT ORAL DOSE AND FREQUENCY	INDICATIONS	COMMENTS
Codeine	0.5–1.0 mg/kg q4–6h	15 mg q4–6h	Mild to moderate pain	By mouth only. Should be avoided because effect is unpredictable. Metabolism is dependent on cytochrome P-450 enzyme, CYP2D6, which has a high degree of genetic polymorphism. Risk for overdose in ultrarapid metabolizers and no effect in slow metabolizers.
Oxycodone—immediate release	0.1 mg/kg q4–6h	5 mg q4–6h	Moderate to severe pain	Usually prescribed with acetaminophen By mouth only Less nauseating than codeine Usually prescribed with acetaminophen in adults
Morphine—immediate release	0.3 mg/kg q4–6h	5–15 mg q4–6h	Moderate to severe pain	May cause seizures in high doses Causes histamine release, vasodilation; avoid in patients with asthma. Avoid in patients with renal insufficiency because accumulation of active metabolite (M6G) may result in respiratory depression.
Hydromorphone	0.03 mg/kg q4–6h	2–4 mg q4–6h	Moderate to severe pain	
Methadone	0.1 mg/kg q6–24h (q6–8h interval: careful observation required)	2.5–10 mg q6–24h	Severe chronic pain when opioids are needed for a prolonged period Pain refractory to other opioids	QT prolongation possible in susceptible patients Toxicity caused by accumulation within 3–5 days Do not increase more often than every 5–7 days Use only in opioid-tolerant patients
Oral transmucosal fentanyl citrate		200 mcg; 200- to 1,600-mcg lozenge units	Breakthrough pain in opioid-tolerant patients	Should only be used in opioid-tolerant patients

pain, which is known as breakthrough pain. In these situations, adding a short-acting opioid to the long-acting form might be indicated, particularly when other nonpharmacologic or nonopioid measures have failed. Frequent need for a short-acting opioid in addition to the long-acting form requires a reassessment: Is the dose of the long-acting opioid too low? Is the patient more active than before therapy started? Does the patient feel only the short-acting opioid *really works*? As the serum blood level changes rapidly with the short-acting opioid, patients might experience a higher degree of euphoria and decide that only the short-acting drug helps. A frank and honest discussion of these effects can prevent unnecessary changes by the pediatrician.

Although usually reserved for oncologic and palliative care patients, long-acting opioids can be combined with intravenous patient-controlled analgesia (PCA). The PCA device is programmed without a continuous rate because the long-acting opioid provides baseline analgesia throughout the day. Intermittent

patient-initiated doses will relieve episodic pain. Occasionally, when no other intravenous fluids are administered, a low continuous rate is required to maintain the patency of the venous access.

Adverse effects associated with opioid administration, such as sedation, drowsiness, nausea, and vomiting, can be apparent during the first few days when opioids are initiated but often resolve in patients taking opioids in the long term. Increases in dose may be accompanied by a temporary recurrence of adverse effects. Reaction time can be slowed even when the patient does not subjectively feel drowsy or sleepy. Teenage drivers and their parents have to be advised of this effect. Bowel motility will be affected even after a prolonged administration of opioids, and constipation is a common complaint. Combining opioid therapy with a bowel regimen is advisable. Adolescent patients taking opioids for years may experience delayed puberty because testosterone and estrogen levels can be decreased. Hormonal supplements might be necessary.

**Table 55-3** Dosing Strategies for Frequently Used Sustained-Release Opioid Analgesics

GENERIC NAME	PEDIATRIC DOSE AND FREQUENCY	INITIAL ADULT DOSE RANGE AND FREQUENCY	INDICATIONS	COMMENTS
Morphine—sustained release	No specific pediatric dosing has been established, follow adult dosing	Dose dependent on previous opioid requirement; lowest dose: 15 mg q12h Interval: MS Contin and Oramorph q8–12h	Moderate to severe pain when opioids are needed for a prolonged period	Patient needs to be able to swallow whole pill Fatal overdose possible if chewed
Oxycodone—sustained release	No specific pediatric dosing has been established, follow adult dosing	Dose dependent on previous opioid requirement; lowest dose: 10 mg q12h	Moderate to severe pain when opioids are needed for a prolonged period	Patient needs to be able to swallow whole pill Fatal overdose possible if chewed
Fentanyl transdermal system (Duragesic)	No specific pediatric dosing has been established, follow adult dosing	Dose dependent on previous opioid requirement Lowest dose: 12 mcg/hr Patch needs to be changed q72h	Moderate to severe pain when opioids are needed for a prolonged period	Initial dose should not exceed 25 mcg/hr Unauthorized simultaneous use of multiple patches can lead to fatal overdose

Once patients have received opioids on a regular basis for more than a week to 10 days, they cannot simply stop using these drugs; they need to be weaned off of them. The body has developed a physical tolerance, receptors have changed in response to the long-term administration, and immediate discontinuation of drug therapy would lead to withdrawal symptoms. Decreasing the total dose by 10% every day to every other day is a common approach to weaning opioids, although this area is one of continuing research. For children who have received opioids for weeks or months, this approach might be too aggressive. Weaning just once or twice a week might be more adequate, especially in an outpatient setting where symptoms of withdrawal might be missed. Parents should be informed that signs of withdrawal include subtle ones, such as yawning, lacrimation, rhinorrhea, nasal stuffiness, or insomnia, as well as the more commonly associated, extreme ones of restlessness, chills, tachycardia, hypertension, nausea and vomiting, crampy abdominal pains, and diarrhea. When the parent reports subtle signs of withdrawal, stopping the weaning process for a few days before resuming it at a slower rate is best. More severe signs of withdrawal require a return to a higher dose, stabilization at the higher dose for a few days, and then return to a slower rate of continued weaning.

#### **Controlled Substances, Patient Care, and the Law**

The use of opioids for chronic pain has been controversial. Some authors have argued that opioids should never be used for chronic, nonmalignant pain because their use would only lead to dependency, tolerance, and dose escalations. Clearly, daily use of opioids always results in physical dependence, although not psychological addiction, tolerance, and a potential

need for a higher dose. The use of opioids may be justified when it can be demonstrated that the pain has been reduced and the patient's function has significantly improved. When initiating opioid therapy, the status of the patient should be clearly documented, and therapy should be objectively assessed later. The physician is advised to sign contracts with the families detailing who can write prescriptions for opioids, where these prescriptions can be filled, whom to contact when the prescribed doses are inadequate, and what happens if patients run out of medications early or lose their medications. The individual patient's and the family's risk for abuse and diversion of medications needs to be reviewed carefully. State medical boards and the US Drug Enforcement Administration provide further information on their respective Web sites.

#### **Adjuvant Analgesics**

Adjuvant analgesics are most commonly used in the treatment of chronic neuropathic pain. Few randomized controlled studies have examined the efficacy of these analgesics in chronic pain management, although they have been used for at least 20 years. Experiences in adults have been extrapolated to administration in children because no comparable studies in children have been conducted. Physicians accustomed to the efficacy of NSAIDs or opioids in acute pain management are often surprised by how little and varied improvement these medications seem to provide (for every 100 patients taking antidepressants for chronic pain, only 30 experience at least a 50% reduction in pain).

In adult patients, there are FDA indications for several medications for particular pain syndromes, such as postherpetic neuralgia, diabetic peripheral neuropathy, and fibromyalgia. None of the adjuvant analgesics

has specifically been approved for the treatment of chronic pain in children. Thus all current use remains off label. The child and the family need to be advised that treatment often involves trial and error. Gradual titration to effect is recommended to limit early adverse effects on orthostasis or cognition, effects that may resolve with time.

**ANTICONVULSANTS.** Anticonvulsants suppress neural hyperexcitability, which might explain their effectiveness in chronic pain management. Gabapentin has been indicated for the adjunctive treatment of partial seizures in children as young as 3 years. Therefore, the experience in children with this particular drug is more extensive than with others in this class. Gabapentin is a widely used adjunctive analgesic in children and is usually well tolerated. The most common adverse effects are dizziness, somnolence, ataxia, fatigue, and weight gain. Weight gain can be particularly concerning in the treatment of lower extremity pain because it may complicate the rehabilitation process. Therapy is usually initiated on a once-a-day basis and advanced up to 3 doses per day if necessary. Doses can be increased every 2 to 5 days. Many physicians begin with nighttime dosing and also increase the nighttime dose first so that potential sedation and dizziness may be less apparent. If patients experience an improvement in pain relief, doses can be raised as long as no significant adverse effects occur. The patient and family should be told that these medications do not work immediately; a week might pass before patients note any improvement at all. Pregabalin is currently indicated for treatment of pain caused by diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia in adults, but it is commonly used off label for other neuropathic pain disorders. Experience in children continues to be limited. It remains to be seen whether initial reports of pregabalin treatment of dysautonomic crisis can be extended to an amelioration of autonomic symptoms commonly associated with painful congenital connective tissue disorders. Adverse effects and toxicity have limited the use of other anticonvulsants. Lamotrigine has been associated with Stevens-Johnson syndrome, tiagabine with seizures, and topiramate with hyperthermia. Older anticonvulsants such as phenytoin, carbamazepine, and valproate require periodic monitoring for potential end-organ toxic effects.

**ANTIDEPRESSANTS.** Evidence of the efficacy of antidepressants in chronic pain management has been best for agents that have a local anesthetic-like effect on neural sodium channels and interfere with the reuptake of norepinephrine. These drugs include TCAs such as nortriptyline and amitriptyline and SNRIs such as duloxetine and milnacipran. SSRIs seem to be less effective but are helpful when associated depression, sleep disturbance, and anxiety are present.

All antidepressant drugs carry an FDA-required boxed warning label alerting health care providers to an increased risk for suicidality (suicidal thinking and behavior) in children and adolescents being treated with these agents. When initiating antidepressant therapy, the FDA advises health care providers to evaluate children and adolescents every week for the first 4 weeks, then every other week for the next 4 weeks, and again at 12 weeks to assess for potential mood changes.

Other side effects of TCAs include dry mouth, constipation, urinary retention, sedation, and cardiovascular effects such as hypotension and disturbances of conduction. Rare reports have surfaced of sudden death associated with TCA therapy. A baseline electrocardiogram should be obtained to identify children with a pre-existing conduction defect. The side-effect profile varies between the drugs: Nortriptyline has fewer anticholinergic side effects than amitriptyline, whereas amitriptyline is the more sedating. Sedation can be turned into a therapeutic advantage when treating patients who complain of nighttime awakenings caused by pain. Patients should be advised to avoid high-calorie drinks to relieve the sensation of dry mouth because they can contribute to undesirable weight gain.

As is the case with anticonvulsants, pain relief is delayed and cannot be expected for at least a week or more. No established correlation exists between plasma concentration of TCAs and analgesic efficacy. Routine measurement of plasma drug levels is rarely indicated. If use of the drug needs to be discontinued, then the dosing should be tapered over a few weeks to avoid irritability and agitation.

**MEMBRANE STABILIZERS.** Membrane stabilizers are drugs that interfere with the ionic fluxes required for initiation and conduction in peripheral and central neurons. These medications are available in a variety of applications: intravenous lidocaine, oral mexiletine, and transdermal lidocaine patches. All of these drugs are thought to be particularly helpful in the treatment of neuropathic pain. Intravenous lidocaine and oral mexiletine are second-line therapy usually reserved for patients who show insufficient improvement after therapy with other adjuvants such as anticonvulsants or antidepressants. Adverse effects include nausea, vomiting, sedation, and ataxia, which limit the usefulness of membrane stabilizers. Initiation of this therapy will most frequently occur after consultation with a pediatric pain specialist; however, the application of transdermal lidocaine might be considered by the pediatrician. As with many therapies, these patches have not been specifically evaluated in children. Their indication, at this point, is solely for postherpetic neuralgia, but they are useful in a variety of other localized neuropathic pain conditions associated with allodynia and hyperesthesia. The patches are applied to the area for 12 continuous hours a day. Cutting patches to size and gradually moving two cut strips from the periphery to the center of a hyperesthetic area may permit therapy in patients who initially cannot tolerate the direct application of a patch in a sensitive area. Adverse effects are usually limited to local irritation because the systemic absorption of lidocaine through intact skin is low. Parents should be warned, however, to keep the patches out of reach of small children because overdose can occur when the patches are chewed or swallowed. At least 95% or 665 mg of lidocaine will still be present in the patch after 12 hours of application.

**ALPHA AGONISTS.** Drugs such as clonidine are centrally and peripherally sympathoplegic. They stimulate  $\alpha$ -adrenoreceptors in the brainstem, resulting in reduced sympathetic outflow from the central nervous system, and they stimulate prejunctional receptors on peripheral



neurons, reducing norepinephrine release. Epidural use of clonidine has been found to be effective for neuropathic pain syndromes. Transdermal clonidine prophylaxis has also been evaluated as an adjunct, preventing withdrawal symptoms in children who were sedated in the intensive care units for a prolonged period. Adverse effects may include sedation, bradycardia, and hypotension. A list of the most frequently used adjuvant analgesics can be found in Table 55-4.

### Interventional Therapy

If the patient's condition rapidly deteriorates or does not improve after a period of several weeks despite a

multidisciplinary approach, including psychological and pharmacologic interventions and physical therapy, the pain specialist might consider a regional anesthetic. A regional anesthetic may be particularly helpful if the painful condition is limited to a single extremity, as is often the case in CRPS type 1. Interventional therapy extends from the injection of a single peripheral nerve with local anesthetics and steroids, to a more extensive intravenous regional or sympathetic nervous system block of an extremity, and finally to a hemi-body neuraxial block through an epidural injection. Most young children will require sedation for these procedures; thus, pediatricians

**Table 55-4** Dosing Strategies for Frequently Used Adjuvant Analgesics

GENERIC NAME	PEDIATRIC DOSE AND FREQUENCY	INITIAL ADULT DOSE RANGE AND FREQUENCY	INDICATIONS	COMMENTS
Gabapentin	5–60 mg/kg divided into 2–3 daily doses Start at 5 mg/kg for <20 kg, 100 mg for <50 kg, 300 mg for >50 kg Titrate q1–3d as needed	300 mg Titrate 300 mg/day q1–3d, up to 3,600 mg divided 3 times daily	Postherpetic neuralgia Neuropathic pain, migraine prophylaxis	CNS effects (somnolence, dizziness, etc) Do not stop abruptly—risk for seizure in susceptible patients
Pregabalin	No specific pediatric dosing established	50 mg; 50 mg tid or 75 mg bid Titrate up to 300 mg/day in 1 wk as needed	Postherpetic neuralgia, diabetic peripheral neuropathic pain, neuropathic pain, fibromyalgia	CNS effects (somnolence, dizziness, etc) Do not stop abruptly—risk for seizure in susceptible patients Discontinuation syndrome
Topiramate	No specific pediatric dosing established	25 mg Titrate to 50 mg q12h in 4 wks as needed	Migraine prophylaxis	Risk for metabolic acidosis, oligohidrosis, hyperthermia
Amitriptyline Nortriptyline	10–25 mg qhs Titrate up to 2–3 mg/kg (max. 150 mg), qhs or twice-daily dosing	25–50 mg qhs Titrate up to 150 mg/day	Neuropathic pain, chronic pain	Sedation, anticholinergic, and cardiac effects, ECG recommended before initiation of therapy
Paroxetine	No specific pediatric dosing established	20–60 mg/day	Diabetic peripheral neuropathic pain, fibromyalgia, chronic musculoskeletal pain	Hepatic toxicity, discontinuation syndrome
Doxepin	12.5 mg/kg qhs Titrate up to 100 mg/day in 1–3 doses	75 mg, divided in 1–3 doses Titrate up to 150 mg/day	Neuropathic pain, chronic pain	Do not use in children <12 years of age
Trazodone	No specific pediatric dosing established	50 mg qhs Titrate up to 200 mg qhs or 400 mg/day in divided doses	Chronic pain	Risk of priapism—avoid in male patients

CNS, central nervous system.

should refer the patient to a pain management facility that is capable of providing this kind of care.

### **Intravenous Regional Block (Bier Block)**

Intravenous regional anesthesia is indicated for painful conditions of the arm below the elbow or the leg below the knee. An intravenous cannula is inserted in a distal vein in the limb, and a tourniquet is applied to the upper arm or thigh. Before inflation of the tourniquet, the limb may be exsanguinated (blood removed) by wrapping the distal part of the limb with an elastic bandage. This procedure can increase the efficacy of the block but may be poorly tolerated in patients with chronic pain. Local anesthetic and ketorolac infusion have been found to be efficacious in some children with CRPS type 1. Complications, although rare, can occur if the tourniquet suddenly deflates soon after the local anesthetic has been injected. The sudden increase in serum level of the local anesthetic will lead to the well-known neurologic adverse effect of an overdose: dizziness, tinnitus, loss of consciousness, and convulsions. Serious cardiac adverse effects are rare but can occur if bupivacaine is the local anesthetic or if convulsions are inadequately treated.

### **Sympathetic Blocks**

Sympathetic blocks are injections of local anesthetic into a particular area of the ganglionic chain of the sympathetic nervous system: at the stellate ganglion for the upper extremity and at the lumbar sympathetic plexus for the lower extremity. The pain specialist may use ultrasound, fluoroscopy, or computed tomography for guidance in the placement of the block. Indications for this intervention are chronic pain syndromes such as CRPS type 1, in which the sympathetic nervous system may contribute to the painful condition. After the block, the patient experiences a warming in the extremity, and the physician can register a measurable increase in temperature in the extremity, which helps in assessing the efficacy of the block in multiple ways. If temperature is increased and the patient reports pain relief, then the pain is considered as sympathetically maintained. If the pain relief lasts beyond the expected duration of the local anesthetic block, then the injection will be considered not only diagnostic but also therapeutic. Depending on the duration of pain relief, the block can be repeated. Repeated injections might provide progressively longer periods of pain relief. If the injection resulted in an increase in temperature, but no improvement in pain occurred, then the condition has to be considered sympathetically independent. Repeating the block has no benefit. If the injection did not result in a temperature change in the extremity the block was technically inadequate. Even in this condition, the patient might report an improvement in pain, a so-called placebo response, a situation the specialist will have to contemplate when deciding on further interventions. Lumbar sympathetic blocks in children with CRPS can lead to measurable reductions in allodynia, although the individual response varies with almost as many patients reporting increases in overall pain scores as decreases.

Adverse effects of sympathetic blockade include typical findings of Horner syndrome in case of a

stellate ganglion block: drooping of the eyelid, conjunctival injection, and stuffy nose on the injected side. Hoarseness can also occur. These effects will persist only for the duration of action of the injected local anesthetic. Other adverse effects include local anesthetic overdose after unintentional intravascular injection or injury to adjoining structures such as a pneumothorax. If a sympathetic nerve block has repeatedly provided good analgesia but was of insufficient duration, then a surgical sympathectomy may be considered.

### **Implanted Devices**

In children, therapeutic interventions will only occasionally progress to the invasiveness of an implanted device. Pediatricians are already familiar with these forms of therapy as an advanced mode in the management of spasticity in a child with cerebral palsy. An intrathecal catheter is surgically implanted at the lumbar level of the spinal cord. It is then tunneled to a reservoir device, which is usually placed in a subcutaneous pocket in the lower abdomen. The reservoir can be filled with local anesthetic, opioids, and clonidine. Because the drugs are delivered directly into the spinal fluid, drug doses can be much smaller than is the case with enteral or parenteral delivery. Patients have to return to the pain management center every 4 to 8 weeks for a refill. The device is programmable through telemetry. Program modes can range from a simple continuous infusion to more complex modes with additional boluses at particular times of the day when increased pain-associated activities are anticipated.

In the case of spinal cord stimulation, electrodes are surgically placed in the epidural space by a minimally invasive approach and connected to an implanted controller. A similar device is used for peripheral nerve stimulation, with electrodes positioned in the direct vicinity of a nerve such as the occipital nerve. Multiple parameters of the repetitive electrical impulses such as duration, intensity, and pulse width can be manipulated. Patient cooperation during implantation is paramount to achieve an optimal result. Therefore, this device is reserved for the occasional older adolescent with severe, unrelenting pain. Discussions of adverse effects for these therapies have to include not only possible immediate surgical complications but also the need for long-term maintenance.

### **Referral to a Pediatric Pain Specialist**

Patients with complex disease processes and significant disability and impairment in function will challenge the pediatrician. Patients who have uncontrolled pain or loss of function despite therapy, significant comorbid diseases, a need for more invasive testing or treatment, or a family who are looking for another opinion should be referred to a pain specialist. The pediatrician has 2 options in this case: either remain the primary coordinator of the multimodal treatment team with the pain specialist as one of the providers, or allow the pain specialist to become the coordinator of the team. Which option is optimum will depend not only on the complexity of the patient's problem but also on the distance the family will have to travel to see the specialist. A listing of pediatric pain treatment centers available from the American Pain Society

reveals that many families need to cross state lines to obtain this kind of care for their child. Ideally, the pediatrician, who is familiar with the patient, the family, and the local resources, will work in close consultation with the pain specialist.

### Discontinuing Treatment

Periodically, all treatment modalities should be assessed to see whether they are still effective or even necessary. A change in function may no longer be dependent on a particular therapy because the overall physical status of the patient has improved. Discontinuing therapy can be a challenge because many patients and families fear that the painful condition will recur. A gradual weaning of therapy is an option even when no clear pharmacologic necessity exists.

Patients who require long-term management of their pain and coordination of multidisciplinary therapies beyond their adolescent years will benefit from a planned, gradual, and collaborative approach to the transition of care. Many of these patients have underlying processes such as congenital diseases, neuromuscular impairments, or post-traumatic conditions.

### Palliative Care

Insufficient relief of pain is one of the most common patient complaints in the management of progressive cancer or other life-threatening/life-limiting illnesses. All therapeutic interventions that have been discussed in this chapter should be considered in the management of a patient with a potentially life-threatening disease. Waiting until the child has only days to live to consider more invasive therapy will lead to needless, avoidable suffering. Components of palliative care should be offered at diagnosis and throughout a potentially life-threatening disease. For placement of an implantable device, the child should have a life expectancy of 3 to 6 months. If the life expectancy is less than 3 months, then a tunneled catheter connected to a conventional infusion pump or a PCA device is an option. Neurolytic blocks can provide the patient and family with valuable pain-free or painless time.

### CONCLUSION

The prevalence and significance of chronic pain in children and adolescents have only recently been recognized. Chronic pain can limit the functional abilities of the child, prevent normal age-appropriate development, and have a significant impact on other members of the family. A multidisciplinary approach is preferred when assessing the patient and providing therapy. A team comprising the pediatrician, who has an established rapport with the family, and specialists, such as a physical therapist, psychologist, and pain management consultant, may be most effective in providing care even for the challenging patient.

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## Chapter 56

# SELF-REGULATION THERAPIES: HYPNOSIS AND BIOFEEDBACK

Denise Bothe, MD; Karen Olness, MD

Children learn self-hypnosis easily and can apply it to help solve problems such as acute and chronic pain, undesirable habits, anxiety associated with chronic illnesses such as hemophilia or cancer, performance anxiety, and enuresis. Self-regulation techniques can also be used to help children manage everyday life stressors better. Training in hypnosis has been used for many years by athletes and other performers. The teaching and application of self-hypnosis is enhanced by the addition of biofeedback, which provides proof to the child that changes in thinking result in changes in body responses. Children, adolescents, and their families can gain an increased sense of control and participation in their treatment by learning effective coping strategies such as those available through self-hypnosis, with or without biofeedback.

### HISTORY

Hypnosis techniques have been used since the late 18th century. The Franklin Commission, which investigated the claims of Franz Mesmer, included experiments involving children. In the 1840s, two British surgeons, John Elliotson and James Braid, both reported surgical procedures on children during which hypnosis was the sole anesthesia method. In the late 19th century, European clinicians reported successfully treating negative habits and pain in children with hypnosis. The first research studies in children using hypnosis were in the 1960s and assessed hypnotizability. Since then, researchers have recognized that children generally learn hypnosis more



quickly and easily than do adults. The first use of biofeedback with children was reported in the 1970s, and since the 1970s, increasing research has documented the ability of children to use hypnosis, with or without biofeedback, to treat many clinical conditions.

Three-day training workshops on hypnosis with children were first taught in 1976 and have been available annually since then.

## DEFINITIONS

*Hypnosis* is defined as a focused state of awareness, sometimes involving relaxation, during which the individual has enhanced ability to facilitate specific physiologic and behavioral outcomes. *Hypnotherapy* is defined as a treatment modality that uses hypnosis by integrating that focused state of awareness into treatment.

Many terms have been used to describe the process of hypnosis (Box 56-1). *Mesmerism* was the original term used to describe the clinical work of Franz Mesmer. James Braid, an English surgeon, first coined the term *hypnosis*. This designation was unfortunate because *hypnos* came from the Latin root for sleep, implying that the person in hypnosis is asleep. However, this is not the case, and hypnosis remains misunderstood. Since then, many other terms (see Box 56-1) such as *self-regulation* and *mind-body skills training* have been used. *Cyberphysiology* is another term coined in the 1980s to describe these same techniques. The prefix *cyber* is derived from the Greek *kybernan*, which means to steer or take the helm; thus cyberphysiology refers to a person's ability to steer or regulate a physiologic or behavioral response.

Some of the more common misconceptions about hypnosis include the following:

- Hypnotists exert mind control over passive subjects.
- Hypnosis is magic.
- When under hypnosis the subject is sleeping.
- Only a few people are able to be hypnotized.

None of these statements is true. The subject is fully awake during hypnosis and aware of the environment. The mind and mental imagery of the person using these mind-body skills causes the physiologic changes. Although some people find these skills easier to acquire than other people, anyone can learn self-hypnosis.

*Biofeedback* is a term coined in 1969 to describe the procedure of using a physiologic response measure, or signal from the body, to give feedback to the

person. This feedback increases the awareness of the body and how it is functioning. Biofeedback is a useful tool in training individuals to strengthen their mind-body connection and learn self-regulation skills. Although biofeedback is a useful adjunct, training in biofeedback requires self-hypnosis instructions, which lead to the desired physiologic changes.

Measures of physiologic response include skin temperature, galvanic skin resistance (GSR) or electrodermal activity, electroencephalographic (EEG) data, breathing, heart rate, and heart-rate variability. Simple skin-temperature monitors make an inexpensive and effective biofeedback tool. Nocturnal enuresis alarms are essentially biofeedback tools.

Another biofeedback computer program that was originally designed for adults and has also been successful with children is the emWave (formerly Freeze Framer) program ([www.heartmath.com](http://www.heartmath.com)) (Figure 56-1). A finger sensor connected to the computer measures the heart-rate variability. As the person relaxes, the image on the computer screen gives positive feedback. For example, a rainbow comes down and fills a pot with coins, and in another a hot-air balloon floats up and across a field as the player relaxes. This program calculates heart rate variability and shows the patient and practitioner how well the patient was able to relax. The program has a graphical representation that shows the details of the session with heart-rate variability over time and percentage of time during which the subject was at low, medium, and high levels of relaxation. Feedback can then be compared with the data from other sessions from the same subject to determine progress. Heartmath also makes a portable emWave personal stress reliever biofeedback device.

## COMMON GROUND

Health professionals use many terms such as *imagery*, *relaxation imagery*, *progressive relaxation*, and *meditation*, among others, all of which refer to the same process by which hypnosis is induced. Although

### BOX 56-1 Terms Used to Describe Self-Regulation Techniques Involving Hypnosis

- |                             |                          |
|-----------------------------|--------------------------|
| • Self-hypnosis             | • Relaxation             |
| • Mind-body skills training | • Progressive relaxation |
| • Self-regulation           | • Meditation             |
| • Biofeedback               | • Visual imagery         |
| • Diaphragmatic breathing   | • Guided imagery         |
|                             | • Cyberphysiology        |



**Figure 56-1** Biofeedback program measures heart rate variability through a finger sensor connected to the child's finger.



great confusion and disagreement exist in the definitions of the variety of terms used, common ground can be found among terms. For example, hypnosis often uses relaxation and imagery techniques, and biofeedback can be used to augment a person's body-physiologic awareness during hypnosis. In addition, imagery and relaxation techniques, which are hypnosis methods, are used in biofeedback to help increase the person's focus and awareness. Culbert and colleagues describe the biofeedback-hypnosis interface and the rationale for integrating these self-regulation or cyberphysiologic techniques with children and adolescents. These skills all foster empowerment, mastery, and self-control. Many athletes use these skills to improve performance, and many patients use them to improve their health and body functions.

## GUIDELINES FOR LEARNING AND TEACHING SELF-HYPNOSIS

Before training a child in self-regulation skills, the pediatrician or other child health professional should prepare the child and family (Box 56-2). The choice of strategies for teaching self-hypnosis to children varies, depending on the child's age and developmental stage, the preferred type of mental imagery (ie, visual, auditory, kinesthetic, olfactory), learning style, preferred activities, dislikes, and personality. The pediatrician who provides coaching or teaching of hypnosis should emphasize that the child is in control and can choose when and where to use self-hypnosis. The pediatrician should be knowledgeable about the basic problem of the child before embarking on a hypnotherapeutic intervention. For example, a general pediatrician should be able to assess whether all necessary diagnostic tests have been completed for the presenting problems of abdominal pain, headache, or enuresis before offering training in self-hypnosis. A general pediatrician would not teach self-hypnosis to a child with posttraumatic

stress disorder (PTSD) unless working closely with a child psychiatrist or psychologist who was experienced in assessment and treatment of PTSD.

Training in self-hypnosis is helpful to a pediatrician or other clinician interested in using these skills to help children. Much can be learned about the language used to promote mind-body control and self-confidence in a child. The language used should be permissive, allowing the child to feel a sense of control. However, many techniques that use mind-body or hypnosis methods can be used in a primary care setting without formal training. Understanding a child's needs, increasing the child's understanding of mind-body control, and helping the child feel comfortable will promote a sense of control and increase the child's ability to regulate her or his body and behavior. Techniques that help a child focus and relax may be taught as part of hypnosis (Box 56-3). Deep breathing, often called *diaphragmatic breathing*, or *belly breathing*, is a powerful way to focus the child's attention and start the relaxation process. Progressive muscle relaxation is useful for older children who understand the instructions. Young children may respond better to *becoming floppy* as they relax. Leora Kuttner has described strategies for working with preschool children in pediatric practice.

Imagery techniques work best when the clinician has an understanding of the child's developmental stage, likes, dislikes, and fears. The clinician should help each child choose relaxation and imagery methods that suits him or her. It is recommended that a child practice 10 to 20 minutes twice daily for 1 month then once daily for the second month. Because biofeedback and hypnosis are designed to promote self-control, the parents should not remind their child to practice; children should develop their own reminder system (eg, a ribbon around the neck of a favorite stuffed animal). Adding a biofeedback measure (eg, to monitor pulse and heart rate variability, peripheral temperature, or GSR) may help the child improve. An audio recording may also be an effective reinforcer.

### BOX 56-2 When Teaching a Child Self-Regulation Techniques

1. Conduct a thorough diagnostic evaluation to understand the effects of the problem on the child and the significance of symptoms for the family.
2. Understand the child by learning about the child's personality, interests, likes, dislikes, and developmental stage, and any learning disabilities.
3. Emphasize the need for practice by explaining that becoming proficient in self-hypnosis requires practice, similar to learning, for example, a sport or music skill.
4. Emphasize that the child, not the parent, is the client; thus parents should be supportive but should not remind their child to practice.
5. Throughout the process, emphasize the child's control because the *child being in control* is the principal key to success.

Derived from Kohen DP, Olness KN. Self-regulation therapy: helping children help themselves. *Ambul Child Health*. 1996;2:43-58.

## CLINICAL APPLICATIONS

Mind-body interventions constitute a major portion of the overall use of complementary and integrative medicine by the public. National survey data published in 2004 showed that five relaxation techniques along with imagery, biofeedback, and hypnosis, taken together, were used by more than 30% of the adult US population.

### BOX 56-3 Techniques to Help a Child Focus and Relax

- Deep breathing
- Relaxation (eg, progressive muscle relaxation)
- Mental imagery
- Guided imagery
- Therapeutic suggestions
- Adjunct biofeedback

### BOX 56-4 Clinical Applications of Child Hypnosis

- Pain:
  - Acute (eg, injury, illness, procedural)
  - Chronic or recurrent (eg, chronic illness, disability, trauma, recurrent procedures)
- Habit problems and disorders (eg, thumb sucking, nail biting, hair pulling [trichotillomania], habitual coughs, tics)
- Behavioral problems (eg, attention problems, anger management)
- Medical-biobehavioral disorders (eg, asthma, migraine, Tourette syndrome, inflammatory bowel disease, warts, pruritus)
- Anxiety (eg, performance [examinations, stage fright, sports], anxiety disorders, PTSD, phobias)
- Psychophysiologic problems (eg, enuresis, encopresis, conditioned nausea and vomiting, irritable bowel syndrome, sleep disorders)
- Chronic disease, multisystem disease, terminal illness (eg, cancer, hemophilia, AIDS, cystic fibrosis, diabetes, chronic renal disease)

Derived from Kohen DP, Olness KN. Self-regulation therapy: helping children help themselves. *Ambul Child Health*. 1996;2:43-58.

Hypnosis and biofeedback are generally categorized in the mind-body aspects of complementary and integrative medicine; however, increasingly, medical institutions are considering hypnosis and biofeedback as part of mainstream medicine. Pediatricians and other health care professionals see many children who exhibit symptoms of high stress levels, including such symptoms as anxiety, depression, headaches, abdominal pain, and school avoidance. Children and parents often feel out of control, with busy lives, worries, or chronic health problems. Children and adolescents may attempt to cope in self-injurious ways, such as with the use of alcohol, nicotine, and drugs.

A thorough medical evaluation should precede hypnosis, with or without biofeedback treatment. Children referred for integrative treatment may not have had adequate diagnostic evaluations. In a study that reviewed 200 cases of children referred specifically for treatment with hypnosis, biofeedback, or both, 25% of the children had unrecognized biologic bases for symptoms such as enuresis, headache, anxiety, and recurrent abdominal pain. Some of the children referred for hypnosis to control headaches proved to have sinusitis, food allergies, brain tumor, or carbon monoxide poisoning.

Children have been taught self-hypnosis for a wide range of problems (Box 56-4). The mind-body skills learned with hypnosis can give a child the capacity to change attitudes, emotions, behavior, habits, autonomic reactivity, and biologic functions. This self-regulation offers techniques that facilitate their ability to:

- Direct their behavior
- Modulate physiologic changes in desired directions
- Control their thoughts for the purpose of symptom control

- Attain and maintain health and wellness
- Improve function or enhance performance

## PAIN MANAGEMENT

Pain is a subjective experience, and children exhibit different tolerance levels. Hypnosis techniques can be used for pain control, for example, in emergency rooms or for children with cancer who are undergoing procedures. When in acute pain, children are in a more focused state of awareness and are highly motivated to feel better. Because of this motivation, they may be more likely to respond to suggestions that increase their sense of control, which they can then use to decrease their sensation of pain. Helping children *dissociate* by imagining that they are in a favorite place can have a calming effect. In some situations, such as a first-time migraine headache, it can be difficult to work with a child who is acutely miserable. While not always possible, it is preferable overall to teach children these techniques when they are well, allowing them to prepare themselves for the possible acute episode. Some of these effective self-regulatory techniques are described in the literature. A book by Kuttner offers guidance for health professionals to help children in pain using self-regulation techniques.

Chronic pain and recurrent pain are more difficult to manage than acute pain. A child who experiences pain over a long period or learns to expect the pain to return again and again may become increasingly anxious and develop feelings of hopelessness. Teaching self-regulation is more complicated in these situations because of the need to address the severity and the negative expectancy that accompanies chronic pain. It has been shown that children will benefit more and require less training if they are offered training very early, ideally within a few days, after diagnosis of a chronic or life-threatening disease. *No Fears, No Tears* and *No Fears, No Tears—13 Years Later* are 2 video productions that illustrate the use of self-regulation strategies with children who have cancer.

If the self-regulatory techniques seem ineffective for the child with chronic or recurrent pain, then the pediatrician should re-evaluate the situation. The pain may be serving a protective psychological purpose. Significant mental health issues, such as PTSD, depression, or abuse, may exist, and psychotherapeutic evaluation and intervention may be needed. (See Case Report, Box 56-5.)

## HABIT DISORDERS

Habit problems are common in children. Habit problems such as thumb sucking, nail biting, hair pulling (trichotillomania), or habitual cough are potentially responsive to hypnotherapy. In a retrospective study, a significant number of children with habitual cough responded well to hypnosis with resolution of their symptoms of cough.

Some types of habits, such as tics or hair pulling, often begin during a stressful experience and initially carry with them emotional significance. In most instances, the emotional significance disappears, yet the habit remains. Habits such as habitual cough may begin with an upper respiratory tract infection but

**BOX 56-5 Case Report—Abdominal Pain**

Sarah, a 6-year-old girl, was brought to the pediatrician by her mother because of severe abdominal pain of 2 months' duration. The pains started suddenly one day in the morning after breakfast and before school. They occurred many mornings of the week and lasted for 1 to 2 hours. Sarah would clutch her abdomen and double over with pain. She did not have vomiting or diarrhea or fever. After the pain resolved, each day she appeared healthy. She had no history of constipation. Medical workup was negative for any medical causes of her pain.

A complete history revealed that Sarah did not want to go to school. She was afraid because a classmate on her school bus was saying things to scare her. The abdominal pain kept her home and protected her from the child who was scaring her.

Sarah's pediatrician spoke with her mother about addressing this issue with school officials and then asked Sarah if she wanted to learn a way to help herself prevent the pain from arising and decrease the intensity when it did occur. Sarah was interested. She liked dolls and stuffed animals; thus she was asked if she had one that was very soft and squishy, and she did. Sarah was taught to take slow, deep breaths "into her belly," and then advised to "make her belly very soft" like her squishy stuffed animal. This exercise would help her belly work better and prevent the pain from coming. Sarah demonstrated in the office that she was able to perform this task. She was then advised to practice this deep breathing and making her belly soft at home. (This teaching took approximately 5 minutes of the office visit.)

One month later, Sarah's mother brought her back for a well-child check. Sarah had had only one more episode of abdominal pain after learning how to relax herself and her abdomen. She has not had similar recurrent abdominal pains since. Sarah's mother also addressed the issue of the child who was scaring Sarah by talking to the principal, teacher, and bus driver. Sarah now enjoys going to school and does well with her friends and schoolwork.

persist long after the infection is gone. Others, such as thumb sucking, may have begun as a comfort measure in young childhood and have become habitual. Unless a motivation exists behind the habit (eg, if the habit helps the child avoid school), and provided that the child is motivated to change (not just the parent), hypnosis techniques are effective in extinguishing the habit. Emphasizing the child's control in mastering the problem is crucial to success in eliminating the problem.

**ENURESIS**

Before considering hypnotherapy for enuresis, the pediatrician should distinguish whether the enuresis is primary or secondary and whether the enuresis occurs during both day and night or at night only (see Chapter 249, Enuresis). Organic causes such as urinary tract infection, diabetes, and constipation must be ruled out. Primary enuresis may be considered a maturational issue, whereas secondary enuresis, after

a period of dryness, may be associated with a significant stressor in the child's life. Enuresis that has no organic cause is expected to resolve spontaneously over time. Depending on the age of the child, enuresis can be quite frustrating and interfere with activities such as sleepovers. Children with nocturnal enuresis often feel shame or guilt. Various methods have been used for children and parents who wish to stop enuresis; these include motivational behavior management (including reward systems, the child helping in cleanup of the wet bed, and bedwetting alarms) and medications such as desmopressin. Hypnotherapy is helpful for many children with enuresis. In a study that compared two groups of children treated with hypnotherapy versus imipramine, comparable results were seen with each group. At long-term follow-up, the group treated with hypnotherapy had a significantly larger positive response. Drugs such as imipramine can have significant side effects and can be life threatening. Desmopressin has negligible known side effects, but some parents are reluctant to give their child medication. The bed-wetting alarm is a type of conditioning device and is quite effective, although some children find the alarm to be aversive. Hypnosis as a treatment is at least as effective, has longer duration, and is not life threatening. As a treatment option for enuresis, self-regulation therapy or hypnosis is the least invasive, and many children respond favorably.

**BEHAVIORAL AND ATTENTION DISORDERS**

Self-regulation has value as an adjunct in management of behavioral problems. In addition to therapeutic interventions, such as counseling and behavioral modification, teaching self-regulation techniques to a child can be a constructive way to build self-esteem and more effectively control the maladaptive behaviors. Attention-deficit/hyperactivity disorder (ADHD) is one of the most common behavioral problems encountered in children. Recommended management usually involves behavioral modification and primarily stimulant medication. A review of research studies that use neurofeedback for ADHD shows potential for short- and long-term improvement from ADHD symptoms. One study using biofeedback and hypnosis techniques has demonstrated beneficial effects of EEG biofeedback on measures of intelligence, behavioral rating scales assessing the frequency of core symptoms of ADHD, computerized tests of attention (eg, the Test of Variables of Attention [TOVA]), and quantitative EEG measures of cortical arousal. Evidence is promising for neurofeedback as a treatment alternative for ADHD, but more research needs to be done to be certain about efficacy for neurofeedback.

**STRESS MANAGEMENT AND ANXIETY**

Self-regulation skills are an excellent way to manage stress. Relaxation and hypnosis are useful for helping children and adolescents with symptoms of anxiety. Many parents bring children to their pediatricians for symptoms related to high stress levels. Stress and anxiety can manifest in a variety of ways, including



**BOX 56-6 Case Report—Anxiety**

Dan, age 16, was referred to learn self-hypnosis for control of test anxiety. He had been an excellent student during all his school years until a year earlier, when he began to perform poorly on examinations. No changes occurred in his studying habits. He did very well on homework. No family changes had occurred. He got along well with two older siblings, both of whom are now in college. Dan had a girlfriend, a classmate, who was also a good student and was looking forward to college.

Dan's mother described him as having always been "perfectionistic." She said that he began expressing worry about examinations when his older brother was taking student aptitude tests. Dan said that he studied and felt that he knew the material but that he froze during the examinations and was unable to think clearly. He also said that he slept poorly on nights before examinations.

Dan said that he enjoyed reading, drawing, playing computer games, swimming, and soccer. He said that his dream was to become an architect. He said that he had been afraid of dogs when a young child but this was no longer so. Dan also said he got approximately 6 hours of sleep on school nights and slept 10 to 12 hours a night on weekends.

The pediatrician explained to Dan that she was able to teach him self-hypnosis to reduce test anxiety and

that his daily practice would be required. She described the use of self-hypnosis by Olympic athletes and the type of practice that was required. The pediatrician emphasized that Dan's parents were not allowed to remind him to practice. Dan said that he wished to learn and was willing to practice.

The pediatrician taught Dan a self-hypnosis method involving progressive relaxation and focus on a winning soccer game. She asked that he practice this method twice daily and return in a week. When Dan returned, he said he had been practicing regularly. At this visit, Dan was hooked to a temperature sensor and was able to watch a screen that demonstrated the increase in his peripheral temperature as he relaxed and achieved self-hypnosis. The pediatrician then taught him specific suggestions to use before his examinations, including suggestions related to sleeping well, and to include future programming of pleasant events associated with successful examinations.

Dan continued to practice daily and was followed up by telephone every 2 weeks for 2 months. At that time, Dan had no further test anxiety, was achieving high scores on tests, and had good grades.

somatic complaints, behavior issues, and poor sleep. Helping children learn self-hypnosis can give them a coping skill they can use anywhere and anytime. When learned at a young age, these stress-management skills can be used for a lifetime to help with daily or extraordinary stressors. Culbert and Kajander have written a book that includes a kit to help children manage stress, sleep problems, and pain. (See Case Report, Box 56-6.)

With children who have an anxiety disorder, such as general anxiety, separation anxiety, or selective mutism, hypnosis techniques can be a useful adjunct along with therapeutic counseling.

**MEDICAL PROBLEMS**

Some diseases respond well to self-regulation techniques. One group of diseases can be classified as *biobehavioral disorders* in that they have clear pathophysiologic origins as well as significant psychoemotional components. Examples of these conditions include asthma, migraine, and irritable bowel syndrome. Relaxation and self-hypnosis help promote a sense of self-control and a reduction of symptoms in children with biobehavioral disorders.

Children and adolescents with asthma can learn self-hypnosis to reduce wheezing in acute episodes. Research using hypnosis, both with and without biofeedback, has demonstrated decreased functional morbidity, with fewer emergency department visits, fewer missed school days, and a better sense of control in children who were taught to use these techniques.

Children with migraine headaches have been shown to respond well, with a significant decrease in frequency of their headaches after self-regulation training when compared to propranolol and placebo. (See Box 56-7.)

Warts are another common condition seen in primary-care pediatrics. Warts are reported to respond to many interventions and often resolve by themselves. In many instances, children will undergo numerous topical treatments without success or with recurrence. Many case studies of successful wart treatment using hypnotherapy have been conducted. (See Box 56-8.)

**DIABETES**

A child with diabetes must cope with frequent blood tests, a special diet, and daily injections. When a child with diabetes feels out of control, compliance with diet and medicines can prove inadequate. Hypnotherapy can provide a child with a way to learn to cope and gain a sense of mastery, both of which may help reduce anxiety and improve compliance.

**MEDICAL PROCEDURES**

Medical procedures are usually a source of anxiety for children and are often painful. These procedures include routine immunization injections, venipuncture, and pelvic examinations. Reductions in anxiety and pain have been noted in children who were taught skills using hypnosis techniques. A randomized controlled study assessing the effects of hypnosis on distress of children undergoing a voiding cystourethrogram procedure found significant reductions in distress for the group of children who received hypnosis.



**BOX 56-7 Case Report—Migraine Headache**

Anne, an 11-year-old girl, had a history of migraine headaches for 3 years. Her mother also had migraines since childhood. Anne was evaluated by a child neurologist who, at various times, had prescribed propranolol, Periactin, and Elavil. He also suggested regular sleep and avoidance of certain foods.

Anne did well in school and had many friends. She enjoyed music and played the piano. She had two younger siblings, ages 8 and 6. She said that she was afraid of thunder.

At the initial visit, Anne was having a migraine episode at least once a week. Most episodes were preceded by a visual aura, and they lasted approximately 12 hours. They were accompanied by nausea and sometimes vomiting. Anne said that she would sleep as soon as possible after a migraine began and would usually awaken without the pain, but with a shaky feeling that lasted for several hours thereafter.

Anne was interested in learning self-hypnosis for control of her migraines. Anne chose to focus on music for her hypnotic induction. She imagined her favorite music as she gradually relaxed all of her muscles. She did well during the first practice.

At her second visit, Anne's finger temperature was monitored during her examination. Her peripheral temperature increased 4°F during this practice, proof that she was relaxing. She learned about pain signals and was offered options for turning the signals off if she should develop a migraine episode.

The third visit took place 3 weeks later. Anne had had 1 migraine during the period between visits, a significant decrease. Subsequently, she was followed up by telephone. In the 6-month follow-up period, she had 2 migraine episodes, both associated with sleep deprivation.

**BOX 56-8 Case Report—Warts**

David, age 7, had had warts on his hands and legs for 2 years. He had been treated by a dermatologist with topical treatments and freezing the warts. Each time, the warts recurred. David had 3 warts on his left leg, 3 on the right leg, 2 on the left hand, and 5 on the right hand.

David was in second grade. He enjoyed school and had friends in both school and the neighborhood. He liked bicycle riding, playing soccer, and ice skating. David had an older sister and a younger brother. He said he wanted to get rid of the warts because he did not like the way they looked and because the previous treatments hurt.

David was told that many children had eliminated warts by doing a relaxation exercise and giving a message to themselves to stop feeding the warts. He was told about practice at home and about the need for a good reminder system for the practice; his mother was told not to remind him to practice.

David imagined himself playing soccer as a hypnotic induction and was asked to imagine playing until the game was won, and then to tell himself to stop feeding each of the 13 warts.

David returned in 2 weeks. At this point, David had 7 warts and was very pleased. He continued practice for another month, and 12 of the warts were gone. No new warts appeared. After 3 months, all the warts were gone.

**HYPNOSIS IN THE ROUTINE PEDIATRIC OFFICE VISIT**

Integrating self-regulation techniques into primary care practice offers the opportunity for pediatricians and other child health professionals to facilitate a sense of mastery and competency in the children under their care. Although many physicians may not realize it, they have long been applying some of the hypnotic principles and using some of the sensitive language in their clinical work with children. In an introductory course on hypnosis, clinicians become aware of the importance of carefully selecting their language and monitoring the timing and pacing with which to introduce new words in their encounters with children. Clinicians often realize that integrating these techniques will be easier and faster than they may have originally believed.

Brief self-regulation interventions can be integrated into primary care practice. Following are some examples of simple techniques that can be used to

make a child more comfortable during routine office procedures such as receiving shots or throat cultures, or just being examined by a stranger.

- Having a child *blow away* pain by using a pinwheel, bubbles, or a pretend candle is an effective tool for decreasing a child's experience of pain during injections or venipuncture.
- Bubbles can also be used to get the attention of the young child who starts screaming as soon as the pediatrician walks into the room and to help the child to feel more comfortable.
- A stuffed animal or doll can be used as an example before examining a child. By pointing out how the doll or stuffed animal is comfortable being examined, the pediatrician can often help the child become more comfortable when being examined.
- A child who needs a throat culture may be able to use slow, deep breaths while focusing on a pleasant thought to keep still while keeping his or her mouth open.
- Favorite music can also be a good way to help the child focus and relax during procedures.

**BOX 56-9 Training Organizations**

- National Pediatric Hypnosis Training Institute ([www.nphti.org](http://www.nphti.org))
- Society for Clinical and Experimental Hypnosis ([www.sceh.us](http://www.sceh.us))
- American Society of Clinical Hypnosis (training workshops bimonthly) ([www.asch.net](http://www.asch.net))

How can the pediatrician or child health professional learn to use hypnosis in the practice?

1. *Take a basic 3-day hypnosis-training workshop.* See Box 56-9.
2. *Identify and stay in touch with a mentor after the first workshop.* Most of the workshops will offer mentoring assistance to encourage the new learner and provide advice regarding clinical situations. Workshops also have an active listserv resource for child health professionals who share knowledge about using hypnosis in a pediatric setting.
3. *Take follow-up workshops, read textbooks and hypnosis journals, and attend annual hypnosis scientific meetings.*
4. *Take board-certified examination in hypnosis.* Tests from the American Board of Medical Hypnosis, Hypnosis in Psychology, Hypnosis in Dentistry, and Hypnosis in Social Work are available. Information can be obtained from the American Society of Clinical Hypnosis or the Society for Clinical and Experimental Hypnosis.

**RESEARCH IN CHILD HYPNOSIS**

Active research in child hypnosis has taken place over the last 40 years. Initial research examined measures of child hypnotic susceptibility, such as the Stanford Children's Hypnotic Susceptibility Scale. Most subsequent research has been clinical research documenting the efficacy of hypnosis with children in areas such as pain management, habit problems, wart reduction, and performance anxiety. The variability in preferences, learning styles, and developmental stages complicates the design of research protocols for the study of hypnosis with children. These protocols are often written to describe identical hypnotic inductions, often recorded, to be used at prescribed times. Measured variables do not address whether a child likes the induction or listens to the tape, or whether the child focuses on entirely different mental imagery of the child's own choosing. Furthermore, learning disabilities are often subtle and may not be recognized without detailed testing that is not usually done before research studies involving child hypnosis. Learning disabilities, such as auditory processing disorder, may interfere with the ability of children to learn and remember self-hypnosis training. Each of these variables complicates efforts to perform meta-analyses on hypnosis and related interventions. Interventions called *relaxation imagery*, *imagery*, *visual imagery*, or *progressive relaxation* each lead to a hypnotic state. The proper analysis of studies on the efficacy of hypnosis in children should combine all

studies that describe strategies for inducing hypnosis in children.

Some research studies are defined as controlled but mix therapeutic interventions. For example, Scharff, Marcus, and Masek reported on "[a] controlled study of minimal-contact thermal biofeedback treatment in children with migraine." Children were randomly assigned to thermal biofeedback, attention, or wait-list control groups. The hand-warming biofeedback group received four sessions of cognitive behavioral stress management training, thermal biofeedback, progressive muscle relaxation, imagery training of warm places, and deep-breathing techniques. Thus, children were also being taught self-hypnosis.

Several controlled laboratory studies have demonstrated that an association exists between learning self-hypnosis and changes in humoral or cellular immunity (or both) in children. In one study, Karen Olness and colleagues examined the self-regulation of salivary immunoglobulin A by children, demonstrating that self-hypnosis can facilitate some immunomodulation in children. This work was the basis for a clinical trial by Hewson-Bower, who demonstrated that training in self-hypnosis for children with frequent upper respiratory tract infections resulted in a reduction of infectious episodes and fewer illness days when upper respiratory tract infections did occur.

An overview describing clinical and research evidence was recently published. The International Society of Hypnosis is currently sponsoring Cochrane reviews of hypnotherapeutic interventions, including those with children.

**TOOLS FOR PRACTICE****Medical Decision Support**

- *American Society of Clinical Hypnosis* (Web site), ([www.asch.net](http://www.asch.net))
- *Harry the Hypno-potamus: Metaphorical Tales for the Treatment of Children* (book), Crown House Publishing
- *Hypnosis and Hypnotherapy with Children*, 4th ed (book), Routledge 2011
- *International Society of Hypnosis* (Web site), ([www.ishhypnosis.org](http://www.ishhypnosis.org))
- *No Fears, No Tears—13 Years Later* (video), Crown House Publishing
- *Pediatric Hypnosis Workshops* (Web site), National Pediatric Hypnosis Training Institute ([www.nphti.org](http://www.nphti.org))
- *Society for Clinical and Experimental Hypnosis* (Web site), ([www.sceh.us](http://www.sceh.us))

**SUGGESTED READINGS**

- Barabasz AF, Olness K, Boland R, Kahn S, eds. *Medical Hypnosis Primer: Clinical and Research Evidence*. Routledge: New York, NY; 2010
- Kohen D, Olness K. *Hypnosis and Hypnotherapy with Children*. 4th ed. Routledge: New York, NY; 2011
- Kuttner L. *A Child in Pain: What Health Professionals Can Do to Help*. Bethel, CT: Crown House Publishing; 2010

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## Chapter 57

# COMPLEMENTARY AND INTEGRATIVE MEDICAL THERAPIES

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Interest in complementary and integrative medicine (CIM) has redefined modern Western medicine. Formerly unconventional therapies such as acupuncture, biofeedback, guided imagery, and hypnotherapy have been integrated into pediatric care in many clinics and hospitals (see Chapter 56, Self-Regulation Therapies: Hypnosis and Biofeedback). Other therapies such as herbs, dietary supplements, massage, and chiropractic care are widely used by the public and are increasingly available at conventional hospitals. Formal definitions of health care quality now acknowledge the importance of respecting spirituality and culturally based healing traditions in daily practice. The growing practice of providing care in a medical home emphasizes the importance of patient- and family-centered, relationship-based care that is at the heart of both pediatrics and integrative medicine. Pediatrics, more than most other specialties, embraces integrative medicine's emphasis on prevention and health promotion.

As found by Kemper and O'Connor, most pediatricians reported that they have limited knowledge of CIM and desired to know more; 70% of pediatricians reported having patients who use CIM therapies, 51% reported that they were concerned that CIM use by patients might delay standard medical care, and 36% were concerned that CIM use occasionally impairs physician-patient communication. However, fewer than 20% of pediatricians routinely ask about the use of CIM therapies. Most (83%) wanted to learn more about complementary and alternative therapies so that they might appropriately counsel families interested in them. Specialists as well as generalist pediatricians need to know about integrative care because the use of CIM therapies is particularly high among children with multiple chronic conditions who seek specialist care.

Similarly, most parents report the desire to discuss CIM with their pediatrician. This group includes more than 80% of those who use CIM for their children. However, fewer than one-half of these parents report having done so. Lack of communication may compromise the quality of care.

Pediatric integrative medicine (PIM) represents one of the newest subspecialties in the care of children. In North America alone, there are more than 15 academic

pediatric programs where clinical care, resident teaching, and research are conducted. However, pediatricians do not need to be content experts on every CIM therapy and product or seek specialized training. Nor do they need to reject their training in biopsychosocial medicine or critical thinking. However, the tremendous growth in demand for CIM plus use of the Internet and mass media for health information suggests the necessity for new competencies in pediatric care. The 21st century pediatrician should have the capacity to do the following:

- Focus on patient and family health goals in addition to diagnostic labels
- Inquire regarding CIM use
- Counsel on CIM from an evidence-based perspective using proven behavioral techniques to foster healthy lifestyles
- Partner with and refer appropriately to CIM practitioners
- Monitor for potential adverse side effects

This chapter defines CIM and describes how to inquire, counsel, partner, and refer. For physicians who seek further skills development, Box 57-1 also cites additional physician training opportunities.

## WHAT IS COMPLEMENTARY AND INTEGRATIVE MEDICINE?

Complementary and integrative medicine includes all health care systems, therapies, and products that are not considered part of conventional medicine as

### BOX 57-1 Continuing Education Opportunities in Mind-Body-Spirit Self-Care

#### HYPNOSIS AND BIOFEEDBACK

- American Society for Clinical Hypnosis ([www.asch.net](http://www.asch.net))
- Association for Applied Psychophysiology and Biofeedback ([www.aapb.org](http://www.aapb.org))
- Biofeedback Certification Institute of America ([www.bcia.org](http://www.bcia.org))
- National Pediatric Hypnosis Training Institute ([www.nphiti.net](http://www.nphiti.net))
- Society for Developmental and Behavioral Pediatrics ([www.sdbp.org](http://www.sdbp.org))

#### MEDITATION

- Center for Mind-Body Medicine ([www.cmbm.org](http://www.cmbm.org))
- Center for Mindfulness in Medicine, Health Care, and Society ([www.umassmed.edu/cfm](http://www.umassmed.edu/cfm))
- Mind-Body Medical Institute ([www.mbmi.org](http://www.mbmi.org))

#### SPIRITUALITY

- George Washington Institute on Spirituality and Health ([www.gwish.org](http://www.gwish.org))

#### ACUPUNCTURE

- American Academy of Medical Acupuncture ([www.medicalacupuncture.org](http://www.medicalacupuncture.org))
- Helms Medical Institute ([www.hmieducation.com](http://www.hmieducation.com))

practiced in the United States. These therapies can be used to supplement conventional care, thus the term *complementary*. When prescribed by physicians as part of a comprehensive treatment plan, they are considered integrative. Because the term *alternative* meant in place of conventional medical care, the term has been dropped by both physicians and the National Institutes of Health. The term *integrative medicine* has been adopted by the American Academy of Pediatrics and is represented by the Section on Integrative Medicine.

Integrative medicine represents the ideal of a higher-order system of care rather than simply the addition of complementary therapies to conventional care. The Consortium of Academic Health Centers for Integrative Medicine, which consists of 56 academic medical centers, defines integrative medicine as follows:

[T]he practice of medicine that reaffirms the importance of the relationship between physician and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic approaches, health care professionals and disciplines to achieve optimal health and healing.

Integrative medicine emphasizes the centrality of the therapeutic relationship, the importance of prevention, and the healing power of nature. Integrative medicine seeks to use the best of scientifically based medical therapies along with compassion and attention to the patient's spiritual and emotional needs, as well as appropriate complementary and alternative approaches when they enhance conventional medicine. Some argue that integrative medicine is simply good pediatric care.

The National Institutes of Health 2001 survey of 31,044 adults assessed and ranked the use of 5 categories of CIM: mind-body medicine, biologically based therapies, manipulative and body-based methods, alternative medical systems, and energy therapies. However, since 1996, pediatricians have embraced a more synergistic model of 4 categories of integrative complementary and alternative medicine and conventional therapies: lifestyle (healthy habits in a healthy habitat); biochemical (medications and supplements); biomechanical (surgery, massage, manipulative therapies); and biofield (acupuncture, prayer, and homeopathy).

### Lifestyle Strategies

Healthy lifestyle habits are the keys to good health throughout the life span. Healthy habits include the following:

- Healthy nutrition (and avoiding toxins like tobacco)
- Healthy physical activity
- Healthy sleep
- Healthy emotional and mental self-regulation
- Healthy social relationships

A healthy habitat refers to the physical, psychological, social, educational, and political environment. For example, music and spending time in nature offer therapeutic benefits to children of all ages.

Because pediatricians are familiar with most of these habits, this chapter will focus on healthy emotional and mental self-regulation. Although conventional care typically refers to mental and behavioral

health, psychotherapy, and support groups, integrative care also includes mind-body strategies such as biofeedback, meditation, hypnosis, guided imagery, and yoga. The purpose of using these strategies is to achieve optimal mental and emotional health and enhance resilience.

Mind-body medicine includes all therapies that activate emotional, mental, spiritual, and behavioral factors to modulate positively physiologic mechanisms, including immune and endocrine function. Over 35 years ago, Green, Green, and Walters stated that

... every change in the physiologic state is accompanied by an appropriate change in the mental-emotional state, conscious or unconscious, and every change in the mental-emotional state is accompanied by an appropriate change in the physiologic state.

The bidirectional influences of mind on body and body on mind can have significant mediating effects, both positive and negative, on health outcomes for children. In the past 20 years, mind-body therapies have become recognized as safe and effective for many pediatric conditions, including headaches, asthma, enuresis, sleep problems, pain, and stress-related symptoms.

According to the National Institutes of Health, spiritual and religious practices such as prayer represent the most prevalent complementary therapies in the United States. Nearly 80% of US adults think that religion, to a large extent, helps patients and families cope with illness. Nearly 75% of the public think that praying for someone else can help cure that person's illness, and 56% of adults state that faith has helped them recover from illness, injury, or disease. Spirituality may or may not involve formal religion. Spiritual concerns arise in clinical settings when important connections with self, with others, with nature, and with a higher power are threatened or disrupted. Spiritual beliefs are frequently important in medical decisions. Spiritual well-being is closely linked to successful coping, faster recovery, and higher quality of life. Many patients may want help with meaning, hope, or overcoming fears, and unmet spiritual needs are associated with despair and increased mortality. Parents often have significant spiritual needs around the life-threatening illness or death of a child.

A growing body of research has demonstrated the benefits of various kinds of meditative practices to train the mind and regulate the emotions, resulting in less pain and fewer symptoms in children and adults. For example, training in mindfulness-based stress reduction and mindfulness-based cognitive behavioral therapy decreased psychological distress among adolescents with psychiatric disorders and decreased hostility and stress among urban youth. Moving meditation practices such as tai chi and yoga can also improve behavior, mental health, physical symptoms, and physical fitness.

Music and music therapy—the intentional use of melody, rhythm, harmony, timbre, form, and style for healing—are important contributors to well-being. In premature infants, music therapy can lower heart and respiratory rates, increase oxygen saturation, improve sleep patterns, improve sucking behaviors, improve caloric intake and weight gain, and decrease



salivary cortisol and distress behaviors. Music also can significantly reduce the stress parents associate with premature infant care. In postsurgical patients, intraoperative and postoperative music reduces both pain and pharmaceutical requirements, including use of both sedatives and analgesics. This seems to be true for procedures as well. In pediatric oncology patients, music therapy can reduce pain and suffering and improve both mood and attitude. In intensive care units, music reduces patient anxiety and depression; and for dying patients, music therapy has been shown to improve the quality of life.

Mind-body therapists may include physicians, psychologists, meditation instructors, nurses, social workers, chaplains, music therapists, and registered yoga teachers. Frequently, master's level and higher levels of education in these fields include training in 1 or more mind-body therapies. Formal graduate-level training is required for both chaplaincy and music therapy certification.

### Biochemical Therapies

Biochemical therapies include both medications and natural products such as herbs, vitamins, and other supplements. Vitamin K is recommended for all children to prevent hemorrhagic disease of the newborn, and supplemental vitamin D is recommended for breastfed infants. The most recent data show that 46.2% of 1,280 interviewed adolescents had used dietary supplements in their life, with 29.1% having used a supplement in the previous month. Nearly 10% of adolescents report using supplements with prescription medications in the previous month. Children with chronic or recurrent illnesses often turn to herbs and other dietary supplements.

The most frequently used supplements in children (aside from vitamins D and K) are multivitamins, single vitamins, and minerals (eg, vitamin C, iron, and calcium). The most frequently used herbal products in children include chamomile, peppermint, echinacea, and aromatherapies such as lavender. In adolescents, the use of weight-loss supplements and creatine are closely linked to attempts to change body shape.

Since the passage of the Dietary Supplement Health and Education Act of 1994 (DSHEA), supplements have been regulated by the US Food and Drug Administration (FDA) with requirements more akin to foods than drugs. Good Manufacturing Practice (GMP) regulations are identical to those for food. Unlike food and drugs, dietary supplements can be sold without premarket approval and do not require a specific post-marketing study. Supplements can be sold based on evidence of safety in the possession of the manufacturer. Supplements can only be removed from the market if the FDA can prove them to be unsafe under ordinary conditions of use. This ban recently occurred with the sympathomimetic herb ephedra (*Ephedra sinica* and related plants), which had been widely marketed for weight reduction. The FDA ruling was later overturned in a court ruling.

Under DSHEA, herbal medicines can be sold for *stimulating, maintaining, supporting, regulating, and promoting health* rather than for treating disease. As

dietary supplements rather than drugs, herbal medicines may not claim to restore normal or to correct abnormal function. Additionally, herbs may not claim to *diagnose, treat, prevent, cure, or mitigate*. For example, herbal medicine companies can assert that their product supports cardiovascular health but not that it lowers cholesterol. To do so would suggest that the product is for treating a disease (hypercholesterolemia) and is therefore subject to FDA pharmaceutical regulations. However, most herbs are used by the public for the treatment of a disease or symptoms of a disease (Table 57-1). Only functional foods (eg, oat bran, soy, cranberries, certain processed butter-like spreads) can claim specific health benefits. Such approvals require significant supporting clinical data and FDA approval.

Licensed practitioners who promote herbal medicine use include naturopaths and chiropractors for whom advanced training often exists as part of their degree programs or continuing education programs. Not all naturopaths, however, are graduates of accredited naturopathic medical schools. International Board Certified Lactation Consultants frequently prescribe herbs such as fenugreek to nursing mothers to stimulate milk production. Reliable resources (Box 57-2) describing herbal medicine and supplements are useful.

### Biomechanical Therapies

Manipulative and body-based methods include all therapies that focus on manipulation and movement of one or more parts of the body. The best-known examples are chiropractic, osteopathy, and massage. All examples incorporate touch, an essential human need with therapeutic, interpersonal, and cultural dimensions. Massage is one of the oldest health care practices and was used in ancient times in India, China, Arabia, Egypt, and Greece. Experience at one of the largest pediatric CIM programs at a children's hospital in the Midwest suggests that massage and other forms of bodywork are among the most popular options—inpatient or outpatient—selected by children and teens. Similar observations have been documented in pediatric oncology patients and adolescents. Massage may be provided most often by parents or other family members. The appropriate amount of massage has not yet been measured, but family members frequently appreciate the chance to learn a skill that can contribute to the comfort and well-being of the patient. Massage can also include many different techniques and forms that require more significant training, including structural integration (Rolfing), movement integration (Feldenkrais technique, Alexander technique), pressure point techniques (shiatsu, acupressure), cranial sacral therapy, reflexology, and many others.

The manipulation, compression, and stretching of the skin, muscles, and joints activates a variety of mechanisms that support and promote health, including the following:

- Mechanical—enhances blood flow to the muscles and soft tissues and enhances lymphatic flow
- Immunologic—enhances specific immune cell functions such as natural killer cell activity

**Table 57-1** Commonly Used Herbal Therapies

COMMON NAME (LATIN NAME)	COMMON USES
Aloe ( <i>Aloe vera</i> )	Burns, minor wounds, skin irritations, aphthous stomatitis, constipation, gastric and duodenal ulcers
Astragalus ( <i>Astragalus</i> species)	Immune booster
Calendula ( <i>Calendula officinalis</i> )	Skin soother
Cascara ( <i>Rhamnus purshiana</i> )	Constipation
Cayenne ( <i>Capsicum frutescens</i> )	Topical treatment for pain, postherpetic neuralgia, nasal spray for migraines and cluster headaches
Chamomile ( <i>Matricaria recutita</i> )	Sedative, colic, anti-inflammatory, antispasmodic
Clove oil ( <i>Syzygium aromaticum</i> )	Teething pain
Coffee ( <i>Coffea</i> species)	Stimulant, attention-deficit/hyperactivity disorder, bronchodilator
Curcumin ( <i>Zingiberaceae</i> )	Anti-inflammatory, antioxidant
Dandelion ( <i>Taraxacum officinale</i> )	Mild diuretic, liver tonic
Dill ( <i>Anethum graveolens</i> )	Antispasmodic, provides colic relief, decreases flatulence
Echinacea ( <i>Echinacea</i> species)	Immune stimulation, anti-inflammatory
Ephedra (ma huang) ( <i>Ephedra</i> species)	Vasoconstriction; allergy, upper respiratory infection; asthma; appetite suppressant
Evening primrose oil ( <i>Oenothera biennis</i> )	Eczema, premenstrual syndrome
Fennel ( <i>Foeniculum vulgare</i> )	Colic
Feverfew ( <i>Tanacetum parthenium</i> )	Migraine headaches, rheumatoid arthritis
Garlic ( <i>Allium sativum</i> )	Antimicrobial, cholesterol lowering
Ginger ( <i>Zingiber officinale</i> )	Antiemetic, antinausea
Ginkgo ( <i>Ginkgo biloba</i> )	Enhances blood flow past clogged arteries; prevents memory loss; marketed to treat attention-deficit/hyperactivity disorder
Ginseng ( <i>Panax</i> species)	Stimulant, adaptogen; enhances endurance and performance
Hawthorn ( <i>Crataegus oxyacantha</i> )	Cardiac stimulant; enhances cardiac contractility
Hops ( <i>Humulus lupulus</i> )	Sedative
Kava kava ( <i>Piper methysticum</i> )	Anxiolytic
Lavender ( <i>Lavendula</i> species)	Sedative
Licorice ( <i>Glycyrrhiza</i> species)	Anti-inflammatory, antiviral, demulcent
Milk thistle ( <i>Silybum marianum</i> )	Hepatoprotection against cirrhosis, hepatitis
Oats ( <i>Avena sativa</i> )	Antipruritic; eczema, varicella
Pine bark extract ( <i>Pinus</i> species)	Antioxidant promoted to treat attention-deficit/hyperactivity disorder
Rhubarb root ( <i>Rheum officinale</i> )	Constipation, chronic renal failure
Saint John's wort ( <i>Hypericum perforatum</i> )	Depression, antiviral
Skullcap ( <i>Scutellaria</i> species)	Sedative
Slippery elm bark ( <i>Ulmus fulva</i> )	Demulcent; pharyngitis
Stinging nettle ( <i>Urtica dioica</i> , <i>Urtica urens</i> )	Hay fever
Tea tree oil ( <i>Melaleuca alternifolia</i> )	Topical antimicrobial; treats acne, minor skin infections, including fungal and yeast infections
Thyme ( <i>Thymus vulgaris</i> )	Antimicrobial, expectorant; treats colds, sore throats, cough
Valerian ( <i>Valeriana officinalis</i> )	Sedative
Witch hazel ( <i>Hamamelis virginiana</i> )	Topical antiseptic, anti-inflammatory

- Neurologic—triggers relaxation response and lowers sympathetic nervous system arousal, reduces serum cortisol, enhances endogenous serotonin and dopamine levels, and modulates pain perception
  - Energetic—according to traditional thought, certain massage practices can provide balance and improve the flow of life force energy or *chi*
- Massage can be enhanced with a biochemical therapy—aromatherapy—the therapeutic application of essential oils distilled from plants. Specific scents are targeted to specific symptoms, such as lavender or chamomile for relaxation, ginger or spearmint for nausea, and peppermint or lemon for fatigue.

Chiropractors are licensed in all 50 states, and their services are widely covered by insurance, including

Medicaid. Most chiropractic schools offer courses in pediatric care. Chiropractors can use special pediatric tables and gentle techniques, or treat the children in their parents' laps. Massage therapists are also licensed in all 50 states, but training and licensure requirements are quite variable. The largest professional national organization of bodyworkers is the American Massage Therapy Association. Membership requires training in an accredited school and completion of 500 hours of training.

### Biofield Therapies

Biofield therapies include practices that invoke, stimulate, or alter an invisible energy, spirit, or information to achieve a health goal. In conventional medicine,

### BOX 57-2 Web Resources for Herbal Medicines and Dietary Supplements

- American Botanical Council ([www.herbalgram.org](http://www.herbalgram.org))
- ConsumerLabs ([www.consumerlabs.com](http://www.consumerlabs.com))
- Memorial Sloan Kettering Cancer Center “About Herbs” ([www.mskcc.org/cancer-care/integrative-medicine/about-herbs](http://www.mskcc.org/cancer-care/integrative-medicine/about-herbs))
- Natural Medicines Comprehensive Database ([www.naturaldatabase.com](http://www.naturaldatabase.com))
- Natural Standard ([www.naturalstandard.com](http://www.naturalstandard.com))
- National Library of Medicine MedLine Plus ([www.nlm.nih.gov/medlineplus](http://www.nlm.nih.gov/medlineplus))
- National Institutes of Health Office of Dietary Supplements ([www.ods.od.nih.gov](http://www.ods.od.nih.gov))
- US Pharmacopeia ([www.usp.org](http://www.usp.org))

radiation therapy is used to treat cancer and invisible rays are used to diagnose illnesses with x-rays and ultrasound. In Asian cultures, an invisible energy or life force is known as chi, which can be affected by acupuncture and related practices. In some religious and secular traditions, healing energy can be sent by prayer, good wishes, laying on of hands, Therapeutic Touch, Healing Touch, or Reiki. In homeopathy, an original compound that causes a symptom is diluted so much that what remains has energy or information to combat that symptom.

Among major teaching hospitals that have a pediatric pain service, 33% offer acupuncture therapy to treat pain. Additional indications may include constipation and traumatic brain injury. Acupuncture is quite safe, even with cancer-associated thrombocytopenia, and can be an effective and well-accepted intervention with children and teens. Use of the term *acupoint stimulation* avoids eliciting fear of needles. Acupoint stimulation can be achieved by massage, comfortable electrical stimulation, stickers with beads, or very thin (>30 gauge) nonhollow acupuncture needles. In many instances, after gradually establishing comfort and trust with a noninvasive approach, children and teens will agree to needle insertion. Acupuncture, when done correctly, is virtually painless and well tolerated for older children.

Acupuncturists are licensed in more than 40 states. In most states, licensed health professionals such as physicians can practice acupuncture. Insurance plans increasingly offer acupuncture for chronic pain and chemotherapy-induced nausea and vomiting.

### Therapeutic Touch

Therapeutic Touch, Healing Touch, and Reiki are all secular forms of laying-on-of-hands healing. Actual touching the patient does not always take place because the human energy field, like the electromagnetic field, extends beyond the skin into the space surrounding the body. Therapeutic Touch was invented in the 1970s by a New York University nursing

professor, Dolores Krieger, and a lay healer, Dora Kunz. Based on their observations of numerous religious healers, they distilled the process into 5 steps that practitioners might bring to healing outside of a specific religious faith or belief. These steps are:

1. Having a clear and conscious intent to be helpful and heal
2. Being centered in a peaceful state of mind
3. Using hands to assess the patient's energy (typically moving the hands 1 to 3 inches away from the body in a slow downward sweep from the head to the toes)
4. Using hands to help restore the patient's energy to a balanced, harmonious, peaceful state
5. Releasing the patient to complete the healing process while the healer returns to the healer's own centered, peaceful state of mind

Nurses and other health professionals in more than 80 countries have received training in Therapeutic Touch from its founders. It is currently taught in nursing schools across the United States. Nursing practice in many hospitals, including children's hospitals, includes policies and procedures for performing Therapeutic Touch.

Additional techniques have been added to Therapeutic Touch in a group of treatments called Healing Touch, which is largely practiced by holistic nurses. Small studies have suggested that Healing Touch can help decrease stress and improve autonomic balance in pediatric oncology patients.

Reiki is a similar practice that comes from a Japanese tradition. Practitioners are trained by a Reiki master through apprenticeship and spiritual and energetic initiation. Neither Therapeutic Touch nor Reiki has national certifying examinations or state licensure. Therapeutic Touch and Healing Touch are typically provided by nurses in both inpatient and outpatient settings. Reiki is typically provided by lay practitioners outside of medical settings. No reports of side effects have been documented from such treatments. The primary clinical benefits of Therapeutic Touch are increased relaxation, diminished anxiety, diminished pain, and enhanced sense of well-being.

In addition to Therapeutic Touch and Reiki, some practitioners use electromagnetic or static magnetic fields to reduce pain or speed healing. For example, pulsed electromagnetic fields are used to promote union of long-bone fractures. There is growing research on the use of pulsed electromagnetic fields for fracture and wound healing in pediatrics. Growing research also supports the use of static magnetic fields to reduce pain and inflammation.

### Homeopathy

Homeopathy is a system of medical treatment invented in the early 1800s by the German physician Samuel Hahnemann. Homeopathy was frequently taught and practiced in US medical schools until criticized in the 1910 Flexner Report. Currently, homeopathy is popular in Europe, Russia, India, and South America.

Homeopathy is based on 2 principles: the *Law of Similars* or *like cures like* and the *Law of Dilutions*. The Law of Similars means that a remedy that would cause

a symptom in a healthy person is used to treat the same symptom in a sick person. For example, a treatment, termed remedy, made from the poison ivy plant (*Rhus toxicum*) might be used to treat a child suffering from eczema. Although pediatricians might be concerned about dangerous-sounding homeopathic medications such as *belladonna*, serious side effects from homeopathic treatment are exceedingly rare, far less common than side effects from standard over-the-counter and prescription medications.

Homeopathy's safety is attributable to homeopathy's second principle, the Law of Dilutions, which states that the more a remedy is diluted, the more powerful it becomes. Dilutions of 1 to 10 are designated by the Roman numeral X (1X = 1/10, 3X = 1/1,000, 6X = 1/1,000,000). Similarly, dilutions of 1 to 100 are designated by the Roman numeral C (1C = 1/100, 3C = 1/1,000,000, and so on). Most remedies today range from 6X to 30X, but some products are as dilute as 200C. Dilutions beyond 12X or 24C contain none of the original molecules. Common over-the-counter remedies include combination products for teething, colic, allergies, and bedwetting.

Homeopaths think that these highly dilute solutions contain an energy, or information, that the patient uses to heal symptoms. Many physicians think that the remedies are placebos that trigger the patient's psychoneuroimmunologic healing systems. Randomized controlled trials suggest some support for homeopathic remedies for diarrhea and otitis media but not for attention-deficit disorder.

The private, nonprofit Council for Homeopathy Education reviews homeopathic programs. Certification in homeopathy is given after testing by the Council. Certification boards exist for health care professionals, including physicians (American Institute of Homeopathy), chiropractors (National Board of Homeopathic Education), and naturopaths (Naturopathic Academy of Homeopathic Physicians). Persons who are not health care professionals are registered with the North American Society of Homeopaths.

## TALKING WITH PATIENTS ABOUT COMPLEMENTARY AND INTEGRATIVE MEDICINE

Although many physicians are concerned that families who use CIM may be dissatisfied with mainstream medical care and fear they may abandon effective therapies in favor of unproved alternatives, data do not support these concerns. Fifty-five percent of all surveyed adults think that CIM therapies would support health when used with conventional medical treatments. For the most part, families seek therapies that are consistent with their values, worldview, and culture, and they seek care from therapists who respect them as individuals and who offer them time and attention. Families continue to value highly the care they receive from compassionate, comprehensive primary care pediatricians, and they seek additional information on healthy lifestyles, dietary supplements, and environmental therapies over which they may exert some control. They also seek care from therapists who offer personal attention, hope,

time, and therapies that are consistent with their culture and values. Families who seek out CIM therapies rarely abandon their pediatrician, but they may not feel comfortable discussing these therapies if they perceive the pediatrician to be antagonistic or judgmental toward them.

To provide the best care, pediatricians should ask all patients about all the therapies they use to promote health. This task is best accomplished in a seamless, structured, and nonjudgmental manner during the medical interview. To set a positive tone, the physician can begin new patient interviews with questions about the number of meals eaten together as a family, fun things the family does together, hopes and dreams for the child, and aspects of the child of which they are most proud. At each return visit, a helpful question would be, "Since the last visit, which other health professionals has your child visited?" As with all good interviewing, listening for understanding rather than agreement or disagreement enhances the therapeutic alliance.

### Social History

During the social history, the physician should inquire about the following:

- Diet, exercise, and environment (including use of music to manage stress) to provide insight about risks and actions taken to promote health
- Illness care at home
- Any special foods, teas, rubs, prayers, or rituals that are helpful for the patient's family
- Any mind-body therapies to manage stress, reduce chronic symptoms, or promote well-being such as deep breathing, yoga, meditation, or prayer

One such question might be, "When you are stressed, what is most helpful for you? Which of your activities do you find is best for your health?" To assess psychological wellness, stress and time management, self-esteem, and self-concept, a thorough academic history and questions about learning style, friends, hobbies, and extracurricular activities should be included.

Questions regarding spirituality can be inserted at this point in the inquiry, as appropriate. Multiple mnemonics exist to guide physicians in their interviews to understand the patient's and family's source of meaning, purpose, richness, and direction (Box 57-3). Conscious choices expressed in the social history represent strengths that can be used for achieving health goals. Clearly, ethical boundaries exist around faith and spirituality. The physician's role is not to provide answers but to support the search for answers.

This point of the inquiry is also the time for assessing all potential environmental factors contributing to health and illness in children. A useful mnemonic for an environmental history is ACHHOO, with each letter representing a potential exposure site to known toxins such as lead, mercury, secondhand tobacco smoke, pesticides, and other contaminants:

- Activities
- Community
- Household
- Hobbies
- Occupation
- Oral behaviors



**BOX 57-3 Spiritual Assessment Tools****FICA****F: Faith or belief**—What is your faith or belief?**I: Importance and influence**—Is faith important in your life? How?**C: Community**—Are you part of a religious community?**A: Awareness and addressing**—What would you want me as your physician to be aware of? How would you like me to address these issues in your care?**HOPE****H: Hope**—What are your sources of hope, meaning, strength, peace, love, and connectedness?**O: Organization**—Do you consider yourself part of an organized religion?**P: Personal spirituality and practices**—What aspects of your spirituality or spiritual practices do you find most helpful?**E: Effects**—How do your beliefs affect the kind of medical care you would like me to provide?**SPIRIT****S: Spiritual belief system**—What is your formal religious affiliation?**P: Personal spirituality**—Describe the beliefs and practices of your religion or spiritual system that you personally accept or do not accept.**I: Integration within a spiritual community**—Do you belong to a spiritual or religious group or community? What importance does this group have for you?**R: Ritualized practices and restrictions**—Are there specific practices that you carry out as part of your religion/spirituality (eg, prayer or meditation)?**I: Implications for medical care**—Would you like to discuss religious or spiritual implications of health care?**T: Terminal events planning**—As we plan for your care near the end of life, how does your faith affect your decisions? Are there particular aspects of care that you wish to forgo or have withheld because of your faith?

Adapted from Puchalski CM, Romer AL. Taking a spiritual history allows physicians to understand patients more fully. *J Pall Med.* 2000;3:129–137; Anandarajah G, Hight E. Spirituality and medical practice: using the HOPE questions as a practical tool for spiritual assessment. *Am Fam Physician.* 2001;63:81–88; and Mougans TA. The SPIRITual history. *Arch Fam Med.* 1996;5:11–16.

**Allergies and Current and Past Medications**

When documenting current and past medication use, additional questions to ask in routine practice include the following:

1. Do you use multivitamins, for example, Poly-Vi-Sol or Flintstones chewable vitamins?
2. Do you use over-the-counter medications, for example, any medications for colds, pain, or constipation?
3. Do you use herbal medicines, for example, any herbs such as echinacea or chamomile?
4. Do you take specific vitamins and minerals, for example, vitamin C, D, or E? Do you take any mineral supplements such as calcium, iron, magnesium, or selenium?
5. Do you take dietary supplements, for example, any supplements such as fish oils, melatonin, or probiotics?

Follow-up questions include the following:

- What brand?
- What dose?
- How often?
- What directions are you following?
- What goals are you hoping to achieve by taking it?
- Are you using any other remedies now?

Understanding the supplements used and the patient's and family's source of information for making treatment decisions can be quite helpful for comprehending what is important to the family.

Interviewing for supplement use is crucial for identifying patients who are at risk for interactions with prescription medications or for excessive bleeding in surgery. Too frequently, professionals and patients follow a *don't ask, don't tell* policy. *Ask, provide an example, then ask again* is a practice policy that is foundational to safe and effective patient care.

Patients should be asked to bring all remedies with them to every visit so that the chart can be updated and usage monitored. Patients with special risks of drug interactions include those who take anticoagulants, hypoglycemics, antidepressants, sedative-hypnotics, antihypertensives, and medications with narrow therapeutic windows such as digoxin and theophylline.

**Medical History**

In addition to immunizations, surgeries, and hospitalizations, the interview for the medical history is a good time to ask about other therapies that often require multiple visits, such as chiropractic, massage, and acupuncture. Understanding what worked or did not work for the patient provides further insights into what is important for the patient and family. Additionally, questioning during this portion of the inquiry can help identify health issues that may be important to address in the context of a holistic approach to health.

**COUNSELING FAMILIES ABOUT COMPLEMENTARY AND INTEGRATIVE MEDICINE**

The goal of counseling is to strengthen the physician–patient relationship through honest dialogue that is clinically responsible, ethically appropriate, and legally defensible. Parental inclusion of CIM therapies for their children, in itself, does not constitute child neglect. Similarly, physician provision of complementary and alternative therapies does not, in itself, represent professional misconduct.

Increasingly, pediatricians will find themselves sharing patients with massage therapists, chiropractors, acupuncturists, and others. Pediatric patient advocacy requires assessing for safety and efficacy and respecting the autonomy of the parent–child relationship. When patients or families report seeing other health professionals and describe current CIM use, physicians should follow 3 steps in response to the answers provided:

Step 1. Determine whether the therapy represents a rejection of standard care for a serious or life-threatening disease for which a reasonable chance exists of cure or if use of the therapy will delay proven treatment. In such cases, the first step is to protect the child while understanding the parents' goals. Reporting requirements for abuse and neglect may apply. (See Chapter 367, Physical Abuse and Neglect.)

Step 2. Determine whether the therapies used are known to be unsafe, ineffective, or both. Excellent Web-based and other resources are noted at the end of this chapter to guide this assessment.

In the event of use of a known toxic agent or an ineffective agent with possible harm, the physician's responsibility is to counsel from the documented evidence that the therapy should be stopped. Resistance to such advice may place the parents at risk for charges of negligence or abuse.

In the absence of data on toxicity or efficacy, the pediatrician's role is to monitor as clinically appropriate. This role can include scheduling telephone follow-up or office visits. In both cases, document the following in the medical record:

- Therapy used and the goal of the therapy
- Patient or family preferences and expectations regarding the therapy
- Physician of the therapy, location, and treatment plan (as known by the family). This information should include names, telephone numbers, any other contact information, and specialties.
- Review of the safety and efficacy issues of the therapy from the medical literature

- Results of counseling including the pediatrician's treatment plan for monitoring the treatment and its results
- Advice provided or resources recommended for further information

Step 3. Ensure that the patient's and family's decision to use a therapy is based on a fully informed judgment and that their verbal consent was obtained and documented. This documentation includes what options have been discussed, offered, tried, or refused. (General guidelines for counseling are found in Box 57-4.) Counseling on spiritual concerns requires special consideration for clinical and ethical reasons. Although not classically part of medical training, adults in the United States consistently report that physicians talking with patients about spirituality is appropriate. When surveyed, 83% of 921 primary care patients surveyed in Ohio reported that they wanted physicians to ask about spiritual beliefs in certain circumstances, such as with serious illness or the loss of loved ones.

Spirituality may be understood as connection with the sources of ultimate meaning. Spirituality may or may not include formal religion. Spiritual concerns arise with threatened losses or disruptions of such connections. These issues can include key relationships with parents, other family members, and friends or what the child thinks God to be. For efficient and effective clinical care when spiritual issues are present, the following guidelines should be kept in mind:

1. Anticipate the presence of spiritual concerns with every illness. These concerns can include those of the patient, the family, and care team members, as well as one's own.
2. Comprehend how the patient's and the family's faith or spirituality can be a resource during illness.
3. Seek to understand how the patient's or the family's cultural and spiritual worldview influence understanding of the disease, the appropriate treatment, and the recovery process.

#### BOX 57-4 How to Talk With Patients About Complementary and Integrative Therapies

1. Do talk about the different kinds of therapies families may have tried to help their child.
2. Do not wait for families to bring it up.
3. Ask in an open-minded, nonjudgmental fashion. Avoid using potentially pejorative terms such as *unproved*, *unconventional*, or *alternative*.
4. Elicit further information with questions about specific therapies. For example, have you tried any *herbal* therapies, such as echinacea or ginkgo? Have you tried any *dietary* therapies, such as avoiding wheat or milk? Have you sought care from any *other health professionals*, such as acupuncturists or chiropractors?
5. Elicit the values, beliefs, and influences that led parents to these therapies. For example, were these suggested by family members? Were they consistent with their religious, spiritual, or cultural beliefs? What is the value of natural or organic approaches? Do they have a fear of side effects of mainstream treatments?
6. Whenever possible, join with the parents and support their decision to pursue avenues that may help their child. Be an ally rather than a tyrant.
7. Ask how well the family thinks the therapies worked or did not work *before* offering your opinion.
8. Offer to talk with other therapists involved in the child's care to maintain coordinated, comprehensive care.
9. Offer to learn more to help answer the family's questions.
10. Offer families additional information and resources to address their questions about alternative and complementary therapies.

4. Determine what effect, positive or negative, the patient's or the family's spiritual orientation or interpretation has on perceived needs.
5. Partner with, and refer to, chaplains or the patient's or the family's preferred spiritual care provider for assistance with significant spiritual concerns.

To achieve these goals, open-ended questions are always helpful. The physician should create a safe environment in which patients and families can articulate their questions. In contrast to the role of physicians in routine medical care, for spiritual concerns, solving problems and providing answers are rarely helpful. For spiritual concerns, the best answers are found rather than given. The physician's role is to support the search for answers.

## HOW TO PARTNER WITH OTHER PRACTITIONERS

Because of increasing interest and evidence of safety and efficacy, pediatricians increasingly want to partner with and refer to a growing number of diverse practitioners. This task is quite easy when credentialed practitioners exist in conventional settings such as hospital-based integrative pediatric clinics or consultation services. However, when a pediatrician provides the therapy or refers to practitioners in the community, the State Medical Board Guidelines apply. Key points include documenting the following in the medical record:

1. Parity of evaluation (medical history and physical examination as thorough as for conventional care)
2. Informed consent (review of diagnosis, all medical options for that diagnosis, discussion of risks and benefits of the recommended treatment, including potential interference with ongoing conventional care, and any applicable financial interests)
3. Treatment plan objectives and goals (expected favorable outcomes and monitoring plan for duration of treatment). Physicians should only refer to licensed or otherwise state-regulated health care practitioners with the requisite training and skills to use the therapy being recommended. Physicians are expected to not sell, rent, or lease health-related products or engage in personal branding. Physicians must also be able to demonstrate a basic understanding of the medical scientific knowledge connected with any recommended therapy.

Physicians are not liable for any negligence on the part of another physician unless the referral delayed necessary conventional treatment, the physician knew the provider was not competent to provide the therapy, or the physician hired the provider or provided joint treatment with the provider.

When making referrals for children with complex chronic illness or chronic pain, pediatricians must carefully prioritize and schedule necessary conventional therapies. They must also coordinate care with all subspecialists. Equally important, however, pediatricians must consider the effect on time and expenses of families who are vulnerable as they seek any available therapies for children. The pediatrician should set appropriate expectations, support appropriate hope, and avoid overscheduling and overtreating children.

## CONCLUSION

Increasingly, the public expects pediatricians to provide wise counsel on all reasonable available therapies and to make appropriate referrals based on scientific evidence and families' values and goals. There are many opportunities for pediatricians to seek additional training to enhance their clinical practice. Additionally, the American Academy of Pediatrics, the National Institutes of Health, and many other organizations provide additional resources to support pediatric service excellence.

## AAP POLICY

- American Academy of Pediatrics Committee on Children with Disabilities. Counseling families who choose complementary and alternative medicine for their child with chronic illness or disability. *Pediatrics*. 2001;107:598–601. Reaffirmed May 2010 ([pediatrics.aappublications.org/content/107/3/598](http://pediatrics.aappublications.org/content/107/3/598))
- American Academy of Pediatrics Committee on Pediatric Workforce. Scope of practice issues in the delivery of pediatric health care. *Pediatrics*. 2013;131(6):1211–1216 ([pediatrics.aappublications.org/content/131/6/1211](http://pediatrics.aappublications.org/content/131/6/1211))
- Kemper KJ, Vora S, Walls R; American Academy of Pediatrics Task Force on Complementary and Alternative Medicine and Provisional Section on Complementary, Holistic, and Integrative Medicine. The use of complementary and alternative medicine in pediatrics. *Pediatrics*. 2008; 122(6):1374–1386. Reaffirmed January 2013 ([pediatrics.aappublications.org/content/122/6/1374](http://pediatrics.aappublications.org/content/122/6/1374))

## SUGGESTED READINGS

- American Academy of Pediatrics Section on Integrative Medicine. [www2.aap.org/sections/chim/default.cfm](http://www2.aap.org/sections/chim/default.cfm). Accessed October 29, 2015
- Children's Hospitals and Clinics of Minnesota. Integrative medicine. [www.childrensintegrativemed.org](http://www.childrensintegrativemed.org). Accessed October 29, 2015
- Columbia University Medical Center/Center for Comprehensive Wellness. Integrative therapies. [ccw.columbia.edu/patient-care/integrative-therapies](http://ccw.columbia.edu/patient-care/integrative-therapies). Accessed October 29, 2015
- National Institutes of Health, National Center for Complementary and Integrative Health. Are you considering using a complementary health approach? [nccih.nih.gov/health/decisions/consideringcam.htm](http://nccih.nih.gov/health/decisions/consideringcam.htm). Updated August 2014. Accessed October 29, 2015
- Pediatric Use of Complementary and Alternative Medicine: Legal, Ethical, and Clinical Issues in Decision-Making. *Pediatrics*. 2011;128(Suppl 4):A1-S212

## Chapter 58

# FLUIDS, ELECTROLYTES, AND ACID-BASE COMPOSITION

Prashant Mahajan, MD, MPH, MBA; Jon R. Felt, MD

Evaluating and managing fluid and electrolyte disorders in children requires an understanding of the composition of the human body and the regulatory mechanisms that maintain homeostasis. The primary care physician will encounter the issue of managing fluids and electrolytes in a large number of patients.

The optimal fluid and electrolyte solution varies depending on the age of the patient, cause of the disease, severity of the condition, and presence of a coexisting morbidity in the patient. Normal homeostasis is maintained by a complex interaction among the solutes, body water, hormonal influence, and the hypothalamic-pituitary-renal axis. Guiding the approach to fluid therapy in any child are a few basic principles of human physiology, including the regulation of body water, electrolytes, and acid-base equilibrium.

### BODY FLUID COMPARTMENTS

The entire body mass is composed of total body water (TBW) and body solids (fat, skeletal muscle, and cellular components). Traditionally, TBW has been viewed as a composite of intracellular fluid (ICF) and extracellular fluid (ECF), and it varies with sex, age, and fat content.

The size of the body's fluid compartments changes significantly in the first year of life. TBW comprises approximately 75% of an infant's mass and approximates the adult figure of 60% by 1 year of age. TBW varies inversely with the fat content of the body. TBW decreases in dehydration, becoming a smaller percentage of body weight.

The ECF is divided into intravascular fluid or plasma (5% of body weight) and interstitial fluid (15% of body weight) (Figure 58-1). The term *effective circulating volume* refers to the blood volume that is perfusing the tissues of the body and is in contact with and stimulating the volume and pressor receptors. The delicate balance between intravascular fluid and interstitial fluid is maintained by hydrostatic pressures (the result of the pumping action of the heart), as well as osmotic pressures and oncotic pressures (the result of the

presence of proteins, mainly albumin, in circulation). Pathologic conditions such as nephrotic syndrome reduce the plasma oncotic pressure and tend to increase the interstitial fluid volume at the expense of intravascular fluid volume, whereas states of dehydration cause a decrease in both interstitial and intravascular volume. ICF constitutes 40% of TBW and is separated from the ECF by cell membranes that are highly water permeable but selectively impermeable to solutes.

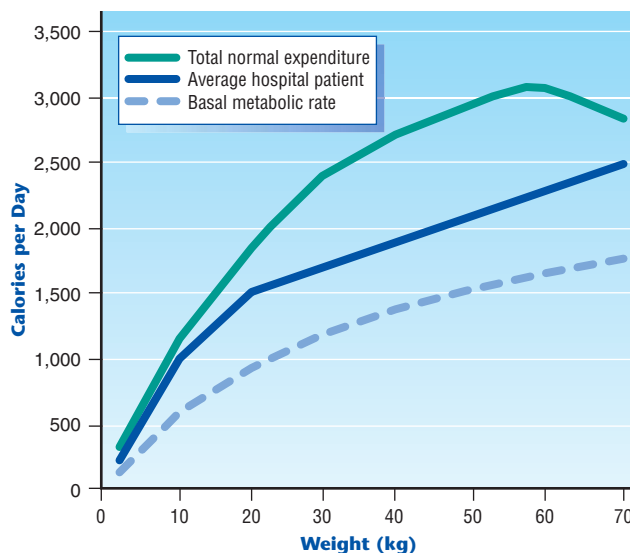
### ELECTROLYTE COMPOSITION

In plasma, sodium is the major cationic particle, with smaller concentrations of calcium, magnesium, and potassium present. Electroneutrality is maintained by an equal number of anionic particles, primarily chloride, bicarbonate, and protein. In addition to these particles are the unmeasured anions that are not part of the laboratory profile (the anion gap), namely phosphate, sulfate, and various organic acids.

The composition of ICF is different from that of plasma (Table 58-1). Potassium is the most abundant intracellular cation, followed by magnesium and a relatively small amount of sodium. The major intracellular anions are organic phosphates and proteins, with smaller concentrations of bicarbonate and sulfate.

The large concentration gradient of electrically charged particles between ECF and ICF is critical to maintaining various cellular functions, such as nerve conductance, muscle movement, and secretory processes. This gradient is maintained by active transport mechanisms found in cell membranes.

The laboratory measurement of serum concentration of electrolytes does not always reflect total body content, and care must be taken when interpreting these results. For example, a shift of intracellular potassium into the intravascular space may lead to a normal serum level while masking a significant decrease in total body content of potassium.



**Figure 58-1** Metabolic requirements of the average hospitalized patient. The center line represents calculated caloric requirements for average hospitalized patients. See text for explanation of the 3 sections of the curve. (Adapted from Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. *Pediatrics*. 1957;19(5):823–832.)

**Table 58-1**

#### Normal Electrolyte Composition of Fluid Compartments

ELECTROLYTES	PLASMA (mEq/L)	INTRACELLULAR FLUID (mEq/L)
<b>CATIONS</b>		
Sodium	140	±10
Potassium	4	160
Calcium	5	3.3
Magnesium	2	26
<b>Total Cations</b>	<b>151</b>	—
<b>ANIONS</b>		
Chloride	104	±2
Bicarbonate	25	±8
Phosphate	2	95
Sulfate	1	20
Organic acids	6	—
Protein	13	55
<b>Total Anions</b>	<b>151</b>	—



## OSMOLALITY AND OSMOTIC PRESSURE

The ICF and ECF are separated from each other by cell membranes that are highly water permeable but selectively impermeable to solutes. The movement of water across the cell membrane is responsible for maintaining osmotic equilibrium. Water will flow along an osmotic gradient from areas of low osmolality to areas of high osmolality, thus maintaining osmotic equilibrium between the ECF and the ICF. Osmolality is a measure of the amount of dissolved solids in the various fluid compartments and is determined by the number of molecules in solution, independent of their size.

By far the most substantial contribution to normal plasma osmolality is made by sodium and its associated anions. Under most circumstances the plasma osmolality is approximately equivalent to twice the concentration of plasma sodium. However, under unusual circumstances, or for precision, the osmolality can be calculated using the following formula:

$$\text{Osmolality} = 2 \times \text{Sodium} + \text{Glucose}/18 + \text{BUN}/2.8$$

Changes in the ECF content of sodium or glucose will cause significant fluid shifts between the ECF and ICF. This shift has important clinical implications, especially in diabetic ketoacidosis, in which hyperglycemia causes a shift of water from the ICF to the ECF and dilutes the plasma sodium (hyponatremia) in spite of an elevated osmolality. In this case, the plasma sodium needs to be corrected for hyperglycemia. The formula for correction is:

$$\text{Corrected sodium} = \text{measured sodium} + [1.6 (\text{glucose} - 100) / 100]$$

Serum sodium concentration falls in proportion to the dilution of the ECF, declining 1.6 mEq/L for every 100 mg/dL (5.55 mmol/L) increment in the plasma glucose level above normal.

Normally, a difference of 10 mOsm/kg exists between the measured and calculated osmolality. This osmolar gap (the result of unmeasured osmoles) should be calculated because it may reflect the presence of unmeasured osmoles such as alcohols (methanol, ethylene glycol, and isopropyl alcohol, or acetone), which often present in toxic ingestions. A mnemonic for some of the more common causes of an elevated osmolar gap is “MAE DIE”: methanol, acetone, ethanol, diuretics (mannitol, sorbitol), isopropanolol, and ethylene glycol. Hypertriglyceridemia (most commonly seen in children with nephrotic syndrome) is another cause of an elevated osmolar gap and should not be overlooked.

## REGULATING TOTAL BODY WATER AND OSMOLALITY

Homeostasis is maintained by independent systems for water balance, which determines osmolality, and sodium balance, which determines volume status. Although the most important determinant of plasma osmolality is sodium, the body maintains normal osmolality not by the regulation of sodium but by the regulation of TBW. Maintaining intravascular fluid volume takes precedence over maintaining osmolality.

## Regulating Osmolality

Normal plasma osmolality is maintained between 275 and 295 mOsm/kg by modification of water intake and excretion. Although some water is produced in the body during oxidation, gastrointestinal (GI) absorption from oral intake is the main source of water. Water loss is primarily regulated via the kidneys and urinary excretion, but other systems play a role, particularly during physiologic states. Evaporative losses through the skin occur with exertion, fever, and increased environmental temperatures. Evaporation also occurs through the lungs with normal breathing, but increases with tachypnea (respiratory illnesses, exertion, or as a compensation for fever). Large losses can occur through the GI tract with infection and inflammatory diseases causing vomiting and diarrhea.

The osmolality in plasma is detected by osmoreceptors in the hypothalamus, which regulate the secretion of antidiuretic hormone (ADH). Thus, during states of elevated plasma osmolality, secretion of ADH is increased, which increases the permeability of the renal collecting ducts to water and maintains normal osmolality by reducing urinary free-water losses. At the same time, a different set of osmoreceptors stimulate the cerebral cortex to facilitate water intake by increasing the sensation of thirst. Healthy adults begin to experience intense thirst at plasma osmolality levels of 290 mOsm/kg, with profoundly increasing intensity as the osmolality reaches 300 to 305 mOsm/kg. At this point, the person consumes large amounts of water (assuming free access, which is not the case with infants and young children) until plasma osmolality is brought back below the thirst-threshold level. The secretion of ADH occurs at a lower threshold than that for thirst and is initiated (thus inhibiting renal water loss) at a plasma osmolality level above 280 mOsm/kg. Similarly a reduction in plasma osmolality leads to the suppression of ADH, increased urinary water loss, and simultaneous suppression of the thirst mechanism.

## Sodium and Sodium Homeostasis

Plasma sodium is the single most important determinant of intravascular volume. Sodium homeostasis depends on the ability of the kidneys to alter its excretion in the urine, which occurs in response to change in effective circulating volume and circulating levels of plasma sodium.

Sodium is the major osmotically active cation in plasma. The total body content of sodium approximates 60 mEq/kg, but almost 43% of this content is contained in bone, most of which plays almost no role in the daily regulation of sodium concentration. Most of the remainder is concentrated in the interstitial and plasma fractions, with only a small amount in the intracellular space.

Sodium homeostasis results from the balance of sodium intake and excretion. Intake is controlled by dietary habits, and although some central regulation for sodium exists given that thirst is present (many patients who lose salt seem to develop a craving for sodium), it seems to be poorly developed and has not yet been localized. The typical American adult's diet contains 100 to 170 mEq of sodium per day; the amount of sodium in an infant's diet varies according

to the amount and composition of formula or human milk the infant receives. Most of the dietary sodium is absorbed actively in the jejunum. Aldosterone secretion increases GI sodium absorption.

Sodium excretion is controlled primarily by the kidneys but also by the GI tract and skin. Although a large amount of sodium is presented to the kidneys during glomerular filtration, almost 99% of it is resorbed in the kidney tubules. In conditions of severe sodium depletion, volume depletion, or both, the amount resorbed may increase to nearly 100%; in cases of sodium and water overload, it may decrease to approximately 90%. The renin-angiotensin-aldosterone system, when stimulated by decreased renal blood flow, facilitates a greater degree of sodium resorption in the distal convoluted tubules and collecting ducts through the action of aldosterone increasing the number of open sodium channels at these sites.

Hyponatremia (serum sodium  $>145$  mEq/L) is often seen in dehydration if the loss of water is greater than that of sodium. These losses may occur through the lungs, skin, stool, or urine (especially in the presence of diabetes insipidus). Another important, although uncommon, cause of hyponatremia in young children is the overuse of commercial enema preparations containing high concentrations of phosphate and sodium. Although elevated sodium content of human milk has been implicated as a cause of hyponatremia in breastfed infants, routine analysis of breast milk composition is unnecessary unless more common causes, such as inadequate milk volume, have been ruled out.

The signs and symptoms of hypernatremic dehydration may be difficult to interpret accurately, and the severity of dehydration may not be apparent based on physical examination alone. ECF volume remains relatively well preserved because of the shift of water from the ICF caused by a change in plasma osmolality; therefore, clinical signs of dehydration are often absent. Hypernatremia results in marked changes in central nervous system function, especially if the electrolyte disturbance occurs rapidly (within a few hours), which is common in small children. Affected infants exhibit marked irritability alternating with severe lethargy. Seizures may occur and may be followed by coma if the condition is not diagnosed and adequate therapy is not initiated. Brain hemorrhage can occur because of the movement of water from the brain cells as subsequent loss of volume in the brain increases the subdural space, which results in tearing of the bridging veins. If the state of hypernatremia persists, then the brain cells react by increasing their intracellular concentrations of osmotically active solutes (previously referred to as *idiogenic osmoles*) glutamate, glutamine, taurine, and the carbohydrate myoinositol. This action reduces neuronal dehydration and has important clinical implications. Rapid correction (ie, reduction of plasma sodium) leads to a shift of free water to the ICF (mainly neurons), leading to cerebral edema, which produces seizures and coma. Thus, carefully lowering the serum sodium level by no more than 10 to 12 mEq/L over a period of 24 hours with frequent monitoring is important. In addition, elevation of the serum sodium concentration may lead to

skeletal muscle rigidity and hyperactive deep-tendon reflexes.

Hyponatremia (serum sodium  $<130$  mEq/L) occurs whenever body sodium stores are diluted or depleted. It is more often related to failure to excrete adequate amounts of water than to simple overhydration; however, in small infants the intake of hypotonic formulas or human milk low in sodium may lower the plasma sodium concentration substantially. Hyponatremic dehydration is less common in children with acute diarrhea and is most often encountered because large stool losses are replaced with solutions containing little or no sodium (eg, water, fruit juices, and colas). Any situation that increases the secretion of ADH may be associated with low serum sodium concentrations. This circumstance is seen in patients who have the syndrome of inappropriate ADH secretion resulting from central nervous system disease, pneumonia, or meningitis. Addison disease and congenital adrenal hyperplasia are associated with excessive loss of sodium in the urine and with retention of potassium. Children who have obstructive uropathy and progressive renal failure are less able to resorb sodium from their renal tubules; therefore, they sustain large sodium losses and may exhibit mild dehydration with a borderline or low serum sodium concentration. Children treated with vasopressin or 1-deamino-8-D-arginine vasopressin may develop iatrogenic hyponatremia, as may children receiving diuretic therapy. The administration of enemas low in saline concentration also may result in hyponatremia. An excessive loss of sodium and water occurs in individuals suffering from heat-related illnesses. The serum sodium concentration reported by the laboratory may be artificially low in the presence of marked hyperlipidemia and hyperproteinemia (pseudohyponatremia). Highly elevated concentrations of blood glucose (as in diabetic ketoacidosis) are associated with real and factitious hyponatremia.

Signs and symptoms of hyponatremia are related to the duration of the lowered serum sodium concentration, the rate of decrease in serum sodium, and the plasma volume status. They are directly related to shifting solute concentrations between the intracellular and extracellular space, and symptoms can be particularly severe if the sodium drop is acute. Hyponatremia associated with diminished plasma volume results in anorexia, muscle cramps, lethargy, and shortness of breath on exertion. With further decreases in sodium concentration, nausea, emesis, and muscle weakness ensue, which may proceed to delirium and seizures. Hyponatremia associated with acute water intoxication is more likely to result in seizures and coma than in conditions in which the plasma volume remains unchanged.

### Potassium

Potassium is the major intracellular cation. The total potassium content is approximately 50 mEq/kg of body weight, with concentrations of intracellular and extracellular potassium of 145 mEq/L and 4 to 5 mEq/L, respectively.

The kidney is the primary organ involved in potassium homeostasis. Potassium is filtered by the glomerulus

and is resorbed and secreted by the tubule. Most potassium absorption occurs in the proximal portions of the GI tract, where it is excreted in the colon in exchange for sodium. Thus, disorders of the kidneys and altered absorption in the GI tract are associated with significant abnormalities in serum potassium levels. Aldosterone is intimately involved in regulating potassium by increasing its excretion from the GI tract, the skin (skin losses are relatively minimal except in patients with cystic fibrosis), and the kidneys. The urinary excretion of potassium results from tubular secretion rather than glomerular filtration. Aldosterone acts at the level of the distal tubule to foster sodium resorption and potassium secretion. Thus, sustained hypovolemic states result in enhanced renal potassium losses. Other examples of renal losses of potassium include renal tubular acidosis (RTA) types I and II, diuretic abuse, and some chemotherapeutics.

Potassium often shifts between the intracellular and extracellular spaces, mediated mostly by alterations in the serum acid-base status. Extracellular potassium concentration increases with systemic acidosis, and alkalosis leads to the movement of potassium into the cell. Other causes of increased cellular potassium uptake include increased insulin activity and  $\beta$ -agonists (albuterol, epinephrine, and dopamine). GI losses are primarily a result of diarrhea and vomiting, but iatrogenic losses occur with nasogastric and gastric tube drainage.

Though relatively uncommon in healthy children, common causes of hyperkalemia are rhabdomyolysis from crush injuries, tumor lysis syndrome, and kidney disease. Acute kidney injury, often present with these conditions, exacerbates hyperkalemia by reducing urinary excretion. Increased potassium levels can be life threatening because of the effect on membrane potential, especially in cardiac muscle. The earliest sign of cardiac toxicity is in the form of tall, peaked T waves (with normal or short QT interval and short PR interval). They are seen at serum concentrations of 5.5 to 6.5 mEq/L. A widened QRS complex with a prolonged PR interval is seen at levels between 6.5 and 7.5 mEq/L. Subsequent increases in serum potassium levels are associated with broad P waves, QT prolongation (7.0–8.0 mEq/L), and absent P waves with a markedly widened QRS (sine wave pattern) at levels above 8.0 mEq/L.

Most patients with hypokalemia are asymptomatic, particularly if the disorder is mild (3.0–3.5 mEq/L). Most commonly the clinical findings in patients with hypokalemia include muscle weakness and ileus. Cardiac effects may also be exhibited on the electrocardiogram by low voltage, flattening of the T waves, depression of ST segments, prominence of U waves, arrhythmias, and asystole. However, these effects are usually not seen until the serum potassium concentration falls below 2.0 mEq/L. When levels fall below 2.0 mEq/L, an ascending paralysis can develop, with eventual respiratory muscle paralysis. The likelihood of symptoms caused by hypokalemia depend on the rapidity of decrease and presence of underlying heart disease; these children should be treated promptly (especially children who are receiving digitalis derivatives).

### Other Ions

Concentrations of chloride, calcium, magnesium, and phosphorous are also critical to the maintenance of cellular function, but their role in typical fluid disturbances is relatively minor and are not discussed here. The remaining ion of interest is bicarbonate, which is crucial to the acid-base buffering system in plasma that is responsible for the close maintenance of a normal pH in the setting of widely varying conditions. Control of the bicarbonate concentration is the result of interactions between its plasma concentration and those of carbon dioxide and water. The concentrations of these components, and thus control and maintenance of pH, are affected by the function of the kidneys and the lungs. In metabolic acidosis, when plasma pH falls in the setting of poor tissue perfusion or increased acid production, the kidney retains bicarbonate ions, whereas the lungs increase their elimination of carbon dioxide by increasing minute ventilation, driving the system toward a higher pH. In respiratory acidosis, usually induced by excessive carbon dioxide production or inadequate elimination by the lungs, the kidney responds by retaining bicarbonate ions. Conversely, with respiratory alkalosis, as in the case of increased minute ventilation and excessive carbon dioxide losses, the kidney excretes increased amounts of bicarbonate ion, lowering plasma pH. A series of conditions that result in the dysregulation of bicarbonate in the kidney are the 4 different forms of RTA. Particularly severe are type 2 RTA and Fanconi anemia, which affect primarily the proximal tubule of the kidney and inhibit bicarbonate resorption. This results in severe acidosis, which the body is unable to correct.

In most situations requiring fluid therapy, a metabolic acidosis prevails as a result of diminished tissue perfusion. Attention to the pH and buffering characteristics of fluids administered is important, but more important is administering sufficient amounts of isotonic fluids that will result in the rapid reexpansion of the ECF. The resulting enhanced tissue perfusion, elimination of tissue acids, and restoration of end-organ function halts the acidosis.

### MAINTENANCE REQUIREMENTS

In clinical practice, maintenance fluids and electrolytes must be provided, and deficits caused by ongoing losses, if any, must be corrected. The key to understanding maintenance fluid and electrolyte requirements is recognizing that they stem from basal metabolism. Metabolism creates 2 byproducts—heat and solute—that need to be eliminated to maintain homeostasis. Heat is lost through insensible evaporation of water from the skin (accounting for two-thirds of insensible water loss; approximately 30 mL/100 kcal) and from the respiratory system (accounting for one-third of insensible water loss; approximately 15 mL/100 kcal). Sensible water losses occur primarily through urine output (55 mL/100 kcal), which is needed by the body to excrete the daily solute byproducts from metabolism. Obligate urine output, the minimal amount of urine needed to eliminate daily solute by-products, is approximately 25 mL/100 kcal.

### Water

Daily water needs are based on insensible losses from the respiratory tract and skin and sensible losses from the



urine and stool. Traditionally, water requirements have been calculated by 1 of 3 methods: body weight, body surface area, or metabolic rate. The water need per unit of body weight changes dramatically with age and size and therefore is not very useful. Body surface area was once thought to correlate well with both metabolic expenditure and fluid needs, but this has been shown not to be the case, especially in neonates and in children between 6 months and 3 years of age. Additionally, surface area is determined by comparing height and weight with a nomogram, which is cumbersome and depends on accurate measurements (height is notoriously difficult to measure in young children and infants). The use of the metabolic rate to calculate fluid requirements is attractive because it is based on physiologic principles and is a constant number; approximately 100 mL (1 dL) of water is needed for every 100 calories consumed. Using an average hospitalized child who has a metabolic rate midway between normal activity and basal metabolic rate as a standard, a fluid requirement can be derived based on calorie expenditure that is quite simple and can be calculated from body weight (Figure 58-2). This value results in a maintenance water requirement of 100 mL/kg per day for each of the first 10 kg, 50 mL/kg per day for each additional kilogram from 11 to 20, and 20 mL/kg per day for each subsequent kilogram. When converting to an hourly fluid rate, the simplest approximation is 4 mL/kg per hour for the first 10 kg, 2 mL/kg per hour for the next 10 kg, and 1 mL/kg per hour for each additional kilogram. This value results, for example, in an hourly maintenance rate of 32 mL/h for an 8-kg infant ( $4 \text{ mL/kg} \times 8 \text{ kg}$ ), 50 mL/h for a 15-kg toddler ( $4 \text{ mL/kg} \times 10 \text{ kg} = 40 \text{ mL}$ , plus  $2 \text{ mL/kg} \times 5 \text{ kg} = 10 \text{ mL}$ ), and 70 mL/h for a 30-kg child ( $4 \text{ mL/kg} \times 10 \text{ kg} = 40 \text{ mL}$ , plus  $2 \text{ mL/kg} \times 10 \text{ kg} = 20 \text{ mL}$ , plus  $1 \text{ mL/kg} \times 10 \text{ kg} = 10 \text{ mL}$ ) (Table 58-2). This simple approach meets the maintenance fluid requirements for most children and should be adjusted up or down depending on factors such as rate of insensible fluid losses (tachypnea, burns) or decreased fluid excretion (renal failure).

### Electrolytes

The maintenance requirement of sodium for the average infant is between 2 and 3 mEq/100 cal, and the

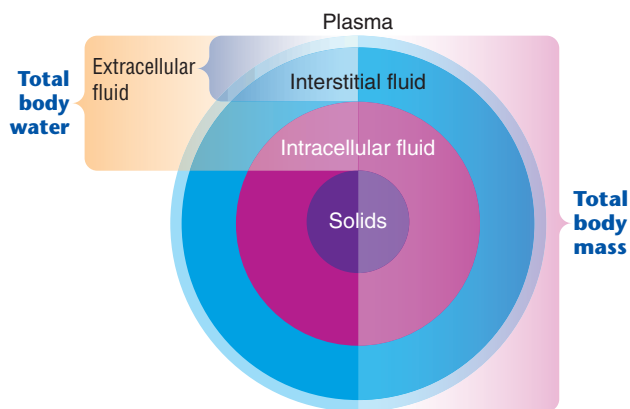
potassium requirement is closer to 2 mEq/100 cal. Because sodium and potassium are supplied routinely in the form of chloride salt, the infant or child receives between 4 and 5 mEq/100 cal of chloride ion, although the absolute chloride requirement probably is very small. An important point to remember is that the amounts of water and electrolytes for maintenance needs are based on the metabolic rate and not body weight. This point is especially important while calculating electrolyte needs in an older child or adolescent.

### Calories

The nutritional component of maintenance therapy should provide a substrate for metabolism. Although optimal nutritional therapy provides an equal number of calories to those expended, for short-term administration of parenteral fluids, little consideration is usually given to replacing caloric expenditure calorie per calorie. Rather, the reason for adding calories in the form of dextrose to parenteral fluids is to prevent ketosis and the breakdown of endogenous protein. This can be accomplished using 5% dextrose containing fluids, which provide between 17 and 20 calories per 100 calories expended. For infants and small children, the absolute glucose requirement to prevent ketosis and overt hypoglycemia is higher (4–6 mg glucose/kg per minute), and these patients may require higher dextrose concentrations.

## COMPOSITION OF MAINTENANCE FLUID FOR PARENTERAL USE

The composition of the parenteral fluid that can be administered under normal circumstances to a hospitalized patient for a short period (up to several days) is calculated based on 1 dL water, 2 to 3 mEq sodium, 2 mEq potassium, and 5 g glucose for every 100 calories expended. The composition of a suitable fluid for maintenance therapy, therefore, would be 20 to 30 mEq sodium, 20 mEq potassium, and 50 g glucose (values expressed per liter) for every 100 calories expended. Values of sodium in parenteral fluids usually are expressed as a fraction of normal saline solution. Normal saline is a 0.9% solution of sodium chloride that provides 154 mEq of sodium per liter of solution. While this calculation would prescribe the use of a quarter-normal



**Figure 58-2** Fluid compartments of the body.

**Table 58-2**

**Holliday-Segar Formula for Determining Daily Maintenance Fluid Requirements**

WEIGHT (kg)	kcal/d OR mL/d	kcal/h OR mL/h
0–10	100 kg/d	4 mL/kg/h
11–20	$1000 + (50/\text{kg/d})^a$	$40 + (2 \text{ kg/h})$
>20	$1500 + (20/\text{kg/d})^b$	$60 + (1 \text{ kg/h})$

<sup>a</sup>For each kg >10.

<sup>b</sup>For each kg >20.

From Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. *Pediatrics*. 1957;19(5):823–832.



saline solution (0.225% sodium chloride containing 38 mEq of sodium per liter), evidence has shown that hypotonic maintenance solutions place hospitalized children at high risk for developing hyponatremia, due in most part to high circulating ADH levels as a result of the stresses of illness. Isotonic parenteral solution (normal saline) or at the very minimum, half-normal saline (77 mEq of sodium per liter) has been recommended for use in maintenance fluid therapy, because it has been shown to significantly decrease the risk of developing hyponatremia. Concerns of inducing hyponatremia by using solutions with up to 5 times the physiologic requirement of sodium, have not been borne out in clinical practice. These solutions are usually formulated with 5% glucose (50 g/L); 20 mEq of potassium can be added to each liter, yielding solutions with a higher osmolality than that of plasma, but this effect is transient and dissipates as glucose is taken up by the cells.

### ADMINISTRATION

Once the appropriate concentration of each solute in the parenteral fluid has been determined, the solution is administered through a peripheral vein at a rate of 100 mL/100 cal of the expected energy expenditure. Procedures for gaining vascular access in children are described in Appendix B, Outpatient Procedures. Although not a new method, the technique of administering fluids and medications into the bone marrow (intraosseous infusion) has been demonstrated to be safe and effective in providing volume replacement and resuscitation drugs in an emergency. It may be used in infants and children when intravenous access cannot be obtained rapidly. Techniques for performing this procedure also are found in Appendix B. Any solution that can be given intravenously may be given via the intraosseous route.

### WHEN MAINTENANCE IS NOT ADEQUATE

In the preceding sections, a rational approach is outlined for supplying children with maintenance fluids. Based on the physiologic mechanism of the illness, the needs of any given child may differ considerably from these maintenance requirements. However, the calculations presented remain valid over a wide range of situations if used as a basis on which unusual losses are added. Any and all of the organs normally involved in water homeostasis may be sought as sources or reasons for water loss: water lost through the GI tract in the form of diarrhea or vomiting; massive renal excretion of water in diabetes mellitus or diabetes insipidus, RTA, or after administration of osmotic or other diuretics; excessive sweating caused by autonomic instability, fever, or high ambient temperature; and an increased loss of lung water with hyperpnea from any cause, including hyperpyrexia. Processes that do not normally contribute to water loss also may be involved, such as losses through a nasogastric tube and acute blood loss. In addition, increased demands for fluids exist in various conditions of elevated metabolic rate (eg, thyrotoxicosis), in situations that create

large shifts in the body's fluid compartments (usually of the vascular space), and in many perioperative conditions (third spacing) that, if uncorrected, may produce shock. The persistence of any of these abnormal conditions in the absence of adequate fluid intake leads to water or electrolyte deficits or both. In addition, the fluid administration scheme must take into consideration ongoing losses and provide appropriate replacement of these lost fluids.

Fluids sometimes need to be supplied in amounts below those estimated for the average hospitalized patient. Any child who has a diminished urine output because of renal failure or acute kidney injury may not require as much free water as the child's healthy counterpart. Children who are placed in mist tents or maintained on ventilators lose less water through their lungs and should have a lower estimate made of insensible water loss. Children whose activity levels are below those predicted for most bedridden patients (eg, those in coma or who are paralyzed) expend fewer calories and therefore require less water (Figure 58-2).

### ESTIMATING AND CORRECTING DEFICITS AND ONGOING LOSSES

The best way to estimate fluid and electrolyte deficits is to determine how much fluid has been lost from each body compartment, the electrolyte concentration of the lost fluid, and the period over which such losses have occurred. In most situations, however, therapy must be initiated before these data can be collected. In addition, the volumes of diarrheal or emetic losses may be extremely difficult to measure.

The first step in evaluating a child who has a fluid and electrolyte deficit is to determine the degree of total body volume that has been lost. Although fluids and electrolytes are lost from all body compartments, the intravascular volume status is the most immediately relevant. Children who have sustained severe losses of intravascular (circulating) fluid volume are at risk for shock, which may result in irreversible organ system damage and death if not addressed promptly.

Table 58-3 contains a systematic approach to estimating fluid losses. Typically, a child may be categorized as mildly, moderately, or severely dehydrated according to clinical findings. (The term *dehydration* is used here in its most common sense, meaning losses of fluid volume. Technically, dehydration refers only to pure water losses, a condition almost never seen clinically.) Attention should be given to the immediate replacement of the estimated fluid losses via the oral (including nasogastric administration), intravenous, or intraosseous routes, depending on the child's overall clinical status. Even before a formal calculation is made, an initial fluid bolus of 20 mL/kg over 20 to 30 minutes should be given to any child who seems to be severely dehydrated or in shock.

When calculating the final amount of fluid to be replaced, either a recent normal weight should be used, if available, or the deficit may be calculated based on an average (50th percentile) weight for the child's age. Formerly, fluid replacements were administered over a 24-hour period, with the aim of restoring one-half of

**Table 58-3** Signs and Symptoms Related to Degree of Dehydration<sup>a</sup>

PARAMETER	DEGREE OF DEHYDRATION		
	MILD	MODERATE	SEVERE
Weight loss in child <1 y (%)	3–5	10	15
Weight loss in patient >1 y (%)	2–3	6–9	>10
Skin color	Pale	Gray	Mottled
Skin turgor	May be normal	Decreased	Tenting
Mucous membranes	Slightly dry	Dry	Dry, parched, collapse of sublingual veins
Eyes	Probably normal	Decreased tears	Sunken, absence of tears, soft globes
Central nervous system	Normal	Irritable	Lethargic
<b>PULSE</b>			
Quality	Strong	Somewhat decreased	Distal pulse not palpable
Rate	Probably normal	Somewhat increased (orthostatic changes)	Markedly tachycardic
<b>OTHER PARAMETERS</b>			
Capillary refill	Normal (<2 s)	2–4 s	>4 s
Blood pressure	No change	Orthostatic decrease	Decreased while supine
Urine	Probably normal or slightly decreased volume	Elevated specific gravity, decreased volume	Less than 0.5 mL/kg/hr over the previous 12–24 hr; may be anuric

<sup>a</sup>Table is most useful for situations involving isotonic dehydration. (See text for adjustments needed for other forms of dehydration.)

the deficit in the first 8 hours of therapy and the second half in the subsequent 16 hours. It is apparent that faster rates of fluid repletion are both more effective and simpler and that complicated formulas for calculating fluid and electrolyte replacements are not necessary. In most cases, dehydration of a mild to moderate degree may be managed on an outpatient basis, often without the use of intravenous therapy. In general, the aim should be to replace the entire calculated deficit in the initial 4 to 6 hours of treatment. This more rapid treatment hastens the restoration of circulating fluid volume, speeds the excretion of tissue acids and ketones that are the result of diminished end-organ perfusion, and contributes to the more rapid resolution of compensatory mechanisms such as renal sodium retention and potassium losses.

In the vast majority of cases, electrolyte determinations do not add useful information to management. The exceptions to this rule include a child who has a severely abnormal mental status (irritable or lethargic), seizures, or clinical signs of hyponatremia or hypernatremia. Furthermore, normal saline should be the initial fluid of choice in virtually all instances, until a specific electrolyte abnormality is detected that mandates a more hypertonic or hypotonic solution. Regardless of the measured serum sodium concentration, a child who is significantly dehydrated usually has a net deficit of *total body sodium*; thus, even a hypernatremic child (as determined by the serum concentration of sodium) will benefit from the initial administration of normal saline.

The fluid volume for an initial rehydration should be based on calculated or estimated healthy weight. After an initial bolus administration of 20 mL/kg over 20 to 30 minutes, the child should be re-evaluated. If evidence of shock persists, then repeated boluses should

be administered, with re-evaluation after each bolus. When heart rate and capillary refill times have returned to normal, the rate of fluid administration may be reduced to an amount calculated to replace the remaining deficit over 4 to 6 hours. In a healthy child who has normal kidneys, this task usually may be accomplished safely by administering half-normal saline (77 mEq of sodium per liter).

### THERAPEUTIC APPROACH TO SHOCK

A severe plasma volume deficit, with actual or impending cardiovascular collapse, is a life-threatening pediatric emergency requiring *immediate* action. Initial therapy replaces the intravascular volume depletion with normal (0.9%) saline. (See Chapter 373, Shock.) Hemorrhagic shock, which must be considered with any history of trauma or any possible internal source of bleeding (eg, a known peptic ulcer or other GI disease that might lead to acute blood loss), must be treated with the administration of packed red blood cells. This treatment is required because administering additional electrolyte solutions to a patient who has an already diminished hematocrit decreases oxygen-carrying capacity further and may result in irreversible damage to vital organs (especially the heart and brain). Therefore, most hospital blood banks keep a ready supply of type O blood, which should be infused as rapidly as possible once the diagnosis of hemorrhagic shock has been considered. A sample of the patient's blood (obtained before transfusion) should be sent to the blood bank so that a properly matched unit of donor blood can be obtained without delay in case it is needed for further therapy. In addition, if the patient's blood type is known, then type-specific non-cross-matched blood, which carries less risk than the use of type O non-cross-matched

blood, may be administered. While awaiting the arrival of blood from the blood bank, normal saline solution should be given. The use of colloid-containing plasma expanders such as albumin or dextran remains controversial and probably provides no benefit over the use of a crystalloid solution unless the shock is the result of protein loss. In addition, if the shock is cardiogenic, then administration of albumin may worsen pulmonary edema. In sepsis, in which volume depletion is caused by leaky capillaries and the exudation of plasma into the extravascular spaces, fresh-frozen plasma may be useful (because it also replaces many clotting factors) and is sometimes used in combination with other fluids. In infants and small children, shock is associated almost invariably with the depletion of glycogen stores. Thus, hypoglycemia often may be present. The administration of 2 to 4 mL/kg of a 25% dextrose solution corrects hypoglycemia and improves the results of further resuscitation efforts. For this reason, rapid bedside determination of blood glucose concentration should always be a part of the initial evaluation of the infant or child in shock (current or impending).

## SERIOUS ELECTROLYTE ABNORMALITIES

Although most patients who are dehydrated may be given the empirical administration of normal saline, and without the measurement of serum electrolytes, in special situations more attention must be given to electrolyte status. Clinically, these situations will become apparent if a child demonstrates signs associated with hypernatremia or hyponatremia or if signs of dehydration do not resolve in response to standard management. This section examines specific electrolyte abnormalities.

### Sodium

The pediatric electrolyte aberrations encountered most commonly relate to sodium balance, and they ordinarily occur with dehydration. When a significant electrolyte disturbance is evident, efforts must be made to determine the cause of the disturbance and any factors that may tend to perpetuate it, so that they can be addressed in the treatment plan.

### Hyponatremia

Hyponatremia is usually associated with hypotonicity. When it is not, the physician must suspect either an artifactual lowering of serum sodium, such as with hyperlipidemia and hyperproteinemia, or the presence of an osmotically active substance such as glucose or mannitol. These compounds cause a shift of intracellular water into the extracellular space to restore osmotic neutrality, thereby lowering effective serum sodium by 1.6 mEq/L for every 100 mg/dL rise in serum glucose or mannitol concentration. Such situations are associated almost universally with the preservation of intravascular volume (except in some extreme cases of diabetic ketoacidosis) and are often apparent from the history, physical examination, or a few simple laboratory tests. Table 58-4 summarizes the causes of hyponatremia. The clinical manifestations of hyponatremia are primarily neurologic and are related

**Table 58-4**

**Causes of Hyponatremia**

TYPE	CAUSE
Pseudohyponatremia (Hyperosmolality)	Hyperglycemia
Hypovolemic hyponatremia	Mannitol
	• Gastrointestinal losses (vomiting, diarrhea)
	• Excessive sweating
	• Renal losses (diuretics, urinary obstruction, salt-wasting nephropathy, etc)
Euvolemic hyponatremia	• Syndrome of inappropriate secretion of antidiuretic hormone
	• Glucocorticoid deficiency
	• Water intoxication (excessive hypotonic intravenous fluids)
	• Child abuse, tap water enemas, psychogenic polydipsia
Hypervolemic hyponatremia	• Congestive cardiac failure
	• Cirrhosis
	• Nephrotic syndrome

to cerebral edema caused by hypo-osmolality. These manifestations occur in the form of headaches, nausea, vomiting, and weakness. As the cerebral edema worsens, patients develop behavioral changes and impaired response to verbal and tactile stimuli.

The most common clinical situation leading to hyponatremia is volume loss. This is usually caused by diarrhea and subsequent volume depletion, which causes a nonosmotic release of ADH. This ADH release increases resorption of free water but not sodium in the kidney, thereby lowering serum sodium levels. If ongoing diarrheal losses are replaced with hypotonic fluids, then hyponatremia will develop, even if the volume deficit is not great. Abnormal accumulations of isotonic fluid from the intravascular space into other body cavities (such as in ascites) is known as *third spacing*. This intravascular volume loss also stimulates ADH release and subsequent free-water resorption and development of hyponatremia.

When volume status is normal, the physician must consider situations that lead to a combination of sodium loss with water intake sufficient to maintain usual hydration. Such a negative sodium balance can result from severe restriction of sodium intake or profound loss of sodium through the skin (cystic fibrosis), GI tract, or kidneys (salt-losing nephropathy or diuretic use).

Mild hyponatremia (serum sodium 128–134 mEq/dL) with normovolemia or hypovolemia is usually undetectable clinically and can be managed by providing isotonic sodium solutions with adequate fluid administration, thereby allowing the excretion of water at an appropriate rate. When simultaneous large deficits of both water and sodium occur, both must be replaced effectively; the usual normal saline solution is sufficient at the outset.

Severe total body potassium depletion, sometimes overlooked, may lead to persistent hyponatremia. Because potassium is the major intracellular cation,

sodium ions enter the cells to replace potassium ions to provide electroneutrality; therefore the concentration of sodium in the extracellular space may fall. Potassium then must be supplied to restore normal sodium balance.

More rapid correction of the sodium deficit may be necessary with serious symptoms (seizures), which may accompany a large or precipitous decline in serum sodium concentration. Rapid correction can be achieved through the administration of 3% saline solution (containing 500 mEq of sodium per liter), which allows rapid replacement of sodium without infusing a large volume of water. The administration of 4 to 6 mL/kg of 3% saline over 1 hour, or alternatively 2 mL/kg boluses of 3% saline (up to 100 mL) over 10 minutes and repeated 1 to 2 times based on response, provides rapid and temporary relief of signs of severe hyponatremia. This temporary relief is achieved by serum sodium level elevations of 4 to 6 mEq/L, thereby reducing cerebral edema. Osmotic equilibrium is established rapidly once intravascular tonicity is restored, because sodium is distributed quickly throughout all body fluid compartments. The intravenous administration of hypertonic sodium chloride solutions is not without risk to the patient, however, especially a patient who has cardiac or renal disease. Such infusions cause a rapid shift of water into the intravascular space and may lead to acute volume overload. This therapy must therefore be reserved for potentially life-threatening situations, and the child must be monitored closely throughout the infusion. Demyelination syndromes have been noted in adults because of the rapid reversal (a rise of more than 12 mEq/L in 24 hours) of long-standing or chronic hyponatremia.

When hyponatremia exists with *expanded* vascular volume, the most likely cause is excessive secretion of ADH, which may occur because of increased intracranial pressure, severe pneumonia, or the stress of certain surgical procedures. Syndrome of inappropriate secretion of ADH (SADH) is diagnosed based on laboratory and physical examination data and requires the presence of hyponatremia with normal or increased intravascular volume. In patients with SADH, sodium excretion in the urine is variable but is usually higher than expected for the level of serum sodium concentration. Treatment of this disorder, whatever the cause, consists of fluid restriction and no sodium administration, unless the patient is convulsing. If fluids must be given, they should be isotonic, with hypertonic fluids for seizures. Concurrent administration of furosemide or other potent diuretics with hypertonic solutions to increase free water diuresis should be avoided unless there is impending heart failure from volume overload, because of an increased risk of hypotension. Some authors, however, have endorsed the use of desmopressin with 3% sodium chloride administration to correct severe, symptomatic hyponatremia. In most cases, however, fluid restriction remains the safest and most efficacious mode of therapy. Once the sodium concentration returns to near normal, moderate fluid restriction (generally to two-thirds of maintenance requirements) may need to be continued, usually for at least 24 hours but sometimes for as long as the underlying disorder persists.

### Hypernatremia

As with decreased serum sodium concentration, hypernatremia may occur with overhydration, dehydration, or normal hydration. However, unlike hyponatremia, an elevated serum sodium level is *always* associated with hypertonicity. Table 58-5 summarizes the causes of hypernatremia.

Hypernatremia associated with overhydration is generally an iatrogenic problem created by administering intravenous or oral solutions with high salt content and failing to provide the requisite free water. Patients treated with large amounts of sodium bicarbonate for metabolic acidosis are also at risk of developing marked hypernatremia (approximately 1 mEq of sodium is administered for every milliliter of bicarbonate solution). Occasionally, when infant formulas are being mixed, mistakes occur, which result in markedly hypertonic solutions that may induce particularly severe hypernatremias. These patients are at risk of developing obvious signs of plasma volume overload, including hypertension, congestive heart failure, and pulmonary edema. Under such circumstances, administering additional fluid is risky and may prove fatal. The most rational approach is to limit sodium and water intake and to attempt to induce sodium loss to a greater extent than water. This task may be accomplished by using a potent loop diuretic such as furosemide, which induces a net sodium loss if the child's renal function is adequate. Concurrently, the physician must watch closely for the development of dehydration, because predicting precisely how much water and sodium will be lost is impossible. Generally, some portion of the induced urine output (50%–75%) should be replaced with intravenous fluid that is slightly hypotonic (ie, 66% or 75% normal saline solution) until normal hydration and tonicity have been achieved. In patients who have severe hypernatremia (ordinarily considered as a serum sodium value >160 mEq/L), serious complications may occur if the sodium concentration falls too rapidly. This action produces marked shifts of extracellular water to the intracellular space and results in cellular swelling. This swelling is most

**Table 58-5**

**Causes of Hypernatremia**

MECHANISM	CAUSE
Excessive sodium	<ul style="list-style-type: none"> <li>• Improperly mixed formula</li> <li>• Intentional (Munchausen syndrome by proxy)</li> <li>• Hyperaldosteronism</li> </ul>
Water deficit	<ul style="list-style-type: none"> <li>• Nephrogenic diabetes insipidus</li> <li>• Central diabetes insipidus</li> <li>• Increased insensible losses (prematurity, phototherapy)</li> </ul>
Water and sodium deficits	<ul style="list-style-type: none"> <li>• Gastrointestinal losses (diarrhea, nasogastric suction)</li> <li>• Skin losses (burns, excessive sweating)</li> <li>• Renal losses (osmotic diuretics, diabetes mellitus)</li> </ul>



worrisome in the central nervous system because of the potential for cerebral edema, which may lead to seizures, coma, or death. Therefore, when the serum sodium value is high and is accompanied by overhydration, the preferred therapeutic approach is to restrict sodium and water, thus permitting a spontaneous diuresis to occur. Serum electrolyte values must be monitored every few hours. If the patient has substantially decreased renal function, then hemodialysis or peritoneal dialysis should be considered, especially in the presence of hypertension or pulmonary edema.

Hypernatremia associated with decreased plasma volume is often encountered in pediatric practice. It is caused most commonly by acute gastroenteritis that induces relatively larger losses of water than sodium. Although these children may have severe hypernatremia, their total body sodium content is usually depleted; they therefore present a therapeutic challenge. Hypernatremia can be seen in the first few days after birth in breastfed infants because of inadequate breast milk ingestion resulting from either decreased production, inverted nipple, or swallowing problems.

Patients with hypernatremic dehydration need to be evaluated carefully. The physician must consider all the aspects of dehydration previously discussed but must remember that because ECF volume is relatively well preserved, the severity of the plasma volume loss may be seriously underestimated. Even with significant fluid losses, these children rarely have signs of incipient vascular collapse. When using the signs and symptoms of dehydration shown in Table 58-3 to determine the degree of dehydration, if the serum sodium concentration is greater than 155 mEq/L, then another 3% to 5% should be added to the weight loss in predicting the degree of dehydration.

Fluid therapy of hypernatremic dehydration is not nearly as straightforward as for other types of dehydration because of the increased risk of creating major fluid shifts and cerebral edema. The physician cannot simply try to remove sodium, because a decrease in the plasma tonicity without an increase in plasma water may induce circulatory collapse. Therefore a cautious rehydration scheme must be developed.

Instead of being rehydrated over a short period, as with isonatremic or hyponatremic dehydration, the child who has a serum sodium greater than 155 mEq/L should have the fluid deficit replaced over 48 to 72 hours. Calculating the actual amount of sodium lost is *not* possible. The physician should estimate the water deficit (based on weight and clinical signs) and plan to replace this volume evenly over 48 to 72 hours. The solution used should be slightly hyponatremic (containing 100 to 120 mEq of sodium per liter). Glucose should be added so that the solution is not hypotonic. As soon as the urine output is judged to be adequate, potassium should be added to the intravenous solution to correct the potassium deficit and to preserve the intracellular osmolality, thus helping to prevent intracellular edema. Particularly important is to monitor serum electrolyte concentrations, serum osmolality, and urine output and osmolality as frequently as possible. Although the physician needs to avoid a persistent

elevation of the serum sodium concentration, ensuring a slow, steady decline in the serum sodium and osmolality levels is also important. Decreases in serum tonicity should be limited to a rate of 5 mOsm/h. Serum sodium concentration should fall at a rate no more rapid than 0.5 mEq/L/h. In many cases, adding up to 40 mEq of potassium per liter to the infused solution and reducing its sodium concentration to 50 mEq/L is feasible.

Sometimes, no matter how carefully hypernatremia is handled, seizures ensue during the rehydration period. They can usually be managed successfully by infusing a solution slightly more hypertonic than the solution being given (ie, normal saline or lactated Ringer solution). If the seizures are particularly severe, or evidence exists of brain herniation, then a hypertonic agent such as mannitol or 3% saline may be required. Unfortunately, the diuresis induced by mannitol may worsen the dehydration substantially. In addition, mannitol should not be used if urine output has not been established.

A relatively uncommon cause of hypernatremia is diabetes insipidus, which usually leads to hypernatremia with a normal plasma volume. This circumstance presupposes an intact thirst mechanism and that the patient has access to the large volume of water required to replace renal losses, which usually allows them to maintain a normal serum sodium level. Such is not the case for small infants and patients who have diabetes insipidus and hypernatremic dehydration. Large renal losses of free water may occur because of deficient ADH (central or pituitary diabetes insipidus) or impairment of the normal renal response to the hormone (nephrogenic diabetes insipidus).

In infants and children, the most common causes of central diabetes insipidus are inherited familial conditions, histiocytosis and other central nervous system diseases of vascular, infectious, or granulomatous origin. The most common causes in older children and young adults are head trauma and idiopathic causes associated with brain malformations. Across all ages, the syndrome may follow brain tumors and intracranial surgical procedures.

Nephrogenic diabetes insipidus may be evident as a congenital disorder, but it is more commonly caused by renal failure (particularly that caused by obstructive uropathy) or electrolyte disorders, drug ingestions, or sickle cell disease. Laboratory findings in patients with diabetes insipidus usually include a moderate to marked hypernatremia (depending on how adequately the lost fluid volume has been replaced) and dilute urine, usually produced in large volumes. Clinically, these patients exhibit a tremendous thirst (often craving ice-cold water) and usually show signs of normal hydration. The laboratory differentiation between central and nephrogenic diabetes insipidus is unnecessary when the cause is apparent (eg, after surgical removal of a craniopharyngioma) but in other situations is essential to help guide the therapeutic approach. This differentiation is generally determined by performing a water deprivation test in adults and older children (monitored closely in the hospital setting). For infants and young children, desmopressin infusion followed by serial

measurement of urine osmolality replaces the water deprivation test.

## Potassium

### Hypokalemia

A low serum potassium concentration seldom represents an emergency unless cardiac effects are seen, which do not typically occur until the serum potassium level is less than 2 mEq/L. In patients receiving digitalis preparations, however, a combined cardiac toxicity may ensue, and the typical T-wave changes and arrhythmias of hypokalemia may occur at serum potassium levels closer to normal. Other patients at risk of exhibiting an exaggerated response to mild hypokalemia include those who have an acid-base disturbance or other ionic aberration that may create a cardiac conduction disturbance by substantially altering the flux of ions between the intracellular and extracellular spaces. At particular risk of developing such alterations are children receiving long-term diuretic therapy. Hypokalemia may occur after large losses of potassium from the kidneys in children with diabetic ketoacidosis and as a manifestation of hyperaldosteronism. (Table 58-6 lists the causes of hypokalemia.)

When emergency therapy for hypokalemia is necessary (usually in the form of intravenous potassium at a dose of 0.5–1.0 mEq/kg usually given over 1 hour and in the preoperative patient who has a serum potassium concentration <3.5 mEq/L), intravenous potassium repletion should be implemented. This task is accomplished either by increasing the concentration of potassium ion in the fluids given intravenously (maximum of 80 mEq/L) or by administering a bolus of potassium into a central vein. The maximal amount of potassium that may be given is 1 mEq/kg over a 1-hour period (with the physician at the bedside and continuous electrocardiographic monitoring), but it is generally safer to deliver only 20% or 25% of this amount and to repeat the dose as necessary to raise the concentration to a safe level. In nonemergent circumstances, enteral potassium supplementation is safer and very effective.

Table 58-6 Causes of Hypokalemia	
MECHANISM	CAUSE
1. Spurious	High white cell counts
2. Transcellular shifts	<ul style="list-style-type: none"> <li>• Alkalosis</li> <li>• Insulin</li> <li>• <math>\beta</math>-agonists (albuterol), toxins (theophylline)</li> </ul>
3. Decreased intake	—
4. Extrarenal losses	Diarrhea, sweating, laxative abuse
5. Renal losses	<ul style="list-style-type: none"> <li>• With metabolic acidosis (renal tubular acidosis)</li> <li>• Without acid–base imbalance (interstitial nephritis)</li> <li>• With metabolic alkalosis (cystic fibrosis, Bartter syndrome)</li> <li>• With high blood pressure (licorice ingestion, Cushing syndrome)</li> </ul>

### Hyperkalemia

Substantial elevations of serum potassium concentration are encountered most commonly in patients with renal failure or systemic acidosis, combined with an increased intake of potassium or a rapid breakdown of tissue or blood products. Table 58-7 summarizes the causes of hyperkalemia.

The treatment of hyperkalemia should focus on stabilizing cardiac conduction and the heart muscle, facilitating a rapid shift of serum potassium intracellularly to temporarily decrease serum potassium levels, and removing potassium from the body to permanently reduce serum levels.

When the potassium concentration reaches 7 mEq/L or more, or if characteristic electrocardiographic abnormalities are noted at any potassium concentration, then the child is in grave danger of cardiac toxicity. Such a patient should have continuous electrocardiographic monitoring, and immediate steps should be taken to protect the heart from the effects of severe hyperkalemia. The first priority is the infusion of intravenous calcium, 0.2 mL/kg of 10% calcium chloride given over 2 to 5 minutes, which can be repeated at 5-minute intervals.

As a temporizing measure, to decrease serum potassium levels rapidly, steps should be taken to drive the potassium intracellularly. First, a combined insulin and dextrose infusion induces movement of potassium ions from the extracellular to the intracellular spaces. This accelerates the usual process by which glucose moves into the cells and is converted to glycogen. A dose of 2 mL/kg of 25% dextrose solution is given along with 1 U/kg of regular insulin. These may be administered over 30 minutes and repeated as necessary. Serum glucose concentration must be monitored closely during and after therapy. Selective  $\beta$ -2 agonists (salbutamol), are very effective in driving potassium into the cell. They may be administered intravenously or by nebulization. The parenteral form is not yet available.

**Table 58-7 Causes of Hyperkalemia**

MECHANISM	CAUSE
1. Spurious laboratory values	Hemolysis, leukocytosis, faulty blood draw techniques
2. Increased intake	Oral or intravenous, blood transfusion
3. Transcellular shifts	<ul style="list-style-type: none"> <li>• Acidosis</li> <li>• Rhabdomyolysis, tissue necrosis, tumor lysis syndrome</li> <li>• Drug toxicity (<math>\beta</math>-blockers, digitalis)</li> </ul>
4. Decreased excretion	<ul style="list-style-type: none"> <li>• Renal failure</li> <li>• Adrenal (Addison disease, congenital adrenal hyperplasia)</li> <li>• Kidney transplant, lupus nephritis</li> <li>• Renal tubular acidosis (pseudohypoaldosteronism)</li> <li>• Medications (angiotensin-converting enzyme inhibitors)</li> </ul>

commercially in the United States. Sodium bicarbonate (2–3 mEq/kg given within a 30-minute period) to raise the serum pH level and help move the potassium into the cells can be considered, but is extremely controversial and is only recommended in cases of severe acidosis or in patients receiving hemodialysis.

Once lifesaving measures have been instituted, attention must be given to removing potassium from the body. One of the most effective means of accomplishing this task is with hemodialysis or peritoneal dialysis. Either one or the other should be initiated without delay in patients who have hyperkalemia accompanied by congestive heart failure and volume overload. The other mechanism used commonly for removing potassium from the body is to bind potassium in the GI tract by using an exchange resin such as sodium polystyrene sulfonate. This exchange resin is usually introduced through a retention enema that contains sorbitol. The physician can expect a decline in serum potassium of 1 mEq/L for each gram per kilogram of resin introduced. The dose is calculated based on the severity of the hyperkalemia, with a maximal adult dose of 60 g. Caution should be used in patients who have renal failure because sodium is absorbed as potassium is excreted, and each gram of resin contains 4.1 mEq of sodium; hyponatremia and hypervolemia may result. In addition, the patient must be monitored for the development of hypocalcemia and hypomagnesemia. Metabolic alkalosis may result from repeated polystyrene sulfonate enemas. When hyperkalemia becomes a chronic but not life-threatening problem, the best approach is to restrict dietary potassium and administer potassium-losing diuretics concomitantly.

## FLUID THERAPY IN SPECIAL SITUATIONS

### Fluid Therapy in the Neonate

Adequate provision of fluid replacement therapy for newborns depends on perinatal alterations in body composition and the infant's size and gestational age. Hydration of sick premature infants who weigh less than 1,500 g is discussed in Chapter 111, Care of the Sick or Premature Infant Before Transport.

The content of TBW decreases progressively throughout gestation and the first year of postnatal life. This decrease is accompanied by increases in the body's content of protein and fat. The shrinkage of the ECF compartment accounts largely for the decrease in TBW. In the first few days of extrauterine life, both term and premature infants normally lose up to 10% of their body weight. Although this loss is considered a physiologic reduction, failure to replace such losses may lead to substantial dehydration.

All newborns show a progressive increase in their metabolic rate. The metabolic rate for full-term infants approximates 32 cal/kg per day at birth and reaches close to 43 cal/kg per day within 3 days. This progressive increase is followed by a slow, steady increase over the first 2 weeks after birth. Premature infants maintain a higher metabolic rate than full-term infants, even when they achieve a similar weight.

In addition to the baseline metabolic expenditure of calories, newborns use energy with cold, stress, and

muscular activity. The growth rate is rapid during this period, and the average newborn requires between 100 and 125 cal/kg per day.

Water requirements are governed by losses through the skin, respiratory tract, and kidneys. Evaporative losses through the skin generally average 20 to 30 mL/kg per day; respiratory losses account for approximately 15 mL/kg per day. Both parameters are affected by ambient humidity, and respiratory losses may actually be reduced by 50% with provision of high humidity to the infant's immediate environment.

The newborn's kidneys, though having a full complement of nephrons, do not have the same surface area and therefore have less filtering and concentrating ability. Though kidney function continues to mature as the infant ages, this difference in concentration ability requires special attention.

As the solute load increases, the free water requirement rises; thus, for a formula-fed infant, urinary water loss may be as high as 120 mL/kg per day. However, the average range probably is closer to 60 to 75 mL/kg per day.

Electrolyte requirements for infants have not been fully established, but infants seem to tolerate a fairly wide range of electrolyte provisions. Fluids that have been used successfully yield between 1 and 3 mEq of sodium per 100 calories per day; this has become the recommended starting range for maintenance fluid therapy.

When preparing a maintenance parenteral fluid formula for newborns, the pediatrician needs to ensure adequate monitoring, which will indicate whether fluid estimates have been adequate. Also important, especially with the sick neonate, is to record weights once or twice per day and to record intake, output, vital signs, urinary osmolality, electrolyte concentrations, and other indications of optimum cardiac and respiratory homeostasis frequently. Frequent changes may be needed; therefore, the physician must never become locked into a particular formula but rather must apply the basic rules of fluid therapy to the situation logically and be ready to compensate for failing systems or increasing losses when necessary.

### Fluid Therapy for Burns

See Chapter 375, Thermal Injuries, for fluid management of children with burns.

### Hydration of the Ambulatory Patient: Alternatives to Parenteral Fluid Therapy

A fairly common practice for pediatricians in the United States is to recommend oral fluids for young patients who have mild diarrhea or vomiting. Such therapy has been suggested for many years on totally empirical grounds. Most physicians have urged the use of a dilute solution that contains sodium and potassium in concentrations of 30 and 20 mEq/L, respectively, and 5% to 7% glucose. When diarrhea leads to moderate or severe dehydration, or if substantial emesis accompanies the illness, then the standard teaching dictated hospitalization of such children and resting the GI tract with the use of parenteral therapy, as outlined in previous sections.

Sodium absorption in the small intestine depends on the presence of glucose or small neutral amino acids such as glycine or alanine. Similarly, the absorption of glucose is enhanced by the presence of sodium salts, and this mechanism of coupled transport is responsible for the efficacy of the ORS. Movement of salt and glucose across the mucosal border is accompanied by an influx of water and other electrolyte concentrations. Maximal rates of absorption are achieved when sodium and glucose are present in a 1:1 to 1:2 molecular ratio, glucose concentration is between 110 and 140 mmol (2%–2.5% solution), and sodium concentration is not substantially less than that of normal jejunal fluid (usually 12 mEq/L). The World Health Organization (WHO) has derived a formula for use with all patients who have diarrheal illness regardless of its cause. It contains 90 mmol of sodium, 20 mmol of potassium, 30 mmol of bicarbonate, 80 mmol of chloride, and 111 mmol of glucose per liter. This formulation provides a solution that has an osmolality of 331 mOsm/L. When given ad libitum to patients who have diarrhea, this formula corrects dehydration rapidly and can return electrolyte concentrations to the normal range regardless of the presence of hyponatremia or hypernatremia on initial evaluation. Large field studies have documented its successful use in patients who have ongoing emesis. No evidence has been found to suggest that the use of such fluid prolongs

the duration of diarrhea; the reverse seems to be the case. In addition, children given this oral rehydration therapy seem to tolerate resumption of a regular diet earlier than those treated solely with intravenous fluids. Use of a solution that has lower osmolality (224 mOsm/L) has been shown to result in superior water absorption and patient weight gain.

The guidelines for managing mild, moderate, or severe dehydration as recommended by the Centers for Disease Control and Prevention, American Academy of Pediatrics (AAP), and WHO are summarized in Table 58-8.

Preparations that meet WHO and AAP guidelines, as indicated previously, are available commercially. Because such preparations are available ready to use, the bicarbonate found in the WHO powder has been replaced with citrate. Studies have documented the equivalent efficacy of the 2 bases in correcting the mild acidosis that accompanies mild to moderate diarrhea. Most of the large-scale evaluations that have been performed in developed countries have excluded the use of oral rehydration solution (ORS) in patients in shock who are treated initially with intravenous fluids. Despite considerable efforts to develop a super ORS, most evidence suggests that the standard WHO solution, accompanied by early return to normal diet and sufficient access to free water, is still the best overall therapy. Treatment consists of 2 phases: rehydration and maintenance. In the rehydration phase,

**Table 58-8****Summary of Treatment Based on Degree of Dehydration**

DEGREE OF DEHYDRATION	REHYDRATION THERAPY	REPLACEMENT OF LOSSES	NUTRITION
Minimal or no dehydration	Not applicable	<ul style="list-style-type: none"> <li>• &lt;10 kg body weight: 60–120 mL ORS for each diarrheal stool or vomiting episode</li> <li>• &gt;10 kg body weight: 120–240 mL ORS for each diarrheal stool or vomiting episode</li> </ul>	Continue breastfeeding, or resume age-appropriate normal diet after initial hydration, including adequate caloric intake for maintenance <sup>a</sup>
Mild to moderate dehydration	ORS, 50–100 mL/kg body weight over 3–4 h	Same	Same
Severe dehydration	Lactated Ringer solution or normal saline in 20 mL/kg body weight intravenous amounts until perfusion and mental status improvement; then administer 100 mL/kg body weight ORS over 4 h or 5% dextrose half-normal saline intravenously at twice maintenance fluid rates	Same; if unable to drink, administer through nasogastric tube or administer 5% dextrose quarter-normal saline with 20 mEq/L potassium chloride intravenously	Same

ORS, oral rehydration solution.

<sup>a</sup>Overly restricted diets should be avoided during acute diarrheal episodes. Breastfed infants should continue to nurse ad libitum even during acute rehydration. Infants too weak to eat can be given breast milk or formula through a nasogastric tube. Lactose-containing formulas are usually well tolerated. If lactose malabsorption seems clinically substantial, then lactose-free formulas can be used. Complex carbohydrates, fresh fruits, lean meats, yogurt, and vegetables are all recommended. Carbonated drinks or commercial juices with a high concentration of simple carbohydrates should be avoided. From Centers for Disease Control and Prevention, Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy for the Centers for Disease Control and Prevention. *MMWR Recomm Rep.* 2003;52:1–16.



fluid deficit is replaced quickly, whereas in the maintenance phase, calories are added along with fluids. The intent of this therapy is to restore an age-appropriate diet as soon as possible while preventing GI rest.

Oral rehydration therapy provides a cost-efficient approach to the problem of childhood diarrhea for the patient who is able to drink, is not in shock, and has a relative or other responsible person who can understand the instructions for using the ORS. Such a therapeutic approach avoids the hospitalization of the child and the consequent disruption in the lives of the family members. This treatment approach eliminates the potential complications of intravenous therapy. (See also Chapter 138, Diarrhea and Steatorrhea; and Chapter 353, Dehydration.)

### WHEN TO REFER

- Abnormal electrolytes refractory to fluid therapy
- Seizure or encephalopathy
- Inability to rehydrate by chosen means (oral or intravenous)

### WHEN TO ADMIT

- Failure to rehydrate completely in 6 hours
- Persistent abnormal mental status
- Inability of parent to maintain hydration at home

### AAP POLICY

Centers for Disease Control and Prevention. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *Pediatrics*. 2004;114(2):507. AAP endorsed (pediatrics). [aappublications.org/content/114/2/507](http://aappublications.org/content/114/2/507)

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## Chapter 59

# BLOOD PRODUCTS AND THEIR USES

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## INTRODUCTION

This chapter reviews the situations in which pediatricians may encounter blood transfusions, and the current standard practice for transfusing different blood components in children. It addresses how products are processed, which product should be administered, when transfusion should take place, and what complications may result.

In 1901 Karl Landsteiner, “the father of blood transfusion,” discovered the major human blood groups A, B, and O and established that blood transfusion needed to occur between persons with the same blood group to avoid destruction of red blood cells (RBCs). This allowed the first successful blood transfusion to occur, and it was later clarified that a fourth blood group, AB, can accept donations from all the other major blood groups (universal recipient), and that type O blood can be transfused into any of the other 3 major blood groups (universal donor) (see Table 59-1). The primary goal of blood transfusion is to normalize oxygen delivery to the tissues. The ability to separate blood into its components and store them appropriately was a subsequent advance that allowed transfusion of only the required blood component, eg, packed red blood cells (PRBCs) for anemia. Transfusion-acquired viral illnesses, specifically human immunodeficiency virus (HIV) and viral hepatitis, became the next challenge in the 1980s, but better donor screening techniques have made such transfusion-transmitted infections extremely rare.

Although transfusion therapy was originally used primarily to treat inadequate oxygen-carrying capacity related to anemia or blood loss, the ability to store separate blood cell components played a second key role in replacing insufficient coagulation proteins or platelets to provide adequate hemostasis. Less common complications of blood transfusions are now better recognized. This has provided an incentive to pursue a more conservative strategy so that blood components are only administered in situations in which the benefit clearly outweighs risk. The transfusion thresholds set by the American Association of Blood Banks (AABB) rely largely on “expert opinion,” and may not be appropriate for all patients and settings. In general, the physician’s goal is not to restore the circulating amount of a blood component to a normal value, but rather to the lowest level that allows normal functioning for the child’s condition. In deciding whether component replacement is necessary for a particular deficit, pediatricians should always ask 2 key questions: (1) is it essential to correct the deficit immediately through transfusion, and (2) does another method exist to correct the deficit?

**Table 59-1** Major Blood Types and Blood Transfusion

BLOOD TYPE	ANTIGENS ON RBC	CAN DONATE BLOOD TO	ANTIBODIES IN SERUM	CAN RECEIVE BLOOD FROM
O	—	O, A, B, AB	Anti-A and Anti-B	O
A	A	A, AB	Anti-B	A, O
B	B	B, AB	Anti-A	B, O
AB	A and B	AB	—	AB, A, B, O

**Table 59-2** Red Blood Cell (RBC) Products

PRODUCT	HEMATOCRIT	VOLUME/UNIT (mL)	INDICATIONS
Packed RBCs	55%	230–330	Anemia, most commonly used product
Whole blood	40%	570	Acute bleeding, exchange transfusion
Washed RBCs	75%	180	Repeated febrile and allergic reactions despite premedication
Frozen RBCs	75%	180	Rare antigens, IgA deficiency, autologous blood donations

## BLOOD BANKING AND PRODUCTS

The current blood transfusion system in the United States is heavily dependent on carefully screened volunteer blood donors. Donor blood is tested for ABO and Rh blood type, as well as for any unexpected RBC antibodies that may cause problems in a recipient. Screening tests are also performed for evidence of donor infection with hepatitis B and C viruses, HIV-1 and HIV-2, human T-lymphotropic virus (HTLV) 1 and HTLV-2, syphilis, Chagas disease, and West Nile virus. As a result, now the overall risk for HIV and hepatitis C in blood obtained within the United States is less than 1 per 1 million units of PRBCs. It is not uncommon for family members or friends to request directed donations to avoid receiving blood from unknown donors who may be perceived as potentially unsafe. However, this practice not only delays transfusion by 2 to 4 days for testing and processing of donor blood, but actually carries a higher risk of transmissible diseases. It can also increase the risk of HLA sensitization that may adversely affect outcomes in a child preparing for bone marrow transplantation.

Each unit of whole blood is separated into several components after collection, which are then stored in a blood bank. These may be cellular (ie, RBCs, platelets, and rarely, granulocytes) and acellular (fresh frozen plasma [FFP], cryoprecipitate). The storage and administration of each of these components will be addressed herein. In addition, other blood products manufactured by commercial companies include albumin, immune globulin, specific immune globulins, and clotting factor concentrates.

Within the United States, hospital blood banks are registered with the US Food and Drug Administration (FDA) and are regulated (21 CFR 607). Physicians should discuss transfusion needs with their local blood bank; most blood bank staff are happy to assist with questions and queries that may be beyond the scope of this chapter.

### Red Blood Cells

Packed red blood cells are administered in various situations and constitute two-thirds of the units dispensed at blood banks. Various RBC products are available (see Table 59-2), including washed RBCs, which contain less than 1% of original plasma and less than 10% of white blood cells (WBCs), and frozen RBCs, which contain less than 0.025% of original plasma and 1% to 5% of original WBCs. Both preparations are rarely used. In addition, most blood banks no longer store whole blood, and if this is indicated, it is usually derived from saline-reconstituted PRBCs or albumin.

As the most commonly transfused products, PRBCs are transfused primarily to treat inadequate oxygen-carrying capacity related to anemia or blood loss, but also in various other situations and for special populations, discussed later in this chapter. Except for emergency situations, type and crossmatch for ABO and Rh groups are mandatory, and for patients with sickle cell disease, extended phenotyping (looking at other blood groups, eg Cc, Ee, or Kell) is recommended by Rosse and colleagues.

For anemia, PRBCs may be infused as a volume of 10 to 15 mL/kg in infants and 5 mL/kg in older children, and this will normally increase the hemoglobin by 2 to 3 g/dL (20–30 g/L; hematocrit increases by 6%–9%). With very severe chronic anemia (hemoglobin <5 g/dL [50 g/L]) in a patient who is clinically stable (eg, severe iron-deficiency anemia), PRBCs should be given in small aliquots of 5 mL/kg over 4 hours, and repeated until the desired hematocrit is reached.

### Platelets

Platelet concentrates are prepared from whole blood (“random donor platelets”) or collected by apheresis from donors (“single donor platelets”) and can be stored at room temperature (20°C–24°C) with continuous agitation for 5 days. The relatively short shelf life means there is often a shortage of platelets at certain

**Table 59-3**      **Non-Red Blood Cell Products**

PRODUCT	CELL COUNT OR CONTENT	VOLUME/UNIT (mL)	INDICATIONS
Single-donor platelets	$3 \times 10^{11}$ platelets/unit	200–400	Preferred platelet product
Random donor platelets	$5$ to $7 \times 10^{10}$ platelets/unit	40–50	Alternative product if single donor unavailable
Fresh frozen plasma	1 unit	200–220	Multiple factor deficiency; disseminated intravascular coagulation; liver disease or unknown coagulation defect
Cryoprecipitate	>150 mg fibrinogen/unit	15 (5–10 units pooled)	Fibrinogen deficiency, also rich in factors VIII and XIII,

times of the year. ABO- and Rh-compatible platelets should be used when possible. Although HLA-antigens are present on platelets, HLA-typing is not routinely needed.

Platelet transfusions are primarily used in patients who are unable to produce adequate platelets or in those with disseminated intravascular coagulation (DIC). The platelet level that warrants transfusion is controversial, as will be discussed in this chapter. Platelets should not be administered in other situations with thrombocytopenia caused by peripheral destruction (eg, immune thrombocytopenia, thrombotic thrombocytopenic purpura, and hemolytic-uremic syndrome).

Platelets are administered as 10 mL/kg of single-donor platelets infused over 1 hour, capped at 1 unit. An equivalent volume of random donor platelets (1 unit per 10 kg) may be infused if single-donor platelets are not available. Indications for platelets and other non-RBC products are shown in Table 59-3.

### Granulocytes

White blood cells are difficult to transfuse because they must be collected from ABO-compatible donors via apheresis and administered fresh, and have significant febrile reactions and pulmonary complications. As a result, they are rarely used and colony-stimulating factors such as granulocyte colony-stimulating factor have largely taken their place. The resolving infection in people with neutropenia with granulocytes (RING) clinical trial was unable to demonstrate benefit from granulocyte transfusions in patients with neutropenia and severe infection.

### Plasma

Plasma includes FFP, which can be stored for a year at  $-18^{\circ}\text{C}$ , as well as thawed plasma, which can be stored for 5 days at  $4^{\circ}\text{C}$  and is instantly available. Infused plasma needs to be ABO-compatible with the recipient's RBCs but the Rh type can be ignored. FFP is rich in clotting factors and is often used to correct coagulation defects in DIC, liver disease, unknown coagulation deficiency, and massive transfusions. In addition, FFP may be infused in nonbleeding patients to provide intravascular volume, to correct a prolonged prothrombin time, or to decrease the risk of bleeding with a

planned invasive procedure. None of these practices, however, is supported by any evidence.

Fresh frozen plasma is second only to PRBCs as the most infused blood product. A consensus conference supported by the AABB found that the primary indication should be treatment of a bleeding patient who has a coagulopathy for which a specific clotting factor concentrate was not available. In addition, 2 other situations in which FFP was indicated were (1) massive transfusion, and (2) patients with warfarin-associated intracranial hemorrhage.

The volume of FFP administered at a time is usually 10 to 15 mL/kg.

### Cryoprecipitate

One unit of cryoprecipitate is derived from the controlled thawing of 1 unit of frozen plasma and is rich in fibrinogen (>150 mg per bag). It has a limited number of other coagulation factors such as factor VIII, von Willebrand factor (vWf), and factor XIII for which commercial concentrates are available. It is therefore primarily used for fibrinogen replacement in consumption coagulopathy (eg, massive transfusion, liver failure, or DIC), or rare patients with congenital hypofibrinogenemia.

The blood bank often issues cryoprecipitate as pooled units so it is important to check the dose when ordering.

### Commercial Plasma Products

Plasma products used to treat coagulation disorders are discussed further in Chapter 230, Coagulation Disorders. Recombinant, genetically engineered, non-plasma-derived factor concentrates are replacing blood-derived factors. Factors VIII, IX, activated VIIa, and XIII are currently available in the United States. Several effective methods for inactivating viruses have made such concentrates much safer in recent years. Recombinant activated human factor VII is approved for the treatment or prevention of bleeding in patients with factor VIII or IX deficiency with inhibitors, congenital factor VII deficiency, acquired hemophilia, and Glanzmann thrombasthenia. Prothrombin complex concentrates (4-factor concentrates) are Baglin and colleague's preferred treatment for bleeding in children receiving vitamin K antagonist anticoagulation or correction of a prolonged PT secondary to warfarin

anticoagulation. Antithrombin III concentrate and protein C concentrate are available to treat children with a congenital deficiency in either of those antithrombotic factors.

Albumin is available as a 5% or 25% solution, the latter for children who have hypoproteinemia and need large amounts of albumin without the added sodium load. Albumin is fractionated from pooled plasma and is pasteurized to inactivate viruses.

Immune globulin preparations are also pooled from large numbers of donors. Intravenous immune globulin is used to treat hypogammaglobulinemia, immune thrombocytopenia, Kawasaki disease, and various immune disorders, including neonatal alloimmune thrombocytopenic purpura. Common complications of intravenous immune globulin are allergic reactions and aseptic meningitis; rarely, renal failure may occur. Other immune globulin preparations are available for intramuscular administration and subcutaneous infusion. Intramuscular anti-Rh globulin is given to nonsensitized Rh-negative women during pregnancy, and after delivery, abortion, amniocentesis, or chorionic villus biopsy to prevent sensitization. Intravenous anti-D immune globulin is sometimes used to treat immune thrombocytopenia in Rh-positive patients, but may result in severe hemolytic anemia and renal failure.

## ORDERING TRANSFUSIONS

When ordering blood products for a child, it is important to understand what recipient sample is needed by the blood bank:

- **Type and screen:** *Accurate identification is critical.* Clerical errors when drawing and labeling blood specimens to be sent to the blood bank (or anywhere along the supply chain) are a major cause of severe hemolytic reaction. Usually 1 to 3 mL of blood in a lavender top (EDTA) tube is adequate. ABO and Rh testing, as well as a screen for antibodies is performed. The results are valid for 3 days for patients getting repeat transfusions (see entry on newborns)
- **Type and crossmatch:** In addition to the aforementioned process, the recipient's serum specimen is actually mixed with cells of a donor unit to confirm compatibility, and that donor unit is then reserved for transfusion. Hence, it is important *not* to order crossmatching for cases with a low probability that the blood product will be needed (eg, elective surgery).
- **Extended phenotyping:** Because of the high frequency with which patients with sickle cell disease develop antibodies after transfusion, it is important to look at less common antigens, such as Cc, Ee, Kidd, Kell, and others, when crossmatching blood. Most smaller blood banks will not do this routinely, so it needs to be specified.
- **Newborn type and screen:** Although ABO antigens on RBCs are fully developed at birth, ABO antibodies in the serum are not produced until 3 to 6 months of age, so the presence of any antibodies represents maternal antibodies. Therefore, when type and screen are evaluated in infants younger than 4 months, it is helpful to know maternal blood type, and to have a maternal blood sample. The initial evaluation is valid for the duration of the hospital admission up to 3 months.

Blood products must be stored and handled properly. Once blood has been issued from the blood bank, it should be used promptly within 4 hours and not stored. If administration is delayed, then the blood should be returned to the blood bank immediately. Blood should not have contact with solutions containing dextrose or calcium, and drugs should never be added to a blood component. RBC products (mainly PRBCs) make up approximately two-thirds of transfused units, with the remainder being FFP and platelets, and a small fraction being cryoprecipitate.

## Preparation of Blood Products

Irradiation of blood products to 25 Gy is recommended for blood products being transfused into immune-suppressed children, including (1) children being treated for a malignancy, (2) bone marrow or organ transplant recipients, (3) preterm infants weighing less than 1,200 g and severely ill neonates, (4) fetuses receiving intrauterine transfusions, and (5) children who have severe congenital immunodeficiency disorders. These children are susceptible to transfusion-associated graft vs host disease secondary to lymphocytes in the transfused blood.

Cytomegalovirus (CMV) infection is a risk to neonates, immune-suppressed children (as listed before), and potential stem cell transplant recipients. These children should receive CMV-negative RBCs and platelets. Because CMV is only present in monocytes, acellular products such as FFP and cryoprecipitate do not require testing. Most blood donors are CMV positive, so if CMV-seronegative blood is not available, then leukocyte-reduced blood may be used.

Leukocyte depletion at source with current third-generation blood filters are able to achieve a 3-log reduction (99.9%) of WBCs in cellular components. It is routine practice for all immune-suppressed children (as listed before), and in Canada, several transfusion services in the United States, and many European countries, it is universally performed. Universal leukoreduction may benefit all patients, especially those receiving chronic transfusion, by decreasing the frequency of febrile reactions, alloimmunization, and transmission of CMV infection.

## INDICATIONS FOR RED CELL TRANSFUSION

### Intensive Care

Adequate hemoglobin level to provide tissue oxygenation is the key goal of RBC transfusion in critical care. Large, prospective, randomized trials in adults and children demonstrated that restrictive transfusion (RBC transfusion given at a lower hemoglobin level) was safe and in some cases resulted in superior clinical outcomes compared with liberal transfusion (RBC transfusion given at a higher hemoglobin level). The available evidence strongly suggests that RBC transfusion in pediatric critical care patients is only needed when hemoglobin drops below 7.0 g/dL (70 g/L). Sick and preterm newborns are at risk for neurologic damage, and therefore, the thresholds for transfusion are higher, as discussed later in this chapter.



### Surgery

Children without sickle cell disease undergoing elective surgery require transfusion with PRBCs for a hemoglobin below 8.0 g/dL (80 g/L; hematocrit <24%) with signs and symptoms of anemia in the perioperative period, or blood loss of more than 15% of the blood volume. The extent of surgery, the likelihood of massive blood loss, and coexisting factors such as impaired pulmonary function or inadequate cardiac output must be considered when deciding about the threshold for transfusion. Children with sickle cell disease undergoing elective surgery should receive preoperative transfusions of up to a hemoglobin of 10 g/dL (100 g/L; hematocrit of 30%) to minimize anesthesia risks, but not higher, to avoid the risk of hyperviscosity and stroke.

Autologous blood donations are increasingly used for elective surgery in adolescents, children, and even in infants (although collection is difficult in children weighing <25 kg). The largest experience has been in orthopedic procedures associated with significant blood loss, in cardiac surgery, and in prospective bone marrow donors. Phlebotomies are performed over several weeks before surgery, and the blood is frozen and stored. Salvaging blood intraoperatively and postoperatively, collecting it with special equipment, and reinfusing it are additional techniques to reduce the use of banked donor blood. The use of erythropoietin and iron supplementation for several weeks before surgery is an important adjunct.

### Acute Blood Loss or Trauma

Acute blood loss of up to 10% to 15% of the blood volume can usually be managed by volume replacement with crystalloid fluids, but loss of more than 15% usually requires transfusion of PRBCs. Massive bleeding involving the loss of more than 1 blood volume (7%–9% of ideal body weight) in 24 hours gives rise to shock, secondary consumption coagulopathy, and high mortality. Massive transfusion protocols have been developed to administer non-crossmatched group O Rh PRBCs, FFP with each unit of PRBCs, and platelet transfusions and cryoprecipitate with every other unit; the role of pediatric massive transfusion protocols remains under investigation.

### Sickle Cell Disease

Children with chronic anemia of sickle cell disease often tolerate hemoglobin levels of less than 7 g/dL (70 g/L), and simple PRBC transfusion is only indicated for symptomatic children with aplastic crisis or unilateral acute chest syndrome. PRBC should be leukoreduced and from HbS-negative donors, irradiation is not indicated. Transfusion is not indicated to ameliorate a vaso-occlusive pain crisis. Children with bilateral acute chest syndrome or incipient stroke warrant exchange transfusion or erythrocytapheresis (see the later discussion of Apheresis and Exchange Transfusion). Some patients with sickle cell disease may be on a chronic transfusion program.

### Chronic Transfusion

Children who are transfusion dependent (eg, thalassemia) or have sickle cell disease and have had a

stroke, wherein chronic transfusions are needed to maintain the circulating HbS level at less than 30% have a unique problem. Each unit of PRBC contains approximately 300 mg of elemental iron (daily requirement in childhood is 1–2 mg per day) and chronic transfusion rapidly causes iron overload. Serum ferritin monitoring is mandatory and chelation therapy is required when the ferritin level is less than 1,000 ng/mL; in addition, magnetic resonance imaging may be used to estimate cardiac and liver iron overload.

### Newborns and Infants Younger Than 4 Months

The threshold for transfusion varies significantly, often driven by concern over clinical condition and long term neuro-cognitive outcomes. Every neonatal intensive care unit has minor variations on transfusion threshold, and although multiple suggested guidelines have been created (see Box 59-1), compliance is often poor.

Several questions remain unanswered in newborn transfusion medicine, including the role of transfusions in triggering necrotizing enterocolitis, whether transfusing blood less than 14 days old is potentially beneficial, and the threshold at which transfusion should be performed (liberal vs restrictive policies yielded contradictory long-term results, as shown in Table 59-4).

#### BOX 59-1 Suggested Guidelines for Transfusion of Red Blood Cells in Infants Younger Than 4 Months<sup>a</sup>

1. Hct <20% with low reticulocyte count and signs of anemia (eg, tachycardia, tachypnea, poor feeding)
2. Hct <30% in an infant:
  - a. On <35% O<sub>2</sub> by hood
  - b. On O<sub>2</sub> by nasal cannula
  - c. On continuous positive airway pressure (CPAP) or intermittent mandatory ventilation (or both) with mean airway pressure <6 cm H<sub>2</sub>O
  - d. With significant apnea or bradycardia
  - e. With significant tachycardia or tachypnea
  - f. With low weight gain
3. Hct <35% in an infant:
  - a. On >35% O<sub>2</sub> by hood
  - b. On CPAP or intermittent mandatory ventilation with mean airway pressure >6–8 cm H<sub>2</sub>O
4. Hct <45% in an infant:
  - a. On extracorporeal membrane oxygenation
  - b. With congenital cyanotic heart disease

<sup>a</sup>Guidelines may vary in different institutions.

H<sub>2</sub>O, Water; Hct, hematocrit; O<sub>2</sub>, oxygen.

From Roseff SD, Luban NLC, Manno CS. Guidelines for assessing appropriateness of pediatric transfusion. *Transfusion*. 2002;42:1398–1413. Copyright ©2002 John Wiley & Sons, Inc. Reprinted with permission.

**Table 59-4** Guidelines for Red Cell Transfusion of Prematures (TOP) Clinical Trial

TIME	HIGH-THRESHOLD (LIBERAL) GROUP		LOW-THRESHOLD (RESTRICTIVE) GROUP	
	RESPIRATORY SUPPORT	NO SUPPORT	RESPIRATORY SUPPORT	NO SUPPORT
Week 1	13.0	12.0	11.0	10.0
Week 2	12.5	11.0	10.0	8.5
Weeks $\geq 3$	11.0	10.0	8.5	7.0

Hemoglobin values are shown in grams per deciliter. Respiratory support is defined as mechanical ventilation, continuous positive airway pressure, fraction of inspired oxygen in excess of 0.35, or oxygen by nasal cannula in excess of 1 L/min.

From Nickel RS, Josephson CD. Neonatal transfusion medicine: five major unanswered research questions for the twenty-first century. *Clin Perinatol*. 2015;42(3):499–513, with permission from Elsevier.

## INDICATIONS FOR PLATELET TRANSFUSIONS

The essential indication for platelet transfusions is to treat or prevent bleeding. It is worth emphasizing that platelet transfusions are not indicated in immune thrombocytopenia, regardless of the platelet count, except in the setting of intracranial bleeding. Platelet transfusions can actually worsen thrombotic thrombocytopenic purpura or hemolytic uremic syndrome and are contraindicated. Prophylactic platelet transfusions have been administered for patients who are not producing platelets because of chemotherapy or stem cell transplantation at a threshold of 10,000/mL for several years. After initial promising data from a no-prophylaxis strategy, the “platelet dose” (PLADO) trial failed to provide data to support lowering that threshold in children.

The International Collaboration for Transfusion Medicine Guidelines continued with the recommendation that prophylactic platelet transfusion should be performed at a threshold of less than  $10 \times 10^3/\text{mL}$  ( $10 \times 10^9/\text{L}$ ) to decrease the risk of hemorrhage. A low dose of platelets ( $1.41 \times 10^{11}/\text{m}^2$ ) was as effective as higher doses, and although single-donor apheresis platelets are preferred, whole blood-derived platelet concentrates can be used. ABO-compatible platelets improve platelet increments and decrease refractoriness, and for Rh-negative girls or women of child-bearing potential who receive Rh-positive platelets, Rh immunoglobulin to destroy any contaminant RBCs is advisable. Rarely, patients develop HLA antibodies toward platelets, and the degree of benefit from HLA-selected platelets for such patients is uncertain.

Coexistent coagulation disorder, trauma, or surgical bleeding may require patients to receive transfusions of higher platelet counts ( $>50,000/\text{mL}$  [ $>50 \times 10^9/\text{L}$ ]). Preferred thresholds in neonates are higher (see Table 59-5).

## COMPLICATIONS OF TRANSFUSION

Transfusion medicine remains remarkably safe with many of the serious risks of the same magnitude as being struck by lightning. (See Figure 59-1.)

### Acute Hemolytic Transfusion Reaction

Severe, immediate hemolytic transfusion reactions are almost always related to ABO incompatibility and clerical errors, such as incorrect labeling of a blood

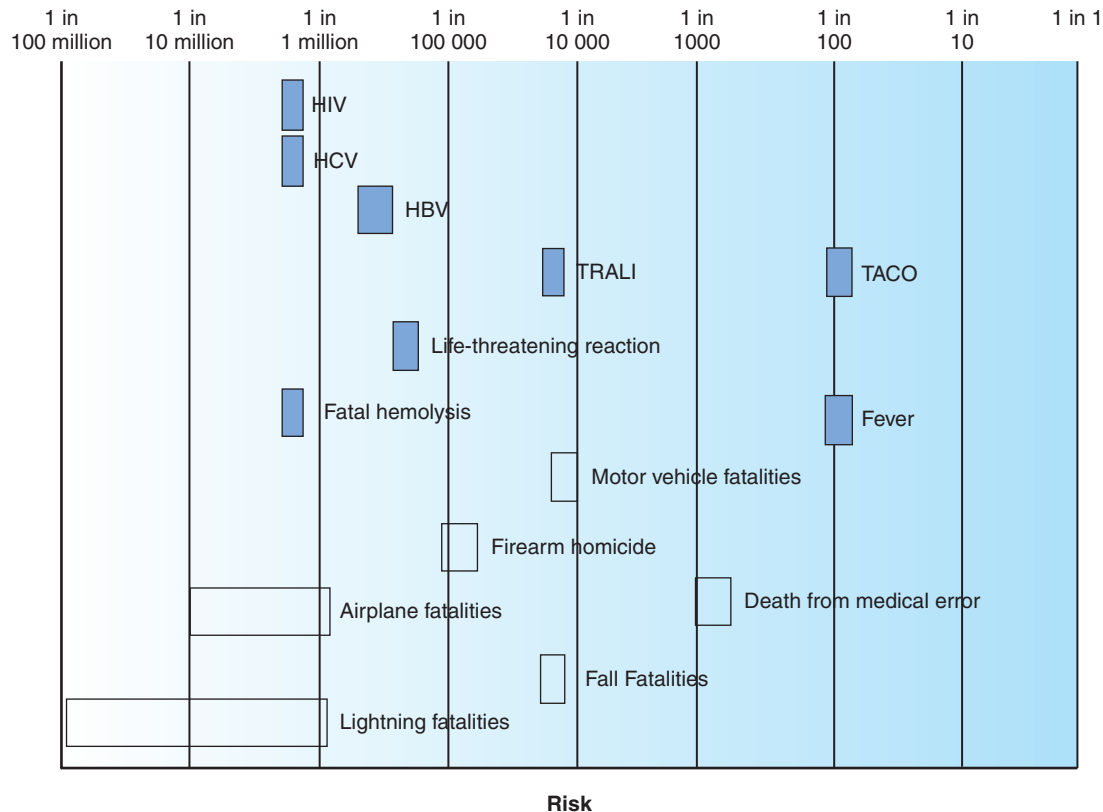
**Table 59-5** Platelet Transfusion Guidelines for Newborns

PLATELET COUNT ( $\times 10^3/\text{MCL}$ [ $\times 10^9/\text{L}$ ])	GUIDELINES
<30 (30)	Transfuse all
30–49 (30–49)	Transfuse if: <ul style="list-style-type: none"> <li>• Birth weight &lt;1,500 g and <math>\leq 7</math> d old</li> <li>• Clinically unstable</li> <li>• Concurrent coagulopathy</li> <li>• Previous significant hemorrhage (ie, grade 3 or 4 IVH)</li> <li>• Prior to surgical procedure</li> <li>• Postoperative period (72 h)</li> </ul>
50–100 (50–100)	Transfuse if: <ul style="list-style-type: none"> <li>• Active bleeding</li> <li>• NAIT with intracranial bleed</li> <li>• Before or after neurosurgical procedures</li> </ul>

NAIT, neonatal alloimmune thrombocytopenia.

From Sparger K, Deschmann E, Sola-Visner M. Platelet transfusions in the neonatal intensive care unit. *Clin Perinatol*. 2015;42(3):613–623, with permission from Elsevier.

specimen tube sent to the laboratory for crossmatching or administering a unit of blood crossmatched to a different patient. Acute onset of fever and chills may be accompanied by nausea, abdominal and lower back pain, dyspnea, and hypotension. Renal failure, DIC, jaundice, and shock may rapidly ensue. If such a reaction is suspected, then the transfusion must be stopped and normal saline administered. A blood specimen from the child together with the remainder of the unit of donor blood or the empty bag and any attached blood tubing should be sent to the blood bank immediately. A rapid screening test can be performed by centrifuging a child's blood specimen, which will show pink, red, or brown plasma; a urine sample will show hemoglobin. If a hemolytic reaction occurs, then adequate venous access should be established and the child transferred to an intensive care unit for close monitoring, aggressive fluid administration, and supportive care. Treatment of DIC and renal dialysis may be needed.



**Figure 59-1** Adverse effects of red blood cell transfusion contrasted with other risks. (From Carson JL, Grossman BJ, Kleinman S, et al. *Clinical Transfusion Medicine Committee of the AABB. Red blood cell transfusion: a clinical practice guideline from the AABB.* Ann Intern Med. 2012;157:49–58. Copyright © 2012, The American College of Physicians. Used with permission.)

### Febrile Transfusion Reaction

Fever is the most common transfusion reaction, usually seen in children who receive multiple transfusions, including platelet transfusions, and secondary to contaminating leukocytes. The onset usually occurs 30 minutes to 2 hours after the transfusion is begun, and the child may also have chills. If the reaction is mild, then stopping the transfusion is unnecessary, but it should be slowed. In more severe reactions, temporary interruption of the transfusion is indicated, with an evaluation for a hemolytic reaction, especially if chills and back or abdominal pain are present. Treatment with acetaminophen and, for more severe reactions, corticosteroids, is helpful; for future transfusions, pretreatment with acetaminophen and diphenhydramine may prevent such reactions. Although it has been common practice in many centers to give prophylactic acetaminophen or diphenhydramine before blood transfusion to prevent febrile and allergic reactions, data to support the routine use of premedication are limited; the use of leukoreduced blood products significantly reduces the incidence and severity of reactions.

### Allergic Reactions

The cause of urticarial reactions is unclear, but is associated with antigens in donor plasma, and cannot be prevented by leukodepletion. About 25% of individuals who have congenital immunoglobulin A (IgA) deficiency have antibodies directed against IgA, and these

patients may develop severe anaphylactic reactions to any blood product containing plasma proteins. Anti-IgA antibodies may also develop in normal individuals and result in urticarial or anaphylactic reactions. Treatment with diphenhydramine, and for more severe reactions, corticosteroids is helpful. People who have repeated minor allergic reactions should be pretreated with an antihistamine; corticosteroids may be used if more severe reactions have occurred. Frozen washed RBCs are rarely needed.

### Delayed Hemolytic Transfusion Reaction

Delayed reactions develop on average 10 days after transfusion (range 3–21 days) in children who have been sensitized to red cell antigens with titers too low to be detected before the recent transfusion. This is most commonly seen in children on a chronic transfusion program. An anamnestic reaction may increase antibody production so that hemolysis ensues and the child becomes anemic, often accompanied by fever, jaundice, and hemoglobinuria. Usually, no specific therapy is required, but an additional transfusion may be needed and steroids have sometimes been advocated for treatment.

### Transfusion-Transmitted Infections

Routine screening of donors for antibodies to HIV has been in effect in the United States since 1985, when 27 per 100,000 donations were found to be HIV positive. With current screening tests for donors, the risk

has been reduced to approximately 1 in 2 million. The risk of hepatitis B virus transmission through blood transfusion is essentially at the same incidence as that in the general (nontransfused) population (< 1:200,000–500,000), whereas that for HIV or hepatitis C virus is approximately 1:1,000,000 to 1:2,000,000. Immune-suppressed children, as discussed previously, are at risk for CMV infection; because 60% to 80% of adult donors in the United States are CMV positive, it might not always be easy to find the right blood product.

Other viruses that may be transmitted by transfusion include hepatitis G (not known to cause disease), hepatitis A, and parvovirus. New-variant Creutzfeldt-Jakob disease and other prion-induced diseases affected 129 cases in the United Kingdom, but no cases in the United States have been associated with blood transfusion. As a result, donors who have spent varying periods in the United Kingdom or Europe are deferred.

Because of the significant decrease in transmission of viral disease and increased use of platelet transfusions, bacterial contamination is now a common transfusion-transmitted infection. It is estimated to occur in approximately 1 in 2,000 units of transfused platelets because platelets are stored at room temperature. The American Association of Blood Banks currently requires testing of platelet units for bacterial contamination with an FDA-approved system to reduce the risk to recipients; the BacT/ALERT system is the most commonly used system.

### Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) is a rare but serious complication of transfusion, occurring most often after transfusion of FFP, but also after other blood products. It has been estimated to occur in 6 in 100,000 transfusions with a 5% mortality, and is the leading cause of transfusion-related death. Patients develop acute respiratory distress caused by noncardiogenic pulmonary edema during or up to 4 hours after transfusion and may require mechanical ventilation. It is caused by anti-HLA or anti-neutrophil antibodies in the donor's plasma, with resultant sequestration of neutrophils in the lung. The treatment is supportive. Mitigation of TRALI has been through preferred use of male donors for plasma and “look back” and removal of donors from the registry who are associated with TRALI.

### Transfusion-Associated Circulatory Overload

Transfusion-associated circulatory overload has an incidence of 1%, but the careful physician should be able to anticipate volume overload in “at-risk” children and minimize the risk by altering the transfusion rate, volume, or the concomitant use of diuretics.

### Transfusion-Related Immunomodulation

Transfusion of stored RBCs has been shown to increase the risk of nosocomial infections and sepsis in children in intensive care units. The cause for this transfusion-related immunomodulatory effect is unknown but may be related to contaminating leukocytes and their cytokines in RBC units or to release of free iron from RBC breakdown from older transfused units. As a result, leukodepletion and use of

fresher units of PRBCs have been tried with varying results.

## APHERESIS AND EXCHANGE TRANSFUSION

One unit of whole blood is equivalent to approximately twice the blood volume of a full-term neonate (ie, a double volume exchange) and will replace approximately 85% of the infant's RBCs. PRBCs can be reconstituted with FFP, and the blood used should be fewer than 3 to 5 days old. Although manual exchange transfusion can also be performed in older children for various indications, this process can be difficult and time consuming.

Using automated cell separators, whole blood is centrifuged and plasma, platelets, leukocytes, and red cells are separated; the desired component is removed, and the remainder is administered back to the patient. Volume can be replaced with saline, albumin, or FFP. With the exception of erythrocytapheresis, the red cells are returned to the patient. Leukocytapheresis may be performed for patients who have leukemia and very high WBC counts to reduce viscosity and leukostasis until chemotherapy takes effect.

Erythrocytapheresis may be performed for symptomatic polycythemia in children who have cyanotic heart disease by using volume replacement with saline or albumin. In sickle cell disease, red cells may be removed and replaced with those containing hemoglobin A. An exchange of one red cell volume (70 mL/kg  $\times$  patient hematocrit) will reduce the Hb S level to approximately 35%. The RBCs should be reconstituted with albumin or FFP, and an additional RBC infusion can reduce the Hb S level further. The final hematocrit should not be more than 30% to 35%.

Plasma exchange can be performed for thrombotic thrombocytopenic purpura by using FFP for replacement. Autoimmune disorders and related conditions have also been treated with plasmapheresis using albumin for replacement, but several of those indications have been discredited.

## ACKNOWLEDGMENT

The assistance of the Albany Medical Center Blood Bank in preparing this chapter is gratefully acknowledged.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Safety of Blood Transfusions* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

## SUGGESTED READINGS

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## Chapter 60

# ANTIMICROBIAL THERAPY

Blaise Congeni, MD; Cecilia Di Pentima, MD, MPH

The use of antimicrobial agents to treat diseases caused by bacteria is part of the day-to-day practice of pediatrics. Antimicrobial therapy continuously evolves; even experts in infectious diseases have trouble staying abreast of new agents and their pharmacologic properties and pharmacodynamics. The physician should know how to use a limited number of antimicrobial agents well rather than have a meager knowledge of many.

## APPROACH TO ANTIMICROBIAL THERAPY

There are 3 important questions that should be answered before antimicrobial therapy is initiated: Where is the infection (anatomic site)? What pathogens usually cause infections at this site? And which antimicrobial agents, given by what route of administration, will achieve effective concentrations at this site? The answers to the 2 initial questions are usually addressed critically by the physician. However, selection of an antimicrobial agent is more likely to be based on a *bug-drug* relationship than on knowledge about a drug's ability to achieve an effective concentration at the site of infection.

The anatomic site of most bacterial infections can be identified by a combination of historical information and findings on physical examination. When the site of infection is more obscure, diagnostic studies such as radiographs, radionucleotide scans, computed tomography scans, magnetic resonance imaging, and ultrasound evaluation are often helpful.

The pediatrician can usually develop a list of potential bacterial pathogens based on the site of infection and the patient's age, habitat, history of exposures,

and clinical signs and symptoms. The site of infection and possible causative agents help the physician decide what (if any) specimens should be cultured for bacteria and whether the laboratory should be alerted to use special culture media or techniques. Selecting an antimicrobial agent based on its ability to achieve effective concentrations at the site of infection requires a working concept of effective concentration. To define an effective concentration, the physician must first review some of the basic pharmacodynamics of antimicrobial agents.

## PHARMACODYNAMICS AND PHARMACOKINETICS

Pharmacodynamics describes the relationship between the serum concentration of the drug and its pharmacologic and toxicologic effects. Pharmacokinetics, on the other hand, describes the absorption, distribution, and elimination of drugs. Physicians are most often interested in the relationship between drug concentration and the antimicrobial effect, the interrelationship between pharmacokinetics and pharmacodynamics. Once administered, an antimicrobial agent is initially distributed throughout the intravascular volume and the extracellular fluid of tissues with high perfusion rates. The drug enters tissues that are not highly perfused at a slower rate. Some antimicrobial agents, such as the  $\beta$ -lactams, are distributed only in extracellular fluid, whereas others distribute intracellularly as well (rifampin, trimethoprim-sulfamethoxazole [TMP-SMX]).

## Correlation of Drug Concentration and Clinical Effect

Antibiotics can be divided into 2 different groups based on their pattern of bactericidal activity. The first group of agents exhibits a greater rate and extent of bactericidal activity the higher the drug concentration. These agents exhibit concentration-dependent killing. Aminoglycosides, fluoroquinolones, metronidazole, and perhaps macrolides exhibit this type of bactericidal activity. In contrast, other antibiotics demonstrate bactericidal activity that is independent of drug concentration as long as the concentration exceeds the minimal inhibitory concentration (MIC) for a certain portion of the dosing interval. These agents demonstrate minimal concentration-dependent killing, but instead, their bactericidal activity depends on the time of exposure. Time-dependent agents include the  $\beta$ -lactam antibiotics, vancomycin, and clindamycin.

## Postantibiotic Effect

For some antibiotics, continued suppression of bacterial growth occurs even after concentrations of the agent have declined below levels that are sufficient to inhibit growth. This circumstance is termed *postantibiotic effect* (PAE). All antimicrobial agents exhibit PAEs in vitro against susceptible gram-positive bacteria. Prolonged PAEs for gram-negative bacteria are observed only after exposure to antibiotics that inhibit protein synthesis or nucleic acid synthesis. A notable

exception is the carbapenems, which produce prolonged PAEs with strains of *Pseudomonas aeruginosa*.

### Relationship of Pharmacokinetic and Pharmacodynamic Parameters and Efficacy

When a time-dependent agent is used, organisms begin to regrow after the serum concentration of the antimicrobial agent has fallen below the MIC. Consequently, the most effective treatment regimens will allow for drug concentrations at the site of infection to be above the MIC for as large a part of the dosing interval as possible. For example, a cure of 85% to 100% can be anticipated when the drug concentration exceeds the MIC for at least 40% of the dosing interval for time-dependent agents such as  $\beta$ -lactams.

Infrequent dosing of concentration-dependent agents such as aminoglycosides and fluoroquinolones is effective. During the 1990s, several studies reported clinical efficacy that was at least equal when the entire aminoglycoside dose was given as a single daily dose compared with divided doses. This approach allows for a single peak concentration at least 10-fold higher than the MIC. Although considerable debate continues, toxicity does not seem to be increased and actually seems more favorable; some investigators have suggested that toxicity depends on the length of time the drug is present in drug-sensitive tissues (eg, the kidney, the inner ear) rather than on the highest concentration attained in the serum at any point.

### Minimal Inhibitory and Minimal Bactericidal Concentrations

An antimicrobial agent's activity against specific bacteria in vitro is expressed as the agent's MIC or minimal bactericidal concentration (MBC). To determine the MIC, bacteria are grown in broth to a concentration of 100,000 ( $10^5$ ) microorganisms per milliliter. The broth containing the bacteria, which is clear to the naked eye, is then placed in a series of test tubes, and a decreasing amount of antimicrobial agent is added to each test tube. The broth containing the bacteria and antimicrobial agent is incubated overnight and then examined for visible turbidity (turbidity represents bacterial growth). The test tube with the smallest concentration of antimicrobial agent that remains clear to the naked eye represents the MIC. To determine whether the antibiotic is bactericidal, the tubes that remained clear are quantitatively subcultured onto agar plates. After overnight incubation, bacterial colonies are counted. Each colony represents 1 bacterium that survived, or 1 colony-forming unit (CFU). The smallest amount of antibiotic that results in the death of 99,900 (99.9%) of the original 100,000 microorganisms per milliliter inoculum (a 1,000-fold reduction) is the MBC. MIC and MBC results are reported in micrograms of antimicrobial agent per milliliter of broth required to inhibit or kill the microorganism, respectively.

### Serum Inhibitory and Bactericidal Titers

Antimicrobial activity in vivo can be approximated by determining the inhibitory or bactericidal titers. Although the test is usually performed using serum, it

can be done with most body fluids that are clear, except urine. The test is performed by growing organisms to  $10^5$  CFU/mL of broth, as in determining the MIC. However, instead of adding known concentrations of antimicrobial agent to each test tube, serial 2-fold dilutions of serum (or other body fluids) are added to sequential tubes (undiluted serum is added to the first tube, serum diluted 1:2 to the second tube, 1:4 to the third, and so on). After incubation overnight, the tubes are examined for visible turbidity; the most dilute sample that has no visible turbidity is the serum inhibitory titer. To determine whether the bacteria are being killed, the broth is cultured quantitatively as for the MBC, and the most dilute specimen that results in the death of 99.9% of the original inoculum is the serum bactericidal titer. Formerly, serum bactericidal levels were used to monitor adequacy of therapy when patients being treated for osteomyelitis or sometimes endocarditis were switched from parenteral to oral therapy. Unfortunately, few laboratories are able to offer this test any longer.

### Tolerance

Tolerance to an antibiotic occurs when organisms are inhibited by the typical concentration of a bactericidal agent but require a higher concentration of the agent to achieve a bactericidal effect. The clinical significance of tolerance is still controversial, but this phenomenon may apparently be important with infections that require bactericidal activity to effect a cure.

### Bacteriostatic versus Bactericidal Agents

Most infections in children do not require a bactericidal antimicrobial agent. In general, bactericidal agents are needed for optimal treatment of bacterial endocarditis, meningitis, and osteomyelitis. The effectiveness of bacteriostatic agents depends on the host's ability to opsonize and phagocytize bacteria that have been inhibited; thus, bactericidal agents are usually necessary to treat bacterial infections in a neutropenic host.

### Role of the Laboratory in Antimicrobial Therapy

Laboratory testing is usually unnecessary for choosing antimicrobial agents for most bacterial infections treated in the ambulatory setting. For example, otitis media is the most common infection of children that is treated with antimicrobial agents in the ambulatory setting. The site of infection is identified by physical examination. The bacterial pathogens that cause otitis media have been well established, and several antimicrobial agents have been shown to produce a clinical and microbiologic cure when given orally. Only if empirical therapy fails might performing a tympanocentesis become necessary to obtain a specimen for isolating the bacteria and performing antibiotic susceptibility tests. The physician can manage common infections such as impetigo, cellulitis, cervical adenitis, local abscesses, and conjunctivitis without obtaining specimens for culture simply by knowing the usual pathogens and their susceptibility to antimicrobial agents.

### Culture and Susceptibility

When therapy fails, when the patient is seriously ill or immunocompromised, or when the clinical situation is unusual, the first step in choosing antimicrobial therapy is to obtain appropriate specimens for culture. When bacterial pathogens are isolated from a normally sterile specimen, antimicrobial susceptibility is tested. Susceptibility is tested either by determining the MIC as described previously or by using the disk diffusion method.

In the disk diffusion method of susceptibility testing, a culture plate is inoculated with the bacteria to be tested, and paper disks containing standardized concentrations of antimicrobial agents are placed on the surface of the culture medium. The culture plates are incubated, and the moisture from the medium allows the antimicrobial agents to diffuse out of the paper disks. The farther from the disk the diffusion reaches, the lower will be the concentration of antimicrobial agent. If the bacteria are inhibited by the antibiotic, then a zone around the disk forms in which the bacteria do not grow. The zone of inhibition is measured after overnight incubation, and based on its diameter, the organism is determined to be *susceptible* or *resistant* to the antimicrobial agent. The interpretation of a result indicating *intermediate* or *indeterminate* is currently undergoing change. Intermediate likely means susceptible but dose dependent. An organism reported to be susceptible by disk means that 95% of the strains of these bacteria are inhibited by serum concentrations of the antimicrobial agent if the antimicrobial agent is given at the usual dose by the usual route of administration for an infection with that organism. This concentration is called the MIC<sub>95</sub>. Clearly, the site of infection, the proposed antibiotic's activity against the pathogen, and the concentration of the antibiotic that can be achieved at the site of infection must all be considered. Pediatric dosages for antibacterial drugs are given in Table 60-1 and Table 60-2.

*Susceptible to ampicillin* has very different meanings, depending on the organism being tested. Gram-negative organisms or enterococci being reported as susceptible to ampicillin (see Table 60-1 and Table 60-2) means that 95% of these organisms are inhibited by serum concentrations of 8 mcg/mL or less of ampicillin. For gram-positive cocci, susceptible means that 95% are inhibited by serum concentrations of 0.2 mcg/mL or less or 40 times less ampicillin than is required to inhibit gram-negative enterics. For *Haemophilus influenzae*, susceptible means that serum concentrations of 2 mcg/mL or less are required to inhibit 95% of all strains. Unless the MIC has been determined for the individual isolate, the physician must assume that MIC<sub>95</sub> must be achieved at the site of infection to inhibit the isolate.

There are 2 modifications of the disk diffusion method that provide additional information when selecting an antibiotic for certain infections. The *e test* uses a strip instead of a disk. An antibiotic gradient is applied, and the zone of inhibition enables the laboratory to determine an approximated MIC by observing where growth occurs on the gradient. This test is most often used to determine MICs for different antimicrobials for *Streptococcus pneumoniae*.

The *D test* is used to determine whether inducible resistance for clindamycin is likely for the offending staphylococcal isolate. The clindamycin disk is placed adjacent to the erythromycin disk. The zone of inhibition between the clindamycin and erythromycin disks is blunted, hence the appearance of a zone that resembles a *D*. Despite the presence of a large zone of inhibition, the staphylococcal isolate is considered resistant to clindamycin (Figure 60-1).

### PROPERTIES OF CLASSES OF ANTIBACTERIAL AGENTS

Because of the large number of antimicrobial agents currently available, usually several are equally effective for a given infection. The antimicrobial agents preferred by a physician reflect the drugs' cost and availability, physician's training, and local practices. In general, knowing how to use a small number of antimicrobial agents well is far better than knowing all of the possible alternatives. The most frequently prescribed antimicrobial agents and their selected pharmacologic and pharmacodynamic information are listed in Table 60-1 and Table 60-2. These tables are an example of the information a physician should have at hand when using antimicrobial agents.

#### Penicillins

##### Mechanism of Action

Although the general mechanism of action of penicillins is to inhibit cell wall synthesis, precisely how they do this is unknown. Current evidence, however, points to inhibition of transpeptidation. Most bacteria have penicillin-binding proteins (PBPs) in their cell membranes. Several PBPs can be found, and the number and type vary from organism to organism. The activity of penicillins generally correlates with the number of high-affinity PBPs the organism has.

#### Bacterial Resistance

Bacterial resistance to penicillins can be based on 3 principal mechanisms: enzymatic degradation, reduced penetration of the agent to the target site, and alteration in the PBP. Inactivation of the penicillin as a result of degradation caused by a penicillinase produced by the bacteria has been the most common mechanism of resistance for this class of agents.  $\beta$ -Lactamase enzymes hydrolyze the  $\beta$ -lactam ring. A variety of  $\beta$ -lactamases have been identified and are classified based on substrate preference. Both gram-positive and gram-negative organisms can produce  $\beta$ -lactamases, and production of these enzymes is mediated by either plasmid or chromosomal mechanisms.

Occasionally, resistance is mediated by failure of the penicillin to reach the site of infection. Some bacteria are resistant because, as a result of shape or electric charge, penicillin cannot reach the binding site. Although this mechanism is clinically less significant, given structural considerations it is more likely encountered with gram-negative organisms such as *Enterobacter*.

**Table 60-1** Antibacterial Drugs for Neonates ( $\leq 28$  Postnatal Days of Age)<sup>a</sup>

DOSE PER KG AND FREQUENCY OF ADMINISTRATION					
DRUG	ROUTE	BODY WEIGHT ≤2 KG		BODY WEIGHT >2 KG	
		≤7 DAYS OF AGE	8–28 DAYS OF AGE <sup>b</sup>	≤7 DAYS OF AGE	8–28 DAYS OF AGE
AMINOGLYCOSIDES <sup>c,d</sup>					
Amikacin	IV, IM	15 mg every 48 h	15 mg every 24h	15 mg every 24 h	17.5 mg every 24 h
Gentamicin	IV, IM	5 mg every 48 h	5 mg every 36 h	4 mg every 24 h	4-5 mg every 24 h
Tobramycin	IV, IM	5 mg every 48 h	5 mg every 36 h	4 mg every 24 h	4-5 mg every 24 h
CARBAPENEMS					
Imipenem/cilastatin <sup>e</sup>	IV	20 mg every 12 h	25 mg every 12 h	25 mg every 12 h	25 mg every 8 h
Meropenem <sup>f</sup>	IV	20 mg every 12 h (≤14 days of age)	20 mg every 8 h (>14 days of age)	20 mg every 8 h (>14 days of age)	30 mg every 8 h (≤14 days of age)
CEPHALOSPORINS <sup>f</sup>					
Cefepime <sup>g</sup>	IV, IM	30 mg every 12 h	30 mg every 12 h	30 mg every 12 h	30 mg every 12 h
Cefotaxime	IV, IM	50 mg every 12 h	50 mg every 8–12 h	50 mg every 12 h	50 mg every 8 h
Cefazolin	IV, IM	25 mg every 12 h	25 mg every 12 h	25 mg every 12 h	25 mg every 8 h
Ceftazidime	IV, IM	50 mg every 12 h	50 mg every 8–12 h	50 mg every 12 h	50 mg every 8 h
Cefoxitin	IV, IM	35 mg every 12 h	35 mg every 8 h	35 mg every 8 h	30 mg every 6 h
Ceftriaxone <sup>h</sup>	IV, IM	50 mg every 24 h	50 mg every 24 h	50 mg every 24 h	50 mg every 24 h
Cefuroxime	IV, IM	50 mg every 12 h	50 mg every 8–12 h	50 mg every 12 h	50 mg every 8 h
PENICILLINS					
Ampicillin <sup>f</sup>	IV, IM	50 mg every 12 h <sup>i,j</sup>	50 mg every 8 h <sup>i</sup>	50 mg every 8 h <sup>i,j</sup>	50 mg every 6 h <sup>i</sup>
Nafcillin, oxacillin <sup>f</sup>	IV, IM	25 mg every 12 h	25 mg every 8 h	25 mg every 8 h	25 mg every 6 h
Penicillin G crystalline <sup>f</sup>	IV, IM	25,000–50,000 U every 12 h	25,000–50,000 U every 8 h	25,000–50,000 U every 12 h	25,000–50,000 U every 8 h
Penicillin G procaine	IM only	50,000 U every 24 h	50,000 U every 24 h	50,000 U every 24 h	50,000 U every 24 h
Piperacillin-tazobactam	IV	100 mg piperacillin component every 12 h	100 mg piperacillin component every 8 h	100 mg piperacillin component every 12 h	100 mg piperacillin component every 8 h
Ticarcillin-clavulanate	IV	75 mg every 12 h	75 mg every 8 h	75 mg every 12 h	75 mg every 8 h
OTHER AGENTS					
Azithromycin	PO	10–20 mg every 24 h	10–20 mg every 24	10–20 mg every 24 h	10–20 mg every 24 h
Aztreonam <sup>g</sup>	IV	10 mg every 24 h	10 mg every 24 h	10 mg every 24 h	10 mg every 24 h
	IV, IM	30 mg every 12 h	30 mg every 8-12 h	30 mg every 8 h	30 mg every 6 h
Clindamycin	IV, IM, PO	5 mg every 12 h	5 mg every 8 h	5 mg every 8 h	5 mg every 6 h
Erythromycin	IV, PO	10 mg every 12 h	10 mg every 8 h	10 mg every 12 h	10 mg every 8 h
Linezolid	IV	10 mg every 12 h	10 mg every 8 h	10 mg every 8 h	10 mg every 8 h



Table 60-1

Antibacterial Drugs for Neonates ( $\leq 28$  Postnatal Days of Age)<sup>a</sup>—cont'd

DOSE PER KG AND FREQUENCY OF ADMINISTRATION					
DRUG	ROUTE	BODY WEIGHT $\leq 2$ KG		BODY WEIGHT $> 2$ KG	
		$\leq 7$ DAYS OF AGE	8–28 DAYS OF AGE <sup>b</sup>	$\leq 7$ DAYS OF AGE	8–28 DAYS OF AGE
Metronidazole <sup>k</sup> [15 mg/kg loading dose all categories (for body weight $\leq 2$ kg or $> 2$ kg, and for $\leq 7$ days of age or 8–28 days of age)]	IV	7.5 mg every 12 h	7.5 mg every 12 h	7.5 mg every 8 h	7.5 mg every 6 h
Vancomycin	IV	See comment <sup>l</sup>			

IM, intramuscular; IV, intravenous; PO, oral.

We gratefully acknowledge the review and comments on this table by John Van den Anker, MD, PhD.

<sup>a</sup>From American Academy of Pediatrics. Antibacterial drugs. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015: 882–883

<sup>b</sup>May use the longer dosing interval in extremely low birth weight ( $< 1,000$  g) neonates until 2 weeks of life.

<sup>c</sup>Dosages for aminoglycosides may differ from those recommended by the manufacturer and approved by the US Food and Drug Administration.

<sup>d</sup>Optimal, individualized dosage should be based on determination of serum concentrations.

<sup>e</sup>Accumulation of cilastatin may occur in neonates with multiple doses.

<sup>f</sup>Higher doses than those listed may be required for meningitis.

<sup>g</sup>50 mg/kg/dose may be required for *Pseudomonas* infections.

<sup>h</sup>Neonates should not receive ceftriaxone intravenously if they also are receiving, or are expected to receive, intravenous calcium in any form, including parenteral nutrition. See Bradley JS, Wessel RT, Lee L, Nambiar S. Intravenous ceftriaxone and calcium in the neonate: assessing the risk for cardiopulmonary adverse events. *Pediatrics*. 2009;123(4):e609–e613.

<sup>i</sup>Some experts recommend 75 mg/kg/dose every 6 h for group B streptococcal meningitis for all weight groups.

<sup>j</sup>100 mg/kg/dose every 12 hours also is acceptable for treatment of presumed early-onset group B streptococcal septicemia without meningitis.

<sup>k</sup>Metronidazole kinetics are best described by postmenstrual (postconceptional) age, which is equivalent to gestational age plus chronologic age. For postmenstrual age  $< 34$  weeks, 7.5 mg/kg every 12 h; for 34–40 weeks, 7.5 mg/kg every 8 h; for  $> 40$  weeks, 7.5 mg/kg every 6 h. All categories should receive a 15-mg/kg loading dose.

<sup>l</sup>Dosing algorithm for vancomycin is based on serum creatinine concentration (which will take approximately 5 days after birth to reasonably reflect neonatal renal function); if  $< 0.7$  mg/dL, then 15 mg/kg every 12 h; if 0.7–0.9 mg/dL, then 20 mg/kg every 24 h; if 1–1.2 mg/dL, then 15 mg/kg every 24 h; if 1.3–1.6 mg/dL, then 10 mg/kg every 24 h; if  $> 1.6$  mg/dL, then 15 mg/kg every 48 h.

During the past decade, alteration in PBPs has become an important mechanism of resistance. This mechanism of resistance is responsible for methicillin resistance seen with *Staphylococcus aureus*. Alteration of PBP also is responsible for the reduced susceptibility of *S pneumoniae* to  $\beta$ -lactams seen in drug-resistant *S pneumoniae* (DRSP). Use of  $\beta$ -lactamase T-stable agents under these circumstances is not effective.

Infections in children caused by DRSP seem to be decreasing as a result of widespread use of the conjugate pneumococcal vaccine. However, community-associated infections with methicillin-resistant *S aureus* (MRSA) have increased dramatically. Infections caused by MRSA may require treatment with antimicrobics that do not inhibit cell wall synthesis by binding to PBPs. Agents frequently used for such infections include vancomycin, linezolid, TMP-SMX, and clindamycin. Tetracyclines and fluoroquinolones may also be used when the age of the patient permits. When selecting a specific antistaphylococcal agent, the physician should be guided by the severity of the infection, as well as by local susceptibility patterns. For example, in life-threatening infections, vancomycin is usually used as a first-line therapy.

### Classification

Based on their specific antibacterial activity, penicillins can be classified loosely as natural, penicillinase resistant, amino, antipseudomonal, and extended spectrum. The physician should be well versed in the use of 1 penicillin from each class.

### Pharmacologic Properties

Penicillins vary greatly in absorption after oral administration, with penicillin V, amoxicillin, cloxacillin, and dicloxacillin having the greatest absorption. Food reduces the absorption of oxacillin and dicloxacillin but not of penicillin V or amoxicillin. Procaine penicillin G and benzathine penicillin G are absorbed slowly after intramuscular injection and are given every 12 to 24 hours and every 15 to 20 days, respectively. Penicillins are excreted by renal tubular cells and have a very short half-life, ranging from less than 30 minutes to slightly more than 1 hour. Penicillins are distributed to most areas of the body if inflammation is present. However, they are poorly lipid soluble and do not enter the central nervous system (CNS) well, even if inflammation is present. Penicillins do not enter cells well. Passage of penicillins from the serum of a

**Table 60-2** Antibacterial Drugs for Pediatric Patients Beyond the Newborn Period<sup>a</sup>

DRUG GENERIC (TRADE NAME)	GENERIC AVAILABLE	ROUTE	DOSAGE PER KG PER DAY		COMMENTS
			MILD TO MODERATE INFECTIONS	SEVERE INFECTIONS	
AMINOGLYCOSIDES <sup>b</sup>					Individualize dose and frequency based on analysis of serum concentrations. <sup>b</sup>
Amikacin	Y	IV, IM	Inappropriate	15–22.5 mg in 2–3 doses, or 15–20 mg in 1 dose	Aminoglycosides may be given once daily, or in divided doses. Measured serum concentrations should guide ongoing therapy. Higher doses are appropriate for patients with cystic fibrosis.
Gentamicin	Y	IV, IM	Inappropriate	6–7.5 mg in 3 doses, or 5–7.5 mg in 1 dose	Aminoglycosides may be given once daily, or in divided doses. Measured serum concentrations should guide ongoing therapy.
Neomycin	Y	PO	100 mg in 4 doses	100 mg in 4 doses	For some enteric infections.
Tobramycin	Y	IV, IM	Inappropriate	6–7.5 mg in 3–4 doses, or 5–7.5 mg in 1 dose	Aminoglycosides may be given once daily, or in divided doses. Measured serum concentrations should guide ongoing therapy. Higher doses are appropriate for patients with cystic fibrosis.
CARBAPENEMS <sup>c</sup>					
Doripenem (Doribax)	N	IV	Inappropriate	60 mg in 3 doses (daily adult dose, 1,500 mg in 3 doses)	Not yet FDA approved for children, but under study. Not studied in meningitis. The generation of each agent is listed as a rough guide to antimicrobial spectrum.
CEPHALOSPORINS <sup>c</sup>					
Imipenem/cilastatin (Primaxin)	Y	IV	Inappropriate	60–100 mg in 4 doses (daily adult dose, 1–4 g)	Caution in use for treatment of CNS infections because of increased risk of seizures. Higher doses for more severe infections or <i>Pseudomonas aeruginosa</i> infections.
Meropenem (Merrem)	Y	IV	Inappropriate	30–60 mg in 3 doses (daily adult dose, 1.5–6 g)	Higher dose (120 mg in 3 doses) used for treatment of meningitis.
Ertapenem (Invanz)	N	IV/IM	Inappropriate	30 mg in 2 doses (adult dose, 1 g, once daily)	Poor activity against <i>Pseudomonas</i> and <i>Acinetobacter</i> species.
Cefaclor (Ceclor)	Y	PO	20–40 mg in 2 or 3 doses (daily adult dose, 750 mg–1.5 g)	Inappropriate	Second-generation.

**Table 60-2** Antibacterial Drugs for Pediatric Patients Beyond the Newborn Period<sup>a</sup>—cont'd

DRUG GENERIC (TRADE NAME)	GENERIC AVAILABLE	ROUTE	DOSAGE PER KG PER DAY		COMMENTS
			MILD TO MODERATE INFECTIONS	SEVERE INFECTIONS	
Cefadroxil (Duricef)	Y	PO	30 mg in 2 doses (daily adult dose, 1–2 g)	Inappropriate	First-generation.
Cefazolin	Y	IV, IM	25–50 mg in 3 doses (daily adult dose, 3 g)	100–150 mg in 3 doses (daily adult dose, 4–6 g)	First-generation. Limited data on dosages above 100 mg/kg/day.
Cefdinir (Omnicef)	Y	PO	14 mg in 1 or 2 doses (max, 600 mg/day)	Inappropriate	Extended-spectrum third generation. Inadequate activity against penicillin- resistant pneumococci.
Cefditoren (Spectracef)	Y	PO	≥12 y: 400–800 mg total daily dose (not per kg) in 2 doses	Inappropriate	Extended-spectrum third general. Contraindicated in patients with carnitine deficiency.
Cefepime (Maxipime)	Y	IV, IM	100 mg in 2 doses (daily adult dose, 2–4 g)	100–150 mg in 2–3 doses (daily adult dose, 4–6 g)	Extended-spectrum fourth generation. Higher dose (150 mg in 3 doses) used for <i>Pseudo-</i> <i>monas</i> infections, or for febrile neutropenia.
Cefixime (Suprax)	N	PO	8 mg in 1 or 2 doses (daily adult dose, 400 mg)	Inappropriate	Extended-spectrum third generation. Inadequate activity against penicillin- resistant pneumococci.
Cefotaxime (Claforan)	Y	IV, IM	50–180 mg in 3 or 4 doses (daily adult dose, 3–6 g)	200–225 mg in 4 or 6 doses (daily adult dose, 8–12 g)	Extended-spectrum third generation. Up to 300 mg in 4 or 6 doses for meningitis.
Cefotetan	Y	IV, IM	60 mg in 2 doses (daily adult dose, 2–4 g)	100 mg in 2 doses (daily adult dose, 4–6 g)	Second-generation. A cephamycin, with en- hanced anaerobic activity. Not FDA approved for use in children.
Cefoxitin (Mefoxin)	Y	IV, IM	80 mg in 3–4 doses (daily adult dose, 3–4 g)	160 mg in 4 doses (daily adult dose, 6–12 g)	Second-generation. A cephamycin, with enhanced anaerobic activity. Active against <i>Bacteroides</i> <i>fragilis</i> .
Cefpodoxime (Vantin)	Y	PO	10 mg in 2 doses (daily adult dose, 200–400 mg, 800 mg for SSTIs)	Inappropriate	Extended-spectrum third generation.
Cefprozil (Cefzil)	Y	PO	15–30 mg in 2 doses (daily adult dose, 0.5–1 g)	Inappropriate	Second-generation.
Ceftaroline (Teflaro)	N	IV	Inappropriate	Adults, 1,200 mg per day in 2–3 doses	Extended-spectrum fifth generation with activity against CA MRSA. Not yet FDA approved for children, but under study.

Continued

**Table 60-2**     **Antibacterial Drugs for Pediatric Patients Beyond the Newborn Period<sup>a</sup>—cont'd**

DRUG GENERIC (TRADE NAME)	GENERIC AVAILABLE	ROUTE	DOSAGE PER KG PER DAY		COMMENTS
			MILD TO MODERATE INFECTIONS	SEVERE INFECTIONS	
Ceftazidime (Fortaz)	Y	IV, IM	90–150 mg in 3 doses (daily adult dose, 3 g)	200 mg in 3 doses for patients with- out cystic fibrosis 300 mg in 3 doses for patients with cystic fibrosis (for both popula- tions, daily adult dose, 6 g)	Extended-spectrum third generation. Anti- <i>Pseudomonas</i> activity.
Ceftibuten (Cedax)	Y	PO	9 mg once daily (daily adult dose, 400 mg)	Inappropriate	Extended-spectrum third generation. Inadequate activity against penicillin-resistant pneumococci.
Ceftriaxone (Rocephin)	Y	IV, IM	50–75 mg once daily (daily adult dose, 1 g)	100 mg in 1 or 2 doses (daily adult dose, 2–4 g)	Extended-spectrum third generation. Larger dosage (up to that used for meningitis) appropriate for penicillin- resistant pneumococcal pneumonia. 50 mg/kg, IM, for 1–3 days for AOM (up to 1 g).
Cefuroxime (Zinacef)	Y	IV, IM	75–100 mg in 3 doses (daily adult dose, 2.25–4.5 g)	100–200 mg in 3–4 doses (daily adult dose, 3–6 g)	Second-generation. Less active than parenteral extended-spectrum cephalosporins against penicillin-resistant pneumococcus.
Cefuroxime (Ceftin)	Y	PO	20–30 mg in 2 doses (daily adult dose, 0.5–1 g)	Inappropriate	Second-generation. Limited activity against penicillin- resistant pneumococcus.
Cephalexin (Keflex)	Y	PO	25–50 mg in 2 or 4 doses (daily adult dose, 1–2 g)	75–100 mg in 3–4 doses (daily adult dose, 2–4 g)	First-generation. The 100 mg/kg/day dos- age has been studied for osteoarticular infections.
<b>CHLORAMPHENICOL</b> (oral formulation not available in the US)	Y	IV only	Inappropriate	50–100 mg in 4 doses (daily adult dose, 2–4 g)	Individualize dose and fre- quency based on analysis of serum concentrations. Usually reserved for serious infections because of rare risk of aplastic anemia.
<b>CLINDAMYCIN</b> (Cleocin)	Y	IM, IV	20–30 mg in 3 doses (daily adult dose, 0.9–1.8 g)	40 mg in 3–4 doses (daily adult dose, 1.8–2.7 g)	Active against anaerobes, especially <i>Bacteroides</i> spe- cies. Active against many multidrug-resistant pneu- mococci and CA-MRSA The 30–40 mg dosage recommended for AOM and CA-MRSA.
		PO	10–25 mg in 3 doses (daily adult dose, 600 mg–1.8 g)	30–40 mg in 3–4 doses (daily adult dose, 1.2–1.8 g)	
<b>DAPTOMYCIN</b> (Cubicin)	N	IV	Inappropriate	6–10 mg, once daily (daily adult dose, 4–6 mg/kg of total body weight)	Not yet FDA-approved for children, but under study



**Table 60-2**      **Antibacterial Drugs for Pediatric Patients Beyond the Newborn Period<sup>a</sup>—cont'd**

DRUG GENERIC (TRADE NAME)	GENERIC AVAILABLE	ROUTE	DOSAGE PER KG PER DAY		COMMENTS
			MILD TO MODERATE INFECTIONS	SEVERE INFECTIONS	
FLUOROQUINOLONES <sup>d</sup>					
Ciprofloxacin (Cipro)	Y Tablet only	PO	20 mg in 2 doses (daily adult dose, 0.5–1 g)	30–40 mg in 2 doses (daily adult dose, 1–1.5 g)	20 mg one time for <i>Neisseria meningitidis</i> prophylaxis (adult dose 500 mg). Also see Fluoroquinolones, p 872.
	Y	IV	Inappropriate	20–30 mg in 2 or 3 doses (daily adult dose, 0.8–1.2 g)	
Levofloxacin (Levaquin)	Y	IV, PO	Inappropriate	16–20 mg in 2 doses (daily adult dose, 500–750 mg)	Also see Fluoroquinolones, p 872.
MACROLIDES					
Azithromycin (Zithromax, Zmax)	Y	PO	5–12 mg once daily (adult single or total course dose, 1.5–2 g); 60-mg single dose of extended-release formulation, Zmax (adult dose 2 g)	Inappropriate	All doses once daily: AOM: 10 mg/kg/day for 3 days; or 30 mg/kg for 1 day; or 10 mg/kg/day for 1 day, then 5 mg/kg/day for 4 days. Pharyngitis: 12 mg/kg/day for 5 days (maximum 1.5 g total course). Sinusitis: 10 mg/kg/day for 3 days or 10 mg/kg/day for 1 day, then 5 mg/kg/day for 4 days. Community associated pneumonia: 10 mg/kg × 1 day, then 5 mg/kg/day for 4 days or 60 mg/kg for 1 day of Zmax extended-release suspension for infants and children >6 months of age. Shigellosis: 12 mg/kg × 1 day, 6 mg/kg/day for 4 days.
	Y	IV	Inappropriate	10 mg/kg, once daily	Administer over at least 60 minutes to potentially prevent local reactions.
Clarithromycin (Biaxin)	Y	PO	15 mg in 2 doses (daily adult dose, 0.5–1 g)	Inappropriate	Similar activity to erythro- mycin; more activity against <i>Mycobacterium</i> <i>avium</i> and <i>Helicobacter</i> <i>pylori</i> .

Continued

Table 60-2

Antibacterial Drugs for Pediatric Patients Beyond the Newborn Period<sup>a</sup>—cont'd

DOSAGE PER KG PER DAY					
DRUG GENERIC (TRADE NAME)	GENERIC AVAILABLE	ROUTE	MILD TO MODERATE INFECTIONS	SEVERE INFECTIONS	COMMENTS
Erythromycin (numerous)	Y	PO	40–50 mg in 3–4 doses (daily adult dose, 1–2 g)	Inappropriate	Available in base, stearate, and ethylsuccinate preparations.
	N	IV	Inappropriate	20 mg in 4 doses (daily adult dose, 2–4 g)	Administer over at least 60 minutes to potentially prevent cardiac arrhythmias.
Fidaxomicin (Dificid)	N	PO	Adults: 400 mg total daily dose (not per kg) in 2 doses	Inappropriate	Minimal systemic absorption; Used for treatment of <i>Clostridium difficile</i> -associated diarrhea. Not yet FDA approved for children, but under study.
<b>METRONIDAZOLE</b> (Flagyl)	Y	PO	30–50 mg in 3 doses (daily adult dose, 0.75–2.25 g)	Same	30 mg in 4 doses for <i>C difficile</i> infection
	Y	IV	22.5–40 mg in 3 doses (daily adult dose, 1.5 g)	Same	
<b>MONOBACTAM</b> Aztreonam (Azactam)	Y	IV, IM	90 mg in 3 doses (daily adult dose, 3 g)	90–120 mg in 3 or 4 doses (maximum daily adult dose, 8 g)	—
<b>NITROFURANTOIN</b> (Furadantin, Macrodantin)	Y	PO	5–7 mg in 4 doses (daily adult dose, 200–400 mg)	Inappropriate	For treatment of cystitis; not appropriate for pyelonephritis. UTI prophylaxis: 1–2 mg once daily.
<b>OXAZOLIDINONES</b> Linezolid (Zyvox)	N	PO, IV	For children <12 y of age: 30 mg in 3 doses For adolescents ≥12 y and adults: 1,200 mg per day in 2 doses	Same	Myelosuppression increases with duration of therapy over 10 days.
<b>PENICILLINS<sup>c</sup></b> <b>Broad-spectrum penicillins</b> Amoxicillin (Amoxil)	Y	PO	25–50 mg in 3 doses (daily adult dose, 750 mg–1.5 g)	High dosage for oral step-down therapy of invasive, non-AOM infections: 80–100 mg in 3 doses, or for highly susceptible pathogens, 90 mg in 2 doses	90 mg/kg in 2 doses recommended for initial therapy of AOM.

Table 60-2

Antibacterial Drugs for Pediatric Patients Beyond the Newborn Period<sup>a</sup>—cont'd

DOSAGE PER KG PER DAY					
DRUG GENERIC (TRADE NAME)	GENERIC AVAILABLE	ROUTE	MILD TO MODERATE INFECTIONS	SEVERE INFECTIONS	COMMENTS
Amoxicillin-clavulanic acid (Augmentin)	Y	PO	14:1 Formulation: 90 mg amoxicillin component in 2 doses (<40 kg) for recurrent AOM, treatment failures 7:1 Formulation: 25–45 mg amoxicil- lin component in 2 doses (daily adult dose, 1,750 mg) 4:1 Formulation: 20–40 mg amoxicil- lin component in 3 doses (daily adult dose, 1,500 mg)	Inappropriate	
Ampicillin	Y	IV, IM	100–150 mg in 4 doses (daily adult dose, 2–4 g)	200–400 mg in 4 doses (daily adult dose, 6–12 g)	Highest doses in treatment of CNS infections
	Y	PO	50–100 mg in 4 doses (daily adult dose, 2–4 g)	Inappropriate	
Ampicillin-sulbactam (Unasyn)	Y	IV	100–200 mg of ampi- cillin component in 4 doses (daily adult dose, 4 g)	200 mg ampicillin component in 4 doses (daily adult dose, 8 g)	
Piperacillin-tazobactam (Zosyn)	Y	IV	Inappropriate	For children ≥9 months of age: 300 mg piper- acillin compo- nent in 3 doses (daily adult dose, 9–16 g)	Lower dose (240 mg piperacillin component in 3 doses) recommended for patients 2–9 mo of age.
Ticarcillin-clavulanate (Timentin)	N	IV	Inappropriate	200–300 mg ticar- cillin component in 4–6 doses (daily adult dose, 12–18 g)	
<b>PENICILLIN<sup>c</sup></b> Penicillin G, crystal- line potassium or sodium	Y	IV, IM	100,000–150,000 units in 4 doses (daily adult dose, 4–8 million units)	200,000–300,000 units in 4–6 doses (daily adult dose, 12–24 million units)	Use highest doses in treatment of CNS infections.
Penicillin G procaine	Y	IM	50,000 units in 1–2 doses (daily adult dose, 300,000–1.2 million units)	Inappropriate	Not safe for IV administration.

Continued

Table 60-2

Antibacterial Drugs for Pediatric Patients Beyond the Newborn Period<sup>a</sup>—cont'd

DRUG GENERIC (TRADE NAME)	GENERIC AVAILABLE	ROUTE	DOSAGE PER KG PER DAY		COMMENTS
			MILD TO MODERATE INFECTIONS	SEVERE INFECTIONS	
Penicillin G benzathine (Bicillin LA)	N	IM	<27 kg (60 lb) 300,000–600,000 units (not dosed per kg) one time ≥27 kg (60 lb) 900,000 units (not dosed per kg) one time	Inappropriate	Not safe for IV administration. Very low but prolonged serum concentrations. 50,000 U/kg for newborns and infants. Major use is treatment of rheumatic fever prophylaxis and treponemal infections.
Penicillin G benzathine/procaine (Bicillin CR) <sup>e</sup>	N	IM	<14 kg (30 lb) 600,000 units (not dosed per kg) one time 14–27 kg (30–60 lb) 900,000–1,200,000 units (not dosed per kg) one time ≥27 kg (60 lb) 2,400,000 units (not dosed per kg) one time		Not safe for IV administration. Major use is treatment of group A streptococcal infections.
Penicillin V	Y	PO	25–75 mg in 3 or 4 doses (daily adult dose, 1–2 g)	Inappropriate	
PENICILLINASE-RESISTANT PENICILLINS <sup>c</sup>					Methicillin (oxacillin)-resistant staphylococci usually are resistant to all semisynthetic antistaphylococcal penicillins and cephalosporins except ceftaroline.
Oxacillin	Y	IV, IM	100–150 mg in 4 doses (daily adult dose, 4 g)	150–200 mg in 4–6 doses (daily adult dose, 6–12 g)	
Nafcillin	Y	IV, IM	100–150 mg in 4 doses (daily adult dose, 4 g)	150–200 mg in 4–6 doses (daily adult dose, 6–12 g)	
Dicloxacillin (suspension no longer available in the US)	Y	PO	12–25 mg in 4 doses (daily adult dose, 0.5–1 g)	100 mg in 4 divided doses (for step-down therapy of osteoarticular infections)	
RIFAMYCINS					
Rifampin (Rifadin)	Y	IV, PO	10–20 mg in 1–2 doses (daily adult dose, 600 mg)	20 mg in 2 doses (daily adult dose, 600 mg)	Should not be used routinely as monotherapy because of rapid emergence of resistance. See p 815–816 for <i>M tuberculosis</i> dosing.
Rifaximin (Xifaxan)	N	PO	≥12 y of age: 600 mg/day (not per kg) in 3 doses	Inappropriate	Treatment of travelers' diarrhea caused by non-invasive <i>Escherichia coli</i> ; should not be used for bloody diarrhea with risk of bacteremia.



**Table 60-2** Antibacterial Drugs for Pediatric Patients Beyond the Newborn Period<sup>a</sup>—cont'd

DRUG GENERIC (TRADE NAME)	GENERIC AVAILABLE	ROUTE	DOSAGE PER KG PER DAY		COMMENTS
			MILD TO MODERATE INFECTIONS	SEVERE INFECTIONS	
<b>STREPTOGRAMIN</b> Quinupristin/ dalfopristin (Synercid)	N	IV	Inappropriate	For children ≥12 y of age: 15 mg in 2 doses (daily adult dose, same)	Moderate activity against <i>Staphylococcus aureus</i> . Limited experience in children.
<b>SULFONAMIDES</b> Sulfadiazine	Y	PO	120–150 mg in 4–6 doses (daily adult dose, 4–6 g)	120–150 mg in 4–6 doses (daily adult dose, 4–6 g)	
Trimethoprim (TMP)-sulfa- methoxazole (SMX) in 1:5 ratio (Bactrim, Septra)	Y	PO, IV	6–12 mg of TMP component in 2 doses (daily adult dose, 320 mg TMP)	same	2 mg of TMP component once daily for UTI prophylaxis. See p 641 for <i>Pneumocystis jirovecii</i> dosing.
<b>TETRACYCLINES</b> Tetracycline (Sumycin)	Y	PO	25–50 mg in 4 doses (daily adult dose, 1–2 g)	25–50 mg in 4 doses (daily adult dose, 1–2 g)	Responsible for staining of developing teeth; routine use only in children 8 y or older. Exceptions for circumstances in which the benefits of therapy exceed the risks and al- ternative drugs are less effective or more toxic found on p 873.
Doxycycline (Vibramycin)	Y	PO, IV	2–4 mg in 1–2 doses (daily adult dose, 50–200 mg)	4 mg/kg per day, divided every 12 hours, intrave- nously or orally (maximum 100 mg/dose)	Adverse effects similar to those of other tetracy- cline products except that risk of dental stain- ing in children younger than 8 y with doxycy- cline is unlikely at the dose and duration recommended to treat serious infections.
Minocycline (Dynacin, Minocin)	Y	PO, IV	4 mg in 2 doses (daily adult dose, 200 mg)	4 mg in 2 doses (daily adult dose, 200 mg)	Responsible for staining of developing teeth; routine use only in children 8 y or older.
<b>VANCOMYCIN</b> (Vancocin)	Y	IV	40–45 mg in 3–4 doses (daily adult dose, 1–2 g)	45–60 mg in 3–4 doses (daily adult dose, 2–4 g)	Measured serum concen- trations should guide ongoing therapy.

AOM, acute otitis media; CA MRSA, community-associated methicillin-resistant *Staphylococcus aureus*; CNS, central nervous system; FDA, US Food and Drug Administration; IM, intramuscular; IV, intravenous; PO, oral; SSTI, skin and soft tissue infection; UTI, urinary tract infection.

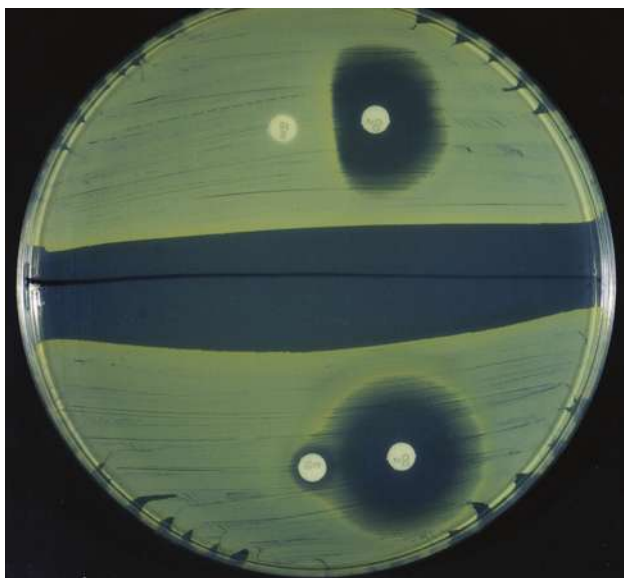
<sup>a</sup>From American Academy of Pediatrics. Antibacterial drugs. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015: 885–895.

<sup>b</sup>Once-daily aminoglycoside dosing may provide equal efficacy with reduced toxicity and may be used as an alternative to multiple daily dosing. See Contopoulos-Iannidis DG, Giotis ND, Baliatsa DV, Iannidis JP. Extended-interval aminoglycoside administration for children: a meta-analysis. *Pediatrics*. 2004;114(1):e111–e118, and Best EJ, Gazarian M, Cohn R, Wilkinson M, Palasanthiran P. Once-daily gentamicin in infants and children: a prospective cohort study evaluating safety and the role of therapeutic drug monitoring in minimizing toxicity. *Pediatr Infect Dis J*. 2011;30(10):827–832.

<sup>c</sup>Children with a history of an IgE-mediated, immediate hypersensitivity reaction to penicillins (urticaria, angioedema, bronchospasm, anaphylaxis) who require treatment with an alternate β-lactam should be considered for skin testing (if available) to confirm the allergy, and/or undergo supervised graded clinical challenge or desensitization with the alternate β-lactam agent under the supervision of an expert in drug allergy and desensitization.

<sup>d</sup>Ciprofloxacin is FDA approved for use in patients younger than 18 years for complicated UTI and postexposure inhalation anthrax but also has been studied in other infections. Levofloxacin is FDA approved for postexposure inhalation anthrax and plague, but has been studied in children and adolescents for treatment of AOM, community acquired pneumonia.

<sup>e</sup>Available in 2-mL prefilled syringes. Each 1 mL contains 300,000 units benzathine plus 300,000 units procaine (600,000 total units per mL).



**Figure 60-1** Positive D test. Petri plate with zone of inhibition surrounding disks.

pregnant woman to her fetus depends on the degree of protein binding present; little of highly protein-bound penicillin reaches the fetus.

### Side Effects

The most important adverse reactions to penicillins are caused by hypersensitivity; they range from skin rashes to anaphylaxis. Anaphylactic reactions to penicillin are immunoglobulin E (IgE) mediated and occur in approximately 1 of every 500 courses of treatment (0.2%); approximately 1 of every 100,000 courses results in a fatality (0.001%). The morbilliform rashes seen during therapy with penicillins probably are IgM mediated and often disappear even when therapy is continued. Less common reactions include serum sickness, exfoliative dermatitis, and Stevens-Johnson syndrome.

Patients who experience significant type 1 reactions such as anaphylaxis following use of a penicillin generally should not be treated with a cephalosporin or other  $\beta$ -lactam. Cross-reactivity, however, is probably less of a problem than previously thought. Patients with non-type 1 reactions can generally be treated with a cephalosporin, for example. Cross-reactivity is not to the shared  $\beta$ -lactam ring but to shared side chains. Using an agent with dissimilar side chains probably poses little risk. Patients who experience idiopathic reactions, such as a morbilliform rash, when treated with a penicillin can be treated with a cephalosporin. It is therefore critical to document the exact nature of the reaction following any antibiotic, including penicillins and cephalosporins.

### Penicillin Desensitization

At times, administering penicillin to a penicillin-sensitive patient may be necessary, for example, in a patient with meningococcal meningitis who is allergic to cephalosporins and penicillins. When penicillin is administered to a patient who may have an anaphylactic reaction, immunotolerance to penicillin can be

achieved by starting with very small doses. An effective protocol is to administer 5 U of penicillin G intracutaneously in the forearm, and then, at 60- to 90-minute intervals increase the dose to 10, 100, 1,000, 10,000, and 50,000 U. If the intradermal doses are tolerated, intravenous penicillin can be instituted.

### Use of Selected Penicillins

The natural penicillins listed in Table 60-1 and Table 60-2 are penicillin G (aqueous, procaine, and benzathine) and penicillin V. These antimicrobial agents are most active against both aerobic and anaerobic gram-positive cocci, *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Fusobacterium* species, *Eikenella* species, *Listeria monocytogenes*, and *Borrelia burgdorferi*. Penicillins are still the mainstay of treatment for infections caused by group A  $\beta$ -hemolytic streptococci, group B streptococci, *S pneumoniae*, *N meningitidis*, and *L monocytogenes*. Penicillin is also the drug of choice for acute infections with *B burgdorferi* (Lyme disease) in children and for infections caused by anaerobes normally found in the mouth.

The potassium salt of penicillin G is usually used and is almost exclusively given intravenously. Either procaine or benzathine preparations are used for intramuscular administration. When given intramuscularly, aqueous penicillin G is excreted very rapidly; when given by mouth, it is poorly absorbed, and very low serum concentrations are achieved with these preparations; they can be used only for exquisitely sensitive organisms and generally should not be used to treat CNS infections. Procaine penicillin can be used in a newborn to treat neurosyphilis. Penicillin V is well absorbed from the gastrointestinal tract and is therefore preferred for oral administration. Peak serum concentrations and MIC<sub>95</sub> equivalents for susceptibility by disk are listed for individual penicillins in Table 60-1 and Table 60-2.

Ampicillin has the same general activity as penicillin, but it also is active against *Escherichia coli*, *Proteus mirabilis*, *Salmonella* species, and *Shigella* species and is more active against group D streptococci and *L monocytogenes*. Amoxicillin differs from ampicillin in molecular composition only by the presence of a hydroxyl group. Because amoxicillin is absorbed much better than ampicillin, peak serum concentrations of amoxicillin after oral administration are equal to those achieved with an equivalent dose of ampicillin given intramuscularly. The antimicrobial activity of amoxicillin is virtually identical to that of ampicillin, except that it is not useful in the treatment of shigellosis; because of the increased absorption of amoxicillin, less drug is available in the intestinal tract.

Several fixed-combination  $\beta$ -lactam- $\beta$ -lactamase inhibitors are available.  $\beta$ -Lactamase inhibitors include clavulanic acid, sulbactam, and tazobactam. There are 4 agents currently available: amoxicillin-clavulanate (Augmentin), ampicillin-sulbactam (Unasyn), ticarcillin-clavulanate (Timentin), and piperacillin-tazobactam (Zosyn). Piperacillin-tazobactam does not have a pediatric indication for its use. The  $\beta$ -lactamase inhibitor extends the activity of the  $\beta$ -lactam to include some organisms that produce  $\beta$ -lactamase. Amoxicillin-clavulanate, for example, is active against  $\beta$ -lactamase-producing *S aureus*, *H influenzae*, *N gonorrhoeae*, and

*Moraxella catarrhalis* that otherwise would be resistant to amoxicillin. The MIC for *E coli*, *Klebsiella* species, *Proteus* species, and *Bacteroides fragilis* ranges from 8 to 16 mcg/mL. This combination is no more active than amoxicillin for *S pneumoniae* strains that are resistant to penicillin. Ampicillin in a fixed combination with sulbactam is marketed as Unasyn for intravenous use only. The activity of ampicillin-sulbactam is similar to that of ampicillin-clavulanate, and this agent is frequently used in adults and children for respiratory infections and infections in which anaerobes are likely to be pathogens, such as intraabdominal or intraoral infections. Safety and efficacy for intraabdominal infections in children have not been established. Ticarcillin-clavulanate and piperacillin-tazobactam use a  $\beta$ -lactam that is an extended-spectrum penicillin with antipseudomonal activity, thereby extending the spectrum of these fixed combinations further. These agents would be more appropriate for infections in which gram-negative organisms, including *Pseudomonas*, are thought to be pathogens.

Nafcillin is one of several penicillinase-resistant penicillins used primarily to treat infections caused by *S aureus*, excluding MRSA. Most strains of *S aureus* are inhibited by concentrations of 2 to 3 mcg/mL. Because nafcillin is highly protein bound, methicillin is preferred for newborns when the possibility of kernicterus is a concern because the amount of albumin available for binding bilirubin will be diminished. Absorption of nafcillin from the gastrointestinal (GI) tract is erratic; it should not be given orally. Dicloxacillin is absorbed from the GI tract more consistently and is a good oral agent for treating *S aureus* infections. The oral suspension of dicloxacillin has a very bitter taste, which can create problems with compliance.

Several antipseudomonal and extended-spectrum penicillins are currently available. In general, *Pseudomonas* infections should be treated with a combination of one of these agents plus an aminoglycoside, both for synergy and for reducing the emergence of resistant bacteria. A possible exception to this rule is for the treatment of a urinary tract infection caused by *P aeruginosa*. Mezlocillin has the antipseudomonal activity of carbenicillin and ticarcillin; it is also more active against enterococci, *Klebsiella* species, *H influenzae*, and *B fragilis*. An important point to remember is that a report of *susceptible to mezlocillin* means that concentrations as high as 64 mcg/mL will be needed to inhibit 95% of the strains tested; this circumstance is compensated for by the high serum concentrations achieved when the drug is given intravenously (the peak serum concentration is 300 mcg/mL after an intravenous dose of 4 g).

Treating multidrug-resistant strains has become more of a problem, especially given the fact that few new antibiotics have been developed during the past decade. A way to address this problem, especially for resistant gram-negative rod infections, such as those seen in nosocomial infections, is to take advantage of pharmacokinetic/pharmacodynamic principles while still employing available agents. For example, a recent retrospective cohort study compared piperacillin-tazobactam given by extended infusion (4 hours) to a 30-minute infusion for treating patients infected with *P aeruginosa* in the intensive care setting. Both 14-day

mortality and length of stay were significantly improved in the prolonged infusion group. These investigators took advantage of the time-dependent killing pharmacokinetic profile seen with this extended-spectrum penicillin.

## Cephalosporins

### Mechanism of Action

Similar to penicillins, cephalosporins are  $\beta$ -lactam antibiotics that interfere with cell wall synthesis. However, the precise mechanism is not known, and the effects of cephalosporins on bacteria range from lysing the organism to producing bacteria that have unusual forms.

### Bacterial Resistance

Bacterial resistance to cephalosporins can arise if the cephalosporin is inactivated by  $\beta$ -lactamase, if it is unable to reach antibiotic-binding proteins, if the organism does not have appropriate binding sites, or if tolerance develops (see the previous discussion of penicillins).

### Classification

In the 1970s and 1980s, more new cephalosporins were introduced for general use than any other type of antimicrobial agent. Currently, ceftriaxone and cefotaxime are 2 of the agents most commonly used for the empirical therapy of the febrile infant. The usual classification system for cephalosporins is based on antibacterial activity and is divided into first, second, and third generations. Some experts have recently added a fourth generation. This classification system seems more useful for parenteral agents and may result in very dissimilar agents being grouped together. In general, the first-generation cephalosporins have good activity against gram-positive cocci except enterococci, coagulase-negative staphylococcal species, and MRSA; they have limited activity against gram-negative organisms except *E coli*, *Klebsiella pneumoniae*, and *P mirabilis*. Activity of these agents against Enterobacteriaceae is unpredictable; the physician should be guided by in vitro susceptibility testing. Organisms susceptible to one cephalosporin of this class are generally susceptible to all. The second-generation cephalosporins have the general activity of the first generation but are somewhat more active against gram-negative organisms, including *H influenzae*. Third-generation cephalosporins are more active than second-generation drugs against gram-negative organisms but are less active against some gram-positive organisms, especially *S aureus*, than are the first-generation drugs.

Cefepime is a fourth-generation cephalosporin with activity similar to cefotaxime, but it additionally demonstrates better activity against some gram-negative organisms, such as *P aeruginosa*.

### Pharmacologic Properties

Because of the number of cephalosporins and the wide variations in pharmacology, each drug should be considered individually.

### Side Effects

The side effects seen with cephalosporins are generally the same as those seen with penicillins. Hypersensitivity reactions are the most common side effects.



Although immunologic studies have shown a substantial cross-reactivity between penicillins and cephalosporins, in practice only 5% to 10% of persons who have hypersensitivity reactions to penicillins have them to cephalosporins. In general, if a patient has had only a nonurticarial rash as the manifestation of penicillin hypersensitivity, then using cephalosporins is safe. For patients who have had urticaria or an anaphylactic reaction in response to penicillins, cephalosporins should be used with great caution. Recent studies have suggested that the frequency of cross-sensitivity between penicillins and cephalosporins is substantially less than the figures cited previously. Allergy to cephalosporins in patients truly allergic to penicillins is more common with first-generation cephalosporins and is seen with agents with identical side chains. The fact that both the penicillins and the cephalosporins share an identical  $\beta$ -lactam ring seems much less important relative to predicting cross-sensitivity than previously thought. Less common side effects with cephalosporins are nephrotoxicity, diarrhea, alcohol intolerance, and bleeding.

### Use of Selected Cephalosporins

**FIRST-GENERATION CEPHALOSPORINS.** First-generation cephalosporins are used to treat infections caused by gram-positive cocci when penicillin cannot be used, to treat infections caused by methicillin-sensitive *S aureus*, and to provide coverage against *E coli*, *K pneumoniae*, and *P mirabilis*. Cefazolin is preferable to cephalothin because it has greater activity against *E coli* and *Klebsiella* species, achieves higher peak serum concentrations, and has a longer half-life. The peak serum concentration of cefazolin after a dose of 1 g given intravenously is 188 mcg/mL; the serum half-life is 1½ to 2 hours. Susceptible by disk means that 95% of the bacteria tested are inhibited by 8 mcg/mL or less. The longer half-life compared with antistaphylococcal penicillins, nafcillin, or cephalothin makes cefazolin a particularly attractive agent for patients who are not hospitalized. Cefazolin can be given 3 times per day compared with the other agents, which require dosing 4 times per day. Cephalexin (Keflex) is a first-generation cephalosporin that can be given orally. A peak serum concentration of 16 mcg/mL can be achieved with a dose of 0.5 g. The antibacterial activity of cephalexin is similar to that of cefazolin. Cefadroxil achieves peak serum concentrations and has antimicrobial activity similar to that of cephalexin but is excreted more slowly, allowing administration at 12- to 24-hour intervals.

**SECOND-GENERATION CEPHALOSPORINS.** Based on activity, second-generation cephalosporins should be divided further into 2 separate groups. The true cephalosporins of the second generation include cefuroxime and cefamandole.

Cefuroxime was used widely in children for the treatment of infection when gram-positive cocci such as *S aureus* and *H influenzae* were considered likely pathogens. Many of these infections are now treated with the third-generation cephalosporins, ceftriaxone, or cefotaxime because of improved penetration into the cerebrospinal fluid and because of the possibility of *S pneumoniae* as a pathogen in these circumstances. Cefuroxime is the only second-generation cephalosporin that achieves therapeutic concentrations

in cerebrospinal fluid (CSF). For a time, cefuroxime was advocated as single-drug therapy for bacterial meningitis in infants and children older than 2 months. However, cefuroxime does not sterilize the CSF as rapidly as does ampicillin plus chloramphenicol or selected third-generation cephalosporins, and should not be used to treat meningitis. Cefuroxime can be used when parenteral coverage for both *S aureus* and *H influenzae* is desirable in a patient who has no CNS infection.

The second-generation cephamycins include cefoxitin, cefotetan, and cefmetazole. These agents are rarely used in children because more suitable agents are available. Cefoxitin is highly resistant to  $\beta$ -lactamases and is more active against anaerobes, especially *B fragilis*, than other cephalosporins. It is not as active as other second-generation cephalosporins against *H influenzae* and Enterobacteriaceae, nor is it as active against gram-positive cocci as first-generation cephalosporins. Cefotetan is more active against aerobic gram-negative bacilli than cefoxitin but is less active against aerobic gram-positive cocci. Cefmetazole seems to be more active against *S aureus* than either cefoxitin or cefotetan but is less active than cefotetan against Enterobacteriaceae and less active than cefoxitin against *B fragilis*. Because of its activity against anaerobes plus some gram-positive and gram-negative aerobes, cefoxitin has proved useful in the treatment of pelvic inflammatory disease and lung abscesses. The peak serum concentration after a dose of 1 g given intravenously is approximately 22 mcg/mL, and the serum half-life is approximately 50 minutes. Susceptible by disk means that the MIC<sub>95</sub> for the organism is 8 mcg/mL or less. Use of cefoxitin declined dramatically in the 1990s because of the development of safer, more effective agents. Fixed-combination  $\beta$ -lactam- $\beta$ -lactamase inhibitors, such as Unasyn, are more active against anaerobes and have better activity against gram-positive cocci, including *S aureus*. Metronidazole and carbapenems are also more active against anaerobes than cefoxitin. Consequently, these agents are preferred in clinical situations in which cefoxitin may have been used in the past.

Second-generation cephalosporins available for oral administration include cefaclor (Ceclor), cefuroxime axetil (Ceftin), cefprozil (Cefzil), and loracarbef (Lorabid). Loracarbef is technically a carbacephem rather than a cephalosporin. These agents are used primarily as the second- or third-line agents to treat upper respiratory infections (eg, otitis media, sinusitis) in patients who have not responded to less expensive first-line agents such as amoxicillin. The structure and spectrum of activity of loracarbef are very similar to those of cefaclor.

**THIRD-GENERATION CEPHALOSPORINS.** The third-generation cephalosporins are more active than even the first- or second-generation drugs against gram-negative organisms, but these agents are less active against *S aureus*. Cefotaxime and ceftriaxone are the most active of the cephalosporins against *S pneumoniae* and other streptococci, including many strains that are resistant to penicillin.

Third-generation cephalosporins can be thought of as those that have a role in treating *Pseudomonas*



infections and those that do not. Cefotaxime and ceftriaxone do not have activity against *P aeruginosa*. Cefotaxime, the initial third-generation cephalosporin to be used widely in the United States, is still useful clinically. Ceftriaxone is very similar to cefotaxime in antibacterial activity but has a much longer half-life. Both cefotaxime and ceftriaxone are active against most gram-positive aerobes except enterococci and *L monocytogenes*. Neither is active against MRSA or coagulase-negative staphylococci. Both are active against most gram-negative aerobic bacteria, except for *Pseudomonas* species. The diacetyl breakdown product of cefotaxime also has a broad range of activity, but specific activity is less than that of cefotaxime itself. The peak serum concentration after intravenous administration of 1 g of cefotaxime is approximately 40 mcg/mL, compared with 150 mcg/mL for ceftriaxone. The serum half-life of cefotaxime is approximately 1 hour, compared with 4 to 6 hours for ceftriaxone. Because ceftriaxone is excreted slowly, a peak serum concentration of 50 mcg/mL is achieved in adults after a dose of 0.5 g is given intramuscularly. Susceptible by disk means that the MIC<sub>95</sub> of either drug for the bacteria tested is 8 mcg/mL or less.

The subsequent third-generation cephalosporins that have good antipseudomonal activity are cefoperazone and ceftazidime. Ceftazidime is more active than cefoperazone against *Pseudomonas* in vitro but is less active than cefotaxime against gram-positive organisms. Whether or not ceftazidime should be used as a single agent to treat *Pseudomonas* infections is still controversial. In adults, the peak serum concentration of ceftazidime after 1 g is given intravenously is 85 mcg/mL; the serum half-life is approximately 1 hour, 48 minutes. Approximately 90% of *Pseudomonas* isolates are inhibited by 8 mcg/mL or less of ceftazidime.

There are 4 third-generation cephalosporins currently available for oral use: cefixime (Suprax), cefpodoxime proxetil (Vantin), ceftibuten (Cedax), and cefdinir (Omnicef). Cefixime and ceftibuten have a similar spectrum; consequently, they are grouped together. They have limited activity against some gram-positive cocci such as *S pneumoniae* and no activity against *S aureus*. Both are active against the gram-negative bacilli responsible for most urinary tract infections. Because *S pneumoniae* coverage is incomplete, these agents are recommended only as second-line agents for the treatment of otitis media and only if treatment with an antimicrobial that has good antipneumococcal activity fails when used alone. Both of these agents are active against *Streptococcus pyogenes* and can be used for pharyngitis. The usual dose of cefixime is 8 mg/kg/day given as a single dose; the usual dose of ceftibuten is 9 mg/kg/day given once daily or divided into 2 equal doses.

Cefpodoxime proxetil and cefdinir have a spectrum of activity for gram-negative microorganisms that is similar to those of other oral third-generation cephalosporins. These agents, however, have good activity against gram-positive cocci, including *S pneumoniae*, *S pyogenes*, and *S aureus*, methicillin-sensitive strains. Cefpodoxime achieves higher tissue concentrations in the lungs and tonsils than do other cephalosporins. The usual dosage is 5 mg/kg every 12 hours, with a maximal dose of 400 mg/day for

otitis media and 200 mg/day for pharyngitis or tonsillitis. The dosage of cefdinir for children 6 months to 12 years of age is 14 mg/kg/day in 1 or 2 divided doses. Although the oral third-generation cephalosporins are effective in treating bacterial pneumonia, otitis media, tonsillitis, and pharyngitis, equally effective and less expensive alternatives are available.

**FOURTH-GENERATION CEPHALOSPORINS.** Currently, cefepime (Maxipime) is available for use in individuals older than 2 months. This agent has been tentatively classified as a fourth-generation cephalosporin. Available only for parenteral use, it is unique compared with other cephalosporins because of its broad spectrum of activity against both gram-positive cocci, including methicillin-sensitive *S aureus*, *S pneumoniae*, and *S pyogenes*, as well as most aerobic gram-negative bacilli, including *P aeruginosa*. This agent has a half-life of 2 hours, which permits dosing twice daily at 100 mg/kg/day. It has been used primarily in adults for the treatment of pneumonia and febrile neutropenia. Although it seems to penetrate into the CSF, it does not have an indication for the treatment of meningitis. Cefepime has been evaluated in pediatric patients with bacterial meningitis and has been found to be effective; however, US Food and Drug Administration approval for this indication has not been obtained.

Recently, a new class of cephalosporin, ceftaroline (Teflaro), has been approved for use in patients older than 18 years with skin and skin structure infections as well as community-acquired pneumonia. Trials are currently underway in pediatric patients. This novel cephalosporin has activity against both methicillin-sensitive and methicillin-resistant *S aureus* and *S pneumoniae* as well as common gram-negative pathogens.

### Other $\beta$ -Lactam Antibiotics

There are 4 other  $\beta$ -lactam antibiotics—imipenem, meropenem, ertapenem (carbapenems), and aztreonam (monobactam)—that have a limited role in the treatment of bacterial infections in children. This class of drugs is generally considered treatment of choice for those extended-spectrum  $\beta$ -lactamase-positive pathogens. Imipenem and meropenem have an extremely broad range of activity that covers most gram-positive organisms, including enterococci, *Listeria* species, and methicillin-susceptible staphylococci, which includes coagulase-negative staphylococci. Strains of *S pneumoniae* that demonstrate intermediate or high levels of resistance to penicillin are frequently susceptible to these agents. Imipenem and meropenem also inhibit most Enterobacteriaceae, *P aeruginosa*, and *Pseudomonas maltophilia*, as well as most anaerobic bacteria. Ertapenem has a longer half-life compared with the other available carbapenems, permitting less frequent dosing. It is not as reliably active against gram-negative aerobes when compared with imipenem or meropenem. Carbapenems are generally considered drugs of choice for organisms producing extended spectrum  $\beta$ -lactamase.

Because imipenem is rapidly destroyed by a renal peptidase, it is supplied in a fixed combination with a dehydropeptidase inhibitor called cilastatin. In adults, 500 mg of imipenem with cilastatin given intravenously produces an average peak serum concentration of 33 mcg/mL; the serum half-life is approximately

1 hour. The MIC<sub>95</sub> of bacteria susceptible by disk is 4 mcg/mL or less. Imipenem's broad spectrum of antimicrobial activity is seldom required in clinical practice.

The major risk factor that has somewhat limited the usefulness of the carbapenems is seizure activity. The risk for seizures seems to be somewhat lower with meropenem compared with imipenem. Consequently, carbapenems should be used with caution in patients who have associated risk factors that may increase the likelihood of seizures, such as renal failure and CNS conditions, including meningitis.

Imipenem recently has been licensed for use in patients as young as 1 week. Meropenem is indicated for use in children 3 months or older. Ertapenem does not have an indication for use in children younger than 3 months, and no indication has been found for patients with meningitis. Given the broad spectrum of activity, these agents are occasionally useful in resistant infections with *S pneumoniae*; in patients with mixed infections, including those caused by anaerobes; and in patients with febrile neutropenia.

Aztreonam, a monobactam, has little activity against gram-positive or anaerobic bacteria because these bacteria have little PBP 3, which is the primary binding site for aztreonam. On the other hand, aztreonam is very active against Enterobacteriaceae (MIC,  $\leq 0.5$  mcg/mL) and moderately active against *P aeruginosa* (MIC,  $\leq 16$  mcg/mL). In adults, 1 g of aztreonam given intravenously results in a peak serum concentration of approximately 125 mcg/mL; the serum half-life is 1 hour, 42 minutes. Susceptible by disk means that the MIC<sub>95</sub> will be 8 mcg/mL or less. The use of aztreonam in children is scant.

## Aminoglycosides

### Mechanisms of Action

Aminoglycosides inhibit bacterial protein synthesis by interfering with bacterial ribosomes at the interface between the smaller and larger ribosome subunits. A second mechanism, not yet known, is necessary to fully explain bacterial killing.

### Bacterial Resistance

There are 3 mechanisms of bacterial resistance to aminoglycosides. Ribosomal resistance occurs when alteration in the smaller ribosomal subunit results in its inability to bind streptomycin. The most common mechanism of resistance is the production of bacterial enzymes that inactivate aminoglycosides. Because aminoglycosides are similar in structure, certain enzymes can inactivate more than one aminoglycoside. The capacity to produce aminoglycoside-inactivating enzymes is inherent among gram-negative aerobic bacteria and seldom occurs by induction. The number and types of enzymes vary among places and populations. As an aminoglycoside becomes used more widely, bacteria that produce inactivating enzymes become more prevalent. The ability to produce inactivating enzymes is carried by plasmids and transferred among gram-negative bacteria. Amikacin seems to be an unsuitable substrate for many of these inactivating

enzymes; consequently, amikacin may be active against some organisms resistant to other aminoglycosides, including gentamicin and tobramycin.

The third mechanism of resistance to aminoglycosides is bacterial impermeability to aminoglycosides. Permeability mutants are generally not very virulent. When an organism is susceptible to tobramycin or gentamicin (or both) but is resistant to amikacin, the amikacin resistance must be based on amikacin's inability to enter the organism. This property must be the reason because the only enzyme produced by gram-negative organisms that inhibits amikacin also inhibits tobramycin and gentamicin.

### Pharmacologic Properties

Aminoglycosides are absorbed poorly or not at all after oral administration. Absorption after intramuscular administration is excellent, with the peak serum concentration occurring 30 to 90 minutes after administration. The serum concentration after intravenous administration over 20 to 30 minutes is approximately the same as after intramuscular administration. Aminoglycosides do not cross cell membranes well and therefore achieve poor concentrations inside most cells except renal tubular cells, which actively transport these agents. In general, only low concentrations of aminoglycosides are achieved in the CNS, eyes, biliary tract, or prostatic fluid. Aminoglycosides do enter synovial fluid well.

Because aminoglycosides are excreted by glomerular filtration, care must be taken to adjust the dose for patients who have renal failure. After filtration, some of the aminoglycoside dose is reabsorbed by the proximal renal tubular cells; this reabsorption probably plays a role in nephrotoxicity caused by these drugs. By convention, the drug is infused over a 60-minute period, and the peak serum concentration is measured 30 minutes after the infusion is completed. With intramuscular administration, the peak serum concentration is measured 1 hour later. Because the therapeutic-to-toxic index is very low for aminoglycosides, the serum concentration should be monitored closely.

### Side Effects

The 2 most common side effects of aminoglycosides are ototoxicity and nephrotoxicity. Ototoxicity is generally considered to be reversible and is caused by destruction of the outer hair cells in the organ of Corti and is possibly related to the concentration of aminoglycoside in the endolymph or perilymph that bathes these cells. The relationship between serum concentrations and the development of ototoxicity remains unclear. Some investigators have suggested that elevated trough concentrations predispose a patient to ototoxicity. Others have recently postulated that once-daily dosing of aminoglycosides may actually reduce the likelihood of ototoxicity by reducing drug accumulation in the inner ear.

Hearing loss generally begins at higher frequencies than those commonly used for conversation. Consequently, routine screening of hearing may be useful in patients at risk for auditory ototoxicity such as those who have cystic fibrosis and are receiving repeated

courses of aminoglycosides. Vestibular toxicity is another manifestation of ototoxicity that is thought to be irreversible and can be very disabling. Transient elevations in aminoglycoside concentrations probably do not affect hearing.

Nephrotoxicity is exhibited as a decrease in the glomerular filtration rate. As with ototoxicity, the relationship between serum concentrations and the development of nephrotoxicity is not completely understood. Nephrotoxicity is generally mild and reversible. Associated risk factors frequently are found in patients who have nephrotoxicity, including concurrent medications and illnesses. Some investigators have suggested that the risk for nephrotoxicity is reduced by administering the entire daily aminoglycoside dose once a day. Both ototoxicity and nephrotoxicity seem to occur less often in children than in adults. Nonetheless, monitoring the serum concentration is important to make sure it is both safe and therapeutic, especially when dosed 2 or 3 times daily.

Aminoglycosides can also cause neuromuscular paralysis, particularly when given along with curare-like drugs, in the presence of botulin toxin, and in patients who have myasthenia gravis. Neuromuscular paralysis does not usually occur if aminoglycosides are given intramuscularly. Neuromuscular paralysis can be treated by administering calcium.

### Use

Streptomycin, the first aminoglycoside used clinically, is used almost exclusively to treat tuberculosis, but it is also used to treat tularemia, plague, and brucellosis. Neomycin is used primarily to reduce the number of bacteria in the large bowel. It is given by mouth, and very little reaches the bloodstream.

Three aminoglycosides—gentamicin, tobramycin, and amikacin—are currently used systemically to treat serious infections caused by gram-negative aerobic bacteria. In general, no evidence has been uncovered that one of these aminoglycosides is clinically superior to another in the treatment of susceptible bacteria. Tobramycin is more active against *P. aeruginosa* than gentamicin or amikacin, but differences in its clinical effectiveness have not been observed. Tobramycin and amikacin are somewhat less nephrotoxic than gentamicin. Amikacin is susceptible to inactivation by one aminoglycoside-inactivating enzyme, whereas tobramycin and gentamicin are inactivated by at least 6 enzymes. Thus, organisms are less likely to be resistant to amikacin than to either tobramycin or gentamicin. Because amikacin is less toxic on a weight basis, a larger dose is given and a higher peak serum concentration is achieved. With a dose of 7.5 mg/kg of amikacin given intravenously, the peak serum concentration averages 38 mcg/mL. At a dose of 2 mg/kg of tobramycin or gentamicin, the peak serum concentration ranges from 3 to 12 mcg/mL. All 3 drugs have a serum half-life of 2 to 2½ hours. The MIC<sub>95</sub> of amikacin for bacteria reported susceptible by disk is 16 mcg/mL or less; the MIC<sub>95</sub> of gentamicin or tobramycin is 4 mcg/mL or less.

Once-daily dosing of aminoglycosides has been found to have several advantages over dosing every 8 to 12 hours. The pharmacodynamic model presented

earlier suggests that because aminoglycosides kill in a concentration-dependent manner, once-daily dosing should offer more rapid and effective killing of bacteria. Once-daily dosing results in a higher peak serum concentration, an acceptably low trough concentration, and possibly a lower incidence of nephrotoxicity and ototoxicity. Dosing once daily also facilitates more convenient administration and reduces costs. Gentamicin and tobramycin are dosed at 4 to 7 mg/kg/day, producing a peak serum concentration that ranges from 10 to 20 mcg/mL and a trough concentration below 2 mcg/mL. Actually, the serum concentration will be below the MIC for a substantial portion of the dosing interval. Amikacin is dosed at 15 mg/kg/day, with a resulting peak serum concentration of 54 mcg/mL and a trough concentration below 5 mcg/mL. Monitoring serum concentrations in patients receiving once-daily dosing is generally accomplished by obtaining a single serum sample 6 hours after the dose. A nomogram is available that then enables the physician to decide whether that dose is administered most appropriately once a day, every 36 hours, or once every other day. Despite studies showing an efficacy equivalent to divided daily doses, once-daily administration of aminoglycosides has not become widespread in pediatrics. Most adult patients, however, are treated using a single daily dose. Some investigators have cautioned that once-daily dosing should not be used for patients who have enterococcal endocarditis, are newborns, or are febrile and neutropenic.

## Sulfonamides and Trimethoprim

### Mechanisms of Action

Sulfonamides inhibit bacterial growth by reducing bacterial synthesis of folic acid, resulting in a decrease in bacterial nucleotides. Trimethoprim inhibits bacterial dihydrofolate reductase, which is the step in folic acid synthesis that follows the step inhibited by sulfonamides. The combination of trimethoprim and sulfamethoxazole results in a synergistic, sequential blockage of folic acid.

### Bacterial Resistance

Resistance to sulfonamides can be based on overproduction of substrate by the bacteria or a change in enzyme structure to one that has diminished sulfonamide binding. Trimethoprim resistance also may be caused by a decline in the bacteria's capacity to bind the drug or to a change in dihydrofolate reductase. Resistance to both drugs can result if an organism develops decreased permeability to the drugs. Resistance occurs less often when the combination TMP-SMX is used.

### Pharmacologic Properties

The sulfonamides currently used in the United States, either alone or in combination with trimethoprim, are sulfisoxazole (Gantrisin), sulfamethoxazole, and sulfadiazine. Sulfonamides are usually given orally, but intravenous preparations of sulfadiazine and sulfisoxazole are available. These sulfonamides are quickly and completely absorbed from the stomach and small intestine. Sulfonamides are distributed throughout the body, including the CSF. They readily cross the



placenta and are found in fetal blood. Sulfonamides are partially metabolized in the liver, and free drug metabolites are excreted by glomerular filtration.

Trimethoprim is also usually given orally and is readily absorbed. It is well distributed throughout the body, with the CSF concentration reaching approximately 40% of the serum concentration. Excretion is primarily by renal tubular secretion.

### Side Effects

A wide variety of toxicities are associated with sulfonamides, ranging from GI upset, headache, and rash to serum sickness and hepatic necrosis. Severe hypersensitivity reactions can occur, such as toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema nodosum, vasculitis, and anaphylaxis. Blood cell disorders, including aplastic anemia, granulocytopenia, thrombocytopenia, and leukopenia, have been attributed to sulfonamides. Patients who have glucose-6-phosphate dehydrogenase (G6PD) deficiency are at heightened risk for aplastic anemia. Sulfonamides should not be taken during the last month of pregnancy because they cross the placenta and compete for bilirubin-binding sites, increasing the risk for kernicterus. All of the side effects associated with sulfonamides can occur with trimethoprim as well, the most common being GI upset and hypersensitivity reactions. With prolonged use, trimethoprim can interfere with folate metabolism, resulting in a megaloblastic anemia. This condition can be prevented by administering folic acid.

### Use of Trimethoprim-Sulfamethoxazole and Selected Sulfonamides

The combination of trimethoprim and sulfamethoxazole was introduced initially to treat urinary tract infections. However, because of its wide range of antibacterial activity, it has proved useful in several bacterial infections. Gram-positive organisms susceptible to TMP-SMX include both coagulase-positive and coagulase-negative staphylococci, *S pneumoniae*, enterococci, and *Listeria* species. Currently, more than 95% of MRSA strains that are community associated are susceptible to TMP-SMX. Hospital-associated strains are not as likely to be susceptible. TMP-SMX also is inhibitory for a wide range of gram-negative aerobic organisms, including *E coli*, *Klebsiella* species, *Salmonella* species, *Shigella* species, *H influenzae*, and *N meningitidis*.

Until recently, TMP-SMX was used primarily in the treatment of acute urinary tract infections and for long-term bacterial suppression in patients who have chronic or recurrent urinary tract infections. Currently, however, TMP-SMX is a preferred agent for the treatment of mild-to-moderate infections caused by community-associated MRSA. Respiratory tract infections, otitis media, sinusitis, prostatitis, orchitis, and epididymitis are also treated on occasion with TMP-SMX. It remains the drug of choice for treating *Pneumocystis jiroveci* (formerly *carinii*) infections and has proved effective in preventing *P jiroveci* infection in children who have malignancies. Many adults infected with human immunodeficiency virus (HIV) do not tolerate TMP-SMX well. To date, however, this situation has not been a major problem in HIV-infected

infants. The peak serum concentrations for both drugs, reached approximately 2 hours after an oral dose, average 2 mcg/mL for trimethoprim and 60 mcg/mL for sulfamethoxazole. After repeated doses, the peak serum concentration of trimethoprim approaches 9 mcg/mL. The MIC<sub>95</sub> for bacteria susceptible to the combination is 2 mcg/mL or less for trimethoprim and 38 mcg/mL or less for sulfamethoxazole. However, the combination usually is synergistic in vivo.

Sulfisoxazole is used primarily to treat acute urinary tract infections or to effect long-term suppression in patients who have chronic or recurrent urinary tract infections. Sulfadiazine is effective prophylaxis for close contacts of patients who have *N meningitidis* infections if the strain is known to be susceptible (see Chapter 366, Meningococcemia). The peak serum concentrations after an oral dose of 2 g range from 30 to 60 mcg/mL for sulfadiazine, 40 to 50 mcg/mL for sulfisoxazole, and 80 to 100 mcg/mL for sulfamethoxazole.

Topical sulfonamides are used primarily in 2 settings. Ophthalmic preparations of sulfacetamide are used to treat acute conjunctivitis and as adjunctive therapy in the treatment of trachoma. Silver sulfadiazine is used in the topical treatment of burns. In this combination, sulfadiazine serves principally as a vehicle for the release of silver ions, which have an antibacterial effect.

### Macrolides and Azalides: Erythromycin, Clarithromycin, and Azithromycin

#### Mechanism of Action

Macrolides inhibit RNA-dependent protein synthesis at the step of chain elongation.

#### Bacterial Resistance

Bacteria that lack the appropriate ribosomal binding site are resistant to erythromycin, as are bacteria that are less permeable to the drug. The presence of an efflux pump results in low-level resistance for streptococcal strains. Methylase resistance, conferred by the *erm* gene, is the most common mechanism of resistance seen in the United States.

### Erythromycin

#### Pharmacologic Properties

Several erythromycin preparations are available for oral administration. Erythromycin base is destroyed by gastric acid and is therefore useful only when given as an enteric-coated tablet. Pediatric preparations use the ester or ester salt derivatives of erythromycin because they are acid stable, soluble, and tasteless. Preparations vary in their rate and degree of absorption from the GI tract. The best absorbed is the estolate ester, which results in a peak serum concentration of approximately 4 mcg/mL. The ethylsuccinate and stearate preparations produce peak serum concentrations that range from 0.4 to 1.9 mcg/mL when given at a dose equivalent to the ester. Erythromycin is distributed throughout the body and persists in tissue longer than in the blood. Therapeutic concentrations are reached in middle ear fluid, paranasal sinuses, tonsils, and pleural fluid but not the CSF, even when the meninges are inflamed. Limited data suggest that entry into synovial fluid is poor.



Erythromycin's route of elimination is not clear. A small percentage of a dose of erythromycin can be found in the urine, and erythromycin is known to be concentrated in and excreted with bile. However, most of an administered dose cannot be recovered.

### Side Effects

The most common side effect of erythromycin is GI upset characterized by abdominal pain, nausea, vomiting, or diarrhea. Erythromycin is actually used primarily to promote GI motility in some adults. Allergic reactions occur but are relatively uncommon. Cholestatic hepatitis occurs after treatment with the estolate ester but can be seen with any of the preparations. This side effect has been seen primarily in adults. The better absorption characteristics of the estolate preparation of erythromycin probably outweigh the slight risk for cholestatic hepatitis in children.

### Use

Erythromycin has a broad range of antibacterial activity and is the drug of choice for infections caused by *Mycoplasma pneumoniae*, *Legionella* species, *Corynebacterium diphtheriae*, *Bordetella pertussis*, *Chlamydia trachomatis*, and *Campylobacter jejuni*. Erythromycin is an alternative drug for the treatment of streptococcal and staphylococcal infections and as prophylaxis for syphilis, urinary tract infections, rheumatic fever, and bacterial endocarditis. Macrolide-resistant *S. pyogenes* have been reported in the United States. However, exactly how this discovery may affect the use of this class of drugs for penicillin-allergic individuals with streptococcal pharyngitis is unknown.

The MIC<sub>95</sub> of erythromycin required to inhibit bacteria reported as susceptible by disk is 0.5 mcg/mL or less. Lactobionate and gluceptate preparations are available for parenteral administration but are not used often. The peak serum concentration after intravenous administration is approximately equal to that achieved when estolate is given by mouth.

### Clarithromycin

#### Pharmacologic Properties

Clarithromycin is stable in gastric acid and is well absorbed from the GI tract; furthermore, its bioavailability is not affected by food. A peak serum concentration of 4 to 5 mcg/mL is reached in 2½ to 3 hours, and concentrations in middle ear fluid and lung tissue exceed serum concentrations. The major route of excretion is in bile, but approximately one-third of an administered dose can be recovered in the urine. A metabolite of clarithromycin, 14-hydroxycarithromycin, achieves a serum concentration that is approximately 60% that of clarithromycin and is approximately twice as active against *H. influenzae*.

### Side Effects

Clarithromycin causes much less gastric upset than erythromycin, but diarrhea (6% of cases), vomiting (6%), abdominal pain (3%), and nausea (1%) are the most common side effects. Children frequently complain that the suspension is unpalatable and leaves an unpleasant aftertaste.

### Use

Clinical trials have demonstrated the efficacy of clarithromycin in the treatment of otitis media, pharyngitis, skin and soft tissue infections, *Mycobacterium avium* complex (MAC) infections, and *Helicobacter pylori* infections. In general, clarithromycin can be used for infections traditionally treated with erythromycin. Because of the activity of its 14-hydroxycarithromycin-breakdown product, clarithromycin may prove useful in *H. influenzae* infections.

### Azithromycin

Azithromycin differs structurally from erythromycin and clarithromycin by having a 15-member rather than a 14-member ring. Because of its unique structure, azithromycin has a much larger volume of distribution, a longer half-life, and greater penetration at the cellular level than erythromycin and clarithromycin. In vitro studies show equivalent antimicrobial activity for gram-positive cocci and atypical pathogens, including *Mycoplasma*. Azithromycin is more effective against *H. influenzae* than erythromycin or clarithromycin. Because of its volume of distribution and longer half-life, once-daily dosing is appropriate, and short-course therapy for streptococcal pharyngitis (ie, 5 days) is recommended. Given its prolonged tissue half-life and concentration-dependent killing, azithromycin has been used with shorter courses and less frequent dosing. Newer preparations such as Tri-pak or Zmax use higher doses, given for 3 days or as a single dose, respectively. These preparations are not available for use in children.

The macrolide antibiotics may interact with other drugs by inducing cytochrome P-450. Commonly used drugs that may interact include theophylline, zidovudine, cimetidine, and most anticonvulsants. Because azithromycin does not induce formation of cytochrome P-450, drug-to-drug interactions do not occur with this formulation.

### Clindamycin

#### Mechanism of Action

Clindamycin shares binding sites with erythromycin and chloramphenicol on the 50S ribosomal subunit and interferes with protein synthesis by inhibiting the transpeptidation reaction.

#### Mechanisms of Resistance

The mechanism of bacterial resistance involves modification of the ribosomal binding site, similar to that seen in erythromycin. Clindamycin, however, is not captured or excreted by the macrolide efflux pump, a significant difference from the macrolides.

#### Pharmacologic Properties

Clindamycin is usually given orally, but preparations for intramuscular and intravenous administration are available. Approximately 90% of a dose of clindamycin is absorbed after oral administration, and peak serum concentrations are reached in 1 hour and are dose dependent. Clindamycin palmitate (oral suspension) and clindamycin phosphate (preparation for intravenous administration) are inactive but are hydrolyzed rapidly in vivo to the active free base. Clindamycin is well distributed throughout the body

except for the CSF. Clindamycin is one of the few antimicrobial agents that is concentrated in polymorphonuclear neutrophils. The serum half-life of clindamycin is approximately 2 hours, 24 minutes. Most clindamycin is metabolized in the liver to products that have variable antibacterial activity. Antibacterial activity in the bile and GI tract is very high and results in a dramatic decline in sensitive bowel flora.

### Side Effects

The most highly publicized complication of clindamycin is colitis caused by the toxin of *Clostridium difficile* (pseudomembranous colitis). This complication has now been associated with many other antimicrobial agents and seems to occur less often in children than in adults. Side effects of clindamycin include allergic reactions, rashes, and minor elevations in transaminase concentrations.

### Use

Clindamycin is highly active against most gram-positive aerobic bacteria and most anaerobic bacteria. The major clinical use of clindamycin is the treatment of anaerobic infections. Clindamycin is used routinely when fecal material spills into the abdomen, and it is also used to treat anaerobic bronchopulmonary infections. When used for the treatment of intraabdominal infections, it is generally given along with an aminoglycoside. Clindamycin is also used as alternate therapy for groups A and B streptococcal infections. Group A streptococci that are resistant to macrolides are almost invariably susceptible to clindamycin. It has also been used as oral therapy to complete a course of antibiotics for *S aureus* osteomyelitis. Under these circumstances, clindamycin is an especially attractive alternative in patients who are allergic to  $\beta$ -lactams. In the United States, many strains of penicillin-resistant *S pneumoniae* remain susceptible to clindamycin. Clindamycin is a preferred agent for the treatment of mild-to-moderate community-associated MRSA infections. However, resistance to clindamycin for this indication is rapidly increasing and varies from location to location. Given the explosive increase in clindamycin use, a significant increase in resistance recently has been noted for MRSA. In contrast to TMP-SMX, clindamycin will provide coverage for both staphylococci and streptococci. Providing such coverage may be necessary before culture and sensitivity data are available. Clindamycin does not enter the CSF in useful concentrations. A peak serum concentration of 2.5 to 3.6 mcg/mL is achieved approximately 1 hour after oral administration, and a concentration of 6 to 9 mcg/mL can be reached after intravenous infusion. The MIC<sub>95</sub> of clindamycin for bacteria reported as susceptible by disk is 0.5 mcg/mL or less.

## Chloramphenicol

### Mechanism of Action

Similar to erythromycin and clindamycin, chloramphenicol binds to the 50S ribosomal subunit and inhibits protein synthesis.

### Bacterial Resistance

Mechanisms of resistance include bacterial production of an acetyltransferase that inactivates chloramphenicol and inability of chloramphenicol to enter bacteria.

## Pharmacologic Properties

Chloramphenicol can be given orally as the free base or as chloramphenicol palmitate, which is hydrolyzed in the intestine to free base. Because chloramphenicol is extremely bitter, oral palmitate suspension is given to patients who cannot take capsules containing free base. The intravenous preparation is chloramphenicol succinate, which is also hydrolyzed to free base. Because the palmitate is hydrolyzed more completely than the succinate, its peak serum concentration is generally higher after oral administration. Chloramphenicol distributes well throughout the body, including the brain and CSF. Chloramphenicol is conjugated by the liver and excreted in an inactive form in urine.

### Side Effects

The major side effects of chloramphenicol are dose-related bone marrow suppression, which is reversible; aplastic anemia, which is idiosyncratic and usually fatal; and gray-infant syndrome. Gray-infant syndrome was first described and occurs most commonly in infants, but it has been reported in all age groups. The syndrome, which is characterized by cyanosis, circulatory collapse, and death, occurs when the chloramphenicol concentration becomes very high.

### Use

The importance of chloramphenicol in the treatment of infectious diseases has waxed and waned since its introduction in the late 1940s. Because of its side effects, physicians have tended to use alternate antimicrobial agents whenever possible. However, because of its antibacterial and pharmacologic properties, it must be often included to optimize treatment. With the introduction of the third-generation cephalosporins, use of chloramphenicol in the United States has declined sharply. Formerly, chloramphenicol frequently was considered the drug of choice to treat brain abscesses, bacterial meningitis in infants and children older than 2 months, typhoid fever, and salmonellosis. Currently, metronidazole frequently is selected for anaerobic coverage in brain abscesses, ceftriaxone or cefotaxime for bacterial meningitis, and either TMP-SMX or ceftriaxone to treat typhoid fever and salmonellosis. Although chloramphenicol, rather than tetracycline, was considered by many to be the drug of choice for rickettsial infections in children younger than 8 years, experts continue to consider tetracyclines to be the drug of choice for children who have rickettsial disease or ehrlichiosis regardless of their age. Chloramphenicol frequently is active against vancomycin-resistant enterococci and is frequently included in regimens to treat such infections.

When chloramphenicol must be used, the peak serum concentration should be measured after 4 or 5 doses to ensure that the concentration is safe and therapeutic and that the drug is not accumulating in the patient. A complete blood count and differential count should be done twice a week while the patient is receiving chloramphenicol to check for dose-related bone marrow suppression. The peak serum concentration is reached 1 to 2 hours after oral or intravenous administration and averages 25 mcg/mL orally

and 19 mcg/mL intravenously. The serum half-life of chloramphenicol is approximately 4 hours. The MIC<sub>95</sub> of chloramphenicol for bacteria reported as susceptible by disk is 4 mcg/mL or less for *H influenzae* and 12.5 mcg/mL or less for other organisms. Although chloramphenicol is bactericidal for *H influenzae*, *S pneumoniae*, and *N meningitidis*, it is bacteriostatic for most other bacteria. When used with a  $\beta$ -lactam to treat organisms inhibited only by chloramphenicol, antagonism may occur.

## Tetracycline

### Mechanism of Action

Tetracycline binds to the 30S ribosomal subunit and blocks aminoacyl-tRNA binding to the receptor site; this action inhibits protein synthesis.

### Bacterial Resistance

The entry of tetracycline into bacterial cells is energy dependent; resistance is usually based on interference with entry into the cell. In general, tetracycline is not altered by resistant bacteria.

### Pharmacologic Properties

Several analogs of tetracycline have been produced, but the range of antibacterial activity is similar for each. The semisynthetic analogs, minocycline and doxycycline, are the most active tetracyclines but are used less often than other tetracyclines because they are considerably more expensive.

Tetracycline has a broad spectrum of activity that includes inhibition of *Streptococcus* species, *S aureus* including many MRSA, *Neisseria* species, *E coli*, and many common anaerobic bacteria. Tetracyclines are well absorbed from the intestinal tract, and the peak serum concentration is achieved 1 to 3 hours after oral administration. Tetracycline distributes in varying concentrations throughout most of the body, with concentrations in synovial fluid, urine, and the maxillary sinuses approaching the serum concentration, whereas the CSF concentration reaches only 10% to 20% of the serum concentration.

### Side Effects

The side effects of tetracycline essentially preclude its use in children younger than 8 years and in pregnant women. Tetracycline causes a permanent gray-brown to yellowish discoloration of the teeth and can be associated with hypoplasia of the enamel. Skeletal growth can be depressed when the drug is given to premature infants. Although bone and tooth defects are associated with the total dose of tetracycline given and occur more often after repeated courses, avoiding use of the drug during pregnancy and in young children is prudent. Although these side effects generally preclude the use of tetracycline in children younger than 8 years, for rickettsial diseases and ehrlichiosis, some experts continue to consider doxycycline the drug of choice because the usual duration of therapy is only 7 to 10 days, and staining of teeth is related to the total dose received. Doxycycline is less likely to stain teeth than other tetracyclines. In addition, tetracyclines are effective against rickettsial diseases and

ehrlichiosis, but chloramphenicol may not be. Other side effects of tetracycline are allergic reactions and skin toxicity.

### Use

For individuals older than 8 years, tetracycline is considered the drug of choice for brucellosis, chlamydial infections, lymphogranuloma venereum, epididymitis, granuloma inguinale, infections with spirochetes (Lyme disease, relapsing fever, leptospirosis), pelvic inflammatory disease, plague, prostatitis, and rickettsial infections. Tetracycline is also an effective alternate drug for many other infectious diseases.

In adults, the peak serum concentrations after oral administration of 500 mg of tetracycline or 200 mg of doxycycline or minocycline are 4 mcg/mL, 2.5 mcg/mL, and 2.5 mcg/mL, respectively. The peak serum concentration is reached 1 to 3 hours after administration. The serum half-life of tetracycline is 8 hours, compared with 16 hours for minocycline and 18 hours for doxycycline. Intravenous administration of tetracycline results in a peak serum concentration about twice that achieved when the same dose is given by mouth. The MIC<sub>95</sub> of tetracycline for bacteria reported as susceptible by disk is 4 mcg/mL or less.

## Vancomycin

### Mechanism of Action

Vancomycin inhibits cell wall synthesis during the second stage by inhibiting formation of peptidoglycan. This action is in contrast to  $\beta$ -lactams that inhibit cell wall synthesis during the final stage by binding to the PBPs, which are enzymes that are crucial to the formation of the cell wall.

### Bacterial Resistance

Currently, vancomycin demonstrates good activity against most gram-positive cocci. However, vancomycin-resistant enterococci have become more common. In addition, vancomycin failures caused by infections with staphylococcal strains demonstrating in vitro susceptibility and the emergence of strains with reduced susceptibility to vancomycin have been a source of concern.

Until safer, more rapidly bactericidal agents are available for use in children, several principles must be considered to ensure appropriate use of vancomycin with regard to concerns of emerging resistance. First, although monitoring vancomycin levels has been reserved exclusively for selected patients such as those with altered renal function, monitoring levels now may apparently be the best predictor of clinical outcome, as discussed later. In addition, the physician must be aware that current disk diffusion methods may not adequately recognize vancomycin-intermediate *S aureus*, heteroresistant vancomycin-intermediate strains, or even vancomycin-resistant *S aureus*.

### Pharmacologic Properties

Vancomycin is absorbed minimally after oral administration and is given orally only to treat pseudomembranous colitis caused by the toxin of *C difficile*. Most experts prefer to use metronidazole for this indication



because increased use of vancomycin has been associated with a marked increase in resistance of commonly encountered gram-positive organisms. After intravenous administration, vancomycin is distributed throughout the body, except for the aqueous humor of the eye and the CSF when the meninges are not inflamed. A bactericidal concentration can be achieved in the CSF in cases of meningitis caused by susceptible organisms. Sometimes, vancomycin must be administered intraventricularly to adequately treat meningitis with or without ventriculitis. Vancomycin is excreted unchanged in the urine by glomerular filtration. Therefore monitoring the serum concentration and adjusting the dose based on renal function are important in certain circumstances. (See Side Effects.)

### Side Effects

When vancomycin initially became available for clinical use, commercial preparations contained as much as 20% of another substance, and its use was limited because of its toxicity. Currently available preparations are more highly purified and less toxic. The most common side effects are fever, chills, and pain at the injection site or, less often, flushing and tingling of the face, neck, and thorax (red neck syndrome). These side effects can be prevented largely by infusing vancomycin slowly in a large volume of fluid and by pretreating the patient with an antihistamine before the first dose. Reports of ototoxicity and nephrotoxicity caused solely by vancomycin have been difficult to confirm. Furthermore, the relationship of toxicity to serum concentrations remains controversial. In children, ototoxicity and nephrotoxicity are apparently uncommon, and no clear correlation between serum concentrations and toxicity has been proved.

### Use

In recent years, infections caused by MRSA, coagulase-negative staphylococci (eg, *Staphylococcus epidermidis*), and ampicillin-resistant enterococci have become major indications for the use of vancomycin as the drug of choice. Vancomycin is active against most aerobic gram-positive cocci, including most *Streptococcus* species and *L monocytogenes* and, in combination with streptomycin or gentamicin, is synergistic against enterococci. Many anaerobic streptococci also are susceptible to vancomycin, whereas most gram-negative bacteria are resistant. Some methicillin-resistant staphylococci have demonstrated tolerance to vancomycin killing, and rifampin or TMP-SMX must be added to kill bacteria. Vancomycin is the drug of choice to treat serious infections with methicillin-resistant staphylococci or coagulase-negative staphylococci and to treat enterococcal endocarditis in patients allergic to penicillin. Patients who have staphylococcal infections that are methicillin susceptible might be treated with an antistaphylococcal penicillin. Patients who have bacterial endocarditis caused by *S aureus* have been observed to clear their bacteremia slowly when treated with vancomycin compared with using an antistaphylococcal penicillin in patients whose strain was methicillin sensitive. The initial dose of vancomycin should be a full therapeutic dose, even in patients in renal failure.

Children with serious or invasive disease because of MRSA should receive vancomycin at a dose of 15 mg/kg/dose given every 6 hours. Monitoring trough concentrations is probably the most accurate guide for using vancomycin, and monitoring peak levels is not recommended. Monitoring trough concentrations is generally recommended for those patients with severe infections, patients with fluctuating renal status or volume of distribution, and patients who are morbidly obese. Improved outcomes have been seen in some adult patients with serious MRSA infections in whom trough concentrations of 15 to 20 mcg/mL are maintained. Although efficacy and safety of trough levels in the 15- to 20-mcg/mL range has not been established in children, such troughs should be considered in pediatric patients with serious infections such as bacteremia, endocarditis, osteomyelitis, meningitis, pneumonia, and severe skin and skin structure infections.

### Metronidazole

#### Mechanism of Action

After being taken up by bacteria, metronidazole is reduced to intermediate products that are toxic to the bacteria; the organism then releases inactive end products.

#### Bacterial Resistance

Resistance to metronidazole develops infrequently and has been associated with decreased entry of the drug into bacteria and a decreased rate of reduction when in bacterial cells.

#### Pharmacologic Properties

Metronidazole is active against most anaerobic bacteria, *Treponema pallidum*, *H pylori*, *Campylobacter fetus*, *Gardnerella vaginalis*, *Actinobacillus* species, *Actinomycetem comitans*, *Capnocytophaga* species, and *Trichomonas vaginalis*, as well as certain parasites. After oral administration, metronidazole is absorbed rapidly and completely, with the peak serum concentration being proportional to the dose administered. Metronidazole is distributed well throughout the body, including the CNS and the aqueous humor of the eyes. The serum half-life is approximately 8 hours. After being metabolized, metronidazole is excreted primarily in the urine.

#### Side Effects

The most common side effect of metronidazole is GI upset. Metronidazole also has been associated with CNS dysfunction (seizures, encephalopathy, ataxia) and peripheral neuropathy, and it can potentiate the effects of warfarin and cause a disulfiram reaction when alcohol is consumed. A major concern with the use of metronidazole has been its carcinogenic potential. Although rats and mice that have received metronidazole for a long period have shown an increase in neoplasms, mutagenicity for human cells has not been demonstrated in vitro, and follow-up studies on women who received metronidazole for trichomonal infections have shown that they did not have an increased frequency of tumors up to 10 years later.



### Use

Originally introduced to treat *T vaginalis*, metronidazole also has proved to be effective in the treatment of amebiasis and giardiasis. More recently, it has gained widespread use in the treatment of anaerobic bacterial infections; it is not effective in treating actinomycosis or *Propionibacterium acnes* infections. Metronidazole also is not optimally effective in the treatment of anaerobic lower respiratory tract infections, perhaps because of the presence of aerobic bacteria; the outcome generally is good if penicillin or ampicillin is given concomitantly.

The peak serum concentration achieved in adults after 0.5 g of metronidazole is given orally averages 11.5 mcg/mL; after an intravenous dose of 0.5 g, the serum concentration ranges from 20 to 25 mcg/mL. The MIC<sub>95</sub> of metronidazole for susceptible bacteria usually is 4 mcg/mL or less. Most diagnostic microbiology laboratories do not test anaerobic bacteria routinely for susceptibility.

### Rifampin

#### Mechanism of Action

Rifampin works by inhibiting DNA-dependent RNA polymerase at the  $\beta$  subunit, preventing chain initiation but not elongation.

#### Bacterial Resistance

Bacterial resistance to rifampin develops rapidly by mutation of the DNA-dependent RNA polymerase. The rates of mutation are so high that they preclude use of rifampin as monotherapy except for very short courses of prophylaxis.

#### Pharmacologic Properties

Rifampin is usually administered orally and is completely and rapidly absorbed, with the peak serum concentration achieved 1 to 4 hours after ingestion. An intravenous form of rifampin is also available. Rifampin is distributed throughout the body, deacetylated by the liver, and excreted in the bile. The serum half-life is 2 to 5 hours early in therapy, but it declines over time because of increased biliary excretion. Rifampin also can enter phagocytes and kill viable intracellular organisms, which may explain why rifampin is better able to enter and sterilize abscesses than are other antimicrobial agents.

#### Side Effects

When rifampin is given daily, the most common side effects are a mild and self-limited rash, mild GI complaints, and hepatotoxicity, especially when used in combination with isoniazid. When rifampin is used intermittently at high individual doses, an influenza-like syndrome with fever, aches, and chills develops in up to 20% of patients. Because rifampin crosses the placenta and teratogenic effects have been observed in rodents, it should not be used during pregnancy except in severe cases of tuberculosis. Patients or parents should be warned that urine, feces, saliva, and tears may turn a red-orange color while they are taking the drug. The patient should not wear contact lenses while taking rifampin therapy because the lenses can become permanently discolored.

### Use

Rifampin is extremely active against a wide range of organisms. Most strains of *S aureus* and coagulase-negative staphylococci are exquisitely sensitive to rifampin, which is also active against most other gram-positive cocci. *H influenzae*, *N meningitidis*, and *N gonorrhoeae* are exquisitely susceptible to rifampin, but other aerobic gram-negative pathogens are less so. Rifampin also is active against *Legionella* species and *Mycobacterium tuberculosis*.

Despite its widespread use for treating tuberculosis and as prophylaxis for *N meningitidis* and *H influenzae*, no pediatric preparation of rifampin is available. Instructions for preparing a suspension for pediatric use are detailed in the *Physicians' Desk Reference*. Results from a single study of pediatric patients 6 to 58 months of age, who received 10 mg/kg of rifampin suspended in syrup or as dry powder suspended in applesauce, are also provided. Internationally, rifampin is used most commonly to treat tuberculosis and leprosy. Rifampin also is recommended for prophylaxis of close contacts of patients who have meningococcal disease and for household contacts of children who have systemic *H influenzae* type b disease. When rifampin is used for the last 4 days along with a 10-day course of penicillin-amoxicillin for the treatment of group A  $\beta$ -hemolytic streptococcal infections, the microbiologic failure rate falls to almost zero. Rifampin in combination with other antistaphylococcal agents has been used to treat severe staphylococcal infections such as *S aureus* endocarditis, osteomyelitis, and CSF shunt infections caused by coagulase-negative staphylococci.

The peak serum concentration of rifampin after oral administration of 600 mg to an adult or 10 mg/kg to a child averages 7 mcg/mL. Because of the long half-life of rifampin, the peak serum concentration and bioavailability are better if the drug is given once a day. The MIC<sub>95</sub> of bacteria reported as susceptible by disk to rifampin is 1 mcg/mL or less.

## INITIAL THERAPY OF SELECTED ACUTE INFECTIONS

In most clinical situations, the physician must decide which antimicrobial agent or agents to use before the offending organism has been positively identified through culture results, serologic tests, or microscopic examination of material obtained from the infected site. The physician should consider the following points before starting treatment:

- Patient's age and immune status
- Whether concomitant disease is a factor
- Patient's history of exposure to infectious agents
- Current or recent administration of antimicrobial agents
- Findings on physical examination

Appropriate specimens for bacterial and viral cultures and specimens for serologic tests and microscopic examinations should be obtained before antimicrobial therapy is started, and specific adjunctive, supportive therapy should be instituted concomitantly. Table 60-3 lists the most likely offending organisms and the antimicrobial agent or agents that might be

**Table 60-3** Initial Empirical Therapy for Selected Infections<sup>a</sup>

CLINICAL DIAGNOSIS	MOST LIKELY OFFENDING ORGANISMS	ANTIMICROBIAL AGENTS
Meningitis	Neonate: group B streptococci, <i>E coli</i> , <i>L monocytogenes</i> Child: <i>S pneumoniae</i> , <i>N meningitidis</i> , <i>H influenzae</i> type b	Ampicillin and cefotaxime (or ceftriaxone)  Ceftriaxone or cefotaxime (plus vancomycin if <i>S pneumoniae</i> is suggested)
Brain abscess	Streptococcal species, anaerobes, <i>S aureus</i>	Penicillin and metronidazole (plus nafcillin or vancomycin <sup>b</sup> if <i>S aureus</i> is suggested [plus cefotaxime or ceftriaxone if gram-negative bacilli are suggested])
Orbital cellulitis	Streptococcal species, <i>S aureus</i> , <i>H influenzae</i> type b	Ceftriaxone or cefotaxime plus clindamycin or nafcillin. Vancomycin would be suggested if life-threatening MRSA infection is suggested. <sup>a</sup>
Epiglottitis	<i>H influenzae</i> type b	Ceftriaxone or cefotaxime
Pneumonia (lobar or segmental)	Neonate: group B streptococci, <i>S aureus</i> , gram-negative organisms Child: <i>S pneumoniae</i> , <i>H influenzae</i> type b, <i>S aureus</i> , <i>S pyogenes</i> , <i>M pneumoniae</i>	Ampicillin plus an aminoglycoside (plus vancomycin if MRSA is considered) Penicillin, amoxicillin, amoxicillin-clavulanate, nafcillin (vancomycin or clindamycin if MRSA considered), <sup>b</sup> or erythromycin
Infective endocarditis	<i>Streptococcus viridans</i> , <i>S aureus</i>	Nafcillin (vancomycin if MRSA considered), <sup>b</sup> and an aminoglycoside
Acute diarrhea (fecal white blood cells present)	<i>Salmonella</i> , <i>Shigella</i> species	If patient is systemically ill, very young, or immunocompromised, cefotaxime or ceftriaxone
Abdominal sepsis	Anaerobes, aerobic enterics, enterococci	Carbapenem, $\beta$ -lactam- $\beta$ -lactamase inhibitor (Unasyn and Timentin), advanced-generation cephalosporin with metronidazole
Urinary tract infection	Acute: <i>E coli</i> , <i>Klebsiella</i> species  Chronic: <i>E coli</i> , <i>Proteus</i> species, <i>Pseudomonas</i> species	Gentamicin or trimethoprim-sulfamethoxazole (TMP-SMX) Await culture and sensitivity results
Osteomyelitis	Neonate: group B streptococci, <i>S aureus</i> , <i>S pyogenes</i> , <i>S pneumoniae</i> Child: <i>S aureus</i> , <i>S pyogenes</i>	Nafcillin (vancomycin if MRSA considered) <sup>b</sup> and an aminoglycoside Nafcillin (clindamycin or vancomycin if MRSA considered) <sup>b</sup>
Pyogenic arthritis	Neonate: group B streptococci, <i>S aureus</i> , <i>S pyogenes</i> , <i>N gonorrhoeae</i>  Child: <i>H influenzae</i> type b (<5 yr), <i>S aureus</i> , <i>S pyogenes</i> , <i>N gonorrhoeae</i>	Nafcillin (clindamycin or vancomycin if MRSA considered) <sup>b</sup> and an aminoglycoside (or cefotaxime) Ceftriaxone or cefotaxime (test MIC for <i>S aureus</i> ) plus nafcillin <sup>b</sup>
Suspected sepsis	Neonate: group B streptococci, <i>L monocytogenes</i> , gram-negative enteric organisms Infant (1–6 wk): as for neonate plus as for child Child: <i>S pneumoniae</i> , <i>H influenzae</i> type b, <i>N meningitidis</i>	Ampicillin and an aminoglycoside (or cefotaxime) Ampicillin and ceftriaxone  Ceftriaxone
<b>COMPROMISED HOST</b>		
Fever only	<i>S aureus</i> , <i>E coli</i> , <i>Pseudomonas</i> species	Cefipime or antipseudomonal extended-spectrum penicillin
Shock (sepsis without source)	Neonate: group B streptococci, enterics  Child: <i>N meningitidis</i> , <i>S pneumoniae</i>	Ampicillin and an aminoglycoside (substitute vancomycin for ampicillin if <i>S aureus</i> considered) Ceftriaxone or cefotaxime (substitute vancomycin if MRSA is considered)

<sup>a</sup>For most clinical diagnoses, an acceptable alternative choice of antibiotics might be proposed.<sup>b</sup>If local prevalence of methicillin-resistant *Staphylococcus aureus* is high, then vancomycin will be empirical drug of choice.

used empirically for various diagnoses under these circumstances. Local susceptibility patterns and other special circumstances always should be considered.

## PROPHYLAXIS

Antimicrobial agents can be given to prevent colonization, to eradicate carriage, to prevent bacteria that colonize one body site from causing disease at a usually sterile site, or to prevent bacteria that have been introduced into a usually sterile site from causing disease. In general, an antimicrobial agent that has the narrowest spectrum that is effective against the most likely pathogen or pathogens should be used at the lowest dose and for the shortest period that will prevent infection. Prophylaxis also should be restricted to situations in which it is known to be effective and in which the risk for infection exceeds the potential risks of the antimicrobial agent or the emergence of resistant bacteria. Recommendations for preoperative antimicrobial prophylaxis are listed in Table 60-4, and clinical situations in which prophylactic antimicrobial agents might be effective and the recommended regimens for prophylaxis are listed in Table 60-5. The *Red Book: Report of*

*the Committee on Infectious Diseases* (American Academy of Pediatrics) has updated dose recommendations for specific antimicrobials in specific situations.

## ANTIMICROBIAL THERAPY FOR VIRAL, FUNGAL, AND PARASITIC INFECTIONS

Currently, only a limited number of agents and a limited number of indications are available for systemic treatment of viral, fungal, and parasitic infections in the United States; most primary care pediatricians are unlikely to be familiar with the use of these agents. Therefore, the pediatrician should consult a specialist in pediatric infectious diseases before treating a patient with these drugs. The antiviral drugs available currently, along with their indications and dosages, are presented in Table 60-6; antifungal drugs (their route of administration, dosages, and adverse reactions) are listed in Table 60-7. Treatment of parasitic infections is discussed in Chapter 308, Parasitic Infections, in the *AAP Red Book*, in *Nelson's Pediatric Antimicrobial Therapy*, and in the *Medical Letter Handbook of Antimicrobial Therapy*.

**Table 60-4**

**Recommendations for Preoperative Antimicrobial Prophylaxis<sup>a</sup>**

OPERATION	LIKELY PATHOGENS	RECOMMENDED DRUGS	PREOPERATIVE DOSE
<b>Neonatal</b> ( $\leq 72$ h of age)—all major procedures	Group B streptococci, enteric gram-negative bacilli, <sup>b</sup> enterococci, coagulase-negative Staphylococci	Ampicillin <b>PLUS</b> Gentamicin	50 mg/kg  2.5 mg/kg
<b>Neonatal</b> ( $> 72$ h of age)—all major procedures	Prophylaxis targeted to colonizing organisms, nosocomial organisms, and operative site		
<b>Cardiac</b> (cardiac surgical procedures, prosthetic valve or pacemaker, ventricular assist devices)	<i>Staphylococcus epidermidis</i> , <i>Staphylococcus aureus</i> , <i>Corynebacterium</i> species, enteric gram-negative bacilli <sup>b</sup>	Cefazolin <b>OR</b> (if MRSA or MRSE is likely) <sup>a</sup> Vancomycin	30 mg/kg  15 mg/kg
<b>GASTROINTESTINAL</b>			
Esophageal and gastroduodenal	Enteric gram-negative bacilli, <sup>b</sup> gram-positive cocci	Cefazolin (high risk only) <sup>c</sup>	30 mg/kg
Biliary tract	Enteric gram-negative bacilli, <sup>b</sup> enterococci,	Cefazolin <sup>d</sup>	30 mg/kg
Colorectal or appendectomy (uncomplicated, nonperforated)	Enteric gram-negative bacilli, <sup>b</sup> enterococci, anaerobes ( <i>Bacteroides</i> species) <sup>e</sup>	Cefoxitin <b>OR</b> Metronidazole <b>PLUS</b> Gentamicin <b>OR</b> Cefazolin <b>PLUS</b> Metronidazole <b>OR</b> Clindamycin <b>PLUS</b> Gentamicin <b>OR</b> Ciprofloxacin	40 mg/kg  15 mg/kg  2.5 mg/kg  30 mg/kg  15 mg/kg  10 mg/kg  2.5 mg/kg (gentamicin); 10 mg/kg (ciprofloxacin)

*Continued*

**Table 60-4** Recommendations for Preoperative Antimicrobial Prophylaxis<sup>a</sup>—cont'd

OPERATION	LIKELY PATHOGENS	RECOMMENDED DRUGS	PREOPERATIVE DOSE
Ruptured viscus (treatment, not prophylaxis)	Enteric gram-negative bacilli, <sup>b</sup> enterococci anaerobes ( <i>Bacteroides</i> species) <sup>c</sup>	Cefoxitin <b>WITH OR WITHOUT</b> Gentamicin <b>OR</b> Gentamicin <b>PLUS</b> Metronidazole <b>PLUS</b> Ampicillin <b>OR</b> Meropenem <b>OR</b> Other regimens for complicated appendicitis <sup>f</sup>	40 mg/kg 2 mg/kg 2.5 mg/kg 10 mg/kg 50 mg/kg 20 mg/kg
Genitourinary	Enteric gram-negative bacilli, <sup>b</sup> enterococci	Ampicillin <b>PLUS</b> Gentamicin <b>OR</b> Cefazolin	50 mg/kg 2 mg/kg (gentamicin); 30 mg/kg (cefazolin)
<b>Head and neck surgery</b> (incision through oral or pharyngeal mucosa)	Anaerobes, enteric gram-negative bacilli, <sup>b</sup> <i>S aureus</i>	Clindamycin <b>WITH OR WITHOUT</b> Gentamicin <b>OR</b> Cefazolin <b>PLUS</b> Metronidazole Cefazolin	10 mg/kg 2.5 mg/kg 30 mg/kg 15 mg/kg 30 mg/kg
<b>Neurosurgery</b> (craniotomy, intrathecal baclofen shunt or ventricular shunt placement)	<i>S epidermidis</i> , <i>S aureus</i>	<b>OR</b> (if MRSA or MRSE is likely) <sup>a</sup> Vancomycin	15 mg/kg
<b>Ophthalmic</b>	<i>S epidermidis</i> , <i>S aureus</i> , streptococci, enteric gram-negative bacilli <sup>b</sup> <i>Pseudomonas</i> species	Gentamicin, ciprofloxacin, ofloxacin, moxifloxacin, tobramycin <b>OR</b> Neomycin-gramicidin-polymyxin B <b>OR</b> Cefazolin Cefazolin <b>OR</b> (if MRSA or MRSE is likely) <sup>a</sup> Vancomycin	Multiple drops topically for 2–24 h before procedure Multiple drops topically for 2–24 h before procedure 100 mg, subconjunctivally 30 mg/kg 15 mg/kg
<b>Orthopedic</b> (internal fixation of fractures, implantation of materials including prosthetic joint and spinal procedures with and without instrumentation)	<i>S epidermidis</i> , <i>S aureus</i>	Cefazolin Cefazolin <b>OR</b> (if MRSA or MRSE is likely) <sup>a</sup> Vancomycin	30 mg/kg 30 mg/kg 15 mg/kg
<b>Thoracic</b> (noncardiac)	<i>S epidermidis</i> , <i>S aureus</i> , streptococci, gram-negative enteric bacilli <sup>b</sup>	Cefazolin <b>OR</b> (if MRSA or MRSE is likely) <sup>a</sup> Vancomycin	30 mg/kg 15 mg/kg
Traumatic wound (nonbites)	<i>S aureus</i> , group A streptococci, <i>Clostridium</i> species	Cefazolin	30 mg/kg

MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *S epidermidis*.

<sup>a</sup>From American Academy of Pediatrics. Antimicrobial prophylaxis in pediatric surgical patients. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015: 961–969.

<sup>b</sup>Selection of antibiotics should take into consideration the institution-specific and patient-specific colonization/infection isolate susceptibility patterns.

<sup>c</sup>Esophageal obstruction, decreased gastric acidity or gastrointestinal motility; see text for additional high risk factors.

<sup>d</sup>Acute cholecystitis, nonfunctioning gallbladder, obstructive jaundice, common duct stones.

<sup>e</sup>High rates of resistance to clindamycin (approx 30%) now reported for *Bacteroides fragilis*. Lowest rates of resistance to carbapenems, ampicillin/sulbactam, and piperacillin/tazobactam. Resistance to cefoxitin reported at 3.5% to 9.4% (Snydman DR, Jacobus NV, McDermott LA, et al. Update on resistance of *Bacteroides fragilis* group and related species with special attention to carbapenems 2006-2009. *Anaerobe*. 2011;17[4]:147–151).

<sup>f</sup>Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America (erratum in *Clin Infect Dis*. 2010;50(12):1695; dosage error in article text). *Clin Infect Dis*. 2010;50(2):133–164.



**Table 60-5** Regimens for Antimicrobial Prophylaxis for a Dental Procedure

SITUATION	AGENT	REGIMEN: SINGLE DOSE 30 TO 60 MIN BEFORE PROCEDURE	
		CHILDREN	ADULTS
Oral	Amoxicillin	50 mg/kg	2 g
Unable to take oral medication	Ampicillin	50 mg/kg, IM or IV	2 g, IM or IV
	<b>OR</b>		
	Cefazolin or ceftriaxone	30 mg/kg, IM or IV (cefazolin); 50 mg/kg, IM or IV (ceftriaxone)	1 g, IM or IV
Allergic to penicillins or oral ampicillin	Cephalexin <sup>a,b</sup>	50 mg/kg	2 g
	<b>OR</b>		
	Clindamycin	10 mg/kg	900 mg
	<b>OR</b>		
	Azithromycin or clarithromycin	15 mg/kg	500 mg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone <sup>b</sup>	30 mg/kg, IM or IV (cefazolin); 50 mg/kg, IM or IV (ceftriaxone)	1 g, IM or IV
	<b>OR</b>		
	Clindamycin	10 mg/kg, IM or IV	900 mg, IM or IV

IM, intramuscular; IV, intravenous.

From American Academy of Pediatrics. Prevention of bacterial endocarditis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015: 970–971.

<sup>a</sup>Or other first- or second-generation oral cephalosporin in equivalent pediatric or adult dosage.

<sup>b</sup>Cephalosporins should not be used in a person with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.

**Table 60-6** Non-HIV Antiviral Drugs<sup>a</sup>

GENERIC (TRADE NAME)	INDICATION	ROUTE	AGE	USUALLY RECOMMENDED DOSAGE
Acyclovir <sup>b,c,d,e</sup> (Zovirax)	Neonatal herpes simplex virus (HSV) infection	IV	Birth to 3 mo	Treatment dosing: 60 mg/kg per day, in 3 divided doses for 14–21 days
		PO	2 wk to 8 mo	Suppressive dosing following completion of treatment dosing: 300 mg/m <sup>2</sup> , 3 times per day for 6 months
	HSV encephalitis	IV	≥3 mo to 12 y	30–45 mg/kg per day, in 3 divided doses for 14–21 days; FDA-approved dose for this indication and age range is 60 mg/kg per day, in 3 divided doses, but nephrotoxicity may be increased at this higher dose <sup>f</sup>
		IV	≥12 y	30 mg/kg per day, in 3 divided doses for 14–21 days
	Varicella in immunocompetent host <sup>g</sup>	Oral	≥2 y	≤40 kg: 80 mg/kg per day, in 4 divided doses for 5 days; maximum daily dose, 3,200 mg/day >40 kg: 3,200 mg, in 4 divided doses for 5 days
		IV	≥2 y	30 mg/kg per day for 7–10 days or 1,500 mg/m <sup>2</sup> per day in 3 doses for 7–10 days
	Varicella in immunocompetent host requiring hospitalization	IV	≥2 y	30 mg/kg per day for 7–10 days or 1,500 mg/m <sup>2</sup> per day in 3 doses for 7–10 days
	Varicella in immunocompromised host	IV	<1 y	30 mg/kg per day, in 3 divided doses for 7–10 days
		IV	≥1 y	1,500 mg/m <sup>2</sup> per day, in 3 doses for 7–10 days; some experts recommend the 30 mg/kg per day dose

Continued

**Table 60-6** Non-HIV Antiviral Drugs<sup>a</sup>—cont'd

GENERIC (TRADE NAME)	INDICATION	ROUTE	AGE	USUALLY RECOMMENDED DOSAGE
	Zoster in immunocompetent host	IV (if requiring hospitalization) Oral	All ages ≥12 y	Same as for varicella in immunocompromised host 4,000 mg/day, in 5 divided doses for 5–7 days
	Zoster in immunocompromised host	IV IV	<12 y ≥12 y	30 mg/kg per day, in 3 divided doses, for 7–10 days 30 mg/kg per day, in 3 divided doses, for 7–10 days
	HSV infection in immunocompromised host (localized, progressive, or disseminated)	IV Oral	All ages ≥2 y	30 mg/kg per day, in 3 divided doses for 7–14 days 1,000 mg/day, in 3–5 divided doses for 7–14 days
	Prophylaxis of HSV in immunocompromised hosts who are HSV seropositive	Oral IV	≥2 y All ages	600–1,000 mg/day, in 3–5 divided doses during period of risk 15 mg/kg, in 3 divided doses during period of risk
	Genital HSV infection: first episode	Oral  IV	≥12 y  ≥12 y	1,000–1,200 mg/day, in 3–5 divided doses for 7–10 days. Oral pediatric dose: 40–80 mg/kg per day, divided in 3–4 doses for 5–10 days (maximum 1.0 g/day) 15 mg/kg per day, in 3 divided doses for 5–7 days
	Genital HSV infection: recurrence	Oral	≥12 y	1,000 mg in 5 divided doses for 5 days, or 1,600 mg in 2 divided doses for 5 days, or 2400 mg in 3 divided doses for 2 days
	Chronic suppressive therapy for recurrent genital and cutaneous (ocular) HSV episodes	Oral	≥12 y	800 mg/day, in 2 divided doses for as long as 12 continuous mo
Adefovir (Hepsera)	Chronic hepatitis B	Oral	≥12 y	10 mg, once daily, in patients with adequate renal function; optimal duration of therapy unknown
Amantadine (Symmetrel) <sup>h</sup>	Influenza A: treatment and prophylaxis (see Influenza, p 476) <sup>h</sup>	Oral  Oral	1–9 y  ≥10 y	Treatment or prophylaxis: 5 mg/kg per day, maximum 150 mg/day, in 2 divided doses Treatment or prophylaxis: <40 kg: 5 mg/kg per day, in 2 divided doses; ≥40 kg: 200 mg/day, in 2 divided doses
Boceprevir (Victrelis)	Chronic hepatitis C	Oral	Dose by weight, not age Adult dose (≥18 years) <sup>i</sup>	Alternative prophylactic dose for children >20 kg and adults: 100 mg/day 800 mg, 3 times per day for 24–44 wk in combination with pegylated interferon alfa and ribavirin for 28–48 wk of total treatment, depending on prior HCV treatment status and HCV viral load during therapy Initiate therapy with pegylated interferon and ribavirin for 4 wk prior to initiating boceprevir
Cidofovir (Vistide)	Cytomegalovirus (CMV) retinitis	IV	Adult dose <sup>i</sup>	Induction: 5 mg/kg, once weekly, × 2 doses with probenecid and hydration Maintenance: 5 mg/kg, once every 2 wk, with probenecid and hydration

**Table 60-6** Non-HIV Antiviral Drugs<sup>a</sup>—cont'd

GENERIC (TRADE NAME)	INDICATION	ROUTE	AGE	USUALLY RECOMMENDED DOSAGE
Entecavir (Baraclude)	Chronic hepatitis B	Oral	≥16 y <sup>i</sup>	0.5 mg, once daily, in patients who have not received prior nucleoside therapy; 1 mg once daily in patients who are previously treated (not first choice in this setting); optimum duration of therapy unknown
Famciclovir (Famvir)	Genital HSV infection, episodic recurrent episodes	Oral	Adult dose <sup>i</sup>	Immunocompetent: 2,000 mg/day, in 2 divided doses for 1 day HIV-infected patients: 1,000 mg, in 2 divided doses for 7 days
	Daily suppressive therapy	Oral	Adult dose <sup>i</sup>	Immunocompetent: 500 mg/day, in 2 divided doses for 1 y, then reassess for recurrence of HSV infection
	Recurrent herpes labialis	Oral	Adult dose <sup>i</sup>	Immunocompetent: 1,500 mg as a single dose HIV-infected patients: 1,000 mg/day, in 2 divided doses for 7 days
	Herpes zoster	Oral	Adult dose <sup>i</sup>	1,500 mg/day, in 3 divided doses for 7 days
Foscarnet <sup>b</sup> (Foscavir)	CMV retinitis in patients with acquired immunodeficiency syndrome	IV	Adult dose <sup>i</sup>	180 mg/kg per day, in 2–3 divided doses for 14–21 days, then 90–120 mg/kg once a day as maintenance dose
	HSV infection resistant to acyclovir in immunocompromised host	IV	Adult dose <sup>i</sup>	80–120 mg/kg per day, in 2–3 divided doses until infection resolves
	VZV infection resistant to acyclovir	IV	Adult dose <sup>i</sup>	120 mg/kg per day, divided every 8 h, up to 3 wk
Ganciclovir <sup>b</sup> (Cytovene)	Symptomatic congenital CMV disease	IV	Birth to 2 mo	12 mg/kg per day, divided every 12 h; duration of treatment is 6 months, but most or all of the treatment should be accomplished with oral valganciclovir (see below)
	Acquired CMV retinitis in immunocompromised host <sup>i</sup>	IV	Adult dose <sup>i</sup>	Treatment: 10 mg/kg per day, in 2 divided doses for 14–21 days; Long-term suppression: 5 mg/kg per day for 7 days/wk or 6 mg/kg per day for 5 days/wk
	Prophylaxis of CMV in high-risk host	IV	Adult dose <sup>i</sup>	10 mg/kg per day, in 2 divided doses for 1–2 wk, then 5 mg/kg per day, in 1 dose for 100 days or 6 mg/kg per day for 5 days/wk
Interferon alfa-2b (Intron A)	Chronic hepatitis B	SC	1–18 y >18 y	6 million IU/m <sup>2</sup> , 3 times/wk for 16–24 wk 5 million IU/day; or 10 million IU, 3 times/wk, for 16 wk
	Chronic hepatitis C	SC; IM	>18 y <sup>i</sup>	3 million IU, 3 times/wk, for 24–48 wk, depending on HCV genotype Note: pegylated interferon preferred over interferon alfa-2b
Lamivudine (Epivir-HBV)	Treatment of chronic hepatitis B	Oral	≥2 y	3 mg/kg once day (maximum 100 mg/day) (children coinfecting with HIV and hepatitis B should use the approved dose for HIV)
Oseltamivir <sup>k</sup> (Tamiflu)	Influenza A and B: treatment (see Influenza, p 476)	Oral	Birth to <9 mo <sup>l</sup>	3 mg/kg, twice daily for 5 days <sup>l</sup>
		Oral	9–12 mo	3.5 mg/kg, twice daily for 5 days

Continued

**Table 60-6** Non-HIV Antiviral Drugs<sup>a</sup>—cont'd

GENERIC (TRADE NAME)	INDICATION	ROUTE	AGE	USUALLY RECOMMENDED DOSAGE
		Oral	1–12 y	≤15 kg: 30 mg, twice daily; 15.1–23 kg: 45 mg, twice daily; 23.1–40 kg: 60 mg, twice daily; >40 kg: 75 mg, twice daily for 5 days
	Influenza A and B: prophylaxis	Oral	≥13 y	75 mg, twice daily for 5 days
		Oral	1–12 y	Same as treatment for patients 1–12 y of age, except dose given once daily for 10 days (following known exposure) or for up to 6 wk (preexposure during community outbreak)
		Oral	≥13 y	75 mg once daily for 10 days (following known exposure) or for up to 6 wk (preexposure during community outbreak)
Pegylated interferon alfa-2a (Pegasys)	Chronic hepatitis B	SC	>18 y <sup>i</sup>	180 µg, once weekly for 48 wk
	Chronic hepatitis C	SC	≥23 kg	180 µg/1.73 m <sup>2</sup> , once weekly for 24–48 wk, depending on HCV genotype, given concomitantly with oral ribavirin <sup>m</sup>
	Chronic hepatitis C	SC	>18 y <sup>i</sup>	180 µg, once weekly for 24–48 wk, depending on HCV genotype
Pegylated interferon-alfa-2b (PegIntron)	Chronic hepatitis C	SC	>18 y >3 to 17 y	1.5 µg/kg, once weekly for 24–48 wk, depending on HCV genotype
				60 µg/m <sup>2</sup> , once weekly for 24–48 wk, depending on HCV genotype
Ribavirin (Rebetol or Copegus)	Treatment of hepatitis C in combination with an alfa interferon	Oral/capsule	≥3 y (Note: capsule doses recommended for use with pegylated interferon alfa-2a and alfa-2b are different)	Fixed dose by weight is suggested for 24–48 wk, depending on HCV genotype 23–33 kg: 200 mg am and pm >34–46 kg: 200 mg am and 400 mg pm >47–59 kg: 400 mg am and pm >60–74 kg: 400 mg am and 600 mg pm >75 kg: 600 mg am and pm
		Oral/solution (Rebetol)	≥3 y	15 mg/kg per day, in 2 divided doses for 24–48 wk, depending on HCV genotype
Rimantadine (Flumadine) <sup>h</sup>	Influenza A: treatment <sup>i</sup>	Oral	≥13 y	200 mg/day, in 2 divided doses
	Influenza A: prophylaxis (see Influenza, p 476) <sup>h</sup>	Oral	≥1 y	1–9 y of age: 5 mg/kg per day, maximum 150 mg/day, once daily ≥10 y of age, <40 kg: 5 mg/kg per day, in 2 divided doses; ≥40 kg: 200 mg/day in 2 divided doses
Simeprevir	Chronic hepatitis C	Oral	Adult dose <sup>i</sup>	150 mg, taken once daily with food, as a component of combination therapy with both pegylated interferon alfa and ribavirin
Sofosbuvir	Chronic hepatitis C	Oral	Adult dose <sup>i</sup>	400 mg, taken once daily with or without food, as a component of combination therapy with ribavirin or with ribavirin plus pegylated interferon
Telaprevir	Chronic hepatitis C	Oral	Adult dose <sup>i</sup>	750 mg, 3 times per day for 12 wk in combination with pegylated interferon alfa and ribavirin for 24–48 wk of total treatment, depending on prior HCV treatment status and HCV viral load during therapy
Telbivudine (Tyzeka)	Chronic hepatitis B	Oral	Adult dose <sup>i</sup>	600 mg, once daily



**Table 60-6** Non-HIV Antiviral Drugs<sup>a</sup>—cont'd

GENERIC (TRADE NAME)	INDICATION	ROUTE	AGE	USUALLY RECOMMENDED DOSAGE
Tenofovir (Viread)	Chronic hepatitis B	Oral	>12 y dose	300 mg, once daily
Valacyclovir (Valtrex)	Varicella	Oral	2 to <18 y	20 mg/kg, 3 times daily for 5 days, not to exceed 1 g per dose 3 times daily
	Genital HSV infection, first episode	Oral	Adult dose <sup>i</sup>	2 g/day, in 2 divided doses for 10 days
	Episodic recurrent genital HSV infection	Oral	Adult dose <sup>i</sup>	1 g/day, in 2 divided doses for 3 days
	Daily suppressive therapy for recurrent genital HSV infection	Oral	Adult dose <sup>i</sup>	1,000 mg, once daily for 1 year, then reassess for recurrences
	Recurrent herpes labialis	Oral	>12 y	4 g/day, in 2 divided doses for 1 day
	Herpes zoster	Oral	Adult dose <sup>i</sup>	3 g/day, in 3 divided doses for 7 days
Valganciclovir (Valcyte)	Symptomatic congenital CMV disease	Oral	Birth to 2 mo	32 mg/kg per day, in 2 divided doses for 6 mo
	Acquired CMV retinitis in immunocompromised host	Oral	Adult dose <sup>i</sup>	Treatment: 900 mg, twice daily for 3 wk Long-term suppression: 900 mg, once daily
	Prevention of CMV disease in kidney or heart transplant patients	Oral	4 mo–16 y	Dose once a day within 10 days of transplantation until 100 days post-transplantation according to dosage algorithm based on body surface area and creatinine clearance Dose (mg) = 7 × body surface area × creatinine clearance (see drug package insert)
Zanamivir (Relenza)	Influenza A and B: treatment (see Influenza, p 476)	Inhalation	≥7 y (treatment)	10 mg, twice daily for 5 days
	Influenza A and B: prophylaxis	Inhalation	≥5 y (prophylaxis)	10 mg, once daily for as long as 28 days (community outbreaks) or 10 days (household setting)

FDA, US Food and Drug Administration; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IM, intramuscular; IV, intravenous; SC, subcutaneous; VZV, varicella-zoster virus.

From American Academy of Pediatrics. Non-HIV antiviral drugs. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015: 919–926.

<sup>a</sup>Drugs for human immunodeficiency virus infection are not included. See [aidsinfo.nih.gov](http://aidsinfo.nih.gov) for current information on HIV drugs and treatment recommendations.

<sup>b</sup>Dose should be decreased in patients with impaired renal function.

<sup>c</sup>Oral dosage of acyclovir in children should not exceed 80 mg/kg per day (3,200 mg/day).

<sup>d</sup>Acyclovir doses listed in this table are based on clinical trials and clinical experience and may not be identical to doses approved by the FDA.

<sup>e</sup>In times of shortage of intravenous acyclovir, the American Academy of Pediatrics Committee on Infectious Diseases recommends that existing supplies of intravenous acyclovir be conserved to improve availability for neonatal HSV infections, herpes simplex encephalitis, or HSV and varicella-zoster virus infections in immunocompromised patients, including more ill pregnant women with visceral dissemination of either virus. If acyclovir is not available, intravenous ganciclovir should be substituted. Alternative regimens to the use of intravenous acyclovir and other options for priority and nonpriority conditions are outlined in an exclusive *Red Book Online Intravenous Acyclovir Shortage Table* ([redbook.solutions.aap.org/selfserve/ssPage.aspx?SelfServeContentId=acyclovir-shortage](http://redbook.solutions.aap.org/selfserve/ssPage.aspx?SelfServeContentId=acyclovir-shortage)).

<sup>f</sup>Monitor for nephrotoxicity and neurologic irritation. Consider involving an infectious diseases or pharmacology specialist if weight-based dosing exceeds 800 mg per dose or if being administered with other nephrotoxic medications.

<sup>g</sup>Selective indications; see Varicella-Zoster Infections in AAP *Red Book*.

<sup>h</sup>Since 2005–2006, almost all influenza A (H3N2) strains and 2009 pandemic H1N1 strains tested have been resistant to adamantanes, and adamantane use therefore has not been recommended. See Influenza in AAP *Red Book* for specific recommendations.

<sup>i</sup>There are not sufficient clinical data to identify the appropriate dose for use in children.

<sup>j</sup>Some experts use ganciclovir in immunocompromised hosts with CMV gastrointestinal tract disease and CMV pneumonitis (with or without CMV Immune Globulin Intravenous).

<sup>k</sup>See [www.cdc.gov/flu/professionals/antivirals/index.htm](http://www.cdc.gov/flu/professionals/antivirals/index.htm) for specific recommendations, which may vary on the basis of most recent influenza virus susceptibility patterns.

<sup>l</sup>Preterm, <38 weeks' postmenstrual age, 1.0 mg/kg/dose, orally, twice daily; preterm, 38 through 40 weeks' postmenstrual age, 1.5 mg/kg/dose, orally, twice daily; preterm >40 weeks' postmenstrual age through 8 months' chronologic age, 3.0 mg/kg/dose, orally, twice daily.

<sup>m</sup>See approved product label for PEGASYS (pegylated interferon alfa-2a).

For more information on individual drugs, see *Physician's Desk Reference* or [www.pdr.net](http://www.pdr.net) (for registered users only).

**Table 60-7** Recommended Doses of Parenteral and Oral Antifungal Drugs

DRUG	ROUTE	DOSE (PER DAY)	ADVERSE REACTIONS <sup>a,b</sup>
Amphotericin B deoxycholate (see Antifungal Drugs for Systemic Fungal Infections, p 905, for detailed information)	IV	1.0–1.5 mg/kg per day; infuse as a single dose over 2 h	Fever, chills, gastrointestinal tract symptoms, headache, hypotension, renal dysfunction, hypokalemia, anemia, cardiac arrhythmias, neurotoxicity, anaphylaxis
	IT	0.025 mg, increase to 0.5 mg, twice/wk	Headache, gastrointestinal tract symptoms, arachnoiditis/radiculitis
	IV	5 mg/kg per day, infused over 2 h	Fever, chills, other reactions associated with amphotericin B deoxycholate, but less nephrotoxicity; hepatotoxicity has been reported with lipid complex
Amphotericin B lipid complex (Abelcet) <sup>c,d</sup>	IV	5 mg/kg per day, infused over 2 h	Fever, headache, nausea, vomiting, diarrhea, leukopenia, hepatic enzyme elevations, and phlebitis
Anidulafungin <sup>c,d</sup>	IV	Adults: 100–200 mg loading dose, then 50–100 mg once daily (higher dose for candidemia) Children: load with 1.5 to 3 mg/kg once, then 0.75–1.5 mg/kg per day	Fever, chills, other reactions associated with amphotericin B, but less nephrotoxicity; hepatotoxicity has been reported
Liposomal amphotericin B (AmBisome) <sup>c,d</sup>	IV	3–5 mg/kg, infused over 1–2 h	Fever, rash, pruritus, phlebitis, headache, gastrointestinal tract symptoms, anemia; concomitant use with cyclosporine is not recommended unless potential benefits outweigh potential risks
Caspofungin <sup>c,d</sup>	IV	Adults: 70 mg loading dose, then 50 mg once daily Children: 70 mg/m <sup>2</sup> loading dose, then 50 mg/m <sup>2</sup> once daily	Gastrointestinal tract symptoms, hepatotoxicity
Clotrimazole	PO	10-mg tablet, 5 times per day (dissolved slowly in mouth)	Rash, gastrointestinal tract symptoms, hepatotoxicity, Stevens-Johnson syndrome, anaphylaxis
Fluconazole <sup>b,d</sup>	IV	Children: 3–6 mg/kg per day, single dose (up to 12 mg/kg per day for serious infections)	
	PO	Children: 6 mg/kg once, then 3 mg/kg per day for oropharyngeal or esophageal candidiasis; 6–12 mg/kg per day for invasive fungal infections; 6 mg/kg per day for suppressive therapy in HIV-infected children with cryptococcal meningitis Adults: 200 mg once, followed by 100 mg/day for oropharyngeal or esophageal candidiasis; 400–800 mg/day for other invasive fungal infections; 400 mg/day for suppressive therapy in HIV-infected patients with cryptococcal meningitis	
Flucytosine	PO	50–150 mg/kg per day in 4 doses at 6-h intervals (adjust dose if renal dysfunction); follow trough levels closely	Bone marrow suppression, renal dysfunction, gastrointestinal tract symptoms, rash, neuropathy, hepatotoxicity, confusion, hallucinations
Griseofulvin	PO	Ultramicrosize: 5–15 mg/kg, single dose; maximum dose, 750 mg Microsize: 10–20 mg/kg per day divided in 2 doses; maximum dose, 1000 mg	Rash, paresthesias, leukopenia, gastrointestinal tract symptoms, proteinuria, hepatotoxicity, mental confusion, headache
Itraconazole <sup>b,d</sup>	IV, PO	Children: 5–10 mg/kg per day divided into 2 doses; confirm therapeutic trough level after 2 wk of therapy to ensure adequate drug exposure ( $\geq 1$ $\mu$ g/mL but $< 10$ $\mu$ g/mL) Adults: 200–400 mg/day once or twice a day; 200 mg, once a day, for suppressive therapy in HIV-infected patients with histoplasmosis	Gastrointestinal tract symptoms, rash, edema, headache, hypokalemia, hepatotoxicity, thrombocytopenia, leukopenia; cardiac toxicity is possible in patients also taking terfenadine or astemizole

**Table 60-7** Recommended Doses of Parenteral and Oral Antifungal Drugs—cont'd

DRUG	ROUTE	DOSE (PER DAY)	ADVERSE REACTIONS <sup>a,b</sup>
Ketoconazole <sup>b,d</sup>	PO	Children <sup>e</sup> : 3.3–6.6 mg/kg per day, single dose Adults: 200 mg, twice a day for 4 doses, then 200 mg, once a day	Hepatotoxicity, gastrointestinal tract symptoms, rash, anaphylaxis, thrombocytopenia, hemolytic anemia, gynecostasia, adrenal insufficiency; cardiac toxicity is possible in patients also taking terfenadine or astemizole
Micafungin <sup>c,d</sup>	IV	Adults: 50–150 mg once daily Children: 2–10 mg/kg per day once daily (higher dose needed for patients <8 y of age), maximum 200 mg per day	Fever, headache, nausea, vomiting, diarrhea, leukopenia, hepatic enzyme elevations, and phlebitis
Nystatin	PO	Infants: 200,000 U, 4 times a day, after meals Children and adults: 400,000–600,000 U, 3 times a day, after meals	Gastrointestinal tract symptoms, rash
Posaconazole <sup>c,d</sup>	PO	Adults: 400 mg, 2 times a day with fatty meals (or liquid nutritional supplement) for treatment; 200 mg, 3 times a day for prophylaxis Children: not known	Gastrointestinal tract symptoms, rash, edema, headache, anemia, neutropenia, thrombocytopenia, fatigue, arthralgia, myalgia, fever
Terbinafine <sup>c</sup>	PO	Adults: 250 mg, once a day Children: <20 kg: 67.5 mg/day; 20–40 kg: 125 mg/day; >40 kg: 250 mg/day	Gastrointestinal tract symptoms, rash, taste abnormalities, cholestatic hepatitis
Voriconazole <sup>d</sup>	IV	Children 2–12 y: 9 mg/kg, IV, every 12 h for 1 day, then 8 mg/kg, IV, every 12 h (maximum dose, 350 mg, every 12 h); follow trough levels closely (>2 µg/mL) Adults and children ≥12 y: 6 mg/kg, every 12 h for 1 day (loading dose), then 4 mg/kg, every 12 h; follow trough levels closely (>1 µg/mL)	Visual disturbance, hallucinations, photosensitive rash, increased liver function tests, encephalopathy; recent reports of aggressive cutaneous malignancy associated with prolonged voriconazole use
	PO	Children 2–12 y: 9 mg/kg, every 12 h; follow trough levels closely (much lower bioavailability in children than adults) Adults: <40 kg: 200 mg, every 12 h for 1 day, then 100 mg, every 12 h; >40 kg: 400 mg, every 12 h for 1 day, then 200–300 mg, every 12 h	

HIV, human immunodeficiency virus; IT, intrathecal; IV, intravenous; PO, oral.

From American Academy of Pediatrics. Recommended doses of parenteral and oral antifungal drugs. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015: 909–912.

<sup>a</sup>See package insert or listing in current edition of the *Physicians' Desk Reference* or [www.pdr.net](http://www.pdr.net) (for registered users only).

<sup>b</sup>Interactions with other drugs are common. Consult [www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/default.htm?utm\\_campaign=Google2&utm\\_source=fdaSearch&utm\\_medium=website&utm\\_term=drug%20interactions&utm\\_content=1](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/default.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=drug%20interactions&utm_content=1) and the *Physicians' Desk Reference* (a drug interaction reference or database) or a pharmacist before prescribing these medications.

<sup>c</sup>Experience with drug in children is limited; 3 mg/kg doses generally used.

<sup>d</sup>Limited or no information about use in newborn infants is available. Voriconazole has now been identified as an independent risk factor for development of cutaneous malignancies in lung transplant patients.

<sup>e</sup>For children 2 years and younger, the daily dose has not been established.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *Child Care Letter* (template letter), Centers for Disease Control and Prevention ([www.cdc.gov/getsmart/community/materials-references/print-materials/parents-young-children/childcare-letter.html](http://www.cdc.gov/getsmart/community/materials-references/print-materials/parents-young-children/childcare-letter.html))
- *Get Smart Brochures* (handouts), Centers for Disease Control and Prevention ([www.cdc.gov/getsmart/community/materials-references/print-materials/index.html](http://www.cdc.gov/getsmart/community/materials-references/print-materials/index.html))

- *Get Smart Posters* (posters), Centers for Disease Control and Prevention ([www.cdc.gov/getsmart/community/materials-references/print-materials/index.html](http://www.cdc.gov/getsmart/community/materials-references/print-materials/index.html))
- *Get Smart: Know When Antibiotics Work: Virus Bacteria Chart* (chart), Centers for Disease Control and Prevention ([www.cdc.gov/getsmart/community/index.html](http://www.cdc.gov/getsmart/community/index.html))

### Engaging Patient and Family

- *Antibiotics and Your Child* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

- *Antibiotics for a Sore Throat, Cough or Runny Nose?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/safety-prevention/at-home/medication-safety/Pages/Antibiotics-for-a-Sore-Throat-Cough-or-Runny-Nose.aspx](http://www.healthychildren.org/English/safety-prevention/at-home/medication-safety/Pages/Antibiotics-for-a-Sore-Throat-Cough-or-Runny-Nose.aspx))
- *Antibiotic Prescriptions for Children: 10 Common Questions Answered* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/safety-prevention/at-home/medication-safety/Pages/Antibiotic-Prescriptions-for-Children.aspx](http://www.healthychildren.org/English/safety-prevention/at-home/medication-safety/Pages/Antibiotic-Prescriptions-for-Children.aspx))
- *Get Smart: Know When Antibiotics Work* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/getsmart/community/index.html](http://www.cdc.gov/getsmart/community/index.html))
- *Get Smart: Know When Antibiotics Work* (Spanish) (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/getsmart/specific-groups/antibioticos.html](http://www.cdc.gov/getsmart/specific-groups/antibioticos.html))

### Medical Decision Support

- *About Antimicrobial Resistance* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/drugresistance/about.html](http://www.cdc.gov/drugresistance/about.html))
- *Appropriate Treatment Summary: Physician Information Sheet* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/getsmart/campaign-materials/info-sheets/child-approp-treatmt.html](http://www.cdc.gov/getsmart/campaign-materials/info-sheets/child-approp-treatmt.html))
- *Careful Antibiotic Use* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/getsmart/campaign-materials/info-sheets/child-approp-treatmt.pdf](http://www.cdc.gov/getsmart/campaign-materials/info-sheets/child-approp-treatmt.pdf))
- *The Common Cold: Rhinitis Vs. Sinusitis: Physician Information Sheet* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/getsmart/campaign-materials/info-sheets/child-rhin-vs-sinus.html](http://www.cdc.gov/getsmart/campaign-materials/info-sheets/child-rhin-vs-sinus.html))
- *Otitis Media: Physician Information Sheet (Pediatrics)* (algorithm), Centers for Disease Control and Prevention ([www.cdc.gov/getsmart/community/materials-references/print-materials/hcp/child-otitismedia.html](http://www.cdc.gov/getsmart/community/materials-references/print-materials/hcp/child-otitismedia.html))
- *Pediatric Treatment Guidelines: Upper Respiratory Tract Infections* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/getsmart/campaign-materials/pediatric-treatment.html](http://www.cdc.gov/getsmart/campaign-materials/pediatric-treatment.html))
- *Pharyngitis: Treat Only Proven GAS: Physician Information Sheet* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/getsmart/campaign-materials/info-sheets/child-pharyngitis.html](http://www.cdc.gov/getsmart/campaign-materials/info-sheets/child-pharyngitis.html))
- *Protecting Patients and Stopping Outbreaks* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/drugresistance/protecting\\_patients.html](http://www.cdc.gov/drugresistance/protecting_patients.html))

### SUGGESTED READINGS

- American Academy of Pediatrics. Antimicrobial resistance and antimicrobial stewardship: appropriate and judicious use of antimicrobial agents. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:874-879
- Bradley JS, Barnett ED, Cantey JB, et al, eds. *2016 Nelson's Pediatric Antimicrobial Therapy*. 22nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2016

## Chapter 61

# PSYCHOSOCIAL THERAPIES

W. Douglas Tynan, PhD; Meghan McAuliffe Lines, PhD

This chapter first provides an overview of the evidence-based nonpharmacologic treatments available for the common mental health disorders of childhood. In the parlance of the mental health community, they may be called *psychotherapy* or simply *therapy*. Here they will be called *psychosocial treatments*. These treatments may be delivered by a variety of mental health professionals (eg, licensed clinical psychologists, social workers, professional counselors, marriage and family therapists, child psychiatrists) trained in the specific techniques of that therapy. Interactive Web-based programs show promise as additional or alternative sources of these therapies.

Second, the chapter draws from these evidence-based psychosocial treatments those common elements that are effective across a number of disorders and potentially applicable to the treatment of children with emerging or undifferentiated symptoms, as they might present in the primary care setting. Practical resources are offered to support physicians in applying these common elements to the care of these children, to children referred for and awaiting care in the mental health specialty system, and to children for whom the appropriate mental health specialty resources are inaccessible.

## HISTORY

The origin of modern psychotherapy with children is usually attributed to the pioneering work of Sigmund Freud at the turn of the 20th century. Freud's ideas about the importance of early childhood experiences and his publication of case studies with both adults and children framed the field, and his influence is still evident. Although these psychoanalytic and psychodynamic concepts date back more than 100 years, behavioral therapy concepts arose soon after, early in the 20th century, in the work on conditioning and learning by Mary Cover Jones and JB Watson, based on Pavlovian conditioning models of learned fears and maladaptive emotional responses. Both psychodynamic and learning theory approaches focused on early traumatic experiences as causal to later behavioral problems, but current approaches to etiology are more complex. It is generally accepted that variations in behavior may have origins in temperamental differences, early patterns of attachment, parent-child interaction difficulties, and social factors, along with early traumatic experience. Work arose on behavioral interventions based both on early Pavlovian theories of learned emotional responses and BF Skinner's writings in the mid-20th century on positive operant conditioning and learning of voluntary responses to improve behaviors. This launched a variety of behavioral approaches, ranging from early reward systems to providing parents and teachers with strategies for



positively oriented behavior modification. During the same era, various play therapies, dramatic therapies, and relationship therapies emerged as additional strategies to help ameliorate children's emotional and behavioral problems. As more was learned about multiple etiologic factors of childhood disorders, multiple therapy approaches were developed to address those factors. By the start of the 21st century, Alan Kazdin identified 551 differently named psychosocial treatment approaches that are used with children. This is a vast number that does not even include eclectic approaches to treatment, in which elements of several therapies are combined, which is the approach most commonly used by physicians.

Clearly, the practice of psychotherapy grew much more quickly than research into its effectiveness. However, in the past decade, research has emphasized documenting the critical elements of therapeutic approaches in treatment manuals and then testing these treatment modalities in representative patients. This research of manualized therapy using written reminders of specific approaches has revealed common elements of effective therapy. More important, these therapies specify what behavior changes need to occur for true treatment progress to be achieved. The American Academy of Pediatrics (AAP) Task Force on Mental Health used the common elements of effective treatment as the basis for the guidance it provided to primary care physicians for the initial management of mental health problems. Within the mental health professions, the concept of modular therapies has been developed, which involves determining elements that have been proven effective in treating specific disorders and then, for individual patients, combining elements drawn from different therapy approaches to address the specific set of symptoms presented. Thus, for a child demonstrating both anxiety and oppositional behavior, elements of evidence-based cognitive behavioral therapy to manage the anxiety and parent training to address the oppositional behavior would be implemented. Chorpita and Daleiden have developed a model including training and treatment monitoring using this modular approach.

## INTERNALIZING VERSUS EXTERNALIZING BEHAVIOR DISORDERS IN CHILDREN

Because all psychosocial disorders are not the same, it is critically important to identify the key symptoms for which children typically present for treatment, to systematically research effective therapeutic strategies. The most commonly diagnosed emotional and behavioral disorders of childhood can be largely divided into 2 broad categories—externalizing disorders and internalizing disorders. Externalizing behavior refers to the group of disorders that are manifested in children's display of negative outward behavior, including aggression, oppositionality, defiance, delinquency, and hyperactivity. Children with these disorders are frequently noncompliant, have difficulty following rules, are restless, and are overly active. The most common referrals for psychotherapy, making up 50% to 75% of all children referred, are for disruptive

behavior problems. The diagnoses that typically fall into this category are attention-deficit/hyperactivity disorder, oppositional defiant disorder, conduct disorder, bipolar disorder, and disruptive behavior disorder not otherwise specified (NOS).

In contrast, internalizing disorders in children represent the group of emotional disorders in which the symptoms primarily affect a child's internal psychological environment. Rather than acting out, children with internalizing disorders often display anxious, depressed, withdrawn, or inhibited behavior. Anxiety disorders are among the most common forms of psychopathology in children and adolescents. Specific internalizing disorders that may emerge in childhood include anxiety disorders (eg, separation anxiety disorder, generalized anxiety disorder, specific phobia, obsessive-compulsive disorder, anxiety disorder NOS) and depressive disorders (eg, major depressive disorder, depressive disorder NOS).

It is noteworthy that although the distinction between the categories of internalizing and externalizing disorders is important for case conceptualization, treatment decisions, and research, these disorders are not necessarily mutually exclusive. In fact, there is often significant comorbidity between externalizing and internalizing disorders in children. However, research on evidence-based treatments for childhood disorders has demonstrated that the most effective types of treatment differ based on the type of problem. A helpful illustration can be seen in Table 61-1, Evidence-Based Child and Adolescent Psychosocial Interventions, which was originally developed by the Hawaii Department of Health and included in the AAP CD-ROM *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit*. This resource demonstrates the particular psychosocial interventions that are most and least helpful for the various categories of child emotional and behavioral difficulties based on a summary of the research in the field. In the case of children who seem to be exhibiting symptoms of both internalizing and externalizing difficulties, a best practice recommendation is to treat the primary symptoms first (ie, symptoms that are causing the most significant impairment).

## PSYCHOSOCIAL TREATMENT FOR EXTERNALIZING DISORDERS IN CHILDREN

### Parent Management Training

An evidence-based treatment for a school-aged child diagnosed with both attention-deficit/hyperactivity disorder and oppositional defiant disorder may include guidance for parents on behavior management and medication for the impulsivity and lack of focus.

Of the therapies used, parent management training (PMT), a therapeutic technique centered around teaching parents to modify their child's behavior through the use of evidence-based strategies, has been proved effective for disruptive behavior in a variety of settings and methods of implementation. PMT is a term that encompasses a number of evidence-based programs. All PMT programs that have been

**Table 61-1** Evidence-Based Child and Adolescent Psychosocial Interventions

	<b>PROBLEM AREA</b>	<b>LEVEL 1: BEST SUPPORT</b>	<b>LEVEL 2: GOOD SUPPORT</b>	<b>LEVEL 3: MODERATE SUPPORT</b>	<b>LEVEL 4: MINIMAL SUPPORT</b>	<b>LEVEL 5: NO SUPPORT<sup>a</sup></b>
<b>INTERNALIZING DISORDERS</b>	Anxious or avoidant behaviors	Cognitive behavioral therapy (CBT), CBT and medication, CBT with parents, education, exposure, modeling	Assertiveness training, attention, CBT for child and parent, cultural storytelling, family psychoeduca- tion, hypnosis, relaxation, stress inoculation	Contingency management, group therapy	Biofeedback, CBT with parents only, play therapy, psychody- namic therapy, rational emotive therapy, social Skills	Assessment/monitoring, attachment therapy, client- centered therapy, eye movement desensitization and reprocessing (EMDR), peer pairing, psychoeducation, relationship counseling, teacher psychoeducation Life skills, play therapy, psychodynamic therapy, psychoeducation, social skills
	Depressive and withdrawn behaviors	CBT, CBT and medication, CBT with parents, family therapy	Client-centered therapy, cognitive behavioral psychoeducation, expressive writing/ journaling/diary, interpersonal therapy, relaxation	None	Problem solving, self-control training, self-modeling	
<b>EXTERNALIZING DISORDERS</b>	Delinquency and disrupt- ive behavior	Anger control, assertiveness training, CBT, contingency management, multisystemic therapy, parent management training, parent management training and problem solving, social skills	CBT and teacher training, communica- tion skills, functional family therapy, parent management training and CBT, parent management training and classroom management, prob- lem solving, rational emotive therapy, relaxation, self-control training, therapeutic foster care, transactional analysis	Client-centered therapy, family therapy, moral reasoning training, outreach counseling, peer pairing	CBT and teacher psy- choeducation, parent management training and classroom management and CBT, parent management training and self-verbalization, physical exercise, stress inoculation	Behavioral family therapy, catharsis, CBT with parents, collaborative problem solving, education, exposure, family empowerment and support, family systems therapy, group therapy (!!), imagery training, parent management training and peer support, play therapy, psychodynamic therapy, self-verbalization, skill development, wraparound

<sup>a</sup>Level 5 refers to treatments whose tests were unresponsive or inconclusive. The symbol (!!) indicates that at least 1 study found negative effects on the main outcome measure. The risk for using treatments so designated should be weighed against potential benefits. Excerpted from PracticeWise Evidence-Based Child and Adolescent Psychosocial Interventions. Reprinted with permission from PracticeWise. For updates and an explanation of PracticeWise determination of evidence level, please visit [www.aap.org/mentalhealth](http://www.aap.org/mentalhealth).

proved effective include all 6 of the following components:

1. **Increasing positive interaction between parent and child through the use of special playtime strategies.** This approach is found in all evidence-based PMT programs and is also common to many other therapies designed to encourage positive parent-child interaction, including Greenspan's Developmental, Individual Differences, and Relationship-based Floortime model, and Brazelton's Touchpoints. For parents who are frustrated with constant arguments and battles with their children, reestablishing a positive relationship is an essential first step.
2. **Teaching parents how to record and monitor behavior accurately.** Change comes with learning, which can be enhanced and accelerated by teaching parents reinforcement and reward skills, but it still requires some time to change patterns of behavior. Parents often respond emotionally in the heat of the moment. It is only when they document and track gradual change that they can maintain their own efforts to bring about change.
3. **The use of reinforcement and rewards to increase the rate of desirable behaviors.** Although parents often present with their list of problem behaviors, they usually have lost sight of what they want their children to do instead. Identifying the desired positive behaviors and using social rewards such as praise, hugs, and more time with parents help reinforce positive behaviors quickly and can change the overall tone of the parent-child relationship.
4. **Teaching parents how to give directions and commands that are effective.** One of the difficulties noted in observational studies of parents and children in conflict is the difficulty some parents have in recognizing what children can comprehend and in simply giving clear, direct, understandable commands. This component, although brief in most programs, is essential.
5. **Coaching and training in the use of mild, non-physical punishments such as time-out to reduce undesirable behaviors.** Research shows that parents use physical punishment inconsistently and that their use of time-out, loss of privileges, or contingent work chores is more effective and less emotionally damaging to the parent-child relationship. This is also in line with current AAP policy on disciplining children.
6. **All of the skills are taught within a context of typical child development for age.** Parents often overestimate their child's abilities, skills, and motivation and require information on typical child development. Thus, effective PMT programs either include specific information about developmental skills or are designed for very specific age ranges. Although various effective programs may place a different emphasis on specific skills, all effective programs implement the complete set of all 6 elements in discussion, role-playing, and the use of video or active coaching to teach parents new behavior patterns. Programs use a variety of strategies, including intensive individual coaching

(Parent-Child Interaction Therapy, Helping the Noncompliant Child), group format with video (Incredible Years), and variations of group and individual family formats (PMT—Oregon Model, Triple P—Positive Parenting Program), as well as these strategies in combination with other therapeutic interventions (Problem Solving Skills + PMT).

## PSYCHOSOCIAL TREATMENT FOR INTERNALIZING DISORDERS IN CHILDREN

### Cognitive Behavioral Therapy

Internalizing disorders in children, encompassing the anxious and depressive disorders, comprise the second core group of psychosocial difficulties that often lead to referrals for mental health treatment. Across diagnostic categories, cognitive behavioral therapy (CBT) has consistently received the best support for reducing internalizing symptoms in children. Although the primary approach for addressing externalizing behavior in children is to provide parents with skills to shape the child's behavior through modifying the environment, research has demonstrated that, for internalizing symptoms, it is critical to address the child's thoughts, feelings, and behaviors directly.

The specific treatment strategies vary by treatment program, but a number of common components are present across CBT programs. According to Phil Kendall, the primary components of all CBT programs are strategies designed to address changes in thinking, feeling, and behavior, as well as an enactive component. CBT programs for children with internalizing difficulties typically address the following:

1. **Cognitions.** Children with anxiety and depression often have faulty cognitions, including distorted thinking about themselves and the world around them and negative, automatic thoughts that cause them to feel fearful or distressed. One aspect of CBT is to help children learn to identify these cognitions and cope with or even change them.
2. **Feelings.** Another important aspect of CBT is to help children learn affective recognition and coping strategies for unpleasant emotions.
3. **Behavior.** Behavioral strategies typically used in CBT include coping skills to help children manage some of their distressing emotional experiences. Behavioral strategies might include relaxation techniques, scheduling of pleasurable activities, and problem-solving strategies.
4. **Practice.** A key element of CBT is opportunities to practice new strategies and evaluate them. Although internalizing disorders are, by definition, manifested in symptoms that are within the child, it is important to consider the social context and provide opportunities for social practice with new strategies. Research has demonstrated that these components can be effectively delivered in individual or group settings.

An example of a well-supported CBT program for anxiety in children is the Coping Cat program. In Coping Cat, children learn to recognize the physiologic and cognitive symptoms of anxiety, learn cognitive

and behavioral strategies for coping with the anxiety, and practice the skills taught.

CBT programs have been developed for the treatment of depression in youth as well. One example includes the TAKING ACTION program, in which children learn to identify emotions, learn coping skills for unpleasant emotions, learn problem-solving strategies, and learn to restructure negative cognitions. This treatment is performed in a group setting, providing opportunities to practice.

For CBT to be an effective treatment strategy, the child must have the cognitive capacity to engage in the treatment. Studies indicate that school-aged children (typically developing children aged 7 years and older) are able to benefit, provided that they have adequate language skills. The therapy requires being able to label emotions, use language to develop an action plan, and use language to evaluate success.

### Common Elements of Evidence-Based Psychosocial Treatments

One of the criticisms of evidenced-based approaches is that they have been developed in randomized controlled trials (RCTs), for single disorders, and often come with a lengthy, detailed manual that leads the therapist and patient through a stepwise series of goals in a specific course of treatment, often for a fixed number of sessions. Clinical practice, however, is marked by comorbidity of more than 1 diagnosis and requires some flexibility in implementation to match the needs of the family. In practice, often the approach is to have the family successfully complete one goal before moving on to the next, and the goal is often determined by immediate need. Thus, a therapist working from an evidence-based perspective needs the elements of each approach available in a modular format that can be presented in the order needed by the patient. The common elements approach is best captured in the PracticeWise program, which incorporates evidence-based approaches to treating anxiety, depression, trauma, and conduct problems in a single set of treatment modules. Included in this program are descriptions of the disorders and detailed guidelines for therapists to guide sessions, as well as handouts for patients and their parents on identifying emotions, problem-solving and cognitive strategies for managing depression and anxiety, and the common elements of PMT (described previously). This program is a comprehensive approach to using modules shown to be effective so that a therapist can construct a treatment approach individualized for each child's particular set of symptoms.

### TREATMENTS LACKING A RESEARCH EVIDENCE BASE

One of the hallmarks of the therapies cited as evidence based are manualized therapies. This kind of systematic approach, which lends itself to standardization across patients, is more easily studied in an RCT than more individualized treatments like play therapy, various creative arts therapies, and individualized psychotherapy. These latter kinds of approaches lend themselves to analysis on a case-by-case, N-of-1, or

anecdotal basis. In some circumstances, the RCT is not an appropriate research method—and highly individualized therapy (eg, treatment individualized to a patient rather than following a manual) is among those circumstances. As a result, a number of therapies show promise with some patients but have no specific evidence regarding their effectiveness. In some situations, therapy can result in harm or worsening of the condition. As with any other type of treatment, there can be iatrogenic effects.

Along with providing information about the treatment methods with the greatest support, a second benefit of recent outcomes research is to provide guidance about which forms of treatment do not work well, or may even potentially cause harm. Across disorders, at this time, there is little to no research support for the use of play therapy or psychodynamic therapy with children, and there is no support for eye movement desensitization and reprocessing.

Mode of treatment delivery can also influence outcomes. CBT and some other treatment modalities addressing anxiety and depression are effective in a group setting. However, research has demonstrated that for children with disruptive oppositional and defiant behavior disorders, some types of group therapy are potentially harmful. A review and study showed that unstructured groups for conduct-disordered adolescents tended to increase deviant and oppositional behavior. More structured groups for children with disruptive behavior that have specific goals for self-control strategies can result in positive therapeutic effects.

Physicians can help to promote the optimal health and well-being of their patients by providing research-informed guidance to parents when selecting mental health providers and by developing a list of established referrals who practice evidence-based approaches to treatment of child psychosocial problems.

In general, although one-to-one individual unstructured psychotherapy with children is the preferred modality of treatment for many physicians, review of research does not support this form of treatment; statistically, it is no better than no treatment. Active, structured therapies, with clear goals and procedures that involve working with parents (and other involved adults) are most effective in shaping behavior. For children aged 7 years and older who have typical cognitive and language skills, teaching coping skills and strategies with targeted goals is also effective. Indeed, these approaches have a more extensive body of supportive research than other treatment, including many medication treatments. Properly carried out, effective psychosocial treatment has excellent long-term benefits that extend years beyond the termination of treatment and can positively influence a child's overall developmental course.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Parents' Guide: A Strengths-Based Approach* (handout), American Academy of Pediatrics, in *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* ([shop.aap.org](http://shop.aap.org))



- *Teaching Good Behavior: Tips on How to Discipline* (handout), American Academy of Pediatrics, in *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* (shop.aap.org)

#### Medical Decision Support

- *Columbia Impairment Scale* (scale), in *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* (shop.aap.org); also in public domain
- *Enhancing Pediatric Mental Health Care: Algorithms for Primary Care* (article), *Pediatrics*, Vol 125, Suppl 3 (pediatrics.aappublications.org/content/125/Supplement\_3/S109.pdf)
- *Evidence-Based Child and Adolescent Psychosocial Interventions* (chart), PracticeWise, American Academy of Pediatrics (www.aap.org/en-us/Documents/CRPsychosocialInterventions.pdf)
- *Generic or Common Factors Intervention: HELP* (mnemonic), American Academy of Pediatrics, in *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* (shop.aap.org)
- *Sources of Specialty Services for Children With Mental Health Problems and Their Families* (chart), American Academy of Pediatrics (pediatrics.aappublications.org/content/125/Supplement\_3/S126.pdf)

#### SUGGESTED READINGS

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## Chapter 62

# PSYCHOTROPIC MEDICATIONS IN PRIMARY CARE PEDIATRICS

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## INTRODUCTION

According to an American Academy of Pediatrics (AAP) survey published in 2008, more than 80% of primary care pediatricians reported that it was their responsibility to identify children with attention-deficit/hyperactivity disorder (ADHD), anxiety, depression,

and substance abuse. Most (70%) also thought it was their responsibility to manage ADHD; however, only about one-fourth thought it was their responsibility to manage anxiety (29%), depression (25%), or substance abuse (21%). In a policy statement published in July 2009, the AAP recommended that primary care pediatricians achieve competence in initiating care not only for children with ADHD, but also for children with anxiety, depression, and substance use or abuse. In addition, the statement recommended that pediatricians achieve competence in providing a medical home for children with the full range of pediatric mental health conditions. Implicit in these recommendations is the necessity for pediatricians to be knowledgeable about pediatric psychopharmacology in general and to use psychotropic medications safely and effectively in certain clinical situations.

The goal of this chapter is to offer a clear, rational, and evidenced-based framework for using psychotropic agents in children with psychiatric diagnoses. Although many pediatricians are already using these medications, there remains a wide variance of comfort with, confidence in, and knowledge about how drugs are initiated, titrated, and monitored across care settings. This chapter, although not a how-to manual, provides a unifying approach grounded in the most up-to-date research, filling in the “who, what, and why” aspects of psychopharmacologic management. The intention is not to dictate practice specifics, but rather to offer a methodologic approach that can best serve a wide range of pediatricians who, after completing a thorough diagnostic assessment in which medication-responsive illness is identified, must then make decisions regarding medication treatment options for children and families.

## GETTING STARTED: PREREQUISITES FOR PRESCRIBING

The safe and effective use of psychiatric medications in the primary care setting requires several conditions, outlined in Box 62-1.

### Determining Whether to Prescribe Medication: The Diagnostic Threshold

An accurate diagnosis of medication-responsive disorders (ie, disorders for which, at a minimum, there is sufficient evidence of a clinically meaningful reduction of symptom severity in response to medication) is important in pediatric psychopharmacology. This diagnostic accuracy ensures that those children who may benefit from medication are offered a trial, and it prevents needless use of medication in children who will not benefit from such treatment. Even with an accurate diagnosis and evidence-based treatments, there is no completely sensitive and specific way to determine which individual child will respond to medication or any other evidence-based therapy for psychiatric disorders, nor is there a way to predict who will experience treatment side effects or what type of side effect may emerge.

The uncertainty underlying these issues presents clinical challenges for the prescribing pediatrician. A relatively simple approach to assessing whether to

### BOX 62-1 Conditions for Safe and Effective Prescribing of Psychotropic Medications by Pediatricians

#### The disorder for which medication is prescribed needs to be

- Sufficiently common to be seen regularly by a pediatrician
- Efficiently and accurately diagnosable by a pediatrician

#### The medication needs to

- Have demonstrated efficacy
- Be relatively safe, as assessed by several parameters
- Have side effects that are reasonably predictable, readily detected, and readily managed

#### The dosing and monitoring of the medication need to

- Follow guidelines that are reasonably established and easily followed
- Include somatic monitoring that is limited to vital signs, height, and weight

#### The prescribing pediatrician needs to have

- Expertise in diagnosing the relevant disorders
- Knowledge of available psychosocial treatments (eg, parent behavior management training, cognitive behavioral therapy)
- Knowledge of the medications prescribed
- Procedures for monitoring medication effects and adherence

#### The system of care needs to provide

- Access to pediatric psychopharmacology expertise for consultation on issues beyond the expertise of the pediatrician
- Adequate payment for services rendered
- Minimal administrative and regulatory barriers

### BOX 62-2 Assessing Whether to Prescribe Medication

1. Does the child have *sufficient* symptoms to support a syndrome or disorder?
2. Have the symptoms been present for a *sufficient* period?
3. Is the child experiencing *sufficient* impairment or distress from the symptoms in ways that negatively affect academic development, family life, interactions with peers, participation in activities, or emotional well-being?
4. Is this disorder *sufficiently* different from normal levels of activity and impulsivity (in contrast with ADHD), worry and concern (in contrast with an anxiety disorder), or demoralization or grief (in contrast with an episode of depression)?
5. Have evidence-based therapies (eg, behavior management training with parents for ADHD; cognitive behavioral therapy for anxiety or depression) been tried, if available?

recommend medication is outlined in Box 62-2. This approach approximates the American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* in terms of essential components or criteria and practice guidelines for therapies.

The term *sufficient* (or *sufficiently*) appears in each of the criteria or components in Box 62-2. Thus, the pediatrician must judge whether each of the 4 components of diagnosis—symptoms, duration,

impairment, and non-normality—crosses a diagnostic threshold that warrants a recommendation for medication.

All pediatricians struggle with threshold when deciding on a diagnosis and determining whether to initiate a specific treatment. A familiar example in pediatrics is ADHD: all 18 symptoms of ADHD in the *DSM-5* include the term *often*, but there is no specific definition of *often*. Comparable examples in general medicine of the struggle with threshold include diagnosis and treatment of pain and insomnia.

Parent reports and self-reports can provide useful information about a child's symptoms and their severity and are often useful in determining threshold. Among the many available reporting tools, the following generally incorporate current *DSM* criteria and are available as open access tools: the Vanderbilt Attention-Deficit/Hyperactivity Disorder Rating Scale for parents and teachers CESj-DC; the Screen for Anxiety Related Disorders (SCARED), parent and child versions, for symptoms of anxiety; and the Patient Health Questionnaire-9 (PHQ-9) Modified for Teens (available at [www.thereachinstitute.org/images/GLAD-PCToolkit\\_V2\\_2010.pdf](http://www.thereachinstitute.org/images/GLAD-PCToolkit_V2_2010.pdf)) for symptoms of depression.

Also critical to threshold is assessment of the child's functioning: determination of whether the child's symptoms are causing impairment of school performance, relationships with peers and family members, and progress toward developmental goals. Several pediatrician-friendly tools are available to assist with this assessment, including the impact scale (second page) of the Strengths and Difficulties Questionnaire and the Columbia Impairment Scale. Use of a tool can break ground for a fuller assessment of functioning and serve

as a baseline for monitoring the child's functioning over time.

### Assessing Common Disorders

It is important to recognize that there is a hierarchy of difficulty in making accurate diagnoses of specific psychiatric disorders. Among the disorders addressed in this chapter, ADHD is generally the easiest and most straightforward to diagnose because the symptoms of ADHD are observable by multiple informants (eg, parents, teachers) in multiple settings (eg, school, home). Yet, even ADHD can often be confused with comorbid intellectual, language, and learning difficulties and with anxiety or the effects of trauma.

Anxiety disorders may be more difficult to diagnose than ADHD. Although anxiety and depression are both considered internalizing conditions, most symptoms of anxiety can be observed or easily elicited. Physical symptoms (eg, abdominal pain, muscle tension) are common in children with anxiety and are familiar to pediatricians. Other symptoms, such as avoiding social situations or phobic stimuli or entering the parents' bedroom or bed at night in response to separation concerns, are either reported by the children to their parents or are readily observed by parents. Asking children what they worry about may reveal anxiety more easily than asking, "Do you worry?"

Depression may be difficult to diagnose because demoralization, grief, and adjustment disorder, which are common in children and adolescents, can mimic the symptoms of depression. Parsing depression from these other conditions requires time and patience. When the differential diagnosis is complex, consultation with a child and adolescent psychiatrist may be needed to confirm the diagnosis of the child or adolescent who is suspected of being depressed.

Information about assessment (and treatment) of various psychiatric disorders can be found in other chapters in this volume.

### Screening for Adverse Childhood Experiences and Substance Abuse

Because symptoms of ADHD, anxiety, and depression can result from or be exacerbated by adverse childhood experiences (ACEs), including trauma, it is important to conduct universal screening for ACEs. ACEs may include single incidents (eg, car accident), ongoing traumas (eg, exposure to domestic violence), or a combination of stresses. ACE screening may identify environmental factors that are contributing to a child's mood and behavior and urgent concerns that require safety planning (eg, child abuse reporting). The Adverse Childhood Experiences study, developed by the Centers for Disease Control and Prevention (CDC), is a useful screening tool ([www.cdc.gov/violenceprevention/acestudy](http://www.cdc.gov/violenceprevention/acestudy)).

A simple screening question that can be incorporated into a standard visit is, "Since the last time I saw you, has anything really scary or upsetting happened to you or your family?" For children younger than 8 years, screening optimally relies on parent report, so the analogous question should be asked to parents, "Since the last time I saw your child, has anything really scary or upsetting happened to your child or

anyone in your family?" Ultimately, the clinical relevance of a reported ACE depends on the pediatrician's judgment.

Substance use and experimentation are very common among adolescents. The CDC reports that approximately 25% of high school-aged adolescents report they have bought, sold, or been given drugs on school grounds in the past 6 months ([www.cdc.gov/features/YRBS](http://www.cdc.gov/features/YRBS)). Preteens and adolescents should be screened for substance use. The CRAFFT substance abuse screening questionnaire is a validated brief pediatric screening tool ([www.ceasar-boston.org/clinicians/crafft.php](http://www.ceasar-boston.org/clinicians/crafft.php)).

Substance abuse and post-traumatic stress disorder (PTSD) may co-occur with other mood or behavioral disorders (eg, ADHD and marijuana abuse; depression and PTSD). Complex psychopathology may require further mental health consultation for diagnostic evaluation or incorporation of specific psychosocial treatments. It is important to note that there are no US Food and Drug Administration (FDA)-approved pediatric medication treatments for either substance abuse or PTSD, but there are evidence-based psychosocial interventions.

### Early Determinants of Need for Referral

Children with undiagnosed learning disabilities may also present with significant mood or behavior problems. These problems may be related to school maladjustment (eg, symptoms occur primarily in a school setting, not at home). Parents may benefit from referral to family advocacy programs or support programs available in the school system that can provide information on obtaining learning disabilities evaluations and advocating for disability services.

Finally, children living with complex psychosocial situations (eg, those whose parents have mental health or substance abuse issues, cognitive impairment, or significantly impaired parenting skills or those who have been maltreated or exposed to significant childhood adversities) may need a more thorough evaluation by a mental health professional because symptoms of ADHD, depression, and anxiety may mimic those of other psychiatric disorders. If a parent's mental illness is affecting the child's mental health, referral of the parent for his or her own care is warranted.

### Psychosocial Treatments

Effective, evidence-based psychosocial treatments, often described simply as therapy, are available for many pediatric psychiatric disorders. See reviews by Ginsburg and Weisz for a summary of these therapies and the evidence supporting them, and Chapter 61, Psychosocial Therapies. Psychosocial treatments are often tried before considering medication and are also used in combination with medication. For very young children, guidelines by the American Academy of Child and Adolescent Psychiatry recommend at least 2 trials of psychosocial treatment before starting medication. Evidence from large studies sponsored by the National Institute of Mental Health (NIMH) demonstrate the advantage of combining psychosocial and medication treatment over medication or therapy alone for ADHD (ages 7 to 9 years), common anxiety



disorders (separation anxiety disorder, social phobia, generalized anxiety disorder; ages 7 to 17 years), and depression (ages 12 to 17 years).

It is important to consider when psychosocial interventions are preferred over medication. Many children and adolescents present to pediatricians with mild depression or anxiety (ie, they meet diagnostic criteria, but symptoms and impairment are minimal) or subthreshold depression or anxiety (ie, they do not meet the diagnostic criteria for the disorder). In general, such a child is likely to benefit from a psychosocial intervention and may not need medication.

Despite the clear effectiveness of psychosocial treatments and the pressing need for them, there are still far too few mental health physicians and therapists with the proper training and experience to provide high-quality evidence-based therapy, and families face many administrative and financial barriers to access. For many pediatricians, these factors add pressure to prescribe psychopharmacologic therapy as a single first-line treatment. Pediatricians can join with families and mental health specialists in their community to advocate for evidence-based psychosocial services in both public and private systems of care. Ideally, psychosocial interventions always accompany pharmacologic interventions.

### Off-Label Prescribing

Before the mid-1990s, there were very few psychiatric medications that had been approved by the FDA for pediatric indications (ie, approved for use in children younger than age 18 years). Those approved included stimulants for ADHD, tricyclic antidepressants for enuresis, a few antipsychotics for psychosis, and lithium for mania in bipolar disorder. Thus, to treat psychiatric disorders in children and adolescents, it was often necessary to prescribe off label. Although many medications still lack FDA-approved pediatric indications across the age span, the number of pediatric indications has increased markedly over the past 20 years. This has occurred in response to federal legislation, including the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). Also, the NIMH began funding large, multisite treatment studies in the mid-1990s.

A number of medications are now available with indications for psychiatric disorders in children, including ADHD, depression, obsessive-compulsive disorder (OCD), mania in bipolar disorder, psychosis in schizophrenia, and “irritability” in children with autism. Thus, prescribing off label, especially for a medication that has no indication for any psychiatric disorder in children and adolescents, should be carefully justified and documented in the medical record.

## CONCEPTUAL FRAMEWORK FOR PRESCRIBING PSYCHIATRIC MEDICATIONS

### Overview

According to an expert task force comprising representatives from major international and regional (ie, American, Asian, and European) organizations, led by

the European College of Neuropsychopharmacology (ECNP), there are 108 psychotropic drugs available for prescribing. (The app “Nomenclature” is available at [play.google.com/store/apps/details?id=il.co.inmanage.nomenclature&hl=en](http://play.google.com/store/apps/details?id=il.co.inmanage.nomenclature&hl=en).) Most of these drugs are approved by the FDA for adults in the United States. This large number of medications can be overwhelming, even for experienced mental health specialists.

The goal of the proposed conceptual framework for prescribing psychotropic medications by pediatricians is to simplify and organize these medications into manageable and targeted groups in accordance with the AAP mental health competencies policy statement.

The first and most important group of psychotropic medications for pediatricians (Group 1) includes medications for the common psychiatric disorders: ADHD, major depressive disorder (MDD), and anxiety disorders. The best epidemiologic data indicate that more than 80% of psychotropic medications prescribed to children are for ADHD, anxiety, and depressive disorders.

Group 1 includes all FDA-approved medications for ADHD in children: 2 stimulants (methylphenidate and amphetamine), 2  $\alpha_2$ -adrenergic agonists (guanfacine and clonidine), and 1 norepinephrine reuptake inhibitor (atomoxetine). It also includes all FDA-approved medications for depression in children: the 2 selective serotonin reuptake inhibitors (SSRIs) fluoxetine and escitalopram. There are no FDA-approved medications for children with anxiety. This is, in large part, because of a discrepancy between FDA rules regarding anxiety disorder indications and the efficacy studies that have been conducted in children and adolescents with anxiety. Thus, for anxiety in children, 3 SSRIs are included—fluoxetine, fluvoxamine, and sertraline—that all have 1 high-quality, positive efficacy study for common anxiety disorders and FDA approval for OCD, an anxiety-related condition.

Thus, there are only 9 medications in Group 1 (Table 62-1). It is important to emphasize that these 9 Group 1 medications are not a formulary or restricted list of possible medications. However, as will be described in greater detail later, they are the only medications with high-quality scientific evidence supporting their efficacy. Also, as will be described later, these medications are relatively safe.

The second group of medications (Group 2) includes all FDA-approved medications for children with other disorders (ie, not ADHD, anxiety, or depression). Group 2 includes 5 antipsychotics (aripiprasole, olanzapine, quetiapine, risperidone, and paliperidone) and the mood stabilizer lithium. These medications are approved for treatment of children with psychosis in schizophrenia, mania in bipolar disorder, and, for aripiprasole and risperidone, “irritability” in autism. However, they are most commonly used in children to treat behavioral problems, especially aggression. Group 2 medications have a higher risk profile and are associated with more concerning acute and chronic adverse effects than Group 1 medications. Pediatricians are ideally suited to monitor the adverse effects of Group 2 medications, and some pediatricians, for various reasons, will be involved in prescribing them.



**Table 62-1**      **Group 1 Medications\***

DRUG (MODE OF ACTION)	INDICATION <sup>c</sup>	FDA APPROVAL/APPROVED AGE
<b>ADHD</b>		
Methylphenidate (stimulant)	ADHD	Yes; ≥6
Amphetamine (stimulant) <sup>a</sup>	ADHD	Yes; ≥6
Guanfacine (α-adrenergic agonist)	ADHD	Yes; ≥6
Clonidine (α-adrenergic agonist)	ADHD	Yes; ≥6
Atomoxetine (NRI)	ADHD	Yes; ≥6
<b>CERTAIN ANXIETY DISORDERS<sup>b</sup></b>		
Fluoxetine (SSRI)	(Anxiety)	No
Sertraline (SSRI)	(Anxiety)	No
	OCD	Yes; ≥6
Fluvoxamine (SSRI)	(Anxiety)	No
	OCD	Yes; ≥10
<b>MDD</b>		
Fluoxetine	MDD	Yes; ≥8
Escitalopram	MDD	Yes; ≥12

ADHD, attention-deficit/hyperactivity disorder; FDA, Food and Drug Administration; MDD, major depressive disorder; NRI, norepinephrine reuptake inhibitor; OCD, obsessive-compulsive disorder; SSRI, selective serotonin reuptake inhibitor.

\*Group 1 medications: evidence of efficacy, favorable side-effect profile, and management of disorder within primary care competencies; for a detailed discussion on pediatric mental health competencies for primary care, see Committee on Psychosocial Aspects of Child and Family Health and Task Force on Mental Health. Policy statement—The future of pediatrics: mental health competencies for pediatric primary care. *Pediatrics*. 2009;124:410–421.

<sup>a</sup>Amphetamine: approved down to age 3 years, “grandfathered” in.

<sup>b</sup>Certain anxiety disorders: generalized anxiety disorder, social anxiety disorder, separation anxiety disorder.

<sup>c</sup>For each of these disorders, there are also evidence-based psychosocial interventions. See *Evidence-Based Child and Adolescent Psychosocial Interventions* at [www.aap.org/mentalhealth](http://www.aap.org/mentalhealth).

The third group of medications includes medications not approved by the FDA for children and thus not included in Groups 1 or 2. For Group 3 medications, there are about 10 that pediatricians are most likely to see in their practices. These 10 medications will be discussed in terms of available efficacy data and adverse-effect profile. Other Group 3 medications, which are not commonly prescribed, will not be discussed, but their adverse-effect profiles can be accessed through electronic media (eg, [drugs@fda.gov](mailto:drugs@fda.gov), Epocrates, Micromedex).

### Evidence Supporting Efficacy

The evidence base for the treatment of ADHD, common anxiety disorders (ie, generalized, social, and separation), and depression has been demonstrated in several multisite randomized clinical trials conducted since the mid-1990s (eg, the MTA Group, Walkup et al, March et al).

The research procedure used to demonstrate efficacy (or not) of a medication is the random assignment, masked (“blinded”), placebo-controlled treatment study (RCT). Additional design features that improve the quality of RCTs include a predetermined primary outcome variable; a sufficiently large number of participants, usually estimated by a power analysis, to accurately test the efficacy hypothesis; multiple performance sites that use comparable methodology; to minimize bias, independent funding (eg, in the United States, the National Institutes of Health (NIH) or another government agency); and use of independent evaluators who do not receive any information about medication side effects.

There is no single gold standard for determining that a medication is efficacious. In adults, 2 well-designed

and conducted RCTs that demonstrate superiority of the active medication over placebo is the generally accepted standard and is used by the FDA as a necessary prerequisite for drug approval. In children and adolescents, because there are fewer funding resources and fewer studies, the FDA sometimes relaxes this standard and approves a medication with just 1 large, high-quality, multicenter RCT along with other supportive data. That approach is also used by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group to evaluate treatments for children and adolescents ([www.gradeworkinggroup.org](http://www.gradeworkinggroup.org)).

One of the widely recognized limitations with this approach to determining efficacy is that, for both ethical and practical reasons, RCTs are short term, although most psychotropic medications are used to treat children and adolescents with chronic disorders that often require long-term treatment. Despite this limitation, the well-designed and conducted RCT is the best method available for demonstrating efficacy.

As noted earlier, the fact that there are no medications with FDA-approved pediatric indications for an anxiety disorder (except for OCD, an anxiety-related condition) is in large part because of a discrepancy between FDA rules regarding anxiety disorder indications and the efficacy studies that have been conducted in children and adolescents with anxiety. The FDA requires that studies used to support an application for an indication focus on a single anxiety disorder, such as social anxiety disorder (SoAD), separation anxiety disorder (SAD), or generalized anxiety disorder (GAD). In children, symptoms of these anxiety disorders often co-occur and change over time. Thus,

several well-designed studies sponsored by the NIH have examined use of an SSRI, such as fluoxetine, fluvoxamine, or sertraline, to treat children with 1, 2, or 3 of these common childhood anxiety disorders (SoAD, SAD, or GAD). Most commonly, the participants in these

studies met criteria for 2 or 3 disorders, not just 1. Therefore, the FDA did not use data from these studies to support an indication.

Table 62-2 summarizes the efficacy data supporting the use of the Group 1 medications. As a proxy for the

**Table 62-2**
**Evidence Supporting Short-term Safety and Efficacy of Group 1 Medications in Children and Adolescents**

DRUG	INDICATION	SUPPORT <sup>a</sup>	AGE (YR)	RATE OF RESPONDERS	IE <sup>b</sup>
Methylphenidate: std. form. <sup>c</sup>	ADHD	Spencer et al (1996): Review	6–12	A: ~70%, P: ~25%	N/A
		MTA Cooperative Group (1999)	7–9	Not specified	No
		The PATS Team (2006)	3–5	A: 21%, P: 13%	No
Methylphenidate: ext'd. rel. <sup>d</sup>	ADHD	Greenhill et al (2002)	6–16	A: 64%, P: 27%	No
		McGough et al (2006): Patch	6–12	A: 71%, P: 16%	No
		Findling et al (2010): Patch	13–17	A: 66%, P: 21%	No
Amphetamine: std. form. <sup>c</sup>	ADHD	Spencer et al (1996): Review	N/A	N/A	N/A
Amphetamine: ext'd. rel. <sup>d</sup>	ADHD	McGough et al (2005)	6–12	Not specified	No
		Domniete, Madaan (2010)	6–12	A: 70%, P: 18%	No
Guanfacine: std. form. <sup>c</sup>	ADHD	Scahill et al (2001)	7–15	A: 53%, P: 0%	No
		Arnsten et al (2007): Review	N/A	N/A	N/A
Guanfacine: ext'd. rel. <sup>d</sup>	ADHD	Biederman et al (2008)	6–17	A: 50%, P: 26%	No
		Sallee et al (2009)	6–17	A: 56%, P: 30%	No
Clonidine: ext'd. rel. <sup>d</sup>	ADHD	Jain et al (2011)	6–17	N/A	No
		Kollins et al (2011)	6–17	N/A	No
Atomoxetine	ADHD	Michaelson et al (2001)	8–18	Not specified	No
Fluoxetine	Anxiety	Birmaher et al (2003)	7–17	A: 61%, P: 35%	No
		Emslie et al (1997)	7–17	A: 56%, P: 33%	No
		Emslie et al (2002)	8–18	A: 65%, P: 53%	No
		TADS Team (2004)	12–17	A: 61%, P: 35%	Yes
	MDD	Riddle et al (1992)	8–15	A: 33%, P: 12%	No
		Geller et al (2001)	7–17	A: 49%, P: 25%	No
		Liebowitz et al (2002)	6–18	A: 57%, P: 27%	Yes
		Wakup et al (2008)	7–17	A: 55%, P: 24%	Yes
Sertraline	Anxiety	Wagner et al (2003)	6–17	A: 36%, P: 24%	No
		March et al (1998)	13–17	A: 42%, P: 26%	No
		POTS Team (2004)	7–17	A: 21%, P: 4%	Yes
		Wagner et al (2006)	6–17	A: 63%, P: 52%	No
Escitalopram	MDD	Emslie et al (2009)	12–17	A: 62%, P: 52%	No
		RUPP Anxiety Group (2001)	6–17	A: 76%, P: 29%	No
Fluvoxamine	Anxiety	Riddle et al (2001)	8–17	A: 42%, P: 26%	No

A, active drug recipients; ADHD, attention-deficit/hyperactivity disorder; IE, independent evaluator; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; P, placebo recipients.

<sup>a</sup>Complete references can be found in the electronic version of this chapter (pediatriccare.solutions.aap.org).

<sup>b</sup>Use of independent evaluators to rate symptom severity may help reduce bias because these individuals are blinded to patient side effects that could reveal their treatment assignment.

<sup>c</sup>Standard formulation.

<sup>d</sup>Extended-release formulation.

magnitude of effect, the rate of responders on active drug and placebo are listed. It is important to note that a responder is not the same as a remitter. A patient who remits no longer meets diagnostic criteria and has no or very mild residual symptoms, whereas a responder generally meets a severity criterion of “much better” or “very much better” but may still have mild to moderate symptoms. Thus, a remitter is generally more improved than a responder. The last column notes whether ratings were done by independent evaluators (IEs). An IE is a rater who is not involved in data collection other than to conduct blinded symptom severity ratings at specified times during a study. The use of IEs is thought to reduce bias because the presence or absence of medication side effects (which are not known to the IEs) can help investigators to guess the participant’s medication status—active or placebo. Finally, all completed NIH-sponsored studies are included in the tables. However, there may be unpublished industry-sponsored studies that are not listed.

### Evidence Supporting Safety

There is no gold standard for assessing safety of medications in children and adolescents. For the purposes of this discussion, 5 parameters will be used for assessing safety.

1. An FDA-approved pediatric indication (a proxy for a minimal standard of research data supporting short-term safety [and efficacy] of a medication for a specified indication)
2. At least 10 years on the market (a proxy for sufficient time to discover rare adverse long-term consequences and rare complications with long-term exposure [ie, greater exposure over time increases the chance to detect rare and harmful events that would not otherwise be detected in brief clinical trials])
3. Minimal overdose harm, determined by a review of the available literature
4. Lack of clinically significant boxed warnings (a formal FDA proxy for rare, major adverse events)
5. Lack of other known or potentially harmful long-term effects, determined by a review of available literature and review of “warnings and precautions” in the FDA package inserts

Table 62-3 applies these safety parameters to the 4 categories of Group 1 medications.

## GROUP 1 MEDICATIONS: SPECIFIC RATIONALE

The Group 1 medications for use in the primary care setting belong to 4 different classes of medications. The rationale for using specific medications is presented here.

### Stimulants

Despite the numerous products available on the market, there are just 2 distinct stimulant chemical entities—methylphenidate and amphetamine. The available literature has not shown advantages of different racemic mixtures (*d* vs *l* vs *d,l*). Thus, different racemic preparations are considered interchangeable, except for dose. Methylphenidate and amphetamine are available in numerous release preparations that provide a treatment effect ranging from 3 to 12 hours. Those with longer time on the market and lower cost may be preferred, but that is a general comment, not a preparation-specific recommendation.

### $\alpha_2$ -Adrenergic Agonists

Guanfacine is approved by the FDA for ADHD in children and adolescents. It is relatively specific to the  $\alpha_{2A}$  receptor subtype, which mediates attention and other executive functions. Clonidine is approved by the FDA for ADHD in children and adolescents. It nonspecifically interacts with  $\alpha_{2A}$ ,  $\alpha_{2B}$ , and  $\alpha_{2C}$  receptor subtypes. The B and C receptors mediate the sedation and hypotension or bradycardia side effects. Thus, clonidine may have a less favorable side-effect profile than guanfacine. There are no direct comparative data regarding this issue. Also, regular (not sustained-release) clonidine is associated with acute drops in blood pressure, syncope, and even death following accidental or intentional ingestions of more than therapeutic quantities.

### Norepinephrine Reuptake Inhibitor

Atomoxetine, a norepinephrine reuptake inhibitor, has an FDA indication for ADHD. Of note, it has more

**Table 62-3** Safety Profile of Group 1 Medication Classes in Children and Adolescents

SAFETY CRITERIA	STIMULANTS	$\alpha$ -ADRENERGIC AGENTS	SSRIs	NRIs
FDA approval	$\geq 6$ yr	$\geq 6$ yr	$\geq 8$ yr	$\geq 6$ yr
Years on market <sup>a</sup>	>50 yr	>30 yr	>25 yr	$\geq 10$ yr
Overdose harm	Low	Low	Very low	Very low
Boxed warning (Major AEs) <sup>b</sup>	Drug abuse potential, cardiac	None	Suicidality	Suicidality
Long-term risk to health <sup>c,d</sup>	Possible growth deceleration	None known	None known	None known

AEs, adverse events; FDA, US Food and Drug Administration; NRIs, norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

<sup>a</sup>Years on the market: measure of exposure in large populations; time to observe potentially harmful events.

<sup>b</sup>SSRIs, NRIs, and suicidality: original FDA meta-analysis: 2% for placebo and 4% active in forced dose titration studies (see Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry*. 2006;63(3):332–339). More recent analysis shows difference of 0.67%, down from 2% difference (see Bridge JA et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA*. 2007;297(15):1683–1696).

<sup>c</sup>Lack of studies to assess long-term risk to health, with the exception of stimulants.

<sup>d</sup>Stimulants and growth deceleration: data are not convincing.

concerning FDA “warnings and precautions” than the other medications for ADHD included in Group 1.

### Selective Serotonin Reuptake Inhibitors

There are 6 SSRIs marketed in the United States: fluoxetine, sertraline, escitalopram, paroxetine, citalopram, and fluvoxamine. Comments regarding the 4 SSRIs included in Group 1 follow:

- Fluoxetine: FDA indications in children and adolescents for depression and OCD; high-quality, NIH-sponsored study demonstrating efficacy for the 3 common anxiety disorders in children; the first SSRI marketed in the United States; longest half-life, so abrupt discontinuation results in slow, safe fall in plasma and brain levels.
- Sertraline: FDA indication in children and adolescents for OCD; second SSRI in the United States; best data for the 3 common anxiety disorders in children; offers alternative to fluoxetine when shorter half-life may be indicated (eg, for a child taking multiple medications with further changes likely) or when fluoxetine cannot be used because of interactions with metabolic isoenzymes (eg, inhibition of CYP2D6).
- Escitalopram: FDA indication in children and adolescents for depression; no clinically relevant interactions with hepatic CYP450 isoenzymes.
- Fluvoxamine: Has an FDA indication for OCD in children and a high-quality, NIH-sponsored study demonstrating efficacy for the 3 common anxiety disorders in children.

## PRESCRIBING GROUP 1 MEDICATIONS IN PEDIATRIC PRIMARY CARE

The general rationale regarding efficacy and safety of psychotropic medications, especially those in Group 1, was described in previous sections. Provided here is a brief introduction to clinical issues associated with prescribing and monitoring of Group 1 psychotropic medications in primary care pediatrics.

### Informed Consent

Obtaining informed consent from the parent or guardian and assent from the patient can be more complicated and difficult for psychotropic medications than for other medications. This is because of parental concerns about the potential effect of medications on the child’s developing brain and controversy in the media regarding psychiatric medications. The basic steps involved in obtaining informed consent and assent are the same, no matter what psychotropic medication is recommended. A description of essential and optional areas to cover in the consent process is provided in Box 62-3. It may be efficient to have a nurse help the prescribing physician with the details of consent, as is commonly done for immunizations and other prescriptions and procedures in outpatient practices. Of note, in addition to the initial consent process, informed consent is usually an ongoing process that unfolds over time as the patient and caregiver develop new questions and concerns about

medications. The initial consent process offers an ideal opportunity to consider a timeline for re-evaluating both medication efficacy and side effects and to note that consent will be revisited in light of the patient’s initial and ongoing responses to and experiences with the medication, both positive and negative. Thus, consent is an ongoing component of an evolving clinical process.

### Dosing

Dosing for all Group 1 medications generally follows the same pattern—start with a relatively low dose, increase in relatively small increments about every week, and continue to increase the dose until an optimal benefit-to-risk ratio is reached. The dosing guidance presented in this chapter for all Group 1 medications is derived from the FDA package inserts, with the authors adding detail on points where the FDA is silent, such as how often or by how much to increase the dose. Dosing recommendations from the FDA can be found in package inserts or at the [drugs@FDA Web site \(www.accessdata.fda.gov/scripts/cder/drugsatfda\)](http://www.accessdata.fda.gov/scripts/cder/drugsatfda).

- Methylphenidate preparations (see Table 62-4): For standard-release preparations, starting doses range from 2.5 mg/dose for preschoolers (ages 4 to 5 years), to 5 mg/dose for school-aged children, to 10 mg/dose for adolescents. Recommended doses for Focalin preparations are half of those for other methylphenidate preparations. Dose increments for increases are generally equivalent to the starting dose. Because response to stimulants may be idiosyncratic, individualized dose titration with interval reports from multiple independent observers is indicated. Optimal benefit-to-risk ratio is common at total daily dose of 0.5 to 1.5 mg/kg per day, although some children respond to lower doses and some adolescents may require higher doses. Some adverse events, such as decreased appetite and insomnia, may be dose sensitive, so higher total daily doses need to be carefully monitored. Most children and families prefer long-acting preparations, which can usually be given once per day. The smallest daily dose of the most popular extended-release methylphenidate preparation (osmotic pump) is 18 mg/day; lower dose increments are available with other formulations.
- Amphetamine preparations (see Table 62-4): 1 mg of amphetamine is approximately equivalent to 2 mg of methylphenidate. Thus, the dosages given previously for methylphenidate can be used for amphetamine preparations, but need to be divided by 2. Long-acting preparations of amphetamine are available in a wide range of doses.
- Guanfacine: For once-daily preparations, which are preferred by children and families, the starting dose is usually 1 mg/day. Doses can be increased by 1 mg every few days to a maximum recommended daily dose of 4 mg.
- Clonidine: 0.1 mg of clonidine is approximately equivalent to 1 mg of guanfacine. Thus, the dosages given previously for guanfacine can be used for clonidine preparations, but need to be divided by 10. Long-acting preparations of clonidine are available in 0.1- and 0.2-mg doses.



**BOX 62-3 A Clinical Approach to Informed Consent for Medication****ESSENTIAL**• **Preamble**

- Conceptualization of signs and symptoms as *illness*
- What are the *risks of not treating* with medication?
- Think *job performance* (home, school, friends)
- Think *development* (emotional, behavioral, social, cognitive)

• **Evidence supporting short-term efficacy and effectiveness**

- A level: 2 placebo-controlled, random-assignment, properly implemented studies (RCTs) or, in some cases for children and adolescents, 1 well-designed RCT
  - *Note:* This applies to all Group 1 medications for attention-deficit/hyperactivity disorder, anxiety, depression.
- B level: 1 RCT
- C level: information from open-label studies, case reports, etc

• **Alternative and additional treatments**

- Evidence-based psychotherapies
- Community, family, school system support
- Other medications

• **Adverse effects**

Severity	Change Needed	Examples
Mild	Requires no change	Dry mouth, transient nausea
Moderate	Requires dose change	Sedation
Severe	Requires stopping drug	Real suicidal ideation or attempt

• **Potential long-term adverse effects**

- Examples: growth restriction (stimulants), diabetes mellitus, or tardive dyskinesia (antipsychotics)
- Unknown

• **Pharmacokinetic issues**

- Convenience: once-daily dosing preferred, no laboratory monitoring preferred
- Drug-drug interactions: especially involving hepatic cytochrome P-450 enzymes

• **Adherence**

- The importance of establishing a convenient daily routine for taking the medication

• **YOUR OPINION ABOUT BENEFIT/RISK RATIO FOR THIS PATIENT**

- Taking into consideration all of the above, what do you recommend?
- Why?
- *Think: if this were your child, what would you do?*

**OPTIONAL**• **Cost**

- Generic vs brand
- This drug vs others in class

• **Evidence supporting long-term efficacy and effectiveness**

- This becomes relevant if/when short-term efficacy and safety are established.

- **Atomoxetine:** Atomoxetine is dosed once daily. For children and adolescents up to 70 kg, the the FDA-recommended initial daily dose is 0.5 mg/kg; target daily dose is 1.2 mg/kg and maximum daily dose is 1.2 mg/kg. For those over 70 kg, initial daily dose is 40 mg; target daily dose is 80 mg, and maximum daily dose is 100 mg. Dosage should be adjusted (lowered) for patients known to be CYP2D6 poor metabolizers.
- **Fluoxetine:** Fluoxetine is dosed once daily. Starting dose ranges from 2.5 to 10 mg, depending on age and weight. Doses are generally increased every week or so by an amount equivalent to the starting dose until a favorable benefit-to-risk ratio is achieved.

Best effective dose is generally 5 to 20 mg, although higher doses are sometimes required.

- **Sertraline:** Sertraline is dosed once daily. Starting dose ranges from 12.5 to 25 mg. Dose increments range from 12.5 to 50 mg. Effective total daily dose is generally 25 to 200 mg.
- **Escitalopram:** Escitalopram is dosed once daily. Starting dose ranges from 2.5 to 5 mg. Dose increments range from 2.5 to 10 mg. Effective total daily dose is generally 5 to 20 mg.
- **Fluvoxamine:** The starting dose is 25 mg at bedtime, with increases of 25 mg every 4 to 7 days as tolerated to maximum effect, not to exceed 200 mg/day (8 to 11 years) or 300 mg/day (12 to 17 years). Daily doses

**Table 62-4** Stimulant Preparations

PREPARATION	DURATION (HR)	METHYLPHENIDATE	AMPHETAMINE
Standard release	3–6	Ritalin Dexmethylphenidate	Dexedrine Adderall
Pulse	7–8	Ritalin SR Metadate ER Methylin ER	Dexedrine Spansule
Pearls	8–12	Metadate CD Ritalin LA FOCALIN XR <sup>a</sup>	Adderall XR
Pump	≤12	Concerta	
Modified standard release (prodrug)	≤12		VYVANSE <sup>b</sup>
Liquid suspension	8–12	QUILLIVANT XR <sup>a</sup>	ProCentra
Patch	≤12	Daytrana <sup>a</sup>	

<sup>a</sup>CAPS indicate that only branded form is available (ie, no generic).

<sup>b</sup>Vyvanse is converted to standard-release dextroamphetamine after the “prodrug” passes through the gut without being metabolized. Thus, it is a “modified” standard-release preparation.

From FDA Listing of Authorized Generics (updated 09/30/2015) ([www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM183605.pdf](http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM183605.pdf))

over 50 mg should be divided. Although an extended-release preparation is available, the FDA package insert states that for “pediatric patients naïve to fluvoxamine maleate—the lowest available dose of Luvox CR capsules may not be appropriate.”

### Side Effects or Adverse Events

Adverse events can be evaluated based on either severity or frequency. In package inserts required by the FDA, potential severity of adverse events is emphasized; that is, “boxed warnings” are more severe than “warnings and precautions” (W&P), which are more severe than “adverse reactions.” In addition, package inserts describe “contraindications” and “drug interactions.”

The most comprehensive and least potentially biased prescribing information about adverse events can be found in FDA-required labels or package inserts. These labels are available in various formats and locations, including in medication packaging and the *Physicians’ Desk Reference*. They are available online at [drugs@fda](http://drugs@fda). Since the FDA modified the format for labels a few years ago, each label or insert has a 1-page “Highlights of Prescribing Information” that includes relatively complete and essential information about boxed warnings, warnings and precautions, adverse reactions, contraindications, and drug interactions. These highlights can be accessed and reviewed quickly and conveniently and are useful resources.

Rather than reiterate all the details regarding all the adverse events associated with all of the medications in Group 1, the following 3 sections provide general guidance regarding boxed warnings, warnings and precautions, and adverse reactions. Because contraindications are essentially prohibitions to prescribing, they are not amenable to summarization and should be specifically and carefully considered before prescribing any medication. Likewise, drug interactions, although not prohibitive, are drug specific and generally not amenable to summarization; they should be carefully considered before prescribing any medication.

### FDA Boxed Warnings

The most concerning adverse events are given boxed warnings by the FDA. There is 1 boxed warning for antidepressants (specifically SSRIs and atomoxetine), 1 for stimulants, and none for  $\alpha_2$ -adrenergic agonists. It is important to keep in mind that all the adverse events described in the boxed warnings listed here occur infrequently and may never be seen by an individual pediatrician. The information in the following sections was taken from the most recent labels available at [drugs@fda](mailto:drugs@fda) as of December 9, 2014.

### Selective Serotonin Reuptake Inhibitors (and Atomoxetine) and Suicidality

The FDA boxed warning about suicidality is an obstacle for many pediatricians who consider prescribing SSRIs or atomoxetine for anxiety and depression. The boxed warning issued in October 2004 stated that all antidepressants pose significant risk for suicidality (suicidal ideation or suicide attempts, not completed suicides) in children and adolescents and recommends close monitoring for increased suicidality. Specific recommendations for frequent monitoring were described in an FDA medication guide, which was revised in 2007 ([www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/ucm100211.pdf](http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/ucm100211.pdf)). This updated guide focuses on information parents need to know regarding suicidality and antidepressants rather than on specific mandates for monitoring frequency.

Antidepressant-induced suicidality is rare. The original FDA estimate, based solely on data from more than 4,300 research participants in 23 studies, was that 2% of children and adolescents receiving placebo and 4% receiving an antidepressant developed suicidal thoughts or attempted suicide. Thus, the risk difference was 2%. A subsequent analysis based on data from 27 RCTs involving more than 5,300 participants found a risk difference of just 0.7% (95% confidence interval [CI]: 0.1% to 1.3%). Of note, the most recent estimate, which was based on data from 35 RCTs involving more than 6,000 participants, found a risk

difference of 0.9% (95% CI: 20.000 to 0.018), just reaching statistical significance.

Clinical prudence indicates the need to educate patients and parents about suicidality and to provide careful monitoring for suicidality and other adverse effects during the initial phase of treatment (when the risk for suicidality is generally greatest from both the depression and the medication) and throughout treatment.

### **Stimulants and Concerns About Abuse and Dependence**

The boxed warnings for both amphetamines and methylphenidate state that they have a high potential for abuse and that prolonged administration may lead to dependence. Fortunately, there are no reports of children who were treated with therapeutic doses of stimulants developing dependence. Available data suggest that children with ADHD who are treated with stimulants are not more likely than those who did not receive stimulant treatment to develop substance abuse later in life. A related problem is diversion; that is, patients selling their prescription stimulants to be used as drugs of abuse.

## **FDA Warnings and Precautions**

### **Stimulants**

Most W&Ps rarely occur in children and adolescents treated with stimulants. Those most relevant to children taking either methylphenidate or amphetamine preparations include the following:

- Serious cardiovascular events (generally only in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems)
- Increase in blood pressure (this is more common than other W&Ps)
- Psychiatric adverse events (primarily emergence of psychotic, manic, or aggressive symptoms)
- Seizures
- Long-term growth suppression
- Exacerbation of tics

Priapism is listed only for methylphenidate preparations.

### **$\alpha$ -Adrenergic Agonists**

- Both guanfacine and clonidine preparations have the following relevant W&Ps: hypotension, bradycardia, syncope
- Sedation and somnolence
- Worsening of some pre-existing cardiac conduction abnormalities

In addition, abrupt discontinuation should be avoided with clonidine preparations.

### **Atomoxetine**

Atomoxetine has the following relevant W&Ps:

- Severe liver injury
- Serious cardiovascular events
- Effects on blood pressure and heart rate
- Emergent psychotic or manic symptoms
- Bipolar disorder
- Aggressive behavior or hostility

- Possible allergic reactions (in addition to the standard contraindication for hypersensitivity)
- Effects on urine outflow
- Priapism
- Growth
- Concomitant use with potent CYP2D6 inhibitors.

### **Selective Serotonin Reuptake Inhibitors**

The SSRIs fluoxetine, sertraline, escitalopram, and fluvoxamine all have the following relevant W&Ps, all of which rarely occur:

- Serotonin syndrome
- Activation of mania/hypomania
- Seizures
- Abnormal bleeding
- Hyponatremia
- Potential cognitive and motor impairment
- Angle closure glaucoma

Fluoxetine has some additional relevant W&Ps—altered appetite and weight, anxiety and insomnia, QT prolongation, long half-life (thus, changes in dose may not be reflected in plasma for several weeks).

Sertraline, escitalopram, and fluvoxamine all have a W&P regarding discontinuation of treatment, specifically concerns about various withdrawal symptoms with abrupt discontinuation.

Fluvoxamine has a W&P regarding potentially important drug interactions, beyond those described in the “drug interactions” section of the label. These are generally related to inhibiting effect of fluvoxamine on several cytochrome P-450 isoenzymes, including 1A2, 2C9, 3A4, and 2C19.

### **Adverse Reactions**

The FDA label uses frequency, rather than severity, to delineate adverse reactions, the most common and least severe of adverse events. Although specifics vary from medication to medication, the label usually describes the most common adverse reactions (>5% and at least twice the placebo rate) reported in RCTs submitted to the FDA. This report may be for adults, children, adolescents, or some combination of these groups.

In Table 62-5, common and less common adverse events for the 4 classes of Group 1 medications are presented. Table 62-5 is based on, but not completely the same as, adverse reactions presented in FDA-approved labels. In addition, withdrawal symptoms are noted. Except for low-dose stimulants and fluoxetine, medications should be tapered in order to minimize withdrawal symptoms.

### **Monitoring Group 1 Medications**

Frequency of monitoring may vary depending on a particular patient's health status, but, in general, it is more frequent during the initial phase of treatment with all Group 1 medications. During this time, dosage is changing frequently as it is being titrated up to an effective and safe dose, and side effects often occur before benefit. Poor adherence is common, so monitoring for adherence is important to prevent unwarranted and potentially unsafe dose escalations in the child who is not adherent. Pediatricians will benefit from access to pharmacy claims data or other medication adherence tools, if available. Finally, more

**Table 62-5** Adverse Reactions Associated With Group 1 Medication Classes

MEDICATION CLASS	ADVERSE REACTIONS <sup>a</sup>	WITHDRAWAL SYMPTOMS <sup>b</sup>
<b>STIMULANTS</b> Methylphenidate (Ritalin and others) Dexmethylphenidate (Focalin) Dextroamphetamine (Dexedrine and others) Amphetamine salts (Adderall and others)	<i>Common: insomnia, appetite suppression, headache, stomachache</i> Less common: cognitive dulling, irritability, exacerbation of tics <b>MONITOR:</b> BP, pulse, BMI	ADHD symptoms “worsen” at end of day when drug wears off. These are not considered withdrawal symptoms.
<b>α<sub>2</sub>-ADRENERGIC AGONISTS</b> Guanfacine (Tenex, Intuniv) Clonidine (Catapres, Kapvay)	<i>Common: somnolence</i> Less common: dry mouth, headache, nausea, decreased BP <b>MONITOR:</b> BP, pulse	Elevated BP, nervousness, headache, confusion
<b>NRIs</b> Atomoxetine (Strattera)	<i>Common: dry mouth, insomnia, nausea, decreased appetite</i> Less common: increased heart rate, BP, palpitations, dizziness, sweating, dysuria, weight change <b>MONITOR:</b> BMI, BP, HR	
<b>SSRIs</b> Fluoxetine (Prozac) Sertraline (Zoloft) Escitalopram (Lexapro) Fluvoxamine (Luvox)	<i>Common: “activation” (restlessness, insomnia, impulsiveness, talkativeness—usually occur early in treatment), GI upset, nausea, diarrhea</i> Less common: autonomic (eg, diaphoresis, mydriasis), cardiovascular (eg, flushing, sinus tachycardia, hypertension), sexual (decreased libido, delayed ejaculation), akathisia <b>MONITOR:</b> BMI, worsening of depression, emergence of suicidal thinking or behavior (especially with initiation or dose escalation), or unusual changes in behavior, such as sleeplessness, agitation, or withdrawal from normal social situations	Especially for shorter half-life SSRIs such as sertraline: flu-like syndrome; dizziness (most common), nausea, emesis, fatigue, headache, gait instability, insomnia, mood changes, myalgia. Tapering not needed for fluoxetine.

ADHD, attention-deficit/hyperactivity disorder; BP, blood pressure; BMI, body mass index; HR, heart rate; NRI, norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

<sup>a</sup>Common adverse reactions in italics.

<sup>b</sup>Tapering suggested for all medications except fluoxetine.

Check for psychopharmacologic medication updates from a reliable source, such as the National Library of Medicine or National Institutes of Health, MedlinePlus Drugs, Supplements and Herbal Information. Available at: <http://www.nlm.nih.gov/medlineplus/druginformation.html>; US Food and Drug Administration. Available at: <http://www.fda.gov>; American Academy of Child and Adolescent Psychiatry. Available at: <http://www.aacap.org>. Practice Parameter on the Use of Psychotropic Medication in Children and Adolescents: The AACAP Practice Parameters describe generally accepted practices. They are designed to assist physicians in providing high-quality assessment and treatment for children and adolescents consistent with best available scientific evidence and clinical consensus. Available at: <http://download.journals.elsevierhealth.com/pdfs/journals/0890-8567/PIIS0890856709601568.pdf>.

frequent monitoring may be indicated for patients with certain medical conditions.

For stimulants, blood pressure, heart rate, height, and weight should be monitored. In addition, patients taking stimulants should be observed for, and parents questioned about, tics. No specific laboratory studies are recommended. The recommendations for guanfacine, clonidine, and atomoxetine are similar.

Patients taking SSRIs should be monitored for several parameters during the first several weeks of treatment: emergence of suicidal thinking or behavior, worsening of depression, gastrointestinal symptoms (pain, nausea, diarrhea), or the activation phenomenon (eg, agitation, insomnia, or increased energy or activity). Over the longer term, height and weight, sexual

dysfunction, and emergence of mania should be monitored. No specific laboratory tests are indicated.

### Phases of Treatment

Medication treatment for ADHD, anxiety, or depression is often initiated during an acute clinical crisis when the child's symptoms are at their worst. Thus, doses that are used in the acute phase of illness and treatment may be higher than are needed later during maintenance treatment. This is especially true if the child and family are responsive to evidence-based psychosocial therapy that is initiated during the acute clinical crisis or shortly thereafter. Improved coping skills, more useful cognitive and behavioral constructs, reduced family tension, or successful behavioral



feedback may reduce the need for medication either partially (eg, lower dose) or completely (eg, discontinuation). Over the longer term, doses may need to be increased in response to growth and maturation.

### Adherence and Persistence

Obviously, medications that are not ingested are not effective. The rate of nonadherence in pediatric psychopharmacology is not well studied or documented except for stimulants, for which the data suggest high levels of nonadherence. Parent reports of adherence to sustained-release stimulant preparations indicate about 10% to 25% nonadherence. Even more concerning, a retrospective comparison of the Multimodal Treatment Study of Attention-Deficit/Hyperactivity Disorder (MTA) found that only 3% of caregivers reported that their child did not receive prescribed stimulant medication on the day of a study visit, whereas child saliva samples indicated that 25% of children were nonadherent. Taken together, studies of parent reports and salivary samples indicate that nonadherence to stimulant medication is high and is underreported by caregivers.

Persistence refers to continuity of treatment. Because ADHD is a chronic disorder, relatively long-term treatment with stimulants would be expected except for drug holidays or when they are discontinued because of unacceptable side effects or lack of adequate effect. However, data from community practice settings suggest that treatment is not persistent. In a study of more than 9,500 pharmacy and medical claims for 6- to 12-year-olds, the mean duration of stimulant treatment episodes was only about 145 days for immediate-release preparations and about 150 to 160 days for longer-acting preparations. In a study using Medicaid claims for more than 40,000 5- to 20-year-olds, 27% to 50% were persistent for 12 months, allowing for a 1- or 3-month gap in use, respectively. These and other studies suggest that a substantial proportion of children receiving stimulants may not receive them for more than 1 year.

Improving adherence and persistence is not a simple or easy task. Discussing adherence and nonadherence in a nonjudgmental manner before prescribing a medication is important. It is important to establish a therapeutic approach through which children and parents feel that assessing adherence is part of the therapeutic process, helpful to clinical decision making regarding dose changes and continuation of a medication, and not a negative judgment.

Procedures for improving adherence and persistence are described in the literature and in Chapter 47, Adherence to Pediatric Health Care Recommendations. They include identification of barriers to adherence, application of motivational interviewing techniques, reminder and monitoring systems, and, when available, aids such as bubble packaging.

### Prioritizing Medications

The following discussion regarding differences between various Group 1 medications is offered as potentially useful information. It is not meant to protocolize or prohibit prescribing of any medication. An individualized decision regarding an individual medication for

an individual patient is always the final responsibility of the individual prescriber.

### Attention-deficit/Hyperactivity Disorder

Clinical guidance from the AAP and practice parameters from the American Academy of Child and Adolescent Psychiatry (AACAP) recommends starting with either methylphenidate or amphetamine. Also, the effect size, a measure of the magnitude of improvement relative to placebo, is greater for these stimulants than for the other medications approved for ADHD. In cases in which there are concerns about starting with a stimulant (eg, specific potential adverse events or parental preferences), guanfacine, clonidine, and atomoxetine are all secondary options and all have generally comparable effect sizes. As described previously, guanfacine and clonidine seem to have a favorable adverse event profile compared with atomoxetine.

### Anxiety

There are no data to suggest any differences in efficacy between fluoxetine, sertraline, and fluvoxamine for anxiety. Fluoxetine has a longer half-life and effect, which is an advantage if there are concerns about adherence, but a disadvantage if there is a need to stop the medication because of adverse effects or drug interactions. Fluvoxamine inhibits cytochrome P-450 isoenzymes that are different from those inhibited by fluoxetine or sertraline.

### Depression

There are no data to suggest any differences in efficacy for depression between fluoxetine and escitalopram. The potential advantages and disadvantages of fluoxetine for depression are the same as described previously for anxiety. An advantage of escitalopram is that it does not have any clinically significant interactions with cytochrome P-450 isoenzymes.

### Switching Medications

If the initial stimulant medication is not effective, data from published studies supports switching to a stimulant in the other category. Likewise, if the initial SSRI is not effective, switching to one of the other Group 1 SSRIs may be successful.

### Multiple Medications

Many children treated in the pediatric primary care setting for ADHD, anxiety, or depression will need only 1 psychotropic medication. Some will need 2 (eg, children with ADHD, anxiety, and depression who require medication as part of the treatment plan). Fortunately, the medications for ADHD (methylphenidate, amphetamine, guanfacine, clonidine, and atomoxetine) can be used safely in combination with the medications for anxiety or depression (the SSRIs fluoxetine, sertraline, escitalopram, and fluvoxamine).

If a child requires 3 or more psychiatric medications to effectively manage symptoms, advanced expertise in pediatric psychopharmacology or consultation with a child and adolescent psychiatrist is strongly advised. The pediatrician can, in either case, play an important

role in monitoring the medications and in promoting a healthy lifestyle.

## GROUP 2 MEDICATIONS FOR OTHER DISORDERS: GENERAL RATIONALE

In addition to prescribing and monitoring Group 1 medications, pediatricians are ideally suited to collaborate with psychiatrists and other mental health specialists in the care of children with more severe or uncommon disorders. They may be asked to take on partial responsibility for monitoring the therapeutic and side effects of a variety of other medications, which are included in Groups 2 and 3.

Group 2 medications can be monitored in primary care settings, but because they generally have a more serious safety profile or more complicated monitoring requirements than Group 1 medications, they are generally prescribed by specialists—child psychiatrists, developmental-behavioral pediatricians, specialists in neurodevelopmental disabilities or adolescent medicine, pediatric neurologists, or adult psychiatrists with additional training in adolescent psychiatry. Depending on an individual pediatrician's skills and experience and availability of specialists for referral (or lack thereof, especially in rural and underserved areas), some pediatricians with additional training in pediatric psychopharmacology may choose to prescribe Group 2 medications.

Group 2 includes all FDA-approved medications for children with other disorders (ie, not ADHD, anxiety, or depression). Group 2 includes 5 second-generation antipsychotics (SGAs; aripiprazole, olanzapine, quetiapine, risperidone, and paliperidone) and lithium, a mood stabilizer. The SGAs (all 5) are approved for treatment of children with psychosis in schizophrenia; all except paliperidone are approved for mania in bipolar disorder; only risperidone and aripiprazole are approved for “irritability” in autism. However, these medications are most commonly used off label (ie, outside the FDA indications) in children to treat behavioral problems, especially aggression. Lithium is approved by the FDA for treatment of acute mania in bipolar disorder. Lithium is also used off label to treat nonbipolar mood instability.

## GROUP 2 MEDICATIONS: SPECIFICS

### Antipsychotics

Antipsychotic medications can reduce the severity of various major psychiatric symptoms and have a variety of effects, including the following:

- Antipsychotic effects for hallucinations, delusions, and disorganized thinking
- Mood stabilizing effects for mania, irritability, and mood instability
- Possible “organizing” or calming effects for agitation and aggressive behavior

However, of all the psychotropic medications used in children and adolescents, SGAs generally have the most concerning adverse effects, including the following:

- Sedation
- Weight gain
- Elevated glucose and insulin resistance

- Elevated triglycerides and cholesterol
- Abnormal movements (neurologic)
- Others (see Table 62-6)

Many of the major adverse effects of SGAs—particularly weight gain, metabolic abnormalities, and involuntary movements—can develop into major health problems (eg, cardiovascular disease and its consequences, tardive dyskinesia) during long-term treatment and may not be reversible. Most disorders that may be treated with SGAs are chronic and generally require long-term treatment. Thus, determining risk versus benefit when initiating SGAs is difficult.

There is no agreement about monitoring for weight and metabolic adverse events in children prescribed SGAs. Neither the AAP nor the AACAP has issued formal guidelines or recommendations for monitoring. The only available formal published guide is for adults; it is presented in Table 62-7.

The following discussion regarding differences between various Group 2 medications is offered as potentially useful information. It is not meant to protocolize or prohibit prescribing of any medication. An individualized decision regarding an individual medication for an individual patient is always the final responsibility of the individual prescriber.

There are no useful data comparing the efficacy of the 5 Group 2 SGAs in children. Paliperidone is the active metabolite of risperidone and seems similar to risperidone in efficacy and adverse event profile. Perhaps the major difference is that risperidone has been in use longer (since 1993) than paliperidone (since 2006) and is available as a generic drug. Generally, clinically meaningful differences between SGAs focus on adverse events. Only a few relevant differences will be highlighted here. Olanzapine, in contrast to the other Group 2 SGAs, is associated with more weight gain and metabolic adverse events. Aripiprazole is associated with the least weight gain and less severe metabolic adverse events. Among the 4, risperidone is most likely to increase prolactin levels and is associated with gynecomastia and amenorrhea. Quetiapine seems to be the most sedating. Detailed information regarding Group 2 SGAs is presented in Table 62-6.

### Lithium

Mood stabilizers (excluding antipsychotics) are used to treat mania, depression, irritability, and problematic mood swings or instability in bipolar disorder and other mood disorders. There are 2 groups of mood stabilizers—traditional (lithium, valproic acid [divalproex sodium], and carbamazepine) and newer anti-convulsants (eg, lamotrigine). Use of mood stabilizers (excluding SGAs) in children appears to be decreasing. This may result from 1 or more factors—available efficacy data are generally negative, regular monitoring of plasma levels is usually required, and the adverse event burden is substantial.

Lithium is the mood stabilizer included in Group 2. It has an FDA indication for mania in bipolar disorder down to age 12 years, and available data for lithium suggest efficacy for acute mania in bipolar disorder. Detailed information regarding lithium is presented in Table 62-6.

**Table 62-6**      **Group 2 Medications**

MEDICATION	WARNINGS, PRECAUTIONS, AND ADVERSE EVENTS	COMMENTS
<b>SECOND-GENERATION ANTIPSYCHOTICS (SGAS)</b>		
<b>Risperidone</b> Class: SGA <i>Indications in children and adolescents:</i> schizophrenia (13–17 yr), acute manic or mixed episodes (10–17 yr), “irritability” associated with autistic disorder (5–16 yr) <i>Uses:</i> schizophrenia spectrum disorders, bipolar spectrum disorders, “irritability” in autism. Also, among many off-label uses: acute aggression, chronic irritability, tics, and other disorders not responsive to other medications <i>Monitoring:</i> height and weight. Fasting glucose and lipid profile. Abnormal involuntary movements.	<i>Box warnings:</i> suicidality with antidepressant drugs <i>Warnings and precautions:</i> increased risk for suicidality in children, adolescents, and young adults with major depressive disorder, neuroleptic malignant syndrome, tardive dyskinesia, hyperglycemia/diabetes mellitus, dyslipidemia, weight gain, orthostatic hypotension, leukopenia, neutropenia, agranulocytosis, seizures/convulsions, potential for cognitive and motor impairment, suicide <i>Adverse events:</i> In children and adolescents clinical trials (incidence $\geq 5\%$ and twice placebo): somnolence, extrapyramidal disorder, fatigue, nausea, akathisia, blurred vision, salivary hypersecretion, dizziness, tremor, sedation, fatigue, increased appetite, drooling, vomiting, pyrexia, decreased appetite, lethargy	Risperidone was the first SGA (other than clozaril, which is rarely used in children) approved by the US Food and Drug Administration (FDA) in 1993 for marketing in the United States. It is generally effective and safe for short-term use, but there are concerns about adverse effects of long-term use, such as obesity, diabetes, metabolic syndrome, and tardive dyskinesia. It can increase prolactin levels and is associated with gynecomastia and amenorrhea.
<b>Aripiprazole</b> Class: SGA <i>Indications in children and adolescents:</i> schizophrenia (13–17 yr), manic or mixed episodes (10–17 yr), “irritability” associated with autistic disorder (6–17 yr) <i>Uses:</i> same as risperidone <i>Monitoring:</i> same as risperidone	Same as risperidone	Marketed since 2002, aripiprazole has a somewhat different mechanism of action than other SGAs. It is associated with less weight gain than other SGAs, except ziprasidone. It also lowers prolactin levels.
<b>Quetiapine</b> Class: SGA <i>Indications in children and adolescents:</i> schizophrenia (13–17 yr), manic episodes associated with bipolar I disorder (10–17 yr) <i>Uses:</i> same as risperidone <i>Monitoring:</i> same as risperidone	Same as risperidone	Marketed since 1997, quetiapine is associated with more somnolence than other SGAs.
<b>Olanzapine</b> Class: SGA <i>Indications in children and adolescents:</i> schizophrenia (13–17 yr), manic or mixed episodes of bipolar I disorder (13–17 yrs) <i>Uses:</i> same as risperidone <i>Monitoring:</i> same as risperidone	<i>Box warnings:</i> none specifically applicable for pediatrics <i>Warnings and precautions:</i> suicide, neuroleptic malignant syndrome, hyperglycemia, hyperlipidemia, tardive dyskinesia, orthostatic hypotension, leukopenia, neutropenia and agranulocytosis, seizures, potential for cognitive and motor impairment, hyperprolactinemia <i>Adverse events:</i> in adolescent clinical trials ( $\geq 5\%$ and at least twice that for placebo): somnolence, dizziness, fatigue, increased appetite, nausea, vomiting, dry mouth, tachycardia, weight gain	Marketed since 1996, olanzapine is associated with more weight gain and related metabolic side effects in adolescents than other SGAs. <sup>a,b</sup>

Continued

**Table 62-6**      **Group 2 Medications—cont'd**

MEDICATION	WARNINGS, PRECAUTIONS, AND ADVERSE EVENTS	COMMENTS
<p><b>Paliperidone</b>  Class: SGA  Indications in children and adolescents: schizophrenia (12–17 yr)  Uses: same as risperidone  Monitoring: same as risperidone</p>	<p><i>Box warnings:</i> none specifically applicable for pediatrics  <i>Warnings and precautions:</i> neuroleptic malignant syndrome, QT prolongation, tardive dyskinesia, hyperglycemia and diabetes mellitus, hyperglycemia, dyslipidemia, weight gain, hyperprolactinemia, gastrointestinal narrowing, orthostatic hypotension and syncope, leukopenia, neutropenia, agranulocytosis, potential for cognitive and motor impairment, seizures, suicide  <i>Adverse events:</i> most common adverse reactions in adolescent clinical trials (<math>\geq 5\%</math>) were somnolence, akathisia, tremor, dystonia, cogwheel rigidity, anxiety, weight increased, tachycardia</p>	<p>Because paliperidone is the major active metabolite of risperidone, it is very similar to risperidone in all respects.</p>
<p><b>MOOD STABILIZER</b>  <b>Lithium</b>  Class: element of the alkali metal group (salt)  Indications in children and adolescents: mania in bipolar disorder (age <math>&gt;12</math> yr)  Uses: acute mania and maintenance therapy in bipolar disorder, mood stabilization  Monitoring: pregnancy testing, electrocardiogram, serum lithium levels, complete blood count, electrolytes, thyroid function, renal function</p>	<p><i>Box warnings:</i> toxicity closely related to serum levels; can occur close to therapeutic dose levels.  <i>Warnings:</i> very high risk for toxicity: significant cardiovascular or renal disease, severe debilitation, dehydration, sodium depletion; taking diuretics or angiotensin-converting enzyme (ACE) inhibitors. Chronic use may lower renal concentrating ability, can present as nephrogenic diabetes insipidus, with polyuria/polydipsia. Encephalopathic syndrome (ie, weakness, lethargy, fever, tremulousness and confusion, leukocytosis, extrapyramidal symptoms, elevated serum enzymes, blood urea nitrogen, and fasting blood sugar) may occur with lithium and a neuroleptic, often haloperidol.  <i>Precautions:</i> hypothyroidism; impaired mental or physical abilities; any concomitant medications, ie, diuretics, ACE inhibitors, carbamazepine, fluoxetine.  <i>Adverse events:</i> Mild <math>&lt;1.5</math> mEq/L; mild/moderate 1.5–2.5 mEq/L; moderate/severe <math>\geq 2.0</math> mEq/L. Less than 2.0 mEq/L: early signs of toxicity, including diarrhea, vomiting, drowsiness, muscular weakness, and lack of coordination; at higher levels: giddiness, ataxia, blurred vision, tinnitus, large output of dilute urine; at <math>&gt;3.0</math> mEq/L: complex clinically with multiple organs and organ systems.</p>	<p>Introduced in the United States in the early 1960s, it was the original mood stabilizer. Clear, documented evidence of effectiveness for acute and maintenance treatment of mania and bipolar disorder in adults. No well-powered, placebo-controlled study for treatment of mania in children and adolescents, in large part because of the ethical and practical difficulties associated with conducting placebo-controlled studies. Evidence is mixed from several smaller studies.<sup>c,d</sup> Indication for 12- to 17-year-olds is not based on rigorous safety and efficacy data. Unpopular with children and adolescents because of common side effects and the need for repeated venipunctures for serum level monitoring.</p>

<sup>a</sup>Correll CU et al. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA*. 2009; 302:1765–1773

<sup>b</sup>American Diabetes Association et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004;27:596–601

<sup>c</sup>Geller B et al. A randomized controlled trial of risperidone, lithium, or divalproex sodium for initial treatment of bipolar I disorder, manic or mixed phase, in children and adolescents. *Arch Gen Psychiatry*. 2012;69:515–528

<sup>d</sup>Robb AS, McNamara N, Pavuluri MN, et al. New Research Poster Presentation 4.47. Lithium in the acute treatment of a manic or mixed episode in pediatric bipolar I disorder: a randomized, double-blind, placebo-controlled study. Abstract from the Annual Meeting of the American Academy of Child and Adolescent Psychiatry; October 2014; San Diego, CA



**Table 62-7****Monitoring Protocol for Adult Patients Taking Second-Generation Antipsychotics**

	<b>BASELINE</b>	<b>4 WEEKS</b>	<b>8 WEEKS</b>	<b>12 WEEKS</b>	<b>QUARTERLY</b>	<b>ANNUALLY</b>	<b>EVERY 5 YEARS</b>
Personal and family history	X					X	
Weight (body mass index)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

Reprinted with permission from American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. *Diabetes Care*. 2004;27:596–601.

### GROUP 3 MEDICATIONS

As noted previously, the third group of medications (Group 3) includes medications not approved by the FDA for children and thus not included in Groups 1 or 2. It should be noted that there are a few other medications that have FDA indications for children, but these are based on premodern data (if there are any data) and were “grandfathered” in by the FDA years ago. Although the FDA has removed most of these grandfathered indications, a few remain. These remaining grandfathered approvals have been excluded from this conceptual framework because they were not subject to the same modern standards of evidence for safety and efficacy as medications included in Groups 1 and 2, discussed previously.

For Group 3 medications, 10 were selected for emphasis because they are commonly used and pediatricians are likely to have patients for whom they have been prescribed. Table 62-8 summarizes available efficacy data and adverse event profiles for these 10 medications. Other Group 3 medications, which are less commonly prescribed, will not be discussed, but their adverse event profiles can be accessed by electronic media (eg, drugs@fda, Epocrates, Micromedex).

#### Other Antidepressants

Four antidepressants—bupropion, citalopram, venlafaxine, and mirtazapine—are commonly prescribed in children and adolescents. None has an FDA indication for use in children or adolescents.

Bupropion has a chemical structure similar to the phenylethylamines, which are stimulants. It is marketed for depression in adults and is sometimes used to treat comorbid depression and ADHD in children.

Although citalopram, an SSRI, is sometimes used for depression or anxiety in children, it offers no

benefit over escitalopram, a Group 1 medication, which is the therapeutically effective s-enantiomer of citalopram. Citalopram has an FDA warning regarding maximum dose in adults because of the risk for QTc prolongation; however, a relevant dosage maximum is not known in children and adolescents. Thus, the need to monitor with electrocardiograms complicates treatment in children.

Venlafaxine is a norepinephrine reuptake inhibitor that acts like an SSRI at lower doses. It is used for anxiety or depression in children. In children and adolescents, venlafaxine is associated with more adverse events than SSRIs. Industry-sponsored efficacy studies for depression and anxiety in children, although almost reaching statistical significance, have not demonstrated clear efficacy.

Mirtazapine has a tetracyclic chemical structure that distinguishes it from other antidepressants. It is marketed for depression in adults. Mirtazapine is associated with more sedation and weight gain than other antidepressants.

#### Other Antipsychotics

Ziprasidone is an SGA (marketed since 2001) that is approved in adults for psychosis in schizophrenia and mania in bipolar disorder. Ziprasidone has the advantage of generally being associated with less weight gain and fewer metabolic adverse events than other SGAs. Probably primarily because ziprasidone is associated with prolongation of QTc, it has not been approved by the FDA for children or adolescents.

#### Other Mood Stabilizers

Divalproex sodium, an anticonvulsant, is commonly prescribed to children as a mood stabilizer. Unfortunately, efficacy data for divalproex sodium suggest no difference from placebo and less efficacy than comparators. Monitoring requires venipunctures.

**Table 62-8**      **Group 3 Medications**

MEDICATION	WARNINGS, PRECAUTIONS, AND ADVERSE EVENTS	COMMENTS
<b>ANTIDEPRESSANTS</b>		
<b>Bupropion</b> Class: atypical antidepressant; chemical structure like phenylethylamines, which are stimulants Indications: <i>adult</i> : major depressive disorder (MDD) C/A: <b>none</b> Uses: depression Monitoring: blood pressure, heart rate, height, weight, suicidality	<i>Boxed warnings:</i> suicidality <i>Warnings and precautions:</i> seizures, hepatotoxicity, agitation and insomnia, psychosis and confusion, weight gain or loss, allergic reactions, hypertension <i>Adverse reactions:</i> agitation, dry mouth, insomnia, headache/migraine, nausea and vomiting, constipation, tremor	Because of its structural similarity to stimulants, bupropion is sometimes used to treat both depression and symptoms of ADHD.
<b>Citalopram</b> Class: selective serotonin reuptake inhibitor (SSRI) Indications: <i>adult</i> : MDD C/A: <b>none</b> Uses: MDD Monitoring: same as other SSRIs (see Group 1)	<i>Boxed warnings:</i> suicidality, electrocardiogram changes <i>Warnings and precautions:</i> similar to other SSRIs <i>Adverse reactions:</i> similar to other SSRIs	Offers no benefit over escitalopram, which is the Group 1 therapeutically effective s-enantiomer of the racemic mixture citalopram. Also, citalopram has a US Food and Drug Administration (FDA) warning regarding maximum dose in adults because of the risk for QTc prolongation; relevant dosage maximum is not known in children and adolescents. Thus, the potential need to monitor with electrocardiograms complicates treatment.
<b>Venlafaxine</b> Class: norepinephrine reuptake inhibitor (NRI) Indications: <i>adult</i> : MDD C/A: <b>none</b> Uses: MDD Monitoring: blood pressure, heart rate, height, weight, suicidality	<i>Boxed warnings:</i> suicidality <i>Warnings and precautions:</i> serotonin syndrome, sustained hypertension, mydriasis, discontinuation symptoms—especially anxiety and insomnia, decreased appetite and weight, height deceleration, activation of mania/hypomania, hyponatremia, seizures, increased risk for bleeding events, serum cholesterol elevation, interstitial lung disease, eosinophilic pneumonia <i>Adverse reactions:</i> asthenia, sweating, nausea, constipation, anorexia, vomiting, somnolence, dry mouth, dizziness, nervousness, anxiety, tremor, blurred vision	Venlafaxine was compared with an SSRI in children and adolescents with depression who had not responded to initial treatment with an SSRI (TORDIA study). The second SSRI and venlafaxine showed comparable efficacy; however, venlafaxine was associated with more adverse events and discontinuations.
<b>Mirtazapine</b> Class: tetracyclic Indications: <i>adult</i> : MDD C/A: <b>none</b> Uses: MDD Monitoring: body mass index, white blood cell lipid panel, transaminases	<i>Boxed warnings:</i> suicidality <i>Warnings:</i> activation of mania/hypomania, agranulocytosis, serotonin syndrome, angle closure glaucoma <i>Precautions:</i> discontinuation symptoms, akathisia, hyponatremia, somnolence, dizziness, increased appetite, weight gain, cholesterol/triglycerides, transaminase elevations, seizures <i>Adverse reactions:</i> somnolence, increased appetite, weight gain, dizziness	Mirtazapine has both serotonergic and noradrenergic actions and is different from other Class 1 and 2 antidepressants in its mechanism of action. It is generally more sedating and causes more weight gain than other antidepressants.

Table 62-8

Group 3 Medications—cont'd

MEDICATION	WARNINGS, PRECAUTIONS, AND ADVERSE EVENTS	COMMENTS
<b>SECOND-GENERATION ANTIPSYCHOTIC (SGA)</b>		
<b>Ziprasidone</b> <i>Class:</i> SGA <i>Indications:</i> adult: schizophrenia, manic or mixed episodes associated with bipolar I disorder, adjunctive maintenance therapy of bipolar I disorder, agitation in schizophrenic patients (intramuscular injection) <i>C/A:</i> none <i>Uses:</i> same as risperidone <i>Monitoring:</i> same as risperidone, plus QTc prolongation on electrocardiogram	<i>Boxed warnings:</i> not applicable for pediatrics <i>Warnings and precautions:</i> QT interval prolongation, neuroleptic malignant syndrome, tardive dyskinesia, hyperglycemia and diabetes mellitus, dyslipidemia, rash, orthostatic hypotension, leukopenia, neutropenia, agranulocytosis, seizures, potential for cognitive and motor impairment, suicide <i>Adverse events:</i> most common adverse reactions in clinical trials (incidence $\geq 5\%$ and twice placebo): somnolence, respiratory tract infection, somnolence, extrapyramidal symptoms, dizziness, akathisia, abnormal vision, asthenia, vomiting, extrapyramidal symptoms, dizziness, akathisia, abnormal vision, asthenia, vomiting, headache, nausea	Marketed since 2001, ziprasidone is associated with less weight gain than other SGAs. Because of potential to prolong the QT interval, electrocardiogram monitoring is needed.
<b>MOOD STABILIZER</b>		
<b>Valproic Acid</b> <i>Class:</i> anticonvulsant mood stabilizer <i>Indications:</i> adult: therapy of complex partial seizures and simple and complex absence seizures <i>C/A:</i> none for psychiatric disorders <i>Uses:</i> mood stabilizer <i>Monitoring:</i> pregnancy testing, serum levels, complete blood count, liver function tests	<i>Boxed warnings:</i> hepatotoxicity can be fatal, usually in first 6 months of use in children $< 2$ years; teratogenic, includes neural tube defects, eg, spina bifida, malformations, decreased IQ; pancreatitis can be fatal, hemorrhagic cases <i>Warnings and precautions:</i> hepatotoxicity, birth defects and decreased IQ following in utero exposure, pancreatitis, suicidality, thrombocytopenia, multiorgan hypersensitivity reaction, hypothermia, hyperammonemia, hyperammonemic encephalopathy, multiorgan hypersensitivity reaction <i>Adverse reactions:</i> most common adverse reactions in clinical trials of mania (incidence $\geq 5\%$ ): abdominal pain, alopecia, amblyopia/blurred vision, amnesia, anorexia, asthenia, ataxia, bronchitis, constipation, depression, diarrhea, diplopia, dizziness, dyspepsia, dyspnea, ecchymosis, emotional lability, fever, flu syndrome, headache, increased appetite, infection, insomnia, nausea, nervousness, nystagmus, peripheral edema, pharyngitis, rhinitis, somnolence, abnormal thinking, thrombocytopenia, tinnitus, tremor, vomiting, weight gain, weight loss	Valproic acid to treat mania in adults is supported by substantial data. Supportive data are lacking in children. An industry-funded, multisite randomized controlled trial in children with mania and bipolar disorder did not show efficacy of valproic acid versus placebo. In a comparison of valproic acid, lithium, and risperidone for bipolar disorder in children, valproic acid had the lowest response rates, which were comparable to those for placebo in the industry-funded study.

Continued

**Table 62-8**      **Group 3 Medications—cont'd**

MEDICATION	WARNINGS, PRECAUTIONS, AND ADVERSE EVENTS	COMMENTS
<b>ANXIOLYTICS</b> <b>Lorazepam</b> Class: benzodiazepine Indications: adult: acute anxiety C/A: none Uses: acute anxiety Monitoring: pregnancy testing	Boxed warnings: none Warnings: worsening or emergence of depression, suicidality, respiratory depression, interference with cognitive and motor performance, physical and psychological dependence, risk of use in pregnancy, withdrawal symptoms Precautions: paradoxical reactions (ie, behavioral disinhibition), should not be used with alcohol Adverse reactions: in a sample of about 3,500 adult patients treated for anxiety, the most frequent adverse reaction was sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%), and unsteadiness (3.4%)	Lorazepam is a short-acting benzodiazepine with a duration of effect of about 4 to 8 hours. Primarily because of the possibility of physical and psychological dependence with prolonged use of benzodiazepines, lorazepam is generally recommended only for short-term use (days to a few weeks) for treatment of acute and severe anxiety following a trauma or preceding a medical procedure or while waiting for an SSRI or other anxiolytic to become effective.
<b>Clonazepam</b> Class: benzodiazepine Indications: adult: panic disorder C/A: none Uses: acute anxiety Monitoring: pregnancy testing	Boxed warnings: none Warnings: interference with cognitive and motor performance, suicidality, physical and psychological dependence, risk of use in pregnancy, withdrawal symptoms Precautions: worsening of seizures, hypersalivation, should not be used with alcohol Adverse reactions: somnolence, abnormal coordination, ataxia, depression	Clonazepam is similar to lorazepam, except for its longer half-life and once-daily dosing.
<b>SLEEP AIDS</b> <b>Trazodone</b> Class: serotonergic potentiator with unclear specific mechanism of action. Indications: adult: MDD C/A: none Uses: insomnia Monitoring: pregnancy testing	Boxed warnings: suicidality Warnings and precautions: serotonin syndrome, angle closure glaucoma, activation of mania/hypomania, QT prolongation, orthostatic hypotension and syncope, abnormal bleeding, interaction with monoamine oxidase inhibitors, priapism, hyponatremia, potential for cognitive and motor impairment, discontinuation syndrome Adverse reactions: somnolence/sedation, dizziness, constipation, blurred vision	Trazodone is sometimes used as a sleep aid in low doses, generally 25 or 50 mg. Because of reports of priapism, its use in adolescent boys is limited.

C/A, children and adolescents.

### Anxiolytics

Two benzodiazepine anxiolytics—lorazepam (short-acting) and clonazepam (long-acting)—are commonly prescribed in children and adolescents. Because dependence may develop with long-term benzodiazepine treatment, they are for short-term use only.

Benzodiazepines may be used before painful or stressful medical procedures. They can be used for short-term treatment of anxiety and distress following an acute traumatic incident or while waiting for an SSRI to have an effect. Also, benzodiazepines are used as an adjunctive treatment of schizophrenia.

Benzodiazepines are generally well tolerated. Sedation is the most common concerning adverse event.

Daytime drowsiness can be dangerous when operating a motor vehicle or machinery. Other concerning side effects are unlikely if benzodiazepines are used in the short term and at appropriately low doses.

### Sleep Aids

Insomnia is a common complaint in children with ADHD, anxiety, depression, and other disorders. In general, treatment of the primary psychiatric disorders plus counseling or behavioral approaches to improving sleep hygiene will relieve the insomnia. If not, further evaluation is warranted. Although research data are lacking, various medications are used to treat insomnia in children and adolescents,



especially those with ADHD or autism spectrum disorders associated with sleep problems. Two potential sleep aids, which are among the most commonly used in children, are included here.

Trazodone is an antidepressant approved for treatment of MDD in adults. It is sometimes used in low doses to treat insomnia in adolescents (and adults). Its mechanism of action is not well understood, but its major effect is thought to be on the serotonergic system. The adverse effects profile of trazodone is similar to that of the SSRIs, but trazodone is also associated with priapism, which may limit its use in adolescent boys.

Melatonin is a hormone produced in the pineal gland that is available over the counter, but not by prescription (and, therefore, is not included in Table 62-8). It can reduce initial insomnia. It is not recommended for long-term use. Studies, primarily in adults, indicate melatonin is effective for only 2 to 3 weeks.

Of note, ramelteon, a relatively new FDA-approved sleep aid that is not commonly prescribed for children, is the first in a new class of sleep aids that are melatonin receptor agonists with high affinity for MT1 and MT2 receptors.

## INDIVIDUAL STATE PROGRAMS FOR IMPROVING PRESCRIBING TO CHILDREN AND ADOLESCENTS

In response to recent federal guidelines, all states in the United States are developing programs to monitor psychotropic medications prescribed to children and adolescents. Specific mandates require child welfare and Medicaid agencies to work collaboratively regarding children in foster care and state custody, for whom psychotropic medications are prescribed at disproportionately high rates. These programs range from consultation models promoting collaboration among providers to drug utilization review processes that restrict access when certain criteria are not met. These programs are too new to support a comprehensive assessment of their effect on children, families, and physicians.

## DISRUPTIVE BEHAVIOR AND AGGRESSION

This chapter has focused on the 3 common medication-responsive disorders identified by the AAP Task Force on Mental Health as potentially managed by pediatricians independently. Symptoms of disruptive behavior and aggression also commonly present to pediatricians and may be manifestations of oppositional defiant disorder, conduct disorder, or other behavioral conditions. These disorders were not addressed in this chapter because they typically require comanagement with a mental health specialist and because there is considerable controversy regarding whether medication, targeted at aggression or disruptive behavior *only*, is an appropriate part of a comprehensive treatment plan.

## SUMMARY

Because of the high prevalence of mental health disorders, pediatricians commonly encounter children whose care may involve assessment for, or treatment

### BOX 62-4 Resources for Clinicians

- Additional information about pediatric psychopharmacology can be found at the Johns Hopkins Bloomberg School of Public Health Center for Mental Health Services in Pediatric Primary Care Web site ([web.jhu.edu/pedmentalhealth/index.html](http://web.jhu.edu/pedmentalhealth/index.html)).
- Children in the child welfare system may have unique needs for therapy treatment. Providers can access a Web site to review the evidence base for psychosocial interventions specifically evaluated for children in child welfare (California Evidence-Based Clearinghouse for Child Welfare at [www.cebc4cw.org](http://www.cebc4cw.org)). This information can be used to guide referrals for psychosocial therapy.
- The National Network of Child Psychiatry Access Programs is a consortium of more than 25 state programs that provide collaborative consultative access to child psychiatry expertise ([www.nncpap.org](http://www.nncpap.org)).
- The National Institute of Mental Health life-charting method facilitates prospective tracking of medication adherence, mood symptoms (activation vs depression), sleep, suicidality, and new stressors ([www.cqaimh.org/pdf/tool\\_edu\\_moodchart.pdf](http://www.cqaimh.org/pdf/tool_edu_moodchart.pdf)).
- The US Department of Agriculture Web site has resources for tracking diet and activity ([www.supertracker.usda.gov/default.aspx](http://www.supertracker.usda.gov/default.aspx)).
- The Centers for Disease Control and Prevention Web site has a simple body mass index calculator ([apps.nccd.cdc.gov/dnpabmi](http://apps.nccd.cdc.gov/dnpabmi)).

with, psychotropic medication. The AAP has released recommendations that pediatricians achieve competence in care of children with ADHD, anxiety, and depression—conditions that may, in some instances, benefit from medication. Moreover, pediatricians may encounter children for whom psychotropic medications are prescribed by behavioral health or other specialty providers and who may require monitoring by pediatricians for therapeutic benefit and potential side effects. Thus, an understanding of pediatric psychopharmacology is necessary for primary care pediatric practice. This chapter has proposed a conceptual framework and general guidance for decision making about prescribing and monitoring psychotropic medications in pediatric primary care. There are also numerous resources for pediatricians available online, including those listed in Box 62-4.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *ADHD and Your School-Aged Child* (fact sheet), American Academy of Pediatrics ([pediatrics.aapublications.org/cgi/data/108/4/1033/DC1/1](http://pediatrics.aapublications.org/cgi/data/108/4/1033/DC1/1))
- *Medicines for ADHD: Questions From Teens* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Parents Medication Guide* (Web site), Parents Med Guide ([www.parentsmedguide.org](http://www.parentsmedguide.org))
- *Understanding ADHD: Information for Parents* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

- *What Is ADHD? Questions From Teens* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)

### Medical Decision Support

- *The CRAFFT Screening Tool* (questionnaire), Center for Adolescent Substance Abuse Research (www.ceasar-boston.org/CRAFFT/index.php)
- *Enhancing Pediatric Mental Health Care: Algorithms for Primary Care* (article), *Pediatrics*, Vol 125, Suppl 3 (pediatrics.aappublications.org/content/125/Supplement\_3/S109.pdf)
- *Evidence-Based Child and Adolescent Psychosocial Interventions* (chart), PracticeWise, American Academy of Pediatrics (www.aap.org/en-us/Documents/CRPsychosocialInterventions.pdf)
- *FDA Listing of Authorized Generics* (Web page), US Food and Drug Administration (www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm126389.htm)
- *Mental Health Screening and Assessment Tools for Primary Care* (chart), American Academy of Pediatrics (www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH\_ScreeningChart.pdf)
- *The Resilience Project: Clinical Assessment Tools* (Web page), American Academy of Pediatrics (www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/resilience/Pages/Clinical-Assessment-Tools.aspx)
- *Scoring Instructions for NICHQ Vanderbilt Assessment Scales* (handout), American Academy of Pediatrics (www2.aap.org/sections/dbpeds/pdf/VanderbiltRatingScaleScoringInstructions.pdf)
- *Screen for Child Anxiety Related Disorders (SCARED): Child Version* (questionnaire), University of Pittsburgh (www.psychiatry.pitt.edu/sites/default/files/Documents/assessments/SCARED%20Child.pdf)
- *Screen for Child Anxiety Related Disorders (SCARED): Parent Version* (questionnaire), University of Pittsburgh (www.psychiatry.pitt.edu/sites/default/files/Documents/assessments/SCARED%20Parent.pdf)
- *Sources of Specialty Services for Children With Mental Health Problems and Their Families* (chart), American Academy of Pediatrics (pediatrics.aappublications.org/content/125/Supplement\_3/S126.pdf)
- *Strengths & Difficulties Questionnaires* (assessment) (www.sdqinfo.com)

### Practice Management and Care Coordination

- *New Patient Referral/Consultation Information* (form), American Academy of Pediatrics, in *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* (shop.aap.org)

### AAP POLICY

American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health and Task Force on Mental Health. The future of pediatrics: mental health competencies for pediatric primary care. *Pediatrics*. 2009;124(1):410–421. Reaffirmed August 2013 (pediatrics.aappublications.org/content/124/1/410)

American Academy of Pediatrics Subcommittee on Attention-Deficit/Hyperactivity Disorder and Steering Committee on Quality Improvement and Management. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2011;128(5):1007–1022 (pediatrics.aappublications.org/content/128/5/1007)

Cheung AH, Zuckerbrot RA, Jensen PS, et al. Guidelines for adolescent depression in primary care (GLAD-PC): II. Treatment and ongoing management. *Pediatrics*. 2007;120(5):e1313–e1326 (pediatrics.aappublications.org/content/120/5/e1313)

Zuckerbrot RA, Cheung AH, Jensen PS, et al; GLAD-PC Steering Group. Guidelines for adolescent depression in primary care (GLAD-PC): I. Identification, assessment, and initial management (AAP endorsed). *Pediatrics*. 2007;120(5):e1299–e1312 (pediatrics.aappublications.org/content/120/5/e1299)

### SUGGESTED READINGS

American Academy of Pediatrics. *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit*. Elk Grove Village, IL: American Academy of Pediatrics; 2010

American Academy of Pediatrics. *Caring for Children With ADHD: A Resource Toolkit for Clinicians*. Elk Grove Village, IL: American Academy of Pediatrics; 2011

Enhancing pediatric mental health care: report from the American Academy of Pediatrics Task Force on Mental Health. *Pediatrics*. 2010;125(Suppl 3)

Riddle MA. *Pediatric Psychopharmacology for Primary Care*. Elk Grove Village, IL: American Academy of Pediatrics; 2016

Rosatto NS, Cornell CU, Pappadapulos E, et al. Treatment of maladaptive aggression in youth: CERT guidelines II. Treatments and ongoing management. *Pediatrics*. 2012;129(6):e1577–e1586

## Chapter 63

## PREOPERATIVE ASSESSMENT

Sarah Tariq, MD; Jayant K. Deshpande, MD, MPH

### INTRODUCTION

Ambulatory or same-day surgery provides significant medical, psychological, and economic benefits to children and their families. Hospitals also benefit from the reduced need for beds, lower infection rates, and lower costs. Moreover, pediatric anesthesia is no longer confined to the operating room, and increasingly children receive anesthesia and deep sedation in other settings. The ability to provide safe anesthesia for outpatients in environments outside the operating room and new technologies have also boosted the use of diagnostic imaging such as magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) scans.

These benefits also pose challenges because of the limited time available for the anesthesiologist to

evaluate the child before the procedure. Often, the anesthesiologist may see the patient for the first time on the day of the procedure. Optimum preoperative or preprocedural assessment, therefore, depends on the effective screening of patients by the primary care physician (PCP). The PCP's assessment serves as a first screen for identifying possible risk factors that could lead to complications during anesthesia and surgery.

The goals of this chapter are:

- To enable the PCP to identify medical concerns that are relevant to the anesthesiologist.
- To help the PCP identify the common risks of anesthesia and recognize factors that can lead to adverse events.
- To discuss the optimal preparation of children for surgery for selected conditions.
- To emphasize the importance of a multidisciplinary approach in formulating a care plan for the perioperative child.
- To advocate the implementation of a quality improvement initiative to make processes safer and more efficient, resulting in better utilization of resources while providing the highest quality of care for children.

## IMPORTANCE OF A THOROUGH PREOPERATIVE ASSESSMENT

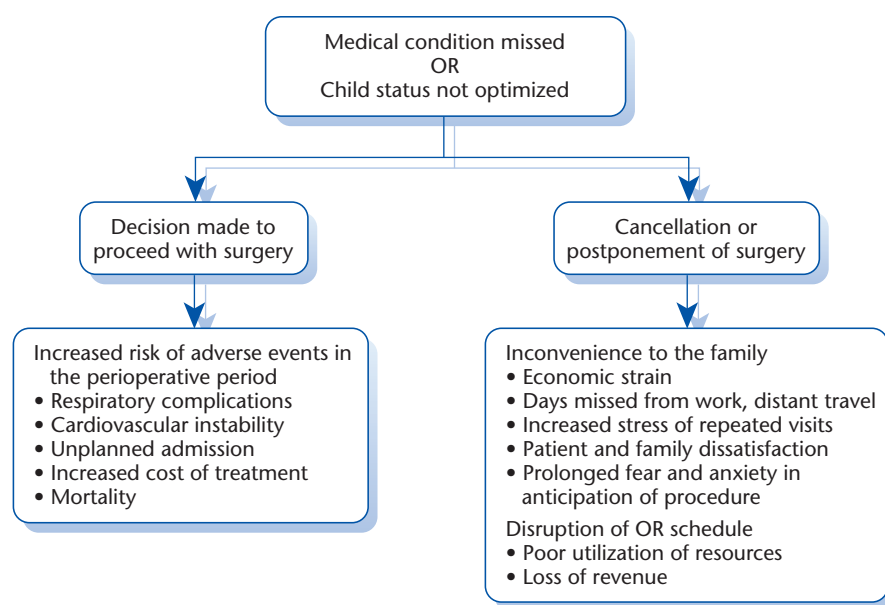
A thorough preoperative assessment is crucial for identifying potential risk factors and optimizing the child's clinical condition, particularly for children with complex medical problems. Inadequate patient preparation before surgery can lead to perioperative complications or to the cancellation of surgery. The last-minute cancellation of surgery has economic and emotional implications for patients and their families. In fact, cancellation of surgery affects all involved—the patients, their families, the physicians, and the

hospital. Common causes of cancellation of surgery are listed in Box 63-1.

An upper respiratory tract infection was cited by Tait and colleagues as the most common cause of same-day cancellation of pediatric surgery. An incomplete medical evaluation was found to be one of the main avoidable causes of day of surgery cancellation in a study by Trentman and colleagues. Another study performed at an Australian pediatric hospital also established that the most common reason for day of surgery cancellation was a medically unfit patient. A comprehensive preoperative evaluation of patients can identify children who need further investigations and children who require optimization of their medical condition before surgery. Patient safety can be severely compromised if a medical condition is overlooked or a decision is made to proceed with surgery despite the inadequate optimization of the child's medical condition. (See Figure 63-1.)

### BOX 63-1 Common Causes of Day-of-Surgery Cancellations

- Upper respiratory tract infections
- Fever
- Lack of intensive care unit (ICU) beds
- Inadequate preoperative investigations
- Medically unfit patients
- NPO (nil per os, nothing by mouth) violations
- Patient nonarrival
- Change in patient's clinical condition
- Cancellation by parents



**Figure 63-1** Effects of inadequate preoperative preparation.

## ANESTHESIA RELATED ADVERSE EVENTS

The risks associated with anesthesia depend on the age and physical condition of the child, the type of surgical procedure, and the choice of anesthesia technique (see Figure 63-2). In a large pediatric anesthesia data review by Cohen and colleagues, neonates were found to have the highest risk for perioperative adverse events. This review also established nausea and vomiting as common complications for children older than 5 years and revealed an overall 35% risk of adverse events in children undergoing anesthesia (as compared to 17% for adults). Another prospective study by Tired and colleagues established a mortality risk of 43 per 10,000 anesthetics in infants younger than 1 year, decreasing to 5 per 10,000 anesthetics in the second year of life.

Some potential anesthetic complications are listed in Box 63-2.

### Pediatric Perioperative Cardiac Arrest Registry

The Pediatric Perioperative Cardiac Arrest (POCA) registry was created in 1994 to better understand the causes, frequency, and risk factors associated with cardiac arrest in children during the perioperative period. Approximately 80 institutions in the United States and Canada voluntarily provided standardized data for each instance of perioperative cardiac arrest. Between 1998 and 2004, the POCA registry reviewed 397 reports of perioperative cardiac arrests in children; of these, 49% were deemed anesthesia related. Cardiovascular causes accounted for 41%, and respiratory issues caused 27% of the arrests, while medication-related causes accounted for 18% of all arrests.

(See Figure 63-3.) Infants and patients with severe systemic disease are at highest risk for perianesthetic mortality.

Flick and colleagues studied the occurrence of perioperative cardiac arrests in 92,881 children who received anesthesia between 1988 and 2005 at a tertiary referral center. They determined the incidence of perioperative cardiac arrest to be 2.9 per 10,000 anesthetics for noncardiac procedures versus 127 per 10,000 anesthetics for cardiac procedures. They further

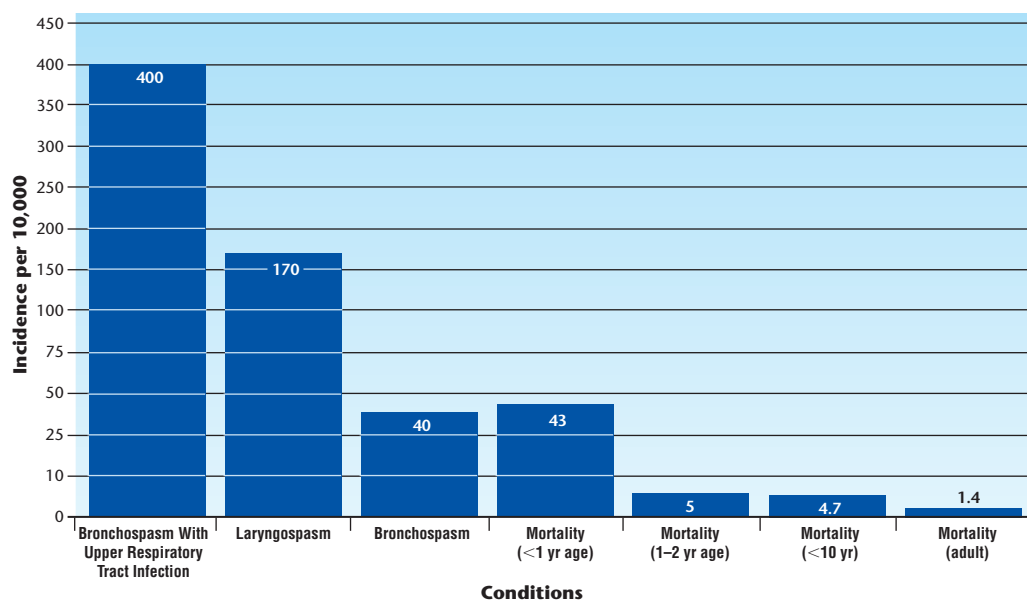
### BOX 63-2 Potential Anesthetic Complications

#### MINOR COMPLICATIONS

- Sore throat
- Nausea, vomiting
- Dental trauma
- Emergence delirium, agitation

#### MAJOR COMPLICATIONS

- Respiratory: laryngospasm, bronchospasm, oxygen desaturation, hypoventilation, apnea, croup, prolonged mechanical ventilation
- Cardiac: bradycardia, hypotension, hypertension, arrhythmias, cardiac arrest
- Neurologic: delayed awakening, seizures, nerve damage, paralysis
- Allergic reactions, anaphylaxis
- Aspiration of gastric contents
- Malignant hyperthermia
- Mortality



**Figure 63-2** Morbidity and mortality from anesthesia in children. (Adapted from Olsson GL, Hallen B: Laryngospasm during anesthesia: a computer-aided incidence study of 136,929 patients. *Acta Anaesthesiol Scand.* 1984;28:567-575; and Morray JP, Geiduschek JM, Ramanmoorthy C, et al. Anesthesia-related cardiac arrest in children. *Anesthesiology.* 2000;93:6-14.)



determined that both the incidence of cardiac arrest and mortality were highest among neonates undergoing cardiac procedures. They concluded that most cardiac arrests were not attributed to anesthesia. (See Figure 63-4.) These findings are divergent from the previous accounts from the POCA data analysis.

### Pediatric Anesthesia Malpractice Closed Claims Registry

The pediatric anesthesia malpractice closed claims registry is another valuable source of information on perioperative risks in children. In this registry, 75% of pediatric claims were made for patients considered generally healthy (American Society of Anesthesiologists physical status [ASA PS] 1 and 2) when undergoing

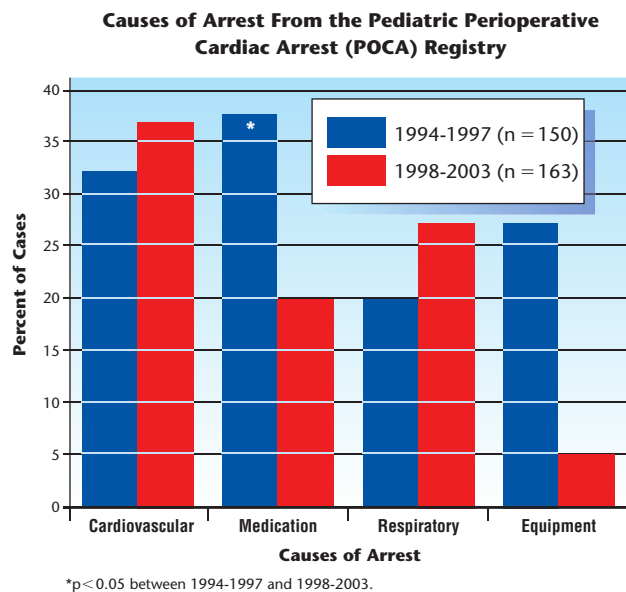
anesthesia. The procedures most commonly cited were dental, ear, nose, throat, and maxillofacial procedures (36%) followed by abdominal procedures (17%). Although these results may be skewed by the frequency of cases performed (ASA PS 1 and 2 children are the most frequently anesthetized, and these are the most common procedures for which children are anesthetized), they suggest that procedures related to the airway are associated with an increased risk of complications and death.

The incidence of anesthesia-related adverse events has been cited as high as 75 per 1,000 anesthetics. The most common adverse events result from respiratory causes during the procedure and vomiting during the recovery period; younger children also are likely to experience respiratory adverse events in the recovery period.

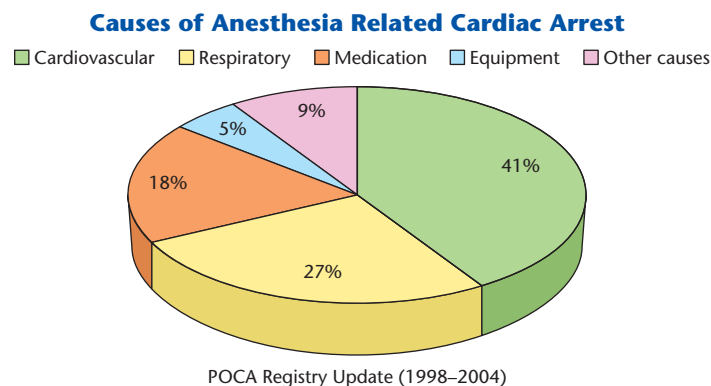
Psychological stress and behavioral complications are additional adverse outcomes in the perioperative experience of the child. The principal risk factors are inadequate family preparation and the lack of preprocedure anxiolysis. Parents who have been inadequately prepared about the process exhibit significant anxiety, which has been demonstrated to be transmitted to the child. Children who experience stressful anesthetic induction often exhibit postoperative maladaptive behaviors, including enuresis, night terrors, and violent behavior. Children requiring repeated invasive procedures can develop a posttraumatic stress-like syndrome.

### The American Society of Anesthesiologists Physical Status Classification

The American Society of Anesthesiologists physical status (ASA PS) classification (Table 63-1) provides a convenient method of summarizing a patient's physical condition and may provide a means of assessing the relative risk of anesthesia. ASA PS 1 patients are healthy and have no underlying disease, whereas ASA PS 4 patients are significantly incapacitated by their underlying disease. Other factors associated with increased preoperative risk are multiple coexisting diseases and the need for emergent surgery. The anesthetic mortality rate in healthy ASA PS 1 children requiring elective surgery is probably less than 1 in 50,000.



**Figure 63-3** Causes of arrest from the Pediatric Perioperative Cardiac Arrest Registry. (From Morray JP, Bhananker SM. *Recent Findings from the Pediatric Perioperative Cardiac Arrest [POCA] Registry*. ASA Newsletter. 2005;69[6]:10-12. Reprinted with permission from the American Society of Anesthesiologists.)



**Figure 63-4** Causes of anesthesia related cardiac arrest

**Table 63-1** American Society of Anesthesiologists Physical Status Classification

CLASS	STATE	CASES
I	Healthy, normal child	
II	Child with mild systemic disease	Controlled asthma, controlled diabetes
III	Child with severe systemic disease	Active wheezing, diabetes mellitus with complications, heart disease that limits activity
IV	Child with severe systemic disease that is a constant threat to life	Status asthmatics, severe BPD, sepsis
V	Child who is moribund and not expected to survive without the procedure	Cerebral trauma, pulmonary embolus, septic shock

Adapted from American Society of Anesthesiologists, ASA physical status classification system. Available at: [asahq.org/resources/clinical-information/asa-physical-status-classification-system](http://asahq.org/resources/clinical-information/asa-physical-status-classification-system). Accessed January 6, 2016.

Children who are candidates for outpatient surgery are generally in the ASA PS 1 and 2 groups. Although initially outpatient surgery was reserved for patients belonging to ASA PS 1 and 2, ASA PS 3 patients increasingly present for outpatient procedures. Because of the increased perioperative risk to these children, direct communication between the PCP and the anesthesiologist is advised well in advance of the planned surgical procedure.

### PREOPERATIVE EVALUATION: NOT “CLEARANCE FOR SURGERY”

Preoperative evaluation of a child going for surgery is not synonymous with clearance for surgery. Clearance for surgery is an outdated concept which often does not relay significant information about a child's condition to the anesthesiologist or perioperative team. Primary care providers can play a significant role in creating a safe perioperative environment by providing an accurate assessment of the child's current medical condition and by working to optimize the child's clinical status in preparation for surgery, thus minimizing the risk to the patient in the perioperative period.

A complete preoperative evaluation comprises the following:

- A thorough history and physical examination
- Laboratory and imaging investigations when indicated
- Management/optimization of the child's medical condition
- Appropriate subspecialty consults when required
- Closed loop communication with the anesthesiologist, surgeon, and other members of the health care team regarding any abnormal findings or special needs. This is particularly required for children with complex medical problems.

### PREANESTHETIC HISTORY

The preanesthetic evaluation should focus on specific elements of the child's medical history and physical examination that may have physiologic consequences during the conduct of an anesthetic. The main concerns involve the pulmonary, cardiovascular, endocrine, hematologic, and neuromuscular systems. The

following information is important to determine the potential risks of anesthesia for each child:

- Birth history: Premature versus full term, complications at birth, neonatal clinical course (particularly respiratory, cardiovascular, and neurologic issues)
- Comorbidities and understanding of the child's optimum clinical condition (for example, best pulmonary functions achievable for a child with asthma on appropriate therapy)
- Current acute illness (eg, upper respiratory infection, asthma exacerbation)
- Developmental delays, autism, or other behavioral-communicative disorders
- Bleeding diathesis (eg, hemophilia, von Willebrand disease, sickle cell disease)
- Allergies, especially to drugs, food, latex
- Current and recent medications
- Child's weight
- Previous surgical procedures and any adverse events
- Previous anesthetics: Ease or difficulty with intravenous access and airway instrumentation, complications
- Family history of anesthesia complications
- Family history of malignant hyperthermia
- History of smoking, alcohol intake, and substance abuse

The remainder of this chapter discusses issues pertinent to the preoperative assessment in a systematic fashion, identifying critical factors that would be of importance to the anesthesiologist caring for children.

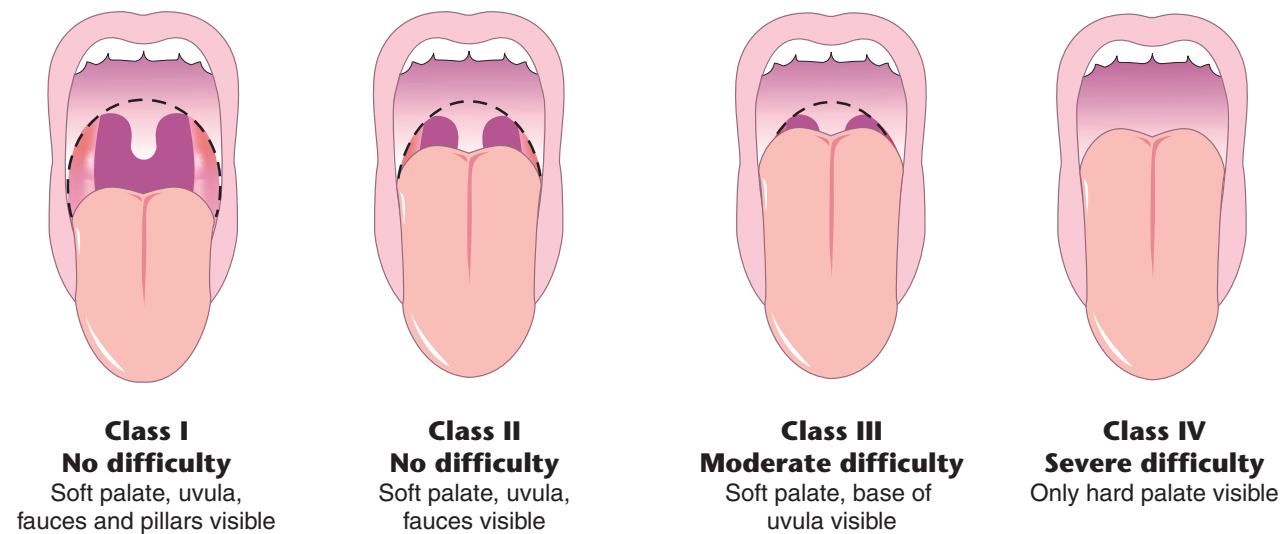
### RELEVANT ASPECTS OF THE PHYSICAL EXAMINATION

The physical examination should determine the patient's general state of health with the aim of specifically discovering any conditions that might complicate anesthesia.

#### General Appearance, Weight, and Vital Signs

The PCP should note the general body habitus, height, and weight (in kilograms). Accurate weight measurement is essential because anesthetic drug dosing is calculated by weight. Preoperative vital signs, including temperature, respiratory rate, heart rate, and blood pressure, should be recorded.

## Mallampati Signs as Indicators of Difficult Intubation



**Figure 63-5** Mallampati airway classification.

### Airway Examination

A thorough examination of the head and neck is essential. The airway examination is especially important. Even when the airway is normal, the PCP should make specific note of adequacy of mouth opening, neck mobility, and the presence of loose teeth. Normal mouth opening, mandibular size, and neck mobility are fundamental to the success of intubation using the most common technique, direct laryngoscopy. Abnormalities in these parameters, either congenital (micrognathia) or acquired (jaw immobility caused by infection, trauma, or irradiation), can lead to great difficulty with intubation, which, if unexpected, can lead to adverse airway events and imperil the life of the child. Alerting the anesthesiologist to these abnormalities helps with appropriate advanced preparation if special anesthetic techniques and equipment (eg, fiberoptic bronchoscope, glidescope, intubating laryngeal mask airway [LMA], etc) are needed for airway management.

Important components of airway examination include:

- Mallampati classification (see Figure 63-5)
- Mouth opening
- Thyromental distance
- Cervical range of motion
- Mandibular or maxillary hypoplasia
- Microsomia
- Presence of loose teeth

The presence of a short neck, large tongue, and a small mandible, midfacial hypoplasia, or maxillary hypoplasia all can lead to difficulty with intubation. In addition to difficulty with intubation, such children may have airway obstruction on induction of anesthesia and difficulty with ventilation. Many congenital syndromes are associated with anatomic abnormalities that may cause difficulty with intubation (see Box 63-3).

### BOX 63-3 Select Conditions Likely to Be Associated With Difficult Airway

- Pierre-Robin syndrome
- Treacher-Collins syndrome
- Mucopolysaccharidosis
- Down syndrome
- Klippel-Feil syndrome
- Choanal atresia (CHARGE syndrome)

### Cardiovascular and Pulmonary Examination

The cardiovascular and respiratory systems are of particular importance because of the significant alterations that take place under anesthesia. For example, children who have significant chest wall or thoracic deformities (eg, severe scoliosis, dwarfism) can have marked cardiorespiratory compromise, exhibited as decreased lung volumes and pulmonary function, and can have myocardial strain evident on electrocardiogram (ECG) or echocardiogram. These children are at a higher risk for intraoperative complications and prolonged postoperative mechanical ventilation. An assessment of preoperative pulmonary and myocardial function is warranted and enables the anesthesiologist to design the optimal anesthetic plan.

### Neuromuscular Examination

An evaluation of the child's neurologic status includes an assessment of the type and extent of preexisting deficits. The child's baseline mental status, especially in children who are developmentally delayed or non-verbal, is important in gauging the child's responses

under anesthesia and in evaluating the progress of the child's recovery afterward. Preexisting neuropathies and neurologic deficits should be documented to differentiate from possible complications from positioning during surgery and regional anesthesia. In particular, muscular dystrophies, myotonic dystrophy, congenital myotonias, and mitochondrial diseases may be associated with life-threatening conditions (malignant hyperthermia, severe hyperkalemia, severe myotonia).

Findings on physical examination that raise concerns for the anesthesiologist include:

- Morbid obesity
- Limited mouth opening, recessed chin, short neck, large tongue, or a small mandible
- Wheezing, rhonchi, or rales on auscultation
- Low baseline room air oxygen saturation
- Presence of a murmur
- Cyanosis
- Fever
- Signs of severe dehydration/hypovolemia, including delayed capillary refill
- Signs of increased intracranial pressure (positional headaches, sundowning, recurrent vomiting, nystagmus)
- Ill appearance
- Poor weight gain
- Excessive bleeding or bruising

## NOTHING BY MOUTH: THE PREOPERATIVE FAST

Patients with large volumes of acidic gastric contents are at risk for pulmonary aspiration and significant morbidity. Because this risk of pulmonary aspiration in healthy children is less than 0.05%, the practice of NPO (*nil per os*) after midnight has been abandoned. The American Society of Anesthesiologists has revised the preoperative fasting guidelines for all age groups (Table 63-2).

Children are encouraged to drink clear liquids to minimize the anxiety, hypovolemia, and possible hypoglycemia that may result from a prolonged preoperative fast. Necessary medications are administered with a sip of water on the morning of surgery. Healthy children are allowed to drink clear fluids until

2 hours preoperatively; breastfed infants can feed until 4 hours preoperatively; nonhuman milk and formula can be consumed until 6 hours before the scheduled procedure. Despite the suggestion of the acceptability of a 6-hour fast after a light meal, most solid food meals have a high fat content, which delays gastric emptying. Because of these factors, many pediatric anesthesiologists require a fast of 8 hours after solid food for elective surgery. Gum chewing increases gastric fluid volume at least two-fold, without clinically significant important buffering of the pH of the gastric fluid, and therefore is generally proscribed in the preoperative period.

Parents often are confused about what constitutes a clear liquid during the preoperative period. Examples of clear liquids include water, clear fruit juices without pulp, carbonated beverages, clear tea, and black coffee.

## PREOPERATIVE LABORATORY EVALUATION

Routine laboratory studies are not required in children for most procedures. Laboratory tests are performed when children have certain clinical conditions or for certain high-risk procedures. Routine preoperative chest radiographs also are not necessary in well children, because they do not detect abnormalities of major anesthetic or surgical consequence.

### Hemoglobin Determination

Serum hemoglobin (Hgb) or hematocrit (Hct) is the most commonly requested preoperative laboratory test. Because the incidence of previously undetected anemia in children undergoing elective surgery is extremely low (0.29%), routine determination of Hgb and Hct is not necessary if the results of studies performed previously as part of well-child care have been normal. A preoperative Hgb or Hct is useful in children with chronic medical illnesses and those about to undergo procedures with the potential for significant blood loss. It may be useful to measure preoperative Hgb in infants younger than 6 months because the physiologic nadir of red blood cell production may cause the Hgb level to decrease to as low as 7 g/dL. Importantly, in infants who were born prematurely, Hgb levels of less than 10 g/dL have been associated with an increased incidence of postoperative apnea. Children of African or African American ethnicity who have not had a Hgb or Hct determination after 6 months of age should have Hgb or Hct determined. Preoperative coagulation studies (prothrombin time, partial thromboplastin time, and platelet count) are useful in children undergoing procedures with an increased risk for intraoperative or postoperative bleeding (eg, posterior spinal fusions, intracranial procedures), even when no history of a bleeding disorder in the child or the child's family exists.

### Electrolyte Abnormalities

Electrolyte abnormalities of any consequence are extremely rare in healthy children; preoperative screening for such deviations is usually unhelpful, and routine preoperative testing is not indicated. However, serum

**Table 63-2**

**NPO Guidelines**

INGESTED MATERIAL	MINIMUM FASTING PERIOD
Clear liquids	2 hours
Breast milk	4 hours
Infant formula	6 hours
Nonhuman milk	6 hours
Light meal	6 hours

From Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures. An updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. *Anesthesiology*. 2011;114:495–511.



electrolytes should be evaluated in children with underlying conditions such as renal insufficiency or in those who are taking diuretics, angiotensin-converting enzyme inhibitors, or other medications that increase the likelihood of an abnormal result. Electrolytes should also be determined in children whose feeding is limited to enteral (nasogastric or gastrostomy tube) feedings or parenteral nutrition.

### Pregnancy Testing

Exposure to anesthetics during pregnancy may be associated with chromosomal abnormalities in the fetus. Therefore, the routine pregnancy screening before anesthesia of all menarcheal females is performed in many institutions. The incidence of a positive pregnancy test result in the preoperative adolescent population ranges from 0.5% to 1.2%. At some institutions it is mandatory to obtain a pregnancy test before anesthesia on all females older than 10 years, using point-of-care urine testing on the day of surgery. When a positive result is obtained the surgical procedure is canceled, and a pediatric social worker is consulted to counsel the patient and family to address the ramifications of the positive test result.

### Miscellaneous Testing

Although the healthy child needs almost no preoperative laboratory tests, the situation is entirely different for children who have the presence or history of an underlying clinical abnormality. For example, a chest radiograph in a child who has a history of chronic aspiration or lower airway disease may point to chronic parenchymal disease or other abnormalities. A child with cardiovascular disease who is taking digoxin or another cardiac medication should have serum sodium, potassium, and digoxin levels measured. An ECG is warranted in a child who has obstructive sleep apnea syndrome (OSAS), bronchopulmonary dysplasia (BPD), congenital heart disease (CHD), or severe scoliosis. Children being treated with anticonvulsants should have serum levels of these medications checked to ensure that they are within the therapeutic range. In these and similar circumstances, preoperative testing is aimed at detecting and quantifying underlying abnormalities associated with known disease that can lead to life-threatening complications during anesthesia.

### Pulmonary Function Tests

Pulmonary function tests are rarely necessary preoperatively in patients with uncomplicated asthma but may be useful in predicting if children who have pulmonary or thoracic cage abnormalities such as scoliosis are at increased risk for anesthetic complications and postoperative respiratory insufficiency. The most common preoperative pulmonary studies are pulse oximetry, forced vital capacity (FVC), and forced expiratory volume in 1 second (FEV1). The absolute values obtained and the ratios of (FEV1/FVC) are useful predictors of the need for postoperative mechanical ventilation among children at risk (eg, in kyphoscoliosis). However, the accurate measurement of FEV1 and FVC requires patient cooperation. Obtaining reliable results in children younger than 6 years is usually not possible.

## PERIOPERATIVE MEDICATION MANAGEMENT

Children may receive medications regularly for many illnesses. Most medications should be given at their usual doses up to and on the day of surgery (see Box 63-4). Some drug regimens need to be adjusted in the perioperative period (see Box 63-5 and Box 63-6).

The decision to stop or continue anticoagulants before surgery is governed by:

- The child's medical condition
- Indication for anticoagulation
- The nature of the surgical procedure

It is prudent to consult with the surgeon, cardiologist, or other involved physicians to guide the decision-making process by weighing the risks of discontinuing the anticoagulant versus the obvious benefit of reduced bleeding complications in the perioperative period. Children taking aspirin or clopidogrel for coronary stents or children who are at increased risk for vascular complications should be evaluated by a cardiologist or other consultant before surgery. Aspirin or clopidogrel should never be discontinued in such cases unless specifically directed by the cardiologist. If deemed appropriate by the cardiologist or another consultant involved, the recommended time frames for discontinuation of medications that can alter hemostasis are given in Box 63-7.

### BOX 63-4 Medications to Continue in the Perioperative Period Including the Day of the Surgery

β-blockers  
 Calcium channel blockers  
 Antiarrhythmics  
 Nitrates  
 Clonidine  
 Digoxin  
 Asthma medications (care may even be escalated 1–2 weeks before surgery)
 

- β-agonists
- Bronchodilators
- Steroid inhalers

 Seizure medications  
 Reflux medications
 

- Proton pump inhibitors
- H<sub>2</sub>-receptor antagonists

 Selective serotonin reuptake inhibitors  
 Insulin (see section on diabetes)  
 Levothyroxine  
 Antithyroid agents  
 Glucocorticoids  
 Benzodiazepine  
 Opioids  
 Tricyclic antidepressants  
 Antipsychotics

### **BOX 63-5 Medications to Continue Until the Day Before Surgery But Hold the Day of the Surgery**

Oral hypoglycemic agents  
Diuretics  
Angiotensin converting enzyme inhibitors and angiotensin receptor blocking drugs (ARBs)

### **BOX 63-6 Medications to Discontinue Preoperatively**

Aspirin (7–10 days)  
Nonsteroidal anti-inflammatory drugs (NSAIDs) (2–3 days)  
Oral contraceptive pills (OCP) (4–6 weeks)  
Monoamine oxidase inhibitors (MAOIs) (2 weeks)  
Hormone replacement therapy (HRT) (4–6 weeks [in conjunction with OCPs])  
Herbal preparations (2 weeks [ASA recommendations])

### **BOX 63-7 Hemostasis Altering Medications to Discontinue Preoperatively**

Aspirin (7 days)  
Coumadin (5 days)  
Clopidogrel (7 days)  
Ticlopidine (10–14 days)  
Dipyridamole (7 days)

Similarly, there is disagreement regarding the decision to continue oral contraceptive pills in the perioperative period. These medications are associated with an increased risk of thromboembolism, so the decision to stop these medications should be weighed against the risk of unwanted pregnancy. For major surgery with high risk of thromboembolism, most experts recommend discontinuing oral contraceptive pills at least 4 weeks before surgery. Most experts favor the withdrawal of hormone replacement therapy 4 to 6 weeks before surgery because of the higher risk of thromboembolism with this therapy.

## **PREOPERATIVE ASSESSMENT AND MANAGEMENT OF SPECIFIC CONDITIONS**

### **Respiratory**

General anesthesia affects pulmonary dynamics profoundly and adversely. Box 63-8 summarizes the effects of general anesthesia on the pulmonary system.

In the setting of preexisting respiratory disease, these effects are exaggerated and can lead to potentially

### **BOX 63-8 Effects of General Anesthesia**

- Decreased functional residual capacity by 15%–20% (this effect can persist for hours after surgery)
- Decreased lung and chest wall compliance
- Increased ventilation perfusion mismatch (V/Q mismatch: increased dead space, increased intrapulmonary shunting)
- Inhibition of hypoxic pulmonary vasoconstriction
- Hypoventilation
- Exacerbation of airway reflexes (laryngospasm, bronchospasm, and increased secretions)
- Decreased contractility of respiratory muscles
- Decreased ciliary clearance
- Depression of central respiratory response to hypoxia and hypercapnia

### **BOX 63-9 Possible Anesthetic Complications in Children with URI**

- Laryngospasm: can lead to negative pressure pulmonary edema
- Bronchospasm: can make ventilation difficult
- Oxygen desaturation
- Severe coughing
- Breath holding
- Post extubation croup
- Unplanned hospital admission
- Prolonged need for mechanical ventilation

life-threatening complications in the perioperative period. The assessment and optimization of a child's pulmonary status is of paramount importance before elective surgery.

### **Upper Respiratory Tract Infection**

*"It's just a cold, why can't my child have surgery?"*

Often pediatric anesthesiologists are faced with the challenge of deciding whether a child with an active or recent upper respiratory tract infection (URI) should undergo anesthesia. No greater difference in perspective exists between the PCP and the pediatric anesthesiologist than in the diagnosis of a URI. To the PCP, the diagnosis is usually one of reassurance. To the anesthesiologist, a URI is a diagnosis that mandates a careful risk, benefit, and consequence analysis (see Box 63-9).

Children with active or recent URI are more likely to have episodes of laryngospasm, oxygen desaturation, bronchospasm, severe coughing, and breath holding during anesthetic induction and emergence. Independent risk factors for adverse perioperative respiratory events in the setting of an active or recent URI are summarized in Box 63-10.

The incidence of perioperative respiratory events is increased 7-fold in children with URI and 11-fold if the child is intubated. The risk of airway complications remains high for up to 6 weeks after a URI, probably

### **BOX 63-10 Risk Factors for Adverse Perianesthetic Respiratory Events Occurring During Acute and Recent Upper Respiratory Tract Infection**

- Age younger than 5 years
- Copious secretions
- Endotracheal intubation required for procedure
- History of reactive airway disease
- History of prematurity
- Parental smoking history
- Upper respiratory infection within the previous 4 weeks
- Wet cough
- Wheezing

Derived from Tait AR, Malviya S, Voepel-Lewis T, et al. Risk factors for perioperative adverse respiratory events in children with upper respiratory tract infections. *Anesthesiology*. 2001;95(2): 299–306.

as a result of altered airway reactivity. Children with URIs undergoing elective cardiac surgery have a 4-fold increased incidence of airway complications at induction of anesthesia, a 2-fold increased incidence of postoperative respiratory complications, a 5-fold increase in postoperative bacterial infections, and an increased risk of an extended stay in the intensive care unit. Mortality during or after administration of an anesthetic in a child with a URI has rarely been reported. Airway events, however, were responsible for almost 30% of all pediatric anesthetic deaths in the most recent summary of pediatric perioperative cardiac arrest registry data. The most common events leading to cardiac arrest in this category are laryngospasm, airway obstruction, inadequate oxygenation, inadvertent extubation, difficult intubation, and bronchospasm, some of which might be related to URI.

Interestingly, several studies have found no significant increase in respiratory complications among children anesthetized during an acute URI, which has led some researchers to advocate against canceling surgery for these children. The physiologic, psychological, and financial implications of delays in surgery must be weighed against the risks of increased perioperative complications of anesthetizing a child who has a URI. Children with systemic manifestations, such as a temperature greater than 101.3°F (38.5°C), purulent nasal discharge, and lower respiratory symptoms such as productive cough, crackles, wheezes, or positive chest radiograph findings, should have the surgical procedure delayed until 4 to 6 weeks after the resolution of symptoms. Surgery and anesthesia can usually be performed safely in children who have none of these symptoms, particularly if they do not require endotracheal intubation. Even in the absence of these symptoms in children with a history of recent URI, adverse events are still possible. Parents should be informed of this possibility and that intra- or postoperative treatment (eg, nebulization of  $\beta$ -agonist for wheezing) may be required.

Parents should also be told that increased adverse perioperative respiratory events occur in children exposed to cigarette smoke at home. (See Figure 63-6.)

### **Asthma**

Asthma is characterized by:

- Chronic inflammation of airway mucosa
- Airway hyperreactivity
- Expiratory airflow obstruction

Many procedures performed routinely during anesthetic management, most notably laryngoscopy and intubation, are potent and intense stimuli that produce bronchospasm in the child with reactive airways. An intraoperative bronchospasm is frightening, is challenging to treat, and can be catastrophic. Ventilation is difficult if not impossible, and may result in hypercapnia, acidosis, hypoxia, cardiovascular collapse, and death. Fortunately, these adverse events need not happen. Maximal preoperative optimization of a child's medical management may prevent, or at the least limit, all of the perioperative complications of asthma. In general, asthma medical therapy must be escalated preoperatively even in asymptomatic children or children with well-controlled asthma to limit or prevent intraoperative bronchospasm. Short courses of corticosteroids in particular are extremely effective in preventing perioperative wheezing, even in patients who have severe asthma. Thus, children who take asthma medications only as needed should use their inhaled  $\beta$ -agonists or oral medications 3 to 5 days preoperatively. Children taking medications on a long-term basis (oral or inhaled) should have steroids added in doses that are normally used for an acute exacerbation. Finally, the child with difficult-to-control asthma and who takes bronchodilators and steroids regularly requires intensification of therapy in preparation for surgery. Under no circumstances should asthma therapy be de-escalated or stopped before surgery.

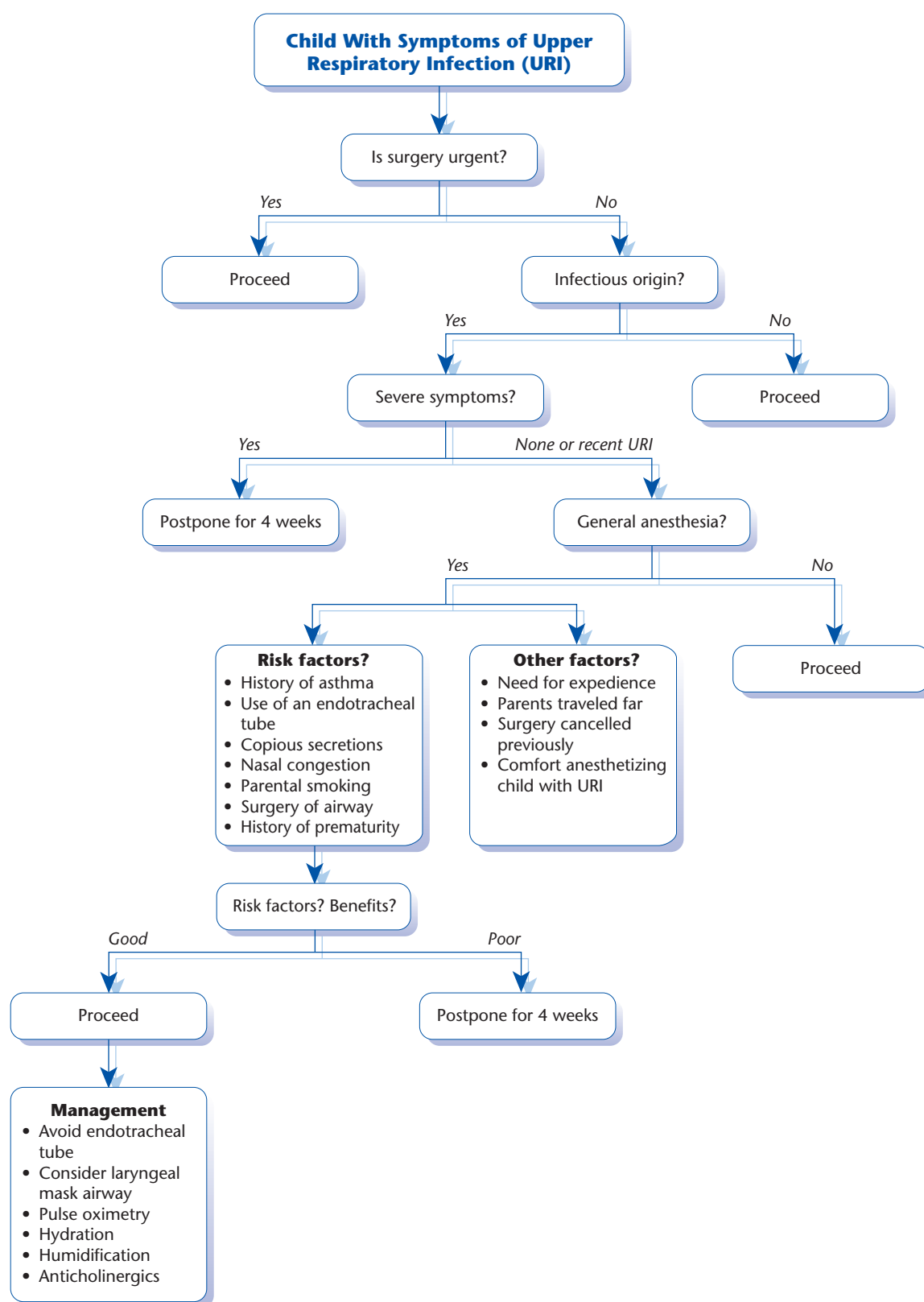
Elective surgery should never be performed in a child who is wheezing actively or who has had a recent asthma exacerbation.

### **Cardiovascular Disease**

A good evaluation begins with a thorough history and physical examination. Compromising this aspect of patient care can lead to adverse outcomes. General anesthesia has several effects on the cardiovascular system (see Box 63-11) that collectively lead to hypotension and decreased cardiac output.

The effects of general anesthesia on the cardiovascular system are more pronounced in the presence of underlying cardiac disease, and the induction of general anesthesia in patients with cardiovascular disease can lead to severe hemodynamic instability and even cardiovascular collapse. Therefore, identifying children with cardiac disease and optimizing their medical condition is of the utmost importance before any elective procedure. Cardiac conditions encountered in the pediatric population include:

- CHD: structural defects and intracardiac shunts (cyanotic, noncyanotic)
- Cardiomyopathy
- Valvular heart disease
- Hypertension



**Figure 63-6** Preoperative decision making in children with upper respiratory infection symptoms. (From Tait AR, Malviya S. Anesthesia for the child with an upper respiratory infection: still a dilemma? *Anesth Analg*. 2005;100:59–65. Reprinted with permission of Wolters Kluwer Health, Inc.)



- Pulmonary hypertension
- Congestive heart failure
- Arrhythmias

The following signs and symptoms may indicate serious underlying cardiac disease and warrant further investigation.

In infants:

- Diaphoresis with feeding or crying (times of increased cardiac demand)
- Poor feeding
- Tachypnea
- Cyanosis/cyanotic spells
- Failure to thrive, poor weight gain
- Certain congenital syndromes (see Table 63-3)

In older children:

- Poor exercise tolerance
- Chest pain
- Palpitations
- Dyspnea on exertion
- Family history of sudden deaths

The finding of a new murmur on examination is concerning. Fortunately, most murmurs (75%–90%) are insignificant or “innocent” and do not require further cardiac workup. Innocent murmurs are also

known as “functional” or “flow” murmurs and have the following characteristics:

- Nature: soft, vibratory, or musical
- Timing: Early systole, an *innocent murmur is never diastolic* (except for a venous hum that is heard during both systole and diastole)
- Grade: Typically not greater than 2/6 in intensity
- Exacerbated during times of increased cardiac output (eg, fever, infection, anemia, and anxiety)

Furthermore, children with innocent murmurs are asymptomatic, have an age-appropriate growth pattern and exercise tolerance, and a normal electrocardiogram. Examples of innocent murmurs include Still’s murmur, pulmonary flow murmurs, venous hum, and the arterial supraclavicular bruit. However, any murmur of questionable status should be evaluated further as it can indicate an intracardiac shunt or valvular heart disease. Moreover, many pediatric syndromes are associated with cardiac anomalies. Children with such syndromes should routinely be screened for the presence of occult cardiac anomalies.

All children who present with signs and symptoms that suggest cardiac disease should undergo a thorough cardiac evaluation before elective surgery, including:

- Hgb and Hct
- Chest radiograph
- ECG
- Echocardiogram
- Consultation with a pediatric cardiologist

In the presence of established heart disease, children should have a recently documented evaluation by the cardiologist (within a year) stating recommendations for perioperative management (the need to continue cardiac medications, etc) and whether infective endocarditis (IE) prophylaxis is required.

### **Infective Endocarditis Prophylaxis**

The American Heart Association guidelines on IE were revised in 2007 (see Box 63-12). These guidelines are

### **BOX 63-11 Effects of General Anesthesia on the Cardiovascular System**

- Slowing of sinoatrial node conduction
- Decreased systemic vascular resistance
- Decreased myocardial contractility

#### **NET EFFECT**

- Hypotension
- Decreased cardiac output ( $CO = HR \times SV$ )

**Table 63-3**

### **Syndromes, Associations, and Disorders With Concomitant Cardiac Involvement**

Down syndrome (trisomy 21)	ASD, VSD, TOF, PDA
DiGeorge syndrome	Conotruncal anomalies
Edwards syndrome (trisomy 18)	VSD, polyvalvular disease, high incidence of CHF
Patau (trisomy 13)	PDA, septal defects, valve abnormalities, dextrocardia
Williams syndrome <sup>a</sup>	Valvular and supravalvular aortic stenosis (which can be critical), coarctation of aorta, coronary artery stenosis
Turner syndrome	Coarctation of aorta, bicuspid aortic valve, HTN
Noonan syndrome	Pulmonary valve dysplasia/stenosis
Marfan syndrome	MVP and mitral regurgitation, ascending aortic dilatation, increased risk for aortic dissection
VACTERL association	VSD, ASD, TOF
CHARGE association	Conotruncal and aortic arch anomalies
Tuberous sclerosis	Cardiac rhabdomyoma, conduction defects
Duchenne muscular dystrophy	Cardiomyopathy
Becker muscular dystrophy	LV dysfunction, cardiomyopathy and heart failure later in life
Mucopolysaccharidases (Hurler, Hunter, Pompe)	Valvular heart disease, cardiomyopathy

<sup>a</sup>Very high risk for perioperative complications

ASD, atrial septal defect; PDA, patent ductus arteriosus; TOF, tetralogy of fallot; VSD, ventricular septal defect.

### BOX 63-12 Highlights of the 2007 American Heart Association Guidelines for the Prevention of Infective Endocarditis

- Bacteremias resulting from activities of daily living are more likely to result in IE than bacteremias from dental procedures
- Even if prophylaxis were completely effective, only an extremely small number of cases of IE may be prevented with antibiotic prophylaxis
- Recommendation of antibiotic prophylaxis is not based exclusively on an increased lifetime risk of developing endocarditis
- Prophylaxis of IE is recommended only in patients with conditions that put them at the highest risk of adverse outcomes should they develop endocarditis
- Antibiotic prophylaxis is no longer recommended for patients with other forms of cardiac conditions not listed
- Antibiotic prophylaxis is recommended only for the dental procedures that involve manipulation of the gingival tissues or periapical tissue of teeth or perforation of the oral mucosa in patients with underlying high-risk cardiac conditions
- Antibiotic prophylaxis is recommended for procedures involving the respiratory tract or infected skin, skin structures, or musculoskeletal tissues only in patients with the underlying cardiac abnormalities outlined
- Antibiotic prophylaxis exclusively to prevent endocarditis is not recommended for gastrointestinal or genitourinary tract procedures
- The recommendation regarding the procedures for which endocarditis prophylaxis was not recommended in the 1997 guidelines remains in effect, including ear or body piercing, tattooing, vaginal delivery, and hysterectomy

Modified from Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis. Guidelines from the American Heart Association. A guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2007;116(15):1736–1754. Copyright © 2007 American Heart Association. Reprinted with permission.

substantially different from previous guidelines and recommend IE prophylaxis for significantly fewer patients. Antibiotic prophylaxis is no longer necessary for genitourinary and gastrointestinal procedures. While previous (1997) guidelines called for antibiotic prophylaxis for patients in high and moderate risk categories, the 2007 guidelines recommend that only patients in the high-risk category require prophylaxis (Box 63-13).

### The Premature Infant

Infants born prematurely (<37 weeks' gestation) are at significant risk of apnea after exposure to sedative drugs and anesthetic agents. (See Figure 63-7.)

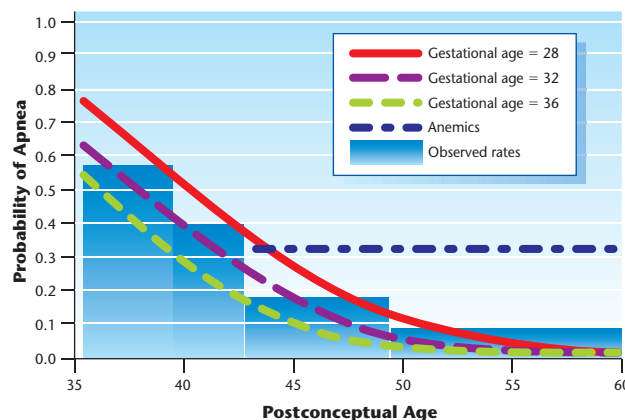
### BOX 63-13 Cardiac Conditions Associated With the Highest Risk of Adverse Outcome From Endocarditis for Which Prophylaxis With Dental Procedures Is Reasonable

- Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
- Previous infective endocarditis
- Congenital heart disease (CHD)<sup>a</sup>
  - Unrepaired cyanotic CHD, including palliative shunts and conduits
  - Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure<sup>b</sup>
  - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
- Cardiac transplantation recipients who develop cardiac valvulopathy

<sup>a</sup>Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.

<sup>b</sup>Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure.

From Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2007; 116(15):1736–1754. Copyright © 2007 American Heart Association. Reprinted with permission.



**Figure 63-7** Predicted probability of apnea in relation to gestational age and postconceptual age. (Cote CJ, Zaslavsky A, Downes JJ, et al. Postoperative apnea in former preterm infants after inguinal herniorrhaphy. A combined analysis. *Anesthesiology*. 1995;82:809–822. Reprinted by permission of Wolters Kluwer Health, Inc.)

This risk of apnea affects the postanesthetic care of infants born prematurely, mandating that those at risk be admitted for monitoring after the procedure. Although most apneic episodes occur within the first 2 hours after an anesthetic, apnea can be seen for up to 12 hours (Box 63-14).

A hemoglobin concentration of less than 10 g/dL increases the risk to greater than the mean for infants of all postconceptual ages.

Nonanemic infants who had been born prematurely and who have attained a postconceptual age (PCA; gestational age added to age after birth) of greater than 56 weeks have less than a 1% risk of developing postoperative apnea.

It is advisable to admit all at-risk patients (those with a PCA of younger than 60 weeks), regardless of the anesthetic technique used, to monitored, high-surveillance inpatient units for 24 hours after anesthesia and surgery. Similarly, infants born at term must be at least 1 month of age to be candidates for outpatient management because postanesthetic apnea has been reported in infants up to 44 weeks PCA. Many centers and some states (eg, Pennsylvania) mandate that children be at least 6 months old to be anesthetized in a freestanding ambulatory surgery center.

More recent studies suggest that postoperative apnea using current anesthetic techniques is much less common than previously reported and recommend overnight observation for premature infants who are younger than 50 weeks PCA (instead of 60 weeks PCA that was the previous recommendation) in the absence of specific risk factors. Factors that were associated with a higher incidence of postoperative apnea include prior history of apnea, low gestational age, very low-birth-weight, low weight at time of surgery, and a complicated neonatal course.

### Down Syndrome

Children with Down syndrome may be at increased risk of atlantoaxial subluxation under anesthesia secondary to ligamentous laxity of the atlantoaxial joint. This predisposes these children to spinal cord injury with airway manipulation during direct laryngoscopy for

endotracheal intubation. The prevalence of atlantoaxial instability (AAI) in patients with Down syndrome is approximately 15%, and an atlantoaxial distance interval of greater than 4 to 5 mm in any lateral view is abnormal. However, the radiographic evaluation of the cervical spine is not accurate before 3 years of age because of inadequate vertebral mineralization and epiphyseal development.

The American Academy of Pediatrics guidelines for health supervision of children with Down syndrome (2011) do not recommend routine cervical spine radiographs for asymptomatic children. The usefulness of lateral cervical radiographs in asymptomatic children is controversial at best. A thorough history and physical examination should be done to search for any signs and symptoms of cervical spine instability. Neurologic manifestations of AAI include neck pain, limited neck mobility, torticollis, numbness and tingling or weakness in an extremity, difficulty walking, gait abnormalities, sensory deficits, spasticity, hyperreflexia, clonus, and bowel or bladder dysfunction. There should be a high index of suspicion for AAI in a child with Down syndrome who presents with deterioration in motor skills, torticollis, or new-onset incontinence.

For the symptomatic child, plain cervical spine radiographs should be obtained in the neutral position. If these show significant abnormalities, no further radiographs should be taken and prompt neurosurgical referral is mandated.

If a child with Down syndrome has signs and symptoms indicative of cervical spine instability, or if the cervical spine radiograph displays an atlantodens interval of greater than 5 mm, elective surgery should be postponed and neurosurgical consultation sought.

Another important consideration for the child with Down syndrome in the perioperative period is the concomitant presence of CHD. Anomalies of the cardiovascular system occur in approximately 40% to 50% of children with Down syndrome. The 3 most commonly associated heart defects are complete atrioventricular canal, ventricular septal defect, and atrial septal defect. Children with Down syndrome should be screened for the presence of heart disease in early infancy. Heart failure may be heralded by tachypnea, feeding difficulties, and failure to thrive. An echocardiogram should be performed, and cardiology consultation should be obtained when appropriate. See Box 63-15 for anesthetic concerns in children with Down syndrome.

#### BOX 63-14 Anesthetic Concerns With Prematurity

##### PERIOPERATIVE CONCERNS

- Postoperative apnea
- Postoperative bradycardia
- Presence of other comorbidities
- Need for admission to hospital after procedure

##### PREDICTORS OF POSTOPERATIVE APNEA

- Low gestational age (<37 weeks premature birth)
- Anemia (<10 g/dL Hgb)
- Previous episodes of apnea
- Complicated neonatal course
- Low weight at time of surgery

#### BOX 63-15 Anesthetic Concerns in Children With Down Syndrome

- Airway: Macroglossia, subglottic stenosis
- Obstructive sleep apnea
- Atlantoaxial instability
- CHD
- Hypotonia
- Hypothyroidism
- GERD

**Table 63-4** Preoperative Considerations for Patients With Cancer**PHYSIOLOGIC EFFECTS OF TUMOR**

Mass effect (anterior mediastinal mass, airway compromise)  
 Tumor lysis syndrome (hyperkalemia, hyperphosphatemia, renal impairment, hypocalcemic seizures, metabolic acidosis, cardiac arrhythmia)  
 Altered hemostasis

Imaging studies (CT, MRI) needed  
 Hydration, correction of acidosis and electrolyte imbalance before elective procedures

Check CBC, increased bleeding risk

**EFFECTS OF CHEMOTHERAPEUTIC AGENTS**

Bone marrow suppression

Anemia

Neutropenia

Thrombocytopenia

Assess need for perioperative blood transfusion  
 Immunocompromised state, increased infection risk, need for protective isolation, perioperative antibiotics  
 Assess need for platelet transfusion, regional anesthesia may be contraindicated  
 Obtain baseline and serial echocardiograms  
 Concern for hypoxia, chest radiograph

Cardiotoxicity

Pulmonary toxicity

Nephrotoxicity

Neurotoxicity

**EFFECTS OF RADIATION THERAPY**

Radiation therapy to the neck or oral cavity can render the airway difficult

**PRESENCE OF CHRONIC PAIN SYNDROMES AND ANALGESIC REQUIREMENT**

Important to determine accurate doses of opioids and other medications used for neuropathic pain

Important to continue opioid analgesics and other medications (antidepressants, anticonvulsants) in the perioperative period to prevent withdrawal

**PSYCHOLOGICAL ISSUES**

Depression, anxiety

Pharmacotherapy, counseling, support groups

Derived from Latham GJ, Greenberg RS. Anesthetic considerations for the pediatric oncology patient—part 1: a review of antitumor therapy. *Paediatr Anaesth.* 2010;20(4):295–304; Latham GJ, Greenberg RS. Anesthetic considerations for the pediatric oncology patient—part 2: systems-based approach to anesthesia. *Paediatr Anaesth.* 2010;20(5):396–420; Haberkern CM, Webel NE, Eisses MJ, Bender MA. Essentials of hematology. In: Cote CJ, Lerman J, Todres ID, eds. *A Practice of Anesthesia for Infants and Children.* 4th ed. Philadelphia, PA: Saunders Elsevier; 2009:191–194.

PCPs can help in the preoperative assessment by:

- Obtaining radiographs of the cervical spine when indicated
- Obtaining echocardiogram and cardiology consultation before a scheduled elective procedure in relevant cases
- Communicating all pertinent findings to the anesthesiologist

**Oncologic Disease**

Children with cancer typically require multiple anesthetics for different procedures, including diagnostic procedures (MRIs, CT scans), major operations for tumor resection, and minor procedures (eg, for central venous access (infusaport placements), radiation therapy, bone marrow biopsies, lumbar punctures).

The anesthetic care of patients with cancer can be particularly challenging and requires a thorough understanding of the physiologic effects of the various childhood tumors, toxicities of chemotherapeutic agents, and systemic effects of radiation treatment. Anesthetic concerns for cancer patients (outlined in Table 63-4) can be categorized as follows:

- Physiologic effects of the tumor
- Toxicities of various chemotherapeutic agents (see Table 63-5)
- Effects of radiation therapy
- Drug interactions between chemotherapy medications and anesthetic agents

- Presence of chronic pain syndromes
- Psychological issues

The preoperative preparation of patients with cancer should take into account both patient factors (eg, type of tumor, complications of therapy) and the complexity of procedure (major surgery versus a minor procedure such as a lumbar puncture). For instance, if a child with cancer is anemic from myelosuppression secondary to chemotherapy, it may be fine to proceed with the anesthetic for a diagnostic procedure (MRI, CT, lumbar puncture, bone marrow biopsy). However, for the same child it may be prudent to plan a preoperative transfusion before a major surgical procedure that can involve blood loss.

Ideally, a multidisciplinary approach involving coordination between the PCP, the pediatric oncologist, the surgeon, and the anesthesiologist should be adopted to ensure the best possible outcome for the patient.

**Endocrine Disease****Hypothyroidism**

The preoperative diagnosis and optimization of patients with hypothyroidism is essential for the provision of safe anesthetic care (see Box 63-16). Untreated hypothyroidism can predispose a patient to serious anesthetic complications, including coma and cardiorespiratory collapse.



**Table 63-5** Adverse Effects of Commonly Used Chemotherapeutic Agents

CHEMOTHERAPEUTIC AGENT	TOXICITY	ANESTHETIC IMPLICATIONS
Bleomycin	Pulmonary fibrosis	Important to elicit history of bleomycin use Obtain chest radiograph in high-risk patients Check room air oxygen saturation Avoidance of high FiO <sub>2</sub> concentration and fluid restriction in the perioperative period
Busulfan	Pulmonary toxicity Hepatotoxicity	
Corticosteroids	Adrenal suppression, hypertension, obesity, hyperglycemia	Need for stress dose steroids perioperatively
Cisplatin	Nephrotoxicity	Check electrolytes
Doxorubicin Daunorubicin	Peripheral neuropathy Cardiomyopathy	Document pre-existing neurologic deficits Baseline echocardiogram before initiating therapy and monitor serial echocardiograms Cardiac consultation in high-risk patients Avoid cardiodepressant drugs
Methotrexate	Myelosuppression Mucositis	Check complete blood count Increased risk of aspiration and airway compromise with mucositis
6-Mercaptopurine (6-MP)	Hepatotoxicity Mucositis	
Vinblastine Vincristine	Hepatotoxicity Neurotoxicity, peripheral neuropathies SIADH	Document existing sensorimotor deficits to distinguish between neuropathies from positioning and complications of regional anesthesia

Derived from Haberkern CM, Webel NE, Eisses MJ, Bender MA. Essentials of hematology. In: Cote CJ, Lerman J, Todres ID, eds. *A Practice of Anesthesia for Infants and Children*. 4th ed. Philadelphia, PA: Saunders Elsevier; 2009:191–192; Maxwell LG, Goodwin SR, Mancuso TJ, et al. Systemic disorders. In: Davis PJ, Cladis FP, Motoyama EK, eds. *Smith's Anesthesia for Infants and Children*. 7th ed. Philadelphia, PA: Mosby Elsevier; 2011:1064–1067.

### BOX 63-16 Anesthetic Concerns in Children With Hypothyroidism

- Cardiac: Bradycardia, myocardial depression, hypotension, torsades de pointes
- Sleep apnea: increased sensitivity to sedatives and narcotics
- Blunted ventilatory response to hypoxia and hypercarbia
- Respiratory muscle weakness
- Airway obstruction resulting from macroglossia and obesity
- Increased sensitivity to anesthetic agents
- Slow drug metabolism (prolonged effects of anesthetic agents)
- Hypothermia
- Resistance to catecholamines

### Hyperthyroidism

Anesthetic concerns in children with hyperthyroidism are summarized in Box 63-17.

Thyroid storm is a hypermetabolic state manifested by hypertension, tachycardia, arrhythmias, and hyperthermia. Differential diagnosis includes malignant hyperthermia and pheochromocytoma.

The primary objective for the child with thyroid disease (hypo- or hyperthyroidism) is for the child to be clinically euthyroid. Children who are euthyroid are generally at no increased perioperative risk.

### BOX 63-17 Anesthetic Concerns in Children With Hyperthyroidism

- Arrhythmias
- Atrial fibrillation
- Hypertension
- Angina, ischemia
- High output cardiac failure
- Exaggerated response to catecholamines
- Thyroid storm
- Goiter (may cause airway compromise)

Children with thyroid disease should have a recent evaluation of thyroid-stimulating hormone and free T<sub>4</sub> levels. In the case of clinical evidence of thyroid disease or abnormal laboratory values, elective surgery should be postponed until a euthyroid state is achieved. This can be done in conjunction with a pediatric endocrinologist. If patients have any cardiac symptoms or if there is any indication of an arrhythmia on physical examination, an ECG should be performed to look for atrial fibrillation, ischemia, or ventricular hypertrophy. Furthermore, any child with a goiter should have radiologic evaluation of the airway; usually a CT scan or MRI is indicated to determine the extent of airway involvement. A large retrosternal goiter or airway involvement can have profound anesthetic implications and significantly alter the anesthetic plan.

**Table 63-6****Anesthetic Concerns in Children With Diabetes Mellitus****DELETERIOUS EFFECTS OF HYPERGLYCEMIA**

Delayed wound healing	Increased infection risk
Impaired phagocyte function	
Hyperosmolarity	Osmotic diuresis leading to Ketosis

Acidosis  
Electrolyte imbalance

**HYPOGLYCEMIA**

Altered mental status	Central nervous system damage
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Tachyarrhythmias  
Hemodynamic instability

**DIABETIC STIFF JOINT SYNDROME**

Immobility of the atlantoaxial joint	Potentially difficult intubation
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**AUTONOMIC NEUROPATHY**

Gastroparesis	Increased aspiration risk
Peripheral neuropathy	Documentation of existing deficits prior to performing regional anesthesia

Silent myocardial infarction

Derived from Copeland KC, Silverstein J, Moore KR, et al. Management of newly diagnosed type 2 Diabetes Mellitus (T2DM) in children and adolescents. *Pediatrics*. 2013;131:364–382; Butterworth JF IV, Mackey DC, Wasnick JD. Anesthesia for patients with endocrine disease. In: Butterworth J, Mackey DC, Wasnick J. *Morgan & Mikhail's Clinical Anesthesiology*. 5th ed. Blacklick, OH: McGraw-Hill Education; 2013:730–731; Specthrie LK, Reed AP. Case 29: diabetes mellitus. In: Reed AP, Yudkowitz FS, eds. *Clinical Cases in Anesthesia*. 3rd ed. Philadelphia, PA: Saunders Elsevier; 2005: 149–154; Salzarulo HH, Taylor LA. Diabetic “stiff joint syndrome” as a cause of difficult endotracheal intubation. *Anesthesiology*. 1986;64(3): 366–368.

**Diabetes Mellitus**

Diabetes mellitus is the most common endocrine disorder in children. It is a metabolic disorder characterized by hyperglycemia secondary to relative insulin deficiency or resistance, or both. The incidence of type 1 diabetes or IDDM has been steady at 5% to 15% in the United States, whereas the incidence of type 2 diabetes or NIDDM has been rising; this has been linked to the increasing obesity rates. See Table 63-6 for anesthetic concerns in children with diabetes mellitus.

Parents and patients should be involved in the planning process. Preoperative assessment and preparation should entail:

- Accurate documentation of pharmacologic regimen (medication type: insulin, oral hypoglycemic agent, dosage, timing)
- Maintaining good glycemic control
- Monitoring and recording the occurrence of hypoglycemic episodes (frequency, severity)

Furthermore, preoperative evaluation of the child with diabetes should also focus on the long-term complications of diabetes. These can be broadly categorized as shown in Box 63-18.

**BOX 63-18 Long Term Complications of Diabetes****MACROVASCULAR COMPLICATIONS**

- Stroke
- Myocardial infarction
- Peripheral vascular disease

**MICROVASCULAR COMPLICATIONS**

- Retinopathy
- Nephropathy
- Autonomic and somatic neuropathy

Laboratory investigations for the diabetic child include blood glucose, urea, creatinine, and electrolytes. Urine analysis should be performed to look for ketonuria. HbA1C measurement is not routinely performed; however, it is a good indicator of long-term glycemic control.

The goals of perioperative management are to avoid hyperglycemia and hypoglycemia. Traditionally, the perioperative target for serum glucose was 120 to 200 mg/dL. However, multiple adult studies have demonstrated that hyperglycemia is an important factor that contributes to increased perioperative morbidity and mortality, and that stringent glycemic control improves perioperative outcomes. A pediatric study by Pham et al (2005) analyzed the effect of tight glycemic control in severely burned children. They established that intensive insulin therapy to maintain normoglycemia was associated with decreased infection rates and improved survival. These recent studies recommend tighter glycemic control (80 to 110 mg/dL), and several protocols for tight glycemic control are emerging.

The disadvantage of maintaining tight glycemic control is the risk for developing hypoglycemia. Close monitoring of serum glucose levels is therefore required.

The general principles for the perioperative management of the patient with diabetes are as follows:

- All efforts should be made to schedule patients with diabetes as the first cases of the day to minimize the fasting period and to minimize disruptions in the treatment regimen.
- Children should have their blood glucose checked on arrival to the hospital the morning of surgery. Ideally, blood glucose level should be lower than 200 mg/dL and elective surgery should be postponed for levels higher than 300 mg/dL.
- Oral hypoglycemic agents are discontinued preoperatively. Metformin should be stopped 48 hrs before surgery because of its potential to cause lactic acidosis. These children can be treated with short-acting insulin preparations given subcutaneously, or a sliding-scale insulin protocol can be started to prevent hyperglycemia.
- Insulin is generally continued in the perioperative period. Typically, the morning dose of insulin is halved on the day of surgery or a sliding-scale

**Table 63-7** Multisystem Effects of Sickle Cell Disease

Hematologic	Hemolytic anemia
Respiratory	Acute chest syndrome: cough, dyspnea, hemoptysis, pleuritic chest pain
Cardiovascular	High-output cardiac failure secondary to anemia, cardiomegaly
Neurological	Increased risk of stroke/CVA
Renal	Renal concentrating defect, hematuria, renal insufficiency
Liver	Chronic hemolysis: jaundice and gallstones
	Frequent blood transfusions: hemosiderosis
Skeletal	Shortening of limbs, gross deformity of joints, osteomyelitis
Dermatologic	Skin ulcers (primarily leg ulcers)
Immunologic	Increased infection risk
Pain crisis	Vaso-occlusive pain crisis involving different sites
Psychological	Depression from chronic pain, chronicity of illness, multiple hospitalizations

Derived from Henderson K. Sickle cell disease and anaesthesia. *Update in Anaesthesia*. 1994. Available at: [www.wfsahq.org/components/com\\_virtual\\_library/media/b3992d0cbf6512b8679cd284616b1235-Sickle-Cell-Disease-and-Anaesthesia--Update-4-1994-.pdf](http://www.wfsahq.org/components/com_virtual_library/media/b3992d0cbf6512b8679cd284616b1235-Sickle-Cell-Disease-and-Anaesthesia--Update-4-1994-.pdf) Accessed January 25, 2016.

insulin regimen is instituted along with an intravenous infusion of 5% dextrose. However, checking the serum glucose level is mandatory and guides management.

- Increasingly, children with IDDM are managed with insulin pumps. Communication between the anesthesiologist and the endocrinologist regarding the perioperative management of insulin pumps may be necessary.
- Blood glucose is checked at regular intervals during the surgery and continued during the postoperative period. A good strategy for improving outcomes is the achievement of tight glycemic control preoperatively and then maintaining the same during surgery and the remainder of the hospital course. A collaborative plan can be devised by the PCP, pediatric endocrinologist, anesthesia physician, and surgeon.

### Sickle Cell Disease

Sickle cell disease is a hemoglobinopathy that is inherited in an autosomal recessive manner. Hemoglobin A (Hb A) constitutes 97% of the normal adult hemoglobin; it comprises 2  $\alpha$  chains and 2  $\beta$  chains. Sickle cell disease results from a single amino acid substitution (valine for glutamic acid) at the sixth position of the  $\beta$  globin chain. Those who are heterozygous for this condition (Hb AS) have sickle cell trait whereas those who are homozygous (Hb SS) have sickle cell disease. The structurally abnormal Hb, *Hb S*, is unstable and polymerizes when deoxygenated, causing the red blood cells to *sickle*. Sickling leads to:

- RBC hemolysis, which leads to anemia
  - Impaired passage of cells through the microcirculation, leading to small vessel obstruction and tissue damage. This causes recurrent episodes of vaso-occlusion and severe pain.
  - Progressive end organ damage
- Sickle cell disease is characterized by progressive end organ dysfunction. Pulmonary and neurologic complications are the leading cause of morbidity and mortality. The table and boxes that follow list the multisystem effects of sickle cell disease (Table 63-7), factors precipitating sickling (Box 63-19), goals for perioperative management (Box 63-20), high-risk patients with

### BOX 63-19 Factors Precipitating Sickling

- Hypoxia
- Infection
- Dehydration
- Acidosis
- Hypothermia

sickle cell disease (Box 63-21), and the investigations needed for these high-risk patients (Box 63-22).

### Mitochondrial Myopathies

Commonly encountered mitochondrial syndromes in the perioperative setting include:

- Leigh disease
- Kearns-Sayre syndrome
- Leber hereditary optic neuropathy

The genetics of mitochondrial myopathies is complex. Mitochondria are inherited from the mother. However, there is variable expression of the disease, because different populations of the mitochondria are transmitted to the offspring. Mitochondria are the major source of energy metabolism in the cell. The muscles and nerve tissue are particularly dependent on mitochondria for energy. The process of oxidative phosphorylation within the mitochondria is the major source of ATP. Conditions that cause the depletion of ATP stores lead to cell breakdown and acidosis. Affected patients are at increased risk of metabolic decompensation, especially during times of increased stress.

The clinical features of mitochondrial diseases include myopathy, cardiomyopathy, encephalopathy, seizures, cerebellar ataxia, and GI symptoms. The preoperative assessment of patients with mitochondrial diseases should entail a thorough assessment of cardiac and respiratory function and the measurement of baseline lactate, electrolytes, and creatine kinase (CK) levels. Increased serum and cerebrospinal fluid lactate and pyruvate levels are seen in these patients. Box 63-23

**BOX 63-20 Objectives in the Perioperative Period**

- Thorough assessment of the patient to identify the presence of multisystem involvement:
  - History of acute chest syndrome
  - History of vaso-occlusive pain crisis, hospitalizations
  - Neurologic assessment (hemiparesis, cognitive impairment)
  - History of chronic analgesic use and requirement
  - History of hematuria, renal insufficiency
- Optimization of cardiopulmonary status:
  - Treatment of acute chest syndrome: hydration, supportive treatment, supplemental oxygen, aggressive bronchodilator therapy, antibiotics, chest physiotherapy, incentive spirometry, and often transfusion.
  - Hydroxyurea therapy and chronic transfusion therapy: these have been shown to decrease the frequency of acute chest syndrome episodes. Inhaled nitric oxide (NO) has been proved to be beneficial for acute management.
- Correction of anemia:
  - The National Institute of Health in their 2002 publication on the management of sickle cell disease recommend: "In patients with SCD-SS, simple transfusion to achieve a hemoglobin of 10 g/dL should be performed before all but the lowest risk procedures."<sup>a</sup>
  - Very high-risk patients may require a more aggressive transfusion approach. Cerebrovascular disease occurs in approximately 8% of patients with SCD. Transfusion programs aimed at maintaining HbSS level below 30% reduce the risk of recurrent stroke from 60%–70% to less than 10%.<sup>b</sup> Children at high risk for cerebrovascular accidents (as identified by abnormalities on MRI and transcranial Doppler exams) are usually maintained on chronic intermittent transfusions, and this regimen should be continued in the perioperative period.
- Prevention of vaso-occlusive crisis:
  - Prolonged fasting should be avoided to prevent dehydration and subsequent vascular stasis that can promote sickling.
  - Ideally, these patients should be admitted before surgery and intravenous hydration should be initiated during the fasting period.
  - Optimize analgesia: a strategy for pain control should be devised, and pediatric pain service (if available) should be involved early in the care of these patients, especially those with frequent pain crisis.
- Any ongoing infections should be treated before elective procedures.

<sup>a</sup>National Institutes of Health, National Heart, Lung, and Blood Institute Division of Blood Diseases and Resources. *The Management of Sickle Cell Disease*, NIH Publication No. 02–2117, Revised June 2002

<sup>b</sup>Lane PA. Sickle cell disease. *Pediatr Clin North Am*. 1996;43:639–664

**BOX 63-21 High-Risk Patients With Sickle Cell Disease**

- Sickle cell chronic lung disease
- Frequent acute chest syndrome
- Reactive airway disease
- Abnormal chest radiograph
- Abnormal pulmonary function test
- History of stroke
- High transcranial Doppler velocity
- On chronic transfusion protocols

**BOX 63-22 Investigations for High-Risk Patients**

- CBC: Baseline Hb and Hct
- Chest radiography
- Pulmonary function tests
- ECG
- Echocardiogram
- Serum BUN and creatinine
- Neurologic imaging
- Liver function tests

BUN, blood urea nitrogen; CBC, complete blood count; ECG, electrocardiogram; Hb, hemoglobin; Hct, hematocrit.

lists the anesthetic considerations for patients with mitochondrial myopathies.

## IMPORTANCE OF MULTIDISCIPLINARY APPROACH

At present, the delivery of health care services is fragmented. There is a need to transition to an integrated model with coordination of patient care services. Information regarding the child's history may be scattered. An important role of the PCP is the compilation of the medical record so that the information is easily available to the child's caregivers on the day of surgery. Also, the communication of abnormal findings, laboratory results, and recommendations of specialists to other health care personnel (anesthesiologists, surgeons) is crucial. A collaborative effort is required to attain improved patient outcomes.

## CONTINUOUS QUALITY IMPROVEMENT MEASURES

Quality and process improvement efforts aim to improve outcomes and promote efficiency and maximal use of resources with the added benefit of cutting costs.

The use of benchmarking systems pertaining to quality-of-care measures is needed. These will help identify and analyze problems in health care delivery. Once issues are recognized, solutions can be implemented. To



### BOX 63-23 Anesthetic Considerations in Children With Mitochondrial Myopathies

- **Respiratory muscle weakness:** Increased sensitivity to volatile anesthetics and narcotic medications predisposes to development of postoperative respiratory insufficiency.
- **Cardiomyopathy:** Warrants judicious use of agents that can further depress myocardial function. Preoperative assessment of cardiac function by echocardiogram is required, and cardiac consultation should be sought when required.
- **Cardiac conduction defects:** Baseline ECG should be obtained preoperatively, and drugs with arrhythmogenic potential should be avoided intraoperatively.
- **Avoid prolonged fasting,** which can lead to an exaggerated metabolic response, causing acidosis. Intravenous hydration with glucose-containing fluids should be initiated while the patient is NPO to avoid anaerobic metabolism. Avoidance of lactated ringer's solution to prevent additional lactate load is advisable.
- **Maintain normothermia:** Shivering secondary to hypothermia can have deleterious effects on already compromised cellular metabolism. Also, hyperthermia is undesirable.
- **Maintain hematocrit** near normal levels to ensure adequate oxygen delivery.
- **Avoid hypotension and hypoxia.**
- **Pain can increase sympathetic tone,** leading to increased oxygen demand, so appropriate pain management is necessary.

improve outcomes for the perioperative child, physicians can use:

- Patient satisfaction surveys
- Data collection and analysis for adverse perioperative events
- Data collection regarding surgery cancellations

### SUMMARY

A comprehensive preoperative evaluation not only entails the identification and management of a child's medical condition but also requires communication with other members of the health care team to formulate a perioperative care plan that best suits the child's needs. The evaluation is fundamental to minimizing the inherent risks of anesthesia and surgery and to improving outcomes. The PCP can contribute by understanding the effects of general anesthesia on physiologic processes and by having an appreciation of the anesthesiologist's concerns. Ideally, a multidisciplinary approach should be adopted to ensure the delivery of the best care and the most efficient use of resources.

### ACKNOWLEDGMENT

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### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Anesthesia and Your Child* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *What Is a Pediatric Anesthesiologist?* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

#### Medical Decision Support

- *National Center for Complementary and Alternative Medicine* (Web site), National Institutes of Health ([nccam.nih.gov](http://nccam.nih.gov))
- *Office of Dietary Supplements* (Web site), National Institutes of Health ([dietary-supplements.info.nih.gov](http://dietary-supplements.info.nih.gov))
- *Pediatric Perioperative Cardiac Arrest (POCA) Registry* (Web page), University of Washington ([depts.washington.edu/asaccp/about-us/other-projects/pediatric-perioperative-cardiac-arrest-poca-registry](http://depts.washington.edu/asaccp/about-us/other-projects/pediatric-perioperative-cardiac-arrest-poca-registry))

### AAP POLICY

American Academy of Pediatrics Section on Anesthesiology and Pain Medicine. The pediatrician's role in the evaluation and preparation of pediatric patients undergoing anesthesia. *Pediatrics*. 2014;134(3):634–641 ([pediatrics.aappublications.org/content/134/3/634](http://pediatrics.aappublications.org/content/134/3/634))

### SUGGESTED READINGS

- American Society of Anesthesiologists Committee. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. *Anesthesiology*. 2011;114:495–511
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## Chapter 64

## POSTOPERATIVE CARE

Jennifer Aunspaugh, MD; Jayant K. Deshpande, MD, MPH

### INTRODUCTION

During the past 25 years, outpatient (ambulatory) anesthesia and surgery have revolutionized the way surgery and anesthesia are practiced in North America. Safe, reliable, inexpensive, and convenient outpatient surgery is an attractive option for parents,

children, their physicians, and perhaps most importantly, their insurers. Surgical procedures that routinely required 1 or 2 days of preadmission hospitalization and 1 to 7 days of postoperative recuperation are now commonly performed without any inpatient hospitalization at all. The cost savings are substantial; the average cost of 1 day in an American hospital is approaching \$5,000 in some areas. Government and private health care insurers are demanding increased use of ambulatory surgery services and will pay for even fewer inpatient procedures. Besides cost savings, outpatient surgery has additional advantages. Ambulatory anesthesia and surgery reduce the psychological trauma of hospitalization and family separation, cause fewer nosocomial infections, and hasten recovery. Examples of surgical procedures that now are routinely performed in children on an outpatient basis are listed in Box 64-1.

### COMPLICATIONS

The incidence of serious postoperative complications in healthy children undergoing ambulatory surgery is relatively low. Common anesthetic and surgical postoperative problems can be classified into early and late, depending on the time of onset. In many instances, the family will call on the larger center hospitalist (general pediatrics), rather than the surgeon or anesthesiologist, to diagnose and treat these problems. The hospitalist must therefore be aware of the

existence of and recommended treatment for these complications.

### SELECTION OF PATIENTS

Guidelines for selecting appropriate procedures and patients for outpatient surgery and anesthesia are continually evolving and are discussed in greater detail in Chapter 63, Preoperative Assessment. In general, the procedure itself should not involve excessive bleeding or open entry into a major body cavity. Patients with comorbidities such as obesity, uncontrolled asthma, upper airway problems, central nervous system (CNS) dysfunction, technology dependence (eg, ventilator-dependent patients) should not be selected to receive anesthesia in a free-standing outpatient surgery center. Additionally, the patient should not require any special postoperative nursing care and must have a responsible adult at home who will be available to provide care until recovery is complete.

### EARLY POSTOPERATIVE ANESTHETIC PROBLEMS

The most frequent complications of general anesthesia are postoperative nausea and vomiting (PONV). These adverse effects are the most common cause of delayed discharge from the postanesthesia care unit (PACU, formerly called the recovery room) and unanticipated hospitalization after outpatient surgery. Risk factors associated with PONV are listed in Box 64-2.

Certain surgical procedures are associated with a greater than 50% incidence of postoperative vomiting. These are listed in Box 64-3.

#### BOX 64-1 Common Outpatient Surgical Procedures by Specialty

##### GENERAL SURGERY

- Incision and drainage of abscesses
- Femoral, inguinal, and umbilical herniorrhaphies
- Lymph node and other diagnostic biopsies
- Central line insertion
- Fistulotomy

##### GENITOURINARY SURGERY

- Orchiopexy, hydrocele
- Circumcision
- Hypospadias repair

##### OTORHINOLARYNGEAL SURGERY

- Myringotomy and tube placement
- Adenoidectomy
- Tonsillectomy
- Bronchoscopy

##### OPHTHALMOLOGIC SURGERY

- Strabismus
- Examination under anesthesia

##### ORTHOPEDIC SURGERY

- Tendon lengthening
- Spica changes
- Fracture reductions

#### BOX 64-2 Patient Risk Factors for Postoperative Nausea and Vomiting

- Female gender
- Obesity
- Age, with risk increasing as the child enters puberty
- Previous history of Postoperative Nausea and Vomiting or motion sickness
- Poorly controlled pain
- High levels of anxiety

#### BOX 64-3 Surgical Procedures Contributing to Postoperative Nausea and Vomiting

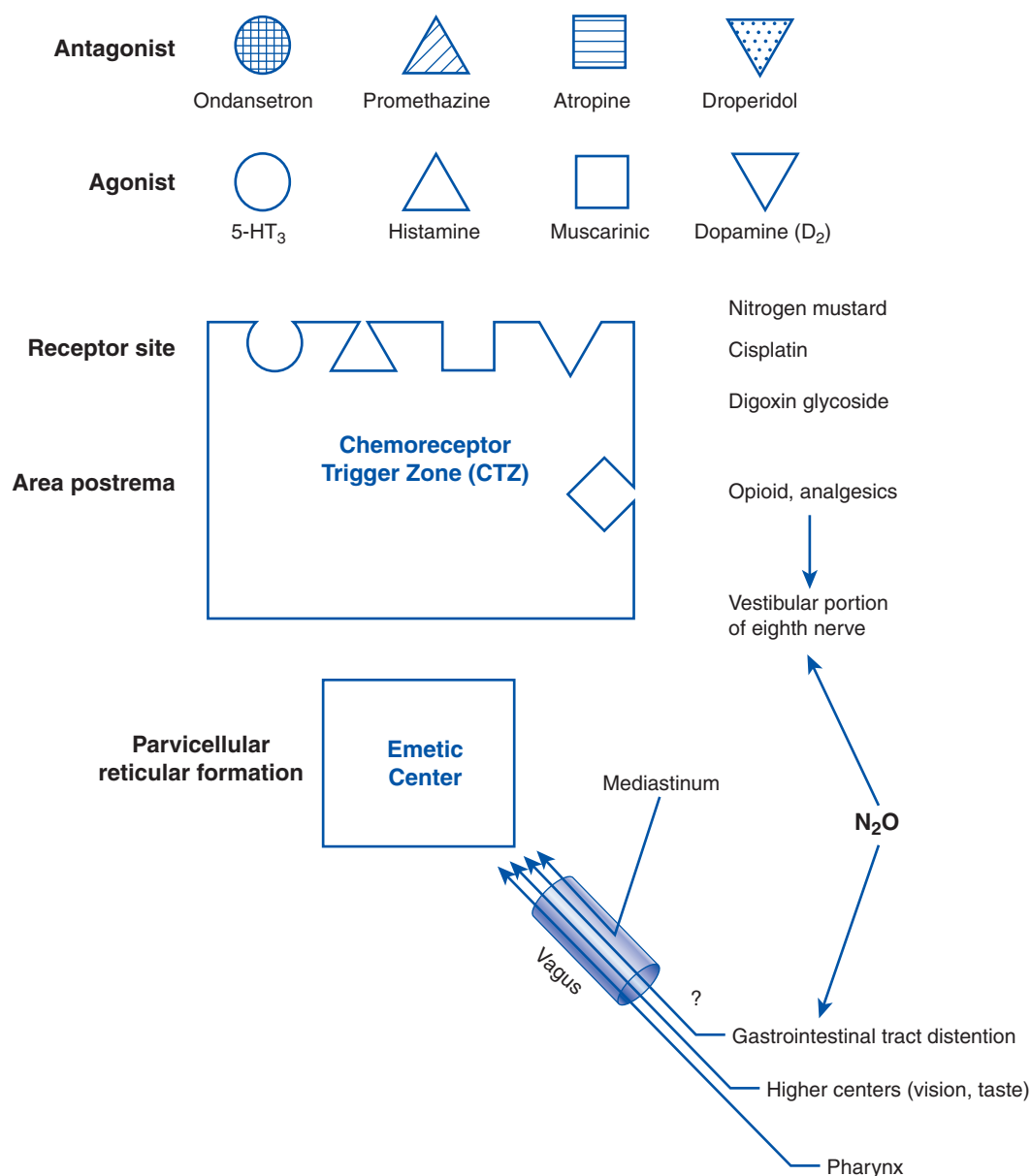
- Tonsillectomy and adenoidectomy
- Tympanoplasty or any middle ear surgery
- Strabismus repair
- Orchiopexy
- Inguinal or umbilical hernia repairs
- Penile surgery
- Major gynecologic surgery

The complex act of vomiting involves coordination of the respiratory, gastrointestinal, and abdominal musculature and is controlled by the emetic center. Stimuli from several areas within the CNS can affect the emetic center. These stimuli include afferents from the pharynx, gastrointestinal tract, and mediastinum, as well as afferents from the higher cortical centers (including the visual center and the vestibular portion of the eighth nerve) and the chemoreceptor trigger zone in the area postrema of the ventral lateral nucleus. The area postrema of the brain is rich in dopamine, opioid, and serotonin receptors. Therefore, blockade of these receptors is an important mechanism of action of the most commonly used antiemetics (Figure 64-1 and

Table 64-1). Several techniques are available to treat or prevent postoperative nausea and vomiting, including altering the anesthetic technique (eg, avoiding the perioperative use of opioids), providing adequate fluid hydration with isotonic solutions intraoperatively, administering antiemetics perioperatively either prophylactically or as treatment (eg, droperidol, phenothiazines, ondansetron, or antihistamines; Table 64-2), and limiting oral intake postoperatively.

### Contribution of Anesthetic Technique to Postoperative Nausea and Vomiting

Certain anesthetic agents and techniques produce more vomiting than others. These are listed in Box 64-4.



**Figure 64-1** The chemoreceptor trigger zone and the emetic center with the agonist and antagonist sites of action of various anesthetic-related agents and stimuli. (From Watcha MF, White PF. *Postoperative nausea and vomiting: its etiology, treatment, and prevention*. Anesthesiology. 1992;77:162-184. Reprinted with permission from Lippincott Williams & Wilkins.)

**Table 64-1** Receptor Site Affinity of Antiemetic Drugs

PHARMACOLOGIC GROUP	DOPAMINE	MUSCARINIC CHOLINERGIC	HISTAMINE	SEROTONIN
<b>PHENOTHIAZINES</b>				
Chlorpromazine	++++	++	++++	+
Prochlorperazine	+++	+	++++	+
<b>BUTYROPHENONES</b>				
Droperidol	+++	—	+	+
Haloperidol	+++	—	+	—
<b>ANTIHISTAMINES</b>				
Promethazine	++	+++	++++	—
Diphenhydramine	+	++	++++	—
<b>BENZAMIDES</b>				
Metoclopramide	++	—	+	++
<b>ANTICHOLINERGICS</b>				
Scopolamine	+	++++	+	—
<b>ANTISEROTONIN</b>				
Ondansetron	—	—	—	++++

Derived from Altman DF. Drugs used in gastrointestinal diseases. In: Katzung BG, ed. *Basic and Clinical Pharmacology*. 8th ed. New York, NY: Lange Medical Books/McGraw-Hill; 2001.

Volatile anesthetics have repeatedly been shown to cause more PONV than intravenous (IV) anesthetic techniques; however, of all of the volatile agents, desflurane has been touted to be associated with less PONV than previous agents. An IV general anesthetic agent, propofol, produces significantly less vomiting and nausea than others, if opioids are not given concomitantly. Indeed, opioids, including morphine, meperidine, fentanyl, codeine, oxycodone, and hydromorphone, have been consistently shown to cause nausea and vomiting. Individual patients may find one opioid drug more nauseating than another; sometimes, changing from one drug to another may decrease the amount of nausea and vomiting. Finally, although regional anesthetic techniques that use local anesthetics either centrally (eg, epidural) or peripherally (peripheral nerve block) produce less vomiting than general anesthetic techniques, using these techniques is rarely possible without concomitant general anesthesia in children.

Avoiding opioids perioperatively may solve only part of the puzzle. Obviously, pain control is essential in children who undergo surgery, and opioids are the most common analgesic drugs used for this purpose (see Chapter 54, Managing Acute Pain in Children). An alternative may be ketorolac, a powerful nonsteroidal anti-inflammatory drug (NSAID), which is almost as potent as morphine as an analgesic but does not produce nausea, vomiting, or respiratory depression. Because NSAIDs affect platelet aggregation and adhesiveness, their use is limited in many patients who are at risk for postoperative bleeding, particularly children who have undergone tonsillectomy. In addition, many orthopedic surgeons forbid the use of NSAIDs during and after operations in which new bone formation is important (fractures, spine fusions)

because NSAIDs have been shown to impair osteoblastic activity. The extent to which this effect is clinically important is controversial. Another alternative to opioids in children is IV acetaminophen, which has just recently been released for clinical use by the US Food and Drug Administration (FDA) for children older than 2 years. Studies with IV acetaminophen have shown that it decreases the need for opioids significantly, therefore lowering the threshold for PONV.

### Contribution of Postoperative Oral Intake to Postoperative Nausea and Vomiting

Many anesthesiologists prefer to restrict patients from taking anything by mouth until they are ready and willing to drink and eat, even if this restriction means that the child leaves the hospital while still fasting. Basically, children must say that they are thirsty, or better still, hungry, and must specifically ask for something to drink or eat before any food or liquid is offered. Even in the youngest patients, the risk for dehydration is low, particularly if IV fluids were appropriately administered perioperatively. In current anesthetic practice, virtually all children undergoing surgery and anesthesia receive hypotonic electrolyte-containing solutions intravenously in the operating room and PACU. If fluids sufficient to supply maintenance and replacement requirements were given during this period, a postoperative fast will be readily tolerated. Thus, just as anesthesiologists are abandoning stringent, prolonged preoperative fasts, they are increasingly appreciating their benefits postoperatively. The studies that questioned mandatory oral fluids before discharge in pediatric patients revealed that neither drinking nor nondrinking worsened



**Table 64-2** Dosage Guidance for Commonly Used Antiemetics

PHARMACOLOGIC GROUP (GENERIC)	BRAND NAME	DOSAGE (mg/kg)	ADVERSE EFFECTS
<b>PHENOTHIAZINES</b>			
Chlorpromazine	Thorazine	IV, PO: 0.5–1.0 every 6–8 hr	Drowsiness, hypotension, arrhythmias, extrapyramidal symptoms; potentiates effects of opioids, sedatives
Prochlorperazine	Compazine	PO, PR: 0.1 every 6–8 hr (maximum dose, 10 mg)	
<b>BUTYROPHENONES</b>			
Droperidol	Inapsine	IV: 0.01–0.03 every 6–8 hr	Drowsiness, hypotension, arrhythmias; droperidol has black box warning: prolongs QT interval, extrapyramidal symptoms; lowers seizure threshold; potentiates effects of opioids, sedatives
Haloperidol	Haldol	IV: 0.01 every 8–12 hr	
<b>ANTIHISTAMINES</b>			
Promethazine	Phenergan	IV: 0.25–0.5 every 6 hr	Drowsiness, hypotension, arrhythmias; contraindicated in patients taking MAO inhibitors; Phenergan contraindicated in children <2 years old because of cases of fatal respiratory depression. <sup>a</sup> Constipation, restless legs, paresthesia, dry mouth, vertigo
Diphenhydramine	Benadryl	0.5–1.0 every 4–6 hr (maximum dose, 50 mg)	
<b>BENZAMIDES</b>			
Metoclopramide	Reglan	IV, PO: 0.05–0.1 every 6 hr	Adverse effects include extrapyramidal symptoms
<b>ANTICHOLINERGIC</b>			
Scopolamine	Hyoscine transdermal scopolamine	IV, PO: 0.005 every 4–6 hr; apply behind ear 4 hr before needed; lasts 72 hr	Adverse effects include dry mouth, blurred vision, fever, tachycardia, constipation, urinary retention, drowsiness, amnesia
<b>STEROIDS</b>			
Dexamethasone	Decadron	IV: 0.1–0.5 every 4–6 hr; most effective when given in conjunction with ondansetron	Adverse effects include hyperactivity and insomnia, but are rarely observed at this dose range
<b>ANTISEROTONIN</b>			
Ondansetron	Zofran, Zofran ODT	IV, PO: 0.15 every 8 hr, (maximum dose, 4 mg)	Adverse effects include bronchospasm, tachycardia, headaches, lightheadedness, may prolong QT interval

IV, intravenous; MAO, monoamine oxidase; ODT, oral dissolving tablet; PO, oral.

<sup>a</sup>FDA MedWatch, [www.fda.gov/Safety/MedWatch/default.htm](http://www.fda.gov/Safety/MedWatch/default.htm). Accessed October 21, 2015.

The chemoreceptor trigger zone and the emetic center with the agonist and antagonist sites of action of various anesthetic-related agents and stimuli.

postoperative nausea or vomiting or prolonged hospital stay. Therefore, drinking oral fluids should not be required before discharge. These changes have been incorporated in the American Society of Anesthesiologists practice guidelines for postanesthetic care. Mandating oral fluid intake before discharge should be done only for selected patients on a case-by-case basis. Unfortunately, many institutions continue to require that patients drink and ambulate before they can be discharged from the hospital or same-day care unit. This restriction almost certainly contributes to the incidence of unanticipated admission to the hospital after outpatient surgery because of vomiting.

### Treatment of Postoperative Nausea and Vomiting

The treatment of PONV is the same as that used for viral gastroenteritis. A cooling-off period of 2 to 4 hours is followed by sips of clear fluids that contain electrolytes (eg, oral rehydration solution, Pedialyte [see Chapter 353, Dehydration]). Each sip is separated by several minutes. Giving fluids or solids prematurely may aggravate the problem. Antiemetics can be used either prophylactically or to treat the problem once it develops. The most common antiemetics are those that block receptors within the vomiting center. Four major neurotransmitter systems play a role in mediating the emetic response: dopaminergic, histaminic,

### **BOX 64-4 Anesthetic Agents That Contribute to Postoperative Nausea and Vomiting**

- Volatile agents such as sevoflurane, isoflurane or desflurane
- Nitrous oxide
- Opioids—these drugs stimulate the chemoreceptor trigger zone in the brain for nausea and vomiting. It is possible that intravenous morphine produces more nausea and vomiting than intravenous hydro-morphone. In respect to oral opioid medications, codeine has been noted to produce more nausea and vomiting than oxycodone.

cholinergic, and serotonergic. Antiemetic drugs may act at more than 1 receptor, but they tend to have a more prominent action at 1 or 2 receptors.

Unfortunately, most of these antiemetic classes, with the exception of the serotonin antagonists, produce sedation, which can interfere with rapid return to baseline function and therefore hospital discharge. In addition, promethazine has been identified as a contributing cause in a significant number of deaths in children younger than 2 years to whom it had been administered for vomiting that occurred either in the postoperative period after hospital discharge or because of gastroenteritis. For this reason, in 2004, the FDA mandated a black box warning. The original warning seemed to apply only to brand-name suppository formulations; the warning was clarified in 2006 to make sure that both health care professionals and parents understood that the warning applies to all formulations.

Medications containing promethazine hydrochloride (HCl) should not be used for children less than 2 years of age because of the potential for fatal respiratory depression. This includes promethazine HCl in any form: syrup, suppository, tablet, or injectable. Cases of respiratory depression including fatalities have been reported with use of promethazine HCl in children less than 2 years of age. Caution should also be exercised when administering promethazine HCl in any form to pediatric patients 2 years of age and older.

This warning is especially germane in children after surgery because they may be receiving opioids for analgesia, which may cause respiratory depression.

In September of 2009, the FDA mandated an additional black box warning for promethazine hydrochloride:

Perivascular extravasation, unintentional intra-arterial injection and intraneuronal or perineuronal infiltration of the drug may result in irritation and tissue damage, including gangrene.

The black box warning will remind physicians that because of the risks of IV injection, the preferred route of administration is deep intramuscular injection and that subcutaneous injection is contraindicated.

This action is based on FDA analysis of postmarketing reports of severe tissue injury, including gangrene, requiring amputation following IV administration of promethazine as well as on FDA review of the current prescribing information for these products. The FDA has determined that the presentation, organization, and content of the prescribing information should be revised to more effectively communicate the risk for severe tissue injury following IV administration.

In addition to the black box warning, the FDA is requiring a revision to the *Dosage and Administration* section to increase the visibility and accessibility of specific recommendations for the maximal concentration (25 mg/mL) and rate of administration (25 mg/min) when IV administration of promethazine is required.

As a result of this most recent black box warning, many pediatric institutions have removed IV promethazine from their formulary or have written specific protocols to follow when administering IV promethazine.

On December 5, 2001, the FDA issued a new black box warning on droperidol, a popular antiemetic for the treatment or prevention of PONV. Droperidol previously carried a warning regarding the potential for sudden cardiac death at high doses (>25 mg) in psychiatric patients. The revised warning suggests that even low doses of droperidol should be used only when other first-line drugs fail.

### **Pharmacology of Commonly Used Antiemetic Drugs**

Site of action, dose, and route of administration of the most commonly used antiemetics are listed in Table 64-1, Table 64-2, and Table 64-3. A new dose form of ondansetron, the oral dissolving tablet, has been found to be an effective and acceptable formulation in children undergoing adenotonsillectomy, as well as in infants and children with gastroenteritis treated in an emergency department. This drug, as with all serotonin antagonists, is slightly more expensive than older antiemetics, but it has the advantage of oral dosing and lack of side effects such as sedation and the extrapyramidal reactions seen with metoclopramide. The effective dose and therefore cost of serotonin antagonists can be reduced by the coadministration of IV dexamethasone in the perioperative period, which has also been shown to prolong the duration of the antiemetic effect of these drugs.

### **Prolonged Nausea and Vomiting**

Nausea and vomiting that persists beyond 12 to 24 hours is unusual and requires evaluation to determine the state of hydration and possible necessity of IV rehydration and to rule out alternative conditions. In rare instances, excessive air swallowing in the postoperative period may lead to acute gastric dilation in young children. Recognition of the characteristic distended abdomen, if present, should be followed by nasogastric decompression.

### **Effect of Postoperative Vomiting on Concomitant Medications**

Postoperative vomiting may interfere with the resumption of long-term oral medication regimens. With few exceptions (monoamine oxidase inhibitors,

**Table 64-3** Most Commonly Used Antiemetics in Order of Use

CLASS	DRUG AND COST PER DOSE
Serotonin antagonists: first choice	Ondansetron (\$0.58/4 mg), dolasetron (\$18.74/12.5 mg)
Steroids	Dexamethasone (\$0.99/4 mg) (most effective if given in conjunction with a serotonin antagonist and has been shown to extend the period of effective treatment up to 24 hrs)
Benzamides	Metoclopramide (\$0.88/10 mg), trimethobenzamide hydrochloride (\$15.03/100 mg)
Phenothiazines	Prochlorperazine (\$3.60/10 mg), promethazine (\$1.18/25 mg)
Butyrophenones	Droperidol (\$4.08/5 mg), haloperidol (\$7.49/5 mg)
Anticholinergics	Scopolamine (\$5.63/0.4 mg), atropine (\$0.96/0.4 mg)

**Table 64-4** Harmful Effects of Undertreated Severe Acute Pain

SYSTEM	EFFECTS
Respiratory	Decreased lung volumes, cough, atelectasis
Cardiovascular	Tachycardia, hypertension, increased myocardial oxygen consumption
Gastrointestinal	Decreased gastric and bowel motility
Genitourinary	Urinary retention
Endocrine	Vagal inhibition, increased adrenergic activity, increased metabolism and oxygen consumption
Central Nervous System	Anxiety, fear, fatigue
Immunologic	Infection, delayed wound healing

oral hypoglycemics, and diuretics), all long-term administered oral medications should be taken on the morning of surgery. Indeed, the question of whether patients should take oral medications on the morning of surgery has become moot because of the liberalization of preoperative fasting guidelines. This ability of patients to take their medications preoperatively has greatly reduced the stress associated with deciding when the use of oral medications can be restarted postoperatively. Most drugs administered in the long term, such as anticonvulsants, bronchodilators, and digitalis, have half-lives of elimination that are long (>12 hr), which means that missing a dose of these drugs for 1 or 2 half-lives (12–24 hr) will have minimal, if any, effect on blood levels. Of course, this situation assumes that therapeutic blood levels existed before surgery began. If vomiting persists beyond 24 hours, then parenteral drug administration may be required.

## POSTOPERATIVE PAIN MANAGEMENT

The treatment and alleviation of pain is fundamental to medical care, and a pain score has been added to clinical assessment as the fifth vital sign. The physician's obligation to manage pain and relieve patient suffering is a crucial element of the professional commitment to patient care. This concept is not merely a lofty ideal; effective pain management produces myriad patient benefits, including reduced morbidity and mortality, early mobilization, and more rapid recovery and return to work, school, and play (see Table 64-4 and Box 64-5.) (A detailed discussion of pain management can be found in Chapter 54, Managing Acute Pain in Children.)

### BOX 64-5 Benefits of Effective Pain Control

- Reduced morbidity and mortality
- Early mobilization
- More rapid recovery
- Rapid return to work
- Rapid return to school and play

## EMERGENCE PHENOMENA AFTER GENERAL ANESTHESIA

Emergence from general anesthesia in healthy patients is often accompanied by transient symmetrical neurologic changes that, under other circumstances, are considered pathologic reflexes. These otherwise pathologic reflexes include sustained and nonsustained ankle clonus, bilateral hyperreflexia, the Babinski reflex, and decerebrate posturing. These reflexes can often be detected within minutes of discontinuing a general anesthetic and may persist for hours, the reason for which is unknown. However, the discovery of focal neurologic deficits in a postoperative patient is never normal. Such neurologic deficits should point to a possible central or peripheral nervous system injury and requires investigation.

Children are prone to disorientation, hallucinations, and, at times, uncontrollable physical activity during emergence from general anesthesia. This hyperexcitable, hyperactive state is sometimes referred

**BOX 64-6 Causes of Emergence Delirium**

- Patient awakens in pain after receiving a vapor anesthetic (eg, sevoflurane, isoflurane, desflurane)
- Patient receives a vapor anesthetic such as sevoflurane independent of any painful stimulus (eg, for magnetic resonance imaging or computed tomography)
- Sensory deprivation (eye bandages or eye lubricant)
- Residual anesthetic
- Awakening in a strange environment (postanesthesia care unit) without parents
- Perioperative use of ketamine
- High level of anxiety preoperatively

Derived from Davis PJ, Greenberg JA, Gendelman M, Fertal K. Recovery characteristics of sevoflurane and halothane in preschool-aged children undergoing bilateral myringotomy and pressure equalization tube insertion. *Anesth Analg*. 1999;88(1):34–38; White PF, Way WL, Trevor AJ. Ketamine—its pharmacology and therapeutic uses. *Anesthesiology*. 1982;56(2):119–136.

**BOX 64-7 Characteristics of Emergence Delirium**

- Thrashing
- Disorientation
- Crying
- Screaming
- Inability to recognize parents or surroundings
- Inconsolability
- Talking irrationally during early emergence from anesthesia

**BOX 64-8 Treatments for Emergence Delirium**

- Small doses of analgesics (eg, fentanyl)
- Flumazenil, if midazolam was administered
- Small doses of dexmedetomidine

to as *emergence delirium* (Box 64-6 and Box 64-7) or *agitation*. Regardless of cause, before discharge from the PACU, most of the disorientation, hyperactivity, excitability, and hallucinatory visual disturbances should be completely resolved (Box 64-8).

Some anesthesiologists may use atropine during induction to counteract the bradycardia seen with succinylcholine in children. Therefore, atropine may be responsible for the characteristics of emergence delirium, in which case it will be accompanied by other features of anticholinergic syndrome (flushed cheeks, mydriasis, and low-grade fever). This reaction may be treated by administration of physostigmine, an anticholinesterase that crosses the blood-brain barrier and reverses the CNS effects of atropine by

**BOX 64-9 New-Onset Postoperative Maladaptive Behaviors**

- Sleep disturbances
- Nightmares (terrors)
- Separation anxiety
- Aggression toward authority
- Loss of nighttime bladder control on the night after surgery
- General anxiety

Derived from Kain ZN, Caramico LA, Mayes LC, et al. Preoperative preparation programs in children: a comparative examination. *Anesth Analg*. 1998;87(6):1249–1255.

potentiating the action of acetylcholine at nerve terminals. However, as a cautionary note, physostigmine has potential for severe side effects and/or risks to the patient if not used by providers who are experienced with this drug. Consultation with an experienced physician is recommended when considering the use of physostigmine. The prevalence of such anticholinergic reactions has been reduced since the replacement of halothane with sevoflurane as the primary gas for mask anesthetic induction in children. Sevoflurane does not cause the bradycardia seen with halothane, making routine use of atropine unnecessary in pediatric anesthetic practice, except when used to counteract the muscarinic effects of anticholinesterase administration for reversal of nondepolarizing muscle relaxant.

Occasionally, some lingering evidence of these behavioral perturbations may persist for 12 to 24 hours. Indeed, children who are extremely anxious before surgery and during the induction of anesthesia are more at risk for developing postoperative negative behavioral changes (Box 64-9) compared with children who seem calm before surgery and during the induction process. Anxious children would benefit from premedication with a benzodiazepine (midazolam) before the induction of anesthesia. Kain and colleagues have clearly demonstrated that oral premedication with midazolam is more effective than either parental presence or extensive preoperative behavioral programs at reducing preoperative anxiety and postoperative delayed alterations in behavior.

Ketamine, in particular, is associated with sleep disturbances after its administration. Although the incidence of nightmares after ketamine administration is lower in children than adults, it has been reported to occur in 5% to 10% of patients who receive it. However, the incidence is mitigated by the concomitant administration of benzodiazepine, usually midazolam. Fortunately, regardless of the cause, sleep disturbance is time limited and rarely persists beyond 48 hours after surgery and general anesthesia. If sleep disturbances become overwhelming, they can then be treated with oral diazepam. In most cases, 1 dose given at bedtime cures the problem completely.

Kain and colleagues state that reducing parental anxiety is an important factor in reducing these



### BOX 64-10 Characteristics of Children at High Risk for Developing Postoperative Maladaptive Behaviors

- Younger children
- Emotional children
- Impulsive children
- Less social children

The parents of these children are significantly more anxious in the waiting area and on separation to the operating room. Derived from Kain ZN, Caramico LA, Mayes LC, et al. Preoperative preparation programs in children: a comparative examination. *Anesth Analg*. 1998;87(6):1249–1255.

postoperative clinical phenomena and preoperative preparation programs directed at parents should be considered (Box 64-10).

## INTUBATION-RELATED COMPLICATIONS

On emerging from a general anesthetic, many children who have been endotracheally intubated or who have experienced either airway manipulation or instrumentation (laryngeal mask airway) will complain of a sore throat. This discomfort can be alleviated with fruit-flavored ice pops, ice chips, or common throat lozenges or sprays once cough, gag, and swallowing reflexes have returned to baseline. Analgesics are rarely required, but if they are, then acetaminophen will usually suffice.

## POSTEXTUBATION STRIDOR

Postextubation stridor, or postextubation subglottic edema, has been a well-recognized entity since airways were first secured by intubation. Children are more prone to develop croup after intubation than are adults because of differences in their airway anatomy. Children have narrower laryngeal and tracheal lumens that are more easily compromised by mucosal edema. Additionally, the narrowest portion of the younger child's airway is at the level of cricoid cartilage and not at the level of the larynx. Given that an endotracheal tube can easily pass through the vocal cords and become wedged in the subglottic area, internal tracheal mucosal injury can occur. Other contributing factors to the development of postextubation stridor are pre-existing subglottic stenosis or airway reconstructions, traumatic or repeated intubations, coughing (*bucking*) on the tube, changing the patient's position after intubation, and providing general anesthesia to children who have a current or recent upper respiratory tract infection.

The incidence of postintubation croup has decreased from 6% to 1% of all endotracheally intubated children. This reduction has occurred through the use of sterile, implant-tested endotracheal tubes and the routine intraoperative use of humidification of the administered gases and, in children younger than 5 years, by using appropriately sized (air leak pressure

<30 cm of water), uncuffed endotracheal tubes. Children who have Down syndrome may be at increased risk for this complication because of the increased incidence of occult subglottic narrowing.

The treatment of postintubation croup is similar to treatment of viral laryngotracheitis. Humidification of inhaled air is effective in most cases. In rare cases, positive pressure (noninvasive or invasive) or heliox may be required. Nebulized racemic epinephrine therapy is rarely necessary. If it is, then these patients should not be discharged from the PACU to their homes. Rather, they should be admitted for several hours of observation because of the potential for rebound edema formation. The efficacy of corticosteroids in treating postintubation croup has been controversial, although most studies have shown it to be effective. Most anesthesiologists will prescribe dexamethasone for this problem, even though no controlled, prospective trials have validated its use for this purpose.

## SUCCINYLCHOLINE-INDUCED MYALGIA

In the past, many anesthesiologists commonly used succinylcholine, a short-acting, depolarizing muscle relaxant, to facilitate intubation of the trachea in children. Because of the risk for fatal hyperkalemia in children with undiagnosed Duchenne muscular dystrophy when succinylcholine is administered, it is used less frequently. The use of succinylcholine by anesthesiologists caring for children has declined in favor of relatively fast-onset, nondepolarizing muscle relaxants such as rocuronium. Use of succinylcholine is now reserved for patients who have no known risk for malignant hyperthermia or hyperkalemia and who need true rapid-sequence intubation because of intestinal obstruction or increased gastric contents from a recent meal. Succinylcholine administration in all children normally will result in some damage to the muscle cell, with leakage of intracellular potassium. Some degree of myalgia and increased blood levels of creatinine phosphokinase and myoglobin are expected complications of succinylcholine administration. To some degree, the magnitude of these perturbations can be avoided by pretreating the patient with small doses of a nondepolarizing muscle relaxant or calcium. The myalgia can be intense and as debilitating as the myalgia produced by an influenza infection. Treatment is supportive, and the pain usually resolves over several days.

## EARLY POSTOPERATIVE SURGICAL PROBLEMS

### Fever

Postoperative fever has several possible causes, which can be remembered as the 4 Ws: wind, wound, water, and walker (Table 64-5). Pyrexia (rectal temperature >101.2°F [38.5°C]) within 24 hours of operation and general anesthesia is common and usually caused by atelectasis. Postoperative atelectasis has many causes. Endotracheal intubation, inhalational general anesthetics, and the use of nonhumidified gases all depress ciliary motion within the tracheal-bronchial tree and

**Table 64-5** Common Causes of Postoperative Fever

SITE	ETIOLOGY	TIME	INCIDENCE	SIGNS AND SYMPTOMS	DIAGNOSIS	THERAPY
Wind (lungs)	Atelectasis	24–48 hr	Very common	Cough, shortness of breath, retractions	Examination, chest radiograph	Cough, deep breathing, incentive spirometer
Wound (operative site)	Infection	>24 hr to 7 days	Rare	Pain, erythema, induration	Examination, wound cultures	Antibiotics, open wound
Water (urinary tract)	Urinary tract infection	3–5 days	Very rare	Dysuria, hematuria	Examination, urinalysis, culture	Remove indwelling catheter, antibiotics
Walker (legs)	Deep vein thrombosis	>3 days	Extremely rare	Swelling, heaviness of lower extremities, superficial venous congestion, palpable cord	Examination, duplex Doppler, venogram	Bed rest, elevation, heparin (Coumadin), thrombolytics

thereby interfere with normal pulmonary clearance mechanisms. When these factors are combined with small tidal volume breathing, somnolence, splinting caused by pain, and cough suppression caused by pain or opioid analgesics, atelectasis occurs. Incentive spirometry alone is not recommended for routine use in the preoperative and postoperative settings to prevent postoperative pulmonary complications. It is recommended that incentive spirometry be used with deep breathing techniques, directed coughing, early mobilization, and optimal analgesia to prevent atelectasis and postoperative fever. Indeed, this feature may be one of the important medical advantages of ambulatory surgery because patients are more likely to be up and about when they are at home rather than in the hospital.

Other causes of postoperative pyrexia are rare. Yeung, Buck, and Filler, in a retrospective analysis of the postoperative course of 256 febrile children at the Hospital for Sick Children in Toronto, Ontario, found that only 4 had infections that required treatment. Interestingly, all 4 of these children had significant and obvious associated signs of infection (local tenderness, crepitation, or erythema at the incision site; tachypnea, cough, dysuria, and headache). Most patients with low-grade postoperative fever require only a physical examination to differentiate between a septic and non-septic process. Extensive (and expensive) diagnostic workups are rarely indicated. Indeed, in most patients, fever in the early postoperative period is so common that it can be regarded as a normal response to operative trauma and general anesthesia. Other unusual causes of postoperative fever include urinary tract infection, dehydration, infected IV access sites, thyroid storm, pheochromocytoma, and malignant hyperthermia. Urinary tract infections do not usually produce symptoms in the immediate postoperative period. Rather, they are a cause of late postoperative fever, usually occurring 3 to 5 days after operation. These children generally are symptomatic and complain of dysuria. Infants may have hematuria. The fever associated with malignant hyperthermia usually starts intra-operatively. Malignant hyperthermia is discussed in more detail in Chapter 63, Preoperative Assessment.

Postoperative wound infections are a potential serious complication. Surgical consultation is recommended as soon as possible so that the appropriate treatment and wound care is provided in a timely fashion.

### Drainage

A small amount of serosanguineous drainage in the postoperative dressing is normal and should not be a cause for alarm. Persistent bleeding requires immediate surgical attention.

Serosanguineous discharge from the operative site 2 to 3 days after the operation may be caused by a superficial hematoma just below the incision site. A hematoma can be recognized by its characteristic ecchymosis and fluctuance. Small hematomas directly below a wound, umbilicus, or scrotum, usually spontaneously drain or resorb. If the hematoma progressively expands, it may then require operative exploration to evacuate the clot and control any ongoing bleeding. In general, a nonexpanding hematoma will usually resolve within 4 to 6 weeks after surgery. If the wound hematoma is associated with pain, then the child should be examined by the operating surgeon.

Serous drainage from a wound may be caused by creation of a large dead space during the operative procedure or by liquefaction of adipose tissue. In general, seromas caused by dead space usually drain 4 to 7 days after surgery, whereas liquefaction of adipose tissue, characterized by yellow drainage, occurs 2 to 3 weeks after surgery.

Regardless of size, hematomas and seromas are excellent culture media for bacteria and increase the likelihood of wound infection. Both of these postoperative problems should be closely watched for and are usually characterized by the triad of pain, wound dehiscence, and persistent drainage.

### Postoperative Bleeding

Persistent bleeding is defined as bleeding or ooze that continues for more than 6 to 8 hours after the operation or a need to change a blood-soaked wound dressing more than twice in the first 6 to 8 hours after

surgery. It almost always indicates inadequate hemostasis and is usually caused by a superficial skin arterial bleeding site, although coagulopathy might also be responsible. Until the bleeding site is investigated and controlled by the operating surgeon or the surgeon's designee, direct digital pressure applied to the wound will slow or stop the flow of blood.

### Post-tonsillectomy Hemorrhage

The incidence of post-tonsillectomy hemorrhage is estimated to be 2% to 4%, with 1% to 2% of patients who have tonsillectomy requiring additional operation. The mortality rate is 1 in 15,000 bleeding episodes. Bleeding that occurs after tonsillectomy may occur early (in the first 24 hours) or late (5–14 days after surgery). Early bleeding is generally caused by failure of hemostasis and may be because of coagulopathy, whereas late bleeding results from dislodgement of the scab from the operative bed. Either form may be severe and life threatening and requires immediate emergency evaluation. Blood clots in the airway may acutely compromise the airway and can be life threatening. Rehydration with isotonic fluid is always required because hemorrhage is frequently associated with history of poor postoperative fluid intake and volume contraction resulting from blood loss. Transfusion, although unlikely, may be required even if a subsequent operation is performed and control of bleeding is achieved.

## MISCELLANEOUS EARLY POSTOPERATIVE PROBLEMS

### Awareness

Awareness refers to a patient's explicit postoperative recall of events during a procedure performed under general anesthesia. The incidence of this phenomenon in adults has been found to be 0.1% to 0.2% in low-risk surgical procedures, but as high as 43% during traumatic surgery. Lopez and colleagues found the incidence of recall in pediatric patients to be 1.2% and as high as 2.7%. Auditory and tactile sensations are most frequently recalled more than pain, anxiety, and paralysis, as in adult patients. Lopez and colleagues also found that the only predictive factor identified was multiple manipulations of the airway. Those children were at an eight times higher risk for developing awareness. This is unlike adults, in whom it has been reported that the use of muscle relaxant or the absence of nitrous oxide in the anesthetic management is a predicting factor for the development of recall.

Many earlier studies have suggested that an extended follow-up is relevant for the detection of awareness. Lopez and colleagues interviewed patients twice during the study, once within 36 hours of the procedure and again 1 month after the procedure. The later interview could help a child elaborate a more coherent and structured representation of the events that took place during the pre-, intra- and postoperative periods.

Previous studies have used the Brice Interview tool for detecting recall in adults. This tool is hardly applicable to children because its contents are not adapted to their cognitive abilities. Lopez and colleagues took

### BOX 64-11 Low Risks for Urinary Retention

- General anesthesia, peripheral nerve blocks, monitored anesthesia care
- Nonpelvic and nonurologic surgery
- Most patients undergoing outpatient gynecologic surgeries (transvaginal, or pelvic laparoscopy) who undergo intraoperative bladder drainage
- Most patients having a spinal, caudal, or epidural anesthesia with short-acting local anesthetic such as lidocaine, procaine, or 2-chloroprocaine

Derived from Souter KJ, Pavlin DJ. Bladder function after ambulatory surgery. *Ambulator Surg.* 2005;12:89–97.

the Brice Interview tool and adapted it to the cognitive capacities of the child being interviewed. They found that this enhanced the detection of awareness in the population studied. (See the Tools for Practice Section for the questionnaire used by Lopez and colleagues.)

### Urinary Retention

In contrast to adults, urinary retention is rare in pediatric surgical outpatients. Most children who undergo surgery through the inguinal canal void within 8 hours of the operation, regardless of their intraoperative anesthetic technique or their postoperative analgesic regimen, which included parenteral and enteral opioids or regional anesthesia (caudal epidural blockade or ilioinguinal-iliohypogastric nerve blocks), or both. This finding is significant because, theoretically, opioids and regional anesthetics, particularly caudal epidural blockade, may interfere with the neural mechanisms responsible for emptying of the bladder. In fact, many investigators who argued against the routine use of caudal anesthesia or opioids (or both) for the treatment of postoperative surgical pain based their opinions on the theoretical risk for urinary retention. Many surgeons, anesthesiologists, and ambulatory care administrators have insisted that children void before discharge after outpatient procedures that require anesthesia. However, many patients simply cannot void on command, particularly in the strange setting of a PACU or hospital. The knowledge that all patients void within 24 hours of operation and virtually all spontaneously void within 10 hours of a procedure strongly suggests that voiding before discharge is unnecessary. Box 64-11 lists common low-risk surgical scenarios for urinary retention; Box 64-12 lists some high-risk scenarios.

To minimize bladder distention, children and adolescents should be encouraged to urinate immediately before coming to the operating room and as soon as possible postoperatively. In some practices, pediatricians and other physicians do not routinely require patients to void before postoperative discharge from the PACU. Exceptions to this rule include patients who complain of lower abdominal distention and discomfort. These patients are initially treated with ambulation, in the case of the older child or adolescent,

**BOX 64-12 High Risks for Urinary Retention**

- Pelvic surgery (hernia, rectal, penile, or urologic)
- Positive family history of retention or spinal cord disease
- Spinal, caudal, or epidural anesthesia with agents of long-acting duration such as bupivacaine, tetracaine, and ropivacaine
- Use of neuraxial opioids combined with local anesthetics

Derived from Souter KJ, Pavlin DJ. Bladder function after ambulatory surgery. *Ambulator Surg.* 2005;12:89–97.

or gentle pressure on the lower abdomen, in the case of infants. If these measures do not lead to voiding and amelioration of symptoms, then bladder catheterization should be performed. Patients requiring bladder catheterization should then be observed for their ability to urinate spontaneously. If bladder function does not return, then the anesthesiologist and the patient's surgeon should decide whether a bladder catheter should be reinserted and if hospitalization is indicated. Nevertheless, the need for bladder catheterization is rare. In the experience of some physicians, urination after outpatient surgery requires a *less is more* attitude; that is, the more attention the physician pays to this issue, the more problems are created.

**Scrotal Swelling**

Scrotal swelling and concomitant discoloration of the scrotum commonly occur after inguinal herniorrhaphy and hydrocelectomy. Initially, this process can produce swelling alone and may progress to bluish discoloration as bleeding and clot lysis occur. In general, the problem is usually the result of bleeding from the cut edge of the peritoneal sac derived from either a hernia or hydrocele. The swelling and color change should resolve in 4 to 6 weeks. However, if fever, erythema, tenderness, and progressive enlargement of the hemiscrotum occur, then an urgent consultation with the patient's surgeon is needed. In many instances, such patients require additional exploratory surgery and operative evacuation of the hematoma through a suprainguinal or trans-scrotal approach.

**LATE POSTOPERATIVE SURGICAL PROBLEMS**

Pyrexia (rectal temperature greater than 101.2°F [38.5°C]) 48 hours or more after outpatient surgery is unusual and may indicate a serious wound infection (see Table 64-5). This circumstance requires evaluation and examination by the patient's physician or, preferably the patient's surgeon. The wound is examined for signs of inflammation, such as heat, pain, redness, and swelling. If any of these signs or symptoms is present, then the operating surgeon should be informed immediately so that appropriate treatment and wound care can be provided.

**BOX 64-13 Risk Factors for Venous Thromboembolism (VTE) in the Postoperative Period**

- Immobility
- Major lower extremity orthopedic surgery
- Spinal cord injury
- Major trauma or trauma to the lower extremities
- Previous history of deep vein thrombosis, VTE, or pulmonary embolism
- Pregnancy
- Oral contraceptive use
- Inflammatory bowel disease
- Nephrotic syndrome
- Burns
- Obesity
- Central venous catheter in the lower extremity
- Known acquired or inherited thrombophilia
- Acute infection

**VENOUS THROMBOEMBOLISM**

Although not as common as in adults, venous thromboembolism (VTE) occurs in children in the postoperative period, with the incidence increasing in adolescence. The physician should be alert to symptoms of VTE, such as extremity pain, swelling, and discoloration, which may indicate deep vein thrombosis and should be referred for immediate evaluation. Patients at highest risk are those who are immobilized after surgery and have at least 1 other risk factor. Risk factors for VTE are listed in Box 64-13. Patients who develop VTE are at risk for pulmonary embolism, which has a mortality rate as high as 20%. Symptoms of pulmonary embolism include dyspnea, chest pain, cough, hemoptysis, and fever. Patients at risk for VTE should receive prophylactic measures, which may include compression stockings or pneumatic sequential compression devices (or both) until ambulatory. Patients with 3 or more risk factors may be treated with pharmacologic prophylaxis: subcutaneous heparin or low-molecular-weight heparin.

**PRACTICAL ASPECTS OF THE POSTSURGICAL WOUND**

Wound healing represents a highly dynamic, integrated series of cellular physiologic and biochemical events. The morphologic events that make up the healing of closed wounds include the following: inflammation, epithelialization, cellular influx, and fibroplasia. The inflammatory phase begins immediately. During its early stages, white blood cells migrate into the wound and engulf and remove cellular debris and tissue fragments. This phase sets the stage for subsequent events in the healing process.

After dead material is removed, the epidermis and dermis immediately adjacent to the wound edges begin to thicken within 24 hours after injury. Within



48 hours, the entire wound surface is reepithelialized. During this critical period, the wound should be kept dressed and dry. Thus, wound dressings are not required after 48 hours. Wound contamination with stool and urine should be cleansed with water or saline, and the overlying dressing should be replaced. Detergent soaps and peroxide should be avoided.

Between days 2 and 3, an influx of fibroblasts into the wound occurs deep in the epithelium. By day 4 or 5, the fibroblasts begin to lay down collagen fibers, which continues for several months. However, remodeling of collagen takes place for more than 1 year. Practically speaking, by postoperative day 4, the wound may be washed with warm water and a bland soap (eg, Ivory, Dove, or Neutrogena). From the surgeon's point of view, all of the morphologic events of wound healing lead to a single important conclusion: wounds become stronger with time. Closing the wound with suture material only serves to hasten the process. Normally, a simple wound will attain 50% of the strength of surrounding uninjured tissue by 28 days. Most wounds are closed using absorbable suture material, which maintains tensile strength for 60 to 90 days, supplies an appreciable amount of wound strength to allow for the normal healing process to take place, and does not require suture removal. Closing wounds with absorbable suture material allows the child to return to activity at an earlier time. For instance, adolescents with uncomplicated inguinal hernia repair may return to nonstrenuous activity 7 to 10 days after surgery and may return to full activity by 4 to 6 weeks. Whenever possible, toddlers are kept off tricycles and bicycles for 7 to 10 days. Infants may be treated with a full bath by postoperative day 4, and there are no restrictions for carrying the infant.

## SCAR FORMATION

Black and white people of Mediterranean descent are predisposed to hypertrophic scars and keloid formation. Keloids are tumors characterized by massive formation of scar tissue in and beneath the skin after any trauma, including surgery. The keloid grows well beyond the borders of the incision, which is what differentiates it from hypertrophic scar formation. Furthermore, a hypertrophic scar tends to resolve with time and, as a rule, is not associated with prolonged itchiness. Keloids tend to recur after excision. Children have a greater tendency to form and re-form keloids than adults. A thorough family history may be a predictor of this pathologic process. An abnormal scar should be observed for a minimum of 6 months postoperatively. If it does not resolve, then a trial excision should be attempted, staying within the confines of the lesion to see what response is obtained. If it recurs, then it should be re-excised and 1% triamcinolone injected beneath the scar, which will produce some keloid resolution. A hypertrophic scar, on the other hand, should be treated with pressure. Overall, the management of the abnormal scar should be determined by the anatomic position of the wound, the age of the patient, and any underlying associated diseases.

Finally, all skin wounds and surgical skin incision sites will scar regardless of the expertise of the surgeon or the use of plastic surgical techniques in closing the skin. Indeed, the notion that plastic surgery is scarless is a myth. Furthermore, the scar tissue will permanently pigment (it will usually become red to dark brown-black) when exposed to intense sunlight during the first 6 months of its formation. Thus, patients and their families should be advised that when going outdoors and exposing the surgical incision site to the sun, the incision site should be completely covered or protected with zinc oxide or a sunblock with a sun-protection factor number higher than 30 for 6 months after surgery.

## MYTHS IN ANESTHESIOLOGY

All clinical practice includes myths and beliefs that are not necessarily founded on hard evidence. False beliefs or myths of any type are rarely written down; rather, they are passed down through generations, leading one to ask: How do these myths or false beliefs develop? Much of the practice of anesthesiology still remains largely a clinical art, with further advancement dependent on quality of research and education.

Some of the more commonly heard myths associated with postoperative care are in regards to pain and are listed below:

- Pain is not harmful.
- Pain relief obscures signs of complications.
- Patients will become addicted to opioids.
- PRN means: "given as infrequently as possible" rather than "give as needed."

Daily activities are not always based on scientific methods. Institutional biases and attending anesthesiologists' personal experiences affect daily practice, and residents are not always taught material that has supporting evidence.

Old myths exist, and new myths will inevitably be born. To minimize their impact on patient care, we must closely scrutinize results of scientific experiments before applying them into our daily clinical practices.

*The authors acknowledge the work of Drs Myron Yaster, Charles Paidas, and Lynne Maxwell in previous editions of this book.*

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Anesthesia and Your Child* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Intra-operative awareness in children: the value of an interview adapted to their cognitive abilities* (article), *Anaesthesia*, Vol 62, Issue 8, 2007

### Medical Decision Support

- *Pediatric Pain Management for Primary Care*, 2nd ed (book), Tobias JD, Deshpande JK, American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

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## Chapter 65

# PEDIATRIC REHABILITATION

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*Rehabilitation* is the process of restoring a person with a disability to the fullest physical, mental, social, vocational, and economic usefulness of which the person is capable. When individuals experience neurologic, neuromuscular, or musculoskeletal injuries or dysfunction caused by acquired disease processes (eg, stroke, tumors, severe illness) or trauma (eg, traumatic brain and spinal cord injuries), they are generally candidates for a program of rehabilitation.

*Habilitation* is the process of developing a skill to be able to function in an environment. It may be defined as the process by which various professional services are used to help a person with a disability make maximal use of his or her capacities to function more effectively. The term is also used to refer to various medical, therapeutic, and educational interventions that children with developmental disabilities receive. *Habilitation*, by definition, would be the appropriate term to use in discussing therapeutic planning for children with congenital disorders such as cerebral palsy, spina bifida, or developmental delay. However, using the term *rehabilitation* to refer to both rehabilitative and habilitative services is common practice, given that both processes have the same ultimate goal of optimizing the functioning of the child with a disability.

A *physiatrist* is a rehabilitation physician with expertise in neuromuscular and musculoskeletal disorders. Physiatrists treat injuries and conditions that affect mobility, diagnose and treat pain, and work with individuals to restore maximal function lost through injury, illness, or disability. They treat the whole person and not just the problem area. Physiatrists often lead a team of medical professionals providing nonsurgical treatments for disability.

*Impairment* is defined as any loss or abnormality of physiologic, psychological, or anatomic structure or function. *Disability* is any restriction, limitation, or lack of ability to perform an activity in the manner or within the range considered normal for participation

in life situations. The current World Health Organization Classification of Functioning, Disability and Health (ICF) focuses on comprehensive assessment of disability, combining both medical and social models. The classification system characterizes an individual's *ability for activity and participation* within his or her environment. The goals of treatment include decreasing disability as well as enabling individuals to function optimally in any setting despite their disability by overcoming barriers related to both environmental factors and societal attitudes. For example, in this framework, a child with cerebral palsy would have an *impairment* in terms of motor function, a *disability* or *activity limitation* related to difficulty with ambulation, and *participation restriction* because of difficulty gaining access to buildings that are not wheelchair accessible. However, the child's impairment need not lead to participation restriction if environmental modifications are made (eg, the installation of ramps) that would allow the child to access buildings with ease. This model recognizes that environmental factors and societal attitudes can either limit opportunities for individuals with impairments or facilitate them, thereby eliminating or reducing the participation restrictions resulting from various impairments.

The number of specific disorders resulting in childhood disabilities is vast. Box 65-1 lists a variety of conditions associated with childhood disabilities that are treated with interventions that fall within the realm of pediatric rehabilitation.

Pediatric rehabilitation is also used to treat disabilities that arise as a result of chronic illnesses in children,

## BOX 65-1 Disorders Treated With Pediatric Rehabilitation and Habilitation

### NEUROMUSCULAR DISORDERS (CONGENITAL AND ACQUIRED)

- Cerebral palsy
- Spina bifida
- Myopathies and muscular dystrophies
- Neuropathies (congenital or hereditary, inflammatory, infectious, metabolic) and peripheral nerve injuries
- Congenital and traumatic spinal cord injuries
- Traumatic brain injuries (eg, unintentional injuries, stroke, inflicted neurotrauma)

### MUSCULOSKELETAL DISORDERS

- Arthropathies (eg, juvenile idiopathic arthritis)
- Congenital and acquired limb deficiencies
- Congenital and traumatic orthopedic deformities
- Burns

### DEVELOPMENTAL DISORDERS

- Genetic syndromes
- Developmental delay, intellectual disability
- Developmental language disorders, autism
- Learning disabilities, attention-deficit/hyperactivity disorder

such as sickle cell anemia, human immunodeficiency virus infection, pediatric tumors and malignancies, diabetes, asthma and chronic pulmonary disease, renal disease, and cardiac disease. The following areas are common to approaches in both habilitation and rehabilitation for childhood disabilities: evaluation and management by an interdisciplinary team; identification of areas of functional impairment; development of an intervention plan; and implementation of the intervention plan.

## INTERDISCIPLINARY TEAM

Children with disabilities and their families have multiple, complex needs. Typically, no single professional can manage all of the issues; the care of the child with a disability is best handled by a team of professionals. An interdisciplinary team is made up of professionals from multiple disciplines who collaborate in a climate of mutual respect. The team addresses the full spectrum of the complex needs of the child with a disability by using a family-centered approach. Members of the team dynamically bring together their differing expertise and perspectives to complete a diagnostic workup, create a plan for intervention, and resolve ongoing management issues. The family is a vital member of the team, able to provide information about the settings in which the child spends time, insight into the child's functioning and motivating factors, and clarification of family priorities.

A single member of the team is designated as the primary physician or case manager to serve as the main contact for the family regarding management issues and to bring the family's priorities and concerns to the team. Interdisciplinary teams vary in terms of the professionals involved, depending on the setting and the mission of the team. Interdisciplinary teams function in a range of settings, including acute care hospitals, transitional care units, rehabilitation programs, outpatient rehabilitation facilities, clinics, and home-based programs. Specialty or regional centers may have funding to create larger, more comprehensive teams. In individual communities, a team of a few professionals at different sites may work together, collaborating to create an ad hoc team to assist children and families. Box 65-2 lists common members of the team for children with physical and developmental disabilities.

## IDENTIFYING SPECIFIC AREAS OF FUNCTIONAL IMPAIRMENT, ACTIVITY LIMITATION, AND PARTICIPATION RESTRICTION

After the interdisciplinary team has clarified the diagnoses and impairments for a child with a disability, analysis of function takes priority. Diagnostic evaluation should address all areas of impairment, including the child's general health, sensory impairments, and cognitive impairments because each factor separately, and the impairments collectively, affect the child's ability to execute activities and participate in life situations. Functional evaluation by the interdisciplinary team is essential for establishing treatment goals. Such assessments are typically performed by physicians (eg, pediatric physiatrists and developmental

pediatricians) as well as by physical, occupational, and speech and language therapists. Physical therapists are the experts in interventions to address impairments in gross-motor functioning and mobility, and occupational therapists are the experts in interventions to address impairments in fine-motor and adaptive functioning and self-care skills, whereas speech and language therapists' expertise is in facilitating communication and feeding skills.

The evaluation of gross-motor functioning involves assessing muscle tone, muscle strength, reflexes, sensation, movement patterns, postural status, motor coordination, gait, and joint ranges as well as documenting deformities. This information provides the basis for clarifying impairments and skill level relative to peers. Functional analysis examines the effect of the set of impairments on the child's ability to carry out activities. In the gross-motor domain, the functions of interest include attaining gross-motor skills relating to stability and mobility (sitting, crawling, pulling to stand, ambulating) and transitions from one position to another.

### BOX 65-2 Disciplines Typically Included in an Interdisciplinary Team for Children With Physical Disabilities

- Physiatrist (pediatric rehabilitation specialist)
- Developmental pediatrician
- Primary care physician
- Orthopedist
- Neurologist
- Geneticist
- Otorhinolaryngologist
- Ophthalmologist
- Neurosurgeon
- Urologist
- Pulmonologist
- Physician assistants
- Nurse practitioner and other nurses
- Dentist
- Physical therapist
- Occupational therapist
- Speech and language pathologist
- Feeding therapist
- Psychologist or neuropsychologist
- Special education professional
- Social worker
- Adaptive technology specialist
- Therapeutic recreationalist
- Audiologist
- Nutritionist
- Orthotist
- Prosthetist
- Home health worker

Evaluating fine-motor and adaptive functioning typically involves a detailed history. Children should participate in providing the history as they are able. Functional assessment should involve assessing the child's ability for self-care: feeding, grooming, toileting, hygiene, and dressing. Functional histories should include information regarding areas of competence as well as impairment. Parents are in a unique position to provide details to the team regarding how and where the child currently carries out adaptive tasks, highlighting strengths and strategies that may prove useful in planning interventions.

Many assessment tools can be used to examine motor and adaptive skill attainment. Norm-referenced, standardized tests are primarily diagnostic; they document a set of delays relative to norms, thereby justifying the need for intervention. Examples include the Bayley Scales of Infant Development, Peabody Motor Scale, Vineland Adaptive Behavior Scale, and Bruininks-Oseretsky Test. Functional or qualitative assessments are criterion referenced; they assess how a child performs a task from a functional perspective. Such instruments are useful for intervention planning and follow-up to assess improvement from intervention and ultimately in establishing evidence-based outcomes research. Table 65-1 lists some of the frequently used assessment and functional outcome measures.

## DEVELOPING AN INTERVENTION PLAN

When planning an effective rehabilitation program for a child with a disability, many factors need to be considered. These factors include severity of motor impairment; anticipated functional potential; age, mental capacity, and developmental status; home and family environment; and ethnic and cultural factors.

Realistic goals should be established based on these factors and the lifelong nature of most physical disabilities. The multisystem nature of disabilities often

requires an interdisciplinary approach to treatment with a team of therapists, each therapist using a variety of techniques. The interdisciplinary approach should address the following components:

- Medical management
- Therapeutic management
- Durable medical equipment, orthotics, and prosthetics
- Sports and recreation
- Psychosocial support to the family, caregiver, and patient
- Education and vocational planning
- Transitional and long-term planning

## MEDICAL MANAGEMENT

Medical management of the child with a disability involves the diagnosis and treatment of associated medical issues, pain management, management of spasticity, and complications of tonal abnormalities.

### Associated Medical Conditions

The diagnosis and treatment of associated medical issues are important components of the care of the child with a disability because many common conditions can greatly affect functioning. Common medical issues in children with disabilities relate to growth, feeding and nutrition, vision and hearing, seizures, pulmonary disease (eg, asthma, chronic lung disease), gastrointestinal functioning (eg, gastroesophageal reflux, oral-motor dysfunction, constipation), dentition, behavior, and sleep.

### Pain Management

Managing pain is also an important part of the intervention plan for a child with a disability. Pain can be related to spasticity in neuromuscular disorders such as traumatic brain injury and cerebral palsy; it can be the result of joint inflammation in juvenile idiopathic

**Table 65-1** Functional Outcome Measures in the Assessment of Motor Disability

ASSESSMENT TOOL	AGE GROUP	AREAS OF MEASUREMENT
<b>DIAGNOSTIC ASSESSMENT TOOLS</b>		
Pediatric Evaluation of Disability Inventory (PEDI) <sup>a</sup>	6 mo–7 yr	Assessment: gross-motor, adaptive function Outcome measures: activity and participation
Peabody Developmental Motor Scales <sup>b</sup>	0–9 yr	Assessment: gross-motor, fine-motor, adaptive function Outcome measure: activity
Motor Assessment of Infants (MAI) <sup>c</sup>	0–12 mo	Assessment: gross-motor, reflex function
<b>FUNCTIONAL OUTCOME ASSESSMENT TOOLS</b>		
Functional Independence Measure for Children (WeeFIM) <sup>d</sup>	0–18 yr	Assessment: gross-motor, fine-motor, adaptive function Outcome measure: activity
Gross Motor Functional Measure (GMFM) <sup>e</sup>	15 mo–16 yr	Assessment: gross-motor and fine-motor function
Pediatric Quality of Life Inventory <sup>f</sup>	2–18 yr	Assessment: health-related quality of life

Based on Deitz Curry JE. Promoting functional mobility. In: Dormans JP, Pellegrino L, eds. *Caring for Children With Cerebral Palsy*. Baltimore, MD: Paul H. Brookes Publishing; 1998; 283–322

<sup>a</sup>Coster WJ, Haley SM. Conceptualization and measurement of disablement in infants and young children. *Infants Young Child*. 1992;4:11–12

<sup>b</sup>Folio M, Fewell R. *Peabody Developmental Motor Scales*. Hingham, MA: DLM; 1983

<sup>c</sup>Chandler L, Andrews M, Swanson M. *The Movement Assessment of Infants*. Rolling Bay, WA: Rolling Bay Press; 1980

<sup>d</sup>Msall ME, DiGaudio KM, Duffy LC. Use of functional assessment on children with developmental disabilities. *Phys Med Rehabil Clin North Am*. 1993;4:517–527

<sup>e</sup>Russell DJ, Rosenbaum PL, Cadman DJ, et al. The gross motor functional measure: a means to evaluate the effect of physical therapy. *Dev Med Child Neurol*. 1989;31:341–356

<sup>f</sup>Varni J, Seid M, Rode C. The PedsQL: measurement model for the Pediatric Quality of Life Inventory. *Medical Care*. 1999;37(2):126–139



arthritis (see Chapter 324, Rheumatologic Diseases), or it can be caused by sickle crises in sickle cell disease (see Chapter 262, Hemoglobinopathies and Sickle Cell Disease). Pain management is also an integral part of the treatment of burns. For further discussion of pain management, see Chapter 54, Managing Acute Pain in Children; and Chapter 55, Managing Chronic Pain in Children.

### Management of Tonal Abnormalities

Medical management also involves managing tone abnormalities that affect function. This area includes the management of spasticity. The assessment of spasticity should include identifying treatable conditions that can be contributory, such as urinary tract infection, decubitus ulcers, fecal impaction, constipation, and gastroesophageal reflux. Spasticity should not be treated for its own sake but rather when it hinders functioning, causes pain, or interferes with hygienic nursing care or positioning. In many instances, spasticity is beneficial. For example, a child with spinal cord injury may use spasticity in standing. A patient with cerebral palsy may be able to use spasticity to walk.

The spectrum of interventions for managing spasticity includes the use of medication and surgery. Treatment differs depending on whether the spasticity is diffuse or localized. Oral medications such as diazepam, dantrolene sodium, baclofen, and tizanidine have been used for diffuse spasticity, although the functional improvement reported has been modest, in part because of limitation in the dosage that can be used secondary to side effects (mainly sedation). Baclofen, which is administered intrathecally through a programmable pump, achieves higher levels in the cerebrospinal fluid and thus can be effective in managing diffuse spasticity of central origin. Chemodenervation agents such as botulinum toxin A, phenol, and alcohol through injection are indicated for more localized spasticity, especially in younger patients without fixed contractures. Reduction of spasticity is temporary, lasting between 3 and 8 months. Surgical treatment, in the form of selective dorsal rhizotomy, interrupts the afferent limb of the reflex arc, reducing spasticity without causing motor paralysis. Improved range of motion and muscle strength have been reported.

Orthopedic interventions are indicated when medication, splints, casts, and physical therapy have failed to deter the progression of deformities and when spasticity interferes with functioning. Release or lengthening of muscles and tendons can reduce the restricted joint motion or malalignment. Orthopedic interventions should also be considered when fixed contractures interfere with function or when they hinder the provision of nursing care.

Dystonia can occur as a result of genetic causes and in cerebral palsy. It is commonly seen in patients who sustain traumatic brain injury as children rather than adults. The interval between injury and the onset of dystonia varies. Medications such as trihexyphenidyl hydrochloride, carbidopa-levodopa, and bromocriptine are used in treatment of dystonia. Intrathecal and oral baclofen have also been used effectively in treatment of dystonia.

### Complications of Tonal Abnormalities

Orthopedic management also addresses the complications of tonal abnormalities. Spasticity in hip adductors and hip flexors can cause subluxation of hips progressing to hip dislocation or dislocation with degenerative changes of the femoral head with pain. Progressive bony deformities can cause pelvic obliquity and scoliosis of the spine. When hip subluxation is detected, soft tissue release or lengthening can be performed. Comprehensive hip reconstruction may be performed in severely affected children. Orthopedic surgical procedures should be followed by physical therapy and orthotics management to maintain range of motion, strengthen weak muscles, and prevent recurrence of deformities.

## THERAPEUTIC MANAGEMENT

The primary goals of intervention are to maximize functional skills, foster independence, and prevent or minimize complications. The emphasis must be on improved function rather than on improvement in the impairment. No single therapeutic method is suitable for all children; thus, the therapeutic regimen must be individualized to the child.

Components of therapeutic management include physical therapy, occupational therapy, functional activity training, speech and communication therapy, and feeding therapy for oral-motor dysfunction.

### Physical and Occupational Therapy and Functional Activity Training

Children with disabilities often have decreased or limited exercise capacity relative to their typically developing peers. This incapacity may result from the specific pathologic features of their disability, deconditioning, or decreased muscle strength and endurance. In therapeutic management of children, physical and occupational therapists use traditional exercises and specific treatment techniques (both traditional and nontraditional) as well as adaptive equipment and assistive devices to improve muscle strength, endurance, flexibility, and range.

Traditional exercises are often not applicable in the treatment of infants, young children, and older children with significant cognitive impairment because they are unable to cooperate and participate in structured exercises typically prescribed for adults. Therefore, using developmentally appropriate games, toys, and play activities to engage such children is important for improving strength, flexibility, and posture.

Maintaining passive range of motion, flexibility, and joint mobility, as well as preventing soft tissue tightness, is especially important in children with muscle tone abnormalities. Limitation in joint mobility interferes with normal movement and activities. Therapy to elicit active movements in infants is done by handling the child or by inducing spontaneous interaction. Normal movement patterns are facilitated by using developmentally appropriate, colorful toys and equipment. Parents are encouraged to be actively involved because exercise programs must carry over to the home with parents or caregivers performing the exercises daily to maximize benefit.

In preschool- and school-aged children, coordination of therapy with education is increasingly used. Participation of therapists in classroom consultation can enhance the child's education potential. Occupational therapists can assist teachers in improving graphomotor skills, activities of daily living (ADLs), and fine-motor adaptive skills. Physical therapists can assist the child in achieving optimal positioning, trunk alignment, and mobility.

When treating adolescents with disabilities, therapeutic programs are geared toward preventing contractures; maintaining strength, flexibility, and endurance; improving postural alignment; and facilitating mobility. Improving functional skills and increasing independence should be emphasized within the limits of the disability.

In addition to strength training and improvement in range of motion, physical and occupational therapists use specific therapeutic techniques. They rarely use a single approach; rather, therapists combine a variety of approaches to develop a program suitable for a particular child's needs. Many of these treatment approaches have little reliable clinical or scientific evidence to indicate efficacy of one method over another. The outcomes

of various treatments have not been well studied, and assessment tools do not separate the effects of treatment from developmental progress as a result of maturation. The recent emphasis on functional assessment measures and functional outcomes of interventions, along with greater inclusion of children as subjects in outcome studies, have led to an increase in the availability of data that will over time allow for better determination of the effectiveness of various treatment techniques and modalities for children with disabilities. This trend is evident in the relatively large number of recent studies on the use of novel technology-based interventions for physical disability such as the use of virtual reality systems (eg, the Wii) and robotics.

Pediatricians and other primary care physicians are often called on to prescribe therapeutic services for children. Prescribing physicians should have contact with the treating therapists, and be familiar with the goals of the therapeutic program and the techniques that will be used to achieve these goals. If such information is lacking, then the physician should consult with a physiatrist or a developmental pediatrician.

Table 65-2 lists current physical and occupational therapeutic techniques, the populations appropriate

**Table 65-2** Specific Physical and Occupational Therapy Treatment Techniques

TYPE	AGE AND DISABILITY	EMPIRICAL SUPPORT
<b>STANDARD THERAPEUTIC APPROACHES</b>		
<i>Passive stretching:</i> used to prevent deformities and maintain muscle and joint range of motion in children with muscle weakness, spasticity, or medical conditions causing immobility	All ages Used in neurologic, musculoskeletal, and neuromuscular conditions	No clear evidence to support efficacy, or guidance on frequency or duration <sup>a</sup>
<i>Neurodevelopmental treatment<sup>b</sup>:</i> specific patient handling skills, guiding patients through initiation and completion of intended tasks	All ages All neurologic conditions	Few studies Conflicting results
<i>Sensory integration<sup>c</sup>:</i> exercises are used to strengthen the patient's sense of touch, of balance, and of where the body and its parts are in space	Children with CP, ID, autism, developmental delay, ADHD, LD, developmental coordination disorder	Many studies Conflicting results <sup>d</sup>
<i>Conductive education<sup>e</sup>:</i> methods focus on educating the child to learn how to gain control over his movements; uses unique equipment and group instruction with a specially trained "conductor"	Preschool- to school-aged children with CP, spina bifida, neurologic disorders	Many studies Conflicting results
<i>Constraint-induced therapy:</i> for hemiparesis; the technique involves restraining the uninvolved arm and engaging the paretic arm in intensive motor practice and shaping	Adults and children with hemiparesis because of CP or stroke	Evidence based <sup>g, h, i</sup>
<b>TECHNOLOGY-BASED APPROACHES</b>		
<i>Partial body weight–supported treadmill training (PBWSTT):</i> twice-weekly sessions targeting walking speed and endurance	Children through age 6 yrs with CP, developmental delay, ID	Emerging evidence <sup>j</sup>
<i>Virtual reality systems:</i> for example, Wii habilitation	Adults and children with TBI, CP, hemiparesis	Few studies Conflicting results <sup>k-n</sup>
<i>Robot assistive therapy:</i> use of robotics to move the child's body through normal movement patterns	All ages with spasticity	Few studies, but promising <sup>o-q</sup>
<i>Aquatic therapy:</i> pool-based treatment program provided by a licensed therapist focusing on strength training, muscle relaxation, stretching, and opportunity and motivation for activities the patient may be unable to perform on land. Indications include muscle weakness, decreased range of motion, impaired coordination, and poor endurance.	CP, spina bifida, arthritis, TBI, strokes, burns, fractures, and asthma Contraindications: open wounds, infectious skin conditions, temperature instability, uncontrolled seizures, hypertension, hypotension	Some evidence <sup>r</sup>

**Table 65-2** Specific Physical and Occupational Therapy Treatment Techniques—cont'd

TYPE	AGE AND DISABILITY	EMPIRICAL SUPPORT
<i>Hippotherapy</i> : a licensed therapist uses the characteristic movement of a horse to provide graded motor and sensory input designed to increase muscle strength and motor skill achievement	CP, spina bifida, TBI, spinal cord injury, amputations, neuromuscular disorders, Down syndrome Contraindications: spinal pathology, poorly controlled seizures, severe cognitive or behavior impairment	Improvement in function in CP, decreased frustration and aggression <sup>s-u</sup>
<b>ALTERNATIVE MEDICINE APPROACHES</b>		
<i>Craniosacral techniques</i> <sup>v</sup> : manipulative hands-on technique, whole-body method of relaxing restrictions around the brain and spinal cord to enhance CNS perfusion and allow the body to self-correct	Originally used for adults, now used in children with cerebral palsy	Few studies No evidence of efficacy in children with CP
<i>Adeli Suit therapy</i> : a device developed in Russia resembling a cosmonaut suit. The suit's components are connected by bands that can be adjusted to imitate flexor and extensor patterns of major muscle groups to correct abnormal alignment. Treatment is given multiple times per week at high intensity for a 4–6 week period.	CP	No evidence of efficacy in children with CP <sup>w</sup>
<i>Hyperbaric oxygen therapy</i> : based on the theory that there are dormant areas surrounding the injured areas of the brain in children with CP and related neurologic disorders that can be stimulated with higher concentration of oxygen. Treatment consists of delivery of oxygen at high pressures for up to 40 1-hour sessions.	CP and other neurologic disorders	No evidence of efficacy; risks of treatment include rupture of ear drums, bleeding, and in rare circumstances death <sup>x</sup>

ADHD, attention-deficit/hyperactivity disorder; CP, cerebral palsy; ID, intellectual disability; LD, learning disability; TBI, traumatic brain injury.

<sup>a</sup>Pin T, Dyke P, Chan M. The effectiveness of passive stretching in children with cerebral palsy. *Dev Med Child Neurol*. 2006;48:855–862

<sup>b</sup>Bobath K, Bobath B. The neuro-developmental treatment. In: Scrutton D, ed. *Management of Motor Disorders in Children with Cerebral Palsy*. Philadelphia, PA: JB Lippincott; 1984: 6–18

<sup>c</sup>Ayers AJ. *Sensory Integration and Learning Disabilities*. Los Angeles, CA: Western Psychological Services; 1972

<sup>d</sup>American Academy of Pediatrics Council on Children With Disabilities, Zimmer M, Desch L. Sensory integration therapies for children with developmental and behavioral disorders. *Pediatrics*. 2012;129(6):1186–1189

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<sup>g</sup>Taub E, Landesman Ramey S, DeLuca S, et al. Efficacy of constraint-induced movement therapy for children with cerebral palsy with asymmetric motor impairment. *Pediatrics*. 2004;113:305–312

<sup>h</sup>Naylor CE, Bower E. Modified constraint-induced movement therapy for young children with hemiplegic cerebral palsy: a pilot study. *Dev Med Child Neurol*. 2005;47:365–369

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<sup>j</sup>Valentin-Gudiol M, Mattern-Baxter K, Girabent-Farres M, et al. Treadmill interventions with partial body weight support in children under six years of age at risk of neuromotor delay. *Cochrane Database Syst Rev*. 2011;12:CD009242

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to receive these therapies, and the availability of data to support them. Many of these therapy techniques were originally used in adults and have been modified for children.

Physical and occupational therapists use various modalities in conjunction with therapeutic exercises, such as electrical stimulation, biofeedback, therapeutic cold and heat, hydrotherapy, and dry heat therapy. Electrical stimulation can be used to treat muscle spasms and to improve functional skills as part of gait training or programs targeting upper extremity usage. Biofeedback, with and without electromyography feedback, can help patients learn ways to gain control over motor function. Therapeutic cold decreases the muscle stretch reflex excitability and clonus and improves range of motion. It can be used to decrease spasticity temporarily and to allow mobility of extremities during therapy. In children with arthropathies such as juvenile idiopathic arthritis, hydrotherapy, hot packs, and dry heat therapy can relieve joint stiffness and pain and allow active range of motion of involved joints.

Hyperbaric oxygen therapy, intensive suit therapy (Adeli), magnetic therapy, and acupuncture are non-traditional therapy techniques used in many children with neurologic disease that lack evidence-based support.

Functional activities training is a critical component of the therapy program, especially for older children and adolescents. The training focuses on age-appropriate ADLs, such as dressing, feeding, brushing teeth, and personal hygiene. Actual training goes on during therapy sessions. Adaptive equipment such as long-handled hairbrushes, modified toothbrushes, and special utensils should be provided. Carryover to home and practice are critical. Bicycling, stair climbing, treadmill walking, and virtual reality system activities should be encouraged as tolerated to improve mobility, endurance, and strength.

### Speech and Communication Therapy

The indications for speech and language therapy in children include developmental language delays such as those associated with intellectual disability, autism, and hearing impairment; acquired language disorders caused by neurologic disorders such as traumatic brain injury, stroke, brain tumor, or encephalopathy; and speech disorders resulting from neuromuscular processes that involve respiration, phonation, articulation, structure, and function, such as in cerebral palsy, myopathies, tracheostomy, ventilator dependency, and high spinal cord injuries. (For further information, see Chapter 195, Speech and Language Concerns; and Chapter 226, Cerebral Palsy.)

### Oral-Motor and Feeding Therapy

These same groups of children and adolescents should be assessed for oral-motor dysfunction, which affects feeding and swallowing. Oral-motor dysfunction can be temporary (debilitative illness) or long term (neuromuscular disorder). Successful feeding involves the coordinated action of multiple systems. Normal feeding requires anatomic integrity of the oropharyngeal cavity, neuromotor control and coordination, sensory

perception, adequate gastrointestinal function, sufficient cardiorespiratory support, intact autonomic nervous system, and integration of normal behavioral responses. Therefore, assessment and intervention in feeding disorders require an interdisciplinary approach. The team of specialists with expertise in feeding may include speech and language pathologists, occupational therapists, nutritionists, gastroenterologists, otorhinolaryngologists, radiologists, physiatrists, and developmental pediatricians.

Warning signs for the pediatrician regarding the possibility of a feeding or eating disorder include the following:

- History of frequent respiratory infections
- Difficulty handling oral secretions and drooling
- Coughing and choking
- Multiple swallows to process a bolus of food
- Noisy breathing
- Food refusal
- Failure to thrive

Assessment of oral-motor function includes a detailed feeding history, observation and assessment of current feeding behavior and skill level, and nutritional status. The oral-motor structures should be examined for anatomic abnormalities of the oral cavity and for functional abnormalities of the lips, tongue, and jaw. Such abnormalities may be caused by the presence or absence of normal or abnormal oral reflexes necessary for coordinated feeding (eg, tongue thrust), weakness or incoordination (eg, poor lip seal), or pain (eg, temporomandibular joint syndrome). The evaluation may require assessment of oropharyngeal structure and function with video fluoroscopy or fiberoptic endoscopic evaluation of swallowing (FEES) to assess for structural abnormalities or evidence of aspiration. This information is often required before feeding therapy can safely be initiated. The child should be evaluated for the ability to manage oral and pharyngeal phases of swallow as well as the ability to swallow foods of different consistencies.

Poor motor control of the head, trunk, and extremities can also interfere with feeding. Muscle tone abnormalities, opisthotonic posturing, obligatory primitive reflexes, and abnormal movements can all interfere with proper positioning. Sensory abnormalities such as hypersensitivity or hyposensitivity to food texture or utensils used for feeding or inability to tolerate being handled or held can also interfere with successful feeding. Medical factors such as gastroesophageal reflux disease, seizures, swallowing dysfunction, or respiratory distress can cause pain, lethargy, and agitation, all leading to food refusal. When feeding difficulties are longstanding as a result of any of the previously mentioned abnormalities, behavioral feeding problems can result, including refusal to participate in oral feeding or selective or restricted intake, leading to inadequate nutrition.

Treatment of feeding difficulties includes an initial decision regarding the child's ability to eat safely and effectively. If significant obstacles to safe oral feeding are identified, then enteral feeding may be indicated. Feeding competency can be encouraged through the use of adaptive positioning chairs with head and trunk supports for positioning of children



with poor head control and impaired trunk balance; the use of specialized nipples, bottles, feeders, or adaptive shallow spoons; the use of special cups to improve lip closure and sucking movements; and the use of brushes for oral stimulation to diminish hypersensitivity. For the child with food refusal, any medical factors affecting motivation for feeding must be addressed. After medical conditions have been treated and positioning and adaptive feeding equipment optimized, if feeding refusal persists, a behavioral feeding program is recommended. Such programs are often intensive, with inpatient and outpatient models.

The inability to feed and swallow is a difficult experience for children and families, and it can have far-reaching consequences. It can interfere with parent-child interaction and attachment, especially in infants. In older children, it can result in isolation owing to an inability to share social experiences at mealtimes with friends and family.

## DURABLE MEDICAL EQUIPMENT

*Assistive technology* or *durable medical equipment* (also called adaptive equipment) refers to equipment designed to enhance the independence of children with chronic illnesses and disabilities, thus improving their quality of life. Assistive devices can be divided into categories based on their intended function: positioning, mobility, ADLs, communication, and support.

*Positioning devices* promote optimal posture and alignment of joints in children who have not achieved adequate head or trunk control. They prevent contractures and decubitus formation by decreasing pressure on bony prominences. Devices such as *positioning chairs* serve as an alternative to beds or wheelchairs and allow the child to be optimally positioned during interactions with others, such as at mealtime or during other family activities. *Standers* provide supported passive standing for children who cannot independently bear their own weight.

*Mobility devices* can be subcategorized into ambulatory aids, transfer aids, and wheeled mobility aids. Ambulatory aids such as walkers help children improve balance and posture, provide support during walking, and decrease energy expenditure. *Forward* or *anterior walkers* promote trunk flexion; *reverse* or *posterior walkers* facilitate more erect posture and trunk extension. Crutches and canes are mobility aids that can be used by children who have better trunk control. Before children use ambulatory aids at home, they should be trained by a physical therapist. The devices must be checked and adjusted regularly to accommodate the growth of the child.

Transfer aids are used to assist children in changing their position on one surface or in transferring from one surface to another. An example is a *trapeze bar* over a bed.

Wheeled mobility devices, such as wheelchairs, scooters, and strollers, are designed to meet the diverse needs of children with differing levels of physical disabilities, cognitive limitations, and recreational interests.

Proper selection of a wheelchair is essential. Manual and powered wheelchairs share the same basic

components: frame, seat, wheels and tires, armrests and footrests, brakes, and seat belts. Powered wheelchairs should be considered for children with adequate cognition (a developmental level of at least 24 months) whose upper body strength or endurance is insufficient to propel a manual chair effectively. The child must be able to understand the concept of cause and effect, be able to follow 1-step commands, have adequate visual skills, and have at least one reliable movement for activating a switch to operate the powered chair. Powered chairs can be operated with joysticks, head or chin switches, track balls (in the setting of weak grasp), and sip-and-puff mechanisms. There are mechanisms to elevate and recline seats, change position from sitting to standing. There are 3-wheel and 4-wheel power scooters available when there is insufficient space at home to maneuver a power wheel chair.

*ADL devices* help patients during feeding, bathing, grooming, and toileting. Occupational therapy evaluation determines the need for such devices, which are used in conjunction with a therapeutic program appropriate for the child's age and functional level. Parents should be involved in the therapeutic program to provide implementation assistance and supervision of these activities.

*Communication devices* use augmentative and alternative communication strategies when a child's ability to speak is impaired. Taking into account the child's cognitive ability, these devices range from simple to complex and should allow expansion if the child's communication abilities improve.

*Support Orthoses* are externally applied devices that are used to modify structural and functional characteristics of the neuromuscular and skeletal system of the body. In clinical practice, orthoses generally take the form of splints or braces. Common aims in prescribing orthoses are to provide optimal positioning and maintain correct alignment of an extremity, prevent deformities by restricting abnormal joint motion, correct joint contracture, relieve discomfort, and assist in function and stability. An orthosis may be rigid and support an affected extremity in one position (static), or it may allow movement in a controlled manner (dynamic). Orthoses can be used for both upper extremities (eg, finger-thumb adductor splints, elbow extension orthoses, shoulder stabilization orthoses) and lower extremities (eg, supramalleolar orthoses, ankle-foot orthoses).

*Splints* are commonly made of low-temperature thermoplastic materials that are heated and molded directly onto an extremity. They are flexible and less durable. Splints are generally used for upper and lower extremities in infants and young children and for upper extremities in older children. They can be easily modified and adjusted to accommodate rapid growth and are cost-effective. *Braces* are usually custom made from high-temperature plastic materials cast from a plaster mold, metal joints, and leather or canvas straps with buckles or Velcro. Braces are durable, but they cannot be easily adjusted to accommodate growth; therefore they need to be replaced after a growth spurt or a change in neuromuscular or functional status.

A recent assistive technology innovation with promising results involves the use of a functional

electrical stimulation (FES) device. Generally, FES is used in cerebral palsy, in poststroke patients to improve function in hemiplegic upper and lower extremities, and in spinal cord injuries. In multiple sclerosis, FES is used for foot drop. FES is used to complement physical therapy to improve strength. A recent study in the *Journal of Spinal Cord Medicine* suggested that lower extremity FES cycling promotes physical and neurologic recovery in chronic spinal cord injury.

With the assistance of the treating therapist, physicians provide a letter of medical necessity and prescription for orthoses. Orthoses are fabricated either by an orthotist or by qualified and experienced physical and occupational therapists. Comfortable fit will improve acceptance. Cotton socks or stockings should be worn under the orthosis to absorb perspiration. A realistic wearing schedule must be outlined with gradually increased periods of use, from a few minutes to the desired number of hours. Skin should be examined for evidence of increased pressure (especially over bony prominences), edema, or other inflammatory responses.

Unbiased clinical research regarding the effectiveness of orthoses or even the spectrum of their application has been sparse. In children with cerebral palsy, a short-term effect on passive range of movement and diminished toe walking have been reported, but the long-term clinical significance is unclear.

## SPORTS AND RECREATION PROGRAMS

Physical benefits of exercise in adults with disabilities (eg, adult paraplegia) have been documented. Individuals with disabilities who are involved in exercise programs have fewer decubitus ulcers, decreased incidence of urinary tract infections, and fewer hospitalizations. Improved strength, endurance, range of motion, and flexibility have been described in patients with cerebral palsy, as have increased socialization and higher self-esteem.

Less information is available regarding effects of sports and recreation activities on children with disabilities. Children with disabilities are found to generally watch more television than their peers. Encouraging data show that self-concept scores of young athletes with disabilities were similar to their able-bodied peers. Sports can be a significant part of an active lifestyle for children with disabilities. Adapted sports are activities that have been modified to meet the needs of children with disabilities. Adapted physical education was developed as a result of the Individuals With Disabilities Education Act of 1973 (IDEA), which includes instruction in physical education as a part of the child's individualized education plan.

Sports for youth with disabilities are available in many communities through community centers, summer camps, and after-school programs and through adapted physical education programs. Such activities can be therapeutic, recreational, or competitive.

Training is provided for teachers, therapeutic and recreational specialists, and physical and occupational therapists in identifying needs, developing curricula, and providing direct instruction in adapted sports.

Physical education teachers provide early exposure to sports and recreational activities for children with special needs, and they encourage participation at local, regional, and national levels as the children mature.

Therapeutic sports include hippotherapy (horseback riding for individuals with disabilities), aquatic therapy, dance therapy, yoga, tai chi, and karate. Hippotherapy has been popular in Europe since the 1950s and has been used in the United States since the 1970s for children with cerebral palsy. The concept behind the intervention is that the movement of the horse induces a pattern of movement in the rider similar to human walking. Reported benefits include improvement in muscle tone, posture, balance, and strength as well as improved concentration, language skills, self-confidence, and peer relations. Aquatic therapy uses water therapeutically. The increased buoyancy of water diminishes the effect of gravity; thus, less effort is required to move. The temperature of the water can therapeutically relax muscles. Increased range of motion and improvement in coordination, cardiorespiratory endurance, and muscle tone have been noted.

Many children with disabilities participate in organized athletic events. The Special Olympics, Paralympics, National Wheelchair Athletic Association, National Wheelchair Basketball Association, American Athletic Association of the Deaf, and United Cerebral Palsy Athletic Association have established junior-level participation and programs for athletes with disabilities 6 to 18 years of age.

With the expansion of the range of competitive sports for athletes with disabilities, sports classification systems have been developed to allow for competition among athletes with various disabilities. Early classification was based on medical diagnoses. The current classifications are based on functional skills; therefore, athletes with different disabilities compete in a single system.

Children with disabilities face many challenges when participating in adapted sports as a result of their medical conditions, varying functional skill levels, and sometimes the need for sophisticated and expensive individualized equipment. For example, a child with spina bifida or a spinal cord injury can have decreased or absent sensation, which may result in pressure ulcers or skin breakdown as a result of minor stresses. An athlete with cerebral palsy may be predisposed to developing muscle strains and injuries as a result of abnormal stresses on spastic muscles and joints with decreased range of motion. A child with mobility impairment may require a racing or sports wheelchair, adapted skis, special balls, or safety devices for participation in the child's chosen activity.

Athletes must first be evaluated to assess their muscle strength and coordination and then to assess their ability to participate in the specific competitive sport. As with able-bodied athletes, children with disabilities should have a preparticipation history taken and a physical examination performed. Medical issues, disability-specific concerns, and developmental and behavioral issues should be addressed. General

health, conditions limiting participation, and predisposing factors to injury should also be assessed.

## PSYCHOSOCIAL SUPPORT TO THE FAMILY AND PATIENT

The family is a pivotal member of the interdisciplinary team. The principles of family-centered care are central to the planning and delivery of care for a child undergoing rehabilitation. These principles include treating families with respect and dignity and listening to and honoring family perspectives, choices, values, beliefs, cultural background, and knowledge. Families are encouraged and supported in participating in care and decision making at the level they choose. Although family members are experts on their child and the priorities and concerns of the family, they are often students—at least initially—in the diagnostic and treatment aspects of rehabilitation. Psychosocial support is needed to address parents' thoughts, feelings, questions, and concerns as they make their way through the rehabilitation process. The patient, depending on age and developmental capacity, should also be included in the psychosocial support plan. The individual learning styles and educational levels of the caregivers and the patient need to be taken into account when working with families, and education should include presentation of materials through different modalities. Because of anxiety and stress during the course of treatment, remembering complicated information may be hard for a caregiver; therefore, staff members should teach skills gradually and repeatedly. Families are most satisfied when care is offered in a respectful and supportive manner.

Providing psychosocial support to the family and child is an integral part of the rehabilitation plan. Support must be flexible and individualized to meet the family's changing needs. The times of greatest need are typically at the initial diagnosis and at points of transition. When a child is newly diagnosed with muscular dystrophy or has experienced traumatic brain injury, the family may cope with guilt, anger, and the loss of what might have been. Transitions from one setting of care to another, such as the discharge of a premature infant from the neonatal intensive care unit or the transition from the hospital setting to the home, a rehabilitation facility, or a transitional care unit after traumatic brain injury, are points of particular stress for families. Parents may feel anxiety or stress as a result of changes in their child's level of care. They may feel unprepared for the new setting, time of discharge, or management of their child's new medical and equipment needs.

To provide support to the family most effectively, family members should be engaged in the planning process early on to ensure coordination and continuity of care from one setting to another. Optimal support to families includes an effective and collaborative discharge plan. This plan includes the identification of the patient's primary caregivers and an understanding of family beliefs, attitudes, motivations, competency, social supports, and biopsychosocial stressors in the home environment. In addition, an assessment of the home environment, home equipment, and service

needs and provision of appropriate home care and community support services (eg, nursing services, home-based therapies, durable medical equipment, school accommodations, backup care in the community) will facilitate a smoother transition process for the patient and family. Alternative therapeutic plans may need to be explored with the family and interdisciplinary team when barriers preclude a safe and agreed-upon treatment plan.

In-hospital supportive counseling, parent-to-parent groups, home modifications, and training in equipment use and rehabilitation needs can support, strengthen, and encourage the family's ability to care for the child at home or during transition from the acute care setting to a transitional or rehabilitation unit. A trial home visit from a rehabilitation facility may build the family's confidence and self-determination in preparation for discharge, with the availability of the interdisciplinary team to provide support and further education to the patient and family as needed.

## EDUCATIONAL AND VOCATIONAL PLANNING

When transitioning a child to the home, additional support in the community must extend to the academic setting to ensure appropriate placement, related services, and accommodations as needed. State agencies such as Vocational and Educational Services for Individuals With Disabilities provide vocational training to prepare the adolescent or young adult for suitable jobs. (See Chapter 52, School-Related Issues for Children With Special Health Care Needs.)

## IN THE COMMUNITY: ACCESSING THERAPEUTIC AND MEDICAL SERVICES

Beginning in the neonatal intensive care unit and continuing through adulthood, entitlements exist that families can access to obtain therapeutic services for their children with disabilities and to fund these services. Early Intervention, Part C of IDEA, funds evaluation of children from birth to 3 years for developmental disabilities, designation of a service coordinator, and provision of a wide range of therapeutic services for the eligible child and the child's family. Typically, children who are 3 years of age and showing continued impairment may enter either a therapeutic nursery setting or a regular child care or nursery and receive therapies at those sites. IDEA ensures that rehabilitation services continue into elementary school and through 21 years of age. Although these entitlements can provide an array of therapies to children with disabilities, they only address a portion of the necessary intervention plan for the child with a disability as described in this chapter. Meeting the needs of the child with a disability requires an interdisciplinary team that is able to integrate health care and therapeutic services in a coordinated fashion. This task is best accomplished through care coordination centered in the medical home.

Many potential obstacles can hinder families attempting to obtain care for children with special health care needs. The American Academy of Pediatrics policy statement Care Coordination in the Medical



Home: Integrating Health and Related Systems of Care for Children With Special Health Care Needs cites multiple barriers to effective care coordination, including:

- Lack of knowledge and information about the chronic condition
- Lack of community resources and a coordination process on the part of the primary care physician
- Primary care physicians who feel unprepared to be involved in equipment decisions for physically impaired children in their care
- Lack of communication between health care providers and other organizations involved in the child's care
- Lack of clearly defined roles for each team member, leading to redundancy of efforts and gaps in care
- Inadequate time and reimbursement for the administrative tasks associated with care coordination
- Language and cultural barriers between health care providers and families

Obstacles to accessing services can also be related to the family of a child with a disability. Although families who are knowledgeable about their child's condition can often effectively coordinate care, some families require more assistance with this task as a result of language barriers, educational level, economic situations, lack of insurance, or living far from sites of available specialty medical care. An effective, coordinated system of care must address these obstacles.

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## Chapter 66

## TRANSITIONS TO ADULTHOOD

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Sections of this chapter have been excerpted from the clinical report Supporting the Health Care Transition From Adolescence to Adulthood in the Medical Home, published in *Pediatrics* in 2011, with the permission of the American Academy of Pediatrics (AAP). The author of this chapter was a co-lead author of the clinical report and wishes to acknowledge the contributions of that document's authoring group to this chapter.

### INTRODUCTION

Transitions occur throughout life and are often highly anticipated: fetus to newborn, preschool to kindergarten, high school to college, single to married, and so on. The foremost responsibility of parenthood is the provision of a safe and stimulating environment wherein children can gain experiences and acquire those skills that will allow them to transition into a successful and productive adult life.

The ability of a child to fully achieve his or her potential is among the cornerstones of good pediatric health care. Delivery of developmentally appropriate



health care before, and continuing throughout, the transition from adolescence into young adult life is paramount to maximizing lifelong function, both physically and psychosocially. This is true for all youth with and without special health care needs. Paramount to a successful health care transition, pediatric and adult providers must clearly differentiate between the terms *transition* and *transfer*. *Transition* is a “process,” occurring over time, which may vary from patient to patient. *Transfer of care* is an “event,” which involves the actual handing off of patient care responsibilities from the pediatrician to the physician.

This chapter aims to facilitate the practice-based implementation of planning, decision-making, and documentation processes for youth who are approaching transition—including those who have special health care needs and those who do not. It summarizes the intent of the 2011 AAP clinical report *Supporting the Health Care Transition From Adolescence to Adulthood in the Medical Home* to provide a structure for training, continuing education, and research to further the understanding of best practices for transition of adolescents to adult care. It does not detail the activities conducted by *receiving* providers who accept patients into an adult model of medical home care.

## 2002 CONSENSUS STATEMENT

A consensus statement coauthored by the AAP, the American Academy of Family Physicians (AAFP), and the American College of Physicians—American Society of Internal Medicine (ACP-ASIM) published in 2002, clearly supports a timely and integrated transition of special needs youth into adulthood. This consensus statement focused on transition from the perspectives of pediatric and adult medical providers, patients, and caregivers. Barriers to transition were identified, and gaps in social, political, and fiscal viability for transition programs were addressed. The consensus statement identified 6 critical steps (Box 66-1) to improving adolescent transition, which have become widely recognized tenets of research, practice models, and policy implementation in the years since its publication.

After more than a decade of effort, the widespread implementation of health transition supports as a basic standard of high-quality care as part of the medical home approach has not been realized. To date, there has been only limited achievement of national health policy goals related to transition. Outcomes-related research efforts have, so far, failed to fully address the transition needs of adolescents with or without chronic conditions. A recent national survey demonstrated that pediatricians remain poorly informed about the conclusions of the consensus statement and that most pediatric practices neither initiate transition planning early in adolescence nor offer transition support services, which have been found to be critical for ensuring a smooth transition to the adult health care model. The survey authors note that “gaps in transition support are due in part to limited staff training; lack of an identified staff person responsible for transition; financial barriers; and anxiety on the part of

### BOX 66-1 2002 Consensus Statement: Six Critical Steps

- Ensure that all young people with special health care needs have an identified health care professional who attends to the unique challenges of transition and assumes responsibility for current health care, care coordination, and future health care planning. This responsibility is executed in partnership with other child and adult health care professionals, the young person, and his or her family. It is intended to ensure that as transitions occur, all young people have uninterrupted, comprehensive, and accessible care within their community.
- Identify the core knowledge and skills required to provide developmentally appropriate health care transition services to young people with special health care needs and make them part of training and certification requirements for primary care residents and physicians in practice.
- Prepare and maintain an up-to-date medical summary that is portable and accessible. This information is critical for successful health care transition and provides a common knowledge base for collaboration among health care professionals.
- Create a written health care transition plan by age 14 years together with the young person and family. At a minimum, this plan should include what services need to be provided, who will provide them, and how they will be financed. This plan should be reviewed and updated annually and whenever there is a transfer of care.
- Apply the same guidelines for primary and preventive care for all adolescents and young adults, including those with special health care needs, recognizing that young people with special health care needs may require more resources and services than do other young people to optimize their health.
- Ensure affordable, continuous health insurance coverage for all young people with special health care needs throughout adolescence and adulthood. This insurance should cover appropriate compensation for health care transition planning for all young people with special health care needs, and care coordination for those who have complex medical conditions.

pediatricians, adolescents, and their parents about planning for their future health care.” Other authors have cited, as a barrier to transition, the lack of developmentally appropriate tools to assess child and family readiness for transition. The result is that many pediatricians, youth, and families have found a limited availability of adult providers with whom to partner to arrange a smooth transition of care.

Where there are obstacles, there are also opportunities. Lacking a nationally accepted “gold standard” for transition, foremost among these opportunities is the flexibility to create transition platforms that may have a few common modalities but respond to the individual needs of the adolescent patient. Providers have opportunities to establish their own local and regional networks with adult medical services, with

the aim of building and establishing systems that can then be used by others. This chapter provides pediatricians a starting point for brainstorming ideas that might work best within their own unique medical home environments. The need is stronger than ever for the seamless transfer of care and personal health information from pediatric care settings to more adult settings and for all youth to function as independently as possible in promoting their own health as adults. The 2007 AAP Annual Leadership Forum designated as a top 10 priority the resolution “transitioning youth with special health care needs to adult health care.” *Bright Futures* provides a framework for anticipatory guidance throughout childhood and adolescence that encourages parental support of self-management and independent decision-making about health.

## AMERICAN ACADEMY OF PEDIATRICS CLINICAL REPORT

In 2011, the AAP convened an authoring group that produced the clinical report *Supporting the Health Care Transition From Adolescence to Adulthood in the Medical Home*. Like its predecessor consensus statement, the clinical report authors represented the 3 primary care medical societies (AAP, AAFP, ACP-ASIM), as well as patient and parent advocacy organizations and the federal government’s Maternal and Child Health Bureau. All 3 professional groups recognize the need to translate the principles of the 2002 Consensus Statement into practical operational guidance for the care of all children and youth as they transition to adulthood. Although youth with special health care needs require a broader range of considerations during their transitions, all youth need education, guidance, and planning to prepare to assume appropriate responsibility for their own health and well-being in adulthood. Most youth with chronic illnesses will survive into adulthood and, depending on the severity and specifics of their disability, should transition to an adult model of care for primary and most specialty care in both outpatient and inpatient settings. After the age of majority, all youth deserve to be treated as adults and to experience an adult model of care—although some individuals may require some level of decision-making support from a third-party proxy, such as through guardianship or power of attorney. Recent evidence has shown that higher executive function affecting impulsivity and decision-making continues to mature through the mid-20s. Older adolescents and young adults may require guided decision-making assistance from physicians and family members as they enter adult systems of care. Nevertheless, most youth will benefit from advance planning and preparation for that experience, regardless of whether they remain with their pediatrician or medical subspecialist after 18 years of age.

The AAP *Clinical Report* advocates an algorithmic approach that focuses on addressing issues from the viewpoint of the 3 main stakeholders in transition: the patient, the patient’s family, and the medical providers (both the outgoing pediatrician and the incoming physician). This report assumes that it is the youth, not the

physician, who is transitioning in his or her movement from one stage of life and development to another. The actions of the youth’s medical home involve not only planning for the *transition* of care by defining roles with the youth and family but also the *transfer* of some or all elements of care to an adult medical home setting or, in the case of a family medicine practice, to an adult medical home model. The medical home visit is a different process when the patient has reached the age of majority; adult patients have specific considerations and necessitate attention to new requirements, such as adopting consent for treatment processes and Health Insurance Portability and Accountability Act (HIPAA)-compliant forms. Health care transfer is one element of transition and has a defined content endpoint that may vary in age from patient to patient. Because both transition and transfer are influenced by environmental, socioeconomic, medical, and other factors, it is the responsibility of the medical home—in partnership with patients and their families—to coordinate efforts that ensure optimal outcomes for every patient.

## TRANSITION PLANNING

### Pediatrician and Physician Readiness

A key component in the primary care medical home’s support of the transition process is an explicit office policy describing the practice’s approach to health care transition, including the age and process by which youth shift to an adult model of care. This office policy applies to all youth (both with and without special health care needs), guides the process, and helps the youth and family members (or other caregivers) understand the medical home team’s roles and responsibilities as well as their own. The office transition policy should be visible and readily available to both patients and their families; it may be included in brochures, posters, or Web-based information about the practice. This office policy should clearly describe the goal of transition as part of lifelong preparation for a successful adult life and articulate how the early and ongoing process of transition planning facilitates the patient’s movement from a pediatric to an adult care mode.

### Family Readiness

The transition process is complex and potentially emotional for parents and other caregivers and guardians. Medical home team members must understand patients’ and parents’ perspectives and address their needs during transition. Although families make multiple transitions during their children’s lives, for many parents the pediatrician has been a constant, and departure from the known to the unknown may be stressful. This is particularly likely for parents of children with special health care needs. To make the process smoother for all involved, transition planning must anticipate challenges that parents may face as the youth enters adulthood.

Pediatricians should educate parents and youth and school staff about their roles in supporting the transition process. This education should include information about how the health care environment changes

when the youth legally becomes an adult and differences between pediatric and adult medicine models. The physician's goals are to normalize the transition process, address the families' concerns and questions, and foster a team approach to help facilitate the acquisition of skills and tools that the youth can use in transition and beyond. The family members or other caregivers should be engaged and open to the process (eg, learning about any upcoming changes in health coverage), encourage autonomous decision-making and self-care on the part of the youth, and share their questions or concerns with the physician as they adjust to their shift from primary decision maker and caregiver to a more supportive role.

### Youth Readiness

For transition planning to succeed, pediatricians, physicians, and parents or caregivers must view the youth as drivers in the process, encouraging youth to assume increasing responsibility for their own health care. Empowering youth through transitions fosters the development of self-management skills and tools needed for individuals to gain more control over their lives. This is particularly critical for youth with special health care needs, who may require a broader range of considerations during the transition process.

Although the clinical report presents optimal ages for initiating and conducting transition planning, it is never too early to begin conversations among the pediatrician, family or caregivers, school staff, and patient about planning for the future—again, especially for children with special health care needs. For this population, similar conversations may occur in the educational system regarding Individualized Education Plans (IEPs), when appropriate. These conversations should reinforce and buttress each other. Prioritizing and reinforcing the value of independence and decision-making as part of the transition planning process not only reinforces such messages on the part of providers, family members or other caregivers, and the broader community but also facilitates the individual's successful transition to adult medical care and active participation in maintaining his or her own health.

## AN ALGORITHM TO GUIDE TRANSITION

Figure 66-1 and Figure 66-2 show an algorithm that specifies the protocol for managing the transition process, assists providers in implementing the transition process, and provides a transition structure for youth and their families. It is intended for use by physicians within a medical home setting as a starting point for identifying youth who have reached a time in their lives in which health care transition should be integrated as a routine part of the office visit. Individual steps along the transition process will vary from one youth to the next depending on individual patient, family or caregivers, pediatrician, and community-resource factors. Discussion of the transition process is best introduced to a patient and his or her parents by the time a child is roughly 12 years of age

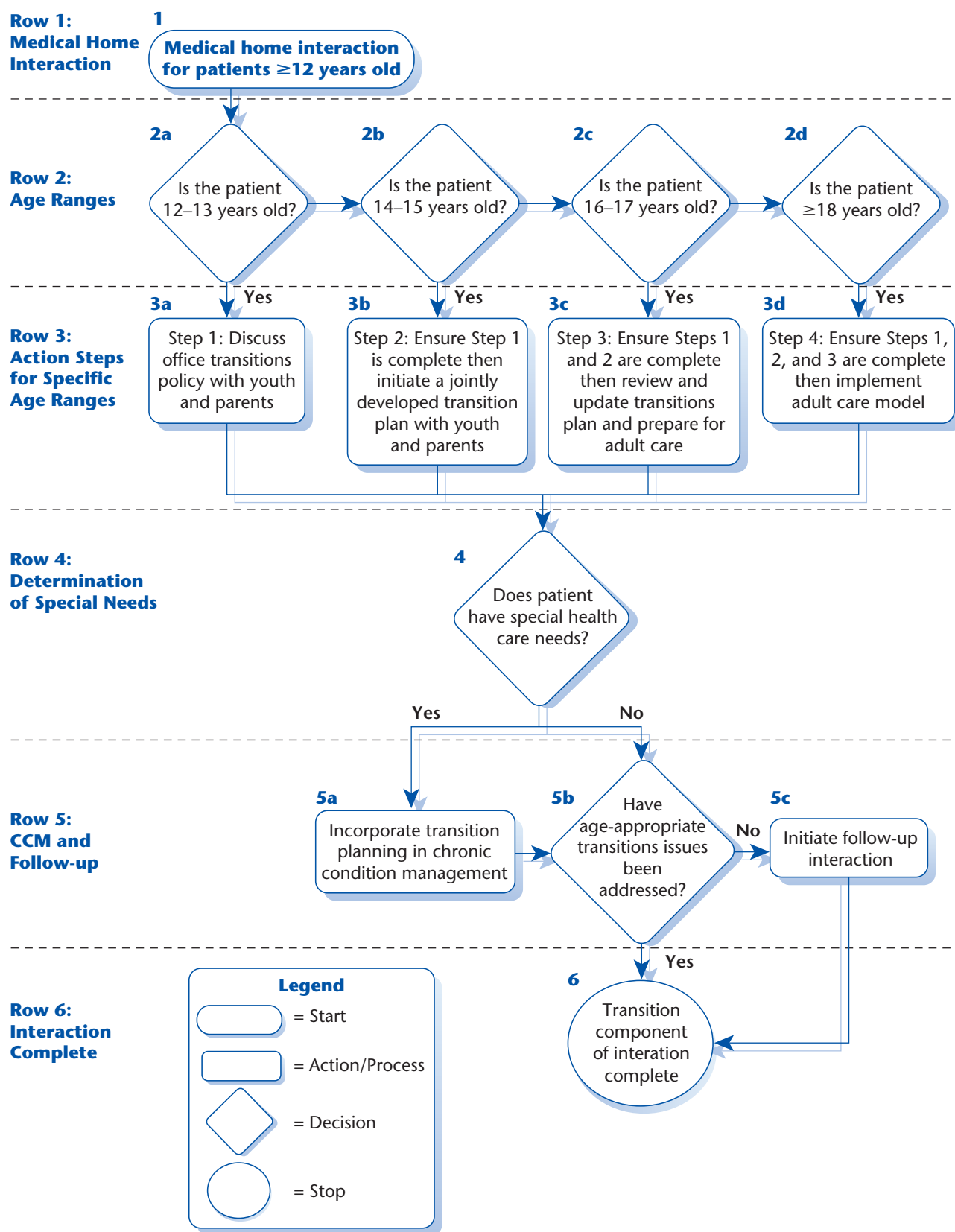
(corresponding to “middle school” development) and ideally should occur during a health maintenance or a chronic care management visit. The AAP clinical report authoring group thought this age was especially important for children with special health care needs and that children without chronic medical issues could wait until 14 years of age (corresponding to “high school” development) to begin the transition process. Transfer itself should typically occur within the 18- to 21-year age range, although it can occur earlier because some internists accept new patients at 15 years of age, particularly if they see other family members as well. Some youth may experience a variety of health care settings as they move from pediatric to adult models of care—for example, while in college or military service—but these settings are not likely to provide a comprehensive medical home. Youth should either remain in their pediatric medical home or be well established in their adult medical home while receiving episodic care in these settings.

Every youth who reaches the age of transition from a pediatric medical home or becomes a legal adult within his or her current medical home needs to have a basic transition plan developed through collaboration among the youth, family, and physician. Those with special health care needs require additional components specifically to address their chronic care management and often in conjunction with school staff.

## TRANSITION PLAN COMPONENTS FOR EVERY CHILD AND YOUTH

There are 4 recommended components for a transition plan, each of which can be augmented by the use of specific tools to facilitate the work of the physician, youth, and family (Box 66-2).

1. **Assess for transition readiness.** The physician, family, school staff, and youth begin by articulating realistic goals for transition and identifying new skills that will be needed by the patient to meet those goals successfully. Although it is not the main focus of the medical home, the readiness assessment should be “person centered” and include identification of other areas of readiness for transition into the adult world in general, including education or vocation, independent living, and patient awareness of medical needs and age-appropriate preventive care, as outlined by such resources as *Bright Futures*. Numerous tools are available in the form of “readiness checklists” that allow providers to obtain a baseline idea of the current capacity of the youth, family, and providers to successfully achieve the outlined goals. Transition progress should be measured through periodic reassessment using the same checklists at each visit. (See Tools for Practice for selected transition-readiness materials.)
2. **Plan a dynamic and longitudinal process to accomplish realistic goals.** The first step of transition planning is the establishing goals that allow the youth to achieve as seamless a transition as possible. A formal transition plan, written in partnership with the youth and outlining specific actions that are necessary to meet the stated goals, should be part of



**Figure 66-1** Transitions algorithm. (From American Academy of Pediatrics, American Academy of Family Physicians, American College of Physicians-American Society of Internal Medicine. Clinical report—supporting the health care transition from adolescence to adulthood in the medical home. *Pediatrics*. 2011;128:1–20.)



ALGORITHM COMPONENT	DESCRIPTIVE TEXT
<b>Medical home interaction for patients <math>\geq 12</math> years old</b>	<b>1.</b> Initiate first step in the health care transition planning process at age 12.
	<b>2a, 2b, 2c, 2d. Age Ranges.</b> By age 12, conduct surveillance to assess any special health care needs. Start actual transition planning by age 14. By ages 16–17, transition planning should be well established. At age 18, initiate an adult model of care for most youth, even if there is no transfer of care. If transition planning does not occur on the schedule described by the algorithm, a concentrated effort is required (eg, special visits) to complete the process successfully.
<b>Step 1:</b> Discuss office transitions policy with youth and parents	<b>3a.</b> Every practice should have a written transition policy that is prominently displayed and discussed with youth and families. The policy should explicitly state the practice's expectations and care process for the health care transition of their adolescent patients to an adult model of care.
<b>Step 2:</b> Ensure Step 1 is complete then initiate a jointly developed transition plan with youth and parents	<b>3b.</b> The practice should use a standard transition plan that can be adapted for each patient's needs. This tool should include components to obtain an accurate assessment of the patient's ability to transition successfully. Providers should interview youth and family members to identify needs and assess the intentions and motivations for youth independence.
<b>Step 3:</b> Ensure Steps 1 and 2 are complete then review and update transitions plan and prepare for adult care	<b>3c.</b> Transition plans must be reviewed regularly and updated as necessary. The provider must also perform surveillance for changes in the youth's medical status and address youth and family concerns that may warrant changes in transition goals. Failure to achieve transition-readiness goals warrants reevaluation of the existing plan and increased frequency of medical home interventions/visits. A "pretransfer" visit to the adult medical home could be conducted during the year before the transfer.
<b>Step 4:</b> Ensure Steps 1, 2, and 3 are complete then implement adult care model <sup>a</sup>	<b>3d.</b> Transition to an adult model of care occurs appropriate for youth's developmental level, which is followed as appropriate by transfer to an adult medical home. Complete medical records should be delivered to the adult provider, along with a portable summary, which is also provided to the patient or guardian. For children and youth with special health care needs, direct communication between pediatric and adult providers is essential, because adult medical personnel may be unfamiliar with certain pediatric conditions.

**Figure 66-2** Algorithm descriptors. (From American Academy of Pediatrics, American Academy of Family Physicians, American College of Physicians-American Society of Internal Medicine. Clinical report—supporting the health care transition from adolescence to adulthood in the medical home. Pediatrics. 2011;128:1–20.)

Continued


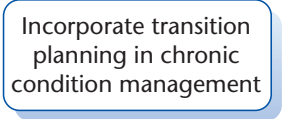

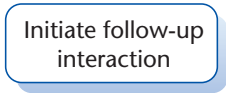
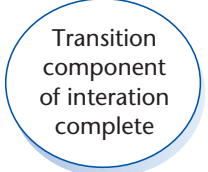
ALGORITHM COMPONENT	DESCRIPTIVE TEXT
 <p>Does patient have special health care needs?</p>	<p><b>4.</b> Transition planning for children and youth with special needs should include specific chronic care management (CCM) activities such as use of registries; care plans; care coordination; CCM office visits; and comanagement with medical subspecialists. Transition goals must be individualized to account for variations in the complexity of a youth's condition and in the youth's intellectual ability and guardianship status.</p>
 <p>Incorporate transition planning in chronic condition management</p>	<p><b>5a.</b> Youth with special health care needs requires an expanded transition-planning process. Transition planning in CCM includes addressing the exchange of complex health information; competencies for self-care; transfers of specialty care; and issues related to insurance entitlements, guardianship, and eligibility for adult services. In a medical home, such youth may have a written care plan as part of the medical record. At age 14, this plan should include a section titled "transition plan," which should be expanded and developed as the youth approaches age 18 and beyond.</p>
 <p>Have age-appropriate transitions issues been addressed?</p>	<p><b>5b.</b> Use of transition-planning tools and readiness checklists facilitate the provider's ability to ensure that all age-appropriate transition issues have been addressed. Each action step must be completed in order, even if it means the provider has to schedule specific visits to initiate and complete steps missed earlier in the process to catch up before the next visit.</p>
 <p>Initiate follow-up interaction</p>	<p><b>5c.</b> Focused tasks involving little detail or complexity can be addressed by the medical home care coordinator, medical provider, or other appropriate staff through telephone or electronic media. More complex issues may necessitate face-to-face office visits.</p>
 <p>Transition component of interaction complete</p>	<p><b>6.</b> The provider is finished with the transition tasks for that specific interaction or visit; transition planning is an ongoing activity that occurs at every interaction.</p>

Figure 66-2, cont'd

the patient's medical record by age 14 years. The written transition plan should account for cultural, developmental, organizational, and contingency-related concerns. These last would arise specifically out of the child's individual health care needs, requiring plans and processes to address any "contingency" that may develop for that individual. In general, recommended categories within the transition plan include the plan's main goals; identification of whom, within the medical home, will be responsible for overseeing or coordinating the plan;

the timeline for accomplishing stated goals; the skills required by the youth to achieve maximum self-management; the family or other caregivers' role; and proposed financing of the youth's adult health care.

3. *Implement* the plan through education of all involved parties and empowerment of the youth in areas of self-care. After the transition plan has been outlined and goals have been established, specific activities should be initiated to ensure the youth acquires needed skills: for instance, scheduling

**BOX 66-2 Transition Plan Components**

- Assess for transition readiness.
- Plan a longitudinal process to accomplish realistic goals.
- Implement the plan through education of youth, family, and medical providers.
- Document progress to facilitate ongoing reassessment.

one's own medical appointments, obtaining medications, having a one-on-one dialogue with a physician, and being familiar with one's medical history and any needed medications. Ongoing discussion of the transition plan at all health care visits is a key step in accomplishing transition goals. This should be a dynamic process that begins gradually and is assessed at regular intervals. The timing of these reassessments depends on the capacity of the youth, the youth's family and other caregivers, and the amount of time remaining until the anticipated transfer of care to the adult medical home. The transition readiness checklists used during the initial assessment are the tools of choice to document accomplishment of specific goals and tasks. It is highly recommended that a medical home use the same checklists throughout an individual patient's entire transition process to provide continuity over time and assist youth, families, school staff, and providers to remain on track regarding specific goals that have yet to be accomplished. School staff can assist youth with acquiring needed skills. Throughout this process, the physician should continually strengthen the partnership with the patient, the family members, and other caregivers by engaging in active dialogue and information sharing, empowering the youth to take on the appropriate new roles. It is important to recognize that, at the age of maturity, the youth becomes a legal adult (except when guardianship by another person has been obtained). As a result of confidentiality laws, the youth should be seen alone unless other arrangements have been legally made. One to 2 years before the anticipated transfer of medical care, the pediatrician should assist the youth, family, or caregivers in identifying potential adult practices, prepare the appropriate documentation for transition, and suggest that the youth interview the adult practice before making a final transfer.

4. *Document* progress to enable ongoing reassessment and movement of medical information to the receiving physician. Many excellent tools are available to document the transition process, including some that can be used within an electronic health record (EHR) system and others that are paper based. For example, providers might place a transition front sheet on the patient's chart or use a "dashboard" tool in the patient's EHR at age 12 years. Both of these methods work well to flag

**BOX 66-3 Portable Medical Summary Items for All Children and Youth**

- Allergies
- Basic demographics
- Current communication preferences, as applicable (eg, e-mail, cell phone)
- Current medications and alternatives (eg, herbals, complementary and alternative medicine)
- Family history
- Focused screening data as indicated: family history of heart disease, diabetes, associated laboratory tests
- General status: nutrition, physical activity, education, work, living status
- Immunization history
- Social history: independent living arrangements, custodians, emergency contacts
- Medical insurance coverage plan information
- Medical, mental health, and dental providers with contact information
- Medical issues (current) and past medical history with dates: diagnoses, surgeries, imaging studies, laboratory tests
- Risk assessments: smoking, alcohol, substance use, mental health, sexual health, oral health

From American Academy of Pediatrics, American Academy of Family Physicians, and American College of Physicians, Transitions Clinical Report Authoring Group. Supporting the health care transition from adolescence to adulthood in the medical home. *Pediatrics*. 2011;128(1):182–200.

important actions that have occurred or need to be scheduled as part of the transition process. Regardless of the specific tool used, it should provide a flexible method for assessing the youth's readiness for transition and progress made toward that goal. Gathering relevant information to document the patient's transition progress is of paramount importance as the anticipated transfer date approaches. A well-documented barrier to adult medical providers' acceptance of transitioning youth is a lack of accompanying medical documentation. Medical documentation should be portable and include 3 critical components: the transition plan (see earlier), longitudinal readiness checklists (see earlier), and a portable medical summary. The portable medical summary contains basic medical and social data to give adult medical providers the information necessary to begin assuming care for the patient. All youth should help create and receive this portable medical summary because these are essential topics and elements that are critical to transition. Although the categories of the medical summary are appropriate for all chronic health conditions, specific information should be tailored to the individual's conditions. A representative, although not necessarily exclusive, list of items that should be found in the portable medical summary is detailed in Box 66-3 and Box 66-4.

### BOX 66-4 Additional Portable Medical Summary Items for Youth With Special Health Care Needs

- Additional current providers, including subspecialists, therapists, and dental professionals
- Agency providers, including medical supplies, home health agencies, and day services
- Anticipatory disease-related information and planned surgeries
- Care coordinators and case managers, including those from insurance companies
- Communication preferences: literacy levels, preferred language, preferred communication methods
- Condition-related nutritional issues
- Condition-related periodic screening results and recommendations
- Current and planned future assignment of legal decision-making status
- Emergency care plan: actions and contacts in case of emergency and emergency information form
- Enhanced medication history, including preferred means of delivery (eg, liquids only), medications successfully used for flare of condition, previous failed medication trials, and known formulary and authorization issues
- Equipment and device information (including durable medical equipment and implantable devices): contact information for providers, date of receipt, and date of insertion of equipment
- Functional status, including the individual's appearance when content versus stressed or pained
- Laboratory data and other studies (including molecular and genetic testing; past evaluations conducted)
- Nutritional considerations (eg, dietary restrictions, feeding schedules)
- Pertinent test results, including molecular and genetic testing and important radiology results
- Pharmacy phone and fax numbers
- Primary and secondary medical conditions and comorbidities
- Status of prior advance care planning discussions

From American Academy of Pediatrics, American Academy of Family Physicians, and American College of Physicians, Transitions Clinical Report Authoring Group. Supporting the health care transition from adolescence to adulthood in the medical home. *Pediatrics*. 2011;128(1):182–200.

## INTEGRATING TRANSITION PLANNING INTO CHRONIC CONDITION MANAGEMENT FOR CHILDREN AND YOUTH WITH SPECIAL HEALTH CARE NEEDS

Transition planning applies to all children and youth and should follow the steps defined in Figure 66-1 and Figure 66-2. The presence of chronic health conditions or developmental disabilities imposes specific primary

### BOX 66-5 Five Tenets of Chronic Care Management Within the Medical Home

- Registry of youth with special health care needs
- Care plan
- Care coordination
- Chronic care management visits
- Comanagement

care requirements on the family-centered medical home characterized as chronic care management (CCM). Effective CCM, in turn, demands additional considerations related to transition planning. CCM involves an explicit, planned process of coordinated, proactive care aimed at achieving the best possible clinical and functional outcomes for the individual patient and for the population of patients with chronic conditions. While following the general sequence and timing of the transition algorithm, transition planning for children or youth with special health care needs will usually be incorporated into the broader CCM process. Early in the transition planning process, it is important to determine whether or not the youth is likely to be a completely independent decision maker as an adult or require decision-making support from a third-party proxy, such as through guardianship or power of attorney. Even with these considerations in mind, it is important to plan with the youth and family or caregivers to achieve the maximum possible participation of the youth in the transition planning process (Box 66-5).

1. **Registry:** The family-centered medical home CCM process may include a registry of the practice's patients with special health care needs. The registry should be searchable on the basis of patient age so that youth who are ready for each stage of the transition process (see algorithm) can be identified. The registry might also include fields indicating which steps in the transition process are due for completion, have been completed, or are past due for completion. Additional fields unique to the transition of children or youth with special health care needs might include "discussed guardianship" or "identified adult specialists."
2. **Care plan:** Some children or youth with special health care needs will have an action-oriented care plan for tracking current problems and health-related needs, including what action is needed, who will be responsible, and by when the action should have occurred. When a child or youth with special health care needs enters the age group covered in the transition algorithm, the action-oriented care plan should add a transition section that becomes the youth's transition plan. The incorporation of the transition plan into the general action-oriented care plan assists the integration of transition planning with other health-related actions.
3. **Care coordination:** One of the foundations of the family-centered medical home, care coordination



assumes special importance for children or youth with special health care needs who use the health care system frequently and may have multiple service providers. The coordination of health care for the child or youth with special health care needs should take into consideration the youth's transition plan and the current stage of the transition planning process. Care coordination may be instrumental in supporting the transfer of care from various pediatric medical subspecialists to their adult specialty counterparts.

4. *Chronic care management visits:* The family-centered medical home provides periodic CCM visits that may occur in addition to health maintenance and acute illness management visits to monitor the status of patients with chronic conditions and implement or update their care plans. These CCM visits provide occasions for transition education and planning.
5. *Comanagement:* Explicit comanagement between primary care physicians and specialists (medical and mental health) ensures communication and prevents omissions and redundancies of care. It explicitly identifies the respective roles of the primary care medical home and the subspecialists in a manner that is clear to each physician, to the youth, and to the family and other caregivers, including those at school. The locus of management may shift from time to time between primary care and specialty care depending on the youth's age and on the complexity and acuity of specific health problems. Comanagement with subspecialists assumes particular importance in transition planning because it provides the framework in which to plan for and implement the transfer of care from pediatric subspecialists to adult medical subspecialists, surgical specialists, and mental health specialists. Comanagement may also be the context for a dialogue of explicit communications between the youth's pediatric medical home and future adult medical home physician. Comanagement planning with respect to transition planning should include the timing and process for specific transfers of care in each relevant specialty area. In some cases, the plan may be to retain a pediatric subspecialist into adulthood because of the absence of appropriately qualified adult medical subspecialists. Some diagnosis-specific programs, including clinics for hemophilia and cystic fibrosis, have established strong programs to guide subspecialty transfer. The National Hemophilia Foundation established a nationwide network of hemophilia diagnostic and treatment centers and, in 2003, adopted transition guidelines that provide age-related recommendations. These models and transition guidelines acknowledge that there are continuing areas for improvement such as addressing preventive health needs or promoting the adult model of decision-making by young adult patients.

## ROLE OF THE ADULT MEDICAL HOME AS RECEIVING PROVIDER

The transition of a young adult makes it necessary to identify an adult practice that is prepared to accept the patient and provide the full range of care and care

coordination in an appropriate, patient-centered care model. Most young adults are healthy and require only the continuation of health maintenance and promotion and the availability of an adult medical home when acute illnesses arise. Yet even the population of young adults without special health care needs includes those with adolescent-type risky behaviors, mental health and substance use issues, and reproductive health needs that require enhanced attention. Young adults with disabilities and chronic medical and mental health conditions are more vulnerable to failures in the transition of health care services and require more attention from providers and the health care system. Fundamentally, *clinical hurdles* and *process hurdles* present major challenges for a successful move to adult-oriented care for young adults with special health care needs.

Shortages in the adult medical home workforce may limit future capacity to accommodate this diverse patient population. Thus *clinical hurdles* largely encompass deficits in education or experience of some physicians to effectively care for patients with special health care needs, as well as financial disincentives that limit access to adult-oriented care. Reviews of the perspectives of physicians participating in the medical transition of young adults with special health care needs found that, when physicians were exposed to the process of transitioning young adults in the context of their residency training experiences, they were much more likely to incorporate it into their practices following residency. Anecdotally, however, these residency training experiences are not common, and many practicing physicians have learned on the job to manage patients with complex needs. A recent survey of internists' needs when accepting a transitioning youth reported that education in congenital and childhood-onset conditions was critical. Additionally, respondents cited the need for identified specialists to help with management decisions. Although physicians have the role of assuming the care and management of these youth, they should not be expected to do so without supports that are more readily available to pediatricians (eg, state Children's Health Insurance Programs [CHIPs], special education services and resources through public school systems, and Social Security benefits for children with specified conditions); yet too often, they are.

Further work is needed to promote an adult model of care that is responsive to the particular needs of all young adults and sensitive to the specific challenges associated with providing high-quality care to young adults with specific chronic conditions (eg, autism, cerebral palsy, intellectual disability, sickle cell disease, mental health disorders). Ideally, the health care payment system would encourage early and ongoing professional relationships with pediatricians in anticipation of transitions and support comanagement with primary care and specialty pediatricians while the patient is becoming established with the adult practice. At some point, the responsibility for the transitioning young adult will come to rest with the physician, at which time the physician and clinical team should assume a key role in supporting the young adult and his or her family in finding a new balance in

the adult medical setting. The transitioning youth's developmental and functional abilities may influence the transition's success. The continued involvement of the family or caregivers, and school staff as appropriate, should be encouraged during this transition period. Working with the family, caregivers, and other supports to ensure adequate health care insurance and financing for these youth is another major goal of transition.

*Process hurdles* include challenges in the communication of appropriate medical records; lack of adult-focused state, regional, and local resources to provide adults with disabilities; preparation of the young adult and his or her family or caregivers to integrate into an adult-focused medical system; issues related to payment (some addressed by provisions of the Patient Protection and Affordable Care Act of 2010); and young adults' lack of knowledge about health insurance. Adult providers should not expect a "handoff" from pediatric practices but rather a "handshake." Establishing collegial relationships between pediatric and adult medical providers facilitates ongoing access to medical care for patients in transition. Although every transition is different, the best transitions include several core elements. Receivers (the adult medical home team) may reasonably expect that they will be provided with concise and accurate medical information about the youth and his or her condition, as described previously. In addition, receivers should ensure the following:

- The responsible party for medical decision-making has been clearly identified.
- Unambiguous adult consent and confidentiality policies have been explained to the patient and his or her family and other caregivers.
- Communication has occurred about how the practice operates for issues such as paperwork and medication refills.
- Access to the practice for routine and after-hours care has been discussed with the patient and his or her family and other caregivers.

Although many young adult patients transition to adult practices from pediatric-based practices, the unique relationship that many family physicians have with their patients allows for ongoing care throughout the life span. Even though transfer of care may not occur in these situations, it is likely that young adults with special health care needs have pediatric specialists who may wish to facilitate transfer to their adult counterparts. The family physician has the special responsibility to be aware of these needs and, in some situations, play the role of both the "sender" and "receiver."

Certainly, successful transition is a test of the degree to which a practice operates within the ideals encompassed in the medical home model of care. A team approach to the challenges of transition is necessary to facilitate the level of care for which adult providers strive. Inclusion of local public health and community-based resources should be considered wherever possible to ensure that the medical home approach is followed, particularly for vulnerable patient populations with special health care needs.

## GOT TRANSITION: AN IMPORTANT RESOURCE FOR PHYSICIANS

Established in 2010 through a cooperative agreement between the US Maternal and Child Health Bureau/Health Resources and Services Administration and the Center for Medical Home Improvement (CMHI) at Crotched Mountain Foundation, *Got Transition* is the National Health Care Transition Center, focusing on the implementation and dissemination of health care transition best practices in primary care medical homes and specialty settings. This center has become the national resource for health care professionals, families, youth, and state policymakers whose effort focuses on transitioning youth to adult medical homes. Information for medical providers, youth, families, and other stakeholders, including resources for establishing transition plans, portable medical summaries, and ongoing research in the field of transitioning, can be found at [www.gottransition.org](http://www.gottransition.org).

## SUMMARY

A well-timed, well-planned, and well-executed transition from child- to adult-oriented health care, ideally occurring between the ages of 18 and 21 years, enables youth to optimize their ability to assume adult roles and activities. For this reason, transition planning should be a standard part of providing care for all youth and young adults, and every patient should have an individualized transition plan, regardless of his or her specific health care needs. A series of consensus activities has emerged, designed to ensure that uninterrupted, high-quality, and developmentally appropriate health care services are available to patients moving from adolescence to adulthood. This chapter provides a clear timeline, beginning at 12 years of age, to assist providers in implementing transition's 4 specific activities: discussion of medical home transition policy, initiation of transition plan, review and update of the transition plan, and implementation of an adult care model. The Health Care Transition Planning Algorithm from the 2011 AAP clinical report specifies the protocol for managing the transition process, helps providers implement the transition process, and provides a transition structure for patients and their families. The algorithm includes a branch with expanded, generic guidelines for transitioning youth with special health care needs who require chronic condition management. Primary care providers and specialists are encouraged to make this process specific for their own needs and those of their patients.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *Building the Legacy: IDEA 2004* (Web site), US Department of Education ([idea.ed.gov](http://idea.ed.gov))

### Engaging Patient and Family

- *Building Your Care Notebook* (Web page), National Center for Medical Home Implementation ([medicalhomeinfo.aap.org/tools-resources/Pages/For-Families.aspx](http://medicalhomeinfo.aap.org/tools-resources/Pages/For-Families.aspx))

- *Emergency Information Form* (template), American Academy of Pediatrics ([www.aap.org/advocacy/blankform.pdf](http://www.aap.org/advocacy/blankform.pdf))
- *Frequently Asked Questions About Section 504 and the Education of Children with Disabilities* (fact sheet), US Department of Education ([www.ed.gov/about/offices/list/ocr/504faq.html](http://www.ed.gov/about/offices/list/ocr/504faq.html))
- *Transitioning Youth to an Adult Care Provider* (booklet), Got Transition ([www.gottransition.org/resourceGet.cfm?id=208](http://www.gottransition.org/resourceGet.cfm?id=208))

### AAP POLICY

American Academy of Pediatrics, American Academy of Family Physicians, and American College of Physicians, Transitions Clinical Report Authoring Group. Supporting the health care transition from adolescence to adulthood in the medical home. *Pediatrics*. 2011;128(1):182–200 ([pediatrics.aappublications.org/content/128/1/182](http://pediatrics.aappublications.org/content/128/1/182))

American Academy of Pediatrics, American Academy of Family Physicians, American College of Physicians–American Society of Internal Medicine. A consensus statement on health care transitions for young adults with special health care needs. *Pediatrics*. 2002;110 (Suppl 3):1304–1306 ([pediatrics.aappublications.org/content/110/Supplement\\_3/1304](http://pediatrics.aappublications.org/content/110/Supplement_3/1304))

### SUGGESTED READINGS

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## Chapter 67

## PALLIATIVE, END-OF-LIFE, AND BEREAVEMENT CARE

Alexander L. Okun, MD

*Most physicians caring for children have not pursued the study of handling death as diligently as they have pursued the treatment of the diseases which cause it.*

VERNICK AND KARON (1965)

This observation remains as true today as it was 50 years ago when it appeared in the sentinel paper, “Who’s Afraid of Death on a Leukemia Ward?” Yet in the intervening half century, the world of pediatrics

has experienced the birth, growth, and development of the field known as palliative and hospice care. In 1997, the Institute of Medicine (IOM) produced the landmark report, *Approaching Death: Improving Care at the End of Life*, followed in 2003 by *When Children Die: Improving Palliative and End-of-Life Care for Children and Their Families*, which focused on children with life span-limiting conditions and their families. Progress in the interim is reviewed in the 2014 IOM report, *Dying in America: Improving Quality and Honoring Individual Preferences Near the End of Life*.

Along with a collection of outstanding textbooks published in the past 15 years, influential research and guidance that form the basis for this chapter have emerged from the pediatric subspecialty fields of oncology, emergency medicine, pulmonology, critical care, palliative and hospice medicine, and neonatology. Specific citations to a list of references can be found in the online version of this chapter. For information on neonatal palliative and hospice care and bereavement, the reader is referred to Chapter 117, *Support for Families Whose Infant Is Sick or Dying*.

The American Academy of Pediatrics (AAP) calls for ensuring that “all clinicians can provide basic palliative care” and are “trained in basic approaches to prevent, assess and manage symptoms and to communicate in a clear, caring and collaborative manner with patients and families.” This chapter is aimed at general pediatricians and subspecialists seeking to acquire the knowledge and skills needed to do just that. The greatest emphasis is placed on what has recently been learned from empirical studies on the experiences of children with life span-limiting conditions and their families; what these children and families say are the most helpful things pediatricians and other health professionals can do for them; and ways that pediatricians can provide that help.

Throughout this chapter, the term *pediatrician* will be used to refer to the pediatrician, general practitioner, family physician, nurse practitioner, physician assistant, or other health professional acting as the primary care, subspecialty care, outpatient, or inpatient care provider or practitioner. The term *caregiver* will be used to refer to the child’s parents or family members providing the bulk of care. The terms *family* and *families* will be used to refer to the larger collection of those closely related to the child and caregivers, together regarded by the National Hospice and Palliative Care Organization as the “unit of care.”

### DEFINITION OF TERMS

Contemporary practice of *palliative care* embraces a broad scope of services from a point early in the illness, ideally close to the time of diagnosis of a life span-limiting condition. As described by the IOM in 2003, pediatric palliative care seeks to “prevent or relieve the physical and emotional distress produced by a life-threatening medical condition or its treatment; help patients with such conditions and their families live as normally as possible; and provide them with timely and accurate information and support in decision making.” The World Health Organization



(WHO) defines palliative care for children as “the active total care of the child’s body, mind and spirit, and also involves giving support to the family.”

Since the late 1990s, the WHO has advised that palliative care be delivered as an integrative approach to curative care, alongside it, rather than instead of it. The AAP recommends that pediatric palliative care and pediatric hospice care be “provided as integrated multimodal care,” “including cure-seeking, life-prolonging (when in the child’s best interest), comfort-enhancing, and quality-of-life enriching modes of care, along with psychological, spiritual and social support for the family.” Still commonly misunderstood to pertain only to the care of persons who are dying, palliative care is an approach to care that is appropriate for all persons with serious, chronic, life span-limiting conditions.

*End-of-life care* is a type of palliative care that is focused on more intensive assessment and control of symptoms, maintenance of comfort, and psychological and spiritual support in the period before an anticipated death. This period may be brief, as in hours or days, or more prolonged, weeks to months. The duration of end-of-life care among children with chronic neurologic illnesses is longer and less predictable than among those with cancer. Its orientation and organization share many features of palliative care, but it is intended, in the words of Feudtner and colleagues in a 2014 IOM report, for children whose “illness, injury or condition progresses to the point where the health status . . . is diminished below a level that would make it possible to live with . . . meaningful or acceptable quality of life.” In most cases, palliative care interventions should have been implemented long before this stage has been reached. In a 10-year retrospective study using a database capturing pediatric hospitalizations, among more than 24,000 children who died following a hospitalizations of 5 days or longer, the receipt of palliative care services was associated with shorter hospital stays, fewer interventions, and fewer admissions to and deaths in the critical care unit.

Several sets of guidelines and practice recommendations have been promoted by national and international organizations. Some are listed in Box 67-1.

The term *hospice* refers to a combined philosophy of care, program of care, and site of care (the child’s home, hospital room, or an independent facility devoted to care for patients in the last stages of life). In the United States, hospice most commonly refers to a set of services delivered by organizations approved by Medicare, in the home or inpatient settings.

Hospice care shares the priorities of end-of-life care but in the past was restricted to persons willing to forgo life-sustaining interventions or treatments. The Concurrent Care for Children requirement of the Patient Protection and Affordable Care Act of 2010 eliminated the requirement that children with life span-limiting conditions who were insured by Medicaid or the state Child Health Insurance Plans forgo curative or life-prolonging medical treatment to receive hospice care. This advance requires extensive work on the part of pediatricians and collaborating team members to coordinate and

### BOX 67-1 Some Guidelines and Practice Recommendations for Pediatric Palliative and End-of-Life Care

- American Academy of Pediatrics Section on Hospital Medicine and Committee on Hospital Care. Pediatric palliative care and hospice care commitments, guidelines and recommendations. *Pediatrics*. 2013;132:966–972
- NHPCO 2009: National Hospice and Palliative Care Organization. *Standards of practice for pediatric palliative care and hospice*. Alexandria, VA: NHPCO; 2009
- Ethier AM, Rollins J, Stewart J. *Pediatric oncology palliative and end-of-life care resource*. Chicago, IL: Association of Pediatric Hematology/Oncology Nurses; 2010
- National Cancer Institute. 2014. *Pediatric supportive care for health professionals (PDQ)*. ([www.cancer.gov/types/childhood-cancers/pediatric-care-hp-pdq](http://www.cancer.gov/types/childhood-cancers/pediatric-care-hp-pdq))

ensure coverage for the array of services often needed in the home toward the end of a child’s life.

Although dying at home is widely preferred by adults in hospice, children’s and families’ preferred place of death may or may not be the home. With meticulous advance planning for symptom assessment and management, transfer home can be arranged for children who are assisted by practically any technology, short of extracorporeal membrane oxygenators, even with the intent of discontinuation a short while after transfer.

*Grief* comprises a collection of feelings and sensations, among the most powerful in life, resulting from loss. When these begin before an expected loss, it is referred to as *anticipatory grief*. *Bereavement* is a process that continues lifelong after the loss, beginning with *mourning*, in which the loss is incorporated into the lives of those who survive. Grief and bereavement are further explored later in this chapter.

## CHILDREN INVOLVED

Depending on the degree of involvement in the care of children with complex chronic conditions, a primary care pediatrician based in a resource-rich country might work with children with life span-limiting conditions and their families as seldom as once or twice every 10 years or as often as once or twice a month. Pediatric subspecialists would be expected to be involved much more frequently.

Each year in the United States, roughly 45,000 children die. Just over half of these deaths occur during the first year of life. Two-thirds of infant deaths (those before the child’s first birthday) occur during the first 28 days of life (birth to 27 days); nearly half of these deaths occur during the first hour or day of life. At any given time in the United States, a similar number of children, about 45,000, are estimated to have life span-limiting conditions. Following guidance of the IOM,



WHO, National Hospice and Palliative Care Organization, National Cancer Institute, and Children's Oncology Group and Association of Pediatric Hematology and Oncology Nurses, the principles of palliative care presented in this chapter should be incorporated into the treatment of all these children.

### Childhood Deaths

In resource-rich countries like the United States and United Kingdom, accidents, congenital malformations, and malignancy are the primary causes of death after the first year of life. After accidents, assault and suicide are the second and third most common causes of death among adolescents. Cause-specific death rates for African American children remain as much as 1.5 to 3 times higher than those for white children in most 5-year age groups for conditions originating in the perinatal period, congenital anomalies, accidents, and the category classified as "all other causes."

Childhood deaths in low-resource countries and developing regions are more common and have different causes compared with those in resource-rich countries. Although mortality rates in children younger than 5 years of age have dropped to half of 1990 levels, as calculated by Liu and colleagues in 2012, more than 6 million children still die each year worldwide. More than 98% of these deaths occur in developing regions. Globally, 44% of deaths among children younger than 5 years occur in the first month of life, principally caused by prematurity, birth asphyxia, and infection. Pneumonia, diarrhea, malaria, and congenital anomalies account for most deaths between 1 month and 5 years of age.

### Children With Life Span–Limiting Conditions

Beyond those described previously, children living with a broad range of illnesses, prognoses, and potentials for cure are considered to have life span–limiting conditions. Incorporating principles of palliative care is appropriate for them throughout the illness trajectory, not just at the end of life. Together for Short Lives, formerly the Association for Children's Palliative Care in the United Kingdom, and the National Hospice and Palliative Care Organization in the United States endorse 4 classes of life span–limiting conditions originally described by Goldman, affecting children whose treatment should incorporate the principles of palliative care discussed in this chapter: (1) diseases such as cancer, in which attempts at cure may fail; (2) diseases that will result in premature death, but for which life-extending treatments may prolong life with good quality, such as cystic fibrosis and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS); (3) progressive diseases for which treatment can only be palliative, such as the muscular dystrophies, mitochondrial disorders, and other neurodegenerative conditions; and (4) conditions with substantial static neurologic disability that results in vulnerability that may result in death, such as severe cerebral palsy.

A conceptualization called *pediatric complex chronic conditions*, developed in 2000 by Feudtner and colleagues, harmonizes with this traditional

classification of life-limiting conditions. These are conditions likely to last 6 months or longer in children who require care by pediatric subspecialists and often a period of hospital care. Many are complications stemming from prematurity or are congenital conditions, cardiovascular or neurologic conditions, or malignancies.

### Children Receiving Palliative and End-of-Life Care

In a 10-year retrospective study reported in 2013 by Keele and colleagues, of more than 24,000 pediatric in-hospital deaths in more than 40 children's hospitals, close to 10% of children receiving palliative care consultation had primary neurologic conditions, and 5% had hematologic malignancies. Feudtner and colleagues reported in 2011 that among children receiving palliative care services in 6 US children's hospitals in 2008, 40% had neuromuscular conditions, 20% had cancer, and 13% had primary lung disease. Half were assisted by technologies such as feeding tubes (most commonly), central venous lines, tracheotomies, and mechanical ventilation. Only one-third of this cohort died in the 12 months that followed the survey. The most common impairments and symptoms experienced by these children included differences in cognition and speech, fatigue, sleep disturbance, difficulty eating and drinking, seizures, pain, and shortness of breath. Across Canada since 2000, children with progressive, noncurable neurologic conditions make up half the children who die each year as described by Steele and colleagues in 2014. The most common symptoms reported by their caregivers were sleep problems; pain and feeding difficulties, with many experiencing constipation; respiratory difficulties; and alterations of alertness or interactions with caregivers.

In lower resource countries and developing regions, where out-of-pocket payments are required for cancer treatment for children, palliative care is seldom provided because of the scarcity of professional resources. The limited availability of opioids contributes to the estimate by Delgado and colleagues in 2010 that 80% of the 250,000 children diagnosed with cancer each year worldwide die without even rudimentary treatment or pain relief.

## COMPONENTS OF BASIC PEDIATRIC PALLIATIVE AND END-OF-LIFE CARE

Palliative and end-of-life care share with curative care a focus on quality of life for the child. They strive to maximize physical and emotional comfort, enable as normal a life as possible for the child and family, facilitate optimal family function, respect and support the child's and the family's cultural and spiritual values, and, in the care of children who are not expected to survive, help the child and family prepare for the child's death (Box 67-2).

Understanding *quality of life* is central to weighing benefits and burdens of proposed therapies toward deriving consensus about which choices for treatment are most likely to promote a child's best interests. Soliciting the child's own assessment of her quality of life, when possible, is strongly urged. Quality of life

### BOX 67-2 Components of Basic Pediatric Palliative and End-of-Life Care

#### PALLIATIVE CARE

- Information and support with decision making
- Thorough assessment, treatment, and monitoring of pain and other symptoms experienced by the child
- Appraisal and reassessment of the child's quality of life, ideally from the child's perspective together with that of the caregivers
- Help for children and caregivers with practical needs
- Psychosocial support and counseling for children and their families
- Attendance to the child's and family's spiritual and religious needs
- Planning for the site of ongoing and future care
- Regular reassessment of care plans based on discussion of the goals of care
- Referral to expert-level pediatric palliative care, as needed
- Ensurance of smooth transitions across the continuum of care, between inpatient and outpatient settings, between primary and specialty care, and at all stages of the child's life

#### END-OF-LIFE CARE

All of the components of palliative care, *plus*

- More intensive assessment of the child's physical well-being and the child's and caregivers' emotional, social, and spiritual needs
- More focused support in advance care planning, including help anticipating the nature and site of death
- Information about and support through the dying process
- Access to advice on symptom management and comfort and care coordination 24/7
- In the United States, referral to hospice services if the child's condition, following a typical course, could be expected to result in death within 6 months
- Planning for arrangements after death

From Institute of Medicine. *Dying in America: Improving Quality and Honoring Individual Preferences Near the End of Life*. Washington, DC: National Academy Press; 2014; adapted from Himelstein BP, Hilden JM, Boldt AM, et al. Pediatric palliative care. *N Engl J Med*. 2004;350:1752–1762.

has been rated higher by children with neuromuscular disabilities, particularly in subjective domains such as emotional and psychosocial well-being, than by their parents, as reviewed by Jardine and colleagues in 2014. Bjornson and McLaughlin showed in 2001 that self-reported quality of life among children with cerebral palsy does not correlate with the degree of spasticity. Pediatricians may appraise quality of life less favorably among hospitalized patients than their families do, as demonstrated in 2014 by Nolan and colleagues.

The life course of many children with life span-limiting conditions changes at critical junctures, some predictable and others surprising, often coinciding with

### BOX 67-3 Opportunities to Discuss the Child's Condition and Prognosis, Quality of Life, and Goals of Care

- Hearing bad news
- Acute decompensation
- Worsening symptoms that are becoming harder to manage
- Increased time spent in the hospital or the critical care unit
- Progression of the disease or condition or its secondary complications
- Recovery from acute decompensation to a lower level of overall function
- When families face decisions about the initiation of new technologies or treatments
- Slow decline preceding death
- When the child and family face decisions about starting a new technology or agreeing to a major invasive procedure
- Any other sustained, significant diminution in the child's quality of life
- End of life

Derived in part from Friebert S, Osenga K. Pediatric palliative care referral criteria. Center to Advance Palliative Care; 2009; and Klick JC, Hauer J. Pediatric palliative care. *Curr Probl Pediatr Adolesc Health Care*. 2010(July):120–151.

encounters that the child and family have with pediatricians and health systems. These visits present opportunities to begin or reopen discussions about the child's overall condition, prognosis, and quality of life; the child's and family's goals for care; and the most likely means to achieve those goals (see Box 67-3).

#### On Teams

Palliative and end-of-life care ideally consists of team-based, multidisciplinary, longitudinal support. More and more, palliative care is being provided in children's hospitals by consult services comprising anywhere from a single pediatrician to a multidisciplinary team of professionals as surveyed by Feudtner and colleagues in 2013. Regarded as the "unit of care," the family is assessed for coping, psychological stressors, sources of support, spiritual needs, and crises in family unity. The roles of team members are complementary, overlapping, and interdependent, as reviewed in several recent publications. These teams may include social workers, chaplains, other spiritual care workers, child life specialists (including expressive arts and music therapists), care managers, bereavement specialists, psychologists, psychiatrists, pharmacists, nurses, physicians, and advance practice nurses.

According to the AAP, child life specialists aim to provide developmentally focused support, promote children's adjustment, reduce their anxieties, diminish their sense of helplessness, and organize peer to peer support. Their well-known expertise in the use of non-pharmacologic techniques around procedures leads to

reduction of children's pain and anxiety. As outlined as well by Sutter and Reid in 2012, they can help caregivers create mementos through photography, art, crafts, and music that may be difficult to collect at emotionally stressful times, but will be treasured later.

Social workers provide emotional and psychosocial support, share resources with families, and assist with referrals to community-based agencies that may enable smooth transitions to care at home or hospice. Their skills and roles overlap with and complement those of others on the team. Chaplains and spiritual care workers play a critical role, together with community-based religious leaders, addressing spiritual and existential crises that may fall outside the boundaries of established religious constructs or the expertise of other members on the care team.

### Advance Care Planning

Since the development and implementation over the past 15 years of adult-oriented advance care plans known as *physician orders for life-sustaining treatment*, or POLST (or, in some states, MOLST, with *medical* substituted for *physician*), methods for soliciting and honoring the values and priorities of children have received increasing attention. In the United Kingdom, *personal resuscitation plans* list individualized details addressing what interventions to provide, the preferred place of death, organ donation, autopsy, care of the body, and funeral or memorial rites. A similar instrument in use in the United Kingdom and New Zealand is called "Child and Family Wishes." These plans frame the child's and family's choices positively, as opposed to more traditional orders "not to" carry out 1 or more interventions, such as *do-not-resuscitate* orders.

In the United States, tools known in the past as "My Thoughts," "My Wishes," and "My Voice" were revised and merged into "Voicing My Choices," available through Aging With Dignity ([www.agingwithdignity.org](http://www.agingwithdignity.org)) for use with children and families. They have been the subject of study among children and young adults with advanced HIV disease and cancer. Considered a "vehicle for information exchange" by the British Thoracic Society in its 2012 guideline for respiratory management of children with neuromuscular weakness, advance care plans permit adolescents and young adults to choose and document the medical treatment they do and do not want, how they want to be cared for, what they want their friends and family to know, and how they want to be remembered. Liberman and colleagues showed in 2014 that basic knowledge about advance care planning remains limited among parents and many pediatricians.

Children's awareness that they are dying becomes more focused and pronounced during the terminal phase of their illness. The British association Together for Short Lives suggests that pediatricians and any member of the health care team ask themselves 4 questions as prompts to junctures when discussions about the wishes of a child and family are appropriate (see Box 67-4).

This organization offers an outstanding guide for families with children with life span-limiting conditions, referenced in the box. The Institute for Health

#### BOX 67-4 Prompts for When Discussions About Advance Care Plans Are Appropriate to Begin or Revisit

The pediatrician and other members of the health care team should ask themselves the following questions:

- Would you be surprised if this child died prematurely because of a life-limiting illness?
- Would you be surprised if this child died within a year?
- Would you be surprised if this child died during this episode of illness care?
- Do you know what the child's and family's wishes are for the end of life?

If the answer to any of these questions is "no," it may be an appropriate time to begin or revisit discussions about advance care plans.

Adapted from Bennt H. *A Guide to End-of-Life Care: Care of Young People Before Death, at the Time of Death and After Death*. Bristol, UK: Together for Short Lives; 2012. Accessed March 8, 2015, from [www.togetherforshortlives.org.uk/assets/0000/1855/TfSL\\_A\\_Guide\\_to\\_End\\_of\\_Life\\_Care\\_5\\_FINAL\\_VERSION.pdf](http://www.togetherforshortlives.org.uk/assets/0000/1855/TfSL_A_Guide_to_End_of_Life_Care_5_FINAL_VERSION.pdf); and Fraser J, Harris N, Beringer AJ, Prescott H, Finlay F. Advanced care planning in children with life-limiting conditions: the Wishes document. *Arch Dis Child*. 2010;95:79–82.

Care Improvement in the United States has published *The Pediatric Starter Kit: Having the Conversation With Your Seriously Ill Child* as a guide to caregivers seeking to initiate discussions about advance care planning.

### ETHICAL ISSUES

The imperative to provide effective and timely palliative and end-of-life care is grounded in pediatricians' fidelity to their patients and obligations to promote the best interests of the child. Attention paid to the principles of palliative care can lessen the risk for iatrogenic harm through vigilance for the adverse effects of polypharmacy and careful consideration of proposed surgical and medical interventions whose benefits and burdens may be unfavorably balanced.

Respecting children's autonomy and that of their caregivers serves as the impetus for collaborative decision making. It creates an obligation, called *veracity*, for the pediatrician to inform children about their health status as fully and sensitively as possible, with respect for each family's culturally rooted and personal health beliefs and practices. The development of tools to facilitate advance care planning and honor the wishes of children and families grew from these obligations.

Decisions about withholding or withdrawing (together called *forgoing*) life-sustaining medical or surgical treatments are best made through examining the balance of potential benefit and harm or distress resulting from the pursuit of each proposed treatment. The interests of family members are also critical and should be considered among the burdens and benefits of treatment choices when examination of the child's best interests does not lead to a clear path of action.



Although withholding and withdrawing specific life-sustaining interventions are considered to be legally and ethically equivalent, they are experienced differently by many health professionals and family members. Pediatricians and caregivers unsure of the benefits of specific interventions near the end of life can plan time-limited trials of these treatments; if, after a suitable period, the burdens of a particular intervention seem to outweigh its benefits, then it can be withdrawn.

As shown by Lee and colleagues in 2010, most deaths in pediatric critical care units are preceded by some limitation of care. As life-sustaining medical treatments are forgone, it may be advisable to have formal orders in place not to attempt resuscitation. In a 2014 study by Burns and colleagues of 133 pediatric deaths across 5 pediatric critical care units in the United States, where 70% of the deaths examined were preceded by withdrawal of life-sustaining medical treatment, one-third did not have formal do-not-resuscitate orders in place at the time of death. The authors raised questions as to the necessity for such formal orders when it was understood that forgoing life-sustaining medical treatment would be followed, in most cases, by death. It has been argued that the common institutional default in US hospitals to provide cardiopulmonary resuscitation unless explicitly precluded by a formal order contributes, in the words of Clark and Dudzinski, to a “culture of dysthanasia,” or prolongation of suffering as death is postponed.

According to the AAP Committee on Bioethics, “it is not ethically mandatory to provide medically administered fluids and nutrition to a child in a permanent vegetative state or other condition that results in a permanent lack of conscious awareness.” Pediatricians need to work to dispel misunderstandings among caregivers and colleagues about any suffering that is thought to be associated with dehydration among children in these states. In a small follow-up study by Rapoport and colleagues in 2013, with families who had limited or discontinued medically provided hydration or nutrition as their children approached death, parent participants reported satisfaction with their decisions but expressed concerns about feeling negatively judged by health professionals. The notion that medically provided nutrition and hydration need to be an “all or nothing” matter can be moderated by an approach that provides small amounts, as tolerated, known as “comfort feeds,” or in the geriatrics literature, “feeding for comfort.”

The forgoing of life-sustaining medical treatment for critically ill or extremely premature newborns has received much legislative attention in the United States. According to the American Medical Association Council on Ethical and Judicial Affairs, “when consensus about what is in the best interest of the child cannot be reached despite reasonable efforts to do so, the wishes of the parent[s] should prevail” unless they “clearly are not committed to serving the child’s interests, are emotionally unstable or lack capacity to make informed decisions.” Hospital ethics committees and community-based ethics consultants can help to clarify the ethical issues pertaining to specific cases and support efforts at mediating

disagreement or conflict between and among professional staff, patients, and caregivers.

Concerns about the future quality of life for children with significant neurodevelopmental disabilities may be influenced by beliefs that caregivers and pediatricians have about the effect these disabilities have to diminish it. Graham and Robinson expressed concern “that many clinicians may unconsciously use the phrase, ‘quality of life’ to mask a set of more complicated, unspoken assumptions about the lives” of children and youth with disabilities. In the care of some children with trisomy 13, trisomy 18, and other combinations of complex congenital anomalies traditionally considered to constitute “lethal conditions,” Koogler, Wilfond, and Ross pointed out that what possibly “make[s] them lethal is the decision not to repair the anomalies or treat the disabilities.” Maintaining a child- and family-centered focus in the appraisal of quality of life is critical to balanced, unbiased discussions of goals of care.

Some treatments intended to relieve pain and suffering may seem to hasten death. Treatment of severe pain with high doses of opioid analgesics often raises concerns about the risk for causing respiratory depression. Even when doses are carefully titrated in response to the patient’s pain, opioids may have a foreseeable and unintended effect to diminish respiratory drive. Under the Principle of Double Effect, the unintended side effect is ethically permissible on the conditions that only the beneficial effect of the treatment (comfort) is intended and that the mechanism by which the intervention relieves suffering (lessening pain) is not the adverse effect itself (respiratory depression that leads to death).

Euthanasia and physician-assisted suicide are not endorsed by any advisory or governing body of physicians treating children in North America, although other countries may permit these measures under certain circumstances. The AAP suggests that requests for euthanasia “should be acknowledged and serve as a starting point of a conversation to elucidate the sources of suffering that underlie such requests.”

## FUNDAMENTALS OF WORK WITH CAREGIVERS, SIBLINGS, AND FAMILIES

To work with families in ways that are most effective and supportive, pediatricians should be knowledgeable about the range of experiences that have been described in empirical research with caregivers, siblings, and families close to children with life span-limiting conditions.

Parents strive to be “good parents” for their children with life span-limiting conditions by providing support, presence, and sacrifice for the child. The work of Hinds and colleagues demonstrates that they make informed, unselfish decisions in the child’s best interests, meet the child’s basic needs, remain at the child’s side, show the child love, try to protect the child’s health and prevent suffering, teach the child moral values, and advocate for the child.

As reported by Rallison and Raffin-Bouchal in 2013, parents of children living with progressive neurodegenerative illness described their “pervasive grief”



from the experience of “living in the in-between,” facing the day-to-day dualities of joy and sorrow, having a sense between illness episodes of both stability and unpredictability, mastering intricate home care regimens and feeling loss of control amid their complexity, and, ultimately, having ambivalent wishes as the child’s death approaches that the child will not die, but be relieved of his suffering.

Siblings experience many unmet needs over the course of the child’s illness. Davies in 1999 described their multifaceted pain, confusion, alienation, and feelings of inadequacy. Siblings may feel “unnoticed or unacknowledged” at hospital visits and other appointments for the child’s care, left out of communication about the child, or “falsely protected” during the child’s deterioration and other critical times, according to the work of Jones and colleagues in 2014. Their privacy may be intruded on as they meet the need to adopt new responsibilities and roles. As Lapwood and Goldman wrote in 2012, they may feel criticized by others when they react with aggression and disruptive behaviors. For many reasons, parents may be unaware of many of these experiences and how challenging the coping process is for siblings.

Children who are dying sometimes worry that they will be forgotten. Many are troubled by imagining their parents’ pain and sadness after they are gone. Some feel preoccupied with their own safety and security. For some older children, as for some adults who face dying, the main goal of living during the terminal stage is, in the words of Nitschke in 2000, to find “new meaning in life and to live in a new mindset.”

For adolescents and young adults as described by Linebarger and colleagues in 2014, crucial developmental tasks related to autonomy, identity formation, and sexual expression, among others, may be thwarted by changes in stamina and appearance and the isolation and confinement to treatment routines imposed on them. Most will have achieved an understanding of the attributes of death—irreversibility, nonfunctionality, universality, and causality—that permit higher level discussions around advance care planning than are possible with younger children.

From a family systems perspective, pediatricians should recognize how the roles of parents, siblings, and other loved ones change over the course of care for a child with a life span-limiting condition. As reviewed by Lapwood and Goldman in 2012, the effectiveness and style with which various family members cope may be different and out of sync. Family members may need and receive different levels and types of external support. One parent or a sibling may feel the need to care for the other parent in addition to the meeting the needs of the child. Pre-existing strains in the marriage, or in relationships between family members and the child who is ill, complicate the calibration of family roles required to care for the child. The normal balance of loyalty, affection, rivalry, and aggression between siblings needs to be reestablished. Resilience among families is promoted by shared belief systems, established patterns of organizing their day-to-day lives, strong communication processes, cohesiveness, flexibility, and expressiveness.

### Spiritual Support

Spiritual needs of children and families involved in palliative, end-of-life, and bereavement care are based in traditional religions, unique religious affiliations and interpretations, and nonreligious paradigms. All give meaning to individuals’ lives. The decline in health of a child can be among the greatest spiritual and existential crises for a parent, yet it is possibly the spiritual domain in which the least training is provided to pediatricians. Addressing children and families’ spiritual needs requires exploration and understanding in domains of professionalism and humanism that are disquieting and profound. Membership in the same religious group or sect as the family or belief in God is not required for professionals to be able to offer spiritual support. Collaboration with the family’s religious leaders or hospital-based chaplains may enrich support.

### Communication Methods That Help

Many physicians feel anxious and inexperienced when initiating talks with caregivers about end-of-life care. They may postpone or defer such discussions because of their own discomfort, lack of training, lack of reimbursement, competing demands, or language barriers. Davies and colleagues showed in 2010 that in some settings, families with limited English proficiency have received no information or only basic information about their child. As shown in a series of studies published between 2008 and 2014 by Davies, Junger, Durall, and their colleagues, pediatricians may hesitate to discuss poor prognosis because of the inherent uncertainty, a belief that the family is not ready to acknowledge that the condition cannot be cured, or concern that doing so will take away hope. In a series of recorded discussions around informed assent to enroll children with advanced cancer in phase I treatment trials, 85% of pediatric oncologists failed to mention that the cancer was incurable, and two-thirds did not offer the option of comfort-oriented end-of-life care as reported by Miller and colleagues in 2014.

In research on discussion of prognosis and preservation of hope among parents of children with cancer, Mack and colleagues in 2007 were able to demonstrate that conversation about poor prognosis was not associated with a loss of hope. Hopeful ways of thinking were associated in a study published by Feudtner and colleagues in 2010 with greater odds of parental assent to limit life-sustaining medical treatment. Hopefulness does not necessarily equate with expectations of cure, but rather with the belief that particular goals can be reached and that the child and family will have some sense of agency in getting there.

In many reports, parents say that they want pediatricians to discuss prognosis in conversations centered on the child and, in the words of Morrison and Meier in 2004, “focused on empathy, openness and reassurance.” We know from work published between 2005 and 2010 by Davies, Mack, Meyer, and their colleagues that they value pediatricians who offer clear, compassionate, informative explanations; tolerate denial and expression of emotion; demonstrate interest in family members; attend to cultural values; work

to preserve the parent-child relationship; remain accessible and committed to follow-up; and prepare the parents for circumstances surrounding the child's death. In conversations about prognosis, wrote Schwantes and O'Brien in 2013, "the goal is not to be brutally honest but to have honest conversations."

Parents told Weidner and colleagues in 2011 that factors that mattered most to them in the course of their children's end-of-life care included respect for the family's role, support for parental decision making, the demonstration of humanistic and compassionate communication, and the provision of comfort, spiritual care, and access to care and resources. Those speaking with Tan and colleagues in 2012 emphasized the presence of a "dependable" person and consistent "witness" to conversations. In a longitudinal study underway with families of children with life span-limiting conditions, Hill and colleagues reported in 2014 that they are investigating ways to best support a process they call "regoaling," in which parents realize that their initial hopes for the child's health trajectory may no longer be realistic and choose to pursue or engage in a new set of goals. At a minimum, families with limited English proficiency told Davies and colleagues in 2010 that they seek "comprehensive information from sensitive providers who respect parents' roles in their child's life."

Although more open communication with children has been generally embraced, conflicts persist about the timing of disclosure to the child that she is dying. In a 2004 follow-up study based in Sweden by Kreicbergs and colleagues of families whose children died of cancer, no parents who discussed the anticipated death with the child who died reported that they regretted doing so, but some who chose not to broach the topic wished they had. Some basic suggestions for facilitating conversations with children and families are listed in Box 67-5.

Parents and siblings have indicated, as reported by Steele and colleagues in 2014, that it is helpful to ask siblings directly about their experience, engage them in care discussions, and provide roles for them in the child's care. They recommend, as described by Lapwood and Goldman, that siblings remain engaged in their usual activities to the greatest extent possible and that at least 1 adult be identified in their world with whom they can talk to openly about their feelings and fears and why their lives have been so disrupted. Portnoy and Stubbs wrote in 2012 that resilience in siblings is promoted by close connections with at least 1 family member and the availability of support systems outside the family. When possible, parents advised that a child life specialist or worker with similar skills be assigned specifically to work with siblings.

Families cite the importance of parent-to-parent support. They can often identify sources through the care team and regional or national organizations, some of which are listed in Box 67-6.

### Common Types of Conversations With Children and Families

Although every conversation with each child and family is unique, there are several categories or types of discussions and meetings that take place frequently.

In interviews with children and families, Kane and colleagues offered suggestions for some "exploratory questions" around the effect on the child and family of the child's condition. These and the suggestions of other authors are reproduced in Box 67-7.

In the words of Block, "A family meeting is a procedure, and it requires no less skill than performing an

#### BOX 67-5 Facilitating Conversations With Children and Families

**General suggestions:** In speaking with children and families, the pediatrician should

- Plan for more than a single conversation over time
- Get a sense of the child's and family's information needs and styles of communication
- Explore the child's and family's hopes and concerns
- Check comprehension frequently
- Tolerate negative emotional responses from caregivers
- Accept differences of opinions between caregivers
- Remain comfortable with nonacceptance and try to identify areas of consensus understanding
- Not be afraid to say that he doesn't know
- Reflect on and manage her own anxieties and fears

**When speaking with children who are ill and their siblings,** to get the best sense of the child's developmental level and understanding of illness or death,

- Ask what they understand
- Ask clarifying questions
- Take cues from the child as to where to bring the conversation next
- Talk in language the child can understand, avoiding euphemisms
- Break information down into very small portions
- Listen more, speak less
- Support the child's voice in decision making and involvement in rituals
- Reassure the child that he is loved and will not be abandoned

**When speaking with caregivers and families,** to help improve the family's quality of life and comfort, ask them

- About effects of the child's condition on his or her abilities
- How various family members are being affected emotionally, socially, and financially
- What they think the siblings know and understand
- What they feel would be most important for the team to know

Derived in part from Bluebond-Langner M, DeCicco A, Schwallie MN. Children's views of death. In: Goldman A, Hain R, Liben S, eds. *Oxford Textbook of Palliative Care for Children*. 2nd ed. New York, NY: Oxford University Press; 2012; Lapwood S, Goldman A. Impact on the family. In: Goldman A, Hain R, Liben S, eds. *Oxford Textbook of Palliative Care for Children*. 2nd ed. New York, NY: Oxford University Press; 2012; Nelson KE, Mahant S. Shared decision-making about assistive technology for the child with severe neurologic impairment. *Pediatr Clin North Am*. 2014;61:641-652; Arnold R, Nelson J, Predergast T, et al. *Education Modules for the Critical Care Communication (C3) Course: A Communication Skills Training Program for Intensive Care Fellows*. 2010; Friebert S, Bower KA, Lookabaugh B. *Caring for Pediatric Patients*. In: Storey CP, ed. *UNIPAC 8: A Resource for Hospice and Palliative Care Professionals*. Glenview, IL: American Academy of Hospice and Palliative Medicine; 2012.

### BOX 67-6 Organizations and Web Sites Devoted to Parent and Family Support Around Palliative and End-of-Life Care and Bereavement

- Candlelighters NYC ([www.candlelightersnyc.org](http://www.candlelightersnyc.org))
- Mothers in Sympathy and Support (MISS) Foundation ([www.missfoundation.org](http://www.missfoundation.org))
- The Compassionate Friends ([www.compassionatefriends.org](http://www.compassionatefriends.org))
- Stepping Stones of Hope ([www.steppingstonesofhope.org](http://www.steppingstonesofhope.org))
- Winston's Wish ([www.winstonswish.org.uk](http://www.winstonswish.org.uk))
- Together for Short Lives ([www.togetherforshortlives.org.uk](http://www.togetherforshortlives.org.uk))
- The Conversation Project ([www.theconversationproject.org/starter-kit/intro](http://www.theconversationproject.org/starter-kit/intro))
- Compassion and Support at the End of Life ([www.compassionandsupport.org/index.php/for\\_patients\\_families](http://www.compassionandsupport.org/index.php/for_patients_families))
- Partnership for Parents ([www.partnershipforparents.net](http://www.partnershipforparents.net))

operation." In the field of communication with patients and families, more tips, acronyms, and 4- to 10-step processes have been developed to guide professionals in giving bad news and holding family meetings than probably any other aspect of communication. Notable examples include "Ask-Tell-Ask," "NURSE," VALUE," "SPIKES," "SEGUE," and "ASCEND." Some basic elements in common are listed in Box 67-8.

### WORKING WITH FAMILIES AROUND THE TIME OF THE CHILD'S DEATH AND DURING BEREAVEMENT

The focus in this chapter has been predominantly on work that pediatricians who have ongoing relationships with families can engage in over time. Johnson and colleagues provide advice for communicating with families after the serious traumatic injury or death of a child, which includes doing interdisciplinary work to collect the facts, enabling communication that is clear and simple, providing time for clarification and the expression of emotion, preparing for parental responses and need for support, helping parents with final decisions and understanding procedures, maintaining contact after the death, and providing

### BOX 67-7 Exploratory Questions to Ask in Interviews With Children and Families About the Effect of the Child's Illness or Condition

#### To start:

- For children with static conditions from birth or early infancy: Tell me about your child on a good day.
- For children with acquired conditions: Tell me about your child before he or she got sick.
- What sorts of things does your child like to do or enjoy?
- What kinds of activities and things are most important for your child to be able to do?
- How does your child communicate with you and let you know what she wants or needs?
- Is your child currently feeling all right? If not, what symptoms are bothering him the most?
- How would you describe your child's quality of life nowadays?

#### Hopes, goals, and priorities:

- What goals are most important to you and your family nowadays?
- As you think back, how do you see your child's health over time (eg, the past month, the past 6 months)?
- As you think about your child's condition, now and in the future, what are you most hoping for?
- What have been the most challenging or frustrating aspects of your child's medical care?

- What makes you feel the most worried, thinking about your child? How often do you find yourself thinking about that?
- Are you comfortable with the health care decisions you have made for your child?

#### Spirituality and supports:

- Do you have a set of beliefs that guides you or supports you? It could be based in religion, or not.
- Does your faith or religion provide any guidance in the decisions you are facing?
- Who provides you with the most support nowadays? Who do you call on or reach out to when you need to talk or need help?

#### Emotional effect:

- How has your child's condition affected her emotionally?
- How has it affected you in your own life?
- How are you coping? How about your spouse, partner, or other loved ones?
- (Alternative: How are you handling everything that's been going on?)
- What worries you the most nowadays?
- (As appropriate: What worries your child the most?)

Throughout, it is preferable to use the child's name in place of "your child."

"Nowadays" may be a term in common use in some settings but not others. Substitutes include "right now," "recently," "these days," and more. "Condition" is one way of referring to what makes the child "unwell." Substitutes include "illness," "medical problems," "situation," "circumstances," and more. Derived from Kane JR, Joselow M, Duncan J. Understanding the illness experience and providing anticipatory guidance. In Wolfe J, Hinds PS, Sourkes BM, eds. *Textbook of Interdisciplinary Pediatric Palliative Care*. Philadelphia, PA: Elsevier Saunders; 2011.



### BOX 67-8 Commonalities Across Different Methods and Frameworks for Giving Bad News and Holding Family Meetings

The pediatrician should

- Prepare ahead of time with all the pertinent facts.
- Plan the setting in which the conversation will be held and arrange that all important persons are there for the conversation.
- Get a sense of how much the family and child already know and expect or are prepared to hear.
- Explain what the pediatrician has learned in ways that are effective and compassionate.
- Permit the child and family to respond.
- Address their emotions and solicit questions.
- Plan the next steps, including when the pediatrician will see the child and family next.

Derived from Mack JW, Hinds PS. Practical aspects of communication. In: Wolfe J, Hinds PS, Sourkes BM, eds. *Textbook of Interdisciplinary Pediatric Palliative Care*. Philadelphia, PA: Elsevier Saunders; 2011; von Gunten CF, Ferris FD, Emanuel LL. The patient-physician relationship. Ensuring competency in end-of-life care: Communication and relational skills. *JAMA*. 2000;284:3051–3057; Masera G, Chesler MA, Jankovic M, et al; SIOP Working Committee on psychosocial issues in pediatric oncology. Guidelines for communication of the diagnosis. *Med Pediatr Oncol*. 1997;28:382–385; Beale EA, Baile WF, Aaron J. Silence is not golden: communicating with children dying of cancer. *J Clin Oncol*. 2005;23:3629–3631; Makoul G. The SEGUE Framework for teaching and assessing communication skills. *Patient Educ Couns*. 2001;45:23–34; Baile WF, Buckman R, Lenzi R, et al. SPIKES: a six-step protocol for delivering bad news. Application to the patient with cancer. *Oncologist*. 2000;5:203–311; and Knops K, Lamba S. Clinical application of ASCEND: a pathway to higher ground for communication. *J Palliat Med*. 2010;13:825–830.

information about arrangements for bereavement-associated needs. Similar guidance is formalized in a joint statement from the AAP Committee on Pediatric Emergency Medicine, American College of Emergency Physicians, and the Emergency Nurses Association, which also addresses family presence during attempted resuscitation, continued contact with surviving family members, and ways to provide the most effective communication training for pediatricians.

The pediatrician has an essential role in providing practical and emotional support after death, both on his own and as part of a bereavement team. A pediatrician may wish to go to the wake, funeral, or memorial service for her patient. Families feel moved that their child meant so much to health care professionals in attendance. Many hospitals and hospices organize memorial services or other annual events for children who have died while in care there. Sending notes or calling to acknowledge the child's birthday or anniversary of death, often comforting for the family, can be facilitated by maintaining a calendar of these dates and the organized activities of bereavement teams. Providing psychoeducation about the prolonged nature of grief and referral to bereavement specialists or teams can be helpful.

Surviving siblings who receive care from the same pediatrician will be returning for visits that provide an opportunity for all to remember the child who died.

The pediatrician may want to bring the siblings back into the office soon to assess how the siblings, parents, and extended family are coping.

Death of the child leaves an enormous void and is widely acknowledged as among the most painful losses anyone can experience. As described by Portnoy and Stubbs and by Gaab and colleagues in 2014, the bereaved typically experience overwhelming grief and other feelings, physical sensations, thoughts, social difficulties, and spiritual searching. The death may come as a surprise to siblings who, despite knowing that the child was worsening, did not expect the child to die. Children may demonstrate what Wilkins and Woodgate in 2005 termed “stop-and-start” grieving, called “puddle jumping,” as they seem to be immersed in sadness, despair, loneliness, yearning, disbelief, confusion, guilt, anger, or anxiety one moment and then seem to be playing normally the next. They may experience a sense of worthlessness and pointlessness and resent their parents’ “absorption in their own grief” as depicted by Portnoy and Stubbs.

Just at the times when the greatest degree of support is needed, families lose relationships with home care personnel, pediatricians, and hospital staff who have often been the core source of support. Their self-concept as caregivers and the organization of their daily existence and purpose are gone. As others in families’ lives begin to speak or ask less often about the deceased child or sibling, this creates another loss of support for the bereaved, who might otherwise be helped by opportunities to continue talking about the deceased as a way of keeping the relationship alive.

In contrast to some of the teachings of Freud, Bowlby, Parkes, and others, individuals’ grief experiences often do not follow a stepwise progression through stages and do not end in resolution, “coming to terms,” or closure. Grief continues to be present in the life of the bereaved, described by Roos in 2002, requiring “continual energy and adaptation,” in the words of Rallison and Raffin-Bouchal. Bonds with the deceased continue as the bereaved learn to “hold on while letting go.” Contemporary models of understanding bereavement depict grief as something that doesn’t lessen, but that the bereaved “grow around.” The focus of help is on finding ways the bereaved can incorporate the pain and loss into their daily lives.

Parents who experienced prior losses, economic hardship, psychiatric comorbidity, poorer perception of medical care, and less preparedness for the child’s death, together with those whose children experienced more intense suffering and poorer quality of life, are at risk for worse outcomes of grief, according to a 2012 study by Rosenberg and colleagues. In a follow-up study of bereaved parents published in 2013 by Youngblut and colleagues, 89 hospitalizations among 56 mothers and 9 hospitalizations among 7 fathers were reported in just the first 13 months after the child’s death; up to one-third of these hospitalizations were classified as stress related. Death of a child is associated with a great deal of financial hardship as well, with poor families in a 2011 study by Dussel and colleagues experiencing the greatest financial loss. Some parents find comfort in altruistic engagement,



### BOX 67-9 Advice for Families That May Help Siblings Anticipating Loss or Grieving After Death

- Spend plenty of time with the children.
- Encourage children to express their feelings and thoughts in their own ways.
- Explain what happened, and be prepared to answer questions again and again.
- Appreciate children's understanding of death at different developmental levels.
- Facilitate children's involvement with friends and activities.
- Continue the usual routine of family responsibilities and discipline as a way of "normalizing" life.
- Let children know that adults also feel anger, sadness, and fright and may express it, and that crying is okay.
- Share your own feelings and memories.
- Allow time for fun and laughter.
- Tell children how much the sick or deceased sibling loves or loved them.
- Avoid comparisons between survivors and the deceased.
- Let children know they will be cared for and loved by a consistent adult.

Derived from Davies B, Wordon JR, Orloff SF, et al. Bereavement. In: Carter BS, Levetown M, eds. *Palliative Care for Infants, Children and Adolescents: A Practical Handbook*. Baltimore, MD: Johns Hopkins University Press; 2004; American Academy of Pediatrics, Committee on Psychosocial Aspects of Child and Family Health. The pediatrician and childhood bereavement. *Pediatrics*. 2000;105:445–447; and Davies B. After a child dies: helping the siblings. In: Armstrong-Daily A, Zarbock S, eds. *Hospice Care for Children*. 2nd ed. New York, NY: Oxford University Press, 2001:168.

in giving to others after the child's death, as reported by Tan and colleagues.

Many siblings experience anxiety, depression, and, among older siblings, illicit substance use, particularly in the first year of bereavement. Those who reported dissatisfaction with communication, poor preparation for the sibling's death, or missed opportunities to say goodbye experienced greater distress and less adequate support, as shown by Rosenberg and colleagues. In addition to these intense feelings, the changes in siblings' lives involve numerous losses—less time with parents, diminished tolerance by parents, emotional unavailability, loss of companionship with the sibling who has died, and disintegration of family dynamics. As described in Wilkins' and Woodgate's review, many report gains as well—increased family closeness and cohesion for some, greater independence and maturity, and an enhanced capacity for empathy and desire to help others. Efforts to protect siblings from the pain of the loss and the parents' grief are often ineffective and may worsen short- and even long-term outcomes. Some advice for families that may help siblings anticipating loss or grieving after death is included in Box 67-9.

Bereavement care calls for sustained connection between the pediatrician and the surviving family after the child's death. It begins with acknowledgment

of the child's death and continues through attention to parental grief, stressors that may intensify the grief, and the experiences of surviving siblings. Some pediatricians find that meeting with families several weeks after the child's death brings a sense of closure for them and thus can be helpful in the pediatricians' own self-care.

## SYMPTOM MANAGEMENT

In-depth attention to the assessment and management of pain and other symptoms is central to palliative and end-of-life care. Great suffering is often present, especially in children with cancer, who may experience pain, dyspnea, and other troubling symptoms that are not sufficiently relieved by medications provided. As described earlier, children with severe neurologic impairment and those dying from conditions other than cancer tend to experience less frequent or severe pain and a different array of symptoms. As demonstrated in 3 separate 2010 studies by Knapp, McCarthy, Jalmesell, and their colleagues, inadequate treatment of suffering in the care of children with life span-limiting conditions has significant effect on caregivers and can have lasting effects on bereavement.

This section provides a basic orientation to symptom assessment and management. Detailed description of intensive assessment methods and advanced management of the range of symptoms experienced by children with life span-limiting conditions is beyond the scope of this chapter. Readers are referred to excellent contemporary reviews by Kang and colleagues, Schwantes and O'Brien, Levine and colleagues, and Johnson and colleagues.

## Recognition and Effective Treatment of Pain

Physicians should follow an approach to analgesic use, introduced about 20 years ago, that is organized by "the ladder," by the clock, by the child, and by mouth (or by the least intrusive route) (Box 67-10). Since 2012, the WHO has promoted a 2-step approach to use of analgesics in children with medical illness who experience persistent or recurrent pain, in which acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID), such as ibuprofen, is used for mild pain, and an opioid is added for moderate to severe pain. Analgesics should be ordered on a standing basis (*by the clock*), according to the chosen analgesic and route of administration, rather than on an as-needed basis. Additional doses are available for breakthrough pain. When analgesics are provided only if the patient requests them, pain escalates between doses, the cumulative amount of analgesic administered is higher, and the potential for adverse effects is increased compared with when they are provided by the clock. The widespread undertreatment of pain, when ordered only on an as-needed basis, has led Friedrichsdorf to reinterpret the abbreviation "prn" to mean "patient receives nothing."

Unwarranted fears of addiction and confusion about the nature of tolerance and dependence inhibit some pediatricians from ordering opioid analgesics optimally for children and make some families reluctant to agree to their use. Tolerance to the analgesic

### BOX 67-10 Principles of Pain Management in Children

#### 1. By the ladder

Step	Pain Severity	Treatment
1	Mild	Oral acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs)
2	Moderate to Severe	Opioid analgesics; continue acetaminophen or NSAIDs

#### 2. By the clock

Analgesic treatment around the clock, rather than on a purely as-needed basis, results in

- Less frequent breakthrough pain
- Improved pain relief overall
- Fewer peaks and troughs of analgesic levels
- Less sedation

#### 3. By the child

Maximal suggested doses for acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are based on the child's weight. In contrast, most opioid analgesics have no maximal dose. The appropriate dose of an opioid is that which relieves pain without unacceptable adverse effects.

#### 4. By mouth (or by the least intrusive route)

Analgesic medication should be given by mouth, whenever possible, or by the least intrusive route, for mild to moderate pain. The parenteral route offers no advantages over the oral route other than more rapid onset of action.

Adapted from World Health Organization. *WHO Guidelines on the Pharmaceutical Treatment of Persistent Pain in Children with Medical Illness*. Geneva, Switzerland: World Health Organization; 2012. Available at: [apps.who.int/iris/bitstream/10665/44540/1/9789241548120\\_Guidelines.pdf](https://apps.who.int/iris/bitstream/10665/44540/1/9789241548120_Guidelines.pdf). Accessed January 5, 2016.

effects of opioids will develop after as little as 1 week, but usually after 2 or 3 weeks, of continuous use. Symptoms of dependence may appear if the drug is abruptly withdrawn after as little as 1 to 2 weeks. The complex psychosocial dysfunction and self-destructive pursuits that characterize addiction do not appear more frequently in children with life-limiting illnesses than in others.

Tolerance develops not only to the analgesic effects of opioids, but also to some of their adverse effects, such as sedation and pruritus. Unfortunately, constipation rarely lessens and should be managed proactively with laxatives, softeners, or both. If doses of opioids are increased and unacceptable adverse effects persist, then an alternative opioid agent can be substituted (a process called *opioid rotation*).

Appropriate pain control begins with proper assessment. Several validated scales for the appraisal of pain are readily available (eg, Face Legs, Activity, Cry, Consolability [FLACC]), including instruments adapted for use with children who cannot communicate easily. These scales must be used consistently and correctly. Observation of behavior is necessary for preverbal or nonverbal children, together with the use of validated

scales such as FACES and others listed in the review by Schwantes and colleagues. Self-report scales may be used for verbal children 3 years and older that use colors, poker chips, or cartoon faces to help children indicate the severity of their pain. Scales incorporating numerical ratings or visual analogs may be used in children older than 7 years who understand order.

The advice of pediatric pain specialists, more widely available in recent years, should be sought when analgesic regimens pose challenges. For children who quickly develop tolerance to the analgesic effects of opioids, who experience neuropathic pain, or who experience pain that might be amenable to regional epidural or nerve block, a pediatric pain expert should be a part of the care team.

### Recognition and Management of Other Symptoms

Fatigue is a prevalent and bothersome symptom near the end of life. It can be lessened by planned naps, limited interruptions during hospitalization, and efforts on the child's part to conserve energy. When excessive sedation is a persistent complication of opioid analgesics required for pain control, drug rotation or the addition of a stimulant such as caffeine or methylphenidate can be considered.

Anorexia is a subjective experience expected toward the end of life. By its nature, anorexia is unassociated with hunger. Traditional assessments of nutrition and hydration in these instances need not lead to medically provided interventions, such as intravenous fluids or nasogastric feeding. Forced hydration may lead to edema, dyspnea, and skin breakdown. Mouth care with moistening swabs, ice chips, and gentle hygiene is sufficient for many children with advanced disease.

Dyspnea can occur as the result of several processes related to the child's underlying condition, complications of treatment, and unrelated comorbidities. In addition to treating the underlying causes of the dyspnea, an approach focused on symptom assessment and palliation can lead to even greater relief. Opioid doses effective at relieving shortness of breath are smaller than those used for analgesia. Opioids are recommended for consideration in children with dyspnea on the basis of neuromuscular disease, whether or not the child is supported by mechanical ventilation. Simple environmental measures can be helpful, such as introducing fresh air and using fans to circulate air.

As is the case with dyspnea, pruritus may arise from the effects of the underlying disease, its treatment, and unrelated comorbidities. Environmental alterations, soothing baths and compresses, oral antihistamines, and topical corticosteroids and moisturizers, chosen as appropriate, can improve quality of life. In the setting of cholestasis, medications that bind bile salts are helpful.

The most successful management of constipation is anticipatory and often multimodal. It includes the use of softeners and laxatives, incorporation of high-fiber foods, and encouragement of physical activity as much as possible.

Nausea and vomiting can be lessened with antiemetic medication, the choice of which is guided by the

cause, and by dietary and environmental modifications. Some cognitive-behavioral methods and complementary and integrative treatments may be beneficial. Seizures are distressing to observe and may or may not warrant treatment, depending on frequency, intensity, and desire on the caregivers' part to minimize sedation.

Anxiety is common in children receiving treatment for serious illness and, in the care of children at the end of life, can complicate subsequent bereavement among caregivers, as reported by Jalsmell and colleagues. Interventions and support aimed at the cause are central. Delirium may be caused by metabolic abnormalities, infections, or adverse effects of drugs. Depressive symptoms are nearly universal among children with advanced illness and may be worsened by the adverse effects of disease treatment.

Increased attention is being paid to signs of autonomic instability, also called *dysautonomia*, which for years was recognized in survivors of traumatic brain injury and now is appreciated in many in children with severe neurologic impairment from a variety of causes. The signs can include irritability, crying, temperature instability, tachycardia, hypertension, tachypnea, sweating, and feeding intolerance. Because of the resemblance of these signs to manifestations of serious bacterial infection, children with autonomic instability undergo frequent evaluation and interventions aimed at diagnosis and treatment of infection, with the attendant pain and suffering associated with these interventions. Treatments aimed at moderating the instability, using gabapentin, clonidine, and other agents, can be immensely beneficial, but sedating as well.

Although much of the suffering experienced by children with life span-limiting conditions can be addressed with medication, the addition of numerous medications brings with it the risk for compound adverse effects resulting from polypharmacy. Sedative and anticholinergic side effects predominate.

## CONCLUSIONS

Improvements in palliative and end-of-life care for children have taken hold in the United States, decades after improved survival and disease-combating therapeutic successes. New palliative care pediatricians and teams are providing consultative care, guided by emerging knowledge about the epidemiology of life span-limiting conditions in childhood, children's and families needs and interventions that help, together with legislation requiring access to treatments formerly restricted for hospice enrollees. As pediatricians recognize children's need for palliative care and learn from the emerging data, they will be better able to provide basic palliative care to greater numbers of patients and families by addressing their emotional and spiritual needs, assessing and managing common symptoms and forms of suffering, facilitating advance care planning, participating in bereavement care, and recognizing indications for referral to specialists in pediatric palliative and hospice care.

Individuals involved in providing care to seriously ill children require support in processing their own experiences of loss. For some people, the rewards of working with devoted members of other disciplines and of the extreme closeness that can develop with

children and their families make providing this care the best work they can imagine. With attention to the information and guidance reviewed in this chapter, pediatricians can vastly improve care and caring for some of the sickest children and their families.

## TOOLS FOR PRACTICE

### Medical Decision Support

- *Standards of Practice for Pediatric Palliative Care and Hospice* (guideline), National Hospice and Palliative Care Organization ([www.nhpco.org/quality/nhpco%E2%80%99s-standards-pediatric-palliative-and-hospice-care](http://www.nhpco.org/quality/nhpco%E2%80%99s-standards-pediatric-palliative-and-hospice-care))
- *UNIPAC 8: Caring for Pediatric Patients* (book), American Academy of Hospice and Palliative Medicine ([aahpm.org/self-study/unipacs](http://aahpm.org/self-study/unipacs))
- *When Children Die: Improving Palliative Care and End-of-Life Care for Children and Their Families* (book), Field M, Behrman R, eds ([books.nap.edu/catalog.php?record\\_id=10390](http://books.nap.edu/catalog.php?record_id=10390))

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## SECTION FOUR

# Care of Special Populations

### Chapter 68

## CHILDREN EXPOSED TO ADVERSE CHILDHOOD EXPERIENCES

Andrew Garner, MD, PhD

Childhood adversity plays a prominent role in influencing a child's development and eventual life course. A wide array of adverse experiences in childhood have been associated with poor developmental outcomes as diverse as depression, substance abuse, teenage pregnancy, incarceration, emphysema, obesity, type II diabetes, and cardiovascular disease. Only recently, however, have advances in the neurosciences, epigenetics, and the physiology of stress begun to reveal the biologic mechanisms that might underlie these well-established associations. This chapter briefly reviews the epidemiologic associations between childhood adversity and unhealthy life course trajectories, and then defines toxic stress and discusses its effect on brain development. It also discusses ways in which pediatricians might intervene to minimize the potentially lifelong effects of childhood adversity.

### CHILDHOOD ADVERSITY AND LIFE COURSE TRAJECTORIES

Adversity can take many forms and can be either catastrophic/traumatic (eg, being abused or witnessing violence) or almost routine (eg, experiencing poverty or parental separation). Defining and measuring what makes an event “adverse” for a particular individual can be problematic. Is adversity dependent upon characteristics unique to the child (eg, the child's previous experiences, temperament, developmental state, or unusual physical or personal traits), the family situation (eg, childhood experiences of the parents, parental mental illness, or intimate partner violence), or broader societal issues (eg, poverty, unemployment, poor housing, neighborhood violence, or limited access to medical or mental health care)? Or, more likely, is adversity caused by complex interactions between all 3 ecologic levels? The perception of adversity or a threat can be quite variable, in that some children might have horrific experiences (witnessing interpersonal violence, for example) yet do very well, whereas other children might have long-lasting physiologic and behavioral changes resulting from relatively minor trauma (like seeing a barking and growling dog, or falling off a bike).

Despite this ambiguity about what constitutes adversity, numerous epidemiologic studies have demonstrated clear associations between various forms of

childhood adversity and multiple markers of poor physical and mental health as an adult. The Adverse Childhood Experiences (ACE) Study looked at more than 17,000 middle-class, middle-aged Americans (average age in the 50s) and found dose-dependent associations between the number of ACEs (see Table 68-1) and a wide array of outcomes, including markers for social functioning, sexual health, and mental health; risk factors for common diseases; and prevalent diseases (Box 68-1). The retrospective ACE Study and several smaller, prospective studies indicate that adverse experiences in childhood influence behavior, learning, mental wellness, physical health, and economic productivity decades later.

Because these epidemiologic studies are descriptive, no causal mechanisms can be asserted. However, interventional studies like the Perry Preschool Project and the Abecedarian Project have demonstrated that alterations in a child's developmental milieu have profound and enduring effects on behavior and health decades later, suggesting that early childhood experiences do alter life course trajectories in a meaningful way. Although econometric analyses of these early childhood interventions suggest a high return on investment, the salient features of these programs (child centered versus family or community centered) and the mechanisms underlying their success (promoting cognitive versus noncognitive skills) remain a topic of much debate.

### MEASURING ADVERSITY: THE PHYSIOLOGIC STRESS RESPONSE

Among the problems with quantifying childhood adversity are its subjective nature and the variability of individual responses. This suggests that the metric of adversity cannot be the precipitants of stress (or the adverse experiences themselves), but rather the individual's physiologic response to those precipitants. The physiologic mediators of stress (cortisol, adrenaline, etc) are quantifiable and can be measured both acutely (as stress reactivity—the magnitude of an acute stress response) or chronically (as elevated basal levels). Boyce and colleagues have looked at stress reactivity in children and have shown a high degree of variability. Traditionally, genetic predispositions were thought to play a major role in determining stress reactivity, but more recent data suggest that previous experiences also play an important role. Stress reactivity, much like brain development itself, results from a complex, dynamic interaction between genes (nature) and the environment (nurture) over time. Neural pathways activated in response to frequent environmental stimuli are strengthened by use. Frequent, strong, or prolonged stress responses early in life are thus able to “set” a relatively lower threshold for future stress responses and to promote a high degree of

**Table 68-1** Adverse Childhood Experiences Are Not Rare

	<b>WOMEN</b> ( <i>n</i> = 9,367)	<b>MEN</b> ( <i>n</i> = 7,970)	<b>TOTAL</b> ( <i>n</i> = 17,337)
<b>ABUSE</b>			
Emotional	13.1%	7.6%	10.6%
Physical	27.0%	29.9%	28.3%
Sexual	24.7%	16.0%	20.7%
<b>HOUSEHOLD DYSFUNCTION</b>			
Mother treated violently	13.7%	11.5%	12.7%
Household substance abuse	29.5%	23.8%	26.9%
Household mental illness	23.3%	14.8%	19.4%
Parental separation or divorce	24.5%	21.8%	23.3%
Incarcerated household member	5.2%	4.1%	4.7%
<b>NEGLECT<sup>a</sup></b>			
Emotional	16.7%	12.4%	14.8%
Physical	9.2%	10.7%	9.9%

<sup>a</sup>Wave 2 data only (*n* = 8,667)

Data from [www.cdc.gov/ace/prevalence](http://www.cdc.gov/ace/prevalence).

The Adverse Childhood Experiences (ACEs) Study asked more than 17,000 middle-class adults to recall if they had experienced any of these 10 ACEs prior to the age of 18 years. The prevalence of each ACE is given for both women and men. To determine an individual's ACE score, 1 point was given for each type of ACE recalled (for a maximum score of 10). Only 36% of the participants had an ACE score of 0, and 1 in 8 had an ACE score of 4 or more.

### **BOX 68-1** Adverse Childhood Experiences Are Associated With Numerous Measures of Poor Health

#### **A. SOCIAL FUNCTIONING**

1. High perceived stress
2. Relationship problems
3. Married to an alcoholic
4. Difficulty with job

#### **B. MENTAL HEALTH**

1. Anxiety
2. Depression
3. Poor anger control
4. Panic reactions
5. Sleep disturbances
6. Memory disturbances
7. Hallucinations

#### **C. SEXUAL HEALTH**

1. Young age of first intercourse
2. Unintended pregnancy
3. Teen pregnancy
4. Teen paternity

5. Fetal death

6. Sexual dissatisfaction

#### **D. RISK FACTORS FOR COMMON DISEASES**

1. Obesity
2. Promiscuity
3. Alcoholism
4. Smoking
5. Illicit drugs
6. Intravenous drugs
7. High perceived risk of human immunodeficiency virus (HIV)
8. Multiple somatic symptoms

#### **E. PREVALENT DISEASES**

1. Ischemic heart disease
2. Chronic lung disease
3. Liver disease
4. Cancer
5. Skeletal fractures
6. Sexual transmitted infections

All of these adolescent and adult outcomes are associated with Adverse Childhood Experiences (ACE) scores in a dose-dependent and statistically significant manner. From Garner AS. Home visiting and the biology of toxic stress: opportunities to address early childhood adversity. *Pediatrics*. 2013;132[Suppl 2]:S65-S73.

stress reactivity. Thus, although stress reactivity may be, to an extent, genetically programmed, it is nonetheless shaped by early individual experiences as well. This individual variability in stress reactivity might explain, at least in part, the wide range of long-term responses to adversity. In sum, it may not be the adverse entity itself that matters as much as the nature of the physiologic stress response that it invokes.

### **ADVERSITY AND STRESS ARE NOT ALWAYS NEGATIVE**

High stress reactivity, however, is not always a negative trait or one that invariably leads to maladaptive behavioral responses. In the context of low adversity, children with a high reactivity to stress (the so-called “orchids”) are actually more social and academically

successful than their peers with a low reactivity to stress (the so-called “dandelions”). However, in the context of high adversity, children with high reactivity to stress fare worse than their peers with low reactivity to stress. Hence, the consequences of high stress reactivity are contextual, with high reactivity promoting adaptive responses in the context of low adversity, but maladaptive responses in the context of high adversity. The relationship between adversity and stress is, therefore, complex. Adversity can promote stress reactivity, but stress reactivity can be beneficial in the context of low adversity.

In an attempt to refine this complex relationship between adversity and stress, the National Scientific Council on the Developing Child has proposed a taxonomy of stress based on the physiologic response to the event (Figure 68-1). Physiologic stress can be positive, tolerable, or toxic. Positive stress is infrequent, mild, or brief and is characterized by strong social-emotional (SE) supports. These strong SE supports—engaged, nurturing and invested caregivers—allow the child’s physiology to return to baseline, and they minimize the child’s exposure to the physiologic mediators of stress (like cortisol and adrenaline). Examples of adverse experiences that could trigger a positive stress response (and the SE supports needed to buffer that stress) include a toddler’s stumble or fall (under the reassuring eyes of a caregiver), a child’s anxiety over beginning kindergarten or child care (and an invested parent’s firm but sympathetic response), or the adolescent’s fear of failure on a long-term school project (that is overcome by a parent’s assistance in organizing time). SE supports effectively buffer the potentially “toxic” consequences of prolonged exposure to the physiologic mediators of stress (see the following section on Brain Development and Toxic Stress). More importantly, strong SE supports model effective social interactions and promote emotional regulation in the face of adversity, thereby building resilience. It is important to note that positive stress is not the absence of physiologic stress; rather, it reflects an ability to adapt to that stress in a healthy manner.

When compared to positive stress, tolerable stress is more frequent, intense, or sustained. Precipitants of tolerable stress might include the death of a loved one, a natural disaster, or a bully on the bus. Although these experiences have the potential to trigger physiologic responses that are stronger or more sustained, caregivers who are engaged, nurturing, and invested usually allow the child’s physiologic stress response to return to baseline. When compared to toxic stress, tolerable stress is distinguished by the presence of sufficient SE supports.

Conversely, toxic stress results from the frequent, strong, or prolonged activation of the body’s stress-response system in the absence of sufficient SE supports. Physiologic stress becomes toxic when it overwhelms the available SE supports and the child’s physiologic stress response is unable to return to baseline. The 10 childhood adversities studied in the ACE Study (see Table 68-1) are examples of potential precipitants of toxic stress. When a child’s SE supports are not engaged (eg, a caregiver who is impaired by

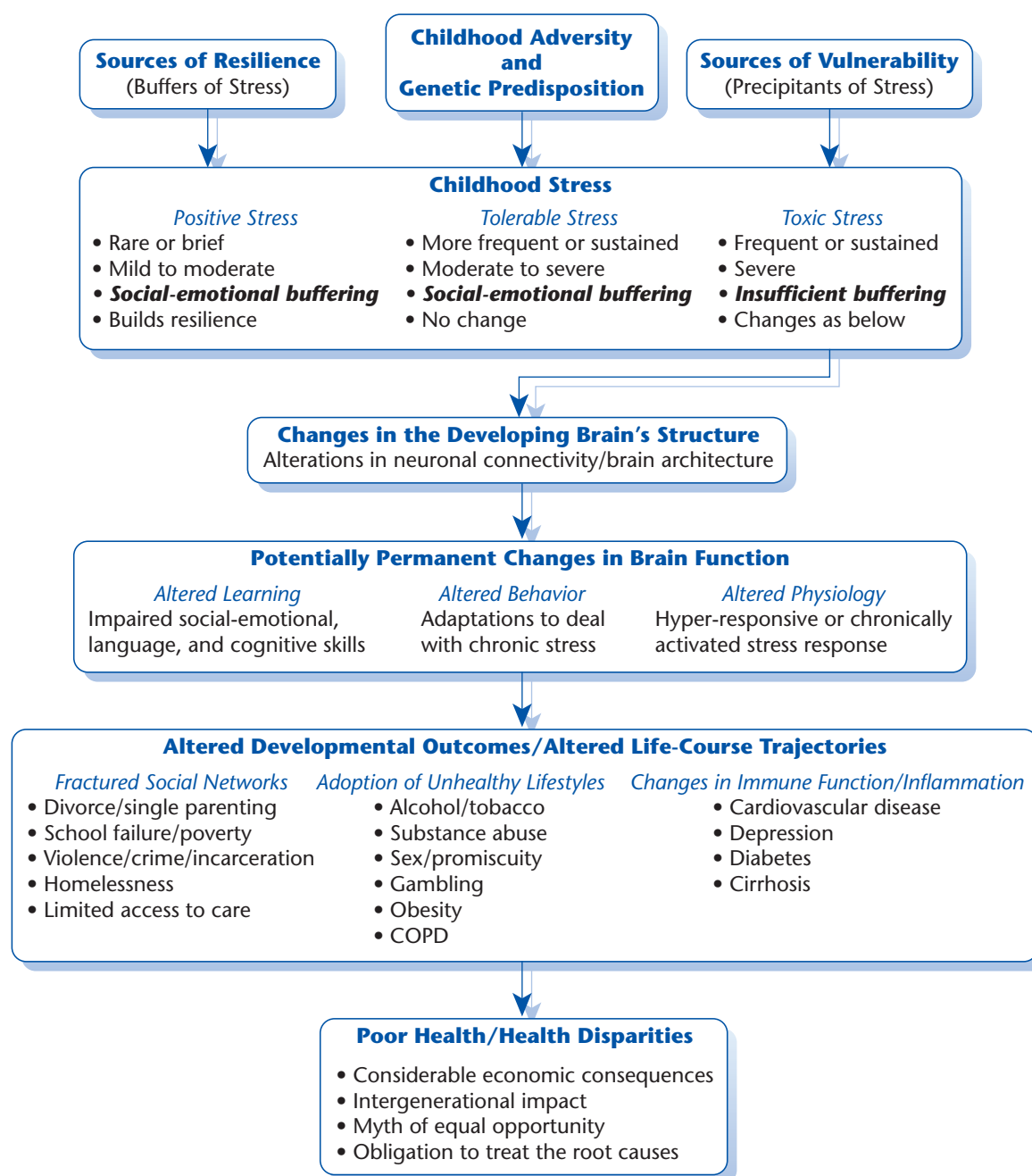
mental health or substance abuse issues) or nurturing (eg, a caregiver’s use of corporal punishment or verbal abuse), the child’s physiologic stress response is sustained, and biologic adaptations and disruptions begin to occur. Disengaged, non-nurturing caregivers may actually become sources of vulnerability, whereas engaged, nurturing caregivers are important sources of resilience. In sum, the relationship between adversity and stress is both complicated and dynamic. The type of stress response precipitated by adversity is influenced by the nature of the adversity, the individual’s stress reactivity, and the level of SE supports. (Are caregivers engaged and nurturing and building resilience, or are they disengaged, non-nurturing and generating additional vulnerabilities?)

## BRAIN DEVELOPMENT AND TOXIC STRESS

The process of brain development is driven by a dynamic interaction between the genome (nature) and the environment (nurture). Epigenetic mechanisms such as DNA methylation and histone acetylation are able to transduce experiences with the environment into long-lasting, even intergenerational changes in gene expression. Thus, while the inherited genetic program is thought to provide a general blueprint for brain architecture, the environment is able to influence which genes are expressed, when they are expressed during the course of development, and where they are expressed within the developing brain. Environmental experiences and the neuronal activity that they generate literally sculpt brain architecture and neuronal connectivity.

Understanding the effect of adverse experiences on the developing brain requires a brief review of where the physiologic mediators of toxic stress are acting in the brain. Glucocorticoid receptors are numerous in 3 prominent brain structures: the amygdala, the hippocampus, and the prefrontal cortex. The amygdala is part of the limbic system, is activated during stress, and is thought to play an important role in generating impulsive or aggressive behaviors. The fact that the amygdala is enlarged and more reactive in patients with post-traumatic stress disorder (PTSD) reinforces the notion that the neuronal pathways underlying the stress response (like those in the amygdala) are built up, reinforced, and strengthened by adverse experiences, leading to a hyperresponsive or chronically active stress response.

Another example of how stress might alter brain architecture is seen in the hippocampus. Although neuronal proliferation was once thought to occur only prenatally, new neurons are continuously being generated in the adult hippocampus, and these new neurons play an important role in learning and in the formation of new memories. In animal studies, chronic stress decreases this neuronal proliferation and results in impaired learning. Recent magnetic resonance imaging (MRI) data suggest that decreased hippocampal neurogenesis may well play a role in patients with PTSD, as they have selective volume losses in specific hippocampal areas known to be important for learning. While acute deficits in learning and memory might



**Figure 68-1** Toxic stress in childhood links adversity with poor health and health disparities. Adverse childhood experiences and genetic predispositions regarding stress reactivity interact to determine the type of childhood stress. Sources of resilience (strong social-emotional supports, previous adaptive experiences where adversity was successfully overcome, and the 7 Cs of resilience—Competence, Confidence, Connectedness, Character, Contribution, Coping, and Control) buffer this stress, whereas sources of vulnerability (poor SE supports, previous maladaptive experiences where adversity was not dealt with in a healthy manner, and harsh or abusive parenting) precipitate even more stress. Positive stress is rare or brief, mild to moderate in intensity, and builds resilience due to appropriate levels of SE buffering by invested, caring adults. Tolerable stress is more frequent or sustained, moderate to severe in intensity, and has the potential to alter life courses, but does not because of adequate levels of SE buffering. Toxic stress is often frequent, sustained, and severe in intensity, but is distinguished by the lack of sufficient levels of SE buffering. As a consequence, the physiologic mediators of stress (such as cortisol and adrenaline) become “toxic” to the developing brain, resulting in changes in brain architecture and functioning. These changes in brain structure and function are in turn associated with many of the adolescent and adult outcomes seen in the ACE study (see Box 68-1). Taken together, these altered developmental outcomes and maladaptive life course trajectories contribute to poor adult health and the intergenerational propagation of health disparities. (Adapted from Garner AS. Home visiting and the biology of toxic stress: opportunities to address early childhood adversity. *Pediatrics*. 2013;132[Suppl 2]:S65.)



be an evolutionarily advantageous, protective mechanism that allows individuals to “get over” very traumatic experiences, chronic or ongoing impairments in learning might also delay the development of critical social, emotional, language, and cognitive skills.

The prefrontal cortex is also altered by stress. The prefrontal cortex is thought to play an important role in executive function, including the regulation of behavior by suppressing impulses and emotions arising from the amygdala and other parts of the limbic system. In animal studies, exposure to chronic stress or glucocorticoids alters the synaptic connectivity within the prefrontal cortex, and this may limit the ability of the prefrontal cortex to suppress the impulsivity and aggression of the limbic system and to execute adaptive responses (rather than maladaptive responses) to future stress. Toxic stress-induced changes in brain structure explain, at least in part, the well-described effect of adversity on a variety of brain functions, including dysregulated physiologic responses (a hyperresponsive or chronically active stress response), poor learning (impaired memory), and maladaptive behaviors (difficulty in adopting adaptive responses to adversity).

### **TOXIC STRESS, DEVELOPMENTAL OUTCOMES AND LIFE COURSE TRAJECTORIES**

The toxic stress-induced changes in brain structure and function discussed earlier mediate, at least in part, the well-described relationship between adversity and altered life trajectories. A hyperresponsive or chronically activated stress response is likely to contribute to the dysregulated immune function and inflammation that are seen in those chronic diseases often associated with childhood adversity, like chronic obstructive pulmonary disease (COPD), cirrhosis, type II diabetes, depression, and cardiovascular disease. Toxic stress-induced impairments in critical SE skills and executive functions are likely to contribute to the fractured social networks associated with adults who have experienced childhood adversity. Examples include school failure, divorce, homelessness, poverty, violence, and limited access to health care. Finally, the adoption of maladaptive behaviors to deal or cope with chronic stress explains, at least in part, the association between childhood adversity and unhealthy lifestyle choices, such as alcohol, tobacco, and substance abuse; promiscuity; gambling; and obesity. Taken together, these 3 general classes of altered developmental outcomes or altered life trajectories (changes in immune function, fractured social networks, and unhealthy lifestyles) encompass many of the morbidities associated epidemiologically with childhood adversity.

### **IMPLICATIONS OF CHILDHOOD ADVERSITY AND TOXIC STRESS**

Childhood adversity and toxic stress are fundamental concerns for the medical community because unhealthy lifestyles, changes in immune function, and

fractured social networks are important markers of higher mortality, morbidity, and medical expenditures. Up to 40% of premature deaths are caused by behavioral patterns. The unhealthy lifestyles associated with childhood adversity are, at least in part, maladaptive coping responses to toxic stress. Another 25% to 30% of premature deaths are thought to be attributable to either social circumstances or shortfalls in medical care. Many of the consequences of fractured social networks associated with childhood adversity are known to contribute to these health care disparities. Toxic stress is also known to alter immune function and increase inflammatory markers, changes that are associated with morbidities as diverse as cardiovascular disease, viral hepatitis, liver cancer, asthma, COPD, autoimmune diseases, and depression. Childhood adversity and toxic stress are inherently medical concerns because they contribute significantly to poor health across the lifespan by encouraging the adoption of unhealthy lifestyles, widening social inequities and health disparities, and increased incidence of stress-associated, inflammatory diseases. Physicians in general and pediatricians in particular have an ethical obligation to address childhood adversity and toxic stress because they are important childhood antecedents, perhaps even determinants, of adult disease.

The consequences of toxic stress are enormous medically, socially, and economically. Advances in epigenetics demonstrate that early adverse experiences can alter gene expression patterns not only in the current generation, but in subsequent generations as well. Moreover, the fractured social networks and social inequities that often result from childhood adversity are prominent sources of toxic stress vulnerability for the next generation. These 2 facts, the epigenetic imprinting of the genome and the intergenerational cycle of social inequities, challenge assertions of “equal opportunity” and underscore the urgent need to address childhood toxic stress as a public health crisis.

### **CHILDHOOD ADVERSITY, TOXIC STRESS, AND PEDIATRIC CARE**

Pediatricians cannot address childhood adversity alone. Many of the systems that generate adversity for children (or serve as sources of vulnerability, such as family structure, income, housing, violence, etc) lie outside the walls of the pediatric clinic. Productive collaborations between pediatricians, family advocates, educators, judges, business leaders, and other stakeholders are needed to drive fundamental shifts in public policy and to promote more nurturing environments for children to live, grow, and learn.

Childhood toxic stress is a public health crisis, and addressing it will require a public health approach that includes treatment, targeted interventions for those at risk, and universal preventive measures. For children who have already experienced significant adversity, or have had previously supportive connections to family and community interrupted or severed by foster care or adoption, pediatricians play several critical roles. These include the recognition of potential signs of toxic

stress at various developmental stages, comfort in discussing possible precipitants of toxic stress with families, and familiarity with the available community resources that support the needs of families with children.

In addition to treatment, a public health approach to toxic stress would also embrace targeted interventions for those at risk. Routinely screening families for risk factors such as the parent's experiences as a child, substance abuse, mental illness, intimate partner violence, or food insecurity could identify children at risk for toxic stress. When linked to interventions, as in the Safe Environment for Every Kid model, these targeted screens are able to decrease important measures of childhood adversity like harsh parenting, maltreatment, and referrals to child protective services.

A public health approach to toxic stress must also include universal primary preventive measures. From a practical standpoint, however, eliminating all childhood adversity is both unfeasible and unadvisable. Some degree of adversity, once overcome, builds resilience, and some degree of stress, if not toxic, motivates behavioral change and learning (adaptation). The issue facing pediatricians and all other professionals caring for children is how to turn toxic stress into tolerable stress, and how to turn tolerable stress into positive stress. Recall that the 3 different types of stress are not defined by the stressors or adverse experiences themselves, but by the frequency, duration, and intensity of the physiologic stress response to those stressors. As seen in Figure 68-1, a very important determinant of the physiologic stress response is the degree of SE support or buffering.

At the practice level, then, pediatricians must assist parents and caregivers in providing developmentally appropriate forms of SE support. For example, beginning as early as the 2-month visit (see Connected Kids and Bright Futures in the Tools for Practice section at the end of this chapter), anticipatory guidance could address the appropriate response to the developing social smile, particularly for parents who might be depressed or overwhelmed. By nurturing the serve-and-return or transactional nature of the social smile, parents are strengthening attachment, promoting rudimentary social skills, and setting the foundation for language. As infants begin to coo and make happy vocalizations, parents need to reinforce those efforts (by cooing and smiling back) as effective alternatives to crying for attention. Attentive, calm, reassuring, and nurturing responses to infant distress model and promote emotional regulation.

In the second year of life, parents need to acknowledge and encourage the toddler's attempts to be competent and independent, while at the same time acknowledging that some important and consistent limits need to be maintained for safety. Continued vigilance for and reinforcement of emerging verbal and nonverbal modes of communication will stop or shorten many tantrums. As children reach their third and fourth years, tantrums and conflicts are opportunities to address the behavior ("no biting") and, more importantly, to demystify the strong emotions that are often underlying the behavior ("I understand that you are angry, but biting doesn't help anger. Next time you are angry, let's try to use our words, or maybe we

can take turns, or maybe we can find something else to do"). This sort of emotion coaching models problem solving, teaches new coping strategies, buffers future stress, and builds resilience, even in the face of severe adversities. These positive parenting techniques (building on strengths while teaching and nurturing emerging new skills) build resilience, in contrast with harsh or physical means of discipline that, while sometimes effective in the short term, only promote aggression and serve as sources of vulnerability in the future.

For young children, SE supports are primarily external. Parents and invested caregivers provide a predictable, nurturing environment to minimize the child's exposure to the physiologic mediators of stress; model healthy, adaptive responses to stress; and reinforce the child's rudimentary or emerging SE skills (engaging others, language skills, self-soothing, etc). For parents and caregivers who are unable to provide these supports, medical homes must be familiar with evidence-based parenting programs (eg, Triple P), home visitation programs (eg, the Nurse Family Partnership), and quality early childhood education services (eg, Head Start).

In adolescence, however, the peer group may become a major source of SE support, in some cases eclipsing the support provided by family. This can leave some youths susceptible to peer pressure and to the temptation to act in a certain way to receive additional SE support. Youths who are experiencing toxic stress may be more likely to seek this additional SE support from their peer group, even if those peers are less than ideal SE role models.

The primary goal for older children, therefore, is to build internal SE supports prior to adolescence. Internal SE skills (like the 7 Cs of resilience—a child's internal sense of competence, confidence, connectedness, character, contribution, coping, and control) need to be the objectives of parents, pediatricians, teachers, and all other professionals who care for children. These critical SE skills will not insulate children from all adversity, but they may turn tolerable or even toxic stress responses into positive ones.

## SUMMARY

Framing childhood adversity in the context of the physiologic response begins to explain the strong associations between adverse experiences in childhood and a wide array of altered developmental outcomes and life course trajectories. This physiologic framework also suggests a generalizable, proactive approach to mitigating the potentially lifelong consequences of childhood adversity—minimize toxic stress by assisting families of young children and strengthening critical SE supports early in life.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *Trauma Guide* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/healthy-foster-care-america/Pages/Trauma-Guide.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/healthy-foster-care-america/Pages/Trauma-Guide.aspx))

### Engaging Patient and Family

- *Partnering With Parents: Apps for Raising Happy, Healthy Children* (booklet), Institute for Safe Families

([www.instituteforsafefamilies.org/sites/default/files/isfFiles/20130324-Partnering-With-Parents-Brochure-WEB.pdf](http://www.instituteforsafefamilies.org/sites/default/files/isfFiles/20130324-Partnering-With-Parents-Brochure-WEB.pdf))

- *The First 1,000 Days: Bright Futures Examples for Promoting EBDCD* (booklet), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/EBDCD/Documents/EBDCD\\_Well\\_Child\\_Grid.pdf](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/EBDCD/Documents/EBDCD_Well_Child_Grid.pdf))
- *What Is Child Traumatic Stress?* (fact sheet), National Child Traumatic Stress Network (NCTSN) ([www.nctsn.org/nctsn\\_assets/pdfs/what\\_is\\_child\\_traumatic\\_stress.pdf](http://www.nctsn.org/nctsn_assets/pdfs/what_is_child_traumatic_stress.pdf))

### Medical Decision Support

- *Bright Futures* (Web site), American Academy of Pediatrics ([brightfutures.aap.org](http://brightfutures.aap.org))
- *Connected Kids Clinical Guide* (booklet), American Academy of Pediatrics ([www2.aap.org/connectedkids/clinicalguide.pdf](http://www2.aap.org/connectedkids/clinicalguide.pdf))
- *Enhancing Pediatric Mental Health Care: Algorithms for Primary Care* (article), *Pediatrics*, Vol 125, Suppl 3, 2010 ([pediatrics.aappublications.org/content/125/Supplement\\_3/S109](http://pediatrics.aappublications.org/content/125/Supplement_3/S109))
- *Evidence-Based Child and Adolescent Psychosocial Interventions* (chart), PracticeWise, American Academy of Pediatrics ([www.aap.org/en-us/Documents/CRPsychosocialInterventions.pdf](http://www.aap.org/en-us/Documents/CRPsychosocialInterventions.pdf))
- *Feelings Need Check Ups Too* (booklet), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/children-and-disasters/Documents/Feelings-Need-Checkups-Toolkit\\_0823.pdf](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/children-and-disasters/Documents/Feelings-Need-Checkups-Toolkit_0823.pdf))
- *Pediatric Medical Traumatic Stress Toolkit for Health Care Providers* (toolkit), National Child Traumatic Stress Network (NCTSN) ([www.nctsn.org/trauma-types/pediatric-medical-traumatic-stress-toolkit-for-health-care-providers](http://www.nctsn.org/trauma-types/pediatric-medical-traumatic-stress-toolkit-for-health-care-providers))
- *SEEK Parent Questionnaire* (questionnaire), Safe Environment for Every Kid ([www.uspreventiveservicestaskforce.org/Home/GetFileByID/859](http://www.uspreventiveservicestaskforce.org/Home/GetFileByID/859))
- *Sources of Specialty Services for Children With Mental Health Problems and Their Families* (chart), American Academy of Pediatrics ([pediatrics.aappublications.org/content/125/Supplement\\_3/S126](http://pediatrics.aappublications.org/content/125/Supplement_3/S126))
- *Tools to Identify CEV* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Medical-Home-for-Children-and-Adolescents-Exposed-to-Violence/Pages/Diagnostic-Tools.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Medical-Home-for-Children-and-Adolescents-Exposed-to-Violence/Pages/Diagnostic-Tools.aspx))

### AAP POLICY

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American Academy of Pediatrics Committee on Early Childhood, Adoption, and Dependent Care. The pediatrician's role in family support and family support programs. *Pediatrics*. 2011;128:e1680–e1684 ([pediatrics.aappublications.org/content/128/6/e1680](http://pediatrics.aappublications.org/content/128/6/e1680))

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- Milteer RM, Ginsburg KR; American Academy of Pediatrics Council on Communications and Media, Committee on Psychosocial Aspects of Child and Family Health. Clinical report—the importance of play in promoting healthy child development and maintaining strong parent-child bond: focus on children in poverty. *Pediatrics*. 2012;129(1):e204–e213 ([pediatrics.aappublications.org/content/129/1/e204](http://pediatrics.aappublications.org/content/129/1/e204))
- Shonkoff JP, Garner AS; American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health, Committee on Early Childhood, Adoption, and Dependent Care, and Section on Developmental and Behavioral Pediatrics. Technical report—the lifelong effects of early childhood adversity and toxic stress. *Pediatrics*. 2012;129(1):e232–e246 ([pediatrics.aappublications.org/content/129/1/e232](http://pediatrics.aappublications.org/content/129/1/e232))

### SUGGESTED READINGS

- Ginsburg KR, Jablow MM. *A Parent's Guide to Building Resilience in Children and Teens: Giving Your Child Roots and Wings*. Elk Grove Village, IL: American Academy of Pediatrics; 2006
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### Chapter 69

## CARING FOR FAMILIES NEW TO THE UNITED STATES

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### INTRODUCTION

The United States is a nation of immigrants. Since 1820, an estimated 75,356,720 people have immigrated to the United States. Currently, almost 3 million foreign-born children live in the United States, accounting for 1 in 27 American children. Twenty percent of children under the age of 6 are the children of immigrants, and are the



fastest growing population of children in the United States. This chapter provides a comprehensive approach to providing high-quality health care to immigrant children. Recent detailed reviews of immigrant health care have focused on screening tests and checklists. In addition to reviewing important medical and health-promotion topics for immigrant children, this chapter addresses basic demographics, barriers to health care, and linguistic and cultural issues for immigrant and refugee children in the United States.

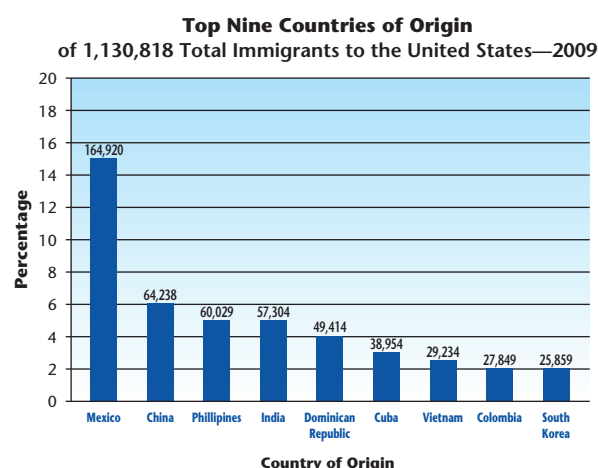
## DEMOGRAPHICS OF IMMIGRANTS AND REFUGEES

In 2009, 1,130,818 immigrants received legal resident status in the United States, of which 177,368 were refugees or asylees. The 5 largest countries of origin of immigrants to the United States are (in order) Mexico, China, the Philippines, India, and the Dominican Republic (Figure 69-1). Most US immigration is through sponsorship by relatives, with 47% being immediate family members of US citizens and 19% receiving family sponsorship (Figure 69-2).

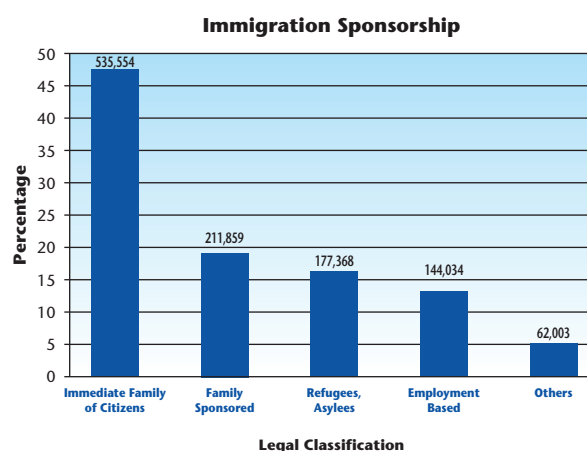
Official immigration figures, however, do not account for the large numbers of undocumented immigrants living and working in the United States. Among the estimated 11.1 million undocumented immigrants in the United States, 10%, or 1.1 million, are children. The annual flow of undocumented immigrants into the United States declined from 2007 to 2009.

## ACCESS TO HEALTH CARE IN THE UNITED STATES

The pediatric primary care physician should consider financial issues and insurance coverage when providing care to immigrant families. With implementation of the federal Patient Protection and Affordable Care Act (PPACA), financial issues and insurance coverage should become less of a problem for documented immigrants. At present, they pose significant barriers to care for many families. For example, 52% of foreign-born noncitizen children are uninsured, compared with 15% of US-born children in citizen families. More than one-fourth (28%) of foreign-born noncitizen children have no usual source of care (other than the emergency department), compared with approximately 6% of US-born children in citizen families. Foreign-born noncitizen children also are less likely than US-born children to have visited a doctor, dentist, or mental-health specialist. Low-income noncitizen children are approximately 5 times as likely to be uninsured as similar children in citizen families, and only 20% of low-income noncitizen children participate in Medicaid or the Children's Health Insurance Program (CHIP), compared with approximately one-half of low-income citizen children (49% for citizen children in noncitizen families and 41% for citizen children in citizen families). The American Academy of Pediatrics advocates for "comprehensive, coordinated, and continuous health services provided within a medical home..." for immigrant children, and awareness of and sensitivity to financial and other barriers that "interfere with achieving optimal health status." An unfortunate start to a



**Figure 69-1** Top countries of origin of immigrants to the United States—2009.



**Figure 69-2** Distribution of legal classifications of immigration visa sponsorship for immigrants to the United States in 2009.

pediatrician's relationship with new patients who are uninsured immigrants would be to perform a large battery of screening laboratory tests and unintentionally cause financial burden to the family.

Studies of Latino children indicate a wide variety of other access barriers to care for immigrant children. For example, a study of a predominantly immigrant Latino population revealed that more than one-quarter of parents (26%) said that language problems were the single greatest barrier to getting health care for their child (specifically, 15% of parents said that the greatest obstacle was physicians and nurses who do not speak Spanish, and 11% cited lack of interpreters). A long wait at the physician's office was reported as the greatest barrier by 15%, 13% mentioned the lack of medical insurance, 7% cited difficulty paying for medical bills, and 6% identified transportation. Parents who participated in the study also identified several barriers to care that had caused them not to bring their child in for medical visits in the past; transportation problems



were reported most often (21%), followed by not being able to afford health care (18%), excessive waits to see the physician (17%), lack of health insurance (16%), inconvenient clinic hours (14%), difficulty making appointments (13%), and culture and language problems (11%).

Access to primary care and other medical services can be highly variable among immigrant communities. Racial/ethnic minorities and low-income children in the United States consistently have had significantly worse rates of having a usual source of care and other health care indicators. In addition, specific ethnic groups have varying levels of access to and use of health care even within their own communities. These differences, independent of income and educational levels, underscore the importance of cultural and linguistic barriers to healthcare access. Accordingly, outreach to ethnic communities and the provision of comprehensive language services to all those who need them are important steps in improving access to healthcare.

Other research on the largest racial/ethnic group among US immigrants, Latinos, suggests that health insurance coverage is a major determinant of access to and use of care. A large study of Latinos in Los Angeles found that a lack of employment-linked health insurance posed a significant barrier to care for children. Many Latino immigrant children live in 2-parent households, with parents (particularly non-citizens) working in entry-level jobs without benefits or the ability to afford health care insurance premiums. Similarly, children with working parents who were eligible for Medicaid were less likely than others to be continuously enrolled. Children in this category also had less access to care in all measures studied. Indeed, research documents that, after adjustment, parental noncitizenship, having 2 parents work, low family income, and older child age are associated with being an uninsured child, but Latino ethnicity is not. In states where undocumented immigrant children are eligible for at least limited health insurance coverage, *promotoras* and other community health workers can be highly effective means of insurance outreach and enrollment. For example, one randomized, controlled trial of an insurance intervention for Latino children that included many immigrant families documented that community healthworkers were substantially more effective than traditional Medicaid and CHIP outreach and enrollment in insuring children (at 96% vs 57%, respectively), and community health workers insured children significantly faster, more continuously, and with higher parent satisfaction with the process.

Federal welfare and immigration reform legislation in 1996 further restricted access to Medicaid for noncitizens to reduce expenditures and discourage immigrants from becoming public charges. Nonetheless, research has documented that in the 2 years before enactment of this legislation, immigrants had substantially lower *per capita* healthcare expenditures (55%) than their US-born counterparts. Among children, expenditures were 74% lower among immigrants, yet emergency-department expenditures were 3 times higher. The latter finding suggests that immigrant children are going without basic primary care services and are missing out on the benefits of

a medical home. A recent study of immigrant children's use of public health insurance since reform legislation shows that foreign-born children were 1.6 times more likely to be uninsured after 2001 than before 2001, and are 3 times more likely to be uninsured than to have public insurance. The PPACA of 2010 increases Medicaid coverage to 133% of federal poverty level and restricts access to the health-insurance exchange to US citizens and legal residents. It does not alter current restrictions on Medicaid and CHIP eligibility for legal permanent residents within the first 5 years of residency, or for undocumented immigrants. Although the ACA contains a provision for the development of guidelines to reduce health disparities through methods such as the use of language services and cultural competency training, the payment mechanism for these services will be incentive-based. The Act does not require insurance plans to reimburse for language services or translation of materials into languages other than English, and only 13 states and the District of Columbia currently provide third-party reimbursement for interpreter services.

Of note, there are nearly 4 million children born in the United States to undocumented immigrants who may encounter even further barriers to productive and healthy futures, despite their citizenship status. Recent research found that children of undocumented immigrants may have lower early cognitive and language skills than children of documented immigrants of similar socioeconomic backgrounds. Undocumented parents may share circumstances that adversely affect their children's outcomes such as avoidance of programs and authorities, social isolation, and poor work conditions. Fearing deportation, undocumented immigrants may be reluctant to access services such as early education programs and food subsidies that could be essential to improving child development. Poor work conditions, including lower rates of benefits and lower wages, may also lead to less access to child care subsidies and center-based care. These factors may contribute to ongoing parental stress and economic hardship, which may result in less of the parent-child interaction that is critical to early skill development in children.

Pediatricians and hospitals that care for children increasingly are facing the dilemma of rationing care to uninsured, undocumented immigrant children, particularly for expensive, life-saving pediatric care, including transplants, chemotherapy, and dialysis. For example, some hospitals have policies to provide neither dialysis nor kidney transplantation to undocumented, uninsured end-stage renal-failure patients. In such cases, it can be argued that the high costs associated with providing expensive lifesaving care to undocumented children can compromise existing or new clinical programs. On the other hand, denying acute and chronic care to undocumented immigrant children may result in higher overall expenditures related to preventable hospitalizations and more expensive therapies and have unintended public-health consequences, including significant long-term morbidity and a high risk of early mortality. One potential solution which has been suggested is to have hospitals and clinics establish a structured process with a panel

of pediatricians and hospital staff who would evaluate these considerations and make a recommendation on a case-by-case basis. This approach could result in formulating a medical individual expense plan for uninsured, undocumented children that could include providing financial aid, discounted treatment, payment plans, and philanthropic support and active fund-raising for lifesaving care.

## HEALTH PROMOTION

Primary care physicians working with families new to the United States must first establish relationships with the families that are linguistically and culturally effective (see details on cultural competency action steps later in this chapter). By showing interest in the families' background, culture, and community issues, the physician may also gain a reputation as a sympathetic and supportive healthcare provider whom other members of that ethnic community can trust. The following section describes in more detail the issues associated with this task. An important point to remember is that postponing medical screening is reasonable if it seems inappropriate based on cultural, linguistic, or economic reasons.

The process of health promotion and preventive medicine may be new to the family. This process is informed by knowledge of the family's home and social circumstances, with which the physician can assess the family's previous experience with the health care system as well as the level of need for environmental intervention, injury prevention, and mental-health services. In trying to understand the cultural expectations of immigrant patients and families and introducing concepts of health promotion and preventive medicine, the physician will embark on a journey of communication with new Americans. This journey may be relatively straightforward and brief with patients and families who share more Western beliefs, or it may involve multiple levels of complexity that will require a fair amount of time and effort. Efforts should be made to understand immigrant families' previous experiences with the health care system in their native countries; educate them about basic issues in the American health care system, such as assessing eligibility for and access to health insurance; and to provide practical tips, such as instructions on where to go for urgent care and when to go the emergency department.

## LANGUAGE BARRIERS TO CARE AND PROVIDING ADEQUATE LANGUAGE ACCESS

Approximately 57 million Americans speak a language other than English at home, and 24.6 million are limited in English proficiency (LEP), defined as a self-rated English-speaking ability of less than "very well." As of 2009, approximately 11 million (21%) US school-aged children (5 to 17 years old) spoke a language other than English at home, almost triple the number reported in 1979, and 2.6 million (5%) were LEP. Between 1980 and 2009, the number of people in the United States speaking a language other than English at home increased from 23 million to 57 million. The number of Americans who are LEP rose from 14 million in 1990 to 24.6 million in 2009.

This marked growth in the number of Americans who speak a language other than English at home or who are LEP can be attributed to the rapid increase in the foreign-born population in the United States, which grew from 9.6 million in 1970 to 38.5 million in 2009. Most Americans considered to be LEP (66%, or 16.2 million) speak Spanish; Asian and Pacific Island languages (led by Chinese) are the next most common among LEP Americans (comprising 17%, or 4.2 million), followed by other Indo-European languages (14%, or 3.4 million), and all other languages (3%, or 750,000).

Language barriers have many adverse consequences in health care, including impaired health status, a lower likelihood of having a usual source of medical care, lower rates of screening and other preventive services, nonadherence with medications, a greater likelihood of a diagnosis of more severe psychopathology and leaving the hospital against medical advice among psychiatric patients, a lower likelihood of being given a follow-up appointment after an emergency-department visit, an increased risk of intubation in asthmatic children, an increased risk of drug complications, higher resource utilization for diagnostic testing, lower patient satisfaction, impaired patient understanding of diagnoses, medications, and follow-up, fewer telephone calls to physicians' offices, fewer referrals to specialists, and an increased risk of medical errors and injuries. Latino parents consider the lack of interpreters and Spanish-speaking staff to be the greatest barriers to health care for their children, and 1 out of every 17 parents in one study reported not bringing his or her child in for needed medical care because of these language issues.

To assess the language needs of patients and caregivers accurately, determining whether a child's caregiver is LEP is essential. Determining English proficiency has been shown to be superior to the primary language spoken at home as a measure of the effect of language barriers on children's health and health care. The following questions, which come from the US Census, are an excellent means of quickly assessing English proficiency and language needs and should be asked routinely of the primary caregiver during the 1st visit:

1. Does this person speak a language other than English at home?
  - Yes
  - No [*Stop here; person is considered English proficient*]
2. What is this language?  
(*For example: Korean, Italian, Spanish, Vietnamese*)
3. How well does this person speak English?
  - Very well
  - Well
  - Not well
  - Not at all

[*Person is LEP if reply is anything other than "very well" and requires medical interpreter or bilingual provider.*]

Although millions of Americans are LEP, many patients who need medical interpreters are not provided with interpreters. Every LEP patient should have access to a trained medical interpreter or bilingual health care provider. Ample scientific evidence documents that optimal communication, patient satisfaction, and

outcomes, and minimal interpreter errors occur when LEP patients have access to trained professional interpreters or bilingual providers. In addition, federal guidance on Title VI of the Civil Rights Act of 1964 has established that denial or delay of medical care for patients who are LEP because of language barriers constitutes a form of discrimination and requires all recipients of federal funds, including Medicaid, CHIP, and Medicare, to provide adequate language assistance to those who need it. Key mechanisms for ensuring adequate language access for patients and families who are LEP are summarized in Box 69-1.

Detailed information on improving language access in health care is available in the Office of Minority Health's "A Patient-Centered Guide to Implementing Language Access Services in Healthcare Organizations."

## CULTURAL ISSUES

Cultural issues affect multiple aspects of pediatric care, including outcomes, quality, costs, satisfaction with care, and patient safety. Failing to appreciate the importance of culture in pediatrics can result in a variety of adverse consequences, including difficulties with informed consent; miscommunication; inadequate understanding of diagnoses and treatment plans by families; dissatisfaction with care; preventable morbidity and mortality; unnecessary child-abuse

evaluations; and disparities in prescriptions, analgesia, and diagnostic evaluations. On the other hand, providing culturally competent health care to children is associated with better health outcomes. For example, pediatric patients with asthma receiving care at practice sites with the highest cultural competence scores are significantly less likely to be underusing preventive asthma medications and have better parental ratings of the quality of care.

Because culture can profoundly affect the care of immigrant children, pediatricians should be familiar with the most important cultural issues that affect clinical care, including folk illnesses with symptoms that overlap with biomedical conditions, biomedical conditions that can result from harmful folk illness remedies or parental beliefs and practices, and cultural healing practices that can be confused with child abuse. Table 69-1 through Table 69-3 are organized by folk illnesses based on regional origin. Although this is not a comprehensive list of folk illnesses and there may be some overlap between regions, the tables can allow physicians to immediately locate cultural information relevant to their prevalent patient populations. These 3 tables can be helpful in obtaining accurate histories and improving patient satisfaction through the use of culturally acceptable alternative treatments (see Table 69-2), generating

### BOX 69-1 Key Mechanisms for Ensuring Adequate Language Access for Patients, Caregivers, and Families With Limited English Proficiency

- **Ensure that a trained medical interpreter or bilingual provider is available for each medical encounter.** Making language available throughout the encounter is especially important, including during registration, the history and physical, procedures, visits to the laboratory and radiology, and scheduling of follow-up appointments.
- **Use telephone or video interpreter services when in-person interpreters or bilingual providers are unavailable.**
- **Ensure adequate language access *door-to-door* (ie, at all points of interaction with the health care system).** This provision includes multilingual operators, telephone trees, or both (for scheduling appointments, leaving messages and getting phone advice), multilingual signage at all key wayfaring points (parking garages, clinic entrances, registration, paths to the emergency department, laboratory, radiology, and pharmacy), and multilingual registration clerks.
- **Routinely collect and record patient and family data on primary language spoken at home and limited English proficiency.** This provision permits efficiently meeting the language needs of the patient population and scheduling interpreters in advance for all future medical visits.
- **Use pharmacies that can print prescription labels, provide medication information packets, and communicate in non-English languages.** Failure to do so can result in medical errors and injuries. Printing clinic prescription pads with checkboxes such as ☐ *Spanish* or ☐ *Chinese* is particularly helpful and is a useful reminder.
- **Have patient information and anticipatory guidance pamphlets available in non-English languages common in the physician's practice.** Ideally, certified translators should be available to translate written documents for patients. Useful Web resources with materials already translated include the National Network of Libraries of Medicine Other Language Resources site ([nnlm.gov/outreach/consumer/multi.html](http://nnlm.gov/outreach/consumer/multi.html)), US Department of Health and Human Services' Español-Healthfinder ([www.healthfinder.gov/espanol/](http://www.healthfinder.gov/espanol/)), CDC en Español ([www.cdc.gov/spanish/](http://www.cdc.gov/spanish/)), and Selected Patient Information Resources in Asian Languages ([www.spiral.tufts.edu/](http://www.spiral.tufts.edu/)).
- **Translate consent forms into all relevant non-English languages for your patient population.**
- **Help patients and families who are LEP to learn English through referrals to free or low-cost English as 2nd-language courses.** This excellent resource ([www.literacydirectory.org](http://www.literacydirectory.org)) locates classes according to zip code.
- **Increase the number of bilingual health care providers and staff.** This provision can be achieved through enhanced efforts to recruit bilingual staff, continuing professional education, intensive language courses, and bonuses for demonstrating foreign language fluency.

**Table 69-1** Selected Folk Illnesses With Symptoms That Overlap With Biomedical Conditions Affecting the Health Care of Children

REGIONAL ORIGIN	FOLK ILLNESS	ETHNICITY OR NATIONALITY THAT MAY HAVE FOLK ILLNESS BELIEF		SYMPTOMS OF FOLK ILLNESS	BIOMEDICAL CONDITIONS THAT OVERLAP WITH FOLK ILLNESS
Latin America	<i>Empacho</i> (and <i>pega</i> )	Latino		Vomiting, stomach pain, headache, abdominal distention, loss of appetite, diarrhea, fever, crying	Gastroenteritis, viral infections, milk allergy, appendicitis, intussusception, anatomic obstruction, lead poisoning
	<i>Caida Mollera</i>	Latino		Diarrhea, excessive crying, fever, loss of appetite, irritability, fallen fontanelle	Gastroenteritis, dehydration, sepsis, meningitis
	<i>Susto</i>	Latino		Drowsiness, insomnia, irritability, exaggerated startle reflex, diarrhea, anorexia, fever, nightmares	Persistent symptoms after pesticide toxicity
	<i>Mal Ojo, Quebrante or Olhado</i>	Latino Brazilian		Inconsolable crying, fever, diarrhea, vomiting, pain, gassy stomach	Gastroenteritis, dehydration
	<i>Quebranto</i>	Costa Rican		Irritability, crying, leg-length discrepancy	Developmental dysplasia of the hip
Africa	<i>Doença de Criança</i>	Brazilian		Diarrhea, fallen fontanelle, convulsions, cyanosis, crying, vomiting (and 17 other less common symptoms)	Gastroenteritis, dehydration, malaria, bacterial meningitis, dengue, measles, pneumonia, methemoglobinemia, pesticide poisoning
	<i>Ventre Caído</i>	Brazilian		Vomiting, diarrhea, loss of appetite, fatigue, cough	Gastroenteritis, dehydration
	<i>Nyènkèhè biènkè</i>	Mali		Red urine	Schistosomiasis
	<i>Umsheko</i>	Swaziland		Wet, loose, nongreen stools accompanied by grumbling stomach, loss of appetite, vomiting	Gastroenteritis, dehydration
	<i>Kuhabula</i>	Swaziland		Sunken fontanelle, loss of strength, vomiting, crying, ribs <i>appear</i> to come together	Gastroenteritis, dehydration
Indian subcontinent	<i>Umphezulu</i>	Swaziland		Green or yellow diarrhea, unusual crying, loss of appetite, distended stomach or navel, grumbling stomach, sunken fontanelle, blood vessels visible on stomach or forehead	Gastroenteritis, dehydration
	<i>Mandama</i>	Singhalese (Sri Lanka)		Diarrhea, abdominal distention, lethargy, <i>lean</i> legs	Gastroenteritis, dehydration
	<i>Dud haga</i>	Rural Bangladesh		Watery stools, crying, abdominal pain	Gastroenteritis, dehydration
	<i>Ajirno</i>	Rural Bangladesh		Diarrhea, abdominal distention, gripping of the stomach	Gastroenteritis, dehydration
	<i>Amasha</i>	Rural Bangladesh		Mucoid and sometimes bloody diarrhea	Gastroenteritis, dehydration, dysentery
	<i>Daeria</i>	Rural Bangladesh		Frequent stools with rice-water appearance, sunken eyes, thirst, vomiting, reduced urine output, weakness	Cholera, gastroenteritis, dehydration



Table 69-1

Selected Folk Illnesses With Symptoms That Overlap With Biomedical Conditions Affecting the Health Care of Children—cont'd

REGIONAL ORIGIN	FOLK ILLNESS	ETHNICITY OR NATIONALITY THAT MAY HAVE FOLK ILLNESS BELIEF	SYMPTOMS OF FOLK ILLNESS	BIOMEDICAL CONDITIONS THAT OVERLAP WITH FOLK ILLNESS
Asia and Pacific Islands	<i>Phrooy</i>	Northern Pakistan	Green diarrhea, blisters on body, infections of the ear and eye	Gastroenteritis, dehydration
	<i>Sarishna</i>	Northern Pakistan	Green watery stools, burning yellow urine, weakness, eyes turned upward	Gastroenteritis, dehydration
	Loose motions	Northern Pakistan	White watery stools, fallen fontanelle	Gastroenteritis, dehydration
	<i>Sardawan</i>	Northern Pakistan	Frequent green watery stools, sunken eyes, weakness	Gastroenteritis, dehydration
	<i>Maleeh</i>	Northern Pakistan	Yellow or green watery stools	Gastroenteritis, dehydration
	<i>Saya</i> or <i>parchawan</i>	Northern Pakistan	Persistent green, white, or yellow diarrhea	Gastroenteritis, dehydration
	<i>Nazar</i> (evil eye)	Northern Pakistan	Green watery stools, fever, sunken eyes, dry lips, weak extremities	Gastroenteritis, dehydration
	<i>Kand-pota</i> (fallen fontanelle)	Northern Pakistan	Watery green stools, vomiting	Gastroenteritis, dehydration
	<i>Sardi</i> or <i>Padsa</i>	Marathas (India)	Cough, runny nose, congested chest, fever	Mild upper respiratory infection
	<i>Potat ala</i>	Marathas (India)	Labored respirations, stomach "going up and down," fever, phlegm, cough, congested chest	Moderate to severe respiratory infections, including pneumonia
	<i>Paltha dabba</i>	Marathas (India)	Tight or hard stomach (worse at night), cough, eyes closed, nostrils flare, fisted hands	Severe pneumonia
	<i>Phagya vat</i>	Marathas (India)	Tight or hard stomach, anorexia, constipation	Moderate to severe respiratory infections, including pneumonia, lead poisoning
	<i>Kitsune-tsuki</i> (fox possession)	Japanese	Delusions, disordered thinking, auditory hallucinations, paranoia	Psychosis, schizophrenia, mercury poisoning
	<i>Piang</i>	The Philippines	Cough, fever	Acute respiratory infection, including pneumonia
	<i>Naeng</i>	Korea	Vaginal discharge, back pain, cold hands and feet, abdominal pain, vaginal itching	Vaginal candidiasis, sexually transmitted diseases

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**Table 69-2** Biomedical Conditions in the Health Care of Children That Can Result from Harmful Folk Illness Remedies or Parental Beliefs and Practices

REGIONAL ORIGIN	CONDITION	ASSOCIATED FOLK ILLNESS, PARENTAL BELIEF, OR SYMPTOM	ETHNICITY OR NATIONALITY THAT MAY HAVE FOLK ILLNESS OR PARENTAL BELIEF	HARMFUL TREATMENT ASSOCIATED WITH CONDITION	CULTURALLY ACCEPTABLE ALTERNATIVE FOLK TREATMENTS
Latin America	Lead poisoning	<i>Empacho</i>	Latinos	Powders containing lead oxides ( <i>azarcón, greta, albayalde</i> )	Abdominal massage with warm oil, mint tea
	Subdural hematoma	<i>Caida de mollera</i>	Latinos	Infant shaken while held upside down with head partially immersed in boiling water	Put soap foam on fontanelle
	Gonococcal conjunctivitis	Conjunctivitis	Latinos <sup>a</sup>	Adult urine as treatment for conjunctivitis in children	Gently push up on palate
	Disseminated <i>Salmonella arizonae</i> infections	Sinus and skin conditions, diarrhea, infections, itchy feet, AIDS, diabetes, connective tissue diseases, heart disease, cancer	Latinos	Capsules or powder containing dried ground rattlesnake, raw dried rattlesnake meat: <i>polvo de vibora, carne de vibora, vibora de cascabel</i>	Special diet: vegetable soup and fresh fruits, carrot juice, eliminate flour tortillas, bread, soda
	Hepatic veno-occlusive disease	Cough	Latinos		Variety of harmless, disease-specific herbal preparations
Africa	Wound infection or cellulitis around infant's umbilicus	<i>Umphezulu</i> (type of diarrhea)	Swaziland (Africa)	<i>Gordolobo yerba</i> , tea made from herb <i>Senecio longilobus</i> , which contains hepatotoxic pyrrolizidine alkaloids <i>Traditional vaccination (kugata)</i> : razor blade cuts made around infant's umbilicus rubbed with ashes	Herbal teas using small amounts of oregano, cinnamon, or chamomile (not sweetened with honey) Herbal teas
	Urinary retention, dysuria, urinary tract infections, incontinence, fever, menstrual difficulties, cysts, abscesses, fistulae, obstetric complications, vaginal pain, bleeding discharge	Reasons cited by cultures for practice: tradition, group identity or norms, chastity, marital reasons, hygiene	Widespread in 33 African nations, most commonly Somalia, Djibouti, Ethiopia, Eritrea, Sudan, Sierra Leone; certain Islamic peoples in Asia, Middle East	Female circumcision, genital mutilation, <i>Sunna</i> , infibulation, Pharaonic circumcision, traditional or ritual female genital surgery	Education regarding health risks; discuss culturally-acceptable alternatives with community or religious groups; advocacy against procedure by community, religious, women's and law organizations; use of least damaging procedure (such as small nick/incision of prepuce) in families insisting on practice

**Table 69-2** Biomedical Conditions in the Health Care of Children That Can Result from Harmful Folk Illness Remedies or Parental Beliefs and Practices—cont'd

REGIONAL ORIGIN	CONDITION	ASSOCIATED FOLK ILLNESS, PARENTAL BELIEF, OR SYMPTOM	ETHNICITY OR NATIONALITY THAT MAY HAVE FOLK ILLNESS OR PARENTAL BELIEF	HARMFUL TREATMENT ASSOCIATED WITH CONDITION	CULTURALLY ACCEPTABLE ALTERNATIVE FOLK TREATMENTS
Indian subcontinent <sup>b</sup>	Dehydration	<i>Dud haga</i>	Bangladesh	1. Breastfeeding discontinued because (a) breast milk considered <i>poisoned</i> by shadow, evil eye, black magic, new pregnancy, illness, diet, cold; (b) pseudoscientific laboratory <i>breast milk analysis</i> reveals pus, germs, mobile bacteria, or blood (Pakistan) 2. Reduce child's oral intake of liquid because liquid believed to worsen diarrhea or vomiting feared Give formula until breast milk no longer considered <i>poisonous</i>	Mother avoids eating green vegetables, fish, meat
		<i>Nazar</i>	Pakistan		Apply <i>chanted oil</i> (available from folk healers, Buddhist priests); Education
		<i>Eshwaha</i> , diarrhea in general	Sri Lanka		Rub ghee (clarified butter) on abdomen Education; ascertain whether multivitamin drops are acceptable replacement Replace with saline drops
	Burns in circular pattern on abdomen Lead poisoning (including death) Lipoid pneumonia, bronchiectasis	<i>Phugrya va</i> (respiratory illness) Maintenance of infant health Cleaning airway of newborn; treatment of respiratory infections	India India	Burning acidic seed ( <i>biba</i> ) in circle on abdomen Lead-containing tonics, such as <i>ghasard</i> , with lead concentration up to 1.6% Apply butter or oil to nostrils or oropharynx	
Middle East <sup>b</sup>	Lead poisoning (including encephalopathy, death)	Teething; cosmetics	Saudi Arabia Kuwait Oman	Teething powders: <i>Saooti</i> , <i>Cebagiri</i> ; Cosmetics: <i>Koh</i> ; Other: <i>Bint al dahab</i>	Teething powders or solutions without lead
	Lipoid pneumonia, bronchiectasis	Cleaning airway of newborn; treatment of respiratory infections	Saudi Arabia	Apply butter or oil to nostrils or oropharynx	Replace with saline drops
	Hypematremia (fatal)	Healthy newborn skin	Turkey	Salting infant's skin or placing salt in swaddling material before swaddling	Education regarding health risks

Continued

**Table 69-2** Biomedical Conditions in the Health Care of Children That Can Result from Harmful Folk Illness Remedies or Parental Beliefs and Practices—cont'd

REGIONAL ORIGIN	CONDITION	ETHNICITY OR NATIONALITY THAT MAY HAVE FOLK ILLNESS OR PARENTAL BELIEF			HARMFUL TREATMENT ASSOCIATED WITH CONDITION	CULTURALLY ACCEPTABLE ALTERNATIVE FOLK TREATMENTS
		ASSOCIATED FOLK ILLNESS, PARENTAL BELIEF, OR SYMPTOM	ILLNESS OR PARENTAL BELIEF			
Asia and Pacific Islands <sup>c</sup>	Lead poisoning	Fever, rash	Hmong (Cambodia)		<i>Pay-loo-ah</i> , a red or orange powder with lead concentration of 1%-80% (and occasionally arsenic)	Education regarding risks; replacement with culturally acceptable harmless herbal preparations
	Life-threatening bradycardia; respiratory and central nervous system depression	Chinese herbal medicine used for analgesia by parents	Chinese		Unintentional poisoning due to ingestion of <i>Jin Bu Huan</i> tablets, Chinese herbal medicine used for analgesia by adults, containing L-THP (potent dopamine receptor antagonist, sedative)	Parental education regarding potential toxicity for children
	Opiate toxicity in infants	Diarrhea	Hmong		Enema made from opium seeds, unidentified capsule	Education regarding risks; culturally acceptable harmless herbal preparations

<sup>a</sup>Ethnicity of affected children not explicitly stated in study.

<sup>b</sup>Certain ethnic groups from these regions may also practice female circumcision, which is described as one of the conditions in the African region.

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**Table 69-3** Cultural Healing Practices That Can Be Confused With Child Abuse

REGIONAL ORIGIN	CLINICAL PRESENTATION	CULTURAL PRACTICE	ETHNICITY OR NATIONALITY ASSOCIATED WITH PRACTICE	SYMPTOMS OR ILLNESSES TREATED
Latin America	Patterned circular erythema, petechiae, occasional burns	Cupping ( <i>ventosas</i> ): create vacuum in cup by burning alcohol over inverted cup, place cup on affected anatomy	Latino	Pain, fever, poor appetite, congestion
Asia and Pacific Islands	Circular burns (2nd or 3rd degree) and scars	Moxibustion: moxa herb or yarn rolled into ball or cone, ignited, applied to body part and allowed to burn to point of pain	Laotian Cambodian Chinese Japanese	Fever, abdominal pain, ear infections, enuresis, temper tantrums
	Linear ecchymoses, hyperpigmentation, transient microscopic hematuria	<i>Cao Gio</i> ( <i>scratch the wind</i> ), or coin rubbing: symptomatic area covered with mentholated oil or balsam, then rubbed linearly with coin or other object until ecchymoses occurs	Vietnamese	Fever, cough, vomiting, headaches, chills, seizures, myalgias
	Linear ecchymoses	<i>Quat Sha</i> ( <i>spoon scratching</i> ): porcelain spoon used to rub skin on back (after water or saline applied) until ecchymoses appear	Chinese	Fever, headache

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rapid differential diagnoses and treatment plans (see Table 69-1), and making informed decisions about child abuse (see Table 69-3).

*Cultural competency* is defined as the recognition of and appropriate response to key cultural features that affect clinical care. Providing culturally competent health care should be the goal of every physician caring for immigrant children. Box 69-2 summarizes a model of cultural competency that can be helpful in clinical encounters with patients from any cultural group.

Helpful Web-based resources for addressing the cultural issues in pediatric care include DiversityRX ([www.diversityrx.org](http://www.diversityrx.org)), the Office of Minority Health's Web site ([www.omhrc.gov](http://www.omhrc.gov)), and the University of Michigan Health System's Program for Multicultural Health ([www.med.umich.edu/multicultural/](http://www.med.umich.edu/multicultural/)).

## GROWTH AND NUTRITION

Growth abnormalities and nutritional disorders are among the most common health problems of immigrant children, particularly refugees, adoptees, and immigrants from similarly deprived backgrounds. Common nutritional disorders, such as iron deficiency, may be seen in a significant portion of some populations of immigrant children, such as young refugees. Nutritional deficiencies, such as in iron and calcium, may also increase the susceptibility of immigrant and refugee children to environmental toxins, such as lead. Other disorders, such as rickets, vitamin A deficiency, and iodine deficiency and goiters, may also be

quite common in some populations. More recently, concerns have been raised about vitamin D deficiency among many refugee populations and B12 deficiency among refugees from Bhutan.

With hunger and food insecurity well documented among US immigrant and refugee populations, the primary care physician must assess growth and nutritional status of immigrant and refugee children. Eligible families should be referred for nutritional support to available programs, such as The Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) and subsidized school meals programs. A multivitamin with iron and minerals is likely to be beneficial for most immigrant children. Physicians should closely monitor nutritionally deprived children for catch-up growth (seen even in longitudinal growth in some cases) and developmental disorders, such as precocious puberty, that have been associated with rapid catch-up. Conversely, overweight may be seen in some immigrant populations, reflecting socioeconomic conditions and lifestyles in countries of origin that range from the formerly socialist countries of Eastern Europe to the urban environments of Sub-Saharan Africa.

All immigrant children should have complete blood counts performed, and those younger than 17 years old should have their blood lead levels evaluated. Children born outside the United States are more likely to have elevated blood lead levels than US-born children. Because a risk of acquiring elevated blood lead after arrival in the United States has been documented

### BOX 69-2 Model for Cultural Competency in Health Care

1. Normative cultural values
  - Identify values that affect care.
  - Accommodate for these values in clinical encounter.
2. Language issues
  - Use interpreter services unless fluent in patient's primary language.
  - Follow guidelines for effective interpreter use.
  - Encourage efforts to increase foreign language skills of staff and English skills of patients who are LEP.
3. Folk illnesses
  - Recognize those that may affect clinical care.
  - Suggest alternatives to harmful folk remedies.
  - Accommodate nonjudgmentally into clinical encounter.
  - Integrate into biomedical treatment plan whenever possible.
4. Parent and patient beliefs
  - Identify beliefs that may affect clinical care.
  - Suggest alternatives to harmful home remedies.
  - Carefully explain etiology and treatment rationale for given biomedical condition.
5. Provider practices
  - Maintain vigilance for ethnic disparities in screening, prescriptions, procedures, and outcomes.
  - When disparities occur, determine problem's source and address practices that might be responsible.

From Flores G, Abreu M, Schwartz I, et al. The importance of language and culture in pediatric care: case studies from the Latino community. *J Pediatrics*. 2000;137:842–848, with permission from Elsevier.

among refugees, testing should be repeated after 90 days. This testing is appropriate even in parts of the United States that generally do not have significant environmental lead contamination. Regardless of the region in the United States, new American children face the unknown risk posed by the use of traditional medicines, lead-contaminated foods and cookware, and other culturally specific practices that may expose children of many different immigrant populations to lead. These types of exposures for immigrant children have been documented repeatedly over the years in the *Morbidity and Mortality Weekly Report*. The Centers for Disease Control and Prevention's (CDC) Web site ([www.cdc.gov/nceh/lead/](http://www.cdc.gov/nceh/lead/)) contains information about lead poisoning among refugee and immigrant children. Because of the particularly high risk of elevated lead levels in refugee children, the CDC recommends testing all refugee children younger than 17 years.

## ORAL HEALTH

A high prevalence of dental caries has been documented among immigrant and refugee children. Many immigrants will lack experience with preventive oral health measures, including topical fluoride and water

fluoridation, and face significant barriers to care in the United States. Research on the association of acculturation with oral-health practices among refugees and immigrants has demonstrated that the many LEP immigrants adopt American lifestyle behaviors that are associated with poor oral health outcomes while giving up protective behaviors from their home countries. Because of LEP and partial acculturation, however, these immigrants do not fully adopt Western preventive oral health practices.

The primary care physician can play an important role in promoting healthy personal oral hygiene practices and supporting traditional customs and related behaviors (eg, breastfeeding, diets low in refined sugar, and use of chewing sticks with antimicrobial properties) that may provide oral health, nutritional, and other benefits to the child while also promoting proven oral hygiene practices in the United States (eg, ensuring consumption of fluoridated water or oral supplementation, use of fluoride-containing toothpaste). The primary care physician should conduct periodic oral health risk assessments, provide dietary counseling on limiting sugary food, assess all sources of fluoride exposure, and facilitate the establishment of a dental home by 6–12 months of age for low-income and other high-risk children and 12 months of age for all children. Application of fluoride varnish in the primary care setting should be conducted for children with no access to a dental home and those with moderate or high caries-risk until a dental home is established. In addition, in some practice settings, the targeted use of fluoride varnish for low income and other high risk immigrant and refugee children is warranted.

## BEHAVIORAL HEALTH AND FUNCTIONAL HEALTH SCREENING

Mental health and behavioral problems are common among immigrant and refugee children, in part, because many such families experience traumas. Prior violence exposure in the country of origin, ongoing exposure to violence in their neighborhoods in the United States, and migration-related stress increase the risk for posttraumatic stress disorder, adjustment disorder, depression, and other mood disorders in immigrants. In a large meta-analysis of studies of internationally adopted children, researchers found an elevated prevalence of behavioral problems and use of mental health services compared to nonadopted children. Behavioral disorders among traumatized immigrant families may be difficult to diagnose and treat in primary care settings. Even in situations in which parents identify behavioral symptoms in their children, parents may be reluctant to have children treated for behavioral disorders because of cultural beliefs or concerns about immigration status. Cultural factors may present similar challenges for diagnosing and treating behavioral disorders among nontraumatized children as well. Many immigrants and refugee families will visit their physicians with symptoms or complaints such as headache or stomachache because of underlying behavioral or emotional problems or somatization.

Somatization is common in many cultures around the world. Studies have documented the high prevalence of somatization and its association with increased clinic visits in immigrant and refugee communities in the United States. Caring for patients with somatization may be challenging. The physician's validation of the impairment from somatic symptoms and focus on functional improvement, however, may facilitate the establishment of trust necessary for uncovering the emotional basis for the symptoms. In the setting of pediatric primary care, the physician may find simple screening instruments, such as the Pediatric Symptom Checklist ([www2.massgeneral.org/allpsych/psc/psc\\_home.htm](http://www2.massgeneral.org/allpsych/psc/psc_home.htm)) or the Child Health Questionnaire ([www.healthact.com](http://www.healthact.com)), helpful in documenting functional impairment from somatization and behavioral-health problems, although language and literacy barriers can be problematic with immigrant and refugee communities. Such screening may obviate the need for disease-specific diagnostic questionnaires that are either too lengthy for practical use or may be emotionally upsetting to patients and families. Resources and online training for primary care physicians wishing to work with traumatized immigrants (or any patients who are survivors of significant violence) are also available from the Harvard Program in Refugee Trauma ([www.hprrt-cambridge.org](http://www.hprrt-cambridge.org)). A child-specific resource available to help pediatricians handle mental health issues is the Refugee Services Toolkit (RST) designed by the Children's Hospital Center for Refugee Trauma and Resilience ([www.chcrrt.org/toolkit/](http://www.chcrrt.org/toolkit/)). The RST is a Web-based tool designed to help providers understand the experience of refugee children and families, identify the needs associated with their mental health, and ensure that they are connected with the most appropriate available interventions.

## SCREENING TESTS FOR INFECTIOUS DISEASES

### Parasitic Infections

Many important diseases have nearly worldwide distributions and high prevalence among immigrant and refugee populations. When considering laboratory testing, the physician must weigh the degree of risk posed by the condition to the patient (including its level of acuity), the patient's insurance status, and the prevalence of the condition among populations from the geographic origin of the patient. For example, stool microscopy for ova and parasites will be indicated for many immigrants; however, physicians might consider ordering only fluorescent antibody staining or stool antigen testing for *Giardia* for patients from the formerly socialist, industrialized countries of Eastern Europe in which the risk of helminth infection is quite low. Additionally, the peripheral eosinophil count is a simple test that can give the physician insight into the possibility of invasive parasite infections that may not be detected in stool specimens.

For patients from tropical climates in which the risk of helminths is high, empiric treatment with albendazole has been shown to be cost effective and is used overseas by the CDC for refugees. The CDC has also recommended empiric treatment of some African

refugee populations (Southern Sudanese and Somali Bantu) for strongyloidiasis and schistosomiasis ([www.cdc.gov/immigrantrefugeehealth/index.html](http://www.cdc.gov/immigrantrefugeehealth/index.html)) and is phasing in more extensive antihelminth empiric treatment overseas. Empiric treatment for helminths, strongyloides, and *Schistosoma* infection can be accomplished in a single day with 1 oral dose of albendazole, 1 dose of ivermectin, and 2 doses of praziquantel. Because of a rare but potentially life-threatening side effect of ivermectin when used in patients with *Loa loa* infection, an alternate regimen for African immigrants from regions with endemic loiasis includes albendazole twice per day for 3 to 7 days and praziquantel as described previously. Empiric therapy with albendazole is contraindicated in children less than 1 year old, ivermectin is contraindicated in children weighing less than 15 kilograms, or less than 90 centimeters in height, and praziquantel is contraindicated in children younger than 4 years old. Increasing concerns about the high prevalence of strongyloidiasis in refugees and immigrants from tropical regions make empiric treatment a favored option in lieu of testing.

### Malaria

Recent literature has documented a high prevalence of malaria parasitemia among recent refugee arrivals from Africa. Among symptomatic cases, the triad of fever, splenomegaly, and thrombocytopenia were highly specific for malaria. Of note, a fairly high proportion of children with malaria was asymptomatic. In the report by Maroushek et al, 29% of children with malaria were asymptomatic. Because of the predominance of *Plasmodium falciparum* in most of Africa, individuals often will develop some immunity over time, thus reducing symptoms. Such is not the case with other forms of malaria that predominate in other parts of the world, particularly in Southeast Asia. As for helminths, the CDC is expanding and updating predeparture empiric treatment for malaria among refugees overseas. Newer protocols expand the use of such treatment and also switch from the use of sulfadoxine and pyrimethamine to newer artemisinin-based combination therapy, such as artemether-lumefantrine or amodiaquine-artesunate.

Primary care physicians should consider malaria testing of all refugees and immigrants from Sub-Saharan Africa and those from any malaria-endemic country who exhibit symptoms suggestive of malaria. Physicians should test liberally, given that the Maroushek study found that no symptom, either alone or in combination with other symptoms, was predictive of the presence or absence of malaria. Guidelines for treatment of malaria, including criteria for determining severity level and eligibility for outpatient treatment, are available from the CDC ([www.cdc.gov/malaria/diagnosis\\_treatment/index.html](http://www.cdc.gov/malaria/diagnosis_treatment/index.html)). In addition, 24-hour consultation is available from the CDC at 770-488-7788 during weekday business hours and by page at 770-488-7100 after hours and on weekends and holidays.

### Tuberculosis

Finally, tuberculosis (TB) infection is a major health issue for immigrant children. The foreign-born population increasingly comprises a disproportionate share of cases of active TB infection in the United States,

accounting for almost 60% of tuberculosis cases in the United States in 2008, and with a case incidence closer to that of their country of origin for the first 5 years in the United States. Children, particularly younger children, are usually in the early stages of latent TB infection, with high likelihood of progression to active disease. All immigrant children from developing and formerly socialist countries should have tuberculin skin testing (TST). If the child is significantly malnourished or immunocompromised, then the physician should consider placing control tests (eg, *Candida* antigen) as well. Prior bacille Calmette-Guerin (BCG) vaccination is not a contraindication to tuberculin skin testing. Internationally-adopted children should receive tuberculin skin testing immediately post-adoption and 6 months later. As an alternative, interferon-gamma release assay (IGRA) testing may be used in place of TST to detect tuberculosis in children over 5 years old. IGRA may be preferable to TST in children over 5 years old with previous BCG vaccination.

Other highly prevalent infectious diseases that may warrant screening tests include hepatitis B, hepatitis C, HIV, syphilis (both congenital and sexually acquired), and other sexually transmitted infections. In particular, HIV testing of refugees is no longer required prior to admission to the United States; however, it is recommended that all refugees be tested for HIV. Additionally, some refugee and internationally-adopted children may be unimmunized or under-immunized for common diseases such as hepatitis B. Immigrants and refugees from areas with endemic hepatitis B, such as Asia and Africa, should be screened with HBsAg and anti-HBs within a few weeks of arrival and again 6 months later. Children with negative serologies should be given the appropriate immunization schedule, and those with positive serologies should receive appropriate follow-up and management. Physicians, again, should weigh individual and geographic risk, as well as the expense and benefits for the patient, when considering such testing.

## IMMUNIZATIONS AND SEROLOGIC TESTING

A safe presumption is that very few immigrant or refugee children seen as new patients in a pediatric practice will be up to date with US vaccine standards set by the CDC Advisory Committee on Immunization Practices (ACIP) (see [www.cdc.gov/vaccines/](http://www.cdc.gov/vaccines/)). Such is the case simply because newer vaccines used commonly in the United States are not available or used in most other countries. Examples include vaccines for *Haemophilus influenzae*, pneumococcus, human papillomavirus, and varicella. In addition, many immigrants will not have adequate documentation of past vaccines. In some cases, documents may actually be fraudulent. Common problems include incomplete or inaccurate documentation of vaccine records, receipt of vaccines at unacceptable intervals or times, and poor immune response as a result of malnutrition. The public health imperative for completing immunization is also illustrated by recent outbreaks of imported measles in Indiana and Boston, the multistate mumps outbreak in the Midwest, and

congenital rubella syndrome in a refugee infant born in New Hampshire. Regarding measles, mumps, and rubella, physicians should be alert when reviewing records to receipt of vaccines with only 1 or 2 components and receipt of measles vaccine before the first birthday, as recommended by the World Health Organization for countries with endemic measles but not considered a valid dose by ACIP.

Immunization should be a priority for new immigrant children who may have school enrollment delayed pending completion of immunizations. Similarly, immunization with a multi-dose series for highly prevalent disease antigens, such as hepatitis B in some populations, should not be delayed pending serologic testing. If immune (either from naturally-acquired infection or a completed primary vaccine series), further doses are not needed. Refugees with partial series but positive serologic tests of immunity still should finish the primary series.

For younger children, physicians should begin primary or catch-up immunization according to ACIP schedules. For school-aged children and adolescents who have insurance coverage, physicians may choose a mixture of immunization and serologic testing for immunity to satisfy school and other requirements for proof of immunity. Studies of serotesting among refugees and immigrants have documented high levels of immunity to some diseases such as hepatitis B, varicella, measles, and rubella. In the case of varicella, serotesting before immunization is a cost-effective strategy. Typically, seroprevalence will increase throughout childhood, with large increases at 1 year old (for measles in particular) and at school age. By early adolescence, most immigrants will have either naturally acquired immunity or prior immunization for these diseases, except for hepatitis B, which will reflect the level of endemicity in the immigrant's country of origin. For hepatitis A vaccine, recommended for universal immunization by ACIP in 2006, most immigrants will have naturally acquired immunity if they lived in endemic regions until school age.

## CONCLUSION

Primary care physicians caring for children new to the United States serve an important role as the gateway to the medical home. Language and cultural divides that separate physician from patient may be bridged by providing access to language services for LEP patients and ensuring the delivery of culturally competent care. At the same time, physicians should be attentive to the acute and chronic health issues specific to immigrant children and their families. Foreign-born children and children of immigrants may continue to encounter significant challenges to their health and well-being due to the numerous cultural, linguistic, and legal barriers to accessing services discussed in this chapter. Immigrant children and adolescents may experience significant stress, anxiety, and depression related to issues of acculturation and immigration. LEP children attending schools with limited experience with this population may have academic difficulties related to English proficiency



that may be mistaken for pathology, such as learning disabilities or developmental delay. These children therefore may need continued follow-up in primary care to discuss school progress and related issues.

Primary care physicians should work to anticipate and integrate potential health and development issues into the health screening and long-term care of immigrant families. By effectively screening for and treating these issues and promoting wellness with cultural sensitivity, the primary care physician can create strong bonds with immigrant families and communities and ensure that immigrant children receive the highest quality pediatric primary care with high levels of patient and parent satisfaction.

## TOOLS FOR PRACTICE

### Community Coordination and Advocacy

- *America's Literacy Directory* (Web page), ([www.literacydirectory.org](http://www.literacydirectory.org))
- *Centers for Disease Control and Prevention (Spanish)* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/spanish](http://www.cdc.gov/spanish))

### Engaging Patient and Family

- *DiversityRX* (Web page), ([diversityrx.org](http://diversityrx.org))
- *Immigrant and Refugee Health* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/immigrantrefugeehealth/index.html](http://www.cdc.gov/immigrantrefugeehealth/index.html))
- *Other Languages Resource* (Web page), National Network of Libraries of Medicine ([nnlm.gov/outreach/consumer/multi.html](http://nnlm.gov/outreach/consumer/multi.html))
- *Selected Patient Information Resources in Asian Languages* (Web page), Tufts University ([spiral.tufts.edu](http://spiral.tufts.edu))

### Medical Decision Support

- *Child Health Questionnaire* (questionnaire), HealthActCHQ ([www.healthact.com/chq.html](http://www.healthact.com/chq.html))
- *Espanol-Healthfinder* (Web page), US Department of Health & Human Services ([www.healthfinder.gov/espanol](http://www.healthfinder.gov/espanol))
- *Lead* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/lead](http://www.cdc.gov/lead))
- *Malaria* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/malaria/diagnosis\\_treatment/index.html](http://www.cdc.gov/malaria/diagnosis_treatment/index.html))
- *Measuring Trauma, Measuring Torture* (book), Harvard Program in Refugee Trauma ([www.hprrt-cambridge.org](http://www.hprrt-cambridge.org))
- *Multicultural Health Generalizations* (Web page), University of Michigan Health System ([www.med.umich.edu/multicultural](http://www.med.umich.edu/multicultural))
- *Pediatric Symptom Checklist* (checklist), Jellenik M, Murphy JM ([www2.massgeneral.org/allpsych/psc/psc\\_home.htm](http://www2.massgeneral.org/allpsych/psc/psc_home.htm))
- *Refugee Trauma and Resilience Center* (Web page), Children's Hospital Boston ([www.childrenshospital.org/centers-and-services/refugee-trauma-and-resilience-center-program](http://www.childrenshospital.org/centers-and-services/refugee-trauma-and-resilience-center-program))
- *Vaccines & Immunizations* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/vaccines](http://www.cdc.gov/vaccines))

## AAP POLICY

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## Chapter 70 ADOPTION

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## WHO ARE THE CHILDREN?

Most children adopted in the United States today are not adopted as newborns. With easy availability of family planning and general acceptance of single motherhood, fewer newborns are placed for adoption than in generations past. Instead, most adopted children join their families after being in the domestic child welfare system or in foster or institutional care overseas. Many children with medical or developmental disabilities who were, in previous times, considered unadoptable are now being successfully placed with adoptive families. Today, adopted children come with a history of life before their adoption, and this history has a tremendous effect on their needs and outcomes, both in the short term and over time.

Some children adopted from the domestic foster care system come to their adoptive families as infants, placed first as foster children, then later adopted by their foster parents. These children have the benefits of nurturing care from infancy but may still experience the long-term sequelae of prenatal adversity, particularly substance exposure. More commonly,

children adopted from foster care are older and have experienced significant abuse and neglect before adoption. Their long-term physical, mental, developmental, and behavioral health risks and needs are determined by the specifics of these insults, but are frequently complex. (See Chapter 72, Children in Foster or Kinship Care.)

Child care circumstances vary tremendously among the countries from which children are adopted internationally. Some children are cared for in high-quality, family-setting foster care, whereas others are cared for in institutional settings that can vary from small group homes with reasonable resources to large, extremely resource-poor orphanages. Some children enter care as newborns because of poverty, social adversity, or political circumstances; others enter as older children after experiencing the same sorts of abuse and neglect that place children into the foster care system in the United States.

More international children than ever before are being adopted with identified special health needs. These can range from fairly simple problems such as orthopedic deformities, isolated cleft lip and palate, or ventricular septal defects, to chronic infectious illnesses such as hepatitis B and HIV, or complex syndromes with multiple medical and developmental disabilities. Health care for these needs may or may not have been available before adoption, and medical procedures may have been traumatic for the child who experienced them without the love or support of a parent.

With or without identified special needs, most children are at least older infants or toddlers before they are eligible for international adoptive placement. Knowing how and why a child came into care is important, as is knowing the type of care a child experienced, because the history before adoption often sheds light on the physical, mental, and developmental health issues a child might be expected to face immediately and over the long term.

Children come to the United States from many countries through adoption. Although some countries have sent substantial numbers of children for many years, the list of sending countries is continually changing as a result of political and social circumstances both in the United States and abroad. The US State Department listing of orphan visas issued provides a concise listing of the numbers of children adopted from the top 20 countries of origin each year. The circumstances of individual children available in each country are varied, but general considerations are listed in Table 70-1 for the current top 10 countries of origin.

Other common adoptions today include kinship placements and second-parent or coparent adoptions. Current child welfare practice emphasizes finding permanency for children more quickly than in the past and keeping children within their communities and cultures of origin whenever possible. Estimates indicate that approximately 200,000 children, or approximately one-third of those in foster care, are placed in foster care with extended family members. If they are not able to return to the custody of their birth parents, then many of these children are adopted by their

extended family members or cared for in permanent legal guardianship relationships. This approach allows children to maintain family connections but can pose unique challenges to the adopting parents, who must negotiate complicated relationships among the children, the birth parents, and other extended family members. Second-parent adoptions refer to the adoption of a child who already has one legal parent by the spouse or partner of that parent. Coparent adoption is the adoption of a child by 2 unmarried adults, often gay or lesbian partners.

## ADOPTION PROCESS

Pediatricians can be most helpful to adopting parents if they are knowledgeable about the processes and types of adoptions. Adoption laws vary by state, but the basic legal requirements are the same. Adopting parents must undergo a social work evaluation (commonly referred to as the *homestudy*) to verify that they are minimally fit to be parents, have minimal resources to support a child, and do not have records of child abuse or significant criminal records. Families do not have to be wealthy or highly educated, but simply have to prove that they would be able to love and nurture a child. The homestudy must typically be provided by a social worker licensed to work in a particular state, who produces a written document verifying the adults' suitability for parenthood, which becomes part of the legal record of the adoption. Families adopting across state lines must satisfy the requirements of both states, and families adopting internationally must meet all requirements of the state and federal governments and those of the child's birth country.

Adoption placements can be arranged and carried out by licensed agencies or independent facilitators, depending on the laws of individual states and countries. Adoption agencies may be public agencies acting as an arm of the public child welfare system or may be licensed private agencies. Facilitators may be of any training background but are commonly social workers or attorneys who specialize in connecting would-be adoptive parents with available children. For international adoptions, most countries of origin require that their children be placed by a licensed nonprofit agency. In addition, the Hague Convention on Intercountry Adoption (a multinational treaty that was signed by the United States in 1994 and entered into force in 2008) requires that all child placements between participating countries be governed by a strict set of ethical guidelines and be carried out by licensed and accredited agencies that have enforceable government oversight. Approximately 80 countries have signed on to the convention so far, meaning that adoptions between these countries must meet ethical and procedural guidelines that provide greater protections for children, birth parents, and adopting parents.

Families adopting newborns are often in touch with the child's birth parents before the adoption because most birth parents today participate in the choosing of their child's adoptive parents. Many adoptive parents travel to be at their child's delivery and often participate in ongoing, open relationships with the child's birth parents. Some adoptions are finalized very

**Table 70-1** Top Ten Countries of Origin of Internationally Adopted Children (2009)

COUNTRY	PREDOMINANT AGE AND GENDER	REASONS IN CARE <sup>a</sup>	TYPE OF CARE	AVAILABILITY AND RELIABILITY OF RECORDS <sup>b</sup>	COMMON HEALTH CONCERNS <sup>c</sup>
China	Girls—infants to teens and older boys with special health care needs	One-child policy or social need for male children	Mostly institutional; some foster care	Minimal—sometimes more information available for children with physical disabilities; reliability variable	Lead intoxication, dental enamel insufficiency
Ethiopia	Boys and girls—infants and older	Children orphaned by parental death from HIV infection	Institutional	Variable quality. Laboratory studies from Addis Ababa usually reliable	Prenatal HIV exposure, profound malnutrition
South Korea	Boys and girls—infants and older	Lack of social acceptance of single parenthood	Foster care	Usually detailed records, very reliable	—
Ukraine	Boys and girls—toddlers and older	—	Institutional	Minimal	Prenatal alcohol exposure
Vietnam	Boys and girls—infants and older	—	Institutional	Variable quantity and reliability	
Haiti	Boys and girls—toddlers and older	—	Institutional	Limited information, variable reliability	Profound malnutrition
India	Boys and girls—infants and older	—	Institutional	Often very detailed records, usually fairly reliable	
Kazakhstan	Boys and girls—toddlers and older	—	Institutional	Minimal	Prenatal alcohol exposure

<sup>a</sup>The reasons children are eligible for adoption in all countries can include severe poverty, social adversity (maternal drug or alcohol addiction, incarceration, homelessness, mental health disabilities), and child abuse and neglect, with government termination of parental rights. The *Reasons in Care* column lists additional factors common to the country.

<sup>b</sup>Availability of reliable records does not mean that recommended new-arrival testing can be eliminated, but rather that preadoptive parents can feel reasonably confident that the information they have will accurately reflect the history of the child they are bringing home.

<sup>c</sup>The Common Health Concerns column is not an all-inclusive list, but rather a note of conditions that are even more common for children from that country than for all international adoptees.

quickly, whereas others take significantly longer, depending on the laws of the state where the child was born and of the state where the adoptive parent or parents live. Financial costs for domestic newborn adoptions are extremely variable, but can be significant when all of the individual services performed are tallied. Costs may include legal and social work fees, travel expenses, and, in some states, payment of room and board or health care expenses for the birth mother before the delivery.

Families adopting children from the child welfare system may have the child in foster care from birth, but only become eligible to adopt after the child's birth parents are unable to resume custody. Other children come into the child welfare system later after experiencing abuse or neglect. If birth parent rights are later terminated (see Chapter 72, Children in Foster or Kinship Care), then the child may be adopted by the child's foster parents or by another family. Adoptive families have ongoing contact with birth parents less frequently in this kind of adoption, although some adoptions, especially kinship placements, do maintain ongoing contact with birth parents. Many of the children who are waiting in the child welfare system for

adoptive families are older, are part of sibling groups, and have significant psychological scars from their earlier life experiences. Families rarely have to travel to adopt from the public system because most communities have more children in care who are in need of permanent homes than families waiting to adopt them. Adoptions from the public child welfare system are often finalized months, or even years, after the child is placed in the home as due process is carried out to protect the rights of birth parents. Financial costs for this type of adoption are typically much more modest, with many of the services provided free of charge to the adopting family by the public agency, its mission being to find the best home for each child on behalf of the state or local government.

Parents adopting internationally most often travel to adopt their child, with adoptions from some countries requiring 2 or 3 trips. Although this process can be stressful and financially costly, it offers adopting parents the opportunity to get to know the people and culture of their child's birth country. In addition to a valid homestudy, families are required to pass criminal record clearance from the Federal Bureau of Investigation, document that the child meets the US definition

of an adoptable orphan, and complete immigration paperwork for the child. Families adopting from Hague Convention countries must also complete at least 10 hours of training on the needs of internationally adopted children, and the child must be deemed eligible for international placement by the sending country after reasonable efforts to place the child in country have been documented.

On finalization of the adoption by US citizen parents, the child is automatically granted US citizenship, although parents must complete yet more paperwork to claim this legal status. It is critical that parents complete this process in order to ensure the child's full legal rights as a US citizen.

## ROLES OF THE PEDIATRICIAN IN PREADoption CARE

Unless the physician has a special interest in adoption medicine, a family adopting its first child might not meet the physician until the parent or parents receive information about a specific child or even until the child is home with the parents. Most pediatricians, however, will have families already in their practice who decide to adopt, and these physicians can play an important role in helping the entire process to be a success. Pediatricians should be familiar with common adoption concerns and can contact members of the American Academy of Pediatrics (AAP) Council on Foster Care, Adoption, and Kinship Care for help.

Parents who are wondering what type of adoption to pursue should consider the potential needs of the children. By looking at the intersection of 3 variables, families and their physicians can anticipate at least some of the needs a child might be expected to have and some of the adoption process issues.

First, families need to consider the age of a child: children beyond infancy bring with them psychological, physical, and social consequences from previous circumstances. Professional mental health services may be needed to allow a child to reach full potential, in addition to developmental and educational supports. The second variable is whether a child is of the same or another race as the adopting parent or parents. The third variable is whether the child is in the same or a different country or culture. Although transracial adoption is not associated with poor outcomes, helping a child develop a strong sense of racial and cultural identity is important to the child's self-esteem and psychological well-being and can be challenging, especially in communities with little racial or cultural diversity.

Parents may also request help in deciding on an agency or facilitator to conduct the adoption. In general, parents should be encouraged to use agencies that are licensed (and, therefore, subject to minimal ethical and practice standards) with a mission to promote the welfare of children. Agencies with the mission of finding the right family for each child often cost more and require more of adopting parents, but will also provide appropriate education and long-term support for families. Agencies with the mission of conducting an adoption rapidly may seem appealing at first glance, but often do not share the complexities

or risks of the children with adopting parents and are rarely there for long-term support.

Pediatricians may also be asked to review the information a family receives about a particular child whom they are considering adopting. Reviewing this information with a family is not to screen out children, but rather to help the prospective family understand the information given to them, know what additional information they need to gather, and then make a well-informed decision as to their ability to be the best parents for the child, given the predictable needs or risks. This service is often best performed by physicians familiar with all the types of adoptions, the information available for children coming from different countries, and the common risks seen in different groups of available children. Many agencies provide families with lists of physicians specializing in adoption medicine, and these can also be found through the AAP Council on Foster Care, Adoption, and Kinship Care Web site.

Finally, pediatricians need to know the infectious disease and travel health issues involved for families traveling internationally to adopt. Even family members who are not traveling, but who will be in close household contact with the newly arrived child, can be affected and need to be protected. Recent increases in the numbers of older children and children from countries with endemic hepatitis A have resulted in numerous cases of hepatitis A being spread to family members, whose risk for hepatitis A is more than 100 times greater than that of the general population. There have been several outbreaks of measles as well, spreading from newly adopted children infected at the time of travel to both family members and other travelers on airplanes. Parents should be counseled early on to review and update the immunizations of all family members before they travel to adopt; this includes hepatitis A, hepatitis B, Tdap (tetanus, diphtheria, and pertussis), and seasonal influenza vaccines, all of which many adults have never received. Parents will also need to plan for any chronic health needs of their own, bringing an ample supply of necessary medications in carry-on luggage. Families adopting a child with special medical needs will need to plan for those as well, bringing items such as cleft palate bottles, and learning relevant clinical warning signs, such as those of congestive heart failure when adopting a child with congenital heart disease.

Families should also be advised to follow strict food and water precautions, to prepare a travel first-aid kit, and to have emergency health contact information for themselves, their new child, and any other family members who are traveling. Families traveling to very remote locations or very impoverished countries may need to bring antibiotics or other medications for themselves and their new child, given that medical care may be difficult or impossible to obtain. Educating the family that antibiotics are being prescribed without seeing the child only for this unusual circumstance can help prevent inappropriate expectations later. Physicians should provide a means for families to contact them in an emergency and written directions as to when and under what circumstances



they might consider using the medications they are carrying.

## NEW-ARRIVAL ISSUES

### Social and Emotional Issues

The arrival of a newly adopted child into a family brings joys and stresses similar to those that accompany the birth of a child. In addition, however, all of the circumstances that led to the adoption must be managed by adopting parents, birth parents, siblings, extended family, and the child. Adopting parents who have experienced infertility or the loss of previous children may have unresolved grief, which can complicate the feelings of joy accompanying the arrival of this child. In addition, long waits for parenthood can create unrealistic expectations, which are often in stark contrast with the reality of parenting any child, let alone one who has lived through adversity and whose whole world has just changed. Postadoption depression is as real an entity as postpartum depression, and pediatricians should be prepared to identify and refer affected parents.

For children adopted outside of the immediate newborn period, the transition into the new adoptive family is often bewildering, frightening, and full of loss. Ideally, children should be given as much preparation as possible, with older children even participating in the decision to join a particular family. In reality, however, many children are simply taken one day from everything that is familiar and handed to strangers. Children who have been in foster care or who have developed strong attachments to orphanage caregivers will usually grieve the loss of these significant people, and older children may worry about their well-being or wonder if the caregivers are searching for them. Even children who have not been treated well by previous caregivers still have connections to them and may still grieve their loss. Adoptive parents and pediatricians need to understand this process, comfort the grieving child, and help the child develop a strong sense of connection and security with the new parents. Allowing the child to talk about the previous caregivers, to look at pictures of them, and even to telephone or write to them can help the child process this grief. Parents may need encouragement to allow children to share their grief, given that not talking about it may seem easier. Allowing children to share these strong feelings can help build strong bonds of new attachment.

All children have to adjust to the arrival of a new sibling, but an adopted sibling brings challenges that a newborn does not. Most often, the new child is not a helpless newborn, but rather a mobile, demanding competitor for not only parental time and attention, but also toys, food, and space. Extra love, understanding, and attention are in order, which can be hard to attain when the demands of the newly transitioning adoptee are high.

Extended family members also have a significant effect on the new-arrival period. Some may be eager to shower love and attention on the bewildered, overwhelmed, grieving child, whereas others may not accept the child as a true member of the family. Sharing

information about adoption and the child's expected transition needs with extended family members before the adoption can help create a nurturing acceptance into a warm extended family without overwhelming the child.

Adopting parents should plan for plenty of quiet, uninterrupted time with their newly adopted child, regardless of the age of the child at arrival. Helping the child develop a strong attachment to the parents is of utmost importance because this groundwork is the foundation of healthy parent-child relationships and, ultimately, of all human relationships. Parents should think of their child as a newborn emotionally in an older child's body. Parents should be the ones to meet physical needs and to provide comfort so that the child learns to use them as a secure base in the world. Some parents are granted parenting leave by employers, whereas others must fight for it, given that many employers finance parenting leave through medical disability coverage, which does not apply when a woman has not given birth. Pediatricians should work with parents to convince employers that time at home with their newly adopted child is vital to the child's long-term physical and emotional health, and parents should be encouraged to use as much leave time as possible.

### Medical Issues

The most important considerations in planning a child's postadoption medical evaluation are the risks inherent to the child's previous circumstances. Whether the child was adopted domestically as a newborn, from the foster care system, or internationally, the social and medical risk factors of the child's birth parents and prior circumstances should guide medical and developmental assessments.

Parents adopting newborns domestically may receive extensive records on the child, birth parents, and extended biologic family, or they may receive nothing at all. Pediatricians should assess not only the available extended family medical history, but also the birth parent social history, paying special attention to risk factors for adverse outcomes for the fetus and child, including issues such as alcohol or other drug use during pregnancy, high-risk sexual behavior, and domestic violence. Records of birth mother prenatal testing for infectious diseases may or may not be available or reliable. Unknown or missing information, including unknown birth father information, should be presumed to be high risk. Decisions regarding testing for HIV, hepatitis B and C, syphilis, and other perinatally transmissible diseases should be made on an individual basis after considering the available information. Testing may need to be repeated after the child is 6 months old, to rule out late-term infection, depending on the specific history and available birth mother test results.

Children adopted from the foster care system have, by definition, experienced significant abuse or neglect and are at high risk for long-term mental health and developmental sequelae. They are also at very high risk for infectious exposures and malnutrition, dental problems, and physical health needs resulting from previous trauma. (See Chapter 72, Children in Foster

or Kinship Care.) Medical evaluation of these risks should be guided by available records, with unknown or missing information being assumed to be high risk.

Children adopted from overseas have most often been cared for in institutional settings, where infectious diseases, including many which may not be obvious on physical examination, are easily spread. In addition, significant infectious and environmental health risks often exist in sending countries, but are unfamiliar to physicians in the United States. These must be remembered especially in the differential diagnosis of febrile, neurologic, or gastrointestinal symptoms, not only at the time of arrival but also for several years afterward. Nutrition is rarely adequate for children in institutional care, making macronutrient and micronutrient deficiencies common. Because a specific, detailed, reliable history is rarely available for a given child, the medical evaluation must be based on known significant risks, rather than individual history.

All newly arrived international adoptees should have a detailed, thorough evaluation soon after arrival, including assessment of overall health, nutritional status, developmental delays, psychosocial adjustments, hearing and vision, and laboratory studies to assess for infectious diseases, nutritional deficiencies, and toxin exposures. Medical records from the child's country of origin should be reviewed but can rarely be taken as guaranteed truth, given that record-keeping, transfer, and translation systems are notoriously unreliable and cannot be verified (see Table 70-1).

As outlined in the AAP *Red Book*, laboratory studies for all internationally adopted children should include at least hepatitis B (surface antibody, surface antigen, and core antibody), HIV, syphilis, stool for parasites, and tuberculosis testing. Most children (especially those adopted from Eastern Europe or Asia and children whose birth parents were intravenous drug abusers) should also be tested for hepatitis C. Prior Bacille Calmette-Guérin (BCG) vaccination is *not* a contraindication to purified protein derivative (PPD) testing, and *all* internationally adopted children fall into at least the moderate-risk category when interpreting PPD test results. Children older than 2 years of age who are adopted under the Hague Convention on International Adoption (see Adoption Process) may have a PPD placed and read by a US Embassy panel physician before being granted a visa to enter the United States. When parents have documentation of the PPD being given and being read, this PPD can "count" and does not need to be repeated again just a few weeks later. All of these infections can be completely asymptomatic but have significant individual, family, and public health implications if left undetected and untreated.

Deciding what to do about a child's immunizations can be challenging. If no written records are available, then a new series should be initiated according to the consensus catch-up schedule, given that even strongly positive antibody titers cannot, at one point in time, guarantee a steady-state level of immune protection. Although considerable controversy and ongoing research exist on this question, written records generally cannot be taken at face value because whether the

child received the injection cannot be verified, nor can the storage or handling of the vaccines be verified, given that orphanages around the world frequently receive old, outdated vaccine supplies. Records should be reviewed carefully, with attention to the timing of doses and the appearance of the records. For example, is it an original, with tattered edges and different inks, or a pristine, brand new copy? Are there doses given before the child was born? Are the vaccines stated available in the sending country? When records seem legitimate and show vaccine timing that meets the guidelines provided by the AAP and the Advisory Committee on Immunization Practices, titers can be checked, and, if positive, these doses can then be counted for the child, with any remaining doses or missing vaccines following the *Red Book* catch-up schedule. Children older than 2 years of age who are adopted under the Hague Convention on International Adoption (see Adoption Process) may receive vaccines by a US Embassy panel physician before they travel home with their new parents. Parents are usually given records of exactly what the child received, and proper storage of these vaccines is guaranteed by the US Embassy. Unfortunately, however, receiving these doses effectively takes away the option of checking titers to verify doses given while the child was in the orphanage because serial titers would be required to prove that immunity shortly after arriving home is long lasting. Doses given at the US Embassy can be "counted" as the first dose of each vaccine, and the series can be completed from there according to the consensus catch-up schedule.

Nutritional deficiencies also are common, with the diet of most children before their international adoption being inadequate in overall calories, protein, and micronutrients. Most children are at least mildly malnourished at the time of adoption, as demonstrated by the rapid catch-up growth of even those who are on the growth curve at the time of adoption. Some children are well below the first percentile for birth weight and height. Most often, this circumstance is the result of combined malnutrition and profound social and emotional neglect, but hypothyroidism must be ruled out, as must true growth hormone insufficiency, if rapid catch-up growth does not occur. Laboratory evaluation should include a complete blood cell count to assess for iron deficiency and calcium, phosphorus, and alkaline phosphatase assessments for rickets. Hemoglobin electrophoresis should be included in follow-up for any child who has microcytic anemia, especially a child from Asia or Africa. Thyroid function tests should be obtained for children with significant growth or developmental delays. Lead intoxication is also common, especially in children adopted from China, and all children should have serum lead levels checked. Box 70-1 highlights components of the medical evaluation of newly internationally adopted children.

All newly adopted children, regardless of the type of adoption, should have a thorough assessment of development, including hearing and vision. For newborns, this assessment will be the same as for any other routine well child care, with special attention to any known long-term risk factors. Children

**BOX 70-1 Medical Evaluation of New Internationally Adopted Children**

On arrival, *all* children should have the following:

- Thorough physical examination
- Purified protein derivative test (PPD) (may need to alter timing if child received Bacille Calmette-Guérin [BCG] vaccination within the previous several months or received repeated, recent PPD tests)
- Hepatitis B surface antigen, surface antibody, and core antibody testing
- Human immunodeficiency virus (HIV)-I and -II enzyme-linked immunosorbent assay (ELISA) (consider DNA polymerase chain reaction in infants)
- Assessment for syphilis—nontreponemal testing (rapid plasma reagin or Venereal Disease Research Laboratory test) for all adoptees. Treponemal testing (microhemagglutinin *Treponema pallidum* or fluorescent treponemal antibody absorbed) if history of exposure or positive nontreponemal test results
- Assessment of stool for ova and parasites (3 samples taken at least 48 hours apart)
- Complete blood cell count
- Lead level testing
- Assessment for rickets: calcium, phosphorus, and alkaline phosphatase
- Detailed review of immunization status, with testing as needed to confirm immunity
- Detailed developmental assessment
- Assessment of hearing and vision

On arrival, risks should be assessed and the following checked appropriately:

- Hepatitis C ELISA for all children from Eastern Europe or Asia or those with history of risk factors
- Thyroid function test for children with significant growth or developmental delays
- Hemoglobin electrophoresis for children from Africa or Asia who have microcytic anemia
- Stool bacterial infection assessment for children with diarrhea or other gastrointestinal symptoms
- Stool testing for *Strongyloides* and *Schistosoma* spp for children from endemic regions who have unexplained eosinophilia
- Serologic testing for *Trypanosoma cruzi* for children from endemic countries in South and Central America
- Thick and thin blood films for malaria for febrile children from endemic areas

Six months after arrival, *all* children should have the following:

- PPD test
- Hepatitis B surface antigen, surface antibody, and core antibody testing
- HIV-I and -II ELISA
- Hepatitis C ELISA (for previously identified risk groups)

adopted after the newborn period should have a careful assessment of all domains of development soon after placement. Most children make rapid developmental progress after they are in a nurturing family environment. Children whose delays are profound or persist beyond the first 2 to 3 months should be referred to formal developmental support services.

Many children have significant medical needs on their arrival to their new families, some of which are known before the adoption, and some of which will be revealed by the new-arrival evaluation. Further diagnostic workup and treatment of these medical needs should be planned carefully, balancing medical urgency with the child and family's need for quiet nesting time in the early days of the adoption. Simple treatments, such as antibiotics or iron supplements, can begin right away. Potentially transmissible infections, such as intestinal parasites, hepatitis, and tuberculosis, should also be treated quickly. Urgent, time-sensitive, or potentially life-threatening medical conditions must be treated immediately (eg, congestive heart failure, dehydration, extremely high lead levels, untreated syphilis, dense cataracts). Treatment

of nonurgent medical concerns, however, can and should be deferred until the family has had some time together and the child has begun to learn to use the parents for comfort and support. Common problems in this category include repair of cleft lip and palate, orthopedic conditions, congenital heart defects, dental work, and strabismus surgery. Truly elective procedures, such as circumcision or repair of minor anomalies, should always be deferred until the child has developed a secure bond with the new family.

### First Year Home

The first months in the adoptive home represent a transition time for the adopted child and the rest of the family, during which the groundwork is laid for the long-term success of the adoption. Regardless of age, the child should be seen at least several times over the first year home to monitor catch-up in growth and development, child and family mental health needs, and the attachment of the child to the new family. In addition, all children should have age-appropriate hearing and vision screens, given that children adopted from foster care or orphanages have high rates of auditory and visual impairments. These

visits can be timed to accommodate catch-up on immunizations and follow-up of identified medical needs.

Perhaps most important, careful attention should be paid to attachment-related behaviors in newly adopted children. Children who have always had loving, nurturing care understand how to use an adult as a secure base in the world and will transfer this designation to a new parent quickly, usually within several weeks. Children who have never experienced one-on-one, emotionally attuned caregiving, however, have often learned to cope with life's hardships on their own, without relying on an adult. These children need to be overtly taught to use their new parents as their base in the world because secure attachments are the foundation of healthy long-term relationships. Parents may be impressed with the child's self-sufficiency, but they should be encouraged to intervene frequently, teaching the child to see the parent as the active provider of food, comfort, and entertainment. Pediatricians should closely monitor newly adopted children for signs of developing strong attachments. If, after several months, the child does not preferentially use the parent or parents as a source of safety, security, and joy, then the pediatrician should refer the family to a therapist experienced in attachment disturbances.

Most children adopted out of foster care or internationally have significant developmental delays at the time of placement. These delays usually resolve rapidly after the child is in the care of loving, nurturing parents; therefore, delays that persist beyond the first 2 to 3 months should be carefully evaluated. Young children learn new languages very quickly; thus, language delays that persist should not be presumed to be the result of learning a new language but rather should be carefully investigated, with early initiation of speech and language therapy. Younger children qualify in most states for early intervention services, and older children can be evaluated and treated through local school districts or privately. For internationally adopted school-aged children, having academic assessments performed in the native language can be advantageous within the first 1 to 2 months home, before fluency in that language is lost, given that full fluency in the new language may take several years.

Deciding when to start a newly adopted school-aged child in school can be difficult and needs to be an individual decision for each child, balancing the need for family bonding time with the child's academic needs and social desires. Children who have never been to or have missed substantial portions of school may need to work on academic basics typically taught to younger children, while being afforded social opportunities and enrichment classes with same-aged peers. Many children do well to start school part-time, gradually working up to full-time attendance as they develop greater comfort with all of their new surroundings. Some children do well starting at a lower grade level to be taught academic basics, and move rapidly through several grade levels as they acquire skills and catch up to their same-aged peers. School-aged international children will qualify for English as a Second Language (ESL) services, in addition to any

learning supports that they may need. Parents and pediatricians should not let schools opt out of learning supports because a child is not a native English speaker; internationally adopted school-aged children frequently have *both* learning support and second-language needs.

Most newly adopted children struggle in some way with the routines of daily living, including eating, sleeping, bathing, and toileting, among other routines. Even a child placed as a newborn may have these issues if exposures were encountered prenatally from which the child experiences withdrawal symptoms. (See Chapter 104, Prenatal Drug Use: Neonatal Effects and the Drug Withdrawal Syndrome.) Children who have not had enough food (particularly those cared for in institutional settings where, in addition to inadequate volumes, food is never available to satisfy individual hunger) often eat huge volumes of food and may hoard food, alarming parents and physicians alike. This circumstance should be recognized as an adaptive survival behavior from the prior life circumstances and should be not restricted or punished. When children are allowed unlimited access to healthy, age-appropriate food, most will learn within several months that enough is now available and that they can have it whenever they need it, and will slow down to more typical levels of intake. If, on the other hand, the child's intake is restricted, then the previously learned strategy of taking all that is available whenever it is available will continue, often developing into more secretive food-hoarding behaviors and other long-term eating disorders. Given all of the information currently targeted at parents around preventing childhood obesity, pediatricians may need to help parents understand this seemingly paradoxical advice and realize that healthy eating habits in the family will prevail after the child truly believes that there will always be enough food.

Sleep problems are obviously a common concern for all children but are almost universal among newly adopted children. Many of these children have never slept alone, in a dark room, or with any notion of safety at night, and internationally adopted children may have traveled through many time zones to arrive at their new home. Sleep deprivation quickly takes its toll on parents and children alike, complicating all of the other new-arrival transitions. Until a child has developed strong attachments to the parent or parents, however, this time is inappropriate for sleep strategies that encourage parents to leave a child alone. Until the child has thoroughly internalized the notion that the parent or parents will always be available when the child needs them, parents should be encouraged to be as physically and emotionally present at nighttime as the child needs to feel safe and secure. This task can be accomplished, however, in the child's room and bed, using the desired long-term sleep routines so that parents can wean themselves out of the child's bedtime routine as the child develops a sense of safety and security. Older children, especially those who have experienced abuse, may need explanations from parents of nighttime noises before they will feel safe enough to sleep. By balancing these short- and long-term goals from the beginning, most children



can be helped to sleep peacefully all night in their own bed within several months.

Sensory-seeking or avoiding behaviors, as well as autistic-like repetitive behaviors, are common among children who have experienced severe deprivation before adoption. As with overeating mentioned earlier, these are adaptive behaviors in a setting with little or no stimulation and usually resolve quickly when more stimulation and human interaction are made available. Many children revert to these behaviors when tired, stressed, or bored, and parents can learn to read these behaviors as cues to these feelings. Reverting to self-stimulating behaviors to cope with fatigue or stress may continue for years after adoption, with no other pathologic behavioral concerns. On the other hand, children who do not respond to nurturing parenting, but instead continue to self-stimulate regularly rather than interact with the world, should have a full developmental and behavioral evaluation.

Another common dilemma, particularly for internationally adopted children, is an uncertain date of birth. Many children come into care after being born at home, with no official record of the birth or, more commonly, after being abandoned. Assigned birthdates may or may not be accurate, particularly for older children, given that the growth and developmental delays that result from malnutrition and neglect make children seem to be younger than they really are. Older children are occasionally deliberately assigned a younger age for well-intended reasons, such as increasing the child's chances of being adopted or enabling an oldest child to remain with younger siblings. As previously reviewed, most children are significantly delayed in their growth and development on arrival, and these delays, combined with knowledge of an assigned birthday, often tempt new parents and pediatricians to consider changing the child's date of birth. Because these delays usually quickly resolve, however, the notion to consider legally changing the child's birth date in the first or second year after arrival is rarely advisable. Bone age testing or dental age assessments are not helpful early on, given that both malnutrition and neglect cause delays in bone and dental age as they do in the rest of the child's development, and thus should not be used as justification for changing a birth date. When concerns about age discrepancy persist a year or more after adoption, parents and pediatricians should carefully consider what would be gained and lost for the child if the date were to be changed. This situation is obviously more common for children adopted after the infant and toddler ages, and, as such, children should be included in the decision making about this important piece of their identity.

### Long-Term Issues

In addition to any health issues identified before or immediately after adoption, long-term health issues common to adopted children should be considered. Recognizing these risk factors in a child's history can help pediatricians maintain appropriate surveillance above and beyond the usual well child care routine and provide referrals and support proactively.

Most important, the long-term effects of early adversity cannot be forgotten. Early malnutrition, abuse, neglect, or trauma can cause significant long-term cognitive, developmental, behavioral, and mental health struggles, even after years in a warm, nurturing adoptive family. Developmental disabilities, mental health problems, and substance abuse are not uncommon factors in unplanned pregnancies or inability to care for their children in the first place, leaving adopted children as a group with a higher frequency of genetic predispositions to these diagnoses than the general population. Prenatal substance exposure, especially to alcohol, also carries significant long-term risks. Teasing out which of these factors is responsible for a given child's struggles is often difficult or impossible; but, for most adopted children, a safe assumption is that any of these predisposing issues might be a causative factor.

Many children experience significant struggles as they enter school age. Difficulties with attention and impulse control often lead to the diagnosis of attention-deficit/hyperactivity disorder (ADHD), although they frequently are far more complex. Children should have a thorough psychoeducational or neuropsychological evaluation to tease out complex visual, auditory, language, and sensory processing differences, difficulties with executive functioning, and specific learning disabilities before being assumed to have simple, uncomplicated ADHD. In addition, many children who spent their early lives in institutional care, lacking much direct human contact, have difficulties reading nonverbal social cues. As a result, they often have great difficulties with peer relationships and can benefit from direct teaching on social skills and reading body language.

Children who experience serious malnutrition, followed by significant catch-up growth, have a significantly higher risk for precocious puberty compared with the general population. In addition to a young age of onset, these children typically proceed through the stages of puberty at a very rapid rate, making early recognition and treatment imperative. Uncertainty about a child's true age can further complicate the evaluation.

Children who have experienced malnutrition also frequently have very weak dental enamel, which is often compounded by circumstances that lack even marginal oral hygiene. Many children experience severe dental decay despite good dental hygiene in the adoptive home. Early recognition and treatment of these conditions is obviously paramount.

Many adoptees have little or no knowledge of the biologic family medical history, and those who do often have only the information that was available at the time of their birth. This missing history can be a source of social and emotional distress to adolescents and their families, but for children of any age, it can also be a significant impediment to providing appropriate health care, particularly in the case of serious illness. Some states now provide registries of birth parent and adoptee information, with access granted by mutual consent. (See Tools for Practice for resources for adoption information.) Laws vary from state to state regarding who may have access to this

information and under what circumstances. Some adoption agencies also maintain and update health records of birth parents whose children they have placed, and some will help families locate birth parents. Children who were adopted from overseas generally have little or no information about birth family medical history, and records may or may not be maintained, thus precluding further investigation. Children who were abandoned have no way to know any family medical history. Lack of birth family medical history should be considered when determining risk factors for routine screening (eg, for hypercholesterolemia).

### **BILLING AND PAYMENT INFORMATION FOR ADOPTION PHYSICIAN SERVICES**

Preadoption consultation services are not billable to third-party payers because the child in question is not yet part of the policy. Pediatricians with a special interest in adoption medicine who perform these services frequently have fee-for-service fee scales that reflect the time spent, the complexity of information reviewed, and local prevailing payment rates. Pediatricians who perform these services only occasionally may choose to provide these services free of charge to families who are already in their practices, or they may devise a pay scale that reflects the same variables. Payment for these services may be available to some families by means of employer adoption subsidy plans or flexible spending accounts.

Office visits for newly adopted children require more time than standard well child visits, involve far more complex issues, and generally need to occur more frequently. Payment for these services can be accomplished by appropriately coding for the diagnoses involved and the complexity of medical decision making. When counseling or care coordination takes up more than 50% of the face-to-face time spent with a patient, the physician can use time as the controlling factor for assigning a procedure code.

### **ISSUES UNIQUE TO ADOPTIVE FAMILIES**

Adoptive families come in all shapes and sizes. These families may include children by birth and adoption, children and parents of different races, single parents, gay and lesbian parents, grandparents and other relatives raising children, and stepparents adopting a new spouse's children, just to name a few. Depending on the size and diversity of the community, some of these families may stick out, and parents and children will need to learn how to handle questions from strangers and acquaintances. Parents and pediatricians need to help children learn to interpret which questions are ill intended versus simply curious, what information is appropriate to share (with whom, when, and where), and what information is private. Children can and do thrive in all of these varieties of families, especially when parents are open and honest with children about these topics that are unique to adoptive families.

All pediatricians should be familiar with basic issues that are common to all adopted children and

should ensure that they and the entire office staff use language that reflects respect for adopted children and their birth and adoptive families. Box 70-2 provides appropriate language to use when speaking about adoption. Numerous resources are available to help parents, professionals, and children negotiate the complexities of grief, loss, and joy that come when a child is relinquished by one set of parents and claimed by another. (See Tools for Practice for these resources.)

Pediatricians should help and encourage adoptive parents to talk with their children about adoption from a very young age, given that all available research has shown that children do far better when they come to understand adoption over time, rather than as a single, bombshell discussion. Adoptive parents often struggle with how to begin these discussions and how to handle children's questions, fearing that they might jeopardize the child's sense of security or belonging in the family or that they might overwhelm the child with difficult-to-comprehend details. Just as with any other complicated matter, however, children come to understand the complexities of adoption over time and in more detail as they progress developmentally. Young children simply need to learn the language and can begin to understand that, "I didn't grow inside Mommy's tummy." Preschoolers ask many questions, and adoptive parents who respond openly to their inquiries are setting the stage for more in-depth, open dialogue as time goes on. School-aged children begin to understand that they have 2 sets of parents and spend a great deal of time thinking about their birth parents. They often fear talking about this subject with their adoptive parents, worrying that these questions will hurt the feelings of or minimize their love for their adoptive parents. Parents need to offer many opportunities for children to talk and clearly tell them that this topic of conversation is acceptable. Teens begin to incorporate what they know about their birth parents and their own stories into their developing identity and may experiment with lifestyles that they know or imagine their birth parents to be living. Anticipatory guidance for adopted children should include encouraging parents to talk openly and honestly in simple, direct, developmentally appropriate language to help the children understand and deal with the specific details of their own life's story.

Many adoptions, particularly domestic adoptions, include some degree of openness or ongoing contact between children and their birth parents. Although this idea is frightening at first to many prospective adoptive parents and might seem harmful to those unfamiliar with adoption, research and experience have shown that children thrive when birth and adoptive parents carefully and lovingly maintain relationships over time. Although these relationships can at times be complicated, the benefit to children of being able to know exactly why their birth parents chose not to raise them and of knowing details such as who they resemble, whose musical talent or crooked toes they inherited, and how their birth parents are doing today is beyond measure.

Children who do not have ongoing contact with their birth parents often, as they become adolescents

**BOX 70-2 Appropriate Language to Use When Speaking About Adoption**

The language we use to talk about adoption can have significant positive or negative effects on children and their families. Physicians and office staff members who speak respectfully and supportively about adoption not only nurture the self-esteem of their patients, but also win the respect of parents and receive word-of-mouth referrals of other adoptive families to the practice. Carefully worded office forms and publications provide further support for adoptive families.

The following list presents respectful ways to talk about adoption with families, as well as language and phrases to avoid.

- **DO:** Use the words “birth child” and “adopted child” **only** when they are relevant to the discussion (eg, in discussing family medical history); otherwise simply use “child.”
- **DON’T:** Refer to a child born to his parents as the parents’ “real child,” “own child,” or “natural child.” A child who was adopted is very real and not at all unnatural; she is very much her parents’ “own child.”
- **DO:** Use the words “birth parents” or “biologic parents” **only** when asking about them is relevant (eg, in discussing family medical history).
- **DON’T:** Refer to the child’s birth parents as his “real parents” or “natural parents.” Adoptive parents are very real and not at all unnatural.
- **DO:** Treat siblings who joined families by birth or adoption equally. They are loved equally by their parents and experience all of the joys and trials of any sibling relationship.
- **DON’T:** Distinguish between children who were adopted into the family and children who were born into the family unless it’s relevant.
- **DO:** Describe birth parents as choosing “to make an adoption plan for the child” or “to place the child for adoption.”
- **DON’T:** Refer to a child as being “put up” or “given up” for adoption. Most birth parents have thought long and hard about their decision to place a child for adoption. It is very important to a child’s self-esteem to know that her birth parents loved her and worked hard to reach a decision that they felt to be in her best interest. Even when birth parent rights are terminated involuntarily, the child needs to know that it wasn’t her fault that her birth parents could not take care of her at the time and that other adults are looking out for her best interests.
- **DO:** Recognize that families come in all shapes and sizes. Create forms, policies, and other office materials that refer to “parent or guardian” not “mother or father.” Some families may have a single adoptive parent or permanent legal guardian and no other legal parent. Other families have same-sex parents. Forms that ask for information from a parent or guardian acknowledge that families of all varieties are welcome.
- **DON’T:** Assume that the child has 2 opposite-sex parents.
- **DO:** Refer to birth parents as “choosing to parent” their child. This implies to the child who was adopted that birth parents made their decisions based on what they felt was in the best interest of each child when they made their decision.
- **DON’T:** Refer to birth parents as “choosing to keep” their child. This implies to a child who was adopted that he was “not worth keeping.”
- **DO:** Talk with a family about how it celebrates the intercultural and/or interracial nature of the family. Many families make special efforts to include their children’s culture and heritage in daily routines and traditions. Available research shows that children clearly benefit from this practice.
- **DON’T:** Ignore a child’s birth country, race, or genetic heritage. Especially in communities where there is limited ethnic diversity, children from racial or ethnic minorities need family and physician support to overcome racism and develop a strong, positive racial identity.
- **DO:** Recognize that a child understands adoption gradually as she grows, just as with all other developmental tasks. Ask the family whether it is dealing with any difficult adoption-related issues and be familiar with common issues of different developmental stages so that the family feels comfortable using office staff members as resources for information.
- **DON’T:** Ask, “Are you going to tell your son that he’s adopted?” Adoptive parents are encouraged to talk freely and honestly about adoption from the time their child is very young so that there is never a time in the child’s life when this information comes as shocking news.
- **DO:** Be sympathetic with the long and sometimes arduous path that parents have traveled to become parents. Some may be experiencing significant financial stresses after the adoption, some may still be grieving infertility losses, and some may be coping with extended family members who do not accept the new member of the family. Recognize that even though the child may not be a newborn, the adults may be new parents. Recognize that postadoption depression exists and is similar to postpartum depression.
- **DON’T:** Ask, “How much did you pay for your daughter?” Children are not bought. Fees go to pay social workers and attorneys, to complete court and government paperwork, to cover travel, medical, foster/orphanage care, and other expenses, not to “buy children.”

or adults, choose to search for them. Many adoption agencies and therapists offer help and support to adopted persons and their families as they proceed through this process. The emotional and legal complexities of this process vary from family to family and state to state, with some states allowing adoptees full access to records, some having mutual consent registries, and some allowing limited or no information to be obtained from sealed records. Pediatricians can help parents understand that the desire to search does not imply a rejection of the adoptive parents, but rather a need for the adopted person to fully understand himself. Some adoptees find and develop good relationships with their birth families, some find them but do not develop strong relationships, and others are never able to locate biologic relatives. Pediatricians need to support families as they negotiate all of these possibilities. (See Tools for Practice.)

Although most adoptive placements generate positive outcomes for both children and their families, not all adoptive placements achieve permanency for children or happy long-term outcomes. Although exact numbers are unclear because of variable state reporting systems, estimates indicate that between 10% and 25% of adoptive placements are disrupted (ended before the adoption is finalized), and 1% to 10% are dissolved (legally reversed, similar to a divorce, after the adoption was final). Most commonly, this event happens with children who are older, with a complicated, traumatic history and complex behavioral and mental health needs, who were placed with families who were either unaware of these needs or inadequately prepared to meet them. Such occurrences are traumatic for everyone involved, especially the child, and are best avoided by full disclosure of information before the adoption and long-term, ongoing support for the family after the adoption is finalized. Families who are considering or pursuing a disruption or dissolution of their adoption should be referred to an experienced adoption professional. (See Tools for Practice for parent resources about disruption and dissolution.) These same stresses, combined with unrealistic expectations, can also leave children at risk for abuse or neglect in their adoptive homes, just as can occur in any other family. Pediatricians should maintain the same surveillance for these possibilities as they would for any other child and family.

## CONCLUSION

Caring for adopted children and their families can be among the most rewarding experiences of a pediatrician's career. By working closely with parents to address the special needs of their adopted children, pediatricians can help ensure a bright future for children whose futures might otherwise have been bleak.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *Access to Adoption Records* (Web page), Child Welfare Information Gateway ([www.childwelfare.gov/topics/systemwide/laws-policies/statutes/infoaccessap](http://www.childwelfare.gov/topics/systemwide/laws-policies/statutes/infoaccessap))

- *Connected Kids Clinical Guide* (booklet), American Academy of Pediatrics ([www2.aap.org/connected-kids/ClinicalGuide.pdf](http://www2.aap.org/connected-kids/ClinicalGuide.pdf))
- *Trauma Guide* (Web page), American Academy of Pediatrics ([www.aap.org/enus/advocacy-and-policy/aap-health-initiatives/healthy-foster-careamerica/Pages/Trauma-Guide.aspx](http://www.aap.org/enus/advocacy-and-policy/aap-health-initiatives/healthy-foster-careamerica/Pages/Trauma-Guide.aspx))

### Engaging Patient and Family

- *Adoption: Guidelines for Parents* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Coping With Disruption/Dissolution* (Web page), Child Welfare Information Gateway ([www.childwelfare.gov/topics/adoption/adopt-parenting/disruption](http://www.childwelfare.gov/topics/adoption/adopt-parenting/disruption))
- *The First 1,000 Days: Bright Futures Examples for Promoting EB CD* (booklet), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-healthinitatives/EB CD/Documents/EB CD\\_Well\\_Child\\_Grid.pdf](http://www.aap.org/en-us/advocacy-and-policy/aap-healthinitatives/EB CD/Documents/EB CD_Well_Child_Grid.pdf))

### Medical Decision Support

- *Enhancing Pediatric Mental Health Care: Algorithms for Primary Care* (article), American Academy of Pediatrics, Pediatrics, Vol 125, Suppl 3 ([pediatrics.aappublications.org/content/125/Supplement\\_3/S109](http://pediatrics.aappublications.org/content/125/Supplement_3/S109))
- *Evidence-Based Child and Adolescent Psychosocial Interventions* (chart), PracticeWise, American Academy of Pediatrics ([www.aap.org/enus/Documents/CRPsychosocialInterventions.pdf](http://www.aap.org/enus/Documents/CRPsychosocialInterventions.pdf))
- *Feelings Need Check Ups Too* (booklet), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/children-and-disasters/Documents/Feelings-Need-Checkups-Toolkit\\_0823.pdf](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/children-and-disasters/Documents/Feelings-Need-Checkups-Toolkit_0823.pdf))
- *International Adoption: Health Guidance and the Immigration Process* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/immigrantrefugeehealth/adoption](http://www.cdc.gov/immigrantrefugeehealth/adoption))
- *Mental Health Screening and Assessment Tools for Primary Care* (chart), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-healthinitatives/Mental-Health/Documents/MH\\_ScreeningChart.pdf](http://www.aap.org/en-us/advocacy-and-policy/aap-healthinitatives/Mental-Health/Documents/MH_ScreeningChart.pdf))
- *Pediatric Symptom Checklist* (screen), Bright Futures ([www.brightfutures.org/mentalhealth/pdf/professionals/ped\\_sympton\\_chklst.pdf](http://www.brightfutures.org/mentalhealth/pdf/professionals/ped_sympton_chklst.pdf))
- *The Resilience Project: Clinical Assessment Tools* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/resilience/Pages/Clinical-Assessment-Tools.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/resilience/Pages/Clinical-Assessment-Tools.aspx))
- *Strengths and Difficulties Questionnaires* (screen), Youth in Mind, Ltd ([www.sdqinfo.com](http://www.sdqinfo.com))
- *Vaccines. Medicines. Advice.* (Web page), Centers for Disease Control and Prevention ([wwwnc.cdc.gov/travel/default.aspx](http://wwwnc.cdc.gov/travel/default.aspx))

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## Chapter 71

# CHILDREN OF DIVORCE

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Approximately 1 million children experience divorce in the United States each year. In the early 1960s, almost 90% of children spent their childhood and adolescence with 2 biological parents. Now, that number has decreased to 40%. For adults, divorce is second only to the death of a spouse or a parent in terms of its intensity as a stressor and the length of time required to adjust to it. Divorce often produces anger and a sense of failure for parents; conflicted loyalties, guilt, grief, and anxiety for children; and concern on the part of all about whether the children will suffer long-term harm. Most children of divorce experience, at the least, a potent transient stress. It should never be viewed, therefore, as an isolated event, but rather as a step in a series of family transitions that significantly affects both of the parents and the children. Many people accommodate to their new circumstances successfully, but a substantial percentage suffer long-term negative effects. Many of the problems of these children and their families can be anticipated, prevented, or alleviated by thoughtful and timely intervention.

## FAMILY CHANGES PRECIPITATED BY DIVORCE

In most cases, both parents are awarded joint legal custody, but the children's primary physical residence is with their mother in more than 80% of cases. Divorce often has devastating financial consequences for these children and their mothers, and children in postdivorce families are 4 times as likely to live in poverty compared with children overall. A significant number of divorced mothers have few financial and personal resources to direct toward the children, and many take on new employment arrangements. This circumstance may result in new child care arrangements for younger children, older children taking care of themselves or siblings for greater parts of the day, and curtailment of certain activities because of expense or parental time constraints.

For nonresidential parents, who are most often fathers, problems range from what to do with children on visiting days to profound concern about the emotional consequences for their children. Some nonresidential parents fear that their children will abandon them, some have unrealistic expectations about the kind of relationship they will have with their children, and some believe divorce deprives them of the right to exercise authority and to discipline the children. Much public attention has deservedly focused on issues of failed child support, nonresidential fathers who do not visit, and the economic plight

of single-parent households. The importance of long-term paternal involvement in a meaningful and unconflicted relationship with their children cannot be overstated.

## STAGES OF DIVORCE

The period immediately before and after the separation is referred to as the acute stage; it is characterized by maximal turmoil and generally lasts up to 2 years. The family then moves into the transitional stage, which is characterized by more controlled changes. The final stage is the postdivorce stage, when major family restructuring ceases.

During the acute stage, all family members are confronted with disruptions of their expectations, relationships, and support systems. Parents may be depressed, may be preoccupied with personal concerns, and may exhibit diminished parenting abilities. During this stage, 2 events appear to be most stressful to most children: learning about the divorce, and the actual departure of a parent. The first year after divorce is the year of maximal negative behavior by children and the poorest parenting by parents. The apparent intensity of a child's reaction to this stage, however, does not predict long-term adjustment. Initially, many parents make fewer demands on the children, communicate less effectively, are less affectionate, and have difficulty disciplining children. In a significant minority of divorces, the troubled relationship between parents continues indefinitely. In these cases, children have the greatest incidence of postdivorce maladjustment.

The transitional stage is marked by new undertakings for the single-parent household and more stability than the acute stage. Children must accommodate to their parents' new relationship with each other, to new friends, and often to new romantic partners of one or both parents. During this stage, children are often concerned about the well-being of, and their relationship with, the nonresidential parent. Visitation patterns tend to have become more stable, whether they are acceptable to all parties or not. The major exception to the general pattern of increased stability is the family in which the parents still are actively in conflict, either informally with each other and the children or formally through the legal system.

In the postdivorce stage, relative stability is achieved. The family may still be headed by one parent, or a stepparent may now be present. Remarriage does not convey automatic stability but rather requires new adjustments as a result of the reawakening of unresolved issues and new roles in the new family.

## EFFECTS OF DIVORCE ON CHILDREN

On average, small but detectable negative emotional, cognitive, social, and physical effects, both short term and long term, are found among children of divorce. Of course, these effects vary greatly and depend on many factors.

### Initial Effects

Initial responses are greatly influenced by the developmental level of the child; the child's temperament; the level of parental conflict; and the emotional,

cognitive, and economic support available to the child. The effects of divorce on children are similar for male and female family members.

Infants and toddlers have minimal to no comprehension that divorce has occurred and may not have a direct reaction to the divorce. Preschoolers, aged 2 to 5 years, initially tend to display regressive behaviors that can be highly stressful for parents, such as sleep disturbances, temper tantrums, separation anxiety, loss of bowel and bladder control, and increased need for parental attention. School-aged children, 5½ to 12 years of age, may experience sadness, grief, or intense anger at one or both parents. School performance and peer relationships may deteriorate, and phobias may emerge among both early and late school-aged children. Adolescents of divorcing parents find themselves without the expected home base from which to move away. This situation may result in insecurity, loneliness, decreased self-esteem, and depression. These feelings may be overtly or covertly expressed in diminished school performance, school failure, truancy, violent and nonviolent criminal behavior, substance use, eating disorders, or sexual promiscuity. Children of any age may exhibit psychosomatic symptoms as a reaction to the stressors placed on them by the divorce. These children may play one parent against the other to gain more control.

### Long-Term Effects

Prior studies revealed long-lasting effects of parental divorce in a significant minority of cases. Adults who experienced divorce as children tend to score lower on a variety of indicators of psychological, interpersonal, and socioeconomic well-being. Although the majority of adults who experienced divorce as children appear to do well, as a group overall, they have higher rates of depression, job changes, premarital pregnancies, and divorce. The degree of marital conflict before the divorce has been shown to be a stronger predictor of adjustment than the divorce itself or the conflicts after the divorce.

A 25-year follow-up study confirmed that children of divorced parents are less likely to marry and when they do marry are more likely to divorce. They are also less likely to enter and complete college. The gap between children of divorced and married parents with respect to academic achievement, psychological well-being, self-concept, and social relations was small in both the 1980s and 1990s, although a trend for a wider gap occurred in the 1990s. The differences in outcomes between children of married and divorced parents may be influenced by ethnicity, with smaller differences seen in black families than in European American families. The long-term negative effects of divorce are mitigated by a variety of social factors: support of parents and grandparents, social support in adulthood, educational attainment by the child and mother, and socioeconomic status of the family.

Not all effects of divorce are negative, however. Children from divorced families demonstrate less stereotyped sexual behavior, greater maturity, and greater independence.

## TASKS FOR THE CHILDREN AND PARENTS OF DIVORCE

Children of divorce have several specific tasks on which they work simultaneously and with varying degrees of success. These tasks greatly depend on the child's development and age. Mastery of these tasks is facilitated by support and cooperation of both parents. Parents can better help children cope with divorce if they are aware of the child's developmental age and respond to them accordingly.

### Understanding the Meaning of Divorce and Custody

Toddlers and preschoolers may have a difficult time understanding the meaning of divorce. Because these children view their world very concretely, they may not be able to comprehend the changes in relationships and the alterations within their household. Confusion about the actual meaning of divorce is the rule rather than the exception. Parents should provide simple explanations about the meaning of divorce and custody and should never avoid the subject. Parents should maintain routines so that the child does not equate divorce with instability or loss of normalcy.

### Accepting the Permanency of Divorce

The task of acceptance requires the child to accept the reality of the divorce despite tendencies to deny the dissolution of the family and fears of abandonment. These tendencies and fears may persist, leading to repeated efforts by children to persuade their parents to reconcile, even after one or more has remarried. Young school-aged children fantasize about being able to reunite their parents. Parents need to recognize that their children have these fantasies and that they will try to get them to interact with each other in any way and as often as possible. Older children and adolescents who have lived in persistent high-conflict or violent marriages, however, are more likely to be relieved about parental separation and are less likely to wish for parental reunion.

### Regaining a Sense of Direction

Immediately after divorce, many children experience emotional and behavioral difficulties, and many seem to lose interest in school, friends, and leisure time activities. Approximately one-third of adolescents, particularly boys, in divorced and remarried families separate from the family unit, spend little time at home, and avoid interactions with family members. Generally, the return to more typical activities for the child takes approximately 1 year. If this transition has not occurred within this period, then referral of the child or family for psychotherapy may be indicated. During this time, parents must maintain discipline and avoid allowing their own emotions surrounding the divorce to cloud their judgment and authority. If a child is having a particularly difficult time adjusting in one home, parents may then consider a trial of living with the noncustodial parent. Children who are better adjusted before the marital breakup, those who are not enmeshed in a prolonged battle between the parents, and those who are supported in their efforts to

understand their feelings are better able to accomplish this task.

### Dealing With Painful Feelings

Departure of a parent through divorce is experienced by children of all ages as a major assault on their self-esteem and sense of security. Because of preschoolers' egocentric thinking, they may believe that they are responsible for the divorce, must therefore be bad, and consequently are at risk for further abandonment by the other parent. Older children, appreciating that the departing parent is exercising a choice to leave, often feel anger as well as other negative aspects of grief. These feelings result in a complex interplay of negative emotions and their consequences. Parents should explain the situation to their children in simple, age-appropriate language and assure them that they are not the cause of the divorce. Despite parents' best efforts, however, long-term follow-up studies indicate that this important task may never be accomplished by a significant number of individuals who experienced divorce as children.

### Not Choosing Sides

Children, especially school-aged children, may see divorce as posing a problem of conflicting loyalties. Parents must consistently reassure children that they are equally loved by both of them and that divorce is not going to change these feelings. Parents should also refrain from buying excessive gifts to prove their affection.

### Remaining a Child

Divorce leads to many changes, but one of the most obvious is the physical absence of one parent in the home. Older adolescents often feel responsible for the happiness of their parents and the well-being of their younger siblings. They may make attempts to comfort and console their parents. Parents should avoid treating their children as adults. Boys should not be expected to become the men of the house, and girls should not be expected to become the cooks. Children's lives will undergo enough changes without also relinquishing their childhood.

### Forgiving the Parents

Forgiving the parents is often a task for older children. Adolescents often struggle with chaos in their own lives and are often angered by having to deal with their parents' lives. Forgiving their parents therefore requires their ability to appreciate the parents' need to separate as being more important than any reason to stay together, including the desires of the children. Children must then overcome grief over the loss of the intact family as well as the anger and resentment generated by the resulting changes in their life. Parents should be flexible and understanding of the adolescent's need for space as well as available for comfort and maintenance of discipline.

### Resolving Issues of Relationship

As Judith Wallerstein has observed, divorce often leaves children fearful and unable "to reach, sustain, and support the personal vision that love, mutual

understanding, and constancy are expectable components of human relationships. Perhaps the major developmental task posed by divorce is this: to achieve realistic hope regarding future relationships and the enduring ability to love and be loved." "At young adulthood, when love, sexual intimacy, commitment and marriage take center stage, children of divorce are haunted by the ghosts of their parents' divorce and are frightened that the same fate awaits them." This task is difficult for a significant number of adults who experienced divorce as children. As children get older, parents should discuss the reasons for the divorce so that the young person learns to view the divorce "not as inevitable but as a result of avoidable human error."

### CUSTODY

If the noncustodial or nonresidential parent has not abandoned the family and wants to remain involved with the children, then the custodial or residential parent must not attempt to sabotage this relationship.

### REMARRIAGE AND STEPFAMILIES

Within 4 years, 50% of divorced adults remarry, and one-third of American children will eventually become members of a stepfamily. More than 80% of these stepfamilies are composed of a biological mother and a stepfather. In many cases, it restores a secure, 2-parent environment, and it may provide children with a model of a loving, caring adult relationship. Despite the wicked stepmother figure portrayed in fairy tales, most stepchildren like their stepparents and report that they get along with them well. Most studies have shown that stepchildren do not appear to differ from other children in personality characteristics or in cognitive or intellectual accomplishments.

Remarriage does, however, have the potential of creating new tensions and stresses for both the parent and the child. When one parent remarries, the other may fear that the children will abandon them for the new stepparent. Lutz's interviews of adolescents between 12 and 18 years of age living in stepfamilies revealed that the areas causing the most difficulty are those of divided loyalty and discipline. Many children may feel conflicted about loving their stepparent and may even see it as a source of betrayal of their biological parent. In addition, many children may continue to wish for parental reunion. Regarding discipline, stepparents are often unsure of their roles and may feel awkward in these situations. Discussing these issues with the custodial biological parent and conforming to their approaches is important for stepparents.

Adults can help children adapt better to remarriage. Children adjust better to remarriage with decreased conflict among family members and a supportive residential parent and stepparent. The stepparent should not exert authority immediately but instead be supportive of the residential parent. Social support from peers, grandparents, and school personnel may positively influence the child's adjustment.

Two other factors may play significant roles in the adjustment of children within stepfamilies. First, the child's age is an important aspect to consider in the evaluation. Although a toddler may not fully

understand the implications of a stepparent, the school-aged child has been found to be the most vulnerable to the stresses associated with the remarriage. Second, timing is equally important to the overall adjustment. If the remarriage occurs abruptly or before the child is ready to accept a new parent in the child's life, the stress may be magnified. Unfortunately, the divorce rate of second marriages is still higher than that of first marriages.

### PREVENTIVE INTERVENTIONS FOR DIVORCING FAMILIES

Different interventions have been attempted to help alleviate the deleterious effects of divorce on families. Court-connected divorce education programs have been developed to inform parents how children respond to divorce and to help parents respond to the child's needs. Evaluations of these programs are sparse. Mediation of divorce and custody issues promotes higher levels of agreement among parents before the court hearing than the adversarial process. Therapy for the mother and child can reduce symptoms of mental disorders; reduce marijuana, alcohol, and other drug use; and reduce sexual promiscuity. An intervention to improve the quality of the mother-child relationship was shown to improve long-term coping in children.

### THE PEDIATRICIAN'S ROLE

The pediatrician can help the family anticipate, prevent, or address problems that frequently accompany divorce by providing anticipatory guidance and counseling for problems as they arise, and assessing and referring children and family members for more extensive or detailed psychosocial intervention when needed. Parents and courts also may ask that pediatricians offer expert witness testimony when custody is questioned.

The first year after divorce is often the worst; parents often feel depressed and angry. If the parents are not otherwise receiving counseling, then the pediatrician may offer to meet with one or preferably both of them to facilitate cooperation regarding child-related issues, such as helping the parents formulate an approach to informing the children about the divorce. Pediatricians need to be the advocate for the child. They should avoid taking sides between parents, and they should be aware that one parent may manipulate the other by using the pediatrician.

Parents should be encouraged to avoid placing the children in the difficult position of choosing which parent to believe or side with when the 2 most significant adults in their lives have widely differing views. They should also be informed that behind many of their questions, children are asking, "Do you still love me, and can I trust you?" Parents should explain the divorce process to children in a developmentally appropriate manner. Also suggested is that parents be *concrete* about the children's future: where they will live, who will care for them, where the nonresidential parent will live, and how often he or she will visit. Parents should be encouraged to maintain children's routines, including going to school and taking on



responsibilities in and outside the home. Parents should maintain consistent discipline strategies.

Both before and after the divorce, children need reassurance that they are not unique as offspring of divorced parents. They may find comfort in discovering that many other children have divorced parents, live in stepfamilies, and have the feelings they are having, and that nothing is wrong with feeling this way. They should also be encouraged to ask questions and express feelings, and they should be brought to realize that expending a great amount of energy hoping their parents will be reunited is useless. Visitation with the nonresidential parent may be court mediated. Pediatricians need to be aware of the visitation agreement that is permitted; the pediatrician can then offer guidance about how to make visits more comfortable for the child. Suggestions that can be given to make this visitation easier include allowing the child to bring a friend along so that the child will not be bored, setting up the child's room as it was in the original home, spending time with the child, and not expecting the child to fit into the noncustodial parent's new world.

If a child does not wish to visit, then parents should be informed that the child should not be made to feel guilty, and the offer to visit soon should be extended. The nonresidential parent should be counseled to avoid forcing visitation if the child refuses. Persistent refusals to visit the nonresidential parent may suggest that the child is enmeshed in parental difficulties or is siding with the residential parent, or that the residential parent may be using the child to hurt the nonresidential parent.

Pediatricians should work with both parents; if abuse by a parent is thought to exist, however, then the appropriate action should be taken. Pediatricians should be knowledgeable about confidentiality laws; sharing medical information with any party during a divorce proceeding requires written permission by both parents or a court order. Pediatricians should maintain an accurate record of the custody arrangements.

Visits for well-child care and for acute illnesses can be used routinely to assess children's adjustment and to determine the need for further counseling by the primary care physician or for referral for individual or family therapy.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Divorce and Children* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *How to Support Children After Their Parents Separate or Divorce* (Web page), American Academy of Pediatrics (www.healthychildren.org/English/family-life/family-dynamics/types-of-families/Pages/Making-the-Divorce-Livable-for-Your-Child.aspx)
- *Marital problems and Divorce* (handout), American Academy of Pediatrics (www2.aap.org/sections/dbpeds/pdf/marital%20problems%20and%20divorce.pdf)

#### Medical Decision Support

- *Enhancing Pediatric Mental Health Care: Algorithms for Primary Care* (article), American Academy of

Pediatrics, *Pediatrics*, Vol 125, Suppl 3 (pediatrics.aapublications.org/content/125/Supplement\_3/S109)

- *Evidence-Based Child and Adolescent Psychosocial Interventions* (chart), PracticeWise, American Academy of Pediatrics (www.aap.org/en-us/Documents/CRPsychosocialInterventions.pdf)
- *Feelings Need Check Ups Too* (booklet), American Academy of Pediatrics (www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/children-and-disasters/Documents/Feelings-Need-Checkups-Toolkit\_0823.pdf)
- *Mental Health Screening and Assessment Tools for Primary Care* (handout), American Academy of Pediatrics (www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH\_ScreeningChart.pdf)

### AAP POLICY

American Academy of Pediatrics, Cohen GJ, Committee on Psychosocial Aspects of Child and Family Health. Helping children and families deal with divorce and separation. *Pediatrics*. 2002;109:1023. Reaffirmed January 2006 (pediatrics.aapublications.org/content/110/5/1019)

American Academy of Pediatrics, Committee on Psychosocial Aspects of Child and Family Health. The pediatrician's role in helping children and families deal with separation and divorce. *Pediatrics*. 2005;115(4):1092-1094 (pediatrics.aapublications.org/content/94/1/119)

### SUGGESTED READING

Emery R. *Renegotiating Family Relationships: Divorce, Child Custody, and Mediation*. New York, NY: Guilford Press; 1994

## Chapter 72

## CHILDREN IN FOSTER OR KINSHIP CARE

Maira Szilagyi, MD, PhD; Sandra H. Jee, MD, MPH

In an ideal world, every child would be reared by nurturing and caring birth parents. Many children and adolescents, however, cannot reside with their birth families for reasons of health and safety, and they require care in other settings. In 2013, approximately 3.5 million reports alleging child abuse and neglect and involving 6.4 million children were investigated by child protective services, resulting in 679,000 children identified as victims. About 144,000 child victims were removed to out of home care, as were another 95,000 nonvictims, mostly adolescents. In most states, kinship care remains a less formal arrangement and includes care by extended family, neighbors, or friends, frequently without the oversight of child welfare services. Foster and kinship care are intended to be a temporary respite for a family in crisis, and there is an increasing trend toward keeping children with their parents or extended family in lieu of foster care.

Although adolescents in out-of-home care frequently enter because of parental inability to cope with their behavioral or emotional issues, they have often experienced abuse and neglect during their childhoods. When children or adolescents are removed from their family of origin by child welfare services, they may be placed in either foster family care, kinship care, or group care. Although this chapter focuses on children and adolescents in out-of-home care, the information applies to the larger population of children and teens whose families are involved with child welfare because they experience similar childhood adversities and trauma as children in foster and kinship care.

In the United States, on September 30, 2014, approximately 402,378 children and adolescents resided in foster care, with approximately 28% in care with extended family members. Furthermore, estimates suggest that more than 600,000 individual children resided in foster care during the preceding 12 months and that approximately 4 times as many children and teens live in informal, unregulated kinship care. These children are, by and large, the children of the indigent, and 70% have a documented history of child abuse or neglect. However, children enter foster or kinship care after experiencing many other severe childhood adversities and trauma that can result in toxic stress and negatively affect health and well-being. More than 80% have been exposed to high levels of violence in their homes or communities, with more than 40% living in homes with active domestic violence at the time of removal. Close to one-half (48%) have a caregiver with a significant mental health impairment, and rates of parental substance and alcohol abuse are enormous, ranging up to 80% for the youngest children. These children have often had multiple caregivers even before removal and have not experienced the predictable, responsive parenting that promotes well-being. Despite such high levels of family dysfunction, removal from their family of origin and all that is familiar is emotionally traumatic for almost all children. Placement in foster or kinship care is intended to nurture and heal children while facilitating the rehabilitation of their families. In reality, foster care has become a system of last resort for the most vulnerable children and challenging families.

Most pediatric practitioners will encounter children and adolescents in foster or kinship care, or otherwise involved with child welfare, during the course of their practice; thus, it is important to be familiar with the effects of and treatment for child abuse and neglect, as well as the effects of early childhood trauma, removal, and placement in foster or kinship care on children, adolescents, and their families.

## SUMMARY OF KEY LEGISLATION

The foster care system seems always to be in a state of flux, burdened by huge caseloads, birth families with multiple intractable problems, inadequate funding, and complex and often conflicting bureaucratic, legal, and ethical demands. The recognition that separating children from their families only to leave them lingering in foster care without permanency was harmful to children, together with burgeoning costs, led to several attempts at reforming child welfare. In 1980 the Adoption

Assistance and Child Welfare Act (PL 96–272) mandated states to provide preventive services (eg, counseling, child care, parenting education, drug rehabilitation) to avert the removal of children from their birth families. Agencies were also mandated to conduct semiannual case reviews and to develop permanency plans within 18 months of placement. In an effort to move children out of the system, adoption subsidies were funded so that a marginal family income would be less of a hindrance to the adoption of children out of foster care. After enactment of PL 96–272 the size of the foster care population transiently declined until the cocaine epidemic led to a dramatic increase in the number of very young children in foster care in the late 1980s and early 1990s.

More recent federal legislation, rooted in emerging research and knowledge about the effect of foster care, childhood trauma, and lack of permanency, now largely defines the goals and operations of foster care. First, the Adoption and Safe Families Act (ASFA) of 1997 (PL 105–89) shifted the emphasis in child welfare toward the health and safety of the child and timely permanency planning. States are now obligated to pursue termination of parental rights for any child who has been in foster care for 15 of the prior 22 months, unless there is a compelling reason not to, such as impending reunification. Under ASFA, adoption subsidies were further enhanced, leading to a surge in adoptions in many states in the late 1990s and the early years of this century. The shorter timelines for permanency and termination of parental rights competed with the goal to reunify children with their families and led to the concept of *concurrent planning* for reunification and alternative permanency arrangements, now the hallmark of foster care work.

The second piece of legislation, the Chafee Foster Care Independence Act of 1999, allowed states the option of extending certain benefits, such as Medicaid, to youth aging out of foster care until they turned 21 years of age. Although many states took advantage of this option to enhance resources for adolescents in their independent living programs, it had less effect than other legislation because it was largely optional and inadequately funded.

During the period between 1995 and 2007, several studies reported that children and adolescents achieve more stable placement in kinship care and kin caregivers report fewer behavioral problems. This resulted in an increased emphasis on assessing and using extended family and *kin* as potential placement resources and a dramatic increase (300%) in kinship care placements during the period between 1995 and 2005. Two major pieces of child welfare legislation, the Fostering Connections to Success and Increasing Adoptions Act of 2008 (PL 110–351) ([www.fosteringconnections.org](http://www.fosteringconnections.org)), and the CAPTA Reauthorization Act of 2010 (PL 111–320) addressed the issues of kinship care, independent living, education, tribal foster care, and adoption supports for children in foster care. Foster care agencies must identify kinship resources at entry to foster care, promote and support kinship care, maintain children in their schools of origin, and support Native American tribes in keeping children within their own foster care systems. Resources for youth with a goal of independent living were also increased.

Of particular relevance to pediatric professionals, the Fostering Connections Act, the Child and Family Services Improvement and Innovation Act (PL 112–34) and the Patient Protection and Affordable Care Act (ACA) (PL 111–148) specifically address health care services and resources for children in foster care. Together, these federal laws require states to develop health oversight systems for children in foster care, monitor and treat emotional trauma, coordinate health care, monitor psychotropic medication use, connect children with medical homes, and measure outcomes. The ACA, in particular, grants those who emancipate from foster care at age 18 years or older automatic Medicaid eligibility until age 26 years.

### TRENDS IN OUT-OF-HOME CARE

Legislative and policy changes and scientific studies ultimately affect foster care practice. With the emphasis on kinship care, increasing numbers of children are entering foster care for very short stays while the child welfare agency attempts to identify and investigate kinship resources. The definition of kin has expanded to include nonrelatives with some familiarity with the child or family. Children residing in kinship homes achieve permanency in these placements at a higher rate than those in foster care, although an unknown percentage of kinship homes disrupt, leading to subsequent foster or other kin care placement.

Adoptions out of foster care peaked in the early part of the millennium. The children who remain in care awaiting adoption are older, minority, part of large sibling groups, or disabled. In some locales, parental methamphetamine abuse has become an increasingly important reason for removing children. The system has become more focused on the effect of childhood trauma and evidence-based interventions to treat children and families, although resources are often scarce. Foster parents remain the major therapeutic intervention of the foster care system, and there are some elegant studies about specific education and supports for foster parents and birth parents that improve outcomes for children, although they have yet to be adopted widely. A recent study that looked at child welfare trends over the past decade demonstrated that child maltreatment referrals have increased but foster care admissions have decreased. During this time frame, the complexity of children in foster care has increased as measured by the larger number of children with multiple forms of maltreatment and diagnosed as emotionally disturbed.

### RISK FACTORS FOR PLACEMENT

Families whose children reside in foster care are, in general, impoverished and living on the fringes of society, with few social supports. Child neglect, including neglect of basic nutritional needs, educational and medical neglect, and lack of supervision, is the most commonly cited reason for placement. Reports of child physical abuse and sexual abuse have declined in the past decade but, along with abandonment, remain reasons for placement. More children, however, reportedly experience multiple forms of maltreatment, although it is unclear whether this reflects a true increase or improved reporting. Although child abuse

and neglect occur in all sociodemographic groups, young people placed in foster care come from the most economically deprived segments of society; thus, extreme poverty remains the pervasive common factor underlying foster care placement. Parental mental illness, substance abuse, active domestic violence, and criminal activity permeate the environments in which children have lived before removal. More than 80% of young children entering foster care have a parent who abuses drugs, alcohol, or both. Many children come from homes and neighborhoods in which drug sales and the presence of drug paraphernalia are common. National data indicate that 48% of parents have a mental illness and 10% are cognitively impaired. Before foster care, 44% of children were living in homes with active domestic violence, and 84% experienced significant levels of violence in their homes, schools, or neighborhoods. In one national dataset, child protective services caseworkers identified 80% of birth parents as having significantly impaired parenting skills at the time of the child protective services investigation. Other social stressors in these families include single parenthood, lack of education, and unemployment. Approximately one-third of birth parents admit to being abused or neglected as children, and approximately the same number spent time in foster care. Removal of a child often occurs after prolonged involvement with social service agencies, including child protective services, when preventive strategies have been exhausted and the child's health and safety are at imminent risk.

Early childhood trauma or multiple adverse childhood experiences and chronic stress have been shown in multiple studies to be associated with very poor long-term mental health, developmental, and physical health outcomes. Trauma and chronic stress, especially in the absence of protective factors, alter the neurobiology of the brain, especially in the young child, affecting those areas involved in cognition, rational thought, emotional regulation, activity level, and the relationship between thought and emotion. (See Chapter 68, Children Exposed to Adverse Childhood Experiences.) Thus, children entering foster care, with their cumulative and often chronic adverse experiences and early life traumas, are a group with immense emotional, developmental, and physical health needs. Studies on resiliency and recovery from traumatic experiences are just now accumulating, but early data indicate that children need stability in nurturing and responsive families and communities for healing after such experiences.

### FOSTER CARE SYSTEM

The foster care system, simple in its conception of providing needy children with nurturing families, is in fact a complex bureaucracy. Federal legislation determines patterns of funding and regulatory guidelines, but responsibility for the structure and implementation of foster care programs resides with state social service agencies, which may delegate daily management to county or private child welfare agencies.

#### Role of Caseworkers

Each child welfare agency retains the responsibility for hiring caseworkers and training foster families.



There are 2 foster care systems, public and private. In the public system, children are placed in care of the public agency that hires and trains both caseworkers and foster parents. The private system in each state consists of individual foster care agencies that hire and train their own caseworkers and foster parents. The public system has administrative oversight of the private system. In recent years, there has been a move toward privatization, despite occasional reports of poor training and oversight of such agencies. Child welfare casework is a demanding job requiring multiple skills. Although the professional demands of casework are more commensurate with master's-level social work skills, casework positions are entry-level jobs in most child welfare agencies, requiring no more than 2 years of college education. As advocates for the biologic family, caseworkers must engage the parent around the care of their child while undertaking a *diligent effort* to rehabilitate the parent or parents, ensuring the accessibility of whatever educational or service resources are necessary (eg, housing, counseling, medical care, drug and alcohol rehabilitation) for reunification. Meanwhile, they must also coordinate educational, developmental, medical, and mental health services for children and teens in their care. When birth parents are noncompliant or unable to undertake the work necessary for reunification, caseworkers have the delicate task of supporting them through the process of developing an alternate permanency plan and enabling the child to develop secure attachments and a sense of belonging in a different family than the family of origin. Caseworkers also recruit, train, monitor, annually recertify, and investigate minor complaints about foster homes.

Caseworkers must have a working familiarity with the legal system in their state, particularly the family court and juvenile justice systems. Within 72 hours of removal of the child from the home, the foster care agency's attorney working with the caseworker must prepare a petition for the court documenting the reasons for removal. Many children are returned to the birth parents within this time frame if the court finds insufficient basis for the removal. When the child or adolescent remains in foster care the caseworker must return to court at intervals to provide ongoing documentation for the continuation of placement and to detail their own efforts at rehabilitation of parents, reunification, and alternate permanency planning. Children may have multiple caseworkers while in foster care. Initially, they have an investigative caseworker, but they are transitioned to a foster care caseworker in approximately 90 days. This caseworker is also assigned to the birth parents. Caseworker turnover is high in most systems, so even when a child stays on a specific foster care team, he or she may transition through several caseworkers. If a child is freed for adoption, the case moves to an adoption team. A youth preparing for emancipation may transition to an independent living team. Each team transition involves a change in caseworker. Multiple transitions add to the losses children experience and can be frustrating in terms of case continuity.

### Other Child Advocates

Representation of children in foster care in court varies by state. Currently, about 30 states require the appointment of attorneys for abused and neglected children. In other states, the dependency court may appoint a guardian ad litem who may or may not be an attorney. The court may also designate a court-appointed special advocate (CASA) on behalf of the child in particularly difficult cases, although CASAs are not available in every state or community. As trained volunteers who are not attorneys, CASAs devote many hours to investigating the child's circumstances for presentation to the court. In some states, CASAs are the nonattorney guardians ad litem. Youth in foster care who are also involved with the juvenile justice system may lose legal representation after their probation ends, but hearings in dependency court will continue, with or without legal representation for the youth, on a prescribed schedule as long as the youth is in foster care. Pediatricians caring for children in foster care may wish to develop an understanding of the laws governing child representation in dependency court in their state, or at least determine whether their patients who are in foster care have representation.

### Termination of Parental Rights

Legally, parents retain guardianship of their children who are residing in the *care and custody* of the state or county commissioner of social services. Guardianship can only be terminated as part of a legal process, in which the commissioner then becomes the child's legal guardian until the child either reaches the age of majority or is adopted. Parents sometimes choose to surrender their children for adoption, but more often, termination of parental rights (TPR) occurs involuntarily after all efforts at reunification have failed. The TPR process can take years, during which time concurrent, but conflicting, efforts at reunification and alternative permanency planning occur. The time constraints imposed by ASFA legislation on beginning the TPR process and the increased focus on children's health and safety were intended to shorten the time between placement and TPR (and thus adoption) for children for whom reunification is not an option.

### CHILDREN IN FOSTER CARE

Entry into foster care is fraught with uncertainty, upheaval, and losses for children and for parents. The family, no matter how dysfunctional, is the center of the child's world. The child or adolescent is removed from family and all that is familiar. Except for the youngest infants, removal is an emotionally traumatizing experience for almost all children. Nonetheless, it is required for the child's health and safety, and in fact it is only after removal that some children and teens feel safe for the very first time.

Child protective services are now required by federal law to identify kinship resources before placement in nonrelative foster care. However, in emergent removals, agencies may first place children in a shelter or an emergency foster home pending the availability of a traditional foster home. Most foster parents are kind and welcoming but unfamiliar to the child.



Placement with kin caregivers can be less traumatic if the child already has a meaningful relationship with them. Within the first few days the child meets a variety of strangers, from child protective service personnel and foster care caseworkers to police officers, health care providers, and members of the foster home. Little privacy is afforded, and most children, grieving the loss of their home and families, are uncertain when they will see them again, are afraid to ask questions, and feel alone and isolated. Most child welfare professionals view this period as one of traumatic grief for the overwhelmed and confused child. Some children will externalize that grief, while others internalize it and seem compliant and passive. As children and teens adjust to their new circumstances, some will act out their anger, frustration, and sadness. Children with severe trauma histories may have developed certain behaviors that were adaptive in their previous environments but are highly maladaptive in their new environments. Most children are simply overwhelmed by feelings they do not understand and cannot express in healthier ways or control. Pediatric professionals can help caregivers understand children's behaviors and grief responses in terms of their trauma experiences. The American Academy of Pediatrics (AAP) has produced a guidebook on *Helping Foster and Adoptive Families Cope With Trauma*.

Children removed from their families spend varying lengths of time in foster care. Although many children (approximately 50%) cycle through foster care in weeks to months, approximately 10% to 20% remain in the system for years—as their families repeatedly fail to meet the goals set for reunification—and resist other permanency options. In 2014, 48% of children were in care for fewer than 12 months, but this may not have included, in some states, those who spent a few days in care but never reached the status of court adjudication. The mean length of stay in foster care was 22 months, whereas the median was 13 months. In 2014, 17% of children had been in foster care for more than 3 years and 8% for more than 5 years. The largest determinant of length of stay is the biologic family's level of cooperation with the individualized case plan for their child or children, although reports indicate that minorities, older children, and children with severe behavioral and developmental disabilities are almost twice as likely to remain in care. The average length of stay in the foster care system has declined from its high of just more than 5 years to approximately 2.5 years, attributed in part to increased efforts at reunification, greater dependence on relatives as resources, and more intensive permanency planning.

Longer stays in foster care are associated with a reduced likelihood of reunification and an increased number of placements. Changes in foster care placement are almost always traumatic for children, given that each transition involves a loss that reinforces feelings of rejection and worthlessness. Approximately 50% of children and teens in foster care will experience more than 1 placement, with approximately 25% having 3 or more placements. Reasons for disrupted placements vary; however, most frequently, a child's behavior problems are beyond the skills of a particular foster parent or deteriorate to the point at which the

child needs a higher level of care. Stable foster or kinship care is associated with improved outcomes. Less often, placements disrupt because foster parents retire, become ill or die, feel threatened by the birth parent, or move out of the child's community. Some placement changes occur in order to reunify siblings. Approximately 20% of all foster homes close each year, and about half of this number are closed by child welfare agencies for inadequate care.

Although the genders are fairly equally represented in foster care, the preponderance of children of black and mixed racial heritage in out-of-home care is high, reflecting, in part, their numbers in the poorer segments of society. As foster care numbers have declined 25% over the last decade, the numbers of African-American children have declined even more (about 40%) as child welfare has focused on reducing bias in investigation and removal. However, concern exists that the overrepresentation of minority children in foster care reflects overselection in investigation and removal. In 2014, 24% were black/non-Hispanic, 20% were Hispanic, 6% were multiracial or of other races, and 45% were white. The average age of a child in foster care in 2014 was 7.5 years. Although 53% of children live in nonrelative foster care and 13% reside in preadoptive homes, 24% reside in kinship homes and 8% live in group home or residential care. Unaccompanied refugee minors, especially from Central America, Africa, and Haiti, represent a very small proportion of the total foster care population.

Uncertainty, powerlessness, and guilt pervade the life of the child in foster care. Children in foster care often deny awareness of the reason for placement, and younger children may blame themselves for the disruption of their families. Children do not know how long they will be in care, whether their parent will arrive for visits, or when their parent will get out of jail or rehabilitation. Most children worry about the well-being of their parents and siblings. Birth parents may make promises they do not or cannot keep. Children are sometimes discharged from foster care or transitioned between placements without preparation. Other children tease them about being in foster care, contributing to their already poor self-regard and sense of alienation. Younger children and infants quickly form attachments to foster parents and may view their less frequently seen birth parent as a stranger. Differences in parenting style, as well as outright conflict between birth parents and current caregivers, creates confusion for children and teens.

## ADOLESCENTS IN FOSTER CARE

Adolescents in foster care are a varied group; most enter foster care through juvenile detention or Persons in Need of Supervision (PINS) petitions. Those placed through PINS petitions are placed because they have failed to attend school or have repeatedly run away from home or defied curfew or otherwise placed themselves at risk. Occasionally, teens are placed when a parent is unable to afford appropriate mental health care. Some adolescents have grown up in foster care, and this group is likely to have experienced a variety of foster care settings over time. Some members of this group are intellectually disabled or developmentally

delayed, with significant behavior issues. They may have lingered in care because a suitable adoptive home was never identified. Pregnant or parenting teens are a small group who may be living with their children in foster care or placed separately if they have significant mental health issues or constitute a risk to their offspring. A small group enters foster care as emancipated refugee minors, having immigrated to the United States from a variety of war-torn countries after surviving war, rape, injury, or the death of their families. Most emancipated refugee minor teens are now arriving from various regions of Central America.

Most adolescents in foster care reside in group homes or residential treatment facilities where their activities are restricted, their education is structured, and they receive mental health services and substance abuse treatment, if needed. The outcomes of residential and group home care have not been adequately studied, and little is known about the prevalence of evidence-based treatment in such settings. A minority of teens in foster care reside in foster families. In general, adolescents in foster care have had adverse life experiences similar to those of younger children entering foster care but have also experienced many transitions and engaged in high-risk behaviors, including substance abuse, sexual activity, school truancy, and petty criminal mischief.

Adolescents in foster care are less likely to be adopted than younger children. When they do leave foster care, they do so to return home or because they *age out* at age 18 years (an increasing number of states allow teens who are in school or job training to remain in foster care until age 21 years), run away, or are moved to another agency or placement setting (residential care or group home care, jail, or inpatient mental health or drug and alcohol treatment). Foster care caseworkers are charged with preparing adolescents who are aging out of care for independent living by offering them education regarding finances, job training, and health insurance. However, resources for independent living education are limited, transitional services are few, and youth aging out of care often find their way back to their family of origin if they have no sense of belonging elsewhere. Foster or kin families who remain invested in youth are their best resource, and youth who identify and remain connected to adult mentors seem to fare better. A recent study showed that about half of teens can form a stable attachment relationship to a long-term foster caregiver despite ongoing unstable attachment to their birth parent.

Little is known about the outcomes of youth who have aged out, and what is known is discouraging. There are no studies that look at the spectrum of young adults who once lived in foster care. In the few prevalence studies available, young adults who are a decade removed from foster care are underemployed and undereducated, have difficulty with trust in intimate relationships, and blame the child welfare system for the disruption of their families. In prevalence studies, adults with a history of foster care are over-represented among the homeless and the incarcerated. It is not known, in general, whether young adults who were adopted fare better than those who remained in foster care or reunified or lived with kinship caregivers.

Adolescence is the time during which the individual is supposed to form a stable identity rooted in self-esteem, a sense of autonomy rooted in self-efficacy, and a larger sense of commitment and comfort in relatedness to peers. For young people in foster care, especially minority youth, negative self-concept, lack of self-esteem, and a lack of self-efficacy are likely outcomes because of early adverse experiences, the accrual of multiple losses over time, and a sense of helpless dependence developed from living in the uncertain world of foster care. Early abuse and neglect coupled with impaired caregiving, repeated separation and losses, unpredictability, and a lack of role models for healthy relationships result in a high prevalence of young adults who are isolated, alienated, dependent, and prone to distrust.

## VISITATION

For the child who remains in foster care, even in a stable placement, major issues must be addressed. Although consistent visitation with the biologic family is the best predictor of reunification, visits are laden with difficulty for the child. The tenor of the parent-child relationship is variable. Children who have been abused or severely neglected by their parents may not feel safe even in a supervised visitation setting. Birth parents may attempt to sabotage the relationship of the child with his or her current caregivers, and vice versa. Parents may visit inconsistently, which is confusing and frightening for children. When the parent does come, the visit ends with the child reliving the initial separation from his or her parent. When the parent fails to show, feelings of rejection and abandonment are reinforced.

Visitation usually progresses through stages, beginning with visits supervised by caseworkers in a neutral setting. Visits then transition to the parent's home, where they may be monitored before eventually becoming unsupervised. Kinship placement may allow for more frequent contact with the birth parent, but kin caregivers may also be in a particularly difficult situation regarding visitation if they harbor resentment toward the birth parent, are conflicted about visitation, or have to enforce court-ordered restrictions to which the parent and other relatives object.

Evidence is mounting for models of visitation in which a mental health professional provides child-parent psychotherapy or child-parent interactive therapy. Such models focus on helping the parent identify the child's cues, understand his or her developmental capacities, practice parenting skills learned in court-ordered parenting education, and respond to the child in an appropriate manner. This is time and labor intensive but has increased successful reunification in those communities that have adopted it. Another promising model is Visitation Coaching, in which trained visitation specialists prepare birth parents for visits, help the parents stay on track during the visit, and debrief with them afterward.

## FOSTER FAMILIES

Foster families are the major therapeutic intervention and the unsung heroes of the foster care system. Most of these families are warm, caring, dedicated

individuals who open their homes to society's most fragile and needy children, taking them into their own families and nurturing them through multiple crises. Although foster parents vary in the skills they bring to caring for children, they are generally motivated by religious conviction, altruism, or personal need. They tend to be *child centered*, often having raised children of their own, and see foster care as a mission because of their love for children. Some families become foster parents as a path to adoption, although a guarantee that a child placed with them will become eligible for adoption seldom exists. Foster parents are usually married, have a middle or lower-middle income, come from tradition-rich backgrounds, are deeply religious, and have a fairly open definition of who constitutes family. A very small percentage of foster parents are same-sex couples. Almost every state allows same-sex couples to foster and adopt, although at this writing there remains at least one state that only allows one member of a same-sex couple to adopt. Approximately 5% of foster families have specialized training or skills and act as resources for severely emotionally disturbed or medically fragile children. Many states now have designated skilled homes that provide care for children with human immunodeficiency virus (HIV) infection or other complex medical problems.

Reimbursement for foster parenting varies widely. Families are paid a daily *board rate* for each child in their care. The rate, set by individual states, is determined by the child's age and health needs and the complexity of the parenting tasks. Average monthly board rates hover around approximately \$400 and are expected to cover food, shelter, personal needs, recreation, and most transportation and educational costs. A study from 2008 showed that board subsidies cover about two-thirds of the cost of caring for a child and that most foster parents "chip in" their own funds. Many agencies reimburse for some transportation (involving medical or mental health visits) and pay an additional stipend for clothing. The highest foster family board reimbursements are for children with extremely complex medical conditions or severe behavioral and emotional issues; these may exceed \$1,000 per month in foster family care. Approximately 15% of children in foster care, mostly adolescents, reside in residential or group home placements, the most costly form of care, which can cost upward of \$100,000 per child annually.

Recruitment, adequate training, and retention of suitable foster families are some of the most compelling tasks facing child welfare agencies. Agencies are supposed to provide potential foster parents with education in the areas of child development, child abuse and neglect, behavior problems, discipline, safety issues, and their roles in relation to the agency and birth families, but training is often minimal. Certification is not supposed to occur until the agency has conducted a home visit, a criminal background check, and a review of the state's child abuse registry. Agencies lack adequate staff to scrutinize foster homes carefully, and annual recertification is less rigorous than the original certification process. Several studies have shown that increased education and support for foster parents can have a dramatic positive effect on children. Currently,

there are only a few localities that have the resources for such intensive efforts. Most communities do not even require foster parents to participate in an evidence-based parenting education program before or while fostering. Although there has been an emphasis on trauma training for foster parents and caseworkers, many agencies continue to provide the bare minimum in terms of education and support.

Boundaries are blurred in the foster care system in terms of authority, responsibility, and accountability. Foster families retain the bulk of the daily responsibility for children and teens but are accountable to caseworkers, the legal system, and the birth family for the child's care. Foster parents may feel excluded from planning on the child's behalf, given that birth parents retain legal custody, child welfare agencies have authority to make decisions on behalf of the child and generate permanency plans, and courts make placement decisions. However powerless, foster families often remain the individual child's strongest advocate.

Foster parents usually have only limited information about children in their care. Placement in a foster home is often regarded as the only necessary therapeutic intervention a child needs, and agencies vary widely in the amount of guidance and services they provide to foster parents and children in their care. Foster families may be overwhelmed, and placements may fail when foster families feel isolated in dealing with a child's complex behavioral and emotional problems. Because of foster home shortages in many areas, particularly large urban centers, most homes maintain the maximum number of children allowed under regulations, further stressing a family's emotional resources. Abuse and neglect occasionally occur in foster or kinship care, and the physician needs to remain alert for signs of inadequate care.

Foster families, like children in foster care, experience multiple separations and losses as children enter and then leave their homes, often for a living situation that the foster parent deems unsuitable. Relationships between foster and birth families range from adversarial to mutually supportive. Foster parents often bear the brunt of a child's anger over a failed visit or a parent's telephone call, or they may be unjustly accused of neglect or abuse by an angry birth parent. They may feel scrutinized, but simultaneously unsupported, by child welfare staff.

## KINSHIP CARE

In the past decade, the numbers of children placed in kinship care increased dramatically (>300%). Unofficial placement with kin caregivers is more common than *relative resource care*, defined as care provided by a relative who has become certified as a foster parent. Although driven by a commitment to maintaining a child within their family of origin, kinship care providers have often made this choice under some duress and with the recognition that a member of their own family, who is often their adult child, has neglected or abused the child. Kin caregivers often are older, are poorer, and have access to fewer resources than foster caregivers. Unless they have become certified foster parents, they are not subject to the same review or oversight as foster caregivers, nor do they have access to the same supports.



Placement with a relative, however, offers significant advantages to children, the most obvious of which is that it maintains their ties with their larger family of origin, their community, and their culture. A few studies have also shown that kinship care is associated with fewer placement disruptions and, in one study, a reduced incidence of abuse or neglect, compared with placement with a nonrelative. Compared with nonrelative foster parents, relative caregivers report that children have fewer behavioral problems. Kin caregivers with marginal incomes have the option of applying for foster care certification in many states, making them eligible for foster care stipends, but with all the oversight of foster care.

### BIRTH FAMILIES

Removal of a child is a traumatic event for the birth parent. For some, the shock of the removal is sufficient to precipitate cooperation with child welfare, family court, and prescribed therapies, resulting in speedy reunification. Approximately one-half of children in foster care are returned to their birth families within the first 6 months. For other families, even the removal of a child does not alter ingrained patterns of substance abuse, violence, and child neglect.

Parents, while battling addiction, mental illness, and poverty, often have to contend with feelings of guilt, powerlessness, inadequacy, anger, frustration, and resentment when children are removed. Even though they retain legal custody, their contact with their children is constrained, with only several hours of supervised visitation per week initially. Parents may fail to show up for visitation, whether because of substance use, mental illness, guilt, the pain of separation, fear of confronting their child or children, or barriers such as transportation.

Although one of the goals of the foster care system is reunification, and although caseworkers are mandated to provide a range of services supporting this goal, some birth parents become locked in an adversarial relationship with child welfare staff, resentfully refusing all help offered. In the past, some parents effectively abandoned their children to the system, maintaining contact just sufficient to prevent termination of their rights. Many of these same parents refused to surrender their children for adoption, even when reunification was clearly not an option. The ASFA legislation has made the TPR process easier in such situations. This legislation also reinforces the concept of open adoptions, thought to benefit the child by providing some ongoing limited supervised contact with the family of origin.

### DEVELOPMENTAL AND EDUCATIONAL ISSUES

Multiple studies have shown that approximately 60% of young children entering foster care have developmental delays, especially in the areas of language, social, and self-help skills, although they have been shown to benefit from placement in a nurturing foster home and early intervention services. Before foster care placement, children and teens have experienced high rates of absenteeism, suspension, school failure, grade

retention, and multiple school transitions. Children and youth in foster care are an educationally vulnerable population that continues to perform below grade level (75%), perform poorly on standardized testing, and exhibit significant behavior issues. Forty-four percent of children and youth in foster care are in special education settings, one-half for behavioral concerns. Stable placement in foster care has been shown to result in predictable school attendance for the first time and is often accompanied by improved academic performance for younger children. A national study of 20,000 young adults who had aged out of foster care in 1998 showed that only 35% graduated from high school and only 11% went on to college or vocational school; 37% of foster teens in another study dropped out of high school. Of seniors in high school who were also in foster care, 65% said that a parent or guardian had never attended a parent-teacher conference. Teens in foster care are as likely to drop out or attain a general education degree as to graduate from high school.

### OUTCOMES FOR CHILDREN IN FOSTER CARE

Foster care and its outcomes for children remain mixed. Minority children remain over-represented in foster care. Just more than 60% of children exiting foster care were reunited with their parent or caregiver, 15% were placed with kin, 19% were adopted, 10% aged out of foster care, and the remaining 3% were mostly transferred to the care of other agencies. The overall recidivism (return to foster care) rate is 20% during the first year after reunification but approaches 30% for infants.

The children in foster care who are eventually adopted are usually adopted by their foster parent (56%) or by a member of their extended family (30%). Almost all adoptions out of foster care involve some subsidy, reflecting the child's physical health, mental health, and developmental needs. Many children also retain their Medicaid insurance, although this retention depends on laws in individual states. An adoption subsidy, once granted, continues until the child reaches 18 years of age.

Of the 102,000 children and teens residing in foster care who are available for adoption, only one-half of them have an adoptive home identified. Children awaiting adoptive homes are mostly adolescents, children considered difficult to adopt by virtue of their significant medical or behavioral problems, older minority children, or those who are part of large sibling groups.

More than 20,000 teens and young adults age out of foster care's independent living programs annually; many leave the system without family resources, although some maintain contact with their families of origin or foster families. Current child welfare practice dictates that agencies assist youth in identifying meaningful adult resources as part of the emancipation process. A small percentage (3% of adolescents) are lost to care through elopement, and a similar number become involved with the criminal justice system or are placed in long-term residential care because of



their intellectual disabilities. The outcomes of adolescents leaving foster care for independent living are very poor.

## ADOPTION

The foster family is most often the party to whom the system turns for adoption when reunification is no longer considered an option. Long-term foster care placement is no longer an option under ASFA, although some foster families make a long-term commitment to one or several of the children and teens who have been freed for adoption but for whom belonging in a *forever family* remains an elusive goal. Termination of rights severs the child's legal ties to their birth family, but not their emotional ones, and the child may be torn between conflicting loyalties to birth and adoptive families. Behavioral problems may escalate or resurface around termination or as adoption nears, as the child re-experiences rejection and loss of his or her original family. Agencies work closely with parents who choose to free children for adoption voluntarily to ease the grief and loss for both parents and children, but the child may view voluntary surrender by the parent as the ultimate rejection. On the other hand, for children who have had a limited and chaotic relationship with their birth family, adoption by their foster or kinship parents is often welcomed.

## HEALTH CARE ISSUES AND RECOMMENDATIONS FOR CHILDREN IN FOSTER AND KINSHIP CARE

Children in foster care represent a highly vulnerable, medically complex population, suffering high rates of chronic medical illness, developmental disabilities, educational disorders, dental problems, and behavioral, emotional, and mental health problems. All children in foster care should be considered *children with special health care needs*. In general, for older children and adolescents, these conditions predate placement and are rooted in their experiences of childhood trauma and loss. Prenatal drug exposure, poor maternal nutrition, genetic risks for mental health problems, and poor prenatal care lead to an increased incidence of premature and small-for-gestational-age infants. Postnatally, psychosocial deprivation, poor nutrition, maltreatment, and failure to attend to the child's health and developmental needs exacerbate problems. Limited use of preventive health services, fragmentation of health care, and underimmunization are typical of children entering foster care. Children also enter foster care with a history of complex trauma, including child maltreatment, and toxic stress that adversely affects their physical, emotional, and developmental well-being.

Studies of the health status of the foster care population have yielded fairly bleak results. Approximately 45% have at least 1 chronic medical condition, with approximately one-fourth of all children in care having 3 or more chronic problems. The most commonly encountered diagnoses include growth failure, neurologic problems, dermatologic problems, anemia and hematologic problems, respiratory problems, parasitic infections, asthma, and gastroesophageal problems. Obesity has become the major type of malnutrition

seen in foster care. Hematologic disorders, mostly attributable to anemia, are present in approximately 20% of children. Burn scars or scars from physical abuse are encountered in 10% to 15% of children younger than 12 years. Visual and hearing impairment and neurologic disorders (varying from mild motor delay to seizures and cerebral palsy) are more prevalent in this population and may be the result of prior physical abuse or medical neglect, or they may be the reason for voluntary placement in foster care. Congenital anomalies occur at higher rates than in the general pediatric population. Sexually transmitted infections and other infectious diseases, whether vertically or horizontally transmitted, are more frequent. Approximately 8% of children in foster care are high-cost patients because they are technology dependent, multiply handicapped, or heavy users of ancillary services.

After children enter foster care, their overall health does not seem to improve significantly. A recent study in New York State reported that less than 30% of children in foster care had access to preventive health services before foster care and had minimally improved access while in foster care. The high mobility of this population contributes to poor preventive health care access. The same study reported that this population accesses high-cost services, such as the emergency department and inpatient medical and psychiatric services, at very high rates. Health information on admission is almost universally lacking, and it can be difficult to identify who previously provided medical care. Neither caseworkers nor foster parents have the level of knowledge necessary to serve as the health care manager, yet the system relies on them to perform this complex task. The *Fostering Connections to Success and Increasing Adoptions Act* of 2008 now requires states to develop health care systems for children in foster care, to work with pediatricians to accomplish this, and to promote the medical home as a source of care. This process is, however, in its infancy in most states. Health systems are essential because inadequate health care management underlies the pattern of inadequate, fragmented, and occasionally redundant care received. Medicaid programs in some states limit access to health care because of inadequate financing, delays in payment, and limited numbers of medical subspecialists willing to accept payment. Some Medicaid managed care programs increase access to medical subspecialists for children in foster care but significantly reduce access to mental health care, although this is the most significant health care need of the foster care population. Complex consent and confidentiality procedures required by the foster care system often limit access to health care, delay evaluations and treatment, and confound communication among professionals. Failure to support and educate foster parents about a child's medical, developmental, and mental health needs and failure to secure appropriate treatment can lead to disruptions in placement when foster parents are overwhelmed. As states move toward the implementation of recent legislation, pediatric practitioners may have the opportunity to engage state and county officials to improve outcomes for children in foster care.

The AAP has a number of resources to help pediatric professionals in this role (Box 72-1; see also [www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/healthy-foster-care-america](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/healthy-foster-care-america)).

## OPTIMIZING HEALTH CARE FOR CHILDREN IN FOSTER CARE

Ideally, children in foster care receive their health care in the context of a medical home. For the child in foster care, the medical home ideally includes a foster care–friendly office with providers who understand the effect of childhood trauma and loss on health, development, and well-being; education and support for caregivers in the context of such trauma; and collaboration and communication with child welfare

personnel around a child's needs. The AAP Task Force on Foster Care has developed a number of resources for pediatric professionals regarding health care for children in foster care. Resources, including *Fostering Health: Health Care Standards for Children and Adolescents in Foster Care*, are now available on a Web site, *Healthy Foster Care America* (HFCA) ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/healthy-foster-care-america](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/healthy-foster-care-america)). This resource was designed for use by interdisciplinary professionals, health care providers, and families and children. Because many states have only broad guidelines governing the provision of health services to children in foster care, these detailed standards may be helpful to pediatricians advocating with foster care agencies for improved care. Unfortunately, multiple barriers still

### BOX 72-1 Guidelines for Health Care of Children Entering Foster or Kinship Care

Children entering foster care should have an admission health evaluation, which includes the following:

1. Infants and preverbal children and those with chronic or acute medical problems or on medication should be seen within the first 24 hours whenever possible. All other children and adolescents should receive a health screen within 72 hours of placement to assess and document:
  - Symptoms or signs of child abuse and neglect, with referral as needed
  - Growth parameters
  - Symptoms or signs of acute illness and use of any over-the-counter or prescribed medications
  - Symptoms or signs of chronic illness and use of any over-the-counter or prescribed medications
  - Developmental screening results and referral for evaluation
  - Behavioral and mental health screening results (focusing on suicidal or homicidal ideation or intent, history of aggressive behaviors, substance abuse or addiction) and referral for evaluation
  - Appropriate referral for emergent health issues or sexual abuse evaluation
  - Appropriate treatment of identified issues
  - Health education of foster or kinship caregiver
2. Health information gathering: an ongoing process that begins at admission to foster care
3. Comprehensive health evaluation within 30 days of placement to:
  - Review all available health history
  - Address health concerns
  - Assess adjustment to foster or kinship care, child care, school, and visitation
  - Address behavior concerns and daily schedule
  - Assess growth parameters
  - Review systems
  - Perform a developmental or educational evaluation or review of evaluation or referral for evaluation if not previously completed
- Perform a mental health evaluation or review of evaluation or referral for evaluation if not previously completed
- Perform a complete physical examination
- Screen for signs and symptoms of child abuse and neglect
- Undertake all recommended screening tests (hearing, vision, lead, complete blood count and differential, purified protein derivative, rapid plasma reagin, hepatitis B and C, and HIV)
- Administer immunizations (consider catch-up immunizations if no history is available)
- Provide age-appropriate anticipatory guidance, focusing on transition issues
- Provide appropriate or indicated treatment and referrals, including dental treatment
- Provide communication in writing of health plan to foster care agency
4. Follow-up admission assessment within 60 to 90 days of placement to:
  - Review all available health history, including results of mental health assessment, developmental and educational evaluations, and dental assessment
  - Address interval concerns
  - Document growth parameters
  - Assess adjustment to foster care, child care, school, and visitation
  - Conduct behavioral screening
  - Conduct developmental screening and review
  - Perform a focused physical examination
  - Screen for child abuse and neglect
  - Administer immunizations as indicated
  - Ensure that all referrals and recommended treatments are in process or have been completed
  - Schedule or plan next visit

prevent translation of these guidelines into accessible, effective, and efficient health care. The barriers include inadequate funding, insufficient caseworker and foster family knowledge, limited understanding of the foster care experience by health professionals, and blurred boundaries of responsibility for the health care management of this complex population. The AAP guideline for pediatricians regarding helping foster and adoptive parents cope with trauma in caring for traumatized children is also available on the HFCA Web site.

Every preventive health visit with a child in foster care ideally includes anticipatory guidance around issues specific to foster care: transition issues, visitation issues, the need for routines and reasonable expectations, the effect of prior trauma on emotional

and developmental well-being, and appropriate discipline, among others.

Recommendations for optimizing health care in the medical home and promoting healing for children and adolescents in foster care (Box 72-2) are available on the HFCA Web site and include the following:

1. The pediatrician ideally has a relationship with the foster care agency (Box 72-3) in which established methods of communication and information exchange facilitate the child's care.
2. The caseworker is the case manager, whose responsibilities include the child's health. The caseworker is responsible for obtaining appropriate releases of information and medical consents from the birth family and sharing copies with health providers, including the pediatrician. The pediatrician may wish

### BOX 72-2 Special Considerations in Caring for Children and Adolescents in Foster Care

Every health encounter in foster care requires extra diligence on the part of the physician, including the following:

- Children in foster care are screened for abuse and neglect at each health care encounter, and the physician should bear in mind that inadequate weight gain is often the first sign of inadequate parenting in a foster home.
- Children entering foster care should ideally receive a full mental health (ideally, including trauma history) and behavioral health evaluation performed by professionals in the field of mental health within 60 to 90 days of entry to foster care. If insufficient resources exist in the community, then the pediatric professional may need to be guided by a validated mental health screen, parental concerns, patient trauma history, and clinical judgment about whom to refer for fuller assessment. Periodic monitoring of mental health is encouraged in all populations, but especially those in which adverse experiences continue to accumulate. (See the AAP Mental Health Toolkit at [www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/Addressing-Mental-Health-Concerns-in-Primary-Care-A-Clinicians-Toolkit.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/Addressing-Mental-Health-Concerns-in-Primary-Care-A-Clinicians-Toolkit.aspx).)
- Children entering foster care should ideally receive a full developmental or educational evaluation performed by professionals in the field within 60 to 90 days of entry to foster care. If insufficient resources exist in the community, a validated developmental screening tool or information from school professionals may help the physician to decide which children will benefit from fuller evaluation.
- Children in foster care should be referred for dental care at the first health encounter or by 1 year of age.
- The physician should attend to the quality of the interaction between caregivers and children. The pediatrician may wish to relay concerns to child welfare if a caregiver lacks warmth toward a child, displays a negative affect toward the child, or speaks harshly to or about the child. A child who repeatedly looks to the caregiver for cues or seems fearful in the presence of the caregiver should be an alert of deeper relationship difficulties.
- Because of their importance in the child's life, the physician is encouraged to review recent changes in the child's visitation and contact with birth family, school attendance and performance, and participation in normalizing activities, among other issues.
- Every encounter should be considered an opportunity to immunize the child.
- The physician should maintain a well-documented health record for the child in foster care.
- The pediatrician ideally has a foster care–friendly office and offers anticipatory guidance with an additional focus on normalizing activities, predictable routines, positive parenting strategies, helping children deal with transitions such as visitation, and the effect of trauma and separation on emotional and developmental well-being, among other issues. (See [www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/healthy-foster-care-america](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/healthy-foster-care-america).)
- A system for tracking health care use and compliance for children in foster care is useful for ensuring that children's needs are met and for alerting the agency when noncompliance exists.
- Referrals should be made promptly when an issue is identified.
- Children leaving foster care benefit from a discharge health visit that includes their new caregiver. This visit is an opportunity to summarize health information and transfer it to the new health care provider and caregiver or to the individual patient who is aging out of foster care.
- Systems for information exchange improve coordination of care between the foster care agency and the physician.
- Up-to-date health summaries that include diagnoses, recommended treatment, and follow-up enable the caseworker to keep the health plan current.
- The foster care agency should provide the physician with as complete a health history as is available for the child, copies of appropriate consents and releases, notification of changes in placement or caseworker assignment, and notification of referrals made by the agency shortly after the child enters foster care.

**BOX 72-3 Pediatrician's Role in Caring for Children in Foster Care**

This list is intended to show 2 possible separate, but overlapping, roles for pediatricians. Of course, the pediatrician who is the medical home health care provider may choose to serve any or all of the consulting roles.

**CONSULTANT ROLE FOR CHILD WELFARE AGENCY REGARDING CHILDREN IN FOSTER CARE**

1. Ensure that the foster care agency understands all AAP standards for health care.
2. Help the foster care agency ensure that each child has a medical home with access, insurance, consents, continuity, and other avenues of support.
3. Develop systems for communication and information exchange among caseworkers, mental health professionals, the court system, other health care providers, and school personnel.
4. Provide or refer to health education resources for foster parents, caseworkers, the court system, attorneys, and school personnel.
5. Develop systems for merging health information and planning into child welfare permanency plan.
6. Develop systems for transitioning health care when the child or teen transitions or leaves foster care.
7. Develop systems for tracking patients that include information on their health needs and data, monitoring outcomes, and any other information.

**MEDICAL HOME PROVIDER ROLE FOR CHILDREN IN FOSTER CARE**

1. Deliver care by the AAP Foster Care Standards. Identify and attend to the child's health care needs.
2. Accept patients in foster care and provide a medical home for them.
3. Communicate and coordinate with caseworker, foster parents, school personnel, subspecialists, and the court system regarding individual patients in foster care.
4. Educate the foster parents, caseworkers, or anyone else involved regarding the child's health care needs.
5. Advocate on behalf of patients in foster care to ensure that health care needs are met.
6. Share health information and plan for the child with the caseworkers, foster parents, court system, and older children in foster care.
7. Ensure that information on the patient is transmitted to the appropriate professionals when the patient transitions out of foster care or from one foster care placement to another.
8. Monitor and track the patient's health needs and care.

to become familiar with the foster care agency's guidelines regarding consent and confidentiality. The foster care agency should have the authority to provide consent in the absence of the birth parent. Certain adolescent health issues, such as pregnancy, sexually transmitted infections, birth control, and substance abuse, are governed by separate confidentiality laws in most states.

3. Gathering health information is a challenging task. The caseworkers, who should have contact with the birth parents, are invaluable in this respect, although they may also be stymied by a dearth of contact and of records. A standardized health information form can help with information collection. The pediatrician may have access to information from prior health providers, schools, Regional Health Information Organizations, and immunization registries. In addition to the usual health history, information that should be sought includes prenatal and perinatal history, developmental history, history of early intervention, mental health history including the use of psychotropic medications, growth curves, immunization records, risk factors for HIV, accounts of other vertically transmitted infections, allergies, chronic illnesses, and medications. For older children, additional information should also include any educational or mental health problems. A paucity of such information may exist because the child may not have received adequate services before foster care or may have had multiple providers.

4. Children entering foster care should have a series of health care encounters over the first 3 months (see Box 72-1). Multiple encounters during this transitional phase often reveal more than one isolated evaluation.
5. Routine primary preventive health care should be scheduled according to AAP guidelines, although experts recommend that children in foster care have more frequent monitoring visits because of their health needs and high mobility. Ideally, infants in foster care should receive monthly visits until age 6 months. Toddlers should receive a health visit at 21 months to monitor development and emerging behavior concerns. After age 2 years, children should have a health encounter between annual preventive health visits until they exit foster care.
6. Comprehensive preventive health care for the foster care population requires diligent effort on the part of the physician. Extended appointment slots and a tracking system are strongly suggested. Ideally, the caseworker should inform the physician about changes in placement and casework assignment and about any referrals made by the caseworker. The physician, in turn, provides the caseworker periodic updates around health care encounters to keep the health plan current.
7. Approximately 70% of children and adolescents entering foster care have been physically abused, sexually abused, or neglected. Physicians should be



familiar with the signs and symptoms of abuse and neglect and should screen all children and teens at the time of admission to care. Children with suspected sexual abuse should be referred to a center specializing in child sexual abuse, if one is available, to prevent the trauma of repeated interviews and examinations. Monitoring for abuse or neglect at every health encounter is part of the pediatrician's responsibility and includes addressing concerns about the adequacy of parenting in a foster home. Some red flags for poor care include inadequate weight gain in a foster home (often the first sign of neglect); lack of warmth between the child and the caregiver; hypervigilance by the child around the caregiver; and caregiver reluctance to allow a private conversation between the child and the pediatrician. In addition, ancillary office staff may sometimes witness and should be encouraged to report concerning caregiver-child interactions to the physician. Although poor compliance with recommended health visits may represent scheduling difficulties, it is often a sign of poor overall care in a foster home.

8. Children in foster care have a high prevalence of dental problems, especially dental caries and malocclusion. Changes in placement may result in a lapse in dental care; therefore, continued monitoring of dentition and reminders to foster parents about the importance of routine dental care are important. Referral for dental care should begin at age 1 year.
9. Children entering foster care tend to be underimmunized, even compared with other poor children, and every health encounter should be viewed as an opportunity to immunize a child in foster care.
10. The underuse of routine preventive health care services before foster care placement implies a deficiency of screening for lead, iron deficiency anemia, and tuberculosis exposure. Many children in foster care reside in or have resided in older housing stock, and pica is a commonly encountered behavioral issue in this population, increasing the risk for elevated plasma lead levels. Poor nutrition before foster care places children at risk for iron deficiency anemia and other micronutrient deficiencies; thus, physicians should obtain plasma lead levels and screen all children younger than 6 years for anemia at least annually. Obesity is now a prevalent form of malnutrition, and appropriate diet and exercise should be addressed with caregivers and children. Children entering foster care have an overall obesity rate of 27%. Of obese children who remain in foster care for at least 1 year, only 12% lose weight in care, whereas 7% gain weight. Youth residing in congregate care have higher rates of obesity than other children in care. Menstruating adolescent girls should have annual hemoglobin screening. Universal tuberculosis screening is recommended using the PPD test at admission and every 3 to 5 years thereafter because children may have had high-risk exposures before foster care and visit in high-risk situations (eg, jail) while in foster care. Hemoglobin electrophoresis should be considered in at-risk children with no documentation of sickle cell screening at birth.
11. Maternal lifestyles during pregnancy, including substance abuse and promiscuity, place children in foster care at increased risk for a variety of vertically transmitted infectious diseases, including HIV, hepatitis B and C, congenital syphilis, and herpes. Every child placed in foster care should be screened for these infections early in placement. Up to 80% of young children placed into foster care are at high risk for vertically transmitted HIV infection, but fewer than 10% are screened because of the complexities of risk assessment, obtaining informed consent, and confidentiality barriers. Guidelines for HIV risk assessment and screening of children in foster care vary from state to state. Some agencies use risk-assessment tools to determine a child's risk for HIV infection, although the accuracy of such tools depends on the birth parent's availability and truthfulness. In general the biologic parent retains the right to consent to testing or not, unless the child has been freed for adoption or parental rights have been terminated. Agencies vary in their policies regarding consent procedures when a parent declines screening but the child meets high-risk criteria. Identifying children who are HIV positive is critical to appropriate medical management, including pneumocystis pneumonia prophylaxis, modification of the immunization schedule, and early antiretroviral therapy. Pediatricians may wish to become familiar with the HIV policies in their state and promote appropriate risk assessment and screening for the individual child.
12. Adolescents in foster care also represent a high-risk group for HIV and other sexually transmitted infections, because of either unprotected sex with multiple partners or prior sexual abuse. In general, adolescents in foster care are allowed by law to give consent for HIV testing, unless they are cognitively impaired. Confidentiality laws vary, however. In some states the adolescent has the right to designate who has access to HIV-related information, whereas in others, social service agencies and their representatives have access to such data on any child in their care and custody, including adolescents. Obviously, pediatric professionals need to provide detailed anticipatory guidance around healthy and safe sexuality. Screening for gonorrhea and chlamydia is recommended at admission and at each preventive health care visit. Testing for other sexually transmitted infections should be considered based on history and local epidemiology.
13. Because of the high prevalence of developmental (60% of children <6 years) and educational (45% of children >6 years) problems, screening with the use of standardized instruments is recommended at the time of the comprehensive admission visit, with periodic reassessments at preventive and monitoring visits. Ideally, all children receive a full developmental-educational evaluation within 3 months of placement, but lack of resources

usually precludes this. Developmental delays are most prevalent in communication, social-emotional, and cognitive skills. With services and an appropriate home environment, many children make developmental strides in foster care. For children who are undereducated because of a lack of schooling, catch-up can be dramatic with increased school attendance, although learning disabilities, behavioral disorders, and limited cognitive ability remain major challenges. Upward of 40% qualify for special education services or an educational plan. Some children in foster care qualify for special education for emotional rather than cognitive concerns, given that attentional difficulties, poor impulse control, and aggressive behaviors often preclude placement in a regular classroom. The high prevalence of language disorders (50% to 60% of preschool children) implies that universal hearing and speech evaluations of toddlers and preschool children may be beneficial in identifying children who would benefit from such services. The primary care physician and caseworker ideally maintain contact with the case manager for developmental-educational services and receive copies of all evaluations. Pediatric professionals may be asked to medicate children for presumed attention deficit/hyperactivity disorder (ADHD) but should be aware that inattention, hyperactivity, and distractibility may be behavioral manifestations of prior trauma, anxiety, or depression rather than ADHD and proceed cautiously. (See Chapter 62, Psychotropic Medications in Primary Care Pediatrics.)

14. Mental health care is the greatest health care need of most children in foster care. The prevalence of severe disturbance ranges from 35% to 85%. Children in foster care use both inpatient and outpatient mental health services at rates 15 to 20 times those of other children of similar backgrounds but are still thought to be underserved. Oppositional defiant disorder, ADHD, attachment disorder, and anxiety disorders are the most commonly cited mental health diagnoses for children in foster care. One study in the Midwest reported that 45% of teens in foster care used alcohol or illicit substances in the prior 6 months, whereas 49% acknowledged past use and 35% met criteria for a substance abuse disorder. Those at highest risk are those with conduct disorder or post-traumatic stress disorder and those residing in independent living situations. This may not reflect actual use because youth may have under-reported or the reporting population may not have been adequately representative of all teens in foster care. What is known about the effect of childhood trauma suggests that substance abuse is often a form of self-treatment. Professionals experienced in foster care think that the prevalence and severity of mental health disabilities have increased dramatically in the past decade, although some of this may be attributed to heightened awareness among child welfare, pediatric, and mental health professionals. The burden of early childhood trauma and toxic stress predating foster care

placement is enormous. Entry to foster care and placement in a good home environment may remediate emotional disorders or may exacerbate them because of the trauma of separation from families and the emotional turmoil of living as a child in an uncertain world. Although marijuana is the most commonly abused drug among those in foster care, youth using addictive substances may experience acute withdrawal at entry to foster care. Thus, physicians should screen for emotional and behavioral issues using standardized instruments at admission and at each preventive health and monitoring of care visit. Every child in foster care should ideally have a full mental health evaluation by 2 years of age or within 3 months of placement. Children with newly identified mental health or behavioral issues should be referred to appropriate mental health services, ideally with pediatric mental health providers who use evidence-based, trauma-informed practice. Those children previously involved in the mental health system, including those for whom psychotropic medications have been prescribed, should have a thorough review of the mental health treatment plan, ideally through direct contact with the mental health professionals who previously assessed the child and who prescribed the medication. All children in foster care have to deal with ongoing separation and loss issues, as well as feelings of anger, sadness, rejection, powerlessness, alienation, and guilt. Even children who do not initially seem to need mental health services should be rescreened at intervals to assess for changes in their emotional well-being. Some of the common stressors that upend the lives of children in foster care include inconsistent visitation, resumption of regular visits after a prolonged lapse, cessation of visitation, incarceration of a parent, illness of a foster parent, and being freed for adoption. These critical junctures are times at which resumption of lapsed counseling or increased frequency of counseling visits is beneficial. It may also be challenging for mental health professionals to know which of a child's parents (foster, birth, or kin) should be involved in therapy with the child. The California Evidence-Based Clearinghouse maintains a list of evidence-based therapies for children in foster care and their caregivers ([www.cebc4cw.org](http://www.cebc4cw.org)).

15. Many foster families have a wealth of childrearing experience, but the physician should not presume that knowledge about child development, behavior, discipline, safety, and parenting a traumatized child are adequate. Anticipatory guidance should be a routine part of well-child care and should include issues specific to foster care, such as behavior problems related to visitation and the permanency planning process, significant sleep disorders, confused loyalties, attachment, violence, and coercion. Adolescents should be counseled not only about safe behaviors but also about healthy activities, planning for their future, and developing relationships with adult mentors. Many teens in foster care, fearing yet another disappointment, have exhausted their capacity to

attach to a parental figure, and families need to be offered guidance in promoting attachment relationships with teens in foster care. Pediatric professionals can help foster parents understand the teen's emotional world while supporting an authoritative parenting style. Support for foster families and older children in foster care around transitions and other stressors can stabilize a foster care placement for a child.

16. All medical information, unless specifically prohibited by law, should be shared with the child's caseworker and foster parent and, when not disallowed, with birth parents in appropriate lay language. The caseworker has the responsibility for communicating the information to the birth parent in the likely event that the parent was not present at the medical visit. If possible, the physician should provide a written summary of each health encounter, including the assessment, treatment plan, and any scheduled follow-up. Caseworkers are required to have at least semiannual *Child and Family Service Reviews*, during which health information can be incorporated into planning for the child.
17. In caring for a child in foster care, the primary care physician might sometimes need to assume the role of advocate for appropriate health care for the child.

## PSYCHOTROPIC MEDICATION

The use of psychotropic medication has become controversial in the foster care population. Studies show that children and teens in foster care are more likely to be on psychotropic medications than peers not in foster care. They are also more likely to be on multiple medications and sometimes on multiple medications from the same class. Studies also indicate that psychotropic medications may not match the major symptom of concern or diagnosis. At least 2 states, Texas and New York, have developed comprehensive guidelines regarding the prescription and management of psychotropic medications in the foster care population, and the reader is directed to these or their individual states for further information. In general, psychotropic medications should be used as part of a comprehensive mental health treatment plan and are best prescribed for patients in foster care by a qualified pediatric mental health professional or a primary care physician with extensive foster care experience. A detailed health history, including mental health, behavior, development, trauma history, medication use, social and family history, and a full mental health evaluation should be obtained before beginning medication. Therapy should be initiated with a single agent in the lowest dose for a specific and appropriate mental health diagnosis. Dosage increases should be gradual and closely monitored for efficacy and side effects. Single-agent therapy should be used whenever possible. Close monitoring is the essence of good care for children and teens who are prescribed psychotropic medication. Pediatric professionals also need to be acutely aware that not every child in foster care who presents with school or parent concerns of hyperactivity and inattention has ADHD because such

behaviors may be a manifestation of early childhood trauma experiences. Caution should be exercised before instituting any psychotropic medication. Referral to mental health professionals for evidence-based, trauma-informed mental health evaluation and services is the ideal initial intervention for the child or teen in foster care presenting with emotional and behavioral problems. (See Chapter 62, Psychotropic Medications in Primary Care Pediatrics.)

## SUMMARY

Children and adolescents removed from their families for reasons of health and safety enter foster or kinship care having experienced multiple adversities and trauma that negatively affect their health and well-being. As a result, these children and adolescents have a high prevalence of medical, mental health, developmental, educational, and dental conditions. Pediatricians should use foster care as a window of opportunity in which the child or teen can heal. The pediatrician can provide the medical home while the child or teen is in foster care, following recommended standards of health care to identify and treat all of the child's health needs. The pediatrician should be proactive in engaging child welfare agencies to ensure that health planning is integrated into the child's permanency plan in a meaningful way. Pediatric professionals also have a role in educating child welfare professionals, foster and kinship parents, birth parents, and youth about health issues and in advocating for and coordinating health care to this vulnerable population.

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## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *Connected Kids Clinical Guide* (booklet), American Academy of Pediatrics ([www2.aap.org/connectedkids/ClinicalGuide.pdf](http://www2.aap.org/connectedkids/ClinicalGuide.pdf))
- *Healthy Foster Care America* (Web site), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/healthy-foster-care-america/Pages/default.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/healthy-foster-care-america/Pages/default.aspx))
- *Trauma Guide* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/healthy-foster-care-america/Pages/Trauma-Guide.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/healthy-foster-care-america/Pages/Trauma-Guide.aspx))

### Engaging Patient and Family

- *Fostering Connections* (Web site), National Resource Center for Permanency and Family Connections ([www.nrcpfc.org/fostering\\_connections](http://www.nrcpfc.org/fostering_connections))

### Medical Decision Support

- *Mental Health Screening and Assessment Tools for Primary Care* (chart), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH\\_ScreeningChart.pdf](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH_ScreeningChart.pdf))



- *Pediatric Symptom Checklist* (screen), Bright Futures ([www.brightfutures.org/mentalhealth/pdf/professionals/ped\\_sympton\\_chklst.pdf](http://www.brightfutures.org/mentalhealth/pdf/professionals/ped_sympton_chklst.pdf))
- *Strengths and Difficulties Questionnaires* (Web site) Questionnaire ([www.sdqinfo.com](http://www.sdqinfo.com))
- *Feelings Need Check Ups Too* (booklet), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Children-and-Disasters/Pages/Feelings-Need-Checkups-Too-Toolkit.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Children-and-Disasters/Pages/Feelings-Need-Checkups-Too-Toolkit.aspx))
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- *Tools to Identify CEV* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Medical-Home-for-Children-and-Adolescents-Exposed-to-Violence/Pages/Diagnostic-Tools.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Medical-Home-for-Children-and-Adolescents-Exposed-to-Violence/Pages/Diagnostic-Tools.aspx))
- *Standards of Excellence for Child Welfare Services* (Web page), Child Welfare League of America ([www.cwla.org/our-work/cwla-standards-of-excellence/standards-of-excellence-for-child-welfare-services](http://www.cwla.org/our-work/cwla-standards-of-excellence/standards-of-excellence-for-child-welfare-services))
- *Patient Health Questionnaire-9 Modified for Teens* (questionnaire), American Academy of Pediatrics, in *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* ([shop.aap.org](http://shop.aap.org))
- *Enhancing Pediatric Mental Health Care: Algorithms for Primary Care* (article), American Academy of Pediatrics ([pediatrics.aappublications.org/content/125/Supplement\\_3/S109](http://pediatrics.aappublications.org/content/125/Supplement_3/S109))
- *Screen for Child Anxiety Related Disorders (SCARED): Child Version* (questionnaire), University of Pittsburgh ([www.psychiatry.pitt.edu/sites/default/files/Documents/assessments/SCARED%20Child.pdf](http://www.psychiatry.pitt.edu/sites/default/files/Documents/assessments/SCARED%20Child.pdf))
- *Screen for Child Anxiety Related Disorders (SCARED): Parent Version* (questionnaire), University of Pittsburgh ([www.psychiatry.pitt.edu/sites/default/files/Documents/assessments/SCARED%20Parent.pdf](http://www.psychiatry.pitt.edu/sites/default/files/Documents/assessments/SCARED%20Parent.pdf))
- *The CRAFFT Screening Tool* (questionnaire), Center for Adolescent Substance Abuse Research ([www.ceasar-boston.org/CRAFFT/index.php](http://www.ceasar-boston.org/CRAFFT/index.php))

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- American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health, Committee on Early Childhood, Adoption, and Dependent Care, and Section on Developmental and Behavioral Pediatrics. Early childhood adversity, toxic stress, and the role of the pediatrician: translating developmental science into lifelong health. *Pediatrics*. 2012;129(1):e224–e231 ([pediatrics.aappublications.org/content/129/1/e224](http://pediatrics.aappublications.org/content/129/1/e224))
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### SUGGESTED READINGS

*The California Evidence-Based Clearinghouse for Child Welfare*. Available at: [www.cebc4cw.org](http://www.cebc4cw.org)

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## Chapter 73

# CHILDREN IN THE JUVENILE JUSTICE SYSTEM

Robert E. Morris, MD; Evalyn Horowitz, MD

## HISTORY OF THE JUVENILE JUSTICE SYSTEM

Policies and regulations for juvenile detention and rehabilitation in the United States have been refined, then redirected toward newer philosophies, and then returned to older ways. Today's methods for directing behavior and those of 1910 are not unlike. A review of this history provides insights into the opportunities and challenges physicians experience today in interacting with the juvenile justice system.

Under English law, parental control was primary. In 1797, the first New York penitentiary opened. Because the state presumed its potential was to provide rehabilitation, juveniles were brought to criminal court. Community groups began lobbying for children to be



handled separately from adults, and, in 1824, the first House of Refuge for delinquent children was founded in New York. Shortly before the Civil War, in 1851, a separate detention for children younger than 12 years was founded.

The Civil War brought immigrants, poverty, violence, and chaos to the United States. Parents worked long hours, and children ran the streets, causing passage of disorderly conduct laws and more incarceration of youths. Children older than 7 years were housed with adults in jails and prisons. In 1875, the Society for the Prevention of Cruelty to Children was formed, defining child neglect and holding parents responsible. By 1892, a separate juvenile court system was founded.

With the Progressive Era of US history (1900 to 1918) came women's suffrage, child labor laws, and the 8-hour workday. Journalism and political satiric cartoons became a tool for public persuasion, and psychological theories for managing children flourished. These forces helped to shape the rights of incarcerated juveniles, and society began to feel responsible to reform youthful offenders before their criminal activity was entrenched or strengthened through incarceration.

Over the next 75 years, juvenile justice law was honed. Incarcerated girls were separated from boys, and their housing was improved. In most cases, juvenile hearings were conducted apart from adult courts, and proceedings were considered civil rather than judicial cases.

In the late 1960s, in *Kent v the United States*, it was decided that the informal process of determining whether a juvenile should be tried in juvenile or adult court failed to provide sufficient due process protection for children. A year later, an Arizona juvenile court placed a sentinel youth—the Mr Gault case—at 15 years old, in detention until age 21 years for a status offense. (A status offense is behavior that is unique to the juvenile status, such as truancy or running away.) On appeal, the US Supreme Court held, based on Article 5 of the Bill of Rights (ratified in 1791) and the 14th Amendment (ratified in 1868) regarding due process, that children had a right to receive fair treatment under the law, including the following rights:

- To receive notice of charges
- To obtain legal counsel
- To confront and cross-examine their accuser
- To avoid self-incrimination
- To receive a transcript of the proceedings
- To appeal

The 1970s brought several new developments. The 1970 case *In re Winship* held that when a juvenile is held responsible for criminal behavior, the previous standard of a *preponderance of evidence* (ie, the facts indicate the juvenile's behavior was "likely" to be true) now rose to a standard of *beyond a reasonable doubt* (ie, the evidence must be proved beyond any other logical explanation, similar to adult law). The 1971 case *McKeiver v Pennsylvania* found that juveniles charged with a criminal law violation and adjudicated in juvenile court are not entitled to a jury trial. In 1974, Congress passed the Juvenile Delinquency Prevention and Control Act, providing federal funding to states

with community programs to discourage juvenile delinquency. The law created the following:

- The Office of Juvenile Justice and Delinquency Prevention
- The Runaway Youth Program
- The National Institute for Juvenile Justice and Delinquency Prevention

The law required separation of "young and impressionable" juvenile delinquents from convicted adults. Part of the rationale behind the separation of juvenile and adult offenders was the evidence that youth learned to behave as more skillful criminals.

By the late 1980s, violent crime rose, peaking in 1994. Highly publicized shootings and shocking crimes by juveniles led citizens to fear that, for some juveniles, violence was a way of life. Retrospectively, it seems media claims greatly exaggerated the role of juveniles in perpetrating crime. In response to this perception of a crime wave, legislation swung back to "get tough on crime," and the Juvenile Justice Act was amended, allowing states to try younger juveniles as adults for certain violent crimes with resulting lengthy prison sentences. The juvenile justice system became increasingly similar to the adult criminal justice system, reflecting the sentiment that children who commit serious crimes must be held accountable and punished for their crimes, not just "reformed."

Throughout the 50 states, correctional facilities for children, much like those for adults, have vastly different infrastructure and focus. Beyond simply corralling children with aberrant behavior, their management points toward different goals, from simple containment, to punishment, to attempts to model nurturing and rehabilitation. Some systems are centralized and run by the state, including both preadjudication and post-adjudication facilities. Other states have decentralized systems, allowing counties or other jurisdictions to presort and house juveniles during preadjudication, as determined appropriate by the local courts. In nearly all states, depending on age, a youth may be remanded to adult court for certain serious crimes.

## PROCESSING CHILDREN THROUGH THE JUVENILE JUSTICE SYSTEM

The arresting officers are the first "judges" of what is best for the child and community, dealing with non-violent crime based on their best judgment. The officer may issue a "warning" and accompany the child home to discuss with the parents, usually maintaining a record of the contact. Or, the officer may take the child to the police station and ask the parent to come there to discuss the situation.

In cases in which the child does not have a parent or guardian who can or will control her, resides in a house that is not fit to live in, is abused or neglected, or is threatening persons or property, the child may be placed in a community shelter or foster care. For more serious crimes or for a reoffense, the child may be sent to a juvenile hall that generally holds preadjudicated youths; the hall may also be used for short-term incarceration as a punishment or deterrent to further offending or for placement when other release settings have failed.

If the child's offense leads to more than an officer's warning, variable legal processes occur, usually culminating in a juvenile court hearing. Children may not be incarcerated for status offenses. More serious offenses irrelevant to age range from minor offenses such as petty theft or property destruction to more serious crimes involving violence, bodily harm, sexual offenses, and other felonies.

Before disposition, referred to as the hearing, an evaluation of the child is usually performed by a social worker or probation officer who recommends to the judge the appropriate disposition of the case. This may include structured assessment tools, such as the Youth Assessment and Screening Instrument (Orbis Partners, Ottawa, Ontario, Canada); a review of family and school history; mental or physical health records; past criminal history; and statements from parents, friends, teachers, faith leaders, or the victim, plus the youth's own statement. At this point, it is important for the youth's physician to provide records, to support and encourage the parents and child, and to make suggestions about actions parents or community members may take to advocate for the child and to provide support and control of the child after release.

At the disposition hearing, the sentence depends on the offense and the state in which the crime occurred. The child may be released to the parent or guardian, community service may be required, and there may be ongoing supervision by a probation officer, social workers, or other youth workers, or multisystemic therapy. A youth on probation in the community may be required to attend a special, segregated school. Courts often order individual, group, or family counseling, structured after-school programs, or weekend or other short-term detention in a county restricted, locked facility. If there is a splintered or unsupportive family situation, the youth can be made a ward of the court, allowing the judge to control the care in an out-of-home or locked setting, assisting with the treatment and guidance of the minor and limiting or ending parental control.

Children who reoffend—in some cases, those who are involved in gang activity or who have little or no family support—may then be placed in a community juvenile “jail” or “ranch.” As noted previously, these facilities can be centralized (regional, or even state run) or community centered and may involve schooling. Depending on the offense, detention may vary in duration, with eventual release to family or foster care on probation.

States have developed increasingly more severe programs for violent or recalcitrant children (eg, high-discipline or “boot” camps). These military-like work camps seek to provide a highly structured environment with the aim of instilling responsibility and self-discipline. Such programs have failed uniformly, sometimes with tragic consequences. One such example was the death resulting from staff neglect of a 14-year-old boy sent to a Florida boot camp for trespassing at a school—a probation and parole violation related to a previous charge, but itself a relatively minor offense. After this 2006 episode, the Florida boot camps were closed.

There are far fewer resources and less discretion in adult courts, whose primary goal is to punish offenders and protect society. If a child is remanded directly to adult criminal court because of repeated crimes or a serious crime and convicted in a jury trial, the youth will receive an adult sentence, including possibly life without parole in a case of murder. This sentencing practice is currently being challenged in the Florida supreme court.

## HEALTH CARE IN JUVENILE JUSTICE FACILITIES

In the 1970s, congressional attempts at health care reform called for standards of care throughout the health care system, leading the American Medical Association (AMA) to investigate health care standards in correctional institutions. The AMA found a lack of standards, and this resulted in the development of correctional health care standards by various national organizations. By the 1990s, medical, dental, and mental health standards became formalized for correctional institutions of all sizes and in all jurisdictions. However, accreditation and adherence to the standards is voluntary. Often, compliance with standards is forced on states or jails through lawsuits brought by federal authorities or prisoner rights organizations.

Health care is considered a universal right within the United States for all incarcerated persons. In most cases, the physicians are caring and resourceful and may receive special certification as correctional health care workers. In those facilities that have chosen to undergo accreditation, the care often exceeds community standards. Tools for rationale of care (see *Tools for Practice* at the end of this chapter) have been developed by these organizations in collaboration with the AMA and with members of the recognized certification boards. For example, the Institute for Medical Quality in California ([www.imq.org](http://www.imq.org)) in conjunction with the California Medical Association and the National Commission on Correctional Healthcare ([www.ncchc.org](http://www.ncchc.org)) regularly network with physicians in updating their published guidelines for correctional medical, mental health, dental, and administrative functions. In some facilities, the physicians are contracted through private correctional health care corporations. If these companies do not maintain the standards of accreditation, they may lose their contract or can be fined by the governmental organization responsible for the facility.

The facility health care workers may be on site for a portion or the entirety of the day, depending on the size and population of the facility. It is well known that one poor outcome will cause years of financial and political upheaval for the facility; thus, the correctional administration generally facilitates access to health care, enabling the incarcerated individuals to receive appropriate health benefits. However, in some institutions, because of budget, culture, and lack of oversight, health care may be “doled out” in parcels. Federal Medicaid rules currently prohibit payment for the incarcerated inside their facilities, and many private insurance companies also decline to cover care of the incarcerated; thus, health care costs can strain the

budgets of the governmental jurisdiction responsible for the facility. More assistance, although not uniformly, is offered for hospitalizations, but not for urgent care or emergency visits. Difficulties in providing care often occur because of insufficient internal staffing during lean funding years and when outside specialty services are needed. Specialty health care outside the facility is expensive, even though fees are often discounted: inmates may be seen as threatening to the outside physicians' other patients, and payment to providers can be slow. For these reasons, some private specialty physicians refuse to see prisoners in their practices. University or public facilities often become the default care providers. In the absence of mandatory national adherence to accreditation standards, variability in quality of care for small, decentralized, and state-run juvenile detention centers persists.

Recently, a series of initiatives has taken juvenile detention into the "case management" realm in many parts of the United States. Behavioral therapy with preinterment and postinterment options, including counseling, group homes, work camps, and locked schools, has been considered part of juvenile justice. Therapeutic interventions, such as cognitive behavioral therapy, multisystemic therapy, functional family therapy, or dialectical behavioral therapy, attempt to redirect erring children to a more productive lifestyle. In the past decade, attempts were made to classify these programs by effectiveness, with some recent decreases in overall juvenile incarceration. The states have various levels of commitment. One example is the Impact program in Boulder, CO, which uses evidence-based motivational and behavioral intervention skills to engage clients in treatment to stabilize their mental health and substance abuse. Other states have no apparent interventional involvement beyond physical incarceration. Community development of youth programs involving local mental health, recreational, and social service workers have the potential to be plausible rehabilitation programs.

The concept of *restorative justice* involves reciprocal relationships between the offended community and the youth offender, who is required to engage in activities to restore the community to its preoffense status. In return, the community takes some responsibility for rehabilitation and care of the youth.

## IDENTIFICATION OF YOUTHS AT RISK FOR FUTURE DELINQUENCY

Delinquent children rarely begin to offend without an early history of maladaptive behavior, often beginning before age 12 years. Behavioral problems are often present for at least 5 years before coming to the attention of juvenile courts; in one study, one-third of offenders were diagnosed with disruptive behavior by age 13 years. Specific professional help is rarely provided to these children.

Many factors may contribute to later delinquency. In early life, these may include fetal complications, brain injury, toxic exposures to chemicals, experiences of violence in the environment, physical or mental abuse, difficult temperament, and hyperactivity. In addition, a wide variety of pathologic family structures

and functions may contribute to future delinquency. Toddlers and older children who exhibit aggression, repeated lying, risk taking, lack of empathy, or animal cruelty, and those whose parents practice harsh, erratic discipline are at risk for later delinquency. Substance use disorder, depression, victimization, and exposure to violence are often proximal to overt delinquency. Problems at school, peer rejection, association with deviant peers, unemployment, school dropout, and residence in neighborhoods with gang warfare, high rates of violence and crime, prostitution, or visible illegal substance or alcohol use compound the risk for delinquency. When children are carrying weapons, dealing drugs, or involved in gangs, their behavior becomes obviously delinquent. The pediatrician who is alert to risk factors can make early referrals to programs that work to prevent later delinquency. A number of "TIPPS" for assessing youth at risk for delinquency can be found in the American Academy of Pediatrics (AAP) publication, *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit*. Chapter 34, Promoting Mental Health. This discusses promotion of mental health, surveillance of children and families for mental health problems, and psychosocial screening of children and their families. Chapter 139, Disruptive Behavior and Aggression, offers clinical guidance for the care of children with disruptive behavior and aggression. Children also benefit from evaluation and appropriate treatment of traumatic stress syndromes, as many had experienced horrific situations before becoming incarcerated.

Because there is evidence that very early childhood experiences have profound and long-lasting effects on an individual's behavior throughout life, programs early in life, even during the prenatal period, may be the most effective interventions to provide protection from developing delinquency. Olds and others developed a model program of home visits by trained public health nurses; these visits begin during the prenatal period and continue until the child is 18 months old. Follow-up conducted years after the program, in some cases 20 years later, has shown multiple benefits for these children, including significantly reduced delinquency and improved school outcomes compared with controls.

A Chicago-based program that provided an enhanced grade school experience and comprehensive family services from kindergarten through third grade resulted in higher rates of school completion, more college attendance, and fewer felony arrests compared with the control group. This intervention began later in life and had fewer positive effects compared with the early childhood nurse visitors. The Rand Corporation has published information about a number of effective preschool programs.

Pediatricians faced with disruptive children who are living with dysfunctional families with overly punitive parents or families suffering from major disruptions may benefit from referral to a parenting program. These have a number of titles, including New Beginnings, Positive Parenting, and Parent Training programs. Chapter 61, Psychosocial Therapies, provides a list of evidence-based programs for young children with social-emotional problems and their families.



Children who have begun to offend against laws are more likely to become involved in the juvenile justice system, which will largely determine both sanctions and rehabilitation programs to which they are referred. Some programs include outpatient therapy. For example, multisystemic treatment of antisocial behavior in children and adolescents is variably available in the United States. The treatment uses trained case managers and their supervisors to evaluate the challenges facing the child and family. Plans are developed in conjunction with the family, instituted, and evaluated, usually over a 3- to 5-month period. The program is action oriented, with a solution for each problem. For example, if the teenager is not getting to school, a person—relative, coach, or neighbor—is identified to be responsible for getting the youth to school. Curfew problems could be addressed by engaging the youth in appropriate evening activities. Individual cognitive behavioral therapy, drug counseling, and effective parenting training are often part of the program. The case manager should be available by phone 24 hours a day for crises. A team of several case managers and their supervisors meets weekly to address successes and failures. Family meetings with the case manager are conducted at a time convenient for the family. Under some circumstances, the child's pediatrician may be asked to participate; for example, there could be a health condition that affects the youth and requires optimal medical management so that the youth can regularly attend school.

A number of states and local jurisdictions have programs aimed at young offenders 10 to 12 years old. All programs involve case managers and provide integrated services (see Box 73-1).

#### **BOX 73-1 Typical Services Offered by Intensive Outpatient Rehabilitation Programs Provided to Young Offenders**

- Crisis management services
- Comprehensive assessment of all aspects of the child: physical health, mental health, substance abuse, school functioning, family economic problems or strengths, vocational needs, family and social functioning
- Skills training for youth and family
- Cognitive problem solving
- Self-control methods
- Behavior cognitive training
- Family training
- Tutoring
- School involvement
- Adult role models

From Burns BJ, Howell JC, Wilg JK, et al. Treatment, services and intervention programs for child delinquents. Child Delinquency Bulletin Series March, 2003; NCJ 193410. Washington DC: US Department of Justice, Office of Justice Programs, Office of Juvenile Justice and Delinquency Prevention. Available at: [www.ncjrs.gov/html/ojjdp/193410/contents.html](http://www.ncjrs.gov/html/ojjdp/193410/contents.html). Accessed October 30, 2015.

Several other evidence-based outpatient programs are therapeutic foster care, dialectic behavior therapy, functional family therapy, and motivational enhancement therapy; these are available for children with certain mental health diagnoses or who have committed certain types of crimes. These therapies are sometimes used while the children are incarcerated.

#### **Children Incarcerated for a First Offense**

For more involved delinquents who are incarcerated, rehabilitation becomes part of the therapeutic milieu. Generally, smaller institutions with only 25 to 30 children have better outcomes and less violence, as demonstrated by the Missouri State System and others.

A variety of theoretical frameworks support programs for incarcerated children. A widely accepted set of principles that guide rehabilitation programs for incarcerated children involve attention to the criminogenic risks of each youth (see Box 73-2). Evidence shows that the criminogenic risks are the most important issues to address during rehabilitation, while excluding other factors often found in delinquent youth that research shows are not relevant to reducing recidivism. When addressing criminogenic risks, counselors must consider the degree of risk to reoffend (ie, high-risk youths, defined as those with more criminogenic risk factors in their history, require more intensive services). Also important during rehabilitation are the principles of responsivity (ie, interactions are tailored to learning styles and abilities) and professional override (ie, trained professional staff make decisions based on the current situation) (see Box 73-2). A logical inference of this theoretical framework supports the notion that low-risk youths require little or no services because they are unlikely to reoffend.

Despite the enthusiasm for using this criminogenic risk evaluation during incarceration, Lipsey recently reported on a meta-analytic overview designed to assess the factors that make up effective rehabilitation interventions. He found that the criminogenic risk principles were important first steps, but that programs were most effective if done in the child's community as opposed to during incarceration. The data showed that the best interventions included cognitive behavioral therapy, mentoring, and group counseling. Not surprisingly, high-quality programs worked best for high-risk offenders, and these programs were usually research or demonstration programs. Evaluations of

#### **BOX 73-2 Criminogenic Risks for Youths to Reoffend**

- History of antisocial behavior or low self-control
- Personal attitudes, values, or beliefs supportive of crime
- Procriminal associates and isolation from anticriminal peers and role models
- Current dysfunctional family features
- Callous personality factors
- Substance abuse



routine practices generally had about half the effect of high-quality programs because they were not conducted with fidelity to the original program.

Aggression is a significant issue for many incarcerated children. Aggressive replacement training uses a number of short problems that illustrate issues in moral reasoning, anger control, or prosocial skill building. Small groups of youths are guided through these exercises by trained staff over about a 10-week period.

A complete discussion of various rehabilitation strategies in use throughout the United States is beyond the scope of this chapter. However, many physicians believe that all effective interventions must, at a minimum, address the intrinsic and extrinsic factors known as criminogenic risks to effectively reduce the risk for reoffending.

Pediatricians are unlikely to be extensively involved in the lives of children who are incarcerated. However, the parents may turn to their child's doctor for advice. Alternatively, the youths may form an attachment to physicians or therapists after repeated or extended incarcerations, especially if these doctors also work outside of the juvenile detention facility in the community. Because many youths (as many as 50% or more) have co-occurring mental health and substance use disorders, the National Commission on Correctional Health Care Standards for Health Services in Juvenile Detention and Confinement Facilities mandate that youths with these co-occurring disorders should be assessed and managed by appropriate physicians while in detention. The parents should be urged to advocate for treatment of these disorders while their child is incarcerated and prepare to continue treatment for the youth after release. Parents, even if they are geographically far removed from their child, should work to maintain contact with both their child and the staff at the correctional facility. When a child with a substance abuse disorder is released, the court will often mandate that the child attend a substance abuse treatment program that the court or jurisdiction will reimburse. Generally, it is the probation or parole officer who is responsible for ensuring that the youth attends any mandated treatment programs after release.

Failure to ensure continuing care after release remains a major problem for incarcerated children. When pediatricians become aware that their patient will soon be released, they should contact the facility's medical department to plan for a smooth transition back to community care. The youth's probation or parole officer can be a useful ally in working to keep the youth in care. Most correctional facilities provide the medical and mental health records to the child's community pediatrician if the child and parents consent. If the child is released on psychotropic medication, the pediatrician may play an important role in helping the child remain on medication until psychiatric evaluation.

## ADVOCATING FOR THE HEALTH CARE OF CHILDREN IN THE JUVENILE JUSTICE SYSTEM

The AAP Committee on Adolescence published a comprehensive policy statement in 2011 that advocates for involvement of the child's community pediatrician

during and after incarceration so that medical and behavioral health is optimized. Therefore, the institution should refer the youth back to the physician in the community. When the youth does not have an existing community physician, the institutional staff should work with the family (or foster family), parole agents, local public health agencies, and community physicians to develop a plan to coordinate care after release. The institutional staff, in planning for the youth's release, should help the youth and family apply for appropriate health insurance. In some jurisdictions, children in the correctional system remain in the foster care system. If this is the case, the youth may be eligible for Medicaid insurance beyond the usual cutoff age. The AAP policy statement also discusses the need for adequate funding of medical and behavioral health and education in juvenile facilities and suggests that pediatricians should advocate for a reversal of federal law to allow Medicaid and other insurance funding of incarcerated juveniles. Finally, pediatricians working individually and through their organizations should advocate for delinquency intervention programs in the community to decrease the number of incarcerated children.

## CONCLUSION

Pediatricians can help to prevent delinquency by providing parenting support to at-risk families and treatment to young children with disruptive behavior. After a child becomes involved with the juvenile justice system, pediatricians can provide support and counseling for the child's parents as the child traverses the system from arrest to adjudication, sanctions, and rehabilitation. Pediatricians who understand the juvenile justice system in their geographic location are prepared to assist delinquent youths and their families before, during, and after incarceration. Juvenile correctional facilities generally welcome the involvement of the child's community pediatrician if the parents and child consent.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *Connected Kids Clinical Guide* (booklet), American Academy of Pediatrics ([www2.aap.org/connectedkids/ClinicalGuide.pdf](http://www2.aap.org/connectedkids/ClinicalGuide.pdf))
- *Trauma Guide* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/healthy-foster-care-america/Pages/Trauma-Guide.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/healthy-foster-care-america/Pages/Trauma-Guide.aspx))

### Medical Decision Support

- *The CRAFFT Screening Tool* (questionnaire), Center for Adolescent Substance Abuse Research ([www.ceasar-boston.org/CRAFFT/index.php](http://www.ceasar-boston.org/CRAFFT/index.php))
- *Data Collection and Technical Assistance Tool (DCTAT)* (reporting system), Office of Juvenile Justice and Delinquency Prevention National Training and Technical Assistance Center ([www.ojjdp-dctat.org](http://www.ojjdp-dctat.org))
- *Enhancing Pediatric Mental Health Care: Algorithms for Primary Care* (article), *Pediatrics*, Vol 125, Suppl 3, 2010 ([pediatrics.aappublications.org/content/125/Supplement\\_3/S109](http://pediatrics.aappublications.org/content/125/Supplement_3/S109))
- *Evidence-Based Child and Adolescent Psychosocial Interventions* (chart), PracticeWise, American Academy

of Pediatrics ([www.aap.org/en-us/Documents/CRP\\_sychosocialInterventions.pdf](http://www.aap.org/en-us/Documents/CRP_sychosocialInterventions.pdf))

- *Feelings Need Check Ups Too* (booklet), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/children-and-disasters/Documents/Feelings-Need-Checkups-Toolkit\\_0823.pdf](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/children-and-disasters/Documents/Feelings-Need-Checkups-Toolkit_0823.pdf))
- *Mental Health Screening and Assessment Tools for Primary Care* (chart), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH\\_ScreeningChart.pdf](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH_ScreeningChart.pdf))
- *Modified Patient Health Questionnaire-9* (screen), Pfizer, Inc and Columbia University, in *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* ([shop.aap.org](http://shop.aap.org))
- *Pediatric Symptom Checklist* (screen), Bright Futures ([www.brightfutures.org/mentalhealth/pdf/professionals/ped\\_sympton\\_chklst.pdf](http://www.brightfutures.org/mentalhealth/pdf/professionals/ped_sympton_chklst.pdf))
- *Practice Parameter for the Assessment and Treatment of Youth in Juvenile Detention and Correctional Facilities* (article), *Journal of the American Academy of Child & Adolescent Psychiatry*, Vol 44, Issue 10, 2005
- *Screen for Child Anxiety Related Disorders (SCARED): Child Version* (questionnaire), University of Pittsburgh ([www.psychiatry.pitt.edu/sites/default/files/Documents/assessments/SCARED%20Child.pdf](http://www.psychiatry.pitt.edu/sites/default/files/Documents/assessments/SCARED%20Child.pdf))
- *Screen for Child Anxiety Related Disorders (SCARED): Parent Version* (questionnaire), University of Pittsburgh ([www.psychiatry.pitt.edu/sites/default/files/Documents/assessments/SCARED%20Parent.pdf](http://www.psychiatry.pitt.edu/sites/default/files/Documents/assessments/SCARED%20Parent.pdf))
- *Strengths and Difficulties Questionnaires* (screen) ([www.sdqinfo.com](http://www.sdqinfo.com))
- *The Resilience Project: Clinical Assessment Tools* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/resilience/Pages/Clinical-Assessment-Tools.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/resilience/Pages/Clinical-Assessment-Tools.aspx))

### AAP POLICY

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## Chapter 74

# CHILDREN IN SELF-CARE

Robert Needleman, MD

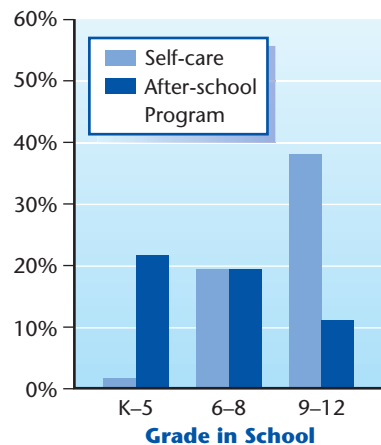
The after-school hours trouble many parents. They may be uncomfortable leaving children to care for themselves or in the care of siblings, but quality after-school programs are often inaccessible or expensive. Pediatricians, aware of the potential stresses and dangers associated with self-care, can help parents find acceptable solutions.

Many, if not most, parents are at work when school lets out (Figure 74-1). According to a 2009 mail survey of nearly 30,000 households selected to mirror the US population, 15% of children aged 5 to 18 participate in after-school programs, while 26% spend time each week in self-care. With increasing age, self-care rises while after-school program participation falls (Figure 74-2). The true prevalence of unsupervised care is difficult to estimate. Parents may under-report children in self-care to avoid stigma or feared legal action; they may even be reluctant to disclose self-care arrangements to their child's doctor.

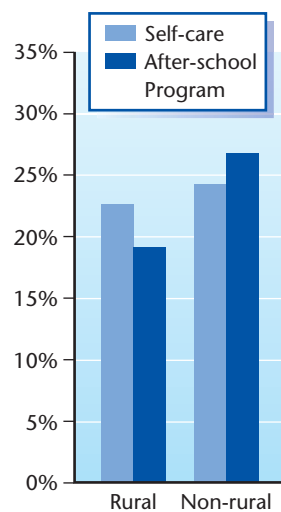
Self-care represents a spectrum of arrangements. For example, a parent may phone home every hour, may be reachable by phone at any time, reachable only in emergencies, or not reachable at all. The nearest responsible neighbor may be across the hall or a mile away. A child may be home alone, or in the care of an older sibling, or caring for a younger one. Many children spend the after-school hours at the library, which may provide a formal after-school program, informal guidance by a concerned librarian, or merely grudging toleration. Some children go to friends' homes, where there may or may not be a responsible adult. Others meet at the mall, in parks, or elsewhere in the community. It is typical for a child to experience different arrangements on different days of the week, and for arrangements to change from year to year, if not more frequently. Similarly, after-school programs vary in content and quality. This variability needs to be taken into account when counseling parents and when interpreting the research literature.

## EFFECTS OF SELF-CARE: SCHOOL-AGED CHILDREN

Many parents and professionals believe that self-care is harmful. James Garbarino, a well-known researcher and author, has suggested that children in self-care struggle in 4 ways: they feel bad (emotional effects), act badly (high-risk behaviors), develop badly (academic deficits), and are treated badly (risk of victimization).



**Figure 74-1** After-school care, by grade. All numbers are based on findings from the 2014 *America After 3PM* survey. (Reprinted with permission from Afterschool Alliance [2014]. <http://afterschoolalliance.org>.)



**Figure 74-2** After-school care, both parents in work-force, by location. All numbers are based on findings from the 2014 *America After 3PM* survey. (Reprinted with permission from Afterschool Alliance [2014]. <http://afterschoolalliance.org>.)

The research literature, however, is equivocal. For example, studies are divided on the question of whether children are frightened when they stay at home alone. Not surprisingly, children who live in the relatively safe suburbs are less prone to fearfulness than children from violent urban neighborhoods. Increased time in self-care has been associated with poorer classroom adjustment, but not consistently with poorer grades. Children's self-esteem, locus of control, peer relationships, and classroom conduct are similar in self-care and parent care, although some parents report that self-care builds self-confidence.

The diversity of findings likely reflects differences among the populations studied, the definitions of self-care, and the selection of outcome measures. Most of

the studies are cross-sectional, limiting conclusions about causality. Multiple factors go into determining whether a child might be exposed to aftercare and, if so, what type. The salient factors are likely to be hard to quantify, such as a parent's sense that his child is mature enough to handle self-care, or the strength of a parent's guilt or fear about leaving her child unsupervised. There are no randomized studies to provide definitive answers. For children with special health care needs, issues of mobility, communication, judgment, and potential need for administration of medication are likely to be salient, but little if any published information is available to guide the pediatrician and parent in weighing these factors.

## EFFECTS OF SELF-CARE: TEENS

One area in which there is a fairly high level of agreement concerns the association of less adult supervision with increased substance use and other risk-taking behaviors among teens. At home after school is a common time and place for unsupervised youths to take drugs and have sex. Adolescents unsupervised at friends' homes are more at risk of succumbing to negative peer pressure than those who stay in their own homes. Those who hang out with friends without a set location are at greatest risk. Nonpermissive parenting style, family rules prohibiting substance use, and increased supervision (eg, through required telephone calls) lower, but do not eliminate, the risk associated with self-care.

Early adolescents may be particularly vulnerable to the stresses and temptations of self-care. Compared with parent-supervised eighth graders, those in self-care for 11 or more hours per week reported 1.5 to 2 times higher levels of risk taking, anger, family conflict, peer influence, attendance at parties, and substance use. Moreover, earlier initiation of self-care was associated with increased rates of these negative behaviors. For example, 11% of eighth graders in parental care reported heavy alcohol use, compared with 19.5% in self-care since junior high school, and 25.5% in self-care since elementary school. While some adolescents report feeling increased self-reliance and responsibility, others experience loneliness and sadness.

## AFTER-SCHOOL PROGRAMS

Alternatives to self-care include care provided by relatives or hired sitters or structured after-school programs. The Afterschool Alliance ([www.afterschoolalliance.org](http://www.afterschoolalliance.org)), an advocacy group, has compiled numerous studies linking participation in after-school programs with higher academic achievement and less deviant and risky behavior. One critical review of the data, however, was less enthusiastic. Programs aimed at obesity prevention are increasingly common, and the evidence for beneficial effects on activity level, fitness, and lipids is growing. Benefits may extend also beyond the children. High-quality after-school programming may make it easier for parents to remain in the workforce. Conversely, parents often cite inadequate after-school arrangements as a significant source of stress.

The number of after-school programs has grown rapidly in the past decade. For example, the US



Department of Education's 21st Century Community Learning Centers funds after-school academic enrichment programs in low-income neighborhoods across the country. However, while participation in after-school programs is higher among ethnic minority children than in the population as a whole, the need for additional programs in low-income areas is also greater. For example, 61% of African American parents report that they would enroll their children if they had access to programs, compared with 38% of parents overall. Safety, transportation, and access to information about programs are also barriers for underserved groups. Children and youth with special health care needs (CYSHCN) may have special difficulty accessing after-school programs, which may not be equipped to accommodate their medical, developmental, or behavioral needs. Information on program accessibility is not readily available, nor is it tracked nationally. Nonetheless, CYSHCN do participate in a wide range of community activities, dictated more by their personal characteristics than by their category of special need.

As with self-care arrangements, there is great diversity among after-school programs. Cost and quality vary widely. Among indices of program quality, warm interpersonal relationships between staff members and child participants appear to be especially important, supporting both academic and personal-social outcomes. The goal for all children is not merely attendance at after-school programs, but fully engaged participation.

## DECISIONS ABOUT AFTER-SCHOOL CARE

Parents' decisions about after-school care can be relatively straightforward, or can be difficult and fraught with guilt and worry. Self-care can be a positive experience, assuming the child is mature enough, the neighborhood safe enough, and the hours short enough. Box 74-1 presents a common-sense checklist to help parents decide if self-care is right for their children. Many states have adopted guidelines that attempt to help draw the line between acceptable unsupervised care and neglect, although the wording of these documents is sometimes vague; actual laws on the subject exist in only a few states. In many communities, service agencies offer "survival training" to prepare children to cope with self-care. The efficacy of such classes has been questioned, however.

## THE PEDIATRICIAN'S ROLE

Parents are hungry for information about after-school care. Among parents using a family help desk at an urban clinic, the most frequent need (29% of visits) was information about after-school programs. Pediatricians can ask about child care arrangements at health supervision visits for children of all ages. These discussions may be particularly important with respect to children with special health care needs. Parents of school-aged and adolescent children may have questions about care outside of school hours, but may hesitate to bring up the subject. Parents need to understand that the effect of self-care varies depending

### BOX 74-1 Signs of Readiness for Self-care

- **Age:** A sensible 8-year-old should be fine for a half hour or so once in a while, but most children will not be mature enough to manage being alone on a regular basis until they are 10 or 11 years of age.
- **Interests:** The child is able to keep busy reading, drawing, making music, doing homework, and playing with toys among other things (not just watching television or playing video games).
- **Memory:** The child remembers common-sense safety rules, such as not opening the door and not telling telephone callers that he is alone.
- **Common sense:** The child can relate how to respond to a fire, gas leak, or other emergency.
- **Caution:** The child generally shows caution, thinking before acting. This is particularly important for young teens, who are tempted to engage in sexual and other experimentation.
- **Comfort:** The child seems to be truly OK with the idea of being home alone.

on the child and the specific circumstances. Pediatricians can help parents think through the issues as they apply to their individual situation. Awareness of the increased rates of substance use and other risk taking among unsupervised adolescents may lead parents to reconsider self-care for their teenage children. To date, the efficacy of pediatric guidance about out-of-school care has not been demonstrated empirically.

Pediatricians can also help connect parents with community resources such as high-quality after-school programs, latchkey training programs, and telephone "warm lines" that provide safe human contact and support to children alone after school. Locally, service agencies such as the YMCA and Boys and Girls Clubs are likely to be good resources, as are public libraries. Guidance and referrals can be found through the Child Care Resource and Referral Programs in most states, easily located through a national toll-free number (1-800-424-2246). The National Child Care Information Center ([www.icfi.com/insights/projects/families-and-communities/national-child-care-information-center](http://www.icfi.com/insights/projects/families-and-communities/national-child-care-information-center)), has a computerized listing; however, it may be difficult to find online. Where local services are inadequate, pediatricians can play an important role in advocating for more high-quality out-of-school programs for school-aged children and adolescents. Finally, pediatricians can advise parents to learn about the Federal Child and Dependent Care tax credit, which applies to all children younger than 13 years of age and to older children who have special health care needs, and which can substantially lower the cost of after-school care.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Choosing Quality Child Care: What's Best for Your Family?* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))



## AAP POLICY

American Academy of Pediatrics Committee on Early Childhood, Adoption, and Dependent Care. Quality early education and child care from birth to kindergarten. *Pediatrics*. 2005;115(1):187–191. Reaffirmed December 2009 ([pediatrics.aappublications.org/content/115/1/187](http://pediatrics.aappublications.org/content/115/1/187))

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## Chapter 75

# GAY- AND LESBIAN-PARENTED FAMILIES

Cindy Schorzman, MD; Melanie A. Gold, DO

Family structures in the United States, as in much of the world, are changing. The traditional structure of a working father and a homemaker mother with 1 or more children no longer describes most of the families in the United States. Alternate family structures are diverse. Unmarried couples may live together with or without children. Single mothers and fathers, stepparents, and blended families may be created by design, by divorce, or by death. These family structures may include gay men and lesbian women, with or without children.

Recent estimates of children in the United States with at least 1 gay or lesbian parent range from 1 to 10 million. According to US Census data from 2000, same-gender couples live in more than 99% of US counties, and nearly 25% of all same-gender couples are raising children. These estimates are limited by barriers to obtaining accurate numbers, in part, because many gay and lesbian parents fear discrimination and do not report their sexual orientation.

Specific research on issues regarding gay and lesbian parenting has been driven by legal issues, chiefly concerning custody. This research has focused on assessing the development and well-being of children raised by gay or lesbian parents. (Box 75-1 contains a glossary of terms.)

## CHILD DEVELOPMENT IN THE CONTEXT OF GAY- AND LESBIAN-PARENTED FAMILIES

No consistent differences exist in the psychological profiles of children raised by gay and lesbian parents compared with children raised by heterosexual parents.

## BOX 75-1 Glossary of Terms

- **Gender identity:** Personal sense of one's integral maleness or femaleness
- **Gender roles:** Behaviors within a culture commonly thought to be associated with maleness or femaleness
- **Homophobia:** Unprovoked fear, distrust, or hatred of lesbian, gay, or bisexual persons
- **Sex:** Classification as either male or female based on external anatomy such as the penis and testes or vulva
- **Sexual orientation:** Persistent pattern of emotional or physical attraction to members of the same or opposite sex. Included are homosexuality (same-sex attractions), bisexuality (attractions to members of both sexes), and heterosexuality (opposite-sex attractions)

During the 1990s, research became increasingly available on children conceived in the context of gay and lesbian relationships.

Children who have gay or lesbian parents do not differ from children who have heterosexual parents in terms of psychological health, social relationships, or cognitive or emotional functioning. The best predictors of child behavior problems are higher levels of parental stress and interparental conflict.

The sexual orientation of parents has not been found to affect the gender identity of their children. Furthermore, adolescent sexual orientation is similar among adolescents raised by gay or lesbian parents and those raised by heterosexual parents. Children raised by lesbian mothers are more likely to explore same-gender sexual relationships, particularly if their childhood family environment is characterized by an openness and acceptance of lesbian and gay relationships. However, these children are no more likely than the children of heterosexual mothers to identify themselves as gay or lesbian.

Pediatricians should be aware that the psychological experience might differ for children raised in heterosexual versus homosexual parenting environments. The greatest difference reported is bullying. Although no overall increase in stigmatization may exist, children of nonheterosexual couples are more likely than those of heterosexual couples to be teased and to be concerned about being harassed. Some children experience shame because of conflicts between loyalty to their parent and the perceived need to conceal their parents' sexual orientation for self-preservation.

The conclusion that research to date demonstrates few discernible differences in parenting based on parental sexual orientation is not universally accepted. Outspoken critics of the literature have highlighted the limitations of these studies, including small sample size (these studies may be more likely to conclude that no differences exist when some differences do indeed exist), lack of generalizability (participants were mostly lesbian, white, well-educated, and upper-middle class), lack of randomization of study populations, and lack of appropriate comparison groups.

However, no studies have been published in the peer-reviewed literature that demonstrate differences

in a child's development based on the sexual orientation of the parents or show any evidence that gay and lesbian parenting causes significant deleterious effects on children. Taken together, the overwhelming number of studies (despite their limitations) demonstrate no differences in children's development based on the sexual orientation of their parent or parents.

The American Academy of Pediatrics (AAP) Committee on Psychosocial Aspects of Child and Family Health reviewed the available data on children of gay and lesbian parents and published a technical report in 2002 with a policy statement supporting co-parent or second-parent adoption by same-gender parents. Their conclusion was that "a growing body of scientific literature demonstrates that children who grow up with 1 or 2 gay and/or lesbian parents fare as well in emotional, cognitive, social, and sexual functioning as do children whose parents are heterosexual," and that "children's optimal development seems to be influenced more by the nature of the relationships and interactions within the family unit than by the particular structural form it takes." Despite some reservations based on the limitations of the studies, such as those noted previously, the Committee thought that the weight of the available evidence was strong enough to demonstrate "that there is no systematic difference between gay and nongay parents in emotional health, parenting skills, and attitudes toward parenting."

## SOCIAL RELATIONSHIPS AND DISCLOSURE

All children, especially as they reach school age, must develop a wide range of relationships outside their nuclear family. Children who have gay or lesbian parents may be assumed to be homosexual and experience stigmatization by peers when their parents' sexual orientations become known. The difference between dominant cultural values in the community and the family constellation may be distressing to children and add to their social isolation and uncomfortable relationships with peers. Gay and lesbian parents often fear that school staff will treat their children differently if they disclose their sexual orientation. As a result, many parents help children learn *differential disclosure*—to be open about their parents' sexual orientation to some people but not to others—so that harassment and social isolation can be minimized. Parents should understand that both secrecy and disclosure represent potential burdens for their children. Further, many families parented by gay and lesbian parents, including those families created by adoption, may be transracial in nature. Physicians should note that this can further contribute to the stressors experienced by the child and the family.

Physicians can act as supportive listeners for families with difficult interactions with their school system. Some physicians with long-standing school relationships may choose to act as intermediaries between the family and the school to help make the educational environment more supportive. They can educate child care providers and teachers and encourage schools to include information about diverse family structures in their libraries and curricula. Physicians can also

encourage families to develop a social support network in the interest of their children. In many larger cities, an active network of gay and lesbian parents works to create an environment of peer support in which their children feel more accepted than they might in other social contexts. Parent-child discussion or playgroups, story hours, and periodic communal meals have helped some parents and children seeking mutual support.

## LEGAL ISSUES

Controversy regarding securing legal parental rights for gay and lesbian parents is ongoing. Legislation constantly shifts the parameters of parental rights and responsibilities. For example, laws in the state of Florida changed in September 2010; Florida's Third District Court of Appeals ruled that the previously established statute, which explicitly stated that homosexuals are not eligible to adopt, violated the state constitution. This resulted in single lesbian, gay, and bisexual individuals being able to petition to adopt in that state; however, same-sex couples in Florida are not able to jointly petition to adopt. It is unclear whether a same-sex partner may petition to adopt his or her partner's adopted child. The spectrum of parental rights for lesbian, gay, and bisexual parents ranges from the 29 states and the District of Columbia that have granted adoptions (either individual/single, joint, or second parent) to gay and lesbian individuals as well as same-sex couples, to states such as Mississippi and Utah, where same-sex couples are prohibited from adopting. Many states have no formal statutory policy on adoption by a gay or lesbian person, and this ambiguity often leaves decisions in the hands of individual judges.

Because courts have continuing legal authority to protect children until they reach 18 years of age, most questions of custody can be reopened in any state in which the child resides. A court can determine what custodial arrangement it finds to be in the child's best interest and can remove the child from the home when parental custody is challenged (eg, by a former spouse or grandparents), particularly when a gay or lesbian parent's sexual orientation was unknown in a previous custody decision. Furthermore, even with court precedents declaring that parents cannot be deprived of child custody based solely on parental sexual orientation, a heterosexual parent is still more likely than a gay or lesbian parent to be granted custody and visitation rights unless the heterosexual parent is unavailable or obviously unfit.

In the frequent circumstance that only one person from the same-gender couple is legally recognized as a child's parent, the physician should clarify how responsibility for the medical decisions and consent for treatment for the child will be shared and document this in the medical record. In the event of serious injury, illness, death, or voluntary separation of the legal parent, a prior written agreement giving the other parent power of attorney in making medical decisions for the child is necessary.

In general, when gay or lesbian couples first contemplate raising a child together, they should agree in writing on issues concerning child custody, support, and consent for treatment. Curry, Clifford, and Hertz

give guidelines for writing agreements that specify parental rights and responsibilities. Without a written agreement, nonbiologic or nonadoptive parents may have difficulty proving their status as parents.

## CLINICAL ISSUES IN PROVIDING PEDIATRIC CARE

The challenge for the pediatrician who cares for these children lies in addressing practical concerns faced by individual families. Meeting the needs of children of gay and lesbian parents means addressing the needs of the children themselves, as well as understanding the particular issues within the context of their family as a whole. Gay or lesbian parents may choose not to identify their sexual orientation to their child's pediatrician. They may worry that latent homophobia or bias among professional or nonprofessional staff will jeopardize the care their children receive or that the pediatrician will not honor their confidentiality, particularly if the parents are concerned about legal threats to their custody rights. The challenge for the pediatrician caring for these children often lies in creating an environment in which members of the family feel comfortable enough to disclose and discuss the parents' sexual orientation and the family constellation. Health care professionals have traditionally received little or no training about homosexuality. In fact, evidence suggests that gay and lesbian adults find the health care system to be unresponsive and sometimes antagonistic to their unique needs and concerns.

Little information exists about how lesbian and gay parents view pediatric care. One study found that most gay and lesbian parents perceived that their children received pediatric care that was affirming, supportive, and satisfactory. However, many specific deficiencies were noted, such as heterosexist assumptions on office forms, exclusion of the nonbiologic parent from the evaluation and treatment process, and explicit insensitivity to particular family involvements. In addition, parents who had not disclosed their sexual orientation to their child's pediatricians had concerns that such disclosure might compromise their child's care, result in negative judgments about their parenting, and infringe on their confidentiality. They described a significant number of concerns regarding physicians, such as prejudice against their children, providing disparate care, lack of communication about the child's health with the nonbiologic parent, and identifying parental lifestyle as the cause of any child physical or behavioral problems.

Pediatricians can create a safe and inclusive environment for same-gender parents and their children. Establishing a supportive health care environment requires that pediatricians first examine their own attitudes toward gay and lesbian parenting. Perrin and Kulkin assert that physicians "who cannot reconcile their personal beliefs with their professional obligation to provide supportive, understanding, and respectful care to gay and lesbian families should recognize this limitation and refer these families to a pediatrician who can better meet their needs." Once the pediatrician has addressed these issues personally, then health care staff attitudes can be similarly

addressed with interventions such as diversity training and strict guidelines regarding confidentiality.

Pediatricians can convey their support of all forms of families, and the office environment can reflect a supportive, safe environment for children of diverse families. Hospital and office policies regarding the use of gender-neutral language and the inclusion of nonbiologic parents during the child's office visits can be discussed and enforced. Box 75-2 illustrates examples of questions to clarify family constellation in ways that can be applied to any family system, including blended and adoptive families. In their work, Perrin and Kulkin identified several changes in the office or hospital environment that demonstrate support for diversity of family structures. These efforts include displaying posters, magazines, books, and pamphlets that portray a wide range of family constructs. A nondiscrimination policy, prominently displayed in the waiting area, can do much to assure members of a diverse array of family structures, including, but not limited to, gay and lesbian parents and their adolescent children, that the office is a safe environment for disclosure of sensitive issues (Figure 75-1). Standard office forms can be modified to include gender-neutral terms, such as *parent*, *caregiver*, and *family member*. Resources can be made available in the office, such as books about gay and lesbian parenting, information regarding community and national support groups, and standard medical forms such as medical power of attorney designation.

As the child grows and develops, in addition to standard anticipatory guidance issues, particular concerns tend to surface at different developmental stages. In the preschool period, common concerns include how to explain the composition of their own family and the methods of reproduction. Gold and colleagues suggest that early childhood "is a good time to

### BOX 75-2 Questions to Clarify the Family Constellation

- Is there anything about your family that would be helpful for me to know?
- Who are the adults who make up your family?
- Who are the important people in your child's life?
- Who lives at home? What is your relationship with each child caretaker?
- By what name does your child call each family member?
- Who are the other important members of your family or support system who help care for your child?
- Do you share parenting responsibilities with anyone else?
- Who helps you with parenting?
- Is there anyone else who participates in parenting?
- Do(es) the biologic parent(s), if not part of the current constellation, have any involvement in child care?
- Which of your child's caretakers can give legal consent for medical care?
- Do any of your child's biologic relatives have any medical conditions?



### Office Nondiscrimination Policy

This office appreciates diversity and does not discriminate based on race, national origin, age, religion, ability, sexual orientation, or perceived gender.

**Figure 75-1** Example of nondiscrimination policy for the pediatric office.

initiate explanations to the child about his own origin and to introduce concepts of the variety of loving relationships.” Pediatricians can help parents empower their children to deal with these issues by encouraging them to allow the child to control the information she discloses to friends or teachers; parents should simultaneously help their children prepare for the possible negative consequences of disclosure.

Parents should be encouraged to help their children come up with their own creative ways to describe their family in positive terms. A gay or lesbian couple might celebrate their essential roles as 2 loving supportive parents while additionally recognizing the other important adult role models and caretakers who comprise the child’s extended family. For example, in the context of a lesbian couple with children, one approach to Father’s Day might be to redefine it as a celebration of the child’s male role models, such as writing cards to an uncle or close male family friend.

The transition to school years also poses particular challenges for children from a nontraditional family background. For parents and children alike, this transition involves deciding whether to disclose their nontraditional family status to teachers and the families of the child’s friends. During the early school years, peer acceptance and teasing often become concerns. In the National Lesbian Families Study, 18% of children had experienced some form of discrimination by age 5, and 43% had experienced homophobia by age 10. Empathic listening, role playing about how to respond to teasing, and providing information to parents and their children through support groups can assist both parents and children in coping with stigma and discrimination.

During adolescence, issues of sexuality tend to come to the forefront regardless of family structure; teenagers in households with lesbian and gay parents are certainly no exception, and they may have their own unique challenges. Early adolescents may feel marginalized and stigmatized by being seen as part of a nontraditional family. Teenagers may feel guilty, torn between their loyalty to their family and pride in their family structure, and their intense desire to form and maintain relationships and fit in with their peers. Physicians can help adolescents and their parents by listening in a nonjudgmental fashion and by offering lists of resources and support groups. Although individual situations vary, some evidence supports encouraging adolescents to disclose their nontraditional family status to their friends. Gershon

and colleagues found that adolescents who disclosed their mother’s lesbianism to their friends reported closer friendships and higher self-esteem than those who did not.

To meet the ever-changing needs of patients and their families, pediatricians should have available a list of local and national support groups and community resources (see Tools for Practice). They might also consider taking a proactive approach in their patients’ lives by not only providing a safe, nurturing office environment, but also taking steps in the community to help counteract the generalized homophobia that children of gay and lesbian parents continually face.

## PHYSICIAN ADVOCACY

Although no evidence has been found that children raised by gay or lesbian parents will develop abnormally or be less well adjusted than other children, these children may be faced with criticism and isolation, which may affect their self-esteem. Pediatricians have an opportunity to help change social attitudes and restrictive legal codes that are damaging to their patients with gay and lesbian parents. Pediatricians who care for these children should be informed about community resources and may choose to be available as consultants to schools and to gay and lesbian support groups. They can learn which community and national programs are supportive of gay and lesbian parents. Pediatricians may choose to be available as consultants to schools and to gay and lesbian support groups and to provide guidance to gay and lesbian parents regarding child care and school selection. Pediatricians can also provide a bibliography of books for children and parents (see Box 75-3) and a list of local and national resource groups (see Box 75-4). Above all, pediatricians have the opportunity and the responsibility to support and advise all families in achieving their maximal nurturing potential.

## CONCLUSION

Children will flourish in various family environments as long as these settings include adequate nurturance and guidance for optimal development. Although no data have been found to suggest that children with gay or lesbian parents are different from other children with regard to their cognitive, psychosocial, and sexual development, these children and their families face social challenges that pediatricians can help address. These challenges are best met within the context of the child’s life as a whole, and the routine medical care of children and adolescents should not be overshadowed by their nontraditional family status. The diversity of the family structures of the gay and lesbian community should be recognized, and anticipatory guidance and care should be tailored to individual needs.

*The authors gratefully acknowledge the expert contributions of Debra L. Bogen, MD, and Mark S. Friedman, PhD.*

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Gay, Lesbian or Bisexual Parents: Information for Children and Parents* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))



**BOX 75-3 Selected Books and Resources for Families****STORIES OF LESBIAN, GAY, BISEXUAL, AND TRANSGENDER FAMILIES**

- Drucker J. *Families of Value*. New York, NY: Plenum Press; 1998. A collection of stories depicting LGBT parents and their children.
- Gillespie P, ed. Kaeser G, photog. *Love Makes a Family: Portraits of Lesbian, Gay, Bisexual, and Transgender Parents and Their Families*. Amherst, MA: University of Massachusetts Press; 1999. Combines interviews and photographs to document the experiences of LGBT parents and their children.
- Herrera D, Seyda B, photog. *Women in Love: Portraits of Lesbian Mothers & Their Families*. Boston, MA: Bulfinch Press; 1998. A collection of photographs and stories of lesbian mothers and their families.
- Rizzo C, Schneiderman J, Schweig L, et al, eds. *All The Ways Home*. Norwich, VT: New Victoria Publishers; 1995. A collection of stories written for and by lesbian and gay parents exploring what it means to be a parent in the LGBT community.
- Strah D, Margolis S. *Gay Dads: A Celebration of Fatherhood*. Putnam, MA: JP Tarcher; 2003. The stories of 24 families, including family-building resources for gay men.

**COMING OUT**

- MacPike L. *There's Something I've Been Meaning to Tell You*. Tallahassee, FL: Naiad Press; 1989. True-life stories from 25 lesbians and gay parents who have come out to their children.

**LEGAL ISSUES**

- Curry H, Clifford D, Hertz F. *A Legal Guide For Lesbian and Gay Couples*. 13th ed. Berkeley, CA: Nolo Press; 2005. An excellent resource for all lesbian and gay couples; includes information on custody, parental rights, and domestic partner benefits.
- Lambda Legal Defense and Education Fund. A national organization focusing on full recognition of the civil rights of LGBT people, including legal resources such as examples of hospital visitation documentation for LGBT family members. [www.lambdalegal.org](http://www.lambdalegal.org).
- American Civil Liberties Union. A national organization with state-by-state reference information regarding

legislation affecting LGBT families. [www.aclu.org/resources-lgbt-equality](http://www.aclu.org/resources-lgbt-equality).

- The Evan B. Donaldson Adoption Institute. Resources regarding adoption, including specific section on gay and lesbian adoption. [www.adoptioninstitute.org/index.php](http://www.adoptioninstitute.org/index.php).

**PARENTING RESOURCES**

- Davis L, Keyser J. *Becoming The Parent You Want To Be: A Sourcebook of Strategies for the First Five Years*. New York, NY: Broadway Books; 1997. A guide to parenting that addresses a broad range of issues, including toilet training, punishment, parenting with a partner, and gender roles.
- Clunis DM, Green GD. *The Lesbian Parenting Book: A Guide to Creating Families and Raising Children*. Washington, DC: Seal Press; 2003. Detailed, chapter-by-chapter information on each stage of parenthood and child development.
- Martin A. *Lesbian and Gay Parenting Handbook*. New York, NY: Harper Collins; 1993. A guide to parenting, with many examples of gay and lesbian parents and their children.

**BOOKS FOR CHILDREN**

- Aldrich A, Motz M. *How My Family Came to Be: Daddy, Papa and Me*. Oakland, CA: New Family Press; 2003. For ages 4–8. Loving story of how 2 men and a baby came together to make a family.
- de Haan L, Nijland S. *King & King*. Berkeley, CA: Tricycle Press; 2000. For ages 4–8. A prince “who has never cared much for princesses” finds true love with another prince.
- Newman L. *Heather Has Two Mommies*. 10th ed. Los Angeles, CA: Alyson Publications; 2000. For ages 2–6. Originally self-published in 1989, the story of a little girl named Heather and her 2 lesbian mothers.
- Parnell P, Richardson J. *And Tango Makes Three*. New York, NY: Simon & Schuster Children's Publishing; 2005. For ages 4–8. This tale is based on a true story about Roy and Silo, 2 male penguins living in New York City's Central Park Zoo who raise a penguin daughter.

**BOX 75-4 Selected Web Sites for Resource Groups**

- COLAGE: Children of Lesbians and Gays Everywhere ([www.colage.org](http://www.colage.org))
- Family Equality Council (formerly Family Pride Coalition) ([www.familyequality.org](http://www.familyequality.org))
- Human Rights Campaign ([www.hrc.org](http://www.hrc.org))
- Pinkbooks ([www.pinkbooks.com](http://www.pinkbooks.com))
- PFLAG (formerly Parents, Families, and Friends of Lesbians and Gays) ([www.pflag.org](http://www.pflag.org))
- Gay, Lesbian & Straight Education Network ([www.glsen.org](http://www.glsen.org))

**AAP POLICY**

Perrin EC; American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health. Coparent or second parent adoption by same-sex parents. *Pediatrics*. 2002;109(2):341–344. Reaffirmed May 2009 ([pediatrics.aappublications.org/content/109/2/341](http://pediatrics.aappublications.org/content/109/2/341))

**SUGGESTED READINGS**

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 Perrin EC. *Sexual Orientation in Child and Adolescent Health Care*. New York, NY: Kluwer/Plenum Publishers; 2002

## Chapter 76

## LESBIAN, GAY, AND BISEXUAL YOUTH

Robert J. Bidwell, MD

In 2004, the American Academy of Pediatrics (AAP) issued its clinical report on sexual orientation and adolescents. This report was followed, in 2013, by an AAP policy statement titled “Office-Based Care for Lesbian, Gay, Bisexual, Transgender, and Questioning Youth,” which broadened the scope of interest to youth dealing with issues of both sexual orientation and gender identity. Together, these affirm the physician’s responsibility to provide supportive and comprehensive health care to all youth, including those who are lesbian, gay, bisexual, transgender, and questioning (LGBTQ). They also provide physicians with the understanding and tools to do so in a respectful and relevant manner. Because LGBTQ adolescents are present in every pediatric setting, an understanding of sexual orientation and gender identity and the unique experiences and needs of LGBTQ youth is essential to the practice of pediatrics.

## DEFINITIONS

*Sexual orientation* is an integral part of human sexuality; it refers to an individual’s pattern of affectional, romantic, or sexual attractions to the same sex (homosexual), opposite sex (heterosexual), or both sexes (bisexual). Homosexual men are generally referred to as *gay*, homosexual women as *lesbian* (or *gay*), heterosexual individuals as *straight*, and bisexual individuals sometimes as *bi*. Sexual orientation is generally represented as a continuum from completely homosexual to completely heterosexual, with many individuals finding themselves somewhere in between. Some individuals describe themselves as asexual, attracted to neither sex. Some youth are not yet certain of their sexual orientation or gender identity and are referred to as *questioning*. Others may engage in same-gender sexual behavior, but not describe themselves as lesbian, gay, or bisexual. They are sometimes referred to as *men who have sex with men (MSM)* or *women who have sex with women (WSW)*. *Gender identity* is another important aspect of human sexuality, distinct from sexual orientation; it refers to a person’s inner sense of being female, male, or another gender. Although too simplistic a definition, *transgender* individuals are generally described as those whose genetic and anatomic sex may be female or male, but whose inner identity is of another gender. *Transgender* may also be used as an umbrella term encompassing the many forms of gender identity and gender expression that are anything other than *cisgender* (when birth gender and experienced or expressed gender are the same). Although the experiences and needs of transgender youths are not discussed in this chapter, a growing number of clinical guidelines address these issues (see Chapter 156, Gender Expression and Identity Issues). Although the term *queer* has historically

been considered pejorative, an increasing number of LGBTQ and other individuals across the broad spectrum of gender and sexuality are claiming this term, along with *genderqueer*, as positive descriptors of their identity.

## PREVALENCE

The percentage of adolescents who recognize or eventually will recognize their lesbian, gay, and bisexual (LGB) identities is uncertain. Estimates for gay and lesbian individuals within adult populations range from approximately 3% to 10%, with an even larger percentage being bisexual. Whatever the exact percentage, LGB adolescents are present in all pediatric practices. They exist within all ethnic, religious, and socioeconomic groups and may be more highly represented among homeless and runaway youths and those in the juvenile justice and child welfare systems. However, LGB adolescents are often unrecognized, either because they do not fit LGB stereotypes, because they have not yet labeled their orientation as LGB, or because they are reluctant to reveal in health care settings their sexual orientation for fear of primary care physician (PCP) disapproval or lack of confidentiality. Many of these individuals likely remain unrecognized because PCPs do not routinely address sexual orientation with their adolescent patients.

## DEVELOPMENT

The process of LGB identity acquisition is long, complex, and often difficult because of the generally negative societal stance toward nonheterosexual orientations. Several models of LGB identity formation have been proposed, each citing stigma as a major factor influencing development. Troiden and Cass offered early models of identity acquisition, proposing stages of increasing self-acceptance as an individual moves from childhood through adolescence into adulthood. Later research suggests these models were perhaps too linear, requiring an individual to pass through one stage to the next on the path to full self-acceptance. More recent models suggest much more complex and varied developmental paths. They take into account the many factors involved in sexual identity development which, in addition to biology, include ethnicity, gender, social class, geography, degree of family and community acceptance, life experiences, and personality traits. The PCP should, therefore, not assume a predefined developmental trajectory for any given patient.

As reflected in the 2004 AAP clinical report and 2013 AAP policy statement, the pediatric profession views heterosexuality, homosexuality, and bisexuality as equally valid and healthy developmental outcomes for youth. This view is consistent with the American Psychiatric Association position that homosexuality is part of the spectrum of normal human sexuality. Homosexuality and bisexuality seem to be well established by early childhood and are not a choice or a matter of something gone wrong. Sexual orientation is likely shaped by biologic, genetic, and environmental factors, and these influences may differ for different individuals. Biologic theories seem to have received the strongest research support in recent

years. Despite supportive AAP statements and a growing understanding of the biologic underpinnings of sexual orientation, significant sectors of American and other societies do not accept the normalcy of homosexuality and bisexuality, seeing them as shameful, sinful, or pathologic. This negative view has significant adverse implications for the development of LGB youths.

## ENVIRONMENTAL EFFECTS

LGB youths are ordinary adolescents in every regard, except that most grow up in environments that are deeply disapproving of their sexual orientation, a fundamental part of who they are. Research strongly suggests that societal stigma and the resultant victimization and discrimination under which LGB youths grow up are the primary reasons for the unique physical, emotional, and social problems they face. While increasing numbers of LGB youth are finding support within their families and communities, many still experience an adolescence of profound isolation, believing they are absolutely alone in their feelings of same-sex attraction. They have little or no access to accurate information about sexual orientation, yet they may be surrounded by a multitude of negative messages about homosexuality coming from their families, schools, churches, and communities and often from people they love and respect. Many LGB youths have little or no access to LGB-supportive PCPs, counselors, or community programs. Some grow up in families and communities where prejudice, discrimination, and violence against LGB individuals are approved or tolerated. Home and school can be especially dangerous places for LGB youths whose sexual orientation is known or presumed. Gender-nonconforming youths seem to be especially vulnerable to victimization and risk for suicidal symptoms.

Given the stigma related to homosexuality and their own fears about their emerging same-sex attractions, many LGB youths repress their same-sex feelings or decide to keep them hidden from others, some expending great energy attempting to pass as heterosexual. They may avoid any exploration of their LGB orientation, thereby delaying an essential part of their identity development. Most LGB youths are denied socially approved dating rituals through which adolescents begin to explore, understand, and become comfortable with their sexuality. Many LGB youths have never had sex with another person; others have been only heterosexually active. Some LGB youths realize that the only way to begin exploring their same-sex attractions is through secretive or anonymous sexual encounters; such encounters are likely increasingly facilitated through the Internet. Although these situations are understandable given the lack of opportunities for sexual socialization enjoyed by heterosexual youths, they are potentially dangerous and may engender feelings of anxiety, guilt, and self-hatred. A small minority of LGB youths are fortunate to live in communities where schools and agencies have begun to provide safe, healthy, and accepting venues, such as school-based gay-straight alliance (GSA) clubs, support groups, drop-in centers, dances, and leadership retreats, for LGB adolescents to meet one another and engage in a process of healthy peer socialization.

LGB youths of color, immigrant youths, disabled youths, rural youths, and youths belonging to conservative religious faiths may have an especially difficult time understanding and accepting their sexual orientation. This intersection of multiple, often stigmatized or conflicting identities is thought to place these LGB youths at even greater risk than their LGB peers. In many instances, they have few LGB-supportive resources within their communities and risk rejection if they openly acknowledge or explore their LGB identity.

Some LGB youths, as with other adolescents who are alone, fearful, and stigmatized, respond in predictable ways, by dropping out of school, running away from home, engaging in risky sex, using drugs, and turning to street life and prostitution. Persons struggling for survival on the streets often encounter violence and sexual exploitation, with the attendant risks of sexually transmitted infections (STIs) and pregnancy. A significant percentage of LGB youths consider suicide to be their only choice. PCPs should realize that these risky behaviors are not a necessary part of the script for growing up LGB. Research has shown that vulnerable adolescents who grow up in stigmatizing or risky environments thrive when they are connected to safe and supportive families, friends, and communities. One of the most important roles for PCPs in working with LGB youths is to participate in creating safe environments and supportive networks of family, peers, teachers, counselors, clergy, PCPs, and others to buffer the often hostile society in which LGB youths grow up. An equally important role of the PCP is to remind LGB youths and their families of the very positive social changes that are occurring. These are evidenced by the expansion of civil rights on many fronts, including same-sex marriage, the increased presence of respected and openly LGB people in media and across many occupations, and the growing acceptance of LGB people across many sectors of American society, including communities of faith.

## EVALUATION

The 2013 AAP policy statement on office-based care of LGBTQ youth, together with its accompanying technical report and *Bright Futures* guidelines for health supervision, provides detailed guidance on providing respectful and relevant care to LGBTQ adolescents. These and other guidelines also describe ways in which physicians can provide care that is respectful of LGB patients and relevant to their needs. PCPs should not presume an adolescent's sexual orientation on the basis of stereotypes or reported sexual behaviors. One of the greatest barriers LGB youths face in receiving appropriate health care is PCPs' belief that they have no LGB adolescents in their practices. Many LGB adolescents will deny same-sex attractions or behaviors even when directly asked. This tendency may be the result of fear of physicians' disapproval or lack of confidentiality or of their own uncertainty about their sexual feelings. Fortunately, the goal of pediatric practice is not to identify all LGB adolescents. Instead, the objective is to create a safe and comfortable clinical setting in which adolescents can discuss sexual orientation issues when they are ready to do so. This task can be accomplished indirectly through posters,

brochures, health questionnaires, and other clinic forms that demonstrate respect for diversity, including diversity of sexual orientation and gender identity. More direct messages come from office staff and PCPs who model respectful attitudes and make no assumptions about sexual orientation or gender identity in their interactions with patients.

Perhaps the strongest message that would allow an LGB adolescent to open up and discuss these issues is when these issues are raised routinely, in a genuinely interested and nonjudgmental manner, at all well-teen visits and any visit suggestive of an adolescent in distress. It is important that the PCP open the door to discussion, because adolescents, uncertain of how their PCP may respond, will seldom raise these issues on their own. A candid discussion of sexuality and other personal issues is facilitated further by meeting with the adolescent alone, without parents or friends present, and accompanied by appropriate assurances of confidentiality. Revealing an adolescent's LGB orientation to others, including parents, without the youth's consent is unethical and potentially dangerous. If issues of LGB orientation arise, then adolescents should be asked whether they are comfortable with the PCP recording these in the chart. Although there are increased recommendations to record sexual orientation and gender identity in the medical record to provide optimal care, adolescents in particular may have concerns about confidentiality that are justifiable and should be respected. Even with permission, these notations should be made carefully and perhaps indirectly, because parents often have the ability to obtain or review their adolescent's medical record, including specific parts that should remain confidential.

PCPs must reflect on their own attitudes and comfort around issues of sexual orientation and consider how their personal biases might affect their ability to provide quality care. Research has shown that many pediatric PCPs are uncomfortable in discussing sexuality, including sexual orientation, with their adolescent patients, and this discomfort limits their ability to provide appropriate care. Studies of LGB adolescents reveal that only a small minority of them have ever been asked about or discussed sexual orientation with their pediatricians. Research has also demonstrated that many PCPs disapprove of homosexuality. This disapproval makes the provision of appropriate health care and counseling to LGB youths nearly impossible. The failure of PCPs to discuss relevant health issues knowledgeably, comfortably, and nonjudgmentally has been a major barrier to accessing health care for LGB youths. Only when issues of sexual orientation are addressed openly and supportively can appropriate medical screening, treatment, education, counseling, and advocacy be provided. Physicians who recognize their discomfort or disapproval around issues of sexual orientation should refer adolescents who may be dealing with these issues to accepting and supportive pediatricians.

### History

Every annual well-teen health evaluation should include a sexual history. Sexual activity, sexual orientation, and sexual decision-making skills should be routinely

assessed at these visits. Sexual orientation also should be addressed with youths having chronic or recurring somatic complaints or at any acute care visit suggestive of an adolescent in distress (eg, parent-teen conflict, school problems, substance use, increased heterosexual or homosexual activity, depression, self-harm, or unusual displays of anger or frustration). Signs and symptoms of STIs should also prompt an inquiry into sexual practices and orientation.

In addressing sexuality with an adolescent patient, the PCP should begin by using gender-neutral language, letting the adolescent know that no assumptions are made about the patient's sexual orientation or practices. For example, the use of terms such as *partner* rather than *boyfriend* or *girlfriend* and *protection* rather than *birth control* is important until a more complete history has been obtained. The PCP can approach the issue of sexuality first by asking if an adolescent has ever been in a dating or romantic relationship with another person. If yes, have these relationships been with girls, boys, or both girls and boys? To learn whether an adolescent has been in a dating or romantic relationship, the physician also should ask, "Have you ever had sex with another person, including just kissing or touching?" If the answer is yes, again, the PCP should ask, "Has this been with girls, boys, or both boys and girls?" An important point to remember is that the question, "Have you ever had sexual intercourse?" may be interpreted as meaning only vaginal intercourse and may not identify youths who have engaged only in petting, oral sex, or anal intercourse.

PCPs should remember that many LGB youths may only have been heterosexually active or not sexually active with others at all. Youths who have been homosexually active may be afraid to acknowledge same-sex behaviors. Therefore, the PCP should search beyond dating relationships and sexual behaviors and ask all adolescents if their feelings of attraction are generally to girls, boys, or both boys and girls, and should also ask about their comfort around these feelings. Many LGB adolescents have not yet labeled their sexual feelings, and, therefore, asking patients early in the interview whether they consider themselves gay, lesbian, or bisexual is usually an ineffective and sometimes frightening screening approach for LGB adolescents. However, as part of a broader discussion over time, asking an adolescent in a supportive and nonjudgmental manner, "Have you ever wondered if you might be lesbian (gay, bisexual)?" may be appropriate at some point. Finally, use of the word *homosexual* as a label ("Are you a homosexual?") is thought to be stigmatizing by many LGB patients and should be avoided.

In interviewing adolescents who acknowledge same-sex behaviors or attractions, the PCP should not focus only or even primarily on their sexual practices and the degree to which they employ safer sex. Because most of the health risks faced by LGB youths are related not to their sexual behavior, but to growing up in a hostile environment, the PCP should address these latter issues in depth before engaging in a detailed discussion of sexual behaviors. For example, the PCP should ask how comfortable LGB adolescents feel about their same-sex attractions and relationships.



How do family background, religion, ethnicity, or community norms play a role in their degree of self-acceptance? The PCP also should ask whether the patient has told others of his or her LGB orientation and whether family members, friends, school counselors, and others have been supportive or rejecting in their responses. In other words, knowing whether an LGB youth is isolated or has a network of supportive family, friends, and adults already in place is important. Another area to explore with LGB adolescents is the degree to which they think their sexual orientation will limit or enhance their future in terms of career, relationships, or acceptance in the community. Can they envision themselves as happy, healthy, and productive LGB adults? What are their concerns or fears, if any? What are their hopes and dreams?

Because some LGB adolescents respond to stigmatization and rejection by engaging in risky behaviors, the PCP should inquire directly about the possibility of parent–teen conflict, school problems, runaway behavior and street life, sexual exploitation, substance use, eating disorders, depression, suicidal ideation or behavior, and involvement in the child welfare or juvenile justice systems. Because many LGB adolescents grow up in nonaccepting or even hostile environments, the PCP should ask specifically about their experience of violence in the home, school, and community. When providing care to LGB youths in the child welfare or juvenile justice systems, PCPs should be aware that although there are standards of care recommending respectful and supportive treatment of LGB youths in foster care and other out-of-home settings, they are not always met. Therefore, PCPs should respect the confidentiality of LGB youths in these systems, recognizing that disclosure of sexual orientation and gender identity through verbal and written communications and documentation could put these youths at greater risk related to safety and the receipt of appropriate care.

As when treating other sexually active adolescents, the PCP should ask sexually active LGB youths how comfortable they are with their sexual behaviors and relationships. Specifically, have these behaviors and relationships been healthy and fulfilling or unpleasant and exploitative in nature? A comprehensive health history should also include a detailed sexual history. It should be preceded by an explanation from the PCP that obtaining personal information about sexuality is helpful in providing patients quality care that meets their specific needs. At the same time, the adolescent patient should be assured that they have a right to answer only specific questions they are comfortable answering. The sexual history should include a discussion of specific sexual behaviors in which the adolescent is engaged, frequency of activity, consensual and nonconsensual encounters, safer-sex practices, number and nature of partners (age, boyfriend or girlfriend vs acquaintance or anonymous), and how contact with potential partners is made (school, church, malls, parties, the Internet). Few sexual practices exist that are unique to LGB youths; thus, history taking related to this specific issue is similar for both LGB and heterosexual youths. Symptoms of STIs also should be elicited, as should any history of combining

substance use and sexual activity or exchanging sex for money, drugs, or shelter.

### Physical Examination

The physical examination of LGB adolescents, whether sexually active or not, does not differ from that of heterosexual adolescents. At the same time, PCPs should remember that many LGB youths are *invisible*, so that any adolescent may have a history of same-sex activity, although it may not always be acknowledged. PCPs should also remember that some gay and lesbian youths have been heterosexually active. The content of the physical examination should be determined by a comprehensive health history, including sexual and other risk behaviors, and not by sexual orientation. If indicated by history, a thorough anal examination should be performed because people of both sexes with a history of receptive anal intercourse are at higher risk for anal STIs, including human papilloma-virus infection, which may lead to anal dysplasia, anal warts, and subsequent anal carcinoma.

Lesbian adolescents should be offered the same gynecologic care as other young women, as guided by a complete and accurate general health and sexual history. Lesbian adolescents who exclusively have sex with other women are not at risk of pregnancy and usually have a lesser risk for STIs than girls who are bisexually or heterosexually active. Although generally not considered STIs, bacterial vaginosis and candidal vulvovaginitis are considered potential STIs between female sexual partners. Many lesbian youth have had male sexual partners, either consensually or through coerced or forced sex, and therefore are at increased risk of pregnancy and STIs. The patient may choose not to share these encounters with the PCP, who must remain open to the possibility of discovering signs of pregnancy and a broad range of STIs on physical examination. Many lesbians, including some adolescents, choose pregnancy as a route to parenthood and will require prenatal care that takes into account their specific life circumstances.

### Laboratory Evaluation

Any decision to offer laboratory or other diagnostic testing to LGB adolescents should be based on a complete and accurate health history (including sexual behaviors) and physical examination and not on sexual orientation. In considering laboratory and other evaluative studies, the PCP should remember that any adolescent may have a history of same-sex encounters and yet be fearful of disclosing them. If a sexually active adolescent is considered at lower risk for STIs (eg, only a single sexual partner and consistent condom use), STI testing may be offered annually. Higher-risk sexual activity, including having multiple sexual partners and the use of drugs or alcohol around the time of sexual activity, warrants more frequent testing. For sexually active gay male youths and MSM, the 2013 AAP technical report on office-based care of LGBTQ youth recommends (1) human immunodeficiency virus (HIV) serology if HIV negative or not tested in the past year; (2) syphilis serology; (3) urethral testing for *Neisseria gonorrhea* and *Chlamydia trachomatis* using a nucleic acid amplification test (NAAT) if the patient has engaged

in insertive anal intercourse in the past year; (4) rectal testing for *N gonorrhea* and *C trachomatis* if the patient has engaged in receptive anal intercourse in the past year; and (5) pharyngeal testing for *N gonorrhea* if the patient has engaged in receptive oral intercourse in the past year. Some recommend herpes simplex virus (HSV) serology testing for all sexually active gay and bisexual male youths and an anal Papanicolaou smear for any adolescent reporting receptive anal intercourse. All sexually active gay and bisexual male youths and MSM should be screened for Hepatitis B (HB<sub>s</sub>Ag). The evaluation and treatment of STIs are discussed in Chapter 330, Sexually Transmitted Infections.

## MANAGEMENT

As stated in the 2004 AAP clinical guidelines, the goal of care in working with LGB youths is “to promote normal adolescent development, social and emotional well-being, and physical health.” PCPs can help realize this goal not only by focusing on the risks that LGB youths face, but also by identifying specific strengths that have allowed them to survive and often thrive in the face of often hostile environments. Historically, because of the serious risks faced by LGB youths, PCPs and allied youth service providers have employed a *risk-reduction model* in addressing the experience and needs of these young people. This model focuses on the vulnerabilities of LGB youth and the need to ameliorate the risks and manage the problems they face. Under this model, healthy adolescent development often seemed to be defined primarily as an avoidance of risk and an absence of negative activities, such as substance use, unsafe sex, dropping out of school, running away from home, or suicidal behavior. Unfortunately, this approach tended to underestimate the strength and resiliency of LGB youths, many of whom presented to their PCPs after having overcome enormous obstacles, including parental rejection, bullying, and internalized homophobia. In working with LGB adolescents, PCPs should adopt an approach that recognizes and builds on the developmental potential of most LGB youths to overcome the risks and obstacles they encounter. This approach is reflected in the *Youth Empowerment* and *Positive Youth Development* models of supporting healthy adolescent development. These approaches seek to support youths in recognizing their strengths and gaining the self-confidence and skills needed to address challenges and create change in their own lives and in the world around them. PCPs can employ this approach in their counseling and encouragement of individual patients. They can also join with others in providing opportunities for LGB youth to assume a leading role in sharing the stories of their lives with others, in creating LGB youth support activities, in achieving leadership skills, and in engaging in civic affairs that address their specific experience and needs. This approach is directly related to risk reduction, but also transcends this narrow goal by providing opportunities for LGB youths not just to survive, but to achieve their full developmental potential and thrive.

### Physical Well-being

LGB adolescents face the same kinds of health issues as other adolescents. Therefore, PCPs should follow

AAP policy and *Bright Futures* guidelines in providing prevention and screening services to LGB youth. The health screening, immunizations, and treatment provided to LGB adolescents should not be based on sexual orientation, but rather on information obtained from an accurate history, physical examination, and evaluative studies. Nevertheless, many LGB youths face increased risks to health because of societal non-acceptance. Patients who show evidence of drug dependency, eating disorders, depression, anxiety, and other mental health concerns should be referred to appropriate LGB-supportive community resources. As an LGB adolescent approaches adulthood, discussions about transition to an LGB-supportive adult health care provider should begin.

### Developmental, Social, and Emotional Well-being

Although providing appropriate health care is important, for many LGB adolescents, the most important role a PCP can play is that of supportive counselor. Adolescents who acknowledge same-sex or bisexual attractions exhibit varying levels of self-acceptance and differing issues of concern. Therefore, a first step in counseling LGB adolescents is to listen carefully to their stories, because these will help shape the content of issues to be discussed during the present and subsequent visits. In general, the counseling of LGB adolescents addresses the following 6 areas: self-acceptance and validation of same-sex attractions; safety; connectedness to supportive others; self-disclosure, or *coming out*; healthy relationships and sexual decision making; and optimism for the future. PCPs often focus their counseling of LGB adolescents only on sexual activity, risk for STIs, and safer-sex practices. However, addressing each of the 6 areas listed here is important in ensuring the healthy development of LGB adolescents.

### Self-acceptance and Validation

Most adolescents grow up surrounded by negative messages about LGB sexual orientation and the presumption that heterosexuality is the only acceptable orientation. These messages often come from people they love and respect and have a profoundly negative effect on the health and development of LGB youths. LGB adolescents often think they are sick or sinful because of their emerging sexual feelings and are filled with shame and self-hatred. The PCP should try to determine the degree of comfort each LGB youth has with emerging sexual feelings and discuss the adolescent's specific concerns or fears. While acknowledging that some cultures and communities may view LGB orientation as unhealthy or wrong, the PCP should state clearly that the pediatric profession considers homosexuality and bisexuality to be healthy and normal. They are not a choice and do not represent something gone wrong. This emphatic reassurance of normalcy from the pediatric perspective is perhaps the most powerful and important statement that a PCP can make to a LGB youth. The PCP should also determine an adolescent's accuracy of knowledge about sexual orientation and correct any misconceptions. Some LGB youths are frightened by LGB stereotypes,

thinking these somehow represent who they are as a person. The PCP should remind LGB adolescents that the stereotypes do not define who they are; rather, they, in their own individuality, help define what it means to be LGB. Ethnic and other minority LGB youths may have an especially difficult time as they try to manage more than 1 type of stigma. The PCP should recognize and discuss this difficult reality with the patient. Letting the LGB adolescent know that growing self-acceptance of a person's sexual orientation is an evolutionary process is helpful. The uncertainty and discomfort they experience now will likely diminish or disappear as they move into adulthood.

If an adolescent denies same-sex attractions, and yet the PCP or others think that it is an issue that may emerge later in an adolescent's life, then the PCP can simply say, "This may or may not ever be a part of your life, and I hear you telling me clearly today that it is not. I just want you to know that, as your doctor, I will always be here for you and available to discuss any issues that come up in your life as you grow older."

For adolescents who express uncertainty about their sexual orientation, the PCP can say, "It's not my place to tell you if you are gay, lesbian, bisexual, or straight; only you can decide this for yourself. What I can do is provide you information and support, and let you know that whoever you finally discover you are is all right. The most important thing is that you are happy and comfortable with who you are, no matter what your sexual orientation might be." It is not unusual for some adolescents to go through stages during which they think they are gay, then straight, then bisexual, then gay again. This uncertainty is part of the normal process of self-discovery and will eventually be resolved, although not necessarily during adolescence. The PCP should not tell adolescents who are experiencing same-sex attractions that they are "just going through a phase." For a significant percentage of adolescents, these feelings do, in fact, represent an emerging LGB identity, and false reassurances to the contrary can be harmful. PCPs should be ready to link adolescents who are LGB or questioning with supportive national organizations that maintain Web sites providing accurate and validating information and resources for teens. Other organizations provide tools for physicians to help them engage LGB adolescents and their families (see Tools for Practice).

## SAFETY

Many LGB youths grow up in environments that are potentially harmful to their physical, emotional, and developmental health. Many of these individuals endure harassment and bullying, discrimination, or social rejection; at the very least, many are surrounded by negative messages about LGB orientation. These dangers may arise at home, school, or church, and within the peer group or the broader community. PCPs should ask LGB adolescents about their safety in each of these settings. If an adolescent acknowledges teasing, harassment, or other harmful treatment, then the PCP should work with the youth to identify and implement appropriate strategies to end the violence. Unfortunately, many LGB adolescents

are filled with shame and are afraid to advocate for their own safety. They may feel that reporting harassment will only make the situation worse. They often think that they deserve the harm inflicted on them, or they simply accept the situation as normal. The PCP should tell adolescents clearly that they have done nothing to deserve such treatment and that they should expect and demand safety and respect from everyone in their lives and in all settings. Because LGB youths have so few advocates, the PCP should offer to join with the adolescent in approaching every venue in which the adolescent experiences violence, including the home and school, to work out a plan to end violence immediately and completely. If necessary, the PCP should call on the state child protective services or advocacy organizations such as the American Civil Liberties Union to join in the effort to keep the adolescent safe.

## ISOLATION

LGB adolescents are among the most isolated of youths. Although there have been significant societal changes in attitude toward homosexuality, many LGB adolescents continue to have little or no access to accurate and supportive information about sexual orientation, and many know of no accepting and supportive counselors in their schools or communities. At a time when they should begin exploring their sexuality, most LGB adolescents have no safe venues in which to meet other LGB youths. Many of them have distanced themselves emotionally or become estranged from their parents and siblings. Many LGB adolescents believe they are the only ones they know who are experiencing same-sex attractions. Few of them have visible LGB adult role models in their communities to provide reassurance that a happy and rewarding adulthood is attainable. As with any other adolescents, isolation and loneliness can lead to compromised physical and emotional health, including increased risk for anxiety and depression. PCPs should routinely screen for these possibilities (see Tools for Practice) and address the issue of isolation by giving accurate information about sexual orientation. They should provide supportive and reassuring counseling, or they should refer the adolescent to LGB-supportive colleagues who have the time, comfort, and expertise to do so. They should connect LGB youths to local community resources, such as support groups and other youth programs for LGB adolescents. LGB youths who do not have access to local programs should be informed about Web sites created for LGB adolescents, such as the Trevor Project, where they can receive accurate information and communicate with other LGB youths in a safe, monitored setting (see Tools for Practice). PCPs can also point out positive LGB youth and adult role models in the community or nationally. In certain circumstances, for LGB PCPs to present themselves openly as role models to LGB youths and their families is also appropriate. Such disclosure should be done only after careful consideration of the physician's own confidentiality needs and how sharing such information might affect, either positively or negatively, the physician-patient/family relationship.



## SELF-DISCLOSURE, OR COMING OUT

LGB adolescents often reach a point in their development at which they feel a strong urge to disclose their sexual orientation to others, referred to as *coming out*. The process of disclosure to family and friends is often emotional and frequently traumatic. Adolescents who come out risk condemnation and rejection by family and peers. Disclosure can also result in physical violence both at home and at school. Therefore, coming out should be considered carefully, weighing the risks and benefits. If an adolescent expects a negative response from the youth's parents, then the adolescent should wait to disclose until legally and financially independent. However, many adolescents think that continuing to "live a lie" is intolerable and harmful to their self-esteem, and, therefore, they come out to their parents much earlier. Under no circumstances should a PCP reveal an adolescent's orientation to parents without permission. A PCP can play an important role in the process of disclosure by helping adolescents decide whether they are ready to come out to family or friends and helping them choose an appropriate time, place, and approach for disclosure.

## HEALTHY RELATIONSHIPS AND SEXUAL DECISION MAKING

Although some LGB youths manage to meet other LGB adolescents and establish friendships and dating relationships, most do not. PCPs should help connect LGB adolescents to local LGB teen support groups and LGB-supportive programs in the community if they exist. This task can be accomplished ethically without parental notification. PCPs can suggest national telephone hotlines or Web sites where LGB youths can receive accurate information and supportive counseling and communicate with other LGB youths. If these options are not available, then the PCP can serve as a supportive and reassuring lifeline until the adolescent is old enough to become independent and possibly move away to work or go to school in a community more accepting of LGB people.

LGB youths who are in relationships face many of the same questions as their heterosexual peers. "Am I in love?" "What do I want from a relationship?" "Do I really want to be in this relationship?" "How do I know if this is a good relationship?" "How do I get out of this relationship?" A LGB-supportive PCP or counselor can help adolescents reflect on and find answers to these questions.

As with other adolescents, many LGB youths know little about sexuality and how to make healthy sexual choices. Abstinence is always the appropriate option for adolescents who do not feel ready for a sexual relationship. LGB adolescents should understand that when they are ready for a sexual relationship, they can expect to lead healthy and fulfilling sexual lives. All adolescents who have decided that they are ready for a sexual relationship should be advised to limit their number of sexual partners and avoid mixing sex and alcohol or drugs so as to reduce their risk for infection, trauma, and sexual assault. Safer sex practices related to oral, vaginal, and anal sex should be reviewed in detail. LGB youths should also be aware that

*no always means no* in negotiating sex, and any forced or coerced sexual experience represents sexual assault. LGB youths should also understand that no set LGB repertoire of sexual behaviors exists and that they should engage only in those sexual practices with which they are comfortable.

## OPTIMISM FOR THE FUTURE

PCPs should challenge the belief of many LGB adolescents that their futures will be significantly limited by their sexual orientation. Referral of LGB adolescents to the *It Gets Better Project* Web site can be especially helpful (see Tools for Practice). Although some communities are clearly more accepting of LGB people than others, most LGB adults lead happy, healthy, and productive lives. LGB youths should be encouraged to pursue any career they wish. They should expect to have deep, long-lasting, and fulfilling relationships throughout their lives. They should expect to be respected and valued members of their communities. They also should understand that marriage and parenthood are enhancing the lives of thousands of LGB adults across the United States. Although growing up LGB is often challenging, the future should be seen as hopeful and exciting.

## PARENTS

Parents who learn of their child's LGB orientation often experience an intense mix of emotions. Some respond to this new understanding of their child with ready support and expressions of love. Many others feel varying degrees of guilt, shame, fear, anger, repulsion, and profound sadness. Many parents go through a deep mourning period, feeling as if they have lost the child they knew and loved. Some parents will reject or physically and emotionally abuse an LGB child. Parents are often as isolated from accurate information and supportive resources as are their children. PCPs should listen patiently and respectfully to parents' concerns and fears, acknowledging their pain and sense of loss. The PCP should emphasize the importance of their continued expressions of love for their child, especially at this time when many adolescents think that they will lose their parents' love and support. At the same time, the PCP can acknowledge that understanding and acceptance of their child's sexual orientation is an evolutionary process and will take time. Nevertheless, parents should be informed of the growing research-based understanding that parental rejection is a predictor of negative health outcomes for LGBTQ youth, including substance use, risky sexual behaviors, suicidal ideation and limited hopes for a happy future. Therefore, while acknowledging that negative responses to a child's disclosure of LGB identity may come from a place of genuine concern and love, it is essential that PCPs engage families in supporting their LGBTQ children through increased acceptance. Parents should be reassured that they did nothing wrong and that the pediatric profession has come to accept homosexuality and bisexuality as normal and healthy developmental outcomes. To decrease their isolation, parents should be referred to the online AAP patient education document titled *Gay, Lesbian, and Bisexual Teens: Facts for*



*Teens and Their Parents* (see Tools for Practice). They should be referred to relevant books, Web sites, and support programs for parents and families of LGB children. One of the most prominent national parent support organizations is Parents, Families and Friends of Lesbians and Gays (PFLAG), which has many local affiliate groups across the country. Parents should be reassured that American society as a whole is becoming increasingly accepting of LGB people. By providing love, support, and protection, parents should expect their child to achieve a happy, healthy, and rewarding adulthood.

The PCP should discourage any parental search for treatment that is directed at changing their child's sexual orientation. Such *reparative therapy* or similar religion-based *transformational ministries* are considered by the pediatric profession to be both unethical and dangerous. Finally, PCPs who think that they are unable to give LGB-supportive counseling to families should refer them to colleagues who have the time, comfort, and expertise to provide such support.

## ADVOCACY

One of the most important roles that PCPs can play in ensuring the health and safety of LGB adolescents is that of advocate. The advocacy role is essential, even lifesaving, because many LGB youths grow up in extremely hostile environments and have few, if any, advocates in their families or communities. PCPs' expertise is respected, and their offering of visible and confident support for LGB adolescents can promote increased community awareness, understanding, and acceptance, which are essential for the healthy development of these youths.

Advocacy can take place on many levels. On an individual patient level, PCPs can meet with families, school officials, social welfare agency staff, mental health care providers, and others to ensure that their patient is safe and accepted in the home, school, and community. They should also ensure that clinic and hospital policies and practices reflect respect for LGB patients. At a community level, PCPs can participate in educational forums that present the pediatric perspective that LGB orientations are normal and healthy. PCPs should be willing to go to schools and school boards, child welfare agencies, juvenile detention and correctional institutions, city councils, legislatures, and faith communities to advocate for policies and programs that specifically ensure the respectful treatment and address the special needs of LGB adolescents. National guidelines have been developed addressing these issues.

In addition, PCPs can advocate for school curricula and library holdings that reflect the diversity of students and their families, including diversity of sexual orientation and gender identity. Furthermore, they should advocate for the development and implementation of robust medical school, residency training, and continuing medical education curricula that include an in-depth consideration of the development, life experiences, and health needs of LGB adolescents and adults and provide the skills to work with these populations respectfully and effectively. This effort is especially important because, for many LGB youths, a supportive PCP may be the only lifeline they have

ensuring safe passage into a happy, healthy, and rewarding adulthood.

## WHEN TO REFER

- When an adolescent has acute or recurrent suicidal ideation
- When an adolescent is engaged in high-risk behaviors
- When the PCP decides that time, expertise, or comfort is insufficient to provide LGB-supportive care and counseling
- When an adolescent's physical, emotional, or developmental well-being and safety may be at risk because of family nonacceptance

Referral should be made only to pediatric, adolescent medicine, or mental health specialists who have experience in working with LGB adolescents and who accept same-sex attractions as normal and healthy. Referrals for reparative therapy or to transformational ministries are unethical and potentially dangerous.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Family Acceptance Project* (Web site), San Francisco State University ([familyproject.sfsu.edu](http://familyproject.sfsu.edu))
- *Gay, Lesbian, and Bisexual Teens: Facts for Teens and Their Parents* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *It Gets Better Project* (Web site) ([www.itgetsbetter.org](http://www.itgetsbetter.org))
- *LGBT Youth Resources* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/lgbthealth/youth-resources.htm](http://www.cdc.gov/lgbthealth/youth-resources.htm))
- *Parents, Families and Friends of Lesbians and Gays (PFLAG)* (Web site) ([www.pflag.org](http://www.pflag.org))
- *The Trevor Project* (Web site) ([www.thetrevorproject.org](http://www.thetrevorproject.org))

### Medical Decision Support

- *Anxiety Disorders* (fact sheet), Mental Health America ([www.mentalhealthamerica.net/conditions/anxiety-disorders](http://www.mentalhealthamerica.net/conditions/anxiety-disorders))
- *Depression* (fact sheet), Mental Health America ([www.mentalhealthamerica.net/conditions/depression](http://www.mentalhealthamerica.net/conditions/depression))
- *Enhancing Pediatric Mental Health Care: Algorithms for Primary Care* (article), American Academy of Pediatrics ([pediatrics.aappublications.org/content/125/Supplement\\_3/S109](http://pediatrics.aappublications.org/content/125/Supplement_3/S109))
- *Guidelines for Care of Lesbian, Gay, Bisexual, and Transgender Patients*, Gay and Lesbian Medical Association (GLMA) ([glma.org/\\_data/n\\_0001/resources/live/GLMA%20guidelines%202006%20FINAL.pdf](http://glma.org/_data/n_0001/resources/live/GLMA%20guidelines%202006%20FINAL.pdf))
- *The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding* (book), Institute of Medicine of the National Academies ([books.nap.edu/openbook.php?record\\_id=13128](http://books.nap.edu/openbook.php?record_id=13128))
- *Mental Health Screening and Assessment Tools for Primary Care* (chart), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH\\_ScreeningChart.pdf](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH_ScreeningChart.pdf))

### AAP POLICY

- American Academy of Pediatrics Committee on Adolescence. Office-based care for lesbian, gay, bisexual, transgender, and questioning youth. *Pediatrics*. 2013;132(1):198–203 ([pediatrics.aappublications.org/content/132/1/198](http://pediatrics.aappublications.org/content/132/1/198))
- American Academy of Pediatrics Committee on Adolescence. Sexual orientation and adolescents. *Pediatrics*. 2004;113(6):1827–1832 ([pediatrics.aappublications.org/content/113/6/1827](http://pediatrics.aappublications.org/content/113/6/1827))
- American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health, Committee on Adolescence. Sexuality education for children and adolescents. *Pediatrics*. 2001;108(2):498–502. Reaffirmed October 2004 ([pediatrics.aappublications.org/content/108/2/498](http://pediatrics.aappublications.org/content/108/2/498))

### SUGGESTED READINGS

- Adelson SL. Practice parameters on gay, lesbian, or bisexual sexual orientation, gender nonconformity, and gender discordance in childhood and adolescence. *J Am Acad Child Adolesc Psychiatry*. 2012;51:957–974
- Levine DA; American Academy of Pediatrics Committee on Adolescence. Office-based care for lesbian, gay, bisexual, transgender, and questioning youth. *Pediatrics*. 2013;132:e297
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- Wilber S, Ryan C, Marksamer J. *CWLA Best Practice Guidelines: Serving LGBT Youth in Out-of-Home Care*. Washington, DC: Child Welfare League of America; 2006

## Chapter 77

# CHILDREN IN MILITARY FAMILIES

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### BACKGROUND

The military family is a modern experience. Before the Vietnam War, US service members were discouraged from having families. Entry into the armed services

was primarily through conscription at a young age. When military service became voluntary in 1973, the number of individuals looking for a career increased, and with them came their families. Currently supporting a population of families larger than its serving force, the Department of Defense (DoD) is now responding to the issue that has affected military service members and their families more than any other in the new millennium: the need to understand the effects of lengthy, recurrent, and dangerous deployments. With 2.2% of all US births, and more than 2 million children, military families and their unique concerns are not confined to the mission of the DoD, but extend to local communities, schools, child care, and health care systems. All pediatricians need to be aware of the physical and mental health needs of military children and the supports that are available to them.

In the past, the image of military families evoked a stereotypical profile, sometimes referred to as the “military family syndrome,” which described a rigid, authoritarian active-duty father, a stay-at-home submissive mother and wife, and “out-of-control” children with rootless identities exhibiting severe psychological problems. Subsequent research, including prospective studies of military versus nonmilitary children, failed to validate this profile and found no inherent psychosocial differences between military and nonmilitary children. In fact, 1 study of Navy families, for whom routine 6-month sea-duty deployments have been a way of life for years, indicated that children demonstrated increased responsibility, independence, and confidence compared with their peers without deployment experiences, suggesting that children develop a different and often beneficial parent-child relationship during parental deployment. Despite its varied components, the US military is a unified community with a strong sense of patriotism, pride, and self-sufficiency. Uniform attitudes and values, rank hierarchy, dress, and customs support a robust and resilient military culture.

### MILITARY LIFE

In addition to issues common in all US families, there are many aspects of military family life that are extraordinary: its diversity, frequent geographic relocations, opportunity to live in foreign countries, forced adaptations to new communities and schools, use of the largest single-payer health entitlement program (TRICARE) in the country, peacetime separations, remote unaccompanied assignments of service members, and dangerous, lengthy combat deployments. The DoD has 3.6 million members serving on Active Duty (AD) or Selected Reserve (SR), including the National Guard. Nearly half of these service members have children. Most children in AD households are younger than 6 years, whereas more than 60% of children in SR families are of school age. Geographically, AD families typically live within military communities where resources and support systems for young children are readily available. SR service members may be activated for service from civilian jobs in geographic areas quite remote from military resources and often have individual and family needs during military activation that may be unmet in their communities and specifically their schools. Of the service members with

<sup>a</sup>The views expressed in this article are those of the author and do not necessarily reflect the official policy or position of the Department of the Army, Department of the Navy, Department of Defense, or the US Government.

I am a military service member. This work was prepared as part of my official duties. Title 17, USC § 105 provides that ‘Copyright protection under this title is not available for any work of the US Government. Title 17, USC § 101 defines a US Government work as a work prepared by a military service member or employee of the US Government as part of that person’s official duties.

<sup>b</sup>This information or content and conclusions are those of the author and should not be construed as the official position or policy of, nor should any endorsements be inferred by HRSA, HHS, Department of the Army, Department of the Navy, the Department of Defense, or the U.S. Government. Manuscript preparation was supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) under grant T73MC00041, Excellence in Comprehensive Interdisciplinary Leadership Education: Enabling Children and Youth with Neurodevelopmental Disabilities to Achieve Their Dreams (UW LEND).

children, 5% (AD) to 9% (SR) are single parents. In 7% of families, both parents serve on AD. These families have additional needs when the military mission requires them to step away from parenting responsibilities. Thirty percent of the service members consider themselves nonwhite, non-Hispanic minorities. The diversity of US military families can be compared with that of other American families, and appreciation of various cultural contexts will help enhance understanding of family needs and provision of care.

### Relocation

Frequent relocations are commonplace for the military family and present significant challenges. At least 60% of military families have relocated at least once in the past 3 years. In a 2009 survey of AD families with deployed service members, 47% reported 3 or more moves in the past 5 years, significantly higher than SR families and the general US population. Frequent relocations affect spouse employment, school continuity, and child care, not to mention services needed for children with special health care needs. To help ease the economic burden of renting or owning a home, the AD service member is provided a housing allowance. Additionally, most military installations have housing available. Housing on military bases can provide a significant source of community support and reduce deployment challenges. Military housing neighborhoods are often filled with families and children in similar life stages, and neighbors take on the role of extended family members. Assignment to installation housing is determined by availability. Many times, families must live in the local community for several months before moving to installation housing, which can result in additional school relocations. Overseas assignments are also a common experience for service members and their families. At any given time, approximately 13% of AD members are stationed outside the US and its territories. The military family can move overseas with the service member in many locations, but some assignments require the AD member to be separated from his or her family for a 1- or 2-year unaccompanied assignment. For foreign locations that do allow families, the experience can be enriching. Families have the opportunity to travel and learn about new cultures. Often, overseas military installations provide many services (eg, housing, schools, supermarkets, department stores, restaurants) to families, and they can choose how involved in the local culture they want to be. Previously, communication with families back in the United States was difficult and expensive, but in the current digital age, the largest barrier is the time differences between countries.

### Schooling

Children in military families, on average, attend 6 to 9 different school systems between kindergarten and 12th grade. Many will change high schools more than twice. Traditionally this has led to less academic success and difficulties participating in competitive interscholastic activities. All 50 states and the District of Columbia, however, have now adopted the Interstate Compact on Educational Opportunities for Military

Children to ensure “uniform treatment of military children transferring between school districts and states.” This Interstate Compact addresses issues of enrollment, eligibility, and graduation parity between states. Many military families are unaware of the agreement, and many students resign themselves to less or fragmented school participation.

### Deployment

One aspect of military life that is well known and accepted among all service members is the need of the mission, which often requires time away from home and regular assigned workplace. Deployment is a temporary, 3- to 15-month movement of an individual or military unit away from his or her local work site, resources, and family to accomplish a task or mission. Deployments can occur as a peacetime activity or to support wartime operations. Peacetime deployments (separations other than war) include humanitarian missions such as when activated service members were sent to assist following Hurricane Katrina in 2005 or when more than 12,000 US service members were involved in the global response to the 2010 earthquake in Haiti. Operations other than war usually mean travel to safe locations, short duration, and interludes of rest and recovery between absences, and most military families cope well with these separations. Military families may also expect 3- to 6-month annual separations from their family service member for specialized schooling or training. Traditionally, unaccompanied tours of 1-year remote overseas assignments, when the family remains state-side, have not been defined as deployments. Wartime combat deployments, on the other hand, represent hostile, dangerous activity of usually long duration.

Before the wars in Iraq and Afghanistan, combat deployment was a rare occurrence for most military forces. Most families had never experienced the separation of a loved one to a hostile environment before 2001. Since then, families have experienced the most prolonged and repeated combat deployments in American history. Deployments have 3 main phases, each with predictable dynamics: predeployment, deployment, and postdeployment (or redeployment) (see Table 77-1).

### Effects of Deployment

The years since 2001 have provided most of the research on responses to war by US service members, their spouses, and their children. Complications related to war-combat stress disorder, traumatic brain injury, development of psychiatric illness, and increase in health risk behaviors can complicate family life for a child. Postdeployment emotional and behavioral responses by a soldier can range from typical short-term distress responses, such as change in sleep, decreased sense of safety, or social isolation, to the development of more serious psychiatric conditions such as post-traumatic stress disorder (PTSD) or depression. It is estimated that more than 30% of returning soldiers have experienced PTSD, depression, or traumatic brain injury. Comorbidities, such as aggression and alcohol misuse, are prevalent in up to half of those with impairment. Studies of spouses of service members indicate that deployment affects their well-being and marital

**Table 77-1**      **Phases of Deployment and the Role of the Pediatrician**

STAGES OF DEPLOYMENT	CHARACTERISTICS	PEDIATRICIAN ASSESSMENT	PEDIATRICIAN ANTICIPATORY GUIDANCE
<b>Predeployment:</b> from notification of deployment to actual departure	<ul style="list-style-type: none"> <li>• Often intense preparation of military units; requires extensive time away from family.</li> <li>• Decisions made about careers, financial adjustments, legal issues, and child care.</li> <li>• Experience with previous deployments may interfere with preparation for new deployment.</li> <li>• Can be confusing to children, who may not understand why separation is necessary and have no concept of what this change means.</li> <li>• Children at various developmental ages experience excitement, denial, worry, fear, and anger. Emotional withdrawal is not uncommon immediately before deployment.</li> <li>• Last-minute or recurrent goodbyes often increase tension.</li> <li>• Teens can be angry at the “selfish” nature of a service member’s job that takes the adult away from his or her role as parent, coach, and supporter.</li> </ul>	<ul style="list-style-type: none"> <li>• Assess for preexisting:               <ul style="list-style-type: none"> <li>• Family dysfunction</li> <li>• Mental health issues in parent</li> <li>• Special needs children</li> <li>• Recent family relocation</li> <li>• Recent divorce or remarriage</li> <li>• Previous problems during a deployment</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Discuss responsibilities and expectations of each family member during upcoming deployment.</li> <li>• Make plans and goals for family rather than “put lives on hold.”</li> <li>• Decrease likelihood of misperception and distortion.</li> <li>• Prepare for communication strategies and expectations, perhaps avoiding everyday contact.</li> <li>• Plan to maintain rules, rituals, and routines.</li> </ul>
<b>Deployment:</b> typically lasts between 3 and 15 months	<ul style="list-style-type: none"> <li>• Usually begins with a tearful going-away ceremony, followed by a period (usually 1–6 weeks) of emptiness and loss.</li> <li>• The intensity leading up to a goodbye can be overwhelming.</li> <li>• The sense of relief that the deployment has actually started can be confusing.</li> <li>• After about 6 weeks, most families try to establish and settle into a new routine.</li> <li>• The “midtour” rest and recuperation (R&amp;R) leave:               <ul style="list-style-type: none"> <li>• Is when the deployed service member can come home for 2 weeks.</li> <li>• Is often a difficult time for children.</li> <li>• May occur during the school year.</li> <li>• Is when children are often distracted by anticipation, excitement, and a short period of visitation, then have to say goodbye all over again.</li> </ul> </li> <li>• Many families describe deployment as “surviving, not thriving” despite trying to find resilience and strength.</li> <li>• For the month or 2 before homecoming:               <ul style="list-style-type: none"> <li>• There may be worry as well as excitement as new independence or self-reliance may have emerged into a “new normal.”</li> <li>• Family members are unsure how to reintegrate a deployed parent.</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Assess at-home parent and children for:               <ul style="list-style-type: none"> <li>• Adjustment (1–6 weeks after deployment)</li> <li>• Sleep regularity</li> <li>• School attendance</li> <li>• Mood problems</li> </ul> </li> <li>• Spend time in private conversation with adolescents to assess:               <ul style="list-style-type: none"> <li>• Adjustment</li> <li>• School performance</li> <li>• Mood</li> <li>• Risk taking</li> <li>• Role in family</li> </ul> </li> <li>• Offer free deployment video for youth</li> </ul>	<ul style="list-style-type: none"> <li>• Discuss responsibilities and expectations of each family member during upcoming deployment.</li> <li>• Make plans and goals for family rather than “put lives on hold.”</li> <li>• Decrease likelihood of misperception and distortion.</li> <li>• Prepare for communication strategies and expectations, perhaps avoiding everyday contact.</li> <li>• Plan to maintain rules, rituals, and routines.</li> </ul>



**Table 77-1**      **Phases of Deployment and the Role of the Pediatrician—cont'd**

STAGES OF DEPLOYMENT	CHARACTERISTICS	PEDIATRICIAN ASSESSMENT	PEDIATRICIAN ANTICIPATORY GUIDANCE
<b>Postdeployment (Redeployment)</b>	<ul style="list-style-type: none"> <li>• Often begins with “honeymoon” period of happiness and putting off the chores of the day.</li> <li>• Happiness of reuniting is mixed with needing to get reacquainted and deciding how to share the time lost.</li> <li>• “Block leave” is 30 days of vacation time given to the postdeployment unit, sometimes delayed after the actual return.</li> <li>• May not coincide with when family members have availability to leave school or work.</li> <li>• At-home spouse often wants some much-needed respite after a year of “full-time” parenting.</li> </ul>	<ul style="list-style-type: none"> <li>• Assess family for               <ul style="list-style-type: none"> <li>• Readjustment (1–6 weeks)</li> <li>• Parental mood</li> <li>• Post-traumatic stress disorder</li> <li>• Substance use</li> <li>• Marital discord</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Take time to communicate, get to know each other.</li> <li>• Spend time talking to each other.</li> <li>• Take time to make decisions, discuss changes in routine.</li> <li>• Lower holiday expectations.</li> <li>• Keep plans simple and flexible.</li> <li>• Don’t try to schedule too many things during the first few weeks.</li> <li>• Let absent parent “back into” the family circle.</li> </ul>

relationships. In a review of more than 250,000 Army wives, Mansfield and colleagues found that soldier length of deployment was associated with elevated depression, sleep problems, anxiety, acute stress reactions, and adjustment disorders in their wives. It is not surprising that the toll of lengthy and recurrent deployments has been reflected in marital discord. In 2008, a US Army Mental Health Advisory Team reported that the number of months deployed has a statistically significant linear relationship with married soldier reports on plans for divorce or separation, especially among the junior enlisted ranks. There is well-established literature across a range of populations to inform pediatricians about the effects of parental psychopathology and marital discord on child well-being, separate from the challenges faced by deployed service members and their spouses. Recognizing the increased vulnerability of children in these circumstances is a role general pediatricians have assumed for decades.

### **Coping With Deployment**

Despite limitations in data collection, researchers have compiled a few dozen studies to create the current profile of military children and their families coping with parental combat deployments. In 2008, Chartrand and colleagues studied preschool-aged children with and without a deployed parent and found increased behavioral symptoms in the preschoolers experiencing parental deployment. Flake and Davis found increased psychosocial morbidity in more than one-third of school-aged children with a deployed parent. At-home parental stress was reported to be very high in this group. Aranda and Davis queried military adolescents with and without a deployed parent, and both the teen self-reports and the parental

reports revealed increased stress in the deployed subgroup. Lester and colleagues and Barker and coauthors each provide evidence of the cumulative effects of deployment experiences as well as risk to children associated with psychological stress of either parent. Mansfield studied the electronic medical record data of more than 300,000 Army children and observed a dose-response pattern between deployment of a parent and increased child mental health diagnoses. At a population level, Gorman and colleagues found that rates of mental health, behavioral, and stress problems in children increased by 11% during parental deployment. A similar increase in psychiatric hospitalizations when a parent was deployed was found by Millegan. Two studies of youth, 1 in Washington State (Reed), and another in Iowa (Acion), showed those with a parent in the military had higher rates of risk-taking behaviors, including substance use and school-based violence. Although infants are yet to be studied, there is evidence of increased maternal stress related to pregnancy and childbirth when a service member partner was deployed. The first systematic review of military children, which included 9 studies, was published by White and colleagues in 2011 and, along with other studies, established consistent indicators of increased risk to military children, including emotional and behavioral problems, poorer academic achievement, and risk-taking behaviors. Risk seems to increase in a dose-dependent manner, based on the number and duration of parental deployments.

Although no specific or consistent pediatric diagnoses have emerged as indicators of the severity of chronic wartime stress, there are examples of significant distress: in testimony to Congress, there is evidence of increases in military preteen inpatient mental health stays,

and 2 studies suggested military families experiencing repeated or prolonged deployments, especially in young marriages with young children, were at risk for child maltreatment, specifically neglectful home environments. Over a decade, the extent to which combat deployments affect military children and their families is being compiled across the life span.

Three longitudinal studies are underway, one of which (Millennium Family Cohort Study, [www.millenniumcohort.org](http://www.millenniumcohort.org)) is a 20-year prospective study, and will substantially enhance our understanding of both the risks and resilience of military children during and after parental deployments.

### When a Parent Dies

The death of a parent or significant parenting figure during war is a catastrophically disorganizing event for a child, the surviving parent, and the family. It is one of the unspoken fears that family members endure during wartime deployments. Helping children understand parental injury or death requires a developmentally unique sensitivity. The pediatrician should assess the social-emotional reaction of the child in relationship to his or her developmental stage, follow the child over time, and support the remaining parent or life partner. The severity of parental injury is not directly related to the degree of child distress. It is important to consider not *how* the child is acting, reacting, or overreacting but for *how long*. It is common for children to demonstrate their grief for 4 to 6 weeks. Because of the devastating nature of parental disfigurement or death, most spouses or partners should be referred for social-emotional assessment and therapy to support their personal grief and to understand how to support their children. A specific resource for military families is the Tragedy Assistance Program for Survivors ([www.TAPS.org](http://www.TAPS.org); see Box 77-1). The pediatrician can encourage a surviving parent to seek military support through Decedent Affairs, the Chaplains' Office, or commanders of the military unit. This support is usually made available at the time the spouse or partner is notified of the death of her or his loved one.

## RESILIENCE

Resilience seems to play a major factor in all phases of deployment as well as military life. Protective factors include family readiness, "meaning making" of a situation, receipt of community and social support, acceptance of the military lifestyle, ability of the at-home parent to develop self-reliant coping skills (see Box 77-1), and adoption of flexible gender roles. Children who have supportive caregivers, school environments, and adults who understand their military situation are more able to effectively recruit coping skills that augment family supports. Evolving understanding of these factors supports the role of systematic approaches to prevention and care of the military-connected child. As programs to support children and families are developed, it is important that they are evaluated for their effectiveness similar to the family-centered, preventive care program developed by Lester and colleagues that showed a statistically significant decrease in anxiety and depression measures and led directly to increases in healthy family functioning.

### BOX 77-1 Resources

- For pediatrician
  - *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit*, American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
  - American Academy of Pediatrics Mental Health Initiatives ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/default.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/default.aspx))
  - American Academy of Pediatrics Section on Uniformed Services ([www.aap.org/en-us/about-the-aap/Committees-Councils-Sections/Section-on-Uniformed-Services/Pages/default.aspx](http://www.aap.org/en-us/about-the-aap/Committees-Councils-Sections/Section-on-Uniformed-Services/Pages/default.aspx))
  - Center for the Study of Traumatic Stress ([www.centerforthestudyoftraumaticstress.org](http://www.centerforthestudyoftraumaticstress.org))
  - Military One Source ([www.militaryonesource.com](http://www.militaryonesource.com))
  - TAPS ([www.TAPS.org](http://www.TAPS.org))
  - TRICARE Online ([www.tricare.mil](http://www.tricare.mil))
- For parent
  - American Red Cross ([www.redcross.org](http://www.redcross.org))
  - Ginsburg KR, Jablow MM. *Building Resilience in Children and Teens*. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2014
  - Military One Source ([www.militaryonesource.com](http://www.militaryonesource.com))
  - National Military Family Association ([www.military-family.org](http://www.military-family.org))
  - Zero to Three: Coming Together Around Military Families ([www.zerotothree.org/about-us/funded-projects/military-families/](http://www.zerotothree.org/about-us/funded-projects/military-families/))
    - Education
      - Military K-12 Partners ([www.militaryK12partners.dodea.edu](http://www.militaryK12partners.dodea.edu))
      - Military Interstate Children's Compact Commission ([www.mic3.net](http://www.mic3.net))
      - Military Child Education Coalition ([www.militarychild.org](http://www.militarychild.org))
      - PAVE: Partnerships for Action. Voices for Empowerment ([wapave.org](http://wapave.org))
      - STOMP (Specialized Training of Military Parents) ([www.stompproject.org](http://www.stompproject.org))
- For child
  - Operation Purple (through the National Military Family Association) ([www.militaryfamily.org](http://www.militaryfamily.org))
- Service related
  - Air Force ([www.af.mil](http://www.af.mil))
  - Air Force Reserve Command ([www.afrc.af.mil](http://www.afrc.af.mil))
  - Army Family Readiness Group ([www.armyfrg.org/skins/frg/home.aspx](http://www.armyfrg.org/skins/frg/home.aspx))
  - Army Reserve Family Programs ([www.arfp.org](http://www.arfp.org))
  - Coast Guard ([www.uscg.mil/mwr](http://www.uscg.mil/mwr))
  - Marine Corps Family Team Building ([www.mccscp.com/mcftb](http://www.mccscp.com/mcftb))
  - Marine Forces Reserve MFR Family Readiness ([www.marforres.marines.mil/FamilyReadinessOffice.aspx](http://www.marforres.marines.mil/FamilyReadinessOffice.aspx))
  - National Guard Family Program ([www.jointservices-support.org/fp](http://www.jointservices-support.org/fp))
  - Naval Services FamilyLine ([www.cnic.navy.mil/FamilyLine](http://www.cnic.navy.mil/FamilyLine))

## BENEFITS OF MILITARY SERVICE

Even in the midst of ongoing deployments, military families, regardless of service or component, appreciate the advantages of military life, including adequate free housing, an “on post” community with shopping, accessible child care and schools, low cost or free medical care, community services including free financial and behavioral counseling, emphasis on recreational facilities, subsidized educational opportunities, relatively stable family income, shared identity and mission with peers as well as senior leaders, and a feeling of patriotism and national contribution.

## HEALTH CARE IN THE MILITARY

The AD service members and their families receive significant health care entitlements under TRICARE, including inpatient, outpatient, primary, and subspecialty care; therapies; medications; and equipment. The administrative agent for TRICARE varies with 3 regions (North, South, and West) based on a contracting process and includes both military treatment facility (MTF) or “direct care” and a network “purchased care” component. There are 149 MTFs in the United States and around the world accounting for 63% of DoD pediatric beneficiary care and supporting Army, Navy, and Air Force military pediatric residencies, subspecialty pediatrics, pharmacy, behavioral health, and ancillary care services. The medical coverage exclusions are regulated by Congress and implemented by the regional administrative agents. The Defense Health Agency recently concluded that the Military Health System is generally meeting the needs of pediatric beneficiaries, but outlined several opportunities for improvement. There were recognized gaps noted in several areas, including transferring care when children move between regions, using preventive care programs, and providing habilitative care.

Several options are given to military families regarding their medical entitlements. TRICARE Prime requires the assignment of a primary care manager (PCM). The PCM provides a medical home as the primary care medical provider and must submit authorization requests for consultation and procedure approval. The MTFs and hospitals are the preferred locations for family members under TRICARE Prime. There are no out-of-pocket expenses for TRICARE Prime. Additional options, TRICARE Extra and Standard, allow for more choices to the beneficiary but also require varying levels of out-of-pocket expenses, with copays and deductibles. Perhaps one of the most significant benefits under TRICARE is the mental health option or Behavioral Health Portal. Family members can be seen up to 8 times by any mental health provider in the TRICARE network without a consult from a PCM. This benefit allows for improved access to mental health services for all military family members. Family member dental care is not covered under TRICARE, but additional coverage can be purchased for a nominal fee. Interested providers should consult Web site references listed in Box 77-1 for the most current information regarding TRICARE benefits.

To prevent moving a family with a dependent who requires significant medical or educational services to a medically underserved area, the military requires

AD service members and their families to enroll in the Exceptional Family Member Program (EFMP). The EFMP is designed to help select appropriate service member duty assignments and continue to meet family members’ health care needs without detriment to the service member’s career. Dependents enrolled in EFMP are potentially eligible for services under the Extended Care Health Option (ECHO). Habilitative equipment and skilled nursing care are provided as part of the ECHO program. The Autism Care Demonstration Project provides intensive autism supports such as applied behavioral analysis and respite care for children with autism who are TRICARE eligible.

Children of military members require an identification card at age 10 years and are eligible for care up to age 23 if they remain full-time students. TRICARE Young Adult (TYA) is a premium-based program available for children 23 to 26 years of age. For children with chronic lifelong medical issues resulting in diminished capacity to live independently, the AD or retired service member has the opportunity to request indefinite medical support for that family member. After a service member retires, the family continues to be eligible for TRICARE retired medical benefits.

## RECOMMENDATIONS FOR PEDIATRICIANS

To support children of military families, a nondeployed parent needs to feel in control and to have support. The pediatrician can encourage the at-home parent to stay healthy and connected, including sharing experiences and finding opportunities for personal growth, respite, and spiritual wellness. If needed, the pediatrician can support and help the parent find a mental health professional. One resource, [www.MilitaryOneSource.com](http://www.MilitaryOneSource.com), is available for pediatricians and military spouses to access adult mental health services regardless of location or service. Pediatricians should be familiar with this Web site to help family caregivers with their own emotional needs. Many of the deployment-specific resources available to AD families can be accessed on this Web site for activated National Guard and Reserve families, including Military Family Life Consultants, chaplains, legal assistance, social work services, and New Parent Support services. In addition to direct contact with a case manager or mental health locator, at-home parents can request free parenting and support books from the OneSource library, and can find parent support groups in their local areas.

The needs and concerns of the military family vary depending on the specific phase of deployment. Table 77-1 shows the phases of deployment and the role of the primary care pediatrician in providing appropriate anticipatory guidance. Pediatricians can connect a family struggling with deployment to resources available in the military community. Some military bases have deployment-related respite or child care services available. School-aged children can participate in Operation Camp Purple, which employs peer relationships to build resiliency.

Understanding military culture and asking initial questions of a child or teen who has a military parent can help unveil etiologies of academic problems, poor

**BOX 77-2 Indications for Referral**

Pediatricians should consider referral of a child/family to a mental health professional when

- They have tried reassurance and helping the parent cope using a psychoeducational intervention or generally supportive counseling, which is not working after 2 visits
- They feel uncomfortable about their own counseling and psychoeducational skills
- Child behavior has become more extreme or continues for up to 3 months after the deployed parent has returned home
- There is a significant change in behavior or a drop in school performance
- There has been an injury or death of a deployed parent

peer interactions, or risk-taking behaviors. Pediatricians need to be able to access a “virtual toolbox” containing health and mental health screening tools to help identify children in need of additional services. Box 77-2 contains additional guidelines for pediatricians to consider referral to a mental health professional.

Pediatricians are on the front line in meeting the needs of military families. By understanding the strengths and challenges of living in a military family, physicians can recognize opportunities to respond within the context of the pediatric medical home.

**TOOLS FOR PRACTICE****Engaging Patient and Family**

- *Military Youth Coping with Separation: When Family Members Deploy* (video), American Academy of Pediatrics ([www.aap.org/sections/uniformedservices/deployment/videos.html](http://www.aap.org/sections/uniformedservices/deployment/videos.html))
- *Mr Poe and Friends Discuss Reunion After Deployment* (video), American Academy of Pediatrics ([www.aap.org/sections/uniformedservices/deployment/videos.html](http://www.aap.org/sections/uniformedservices/deployment/videos.html))
- *Talk, Listen, Connect* (videos), Sesame Workshop ([www.sesameworkshop.org/what-we-do/our-initiatives/military-families](http://www.sesameworkshop.org/what-we-do/our-initiatives/military-families))

**Medical Decision Support**

- *A Toolkit for the Well Child Screening of Military Children* (toolkit), Massachusetts General Hospital ([www.homebase.org/media/toolkit-for-provider-UpdatedLogo.pdf](http://www.homebase.org/media/toolkit-for-provider-UpdatedLogo.pdf))

**AAP POLICY**

Siegel BS, Davis BE; American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health and Section on Uniformed Services. Health and mental health needs of children in US military families. *Pediatrics*. 2013;131(6):e2002–e2015 ([pediatrics.aappublications.org/content/131/6/e2002](http://pediatrics.aappublications.org/content/131/6/e2002))

**SUGGESTED READINGS**

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**Chapter 78****HOMELESS CHILDREN**

Patricia McQuilkin, MD; Jason R. Rafferty, MD, MPH, EdM

Although homelessness brings to mind the stereotype of a man panhandling on a street corner, in fact, single women and their children comprise a significant proportion of people who are homeless. Pediatricians will likely encounter children in their practices who are experiencing or have experienced homelessness. With the passage of the McKinney Act in 1987, the US Department of Housing and Urban Development (HUD) defined a homeless individual as one “who lacks a fixed, regular, and adequate nighttime residence.”

This definition has been criticized for not acknowledging the dynamic nature of homelessness, particularly because it tends to exclude families and youth. To avoid the risks of living on the streets, homeless families and youth are more likely to be in and out of shelters, residing in vehicles or motels, or “couch surfing” with friends and relatives. Consequently, by adding the education subtitle to the renamed McKinney-Vento Act, the Department of Education included children living in motels and those who share temporary housing to this definition. In 2011, HUD released the Final Rule Defining Homelessness, which incorporates families who are in unstable housing situations, are fleeing domestic violence, or may face homelessness in the next 14 days.

In some cases, the family unit as a whole experiences homelessness. In others, an “unaccompanied youth” may not be in the custody of his or her family and may be physically disconnected from them. These youth may leave their family, either voluntarily (“run-away”) or because family member(s) force them out (“thrown-away”), have no legal right to where they are staying (“doubling up”), or no access to shelter at all (“street youth”).

Knowledge of a child’s past and present housing status is important to clinical care. Homelessness can contribute to toxic stress; affect the health, psychological, and developmental well-being of a child; and



present barriers to health care access and treatment adherence.

## NUMBERS OF HOMELESS

Between 2.3 and 3.5 million Americans experience homelessness at least once per year. Single adults, some of whom are chronically homeless constitute 49% of this population. Families with children comprise 34% of the homeless population, and as the gap between income and affordable housing widens, the number of families without homes is increasing. As a result, 1.6 million children will experience homelessness during the course of a year. According to HUD “point-in-time” data, on any given night, approximately 200,000 children and youth (defined as those up to 24 years of age) will have no place to stay. About 76% of these children and youth are living with their homeless families. The remaining 23% are “unaccompanied youth.” It should be noted that this point-in-time count used the original, narrow HUD definition of homelessness so these are likely underestimates that do not take into account “doubling up” and other unstable housing situations. This leaves hundreds of thousands of homeless children invisible to policymakers and the public.

The Department of Education is also mandated to keep a count of homeless children enrolled in US public schools. In 2013, approximately 2.5 million children experienced homelessness. This represents approximately 1 in every 30 US children based on census data. Despite the use of a broader definition, this figure also is likely an underestimate, given that such children may not be consistently enrolled in school and there is an incentive against disclosure because it might affect a child’s school district assignment.

### Homeless Families

Who are these homeless families? Among adults in homeless families, 29% are working. A typical sheltered homeless family consists of a mother in her late 20s with 2 children and limited education. Among children in homeless families, 42% are younger than 6 years. An estimated 84% of these families are headed by women. Most are minorities, with 43% being African American, 38% white non-Hispanic, 15% Hispanic, and 3% Native American. Nearly all mothers experiencing homelessness have a history of interpersonal violence, and as a result, suffer from severe depression (50%), posttraumatic stress disorder (PTSD; 33%), and substance abuse.

It is estimated that 75% of homeless children and families may be “doubling up” with friends or relatives, or living in cars or motels. These families often have a strong incentive not to disclose their living situation because it may lead to eviction or complications with the children’s school district.

### Unaccompanied Youth

Homeless or unaccompanied youth comprise approximately 8% of the total homeless population and 23% of all homeless children and youth, according to HUD point-in-time counts. Among programs that count homeless youth, the US Department of Justice (DOJ) Office of Juvenile Justice and Delinquency Prevention data are most often cited. This is because they include

aggregates of diverse and relevant sources, including surveys of households, juvenile residential facilities (detention centers, group homes, etc), and law enforcement agencies. They define “homeless” as being away from home without permission for more than 1 night if the child is younger than 15 years or 2 nights if the child is older. Their most recent study reported an estimated 1,682,900 unaccompanied homeless and runaway youth in 1999. This number is equivalent to estimates by the Research Triangle Institute based on responses to the Centers for Disease Control and Prevention’s Youth Risk Behavioral Survey published in 1998.

According to DOJ data, unaccompanied homeless youth include equal numbers of boys and girls, with the majority of them being 15 to 17 years old. Seventy-one percent of these youths were categorized as being in immediate danger because of factors such as substance dependency, sexual or physical abuse, living in an area of criminal activity, or young age ( $\leq 13$  years). They are 7 times more likely to be victims of violent crimes; 30% stayed within 10 miles of home and 83% remained within their state of residency. Across studies, between 20% and 40% of homeless youth identified themselves as lesbian, gay, bisexual, or transgender (LGBT).

Recently, 9 sites across the country were selected as part of a federal interagency initiative, Youth Count!, to pilot new methods to improve counting of unaccompanied homeless youth, particularly through increased engagement with LGBT services.

## CAUSES OF HOMELESSNESS

Family homelessness is caused by a combination of factors including poverty, low-paying jobs, unemployment, lack of affordable housing, and interpersonal violence. Vulnerable families with little social support can become homeless when seemingly minor triggers result in major catastrophe. A 2005 study by the Vera Institute of Justice found that families who entered the New York City shelter system experienced remarkably high rates of disruption in their lives in the 5 years before becoming homeless. Sixty-nine percent had a job loss, 43% had physical health problems, 39% had emotional health problems, and 21% were victims of interpersonal violence. The economic recession during the period 2007 to 2010 caused one of the deepest downturns in the labor market in postwar history. This resulted in a record high number of housing foreclosures, which compounded the problem of homelessness even further. As a result, the number of homeless children increased by 38% during this period, to include many who were previously in the middle class.

Only 1 in 5 unaccompanied youth are reported missing; of these, 47% to 62% indicated that a family member told them they were no longer wanted. Most unaccompanied youth leave home to escape dysfunctional or abusive family situations, or are coerced into leaving by adults at home. There is a strong relationship between abuse and subsequent homelessness, with estimates of 17% to 35% of such youth reporting sexual abuse and 40% to 60% reporting physical abuse. Other family-related factors include neglect, parental

substance abuse, and conflict over sexual orientation, sexual activity, or pregnancy. Residential instability is another contributing factor, with the majority of unaccompanied youth having a history of out-of-home placement; specifically, 70% of homeless unaccompanied youth have spent time in a foster family, group home, or other residential facility. Nearly half of children in foster care report a history of running away, and 14% to 50% experience homelessness.

### Poverty

A clear and direct correlation exists between poverty and homelessness. The majority of homelessness in the United States is caused by the gap between income and the cost of housing. In 2009, 17% of all American families and 34% of all single-parent families lived below the federal poverty line. According to HUD, families with the following characteristics are in the category of worst-case housing needs: those who rent, have incomes less than 50% of the median family income in their community, pay more than one-half of their income for housing, and do not receive federal housing assistance. These families are at the highest risk for becoming homeless. Since this statistic was tracked in 1991, approximately 5% of households have fallen within this category. Children reside in 36% of households with worst-case housing needs.

Full-time employment is not a guarantee against homelessness. Of families with worst-case housing needs, 41% have at least 1 full-time worker. Despite being employed, many families do not earn adequate wages. Approximately one-fifth of all jobs in the United States do not keep a family of 4 out of poverty. More and more individuals are employed by service industries, such as hotels and restaurants, which pay minimum wage and often provide only part-time work, with few or no benefits. This circumstance puts housing out of reach for many families. Fair market rent is calculated by HUD as “the amount that would be needed to pay the gross rent (rent plus utilities) of privately owned, decent, and safe housing of a modest (nonluxury) nature with suitable amenities.” The National Low-Income Housing Coalition defines housing wage as the “hourly wage necessary to pay the fair market rent for a 2-bedroom home while spending no more than 30% of income on housing costs.” Nationally, the housing wage in 2005 was \$15.78, with a range of \$8.10 to \$29.54. The national housing wage is more than triple the minimum federal wage.

### Housing Shortage

A serious gap continues in the number of units needed to house low-income families and the amount of affordable housing. The National Income and Housing Coalition concluded that the United States is experiencing a significant and prolonged shortage of affordable housing. At least 1.7 million housing units are needed to fill this gap. Housing costs have also been outpacing wages. A full-time worker earning minimum wage currently cannot afford a 1-bedroom apartment at fair market wage anywhere in the United States. This situation has been exacerbated by the federal government’s decreased role in providing low-income housing over the last 20 years. Federal

support for low-income housing fell 49% between 1980 and 2003, and only 30% of persons who are eligible for low-income housing assistance receive this subsidy. Since 1995, more than 200,000 subsidized housing units have been lost.

### Interpersonal Violence

Fifty-four percent of cities surveyed in 2005 identified interpersonal violence as the leading cause of family homelessness. A study in Minneapolis found that 40% or more mothers revealed domestic violence to be a major cause of their family’s homeless situation. These families are often headed by women who are fleeing a violent situation at home, and have little in the way of social or financial support. They often are unable to obtain credit or child support. They may have difficulty accessing resources because they are afraid of being discovered by their abusers. The physician needs to be aware that interpersonal violence is an important cause of homelessness for families.

Interpersonal violence is also a major cause of homelessness for unaccompanied youth. An important subgroup, unaccompanied youth, consists of persons who are asked to leave home or are not allowed back home by a parent or guardian. Family conflict and violence are the primary causes of their homelessness, and nearly half have been physically or sexually abused.

## EFFECT OF HOMELESSNESS ON CHILDREN’S HEALTH

Homeless children have significantly higher rates of acute and chronic illness compared with housed children. Several factors are responsible for this disparity.

Homelessness can cause illness and aggravate existing health conditions. Living conditions in shelters are often crowded; children are more likely to be exposed to contagious diseases, and they often have poor access to health care. Families living in shelters are living under stressful conditions, which can exacerbate illness. Homelessness contributes to toxic stress, which has adverse effects on child health and development. (See Chapter 68, *Children Exposed to Adverse Childhood Experiences*.)

Lack of access to primary and preventive care is a major issue for homeless families. Nearly 1 in 10 homeless children reports that he or she has not seen a physician in the past year. Lapses in care can lead to lapses in treatment of chronic illness and decreased vaccination rates. Many homeless families use the emergency department as their primary source of health care. The lack of preventive care leaves various medical problems untreated, which in turn leads to more use of the emergency department.

Lack of medical insurance coverage is another barrier to homeless children obtaining primary and preventive care. One study showed that 58% of homeless children lacked health insurance compared with 15% of housed children.

### Homeless Children and Rates of Illness

Health risks related to homelessness begin during the prenatal period. Statistics show increased morbidity and mortality rates related to lack of prenatal care,

poor nutrition, stress, and exposure to violence, as well as increased substance abuse. One study revealed that 20% of infants born to homeless mothers were preterm. The risk of a homeless woman giving birth to an infant weighing less than 2 kg was 6 to 7 times that of the control group. Severity of homelessness predicts low birth weight and preterm births beyond its correlation with delayed prenatal care and other risk factors. Among pregnant homeless adolescents, a frequent history of severe sexual abuse and early intravenous drug abuse correlates with poor health outcomes in the newborn.

Homeless children have 4 times as many acute illnesses as housed children. They suffer from twice as many ear infections, 4 times as many respiratory infections, and 5 times more stomach problems. Because homeless families live in crowded conditions, the risk of acquiring upper respiratory tract infections, diarrhea, and otitis media is increased. One study revealed that homeless children had a 50% increased rate of otitis media compared with the national average (27% vs 18%). This increase was probably the result of greater exposure to upper respiratory tract infections and secondhand smoke. Because of a lack of consistent medical care among the homeless, otitis media is often undiagnosed and untreated, leading to possible hearing loss.

Homeless children also suffer from increased rates of chronic illness, exacerbated by their living conditions. Asthma, the most common chronic illness during childhood, is aggravated by the difficult living conditions in shelters, such as crowded conditions, increased exposure to respiratory infections, stress, and poor access to health care. The prevalence of asthma among a random sample of homeless children in New York City was found to be 39.8%, more than 6 times the rate for other children. Asthma in homeless children was more likely to be severe and undertreated.

Other conditions that are more prevalent in homeless children include poor dentition. Homeless children are more likely to have dental caries and severe tooth decay compared with housed children. According to the National Health Care for Homeless Providers, the rates of poor dentition and dental caries are approximately 10 times greater among homeless children than among the general population.

The risk of homeless children acquiring ectoparasitic infections such as lice and scabies is higher. They are also at increased risk for elevated lead levels.

### Oral Health

The most common unmet health need among all children is adequate dental care. This is particularly true among homeless children who are at high risk for tooth decay (5 times more common than asthma in the homeless population). One in 3 homeless children have not had dental care in the past year compared with 1 in 5 among housed children. Major contributing factors include the limited number of dentists who participate in public insurance, a general shortage of the dental workforce, long wait times after scheduling an appointment, and an uneven geographic distribution that neglects low-income areas.

### Homeless Adolescents

Regardless of whether homeless adolescents are with their families or unaccompanied, they represent a particularly high-risk population. Adolescence is a challenging time in any circumstance as teenagers learn to navigate new independence and identity alongside rapid physical change. In addition, decision-making and problem-solving skills are still developing. The lack of economic, social, and emotional resources (including supportive adult relationships) faced by homeless adolescents can interfere with one's developmental trajectory, leading to dangerous consequences and high risk-taking behavior. Adolescents and young adults are overrepresented among unaccompanied youth, and are at an extremely high risk for victimization and are least likely to be connected to service agencies. This can lead to very concerning physical and mental health outcomes. (See section on The Health of Unaccompanied Youth later in this chapter.)

In general, among homeless adolescents, the incidence and prevalence of human immunodeficiency virus (HIV) infection, *Chlamydia*, herpes, and hepatitis B and C are increased. Increases may be caused by lack of access to educational and prevention programs, lack of condom use, multiple partners, increased drug use, and sexual victimization. Homeless youth are at high risk of substance abuse, mental illness, and bloodborne infections. Mortality among homeless youth is approximately 11 times the expected rate based on age and sex and is mainly caused by suicide and drug overdose.

Sexual minorities are overrepresented among homeless adolescents, especially unaccompanied homeless youth. It is estimated that 2% to 40% of homeless youth identify as LGBT and their voluntary or involuntary "coming out" was the most common reason for becoming homeless, specifically a "throwaway." The LGBT homeless youth population is at much greater risk for violence and negative health outcomes than their heterosexual peers. In particular, they are at risk for early onset of sexual activity, involvement in prostitution or survival sex, multiple partners, and other risky behaviors leading to elevated HIV rates, substance abuse, mental health problems, and physical and sexual victimization.

### Homeless Children and Nutrition

Homelessness and hunger commonly coexist. Homeless children suffer from lack of access to food and good nutrition. Children without homes are more than twice as likely as other children to experience hunger. More than one-third have been forced to skip meals and two-thirds of these children worry about having enough to eat. It is well-established that lack of good nutrition can affect a child's behavior, school performance, and cognitive development.

Homeless children are 3 times more likely to experience iron-deficiency anemia caused by poor nutrition. One study reported a 52% rate of obesity, 45% rate of anemia, and 36% rate of failure to thrive among homeless children. Given the importance of adequate nutrition for development in the infant and young child and the risk factors associated with obesity in later life, these findings are disturbing.



### Minority Homeless Youth

Black children in the United States have disproportionately higher rates of homelessness than white and Hispanic children. Minority homeless children also have poorer health outcomes compared with their white counterparts, even when family income and health insurance coverage are controlled. For example, black homeless children are 49% more likely to have asthma and 21% more likely to have activity limitations compared with white children. Racial disparities in health outcomes persist until family income falls below 200% of the poverty line.

Many mechanisms underlie the relationship between race and poor health among homeless children. Interpersonal and institutionalized discrimination contribute to differential access to medical services, dental care, and shelters. In fact, Hispanic homeless children have been found to have the poorest overall access to primary and preventive care. Furthermore, although national studies find no racial or ethnic differences in new homelessness, local studies tend to suggest that such minorities are overrepresented. This discrepancy may be the result of a sampling bias, reflecting the fact that black and Native American youth are more likely to be on the streets because of low shelter access.

Ultimately, internalized discrimination, secondary to a child witnessing first hand the devastating effects of personal and institutional inequalities, is believed to cause physiologic stress, which has a negative influence on chronic disease. In older children, such stress reinforces feelings of injustice, powerlessness, and victimization that lead to violent behaviors and mental illness.

### EFFECT OF HOMELESSNESS ON CHILDREN'S BEHAVIORAL HEALTH

Developmental, educational, and psychological outcomes in homeless children are equally worrisome. Compared with other children, homeless children are 4 times as likely to have developmental delays, twice as likely to have learning disabilities, and twice as likely to repeat a grade because of frequent absences and school changes. The majority of both homeless mothers and their preschool children exhibit delays in at least 1 of the following areas: auditory comprehension, verbal expression, reading, and writing.

Unaccompanied youth are at particularly high risk for victimization, traumatic stress, and poor mental health outcomes, which is discussed specifically in the section entitled "The Health of Unaccompanied Youth."

### School and Homeless Children

Children experiencing homelessness face huge barriers to obtaining education. These children experience significant educational disruption because of multiple relocations and school changes. Such disruption causes lower levels of academic achievement. One study showed that among homeless children in grades 3 to 12, only 48% were proficient in math and 43% were proficient in reading. Thirty-six percent of homeless children will repeat a grade, and less than 25% of homeless children will graduate from high school.

Buckner and coworkers compared the school experiences and academic achievement of adolescents in families who experienced homelessness with permanently housed adolescents whose families received public assistance. Formerly homeless students had more school mobility, were more likely to repeat a grade, and had worse school experiences by maternal report and lower plans for postsecondary education by self-report. Homelessness was associated with declines in achievement during the period of maximal residential disruption. Days absent from school were hypothesized as the mediating link between homelessness and academic achievement.

In an effort to improve the educational opportunities of homeless children, the McKinney-Vento Homeless Assistance Act of 2001 was created. It requires that children and youths experiencing homelessness are immediately enrolled in school and have educational opportunities equal to those of their nonhomeless peers. The statute requires every public school district and charter holder to designate a *homeless liaison* to ensure that homeless students are identified and that their needs are met.

### Homeless Children and Behavioral Health

Children who experience homelessness have 3 times the rate of emotional and behavioral problems as their housed peers. This is largely because of the amount of stress and trauma that these children experience and witness.

Twenty percent of homeless preschoolers have emotional problems requiring intervention. One-third of homeless school-age children have a major mental disorder that interferes with daily activity compared with 19% in the general population. Forty-seven percent have anxiety and depression compared with 18% in the general population, and 36% are aggressive compared with 17% in the general population. Less than one-third who might benefit from treatment are receiving assistance.

Evidence that homeless youth may suffer disproportionately from behavioral and psychological problems is persuasive. Once a child is homeless, an increase can be found in the number of psychological diagnoses, including drug- and alcohol-related conditions. Trauma is a common experience among homeless youth. Trauma resulting from exposure to violence may be a mediating factor, with 83% of homeless youth older than 12 years being exposed to violence and 25% having witnessed violence in their family. The risk of sexual and physical victimization is increased among homeless adolescents, leading to increased risk of posttraumatic stress syndrome. One half of homeless youth report being physically abused, and one third experience sexual abuse. Homeless adolescents are 6 times more likely to meet criteria for conduct disorder, major depressive disorder, posttraumatic stress syndrome, alcohol abuse, or drug abuse. After homelessness, involvement in criminal activity is common.

"Attachment" describes the emotional connection between a child and caregiver, particularly the desire for closeness and security in the face of stress and separation. Therefore, the health and emotional well-being of a child is closely linked to the emotional



well-being of his or her parent. Increased levels of depression in homeless parents adversely affects their ability to provide supportive caregiving (including breastfeeding of infants), consistent social interaction, and engagement in enriching activities. This leads to an increased stress response in the child which contributes to poorer cognitive, emotional, and developmental outcomes. Unaccompanied homeless girls have much higher rates of teenage pregnancy than their peers, which is especially concerning given that homeless adolescents are at elevated risk for mood disorders with little access to resources and supports.

## THE HEALTH OF UNACCOMPANIED YOUTH

Violence is the top reason why youth leave home and disconnect from their families. The DOJ study focusing on unaccompanied homeless youth found that 21% were physically or sexually abused in the year before leaving home. A study in Seattle found that among homeless and runaway adolescents, 82% reported experiencing physical abuse, 43% family neglect, and 26% sexual abuse.

In addition to being exposed to or experiencing violence before leaving home, adolescents are at high risk for being retraumatized in shelters, and especially on the streets. A study in Los Angeles found that 1 in 4 homeless adolescents had been shot at (7% wounded), 1 in 5 had been stabbed, and 1 in 6 sexually abused. In general, as many as 43% of adolescent men and 39% of adolescent women report having been assaulted with a weapon while living on the streets. For men, the greatest risk factor for engaging in aggressive behaviors is having been physically victimized.

Unaccompanied young women and sexual minorities are particularly susceptible to sexual victimization. As many as 43% of homeless adolescents in Los Angeles reported having engaged in “survival sex,” which is the exchange of sexual acts for necessary resources. Risk factors for survival sex include a history of physical or sexual abuse, depression, the need to obtain income (often for medical care), and drug/resource sharing. LGBT homeless youth are 3 times more likely to engage in survival sex than their heterosexual peers. Sexual assault is a particular concern, with rates reported to be as high as 42% among female runaways and 59% among LGBT homeless youth (compared with 33% among their heterosexual peers in that particular study). Such behaviors have contributed to alarmingly high rates of sexually transmitted infection (estimated prevalence 50%–70%). Homeless and runaway adolescents are at 2 to 10 times greater risk for HIV infection. The longer they are homeless, the less motivated they are for HIV prevention, and may report the belief that they would be better off contracting HIV because it would make them eligible for housing funds specifically for HIV-positive people in need.

Unaccompanied youth experience almost constant fear of victimization, which is accompanied by the stressors of living in a shelter or on the streets, obtaining necessary resources to survive, and the loss of routine and predictability in their life. Such experiences

have consequences for mental health (depression, anxiety, and stress disorders), substance abuse, and reduced resiliency, and they may interfere with the individual's ability to identify and develop positive relationships. Most unaccompanied adolescents meet criteria for mood disorders, especially major depression, and more than one-third meet PTSD criteria during their lifetime. Attempted suicide rates (18%–48% across studies) are consistently higher for unaccompanied homeless youth than their normative peers with nearly half of heterosexual homeless youth describing suicidal ideation. Among LGBT homeless youth, that rate is as high as 75%.

Homeless youth may abuse substances to help withstand the severe hardships they face both at home and on the streets. The prevalence of substance use across studies ranges from 70% to 90%. Rates of marijuana abuse were 6 times higher than those for housed peers, and cocaine abuse was 35 times higher. Substance abuse is especially high among “street youth,” with 1 study stating that 94% used tobacco and alcohol, 97% used marijuana, 73.4% used amphetamines, 55.5% used cocaine, and 39.5% used heroin in the last year.

## CARE OF HOMELESS CHILDREN AND FAMILIES

### Homeless Families

Families may not identify themselves as homeless. The children may actually be attending school, yet go “undetected.” It is important to ask questions about housing to identify homeless families. This can be a part of universal previsit screening, using a tool such as Kemper's Family Psychosocial Screen.

Once a family is identified as homeless, the most important issue is ascertaining that all children are living in a safe environment. If not, then the family should be assisted with making contacts with a local family homeless shelter system, welfare agency, or charitable institution that can provide temporary housing. It should be noted that family shelters may not allow adolescent boys or adult fathers to stay, which forces male members to break off and find shelter elsewhere. Two-thirds of cities polled in a 1995 survey reported that they do break up families because of such regulations. These families will also need assistance in applying for health, nutrition, and social services and, if the child is uninsured, for Medicaid.

All children need to undergo a thorough medical, developmental, and psychological history and a physical examination to identify medical conditions associated with homelessness, the factors that led to homelessness, and needs for medical care. Particular attention should be paid to health care maintenance, including immunizations and lead testing, and to the diagnosis and treatment of chronic medical conditions. Clinic care that is offered to children while they are homeless should be comprehensive, meeting the criteria of a medical home. In addition to primary pediatric care, clinic care should include 24-hour telephone access, referral to subspecialty care, developmental and psychological evaluation and treatment, medication and medical devices, and case management.

Asthma is overrepresented among homeless children. Children often require aggressive treatment, and parents may need comprehensive education to avoid hospitalization, excessive emergency department use, and school absenteeism for their children. A child who is not sleeping at night or keeping other family members awake because of coughing can exacerbate the stress of being homeless.

Children of families living in shelters may have frequent acute illnesses as a result of living in close quarters with other families. In treating upper respiratory infection, gastroenteritis, otitis media, and tinea, a helpful approach would be to instruct parents about infection control measures in addition to applying standard treatment regimens. Outbreaks of certain illnesses, such as varicella or hepatitis, may require contacting shelter personnel or the local department of health to initiate infection-control measures.

When a parent brings in a child who has a minor acute illness, it is important to use the visit as an opportunity to perform a thorough medical assessment and initiate any needed treatment and referral. Follow-up can be problematic for homeless families, and any delay in initiating a comprehensive treatment plan may impede needed health care.

Homeless children face constant traumatic stress and uncertainty (lack of routine) as well as high rates of mental health concerns and parental depression. These have all been shown to adversely affect cognitive, emotional, and social developmental trajectories. Therefore, routine behavioral and developmental screening is essential with a validated age-appropriate tool, such as the Pediatric Symptom Checklist for school-age children and adolescents. A licensed mental health clinician who has experience working with homeless families should be identified for follow-up referrals, if necessary.

In addition to referrals for developmental assessment or psychological problems found in children, referring parents for counseling may also be necessary. Some families are homeless because of severe parental mental health problems or substance abuse. A parent may become depressed as a result of being homeless. Mental health concerns and stressors of caregivers should always be addressed so as to optimize the environment needed for a child's well-being.

One of the most common reasons for a woman and her children becoming homeless is interpersonal violence. Women must be queried about this issue. (See Chapter 68, *Children Exposed to Adverse Childhood Experiences*.) Clinicians should be aware of local resources for victims of interpersonal violence so that any necessary referrals can be made. Moving a family into an interpersonal violence shelter may be necessary if the batterer is a threat.

Chronic medical conditions are often not treated properly. This is because homeless families frequently move, resulting in multiple clinicians and discontinuity of care. This circumstance may lead to underreferral, overreferral, and undertreatment. For example, a child may be referred multiple times to specialists for the same problem; the diagnostic workup may be restarted with each referral; the specialist may never reach the point of implementing an adequate treatment plan. While the child is homeless, a more practical

approach may be to initiate the medical workup in the primary care setting, and arrange for specialty referral once the family enters permanent housing.

When a family is moving out of a shelter into permanent housing, they will often need assistance in locating medical care in their new community. This involves helping to identify a new medical home and transferring medical records to the new physician.

### Unaccompanied Youth

Distrust of adults is very common among homeless (especially victimized) youth, which limits initial contact with clinicians, even when they are readily accessible. In addition to victimization by adult figures, distrust may also be based on prior experience or fear of being forced into placement (foster care, hospitals, or detention centers) instead of having their needs met. Therefore, outreach is critical because these youth are unlikely to present to a traditional outpatient clinic.

The US General Accounting Office found that health services were not a reported priority among programs providing outreach and shelter to homeless youth. However, nearly one-quarter of unaccompanied youth reported that they receive medical care directly or through referrals from such programs. Despite the lack of attention to health care, homeless youth utilize and depend on such services being readily available. Studies show that if such programs are available, they are utilized. Homeless youth appear to access care most often for pregnancy, mental health issues, trauma, sexually transmitted infections, substance abuse, chronic conditions, and dental problems.

Homeless youth also report a reluctance to seek care for reasons such as difficulty navigating the health care system, limited clinic sites, lack of coordination among clinicians, specific hours for homeless youth, and long waitlists. They also report embarrassment, denial of any medical problems, and fear of a clinician's implicit and explicit biases.

Unaccompanied youth have various needs, including housing, education, vocational training, preventive health care, mental health care, screening for infectious disease, and substance and alcohol abuse services. Services that target this population rarely address all of them. The concept and principles of the "medical home" are essential to overcome such challenges, but this infrastructure is difficult to support in an outreach or emergency setting where such youth often present.

Once an unaccompanied youth is identified, the priority is to ensure that he or she is living in a safe environment. The youth should be assisted in making contacts that will enable access to safe housing. Resources specific for unaccompanied youth may not be available in all areas, but pediatricians need to be familiar with local service agencies, what they offer, and how to refer patients. Adolescent girls need to be able to access women's or domestic violence shelters (or family shelters if they are pregnant or have a child). Finding shelter for adolescent men may be especially challenging because they are often turned away from family shelters, and usually cannot stay in an adult shelter until they turn 18 years of age.

Whenever possible, unaccompanied youth should have access to routine preventive care, nutrition, and social services and, if uninsured, Medicaid. The youth will also need a thorough medical, developmental, and psychological history with a comprehensive physical examination. Particular attention must be paid to signs of abuse or trauma. They should be counseled on sexual health, offered screening for pregnancy and sexually transmitted infections, and provided with appropriate contraception (including access to plan B). Open-ended questions should be used to avoid assumptions about gender identity, sexual orientation, or sexual behaviors. Mental health screening is essential including assessment for mood disorders, PTSD, suicidality, and substance abuse disorders.

A safety plan should be developed for instances in which the safety of the youth is threatened, and a 24-hour emergency service should be identified. Case management, referrals for subspecialty care, psychological evaluation, and treatment should be available. If the youth resides in a shelter, then the precautions described earlier for infectious disease control should be taken. All visits to the clinic, even for a minor acute illness, are an opportunity to assess safety and high-risk behaviors, and to perform a thorough medical assessment. Continuity of care is a particular challenge among a transient population, but it is essential for effectiveness in the face of distrust and complex presenting problems. In an attempt to develop quality outcome measures through direct interviews with homeless youth, it was found that the vast majority identified continuity of care as important. They desired “. . . rapport with 1 clinician, and ‘not have to start all over again with repeating my story to someone else.’” In addition, they stated that respect was important to “. . . inform me, talk to me like a regular person instead of telling me what to do.”

Having a caring adult figure is developmentally protective for adolescents against hopelessness and emotional distress. Homeless adolescents often lack social connectedness, particularly to adults, because of histories of violence. Therefore, it is essential for clinicians to create a confidential, nonjudgmental “safe space” that consistently promotes autonomy and respect. Over time, this can foster resilience and trust around disclosing sensitive issues, such as sexuality, gender identity concerns, or trauma.

## LONG-TERM EFFECTS OF HOMELESSNESS ON WOMEN AND CHILDREN

Whether the experience of homelessness, in itself, has long-term effects on the health of a child is unknown. Although differences have been identified in the psychological and developmental characteristics of homeless children compared with housed poor children, it is not clear whether this difference is the result of events that occurred before or during homelessness. Nevertheless, it is reasonable to assume that providing needed educational, medical, and psychological services may mitigate toxic stress and limit the potential damaging effects of homelessness on the child.

It is important to keep in mind that many homeless families demonstrate an enormous amount of strength and resilience under adverse conditions and respond positively to the resources found in a medical home. In addition to identifying problems, clinicians can reinforce the strengths of the child and family, because they are crucial to helping them get through the crisis of being homeless.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *Connected Kids Clinical Guide* (booklet), American Academy of Pediatrics ([www2.aap.org/connectedkids/ClinicalGuide.pdf](http://www2.aap.org/connectedkids/ClinicalGuide.pdf))
- *The National School Lunch Program (NSLP)*, US Department Agriculture (Web page) ([www.fns.usda.gov/nslp/national-school-lunch-program-nslp](http://www.fns.usda.gov/nslp/national-school-lunch-program-nslp))
- *School Health* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/healthyyouth/schoolhealth/index.htm](http://www.cdc.gov/healthyyouth/schoolhealth/index.htm))
- *State School Health Resources* (Web page), American Academy of Pediatrics ([www2.aap.org/sections/schoolhealth/contactmap/section\\_contacts.cfm.htm](http://www2.aap.org/sections/schoolhealth/contactmap/section_contacts.cfm.htm))
- *Toolbox* (handouts), National Association of County and City Health Officials ([www.naccho.org/toolbox](http://www.naccho.org/toolbox))

### Engaging Patient and Family

- *Community Health Online Resource Center* (handouts), Centers for Disease Control and Prevention ([nccd.cdc.gov/DCH\\_CHORC](http://nccd.cdc.gov/DCH_CHORC))
- *Data Tools* (Web page), National Center for Children in Poverty ([nccp.org/tools](http://nccp.org/tools))
- *Parent and Family Resources* (Web page), Child Care Aware ([childcareaware.org/parents-and-guardians/resources](http://childcareaware.org/parents-and-guardians/resources))
- *Rental Assistance* (Web page), US Department of Housing and Urban Development ([portal.hud.gov/hudportal/HUD?src=/topics/rental\\_assistance](http://portal.hud.gov/hudportal/HUD?src=/topics/rental_assistance))
- *Social Security Administration* (Web site), ([www.ssa.gov](http://www.ssa.gov))

### Medical Decision Support

- *Pediatric Symptom Checklist* (screen), Massachusetts General Hospital ([www.massgeneral.org/psychiatry/services/psc\\_home.aspx](http://www.massgeneral.org/psychiatry/services/psc_home.aspx))
- *SEEK Parent Questionnaire* (screen), University of Maryland School of Social Work ([theinstitute.umaryland.edu/seek/seek\\_pq.cfm](http://theinstitute.umaryland.edu/seek/seek_pq.cfm))
- *Strengths & Difficulties Questionnaires* (screen), Youth in Mind ([www.sdqinfo.com](http://www.sdqinfo.com))

## AAP POLICY

American Academy of Pediatrics Council on Community Pediatrics. Providing care for children and adolescents facing homelessness and housing insecurity. *Pediatrics*. 2013;131(6):1206–1210 ([pediatrics.aappublications.org/content/131/6/1206](http://pediatrics.aappublications.org/content/131/6/1206))

American Academy of Pediatrics Council on Community Pediatrics. Providing care for immigrant, migrant, and border children. *Pediatrics*. 2013;131(6):e2028–e2034 ([pediatrics.aappublications.org/content/131/6/e2028](http://pediatrics.aappublications.org/content/131/6/e2028))

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## Chapter 79

### CHILDREN IN POVERTY

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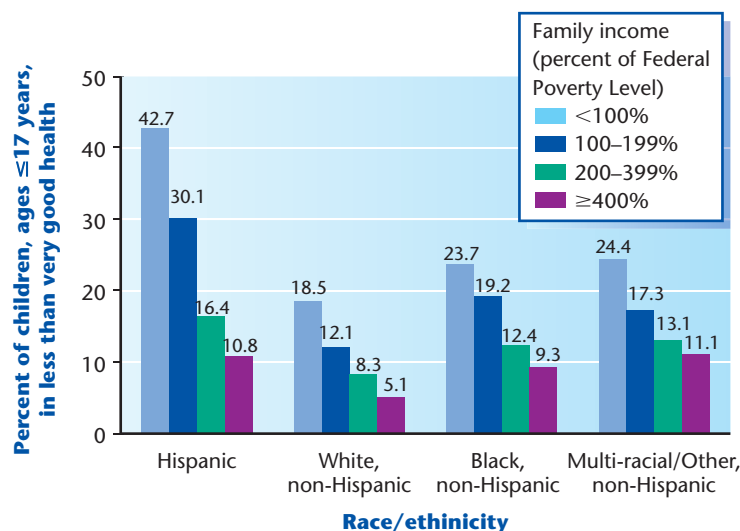
Poverty, a social determinant of health, is a major contributor to adverse child health outcomes. The life-course perspective suggests that the effect of poverty during childhood has associated adverse outcomes into adult years. The negative effects of poverty and low income on health are seen across racial and ethnic groups; however, they disproportionately affect

minority children and result in significant racial and ethnic health disparities (Figure 79-1).

Family income, although not the only measure of poverty, is the measure most commonly used in defining poverty in the United States. Children living in poverty and low-income environments are not homogenous in their resources, either personally or materially. Family structure and dynamics, resilience, gender roles and expectations, education, duration and depth of poverty, health insurance, and access to health care are among the factors associating poverty with health status. It is necessary to recognize a child and family's assets, along with income-related risks, when prescribing interventions to promote positive health and developmental outcomes.

## DEFINING POVERTY AND LOW-INCOME STATUS

Poverty guidelines are issued each year by the US Department of Health and Human Services (HHS) for administrative use in determining family eligibility for certain federal- and state-administered programs. The same guidelines apply across the 48 contiguous states, with separate, slightly higher guidelines for Hawaii and Alaska. Since 1963, when the poverty thresholds were developed, 100% of the Federal Poverty Level (FPL) has been calculated by multiplying the cost of an economy food plan by 3 and adjusting for family size; however, the food share used to develop these thresholds does not represent today's consumption pattern for either the general population or the poverty population. Today, given the comparatively greater cost of housing and other basic needs, families are estimated to need an annual income of about twice the FPL to meet their basic requirements; hence, families at 200% of the FPL are identified as low-income or near-poor families. To view current federal poverty guidelines, go to [aspe.hhs.gov/poverty/15poverty.cfm](http://aspe.hhs.gov/poverty/15poverty.cfm).



**Figure 79-1** Across every racial and ethnic group, children's health varies according to family income. Data from National Survey of Children's Health, 2011–2012.



The percentage of children in poor families is almost twice that of adults aged 18 to 64 years and 2.5 times that of seniors 65 years and older. Young children are more likely to be poor or live in low-income conditions, as are children from racial and ethnic minority populations, children of parents who did not complete high school, and children with unemployed or part-time working parents. Contrary to the traditional stereotypes, 72% of children with at least one parent who works part-time or part-year and 48% of children living with married parents are low-income children.

Determination of poverty based only on annual household income suggests homogeneity of resources across families and denies the effect of other socioeconomic factors, such as assets, investments and liabilities, occupational status, neighborhood conditions, and other socioeconomic measures. All should be considered in determining contributory risk and protective factors for health and development outcomes. For racial and ethnic minorities, discrimination—at the institutional or personal level—may interact with poverty in a way that accounts for a more negative effect.

### WHY INCOME MATTERS: POVERTY AND CHILD HEALTH AND DEVELOPMENT

Children in poor and low-income families are at greater risk for adverse health outcomes from the perinatal period through adolescence. The negative effect on child health status occurs across the income gradients: the lower the income, the greater the effect. (See Table 79-1)

An analysis of poverty, overall health status, and activity limitation using the National Health Interview Status (NHIS) survey demonstrated, among children in poverty, a higher prevalence of chronic conditions, a higher incidence of low birth weight, and a lower percentage of mothers rating their child's health as excellent or very good. Measures of unmet mental health needs also disproportionately affected poor children. Disadvantaged mothers experience depression well beyond the postpartum period. Studies have shown that infants of depressed mothers are at risk for multiple developmental and medical problems. If treated, the mothers' symptoms improve, as do their perception of their child's behavior. Furthermore, mothers of poor children were more likely to perceive their child as being progressively limited over time because of a chronic condition when compared with nonpoor children. This finding points to the potentially enhanced benefit of early intervention and treatment for poor children with chronic conditions.

Morris and colleagues proposed a conceptual framework to explain the vulnerability of child health and development in poor and low-income families. They cited 2 mechanisms: effect of family stress and parenting practices, and inability to invest material (eg, food, housing) and nonmonetary (eg, time) resources. The family stress model proposes that instability of income raises parental stress (eg, hardships such as utility shutoffs, missed rent/mortgage payments,

unstable housing, no primary care physician, inconsistent child care arrangements) and results in a more punitive and inconsistent style of parenting. The inadequate resource model aligns with findings of poorer educational outcomes for children without cognitively stimulating home environments, sufficient food, and availability of books.

Children in families that experience food hardship or housing insecurity are also more likely to have health problems than other children.

In 2000, food insecurity was present in 10.5% of households and increased to 14.9% (17.9 million) of American households by 2011 because of lack of money and other resources for food at some time during the year.

### RESILIENCE

Resilience is defined as “exhibiting a better-than-expected outcome in the face of adversity.”

The concept of resilience is useful in explaining variations among health and educational outcomes of children in low-income families. Families living in poverty are described as resilient when their beliefs about the social and/or spiritual world nourish them, when they know how to take steps to control their destiny, and when they are good at seeking, receiving, and giving support and building interconnectedness. Examples of resilience in surveys show that low-income parents who rate their children as having excellent health are more likely to maintain more structured home environments around meals, follow safety practices, and practice routine dental hygiene. Family resiliency is fostered through individual (eg, belief system, effective coping skills), family (eg, family cohesion, supportive parent-child interaction), and community (eg, adequate housing, access to quality child care and schools) protective factors for at-risk families.

### OTHER PROTECTIVE FACTORS

#### Health Insurance

Fortunately, most poor and low-income children are covered by publicly funded health insurance (Medicaid or their state's Children Health Insurance Program [CHIP]); however, gaps persist between the numbers of children eligible and those enrolled. Immigrant children are less likely to be insured, with citizen children more likely than noncitizen children to have coverage.

Children with public health insurance are more likely to receive preventive health care in the primary care setting than uninsured children and have rates for well-child visits similar to children with private insurance. Uninsured children were 6 times more likely to have unmet medical needs and twice as likely to have unmet dental needs than children covered by Medicaid or CHIP. Being insured provides significant opportunity for children to have positive health outcomes. Unfortunately, as of 2011, 16% of poor and 16% of low-income children remain uninsured, with adolescents aged 12 to 17 years more likely to be uninsured than younger children. If fully implemented and sustained at the state and federal levels, the Affordable Care Act (ACA) has the potential to reduce the number of uninsured children in the United States by another 40% and the number of

**Table 79-1** Health Status of US Children According to Family Income Level

	SAMPLE SIZE (N) <sup>a</sup>	BELOW 100% FPL	100%– 199% FPL	200%– 299% FPL	300%– 399% FPL	400% FPL OR GREATER	LINEAR TREND <sup>b</sup>	DEVIATION FROM LINEARITY <sup>b</sup>
<b>PHYSICAL HEALTH</b>								
Good/fair/poor health (%) <sup>c</sup>	90,601	33.0	19.0	11.3	7.8	6.2	$P < .05$	$P < .05$
Activity limitations (%)	90,491	9.3	6.8	4.8	4.1	3.3	$P < .05$	NS
Good/fair/poor teeth (%) <sup>d</sup>	84,788	51.3	39.6	27.4	22.0	17.1	$P < .05$	$P < .05$
Overweight/obese (%)	73,852	32.8	29.8	25.0	20.9	17.6	$P < .05$	NS
Diabetes (%)	90,564	0.4	0.3	0.3	0.4	0.2	NS	—
Bone, joint, muscle problems (%)	90,532	3.8	3.4	2.8	3.0	3.2	NS	—
Vision/hearing problems (%)	79,796	4.0	2.9	2.6	2.2	2.3	$P < .05$	$P < .05$
Asthma (%)	90,443	13.8	13.0	12.4	12.2	11.3	$P < .05$	NS
• Moderate/severe asthma (%) <sup>e</sup>	7,653	54.2	36.6	34.5	22.5	21.3	$P < .05$	$P < .05$
Severe headaches (%)	75,512	8.1	6.0	4.9	5.2	4.3	$P < .05$	$P < .05$
Ear infections (%)	75,502	7.5	5.4	4.8	3.9	3.5	$P < .05$	NS
Allergies								
• Respiratory/hay fever (%)	90,371	12.8	13.7	15.7	16.4	17.2	$P < .05$	NS
• Digestive/food (%)	90,477	3.5	3.2	3.6	3.7	3.9	$P < .05$	NS
• Skin (%)	90,492	9.1	9.8	9.4	9.6	11.1	$P < .05$	NS
<b>EMOTIONAL, DEVELOPMENTAL, AND BEHAVIORAL HEALTH</b>								
Problems with emotions, concentration, behavior (%)	75,414	24.5	21.3	17.3	14.2	13.2	$P < .05$	NS
Learning disabilities (%)	75,426	14.8	11.0	9.4	7.4	6.8	$P < .05$	$P < .05$
Autism (%)	90,530	0.5	0.4	0.4	0.6	0.5	NS	—
ADHD (%)	79,620	8.2	7.0	7.3	5.9	6.4	$P < .05$	$P < .05$
Behavior/conduct problems (%)	79,823	9.6	6.2	4.5	3.6	2.8	$P < .05$	$P < .05$
Depression/anxiety (%)	79,777	5.8	4.3	3.9	3.8	3.4	$P < .05$	NS
Speech problems (%)	75,545	5.8	3.8	3.3	2.9	2.5	$P < .05$	NS

<sup>a</sup>The sample size (N) is limited to only those individuals with no missing data on the covariates for the logistic regression models. The age range of the sample is 0 to 17 years, although some questions were not relevant and not asked of infants or very young children. There is a variability in sample size across all outcomes because of differences in age and missing data on the outcome variables.

<sup>b</sup>Results from linear polynomial statistical test. A significant linear component indicates a trend of increasing (or decreasing) health across categories of family income. A significant deviation from linearity (quadratic/cubic trend) indicates that the change is not constant across all given categories of family income (eg, gradient may be steeper at lower end of income distribution).

<sup>c</sup>good/fair/poor health vs excellent/very good

<sup>d</sup>good/fair/poor teeth vs excellent/very good

<sup>e</sup>Only among those with asthma.

ADHD, attention-deficit/hyperactivity disorder; FPL, federal poverty level; NS, not significant.

From Larson K, Halfon N. Family income gradients in the health and health care access of US children. *Matern Child Health J*. 2010;14:332–342.

uninsured parents by almost 50%. Using the Urban Institute's nationally recognized microsimulation models, researchers predict that 95% of all children in this nation will have coverage if ACA is fully implemented.

### Food Supplemental Programs

Food supplement programs, such as the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) (described later in this chapter), have been shown to reduce rates of low birth weight and iron deficiency.

Although there is a decline in iron deficiency prevalence among 1-year-old, black, and poor children, overall iron deficiency prevalence in US toddlers has persisted over the last 3 decades, and, despite the decline, it remains disproportionately elevated in certain high-risk groups: Hispanics, 1-year-olds, and overweight toddlers.

### Home Visitation

Home visitation programs, although often variable by content and outcome measure, have shown accumulating evidence that mothers with the fewest resources (ie, low income) often benefit most from the services. Home visiting has been shown to reduce rates of childhood injury, to reduce family welfare dependency, and to improve school readiness in at-risk families.

### Housing Subsidies

Increasingly, the federal government housing authority relies on portable housing subsidies, which provide lower-income households with vouchers to make housing more affordable in higher-quality neighborhoods. Housing subsidies have resulted in improved neighborhood safety and reduced exposure to violence, most successfully in black households, with limited effectiveness in Hispanic and white households.

### Quality Preschool

Early childhood interventions, such as Head Start, that address health and educational needs comprehensively have demonstrated positive health and behavioral outcomes. Head Start's mission acknowledges the influence of positive health care practices on multiple aspects of a child's development. Healthy preschoolers from low-income families have shown consistently to improve vocabulary, early writing, and early mathematics scores. Parents of children in Head Start are more likely to report having health insurance and regular dental care visits for their children. Reductions in mortality among children aged 5 to 9 years have been reported in examined long-term effects of Head Start since its introduction in the 1960s.

## ASSESSING CHILDREN IN THE OFFICE SETTING

The traditional social history obtained in the primary care office is not structured to assess basic needs of poor and low-income families. For these families the history should include more detailed information and encompass actual contributors to poor health, such as hunger and substandard housing. Other social history probes that can provide an assessment of a family's socioeconomic status include identification of social

stressors and support networks, recent change in environment, the ability to control events in one's life, and literacy. Physicians can use a tool like the IHELLP mnemonic described in Table 79-2 to assess these influences in the patient or family.

## CARE OF THE POOR AND LOW-INCOME CHILD

### Routine Health Supervision

Low-income children are at greater risk than their peers for overall poor health status indicators and special conditions such as overweight/obesity, asthma, vision and hearing problems, severe headaches, and ear infections (Table 79-2). In their day-to-day practices in medical homes, primary care physicians can promote optimal nutrition, growth, and physical health as part of health maintenance, including provision of immunizations and anticipatory guidance. Guidance regarding developmental and behavioral issues and concerns can help parents enhance their nurturing relationships with their children, especially those at risk because of limited material resources.

As part of daily practice to stimulate low-income children who have an increased vulnerability to learning and behavioral problems, primary care physicians can promote the "5 Rs" of early education.

- **Reading** together as a daily family activity (using the Reach Out and Read program, for example)
- **Rhyming**, playing, and cuddling together often
- **Routines** and regular times for meals, play, and sleeping, which help children know what they can expect and what is expected from them
- **Reward** with praise for everyday successes
- **Reciprocal** and nurturing relationships, which are the foundations of healthy child development

When anticipatory guidance reveals health-promoting behaviors, physicians can provide positive feedback and encouragement to continue and expand the practices. The Bright Futures selective screening criteria that affect low-income children include those for anemia, lead, tuberculosis, and dyslipidemia screening. Low-income children with environmental risk, including limited access to food, should be screened for anemia at the 18-month visit and 2- to 5-year annual visits in addition to the initial screen at 9 to 12 months of age. Children exposed to old housing, children who are refugees, and children in communities with identified lead exposure require lead screening. Immigrant children born in high-risk countries should be screened for tuberculosis, and physicians should be attentive to guidelines for dyslipidemia screening in overweight low-income children. Physicians can improve identification of children with developmental delays by integrating regular, systematic, developmental screening and surveillance into their practices. Children identified as having developmental delays and children at risk for delays can be referred to community-based services, such as early intervention programs (eg, Birth to 3), home visitation programs, Head Start, and special education programs available through public schools. An appropriate response to identified socioeconomic stressors is to offer potential problem-solving strategies, pose further

**Table 79-2****Examples of Potential Social History Questions (Using the “IHELLP” Mnemonic) to Address Basic Needs**

DOMAIN/AREA	EXAMPLES OF QUESTIONS
<b>INCOME</b>	
General	Do you ever have trouble making ends meet?
Food income	Do you ever have a time when you don't have enough to food? Do you have WIC? Food stamps?
<b>HOUSING</b>	
Housing	Is your housing ever a problem for you?
Utilities	Do you ever have trouble paying your electric/heat/telephone bill?
<b>EDUCATION</b>	
Appropriate education placement	How is your child doing in school? Is he/she getting the help to learn what he/she needs?
Early childhood program	Is your child in Head Start, preschool, or other early childhood enrichment?
<b>LEGAL STATUS</b>	
Immigration	Do you have questions about immigration status? Do you need help accessing benefits or services for your family?
<b>LITERACY</b>	
Child literacy	Do you read to your child every night?
Parent literacy	How happy are you with how you read?
<b>PERSONAL SAFETY</b>	
Domestic violence	Have you ever taken out a restraining order? Do you feel safe in your relationship?
General safety	Do you feel safe in your home? In your neighborhood?

WIC, Special Supplemental Nutrition Program for Women, Infants, and Children.

From Kenyon C, Silverstein SM, Silverstein M, et al. Revisiting the social history of child health. *Pediatrics*. 2007;120(3):e734–e738.

questions for clarification, and offer referral sources, including the safety net programs described in the following text. Pediatricians can monitor children's participation and progress as a result of these referrals.

## SAFETY NET PROGRAMS

Safety net programs offer low-income families opportunities to become more economically stable. Pediatricians need to become knowledgeable about the basics of such programs, to advocate for them and consider them as a resource for low-income and poor families in their care. Safety net programs may be sponsored by nonprofit or faith-based organizations or local, state, or federal government. Several federally funded programs (Temporary Assistance for Needy Families; Earned Income Tax Credit; Child Support; Child Care Subsidies; WIC; National School Nutrition Programs; and Food Stamps) are discussed in the following text. Medicaid and CHIP are described in Chapter 1, Health Care Delivery System.

Not detailed in this chapter are several other safety net programs beneficial to economically disadvantaged populations. Pediatricians should familiarize themselves with those programs, which include Supplemental Security Income, Social Security Disability Insurance, Unemployment Insurance, Early Head Start, and Head Start. Many low-income families depend on the National School Lunch Program and School Breakfast Program to provide food for their school-aged children; these programs provide free and reduced-priced nutritionally balanced meals

to eligible children living below 130% and below 185% of the federal poverty threshold, respectively, for the families to meet the daily food requirements.

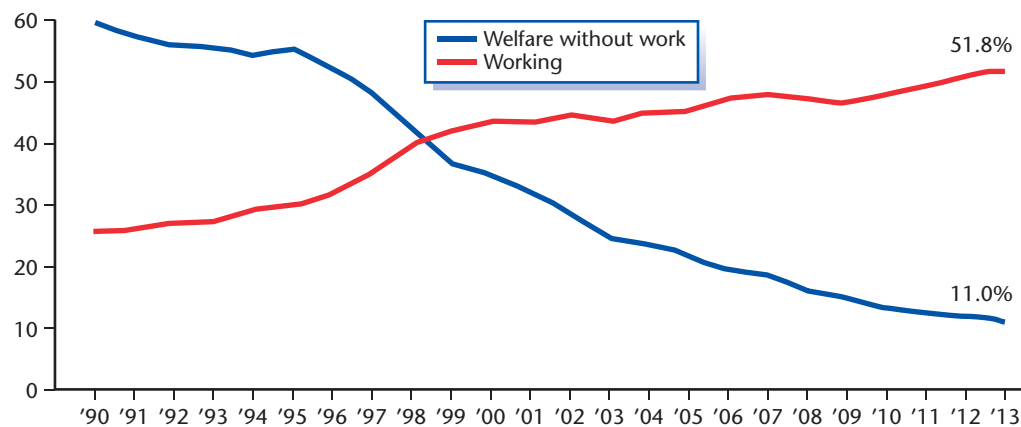
## Temporary Assistance for Needy Families

In 1996, welfare reform legislation replaced the existing welfare programs (Aid to Families with Dependent Children, Job Opportunities and Basic Skills Training, and Emergency Assistance) with Temporary Assistance for Needy Families (TANF). The Personal Responsibility and Work Opportunity Reconciliation Act released the federal government from responsibility to provide direct financial support based on entitlement, and instead provided funds for administration of public assistance at the state level. To receive TANF, adults with dependent children must pursue job opportunities and training. After the benefits begin, the adult has up to 60 months of support, which can be terminated if the state determines the individual is capable of obtaining an entry-level position. Of the 12 million people who receive TANF, most are single mothers.

## Earned Income Tax Credit

The Earned Income Tax Credit (EITC) is a refundable income tax credit for low- to moderate-income working individuals and families, usually for those whose annual income is between \$35,000 and \$48,000. The structure of the federal EITC program and the 24 state-level EITCs allows families to receive money back, based on income, marital status, and number of children. To qualify, an individual must meet certain





**Figure 79-2** Share of SNAP households with children by type of income. (Reprinted with permission from Testimony of Robert Greenstein, President, Center on Budget and Policy Priorities Before the House Committee on Agriculture. February 25, 2015. Available at: [www.cbpp.org/testimony-of-robert-greenstein-president-center-on-budget-and-policy-priorities-before-the-house](http://www.cbpp.org/testimony-of-robert-greenstein-president-center-on-budget-and-policy-priorities-before-the-house). Accessed October 5, 2015.)

requirements and file a tax return, even if he does not owe any taxes. Congress approved this tax credit legislation in 1975 with the goal of rewarding and encouraging working, in addition to helping families offset the burden of Social Security taxes. Many families use EITC refunds to pay for necessities, make repairs to homes or vehicles, or continue with higher education and training.

### Child Support

Child support enforcement occurs at the state level and involves the collection of court-ordered child support payments. More than 60% of child support collected each year occurs by the direct withholding of money from the court-ordered noncustodial parent. If child support monies are not collected from the noncustodial parent, serious penalties can occur, including the retention of federal and state tax refunds, liens on property, freezing of bank accounts, and suspension of driver, occupational, or operation licenses.

### Child Care Subsidy

The Child Care and Development Fund (CCDF) is the key resource that the federal government provides for funding child care subsidies to support work among low-income families. It is administered by the Administration for Children and Families (ACF) in the Department of Health and Human Services. Annually, each state has an allocation of funds for child care subsidies consisting of separate mandatory, matching, and discretionary funds. Child care subsidies provided through CCDF and associated state funding assist nearly 1 million families and 1.6 million children in an average month.

### Supplemental Nutrition Assistance Program (Food Stamps)

The national Supplemental Nutrition Assistance Program (SNAP), historically known as the Food Stamps program, provides more than 46 million poor and low-income Americans with a mechanism to acquire nutritionally adequate food. Since 2004, all states use an Electronic Benefit Transfer (debit card) for all

food stamp benefits. Eligibility for food stamps is based on the following rules: (1) A household's gross monthly income must be at or below 130% of the FPL; and (2) household and vehicle assets must be below \$2,000 to \$3,250 (based on different circumstances), consistent with TANF rules. There is some variability, however, in how states handle the vehicle assets: some exclude the entire value of vehicles; some count the value of vehicles; some exclude the value of 1 vehicle per household. Each state designates the application process for food stamps, although most have a centralized location, and most require able-bodied adults between 16 to 60 years of age to register for work, accept suitable employment, and take part in an employment and training program to receive the nutrition benefit. Figure 79-2 illustrates the proportion of households with children receiving food stamps by working status from 1990 to 2013.

### Special Supplemental Nutrition Program for Women, Infants, and Children

The Special Supplemental Nutrition Program for Women, Infants, and Children is a federally funded program administered by the states for low-income pregnant women, breastfeeding mothers, and infants and children up to the age of 5 years. Families receive monthly checks or vouchers redeemable for baby formula, infant cereal, iron-fortified adult cereal, milk, vitamin C-rich fresh fruit, fruit and/or vegetable juices, eggs, cheese, and certain other foods for their consumption. Soy-based beverages, tofu, baby foods, whole-wheat bread, and other whole-grain options were recently added to the program. A few state agencies distribute WIC foods through warehouses or deliver the food to participants' homes. In addition to making nutritious foods more accessible to families, WIC provides nutrition education, breastfeeding support, health and social service referral, and referrals for health care. The WIC eligible food list is available at [www.fns.usda.gov/wic/benefitsandservices/foodpkgregs.HTM#JUICE\\_\(Women\\_and\\_Children\)](http://www.fns.usda.gov/wic/benefitsandservices/foodpkgregs.HTM#JUICE_(Women_and_Children)).

The nutritional foods supplied by WIC vouchers provide families with access to a balanced diet of specific items.

A study in 2008 found that WIC families who had access to a weekly voucher for fresh foods from either a farmers' market or a supermarket were more likely to increase their daily intake of fruits and vegetables and maintain that increase. Beginning in 2009, WIC participants began receiving vouchers for farmers' market and supermarket use, covering fresh, frozen, and canned fruits and vegetables (minus potatoes and foods provided by their state commodity supplement program). WIC also covers many unprepared foods, whole grains, and brown rice, all of which are high in either protein, calcium, iron, vitamin A, or vitamin C. Additional foods are available for women who are breastfeeding, until their infant turns 12 months old. If a woman chooses not to breastfeed, infant formula is included with the WIC program vouchers, along with infant solid foods.

The medical benefits of providing foods with strong nutritional value include higher birth weights, lower infant mortality rates, lower numbers of preterm births, and a higher rate of preventive health service use. Women enrolled in WIC tend to have healthier pregnancies and deliveries. WIC mothers deliver fewer preterm infants than women not enrolled in WIC. In fact, these women generally tend to have babies of healthy birth weight. Khanani and colleagues demonstrated that WIC participation significantly reduced the disparity in infant mortality rates between African Americans and whites compared with non-WIC participants.

In addition to food vouchers, the WIC program provides some nutritionally at-risk women and children with social service referrals.

## LIMITATIONS OF SAFETY NET PROGRAMS

Many of the safety net programs summarized in the previous text do not coordinate or integrate with each other. For example, as wages increase to elevate a family's income, the family may lose benefits such as child care subsidy and have, effectively, less cash than before the wage increase. The dilemma could be remedied by allowing families to phase out government-sponsored benefits such as EITC, child care, or food stamps. This phasing out of benefits would result in a more gradual loss of benefits to prevent families from slipping back into poverty. To minimize the poverty burden on children and families, policymakers must examine the consequences of lack of coordination of programs that were originally designed to lift families out of poverty and the service gaps created by interstate variability in benefits.

## PUBLIC POLICY OPTIONS FOR CHILD ADVOCATES

Most low-income children have parents who work at low-wage jobs, bringing in insufficient income to pay for basic family expenses. Limitations in social and political power result from low-income status. In addition, work support benefits are inadequate and difficult to access. Physicians can collaborate with policymakers to reframe social and health policies to support low-income families and promote the healthy

growth and development of their children. Examples of such policy reframes might include a reduction or elimination of asset tests for major means-tested benefit programs. Many states have chosen to reduce or eliminate asset tests in work support programs as a means to assist recipients in achieving self-sufficiency. Other states, such as California, Colorado, and Illinois, have restructured their programs by increasing the amount of cash resources and exemptions allowed for certain forms of assets. Physicians also have opportunities to affect their communities through American Academy of Pediatrics (AAP) grant programs, educational resources, and federal and state advocacy strategies. Grants for projects that increase access to health care, preventive health care, and service coordination are just a few of the services funded through the Coordinated Approach to Child Health (CATCH) and Healthy Tomorrows programs. The AAP Council on Community Pediatrics is a source of ongoing direction to physicians about poverty and child health.

In addition, collaboration between physicians and lawyers can ensure that the basic needs of families are met. A national model called "medical-legal partnerships" has emerged as an effective intervention to ensure that low-income families benefit from government-sponsored programs for which they are eligible. In this model, a lawyer on site at a medical practice offers families assistance in advocating for legal and social services, especially those with outcomes that affect health status, such as housing and special education programs. Box 79-1 summarizes public policy

### BOX 79-1 Public Policy Options to Mitigate Economic Insecurity

- Phase out rather than abruptly terminating supplementation programs ("falling off the cliff")
- Promote financial and health literacy
- Invest in early childhood education
- Eliminate asset tests in means-tested programs
- Support Temporary Assistance for Needy Families (TANF) with focus on family-friendly workplaces
- Expand home visitation
- Integrate quality programs across education, workforce, health, housing, neighborhoods
- Develop asset-building programs
- Expand family leave policies
- Expand safety net programs to a greater share of eligible children
- Provide comprehensive health insurance coverage
- Ensure that working at minimum wage covers a family's basic expenses
- Invest in safe neighborhoods
- Coordinate programs for children applying for or receiving multiple government-sponsored benefits (eg, offer a universal application)

Adapted from Kaplan GA. The Poor Pay More: Poverty's High Cost to Health. September 2009. Available at: [hdl.handle.net/2027.42/65007](http://hdl.handle.net/2027.42/65007). Accessed January 7, 2015.

options that various experts have suggested to mitigate economic insecurity for children of low-income families.

## SUMMARY

Although children living in poverty and low-income environments are at greater risk than their peers for adverse health and educational outcomes, a number of home, clinic, school, community, and government interventions have been shown to mitigate these risks successfully. Primary care physicians have opportunities to nurture resilience in low-income children and families, identify and address the health problems they face, and connect them to community services and safety net programs that are likely to improve their health and educational outcomes. Physicians can also serve as advocates for enactment of public policies that support children in low-income environments.

## TOOLS FOR PRACTICE

### Community Advocacy and Care Coordination

- *Connected Kids Clinical Guide* (booklet), American Academy of Pediatrics (patiented.solutions.aap.org)
- *State School and Health Resources* (Web page), American Academy of Pediatrics (www2.aap.org/sections/schoolhealth/contactmap/section\_contacts.cfm.htm)
- *The National School Lunch Program (NSLP)* (Web page), US Department of Agriculture (www.fns.usda.gov/nslp/national-school-lunch-program-nslp)
- *Adolescent and School Health* (Web page), Centers for Disease Control and Prevention (www.cdc.gov/healthyyouth/schoolhealth/index.htm)
- *National Association of County and City Health Officials Toolbox* (Web page), National Association of County and City Health Officials (www.naccho.org/toolbox)
- *USDA Food and Nutrition Services* (Web page), USDA Food and Nutrition Services (www.fns.usda.gov/wic/benefitsandservices/foodpkgregs.HTM#JUICE\_(Women\_and\_Children))

### Engaging Patient and Family

- *National Center for Children in Poverty Data Tools* (Web page) National Center for Children in Poverty (nccp.org/tools)
- *Community Health Online Resource Center* (Web page) Community Health Online Resource Center (nccd.cdc.gov/DCH\_CHORC)

- *Child Care Aware Parent and Family Resources* (Web page), Child Care Aware (childcareaware.org/parents-and-guardians/resources)
- *Rental Assistance* (Web page), US Department of Housing and Urban Development (portal.hud.gov/hudportal/HUD?src=/topics/rental\_assistance)
- *Supplemental Nutrition Assistance Program (SNAP)* (Web page), US Department of Agriculture (www.fns.usda.gov/snap)
- *Office of Child Support Enforcement* (Web page), US Department of Health and Human Services (www.acf.hhs.gov/programs/css)
- *About Head Start* (Web page), Head Start (eclkc.ohs.acf.hhs.gov/hslc/hs/about)
- *Social Security Administration* (Web site), Social Security (www.ssa.gov)

## AAP POLICY

American Academy of Pediatrics Council on Community Pediatrics and Committee on Native American Child Health. Health Equity and Children's Rights. *Pediatrics*. 2010;125(4):838–849. Reaffirmed October 2013 (pediatrics.aappublications.org/content/132/6/e1715)

Milteer RM, Ginsburg KR; American Academy of Pediatrics Council on Communications and Media, Committee on Psychosocial Aspects of Child and Family Health. The importance of play in promoting healthy child development and maintaining strong parent-child bond: focus on children in poverty. *Pediatrics*. 2012;129(1):e204–e213 (pediatrics.aappublications.org/content/129/1/e204)

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## PART 3

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# Maternal and Fetal Health: Effect on Pregnancy Outcomes and Perinatal Health

- 80 Perinatal Preventive Care: Fetal Assessment
- 81 Assisted Reproductive Technologies, Multiple Births, and Pregnancy Outcomes
- 82 Prenatal Diagnosis
- 83 Fetal Interventions
- 84 Maternal Depression



## Chapter 80

# PERINATAL PREVENTIVE CARE: FETAL ASSESSMENT

*E. Rebecca Pschirrer, MD, MPH; George A. Little, MD*

Pediatricians, as primary care physicians and as subspecialist neonatologists, consult and work collaboratively with obstetric providers in preconception counseling, fetal risk identification, and peripartum decisions. Years ago, pediatricians first saw their newborn patients in the nursery, but only after the events of pregnancy and delivery; today their initial interaction with the pregnant woman may be during a prenatal pediatric visit. In addition, pediatricians assume primary responsibility for resuscitation, stabilization, and ongoing care of the neonate from the moment of birth. Knowledge about fetal health includes appreciation of the interaction of the fetus with the mother, her partner, health professionals, and society. Many examples exist of the capacity for fetal medicine, as part of preconception and prenatal care, to prevent or treat problems and improve outcomes.

Parents and professionals have good reason to be concerned about the immediate and long-term effects of agents or processes on the fetus. Infections such as rubella can result in the loss of the fetus or in multisystem disease. The magnitude and seriousness of manifestations of maternal alcohol consumption, tobacco use, or substance abuse during pregnancy may be evident in the infant's physical appearance or behavior in the neonatal period and throughout the child's life course. Furthermore, problems may not appear until a subsequent generation. The effects of diethylstilbestrol, once given to mothers to reduce the risk of pregnancy complication or abortion, for threatened abortion, were not recognized until the appearance of clear cell carcinoma of the vagina in female offspring 10 to 20 years later.

Growth and development are as much a key to fetal medicine as they are to pediatrics, of which study of the fetus is merely the first phase. Human growth and development must be regarded as a continuum that begins with conception (Figure 80-1). This chapter outlines some of the normal physical and interactive aspects of fetal existence, then discusses selected pathophysiologic states that may adversely affect that existence.

## MATERNAL CONDITIONS THAT AFFECT THE FETUS AND NEWBORN

Many authorities have pointed to socioeconomic status and social environment as causes of fetal risk. Delineation of specific influences is difficult, but poverty is undoubtedly important, as are nutrition and hygiene. Intrauterine infection is more frequent in mothers of lower socioeconomic status. Emotional influences on fetal loss have been discussed; in addition, the possibility that medical or socioeconomic deprivation contributes cannot be discounted. Knowledge

of a patient's race, ethnicity, and language and communication needs can assist in the provision of patient-centered care, facilitate appropriate risk assessments, and improve perinatal outcomes. Socioeconomic status, immigration, and health literacy may further moderate the effect of race, ethnicity, and language. Quality maternity and perinatal care can be influenced by a provider's identification and understanding of the cultural beliefs and experiences of the pregnant woman and her family, and by the expression and understanding of health care needs communicated by patients.

The risk for adult health disorders, particularly obesity and metabolic syndrome, can be markedly influenced by early life events, such as maternal preexisting and pregnancy-related health conditions and environmental exposures. These pregestational and gestational factors affect both prenatal and neonatal growth trajectories. Alterations in embryonic and fetal nutrition as well as endocrine status during gestation can result in developmental adaptations that produce permanent structural, physiologic, metabolic, and epigenetic changes, thereby predisposing an individual to adult cardiovascular, metabolic, and endocrine diseases, particularly metabolic syndrome.

## Maternal Nutrition

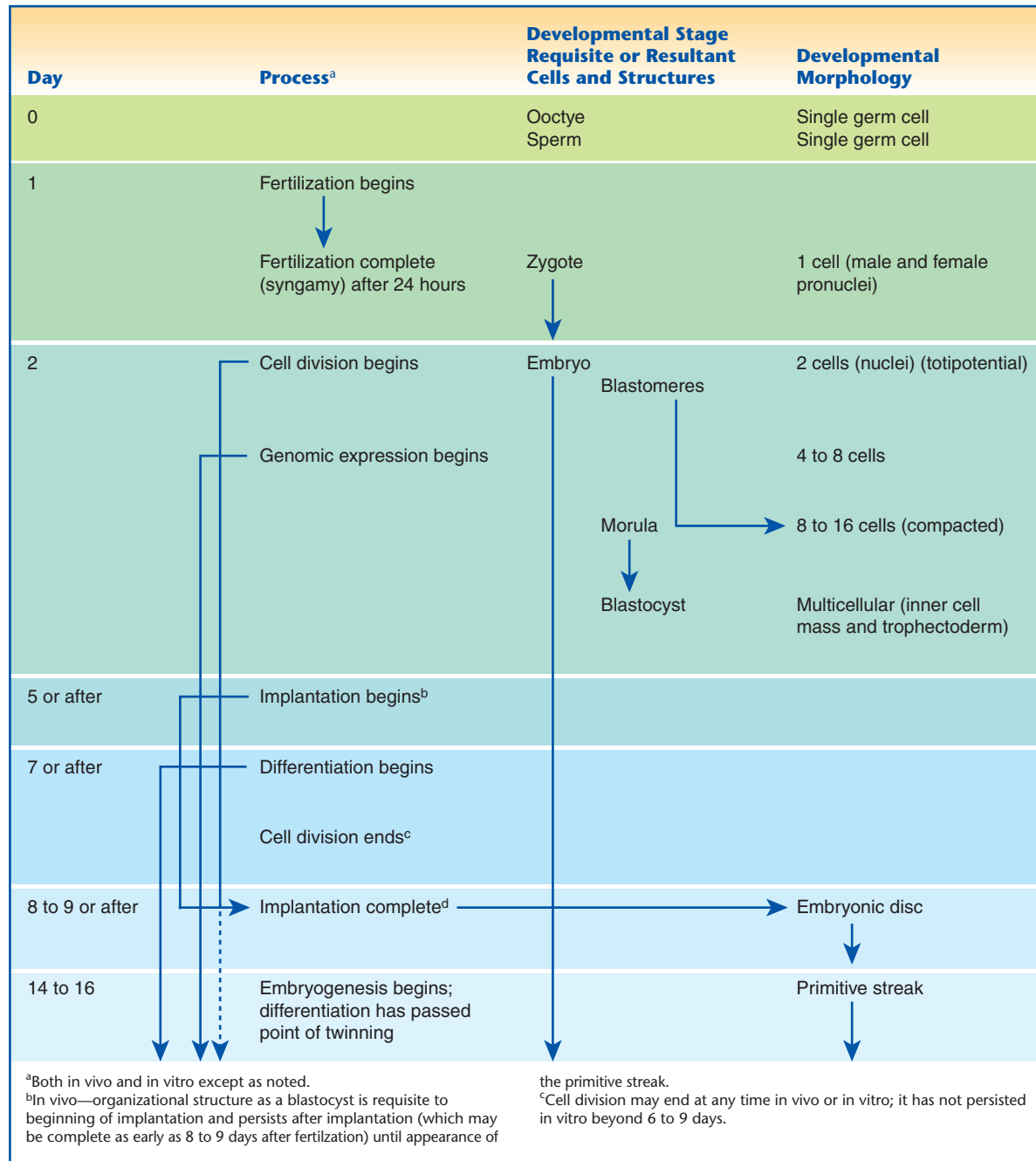
Maternal nutritional disorders represent a definite risk to the fetus, including situations in which gross deprivation is not apparent. The supply of substrate to the fetus for growth originates with the maternal circulation and passes through an interface with fetal tissue at the placenta. Placental insufficiency can result in intrauterine growth restriction (IUGR) that is not of maternal origin. The relationship between maternal and fetal nutrition is complex. Maternal dietary changes usually do not directly or rapidly influence fetal well-being; thus, the positive or negative effects of changes in maternal nutrition are not easily recognized. Maternal weight is an important concern.

Traditionally, 2 types of nutritional deficiency have been conceptualized: general caloric or energy-related deficiency states and specific deficiencies. Deprivation of maternal caloric intake to the point at which fetal growth is markedly impaired also may be associated with specific deficiencies. If maternal caloric deprivation is severe, then fertility is decreased.

Women whose prepregnancy weight is below standard for height tend to have babies whose weight is less than expected. Women who are obese tend to have heavier babies. Problems such as hyperemesis gravidarum can result in fetal caloric deprivation. The mother's expression of eating disorders that often start during late childhood and adolescence is a possible fetal risk.

Specific deficiencies are well recognized; their risk to the fetus can be reduced through public health and individual clinical interventions. Vitamin deficiencies are of interest, and problems such as congenital beriberi (lack of thiamine) and infant calcium disorders (lack of maternal vitamin D) are of historical interest and decreasing incidence. Studies have

### Early In Vivo and In Vitro Human Development Process



**Figure 80-1** Fetal and child development begins with fertilization and is similar in vivo and in vitro for 6 to 9 days. (From American College of Obstetricians and Gynecologists. *Using preimplantation embryos for research*. ACOG Committee Opinion No. 347. Obstet Gynecol. 2006;108:1305–1317. Used by permission.)

confirmed that neural tube defects can be reduced by consuming folic acid, with the best protection achieved when 0.4 mg is ingested from at least 1 month before conception through the first month of pregnancy.

Minerals are a major concern in pregnancy. Iodine deficiency is said to be the most common cause of preventable mental deficiency in the world; treatment

during pregnancy protects the fetal brain, with later treatment being much less beneficial to neurologic status. Zinc deficiency may also be associated with anomalies. Maternal anemia caused by reduced availability of iron is well known; the fetus and infant, as a result, can have low iron stores, making the infant susceptible to iron deficiency if intake after birth is inadequate.



## Environmental Exposures

Adverse reproductive and developmental effects have been linked to environmental exposures. Vulnerability to toxic insult varies with the rate of cell division and with the developmental state of the exposed tissues; rapidly dividing cells, such as spermatocytes, neural stem cells, and embryonic cells, will be especially susceptible. Adverse birth outcomes include preterm birth and low birth weight (IUGR), congenital malformations, spontaneous pregnancy losses, and neurodevelopmental impairments. Environmental factors, such as radiation, chemicals, and drugs, affect people of all socioeconomic classes. A woman's preconception or prenatal history should include review of history of alcohol and smoking as well as secondhand smoke exposure, illicit substance use, and other environmental exposures. These environmental toxicant exposures include mercury intake through fish consumption; well-water nitrate exposures; exposures to chemical, physical, and/or biologic hazards in the workplace or community; and lead and other toxicant exposures in the home. It is important to be aware that males are also vulnerable to environmental toxin exposures. Male-linked factors (referred to as *male-mediated teratogens*) that have been identified as having the potential to cause damage to offspring include cocaine, alcohol, some pesticides and solvents, such as dibromochloropropane and trichloroethylene, and heavy metals such as lead and mercury. Reviewing exposure and risk factors for potential exposure is important, particularly for exposure to mercury, lead, pesticides, and endocrine disruptors, such as phthalates, bisphenol A, and polybrominated diethyl ethers. There are many excellent resources available regarding environmental exposures, which are listed at the end of the chapter. Radiation exposure in mammals causes fetal death, growth retardation, and congenital malformation, with the central nervous system (CNS) commonly affected. The relationship between embryonic or fetal irradiation and carcinogenesis is unclear. Effects are both dose and rate related. Death during the preimplantation period, malformation during early organogenesis, and cell deletion and hypoplasia during fetal life form a general pattern in animal studies. Guidelines exist for limiting radiation to the embryo and fetus during occupational exposure or elective diagnostic techniques; however, dilemmas often arise as a result of lack of foreknowledge about pregnancy, nonelective medical evaluations, and emotional factors. When necessary, a radiation physicist should be consulted.

Air pollution can originate from multiple sources, such as car exhaust, power plants, factories, fires, and fumes from solvents. Of the many chemical components that constitute air pollution, 4 of the most dangerous pollutants are sulfur dioxide, carbon monoxide, nitrogen oxides, and particulate matter. Exposure to air pollution early in pregnancy can affect fetal development. Similarly, exposure to pesticides (organophosphates) and herbicides through contact with contaminated air, food, and ground water can lead to IUGR and anomalies, such as limb reduction deformities and urogenital and musculoskeletal defects. Neurotoxicity can result from prenatal and postnatal exposure to lead and methylmercury, leading to neurodevelopmental and

cognitive impairments, cerebral palsy, sensory deficits (blindness, deafness), and deficits in attention, fine motor function, language, visual-spatial abilities, and memory.

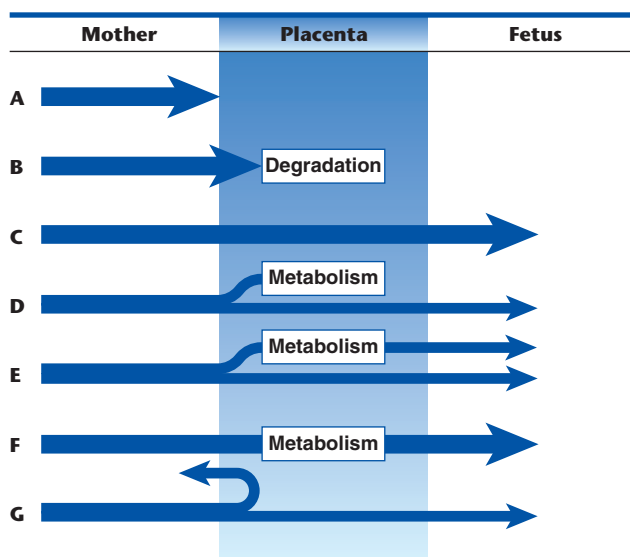
Chemicals in the environment are of natural and synthetic origin. Certain substances, such as pesticides and mercury, have been the focus of attention, although more study of other potential environmental toxins is needed. Many agents are potentially more toxic to the embryo, fetus, and neonate than to older children and adults. Perchlorate, both a naturally occurring and a human-made contaminant increasingly found in groundwater, surface water, and soil, is another environmental toxin of increasing concern because of its interference with thyroid uptake of iodide and potential to affect child health and development. Lead exposure during pregnancy, at both low and high levels, has been associated with adverse fetal and neonatal outcome. Appropriate maternal calcium intake may decrease fetal lead exposure, resulting from decreased mobilization of stored lead in maternal bone.

Mercury exposure is a major issue in environmental health, in large part because of its toxicity to the brain, especially the more susceptible fetal brain. Mercury is common in the environment in small amounts and occurs in 3 forms: the metallic element, inorganic salts, and organic compounds. Predatory fish are the primary exposure, and local fish advisory bans are available from the US Environmental Protection Agency. Women planning pregnancy, women who are pregnant or breastfeeding, and children younger than 15 years have been advised to avoid eating swordfish or shark and to limit the amount of tuna eaten. Updates on information regarding the safety of fish and shellfish, as well as resources for local health departments, may be found through the US Environmental Protection Agency. Research has shown variable amounts of mercury during testing of different brands of tuna. Thimerosal, a mercury-containing preservative used in some vaccines, has been the subject of concern and controversy, resulting in its no longer being used in vaccines despite the lack of evidence of causality. (See Chapter 20, Immunizations.)

## Drugs and Other Substances

Drug use during pregnancy is epidemic and may be on the rise. Physicians must be concerned about all types of drug use: legitimate (nonprescription and prescription), social, illegal, and abusive. All health care professionals, especially the primary care physician, should recognize that the concept of the placenta as an effective toxic substance barrier between maternal and fetal circulation has been discarded.

The maternal-fetal pharmacologic mechanism is complex, with the placenta serving as an organ of exchange (Figure 80-2). Placental diffusing capability or permeability of the simple variety operates for many substances; energy-utilizing transport is also important. Drugs in the maternal circulation should be assumed to cross the placenta and should be evaluated for potential teratogenesis. The risk to the fetus depends on several factors, including concentration of the substance, length of exposure, and when exposure occurs during gestation.



**Figure 80-2** Maternal-fetal transport patterns and the role of the placenta, a fetal organ with active metabolic activity. **A**, Placental barrier with minimal uptake or transfer (eg, succinylcholine, highly charged quaternary compounds). **B**, Active placental uptake and degradation without transfer as seen with insulin. **C**, Placental uptake and transfer without significant change as with bilirubin. **D**, Placenta actively involved in uptake, partial use, and transfer (oxygen, glucose, amino acids, free fatty acids). **E**, Uptake, partial metabolism, and transfer (cyclosporine). **F**, Placenta actively modifies during transfer (25-hydroxyvitamin D<sub>3</sub>). **G**, Carrier-coupled uptake occurs with release of ligand to the fetus and regeneration of carrier on the maternal side (transferrin-iron). (Adapted from Pridjian G. *Feto-maternal interactions: placental physiology and its role as a go-between*. In: Avery GB, Fletcher MA, MacDonald MG, eds. *Avery's Neonatology: Pathophysiology and Management in the Newborn*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999. Reprinted by permission.)

Therapeutic agents, both prescribed and nonprescribed, may be taken before pregnancy is recognized, thereby placing the products of conception at risk during the period of organogenesis in early gestation. An important benefit of preconception or interconception care is the opportunity to identify medication uses that are necessary, such as anticonvulsants, or desirable, such as nonnarcotic analgesics, and to monitor or modify exposure. Examples of problems include fetal hydantoin syndrome and the potential effects on the mother and fetus of aspirin, including clotting abnormalities and disruption of prostaglandin synthesis.

Many of the therapeutic agents indicated during the course of pregnancy and delivery require judicious use because of known and potential risks. Antimicrobial therapy is often necessary when treating maternal conditions, such as urinary tract or gynecologic infections, but must be used with the knowledge that well-recognized fetal problems can result, such as bone and dental dysplasias associated with fetal tetracycline exposure and the potential hearing loss of fetal

aminoglycoside toxicity. Cardiovascular medications that cross the placenta readily, such as digitalis, can be used to treat the fetus or can cause fetal problems. Selective serotonin reuptake inhibitors (SSRIs), such as commonly used antidepressants, have been shown to cause mild neonatal abstinence syndrome. A report has been issued of an increased rate of persistent pulmonary hypertension of the newborn among infants exposed to SSRIs late in pregnancy; however, the absolute risk is likely to be less than 1%. Furthermore, no significant relationship has been found between SSRI exposure and stillbirth, neonatal death, or post-neonatal death.

Pediatricians need to know the effects of obstetric drugs on the fetus, including narcotics, oxytocin, and magnesium sulfate, which can cause depressed respiration, hyperbilirubinemia, and hypotonia, respectively. Socially used and abused drugs are very well known to pediatricians for their deleterious effect on the fetus, newborn, child, and adult. Mothers who smoke have babies who are smaller than those of non-smokers by an average of 200 g. Varied active agents in smoke, such as carbon monoxide and nicotine, have physiologic effects. Evidence suggests that antenatal exposure to environmental tobacco smoke affects early childhood cognitive development. Infants exposed to tobacco smoke prenatally and postnatally are at increased risk for childhood asthma, respiratory infections, otitis media, and sudden infant death syndrome, as well as later behavioral problems and increased rates of adolescent smoking. The clear medical consensus is that smoking is a health hazard for the fetus and newborn. Maternal alcohol consumption is associated with fetal alcohol syndrome and should be discouraged during pregnancy in all trimesters, although demonstrating deleterious effects is difficult when small amounts are consumed.

Addictive drug use during pregnancy creates major medical and societal problems. Many, if not most, users have lifestyles that include factors such as poor nutrition or lack of prenatal care that present significant background risk regardless of the addictive agent. Heroin is known to reach the fetus soon after maternal use, with intrauterine dependency and withdrawal recognized. Treatment programs that use methadone or buprenorphine are preferable alternatives to continued illicit opioid abuse, although neonatal withdrawal requires appropriate evaluation and management. Outcomes of women and infants in treatment programs are significantly better than those of women not enrolled in treatment.

Cocaine is considered to be responsible, directly or indirectly, for many admissions to neonatal intensive care units. Cocaine use can result in problems such as placental abruption that compromise the fetal and neonatal cardiovascular and neurologic systems. Investigative efforts to characterize and quantify long-term neurodevelopmental effects are ongoing. (See Chapter 104, Prenatal Drug Use: Neonatal Effects and the Drug Withdrawal Syndrome.)

Identification of environmental and lifestyle risks relies largely on the maternal medical history. Paternal history is also important to investigate. When specific factors such as radiation or chemical exposure are

detected, assessment of fetal well-being, especially its growth and morphology, may be helpful. In many situations, however, decisions to continue or terminate pregnancy are made based on possible fetal effects, involve parental emotions and values, and require compassionate, nondirective counseling in addition to the presentation of available scientific knowledge.

### Dental Health

The relationship between periodontal disease and pregnancy outcome is controversial. Some studies have shown women with periodontal disease are at increased risk for adverse perinatal events compared to women without periodontal disease, whereas others have shown no relationship. The increasing popularity of oral jewelry, including lip and tongue piercing, has been associated with higher incidence of periodontal disease. Women who are planning a pregnancy should pursue regular dental care, with treatment of poor dentition and gingivitis.

### Maternal Reproductive Capability and Health

Certain maternal factors result in fetal risk. Pregnancy can produce physiologic changes in the mother that may complicate preexisting maternal conditions, thereby jeopardizing the fetus. For example, mothers who have asymptomatic cardiac disease may decompensate when they become pregnant.

Maternal biologic factors, such as age, weight, height, race, parity, and previous obstetric history, directly affect fetal risk. Perinatal mortality increases at the extremes of maternal age; the relative risk for stillbirth increases with maternal age, regardless of medical comorbidity, parity, or race and ethnicity. One large observational study determined the lowest risk to be in the 16- to 19-year range. However, such observations should not be taken to encourage adolescent pregnancies; pregnancy in those younger than 16 years has definite associated risks, and pregnancy throughout the teenage years is associated with medical and social morbidity. Newborn weight and height are related to maternal nutrition, socioeconomic status, and other variables, which may jeopardize the fetus by increasing the incidence of prematurity or intrapartum complications. Race is a complex factor that includes socioeconomic considerations; some congenital anomalies and medical conditions may be racially predisposed. Congenital maternal reproductive tract abnormalities are often associated with spontaneous abortion and with prematurity. Cervical insufficiency occurs in 1 in 500 to 600 pregnancies and can result in premature delivery. The interval between pregnancies is an important contributor to the risk for low birth weight.

Maternal medical disorders carry a significant risk to both fetus and mother. Cyanotic congenital heart disease in a mother is clearly related to fetal problems, including IUGR and prematurity. Termination of pregnancy should be considered if maternal cardiac decompensation later in the pregnancy is anticipated. Asthma can threaten mother and fetus but is commonly well controlled with medication. Tuberculosis demands aggressive management of maternal disease with attention to potential fetal exposure to drugs. Pregnancy

in women who have cystic fibrosis presents the fetus with a variety of medications, maternal pulmonary insufficiency, and possible nutritional deficiency.

Preexisting and new-onset renal disease can complicate pregnancy. Fetal risk increases markedly in the presence of maternal proteinuria, impaired renal function, and hypertension. Hypertension can result in placental changes leading to IUGR. Adverse fetal outcome from urinary tract infection relates primarily to the risk for premature birth. Successful pregnancy is possible in women with kidney transplants, with the best outcomes seen among women who have stable renal function, time since transplantation of at least 2 years, and no evidence of rejection. Some risks are associated with exposure to immunosuppressants, but they do not prohibit a good outcome.

Maternal hematologic problems are common. In developing countries, anemia has been demonstrated to correlate with low birth weight; the effect of moderate maternal iron deficiency on the fetus is unclear. Some hemoglobinopathies can profoundly increase fetal mortality and morbidity as a result of either maternal health status or fetal disease. Pregnant patients who have sickle cell disease require close attention. Immune sensitization problems (Rh, ABO) are discussed later in this chapter and in Chapter 93, Maternal Medical History.

Maternal metabolic disorders can be significant for the fetus. The interaction of mother and fetus seems limitless: Compounds are metabolized actively on both sides of the placenta; fetal organogenesis and development may be affected; and fetal end organs may respond to maternal abnormalities. Two conditions, diabetes and thyroid disorder, deserve special mention.

Diabetes in pregnancy causes a myriad of fetal complications, including stillbirth, increased frequency of congenital anomalies, macrosomia (a large-for-gestational-age state characterized by an increase in fat but not in total body water), and conversely, growth restriction in a small number of infants. Evidence suggests that fetal pulmonary and neurologic maturity may be delayed in these pregnancies. In addition, obstetric problems, including preeclampsia, hydramnios, and intrapartum complications, resulting from excessive size, increase risk further. Glucose is a primary metabolite of the fetus. Pregnancies complicated by diabetes may cause fluctuations in maternal-fetal glucose, with resultant fetal hyperinsulinism and hypoglycemia. The increase in pancreatic islet tissue leads to fetal hyperinsulinism, which may be associated with a growth hormone effect that results in macrosomia. Severe maternal diabetes, especially when complicated by prepregnancy vascular disease, may result in small fetuses rather than macrosomia because of placental insufficiency and fetal nutritional deficit. Close control of maternal diabetes results in a better overall perinatal outcome.

Maternal thyroid disease is much less common than diabetes but also has profound fetal effects. Fetal thyroid function appears by 12 weeks' (12<sup>0</sup>/12<sup>6</sup>/) gestation; thyroxine and triiodothyronine can cross the placenta in small amounts in either direction. Classic cretinism, a reflection of maternal and fetal hypothyroidism, includes obvious fetal neurodevelopmental



problems and is a result of endemic iodine deficiency or autoimmune maternal thyroiditis. Evidence is accumulating that maternal hypothyroidism, even when subclinical, interferes with normal fetal brain development and may be prevented by maternal screening and treatment. Spontaneous loss, stillbirths, anomalies, and prematurity can be associated with hypothyroidism. Increases in maternal thyroid replacement hormone are generally necessary during pregnancy. Hyperthyroidism, when untreated, increases fetal loss. Its treatment, however, carries a definite risk to the fetus because antithyroid drugs may affect the fetal thyroid, and surgical intervention carries an operative risk to fetus and mother. Postoperative treatment with thyroid replacement therapy may minimize fetal complications.

Although seizure disorders are common, their course during pregnancy is difficult to predict with certainty. The status of approximately one-half of those affected is unchanged, and of the remaining number, one-half improve and one-half become worse. Status epilepticus is an emergency for the mother and fetus. Some anticonvulsants, such as trimethadione and valproic acid, are clearly teratogenic. Carbamazepine is associated with an increased risk for neural tube defect. Phenytoin has been linked with a fetal hydantoin syndrome, although the actual incidence is much debated. Phenobarbital, carbamazepine, phenytoin, and other medications have a broad-based effect on fetal enzymatic systems; they are associated with vitamin K-dependent coagulation factor deficiency in neonates. Many perinatologists suggest additional supplementation of vitamin K in the last month of pregnancy. Women who have epilepsy have an approximately 1 in 40 chance that their children will develop the same condition.

Seizures that seem *de novo* in pregnancy must be thoroughly evaluated. Eclampsia usually produces other signs and symptoms and is associated with a high incidence of fetal and neonatal complications.

Maternal emotional status presents too complex a relationship with physical and familial status to be used as a specific fetal risk factor in most situations. Whether maternal emotional illness not related to pregnancy can affect the fetus directly is unclear. Pregnancy-caused or pregnancy-aggravated crises leading to abortion, drug abuse, or poor maternal nutrition generate obvious fetal consequences.

### Placenta and Membrane Disorders

The placenta and associated membranes are tissues on which the fetus depends for respiration, nutrition, protection, and other functions. Manifestations of placental disease are diverse and severe and include fetal death, distress, hypoxia, shock, anemia, polycythemia, infection, congenital anomalies, and neoplasia.

The implantation site is normally in the upper uterus but may be in the lower segment, in the tubes, or, rarely, in the abdominal cavity. Maternal anatomic factors may contribute to abnormal implantations. Abdominal and tubal (ectopic) pregnancies are potential disasters for both mother and fetus; except for a rare surviving abdominal fetus, fetal loss is nearly uniform, and maternal mortality and morbidity are common.

Placenta previa is associated with multiparity and places the fetus at risk in the event of hemorrhage; premature delivery, usually by cesarean section, is necessary. Abruption of the placenta often is associated with maternal problems, including preeclampsia, hypertension, renal disease, and multiparity. Sudden fetal death may occur after an extensive placental separation; lesser degrees of separation can result in hypoxia and acute fetal stress. Bleeding from placenta previa and abruption is usually maternal but can be fetal and sufficient to cause fetal hypovolemia and anemia.

Cord abnormalities are unusual but may have severe consequences. A short umbilical cord may be complicated by abruption. True knots are unusual, but they do occur and can cause fetal stress. Vasa previa and velamentous cord insertion are difficult to identify before labor but can result in fetal compromise or fetal exsanguination. A circumvallate placenta is associated with fetal growth restriction. Vascular abnormalities within the main placental structure occur rarely; fetal risk in monochorionic multiple pregnancies includes the possibility of twin-to-twin transfusion syndrome, in which arteriovenous vascular anastomoses result in blood flow between the fetuses and in severe circulatory problems for recipient, donor, or both.

A vascular abnormality of the cord observed in 1% of pregnancies is a 2-vessel cord with a single umbilical artery, rather than the normal 2. Current evidence suggests that anomalies may be associated with a 2-vessel cord. The risk for associated abnormalities, including fetal growth restriction, renal abnormalities, and aneuploidy, is approximately 7%.

Premature rupture of membranes (PROM) is a major contributor to perinatal mortality and morbidity. It is defined as rupture that occurs before the onset of labor and is usually spontaneous. Artificial rupture of membranes may be accidental during an examination or may be used to augment labor. Regardless of classification, the prenatal care team must be aware that an inevitable process of increased fetal risk begins soon after rupture and that prospective treatment protocols are desirable. Most protocols stipulate evaluation and treatment in relation to the time since rupture. Prolonged rupture of membranes, which most authorities consider to be 18 hours after rupture, is the beginning of increased risk.

The primary cause of fetal and maternal morbidity and mortality in prolonged rupture of membranes is sepsis. At term, labor occurs within 24 hours of rupture in 80% of pregnancies; in preterm pregnancies, labor begins within 24 hours in less than 50%. The cause of preterm PROM is often not clear, and except for entities such as an incompetent cervix or history of a preterm delivery, no statistical correlation has been found with prior risk factors.

The frequency and degree of inflammation of membranes, cord, or fetus vary directly with time and onset of labor. Infection apparently ascends to the fetus through the cervix, with labor accelerating the process. Antibiotics given before delivery are of uncertain value in providing effective maternal treatment, but they do prevent some cases of sepsis in the fetus and newborn. Such is particularly the case of chemoprophylaxis for



prevention of group B streptococcal (GBS) infection. Current practice recommendations include culture of all pregnant women for GBS infection between 35 and 37 weeks' estimated gestational age, with treatment at the time of labor with intravenous antibiotics for those found to be positive. Women with GBS urinary colonization or women who have previously had an infant with invasive GBS disease should receive intrapartum chemoprophylaxis; prenatal culture screening is not necessary.

A dilemma in fetal risk management occurs in the PROM pregnancy that is significantly preterm. The fetus in this situation is at risk not only from infection but also from premature birth and its complications, especially respiratory distress syndrome. The physician has available prepartum agents (corticosteroids) that seem to accelerate pulmonary maturity and improve postpartum status overall in certain populations. A 2000 National Institutes of Health Consensus Development Conference reiterates the previous recommendation for antenatal treatment with corticosteroids for fetuses between 24 and 32 weeks' gestation that have preterm PROM. A single rescue course of antenatal corticosteroids may be considered if the antecedent treatment was given more than 2 weeks prior, the gestational age is less than 32 $\frac{6}{7}$  weeks and the risk for delivery within a week is estimated to be high.

There may be an increased risk for neurologic sequelae among babies born prematurely after PROM. An increased incidence of periventricular leukomalacia and cerebral palsy seems to be at least associated with, if not caused by, intra-amniotic infection. Whether immediate induced vaginal delivery or cesarean section delivery with preterm PROM will decrease these risks is unknown at present.

### Maternal-Fetal Unit

Fetal risk and poor perinatal outcomes are often associated with pathophysiologic processes in which both mother and fetus play an integral role. Causality in some situations is well understood, as in, for example, alloimmunization, but causality for other situations such as preeclampsia is not yet clear. A major factor in the risk for adverse neonatal outcome relates to fetal age at the time of delivery. At present, in the United States and worldwide, the mean gestational age at delivery is 39 weeks. Infants delivered between 37 $\frac{7}{7}$  weeks and 38 $\frac{6}{7}$  weeks are at higher risk for neonatal morbidity and mortality than those born between 39 $\frac{0}{7}$  weeks and 41 $\frac{6}{7}$  weeks. Neonatal mortality and morbidity are higher after 42 $\frac{0}{7}$  weeks compared to 38 $\frac{7}{7}$  weeks through 41 $\frac{6}{7}$  weeks, and also higher at 37 $\frac{7}{7}$  weeks through 38 $\frac{6}{7}$  weeks than at 39 $\frac{0}{7}$  weeks through 41 $\frac{6}{7}$  weeks. Infant mortality is lowest for births at 39 $\frac{0}{7}$  weeks through 41 $\frac{6}{7}$  weeks.

### Premature Birth

Prematurity and its complications are the prime contributors to perinatal mortality and morbidity. The problems of prematurity and low birth weight are similar but not identical.

The prevention and management of premature birth has been and remains the primary objective of

perinatal care providers. Prematurity is multifactorial in origin, and its causes will likely remain unclear for the foreseeable future, inasmuch as the precise mechanisms that cause normal labor have yet to be elucidated. Many factors that contribute to fetal risk precipitate adverse outcomes directly or indirectly through premature birth.

### Pharmacologic Intervention

Tocolysis, or inhibition of uterine activity, is therapy directed at preventing premature birth once labor has begun. Pharmacologic agents have been used with this intent for years with minimal success.

The theoretical basis for the use of  $\beta$ -mimetic drugs as tocolytics is their inhibitory effect on uterine contractions through activation of  $\beta$ -adrenergic receptors.  $\beta$ -Adrenergic receptors are subdivided into  $\beta_1$  and  $\beta_2$  groups, with the latter dominant in blood vessels and the uterus. Isoxsuprine hydrochloride (a derivative of catecholamine), ritodrine hydrochloride, and terbutaline sulfate have been used and are thought to be effective in depressing uterine contractions. A  $\beta$ -mimetic that has a narrow effect on only the uterus has yet to emerge. Thus, maternal and fetal or neonatal side effects do occur, with cardiovascular, pulmonary, and metabolic complications documented. For example, neonatal hypoglycemia is a recognized complication of isoxsuprine therapy.

Calcium antagonists such as nifedipine are now used as an adjunct for tocolysis. Magnesium sulfate is no more effective than other agents but is commonly used because of a better maternal side-effect profile than the  $\beta$ -adrenergic agents, as well as its efficacy as a neuroprotective agent. Prostaglandin synthetase inhibitors may have a future role, but their use is limited because of their potential vasoactive effect on the fetus, especially on the ductus arteriosus.

Tocolytic therapy can be beneficial between 26 and 33 weeks' gestation. Then a relatively short delay of preterm delivery through tocolysis or other interventions is long enough (24–48 hours) to allow administration of corticosteroids for the enhancement of fetal lung maturity and maternal antibiotics for GBS sepsis prophylaxis.

### Prevention of Prematurity

Prevention of preterm birth is an area of ongoing research. Evaluation of lifestyle factors associated with preterm delivery and the subsequent modification of identified risk factors have yielded mixed results. More recent efforts have focused on cervical insufficiency and hormonal effects.

The use of weekly progesterone to decrease the risk for recurrent preterm birth in subsequent pregnancy seems promising because the biggest risk factor for preterm delivery is a history of previous preterm delivery.

Physicians can play a major role in such preventive programs because they ensure that the need for intervention is documented and that intervention occurs. In addition to management of specific medical problems, alterations in work and home environment may be necessary. Good prenatal care and early work leave may be very important. Countries in which such

policies exist, such as Sweden, have low prematurity rates, but whether this circumstance is an association or a contributing relationship is unknown at present.

### Multiple Gestation

The incidence of multiple gestation has recently and remarkably increased because of the application of newer reproductive technologies to treat infertility, although as reproductive technology is refined, the incidence of higher order multiple gestation is decreasing.

Spontaneously occurring multiple gestation is also relatively common (twins occur naturally in approximately 1 in 88 births). Regardless of the source of multiple gestation, fetal risk is increased. These risks range from those that are placental in origin, such as twin-to-twin transfusion, to rare fetal malformations, as in conjoined twins, to the much more frequent problems of prematurity and obstetric complications. Multiple gestation is among the 3 most common causes of prematurity. Complications of labor and delivery increase the risk for hypoxia or trauma, with the second-born twin being more susceptible to damage than the first.

### Obstetric Complications

Obstetric complications jeopardize the fetus, the most dire manifestation being intrapartum fetal death. Even the most healthy fetus is at increased risk during labor and delivery. Stress to the fetus may be documented retrospectively by low Apgar scores, poor recovery after birth, and subsequent complications. A fetus chronically compromised by adverse factors, such as diabetes in pregnancy, may be compromised further by obstetric problems.

Abnormal presentations, such as breech and transverse lie, greatly increase fetal risk, as does cephalopelvic disproportion (a mismatch between the maternal pelvis and the fetal head). Malproportion can be predominantly fetal, as in congenital hydrocephalus, or maternal when congenital pelvic bone abnormalities exist.

### Abnormal Growth and Gestation

Discrepancies between fetal growth and gestation are often manifestations of an underlying disease process but may occur without apparent cause. Regardless of cause, discrepancies in growth and gestation can often result in such severe risk to the fetus as to be more worrisome than the underlying problem. Postmaturity occurs much less often than prematurity, but it presents increased risk to the fetus. Continued growth in utero increases the risk for macrosomia and birth trauma. Placental insufficiency may result in the development of hypoxia and acidosis before or during labor that is characterized by non-reassuring fetal heart rate, poor Apgar scores, and perinatal hypoxic encephalopathy. Meconium passage is common and poses a risk for meconium aspiration syndrome; it may also signal peripartum infection.

Deviations of growth and gestation can be cumulative for fetal risk. The premature infant also affected by IUGR tolerates intrauterine stress poorly, may

exhibit respiratory distress syndrome or apnea after birth, and is at risk for the development of hypoglycemia. New information is emerging about the long-term effects of fetal growth restriction. Fetal nutritional adaptations to placental insufficiency may persist through adulthood because the risk for coronary artery disease and chronic hypertension is increased among adults who were born with IUGR. The physician should appreciate that evaluation of the fetus or newborn by birth weight and gestational age can provide specific information that facilitates diagnosis and treatment.

### Alloimmunization

Alloimmunization is a disease of the maternal-fetal unit that has decreased in incidence because of successful efforts to prevent Rh disease with Rh-globulin (RhoGAM). Passage into the maternal circulation of fetal red cells, which possess antigens not present in the mother, stimulates production of antibodies. Maternal antibodies of the immunoglobulin G (IgG) class cross the placenta, resulting in a hemolytic process in the fetus that can be severe. The initial alloimmunization can occur with blood transfusions, with spontaneous or induced abortion, or with the first or subsequent pregnancy. Small amounts of red cell antigen contained in blood measuring 1 mL or less (especially if repeated) can cause an antibody response even in normal pregnancies. Sensitization risk is increased by complications such as preeclampsia or cesarean delivery.

Rh incompatibility is associated with a variable but often severe sensitization that can cause stillbirth, massive fetal erythrocytosis or erythroblastosis, anemia, hydrops fetalis, and other systemic manifestations. Hyperbilirubinemia occurs in the newborn and to a lesser degree in utero, whereas the maternal liver clears bilirubin.

The incidence of fetal Rh disease varies with the prevalence of Rh negativity. This genetically determined state is not often documented in Asians and Native Americans; however, it occurs in 15% of whites, resulting in the possibility of approximately 9% of their pregnancies involving an Rh-negative woman carrying an Rh-positive fetus. Despite prophylaxis with RhoGAM for the D antigen, alloimmunization still occurs in response to several other red cell antigens for which there is no prophylaxis available, including c, C, e, E, Kell, Kidd, and Duffy. These *minor* antigens can cause very serious hemolysis. Some patients acquire more than 1 hemolytic antibody, typically after blood transfusion.

Since the delineation of the cause of Rh sensitization, a wide range of diagnostic and therapeutic methods have become available that make Rh incompatibility treatment a paradigm for intensive perinatal care. Today's routine procedures for the disease include initial screening for the presence of alloimmunization and for Rh-negative women who are still candidates for prevention with RhoGAM. If hemolytic antibody is detected, then maternal serum levels and amniotic fluid analysis can assess the possibility of severe fetal illness. Amniotic fluid can be analyzed by polymerase chain reaction (PCR) DNA analysis to

determine fetal blood type and the risk for hemolytic disease. Noninvasive methods of diagnosis of fetal anemia have been developed, which use ultrasound assessment of fetal cerebral blood flow in the middle cerebral artery. Peak systolic velocity in the middle cerebral artery increases as anemia worsens. This noninvasive option for monitoring decreases the risk accrued with serial amniocentesis, which can include infection, worsened sensitization, and loss of pregnancy. When a high hemolytic risk is detected, by either ultrasound or amniocentesis, fetal blood sampling by the percutaneous umbilical route can be performed so that an accurate assessment can be made and so that in utero blood transfusion may be administered. The timing of delivery includes consideration of fetal health, the possibility of in utero transfusion, and the degree of prematurity. Immediate, aggressive neonatal intensive care, including exchange transfusion and cardiopulmonary support, may be indicated.

Incompatibilities of the ABO system result from the presence of maternal anti-A or anti-B antibodies when the fetus's blood type is group A or B and the mother's is group O. Severe hemolysis is much less common, even though ABO incompatibility is potentially present in approximately 20% of pregnancies. Fetal erythrocytes seem to have fewer antigenic loci, and maternal antibody appears in IgA, IgM, and IgG forms, with only the latter crossing the placenta. These facts may explain why ABO alloimmunization is usually of greater concern in the newborn than in the fetus. Stillbirths and hydrops fetalis are rare, but prolonged neonatal hyperbilirubinemia occurs often.

### Gestational Hypertension

Hypertension of pregnancy is a major contributor to fetal risk. A group of diseases seen only in pregnancy and presenting with acute and chronic manifestations of hypertension, edema, and proteinuria may be lumped together in this category. *Preeclampsia* is another term for the basic process, which can be severe; when convulsions or coma occur, *eclampsia* is present. Chronic hypertensive vascular disease with pregnancy is thought by many to be a separate disease state that can have superimposed preeclamptic manifestations.

Premature birth is increased in incidence because early delivery is often elected on maternal or fetal indication. As the severity of the disease increases, and particularly when eclampsia develops, stillbirth and maternal death become much more frequent. IUGR is seen in a third of perinatal deaths associated with preeclampsia. For the fetus, this disease process presents a bleak perspective; fetal stress is significant, and labor and delivery are often premature and timed for maternal treatment rather than for fetal well-being. Neonatal complications are many and severe.

Successful perinatal management of preeclampsia relies heavily on early detection during prenatal care. When the process is discovered, intensive perinatal care may be necessary, with seizure prophylaxis with magnesium sulfate a mainstay of therapy. Severe preeclampsia is a significant maternal threat and may require a decision to deliver a premature baby. Proper expectant management requires careful maternal and fetal surveillance, including assessment of fetal well-being

by nonstress testing, biophysical profile, amniotic fluid volume determinations, Doppler studies of umbilical blood flow, and ultrasound studies of fetal growth.

### Intrauterine Infections

The medical community's understanding of the scope of the problem of intrauterine infections and their fetal effects has broadened considerably but is probably far from complete. Expression ranges from fetal loss caused by spontaneous abortion and stillbirth through severely debilitating congenital anomalies resulting from teratogenic effects, to subtle systemic manifestations, including those of the CNS, not detected until later in childhood when problems with higher cerebral function and behavior become apparent.

The important infectious agents include viruses, bacteria, spirochetes, and protozoa. The route for infection varies with the agent and can be transplacental, ascending through the cervix, with or without the rupture of membranes, which provide an imperfect protective cover, as well as through direct contact with the fetus during passage through the vagina.

The pediatric physician needs to have a basic appreciation for the variety of intrauterine infectious agents and the pathophysiologic processes and clinical problems they invoke. Table 80-1 is a modification of the TORCH acronym that has served well for several decades.

### Human Immunodeficiency Virus

Fetal, intrauterine, and peripartum considerations are but a small part of the story of HIV; a complete discussion appears in Chapter 268, Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome. Given the magnitude of the HIV/AIDS problem and that of the 3 predominant modes of transmission in the United States (sexual contact, percutaneous contact with contaminated sharps, and fetal or infant contact with an infected mother), 2 involve reproduction, the pediatrician must know the specifics of transmission and intervention. The newly developed ability to decrease vertical transmission from mother to fetus makes universal screening of pregnant women for HIV imperative. The fetus can be infected in utero, although the exact timing is uncertain; other possibilities for transmission include transplacental or peripartum, as well as postpartum (through breastfeeding). The timing of the expression of disease in children is variable and is thought to be determined by whether the infection was acquired before delivery or during parturition. Without antiviral therapy, approximately 25% of babies born to HIV-infected women will become infected themselves. The use of antepartum, intrapartum, and postpartum multiple-agent antiretroviral prophylaxis may decrease the risk for congenital infection to 2%. Even further decreases in transmission may be associated with cesarean delivery or vaginal delivery within 4 hours after rupture of membranes. Whether cesarean section delivery is protective for fetuses of women who have very low or undetectable viral loads is uncertain. Newborns discovered to be at risk should be continued on antiretroviral agents until their infective status becomes clarified. In the United States, where safe artificial milk is available, breastfeeding is contraindicated in HIV-infected women.

**Table 80-1**      **Maternal-Fetal Infections: TORCH**

INFECTION	ORGANISM	TRANSMISSION	COMMENTS
T Toxoplasmosis	<i>Toxoplasma gondii</i>	Transplacental	Most common congenital parasitic infection in US; domestic cat is primary host; risk of infection is highest in third trimester, but fetal effects are less severe; prenatal diagnosis by PCR or tissue culture
O Other	<i>Listeria monocytogenes</i>	Vertical or horizontal (environmental exposure)	Foodborne, gram-positive bacillus; isolated from livestock and fowl; outbreak related to consuming contaminated cheeses, raw vegetables, milk; infection during first and second trimester associated with high rates of fetal death Diagnosis: + body fluid cultures
	Syphilis ( <i>Treponema pallidum</i> )	Transplacental	Transmission at any stage of pregnancy; prevalence increasing in the US; risk factors: young age, inadequate prenatal care, substance use, multiple partners, history of STIs, inadequate treatment for prior infection; maternal screening (VDRL, RPR) at entry into prenatal care and at delivery is key
	Varicella-zoster	Transplacental	Varicella embryopathy caused by transmission during first 20 weeks of gestation; can cause limb deformities and cicatricial skin scarring
	Parvovirus B 19 (Fifth's disease)	Respiratory (most common), hematogenous (transplacental), vertical	Infection typically more common in spring and summer; transmission risk highest in first and second trimesters; can cause fetal hydrops and increased nuchal translucency in the first trimester Maternal testing for antiparvovirus B 19 IgM and IgG, amniotic fluid PCR
	Group B <i>Streptococcus</i> , <i>Gonococcus</i> , HIV, mumps, enteroviruses, tuberculosis		
R Rubella	Rubella virus	Transplacental	Rare in countries with universal rubella vaccination; fetal infection rates highest with exposure in the first trimester; diagnosis maternal infection by rubella-specific IgM
C Cytomegalovirus	Human Cytomegalovirus (CMV, herpes virus 5)	Congenital, transplacental; 50% infected at birth	Most common congenital infection; transmission more common in primary maternal infection, results in 30%–40% fetal infection; maternal disease typically mild; infection risk increases with young maternal age, single status, non-white race, and exposure to young children Universal prenatal screening is not routine; prenatal diagnosis: anti-HCMV IgM and low avidity anti-HCMV IgG
H Herpes Simplex	Herpes simplex virus (HSV) 1 and 2	Intrapartum Transplacental is rare	Neonatal infection usually from primary genital infection with HSV 2; mother is often asymptomatic; neonatal disease is typically severe Diagnosis: HSV-PCR + HSV cultures



### Rubella

Rubella virus is recognized as a potent teratogen. Infections during the first trimester result in approximately 20% of fetuses being severely damaged or malformed, with second-trimester involvement damaging 10%. Third-trimester infection has presented few clinical problems. The expression of rubella syndrome is variable. Manifestations of first-trimester fetal disease can be severe (eg, abortion, stillbirth, severe rubella syndrome). Severe rubella syndrome includes growth restriction, eye defects (cataracts and microphthalmia), congenital cardiac defects, deafness, thrombocytopenic purpura, hepatosplenomegaly, bone lesions, pneumonitis, and cerebral defects (microcephaly, encephalitis, intellectual disability, and spastic quadriplegia). Infections in the second trimester are variable and tend to be less severe.

The high fetal risk and potentially devastating consequences of intrauterine rubella have stimulated aggressive efforts to prevent maternal rubella. Congenital rubella is a reportable disease. Vaccination of children between the ages of 1 and 12 years is routine. Administration of vaccine to women of childbearing age has been controversial because of concern of possible vaccine effects on the developing fetus. However, a registry of cases in which women received vaccine within 3 months of conception has found no cases of congenital rubella syndrome. Vaccine virus was cultured from fetal and placental tissue, but teratogenic effects were not seen. Preconception counseling should include rubella serotesting to determine the need for vaccination before conception occurs.

### Cytomegalovirus Infections

The cytomegaloviruses (CMVs) may be the most common cause of congenital infections, occurring in somewhat less than 1% of births. This group of viruses is widespread and produces various apparent and inapparent infections in the general population: 58% of women of childbearing age are seropositive. Among uninfected women, 1% to 4% will develop a primary CMV infection during pregnancy, with approximately one-third of these women shedding virus to their fetus transplacentally. Fetal infection usually occurs through the placenta.

The fetal disease has been called *cytomegalic inclusion disease* because of the large inclusion-bearing cells found in urine and many organs. Severe cytomegalic inclusion disease includes hepatosplenomegaly, microcephaly, cerebral calcifications, mental and motor manifestations, and chorioretinitis. Reviews suggest that expression of intrauterine infections is variable and that full recognition of incidence is yet to come. Serologic tests for CMV are available and can provide presumptive evidence for infection; however, reliability is not as good as with rubella titers, and a vaccine is not available. CMV antibody testing of infants reflects the maternal antibody status. Consequently, congenital CMV infection cannot be diagnosed if the infant is tested more than 2 to 3 weeks after birth. Urine CMV culture is a good indicator of recent or active infection. Among infants born with congenital CMV infection, approximately 80% are asymptomatic. One in 750 CMV-infected infants will

develop permanent CMV-related sequelae. CMV is the most common cause of nonhereditary hearing loss in children.

### Herpes Simplex Virus Infections

Herpes simplex virus (HSV) infections in humans result from 2 strains, types 1 and 2, each with distinct serotypes yet some cross-reactivity. Perinatal disease is usually associated with type 2, although type 1 is more common in the general population. Type 2 HSV produces genital lesions and in most instances is transmitted sexually. Herpetic disease in the fetus or newborn is relatively rare but can be devastating. Transmission occurs by direct contact at birth or by ascending transcervical infection after rupture of the membranes. Transplacental infection early in pregnancy with fetal manifestations similar to those of CMV infection has been documented but is rare. Prophylaxis against recurrent HSV outbreak is suggested late in the third trimester through delivery.

Newborn manifestations of intrapartum contact are well known. They range from vesicular lesions of the skin to encephalitis and severe systemic disease, with a mortality of more than 90% without treatment and severe CNS morbidity in those who survive. Expression is probably linked to primary versus recurrent maternal disease, being more intense in the former.

A major recent development is the success of antiviral agents in the treatment of systemic herpes infection, in particular encephalitis. Early diagnosis and treatment are essential. Prevention is desirable and possible. (See the discussion of herpes infections in Chapter 267, Human Herpesvirus-6 and Human Herpesvirus-7 Infections.) Current suggested management for a pregnant mother who has active genital lesions is a cesarean delivery to prevent fetal inoculation by passage through the vagina.

### Toxoplasmosis

Toxoplasmosis is caused by an intracellular protozoan parasite, *Toxoplasma gondii*. Infection is widespread, is congenital or acquired, and varies in expression from almost asymptomatic to generalized and fatal. The fetus is at risk for death when the infection occurs early in pregnancy or may be born with fully developed disease indicative of a long intrauterine course. Chorioretinitis, cerebral calcification, hydrocephalus or microcephaly, hepatosplenomegaly, and a host of systemic manifestations are observed. Long-term sequelae, especially involving the CNS, are present in most of the infants who have severe infection and survive.

Pregnant women are thought to become infected through consumption of raw or undercooked meat or by ingestion of oocysts from soil or contaminated food. They may also become infected by exposure to cat feces. Prevention of toxoplasmosis in pregnancy is possible by careful handwashing after changing cat litter, gardening, or handling raw meat. The incidence of the perinatal disease is higher in certain locales.

Detection of *Toxoplasma* antibody by a reference laboratory can document the onset of infection if IgM antibody appears coupled with a rise of IgG antibody in paired samples over at least 2 weeks. Antibody levels

can remain high for years; unchanging elevated levels indicate old infection. Infection before pregnancy seems to prevent congenital disease; however, maternal coinfection with HIV may result in reactivated maternal parasitemia and congenital infection. If toxoplasmosis is suspected by serologic testing, then amniotic fluid or fetal blood can be tested by PCR for *Toxoplasma* DNA. Treatment with pyrimethamine and sulfadiazine is effective in decreasing the severity of congenital infection. Congenital toxoplasmosis may be inapparent at birth and not recognized until later in infancy or early childhood. (See Chapter 308, Parasitic Infections.)

### Other Intrauterine Infections

Fetal syphilis is caused by transplacental passage of *Treponema pallidum*. Fetal infection has been thought not to occur before the 18th week of gestation, but this assumption is disputed. Pregnancy in a woman who has primary- or secondary-stage disease may result in stillbirth. Other manifestations vary from presentation in the newborn to those appearing in the first 2 years of life or later. In general, the earlier the onset of infection, the more severe the lesions will be. Severe fetal infection manifests in early infancy by osteochondritis and periostitis, rhinitis (snuffles), rash, and mucosal fissures or patches. Premarital and prenatal screening for syphilis, in conjunction with antibiotic treatment, has effectively decreased the incidence of intrauterine disease, especially the more severe or classic manifestations. Unfortunately, a resurgence occurred in the late 1990s. Recently trained physicians have not had the experience in recognizing congenital syphilis that many of their older colleagues have had, which sometimes results in a delayed diagnosis. Detection of disease during pregnancy and treatment with penicillin will arrest development of the fetal disease. Penicillin remains the treatment of choice for syphilis during pregnancy, even if desensitization for penicillin allergy is required. (See Chapter 330, Sexually Transmitted Infections.)

*Listeria monocytogenes* is a gram-positive bacillus that probably plays an important role in overall fetal wastage. Incidence varies widely; infection is associated with ingestion of contaminated ready-to-eat food products. Fetal death may occur after a relatively mild systemic maternal disease. *Listeria* chorioamnionitis can be diagnosed by amniocentesis, and successful antibiotic treatment is possible. Neonatal manifestations include systemic disease at birth or a delayed appearance as meningitis in the second to fifth weeks of life, with a characteristic monocellular cerebrospinal fluid.

GBS disease has many similarities in presentation to that of *Listeria* and is a more common problem (see Chapter 100, Respiratory Distress and Breathing Disorders in the Newborn). Infection is acquired by exposure to organisms during parturition. Maternal immune status and bacterial subtype are important determinants of virulence. The Centers for Disease Control and Prevention, the American College of Obstetrics and Gynecology, and the American Academy of Pediatrics recommend assessing colonization status at 36 weeks' gestation by culture and treating all

colonized women as labor commences. If GBS status is unknown at the onset of labor, then women who have risk factors such as prolonged rupture of membranes, preterm labor, fever or systemic manifestations, or a previous child who had GBS disease should be treated.

All neonatal services should have a structured approach to identifying and treating patients at risk for or having GBS disease in its 2 dominant modes of presentation: a fulminant hemorrhagic pneumonitis in the first hours after birth, or neonatal meningitis that appears a few days or weeks after birth.

Other known intrauterine infections include agents of all known classes; undoubtedly, many others are yet to be discovered. Many viruses can cause fetal infection, including varicella, coxsackievirus, mumps, rubeola, echovirus, and hepatitis. *Mycoplasma pneumoniae* also is an important perinatal agent, and malaria is a significant fetal threat in many areas of the world.

### FETAL ASSESSMENT

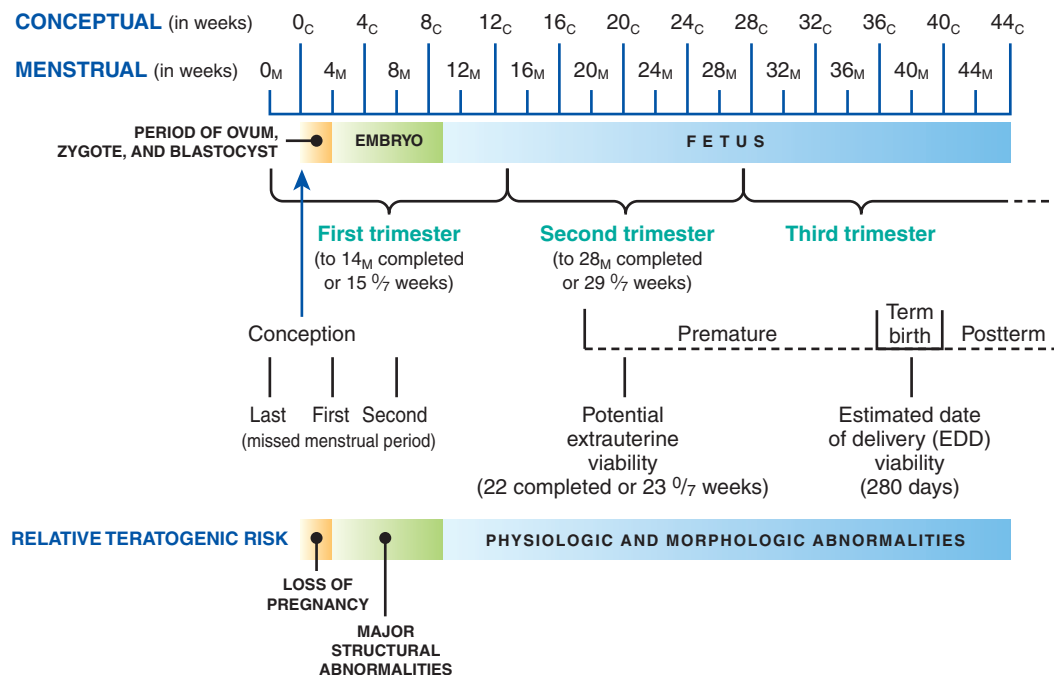
Physicians use menstrual dating when describing the course of human pregnancy, beginning with the first day of the last menstrual period. Others use conceptual dating and a time line that begins with conception or approximately 2 weeks after the last menstrual period. Occasional confusion arises when the differences between these 2 conventions are not appreciated. Furthermore, physicians discuss pregnancy in terms of portions of weeks, such as 36%, or the beginning of the 36th week. By use of menstrual dating, a pregnancy is thus in the 37th week (37%), when it is considered to be at term. This concept is similar to a child not being 1 year of age until the child's first birthday, on the 366th day of life.

The typical human pregnancy lasts 36 to 40 weeks from fertilization or 38 to 42 weeks from the last menstrual period (by menstrual dating). Fetal development begins at fertilization, when a sperm combines with an oocyte to form a zygote. The fetal life span is defined here in the broad sense to include the entire gestational interval (Figure 80-3). The human product of conception technically becomes a fetus at the end of the eighth week after fertilization and remains so until birth.

Development proceeds from conception to birth in 3 stages: the ovum, zygote, and blastocyst; the embryo; and the fetus. The *conceptus*, or product of conception, comprises all the structures that develop from the zygote, both embryonic (the embryo or fetus) and extraembryonic (the membranes and the placenta).

The stage of the ovum, zygote, and blastocyst, illustrated in Figure 80-1, begins with fertilization, wherein a single haploid sperm (23 chromosomes) enters the oocyte (haploid female ovum with 23 chromosomes). This stage usually takes place within the ampulla of the fallopian tube. The fertilization process is complicated and takes up to 24 hours before the genetic material from the 2 haploid cells fuses to form a diploid cell, the *zygote*, with a full complement of genetic material (called the *stage of syngamy*).

The *preembryo* consists of the developing cells, produced by division of the zygote, and lasts until



**Figure 80-3** Fetal life span by conceptual and menstrual dating. Note timing of important events and relative teratogenic risk.

the formation of the *primitive streak*, approximately 14 days after the beginning of fertilization. The pre-embryonic stage has been of special interest clinically and ethically because sustaining human preembryos in vitro is possible for up to 6 to 9 days after fertilization.

Preembryo development, during the interval before implantation in the uterine lining, includes a series of morphologic changes. Progression proceeds from blastomeres, or individual cells, to a tightly compacted group of cells called the *morula*. The blastocyst, a mass of cells with a fluid-filled inner cavity, appears approximately 4 days after syngamy. Early mitotic divisions lead to totipotent cells that are able to produce all the products of conception. During this time, twinning becomes possible; by approximately day 7, differentiation leads to cells becoming individualized. The multicellular blastocyst with a trophoblast and an inner cell mass initially attaches to the maternal endometrial lining at day 8 or 9, and over the next several days it becomes embedded, thereby completing the process of implantation.

By the time of the first missed menstrual period (see Figure 80-3) the primitive streak has been formed in the embryonic disk, embryogenesis is beginning, and a critical time has passed during which up to 50% or more of fertilizations do not complete pre-embryonic development and implantation successfully. Thus, this stage is a period when the product of conception is at very high risk.

The *embryonic* period encompasses approximately weeks 3 to 8 and is characterized by the differentiation of all major organs that will be present in the fetus, the newborn, and the adult. Near the beginning of this interval, the woman usually becomes aware of

cessation of menstruation, and laboratory tests can confirm pregnancy.

During the pre-embryonic period, adverse conditions may cause the death of the products of conception. This event often occurs around the time when a menstrual period would have been expected, and fertilization may not be recognized. Adverse influences during the embryonic period can cause severe interruptions in the pattern of system development, resulting in major congenital anomalies in a surviving fetus. The embryo is recognizable as humanoid toward the end of this period; malformations such as neural tube defects resulting, for example, from maternal ingestion of carbamazepine, may be identified.

The *fetal* stage, the longest of the 3 stages of the fetal life span, ends with delivery. Growth in size is the most apparent change during this interval, but maturation of organ systems and bodily processes is equally important. The high incidence and problems of premature birth make the degree of organ and enzyme system maturation of compelling interest to the pediatrician. The development of pulmonary surfactant is probably the single most important maturational process directly affecting survival in premature infants.

The late fetal stage has become the focus of increasingly sophisticated diagnostic techniques. Ultrasonography not only provides images of the fetus but also facilitates invasive procedures, such as amniocentesis to obtain amniotic fluid, and fetal blood sampling. Magnetic resonance imaging can be used in selected cases to provide further diagnostic information. The pediatrician needs to keep pace with developments in this period because intrauterine treatment of the fetus seems destined to expand someday to include the addition or modification of genetic material.

### Intrauterine Growth and Nutrition

The pediatrician must have a firm conceptual framework of intrauterine growth to effectively evaluate and treat the healthy newborn and the atypical newborn. In particular, the common clinical problem of prematurity can be managed more appropriately if growth patterns as they relate to gestational age are appreciated.

The growth rate of the fetus is especially rapid from 12 to 16 weeks of gestation and again during its final months. Both of these rapid-growth phases are associated with events of immediate concern to the physician. By the end of the 16th week after fertilization, the size and activity of the fetus have reached the point that many multiparous and some primiparous women are able to feel fetal motion (*quickening*). This event can be a valuable marker when assessing fetal age and well-being. The late-growth phase can be monitored by several means, especially physical examination, including the measurement of the height of the fundus above the maternal symphysis pubis and ultrasound measurements.

The period from 8 to 12 weeks after fertilization begins with a fetus whose head makes up almost one-half of the total length. By 12 weeks the total length has doubled, but the head represents a smaller proportion. The 12- to 16-week interval is characterized by extremely rapid growth in length. In the 17- to 20-week interval growth slows somewhat, but extremities assume their relative proportions. The 21- to 25-week interval after fertilization is characterized by significant gains in both length and weight.

Twenty-one weeks after fertilization, or 23 weeks from the last menstrual period, represents an extremely important milestone because the threshold for extrauterine viability is currently recognized as occurring at approximately 22 to 25 weeks (menstrual dating), with neonatal intensive care necessary to sustain that potential. An important point to note is that at the threshold of viability, cognitive and neurologic impairment is common when the child has reached school age, and the level of impairment is greater than previously recognized with the use of standardized norms.

Many studies have attempted to quantify fetal growth through the use of postnatal data. Such growth curves, derived from measuring infants born at varying gestational ages, can give an approximation of intrauterine growth, but they have shortcomings. The baseline population is, by definition, atypical because the babies were born before term. In addition, the population of premature live births is very difficult to standardize for factors such as race, parity, socioeconomic status, maternal smoking, and maternal disease states.

Despite all this circumstance, intrauterine growth curves derived from postnatal data can be of great clinical assistance. The Colorado Intrauterine Growth Charts (Figure 80-4) are among the better known. They provide percentiles of intrauterine growth for weight, length, and head circumference. In addition, a weight-to-length ratio is shown. From weight and length data, a ponderal index can be derived to depict proportionality. The growth curves in Figure 80-4 were derived from a population of hospital-born and

non-hospital-born infants who had mixed racial backgrounds and were living at an altitude of approximately 5,000 feet. Intrauterine growth curves derived from live births in other populations show significantly different values, particularly at some of the higher percentiles. However, the basic sigmoid shape of the curve persists. A few investigators have questioned the sigmoid shape of the growth curve as artifactual because it is based on the inaccuracies of menstrual dating. They suggest that when ultrasound dating is used, the curves become linear. With the use of growth curves and ultrasound, fewer pregnancies now are delivered at 43 and 44 weeks' gestation.

Intrauterine growth curves for the last trimester of pregnancy can be very helpful in both fetal and neonatal medicine. That intrauterine growth is a steady process cannot be assumed without reservation; growth might occur in bursts of undetermined length. Monitoring individual fetuses for growth against the baseline of an intrauterine growth scale can be helpful.

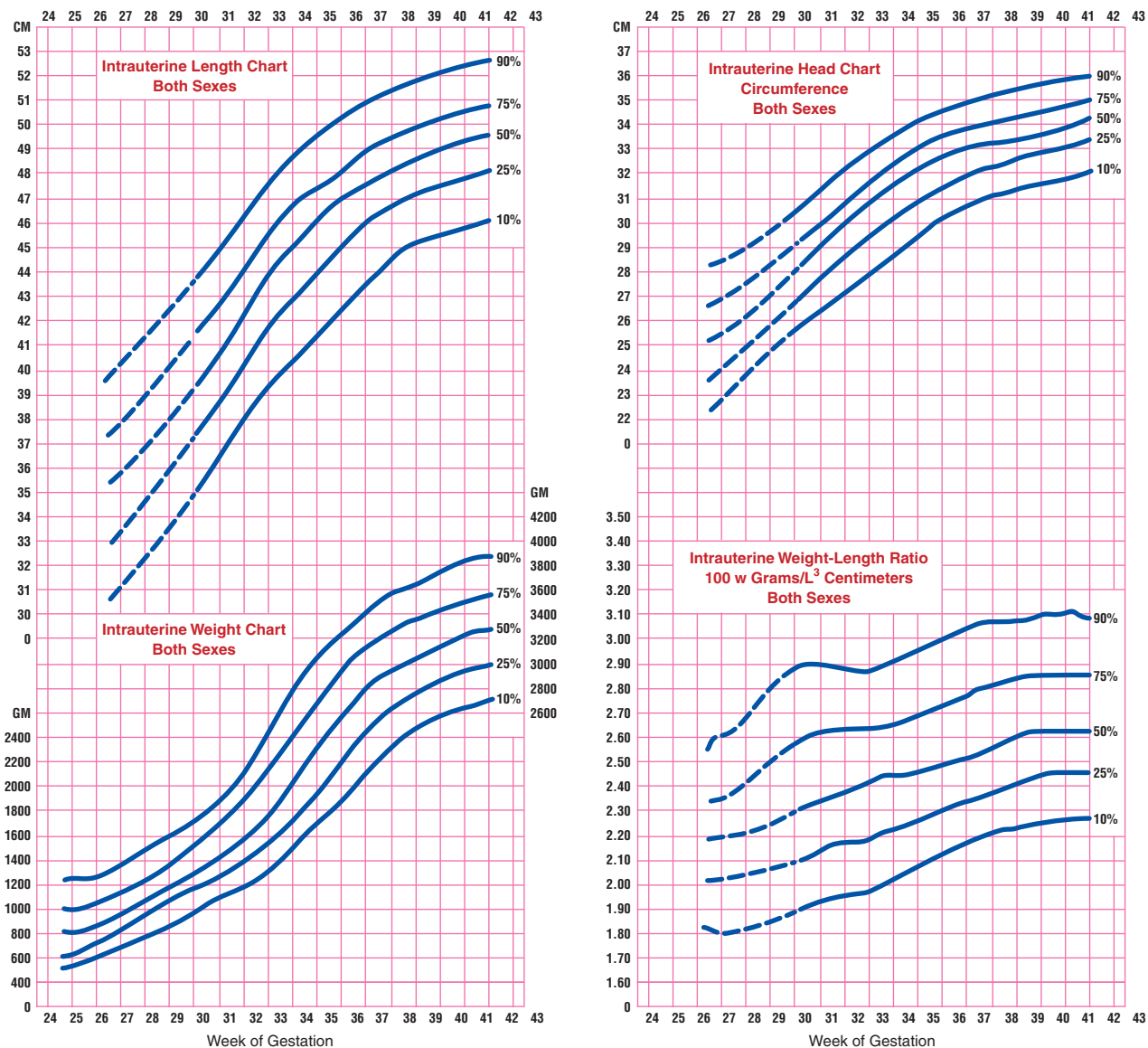
Fetal nutrition can be conceptualized in basic parameters that are familiar to the pediatrician. As with the child, 2 basic processes are underway: accretion of substance for growth of new tissues, and oxidation or energy production for metabolism. Growth and development occur as a continuum from fetal to extrauterine existence, but the physiologic mechanism of nutrition for that continuum changes abruptly at birth when the principal fetal organ for respiration and nutrition (the placenta) gives way to other organs and systems.

Glucose is a primary nutrient for the fetus, with its transplacental passage providing material for energy and for contributions to the fetal carbon pool. Initially, tissue growth is the main location for carbon and other constituents, with the 20-week fetus having little or no fat and approximately 90% water in its body composition. By term, fetal body water has decreased to approximately 76%, a figure high by adult standards; fat, a material of high carbon content, constitutes approximately 16% of the fetus. These observations, coupled with the instability of neonatal glucose metabolism, when the baby is stressed by infection or other problems, should reinforce the importance of glucose metabolism in the perinatal period and particular respect for the relatively depleted stores of energy in the small premature or growth-restricted infant.

Amino acids, both essential and nonessential, are important as the building blocks of fetal protein synthesis. The uptake of essential amino acids through the placenta seemingly serves as a basic requirement for growth. Maternal nutritional state and placental function are crucial to fetal well-being and growth, whereas in the neonate, amino acids and nitrogen originate with digestion of milk and uptake through the portal venous route.

The physician dealing with the newborn must consider the prior fetal nutritional state. Fortunately, when the digestive system of the neonate is unable to function at a level sufficient to provide energy and growth, physicians have the knowledge and technology available to approximate the fetal nutritional state. Total parenteral nutrition effectively returns the baby to the





**Figure 80-4** Colorado intrauterine growth charts. These charts were developed from measurements of babies after birth. They remain useful as a means for determining relative growth status of a baby compared with a reference population. (Adapted from Lubchenco LO, Hansman C, Boyd E. Intrauterine growth in length and head circumference as estimated from live births at gestational ages from 26 to 42 weeks. *Pediatrics*. 1966;37:403–408.)

fetal state, in which all necessary nutrients, including essential and trace substances, enter directly into the circulation. Although this state can be maintained for reasonable intervals, such therapy does have complications, including infection and liver disease, making very long-term parenteral nutrition of the child much more problematic than it is for the fetus.

### Identification and Management of Fetal and Maternal Risk

Any factor that increases the possibility of adverse pregnancy outcomes contributes to risk. Medical risk includes physiologic, nutritional, obstetric, and genetic factors. Psychosocial risk includes psychological, social, environmental, and behavioral factors and personal habits. These 2 broad categories of risk often act

concurrently, and individual risks may overlap, accompany, or follow each other. The relationship between risk factors and adverse outcomes may be obvious, as with a specific toxic agent such as mercury; more often, however, risk is both subtle and cumulative.

### Preconception Care

Health before pregnancy has become increasingly recognized as an important determinant of pregnancy outcome. Preparation for pregnancy should begin before conception for both women and men, including assessment of risk and preventive or therapeutic intervention, including change of behavior. Box 80-1 illustrates the general categories and some specific problems that should be addressed in preconception care.

**BOX 80-1 Preconception Care Inventory****MEDICAL HISTORY**

- Reproductive
- Family
- Genetic
- Current medications
- Substance use, including alcohol, tobacco, and illicit drugs
- Abuse, physical and emotional
- Environmental exposures
- General physical examination
- Immunization when indicated (rubella, hepatitis B, varicella)

**SCREENING**

- Sexually transmissible infections, depending on risk assessment
- Genetic disorders based on racial and ethnic background and family history (sickle hemoglobinopathies,  $\beta$ -thalassemia,  $\alpha$ -thalassemia, Tay-Sachs disease, cystic fibrosis, fragile X syndrome, Duchenne muscular dystrophy)

**COUNSELING**

- HIV prevention and testing
- Abstinence from tobacco and alcohol
- Folic acid supplementation when attempting pregnancy and during first trimester
- Good control of preexisting medical conditions such as diabetes and hypertension

Modified from American Academy of Pediatrics. *Guidelines for Perinatal Care*. 7th ed. Elk Grove Village, IL: American Academy of Pediatrics and American College of Obstetricians and Gynecologists; 2012.

The concept of care before conception is related to, but not the same as, family planning; much more is involved than merely spacing of pregnancies. Wider acceptance of this concept within society may have a major effect on the outcome of pregnancy in such specific populations as adolescents. The role of the pediatrician in preconception and interconception care is vital.

The importance of preconception care was emphasized in 2006 by the Centers for Disease Control and Prevention, which convened a summit to discuss preconception care programs, research, and policy. The recommendations are specific to the implementation of health behavior, access to health care, consumer demand, research and surveillance for monitoring, and improving the health of women, children, and families. Box 80-2 summarizes the primary objectives of the panel recommendations of the Centers for Disease Control and Prevention.

**Prenatal Care**

A report entitled *Caring for Our Future: The Content of Prenatal Care*, published by the US Department of Health and Human Services in 1989, defines the 3 basic

**BOX 80-2 Recommendations to Improve Preconception Health and Health Care**

1. Improve the knowledge, attitudes, and behaviors of men and women related to preconception health.
2. Ensure that all women of childbearing age in the United States receive preconception care services that will enable them to enter pregnancy in optimal health.
3. Reduce risks indicated by a previous adverse pregnancy outcome through interventions during the interconception period, which can prevent or minimize health problems for a mother and her future children.
4. Reduce the disparities in adverse pregnancy outcomes.

From Centers for Disease Control and Prevention. Recommendations to improve preconception health and health care—United States: a report of the CDC/ATSDR Preconception Care Work Group and the Select Panel on Preconception Care. *MMWR Recomm Rep*. 2006;55(RR06):1–23.

components of prenatal care as early and continuing risk assessment, health promotion, and medical and psychosocial interventions and follow-up.

Previous discussion has emphasized that during the prenatal period, the fetus is undergoing rapid and continuous growth and development. Anything that jeopardizes this process must be recognized as a fetal risk factor and assessed. Major contributors to fetal risk are listed in Box 80-3.

Little doubt exists that prenatal care is associated with healthier babies and mothers. Much of the original interest in and emphasis on prenatal care involved pregnancy-induced hypertension and the use of periodic blood pressure determinations. Standardized schedules (with details such as number and timing of visits, procedures, and studies) are available. In addition, the US Department of Health and Human Services offers suggestions, including the addition of preconception care to traditional prenatal care. The tests available for fetal assessment are provided in Box 80-4.

**Assessing Fetal Status Before Labor**

The physician is obligated to make every effort to identify risk and practice expectant fetal medicine. Pediatricians must be familiar with the basic principles of techniques used to gather information. Family and reproductive history, fetal structure and growth, heart rate, and amniotic fluid and fetal blood analyses provide the basis for most of these methods. Some of these measurements are noninvasive, have been part of obstetric practice for years, and provide statistically valid information—for example, taking a history and measuring the size of the uterus. They are used to assess the need for other investigative techniques.

**Fetal Activity**

The duration, amplitude, and frequency of fetal movement after quickening and in the third trimester can provide important information about fetal well-being.

**BOX 80-3 Major Contributors to Fetal Risk****GENETIC**

- Chromosome abnormalities
- Inherited traits

**MATERNAL-FAMILIAL ENVIRONMENT AND LIFESTYLE**

- Socioeconomic status
- Social environment
- Physical environment
- Radiation
- Teratogens
- Nutrition
- Smoking or secondary exposure to smoke
- Drug or alcohol abuse
- Lack of prenatal care

**MATERNAL REPRODUCTIVE CAPABILITY AND HEALTH**

- Age, weight, height
- Reproductive tract abnormalities
- Maternal medical disorders
- Cardiac
- Respiratory
- Renal
- Hematologic disorders (eg, sickle cell disease, thrombocytopenia)
- Metabolic disorders (eg, diabetes, thyroid disorders, phenylketonuria)
- Epilepsy
- Emotional status/mental health

**PLACENTA AND MEMBRANE DISORDERS**

- Implantation (abdominal, tubal, previa)
- Vessel and cord complications
- Abruptio
- Premature rupture of membranes and infection

**MATERNAL-FETAL UNIT**

- Multiple gestation
- Obstetric complications
- Malposition and malpresentation
- Cephalopelvic disproportion
- Abnormal fetal growth and gestation
- Alloimmunization (erythroblastosis fetalis)
- Intrauterine infections
- Pregnancy-induced hypertension

An inactive fetus may be chronically compromised, and the rapid onset of inactivity in a previously active fetus can be ominous. Daily assessment of fetal movement has some value as a test of fetal well-being. Obstetricians often ask women to report if they perceive fewer than 10 fetal movements in a 2-hour period of close observation (*kick counts*). Change in fetal activity does not predict specific fetal abnormalities but warrants follow-up with more standardized tests of fetal well-being.

**BOX 80-4 Fetal Assessment****ANEUPLOIDY SCREENING**

- First-trimester screening
- Second-trimester screening
- Quadruple marker screening
- Genetic sonogram
  - Integrated screening
  - Sequential screening
  - Noninvasive prenatal testing/cell-free fetal DNA

**DIAGNOSTIC PROCEDURES**

- Chorionic villus sampling
- Amniocentesis
- Percutaneous umbilical blood sampling

**FETAL WELL-BEING ASSESSMENT**

- Fetal kick counts
- Nonstress test
- Biophysical profile
- Modified biophysical profile: nonstress test plus amniotic fluid index
- Contraction stress test
- Umbilical artery Doppler velocimetry
- Venous Doppler velocimetry
- Middle cerebral artery Doppler velocimetry

Fetal assessment modalities available at most regional centers. See text for more information.

**Fetal Heart Rate**

The normal fetal heart rate (FHR) settles in the range of 110 to 160 beats/min by the final trimester and is easily monitored by a Doppler device (after 10 weeks), a fetoscope (after 20 weeks), and a stethoscope (after 28 weeks). During labor, continuous electronic fetal monitoring is used widely but has not been conclusively shown to be better than intermittent auscultation, despite many large studies.

FHR decelerations, especially fewer than 100 beats per minute, are of concern because of an association with acute or chronic insult. Explanation for their presence must be sought. The list of possible causes is long and includes many that have a poor outcome, such as placental insufficiency. An intrinsic fetal cause, heart block, is not as ominous. Tachycardia usually occurs as an autonomic response to stimulation and can indicate fetal normality; it also may be associated with a maternal condition, such as pyrexia. Intrinsic fetal arrhythmias, such as supraventricular tachycardia, can result in secondary manifestations, including fetal hydrops.

**Nonstress and Contraction Stress Tests**

Tests that record FHR and the presence, absence, or temporal sequence of uterine contractions are used extensively. The FHR is driven by neurogenic reflex mechanisms similar to those seen in newborns.

The nonstress test (NST) observes FHR patterns by continuous fetal monitoring before the onset of

contractions. The interrelationship between FHR and fetal movement or spontaneous uterine contractions is observed. Such testing can begin at 26 to 28 weeks but is usually performed closer to term. NST is indicated for patients at risk for uteroplacental insufficiency and fetal death. It is repeated once or twice weekly. A normal or *reactive*, or category 1, NST is defined by a normal baseline heart rate (110–160 beats per minute), moderate variability (5–20 beats per minute), 2 or more accelerations of at least 15 seconds' duration, and a 15-beats per minute peak above baseline in a 20-minute period. A nonreactive or abnormal NST is defined as one that does not meet these standardized criteria and may actually show decelerations. The test has a false-positive rate for prediction of adverse fetal outcome of approximately 80%.

The contraction stress test (CST), or oxytocin challenge test, uses oxytocin-stimulated uterine contractions and records the FHR response. The NST is used more commonly; the CST is used by some physicians only after a nonreactive (abnormal) NST result. The presence of repeated late decelerations is considered problematic. Interpretations can be difficult, and relative and absolute contraindications exist for performing CST, in addition to a false-positive rate of approximately 50%. Interpretation requires experience.

### **Fetal Biophysical Profile**

Fetal well-being can be assessed through the use of multiple parameters identified on ultrasound. Items such as muscle tone, body movement, breathing movement, amniotic fluid volume, and results of the NST can be identified and a score derived in a fashion similar to that for determining an Apgar score.

The biophysical profile has been observed to have a reasonable correlation with fetal blood gas scores. Some investigators have found the combination of amniotic fluid volume assessment and NST to have equivalent performance to that of a biophysical profile.

### **Uterine Size**

The uterus and the products of conception are monitored closely at each prenatal visit. Measurements of fundal height above the symphysis are obtained and plotted; the umbilicus is reached by 20 to 22 weeks. Deviations from the expected curve may indicate a significant number of abnormal and high-risk states.

Fundal height at a level greater than expected may be the result of a miscalculation of dates, with the pregnancy being further along than anticipated. Another relatively straightforward cause of unexpectedly large uterine size is multiple pregnancy. Conversely, fetal causes of smaller than expected uterine size include pregnancy less advanced than anticipated and many problems that lead to IUGR.

The amniotic fluid volume deviations, oligohydramnios or hydramnios, may initially be detected by abnormal uterine size or fundal height. Confirmation and further study by ultrasonography should follow because ultrasound imaging can more precisely estimate the volume of fluid present and assess fetal structures.

The pediatrician also needs to be alert to particular fetal situations in preterm pregnancies in which oligohydramnios occurs, inasmuch as this may be associated

with a large number of disease processes, including IUGR and renal abnormalities with severely compromised urinary excretion. Under normal circumstances, amniotic fluid volume increases until 36 weeks and then decreases. Oligohydramnios thus can be associated with both postterm and postmature pregnancies. Renal agenesis (Potter syndrome) or dysplasia and structural and functional renal problems may not become evident until after birth.

Hydramnios may result from maternal problems, such as diabetes, or from fetal causes, such as tracheoesophageal fistula or diaphragmatic hernia. The pediatrician should immediately suspect fetal and neonatal abnormalities of the upper gastrointestinal tract because the normal circulation of amniotic fluid is interrupted on the absorptive side of the loop in these conditions. The baby will require special attention at birth and may require surgical intervention. CNS and neuromuscular abnormalities, such as myotonic dystrophy, impair fetal swallowing and cause hydramnios.

### **Ultrasonography**

Clinical ultrasound has had a profound effect on all aspects of perinatal medicine. A transducer, acoustically linked to the skin surface by a gel, transmits ultrasonic vibrations, and the returning sound echoes are processed electronically to produce a two-dimensional image. New technology is now allowing production of three-dimensional images, but two-dimensional imaging remains the standard of care of diagnostic ultrasound imaging in obstetrics. Three-dimensional imaging may be seen as an adjunct technology.

Two-dimensional images are used to evaluate fetal size and morphology. Doppler ultrasound is used to measure velocity of blood flow in fetal and maternal blood vessels. Color Doppler depicts local flow by color-encoding an estimate of the mean Doppler frequency shift at a particular position, thereby demonstrating direction and velocity of blood flow. This tool is useful in evaluating fetal heart structure on echocardiogram and may be used as an adjunct in antenatal monitoring in the setting of IUGR or maternal alloimmunization. Power Doppler ultrasound is a technique that encodes the amount of blood flow in color. Its usefulness includes evaluation of fetal vasculature and placental abnormalities.

Although no clinically untoward effects of clinical ultrasound have been documented in humans, potential structural and functional biologic effects have been hypothesized. Doppler ultrasound theoretically has greater potential for harm because of the continuous, rather than pulsed, wave and the amount of time in use. The US Food and Drug Administration, together with the American Institute of Ultrasound in Medicine and other organizations, has developed standards for safe information display.

Controversy continues about the usefulness of and indications for routine prenatal ultrasound examination; several large clinical studies provide conflicting results. An American College of Obstetrics and Gynecology *Practice Pattern Review* developed the following conclusions: specificity of ultrasound fetal anomaly survey is high (99%), sensitivity varies widely and depends on clinical setting and professional skill,



ultrasound is safe when used appropriately, specific indications should serve as the basis for the use of ultrasound in pregnancy, and the optimal time for a single ultrasound during pregnancy is between 16 and 20 weeks' gestation. The use of casual ultrasound without a medical indication should be avoided, and patients must be counseled about the limits of ultrasonography for prenatal diagnosis.

A National Institutes of Health consensus development conference in 1984 concluded that when an accepted medical indication exists, ultrasound improves pregnancy outcome, and the consensus committee listed many specific risk situations. Routine screening, identification of fetal sex, and parents' desire to see their fetus were not considered appropriate because of possible risk and ethical concerns. Estimates indicate that approximately 67% of pregnancies undergo ultrasound examination.

Ultrasound evaluations are an important part of evaluation of fetal well-being. Measurements of fetal growth pattern and distribution and amniotic fluid volume are important observations. A fetus for which biometric parameters are concordant and within acceptable range for gestational age and for which amniotic fluid volume is normal has a low risk for adverse outcome, such as stillbirth. Although the sensitivity varies with the type of birth defect and the skill of the operator, ultrasound can detect many birth defects. Ultrasound also is being used as a noninvasive tool to detect minor markers of aneuploidy.

### Fetal Surgery

Fetal surgery is a controversial intervention that has attracted considerable medical and public interest. Pediatricians should be aware of the general level of activity in this field because they may be consulted by families in their practices. The media and increasingly the Internet serve as informants about possible interventions, often without adequate attention to status of investigation and outcomes.

Fetal risk identification through accurate and timely prenatal diagnosis by ultrasound in conjunction with fetal sampling techniques and technical ability to intervene surgically through endoscopic or open techniques has resulted in attempts to correct fetal lesions that interfere with normal development. Fetal problems potentially amenable to surgical correction with resultant continued development in utero include urinary obstruction (urethral valves), twin-to-twin transfusion syndrome resulting from placental vascular abnormalities, and myelomeningocele. Neural tube defects have been subject to randomized controlled studies of intervention and outcome evaluation. Risks and benefit evaluation of fetal surgery should include the mother as well as the fetus. For further information, see Chapter 83, Fetal Interventions.

### Risk Assessment and Diagnostic Testing

An increasingly valuable technique of perinatal risk assessment involves maternal serum screening for markers that correlate with risk for specific outcomes. All pregnant women in the United States should be offered testing for detection of neural tube defects and

trisomy 18 and 21. Second-trimester (15–21 weeks) risk assessment includes analysis of  $\alpha$ -fetoprotein, unconjugated estriol, inhibin A, and human chorionic gonadotrophin—the quadruple, or *quad*, screen. The sensitivity of detection of spina bifida is approximately 80%, with a 3% to 5% false-positive rate. Ultrasound sensitivity for open neural tube defect is up to 95%. Women who have unexplained elevated serum  $\alpha$ -fetoprotein are at risk for adverse pregnancy outcomes other than neural tube defects, including IUGR and stillbirth. The sensitivity of a quad marker study panel for trisomy 21 is 79%, with a false-positive rate of 5%. First-trimester screening using 2 serum analytes,  $\beta$ -human chorionic gonadotrophin and pregnancy-associated plasma protein A, as well ultrasound measurement of the fetal nuchal translucency, allows risk assessment at 11 to 13 + 6 weeks' gestation, with a similar detection rate and false-positive rate. Noninvasive prenatal testing, or directed analysis of isolated cell-free fetal DNA from maternal serum, is also becoming available. This technique measures the relative proportions of chromosomes, giving a detection rate for trisomy 21 of nearly 99%. Ultrasound in the second trimester can be used to modify the risk assessed on either a quad screen or a first-trimester screen; the screen is based on the presence or absence of markers—subtle changes in fetal anatomy that are more likely to be associated with aneuploidy, such as hypoplastic nasal bone or thickening of the nuchal fold. Women whose screening results are positive are offered diagnostic testing, such as amniocentesis, and they often accept the procedural risk to achieve a definitive diagnosis.

### Amniocentesis

Amniotic fluid bathes and is swallowed by the fetus, and it contains fetal cells, urine, and other substances, including pulmonary surfactant. The technique for obtaining a specimen of this fluid by percutaneous aspiration has been made more successful by the use of ultrasonography.

Diagnostic amniocentesis at 15 to 18 weeks' gestation, in conjunction with ultrasonography, confirms placental localization, fetal size, and gestational age, in addition to providing information obtained from fluid analysis. Evaluation of fetal cells through karyotyping can detect chromosomal abnormalities before potential extrauterine viability so that termination can be considered. Fluorescent in situ hybridization studies are available that produce results for some aneuploidies within 48 hours, as opposed to the 10- to 14-day requirement for standard metaphase karyotype analysis. Molecular genetic studies on DNA extracted from fetal cells are expanding so rapidly that the pediatrician is advised to contact a prenatal diagnostic center to determine whether prenatal testing has become available for a specific disorder.

### Chorionic Villus Sampling

Chorionic villus sampling (CVS) involves ultrasound-directed aspiration of trophoblastic tissue surrounding the gestational sac during the first trimester. The approach can be transcervical or abdominal. CVS is usually performed at 10 to 12 completed gestational

weeks, thereby providing information earlier than amniocentesis.

Studies of the safety and efficacy of CVS have found a higher rate of pregnancy loss and procedure failure than midtrimester amniocentesis. Some centers have higher rates of loss with transcervical than with transabdominal CVS. That CVS requires more professional experience than does amniocentesis is generally accepted. The advantage of CVS is more rapid and earlier diagnostic information, which allows more time for consultation and intervention, including abortion. The disadvantages of CVS include the slightly higher loss rate, lack of information about neural tube defect, and the possible need for later amniocentesis to clarify CVS results or to diagnose neural tube defect. Controversy has existed concerning possible limb reduction defects associated with CVS. The procedure is usually not performed before 10 weeks in an effort to minimize this risk.

### **Percutaneous Umbilical Blood Sampling (Cordocentesis)**

Direct aspiration of fetal blood by means of a needle placed transabdominally through maternal skin and into a fetal blood vessel, or percutaneous umbilical blood sampling (PUBS), is another technique facilitated by ultrasound that has improved fetal diagnosis and therapy significantly. Sampling is possible from approximately 17 weeks to term.

Common diagnostic indications for PUBS are the need for rapid fetal karyotype and evaluation of fetal alloimmune hemolytic disease. The main treatment is transfusion for fetal anemia. The PUBS technique is useful because it provides immediate fetal blood specimens for study of hemoglobin, platelets, blood gases, blood typing, and other parameters in the same fashion as studies in the neonate. Risk is a concern, with fetal loss a possibility. This technique requires sophisticated technology and expertise.

### **Fetal System Formation and Malformation**

Pediatricians and other health care providers must be prepared to discuss normal fetal development, as well as fetal malformation, with parents; this discussion increasingly includes management during pregnancy and the peripartum period. *Teratology* is the study of the causes, development, structure, and classification of fetal abnormalities. Modern prenatal diagnosis provides information about the presence of structural abnormalities in a large portion of cases well before birth.

Most major malformations and disruptions of system function can be categorized as being caused by genetic or intrauterine factors, maternal conditions, and drugs or other agents. Genetic factors have their origin in parental cell lines or in aberrations of initial cellular division after fertilization and are discussed in Chapter 96, Common Congenital Anomalies. Evaluation of risk for genetic disease has advanced rapidly as the techniques for prenatal diagnosis (including fetal cell and tissue sampling) have become increasingly sophisticated. Intrauterine factors include problems such as uterine abnormalities, amniotic bands, and umbilical cord or placental abnormalities. Mechanical

pressure from uterine constraint (as in severe oligohydramnios) causes morphologic changes categorized as a deformation sequence. If otherwise normally developing tissue is disrupted, as with the damage caused by amniotic bands from early amnion rupture, then the resulting damage is categorized as a *disruption sequence*. Maternal medical conditions that produce metabolic imbalance, such as diabetes mellitus and phenylketonuria, are teratogenic. The effect of maternal nutrition is of major concern, especially because the relationship between folic acid deficiency and neural tube defects now is well recognized. Drugs and other agents are a major concern because of the recognition that practically any drug is potentially teratogenic and because of the observation that chemical, radiation, or infectious agents may vary in degree of expression, depending on genetic predisposition or gestational age at the time of insult.

The major systems are discussed in the following sections, with attention drawn to the gestational time of origin of the major types of abnormalities.

### **Central Nervous System**

The CNS starts from an ectodermal origin at about day 18 of gestation; development continues through delivery and long after birth. It is susceptible to teratogenic agents throughout the embryonic and fetal periods and is most susceptible during the first half to two-thirds of the embryonic period.

The original neural plate develops into a neural tube that has cranial and caudal ends. The neural tube walls develop to become the brain and spinal cord; the inner part evolves into the ventricles of the brain and the central canal of the spinal cord. Brain development is complex and passes through stages of a forebrain, midbrain, and hindbrain, with subsequent development of the cerebrum, midbrain structures, pons, and cerebellum. Cells that were originally separated from the neural plate and became the neural crest develop into cranial, spinal, and autonomic ganglia, as well as the autonomic nervous system and chromaffin tissue, especially the adrenal medulla.

Malformations of the CNS confront the physician prenatally and postnatally through imaging studies, which may prompt pediatric and neurosurgery consultation. Some of these defects are among the most profound, such as the anencephalic baby or infants who have very large encephaloceles. Application of life-supportive technology, in the form of assisted ventilation and nutrition, to babies who have such problems has been the subject of much public debate, as has the issue of organ donation. Other anomalies, such as microcephaly, may be compatible with life for variable lengths of time but carry extremely bleak prognoses. Congenital malformations of the spinal column, especially those that have defects in overlying tissue, also pose major moral and ethical dilemmas to parents and health professionals, when potentially treatable complications are superimposed on a fundamentally poor prognosis. Some CNS lesions are of known origin, but others, such as meningomyelocele, may be the result of interactions between genetic predisposition and extrinsic factors. Preconception supplementation with folic acid will decrease the risk for neural tube defect.

Of major concern is the evidence that intrauterine exposure of the developing nervous system to substances such as cocaine or alcohol results in permanent functional morbidity, as well as structural changes. Although morphologic and behavioral changes often appear together, thus inviting the postulation of cause and effect, no reason exists to think that they are always related. Pediatricians should be familiar with resources available for management of neonatal abstinence syndrome.

The developing fetal brain is now known to acquire lesions that are clinically important to the infant and child. Spontaneous hemorrhagic lesions have been seen in the presence of alloimmune thrombocytopenia and cocaine exposure. Evidence is increasing of a link among intrauterine infection, preterm PROM, an increased risk for periventricular leukomalacia, and subsequent cerebral palsy.

### **Cardiovascular System**

The cardiovascular system is the first to function, with a rudimentary blood circulation beginning in the third week. Initially, 2 tubes fuse to form a single tube that evolves into the four-chambered heart and great vessels. By the end of the fourth or fifth week, partitioning of the chambers is complete, with 2 atria and 2 ventricles. Equally complex is the initial formation of a truncus arteriosus, aortic sac, and aortic arches, which evolve by the eighth week into a fetal circulatory pattern. This system undergoes changes in flow patterns during adjustment to extrauterine existence.

Schematic representations of the process whereby the initial pair of tubes forms a single tube with subsequent twisting and formation of chambers and very complex vascular structures (some of which become atretic, whereas others become dominant) can help in understanding spatial relationships and the reasons specific lesions develop. The lymphatic system, which develops in a similar time line, is seen initially somewhat later than the cardiovascular system. The lymphatics have connections with the venous side of the developing cardiovascular system. Malformations of the cardiovascular system occur in approximately 7.5 in 1,000 live births. The critical period for teratogenic effects ends relatively early in the intrauterine period, but the process of formation is so complex that a multitude of possibilities for maldevelopment exists. The degree of severity varies considerably.

Some structural malformations, such as the patent foramen ovale type of atrial septal defect, may be functional only when another pathologic condition exists. The patent ductus arteriosus as a pathologic entity occurs when closure fails after birth; in the fetal state, the patent ductus arteriosus is normal. Use of nonsteroidal antiinflammatory agents by pregnant women in the third trimester can cause premature closure of the ductus arteriosus and cardiac failure. Early malrotation of the fused cardiac tubes can result in dextrocardia, which can occur with an otherwise normal heart and great vessel structures and may not be a clinical problem if complete situs inversus of the viscera also is present. Dextrocardia without situs inversus is often a major problem because of a tendency for associated complex intrinsic abnormalities.

Intracardiac malformations, such as septal defects, are very common, especially in the ventricle. Complex problems, with formation of the great vessels evolving from an inappropriate partitioning of the truncus arteriosus, are also fairly common. Coarctation of the aortic arch is an example of a malformation that may be some distance from the heart itself. Manifestations of malformations can occur in utero and are thought in some instances to result in infants who are large for gestational age. In severe and relatively rare instances, they can produce a form of nonimmune hydrops fetalis.

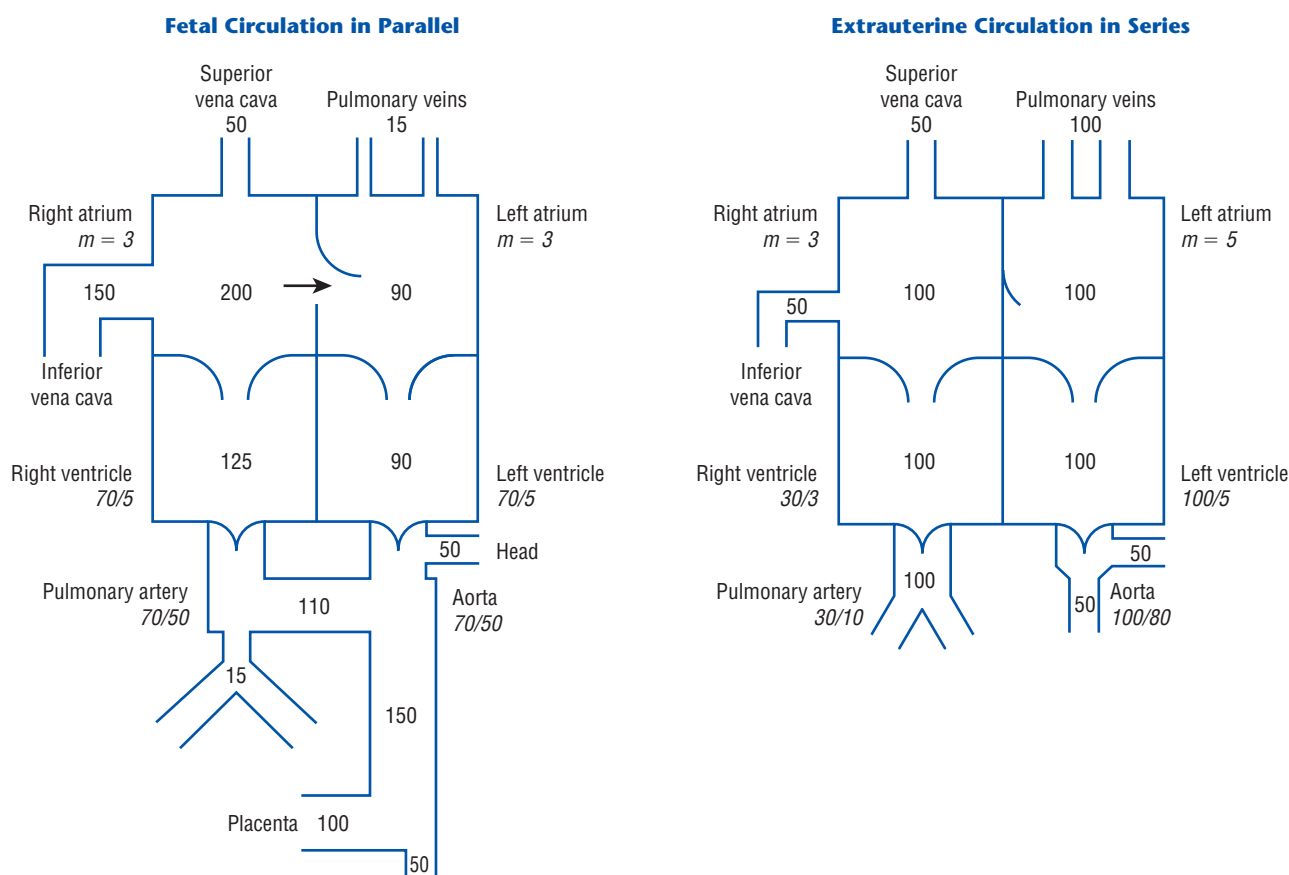
The physiologic aspects of cardiac function in the fetus are basically different from those in the infant, child, and adult. The fetal circulation has several parallel circuits, rather than the series (or sequential) circuitry that is established after the closure of physiologic shunts during or shortly after birth (Figure 80-5). The fetal heart has lower myocardial compliance and ventricular ability to increase stroke work. Increases in heart rate or filling pressure cause little increase in cardiac output.

The pediatrician, pediatric cardiologist, and neonatologist are increasingly becoming involved with cardiac dysfunction before birth. The evaluation of fetal well-being includes cardiac status, with the result that problems such as cardiac arrhythmia or cardiac failure can be detected in utero. Fetal echocardiography can detect specific structural defects, with the interval from 18 to 24 weeks optimum for such an evaluation. Pregnant women who are healthy are admitted to hospitals for treatment of fetal cardiovascular disease; use of antiarrhythmic drugs in the pregnant woman to treat fetal cardiac arrhythmias is an example of fetal treatment by way of the maternal and placental circulations. Medications used to treat fetal arrhythmias in utero may include digoxin, propranolol, flecainide, sotalol, or amiodarone.

### **Musculoskeletal System**

Formation of the musculoskeletal structures becomes apparent in the embryo by at least the fourth week, when limb buds (first the upper and then the lower) become obvious. Muscle structures originate from mesoderm, much of which arises directly from the somites. Bone evolves from mesoderm that undergoes a process of chondrification. Cardiac muscle and other smooth muscles have a different origin in the splanchnic mesoderm of the primitive gastrointestinal tract. The origin of some muscles, such as those of the iris and extrinsic eye, is unclear. The limb buds elongate while forming bone and large-muscle masses. A process of rotation and growth, in which upper and lower extremities rotate in different directions, results in the muscle groupings and dermatome patterns of the child and adult.

Malformations of the limbs are relatively common; otherwise, skeletal and muscular abnormalities are rare. The physician providing newborn care is often struck by the significant attention paid by parents to the extremities, particularly the hands, of newborns. For this reason, relatively minor defects can have major emotional significance. Polydactyly and syndactyly are among the more common human malformations.



**Figure 80-5** In the fetus, blood follows several routes, with a small portion going to the lungs. Oxygenated and nonoxygenated blood is admixed in the fetus, and the placenta serves as the fetal organ of respiration. The risk for expression of cardiovascular disease differs before and after birth because of changes in structure and flow. The numbers inside the diagram represent blood flow (rate), and numbers in italics represent pressure. (Adapted from Flanagan MF, Yeager SB, Weindling SN. Cardiac disease. In: Avery GB, Fletcher MA, MacDonald MG, eds. *Avery's Neonatology: Pathophysiology and Management in the Newborn*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999. Reprinted by permission.)

Many limb abnormalities are genetic in origin, but some malformations result from genetic predisposition interacting with environmental factors. The thalidomide deformities were a specific and perhaps relatively isolated example of limb teratogenesis. Sirenomelia, or caudal regression syndrome, is pathognomonic for poorly controlled maternal diabetes.

### Gastrointestinal System

The alimentary tract, developing from a primitive anlage seen initially at the fourth week, has 3 main divisions: foregut, midgut, and hindgut. Each of these divisions has its own specific blood supply in the celiac, superior mesenteric, and inferior mesenteric arteries. Because development of each tract can be traced, abnormalities of the individual divisions are seen. The foregut, from the pharynx to the insertion of the common bile duct, develops into various structures, including the intestine and the liver and pancreas. Midgut structures include all the small intestines (except for the duodenum proximal to the insertion of the common bile duct) plus the cecum, the appendix, the ascending colon, and approximately two-thirds of

the proximal transverse colon. The midgut structures go through a complex rotation during development, whereby an initial loop develops outside the fetal abdomen and rotates approximately 90 degrees at that time. At approximately the 10th week, these midgut intestinal structures return to the abdomen and go through a further complex rotation of 180 degrees, leading to the final anatomic relationships of the intestine. Hindgut structures include the transverse, descending, and sigmoid colon and rectum through the final portion of the anal canal, which develops from an anal pit. The cloaca (the early expanded end of the hindgut) and tissues of other origin form the perineal structures.

Alimentary tract malformations are fairly common and often are associated with other anomalies. The foregut has an initial tracheoesophageal common origin, with subsequent separation. Tracheoesophageal fistulas resulting from errors in formation of the tracheoesophageal septum occur in 4 basic patterns; early detection is important to prevent extensive aspiration pneumonitis. Errors of midgut development and malrotation lead to many problems, the most



spectacular of which is the lack of return of the bowel to the abdominal cavity, with a resultant omphalocele. Other malrotation presentations include acute intestinal obstruction and ischemia in utero or at varying lengths of time after birth, often after initial feedings. Malformations of the intestinal tube in the form of stenosis, duplication, or atresia are of unclear origin but may result from problems with recanalization or a compromised mesenteric vascular supply. Hindgut malformation occurs most commonly at the most distal portion, resulting in atresia, stenosis, membranous obstruction, or imperforate anus. Many other intestinal malformations can be seen. Of special interest is Meckel diverticulum (an outpouching in the ileum), representing the remnant of the yolk stalk.

### Respiratory System

Respiratory system formation begins at approximately 26 days and goes on long after birth. Initial cell lines arise on the floor of the primitive pharynx and produce a laryngotracheal tube. Endoderm of this tube becomes the lining and glands of the lower respiratory system; connective tissue and cartilage of the respiratory system arise from splanchnic mesoderm. Further growth of the endotracheal tube results in 2 lung buds that divide further into 2 sections on the left and 3 on the right; these correspond to the adult lobes. Branching continues after this point to form the pulmonary segments. Approximately 5 to 7 weeks after fertilization, a pseudoglandular period exists during which major growth of the bronchi and terminal bronchioles occurs.

During the canalicular period beginning at 13 weeks and continuing to approximately 25 weeks, bronchioles and alveolar ducts develop, and significant vascularization occurs. From 24 weeks until birth, terminal sacs arise and become alveoli. These sacs are initially lined by a cuboidal epithelium, which changes to a squamous form at approximately 26 weeks' gestation. Alveolar development continues through early childhood. The association of the development with the threshold of extrauterine viability is obvious.

Surfactant is not produced until alveoli are formed. Complex cell types lining the alveoli have been described. A vacuolated cell, the type 2 pneumocyte, seems to have a secretory function and to be involved in alveolar stabilization through the elaboration of surfactant.

Anatomic malformations of the pulmonary parenchyma are unusual but include many dysplastic and cystic abnormalities. (See Chapter 100, Respiratory Distress and Breathing Disorders in the Newborn.) Because of the nature of fetal respiration, in which gas exchange is not occurring in the lung, these abnormalities are usually not problematic until after birth. Abnormalities of the diaphragm, the most common of which is diaphragmatic hernia, are most frequently seen on the left and often are associated with severe restriction of lung development on 1 or both sides. Some infants who have diaphragmatic hernia exhibit persistent pulmonary hypertension, a complication that includes increased vascular resistance similar to that seen in the fetus.

The pediatrician confronts respiratory problems closely related to the formative and maturational

status of the lung. For example, at 22 to 25 weeks' gestation, alveolar formation may not be advanced to the point of being able to support life, even when exogenous surfactant, mechanical ventilation, and other interventions of present-day neonatal intensive care are used. This situation is encountered in the extremely low-birth-weight infant, or *micropremie*, and is basically a problem of pulmonary immaturity rather than prematurity. Whether respiratory distress syndrome is present after the birth of a premature baby depends largely on the functional cellular maturity of the infant's lungs. Antenatal treatment includes the use of corticosteroids to enhance fetal pulmonary maturity in pregnancies at risk for preterm delivery. Administration of a single course of corticosteroids is recommended for the pregnant woman at risk for preterm delivery, between 24 and 34 weeks' gestation. Postnatal treatment includes administration of exogenous surfactant until endogenous production occurs. (See Chapter 100, Respiratory Distress and Breathing Disorders in the Newborn.)

Prenatal exposure to air pollutants, including heavy metals, tobacco smoke, sulfur dioxide and particulate matter, and pesticides such as polychlorinated biphenyls and dichlorodiphenyltrichloroethane, are known to cause low birth weight, fetal growth restriction, and preterm birth, as well as malformations and neurocognitive deficits. There is a causal relationship between exposure to ambient air pollutants and adverse effects on lung function development. Both reversible deficits of lung function and chronically reduced lung growth rates and lower lung function levels are associated with exposure to air pollution, with clearer relationships for particulates and traffic-related air pollution. A causal relationship has also been shown between exposure to air pollution and aggravation of asthma (mainly resulting from exposure to particulate matter and ozone), as has a causal link between increased prevalence and incidence of cough and bronchitis resulting from particulate exposure. Maternal smoking during pregnancy is associated with poor fetal development. Exposure to secondhand smoke (also referred to as environmental tobacco smoke) during pregnancy might also result in a higher risk for poor fetal development (ie, reduced birth weight and birth length), reduced lung function, respiratory illnesses (eg, asthma), and cognitive deficits (eg, impaired speech, language skills, and intelligence).

### Hematopoietic System

Initial red blood cell formation is seen as early as day 14 after conception, when cells containing embryonic hemoglobin arise from the endothelium of primitive vessels of the yolk sac. Hematopoiesis within the embryo begins in the liver at approximately the sixth week, and this remains the most active site during the early part of the fetal life span. The bone marrow assumes the primary role at approximately the sixth month, and other sites, especially the spleen and lymph nodes, play a contributory role.

Fetal hemoglobin (HbF) predominates for much of intrauterine existence and under normal circumstances is seen to a small degree in early infancy. Beginning at

approximately the third month, some hemoglobin A (HbA) is present (5%–10%), and the proportion of HbA to HbF increases rapidly from approximately 35 weeks to term, when blood is approximately 50% to 65% HbF. HbF has an increased oxygen affinity compared with HbA, probably the result of a differing action of 2,3-diphosphoglycerate, which facilitates oxygen saturation in the intrauterine environment. Blood group antigens are familial in their determination and can be identified as early as the second month of fetal life. Platelets also are seen at approximately the second month. The presence of hematopoietic abnormalities is important for the physician to recognize. Certain hemoglobinopathies may result in intrauterine disease.  $\alpha$ -Thalassemia results in hemoglobin Bart (tetrameric  $\gamma$ -chains), which has a very high oxygen affinity, resulting in intrauterine distress from tissue hypoxia and non-immune hydrops fetalis. Several other significant hemoglobinopathies (eg, homozygous and heterozygous  $\beta$ -thalassemia) and structurally abnormal hemoglobins have been identified, such as HbS and HbC. PCR analysis of DNA from samples obtained by amniocentesis is possible. Hemolytic anemia that results from maternal–fetal blood group incompatibilities and transplacental passage of antibody is an immune disease; however, it has a marked effect on hematopoiesis, resulting in erythroblastosis fetalis and extensive proliferation of hematopoietic tissue. Fetal thrombocytopenia may be primarily of fetal origin, or it may be associated with some form of extrinsic agent or process, such as immune antibody of maternal origin or intrauterine infection. Many fetal intrauterine hematologic manifestations are part of disease processes involving other systems.

Middle cerebral artery Doppler velocimetry, amniocentesis, and PUBS are clinically useful in fetal hematologic disorders. Middle cerebral artery velocimetry is used to noninvasively diagnose fetal anemia, as seen, for example, with alloimmunization. PUBS can be used to diagnose thrombocytopenia and for platelet transfusions or exchange transfusions in the fetus with severe anemia caused by blood group alloimmunization.

### Immune System

Immune system components function very early in fetal life, with some parts present as early as the eighth week and with a total rudimentary system capability by the 12th week. The cellular immune system originates in liver or spleen stem cells that migrate to the thymus at approximately the eighth week. These T cells enter the bloodstream and are distributed to the body, mainly to the lymph nodes and spleen. The antibody immune system generates IgM in lymphoid tissues as early as the 11th week and IgG at approximately the 12th week. IgA, IgD, and IgE are seen in the fetus in small amounts toward the end of pregnancy. Current thinking suggests that specific immunoglobulin synthesis occurs in stem cells or B cells. Passive transfer of maternal antibody has been demonstrated very early in fetal life. Maternal IgG is detectable as early as the 40th

day, and practically all cord IgG is maternal in origin, arising from both passive and active enzymatic transplacental passage. IgM is not transferred passively. The complement system has some fractions present during the embryonic period at the eighth week, and by 12 to 14 weeks' gestation a considerable complement fraction is present. Malformations of the fetal immune system, of either familial or developmental origin, have been described and have contributed to an understanding of the adult system.

Abnormalities are thought to exist in all parts of the immune system, and physicians should understand the basic possibilities because of the fetal and neonatal diseases that result. Fetal graft-versus-host reactions have been documented after intrauterine transfusions. Congenital infections activate the immune system, with an increased cord IgM level possibly being evidence of such infections. Fetal IgM is usually not present until the third trimester. At term, IgM and IgA are detectable but at levels much lower than in the adult. Transplacental antibody passage with effects on the fetus, as seen in alloimmunization (erythroblastosis fetalis), is the classic clinical example of fetal disease resulting from activation of a maternal immune system response.

### Urogenital System

A close interrelationship exists between the development of 2 basic systems: the urinary (or excretory) system and the genital (or reproductive) system. The human embryo has 3 separate excretory organs: the pronephros, the mesonephros, and the metanephros. The metanephros appears at approximately the fifth week after fertilization, functions 2 to 3 weeks later, and remains as the permanent kidneys. The other 2 systems involute, with the mesonephros remaining as a few ducts in the male genital tract and as a vestigial remnant in the female genital tract. The final excretory system has 2 main divisions. The entire collecting system from the kidney to the bladder originates from the ureteric bud; nephrons arise from the mesodermic-metanephric mass. The kidney tissue appears originally in the early pelvic region and ascends into the abdomen. The bladder develops from the urogenital sinus and splanchnic mesenchyme. Excretory system function is present by approximately the ninth week; theoretically, contributions to amniotic fluid are possible at this time and become the major component later in gestation.

The prospective phenotype of the genital system is determined at fertilization. However, an indifferent stage of genital development exists, ending at approximately the seventh week, with the gonads showing specific sexual characteristics. By the 12th week after fertilization, the genitals are distinctly male or female. The Y chromosome seems to be responsible for the differentiation of testes. Masculinizing hormones from the testes stimulate development of mesonephric ducts into genital components and result in the external genitals forming a penis and scrotum. Feminization of the external genitalia seemingly occurs in the absence of androgens. Gonadal tissue has its origin in the lateral abdominal wall,

with the testes descending into the scrotum late in fetal life.

Malformations of the urogenital system are relatively common and result in a myriad of morphologic and microscopic manifestations. Some entities, such as renal agenesis, result in intrauterine manifestations, including oligohydramnios, and in morphologic changes in the fetus. Other problems may occur in the immediate neonatal period. For example, renal abnormalities that result in cystic lesions of the kidneys initially may be detected in the newborn period as abdominal masses found at physical examination or as abnormalities in renal function. Malformations in the vascular supply to the kidneys or the collecting system result in congenital problems such as obstructive uropathy that predispose the person to renal disease, occurring in infancy and childhood. Ultrasound evaluation of the fetal collecting system may demonstrate findings consistent with dilation that does not persist. Fetal observations should be evaluated after birth. Malformations arising from problems of formation of the urogenital sinus and urachus may be severe, as in extrophy of the bladder or, less obviously, as in fistulas between perineal structures.

Abnormalities of kidney function can develop in utero. Maternal exposure to angiotensin-converting enzyme inhibitors in the second and third trimesters can cause renal failure and severe oligohydramnios without structural abnormalities.

Malformations of the genitals also can be complex in origin; those caused by errors in the sex-determining mechanism can result in hermaphrodites but are rare. Errors in sexual differentiation, producing pseudohermaphrodites, are somewhat more common. The presence of neonatal ambiguous genitalia is a true medical emergency, requiring immediate evaluation. Congenital adrenal hyperplasia, which is characterized by fetal androgen excess and masculinization of the female fetus, accompanied by a deficiency of cortisol and leading to salt wasting and shock, is a possible cause. (See Chapter 58, Fluids, Electrolytes, and Acid-Base Composition; and Chapter 243, Disorders of Sex Development.) Exposures to potential endocrine disruptors, naturally occurring compounds, or human-made substances that may mimic or interfere with normal hormonal function, have been linked with developmental, reproductive (fertility; genitourinary anomalies; cancer [diethylstilbestrol]), neural, immune, and other conditions. Some environmental endocrine-disrupting chemicals, such as the pesticide dichlorodiphenyltrichloroethane, dioxins, and polychlorinated biphenyls, are highly persistent and slow to degrade in the environment, making them potentially hazardous over an extended period of time.

### Special Considerations

Certain situations of fetal formation and malformation deserve special mention. The special senses, specifically those of the eyes and ears, are very sensitive to teratogenic activity and result in profound effects on the developing infant and child. Eye formation begins at the fourth week and proceeds very rapidly,

especially through the sixth week. Malformations of the eye and ear may be associated with errors in genetic material; some syndromic conditions have readily identifiable eye and ear malformation patterns. Intrauterine infections, particularly rubella, can affect the eye and inner ear. CMV is a common cause of congenital deafness. Errors in position or morphology of the external ear often are associated with other malformations.

Malformations of the face and palate are of major concern. These malformations have their origin in the embryonic branchial apparatus from which the face, pharynx, and attendant structures develop. Cleft lip often is associated with cleft palate but arises from distinctly different origins. Cleft lip is often recognizable on second-trimester ultrasound, but prenatal diagnosis of cleft palate remains elusive. Three-dimensional ultrasound holds promise for the diagnosis of cleft palate. Difficulties in these areas are probably of mixed genetic and environmental cause. The branchial arch merging in the formation of palate structures is most susceptible to teratogenic factors between 6 and 10 weeks' gestation.

### Fetus, Mother, and Family

The fetus influences the mother and family physically and emotionally. Although expectations regarding conception and childbearing vary, the most positive situation is one of physical reproductive readiness and an anticipated pregnancy. Psychological factors involved in the decision to become pregnant are extremely complex and heavily influenced by societal mores and values. More than 50% of all pregnancies in the United States, and a much higher portion of pregnancies in teenagers and unmarried women, are unanticipated, but not necessarily unwanted, at conception. Psychosocial situations that detract from optimal health before conception should be interpreted as the beginning of potential fetal risk.

Many maternal and familial situations of unfortunate familiarity to the physician provide a bad start for the pregnancy; a common example is pregnancy in the younger adolescent, who is both physically and emotionally immature and who may well not have a stable interpersonal relationship with her male partner. Post-conceptual factors interact after fertilization occurs, with a progression of biochemical, physical, and emotional changes that influence the mother, father, and family. Poverty has a profound effect on the physical, emotional, and cognitive well-being of children, adolescents, and adults. These effects can be mitigated by health and social programs such as Medicaid and the Special Supplemental Nutrition Program for Women, Infants, and Children.

These postconceptual changes, some subtle and some not, permanently alter the parents' lifestyle. New situations demand behavioral adaptations and a process of coping. If the coping process is successful, then major developmental progress has been made, especially by the mother; such is usually true to a lesser extent in the father and to varying degrees in people further removed. However, if attitudes and the coping process are unsatisfactory, then adoption or abortion may be considered.

The first missed menstrual period, an overt sign of change to many women, does not occur until after the stage of the dividing zygote is essentially complete. By the time of the second missed menstrual period, the embryonic stage is one-half over (see Figure 80-3). Although the zygotic stage is relatively unaffected by teratogens, the embryonic stage is one of very high risk. Maternal and familial habits potentially injurious to the fetus are difficult to alter under any circumstances, and of course altering circumstances is impossible when the mother does not yet know that she is pregnant. Pregnancy is often not confirmed in the present medical system until after the second missed menstrual period.

The customary use of trimesters as a means of dividing pregnancy into 3 intervals of equal length of particular personal or medical significance is considered imprecise by obstetricians and is discouraged for clinical situations. Nonetheless, the trimester concept remains in common use in discussions of the progression of pregnancy and its influence.

The first trimester may be the most important phase of adjustment to the fetal presence. Many women experience physical symptoms such as fatigue, nausea, and headache, as well as changes in emotional status. The second trimester is usually marked by less overt signs of physical and emotional adjustment and discomfort. System development in the fetus is basically complete, and major growth is occurring. This development leads to the phenomenon of quickening, when a woman feels fetal movements for the first time at approximately weeks 18 to 20 in the primigravida; in the multigravida, such movement may be felt 1 to 2 weeks earlier. Quickening undoubtedly represents a major milestone in the relationship between a woman and her fetus. This sign is the first overt or direct sign of independent fetal activity. Awareness of fetal movement can provide some information about gestational age. For some women, it also serves as a milestone after which abortion is an even more difficult choice.

The third trimester is marked by an acceleration of the fetal alteration of lifestyle. Maternal physical activity, previously undertaken easily, may become increasingly difficult. Sexual activity between parents may be subject to changes or even cessation. Preparation for delivery becomes more of a part of everyday life; childbirth education, financial planning, and other aspects of preparation and emotional adjustment should be in progress. Ideally, a first appointment with the pediatrician would occur at this time.

### Fetus, Health Professional, and Society

Great concern over the influence of factors such as smoking, alcohol consumption, radiation, and pesticides on the fetus is supported by many studies, and research continues to expand the database. Societies that advocate preconception care and the introduction of employment, nutritional, and lifestyle changes for women as soon as they miss a period (or preferably before conception) are surely enlightened in

their advocacy of improved fetal and pregnancy outcomes.

Amniocentesis, chorionic villus sampling, and percutaneous umbilical cord sampling represent procedures of major interest to individuals and society because they enable physicians to detect conditions incompatible with what is considered normal human existence. These procedures allow families to prepare for the birth of an infant who may have special needs or requirements or to make the difficult and personal decision to terminate a pregnancy. Moral and ethical concerns over these procedures are related to those associated with abortion generally. The debate over legalized abortion has brought to the fore concerns about the legal and interpersonal status of the fetus. Health professionals are embroiled in this debate, especially over whether a physician of perinatal medicine can personally oppose abortion and therefore not mention all alternatives to patients.

*Viability*, or the capability of a fetus to assume an independent extrauterine existence, is a concept that demands attention and thought. Research shows that 23 weeks from the last menstrual period is the time at which some fetuses, if born into an environment in which neonatal intensive care is available, can survive. The role of the family in decision making, especially with regard to the extent of intervention for a baby born at the threshold of viability, is a matter of great interest. In particular, the frequency of somber modes of survival needs to be presented sensitively. Parents and pediatricians have advocated that for premature infants born between 23 and 25 weeks' gestation, parental wishes should be recognized and followed.

The physician must be aware of the close approximation of potential viability and gestation limits on legal abortion in the context of significant variations in clinical estimates of fetal age. The Supreme Court decision (*Roe v Wade*) has been interpreted to support legal abortion, although state laws vary with respect to gestational age limits. Menstrual dating by history and physical examination is only accurate within a range of 2 to 4 weeks. Confirmation of pregnancy dating by ultrasound examination improves the precision of dating to approximately 10%, so that a variation of 10 to 14 days is still possible in the second trimester. Ultrasound dating in the first trimester is associated with the smallest margin of error.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Environmental Exposure Assessment* (form), Katie Huffling, RN, MS, CNM ([prhe.ucsf.edu/prhe/pdfs/Huffling%20prenatal-preconception%20assessment.pdf](http://prhe.ucsf.edu/prhe/pdfs/Huffling%20prenatal-preconception%20assessment.pdf))
- *Fish Consumption Advisories* (Web page), United States Environmental Protection Agency ([epa.gov/waterscience/fish](http://epa.gov/waterscience/fish))
- *Healthy Environment Healthy Child: Prescriptions for Prevention* (handout), Physicians for Social



Responsibility ([www.psr.org/assets/pdfs/toolkit-rxpads-4up.pdf](http://www.psr.org/assets/pdfs/toolkit-rxpads-4up.pdf)) (English); ([www.psr.org/assets/pdfs/toolkit-rxpads-4up.pdf](http://www.psr.org/assets/pdfs/toolkit-rxpads-4up.pdf)) (Spanish)

- *March of Dimes* (Web site), ([www.marchofdimes.org](http://www.marchofdimes.org))
- *MotherToBaby* (Web site), Organization of Teratology Information Specialists ([www.mohtertobaby.org](http://www.mohtertobaby.org))
- *Niños Seguros y Sanos: Safe and Healthy Children* (Web page), Physicians for Social Responsibility ([www.psr.org/resources/ninos-seguros-y-sanos.html](http://www.psr.org/resources/ninos-seguros-y-sanos.html))
- *Prenatal* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/prenatal/Pages/default.aspx](http://www.healthychildren.org/English/ages-stages/prenatal/Pages/default.aspx))

### Medical Decision Support

- *American College of Obstetricians and Gynecologists* (Web site) ([www.acog.org](http://www.acog.org))
- *Guidelines for Perinatal Care* (book), American Academy of Pediatrics and American College of Obstetricians and Gynecologists ([shop.aap.org](http://shop.aap.org))
- *Pediatric Environmental Health* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Pediatric Environmental Health Toolkit* (toolkit), Physicians for Social Responsibility ([www.psr.org/resources/pediatric-toolkit.html](http://www.psr.org/resources/pediatric-toolkit.html))
- *Red Book: 2015 Report of the Committee on Infectious Diseases* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *REPROTOX* (Web site), Reproductive Toxicology Center ([www.reprotox.org](http://www.reprotox.org))
- *Resources for Health Professionals* (Web page), Pediatric Environmental Health Specialty Units ([www.aoc.org/pehsu/training.html](http://www.aoc.org/pehsu/training.html))
- *TOXNET: Toxicology Data Network* (Web site), United States National Library of Medicine ([toxnet.nlm.nih.gov](http://toxnet.nlm.nih.gov))

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## Chapter 81

# ASSISTED REPRODUCTIVE TECHNOLOGIES, MULTIPLE BIRTHS, AND PREGNANCY OUTCOMES

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## INTRODUCTION

The decision to bring a child into the world is a momentous one. For some people, reproductive medicine may be necessary to realize this goal. Infertility rates in industrialized countries have risen for 3 decades, mostly as a result of couples delaying childbirth. Infertility is defined as the inability of a couple to conceive after 1 year of unprotected intercourse. This affects approximately 15% of couples in the United States. Infertility arises from a male etiology in 8%, female etiology in 37%, and a combination of the 2 in 35%. The Centers for Disease Control and Prevention (CDC) report that approximately 12% of women of reproductive age (ie, 7.4 million) have had an infertility-related medical visit within the previous year, and an additional 10% have received infertility services at some time in their lives. Additional CDC data demonstrates infertility in 7.5% of men younger than age 45. Up to 4.7 million men have sought evaluation from a fertility specialist. Typically 18% of men evaluated are diagnosed with a fertility problem. Assisted reproductive technology (ART) has been used in the United States since 1981 to help couples achieve pregnancy, most commonly through ovulation induction and the transfer of fertilized human eggs into a woman's uterus (in vitro fertilization). In fact, over 1% of all infants born in the United States every year are conceived using ART. Assisted reproductive technology includes all fertility treatments in which both eggs and sperm are manipulated. Assisted reproductive technology (ART) procedures most commonly involve surgically removing eggs from a woman's ovaries, combining them with sperm in the laboratory, and returning them to the woman's body or donating them to another woman. The types of ART are in vitro fertilization (IVF), gamete intrafallopian transfer (GIFT), and zygote intrafallopian transfer (ZIFT). The 2 procedures utilized during IVF are ICSI, intracytoplasmic sperm injection, and PGD, preimplantation genetic diagnosis. PGD is a technique that combines molecular genetics and ART, allowing clinicians to identify various genetic diseases in the embryo prior to implantation. Intracytoplasmic sperm injection involves injection of a single sperm directly into an egg; this procedure is commonly used to overcome male infertility problems. Deciding whether to undergo this expensive and time-consuming treatment can be difficult. Ninety-nine percent of ART cycles involve an IVF procedure of a woman hoping to bear a child; less than 1% involve a gestational carrier or surrogate. According to the CDC 2011 ART Success Rates Report,

151,923 ART cycles were performed at 451 reporting clinics in the United States during 2011, resulting in 30,211 live births. This is a decrease of 34.8% in the number of live births as compared to 2008. This results from fewer eggs being implanted during an IVF cycle, on average 2 eggs per cycle irrespective of procedure. This change in practice first recommended in 1998 by the Society for Assisted Reproductive Technology and the American Society for Reproductive Medicine (ASRM), has evolved from the recognition of poorer outcomes for triplet and higher order gestations.

When taking a child's history, the health professional should include the history of the perinatal course, whether a history of infertility exists, and if any assistive measures were used to achieve this or previous pregnancies. In the instances when a multifetal pregnancy occurred, the discussion should include whether any associated fetal or neonatal losses occurred. This information is sensitive as a given family may not want others to know about their fertility issues or the nonmaternity or paternity of their child. Given that this issue is sensitive for many parents, such information may not be divulged spontaneously. The physician must probe gently to elicit this information since a further concern is the increased risk of congenital malformations with ART. For this reason, it is important for those caring for a child to know the means of conception. For example, malformations of the eye, head and neck, heart, and genitourinary system are increased with ART, and even more so with multiple gestation pregnancies.

Our understanding of the outcomes over the life course and into adulthood for children born through assisted conception is evolving. Overall, health and developmental outcomes seem to be comparable with young adults who were naturally conceived although there are concerns about cardiometabolic risks and higher rates of psychological disorders in individuals born through ART.

## TREATMENT OF INFERTILITY

### Artificial Insemination With Donor Sperm and Intrauterine Insemination

Artificial insemination (AI) represents the oldest form of assisted reproduction, with attempts dating back to Princess Joana of Portugal, wife of King Henry IV of Castile, circa 1455. Efforts to develop practical methods for AI began in Russia in 1899. Intrauterine insemination (IUI), a technique involving the injection of collected sperm-containing semen into a woman to cause pregnancy, is used in cases of infertility or impotence or as a means by which a woman without a partner may become pregnant. Approximately 80,000 procedures using donor sperm are performed each year, resulting in the births of 30,000 babies. For many years, artificial insemination with donor sperm (AID) was the only available treatment for male factor infertility. Today, IUI is indicated also for idiopathic or unexplained infertility, to bypass cervical abnormalities, and to offer lesbian couples the option of childbirth. When IUI is combined with ovarian hyperstimulation, the chance of achieving a pregnancy is increased compared with IUI alone.

### In Vitro Fertilization and Related Assisted Reproductive Technologies

In vitro fertilization (IVF), which accounts for 99% of ART procedures performed by fertility clinics in the United States, is an outpatient procedure that uses ovulation induction, ultrasound-guided oocyte retrieval techniques followed by an in vitro fertilization procedure that uses sperm from the male partner or another donor, and transcervical embryo transfer 2 to 3 days after fertilization of the retrieved eggs. The procedure can be performed under sedation without the need for general anesthesia. Although IVF was originally developed to treat women who had absent or irreparably damaged fallopian tubes, use of this procedure has since expanded to treat many other causes of infertility, including tubal obstruction, pelvic adhesions, endometriosis, male factor infertility, and immunologic or idiopathic infertility.

A woman's age is the single most important variable affecting success rates after IVF. Pregnancy rates drop precipitously and miscarriage rates rise in women older than 40 years because of a lack of ovarian reserve (declining number of eggs in the aging female ovary). Low ovarian reserve decreases a woman's chances for conception. To optimize success rates, traditionally many IVF programs in the United States have transferred relatively high numbers of embryos with the hope that at least 1 will result in a pregnancy. The 2008 National Summary and Fertility Clinic Reports of the CDC showed that 38% of ART cycles involved the transfer of 3 or more embryos. The result has been an unprecedented increase in the incidence of multiple births. In the United States, the number of twin births has risen nearly 2-fold between 1971 and 2009, the year with the highest recorded number of twin births. The rates of triplet and higher order births also increased 6.7-fold, reaching a peak in 1998. Over the past 2 decades there has been a 29% reduction in triplet and higher order birth. However, in 2011, 3.5% of live births were multiple gestations, double the incidence in 1971. To lessen the incidence of multiple births and the associated risks of gestational diabetes, preeclampsia, and prematurity, among others, in 2013 the ASRM updated the recommended number of transferred embryos per IVF cycle. Based on the new recommendations, for patients younger than 35 years with a favorable prognosis, a single embryo transfer should occur. Following this recommendation, a decrease in higher order multiple births has already been demonstrated. This is similar to the practice of many European and international communities. In fact, international research supports that single embryo transfer reduces the risk of perinatal mortality with IVF. Detailed information regarding the current status of ART is reviewed annually in the CDC publication *Mortality and Morbidity Weekly Review Surveillance Summaries*.

### Ovulation Induction

Ovulation induction (OI), which uses ovary-stimulating drugs, has been used traditionally for women who have anovulation and oligoovulation, for whom it improves the chance for conception each month by increasing the number of eggs that will ovulate. OI

medications may also control the timing of ovulation, so that intercourse, IUI, and IVF can be scheduled to achieve pregnancy. However because of the uncontrolled nature of OI, there is significantly increased risk of twin and higher order multiple pregnancies. As a result, many states have limited the number of OI cycles prior to IVF initiation, because IVF can more predictably result in a singleton pregnancy. It is important to note that a serious complication of OI is ovarian hyperstimulation syndrome (OHSS). The presentation of OHSS may range from mild to severe with gastrointestinal symptoms, bloating, and weight gain. As symptoms progress, a patient may experience shortness of breath from pulmonary edema and may develop blood clots. These are all attributable to a varying degree of ovarian enlargement.

### Intracytoplasmic Sperm Injection

Representing a true revolution in assisted reproduction, intracytoplasmic sperm injection (ICSI) involves the insertion of a single spermatozoon, selected by a trained embryologist based on its morphology and motility, into the cytoplasm of an oocyte, thereby bypassing all of the inherent obstacles for penetrating the oocyte, such as the zona pellucida.

ICSI is currently the treatment of choice for male factor infertility and for couples who have experienced previous IVF failures or low yield of eggs at egg retrieval. Male factor infertility accounts for nearly one-third of all infertile couples and is caused by low sperm count, poor sperm motility, or poor sperm morphology.

## PREGNANCY RATES AFTER IN VITRO FERTILIZATION

Approximately 20% of IVF pregnancies are lost, most as first-trimester spontaneous abortions. The rate of loss after IVF exceeds that for spontaneous conceptions for several reasons, including the adverse effect of high ratios of estradiol to progesterone on the endometrium, an increased incidence of genetically abnormal oocytes and embryos after OI in an inherently higher-risk population, and a higher risk for ectopic pregnancy. More than 50% of IVF pregnancies are lost in women older than age 40. For older women, diminished ovarian reserve, a condition characterized by a low ovarian egg reserve or impaired development of existing eggs, often accounts for this significantly decreased success rate. Strategies to improve success rates in this population include DHEA supplementation to increase the quantity and quality of eggs and embryos in addition to the use of donor eggs. Although IVF success rates are increased in older women with the use of donor eggs, concerns exist with regard to the basic principles of medical ethics. Specific concerns pertain to autonomy of the egg donor (coercion and uninformed consent) and equality (those who can afford to pay for egg donors are more likely to find a donor).

Of ART cycles in 2008 that used fresh nondonor eggs or embryos, 35% resulted in clinical pregnancy. Approximately 81% of the pregnancies resulted in a

live birth (about 56% singleton birth and 26% multiple birth); about 18% of pregnancies resulted in miscarriage, stillbirth, induced abortion, or maternal death prior to birth.

## MAKING THE DIAGNOSIS OF INFERTILITY

A couple is considered infertile only after unprotected, well-timed intercourse for more than 12 months has failed to result in pregnancy. This rule does not apply to couples when either partner has a history of fertility-related problems. *Primary infertility* refers to those couples who have not become pregnant after at least 12 months of unprotected intercourse; *secondary infertility* refers to couples who have been pregnant at least once, but are not able to get pregnant at present time. Infertility, or a reduced potential for pregnancy, is distinguished from sterility, in which no chance for pregnancy exists. Most childless couples younger than 40 years who are having problems conceiving are infertile but not sterile.

Reproductive endocrinologists attempt to determine the cause of infertility and counsel the infertile couple about realistic expectations and their prognosis for future fertility. Oversimplification of success stories of ART as reported by mass media has raised patient expectations to new, and occasionally insurmountable heights.

The most common causes of infertility are listed in Table 81-1. The cause of infertility is determined by performing a basic infertility evaluation, which includes taking a history and performing a physical examination, semen analysis, and blood tests that include follicle-stimulating hormone, luteinizing hormone, prolactin, testosterone, estradiol, progesterone, 17-OH progesterone, thyroxine, thyroid-stimulating hormone, lupus anticoagulant, anticardiolipin, and complete blood count. In addition, anti-Müllerian hormone assay has become utilized more recently as a more precise test of ovarian reserve. Fragile X testing must also be

**Table 81-1** Causes of Infertility

CAUSES OF INFERTILITY	PERCENT
Male factor	19
Multiple factors, women and men	28 (13% female factors only)
Tubal factor	13
Multiple factors, women only	12.3
Unexplained cause	10
Diminished ovarian reserve	9
Endometriosis	6
Other cause	7
Ovulatory dysfunction	6

Adapted from US Department of Health and Human Services, Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society for Assisted Reproductive Technology. 2011 Assisted Reproductive Technology Fertility Clinic Success Rates Report. Atlanta, GA: DHHS; 2013. Available at: [www.cdc.gov/ART/ART2011/](http://www.cdc.gov/ART/ART2011/). Accessed May 20, 2014.



considered, since carrier status is a potential cause of female infertility. Hysterosalpingogram and laparoscopy are indicated only if necessary to evaluate the anatomy of the endometrial cavity of the uterus and the fallopian tubes.

### PERINATAL OUTCOMES AND NEONATAL ISSUES ASSOCIATED WITH ASSISTED REPRODUCTIVE TECHNOLOGIES

Although dramatic advances in reproductive technologies have offered new hope to childless couples and new opportunities to those who want to postpone childbearing, they also have raised concerns about the ultimate outcomes for infants conceived after fertility treatments such as IVF or ICSI. Parents who conceive after fertility treatments want to know if their children are at higher risk for health problems compared with children who were conceived naturally. Since the birth in 1978 of the first child conceived through the use of IVF, numerous scientific papers have been published on various aspects of IVF, but few reports address perinatal complications, with even fewer studies characterizing the long-term follow-up of children from IVF. In fact, the CDC reports results by state for ART on their Web site based on various modalities and success rates, but do not report long-term follow-up results. This seems to be secondary to a lack of centralized follow-up of ART offspring, since many smaller clinics are administering these therapies without adequate governmental supervision. Identified risks with ART include an increased risk for preterm or low birth weight, multiple gestation, major malformations, growth delay, developmental delay (psychomotor and cognitive), infant mortality, and postnatal health problems. The wide spectrum of clinical sequelae following assisted conception contributes to longer duration of birth hospitalizations and more rehospitalizations during the first 5 years of life and higher health care costs.

Concerns have also been raised regarding increased risks of genetic imprinting disorders, such as Beckwith-Wiedemann syndrome, childhood cancer, as well as cardiometabolic effects in adulthood with ART. Given these reported risks, health care providers face ethical dilemmas about whether families should know these remote risks prior to pursuing ART.

#### IVF and Outcomes

Although many studies have reported reassuring data, because of faults in methods used, study results are considered insufficient to conclude that IVF has no detrimental effect on conceived children's growth or motor and psychological development. Some investigators have not found increased risks for structural abnormalities in offspring from ART pregnancies, whereas others document increased rates of adverse infant outcomes, including higher rates of birth defects. Several recent systematic reviews and meta-analyses of published studies on the outcomes of

ART-assisted pregnancies are limited by the quality of the studies available for analyses. The nature of ART, however, is such that studies typically categorized as the highest quality (level 1 evidence)—randomized controlled clinical trials that compare one treatment strategy with another—have not been considered feasible or appropriate under current clinical practice standards. Consequently, most studies on which these meta-analyses and systematic reviews have been based are lower quality investigations such as controlled trials without randomization and prospective cohort or case-control studies (level 2 evidence) and descriptive studies (level 3 evidence).

Equally important are the risks of adverse pregnancy outcome that result in maternal morbidity, with the potential for a serious effect on fetal and neonatal health. The National Institutes of Health-sponsored FASTER Research Consortium has reported on the outcomes of over 36,000 pregnancies among its participating centers nationwide, noting that OI is associated with significantly increased risks for placental abruption, fetal loss after 24 weeks, and gestational diabetes. Women who are undergoing IVF experience significant increases in rates of gestational hypertension and preeclampsia, placental abnormalities (abruption, placenta previa), and cesarean delivery.

#### Congenital Malformations and Chromosomal Anomalies

There are ongoing concerns regarding the risk for birth defects among infants born as the result of ART. A recent systematic review and meta-analysis identified a 30% to 40% increase with ART in the risk of having a major birth defect resulting in the need for medical or surgical intervention. Although the studies used in this analysis all had some limitation, the analysis does provide some perspective on the increased potential for a significant birth defect among infants of ART pregnancies. The absolute risk of malformations, however, is low.

Significant concerns have been raised over the possibility of adverse effects resulting from the ICSI technique, such as chromosomal abnormalities, congenital malformations, and intellectual disability. Reported outcomes vary. A 2005 study in *Pediatrics* is reassuring for parents who conceived through ICSI or IVF. The findings indicate that the motor and cognitive development of children conceived through these methods is similar to that of naturally conceived children. A meta-analysis conducted by Lie et al assessed the limited data comparing outcomes from ICSI pregnancies with those from conventional IVF. The authors did not find additional risks of major birth defects with ICSI. Nouri et al found in a comparison of neonatal outcomes following pregnancies achieved through IVF or ICSI, that IVF pregnancies were more complicated, yet the neonatal outcomes were better than infants born from ICSI pregnancies. A larger, more comprehensive study conducted in South Australia evaluated perinatal outcomes following assisted conception from 1986 through 2002. Neonatal outcomes varied by ART method. Among singleton



pregnancies following IVF there were higher rates of stillbirth, low- (<2,500 g) and very low-birth-weight (<1,500 g), preterm (<37 weeks' gestation) and very preterm birth (<32 weeks gestation) and neonatal death (<29 days of age). Neonates born of ICSI pregnancies experienced fewer adverse outcomes in comparison with IVF neonates. Infants born from frozen embryos did not exhibit the pattern of adverse outcomes more common among ICSI infants, but were not protected from the sequelae associated with IVF outcomes, preterm birth and reduced birth weight. A notable finding among frozen embryo births was macrosomia among some of the infants. Overall, the underlying infertility status was an important factor in the risk of an adverse outcome.

### Multiple Births

The most common complication of IVF is failure to achieve a successful pregnancy. If pregnancy is achieved, then multiple gestation pregnancy and prematurity are further serious concerns. Since the 1970s, the national twin-birth rates have increased worldwide because of ART. Multifetal gestation may occur resulting from ovarian hyperstimulation from OI or the implantation of multiple embryos. Ovarian stimulation alone also increases the twinning rate from a spontaneous rate of 1.2% to 5.9%. Rates of identical twinning and triplet gestation are also increased. Voluntary guidelines regarding the number of IVF embryos implanted may explain the higher rates of multiple births in the United States as compared with other countries such as Britain, Finland, and Sweden, where regulations typically limit the number of embryos implanted to 1. In the United States, ASRM made the same recommendation for women younger than the age of 35 with a favorable prognosis for pregnancy.

Multifetal pregnancies are at increased risk for preterm delivery or miscarriage and have the potential for significant sequelae in the offspring, including in utero fetal death, low birth weight, and disability among survivors. In a 2003 study, major morbidity—defined as neonatal intensive care admission, surgical intervention, special needs, and delayed speech development—was apparently related to multiple gestation as opposed to ART itself. The risk for perinatal mortality and morbidity is 5-fold and 7-fold higher for twins and triplets, respectively. The average duration of a multifetal gestation decreases by approximately 3 weeks for each additional fetus: 37 weeks for twins, 33.5 weeks for triplets, and 31.5 weeks for quadruplets. This decrease has resulted in a significant debate within the reproductive medicine communities in North America and Europe about the appropriate number of embryos to implant and the role of multifetal reduction.

Multifetal pregnancy reduction (MFPR) offers an alternative to couples who have high-order multiple gestations but poses ethical and religious dilemmas for many couples. Data are limited regarding outcomes of multiple gestations with or without fetal or embryo reduction. However, reports have surfaced that outcomes for both the mother and infant after MFPR are improved. Reports comparing obstetrical

outcome data from quintuplets or quadruplets reduced to twins and nonreduced multiple births suggest that the obstetrical outcome of pregnancies after reduction is improved compared with the data from nonreduced pregnancies. The data regarding reduction from triplet to twin gestation also demonstrates generally improved outcomes. In theory, reduction from triplet to twin decreases the chance of a very early prematurity and short-term morbidity. However, MFPR is itself associated with a risk for preterm delivery and fetal loss, particularly if performed after 15 weeks' gestation.

The risk for multiple gestation may also be reduced by limiting the number of eggs or embryos transferred to 2 or 1 when egg or embryo quality is high. Unfortunately, many clinics continue to implant more than the recommended number of embryos in their patients in an effort to meet patient demands and achieve high success rates. Britain, Germany, Sweden, Switzerland, and other European countries have banned implanting more than 3 embryos in women who are undergoing IVF for fear of multiple pregnancies. In the United States, the ASRM has published guidelines to assist ART programs and prospective patients in determining the appropriate number of cleavage stage (2- to 3-day) embryos that should be implanted. These guidelines specify that women younger than age 35 with a good prognosis should consider only single embryo transfer and that no more than 2 should be transferred in this age group except under extraordinary circumstances. Women between the ages of 35 and 37 should receive 2 embryos unless they have a poor prognosis, in which case 3 embryos should be the maximum implanted.

### Growth and Development

The long-term outcomes of children born using IVF seem similar to those of naturally conceived children when assessing scholastic performance, congenital malformations, and neurologic and psychomotor development. A recent study by the University of Iowa Hospitals and Clinics demonstrated that children from IVF actually scored higher on standardized tests than their matched peers, suggesting that IVF does not have a negative effect on cognitive development.

The growth of children from IVF may lag behind that of naturally conceived children during the first 3 years of life. There may also be an increased incidence of respiratory diseases and diarrhea in the neonatal period. Reported developmental outcomes of children from IVF compared with naturally conceived children are conflicting. The most recent reports of the neurodevelopmental well being of children conceived through ICSI conclude that verbal, performance, and full-scale IQ at 5 and 8 years of age are comparable among a group of children conceived by ICSI and IVF and those conceived spontaneously.

Data on outcomes of pregnancies achieved using frozen-thawed and cryopreserved embryos suggest a slightly lower developmental index with frozen-thawed embryos, but the results were not adjusted for prematurity. Long-term outcomes for children conceived by ICSI using fresh or frozen-thawed surgically

retrieved spermatozoa are not known. However, both sources of sperm are equally efficacious in achieving conception.

### Psychosocial Effect and Family Functioning

An integral component of infertility care is the provision of counseling during the evaluation and treatment cycles. Although the body of literature regarding the mental health issues experienced by couples undergoing infertility treatment and their transition to parenthood is small and primarily women focused, the work continues to grow. In addition, interest has grown in the psychological outcomes for children who are products of reproductive technology related to parent-child relationships and parenting skills in IVF pregnancies and the potential effects of nongenetic parenting when pregnancy is achieved through the use of donor eggs or sperm. The existing literature is limited in that it tends to focus on the parenting relationships with healthy children. Little is known about the mental health issues and burdens faced by parents who have undergone fertility treatments, achieved a pregnancy, but had a sick or disabled child or experienced a fetal or neonatal loss of 1 or more babies in a multifetal pregnancy. Recent reports in the psychological literature suggest that stressors associated with infertility and infertility treatments may contribute to dysfunctional parenting patterns and increased susceptibility to the *vulnerable child syndrome*. Parents who make the difficult choice to reduce a multifetal pregnancy either because of a fetal abnormality in 1 or more babies or to improve the chances for a healthier pregnancy outcome for the mother and the remaining baby or babies experience tremendous grief, anxiety, emotional distress, and guilt. Parents must cope with conflicting feelings of joy for their surviving infant or infants and sadness and grief associated with their remembrances of the babies who died. Recognizing that mothers and fathers often use different coping mechanisms that may influence their perceptions and responses is important. Golombok and Hahn have reviewed recent studies suggesting that ART does not seem to influence parenting and child development unduly. Two recent studies provide additional confirmation that successful ART does not predict mental health problems for adults as they transition to parenthood.

### ETHICAL AND LEGAL CONSIDERATIONS

Although new techniques offer multiple reproductive choices for couples and individuals, they also have created complex ethical and legal issues. For example, in ICSI, the male factor infertility that necessitated ICSI in the first place may be caused by a genetic defect, which the father may then pass unknowingly to his son. Another sensitive issue is that of sperm/gamete donation in which a single man may father many offspring. These offspring may then have multiple genetic half-siblings of whom they are not aware. If offspring become aware of this situation, this may pose quite an emotional burden. Therefore, some

advocate for limiting the number of gamete donations a man can make. Furthermore, there is the issue of preserving the anonymity of the donor and balancing that with the right of the offspring to realize their paternity.

Another controversial matter is that of egg freezing. This may be a chosen route for women who want to delay childbearing in order to pursue personal or career goals. As fertility is known to decline with age, freezing one's eggs at an earlier reproductive age may increase one's chance of future pregnancy. There is abundant information about this in the lay press, but a paucity of medical scientific data exists. When an egg is fertilized, it becomes an embryo. Controversy exists when clinics freeze embryos for later use. For example, what happens if embryo use never takes place? If the parents divorce or die, who gets custody of the embryos? In the United States, clinics request that parents specify how they want unused embryos handled. Some parents will donate them to other infertile couples or to scientists for research; others have them destroyed for fear of creating offspring they will never know. However, many individuals and religious institutions consider these embryos to be human beings and their disposal equivalent to murder.

In the United States, 100 women who are 50 years and older have borne children. Some ethicists think that this circumstance is not fair to the child, and, in the words of Fr. John Paris, Professor of Bioethics, "We're designing orphans by choice." For this reason, few fertility clinics in the United States will treat women older than 49 years. The ethics committee of the ASRM has issued guidelines stating, "Infertility should remain the natural characteristic of menopause." However, these guidelines are voluntary, and no law prevents physicians from treating any woman who requests it. Assisted reproduction is among the least regulated medical specialties in the United States with regard to the number of embryos transferred and age at which donor egg use is considered appropriate, among others.

Unfortunately, IVF is not covered by national health insurance in most of the world. According to the National Conference of State Legislatures, 15 US states have laws that require insurers to cover infertility diagnosis and treatment, with 8 states mandating IVF coverage. Although several European countries have ART covered by national health plans, most of the world does not. In the United States, because each attempt costs \$8,000 to \$10,000, patients often risk multiple births to avoid having to pay for a second visit. In most of the United States, high-quality assisted reproductive care is available mostly to people who have the financial means. The high cost of infertility treatment, especially advanced ART such as IVF, has resulted in reluctance on the part of most insurance companies to provide benefits for infertility and therefore has rendered such medical intervention financially inaccessible to a large portion of the infertile population. For many women then, OI is the primary method feasible to achieve pregnancy, despite the risk of

ovulation hyperstimulation and consequent multiple gestation.

## CONCLUSION

ART has allowed many couples who were once considered barren or beyond childbearing age to now experience the birth of a child. Furthermore, same-sex couples and single mothers or single fathers now have the option of procreating using their own genetic material through assisted reproduction, often involving surrogacy. Unfortunately, technological advances often come with uncertain and often imperfect outcomes; in the case of ART, these would include multiple births, prematurity, and low birth weight. Nonetheless, evidence-based medicine points to an overwhelmingly positive result of the advances in reproductive medicine, provided physicians are responsible and follow reasonable voluntary guidelines. Primary care physicians can be instrumental in guiding families through the information-gathering and decision-making process that is necessary when faced with the obstacle of infertility.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *A Patient's Guide to Assisted Reproductive Technology* (Web page), Society for Assisted Reproductive Technology ([www.sart.org/detail.aspx?id=4020](http://www.sart.org/detail.aspx?id=4020))
- *Born Early (Preterm): Health Concerns* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Resolve* (Web site), National Infertility Foundation ([www.resolve.org](http://www.resolve.org))
- *Urology Care Foundation* (Web site), American Urological Association ([www.urologyhealth.org](http://www.urologyhealth.org))

### Medical Decision Support

- *Assisted Reproductive Technology (ART)* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/ART/index.htm](http://www.cdc.gov/ART/index.htm))

## SUGGESTED READINGS

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## Chapter 82

# PRENATAL DIAGNOSIS

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Fifty percent of early pregnancy losses and 6% to 11% of stillbirths and neonatal deaths are attributed to chromosomal abnormalities. Nonlethal abnormalities can cause significant morbidity and occur in 0.7% of newborns. Although detecting all abnormalities may not be possible prenatally, some screening and diagnostic tests are available.

## GENETIC SCREENING: SERUM TESTING AND FIRST-TRIMESTER ULTRASOUND

Prenatal screening first became available more than 30 years ago and has been evolving ever since. Initially, maternal age and history were the only means of screening available. This practice changed in the mid 1980s when Cuckle demonstrated that combining maternal age with maternal serum alpha-fetoprotein (AFP) increased the detection rate for aneuploidy substantially. This maternal serum screening evolved into what is known as the *quadruple screen* typically performed at 15 to 18 weeks' gestation. Four serum markers (maternal serum AFP, human chorionic gonadotropin [hCG], estriol, and inhibin) are measured, yielding a 75% detection rate and a 5% false-positive rate.

In the early 1990s, Nicolaides reported an association between thickened nuchal translucency (NT) and aneuploidy. NT is a sonographic finding examining the subcutaneous tissue at the back of the fetal neck. NT represents a collection of fluid that appears as an echolucent line. Combining NT with maternal age can provide early detection of these pregnancies in women at higher risk for aneuploidy, with an 80% detection rate.

In 1996, Wald et al found 2 first-trimester serum markers—pregnancy-associated plasma protein A (PAPP-A) and free  $\beta$ -hCG—that stood out as markers for Down syndrome-affected pregnancies. PAPP-A values were found to be low, and free  $\beta$ -hCG values high in affected pregnancies. Using both analytes in combination with age provided a 62% detection rate at an earlier gestational age.

The combination of measuring NT and testing for serum markers is more effective than either of these measurements alone. At 11 weeks' gestation, the detection rate for Down syndrome is 70% using NT alone. This rate increases to 87% when PAPP-A and free  $\beta$ -hCG are added. A fully integrated model of screening in which serum metabolites from the second trimester are measured and the risk is not completely calculated until after this second trimester screen yields the best detection rate, at 96%. The major disadvantage is that the patient is not made aware of the first-trimester results, which not only removes the option of chorionic villus sampling (CVS) for early diagnosis, but also affects management options for



the patient if the decision is made not to continue the pregnancy. Stepwise sequential testing allows for calculation of risk after the first trimester. If the screening is negative, the patient would then undergo the quadruple screen, with a new risk calculated. If the first-trimester screen is positive, then the patient can have CVS for further assessment if so desired. Even with the positive screen, the patient can choose to forego CVS, and the physician should obtain the quadruple screen with a new risk calculated. The patient can then undergo amniocentesis for further determination. The detection rate for the stepwise sequential testing is 95%.

Most recently, maternal plasma tests for cell-free fetal DNA have been clinically validated as screening tests in high-risk populations. Large studies have demonstrated a detection rate of greater than 98% for Down syndrome. Presently, maternal plasma fetal DNA sequencing is best used as a secondary test after positive prenatal screening to determine which patients would benefit from invasive testing. Palomaki's study indicates that a positive result on the maternal plasma fetal DNA test increases the risk from the primary screen 490-fold, whereas a negative result reduces the risk of the primary screen 72-fold. As such, virtually all patients with a positive screen will be carrying a Down syndrome fetus and should be offered confirmatory invasive testing. Conversely, virtually all patients with a negative screen will have an unaffected fetus and they can avoid an invasive procedure. This approach minimizes the risk of procedure-related pregnancy loss of an unaffected fetus. While studies continue to confirm high sensitivity and specificity of maternal plasma DNA sequencing in detecting trisomies 21, 18, and 13 as well as monosomy X, it is important to note that (1) it remains a screening test and all positive results should be confirmed by amniocentesis or CVS; (2) currently, its efficacy is limited to the detection of the aforementioned aneuploidies; (3) as such, for women who are at increased risk of a child with a prenatally diagnosable disorder with Mendelian pattern of inheritance, microdeletion syndrome, and some other conditions, amniocentesis or CVS would still be indicated; and (4) the test has only been evaluated in high-risk populations. Studies demonstrating comparable performance of the test among low-risk populations are needed before it can be used as a primary screening approach.

### Genetic Diseases Specific to Ancestry

Carrier screening for specific genetic diseases is often determined by the individual's ancestry. For example, certain autosomal-recessive diseases are more prevalent in the Ashkenazi Jewish population. These diseases include Tay-Sachs disease, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia, Niemann-Pick disease, mucopolysaccharidosis type IV, Bloom syndrome, and Gaucher disease. Many of these conditions are lethal in childhood and are associated with significant morbidity. As another example, some hematologic disorders are more prevalent in some populations than in others (eg, sickle cell disease in blacks,  $\alpha$ -thalassemia in Southeast Asians,  $\beta$ -thalassemia in patients from Mediterranean countries).

Carrier screening should be offered to couples either preconceptionally or in early pregnancy so that prenatal diagnostic testing is an option for the couple.

### Invasive Testing

Invasive testing should be offered to women of advanced maternal age or with positive first- or second-trimester screening for aneuploidy. It should also be offered to couples at risk for a specific genetic disease. Options for invasive testing include 1 of 2 ultrasound-guided procedures, CVS performed between 10 and 13<sup>7</sup>/<sub>7</sub> weeks' gestation, and amniocentesis done from 15 weeks' gestation onward. CVS is performed by inserting a needle into placental tissue and extracting villi. An amniocentesis is performed by inserting a needle into the amniotic sac and withdrawing amniotic fluid. In experienced hands, the procedure-related loss rate for CVS is approximately 0.5% to 1%. Traditionally the procedure-related loss rate was similar to that of amniocentesis, but newer literature has shown that the loss rate with amniocentesis may be as low as 1 per 1,000. Studies are underway to assess for loss rates with CVS as a direct comparison with amniocentesis.

In addition, the American College of Obstetricians and Gynecologists has published new guidelines for women who have a prenatal ultrasound in which a major fetal anomaly is found. Regardless of maternal age, chromosomal microarray analysis should be performed in addition to routine karyotype analysis.

## SECOND- AND THIRD-TRIMESTER ULTRASOUND

Ultrasound has been the best method for imaging the fetus since the 1950s. With the advent of real-time sonography, higher-frequency transducers, and Doppler sonography, the ability to provide accurate prenatal diagnoses has greatly improved. Most pregnant women in the United States will undergo an ultrasound examination, although the role of routine ultrasound has been a focus of controversy. The American College of Obstetricians and Gynecologists has specific recommendations for the role of ultrasound in each trimester of pregnancy. The focus of this chapter is on the diagnosis and evaluation of major fetal anomalies.

### Central Nervous System

#### Neural Tube Defects

Neural tube defects (NTDs) are congenital structural abnormalities of the brain and vertebral column. These abnormalities can occur as an isolated event, with other malformations, or as part of a genetic syndrome. With an incidence of 1 to 2 per 1,000 live births (LBs) worldwide, NTDs are the second most common major congenital anomaly.

NTD prevalence rates vary geographically and by ethnicity. Isolated NTD is multifactorial in origin; there are contributing genetic and environmental factors that increase risk. Periconceptional dietary supplementation with folic acid significantly reduces the risk of NTDs. In the United States, where folic acid fortification of flour and grain-based cereals is common and women are encouraged to take folate-containing vitamins before becoming pregnant, the prevalence



rate for all NTDs (anencephaly, spina bifida and encephalocele) is 6.38 per 10,000 LBs, adjusted for maternal race and ethnicity. The spina bifida rate is 3.50 per 10,000 LBs (1 in 2,858 births). Hispanic women have the highest risk of having a child with spina bifida in comparison with non-Hispanic black and non-Hispanic white women. Recent data reveal that a declining number of women, particularly minority women, are consuming folic acid supplements before pregnancy.

Embryologically, the neural plate appears during the third week of gestation and gives rise to neural folds that fuse in the midline to form the neural tube. Closure of the neural tube is usually complete by the end of the sixth gestational week. Failure of this process leads to the defect. The cause is a result of genetic, environmental, and dietary influences. Folic acid plays an important role in the proper formation of the neural tube, which is mediated via the enzyme methylenetetrahydrofolate reductase (MTHFR). Deficiency in folic acid has been implicated in part of the mechanism for the formation of NTDs. Such is the case not only in terms of dietary deficiency, but also as a result of the mechanism of teratogenic effects of certain medications, such as antiepileptic drugs. Supplementation with folic acid has been shown to decrease the incidence and recurrence.

NTDs can be separated into 2 categories: cranial and spinal. Cranial defects include anencephaly, exencephaly, encephalocele, and iniencephaly. These defects occur in the skull, scalp, and brain tissue and result in death. Defects in the caudal region are more commonly known as spina bifida. These defects are malformations of the spinal cord, meninges, and vertebrae and are compatible with life. Caudal-region defects that are confined to the spine are further differentiated as open (neural tissue exposed), usually involving the spine or cranium, or closed (neural tissue not exposed).

Maternal serum screening is routinely offered to all pregnant women. AFP is the maternal serum marker that is used as a screening tool for open NTDs. AFP is measured at 15 to 20 weeks and is expressed as multiples of the median (MOM). A value above 2.0 to 2.5 MOM is considered abnormal and necessitates further evaluation, such as a repeat test, ultrasound examination, and possibly amniocentesis. Other factors can affect interpretation, such as knowledge of proper gestational age, maternal weight, multiple gestations, and the presence of other anomalies.

Ultrasound is effective for detecting NTDs as well. In experienced hands, ultrasound can be 97% sensitive and 100% specific, negating the need for maternal serum AFP. NTDs can be identified on ultrasound by the presence of irregularities of the bony spine or a bulging of the contour of the fetal back. The posterior fossa of the fetal brain may also provide clues that an NTD is present. The *banana sign* refers to the shape the cerebellum makes as a result of the herniation of the spinal tissue and is one such clue. Spinal herniation also produces the *lemon sign*, which refers to flattening of the frontal contour of the fetal calvarium. Ventriculomegaly may also be seen. At the time of diagnosis, an amniocentesis should be offered. This test can provide information regarding the karyotype,

particularly if other anomalies are detected; it also serves as a confirmatory test. AFP levels will be increased in amniotic fluid, which can also be tested for acetylcholinesterase (AChE). AChE is an enzyme found in blood cells, muscle tissue, and nerve tissue. An increase in AChE levels suggests an open NTD with 96% accuracy.

Prognosis depends on the type and location of the lesion. As stated previously, lesions involving the brain and skull are lethal; those involving the spine are usually compatible with life. An important point to note is the existence of indications regarding ambulatory, urologic, and bowel function, which is important when counseling parents regarding further interventions or when counseling parents considering termination of the pregnancy. In utero intervention is available for this anomaly (see Chapter 83, Fetal Interventions). The recently published multicenter, randomized MOMS trial (Management of Meningomyelocele Study) demonstrated that fetal intervention may alter the natural history of meningocele. Eligible fetuses randomized to undergo fetal repair between 19 and 26 weeks' gestation experienced lower mortality and morbidity in comparison with fetuses who underwent standard postnatal repair. However, risks to the mother and fetus undergoing prenatal repair were significant. Longitudinal follow-up of these 2 groups of children is ongoing and will provide additional insights into the risks and benefits of prenatal intervention.

### Ventriculomegaly and Hydrocephalus

Ventriculomegaly is defined as an increased diameter of the fetal lateral ventricles of more than 10 mm. Hydrocephalus is defined as a pathologic increase in intracranial cerebrospinal fluid (CSF). These terms are often used interchangeably in prenatal diagnosis, though technically hydrocephalus refers to intracranial pressure, which cannot be measured in the prenatal setting.

CSF is produced within the ventricular system, with one-half from the choroid plexus and the other half from the cerebral capillaries. Circulation is unidirectional and moves from the lateral ventricles through the foramen of Monroe to the third ventricle. It then travels to the fourth ventricle after passing through the aqueduct of Sylvius and ends up in the spinal subarachnoid space or basal cisterns. It is then reabsorbed in the venous sinuses. In the event of either production of CSF that exceeds absorption or mechanical obstruction of flow, ventriculomegaly can result. Ventriculomegaly can be an isolated finding, with an incidence of 1.4 to 20 per 1,000 LBs, or it may be an indicator of other underlying central nervous system (CNS) anomalies (eg, aqueductal stenosis) or associated extra-CNS anomalies (eg, NTDs).

The lateral ventricles can be readily assessed with ultrasound. The atria of the lateral ventricles measure, on average, 7 mm; the upper limit of normal is 10 mm. Once the diagnosis has been made, a thorough ultrasound examination should permit the operator to assess for any other associated anomalies. Amniocentesis for karyotyping should be offered, because a 4% to 14% association has been reported with aneuploidy,

which may also provide additional information if an NTD is suspected. Family history should be carefully reviewed because of the association with some X-linked conditions. Limitations of ultrasound evaluation exist, particularly for cortical malformations. For this reason, fetal magnetic resonance imaging (MRI) is recommended when a CNS anomaly is diagnosed, as it may provide additional information that alters diagnosis and management in up to 40% of cases.

Prognosis depends on the presence of other anomalies. In patients continuing the pregnancy, surveillance of the ventriculomegaly is performed with serial ultrasounds. Although in utero treatment has been attempted, no improvement in outcome has resulted. Most fetuses will have normal head circumference; therefore, cesarean section should be considered only for routine obstetric reasons.

### **Choroid Plexus Cysts**

Choroid plexus cysts (CPCs) are thought to be neuroepithelial folds that fill with CSF and cellular debris. A CPC is a common ultrasound finding in healthy fetuses in the second trimester and has an incidence of 0.2% to 3.6%. The choroid plexus is a major source of CSF. Development begins at 6 to 7 weeks' gestation. They grow rapidly, filling 75% of the lateral ventricles by 9 weeks' gestation and reaching full size by 20 weeks' gestation.

The typical appearance on ultrasound is a sonolucent structure with well-defined borders. CPCs are generally small. When determining the actual risk for trisomy 18 with isolated CPCs, the physician must take into consideration maternal age and adjust it according to the maternal serum screen risk, if available. The risk does not depend on the age at diagnosis, but rather on the size or laterality of the cysts.

Once CPCs are noted on ultrasound, a detailed ultrasound should be performed to determine the presence of other anomalies, particularly those associated with trisomy 18 (ie, congenital heart defects, rocker-bottom feet). In up to 75% of fetuses with trisomy 18, additional abnormalities will be detected. Once the risk of aneuploidy is determined, amniocentesis can be offered. Many physicians suggest invasive testing only in the setting of other anomalies or if the mother is older than 35 years. In the setting of an isolated CPC, the prognosis is good, and most CPCs will resolve by the third trimester; those that do persist are usually benign. However, resolution does not change the small risk of aneuploidy.

### **Craniofacial Defects**

The orofacial cleft is the most common craniofacial malformation found in the newborn. Clefting can be of the lip or palate in isolation or together. Of all cases, 60% to 75% will involve the lip with or without the palate, and 25% to 40% will involve the palate alone. Up to 80% of cases are unilateral; left-side involvement is twice as common as right-side involvement. The overall incidence is population dependent. In the white population, incidence is 1 per 1,000 LBs; in the black population, incidence is 1 per 2,273 LBs. The incidence among Asians is higher, with reported rates of 1 per 500 LBs.

Craniofacial development involves migration, proliferation, and differentiation of facial mesenchyme

derived from neural crest cells. Many genes are involved in the regulation of this process. Normally, fusion of 3 mesodermal processes occurs, which is complete by 7 weeks' gestation. Failure of this process leads to clefting involving the lip, whether it is in isolation or involves the palate. Cleft palate in isolation is different; although fusion must also take place, the formation of a cleft palate also involves other processes, particularly proper movement of palatal shelves and the tongue.

The cause is genetic, as well as environmental. The genes involved, *Dlx* and *sonic hedgehog*, influence cell programming and cell differentiation. Environmental factors are the result of teratogenic effects. Medications, including antiepileptic drugs and steroids, have been implicated. Cigarette smoking, alcohol consumption, and folic acid deficiency have also been found to have an association.

Orofacial clefting can be detected on ultrasound, but only after 14 weeks, because this is the time that the fetal face assumes its normal form. Isolated cleft palate can be extremely difficult to diagnose prenatally. Once detected, a thorough ultrasound examination should be performed to assess for other anomalies, particularly of the CNS and cardiac systems. If another anomaly is detected, then chromosomal abnormalities can be seen in as many as 60% of these fetuses. Cleft lip or palate in isolation is not associated with aneuploidy. However, amniocentesis can be offered, and it may be helpful in finding other anomalies.

No prenatal interventions are available. Management of the pregnancy should otherwise be routine. Parents should meet with the craniofacial surgeons to discuss the steps involved in postnatal surgical management.

### **Neck**

#### **Cystic Hygroma**

Cystic hygroma is a lymphatic malformation or lymphangioma located at the level of the neck. Lymphatic fluid collects in the jugular system because of a blockage to flow. The overall prevalence in the first trimester is 1 per 100 LBs.

Cystic hygromas can be large, single or multiloculated, fluid-filled cavities. They are easily identifiable on ultrasound examination in the first trimester. Cystic hygromas tend to be largest in the nuchal region but can extend the full length of the fetus. Once a cystic hygroma is detected, a thorough ultrasound examination should be performed. The skull and spine should be examined to differentiate cystic hygroma from an NTD. The physician should thoroughly assess for other signs consistent with hydrops fetalis (skin edema, ascites, pericardial or pleural effusions). A 50% chance of aneuploidy exists when diagnosis is made in the first trimester. The most common aneuploidy is Down syndrome (trisomy 21), but it can also be seen with trisomy 13 and 18, as well as Turner syndrome (45,X). Therefore, invasive testing such as CVS or amniocentesis should be performed. A fetal echocardiogram should also be performed to determine the presence of any cardiac defects. No fetal intervention is available. Serial sonograms should be performed to assess for polyhydramnios resulting from

fetal inability to swallow, which can lead to uterine irritability and even preterm labor.

This finding is associated with significant mortality because of the high incidence of coexisting chromosomal abnormalities and other malformations. In the small group of fetuses in which this disorder is found in isolation with normal karyotype, the prognosis can be excellent. The major concern in this group is the ability to maintain the airway at the time of delivery, which may require an ex utero intrapartum treatment (EXIT) procedure, during which uteroplacental blood flow and gas exchange are maintained while the fetal malformation is surgically treated (see Chapter 83, Fetal Interventions).

### Goiter

Fetal goiter, also known as thyromegaly, is an enlargement of the fetal thyroid gland. It can occur in the maternal hyperthyroid, euthyroid, or, most commonly, hypothyroid state. When fetal goiter occurs in the hypothyroid state, it may result from transplacental passage of antithyroid medication, antithyroid antibodies, iodine deficiency, or congenital thyroid metabolic disorders. A fetal goiter that occurs in the hyperthyroid state is most commonly caused by transplacental passage of thyroid-stimulating antibodies, as in maternal Graves disease. Overall, this finding is rare. The fetal thyroid becomes fully responsive to thyroid-stimulating substances only in the second trimester; therefore, diagnosis before 20 weeks is unlikely.

A fetal goiter can be seen on ultrasound examination as a homogenous anterior neck mass. In severe cases, the neck is in a persistent state of hyperextension. Polyhydramnios may also occur as a result of fetal impairment of swallowing. Other abnormal ultrasound findings include fetal tachycardia, intrauterine growth restriction (IUGR), and hydrops. Signs of fetal hypothyroidism include cardiomegaly and fetal heart block. Even with these findings, accurately predicting fetal status may be difficult.

Given the difficulty in accurately determining fetal status with ultrasound alone, periumbilical cord blood sampling should be considered to evaluate thyroid hormone levels in fetal serum. The fetus can then be treated through administration of the proper medication to the mother. If the mother is euthyroid, then she may need supplementation to maintain her thyroid function. In addition, the fetus should be monitored with serial ultrasounds to assess amniotic fluid, signs of hydrops, and growth.

At delivery, the neonatal professionals skilled in neonatal resuscitation should be present and aware of the diagnosis and the therapy that has been instituted. The fetal airway must be maintained; thus an EXIT procedure including tracheostomy or bronchoscopy may be necessary. In such instances, a pediatric otorhinolaryngologist or pediatric surgeon will need to be present at the delivery to secure the newborn's airway.

## Thoracic Defects

### Bronchopulmonary Sequestration

Bronchopulmonary sequestration (BPS) is a rare congenital malformation of the lower respiratory tract. It

is made up of a cystic mass of nonfunctional pulmonary tissue. No communication occurs with the normal bronchopulmonary tree, and it derives its blood supply from anomalous vessels. BPS is thought to comprise 0.1% to 6% of all congenital pulmonary lesions (see Chapter 100, Respiratory Distress and Breathing Disorders of the Newborn).

BPS is believed to originate from a supernumerary lung bud that develops caudally to the normal lung buds and then migrates with the esophagus. Two forms have been described: intralobar and extralobar. Intralobar is more common (75%) than extralobar; it is located in the lobe and lacks its own visceral pleura. Extralobar is seen in the rest of the cases; it is located outside the normal lung and has its own visceral pleura. Extralobar lesions can be intrathoracic or subdiaphragmatic.

On ultrasound examination, BPS is a solid echogenic mass characterized by its location, vascular supply, and association with other abnormalities. Most lesions are located in the lower lobes, but they can be anywhere in the thorax or can be subdiaphragmatic. They have their own blood supply, which tends to arise from the thoracic aorta. Demonstration of the aberrant blood supply by Doppler sonography usually confirms the diagnosis. Other sonographic findings may be pleural effusion, mediastinal shift, and hydrops. Cardiac and vertebral anomalies may also be present. Amniocentesis should be offered if other anomalies are present. A fetal echocardiogram should be performed because of the disorder's association with cardiac anomalies.

The natural history of BPS tends to be variable. Some lesions regress; others can lead to hydrops, usually from vascular compression. The prognosis depends on the other associated findings. Cases complicated by hydrops can be fatal. Survival rates for fetuses with pleural effusion or polyhydramnios have been reported as 22% and 30%, respectively. Because of this, for fetuses that develop hydrops before 30 weeks' gestation, intervention can be considered via shunting. In cases where hydrops develops after 30 weeks' gestation, early delivery should be considered.

### Congenital Pulmonary Airway Malformation

Congenital pulmonary airway malformation (CPAM), formerly known as congenital cystic adenomatoid malformation (CCAM), is a rare lesion of the lower respiratory tract. It is composed of multicystic masses of pulmonary tissue, is unilobar in 80% to 95% of cases, and can affect any lobe of the lung. The incidence has been reported as being 1 per 10,000 to 1 per 35,000 LBs.

CPAM arises from an abnormality in branching and maturation of bronchiolar structures, which begins around 5 to 6 weeks' gestation. Three types of CPAMs have been identified and are thought to originate at different levels of the respiratory tract at different times during development. Type I is the most common and accounts for 50% of these lesions. Lesions are characterized by either single or multiple large cysts (3–10 cm). The cysts are lined by ciliated pseudostratified columnar epithelium; these lesions are thought to be distal in origin because they have well-differentiated



tissue. Type II is the second-most common type and accounts for 40% of CPAM cases. These lesions are made up of smaller cysts (<1 cm) lined with ciliated cuboidal or columnar epithelium. This type of malformation has a high association (60%) with other anomalies, including genitourinary, cardiac, and skeletal anomalies, because the disorder likely occurs earlier in development. Type III is the least common (10%). It is characterized by large homogeneous microcystic masses (<0.5 cm). A mixture of solid and cystic tissue is found from adenomatoid proliferation of the distal airways and spaces. Lesions tend to be large and lack differentiation. This insult is thought to occur between 26 and 28 days' gestation.

CPAMs have been divided into 5 different types based on histologic characteristics (type 0 through type IV). Thus to confirm the type, postnatal histology is needed. Adzick et al proposed a modification to Stocker's classification of CPAMs based on anatomy and sonographic appearance to assist in predicting prenatal outcome. Macrocytic CPAMs have single or multiple cysts larger than 5 mm in diameter and microcystic CPAMs have cysts that are smaller than 5 mm in diameter, giving them a more homogeneous appearance. Microcystic lesions increase the risk of development of hydrops. Because they can be quite large, microcystic lesions can also cause mediastinal shift, pulmonary hypoplasia, and polyhydramnios.

A detailed Doppler ultrasound examination should be performed to differentiate these lesions from others, such as congenital diaphragmatic hernia (CDH) or BPS, as well as to assess for other associated anomalies, particularly if a type II lesion is suspected. A fetal echocardiogram should be performed to rule out cardiac anomalies, particularly in the setting of hydrops. Fetal karyotyping should be offered in the setting of other anomalies or hydrops. Isolated CPAM has a less than 1% association with aneuploidy; however, karyotyping still should be performed if plans are in place for in utero intervention, because an abnormal result may affect the decision to do so. Serial sonography should be performed to look for signs of hydrops. These lesions can occasionally regress.

Prognosis for these lesions depends on the type of CPAM present. Fetuses with type I tend to do well; fetuses with type III disorder have a poorer prognosis. The prognosis for type II depends on the severity of other lesions, if present. In utero treatment with decompression and possible shunt placement may be reasonable when hydrops is present before 32 weeks' gestation. An EXIT procedure should be considered at the time of delivery if there is concern for the airway.

### **Congenital Diaphragmatic Hernia**

Congenital diaphragmatic hernia occurs when a defect develops in the diaphragm that allows the abdominal viscera to herniate into the fetal thorax. Most CDHs are unilateral (98%), with the left side being the most common. The incidence is 1 per 2,200 LBs.

The defect occurs either as failure of closure of the pleuroperitoneal folds or as a defect in migration of muscle fibers during the development of the diaphragm at 9 to 10 weeks' gestation. When the defect is present, it allows herniation to occur. Because this

defect happens so early in lung development, the number of bronchial branches becomes reduced, leading to pulmonary hypoplasia. These changes are more pronounced on the side of the herniation, but the contralateral lung can be affected by compression of a shifted mediastinum.

On ultrasound examination, one of the key clues to diagnosing CDH is the location of the stomach bubble. When viewing the fetal chest, the stomach bubble is seen in the same plane as the heart in cases of CDH. Peristalsis of the bowel in the thorax may also be noted. Determination of potential liver herniation is important for prognosis and the possibility for intervention. MRI may be suitable for this purpose. Fifty percent of CDHs are associated with other anomalies, including cardiac, genitourinary, and gastrointestinal anomalies. A fetal echocardiogram should be performed to assess for cardiac defects. Chromosomal abnormalities can be seen in 10% to 20% of cases; therefore, amniocentesis should be offered, particularly if in utero intervention is being considered.

Prognosis depends on such factors as karyotype, presence of liver herniation, associated anomalies, and ratio of lung area to head circumference. This ratio estimates the contralateral lung size and mediastinal shift at the level of the atria. Originally thought to predict survival, this ratio is more useful in assessing morbidity than mortality. Up to 30% of these fetuses can be stillborn; therefore, close surveillance in the third trimester is warranted. Serial ultrasounds may also be performed to assess growth and amniotic fluid volume. In utero intervention may play a role (see Chapter 83, Fetal Interventions). Delivery should be at an appropriate tertiary care center.

### **Cardiovascular Defects**

Cardiac anomalies are the most common congenital lesion, with an incidence of 5 to 8 per 1,000 LBs. Thus, review of cardiac anatomy is an integral part of the basic fetal anatomic survey and is ideally preformed between 18 and 22 weeks' gestation. Most cardiac lesions are detected in low-risk populations; however, several risk factors call for more detailed evaluation, such as a fetal echocardiogram. These risk factors can be divided into 3 general categories: familial, maternal, and fetal. Familial risk factors include parental congenital heart disease, a previous affected child, or a family history of a syndrome associated with heart disease (eg, Noonan syndrome). Maternal risks include diabetes, lupus, teratogen exposure (eg, lithium), and infection (eg, rubella). Fetal risks include detection of another anomaly, suspicion of aneuploidy, arrhythmia, and evidence of hydrops. A strong association exists between cardiac anomalies and aneuploidy; therefore, amniocentesis should be offered if a cardiac anomaly is discovered. Patients should meet with pediatric cardiologists or a pediatric cardiothoracic surgeon (or both) to discuss prognosis and postnatal treatment, including surgery. The following section will provide a brief review of some of the most common cardiac anomalies.

#### **Atrioventricular Canal Defect**

Atrioventricular (AV) canal defects consist of atrial septal defect (ASD) and ventricular septal defect (VSD)



and a single common AV valve. They are also known as endocardial cushion defects. AV canal defects account for 1% to 5% of all cases of congenital heart disease.

On ultrasound examination, a large defect is noted when looking at the 4-chamber view of the heart, representing the defects in the inferior portion of the atrial septum and the superior portion of the ventricular septum. The normal conduction of the heart is affected by the large defect, often leading to bradyarrhythmia. Additional cardiac malformations may be present, including tetralogy of Fallot, coarctation, and pulmonary stenosis. The prognosis depends on the presence of other associated anomalies, including hydrops and aneuploidy.

### **Truncus Arteriosus**

Truncus arteriosus occurs when a single, large ventricular outflow tract arises from both the left and right ventricles. It is rare, accounting for only 1.5% of heart defects, with an incidence estimated at 3 per 100,000 LBs. Four subtypes were originally described. Type I has a single pulmonary trunk that divides into right and left pulmonary arteries. Type II has 2 pulmonary arteries arising from the posterior of the truncus. Type III has 2 pulmonary arteries from the lateral aspects of the truncus. In type IV, the pulmonary arteries are absent, but collaterals arise from the descending aorta.

When visualizing the outflow tracts using ultrasound, a single, large ventricular outflow tract is seen. The right-ventricular outflow tract is not seen. Abnormalities of the aortic arch may also be seen, as well as the presence of hydrops.

### **Hypoplastic Left and Right Ventricles**

Hypoplastic left ventricle, also known as hypoplastic left heart syndrome, occurs when hypoplasia of the left ventricle, atresia of the aortic and mitral valves, and hypoplasia of the aortic arch are present. Each of these components can occur at varying degrees. Hypoplastic left heart syndrome accounts for 9% of all congenital heart defects, with an incidence of 1 per 10,000 LBs.

Hypoplastic right heart syndrome, also known as pulmonary atresia with intact ventricular septum, occurs when hypoplasia of the right ventricle, pulmonary atresia, and occasionally tricuspid atresia are present. This lesion accounts for less than 3% of congenital heart defects, with an incidence of 1 per 144,000 LBs.

Both lesions are usually easy to detect on ultrasound examination. When looking at the 4-chamber view of the heart, an inequality of the ventricles can be seen. The affected side will appear as a small remnant and will seem hypocontractile. Both lesions may not be as clear on second-trimester ultrasound but will evolve over time. Careful anatomic survey should be performed to assess for other cardiac and extracardiac anomalies.

### **Tetralogy of Fallot**

Tetralogy of Fallot is a malformation that consists of VSD, right-ventricular outflow obstruction, the aorta

overriding the ventricular septum, and right-ventricular hypertrophy. Tetralogy of Fallot is thought to occur as a result of misalignment during embryogenesis. It accounts for 5% to 10% of congenital heart defects and has an incidence of 2 per 10,000 LBs.

On ultrasound examination, an overriding aorta is the key feature for diagnosis. Color Doppler sonography may be helpful in detecting the VSD. Detailed sonography should be performed to assess for extracardiac malformations.

### **Transposition of the Great Vessels**

In transposition of the great vessels, the aorta connects with the right ventricle, and the pulmonary artery connects with the left ventricle. Two types have been identified: complete and corrected. Complete transposition of the great vessels, also known as D-transposition, is the more common of the 2 forms. In this form, the aorta comes off the right ventricle, and the pulmonary artery comes off the left ventricle. ASD and VSD defects are also commonly seen. It usually causes no hemodynamic compromise in utero. The corrected type of transposition of the great vessels, also known as L-transposition, refers to a connection of the right atrium to the morphologic left ventricle that connects to the pulmonary artery, whereas the left atrium connects to the morphologic right ventricle and then to the aorta. It is an abnormality in conotruncal development at 4 to 5 weeks' gestation and accounts for 4% to 6% of congenital heart defects.

The diagnosis is made on ultrasound examination when the aorta is identified as originating from the right ventricle. Demonstrating the vessels supplying the head and neck helps identify the aorta. The normal crossing over of the pulmonary artery and aorta is not seen. The outflow tracts seem to run in parallel, which is of importance, particularly in L-transposition, which can be difficult to diagnose. A detailed ultrasound examination should be performed to assess for other cardiac anomalies, such as pulmonic stenosis and coarctation, as well as extracardiac anomalies.

### **Atrial and Ventricular Septal Defects**

ASD is a malformation in the development of the interatrial septum. Three different types are possible, depending on location. An inlet ASD is located near the entrance of the superior vena cava. A primum or outlet ASD is located in the body of the septum. Secundum ASDs occur because of an absence of the foramen ovale flap. These lesions are usually of no concern in utero because of normal right-to-left shunting. ASDs comprise 7.5% of all congenital heart defects.

A VSD is a malformation in the development of the interventricular septum. It is the most common congenital heart defect. VSDs can occur in the muscular or membranous portions of the septum. Muscular VSDs are bordered on all sides by muscle and may be further categorized as inlet, trabecular, or infundibular. Subvalvular VSDs, which are directly related to the AV and semilunar valves, may also occur.

Prenatal diagnosis of ASD is difficult because of the normal presence of the foramen ovale. VSDs can also be problematic, particularly if the lesion is small. Color Doppler sonography may be useful in demonstrating

flow across the septum. A detailed ultrasound examination should be performed to assess cardiac anatomy further. Serial ultrasounds should be performed to assess growth and to monitor for signs of fetal hydrops.

### **Arrhythmias**

The normal fetal heart rate ranges from 120 to 160 beats per minute (bpm). In bradycardia, the rate is sustained below 120 bpm; in tachycardia, the sustained rate exceeds 160 bpm. Bradyarrhythmias are caused by congenital heart block and are most commonly associated with structural anomalies such as transposition and AV canal defects. Bradyarrhythmia can also be found in a structurally normal heart when transplacental passage of certain maternal antibodies occurs in mothers with connective tissue disorders (ie, anti-Ro and anti-La antibodies in patients with systemic lupus erythematosus). First-, second-, or third-degree heart block can exist, with the last of these 3 blocks being the most common. Echocardiography should be performed to assess for cardiac anomalies. Serial ultrasounds should be performed to assess fetal growth. Bradycardia is generally well tolerated, but can lead to hydrops in up to 25% of fetuses. If evidence exists of fetal compromise after 30 weeks' gestation, then delivery should be considered. Medical treatments have been proposed and are divided into those that suppress maternal immune response, such as corticosteroids, and those that increase fetal ventricular rate, such as  $\beta$ -mimetics.

Tachyarrhythmias are irregular cardiac rhythms caused by extrasystoles, supraventricular tachycardia, atrial flutter, or fibrillation. Extrasystoles may originate in the atria, AV node, or ventricles, and usually resolve spontaneously. The most common are supraventricular tachycardias, many of which are re-entry dysrhythmias. Atrial flutter is from a single re-entry circuit within the atria with varying degrees of block at the AV node. Atrial fibrillation is from multiple small intraatrial re-entry circuits, and organized atrial contraction is absent. These dysrhythmias have the potential for serious sequelae leading to hydrops. Complete cardiac survey should be performed to assess for cardiac anomalies. In utero treatment by administration of antiarrhythmics to the mother can convert the aberrant rhythm. Serial sonograms should be performed to assess fetal growth and to assess for signs of hydrops.

### **Abdominal Wall Defects**

#### **Gastroschisis**

Gastroschisis is a full-thickness defect of the abdominal wall that leads to evisceration of the abdominal contents. The defect is thought to be the result of vascular compromise of either the umbilical vein or the omphalomesenteric artery. It typically arises to the right of the umbilicus. The incidence is reported as 1 per 4,000 LBs.

Increased levels of AFP in maternal serum will be present with gastroschisis and other wall defects. Midgut herniation is normal up until 11 weeks' gestation. Herniation noted on ultrasound examination beyond this time is abnormal. Protruding bowel can be easily seen. Color Doppler sonography can be

used to demonstrate the insertion of the umbilical cord medial to the defect. A thorough ultrasound evaluation should be performed to assess for other anomalies. Gastroschisis is not associated with chromosomal abnormalities. Amniocentesis should be offered if other anomalies are detected. Serial sonograms are performed to monitor growth and bowel integrity.

The prognosis with gastroschisis is generally good. No fetal intervention is available. Mode of delivery is for obstetric indications. Parents should meet with a pediatric surgeon to discuss postnatal surgical treatment.

For more information, see Chapter 108, Surgical Emergencies of the Chest and Abdomen in the Newborn.

#### **Omphalocele**

An omphalocele is a defect of the medial abdominal wall characterized by the lack of abdominal muscles, fascia, and skin. Protrusion of the intra-abdominal contents occurs with a covering membrane that consists of peritoneum and amnion. In contrast to gastroschisis, the umbilical cord inserts into the membrane at its apex. Omphaloceles are categorized as either liver-containing or non-liver-containing.

During development, the embryo undergoes a series of cranial, caudal, and lateral folding events. When failure of lateral folding occurs at the third to fourth week of gestation, omphaloceles can occur. The incidence is 1 per 4,000 LBs. Maternal serum screening can be helpful making this diagnosis.

On ultrasound examination, bowel herniation can be noted. The membranous covering confirms the diagnosis of omphalocele. The presence or absence of liver herniation should be noted, because this finding is important for determining prognosis. Color Doppler sonography can demonstrate the umbilical cord entering the sac. Omphalocele is strongly associated with other anomalies and with chromosomal abnormalities. Therefore, a thorough ultrasound evaluation should be performed, as should amniocentesis. Serial sonograms should be performed to assess fetal growth.

The prognosis depends on finding other congenital anomalies and on chromosome evaluation. Mortality may be as high as 20% to 30%. Large lesions have limited potential for closure. Patients should meet with pediatric surgeons to discuss postnatal surgical treatment.

### **Gastrointestinal Defects**

#### **Duodenal Atresia**

Duodenal atresia is characterized by complete obliteration of the duodenal lumen. It is the most common type of congenital small-bowel atresia. The incidence is 1 per 10,000 LBs.

At 5 weeks' gestation, the lumen of the duodenum is obliterated by proliferating epithelium. Normally, recanalization occurs, and the lumen is restored by 11 weeks. Failure of the recanalization process results in duodenal atresia or stenosis. Three types are described. Type I is membranous mucosal atresia with an intact muscular wall. The proximal duodenum is

ballooned out, and the distal duodenum is narrowed. Type II duodenal atresia is rare. It has a short fibrous cord connecting the 2 ends of the duodenum. Type III has a complete separation between the duodenal ends and can be associated with gallbladder anomalies.

Most cases can be diagnosed by ultrasound but generally not until the third trimester. The duodenum is persistently dilated and the stomach is filled with fluid, leading to the classic *double-bubble* appearance. Significant polyhydramnios is usually present because of the fetal inability to swallow, which can lead to uterine irritability and preterm labor and may often be the reason why a mother presents for an ultrasound evaluation. Thirty percent of fetuses with duodenal atresia will have Down syndrome; therefore, amniocentesis should be performed. A thorough cardiac evaluation should be conducted, because an association exists with heart malformations.

The prognosis is related to associated malformations and karyotype. The risk of preterm labor and its associated morbidity and mortality is increased. Surgical repair is required early in life and in some cases can be performed with a minimally invasive approach.

### **Echogenic Bowel**

Echogenic bowel is a sonographic finding in which the bowel seems to have the same echogenicity as the surrounding bone. The incidence ranges from 0.4% to 1% in the second trimester. Echogenic bowel can be a normal variant. However, it has been associated with chromosomal abnormalities, fetal cystic fibrosis, cytomegalovirus infection, IUGR, intra-amniotic bleeding, and intestinal abnormalities. Once echogenic bowel is detected, an amniocentesis should be considered to enable testing for karyotype, cystic fibrosis, and infection studies. No fetal intervention is available. Prognosis depends on the cause.

## **Genitourinary Defects**

### **Ambiguous Genitalia**

Sexual differentiation does not occur until 6 to 7 weeks' gestation, even though genotype is determined at the time of conception. Before 6 to 7 weeks' gestation, the gonads are undifferentiated. The presence of particular hormones and the expression of specific genes aid in the differentiation process. Masculinization is induced by the activity of dihydrotestosterone, which is formed from testosterone. Absence of or insensitivity to this hormone leads to the formation of female genitalia. Disruption in this pathway can lead to ambiguous genitalia. The overall incidence is 1 per 5,000 LBs.

Abnormalities of sex differentiation are chromosomal, gonadal, or phenotypical. Three categories are described. The true hermaphrodite has both ovarian and testicular tissue present. Female pseudohermaphrodites are overmasculinized females. Male pseudohermaphrodites are undermasculinized males. Many methods have been described to determine sex on ultrasound examination. (See Chapter 243, Disorders of Sex Development.)

Amniocentesis should be performed to determine genotype. Testing for inborn errors of metabolism should be performed. A complete maternal history

and physical examination should be performed to assess for signs of androgen excess, hormone ingestion, or family history of similar findings.

### **Hydronephrosis**

Hydronephrosis is dilatation of the renal pelvises and calyces. It is among the most commonly reported ultrasound findings and comprises 75% of diagnosed renal abnormalities. The severity can range from mild to severe and depends on gestational age. Hydronephrosis may be physiologic or pathologic. Distinguishing the 2 entities requires thorough ultrasound evaluation and close follow-up. The incidence of mild hydronephrosis is reported as 1 per 100 LBs; for severe hydronephrosis, as in ureteropelvic junction obstruction, the incidence is 1 per 100,000 LBs. The finding may be unilateral or bilateral.

When visualizing the kidneys on ultrasound evaluation, the renal pelvises are dilated when measured. The absolute measurement depends on gestational age, because normal dilatation exists with advancing gestational age. A thorough ultrasound evaluation should be performed to assess for any other abnormalities. Amniocentesis should be offered because of the increased risk of aneuploidy in severe cases. In unilateral cases, fetal intervention is not recommended. If severe bilateral hydronephrosis is present and evidence exists of dysplastic kidney or renal agenesis, and if the fetus is older than 30 weeks' gestation, then delivery should be considered after administering corticosteroid therapy to promote fetal lung maturation. In cases of bladder outlet obstruction, intervention by shunting of the bladder can be considered after sampling fetal urine to assess kidney function. Parents should meet with a pediatric urologist for prenatal consultation.

### **Ureterocele**

Ureterocele is a cystic dilation of the intravesicular portion of the ureter—that is, the distal end at the junction of the bladder. Ureteroceles can be classified as simple or ectopic. Simple ureteroceles are at the normal location of the ureteral orifice in the trigone of the bladder. These are more commonly found in adults and may be associated with a varying degree of obstruction. In ectopic ureteroceles, the ureteral orifice is in an ectopic position, usually distal to the trigone. It can be associated with a duplex collecting system (75%). Ectopic ureteroceles tend to be unilateral, but are bilateral in 10% to 20% of cases. The incidence is 1 per 5,000 LBs.

Unilateral hydronephrosis is often noted first on ultrasound examination, with the key feature being a dilated upper pole of the kidney with a normal lower pole. A crescent-shaped line may be seen at the base of the bladder, demonstrating the prolapsing ureterocele. The ureterocele itself is of no consequence unless it is causing bladder outlet obstruction. If obstruction is noted, then bladder decompression via needle aspiration may be indicated. Parents should meet with a pediatric urologist.

### **Multicystic Dysplastic Kidney**

Multicystic dysplastic kidney is an extreme form of dysplasia of the kidney characterized by large dilatations



of the collecting tubules with an atretic ureter. The kidney essentially consists of a group of cysts containing some connective tissue, with no real renal tissue present. Up to 80% of cases are unilateral. The incidence is reported as between 1 per 1,000 to 1 per 4,500 LBs. Multicystic dysplastic kidney is thought to arise from an early error in the development of the mesonephric blastema leading to an early obstructive uropathy.

On ultrasound examination, a cystic paraspinal flank mass is noted. Multiple cysts of varied size exist at the periphery of the kidney. They start out small but will usually get bigger over time. The overall kidney size may be either large or small. If unilateral, hypertrophy of the contralateral kidney may then be noted as a compensatory mechanism. A thorough ultrasound examination should be performed to assess for associated genitourinary and nongenitourinary anomalies. Amniocentesis should be performed because of this disorder's association with chromosomal abnormalities.

The prognosis depends on the presence of other anomalies, particularly in cases of unilateral dysplasia. If no other anomalies are present and the contralateral kidney is normal, then the prognosis is excellent. Bilateral severe cysts result in fetal death. If partial dysplastic involvement of both kidneys is found, then renal impairment may eventually occur.

### Renal Agenesis

Renal agenesis is the congenital absence of either one or both kidneys. At 4 to 6 weeks' gestation, the metanephros fails to develop, which leads to the complete absence of the kidney. The incidence of unilateral agenesis is 1 per 1,000 LBs, and of bilateral agenesis is 12 per 100,000 LBs.

The diagnosis of bilateral renal agenesis is made when severe oligohydramnios or oligohydramnios is noted after 14 weeks' gestation, along with the inability to visualize the fetal bladder or kidneys. Visualization can be difficult in the absence of amniotic fluid. Amnioinfusion may be considered, in which sterile saline is infused into the uterus using the same method as in amniocentesis. This procedure is helpful to rule out ruptured membranes, and it aids in the anatomic survey.

No fetal intervention is available. Up to 40% of fetuses with bilateral renal agenesis are stillborn; the remaining fetuses die shortly after birth from respiratory or renal complications. Unilateral agenesis may be asymptomatic and consistent with life. Unilateral renal agenesis may have other associated birth defects, most commonly involving the genitourinary system. Girls should eventually undergo pelvic ultrasound to assess for müllerian anomalies.

### Umbilical Cord

The umbilical cord normally has 2 arteries and 1 vein. In the case of a single umbilical artery, also known as a 2-vessel cord, one of the arteries is congenitally absent. Its incidence is 0.5% to 0.9%.

The umbilical arteries develop from the allantois, which is a diverticulum of the yolk sac. Single umbilical artery occurs as a result of either primary agenesis of one of the umbilical arteries, secondary atresia of one of the arteries, or persistence of the common allantoic or umbilical artery.

A detailed ultrasound evaluation is necessary to assess for other anomalies, and if they are present, then amniocentesis should be performed, because the risk of aneuploidy is increased. If the workup is normal, then serial sonograms should be performed for the remainder of the pregnancy because this disorder is associated with IUGR.

### Skeletal Defects

#### Achondroplasia

Achondroplasia is a form of short-limbed dwarfism and is the most common form of nonlethal skeletal dysplasia. It is characterized by rhizomelic limb shortening with macrocephaly. Endochondral ossification is decreased. Bones that are initially formed from cartilage, such as long bones, are affected. The incidence is 1 per 26,000 LBs.

On ultrasound examination, all the long bones are noted to be shortened (less than the third percentile), particularly the femur. This finding is first notable at 21 to 27 weeks' gestation. The overall shape of the bones is normal. Additional findings include a large head (macrocrania), an abnormal profile caused by frontal bossing, and a protruding abdomen. Development of mild polyhydramnios may also occur in the third trimester. Once achondroplasia is detected, echocardiography and karyotyping should be performed to rule out other conditions. Finding the *FGFR3* mutation on amniocytes can confirm the diagnosis. A fetus with macrocrania near term may require delivery by cesarean; therefore, serial sonograms should also be performed.

Intelligence and life span are normal. Neurologic sequelae remain a risk because of spinal cord compression. Homozygosity for achondroplasia is lethal, resulting in stillbirth or neonatal death from respiratory failure.

#### Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is a heterogeneous group of brittle bone disorders and is characterized by a tendency to develop spontaneous fractures, both before and after birth. Most individuals are heterozygotes, and most types of OI are caused by type I collagen abnormalities. Osteogenesis imperfecta is considered a heritable condition because it results from genetic changes. Most people with OI (>90%) have a mutation in one of the two copies of the genes (*COL1A1* or *COL1A2*) that carry instructions for making type I collagen—the protein “scaffolding” of bone and other connective tissues. The remaining 10% of cases of OI result from a spontaneous dominant mutation.

Our understanding of this disease from a genetic level has not only allowed for more accurate diagnosis of the disease using collagen molecular testing, but also has allowed us to understand the manifestations of the disease, even as early as the prenatal period. Features that can be seen on prenatal ultrasonography, usually between 14 and 18 weeks' gestation (for types II and III OI; type I cannot be easily diagnosed), include increased NT; reduced echogenicity of bones; multiple fractures of the long bones, ribs, and skull at various stages of healing; and bowing of the long bones (with or without shortening). Once there is a



concern for OI via prenatal ultrasonography, the diagnosis can be made from either CVS demonstrating abnormal type I collagen via electrophoresis, or amniocentesis, which obtains fetal DNA for molecular analysis. Because most mutations will involve COLA1/COLA2 genes, testing is centered around the identification of these genes followed by examination of the other aforementioned genes.

Type I OI, the most common and mildest form of the disease, is nondeforming and results in patients attaining close to a normal height. However, vertebral fractures are common and can lead to mild scoliosis. Patients typically have blue sclera and, infrequently, dentinogenesis imperfecta. Fractures are rarely observed at birth, but begin with ambulation and subsequent falls during juvenile development, then commonly decrease following puberty.

Type II OI is the most severe form, resulting in death in the perinatal period. Infants typically die within weeks from pulmonary insufficiency or cardiac complications. These individuals exhibit multiple intrauterine rib and long bone fractures, and severe skeletal deformities, which eventually result in respiratory failure. Bone histology reveals a marked decrease in both cortical bone thickness and the amount of trabecular bone.

Type III OI is the most severe nonlethal form of the disease. It is characterized by severe progressive skeletal deformities, often starting from birth. Fractures may be present in utero and are very common during the growing period. The incidence of fractures remains high even in adult life. Individuals have severely short stature and, because of their deformities and bone fragility, are often confined to a wheelchair for life. Scoliosis can lead to respiratory problems, which have been identified as a leading cause of death in this patient group. Dentinogenesis imperfecta is often present.

Type IV OI is the most clinically diverse group. The phenotype can vary from severe to mild, with the more severely affected patients presenting with fractures at birth, exhibiting moderate skeletal deformities, and attaining a relatively short stature.

Type V OI is moderately deforming, and patients exhibit moderate to severe bone fragility. Blue sclera and dentinogenesis imperfecta are not present. There are 3 distinctive features: the frequent development of hypertrophic calluses at fracture sites; the calcification of the interosseous membranes between the bones of the forearm; and the presence of a radio-opaque metaphyseal band immediately adjacent to the growth plates on radiograph. Upon histologic examination, the bone organization has an irregular mesh-like appearance, clearly distinct from the normal lamellar pattern. The calcified interosseous membrane often severely limits the pronation/supination of the hand and may lead to secondary dislocation of the radial head. Importantly, the hyperplastic callus that may develop after fractures or surgical interventions may mimic osteosarcoma. Magnetic resonance imaging and computed tomography can be useful to make the distinction in unclear cases. Patients with Type V OI seem to represent 4% to 5% of the OI population seen in hospitals.

Type VI OI patients also present with moderate to severe skeletal deformities, and do not have blue

sclera or dentinogenesis imperfecta. Distinctive histologic features are the fishscale-like appearance of the bone lamellae and the presence of excessive osteoid accumulation on bone-forming surfaces. The latter suggests a mineralization defect reminiscent of osteomalacia, but there is no abnormality in mineral homeostasis, and growth plate mineralization proceeds normally. Inheritance is autosomal recessive. Type VI OI may be present in approximately 4% of moderately to severely affected OI patients.

Type VII OI patients also have moderate to severe skeletal deformities and bone fragility, and lack blue sclera and dentinogenesis imperfecta. Their distinctive clinical feature is a rhizomelic shortening of the humerus and femur. Coxa vara may be present even in infancy. To date, this disorder has only been observed in a community of Native Americans in northern Quebec, where it exhibits autosomal-recessive inheritance. The disease has been assigned to chromosome 3p22-24.17, co-localizing with the gene encoding CRTAP, a cartilage-associated protein, whose expression is 90% reduced in homozygote patients.

The family history will provide clues about diagnosis. If OI is suspected prenatally and no known family history is found, then type II must be considered. Confirmation of diagnosis can be made by biochemical and histologic testing. For the nonlethal forms, cesarean delivery may be of benefit to decrease the risk of fracture.

## Extremities

### Arthrogryposis

Arthrogryposis is a term to describe a group of disorders that are characterized by congenital nonprogressive joint contractures at multiple sites. The muscles in the affected areas are replaced with fat and fibrous tissue. The incidence is 1 per 3,000 to 4,000 LBs.

Four major causes of contractures have been identified. The first is an abnormality in muscle tissue. The second is abnormal nerve function or innervation. The third is an abnormality of connective tissue. The fourth is a mechanical limitation of movement. Clinical features include joint rigidity, short and tight muscles, and joint dislocation.

On ultrasound examination, the diagnosis is made by observation of malposition of the fetal limbs. The bones are morphologically normal, but the range of motion is limited. A detailed ultrasound evaluation should be performed to rule out other associated anomalies and to further delineate the case into possible syndrome categories. Karyotyping should be offered to rule out chromosomal abnormalities.

### Congenital Talipes Equinovarus

Congenital talipes equinovarus (CTEV), or club foot, is a term used to describe an abnormal positioning of the foot and is characterized by equinus and inversion of the foot with associated abnormalities in the musculature of the lower leg. The incidence is 1 per 1,000 LBs with a 2:1 male-to-female predominance; 50% of affected infants will have bilateral foot deformities.

The fetal lower limb begins movement between 9 and 11 weeks' gestation. If neurologic or muscular abnormalities are present, then limb movements may

be impaired, and joints will eventually become stiff and even contracted.

Talipes equinovarus deformities can be identified as early as 16 weeks' gestation by antenatal sonography. On ultrasound examination, the 2 long bones of the lower leg can be seen at the same time as the lateral aspect of the feet; the feet are in a fixed position—plantar flexed, internally rotated, and adducted. Most cases of clubfoot are isolated and idiopathic. If other anomalies are associated, then a syndrome may be present. Although offering amniocentesis is controversial when the finding is isolated, it should be performed if other anomalies are suspected. Parents should consult a pediatric orthopedic surgeon.

### Twins

It is important to determine the chorionicity of twin pregnancies. Monochorionic pregnancies carry a unique risk for twin-twin transfusion syndrome (TTTS) and its associated morbidity and mortality, and thus require greater surveillance throughout the pregnancy. Chorionicity can be determined on both first- and second-trimester ultrasound. This is accomplished via examination of the membrane at its insertion into the placenta. In a dichorionic gestation, the membrane is thick (>2 mm) and its insertion seems triangular and is described as the *lambda* or *twin peak* sign. In a monochorionic gestation, the membrane is thin and inserts flatly into the placenta and is described as the *T* sign.

### Intrauterine Growth Restriction

IUGR is a condition defined as birth weight below the tenth percentile at a given gestational age. The causes of IUGR are fetal, maternal, or placental. At the time of diagnosis, a detailed ultrasound examination is performed to determine whether any anomalies are present. Echocardiography is useful because cardiac anomalies are significantly associated with IUGR. Amniocentesis should be offered, particularly if IUGR is diagnosed early in gestation, because aneuploidy is also strongly associated with IUGR. Infection studies (TORCH [toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex]) can be requested at the time of amniocentesis. Amniotic fluid volume is also assessed as a determination of placental function. Doppler ultrasound may also be performed to ensure fetal well-being. Fetuses are assessed by serial sonograms, because the diagnosis of IUGR carries an increased risk of fetal death.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Prenatal Testing* (Web page), Medline Plus ([www.nlm.nih.gov/medlineplus/prenataltesting.html](http://www.nlm.nih.gov/medlineplus/prenataltesting.html))
- *Prenatal Screen Detects Fetal Abnormalities* (article), *Nature Education*, Vol 1, Issue 1, 2008

### Medical Decision Support

- *Spina Bifida and Anencephaly Before and After Folic Acid Mandate* (report), Centers for Disease Control and Prevention ([www.cdc.gov/mmwr/preview/mmwrhtml/mm5317a3.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5317a3.htm))

- *Help Me Understand Genetics* (handbook), Genetics Home Reference ([ghr.nlm.nih.gov/handbook.pdf](http://ghr.nlm.nih.gov/handbook.pdf))
- *NSGC Practice Guideline: Prenatal Screening and Diagnostic Testing Options for Chromosome Aneuploidy* (article), *Journal of Genetic Counseling*, Vol 22, Issue 1, 2013

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## Chapter 83

# FETAL INTERVENTIONS

Garfield Clunie, MD

## INTRODUCTION

The field of prenatal diagnosis has seen a rapid advancement over the past decade with the improvement in high-resolution ultrasound, including 3D and 4D technologies, fetal magnetic resonance imaging (MRI), improved maternal serum screening for aneuploidy, and genetic prenatal diagnosis. In large part because of these advances, most structural abnormalities previously diagnosed in the newborn period are now diagnosed prenatally. Certain anomalies may lead to fetal deterioration and impairment of normal organ development during the course of the pregnancy, subsequently leading to worse postnatal outcomes in some instances. For these conditions, fetal intervention, if available, may provide a viable option for fetuses otherwise at risk for serious morbidity or mortality.

In the past, parents' options were narrow: termination of pregnancy (if an anomaly was diagnosed early enough) or treatment of the newborn after delivery. Treatment for Rh isoimmunization in the early 1960s was the first example of a successful medical intervention in the fetus, but it was not until the 1980s that the field began to expand. Because of the high rate of complications from early interventions such as open fetal surgery, fetal intervention was initially reserved for conditions that, if left untreated, would lead to a high chance of perinatal mortality and morbidity. Since that time, the field of fetal intervention has greatly progressed, leading to the creation of more alternatives, including minimally invasive approaches, for pregnancy management when a fetus is found to

**Table 83-1** Fetal Interventions

TYPE OF INTERVENTION	DESCRIPTION	CLINICAL INDICATIONS
Open surgery	<ul style="list-style-type: none"> <li>• Hysterotomy under general anesthesia</li> <li>• Requires 3–7 days postoperative hospitalization</li> <li>• Obligates cesarean delivery</li> <li>• Preterm labor and preterm delivery are associated risks</li> </ul>	<ul style="list-style-type: none"> <li>• Large congenital lung malformations</li> <li>• Sacrococcygeal and cervical teratomas</li> <li>• Myelomeningocele repair</li> <li>• EXIT procedure</li> <li>• CDH (EXIT to ECMO)</li> <li>• CPAM (EXIT lobectomy)</li> </ul>
Endoscopic fetal surgery	<ul style="list-style-type: none"> <li>• Fetoscopic surgery using small endoscopes</li> <li>• Performed either percutaneously or through a small laparotomy incision</li> <li>• Preterm labor is a risk but less so than with open surgery</li> </ul>	<ul style="list-style-type: none"> <li>• Balloon occlusion trachea (CDH)</li> <li>• Laser ablation vessels (TTTS)</li> <li>• Cord ligation or division</li> <li>• Cystoscopic ablation posterior urethral valves</li> </ul>
Fetal image-guided surgery	<ul style="list-style-type: none"> <li>• Sonography-guided endoscopic surgery performed through a percutaneous or small laparotomy incision</li> <li>• Performed under regional (epidural, spinal) or local anesthesia</li> <li>• Least invasive, although a risk for preterm labor exists</li> </ul>	<ul style="list-style-type: none"> <li>• Amniotic bands division</li> <li>• Amnioreduction or amnioinfusion</li> <li>• Fetal blood sampling</li> <li>• Twin-reversed arterial perfusion (acardiac or acephalic twin)</li> <li>• Vesicoamniotic shunts for obstructive uropathy</li> <li>• Pleural (thoracic) amniotic shunts for pleural effusions or hydrothorax</li> <li>• Cord monopolar cautery</li> <li>• Balloon dilation aortic stenosis</li> </ul>

CDH, congenital diaphragmatic hernia; CPAM, congenital pulmonary airway malformation; ECMO, extracorporeal membrane oxygenation; EXIT, ex utero intrapartum treatment; TTTS, twin-to-twin transfusion syndrome.

have an abnormality. As these less invasive techniques have become more widespread, the procedural complication rate has also decreased, leading to the application of fetal interventions for a wider variety of fetal conditions.

## TYPES OF FETAL INTERVENTIONS

The first fetal intervention attempted was a fetal transfusion for hemolytic disease in the 1960s. The first open fetal surgery cases, performed during the 1980s, were for bladder outlet obstruction. Open fetal surgery techniques frequently involve administration of inhalation anesthetics to the pregnant woman, to provide deeper than usual sedation in order to achieve uterine hypotonia. Tocolytics are often necessary as well. A hysterotomy is performed, and the fetal malformation is repaired. This type of surgery is associated with a high rate of preterm labor and preterm premature rupture of membranes, and the mother usually needs to be hospitalized for recovery and, as needed, tocolysis.

With the advent of minimally invasive techniques such as fetal endoscopy and ultrasound-guided fetal surgery, maternal recovery time and preterm labor rate have decreased. Fetal endoscopy, also known as fetoscopy, is based on preserving fetal homeostasis by protecting the intrauterine environment. The surgery is performed by introducing a 3- to 5-mm trocar into the uterine cavity to allow for placement of endoscopes or fetoscopic instruments.

Ultrasound-guided fetal surgery, also termed fetal image-guided surgery, is a needle-based or percutaneous procedure. It is the least invasive technique and

can be performed under local anesthesia. This type of intervention was first used for amniocentesis and percutaneous umbilical blood sampling. It can now be used to place a catheter in the fetal bladder, abdomen, or chest and to provide radiofrequency ablation for complications associated with monochorionic multiple gestations. This chapter describes the most common fetal interventions available to treat a variety of fetal abnormalities (Table 83-1).

## FETAL INTERVENTIONS FOR SPECIFIC ABNORMALITIES

### Bladder Outlet Obstruction

Obstructive uropathy is known to affect from 1 in 20 to 1 in 1,000 births and can be the result of ureteropelvic junction obstruction or urethral obstruction. In male fetuses, this obstruction can be seen most commonly with posterior urethral valves. Other causes include urethral atresia and urethral hypoplasia. Lower urinary tract lesions seem to have a higher association than upper urinary tract lesions with morbidity. This abnormality can lead to severe hydronephrosis, progressive renal damage, subsequent decreased fetal urine output, and oligohydramnios. When the abnormality occurs early in the second trimester, pulmonary hypoplasia may result, leading to high rates of in utero or early postnatal demise.

Initially, affected fetuses are monitored with serial ultrasounds. If both kidneys are noted to be affected and the fetus is male, then fetal intervention may be considered to allow for relief of the obstruction and for accumulation of amniotic fluid for fetal lung development.

Because pulmonary hypoplasia results from oligohydramnios, the presence of oligohydramnios is an important consideration in deciding when to intervene. Before intervention, an intensive workup is required to determine whether the fetus is an appropriate candidate for therapy. This includes determination of fetal karyotype and careful sonographic evaluation for any additional abnormalities and to characterize the fetal kidneys. Poor prognostic indicators include echogenic kidneys, kidneys with multiple cysts, and evidence of perinephric urinoma, which indicates rupture of the urinary tract. Finally, fetal urine must be sampled for electrolytes and  $\beta$ -microglobulin. Healthy fetuses usually produce hypotonic urine, whereas renal damage is associated with salt wasting and can lead to isotonic urine production. Fetuses with evidence of isotonic urine are not good surgical candidates because of impaired kidney function. Fetal urine is sampled by draining the fetal bladder in a method similar to amniocentesis. A needle is introduced into the fetal bladder, and the bladder is completely drained. This procedure is repeated twice more, 48 to 72 hours apart. The third sample provides the most accurate assessment of fetal renal function.

The first fetal intervention used for treatment of bladder outlet obstruction was open fetal surgery. In 1982, Harrison and colleagues published the first case report of bilateral ureterostomies performed at 21 weeks' gestation. The surgery itself was successful at reversing the hydronephrosis and bladder distention, and the pregnancy continued until 35 weeks. However, the infant died 1 day after delivery as a result of severe pulmonary hypoplasia.

Ultrasound-guided placement of a catheter for vesicoamniotic shunting involves placement of a tube into the fetal bladder so that urine can flow from the bladder into the amniotic fluid. The most common complication from this procedure, a blocked or dislodged catheter, occurs in up to 40% to 50% of cases, which can lead to impaired shunt function with further worsening of the obstructive uropathy. Although there remains a small increased risk for preterm labor and premature preterm rupture of membranes, ultrasound-guided fetal surgery is far less risky than either open fetal surgery or fetoscopy. In addition, this technique is easier to perform and is more widely available than fetal surgery. However, neither open fetal surgery nor vesicoamniotic shunting addresses the structural anatomic problem (eg, posterior urethral valves). Perinatal mortality rate remains at 40% to 50%, most commonly resulting from pulmonary hypoplasia. Additionally, surviving fetuses have severe bladder abnormalities after birth. Less than 50% of those successfully treated will have normal renal function after birth. Additionally, more than 50% of surviving infants will have severely compromised growth secondary to chronic renal failure. Because of their significant bladder dysfunction, these infants are also poor renal transplantation candidates. Although these fetal interventions may reduce the pulmonary sequelae associated with bladder outlet obstruction and severe oligohydramnios, they do not address the renal sequelae.

The fetoscopic approach involves introducing a small trocar sheath through which a small fiberoptic

endoscope passes into the fetal bladder to identify and possibly ablate proximal urethral obstructions. Reported cases of fetoscopic ablation of posterior urethral valves have been technically successful but are still associated with a high rate of obstetric complications. Long-term safety and efficacy data have yet to be established. After birth, these neonates require follow-up with renal ultrasound and voiding cystourethrograms to determine whether further intervention is necessary.

### **Congenital Diaphragmatic Hernia**

Congenital diaphragmatic hernia (CDH) has been theorized to result from the failure of the normal closure of the pleuroperitoneal folds 4 to 10 weeks after fertilization. It has also been attributed to genetic or environmental factors that affect differentiation of mesenchymal cells during formation of the diaphragm. Most CDH occurs sporadically, with no identifiable familial association. Most of these hernias occur on the left side, and the disorder occurs in approximately 1 in 2,200 to 1 in 3,000 births. Herniation of abdominal contents into the thoracic cavity in the early second trimester causes compression of the hemithorax and can lead to severe pulmonary hypoplasia caused by the interruption of pulmonary development at an early stage of development, thus impairing branching morphogenesis and development of bronchioles and alveoli. Most of these infants are born with a degree of fixed lung hypoplasia and pulmonary hypertension. The severity of lung hypoplasia and secondary respiratory failure can be reduced and potentially prevented if fetal repair is performed early. Current advances in neonatal care have improved outcomes and survival rates for these infants. However, some are born with severe fixed hypoplasia and inadequate gas exchange. Aspects of the clinical presentation and features of congenital diaphragmatic hernia as well as treatment options and outcomes are discussed in Chapter 100, Respiratory Distress and Breathing Disorders in the Newborn; Chapter 108, Surgical Emergencies of the Chest and Abdomen in the Newborn; and Chapter 116, Health and Developmental Outcomes of Selected Medically Complex Neonates.

Antenatal evaluation requires a detailed ultrasound and a fetal echocardiogram to screen for other defects, as well as fetal karyotype to rule out aneuploidy. Diagnosis of CDH at less than 25 weeks' gestation with liver herniation is associated with the poorest prognosis. Liver herniation into the hemithorax is associated with a postnatal survival rate of less than 50%, whereas the absence of liver in the hemithorax is associated with a 90% survival rate. Similarly, diagnosis after 25 weeks' gestation has a near 100% survival rate compared with 56% when the diagnosis is made at or before 25 weeks' gestation. The lung-to-head ratio (LHR), which is the ratio of the lung area contralateral to the hernia defect to the fetal head circumference, has also been shown to be predictive of survival. An LHR of less than 0.6 is associated with a 0% survival rate compared with 100% survival in fetuses with an LHR of more than 1.35. LHR has been validated for use in fetuses between 23 and 26 weeks' gestation. The reliability of LHR for fetuses outside of this range, particularly at greater than 26 weeks' gestation, is debatable. For



those fetuses outside of this gestational age range, an association with increased postnatal mortality has been demonstrated for late-gestation fetal MRI-derived low total lung volume and the need for extracorporeal membrane oxygenation (ECMO) support. Although maturation and development of the lungs continues after birth, fetal lung growth should be complete by 34 weeks' gestation. Fetal MRI for total lung volume performed after 34 weeks' gestation may be used to identify, counsel, and develop a treatment plan for patients diagnosed with fetal CDH (eg, transfer to facility with ECMO capabilities; counseling regarding neonatal mortality rate).

For those fetuses with the poorest prognosis, fetal surgery may be offered as an alternative. The goal of fetal intervention is to assist with the development of the lungs so that these neonates can breathe after birth. The first attempted fetal intervention for CDH was open fetal surgical repair of the diaphragmatic defect. A National Institutes of Health (NIH)-sponsored prospective randomized clinical trial found no benefit to fetal surgery over conventional postnatal care. However, preterm delivery rates were higher among the fetal surgery patients. Focus then shifted to interventions aimed at correcting the pulmonary hypoplasia before birth. Occlusion of the fetal trachea in animal models of CDH demonstrated that tracheal occlusion could reduce the pulmonary hypoplasia associated with CDH. With blockage of the trachea, the fluid produced by the fetal lung remains in the lungs, resulting in expansion and accelerated maturation of the lungs.

Various methods have been described for tracheal occlusion and may be considered for fetuses with very severe CDH in which either the liver is herniated into the chest cavity or the LHR is low. Minimally invasive fetoscopic techniques have since been developed for tracheal occlusion. One approach uses fetoscopic neck dissection to attach obstructing clips to the trachea, a method complicated by the fine dissection required to bring the trachea into view. This fetoscopic approach has been modified to allow for endoscopic placement of a detachable balloon in the trachea that can be deflated after delivery. These newer, less invasive techniques have improved survival rates while decreasing preterm labor rates, the need for tocolytic therapy, and length of maternal hospitalization.

### **Congenital Pulmonary Airway Malformation**

Congenital pulmonary airway malformation (CPAM), formerly known as congenital cystic adenomatoid malformation (CCAM), is a rare abnormality of the lower respiratory tract. The incidence of CPAM is only approximately 1 in 25,000 to 1 in 35,000 pregnancies. CPAM is a congenital cystic lesion that occupies space in the lung field as a result of abnormalities that occur at varying stages of pulmonary development. Although usually unilateral or lobar, CPAMs are found in equal distribution among the right and left lung and in all lobes and may involve multiple lobes. CPAMs can decrease in size, remain stable, or increase in size. CPAMs may lead to nonimmune fetal hydrops by causing a mediastinal shift, compression of the vena

cava, and compromised venous return to the heart. Affected fetuses can have associated polyhydramnios as a result of increasing intrathoracic mass size, leading to esophageal compression and impaired swallowing. In a review of 17 cases of CPAM, the presence of nonimmune fetal hydrops was the only significant negative predictor of outcome, and its presence was associated with a 100% perinatal mortality rate in that series.

CPAMs have been divided into 5 different types based on histologic characteristics (type 0 through type IV). Thus, to confirm the type, postnatal histology is needed. Adzick and colleagues proposed a modification to Stocker's classification of CPAMs based on anatomy and appearance to assist in predicting prenatal outcome. Macrocystic CPAMs have single or multiple cysts more than 5 mm in diameter, and microcystic CPAMs have cysts that are less than 5 mm in diameter, giving them a more homogeneous appearance. Microcystic lesions increase the risk for development of hydrops. Because they can be quite large, microcystic lesions can also cause mediastinal shift, pulmonary hypoplasia, and polyhydramnios.

Before surgical intervention, a detailed ultrasound with color-flow Doppler to demonstrate or exclude systemic blood supply is necessary to confirm the diagnosis and to identify any additional structural abnormalities. Fetal echocardiogram is also recommended because of the increased incidence of associated cardiac anomalies, particularly truncus arteriosus and tetralogy of Fallot. Fetal MRI may be useful for distinguishing CPAM from other abnormalities, such as bronchopulmonary sequestration (BPS) or CDH. Without antenatal surgical intervention, most fetuses with large CPAMs resulting in hydrops will die in utero or in the early neonatal period. However, there are reports of resolution of the hydrops caused by CPAM after maternal steroid administration. Nevertheless, further study is needed to confirm true causality.

The CPAM volume ratio (CVR) is a useful prognostic tool. It is obtained by dividing the CPAM volume by the head circumference, to correct for gestational age. A CVR of greater than 1.6 is associated with an 80% risk for hydrops, whereas a CVR of less than 1.6 carries a 2% risk for hydrops. Fetal surgical resection of the CPAM by open fetal surgery in fetuses with hydrops has been shown to be successful in resolving hydrops, promoting in utero lung growth, and improving perinatal survival rates. Other techniques include thoracocentesis and placement of a thoracoamniotic shunt to decompress large cysts, serial aspirations for hydrops, and administration of a short course of prenatal steroid therapy. If the fetus has a large lesion, a specialized ex utero intrapartum treatment (EXIT) procedure may be considered at delivery. This procedure involves the baby being delivered and remaining attached to the placenta while the CPAM is surgically resected or until ECMO support is provided.

### **Sacroccygeal Teratoma**

Sacroccygeal teratoma (SCT) is the most common fetal neoplasm and one of the most common tumors in

newborns. With an overall incidence of 1 in 40,000 live births and a birth prevalence of 1 in 21,700 to 1 in 27,000 live births, it is more common in females than males (4:1 ratio). In the past, it was suggested that SCT was of germ cell origin. However, more recently, SCT has been thought to arise from a totipotent somatic cell originating from Hensen's node. SCTs are classified into 4 types based on the location of the tumor and degree of extension. This classification, described by Altman, is based on the intra-abdominal extent versus the external extent of the lesion. Although many of these tumors may attain a large size in utero without fetal compromise, in some cases arteriovenous shunting through the tumor can lead to high-output cardiac failure and fetal hydrops. Most studies have shown that the presence of hydrops and placentomegaly is associated with the poorest prognosis, particularly when diagnosed before 30 weeks' gestation. Some studies have shown the highest risk for fetal death associated with the most vascularized tumors, regardless of size, and in the presence of fetal hydrops. In a retrospective review of 12 fetuses diagnosed with SCT, tumor volume-to-fetal weight ratio (TFR) performed between 16<sup>6</sup>/<sub>7</sub> and 32 weeks' gestation was predictive of fetal outcome. A cutoff of TFR greater than 0.12 predicted a poor outcome, defined as development of hydrops or fetal or neonatal demise, whereas TFR less than 0.12 before 24 weeks' gestation predicted an uncomplicated prenatal course with a 100% survival rate.

Fetal hydrops, polyhydramnios, and associated placentomegaly may cause a maternal *mirror syndrome*, in which the mother develops hypervolemia, hemodilution, pulmonary edema, and elevated blood pressure. This condition can be life threatening to the mother and often requires delivery for maternal symptomatic relief. SCTs may also complicate delivery of the fetus resulting from dystocia or traumatic hemorrhage at the time of vaginal delivery. Some have suggested a cutoff of more than 5 cm or a volume of 750 cm<sup>3</sup> as an indication for elective cesarean delivery. Prematurity is another complication of SCTs, usually secondary to preterm labor from polyhydramnios. SCTs may also be associated with abnormalities of the central nervous, cardiac, urogenital, or musculoskeletal systems.

Many SCTs are identified in utero on prenatal ultrasound. SCTs contain solid and cystic components and are highly vascularized. Although 3D ultrasound and MRI may aid in diagnostic imaging, particularly in determination of location, content, and degree of extension of the tumor, ultrasound with Doppler studies remains the primary imaging method. Affected fetuses need detailed serial ultrasounds and echocardiograms to assess growth and to evaluate for the development of fetal hydrops.

Open fetal surgery before 30 weeks' gestation has been successfully performed in fetuses that have developed hydrops. Since the first successful case in 1997, 3 additional cases of open surgery have been performed. Although fetal surgery has been successful at antenatal resection of SCTs, it is also associated with a high preterm labor rate and significant maternal and fetal morbidity and mortality. Based on these earlier cases, the Children's Hospital of Philadelphia developed

criteria for open fetal surgical resection, which take into account any maternal contraindications, the gestational age of the fetus, staging of the teratoma, the presence of hydrops, the presence of significant placentomegaly, fetal karyotype, fetal cardiac status, and the presence of maternal mirror syndrome.

Less invasive methods have since been described that involve inserting a needle or probe into the blood vessels that feed into the tumor and ablating the vessels so that the high-velocity blood flow is disrupted, such as with radiofrequency ablation or thermocoagulation of tumor vessels. Reported cases have had varying degrees of success. Some cases were complicated by fetal hemorrhage, significant skin necrosis, and fetal muscle or hip joint and pelvic bone injury requiring additional surgery after delivery. Despite the theoretical benefit from prenatal intervention for SCTs, particularly in cases with large, well-vascularized tumors and hydropic fetuses, none of the fetal interventions performed has been shown to reliably improve outcome or survival, and they have in fact been associated with significant procedure-related morbidity and risk for preterm delivery.

### **Congenital High Airway Obstruction Syndrome**

Congenital high airway obstruction syndrome (CHAOS), first described by Hedrick and colleagues in 1994, is characterized by large echogenic lungs, flattened or inverted diaphragms, dilated airways distal to the obstruction, and fetal ascites or hydrops. The most common etiology of CHAOS is laryngeal atresia, although isolated tracheal or subglottic atresia has been described. The pathognomonic sonographic findings of CHAOS are the manifestations of upper airway obstruction leading to lung expansion caused by the trapping of lung fluid. This leads to flattening, and ultimately inversion, of the diaphragm and dilation of the upper airways distal to the obstruction. Experience from fetal interventions to treat CDH has demonstrated that the upper airway obstruction must be complete and occur early in development in order to produce the CHAOS phenotype.

The natural history of CHAOS is not well defined. Many affected fetuses die in utero, and many who survive to delivery die in the early neonatal period. Fetuses diagnosed with CHAOS fall into 1 of 3 categories: complete laryngeal atresia without an esophageal fistula, complete laryngeal atresia with a tracheoesophageal fistula, and near-complete high upper airway obstruction. Approximately one-third of affected fetuses will develop progressive nonimmune hydrops and die in utero. In another one-third of fetuses, the lesion will spontaneously perforate through the tracheal or laryngeal atresia or less commonly decompress through a tracheoesophageal fistula. The remaining one-third of affected fetuses tolerate hydrops reasonably well and remain hydropic until 30 to 32 weeks' gestation, at which point preterm labor or fetal distress prompts the need for an EXIT procedure. In cases in which CHAOS is caused by a thin web or laryngeal cyst, spontaneous rupture of the lesion can lead to complete resolution of the condition. Fetoscopy has also been used to treat CHAOS because of an isolated tracheal web.

Ex utero intrapartum treatment (EXIT) is a procedure for securing the fetal airway in fetuses at risk for airway obstruction while maintaining placental support. The EXIT procedure has been used for fetuses with head and neck tumors and for placement of a tracheal plug or clip in cases of CDH. In 1998, DeCou and colleagues reported the first case of CHAOS treated successfully during an EXIT procedure at 35 weeks' gestation with bronchoscopic evaluation and placement of a tracheostomy. Since that time, 11 cases have been reported. In these cases, prenatal ultrasound and MRI were used to determine the location and degree of airway obstruction. If the EXIT procedure was deemed possible, laryngoscopy and bronchoscopy were performed at the time of the EXIT procedure before tracheostomy placement. It is important to note, however, that although the EXIT procedure may improve perinatal survival, it does not treat the underlying abnormality, and for many of these patients the lesion is lethal and EXIT will not salvage those fetuses. Parents should be aware of the significant long-term morbidity associated with CHAOS, including long-term tracheostomy, impaired or delayed speech, chronic respiratory problems, and the need for several operations.

### Neural Tube Defects

Open neural tube defects (NTDs) are characterized by midline vertebral defects and are usually associated with the dorsal portion of the lumbosacral spine. Open NTDs develop when the neural tube fails to completely close. When the meningeal sac protrudes through the defect, it is called a meningocele. When the hernia sac contains nerve roots, the NTD is called a myelomeningocele. The most common NTD, myelomeningocele affects from 1 in 1,000 to 7 in 1,000 infants worldwide depending on ethnic, geographic, and nutritional factors. Open NTDs are associated with an increased maternal serum  $\alpha$ -fetoprotein level that is typically detected in the second trimester. On ultrasound, the frontal bones of the calvarium may take on a concave shape, known as the *lemon sign*. Herniation of the cerebellum into the foramen magnum may also be seen as a banana-shaped cerebellum in the posterior fossa, known as the *banana sign*.

NTDs are known to be associated with paralysis, hydrocephalus, intellectual disability, and loss of control of bowel and bladder function. In addition, most fetuses with open spina bifida will develop hindbrain herniation, also known as Arnold Chiari II malformations, which may then lead to hydrocephalus. Without surgical closure of the defect, these infants are at high risk for central nervous system infection. Before delivery, exposure of the spinal elements to the intrauterine environment may lead to progressive damage. Assessing the progression of the neurologic damage associated with these lesions in utero is difficult because distinguishing between active and passive movement of individual segments of the lower extremities on ultrasound can be difficult.

The first attempts at fetal repair were made in 1994 by a fetoscopic approach and were aimed at providing cover and protection to the NTD in utero in order to preserve neurologic function until a more definitive

repair could be performed postnatally. The outcomes of these initial procedures were poor. Of the 4 cases, 2 fetuses died, and the surviving 2 infants showed no benefit from the procedure. In 1998, fetal repair was once again attempted, this time using an open technique. Of these 4 cases, all 4 survived to birth and had no evidence of hindbrain herniation. Two infants ultimately required ventricular shunts. Compared with historical controls, in utero repair of open NTDs has led to a decrease in the number of neonatal shunts needed (86% versus 54%). An NIH-funded randomized clinical trial, the Management of Myelomeningocele Study (MOMS) trial, was published in 2011. This study compared outcomes of in utero repair with standard postnatal repair over a 7-year period from 2003 to 2010. The study was stopped prematurely because of the efficacy of prenatal surgery. Prenatal surgery for myelomeningocele reduced the need for shunting and improved motor outcomes at 30 months. However, prenatal surgery was associated with an increased risk for preterm delivery and uterine dehiscence at delivery. A second phase of this study that is underway, MOMS2, is evaluating the adaptive behaviors (personal and social skills) of the children enrolled in the MOMS trial between 5 and 9 years of age. Additional outcomes will include cognitive and motor functioning, brain morphology and function, and urologic and other spina bifida-associated outcomes and the child's quality of life.

### Amniotic Band Sequence

Amniotic band sequence (ABS) includes a group of sporadic congenital structural anomalies, typically involving the limbs, craniofacial regions, and trunk, which arise secondary to constriction rings or amputations associated with fibrous amniotic bands present within the amniotic cavity. Amniotic bands may be seen sonographically as early as 12 weeks' gestation. However, ABS is more often diagnosed by the effect of the bands on fetal anatomy. Sonographic findings commonly include absent digits or portions of limbs, or less commonly craniofacial, visceral, or body wall defects.

The incidence ranges from 1 in 1,200 to 1 in 15,000 live births and 1 in 70 stillbirths. The exact pathogenesis of amniotic bands is unknown, although current literature and animal models support the theory that these bands form after rupture of the early amnion, resulting in loose bands of amnion, which may then entangle the fetus and lead to vascular or mechanical disruption. The prognosis in ABS depends on the severity of the anomalies and the organ systems involved. As with any procedure that is associated with a significant risk for perinatal morbidity and mortality, fetal intervention for ABS should be performed when salvage of the affected extremity can be achieved. In 1995, Crombleholme and colleagues demonstrated that fetoscopic release of constrictive bands in a lamb model of amniotic band sequence reversed the hydropic changes in the limbs and prevented the other sequelae of banding, including limb shortening, loss of joint mobility, and absence of wool. The first attempt at fetoscopic release in human fetuses was performed at 22 weeks' gestation for a fetus with bilateral cleft lip and bands attached to the face and left upper extremity. Distal limb edema resolved with



minimal residual scarring at the site of band attachment, and the pregnancy continued successfully to 39 weeks. Several cases of fetoscopic release of amniotic bands have since been performed. A review of these cases showed that the most important fetal prognostic factor is the perfusion of the distal portion of the involved extremity. If there is no demonstrable perfusion of the extremity distal to the constriction, the limb may not be salvageable. It is important to note that intervention for ABS is primarily to salvage extremities and will not affect the outcome for more extensive bands where the deformities have already occurred.

### **Monochorionic Twin Gestations**

Monochorionic diamniotic (MCDA) twin gestations by definition share a single placental mass. Compared with dichorionic diamniotic (DCDA) twin pregnancies, monochorionic twins are at risk for specific pregnancy complications, typically secondary to abnormal vascular connections between the 2 fetuses. These anastomoses may be venous-venous (v-v), arteriovenous (a-v), or arterioarterial (a-a). In addition, although the perinatal mortality rate is greater for twins than for singletons, the rate is highest among monochorionic twins compared with dichorionic. Because of the vascular connections within a monochorionic placenta, there are significant risks for permanent neurologic damage to the surviving twin after a fetal death in up to 20% of cases of single twin demise. Certain complications, such as twin-to-twin transfusion syndrome (TTTS), discordant anomalies, and twin-reverse-arterial-perfusion sequence (TRAP), present a unique challenge because of the risk for morbidity and mortality to not only the abnormal fetus but also the normal twin. Treatment of these conditions in the abnormal fetus must take into account the consequences for the surviving twin.

### **Twin-to-Twin Transfusion Syndrome**

Twin-to-twin transfusion syndrome occurs at a rate of 0.1 to 0.9 per 1,000 live births, and the syndrome complicates approximately 10% to 15% of monochorionic pregnancies. The etiology of TTTS is based on the vascular anastomoses within the single placenta and the unequal sharing of blood flow between the 2 fetuses. These anastomoses can lead to the shunting of blood from one fetus (donor twin) to the other (recipient twin) by arteriovenous anastomoses, leading to intrauterine growth restriction in the donor and hydrops in the recipient. Although all monochorionic twins share some vascular connections within the placenta, the number and type of vascular anastomoses determine whether TTTS will develop in an MCDA pregnancy. The syndrome is diagnosed in monochorionic twins when a marked difference is found in amniotic fluid volume between the 2 sacs, leading to polyhydramnios in one sac and oligohydramnios in the other. Significant size discordance (>20%) can also develop between the twins, with the donor twin growing smaller in size. The donor twin is also referred to as the *stuck twin* because of the resulting oligohydramnios and subsequent collapse of the sac around the fetus, limiting its ability to move. The increase in

blood volume in the recipient twin secondary to shunting of blood within the placenta can cause strain on the fetal heart, leading to heart failure and hydrops from the chronic volume overload. If left untreated, fetal death will ensue, usually of the donor twin. The perinatal mortality rate of severe TTTS without intervention ranges from 60% to 100%.

The first minimally invasive technique employed in the treatment of TTTS was serial amnioreduction. The polyhydramnios surrounding the recipient twin leads to excessive uterine distention, impaired uteroplacental blood flow, pressure on the donor twin, and maternal discomfort. Serial reduction of amniotic fluid under ultrasound guidance can be used to help prolong gestation by improving uteroplacental blood flow and easing maternal discomfort. Survival rates among TTTS patients undergoing serial amnioreduction were improved compared with those pregnancies managed expectantly. Care must be taken not to remove too much fluid because placental abruption may occur secondary to the sudden decrease in intra-amniotic pressure. Amniotic septostomy can also be made in the dividing membrane between the 2 fetuses to allow amniotic fluid to flow between the 2 sacs; however, this can create monoamniotic twins, which also carry a high perinatal morbidity and mortality rate.

For the pregnancies that develop severe TTTS early in gestation, an alternative intervention is fetoscopic laser coagulation of anastomotic placental vessels. In 1997, Quintero and colleagues published a staging system for TTTS based on the sonographic appearance of the bladder, the presence or absence of Doppler abnormalities or hydrops, and in utero fetal demise of one or both twins. This staging system was developed to help distinguish those cases most likely to benefit from early fetal intervention. Since the 1990s, this procedure has become available in more centers throughout the United States. Most centers have developed protocols for the workup of these pregnancies before laser coagulation can be considered. Both fetuses must have a normal karyotype, a normal fetal echocardiogram, a detailed ultrasound, and TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex) laboratory workup to rule out possible infectious causes. Fetoscopic laser coagulation is considered in early-onset TTTS with a high Quintero stage or after failure of amnioreduction. For this procedure, placental vessels are mapped and all intertwined communicating vessels identified. A thin fiberoptic endoscope is introduced through the wall of the uterus and into the amniotic cavity of the recipient twin. The surfaces of the placental vessels are examined directly, and the abnormal vascular connections are coagulated with a laser. By eliminating the anastomoses, significant shunting of blood flow between the twins is stopped.

Serial amnioreduction and fetoscopic laser ablation have demonstrated the most promise for successful treatment of TTTS. In 2004, a study comparing outcomes after serial amnioreduction versus fetoscopic laser coagulation showed that the laser ablation cohort had a higher likelihood of survival of at least one twin to 28 days of life (76% vs 51%). Additionally, in the laser ablation cohort, the chances of a single



survivor and twin survivors were higher, and the median gestational age at delivery was greater. A Cochrane review of 213 pregnancies complicated by TTTS demonstrated that fetoscopic laser ablation results in few deaths of both infants per pregnancy, fewer perinatal deaths overall, and fewer neonatal deaths compared with serial amnioreduction. Thus, fetoscopic laser ablation is currently the recommended management for early-onset severe TTTS.

### **Twin Anemia-Polycythemia Sequence**

Twin anemia-polycythemia sequence (TAPS) is an atypical chronic form of TTTS that does not present with the requisite polyhydramnios or oligohydramnios but instead presents with a large intertwin difference in hemoglobin. Most cases are diagnosed in the late second or the third trimester. TAPS reportedly occurs in 3% to 6% of otherwise uncomplicated MCDA pregnancies. However, the incidence is up to 13% in pregnancies in which laser surgery has occurred. Lopriore and colleagues reported that residual unidirectional arteriovenous anastomoses after laser surgery for TTTS, which are usually less than 1 mm, lead to gradual development of anemia in one twin and polycythemia in the other twin. This process occurs slowly, which allows for hemodynamic compensation, and is hypothesized to be the reason for the absence of amniotic fluid volume discordance. TAPS may progress to TTTS.

Similar to the detection of fetal anemia in isoimmunization, middle cerebral artery (MCA) Doppler ultrasound evaluation can be used to monitor monochorionic pregnancies for TAPS. Middle cerebral artery peak systolic velocity (PSV) of greater than 1.5 multiples of median (MoM) in one twin (donor) and 0.8 MoM in the other twin (recipient) is used to make the diagnosis. As with TTTS, growth discordance may not be present. Postnatally, 3 measures are required to make the diagnosis. First, the difference between the hemoglobin value of the twins must be 8.0 mg/dL or greater, the reticulocyte ratio must be greater than 1.7, and there must be pathologic evidence of superficial atrioventricular anastomosis. Although the optimal treatment of TAPS has yet to be determined, repeat laser, fetal transfusion, and selective feticide are among the options.

### **Twin Reversed Arterial Perfusion Sequence**

Twin reversed arterial perfusion (TRAP) sequence affects approximately 1 in 35,000 live births and arises from abnormal arterial-to-arterial anastomoses on the placental surface. Because of this abnormal sharing, one twin (acardiac twin) receives all of the deoxygenated blood from the other twin (pump twin). As the deoxygenated blood from the pump twin enters the acardiac twin, normal developmental processes are interrupted, leading to atrophy, usually of the upper body (acardia acephalus). However, because of the anastomotic vessels within the placenta, this acardiac twin is sustained by the pump twin. As in TTTS, TRAP sequence can lead to in utero cardiac failure of the normal twin and eventual fetal death. If left untreated, the mortality rate for the pump twin is 50% to 75%, particularly if the acardiac twin is greater than 50% of

the size of the pump twin. Without intervention, even those fetuses who survive to delivery have significant long-term morbidity.

Treatments for TRAP sequence are aimed at disrupting the vascular connections supporting the acardiac twin in order to prevent the complications to the pump twin associated with high-output cardiac failure. Several fetal interventions have been used, including fetoscopic and ultrasound-guided laser ablation, umbilical cord ligation, bipolar or monopolar ultrasound-guided thermocoagulation, and ultrasound-guided radiofrequency ablation.

Fetoscopic laser ablation, as described previously, involves insertion of a fiberoptic endoscope into the uterus and ablation of the vessels supplying the acardiac twin. Alternatively, this procedure may be performed under ultrasound guidance without the use of a fetoscope. Umbilical cord ligation involves the placement of 2 or 3 trocars into the amniotic cavity, insertion of an endoscope to locate the umbilical cord supplying the acardiac twin, and suture ligation of the cord. Cord ligation has also been performed using ultrasound guidance alone with a single trocar for placement of the suture. The technique for monopolar thermocoagulation involves placement of a wire electrode under ultrasound guidance into the acardiac twin and coagulation of the aorta using monopolar energy. Bipolar cord coagulation requires use of a single trocar for insertion of a small-diameter bipolar coagulating forceps that is used to grasp the cord supplying the acardiac twin. In centers experienced in this procedure, bipolar cord coagulation is associated with a high success rate, low rate of complications, and short operative time. Radiofrequency ablation is performed using local anesthesia. A 3-mm radiofrequency ablation needle is placed percutaneously into the abdomen of the acardiac twin at the level of the cord insertion site, and the vessels supplying the acardiac twin are ablated.

Because of the need for highly specialized training and equipment, procedures for in utero therapy for TRAP are not widely available. Further, outcome data are limited to short-term outcomes. Thus far, randomized clinical trials have not been published, making it difficult to preferentially choose one technique over another. However, given the data that are available, both laser therapy and radiofrequency ablation seem to be safe and effective procedures. In general, studies report a survival rate of 80% to 90% for the pump twin after definitive therapy. Radiofrequency ablation is associated with a 22% risk for preterm premature rupture of membranes. Intrafetal laser ablation is associated with a 40% risk for preterm delivery. Maternal complications are uncommon and include bleeding, need for laparotomy to complete the procedure, thermal injury, chorioamnionitis leading to maternal sepsis, and disseminated intravascular coagulation.

### **Monochorionic Twins Discordant for Anomaly**

The rate of fetal anomalies is higher among twin pregnancies than singletons. In a population-based study of more than 2,300 twin pregnancies and 147,000 singletons, the prevalence of congenital anomalies in MCDA twins was 633.6 per 10,000 compared with 343.7 per 10,000 for DCDA twins (RR 1.8). In particular,

the excess risk among MCDA twins was attributable to anomalies of the central nervous system and to chromosomal and musculoskeletal anomalies.

Selective termination of the anomalous fetus using an intracardiac injection of potassium chloride cannot be performed for MCDA pregnancies because of the vascular anastomoses and risk for embolization of toxic materials to the nonanomalous twin. One of the methods described earlier in this chapter may be used to occlude the cord of the anomalous twin, typically at the abdominal cord insertion site.

### Fetal Anemia

Rh sensitization has become increasingly rare since the advent of Rho(D) immune globulin (RhoGAM), but cases of Rh isoimmunization that require fetal intervention can still be found. Rh isoimmunization can develop when an Rh-negative mother is pregnant with an Rh-positive fetus. If the mother has been exposed to Rh-positive cells in the past, then she will have circulating antibodies to the Rh antigen. When re-exposed to the Rh antigen (eg, during a subsequent pregnancy with an Rh-positive fetus), these antibodies rapidly increase in number. These antibodies can cross the placenta and attack the fetal red blood cells, resulting in hemolysis and fetal anemia. In severe cases, the anemia may lead to heart failure and hydrops, and subsequent death. Most cases of Rh isoimmunization causing severe hemolytic disease of the fetus and newborn are the result of incompatibility with the D antigen. However, severe hemolytic disease of the newborn can occur with other red blood cell antigen incompatibility, such as Kell. The overall prevalence of Rh incompatibility varies based on race and ethnicity but is estimated to be 6.8 cases per 1,000 live births based on birth certificate data as reported by the US National Center for Health Statistics in 2003.

Currently, all pregnant women receiving prenatal care are tested for their Rh type at the beginning of pregnancy and treated with RhoGAM when necessary. Additional doses may be given for episodes of vaginal bleeding, after procedures such as chorionic villus sampling and amniocentesis, or after direct abdominal trauma when fetomaternal hemorrhage is suspected. For women who are known to have Rh antibodies and who are at risk for having an Rh-positive fetus, serial antibody titers are followed throughout the pregnancy. A critical maternal titer is the titer associated with a significantly increased risk for fetal anemia. Each laboratory will have an established critical titer, typically between 1:8 and 1:16. If the titer exceeds this critical number before 35 weeks' gestation, the fetus is monitored more closely for anemia. The gold standard for detection of fetal anemia using invasive methods is amniocentesis to check the optical density of the amniotic fluid based on the heme pigment produced by hemolysis. This value, known as the DOD<sub>450</sub> value, was originally plotted on a Liley curve that was divided into 3 zones and designed for use in pregnancies from 27 weeks' gestation to term. The Liley curve was then modified by Queenan in 1993. The Queenan curve consisted of 4 zones and included data for pregnancies as early as 14 weeks' gestation. In 2000, Mari and colleagues found Doppler measurement

of the MCA PSV of greater than 1.5 MoM to be a reliable screening tool for fetal anemia, with a low false-positive rate of only 12%. Subsequent studies have confirmed the reliability and sensitivity of MCA Doppler ultrasound. Compared with amniocentesis for DOD<sub>450</sub>, MCA PSV had a sensitivity of 88% versus 76%, specificity of 82% versus 77%, and accuracy of 85%. These data confirmed that MCA PSV can safely replace DOD<sub>450</sub> in the management of Rh isoimmunization. A meta-analysis in 2009 further confirmed that MCA PSV is the gold standard for noninvasive screening for fetal anemia.

In severe anemia, the current practice for treatment involves a fetal blood transfusion using percutaneous umbilical blood sampling (PUBS) or cordocentesis. PUBS is performed by introducing a needle into the fetal umbilical cord. A small amount of blood is withdrawn, and a Coulter counter determines the opening fetal hematocrit. Based on this initial value, a calculation is made to determine the amount of blood that should be transfused to the fetus. Irradiated, leukocyte-depleted, cytomegalovirus-negative, type O, RhD-negative red blood cells are transfused into the fetus for a target hematocrit of 40% to 50%. On average, the fetal hematocrit will decline approximately 1% per day from hemolysis related to Rh incompatibility. Given this, the procedure may need to be repeated several times during the pregnancy. The risks of PUBS include non-reassuring fetal status, spontaneous rupture of membranes, preterm labor, and intrauterine infection. It is important to note that in order to allow the fetal cardiovascular system to compensate for the acute change in volume and viscosity, the hematocrit should not be raised by more than fourfold in a single transfusion.

### ETHICAL CONSIDERATIONS IN FETAL INTERVENTIONS

Since the 1980s, the fields of prenatal diagnosis and fetal intervention have experienced dramatic advances. Because of the significant risks associated with open fetal surgery and earlier, more invasive procedures, fetal intervention was previously reserved for diseases that would otherwise be lethal without intervention. With improvements in ultrasonography and more widespread use of MRI, fetal abnormalities are being diagnosed at earlier gestational ages. In addition, with the increasing number of centers offering fetal intervention and the improvements in minimally invasive approaches to fetal intervention, the application of fetal intervention has expanded to include a wider number of diseases.

The American College of Obstetricians and Gynecologists (ACOG) released a Committee Opinion in 2011 regarding maternal-fetal intervention and fetal care centers. The statement emphasizes the overarching goal of fetal interventions, which is to improve outcomes for children by intervening before birth to correct or treat prenatally diagnosed abnormalities. Correcting a fetal malformation with open surgery, fetoscopy, or ultrasound-guided procedures can be risky to both fetus and mother, inadvertently increasing both maternal and perinatal morbidity and mortality

rates. The need to balance risks to the mother and fetus against potential benefits to the fetus forms the basis for the fundamental ethical conflict when considering fetal surgery. Additionally, the psychosocial risks to the mother and family of losing the pregnancy or, in the event of iatrogenic injury to the fetus, living with a child impaired with further damage must also be considered. Finally, residual risks to future pregnancies must also be taken into account. For these reasons, ACOG and the American Academy of Pediatrics recognize that these interventions always require the free informed consent of the pregnant woman, who always has the right of refusal.

Criteria have been set for considering fetal intervention, including that prenatal diagnosis techniques should identify the malformation and almost certainly exclude any abnormalities that will result in death; the defect should have a defined natural history and cause progressive injury to the fetus that is irreversible after delivery; repair of the defect should be feasible and should reverse or prevent the injury process; and the surgical risk must not entail excessive risk for the mother or her future fertility. Meeting these prerequisites is extremely important because most fetal malformations do not directly threaten the mother's health.

The investigational nature of these interventions, offered at a limited number of centers under research protocols, necessitates a rigorous, nondirective informed consent process that emphasizes the experimental basis for these interventions. Most of these procedures use a multidisciplinary approach including but not limited to perinatologists, neonatologists, radiologists, pediatric surgeons, pediatric subspecialty surgeons, anesthesiologists, and nurses. As therapies advance, public policy and insurance practices will likely continue to evolve. Centers performing fetal surgery have established *fetal oversight committees* that serve as a multidisciplinary advisory council, which ensures continuous monitoring of quality and function.

### Decision Making

Questions remain about both the safety and efficacy of many fetal surgical corrections. In some disorders, the natural history of the conditions is poorly understood, making outcome comparisons difficult when evaluating fetal therapy versus no treatment or postnatal intervention. In addition, when comparing fetal therapy with postnatal surgery, it is crucial to consider risks to the mother from exposure to anesthesia and surgery during the procedure, drugs used to prevent premature labor and delivery after the procedure, and the emotional burden of consenting to medical interventions with uncertain outcomes. This means that the benefits of these surgeries must be considered in the context of risks to both the pregnant woman and the fetus. Not every pregnant woman seeking fetal treatment is an appropriate intervention candidate. Consequently, the informed consent process should educate expectant parents so that their expectations about likely outcomes match current clinical realities. Precise information about the benefits of fetal approaches in the context of the natural history of the diseases or disabilities being treated, and disclosure of

information about the skill sets, experience, and success rates of medical teams performing each procedure should be provided. These measures would ensure that pregnant women (and their families) have the information necessary for shared decision making about fetal or neonatal interventions for life-threatening neonatal conditions. The pediatrician has an important role in collaboration with the maternal-fetal specialist and other pediatric subspecialists in supporting families through these difficult and delicate processes, balancing hope with the reality of the condition and offering clear, compassionate communication regarding expectations and anticipated outcomes.

A framework for understanding how some families will approach decision making under these circumstances can be extrapolated from studies of parents whose young child has a life-threatening congenital heart defect. Described as "parenting under pressure," the process involves 4 phases: realizing and adjusting to the inconceivable, growing increasingly attached, watching for and accommodating to the unexpected, and encountering new challenges. Families confronting a prenatal diagnosis of a potentially life-threatening condition affecting their fetus must quickly channel through these stages as they gather and process information needed to make decisions for their child. It is equally important to recognize cultural variations in values that inform parental choices regarding their desire for potential fetal or neonatal interventions following a prenatal diagnosis and, in some instances, even decisions regarding whether to undergo extensive fetal assessment to more fully inform the degree of fetal involvement or anticipated illness severity.

### THE FUTURE

In utero transplantation with hematopoietic stem cells can possibly treat fetuses with various congenital disorders. Additionally, the advent of gene therapy will likely transform the management of in utero disease. Today, many potentially lethal inherited conditions have to be treated after birth with bone marrow transplantation, which can be complicated by lack of donor stem cells, irreversible damage in the neonate, or rejection of the donor cells. The idea of transplantation in utero is based on the theory that the fetal immune system is immature and will be more likely to overcome these problems. This treatment is novel and unproven. In utero transplantation will be considered for hemoglobinopathies, immunodeficiency diseases, inborn errors of metabolism, mucopolysaccharidoses, and more. Currently, most fetal interventions are used in situations in which the fetus would die without the intervention, such as Rh isoimmunization or TTTs.

As technology advances and physicians become more proficient with these techniques, ethical considerations will arise. However, most of the available evidence is based on case reports, case series, or reviews. There have been few prospective studies evaluating the superiority of one method over another. Despite the paucity of evidence in the literature, minimally invasive fetal interventions are being offered at more centers and are practiced by more physicians. Interventions originally



reserved for fetal abnormalities that would result in fetal death if untreated are now being offered for a wide variety of non-life-threatening fetal abnormalities. Should these therapies be offered for still more abnormalities, such as polydactyly or cleft lip? Society must weigh the cost of treating these defects in utero against the complications that may occur. Finally, outcomes of interest to parents, such as the child's long-term neurodevelopmental status, quality of life, and future health, as well as maternal health outcomes, are unknown at this point.

Despite these gaps in knowledge, there is a building momentum and body of literature in the field of fetal intervention. Studies evaluating long-term follow-up of these patients and their children will be invaluable in determining the future of fetal intervention.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *What Is Amniotic Band Syndrome?* (Web page) ([amnioticbandsyndrome.com/about](http://amnioticbandsyndrome.com/about))
- *Amniotic Band Syndrome* (Web page), National Organization for Rare Disorders ([rarediseases.org/rare-diseases/amniotic-band-syndrome](http://rarediseases.org/rare-diseases/amniotic-band-syndrome))
- *Prenatal Surgery: Helping Babies Before Birth* (Web page), KidsHealth ([kidshealth.org/parent/positive/issues2012/2012\\_prenatal.html](http://kidshealth.org/parent/positive/issues2012/2012_prenatal.html))
- *An Expectant Parent's Guide to Spina Bifida* (fact sheet), Spina Bifida Association ([spinabifidaassociation.org/project/expectant-parents-guide-to-spina-bifida](http://spinabifidaassociation.org/project/expectant-parents-guide-to-spina-bifida))
- *Prenatal Hydrocephalus: A Book for Parents* (booklet), Hydrocephalus Association ([www.hydroassoc.org/docs/PrenatalHydrocephalus-A\\_Book\\_for\\_Parents.pdf](http://www.hydroassoc.org/docs/PrenatalHydrocephalus-A_Book_for_Parents.pdf))

#### Medical Decision Support

- *A Guide for Medical Professionals* (fact sheet), Spina Bifida Association ([spinabifidaassociation.org/project/a-guide-for-medical-professionals](http://spinabifidaassociation.org/project/a-guide-for-medical-professionals))

### AAP POLICY

American College of Obstetricians and Gynecologists Committee on Ethics, American Academy of Pediatrics Committee on Bioethics. Clinical report: Maternal-fetal intervention and fetal care centers. *Pediatrics*. 2011;128(2):e473–e478 ([pediatrics.aappublications.org/content/128/2/e473](http://pediatrics.aappublications.org/content/128/2/e473))

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### Chapter 84

## MATERNAL DEPRESSION

Marian Earls, MD

Perinatal depression is a pertinent issue for the primary care physician (PCP) because of the significant associated risks to the health and well-being of the infant and family. This chapter specifically discusses postpartum depression for the PCP who is providing care for the child of a depressed mother. Postpartum depression adversely affects early brain development and leads to increased costs of medical care, inappropriate medical care, child abuse and neglect, discontinuation of breastfeeding, and family dysfunction. Pediatric practices, as medical homes, can establish a system to implement postpartum depression screening and to identify and use community resources for the treatment and referral of the depressed mother and support for the mother-child (dyad) relationship.

Up to 12% of all women may experience depression in a given year. Socioeconomic status is a compounding factor, and if a woman has low income, the prevalence of depression is doubled to 25%. Forty to 60% of mothers who have low income report depressive symptoms (but do not necessarily meet criteria for a depressive disorder). Specifically, depression occurs in 8.5% to 11% of women during pregnancy and in 6.5% to 12.9% of women during the postpartum period. Major depression, as a subset of those statistics, occurs in 3.1% to 4.9% and 1% to 6.8%, respectively. The peak for minor depression occurs at 2 to 3 months postpartum, and for major depression at 6 weeks postpartum.

The spectrum of postpartum depression encompasses “postpartum blues” to postpartum mood disorders (PPMDs), which include postpartum depression and postpartum psychosis. Fifty to 80% of all mothers experience postpartum blues after birth. These symptoms are transient (beginning a few days after birth and lasting up to 2 weeks), but they do not impair function. Symptoms include crying, depressed mood, irritability, anxiety, and confusion.

Postpartum depression is categorized as a minor/major depressive disorder in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition. Postpartum psychosis is a relatively rare event. Only 1% to 3% of women experience postpartum psychosis after birth. Occurring in the first 4 weeks after birth, impairment is serious and may include paranoia, mood shifts, hallucinations/delusions, and suicidal/



homicidal thoughts. Postpartum psychosis requires immediate medical attention. If a woman experiences PPMD, she is likely to experience it again with subsequent pregnancies. However, PPMD can also affect mothers even without a previous history with earlier births.

A mother can be placed at risk for depression if the child has difficult temperament, was premature, or has a chronic health condition. If a mother has difficulty reading her baby's cues, bonding may be difficult and interaction impaired.

### EFFECT OF MATERNAL DEPRESSION

In the setting of maternal depression, the effects on the infant's environment can adversely affect early brain development. It is known that migration of neurons and formation and pruning of synapses are affected by both genetics and the environment. Further, physiologic responses to stress in the infant's environment affect the infant's social-emotional development. The activation of the physiologic stress response system results in increased levels of stress hormones. Persistent elevation of cortisol can disrupt the developing brain's architecture in the areas of the amygdala, hippocampus, and prefrontal cortex and therefore ultimately affect learning, memory, and behavioral and emotional adaptation. When an infant lives in an environment of neglect, there can be visible changes on magnetic resonance imaging in the frontal lobes. The infant therefore is at risk for impaired social interaction and delays in language and cognitive development.

Maternal depression compromises bonding. When the mother is emotionally disengaged, an environment is created in which the infant withdraws from daily activities and may avoid interaction. As early as 2 months of age, the infant looks at the depressed mother less and can demonstrate poor state regulation, less interaction with objects, and lower activity level. The infant is at risk for failure to thrive and attachment disorder of infancy (deprivation/maltreatment disorder of infancy).

#### The Infant

Early signs and symptoms in the infant include poor orientation skills and tracking, lower activity level, and negative temperament. The developing infant may appear sad, lethargic, and withdrawn. The infant may have little interest in exploration. There may be feeding or sleeping problems. The infant may cry a lot and have difficulty both with self-comforting and with being soothed. The infant is likely to exhibit no caregiver preference and to go to anyone. The infant may resist touch or be clingy.

#### The Mother

Maternal depression impairs parenting skills. The mother's perception of the child's behavior is less positive. Her interaction is less attuned to the infant's cues and may be more controlling. On the other hand she may have apathy toward the baby and indifference to caregiving. She is likely to have impaired attention and judgment for health and safety. Further, there is an adverse effect on breastfeeding. The

Agency for Healthcare Research and Quality evidence report "Breastfeeding and Maternal and Infant Health Outcomes in Developed Countries" reviewed 6 prospective cohort studies regarding postpartum depression and breastfeeding. It revealed an association between not breastfeeding, or early cessation of breastfeeding, and postpartum depression.

Early response is urgent. If the mother continues to experience depression and there is no intervention for the dyad, the child's developmental issues are likely to persist and be less responsive to intervention over time. As noted previously, infants are at risk for insecure attachment. Children with insecure attachment are more likely to have behavior problems and conduct disorder. Higher cortisol levels in preschoolers are linked with anxiety, social wariness, and withdrawal. Attachment disorders, behavior problems, and depression can occur in childhood and adolescence. When mothers experience depression, the children, as they age, often have poor self-control, poor peer relationships, school problems, aggression, special education needs, grade retention, and early school exit.

### ROLE OF THE PRIMARY CARE PHYSICIAN

Postpartum depression leads to adverse effects on infant brain development, cessation of breastfeeding, family dysfunction, inappropriate medical treatment of the infant, and increased costs of care. To have a positive effect on the health of the child and family, medical homes can be timely and proactive by implementing screening, supporting the mother-child relationship, and identifying and using community resources for referral and treatment. PCPs who care for children need to promote awareness of the need for screening in the obstetric and pediatric periodicity of care schedules, use evidence-based interventions focused on healthy attachment and parent-child relationships, and promote training for professionals who care for very young children.

There is much support for the primary care setting to incorporate screening and interventions. The American Academy of Pediatrics (AAP) policy statement "The Future of Pediatrics: Mental Health Competencies for Pediatric Primary Care" recognizes the unique advantage of the primary care physician for surveillance, screening, and working with families to improve mental health outcomes. The "primary care advantage" derives from the following characteristics:

- Longitudinal, trusting relationship with the family
- Family centeredness
- Unique opportunities for prevention and anticipatory guidance
- Understanding of common social-emotional and learning issues in the context of development
- Experience in coordinating with specialists in the care of children and youth with special health care needs
- Familiarity with chronic care principles and practice improvement

The AAP Task Force on Mental Health promotes the use of a common factors approach to engage families and build an alliance for addressing mental health

issues. Bright Futures health promotion themes include Family Support, Child Development, and Mental Health. Specifically, Bright Futures includes surveillance for parental social-emotional well-being as well. Psychosocial screening and surveillance for risk and protective factors is an integral part of routine care and the relationship with the child and family. Opportunities for prevention and promotion in primary care include the following:

- Prenatal visits (the prenatal visit is the first in the Bright Futures periodicity schedule)
- Psychosocial and maternal depression screening
- Developmental and behavioral screening and surveillance
- Social-emotional screening for children identified at risk

Implementation of these screening opportunities requires a quality improvement approach to office process.

## SCREENING FOR POSTPARTUM DEPRESSION

Based on the peak times for the occurrence of the spectrum of PPMD, the 1-, 2-, and 4-month well-child visits are appropriate times to screen for maternal depression. Screening tools are simple and include the Edinburgh Postpartum Depression Scale (EPDS) or the Patient Health Questionnaire-2 (PHQ-2), both of which are endorsed by the US Preventive Services Task Force. The EPDS has 10 multiple-choice questions and is completed by the mother. A score of 10 or greater indicates possible depression; a score of 20 or greater requires immediate referral for emergency mental health services. The screen is available in English and Spanish and can be accessed online. The PHQ-2 has only 2 questions and is not specific to the postpartum period; it can be used during pregnancy, for surveillance, and to indicate risk for depression in adults in general. The 2 questions are as follows:

- Over the past 2 weeks, have you ever felt down, depressed, or hopeless?
- Over the past 2 weeks, have you felt little interest or pleasure in doing things?

The prenatal visit is an excellent opportunity to discuss strengths and stressors during pregnancy, including depression. The PCP may be able to provide anticipatory guidance and initiate supportive strategies for the mother even before the baby's birth. Communication between the obstetrician and PCP is desirable for this reason.

To follow up on depression concerns and the effect on the mother-infant relationship, use of a screen for infant social-emotional development and interaction is appropriate. The Ages and Stages Questionnaire—Social-Emotional (ASQ-SE) is one such tool. It is completed by the mother and has a single cutoff score. It provides information about infant caregiver interaction and screens affect, self-regulation, adaptive functioning, autonomy, compliance, and communication. The 6-month tool is used for infants who are 3 to 8 months of age. Another infant social-emotional screening instrument that is available and in the public domain is the Baby Pediatric Symptom Checklist (BPSC), available at the Survey of Wellbeing of Young

Children Web site ([www.theswyc.org](http://www.theswyc.org)). It assesses irritability, inflexibility, and difficulty with routines and is to be used for children younger than 18 months.

## WHEN SCREENING SHOWS A CONCERN

When a depression screen is positive, management will vary according to the degree of concern and need. At the very least, it will require support and demystification. Management includes the following:

- Communication
- Demystification
- Support resources (family and community)
- Referrals to integrated/co-located mental health provider
  - For the mother
  - For the dyad
  - For the child (for targeted promotion and early intervention).

Demystification is directed at removing the mystery about maternal depression—emphasizing that postpartum depression happens with many women, that it is not the mother's fault and she is not a bad mother, that she will feel better and depression is treatable, and that the PCP is a resource and other help is available. Having a baby is a time of transition that can be difficult when there are other stressors but can be eased when there are other supports. A brief intervention at the visit could include the following:

- Promote the strength of the mother-infant relationship
- Encourage understanding and responding to the baby's cues
- Encourage routines for predictability and security
- Encourage focus on wellness: sleep, diet, exercise, stress relief
- Acknowledge personal experiences
- Promote realistic expectations and prioritizing important things
- Encourage social connections

Intervention for the mother may include support, therapy, medication, emergency mental health services, and hospitalization. Note that mild depression does not generally require medication. For these services, the mother can be referred to her own PCP, her obstetrician, or an adult mental health provider.

Immediate action is necessary if the EPDS score is 20 or greater, if the mother expresses concern about her or her baby's safety, or if the PCP suspects that the mother is suicidal, homicidal, severely depressed, manic, or psychotic. Referral to emergency mental health services (most communities have mental health crisis teams/services) is needed, and the mother should leave the office with a support person (not alone) and a safety plan.

Intervention for the dyad includes the following:

- Follow-up ASQ-SE, and, if attachment issues are indicated,
- Therapy with a child mental health professional regarding attachment and bonding,
- Referral to Part C, Early Intervention services.

The father may also have depression, and the incidence may be higher if the mother is depressed. A father who is not depressed may be a protective factor.

If the practice has an integrated mental health provider, such as a licensed clinical social worker or counselor, that provider can provide immediate triage for a positive screen, administer secondary screens, offer support and follow-up, facilitate referrals, and coordinate follow-up with the PCP.

Referrals for the mother could be to her own PCP, her obstetrician (who may be the mother's PCP or may have an integrated mental health professional linked with their practice), or an adult mental health professional for individual or couple therapy and, if needed, medication.

Referrals for the dyad should be to a professional who has expertise in the treatment of very young children. Evidence-based treatments include Circle of Security (COS, for children aged 0–5 years), Parent–Child Interactive Therapy (PCIT, for children aged 3–7 years), Child–Parent Psychotherapy (ABC, for children aged 0–5 years), and Attachment and Biobehavioral Catch-Up (ABC, for children aged 0–5 years). Part C services can provide modeling and support for interaction and play with the infant to promote healthy development.

Other community resources for the family include the following:

- Public health nurses
- Lactation specialists
- Parent educators
- Family support groups
- Parent–child groups
- Mother's morning out
- Early Head Start
- Mentoring and home visitation such as Parents as Teachers, Healthy Families America, and faith-based or other volunteers

## CODING AND BILLING

The AAP recognizes the EPDS or PHQ-2 as a measure of risk in the infant's environment; therefore, billing is appropriate at the infant's visit with the infant as the patient. The Current Procedural Terminology (CPT) code for this screen is 99420. The CPT code for the ASQ-SE may be 96110 or 99420, depending on the state. The Diagnostic Classification of Mental Health and Developmental Disorders in Infancy and Early Childhood: Revised Edition (DC 0-3R) coding for Deprivation/Maltreatment Disorder of Infancy is observed in the context of evidence of deprivation or maltreatment manifested by the following:

1. Persistent parental neglect or abuse of a physical or psychological nature, of sufficient intensity and duration to undermine the child's basic sense of security and attachment;
2. Frequent changes in, or inconsistent availability of, the primary caregiver, making an attachment to an individual caregiver impossible; or
3. Other environmental compromises and situations beyond the control of the parent and child that are

prolonged, interfere with the appropriate care of the child, and prevent stable attachments.

These statements describe the possible impact of significant or prolonged maternal depression on attachment.

## SUMMARY

Early brain development research highlights the importance of a healthy mother–infant relationship. Unrecognized and untreated, postpartum depression places this relationship and the infant at risk. The nonstigmatizing, longitudinal pediatric relationship lends itself to identifying maternal depression and supporting maternal and child health. Universal early, routine, structured psychosocial screening opens the door to broader communication with families and medical homes about mental health–related concerns. The PCP–family relationship provides the “primary care advantage” to facilitate healthy attachment and social-emotional development for the infant.

## TOOLS FOR PRACTICE

### Medical Decision Support

- *Screening for Maternal Depression & Infant Toxic Stress* (online course), North Carolina Academy of Family Physicians, North Carolina Pediatric Society, Community Care of North Carolina (md2013.ncafp.com)

## AAP POLICY

- American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health and Task Force on Mental Health. The future of pediatrics: mental health competencies for pediatric primary care. *Pediatrics*. 2009;124:410–421. Reaffirmed November 2013 (pediatrics.aappublications.org/content/124/1/410)
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## PART 4

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# Care of Healthy and High-Risk Infants

### Section One: Routine Care Issues

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- 86 Prenatal Pediatric Visit
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## SECTION ONE

# Routine Care Issues

### Chapter 85

## MEDICAL-LEGAL CONSIDERATIONS IN THE CARE OF NEWBORNS

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### INTRODUCTION AND OVERVIEW OF MEDICAL MALPRACTICE

About 4 million infants are born every year in the United States. Pediatricians, general physicians, and nurse practitioners provide most of the care to these newborns. Throughout this chapter, these physicians will be collectively referred to as *primary care physicians* (PCPs); however, the information presented here is intended for all physicians and other medical professionals who care for infants. Although most of these newborns will be healthy, the PCP will need to manage a variety of common but potentially harmful conditions, such as hyperbilirubinemia, hypoglycemia, and previously unrecognized congenital heart disease. Delays in the initiation of resuscitation and inadequate neonatal resuscitation are among the most common clinical situations leading to litigation against pediatricians and other physicians and nonphysician clinicians who care for newborns. Missed or delayed diagnosis and management of suspected sepsis or meningitis, perinatal injury, developmental dysplasia of the hip, and critical congenital heart disease may also give rise to substantial medical liability. Other issues in newborn care that pose liability for pediatric PCPs include missed newborn blood spot screening, missed hearing screening in the nursery, improper treatment of neonatal hypoglycemia, and delayed response to neonatal seizures or hyperbilirubinemia. Factors that contribute to potential liability encompass failure to perform appropriate screening evaluations or risk assessment, poor communication, incomplete documentation, failure to recognize and appropriately treat high-risk conditions that may contribute to a particular neonatal condition, and inadequate or delayed follow-up care.

Unfortunately, medical malpractice liability is in the midst of a new crisis. Indeed, the American Medical Association (AMA) estimates that 20 states are currently in a medical liability crisis, defined as a situation in which patients lose access to care as a result of the medical liability system. In 2010, both the Illinois and Georgia Supreme Courts struck down their medical malpractice caps as unconstitutional. Additionally, the AMA published a survey in 2010 showing that an average of 95 claims were filed for every 100 physicians.

Although liability problems have occurred in the past, the current effect on young physicians is severe. A 2008 survey of final-year residents found that 69% of residents were significantly concerned about malpractice, up from only 15% in the 2001 survey. Furthermore, many surveys have revealed physicians' increasing dissatisfaction with medical practice, in part because of liability concerns.

The specialty of pediatrics ranks fourth in highest average indemnity from 1985 to 2004, behind neurology, neurosurgery, and obstetrics and gynecology. Furthermore, the Physician Insurers Association of America (PIAA) reports that the average closed pediatric malpractice claim was \$316,521, compared with \$212,722 for all specialties. The high claim amounts result because many of the common diagnostic errors in newborns, such as meningitis, may lead to catastrophic and permanent injuries. Furthermore, the appearance of these permanently handicapped children in court or on video can generate enormous sympathy from juries. Finally, there are substantial costs of care when newborns are permanently injured. In a study conducted by Hickson and colleagues, families whose infants experienced permanent injury or death after a perinatal event were interviewed after the end of litigation regarding their reasons for filing malpractice claims. Important among the reasons cited by parents was a dissatisfaction with the physician-patient (family) communication: 13% did not believe their physician would listen to them, 32% believed that their physician did not speak openly, and 48% expressed feeling that they were intentionally misled. Seventy percent of participants stated that their physician did not inform them about the potential for long-term neurodevelopmental problems in their children. Families who believe that they are uninformed often assume that a complication that occurred is a result of a mistake and that the hospital staff is afraid to acknowledge this error. Issues of blame may be compounded further by parental concerns about their own responsibility for the infant's condition. Ultimately, the family may ascribe blame to the medical caregivers.

This chapter explores medical-legal issues that the PCP encounters in the delivery room, the newborn nursery, and the office. The chapter also addresses common malpractice risks that the PCP faces in dealing with sick newborns, as well as consultation, transport, and referral issues. The final sections of the chapter examine communication issues, patient safety, and ways to minimize liability risk. The goal is to assist practicing physicians in understanding their rights, duties, and liabilities as physicians (see also Chapter 11, Ethical Issues for the Primary Care Physician).

## MEDICAL-LEGAL CONSIDERATIONS IN THE DELIVERY ROOM

Prudent physicians who attend deliveries will be familiar with the various clinical challenges they may face in the labor and delivery area. The care provided in the delivery room has lifelong implications. Quickly recognizing and treating potential complications can help ensure an infant's smooth transition to extrauterine life. Although a PCP will generally not be held to the same standard of care as that of a neonatologist, merely taking call coverage for labor and delivery mandates that the pediatrician be knowledgeable and experienced in the management of common complications of parturition. An important facet of this preparation is maintaining training in the neonatal resuscitation program and understanding the potential pitfalls associated with resuscitating and stabilizing a newborn.

As in other areas of medicine, appropriate preparation, intervention, and documentation are essential. The pediatrician should be well informed concerning the capabilities of the birthing facility and the training of the personnel, given that approximately 10% of newborns require resuscitation after birth. Although most newborns who will require resuscitation can be anticipated based on maternal risks, pregnancy risks, or both, 1% to 3% of low-risk pregnancies will result in an infant who requires resuscitation at birth. If significant pregnancy complications or fetal abnormalities are noted before labor, then the newborn should be delivered at a facility that offers comprehensive care for the newborn. Primary care physicians should ask themselves a series of questions. Can this facility handle this delivery? Are the appropriate equipment and properly trained personnel available? What will be the course of action if the newborn has complications that cannot be addressed at the delivering facility? If circumstances permit, the pediatrician may consult with the woman's obstetric caregiver to convey the concerns for the soon-to-be-born infant. If time permits and the safety of the mother and fetus are not compromised, maternal transport to a facility offering a higher level of care may be possible. In cases in which this transfer is not practical, the pediatrician should consider notifying the neonatologist at the affiliated regional perinatal center for assistance and preparation for transport should the newborn require specialized or neonatal intensive care.

Primary care physicians should immediately familiarize themselves with the labor and delivery room area of any hospital they will be covering. Inadequate resuscitation may result from not anticipating the need for resuscitation, lack of appropriate and functioning equipment, presence of unskilled resuscitators, or errors in sequencing resuscitation steps. The last of these factors often includes delays in establishing an airway and initiating positive pressure ventilation, providing chest compressions, and administering the appropriate medications. If the newborn is being delivered through thick meconium and the head is crowning, this is not the appropriate time to discover that the laryngoscope is not functioning. During a delivery room resuscitation, the pediatrician is typically considered to be in charge of the newborn's care and any

resuscitative measures that may be needed. If the pediatrician is not present, then the obstetrician may be deemed responsible for the newborn's assessment and care. The obstetrician may delegate this responsibility to the anesthetist if one is present and if a pediatrician is not available. Much as the general surgeon may be held responsible for the negligent acts of an operating room nurse, the resuscitating pediatrician may be found to have some degree of liability for malfunctioning equipment or poorly trained staff. Because the supervising pediatrician is in a position to coordinate and direct the activities of others, this physician may have liability for persons who are assisting. Miscommunication and a perception of ineptness by close observers may further contribute to a family's decision to file a malpractice claim. The American Academy of Pediatrics (AAP) and American Heart Association Neonatal Resuscitation Program (NRP; [www.aap.org/nrp](http://www.aap.org/nrp)) is placing increasing emphasis on simulation and active measures to improve communication and teamwork.

A great deal of confusion and potential litigation can be mitigated by thorough analysis, intervention, and documentation (Box 85-1). Primary care physicians should document in the newborn's medical record the reasons for which they are attending the delivery, summarize the risks as known to them, and indicate what interventions were initiated and the newborn's response to these interventions. Was the infant delivered by cesarean section? If so, was there an indication such as suspected placental abruption? What is the estimated gestation? Was the mother febrile? How long have the membranes been ruptured? Was the mother treated with antibiotics before delivery? Does other salient maternal medical information exist that may affect the newborn or the resuscitative measures that might be necessary? What was the condition of the newborn at birth? What were the assessments, and what treatments were initiated? How did the infant respond to these interventions? It is also important that the infant be appropriately monitored after resuscitation. If an infant requires positive pressure ventilation, the NRP recommends that the infant be transferred to a place of "continuing observation." This does not necessarily mean the neonatal intensive care unit (NICU), but it should be a monitored area of the nursery.

### BOX 85-1 Strategies to Minimize Delivery Room Risk

- Maintain resuscitation skills; stay current according to the NRP guidelines.
- Know the capabilities of the other members of the resuscitation team.
- Know the capabilities of the facility.
- Document the situation, interventions, responses, and communications.
- Participate in team-based training and simulation activities that foster communication, skill building, and teamwork.



Other professionals may be in the delivery room to assist with airway management. An anesthesiologist or nurse anesthetist may be able to assist if a particular intubation is problematic. Even though the anesthesiologist's primary responsibility is the newborn's mother, fellow professionals often are willing to assist, so long as it does not mean jeopardizing their primary patient. Resuscitation is a team effort, and it is important that duties be defined before the delivery. Team training and debriefing can help to improve communication skills among team members. Debriefing and discussion after a delivery may ensure that families are given consistent information.

Primary care physicians may have their first interaction with a family in the delivery room. The pediatrician who has had prior contact with the family can bring considerable comfort to the family. Without this prior contact, the pediatrician should attempt to establish rapport with the family. Although parent (family)–professional communication under this circumstance can be quite difficult, it is nonetheless critical to helping parents understand the physician's concerns for the newborn and engaging the parents in medical decision-making plans for the newborn regarding ongoing evaluation and treatment. This factor is particularly important if the resuscitative efforts are not successful, in specific cases in which a problem was not anticipated before the newborn's delivery, and when a neonate requires transfer to another facility for care that is unavailable at the birth hospital.

## MEDICAL-LEGAL CONSIDERATIONS IN THE HEALTHY NEWBORN NURSERY

One of the more challenging aspects of general pediatric practice is determining which newborns are well and which ones are sick. The differential diagnosis and initial management of a newborn can be challenging for a seasoned neonatologist or hospital-based pediatrician with years of delivery room and newborn nursery experience who has the benefit of direct observation. Primary care physicians are often at a significant disadvantage because they may not be present in the nursery when a concern arises and receive a call from the nursery nurse or family relaying symptoms. A common factor that poses a liability risk for the health professional involves failure to diagnose a condition for which early diagnosis and treatment may prevent death or long-term morbidity. Among the risks are missed diagnoses of clinically significant congenital heart disease (eg, ductus-dependent cardiac lesions), detection of birth defects that result in early neonatal illness (eg, gastrointestinal or genitourinary obstruction, congenital hydrocephalus) or require timely intervention (eg, congenital glaucoma, retinoblastoma, developmental dysplasia of the hip), suspected brachial plexus injuries or birth trauma and injury that may result in cerebral palsy and brain damage, congenital conditions that may be detected through newborn screening (eg, for hearing loss), hyperbilirubinemia leading to kernicterus, signs and symptoms of hypoglycemia, infection, and seizures. Nurseries should implement oxygen saturation screening to detect cyanotic heart disease as recommended by the AAP. Failure to follow up on prenatal

information that suggests a potential health risk for the infant is an important issue as well. The use of prenatal ultrasonography, although not necessarily an American College of Obstetrics and Gynecology (ACOG) standard of care, has become a routine component of prenatal care nationwide. As a result, many infants are identified prenatally as having a suspected congenital anomaly. The severity of the anomaly will determine the level of hospital in which the infant should be delivered. A high index of suspicion and appropriate follow through may help to prevent an adverse outcome.

Detailed discussion of these problems is contained in subsequent chapters in this section of the text. Appropriate counseling of the family is important, as is early postnursery follow-up care, to assess the infant's continued postnatal adaptation, evaluate for other signs or symptoms, and address parental concerns. The pediatric professional should also work with the nursery staff to ensure that home or public health nurse visits are coordinated, if covered by the family's insurance, to assist the family with the transition home and to provide an objective, interim assessment of the newborn until the first follow-up office visit with the PCP. If this service is not available, then consideration should be given to an earlier follow-up appointment. Physicians should comply with AAP guidelines regarding follow-up appointments for newborns after discharge from the hospital. It is also essential that the physician-led team assess for any barriers to adherence to recommended care and follow-up visits as required (eg, transportation, child care, language or communication, health insurance, access to primary and specialty care). Physician documentation in the newborn's medical record of the clinical concerns, available and pending test results, recommended plan of care, and content of discussions with the family, which includes their concerns, their understanding of their child's issues, and their expressed barriers to complying with the recommended care, can help reduce liability risks. Ideally, discharge instructions that are given to the parents should also be documented in the medical record.

## MEDICAL-LEGAL CONSIDERATIONS IN CARING FOR SICK NEWBORNS

Before PCPs provide care for sick newborns, they must pay close attention to their hospital's policies. Some nurseries will take care of healthy newborns only. If an infant requires supplemental oxygen beyond a defined period (perhaps >4 hours), positive pressure ventilation, or ventilator assistance, then the baby must often be transferred to an affiliated hospital that can provide the scope of care required. Regionalized perinatal care varies throughout the United States. Regional perinatal centers are typically state health department-designated tertiary care facilities that are capable of caring for the sickest and most medically complex women and infants. Within communities, affiliation agreements will exist between the regional center and community hospitals that are able to provide varying levels of high-risk care to pregnant women and sick or premature infants. These relationships are often codified in individual state public health law statutes. The AAP and ACOG *Guidelines for*

*Perinatal Care* are updated regularly and specify the requirements in facilities, personnel, expertise, and equipment for the level (scope) of care a hospital provides.

Four levels of care have been delineated: basic care (level I; routine maternity and newborn care to low-risk infants and women), specialty care (level II; obstetric and newborn services to care for patients with specific high-risk conditions exclusive of the most critically ill, medically complex, and premature infants), and subspecialty care (levels III and IV; the full range of medical care to the most medically complex women and infants). In many states, subspecialty care facilities, or level IV perinatal centers, also serve as regional perinatal centers with quality assurance, education, and outreach responsibilities. However, some states have a plethora of level III facilities, with a smaller number designated as level IV regional perinatal centers in recognition of their unique role in providing the most comprehensive treatments in addition to care coordination, education, outreach, and quality improvement activities. The AAP has a policy statement outlining a uniform definition for levels of care (see Box 85-2).

In many community newborn nurseries, the requirement for intravenous antibiotics will necessitate a transfer to another facility. Within larger hospitals or select institutions that are equipped to provide a broader spectrum of newborn care, transfer to another facility may not be necessary; instead, the newborn may be transferred to a special care nursery or an NICU. Interhospital and regional perinatal affiliation

agreements guide transfer relationships and the level of care required for particular maternal or newborn care issues. In addition to the pediatric care, physician's experience, and degree of comfort in caring for newborns with a variety of medical problems, hospitals have guidelines that delineate the privileges of its physicians and the scope of care that they may provide.

## MEDICAL-LEGAL ISSUES RELATED TO SPECIFIC NEWBORN CONDITIONS

A PCP often supervises the care of a neonate who requires a higher level of care for a single organ system. Perhaps the newborn has hypoglycemia, requires antibiotics, or requires supplemental oxygen for a brief period. Although many PCPs would choose to transfer these infants to a neonatologist, other PCPs are quite comfortable caring for sick newborns in a specialty or level II neonatal unit. Under certain circumstances, a pediatrician may need to care for a very sick baby until the perinatal center's transport team arrives. These clinicians may need to provide ongoing stabilization care, place umbilical lines, and supervise mechanical ventilation for brief periods. In general, most newborns who require prolonged ventilation (>4–6 hours) or support for more than one organ system will be transferred to the care of a neonatologist.

Several common neonatal medical problems pose an increased liability risk for the PCP because of the potential for long-term sequelae and associated morbidities.

### BOX 85-2 AAP Proposed Uniform Definitions for Capabilities Associated With the Highest Level of Neonatal Care Within an Institution

#### Level I neonatal care (well-born nursery) has the capabilities to:

- Provide neonatal resuscitation at every delivery
- Evaluate and provide postnatal care to stable term newborn infants
- Stabilize and provide care for infants born at 35 to 37 wk gestation who remain physiologically stable
- Stabilize newborn infants who are ill and those born at <35 wk gestation until transfer to a facility providing the appropriate level of neonatal care

#### Level II neonatal care (special care nursery) has Level I capabilities plus:

- Provide care for infants born  $\geq 32$  wk gestation and weighing  $\geq 1,500$  g who have physiologic immaturity or who are moderately ill with problems that are expected to resolve rapidly and are not anticipated to need subspecialty services on an urgent basis
  - Provide care for infants convalescing after intensive care
  - Provide mechanical ventilation for brief duration (<24 h) or continuous positive airway pressure or both
- Stabilize infants born <32 wk gestation and weighing <1,500 g until transfer to a neonatal facility

#### Level III neonatal care (NICU) has Level II capabilities plus:

- Provide sustained life support
- Provide comprehensive care for infants born and weighing intensive care <32 wk gestation and weighing <1500 g and infants born at all gestational ages and birth weights with critical illness
- Provide prompt and readily available access to a full range of pediatric medical subspecialists, pediatric surgical specialists, pediatric anesthesiologists, and pediatric ophthalmologists
- Provide a full range of respiratory support that may include conventional and/or high-frequency ventilation and inhaled nitric oxide
- Perform advanced imaging, with interpretation on an urgent basis, including computed tomography, MRI, and echocardiography

#### Level IV neonatal care (regional NICU) has Level III capabilities plus:

- Located within an institution with the capability to provide surgical repair of complex congenital or acquired conditions
- Maintain a full range of pediatric medical subspecialists, pediatric surgical subspecialists, and pediatric anesthesiologists at the site
- Facilitate transport and provide outreach education

## Hypoglycemia

Transient low serum glucose is a common issue in newborns. Primary care clinicians are regularly consulted about newborns with hypoglycemia. Knowledge about the risk factors that predispose a newborn to the development of hypoglycemia and the normal physiologic changes in energy metabolism and glucose utilization occurring after birth prepare the pediatrician to recognize, appropriately evaluate, and manage the newborn with low blood sugar. One of the challenges facing the pediatrician is the lack of a single, uniform definition of hypoglycemia and the influence of gestational and postnatal age in setting a threshold to define *clinically significant hypoglycemia*. Most nurseries have established patient care policies that detail which infants should be screened for low blood sugar, the frequency of testing, and guidance regarding assessment, feeding, and intervention strategies. Studies reporting on the neurodevelopmental outcome of babies who develop symptomatic hypoglycemia have reported conflicting results. A recent systematic review did not produce conclusive recommendations for clinical practice in the care of neonates experiencing hypoglycemia in the first week of life because of a paucity of quality studies and heterogeneity among the patients included in the reported studies. Among healthy, full-term newborns, transient, mild neonatal hypoglycemia has not been shown to affect later neurodevelopment. In 2011, the AAP issued a clinical report that included an algorithm for the screening and subsequent management of neonatal hypoglycemia that includes which infants to screen, when to screen, laboratory data, clinical signs, and management.

The pediatrician should recognize that failure to identify, evaluate, and treat infants at risk for or exhibiting symptoms potentially caused by hypoglycemia and failure to document the rationale for treatment or nontreatment may be a cause for later litigation if the child develops subsequent neurodevelopmental problems. For newborns experiencing clinically significant episodes of hypoglycemia, the full extent of neurologic injury may not be fully recognized for decades. Being aware of the admitting nursery's policies and documenting identified risk factors, glucose screening (and any confirmatory testing) results, and response to feeding or other interventions initiated are important. Communication with the nursery staff and the family is of paramount importance.

## Perinatal Event

Cerebral palsy (CP) is the most common injury claimed as a result of obstetric or neonatal negligence. Frequent causes cited to account for the development of CP include intrapartum or postpartum asphyxia, birth trauma, brain injury caused by intracranial hemorrhage or ischemia, peripartum infection, kernicterus, and hypoglycemia. Injury may result from chronic, subacute, or intermittent hypoxic-ischemic episodes or acute intrapartum events that may occur at various times during gestation, including the antenatal or immediate peripartum period. Substantial in utero injury can also precede the onset of labor. A relatively common occurrence during labor is an *indeterminate*

or *category II fetal heart rate tracing*, previously referred to as a *nonreassuring fetal monitoring strip*. A problematic monitoring strip can be associated with a variety of in utero issues. Fetal head compression, uteroplacental insufficiency, placental abruption, and other events may be reflected in the fetal monitoring strip. That only 12% to 23% of cases of CP diagnosed in term infants were caused by intrapartum or peripartum events has been well described.

From a legal standpoint, the statute of limitations (SOL) can last decades. This means that in many states, a family can file suit against the obstetrician or pediatrician when the child is of college age. Within this context, the test for SOL is generally when a reasonable plaintiff might have discovered the abnormality if they had investigated. In case of neonatal encephalopathy, the full extent of the injuries may not be clear for decades, which is one of the reasons that the SOL can extend so many years in these cases.

A variety of medical issues need to be considered when an infant is born with suspected encephalopathy. Will the infant develop seizures? Was the mesenteric blood flow compromised? If so, then how long should the physician wait before the initiation of enteral feeds? Is the infant at risk for renal or other organ dysfunction? The pediatrician is well advised to consult with a neonatologist about any newborn who is born after a high-risk delivery. Many of these cases result in malpractice litigation. The care provided by the pediatrician will likely be highly scrutinized. Did the neonate sustain additional injury after birth? Was the pediatrician's care contributory to this additional injury? Maintaining good communication with the family is particularly important in these cases. Minimally, the pediatrician should document the consultation with the family, the consultation with the neonatologist, the assessment, and the plan. Making promises to the family concerning outcome is generally not advised, given that many years may pass before the outcome is completely understood. Therefore, any assurances to the family will be based on incomplete information.

The timing of a suspected perinatal event sufficient to cause CP remains an issue of contention. The ACOG and AAP have published criteria to define an acute intrapartum hypoxic event as sufficient to cause cerebral palsy (Box 85-3).

Primary care physicians should exercise care in their medical documentation and refrain from using the term *perinatal asphyxia* unless appropriate criteria exist to support using this term. Although numerous markers of intrapartum asphyxial injury have been identified, no single marker is diagnostic.

Therapeutic hypothermia for the prevention or reduction of perinatal brain injury provided as head cooling or total body cooling has become the standard practice in many regions of the country. Because the current data indicate that the newborn who experiences a moderate degree of encephalopathy will derive maximal benefit if cooling is initiated within 6 hours of birth, the pediatrician must maintain a high index of suspicion for hypoxic-ischemic encephalopathy (HIE). If HIE is suspected, the pediatrician

### BOX 85-3 AAP/ACOG Criteria to Define an Acute Intrapartum Hypoxic Event as Sufficient to Cause Cerebral Palsy

- |  |   |
|--|---|
| <p>1.1: Essential Criteria (must meet all 4)</p> <ol style="list-style-type: none"> <li>1. Evidence of a metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery (pH &lt;7 and base deficit <math>\geq 12</math> mmol/L)</li> <li>2. Early onset of severe or moderate neonatal encephalopathy in infants born at <math>\geq 34</math> weeks' gestation</li> <li>3. Cerebral palsy of the spastic quadriplegic or dyskinetic type</li> <li>4. Exclusion of other identifiable etiologies, such as trauma, coagulation disorders, infectious conditions, or genetic disorders</li> </ol> <p>1.2: Criteria that collectively suggest an intrapartum timing (within close proximity to labor and delivery,</p> | <p>eg, 0–48 hours) but that are nonspecific to asphyxial insults</p> <ol style="list-style-type: none"> <li>1. A sentinel (signal) hypoxic event occurring immediately before or during labor</li> <li>2. A sudden and sustained fetal bradycardia or the absence of fetal heart rate variability in the presence of persistent, late, or variable decelerations, usually after a hypoxic sentinel event when the pattern was previously normal</li> <li>3. Apgar scores of 0–3 beyond 5 minutes</li> <li>4. Onset of multisystem involvement within 72 hours of birth</li> <li>5. Early imaging study showing evidence of acute nonfocal cerebral abnormality</li> </ol> |
|--|---|

From American College of Obstetrics and Gynecology and American Academy of Pediatrics. *Monograph: Neonatal Encephalopathy and Cerebral Palsy: Defining the Pathogenesis and Pathophysiology*. Washington, DC: American College of Obstetrics and Gynecology; 2003.

should consider immediate consultation with an NICU that provides cooling.

#### Role of Umbilical Cord Blood Gases

Within the obstetric and risk management communities, there is an increasing emphasis on the role of umbilical arterial cord blood gas base deficit in timing fetal hypoxic injury. Umbilical arterial or venous blood gases or an early neonatal arterial base deficit (before significant correction of respiratory acidosis or administration of fluid boluses or bicarbonate) may reflect the level of acidosis at the time of delivery. Increasingly, as part of their quality improvement and risk management programs, hospital obstetric services are implementing protocols by which umbilical arterial cord blood gases are routinely obtained for all deliveries (see Chapter 109, Assessment and Stabilization at Delivery). It is important to recognize that impaired cord blood flow (as with an occluded cord) may provide invalid cord gas results. Additionally, even among newborns exhibiting severe encephalopathy, less than 25% of cases are attributable to fetal hypoxemia. After vaginal delivery, the normal mean umbilical arterial base deficit is 4 to 5 mmol/L (if base excess is reported, then the respective values are  $-4$  to  $-5$  mmol/L). The degree of metabolic acidosis that determines the threshold for injury is generally defined as greater than 2 standard deviations from the mean (10–12 mmol/L) and is accepted as greater than 12 mmol/L. Base deficit levels exceeding 12 mmol/L occur in less than 2% of a normal newborn population. Of note, most newborns with a base deficit above 12 mmol/L do not demonstrate long-term neurologic injury. Among newborns experiencing severe metabolic acidosis with base deficits above 16 mmol/L, most die, or if they survive, are healthy.

#### Seizures

A pediatrician may occasionally be notified that a newborn is suspected of having had a seizure. Additionally, apnea in a term baby should be investigated as

a potential seizure. Although a neonatal seizure will often place the newborn outside of the scope of general pediatric care, the pediatrician may be required to provide the initial evaluation and stabilization. Although many infants will continue to breathe during a seizure, the physician should always keep in mind the ABCs (airway, breathing, and circulation). If the newborn does not require airway management or circulatory support, then the pediatrician may give the newborn antiseizure medications. What are the complications of these drugs? Is phenobarbital the first-line drug? If the pediatrician is ordering these medications, then the potential complications, including apnea, should be considered. Incorrect dosing is a potential source of medication error; attention also needs to be paid to the medication order (loading dose or maintenance therapy), route of administration, and dosing interval. Is the seizure a result of HIE, infection, hypocalcemia, or a brain malformation? Is the neonate hypoglycemic? The prudent PCP will deal with the immediate medical needs of the newborn and promptly consult with a pediatric neurologist, a neonatologist, or both. Beyond immediate stabilization, rarely does a general pediatrician provide continuing care for a neonate with seizures in the immediate neonatal period.

#### Brachial Plexus Injuries

Brachial plexus injury (BPI) is relatively common in neonates, with a reported incidence of clinically significant lesions occurring at a rate of 0.5 to 2.6 per 1,000 live births. Not all BPIs are the result of birth-related trauma; intrauterine malpositioning has also been implicated, especially given that BPI has been documented among healthy newborns born atraumatically by cesarean delivery. A BPI is nonetheless an important cause of malpractice litigation against medical caregivers and therapists. The PIAA reports that nearly 60% of BPI malpractice claims result in monetary damages. Litigation may also result from a failure of the pediatric care physician to recognize medical



**BOX 85-4 Potential Sources of Liability Related to Severe Hyperbilirubinemia and Kernicterus**

- Early discharge
- Not recognizing that bilirubin is rising at the time of discharge
- Failure to educate parents about the dangers of jaundice
- Failure to ensure targeted follow-up after nursery discharge
- Failure to treat a newborn with a TSB or TcB in the high-risk zone
- Failure to recognize the severity of hyperbilirubinemia corrected for age in hours, not days, of life (Bhutani curve)
- Failure to recognize risk factors, such as blood group incompatibility, positive Coombs test, excessive bruising, cephalohematoma, family history of G6PD deficiency, East Asian ancestry, possible sepsis, prematurity, exclusive breastfeeding with evidence of excess weight loss/inadequate feeding skills
- Delay in timely or intensive intervention predischARGE or at readmission
- Not recognizing the inaccuracies of visual assessment of jaundice
- Not responding appropriately to parental concerns about jaundice, poor feeding, or changes in infant behavior

G6PD, glucose-6-phosphate dehydrogenase; TcB, transcutaneous bilirubin; TSB, total serum bilirubin.

conditions associated with BPI. These conditions include diaphragmatic paralysis, cervical spine injury, facial paralysis, vocal cord paralysis, shoulder subluxation, and unilateral clavicular and humeral fractures. Therefore, the newborn suspected of having a BPI should have a thorough physical examination and radiographic studies to evaluate the clavicle and humerus on the involved side. Physical findings will guide the need for other studies. In general, the pediatrician should carefully document normal and symmetrical extremity movement and limb posture or position on the initial physical assessment and again at the time of nursery discharge.

Prognosis for recovery in BPI is typically associated with the severity of the infant's motor deficit. Infants who have moderate motor dysfunction at the time of presentation are less likely to have significant permanent weakness than infants with severe motor dysfunction. The period of recovery may continue for up to a year; however, most infants with milder injuries recover within the first few weeks. A recent meta-analysis found that 20% to 30% of infants who have BPI will have residual neurologic deficits. The provision and timing of initiation of treatment are also important considerations and may contribute to parents' decision to initiate a claim. Initial therapy typically involves a period of immobilization to allow for resolution of edema. This therapy is followed by careful passive range-of-motion exercises to prevent contractures and muscle atrophy. Infants who are not improving by 3 to 6 months of age should be referred for further evaluation (electromyographic assessment and neurosurgery for possible nerve transplantation).

Communication between the health professionals and child's parents is critical and can be an effective risk management tool when the physician uses a proactive approach.

- The pediatrician should not assume that all BPIs are the result of birth trauma.
- Family history should be explored if the suspected BPI cannot be explained based on a difficult delivery or intrauterine malpositioning.
- Neonates with suspected BPI should be evaluated for associated conditions.

- Physical assessments should document extremity posture, position, movement, and symmetry.
- Parents should be informed about the range of recovery possible and that long-term sequela may result from the BPI.
- Close follow-up care is important, including appropriate consultations with a pediatric neurologist and a physiatrist, as well as early intervention referrals as appropriate based on state-specific eligibility requirements.

**Hyperbilirubinemia**

Sixty percent of newborns develop clinical jaundice. (See Chapter 99, Neonatal Jaundice, and 170, Jaundice, for discussion on Jaundice.) Consequently, most PCPs treat newborns with elevated serum levels of indirect (unconjugated) bilirubin. The complications of hyperbilirubinemia have been well described. Cases in which an infant is diagnosed with kernicterus often result in multimillion-dollar legal settlements. In April 2001, the Joint Commission for the Accreditation of Healthcare Organizations (now known as the Joint Commission) issued a sentinel alert about the threat posed by kernicterus, a generally preventable condition, to healthy newborns. In the most severe cases, the newborn can sustain permanent neurologic injury or even death. Box 85-4 summarizes the factors that contribute to the risk for severe hyperbilirubinemia and kernicterus. Any of these factors can warrant more aggressive treatment of hyperbilirubinemia.

A recent publication by Beal and associates highlights an increasing challenge confronting physicians who must identify and treat conditions that typically occur in higher frequencies in specific ethnic groups—the increasing number of multiethnic infants born. In this study conducted at the Henry Ford Health System, a major urban medical center serving a large minority population, the investigators found that racial identification in medical records did not completely overlap with the mother's self-report of her infant's race. When given the opportunity to select more than one race for their child, 41% of mothers of interracial infants described their infants as having

other racial ancestry in addition to that of the mother and father. Therefore, the pediatrician should consider exploring the ancestry of a newborn who exhibits clinical symptoms of a condition not common for the child's perceived race or ethnicity.

Another important cause of neonatal hyperbilirubinemia is glucose-6-phosphate dehydrogenase (G6PD) deficiency. Diverse population groups are affected by G6PD deficiency caused by many gene polymorphisms that result in decreased bilirubin conjugation. Population migration has contributed to a worldwide distribution of babies born with hyperbilirubinemia caused by G6PD deficiency. Black newborns are the largest population group affected by G6PD deficiency in North America. There have been case reports of kernicterus caused by severe hyperbilirubinemia in black G6PD-deficient newborns. G6PD deficiency is an X-linked condition and is less frequently considered to be a causative factor in newborn girls with hyperbilirubinemia. However, G6PD-deficient heterozygote girls have been identified, and their neonatal course may be complicated by hyperbilirubinemia.

Hyperbilirubinemia is common, and the pediatrician should remain current with the literature on this topic. If a particular newborn's course is complicated by serum levels that are increasing quickly, as indicated by inadequate response to phototherapy, hemolysis, anemia, altered neurologic examination or mental status, or other significant finding, then the pediatrician should strongly consider consultation with a neonatologist. The management of these cases can be complex, and the potential for liability is extremely high. If a newborn suffers a severe complication of hyperbilirubinemia, then the pediatrician's treatment will likely be scrutinized. How often were bilirubin levels checked? How quickly was therapy instituted? Was a consultation with a neonatologist obtained? The care and treatment of newborns with severe hyperbilirubinemia can lead to litigation, and both the infant and the pediatrician will likely benefit from the input from a neonatologist. The key to protecting the pediatrician and ensuring optimal care for the newborn is risk assessment, with performance of systematic assessments on all newborns before nursery discharge. Nursery protocols should integrate bilirubin measurement, risk factor identification, and appropriate follow-up. If a parent calls the office and is worried that the infant is jaundiced, the infant should be seen in a timely manner.

### **Late Preterm and Early Term Infants**

In recent years, there has been an increasing recognition that infants from 34<sup>0</sup>/<sub>7</sub> to 36<sup>6</sup>/<sub>7</sub> weeks' gestation are physiologically immature and at higher risk for morbidity and mortality than term infants. Indeed, at a 2005 National Institutes of Health workshop, the decision was made to discourage calling such infants "near term" and instead label them "late preterm" to emphasize that these are premature infants at risk for a number of complications. From a liability standpoint, PCPs need to pay very close attention to

this group of infants both in the hospital and after discharge. Possible morbidities include, but are not limited to, respiratory distress, temperature instability, hypoglycemia, apnea, jaundice, and poor feeding. The rise in elective cesarean deliveries has resulted in increased numbers of infants born in the early term period of 37<sup>0</sup>/<sub>7</sub> to 38<sup>6</sup>/<sub>7</sub> weeks' gestation. Mortality and morbidity rates are higher among these infants as well.

There should be awareness of recommendations such as those promulgated by the AAP Committee on Fetus and Newborn. These recommendations are not meant to create a "standard of care" for liability purposes. Nevertheless, failure to follow them without justification may increase the chance of a malpractice lawsuit.

### **Procedures**

Primary care physicians are occasionally required to perform procedures on newborn patients. General rules for procedures involve competence, training, technique, consent, and documentation. In the non-emergency setting, the risks, benefits, and alternatives should be discussed with the parents, and this discussion should be documented. In the emergency setting, PCPs should use their best judgment. Will the newborn be harmed by delaying the procedure until consent can be obtained? If a newborn requires emergency intubation in the delivery room, then obtaining consent from the parents is unnecessary. This procedure generally falls under the *emergency exception to the informed consent doctrine*. Basically, informed consent is not necessary if the physician's intervention is needed on an emergency basis. For example, when called to a delivery that is complicated by meconium-stained amniotic fluid, the prudent pediatrician will explain to the parents that the neonate may be intubated. In many instances, time for such a discussion is not available. In this case, the pediatrician is well advised to put the interest of the baby at the forefront. Proceeding without consent is acceptable if the physician can clearly demonstrate the necessity of the procedure and the emergency nature of the situation.

Procedures should be accompanied by procedure notes. Box 85-5 contains the essential elements of the procedure note. The Joint Commission (see Tools for Practice) mandates a *time out* before any procedure to ensure patient safety. A time out is a planned period of discussion before the procedure is initiated, during which time the team verbally confirms the identification of the patient, the procedure to be undertaken, and the location. A time out can prevent a procedure from being performed on the wrong patient or on the wrong side. Even if the note is added to the chart later, the pediatrician should still document the indications, procedure performed, success or failure, complications, blood loss (if appropriate), and patient tolerance. If a follow-up study, such as a chest radiograph, is indicated, then the procedure note should include this information as well. Even noting that *chest radiograph is pending*

**BOX 85-5 Essential Elements of a Procedure Note**

- Date and time the procedure is performed and the documentation is completed
- Infant identification using 2 forms of identification
- Name of procedure
- Infant's diagnosis and the indication(s) for the procedure
- Consent (if none, then explain reasons for lack of consent)
- Performance of a *time out*
- Documentation of events, including sterile technique and preparation
- Blood loss, if applicable
- Complications (if none, then document)
- Infant's tolerance
- Results of indicated follow-up studies (eg, radiograph to confirm umbilical line position)

documents that the physician understands the importance of verifying the success or failure of the procedure.

**Umbilical Line Complications**

Some PCPs place umbilical lines as part of their routine practice in level II NICUs. Other PCPs will place umbilical lines on rare occasions and only under emergency situations. In either case, the attending physician needs to understand the potential complications from central venous and arterial access. The most common complications involve vasospasm, thromboembolic events, damage to the vessels being cannulated, exsanguination, and infection. Sterile technique should be used in the placement of central vascular access, and this precaution should be included in the pediatrician's procedure note. Line placement should be confirmed by radiograph, and documentation on all subsequent radiographs should note the line placement. Complications, if any, should be promptly evaluated. A referral to a neonatologist and vascular surgeon is likely appropriate for any infant with a complication related to vascular access.

**Transport and Referral**

If a neonate requires a higher level of care, then the pediatrician will generally arrange for a transfer of service or transport to another facility. The referring pediatrician will occasionally also be the admitting physician at the receiving facility. When is the referring pediatrician no longer responsible for the decision-making? Who is liable if the newborn suffers a complication after the receiving facility has been contacted? Who is liable if the newborn is harmed during transport? The answer is based, at least in part, on the role of the respective physicians. Is the referring physician making management decisions while the receiving physician is making

suggestions, or has the receiving physician taken over management of the patient?

In the case of *Sterling v Johns Hopkins*, a woman with severe preeclampsia died after transport, and the husband alleged that negligent telephone advice was given by the receiving facility. After reviewing the facts of this case, the court determined that the receiving physician was largely functioning in the role of a consultant and that the referring physician was responsible for the management decisions that were made.

**MEDICAL-LEGAL CONSIDERATIONS IN OFFICE CARE OF NEWBORNS**

Pediatricians spend up to 40% of their time providing preventive health care to children. During these health supervision visits, they are expected to provide an increasing number of services, from history taking and physical examination to immunizations to assessing developmental milestones to counseling, in a decreasing amount of time. Furthermore, during these visits, physicians need to diagnose medical problems that may not have been present or detectable in the first few days of life. For example, many ventricular septal defects are discovered only in patients older than 1 month, when pulmonary vascular resistance decreases. Failure to diagnose in a timely manner and failure to provide appropriate preventive care may give rise to liability.

Appropriate and timely follow-up of discharged newborns is essential to ensure safe and high-quality care. Several problems may not become apparent until after discharge but require intervention well before the traditional 1- to 2-week visit. This is especially true with late preterm infants, as discussed earlier in this chapter. Hyperbilirubinemia affects most healthy term newborns. Timely intervention is necessary to prevent severe and irreversible neurologic impairment. Primary care physicians who wish to minimize their liability while providing the best care are advised to follow the AAP Subcommittee on Hyperbilirubinemia clinical practice guideline published in July 2004 and updated in October 2009 (see Tools for Practice).

Newborn screening programs exist in every state, and testing is performed on more than 4 million newborns each year. With the introduction of tandem mass spectrometry, the capability now exists to screen for more than 50 disorders from a single blood spot. Presently, wide variability exists among states with regard to the number and type of disorders to be screened. Primary care physicians need to be aware of the specific screening tests mandated in their state. This awareness is particularly important for infants entering the pediatrician's practice who were born in a different state or outside of the United States. Comprehensive information can be found on the Web site of the National Newborn Screening and Genetics Resource Center ([genes-r-us.uthscsa.edu](http://genes-r-us.uthscsa.edu)). Furthermore, PCPs must be certain that organized systems are in place so that

results outside the reference range receive a timely response. Primary care physicians must also be certain that newborns who missed the newborn screen before nursery discharge, who had an inadequate or untestable specimen, or who had their screens obtained before 24 hours of consuming milk (breast milk or formula) receive the appropriate follow-up testing.

A comprehensive approach applies to newborn hearing screening as well. Given that permanent hearing loss is far more prevalent than most other conditions screened, early intervention is key to optimizing the child's functional and educational outcomes. In 2012, newborn screening for critical congenital heart disease (CCHD) was recommended by the US Health and Human Services Secretary's Advisory Committee on Heritable Disorders in Newborns and Children to promote early detection. Strategies have been published that recommend screening for low blood oxygen saturation through the use of pulse oximetry monitoring to detect CCHD in well-infant and intermediate care nurseries. Follow-up care processes must be incorporated into nursery screening programs to assure timely evaluation and intervention for infants who do not pass the screening protocol. Certain abnormalities, such as congenital adrenal hyperplasia, are considered emergencies and require immediate attention. Maintaining a high index of suspicion is key to making the diagnosis in a timely fashion.

Finally, PCPs must consider whether a diagnosis may affect future pregnancies for the parents or other family members. Primary care physicians should also refer the parents for appropriate genetic counseling when necessary. Appropriate preventive care covers a large number of issues that vary based on age. To ensure that necessary topics are covered during a visit, as well as to ensure that appropriate documentation is maintained, PCPs should consider using preprinted structured documentation forms. Physicians may choose to develop these forms themselves or use the forms that are available from the AAP.

## COMMUNICATION ISSUES

Communication is an integral component of providing excellent patient care. This concept is fundamental from a medical-legal standpoint as well as from an ethical perspective. The AAP and the American Board of Pediatrics recognize the importance of interpersonal and communication skills in providing quality patient care. Furthermore, a poor relationship between a patient and a physician is more likely to result in a lawsuit. (Information on communicating with families is contained in Chapter 49, Discussing Serious Symptoms, Results, and Diagnoses With the Patient and Family; and Chapter 9, Partnering With Families in Hospital and Community Settings.)

In addition to communication with the parents, physicians must make every attempt to ensure effective communication with other members of the health care team. Effective communication and care

transition are essential to safe and effective patient care. (See Chapter 7, Planned Coordinated Care to Support the Medical Home; and Chapter 51, Care of Children With Special Health Care Needs).

## PATIENT SAFETY

Errors in patient care are a major problem in health care. A seminal 1999 report of the Institute of Medicine, *To Err Is Human: Building a Safer Health System*, estimated that 98,000 deaths per year may be attributable to medical errors, and the Institute of Medicine demanded a complete shift in the health care culture. Although progress to date has been mixed, significant efforts have been made to improve patient safety. (See Chapter 5, Quality Improvement in Practice.)

When an error does occur, physicians are ethically and legally bound to disclose it to the patient or parent. Additionally, consoling and apologizing to the family can benefit both the patient and the physician and may help preserve the physician-patient relationship. Many states have adopted "apology laws," which prevent certain physician statements from being used at trial.

## MINIMIZING LIABILITY RISK

Approximately 1 in 7 physicians is sued every year. The current process of litigation is expensive, time consuming, and unpleasant. Even though no guarantees exist, methods can be used to minimize the chances of being named in a malpractice suit.

Maintaining competency is an essential task, not only for risk management, but also as an ethical imperative in its own right. Medicine today is a rapidly changing field. The AAP actively assists pediatricians with keeping current and developed a Web site that provides an individualized learning plan ([pedialink.aap.org](http://pedialink.aap.org)).

Pediatrics has become increasingly specialized, and most subspecialty and tertiary care services are organized into a regionalized system. These systems allow all PCPs to maintain professional ties with one another as well as with larger medical centers. This factor becomes important when appropriate consultation, referral, and transport may be necessary to provide optimal care.

A physician is occasionally faced with a particularly rare or challenging patient. In these situations, obtaining assistance is important. Maintaining contact with former attendees and mentors from residency can be helpful. Furthermore, academic centers with training programs will regularly discuss particularly difficult clinical cases during management conferences, morning report, grand rounds, and other meetings.

Keeping parents involved and informed is absolutely essential. Persons who feel uninformed and ignored can easily become frustrated and upset. Furthermore, they will quickly lose trust in the physicians and other clinicians. Mistrust, dissatisfaction,



and anger, combined with an undesirable outcome, can easily lead to a malpractice suit.

Proper documentation is an important component of risk management. One common mantra notes, “If it wasn’t documented, it wasn’t done.” Furthermore, poor documentation reflects poorly on the physician and can make even appropriate care seem to be shoddy and unorganized. Indeed, the PIAA found that of all the closed claims in 2004 involving a problem with the medical record, a payout occurred in 62%. The physician’s notes should be timed and dated, with *late entries* documented as such. All important events should be documented, along with the physician’s thought process and the rationale for the treatments.

Telephone advice can be a significant source of liability in pediatrics. Especially in the immediate newborn period, determining the clinical picture appropriately over the telephone may be especially difficult. When in doubt, the pediatrician should avoid diagnosing over the telephone. Furthermore, all telephone advice should be documented appropriately.

Finally, although large medical malpractice awards generate national headlines, medical practice is generally regulated by each state. State government legislation and case law cover a wide variety of issues that PCPs encounter, from the age of consent to resuscitation standards to professional licensing and discipline. Therefore, all practicing PCPs need to stay up to date on the laws and regulations that affect their practice. This task can be achieved by referring to the AAP Web site and to information disseminated by the physician’s local AAP chapter. The American Association of Family Physicians also provides its members with federal and state updates. In addition, state medical societies are a good source for current rules and regulations guiding practices. Box 85-6 summarizes strategies to minimize liability risk.

#### **BOX 85-6 Strategies to Minimize Liability Risk**

- Keep current through an individualized learning plan.
- Maintain professional ties with a referral medical center.
- Consult with a colleague when encountering a difficult situation; document these communications.
- Ensure that the consulting professional also provides documentation within the infant’s medical record (electronic or faxed consultation).
- Communicate frequently and honestly with parents.
- Document in a timely and thorough manner; include impressions, thought processes, and plan of care, including the plan for follow-up.
- Document telephone advice.
- If uncertainty exists, then do not diagnose over the telephone.
- Be aware of state laws that affect the practice.

## **CONCLUSIONS**

Physicians should make every attempt to understand their rights, duties, and liabilities. This chapter provides an overview of medical-legal considerations in the care of newborn infants.

Pediatricians and other child health care professionals are appropriately concerned about the liability risks they encounter when treating newborns. Nevertheless, many steps can be taken to minimize liability risk. Most of these steps, such as keeping current, documenting appropriately, and focusing on communication and safety, are also prerequisites for practicing good clinical medicine.

## **TOOLS FOR PRACTICE**

### **Practice Management and Care Coordination**

- *Committee on Medical Liability and Risk Management* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/about-the-aap/Committees-Councils-Sections/Pages/Committee-on-Medical-Liability-and-Risk-Management.aspx](http://www.aap.org/en-us/about-the-aap/Committees-Councils-Sections/Pages/Committee-on-Medical-Liability-and-Risk-Management.aspx))
- *Pediatric Visit Documentation Forms* (forms), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Physician Insurers Association of America* (Web site), ([www.piaa.us](http://www.piaa.us))
- *Safer Health Care for Kids* (Web page), American Academy of Pediatrics ([www2.aap.org/saferhealthcare](http://www2.aap.org/saferhealthcare))
- *The Joint Commission* (Web site), ([www.jointcommission.org](http://www.jointcommission.org))
- *Vaccine Administration Record* (forms), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

### **Medical Decision Support**

- *Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents*, 3rd ed (book), American Academy of Pediatrics ([brightfutures.aap.org/index.html](http://brightfutures.aap.org/index.html))
- *Guidelines for Perinatal Care*, 7th ed (book), American Academy of Pediatrics and American College of Obstetricians and Gynecologists ([shop.aap.org](http://shop.aap.org))
- *National Newborn Screening and Global Resource Center* (Web site), ([genes-r-us.uthscsa.edu](http://genes-r-us.uthscsa.edu))
- *PediaLink Online Center for Lifelong Learning* (Web site), American Academy of Pediatrics ([pedialink.aap.org](http://pedialink.aap.org))
- *Strategies for Implementing Screening for Critical Congenital Heart Disease* (article), American Academy of Pediatrics ([pediatrics.aappublications.org/content/128/5/e1259](http://pediatrics.aappublications.org/content/128/5/e1259))
- *Textbook of Neonatal Resuscitation*, 6th ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

## **AAP POLICY**

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## Chapter 86

# PRENATAL PEDIATRIC VISIT

Deborah E. Campbell, MD

A prenatal pediatric visit during the third trimester of pregnancy is recommended for all expectant families as an important first step in establishing a child's medical home. The pediatric prenatal visit is often scheduled between 32 and 36 weeks' gestation. It provides an opportunity for the physician to gather basic information, provide information and advice to the family, identify high-risk situations, and promote parenting skills. A prenatal visit may be particularly valuable for first-time parents, families in which a long interval exists between births, families new to a practice, and families with high-risk pregnancies,

including pregnancy complications, multiple gestation, anticipated neonatal health problems, or a prior adverse pregnancy outcome. In a randomized controlled trial of prenatal pediatric visits among a group of low-income urban families, the prenatal visit was shown to affect important health outcomes, including the breast-feeding decision, satisfaction with the initial physician–parent relationship, and reduced emergency department use. The prenatal visit affords the prospective parents an opportunity to learn about the pediatric physician's office practice, the physician's approach to child health care, and the newborn's initial medical care during the early weeks after the delivery. Alternatively, parents may not have the opportunity to engage with the health professional in a full prenatal office visit, but they may initiate contact with their child's prospective physician by telephone, a brief office visit, or a group prenatal visit.

Group prenatal visits are an effective and efficient way to introduce prospective families to a practice and permit physicians to meet with prospective parents in a relaxed setting that fosters a free flow of information and discussion. If a group prenatal pediatric visit is the venue offered, then the physician should provide individual parents with an opportunity for a private conversation in order to gather individualized information. Many new parents do not meet their child's pediatrician before the baby's birth. No national data exist on the number of expectant families who complete a prenatal visit. A 2007 study conducted by the Institute for Vaccine Safety reported that 78% of the pediatric physicians surveyed offered a prenatal pediatric visit. Among the parents surveyed, 39% of first-time mothers completed a prenatal pediatric visit. Previous studies have reported that 70% to 90% of pediatricians and family physicians offer prenatal pediatric visits, with wide variation (22%–65%) in the reported rates of mothers completing a prenatal pediatric visit. Among urban poor women, rates as low as 5% have been noted for prenatal pediatric visits.

The National Center for Health Statistics reports that less than 75% of pregnant women in the United States begin prenatal care in the first trimester. However, 93% of women will be in care by the second trimester with only 7% of pregnant women receiving late or no prenatal care. Racial and ethnic disparities in the initiation and rates of utilization of prenatal care persist. Black and Hispanic women remain less likely to enter care in the first trimester or to have adequate prenatal care (complete greater than 80% of prenatal care visits for gestational age). Two-thirds of pregnant women attend a childbirth class. Late entry into prenatal care (after the first trimester) increases the risk that a child will not receive all the recommended immunizations and routine well-child care.

The prenatal pediatric visit has 5 goals: to ascertain pertinent aspects of the prenatal history, to review the family history and identify disease risks for future health problems and genetic or chromosomal disorders that may affect the infant, to identify psychosocial factors that may affect family functioning and the family's adjustment to the newborn, to introduce anticipatory guidance about early infant care and infant safety practices, and to provide a foundation on which to build a

family health professional partnership. Box 86-1 lists goals and topics for discussion. Breastfeeding promotion is another key component of this visit, particularly for expectant mothers who have not yet decided on a feeding method or are unsure about the benefits of breastfeeding or their ability to successfully breastfeed their infant. Breastfeeding education provided in the prenatal setting is a proven strategy that increases the initiation of breastfeeding. Figure 86-1 provides a sample format for discussing and documenting elements of the prenatal pediatric visit.

From a financial and practice management standpoint, debate exists within the medical community regarding whether a fee should be charged for the prenatal pediatric visit. Some advocates argue that the prenatal visit is an important marketing tool to building a physician's practice; opponents counter that the professional's time and expertise are valuable and that a charge should be levied for the visit. Individual professionals and practices will need to make their own decisions regarding benefits derived from this visit and whether payment is

appropriate. Many insurance carriers do include a prenatal pediatric visit as a covered benefit for first-time parents, for high-risk pregnancies, and if the family requests a conference.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Caring for Your Baby and Young Child: Birth to Age 5*, 6th ed (book), American Academy of Pediatrics (shop.aap.org)
- *Heading Home With Your Newborn: From Birth to Reality* (book), Jana L, Shu J, American Academy of Pediatrics (shop.aap.org)
- *New Mother's Guide to Breastfeeding* (book), American Academy of Pediatrics (shop.aap.org)
- *You and Your Pediatrician* (handout), American Academy of Pediatrics (shop.aap.org)
- *Where We Stand: Newborn Discharge From Hospital* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/prenatal/delivery-beyond/Pages/Where-We-Stand-Newborn-Discharge-from-Hospital.aspx](http://www.healthychildren.org/English/ages-stages/prenatal/delivery-beyond/Pages/Where-We-Stand-Newborn-Discharge-from-Hospital.aspx))

### BOX 86-1 Visit Goals and Topics to Discuss at the Prenatal Visit

1. Establish parent–physician relationship
  - a. Parent perspectives on what qualities they are hoping to find in their child's health professional and their expectations of the practice and pediatric physician
  - b. Specific parent concerns or questions
  - c. Health professional reflects on own perspectives about pediatric primary care and expectations about the parents' role in their child's care
2. Obtain family and prenatal history
  - a. Parents' ages and occupations, health insurance coverage for parents, and proposed health insurance coverage for the infant
  - b. Specifics of family relationships, cultural beliefs, and parenting beliefs and experiences
  - c. Perceived impact of impending birth on the family and family functioning—family's preparation for the infant (adequacy of resources)
  - d. Family social habits and potential environmental/occupational exposures, including tobacco, alcohol, lead, and drug use
  - e. Family medical and pregnancy history—known hereditary or genetic conditions
3. Provide information and support
  - a. Identify high-risk situations
    - i. Prenatal evaluations, prenatal diagnoses, family genetic history maternal medical conditions that may affect the timing and mode of delivery or the newborn
    - ii. Multiple gestation
    - iii. Previous adverse pregnancy outcome
    - iv. Mental health, illicit drug, prescription, and/or over-the-counter medication use, tobacco use, and domestic violence issues
  - b. Delivery plans
    - i. Parent concerns: *birth plan*
    - ii. Hospital where delivery will occur: whether the practice provides the baby's care or if other physicians will be responsible
      - (1) Rooming-in
      - (2) What will happen if the infant requires specialized or neonatal intensive care
    - iii. Home birth
  - c. Initial newborn care after the birth
    - i. Normal newborn transition including state regulation
    - ii. Initial assessment, including postnatal evaluations of any prenatal test results of concern
    - iii. Preventive care, including immunizations, newborn screening (blood spot, hearing, jaundice, critical congenital heart disease)
  - d. Infant feeding choices, benefits of exclusive breastfeeding, early skin-to-skin care, and initiation of breastfeeding within the first hour after birth
  - e. Circumcision decision
  - f. Anticipated timing of the baby's discharge from the nursery or birthing center; factors that determine when the baby can go home
4. Build parenting skills; anticipatory assessment and guidance about potential for postpartum depression
5. Provide safety and anticipatory guidance including car seat use, avoidance of second-hand smoke exposure, safe sleep practices, sibling responses
6. Schedule visits: hospital care after the delivery, during the first week of life (first postdischarge follow-up visit by 3–5 days of age) and subsequent well-child care visits
7. Discuss how and when the parents should contact the child's pediatric care professional and specific practice routines

**Medical Decision Support**

- *Protocols and Statements* (Web page), Academy of Breastfeeding Medicine ([www.bfmed.org/Resources/Protocols.aspx](http://www.bfmed.org/Resources/Protocols.aspx))
- *Breastfeeding Handbook for Physicians*, 2nd ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

**AAP POLICY**

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**SUGGESTED READINGS**

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**Prenatal Pediatric Visit Checklist**

Date \_\_\_\_\_ Name of physician/provider \_\_\_\_\_  
 Name of mother \_\_\_\_\_ Name of father or partner \_\_\_\_\_  
 Contact information \_\_\_\_\_ Expected date of delivery \_\_\_\_\_ Home birth? Yes ☐ No ☐

History	Pertinent Details	Follow-up and/or Action Needed
Family constellation		
Family and genetic history		
Pregnancy history		
Current pregnancy concerns, including method of conception, pregnancy, and medical complications, fetal growth, prenatal diagnosis		
Prenatal screening and test results		
Environmental concerns, including toxic habits and exposures		
Family resources and identified needs		

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**Figure 86-1** Prenatal pediatric visit checklist.



**Prenatal Pediatric Visit Checklist—continued**

Topics Discussed With Parent(s)	Yes	No	Follow-up and/or Action Needed
Specific parent questions and concerns			
Process for informing the hospital about the parent's choice for the baby's pediatrician. Procedure for notification of the practice or physician after the infant's birth			
Initial newborn care after the delivery, including the labor and delivery and newborn nursery routines, rooming-in, and in-hospital newborn screenings			
Feeding choice; benefits of breastfeeding; strategies to support early breastfeeding success include initiating skin-to-skin care in the delivery room, breastfeeding within the first hour, and rooming-in			
Common newborn concerns: gestational age at delivery (full term, late preterm, preterm), transition after birth, feeding, elimination, jaundice, low blood sugar (if risks are present), presence of birth defects			
Circumcision decision			
Routine newborn screenings			
Family functioning: adjustment to newborn, sibling reactions			
Infant safety			
Office follow-up after nursery discharge, how and when to contact the physician, practice routines and hours of operation, insurance coverage for the infant			
Other issues			

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**Figure 86-1, cont'd**

**Chapter 87****CARE OF THE NEWBORN  
AFTER DELIVERY**

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Parental concerns after the birth of their infant frequently focus on the health and *normality* of their newborn. These concerns may be heightened by a suspected fetal abnormality diagnosed prenatally, a prior adverse pregnancy outcome, or an unfavorable maternal medical condition. The mother's own health and her experiences during the labor and delivery process also affect her response to her newborn and receptivity to information about the baby. Answering questions and addressing parental concerns will reassure parents and lessen anxiety. Knowing that the physician will be available to them, both in the nursery and after the family leaves the hospital, enhances parental satisfaction.

**NEWBORNS WITH SPECIAL HEALTH  
CARE NEEDS**

Parents of babies who are born preterm or at low birth weight or who are found to have a congenital malformation or other condition that requires specialized medical care experience additional stress and anxiety. The families of otherwise healthy term and late preterm babies who develop an illness in the immediate newborn period (eg, transient tachypnea of the newborn, hypoglycemia, infection, hyperbilirubinemia) may exhibit emotional and psychological distress equal to or exceeding that expected from parents of the most seriously ill neonates. Caring for the parents is therefore as important as caring for the newborn, especially if parents are young or have personal health problems, an inadequate personal support network, or apparent limited coping skills.

Helping parents express an understanding of their child's health needs and the effect the illness has on their family is ideal. Addressing any stated (or implied) assertions of guilt by or toward the mother as being responsible for the baby's health issues is particularly important. Searching for a reason why the newborn became sick after birth is common for mothers and families. In some cultures, illness is viewed as punishment for some wrong committed by the mother or another family member. Some parents need to be given permission to ask questions, express fears, and discuss concerns regarding their hopes and dreams for their child and family and whether these hopes and dreams can remain the same or must change. Depending on the circumstances surrounding the birth and the health concerns for the mother and baby, families can be expected to express a wide range of feelings and emotions, including grief, anger, and fear. Typically these concerns must be addressed before the parents and family can engage in significant discussions about the baby and the proposed evaluation and treatment options.

**INITIAL CARE OF THE NEWBORN****Care of the Healthy Newborn After Delivery**

In addition to the initial assessment and any resuscitation or stabilization performed in the delivery room, the early components of newborn care are oriented toward preventing common conditions that can cause early, serious harm to the neonate. Anticipatory care includes preventing hypothermia, recognizing neonates at risk for hypoglycemia or infection, and administering topical eye care and parenteral vitamin K. Discussion of the initial assessment and care of the sick newborn are provided in Chapter 109, Assessment and Stabilization at Delivery; and Chapter 110, Identifying the Newborn Who Requires Specialized Care.

Babies who transition normally can be transported to the nursery after a period of bonding with their parents that includes early skin-to-skin care and the opportunity to breastfeed within the first hour in the delivery room. Infants may also remain with the mother for the entire length of the hospital stay in centers where all care is provided in the mother's multipurpose labor–delivery–recovery–postpartum room. Irrespective of hospital maternity and newborn unit structure, mothers should be encouraged to room-in with their newborns to promote frequent breastfeeding and support early caregiving activities, including adaptation to parenthood by the new parents.

**Breastfeeding**

Initial postnatal care of the neonate should include the opportunity for breastfeeding soon after delivery. Early initiation of breastfeeding, breastfeeding on demand, and rooming-in have been shown in meta-analyses to have a positive effect on mother–infant bonding and breastfeeding in primiparous women, reducing the occurrence of maternal complications, formula use, and early breastfeeding discontinuation. If feasible, breastfeeding should be initiated within 1 to 2 hours after delivery, optimally within the first hour.

A recent caution has been raised regarding the need for observation of the primiparous woman who is breastfeeding for the first time immediately after delivery. Reports from Israel and France describe several infants who experienced cardiopulmonary compromise while breastfeeding, positioned prone on the mother's abdomen. Supporting and sustaining early breastfeeding efforts includes education regarding the newborn's early feeding skills, positioning, latch-on and suckling, and the frequency of demand feeding in the early postnatal period. Mother–baby pairs should be evaluated during the hospital stay to assess the mother's knowledge about breastfeeding and the adequacy of the breastfeeding process and to identify information and resources needed to support breastfeeding after hospital discharge. A particular challenge is encountered when women express the intent to both breastfeed and bottle (formula) feed and desire to implement this practice while in the hospital.

Mothers receiving epidural anesthesia for postoperative pain control do not experience negative effects on breastfeeding if bupivacaine is used or if they are receiving oral ibuprofen. Buprenorphine use has been

shown to affect early breastfeeding. (See Chapter 88, Breastfeeding the Newborn, for more information on initiating breastfeeding.)

### Eye Care

Prevention of ophthalmia neonatorum by providing topical prophylaxis after birth is an effective prevention strategy. Ophthalmia neonatorum is inflammation of the conjunctivae in the first month of life. Ophthalmia neonatorum is classified as 1 of 4 forms: chemical conjunctivitis, bacterial conjunctivitis, chlamydial conjunctivitis, or viral conjunctivitis. The most severe cases of ophthalmic neonatorum are caused by *Neisseria gonorrhea* and *Chlamydia trachomatis* infections. *C. trachomatis* is the most commonly reported sexually transmitted infection in the United States. Fifty percent of infants delivered vaginally will acquire infection. Of those infants who are infected at delivery, 25% to 50% will develop conjunctivitis and 5% to 20% will suffer from pneumonia. Other bacteria also cause conjunctivitis in neonates, including *Haemophilus influenzae*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus*, and other gram-negative organisms. Contamination with these organisms may occur through horizontal transmission routes postnatally and through contact with nursery and hospital staff, parents, and other caregivers. Gonococcal conjunctivitis will typically develop within 48 hours of birth, in contrast to chlamydial conjunctivitis and herpetic conjunctivitis, which more commonly occur at 4 to 7 days and 1 to 2 weeks of age, respectively.

Credé, in 1881, recognized that application of silver nitrate to newborn conjunctivae greatly reduced the incidence of gonococcal ophthalmia neonatorum. The epidemiology of ophthalmia neonatorum changed over the last century, reflecting the increase in *C. trachomatis* infection worldwide. However, the routine installation of antibiotic eye drops combined with improved prenatal care and preventive treatment resulted in a significant decrease in neonatal conjunctivitis, from 10% to 0.3%.

With appropriate prenatal care that includes cervical cultures, the need for routine eye prophylaxis in light of the risk for chemical conjunctivitis as a complication of prophylaxis may be questioned. Bell et al, in a randomized, double-blind study of low-risk infants (those whose mothers were screened for cervical infection with gonococcus and *Chlamydia*) demonstrated that 1% silver nitrate or 0.5% erythromycin ophthalmic ointment decreased the incidence of conjunctivitis (infectious or noninfectious) compared with no prophylaxis. Of the 630 infants randomized to 3 groups, 17% developed conjunctivitis, with 63% of cases in the first 2 weeks. The rates of conjunctivitis were 15% in the no-treatment group, 9% in the erythromycin group, and 8% in the group treated with silver nitrate. The authors concluded that silver nitrate had no harmful effects and may provide some benefit, although the effect on organisms of low virulence was not robust. Most states require routine eye prophylaxis of all newborns, but the data suggest that elective treatment based on maternal prenatal surveillance for infection may be a reasonable alternative. The

American Academy of Pediatrics (AAP) currently recommends universal prophylaxis of all newborns with 1% silver nitrate, 0.5% erythromycin, or 1% tetracycline. A 2.5% povidone-iodine ophthalmic solution is also effective in preventing ophthalmia neonatorum. Chemical conjunctivitis can develop during the first 24 hours of life in response to topical eye prophylaxis with silver nitrate, but the incidence has declined to approximately 1% since the concentration of the silver nitrate solution was reduced to 1%.

### Vitamin K Prophylaxis

Unexpected bleeding in a healthy newborn may be caused by vitamin K deficiency. Prophylactic administration of vitamin K reduces the incidence of bleeding. Parenteral administration of vitamin K has been the standard of care since the 1961 AAP recommendation. Concern about the possible relationship between parenteral vitamin K and childhood cancer led to debate regarding parenteral administration, but more recent research failed to support these earlier claims. The AAP Committee on Fetus and Newborn continues to recommend that all newborns receive vitamin K prophylaxis via the parenteral route.

Vitamin K is an essential component in the synthesis of 4 coagulant proteins—factors II, VII, IX, and X—and neither vitamin K nor these factors cross the placenta efficiently. At birth the fetal levels of these clotting factors and levels of protein C and protein S are approximately 50% of adult levels. This circumstance, combined with a sterile gut and low levels of vitamin K in human milk, increases the risk for hemorrhage in the newborn.

Hemorrhagic disease of the newborn, also referred to as vitamin K deficiency bleeding (VKDB) occurs in 3 forms: early (first 24 hours), classic (days 2–7 of life), and late (after 1 week of age). Bleeding in the first hours of life is frequently associated with maternal use of drugs such as anticoagulants, barbiturates, carbamazepine, phenytoin, and some cephalosporins, as well as tuberculostatic agents such as rifampicin and isoniazid. Risks to the neonate at this time are intracranial hemorrhage and gastrointestinal bleeding.

During the first week newborns with the classic form of VKDB may develop prolonged bleeding during and after circumcision, cord separation, or phlebotomy. The incidence of classic VKDB is approximately 0.25% to 1.7%, whereas late VKDB, occurring from week 2 through 12, has an incidence of 4.4 to 7.2 per 100,000 live births. Late-onset VKDB occurs primarily among exclusively breastfed infants who have not received adequate vitamin K and in infants who have underlying diseases such as biliary atresia, cholestatic jaundice, or malabsorption syndromes. Late-onset VKDB can cause cerebral hemorrhage with devastating sequelae.

Inception of vitamin K prophylaxis worldwide has greatly reduced the incidence of classic VKDB. Controversy regarding the route of administration has led to development of alternative regimens. The disadvantages of intramuscular vitamin K include local trauma, increased cost, and concern about increased levels of the vitamin potentiating the risk of childhood cancer. Oral preparations are less costly but may be

difficult to administer properly. When a single dose of oral vitamin K is given, the incidence of classic VKDB is nil, with a concomitant reduction in late VKDB from 4.4 to 7.2 per 100,000 live births to an incidence of 1.4 to 6.4 per 100,000. However, parenteral vitamin K prophylaxis prevents both classic and late VKDB, except for those newborns with rare severe malabsorption syndromes.

In 1990, 2 studies reported from Bristol, England, suggested an association between parenteral vitamin K administration and childhood cancer. Golding et al proposed as much as a 2-fold increase in childhood cancer. Subsequent research performed by others has failed to confirm the association. The AAP Vitamin K Ad Hoc Task Force reviewed the Golding study, as well as other contrary research, and concluded that a link between vitamin K administration and childhood cancer was not established. Current recommendations remain unchanged—all newborns receive intramuscular vitamin K at a dose of 0.5 to 1.0 mg. Continued research into the efficacy, safety, and bioavailability of oral preparations and optimal dosing regimens to prevent late VKDB remains an important need.

### PHYSICAL EXAMINATION: HOW MANY EXAMINATIONS ARE NEEDED?

The purposes of the newborn examination are to assess the transition from fetal life to the extrauterine environment, to provide reassurance to parents that their newborn is healthy, and to detect potentially serious conditions in healthy-appearing neonates before discharge from the hospital. However, not all conditions that affect the newborn will be detected in the immediate postnatal period. Routine neonatal examination fails to detect the presence of heart disease in 50% of babies born with a congenital heart defect. In addition, only one-third of infants with congenital cataracts are diagnosed during the course of their newborn nursery stay. This low rate of diagnosis has led some physicians to question the number of assessments that need to be performed before the newborn's nursery discharge and the role of screening tests to assist in early diagnosis of potentially serious health conditions. An evidence review conducted in 1999 found few studies evaluating the efficacy of 1 versus 2 neonatal examinations in detecting congenital anomalies in low-risk, healthy newborns before hospital discharge. One controlled trial did determine that more abnormalities were identified before hospital discharge if 2 examinations were conducted; however, in the group of newborns studied, no difference was noted in specific clinical outcomes evaluated.

Current practice in most US hospitals providing newborn care is for the neonate to undergo at least 2 examinations before nursery discharge. However, the healthy term newborn delivered and discharged home within 24 hours may undergo only a single examination. Neonates whose delivery is attended by a physician will typically have a brief assessment performed in the delivery room and a more comprehensive examination after admission to the newborn nursery. Most births, however, are not attended by a pediatrician.

Therefore most newborns will be examined by a physician within the first 24 hours, with a second examination occurring in preparation for the hospital discharge. Whenever possible, the physician should perform these assessments in the mother's room to facilitate history taking, to provide an opportunity to evaluate parent-infant interactions, and to promote parent involvement. It also affords the physician the opportunity to demonstrate the newborn's abilities, answer parent questions, discuss any variations or abnormalities detected on examination, and provide anticipatory guidance and breastfeeding support.

Discussion about newborn care issues and continuity of care has been shown to enhance maternal satisfaction with early newborn care. Hospitals with rooming-in policies that support complete care delivery in the mother's room facilitate this process. Studies have shown that half of the missed abnormalities were congenital dislocation of the hip. Irrespective of whether the infant is examined once or twice before nursery discharge, a follow-up assessment at 3 to 5 days of age is paramount to ensure that conditions exhibited later during the first week of life are detected so that appropriate interventions can be initiated.

### Glucose Screening

No evidence has been found to justify routine measurement of glucose in appropriately grown, healthy, term neonates. (See Chapter 105, Transient Metabolic Disturbances in the Newborn.) A normal blood glucose level in a neonate during the first days of life may vary from 27 to 108 mg/dL (1.5–6 mmol/L), and approximately 10% of healthy newborns will have a blood glucose level less than 47 mg/dL (2.5 mmol/L) during the first 72 hours of life. Mean blood glucose levels for breastfed infants are slightly lower at 65 mg/dL (3.6 mmol/L) than formula-fed infants at 72 mg/dL (4 mmol/L). In a recent clinical report the AAP Committee on Fetus and Newborn (COFN) noted that current evidence does not support a specific concentration of glucose that can discriminate normal from abnormal or can potentially result in acute or chronic irreversible neurologic damage. However, early identification of at-risk infants (late preterm and term small for gestational age infants and infants of diabetic mothers/large for gestational age infants) with institution of prophylactic measures to prevent neonatal hypoglycemia is recommended. The report provides strategies for screening and management of at-risk neonates within the first 4 hours following birth and for infants between 4 and 24 hours of age. Within the first hour of life asymptomatic, at-risk neonates should breastfeed or formula feed and have their initial glucose screen performed 30 minutes after the feeding. If the initial glucose screen is less than 25 mg/dL (1.4 mmol/L), the asymptomatic, at-risk infant should be fed again and the glucose repeated 1 hour after the second feeding. Management approaches are guided by the presence of clinical symptomatology, specific risks, and glucose levels.

Some nurseries may perform an initial glucose screen on all newborns. Cornblath recommended using an operational threshold of 36 mg/dL (2.0 mmol/L)



for intervention in infants at risk for hypoglycemia, with the goal of raising the blood glucose level above 47 mg/dL (2.6 mmol/L). AAP COFN currently recommends a glucose threshold of 35 to 45 mg/dL (1.94–2.5 mmol/L) in asymptomatic, at-risk infants between 4 and 24 hours of age. The frequency and duration of glucose monitoring for newborns at risk for hypoglycemia typically extends for a period of 12 to 24 hours based on the specific risk factor and the infant's response to feeding. Individual hospital protocols delineate these processes and criteria for transfer of infants to a special or neonatal intensive care unit for intravenous therapy.

### Screening for Congenital Heart Defects

Screening during both the prenatal and the postnatal period to diagnose a variety of conditions with potential short- or long-term consequences for the newborn is increasing in frequency as technology advances and parent advocacy grows. Early identification of potentially life-threatening cardiac defects before the infant develops symptoms is the rationale for implementation of screening for critical congenital heart defects (CCHD). Current guidance supports the examination of a newborn's cardiovascular system with both prenatal ultrasound and physical examination at birth, recognizing that neither screening assessment will identify all newborns with CCHD. For example, predictive value of a heart murmur during the first days of life is reported as 54%. The Secretary of Health and Human Services, with the endorsement of the AAP, now recommends that screening for CCHD with pulse oximetry be included in the uniform newborn screening panel.

Pulse oximetry is recommended as a screening test for the early detection of CCHD based on this assumption that life-threatening heart diseases in newborns may not be detected by physical examination and that many hypoxic heart defects do not have an audible murmur during the early neonatal period. In the US congenital heart defects occur in 9 per 1,000 live births, with approximately 4,800 infants born annually with 1 of the 7 CCHD defects. Development of hemodynamic instability secondary to CCHD leads to multiple organ system compromise, most notably hypoxic-ischemic brain injury. Periventricular leukomalacia has been detected by MRI in up to 39% of neonates with CCHD prior to surgery.

A collaboration of the AAP and the American Heart Association studied the available research addressing the usefulness of pulse oximetry for the detection of CCHD. Techniques and results varied among studies, with some studies demonstrating reasonable rates of detection. Of the infants identified with suspected heart disease, 94% had a structural cardiac lesion (97% specificity), but only 11.4% of these infants had a potentially life-threatening cardiac lesion. Ideally, the rate of false positive results should be minimal to reduce unnecessary echocardiography.

In September of 2011 the HHS Secretary's Advisory Committee on Heritable Disorders in Newborns and Children convened a working group to evaluate and offer strategies for universal newborn screening for CCHD. This group focused on seven specific structural

heart lesions associated with hypoxia: hypoplastic left heart syndrome; pulmonary atresia; total anomalous pulmonary venous return; transposition of the great arteries; tricuspid atresia and truncus arteriosus.

The HHS group published strategies to implement a universal program that includes equipment, training, personnel and specific recommendations using pulse oximetry. This publication provides detailed information and an important screening algorithm for use in nurseries. Sentinel implementation recommendations include targeting healthy newborns, using motion-tolerant pulse oximeters and screening after 24 hours of life. Oxygen saturations should be obtained in both the RIGHT hand and either foot to capture postductal oxygenation. A passing screen should include oxygen saturation of  $\geq 95\%$  in either extremity with  $\leq 3\%$  absolute difference between the upper and lower measurements. If an initial screen finds hypoxia it should be repeated to reduce false positives. Importantly, a saturation of less than 90% requires immediate evaluation. A true positive screen necessitates the exclusion of pulmonary and or infectious causes of hypoxia and diagnostic echocardiogram.

Despite the recommendation of the Secretary of HHS individual states will determine how they will implement pulse oximetry into newborn screening programs. The AAP strongly recommends and supports national screening and surveillance of CCHD to reduce the morbidity and mortality associated with delayed diagnosis.

### Newborn Blood Spot Screening

Newborn blood screening (NBS) is performed on 4 million infants each year in the United States, representing the largest application of genetic testing in medicine. NBS is an essential preventive public-health program to identify disorders that may affect long-term health. Early detection and treatment of a variety of metabolic, genetic, and infectious diseases may lead to a significant reduction in death, disease, and associated disabilities.

NBS began with the pioneering work of Dr Robert Guthrie, who developed a screening test for phenylketonuria by using a drop of blood placed on filter paper. In the succeeding 40 years the technology and scope of screening has led to the ability to test metabolic, infectious, and genetic conditions. In 1990, tandem mass spectrometry (MS-MS) was introduced as a more accurate and expansive mode of testing. MS-MS allows for the detection of more than 30 analyte errors. MS-MS combined with radioimmunoassay, fluoroimmunoassay, enzyme-linked immunosorbent assay, and DNA analysis has greatly expanded NBS potential. Each state public health system has a program to screen, identify, and treat its newborn population. The programs require the involvement of primary-care pediatricians as well as subspecialists. The primary-care physician must be aware of the tests performed, the protocols to repeat testing, and the referral base for infants with positive tests. Great interstate variability exists in the communication systems established between the family of the newborn, the primary-care physician, and the NBS program. Interstate variation also exists in parental education,

NBS consent, and diseases screened and tracking of results. Information is available at state public-health Internet sites, the Health Resources and Services Administration, and the National Newborn Screening and Genetics Resource Center.

However, universal standards exist regarding collection and storage of specimens. Only persons who are properly trained should collect specimens. Blood should be drawn from the newborn via heel stick using the medial or lateral aspect of the lower foot with saturation of the filter paper spots. Capillary tube or venipuncture is also adequate, but central lines or umbilical lines should be avoided to prevent false results. The filter paper must be handled carefully because alcohol, iodine, skin oil, petroleum jelly, urine, or feces may contaminate the specimen. Specimens should be collected before nursery discharge and before 72 hours of age.

NBS samples obtained before 24 hours of life can create false-positive results, although the use of MS-MS may eliminate this problem. If a specimen is collected before 24 hours, then a second specimen should be obtained by 7 days. If a neonate is to receive a blood transfusion, then the NBS sample must be drawn before blood is given and repeated 2 months later. Premature and low-birth-weight newborns may have false-positive results on several of the routine NBS tests, such as those for thyroid function, congenital adrenal hyperplasia, tyrosinemia, and galactosemia. Experts recommend that preterm, low-birth-weight, and very sick neonates be retested later, at 2 weeks of age or before discharge from a neonatal intensive care unit. Filter-paper specimens should dry for at least 3 hours in room air before placement in transport envelopes. The samples should be kept from heat and humidity, given that these environmental conditions may denature enzymes to create false results. All specimens are sent to regional, centralized laboratories where strict standards and controls must be maintained. The hospital of origin and, ideally, the medical home of the infant must be identified so that re-evaluation and intervention for a positive test may happen rapidly and efficiently.

The AAP Task Force on Newborn Screening has made a series of recommendations summarized in the 2000 report *Serving the Family From Birth to the Medical Home*. The Task Force emphasized that NBS is not merely a testing program but rather a tracking, diagnostic, therapeutic, and evaluation program. As technology continues to develop, the ability to recognize more potential diseases will be available through both government-sponsored programs and private industry. However, the ability to treat or alter disease may lag behind. The Task Force's key recommendations include (1) developing adequate public health infrastructure to support advanced testing, tracking, informing and treating disease, (2) advancing the involvement of health professionals, families, and the public in development and oversight of NBS, and (3) charging public health agencies with ensuring adequate infrastructure, financing, and policies for adequate surveillance and research related to newborn screening.

With the extensive availability of MS-MS, almost all states have expanded screening programs to

encompass more disorders. In 2005 the AAP endorsed the report of the American College of Medical Genetics (ACMG) recommending that each state screen newborns for a core panel of 29 treatable diseases and an additional 25 conditions that may be detected with the new technologies. The Federal Advisory Committee on heritable Disorders in Newborns and Children also endorsed the ACMG recommendation. In 2008, 21 states and the District of Columbia fully implemented the ACMG panel. There remains interstate variability in newborn screening panels although the potential for a national policy remains in the future. Because of the rapid expansion in technology primary care pediatricians may soon be required to follow and treat diseases for which there is little familiarity. The ACMG supported by the Maternal and Child Health Bureau of Health and Human Services has developed web supported ACT sheets to assist physicians in the immediate response to out of range newborn screen results. These informational sheets are designed to supplement state sponsored information and follow-up. Physicians, in union with state agencies, must develop office policies for recognition, referral, and follow-up of those children identified by newborn screening. There must also be alliance between local, state and national entities to maximize the positive effects on children and families that this program is intended to provide.

### Prevention of Perinatal HIV Transmission

Perinatal HIV transmission remains the primary source of pediatric HIV/AIDS in the United States. The risk of infection for a neonate born to an HIV-positive mother has been reduced from 25% to less than 2% by the use of currently recommended prenatal antiretroviral therapy and obstetric interventions for women who are aware of HIV infection early in pregnancy. The Institute of Medicine and the Centers for Disease Control and Prevention recommend that all pregnant women receive counseling regarding HIV infection and perinatal HIV transmission and its prevention and that HIV testing be performed on entry into prenatal care and again in the third trimester. For women who have not been tested prenatally, rapid HIV testing in the labor and delivery unit can reduce the risk for mother-to-child transmission. HIV prophylaxis, even when begun during labor and delivery, has been shown to reduce mother-to-child HIV transmission by as much as 50%. Two states, New York and Connecticut, perform HIV screening on the newborn blood spot sample.

### Infants at Risk for Sepsis

The approach to the infant at risk for infection is discussed in detail in Chapter 102, The Newborn at Risk for Infection. New guidelines for the evaluation of infants exposed to intrapartum Group B *Streptococcus* were accepted by the AAP in December, 2010.

### Screening for Developmental Dysplasia of the Hip

Developmental dysplasia of the hip (DDH), if untreated, can lead to the development of osteoarthritis, chronic pain, and activity limitations. Although screening for

DDH has been considered a standard of care for over 4 decades, conflicting recommendations remain regarding the evidence that supports the efficacy of screening for DDH and the appropriate screening strategy and treatment options to improve functional outcomes. DDH represents a spectrum of anatomic abnormalities that involve improper alignment or abnormal growth of the femoral head and acetabulum. Reported rates of DDH vary between 1.5 and 20 per 1,000 live births, with 1% to 10% of affected infants having an identifiable risk factor. A recent review of the available evidence by the United States Preventive Services Task Force assessed the efficacy of early detection methods and intervention outcomes.

Breech presentation, family history of DDH, and female gender have been found in fair-quality, case-controlled and observational studies to be most consistently associated with DDH. Among affected infants, only 10% to 27% of patients diagnosed with DDH have been reported to have a risk factor other than female gender. Notably, 60% to 80% of hips assessed as abnormal on the initial newborn examinations are normal on follow-up examinations between 2 and 8 weeks later. Even among neonates with evidence of mild dysplasia on ultrasonography of the hip, clinical resolution occurs between 6 weeks and 6 months of age. Studies have evaluated the efficacy of universal ultrasound screening of newborns for DDH and have found that the evidence to support this recommendation is insufficient. Neither the AAP nor the Canadian Paediatric Society (CPS) recommends routine ultrasonography.

A recent retrospective, observational study reinforces the value of a positive Ortolani sign in a neonate as signifying that the femoral head is not properly within the acetabulum, warranting further evaluation. Current recommendations from the AAP and the CPS are for serial clinical examination of an infant's hips at all periodic health examinations until 12 months of age and a closely monitored period of observation for newborn infants with clinically detected DDH. Positive Ortolani and Barlow tests are indicators for close surveillance by the pediatric physician, with repeat evaluation by 3 weeks of age to document either resolution or persistence of clinical findings. In those infants with spontaneous resolution, imaging, either ultrasonography at 6 weeks of age or x-ray at 4 months of age, should be performed. If the positive findings persist at the 3-weeks visit, then the newborn should be referred to an orthopedist for management. Age-appropriate imaging is also recommended by the AAP for female newborns born breech or with positive family history of DDH. In contrast, the CPS does not recommend imaging for high-risk infants. Because of the biologic nature of DDH, not all dislocatable hips will be detected at birth. If during periodic visits suspicions are raised by the examination or because of parental concern, confirmation by referral to an orthopedist or by imaging is recommended by the AAP.

### Hearing Screening

Over 90% of newborn infants have their hearing screened before nursery discharge. The Joint Committee on Infant Hearing in its 2007 position paper

created guidelines for early hearing detection and intervention programs. A detailed discussion about infant hearing screening is available in Chapter 26, Auditory Screening.

### Umbilical Cord Care

The umbilicus is rapidly colonized after birth. Up to 90% of newborns whose umbilicus is not treated with umbilical antiseptics show evidence of colonization with *S aureus* at the time of nursery discharge. Although infants with heavy bacterial colonization are at higher risk for developing infection, the overall risk of serious infection is less than 1%. Wide variation exists in hospital practices regarding the use of antiseptics in infant cord care. The most commonly used antiseptics are chlorhexidine, triple dye, hexachlorophene, and 70% alcohol. Dry cord care is associated with higher rates of colonization with *S aureus*, whereas chlorhexidine use has been shown to decrease colonization by 33%. Cord separation typically begins by 4 to 6 days of age, with complete separation by 2 weeks of age. Separation takes longer in preterm infants than in term infants. Delayed separation beyond 3 weeks of age should alert the clinician to a possible immunologic defect or anatomic abnormality, such as a patent urachus. Time to cord separation has also been shown to increase with the use of chlorhexidine, alcohol, and repeated applications of triple dye.

Antiseptic agents on the umbilical cord prevent bacterial colonization and possibly infection. However, recent changes in maternity care practice have resulted in reduced bacterial cross-contamination of infants and have made infections a rare event to the extent that many hospitals have adopted dry cord care. A recent Cochrane review concluded that evidence is insufficient to know whether antiseptics have any additional advantage over keeping the cord clean and dry.

### Hepatitis B Virus Vaccine

The acute and chronic consequences of hepatitis B virus (HBV) infection are major health problems. Acute HBV infection can cause liver failure, leading to death, whereas chronic HBV infection can cause long-term liver damage such as cirrhosis and hepatocellular carcinoma. Approximately 12.5 million persons have been infected with HBV during their lifetime, an estimated 1.25 million Americans have chronic, life-long HBV, and 4,000 to 5,000 deaths occur each year in the United States from HBV-related chronic liver disease, such as cirrhosis and liver cancer.

The risk of chronic infection increases with decreasing age; people who are infected in early childhood experience a disproportionately large burden of disease attributable to HBV infection. As many as 90% of newborns exposed to HBV from their mothers at birth become carriers, 30% to 50% children exposed between 1 to 5 years become carriers, and by adulthood the risk of becoming a carrier is 6% to 10%. Immunization with HBV vaccine is the most effective measure for preventing HBV infection and its consequences. Universal vaccination can control vertical and horizontal transmission of HBV and the sequelae of chronic HBV infection. In populations in which the



infection is highly endemic, routine childhood immunization has led to decreases in the prevalence of chronic infection, as well as declines in childhood mortality from hepatocellular carcinoma. In countries with low prevalence rates the benefits of universal neonatal vaccination will not be apparent until 2 to 3 decades later because infection in these countries occur among adolescents and young adults through percutaneous or sexual routes. The Advisory Committee on Immunization Practices expanded its HBV immunization recommendations in 1991 to include all newborns primarily to stop HBV transmission among children and eventually to prevent HBV infections in adolescents and adults. The currently available HBV vaccines are safe and have an efficacy of above 90%. The vaccines are produced by recombinant DNA technology and have been licensed in the United States in single-antigen formulations and as components of combination vaccines. Long-term studies of adults and children indicate that immune memory remains intact for 15 years or more and protects against clinical acute infections and chronic HBV infection, even though anti-hepatitis B surface antigen (HBsAg) concentrations may become low or undetectable over time. Current recommendations are to administer the first dose of the HBV vaccine to every infant at birth and no later than hospital discharge. This policy eliminates the possibility of missed immunoprophylaxis in newborns of mothers who are HBsAg positive secondary to testing errors, ensures that newborns of mothers whose HBsAg status is unknown at delivery receive appropriate immunoprophylaxis, and reduces the risk of early childhood infection. This policy also protects infants who are discharged home to households with occult HBsAg-positive carriers and has been shown to significantly increase infant immunization completion rates.

### Hepatitis B–Negative Mother

Experts recommend that obstetricians and family physicians routinely screen all pregnant women for HBsAg during each pregnancy regardless of the presence or absence of risk factors and regardless of vaccination history. If the mother is HBsAg negative, then a single-antigen HBV vaccine (0.5 mL intramuscularly) should be given to the infant soon after birth and before discharge from the nursery. If the infant weighs less than 2 kilograms, then the first HBV vaccine dose is given at 30 days of chronologic age if medically stable or at hospital discharge before 30 days of chronologic age. After the birth dose the HBV series should be completed with either single-antigen HBV vaccine (Engerix or Recombivax) or a combination vaccine (Comvax or Pediarix). The second dose should be administered at age 1 to 2 months of age and the final dose at age 24 weeks or more of age. Administering 4 doses of HBV vaccine is permissible when combination vaccines are given after the birth dose.

### Hepatitis B–Positive Mother

If the mother is HBsAg positive, then the baby should receive hepatitis B immune globulin (HBIG; 0.5 mL intramuscularly) and HBV vaccine (0.5 mL intramuscularly) at separate sites within 12 hours of birth.

The HBV vaccination schedule should be completed on time, at 1 to 2 months and 6 months for single-antigen vaccine; at 2, 4, and 12 to 15 months for Comvax; or at 2, 4, and 6 months for Pediarix. Post-vaccination testing for HBsAg and anti-HBsAg should be performed at 9 to 18 months of age to assess immunity. If the newborn weighs less than 2 kilograms, then HBIG and HBV vaccine should be given within 12 hours of birth. However, this administration is not counted as the first dose; the full HBV vaccine series should be initiated at 1 to 2 months of age.

### Unknown Maternal Hepatitis B Status

If the mother's HBsAg status is unknown, then HBV vaccine (0.5 mL intramuscularly) should be given within 12 hours of birth. The mother should have blood drawn as soon as possible to determine her HBsAg status. If the mother is HBsAg positive, then the infant should receive HBIG as soon as possible (no later than 1 week). The HBV vaccination series should be completed on time, and postvaccination testing should be done at 9 to 18 months of age. If the newborn weighs less than 2 kilograms, then HBIG and HBV vaccine should be given within 12 hours of birth. This dose is not counted as the first dose, and the full HBV vaccine series is started at 1 to 2 months of age.

Transmission of perinatal HBV infection can be prevented in approximately 95% of newborns born to HBsAg-positive mothers by early active and passive immunoprophylaxis in the newborn by vaccine and HBIG. HBV vaccine alone, initiated at or shortly after birth, is also highly effective for preventing perinatal HBV infections. HBV vaccine is extremely cost effective not only in preventing HBV infection, but also in preventing the sequelae of chronic HBV infection. Therefore the first dose of HBV vaccine should be administered to every newborn at birth and no later than hospital discharge. This approach offers the best opportunity to prevent unrecognized perinatal transmission and to prevent transmission within families caused by unrecognized chronic HBV infection in the household. It places immunization as an early and visible priority for parents and offers added insurance that an overall immunization series will be completed on time.

### Infants Born to Mothers With Thyroid Disease

Neonatal thyroid function and health outcomes are influenced by maternal thyroid disease. Neonatal thyrotoxicosis is a rare condition caused by the transplacental passage of thyroid stimulating immunoglobulins from mothers with Graves disease or, more rarely, Hashimoto thyroiditis. Infants of mothers with Hashimoto thyroiditis should have the routine thyroid-stimulating hormone (TSH) measurement on day 3 or 4 (newborn blood spot screening [NBS]). The reported incidence of neonatal thyrotoxicosis among infants born to mothers with Graves disease is between 8% and 16%. Infants at risk of congenital hyperthyroidism (maternal Graves disease, family history of activating mutations in TSH receptor) should have the following



screening: Newborn screen between 2 and 5 days of age with a repeat screening test between 10 and 14 days of age. If a mother is on antithyroid medication, the infant should have more complete testing between 10 and 14 days of age, including free T4 (fT4), free T3 (fT3) and TSH.

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## Chapter 88

# BREASTFEEDING THE NEWBORN

Lisa Stellwagen, MD; Richard J. Schanler, MD

## INTRODUCTION

Breastfeeding is nature's standard for infant nutrition and optimal health. Scientific evidence supports human milk feeding as important for mother and child. Pediatricians play a key role in supporting breastfeeding beginning at birth.

## BREASTFEEDING RATES IN THE UNITED STATES

In 1999, by mandate of Congress, the Centers for Disease Control and Prevention (CDC) began surveillance of breastfeeding rates through the National Immunization Survey.

The CDC "Breastfeeding Report Card" for the 2013 birth cohort tells us that 77% of all US women initiated breastfeeding, which is below the Healthy People 2020 objective of 82%, but showing steady gains every year. Although this period had the highest rates in recent years, only 37.7% were *exclusively* breastfeeding at 3 months. By 6 months of age only 49% of infants were receiving any human milk, well below the Healthy People 2020 goal of 61% ([www.cdc.gov/breastfeeding/pdf/2013breastfeedingreportcard.pdf](http://www.cdc.gov/breastfeeding/pdf/2013breastfeedingreportcard.pdf)). Considerable disparity exists among racial and ethnic groups. In the 2007 birth cohort, the tabulated data identified that breastfeeding rates for blacks were 60% for initiation and 28% at 6 months. This group, however, had the most rapid gains in breastfeeding rates in recent years (30% increase from 1996 to 2004). Breastfeeding rates for Latino or Hispanic mothers are greater than those of the total US population (approximately 81%). Although well below the national rates, significant increases in breastfeeding rates have also been reported for mothers 20 years of age or younger (60% initiation and 22% at 6 months), primiparous women, participants in the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) (68% initiation and 34% at 6 months), and mothers of low-birth-weight infants. Breastfeeding rates at 1 year of age have only recently been measured. Whereas the Healthy People 2020 goal for 1 year is 34%, the total US rates in 2012 were 27%. In all populations, married, older, and highly educated women not working outside the home were more likely to initiate and sustain breastfeeding for longer durations.

National efforts are being focused on improving breastfeeding rates and programs to support mother and baby after delivery. The CDC are now collecting data on birth hospital indicators; in 2013 only 7% of infants were born in baby-friendly designated hospitals, and 24% of breastfeeding newborns receive formula in the first 2 days of life. Further efforts are being made by CDC to track maternity care practices that can effect mother/infant breastfeeding success; this National Survey of Maternity Practices in Infant

Nutrition and Care (mPINC) is being conducted every 2 years ([www.cdc.gov/breastfeeding/data/mpinc/index.htm](http://www.cdc.gov/breastfeeding/data/mpinc/index.htm)). Lastly, the CDC and Food and Drug Administration (FDA) are collaborating on the Infant Feeding Practices Survey II; this long-term study will follow mother and baby nutrition, infant feeding patterns, and determinants and benefits of breastfeeding ([www.cdc.gov/breastfeeding/data/infant\\_feeding.htm](http://www.cdc.gov/breastfeeding/data/infant_feeding.htm)).

Considerable need to overcome obstacles and continue breastfeeding-promotion efforts still exists to reach and maintain the modest goals set by the US Department of Health and Human Services in its Healthy People 2020 program. This effort is of particular importance for infant and maternal health because the populations at highest risk are the ones with the lowest breastfeeding rates and stand to gain the greatest health and developmental benefits from breastfeeding. The WIC program has made significant strides in increasing successful breastfeeding. Returning to employment or schooling outside the home by the mother is a major negative influence on both initiation and continuation of breastfeeding. National strategies are continuing to foster breastfeeding in the United States. The 2011 US Surgeon General's *Call to Action to Support Breastfeeding* ([www.surgeongeneral.gov/library/calls/breastfeeding/index.html](http://www.surgeongeneral.gov/library/calls/breastfeeding/index.html)) recommended a roadmap to improve support for breastfeeding mothers that focuses on the following areas:

- (1) *Mothers and their families* should be educated on the importance of breastfeeding, and be provided with ongoing support;
- (2) *Communities* must support breastfeeding, provide peer counseling support, and promote breastfeeding through community organizations and media, and remove all commercial barriers;
- (3) *Health care professionals* must adopt evidence-based practices (Baby-Friendly Hospital Initiative), provide health professional education, ensure access to lactation services, and increase availability of banked donor milk;
- (4) *Employers* must provide paid maternity leave and work-site accommodations;

- (5) *Research and surveillance* are needed and must be expanded, should address disparities, and measure the economic effect of breastfeeding; and

- (6) *Public health infrastructure* must demonstrate enhanced national leadership.

The Joint Commission (TJC) recently added the measure of in-hospital exclusive breastfeeding rates as a Perinatal Care Core Measure. TJC also promotes in-hospital breastfeeding to the public in their SpeakUp campaign. Pediatricians and other pediatric health care professionals should work with their hospitals to support successful breastfeeding initiation. (Box 88-1).

## BENEFITS OF BREASTFEEDING FOR THE INFANT

### Protective Effects

Breastfeeding provides significant benefits to both infant and mother (Box 88-2).

Understanding the benefits of human milk requires knowledge of the multitude of factors in mother's milk. Traditionally we have thought of breastmilk as nutrition with protein, fat, carbohydrate, and water as the principal components. But in reality human milk is more like a biologic fluid, containing hundreds of different biologically active factors: hormones, cytokines, growth factors, large amounts of secretory IgA, and numerous live maternal cells. Recent investigation confirms that human milk has probiotic bacteria as well as prebiotic factors that encourage optimal bacterial flora in the gut of the newborn. Indeed, human milk oligosaccharides are abundant and although not digested by the infant, serve to nourish probiotic bacteria. So it is not surprising that breastfeeding confers significant protection from infectious disease and inflammation in the young child. With improved data collection, these benefits have been looked at in a dose-response form, further adding to the evidence that longer periods of exclusive breastfeeding are optimal. The 2012 American Academy of Pediatrics policy statement on breastfeeding provides detailed information on these benefits (Table 88-1).

### BOX 88-1 Pediatrician Role in Breastfeeding Initiation

- Promote breastfeeding as the norm for infant feeding
  - Exclusive breastfeeding for about 6 months
  - Encourage continuing until at least 12 months of age
  - Add complementary foods at about 6 months of age
- Educate parents about the importance of breastmilk for all infants
  - Human milk and its components
  - Benefits of breastfeeding
  - Correct any false beliefs about infant feeding
- Prepare mother for hospital experience and recommend that:
  - Baby goes skin-to-skin at delivery
  - Erythromycin and vitamin K administration are recommended, but can be delayed up to 6 hours to allow for first nursing
- 24-hour rooming in is practiced
- Elective procedures (eg, bathing and circumcision) are delayed until infant is feeding well
- Encourage unrestricted nursing
  - Baby should nurse whenever interested; 8–12 times per day
  - Educate parents about norms in baby feeding, weight, stooling, and voiding
  - Avoid unnecessary supplements or pacifiers
  - Warn parents about common pitfalls
- Avoid any promotion of commercial infant formula or feeding equipment in your hospital or office

### Infectious Disease

Breastfed infants experience infectious illness at a lower rate than formula-fed infants, and the duration and severity of illness are shortened as well. These effects are observed in both developing and industrialized countries. Significant reductions in respiratory illness including hospitalization for lower respiratory tract infection, respiratory syncytial virus (RSV) severity, serious colds, and ear and throat infections are found in breastfed infants. Gastrointestinal tract infections are also greatly reduced, by 64%, in breastfed infants.

### SIDS Reduction

Breastfeeding has been shown in several large studies to be associated with protection against sudden infant death syndrome (SIDS), reducing the risk by half. Instructions to have the infant sleep in close proximity to mother, while avoiding bed sharing or falling asleep with the infant while nursing, should be a part of anticipatory guidance on safe sleep.

### Chronic Disease

Some epidemiological studies suggest that chronic pediatric disorders such as Crohn disease, leukemia,

## BOX 88-2 Rationale for Breastfeeding

### FOR THE INFANT

#### Reduces Acute Disorders

- Diarrhea and gastrointestinal infections
- Respiratory infections and hospitalizations
- Otitis media, acute and chronic
- Urinary tract infection
- Septicemia and bacterial meningitis
- Necrotizing enterocolitis
- Sudden infant death syndrome
- Postneonatal infant mortality

#### Reduces Chronic Disorders

- Insulin-dependent diabetes mellitus (type 1)
- Noninsulin-dependent diabetes mellitus (type 2)
- Obesity and overweight

- Allergy and asthma
- Inflammatory bowel disease (celiac and Crohn diseases)
- Childhood leukemia (acute lymphocytic leukemia and acute myelogenous leukemia)

### FOR THE MOTHER

- Decreases postpartum bleeding
- Facilitates postpartum weight loss
- Reduces stress hormone levels
- Provides contraceptive effect if used exclusively for 4–6 months
- Decreases risk of breast and ovarian cancer
- Decreases risk of type 2 diabetes mellitus
- Decreases risk of cardiovascular complications

Adapted from American Academy of Pediatrics, American College of Obstetricians and Gynecologists. Rationale for breastfeeding: benefits to infants, mothers, and society. In: Schanler RJ, Krebs NF, Mass SB, eds. *Breastfeeding Handbook for Physicians*. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2014.

**Table 88-1** Dose-Response for Beneficial Effects of Breastfeeding

CONDITION	% LOWER RISK	COMMENT	OR	95% CI
Otitis media	50	EBF $\geq 6$ versus 3 mo	0.50	0.36–0.70
Recurrent otitis media	49	EBF $\geq 6$ versus 4–6 mo	0.51	0.28–0.94
Upper respiratory tract infection	70	EBF $> 6$ versus $< 6$ mo	0.30	0.18–0.74
Lower respiratory tract infection	77	EBF 4–6 versus $\geq 6$ mo	0.23	0.07–0.79
Asthma	40	EBF $\geq 3$ mo, positive atopic family hx	0.60	0.43–0.82
Asthma	27	EBF $\geq 3$ mo, negative atopic family hx	0.73	0.60–0.92
RSV bronchiolitis	74	EBF $> 4$ mo	0.26	0.07–0.90
Necrotizing enterocolitis	77	Exclusive human milk diet	0.23	0.51–0.94
Atopic dermatitis	27	EBF $> 3$ mo, negative family hx	0.84	0.59–1.19
Atopic dermatitis	42	EBF $> 3$ mo, positive family hx	0.58	0.41–0.92
Gastroenteritis	64	Any	0.36	0.32–0.40
Inflammatory bowel disease	31	Any	0.69	0.51–0.94
Obesity	24	Any	0.76	0.67–0.86
Celiac disease	52	$> 2$ mo gluten exposure when BF	0.48	0.40–0.89
Type 1 diabetes	30	EBF $> 3$ mo	0.71	0.54–0.93
Type 2 diabetes	40	Any	0.61	0.44–0.85
Leukemia (ALL)	20	$> 6$ mo	0.80	0.71–0.91
Leukemia (AML)	15	$> 6$ mo	0.85	0.73–0.98
Sudden infant death syndrome	73	EBF	0.27	0.24–0.31

Note: Percent lower risk refers to lower risk while breastfeeding compared with feeding commercial infant formula or referent group specified.

ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; CI, confidence interval; EBF, exclusive breastfeeding; hx, history; OR, odds ratio; RSV, respiratory syncytial virus.

From American Academy of Pediatrics Section on Breastfeeding. Breastfeeding and the use of human milk. *Pediatrics*. 2012;129(3):e827–e841.

lymphoma, and celiac disease occur less often among children who were breastfed as infants. Reduction in celiac disease development by as much as 50% occurs in babies who were breastfeeding when they were first exposed to gluten.

### Allergy

Reductions in clinical asthma and atopic dermatitis, especially in children with a family history of allergy, are seen in exclusively breastfed infants.

### Diabetes

Reduced rates of both type I and II diabetes have been reported for breastfeeding infants. Exposure, especially of high-risk individuals, to cow's milk protein early in life may play a role in the development of islet cell autoantibodies.

### Obesity

Obesity rates are lower in breastfed children, but the amount of protection is not clear. Estimates are that breastfeeding in infancy confers a 15% to 30% reduction in adolescent and adult obesity rates. This benefit may be a result of what breastfed infants are fed, but also how they are fed, since bottle-fed infants take in higher volumes and have been found to gain more weight in the first year of life.

### Premature Infants

For the premature infant, human milk protection against necrotizing enterocolitis and improvement in neurodevelopmental outcomes may be of great importance.

### Other Benefits

Maternal-infant bonding is enhanced during breastfeeding. Some studies indicate a dose-response relationship with IQ, the longer the duration of breastfeeding being associated with a higher cognitive score. The positive effects of breastfeeding on subsequent school performance have been reported into adolescence. Visual acuity, particularly in premature infants, seems to be enhanced by breastfeeding compared with formula feeding. Long-chain polyunsaturated fatty acids have been implicated as factors associated with better visual acuity in breastfed infants. The visual acuity of the breastfed infant is the model for studies of long-chain polyunsaturated fatty acid supplementation. Breastfeeding also provides analgesia to infants during painful procedures. Economic models suggest that the magnitude of health benefits is such that if all US mothers exclusively breastfed for 6 months, there could be a cost savings of \$13 billion per year.

## BENEFITS OF BREASTFEEDING FOR THE MOTHER

A tendency exists to assume that only infants and children benefit from breastfeeding. However, there are many positive effects of breastfeeding for the mother as well.

Breastfeeding in the first hour after delivery increases uterine contractility, reducing maternal blood loss and leading to more rapid involution of the

uterus. Postpartum weight loss may be facilitated in breastfeeding women. Several studies indicate that the greatest effect on weight loss occurs when the duration of breastfeeding exceeds 6 months. Psychological advantages to breastfeeding are obvious, given that bonding is fostered and quiet time is enforced on the nursing mother. Human data show decreased levels of adrenocorticotrophic hormone and corticosterone in lactating women. The blunted response of stress hormones may be an adaptive mechanism for the stress of labor and delivery. Exclusive breastfeeding delays the resumption of normal ovarian cycles and the return of fertility in most mothers. As such, the contraceptive effects of breastfeeding contribute globally to increased child spacing. Amenorrhea is most likely to occur in women who are exclusively breastfeeding, particularly in the first 6 months postpartum, which allows for repletion of maternal iron stores and correction of anemia. World epidemiological data indicate that prolonged breastfeeding into the second year, but not exclusively beyond 6 months, prolongs the interpregnancy interval to 1 year, resulting in the birth of the next infant 20 to 24 months after the previous infant. This longer interval may be a factor in reducing infant mortality.

Women who have a cumulative breastfeeding experience of 12 months have a 28% reduction in the rate of premenopausal breast and ovarian cancer. Each year of breastfeeding reduces a woman's risk of breast cancer by 4.3%. Additionally, women with a total lactation experience of 12 to 23 months enjoy additional reductions in hypertension, hyperlipidemia, cardiovascular disease, and diabetes. Losses in bone density (approximately 5%) are seen during lactation, with remineralization occurring during weaning. Researchers have suggested that the repeated cycles of demineralization-remineralization may strengthen bone.

Informing women and their partners that mother and baby benefit greatly from breastfeeding, and that longer periods of lactation may be even more protective, should be part of standard anticipatory guidance.

## SUPPORTING BREASTFEEDING: PRENATAL VISIT

The successful management of lactation begins during pregnancy. The prenatal office visit is an ideal time to encourage breastfeeding and to provide information so families can make an informed choice regarding infant feeding. Although some studies have shown that infant feeding decisions are made before the third trimester, choices may have been influenced by certain misconceptions or fears held by the expectant mother or father, such as fear of inadequate milk supply because of small breast size, possible loss of sexual breast activity during lactation, cosmetic breast changes as a result of lactation, being a failure at breastfeeding, beliefs that breast milk is not rich enough, and difficulties in learning how to breastfeed, as well as disapproval by the spouse, poor public acceptance, and possible loss of freedom or spontaneity. Many women express an intent to combination (breast and formula) feed their infants. This has been shown to shorten the duration of breastfeeding.



Because decisions are generally made early and few women have pediatric office visits prenatally, the early obstetric visit must take advantage of the opportunity to discuss and promote breastfeeding. As such, during the initial breast examination at an early obstetric visit, the mother should be commended on her choice of breastfeeding and reassured that her breasts are normal.

## SUPPORTING BREASTFEEDING: AFTER DELIVERY

While breastfeeding decisions are often made early, these decisions have been shown to be flexible, and ideal hospital support systems, including the Baby Friendly Hospital Initiative, have been successful at increasing breastfeeding initiation rates. The 10 steps that serve as the foundation for the WHO/UNICEF Baby Friendly Hospital Initiative to ensure breastfeeding success in the hospital are outlined in Box 88-3. The early days of lactation are critical to establishing a good milk supply and proper infant feeding. Many mothers who intend to exclusively breastfeed their babies are not successful, and adherence to the 10 steps may help a mother reach her goals. Education of family and staff, encouragement of exclusive breastfeeding, keeping mother and baby together, discouraging unnecessary supplements, provision of community resources, and close follow up of mother and baby after discharge may help to improve breastfeeding outcomes.

### Initiating Breastfeeding

Early initiation of breastfeeding within the first hour after birth should be practiced unless the medical

condition of the mother or infant indicates otherwise. Early nursing in the delivery room is associated with a marked increase in the percentage of mothers who continue breastfeeding at 2 to 4 months postpartum compared with initiation of nursing 2 hours after birth. Successful lactation management includes encouraging skin-to-skin contact and nursing in the delivery room, and keeping mother and baby together after delivery and during the hospital stay.

Although many infants placed on the mother's chest or abdomen during their usually alert and active first hour after delivery will spontaneously find the mother's nipple and latch on to it, others may require assistance. Eye prophylaxis, vitamin K administration, weighing, and other procedures can be performed after the first breastfeed has been achieved (Vitamin K can be delayed up to 6 hours after birth). Infant bathing is not necessary and may interfere with transition, early breastfeeding attempts, and adaptation of the neonatal skin.

### Position and Latch

The nursing mother can use many different positions. However, regardless of position, she should be comfortable (Figure 88-1). The football or cross cradle positions may provide an advantage for mothers who have undergone cesarean delivery, have a small or premature infant, or an infant who is having trouble latching on. These positions allow for good control of the infant's head, visibility of the infant's mouth on the breast, and avoid contact with mother's incision.

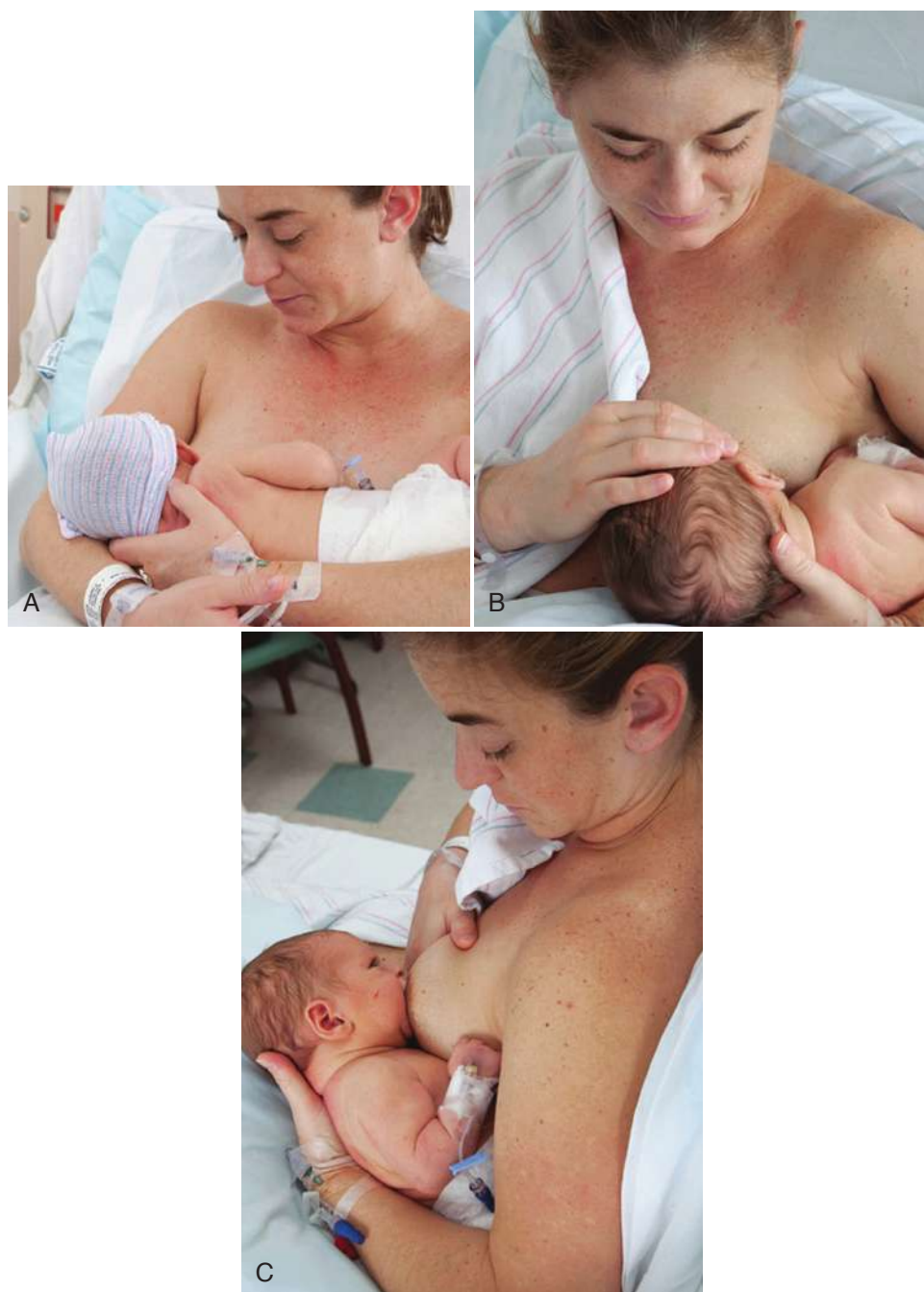
Mothers should understand the importance of achieving a proper latch (Figure 88-2). Note that a mother's fingers should be parallel to the infant's jaws and placed well behind the areola. This hand position allows her to compress her breast to facilitate milk transfer. A link to a complete breastfeeding guide for mothers is included in the Tools for Practice section at the end of this chapter.

If the infant has a deep latch and is sucking well, a mother will be comfortable and milk transfer will be optimized. The buccal mucosa and tongue mold around the breast, leaving no space. The milk is extracted by negative pressure generated from downward movement of the infant's tongue. When the infant is latched correctly, the mother will feel a gentle undulating motion or tugging but no pain with each suck.

If the latch is painful, to prevent additional nipple trauma, the mother can release the suction by inserting her finger gently into the corner of the infant's mouth. After detachment, the nipple should be observed; it should be elongated and have no creases or areas of trauma. Other signs of incorrect latch include dimpling of the infant's cheeks during suckling, clicking noises, lips curled inward, frequent movement of the infant's head, lack of swallowing, and maternal complaint of pain. New fathers or partners can be helpful in looking for these signs of good positioning and latch. Poor latch-on can eventually lead to nipple trauma, pain, poor milk transfer, poor infant weight gain, and low milk supply.

### BOX 88-3 10 Steps to Successful Breastfeeding

- Step 1: Have a written breastfeeding policy that is routinely communicated to all health care staff.
- Step 2: Train all health care staff in skills necessary to implement this policy.
- Step 3: Inform all pregnant women about the benefits and management of breastfeeding.
- Step 4: Help mothers initiate breastfeeding within 1 hour of birth.
- Step 5: Show mothers how to breastfeed and how to maintain lactation even if they are separated from their infants.
- Step 6: Give newborns no food or drink other than human milk, unless medically indicated.
- Step 7: Practice rooming-in—allow mothers and infants to remain together—24 hours a day.
- Step 8: Encourage breastfeeding on demand.
- Step 9: Give no artificial teats or pacifiers to breastfeeding infants.
- Step 10: Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from the hospital or clinic.



**Figure 88-1** Cross cradle (A) or football (B, C) positions help the mother properly position the infant and visually check the latch. (From *Get Ready to Breastfeed*. UC San Diego Health System Mother's Breastfeeding Guide and Log Book.)

### Signs of Milk Transfer

Once the infant is latched to the breast, suckling begins with rapid bursts and intermittent pauses. This action will assist with stimulating the milk ejection reflex. As milk flow is established, the rhythm of suckling, swallowing, and pauses becomes slower and more rhythmic, approximately 1 suckle or swallow per second. Audible swallowing indicates milk transfer to the infant. Swallowing may be difficult to hear when the newborn is taking small sips of

colostrum, but as milk volume increases, swallowing should be heard easily, sounding like “kuh.” At the end of nursing, the infant will often come off the breast spontaneously and if the feeding is adequate, the infant should seem content. As a mother's milk comes in, she should appreciate that her breasts are heavier and fuller before the feeding begins then softer and lighter after feeding is completed; this difference indicates that her infant has emptied her breasts.



**Figure 88-2** Achieving a good latch is key to the mother's comfort and to milk transfer. Note that the mother's fingers are well back on the breast (A) as the infant gapes wide. Avoiding a shallow latch (B) and aiming for a wide, deep latch (C) is the mother's goal. (From *Get Baby on the Breast / Got It Right?* UC San Diego Health System Mother's Breastfeeding Guide and Log Book.)

### Feeding at the Breast Versus Bottle

A distinct difference exists between tongue and jaw movements of breastfeeding and bottle-feeding infants. In breastfeeding, breathing is coordinated with sucking and swallowing, usually in a 1:1:1 pattern. The rapid flow from a bottle may result in respiratory pause and shortened expiration. A common assumption is that breastfed infants who have difficulty obtaining milk will be more likely to prefer bottle feeding if given the opportunity. Some infants may simply prefer the more rapid, gravity-induced flow from a bottle. Because the introduction of a bottle has the potential to disrupt the development of effective breastfeeding behavior, its use should be minimized until breastfeeding is well established.

### Hunger Cues

Many new parents expect their baby to cry when hungry, so they need to be informed that crying is a late sign of hunger and can result in an infant who is difficult to calm and latch to the breast. Anticipatory guidance and rooming in 24 hours a day allows the parents to notice early infant hunger cues, such as increased alertness, flexion of the extremities, mouth and tongue movements, cooing sounds, rooting, bringing the fist toward the mouth, or sucking on fingers or the hand. Signs of satiety also need to be taught, such as non-nutritive sucking with longer pauses between sucking bursts, self-release from the breast, disappearance of hunger cues, relaxed posture, and sleep.

### Feeding Norms

Colostrum is present in small amounts and an infant may desire to suck for a long time or nurse frequently. A mother should be encouraged to follow her baby's lead and refrain from timing or scheduling feeds. Once her milk is abundant, she should try to offer both breasts at each feeding. Falling asleep after the first breast and refusing the second is normal for a newborn. Allowing an infant to drain the first breast before switching to the other breast is preferable. A feeding should not be interrupted just to switch to the second side. Typically, the infant will spontaneously release the first breast after sufficient milk transfer.

Maternal milk supply evolves over the first days of lactation, and feeding frequency will change accordingly. Infants may be sleepy or hungry during the first 24 hours as they recover from the birth process; less frequent small feedings are often seen. Many infants have a transient neonatal ileus as they initiate feeding, active peristalsis and bowel movements. Parents can be reassured that the gagging, spitting clear mucous, and slight abdominal distention will generally abate by 24 hours. Mothers should be told that infant feeding drives their milk supply, and that after the infant is 24 hours old, 8 to 12 feedings a day will help to ensure good milk volumes (Table 88-2). Mothers who are aware that their milk volume is low the first day and increases step wise over the next few days will have more reasonable expectations regarding infant feeding frequency. Understanding infant hunger cues and preparing parents for disorganized nocturnal behavior ("second night syndrome") on the second or third nights after birth can minimize requests for unnecessary formula. Healthy breastfeeding babies do not need water, glucose water, or formula, and unnecessary supplements can interfere with successful breastfeeding.

### Separation

If mother and baby are separated because of the infant's admission to the neonatal intensive care unit, she will need to begin to express her milk. While hand expression should be taught to all breastfeeding mothers, using a double electric breast pump generally leads to higher milk volumes. Milk expressed by mother can be used to feed the infant and will help her in establishing and maintaining her milk production until baby is ready to breastfeed.

### Pacifiers

The use of pacifiers in the early breastfeeding period has been thought to be associated with shorter breastfeeding duration, although the evidence is still not clear. Avoiding pacifiers and other missed opportunities to breastfeed will help mother and baby get off to the best start. Pacifiers have been recommended to decrease the risk of SIDS and may be introduced after breastfeeding is well established, generally at 4 weeks of age.

Table 88-2 Breastfed Newborns Input/Output Norms

DAY OF LIFE	AGE IN HOURS	MILK VOLUME			# FEEDS	# VOIDS <sup>a</sup>	# STOOLS <sup>a,b</sup>	COLOR OF STOOLS	WEIGHT LOSS NORMS <sup>c</sup>	EXCESS WEIGHT LOSS <sup>c</sup>	SUPPLEMENT VOLUME
		MILK VOLUME PER FEEDING	PER FEEDING (MOTHER'S PERSPECTIVE)	MILK VOLUME PER FEEDING							
1	0-24	0-5 ml	drops		6-8	≥1	≥1	Meconium	Birth weight		5-10 ml
2	24-48	5-10 ml	1 tsp		≥8 <sup>d</sup>	≥2	≥2	Meconium	≤3%	>5%	10-20 ml
3	48-72	10-20 ml	1 Tbsp		≥8 <sup>d</sup>	≥3	≥3	Transitional	≤6%	>8%	20-30 ml
4	72-96	20-30 ml	1 oz		≥8	≥4	≥4	Transitional	≤8% (may gain)	>10%	30-40 ml
5	>96	>30 ml	>1 oz		≥8	≥4-12	≥4-12	Yellow	Baby should gain	>10%	40-50 ml

<sup>a</sup>Infant has 24 hours to void and 48 hours to stool after birth.

<sup>b</sup>There may be a lull in stooling after meconium is cleared while baby waits for increased milk volume.

<sup>c</sup>Weight loss norms and excess weight loss numbers are approximations and may be different for more robust or more vulnerable infants.

<sup>d</sup>Infants may feed very frequently (even hourly for the first few nights) before the milk comes in.



## ASSESSING THE BREASTFEEDING INFANT

### History

Maternal history, delivery, gestational age assessment, and infant growth parameters should be reviewed. Risk factors that might herald lactation problems should be queried (Box 88-4 and Box 88-5).

#### BOX 88-4 Mothers Who May Need Help to Successfully Breastfeed

- Intention to breast and bottle feed
- Lack of family or social support
- Psychological problems
- History of poor breastfeeding experience in the past
- Teen mother or advanced maternal age
- Presence of risk factors for poor or delayed milk production (eg, breast surgery, no breast changes in pregnancy, hypoplastic breasts)
- History of medical problems (eg, diabetes, obesity, hypertension)
- Use of medications that may effect milk production or have potential adverse effects on infant
- Perinatal complications (eg, hypertension, blood loss, infection)
- Cesarean section delivery
- Risk factors for latch problems (eg, flat or inverted nipples)
- Mother-baby separation after delivery

#### BOX 88-5 Infants Who May Need Help to Successfully Breastfeed

##### VULNERABLE INFANT

- Late preterm infants (34–36 weeks gestation)
- Multiple births
- Intrauterine growth restricted infants with low reserve
- Hypotonic infant (eg, trisomy 21, achondroplasia)
- Abnormal oral anatomy (eg, cleft palate, ankyloglossia, micrognathia)
- Resuscitation at birth, poor transition, or prolonged labor

##### MEDICAL COMPLICATIONS

- Hyperbilirubinemia
- Hypoglycemia
- Infection/at risk for sepsis
- Birth trauma
- Excessive weight loss/dehydration

##### SUBOPTIMAL FEEDING IN HOSPITAL

- Failure to latch in first 24 hours
- Poor or uncoordinated suck
- Sleepy or infrequent feeder

### Physical Examination

Physical examination of the infant should include an oral-motor examination, with visual inspection of the palate and lingual frenulum. A digital assessment of suck with a gloved finger is invaluable to detect abnormalities in suction pressure, jaw laxity, or tongue movement. Presence of congenital anomalies, tone abnormalities, torticollis, or other physical factors that could effect feeding capabilities should be noted.

### Weight Loss Norms

All breastfed infants lose weight for several days after birth; indeed, even bottle-fed infants do. While feeding volumes are low for the first 24 to 72 hours, infants have obligatory urinary loss and must eliminate the meconium stool. Exact norms in weight loss vary by feeding method, and studies are complicated by traditions of formula use in newborns. However, a weight loss of 3% per day is deemed normal over the first days, and a total weight loss of 6% to 8% by day of life 3 to 4 is commonly seen. Once mother's milk is abundant (generally after 96 hours), the infant should begin to gain weight, at least 15 to 30 g (0.5–1 oz) per day. At this rate, most breastfed infants will exceed their birth weight by 7 to 14 days and gain 150 to 210 g/week (5–7 oz/week) for the first 2 months.

### Elimination Norms

After the first few days, patterns of stooling and voiding are good indicators of the adequacy of milk intake. Urination may be infrequent at first because of the relative dehydration of the baby, but immature renal concentrating ability may result in a baby continuing to void despite dehydration. Urine may initially be dark or contain uric acid crystals, but by day 4 or 5, an infant should pass 6 or more clear, dilute urines each day. Initial elimination of meconium may be unrelated to feeding, but the transition to breast-milk stool is a key indicator of intake. Once an infant has a good milk intake, the stool will begin to transition in color from black to brown to green and then to yellow seedy stools by day 4 or 5 of life. Anticipatory guidance is helpful because stools of the normal human milk-fed newborn are often loose and may be confused with diarrhea if parents are accustomed to seeing the firm, brown stools typical of formula-fed infants. Parents can be told to watch for minimums of 1, 2, and 3 wet and soiled diapers on day of life 1, 2, and 3, respectively. Thereafter, well-nourished breastfed infants usually pass a medium-sized yellow stool at least 3 to 4 times a day, or as often as with every feeding.

A logbook kept by the mother recording feeding and elimination by the infant in the first few weeks can be helpful (see Tools for Practice for a link to a complete breastfeeding guide and log book).

### Breastfeeding Observation

The physician should observe a feeding if any questions regarding adequacy of feeding exist. Alternatively, a trained lactation specialist should examine these couples to evaluate infant positioning at the breast, the ability of infant to latch, quality of latch, milk transfer, presence of audible swallowing, the anatomic and

**BOX 88-6 The First Postpartum Office Visit: 3 to 5 Days of Age (48–72 Hours After Discharge)****BREASTFEEDING ASSESSMENT**

- How many feedings, voids, and stools in past 24 hours?
- Does newborn need to be awakened to feed?
- Does newborn easily latch on to breast and nurse eagerly?
- Is newborn receiving any supplements?
- How is mother doing, and how is she feeling about breastfeeding?
- Are mother's breasts comfortable?
- Has mother previously breastfed?
- Is mother taking any medication?
- How is mother's nutrition?
- How do family members feel about breastfeeding?

**EXAMINING NEWBORN AND MOTHER**

- Calculate newborn's weight gain or loss since birth.
- Observe breastfeeding.
- Examine mother's breasts or refer for examination, if needed.
- Consider using test weight to estimate volume of milk transferred by newborn if concerns exist.
- Perform routine newborn and oral-motor examination.
- Assess state of hydration.
- Observe for jaundice.

**ANTICIPATORY GUIDANCE**

- Encourage breastfeeding on demand.
- Review normal breastfeeding and elimination patterns.

- Avoid long nighttime intervals without feeding.
- Review safe sleep and SIDS prevention.
- Ensure that infant is taking 400 IU of vitamin D.
- Reinforce the importance of the care of the mother.

**BREASTFEEDING INTERVENTIONS**

- Attempt to determine and treat the cause of inadequate milk supply before supplementing.
- For indicated supplementation, use adequate volume.
- If milk transfer is not optimal, mother should express to provide milk for baby.
- Discuss techniques to progress to exclusive breastfeeding.
- Consider referral to lactation specialist or support group if problems are ongoing.

**CLOSING THE VISIT**

- Congratulate parents on decision to breastfeed their newborn.
- Review some of the benefits of breastfeeding and risks of unnecessary supplementation.
- Remind mother to eat when hungry and drink when thirsty.
- Arrange for appropriate follow-up visit until weight gain is adequate and breastfeeding is going well.

physiologic characteristics of the nipple, maternal responses, and whether the caregiver needs to provide assistance with feeding. The hospital staff should observe and document their own breastfeeding observations in the medical record at least twice daily.

**Discharge From the Hospital**

The newborn infant and mother are often in the hospital 2 days after a vaginal delivery, and 3 to 4 days after cesarean delivery. However, discharge readiness of the infant is an important factor to consider prior to sending the couple home. Infants who have significant risk factors for failed breastfeeding, hyperbilirubinemia, or hospital readmission may need more time in the hospital. Increased attention to the morbidities of readmitted infants has led to recommendations that the infant meet minimal discharge criteria. Further observation may be required if the infant is low birth weight or born late preterm. Suggested criteria relative to breastfeeding include that the mother has the knowledge, confidence, and ability to care for the baby, and that the infant has accomplished the following: 2 successful consecutive feedings, coordination of suck-swallow-breathe during feeds, passed an assessment by trained staff for feeding adequacy, passed at least 1 stool, and has urinated regularly. Prior to discharge, infants should also have an assessment of hyperbilirubinemia risk. Consideration of weight loss criteria for discharge may be important. Infants with excessive weight loss should not be sent home without a detailed feeding plan.

**Post-discharge Assessment and Nutrition****Post-discharge Visit**

This first visit should occur 48 to 72 hours after discharge—at 3 to 5 days of life—and should be used to assess the adequacy of hydration, milk intake, and weight gain, the presence of jaundice, and the state of the mother (anxiety, concerns). Vulnerable infants, including late preterm infants, fragile feeders, and infants with excessive weight loss or jaundice may need to be seen 24 hours after discharge. Breastfeeding should be observed during this first visit if any concerns exist. (Box 88-6 provides a checklist for the first postpartum visit.) Telephone contact should be encouraged if further questions arise. Families should be made aware of the availability of community, office, and hospital lactation resources.

Resources exist to aid the pediatric practice with optimal breastfeeding support. The Academy of Breastfeeding Medicine (ABM) clinical protocol (*The Breastfeeding-Friendly Physician's Office*) has been shown to lead to higher rates of initiation and exclusive breastfeeding, and offers practical steps that can be adopted by a pediatric practice (see Box 88-7). The Safe and Healthy Beginnings Toolkit (referenced in Tools for Practice) provides materials to support breastfeeding in the jaundiced newborn.

**Growth Patterns of Breastfed Infants**

The conclusions drawn from plotting the growth of a breastfed infant on older growth charts may be

### BOX 88-7 Elements of a Baby-Friendly Physician's Office

1. Establish a written breastfeeding office policy.
2. Encourage exclusive breastfeeding.
3. Culturally competent care.
4. Offer a prenatal visit.
5. Collaborate with local hospital and the community.
6. Schedule newborn visit within 48–72 hours and provide access to a lactation consultant.
7. Provide educational resources.
8. Encourage open breastfeeding.
9. Discourage formula marketing.
10. Telephone support.
11. Commend breastfeeding.
12. Recommend exclusive breastfeeding to 6 months of age.
13. Work site lactation policy.
14. Establish community resources.
15. Insurance and billing.
16. Assist with workplace support.
17. Formal staff training and on-site IBCLC services.
18. Mentor health care providers.
19. Data tracking.

IBCLC, International Board Certified Lactation Consultant  
Adapted from Academy of Breastfeeding Medicine Protocol Committee.  
ABM Clinical Protocol #14: Breastfeeding-Friendly Physician's Office, Part 1:  
Optimizing Care for Infants and Children. *Breastfeed Med.* 2006;1:115–119.

erroneous if the chart does not adequately reflect the normal growth of the breastfeeding infant. Newer growth curves for exclusively breastfed infants, developed by the WHO, are available online ([www.cdc.gov/growthcharts/who\\_charts.htm](http://www.cdc.gov/growthcharts/who_charts.htm)).

Growth faltering is a concern when the weight for age (or weight for length) is more than 2 standard deviations below the mean or a weight for age that crosses more than 2 percentile channels downward on the growth chart. The WHO growth curve will assist in evaluating an infant whose growth is questionable. Assessments of milk supply and intake, appropriateness of complementary foods, the feeding environment, and the potential for micronutrient deficiencies (eg, iron, zinc, vitamin D) are all part of the nutritional assessment of the infant with slow weight gain or faltering linear growth. The principles in assessing insufficient milk syndrome should also be considered for these infants (see Primary Insufficient Milk Syndrome section).

#### Duration of Breastfeeding

The AAP recommends that infants be exclusively breastfed for about 6 months, followed by continued breastfeeding as complementary foods are introduced, with continuation of breastfeeding for 1 year or longer as mutually desired by mother and infant.

#### Vitamin D

Exclusive breastmilk feeding, highly prevalent maternal vitamin D deficiency, and recommendations to limit sun exposure in infants have led to an increased incidence of vitamin D deficiency. Recommended supplementation

of all breastfeeding newborns with 400 IU of vitamin D daily should start soon after birth.

#### Iron

Healthy term infants generally have sufficient iron stores to meet their needs until 4 to 6 months of age. Because human milk has low amounts of iron, the AAP recommends that exclusively breastfed term newborns be given an iron supplement of 1 mg/kg/day from 4 months of age until these needs can be met by the intake of complementary foods. Infants who have had blood loss at birth or are otherwise at risk for having low iron stores (late preterm infants, growth restricted infants, infants of diabetic mothers) may need earlier iron supplementation or monitoring of laboratory values to assess iron stores.

#### Complementary Foods

The timing of complementary foods introduction into the diet of the breastfed infant is difficult to define with precision, and indeed a single optimal age for all infants may not exist. The recommendations by the WHO and other organizations for exclusive breastfeeding for approximately 6 months are intended for populations and do not dictate the management for individual infants. The AAP recommends exclusive breastfeeding for about 6 months, while recognizing that some infants are developmentally ready to accept complementary foods before this time. Decisions about introducing complementary foods for individual infants need to be based on several considerations, including birth weight, postnatal growth rates, and developmental readiness. Infants who were born prematurely or small for gestational age may need micronutrients, especially iron and zinc, earlier than would be provided by complementary foods. Delay of introducing complementary foods beyond 6 months is not recommended because of increasing risk of micronutrient deficiencies.

### BREASTFEEDING INITIATION: SPECIAL CIRCUMSTANCES

Most women are able to establish and sustain breastfeeding for an extended period if they are motivated, have support from their families, employers, communities, and the medical system. Women with certain medical and psychosocial conditions may not succeed at breastfeeding, and in rare situations, an infant should not be breastfed (see Box 88-4 and Box 88-5).

#### Breast Size

Breast size is not an indicator of breastfeeding success. Small breast size is not a predictor of lactation failure because most of the breast mass is fat tissue, not glandular tissue. Thus even small breasts should have enough glandular tissue to produce sufficient milk. Breast maldevelopment, such as breast hypoplasia or tubular shaped breasts, has been associated with a high frequency of lactation failure and should prompt close monitoring of infant weight gain.

#### Breast Surgery

Breast surgery, whether for reduction or augmentation mammoplasty, removal of a mass, or as a result of trauma, may be a cause for breastfeeding difficulties. In

general, breast augmentation does not cause problems with the establishment of breastfeeding, unless surgery was performed for breast hypoplasia. Women who have had reduction mammoplasty with repositioning of the areolae and nipples are more likely to have difficulty producing adequate milk because of interruption of the ducts and subsequent blockage of milk flow. Newer surgical techniques may improve outcomes, but these mothers require close observation for milk production and monitoring of infant weight gain and hydration.

### Primary Insufficient Milk Syndrome

Breast enlargement during pregnancy is an important factor in predicting lactation success. Failure of breasts to enlarge during pregnancy often presages lactation failure. Approximately 5% of women will not produce adequate milk, known as *primary insufficient milk syndrome*. Generally, breastfeeding should be encouraged and attempted if the mother so desires. The possibility of difficulty in establishing lactation should be discussed with the mother. Additional assistance, monitoring of infant milk intake or weight gain, judicious use of supplemental feedings, and encouragement should be provided to optimize milk production and appropriate infant growth.

### Human Immunodeficiency Virus and Human T-Cell Lymphotropic Virus

Women in the United States who are infected with HIV or human T-cell lymphotropic virus type 1 should not breastfeed because of the risk of transmission to the nursing infant. In developing countries where infectious diseases and malnutrition are the predominant causes of infant mortality, the health risks of not breastfeeding must be balanced with the risk of HIV acquisition. More recent data suggest beneficial effects of breastfeeding in infants of HIV-positive mothers who are also receiving antiretroviral therapy, but no therapy eliminates the risk of transmission through breastmilk.

### Tuberculosis

Women with active pulmonary tuberculosis should not breastfeed until they have received appropriate antibiotic treatment for approximately 2 weeks and are no longer contagious, as determined by their physician or public health official. Because transmission of tuberculosis is primarily by respiratory tract droplet or airborne transmission, separating mother and baby is of primary importance. Whether the tubercle bacillus actually passes into the milk is unclear; most hospitals allow a mother to provide expressed milk to her infant.

### Varicella-Zoster Virus

Neonates should be given varicella-zoster immune globulin if their mothers develop varicella from 5 days before delivery to 2 days after delivery. These infants are separated from mother until her lesions are crusted over but can receive expressed breastmilk. Varicella vaccine may be given to susceptible breastfeeding mothers if the risk of exposure to natural varicella is high.

### Herpes Simplex Virus

Women with herpetic breast lesions should not breastfeed from the infected side until the lesions have healed, although expressed milk can be given to the infant. Proper hand washing and covering the lesions are recommended to prevent infant infection. Women with genital herpes can breastfeed.

### Hepatitis B

Breastfeeding by women who are hepatitis-B surface antigen-positive does not alter the risk of infant infection. Infants born to known hepatitis B-positive mothers should receive both hepatitis B vaccine and hepatitis-B immune globulin within 12 hours after birth. There is no need to delay breastfeeding for infant immunization.

### Hepatitis C

Hepatitis C virus and hepatitis C antibody have been detected in human milk. Infant acquisition of the virus through breastfeeding has not been reported. Maternal hepatitis C infection is not a contraindication to breastfeeding. Some advise abstinence from breastfeeding if the mother has cracked or bleeding nipples.

### Other Infectious Agents

*Cytomegalovirus* (CMV) may be shed in the milk of seropositive mothers. In healthy term infants, symptomatic CMV disease from transmission through human milk is uncommon. However, premature infants may be at greater risk of symptomatic disease characterized by sepsis-like syndromes. Because human milk is of great importance to the premature infant, most neonatal units continue to use milk of mothers who are known to be CMV positive or who have seroconverted during lactation. Pasteurization of milk may inactivate the virus and freezing may decrease but not eliminate viral content of mother's milk; either process may allow baby continued access to human milk. Long-term follow-up of the few premature infants who were presumed to have acquired CMV postnatally have found no abnormalities in brain imaging, hearing tests, and visual function studies.

*West Nile virus* has been detected in human milk but risks to the breastfed infant are not well understood.

*H1N1* virus in acutely infected women can be spread to infants. The CDC recommends that baby be separated from mother until she is afebrile, but may receive her expressed milk.

*Brucellosis* may be transmitted in human milk and infants of mothers with untreated disease should not receive human milk.

### Radiologic Procedures

Therapeutic radiographs, CT scans, and MRIs are not a problem for nursing mothers. Common contrast agents including iodinated intravenous agents or gadolinium are not excreted into milk in sufficient amounts to be problematic, and mothers should not be told to pump and dump their milk for these procedures. Mothers receiving diagnostic or therapeutic radioactive isotopes or who have had accidental exposure to radioactive materials should not breastfeed for as long as radioactivity in milk is present.



### Substance Abuse

Women ingesting drugs of abuse (amphetamine, cocaine, heroin, marijuana, phencyclidine) need counseling and should not breastfeed until their systems are free of the abused drugs that may harm the infant. Narcotic-addicted women who are in treatment may be encouraged to breastfeed if they have no other risk factors.

### Alcohol

Changes in infant feeding patterns have been reported in infants soon after mothers have ingested large amounts of alcohol quickly; it is among the few substances that achieves high concentrations in human milk. The AAP recommends mothers limit alcohol to occasional use of no more than 2 ounces of liquor, 8 ounces of wine, or 2 beers, and further recommend that nursing take place after more than 2 hours have elapsed since alcohol intake.

### Cigarette Smoking

Mothers should be discouraged from smoking during lactation. If a mother continues to smoke, breastfeeding should be encouraged for the protective effects in the infant, especially with respect to protection from respiratory illnesses and SIDS.

### Medications

Most medications are compatible with breastfeeding, or, if not compatible, a substitute medication may exist and should be sought.

Half a million pregnant women each year have been found to suffer from a psychiatric disorder. One in 6 pregnant women and up to 20% of postpartum women suffer from depression. Breastfeeding benefits mother and infant, but concerns exist about infant exposure to psychotropic medication. In general, sertraline, paroxetine, and fluvoxamine are felt to be compatible with breastfeeding, although little data exist on long-term effects. Other drugs should be reviewed for safety and alternative medication sought if concerns exist. The National Library of Medicine maintains an updated Web site (LACTMED) providing detailed information about safety profiles of maternal medication and breastfeeding ([toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT](http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT)).

### Cancer Therapy

Women with breast cancer should not delay treatment so they can breastfeed. Depending on the therapy, women receiving antimetabolite chemotherapy may be able to breastfeed by pumping and discarding their milk until the chemical has been cleared after each treatment. Radiation therapy is generally compatible with breastfeeding. Radiation treatment of the breast, however, may significantly damage sensitive breast tissue and be detrimental to future lactation performance of the affected breast.

### Inborn Errors of Metabolism

Infants with classic galactosemia (galactose-1-phosphate uridyl transferase deficiency) cannot ingest lactose-containing milk. Therefore, because lactose is the principal carbohydrate in human and bovine milk,

infants with classic galactosemia should not breastfeed nor receive formula containing lactose.

Infants with other inborn errors of metabolism may ingest some human milk, but this recommendation would depend on the desired protein intake and other factors. Phenylketonuria has been managed with a combination of partial breastfeeding and phenylalanine-free formula. Human milk contains relatively low levels of phenylalanine compared with formula.

## MATERNAL BREASTFEEDING ISSUES

### Nipple Pain

Sore nipples are the most common complaint of breastfeeding mothers in the immediate postpartum period. Early, mild nipple discomfort is common among breastfeeding women. Severe nipple pain, the presence of nipple trauma, pain that continues throughout a feeding, or pain that is not improving at the end of the first week should not be considered a normal part of breastfeeding. If ignored, nipple pain can then lead to other problems, such as engorgement, mastitis, low milk supply, early cessation of breastfeeding, and alterations in maternal mood or sleep.

Improper breastfeeding technique, specifically, poor position and improper latch, is the most common cause of nipple pain in the immediate postpartum period. Infant tongue-tie or generation of excessive suction pressures may also play a role. Limited milk transfer occurs when the infant is attached incorrectly, resulting in poor infant weight gain and impaired milk production. Limiting the time at the breast will not prevent nipple pain. Treatment for nipple pain depends on the underlying cause. Skilled help with position and latch-on are primary interventions. Frenotomy for tongue-tied infants seems to improve pain for many women. Specific infections and dermatoses require directed therapy. Pain relief medications may be needed. If severe trauma exists, then either manually or mechanically expressing milk may be necessary until the tissue has healed well enough to resume breastfeeding. Nipple healing may be hastened if a small amount of breastmilk is applied to the area after a feeding.

### Delayed or Insufficient Milk Production

Abnormalities in milk production, whether in amount or timing, are problematic because they can lead to excessive weight loss in the infant and early weaning. Identification of women who are at high risk for milk delays and close monitoring of infant weight loss can prevent later problems.

Women can have delayed onset of milk production for many reasons. Brief delays are often seen in mothers who are older, obese, diabetic, hypertensive, had cesarean section, have a history of infertility, or have infants who did not nurse well in the early days after delivery. Other risk factors for delayed milk production include higher postpartum fluid balance and postpartum edema. Factors that decrease breast stimulation, such as unnecessary formula supplementation, mother baby separation or missed feedings, can also cause delays. Recent reports have found that as

many as 44% of primiparous mothers have milk delay, although 98% of mothers eventually produce adequate supply by 7 days postdelivery.

Identifying the etiology of the delay and treating the primary problem is key. Initiating human milk expression for infants who are not feeding well, or brief formula supplementation of infant until mother's milk is in may preserve breastfeeding.

Rarely, mothers have primary lactational failure because of inadequate glandular tissue or hormonal factors. Characteristically these women have a lack of breast growth during pregnancy and may have abnormal breast appearance. Mothers who have had breast surgery are also at risk of insufficient milk transfer, especially if afferent nerves or ducts have been severed. Identifying these mothers before infant discharge is important to prevent dehydration and failure to thrive.

Low milk production may also result if infant does not empty the full breast. Treatment in this case involves expressing milk to feed the infant and to stimulate increased milk production by completely emptying breasts. A full or engorged breast leads to accumulation of serotonin, which is a feedback inhibitor of milk production.

The major goal in management for all of these conditions is to increase milk production, improve milk transfer, and most importantly, to adequately feed the baby.

### Engorgement

Physiologic breast fullness occurs because of vascular congestion during milk production. Pathological engorgement is the firm, diffuse, and painful overfilling and edema of breasts usually caused by inadequate milk removal. If left untreated, engorgement may then lead to difficulties in latch or mastitis. Engorgement may also occur later in the course of breastfeeding related to a missed feeding or an abrupt change in feeding frequency. The swelling and tenderness of engorged breasts are bilateral and generalized, and the condition is rarely associated with high fever or systemic symptoms. The primary treatment is frequent and effective milk removal, by baby or mechanical expression.

### Plugged Ducts

A plugged duct is a localized blockage of milk, often characterized by a painful mass in the breast. This lump may decrease in size with nursing. The condition may be caused by an abrupt change in the feeding schedule, inadequate draining of the breast, failure to vary nursing positions, or wearing tight and constricting clothing (such as a poorly fitting under-wire bra). Some anatomic variations may lead to plugged ducts, especially when the condition recurs in the same breast segment. Rarely, what is considered a plugged duct may be a tumor, benign or malignant, that is blocking the duct. Plugged ducts are easily differentiated from engorgement or mastitis and are not associated with fever or other signs of systemic illness. The treatment for plugged ducts is to apply moist heat before feeding and massage the affected area before and during nursing.

### Mastitis

Mastitis is a unilateral bacterial infection of the breast. Mastitis most commonly produces a single area of localized warmth, tenderness, edema, and erythema in 1 breast more than 10 days after delivery. The infection may be accompanied by a sudden onset of breast pain, myalgia, and fever or with influenza-like symptoms such as fatigue, nausea, vomiting, and headache. Milk stasis resulting from engorgement, obstruction of milk ducts from plugged ducts, or a cracked nipple can lead to mastitis. Most of the causative organisms are penicillin-resistant *Staphylococcus aureus*. The treatment of mastitis includes antibiotics for a 10- to 14-day course; additional therapy includes adequate fluid intake, bed rest, and pain control. Breastfeeding should continue during treatment to allow drainage of the infected breast; this does not pose a risk to the infant. Manual expression or a breast pump may be needed to remove the milk from the breast if severe pain precludes breastfeeding. If surgical drainage of a breast abscess is required, interruption of nursing on the affected breast may be necessary for 24 to 48 hours. However, mother should pump that side and continue nursing on the unaffected breast.

## NEONATAL ISSUES AND BREASTFEEDING

### Hypoglycemia

Hypoglycemia is among physicians' most commonly cited concerns regarding breastfed infants, but healthy term infants with normal feeding patterns have adaptations in place to prevent problematic hypoglycemia. Breastfed infants are known to have lower blood glucose and higher ketone levels than formula-fed infants. Minimizing cold stress by encouraging skin-to-skin care and improving milk intake by early and frequent breastfeeding may decrease hypoglycemia in healthy newborns. Infants who are small or large for gestational age, late preterm, or born to diabetic mothers are most commonly affected by hypoglycemia in the normal newborn population. Screening for hypoglycemia is recommended in symptomatic or at-risk infants only. Current recommendations suggest responding to mild hypoglycemia with prompt feeding (breast, expressed milk, or formula) and treatment with intravenous glucose if infant does not respond to feeding or becomes symptomatic. Routine supplementation of healthy, asymptomatic breastfed infants to prevent hypoglycemia is not indicated.

### Excessive Weight Loss

Healthy term exclusively breastfed infants lose an average of 6% of their body weight in the first 2 days of life. Most infants thereafter lose only another 1% to 2% as mother's milk comes in and commonly will start to gain weight on day 4 or 5 of life. Weight loss of 10% can lead to dehydration, hypernatremia, hyperbilirubinemia, and poor feeding. Recent studies show that many exclusively breastfed babies are losing too much weight—up to 19% of newborns had weight loss of 10% or more. Weight loss in the first days are likely multifactorial, and may reflect poor feeding, low milk supply, and excessive maternal and infant hydration, among other causes. Infants who are at risk for excessive weight loss may

show greater loss early; losing 5% of birth weight in the first day predicts an ultimate 10% weight loss. Predictors of excessive weight loss are not surprisingly similar to risk factors for delayed onset of milk production, which is known to happen in as much as 42% of women and increases the risk of excessive weight loss 7-fold in the infant. Poor breastfeeding in the first day of life triples the risk for excessive weight loss. Current trends in maternal medical complications—including obesity, diabetes, older maternal age, multiple births, hypertension, and cesarean section rates of 35%—are leading to an increased prevalence of delayed maternal milk production and perhaps are contributing to more infants with excessive weight loss.

Practical assessment of an infant's weight loss and fluid status while in the hospital involves reviewing correctness of birth weight and daily weights, baby's feeding ability, maternal milk production/breast fullness, and baby's urination and stooling progression, as well as any complicating medical factors. Assessment of milk transfer to the baby by performing a pre- and post-feeding weight can give valuable information to make a proper feeding plan. Initiation of formula supplementation for excessive weight loss, milk delay or infant medical reasons should be done by looking at the whole picture and discussing risks and benefits with the family. Discharging a newborn with excessive weight loss from the hospital should be done cautiously. A baby with weight loss of 10% or more may be hypernatremic and have secondary poor feeding, and may be at high risk for readmission and hyperbilirubinemia. It may be wise to keep the baby another day to demonstrate weight gain, improved feeding behavior, and good milk transfer.

Once the baby begins to gain weight, expect to see 30 g of weight gain per day, although gains of 100 g per day are common when mother's milk is abundant and infant is feeding well. A breastfed infant who weighs less than birth weight at 2 weeks requires evaluation and intervention.

### Supplementation of Breastfeeding

Breastfed newborns may require supplements of expressed milk, pasteurized donor milk, or formula for several medical conditions. Routine supplements without medical indications are not advisable and may lead to early termination of breastfeeding. Supplements of water, glucose water, or soy formulas have no role in the feeding of healthy term newborns. Parents who insist on supplementing their baby, if it isn't necessary, should be informed of the risks, but allowed to make the final decision for their child.

Box 88-8 details some common reasons for supplementation in a checklist form. Using a stamp or checklist in the chart or electronic medical record for the documentation of necessity and method of feeding may decrease the use of unnecessary supplements.

Much controversy exists over the best method to supplement babies that require additional milk. Many hospitals prefer to avoid the bottle and use a cup or tube at the breast. Allowing baby to receive the supplement at the breast controls the flow of milk, keeps baby oriented to mother's breast, and continues her breast stimulation. Some, but not all, infants may become difficult to nurse after using a bottle nipple.

#### BOX 88-8 Indication for Supplementation of Breastfeeding

Supplementation initiated for:

- ☐ Hypoglycemia: glucose \_\_ mg%
- ☐ Excessive wt loss: \_\_% at \_\_ hours of age
- ☐ Failure to latch at \_\_ hours
- ☐ Delayed milk production
- ☐ Jaundice related to decreased intake (per provider)
- ☐ LBW/IUGR requiring caloric supplementation (per provider or LC)
- ☐ Mother/baby separation; please explain \_\_\_\_\_

☐ Maternal insistence

☐ Other

Education provided re: risks & benefits of formula: YES NO

If NO, explain: \_\_\_\_\_

Supplement given (check all that apply)

- ☐ Expressed breastmilk \_\_ ml
- ☐ Pasteurized donor human milk \_\_ ml
- ☐ Commercial infant formula \_\_ ml
- ☐ Tube at breast
- ☐ Finger
- ☐ Cup
- ☐ Bottle

Mother pumping? YES NO

If NO, explain: \_\_\_\_\_

Supplementing infants with small volumes, appropriate for their age and size may prevent overfeeding, development of ileus in the first 24 hours of life, and allow for ongoing frequent feedings. Suggested volumes shown in Table 88-2 are extrapolated from normal maternal milk production values in the first days of lactation. Tailoring the supplement to each infant's caloric and fluid needs is important, and feeding volumes should be individualized.

Supplement nutrient should always be mother's expressed milk if it is available. While some hospitals offer families access to pasteurized donor human milk from a milk bank, supplies are limited, and donated milk from friends and family is discouraged for safety issues. For mothers with delayed or insufficient milk, the temporary use of a standard term (cow's milk based) infant formula is suggested. Families wishing to avoid cow's milk protein formula can use a hypoallergenic or elemental formula if desired.

### Late Preterm Infants

Infants born at 34 to 36 <sup>6</sup>/<sub>7</sub> weeks are known to be at high risk for feeding problems and hyperbilirubinemia. These infants, if they remain with the mother in couplet care (not in the NICU), may be at additional risk of readmission and poor feeding outcomes. Identification of these infants as fragile feeders, and hospital policies that encourage extra breastfeeding



support, observation for feeding success, monitoring for jaundice, and assessment of discharge readiness, may help to decrease these morbidities.

### Jaundice

The association between breastfeeding and jaundice is observed in 2 distinct entities: *breastfeeding jaundice* and *breast milk jaundice* (see also Chapter 99, Neonatal Jaundice).

#### Breastfeeding Jaundice

Breastfed newborns will often be found to have elevated bilirubin in the first week of life. However, we now know that breastfed infants who are feeding frequently and obtaining proper amounts of mother's milk, will have the same bilirubin levels as formula-fed infants. Infants who are not feeding well are at risk for breastfeeding jaundice, which is essentially a form of starvation jaundice. The combination of low milk intake, relative dehydration, delayed passage of bilirubin-rich meconium, and an active enterohepatic circulation of bile may lead to this phenomenon. Infants with increased rates of bilirubin production caused by hemolytic processes (ABO incompatibility or G6PD deficiency), bruising, or ingested maternal blood may be at higher risk. Additionally, infants with immaturities in conjugating bilirubin typically seen in Asian, late preterm, or infants with Gilbert disease may also develop exaggerated jaundice in the early days of life.

Prevention of breastfeeding jaundice is key. Encouraging exclusive and frequent breastfeeding at least 8 to 12 times per day, avoiding water or unneeded formula supplements, and teaching mother proper latch technique may help prevent poor intake, excessive weight loss and jaundice. Infants who have significant hyperbilirubinemia in the early days of life may at times need supplementation to assist in driving bilirubin levels down, but this is not routinely indicated. Misconceptions about breastfeeding jaundice have led physicians in the past to interrupt breastfeeding in this scenario. There is never a need to interrupt breastfeeding; an appropriate response is to optimize intake by improving milk transfer, having mother express milk to increase milk intake, or judicious use of pasteurized donor milk or formula supplements.

Infants who are readmitted to the hospital with excessive weight loss, dehydration, or hypernatremia often have hyperbilirubinemia as well. These infants require prompt treatment of their fluid and calorie deficits as well as management of hyperbilirubinemia. Assessment of milk transfer or consultation with a lactation specialist may help to preserve breastfeeding if an infant is readmitted to the hospital.

#### Breastmilk Jaundice

Breastmilk jaundice is thought to be a normal exaggeration of physiologic jaundice seen in human milk-fed infants. In these infants, serum unconjugated bilirubin will remain elevated, and a few infants may have elevated concentrations for as long as 6 to 12 weeks. In formula-fed infants, serum bilirubin declines, reaching values of less than 1.5 mg/dL by day 11 or 12 after birth. In contrast, by week 3, two-thirds of normal, thriving breastfed infants have serum bilirubin concentrations

above 1.5 mg/dL, and 30% will be clinically jaundiced. Authorities have suggested that the elevation in serum bilirubin may be protective against oxidative injury because it has been shown to be an effective antioxidant *in vitro*. Given that this elevation is a normal response to breastfeeding, other than jaundice, the infants seem healthy and are thriving. These infants exhibit no abnormal clinical signs suggesting hemolysis, infection, or metabolic disease. The etiology is unknown, but factors in human milk which increase the enterohepatic cycle of bilirubin or genetic variations which impair bilirubin hepatic conjugation, such as occurs in Gilbert disease, are hypothesized. Breastfeeding should be continued, and parents should be reassured.

The physician should ensure that no other causes of prolonged indirect hyperbilirubinemia (eg, galactosemia, hypothyroidism, urinary tract infection, pyloric stenosis, hereditary spherocytosis) are present. These causes may be identified on newborn screening, from the hospital records, or physical examination. Serum total and direct bilirubin and other indicated laboratory values should be measured if the clinical examination indicates an elevated bilirubin level or if jaundice persists for more than 3 weeks. The persistent rise in serum bilirubin or a total bilirubin greater than 20 mg/dL may necessitate phototherapy and consideration of interrupting breastfeeding for 24 to 48 hours. If breastfeeding is interrupted, the mother should be encouraged and helped to maintain her milk supply. The mother may be reluctant to resume breastfeeding because of the association between breastfeeding and jaundice. A positive attitude on the part of the health care professionals and assurance that this circumstance will not recur later may prevent termination of breastfeeding.

### Ankyloglossia

Ankyloglossia (tongue-tie) is the presence of a short or tight lingual frenulum that can restrict proper tongue extension and movement, hindering proper breastfeeding abilities in the infant. It is estimated that 2% to 5% of newborns have tongue-tie. In many, this is a normal variant of no consequence, but some infants demonstrate poor feeding and slow weight gain; the mother may suffer from severe nipple pain. Recent research suggests that frenotomy, when performed for clinically significant ankyloglossia, may lead to fewer problems breastfeeding and reduction in maternal pain.

## SUMMARY

Primary care physicians and other health care professionals should recommend human milk for almost all infants and should provide parents with complete, current information on the benefits and techniques of breastfeeding to ensure that their feeding decision is a fully informed one. Peripartum policies and practices that optimize breastfeeding implementation and maintenance should be encouraged. Healthy infants should be placed and remain in direct skin-to-skin contact with their mothers immediately after delivery until the first feeding is accomplished. All breastfeeding newborn infants should be examined by a pediatrician or other knowledgeable and experienced health care professional at 3 to 5 days of age.



## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *Advocacy Resource Guide* (Web page), American Academy of Pediatrics Section on Breastfeeding ([www2.aap.org/breastfeeding/advocacyResourceGuide.html](http://www2.aap.org/breastfeeding/advocacyResourceGuide.html))

### Engaging Patient and Family

- *Breastfeeding* (Web page), American Academy of Pediatrics ([www.healthychildren.org/english/ages-stages/baby/breastfeeding/Pages/default.aspx](http://www.healthychildren.org/english/ages-stages/baby/breastfeeding/Pages/default.aspx))
- *Breastfeeding* (Web page), Office of Women's Health, US Department of Health and Human Services ([www.womenshealth.gov/breastfeeding/index.html](http://www.womenshealth.gov/breastfeeding/index.html))
- *Breastfeeding Guide and Log Book* (handout), UC San Diego Health System ([health.ucsd.edu/flip-books/wai/breastfeeding-guide/index.html](http://health.ucsd.edu/flip-books/wai/breastfeeding-guide/index.html))
- *Breastfeeding Your Baby: Getting Started* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Families Resource Guide* (Web page), American Academy of Pediatrics Section on Breastfeeding ([www2.aap.org/breastfeeding/familiesResourceGuide.html](http://www2.aap.org/breastfeeding/familiesResourceGuide.html))
- *New Mother's Guide to Breastfeeding* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

### Medical Decision Support

- *Academy of Breastfeeding Medicine* (Web site), ([www.bfmed.org](http://www.bfmed.org))
- *Baby-Friendly USA* (Web site), ([www.babyfriendlyusa.org](http://www.babyfriendlyusa.org))
- *Breastfeeding* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/breastfeeding](http://www.cdc.gov/breastfeeding))
- *Breastfeeding Handbook for Physicians* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Guidelines for Perinatal Care*, 7th ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Safe and Healthy Beginnings Toolkit* (toolkit), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

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## SUGGESTED READINGS

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## Chapter 89

# THE CIRCUMCISION DECISION

Andrew L. Freedman, MD

The choice of whether to have one's newborn son undergo a circumcision has for many new parents become one of the most difficult and anxiety-provoking decisions encountered in the newborn period. Although many parents approach this with relatively little reflection having had their minds made up for a long time, others agonize, often sensitive to the current debate in the larger culture. Although circumcision has ancient roots, dating back 6,000 years to Egypt, and remains the most common operation performed in males in the United States, we are currently witnessing a period of significant reevaluation, in part because of the development of an increasingly vocal opposition to the practice.

This sense of conflict is almost uniquely an American experience. In most of the world the primary indication for circumcision is religious tradition or local culture, but in the United States it is predominantly considered a medical procedure, divorced of religious significance, and greatly influenced by the

parents' beliefs regarding hygiene, health benefits, and potential risks. Although incompletely understood in contemporary American culture, clearly this decision has many influences beyond the medical, including religion, ethnicity, family tradition, paternal status, and aesthetics. Thus, those for whom circumcision is not seen primarily as a medical or public health issue may have no trouble deciding, whereas those who are trying to choose on a purely medical basis are increasingly confronted by a torrent of conflicting messages.

The proper role of the physician is likewise evolving. Increasingly, being the child's advocate means being a source of unbiased information that will help parents navigate this debate and make a multidimensional decision that is right for them. However, the physician may feel uncomfortable discussing the non-medical aspects or worry that their own beliefs may be biasing their discussion. To aid the physician as well as patients, representative professional organizations have developed guidelines for newborn circumcision. The most influential of these guidelines in the United States have been the ones developed by the American Academy of Pediatrics (AAP).

The AAP guidelines, first published in 1971, have undergone several revisions. They most recently underwent an extensive reevaluation and were published in 2012. The AAP guidelines are frequently misinterpreted as having a pro or con stance. The policy states that circumcision has benefits and risks, but overall the benefits outweigh the risks. However, the benefit is not great enough to recommend universal newborn circumcision. The policy does support access to the procedure for families desiring a circumcision. The policy also recommends that circumcision be performed by a trained provider, under hygienic conditions, and with the use of adequate pain management. Thus, the final decision is left in the hands of the well-informed parent.

The purpose of this chapter is not to support or condemn circumcision, nor to provide a comprehensive review of the vast circumcision literature, but rather to provide pediatricians with a brief summary of the most commonly discussed issues along with generally accepted data to allow them to be able to help inform parents. The chapter intends to support the use of the AAP guidelines. All physicians involved in newborn circumcision are strongly encouraged to read the revised guidelines and accompanying technical report (see AAP Policy at the end of this chapter).

## INCIDENCE OF CIRCUMCISION

The rate of newborn circumcision has been steadily falling over the past several decades since hitting its peak in 1965 with 85% of boys being circumcised. There remain significant regional variations as well as variations in access to circumcision through governmental insurance. Rates vary widely among different racial, ethnic, and religious groups. Although significant on the world scene, where 25% of the population is circumcised, in the United States, ritual religious circumcisions represent a tiny component of circumcisions performed.

The overall circumcision rate in the United States in 2006, based on the National Hospital Discharge Survey, was 56%. It was highest in the North Central region at 78%, and lowest in the West at 34%. Nationwide there has been a trend toward a declining incidence of newborn circumcision over the past decade. Review of the National Hospital Discharge Survey has shown a drop from 64.5% in 1979 to 58.3% in 2010. Findings were similar in 2 other national hospital databases. An unknown percentage of boys, however, will obtain their circumcisions outside of the birth hospital, such as in clinics or physician offices.

## ARGUMENTS THAT SUPPORT CIRCUMCISION

The medical portion of a parent's decision making should be based on a factual assessment of the risks and benefits of newborn circumcision. Most parents, however, will have made up their mind before any discussion with their physician. The most common reasons stated are that they believe it promotes better or easier genital hygiene, and the circumcision status of the father. Much of the hygiene concern derives from a lack of knowledge about how to care for the uncircumcised penis and concern about its difficulty. However, when pressed further, the medical benefits most frequently stated by parents are decreased risk for urinary tract infection (UTI) in the first year of life, decreased risk for acquiring a sexually transmitted infection (STI) including HIV, and a decreased risk for penile cancer.

### Hygiene

Parents often express fears about their own ability to care for the uncircumcised penis as well as fears that the child will be unwilling or unable to maintain adequate genital hygiene. Most of the time, they are unaware of what proper hygiene actually entails. Although there are data showing that uncircumcised men wash their penis less than circumcised men, and that many uncircumcised men fail to retract the foreskin during voiding or bathing, there are no good studies systematically evaluating genital hygiene practices in children.

Parents should be reassured that satisfactory hygiene of the uncircumcised penis can be easily achieved at all age levels with no more than simple daily washing with soap and water. There is now an easily available information fact sheet on proper hygiene practices produced by the AAP titled *Care of the Uncircumcised Penis* (see Tools for Practice).

### Urinary Tract Infection

There have been numerous studies evaluating the association between infant UTI and circumcision status. In general, these studies have shown a consistently increased risk for a UTI in boys with an intact prepuce. The reported relative risk varies along with the definition of a UTI, method of urine collection, sample size, and coexisting factors. However, there is a fairly consistent 4- to 10-times relative risk reduction associated with circumcision. The risk for UTI in an intact boy is

in the range of 7 to 14 per 1,000, whereas in circumcised boys, the range is 1 to 2 per 1,000. However, it is clear that the overall absolute risk (about 1%) is lower than the overall baseline risk of asymptomatic bacteriuria in infant boys.

One concern is the possible confounding influence of premature infants, who are much less likely to undergo circumcision but are more likely to have additional medical encounters and obtain more urine cultures. A further confounding issue is the finding of greater bacterial colonization of the urethra and peri-urethral glans in uncircumcised boys, increasing the risk for contaminated specimens when obtained by a bag method. Despite these concerns, there remains a consensus that circumcision has a beneficial effect in reducing the UTI risk in infants. After infancy, the risk for UTI in both circumcised and uncircumcised boys is significantly reduced.

### **Sexually Transmitted Infections (Excluding HIV)**

Numerous studies have evaluated the effect of circumcision on the risk for STI. A meta-analysis of the literature suggests that there is a protective effect of newborn circumcision against ulcerative STIs, most significantly syphilis. There is also a protective effect against chancroid and herpes, though to a lesser degree. However, several other studies have refuted this effect. Circumcision has been thought to have a protective effect against human papillomavirus (HPV) in males as well as in transmission to females, although this effect is much lower in relatively low-risk men with fewer female partners. There is no evidence of a protective effect against the nonulcerative STIs, particularly gonorrhea and chlamydia.

Thus, there is an overall risk reduction in acquisition of certain non-HIV STIs afforded by circumcision, particularly syphilis, chancroid, and HPV, but not in gonorrhea or chlamydia. It is important to stress to parents that this protection alone is insufficient to lessen the practice of effective safe-sex measures.

### **Human Immunodeficiency Virus (HIV)**

The most provocative new information in the circumcision debate is the protective effect of circumcision in preventing male HIV acquisition during high-risk heterosexual activity. Three large randomized controlled trials conducted in Africa demonstrated a 50% reduction in HIV acquisition. This follows many other studies that had previously suggested such an association. Further, there is a plausible biologic theory for the effect based on viral adherence to Langerhans cells in the mucosal aspect of the prepuce as well as greater likelihood of sexual trauma to the intact prepuce creating breaks in the skin barrier. Using current patterns of HIV acquisition and disease prevalence, the Centers for Disease Control and Prevention calculated that circumcision could provide a 15.7% lifetime risk reduction for men in the United States. The current predicted lifetime risk for HIV in US men is 1.87%. Circumcision has been shown to be a cost-effective strategy in the United States despite the fact that no benefit of circumcision has been shown in the men having sex with men

(MSM) population, which is still the primary source of HIV acquisition in the United States.

From a world public health perspective, this has been recognized as an important new tool in the fight against HIV, particularly in those regions with a high prevalence in the female population and poor adoption of safe-sex practices. Whether this is a significant enough benefit to warrant a more positive recommendation in the US population remains a subject of debate.

### **Penile Cancer**

Penile cancer is a rare tumor in the United States and has been becoming rarer, with a recent incidence of 0.58 per 100,000. Geographic variation in incidence has frequently been used to bolster the argument in favor of neonatal circumcision. Many areas with a high incidence of penile cancer, such as Brazil (3.4 per 100,000) and India (1.8 per 100,000), have a low incidence of circumcision compared with populations with a low incidence of cancer and a high rate of circumcision, such as Jews in Israel (0.1 per 100,000). However there are areas with a similarly low incidence of cancer and a low incidence of circumcision, such as Japan (0.3 per 100,000), Finland (0.5 per 100,000), and ethnic Chinese in Singapore (0.6 per 100,000). It is suspected that other aspects of public health such as the availability of clean water and better hygiene practices may play a more important role.

The presence of a foreskin is a risk factor for squamous cell carcinoma but not carcinoma in situ. The overall risk is 2.3 times higher in men with an intact foreskin. However, this is a weaker risk factor than smoking (4.5 times) or history of a penile injury or tear (4 to 5 times). Phimosis is the greatest risk factor (11–16 times), and it accounts for most of the risk caused by the presence of a foreskin. In fact, in uncircumcised men without a history of phimosis, the risk for penile cancer is actually reduced by 50%. This suggests that the means by which circumcision reduces penile cancer is preventing phimosis; a healthy foreskin can have a protective effect.

## **ARGUMENTS OPPOSING CIRCUMCISION**

The main arguments against circumcision include a discounting or disagreement with the medical benefits, surgical risks, effects on sexual functioning and satisfaction, and ethical considerations in altering the bodily integrity of an individual without his consent. It is important to be aware of these issues because parents may have these concerns but be reluctant to address them, thinking that physicians may have a pro-circumcision bias and not be open to these concerns.

### **Discounting Medical Benefits**

The circumcision literature is vast, and it is not hard to find studies that refute or minimize any of the suggested potential benefits. Studies vary greatly in design, populations, definitions, and interpretations. There are few studies that meet the most rigorous



standards, and there is always the potential for bias in interpretation or patient selection. The publication of several meta-analyses and reviews has helped to improve the discussion but there is still plenty of room for continued debate. Unfortunately, most of the battles among researchers have been in this arena, leaving the other areas of concern without sufficient study.

### Surgical Complications

The true incidence of complications after circumcision is unknown, in part because of differing opinions about what constitutes a complication and differing standards for determining when a complication has occurred. Adding to the confusion is the separation of acute complications such as bleeding or infection, which are uncommon, from late complications such as adhesions, meatal stenosis, and an unacceptable cosmetic outcome, which may be more common. Lastly, complications of circumcision in the non-newborn have received little attention.

Based on 2 very large hospital-based series, the risk for a significant acute newborn circumcision complication in the United States is very low, 0.2% or 1 out of 500 circumcisions. Bleeding was the most common complication (0.08%–0.18%), followed by infection (0.06%) and penile injury (0.04%). However, in a smaller series using hand-reviewed medical records, complications were found to be much more common at 3.1%, with bleeding occurring in 2.1%, although most of these were mild in nature and did not require operative intervention.

Late complications of newborn circumcision include excessive residual skin (incomplete circumcision), excessive skin removal, adhesions (natural and vascularized skin bridges), meatal stenosis, phimosis (trapped penis) and epithelial inclusion cysts. Late complications in 1 outpatient-based study were found to include adhesions (25.6%), redundant residual prepuce (20.1%), balanitis (15.5%), skin bridge (4.1%), and meatal stenosis (7%). Although the true incidence of these late complications is not well established because there are few studies of the US experience, their incidence is clearly not trivial.

Most severe or even catastrophic injuries are of such a rare nature as to be reported as case reports without a clear sense of their overall incidence. Significant reported complications include glans or penile amputation, herpes transmission, methicillin-resistant *Staphylococcus aureus* (MRSA) infection, urethral cutaneous fistula, glans ischemia, and death.

### Sexual Effects

A frequent concern among those opposed to circumcision is a perception that there is decreased penile sensitivity. There are few methodologically rigorous studies, which in general do not support any significant loss of sensation or decreased sexual satisfaction. There have been reports of lengthened ejaculatory latency times, but it is unclear whether this leads to an increase or decrease in satisfaction. In an African study of female partner satisfaction, most subjects reported increased satisfaction after circumcision of their adult

male partner. The research in this area remains limited and often contains significant concerns of bias.

### Medical Ethics

One of the most challenging areas is that of the ethics of altering the child's bodily integrity without his consent. Although parents are generally asked to decide the medical course for their children, circumcision is somewhat unique because it is nontherapeutic at the time of its performance and some of the benefits being considered are nonmedical, such as cultural, religious, and aesthetic considerations. Although one can suggest that there may be a prophylactic effect for certain medical conditions, these conditions are generally uncommon and are not present at the time, and it is certainly not clear that any individual newborn is at an elevated risk.

Therefore, in the absence of a clear metric in which to weigh the risks and benefits, it is thought to be most ethical for the parents to determine what is in the best interest of the child. Furthermore, within the pluralistic framework of American society, parents are afforded wide latitude in determining what is appropriate for their child, and thus it is considered legitimate for them to take into account their cultural, religious, and ethnic traditions along with the medical information in making their decision.

Physicians have a moral obligation to avoid any coercion, provide unbiased and complete information, and do everything in their power to reduce the risk or suffering associated with the procedure, such as providing adequate pain management and having the procedure performed by well-trained personnel.

As with many ethical questions, this stance is not universally accepted, but at present it is representative of the organized medical community in the United States.

### THE CIRCUMCISION PROCEDURE

Circumcision in the newborn period should be performed only when the infant is stable and healthy and has urinated. There are 3 devices in common use for newborn circumcision: the Gomco clamp, the Mogen clamp, and the Plastibell. Success and complication rates are similar among the techniques. Contraindications for circumcision include hypospadias, congenital buried penis or other anatomic anomalies of the penis, neonatal illness, and bleeding disorders or a family history of bleeding disorders. After the first month of life, these techniques carry a greater risk. Non-newborn circumcision involves a more formal procedure and is typically done under general anesthesia.

All circumcision procedures should be preformed with adequate pain control. There is no longer any question that the newborns experience pain with circumcision. Pain control measures, including sucrose nipple, analgesics, topical anesthetic creams, dorsal penile nerve block, and subcutaneous ring block, have the ability to significantly decrease the pain associated with the procedure and can be safely used in combination. The most effective measures are the blocks—dorsal penile nerve block and ring block. They should be performed with 1% lidocaine in a buffered solution. The most common complications include



bruising or hematoma, which rarely require any additional treatment. Rare events include intravascular injection or allergic reaction. The topical lidocaine creams are less effective and need to be placed 45 to 60 minutes in advance of the procedure. There is some evidence that circumcision in the first week of life is better tolerated than later in the newborn period. Gentle restraint, especially with upper extremity swaddling, rather than 4-point restraint on a rigid board, is believed to be less stressful for the child.

## CONCLUSION

Newborn circumcision can no longer be considered a routine rite of passage for American boys. While providing some measurable benefits, primarily a decreased risk for HIV infection and infant UTI, it is not without a small but definable surgical risk. The benefits may be enough to justify its performance for those who desire it but likewise are not sufficient to recommend universal application. Because circumcision finds itself somewhere between recommendation and condemnation, ethically it falls to the parent to decide what is in the best interest of the child. The family is best aided by a knowledgeable physician who is able to provide unbiased information, sensitivity to the nonmedical dimensions, and assurance that the procedure is performed in a safe, hygienic, and compassionate manner.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Care of the Uncircumcised Penis* (fact sheet), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org)).
- *Circumcision: Information for Parents* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

### Medical Decision Support

- *Trends in Circumcision for Male Newborns in US Hospitals: 1979–2010* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/nchs/data/hestat/circumcision\\_2013/circumcision\\_2013.htm](http://www.cdc.gov/nchs/data/hestat/circumcision_2013/circumcision_2013.htm))

## AAP POLICY

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## SUGGESTED READINGS

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## Chapter 90

# CARE OF THE LATE PRETERM INFANT

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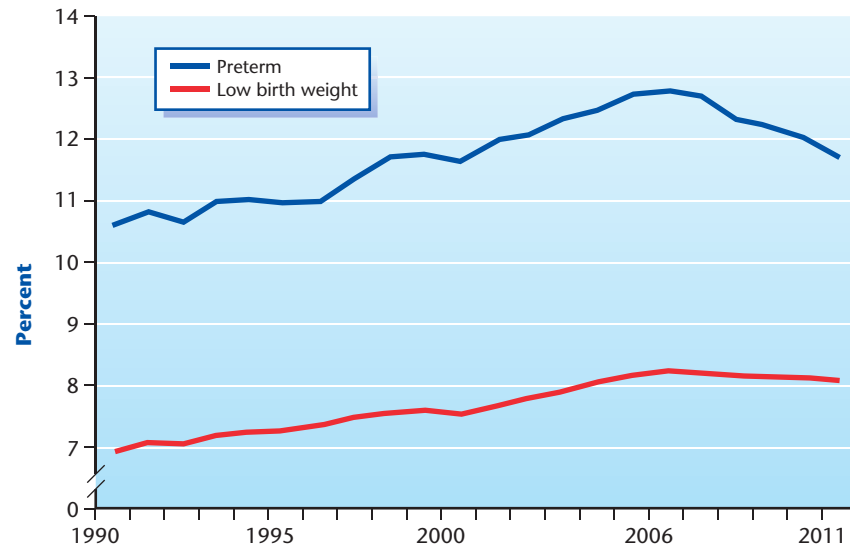
## INTRODUCTION

Prematurity continues to be an issue of major concern. In the United States alone, preterm births account for more than 500,000 infants born each year. From 1990 to 2006, the rate of preterm birth rose dramatically to 12.8%. Fortunately, it decreased consecutively over the following 5 years to 11.72% in 2011 (Figure 90-1). Most premature infants, approximately 70%, are born between 34 and 36 weeks' (34<sup>0</sup>/<sub>7</sub>–34<sup>6</sup>/<sub>7</sub>) gestation and are considered late preterm (LPT).

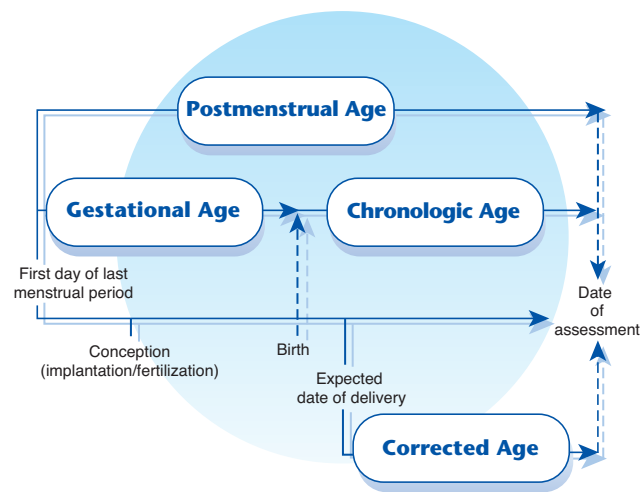
Worldwide, LPT birth rates are similar and make up the vast majority of preterm births. The term *prematurity* is used to describe any infant born before 37 weeks' gestation. Preterm babies are grouped into subcategories based on their degree of prematurity. Previous convention described infants born at 32 to 34 weeks' gestation as moderately preterm and at 35 to 37 weeks' gestation as near term. Recognition of the increased vulnerability associated with birth between 34 and 36 weeks' gestation led to the 2005 Workshop on Optimizing Care and Long-Term Outcome of Near-Term Pregnancy and Near-Term Newborn Infants, which refined the definition of the LPT infant to mean delivery from 34<sup>0</sup>/<sub>7</sub> to 36<sup>6</sup>/<sub>7</sub> weeks' gestation (239–259 days) (Figure 90-2).

The rise in preterm birth rates is a result of many variables. In the United States, advanced maternal age is defined as a woman more than 35 years old. The number of women in this demographic delivering babies has steadily increased over the years. These women have an increased risk for having an LPT infant (adjusted odds ratio, 1.23), and in a recent report, almost 19% of women older than 44 years delivered infants prematurely (Figure 90-3).

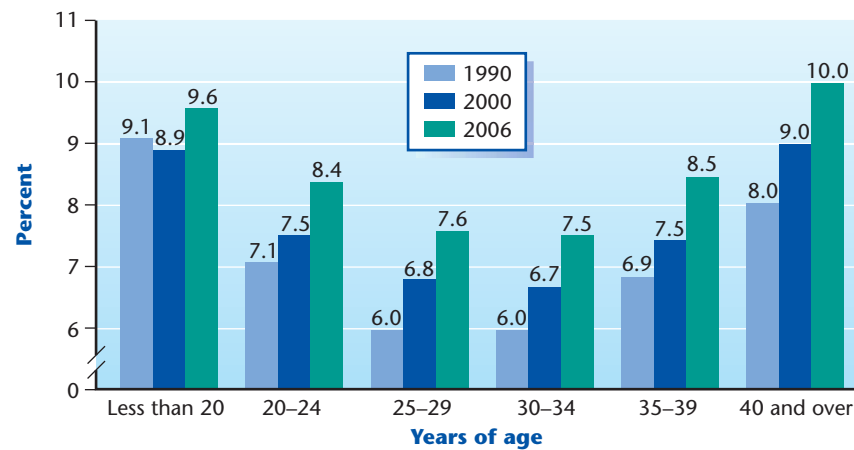
Multiple gestations are another significant contributor to the increased LPT birth rate. The incidence of multiple births has increased significantly over the past 40 years in conjunction with advances in and greater access to assisted reproductive technologies.



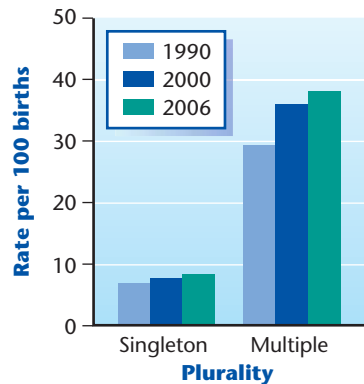
**Figure 90-1** Incidence of preterm birth rate.



**Figure 90-2** Age terminology during perinatal period.



**Figure 90-3** Late preterm birth rates by age of mother: United States, 1990, 2000, and 2006. (From Menacker F, Hamilton BE. Recent trends in cesarean delivery in the United States. NCHS Data Brief. 2010;Mar[35]:1-8)



**Figure 90-4** Late preterm births per 100 total births.

The rate of twinning increased 76% from 1980 to 2009. Although higher order multiples (3 or more) have decreased during the past 3 years because of changes in assisted reproductive practices, twins continue to account for 3% of all births in the United States. Approximately 50% of twins and 44% of triplets are born LPT (Figure 90-4).

### MORBIDITY AND MORTALITY

As a group, LPT infants experience increased morbidity and a higher incidence of mortality than their full-term counterparts. Late preterm infants represent 33% of total neonatal intensive care unit (NICU) admissions. With decreasing gestational maturity, the percentage of preterm infants requiring intensive care increases. Recent studies have shown significant heterogeneity, with reports of 33% to 100% of infants born at 34 weeks, 15% to 43% of infants born at 35 weeks, and 8% to 21% of babies born at 36 weeks requiring NICU admission.

Reasons that LPT infants require NICU admission include difficulty with thermoregulation and control of cardiorespiratory function (apnea, bradycardia, and hypoxic episodes), problems with oral feeding, hypoglycemia, hyperbilirubinemia, respiratory distress, and suspected sepsis.

The LPT infant also has an increased risk for short-term and long-term complications. Approximately 7% to 9% of newborns born at 34 to 36 weeks' gestation require rehospitalization within 14 days of nursery discharge. A significant portion of LPT infants continue to have ongoing health and developmental issues throughout childhood that require rehospitalization, extensive medical visits, and an increased need for social and educational support.

The mortality rate of LPT infants is also significantly higher than that of full-term babies. Infant mortality classified by the postnatal age categories of early neonatal (0–6 days), late neonatal (7–27 days), and post-neonatal (28–364 days) are notable for mortality rates that are 6, 3, and 2 times higher, respectively, than term infants. With each week of gestation, the risk for death decreases significantly. In 2009, the mortality rate for LPT infants was between 2.8 and 7.1 per 1,000 (Table 90-1).

**Table 90-1**

**Neonatal Mortality  
per 1,000 Births**

WEEKS OF GESTATION	RATE	RR (95% CI)
34	7.1	9.5 (8.4–10.8)
35	4.8	6.4 (5.6–7.2)
36	2.8	3.7 (3.3–4.2)

### HEALTH CARE UTILIZATION: ECONOMIC IMPACT

Despite the increased risk for morbidity and mortality, many LPT infants are routinely cared for in regular newborn or well-baby nurseries rather than special (level II) or neonatal intensive (level III) care units and are often discharged home at 2 to 3 days of age. The birth weights of these infants are typically more than 2,500 g, and they may seem physically more mature. This leads to many LPT infants being treated the same as the developmentally more mature full-term infants. The misconception that LPT infants have similar risks as term infants is common. However, it is not uncommon for the initial birth hospitalization stay to be significantly longer than for full-term infants, 2.6 days versus 1.96 days. Irrespective of the initial birth hospitalization, these infants are more likely to be readmitted to the hospital. Causes include dehydration, excessive weight loss, feeding problems, jaundice, and suspected sepsis in the first weeks of life.

According to the revised policy statement on neonatal care from the American Academy of Pediatrics (AAP) Committee on Fetus and Newborn, level I nurseries should provide care for infants born at 35 weeks' gestation or later who remain physiologically stable and stabilize those born earlier than 35 weeks until transfer to a higher level facility is available. Within institutions where regionalized perinatal health systems are in place, neonatal transfer policies determine where care for these babies occurs.

Costs for prolonged birth hospitalizations, rehospitalizations, and associated medical care of LPT infants are greater than for full-term newborns. The higher initial birth hospitalization costs are a common occurrence worldwide and range from \$5,000 to \$15,000. This cost is associated with a number of factors, including equipment for care and treatment, medications, and staffing.

The costs continue to rise well beyond the initial birth hospitalization. On average, LPT infant medical care costs in the first year are 3-fold higher than those for full-term infants. The hospital costs in the first year of life for LPT infants were 3.21 times more likely to be above \$25,000. In addition, outpatient costs for the first year were \$6,981 for LPT infants compared with \$2,158 for full-term babies. The mean total cost for LPT infants during the first 2 years of life continues to exceed the cost for full-term infants. Emergency department (ED) visits, outpatient physician office visits, and hospitalizations are much more frequent among LPT infants.

## HEALTH ISSUES INFLUENCING NURSERY CARE OF THE LATE PRETERM NEWBORN

Transitional issues such as transient tachypnea of the newborn, cold stress caused by hypothermia, and hypoglycemia may be seen during the early hours after birth.

### Cold Stress and Hypothermia

Preterm newborns have an impaired ability to prevent heat loss and increase their body heat production in response to low environmental temperatures. The risk for cold stress is greatest during the immediate transitional period after delivery and is caused by the preterm newborn's immature skin, the decreased amount of brown fat, the high ratio of surface area to birth weight, and the environmental conditions in the delivery room (large temperature gradients between the newborn's body temperature and the ambient temperature of the delivery room, airflow through the room, and contact with cold surfaces that lead to significant evaporative, radiant, convective, and conductive heat losses). Wide variations in delivery room temperatures have been reported to have a significant effect on a newborn's temperature. Approximately 50% of newborns experience some degree of cold stress after birth.

Oxidation of fatty acids is the predominant method of nonshivering heat production in newborns regardless of gestational age or birth weight. Brown fat, the major store of fatty acids in neonates, is located around the mediastinal structures, kidneys, scapulae, axillae, and nape of the neck. Cold exposure activates the sympathetic nervous system, releasing norepinephrine. In turn, norepinephrine stimulates the hydrolysis or breakdown of brown fat, with resultant heat production. LPT infants have decreased brown fat compared with full-term infants. Consequently, they are more prone to develop cold stress and hypothermia. Normal core body temperature for a neonate is 36.5°C to 37.4°C (97.7°F to 99.3°F). Clinical manifestations of cold stress are nonspecific. Common findings include hypoglycemia, tachypnea, peripheral vasoconstriction, pallor, mottling caused by vasomotor instability, and metabolic acidosis. Therefore, maintaining thermoregulation, keeping the newborn warm, and minimizing heat loss and energy expenditure are important components of the preterm newborn's initial care after birth.

Strategies to minimize heat loss include the following:

- Maintain the delivery room and all other patient care rooms at a temperature of 24°C ± 2°C (75°F ± 3°F). (The World Health Organization recommends 25°C or greater.)
- Prewarm the radiant warmer.
- Initiate skin-to-skin contact with the mother to facilitate temperature regulation of the newborn.
- Rapidly dry the newborn after delivery.
- Cover the newborn's head with a hat to reduce heat loss.
- Place the newborn in an isolette when not in skin-to-skin contact with the mother if the newborn is exhibiting difficulty maintaining body temperature.

### Respiratory Disorders and Respiratory Distress

Acute respiratory distress is a common condition experienced by the LPT newborn. Neonates born between 34 and 36 weeks' gestation who exhibit respiratory distress after delivery are at increased risk for associated morbidities. Late preterm newborns exhibit higher rates of transient tachypnea of the newborn (TTN), respiratory distress syndrome (RDS), persistent pulmonary hypertension, and respiratory failure. TTN and RDS are both common in the late preterm newborn and are related to delayed clearance of lung fluid, surfactant deficiency, or both. One-third of LPT newborns will exhibit respiratory difficulties. More than 8% of LPT infants experience severe respiratory disorders, requiring nasal cannula, continuous positive airway pressure (CPAP), or mechanical ventilation.

In utero, alveoli are filled with fluid that must clear during the initial transitional period for effective ventilation to be established. In addition, pulmonary blood flow to the lungs increases to ensure effective pulmonary perfusion and adequate matching of perfusion and ventilation. A significant part of this process includes fluid clearance through transepithelial sodium absorption that occurs during the process of labor and vaginal delivery. Liquid is also driven through the pulmonary epithelium into the vasculature. Maturation and recruitment of epithelial sodium channels occur during the last few weeks of pregnancy in response to endogenous steroid and catecholamine surges that are triggered by the onset of labor. Neonatal transition may be more difficult when the infant is born by cesarean delivery without onset of labor. Impaired function or inactivity of the sodium channels contributes to TTN and RDS. Although administering antenatal corticosteroids results in a significant reduction in mortality and morbidity caused by RDS in premature infants, the American College of Obstetricians and Gynecologists does not recommend routine antenatal steroid use after 34 weeks' gestation.

Strategies to minimize the risk for respiratory morbidity include the following:

- Personnel skilled in the assessment, resuscitation, and stabilization present in the delivery room.
- The use of CPAP and initiation of resuscitation in the delivery room as needed
- Attention paid to maintaining thermoneutrality and glucose homeostasis to avoid additional morbidity that may prolong the newborn's physiologic transition and worsen respiratory symptoms.

### Risk for Infection

One major cause of preterm delivery is infection. Late preterm infants are more susceptible to infection, congenital or acquired, because of immaturity of their immune system. (See Chapter 102, The Newborn at Risk for Infection.) As a group, LPT infants are nearly 4 times more likely to be evaluated for suspected sepsis than the full-term neonate and are more likely to be treated with a 7-day course of antibiotics. In addition, clinical signs during the transitional period may mimic



early signs of systemic infections. These include respiratory distress, temperature instability, low tone, poor feeding, and evidence of hemodynamic instability.

Late preterm infants often experience increased respiratory morbidity during infancy, including RSV infection, wheezing, the need for treatment with inhaled corticosteroids, and greater risk for developing asthma. RSV infection in this group of infants leads to significantly more emergency department visits (3.6- to 6.2-fold higher than for full-term infants) and outpatient physician office visits. Respiratory issues are the leading cause of outpatient visits for LPT infants.

Strategies to minimize morbidity related to infection risks include the following:

- Review the maternal medical history including onset of labor, length of rupture of membranes, and timing of antibiotics. Monitor and thoroughly assess the infant for signs of infection and initiate therapy as appropriate.
- Follow guidelines based on the Centers for Disease Control and Prevention (CDC) Group B Streptococcal Disease Revised Guidelines.
- Encourage early and exclusive breastfeeding, by either direct breastfeeding or the provision of expressed breast milk.
- Consider palivizumab administration for infants born before 35 weeks' gestation who are less than 90 days of age at the start of the RSV season and who have 1 or more additional risk factors (infant is in daycare or has school-aged siblings younger than 5 years).
- Discuss pollutants and adverse effects of second-hand smoke and other environmental exposures at each office visit.

### Hepatitis B Vaccination

According to the 2012 CDC Advisory Committee on Immunization Practices recommendations, all infants born to hepatitis B surface antigen-positive mothers should receive hepatitis B (HBV) vaccine and hepatitis B immune globulin (HBIG) within 12 hours of birth. If the mother is negative, then the infant should receive HBV vaccine before discharge. In neonates whose birth weight is less than 2,000 g, the initial vaccine dose confers lower immunogenicity than in infants born at term. Therefore, infants weighing less than 2,000 g should receive a total of 4 doses of HBV vaccine (birth and 1-2, 3-4, and 6 months). In cases of unknown maternal status at delivery, all infants should receive HBV vaccine within 12 hours after birth. If the infant weighs less than 2,000 g, then the HBIG should also be administered; otherwise, it can be held for 1 week until maternal status is confirmed. The AAP recommends that all neonates should receive the first dose of vaccine in the hospital.

### Hypoglycemia

Glucose is a primary energy source for the newborn infant. Gestational age, hypothermia, hypoxia, maternal diabetes, maternal glucose infusion in labor, intrauterine growth restriction, small for gestational age, and sepsis are all factors that may contribute to the incidence of hypoglycemia. Hypoglycemia occurs more often in premature infants as a result of decreased hepatic

glycogen stores, decreased gluconeogenesis, and ketogenesis. Feeding may also be less efficient in some LPT infants because of easy fatigability and immature feeding skills. Limited enteral intake further complicates the newborn's initial transition, predisposing the LPT newborn to hypoglycemia.

Hypoglycemia has been reported to occur in 25% of LPT infants (see Chapter 105, Transient Metabolic Disturbances in the Newborn). An important element of care in prevention of hypoglycemia in the LPT newborn is appropriate risk assessment with glucose screening. The AAP Committee on Fetus and Newborn released recommendations for glucose screening of at-risk newborns, including LPT infants. In summary, a blood glucose level greater than 40 mg/dL (2.2 mmol/L) is acceptable in the first 4 hours of life. After 4 hours of age, the infant should maintain a blood glucose level above 45 mg/dL (2.5 mmol/L). Late preterm infants are at greatest risk for developing hypoglycemia during the first 12 hours of life, although they should have preprandial glucose monitoring for at least the first 24 hours of life because they remain more vulnerable to low glucose concentrations, particularly if regular feedings are not well established.

Strategies to assess the risk for hypoglycemia include the following:

- Assess all LPT infants for hypoglycemia.
- Initiate early breastfeeding or formula feedings within 60 minutes of birth.
- Monitor glucose 30 minutes after the first feeding.
- Maintain blood sugar higher than 40 mg/dL in the first 4 hours of life and higher than 45 mg/dL thereafter.
- Continue to monitor blood sugar every 3 hours before feeds until 3 stable blood sugars are recorded.

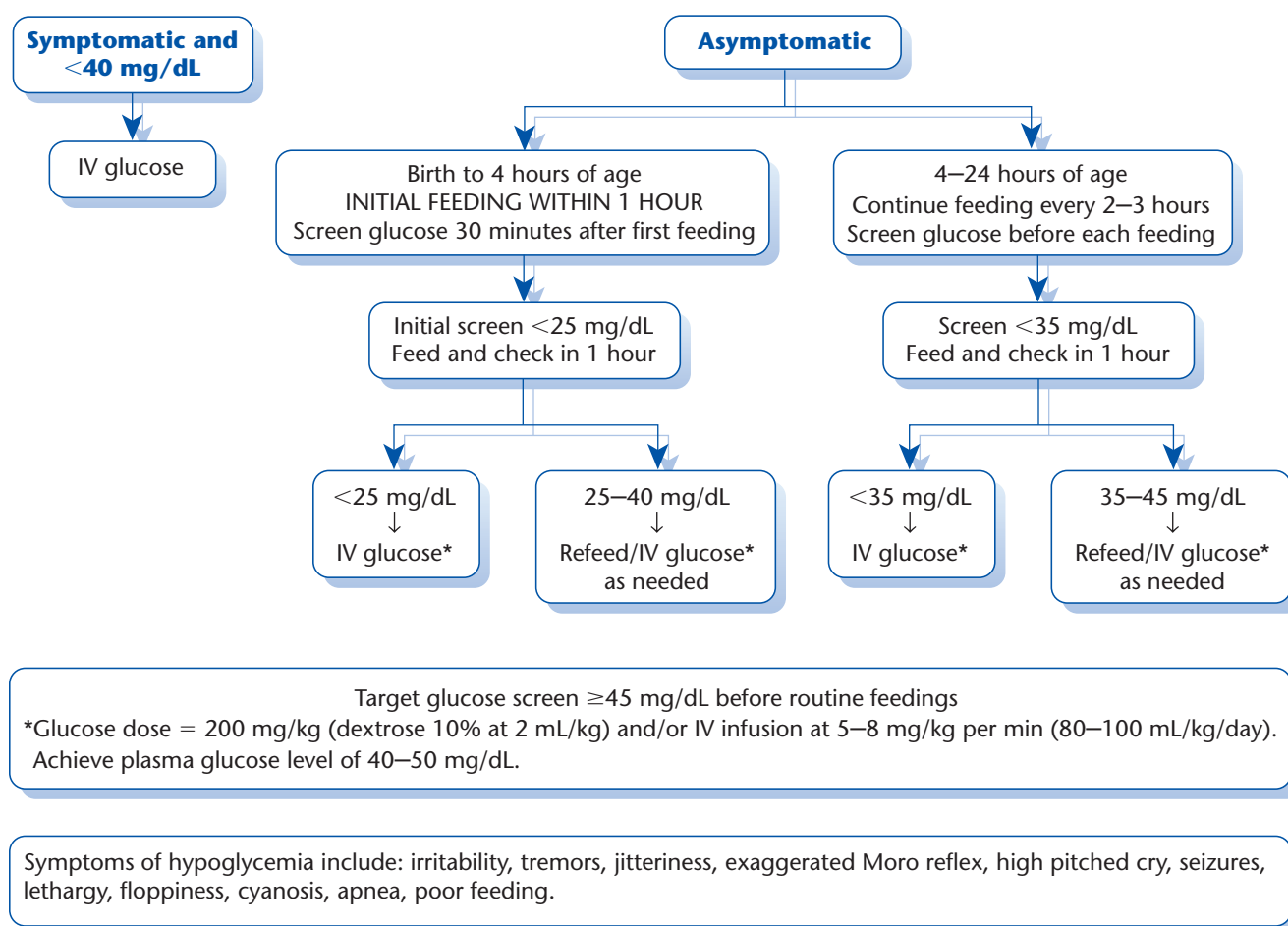
The AAP Committee on Fetus and Newborn offers guidelines for the management of hypoglycemia (Figure 90-5).

### Feeding Issues

#### Feeding Tolerance

Maturation of the gastrointestinal tract is important not only for digestion and absorption but also for endocrine and exocrine function. Significant increases in the intestinal length and surface area, including villus and microvillus growth, occur during the last trimester. Most LPT newborns are able to tolerate human milk and infant formula without difficulty despite these developmental differences. Although LPT infants have low gastric acid secretion and limited pancreatic enzyme activity, they are able to digest whole-protein formulas. Despite decreased bile acid secretion, enterohepatic circulation, and lower lactase activity, LPT infants are generally able to digest fats and carbohydrates. Premature infants often have intestinal motor function immaturity that contributes to feeding intolerance. Intestinal dysmotility is typically present up to 34 weeks' gestation but may persist. Some infants may require a longer interval between feedings because of a delay in motility and gastric emptying.

An important point to consider is the adequacy of the infant's intake and growth pattern. Many LPT infants are not able to demonstrate clear feeding cues, and some may lack suck-and-swallow coordination



**Figure 90-5** Screening and management of postnatal glucose homeostasis in infants who are small for gestational age, infants who are large for gestational age, infants who were born to mothers who have diabetes, and late preterm infants.

skills. The strength and efficiency of the suck patterns and suck, swallow, and breathing coordination may further impede successful oral feeding and contribute to excessive weight loss or poor weight gain. Other feeding problems include latching, feeding fatigue with progressive feeding disorganization, and loss of suction during suckling, in some instances causing respiratory compromise (choking, coughing, duskiness) (Figure 90-6).

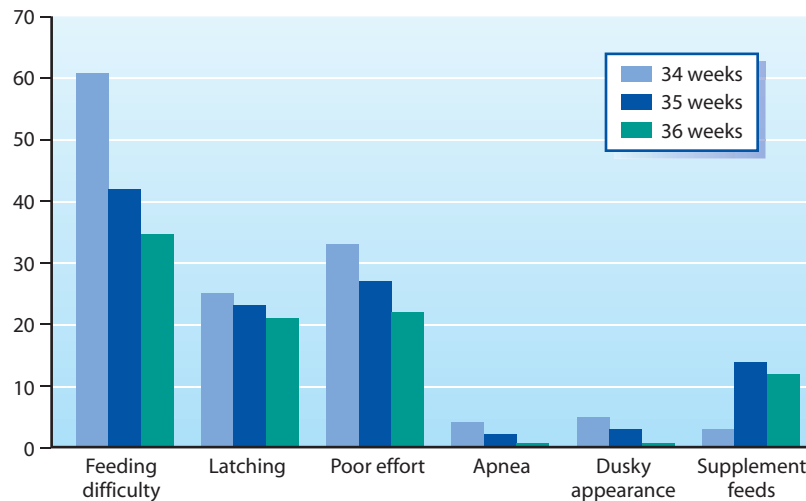
Feeding issues continue after nursery discharge for many preterm infants. The most common problems, which sometimes lead to rehospitalization, are decreased appetite, oromotor dysfunction, and avoidant feeding behavior. Most feeding recommendations are geared toward very preterm infant; little research has been conducted specifically for the LPT infant.

It is important that nutritional intake and feeding plans are discussed during each office visit until effective feeding patterns and adequate weight gain are established. Although LPT infants may lose up to 12% of their birth weight during the first week of life, weight loss of more than 3% in the first 24 hours of life or greater than 7% at 48 hours of age is of concern.

A careful assessment of the infant's state regulation, hydration status, glucose levels, feeding patterns, and feeding skills is necessary, as is review of types of feeding (breastfeeding and/or bottle feeding). Assessment of maternal lactation during this time is also important for the breastfeeding LPT infant.

### Breastfeeding

Human milk provides substantial benefits to infants' health. Human milk feeding is associated with reduced infectious and inflammatory disease, metabolic disease, and obesity, as well as enhanced neurodevelopmental outcome and healthy postnatal growth patterns. The AAP recommends exclusive breastfeeding for 6 months, followed by breastfeeding in combination with the introduction of complementary foods until at least 12 months of age, and continuation of breastfeeding for as long as mutually desired by mother and baby. Initiation of breastfeeding in LPT infants occurs in 59% to 75% of newborns in the United States, and it seems that NICU admission may have a positive effect on continuation and length of breastfeeding among all infants.



**Figure 90-6** Incidence of feeding problems affecting late preterm infants, by gestational age.

Strategies to support optimal nutrition for the LPT infant include the following:

- Human milk should be the first choice.
- Mothers can also combine hand expression of breast milk with the use of an electric breast pump because this technique has been shown to increase milk volumes more rapidly than breast pump use alone.
- Infants should be put to breast within the first 30 to 60 minutes after delivery.
- Lactation consultation should be offered within 24 hours of birth.
- Direct observation and documentation should be undertaken every 12 hours while in the hospital.
- Infants should be breastfed 8 to 10 times in a 24-hour period.
- Expressed breast milk can be stored and offered to the infant following each nursing attempt until lactation is established and the infant is feeding effectively at the breast.
  - Day 1 (Birth–24 hours of age): offer 5 to 10 mL at each feeding
  - Day 2 (25–48 hours of age): offer 10 to 20 mL at each feeding
  - Day 3 (49–72 hours of age): offer 20 to 30 mL at each feeding
- Mothers should maintain a feeding log with the frequency and duration of nursing episodes and the quantity of expressed breast milk or formula fed.

The LPT infant who loses more than 7% of birth weight during the first 2 days of life is at higher risk for excessive weight loss, dehydration, severe hyperbilirubinemia, and rehospitalization within the first 2 weeks of life. The physician will need to decide in consultation with the family whether the infant can be discharged home with close primary care follow-up or requires continued hospitalization until feeding improves and weight stabilizes.

- If the infant is discharged home, the infant should be reevaluated within 24 to 48 hours.
- A postdischarge lactation consultation may be arranged if feasible (LaLeche League and WIC are

valuable community resources that offer lactation support and peer counseling; some hospitals offer lactation support clinics).

- Mothers should continue to keep a log of the infant's feedings, any supplementation given, and the infant's elimination pattern.
- Mothers should have a clear feeding plan for their LPT infant at discharge irrespective of whether the infant is breast or formula feeding.
- Although most formula-fed LPT infants will be fed a 20-cal/oz term infant formula, those who are small for gestational age or who exhibit excessive weight loss and/or poor weight gain may require higher-calorie infant formula.
  - Higher-calorie formula can be transitioned to standard 20-cal/oz infant formula when the infant is demonstrating good weight gain, 30 to 40 g/day, and growth and is above the 10% for postmenstrual age on the CDC or World Health Organization infant growth curves.

The following are indications for concern:

- Feeding duration greater than 30 minutes or fewer than 6 feedings per day
- Fussiness, distress, or difficulty breathing during feedings
- Difficulty waking the infant for feeding or difficulty completing a full feeding
- Infant refusal of feedings or gagging, coughing, cyanosis, or frequent choking while feeding

Soy formulas are not recommended for preterm infants born at less than 1,800 g.

### Hyperbilirubinemia

Prematurity is one of the main risk factors for the development of significant hyperbilirubinemia and is associated with an increased risk for kernicterus. Jaundice in the LPT infant often has a more severe and protracted course than in term infants. Bilirubin levels typically peak between 5 and 7 days in the premature infant and decline slowly thereafter. If bilirubin levels reach critically high values, kernicterus may occur.

In LPT infants, the progression to kernicterus can be insidious. Kernicterus is a preventable brain injury; failure to diagnose and properly treat the LPT infant with significant hyperbilirubinemia may place the physician at medical-legal risk. Pediatricians should consider testing the cord blood of any infant born to a woman who had no prenatal blood grouping or who is antibody positive or Rh negative. It is recommended that all infants be screened for jaundice before initial hospital discharge. The 2004 AAP Clinical Practice Guideline and the National Institute for Health and Care Excellence guidelines are very useful for infants born at 35 weeks' gestation or later. However, one must be careful using this guideline for all LPT infants. (See Table 90-2.) Consensus guidelines were published in 2012 for the clinical evaluation and management of hyperbilirubinemia in preterm infants born before 35 weeks' gestation (see Chapter 99, Neonatal Jaundice).

Strategies to consider for management of hyperbilirubinemia in the LPT infant include the following:

- Obtain transcutaneous or total serum bilirubin before discharge.
- Follow up within 1 to 2 days of discharge and repeat transcutaneous or total serum bilirubin levels as needed.

### Brain Maturation and Neurodevelopment

Most brain growth occurs during the last half of gestation, with 35% of the brain's weight accrued in the last 6 weeks of gestation. Although neuronal proliferation and migration are considered complete by 24 weeks, the brain's gyri and sulci are not fully developed until about 40 weeks' gestation. In addition, a 4-fold (50%) increase in cortical brain volume occurs during the third trimester. Synaptogenesis, dendritic branching, and maturation of oligodendrocytes also continue through the last weeks of gestation. These processes are extremely sensitive and susceptible to hypoxic-ischemic and free radical injury, particularly the oligodendrocytes.

Brainstem function and autonomic and respiratory control are also immature, contributing to periodic breathing, apnea, desaturations, and bradycardia in the preterm infant. As previously described, inefficient feeding skills in conjunction with poor coordination of suck, swallow, and breathing and episodic gastroesophageal reflux precipitate these physiologic responses. The incidence of sudden infant death syndrome in preterm infants between 33 and 36 weeks' gestation is nearly twice as high as that of term infants. For infants between 34 and 37 weeks' gestation, the relative risk for experiencing an episode of prolonged apnea or bradycardia requiring intervention (apparent life-threatening event) is 3 times greater than for the term infant. The Collaborative Home Infant Monitoring Evaluation (CHIME) study found that 30% of the study infants who experienced an apparent life-threatening event were less than 38 weeks' gestation at birth. The younger the preterm infant, the earlier symptoms were exhibited. (See also Chapter 217, Apparent Life-Threatening Events.) Electroencephalogram/sleep patterns are also very different in LPT infants compared with full-term infants.

Some hospital practices and primary care physicians may consider home monitoring for the LPT infant. However, no data are available that support the routine use of home monitoring for this group of infants. Considerations regarding these care recommendations should be based on the infant's clinical and family history. Parents of LPT infants should be counseled about infant safety and safe sleep practices, including that preterm infants should be placed supine for sleep and that all other recommendations regarding safe sleep practices for infants are applicable to their preterm infant.

### Neurodevelopmental Outcomes

There have been numerous studies published in the past 5 years describing neurodevelopmental outcomes for LPT infants. Although the incidence of neurodevelopmental delays and impairment among LPT infants is

**Table 90-2**

**Total Serum Bilirubin Levels at Which Interventions Are Recommended for Late Preterm Infants**

RISK FOR BIND (AAP GUIDELINES <sup>a</sup> )	TSB THRESHOLD AT AGE 48 hr (mg/dL)		TSB THRESHOLD AT AGE ≥96 hr (mg/dL)	
	PHOTOTHERAPY	EXCHANGE	PHOTOTHERAPY	EXCHANGE
High (presence of any BIND risk factors <sup>b</sup> and 35 <sup>0</sup> / <sub>7</sub> to 37 <sup>6</sup> / <sub>7</sub> wk)	11	18	15	19
Moderate (35 <sup>0</sup> / <sub>7</sub> to 37 <sup>6</sup> / <sub>7</sub> wk with no BIND risk)	13	20	18	22.5
Low (term infant with no BIND risk)	15	22	21	25

AAP, American Academy of Pediatrics; BIND, bilirubin-induced neurologic dysfunction; TSB, total serum bilirubin.

<sup>a</sup>American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Clinical practice guidelines. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2004;114(1):297–316

<sup>b</sup>BIND risk factors: isoimmune hemolytic anemia; glucose-6-phosphate dehydrogenase deficiency; significant lethargy, sepsis, acidosis, asphyxia, temperature instability, and serum albumin level.



not as high as in the very preterm infant, it remains a significant problem. As a group, LPT infants have more early intervention needs than full-term infants, yet many of these vulnerable infants do not receive developmental services because of delays in or missed opportunities for diagnosis. LPT infants constitute a group of infants requiring developmental surveillance and periodic developmental screening. Although LPT infants are not routinely referred to early intervention, 30% of LPT infants admitted to the NICU qualify and receive services by 1 year of age.

Although about half of all LPT infants require NICU admission at birth, developmental assessment at 3 years of age is the same as in those who did not need a NICU admission. The studies seem to be consistent showing the increased risk for neurodevelopmental morbidities into school age. Emotional and behavioral issues are significant and challenging for families of LPT infants. At the end of their first year of school, by age 5 years, LPT children had lower personal, social, and emotional developmental scores. Kindergarten is a crucial age for children because it often sets them on their scholastic path. In Florida, risk for suspension from kindergarten is 19% higher for children born LPT. As the LPT population ages, the deficits among this group seem to persist. In New York City, by the third grade 25% of LPT children have educational disabilities requiring special education services. Realizing that these infants continue to have difficulties throughout childhood, it is worthwhile to consider early surveillance and periodic screening for neurodevelopmental and behavioral difficulties and delays.

### Additional Routine Care Issues

#### Car Seat Safety

According to US Federal Motor Vehicle Safety policy, the maximum weight acceptable for use of an infant car seat is 50 lb; however, no minimum weight is specified. Preterm infants may have episodes of oxygen desaturation when placed in a standard upright infant car seat. It is now recommended that all infants younger than 37 weeks' gestation (including those cared for in a regular newborn nursery) have an infant car seat challenge test before hospital discharge. This usually entails the infant being placed on a pulse oximetry monitor for 60 to 120 minutes to evaluate the infant for apnea, desaturations, or bradycardia while in the car seat. This will assist parents with proper positioning of the baby and determine the length of time the infant should remain in a car or infant seat without repositioning or removal from the seat in order to reduce the risk for cardiorespiratory compromise. Rolled towels or blankets may be placed on both sides of the infant for head and neck support. It should be explained to parents that the time the infant spends in an infant (car) seat should be kept to a minimum. Infants who exhibit apnea, bradycardia, or desaturations while upright are advised to travel in a supine position in a car bed. It is thought that infants transported in car beds are less likely to exhibit desaturations. It is prudent to educate parents about proper car seat positioning and limiting the time spent in a car or infant seat to less than

60 minutes when possible. At a minimum, parents and other caregivers should be instructed to check the infant and reposition if travel is in process or remove the baby from the car or infant seat when travel is complete.

Babies discharged with home monitoring should also be monitored during travel. For the infant discharged on oxygen, proper storage of the oxygen tank and apnea monitor during travel includes placing the equipment below the infant seat or on the vehicle floor for safety purposes. As of 2013, the AAP recommends that all infants and toddlers remain rear-facing until they are 2 years old.

#### Specific Newborn Screening Tests in the Hospital

All newborn blood spot screening procedures should be conducted by 3 days of life. Newborn hearing screens using either automated auditory brainstem response or otoacoustic emission testing devices should be completed before discharge from the hospital. If the infant requires more than 5 days of hospital care or received aminoglycosides, it is recommended that the infant undergo automated auditory brainstem response testing to screen for potential auditory neuropathy/auditory dyssynchrony. Universal newborn screening for critical congenital heart disease is now recommended for infants before discharge from the hospital.

#### Discharge of the Late Preterm Infant

Documentation is vital for communication among caregivers and good outcomes.

Strategies to consider for safe discharge include the following:

- Document mode of feeding.
- If breastfeeding, document lactation consult and observation.
- Establish 24 hours of successful feeding before discharge.
- Individual feedings should not exceed 20 minutes in length.
- Early weight loss should not exceed 10% of body weight or 7% of birth weight within the first 48 hours of life.
- Verify voiding and stooling.
- Document stable vital signs and blood sugar.
- Document maintenance of thermoregulation.
- Undertake hyperbilirubinemia assessment.
- Complete the car seat challenge test.
- Complete the hearing screen.
- Administer the HBV vaccine.
- Screen for critical congenital heart disease.
- Complete the blood spot (metabolic) screen.
- First-time mothers in particular require careful supervision and, when infants are leaving from an intensive care environment, should be offered a rooming-in experience.
- Document scheduled appointment for infant follow-up care.

Follow-up care should include a home nurse visit or an office visit with the primary care physician within 48 to 72 hours of discharge from the newborn nursery or 5 to 7 days from the NICU for infants

whose NICU or special care nursery hospitalization is longer than 5 days.

## LONG-TERM OUTCOMES FOR THE LATE PRETERM INFANT

Gestational age-specific long-term outcome data about LPT and heavier low-birth-weight (LBW; 1,500 to 2,499 g) infants are limited. Health outcomes for LPT infants are poorer than for full-term infants. LPT infants have higher rates of emergency department visits and rehospitalization with associated higher health care costs over the first 5 years of life. Rehospitalization for treatment of hyperbilirubinemia and for infection within the first 30 days of life is significantly greater among infants born LPT. Respiratory and gastrointestinal disorders account for over 50% of hospital admissions for this group of children. Persistent feeding difficulties following nursery discharge are also common. LPT infants who are breastfeeding require close follow-up and enhanced lactation support, including evidence-based lactation technologies and lactation strategies to promote effective feeding and growth.

Among infants with birth weights between 1,500 and 2,000 g (3.3–4.4 lb), there is reported to be an increased risk for both behavioral and psychiatric problems. Population-based studies have revealed that the risk for developmental delay or disability is 40% higher for infants weighing between 1,500 and 2,499 g at birth as compared to NBW babies. Infants born LPT and early term have higher prevalence of educational intervention program services enrollment than infants born at term, and may benefit from more frequent monitoring for developmental delays or disabilities. Educational outcomes for children born between 32 and 35 weeks' gestation are similarly affected. Although the greatest effect is among the most immature infants weighing less than 1,000 g at birth, heavier LBW children experience increased adverse educational outcomes such as academic problems, learning disabilities, physical and sensory impairments, and mental handicaps.

School performance has been studied in children born after 32 weeks' gestation. Reading and spelling difficulties are more common among children born at 33 to 36 weeks' gestation than among NBW infants. Huddy et al reported on school performance at age 7 years for a population-based cohort of children born between 32 and 35 weeks' gestation. Up to one-third of these children exhibited school difficulties; nearly 25% required additional school resources. Areas of poor performance included writing and fine-motor skills, reading, mathematics, and physical education. Rates of attention-deficit/hyperactivity disorder are nearly 2.5-fold greater than for NBW children. Behavioral difficulties are twice as common in LBW children and have been related to maternal psychological distress at 40 weeks postmenstrual age and a history of tobacco smoke exposure. Whether the effects of smoking are primary or a proxy for other environmental factors or stressors that influence the parents' well-being and ability to support their child's maturation is unclear. Among preterm children born SGA, adolescents who were under the 3% at birth were more likely than NBW term children to experience

learning and attention difficulties. SGA children between the 3% and 10% for gestational age did not experience similar difficulties. Symmetry or proportionality of growth was not related to these differences.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Car Safety Seats: A Guide for Families 2015* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)

### Medical Decision Support

- *Births: Final Data for 2012* (report), National Center for Health Statistics ([www.cdc.gov/nchs/data/nvsr/nvsr62/nvsr62\\_09.pdf](http://www.cdc.gov/nchs/data/nvsr/nvsr62/nvsr62_09.pdf))
- *Guidelines for Perinatal Care*, 7th ed (book), American Academy of Pediatrics and American College of Gynecologists and Obstetricians ([shop.aap.org](http://shop.aap.org))
- *Multidisciplinary Guidelines for the Care of Late Preterm Infants* (guidelines), National Perinatal Association ([www.nationalperinatal.org/Resources/LatePretermGuidelinesNPA.pdf](http://www.nationalperinatal.org/Resources/LatePretermGuidelinesNPA.pdf))
- *Strategies for Implementing Screening for Critical Congenital Heart Disease* (article), American Academy of Pediatrics ([pediatrics.aappublications.org/content/128/5/e1259](http://pediatrics.aappublications.org/content/128/5/e1259))

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## Chapter 91

# HOSPITAL DISCHARGE OF THE HEALTHY TERM AND LATE PRETERM INFANT

Christina Kan Sullivan, MD; Sonia Dela Cruz-Rivera, MD

### NEWBORN DISCHARGE

The optimal timing of hospital discharge of the newborn and mother has been a subject of debate in recent years. In the United States, newborn length of stay (LOS) has varied considerably in the last 50 years because of changing perinatal hospitalization practices. Before 1920, hospital births were uncommon. By 1945, 80% of births occurred in the hospital, with an average LOS after vaginal delivery ranging from 3 to 5 days. The trend toward shorter LOS was first driven by a consumer-initiated movement between the 1960s and 1980s as an alternative to home delivery. By the 1990s, financial constraints imposed by third-party payers led to even shorter stays because insurers would not pay for hospitalizations extending beyond 24 hours for an uncomplicated vaginal delivery. The average LOS in 1992 was 2.1 days. Nearly 2 decades

later, the mean and median lengths of hospital stay for healthy newborn infants remained 2.1 and 2.0 days, respectively.

The pressure to discharge infants early based on arbitrary financial considerations has been a source of frustration for physicians and families. In addition, many medical issues related to the transition from an intrauterine to an extrauterine environment require a longer period of observation. Serum bilirubin concentration peaks at 3 to 5 days, and lactation is rarely established in fewer than 3 days. In a 1996 survey of pediatricians, 43% of respondents indicated that they had experienced adverse outcomes related to the shortened LOS. The passage of the Newborns' and Mothers' Health Protection Act of 1996 prohibited payers from restricting benefits for hospital stays to less than 48 hours after birth for vaginal deliveries and less than 96 hours for cesarean deliveries.

The American Academy of Pediatrics (AAP) first addressed the management of newborns in the hospital when the Committee on Fetus and Newborn published the first edition of *Standards and Recommendations for Hospital Care of Newborn Infants* in 1948. In 1977, the Committee recommended a 72- to 96-hour hospital LOS. The 1995 AAP policy statement detailing the minimum discharge criteria for healthy, term newborns was issued in response to the shortened hospital stay (<48 hours) with revised policy statements in 2004 and 2010 further emphasizing the concept that the length of stay of a healthy term newborn should be based on the unique characteristics of each mother-infant dyad, including the health of the mother, the health and stability of the infant, the ability and confidence of the mother to care for her infant, the adequacy of support systems at home, and access to appropriate follow-up care.

The timing of the newborn's discharge is best determined by the physician in consultation with the infant's family, and with input from the obstetrician and other care providers including nursing and lactation staff and social workers. (For further details on this subject, see Timing section.) A healthy term newborn may be ready for nursery discharge once the infant exhibits stable vital signs for at least 12 hours, has a physical examination with no abnormalities that require continued hospital care, voids, passes stool, demonstrates appropriate feeding skills, has been assessed for early-onset jaundice, completes all screening tests, and has appropriate follow-up care in place. Despite adherence to these discharge criteria for term infants, detection of significant jaundice, ductal-dependent cardiac lesions, and other problems may require longer periods of observation. Parents should be counseled about signs of illness that warrant immediate medical attention and the importance of routine follow-up care within the first week of life. Infants discharged from the hospital or birthing center within 24 hours of birth should be re-examined by a pediatric professional within 24 to 48 hours (2–3 days of age) and have a repeat newborn blood spot test performed.



### Assessing Readiness

Whether the newborn is the first or fifth child born, all new parents experience some combination of excitement coupled with exhaustion. Lack of experience, limited support systems, competing family needs, and medical complications impose additional stress on the family. Health professionals must be adept at identifying and addressing these issues so that, on hospital discharge, parents feel confident, knowledgeable, and well prepared to care for their newborn.

By the time of discharge, a physician has likely examined the newborn 2 or more times. The recommended number of assessments before newborn nursery discharge is based more on accepted clinical practice rather than on data from randomized clinical trials. From an evidence-based perspective, no well-designed randomized trials have been conducted to evaluate the efficacy of 1 versus 2 routine neonatal examinations. However, serial physical exams of the infant allow for earlier detection of anomalies and problems and give the physician the opportunity for direct communication with the family to provide information, counseling, and reassurance.

### Medical Factors

In addition to reviewing and verifying the maternal, family, and obstetric histories; documenting gestational age, anthropomorphic data, and the appropriateness of growth for the infant's gestational age; and monitoring vital signs and daily weights, the following systems particularly should be noted on physical examination:

- Head shape and signs of trauma (caput, cephalohematoma; facial bruising; asymmetric cry suggestive of nerve palsy)
- Dysmorphic features
- Eyes (red reflex, size)
- Ears (pits, tags, position, shape)
- Palate and alveolar ridge morphology, presence of natal teeth, and shortened frenulum
- Clavicles (crepitus suggestive of fracture)
- Cardiac system (location of apical pulse and murmurs)
- Femoral pulses
- Abdominal area (masses, distension; umbilicus)
- Hip (signs of dislocation or dislocatability)
- Spine (deformities)
- Foot deformities (metatarsus adductus, clubfoot)
- Genitalia and rectum
- Skin (jaundice, rash, mottling, cyanosis, birthmarks)
- General posture and muscle tone; symmetrical reflexes; irritability/consolability; limb posture and position suggestive of brachial plexus dysfunction
- Well-coordinated suck and swallow reflexes
- Ability to fix gaze and follow a human face

Newborn screening is an integral component of a neonate's initial care typically completed before the infant's nursery discharge, although infants born at home or in a birthing center will require these tests to be performed in the days after birth. The newborn blood spot screening test is performed in all hospitals in North America, although the specific conditions

screened for vary by state. Baby's First Test provides a current list of conditions included in newborn screening in each state ([www.babysfirsttest.org/newborn-screening/states](http://www.babysfirsttest.org/newborn-screening/states)). Infants whose newborn screening is performed before 24 hours of age will require an additional newborn blood spot screening test at 3 to 5 days of age. Some states routinely require a second newborn screen at this time.

Good evidence exists to support screening examination of the skin, eyes (red reflex), ears (hearing), and hips of the newborn infant. Although early detection of critical congenital heart defects (CCHD) can improve outcomes, physical examination alone will miss many infants with CCHD. Most CCHD presents with some degree of hypoxia. In 2009, the AAP and the American Heart Association (AHA) reviewed the literature on the use of oximetry screening for the detection of CCHD and concluded that "routine pulse oximetry screening on asymptomatic newborns after 24 hours of life in hospitals that have on-site pediatric cardiovascular services incurs very low cost and risk of harm." In 2011, the US Department of Health and Human Services (HHS) recommended that screening for CCHD by pulse oximetry be added to the recommended uniform screening panel (RUSP), which includes newborn metabolic screening and universal newborn hearing screening. Currently, each state is in the process of implementing this new recommendation.

All newborns should receive a hepatitis B vaccine (and hepatitis B immune globulin within 12 hours of birth if the mother is positive for hepatitis B surface antigen) and have newborn metabolic and hearing screenings as per hospital protocol and state regulations before discharge. There is evidence to support the observation that universal newborn hearing screening using physiological measures (otoacoustic emission or auditory brainstem response testing) leads to earlier identification and treatment of infants with permanent hearing loss. The AAP recommended newborn hearing screening in 1999. The Joint Committee on Infant Hearing endorsed universal screening in 2000, and by 2005 approximately 95% of newborn infants in the United States were screened before discharge. In 2008, the US Preventive Services Task Force reviewed the evidence on benefits and harms of universal screening and recommended continued screening for hearing loss in all newborns.

Maternal screening for the presence of group B streptococcus (GBS) colonization of the vagina and rectum of pregnant women at 35 to 37 weeks of gestation is pivotal to preventing newborn early-onset GBS disease (see Chapter 102, The Newborn at Risk for Infection). The second cornerstone in the prevention of early-onset GBS disease in the neonate is intrapartum antibiotic prophylaxis during labor for women who test GBS positive.

In 2010, the Centers for Disease Control and Prevention (CDC) issued revised guidelines for the neonatal management of GBS-exposed neonates. It provided management recommendations that depend on clinical appearance of the neonate and other risk factors such as maternal chorioamnionitis, adequacy



of intrapartum antibiotic prophylaxis (IAP) if indicated for the mother, gestational age, and duration of membrane rupture (see Table 91-1). Changes were made to the algorithm to reduce unnecessary evaluations in well-appearing newborns at relatively low risk for early-onset GBS disease. Intrapartum prophylaxis is considered optimal if administered at least 4 hours before delivery (Figure 91-1).

Assessment of feeding adequacy whether the infant is breastfeeding or formula feeding is an important determinant of the newborn's readiness for discharge. Coordination of the suck and swallow reflex and the frequency and duration of feeding episodes are influenced by the infant's gestation, postnatal age and physiological transition after birth, neurobehavioral state, and level of alertness. Adequacy of feeding also influences the infant's hydration status and degree of weight loss, important contributors to early or excessive hyperbilirubinemia.

Before discharge, the clinical risk of developing hyperbilirubinemia is assessed in accordance with established guidelines. Parents should be educated about neonatal jaundice—what it is, how to assess its presence, and how to contact their physician if it is noted at home. Discharge counseling gives the physician the opportunity to reinforce the importance of the follow-up visit. This visit ensures a safe transition for the newborn by identifying feeding problems, excessive weight loss, and jaundice, and reevaluating unusual or atypical findings. All abnormalities requiring further testing should be discussed in detail with the family, and appropriate follow-up arranged. Examining the newborn at least once in the parents' presence allows the health professional to point out

significant physical findings and comment on normal variations, and gives parents the chance to have their questions answered. This practice also gives the physician the opportunity to observe parent-infant and parent-parent interactions.

### Family and Environmental Factors

Observing parents' responsiveness to their new infant and their interactions with each other can provide powerful indicators of the family's comfort level with caring for their new infant. Anticipating concerns and providing thoughtful, clear answers will reassure parents and decrease any anxiety they may feel about taking their infant home.

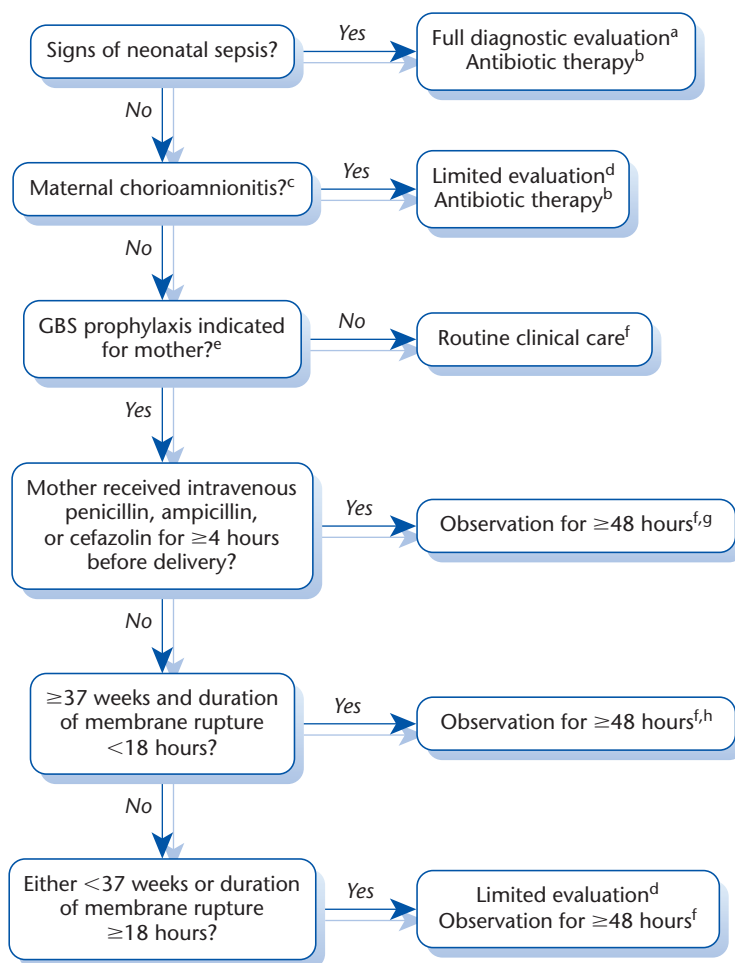
Careful attention to maternal and environmental risk factors should further influence the physician's decision about discharge readiness and may include but is not limited to inadequate social support, especially for first-time, single mothers; lack of knowledge about routine infant care and breastfeeding; adolescent parent; and presence of substance abuse or domestic violence. In addition, assessment of risk factors for postpartum depression in accordance with Bright Futures guidelines and the AAP Committee on Psychosocial Aspects of Child and Family Health must be incorporated into discharge planning. Although most physicians consider these factors, women pediatricians are 2 to 3 times more likely than men to rate these maternal and peripartum factors as highly important determinants of discharge readiness. Significant findings in these domains may not necessarily delay hospital discharge, but visiting nurse services, home visits, or earlier follow-up plans should be instituted as appropriate.

**Table 91-1**

### Strategies in the Assessment and Management of Well-Appearing Infants Born to GBS-Colonized Mothers

ADEQUACY OF INTRAPARTUM PROPHYLAXIS	REQUIRED INFANT EVALUATION	IMPLICATIONS FOR DISCHARGE PLANNING
Infants of any gestational age whose mother received <b>adequate</b> intrapartum prophylaxis (>4 hours of penicillin, ampicillin, or cefazolin).	Should be observed for >48 hours. No routine diagnostic testing is required. Well-appearing infants with a GA 35–36 weeks do not routinely require diagnostic evaluation.	Infants can be discharged home as early as 24 hours after birth, assuming that all other criteria have been met, ready access to medical care exists, and the infant's caregiver is able to comply with home observation instructions.
Mother with <b>no or inadequate</b> intrapartum prophylaxis, infant is >37 weeks' gestation, and rupture of membranes is <18 hours.	Observation for 48 hours. No routine diagnostic testing is recommended.	Infants can be discharged home as early as 24 hours after birth, assuming that all other criteria have been met, ready access to medical care exists, and the infant's caregiver is able to comply with home observation instructions.
Mother with <b>no or inadequate</b> intrapartum prophylaxis and infant is <37 weeks gestation <b>or</b> rupture of membranes is >18 hours.	Limited evaluation (blood culture, CBC with differential) and observation for >48 hours.	Infants can be discharged home after at least 48 hours of observation, assuming that all other criteria have been met, ready access to medical care exists, and the infant's caregiver is able to comply with home observation instructions.

From Verani JR, McGee L, Schrag SJ. Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010. *MMWR Recomm Rep*. 2010;59:1–32.



**Figure 91-1** Algorithm for secondary prevention of early-onset group B streptococcal (GBS) disease among newborns.

<sup>a</sup> Full diagnostic evaluation includes a blood culture, a complete blood count (CBC) including white blood cell differential and platelet counts, chest radiograph (if respiratory abnormalities are present), and lumbar puncture (if patient is stable enough to tolerate procedure and sepsis is suspected).

<sup>b</sup> Antibiotic therapy should be directed toward the most common causes of neonatal sepsis, including intravenous ampicillin for GBS and coverage for other organisms (including *Escherichia coli* and other gram-negative pathogens) and should take into account local antibiotic resistance patterns.

<sup>c</sup> Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically and some of the signs are nonspecific.

<sup>d</sup> Limited evaluation includes blood culture (at birth) and CBC with differential and platelets (at birth and/or at 6–12 hours of life).

<sup>e</sup> See Table 91-1 for indications for intrapartum GBS prophylaxis.

<sup>f</sup> If signs of sepsis develop, a full diagnostic evaluation should be conducted and antibiotic therapy initiated.

<sup>g</sup> If ≥37 weeks' gestation, observation may occur at home after 24 hours if other discharge criteria have been met, access to medical care is readily available, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until discharge criteria are achieved.

<sup>h</sup> Some experts recommend a CBC with differential and platelets at age 6–12 hours.

## COUNSELING THE FAMILY

Part of the newborn discharge process is counseling parents about how to care for their newborn infant and providing anticipatory guidance. Counseling should be tailored to the personality and practice patterns of the physician and the personality of the parents. Style notwithstanding, certain issues (summarized in Box 91-1) need to be kept in mind.

## Feeding

Physicians have the responsibility to encourage breastfeeding and should always reinforce the importance of making the decision to breastfeed.

Human milk is the best nutritional choice, and it is both economical and convenient. The most important advantage is its immunologic benefits. In addition, there is evidence that in infants at high risk for developing

**BOX 91-1 Suggested Topics for Discussion: Newborn Discharge Counseling****Feeding**

- Breastfeeding
- Bottle feeding

**Elimination**

- Urination
- Bowel movement

**Sleep**

- Sleep position
- Sleep location

**Body care**

- Umbilical cord care
- Skin care
- Bathing
- Nail care
- Dressing
- Genitalia care

**Safety**

- Vehicle safety
- Environmental toxins
  - Tobacco smoke
  - Lead
  - Carbon monoxide
  - Mold
  - Pesticides

**Signs of illness****Psychosocial issues**

allergies, exclusive breastfeeding for at least 4 months prevents or delays the occurrence of atopic dermatitis, cow's-milk protein allergy, and wheezing in early childhood. Breastfeeding also protects against obesity. Each month an infant is breastfed decreases the risk of childhood overweight. However, supporting the mother in whatever decision she makes with regard to feeding method is also the responsibility of physicians. (See Chapter 88, Breastfeeding the Newborn.)

**Breastfeeding**

Physicians should work with the nursing and lactation support staff to provide information to mothers to ensure successful breastfeeding. Information should include:

- Proper positioning and latch
- What the let-down reflex is
- What colostrum is, its adequacy for the early feedings, the normal feeding volume during the first days of life, and the newborn infant's stomach capacity
- The process and timing of the transition from colostrum to mature milk
- Ways to explore any culturally based misconceptions about giving the newborn colostrum, especially if the mother is hesitant to give the newborn

colostrum (common among women from Southeast Asia, parts of Africa, and South America)

- Strategies to promote successful initiation of breastfeeding when the mother plans to breast- and formula-feed
- How nursing frequency affects milk supply
- How to tell if the infant is nursing properly
- How to break suction and the meaning of nipple pain or discomfort
- Basic nipple care
- How to manage engorgement
- How to express milk manually or using a breast pump
- How to store expressed milk
- Vitamin D supplementation for the infant
- Signs and symptoms of mastitis
- Breastfeeding support groups (La Leche League, lactation consultants, Special Supplemental Nutrition Program for Women, Infants, and Children)

**Formula Feeding**

Commonly used infant formulas generally fall into 3 main categories: cow's-milk based, soy based, and hydrolyzed. Formulas are readily available in powder, concentrate, and ready-to-feed preparations, and no known advantage exists of one brand or form over another. If the parents are planning to feed their infant formula, then it is important to determine if the parents have particular concerns about one category of formula or another. Vegan parents will refuse cow milk-based formulas, whereas a family with a previous child who exhibited intolerance to a particular type of formula may request another specific formula. This preference is particularly important among immigrant families who may have used animal milk (eg, goat's milk) or formulas not typical for North America. There is modest evidence that using hydrolyzed formulas may delay the onset of atopic dermatitis in infants at high risk for atopy who are not exclusively breastfed for 4 to 6 months. Physicians should emphasize the importance of using iron-fortified infant formulas and the proper dilution of the powder or concentrate preparations (see Box 91-2). Fluoride supplementation should be given only to infants aged 6 months or older who live in communities where the fluoride concentration in the water is <0.3 ppm. Parents need to be informed that sterilizing water, bottles, and artificial nipples is not necessary if the water supply is safe and refrigeration is available. Infant formula need not be warmer than room temperature. The use of the microwave oven to warm the formula should be discouraged because it causes uneven heating. The physician should caution parents against bottle propping so as to prevent choking and aspiration.

**Elimination**

Parents should know what normal urination and bowel elimination patterns are for newborns. Parents need to be informed that after the first 2 to 3 days of life, infants should have at least 4 to 5 wet diapers per day. Stool elimination patterns are variable during this period and will depend on the type of feeding. Breastfed infants tend to have more frequent bowel movements than formula-fed infants. They can initially have as

### BOX 91-2 Preparation Checklist for Iron-Fortified Infant Formula

Please note that this information serves as a guide, but it is important to follow the manufacturer's recommendation for storage and instructions for formula mixing.

1. Wash your hands with soap and water, rinse well, and clean your work space.
2. Wash bottles, nipples, caps, rings, and preparation utensils in hot soapy water. Rinse thoroughly.
3. Place bottles, nipples, caps, and rings in a pot and cover with water, bring to a boil, and boil for 5 minutes. Remove with sanitized tongs. Allow the items to cool and air dry.
4. For READY TO FEED (RTF) formula: After washing and cleaning the top of the can, shake well and then open the can with a clean can opener. Pour the amount of RTF formula for 1 feeding into a clean bottle. Do not add water or any other liquid.
5. For LIQUID CONCENTRATED formula: After washing and cleaning the top of the can, shake well and then open the can with a clean can opener. Pour needed amount of formula into a clean bottle using ounce markings to measure formula and add an equal amount of cooled boiled water. This preparation will yield an infant formula that is approximately 20 calories/oz.
6. For POWDERED formula: Remove plastic lid, wash and clean the top of the can. Using the provided scoop, measure a level scoop of powdered formula. For each 2 oz of cooled boiled water in a clean bottle, add 1 level scoop of powdered formula. This preparation will yield an infant formula that is approximately 20 calories/oz.
7. After mixing the infant formula, attach nipple and ring to the bottle and shake well. Feed prepared formula immediately.
8. If several bottles are prepared, put a clean nipple right side up on each bottle and cover with a nipple cap. Label with date and time of preparation.
9. Refrigerate until feeding time. Follow the manufacturer's storage instructions. To warm the bottle, hold it under running warm water. Do not microwave the bottle. Use within 24 hours.
10. Throw out unused formula leftover after feeding or which has been unrefrigerated for 1 hour or more.

Adapted from *Infant Nutrition and Feeding: A Guide for Use in the WIC and CSF Programs*. Washington, DC: US Department of Agriculture; 2009.

many as 1 stool after every feeding because breast milk is more easily digested than formula. Formula-fed infants may have as few as 1 to 2 bowel movements per day. Stool frequency can change over the first few weeks and, by 1 month of age, can range from over 10 times per day to once every 4 to 7 days. Stool appearance also can change over time. It can transition from normal meconium stools to having a seedy yellow appearance over several days (Table 91-2).

**Table 91-2 Newborn Stool Patterns**

TYPE	CHARACTERISTICS	TIME FRAME
Meconium	Thick and tarry Dark green	Birth–2 days
Normal	Loose Green-brown to yellow-brown Seedy	2–5 days
Breastfed	Mushy and golden Often after each feeding Odor similar to sour milk	After 5 days

Constipation is a major concern for most parents, and the physician should discuss with families what constitutes true constipation. Parents should be reassured that straining is normal and represents the effort needed to pass stools while lying down. The infant is considered constipated if the stools are becoming hard. Regardless of the amount of straining or the interval between bowel movements, as long as the stools are soft, the infant is not constipated. Parents should be encouraged to discuss their infant's elimination patterns and stool characteristics during the follow-up visit if they continue to have concerns. Infants should be carefully examined since anterior anal displacement may be a cause for apparent constipation in infants.

Laxatives are not recommended. The physician should emphasize that honey should not be given to infants younger than 1 year because of the risk of developing botulism.

### Sleep

Newborns vary in their pattern of sleep and wakefulness. Newborns generally need 16 to 20 hours of sleep in a 24-hour period and can sleep for 2 to 4 hours at a time. During the first few weeks of life, having day-night reversal with longer periods of wakefulness during the night is common. Not until approximately 3 to 4 months of age do most infants begin to sleep through the night.

Safe sleep strategies should be emphasized to reduce the risk of sudden unexpected infant death (SUID), including sudden infant death syndrome (SIDS), which describes any sudden and unexpected death of a child under 1 year of age, whether explained or unexplained. Many of the sleep environment risk factors for SIDS, such as bed sharing and soft bedding materials, have accounted for accidental suffocation in many cases of SUID. In 2011, the AAP issued a policy statement regarding the expansion of recommendations for a safe sleep environment to reduce the risk of all sleep-related infant deaths including SIDS, suffocation from soft bedding materials, and entrapment from inappropriate sleep situations, such as becoming lodged between a mattress and headboard. Providing a safe sleep environment has the potential to reduce SIDS risk as well as



**BOX 91-3 AAP Recommendations for a Safe Sleep Environment**

1. Infants should be placed in a supine sleep position for every sleep period.
2. Use a firm sleep surface such as a firm crib mattress with a fitted sheet. Sitting devices such as car seats, strollers, and swings are not recommended for routine sleep.
3. The sleeping room may be shared with parents without bed sharing.
4. Soft objects and loose bedding should be kept out of the crib. This includes pillows, blankets, and bumper pads.
5. Pregnant women should receive regular prenatal care.
6. Avoid prenatal and postnatal tobacco smoke exposure.
7. Avoid prenatal and postnatal alcohol and illicit drug use.
8. Breastfeeding is recommended, preferably exclusive breastfeeding.
9. Consider offering a pacifier at nap time and bedtime. However, introduction of pacifier should be delayed in breastfed infants until breastfeeding has been well established.
10. Avoid overheating by ensuring that infants are dressed appropriately for the environment and avoiding overbundling and covering the face and head.
11. Infants should receive all recommended immunizations.
12. Avoid commercial devices such as wedges and positioners that can increase the risk of suffocation.
13. Do not use cardiorespiratory home monitors.
14. Supervised awake “tummy time” is recommended to allow upper body muscular development and reduce the risk of positional plagiocephaly.

reduce the risk for SUID. The HHS and the US Consumer Product Safety Commission (CSPC) have endorsed the AAP recommendations, summarized in Box 91-3.

Despite these recommendations, parents and caregivers have been resistant to implementation of supine sleep position. Common reasons include fear of choking or aspiration and perception that the infant is uncomfortable and does not sleep well in the supine position. Pediatricians should reassure parents and caregivers that coughing or gagging is a normal protective reflex to prevent choking and aspiration and that sleep arousal is an important protective response to sleep stressors.

The issue of co-sleeping remains controversial. Forms of co-sleeping vary and include bed sharing. The sleep surface can range from sharing a mat, a futon, or the floor to sleeping on a soft mattress, quilt, waterbed, sofa, or couch. These varying surfaces may not pose an equal risk to the infant. Bed sharing is increasing in frequency throughout the United States. Studies have reported that over one-third of new mothers bed-shared frequently,

with another 40% bed-sharing with their infant sometimes. Bed sharing was equally as common among mothers who smoke as those who do not in this study. Another case-controlled study found an association between bed sharing and SIDS when the infant was sleeping between 2 parents. This association was highest for infants younger than 11 weeks. This study has been criticized for having assessed bed sharing alone as a risk factor (rather than the environment within which the bed sharing occurred) and not assessing the presence of parental alcohol use at the time of bed sharing and breastfeeding in the analysis.

Sensitivity to cultural differences is necessary when obtaining sleep histories. Additionally, the assumption should not be made that families are practicing only 1 sleep arrangement over the course of the day and night. Health care professionals should consider this factor when obtaining a history on infant sleep practices and encourage parents to express their views about infant sleep and recommended sleep practices.

An alternative to sharing an adult bed or sharing a mattress is using an infant bed that attaches to the side of the adult bed and provides proximity and access to the infant but has a separate sleep surface. No current, peer-reviewed studies of such devices have been conducted, and the CSPC has not yet established safety standards for these attachable co-sleepers.

**Body Care****Umbilical Cord Care**

Evidence-based care of the umbilical cord in the postnatal period includes effective hand hygiene and keeping the cord dry and exposed to air or loosely covered with clean clothes, with the diaper folded below the umbilicus. If the umbilical cord stump becomes soiled with urine or feces, then cleansing the area with water is adequate. Studies conducted in developed countries have shown that topical antiseptics of the cord stump reduces cord colonization. However, a systematic review of randomized trials that assessed the efficacy of applying topical antimicrobial agents in the prevention of infection has not shown this practice to be superior to simply keeping the cord clean. Chlorhexidine (Hibiclens) or hexachlorophene (pHisoHex), tincture of iodine or povidone-iodine (Betadine), silver sulfadiazine, and triple dye have the most efficacy in reducing umbilical cord colonization. If topical antimicrobial agents are used, then care must be exercised because toxicity has been reported with excess or inappropriate use.

Although some hospitals and physicians continue to recommend application of alcohol to the umbilical cord, alcohol use has been shown to delay umbilical cord drying, is less effective in reducing bacterial colonization, and delays cord separation. Therefore, alcohol application is not recommended for routine umbilical cord care.

The umbilical cord stump usually separates between 8 and 15 days of age (up to 3 weeks may be normal). Minimal discharge is to be expected

thereafter. However, if significant amounts of discharge persist, it should be brought to the physician's attention. Until the cord falls off, the area should be kept dry as much as is possible to promote separation and healing. For this reason, giving infants only sponge baths is best until the cord is well healed.

### **Skin Care**

Skin lubrication is usually not necessary; however, if it is needed, then it should be limited to the use of hypoallergenic lotions. Oil-based preparations, such as petroleum-based lubricants or barriers containing zinc oxide, are more effective than water-based preparations. Talcum powder should not be used because of the danger of aspiration. The diaper area is best cleansed with warm water with each diaper change, although the use of commercially available infant wipes offers many conveniences. Although these wipes may contain chemicals, alcohol, and fragrances that can cause skin irritation, most of these products, particularly those designated as *hypoallergenic* or *sensitive*, are found to be as mild as using a wet washcloth and may be used even in the newborn period. Wipes free of fragrance, alcohol, and other chemicals, except for lotion, have been shown to be gentler than water alone. Most diaper rashes will improve with applications of zinc oxide or an antifungal preparation if the rash is not improving and has the appearance of a candidal infection. Parents should be encouraged to notify their child's health professional for a persistent diaper rash. Evidence-based clinical practice guidelines on the care of neonatal skin have been published by the Association of Women's Health, Obstetric, and Neonatal Nurses.

### **Bathing**

The purpose of bathing during the neonatal period is to remove debris. Daily bathing with soap is not recommended during this time because it may contribute to excessive drying of the skin and can exacerbate skin conditions such as atopic dermatitis. Young infants can be washed with plain water 2 to 3 times per week during the first year. However, if use of a cleanser or soap is preferred, then it should be mild with a neutral pH. Hair can be shampooed a few times weekly using a mild shampoo or body wash.

### **Nail Care**

Scissors should not be used. Nails should be filed using an emery board.

### **Dressing**

Healthy, full-term infants do not need to be dressed more warmly than an older child or adult. Parents can use themselves as a guide to determine the amount of clothing to put on the infant. A good rule of thumb is to dress the infant in 1 more layer of clothing than an adult would be wearing in the same environment. Specific guidance will need to incorporate the ambient temperature of the home where the child resides, as well as reflect the regional environmental temperatures. Questions often arise as to how warmly to dress the late preterm (34 $\frac{0}{7}$  to 36 $\frac{6}{7}$  weeks' gestation) infant. In general, the same principles apply in deciding how much clothing to use. The need

for extra clothing or use of double blankets for these infants will primarily depend on the infant's ability to maintain temperature in the ambient environment. The infant's temperature regulation will be determined, in part, by adiposity, degree of physiologic maturity, and ongoing metabolic demands. Because of high heat losses through the scalp, parents should be encouraged to cover the infant's head when going outside. Care must be exercised when swaddling a young infant. Although this method is effective for soothing a fussy infant and maintaining body temperature, an overbundled infant is at risk for hyperthermia and potentially at increased risk for SIDS if overheated during sleep.

### **Taking the Newborn Outdoors**

As soon after discharge as the mother is ready to go outside, the newborn can go out as well. Many parents are hesitant to take their newborn outside because of fear of exposure to airborne and other communicable illnesses. A common belief among many families is that an infant cannot go outside the home until the first or second set of immunizations has been received. Cultural prohibitions against outings before a certain age may also exist. Korean parents typically keep an infant indoors until the 100th day, the time when the infant's survival is thought to be more assured. Time spent in close contact with crowds should be limited and sick contacts should be avoided. Appropriate protection against excess sun exposure should also be discussed.

### **Genitalia Care—Boys**

The uncircumcised penis should be cleansed simply with water with or without a mild soap or with a diaper wipe. Retracting the penile foreskin is unnecessary because adhesions will spontaneously lyse over the first several years of life. The newly circumcised penis can also be cleansed with warm water and gentle soap with every diaper change. An antibacterial ointment or other lubricant such as vitamin A and D ointment can be applied to the area to prevent the skin from sticking to the diaper as it heals, and can reduce the small chance of infection.

### **Genitalia Care—Girls**

Recommendations suggest washing the area between the labia gently with warm water only. Diaper wipes may be used if they do not cause skin irritation, and parents should be instructed to always wipe girls from the vagina toward the anus (front to back). Parents should be informed that a white caseous discharge or even a bloody discharge from the vagina might occur in the first few days. This discharge is the result of maternal hormones that are absorbed by the fetus before delivery.

### **Safety Issues and Injury Prevention**

#### **Safe Infant Handling**

Infants are at risk for abusive head trauma (also known as shaken baby syndrome). Shaking can cause intracranial bleeding and death. Parents should be counseled to avoid handling an infant when they are overwhelmed, angry, or frustrated.

### Vehicle Safety

Vehicle seat safety should begin with the first ride home from the hospital. The physician should emphasize to parents that a car safety seat must be used at all times. The AAP Committee on Injury and Poison Prevention recommends that all infants and toddlers should ride in a rear-facing car safety seat until they are 2 years of age or until they reach the highest weight or height allowed by the manufacturer of their car safety seat. A seat with a 5-point harness provides the best fit and protection to a newborn; parents may choose an infant-only seat or a convertible car seat that accommodates the child rear facing to a higher weight and height. For AAP patient education resources on car safety seats and transportation safety, see Tools for Practice.

### Environmental Toxins

Several hazards exist in the home environment. Newborns have a unique vulnerability to certain environmental toxins, and their rapidly developing organ systems are particularly susceptible to the harmful effects of toxins. Toxic exposures of newborns differ from other age groups because of their own unique physical environment, food and water consumption pattern, and behavioral developmental stage. Parents should be informed about common environmental toxins that can significantly affect the health of their infant.

**TOBACCO SMOKE.** Tobacco smoke is a common toxic substance that is harmful to everyone, including young infants. Parents should be educated about the harmful effects of inhaled secondhand smoke, which include increased incidence of lower respiratory infections, otitis media, cough, asthma, and SIDS. The physician should stress that smoking not be allowed in the immediate environment of the infant, such as in the house or vehicle.

**CARBON MONOXIDE AND OTHER SOURCES OF INDOOR AIR POLLUTION.** Infants can be vulnerable to the effects of inhaled carbon monoxide. Intoxication from inhaled carbon monoxide can cause tissue hypoxia, which can affect multiple organ systems, with the central nervous and cardiovascular systems being the prime targets. Installing smoke and carbon monoxide detectors in the home can prevent unintentional carbon monoxide inhalation (Box 91-4). The increased popularity of scented candles and incense poses another potential hazard to young children. Burning candles with lead-core wicks have been associated with lead levels above established Environmental Protection Agency standards. Even candles with nonlead wicks pose a hazard because they often release potentially harmful organic chemicals, such as formaldehyde, acetaldehyde, and acrolein. Soot from scented candles and particulate emissions from burning incense have been linked to respiratory symptoms and irritant dermatitis in vulnerable individuals.

**LEAD.** Risk factors for lead exposure in pregnant women differ from those described for young children. The most common route and source of fetal and neonatal lead exposure is pregnancy and breastfeeding. Maternal pica during pregnancy, although rare, is an

### BOX 91-4 Sources of Carbon Monoxide Exposure

- Motor vehicle exhaust
- Unvented kerosene and propane gas space heaters
- Leaking chimneys and furnaces
- Back draft from furnaces
- Woodstoves and fireplaces
- Charcoal grills
- Gas appliances: stoves, dryers, water heaters
- Gasoline-powered generators
- Gasoline-powered equipment: lawn mowers, leaf blowers, floor polishers, snow blowers, pressure washers
- Tobacco smoke

Adapted from American Academy of Pediatrics Committee on Environmental Health. Carbon monoxide. In: Etzel RA, ed. *Pediatric Environmental Health*. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2003.

identified cause of fetal lead intoxication. Although the CDC does not recommend routine blood lead testing of all pregnant women in the United States, it does encourage state or local public health departments to identify populations at increased risk for lead exposure and encourages physicians to use community-specific risk factors as a guide in determining the need for population-based blood lead testing. Routine blood lead testing of pregnant women is recommended in clinical settings that serve populations with specific risk factors for lead exposure. Common risk factors for pregnant women include recent immigration status, practicing pica, occupational exposure, use of alternative remedies or cosmetics, use of traditional lead glazed pottery, and nutritional status. Risk assessment of lead exposure should take place at the earliest contact with pregnant or lactating women. If this has not occurred during the prenatal period, then the pediatric provider should ask the mother about potential risks for lead exposure. The pediatric provider should discuss with the maternity care provider any risk factors elicited from the mother and request maternal lead screening.

Newborns who are given reconstituted infant formula prepared with tap water are at potential risk for lead intoxication. Lead still can be found in some metal water taps, interior water pipes, or pipes connecting a house to the main water pipe in the street. Lead found in tap water usually comes from the corrosion of older fixtures or from the solder that connects pipes. When water sits in leaded pipes for several hours, lead can leach into the water supply. To minimize lead exposure from drinking water, recommendations suggest flushing the water faucet in the morning for 2 minutes before using it to prepare the formula and using only cold tap water for drinking and preparing milk formula. For full recommendations from the CDC, see [www.cdc.gov/nceh/lead/tips/water.htm](http://www.cdc.gov/nceh/lead/tips/water.htm).

**PESTICIDES.** More than 900 chemicals are registered in the United States as pesticides. These substances include insecticides, fungicides, rodenticides, fumigants, and insect repellents. The developing organ systems of

young infants are especially susceptible to the harmful effects of these toxic chemicals. Routes of exposure for newborns are inhalation and skin absorption by contact. Infants of parents with occupational exposures to pesticides such as those who work on farms, pesticide applicators, or landscapers are at increased risk of exposure to pesticides. Prevention includes washing work clothes separately from the infant's laundry, changing out of work clothing, and washing with soap and water before coming into close contact with infants and children (Box 91-5).

### Signs of Illness

Parents should know when and how to contact the physician or the pediatric office in case of an emergency. Parents should be advised to contact the physician for the following reasons:

- Fever (rectal temperature  $\geq 100.4^{\circ}\text{F}$  [ $\geq 38^{\circ}\text{C}$ ])
- Persistent coughing or breathing difficulty
- Cyanosis (Few parents understand what the terms *cyanosis*, *blue*, or *dusky* skin color actually mean. Explanations should also include the differences between peripheral [acrocyanosis], circumoral, and central [body core] cyanosis. The physician should therefore explain these potential concerns and assess the parents' understanding.)
- Sudden change in level of alertness, activity such as persistent irritability, or lethargy
- Feeding difficulties
- Persistent or projectile vomiting
- Diarrhea
- Jaundice
- Seizures
- Decreased urine output
- Umbilical cord problems
- Unusual skin rash or skin mottling

### Psychosocial Issues

The first few weeks at home with a newborn can be stressful to all family members but particularly new

parents. The need for an adequate support system at home cannot be overemphasized. Sources of extra help might be family members, close relatives and friends, or hired help. Close support persons can assist with infant care and household chores. For families who do not have the advantage of having an adequate support system, community agencies are often available to assist them. Information on public and private groups that can provide services to these families is usually available through the social service department. It is reported that 11% to 18% of women experience postpartum depressive symptoms. It is therefore important that the pediatrician assess the mother for depressive symptoms.

Devoting a large amount of time to discharge counseling is often difficult because of time constraints and shorter hospital stays. However, allowing sufficient time for parents to ask questions and for these questions to be addressed is important. Whether it is the initial or a subsequent meeting between the physician and the parents, the physician must be able to ascertain the kind of professional relationship the family desires, as well as anticipate needs relative to care of their newborn and integration as a family unit.

Of paramount importance is the personal interaction between the physician and the parents before the discharge of the infant from the hospital. Providing reading materials to parents is relatively easy, but handouts can never replace personal interaction, which can lay the groundwork for a lasting professional relationship between the physician and the parents.

## FOLLOW-UP NEWBORN CARE

### Timing

Follow-up of newborns within the first week of life—typically within 48 to 72 hours of nursery discharge (by 3–5 days of age) for newborns going home from the hospital within 48 hours of birth, newborns who are breastfeeding, or newborns with health concerns that place them at risk for early medical problems (such as the late preterm infant)—is crucial to assessing the adequacy of hydration and feeding patterns and to assessing bilirubin levels and degree of weight loss. Studies have shown that newborns who receive early follow-up visits were less likely to be rehospitalized within the first 10 days of life for jaundice or dehydration. The AAP recommends that all healthy, full-term (37–41 weeks), singleton newborns whose birth weight is appropriate for gestational age and who are discharged in fewer than 48 hours should have a follow-up appointment preferably within 48 hours, and no later than 72 hours of discharge. For late preterm infants (34–36 weeks), the recommendation for the follow-up visit is within 24 to 48 hours of hospital discharge because they are at greater risk of neonatal morbidity and mortality than term infants. For infants who are discharged more than 48 hours after childbirth, the first office visit may occur within 2 to 4 days of discharge. In some communities, hospitals routinely offer families the option of bringing the infant back to the hospital for a postdischarge visit. These guidelines apply equally to formula-fed and breastfed infants. The AAP Section on Breastfeeding

### BOX 91-5 Safe Pesticide Practices

- Wash work clothes separately from other laundry.
- Wash work clothes with detergent and hot water before wearing them again.
- Wash hands and arms after putting clothing into washing machine.
- Change clothing and wash with soap and water before picking up or playing with your children.
- Store pesticides in an area safe from children.
- Cover children's skin if they are with you at work.
- Keep the children and their toys and playthings indoors when there is nearby aerial spraying or spraying that may drift near the house.
- Children and teenagers should avoid work that involves mixing or spraying pesticides.

Adapted from American Academy of Pediatrics Committee on Environmental Health. Pesticides. In: Etzel RA, Balk SJ, eds. *Pediatric Environmental Health*. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012:515–548.



states: “All breastfeeding newborn infants should be seen by a pediatrician or other knowledgeable and experienced health care professionals at 3 to 5 days of age . . . and again at 2 to 3 weeks of age.”

### Purpose

Although the main purpose of the visit is to detect problems such as jaundice, feeding difficulties, and excessive weight loss or poor weight gain, this visit also provides another opportunity for parents to have their infant examined, to be reassured about minor physical variations, and to have their questions answered, and for the physician to assess parent-infant interaction and the adaptation of the parents to their new role.

The 2010 policy statement from the AAP states that the purpose of the follow-up visit is to:

- Weigh the infant; assess the infant’s general health, hydration, and degree of jaundice; identify any new problems; review feeding pattern and technique; and obtain historical evidence of adequate urination and defecation patterns for the infant
- Assess the quality of mother-infant attachment and details of infant behavior
- Reinforce maternal or family education in infant care, particularly regarding infant feeding and safety such as breastfeeding, back to sleep, and child safety seats
- Review the results of outstanding laboratory tests, such as newborn metabolic screens, performed before discharge
- Perform screening tests in accordance with state regulations and other tests that are clinically indicated, such as serum bilirubin measurement
- Verify the plan for health care maintenance, including a method for obtaining emergency services, preventive care and immunizations, periodic evaluations and physical examinations, and necessary screenings
- Assess for parental well-being including postpartum depression in the mother

Families need reassurance that they are responding adequately to their infant’s cues. Even a simple discussion of the normal variations in a newborn’s schedule with regard to timing of feedings, sleep, and stool consistency and frequency can alleviate concerns and empower parents to be better observers, which can ultimately decrease stress and allow greater enjoyment of parenthood.

### Barriers

On hospital discharge, physicians should ensure at a minimum that the following barriers to adequate follow-up care are identified and addressed:

- Lack of transportation to medical care services
- Lack of easy access to telephone communication
- Non-English-speaking parents

Inadequate communication from the hospital to the community-based provider about a newborn’s birth, medical history, and relevant laboratory data may be the result of a lack of a clear mechanism for communication, as well as the fact that some families have not identified a postdischarge provider at

the time of discharge. Gaps in parental knowledge have been attributable to a decreased opportunity for parental education with shorter LOS and lack of physician awareness for early follow-up.

Despite the published recommendations for follow-up of newborns, many do not have a posthospital follow-up visit within the recommended time frame and do not receive appropriate management of hyperbilirubinemia. Only approximately 50% of healthy term newborns who need phototherapy based on the AAP practice parameter actually receive it. This circumstance results, in part, from the reality that even guidelines based on an evidence-based approach do not translate readily into changes in standards of care and improved practice. The AAP recognizes that “knowledge is essential but not sufficient to produce behavior change” and has developed the *Safe & Healthy Beginnings* toolkit, which contains a discharge readiness checklist. This resource was developed to help physicians prepare a newborn for discharge and to close the gap between theory and practice in the management of issues that are critical to promoting a seamless transition from hospital discharge to home during the critical first week of life.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Breastfeeding Your Baby: Getting Started* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Car Safety Seat Check-up* (fact sheet), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Car Safety Seats: A Guide for Families 2015* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Caring for Your Baby and Young Child: Birth to Age 5*, 6th ed (book), American Academy of Pediatrics (shop.aap.org)
- *Circumcision* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Heading Home With Your Newborn* (book), American Academy of Pediatrics (shop.aap.org)
- *Jaundice and Your Newborn* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *The New Crib Standard: Questions and Answers* (blog entry), US Consumer Product Safety Commission (onsafety.cpsc.gov/blog/2011/06/14/the-new-crib-standard-questions-and-answers/)
- *Protecting Your Baby From Abuse: Important Information About Preventing Brain Injuries in Infants* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Safe Sleep and Your Baby: How Parents Can Reduce the Risk of SIDS and Suffocation* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Safe to Sleep* (Web page), US Department of Health and Human Services (www.nichd.nih.gov/sids)
- *TIPP Safety Slips: Four Steps to Prepare Your Family for Disaster* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Your Baby’s First Year*, 3rd ed (book), American Academy of Pediatrics (shop.aap.org)

## AAP POLICY

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## Chapter 92

# FOLLOW-UP CARE OF THE HEALTHY NEWBORN

Deborah E. Campbell, MD

The timing of initial follow-up care of newborns after nursery discharge is based on several factors: the newborn's gestational age and postnatal age at hospital discharge, whether the newborn is breastfeeding or formula feeding, the quality and efficiency of the newborn's feeding abilities, and the presence of risk factors that predispose to complications or an increased risk for early hospital readmission. In a report by Jackson et al, 8% of indigent urban neonates monitored developed signs of illness in the early postnatal period. Of these, 31% developed symptoms after 24 hours of age, emphasizing the importance for early postdischarge follow-up care. Among insured newborns with access to an integrated system of health care, follow-up care within 72 hours of nursery discharge has been found to be protective against the risk for early rehospitalization. The Pregnancy Risk Assessment Monitoring System (PRAMS) collects data about newborn discharge and the timing and adequacy of postdischarge follow-up care from 27 states participating in this Centers for Disease Control and Prevention program. In 2002 the percentage of newborns discharged from the hospital within 48 hours of birth ranged from 50% to 70%. Significant geographic variation in newborn infant follow-up rates, ranging from 58% to 90%, was noted across the United States. PRAMS also found that during the period between 2000 and 2002, several states improved in the proportion of infants receiving follow-up within the first week of life. Five states (Arkansas, Florida, Illinois, North Carolina, and Utah) made significant strides in improving adherence with first-week follow-up care for newborns during this period of monitoring. Also notable is that only 2 states, New York and Rhode Island, exceeded the 90% threshold for infants having received *sufficient well-baby care* during the first 9 months of life in the time period studied. On average, newborns stay in the hospital for 3.4 days. During 2009 to 2010, 93.2% of mothers reported that their newborns had a follow-up pediatric visit within 1 week after the birth. The proportion of mothers reported pediatric visits within the first week varied by race and ethnicity; the lowest rates being reported by non-Hispanic American Indian/Native Alaska mothers. Recent investigations have focused on the group of infants identified as at greatest risk for early neonatal mortality and morbidity—the late preterm (34<sup>0</sup>/<sub>7</sub> to 36<sup>6</sup>/<sub>7</sub> weeks' gestation) and early term (37<sup>0</sup>/<sub>7</sub> to 38<sup>6</sup>/<sub>7</sub> weeks', gestation) infants. Among late preterm infants there was no change in the rate of early discharge between the years 2000 (40%) and 2005 (39%). Variation in individual state practices regarding the timing of newborn discharge persisted as did variation in discharge timing related to insurance coverage

and hospital type. Nonteaching hospitals were more likely to discharge infants early if they were uninsured or insured through a health maintenance organization. Among infants insured through state Medicaid programs there was a similar, though not statistically significant trend toward earlier discharge. Delayed pediatric follow-up care remains a common problem in both urban and suburban settings. Despite policy guidelines and efforts to increase awareness of the importance of appropriate discharge planning and early postnursery follow-up care for late preterm and term infants discharged home within 48 hours of their birth, delays in the necessary postnatal follow-up continue.

Early follow-up is important in terms of reassessing the newborn for signs of illness related to congenital malformations that are not evident at birth or during the immediate newborn period. New mothers report they experience new physical and emotional problems following technology-intensive births with high rates of cesarean deliveries and other interventions, get limited support from husbands/partners and others, must return to employment within a short period of time, and are often unable to start or continue breastfeeding as they want. Parental adaptation to their new role and an assessment of the mother's and the newborn's readiness to leave the hospital are additional aspects to consider in determining how soon follow-up should occur. Maternal depression and the potential for peripartum abuse of the mother are additional potential risk factors that support the need for early follow-up. Infant care practices of concern, such as co-sleeping, are being reported with increasing prevalence. Research regarding perceptions about mother and baby readiness for discharge from the hospital emphasizes the importance of mutual decision making about the optimal time for discharge and follow-up care. Recommendations concerning the optimal timing for the initial postdischarge pediatric visit are consensus based, formulated from reported cohort and population study outcomes for newborns who have been discharged within 48 hours of birth.

The initial follow-up visit may be provided in the newborn's home, a hospital-affiliated newborn follow-up clinic, or in the pediatrician's office. The guiding principle for this phase of care is that it should be a physician-directed source of continuing medical care for the mother and baby. An important factor in the decision about where and how the initial care should occur is identification of barriers to the parents' ability to comply with early postnatal follow-up. Issues of access to care remain significant despite the 1996 Newborns' and Mothers' Health Protection Act and the Health Insurance Portability and Accountability Act of 1996, which stipulate that access by the mother and her newborn to appropriate follow-up health care must be ensured, and that insurers cannot deny newborns coverage to avoid complying with these federal mandates. Numerous studies document the effect of federal regulations and the newborn's insurance status on health care utilization and the timeliness of postdischarge newborn follow-up. Common factors identified across studies are the level of maternal education, families living in poverty or residing in poor communities with limited

access to care, other children at home, and immigrant or non-English-speaking status.

Barriers to timely follow-up of newborns during the first week of life have been explored through focus groups with families and physicians. Physicians and parents identify issues of communication and information, processes of care, and parent knowledge and education as critical factors. Parents value and can assimilate information about early warning signs in regard to their newborn. Pediatricians play an important role in setting office practices regarding the timing of newborn follow-up care. Despite a long-established recommendation regarding the need for early follow-up after a short newborn nursery hospitalization, many physicians still counsel parents that follow-up within 1 to 2 weeks after nursery discharge is acceptable. Other barriers are limited office hours or inadequate hospital and community resources to provide timely home health or public health nursing visits, particularly on weekends and holidays. This barrier can prevent a family's adherence with a recommended 24- to 48-hour (3–5 days of age) follow-up visit or home visit. Assistance with scheduling the initial follow-up appointment, particularly among Medicaid recipients, has been shown to be an effective strategy to parental adherence with infant follow-up.

Goals of 48- to 72-hour follow-up care appointment include the following:

- Assess the newborn's general health, hydration, and degree of jaundice, and identify any new problems.
- Review the newborn's feeding pattern and feeding skills, including observation of a breastfeeding episode for appropriate positioning, latch-on, coordinated sucking and swallowing, and any maternal concerns regarding clinical problems that can disrupt effective breastfeeding (newborn state regulation; cracked or sore nipples; mastitis; engorgement, flat, or inverted nipples, prior breast surgery).
- Review the pregnancy and family (including genetic) history, pertinent prenatal diagnostic test results, and the newborn's nursery course to ensure identification of risk factors requiring further assessment and follow-up care. (This review is particularly important if the infant is new to the practice.)
- Assess the infant's voiding and stooling patterns.
- Assess maternal/caregiver–infant interaction and details of newborn behavior (state regulation and adaptation), maternal and family adaptation to the infant, family functioning, and signs of maternal/caregiver depression or family distress.
- Reinforce education about newborn care, exclusive breastfeeding, appropriate newborn feeding practices, and safety, including safe sleep practices.
- Combination breastfeeding and formula feeding shortens the duration of breastfeeding.
- New mothers experience a variety of perceived barriers and challenges that contribute to early breastfeeding cessation.
- Review which newborn screening tests were performed during the infant's newborn hospitalization. Infants discharged home before 24 hours of milk feedings require a repeat blood spot test by



3 to 5 days of age. Some states routinely require a second blood spot test be obtained when the infant is 3 to 5 days of age.

- The optimal time for screening for congenital hypothyroidism is between 48 and 96 hours of life. Specimens collected in the first 24 to 48 hours of life may lead to false-positive thyroid-stimulating hormone elevations when using screening test methods.
- If the infant referred on initial newborn hearing screening or if screening was not performed during the birth hospitalization, ensure that the family has an outpatient appointment for a hearing screening.
- Review or, if not done during the newborn hospitalization, complete the risk assessment for severe

hyperbilirubinemia. The determination of risk factors for hyperbilirubinemia in conjunction with physical examination and transcutaneous or total serum bilirubin level are effective in reducing the risk for acute bilirubin encephalopathy (Figure 92-1).

- In 2011, the US Department of Health and Human Services issued recommendations that screening for critical congenital heart disease (CCHD) should be added to the panel of conditions for which all newborn infants are screened. Many states have passed legislation requiring universal screening for CCHD before newborn nursery discharge. Physicians should be aware of the regulations in their state and affiliated delivery hospital practices, and perform a careful physical examination on all newborn infants, since

## Is the Baby at Risk for Severe Hyperbilirubinemia?

### Predischarge Assessment of the Risk for Severe Hyperbilirubinemia in Newborns 35 or More Weeks of Gestation

Newborn name \_\_\_\_\_

Hospital \_\_\_\_\_

Bar code space \_\_\_\_\_

Gestational age \_\_\_\_\_ weeks

#### Risk Factors for Development of Severe Hyperbilirubinemia<sup>a</sup>

Risk Factors	Major Risk	Minor Risk	Decreased Risk
<b>Gestational age</b>	<input type="checkbox"/> 35–36 wk	<input type="checkbox"/> 37–38 wk	<input type="checkbox"/> ≥41 wk
<b>Predischarge TSB/TcB</b>	<input type="checkbox"/> >95th Percentile	<input type="checkbox"/> >75th–95th Percentile	<input type="checkbox"/> <40th Percentile
<b>Visible jaundice</b>	<input type="checkbox"/> First 24 h	<input type="checkbox"/> Before discharge	
<b>Feeding</b>	<input type="checkbox"/> Exclusive breastfeeding (↑ risk if poor feeder or ↑ weight loss <sup>b</sup> )	<input type="checkbox"/> Breastfed, nursing well	<input type="checkbox"/> Exclusive formula feeding
<b>Previous sibling</b>	<input type="checkbox"/> Received phototherapy	<input type="checkbox"/> Jaundiced, no phototherapy	
<b>Blood groups Hemolytic disease</b>	<input type="checkbox"/> Blood group incompatibility + DAT Other hemolytic disease (eg, G6PD)		
<b>Race</b>	<input type="checkbox"/> East Asian	<input type="checkbox"/> Latina/Latino	<input type="checkbox"/> African American unless G6PD deficiency (12%)
<b>Other factors</b>	<input type="checkbox"/> Cephalohematoma, significant bruising, or vacuum delivery	<input type="checkbox"/> LGA newborn, male, maternal, age ≥25 y, oxytocin in labor	<input type="checkbox"/> Discharged from hospital after 72 h

TSB, total serum bilirubin; TcB, transcutaneous bilirubin; DAT, direct antiglobulin test; G6PD, glucose-6-phosphate dehydrogenase; LGA, large for gestational age.

The risk factors highlighted in yellow are those most predictive for subsequent hyperbilirubinemia.

<sup>a</sup>The more risk factors present, the greater the risk of developing severe hyperbilirubinemia.

<sup>b</sup>Weight loss of more than 7% to 10% in a breastfeeding newborn requires assessment and plan.

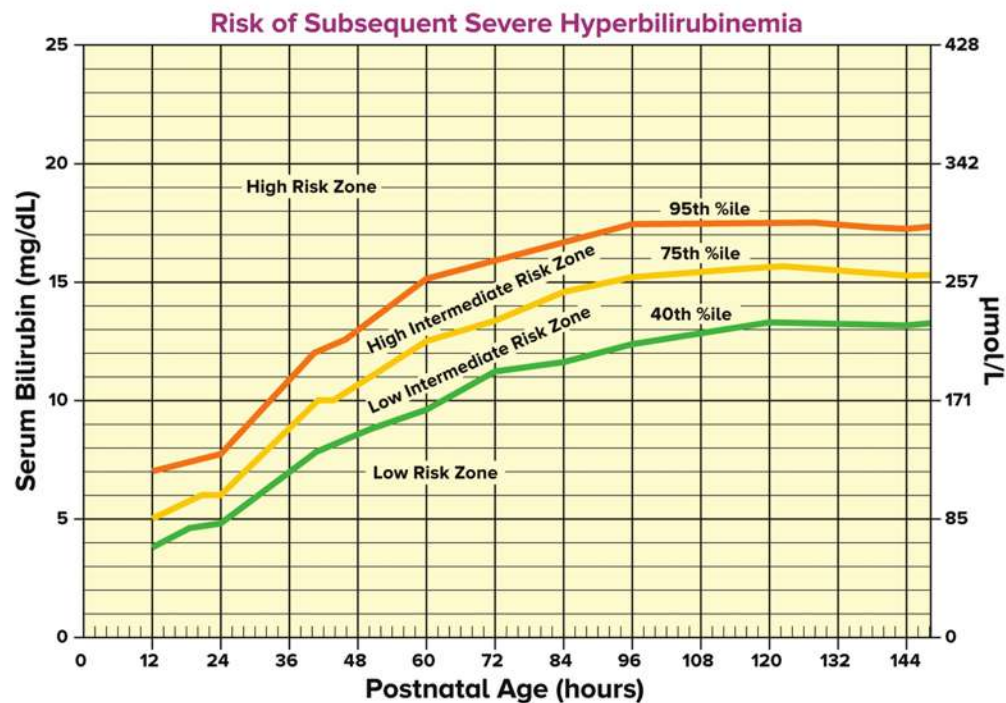
**Figure 92-1** Predischarge assessment for risk of severe neonatal hyperbilirubinemia.



**Predischarge Bilirubin**

Date	Time	Age (h)	TcB	TSB	Initials

TcB, transcutaneous bilirubin; TSB, total serum bilirubin.

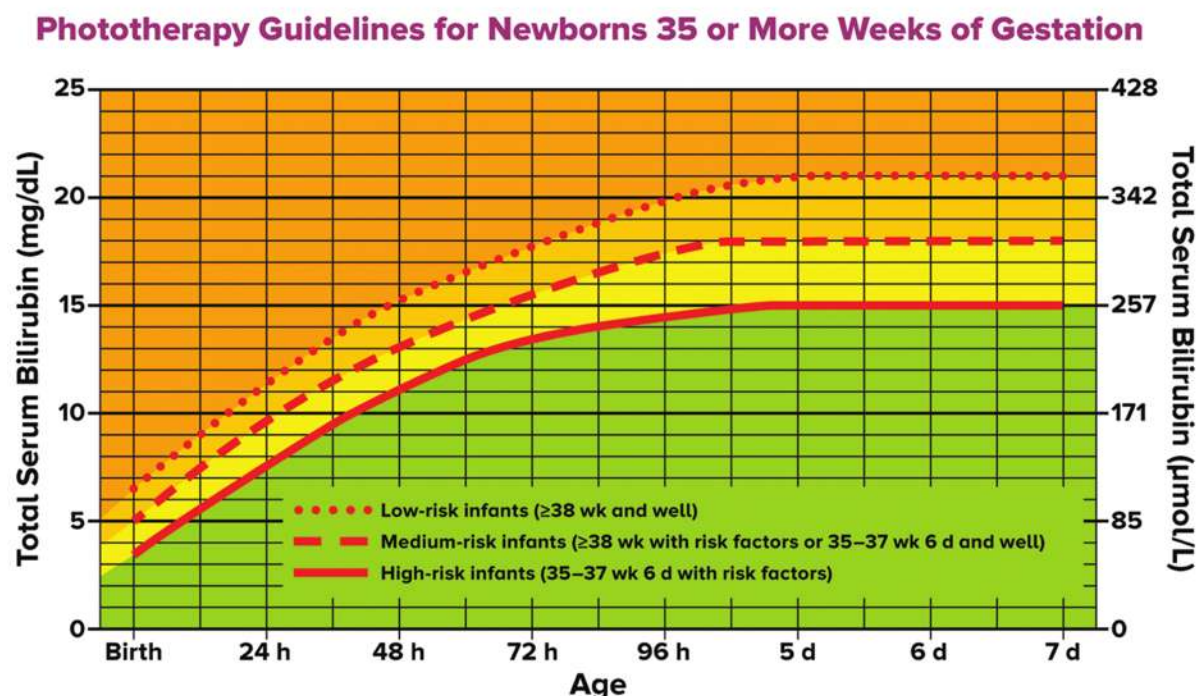
Bhutani et al. *Pediatrics*. 1999;103:6–14

It is recommended that a newborn discharged before 72 hours of age be assessed by a licensed health care professional within 2 days of discharge.

**Follow-up Plan** ☐ Primary Care Practitioner Office ☐ Nurse Home Visit ☐ Newborn Nursery  
☐ Lactation Consultant ☐ Emergency Department

**Figure 92-1, cont'd***Continued*

## Does This Baby Need Phototherapy?



Source: Maisels MJ, McDonagh AF. Phototherapy for neonatal jaundice. *N Engl J Med*. 2008;358:920–928

- These guidelines are based on limited evidence.
- Guidelines refer to use of *intensive* phototherapy, which is the use of high levels of irradiance in the 430- to 490-nm band (usually  $30 \mu\text{W}/\text{cm}^2$  per nm or higher) delivered to as much of the newborn's surface area as possible.
- *Use total bilirubin.* Do not subtract direct reacting or conjugated bilirubin.
- ***Risk factors referred to in the graph key indicate specific risk factors that increase the likelihood of brain damage at different bilirubin levels.*** These risk factors include isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase deficiency, asphyxia, respiratory distress, significant lethargy, temperature instability, sepsis, acidosis, or albumin less than 3.0 g/dL (if measured).
- For well babies born between 35 and 36 6/7 weeks, you can adjust total serum bilirubin (TSB) levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for newborns closer to 35 weeks and at higher TSB levels for those closer to 37 6/7 weeks.
- It is an option to provide phototherapy in the hospital or at home at TSB levels 2 to 3 mg/dL below those shown, but *home phototherapy should not be used in any newborn with risk factors listed herein.*

**Figure 92-1, cont'd**

neither prenatal nor postnatal screening will detect all congenital cardiac disease.

- Review with the mother or caregiver the baby's ongoing preventive health care needs, including immunizations and scheduling of other evaluations as needed, based on prenatal testing or postnatal assessment.
- Review the importance of parental, sibling, and other caregiver vaccinations against influenza, pertussis, and other communicable diseases in providing additional protections for the young infant. Late preterm infants born between 34 and 35 weeks' gestation may also be eligible for prophylaxis against RSV infection if they have siblings under age 5 or will be in day care during the height of RSV season (November through March) and are less than 90 days of age.
- Review with the mother/caregiver how to access care in an emergency and for routine or nonurgent issues.
- Review with the mother/caregiver the adequacy of family resources, including the newborn's health care coverage. Solicit and discuss any parent-identified concerns or issues related to the newborn or family.

Neonatal weight loss is often an issue of concern for families and physicians, particularly because dehydration and failure to thrive are significant risks for the newborn who is experiencing feeding difficulties or whose mother has lactation failure. Controversy exists about routine monitoring of a newborn's weight because some physicians express concern about unnecessary interventions, interruption of exclusive breastfeeding, and parental anxiety in response to early weight loss. McKie et al noted that implementation of regular neonatal weight monitoring among a cohort of infants in Scotland did not reduce breastfed among the cohort of women and infants studied. Another recent cohort observational study of 961 term newborns born in Scotland found that, by 5 days of age, 34% had regained their birth weight; 17% were more than 5% below birth weight, with 3% of these infants more than 10% below birth weight. The mean weight loss for this group of babies was 50 g (1.67 oz). At 12 days of age, more than 80% had regained birth weight, with most gaining an average of nearly 200 g.

The degree of weight loss was correlated with newborn birth weight; term neonates with lower weights exhibited minimal weight loss. Comparison of early neonatal weight-loss patterns between breastfeeding and formula-feeding term newborns demonstrated a median weight loss of 6.6% among those breastfed versus 3.5% for those formula-fed. Typically, breastfed babies lose more weight and take longer to regain their birth weight compared with formula-fed babies; upper limits of weight loss were 12% of birth weight for breastfed babies versus 8% for formula-fed babies. The median time of maximal weight loss and time to regain birth weight were also longer for the breastfed infant. Flaherman et al determined that

breastfed infants who lose 4.5% or more of their body weight during the first 24 hours of life are 3.6 times more likely to exhibit weight loss in excess of 10% of their birth weight during the newborn nursery hospitalization. In general, weight loss of more than 3% in the first 24 hours of life or greater than 7% at 48 hours of age warrants careful assessment.

A complete physical examination should be performed. Key aspects of the examination include the following:

- Eyes for opacities including cataracts (red reflex)
- Heart and lungs for congenital heart disease (cyanosis, murmur, tachypnea, femoral pulses, tachycardia)
- Hips for dysplasia (Barlow and Ortolani tests)
- Skin for evidence of jaundice, drying of the umbilical cord, lesions suggestive of infection, and pallor
- Nervous and musculoskeletal systems for state regulation, activity and response to stimulation, tone and reflexes, asymmetry limb posture, position, and movement
- Assessment of the newborn's hydration status, particularly for newborns at risk for feeding difficulties (prematurity, poor feeding or poor cuing in regard to hunger, signs of illness or anomalies not previously identified)

Subsequent follow-up primary care appointments are typically based on specific newborn and parent needs. Routine follow-up after the first week postdischarge newborn visit for the healthy term newborn without health issues is scheduled for 6 to 8 weeks of age. Components of the assessment at that health visit include a thorough physical examination, with special attention focused on evaluation of the eyes for opacities including cataracts (red reflex), heart for congenital heart disease (cyanosis, murmur, tachypnea, femoral pulses), neurodevelopmental screening, and hips for dysplasia (Barlow and Ortolani tests). Results of the newborn screening test and any other interim screening or diagnostic studies performed should be reviewed to ensure that further evaluation or treatment is not required.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Breastfeeding Your Baby—Getting Started* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Crying and Your Baby: How to Calm a Fussy or Colicky Baby* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Immunizations* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Jaundice and Your Newborn* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Newborn Hearing Screening and Your Baby* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Newborn Screening Disorders: What Parents Want to Know About Newborn Screenings Disorders* (handout), American Academy of Pediatrics (www.medicalhomeinfo.org/downloads/pdfs/Newborn-screeningdisorders.pdf)

- *Bright Futures Parent Handout: 2 to 5 day (First Week) Visit* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Safe Sleep and Your Baby: How Parents Can Reduce the Risk of SIDS and Suffocation* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Newborn Screening Tests* (handout), American Academy of Pediatrics (www.medicalhomeinfo.org/downloads/pdfs/NewbornScreeningtests.pdf)
- *Caring for Your Baby and Young Child*, 6th ed (book), American Academy of Pediatrics (shop.aap.org)
- *Heading Home With Your Newborn*, 3rd ed (book), American Academy of Pediatrics (shop.aap.org)
- *New Mother's Guide to Breastfeeding*, 2nd ed (book), American Academy of Pediatrics (shop.aap.org)

### Medical Decision Support

- *Edinburgh Postnatal Depression Scale* (scale), Cox JL, Holden JM, Sagovsky R (www2.aap.org/sections/scan/practicingsafety/Toolkit\_Resources/Module2/EPDS.pdf)
- *Pregnancy Risk Assessment Monitoring System (PRAMS)* (Web site), Centers for Disease Control and Prevention (www.cdc.gov/PRAMS)
- *Safe and Healthy Beginnings: A Resource Toolkit for Hospitals and Physicians' Offices* (toolkit), American Academy of Pediatrics (shop.aap.org)
- *Newborn Screening ACT Sheets and Confirmatory Algorithms* (tool), American College of Medical Genetics (www.ncbi.nlm.nih.gov/books/NBK55827)

### AAP POLICY

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- US Preventive Services Task Force. Primary care interventions to promote breastfeeding: A US Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2008; 149:560–564



## SECTION TWO

# Assessment and Physical Examination of the Newborn

### Chapter 93 MATERNAL MEDICAL HISTORY

*Harpreet Kaur, MD; Deborah E. Campbell, MD*

Familiarity with the maternal history is crucial to identifying risk factors that can contribute to illness in, or later health risk for, the infant. The health of the mother directly affects the well-being of the fetus and newborn. The physician should learn about the family constellation and the mother's physical and mental health, life stressors, support systems, and developmental adaptation to the prospect of becoming a parent. The physician should also inquire about the family's preparations for the infant, including infant safety, and identify resource needs and the availability of family and community support. Anticipatory guidance will encompass care of the infant in the hospital after delivery (including any specialized testing), infant feeding choice, early infant state regulation and temperament, newborn screening routines, and the timing of postdischarge follow-up care for the infant.

### PRECONCEPTION AND ANTENATAL HISTORY

Comprehensive care for a newborn requires a thorough review of the maternal history in preparation for examination of the newborn. Unfavorable maternal social history, poverty and limited education, lack of adequate prenatal care, poor nutrition, and inadequate pregnancy weight gain, as well as exposure to nicotine, alcohol, prescription medications and illicit substances, domestic violence, and other environmental or occupational exposures, contribute to adverse pregnancy outcomes. Evidence of the harmful effects of maternal exposure to environmental toxins on fetal well-being is increasing. Infant mortality and other adverse birth outcomes (congenital defects, premature birth, and low birth weight) have been linked to various environmental toxins (pharmaceuticals, alcohol, nicotine, mercury, lead, nitrates, manganese, polychlorinated biphenyls, and other pollutants). Maternal race, ethnicity, and history of recent immigration are additional factors that influence pregnancy risks and outcomes. Acculturation over time moderates the benefits seen among recent immigrant women who benefit from close community support during pregnancy. The literature that documents the adverse health effects of chronic stress and its effect on minority, particularly black, women is also increasing. Fetal growth

is affected by generational influences with regard to both low birth weight and cardiovascular risk.

### Alcohol Use and Binge Drinking

The physician examining the newborn may suspect maternal drug abuse when treating an infant exhibiting irritability, poor feeding, vomiting, high-pitched crying, or tremors. Fetal alcohol spectrum disorders remain the largest cause of nongenetic disability worldwide and are 100% preventable. Among developed countries, the rate of fetal alcohol syndrome (FAS) is reported as 1 in 1,000 live births. In the United Kingdom, where two-thirds of pregnant women admit to alcohol consumption during pregnancy, 1 in 100 infants born is diagnosed with fetal alcohol syndrome. Studies conducted by the Centers for Disease Control and Prevention (CDC) have shown that 0.2 to 1.5 cases of FAS occur for every 1,000 live births in certain areas of the United States. The CDC 2010 Behavioral Risk Factor Surveillance System survey found that 7.6% of pregnant women (1 in 13) and 51.5% of nonpregnant women reported drinking alcohol in the past 30 days; 1.4% of pregnant women report binge drinking (4 or more drinks on an occasion at least 1 time in the past 30 days). Among women of childbearing age who are not practicing birth control, more than 50% report using alcohol, and 12.4% report binge drinking. (See Chapter 104, Prenatal Drug Use: Neonatal Effects and the Drug Withdrawal Syndrome.)

### Assisted Reproduction

The mode of conception is an additional aspect of the pregnancy history that provides the physician with valuable information. Assisted reproductive technology (ART) has become a routine aspect of fertility care for families worldwide. Based on data from the National Survey of Family Growth (NSFG), the percentage of women aged 15 to 44 who had ever used infertility services increased from 9% in 1982 to 15% in 1995, then declined to 12% in 2002, and remained at that level in 2006 to 2010. Estimates suggest that between 1% and 5% of all neonates born are conceived through ART. Outcomes for these pregnancies vary with assistive reproductive technique, the underlying cause for the female or male infertility, and the need to use donor eggs. This information is important in determining the infant's future care and may influence the parents' adaptation to parenthood and necessitate extra care on the part of the pediatrician should the parents choose to keep this information confidential from other family members. Singleton infants born from ART pregnancies are more likely to be preterm or low birth weight and experience

similar complications related to these conditions. ART pregnancies that result in multiple births are also at risk for prematurity, low birth weight, and increased perinatal mortality and morbidity and have higher rates of congenital malformations and epigenetic alterations (imprinting defects). (See Chapter 81, Assisted Reproductive Technologies, Multiple Births, and Pregnancy Outcomes.)

### Pre-existing Health Conditions

A maternal history of chronic medical conditions such as diabetes, hypertension, severe anemia, and thyroid disease can have perinatal effects on the fetus and can influence the postnatal course for the newborn. Box 93-1 provides an outline of maternal and family factors that can affect pregnancy and infant health. A woman with poorly controlled diabetes is at risk for pregnancy complications that can affect the neonate in several ways, causing fetal macrosomia that places the infant at risk for dystocia at delivery, metabolic derangements after birth, respiratory distress, hyperbilirubinemia, and, if the mother has pre-existing diabetes, a variety of birth defects. Obesity, recognized as an important health concern, disproportionately affects blacks, Hispanics, poor people, and those with a low level of education. In addition to the well-established health risks, obesity in pregnancy confers additional risks to the mother, fetus, and newborn that continue into childhood as well as adult life. Obesity has been shown to be an independent risk factor for a multitude of adverse outcomes, including maternal, fetal, and neonatal death.

Chronic hypertension and hypertensive disorders of pregnancy increase the risk for preterm delivery and fetal growth restriction. Abruptio placenta can cause neonatal anemia, perinatal distress, and permanent neurologic injury. Maternal asthma increases the risk for fetal death and spontaneous abortion. Infants born to women with Graves disease may develop neonatal thyrotoxicosis as a result of transplacental passage of maternal antibodies. Similarly, infants born to women with autoimmune thrombocytopenia are at risk for intraventricular hemorrhage. An infant diagnosed with congenital heart block may be the first indication that the mother has an underlying autoimmune disorder.

The maternal medical history can also influence the counseling provided to the mother and family. A woman with a history of epilepsy, particularly if she continues to experience seizures, requires specific guidance on how to care for her infant safely, especially if she is alone with the infant. The paternal history also influences considerations regarding risks to the infant's health and need for follow-up evaluations. A paternal history of a genetic disorder or carrier status may necessitate specific infant screening. Paternal age (young or advanced) has been associated with the risk for infant low birth weight in addition to de novo or abnormal methylation of paternally imprinted genes. Environmental exposures may affect both parents, with exposure to organic solvents, pesticides, and radiation causing the greatest concerns for fetal development.

Infants born to women on medications may experience complications from drugs that cross the placenta and accumulate in fetal tissues. A baby born to a woman with hypothyroidism who is taking propylthiouracil may exhibit transient neonatal hypothyroidism. Maternal

medication use can further affect the clinical care of an infant and can assist in the diagnosis of an infant born with specific signs or stigmata. A history of antiepileptogenic medication use with carbamazepine, valproic acid, or phenytoin is associated with risk for embryopathy. Maternal depression has the potential to affect the fetus and newborn, as does the treatment of this condition in the pregnant woman. The increasing use of antidepressant therapy during pregnancy, particularly selective serotonin reuptake inhibitors, for treatment of depression has not been associated with an increased risk for major congenital malformations but is linked to an increased incidence of neonatal abstinence syndrome and poor neonatal adaptation.

### PRENATAL TESTING AND DIAGNOSIS

Approximately 10% of all infants born will be found to have a birth defect. Maternal prenatal screening can therefore provide valuable information that can identify potential risk factors for the infant, as well as detect conditions that are treatable during pregnancy, with the opportunity to improve the perinatal outcome. For a variety of reasons, many pregnant women undergo sonography during their pregnancy. The information gathered from 1 or more sonographic studies may identify a fetal abnormality or aberrant fetal growth. In some instances, further evaluations and a diagnosis will have been known before the infant's birth. In other cases, a suspected abnormality will require evaluation after the infant's birth to confirm its presence, to identify other abnormalities, and to determine a course of care. Advances in prenatal sonography, magnetic resonance imaging, and prenatal genetic diagnosis have contributed to the identification of suspected or confirmed anomalies in many more infants at the time of their birth. Depending on the suspected anomaly or problem, the infant may be cared for in the newborn nursery and undergo evaluation there rather than be separated from the mother in a neonatal unit.

For some infants, prenatal diagnosis may provide an opportunity for fetal therapy to correct an abnormality, with the goal of improving the chance for fetal survival or improving the long-term outcome for the infant after birth by preventing or reversing a process that can affect organ function. Monochorionic twins are at risk for twin-to-twin transfusion syndrome because of vascular interconnections. Fetal therapy involving laser ablation of these vessels can improve the chance for survival of the donor twin. A variety of fetal interventions for potentially life-threatening fetal malformations offers promise in improving survival rates and functional outcomes. Maternal testing may also provide valuable information. Discordancy in a twin gestation or abnormal umbilical vessel Doppler studies should alert the physician to potential postnatal problems. A report of polyhydramnios or oligohydramnios should raise specific differential diagnoses for consideration.

### FAMILY HISTORY

The family medical history provides the physician with valuable information. Numerous hereditary conditions can affect the newborn. The physician should obtain a detailed history regarding illnesses or conditions that are present in family members. Congenital heart disease, pyloric stenosis, or Hirschsprung disease in a

**BOX 93-1 Maternal Medical and Family History****AUTOIMMUNE DISORDERS**

- Systemic lupus erythematosus
- Rheumatoid arthritis

**CARDIOVASCULAR DISORDERS**

- Hypertension, chronic and/or hypertensive disorders of pregnancy
- Dysrhythmias
- Atherosclerosis, metabolic syndrome
- Cardiomyopathy
- Congenital heart disease
- Rheumatic heart disease
- Thromboembolic disease

**ENDOCRINE AND METABOLIC DISORDERS**

- Thyroid, parathyroid
- Adrenal
- Diabetes
- Inborn errors of metabolism, eg, maternal phenylketonuria
- Multiple endocrine adenomatosis

**GASTROINTESTINAL DISEASES**

- Hepatitis
- Gallbladder disease
- Inflammatory bowel disease

**GYNECOLOGIC HISTORY ISSUES**

- Breast or other genital tract disorders
- Breast surgery or other genital tract procedures
- Abnormal Papanicolaou smear
- Diethylstilbestrol exposure

**HEMATOLOGIC-ONCOLOGIC CONDITIONS**

- Anemia
- Coagulation disorders
- Thrombocytopenia (immune thrombocytopenic purpura)
- Cancer history
- Hemoglobinopathy

**INFECTIOUS DISEASES**

- Chlamydia
- Cytomegalovirus
- Gonorrhea
- Herpes
- HIV
- Human papillomavirus
- Syphilis
- Toxoplasmosis

**NEUROMUSCULAR AND NEUROLOGIC CONDITIONS**

- Seizure disorder
- Myotonia
- Aneurysm
- Arteriovenous malformation

**PULMONARY DISORDERS**

- Asthma
- Tuberculosis
- Sarcoidosis

**RENAL CONDITIONS**

- Renal anomalies
- Urinary tract infection
- Pyelonephritis
- End-stage renal disease
- Renal transplantation

**MENTAL HEALTH PROBLEMS**

- Depression
- Eating disorders
- Psychosis
- Substance abuse

**OTHER ISSUES**

- Allergies
- Environmental and occupational exposures
- Medications (prescription and over-the-counter), complementary (herbal) products
- Prior surgeries, including prior breast augmentation or reduction
- History of trauma, including domestic/intimate partner violence
- History of prior blood transfusion

**FAMILY GENETIC HISTORY ISSUES**

- Congenital anomalies
  - Neural tube defects
  - Congenital heart disease
  - Cleft lip or palate
  - Other
- Chromosomal anomalies
  - Aneuploidy—trisomy 21, 13, 18
  - Intellectual disability
    - Fragile X disease risk
    - Prader-Willi syndrome
  - Recurrent pregnancy loss
  - Other
- Maternal age older than 34 years or advanced paternal age
- Inherited disorders
  - Cystic fibrosis
  - Hemoglobinopathy
  - Hemophilia
  - Metabolic disorders
  - Neuromuscular disease
    - Muscular dystrophy
    - Huntington chorea
    - Familial dysautonomia
    - Tay-Sachs disease, Canavan disease
  - Renal disease
- Conditions linked to ethnic background or consanguinity

previous child increases the risk for these conditions in subsequent pregnancies. Diseases such as hemophilia, sickle cell disease, Tay-Sachs disease, and cystic fibrosis are inherited. Parents should be asked if they are related because consanguinity increases the risk for autosomal recessive disorders. The increased availability of genetic counseling and testing affords families the opportunity for a more comprehensive evaluation when a history of multiple pregnancy losses exists. As a result, genetic information is available for many more infants who have chromosome-related syndromes and balanced translocations at the time of their birth. Routine pregnancy testing includes a quad screen (see Chapter 80, Perinatal Preventive Care: Fetal Assessment) and may entail serial sonography for fetal growth, as well as a fetal evaluation for the presence of anomalies.

Review of the pregnancy history should also include the results of maternal screening during pregnancy, including maternal syphilis serology, group B *Streptococcus* colonization, and hepatitis B status, as well as possibly HIV and tuberculosis status (depending on specific state public health law requirements and maternal risk factors), blood type, and Rh and antibody (Coombs) tests. Additional test results to consider are the maternal complete blood count, blood chemistries, studies performed in the evaluation of the mother with hypertensive disease in pregnancy, diabetes-screening studies (glucose challenge and glucose tolerance tests), and a test for thyroid disease. The physician should inquire about a maternal history of herpes infection, treatments received, and any episodes during the current pregnancy (Table 93-1). Perinatal HIV prevention is a critical component of prenatal care required for all women, given that women are the fastest growing group of individuals with HIV diagnoses in the United States and in many countries worldwide. It is estimated that the percentage of pregnant women tested over a 12-month period ranged from 51.2% to 60.7% in 3 recent surveys.

Estimates indicate that 6,000 to 7,000 HIV-positive women give birth annually in the United States. Of particular importance is the fact that 40% of infected infants are born to women whose HIV status was not known during the pregnancy. Knowledge about the

woman's HIV status is also important because this status will guide breastfeeding counseling and identify infants who are in need of perinatal treatment with zidovudine to reduce the rate of HIV transmission to the infant, as well as postnatal testing to determine whether HIV infection of the infant has occurred. Specific state public health policies augment the CDC and Institute of Medicine recommendations regarding requirements for maternal counseling and testing during pregnancy and labor and requirements for postnatal evaluation and treatment of at-risk infants.

Congenital syphilis, a serious, preventable disease, continues to be an important public health and clinical care challenge. Up to 40% of pregnancies in women with untreated syphilis result in fetal or perinatal death. Despite the continued increase in rates of primary and secondary syphilis among both men and women, intensive state public health surveillance programs for pregnant women have reduced the number of congenital syphilis cases. The CDC recommends screening women at high risk for syphilis during the first and third trimesters of pregnancy. Screening for syphilis at delivery primarily ensures that infants born to women in whom syphilis previously was either unidentified or untreated are identified and treated. Follow-up evaluation of an at-risk infant born to a woman with positive serologic testing is necessary to ensure appropriate management.

Maternal immunization history should be reviewed. Vaccination of pregnant women is permissible with inactivated virus or bacterial vaccines or toxoids. Live-virus vaccines are generally contraindicated during pregnancy because of the theoretical risk for virus transmission to the fetus. Inactivated influenza vaccination is recommended during the winter season. Routine administration of a dose of Tdap during each pregnancy irrespective of the patient's prior history of receiving Tdap is now recommended. To maximize the maternal antibody response and passive antibody transfer to the infant, the optimal timing for Tdap administration is between 27 and 36 weeks of gestation although Tdap may be given at any time during pregnancy. For women not previously vaccinated with Tdap, if Tdap is not administered during pregnancy, Tdap should be administered

**Table 93-1** Effect of Maternal Infections on the Newborn

INFECTION	EFFECT
Rubella	IUGR, microcephaly, rash, congenital heart disease
Tuberculin test	Asymptomatic mothers with positive purified protein derivative require a chest radiograph to rule out active tuberculosis (TB). Active TB is a contraindication to breastfeeding.
Hepatitis B surface antigen	Babies born to mothers with infection need hepatitis B vaccine immediately after birth and hepatitis B immune globulin within 7 days. These infants require hepatitis B surface antigen (HBsAg) and anti-HBsAg at 9–18 months to check for infection.
Serologic test for syphilis	Increased risk for stillbirth, IUGR, hydrops, and premature labor. Treatment with penicillin if (a) physical laboratory or radiographic evidence of active disease, (b) positive testing on direct fluorescent antibody staining on cord blood, (c) cerebral spinal fluid–VDRL is positive, or (d) serum nontreponemal titer is at least 4-fold higher than that of the mother.
HIV	Treatment during pregnancy and delivery decreases the incidence. Newborns are screened at birth and started on prophylactic therapy.
Group B <i>Streptococcus</i>	Greatest risk for sepsis
Gonorrhea, chlamydia	Conjunctivitis

IUGR, intrauterine growth restriction; VDRL, Venereal Disease Research Laboratory.



immediately postpartum. Breastfeeding mothers may receive Tdap; there is no risk to the infant. Specific guidance regarding current CDC Advisory Council on Immunization Practices recommendations is available at [www.cdc.gov/vaccines/pubs/preg-guide.htm](http://www.cdc.gov/vaccines/pubs/preg-guide.htm).

## INTRAPARTUM COURSE

The intrapartum course can also influence the infant's care and anticipated postnatal course. A maternal history of prolonged rupture of the membranes or meconium-stained amniotic fluid provides important details that guide the newborn's initial management and alert the physician to the level and scope of observation or assessment required. A meconium-stained neonate who exhibits intrapartum fetal distress is at increased risk for hypoglycemia, respiratory distress, pulmonary hypertension, and pulmonary air leak (pneumothorax, pneumomediastinum). Female infants born by cesarean delivery as a result of breech presentation require close surveillance for developmental dysplasia of hips.

## DURATION OF PREGNANCY

Gestational age is calculated in completed weeks as the time elapsed between the first day of the last menstrual period and the day of delivery. If pregnancy was achieved using ART, then gestational age is calculated by adding 2 weeks to the conceptional age. Ultrasound in the first trimester provides a reliable estimation of the gestational age. *Full term* is defined as any neonate whose birth occurs from the beginning of the first day of the 38th week (day 260) through the end of the last day of the 42nd week (day 294) after the onset of the last menstrual period. By convention this means that an infant born from 37½ to 42½ weeks' gestation is classified as *term*. Prematurity is defined as less than 37½ weeks' gestation. Postterm infants are at greater risk for perinatal morbidity and death.

## TOOLS FOR PRACTICE

### Medical Decision Support

- *Alcohol Consumption Among Women Who Are Pregnant or Who Might Become Pregnant—United States, 2002* (article), Centers for Disease Control and Prevention ([www.cdc.gov/mmwr/preview/mmwrhtml/mm5350a4.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5350a4.htm))
- *Antenatal Care: Routine Care for the Healthy Pregnant Woman* (booklet), NHS National Institute for Health and Clinical Excellence ([www.nice.org.uk/nicemedia/pdf/CG062NICEguideline.pdf](http://www.nice.org.uk/nicemedia/pdf/CG062NICEguideline.pdf))
- *Exposure History Form* (booklet), Agency for Toxic Substances and Disease Registry ([www.atsdr.cdc.gov/csem/exphistory/docs/CSEMExposHist-26-29.pdf](http://www.atsdr.cdc.gov/csem/exphistory/docs/CSEMExposHist-26-29.pdf))
- *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* (guideline), Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children ([aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf](http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf))
- *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States* (guideline), Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission ([aidsinfo.nih.gov/contentfiles/lvguidelines/perinatalgl.pdf](http://aidsinfo.nih.gov/contentfiles/lvguidelines/perinatalgl.pdf))

- *Guidelines for Vaccinating Pregnant Women* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/vaccines/pubs/preg-guide.htm](http://www.cdc.gov/vaccines/pubs/preg-guide.htm))
- *Obstetric Guideline 19: Maternity Care Pathway* (guideline), BC Perinatal Health Program ([www.perinatalservicesbc.ca/NR/rdonlyres/4C4892B0-BF43-496A-B113-5A50471B9C4B/0/OBGuidelines-MaternityCarePath19.pdf](http://www.perinatalservicesbc.ca/NR/rdonlyres/4C4892B0-BF43-496A-B113-5A50471B9C4B/0/OBGuidelines-MaternityCarePath19.pdf))
- *Routine Prenatal Care* (guideline), Akkerman D, Cleland L, Croft G, et al; Institute for Clinical Systems Improvement ([www.icsi.org/\\_asset/13n9y4/Prenatal.pdf](http://www.icsi.org/_asset/13n9y4/Prenatal.pdf))
- *Routine Tests in Pregnancy* (booklet), American College of Obstetricians and Gynecologists ([www.acog.org/~media/For%20Patients/faq133.pdf](http://www.acog.org/~media/For%20Patients/faq133.pdf))
- *Sexually Transmitted Disease Surveillance 2012* (booklet), Centers for Disease Control and Prevention ([www.cdc.gov/std/stats12/Surv2012.pdf](http://www.cdc.gov/std/stats12/Surv2012.pdf))
- *LactMed* (mobile app), National Institutes of Health ([toxnet.nlm.nih.gov/help/lactmedapp.htm](http://toxnet.nlm.nih.gov/help/lactmedapp.htm))

## AAP POLICY

- American Academy of Pediatrics Committee on Fetus and Newborn. Controversies concerning vitamin K and the newborn. *Pediatrics*. 2003;112(1):191–192. Reaffirmed September 2014 ([pediatrics.aappublications.org/content/112/1/191](http://pediatrics.aappublications.org/content/112/1/191))
- American Academy of Pediatrics Committee on Pediatric AIDS. HIV testing and prophylaxis to prevent mother-to-child transmission in the United States. *Pediatrics*. 2008;122(5):1127–1134. Reaffirmed November 2014 ([pediatrics.aappublications.org/content/122/5/1127](http://pediatrics.aappublications.org/content/122/5/1127))
- American Academy of Pediatrics Committee on Substance Abuse. Substance use screening, brief intervention, and referral to treatment for pediatricians. *Pediatrics*. 2011;128(5):e1330–e1340. Reaffirmed December 2014 ([pediatrics.aappublications.org/content/128/5/e1330](http://pediatrics.aappublications.org/content/128/5/e1330))
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## Chapter 94

# PHYSICAL EXAMINATION OF THE NEWBORN

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Examining the newborn in the presence of the parents provides an opportunity to demonstrate the infant's physical and developmental characteristics and to model positive infant–caregiver behaviors. This interaction with the family also affords the physician the chance to initiate a health supervision partnership with the family.

## ASSESSING THE NEWBORN IN THE DELIVERY ROOM

The first assessment of the newborn infant, including assignment of the Apgar score, is usually performed in the delivery room to identify any signs of distress or delay in the infant's initial transition and to assess for the presence of visible malformations. Inspection of the newborn for obvious malformations is important because this will further guide the immediate care needs of the newborn and determine the level of nursery care required. A newborn with a cleft palate will require admission to a special or neonatal intensive care unit for evaluation and specialized feeding management. In contrast, a baby born with an isolated

limb deformity may be admitted to a newborn nursery for care and evaluation. Healthy newborns who do not exhibit transitional difficulties are able to remain with their parents in the labor-delivery-recovery suite for an extended period before admission to the newborn nursery. This allows for early initiation of skin-to-skin care immediately after birth and supports breastfeeding within the first hour following delivery. During the first 30 to 60 minutes after birth, infants are typically quite alert and active; thus this period is an opportune time to initiate breastfeeding. Otherwise healthy infants who are at risk for early neonatal hypoglycemia, small-for-gestational-age babies, infants of diabetic mothers, and late preterm infants (34<sup>0</sup>/<sub>7</sub> to 36<sup>6</sup>/<sub>7</sub> weeks' gestation) should feed, either breastfeeding or with infant formula, within the first hour following delivery.

Most (85%–90%) newborns do not exhibit any difficulty in their postnatal physiologic transition. Among the 10% to 15% who do experience problems are infants who are preterm, those who are delivered by cesarean section or who require instrument-assisted delivery, and newborns who exhibit signs of perinatal distress or whose mothers have pregnancy complications that affect the fetal environment and placenta function. Chapter 109, Assessment and Stabilization at Delivery, provides a comprehensive discussion about resuscitation and stabilization of the newborn who is having difficulty with the initial postnatal transition.

In the delivery room, rapid assessment of the newborn's gestational age may be performed using a rapid scoring system that assesses maturity by examining the creases in the sole of the foot, size of the breast nodule, nature of scalp hair, cartilaginous development of the earlobe, labial development in female newborns, and scrotal rugae and testicular descent in male newborns (Table 94-1). In addition to inspecting the infant for malformations or signs of distress that may necessitate admission to a special or neonatal intensive care unit, the examiner should review the prenatal history for antenatal findings that warrant further evaluation.

## Assessing the Gestational Age

The Ballard score provides neuromuscular and physical maturity scores to determine gestational age (Figure 94-1). Studies have shown that the Ballard

**Table 94-1**

**Gestational Age Assessment in the Delivery Room**

PHYSICAL CHARACTERISTIC	GESTATIONAL AGE		
	≤36 WEEKS	37–38 WEEKS	≥39 WEEKS
Creases in the sole of the foot	1 or 2 transverse creases in anterior one-third of the sole; posterior two-thirds smooth	Multiple creases in anterior two-thirds of the sole	Entire sole covered with creases
Ear lobe	No cartilage	Moderate cartilage	Thick cartilage, stiff ear
Scalp hair	Fine and woolly	Fine and woolly	Coarse hair; each hair single stranded
Breast nodules	2 mm	4 mm	7 mm
Testes and scrotum	Few rugae; testes partially descended	Prominent rugae; testes fully descended	Prominent rugae; testes fully descended

**MATURATIONAL ASSESSMENT OF GESTATIONAL AGE (New Ballard Score)**

NAME \_\_\_\_\_ SEX \_\_\_\_\_  
 HOSPITAL NO. \_\_\_\_\_ BIRTH WEIGHT \_\_\_\_\_  
 RACE \_\_\_\_\_ LENGTH \_\_\_\_\_  
 DATE/TIME OF BIRTH \_\_\_\_\_ HEAD CIRCUMFERENCE \_\_\_\_\_  
 DATE/TIME OF EXAM \_\_\_\_\_ EXAMINER \_\_\_\_\_  
 AGE WHEN EXAMINED \_\_\_\_\_  
 APGAR SCORE: 1 MINUTE \_\_\_\_\_ 5 MINUTES \_\_\_\_\_ 10 MINUTES \_\_\_\_\_

**NEUROMUSCULAR MATURITY**

NEUROMUSCULAR MATURITY SIGN	SCORE							RECORD SCORE HERE
	-1	0	1	2	3	4	5	
POSTURE								
SQUARE WINDOW (Wrist)								
ARM RECOIL								
POPLITEAL ANGLE								
SCARF SIGN								
HEEL TO EAR								
TOTAL NEUROMUSCULAR MATURITY SCORE								

**SCORE**

Neuromuscular \_\_\_\_\_  
 Physical \_\_\_\_\_  
 Total \_\_\_\_\_

**MATURITY RATING**

SCORE	WEEKS
-10	20
-5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

**PHYSICAL MATURITY**

PHYSICAL MATURITY SIGN	SCORE							RECORD SCORE HERE
	-1	0	1	2	3	4	5	
SKIN	sticky friable transparent	gelatinous red translucent	smooth pink visible veins	superficial peeling and/or rash, few veins	cracking pale areas rare veins	parchment deep cracking no vessels	leathery cracked wrinkled	
LANUGO	none	sparse	abundant	thinning	bald areas	mostly bald		
PLANTAR SURFACE	heel-toe 40-50 mm: -1 <40 mm: -2	>50 mm no crease	faint red marks	anterior transverse crease only	creases ant. 2/3	creases over entire sole		
BREAST	imperceptible	barely perceptible	flat areola no bud	stippled areola 1-2 mm bud	raised areola 3-4 mm bud	full areola 5-10 mm bud		
EYE/EAR	lids fused loosely: -1 tightly: -2	lids open pinna flat stays folded	sl. curved pinna; soft; slow recoil	well-curved pinna; soft but ready recoil	formed and firm instant recoil	thick cartilage ear stiff		
GENITALS (Male)	scrotum flat, smooth	scrotum empty faint rugae	testes in upper canal rare rugae	testes descending few rugae	testes down good rugae	testes pendulous deep rugae		
GENITALS (Female)	clitoris prominent and labia flat	prominent clitoris and small labia minora	prominent clitoris and enlarging minora	majora and minora equally prominent	majora large minora small	majora cover clitoris and minora		
TOTAL PHYSICAL MATURITY SCORE								

**GESTATIONAL AGE (weeks)**

By dates \_\_\_\_\_  
 By ultrasound \_\_\_\_\_  
 By exam \_\_\_\_\_

**Figure 94-1** Maturational assessment of gestational age (new Ballard score). (From Ballard JL, Khoury JC, Wedig K, et al. New Ballard score, expanded to include extremely premature infants. *J Pediatr*. 1991; 119:417-423. Reprinted by permission of Dr Ballard and Mosby-Year Book, Inc.)

score is most consistent with the prenatal ultrasound and last menstrual period in estimating the gestational age within a 2-week range and is most accurate when performed within the first 12 hours of life. Newborn infants who experienced intrauterine stress related to a variety of maternal medical conditions (hypertension, preterm labor) or environmental exposures (nicotine, cocaine, heroin, antenatal steroids) may demonstrate accelerated neurologic maturation in comparison with the level of physical maturity.

## Approach to Physical Examination of the Newborn

### Clinical Observation

Initial observation should occur with the newborn undressed and in a quiet state. The color, spontaneous movements, cry, posture, tone, and respiratory pattern should be observed. The infant should be observed for symmetry of movements of the arms and legs. The optimal time to conduct this examination is following a feeding when the baby is in a quiet, alert state.

The examiner should observe the newborn's appearance. Does the baby seem normal and comfortable? What is the infant's color? Are any skin lesions present? What is the newborn's tone and activity level? Is the baby alert and responsive? Are any atypical or abnormal eye movements noted?

Observing the infant's transition through different states can assist in the identification of some abnormalities, such as a facial palsy. This can occur because of fetal compression against the maternal pelvis affecting a branch of the facial nerve or because of hypoplasia or agenesis of the depressor anguli oris muscle. These infants exhibit asymmetry of the mouth during crying or inability to close the eyelid on the affected side.

Engaging the parents during the assessment of the infant enhances communication and parental involvement. The room should be warm and have adequate lighting available to facilitate examination of the skin for jaundice or lesions. It is important when performing the neurologic examination to make sure the infant is alert and awake. Examining the baby at the mother's bedside also provides an opportunity to talk to the parents about the infant's immediate care needs and health concerns during the first week of life, including neonatal jaundice, early weight loss, and common skin findings such as erythema toxicum, milia, benign pustular melanosis, and various birth marks. The parents can be encouraged to ask questions they may have about their newborn's development and health. The parents can also be educated about conditions that require immediate medical care.

Allowing the newborn to grasp the parent's or examiner's finger provides an opportunity to assess the strength of the newborn's grasp and reduces the tendency for reflexive startle response to exogenous stimulation. The resting posture for the healthy full-term newborn is generally symmetrically flexed. A newborn who has sustained a clavicular fracture or brachial plexus injury may seem to have an abnormal or atypical posture or limb position. Preterm newborns, babies who are ill, or neonates with conditions affecting their neurologic function may seem hypotonic.

### Listening to the Cry

Physicians should train themselves to listen to and assess an infant's cry. A normal cry is strong. Hoarseness, weakness, or an unusual high- or low-pitched cry may indicate a laryngeal or neurologic abnormality. A repetitive, inconsolable cry is considered abnormal. A high-pitched cry is often related to a central nervous system problem, whereas a low, throaty cry suggests congenital hypothyroidism; a *catlike* cry is significant for cri du chat syndrome. A weak, poorly sustained cry may occur in an infant who is ill, neurologically impaired, or born with Down syndrome. Babies experiencing neonatal abstinence may be extremely irritable and difficult to console. Infants who remain inconsolable with comforting measures warrant assessment for an underlying cause, such as pain, sepsis, drug withdrawal or in utero substance exposure, and neurologic abnormalities.

### Body Measurements

In all newborns, weight, length, and head circumference are part of an assessment of the adequacy of fetal growth and are a baseline for evaluation of subsequent growth. Measurements should be plotted on standardized, gestational age-specific growth charts. Three major sets of growth charts have been developed that are most commonly used around the world: British/European (Tanner and Whitehouse), the 2000 Centers for Disease Control and Prevention (CDC) Sex-Specific Growth Charts in the United States, and the World Health Organization International Reference charts. Although the 2000 CDC Sex-Specific Growth Charts may be used for this initial evaluation, the physician should recognize that the data points for term gestation are a composite of data derived for infants weighing more than 1,500 g at birth and do not reflect gestation-specific data that are necessary to properly evaluate adequacy of fetal growth and to identify infants at particular risk based on inadequate or excessive fetal growth. This distinction is particularly important for the late preterm infant, 34 to 36 weeks' gestation, who is often cared for in a regular newborn nursery. No evidence has been found demonstrating large genetic differences in birth weight among various populations; thus the use of separate, race-specific reference curves, even in situations in which race is associated with other risk factors such as poor nutrition or low socioeconomic status, is not supported. A newborn whose birth weight is below the 10th percentile or more than 2 standard deviations below the mean is considered small for gestational age. Large-for-gestational-age infants have birth weights above the 90th percentile (weights more than 2 standard deviations above the mean) for their gestational age. The National Center for Health Statistics reports that the mean birth weight ( $\pm 1$  standard deviation) for singleton infants born in the United States during 2004 was 3,316 g ( $\pm 570$  g) or 7 pounds, 5 ounces. Of note, this represents a gradual reduction in the mean birth weight among healthy, term infants over time.

Racial and ethnic variations can be found in birth weight, with non-Hispanic white and Hispanic infants having higher mean birth weights than non-Hispanic black infants. Mean ( $\pm 1$  standard deviation) birth weights were reported as 3,375 g ( $\pm 554$ ), 3,316 g ( $\pm 548$ ), and 3,115 g ( $\pm 628$ ) for non-Hispanic white,



Hispanic, and non-Hispanic black infants, respectively. Of note, since 1990, the birth weight among singleton infants has declined by 1%, with the highest declines in birth weight among non-Hispanic white infants.

Length is measured by placing the baby supine on a commercially available measuring device. Care must be taken to ensure that the baby's head is touching a fixed object and the body and legs are extended. Normal measurement of length ranges between 47 and 55 cm. The midpoint of a newborn's body is typically considered to be at the level of the umbilicus, and the crown-pubis-to-pubis-heel ratio is 1.7:1. This ratio is altered in disorders such as chondrodystrophy.

Measuring the baby's head circumference requires placing a disposable measuring tape around the occipital-frontal circumference (OFC): across the forehead, just above the eyes, and over the most prominent part of the occiput. This measurement should be repeated 2 or 3 times and the results averaged to yield the OFC. A normal OFC measures 33 to 37 cm in a full-term infant. Benign familial megalencephaly, a normal variant, is the most common cause of a large head, a trait typically inherited from the father. Chest circumference, if measured, is usually 1 to 2 cm less than the head circumference.

### Skin

Newborn skin is pink and uniform. (See Chapter 95, Neonatal Skin.) Vernix is a white, cheesy material composed of cellular and other debris that is usually present at birth, although it is absent in postterm (>41 weeks' gestation) infants. Lanugo is fine body hair visible on a newborn that begins to thin after 28 weeks. Abundant earlier in gestation, lanugo diminishes with increasing gestation. Acrocyanosis is a bluish discoloration of a newborn's extremities, which is normal for a healthy newborn during the first few hours after delivery, disappearing over the course of the next 24 hours, and represents relatively sluggish circulation of blood through the peripheral structures when they are cold. Acrocyanosis is not a valid indicator of an infant's oxygen status.

Mongolian spots are bluish-green, well-demarcated areas of pigmentation visible most often on the buttocks, back, or shoulders of darker-skinned infants. The skin should be examined for evidence of jaundice, meconium staining, edema, petechiae, and hemangiomas. Skin mottling may be a sign of sepsis or shock.

Erythema toxicum is a common neonatal rash that typically appears during the first week of life and resolves without treatment by 5 to 7 days of age. It begins as an erythematous, macular rash that develops into a small papule on an erythematous base. The papule can sometimes become vesiculopustular. Transient neonatal pustular melanosis is another common skin finding, with characteristic lesions that evolve from small vesiculopustules to hyperpigmented macules, flat dark areas that resemble freckles that may be surrounded by fine desquamating skin. Some infants are born with hyperpigmented macules, whereas others develop pustules after birth that rupture during the first few days, with subsequent formation of the hyperpigmented macules. These lesions fade over the course of 3 weeks to 3 months without treatment. Milia are small white, firm papules noted on the upper cheeks, nose, and chin that are caused by blockage of the sweat ducts

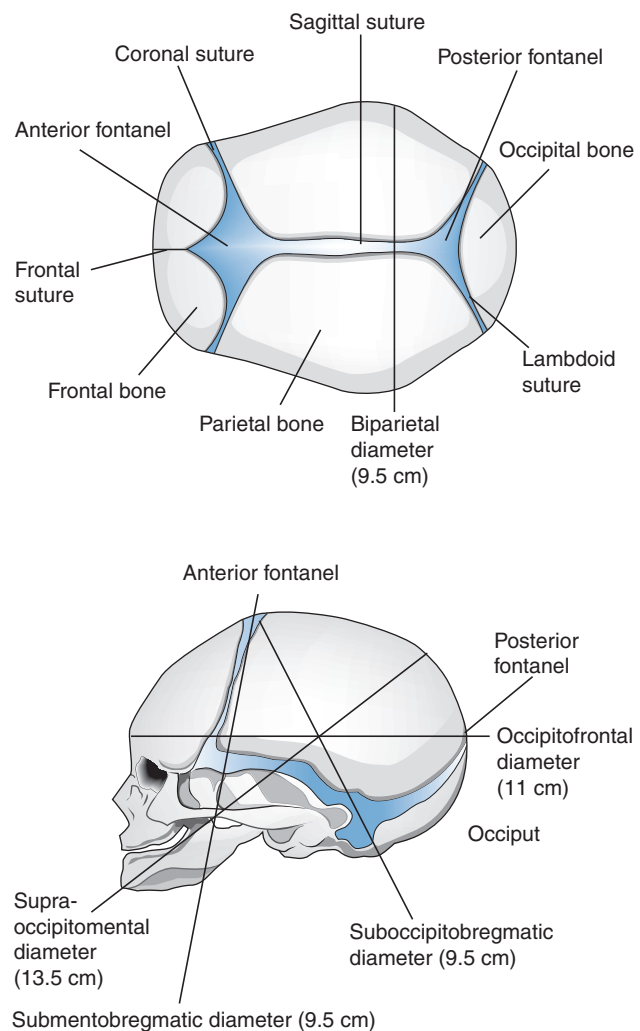
in the skin. Nevus simplex is a pink discoloration of the skin, typically involving the eyelids, glabella, and nuchal areas and resulting from vascular ectasia.

### Head

The newborn's head can vary in shape and symmetry, depending on the intrauterine position, presentation at delivery, degree of molding, or need for an instrument-assisted delivery (forceps or vacuum extraction). Infants born by cesarean or breech delivery often have a symmetrical, round head, in contrast to infants born vaginally, whose head shape is often elongated in the occipital area, with overriding sutures.

### Sutures and Fontanels

Sutures are strong, flexible fibrous tissue connecting the 6 major bones of the skull. The coronal, lambdoid, sagittal, metopic (frontal), and squamosal sutures are shown in Figure 94-2. Fontanels are the points at which the suture lines intersect. The sutures and fontanels are necessary for the infant's brain growth and development. As the brain grows, it exerts pressure on the skull bones, causing new bone deposition along the suture lines. Remolding of bone along the periosteal and dural surfaces of the sutures shapes the head as it grows.



**Figure 94-2** Normal skull sutures and fontanels.

Skull growth occurs perpendicular to a suture such that growth along the coronal suture increases the skull's anterior-posterior diameter; whereas growth along the sagittal suture increases the skull's width. After brain growth is complete at approximately 2 years of age, the fibrous sutures are replaced by rigid bone.

During childbirth, the flexibility of the fibers allows the bones to overlap their edges, without compressing and damaging the infant's brain, as the head passes through the birth canal. Sutures are easily palpable at birth when the bone edges are not widely separated. Overriding sutures palpated after delivery typically resolve with time. Premature fusion of sutures may be palpable as a prominent edge.

Fontanels, the wider spaces at the intersections of the sutures, are usually felt as *soft spots* on the head and vary in size. Large fontanels may indicate hypothyroidism, hydrocephaly, in utero malnutrition, rickets, or a genetic disorder. The posterior fontanel is located at the junction of the lambdoid and sagittal sutures. It is usually triangular, less than 0.5 cm at birth, and closes shortly after birth. The diamond-shaped anterior fontanel is located at the junction of the sagittal and coronal sutures, measures approximately 4 to 6 cm at birth, and closes at about 18 months of age. A depressed anterior fontanel is a late sign of dehydration, whereas a bulging fontanel can be normal in a crying baby but may be associated with hydrocephalus, birth injury, intracranial bleeding, or infection, or it may be present as a late sign of raised intracranial pressure. A third fontanel may sometimes be present between the anterior and posterior fontanels and can be associated with congenital anomalies.

Molding is a common occurrence associated with cephalic presentation during vaginal delivery, although it may also be present in a neonate delivered by cesarean section after a prolonged labor. Molding typically resolves 2 to 3 days after birth (Figure 94-3). Birth-related deformations (deformational, positional or nonsynostotic plagiocephaly) of the skull may also be present at birth. Characterized by forehead asymmetry, this deformation is caused by compressive or restrictive forces along the coronal or lambdoid sutures in utero or during the birth, or is related to subsequent positioning. Prematurity and low birth weight, multiple fetuses, congenital muscular torticollis, a restrictive uterine environment, congenital anomalies, neurologic disorders, and medical conditions that limit fetal head movement are risk factors for deformational plagiocephaly. Infants with positional molding will have an open suture and frontal and temporal prominence on the same side as the affected suture, and frontal flattening on the opposite side. The skull has the appearance of a parallelogram.

Caput succedaneum is caused by constricting pressure on the fetal head during passage through the birth canal. It produces a diffuse subcutaneous edematous swelling of the soft tissue that may cross suture lines and usually resolves within several days. Neonatal extracranial hemorrhages occur in 2 forms: as a cephalohematoma or a subgaleal hemorrhage. A cephalohematoma is a subperiosteal hemorrhage that is a soft, fluctuant cyst-like swelling usually occurring after a difficult or instrument-assisted delivery. Cephalohematomas occur in 1% to 2% of live births and are more common in male first pregnancies (Figure 94-4). Most resolve within a period



**Figure 94-3** Molding.



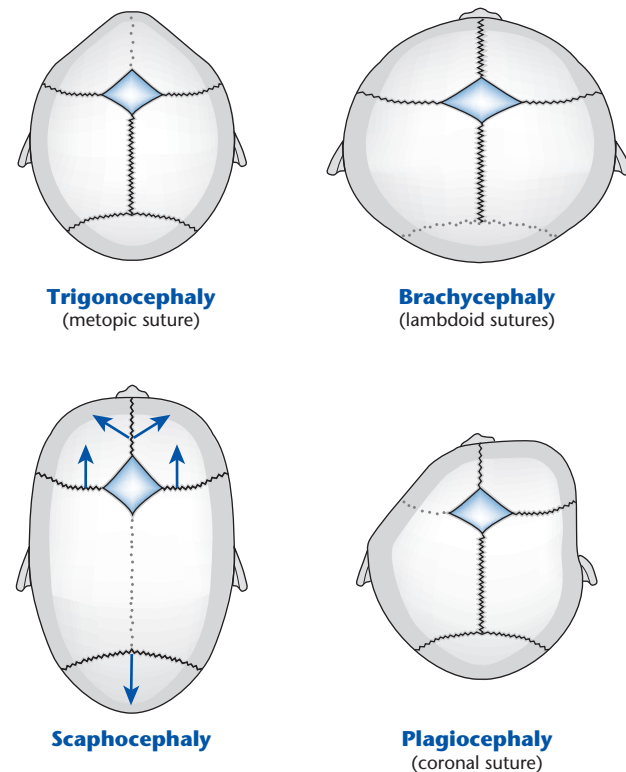
**Figure 94-4** Cephalohematoma.

of 6 weeks to several months. Babies who sustain a large cephalohematoma require monitoring of hematocrit and bilirubin levels. Cephalohematomas typically calcify at the edges during resolution, giving an impression of a depression of the skull in the center, with eggshell-like bony margins on palpation. Skull films should be obtained only if fracture is suspected.

Subgaleal hematoma is a serious, but less common, complication usually associated with vacuum-assisted delivery. It is caused by rupture of the emissary veins, which are connections between the dural sinuses and the scalp veins. Blood accumulates between the epicranial aponeurosis of the scalp and the periosteum. This potential space extends forward to the orbital margins, backward to the nuchal ridge, and laterally to the temporal fascia. This potential space can easily accommodate up to one-half of the blood volume of a neonate; therefore, monitoring blood pressure, hematocrit, bilirubin, and signs for hypovolemia, bleeding, and shock is necessary. Table 94-2 provides a comparison of the characteristics that differentiate caput from extracranial hemorrhages.

Craniosynostosis is the premature fusion of 1 or more of the cranial sutures; it can occur as part of a syndrome or as an isolated defect. Typically, an infant exhibits an asymmetrical head shape and has a palpable ridge along a suture line. The premature closure or absence of 1 or more of the sutures prevents normal head growth and may constrain brain growth. Compensatory growth occurs along the open sutures, resulting in craniosynostosis and distortion of the head shape. Head growth is restricted in the plane that is perpendicular to the fused suture and enhanced in the plane parallel to the fused suture (Figure 94-5). Synostosis involving more than 1 suture is often associated with a syndrome and requires early intervention to limit the risk for increased intracranial pressure and neurologic impairment. Sagittal synostosis caused by premature closure of the metopic suture is the most frequent form of craniosynostosis,

with a male predominance (3:2 male-to-female ratio) and occurs most commonly in white infants. Numerous syndromes and chromosomal mutations are associated with craniosynostosis. Table 94-3 describes the differences between craniosynostosis and nonsynostotic plagiocephaly.



**Figure 94-5** Cranial shapes associated with premature suture closure.

**Table 94-2** Characteristics of Caput Succedaneum, Cephalohematoma, and Subgaleal Hematoma

FEATURE	CAPUT SUCCEDANEUM	CEPHALOHEMATOMA	SUBGALEAL HEMORRHAGE
Cause	Pressure of the fetal head on the cervix during labor; causes decreased blood flow to the area and results in edema	Subperiosteal hemorrhage	Suture diastasis; ruptured emissary vein caused by fragmentation of parietal bone; skull fracture
Suture line Appearance	May extend suture lines Localized soft tissue edema, with poorly defined outline; pitting edema	Does not cross suture line Soft, fluctuant, localized swelling, with well-defined outline; initially firm but more fluctuant after 48 hr	Can extend to orbits and neck Firm to fluctuant; ill-defined borders; may have crepitus or fluid waves
Timing	Usually present at birth; does not progress and resolves in 48–72 hr	Increases after birth for 24–72 hr and resolves over 2–3 wk; sometimes not evident immediately after birth	Progressive after birth and resolves over 2–3 wk
Blood loss	Minimal	Occasionally severe; coagulopathy suspected	May be massive, especially if coagulopathy is present
Complications	Rare	Intracranial bleed; jaundice	Hypovolemic shock



**Table 94-3** Features of Craniosynostosis Versus Nonsynostotic Plagiocephaly

	CRANIOSYNOSTOSIS	NONSYNOSTOTIC PLAGIOCEPHALY
Head shape	Asymmetrical head because the growth is restricted perpendicular to the fused suture	Flat spot on the back or 1 side of the head caused by remaining in a single position for too long
Cranial suture	Fusion of sutures	Normal sutures
Diagnosis	Radiographic examination or computed tomographic scan	History and physical examination
Treatment	Surgery	Positioning, helmets
Cause	Unknown	External molding caused by back sleeping, restrictive intrauterine environment, muscular torticollis, prematurity

Craniotabes is an abnormal softening or thinning primarily of the parietal bones in preterm infants that gives a sensation of a ping-pong ball on gentle pressure. It normally disappears in a few weeks. Persistence beyond a few weeks is considered pathologic and should alert the physician to suspect rickets, syphilis, osteogenesis imperfecta, marasmus, hypervitaminosis A, and hydrocephalus. A bruit on auscultation over the temporal arteries and anterior fontanel can be heard in cases of high-output cardiac failure or neuro-pathologic abnormality. Transillumination is not part of the routine examination but should be performed in a newborn with an unusually large or asymmetrical head or if a widely patent suture or fontanel is present. Diagnoses associated with craniotabes include subdural effusion, subdural hematoma, hydrocephalus, hydranencephaly, porencephaly, increased intracranial pressure, and even skull fractures and nutritional deficiencies. Imaging studies such as neurosonography, computed tomography, and magnetic resonance imaging are important tools in evaluating the newborn to identify potential intracranial disease.

### Scalp

The scalp should be inspected for abrasions or lacerations caused by internal monitor placement or birth-related injury. Aplasia cutis congenita is a skin disorder in which an infant is born with a missing patch of skin. The affected area is usually covered with a thin transparent membrane, is well defined, and is not inflamed. Although aplasia cutis congenita may occur anywhere on the body, 80% of these lesions occur on the scalp. When aplasia cutis congenita occurs on the scalp, an associated skull defect may be present underneath, which may be an isolated finding or associated with other syndromes or disorders.

The physician should examine the hair for its color, texture, distribution, and directional pattern. Reddish or blond hair in a black infant may indicate albinism. Hair color is usually uniform; random patches of white hair may be familial in origin, but a white forelock should alert the physician to consider Waardenburg syndrome (associated pigment defect, deafness, and retardation). The frontal margin of the hairline may vary. Some infants will have extensive hair distribution involving the face, arms, and torso, which typically resolves over a few months. These infants may

also have synophrys—fusion of the eyebrows in the midline—a finding that should prompt the physician to consider whether the infant has other stigmata of Cornelia de Lange syndrome. The posterior hairline has a more consistent limitation. Hair roots distributed below the neck creases, particularly at the lateral margins, can be associated with syndromes involving a short and webbed neck. Normally the direction of hair growth is consistent with a single parietal hair whorl positioned off center, 1 to 2 cm anterior to the posterior fontanel and most often to the left. If the hair whorl is in the midline, if more than 1 whorl is present, or if the whorl is located inferior to the posterior fontanel, then it may be associated with an underlying brain abnormality. Unusual or extremely wiry or unruly hair in a small-for-gestational-age infant with microcephaly and unusual facies suggests the presence of a genetic disorder.

Encephalocele is a neural tube defect characterized by saclike protrusions of the brain and the membranes that cover it through openings in the skull. These defects are caused by failure of the neural tube to close completely during fetal development. Encephaloceles cause a groove down the middle of the skull, or between the forehead and nose, or on the back side of the skull.

### Face

The face should be inspected in its entirety, and the individual facial structures should be closely examined as well. The examiner should evaluate the size, shape, and position of the eyes, ears, nose, mouth, and chin. The face can be divided into thirds, with one-third encompassing the forehead, one-third the eyes and nose, and one-third the mouth and chin. Abnormalities of individual features in isolation are generally not significant, but a combination of atypical features increases the likelihood of an associated syndrome.

### Eyes

Examination of the newborn eye can sometimes be difficult. Examining the eyes is easiest when the baby is in a quiet alert state because the eyes are often open spontaneously. The physician can also take advantage of the vestibular reflex that is elicited by holding the newborn upright, supporting the baby's head with a hand, and gently rocking the neonate back and forth.



If the baby is in a quiet state, then the eyes will open. Occasionally, a newborn will open the eyes when given a finger or pacifier on which to suck. Newborns typically exhibit a dysconjugate gaze, given that eye movements are often not coordinated until approximately 3 to 4 months of age.

The sclera is usually white, although it may appear blue in a premature newborn or yellowish in a jaundiced newborn. Neonates with osteogenesis imperfecta also have a blue sclera. Subconjunctival hemorrhages can occur normally during labor and delivery and resolve over time. These hemorrhages are the result of rupture of small blood vessels near the surface of the bulbar conjunctiva. The iris appears dark blue until 3 to 6 months of age, when eye color may change. The iris should be perfectly circular, with the pupil located centrally and visible striations radiating out from the center. The iris should be examined for evidence of a defect or coloboma. A coloboma is a hole in a structure of the eye, such as the lens, eyelid, iris, retina, choroids, or optic disc. The hole is present from birth and can be caused when a gap between 2 structures in the eye in the fetus fails to close up completely before birth. It can be an isolated abnormality or a feature of CHARGE syndrome (coloboma, heart disease, atresia choanae, retardation of growth or development, genitourinary tract anomalies, and ear anomalies) when it occurs in association with other anomalies. The presence of white spots may be abnormal and should prompt a formal ophthalmologic evaluation. Pupil response to a light stimulus occurs consistently after 32 weeks' gestation but may be present from 28 weeks' gestation. The pupillary response to light and symmetry of eye movement should be checked. The cornea and lens should be clear. Opacification can occur as a consequence of congenital glaucoma, infection, cataract, or trauma. Brushfield spots, also referred to as a *speckled iris*, are small white spots that are slightly elevated on the surface of the iris arranged in a concentric ring around the pupil. These spots occur in healthy children but are far more common among those with Down syndrome.

All infants and children should have an examination of the eye's red reflex performed by a physician or trained professional before discharge from the nursery and during subsequent routine health supervision visits. Current recommendations are that an infant's eyes should be examined for the red reflex from the newborn period through 3 months, then at 6 months, continuing on episodically through early childhood. The red reflex test uses light transmitted from an ophthalmoscope through all the transparent parts of the eye, including the tear film, cornea, aqueous and vitreous humor, and lens. An ophthalmoscope with the lens power set at zero is focused on the pupil from a distance of 18 inches. To be considered normal, the red reflex in both eyes should be symmetrical. Dark spots in the red reflex, a blunted red reflex on 1 side, lack of a red reflex, and the presence of a white reflex (retinal reflection) are all indications for immediate referral to an ophthalmologist for a dilated examination. Leukocoria, a white pupillary reflex visible on the ophthalmoscopic red reflex test, is the most common

presenting clinical sign in retinoblastoma. Newborns in high-risk groups, including those with a family history of retinoblastoma, congenital cataract or glaucoma, congenital retinal dysplasia, and genetic or familial eye disease, should have a dilated eye examination, preferably by an ophthalmologist. Newborns in whom the parent or the observer describes a history suspicious for presence of leukocoria should be referred to an ophthalmologist because a small retinoblastoma or other serious lesion may develop in a subtle fashion.

Congenital cataracts may result from intrauterine infection or can be inherited as a dominant trait from an affected parent. Gonococcal ophthalmia neonatorum tends to develop after the first few days of life but can occur later. *Chlamydia trachomatis* infection, another cause for eye drainage, occurs after the first week. Chemical conjunctivitis caused by silver-nitrate ointment instillation in the eyes is usually self-limited. Tearing is not normal until 2 months of age. Tearing or persistent crusting after the first 2 days requires evaluation for congenital glaucoma (associated photophobia and cloudy cornea), infection, corneal abrasion, and obstruction of the nasolacrimal duct (NLD). In congenital glaucoma, elevated eye pressure pushes fluid into the cornea, causing it to swell and become hazy. Parents may be the first to notice clouding or whitening of the cornea.

An epicanthal fold, a small web of tissue overlapping the nasal corner of the eye, is typical among infants of Asian descent, may be familial in 1% of the non-Asian population, and is a clinical feature in several conditions: Down syndrome, fetal alcohol syndrome, Turner syndrome, phenylketonuria, Williams syndrome, Noonan syndrome, Rubinstein Taybi syndrome, and blepharophimosis syndrome. Upward slant of the outer edge of the eye is another ocular finding associated with trisomy 21. Hypertelorism (widely separated eyes) and hypotelorism (narrowly separated eyes) are other features to be assessed.

### Ears

The normal ear location is determined by drawing an imaginary horizontal line from the inner canthi of the eyes perpendicular to the vertical axis of the head. If the helix of the ears lies below this line, then the ears are low set and can be associated with other syndromes or anomalies. Hairy ears are seen in infants of diabetic mothers. Visualizing a tympanic membrane is not an essential part of a newborn examination and is often not possible because of the presence of vernix or amniotic fluid.

Abnormalities of the external ear include malformation such as microtia, malposition, preauricular pits, tags, and sinus tracts. Malformations may be familial, an isolated finding, or part of a syndrome. The degree of development of the external ear is among the physical characteristics used in determining a neonate's maturity at birth. The physician should examine the ears' size, shape, and position and assess for the presence of abnormalities such as a preauricular skin tag or sinus (ear pit).

Preauricular tags and sinuses are reported to occur in 5 to 10 infants per 1,000 live births. An isolated

preauricular sinus is typically considered a benign malformation. Although these are considered common minor anomalies, the physician should thoroughly examine the affected newborn and review the prenatal and family history for evidence of other malformations or a history of hearing impairment. Renal ultrasonography should be performed in any newborn with an ear anomaly accompanied by other dysmorphic features, family history of deafness, maternal history of gestational diabetes, or a defined syndrome.

Although there is consensus regarding the need to evaluate the urinary tract of a newborn with a major ear malformation or a preauricular tag or sinus accompanied by other abnormalities, controversy exists regarding the need for renal sonography if the newborn's only anomaly is a preauricular tag or sinus. Two publications argue against the need for renal sonography in babies with isolated minor ear anomalies, reporting that the prevalence of renal anomalies among individuals with preauricular tags and sinuses is similar to the reported incidence of renal abnormalities in the general population. The most prudent approach in view of the current lack of a definitive conclusion is for the physician to thoroughly examine the newborn with an isolated minor ear anomaly for evidence of other malformations or dysmorphism, the presence of which should prompt evaluation with a renal ultrasound.

### Nose

Nasal flaring is a frequent finding in the neonate who is transitioning from the fetal physiologic environment to independent extrauterine cardiorespiratory function and denotes the newborn's attempt to decrease airway resistance. Because newborn infants are obligate nose breathers, nasal patency should be verified. Gently blocking each nostril while the mouth is closed and then listening for air movement through the unobstructed nare is an important part of the physical examination. Alternatively, a wisp of cotton can be placed in front of each nostril and observed for movement. If the physician is unsure from these maneuvers that the nasal passage is patent, then a soft 6-French catheter may be inserted into each nare to check for patency. Babies with bilateral choanal atresia exhibit respiratory distress and cyanosis immediately after delivery; the distress is relieved with crying or if the mouth is opened.

The nasal bridge should be inspected for flattening and the presence of any midline defects. Flattened nasal bridge can be a normal variation or associated with congenital syphilis, Down syndrome, or Williams syndrome. Congenital obstruction of the nasolacrimal drainage system is common, although symptomatic infants with signs of nasal obstruction or respiratory distress are rare. The 2 forms of lacrimal system obstruction observed are NLD obstruction and dacryocystocele. Reports suggest that up to 20% of newborns develop symptoms of obstruction of the nasolacrimal system. It is usually caused by persistent membranous obstruction near the lower end of the NDL; the most distal portion of the duct near its exit to the nose is most typically involved. The obstruction may be unilateral or bilateral. Presenting signs include

either or both eyes appearing moist, tearing, crusting on the eyelashes, and, over time, chronic or intermittent infections and periocular redness and irritation. Lacrimation increases during the first 2 to 3 weeks of life. Consequently, NLD obstructions may not become evident until the newborn is 3 weeks of age. Spontaneous resolution occurs in more than 95% of affected infants. Differential diagnosis of the newborn with persistent tearing and mucopurulent discharge includes congenital glaucoma, an eyelash or eyelid abnormality, and conjunctivitis. Congenital dacryocystocele is a less common form of NLD obstruction that is caused by distention of the nasolacrimal sac. It is characterized by a bluish-gray cystic swelling below the medial canthus of the eye and may be confused with a vascular malformation. Acute inflammation in and around the lacrimal system develops in 20% to 60% of neonates within the first days of life.

Studies have demonstrated the efficacy of medical management with warm compresses, massage, and topical antibiotics, with 76% of dacryocystoceles resolving after 6 days of medical management. Babies born with dacryocystoceles may have intranasal extension and develop respiratory distress after birth. Current recommendations include early probing at 4 to 6 months of age if symptoms persist.

### Mouth

The mouth should open at equal angles bilaterally. Unilateral facial nerve palsy is associated with an asymmetrical cry (Figure 94-6), inability to close the eye, flattening of the nasolabial fold, and drooping of the corner of the mouth on the affected side. When muscle activity of the tongue against the hard palate is limited or nonexistent during fetal life, the mandible does not develop fully, resulting in micrognathia. This anomaly occurs as part of the triad of retrognathia or micrognathia, glossoptosis, and airway obstruction in the Pierre Robin sequence. Babies with micrognathia can have respiratory distress, airway obstruction, and feeding difficulties. An important part of the mouth examination is inspection and palpation of the hard and soft palate and uvula for evidence of a cleft. A posterior cleft palate may be missed if complete inspection of the palate is not performed. Cleft lip and palate can be hereditary or associated with syndromes. A bifid uvula may be a sign of underlying submucous cleft palate.



**Figure 94-6** Asymmetrical crying facies.

Natal teeth are present at birth and are different from neonatal teeth, which erupt during the first post-natal month. Mobile natal or neonatal teeth should be assessed first for mobility. Only in the presence of one of the following 3 conditions should these teeth be removed: (1) the tooth is so loose that it needs to be removed to prevent aspiration, (2) the tooth is injuring the mother at breastfeeding, (3) the baby is injuring himself or herself when feeding. These are the specifics of extracting natal or neonatal teeth. Be aware that these might be the only primary teeth the baby has, so a radiograph is indicated to diagnose the presence of supernumerary teeth.

Ankyloglossia, commonly referred to as *tongue-tie*, is caused by a short frenulum on the underside of the tongue that prevents complete protrusion of the tongue. It is a common oral anomaly that can interfere with breastfeeding, speech articulation, and mechanical tasks. Macroglossia can be congenital or acquired; it can be localized when caused by a congenital hemangioma, or it can involve the entire tongue in such disorders as hypothyroidism, Beckwith-Weidemann syndrome, Pompe disease, and Down syndrome.

Mucocoeles are lesions of the oral mucosa that occur as a result of leakage of salivary mucin into the surrounding soft tissues, producing a granulomatous tissue response. Mucocoeles lack a true epithelial lining and are classified as pseudocysts. The most common location for a mucocoele is the lower lip. Clinically, mucocoeles are usually small, fluctuant, asymptomatic mucosal swellings that are benign and thought to occur in response to salivary gland trauma. Ranulae are benign sublingual cysts that may rupture with vigorous sucking. Epstein pearls are small, white inclusion cysts present at the junction of soft and hard palate. These cysts usually resolve spontaneously with sucking. Excessive drooling from the mouth can be normal, or it may be an early sign of esophageal obstruction or isolated neuromuscular swallowing difficulties. Esophageal obstruction can be easily diagnosed by the inability to pass the feeding tube to the stomach.

### Neck

A newborn should be able to turn the head to both sides of the shoulder. The rooting reflex can elicit this movement when the baby turns the head to the side when stimulated. Inability to turn the head should raise the concern about congenital torticollis. Persistent limitation of neck movement requires a referral for physical therapy evaluation. Webbing of the neck can be associated with Turner or Noonan syndrome. The examiner should inspect the clavicles for crepitus, mass, or tenderness, which is suggestive of a fracture. Newborns with a clavicular fracture exhibit limited movement of the arm on the affected side. The sternocleidomastoid muscles should be palpated for evidence of hematoma or fibroma, and the range of rotation of head to each side should be checked. The neck should be examined for the presence of thyroid enlargement and thyroglossal or brachial cleft cysts. A branchial cleft cyst is a developmental defect that occurs as a result of incomplete closure of the brachial plate between the cleft and the pouch. Cystic hygromas are multiloculated, benign cystic structures arising from

lymphatic channels that can occur anywhere in the body. A cystic hygroma is the most common neck mass, typically arising posterior to the sternocleidomastoid muscle. Thyroglossal duct cysts are caused by dilation of a remnant at the site where the primitive thyroid descended from its origin at the base of the tongue to its permanent location, low in the neck. Failure of subsequent closure and obliteration of this tract predisposes a newborn to thyroglossal cyst formation. The resulting neck mass moves during swallowing.

### Cardiovascular System

Examination of the cardiovascular system includes assessment of the heart's rate, rhythm, and position; the pulse volume; adequacy of perfusion; and other signs of cardiovascular compromise. The normal heart rate is 120 to 160 beats per minute in the alert newborn. Some babies, particularly those exposed to a suboptimal intrauterine environment, may have low resting heart rates when at rest and during sleep. Bradycardia in a neonate is defined as a heart rate less than 100 beats per minute. Infants born to mothers with systemic lupus erythematosus will exhibit symptoms of congenital heart block and a fixed heart rate. Tachycardia occurs when the newborn heart rate exceeds 170 beats per minute. A heart murmur on the first day of life is usually benign and reflects blood flow across a patent ductus arteriosus. (See Chapter 101, The Newborn With a Heart Murmur or Cyanosis.) Both femoral pulses should always be palpated and compared with the brachial pulses. Weak femoral pulses or decreased blood pressure measured in the lower extremities must be immediately evaluated for coarctation of aorta. Weak pulses may also indicate hypotension or other significant heart disease. Bounding femoral pulses may indicate hypertension or patent ductus arteriosus.

### Chest and Lungs

The normal respiratory rate for a newborn is 40 to 60 breaths per minute. Newborns, especially preterm babies, often exhibit periodic breathing, with cycles of 5- to 10-second respiratory pauses. This phenomenon is simply a reflection of the immature breathing center of the baby's brain. Apnea, the cessation of respiration for more than 20 seconds, is associated with bradycardia and color change and requires rapid assessment and intervention.

Newborns experiencing respiratory distress may exhibit tachypnea, nasal flaring, grunting, and intercostal retractions. Subcostal retractions occur as a result of a newborn's primary use of the diaphragm during respiration. (For a detailed discussion of respiratory disorders in the newborn, see Chapter 100, Respiratory Distress and Breathing Disorders in the Newborn.) Asymmetry of the chest may signify tension pneumothorax, diaphragmatic hernia, skeletal disorder, and intrathoracic mass. A barrel-shaped chest suggests the presence of a pneumomediastinum (particularly in the newborn with a history of meconium staining), the need for positive pressure ventilation in the delivery room, or a newborn who exhibits respiratory distress.

Malformation of the rib cage may be seen with chondrodystrophies. Pectus excavatum is a congenital

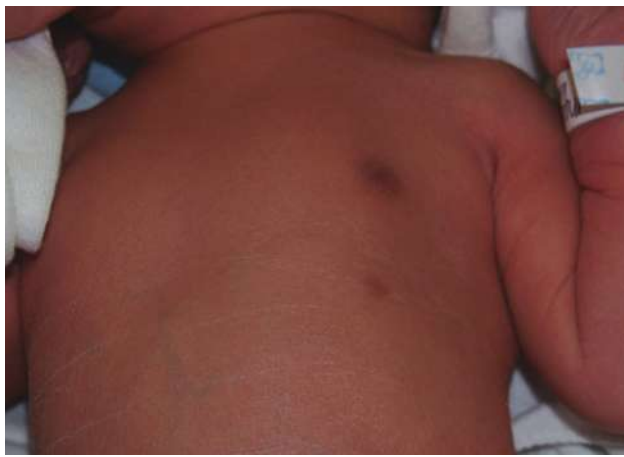


depression of the sternum and is usually insignificant. Both male and female infants may have breast enlargement or may exhibit galactorrhea in the initial postnatal period. Widely spaced nipples (internipple distance greater than 25% of the chest circumference) can be associated with congenital disorders such as Turner syndrome.

Supernumerary (or accessory) nipple, also known as polythelia, is a congenital developmental abnormality that occurs most commonly over the anterior aspect of the trunk (Figure 94-7). Supernumerary nipples are found along the embryonic milk line that extends from the axilla to the pubic region. Supernumerary nipples can vary in their structure, ranging from a fully developed accessory breast, areola, or nipple to a minute, rudimentary hyperpigmented structure. Incidence of supernumerary nipple is 25 per 1,000 live births, with a higher prevalence for the left side and male infants.

### Abdomen

The newborn abdomen is soft and slightly protuberant. Diaphragmatic hernia is a defect in the diaphragm that allows the abdominal contents to move into the chest cavity, resulting in a scaphoid abdomen. Diastasis rectus is caused by separation between the left and the right side of the rectus abdominis muscle. Diastasis recti is a common, normal condition in newborns and occurs more frequently in premature and black babies. The abdominal musculature should be examined for evidence of laxity, which can be associated with gastrointestinal and genitourinary anomalies, such as are seen in infants with prune belly syndrome. The examiner should auscultate for the presence of bowel sounds. The presence of a bruit on auscultation over the liver indicates an arteriovenous malformation; if heard over the kidneys, then renal artery stenosis is suggested. The spleen is not usually palpable. The liver can be palpated 1 to 2 fingerbreadths below the right costal margin, and the lower pole of the left kidney may be felt in the pelvic gutter. Enlarged kidneys are the most frequent cause of an abdominal mass in newborns. Dilated veins are sometimes visible on the abdominal wall, indicating venous distention.



**Figure 94-7** Infant with rudimentary supernumerary nipple.

**UMBILICAL CORD.** The examiner needs to review the delivery history for notations regarding the umbilical cord length and abnormalities related to nuchal cord, cord wrapped around the infant's body, or other abnormalities such as knots in the cord. The average umbilical cord length is 55 to 61 cm, with 85% of cords measuring between 46 and 79 cm (18 and 31 inches). Six percent of umbilical cords are considered to be short (<35 cm), and 9% are long (>80 cm). The umbilical cord length is related to the degree of fetal movements: the greater the fetal movement, the longer the cord. The degree of fetal movement also correlates with the degree of twisting of the cord. Umbilical cord complications are more common with abnormal cord lengths. Longer cords are more susceptible to knotting, entanglement, and prolapse. True knots in an umbilical cord are rare, occurring in less than 1% of live births. Knots are more common in monoamniotic twins, infants with long cords, and pregnancies complicated by polyhydramnios. Wasted umbilical cords are observed in neonates with fetal growth restriction, whereas macrosomic neonates are more likely to have bulky cords. The diameter of the umbilical cord varies in relation to the quality of Wharton jelly and is an indicator of fetal nutritional status. Abnormal marginal and velamentous cord insertion into the placenta also increases the risk for fetal growth restriction and single umbilical artery.

If the cord is broad at the base, then the newborn should be checked for the presence of a small omphalocele before the cord is cut in the delivery room. An omphalocele is a congenital malformation in which variable amounts of abdominal contents protrude into the base of the umbilical cord. The intestines are covered only by a thin layer of tissue and can be easily seen. Gastroschisis is an abdominal wall defect that occurs when the anterior abdomen does not close properly, allowing the intestines to protrude outside the fetus. Unlike the omphalocele, the bowel is not covered by the membrane and is located to the right of the intact umbilicus.

An umbilical hernia is a small defect in the abdominal wall at the umbilicus. It is most often visible when a newborn cries or strains because the pressure pushes the abdominal contents or fluid through the defect, causing it to bulge. The size of the umbilical hernia is determined by palpating the opening in the abdominal muscle, not by the amount of skin protruding. Umbilical hernias are also more prevalent in black infants and typically resolve over the first years of life. Prune belly syndrome is caused by laxity of the abdominal musculature and is associated with gastrointestinal, genitourinary system, and lung hypoplasia. Edema, discharge, redness, or foul odor around the umbilical cord are signs of omphalitis.

**SINGLE UMBILICAL ARTERY.** The normal umbilical cord contains 2 arteries and 1 vein. An isolated single umbilical artery (SUA) occurs in up to 2% of all live-born infants. It may be detected antenatally or identified on examination of the newborn after birth. Prenatally, only two-thirds of the SUA will be identified sonographically. An SUA is thought to result from either aplasia or atrophy of the second umbilical artery or from persistence of the normally transient early embryonic SUA. Associated structural

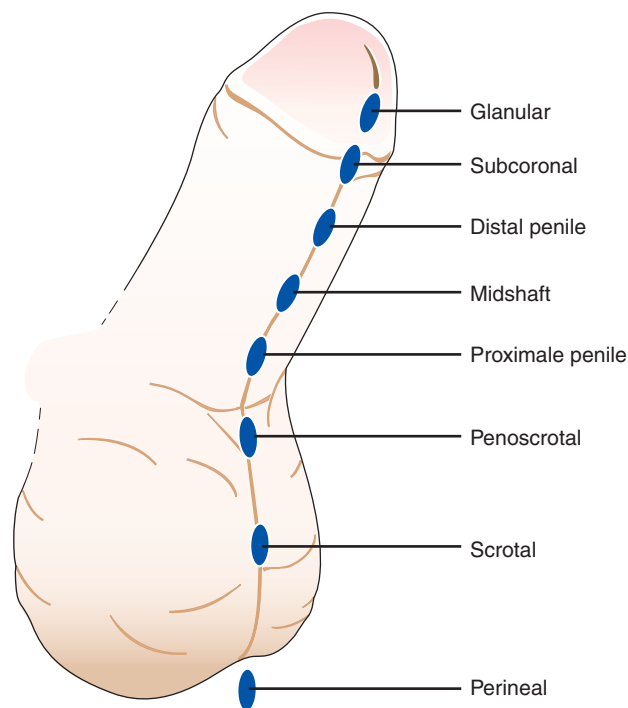


or chromosomal anomalies are found in 27% of infants with an SUA, with renal malformations being the most common finding. SUA is seen more frequently in monoamniotic twins, and intrauterine growth restriction was observed in 15% to 18% of newborns with an SUA.

A newborn found to have an SUA should be thoroughly examined for dysmorphic features, abdominal masses, and the presence of heart disease. Postnatal screening for other malformations is warranted if additional abnormalities are present on examination or if prenatal evaluation identified other anomalies. In the absence of identified physical abnormalities on antenatal ultrasound screening, the available research suggests a low yield from investigations after delivery in infants without positive examination findings, suggesting the presence of other anomalies.

### Genitalia and Anus

**MALE.** Usually at birth the glans is completely covered by the foreskin. The foreskin should not be retracted until the child is 3 to 10 years of age. The skin on the underside of the penis may be tethered to the scrotum, called the chordae, and may or may not be associated with hypospadias. Hypospadias is a defect of the urethra in a male infant that involves an abnormally placed urethral meatus. Instead of opening at the tip of the glans, a hypospadiac urethra opens anywhere along a line running from the tip along the ventral aspect of the shaft to the junction of the penis (Figure 94-8). Infants with hypospadias should not undergo circumcision because the foreskin is often used during the surgical repair. Epispadias is an opening on the dorsal surface of the penis. A malpositioned meatus may be associated with urethral or kidney abnormalities and may result in poor urinary stream.



**Figure 94-8** Schematic of urethral orifice in hypospadias.

Penile length varies from 2.5 to 3.5 cm. The penis may appear short in an obese infant with suprapubic fat. A microphallus, or micropenis, should be suspected if the stretched penile length is less than 2 standard deviations below the mean for age; measurements of less than 2.5 cm in a term newborn male meet the definition of micropenis. The examiner should observe infants with micropenis (especially if other abnormalities associated with hypopituitarism are present) for evidence of metabolic derangements. Among neonates with pituitary dysfunction an early clinical sign is hypoglycemia. If hypoglycemia occurs, then glucose, insulin, growth hormone, and cortisol levels should be immediately obtained.

The scrotum is smooth or has a rugated appearance. Confirmation of descended testes is important for the infant with a bifid scrotum. If the testicles are not felt in the scrotum, then the inguinal canal should be palpated for the testicles. Black, Asian, and Hispanic infants can have darker scrotum (Figure 94-9). Pigmentation of scrotum can be a sign of congenital adrenal hyperplasia. Testicular size, noted as a volume, is 1 to 2 mL. Transillumination should be performed if the scrotum seems distended to determine whether a hydrocele is present. If the scrotum does not transilluminate, then the infant should be examined closely for a tumor or torsion.

Discoloration of the scrotum may be present in a neonate born after breech presentation or may be caused by testicular torsion or hematoma. Testicular torsion results in vascular compromise to the testes, and if blood flow is not restored in a timely fashion, testicular ischemia, infarction, and subsequent atrophy will occur. Prenatal testicular torsion is an in



**Figure 94-9** Full-term male genitalia. The scrotum of the term infant with descended testes will be pendulous with well-developed rugae. The scrotum of infants with deeper skin pigmentation (black, Native American, and nonwhite Hispanic infants) will appear darker than the rest of their skin.

utero event, and the torsion is generally detected at the initial newborn examination. The neonate does not demonstrate any clinical signs of distress, but on examination the testicle typically is enlarged, firm, and nontender with a discolored and fixed hemiscrotum. In rare cases, if the torsion occurred early in utero, the neonate may present with a firm, small testicle or even with an absent or nubbin testicle.

Cryptorchidism is common in the newborn infant, given that most undescended testicles are present at birth. (See Chapter 272, Hypospadias, Epispadias, and Cryptorchidism.) Three percent to 5% of term male infants are affected. Predisposing factors include prematurity, low birth weight, twin gestation, and first-trimester exposure to estrogen. Up to 30% of premature male newborns can be affected. Undescended testicles may be true undescended testicles, ectopic testicles, or retractile testicles. A newborn who seems phenotypically male but does not have palpable testes bilaterally should be considered to be a virilized female infant with congenital adrenal hyperplasia until proved otherwise. Congenital adrenal hyperplasia may rarely produce a normal male phenotype and is a life-threatening condition.

**FEMALE.** The labia can be swollen or ecchymotic after a breech delivery. In a term infant, the labia majora is enlarged and covers the labia minora, clitoris, urethral meatus, and external vaginal vault. Infants can have a creamy white to a slightly blood-tinged discharge 2 to 3 days after birth caused by maternal estrogen withdrawal. An enlarged Bartholin gland can appear as an imperforate hymen. Vaginal mucosal skin tags are a common finding and may extend beyond the rim of the hymen. They usually disappear within the first few weeks of life. Occasionally, small vesicles with no erythema may be clustered around the genitalia, and their surface is frequently broken. The hymen should be gently inspected to assess for the presence of an opening. An imperforate hymen can cause hydrometrocolpos, which usually appears as a bulging hymen, especially with crying.

Virilization of the genitalia may be difficult to identify; both labia need to be spread to ensure that no labioscrotal fusion is present, and the labia majora should be palpated to be sure that no gonads are present. Infants with ambiguous genitalia need a multidisciplinary workup before assigning the gender. Gender assignment should be delayed if the genitalia are incompletely developed or seem indeterminate. (See Chapter 243, Disorders of Sex Development.)

### Anus and Rectum

In female newborns, anal position index is the distance between the posterior fourchette and the anus divided by the distance from the coccyx to the fourchette—usually 0.44 cm ( $\pm 0.05$  cm). In male newborns it is the distance from the anus to the scrotum divided by the distance from the coccyx to the scrotum—usually 0.58 cm ( $\pm 0.06$  cm).

Measurement of the anal position index is helpful in identifying ectopic anus, which is mild mislocation of the anus often missed in the newborn exam; these patients present later in life with constipation. Anterior ectopic anus is different from imperforate anus with perineal fistula in that the anal opening is usually of normal size and only mildly misplaced.

Occasionally a large fistula may be mistaken for an anus. Fistulae may be located anterior or posterior to the anus and may connect to the bladder. An imperforate anus occurs in approximately 1 in 5,000 newborns. The rate is slightly higher among boys than girls, and it can occur as an isolated anomaly or in association with other abnormalities of the rectum and anus.

### Musculoskeletal System

**SPINE.** The newborn's spine should be examined with the infant in the prone position. Infants are often noted to have a nevus simplex (*stork bite*) at the nape of the neck that is insignificant and disappears with time. Asymmetry in the creases at the thigh or buttock may be evident in a neonate with developmental dysplasia of the hip. The examiner should palpate the spine to check the curvature; any midline defect on the dorsal surface can be an indication of spine anomalies. The examiner should assess for symmetrical motion of the major joints, including the shoulders, hips, knees, elbows, ankles, and wrists.

A pilonadal sinus (sacral dimple) may be present at the base of the spine between the buttocks. It is typically benign although, rarely, a true sinus tract associated with a meningocele may exist. Abnormal pigmentation, overlying hemangioma, pigmented nevus, or a hair tuft over the lower spine may be associated with vertebral anomalies (Figure 94-10). Lipomas are palpable masses that move with the skin. Spinal dysraphism is usually a midline defect, whereas a sacrococcygeal teratoma tends to be located lateral to the midline. The scapulae should also be palpated to check their size, symmetry, and location. A scapula that is smaller and higher in position on 1 side should alert the physician to Sprengel deformity.



**Figure 94-10** A hair tuft over the spine may be associated with vertebral anomalies.

**EXTREMITIES.** The physician should examine the palmar creases. Simian creases (single transverse creases) occur normally in 5% to 10% of the population, although the presence of a simian crease is highly associated with a chromosomal and congenital abnormality. The upper extremities should be examined thoroughly for evidence of any brachial plexus injury;

limb position, posture, symmetry, and range of motion should be assessed. Figure 94-11 provides a checklist for use in the assessment and follow-up care of an infant with a suspected brachial plexus injury.

**LIMB AND DIGIT ABNORMALITIES.** Congenital deformities affect 1% to 2% of all newborns, and 10% of these deformities involve the upper extremity. Congenital

### Suspected Brachial Plexus Injury (BPI): Evaluation and Management Form

	Date _____ Admission		Date _____ Discharge		BPI Typical Clinical Findings		
Physical Examination:	Left	Right	Left	Right	Erb's		Klumpke
					Palsy	Paresis	
• Shoulder abduction					Absent	Decrease	Present
• Shoulder external rotation					Absent	Decrease	Present
• Elbow flexion					Absent	Decrease	Present
• Supination					Absent	Decrease	Present
• Wrist and finger extension					Present		Absent
• Biceps reflex					Absent	Decrease	Present
• Grasp reflex					Present		Absent
• Moro reflex					Abnormal		Abnormal
• Hand movement					Present		Absent
• Sensory					Varies		Varies
					"Waiter's tip position"		
<b>Pain Management:</b>					<b>Erb's + Klumpke = Total BPI</b>		
• Pain assessment	Present	Absent	Present	Absent	<b>Comments:</b>		
• Comfort care	Yes	No	Yes	No			
• Pain medication	Yes	No	Yes	No			
<b>Diagnosis:</b>							
• Attending name ( <i>print</i> )							
• Attending signature							
<b>Imaging:</b>							
• Clavicles and chest x-ray							
• Upper extremity x-ray							
• Other							
<b>Recommendations, Consultations, and Referrals</b>							
<b>Pediatrics neurology consultation:</b> Date _____ Time _____ Name _____							
I O NN H							
<b>Orthopedic consultation:</b> Date _____ Time _____ Name _____							
I O NN H							
<b>Primary-care follow-up:</b> Phone _____ Date _____ Time _____							
<b>Physical therapy and/or occupational therapy consultation:</b> Date _____ Time _____ Name _____							
Yes No							
<b>Home care referral:</b>							
Yes No							
<b>Early intervention referral:</b>							
Yes No							
<b>EIP child find (At-risk registry) referral:</b>							
Yes No							

↑, Increased; U, unchanged; I, inpatient; H, HMO (referral by primary-care provider); ↓, decreased; N, normal; O, outpatient; NN, Not needed.

Developed by Carlos Vega-Rich, MD, and the Division of Neonatology, Children's Hospital at Montefiore (2003)

**Figure 94-11** Suspected Brachial Plexus Injury (BPI): Evaluation and Management Form.

limb anomalies are classified according to the pattern of abnormal embryonic development. This includes the failure to form limb parts, failure of differentiation, duplication, overgrowth, undergrowth, congenital constriction band syndrome, and generalized skeletal abnormalities. Syndactyly (abnormal fusion of digits) or polydactyly (supernumerary or duplicated digits) and clinodactyly (radial deviation of the fifth digit) can be associated with syndromes. (See Chapter 96, Common Congenital Anomalies.) Polydactyly may be pre- (located on the radial aspect of the hand or tibial side of the foot) or post-axial (located on the ulnar side of the hand or fibular side of the foot). Post-axial polydactyly occurs at approximately twice the frequency as pre-axial polydactyly and varies by race. Post-axial polydactyly occurs more commonly than the other abnormalities, particularly among individuals of African descent, and is typically an isolated defect. In contrast, pre-axial polydactyly occurs more commonly in individuals of European descent and is frequently associated with other abnormalities or syndromes. The extra digit should be palpated for the presence of bony structures; often, the extra digit is attached to the hand by a thin stalk that can be easily ligated before the infant's discharge from the hospital. The inheritance pattern is most often autosomal dominant with incomplete penetrance, although recessive inheritance patterns have been identified. Phenotypic presentations of ulnar polydactyly range from a small skin appendage on the ulnar aspect of the hand to a fully formed ulnar digit. Syndactyly affects 1 per 1,000 live births and may occur sporadically or in families or in association with other abnormalities. Syndactyly is considered to be simple when skin alone is involved, complex when there is bone connection, complete when the web involvement includes the nail, incomplete or partial when the nail is not involved but when the web depth is not normal, and complicated when there are multiple tissue abnormalities. The newborn with apparent syndactyly should be closely assessed for evidence of constriction band (amniotic band) sequence. The nails should also be examined for abnormalities.

Each year approximately 4 of every 10,000 babies will have upper limb reductions, and approximately 2 of every 10,000 babies will have lower limb reductions. Some of these babies will have both upper and lower limb reduction defects. Limb deficiencies have been associated with teratogenic exposures during pregnancy, such as thalidomide and misoprostol, and reported to rarely occur following prenatal diagnostic procedure (chorionic villus sampling, amniocentesis). Infants exposed early in pregnancy to misoprostol or chorionic villus sampling have a small, but higher than the general population, risk for developing a vascular disruption that results in asymmetrical digit loss, constriction rings, and syndactyly. Among the spectrum of radial limb deficiencies that may be seen in the newborn is an absent or hypoplastic thumb. Radial deficiencies are often associated with other anomalies. Infants with limb deficiencies should be referred to an orthopedic or plastic surgeon for evaluation and management planning.

The presence of a dimple on the anterior leg suggests the presence of an underlying bony abnormality

and warrants further evaluation. Alignment of the legs from the hips to the toes should be assessed to identify rotational misalignment. The number and appearance of the newborn's toes should be assessed for the presence of polydactyly, syndactyly, hypoplasia, overlap, and abnormal alignment. The extremities should also be observed for symmetry in limb size and muscle bulk. Genu recurvatum is a congenital anomaly of the lower limb, with hyperextension of the knees (Figure 94-12). Genu recurvatum can be associated with congenital dislocation of hips, cerebral palsy, joint hypermobility, or clubfoot. Dislocation of the patella should be suspected if lateral displacement of the patella and limited knee motion are present.

A healthy newborn's foot is usually supinated and adducted at the forefoot, with increase in the distance between the first and the second toe. The range of motion of the ankles and subtalar joints should be examined. Metatarsus adductus is typically a positional deformation that occurs in varying degrees of severity and is frequently correctable with passive range-of-motion exercises. Metatarsus adductus may occur as a structural abnormality, with a fixed position that does not allow abduction of the foot beyond a neutral position. Talipes equinovarus (clubfoot) is inward with medial rotation of the foot, mild calf atrophy, and hypoplasia of the foot, tibia, and fibula. Another component of clubfoot is cavus midfoot deformity. Limited dorsiflexion or a fixed equinus position of the foot occurs with congenital foot anomalies. Orthopedic evaluation and follow-up are required for a newborn with an equinovarus deformity.

All newborns should be examined for developmental dysplasia of the hip. A positive Galeazzi sign is a functional leg-length discrepancy when the knees and hips are flexed. Also, the hip examination should be done carefully in a relaxed baby—gently and without any force (Figure 94-13). The Barlow test dislocates an unstable hip. With the newborn placed in a supine position and the hips in flexion, the hips are grasped and adducted, with simultaneous downward pressure applied. The Ortolani test is performed to assess the relocation of a dislocated hip. In this maneuver, the hip and knee are flexed while the thigh is grasped and the pelvis is stabilized by the examiner's other hand. The thigh is abducted as pressure is applied on the greater trochanter to reduce a dislocated hip. On dislocation of the femoral head against the acetabulum, a *clunk* is felt. Benign clicks are more commonly observed, caused by movement of the ligamentum teres in the acetabulum or a tendon such as the iliopsoas popping over the femur. Any hip instability should result in an orthopedic referral. Breech position and a family history of developmental hip dislocation are major risk factors for hip instability.

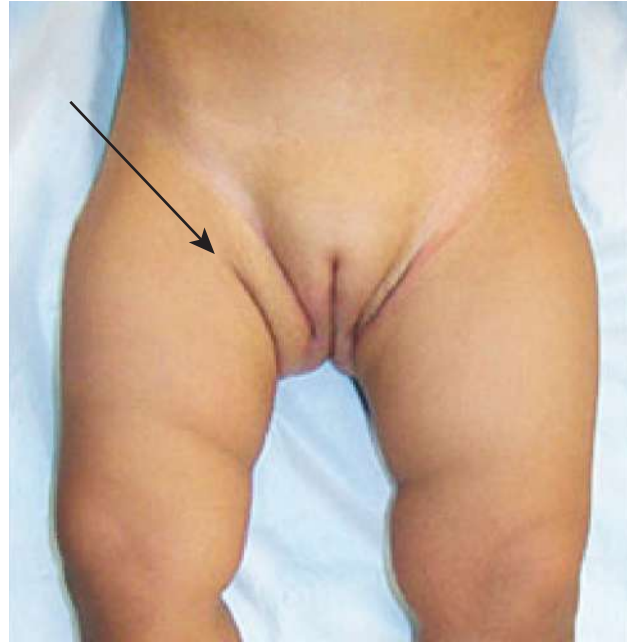
### Neurologic Examination

The neurologic assessment includes examining the motor system, reflexes, sensory system, and cranial nerves (Table 94-4). A full-term newborn's posture in a quiet state is typically abducted, with partial flexion





**Figure 94-12** Genu recurvatum.



**Figure 94-13** Asymmetrical thigh creases in developmental dysplasia of the hip.

**Table 94-4**

**Neonatal Neurologic Evaluation**

TEST	TECHNIQUE	NORMAL FOR TERM	DEVIANT FOR TERM
Resting posture	Observe unswaddled infant without contact in quiet awake, quiet active, or light sleep states	Moderate flexion of 4 limbs, held off bed  Equal side to side and upper to lower if head is in midline Extension of neck in face presentation or legs in breech	Constant tight flexion  Full extension, flaccid or forced Knees abducted to bed (ie, frog leg)  Elbows flexed with dorsum of hands on bed Tight, persistent fisting ATNR persistent 30 sec Strong lateral preference
State	Deep sleep to light sleep Awake, light peripheral movements Awake, large movements, not crying Awake, crying	Moves from 1 to the other with appropriate stimuli Self-calms  Modulated cry with expression	Is difficult to move from 1 to the other Stays too alert or cries without physical reason Does not come to fully awake state Weak or monotonous cry
Motor activity	Observe throughout physical examination	Appropriate for state of alertness  Symmetrical, fairly smooth Expressive face with yawn or cry	Bicycling, swatting without stimulus Asymmetrical, weak Jittery while sucking Flat facial expression
Phasic (ie, passive)	Measure resistance to extension (limb recoil)	Response appropriate for gestational age	Resists too much or too little

*Continued*

**Table 94-4 Neonatal Neurologic Evaluation—cont'd**

TEST	TECHNIQUE	NORMAL FOR TERM	DEVIANT FOR TERM
Tone: resistance to movement	Scarf, heel to ear	Patellar is only reflex reliably present at birth	Asymmetry
Tendon reflexes	Test patellar reflex with head midline		Sustained clonus
Postural (ie, active)	Pull to sitting while grasping infant's hands	Infant pulls back with flexion at elbows, knees, and ankles	Asymmetry in pulling back
Tone: resistance to gravity		Head comes with body with minimal lag and falls forward when sitting is obtained	No resistance, full head lag
Traction response			Pull to stand instead Head does not fall forward as infant goes past upright
Upright suspension	Suspend infant facing examiner with both hands in axillae	Infant supports self then yields slowly	Infant falls through immediately
		Holds head erect, flexes hips, knees, and ankles Eyes open	Legs extend, eyes fail to open Infant fails to relax and fall through after 1 min
Ventral suspension	Hold infant under chest and suspend in prone position	Flexes arms, extends neck, holds back straight	Hangs limply or excessively rigidly
	Galant: stroke adjacent to spine	Curves toward side of stimulus	Asymmetrical incurving
	Landau: stroke caudocephalad along spine	Extends back, lifts head and pelvis, micturates	Weak or absent response
Positive support	Hold infant to support trunk with feet touching firm, flat surface	Infant extends hips to bear his or her own weight and relaxes after 1 min	Infant fails to bear weight or extends too much or too long
Integrated reflexes	Hold infant in supine position	Spreading: arms abduct and extend; hands open	Unequal laterality
Moro reflex	Support head and neck with hand; allow head to drop while still supporting it	Hugging: arms adduct and flex; hands close	Asymmetry; exaggeration with disorganization in state
Tonic neck reflex	Infant in supine, neutral position; turn head to 1 side; repeat with opposite side	Mental extension, occipital flexion primarily of arms; does not remain in position for >30 sec	Exaggerated response and stays in position >30 sec
Withdrawal reflex	Painful stimulus to 1 foot	Withdrawal of stimulated foot; variable extension of opposite leg	Absence of flexion in stimulated leg

at the hips and knees; the arms are adducted and flexed at the elbow. Newborns have their fists loosely clenched with the thumb on the palm. Neurologic maturity is evaluated as part of gestational age assessment, as described previously. The posture, state regulation and behavior, muscle tone, responses, and reflexes provide valuable information about the newborn's adaptation to extrauterine life and may provide clues to the newborn's intrauterine experiences. Signs on neurologic examination that warrant further evaluation include fisting or abnormal posturing of the trunk, hands, or feet; excessive tremulousness; clonus or atypical movements suggestive of seizure activity; abnormal eye movements; and a decreased or absent response to

visual or auditory stimuli. (Refer to Chapter 107, The Newborn With Neurologic Findings, for a more detailed discussion.)

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Hip Dysplasia (Developmental Dysplasia of the Hip)* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Jaundice and Your Newborn* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Breastfeeding Your Baby: Getting Started* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)

- *How to Prevent Tooth Decay in Your Baby* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Newborn Hearing Screening and Your Baby* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)

### Medical Decision Support

- *Centers for Disease Control and Prevention Clinical Growth Charts* (growth charts), (www.cdc.gov/growthcharts); also available at AAP bookstore (shop.aap.org)
- *New Ballard Score* (Web page), Ballard JL (www.ballardscore.com)
- *World Health Organization International Reference Charts* (growth charts), World Health Organization (www.who.int/childgrowth/en)
- *International Hip Dysplasia Institute* (Web site), (www.hipdysplasia.org)
- *Current Concepts Review: Upper-Extremity Congenital Anomalies* (article), *Journal of Bone and Joint Surgery*, Vol 85, Issue 8, 2003
- *Handbook of Normal Physical Measurements*, 2nd ed (book), Oxford University Press

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## Chapter 95

## NEONATAL SKIN

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By the end of the third trimester of pregnancy, the skin structure and composition of a fetus are similar to that of an adult. The skin contains a mature lipid bilayer, substantial subcutaneous fat, and differentiated epidermal layers. The primary functions of neonatal skin are mechanical protection, maintenance of thermoregulation, immune surveillance, and prevention of insensible loss of body fluids. Skin of premature infants is thinner and much less effective than skin of term infants in these functions.

### SKIN CARE OF NEWBORNS

The developmentally immature skin barrier in premature infants can result in increased transepidermal water loss, difficulties in thermoregulation, higher risk for infection, increased absorption of environmental toxins, and predisposition to injury from minor skin trauma. Hand washing by caregivers is the most effective way to prevent skin colonization and nosocomial infection. Mild, alkaline to neutral pH cleanser (eg, chlorhexidine) is suggested for hand decontamination.

Premature infants are at marked risk for percutaneous toxicity compared with term infants. A conservative approach to applying topical products to the skin of preterm infants must be undertaken. Only essential products should be used, and these should be washed off once their purpose has been achieved.

Sterilization of the skin before invasive procedures are performed on the neonate is assumed to eliminate pathogens from the local site and reduce the risk for subsequent bacteremia and sepsis. Chlorhexidine seems to be the safest and most effective agent for local skin sterilization. Chlorhexidine has also been found to be a safe and effective agent for reducing bacterial colonization of the umbilical cord stump.

Bathing of neonates should be delayed until vital signs have been stable for several hours. Excessive vernix is best left on the skin. For preterm infants, particularly those with compromised barriers, water-only nonimmersion bathing up to 3 times a week is suggested for the initial 2 to 4 weeks of life. Rubbing or scrubbing the skin should be avoided. If soap is required, then only mild, neutral-pH soaps without additives should be used in heavily soiled areas; these soaps should be promptly rinsed from the skin.

Although treatment with emollient theoretically promotes the integrity and function of the stratum corneum, studies have revealed a trend toward increased risk for bacterial infection in infants prophylactically treated with emollient. Based on these studies, topical ointment should not be used routinely in preterm infants.

Neonatal skin, especially that of preterm neonates, is highly susceptible to injury. Routine precautions such as care in handling, minimal use of skin adhesives, hydrogel-based chest leads, and masks should be routinely followed.

## PIGMENTARY BIRTHMARKS

### Congenital Disorders of Hypopigmentation and Depigmentation

*Nevus depigmentosus* refers to macular hypopigmentation that is present at birth and stable throughout the lifetime (Figure 95-1). Lesions are usually unilateral and block- or flag-shaped. Hypopigmented linear or segmental macules are seen in patients with hypomelanosis of Ito. Lesions can be present at birth, or they can develop during infancy or childhood. The spectrum of this disorder ranges from those with only cutaneous involvement (most common) to those in which cutaneous lesions are associated with ocular, musculoskeletal, or neurologic disorders. This disorder is hypothesized to be the result of chromosomal mosaicism.

Hypomelanotic macules are generally the first cutaneous clue to the diagnosis of tuberous sclerosis. These lesions are often present at birth, although in individuals with light skin types, a Wood lamp may be needed to demonstrate their presence. The most common hypopigmented lesion is an elliptical or ash-leaf macule. Less commonly, guttate hypopigmented macules of the pretibial areas or segmental hypopigmented lesions may be present. As patients age, additional cutaneous manifestations of tuberous sclerosis (facial angiofibromas, periungual fibromas, and connective tissue nevi) often become evident.

*Piebaldism* is an autosomal dominant disorder characterized by depigmented patches of skin on the forehead, anterior trunk, and extremities. Forehead lesions may be associated with a white forelock (poliosis). In rare cases, patients with piebaldism can have associated problems, including intellectual

disability. This disorder results from mutations in the *KIT* gene.

### Hyperpigmented Lesions

Congenital hyperpigmented lesions are the result of accumulation of melanin in melanocytes or keratinocytes, melanin incontinence, proliferation of nevus cells in the epidermis or dermis, or thickening of the stratum corneum.

Proliferation of dermal melanocytes produces brown, blue-gray, or blue-black patches. Such lesions are termed congenital dermal melanosis. Mongolian spot is an outdated term used to describe congenital dermal melanosis in the sacrogluteal area. Less commonly, these spots can be located on the dorsal trunk, extremities, and scalp. These lesions are the most common birthmarks in patients with highly pigmented skin, being present at birth in 85% of Asians, 96% of blacks, and 46% of Hispanics. Congenital dermal melanosis typically increases in size during the first year and subsequently fades during childhood. *Nevus of Ota* is a blue-gray patch in the distribution of the ophthalmic or maxillary branch of the trigeminal nerve. This patch can be associated with glaucoma, and rare cases of ocular melanoma have been found in these patients. *Nevus of Ito* is a unilateral hyperpigmented patch over the deltoid or scapula. The nevus of Ota and nevus of Ito do not involute with time. The pathogenesis of dermal melanocytosis is thought to be caused by a defect in melanocyte migration from the neural crest to the skin.

One to 3 *café-au-lait macules* (CALMs) are present in 10% to 28% of the general population. More than 3 and particularly more than 6 CALMs may indicate an underlying disorder. Neurofibromatosis type 1 is the most common associated disorder. Large, linear, or segmental CALMs are seen in McCune-Albright syndrome. Additional features characteristic of McCune-Albright syndrome are polyostotic fibrous dysplasia and endocrine abnormalities, which unusually exhibit as precocious puberty.

*Congenital melanocytic nevi* (moles) are classified as small (<1.5 cm diameter), medium (1.5–19.9 cm diameter), and large (>20 cm diameter) (Figure 95-2). Although small congenital nevi occur in up to 1% of infants, large congenital nevi are rare, occurring in 1 in 20,000 infants. In addition to the psychosocial aspects associated with having large nevi, complications include neurocutaneous melanosis, limb hypoplasia, cutaneous melanoma (lifetime risk of 6%–8% in those with large congenital nevi), and extracutaneous melanoma. Congenital nevi larger than 40 to 60 cm are at highest risk for the previously mentioned complications. Furthermore, large congenital nevi on the trunk are at greater risk for developing into cutaneous melanoma, and patients with numerous satellite nevi are at highest risk for developing neurocutaneous melanosis. More than 70% of cases of cutaneous melanoma in patients with large congenital melanocytic nevi are diagnosed before the age of 10 years. Neurocutaneous melanosis can initially be asymptomatic. Magnetic resonance imaging (MRI) is the modality of choice for identifying neurocutaneous melanosis. However, the necessity for brain imaging in asymptomatic patients



**Figure 95-1** Nevus depigmentosus. (Copyright © Johnell Kolve, Dermatlas; www.dermatlas.org.)



remains controversial. In symptomatic patients, imaging with MRI is important in addition to serial clinical neurologic examination. In patients with large congenital melanocytic lesions located over the midline lumbosacral area, MRI can be used to rule out tethered spinal cord. Management of patients with large congenital nevi needs to be individualized and often requires multidisciplinary care. Partial or complete excision is sometimes suggested for large congenital nevi. Although prophylactic surgical intervention theoretically reduces the risk for malignant transformation and improves cosmesis, it is important to note that critical review of the current literature is not able to answer whether surgical intervention reduces the true risk for cutaneous melanoma. Surgical treatment of large congenital nevi does not affect the risk for neurocutaneous melanosis. Small- and medium-sized congenital nevi should be followed with serial examinations and removed if they manifest clinical changes that cause concern.

*Nevoid hypermelanosis* is macular hyperpigmentation in a segmental or whorled pattern. This usually presents in the first few weeks of life and spreads until the end of the second year. Nevoid hypermelanosis can be an isolated cutaneous condition or part of a genetic disease, which is the result of cutaneous mosaicism.

#### WHEN TO REFER

- Large congenital nevi
- Small or medium congenital nevus with concerning clinical features (ie, asymmetry, border irregularity, color variegation)

### VASCULAR ANOMALIES

Vascular anomalies can be classified as either tumors or vascular malformations. *Infantile hemangiomas* (IH) are the most common vascular tumors found in newborns and infants, are rarely present at birth, and usually develop at a few days to a few weeks of life (Figure 95-3).



**Figure 95-2** Large congenital nevus.

These benign proliferations of vascular endothelium are characterized by a predictable growth pattern and a tendency toward spontaneous involution. *Vascular malformations* are congenital lesions composed of mature vessels (arterial, venous, capillary, lymphatic, or combinations). Malformations generally do not spontaneously involute. Examples of vascular malformations include nevus simplex (salmon patch) and nevus flammeus (port wine stain).

Infantile hemangiomas develop in 1.1% to 2.6% of newborns; incidence figures at the end of 1 year are 10% to 12% of white infants. The prevalence is highest in low-birth-weight, white, female infants. Many hemangiomas are heralded by precursor lesions—well-demarcated red macules or telangiectasia, often surrounded by an area of pallor. Fully developed hemangiomas range from soft, bright-red lobulated plaques (*superficial hemangiomas*, formerly known as strawberry hemangiomas) to purplish-blue, poorly defined, compressible subcutaneous nodules or tumors (*deep hemangiomas*, formerly known as cavernous hemangiomas). Most IH have both a superficial and deep component. Most IH present as single round or oval papules or plaques from a few millimeters to a few centimeters in size, referred to as *focal IH*. Fifteen percent to 30% of affected infants have more than 1 focal IH, referred to as *multifocal IH*. Large IH, which account for fewer than 5% of IH, often present as unusual block-like patterns, referred to as segmental IH.

Most IH undergo a proliferative growth phase lasting typically 2 to 4 months, followed by a period of stabilization, and finally an involutional phase. Most IH reach maximal size by 4 months and begin to regress during the second half of the first year of life. Some IH, particularly deep IH, may have a prolonged growth phase that extends to the first birthday or a few months beyond.



**Figure 95-3** Hemangioma of infancy.

Involuting hemangiomas are characterized by loss of bright red color, acquisition of a grayish hue particularly in the center, and loss of volume. Although considerable variation exists in involution, generally 50% of hemangiomas have completely involuted by age 5 years; approximately 10% involute each year thereafter such that, by age 9, approximately 90% have undergone complete involution. Up to 50% of affected patients will have residual skin changes, most commonly telangiectasias, pallor, or redundant atrophic skin.

Management for most IH is watchful waiting and parental education. Parents should be advised to notify the physician if any of the following occur: sudden, rapid growth of the hemangioma; development of a hard, woody texture; prolonged bleeding from the hemangioma; or development of erosions, ulcerations, or crusts. Hemangiomas that may be associated with complications include large IH of the face or beard area, perioral hemangiomas, segmental hemangiomas, and hemangiomas involving the midline spine. Unfortunately, small, subtle IH may grow quickly and suddenly after discharge from the nursery and before the follow-up visit with the primary care pediatrician, so IH in strategic areas often require parent counseling in the nursery or early referral for consultation during the first few weeks of life. PHACE and LUMBAR syndrome should be considered in infants with large segmental hemangiomas. PHACE syndrome describes the association between large (>5 cm in diameter) facial hemangiomas with structural abnormalities of the brain, cerebral vasculature, eyes, sternum, and/or cardiac vasculature and large vessels arising from the aorta. Infants with suspected PHACE syndrome should have brain MRI and magnetic resonance angiography, cardiovascular imaging, and an eye examination. LUMBAR syndrome describes the association between lower body hemangiomas and urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies, and renal anomalies. Initial evaluation of infants younger than 3 months with a hemangioma on the lower half of the body should include color Doppler ultrasound imaging of the spine, abdomen, and pelvis. The recommendations for additional imaging vary based on the exact anatomic location of the hemangioma. Additionally, infants with multiple hemangiomas may require evaluation to exclude the presence of internal hemangiomatosis (especially hepatic). Magnetic resonance imaging, therapeutic intervention with systemic corticosteroid therapy, laser treatment, or any combination of these modalities may be necessary in severe cases. Since its initial report as a successful treatment in steroid-refractory hemangiomas, there have been multiple successful case series documenting the effectiveness of off-label propranolol, a nonselective beta blocker, in the treatment of both cutaneous and visceral IH. In May 2015, a special formulation of propranolol, hemanageol, was approved by the FDA for the treatment of IH at a dose of 3 mg/kg/day in 2 divided doses. In North America many physicians use a lower dose of 2 mg/kg/day in 2 or 3 divided doses. In general, propranolol is well tolerated. However, serious adverse effects such as bradycardia, hypoglycemia, hypotension, and bronchospasm have rarely been reported in those treated

with propranolol. Caution should therefore be exercised when administering propranolol for IH.

### WHEN TO REFER

- Large IH of the face or beard area
- Periorificial IH (especially perioral and periocular IH)
- Lumbosacral IH
- Ulcerated IH
- IH at risk for ulceration in the diaper area and other skin creases
- Multiple hemangiomas
- Segmental hemangiomas
- Disfiguring IH
- IH in strategic areas during the first few days of life (should be monitored closely during the first 2 weeks of life)

### VASCULAR MALFORMATIONS

*Nevus simplex* (salmon patch) is a capillary vascular malformation seen in approximately 40% to 80% of infants (Figure 95-4). These lesions are pink, blanch completely, have indistinct borders, and usually darken in color with crying, vigorous activity, or changes in ambient temperature. Common locations are the glabella, upper eyelids, and nape of the neck. The lesion is presumed to be composed of ectatic dermal capillaries representing persistent fetal vessels. Virtually all eyelid lesions will involute; a small number of glabellar lesions will persist. Nuchal lesions generally lighten during the first or second year, but careful observation will usually reveal some subtle lesions into adulthood. Persistent salmon patches will generally respond to treatment with the pulsed dye laser if necessary in psychosocially important areas.

*Port wine stain* (nevus flammeus) is a less common capillary malformation that occurs in 0.3% of newborns (Figure 95-5). The initial manifestation is a red to purple-red discrete patch with irregular borders,



**Figure 95-4** Glabellar salmon patch and nevus sebaceous.

usually unilateral in distribution. If left untreated, port wine stains will become purple and nodular in adulthood. It is a permanent mark and has no tendency toward involution. The most common site is the face with 50% involving the head and neck. A port wine stain represents a malformation of mature capillaries of the upper dermis. Although a port wine stain can occur as an isolated abnormality, some are associated with serious extracutaneous findings. Sturge-Weber syndrome (SWS) is characterized by a port wine stain in the trigeminal distribution in association with cerebral calcifications, glaucoma, seizures, and mental retardation. A recent study shows that the pattern may actually follow embryologic developmental patches rather than a trigeminal pattern and the GNAQ genetic mutation was identified as a trigger of SWS and a marker of somatic genetic mosaicism. Interestingly, the same mutation was identified in patients with isolated port wine stains. Port wine stain of an extremity, venous varicosities, and hypertrophy of soft tissues and bones are seen in Klippel-Trénaunay syndrome. The triad of findings in Klippel-Trénaunay syndrome plus the presence of an arteriovenous malformation constitutes Parkes-Weber syndrome (associated with RASA1 genetic mosaicism). Cobb syndrome is characterized by a port wine stain in a dermatomal distribution, a vascular malformation of the corresponding segments of the spinal cord, and neurologic manifestations of cord compression. Port wine stains, especially facial lesions, generally improve with laser treatment. If the distribution of the port wine stain and attendant findings suggest any of the aforementioned syndromes, then further evaluation, including MRI and consultation with a neurologist or an ophthalmologist (or both), is necessary for management.

### WHEN TO REFER

- Port wine stain involving the forehead, scalp, temple, or eyelids
- Large port wine stain of an extremity or overlying the midline
- Since port wine stains respond better to treatment early in life, any lesion in a strategically important area should be referred for evaluation shortly after birth



**Figure 95-5** Extensive vascular malformation.

## HAMARTOMAS AND MISCELLANEOUS LESIONS

*Hamartomas* are benign growths consisting of an excess amount of tissue (eg, smooth muscle, sebaceous glands) to that normally found in the location. They are usually not cancerous or hyperproliferative.

*Epidermal nevus* is a benign epidermal hamartoma that usually exhibits at birth or in early childhood (Figure 95-6). It is usually an isolated, small, hyperpigmented, slightly verrucous lesion, but it can be linear or extensive. Rarely, extensive epidermal nevi may be associated with skeletal, neurologic, cardiovascular, and ocular abnormalities (epidermal nevus syndrome). A biopsy is often performed to exclude the possibility of epidermolytic hyperkeratosis, which is a more severe skin condition that may be passed to offspring of affected patients. In rare instances, malignant proliferation has been reported. Treatment is not necessary, but options for symptomatic or cosmetically disfiguring lesions include destructive measures such as excision, cryotherapy, laser ablation, or electrosurgery.

*Nevus sebaceous* is a benign sebaceous hamartoma that manifests at birth or early childhood. It starts as a flesh-colored to yellow smooth plaque found mostly on the face and scalp. Associated alopecia is a common feature of scalp lesions. During and after puberty, the nevus enlarges and becomes more verrucous, corresponding to maturation of sebaceous glands. Benign and malignant neoplasms (including basal cell carcinomas) may develop within these lesions. Although some studies doubt the need for prophylactic excision of nevus sebaceous, authors of a 2009 review recommend that all nevi sebaceous should be excised because of the real (although low) risk for malignant transformation and concern of cosmesis. In their study, youth and the absence of clinical changes within the lesion also do not guarantee benignity. The timing of excision is based on risk of anesthesia, symptoms, and patient's medical history. It is best determined between the patient, parents, and surgeon.

*Smooth muscle hamartoma* is a congenital, skin-colored to hyperpigmented plaque that is present mostly on the trunk and proximal extremities (Figure 95-7). Hypertrichosis is a common finding. This lesion is



**Figure 95-6** Epidermal nevus.



benign; removal is indicated if it is symptomatic or for cosmetic reasons.

### DEVELOPMENTAL ANOMALIES

Developmental anomalies result from faulty morphogenesis at some point during embryonic development. These anomalies can affect any organ system, including the skin. Cutaneous defects may be an isolated, incidental finding or associated with other, possibly severe or life-threatening, abnormalities. They are also potential indicators of underlying defects or a manifesting feature of a syndrome.

*Branchial cleft cysts* present on the preauricular area, mandible, or lateral neck anterior to the sternocleidomastoid muscle during early childhood or adolescence. These cysts result from incomplete resolution of the second and third branchial clefts. Fistula or sinus formation is a common complication and must be delineated with an MRI or computed tomographic scan. These cysts must be differentiated from enlarged lymph nodes and thyroglossal duct cysts (remnants of the thyroglossal duct, which are located on the midline neck and often move with swallowing).

*Aplasia cutis congenita* is a congenital absence of skin that occurs most commonly on the vertex of the scalp but can be found anywhere (Figure 95-8). The lesion appears as a punched-out ulceration (that heals as a scar), or as a scar. Within the scar, no hair or appendages are present. The lesion is usually isolated, but multiple areas may be present. The lesion may involve deeper structures (absence of subcutaneous tissue or bony defects) or be associated with other congenital anomalies (neurologic, skeletal, gastrointestinal) or disorders (trisomy 13). Management involves routine wound care and prevention of infection. Once healed, no further care is necessary, but surgical excision is an option for improved cosmesis. For medicolegal reasons, the physician should recognize aplasia cutis congenita as an intrauterine event



**Figure 95-7** Smooth muscle hamartoma.

that is not related to birth trauma, electrode monitors, or forceps delivery.

The skin and the nervous system are both derived from the ectoderm. Therefore any midline lesion along the posterior axial skeleton can potentially indicate an underlying spinal abnormality and a need for further evaluation. Some common cutaneous posterior midline lesions suggestive of an underlying spinal defect include congenital nevi, vascular malformations, hemangiomas, hair tufts, lipomas, skin tags, dimples above the gluteal cleft, and subcutaneous nodules. An ultrasound (if within first few months) or MRI is necessary to assess for the presence of underlying spinal disease.

*Dermoid cysts* result from trapped ectodermal-derived tissue along embryonic fusion planes. These cysts appear as subcutaneous nodules mostly on the nose or around the eyes, especially near lateral eyebrows (Figure 95-9). A small percentage of midline nasal dermoid cysts will have intracranial involvement. Such lesions require imaging before they are excised.

*Nasal gliomas* represent ectopic neuroectoderm that was sequestered during bony fusion. No intracranial connection is found. Nasal gliomas exhibit as firm,



**Figure 95-8** Aplasia cutis congenita.



**Figure 95-9** Dermoid cyst of lateral eyebrow.



red, telangiectatic dermal nodules located on the nasal root. Less commonly, they can be located intranasally, causing distortion of the nose and obstruction. MRI is the imaging modality of choice.

*Cephalocele* is a generic term referring to herniation of any intracranial tissue through a skull defect resulting from faulty closure. Thus all cephaloceles have an intracranial connection. The most common cephaloceles are meningoceles (meninges only) and encephaloceles (meninges and brain). Most cephaloceles occur along the midline of the occiput or vertex. These appear as a soft, bluish, pulsatile nodule and rarely can be confused for deep hemangiomas or vascular malformations. If a cephalocele is clinically suspected, imaging must be done to define the extent of the tumor. Repair, often requiring collaboration between otolaryngology and neurosurgery, is indicated.

*Accessory tragi* are common anomalies that result from an extra tubercle or remnant of the first branchial arch. These anomalies are most often present in the preauricular area, but they can be seen on the cheek and lateral neck. Accessory tragi are usually an isolated defect, but they can be associated with cleft lip or cleft palate or with several syndromes. The infant must be assessed for other dysmorphic features, and the newborn hearing screen is important for evaluating potential hearing loss.

*Ear pits* are a common congenital defect resulting from defective embryonic fusion of the tubercles of the first 2 branchial arches. Cyst formation and infection are common complications. Rarely, ear pits are associated with hearing loss, renal abnormalities, and several syndromes.

*Supernumerary digits* (postaxial polydactyly) are soft tissue duplications that produce a papule or nodule, most often on the ulnar aspect of the fifth digit. No bone development is present. These are usually isolated anomalies without systemic associations. Supernumerary digits of the hand are a common isolated finding in black children, occurring with a frequency approximately 10 times that of white children and are seen more often in boys. Transmission is presumed to be autosomal dominant. In contrast, when seen in white children, supernumerary digits are more commonly found in association with a syndrome and autosomal recessive inheritance. Treatment of supernumerary digits consists of surgical excision.

*Accessory nipple* results from persistence of nipple or areola, or both, anywhere along the embryonic milk line (anterior axillary fold to medial upper thigh). These lesions are usually asymptomatic and may be single, multiple, unilateral, or bilateral. They are light brown and persist throughout life. Routine examination is essential because individuals with associated breast tissue have a similar risk for malignant transformation as with normal breast tissue. No treatment is necessary.

## VESICULOPUSTULAR DISEASES OF THE NEWBORN

*Erythema toxicum neonatorum* is a benign disorder occurring in 20% to 60% of term newborns and 5% of preterm neonates. Characteristically, the eruption begins during the second 24 hours of life; it is rarely present at birth. However, this eruption may begin

anytime from birth to 2 weeks of age and typically lasts several days to several weeks. A polymorphous eruption is present, consisting of erythematous macules, papules, pustules, and wheals. Lesions are most commonly found on the face, trunk, proximal arms, and buttocks. The palms and soles are usually not involved. The cause is unknown. The diagnosis is usually based on the clinical appearance of the rash in an otherwise healthy term newborn. In cases in which the diagnosis is in doubt, scrapings of pustules stained with Wright stain will reveal large numbers of eosinophils. Fifteen percent of cases are accompanied by peripheral eosinophilia. This disorder is self-limited and requires no treatment; parents should be reassured about the benign and noninfectious nature of this condition.

*Transient neonatal pustular melanosis* is a benign condition occurring in 0.2% to 4% of term babies and is more commonly seen in black newborns. Boys and girls are equally affected. Lesions are present at birth; new lesions do not usually appear after birth. The eruption generally resolves in 24 to 48 hours. Pustules, vesicles, or pigmented macules with or without a surrounding collarette of scale are present. The eruption typically affects the chin, neck, upper back, buttocks, abdomen, thighs, palms, and soles. The cause is unknown. This diagnosis is usually based on the time of onset, clinical appearance, and absence of other findings. Gram stain of pustules demonstrates neutrophils, rare eosinophils, and an absence of bacteria. No treatment is necessary; however, hyperpigmented macules may last for several weeks to months before resolving.

*Miliaria* are a common finding in neonates and infants. In warm climates, they may be present in up to 15% of newborns. Two types of miliaria commonly occur during the newborn period—*miliaria rubra* (known as *prickly heat*) and *miliaria crystallina*—with the former being more common. Incidence is equal among the sexes and races. Both types of miliaria can occur within the first weeks of life and can persist from hours to days. Vesicles, pustules, or papules occur in crops on the face, trunk, and intertriginous areas. Miliaria arise as a result of obstruction within the eccrine duct, followed by rupture of the duct and leakage of eccrine sweat into the skin. Precipitating factors include excessive warming in an incubator, fever, occlusive dressings, or dressing in inappropriately warm clothing. The diagnosis is usually based on lesion location, time of onset, and history of excessive warming. Miliaria usually resolve spontaneously. Providing cool baths and avoiding excessive warming can prevent recurrences.

*Eosinophilic pustular folliculitis* has been reported in neonates. Recurrent crops of white to yellow pustules occur on the scalp and forehead. Lesions crust within 2 to 3 days of onset and resolve without scarring. The course can be months to years in duration. The cause is unknown. The strong association with HIV seen in adults is not observed in neonates, although associated immunodeficiency has been reported. Multiple eosinophils are present on Giemsa stain of a lesion. Topical corticosteroids, erythromycin, or both have been reported to be effective treatments.

*Acropustulosis of infancy* is a chronic, recurrent eruption of vesicles and pustules occurring on the hands and feet. The onset is usually hours after birth, but it can occur anytime during the first year of life.

Lesions last 5 to 10 days; however, crops can appear every 2 to 4 weeks for 2 to 3 years in persistent cases. Erythematous papules rapidly progress to intensely pruritic vesicles or pustules (or both) on the hands, feet, ankles, and wrists, and occasionally on the chest, back, and abdomen. The cause is unknown. An association with scabies is suspected because both have similar clinical presentations. Scabies preparations in acropustulosis will be negative. Gram stain reveals numerous neutrophils and occasional eosinophils. The disease usually spontaneously remits within 1 to 2 years. Symptomatic treatment includes topical corticosteroids and systemic antihistamines. Severe disease may be treated with dapsone, which requires pretreatment screening for glucose-6-phosphate dehydrogenase deficiency and monitoring of complete blood count (CBC) and chemistry profile during treatment.

*Neonatal acne* occurs in 20% of healthy newborns. Onset is at approximately 2 weeks of age, and lesions generally resolve within 3 months. Small, inflamed papules occur on the nasal bridge and cheeks. Reports have implicated the yeast *Malassezia furfur* in the pathogenesis of neonatal acneiform eruptions. Given its benign and transient nature, reassuring the parents is generally adequate. If treatment is necessary, then benzoyl peroxide preparations or topical ketoconazole are effective.

*Incontinentia pigmenti* is an X-linked dominant genodermatosis caused by mutations in the *NEMO* gene. More than 700 cases have been reported; 97% of those affected are girls. The disease has 4 phases: vesicular (Figure 95-10), verrucous, hyperpigmentation (Figure 95-11), and hypopigmentation. In the vesicular phase, lesions are present at birth in 50% of those affected and in 90% of cases by age 2 weeks. Erythematous macules, papules, vesicles, and bullae follow the lines of Blaschko on the extremities, trunk, and scalp. The verrucous phase typically occurs between 2 and 6 weeks of age. Streaks of hyperkeratotic papules and pustules develop in the aforementioned areas. The third phase, hyperpigmentation, usually develops by 3 to 6 months of age. Hyperpigmented macules and patches are present along Blaschko lines. The final phase, hypopigmentation, exhibits during the second to



**Figure 95-10** Incontinentia pigmenti—vesicular phase.

third decades of life. Previously hyperpigmented areas develop hypopigmentation with or without follicular atrophy. Additional findings include scarring alopecia, abnormal teeth (anodontia; peg or conical teeth), eye abnormalities (strabismus, cataracts, optic atrophy, retinal vascular changes), dystrophic nail changes, and seizures. These patients typically have a normal life span. After the diagnosis has been made, a detailed family history and complete skin examination of the mother and of the child's sisters should be performed. Patients should have periodic complete physical examinations, ophthalmologic and neurologic examinations at diagnosis, and a dental examination by 1 year.

## INFECTIOUS LESIONS OF THE NEONATE

Skin infections of the neonate can be uncomplicated and benign or complex and life threatening. Most cutaneous infections are part of a distinct clinical spectrum. Generally, additional clinical clues assist in making a definitive diagnosis. Following are some commonly encountered skin infections that occur either at birth or during the first few weeks of life.

Sepsis is a potentially life-threatening diagnosis in the neonate. If a neonate is exhibiting signs of lethargy, irritability, fever, temperature instability, or poor feeding, then a sepsis workup is almost universally indicated. When present, cutaneous lesions of sepsis usually appear as polymorphic lesions, for example, erythematous macules, petechiae, or, less commonly, small nodules or vesicles. The workup includes cultures of blood, cerebrospinal fluid (CSF), and urine. Empirical antibiotics for the most common organisms should be initiated while awaiting culture results.

### Bacterial Infections

Neonates may exhibit cutaneous infections commonly encountered in school-aged children. Impetigo can be



**Figure 95-11** Incontinentia pigmenti—hyperpigmented phase.

seen during the neonatal period. Infection presents as well-demarcated areas of erythema that progress to vesicles and then pustules, which rapidly rupture or ulcerate, leaving a characteristic honey-colored crust. The most common pathogens are *Staphylococcus aureus* and *Streptococcus pyogenes*. Extremely limited local infections may be treated with topical antibiotics such as mupirocin; more diffuse involvement may require oral or intravenous antistaphylococcal penicillin or cephalosporin.

Bullous impetigo may occasionally be seen. It is caused by specific strains of toxin-producing *S aureus*. The lesion begins as an erythematous patch and progresses to bulla formation when exfoliative toxins are elaborated locally. Fluid obtained from these bulla may show gram-positive cocci in clusters. A diffuse eruption of superficial skin exfoliation is seen in staphylococcal scalded-skin syndrome. This form of staphylococcal infection is seen with the elaboration of exfoliative toxins secreted by phage-2 *S aureus* that is hematogenously disseminated. At the examination, the patient is febrile and seems ill. The patient's skin is diffusely tender and erythematous. Superficial bullae soon develop and quickly rupture. Application of pressure to the edge of intact skin will often result in separation of the epidermis from underlying skin layers (positive Nikolsky sign). Although Gram stain of this fluid will be sterile, neonates with suspected staphylococcal scalded-skin syndrome should have cultures obtained from their blood, urine, nasopharynx, or other suspected focus of infection. Patients with scalded-skin syndrome should be treated with parenteral antistaphylococcal antibiotics.

### Syphilis

With the advent of strict perinatal surveillance, the incidence of congenital syphilis has dramatically decreased. Occasionally, mothers without prenatal care can deliver a child with congenital syphilis. In early congenital syphilis, the neonate will exhibit symptoms similar to those of a patient with secondary syphilis. A generalized papulosquamous eruption can be found, including on the palms and soles. Additional features include rhinitis, hepatosplenomegaly, lymphadenopathy, fever, pseudoparalysis, and CSF abnormalities. Evaluation of patients with congenital syphilis includes serologic studies, CSF VDRL (Venereal Disease Research Laboratory) test, and CBC with platelet count. The treatment of choice is intravenous penicillin G.

### Viral Infections

Neonatal herpes simplex virus (HSV) infection can range from a mild, self-limited disease to one with potentially devastating neurologic consequences and even death. Approximately 70% to 85% of neonatal HSV infections are caused by the mother's primary HSV-2 infection being transmitted to the neonate; often, the mother has no evidence of genital herpes-like lesions at the time of delivery. HSV-1 is implicated in the remaining cases. Reactivation of the virus has very low rates of transmission to the infant. Neonatal HSV infection can exhibit in several forms. First, and potentially the most deadly, is central nervous system (CNS) disease. During a sepsis workup, HSV polymerase chain reaction (PCR) is usually performed on CSF obtained by lumbar puncture. PCR is now the method of

choice for documenting HSV CNS involvement. Because children generally tolerate intravenous acyclovir well, this drug should be provided after the lumbar puncture while awaiting the results of viral PCR. Second, neonatal HSV can produce classic skin lesions of grouped vesicles on an erythematous base seen anywhere on the body that may have been exposed to HSV during delivery. Tzanck preparations may show multinucleated cells if HSV is present. Viral culture of these lesions is the most definitive diagnostic method to establish the diagnosis of HSV. Finally, and least commonly seen, is disseminated infection, the symptoms of which often overlap those described previously. The physician must think of HSV infection as a clinical spectrum. Half of the cases of neonatal herpes in the United States are localized to the skin, eye, and mouth, which responds well to systemic acyclovir. However, in 20% to 25% of cases, dissemination to visceral organs occurs.<sup>72</sup> Lumbar puncture should be performed in any patient suspected of having neonatal HSV because of the possibility of CNS involvement. Intravenous acyclovir therapy should be initiated empirically while awaiting culture results.

Maternal infection with varicella-zoster virus during the first 20 weeks of gestation can result in congenital varicella syndrome. Affected infants can exhibit ophthalmologic complications, neurologic defects, limb hypoplasia, and genitourinary and gastrointestinal defects. Characteristic cutaneous findings are vesicles or scarring in a dermatomal distribution. Maternal varicella with onset during the last few weeks of pregnancy or during the early postpartum period can result in neonatal varicella. Affected infants have an eruption consisting of disseminated papules, vesicles (*dewdrop on a rose petal*), and erosions. Diagnosis can be made by Tzanck preparation, viral culture, or direct immunofluorescence assay. Infants are more likely to have severe disseminated disease with systemic complications if maternal onset of varicella is within 5 days of delivery to 2 days after or if the newborn exhibits the disease between 5 and 10 days of life. Neonatal varicella is treated with intravenous acyclovir.

Congenital rubella syndrome (CRS) occurs in infants of mothers exposed to rubella during the first portion (generally the first 16 weeks) of pregnancy. Increased risk for CRS is associated with earlier gestational exposure. The incidence of CRS has greatly declined as a result of widespread rubella vaccination; however, occasional outbreaks continue to be reported in populations with low vaccination rates. CRS is characterized by the triad of congenital cataracts, deafness, and cardiac defects (most commonly patent ductus arteriosus). Additional features include intrauterine growth restriction, various CNS manifestations, jaundice, hepatosplenomegaly, thrombocytopenia, and radiolucent metaphyseal bone lesions. The characteristic cutaneous finding is a diffuse eruption of blue-red papules and nodules (called *blueberry muffin lesions*). These lesions generally appear at birth or in the first 24 hours of life. Blueberry muffin lesions are not unique to CRS and can be seen in several additional congenital infections (toxoplasmosis, cytomegalovirus, parvovirus B19), erythroblastic fetalis, and neoplastic disorders (congenital leukemia, histiocytosis). Evaluation to determine the etiology



of blueberry muffin lesions should include a CBC, TORCH serologies, viral cultures, and Coombs test. A skin biopsy may also aid in the diagnosis. Additional nonspecific cutaneous features of CRS include nonspecific generalized maculopapular eruption, hyperpigmentation, and recurrent urticaria. The diagnosis of CRS should be suspected in infants with the appropriate constellation of findings. Confirmation is made by isolation of rubella virus from sputum, urine, CSF, or tissue, or by findings of increased titers of immunoglobulin M antibodies to rubella. Treatment is supportive. A high percentage of infants with CRS will experience significant neurologic and auditory complications. Prevention is through immunization with a live rubella virus vaccine.

### Yeast

Congenital *Candida* infection can be present at birth, or it can manifest within the first 6 days of life. Affected neonates typically have widespread eruption of macules, papules, and pustules with relative sparing of the diaper area. Thrush is uncommon in congenital candidiasis. Pustules of the palms and soles are a helpful diagnostic sign. Changes in the fingernails, including yellow discoloration and paronychia, are occasionally present. Diagnosis is made by potassium-hydroxide test or culture. The course tends to be benign in healthy neonates, but it may be complicated by systemic involvement in preterm neonates. Treatment for skin-limited disease in otherwise healthy neonates is with topical antifungal agents.

Neonatal candidiasis is most commonly caused by *Candida albicans* and is observed during the first and second week of life. Infection should be suspected in patients with white hypertrophic plaques within the oral cavity. Another common presentation is a localized perianal eruption consisting of erythematous macules and papules that become confluent. This eruption is often beefy red in color and characterized by the presence of satellite lesions (papules, pustules, or vesicles). The diagnosis can be made by potassium-hydroxide test and observing the characteristic pseudohyphae. Treatment of localized disease is with topical antifungal preparations.

Systemic candidiasis is typically seen in low-birth-weight infants between the second and sixth weeks of life. Features include temperature instability, lethargy, hypotension, and hyperglycemia. Cutaneous involvement may or may not occur. Diagnosis is confirmed by cultures of blood, urine, and CSF. High morbidity and mortality rates are seen in patients with this condition. Treatment is with amphotericin B.

### TOOLS FOR PRACTICE

#### Medical Decision Support

- *Dermatology: Newborn Skin Conditions* (online course), American Academy of Pediatrics (pedialink.aap.org)
- *Pediatric Dermatology: A Quick Reference Guide* 2nd ed (book), American Academy of Pediatrics (shop.aap.org)
- *American Academy of Dermatology* (Web site), (www.aad.org)
- *Society for Pediatric Dermatology* (Web site), (www.pedsderm.net)

### SUGGESTED READINGS

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### Chapter 96

## COMMON CONGENITAL ANOMALIES

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The diagnosis of an anatomic abnormality in an infant at or around the time of delivery can be devastating for a family. From the time that a concern is raised, the parents, who have been anticipating the birth of a normal, healthy newborn, must contend with a series of uncertainties. They must comprehend the meaning of their child's diagnosis and adjust to the reality that their infant or their prospects for parenthood may be different from what they expected. Individual families handle this crisis in differing ways. The infant's primary care physician may need to assume different roles to assist and support the family.

Once a diagnosis has been made, identifying a cause for the malformation is essential for 3 reasons: to guide the workup in an attempt to identify associated hidden anomalies, provide anticipatory guidance for the family to aid in the decision-making process, and permit appropriate genetic counseling regarding the risk of a similar anomaly occurring in future pregnancies. In nearly 50% of cases, no clear cause will be found for the anomaly. In the other half, the anomaly is caused by either genetic disorders, consisting of both single gene mutations and chromosomal anomalies (Table 96-1), accounting for approximately 15% of cases; environmental exposures to teratogens, such as drugs and infectious agents, accounting for approximately 8%; or multifactorially inherited conditions, anomalies caused by an interplay between genetic and environmental factors, accounting for approximately 25% of anomalies.

Congenital anomalies, defined as abnormalities in form or function, occur in 2% to 4% of all infants born in the United States and are the leading cause of neonatal mortality and long-term chronic illness.

### DEFINITIONS

Birth anomalies can be classified as malformations, deformations, or disruptions. *Malformations* are localized



**Table 96-1** Common Genetic Disorders

DISORDER	MANIFESTATION	FREQUENCY PER 10,000 BIRTHS
<b>CHROMOSOMAL</b>		
Trisomy 21	Congenital heart disease, Brushfield spots, short hands, clinodactyly, simian crease, hypotonia, dysmorphic facies	16
Trisomy 18	Congenital heart disease, small for gestational age, clenched fist, rocker-bottom foot, dysmorphic facies	3
Trisomy 13	Congenital heart disease, small for gestational age, polydactyly, holoprosencephaly, dysmorphic facies	2
XO (Turner syndrome)	Congenital peripheral edema, webbed neck, short stature, primary amenorrhea	3
XXY (Klinefelter syndrome)	Behavior problems, small testes, infertility, clinodactyly	5
<b>AUTOSOMAL RECESSIVE</b>		
Sickle cell disease	Anemia, infection	20 (black)
$\beta$ -Thalassemia	Anemia	20 (Mediterranean)
Cystic fibrosis	Failure to thrive, malabsorption, cough, recurrent pneumonia	5 (white)
<b>AUTOSOMAL DOMINANT</b>		
Familial hypercholesterolemia	Family history of early coronary artery disease	20
Neurofibromatosis	Café-au-lait spots	3
<b>X-LINKED RECESSIVE</b>		
Fragile X	Mental retardation, large testes, dysmorphic facies	5
Duchenne muscular dystrophy	Muscle weakness, pseudohypertrophy of calf	1

errors in the morphogenesis of an organ that result in abnormal form or function from damage that has occurred to the primordial tissue during the first trimester of pregnancy. Malformations can be further classified as *minor* or *major*. Minor malformations, which occur in 1 of 10 newborns, are not associated with severe malfunction. They usually represent a cosmetic rather than a functional concern. In contrast, major malformations are far less common and cause severe functional consequences.

An *association* occurs when 2 or more malformations occur together more often than would be expected by chance. The underlying genetic cause of an association may not be known. VACTERL is an example of an association in which vertebral anomalies, anal atresia, cardiac anomalies, tracheoesophageal fistula, and renal and limb anomalies are combined.

A congenital structural abnormality or variation that occurs as a result of external physical forces will lead to a *deformation*. Oligohydramnios, uterine fibroids, and a multifetal pregnancy may each contribute to uterine compression that can result in clubfoot. A *disruption* is a congenital abnormality that occurs because of a destructive event or process that leads to incomplete or abnormal fetal development. Disruption of blood flow to a portion of the brain may result in porencephaly, whereas rupture of the amniotic sac produces tissue strands that entangle limbs, digits, or other fetal parts, leading to amputation of the affected fetal part and amniotic band syndrome. Malformations can occur alone or with other malformations (see Chapter 148, Facial Dysmorphism). They can be part of a *malformation sequence*, such as the Pierre Robin malformation sequence, or occur as part of a multiple malformation syndrome, in which all the anomalies

can be traced to a single identifiable cause (eg, an extra copy of chromosome 18 in trisomy 18, a mutation in a single copy of the *FBN1* in Marfan syndrome, exposure to alcohol in fetal alcohol syndrome).

## APPROACH TO THE NEONATE WITH CONGENITAL ANOMALIES

Identifying a congenital malformation in a newborn should begin a well-defined process of evaluation and information gathering. The physician should review the pregnancy and family history with the neonate's parents, perform a thorough physical examination, and order tests that will provide the information necessary to arrive at the decisions vital to the child's future.

Appropriate care, including resuscitation, should be initiated in the delivery room after the birth of a baby with congenital anomalies. The decision to withdraw treatment should be deferred until a full diagnostic evaluation has been completed and a diagnosis has been made, unless resuscitative efforts prove unsuccessful. Under certain circumstances an advanced care plan may be developed based on a confirmed prenatal diagnosis of a condition not compatible with survival and a family's decision made in consultation with their obstetric and pediatric care physician for their newborn to receive only comfort care. The parents must be involved from the beginning and have a major role in the decision-making process.

## Care of the Newborn With a Condition Not Compatible With Life

When a newborn is found to have an anomaly or syndrome that, in the judgment of the physicians, is

incompatible with life, some parents may have a difficult time accepting these facts and may resist the medical staff's counsel to withdraw life support or to consent to a *do not resuscitate* order. Parents may have difficulty agreeing to these types of recommendations for many reasons: some parents will be in denial about the child's condition, a normal part of the grieving process; others may object to withdrawal of care because of religious beliefs or personal values; still others may believe that, if given enough time, a miracle might occur or a new treatment might be developed that will save the infant's life. In such cases, to prevent the relationship between staff and family from becoming contentious, the medical staff must be as supportive of the family as possible. The caregiving team should maintain patience, empathy, and respect for the parents and for their values and preferences.

In all instances, particularly when disagreement exists between the medical team's management plan and the parents' wishes, lines of communication must be kept open. Daily meetings among the parents, their representatives (including members of the clergy), and the medical staff should be arranged; during these meetings, information about the child's condition should be discussed in detail and care options presented. The neonatal intensive care unit's social worker or hospital liaison psychologist should attend these meetings as a mediator or ombudsman. Parents may feel more comfortable discussing their feelings with a social worker or nurse than with the physician.

Under some circumstances, if no consensus can be reached, the team may have to engage the hospital's bioethics consultation team for mediation purposes or to provide an outside assessment of the information regarding the newborn's prognosis and appropriate treatment options, including the termination of therapy. Given adequate time, however, when the situation is handled with empathy, caring, and respect, the majority of disagreements between parents and physicians can be resolved without the intervention of a bioethics consultation committee or the involvement of the courts. In many instances, time, information, and support are the important elements that allow parents to come to terms with their child's diagnosis and the lack of corrective or palliative treatments, and to weigh the option of continuing care without the benefit of improvement versus discontinuing treatment except for comfort care and allowing their infant to die. If the child's death is not imminent, the parents may choose to take their newborn home to die or consider transfer to a chronic care hospital capable of providing hospice care. Engaging a family in a community- or hospital-based perinatal hospice program is another option. Although perinatal hospice is relatively new in the field of hospice care, the increasing frequency of prenatal diagnosis has created a need for this support for the family of the dying infant. (See Chapter 117, Support for Families Whose Infant Is Sick or Dying.)

### Role of the Medical Geneticist and Genetic Counseling

The genetic team plays an important role in the diagnosis and management of a newborn with congenital anomalies. By assisting in establishing the diagnosis

and providing counseling to the family, the geneticist and genetic counselor provide an important component of care. During the process of genetic counseling the genetic team supports the family, helping the parents and other family members cope with the issues that confront them. The team members serve as advocates for the patient, helping the parents process medical information and treatment options and assisting as needed with decision making. The genetic team becomes an ongoing source of assistance to the child and family by providing information in written and oral forms, making referrals to family support groups, and offering assistance with care coordination, financial aid, and social service needs.

## DIAGNOSIS

To reach a conclusive diagnosis in a newborn with congenital anomalies, 3 major aspects should be pursued: the medical history, the physical examination, and the appropriate laboratory tests.

### Medical History

A comprehensive history is an essential part of the evaluation of the baby with congenital malformations. Three elements that should be included in the history are the pregnancy history and prenatal course, the family history, and the delivery process.

Questions about the pregnancy should assess several areas (Box 96-1). First, how was the infant conceived? Evidence is growing that conditions caused by defects in gene imprinting, such as Beckwith-Wiedemann syndrome, occur more often in newborns conceived via in vitro fertilization.

Information about the nature of fetal movements can provide clues to the functioning of the newborn's central nervous system. Decreased fetal movements or delayed quickening suggests a neuromuscular disease, whereas a mother's report that her fetus had recurrent hiccups during the second or third trimester suggests possible intrauterine seizure activity. Oligohydramnios is suggestive of anomalies of the urinary tract, such as renal agenesis and obstructive uropathy, whereas polyhydramnios may point to an obstruction in the gastrointestinal tract, such as duodenal atresia or a disorder of the central nervous system that prevents normal fetal swallowing. The possibility of fetal exposure to a teratogenic substance should also be reviewed. Intrauterine exposure to alcohol raises concern about fetal alcohol syndrome, whereas exposure to drugs such as sodium valproate, carbimazole, vitamin A analogues, warfarin, and fluconazole is associated with specific malformation syndromes. Similarly, maternal infection with toxoplasmosis, rubella, cytomegalovirus, or varicella is responsible for well-defined patterns of malformations. Finally, chronic illnesses in the mother, such as poorly controlled diabetes mellitus and untreated phenylketonuria, can cause multisystem abnormalities in the fetus.

Results of prenatal testing can be helpful in determining the cause of a newborn's malformations. Prenatal karyotypes should be confirmed with a postnatal blood test from the baby. Antenatal alpha-fetoprotein levels that are too high or too low can direct the physician toward a specific diagnosis. An alpha-fetoprotein

**BOX 96-1 Areas to Cover When Taking a History****ISSUES ABOUT THE PREGNANCY**

1. Conception: Natural or assisted? If assisted, then what method was used to achieve this pregnancy? Were fertility issues raised related to maternal factors, paternal factors, or both?
2. Fetal movements: When did quickening occur? Were movements similar to, greater than, or less than those felt during previous pregnancies?
3. Amniotic fluid: Amount (polyhydramnios vs. oligohydramnios)—color, fluid leakage
4. Exposure: To teratogenic agents or maternal illnesses (diabetes, infection), maternal drugs or chemical use (street and prescription drugs), and environmental exposure (work or community exposures, radiation, hyperthermia)
5. Prenatal testing: Biochemical screening: Pregnancy-associated plasma protein-A, *Quadruple Screen* (Alpha-feto-protein, beta subunits of human chorionic gonadotropin, estriol, and inhibin-A). Use of maternal plasma-cell free DNA (cfDNA testing) in high-risk pregnancies to detect fetal autosomal aneuploidy has been recently reported.<sup>a</sup> Ultrasound screening for nuchal lucency, fetal growth, anatomy, blood flow in umbilical vessels, placental position, etc. Additional prenatal testing such as amniocentesis and chorionic villus sampling is available

6. Other: Parity, maternal weight gain, evidence of maternal uterine pathology (bicornuate uterus, fibroids, etc.), bleeding
7. Fetal growth: Appropriateness of growth, discrepancy in growth parameters—symmetric or asymmetric growth restriction, macrosomia or appropriate growth for gestational age

**ISSUES ABOUT THE FAMILY**

1. Complete pedigree
2. Presence of similar or dissimilar anomalies in first- and second-degree relatives
3. History of pregnancy losses: Spontaneous abortions, stillbirths, and neonatal demise in first- and second-degree relatives
4. Consanguinity in the parents

**ISSUES ABOUT THE DELIVERY**

1. Length of gestation
2. Type of delivery: If by cesarean section, then what was the indication?
3. Fetal presentation: Vertex, breech, or transverse lie?
4. Presence of placental or umbilical cord abnormality

<sup>a</sup>Bianchi DW, Parker RL, Wentworth J, et al. DNA sequencing versus standard prenatal aneuploidy screening. *N Engl J Med*. 2014;370:799–808  
 From: Marion RW, Fleischman AR. The assessment and management of neonate with congenital anomalies. In: Evans M, ed. *Reproductive Risks and Prenatal Diagnosis*. Norwalk, CT: Appleton and Lange; 1991. Reprinted by permission of The McGraw-Hill Companies, Inc.

level that is high raises a concern about a neural tube defect, abdominal wall defects, poor placental function or nephrosis in the fetus. A level that is too low could be caused by fetal death, increased maternal weight, overestimated gestational age, gestational trophoblastic disease, or trisomies. Ultrasound scans revealing shortening of long bones suggest a possible skeletal dysplasia. The presence of polyhydramnios and an ultrasound scan that shows a *double bubble* in the bowel suggest the diagnosis of duodenal atresia.

In gathering information about the family history, a pedigree consisting of at least 3 generations should be constructed (see Box 96-1 for questions to ask in taking the history). Detailed information about any malformations in family members should be obtained; any health problems, instances of intellectual disability, or known conditions should be noted. A history of still-born infants and spontaneous abortions suggests the presence of a balanced translocation in one of the parents, and should cause the physician to suspect that the newborn may have an unbalanced chromosome rearrangement. The presence of similar features in siblings may suggest that the disorder is genetic or a consequence of a teratogen. The physician should consider an inherited autosomal-recessive condition if parental consanguinity exists. Ethnic background, as well as country and city of origin, may suggest a specific genetic disorder that is more common in the

specific population or gene pool. Medical records of parents, siblings, or other family members should be reviewed to corroborate any significant positive findings elicited through the history.

Finally, information about the perinatal period should be obtained. How long was the gestation? Did the mother consume any medications, vitamins, or herbal or over-the-counter products before and during her pregnancy? Did the mother smoke, drink, or use any illicit drugs? Was the mother exposed to any environmental toxins (chemicals, vapors, or fumes, heavy metals or mercury, radiation)? Did the mother have any illnesses or chronic medical conditions? Did the mother have fever? Did any prenatal tests indicate a possible problem? How was the infant delivered? If delivery was via cesarean section, then what was the reason? What complications occurred during the delivery? What were the Apgar scores? Was resuscitation of the newborn needed? Was the placenta normal? Birth weight is particularly important, given that infants with chromosome anomalies, such as trisomy 18, and teratogenic syndromes, such as fetal alcohol syndrome, are typically small for gestational age, whereas babies with multifactorial disorders, such as cleft palate or meningomyelocele, or single gene mutations, such as Marfan syndrome, usually have normal birth weight, and infants born to diabetic mothers, as well as those with rare overgrowth syndromes, such

as Beckwith-Wiedemann syndrome, are typically large for gestational age.

### Physical Examination

A detailed, systematic physical examination should be performed. The newborn's weight, height, and head circumference should be recorded and plotted on an appropriate growth curve. Measurements that are not part of the standard newborn physical examination should be included in the evaluation of the neonate with congenital anomalies. These measurements include interpupillary distance and interpupillary distance, length of philtrum, and ear size and position. Each part of the limbs should be measured. In the newborn period the upper body/lower body ratio is approximately 1.7:1. If this ratio is too high, then the extremities are short; if the ratio is too small, then either the limbs are long or the trunk is too short. During the physical examination, when the upper extremities are in extension and adducted against the body, the tips of the fingers should reach approximately mid-thigh. If the fingertips only reach the hip joint, then the limbs are too short. Comparison of limb length and the ratio of upper body to lower body segment with standard measurements for a newborn may lead to a diagnosis of skeletal dysplasia.

Features that are important in diagnosing the newborn with major congenital malformations are reviewed in the following sections.

### Skull

Evaluation of the skull in the immediate newborn period may be difficult because the journey through the birth canal may produce a molded or misshapen skull. In most cases the skull will revert to its more normal shape within 48 hours.

Craniosynostosis is the premature closure of 1 or more sutures of the skull. The newborn with craniosynostosis will have an unusual skull shape that does not resolve during the first few days of life. The shape of the skull depends on the suture or sutures that have fused: scaphocephaly or dolicocephaly, a long, *boat-shaped* head, results from closure of the sagittal suture; brachycephaly, a short, broad skull, results from coronal suture closure; plagiocephaly, a rhomboid-shaped skull, results from premature closure of either a single lambdoidal or coronal suture (see Chapter 316, Positional Deformational Plagiocephaly); Kleeblattschädel or cloverleaf skull occurs when multiple sutures fuse early during gestation. Craniosynostosis can be an isolated finding in an otherwise normal infant, arise because of an underlying metabolic or endocrinologic disorder, such as hyperthyroidism, or be part of a multiple malformation syndrome, such as Crouzon, Apert, or Pfeiffer syndromes.

An unusual skull shape is not always associated with premature closure of sutures. Brachycephaly is a feature of Down syndrome; scaphocephaly or dolicocephaly can be seen in neonatal Marfan syndrome. Other malformations of the skull or scalp can provide important clues to the diagnosis. For instance, newborns with trisomy 13 often have aplasia cutis congenita, a punched-out-appearing scalp defect

usually seen in the occipital region. The presence of such a lesion in a child with polydactyly and other malformations is virtually pathognomonic for this lethal chromosomal disorder.

### Face

A detailed discussion of facial dysmorphism is found in Chapter 148, Facial Dysmorphism. The approach to evaluating infants with minor (common) facial malformations is reviewed below.

The eyes should be measured to obtain the palpebral fissure size (measured from inner to outer canthus) and interpupillary and inner canthal distances and to determine if the infant has hypotelorism or hypertelorism that is associated with many syndromes. Syndromes with hypotelorism as a feature include trisomy 13 and 21, holoprosencephaly, Meckel-Gruber syndrome, and Williams syndrome, among others. Corneal opacity suggests the possibility of many genetic disorders or a metabolic disorder like mucopolysaccharidosis syndrome. Upper slanting eyes, epicanthal folds, a flat nasal bridge, and short nose with anteverted nares that occur in combination are indicative of midfacial hypoplasia and are seen in infants with Down syndrome and fetal alcohol syndrome, whereas downward slanting of eyes is present in the infant with Treacher Collins.

The ears should be thoroughly examined. The length and shape of each ear should be measured and assessed for low set ears and preauricular skin tags or pits. Ear anomalies are commonly associated with genetic syndromes. Preauricular tags and pits are common findings on the newborn examination. Ear pits and tags can be inherited in an autosomal-dominant pattern. The physician should therefore check other family members for ear pits and tags, as well as to screen the newborn for hearing loss. Defects in middle ear and inner ear can accompany external ear abnormalities. The neck should be examined for branchial pits. If present, then it may be part of the branchio-oto-renal syndrome, and a renal ultrasound should be performed. Renal sonography should be considered when at least 3 minor anomalies exist that include preauricular pits or tags. The diagnostic yield of renal sonography is low for babies who have isolated pits or tags.

The mouth, including philtrum length, should be measured. A large mouth (macrostomia) or small mouth (microstomia) may be seen in various genetic syndromes. Some newborns will exhibit an asymmetric cry caused by the absence of the depressor anguli oris muscle. The cause of this defect is considered to be multifactorial. Research has shown that babies with asymmetric cry have a higher incidence of congenital heart disease; the most common defects include ventriculoseptal defect, atrial septal defect, patent ductus arteriosus, and tetralogy of Fallot. An asymmetric cry is associated with anomalies in other systems, including the central nervous, gastrointestinal, urinary, and skeletal systems. Association with velocardiofacial syndrome (22q11 deletion syndrome) has been reported. Some children have developmental disabilities and failure to thrive. Babies who are born with asymmetric cry should be checked thoroughly for cardiac and other anomalies. Prominent



lips suggest Williams syndrome, whereas a thin upper lip is seen in fetal alcohol and Cornelia de Lange syndromes.

Cleft lip, with or without a cleft palate, occurs in approximately 1 in 750 live births among white infants and is more common in male infants than in female infants. The incidence is highest among Asian infants and lowest in black infants. Cleft lip is usually located laterally at the philtrum ridges. A cleft located in the midline should alert the physician to suspect holoprosencephaly and to assess for other midline central nervous system defects. Cleft lip and palate can occur sporadically as part of a malformation syndrome or as the consequence of maternal drug exposure or a genetic trait. Isolated cleft palate occurs less frequently, at a rate of 1 in 2,500 live births. Cleft defects are associated with other malformations in 25% to 50% of affected infants. An isolated cleft lip does not typically cause functional problems. The primary concern is cosmetic, and this defect may cause a great deal of anxiety for the family. Parents need support and reassurance about the frequent success of cosmetic repair. Feeding problems in the neonatal period often present a significant challenge. Infants who have a cleft palate often cannot adequately generate the negative pressure during sucking to feed efficiently using a standard infant nipple. Many techniques may be tried; however, use of a soft nipple with larger holes and squeezable bottle is often sufficient to solve the problem. Infants with cleft palates can successfully breast-feed with proper support, education, and assistance from a lactation consultant. The mandible is usually retruded in the neonatal period. If the mandible is underdeveloped but the infant has a normal-size tongue, then space is insufficient to contain the tongue properly, leading to pressure on the palate. This process may produce a U-shaped cleft, similar to that seen in infants with Pierre Robin sequence.

Cleft lip repairs are typically performed when the infant is 2 to 3 months of age, after the baby has gained weight and adjusted to extrauterine life. Correction of cleft palate occurs between 9 and 12 months of age.

### **Chest**

The chest circumference and the internipple distance should be measured and plotted on an appropriate growth curve. The nipples may be widely spaced in Turner and Noonan syndromes. A constricted chest with a smaller than normal circumference often occurs in skeletal dysplasias involving the spine, such as Jeune asphyxiating thoracic dystrophy and Ellis van Creveld syndrome; these disorders are often associated with lung hypoplasia, a feature that may impair the infant's ability to survive. Under normal circumstances the head circumference is larger than the chest circumference by 1 to 4 cm; if these proportions are different, then a cause should be sought. Shortening of the sternum is a common feature in trisomy 18, whereas short trunk is seen in skeletal dysplasias such as osteogenesis imperfecta.

### **Spine**

Open neural tube defects are common congenital anomalies, although their frequency has decreased

significantly since the advent of folic acid supplementation of grains and grain products. Since 1998 the availability of periconceptual folic acid has decreased the occurrence of open neural tube defects by approximately 70%. Open neural tube defects include meningocele (the presence of both neural elements and cerebrospinal fluid in a sac protruding from the midline of the back), meningocele (the presence of just cerebrospinal fluid with no neural elements), anencephaly, and encephalocele (essentially, meningocele of the skull). Spina bifida occulta, a condition in which the vertebral arches are not complete and the spinal cord is intact, is a common minor malformation that is of little clinical consequence. Not etiologically related to open neural tube defects, spina bifida occulta may, in rare cases, be associated with tethering of the spinal cord. Similarly, skin lesions or minor abnormalities such as tufts of hair in the lumbosacral region can be an occult marker of underlying cord disease, such as lipomas, or tethers.

When the primary care physician examines a neonate and observes 1 or more of the skin manifestations mentioned previously, the question arises as to whether an ultrasound of the spine is required to rule out a spinal anomaly. Kriss and Desai described a 3.5% incidence of simple sacral dimples (<5 mm, midline position, not farther than 2.5 cm from anus, and no other skin lesions) among 1,449 term infants; none of these infants had spinal abnormalities. They did observe that the infants with other lower back skin lesions (hemangiomas, tail-like skin appendages, raised skin lesions, hairy patches, and cutis aplasia) and a more complex sacral dimple (>5 mm and farther than 2.5 cm from the anus) are at high risk for spinal dysraphism, more so if the baby has more than 1 finding. (See Chapter 332, Spina Bifida.)

### **Trunk and Limbs**

The limbs are involved in many congenital malformation syndromes. In the initial examination the newborn should be examined for symmetry, mobility, and length. Are the head and the trunk appropriate in size for the body? If not, then are the limbs too short (suggesting a skeletal dysplasia such as achondroplasia), or is the trunk too short for the limbs (suggesting a skeletal dysplasia of the spine, such as Jeune syndrome or spondyloepiphyseal dysplasia congenita)?

Asymmetry of the limbs can be caused either by atrophy, often the result of an intrauterine vascular disturbance such as Poland sequence, or by hypertrophy, as can be seen in Beckwith-Wiedemann syndrome or hemihypertrophy, each of which may be associated with Wilms tumor and other malignancies.

Decreased mobility of joints and congenital contractures, often termed arthrogryposis multiplex congenita, results from conditions that interfere with normal fetal movements. Congenital contractures can result from a primary neuromuscular disorder or occur secondary to fetal crowding in the uterus (caused by oligohydramnios, bicornuate uterus, other uterine malformations, or multiple fetuses).

Talipes equinovarus, more commonly known as clubfoot, is a deformity that includes hindfoot plantar flexion, midfoot cavus, and adduction and supination

of the forefoot. It is a common anomaly, occurring in 1 to 2 per 1,000 live births. The most common form is idiopathic clubfoot, which is most likely the result of a combination of environmental and genetic factors. A positional clubfoot may result from intrauterine crowding with restriction of foot motion, and lacks the stiffness of an idiopathic clubfoot. Similarly, a paralytic clubfoot results from intrinsic lack of intrauterine motion. The most rigid and deformed clubfeet are usually teratogenic or syndromic; as the name suggests, these foot deformities are associated with other congenital anomalies such as arthrogryposis and skeletal dysplasias. Talipes is a common feature of a number of multiple malformation syndromes, including trisomy 13 and 18. Tredwell reported association of talipes equinovarus with early amniocentesis. Casting is available as a nonoperative treatment. The cast is changed every 1 to 2 weeks with the expectation of repair within 3 months. The patient continues to wear a cast for 3 to 6 months, followed by corrective shoes. If casting fails, then surgical repair is undertaken. Recently, the Ponseti casting technique involving tenotomy of the Achilles tendon has become well accepted. The casting is followed by bracing for 2 to 4 years.

Isolated puffiness of the hands and feet, particularly on the dorsal side, suggests lymphedema; the physician should suspect Turner syndrome or Noonan syndrome.

Polydactyly, the presence of extra fingers or toes, a common finding, is often inherited in an autosomal-dominant fashion. Polydactyly is usually an isolated finding in an otherwise healthy newborn, occurring in approximately 1 in 700 live births. However, the finding of extra digits can also be part of a more complex multiple malformation syndrome. Classification of polydactyly is based on the position of the extra digit on the hand or foot. The extra digit can be on the radial (preaxial) side of the hand or, more commonly, on the ulnar aspect (postaxial); the digit can be represented by boneless soft tissue attached by a rudimentary pedicle (postminimus) or can be a normally functioning digit. Postaxial polydactyly occurs more often than preaxial polydactyly, particularly among black individuals. When preaxial polydactyly is present, a possible syndromic association should be sought, particularly if a triphalangeal thumb is present. Holt-Oram syndrome, short ribs–polydactyly syndromes, Carpenter syndrome, trisomy 21, VACTERL association, and Fanconi anemia are conditions that may be associated with preaxial polydactyly. Rarely, central polydactyly affecting the 3 central digits may occur. The least common type of polydactyly, it is often associated with another malformation or a syndrome.

Syndactyly, an abnormal connection between adjacent digits, can involve only soft tissues (simple) or include bones (complex). It may be either complete, along the entire length of the finger, or incomplete, sparing the distal part of the fingers. Any number of digits can be linked. Syndactyly is relatively common, affecting 2 to 3 of 10,000 live births. The anomaly can be sporadic, familial, or associated with other abnormalities. Familial syndactyly usually affects the second and third digits and is not associated with other

abnormalities; transmission is autosomal dominant, with variable expressivity and incomplete penetrance. Associated or complicated syndactyly can be syndromic or secondary to a constriction band (amniotic band) sequence. Syndromes described in association with complicated syndactyly include acrocephalosyndactylies and the Poland sequence.

Brachydactyly, or foreshortening of digits, can be isolated or part of a large number of syndromes, or elongated (usually referred to as arachnodactyly), a feature of Marfan syndrome. The position of digits can be abnormal. Clinodactyly, referring to an incurving of 1 or more digits (most often the fifth finger), is a common finding in healthy individuals but is associated with Down syndrome and Russell-Silver syndrome. Camptodactyly, a contracture of the proximal interphalangeal joint most commonly affecting the third and fourth digits, is caused by shortening of the tendons, can be an isolated finding, and is often inherited as an autosomal-dominant trait or part of a more complex condition such as Beals contractural arachnodactyly syndrome or trisomy 18.

### Genitalia

Immediately after birth, the first question asked by parents is whether their infant is a boy or girl. When the answer to this question is not clear, the parents will be understandably anxious and confused. Because of the delicate nature of this problem and the need to communicate with the family in a timely and accurate manner, the management of the infant with ambiguous genitalia is considered a true medical emergency. The evaluation and management of the infant with ambiguous genitalia require a coordinated approach to care that includes a neonatologist, an endocrinologist, a pediatric urologist, a geneticist, a social worker, and mental health professionals. Throughout the evaluation and treatment process, open and frequent communication with the infant's family is essential. In the past, if a baby had a micropenis or severe hypospadias, then the recommendation was for gender reassignment with genital surgery started as soon as possible. Today, controversy exists regarding gender reassignment. The current approach avoids any irreversible surgeries to the genitalia until the child's own gender identity is clear. (See Chapter 243, Disorders of Sex Development.)

Hypospadias is a common malformation of the male genitalia occurring in 1 in every 200 male infants. (For a complete discussion see Chapter 94, Physical Examination of the Newborn; and Chapter 272, Hypospadias, Epispadias, and Cryptorchidism.)

Testicular location is an important clue to whether hypospadias is an isolated defect or part of a more complex condition. Hypospadias is more likely to be an isolated defect in the individual in whom the testes are both descended. Isolated hypospadias, as with clefting of the lip and palate, is a multifactorial trait that shows clustering in families. As such, in these individuals, finding a positive family history is not unusual. The finding of cryptorchidism in an individual with hypospadias should trigger a more extensive workup than would be performed on the child with isolated hypospadias. Such individuals

may actually be virilized girls, caused by such underlying conditions as congenital adrenal hyperplasia resulting from 21-hydroxylase deficiency, partial androgen insensitivity, abnormalities of the sex chromosomes, or another endocrinologic or genetic syndrome. The physician should inquire about the use of progestin and other hormonal treatment in the first trimester; the child should be evaluated for the presence of ovaries and uterus, and renal and other somatic anomalies, and also tested immediately to rule out congenital adrenal hyperplasia. Finally, a karyotype and endocrinologic testing are necessary if intersex is suspected.

Clitoromegaly, enlargement of the clitoris, is not a common finding. In premature babies the labia majora are not yet fully developed, and the normal-size clitoris seems unusually prominent. As described by Oberfield, the paired diameter of the corpora cavernosa should be measured. When enlargement is caused by trauma (edema caused by the birth process), then the diameter will be less than 6 mm. When the enlargement is caused by excess of androgens, then the diameter of the paired corpora cavernosa is more than 6 mm. The infant must be evaluated for congenital adrenal hyperplasia, given that replacement therapy is lifesaving.

## DIAGNOSTIC PROCEDURES

### Chromosome Analysis

Recently, clinical genetic testing using microarray technology has made it possible to detect much smaller chromosomal deletions and duplications (copy number changes) than was possible by standard or high resolution chromosome analysis. Chromosomal microarray (CMA) involves extraction of DNA from peripheral blood and comparison of DNA copy number with a “normal” DNA sample. While similar to fluorescent in situ hybridization (FISH), this technique allows the detection of DNA copy number changes throughout the genome, rather than only at a specifically designated locus. A caveat to the use of microarray testing is that many copy number variants (CNVs) have been discovered, which are benign variants and not disease-causing. The interpretation of test results may require comparison with parental DNA or discussion with a molecular cytogeneticist, or may remain inconclusive. Additionally, CMA cannot detect balanced rearrangements, including translocations or inversion. CMA should be ordered for any child with 2 or more major anomalies, many minor anomalies, intellectual disability, or autism spectrum disorders.

Chromosome analysis is performed on any cells that have the ability to actively divide in culture. As such, although the test is usually performed on lymphocytes from peripheral blood, bone marrow cells or fibroblasts from skin biopsy can also be used. When lymphocytes are used, results should be available after 3 to 4 days; karyotype from fibroblasts takes much longer, on the order of 4 weeks or more. If chromosome analysis can be performed on bone marrow, the results will be ready in 1 day. This method is usually reserved for cases in which critical decisions regarding management need to be made. Chromosome analysis is used to

detect major numerical or structural chromosomal abnormalities, and should be performed in any newborn with ambiguous genitalia or features of a known chromosomal abnormality such as trisomy 21, or if a balanced chromosomal translocation is suspected.

If trisomy 21 or another condition caused by aneuploidy is suspected, then routine chromosome analysis should be ordered. If the child’s features do not fit one of these well-described conditions, then it is more appropriate to order high-resolution chromosome testing, which will provide a more detailed analysis of the chromosomes. Some diseases are caused by a large deletion of an entire gene that can be detected by FISH and other molecular cytogenetic methods.

### Single Gene Testing

Polymorphisms, the most common cause of changes in DNA base pairs, do not cause disease. When an alteration in a gene leads to an alteration in function with clinical symptoms and signs, it is called a *mutation*. Most genetic diseases are caused by single base pair deletions, duplications, or substitutions.

DNA analysis permits the identification of a growing number of conditions caused by single gene mutations. Updated information can be found at GeneTests ([www.genetests.org](http://www.genetests.org)), a Web site that provides information about the availability of testing for specific genetic conditions. New technology, referred to as next-generation sequencing, is being developed to analyze the sequence of multiple genes in a single test. This will aid in the diagnosis of disorders that can be caused by mutations in many different genes and in the discovery of genes responsible for currently unexplained genetic syndromes.

### Fluorescent in Situ Hybridization

FISH is a useful technique in babies born with congenital malformations that suggest one of a group of conditions known to cause small chromosome deletions or duplications. FISH should be ordered in infants in whom the following conditions are being considered: Velocardiofacial or DiGeorge syndrome (deletion 22q11.2), Williams syndrome (deletion 7q11.23), cri du chat (deletion 5p), and lissencephaly and Miller-Dieker syndrome (deletion 17p13.3).

### Methylation Testing

Addition of a methyl group to cysteine and adenine nucleotides can silence or down-regulate gene expression. There is a differential pattern of methylation based on whether the chromosome is of maternal or paternal origin. Through genetic analysis, this change can be exploited to determine the methylation pattern that exists on the genome. Diseases that are caused by methylation abnormalities such as Beckwith-Wiedemann, Prader-Willi, and Angelman syndromes can be diagnosed by determining the methylation pattern in the genome.

### Metabolic Tests

Metabolic tests are additional tools to confirm a diagnosis in a baby with congenital anomalies or a suspected syndrome. Increasing numbers of conditions exist in which a connection between the clinical diagnosis and



the biochemical abnormality has been established. For instance, hypocalcemia is seen in velocardiofacial (DiGeorge) syndrome, whereas hypercalcemia is not uncommon in Williams syndrome; hypoglycemia, caused by hyperinsulinism, is seen in Beckwith-Wiedemann syndrome, whereas low cholesterol and increased level of 7-dehydrocholesterol is a confirmatory test for Smith-Lemli-Opitz syndrome.

### Imaging

Imaging studies are indicated when a baby has more than 1 major anomaly or several minor abnormalities. The finding of internal abnormalities will help in establishing a diagnosis and optimizing treatment of the newborn. Ultrasound of the head and abdomen may detect major anatomic defects. The kidneys should be checked as well. A magnetic resonance imaging study for the brain is the preferred diagnostic tool rather than cranial sonography; however, if a newborn is unstable, then sonography may be the appropriate first screening tool. A skeletal survey is indicated when shortening of limbs or significant short stature at birth is present. Review of a chest radiograph for the presence of the thymus is helpful if 22q11 deletion is suspected; in many syndromes the number of ribs is abnormal. In suspected craniosynostosis a skull film or three-dimensional head computed tomography is helpful, whereas patellar or epiphyseal stippling can be seen in Zellweger syndrome. Periosteal cloaking of long bones is present in I-cell disease even if the baby is preterm. An echocardiogram should be obtained on any neonate with a heart murmur who has other malformations. Ophthalmologic evaluation is helpful as well. Corneal opacity is seen in mucopolysaccharidosis and trisomy 18, colobomata of the iris in CHARGE syndrome (coloboma, heart disease, atresia choanae, retardation of growth or development, genitourinary tract anomalies, and ear anomalies), trisomy 13, cataracts in Sotos syndrome, and Stickler syndrome, as well as other syndromes.

### Other Diagnostic Tools

The diagnosis of a malformation syndrome is sometimes apparent on the basis of the infant's clinical features. A diagnosis will sometimes be determined after additional testing. To address the difficulty in determining a diagnosis, dysmorphologists have developed scoring systems for various genetic syndromes. Scoring systems have been developed for trisomy 18, as well as trisomy 21, Williams, Cornelia de Lange, and Noonan syndromes. The limitation of a scoring system is the subjective judgment of the examiner. Another helpful tool is *Smith's Recognizable Patterns of Human Malformation*, which describes lists of anomalies that appear in different syndromes. Computer systems such as POSSUM (Pictures of Standard Syndromes and Undiagnosed Malformations), LDDb (London Dysmorphology Database), and SYN-DROC (Syndrome Congenital Malformation Database) have been developed; these programs can be helpful in identifying malformation syndromes.

### Special Concerns

Genetic testing should not occur before pretest counseling of the family. Counseling should include discussion that genetic test results may disclose

information about the extended family and even lead to revelation of family secrets about paternity or adoption. Both family members who are carriers of the disease and those who are healthy may experience a range of feelings, including anger and guilt. In October 2009, the federal Genetic Information Nondiscrimination Act (GINA) was signed into law, preventing citizens from being discriminated against by health insurers or employers because of their genetic test results. However, genetic test results can affect family members' ability to obtain life and disability insurance, or to adopt children. Special consideration should be given to genetic testing in children who are not capable of giving informed consent; for this reason, several national organizations, including the American Academy of Pediatrics, published recommendations under which children should be allowed to have genetic testing: "(1) When there are immediate medical benefits, such as institution of measures that can prevent the disease, delay its onset, or prevent secondary disabilities; and (2) when there is benefit to another family member and no harm to the minor." When parents request genetic testing and no benefits exist for the child, or if the genetic testing will be used solely for future reproductive decision making, then in most circumstances the test should be deferred. Genetic testing brings complex social, ethical, and emotional issues, particularly in adolescents. Before ordering any genetic tests the physician must understand the above complexities, consult with the appropriate specialists, and prepare the family for the possible consequences of the genetic testing results.

## TOOLS FOR PRACTICE

### Medical Decision Support

- *GeneTests* (Web site), ([www.genetests.org](http://www.genetests.org))
- *Committee opinion on evaluation of prenatally diagnosed structural congenital anomalies* (article), *Journal of Obstetrics and Gynaecology Canada*, Vol 31, Issue 9, 2009
- *Indications for genetic referral: a guide for health care professionals* (article), *Genetics in Medicine*, Vol 9, Issue 6, 2007

## AAP POLICY

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**Chapter 97****POSTNATAL ASSESSMENT  
OF COMMON PRENATAL  
SONOGRAPHIC FINDINGS**

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Approximately 10% of all neonates are born with a birth defect. Three percent will have a serious, potentially life-threatening anomaly, and an additional 7% to 8% of neonates are born with a minor malformation. Advances in prenatal screening, diagnosis, and intervention have contributed to an increased awareness at the time of birth of newborns in need of postnatal evaluation to confirm a prenatal diagnosis. For those newborns with a confirmed prenatal diagnosis, this information permits more rapid initiation of treatment and can help guide the evaluations necessary to optimize care. The patterns of malformations seen among newborns have changed over time because of prenatal diagnosis, availability of fetal interventions (including many experimental protocols), and families choosing termination of pregnancy in instances in which the fetus has multiple or complex malformations with an associated poor prognosis or a lethal chromosomal or genetic condition. The spectrum of antenatal sonographic findings is extensive and beyond the scope of this chapter, the focus of which is on the healthy-seeming newborn whose prenatal history is notable for a suspected antenatal abnormality. For further information, see Chapter 96, Common Congenital Anomalies; and Chapter 154, Foot and Leg Problems.

Prenatal diagnosis, though offering the potential for earlier intervention and correction of potentially serious abnormalities, also presents a significant psychological burden on expectant women and their families that may have long-lasting effects. Prospective parents are aware that prenatal ultrasound is a tool for early diagnosis of some abnormalities; however, often they are primarily interested in confirmation of pregnancy and a connection to their baby. The benefits of prenatal sonographic screening on neonatal outcomes remain largely unproven because the sensitivity and specificity of prenatal sonographic screening varies with the conditions screened for, the maternal habitus, and the time at which testing is performed. Routine prenatal screening is useful in the estimation of gestational age, detection of multiple gestations, and identification of fetal anomalies. Accurate pregnancy dating is important in preventing unindicated late preterm and early term deliveries (before 39 weeks' [39 $\frac{0}{7}$ –39 $\frac{6}{7}$  weeks] gestation) and in appropriate diagnosis of intrauterine growth restriction, and in reducing intervention for postterm pregnancy. Appropriate pregnancy dating is also important for more accurate detection of aneuploidy because the significance of the first trimester maternal serum screening test results (free- $\beta$  human chorionic gonadotrophin and

pregnancy-associated plasma protein-A) is based on the estimated gestational age. Generally, 1 to 2 prenatal ultrasounds are performed during every pregnancy. The first study is usually performed between 11 and 14 weeks' gestation in order to confirm an intrauterine pregnancy and to assess for evidence of nuchal translucency (sonographic appearance of a subcutaneous fluid collection behind the fetal neck). Fetal nuchal translucency thickness measurements combined with maternal serum screening markers can detect over 90% of fetuses with trisomy 21. Fetal anatomic scans are typically performed during the second and third trimesters of pregnancy. The sensitivity of sonography performed during the second trimester for detecting fetal anomalies ranges from 35% to 75%. When performed during the second trimester, prenatal sonography identifies approximately 92% of central nervous system (CNS), 80% of musculoskeletal, 60% of genitourinary, 50% of craniofacial, and 24% of cardiovascular malformations (38% if the child's underlying condition is associated with congenital heart defects), with many of these abnormal findings not being of clinical significance. (See Table 97-1.)

Some anomalies may not yet have developed, such as microcephaly. Detection rates are variable and dependent on gestational age at examination, type of malformation, sonographer experience, number of ultrasounds performed, quality of the equipment used, and population characteristics. Fetal magnetic resonance imaging and fetal karyotyping may be used to further delineate clinical findings and aid in the formulation of the initial clinical care plans for the fetus and neonate. Some infants with prenatally diagnosed conditions will be healthy when evaluated postnatally. Despite explanations from obstetric caregivers and sonographers that prenatal ultrasonography will not identify all anomalies, families often expect that any and all problems should have been detected if the mother had 1 or more prenatal sonographic studies or underwent an amniocentesis. This expectation can present a challenge to the pediatrician who must assist the parents as they come to terms with their newborn's diagnosis and try to understand the limits of technology.

Screening ultrasonography has not been shown to be more effective in improving perinatal outcomes

**Table 97-1****Likelihood of Malformation  
Detection on Prenatal  
Sonography**

ANOMALY	CHANCE OF DETECTION
Anencephaly	99%
Hydrocephalus	60%
Spina bifida	90%
Major cardiac anomalies	25%
Diaphragmatic hernia	60%
Omphalocele/gastroschisis	90%
Major renal anomalies	85%
Major limb anomalies	90%
Trisomy 21	40%

compared with selective use of ultrasonography based on clinical judgment. However, if fetuses with severe malformations whose pregnancies are terminated are excluded from statistical analyses, then an improvement in reported outcomes can be found. Controversy exists with regard to the benefits of prenatal diagnosis, given that decision making about the choice of delivery hospital, level of neonatal and subspecialty care, and initial scope of care provided are influenced by the available prenatal data. The infant with a serious malformation, such as a gastroschisis or congenital diaphragmatic hernia (CDH), can benefit from delivery at a tertiary care center, while knowledge that an infant has a ductus-dependent cardiac lesion can afford the pediatric primary care physician the opportunity to have prostaglandin therapy available for use during the infant's stabilization. In contrast, postnatal diagnosis of significant birth defects, such as pulmonary atresia, may not necessarily lead to greater mortality or morbidity in comparison with infants who are identified through prenatal screening. Understanding the complexities of screening is important in assisting parents as they assimilate information about health conditions for their baby, their awareness of the potential problem in the prenatal period, and subsequent evaluation of the infant to characterize more fully the infant's health care needs.

Surveillance programs in the United States report that orofacial clefts and Down syndrome are the most common major birth defects to occur among liveborn infants. The Metropolitan Atlanta Congenital Disorders Program is a Centers for Disease Control and Prevention (CDC)-supported initiative that tracks birth defects in that city. When all neonatal birth defects are considered, malformations involving the heart, genitourinary, and musculoskeletal systems, as well as the chromosomal anomaly trisomy 21, are among the more common abnormalities observed. The most frequently observed cardiovascular malformations are atrial septal defects, patent ductus arteriosus, and ventricular septal defects, in increasing order of prevalence. Rates of gastroschisis are also reported to be increasing, particularly among teen mothers. Regional variation has been reported in the incidence of these and other malformations; the reasons for the changing prevalence rates are not easily determined in many instances. It is important to recognize the variability in the clinical significance of the various findings detected by prenatal sonography, the potential psychological effect for families, which prenatal findings require postnatal assessment, and the scope of evaluation required.

## POSTNATAL EVALUATION IN OTHERWISE HEALTHY NEWBORNS

### Abnormalities in Amniotic Fluid Index

Amniotic fluid helps to protect the fetus in utero from impact, allows the fetus to move freely around the uterus, and promotes fetal lung development. Amniotic fluid is produced by the mother until about the fourth month of pregnancy when the fetal kidneys begin to produce urine. Amniotic fluid volume increases until about 32 weeks' gestation, and then proportionately decreases as the fetal size increases. The amniotic

fluid index is measured by the sum total of the deepest vertical pockets in each of the 4 quadrants into which the uterus is divided. Normal amniotic fluid index (AFI) is 5 to 24 cm. Infants who have abnormal amniotic fluid volumes require careful review of prenatal history and a thorough physical examination.

Oligohydramnios, defined as an AFI less than 5 cm, occurs in about 4% of pregnancies. A strong correlation has been reported between an AFI less than 5 cm and abnormal fetal heart rate, meconium passage during labor, and the need for cesarean delivery. Decreased production of amniotic fluid may be associated with renal anomalies. In the absence of malformations, borderline or low AFI is more likely to be complicated by fetal growth restriction and preterm birth. Decreased volume of amniotic fluid inhibits the activity and movement of the unborn infant. This is associated with a greater prevalence of congenital torticollis and developmental hip dysplasia compared to controls. Oligohydramnios may result from renal malformations; therefore, in instances where an underlying cause for the oligohydramnios has not been determined prenatally, a postnatal sonogram is recommended and consideration should be given to measurement of serum chemistries and perhaps additional imaging (voiding cystoureterography [VCUG], Mag3 renogram) based on the results of the initial evaluation. Postnatal hip ultrasounds and/or radiographs should be ordered for cases of prenatal diagnosis of oligohydramnios and breech positioning. Careful newborn and periodic physical examinations of the hips should be done for these children as well as hip ultrasound between 4 weeks and 4 months of age and/or radiograph after age 4 months.

Polyhydramnios, defined as an AFI greater than 24 cm, occurs in 1% to 3% of pregnancies. Polyhydramnios is a common finding in diabetic pregnancies, when the fetus is macrosomic, as well as in multiple gestation pregnancies. There is an increased risk for minor (4.2%) as well as major (20%) congenital malformations in pregnancies where polyhydramnios is present including GI (40%), CNS (26%), cardiovascular (22%), or genitourinary system anomalies (13%). Gastrointestinal malformations include GI tract obstruction, such as duodenal atresia and tracheoesophageal fistula. Approximately 50% of affected pregnant women had no associated risk factors. Among monoamniotic-monochorionic twin gestations complicated by twin-to-twin transfusion, the donor twin may develop oligohydramnios while the recipient twin develops polyhydramnios. Fetal or neonatal hydrops with anasarca, ascites, or pleural or pericardial effusions is also associated with polyhydramnios. CNS disease that compromises the brain's control of fetal swallowing can result in polyhydramnios.

### Antenatal Single Umbilical Artery

The number of umbilical vessels, 2 arteries and 1 vein, is usually assessed as part of the routine anatomic survey during the prenatal ultrasound. A single umbilical artery (SUA) is identified in 0.2% to 2% of fetuses. There is a known association of SUA with congenital anomalies, intrauterine growth restriction, and fetal demise. Cardiac anomalies, renal anomalies, and preterm birth

are significantly higher among infants with an SUA. SUAs diagnosed in the first trimester are highly associated with trisomy 18 and other chromosomal anomalies. Laterality has been examined to determine whether there may be an association for congenital anomalies. The absence of the left umbilical artery is more common than the right. An absent right umbilical artery has been associated with a higher incidence of genitourinary and gastrointestinal anomalies. A detailed anatomy scan including fetal echocardiogram is recommended for infants with an SUA. A recommended screening protocol for genitourinary malformations in patients with SUA should consist of routine prenatal ultrasound, a postnatal physical examination, a postnatal abdominal ultrasound, and possibly a postnatal VCUG. This screening likely would detect all significant urologic disease in a fetus or neonate.

### Antenatal Sex Determination

Although many families' primary interest in the prenatal ultrasound is to discover the sex of their infant, for the physician the prenatal ultrasound affords an opportunity to detect genitourinary anomalies. In some cases, congenital adrenal hyperplasia can be diagnosed with ultrasound by an initial finding of genital ambiguity. Treatment can be initiated prenatally to avoid further complications.

The CDC reports that the rate of hypospadias has increased dramatically in the last 2 decades, confirming similar findings in Europe. Hypospadias may lead to an incorrect prenatal gender assignment. After the first trimester, accuracy of sex determination via ultrasound is 99%; however, incorrect fetal sex determination may have significant emotional repercussions for the family. It has been associated with marital conflicts, domestic violence, negative perceptions of ultrasound, and a desire for reversal of tubal ligation.

### Antenatal Limb Anomalies

The frequency of limb anomalies is 6 in 10,000 with a higher occurrence in the upper limbs. Clubfoot or talipes equinovarus deformity is the most common musculoskeletal defect, followed by upper limb reduction abnormalities (Figure 97-1). Limb anomalies

detected early are often associated with serious congenital conditions.

The literature on prenatal diagnosis of common limb anomalies is extensive. Ermito et al. describe many of the upper limb anomalies that can be visualized via ultrasound, including clinodactyly, radial clubhand, terminal transverse limb defects (upper limb transverse deficiency is the most common), syndactyly, postaxial polydactyly (Ellis-van Creveld syndrome), and phocomelia. Detecting limb anomalies is useful for overall syndrome identification and making the family aware in advance of the delivery where possible so as not to be surprised.

Prenatal diagnosis of congenital clubfoot has been extensively studied. Glotzbecker et al. recently described a severity scale, with the more severely deformed foot having a higher level of prenatal accuracy. This can provide a higher degree of confidence in the prenatal diagnosis when counseling families. However, parents should be counseled that a clubfoot can still occur although it was not detected prenatally by ultrasound. In addition, there may be associated anomalies present that are not detected by the ultrasound. It is important to avoid terms such as "missed" or "misdiagnosis" when talking to parents. Ultrasound is also useful to detect skeletal dysplasias. These include diastrophic dysplasia, achondroplasia, thanatophoric dysplasia, Kniest, campomelic dysplasias, chondroectodermal dysplasia, and arthrogryposis congenita. Upper and lower limb deformities that result from amniotic band sequence (also referred to as amniotic deformity, adhesion, and mutilation [ADAM] sequence) are detectable by prenatal sonography, as are limb deficiencies that arise from hypoplasia or agenesis of 1 or more long bones. Three-dimensional ultrasound is a newer modality to visualize the infant in a more panoramic view. Accuracy of diagnosis is not 100%, but is more accurate if the diagnosis is a lethal condition.

### Antenatal Hydronephrosis and Pyelectasis

Antenatal hydronephrosis (ANH) is among the most common abnormalities detected on prenatal sonography and has a reported incidence of 1% to 5%. Etiologies of ANH include transient dilation of the collecting system, upper and lower urinary tract obstructive uropathy, and nonobstructive conditions such as vesicouterine reflux (VUR) and less commonly cystic kidney disease, congenital strictures, megaureters and prune belly syndrome (see Table 97-2). Pyelectasis, dilation of the renal pelvis, is a more common finding on prenatal sonography. The reported incidence of pyelectasis is 2% to 7%. Pyelectasis is most commonly caused by ureteropelvic junction obstruction (UPJO), VUR, posterior urethral valves, and ureteral obstruction. Less commonly, antenatal hydronephrosis may be associated with prune belly syndrome, VATER syndrome, solitary kidney, and renal mass. As the pregnancy progresses, pyelectasis can develop into hydronephrosis or resolve spontaneously. An association also exists between pyelectasis occurring later in gestation and Down syndrome.

Defining the severity of ANH can be challenging. At present, measurement of the anterior-to-posterior



**Figure 97-1** Prenatal ultrasound of a clubfoot.



**Table 97-2****Etiology of Antenatal Hydronephrosis**

ETIOLOGY	INCIDENCE
Transient hydronephrosis	41%–88%
UPJ obstruction	10%–30%
Vesicoureteric reflux (VUR)	10%–20%
Ureterovesical junction obstruction/ megaureters	5%–10%
Multicystic kidney disease	4%–6%
Posterior urethral valves/ureteral atresia	1%–2%
Ureterocele/ectopic ureter/duplex system	5%–7%

From Nguyen HT, Herndon CDA, Cooper C, et al. The Society for Fetal Urology consensus statement on the evaluation and management of antenatal hydronephrosis. *J Pediatr Urol.* 2010;6:212–231, with permission from Elsevier.

diameter (APD) of the renal pelvis is used to assess ANH in utero. Gestational age, maternal hydration status, and the degree of maternal bladder distention can affect the APD measurements. An APD greater than 15 mm is considered indicative of severe fetal hydronephrosis. Prenatal grading of ANH severity includes characterization of the hydronephrosis as mild, moderate, or severe, and specifies the extent of renal pelvis and calyces involvement (pelviectasis, pelvicaliectasis, caliectasis). Postnatally, a different grading system is used based on the appearance of the renal pelvis, calyces, and renal parenchyma. Oligohydramnios is an important factor in predicting the likelihood of postnatal pathology.

Wide variation can be found in the prenatal assessment and postnatal management of infants with ANH. A meta-analysis conducted to determine the risk of postnatal disease in infants with ANH found that the risk of VUR among infants born with ANH was 8.6%, nearly 9 times higher than the incidence found among infants without ANH. Infants born with severe ANH have a high risk (88.3%) of underlying genitourinary tract pathology. In comparison, infants with mild or moderate ANH have been shown to have lower rates of postnatal pathology; however, the rates of associated abnormalities remain highly significant at 11.9% and 45.1%, respectively. Transient hydronephrosis caused by renal pelvis or calyceal dilation resolves over time without intervention in most children. It is reported that most children with antenatal renal pelvic dilation less than 6 mm in the second trimester or less than 8 mm in the third trimester have transient hydronephrosis. The incidence of transient hydronephrosis decreases with increasing anterior-posterior diameter detected during the third trimester. Figure 97-2 is a prenatal ultrasound of severe hydronephrosis.

Infants with significant hydronephrosis are more often male and have evidence of left kidney involvement. Additional information garnered from the prenatal evaluation that informs the diagnostic and management considerations includes renal calyceal dilation, echogenicity of the kidneys, thinness of the renal parenchyma, presence of hydroureteronephrosis,

**Figure 97-2** Prenatal ultrasound of hydronephrosis.

bladder dilation, posterior urethral dilation, fetal gender, laterality of the involved kidney, and amniotic fluid volume. Oligohydramnios is associated with a poorer prognosis. Bladder distention or the presence of lower urinary tract obstruction suggests posterior urethral valves, VUR, or megacystis, particularly in a male fetus. The presence of prenatal renal dysplasia (renal cysts and hyperechoic renal parenchyma) can indicate poor kidney function. Renal cysts are highly specific for kidney dysplasia, whereas kidney hyperechogenicity is a more sensitive, but less specific, sign. Spontaneous urinary tract decompression can occur in infants with severe urethral obstruction, causing ascites or a perinephric urinoma.

The timing of the prenatal ultrasound is also important in predicting the importance of the findings. Infants with isolated ANH have varying degrees of renal pelvis or calyceal dilation, referred to as pelviectasis or pelvicaliectasis. Postnatal sonography is usually performed 5 to 7 days after the infant's birth to reevaluate the kidneys. At 5 days of age, 25% of newborns with ANH show no evidence of residual hydronephrosis. While half of the newborns with pelviectasis exhibit mild dilation, pelviectasis has resolved in 50% of babies with dilation on the initial postnatal renal sonogram.

Newborns with ANH should be thoroughly examined for the presence of other anomalies and assessed for adequate urine output. Postnatal evaluation and management remains controversial; there is significant variation in administration of antibiotic prophylaxis. Postnatal sonography performed within 48 hours of birth may underestimate the degree of hydronephrosis. Depending on the sonographic results, further evaluation may be indicated, including VCUG and nephrology and/or urology consultation. Initiating postnatal antibiotic prophylaxis to reduce the risk of infection before performing postnatal imaging to confirm the presence of associated VUR is controversial. Though recommendations regarding management of a first urinary tract infection in infants between 2 and 24 months have been recently published, the physician should be careful applying these recommendations to the newborn. The clinician



should consider consultation with a pediatric urologist to discuss optimal evaluation and management plans. Current recommendations include the following:

- Newborns with bilateral severe ANH ( $\geq 10$  mm in second trimester or  $\geq 15$  mm in third trimester) or a single kidney with any grade of hydronephrosis should undergo postnatal renal sonographic evaluation before hospital discharge.
- Newborns with any other grade of ANH should have a postnatal renal ultrasound examination performed within the first month of life (after the first 5 days of age).
- Newborns with persistent moderate to severe ANH should undergo a VCUG evaluation and functional studies as needed.
- Decisions regarding postnatal evaluation of newborns with mild persistent ANH or isolated ANH that resolves should be individualized based on the specific infant issues.
- Pyelectasis that resolves spontaneously before birth does not require postnatal evaluation.
- Newborns with persistent pyelectasis should have postnatal renal sonographic evaluation performed within the first month of life with additional evaluation (VCUG evaluation and functional studies) and antibiotic prophylaxis based on sonographic and clinical findings.

### Antenatal Identification of Central Nervous System Variants

Cerebral malformations occur in approximately 1% of live births and are the second most common congenital abnormality following congenital heart disease. Suspicion of a CNS abnormality requires a multidisciplinary evaluation. Testing may include evaluation for TORCH infections, screening and amniocentesis for karyotyping and microarray analysis. The corpus callosum becomes clearly visible by 20 weeks' gestation. Major sulci are identifiable from 26 weeks of development. The lateral ventricle is typically larger in male fetuses. Transabdominal or transvaginal sonography in mid-trimester allows for visualization of most cerebral and cerebellar structures. The addition of color Doppler flow imaging and 3D or 4D imaging enhances detection rates. Fetal magnetic resonance imaging (MRI) may be needed to enhance delineation of suspected CNS anomalies. Isolated mild to moderate ventriculomegaly, defined as a lateral ventricle that measures between 10 and 15 mm, is the most common nonspecific nervous system anomaly identified, with a reported incidence of 1.4 per 1,000 live births in low-risk populations. Ventriculomegaly and cysts of the choroid plexus and subependyma are prenatal sonographic findings with an uncertain significance that warrant postnatal evaluation and follow-up. Ventriculomegaly is the most common CNS abnormality identified on prenatal sonography. It is an excess of fluid in the lateral ventricles within the developing cerebrum. Figure 97-3 is a prenatal ultrasound with ventriculomegaly. The diagnosis is most often identified at a routine fetal anatomy scan, traditionally undertaken at 18 to 22 weeks' gestation. An estimated 70% to 85% of fetuses with ventriculomegaly have associated structural or chromosomal anomalies, including neural



**Figure 97-3** Prenatal ultrasound of ventriculomegaly.

tube defects, structural and cortical brain malformations, hemorrhage, and porencephaly. Clinical risk is further influenced by additional factors such as maternal age and the results of maternal serum markers for aneuploidy. Though some of these cases resolve spontaneously, serial exams should be undertaken to follow the course. One-third of infants with isolated ventriculomegaly have been found to subsequently exhibit developmental delay in comparison with over 84% of infants with ventriculomegaly and associated anomalies. Mild, isolated ventriculomegaly (15 mm or less) is associated with normal school-age outcomes. In contrast, unilateral isolated ventriculomegaly and asymmetric ventricles (suggestive of infarction or ischemic injury) are identified risk factors for behavioral and neuropsychiatric disorders.

Choroid plexus cysts are detected on prenatal sonography in approximately 1% of pregnancies and are associated in a small percentage of infants with aneuploidy; 40% to 50% of infants with trisomy 18 and 1.4% of babies born with Down syndrome have choroid cysts. The risk for aneuploidy is unrelated to the location (laterality), size, number, or complexity of the choroid plexus cysts, or whether the cysts spontaneously regress. Advanced maternal age increases the infant's risk as well. Many choroid plexus cysts regress by 28 weeks of gestation. A multidimensional assessment of developmental status, emotional regulation and social engagement, motor control and activity level under conditions of activation and inhibition, and autonomic regulation failed to reveal significant differences between children with a choroid plexus cyst detected prenatally and those without detection, as long as the karyotype was normal.

Subependymal cysts are thought to represent hemorrhagic-ischemic injury in a portion of the periventricular region of the brain. Infants born preterm exhibit associated neurodevelopmental sequelae. The true incidence of cranial sonographic abnormalities in term infants is unknown; however, approximately 8% of infants have evidence of ischemic injury. The short-term neurodevelopment of these infants seems comparable to that of infants without cranial sonographic

abnormalities at birth. The detection of neural tube defects (NTDs) during pregnancy has been increased through the combination of maternal serum and amniotic fluid alpha-feto protein (AFP) levels in conjunction with fetal anatomy scanning. Identification of “lemon” (scalloping of the frontal bone) and “banana” (hypoplastic cerebellum) signs on fetal sonography has increased detection rates to more than 90%. Neural tube defects may be diagnosed as early as 11 to 13 weeks. Open defects are more commonly associated with hydrocephalus and Arnold-Chiari II malformations. Spina bifida occulta or closed NTDs are less likely to be associated with hydrocephalus or other anomalies. Midline malformations, such as semilobar and lobar holoprosencephaly, can be diagnosed in the first trimester. Fetal MRI can augment 3D sonographic imaging to further characterize the abnormality. Partial or complete agenesis of the corpus callosum occurs in approximately 5 in 1,000 births and can also be identified by fetal imaging, optimally in the second trimester. Agenesis of the corpus callosum may be isolated or occur in conjunction with chromosomal defects, genetic syndromes, and metabolic and environmental disorders.

Recommendations include the following:

- After birth, head circumference must be measured accurately and plotted on percentile charts.
- Infants with prenatal cranial sonographic abnormalities require a postnatal cranial sonogram and a thorough physical examination for evidence of dysmorphism and other malformations.
- The prenatal information should be reviewed to ascertain whether the mother was evaluated prenatally for a TORCH infection (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex).
- Consultation with a pediatric neurologist and additional neuroimaging may be warranted based on the sonographic findings and clinical examination.
- Careful monitoring of the infant’s head growth and neurodevelopment is required.

### Antenatal Echogenic Intracardiac Focus

A bright echogenic focus within the cardiac ventricles was first described in 1987. Prevalence rates reported are between 0.5% and 20%. It is defined as a small structure within the fetal heart with similar or greater echogenicity compared to the surrounding bone. It may be related to increased mineralization or even calcification. This echogenic focus is usually in the vicinity of the papillary muscle, chordae tendinae, and atrioventricular valves. This is thought to be a normal finding in low-risk populations, although the presence of cardiac echogenic foci may be associated with trisomy 21 in high-risk pregnancies. Results from high-risk groups (advanced maternal age, abnormal biomarkers [triple or quad screening], prior affected offspring) suggest that isolated cardiac echogenic foci may be associated with a higher risk of fetal aneuploidy. When a mass is seen associated with a bright focus or calcification, a tumor such as a rhabdomyoma or teratoma should be considered. Cardiac echogenic foci usually regress with age, with most resolving by age 5. In low-risk pregnancies, isolated intracardiac

echogenic foci are not associated with impaired ventricular function, valvular disease, or childhood myocardial dysfunction. No specific postnatal follow-up assessment is required.

### Postnatal Evaluation of Lung Anomalies

Fetal lung masses that cause respiratory distress are reviewed in detail in Chapter 100, Respiratory Distress and Breathing Disorders in the Newborn. Antenatally diagnosed lung lesions are most commonly congenital cystic adenomatoid malformations or bronchopulmonary sequestrations. Many echogenic fetal lung masses regress antenatally, whereas other lesions will enlarge in size. Postnatal evaluation of the asymptomatic infant with a history of an antenatal fetal lung mass should include chest radiograph and a computed tomographic (CT) scan. Residual lesions are often visible on CT scan despite apparent resolution on prenatal sonography.

Recommendations include the following:

- Thorough examination of the infant for evidence of respiratory compromise
- Postnatal chest radiographs and chest CT scan
- Pediatric surgical consultation and close follow-up

A defect in the fetal diaphragm causes CDH, which occurs 1 in 2,400 newborns. The number is likely higher if fetal losses and terminations are included. This defect is usually diagnosed prenatally via ultrasound. When a prenatal diagnosis is made, it is important for the pregnant woman to seek consultation at a tertiary center experienced in treating infants with CDH. Consultations with a pediatric general or cardiothoracic surgeon and neonatologist provide an opportunity to discuss prenatal and postnatal medical treatment options.

### Postnatal Evaluation of Intra-abdominal Fetal Echogenic Masses

Fetal echogenic lesions in the abdomen are common prenatal sonographic findings. Formulation of a presumptive diagnosis is based on a thorough evaluation of the lesion’s characteristics and structure, and on the presence of calcifications. Echogenic bowel is the most common echogenic mass in the fetal abdomen, identified in 1% of second-trimester fetuses that are evaluated. Spontaneous resolution occurs in 50% of affected infants. Echogenic bowel may be associated with fetal growth restriction. Differential diagnosis of echogenic bowel includes cystic fibrosis, chromosomal abnormalities, intra-amniotic bleeding, and congenital infection (cytomegalovirus, herpes). Prenatal detection of echogenic bowel, other echogenic masses, and/or intra-abdominal calcifications typically prompts a detailed review of the maternal history and assessment for additional findings. Evaluation may include genetic counseling and fetal karyotyping, viral studies, and parental testing for cystic fibrosis genes. Bowel echogenicity seen on a third-trimester sonogram is a common variant and reflects meconium in the intestine.

Intra-abdominal calcifications are often present in infants with meconium peritonitis caused by an intestinal perforation that develops in response to a vascular insult or cystic fibrosis. Enterolithiasis,

intraluminal calcified meconium, may occur in the presence of cloacal anomalies. Infants with isolated abdominal calcifications generally have a normal outcome. Other sites of calcification include the liver, where calcifications may be associated with congenital viral infections (TORCH), or more rarely in the presence of hepatoblastoma or metastatic neuroblastoma. Fetal gallstones and gallbladder sludge may be detected after 28 weeks' gestation on sonography. Often fetal gallstones are an incidental finding during a sonogram performed for another indication. Postnatal sonography may be indicated to confirm resolution. Noncalcified lesions may also be detected on fetal abdominal sonography. These lesions include hemangioma, hamartoma, enteric duplication cysts, adrenal lesions (hemorrhage, neuroblastoma), subdiaphragmatic extrapulmonary sequestration, and mesoblastic nephroma. Neuroblastomas are the most common adrenal neoplasm typically identified late in gestation, as a solid, usually right-sided mass with cystic components that is displacing the kidney. Spontaneous regression occurs in up to 40% of affected patients, though calcifications may persist. Mesoblastic nephroma is the most common primary renal tumor presenting in the first month of life. Although it is benign, affected infants often develop heart failure and require early nephrectomy.

Recommendations for postnatal evaluation of suspected meconium peritonitis include the following:

- Postnatal abdominal radiography with additional upper and lower gastrointestinal tract studies may be performed to evaluate for perforation.
- Consider surgical consultation to assist in evaluation of the infant.
- If the radiographic studies are normal and the infant passes meconium, then further evaluation is not required.
- Consider screening for cystic fibrosis if this testing was not performed prenatally.

Dilated bowel loops are another common finding on second- and third-trimester prenatal sonography. The fetal bowel can be altered by a number of pathologic processes. The most common pathology is a bowel dilatation characteristically recognized as 1 or more tubular structures within the fetal abdomen. Bowel dilatation is caused by obstruction that may be either mechanical (atresia or stenosis, malrotation, volvulus, aganglionosis) or functional (microcystis-megacolon intestinal hypoperistalsis syndrome). Normal large intestine may be misidentified as dilated small bowel. The extent of postnatal evaluation of infants with a history of dilated fetal bowel loops depends on the clinical condition of the infant at delivery and the specific sonographic findings on third trimester scanning (see Box 97-1). A well-appearing infant with high suspicion criteria should have an abdominal radiograph taken within the first 4 to 6 hours of life. The infant, if healthy and hemodynamically stable without transitional issues, may be allowed to remain with the mother for the first hour for skin-to-skin care and the first breastfeeding. The initial colostrum intake is typically no more than 1 to 2 mL. An infant with abdominal distention evident at

### BOX 97-1 Antenatal Sonographic High Suspicion Criteria for Intestinal Obstruction

**Small bowel** (smooth internal wall without haustral folds) >10 mm in third trimester (>28 weeks' gestation) at the time of the study with 1 of the following:

1. Hyperperistalsis
2. Polyhydramnios
3. Echogenic bowel
4. Increase in dilation over time or loop >20 mm in diameter
5. Whirlpool sign (suspicious for volvulus) Or, **dilated large intestine** (>20 mm)

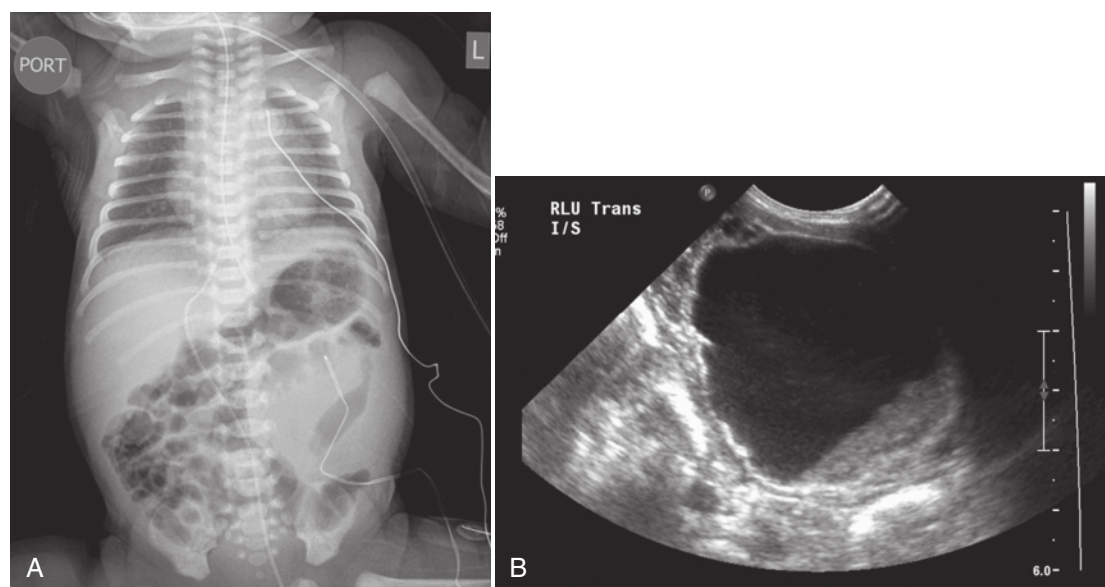
delivery, respiratory distress, or transitional difficulty should be immediately transferred to the neonatal unit for stabilization, surgical consultation, evaluation, and management. Second-trimester findings that have resolved on the third trimester follow-up do not warrant radiographic imaging after delivery.

### Fetal Ovarian Cysts

Ovarian cysts are the most common cystic abdominal mass in newborn girls; however, a palpable cystic mass in the newborn is more likely to be of renal than ovarian origin. The incidence of clinically significant ovarian cysts diagnosed antenatally is approximately 1 in 2,500. Because of the hormonal influence at birth (fetal gonadotropins, maternal estrogen, and placental human chorionic gonadotropin), 98% of newborn girls may have ovarian cysts on ultrasound. Under the influence of these hormones, follicular cysts develop and can be detected as early as 28 to 32 weeks of gestation. Cysts are also more common in conditions such as maternal diabetes mellitus where there is an increased production of human chorionic gonadotropin (hCG) by the placenta. During the last trimester of pregnancy, there is a fall in fetal follicular stimulating hormone (FSH) and luteinizing hormone (LH), with a subsequent postnatal rise in these hormones, possibly in response to the drop in maternal hCG and estrogen levels at birth. Most ovarian cysts resolve spontaneously because of this drop in gonadotropin levels.

The cysts may achieve considerable size, reaching up to 5 cm. They may be unilateral or bilateral, unilocular or multilocular. A tendency exists for cysts less than 3 cm in size to regress near term or in the early neonatal period. Serial ultrasound of fetal ovarian cysts is indicated because approximately 35% of patients develop symptoms of torsion or rupture of the cyst, either prenatally or in the postnatal period. Torsion of cyst is suspected when changes on ultrasound findings occur that are consistent with intracystic hemorrhage. This circumstance is an indication for immediate surgical intervention. Diagnosis is confirmed by a postnatal abdominal ultrasound (Figure 97-4). On ultrasound, cysts may appear as





**Figure 97-4** A. Ovarian cyst. Plain abdominal radiograph shows a mass effect in the left abdomen with displacement of the bowel loops. B. Ovarian cyst. Postnatal abdominal ultrasound shows a large cystic mass in the ovary.

simple or complex with debris, internal echoes, or solid elements in them.

Recommendations include the following:

- Postnatal evaluation should consist of a thorough abdominal examination for a palpable mass; abdominal sonographic evaluation is also recommended.
- Surgical consultation and follow-up are required if an ovarian cyst is identified, particularly if evidence is found of a large complex cyst, hemorrhage, or torsion, or if the lesion is causing bowel obstruction.

### Antenatal Gastrointestinal Findings

A history of polyhydramnios should alert the physician to suspect a proximal intestinal obstruction, such as tracheoesophageal fistula, or esophageal, duodenal, or jejunoileal atresia. A thorough physical examination should be performed with emphasis on inspection and palpation of the abdomen and perineum and assessment of the infant for evidence of other anomalies.

Newborns with tracheoesophageal fistula or esophageal atresia often have copious secretions after birth. This can be easily diagnosed with a radiograph after placing an orogastric tube. Duodenal and jejunoileal atresias often exhibit symptoms in the immediate postnatal period with the onset of vomiting, with or without prior feeding. Duodenal atresia occurs in 1 in 5,000 live births; 25% of affected infants have Down syndrome. Neonates with duodenal atresia develop bilious vomiting in the first hours after birth and may not exhibit abdominal distention. A *double bubble* is the characteristic finding on abdominal radiography. Jejunoileal atresias are caused by intrauterine vascular accidents and occur in 1 in 3,000 live births. Neonates with jejunoileal atresia also are typically symptomatic

within the first day of life, exhibiting vomiting and abdominal distention. Abdominal radiographs demonstrate air-fluid levels and dilated bowel.

Gastroschisis is a prenatal evisceration of the fetal bowel through a defect in the abdominal wall. It occurs in 1 in 4,000 live births. Common associated anomalies are gastrointestinal (intestinal atresia and malrotation). Sonographic findings include small and large bowel loops outside the abdominal cavity and in the amniotic fluid. The smaller the defect, the greater propensity to have intestinal blood flow restriction, and more damage can be expected, but with prompt surgical intervention the prognosis is excellent. In many cases polyhydramnios develops as a result of the intestinal obstruction, and intrauterine growth restriction coexists. Surgical intervention, close monitoring and correction of fluid and electrolyte abnormalities, and administration of broad-spectrum antibiotics are warranted.

Omphalocele is another defect in the abdominal wall often detected prenatally by ultrasound. Many babies with this condition also have other birth defects. Small defects are more common (1:5,000) than giant omphaloceles (1:10,000). The size of the defect and the presence of comorbidities affect the outcome of these infants. Figure 97-5 is a prenatal ultrasound of an omphalocele.

For a full discussion of related topics, see Chapter 108, Surgical Emergencies of the Chest and Abdomen in the Newborn.

### Neonatal Gastrointestinal Anomalies Causing Early Serious Illness

Bowel obstruction may be caused by intestinal atresias, malrotation with midgut volvulus, and Hirschsprung disease. Vomiting during the neonatal period should





**Figure 97-5** Prenatal ultrasound of an omphalocele.

alert the physician to a potential intestinal anomaly. Although initial symptoms may be nonspecific, the onset of bilious vomiting constitutes a medical emergency that warrants immediate assessment and intervention. Review of prenatal sonography may help inform the diagnosis.

Newborns with a malrotation and midgut volvulus exhibit bilious emesis and poor feeding and may rapidly develop lethargy and shock. In addition to placement of a nasogastric tube and initiation of intravenous fluid resuscitation and antibiotic therapy, abdominal radiographs and an upper gastrointestinal series must be obtained immediately. Concurrent surgical consultation and arrangements for transfer to a neonatal or pediatric critical care unit are paramount.

Newborns with esophageal atresia and tracheoesophageal fistula often have a prenatal history of polyhydramnios. These babies may exhibit symptoms shortly after birth, particularly during the first attempt at feeding. Placement of a nasogastric tube before obtaining a radiograph of the chest and abdomen will show the feeding tube coiled in the upper esophageal pouch. If air is present in the stomach, then the infant has an associated tracheoesophageal fistula.

The infant with Hirschsprung disease typically exhibits constipation or failure to pass meconium in the first 24 hours of life. Affected infants exhibit poor feeding, vomiting, progressive abdominal distention, irritability, and bloody stools. Stabilization including fluid resuscitation and broad-spectrum antibiotic administration should be performed in conjunction with obtaining imaging studies, transfer to a neonatal or critical care unit, and surgical consultation. Abdominal radiographs typically demonstrate a markedly dilated colon. The diagnosis is confirmed with a rectal biopsy.

Bowel obstruction may also occur as a result of meconium ileus, meconium plug syndrome, or a small left (micro) colon. Meconium ileus occurs in 10% to 20% of infants with cystic fibrosis (CF) and may be the earliest manifestation of CF. Enemas are used to decompress the intestinal obstruction. Perforation and pseudocyst formation may complicate the infant's course. The presence of calcifications on abdominal imaging indicates an intrauterine perforation occurred. Newborns with meconium plug syndrome are otherwise healthy neonates with plugs of meconium in the colon. Meconium plug syndrome is not associated with CF but occurs in

infants with intestinal dysmotility—infants of diabetic or preeclampsia mothers, those exposed in utero to magnesium sulfate, and those who are preterm with sepsis or hypothyroidism. Small left colon syndrome occurs in infants of diabetic mothers. Maternal lithium use is also associated with small left colon syndrome.

### Summary

As technology continues to improve, prenatal ultrasound assessments are becoming more informative. Although ultrasonography has vastly improved the field of prenatal medicine, families and caretakers alike should keep in mind that it is a screening test and not as definitive as chorionic villi sampling or amniocentesis for diagnosing aneuploidy. When there is an abnormal prenatal ultrasound finding, a timely consultation with a specialist is recommended.

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### TOOLS FOR PRACTICE

#### Medical Decision Support

- *Birth Defects* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/ncbddd/bd/default.htm](http://www.cdc.gov/ncbddd/bd/default.htm))

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## SECTION THREE

# Neonatal Medical Conditions

### Chapter 98

## ABNORMALITIES OF FETAL GROWTH

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Fetal growth is determined by fetal genotype and, to a large extent, by the uterine environment. The in utero environment is predominantly influenced by maternal genetics, the size of the mother, the capacity of the placenta to provide nutrients to the fetus, and, to a modest degree, paternal genetics. Although several genes have been described as maternally or paternally imprinted, 2 growth disorders, Beckwith-Wiedemann syndrome (macrosomia) and Russell-Silver syndrome (fetal malnutrition), represent well-characterized phenotypes that arise as a consequence of disrupted imprinting. Two protein products of genes, such as insulin-like growth factors I and II, play a specific role in the growth of trophoblastic cells, which form the placenta. Abnormalities in genes affecting growth may result in adverse effects. Various factors affecting fetal growth are listed in Table 98-1.

### INTRAUTERINE GROWTH RESTRICTION

Intrauterine growth restriction (IUGR), or fetal growth restriction, is a common complication of pregnancy with significant short- and long-term sequelae that reach out to adulthood. IUGR is the second leading cause of perinatal mortality, with a 10-fold increase in rates for all cases of IUGR compared with normally grown fetuses after exclusion of aneuploidy and anomalous fetuses. Up to 50% of survivors will experience intrapartum asphyxia, which adds to the already increased risk for end-organ injury.

At present, many physicians do not distinguish between the terms *small for gestational age* (SGA) and IUGR. However, these 2 clinical entities are not the same. SGA newborns traditionally have been defined as those whose birth weights are more than 2 standard deviations below the mean or less than the 10th percentile of population-based weight data obtained from newborns at the same gestational age. Conversely, a newborn with IUGR has not reached genetic growth potential as a result of an insult that occurred in utero. An IUGR fetus may or may not be SGA, but IUGR always implies a pathologic process. The decreased fetal growth rate in IUGR is an adaptation to an unfavorable intrauterine environment

**Table 98-1** Factors Affecting Fetal Growth

FACTOR	COMMENT
Fetal genetic potential	Specific genes must be expressed for fetal and placental growth.
Maternal size and uterine size	Fetal growth constraint from the maternal environment is a physiologic process that includes the maternal-specific capacity of uterine size, placental implantation surface area of the uterus, and uterine circulation, which together support the growth of the placenta and its function. <sup>a</sup>
Patterns of gestational age	Length of gestation is proportional to fetal weight but is more strongly correlated to neural growth.
Fetal nutrient uptake and metabolism; regulation of fetal growth	Decreased rates of fetal growth represent an adaptation to inadequate nutrient supply (intrauterine growth restriction).
Maternal nutrition	Only severe starvation limits fetal growth; growth may be limited by 10% to 20%.
Placenta	True placental hormones, particularly placental lactogen, play an important role in fetal growth. Placental insufficiency leads to fetal growth restriction. Placental size and fetal size are directly related. <sup>b</sup>
Glucose, amino acids, and fat transport across placenta	Intrauterine growth-restricted infants have lower glucose levels. Amino acids and energy supply are important for fetal growth. Fat accumulation occurs predominantly in the third trimester.
Maternal and fetal endocrine regulation	Maternal growth hormone and human placental lactogen increase during pregnancy, which induces insulin resistance and increased facilitated glucose transport to fetus. In infants of diabetic mothers, increased supply of glucose stimulates fetal insulin and promotes fetal adiposity (macrosomia).

<sup>a</sup>Regnault TRH, Limesand SW, Hay WW Jr. Factors influencing fetal growth. *NeoReviews*. 2001;6:119-128

<sup>b</sup>Molteni RA, Stys SJ, Battaglia FC. Relationship of fetal and placental weight in human beings: fetal/placental weight ratio at various gestational ages and birth weight. *J Reprod Med*. 1978;21:327-334

and may cause permanent alterations in metabolism, growth, and development.

IUGR is commonly defined as birth weight under the 10th percentile on intrauterine growth curves. Some perinatologists have defined IUGR as birth weight lower than 2 standard deviations below the mean, which roughly corresponds to less than the third percentile on intrauterine growth curves. Low birth weight is defined by the World Health Organization as a birth weight below 2,500 g, but this does not consider gestational age. Other weight-based definitions include *very low birth weight* (<1,500 g), *extremely low birth weight* (<1,000 g), and, more recently, *micropremie* (<750 g).

However, some infants are constitutionally small. These infants have no increased obstetric or neonatal risks. Availability of continuous fetal growth curves, developed from information gathered by ultrasound, has helped in diagnosing IUGR earlier. Race and ethnicity also play an important role. The growth curves should ideally be tailored to the patient population and geographic region.

Another concept relates to *symmetrical* (proportionately small) versus *asymmetrical* (relative head-sparing) growth restriction. Symmetrical IUGR is likely to result from an early fetal insult caused by chemical exposure (eg, nicotine from cigarette smoking), viral infection, or inherent developmental abnormalities caused by aneuploidy, whereas asymmetrical IUGR is likely to be the result of uteroplacental insufficiency, with preferential shunting of fetal blood to the brain. IUGR is associated with a significantly higher stillbirth rate and infant mortality rate in preterm, term, and postterm infants.

Another subset of newborns with IUGR who are born preterm is at a significant risk for hypoglycemia. The risk factors that predispose preterm IUGR infants to hypoglycemia are reduced glycogen and fat stores, increased consumption of glucose, hyperinsulinism, immaturity of hepatic enzymes, reduced

expression of glucose-6-phosphatase, reduced ketogenesis, and failure of counterregulation. These infants require regular monitoring of blood glucose levels even after full feeds have been established.

Recent epidemiologic studies have shown that the “metabolic syndrome,” including obesity, insulin resistance, diabetes, and cardiovascular disease, is more common among adults who were growth restricted at birth.

### Causes of Fetal Malnutrition and Intrauterine Growth Restriction

Fetal growth is a complex, dynamic process controlled by a wide range of factors of maternal, placental, and fetal origin. In early fetal life, the major determinant of growth is the fetal genome; however, later in pregnancy, environmental, nutritional, and hormonal influences become increasingly important. The known clinical, genetic, and environmental factors associated with IUGR are listed in Table 98-2.

### Preventive Strategies

Strategies to predict and prevent the recurrence of IUGR are critical in perinatal management. Effective interventions for prevention of recurrent fetal growth restriction may include a reproductive plan for spacing of pregnancies, optimization of maternal medical conditions, smoking cessation, accurate dating by first-trimester sonography and monitoring of fetal growth with serial sonograms, and low-dose aspirin (80–160 mg) started before 20 weeks. In women with nutritional deficiencies, optimizing caloric intake with low-protein (<25%) supplementation of 500 to 1,000 calories may prevent recurrent fetal growth restriction. In women living in areas endemic for malaria, antimalarial prophylaxis diminishes risk for recurrent fetal growth restriction.

It is important to be aware that maternal environmental exposures can be preconceptional or “noncurrent” fetal exposures that result from maternal

**Table 98-2**

**Clinical, Genetic, and Environmental Factors Associated With Intrauterine Growth Restriction**

FETAL	MATERNAL	PLACENTAL
Chromosomal abnormality	Substance abuse	Partial placental separation
Aneuploidy	Smoking	Uteroplacental insufficiency
Multifactorial congenital malformations	Alcohol	Unexplained elevated alpha
Cardiovascular abnormalities	Drugs: amphetamines, corticosteroids,	feto-protein, preeclampsia
Renal agenesis	heroin, hydantoin, propranolol,	Placental infarction
Multiple fetus pregnancy	warfarin	Placenta previa
Infection	Chronic disease	Multiple gestation, twin-to-twin transfusion
Cytomegalovirus	Cyanotic heart disease, cystic fibrosis,	Small placenta
Toxoplasmosis	asthma, renal disease, sickle cell disease,	Chronic vascular disease
Herpes simplex	lupus, inflammatory bowel disease,	
Rubella	advanced diabetes, hyper thyroidism	
Malaria	Constitutionally small mother	
Aberrant genomic imprinting	Lack of second-trimester weight gain	
Uniparental disomy	High-altitude pregnancy (hypoxia)	
Epimutations	Malnutrition	

Derived from Peebles DM. Fetal consequences of chronic substrate deprivation. *Semin Fetal Neonatal Med.* 2004;9:379–386.



excretion or mobilization of chemicals (lead). Additionally, exposures should be assessed for the father as well (even as a possible “paraoccupational” exposure whereby the father may have residual chemicals on clothing that a woman may be exposed to).

### Timing of Delivery

Close collaboration between obstetricians and neonatologists is essential for proper care of the growth-restricted fetus. When persistent fetal growth restriction is detected, antepartum surveillance should always include weekly serial Doppler studies of the umbilical artery because this testing has been associated with a significant reduction in perinatal mortality in women with fetal growth-restricted infants.

A joint decision on the appropriate timing of delivery is made based on the risk for fetal compromise compared with that of neonatal morbidity. The management of a fetus with growth restriction must include a balance of the risks of intrauterine chronic hypoxia with those of preterm delivery. Delivery may be indicated if the fetal growth-restricted infant has absent or reversed diastolic flow in the umbilical artery Doppler at 30 to 32 weeks (30%–32% weeks) or later, especially after steroids for fetal lung maturity have already been given if the fetus is less than 34 weeks’ gestation.

### Management in the Delivery Room

Competent personnel trained in neonatal assessment and resuscitation should be present at the time of delivery. Care should be taken to prevent hypothermia. Assuring an optimal environmental ambient air temperature and covering the infant with plastic wrap and a hat soon after delivery maintain core body temperature well. In the event of a stillborn fetus, karyotyping, serologic testing for congenital infection, and complete autopsy should be performed. The placenta should be examined for the presence of infarcts and gross abnormalities and sent for histopathologic evaluation. Careful evaluation of the placenta at the gross and microscopic level may aid in either confirming or elucidating the cause for fetal growth restriction.

Perinatal hypoxia occurs with increased frequency among SGA infants, particularly those who have severe IUGR, which may cause fetal death or perinatal compromise. The rate of cesarean delivery is increased, and the need for resuscitation is frequent.

### Neonatal Management

Newborns with IUGR who have symptoms that result from respiratory distress, hypoglycemia, or polycythemia or who require resuscitation should be admitted to the neonatal intensive care unit. Asymptomatic newborns with IUGR of less than 35 weeks’ gestation or who weigh less than 1,800 g at birth should also be admitted to the neonatal intensive care unit for management.

### Examination of the Neonate

On physical examination, the skin is often dry, rough, desquamated, wrinkled, and at times covered in meconium. The skin may look plethoric, or the newborn may look pale in the presence of peripheral vasoconstriction.

The neonate may seem more mature as a result of a reduced amount of vernix caseosa. Fingernails may be long. The newborn is often alert looking and jittery, even without hypoglycemia or hypocalcemia. Cranial sutures may seem wide, with large fontanels. The umbilical cord is usually thin and can be stained yellow or green if meconium is passed in utero. Newborns can be hyperexcitable and exhibit aberrations in muscle tone. The Moro reflex may be exaggerated, with more extension and abduction. However, newborns with severe IUGR may be floppy because they become easily exhausted when they are handled. Severe symmetrical IUGR neonates should be checked for chromosomal abnormalities and evidence of any intrauterine infection (skin rash, hepatosplenomegaly, and ocular abnormalities such as cloudy cornea, cataract, or chorioretinitis).

Gestational assessment may be affected by the presence of many creases on the sole of the foot, small breast nodules, less well-formed ear cartilage, and less fat on female genitalia. The IUGR process does not greatly affect the neurologic assessment. The weight, length, and head circumference should be recorded. In addition, the ponderal index (PI) should be calculated as follows:

$$PI = \frac{\text{weight (g)} \times 100}{\text{crown-heel length (cm)}^3}$$

PI at lower than the tenth percentile reflects fetal malnutrition; PI at lower than the 3rd percentile indicates severe wasting. In cases of asymmetrical growth restriction, birth weight and occasionally length are less than the 10th percentile, but head circumference is preserved. The neonate will have a low ponderal index. Growth rates of adipose tissue and skeletal muscle are less than normal, although bone and probably brain growth are not. In cases of symmetrical growth restriction, a proportionate decrease in weight, length, and head circumference is present; the ponderal index will be normal. Combined IUGR shares features of both asymmetrical and symmetrical IUGR. Skeletal shortening and some reduction in soft tissue mass are seen. Causes include severe maternal disease from the first trimester of pregnancy, skeletal dysplasia, and metabolic bone disease. In dysmorphic IUGR, infants have disproportionately sized head, trunk, and limbs as a result of congenital abnormalities.

### Evaluation of the Neonate

Initial evaluation and stabilization should include preventing stress from the cold and observing the neonate for complications. If congenital infection is suspected, or if dysmorphic features are present, then appropriate evaluation should be undertaken, including laboratory testing for TORCH infections (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex) urine for cytomegalovirus, and genetic assessment. Temperature should be monitored every 30 minutes until stable for 2 hours, then at least every 4 hours. The infant should be kept warm with bundling, and a hat should cover the head to avoid heat loss.

Blood glucose should be monitored within the first 1 to 2 hours of life by capillary glucose measurement, even if the child is asymptomatic. Early feedings,

within the first hour, including breastfeeding, should be encouraged to prevent hypoglycemia in newborns who are vigorous at birth. In the presence of asymptomatic borderline hypoglycemia (25–40 mg/dL or 1.39–2.22 mmol/L), the infant should be nursed frequently. Formula supplementation may be necessary until adequate mother's milk is available. Symptomatic newborns who are being exclusively breastfed may require intravenous glucose supplementation.

In the well-appearing SGA infant, hemoglobin level or hematocrit level should be measured at 6 to 8 hours of life by free-flowing venipuncture to evaluate for polycythemia. A hematocrit value of more than 65% or a venous hemoglobin concentration in excess of 22.0 g/dL indicates polycythemia. In the symptomatic infant, the timing of the initial hematocrit sampling should be determined by clinical signs.

### **PATHOPHYSIOLOGIC FEATURES AND MANAGEMENT OF PROBLEMS ASSOCIATED WITH GROWTH-AFFECTED NEONATES**

Infants who are SGA or IUGR may experience various problems that require different degrees of support based on their metabolism. Table 98-3 defines the most common problems and describes their management.

#### **Nutritional Management and Follow-up**

SGA infants have a relatively increased energy requirement caused by low muscle mass and fat content and metabolically active organs. Thus, feeding them aggressively seems logical so that they can catch up in growth. Clinically, this strategy seems to work in mild to moderate growth restriction, with the anticipation of catch-up growth by providing high caloric and protein administration. However, in the severely affected infant, the intrauterine environment may have altered organ and endocrine development, placing the infant at risk for later complications from hypertension, type 2 diabetes, and lipid abnormalities. Thus, in severe IUGR infants, rapid catch-up growth with high caloric intakes may not be advisable. Animal studies of fetal IUGR caused by maternal protein restriction demonstrated a shortened life span, particularly in male infants, when a catch-up strategy of markedly increased protein intake was administered after birth. Long-term clinical trials are needed to resolve this issue.

Given the risk for some degree of in utero intestinal ischemia in IUGR infants, it is unwise to tube feed the term growth-restricted infant. For the most part, feed advancement should use nipple feeds. Tube feeds can be used to advance feeds cautiously in the growth-restricted late preterm infant.

Fewtrell et al randomized 199 term SGA infants to receive either a 22 kcal/oz enriched formula (EF) or standard term formula. The EF group had better length and head circumference gains than the control group, with the largest benefit seen in females. No differences in weight were noted. Breastfed infants had slightly greater gains in weight and head circumference than the term formula-fed group, but these differences disappeared when confounding factors were accounted for. It is unclear whether catch-up growth

is beneficial or detrimental to long-term outcomes; therefore, a definitive recommendation cannot be made. However, it is worth noting that breastfed infants have high ketone body levels when blood sugar levels are low, and it is likely that these alternative fuels protect them from neurologic injury. Formula feeding is associated with lower ketone body levels.

#### **Outcomes of Growth-Restricted Infants**

Growth-restricted infants have a higher incidence of sudden infant death syndrome (SIDS), increased perinatal mortality rates, more frequent hospitalizations including for serious respiratory infections, increased incidence of neurologic disorders, and other morbidities requiring follow-up.

Growth and development depend on the degree of insult in utero and on the cause of growth restriction. Infants who are small as a result of family disposition will likely experience normal growth. Infants who are symmetrically growth restricted are not likely to catch up, but asymmetrical IUGR infants have a reasonable chance of normal growth and development.

Infants with a small head circumference along with growth restriction have associated poor neurologic and psychological outcomes, especially if the catch-up growth in head circumference has not occurred by 8 months of life. The prognosis for preterm SGA infants is relatively poor, especially preterm infants whose brain growth failure occurred before 26 weeks' gestation. In general, subnormal intellectual outcomes are more common among preterm SGA infants than term SGA infants. SGA infants may not exhibit delay in bone development, puberty, or sexual maturation at adolescence, although they may be shorter and lighter and have smaller heads.

IUGR infants with major chromosomal disorders have an extremely high incidence of handicap. Infants with congenital rubella or cytomegalovirus infection with microcephaly have poor outcomes, with a disability rate of more than 50%. Socioeconomic class significantly influences the school performance of children with IUGR: children from higher socioeconomic classes score better than those from low socioeconomic classes on achievement tests.

Interest in the short-term and long-term consequences of fetal growth restriction on cardiovascular, neurologic, and lung functions is increasing. Catch-up growth is potentially beneficial in the short term, but it may be detrimental to long-term fitness and survival. Adults who experienced severe growth restriction in utero have an increased incidence of hypertension, insulin resistance, type 2 diabetes, lifelong alterations in growth and development, obesity, and possibility of the development of metabolic syndrome.

#### **Key Points**

- Close collaboration between obstetricians and health professionals caring for neonates is essential for proper care of the neonate with IUGR, especially with the timing of delivery.
- Prenatal corticosteroid therapy remains effective and safe in preterm labor in the presence of IUGR.
- Delivery may be indicated if the fetal growth-restricted infant has absent or reversed diastolic

**Table 98-3** Problems Associated With Growth-Affected Neonates

PROBLEM	PATHOPHYSIOLOGIC FEATURES	MANAGEMENT AND PREVENTION
Intrauterine death	<ul style="list-style-type: none"> <li>• Chronic hypoxia</li> <li>• Placental insufficiency</li> <li>• Malformation</li> <li>• Infection</li> <li>• Infarction or abruption</li> </ul>	<ul style="list-style-type: none"> <li>• Perform careful prenatal monitoring, including biophysical profile.</li> <li>• Accurate dating is essential and may best be accomplished with a first-trimester ultrasound examination. An ultrasound at 18 to 22 weeks may be helpful to rule out fetal anomalies.</li> <li>• When fetal growth restriction has been diagnosed, weekly Doppler velocimetry should be performed.</li> <li>• Consider early delivery for worsening fetal distress.</li> <li>• Provide adequate neonatal resuscitation.</li> </ul>
Asphyxia	<ul style="list-style-type: none"> <li>• Acute and chronic hypoxia</li> <li>• Placental insufficiency</li> <li>• Acidosis</li> <li>• Glycogen depletion</li> <li>• Cord blood lactate often increased despite normal cord pH</li> <li>• Hypoxia</li> </ul>	<ul style="list-style-type: none"> <li>• See Chapter 100, Respiratory Distress and Breathing Disorders in the Newborn.</li> </ul>
Meconium aspiration syndrome and persistent pulmonary hypertension of newborn		
Hypothermia	<ul style="list-style-type: none"> <li>• Cold stress</li> <li>• Hypoxia</li> <li>• Hypoglycemia</li> <li>• Decreased fat stores</li> <li>• Decreased subcutaneous insulation</li> <li>• Increased surface area</li> <li>• Catecholamine depletion</li> <li>• Reduced fat stores</li> </ul>	<ul style="list-style-type: none"> <li>• Prevent heat loss.</li> <li>• Provide thermoneutral environment.</li> <li>• Provide adequate nutritional support.</li> </ul>
Hypoglycemia	<ul style="list-style-type: none"> <li>• Increased brain-to-body mass ratio (with increased consumption of glucose)</li> <li>• Hyperinsulinism</li> <li>• Immaturity of hepatic enzymes</li> <li>• Reduced expression of glucose- 6-phosphatase</li> <li>• Reduced ketogenesis</li> </ul>	<ul style="list-style-type: none"> <li>• Provide frequent glucose monitoring.</li> <li>• Provide early enteral feeding.</li> <li>• Administer intravenous glucose (4–8 mg/kg/min) soon after birth.</li> <li>• Adjust infusion rate based on glucose measurement.<sup>b</sup></li> </ul>
Hyperglycemia	<ul style="list-style-type: none"> <li>• Failure of counterregulation<sup>a</sup></li> <li>• Very preterm SGA infants have developmentally low insulin secretion rates and plasma insulin concentrations that can lead to hyperglycemia, which complicates the administration of adequate parenteral nutrition.</li> </ul>	<ul style="list-style-type: none"> <li>• Provide frequent glucose monitoring and total parenteral nutrition modification.</li> </ul>
Respiratory distress syndrome	<ul style="list-style-type: none"> <li>• Prematurity</li> <li>• Maternal diabetes</li> <li>• Multiple births</li> <li>• Cesarean delivery</li> <li>• Perinatal asphyxia</li> </ul>	<ul style="list-style-type: none"> <li>• Provide surfactant and respiratory support (mechanical ventilation, nasal continuous positive pressure ventilation).</li> </ul>
Pulmonary hemorrhage	<ul style="list-style-type: none"> <li>• Cold stress</li> <li>• Hypothermia</li> <li>• Polycythemia</li> <li>• Hypoxia</li> <li>• Disseminated intravascular coagulation</li> </ul>	<ul style="list-style-type: none"> <li>• Prevent cold stress and hypoxia.</li> <li>• Administer endotracheal epinephrine, fresh-frozen plasma, factor 7 (in severe, life-threatening conditions).</li> <li>• Provide higher positive end-expiratory airway pressure if patient is on mechanical ventilation. High-frequency ventilation may be beneficial.</li> </ul>

Continued

**Table 98-3** Problems Associated With Growth-Affected Neonates—cont'd

PROBLEM	PATHOPHYSIOLOGIC FEATURES	MANAGEMENT AND PREVENTION
Polycythemia and hyperviscosity Other hematologic or coagulation abnormalities	<ul style="list-style-type: none"> <li>Chronic hypoxia</li> <li>Maternal-fetal transfusion</li> <li>Increased erythropoiesis</li> <li>Thrombocytopenia</li> <li>Neutropenia</li> <li>Prolonged thrombin and partial thromboplastin times</li> <li>Increased fibrin degradation products</li> <li>Low iron stores</li> </ul>	<ul style="list-style-type: none"> <li>Provide hydration, glucose, and oxygen.</li> <li>Provide partial exchange transfusion.</li> <li>Check liver function tests for abnormalities.</li> <li>Check coagulation profile.</li> </ul>
Necrotizing enterocolitis (NEC)	<ul style="list-style-type: none"> <li>The postulated mechanism is in utero bowel ischemia caused by shunting of blood in response to hypoxia to vital organs. The incidence of NEC is increased in infants with fetal absent or reversed end-diastolic flow in the umbilical artery.</li> </ul>	<ul style="list-style-type: none"> <li>Provide cautious enteral feeding and gradual advancement of feeds.</li> </ul>
Ischemia-induced necrosis leading to focal perforation Acute renal tubular necrosis and renal failure Immunodeficiency	<ul style="list-style-type: none"> <li>Decreased splanchnic blood supply and hypoxia</li> <li>Hypoxia or ischemia</li> <li>Malnutrition</li> <li>Congenital infection</li> <li>Decreased lymphocyte number and function</li> <li>Lower immunoglobulin levels during infancy</li> <li>Attenuated antibody response to oral polio vaccine</li> </ul>	<ul style="list-style-type: none"> <li>Provide cautious enteral feeding.</li> <li>Provide cardiovascular support.</li> <li>Provide early, optimal nutrition.</li> <li>Provide specific antibiotic and immune therapy.</li> </ul>
Congenital, anatomic, and genetic abnormalities	<ul style="list-style-type: none"> <li>Growth restriction (a feature of various syndromes)</li> </ul>	<ul style="list-style-type: none"> <li>Provide genetic consultation.</li> <li>Provide appropriate TORCH and genetic management.</li> </ul>
Decreased bone mineral density	<ul style="list-style-type: none"> <li>Possible substrate deficiency or altered vitamin D metabolism</li> <li>Low calcium stores (chronic decreased placental blood flow, insufficient nutrient supply)</li> </ul>	<ul style="list-style-type: none"> <li>Provide appropriate postnatal oral calcium and vitamin D intake.</li> </ul>
Increased retinopathy of prematurity in preterm IUGR infants	<ul style="list-style-type: none"> <li>Intrauterine hypoxia, altered levels of growth factors, and diminished antioxidant capacity<sup>c</sup></li> </ul>	<ul style="list-style-type: none"> <li>Monitor closely in consultation with retina specialists.</li> </ul>

TORCH, toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex.

<sup>a</sup>Hussain K, Aynsley-Green A. The effect of prematurity and intrauterine growth restriction on glucose metabolism in the newborn. *NeoReviews*. 2004;5:e365–e368

<sup>b</sup>Severe hypoglycemia (<20 mg%) may require bolus of 10% dextrose 2 mL/kg followed by 10% glucose infusion at 4–8 mg/kg/min. Asphyxiated and intrauterine growth-restricted infants with low ponderal index are at the highest risk for hypoglycemia; see Chapter 105, Transient Metabolic Disturbances in the Newborn.

<sup>c</sup>Rosenberg A. The IUGR newborn. *Semin Perinatol*. 2008;32:219–224

Modified from Anderson MS, Hay WW Jr. Intrauterine growth restriction and the small-for-gestational-age infant. In: Avery GB, Fletcher MS, MacDonald MG, eds. *Avery's Neonatology: Pathophysiology & Management of the Newborn*. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006. Reprinted with permission.

flow in the umbilical artery Doppler at 30 to 32 or more weeks' gestation, especially after antenatal steroid administration to promote fetal lung maturity, if less than 34 weeks' gestation.

- The cause of small size at birth carries great prognostic value.
- Close monitoring of temperature, glucose, and hematocrit is important for management. Blood glucose should be closely monitored even after full feeds have been established.
- Early feeding of these newborns should be encouraged to prevent hypoglycemia. In the event of asymptomatic hypoglycemia, breastfeeding infants

should nurse frequently. Formula supplementation may be necessary until the mother's milk volume has been established.

- Cautious advancement of feeds is recommended in preterm IUGR infants.
- IUGR is associated with significantly higher rates of stillbirth, mortality, and SIDS.
- Rapid catch-up growth is potentially beneficial in the short term, but it may be detrimental to long-term fitness and survival with the possibility of an increased incidence of hypertension, insulin resistance, type 2 diabetes, and obesity, and a possibility of the development of metabolic syndrome.



# **LARGE-FOR-GESTATIONAL-AGE INFANTS AND INFANTS OF DIABETIC MOTHERS**

## **Large for Gestational Age**

At the other end of the spectrum of fetal growth abnormalities are newborns who are large for gestational age (LGA). The risk to the LGA baby is not so much antepartum hypoxemia and acidosis as the problem of prolonged labor and intrapartum trauma. LGA infants may have associated metabolic abnormalities (hypoglycemia, hypocalcemia), traumatic birth injuries, polycythemia, hyperviscosity, and hyperbilirubinemia, as well as the possibility of various congenital anomalies. Newborns are considered to be LGA if they weigh more than the 90th percentile for their gestational age or if they weigh more than 4,000 g (8 lb, 13 oz). *Macrosomia* is a clinical term describing excessive weight for gestational age; it results from increased adiposity caused by adipocyte hyperplasia and hypertrophy. Infants whose birth weight exceeds the 97th percentile (>4,500 g, or 9 lb, 4 oz) are at greater risk for neonatal morbidity, with babies weighing more than 5,000 g (11 lb) at highest risk for death. A subpopulation of LGA infants born to mothers with diabetes mellitus (before or during pregnancy) has various abnormalities. These infants are labeled under a syndrome known as *infant of diabetic mother* (IDM). Some of the IDMs born to mothers with long-standing diabetes mellitus and vascular disease may be SGA.

Most macrosomic babies are not associated with diabetes but rather with large mothers. LGA infants can result from being born to obese mothers (constitutional), from gestations longer than 42 weeks (postmaturity), or as the result of overstimulation of growth in utero. Additional risk factors include maternal weight gain during pregnancy, multiparity, a male fetus, and ethnicity. Infants of mothers with pregestational diabetes mellitus or gestational diabetes are exposed to high blood sugar during fetal development, or they may develop high circulating insulin levels and may therefore grow excessively. Women with gestational diabetes with glucose tolerance during late pregnancy (a positive glucose challenge test with a negative glucose tolerance test) may remain undiagnosed and may deliver a macrosomic infant with greater perinatal complications. Infants with Beckwith-Wiedemann syndrome and other genetic disorders with early excessive fetal growth, as well as infants with erythroblastosis fetalis, may exhibit as LGA with or without hyperinsulinism.

## **Infants of Diabetic Mothers**

Although many IDMs have an uneventful perinatal course, other such infants have an increased risk for complications. Better management of diabetes mellitus during pregnancy has led to a marked improvement in perinatal morbidity and mortality; however, opportunities for improvement in various outcomes remain. Perinatal mortality varies directly with severity of maternal diabetes, as judged by 2 commonly used maternal classification schema: White's revised classification of diabetes in pregnancy, based on duration of diabetes and presence of vascular complications (Table 98-4), and Pedersen's Prognostically Bad Signs in Pregnancy

Table 98-4	White's Classification During Pregnancy
CLASSIFICATION	DESCRIPTION
Gestational diabetes	Abnormal glucose tolerance test, but euglycemia maintained by diet alone; if diet alone insufficient, insulin required
Class A	Diet alone, any duration or age at onset
Class B	Age at onset, >20 yr; duration, <10 yr
Class C	Age at onset, 10–19 yr; duration, 10–19 yr
Class D	Age at onset, <10 yr; duration, >20 yr; background retinopathy or hypertension (not preeclampsia)
Class R	Proliferative retinopathy or vitreous hemorrhage
Class F	Nephropathy, with <500 mg/dL proteinuria
Class RF	Criteria for both classes R and F coexist
Class H	Arteriosclerotic heart disease clinically evident
Class T	Prior renal transplantation

Reprinted from Cowett RM. The infant of diabetic mother. *NeoReviews*. 2002;3:e173–e189.

classification, which includes complications of current pregnancy, that is, the presence of chemical pyelonephritis, precoma or severe acidosis, toxemia, and pregnant diabetic women who are noncompliant with recommended care. Preeclampsia often complicates diabetic pregnancy and results in higher incidence of preterm delivery with consequent increased morbidity and mortality.

## **Pathophysiologic Features**

Although no single pathogenetic mechanism has been clearly identified to explain the diverse problems seen in IDMs, many of the effects can be attributed to maternal metabolic control. Pedersen's maternal hyperglycemia–fetal hyperinsulinism hypothesis recognized that maternal hyperglycemia resulted in fetal hyperglycemia, which stimulates the fetal pancreas, resulting in islet cell hypertrophy and  $\beta$ -cell hyperplasia with increased insulin availability. Neonatal macrosomia results from increased adiposity (hyperplasia and hypertrophy) and increased liver and skeletal mass as a result of insulin-stimulated fetal growth. The acceleration in growth begins about the 25th to 28th week of gestation, which explains why very preterm IDMs do not exhibit macrosomia.

After delivery, the neonate develops neonatal hypoglycemia as a result of the absence of continuous glucose supply across the placenta. The presence of increased C peptide and reactive immunoinsulin concentrations with hypoglycemia suggests that the control of maternal hyperglycemia in the third trimester may decrease the incidence of neonatal hypoglycemia. Other factors that

**BOX 98-1 Components for Hyperinsulinism in Infants of Diabetic Mothers**

- Islet cell hyperplasia and  $\beta$ -cell hypertrophy
- Obesity and macrosomia
- Hypoglycemia with low free fatty acid concentration
- Rapid glucose disappearance rate
- Higher plasma insulin-like activity after glucose administration
- Umbilical vein reactive immunoinulin increase
- Increased C peptide and proinsulin concentrations

Reprinted from Cowett RM. The infant of diabetic mother. *NeoReviews*. 2002;3:e173–e189.

may cause hypoglycemia in IDMs include decreased catecholamine and glucagon secretions as well as diminished hepatic glucose production and decreased oxygenation of fatty acids (Box 98-1).

The pathogenesis of the increase in congenital anomalies among IDMs is probably related to poor glycemic control at conception and during the first trimester of pregnancy. Hyperglycemia in the fetus alters lipid metabolism, generates an excess of reactive oxygen species, and activates apoptosis, all of which can result in fetal malformations. Uteroplacental vascular disease and genetic predisposition may play roles as well. The most common malformations are noted in the heart, central nervous system, and urinary system.

**Delivery**

Mode of delivery is determined by estimated fetal weight on ultrasound, maternal and fetal condition, and obstetric history. Personnel trained in the AAP-AHA Neonatal Resuscitation Program should be available during delivery.

The maternal blood glucose concentration is tightly controlled during labor and delivery. Blood glucose levels higher than 120 to 140 mg/dL (6.66–7.77 mmol/L) are managed with infusion of short-acting insulin.

Continuous fetal monitoring is essential during labor. The American College of Obstetrics and Gynecology recommends elective cesarean section when estimated fetal weight is more than 5 kg in nondiabetic pregnancies, when the estimated weight is more than 4,500 g in diabetic pregnancies, and in cases of arrest of the descent of the fetal head and prolonged second stage of labor in a fetus estimated to be more than 4,500 g. Forceps and vacuum deliveries increase the incidence of shoulder dystocia in macrosomic infants. Patients with advanced microvascular disease are at increased risk of delivery by cesarean.

Infants should be evaluated for presence of any birth injury, congenital malformations, evidence of macrosomia, hypoglycemia, and respiratory distress.

**Evaluation**

IDMs with evidence of perinatal depression, congenital malformations, history of maternal insulin administration, and/or hypoglycemia should be monitored carefully. Infants should be evaluated for hypoglycemia,

hypocalcemia, polycythemia, and hyperbilirubinemia. Careful physical examination should be performed to assess the infant for anomalies. Supportive care should be provided while a continuous evaluation is undertaken.

Infants born to mothers with diabetes may develop asymptomatic neonatal hypoglycemia as early as 1 hour after birth and usually by 12 hours of age. Infants who are LGA may develop low plasma glucose concentrations as early as 3 hours of age.

Asymptomatic IDMs should be fed within the first hour and have a glucose screen 30 minutes after the first feeding. Symptomatic infants who exhibit clinical signs such as jitteriness, cyanosis, seizures, apneic episodes, tachypnea, weak or high-pitched cry, floppiness, lethargy, or poor feeding should have an immediate glucose screen. A glucose level in a symptomatic infant requires intravenous glucose therapy. Clinical laboratory confirmation should immediately check glucose readings less than 47 mg/dL (2.6 mmol/L). Extended monitoring beyond 12 hours of life requires consideration of transfer to a neonatal special or intensive care setting. Hematocrit levels should be checked at 6 to 8 hours and at 24 hours (Figure 98-1). Calcium levels should be checked at 24 hours. Risk assessment for the development of severe hyperbilirubinemia should be performed and include transcutaneous and/or total serum bilirubin testing.

**Physical Examination**

Physical examination should focus on detection of traumatic birth injuries, including a thorough neurologic examination to detect any nerve palsies. Most facial nerve palsies will resolve without intervention, but suspected brachial plexus injuries need thorough evaluation and neurologic follow-up. Cardiac examination should focus on detecting any cardiac murmur, abnormal pulses, and cyanosis. Persistence of symptoms warrants evaluation of the newborn, including electrocardiogram, chest radiograph, 4-limb blood pressures, oxygen saturation, echocardiogram, and consultation with a pediatric cardiologist. Abdominal examination should be performed for detection of any masses and evaluation for any abdominal injuries. An enlarged liver may result from glycogen deposits. Renal masses may be present, especially in the presence of a single umbilical artery.

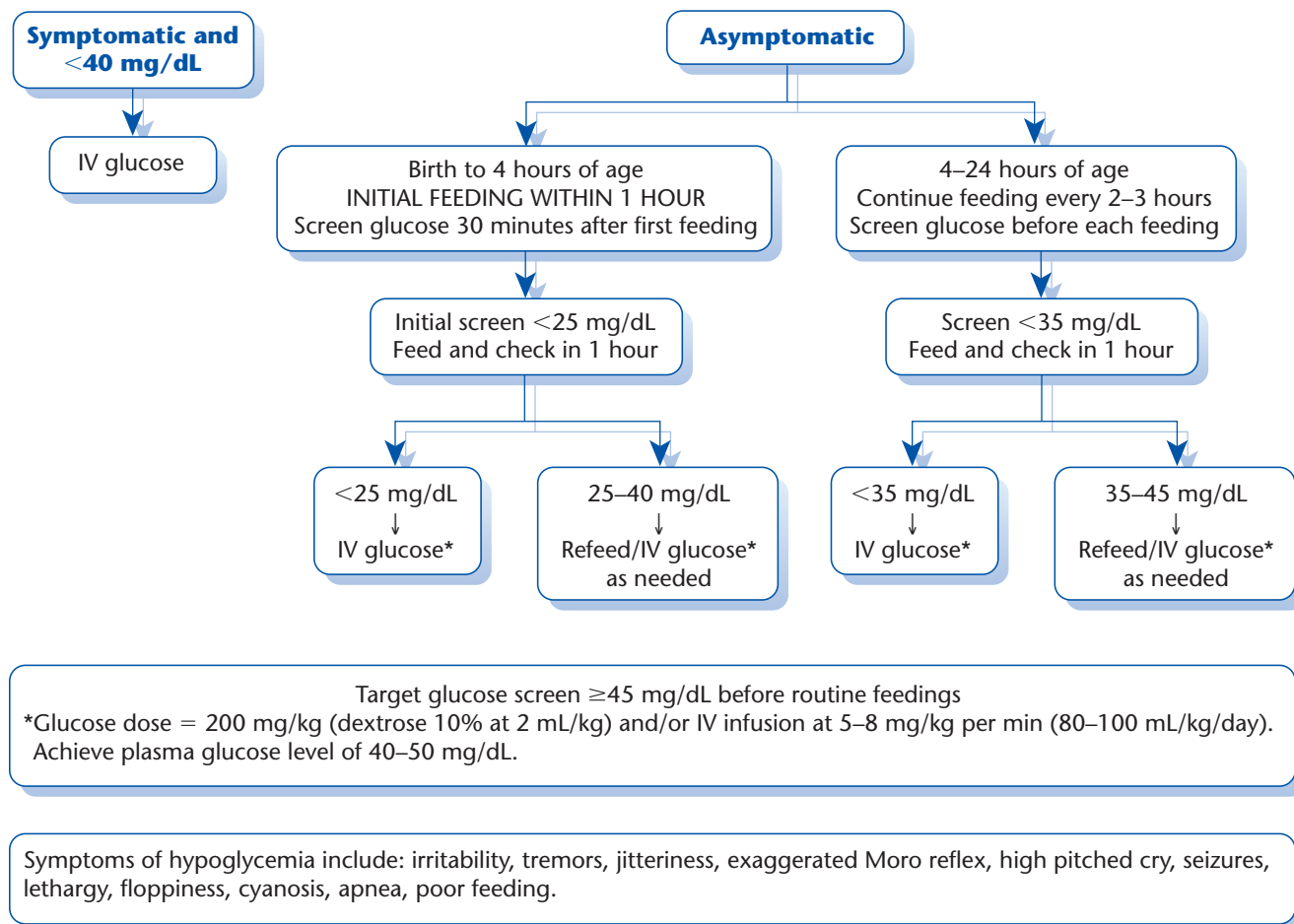
**Frequently Observed Specific Problems**

Rates of adverse neonatal outcomes are 3 to 9 times greater in IDMs compared with infants of nondiabetic mothers. Neonatal complications found in IDMs and LGA infants are listed in Table 98-5.

**Hypoglycemia**

The risk for development of neonatal hypoglycemia increases when there are multiple risk factors such as IDM/LGA, late preterm, and term SGA infants.

The asymptomatic infant should begin breast or formula feeding within the first hour after delivery. The screening and management of postnatal glucose homeostasis is outlined in Figure 98-1.



**Figure 98-1** Glucose monitoring and management in growth-restricted infants, infants of diabetic mothers, and large-for-gestational-age infants. (From Adamkin DH, Committee on Fetus and Newborn. Clinical report—postnatal glucose homeostasis in late preterm and term infants. *Pediatrics*. 2011;127:575–579.)

### Hypocalcemia

IDMs whose mothers had poor glycemic control in the first trimester had decreased bone mineral content at birth secondary to decreased transplacental transfer. Parathyroid function has been shown to be suppressed as well in these infants. Noguchi and colleagues showed hypomagnesemia in 33% of IDMs and speculated low parathyroid function may be related to low magnesium. Excessive jitteriness, alteration in muscle tone, and seizures should warrant investigations for hypoglycemia or hypocalcemia; if these symptoms are present, then ionized calcium levels should be checked. Symptomatic hypocalcemia should be treated with calcium gluconate. If symptoms are mild, then enteral supplementation may be provided. If the hypocalcemia is severe or protracted, the presence of hypomagnesemia should then be ruled out.

### Macrosomia

Hyperinsulinemia in utero affects diverse organ systems, including the placenta. Insulin acts as the primary anabolic hormone of fetal growth and development, resulting in visceromegaly, especially of

the heart and liver, and macrosomia. Fetal macrosomia is reflected by increased body fat, muscle mass, and organomegaly, but not by increased brain or kidney size. Evaluation of nonfasting glucose rather than the fasting glucose in the third trimester of pregnancy is an important measure in preventing macrosomia.

### Traumatic Birth Injuries

As a result of their large size, LGA newborns experience complications of birth trauma, which include shoulder dystocia, and they are also at greater risk for perinatal depression. LGA neonates are more likely to be delivered by cesarean. Injury to the brachial plexus, sometimes associated with phrenic nerve injury, may occur as a result of macrosomia and shoulder dystocia. Injury to abdominal organs may lead to hepatic and adrenal hemorrhage. Injury to external genitalia has occasionally been seen.

### Asphyxia

Although the specific cause of perinatal asphyxia is unclear, it may be caused by difficulty in the

Table 98-5

### Presence of Complications in Large-for-Gestational-Age Infants and Infants of Diabetic Mothers

COMPLICATION	LARGE FOR GESTATIONAL AGE	INFANTS OF DIABETIC MOTHERS
Birth trauma (shoulder dystocia, abdominal organ injury, brachial plexus injury, clavicular fracture, cephalohematoma, diaphragmatic paralysis, facial nerve palsy, ocular hemorrhage, external genitalia hemorrhage, subdural hemorrhage)	X	X
Asphyxia	X	X
Hypoglycemia	X	X
Hyperbilirubinemia	X	X
Macrosomia	X	X
Polycythemia and hyperviscosity		X
Respiratory distress syndrome, transient tachypnea of newborn, meconium aspiration, air-leak syndromes, diaphragmatic paralysis		X
Congenital anomalies (caudal regression, small left colon syndrome, hypertrophic obstructive cardiomyopathy, septal hypertrophy, double-outlet right ventricle, truncus arteriosus, anencephaly, spina bifida, hydrocephalus)		X
Neurologic instability (short and long term)		X
Hypocalcemia, hypomagnesemia		X
Organomegaly		X
Renal vein thrombosis, transient hematuria		X

Modified from Cowett RM. The infant of diabetic mother. *NeoReviews*. 2002;3:e173–e189; Cowett RM. Neonatal care of the infant of diabetic mother. *NeoReviews*. 2002;3:e190–e196.

intrapartum period resulting from relative macrosomia. Umbilical arterial cord blood pH and base deficit and cord lactate levels can provide early biochemical assessment of the fetus's physiologic status. Asphyxia may have diverse consequences. It may acutely affect respiratory, renal, central nervous system, and gastrointestinal functioning. Restriction of fluids may be indicated until the degree of injury to the central nervous system and kidneys has been ascertained.

#### Polycythemia

Polycythemia (venous hematocrit >65% [ $>0.65$  fraction of red blood cells]) may be associated with acrocyanosis, hypoglycemia, irritability, or poor feeding. A higher than normal incidence of neonatal necrotizing enterocolitis is seen in IDMs with polycythemia and concurrent hypoglycemia; therefore, they should be fed cautiously. Hyperviscosity resulting from polycythemia may cause renal vein thrombosis, stroke, and other organ damage.

The mechanisms responsible for increased fetal erythropoiesis are not clear, but erythropoietin does not seem to be responsible for polycythemia in IDMs. Late erythroid progenitor colonies are particularly sensitive to insulin, leading to polycythemia and an increase of nucleated red blood cells in IDMs.

#### Jaundice

Hyperbilirubinemia is observed more often in IDMs than in healthy neonates, possibly because of increased bruising secondary to macrosomia and

polycythemia. Management of neonatal hyperbilirubinemia in IDMs and LGA newborns is done according to the guidelines for managing jaundice in other term newborns (see Chapter 99, Neonatal Jaundice).

#### Respiratory Distress

IDMs born only slightly preterm (36 to 37 weeks' gestation) may have respiratory distress syndrome as a result of delayed maturation of surfactant, especially in mothers with class A, B, and C diabetes. Fetal hyperinsulinism may adversely affect the lung maturation process in IDMs by antagonizing the action of cortisol, restricting substrate availability for surfactant biosynthesis, and impeding fibroblast-pneumocyte factor, which stimulates type II alveolar cells to produce surfactant.

IDM neonates may also exhibit respiratory distress resulting from transient tachypnea of the newborn, meconium aspiration, air-leak syndromes, or diaphragmatic paralysis.

#### Poor Feeding

Poor feeding is a major problem in IDMs; it occurs in almost one-third of infants and is often present in the absence of other problems. Poor feeding may occasionally be related to prematurity, respiratory distress, or other problems and is a major cause of prolonged hospital stay and parent-infant separation. Some IDMs have been reported to have increased concentrations of amylin peptide, an inhibitor of gastric motility that is co-secreted with insulin, which may explain the poor feeding in these neonates.



### **Congenital Anomalies**

IDMs are at 3 times the risk for malformations compared with infants of nondiabetic mothers. Poor metabolic control in the first trimester is correlated with major anomalies in IDMs. The recognized complications in IDMs include sacral agenesis, femoral hypoplasia, heart defects, and cleft palate. Others include preaxial radial defects, microtia, cleft lip, microphthalmos, holoprosencephaly, microcephaly, anencephaly, spina bifida, hemivertebrae, urinary tract anomalies, and hallucal polydactyly. Strategies to reduce the risk for congenital anomalies have focused on normalizing the intrauterine metabolic environment before conception, especially in women who have diabetes.

### **Congenital Heart Disease and Cardiomyopathy**

The strongest associations with maternal type 1 diabetes have been noted for double-outlet right ventricle and truncus arteriosus. No such associations have been noted with gestational diabetes. IDMs are at increased risk for congestive or hypertrophic cardiomyopathy. Hypertrophic cardiomyopathy in the neonate results from a fetal hyperinsulinemic state. Most of the infants are asymptomatic, and the diagnosis is made by echocardiography. In a small fraction of neonates, outflow tract obstruction may cause left ventricular failure. Propranolol seems to be the therapeutic drug of choice. Resolution of symptoms occurs within 2 to 4 weeks, and resolution of the hypertrophy occurs within 2 to 12 months, with no permanent effect on the myocardium.

### **Renal Vein Thrombosis**

The pathogenesis of renal vein thrombosis remains obscure, although most speculation has centered on the possible role of polycythemia. Sludging of red blood cells, combined with a further reduction in cardiac output as a result of diabetic cardiomyopathy, may be a contributing factor.

### **Small Left Colon**

Neonatal small left colon syndrome is a transient and unique anomaly affecting about 5% of IDMs. Hypoplastic left colon should be ruled out in case of feeding intolerance and inability to pass meconium. The cause of this anomaly is not clear, although hormone imbalance affecting the autonomic nervous system has been proposed as a mechanism. Increased concentrations of amylin peptide may be contributory. The condition usually resolves spontaneously with conservative medical management within the neonatal period.

### **Perinatal Survival**

Despite the problems associated with pregnancy, a mother with diabetes has a 95% chance of having a healthy baby if she participates in a pregnancy management and surveillance program at an appropriate perinatal center.

### **Follow-up**

Postnursery pediatric follow-up care should be based on the specific complications noted during the

neonatal period. Pediatric cardiology follow-up is required for infants with hypertrophic cardiomyopathy or congenital heart disease. Newborns with repeated episodes of hypoglycemia or with any neurologic signs or symptoms should have close neurodevelopmental follow-up and referral to the local early intervention Child Find registry for at-risk infants. Physical therapy and referral to early intervention may be required for newborns with nerve palsies. Urologic consultation may be required for those with renal abnormalities. Long-term follow-up, with particular attention to neurodevelopment and nutrition to lessen the risk for late metabolic problems, is recommended.

### **Long-term Outcome**

#### **Neurodevelopment**

Achieving optimal metabolic control during pregnancy reduces but may not absolutely prevent the risk for poor neurodevelopmental outcome in offspring. Even with improved maternal care, higher maternal fasting  $\beta$ -hydroxybutyrate concentrations in the second and third trimesters are associated with some limitations in intelligence and psychomotor development independent of perinatal complications in offspring. Adverse outcomes are likely with prolonged and severe hypoglycemia. Psychological evaluations show that IDMs are more vulnerable to intellectual impairment, especially if the neonate was born SGA or if the pregnancy was complicated by acetonuria. Children who have a history of growth delay in early diabetic pregnancy should be screened at 4 to 5 years of age for possible developmental impairment using a norm-referenced screening tool, such as the Denver Developmental Screening Test.

#### **Obesity**

Some evidence suggests that the risks for obesity, impaired glucose tolerance, blunted insulin secretion, and hypertension developing during late childhood or adolescence and persisting into adult life are increased in offspring of diabetic mothers.

#### **Insulin-Dependent Diabetes Mellitus**

The risk for developing insulin-dependent diabetes mellitus (IDDM) by 20 years of age in infants born to pregestational diabetic mothers is  $2.1\% \pm 0.5\%$ . The risk for diabetes in offspring of mothers with diabetes is increased in young mothers and is independent of the risk factors for perinatal mortality. The incidence of IDDM is found to be slightly increased in infants born to fathers with IDDM. The mechanism by which alterations in maternal glucose metabolism alter fetal  $\beta$ -cell function is unknown. Infants born to women with gestational diabetes are at increased risk for metabolic syndrome, obesity, and type 2 diabetes in childhood and adolescence.

#### **Cerebral Palsy, Epilepsy, and Intellectual Disability**

The incidence of cerebral palsy and epilepsy is 3 to 5 times higher in IDMs compared with infants of nondiabetic mothers.

### Key Points

- IDMs with evidence of perinatal depression, congenital malformations, history of maternal insulin administration, and hypoglycemia should be monitored carefully.
- Neonatal hypoglycemia (transiently low blood glucose levels) is common in the immediate neonatal period and may be considered a normal feature of adaptation to extrauterine life. No evidence has been found that this condition causes brain injury in the absence of concurrent clinical manifestations.
- Persistent and severe hypoglycemia may be associated with underlying diseases that themselves predispose newborns to brain injury.
- Careful documentation of the clinical and biochemical state, response to treatment, and the pattern of any cerebral injury in neonates with hypoglycemia should be undertaken.
- Poor metabolic control in the first trimester is correlated with major anomalies in IDMs.
- Some evidence exists of increased incidence of obesity and subsequent IDDM in IDMs, particularly children and adolescents born to women with gestational diabetes.
- Long-term follow-up, with particular attention to neurodevelopment and nutrition to lessen the risk for late metabolic problems, is also important.

### TOOLS FOR PRACTICE

#### Medical Decision Support

- *Bilirubin Calculator* (Component of American Academy of Pediatrics mobile app) ([itunes.apple.com/us/app/american-academy-pediatrics/id526086606?mt=8](https://itunes.apple.com/us/app/american-academy-pediatrics/id526086606?mt=8))
- *MotherToBaby Fact Sheets* (Web page), Organization of Teratology Information Specialists ([www.otispregnancy.org/otis-fact-sheets-s13037](http://www.otispregnancy.org/otis-fact-sheets-s13037))
- *Pediatric Environmental Health, 3rd ed* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Pediatric Environmental Health Specialty Units* (Web site), ([www.pehsu.net](http://www.pehsu.net))
- *TOXNET: Toxicology Data Network* (Web site), National Library of Medicine ([toxnet.nlm.nih.gov](http://toxnet.nlm.nih.gov))

### AAP POLICY

American Academy of Pediatrics Committee on Fetus and Newborn. Postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics*. 2011;127(3):575–579 ([pediatrics.aappublications.org/content/127/3/575](http://pediatrics.aappublications.org/content/127/3/575))

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## Chapter 99

# NEONATAL JAUNDICE

Vishal Subodhbhai Kapadia, MD; Luc P. Brion, MD

### DEFINITION

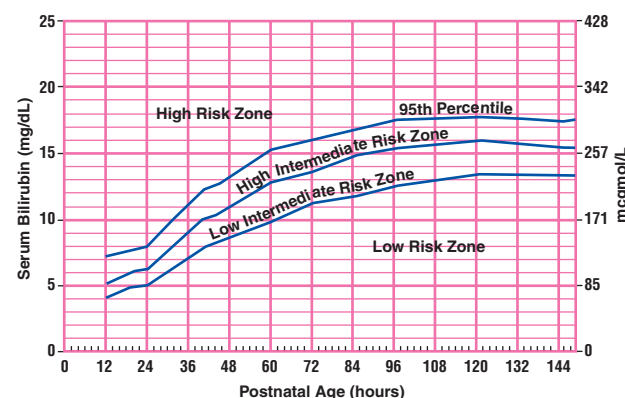
The term *jaundice*, derived from the French *jaune* for yellow, is defined as yellow pigmentation of sclera, skin, and urine caused by hyperbilirubinemia. Hyperbilirubinemia in the term or late preterm infant greater than 35 weeks' gestation is classified as either physiologic or pathologic based on age-specific statistical analysis of serum bilirubin measurements.

### FREQUENCY

Jaundice occurs in approximately 60% of the 4 million neonates born yearly in the United States. The largest data set on neonatal bilirubin levels in term or near-term infants was obtained by Bhutani and collaborators in 2,840 well newborns (Figure 99-1). This nomogram is reflective of the natural history of neonatal hyperbilirubinemia during the first 48 to 72 hours of life. Thereafter, the low-risk-zone threshold is less accurate because of the sampling bias that resulted in spuriously elevated levels in the lower zones (more than the high-risk-zone 95th percentile in the study). The approximate frequency of high bilirubin levels compiled from several studies is shown in Table 99-1. In a population study in Denmark, hyperbilirubinemia with a serum concentration justifying an exchange transfusion occurred in 25 per 100,000 (1:4,000) term or late preterm infants.

### DIFFERENTIAL DIAGNOSIS

Yellow skin color can develop in children with carotenemia. In contrast with jaundice, carotenemia does



**Figure 99-1** Nomogram for designation of risk in term and late preterm infants. (From Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischARGE hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics*. 1999; 103[1]:6–14.)

not affect the color of the sclera and has not been reported in neonates.

EVALUATION

Clinical practice guidelines for managing hyperbilirubinemia in the newborn of 35 weeks’ gestation or more were published by the American Academy of Pediatrics (AAP) in 2004. The key elements and the diagnostic and therapeutic algorithm are shown in Box 99-1 and Figure 99-2, respectively.

Relevant History

Major risk factors for developing severe hyperbilirubinemia are listed in Box 99-2. The best documented prediction of severe hyperbilirubinemia is a total serum bilirubin or transcutaneous bilirubin level that falls within the high-risk zone of the Bhutani curve. A serum or transcutaneous bilirubin level is measured and plotted on the Bhutani curve. This process allows for determination of the degree of risk of the infant to develop significant hyperbilirubinemia. In combination with identified risk factors for neonatal jaundice, the degree of risk can guide the physician’s treatment planning. Relevant history should also include questions

about the potential use by the mother or administration to the neonate of herbs as well as drugs and medications (eg, sulfonamides, many cephalosporins, benzyl alcohol, parabens, methylparaben) that affect bilirubin binding. Box 99-3 lists agents that displace bilirubin from albumin. Family history may reveal 1 or more hereditary disorders of bilirubin production (eg, increased hemolysis), bilirubin metabolism (mutations of the promoter or of the gene coding uridine diphosphate glucuronosyl transferase, causing, respectively, Gilbert and Crigler-Najjar syndromes), or bilirubin excretion (Dubin-Johnson syndrome). The risk for neonatal jaundice is higher when the neonate has Gilbert syndrome and another factor of jaundice, for example, hemolysis or breastfeeding. The risk for severe hyperbilirubinemia is increased in infants of East Asian descent and decreased in black infants. Correct identification of race and ethnicity by asking the mother about the maternal and paternal ancestry is important in assessing the risk to an infant.

The increased risk for severe hyperbilirubinemia in Asian neonates (with 2 parents of Asian origin) may result from hemolysis, frequently caused by glucose-6-phosphate dehydrogenase (G6PD) deficiency, and

Table 99-1 Proposed Definitions for Severity of Hyperbilirubinemia and Its Estimated Occurrence			
TSB LEVEL (mg/dL)	PERCENTILE AFTER 72 HOURS OF AGE	PROPOSED DEFINITIONS	ESTIMATED OCCURRENCE
≥17.0 (291 mcml/L)	>95th	Significant	~1:10
≥20.0 (342 mcml/L)	>99th	Severe	~1:70
≥25.0 (427 mcml/L)	>99.9th	Extreme	~1:700
≥30.0 (513 mcml/L)	>99.99th	Hazardous	~1:10,000

TSB, total serum bilirubin.  
To convert bilirubin concentration from mg/dL into mcml/L, multiply by 17.1.  
Percentiles are approximate. Occurrence is estimated in screened and treated infants based on data reported in Bhutani et al, Stevenson et al, Martinez et al, and Khurana et al. Precise data cannot be compiled because of differences in methodologies, patient selection, and thresholds for intervention.  
From Bhutani VK, Johnson LH, Maisels MJ, et al. Kernicterus: epidemiological strategies for its prevention through systems-based approaches. *J Perinatol.* 2004;24(10):650–662. Reprinted with permission from Macmillan Publishers.

BOX 99-1 Key Elements in Managing Hyperbilirubinemia

1. Promote and support successful breastfeeding.

2. Establish nursery protocols for the identification and evaluation of hyperbilirubinemia.

3. Measure the total serum bilirubin or transcutaneous bilirubin level in newborns jaundiced in the first 24 hours.

4. Recognize that visual estimation of the degree of jaundice can lead to errors, particularly in darkly pigmented infants.

5. Interpret all bilirubin levels according to the newborn’s age in hours.

6. Recognize that newborns at less than 38 weeks’ gestation, particularly those who are breastfed, are

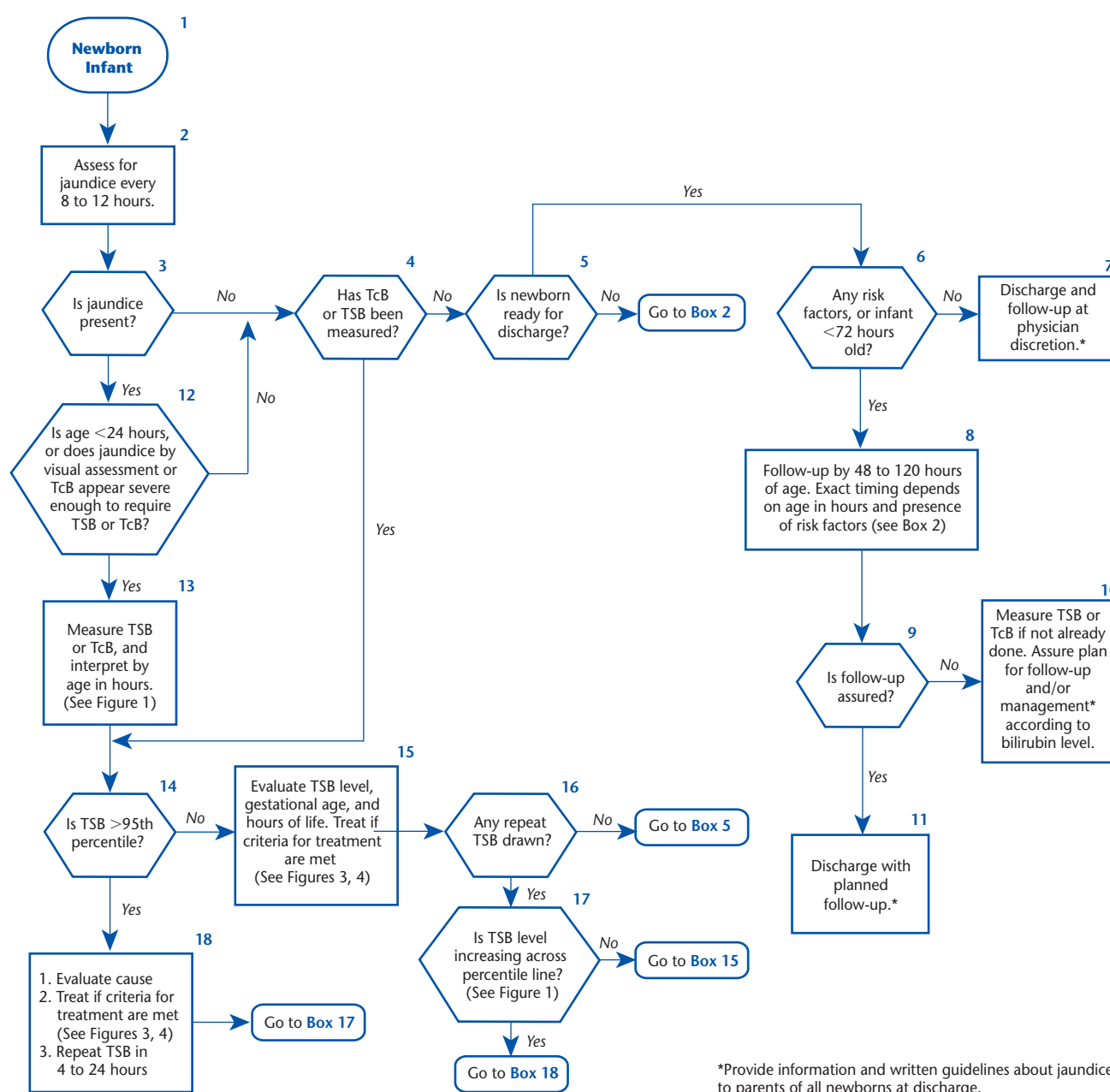
at high risk of developing hyperbilirubinemia and require close surveillance and monitoring.

7. Perform a systematic assessment of all newborns before discharge for the risk for severe hyperbilirubinemia.

8. Provide parents with written and verbal information about newborn jaundice.

9. Provide appropriate follow-up based on the time of discharge and the risk assessment.

10. Treat newborns, when indicated, with phototherapy or exchange transfusion.



**Figure 99-2** Diagnostic and therapeutic algorithm for jaundice in the newborn nursery. TcB, transcutaneous bilirubin level; TSB, total serum bilirubin level. (From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Clinical practice guideline: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114[1]:297–316.)

from abnormal bilirubin metabolism (eg, mutations affecting abundance or function of uridine diphosphate glucuronosyl transferase, thereby limiting glucuroconjugation). Neonates who carry the nucleotide 211 GA or AA variation within coding region in the *UGT1A1* gene are more susceptible to developing early-onset neonatal breastfeeding jaundice. In addition, increased risk for bilirubin toxicity in Asian neonates may result from displacement of bilirubin from albumin caused by exposure to herbals given to the

neonate (eg, Chuen-Lin, [*Coptis chinensis/japonicum*], a popular herb given to 28% to 51% of Chinese neonates) or taken by pregnant or breastfeeding mothers (eg, berberine, the major ingredient of the Chinese herb huanglian [*Coptis chinensis*]).

Sporadic genetic mutations affecting the gene encoding G6PD on the X chromosome occur in all ethnic and racial groups; more than 400 gene mutations have been identified. In the United States, black male infants are most often affected. Although black neonates



**BOX 99-2 Risk Factors for Development of Severe Hyperbilirubinemia in Newborns of 35 Weeks' Gestation or More (in Approximate Order of Importance)**

**MAJOR RISK FACTORS**

- PredischARGE total serum bilirubin or transcutaneous bilirubin level in the high-risk zone (best documented method)
- Jaundice observed in the first 24 hours
- Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (eg, glucose-6-phosphate dehydrogenase deficiency), elevated end-tidal carbon monoxide
- Gestational age of 35 to 36 weeks
- Previous sibling required phototherapy
- Cephalohematoma or significant bruising
- Poor feeding
- Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive
- East Asian race (race as defined by mother's description)

**MINOR RISK FACTORS**

- PredischARGE total serum bilirubin or transcutaneous bilirubin level in the high- to intermediate-risk zone
- Gestational age 37 to 38 weeks
- Jaundice observed before discharge
- Previous sibling with jaundice
- Macrosomic infant of a diabetic mother
- Maternal age  $\geq 25$  years
- Male gender

**DECREASED RISK\***

- Total serum bilirubin or transcutaneous bilirubin level in the low-risk zone
- Gestational age 41 weeks or more
- Exclusive bottle feeding
- Black race (race as defined by mother's description)
- Discharge from hospital after 72 hours

\*These factors are associated with decreased risk for significant jaundice, listed in order of decreasing importance. From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Clinical practice guideline: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2004;114(1):297–316.

**BOX 99-3 Chemicals That Displace Bilirubin From Albumin**

- |   |   |
|---|---|
| • Chuen-Lin ( <i>Coptis chinensis/japonicum</i> )                         | • Ibuprofen   |
| • Berberine ( <i>Coptis chinensis</i> )                                   | • Long-chain fatty acids  |
| • Some cephalosporins (eg, ceftriaxone, cefonicid, cefotetan, moxalactam) | • Pancuronium   |
| • Benzyl alcohol  | • Salicylates   |
| • Chloral hydrate   | • Sulfonamides—sulfisoxazole, sulfamethoxazole                                    |
| • Ethacrynic acid   | • Maternal intrapartum medication administration—oxytocin, diazepam, promethazine |

have a low risk for severe hyperbilirubinemia, a subgroup of G6PD-deficient black neonates (12.8%) has a 3-fold increase in risk for hemolysis and jaundice compared with controls.

**Physical Examination**

Jaundice may be diagnosed at a bilirubin level of 5 mg/dL. Interobserver agreement about the presence of jaundice in neonates is only moderate (pairwise  $\kappa$ , 0.48), except for infants with bilirubin levels greater than 12 mg/dL, which is the threshold at which all infants are correctly identified as jaundiced by all examiners. Other important parts of the physical examination include vital signs, size for gestational age, either pallor or plethora, petechiae, bruising, subcutaneous edema, blueberry muffin lesions, vasoconstriction, scalp swelling, cataract, goiter, abdominal mass, hepatosplenomegaly, activity, tone, and neurologic examination. Patients with extreme hyperbilirubinemia are at risk for bilirubin encephalopathy. Acute bilirubin

encephalopathy occurs when bilirubin levels become neurotoxic in infants. Three phases of acute bilirubin encephalopathy have been described. The early acute phase is characterized by lethargy, hypotonia, and poor suck; the intermediate phase by hypertonia alternating with hypotonia (including opisthotonus and retrocollis), high-pitched cry, fever, moderate stupor, and irritability; and the advanced phase by seizures, coma, apnea, pronounced retrocollis, and opisthotonus, with death occurring in severe cases. Although the acute neurologic abnormalities of hyperbilirubinemic infants can be transient, the intermediate and advanced phases have been strongly linked to long-term neurologic sequelae. The intermediate phase may be reversible with exchange transfusion, whereas the advanced phase is irreversible. Kernicterus (yellow discoloration of the basal ganglia and brainstem nuclei caused by bilirubin deposition), or chronic, irreversible sequela of bilirubin toxicity, is characterized by athetoid cerebral palsy, auditory dysfunction, dental enamel dysplasia,

paralysis of upward gaze, and, less often, intellectual and other disabilities.

### Laboratory Testing

The AAP recommendations for evaluating jaundiced infants are listed in Table 99-2. The World Health Organization recommends neonatal screening for G6PD in populations with a prevalence of 3% to 5% or more in boys. Some neonatal screening programs also include testing for hemoglobinopathy.

The total serum bilirubin level is the most important measurement. The physician should be aware that bilirubin measurements on automatic analyzers used in most clinical laboratories can be erroneous if the specimen is hemolyzed or turbid.

If phototherapy is indicated, or if the bilirubin level crosses percentiles on the Bhutani nomogram and is unexplained by the history and physical examination, then a serum level of direct or conjugated bilirubin should be obtained. Conjugated hyperbilirubinemia is defined by a serum conjugated bilirubin concentration greater than 1.0 mg/dL (17.1  $\mu$ mol/L) if the total bilirubin is less than 5.0 mg/dL (85.5  $\mu$ mol/L) or more than 20% of the total bilirubin if the total bilirubin is greater than 5.0 mg/dL (85.5  $\mu$ mol/L). Neonatal cholestasis is defined as conjugated hyperbilirubinemia that occurs in the newborn period. It is caused by diminished bile flow or excretion (or both) of conjugated bilirubin from the hepatocyte into the duodenum. The incidence of neonatal cholestasis is approximately 1 per 2,500 live births. Jaundice is further discussed in Chapter 170.

A comprehensive program of prevention, including universal predischarge neonatal bilirubin screening, significantly reduces the subsequent development of bilirubin levels that are known to place newborns at risk for bilirubin encephalopathy.

The new methods of transcutaneous bilirubin assessment, valid in many populations regardless of skin

color, have led to a decrease in the number of blood samples required before and after discharge in term or late preterm infants. Importantly, transcutaneous bilirubin assessment and clinical examination of jaundice are unreliable after phototherapy.

Additional tests indicated in newborns with early or severe hyperbilirubinemia (see Table 99-2) include blood type and Coombs test, complete blood count and smear, reticulocyte count, end-tidal carbon monoxide concentration (if available), and G6PD. Testing for G6PD deficiency is warranted when the newborn is of African, Asian, Mediterranean, or Middle Eastern descent. Among babies with G6PD deficiency (male infants with the defective gene and homozygous female infants) the rate of hyperbilirubinemia is twice that for unaffected newborns. G6PD deficiency should be considered in neonates who develop jaundice during the first day of life, have a family history of a sibling with unexplained hyperbilirubinemia, or have a bilirubin level greater than the 95th percentile on the Bhutani nomogram, and in Asian male infants. The smear may show anomalies such as abnormal erythrocyte volume, ovalocytosis, elliptocytosis, spherocytosis (seen in congenital spherocytosis and in ABO disease), Heinz bodies (suggestive of G6PD deficiency), stomatocytosis, pyropoikilocytosis, thrombocytopenia, or an abnormal white cell count suggestive of sepsis. If hemolysis is confirmed, additional tests to consider may include tests for minor group incompatibility, a workup for congenital or acquired infection, and hemoglobin electrophoresis to rule out thalassemia or thalassemia trait (which could cause hemolysis in association with G6PD deficiency). The newborn screening program may include hemoglobin electrophoresis. Additional tests may be considered, such as autoimmune antibodies, vitamin E level, and tests for pyruvate kinase deficiency and other rare deficiencies of the glycolytic, hexose monophosphate, and

**Table 99-2**

### Laboratory Evaluations for the Jaundiced Newborn of 35 Weeks' Gestation or More

INDICATIONS	ASSESSMENTS
Jaundice in first 24 hr	Measure TcB, TSB, or both
Jaundice appears excessive for age	Measure TcB, TSB, or both
Infant receiving phototherapy or TSB rising rapidly (ie, crossing percentiles and unexplained by history and physical examination)	Blood type and Coombs test, if not obtained with cord blood Complete blood count and smear Measure direct or conjugated bilirubin Option: perform reticulocyte count, G6PD, and ETCOc, if available Repeat TSB in 4–24 hr depending on age and TSB level Perform reticulocyte count, G6PD, albumin, ETCOc, if available
TSB concentration approaching exchange levels or not responding to phototherapy	
Elevated direct (or conjugated) bilirubin level	Perform urinalysis and urine culture. Evaluate for sepsis if indicated by history and physical examination
Jaundice present at or beyond age 3 wk, or newborn is sick	Total and direct (or conjugated) bilirubin level; if direct bilirubin elevated, evaluate for causes of cholestasis Check results of newborn thyroid and galactosemia screen and evaluate newborn for signs or symptoms of hypothyroidism

ETCOc, end-tidal carbon monoxide concentration; G6PD, glucose-6-phosphate dehydrogenase; TcB, transcutaneous bilirubin level; TSB, total serum bilirubin level. From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Clinical practice guideline: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2004;114(1):297–316.

erythrocyte metabolic pathways. Measuring serum albumin is indicated if the bilirubin approaches exchange transfusion level. Prolonged jaundice should raise the suspicion of hypothyroidism, galactosemia, and cholestatic jaundice.

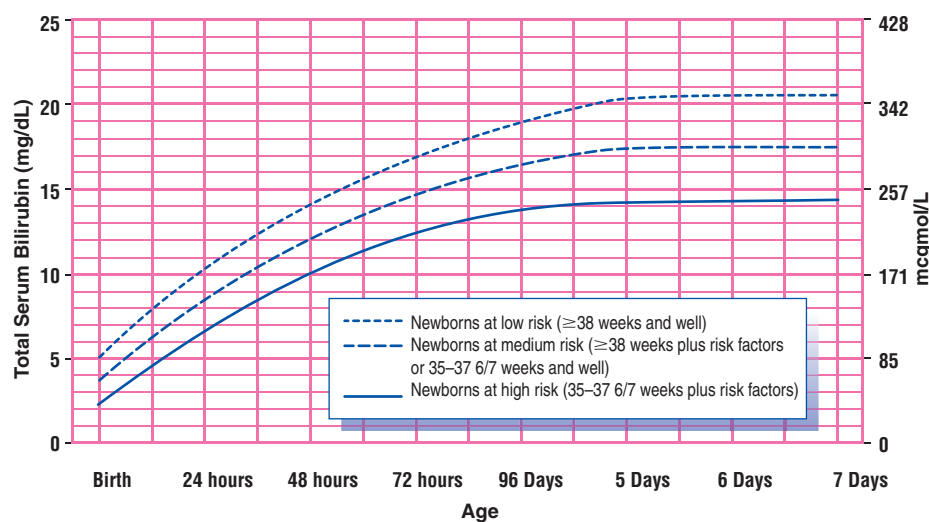
## MANAGEMENT

The AAP and The Joint Commission recommend a universal systematic approach to reduce the risk for severe hyperbilirubinemia and kernicterus. The key elements of the AAP recommendations are summarized in Box 99-1.

Postnatal age-, gestational age-, and risk factor-specific criteria for phototherapy are shown in Figure 99-3. Low-intensity phototherapy can be provided at home to newborns for whom phototherapy is optional, whereas high-intensity phototherapy requires hospital care. Phototherapy reduces the risk that bilirubin levels will reach a level at which exchange transfusion is recommended. Approximately 5 to 10 newborns with serum bilirubin levels ranging from 15 to 20 mg/dL (257–342  $\mu\text{mol/L}$ ) will receive phototherapy to prevent bilirubin in 1 newborn from reaching 20 mg/dL (a number at which exchange transfusion may be recommended). The efficacy of

phototherapy is best with special blue or with blue-green lights and increases with increasing spectrum irradiance, spectrum power (irradiance by unit of surface), and total serum bilirubin. The efficacy is reduced in patients with hemolysis and in infants with cholestasis. Side effects of phototherapy include weight loss, gastrointestinal problems, parental anxiety related to the need for protective eye patches, development of bronze baby syndrome in newborns with cholestasis, and, rarely, purpura, possible growth of melanocytic nevi, and bullous eruptions. Phototherapy is contraindicated in infants with congenital erythropoietic porphyria, in whom it causes severe blistering. Given that the recently developed phototherapy devices do not significantly increase insensible water loss, routine increase in fluid administration is not necessary for patients who undergo phototherapy. However, newborns with clinical or laboratory evidence of dehydration should receive additional fluid.

Postnatal age-, gestational age-, and risk factor-specific criteria for exchange transfusion are shown in Figure 99-4. The ratio of bilirubin to albumin can be used together with the total bilirubin level as an additional factor in determining the need for exchange transfusion.



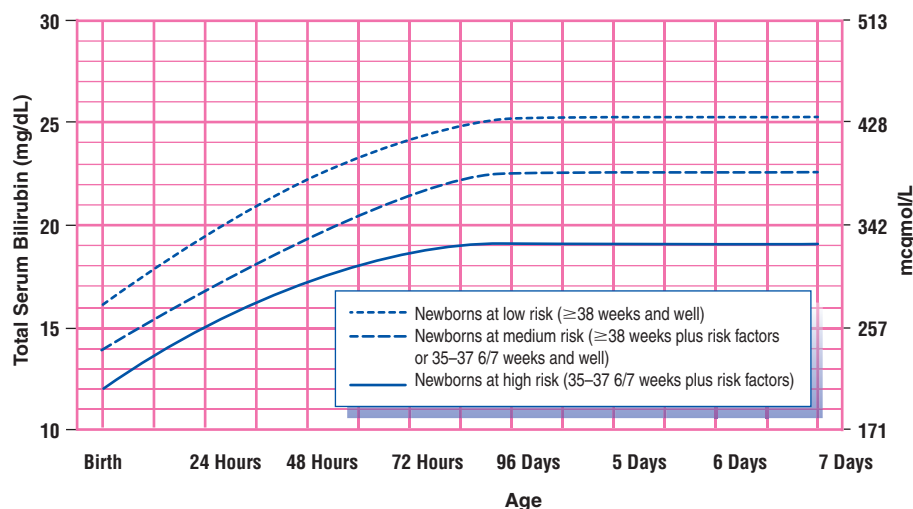
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors: Isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin  $<3.0$  g/dL (if measured).
- For well infants 35–37 6/7 weeks can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 weeks and at higher TSB levels for those closer to 37 6/7 weeks.
- It is an option to provide conventional phototherapy in the hospital or at home at TSB levels 2–3 mg/dL (30–50  $\mu\text{mol/L}$ ) below those shown, but home phototherapy should not be used in any infant with risk factors.

**Note:** These guidelines are based on limited evidence, and the levels shown are approximations. The guidelines refer to the use of intensive phototherapy, which should be used when the TSB exceeds the line indicated for each category. Infants are designated as at high risk because of the potential negative effects of the conditions listed on albumin binding of bilirubin, the blood-brain barrier, and the susceptibility of the brain cells to damage by bilirubin.

Intensive phototherapy implies irradiance in the blue-green spectrum (wavelengths of approximately 430–490 nm) of at least 30  $\text{mcgW/cm}^2$  per nm (measured at the infant's skin directly below the center of the phototherapy unit) and delivered to as much of the infant's surface area as possible. Note that irradiance measured below the center of the light source is significantly greater than that measured at the periphery. Measurements should be made with a radiometer specified by the manufacturer of the phototherapy system.

If total serum bilirubin levels approach or exceed the exchange transfusion line, the sides of the bassinet, incubator, or warmer should be lined with aluminum foil or white material, which will increase the surface area of the newborn exposed and will increase the efficacy of phototherapy. If the total serum bilirubin does not decrease or if it continues to rise in a newborn who is receiving intensive phototherapy, then these results strongly suggest the presence of hemolysis. Newborns who receive phototherapy and have an elevated direct-reacting or conjugated bilirubin level (cholestatic jaundice) may develop the bronze-baby syndrome.

**Figure 99-3** Guidelines for phototherapy in infants of 35 or more weeks' gestation. *B/A*, Bilirubin/albumin; *TcB*, transcutaneous bilirubin level; *TSB*, total serum bilirubin level; *G6PD*, glucose-6-phosphate dehydrogenase. (From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Clinical practice guideline: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114[1]:297–316.)



- The dashed lines for the first 24 hours indicate uncertainty as a result of a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if newborn shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high-pitched cry) or if TSB is  $\geq 5$  mg/dL (85 mcgmo/L) above these lines.
- Risk factors: Isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin, and calculate B/A ratio.
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- If newborn is well and 35–37 6/7 weeks (median risk) can individualize TSB levels for exchange based on actual gestational age.

**Note:** These suggested levels represent a consensus of most of the committee but are based on limited evidence, and the levels shown are approximations. During birth hospitalization, exchange transfusion is recommended if the TSB rises to these levels despite intensive phototherapy. For readmitted infants, if the TSB level is above the exchange level, then repeat TSB measurement every 2 to 3 hours, and consider exchange if the TSB remains above the levels indicated after intensive phototherapy for 6 hours.

If the TSG is at or approaching the exchange level, then send blood for immediate type and crossmatch. Blood for exchange transfusion is modified whole blood (red cells and plasma) crossmatched against the mother and compatible with the infant.

**Intensive phototherapy** implies irradiance in the blue-green spectrum (wavelengths of approximately 430–490 nm) of at least 30 mcgW/cm<sup>2</sup> per nm (measured at the infant's skin directly below the center of the phototherapy unit) and delivered to as much of the infant's surface area as possible. Note that irradiance measured below the center of the light source is significantly greater than that measured at the periphery. Measurements should be made with a radiometer specified by the manufacturer of the phototherapy system.

If total serum bilirubin levels approach or exceed the exchange transfusion line, the sides of the bassinet, incubator, or warmer should be lined with aluminum foil or white material, which will increase the surface area of the newborn exposed and will increase the efficacy of phototherapy. If the total serum bilirubin does not decrease or if it continues to rise in a newborn who is receiving intensive phototherapy, then these results strongly suggest the presence of hemolysis. Newborns who receive phototherapy and have an elevated direct-reacting or conjugated bilirubin level (cholestatic jaundice) may develop the bronze-baby syndrome.

The following B/A ratios can be used together with but not in lieu of the TSB level as an additional factor in determining the need for exchange transfusion:

Risk Category	B/A Ratio at Which Exchange Transfusion Should Be Considered	
	TSB mg/dL/Alb, g/dL	TSB mcgmo/L/Alb, mcgmo/L
Newborns $\geq 38$ 1/7 wks	8.0	0.94
Newborns 35 0/7–36 6/7 weeks and well or $\geq 38$ 0/7 wks if higher risk or isoimmune hemolytic disease of G6PD deficiency	7.2	0.84
Newborns 35 0/7 wks if higher risk or isoimmune hemolytic disease or G6PD deficiency	6.8	0.80

**Figure 99-4** Guidelines for exchange transfusion in infants of 35 or more weeks' gestation. B/A, Bilirubin/albumin; TcB, transcutaneous bilirubin level; TSB, total serum bilirubin level; G6PD, glucose-6-phosphate dehydrogenase. (From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Clinical practice guideline: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114[1]:297–316.)

Double-volume exchange transfusion has a low but significant risk for complications and should be performed only by trained personnel in a neonatal intensive care unit with full monitoring and resuscitation capabilities.

Based on Gottstein's systematic review (which included 4 small trials) the Subcommittee on Hyperbilirubinemia concluded in 2004: "Intravenous gamma globulin administration is effective in reducing the need for exchange transfusion in infants with isoimmune hemolysis caused by Rh or ABO incompatibility. It is indicated for neonates with isoimmune hemolysis if the serum bilirubin level is rising despite intensive phototherapy or if the bilirubin level is within 2 to

3 mg/dL of the level of bilirubin at which the determination is made that an exchange transfusion becomes necessary to prevent the risk of developing kernicterus." The evidence for the use of intravenous immunoglobulin for isoimmune hemolysis in the neonate will need to be reviewed to take new trials into account.

Jaundice is a frequent reason for readmission of neonates during the first 2 weeks after newborn nursery discharge. Criteria to refer and to admit are listed at the end of this chapter, and guidance for the timing of follow-up care is provided in Table 99-3. The rate of readmission for healthy infants for the treatment



Table 99-3 Follow-up of Newborn With Hyperbilirubinemia	
NEWBORN DISCHARGED	TIMING OF FOLLOW-UP VISIT
Before age 24 hr Between 24 and 47.9 hr Between 49 and 72 hr Before 48 hr <sup>a</sup>  Few or no risk factors <sup>a</sup> Elevated risk factors Elevated risk factors AND appropriate follow-up cannot be ensured	By 72 hr By 96 hr By 120 hr Two follow-up visits may be required: The first at 24–72 hr The second at 72–120 hr Can be seen after longer intervals Earlier or more frequent follow-up Delay discharge either until appropriate follow-up can be ensured or the period of greatest risk has passed (72–96 hr)

<sup>a</sup>Clinical judgment should be used in determining follow-up.

**BOX 99-4 Example of a Clinical Pathway for Management of the Newborn Readmitted for Phototherapy or Exchange Transfusion**

**TREATMENT**

- Use intensive phototherapy or exchange transfusion (or both) as indicated in Figure 99-3 and Figure 99-4.

**LABORATORY TESTS**

- TSB and direct bilirubin levels
- Blood type (ABO, Rh)
- Direct antibody test (Coombs test)
- Serum albumin
- Complete blood cell count with differential and smear for red cell morphology
- Reticulocyte count
- End-tidal carbon monoxide (if available)
- G6PD if suggested by ethnic or geographic origin or if poor response to phototherapy
- Urine for reducing substances
- If history, presentation, or both suggest sepsis, perform blood culture, urine culture, and cerebrospinal fluid for protein, glucose, cell count, and culture.

**INTERVENTIONS**

- If TSB ≥25 mg/dL (428 mcmol/L) or ≥20 mg/dL (342 mcmol/L) in a sick newborn or newborn
- In newborns with isoimmune hemolytic disease and TSB level rising despite intensive phototherapy or within 2 to 3 mg/dL (34–51 mcmol/L) of exchange

level, administer intravenous immunoglobulin 0.5 to 1 g/kg over 2 hours and repeat in 12 hours if necessary.

- If newborn's weight loss from birth is >12% or clinical or biochemical evidence of dehydration exists, then recommend formula or expressed breast milk. If oral intake is in question, then give intravenous fluids.

**FOR NEWBORNS RECEIVING INTENSIVE PHOTOTHERAPY**

- Breastfeed or bottle feed (formula or expressed milk) every 2 to 3 hours.
- If TSB ≥25 mg/dL (428 mcmol/L), repeat TSB within 2 to 3 hours.
- If TSB 20 to 25 mg/dL (342–428 mcmol/L), repeat within 3 to 4 hours.
- If TSB <20 mg/dL (342 mcmol/L), then repeat in 4 to 6 hours. If TSB continues to fall, then repeat in 8 to 12 hours.
- If TSB is not decreasing or is moving closer to level for exchange transfusion or the TSB/albumin ratio exceeds levels shown in Figure 99-4, then consider exchange transfusion (see Figure 99-4 for exchange transfusion recommendations).
- When TSB is <13 to 14 mg/dL (239 mcmol/L), discontinue phototherapy.
- Depending on the cause of the hyperbilirubinemia, measuring TSB 24 hours after discharge to check for rebound is an option.

G6PD, glucose-6-phosphate dehydrogenase; TSB, total serum bilirubin level. From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Clinical practice guideline: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2004;114(1):297–316.

of jaundice in California in 1991 to 1998 ranged between 10% and 15% for full-term infants and between 24% and 32% for late preterm infants. The clinical pathway for management of the newborn readmitted for phototherapy or exchange transfusion is shown in Box 99-4. The AAP recommends not delaying discharge from the hospital to observe the newborn for rebound

bilirubin level. Instead, a follow-up bilirubin measurement within 24 hours after discharge is recommended if phototherapy is used for hemolytic disease or initiated early and discontinued before 3 to 4 days of age. A recent study suggested a significant association with a higher rebound bilirubin level among newborns with a positive direct Coombs test, for

newborns with a gestational age younger than 37 weeks, and in instances in which phototherapy is initiated before 72 hours of life.

## PREVENTION

Because breastfeeding is the second independent risk factor for the development of hyperbilirubinemia, optimizing breastfeeding is an essential component in the prevention and management of neonatal hyperbilirubinemia. One major aspect of prevention is early initiation and frequent breastfeeding, at least 8 to 12 times per day for the first several days. Two types of hyperbilirubinemia may be observed in breastfed infants: (1) breastfeeding jaundice (also called *breast-non-feeding jaundice*) and (2) breast milk jaundice. (See Chapter 88, Breastfeeding the Newborn.) Breastfed infants who develop jaundice should be continued on frequent breastfeeding. Supplementation with expressed milk or formula is indicated only if the intake seems inadequate despite intervention, if weight loss is excessive, if the newborn appears dehydrated, or for breast milk jaundice when levels reach greater than 20 to 25 mg/dL in an otherwise healthy infant and when a diagnostic interruption of breastfeeding may be helpful.

The US Food and Drug Administration (FDA) has approved no medication for preventing hyperbilirubinemia. A small randomized trial has shown that hyperbilirubinemia in breastfed infants can be reduced by inhibiting  $\beta$ -glucuronidase, thereby reducing the enterohepatic cycle of bilirubin. Glycerin suppositories during the first 48 hours do not significantly affect the level of bilirubin at 38 hours of life. Several studies have shown that in patients with hemolytic anemia, the early postnatal administration of a single dose of tin mesoporphyrin, an inhibitor of heme oxygenase, is highly effective in reducing the risk for hyperbilirubinemia. However, this inhibitor is nonspecific, thereby potentially inhibiting heme oxygenase in the brain. Long-term follow-up data are required before this drug receives FDA approval for this indication.

## LONG-TERM OUTCOME, NEURODEVELOPMENTAL FOLLOW-UP, AND MEDICAL-LEGAL RISKS

The clear guidelines of the AAP and The Joint Commission for prevention, intervention, and follow-up for hyperbilirubinemia in the term or late preterm neonate based on risk factors and total serum bilirubin levels help the physician minimize the medical-legal risk for kernicterus. However, the US Preventive Task Force found only limited evidence supporting efficacy of screening and therapy to prevent chronic bilirubin encephalopathy.

Any term or late preterm neonate who develops acute or chronic bilirubin encephalopathy or presents with a peak bilirubin  $>25$  mg/dL should be entered into the pilot Kernicterus Registry, which in 2013 had records of 216 patients. Peak or admission serum bilirubin concentrations in these patients ranged from 20.7 to 59.9 mg/dL. In this registry, 8% of those who died with kernicterus or developed residual neurologic sequelae had a total serum bilirubin level of 20.7 mg/dL to 25.0 mg/dL, and 50% had a value less than 30.1 mg/dL.

The major underlying root cause for kernicterus in this registry is systems failure of services by multiple providers at multiple sites and inability to identify the at-risk infant and manage severe hyperbilirubinemia in a timely manner. Experimental and clinical data strongly suggest that measurement of free bilirubin may improve risk assessment for long-term neurotoxicity. In a neonate exposed to an agent that unbinds bilirubin, using (measured or estimated) unbound bilirubin levels rather than total serum bilirubin levels to assess the need for phototherapy or exchange transfusion seems prudent. Metabolic acidosis increases free bilirubin levels in the blood.

In patients readmitted with serum bilirubin concentration greater than 25 mg/dL (26.4 to 36.9 mg/dL), most with acute signs of encephalopathy, magnetic resonance imaging may show increased T1 signal at the level of the basal ganglia or brainstem nuclei. In one series, neurologic signs normalized in 4 of 5 infants and magnetic resonance imaging results normalized in 2 of 3 infants by 2 years of age.

Healthy neonates with nonhemolytic hyperbilirubinemia and moderately elevated serum bilirubin levels (13.6 to 26.0 mg/dL) may exhibit minor neurologic dysfunction when examined during the first year of life. In one series, a strong dose-response relationship between the degree of hyperbilirubinemia and the severity of minor neurologic dysfunction was present at 12 months of age.

In contrast, in a series of 132 neonates with peak serum bilirubin levels of at least 25 mg/dL (most up to 29.9 mg/dL) and treated with phototherapy or exchange transfusion, neurodevelopment was normal beyond 2 years of age when examined at a median age of 5.8 years.

Severe anomalies of the brainstem-evoked response are observed in patients with serum bilirubin levels greater than 20 mg/dL. Patients with hyperbilirubinemia at a serum level requiring exchange transfusion should be tested for sensorineural hearing loss by brainstem auditory evoked response, regardless of the results of hearing screening using otoacoustic emission, and should have audiologic monitoring every 6 months until the age of 3 years. Long-term neurodevelopmental follow-up appears justified in patients suspected of or confirmed with bilirubin encephalopathy and those with total serum bilirubin greater than 25 mg/dL. The toxic effect of hyperbilirubinemia on auditory brainstem pathways might be transient provided that prompt treatment is initiated. A recent study found no relationship between the abnormalities of the brainstem auditory evoked potentials and neurodevelopmental status. Accumulating evidence suggests an association between exposure to neonatal jaundice and autistic disorders, as well as perhaps other disorders of psychological development. Gestational age, parity, and season of birth seem to play important roles in this association.

## WHEN TO REFER

- Preparation for possible exchange transfusion: total serum bilirubin greater than the level recommended for exchange transfusion or total serum bilirubin greater than 25 mg/dL

(428  $\mu\text{mol/L}$ ) at any time or signs of bilirubin encephalopathy

- Need for intravenous immunoglobulin therapy: isoimmune hemolytic disease with a total serum bilirubin level rising despite intensive phototherapy or within 2 to 3  $\text{mg/dL}$  (34–51  $\mu\text{mol/L}$ ) of exchange transfusion level
- Sick newborn who needs to be evaluated and treated for possible sepsis
- Cholestatic jaundice, defined as a direct or conjugated bilirubin level greater than 1  $\text{mg/dL}$  if total bilirubin is less than 5  $\text{mg/dL}$ , or above 20% of total serum bilirubin if the latter is greater than 5  $\text{mg/dL}$
- Prenatal diagnosis of isoimmune hemolysis
- Newborn with poor response to high-intensity phototherapy
- Suspicion of bilirubin neurotoxicity

### WHEN TO ADMIT

- Emergency admission: total serum bilirubin greater than the level recommended for exchange transfusion or total serum bilirubin greater than 25  $\text{mg/dL}$  (428  $\mu\text{mol/L}$ ) at any time
- Need for intravenous immunoglobulin therapy: isoimmune hemolytic disease with a total serum bilirubin level rising despite intensive phototherapy or within 2 to 3  $\text{mg/dL}$  (34–51  $\mu\text{mol/L}$ ) of exchange transfusion level
- Routine admission or home phototherapy: total serum bilirubin above the level recommended for phototherapy (usually total serum bilirubin >18  $\text{mg/dL}$ )
- Sick infant who needs to be evaluated for and treated for dehydration or possible sepsis
- Suspicion of bilirubin neurotoxicity

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Jaundice and Your Newborn* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Jaundice in Newborns Q&A* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/news/Pages/Jaundice-in-Newborns.aspx](http://www.healthychildren.org/English/news/Pages/Jaundice-in-Newborns.aspx))

#### Medical Decision Support

- *Algorithm for the Management of Jaundice in the Newborn Nursery* (algorithm), American Academy of Pediatrics ([pediatrics.aappublications.org/content/114/1/297](http://pediatrics.aappublications.org/content/114/1/297))
- *BiliTool* (interactive tool), BiliTool, Inc. ([www.bilistool.org](http://www.bilistool.org))
- *Revised Guidance to Help Prevent Kernicterus* (fact sheet), The Joint Commission ([www.jointcommission.org/sentinel\\_event\\_alert\\_issue\\_31\\_revised\\_guidance\\_to\\_help\\_prevent\\_kernicterus/](http://www.jointcommission.org/sentinel_event_alert_issue_31_revised_guidance_to_help_prevent_kernicterus/))

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## Chapter 100

# RESPIRATORY DISTRESS AND BREATHING DISORDERS IN THE NEWBORN

Suhas M. Nafday, MD, MRCP(Ire), DCH; Christina Long, DO

## INTRODUCTION

### Physiologic Changes at Birth

The transition from intrauterine to extrauterine life requires establishment of effective pulmonary gas exchange. The process of changing from placental to pulmonary gas exchange at birth requires rapid removal of fetal lung liquid from the potential air space. It is a complex process rather than simple mechanical compression of the chest at delivery that results in oral drainage of lung liquid. It is controlled primarily by ion transport across the airway and pulmonary epithelium that entails a supporting role for sodium uptake in alveolar fluid clearance, particularly under stimulated conditions, and the role of glucocorticoids, catecholamines, and oxygen in regulating the activity of this uptake.

During fetal life, pulmonary vascular resistance (PVR), is high and pulmonary blood flow is low; thus, most of the blood from the right side of the heart flows through the ductus arteriosus into the aorta. At birth, clamping the umbilical vessels removes the low-resistance placental circuit and increases systemic

blood pressure, while blood vessels in the lungs relax. As a result, pulmonary blood flow increases immediately by 8- to 10-fold, and the blood flow through the ductus arteriosus decreases. The most important stimuli for increasing pulmonary blood flow are ventilation of the lungs and an increase in oxygen tension.

Significant changes occur during the first 6 hours after birth as part of the process of cardiorespiratory adaptation that lead to a significant increase in oxygenation and a decrease in the arterial pressure of carbon dioxide ( $\text{PaCO}_2$ ). Throughout this period, there are intrapulmonary shunts that persist as the lungs become air filled and the newborn's functional residual capacity (FRC) is established. The initial respiratory pattern is irregular, but respiratory cycles become increasingly rhythmic with modulation of chemoreceptors and stretch receptors. Both term and preterm infants frequently exhibit incomplete or halting expiratory effort during the first minutes of life. Crying is an important part of the transitional process, helping to promote lung expansion and protect lung volume. Breathing patterns in preterm infants are especially vulnerable because of poor respiratory drive, weak muscles, flexible ribs, surfactant deficiency, and impaired lung liquid clearance.

Successful initiation of respiration requires a sufficient pulmonary gas exchange surface area in the lung in conjunction with an adequately developed pulmonary vasculature that supports transport of oxygen and carbon dioxide through the lungs. The lungs must be compliant and able to respond to the metabolic needs of the infant with minimal respiratory effort. The airways, chest wall, respiratory muscles, and neural mechanisms that control respiration must be structurally mature to allow for optimal respiratory function. Three groups of skeletal muscles—the diaphragm, intercostal and accessory muscles, and abdominal muscles—are involved in ventilation. The diaphragm is the primary muscle used during quiet breathing. Respiratory muscle fatigue occurs when the work of breathing increases, when muscle strength is reduced, or when breathing is inefficient. Respiratory fatigue will lead to progressive hypercapnia and apnea. In most instances, this complex series of events goes quite smoothly. However, some babies develop respiratory distress, necessitating evaluation and possible neonatal intensive care.

During the first 2 months after a full-term birth, significant increases occur in lung size, surface area, and lung volume. Changes in the control of breathing and maturation of neural control mechanisms coincide with this rapid phase of lung growth. Development of the respiratory system continues after birth and into childhood. Alveolar remodeling continues until a child is 6 to 7 years of age, with continued alveolar growth into adolescence.

### Normal Physical Findings

Normal physical findings in a newborn include a respiratory rate of 40 to 60 breaths per minute. During active or rapid eye movement (REM) sleep, infants often exhibit irregular respirations with respiratory pauses of 5 seconds or less. In contrast, during non-REM or quiet sleep, a newborn's respiratory rate is

5 to 10 breaths per minute slower than in the awake or REM sleep states. Infants attempt to minimize their work of breathing by adjusting their respiratory rate. In full-term neonates, respiratory rates average around 45 breaths per minute when awake and 35 breaths per minute during sleep, with wide rates of respiration variation. Respiratory rates are typically higher in preterm infants.

### Respiratory Distress Defined

*Respiratory distress* can be defined as tachypnea with respiratory rate greater than 60 breaths per minute, nasal flaring, chest retractions (intercostal, subcostal, and substernal), and expiratory grunting. Respiratory distress may be present with or without cyanosis. Peripheral or acrocyanosis is common in the neonatal period. Central cyanosis, signifying greater than 3 to 5 g/dL of desaturated hemoglobin, is often visible by looking at the newborn's mucous membranes and tongue and, depending on the skin pigmentation, the lips and trunk. Evaluating nail beds is not helpful in neonates; pigmentation of the vermilion border of the lip and facial bruising may also masquerade as cyanosis. Polycythemic infants may appear cyanosed at higher oxygen saturation levels, whereas infants who are severely anemic will appear pale and may not look cyanotic when they are hypoxic. Decreased oxygen saturation, apnea, or both may also be present. Irregular (*seesaw*) or slow respiratory rates of less than 30 breaths per minute, particularly if associated with gasping, are a worrisome sign.

The cause of respiratory distress can be either pulmonary or nonpulmonary in origin. Nonpulmonary causes of respiratory distress include airway, cardiac, or central nervous system (CNS) abnormalities, sepsis, infection, and hematologic, metabolic, or other conditions. Respiratory depression as the result of maternal medications or illicit substance use may also be a contributing factor. The gestational age of the newborn at birth is another factor that influences the risk for respiratory distress after birth. Late preterm neonates between 34 and 37 weeks' gestation, in comparison with full-term infants, experience increased respiratory difficulties. These newborns exhibit higher rates of low Apgar scores, transient tachypnea of the newborn (TTN), respiratory distress syndrome (RDS), persistent pulmonary hypertension, and respiratory failure. Respiratory distress is associated with cesarean delivery, particularly in the absence of labor. Delivery by elective cesarean is associated with higher rates of respiratory morbidity, necessitating neonatal intensive care, oxygen therapy, and cardiorespiratory support (eg, continuous positive airway pressure [CPAP], mechanical ventilation, extracorporeal membrane oxygenation [ECMO]) because of prematurity and surfactant deficiency.

### APPROACH TO THE PATIENT WITH RESPIRATORY DISTRESS

Respiratory distress can be difficult to determine immediately after birth. Many newborns may initially be cyanotic or tachypneic. These symptoms usually



resolve spontaneously in the first 10 to 15 minutes after birth. A thorough history and physical examination are important to distinguish cardiac and noncardiac causes of cyanosis and respiratory distress. The prenatal and perinatal histories, including maternal medication and substance use, are important in the evaluation for respiratory distress. Labor course and evidence of fetal distress provide important information regarding risk factors for a prolonged or difficult transition after birth. Complications occurring during delivery related to meconium passage, perinatal depression, or birth injury may also lead to transitional difficulties and respiratory distress. Many conditions that produce respiratory distress occur in preterm infants, whereas others may occur in full-term infants. In addition, many congenital anomalies may be suspected prenatally because of the presence of maternal complications that develop. Tracheoesophageal fistula, which may cause respiratory distress, is often associated with polyhydramnios, whereas an underlying condition that causes oligohydramnios may lead to pulmonary hypoplasia. Box 100-1 lists various maternal and obstetric conditions associated with neonatal causes of respiratory distress.

### Physical Examination

After a complete history, the newborn should be examined thoroughly. Urgent evaluation and treatment are needed for the infant who appears ill; is apneic; is choking; exhibits poor, labored, or gasping respirations; or has marked retractions or stridor, poor perfusion, or cyanosis. Bradycardia and hypotension also signify serious illness. The newborn's general appearance may provide useful clues to the cause of the child's symptoms. The physician should observe the neonate's color, activity, level of alertness, cry,

posture, and perfusion and assess for dysmorphism. Upper airways obstruction should be suspected in the infant who develops inspiratory stridor. A barrel-shaped chest suggests an air leak, whereas a scaphoid abdomen should lead the physician to consider that the newborn may have a diaphragmatic hernia. Grunting respirations and retractions signify poor lung compliance and often indicate the presence of parenchymal lung disease.

If cyanosis is present, the newborn should be examined while quiet and in a neutral thermal environment to ascertain whether the cyanosis is central or peripheral (acrocyanosis). Acrocyanosis, blue color of the hands and feet when the rest of the body is pink, is frequently seen in newborns. Acrocyanosis is usually normal and is likely to be seen with exposure to cold and in the presence of polycythemia, but it may also be a presenting sign of serious conditions such as sepsis, hypoglycemia, or hypoplastic left heart syndrome. When the baby's temperature has stabilized, it can be determined whether the cyanosis is central or is acrocyanosis. Central cyanosis of the trunk, mucosal membranes, and tongue can occur at any time after birth and is a manifestation of an underlying problem. Different conditions may affect the appearance of cyanosis, including anemia and hyperbilirubinemia. Causes of cyanosis are listed in Table 100-1.

The oxygen saturation level by pulse oximetry is important to check because clinical signs of hypoxemia or cyanosis may be difficult to detect. Oxygen saturations measured by pulse oximetry typically reflect an arterial pressure of oxygen ( $\text{PaO}_2$ ) between 60 and 90 mm Hg. Although oxygen saturation is less than 90% when the  $\text{PaO}_2$  is below 60 mm Hg in the adult with predominantly adult hemoglobin, in the newborn infant, the hemoglobin-oxygen dissociation curve is shifted to the left. Thus, the saturation in a neonate will be less than 90% when the  $\text{PaO}_2$  is below 40 mm Hg. In the rare condition of methemoglobinemia, the infant appears cyanotic but has a high oxygen saturation level. See Figure 100-1 for typical oxygen dissociation curve.

Accurate monitoring of respiratory rate is important. The physician should look for signs of respiratory distress such as nasal flaring, intercostal or subcostal retractions, and grunting. Grunting, the result of partial closure of the glottis during expiration, may be intermittent or continuous. Suprasternal retractions may be another indication of upper airway obstruction. Capillary refill time greater than 2 seconds may indicate poor perfusion, which may contribute to the respiratory distress.

Further examination of the neonate can reveal whether any obvious malformations are present, such as a barrel-shaped chest with meconium aspiration syndrome or pneumomediastinum and a small, narrow chest in cases of asphyxiating thoracic dystrophy, or a scaphoid abdomen if a congenital diaphragmatic hernia is present. The patient may have inspiratory stridor, which can be associated with vocal cord paralysis or laryngotracheomalacia. The chest must be auscultated to listen to heart and breath sounds. Heart sounds may be loud or diminished

### BOX 100-1 Maternal and Obstetric Conditions Associated With Neonatal Causes of Respiratory Distress

#### MATERNAL CONDITIONS

- Drug abuse: drug withdrawal
- Diabetes mellitus: RDS, hypoglycemia, polycythemia, cardiomyopathy
- Infections: pneumonia, sepsis

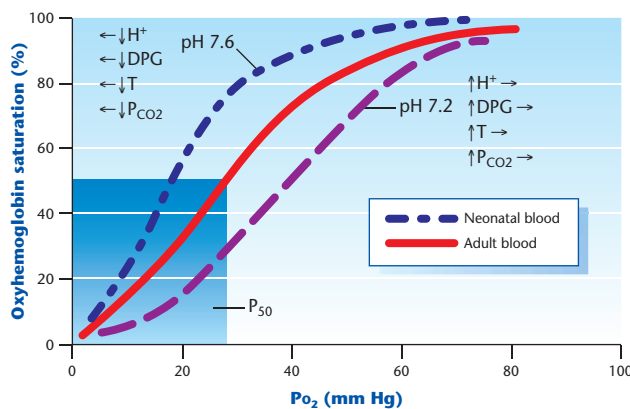
#### OBSTETRIC CONDITIONS

- Use of general anesthesia: central depression
- Hydrops fetalis: pleural effusion
- Preterm delivery: RDS
- PROM, maternal fever, chorioamnionitis: pneumonia, sepsis
- Meconium-stained amniotic fluid: meconium aspiration syndrome
- Antepartum hemorrhage: anemia, hypovolemia

PROM, premature/prolonged rupture of membranes; RDS, respiratory distress syndrome.

**Table 100-1** Causes of Cyanosis in the Neonate

	ACROCYNANOSIS	CENTRAL CYANOSIS	DIFFERENTIAL CYANOSIS	REVERSE DIFFERENTIAL CYANOSIS
<i>Appearance</i>	Blue color of the hands and feet when the rest of the body is pink	Blue color of the trunk, mucosal membranes, and tongue	Upper part of the body remains pink, and the lower part is cyanotic	Upper part of the body is cyanotic, whereas the lower part remains pink
<i>Possible Causes</i>	Usually normal Exposure to cold Polycythemia Serious conditions such as sepsis, hypoglycemia, or hypoplastic left heart syndrome	Serious pulmonary parenchymal as well as nonparenchymal abnormality Persistent pulmonary hypertension of newborn Cyanotic congenital heart disease	Right-to-left shunt through the patent ductus arteriosus (PDA)	Transposition of great arteries with pulmonary hypertension and shunt through the PDA TGA with PDA and preductal aortic interruption or coarctation Total anomalous pulmonary venous return above the diaphragm with shunt through the PDA



**Figure 100-1** Oxygen dissociation curve. (Modified from the *Merck Manual of Diagnosis and Therapy*, edited by Robert Porter. Copyright © 2013 by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co, Inc, Whitehouse Station, NJ. Available at: [www.merckmanuals.com/professional/](http://www.merckmanuals.com/professional/). Accessed July 14, 2014.)

(eg, pneumopericardium), or a heart murmur may be present. Cardiac murmur may be absent in a neonate with serious cardiac disease. Breath sounds may be unequal bilaterally, with rales, rhonchi, or wheezing (rare). Breath sounds may be diminished or distant in situations that involve pneumothorax, atelectasis, or pleural effusion. Transillumination of the chest may be a useful tool to rule out pneumothorax. Abdominal distention may be present in cases of ascites or bowel obstructions or those caused by hepatosplenomegaly, which may contribute to respiratory distress. Neurologic status is also important. Hypotonia is often a sign of sepsis, asphyxia, or depression as a result of maternal narcotics. Phrenic nerve injury that occurs during a difficult delivery or as a consequence of thoracic surgery may lead to

paralysis of the diaphragm. The differential diagnosis of respiratory distress is listed in Box 100-2.

## EVALUATION OF A PATIENT WITH RESPIRATORY DISTRESS

### Pulse Oximetry and Blood Gas Studies

Evaluation of a newborn with respiratory distress includes pulse oximetry and blood gas analysis. A pulse oximeter measures the oxygen saturation by comparing the amount of red light absorbed by deoxygenated hemoglobin with the amount of infrared light absorbed by oxygenated hemoglobin. If cyanosis is present, preductal (right hand) and postductal oxygen saturations (probe placed on a lower extremity) should be measured. Preductal and postductal saturation differences may indicate intracardiac shunting as a cause of respiratory distress and cyanosis. Interpreting blood gas values based on normal values for newborns is important. Refer to Table 100-2 for normal blood gas values at different ages. If serial blood gas monitoring is required, then the newborn should be transferred to a special care or neonatal intensive care unit (NICU). While interpreting the blood gas results, attention must be paid to errors caused by air bubbles (high  $\text{PaO}_2$  and low  $\text{PaCO}_2$ ), excessive heparin (metabolic acidosis), dilution of samples by intravenous fluids in samples obtained from intravascular lines, and blood gases obtained by arterial puncture (decreased  $\text{PaCO}_2$  with crying).

If signs of respiratory distress are present, then a hyperoxia test can aid in differentiating between cardiac and noncardiac diseases. The test consists of obtaining a baseline right radial (preductal) arterial blood gas measurement with the baby breathing room air and repeating the measurement while the baby is receiving 100% oxygen. A  $\text{PaO}_2$  measurement greater than 300 mm Hg on 100% oxygen is normal, more than 150 mm Hg suggests pulmonary disease,

**BOX 100-2 Differential Diagnosis of Respiratory Distress in the Newborn****AIRWAY OR LUNG PARENCHYMAL DISORDERS**

**Congenital anomalies:** tracheoesophageal fistula, congenital diaphragmatic hernia, pulmonary sequestration, congenital pulmonary airway malformations, pulmonary hypoplasia, choanal atresia or stenosis, laryngeal web, subglottic stenosis, congenital lobar emphysema, chylothorax, external compression of upper airway (vascular ring, tumors, and cysts), laryngotracheomalacia

**Acquired disorders:** transient tachypnea of the newborn, respiratory distress syndrome, meconium aspiration syndrome, pneumonia, pulmonary edema, pulmonary hemorrhage, pneumatocele, pulmonary lymphangiectasia, air leak syndromes (pneumothorax, pneumomediastinum), pleural effusion including hydrops fetalis, trauma (postextubation laryngeal edema, atelectasis, and subglottic stenosis)

**CARDIAC DISORDERS**

**Cyanotic heart lesions:** transposition of the great arteries, total anomalous pulmonary venous return,

truncus arteriosus, tricuspid atresia, pulmonary atresia, Ebstein anomaly

**Acyanotic heart lesions:** left-to-right shunts (patent ductus arteriosus, ventricular septal defect, and, rarely, atrial septal defect), atrioventricular canal defect, coarctation of aorta, aortic stenosis

**MECHANICAL ANOMALIES**

Rib cage anomalies (eg, Jeune syndrome), abdominal distention

**CENTRAL NERVOUS SYSTEM DISORDERS**

Cerebral edema, asphyxia, infection, vocal cord paralysis, diaphragmatic paralysis, intracranial hemorrhage

**MISCELLANEOUS**

Metabolic acidosis, sepsis, polycythemia, anemia, hypoglycemia, hypermagnesemia

**Table 100-2** Range of Blood Gas Values for Healthy Children

	<b>PRETERM INFANTS (at 1–5 hr)</b>	<b>TERM INFANTS (at 5 hr)</b>	<b>PRETERM AND TERM INFANTS (at 5 days)</b>	<b>CHILDREN, ADOLESCENTS, ADULTS</b>
pH	7.33	7.34	7.38	7.40
Range	7.29–7.37	7.31–7.37	7.34–7.42	7.35–7.45
PaCO <sub>2</sub> (mm Hg)	47	35	36	40
Range	39–56	32–39	32–41	35–45
PaO <sub>2</sub> (mm Hg)	60	74	76	95
Range	52–67	62–86	62–92	85–100
HCO <sub>3</sub> (mEq/L)	23	19	21	24
Range	22–23	18–21	19–23	22–26
BE	–4	–5	–3	0
Range	–5 to –2.2	–6 to –2	–5.8 to –1.2	–2 to 2

BE, base excess; HCO<sub>3</sub>, bicarbonate; PaCO<sub>2</sub>, arterial pressure of carbon dioxide; PaO<sub>2</sub>, arterial pressure of oxygen.

and 50 to 150 mm Hg suggests cardiac disease (or severe pulmonary hypertension). Significant metabolic acidosis requires evaluation for evidence of tissue hypoxia, cold stress, an inborn error of metabolism, sepsis, acute renal failure, or loss of pH buffering ions as a result of diarrhea, parenteral nutrition, or renal insufficiency.

**Other Laboratory Tests**

In addition to evaluating the newborn's blood gas values, laboratory studies such as complete blood count with differential, blood culture, C-reactive protein, calcium and magnesium levels, urine drug screen, and metabolic screening of urine and blood may be useful in finding a cause for respiratory distress.

**Imaging**

Any neonate with respiratory distress should also have a chest radiograph performed. The spectrum of diseases that affect the neonate's chest has significant overlap in their radiographic and clinical appearances; therefore, interpreting the radiologic images with the clinical picture is important. Appropriate shielding is necessary to limit radiation-associated risks. A systematic approach to the evaluation of a chest radiograph should include review of the radiograph to confirm the patient's name and medical record number, laterality side markers, film exposure (quality), rotation, inspiratory effort, and the presence of motion and other artifact. The typical radiograph view obtained is the anterior-posterior (AP) view. A

nasogastric tube should be inserted to confirm esophageal continuity, stomach position, and situs. The utility of obtaining a lateral view chest radiograph has been questioned in the past. Addition of a lateral chest radiograph does not increase the diagnostic efficacy of routine chest films in symptomatic infants. No recent studies investigating the value of the lateral chest radiograph have been conducted. However, each case should be evaluated individually, given that valuable information may be obtained for some infants.

The physician must check the position of any tubes, catheters, and lines. The chest wall (thoracic cavity), bones (clavicles, ribs, scapulae, and vertebrae), airway, and diaphragms should also be assessed. The cardiac and thymic silhouettes often appear to be one, although careful inspection will reveal the borders of each. In a newborn, the thymus is often large, but involution may occur rapidly when an infant is ill. The lung fields should be evaluated for the lung volume and position. The lungs may be hyperinflated, underinflated, opaque, or lucent. Each of these descriptions may suggest an underlying condition that aids in formulating a differential diagnosis. The physician may suspect lung hyperinflation and possibly the presence of a pneumomediastinum in a newborn who exhibits a barrel-shaped chest in the hours after birth, particularly if positive pressure ventilation was required in the delivery room. In sick as well as vigorous neonates, obtaining a completely symmetrical radiograph may be difficult. Radiologic findings may change over the first 24 to 48 hours after birth. Consequently, obtaining additional radiographs may be necessary to evaluate for disease progression or improvement.

Evaluating lung density includes evaluating the lungs for evidence of consolidation or atelectasis/collapse. In instances of lung atelectasis/collapse, tracheal and cardiac deviation to the side of the atelectasis/collapse may be seen. Lucency of the lungs is often the result of air trapping, although it may also signify the presence of air leak into the mediastinum (*sail sign* outlining the right lobe of the thymus), pleural or pericardial spaces, or hemithorax. In cases of massive air leak syndrome, lucencies (dissection of pleural air) may be seen in the neck and peritoneal spaces as well. The heart size, shape, and position and pulmonary circulation should also be assessed. The cardiac silhouette (cardiothoracic ratio) may occupy as much as 65% of the hemithorax during the first days of life. The cardiac apex, aortic notch, and gastric bubble are important orientation features that assist in determining the underlying cause for the newborn's respiratory difficulty. Evaluating the pulmonary circulation is important if congenital heart disease or persistent pulmonary hypertension is suspected. Lucent or dark lung fields suggest diminished pulmonary blood flow caused by anatomic or vascular abnormalities.

The position of the diaphragm is helpful in ascertaining lung volume as well as identifying newborns with diaphragmatic hernias. In the latter instance, the diaphragm will be elevated, and the abdominal contents are visible in the hemithorax. Pulmonary hypoplasia that results from limited thoracic space for lung growth will lead to significant respiratory compromise and distress after birth. A newborn

who sustains damage to the phrenic nerve as a result of birth or surgical injury will exhibit respiratory symptoms and elevation of the diaphragm on the affected side. Elevation of the diaphragm may also be seen in eventration of the diaphragm. A nasogastric or orogastric tube should be placed before obtaining a chest radiograph. The presence of a tracheoesophageal fistula is confirmed by seeing a coiled tube in an upper esophageal pouch. Prenatal diagnosis of congenital lung masses may have included fetal sonography and fetal magnetic resonance imaging (MRI). However, most cases of congenital lung masses will be identified after birth as the newborn exhibits respiratory distress. Sonography, computed tomography (CT), or MRI of the chest is used to help characterize congenital lung lesions and aid in diagnosis. These studies also assist in defining the extent of the lesion and identifying associated anomalies.

### Cardiac Tests

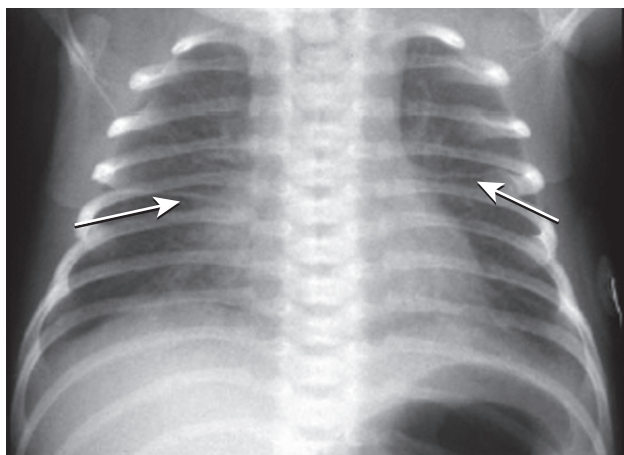
If cardiac disease is suspected, then the physician should obtain an electrocardiogram, 4-limb blood pressures, and preductal and postductal oxygen saturation levels. Echocardiography is the definitive investigation for diagnosing congenital heart disease, if available (see Chapter 101, The Newborn With a Heart Murmur or Cyanosis).

## COMMON CAUSES OF EARLY RESPIRATORY DISTRESS IN THE NEWBORN

### Transient Tachypnea of the Newborn

Transient tachypnea of the newborn (TTN) is a common, relatively benign, self-limited disease diagnosed shortly after birth (Figure 100-2). It is more common in newborns delivered by cesarean section in the absence of labor. Other risk factors include male sex, perinatal asphyxia, history of umbilical cord prolapse, and maternal complications such as asthma, diabetes, and anesthesia or analgesia during labor. Although TTN occurs in preterm infants, it is most common in infants delivered between 37 and 42 weeks' gestation. Complications may occur, such as air leaks, with or without the provision of positive pressure ventilation. Neonates with mild TTN symptoms who transition quickly may be monitored closely in a regular or observation nursery. Newborns who continue to exhibit respiratory distress after a period of transition should be admitted to the NICU for further evaluation, monitoring, and treatment. The pathophysiologic mechanism of TTN involves delayed clearance of fetal lung fluid by the lymphatics and pulmonary circulation with resultant transient pulmonary edema. At birth, the pulmonary epithelium switches from predominantly facilitated  $\text{Cl}^-$  secretion to predominantly active  $\text{Na}^+$  reabsorption with the increased expression of epithelial  $\text{Na}^+$  channels (ENaC). Diminished activity or immaturity of this process may contribute to the development of TTN. Familial clustering of some TTN cases shows a genetic predisposition in the development of this disorder. Antenatal glucocorticoids induce lung  $\text{Na}^+$  reabsorption by increasing the number and activity of





**Figure 100-2** Chest radiograph of neonate with transient tachypnea of the newborn.

channels, even in hypoxia. Because a large release of fetal adrenaline occurs late in labor, stimulating ENaC to start reabsorbing lung fluids, aerolized  $\beta$ -agonists may be used in the treatment. Genetic predisposition for  $\beta$ -adrenergic hyporesponsiveness may cause TTN in the newborn period and asthma or wheezing in older age groups. The clinical findings associated with TTN and treatment strategies are listed in Box 100-3.

### Respiratory Distress Syndrome

Respiratory distress syndrome (RDS) is primarily a disease of preterm infants, although it may affect term neonates, especially infants of diabetic mothers. RDS complicates approximately 1% of pregnancies. The risk for RDS decreases with increasing gestational age: 60% of babies born at fewer than 28 weeks' gestation, 30% of babies born between 28 and 34 weeks' gestation, and fewer than 5% of babies born after 34 weeks' gestation develop RDS.

Late preterm infants born between 34 and 37 weeks' gestation experience a higher risk for respiratory distress after birth than full-term infants because of TTN and RDS.

Other factors that increase the risk for RDS include male sex, maternal gestational diabetes, perinatal asphyxia, hypothermia, multiple gestations, and a family history of a sibling who developed RDS. The disease is more prevalent among white infants. Hemodynamic instability caused by hypothermia or hypoglycemia may worsen preexisting respiratory difficulties. Antenatal steroids and prolonged rupture of membranes decrease the risk for RDS.

### Pathophysiology

Preterm infants have underdeveloped alveolar sacs and experience a delay in production and secretion of functional surfactant. Such surfactant deficiency leads to noncompliant, stiff lungs resulting in the development of atelectasis (alveolar collapse) at the end of expiration with low FRC and lung injury. Lung injury leads to protein exudation and edema, which can

### BOX 100-3 Findings and Treatment of Transient Tachypnea of the Newborn

#### CLINICAL PRESENTATION

- Tachypnea appears shortly after birth and resolves in 1 to 5 days.
- Nasal flaring, grunting, and retractions occur; crackles or rales are heard on auscultation.
- Hypoxemia occurs.
- Chest radiograph hyperinflation, prominent perihilar vascular markings, and fluid may be present in the fissures. Small pleural effusions may also be present (see Figure 100-2).

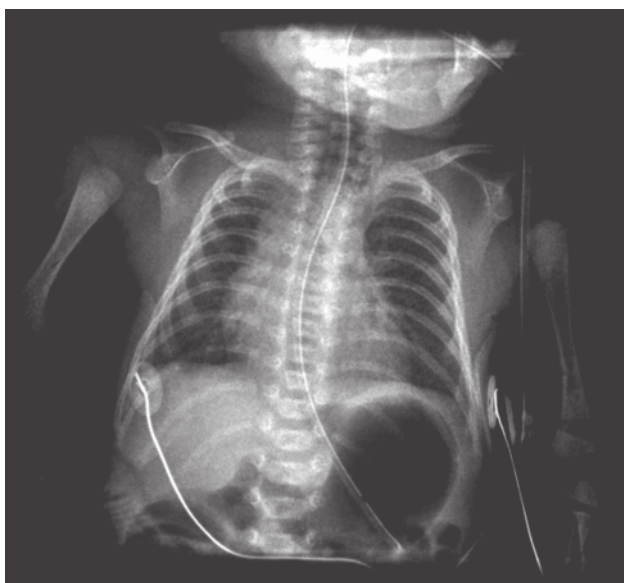
#### TREATMENT

- Most infants with transient tachypnea of the newborn do not require treatment.
- Supplemental oxygen: nasal cannula and continuous positive airway pressure providing 5 to 7 cm water may be useful when fractional inspired oxygen requirements exceed 0.4 to 0.5 (40%–50% oxygen). Mechanical ventilation is rarely required.
- Antibiotics may be considered until sepsis has been excluded.
- Provide intravenous hydration and nutrition.
- Avoid fluid overload.
- Diuretics offer little or no benefit.
- Aerosolized  $\beta$ -agonists may have a role in the treatment.

inactivate surfactant further. The acidosis and hypoxia that result from atelectasis and lung injury further interfere with surfactant production. The combination of these events leads to respiratory failure. Ventilation-perfusion mismatch occurs because of the relatively well-perfused but poorly ventilated areas of the lungs that cause hypoxemia and hypercarbia. Hypoxemia promotes pulmonary vasoconstriction that can trigger persistent pulmonary hypertension. In premature infants, respiratory muscle fatigue and a compliant chest wall further impair alveolar ventilation. Surfactant is a mixture of phospholipids and proteins. The most abundant surface-active phospholipid in mature lungs is phosphatidylcholine. In addition to phospholipids, surfactant contains 4 major proteins: surfactant proteins (SPs) A, B, C, and D. Surfactant protein deficiency occurs in a small group of term infants with severe respiratory distress that leads to intractable respiratory failure and death. SP deficiency type B is the most common form of SP deficiency and occurs as an autosomal recessive trait.

### Clinical Presentation

RDS presents at the time of or soon after birth, and symptoms worsen over time. Clinical symptoms of RDS are the same as those of any other respiratory distress: tachypnea, nasal flaring, chest wall retractions, expiratory grunting, and central cyanosis. In the extremely preterm infant, the only clinical symptom of RDS may



**Figure 100-3** 34-weeks' gestation twin born to a 28-year-old primiparous woman with preeclampsia. Baby had progressive respiratory distress requiring nasal continuous positive airway pressure and oxygen.

be apnea. Some infants who have RDS exhibit all of these symptoms, and others may show none.

The typical chest radiograph shows diffuse atelectasis and the classic reticulogranular ground-glass appearance of the lung fields (Figure 100-3). Air bronchograms, which are air-filled bronchi superimposed on the relatively airless parenchyma of the lung tissue, also are seen commonly on chest radiograph. Importantly, the appearance of group B streptococcal pneumonia on chest radiograph can be identical to that of RDS.

### Prevention and Treatment

For prevention, stabilization strategies, and treatment of RDS, see Box 100-4.

### Long-term Prognosis

Survival of patients with respiratory distress is inversely proportional to the gestational age at birth. Long-term morbidities associated with RDS include bronchopulmonary dysplasia, increased risk for pulmonary infection such as respiratory syncytial virus, and increased incidence of retinopathy of prematurity. The introduction of prenatal steroids for acceleration of lung maturity and the development of exogenous surfactant have improved outcomes and decreased mortality in patients with RDS.

### Meconium Aspiration Syndrome

Meconium aspiration syndrome (MAS) is a respiratory disorder that occurs in a newborn who is born through meconium-stained amniotic fluid and whose symptoms cannot otherwise be explained. MAS occurs most frequently in infants who are term, postterm, or small for gestational age. Meconium-stained amniotic fluid occurs in approximately 13% of

live births, with MAS occurring in 5% to 10% of infants born through meconium-stained amniotic fluid with significant neonatal morbidity and mortality. Neonates born through meconium-stained amniotic fluid may have other causes for respiratory distress such as TTN, delayed transition, infection, persistent pulmonary hypertension, air leak, hypovolemia, pulmonary edema, or aspiration of blood. Up to one-third of these infants exhibit perinatal depression at birth. The incidence of MAS has decreased during the past decade in response to improved intrapartum and and postnatal management in developed countries.

Meconium is composed of water and debris from the intestinal tract, including skin, lanugo, bile pigments, lipids from vernix, amniotic fluid and intestinal secretions, glycoproteins, and mucopolysaccharides. Aspiration of meconium occurs during fetal gasping or with the initial breaths after delivery. Although sterile, when meconium is aspirated into the lung, it triggers an inflammatory response through stimulation of cytokine and vasoactive substance production. Respiratory failure and hypoxia develop as a result of poor lung compliance, increased airway resistance, and smaller tidal volumes. Marked ventilation-perfusion abnormality secondary to airways plugged by meconium also occurs. This condition promotes persistent pulmonary hypertension with right-to-left shunting through the ductus arteriosus or the foramen ovale. Aspirated meconium may cause airway obstruction with air trapping, chemical irritation, pneumonia, and inactivate endogenous surfactant. The pathophysiologic mechanisms related to airway obstruction and pulmonary vascular resistance are understood better than issues related to meconium-induced inflammation and subsequent meconium-induced lung injury.

The diagnosis of MAS is confirmed by radiography (Figure 100-4). Streaky, linear, or patchy infiltrates (densities) are present on the initial chest film, and the lungs may appear hyperinflated. Radiologic changes resolve over a 7- to 10-day period, although the chest radiograph may take weeks to normalize in rare instances. A 10% to 30% risk exists for air leak among newborns with MAS. These newborns may often be in the nursery and become acutely tachypneic or cyanotic. Air leak typically occurs within 72 to 96 hours of birth. Box 100-5 summarizes treatment and prevention strategies. Although depressed infants born through meconium-stained fluid are at risk for developing MAS, there is no evidence that endotracheal suctioning of these infants reduces MAS.

### Pneumonia

Pneumonia may be acquired in utero, during delivery, or postnatally. It is classified as early or late. Causes of neonatal pneumonia depend on whether the infection is acquired before, during, or after birth. An extensive range exists of bacterial, parasitic, and viral organisms that are responsible for infection along the pregnancy continuum and are summarized in Box 100-6. Prenatally, the fetus may be exposed to many different pathogens if a maternal infection is present. In addition, a variety of risk factors can be found related to preexisting maternal infection, premature or prolonged membrane rupture, and signs of fetal

**BOX 100-4 Prevention and Treatment Strategies in Respiratory Distress Syndrome****PREVENTION**

- Preterm babies at risk for respiratory distress syndrome (RDS) should be delivered in centers where appropriate skills are available for stabilization and ongoing respiratory support, including NCPAP, intubation and mechanical ventilation.
- Prenatal administration of a single course of prenatal betamethasone to all women at risk for preterm delivery (between 24 and 34 weeks' gestation) including threatened preterm labor, antepartum hemorrhage, preterm rupture of membranes, or any condition requiring elective preterm delivery. There is continuing controversy over the use of repeated courses of prenatal corticosteroids.
- Prevention of prematurity, prevention of asphyxia, avoiding drug depression during preterm labor, avoidance of maternal fluid overload.

**DELIVERY ROOM STABILIZATION**

- Administration of 100% oxygen may be harmful to preterm infants; uncontrolled tidal volumes, either too large or too small, may also be detrimental to the immature lung.
- Delivery room continuous positive airways pressure (CPAP) has come into widespread use, although it is not clear at present if this will reduce the need for subsequent surfactant treatment or mechanical ventilation. Start resuscitation with CPAP of at least 5 to 6 cm H<sub>2</sub>O via mask or nasal prongs to stabilize the airway and establish functional residual volume. Avoid excessive tidal volumes by incorporating resuscitation devices (T-piece resuscitator) that measure or limit the peak inspiratory pressure because this might reduce the risk for lung injury.
- Intubation should be reserved for babies who have not responded to positive pressure ventilation by mask and those requiring surfactant therapy.
- Pulse oximetry in the immediate newborn period provides useful information on heart rate during resuscitation and may help to avoid hypoxemic peaks. During the transitional phase after birth, saturations should rise gradually from about 60% to 90% over 5 minutes. The lowest concentration of oxygen possible should be used during resuscitation, provided there is an adequate heart rate response (>100 beats/minute) because this reduces cerebral vasoconstriction and may reduce mortality.

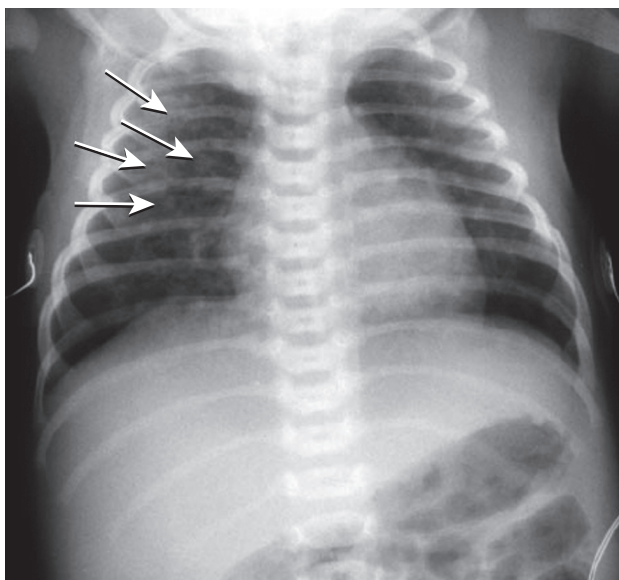
**TREATMENT**

- Multidisciplinary approach applying basic principles of neonatal care, such as thermoregulation, cardiovascular and nutritional support, treatment of early neonatal infection, and prevention of nosocomial infections.
- Provision of respiratory support: mechanical ventilation or nasal CPAP. Mechanical ventilation is harmful to immature lungs and should be avoided if possible. CPAP of at least 5 cm H<sub>2</sub>O pressure reduces the need for reintubation if applied after extubation from mechanical ventilation. CPAP should be initiated in all babies at risk for RDS, such as those <30 weeks' gestation who are not receiving mechanical

ventilation, until their clinical status can be assessed. Avoiding CPAP levels of  $\geq 8$  cm H<sub>2</sub>O reduces the risk for overdistention and air leak. Heated and humidified high-flow nasal cannula has been incorporated in many neonatal intensive care units because of ease of administration and possibly improved patient tolerance. However, randomized controlled trials are not available to guide therapy. Concerns have been raised, especially in preterm infants weighing <1000 g, regarding lack of measurement of delivered pressure and a potential for increased infection. It may be prudent to use the smallest acceptable nasal cannula in smaller infants to allow for leak around the nares. Adequate infection control surveillance programs should be established.

- Surfactant replacement therapy: meta-analysis of various trials in which natural or synthetic surfactant was used, either as a prophylactic or rescue treatment, shows that surfactant improves oxygenation, decreases air leaks, and reduces infant mortality caused by RDS.
- Prophylaxis (within 15 minutes of birth) may be considered in babies <27 weeks' gestation. Prophylactic surfactant for babies >26 weeks' but <30 weeks' gestation if intubation is required in the delivery suite or if the mother has not received prenatal corticosteroids may be considered.
- Prophylactic surfactant has not been found superior to nasal CPAP and early selective surfactant in decreasing the need for mechanical ventilation in the first 5 days of life and the incidence of main morbidities of prematurity in spontaneously breathing very preterm infants on nasal CPAP.
- Combination of early CPAP with early or prophylactic surfactant administration can lead to further therapeutic improvement (intubation surfactant extubation, or INSURE). When possible, duration of mechanical ventilation should be shortened by immediate (or early) extubation to CPAP after surfactant administration provided the baby is otherwise stable.
- Many institutions practice only rescue surfactant therapy. Initial stabilization with CPAP and rescue surfactant administration, if necessary, is not worse than intubation, mechanical ventilation, and surfactant administration immediately after birth.
- Alternative method of administration of surfactant via an endotracheal catheter while a baby is on CPAP has been reported.
- Natural surfactants should be used in preference to synthetic because they reduce pulmonary air leaks and mortality.
- CPAP can be considered as an alternative to intubation and surfactant therapy.
- In babies receiving oxygen, saturation should be maintained at all times between 90% and 95% because this may reduce retinopathy of prematurity and bronchopulmonary dysplasia and reduce mortality.
- Babies with RDS should routinely have blood cultures preformed before starting treatment with intravenous antibiotics.
- The benefits of inhaled nitric oxide in preterm infants for hypoxemic respiratory failure are being investigated at present.





**Figure 100-4** Term newborn with meconium aspiration syndrome. Arrows highlight meconium infiltrates in the lung.

compromise that, singly or in combination, increase the opportunity for a fetus to develop congenital pneumonia (Box 100-7).

Clinical manifestations of pneumonia are similar to other respiratory disorders in the newborn. Signs of respiratory distress may be seen. Fever or other systemic signs may be present. Systemic findings often mirror manifestations seen with sepsis or other severe infections. A variety of chest radiograph findings may be present in a newborn with pneumonia, such as air bronchograms, diffuse parenchymal infiltrates, lobar consolidation, and pleural effusions. Radiographic findings in group B streptococcal pneumonia may be similar to the reticular granular pattern seen in RDS.

Treatment consists of respiratory support, including oxygen and ventilation if necessary. Broad-spectrum antibiotics must be started expeditiously. If an infecting organism is identified, then antibiotic therapy can be adjusted to the specific organism. Failure to consider the diagnosis in the absence of maternal risk factors for infection and failure to initiate neonatal antibiotics in a timely manner may be a medical-legal pitfall.

Blood counts and blood culture should be obtained. Routine culture of spinal fluid is controversial. Endotracheal culture soon after intubation may be useful. Quantitative measurements of C-reactive protein and other acute-phase reactants have limited positive predictive value. Decisions about antimicrobial treatment should not be based on inflammatory markers alone. Neonates should receive adequate nutritional support and hydration.

*Ventilator-associated pneumonia (VAP)* is a significant cause of nosocomial infection in infants with associated high mortality and morbidity. The exact rate of neonatal VAP is difficult to establish, because

radiographic identification of pneumonia is difficult, especially amongst neonates with significant underlying lung disease such as bronchopulmonary dysplasia (BPD) with high incidence of airway bacterial colonization. Surveillance studies of nosocomial infections amongst NICU patients indicate that the VAP represents 6.8% to 32.3% of nosocomial infections in NICU with significant variability amongst various birth-weight and gestational age categories. Ventilator associated pneumonia has assumed significance because of increasing survival of extremely low-birth-weight neonates in the NICU who require prolonged mechanical ventilation. It is a leading cause of death among hospital-acquired infections and prolongs ventilator time and length of stay.

Stringent clinical criteria to define VAP have been developed by the CDC and the National Hospital Safety Network (NHSN). Criteria include mechanical ventilation within 48 hours of onset of suspected VAP; worsening gas exchange with an increase in oxygen or ventilatory requirements; 2 or more chest radiographs that show new infiltrates, consolidation, cavitation, or pneumatoceles; and at least 3 signs and symptoms. Signs and symptoms may include temperature instability, wheezing, tachypnea, cough, abnormal heart rate, change in secretions, or an abnormal leukocyte count. Current CDC definitions of pneumonia for infants younger than 1 year do not address the uniqueness of mechanically ventilated very low-birth-weight infants who seldom develop fever, wheezing, rhonchi, or cough. Furthermore, radiographic changes and the presence of a respiratory pathogen in blood alone as criteria have low specificity, low sensitivity, and low negative predictive value for the definition of pneumonia.

Recently, many institutions have adopted VAP prevention strategies in the form of a “bundle” approach comprising strict hand hygiene, elevating the head of the bed by 15 to 30 degrees, oral care protocol, suctioning the mouth before endotracheal tube insertion, endotracheal tube suctioning when clinically indicated, and draining ventilator circuits before turning the neonate.

### Chronic Lung Disease of Infancy

Chronic lung disease of infancy (CLDI) represents a heterogeneous group of pulmonary disorders originating in the neonatal period.

Chronic lung disease of infancy is a disorder of intrauterine inflammation and atypical (premature) extrauterine lung development characterized by alveolar simplification. Airway and parenchymal inflammation, a hallmark of CLDI, may also develop following pneumonia/sepsis, meconium aspiration, pulmonary hypoplasia, persistent pulmonary hypertension, apnea, tracheoesophageal fistula, congenital diaphragmatic hernia, congenital heart disease, and congenital neuromuscular disorders. Major contributing factors also include the effects of treatment, including mechanical ventilation, barotrauma, and oxygen toxicity. However, a variety of other issues, such as genetic predisposition, perinatal asphyxia, perinatal infection, and inflammation, may



**BOX 100-5 Management Strategies in the Treatment of Meconium Aspiration Syndrome**

Many newborns with meconium aspiration syndrome (MAS) at birth will transition and have no evidence of respiratory distress. Management of most newborns with MAS is supportive. For newborns with signs of respiratory distress after a meconium delivery, admission to the neonatal intensive care unit is necessary.

**RESPIRATORY SUPPORT**

- Oxygen therapy via oxygen hood: maintain oxygen saturation >95% ( $\text{PaO}_2 = 55\text{--}90$  mm Hg).
- CPAP providing at a level of 5 to 6 cm  $\text{H}_2\text{O}$  may be useful when fractional inspired oxygen requirements exceed 0.4 to 0.5 (40%–50% oxygen).
- Assisted ventilation: pH should be maintained above 7.3,  $\text{PaCO}_2$  in the 40 to 50 mm Hg range, and  $\text{PaO}_2$  targeted at 70 to 80 mm Hg. This may be achieved with a moderate peak inflating pressure preferably not exceeding 25 cm  $\text{H}_2\text{O}$ , a relatively rapid ventilator rate (40–60 breaths/minute), a moderate PEEP (4–6 cm  $\text{H}_2\text{O}$ ), and an adequate expiratory time (0.5–0.7 second) to prevent air trapping. This strategy requires a relatively short inspiratory time of 0.3 to 0.4 second. If the diaphragms on chest radiograph are flat and gas trapping is suspected, the expiratory time should be increased to 0.7 to 0.9 second, PEEP decreased to 3 to 4 cm  $\text{H}_2\text{O}$ , and the rate decreased to allow at least a 0.25-second inspiratory time.
- Close monitoring is important because air trapping may result in hyperinflation and air leak (pneumomediastinum, pneumothorax).
- High-frequency ventilation may be used if the newborn is not responding to conventional ventilation.

- Exogenous surfactant and surfactant lavage
- Sedation
- Inhaled nitric oxide to improve oxygenation, especially in patients with persistent pulmonary hypertension of the newborn
- Experimental therapies: phosphodiesterase (PDE) inhibitors (milrinone, dipyridamole, zaprinast, sildenafil), superoxide dismutase, vasoactive intestinal peptide, adrenomedullin, arginine
- Extracorporeal membrane oxygenation
- Antibiotics
- Maintain fluid and electrolyte balance
- Monitor with serial chest radiographs: watch for air trapping, flat diaphragm, and signs of air leak.

**PREVENTION: ROLE OF SUCTIONING**

Intrapartum suctioning: routine intrapartum oronasopharyngeal suctioning before delivery of shoulder in neonates born through MSAF is not recommended.

Tracheal suctioning: One-third of infants born through MSAF will have meconium in their trachea after delivery even with intrapartum suctioning.

Suctioning is not recommended for the vigorous infant born through MSAF because it does not improve outcomes and may cause complications.

Tracheal suctioning should be performed before positive pressure ventilation in infants born through MSAF who are apneic or nonvigorous (depressed), even if previously vigorous.

CPAP, continuous positive airway pressure; MSAF, Meconium stained amniotic fluid;  $\text{PaO}_2$ , arterial pressure of oxygen; PEEP, positive end-expiratory pressure.

**BOX 100-6 Pathogens Causing Pneumonia in Neonates****PRENATAL**

- Adenovirus
- Rubella
- Herpes
- Mumps
- Cytomegalovirus
- *Toxoplasma gondii*
- *Mycobacterium tuberculosis*
- *Listeria monocytogenes*
- Varicella
- HIV

**INTRAPARTUM**

- Group B *Streptococcus* species

- *Escherichia coli*
- *Klebsiella* species
- Syphilis
- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis*—typically does not occur until after 2 weeks of age

**POSTNATAL**

- Various gram-negative and gram-positive bacteria
- Viruses (respiratory syncytial virus, adenovirus, influenza virus, and others)

**BOX 100-7 Prenatal Risk Factors for Congenital Pneumonia**

- Unexplained preterm labor
- Rupture of membranes before onset of labor
- Membrane rupture more than 18 hours before delivery
- Maternal fever ( $>38^\circ\text{C}$  [ $100.4^\circ\text{F}$ ])
- Uterine tenderness
- Foul-smelling amniotic fluid
- Infection of the maternal genitourinary tract
- Recurrent maternal urinary tract infection
- Gestational history of illness consistent with an organism known to have transplacental pathogenic potential
- Nonreassuring fetal well-being test results
- Fetal tachycardia
- Meconium in the amniotic fluid
- Infant with previous neonatal infection

all contribute to the process. Some full-term infants can develop CLDI following mechanical ventilation used to treat other neonatal respiratory conditions. These pathophysiological changes lead to chronic airflow obstruction, increased work of breathing, and airway hyper-reactivity.

### Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia, first described by Northway in 1967, is a form of CLDI that typically develops in very low-birth-weight infants weighing less than 1,500 g, particularly infants born weighing less than 1,000 g. In 2001, a NIH workshop developed a consensus on a definition of BPD based on gestational age at birth, time of assessment, and severity of disease (see Box 100-8). Bronchopulmonary dysplasia evolves after respiratory distress syndrome (RDS), a disorder of surfactant deficiency in preterm infants treated with oxygen and/or mechanical ventilation ("classic" or "old" BPD). Some extremely preterm infants develop lung disease after an initial period without an oxygen or ventilatory requirement. This condition is also referred to as *chronic lung disease of prematurity*. Advances in neonatal care since the early 1990s have contributed to increased survival of extremely preterm, extremely low-birth-weight infants. Systematic use of antenatal corticosteroids to promote lung maturity and postnatal administration surfactant in very preterm infants with RDS and significant respiratory support requirements has resulted in the identification of a different, "new" form of BPD that is associated with a disruption of lung organogenesis, specifically an arrest of alveolar septation and vascular development in the distal lung and impaired pulmonary function during the first years of life. This form of lung disease, "new BPD," has become the most common cause of CLDI. It is not clear if this new BPD represents a single different disease entity in extremely preterm infants with lung injury, or whether it is a group of entities associated with complex epigenetic, environmental (especially antenatal and postnatal infections), inflammatory-mediated dysregulation of lung maturation, or other factors. Table 100-3 compares the findings in "classic" (old) BPD and the "new" BPD. Figure 100-5 is a radiograph of an infant with classic BPD characterized by diffuse cystic changes, hyperinflation and fibrosis. In contrast, Figure 100-6 illustrates the characteristic finding in the extremely preterm infant who has developed BPD. The changes include minimal airway lesions, pulmonary edema, and arrest of alveolarization.

Thus CLDI contributes to childhood, adolescent, and adult chronic lung disease. Neonatologists, pediatricians, and pediatric pulmonary and cardiology specialists are faced with caring for infants with residual complex lung conditions. Improved ventilation management techniques and the use of surfactant, caffeine, and antenatal steroids have improved outcomes for preterm infants greater than 28 weeks' gestation, yet less mature preterm infants born at the late canalicular stage of lung development continue to pose a challenge (See Figure 100-7 for stages of lung development). Many infants with CLDI go on to have long-term respiratory sequelae; however,

### BOX 100-8 NIH Consensus Definition of BPD: Jobe and Bancalari

BPD is defined as the need for supplemental oxygen for at least 28 days after birth, and its severity is graded according to the respiratory support required near term. Grading at 36 weeks post menstrual age for infants born at <32 weeks or at 56 days of life of infants born at ≥32 weeks.

- Mild:  $\text{FiO}_2$  0.21
- Moderate:  $\text{FiO}_2$  0.22–0.29
- Severe:  $\text{FiO}_2$  ≥0.30 or continuous positive airway pressure or mechanical ventilation

prolonged oxygen dependency in the neonatal period does not predict long-term respiratory outcome. Late respiratory symptoms and pulmonary function abnormalities may appear even in patients who did not require prolonged oxygen supplementation as neonates.

### Incidence

The incidence of bronchopulmonary dysplasia varies with gestational age, respiratory disease and illness severity, duration of oxygen and ventilatory support requirement, and the fractional inspired oxygen concentration needed to maintain  $\text{SpO}_2$  >90%. In a study from 2007 by Fanaroff and colleagues, the incidence of BPD when defined as an oxygen requirement at 28 days of age was 42% (BW 501–750 g), 25% (BW 751–1,000 g), 11% (BW 1,001–1,250 g), and 5% (BW 1,251–1,500 g), respectively, for the birth-weight categories noted. The majority of BPD occurs in infants with a birth weight less than 1,250 grams. Application of a definition that assesses the adequacy of oxygenation and ventilation at 36 weeks postmenstrual age and the level of the infant's need for supplemental oxygen and/or ventilatory assistance reduces the incidence by 10%.

### Pathology

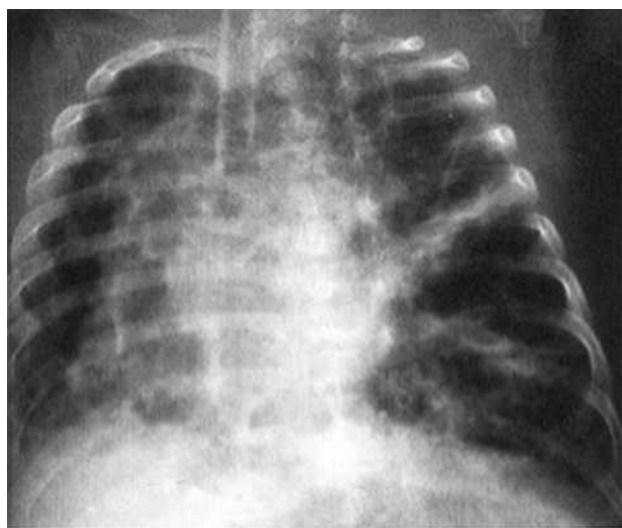
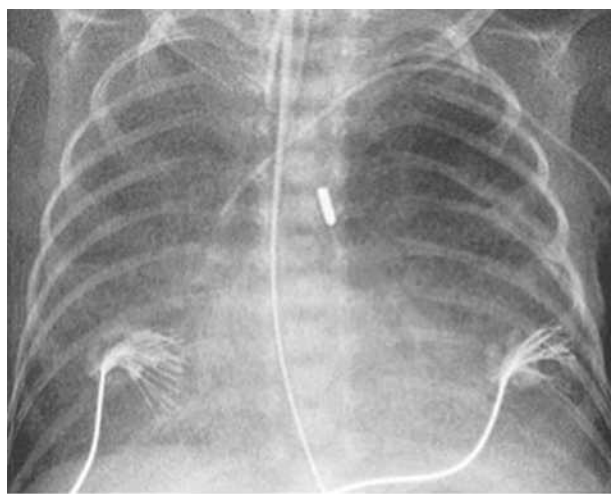
Classic (old) BPD, seen mostly during the 1980s and early 1990s, was characterized by heterogeneous airway injury, smooth-muscle hypertrophy, and areas of parenchymal lung fibrosis alternating with areas with emphysematous changes. Pathologic findings of new BPD in the lung reveal more uniform inflation and less fibrosis with the absence of small and large airway epithelial metaplasia and smooth-muscle hypertrophy compared to classic BPD. The pulmonary vasculature is dysregulated in new BPD; vascular changes observed include marked angiogenesis, abnormal distribution of alveolar capillaries, prominent corner vessels with variable capillary density in adjacent alveoli, and vessels that are more distant from the air surface.

### Pathophysiology

Bronchopulmonary dysplasia has a complex, multifactorial etiology. Depending on the timing, extent, and duration of exposures, different patterns of pulmonary damage may occur (Figure 100-5). Within

**Table 100-3** Comparative Differences Between Classic and New BPD

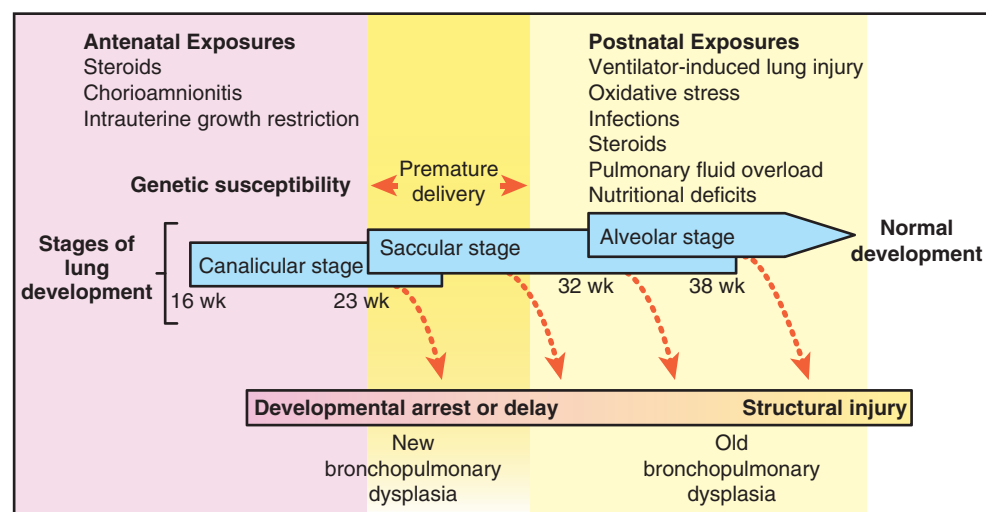
	<b>CLASSIC BPD (Northway 1967)</b>	<b>NEW BPD (90s–current)</b>
Patients	Large preterm	Extremely low birth weight
Prenatal steroids	No	Yes
Surfactant	No	Yes
Initial ventilation	Aggressive, high O <sub>2</sub>	Gentle, low O <sub>2</sub>
<b>EVOLUTION</b>		
	Severe RDS	Mild to moderate RDS
	Severe CLD	Honeymoon period
	Respiratory/heart failure	Worsening: ductus/infection
<b>COMPLICATIONS</b>		
	Ductus arteriosus	Ductus arteriosus
	Infections	Infections
	Air leaks	Apnea, poor respiratory effort
	Cor pulmonale	
<b>RADIOLOGY</b>		
	Severe RDS	Mild RDS
	Condensations (PDA, edema, hemorrhage)	Almost normal/PDA
	Bubble-like	Hazy
	Hyperinflation/fibrosis/CHF	
<b>PATHOLOGY</b>	<b>See Figure 100-5</b>	<b>See Figure 100-6</b>
	Atelectasis, edema, Fibrosis/emphysema	Minimal airway lesions
	Smooth muscle disease	Pulmonary edema
	RVH	Arrest of alveolarization
Incidence	Decreasing	Increasing
Present distribution	<1/4	>3/4
Treatment	Ventilator	Oxygen/CPAP

**Figure 100-5** Radiologic findings in classic BPD.**Figure 100-6** Radiologic findings in new BPD.

1 and 4 days after preterm birth, inflammatory biomarkers (chemokines, adhesion molecules, pro- and anti-inflammatory cytokines, proteases and their inactivated inhibitors, and growth factors) have complex interactions that alter subsequent lung maturation. An imbalance between pro- and anti-inflammatory cytokines released secondary to antenatal and postnatal factors leads to activation of the cellular death

pathways in the lung, which is followed by healing or repair. The latter is characterized by impaired alveolarization and dysregulated angiogenesis, which lead to fewer, larger, more simplified alveoli and a dysmorphic pulmonary vasculature, the pathologic hallmarks of BPD.

Thus, chronic lung disease among very preterm infants is not simply synonymous with ventilator-induced



**Figure 100-7** Stages of lung development and types of injury. (From Baraldi, E, Filippone, M. Chronic lung disease after premature birth. *N Engl J Med.* 2007;357:1946–1955 Copyright © Massachusetts Medical Society. Reprinted with permission.)

damage associated with high concentrations of supplemental oxygen or stretch injury caused by the need for large tidal volumes (or high peak inspiratory pressures), but the final result of a range of complex insults including intrauterine inflammation, postnatal infection, lung immaturity, the effects of the patent ductus arteriosus, resuscitation maneuvers, and ventilator-associated injury. Genetic factors have been implicated in the severity of acute respiratory disease as well as the development of BPD. Additionally, inadequate nutrition is thought to lead to decreased alveolar development, impaired surfactant production, and a catabolic state that inhibits growth and repair of the premature lung. The heterogeneous damage to airways and lungs results in marked ventilation-perfusion (V/Q) mismatch. Lung compliance is reduced secondary to fibrosis and edema. Tracheobronchomalacia and increased airway resistance of both small and larger airways is common. As the course of BPD progresses, initial low lung volumes secondary to atelectasis are often at least partially replaced by hyperinflation from air trapping caused by airway inflammation.

### Management

**IN-HOSPITAL (NICU) CARE.** In-hospital management of infants with BPD requires a coordinated approach that minimizes the duration of mechanical ventilation, using noninvasive respiratory support to avoid ventilator-induced lung injury (barotrauma and volutrauma), which, in turn, reduces the incidence of hyperoxemia and hypocapnea. Careful fluid management and bronchodilator therapy can improve lung function and reduce the need for supplemental oxygen and high ventilator settings, even though it will not change the ultimate course of these infants. A trial of diuretic therapy is often added to the infant's medication regimen although there is limited evidence of efficacy. Among the available interventions, antenatal steroids, caffeine (recently demonstrated to be efficacious in the

prevention of BPD in addition to its known benefit in ameliorating apnea of prematurity, vitamin A (currently in short supply in the United States), and surfactant have the best risk-benefit profile. Postnatal corticosteroids also improve lung function and accelerate weaning from oxygen and mechanical ventilation, but their use during the first weeks of life is associated with worsened neurological outcome. Thus, systemic postnatal corticosteroids should be reserved for use only in ventilated infants who cannot be weaned from the ventilator.

Treatment with diuretics and bronchodilators has been used for symptomatic management of BPD, but the studies have shown that responses to these medications are variable and transient. Use of inhaled steroids has also been evaluated in an effort to gain the benefits of corticosteroids and minimize unacceptable systemic side effects. The trials did not demonstrate significant change on the BPD rate at 28 days of age or at 36 weeks' PMA regardless of whether the therapy was given early (<7 days) or late (>7 days). Adequate nutrition plays an important role in lung injury protection and recovery. Infants with severe BPD often develop pulmonary hypertension (PH) and should be evaluated periodically for PH as this significantly increases the risk of late and postdischarge mortality; these infants may benefit from the use of pulmonary vasodilators. Use of inhaled nitric oxide for prevention of CLD of infancy has not been validated in clinical trials. Recent insights into stem cell biology have revealed the therapeutic potential of these cells to repair damaged organs, including the lungs. In combination with strategies that already exist, cell-based therapies may allow improvements in survival with very limited disability.

**POST-DISCHARGE CARE.** Outpatient management must be carefully planned, coordinated, and carried out by experienced multidisciplinary teams. Social and financial issues must be addressed with the family



and caregivers. Maintenance of oxygenation and proper nutritional support are critical aspects in the postdischarge management of these infants. Home oxygen and mechanical ventilation therapy are used commonly after discharge and require specialized staff and equipment. The AAP Committee on Fetus and Newborn report on Hospital Discharge of the High-Risk Neonate provides guidance about discharge planning and follow-up care needs. Up to two-thirds of infants with BPD continue to have growth failure after discharge. Among the explanations for this observation are the infant's poor ability to feed orally, the occurrence of gagging, choking, and vomiting, gastroesophageal reflux, and other issues related to oromotor coordination. Increased metabolic demands can also cause growth failure. Metabolic bone disease, ranging from osteopenia to nutritional rickets, results from chronic or prolonged diuretic use. In addition, these infants are at higher risk for nephrocalcinosis and abnormal dentition, with tooth enamel hypoplasia also the result of prolonged diuretic therapy and inadequate mineral intake.

The respiratory syncytial virus (RSV) prophylaxis is recommended for all children less than 2 years of age who have required medical therapy of any chronic lung disease within 6 months prior to the start of RSV season. Preterm infants, especially those with BPD, are at increased risk for significant morbidity and mortality from influenza virus infection. Administration of influenza vaccine to all caregivers and to the infant after 6 months of age is recommended. Avoidance of second hand smoke should be explained to the parents. Infants with BPD have higher rates of rehospitalization (up to 50%) in the first year of life. Respiratory symptoms in patients with BPD may persist beyond the first 2 years of life into the preschool years, adolescence, and early adulthood. Although preterm infants have an increased risk of neurodevelopmental impairment, BPD is an additional risk factor. Readers are also referred to the guideline issued by American Thoracic Society on the Care of the Child with Chronic Lung Disease of Infancy and Childhood.

Most preterm neonates experience a relatively benign respiratory course, but in some patients the disease progressively worsens and culminates in severe respiratory failure, pulmonary hypertension, and in some cases right heart failure. Further intensive care may prolong a distressing death rather than offer any hope of survival. An end-of-life decision may be made after discussions with parents. Assisted ventilation may be withdrawn, or care redirected to withhold further episodes of assisted ventilation.

## APNEA IN NEWBORNS

### *Definition and Fundamentals*

Apnea may occur in all infants and is considered normal if it occurs infrequently, is brief, and is not associated with any underlying conditions or other signs.

Apnea of prematurity (AOP) is a significant clinical problem manifested by an unstable respiratory rhythm reflecting the immaturity of respiratory control systems. It is defined as cessation of breathing

that lasts for at least 20 seconds. All apneic episodes are not associated with cessation of breathing, and some of these episodes occur in the presence of breathing efforts but are associated with airway obstruction and cessation of airflow. On the basis of respiratory efforts and airflow, apnea has been classified as central, obstructive, or mixed. Mixed apnea constitutes most apneic episodes. Definitions of terminology are found in Box 100-9. Gastroesophageal reflux (GER) has been implicated as a cause of apnea in premature infants for decades. Yet, there has been no compelling evidence supporting a causal relationship between them. Further, antireflux medications do not reduce bradycardia episodes in preterm infants with GER. The triad of apnea, bradycardia, and oxygen desaturation occurs frequently in NICUs. Prolonged apnea may occur as a nonspecific sign of illness in both full-term and premature infants. Box 100-10 lists common conditions associated with apnea in neonates. (See also Chapter 337, Sudden Unexpected Infant Death, and Chapter 217, Apparent Life-Threatening Events.)

### *Pathophysiology*

The neuronal mechanisms leading to apnea are still not well understood. Neonatal respiratory rhythm generation is modulated by afferent signals and is the result of integration of signals from peripheral and central chemoreceptors, airway afferents, and state-dependent controls. Ventilatory responses to hypoxia and hypercarbia are impaired, and inhibitory reflexes are exaggerated in the neonate. These unique characteristics predispose the neonate to the development of apnea.

### *Evaluation*

Evaluation of the neonate who exhibits apnea is warranted if apnea develops within 24 hours of birth; if the infant is born after 36 weeks' gestation or requires vigorous resuscitation; if the episode is preceded by or associated with marked cyanosis, pallor, or change in muscle tone; or if the episodes become more frequent and increase in severity. The specific diagnostic tests are chosen based on the newborn's gestational and postmenstrual age, presenting symptoms and physical examination, underlying medical problems, and extent of resuscitation or intervention required to stabilize the newborn. Typical testing of a symptomatic neonate with unexplained apnea, bradycardia, or cyanosis includes a complete blood count, glucose and electrolyte determinations, sepsis evaluation (blood, urine, and cerebral spinal fluid cultures), and continuous multichannel recording with esophageal pH monitoring. A thorough review of the maternal history for evidence of medication use that can induce fetal CNS and respiratory depression (over-the-counter products [including herbal agents], illicit drugs, or prescribed medications and labor pain relief) is necessary. Consideration should also be given to sending a sample of the newborn's urine for toxicologic testing for drugs of abuse based on the newborn's signs and clinical history. (See Chapter 104, Prenatal Drug Use: Neonatal Effects and the Drug Withdrawal Syndrome.) If seizures or other CNS abnormalities are suspected, then the newborn should undergo a

**BOX 100-9 Apnea Terminology**

- *Pathological apnea* is apnea exceeding 20 seconds' duration or apnea of shorter than 20 seconds' duration accompanied by bradycardia, pallor, cyanosis, hypotonia, or oxygen desaturation. Apnea is classified as *central*, *obstructive*, or *mixed*.
  - *Central apnea* is the cessation of both airflow and respiratory effort.
  - *Obstructive apnea* is the cessation of airflow in the presence of continued respiratory effort.
  - *Mixed apnea* contains elements of both central and obstructive apnea, either within the same apneic pause or at different times during a period of respiratory recording. It may start as an obstructive apnea but is followed by central apnea.
- *Periodic breathing* is a respiratory pattern characterized by 3 or more consecutive respiratory pauses that are greater than 3 but less than 20 seconds in duration separated by less than 20 seconds of breathing between each pause. Periodic breathing is centrally mediated as a result of immaturity of the central nervous system respiratory control center.
- *Apnea of prematurity* usually begins after the first day of life and resolves when the infant reaches 37 weeks' postmenstrual age. AOP may occasionally persist to 44 to 48 weeks' postmenstrual age. It is defined as cessation of breathing that lasts for at least 20 seconds.
- *Apnea of immaturity* occurs in infants who are more than 37 weeks' gestation. No specific cause is identified in these infants.
- *Apparent life-threatening event* refers to an event that is characterized by some combination of apnea, color change (pallor, cyanosis), choking, or gagging and marked change in muscle tone (limp or hypotonic or arching or hypertonic).

**BOX 100-10 Common Conditions Associated With Apnea in Neonates****ACUTE CONDITIONS**

- Airway obstruction
- Neck flexion
- Laryngospasm
- Structural abnormality—glossoptosis, laryngomalacia, tracheomalacia
- Central nervous system disorders
- Intracranial hemorrhage
- Seizures
- Hypoxic ischemic injury
- Congenital malformations of the brain—Arnold-Chiari malformation
- Drugs administered to the mother or to the baby
  - Narcotics or central nervous system depressants
  - Prostaglandin E<sub>1</sub>—used to maintain patency of the ductus arteriosus in infants with suspected duct-dependent congenital heart disease
- Infection
  - Sepsis, meningitis, necrotizing enterocolitis
  - Respiratory syncytial virus infection, pertussis, infantile botulism

- Impaired oxygenation, hypoxemia, severe anemia, and shock or marked systemic-to-pulmonary circulatory shunt (eg, patent ductus arteriosus)
- Metabolic disorders
  - Hypoglycemia
  - Hypercalcemia
  - Hyponatremia, hypernatremia
  - Hyperammonemia—inborn errors of metabolism
  - Postoperative status following general anesthesia
  - Thermal instability (ie, rapid increase or decrease of temperature)

**CHRONIC CONDITIONS**

- Chronic lung disease
- Congenital central hypoventilation syndrome (formerly known as *Ondine curse*)
- Gastroesophageal reflux disease
- Marked anemia

Adapted from Spitzer A. Apnea syndromes. In: Donn SM, Sinha SK (eds). *Manual of Neonatal Respiratory Care*. 2nd ed. St Louis, MO: Mosby; 2006.

cranial ultrasound and MRI of the brain as well as have an electroencephalogram performed. If a dysrhythmia is suspected, then the newborn will require chest radiograph, electrocardiographic, and Holter monitoring studies. The newborn with a choking episode will benefit from evaluation of the airway and feeding skills by a speech pathologist and ENT specialist and evaluation for the presence of symptomatic gastroesophageal reflux disease. Subspecialist consultations may include cardiology, neurology, pulmonary, or other specialists

as needed based on the newborn's clinical condition. In cases in which apnea remains unexplained, infant polysomnography, if available, can be useful in helping to determine etiology and management.

**Management**

The initial nursery management of the neonate with apnea will include specific therapies needed to reestablish adequate oxygenation and ventilation as well as cardiac and hemodynamic stability. Treatment may

range from simple tactile stimulation and supplemental oxygen to intubation and assisted ventilation. Pharmacologic therapy will be based on the assessment of the condition causing the apnea and may include methylxanthines, antiepileptic drugs, or medications for correcting metabolic abnormalities. CPAP is an effective nonpharmacologic therapy.

See Chapter 337, Sudden Unexpected Infant Death, for treatment guidance, including indications for methylxanthines therapy and home monitoring.

## OTHER CAUSES OF RESPIRATORY DISTRESS IN NEWBORNS

### Pulmonary Air Leak Syndrome: Pneumomediastinum and Pneumothorax

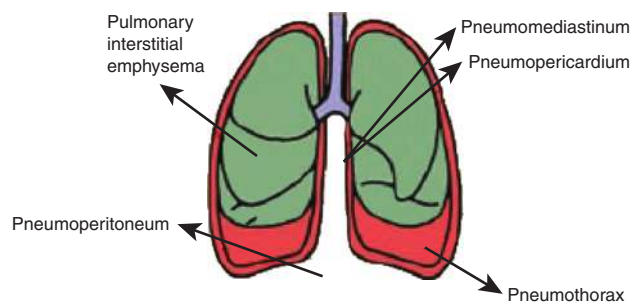
Pulmonary air leak is caused by alveolar rupture with leakage of air into extra-alveolar spaces within the lung. Air leaks occur more commonly during the newborn period than at other times in life. Forms of air leak include pneumothorax, pneumomediastinum, pulmonary interstitial emphysema, pneumopericardium, and, less frequently, pneumoperitoneum and subcutaneous emphysema. Figure 100-8 depicts various forms of air leak.

#### Pneumothorax

Pneumothorax is one form of air leak syndrome that may occur in neonates either iatrogenically or spontaneously. Pneumothoraces may remain undetected in asymptomatic neonates or may cause respiratory distress. Several factors may cause a pneumothorax, including overly vigorous stimulation and resuscitation at birth, RDS, MAS, pneumonia, pulmonary hypoplasia, and assisted ventilation (CPAP and positive pressure ventilation). Generalized air trapping or uneven ventilation leads to overdistention of the lung and predisposes the infant to alveolar rupture with dissection of air along the perivascular or peribronchial tissue toward the hilum, producing a pneumomediastinum, or into the pleura, thereby causing a pneumothorax. Figure 100-5 depicts the forms of air leak.

The incidence of spontaneous pneumothorax varies from 0.3% to 1.3% based on clinical symptoms or radiographic findings. A spontaneous pneumothorax may result from rupture of alveoli secondary to high inspiratory pressures needed to expand uninflated lungs. The incidence of air leak is higher among all gestational age groups of premature infants as a result of their increased risk for lung disease and need for resuscitation and assisted ventilation.

A newborn who develops a pneumothorax may exhibit signs such as tachypnea, grunting, pallor, or cyanosis. Physical examination may reveal chest asymmetry with enlargement on the affected side, decreased breath sounds on the side with the pneumothorax, and a shift of the maximal cardiac impulse away from the affected side. A newborn who develops a tension pneumothorax may deteriorate rapidly, exhibiting bradycardia, hypotension, and hypoxemia caused by decreased venous return to the heart, thereby causing a drop in cardiac output. If a pneumothorax is suspected, then transillumination of the



**Figure 100-8** Air leak syndrome. (From Aly H. *Respiratory disorders in the newborn: identification and diagnosis*. *Pediatr Rev.* 2004;25(6):201–208.)

chest is a useful technique for immediate diagnosis. Neonates diagnosed with an air leak, whether a pneumothorax or pneumomediastinum, should be admitted to the NICU for further monitoring and treatment.

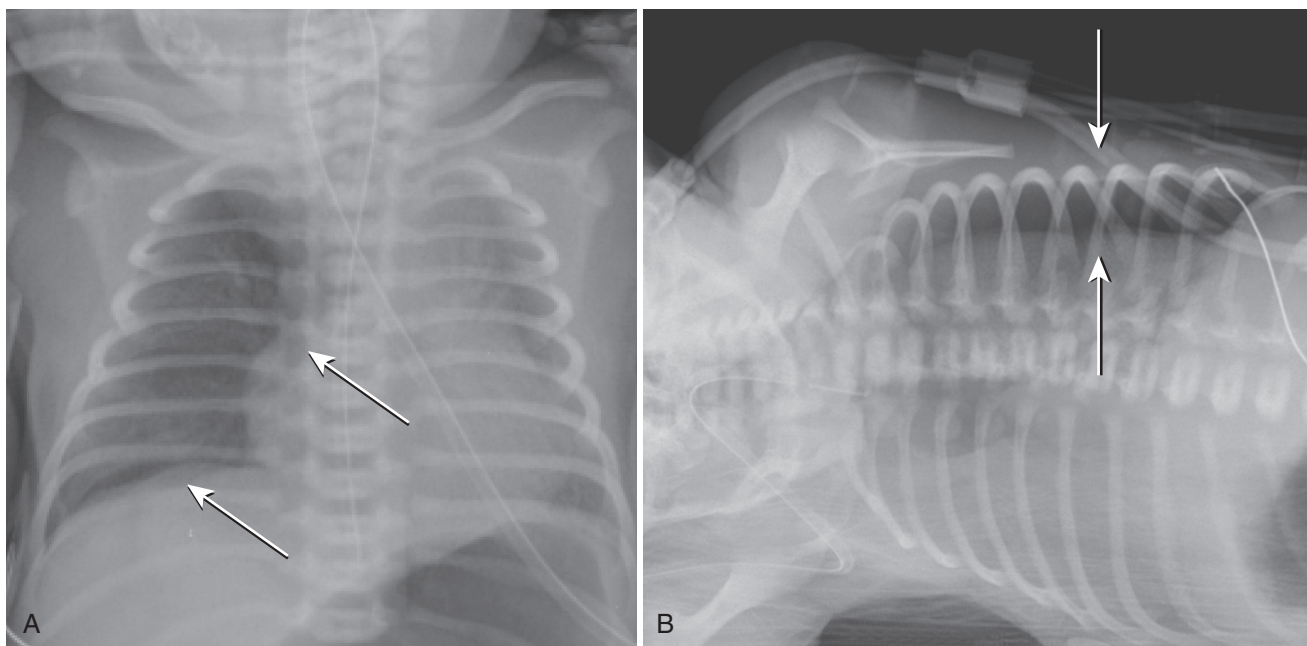
#### Pneumomediastinum

Although most newborns with a pneumomediastinum are not symptomatic, newborns with larger collections of mediastinal air exhibit tachypnea and cyanosis. The heart sounds may sound distant on auscultation. A chest radiograph will confirm the presence of a pneumothorax and other forms of air leak (Figure 100-9 and Figure 100-10). If the infant is stable, without signs of respiratory distress or a continuous air leak, and the pneumothorax is isolated and small, then the infant can be monitored closely without specific intervention. Administration of 100% oxygen to a term or late preterm infant with an air leak accelerates the resolution of pneumothorax. Oxygen should be administered for 8 to 12 hours and the chest radiograph repeated after oxygen therapy. Most infants can be managed conservatively. Thoracentesis is necessary when the infant has a tension pneumothorax or requires ventilation. A thoracostomy, or chest tube, is placed into the anterior pleural space and connected to an underwater seal with continuous-suction pressure of 10 to 15 cm H<sub>2</sub>O. The chest tube remains in place until the air leak has resolved.

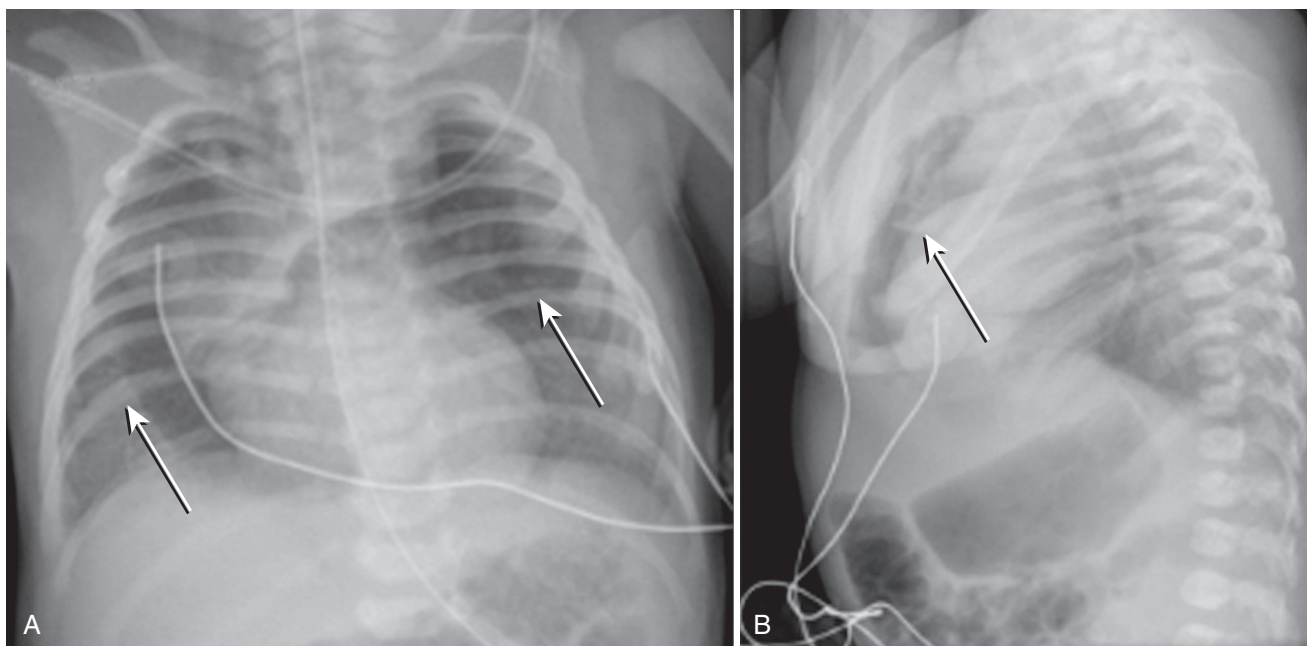
## DISORDERS OF LUNG DEVELOPMENT

Congenital errors in lymphatic development are a group of rare conditions that result in primary pulmonary lymphatic disorders and are often misdiagnosed. The constellation of conditions includes lymphangiomas, lymphangiectasis, lymphangiomatosis, and lymphatic dysplasia syndrome. Pulmonary lymphangiectasia is caused by pathologic dilation of the lymphatics and has primary and secondary forms. The primary, or congenital, form occurs in neonates, is typically fatal, and is presumed to result from failure of the pulmonary interstitial tissue to regress. This form results in dilation of the lymphatic capillaries in the developing lung. Secondary lymphangiectasia in neonates is a complication that may occur after surgery, infection, or trauma. Infants with total anomalous pulmonary venous return or hypoplastic





**Figure 100-9** Anterior-posterior and lateral chest radiograph: full-term newborn with respiratory distress caused by right-sided pneumothorax. Note the flattening of the diaphragm and shift of the cardiothymic silhouette into the left hemithorax.



**Figure 100-10** Full-term infant with large pneumomediastinum: characteristic halo around the heart with lifting of the right lobe of the thymus on the anterior-posterior view and lucency in the mediastinal space on the lateral film.

left heart syndrome may develop dilated lymphatics as a result of increased lymphatic circulation.

### Lymphatic Dysplasia Syndrome

Lymphatic dysplasia syndrome is a heterogeneous group of disorders that includes idiopathic or primary lymphedema and congenital chylothorax. The neonatal form of primary lymphedema is termed *lymphedema congenita*.

Abnormal lymphatic development is associated with genetic disorders and variable inheritance patterns. Most chylous effusions in neonates are congenital.

Treatment is determined by the underlying condition. Congenital lymphangiomas do not resolve spontaneously and require resection or sclerosis. Congenital chylothorax and lymphangiectasis are treated with a combination of a high-protein, low-fat



diet that provides medium-chain triglycerides as the fat source. Portagen is the usual infant formula used for infant nutrition. Supplemental vitamins are also needed. Large pleural effusions need drainage and may require chest tube placement, if persistent.

### **Congenital Diaphragmatic Hernia**

Congenital diaphragmatic hernia (CDH) is a developmental abnormality of the diaphragm that allows abdominal organs to herniate into the chest. CDH occurs in 1 in 2,000 to 4,000 live births and has a male predominance among affected infants. Newborn infants typically show signs of respiratory distress in the delivery room or during the first hours of life. The degree of respiratory distress will vary with the severity of the defect and degree of pulmonary compromise as a result of lung hypoplasia. The most common defect responsible for development of CDH is failure of the posterior growth of the diaphragm at the left Bochdalek foramen. This defect occurs at approximately 8 weeks' gestation during embryogenesis. The extent of abdominal organ herniation into the chest will influence the severity of lung hypoplasia and severity of infant symptoms. Lung hypoplasia is most severe on the side with the hernia, but it may also involve the contralateral side. Although most CDH involves the left-sided diaphragm, right-sided lesions occur in approximately 11% of affected infants. Right-sided lesions tend to be less severe, given that the liver prevents the other abdominal organs from migrating into the chest. Bilateral diaphragm involvement occurs infrequently (2% of patients with CDH). Pulmonary hypoplasia predisposes infants born with CDH to the development of persistent pulmonary hypertension and respiratory failure.

Physical examination is notable for a barrel-shaped chest with a scaphoid abdomen. Breath sounds are absent on the affected side, and the heartbeat is displaced to the right as a result of mediastinal shift to the right. Fifty percent of infants with CDH have associated anomalies, including chromosomal abnormalities, congenital heart disease, and neural tube defects. Many infants with CDH are diagnosed prenatally. (See Chapter 82, Prenatal Diagnosis, and Chapter 83, Fetal Interventions.) Among cases that have not been diagnosed through prenatal ultrasonography, the diagnosis is confirmed by chest radiograph. Characteristic findings include herniation of the abdominal contents (intestine, liver, and spleen) into the chest. The heart and mediastinum are displaced, and the involved lung appears small.

Initial treatment involves stabilization of respiration with support for hemodynamic and cardiac function as needed. Neonates with a prenatal diagnosis of CDH should be immediately intubated (see Chapter 108, Surgical Emergencies of the Chest and Abdomen in the Newborn). Low-volume ventilation strategies using higher ventilation rates are used to minimize lung injury. The PaO<sub>2</sub> should be maintained above 55 mm Hg (oxygen saturation >90%), and mean arterial blood pressure should be above 50 mm Hg to reduce right-to-left shunting that will promote pulmonary hypertension. A nasogastric tube should also be placed expeditiously to reduce intestinal distention

because this will further compromise respiratory function. Maintaining adequate oxygenation, blood pressure, and acid-base status are critical steps in the early care of infants with CDH. Adjunctive therapies used with surgical repair include high-frequency ventilation, inhaled nitric oxide, and ECMO. Before initiating ECMO, infants require a full evaluation that includes echocardiography, cranial and renal sonography, and an electroencephalogram. Eligibility criteria for ECMO therapy require an infant to be older than 34 weeks' gestation with a weight above 2,000 g. Infants cannot have more than a grade 1 intraventricular hemorrhage or any congenital or chromosomal anomalies. Survival rates among neonates deemed surgical candidates are 60% to 80% (see Chapter 116, Health and Developmental Outcomes of Selected Medically Complex Neonates).

Other developmental lung anomaly lesions should also be considered when a CDH is suspected prenatally. These congenital lung masses, often identified as echogenic structures on prenatal sonography, are congenital pulmonary airway malformation (CPAM), congenital lobar emphysema (CLE), pulmonary sequestrations, and bronchogenic cysts.

### **Congenital Pulmonary Airway Malformation**

Congenital pulmonary airway malformation is a rare anomaly that is estimated to occur at a rate of 1 in 25,000 to 35,000 pregnancies involving abnormal lung branching. The resulting hamartomas are composed of cystic and adenomatous overgrowth of the terminal bronchioles. CPAMs typically connect to the tracheobronchial tree and may be found in any lobe of either lung. The connecting bronchi are typically abnormal. Four types of CPAM have been identified, and these are classified depending on the affected area of the tracheobronchial tree and the stage of lung development when the abnormality occurs. The occurrence of CPAM is sporadic, has no racial preference, and affects male and female infants equally. Hydrops may occur in up to 40% of infants with a CPAM. Serial prenatal sonography has shown that nearly 60% of CPAMs will regress over the period of gestation (see Chapter 108, Surgical Emergencies of the Chest and Abdomen in the Newborn).

Approximately two-thirds of neonates with a CPAM will present at birth with tachypnea, grunting, retractions, cyanosis, and increased respiratory effort. The severity of the symptoms correlates with the lesion's size. The prognosis depends on the type of CPAM. Most CPAMs that occur in the neonatal period are type 1. Type 2 lesions also occur in the neonatal period but are associated with other congenital anomalies in 60% of affected infants. Type 3 CPAM is the most severe, with resultant fetal hydrops, pulmonary hypoplasia, and high mortality rate. Treatment involves resection of the CPAM postnatally.

### **Congenital Lobar Emphysema**

Congenital lobar emphysema (CLE) is typically diagnosed after birth and is characterized by air trapping with progressive hyperinflation of lobar segments of the lungs that leads to airway obstruction. It is a rare malformation that seems to have a male predominance

and commonly involves the left upper lobe. The reported prevalence rate is 1 in 20,000 to 30,000 births. Causes can include extrinsic or intrinsic bronchial cartilage deficiencies or dysfunction, as well as abnormal mucosal folds contributing to obstruction, although in the majority of cases, no abnormalities are found. Anomalous cardiopulmonary vascularities such as PDA, pulmonary artery sling, and anomalous pulmonary venous return, or more rarely bronchogenic cysts, esophageal duplication cysts, teratoma, neuroblastoma, and mediastinal cysts, have been described as causes of extrinsic obstruction. Most infants with CLE have symptoms by 6 months of age. Up to one-third of affected infants exhibit symptoms at birth, and 50% have symptoms by 1 month of age. Respiratory distress may be mild or rapidly progressive.

Physical examination is notable for tachypnea, increased work of breathing, and wheezing. Breath sounds over the involved lobe of the lung are diminished with hyperresonance on chest percussion. If mediastinal shift is present, then the cardiac impulse may be displaced. Some infants will have associated congenital anomalies affecting the heart, kidneys, gastrointestinal tract, musculoskeletal system, and skin. Difficulty with weight gain caused by poor feeding and recurrent pneumonias may comprise the presenting symptoms in the infant with a milder form of CLE. Diagnostic imaging includes chest radiography and CT or MRI. On chest radiograph, the affected lobe may appear either consolidated or hyperinflated depending on the degree of lobar expansion. Additional findings include mediastinal shift with compression and atelectasis of the contralateral lung. CT scanning may be helpful in identifying the diagnosis in infants with persistent respiratory distress and is also useful in the postnatal assessment of the neonate with a prenatal sonographic finding of a pulmonary lesion. Included in the differential diagnosis of infants with CLE are pneumothorax, isolated pulmonary interstitial emphysema, CPAM, CDH, pulmonary sequestration, and bronchogenic cysts. Treatment in infants who have symptoms is resection of the affected lobe.

### Bronchopulmonary Sequestrations

Bronchopulmonary sequestrations are lobar sequestrations of abnormal, nonfunctioning lung tissue found in the lower respiratory tract. Extremely rare, sequestrations do not connect to the tracheobronchial tree, and they derive their blood flow from the systemic circulation, usually through a blood vessel originating from the aorta. Sequestrations are composed of normal lung tissue that contains both airway and alveolar elements. Sequestrations are of 2 types. Intralobar sequestrations are localized within a normal lobe of the lung but without separate pleura. They are typically located in a lower lobe and are slightly more common on the left side. Intralobar sequestrations are more common than the extralobar form of sequestration. Extralobar sequestrations are composed of lung tissue encased in its own pleura that is located outside the normal lung lobe. Lesions are more likely to be found on the left side, often located between the lower lobe and diaphragm. Male infants seem to be affected more often than female infants, and 2 out of 3 infants have associated

anomalies (CDH, pericardial defects, and anomalous pulmonary venous return). A gene has been identified that is necessary for normal airway development and branching (homeobox protein HOXB-5).

Respiratory symptoms at birth are variable and are related to the lesion's location, size, and type. Lesions may be identified on prenatal sonography. Most lesions regress over the course of gestation. If vascular compression develops because of a large lesion, then hydrops may develop. Extralobar sequestrations tend to present earlier than intralobar lesions. Chest radiographs show a sequestration as a dense mass in the thoracic cavity or lung parenchyma. Sonography will also demonstrate an echogenic homogeneous mass. CT and MRI characterize associated abnormalities and identify the aberrant arterial and venous blood supply to the sequestered lobe. Treatment involves immediate surgical resection in symptomatic infants.

Overall, disorders of lung development, particularly cystic lung masses, have a favorable prognosis among infants who do not have severe respiratory distress or hydrops. The generalized use of prenatal sonography has led to earlier and more frequent diagnosis of suspected fetal anomalies. Questions arise as to the need for postnatal evaluation of pulmonary lesions that appear to be regressing on serial fetal sonography. In addition, investigators have reported continued postnatal regression of congenital lung lesions. The current consensus is that prenatal ultrasonography is limited in its ability to assess fully echogenic lesions and that apparent involution of these lesions on prenatal sonography and postnatal chest radiography may miss residual lung lesions. Therefore, in the postnatal period, early evaluation is warranted.

### Tracheoesophageal Fistula and Esophageal Atresia

Esophageal atresia and tracheoesophageal fistula (discussed in Chapter 83, Fetal Interventions; and Chapter 108, Surgical Emergencies of the Chest and Abdomen in the Newborn) may occur as separate lesions but more often occur together. The classification is based on anatomy as well as certain features that are therapeutically important. Important features are the presence or absence of a fistula and the location of the fistula. The most common type (85%) consists of an upper esophageal segment that ends in a blind pouch, with the lower esophageal segment is connected to the trachea by a fistulous tract. The anomaly should be suspected in the presence of maternal polyhydramnios, excessive oral secretions, and choking, coughing, and cyanosis after the first feeding. Associated malformations such as cardiovascular abnormalities, imperforate anus, intestinal malrotation, and duodenal anomalies may occur. An association among vertebral anomalies, anal atresia, tracheoesophageal fistula, and radial limb dysplasia is also known as *VATER syndrome*. The diagnosis is confirmed by radiopaque catheter and observing coiling in the esophageal pouch on radiographic examination. The surgical correction is undertaken when the infant is stable. Complications include dysfunction of the esophageal motility, gastroesophageal reflux, chronic cough, wheezing, and recurrent pneumonia.

### Interstitial Lung Disease Unique to Infancy

Interstitial Lung Disease (ILD) in infants and young children is caused by a heterogeneous group of conditions characterized by impaired gas exchange and diffuse pulmonary infiltrates on chest imaging. Diffuse lung disease (DLD) can be caused by numerous diseases, including cystic fibrosis, congenital or acquired immunodeficiency, congenital heart disease, bronchopulmonary dysplasia (BPD), pulmonary infection, primary ciliary dyskinesia presenting with newborn respiratory distress, and recurrent aspiration. For neonates and infants younger than 2 years of age with the appearance of DLD on chest imaging, these causes should first be excluded as the primary diagnosis. Following this, the neonate or infant may be regarded as having ILD in the presence of at least 3 of the following: respiratory symptoms (cough, exercise intolerance, rapid breathing, difficult breathing); respiratory signs (adventitious breath sounds, clubbing of the fingers or toes, tachypnea, retractions, failure to thrive, respiratory failure); hypoxemia; chest radiograph or computed tomography (CT) scan showing diffuse abnormalities. A classification scheme that has evolved over the last decade distinguishes the causes of ILD in children (and especially infants) from the conditions that cause ILD in adults and adolescents. Categories primarily prevalent in infancy include diffuse developmental disorders of lung development, growth abnormalities reflecting deficient alveolarization, specific primary ILDs of undefined etiology (neuroendocrine cell hyperplasia of infancy, pulmonary interstitial glycogenosis) and disorders affecting surfactant protein metabolism (surfactant protein B, C, and ABCA3 mutations). The most common clinical signs among affected infants are hypoxia, tachypnea and retractions, as well as abnormal lung examination (crackles) and cough. Commonly associated abnormalities include gastroesophageal reflux, pulmonary hypertension, and failure to thrive. Expansive discussion of the spectrum of disorders that cause DLD and ILD in neonates is beyond the scope of this chapter. The discussion that follows will highlight the more common conditions responsible for DLD and ILD in neonates.

Rarely, one may encounter neonates or infants with persistent respiratory distress, and it is important to be aware of a broad group of disorders of childhood interstitial lung diseases. These include persistent tachypnea of infancy or neuroendocrine cell hyperplasia of infancy, alveolar capillary dysplasia associated with misalignment of pulmonary veins (ACD/MPV), pulmonary interstitial glycogenosis, and genetic abnormalities of surfactant function. Disorders in this category arise early in lung development and are diagnosed from lung biopsy or postmortem tissue based on histologic criteria.

Most childhood interstitial lung diseases share structural remodeling of the distal air spaces leading to impaired gas exchange.

Molecular defects are being increasingly identified. Whether mutations cause a fundamental derangement (eg, lack of surfactant protein), induce cellular stress (protein misfolding), or affect response to an environmental agent (disordered innate immunity) is likely to affect the age at presentation. Many

genetic syndromes identified in the past decade include deletions of or mutations in genes encoding proteins important in surfactant production and function (SP-B, SP-C, and ABCA3) or surfactant catabolism (GM-CSF receptor), as well as transcription factors important for surfactant production (TTF1) or lung development (Fox F1), with heterozygous deletions or loss-of-function mutations of the latter resulting in alveolar capillary dysplasia (ACD) with misalignment of the pulmonary veins.

Hereditary SP-B deficiency is usually a severe, rapidly progressive respiratory disease in newborns, often fatal by 3 to 6 months of age. The 10% to 15% of affected patients develop respiratory symptoms within the first month of life, whereas 40% develop symptoms between 1 and 6 months of life. Mutations in genes encoding 3 different proteins with important roles in surfactant function and metabolism, SP-B, SP-C, and ABCA3, result in lung disease with overlapping clinical, radiographic, and lung histopathologic features.

Mutations in the ABCA3 gene, which cause surfactant dysfunction, are currently the most common genetic cause of respiratory failure in full-term infants, with 150 distinct mutations identified.

ACDMPV is a disorder of lung development involving inadequate development of the pulmonary capillary bed, with the pulmonary veins found in the same bronchovascular bundles as pulmonary arteries rather than associated with pulmonary lymphatics. Affected infants typically present with severe pulmonary hypertension in the neonatal period that is unresponsive to medical management and ultimately fatal. Neonates with ACD may be placed on ECMO and require a lung biopsy before being taken off ECMO. Because ACD-MPV is universally fatal, lung transplantation is the only viable treatment option, but it is frequently limited because of the severity and rapidly progressive nature of the lung disease, which limits patient transport to a pediatric lung transplantation center. Once a definitive diagnosis is established, many families currently elect to discontinue support.

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**Chapter 101****THE NEWBORN WITH A HEART MURMUR OR CYANOSIS***Nicole J. Sutton, MD; Christine A. Walsh, MD*

In the newborn, certain physical findings, such as heart murmur, arrhythmia, congestive heart failure, or cyanosis, lead to the suspicion of heart disease. Evaluation of these findings can be performed in the primary care setting.

**PREVALENCE OF CONGENITAL HEART DISEASE**

The prevalence of congenital heart disease in infants in the United States is approximately 5 to 8 per 1,000 live births. Of these patients, approximately 2.5 to 3 per 1,000 live births will have critical heart disease that requires an intervention in the first year of life. Virtually all pediatricians will see patients with congenital heart disease in their practice. The gender distribution is equal for congenital heart disease as a whole, but the male-to-female ratio varies widely among defects, with aortic stenosis, for example, more common in boys than in girls.

Several population-based studies have been conducted in the United States to examine the prevalence of congenital heart disease. The Baltimore Washington Infant Study (BWIS) is thought to be one of the most complete. The prevalence of congenital heart disease and associated risk factors were examined. The BWIS showed a significantly increased risk for congenital heart disease in children born to diabetic mothers (tetralogy of Fallot, truncus arteriosus), mothers with phenylketonuria, and mothers who abused alcohol (muscular ventricular septal defects). Overall, no racial differences were noted, but a subset analysis showed an increased proportion of white infants with Ebstein anomaly, aortic stenosis, coarctation of the aorta, transposition of the great vessels, and pulmonary atresia. No difference associated with the presence or lack of early prenatal care was found, most likely because the heart is completely formed by 12 weeks of pregnancy, before most women know they are pregnant and have started prenatal care. The study also showed no effect of maternal or paternal age on the prevalence of congenital heart disease. The BWIS found a significant risk for heart disease in infants with a family history of congenital heart disease, especially if the affected relative was the mother or a full sibling. A strong correlation was found between heart disease and other congenital anomalies, with 28% of all cases having a chromosomal abnormality, a heritable syndrome, or another major organ system defect. Down syndrome was the most common association, representing 9% of all infants with congenital heart disease.

**MURMURS**

Murmurs are the product of turbulent blood flow. Approximately 60% of newborns will have a murmur auscultated in the newborn period. If babies were

auscultated continuously from birth, nearly 100% of them would have the murmur of a closing patent ductus arteriosus (PDA). Most murmurs of the neonatal period are benign in nature. An important point to remember is that a newborn may have a severe heart defect, for example, transposition of the great vessels, without having a murmur.

**Benign Murmurs**

The most common benign murmur is a peripheral pulmonary stenosis (PPS) murmur. This murmur is caused by turbulence in the branch pulmonary arteries after closure of the ductus arteriosus. It is generally a grade 1/6 to 2/6 short, early to mid systolic ejection murmur heard best over the axillae or the back. This murmur can be present bilaterally or unilaterally, and it can be heard at birth or soon after. It should resolve by 6 months of age; if it does not, the infant should be referred to a cardiologist to exclude pathologic pulmonary artery branch stenosis, which may be associated with Williams syndrome or rubella syndrome.

The Still murmur can appear in neonates, although it is not as common in the newborn as it is in the older child. This early systolic ejection murmur is located at the left lower sternal border or near the apex and is distinguished by its low-pitched, vibratory, or humming quality. It sounds the same in the newborn and older child. If the pediatrician is comfortable with diagnosing a Still murmur, then these patients do not require a cardiology evaluation. The murmur is not associated with any underlying pathologic condition and typically disappears by puberty.

A common cause of a murmur in the newborn period is a PDA. The PDA murmur of a newborn is different from the *machinery-type* murmur that is described in older children because the pulmonary vascular resistance is still high in the newborn period. The murmur becomes louder and longer as the ductus closes and the pulmonary vascular resistance falls. It generally starts as a short, low- to medium-pitched systolic crescendo murmur at the left upper sternal border that radiates to the left infraclavicular area. If the ductus arteriosus remains patent, the murmur will eventually become the medium- to high-pitched continuous machinery-type murmur of the older child. The normal PDA murmur should resolve in the first few days to weeks of life. If it persists past the first few months of life, the PDA is unlikely to close on its own, and the infant should be referred to a cardiologist.

**Pathologic Murmurs**

The murmurs of congenital heart disease can be divided into 3 categories: stenosis, regurgitation, and left-to-right shunt (Table 101-1).

The intensity of a murmur is not a good marker of the severity of the cardiac disease that is producing it. For example, the small amount of flow through a very small and restrictive ventricular septal defect (VSD) is very turbulent and produces a much louder murmur than the much greater but less turbulent flow through a very large VSD, which is likely to cause congestive heart failure. This feature is in sharp contrast to the murmurs of outflow tract obstruction, which become increasingly louder with increasing degrees



**Table 101-1** Pathologic Murmurs

LESION	PHYSICAL FINDINGS	ELECTROCARDIOGRAM	CHEST RADIOGRAPH
<b>STENOSIS</b>			
Aortic stenosis	Grade 2/6 to 5/6 SEM at RUSB ± Systolic ejection click ± Thrill at suprasternal notch Radiates to carotids	LVH	Dilated aorta Normal PVMs
Pulmonic stenosis	Grade 2/6 to 5/6 SEM at LUSB ± Ejection click ± Thrill at LUSB Radiates to back	RVH, ± RAD	Dilated MPA Normal PVMs
<b>REGURGITATION</b>			
Mitral regurgitation	Grade 2/6 to 3/6 early systolic murmur, can be holosystolic at apex May be associated with midsystolic click if MVP Radiates to midprecordium	LAE, LVH	LAE, LVE
Tricuspid regurgitation	Grade 2/6 to 3/6 early systolic murmur, can be holosystolic at LLSB	RAE, IRBBB	Normal PVMs Possible RAE when severe
<b>LEFT-TO-RIGHT SHUNT</b>			
Atrial septal defect	Grade 2/6 to 3/6 SEM at LUSB; may not be present in infant ± Widely split, fixed second heart sound	RAD, IRBBB, RVH	Normal or cardiomegaly and increased PVMs
Ventricular septal defect	Grade 2/6 to 5/6 holosystolic murmur at LLSB; murmur may not be holosystolic with small VSD ± Thrill ± Loud P <sub>2</sub>	Normal or LVH, BVH	Normal or cardiomegaly and increased PVMs

BVH, biventricular hypertrophy; ECG, electrocardiogram; IRBBB, incomplete right bundle branch block; LAE, left atrial enlargement; LLSB, left lower sternal border; LUSB, left upper sternal border; LVE, left ventricular enlargement; LVH, left ventricular hypertrophy; MDR, mid-diastolic rumble; MPA, main pulmonary artery; MVP, mitral valve prolapse; PVMs, pulmonary vascular markings; RAD, right axis deviation; RAE, right atrial enlargement; RUSB, right upper sternal border; RVH, right ventricular hypertrophy; SEM, systolic ejection murmur; VSD, ventricular septal defect.

of stenosis and turbulence. However, with a critical stenotic lesion, a complete loss of the murmur can occur because so little flow exists through the stenotic area that the turbulence generating the murmur is very low. Newborns in severe congestive heart failure may not have a murmur until cardiac output is improved with anticongestive therapy. The loudness of the murmur must be placed in the larger context of the physical examination and presentation of the infant.

The murmur of transient tricuspid regurgitation can be heard in the newborn period. The regurgitation causing this murmur is generally not caused by a structural problem of the tricuspid valve itself, but instead by poor right ventricular function from severe pulmonary hypertension, persistent fetal circulation, neonatal asphyxia, or fetal distress. It is a grade 1/6 to 3/6 medium-pitched regurgitant murmur best auscultated at the right lower sternal border. It is occasionally holosystolic and can be very prominent in the setting of severe pulmonary hypertension. This murmur is most frequently heard in the neonatal intensive care unit (NICU) and is generally not a murmur that is observed at an outpatient visit.

### Physical Examination

In a healthy newborn, peripheral cyanosis (acrocyanosis) is common. In the normal neonatal cardiac

examination, the point of maximal intensity may be at the left lower sternal border because of the hyperactivity of the right ventricle. The second heart sound may be single, and an ejection click indicative of pulmonary hypertension may be heard. Peripheral pulses are generally easy to palpate in the newborn and are accentuated in premature infants because of the lack of subcutaneous tissue.

When a murmur is heard, the examiner should analyze it in terms of intensity (grade 1/6 to 6/6), timing (systolic vs diastolic), location (of maximal intensity), transmission (eg, to the back), and quality (blowing, vibratory, harsh, or other qualities). These characteristics will suggest a differential diagnosis. For example, the Still murmur is a grade 2/6 to 3/6 vibratory, systolic ejection murmur heard best between the left lower sternal border and the apex without radiation. Abnormal physical findings that are vital to note are cyanosis, tachycardia, tachypnea, hepatomegaly, poor perfusion, and poor or discrepant pulses. These findings are discussed in more detail in the section on congestive heart failure.

### Evaluation

If a murmur or other suggestion of heart disease is present, blood pressures must be obtained in the arms and a leg to rule out a coarctation of the aorta. In a healthy child, the lower extremity blood pressures are approximately

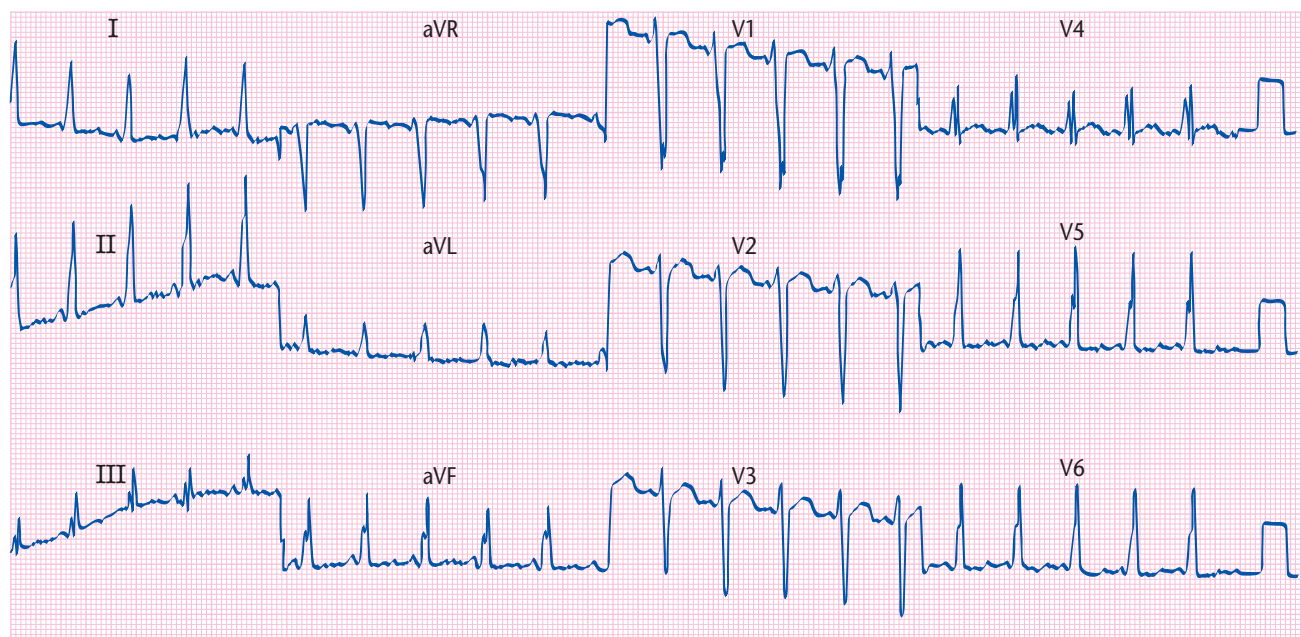
10 mm Hg higher than the right arm pressure. In an infant, the right upper extremity and lower extremities may have a similar systolic blood pressure. The left subclavian artery can be involved in a coarctation, so the right arm blood pressure must be obtained. It is also important to obtain a left arm blood pressure because of the association of coarctation of the aorta with an aberrant right subclavian artery coming off the descending aorta below the coarctation, which would result in equal pressures in the right arm and the leg despite a coarctation. All of the blood pressures must be taken with the baby in the same state, for example, sleeping; otherwise, differences in the blood pressures may not be valid. In addition, the heart rate should be approximately the same throughout the process.

An electrocardiogram (ECG) evaluation should be performed on all patients with a heart murmur or other suggestion of heart disease. The ECG findings must be interpreted with regard to the axis of the P wave and QRS complex, right and left atrial and ventricular enlargement, ST-T changes, conduction abnormalities, rate, and rhythm. It must be read with knowledge of normal values for age because of the many changes that occur in the first weeks of life. The normal ECG of a newborn will show sinus rates of up to 180 beats per minute. The axis can be as far rightward as +180 degrees. Right ventricular dominance is normal, even to the point of an occasional neonate having Q waves in V<sub>1</sub>. The examiner should make sure that any infant with a murmur or signs of congestive heart failure is in sinus rhythm (positive P waves in leads I, II, and aVF). A superior axis (0 to -150 degrees) is consistent with an endocardial cushion defect. A positive T wave in V<sub>1</sub> after 3 days

of age and a qR pattern in V<sub>1</sub> are indicative of right ventricular hypertrophy. Specific voltage criteria exist for right and left ventricular hypertrophy at various ages. Right atrial enlargement is suggested by a P wave that is 3 mm tall or greater in any lead. In a newborn, left atrial enlargement is suggested by a P wave that is greater than 0.07 second wide, often associated with notched P waves in the limb leads and biphasic P waves in V<sub>1</sub>. An incomplete right bundle branch block can be seen with an atrial septal defect, Ebstein anomaly, or coarctation of the aorta in the newborn. A delta wave and short PR interval are hallmarks of Wolff-Parkinson-White (WPW) syndrome (Figure 101-1).

Oxygen saturation should be obtained in a preductal (right arm) and a postductal (foot) area to detect right-to-left shunting through the patent ductus arteriosus. This test is especially important in the immediate neonatal period. In addition, if the oxygen saturations are abnormal, a hyperoxia test should be performed. This test is described later in the discussion of cyanosis. A healthy 1-day-old infant may have an arterial pressure of oxygen (PaO<sub>2</sub>) as low as 60 mm Hg.

Finally, a chest radiograph is frequently taken in the neonatal period when the patient is still in the hospital. A chest radiograph is less frequently performed when a murmur is detected in an office setting than it is in the hospital setting. Useful information can be gleaned from the chest radiograph, including the size, shape, and location of the heart; the status of the pulmonary vascular markings; and on which side the aortic arch is located. However, the size of the cardiac silhouette on chest radiograph is a poor predictor of the actual heart size.



**Figure 101-1** ECG showing a short PR interval and delta waves during normal sinus rhythm (Wolff-Parkinson-White syndrome) in a newborn.

## ARRHYTHMIAS

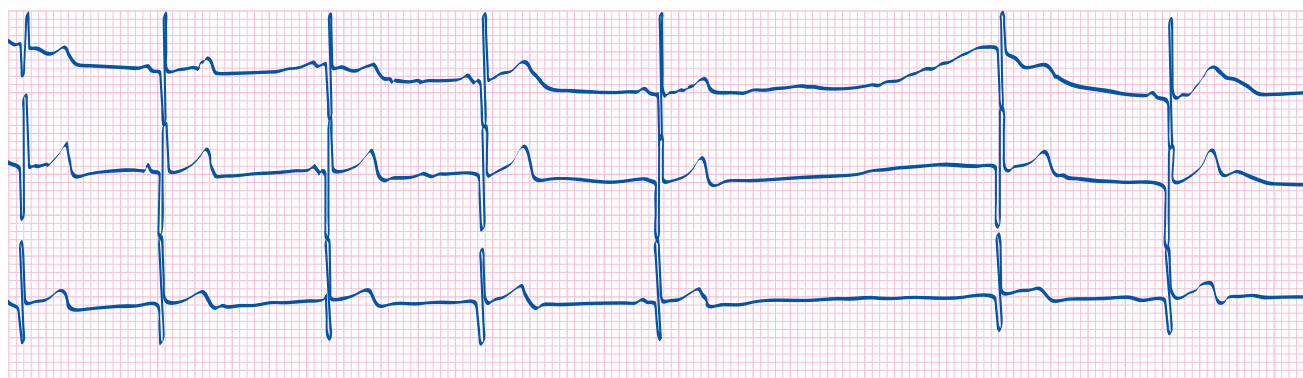
The easiest method of differentiating rhythm disturbances is to listen with a stethoscope. Is the rhythm too fast, too slow, or irregular but close to the normal rate?

### Bradyarrhythmias

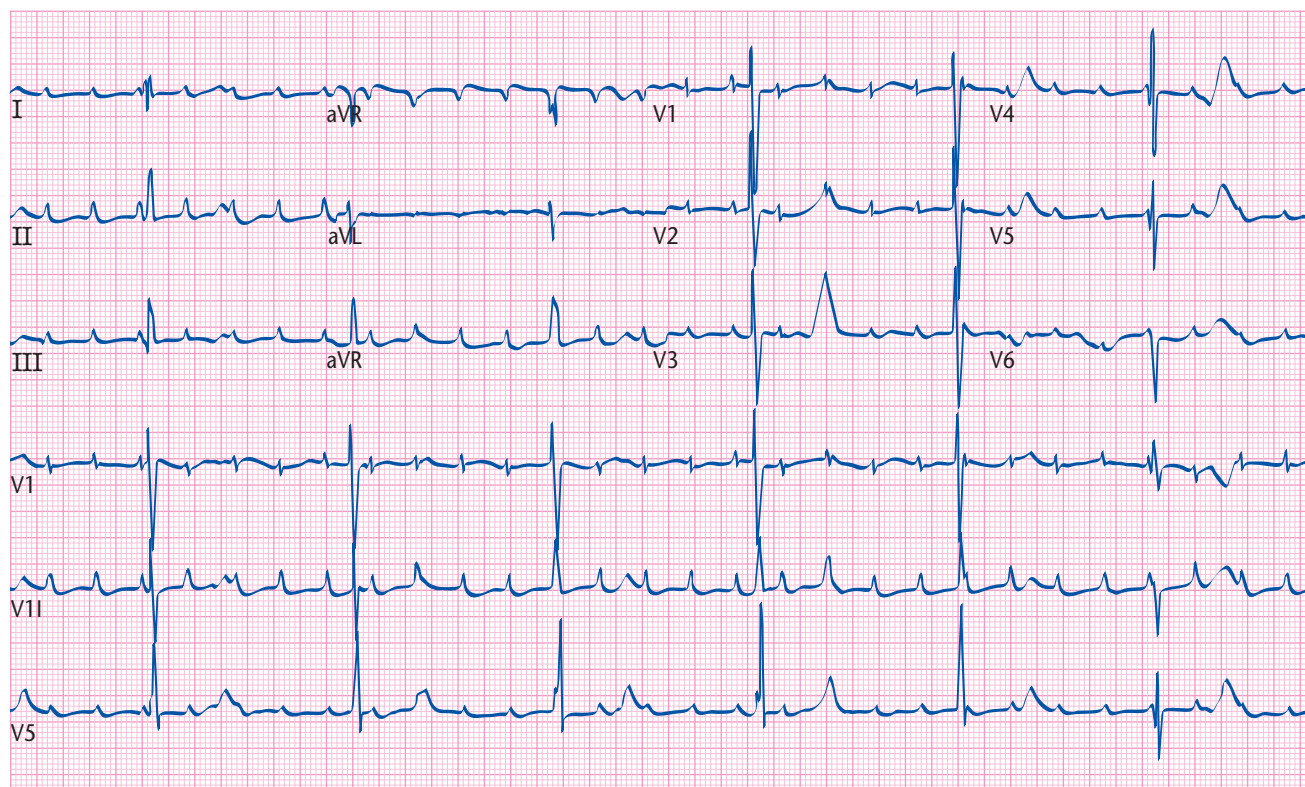
A slow heart rate is defined as being less than the fifth percentile for the age of the patient. A persistent heart rate less than 80 beats per minute is considered bradycardia in a newborn (Figure 101-2). Sinus bradycardia is seen more frequently in preterm than in term infants. Causes include maternal medication,

neonatal asphyxia, increased intracranial pressure, sepsis, hypothyroidism, hypothermia, and hyperkalemia. The underlying cause of sinus bradycardia must be discovered and treated.

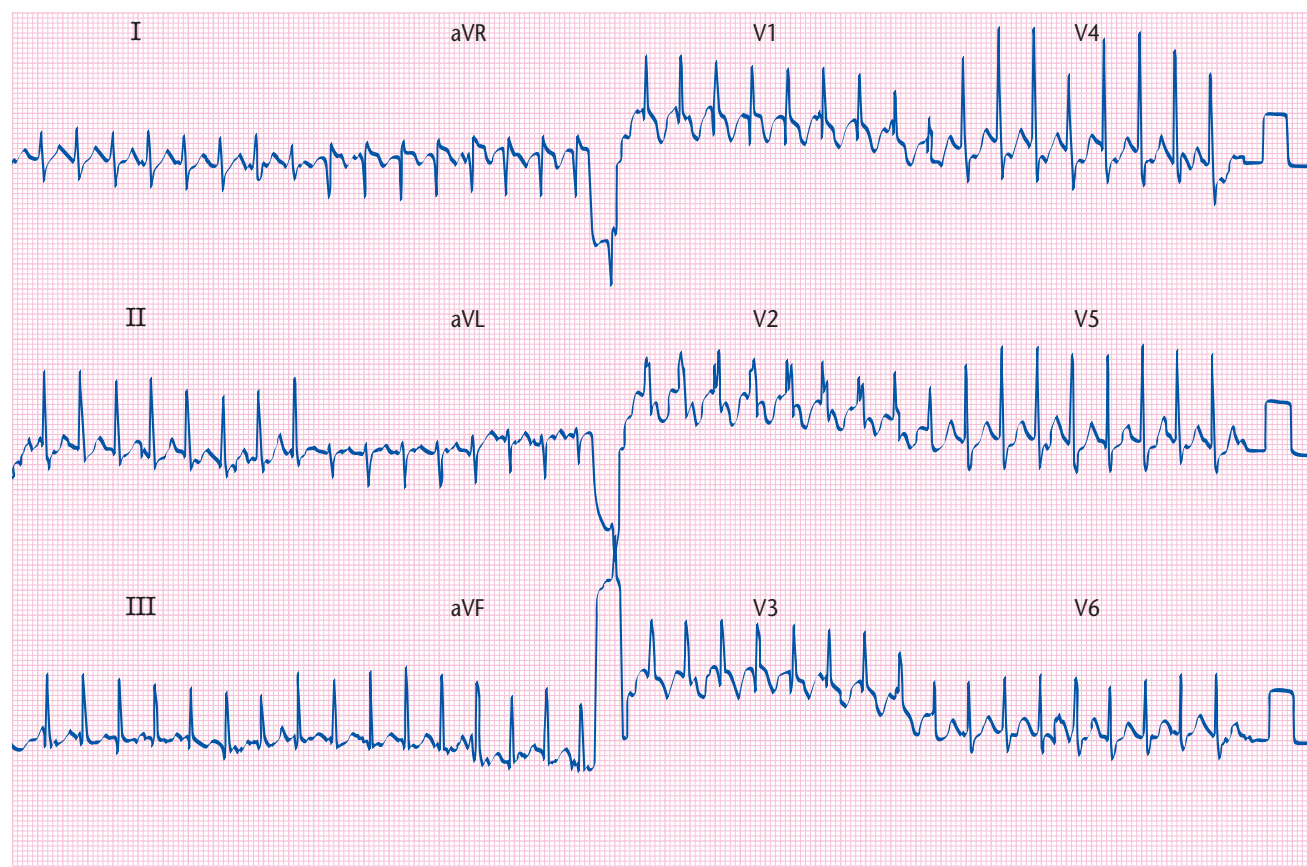
After sinus bradycardia, the most common cause of a slow heart rate in a neonate is congenital complete heart block (Figure 101-3), which is usually first noted during routine prenatal care. Congenital complete heart block is generally associated with maternal systemic lupus erythematosus, more specifically with anti-Ro and anti-La antibodies that attack the conduction tissue of the fetal heart. No correlation has been



**Figure 101-2** ECG showing sinus bradycardia with a 1.8-sec pause followed by a junctional escape beat in a premature newborn.



**Figure 101-3** ECG reflecting complete heart block in a newborn.



**Figure 101-4** Supraventricular tachycardia in a newborn.

found between this pathologic abnormality and structural heart disease. The low heart rate is generally well tolerated, and the fetus does not usually develop hydrops. When the babies are born, they appear clinically well, with a low resting heart rate, often in the range of 60 to 70 beats per minute. They usually do not require a pacemaker in the newborn period, but they need to be evaluated by a cardiologist when they are born. A pacemaker is indicated if the QRS is wide or if the heart rate is less than 50 to 55 beats per minute in an infant with a normal heart, or less than 70 beats per minute in an infant with congenital heart disease. An echocardiographic examination should be performed after birth to evaluate structure and function, even if fetal echocardiograms were performed.

### Tachyarrhythmias

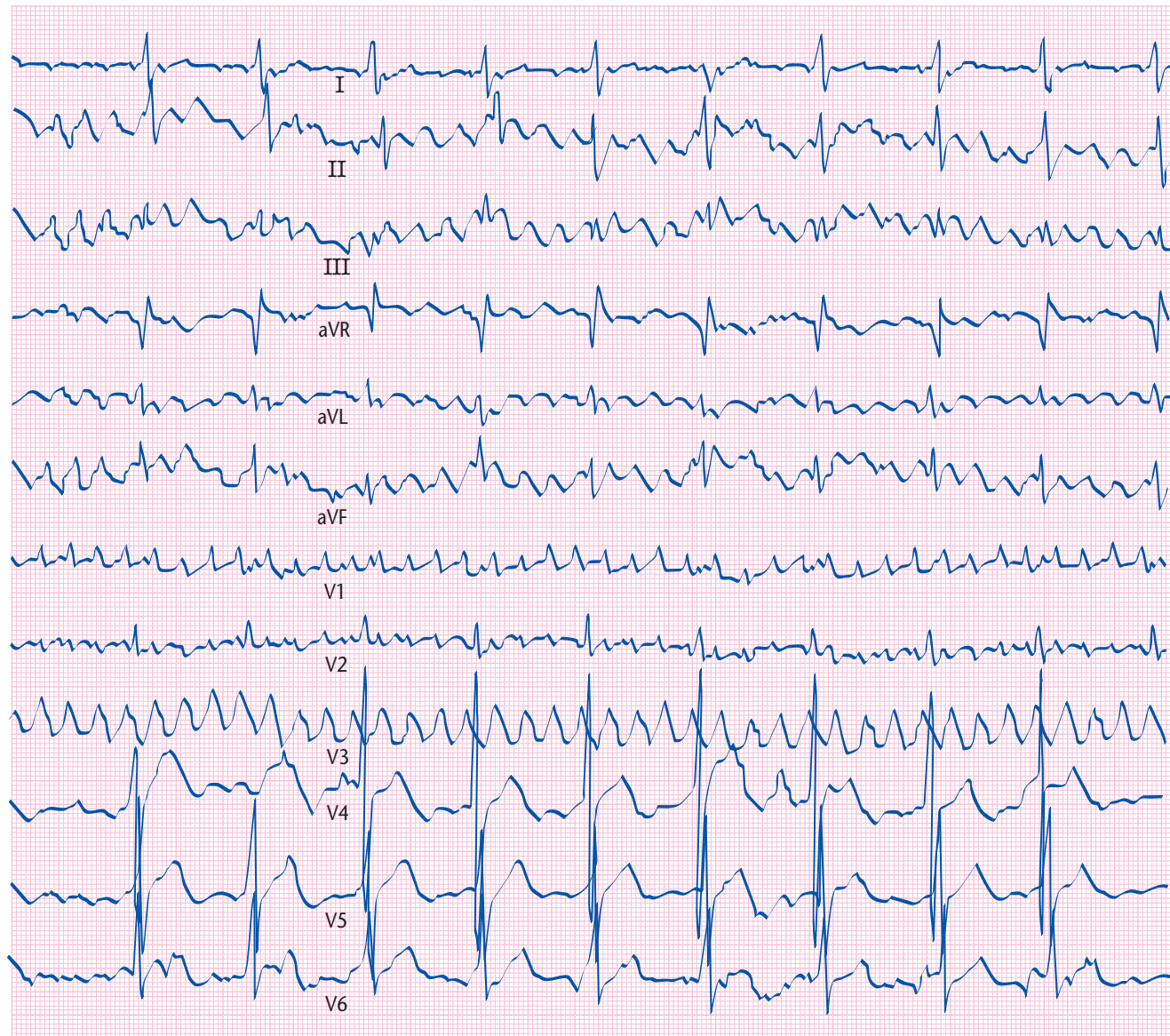
A fast heart rate is greater than the 95th percentile for the age of the child. Transient sinus tachycardia up to 190 beats per minute is often seen in healthy newborns. However, the maximal rate should not exceed 220 to 230 beats per minute in an infant. Rates above this level are not sinus because the sinus node is generally incapable of faster rates.

The most common childhood tachyarrhythmia (after sinus tachycardia) is supraventricular tachycardia (SVT), usually with a heart rate greater than 220 beats per minute (Figure 101-4). The baseline ECG can be normal, or it can have a short PR interval and delta

waves indicative of WPW syndrome that is present in 50% of newborns with SVT (see Figure 101-1). In addition to SVT, babies can also have atrial tachyarrhythmias such as ectopic atrial tachycardia, atrial flutter (Figure 101-5), and much less commonly atrial fibrillation. Other less common neonatal tachyarrhythmias are junctional ectopic tachycardia and ventricular tachycardia.

The normal QRS duration in a neonate is 70 msec or less, which is important when deciding whether a narrow- or wide-complex tachycardia is present. A QRS duration of 90 msec, which is normal for an adult, is wide for a baby and can indicate ventricular tachycardia (Figure 101-6). Ventricular tachycardia is often misdiagnosed as SVT in the newborn because of this feature. The rate of ventricular tachycardia can be as high as the SVT rate in neonates; therefore, the rate will not differentiate between the 2 tachyarrhythmias. The treatment and implications are very different for a narrow-complex SVT and a wide-complex ventricular tachycardia. In either case, a pediatric cardiologist must evaluate these patients as soon as possible because congestive heart failure can develop from a persistent tachyarrhythmia. An echocardiographic examination is required to evaluate the structure and function of the heart. Acute treatment of a tachyarrhythmia may be medical or electrical cardioversion, followed by an antiarrhythmic agent to prevent recurrence.





**Figure 101-5** ECG showing atrial flutter in a 4-month-old boy.

Radiofrequency ablation is not usually performed in newborns because the arrhythmia may spontaneously resolve, because of technical difficulties related to the size of the patient, and because of the possibility that radiofrequency lesions may expand with time in this age group.

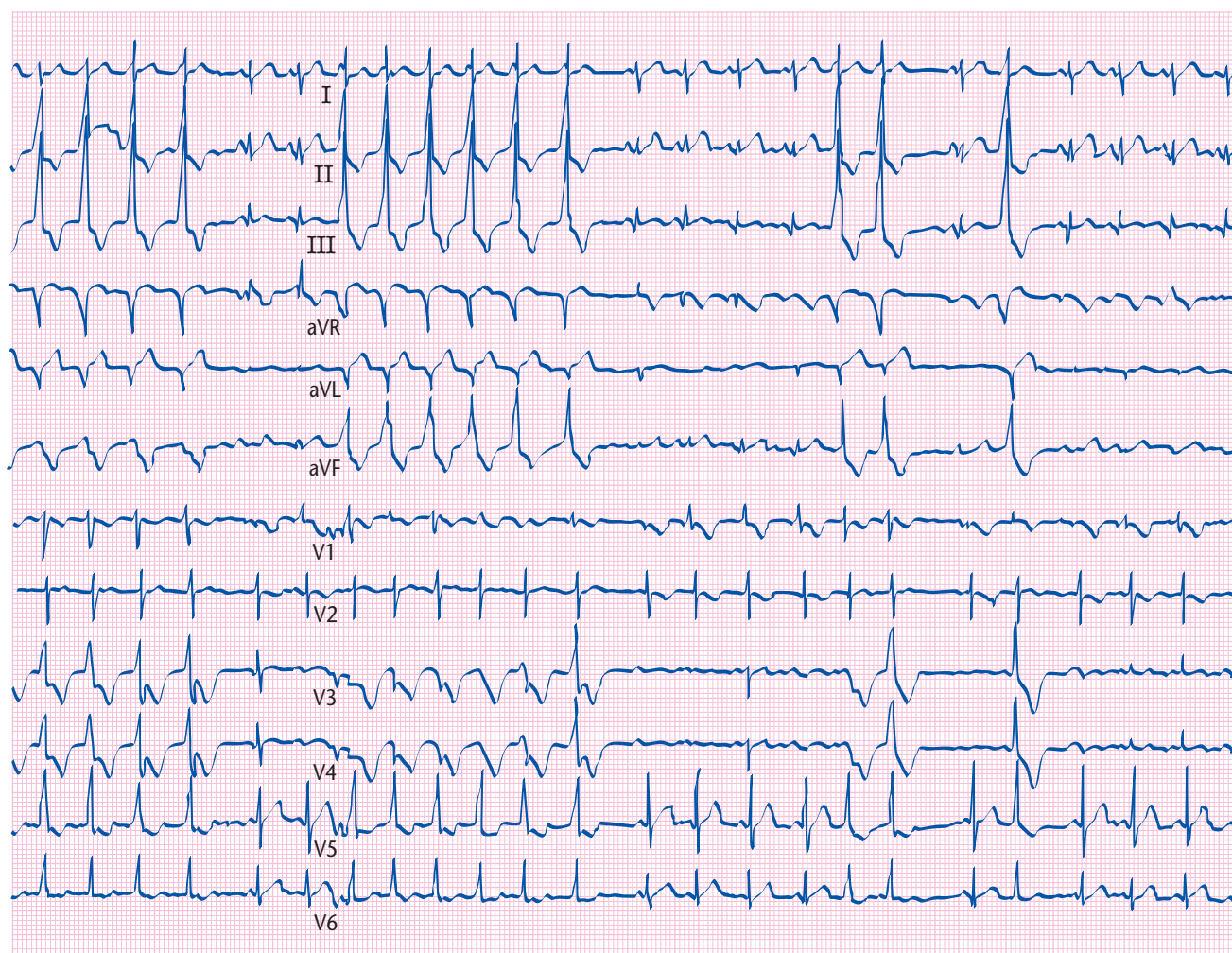
### Irregular Rhythms

The most common cause of an irregular rhythm in the child or adolescent is sinus arrhythmia. Sinus arrhythmia is a normal finding in which a variation exists in the heart rate with respiration. A 12-lead ECG with a rhythm strip will show positive P waves of the same morphology in leads I, II, and aVF, each followed by a QRS complex. In newborns, however, an irregular heartbeat is more often caused by premature atrial or ventricular beats, which are usually single and uniform. The overall heart rate is normal. These patients

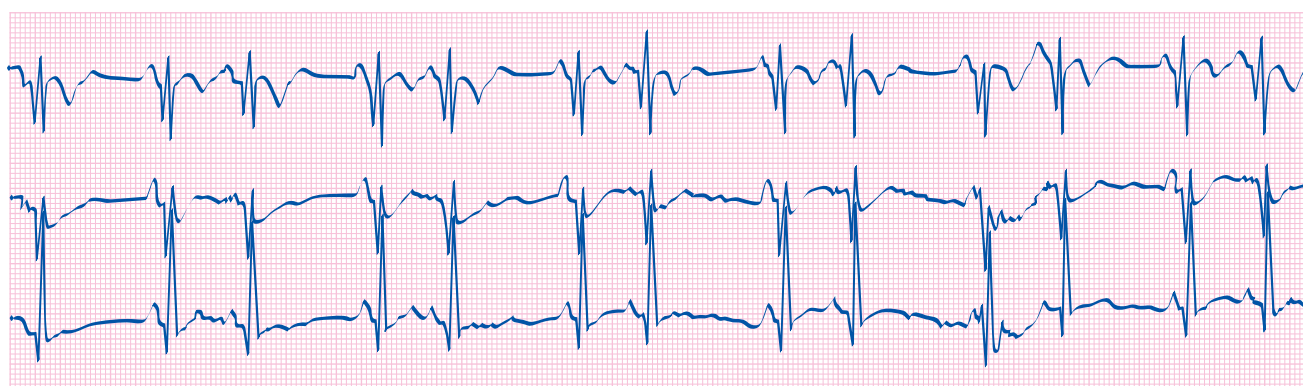
usually have structurally normal hearts. No intervention is needed, and the premature beats usually resolve with time.

Atrial premature contractions (APCs) may be conducted normally resulting in a normal narrow QRS (Figure 101-7), or they may be conducted aberrantly resulting in a wide QRS (Figure 101-8). Both normally conducted and aberrantly conducted APCs have a preceding P wave, which is different from the sinus P wave. Nonconducted (blocked) APCs have an abnormal early P wave but no QRS, and if they are frequent, they may result in a low heart rate (Figure 101-9).

Premature ventricular contractions (PVCs) are early beats that are wide and not preceded by a P wave (Figure 101-10). After a PVC, a full compensatory pause usually occurs before the next sinus beat, meaning that the length of 2 cycles, including the premature beat, is equal to that of 2 normal cycles. PVCs are considered



**Figure 101-6** ECG reflecting nonsustained monomorphic ventricular tachycardia in a newborn.



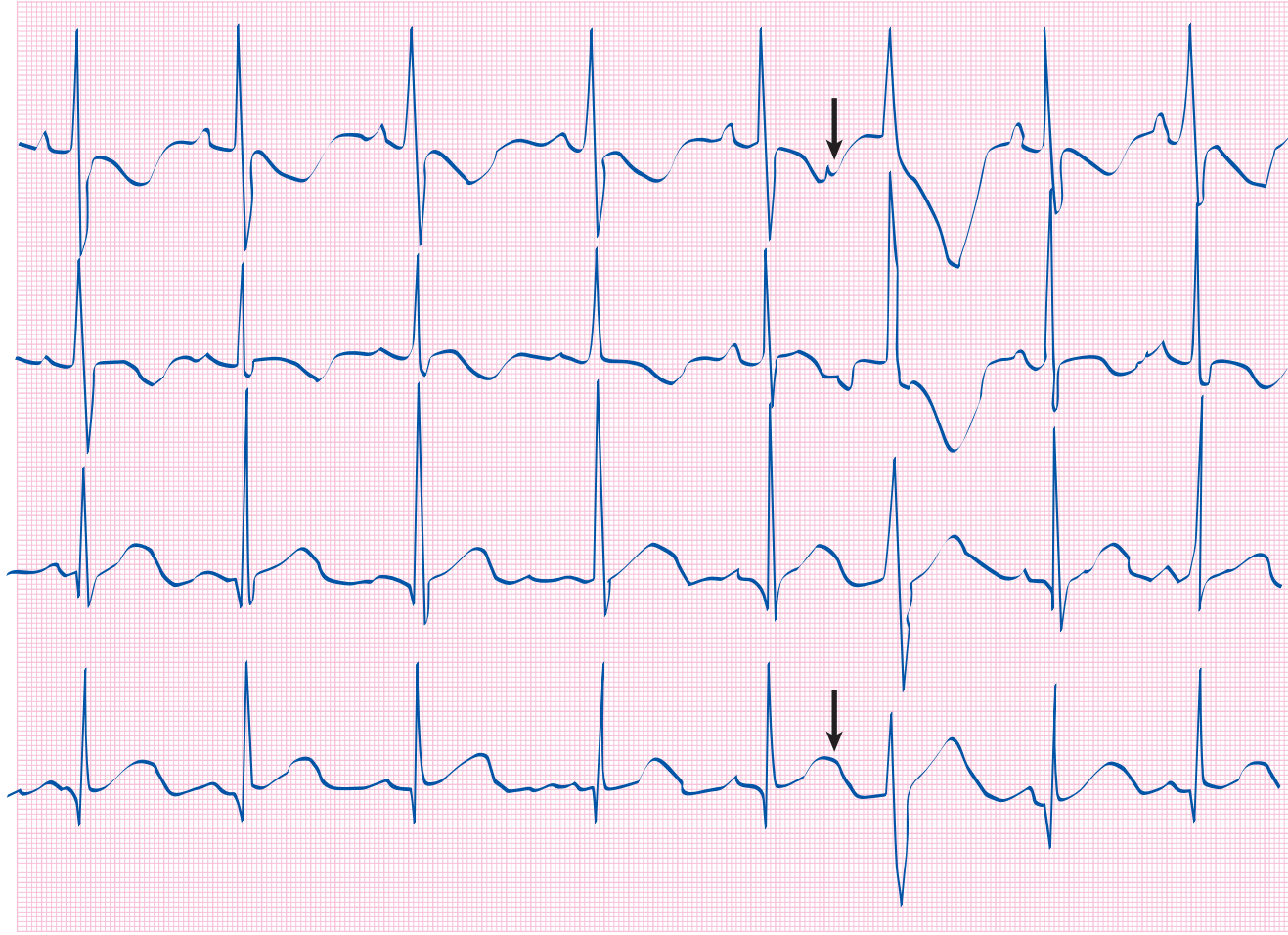
**Figure 101-7** ECG showing atrial premature contractions with normal conduction as atrial bigeminy in a newborn.

significant if they are frequent, multiform, occur as couplets or runs, or are associated with a long QT interval.

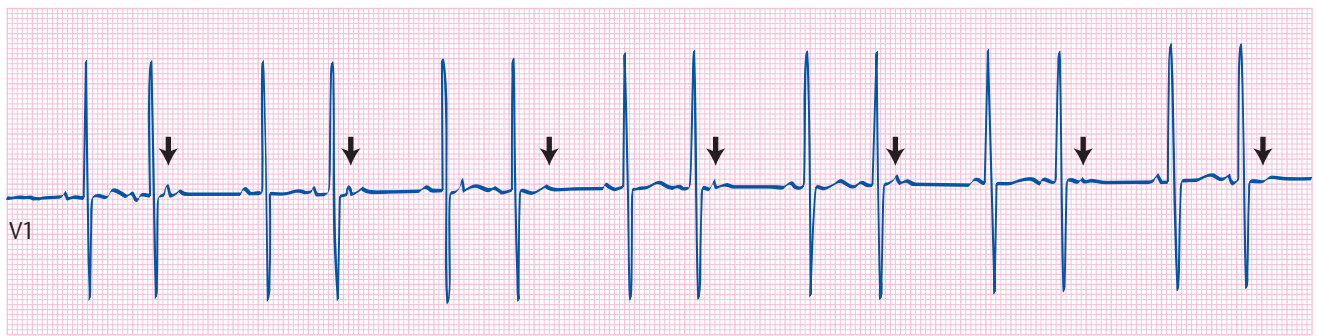
### Evaluation

When an arrhythmia is appreciated, a standard 12-lead ECG evaluation should be performed with a rhythm

strip that is 30 seconds to 1 minute long, preferably with 12 simultaneous leads. The rhythm strip is essential to diagnosis and can be obtained with all ECG machines or ordered specifically from any ECG laboratory. The rest of the physical examination of the baby with an arrhythmia is generally normal, but an



**Figure 101-8** ECG showing atrial premature contractions with aberrant conduction in a newborn.



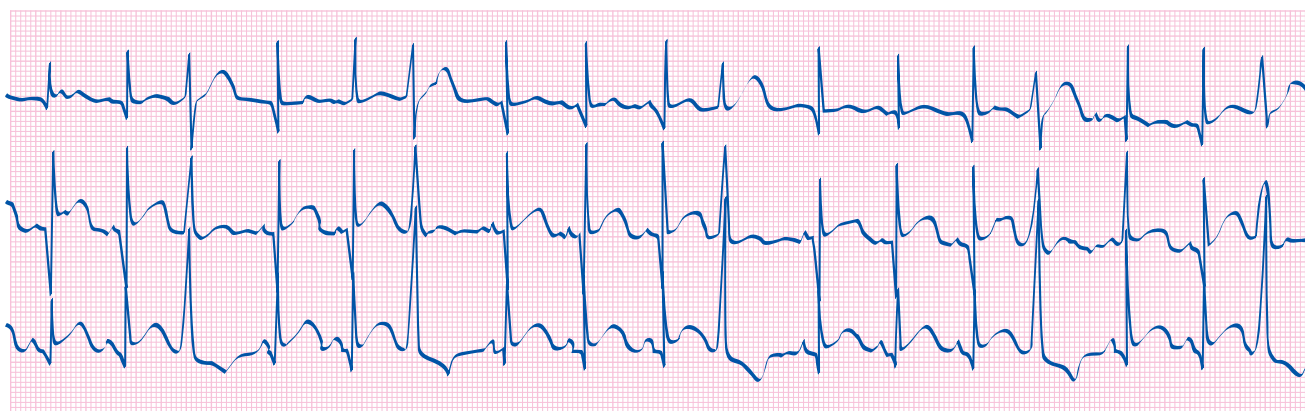
**Figure 101-9** ECG showing blocked atrial premature contractions (down arrows) as atrial trigeminy.

association can be found with acquired heart disease or congenital heart disease. A common and important association is Ebstein anomaly of the tricuspid valve and SVT. These patients have an accessory pathway that can sometimes be manifested on the ECG as a short PR interval and delta wave of WPW syndrome (see Figure 101-1). Other associations are infection (eg, myocarditis), neurologic disease (eg, asphyxia), and metabolic disorders (eg, electrolyte abnormalities).

Infants with heart disease often decompensate with an arrhythmia. Any sign of congestive heart failure in a baby with an abnormal rhythm requires an immediate evaluation by a pediatric cardiologist.

### CONGESTIVE HEART FAILURE

Congestive heart failure (CHF) is the inability of the heart to do the work required. This inability can be caused by abnormal muscle function with



**Figure 101-10** ECG reflecting single uniform premature ventricular contractions as ventricular quadrigeminy in a newborn.

a normal workload or by an increased workload with normal muscle function. (Box 101-1 lists the causes of CHF.)

The history is critical in making the diagnosis of CHF. Babies with CHF have poor feeding; they are very hungry and start to eat ravenously but tire quickly and get very short of breath. They need to rest frequently while feeding and may want to eat again shortly afterward because they cannot ingest enough at any one sitting. A detailed feeding history should be elicited, including frequency of feedings and how many minutes each feeding lasts. Babies with CHF may also have sweating with feeds, which is a sign of how hard they are working when they feed. They need more calories than normal babies but are consuming fewer. A history of poor weight gain will be found, with head circumference and length being spared to some degree.

Signs of CHF include underweight and tachypnea. Infants may exhibit retractions, nasal flaring, and grunting. A cardiac examination may show tachycardia, a gallop, or a hyperactive or hypoactive impulse. Any rhythm disturbance must be investigated to determine whether the arrhythmia is the cause or result of CHF. Murmurs may or may not be appreciated in a baby with CHF. Some conditions causing CHF are not associated with heart murmurs. Even murmurs caused by structural heart disease may not be heard if the baby has low cardiac output; these murmurs become evident when anticongestive therapy is effective. Crackles in the lungs from pulmonary edema and hepatomegaly are presenting signs of CHF. Signs of poor perfusion include mottling, slow capillary refill, cool extremities, and poor pulses. Good upper extremity pulses and poor femoral pulses indicate a coarctation of the aorta; however, this difference may not be evident if low cardiac output is present. The examiner should feel the right brachial pulse and femoral pulse simultaneously to detect a delay, suggesting a coarctation.

A pediatric cardiologist must evaluate a baby with CHF as soon as possible. Echocardiography, ECG, and chest radiography must be performed. Some infants may need to be stabilized and transported emergently

### **BOX 101-1 Causes of Congestive Heart Failure**

#### **NONCARDIAC CAUSES**

- Birth asphyxia with myocardial ischemia
- Sepsis
- Anemia
- Hypoglycemia
- Hypocalcemia
- Adrenal insufficiency
- Maternal diabetes mellitus
- Barth syndrome
- Cerebral arteriovenous malformation

#### **PRIMARY MYOCARDIAL DISEASE**

- Hypertrophic cardiomyopathy
- Myocarditis
- Endocardial fibroelastosis

#### **ARRHYTHMIAS**

- Supraventricular tachycardia
- Ectopic atrial tachycardia
- Atrial flutter or fibrillation
- Junctional ectopic tachycardia
- Ventricular tachycardia
- Complete heart block

#### **STRUCTURAL HEART DISEASE**

- Anomalous left coronary from the pulmonary artery
- Pressure overload lesions
  - Coarctation of the aorta
  - Aortic stenosis
  - Hypoplastic left heart syndrome
- Volume overload lesions: left-to-right shunt
  - Ventricular septal defect
  - Atrial septal defect
  - Patent ductus arteriosus
  - Complete atrioventricular canal



to a tertiary-care NICU or emergency department, especially if shock is present. (See Chapter 111, Care of the Sick or Premature Infant Before Transport.)

### Abnormal Muscle Function

Abnormal muscle function in newborns may be caused by a primary cardiomyopathy (eg, myocarditis, endocardial fibroelastosis), or it can be secondary in nature. Some causes of secondary cardiomyopathy are arrhythmias (eg, tachyarrhythmias, complete heart block), metabolic disorders (eg, adrenal insufficiency, hypocalcemia, hypoglycemia, Pompe disease), sepsis, and anemia. A gallop and the murmur of mitral or tricuspid regurgitation may be heard in these patients.

### Increased Workload

The other category of patients who develop CHF have normal muscle function but have increased workload. The increased workload can be divided into pressure overload and volume overload.

#### Pressure Overload

Common causes of increased pressure work are aortic stenosis, pulmonary stenosis, and coarctation of the aorta. Hypoplastic left heart syndrome will often exhibit as a severe version of coarctation of the aorta.

Coarctation of the aorta is a stenosis of the upper thoracic aorta, usually just opposite the insertion of the ductus arteriosus (juxtaductal). Depending on the severity of the stenosis, the effect on cardiac output can vary from very minimal to severe. The degree of stenosis is hard to predict clinically or by echocardiographic evaluation before the PDA has completely closed, given that the ductal tissue can be involved in the site of the coarctation. The stenosis leads to increased pressure in the proximal aorta, causing increased systolic pressure and wall stress in the left ventricle, resulting in left ventricular hypertrophy. However, when the stenosis is severe and increases suddenly, such as occurs when the PDA closes in a patient with a critical coarctation, the left ventricular wall stress rises very sharply over a short period. The left ventricle does not have time to compensate with hypertrophy and can fail in hours or days, resulting in low cardiac output and shock. Prostaglandin is used to keep the ductus open until surgery is performed.

On cardiac examination, a suprasternal notch thrill may be present. The first and second heart sounds are generally normal. Occasionally, a systolic ejection click from a bicuspid aortic valve is heard. Some newborns have a grade 2/6 to 3/6 systolic ejection murmur at the left upper sternal border radiating to the back from the coarctation itself, but this finding is uncommon. The most prominent finding is the discrepancy between the upper and lower extremity pulses and blood pressures. In these babies, the PDA shunts right to left and represents the only source of blood flow to the lower extremities. The saturation in the feet may therefore be lower than those in the right arm while the PDA is open. When the PDA closes, the right-to-left shunt resolves, and the saturation in the feet will

be same as that in the right arm, but the perfusion will be much worse.

The ECG in the newborn is often normal without evidence of left ventricular hypertrophy. The ECG can show right ventricular hypertrophy in the neonatal period because the right ventricle is still responsible for pumping most of the cardiac output to the body through the PDA. Patients who present later with coarctation generally have a murmur or hypertension, with left ventricular hypertrophy on the ECG. They do not have as severe a coarctation and therefore still have forward cardiac output around the aortic arch without a PDA. A chest radiograph shows the nonspecific findings of cardiomegaly and increased pulmonary vascular markings. Rib notching is not present because the collateral circulation has not yet developed sufficiently.

Babies with critical aortic stenosis and hypoplastic left heart syndrome can also present in shock. In these patients, the pulses are quite thready, but the brachial and femoral pulses will be equally poor, and blood pressures will be the same in upper and lower extremities. However, some babies in shock from a coarctation will have such poor pulses that detecting a difference between upper and lower extremities is difficult. Infants with coarctation often have a normal ECG or right ventricular hypertrophy, whereas neonates with aortic stenosis will have left ventricular hypertrophy, and those with hypoplastic left heart syndrome will have decreased or absent left ventricular forces with right ventricular hypertrophy.

#### Volume Overload

The volume overload lesions are atrial septal defect, VSD, PDA, and common atrioventricular canal. VSD is discussed here because it is the most common volume overload lesion to cause CHF in infants.

VSDs are the most common form of congenital heart disease, if bicuspid aortic valve is excluded. The amount of shunting across a VSD is determined by the size of the defect and the relative resistances of the systemic and pulmonary circulations, but not the location of the VSD in the septum. CHF can occur with a moderate to large VSD.

On cardiac examination of an infant with a VSD, a systolic thrill may be palpable at the left lower sternal border. A hyperactive precordium and loud  $P_2$  are present with a large shunt. A grade 2/6 to 5/6 pansystolic or early systolic murmur is audible at the left lower sternal border. An apical diastolic rumble of relative mitral stenosis may be present with a moderate to large shunt. (For a complete discussion of VSD, see Chapter 234, Congenital and Acquired Heart Disease.)

## CYANOSIS

Cyanosis is a bluish discoloration of the skin and mucous membranes and is either peripheral (acrocyanosis) or central. Peripheral cyanosis can occur with hypovolemia or shock, but it is a common finding in healthy infants who are vasoconstricted from the cold or a fever. Circumoral cyanosis refers to bluish skin around the mouth and, if isolated in a cold baby, is of no concern. Central cyanosis requires desaturation

of 5 g/100 mL of hemoglobin and is usually not detectable until the arterial oxygen saturation is 85% or lower in an infant with a normal hemoglobin. Cyanosis can be seen at a higher level of oxygen saturation in patients with polycythemia and at a lower level in patients with anemia. Cyanosis can be difficult to detect in dark-skinned infants. The best place to assess for cyanosis is the tongue, which has a rich vascular supply and is free of pigmentation. Clubbing describes thick, wide, spoon-shaped fingertips and toes with convex nail beds; it usually does not start to develop until the child is 6 months or older.

Central cyanosis can be caused by upper airway (eg, laryngeal web) or lower airway (eg, pneumonia) disease. Upper airway disease is characterized by marked hypercarbia, inspiratory stridor, and retractions. Hypercarbia develops later in lower airway disease, and findings include tachypnea, expiratory wheezing, grunting, crackles, and retractions. Apnea or shallow irregular respirations and hypercarbia are seen in the cyanotic infant with central nervous system disease (eg, birth asphyxia). Babies with methemoglobinemia are only tachypneic; their arterial blood gas shows a normal PaO<sub>2</sub> and low oxygen saturation. In newborns with persistence of the fetal circulation, right-to-left shunting occurs through the patent foramen ovale and PDA because of persistent pulmonary hypertension, which may be idiopathic or a result of conditions such as meconium aspiration, hypoglycemia, and perinatal asphyxia.

Infants with cyanosis from congenital heart disease can be divided into those with acyanotic congenital heart disease with CHF (eg, large VSD) producing abnormal diffusion and  $\dot{V}/\dot{Q}$  mismatch in the lungs (similar to lower airway disease) and those with true cyanotic congenital heart disease with a right-to-left shunt.

Patients with a true right-to-left shunt can be differentiated with a hyperoxia test. As close to 100% oxygen as possible is administered for 10 minutes. When a right-to-left intracardiac shunt is significant, the PaO<sub>2</sub> does not usually increase to greater than

100 mm Hg, and the rise is not usually more than 10 to 30 mm Hg. However, in defects with markedly increased pulmonary blood flow, such as total anomalous pulmonary venous return, the PaO<sub>2</sub> can rise as high as 150 mm Hg.

When possible, simultaneous blood gases should be obtained from the right upper extremity and umbilical artery or lower extremity to determine the presence of a right-to-left ductal shunt. A 10- to 15-mm Hg difference between the right radial artery and umbilical artery is considered significant.

Cyanotic congenital heart defects can be divided into those with decreased pulmonary blood flow and those with increased pulmonary blood flow (Table 101-2). Defects with decreased pulmonary blood flow have in common right-sided obstruction (eg, tricuspid atresia, pulmonary atresia, pulmonary stenosis) to pulmonary flow with a right-to-left shunt through a normal patent foramen ovale or abnormal intracardiac communication (VSD). Tetralogy of Fallot will be discussed as an example. Defects with increased pulmonary blood flow have intracardiac mixing of saturated and desaturated blood, but no obstruction to pulmonary blood flow. Transposition of the great arteries will be discussed as an example.

### Tetralogy of Fallot

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart defect, representing 5% to 7% of all congenital heart disease. Most patients with TOF will exhibit symptoms in the immediate newborn period with cyanosis and a murmur. The degree of cyanosis is determined by the severity of the pulmonary stenosis. Some infants will not be cyanotic at birth but will develop increasing obstruction and cyanosis over the first year of life. Other infants have such severe cyanosis that they are dependent on the PDA for blood flow to the lungs and become severely ill when the PDA closes.

On physical examination, a systolic thrill at the left upper and midsternal borders and an increased right

**Table 101-2** Cyanotic Congenital Heart Disease

DISEASE	ECG	CHEST RADIOGRAPH	
		HEART SIZE	PVMs
Tetralogy of Fallot	RVH, RAD	Boot-shaped heart	Decreased
Tricuspid atresia	Superior axis, decreased RV forces, LVH	Normal to slightly increased heart size	Decreased
Pulmonary atresia	Normal axis, decreased RV forces; LVH	Normal to slightly increased heart size	Decreased
Critical pulmonic stenosis	RAD, RVH	Normal to slightly increased heart size	Decreased
Ebstein anomaly	RAE, RBBB, delta wave of WPW syndrome	Extremely enlarged heart size (mainly from RA dilation)	Decreased
Truncus arteriosus	BVH	Cardiomegaly	Increased
TGA	RAD, RVH	Egg-shaped heart with narrow superior mediastinum	Increased
TAPVR	RAD, RVH with RSR'	Cardiomegaly	Increased

BVH, biventricular hypertrophy; ECG, electrocardiogram; LVH, left ventricular hypertrophy; PVMs, pulmonary vascular markings; RA, right atrial; RAD, right axis deviation; RAE, right atrial enlargement; RBBB, right bundle branch block; RV, right ventricular; RVH, right ventricular hypertrophy; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; WPW, Wolff-Parkinson-White.

ventricular impulse are usually present. The second heart sound is single, and a systolic ejection click may be heard. Typically a long, loud crescendo-decrescendo systolic murmur of right ventricular outflow tract obstruction is audible at the left upper and midsternal borders. The infant may be tachypneic but not particularly dyspneic, and the pulses are usually good.

The ECG will show isolated right ventricular hypertrophy with a rightward axis. A chest radiograph classically shows a boot-shaped heart with decreased pulmonary vascular markings. Approximately 25% of patients with TOF have a right aortic arch. (For a full discussion of TOF, see Chapter 234, Congenital and Acquired Heart Disease.)

### Transposition of the Great Arteries

Transposition of the great arteries (TGA) represents approximately 3% to 5% of all congenital heart defects. A strong male predominance exists in this disorder, but it is not usually associated with other congenital anomalies or chromosomal abnormalities. Newborns with TGA have severe cyanosis. The rest of the physical examination is often normal except for tachypnea. The baby may be large because TGA is found more commonly in infants of a diabetic mother. The typical patient is a *big, blue, baby boy*. Murmurs are not prominent in the absence of a VSD and pulmonary stenosis.

Initially, the chest radiograph may be completely normal. With time, the chest radiograph will show overcirculation of the pulmonary vasculature. The classic description of the heart on chest radiograph evaluation is an *egg on a string*. The ECG may be normal or show right ventricular hypertrophy.

The most classic, but infrequently seen, finding in TGA is reversed differential cyanosis, that is, greater cyanosis of the upper half of the body than the lower half of the body. This finding is caused by shunting of blood with a higher saturation from the pulmonary artery to the descending aorta through the PDA. Usually the  $\text{PaO}_2$  is less than 35 mm Hg in room air and 35 to 40 mm Hg on 100% oxygen.

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## Chapter 102

# THE NEWBORN AT RISK FOR INFECTION

Tsoline Kojaoghlanian, MD

Neonatal infections can be broadly categorized as either congenital, indicating their presence at birth and likely acquisition in utero; or perinatal, indicating acquisition late in pregnancy or during the delivery. Outcomes for the neonate after infection can vary widely based on the organism involved, the time during gestation when infection occurs, and whether the mother has any protective antibodies that can provide the fetus with passive protection, reducing the disease severity for the infant.

Transplacental spread of maternal infection is the common route by which the fetus acquires infection. Placental infection is often associated with systemic illness in the neonate; thus, molecular, microbiologic, and pathologic examination of the placenta is important in the critically ill newborn. In the perinatal period, acquired early-onset infection (before 72 hours) is almost always caused by organisms acquired in the maternal birth canal. After this period, most infections are acquired through close contact with members of the baby's environment and through human milk. The manifestations of infection vary with the infecting organism. The mechanism of damage and response by the host, as well as the stage of the pregnancy, determine the effects on the neonate. Some pathogens can have deleterious effects throughout gestation. Fetal organogenesis is complete by 12 weeks' gestation; thus, damage incurred during this period will likely result in anomalies. The mother does not transfer T-cell-specific immunity, crucial in the control of many viruses, to the fetus. Maternal IgG antibodies, conversely, are transferred to the fetus and reach one-half the normal serum concentration by 30 weeks' gestation and more normal values at term. Furthermore, the transferred antibodies must be of a certain concentration to be protective. In some bacterial infections, the mother may not have enough circulating antibodies, and this factor is complicated by the fact that newborns cannot mount an antibody response to polysaccharide antigens, such as those found on bacterial capsules (eg, those of group B *Streptococcus* [GBS]). Newborns who experience a sufficient period of antigenic stimulation (usually 7–14 days) will exhibit a measurable IgM response to some viruses and parasites, which can be used diagnostically. In addition, antigen-specific T-cell responses are significantly reduced or delayed in neonates, and this also translates to delays in B-cell and antibody responses.

In the neonate, the factor associated most significantly with sepsis caused by any microorganism is low birth weight. Very low-birth-weight (VLBW) and premature infants are especially susceptible to infections. Other factors include prolonged rupture of membranes, traumatic delivery, maternal infection, chorioamnionitis, and fetal hypoxia. The incidence of

bacterial meningitis is greater in the neonatal period than in any other period in life. Furthermore, these infants are predisposed to a number of acquired infections by the use of modern neonatal intensive care techniques that include endotracheal intubation, parenteral nutrition, chronic blood vessel cannulation (umbilical, percutaneous intravenous, and other central vessel catheterization), disruption of skin integrity, delay in feeding, formula rather than human milk feedings, and administration of broad-spectrum antibiotics and other medications that alter the infant's intestinal and skin flora. Deficiencies in mucosal barrier function, and in both the innate and adaptive arms of the immune response, including serum complement components, defensins, and abnormalities in cytokine production, plus deficiencies of chemotaxis, phagocytosis, and microbial killing, contribute to the vulnerability of preterm neonates to systemic infections. Globally, the major burden of preterm birth is in the developing world, where infectious diseases such as malaria, human immunodeficiency virus (HIV), tuberculosis, and intestinal parasites cause much of the mortality and morbidity. Women and their infants also disproportionately bear the long-term consequences of sexually transmitted infections, including syphilis, herpesviruses, and *Chlamydia*.

Neonatal infections are caused by a variety of microorganisms. By convention, *congenital* infections have been assimilated into the acronym TORCH: toxoplasmosis, other agents (including syphilis, parvovirus B19, hepatitis B virus [HBV], enterovirus and HIV), rubella, cytomegalovirus (CMV), and herpes simplex virus (HSV). However, unlike most TORCH infections, which are acquired transplacentally, 90% of HSV and 80% of HIV infections are transmitted perinatally at the time of delivery. Many viruses that are transmitted from mother to child must find a way to persist in the infected mother for her to pass it on to her offspring.

Toxoplasma, CMV, rubella, and syphilis are the primary pathogens acquired in utero that result in congenital infection. Antenatal imaging has been a useful adjunct in prenatal diagnosis, and the most common fetal ultrasound findings to be associated with congenital infections are echogenic bowel, ascites, pleural effusions, cardiomegaly, and oligohydramnios; intrauterine growth restriction (IUGR) and ventriculomegaly coexist with other features. The yield of screening

infants born with IUGR or ventriculomegaly for all TORCH serology is low, even among infants screened for TORCH because of the presence of thrombocytopenia, neutropenia, direct hyperbilirubinemia, or dysmorphic features. Maternal hypertensive disorders of pregnancy, smoking, and drug or alcohol use are more likely culprits for IUGR. In all circumstances, postnatal screening for congenital infections must be cost-beneficial and -effective to be implemented. Table 102-1 summarizes the estimated relative incidence of some neonatal infections.

## CONGENITAL INFECTIONS

### Cytomegalovirus

CMV is the most common congenital infection and the leading infectious cause of damage to the developing fetus in developed countries. In the United States, 35,000 newborns (0.7%–1% of births) are infected annually, 6,700 of whom will have CMV-related damage. Among all children with bilateral moderate to profound sensorineural hearing loss (SNHL), an estimated 20% are attributable to congenital CMV infection. As is true of all herpesviruses, after primary infection, CMV establishes latency and can replicate actively at epithelial sites throughout the lifetime of the host. Intrauterine infection after primary maternal infection is 40% to 50%, compared with 0.5% to 2% after reactivation of latent virus. The existence of multiple strains of the virus is responsible for a small number of congenital infections acquired by reinfection with a new strain during pregnancy. CMV infects placental cytotrophoblasts and is transferred to the fetus through placental infection. The mechanisms by which CMV injures the fetus likely include a combination of direct fetal injury induced by pathologic, virally encoded gene products, an inability of the maternal immune response to control infection, and the direct effect of infection on placental function.

CMV is transmitted via breastfeeding, close contact with young children, and sexual contact. Improved hygiene and formula feeding in the developed world have delayed acquisition of CMV to the childbearing years. From 1988 to 2004, the overall age-adjusted CMV seroprevalence for individuals 6 to 49 years old in the United States remained stable at 50%. CMV seroprevalence is higher among non-Hispanic black and

**Table 102-1** Estimated Relative Incidence of Some Neonatal Infections (per 100,000 Live Births) in the United States

INFECTIOUS AGENT	OVERALL INCIDENCE PER 100,000 LIVE BIRTHS	SYMPTOMATIC AT BIRTH
Cytomegalovirus	1,000	100
<i>Toxoplasma gondii</i>	10–40	2–8
Rubella virus	<1	<1
Varicella virus	<1	<1
<i>Treponema pallidum</i> (syphilis)	13	4
Human Immunodeficiency Virus (HIV)	5	<1
Herpes simplex virus	10–40	10–40
Group B <i>Streptococcus</i>	30–50	30–50



Hispanic women compared with non-Hispanic white women, and in those who are older, foreign-born, have low household income, and have high household crowding. Infection rate is 2.5% during pregnancy, 5.5% between pregnancies, and 10% per year in women of childbearing age who are child care employees.

The highest risk of transplacental transmission resulting in congenital infection is during the third trimester of pregnancy (75%); however, most of these neonates will be born asymptomatic. On the other hand, 25% of newborns who acquire infection during the first trimester will have central nervous system (CNS) involvement. Overall, 90% of infected newborns will be asymptomatic, but 10% to 15% of these asymptomatic infants will still develop SNHL and, less commonly, other CNS sequelae. Of the 10% of newborns who have symptoms at birth, 20% will die; 70% will have hearing loss with varying degrees of developmental delay, motor or cognitive impairment, and seizures; and only 10% will survive without sequelae. Hence, overall, 20% of infected infants will have some degree of hearing or CNS disability. Symptomatic disease may manifest as premature delivery (35%), IUGR (50%), microcephaly (55%), periventricular calcifications, polymicrogyria, jaundice (65%), petechiae (75%), hepatosplenomegaly (60%), thrombocytopenia (77%), hyperbilirubinemia (70%), and mild hepatitis (85%). CMV has a predilection to the rapidly multiplying cells of the germinal matrix. If overt CNS findings are present at birth, almost all will have major neurodevelopmental sequelae. Microcephaly is the most specific predictor of intellectual and motor disability, followed by abnormal computed tomographic scan findings. The developing CNS remains vulnerable to damage from persistent virus replication after birth. SNHL is characteristically progressive, such that only about one-half of those who will eventually develop hearing loss are captured by universal hearing screening at birth. The 2007 American Academy of Pediatrics (AAP) and Joint Committee position statement on infant hearing called for hearing tests and neurodevelopmental assessments until school age.

Perinatal CMV infection can occur intrapartum because CMV may be in the cervix during late pregnancy and transmitted postpartum via human milk. Perinatal disease is mostly asymptomatic but may manifest as transient mild thrombocytopenia or transaminitis at 2 to 8 weeks of age. Among CMV seropositive women, 32% to 96% will excrete CMV into their milk; the peak period of excretion is 3 to 4 weeks after delivery. The risk-benefit ratio of pasteurizing human milk for the prevention of infection is unclear, and it is not recommended to withhold milk produced by CMV-seropositive mothers from healthy term infants.

To diagnose congenital infection, urine or saliva obtained within 14 days of birth is the best sample from which to isolate the virus by culture because of high titers shed from these fluids. Cultures obtained after 10 to 14 days do not differentiate congenital from perinatal acquisition of infection. Polymerase chain reaction (PCR) amplification of viral DNA is rapidly replacing viral culture as the most sensitive and efficient method for the detection of CMV. Real-time PCR assays of both liquid and dried saliva samples have reported sensitivities of 97% and 99.9%, respectively, compared with saliva rapid culture.

For prenatal diagnosis, isolated IgM titers in pregnant women are not sufficient; viral DNA in amniotic fluid together with ultrasound findings such as echogenic bowel and CNS abnormalities with IUGR, are most suggestive. Abnormal prenatal findings on ultrasound are associated with increased risk of sequelae. No guidelines exist for the treatment of CMV during pregnancy; using antepartum CMV hyperimmune globulin requires further assessment.

Treatment of congenital infection remains limited and suboptimal. Therapy of symptomatic disease involving the CNS with intravenous ganciclovir for 6 weeks results in modest improvement in hearing outcomes and developmental delays. Its use is associated with adverse effects, including neutropenia, complications of prolonged central venous catheterization, and the potential for sterility (in animal models). Valganciclovir, the oral prodrug of ganciclovir, is currently being investigated for treatment. A randomized, controlled trial is being performed by the National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CASG), using SNHL as its primary endpoint.

The Institute of Medicine has classified a CMV vaccine at the highest priority to prevent congenital infections, neurologic damage, and deafness, and to avoid major economic costs. Assessing the risk-benefit ratio of universal screening of all infants has significant obstacles including the lack of a standardized, high-throughput screening test and a protocol for follow-up of CMV-infected children. The substantial disparities in CMV risk among seronegative women suggest that prevention strategies should include an emphasis on reaching racial or ethnic minorities and women of low socioeconomic status. Increasing awareness of CMV's public health importance will foster the development of vaccines and drive the industry and regulatory agencies. Education of women and health care professionals about modes of transmission is key for prevention. Avoid kissing toddlers on their mouths, sharing utensils, and lapses in effective hand-washing practices, especially after changing diapers and handling toys.

### **Toxoplasma gondii**

Congenital toxoplasmosis is estimated at 10 to 40 per 100,000 live births, resulting in a large economic burden caused by mental and visual disabilities. Although congenital toxoplasmosis is not a nationally reportable disease, it is potentially preventable through education, screening of mother or newborn, and treatment of the pregnant woman. The implementation of screening interventions has been debated mainly because of differences in seroprevalence rates in different geographic areas and the unknown true burden of disease. The estimated seroprevalence rate in women of childbearing age in the United States is 15%. *Toxoplasma gondii* exposure is attributed to either consuming contaminated pork meat (the microorganism is destroyed by heating) or ingesting oocysts passed in the feces of cats in warm, moist climates. A risk of transmission exists with primary infection across the placenta, but not if infection is acquired before conception. The transmission rate is higher late in gestation (50%–80% vs <10% early in gestation), but anomalies are most severe (50%–80%)

if infection is acquired at 10 to 24 weeks' gestation. Treatment during pregnancy has been shown to reduce the rate of transmission, and seems to reduce serious neurological sequelae in the infant.

Congenital infection may result in fetal loss, be asymptomatic at birth (75%), manifest with symptomatic disease in the neonate within the first few months of life, or present later in life with relapse of undiagnosed infection, most commonly as retinochoroiditis. If untreated, up to 85% of all infected infants (including asymptomatic) will develop visual and learning disabilities with or without seizures later in life. Symptomatic newborns may have 1 or more of the following, which overlap with symptoms of other congenital infections: chorioretinitis, hydrocephalus, and intracranial calcifications (the classic triad of congenital toxoplasmosis); prematurity; cytopenias; jaundice; and maculopapular rash. Markedly increased cerebrospinal fluid (CSF) protein concentration that results from autolysis of necrotic brain tissue is a hallmark of congenital toxoplasmosis. A database on congenital toxoplasmosis in the United States has been accumulated through the National Collaborative Chicago-based Congenital Toxoplasmosis Study (NCCCTS), in collaboration with the Palo Alto Medical Foundation Toxoplasma Serology Laboratory (PAMF-TSL). Taking into account potential referral bias from 1991 to 2005 in 164 confirmed infected infants whose mothers had not been treated during gestation, severe clinical manifestations were reported in 84% and included eye disease (92%), brain calcifications (79%), and hydrocephalus (67%). In 61% of the infants, the triad occurred concurrently. The prevalence of clinical signs at birth might also vary among geographic areas of the world depending on the strain of the infecting parasite.

Serology remains the mainstay of diagnosis of infection in the neonate. Commercial kits, with specificity of 80% for detecting IgM, are used and thus should be interpreted with caution and confirmed, preferably in the reference PAMF-TSL. Testing for IgM and IgA antibodies increases the sensitivity to 93% compared with testing for IgM or IgA individually. Infections acquired late in the third trimester of pregnancy may be missed because antibodies have not yet been formed. The presence of IgM antibodies can also be detected in CSF. In addition, CSF, blood, urine, and placenta can be sent for detection of the organism by PCR. Prenatal diagnosis is made based on ultrasound findings and amniocentesis between 17 and 21 weeks' gestation for PCR testing in the presence of IgM, increased IgG, or both.

Affected children who receive treatment have favorable outcomes. Treatment of infants without substantial neurologic disease at birth with pyrimethamine and sulfadiazine for 1 year results in normal cognitive, neurologic, and auditory outcomes, while treatment of infants who have moderate or severe neurologic disease at birth leads to normal neurologic and/or cognitive outcomes for most of the patients, and normal auditory function in all.

Systematic serologic screening of either the newborn or the mother should be considered, given that improved outcomes result when infants receive proper therapy. In countries such as France, where seroprevalence rates are higher than those in the United States, prenatal screening has proven cost effective.

Massachusetts, New Hampshire, and Minnesota perform newborn screening and reporting of toxoplasmosis. Until consensus is reached, raising awareness and educating health care professionals and their patients (eg, using hot water to wash utensils after handling raw or undercooked meat, using gloves during gardening) are imperative to decrease the burden of disease.

### Rubella Virus

Although universal screening and vaccination programs have made congenital rubella syndrome (CRS) a rare occurrence in developed countries, susceptibility rates in women of childbearing age in Southern Asia, Africa, and some parts of Latin America are 20%. The national objective of elimination of rubella and CRS by 2010 from the United States has been attained. Zero to 6 cases are reported per year, most born to foreign-born mothers. Classically, rubella affects the heart, eyes, and ears because virus replication leads to tissue necrosis and damage to endothelium, but thrombotic thrombocytopenic purpura, osteitis (areas of translucency in metaphysis of long bones), and meningoencephalitis may occur in 25% of affected infants. Manifestations can be delayed in the form of purpuric rash, persistent diarrhea, pneumonia, and diabetes. Thus, similarly to congenital CMV, CRS is not a static disease, given the spectrum of time of onset of symptoms. Infants with rubella secrete virus in high titers in their urine for up to 2 years.

### Syphilis (*Treponema pallidum*)

Congenital syphilis is a preventable disease. The seroprevalence rate of syphilis in the United States is 4.5%, but is disproportionately higher in large urban areas, the rural southern states, and the black population (eightfold). Access to adequate prenatal care results in the relatively low national number of about 10 cases of congenital syphilis per 100,000 live births, with a case fatality rate (stillbirths and deaths) of 6.4%. Worldwide, however, congenital syphilis remains a major problem that affects 1 to 2 million pregnancies yearly, and is the second most common cause of stillbirth. Seroprevalence rates in some African countries, where resources for screening and treatment are most needed, exceed 15%. A World Health Organization initiative to eliminate mother-to-child transmission of syphilis aims for 90% or more of pregnant women to be tested for syphilis and 90% or more to receive treatment by 2015.

Prenatal screening is cost beneficial and cost effective. In 2004, the US Preventive Services Task Force strongly recommended that physicians screen all pregnant women for syphilis infection, and new evidence supports the effectiveness of such screening. Ideally, all women should be screened with nontreponemal serologic titers (Venereal Disease Research Laboratory [VDRL] or rapid plasma reagin [RPR] test) during the first trimester, then early in the third trimester and again at delivery for high-risk women (HIV-infected women, those who abuse drugs, those who reside in high-prevalence areas). Testing of women of unknown serostatus at delivery is necessary to identify potentially infected infants. Providers miss well-defined opportunities to prevent congenital syphilis for most cases in the United States.

The various manifestations of congenital syphilis depend on the stage and adequacy of treatment of

maternal syphilis and the gestation and immunologic response of the fetus. Transmission can occur any time during pregnancy, and intense inflammatory responses and prostaglandins induced by disseminated fetal infection may be responsible for fetal death, preterm delivery, and severe growth restriction. Congenital syphilis is more likely to occur with maternal primary and secondary syphilis (60%–100%), if maternal disease is of unknown duration or untreated, if fewer than 4 weeks have elapsed between therapy and delivery, and if maternal plasma nontreponemal titer (VDRL or RPR) is more than 1:16 after therapy or at delivery. A potentially higher rate of treatment failure exists in HIV-positive pregnant women.

Evaluation for congenital syphilis is warranted if the infant's nontreponemal titer (noncord blood) is 4-fold higher than the mother's or if the mother's titer has increased 4-fold; nevertheless, any increase in the infant's titer should be considered for evaluation. Using the same nontreponemal tests for the mother-infant pair is imperative. Treponemal tests (FT-ABS, MHA-TP, TP-PA) are not useful for the infant. Signs of congenital syphilis are nonspecific and include prematurity and low birth weight (10%–40%); hepatomegaly, with or without splenomegaly (33%–100%); a blistering, scaly, copper-colored skin rash (40%); periostitis and osteochondritis (75%–100% vs 20% in asymptomatic infants); pseudoparalysis (12%); respiratory distress (35%); CNS involvement with high CSF protein and pleocytosis (25% vs 10% in asymptomatic infants); Coombs-negative hemolytic anemia with hydrops; and thrombocytopenia and fever (10%–45%). Although more than one-half of affected infants are asymptomatic at birth, lumbar puncture and long-bone radiographs are often justified because 60% of these infants may be infected and develop disease at 4 to 8 weeks of life manifesting as snuffles, hepatosplenomegaly, lymphadenopathy, rash, or osteochondritis; or the disease may develop much later in life. Treatment of confirmed or highly probable congenital syphilis is with penicillin (intravenous or intramuscular) for 10 days; ampicillin is not acceptable. Follow-up with serologic assays should be carried out for at least 6 months. In the presence of mucocutaneous skin lesions or nasal discharge, gloves should be worn until 24 hours after initiation of therapy.

### Parvovirus B19

Parvovirus B19 virus is transmitted in utero and has been identified as a cause of adverse fetal and neonatal outcomes. The virus is cytotoxic to erythroid progenitor cells inhibiting erythropoiesis. Seroprevalence rates vary from 50% to as much as 70% in day care educators. Transmission rate during pregnancy is 30%, and although most newborns are asymptomatic and healthy, some evidence suggests that a high rate of intrauterine viral infection occurs throughout gestation and the virus persists until birth and beyond. Adverse outcomes such as fetal anemia, IUGR, neurologic anomalies, and nonimmune hydrops fetalis, as well as fetal death (overall risk 5%), are more likely if infection is acquired in the first half of pregnancy. The virus is not transmitted through breastfeeding. Prenatal diagnosis is made by maternal IgM antibodies and

viral DNA in fetal blood. Detection of B19-specific IgM in infant serum (EIA) is the preferred test postnatally, but sensitivity and specificity vary; viral DNA from serum or tissues can be confirmatory.

## PERINATAL INFECTIONS

### Human Immunodeficiency Virus

Maximal reduction of perinatal HIV infection is among the goals of the Centers for Disease Control and Prevention (CDC) Advancing HIV Prevention Initiative, which was updated in 2013. In order to reach this goal, HIV testing and antiretroviral (ARV) prophylaxis and treatment are essential. The CDC recommends that all states require public health reporting of all cases of perinatal HIV exposure in infants. With maternal diagnosis and prophylaxis during the perinatal period, perinatal HIV transmission is usually preventable in all but 2% or less of cases, adding up to approximately 150 cases in the United States yearly, mostly because of missed prevention opportunities. The AAP recommends routine education and HIV testing, with consent, of all pregnant women in the United States. Third trimester repeat testing should be done if a woman has risk factors, is in an area of high prevalence, or has previously refused. Current guidelines recommend using highly active antiretroviral therapy, preferably a regimen that includes zidovudine, for women whose plasma HIV RNA levels are greater than 1,000 copies/mL. If the mother's status is unknown, testing during labor or immediate testing of the newborn by a rapid HIV antibody test are recommended. In some states, rapid testing is required by law. The infant's primary care physician plays a key role in preventing mother-to-child transmission of HIV by identifying HIV-exposed infants, prescribing ARV prophylaxis for these infants, and promoting avoidance of HIV transmission through human milk. Continued efforts should focus on collecting data to identify the missed opportunities and to modify practices accordingly, sustaining the commitment to reinforce recognized factors such as increased accessibility to prenatal care, enhancing counseling, and lowering barriers such as social stigma and informed consent.

Most transmission of HIV is peripartum (80%), but it can occur in utero, especially in the third trimester, or postpartum via breastfeeding. Newborns are asymptomatic but if untreated will progress to AIDS within a year. The higher the maternal HIV RNA levels, the higher the risk of transmission. The preferred test for diagnosis of HIV infection in infants is HIV nucleic acid detection by PCR assay of DNA extracted from peripheral blood mononuclear cells, not umbilical cord blood. Approximately 93% of infected newborns have detectable HIV DNA by 2 weeks of age. A third PCR should be performed at 1 to 2 months of age. Prophylaxis with zidovudine alone for 6 weeks is indicated for most exposed infants.

### Hepatitis B Virus

Five percent of the US population and 350 million people worldwide are infected with hepatitis B virus (HBV), and 1 million people die each year of HBV-associated disease. HBV is highly endemic in China and Southeast Asia, among other places. Because only



1 serotype of HBV has been found, a protective vaccine has been developed, and routine immunization programs have decreased HBV prevalence. Most states require that all mothers be tested for serologic evidence of HBV infection. Because of its lipoprotein envelope, HBV resists enzymes in the blood. The blood of carriers often contains approximately 100 million infectious particles per milliliter, making it among the most infectious of all viruses: 1  $\mu$ L of blood is sufficient for spread.

Most transmission occurs through the blood of the infected mother mixing with that of her child during childbirth. Without intervention, 70% to 90% of infants will be infected at birth if the mother tests positive for both the hepatitis B surface antigen and the hepatitis B e antigen; the transmission rate drops to 35% if the mother tests negative for the hepatitis B e antigen. Hepatitis B vaccine administered within 12 hours of birth to exposed newborns, together with hepatitis B immune globulin (HBIG), reduce the vertical transmission rate by almost 90%. This combination provides sufficient protection against any further theoretical risk. Ninety percent of infected newborns become chronic carriers because of their immature immune system. Carriers who acquire the virus at birth comprise the largest cohort to spread the virus to others.

### Hepatitis C Virus

Two percent of the US population and 170 million people worldwide are infected with hepatitis C virus (HCV). Similar to HBV, HCV is highly infectious. Unlike HBV, HCV has many serotypes because of its high mutation rate; hence creating a universally effective vaccine has been difficult. Maternal-fetal transmission of HCV likely occurs either in utero or intrapartum, and 7% to 10% of newborns of affected mothers will be infected at birth. The risk of vertical transmission is greatly increased if the mother is coinfecting with HIV unless she is receiving highly active antiretroviral therapy, which eliminates the difference in risk. No current recommendations have been issued to screen mothers for HCV, given the absence of an intervention to prevent vertical transmission. Testing for the presence of anti-HCV antibody is recommended for HIV-positive mothers in addition to those with past or current intravenous drug use, known HCV exposure, and history of blood transfusions before 1992. HCV-infected mothers can breastfeed their infants; HCV transmission rates in milk of HCV antibody-positive but HCV-RNA-negative mothers are reported to be near zero. HCV antibodies in colostrum and mature human milk seem protective for infants born to HCV antibody-positive but HIV-negative mothers. However, as these antibody levels wane, the risk for HCV transmission in human milk has been documented to increase. Because of the 50% chance of viral reactivation (conversion to HCV-RNA-positive status) in HCV antibody-positive women, additional HCV-RNA testing is recommended during breastfeeding.

Infected infants are asymptomatic. They may have transient viremia and maternal anti-HCV antibodies during the first year of life. PCR for HCV can be obtained as early as 1 month of life to confirm infection of the infant. Alternatively, anti-HCV antibody testing should be performed in the infant during the first 12 to 18 months of life.

### Herpes Simplex Virus Types 1 (Mucosal) and 2 (Genital)

Neonates have the highest frequency of visceral and CNS infection of any HSV-infected population of patients. The morbidity and mortality associated with this virus cannot be overemphasized: the untreated case-fatality ratio is 60%. Early detection and treatment are required to reduce neurologic sequelae in surviving infants. A third of the world is infected with HSV. Sixty percent of women of childbearing age are seropositive for HSV-1, and 25% of the US population is seropositive for HSV-2. The seroconversion rate during pregnancy is 1% to 2%. The estimated number of neonatal herpes infections in the United States is 10 to 40 cases per 100,000 live births (~1,500 cases annually), with up to one-quarter of cases caused by HSV-1 infection.

Virus reproduction initiates rapidly in epithelial cells. Subsequently, the virus establishes latency in the surrounding sensory nerve cells. From time to time, reactivation occurs and leads to infection of the surrounding epithelial cells. Perinatal transmission occurs via contact between the virus produced in the epithelial cells and genital secretions (or saliva) of the mother and the baby's abraded skin, which is denuded of keratin, thus exposing epithelial cells during (or after) birth. Approximately 90% of transmission occurs during delivery and less than 10% postnatally. The mother may have primary or recurrent active genital lesions or subclinical virus shedding. Maternal IgG is somewhat protective. With first-episode primary maternal infection and shedding at delivery, an estimated 60% of babies acquire neonatal HSV disease; with first-episode nonprimary maternal infection and shedding at delivery (ie, mother is positive for HSV-1 antibody but she is having her first HSV-2 disease or vice versa), an estimated 25% of babies acquire neonatal HSV disease; and with recurrent maternal infection and shedding at delivery, about 2% of babies acquire neonatal HSV disease. Since disease may be subclinical in the mother, more than 70% of infants with neonatal HSV are born to mothers with no symptoms or signs of HSV lesions at delivery.

In the immune-immature host, the virus can reproduce in high numbers and spread systemically from the eye, skin, and mouth to the CNS, adrenals, liver, and lungs. Liver involvement is marked by fever in the newborn. Disease is most commonly evident by approximately 12 days of life (range, 3–21 days of life). If acquired postnatally, it can occur as late as 28 days. HSV disease manifests in 1 of 3 forms: skin, eye, and mouth (SEM) disease, usually with a vesicular rash, occurring at approximately 7 to 10 days; CNS disease, which presents at approximately 17 days with irritability, lethargy, poor feeding, apnea, and seizures; and disseminated disease, which occurs at 5 to 9 days of life, mimicking sepsis, with fulminant hepatitis, respiratory failure, meningoencephalitis, and mortality rate of 30%. With disseminated disease, the brain is probably infected via blood, whereas in CNS disease, infection is probably the result of neuronal spread. If untreated, 70% of SEM disease progresses to CNS or disseminated disease. The sequelae of CNS disease are less severe with HSV-1 than with HSV-2,



but disseminated disease with either virus carries the same death prognosis.

Skin, conjunctivae, oropharynx, rectum, and urine can be cultured for herpes. Growth in cell culture is fast, generally 48 to 72 hours. Detection of HSV 1 and 2 DNA by PCR from CSF has significantly enhanced the detection of CNS disease. A high index of suspicion should be present in all ill infants in the absence of skin lesions. Viral DNA can be detected in CSF for up to 2 weeks, although with decreasing sensitivity over time. The application of PCR testing to blood specimens seems promising.

Despite therapy with acyclovir, 70% of infants with CNS disease will have various degrees of disabilities; therefore, the physician must make an early diagnosis and promptly intervene, given the potential of timely therapy. CSF PCR is suggested for all babies with CNS disease at the end of therapy because failure to clear viral DNA warrants continuation of therapy. Data are insufficient at the current time to allow the use of serial PCR assays of blood to establish response to or duration of antiviral therapy.

Cesarean delivery in a woman with active genital herpes lesions significantly reduces, but does not eliminate, the risk of infection. In 2013, the AAP reported guidance on the management of asymptomatic neonates born to women with active lesions using both serologic and virologic studies, if available to the physician, to determine the risk of HSV transmission. Infant HSV surface cultures, and blood PCR if available, should be obtained at 24 hours of life. If the mother has history of genital herpes preceding pregnancy, one can evaluate the infant with surface cultures or blood PCR and treat empirically to prevent progression from neonatal infection to disease only if those results are positive with intravenous acyclovir for 10 days. Ten days of preemptive therapy is also recommended if the mother has a documented or assumed first-episode primary or first-episode nonprimary infection regardless of the neonate's evaluation results (Figure 102-1, Figure 102-2). Preterm babies are more vulnerable, and prematurity generally predicts mortality; thus, infants born at less than 37 weeks may benefit from earlier evaluation and treatment.

It has been reported that neonates surviving HSV disease with CNS involvement had improved neurodevelopmental outcomes when they received suppressive therapy with oral acyclovir for 6 months. Most also use suppressive oral acyclovir therapy for recurrent SEM disease that may be associated with CNS involvement in 10% of instances. Neutropenia is a known but reversible adverse effect of such treatment.

### Enteroviruses

Enteroviral infections of the neonate are common. In most cases, infection is acquired from the mother perinatally in the summer months and less often from the hospital via caretakers in close contact with the infant. Coxsackievirus group B serotypes 2 to 5 and echovirus type 11 can cause fulminant, sometimes fatal, disease in the neonate, especially if it occurs early (between 3 and 7 days of age). Early symptoms are poor feeding and respiratory distress; generalized disease mimics sepsis or disseminated herpes infection,

with myocarditis and meningoencephalitis or fulminant hepatitis. More than one-half of patients may die despite adequate supportive therapy. Although neonates respond by mounting an antibody reaction, macrophage function, which is necessary to limit initial enteroviral replication, is not sufficiently mature in the neonate. Premature infants are more susceptible than term infants because of the absence of passively acquired maternal antibody. Diagnosis can be made rapidly by culturing oropharyngeal secretions, feces, or urine, or by detection of viral DNA by PCR from various sites including CSF.

### Chlamydia and Ureaplasma species

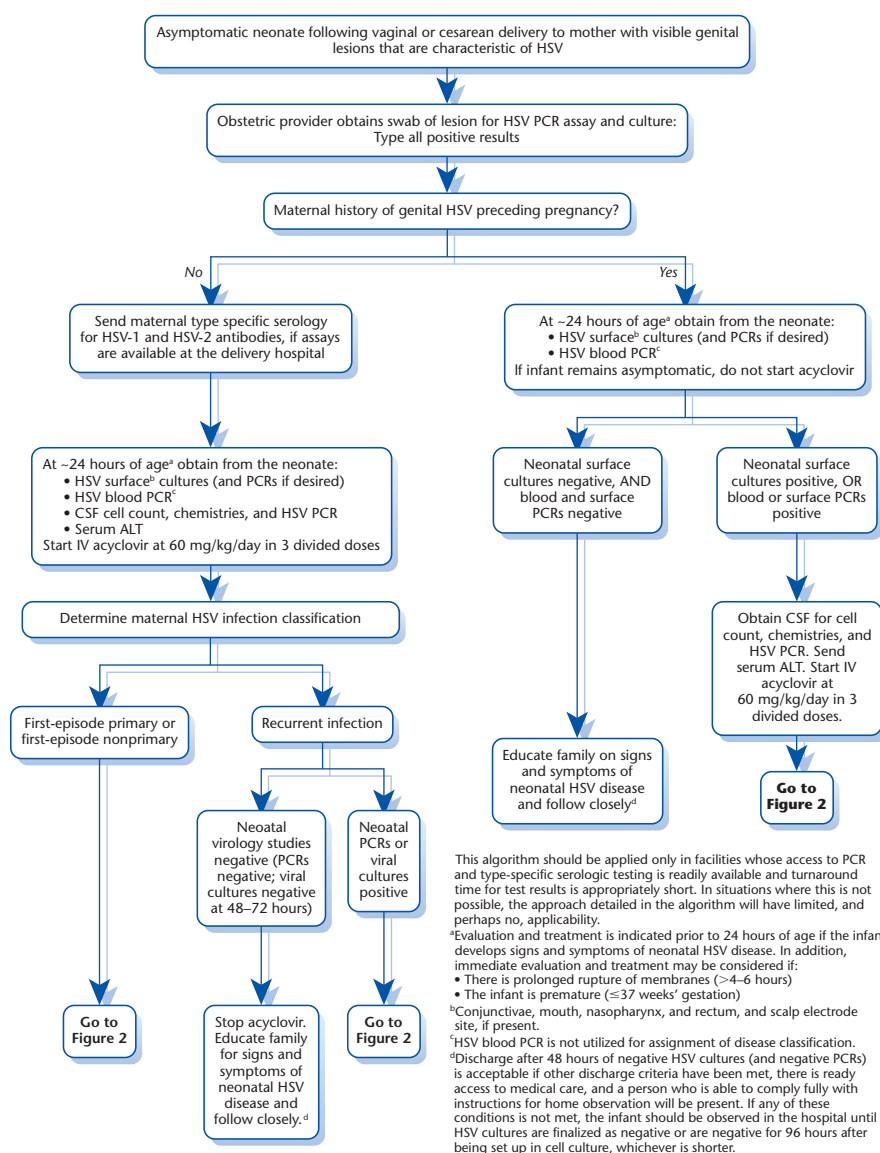
*Chlamydia trachomatis* is the most common cause of sexually transmitted infection, resulting in 100,000 annually exposed neonates in the United States. The infant of an untreated mother has a 35% chance of developing mucopurulent conjunctivitis and a 15% chance of developing pneumonia in the first few months of life.

*Ureaplasma* species can be acquired by the fetus at any time during pregnancy or at birth by passage through an infected birth canal. Several studies have shown that *Ureaplasma* species can cause congenital and neonatal pneumonias, especially in preterm infants; however, controversy remains on whether *Ureaplasma* infection of the respiratory tract contributes to the development of bronchopulmonary dysplasia. The fastidious nature and susceptibility of these organisms to drying mandate careful attention in specimen collection. Isolation from normally sterile sites in an ill infant with otherwise unexplainable causes is suggestive of disease. Antibiotic therapy may be efficacious in such instances.

### Tuberculosis

One-third of the world's population is estimated to be infected with *Mycobacterium tuberculosis*. The mother-to-child transmission rate in resource-limited settings is 15%. Given the increasing number of immigrants to the United States from countries where tuberculosis (TB) is endemic, a high index of suspicion for congenital and perinatal TB must be maintained for ill neonates born to women at risk for TB. Prompt treatment of disease in the mother greatly diminishes the risk of disease in the infant. Congenital TB is rare and is acquired in utero by hematogenous spread or by aspiration or ingestion of infected amniotic fluid. The more common perinatal disease occurs at birth by aspiration of infected amniotic fluid or, more commonly, by airborne transmission from the mother or any adult with TB disease in close contact with the newborn, including health care providers. The incidence of TB disease among foreign-born health care providers in New York State, for example, is 18 per 100,000. Such transmission of *M. tuberculosis* emphasizes the importance of effective latent TB infection testing and prophylaxis programs in health care settings.

Symptoms of congenital TB are nonspecific and include hepatosplenomegaly, respiratory distress with abnormal chest radiograph, fever, and lymphadenopathy, which appear at approximately 2 to 3 weeks of life. Perinatal infection exhibits similarly and, if untreated, often results in local progression



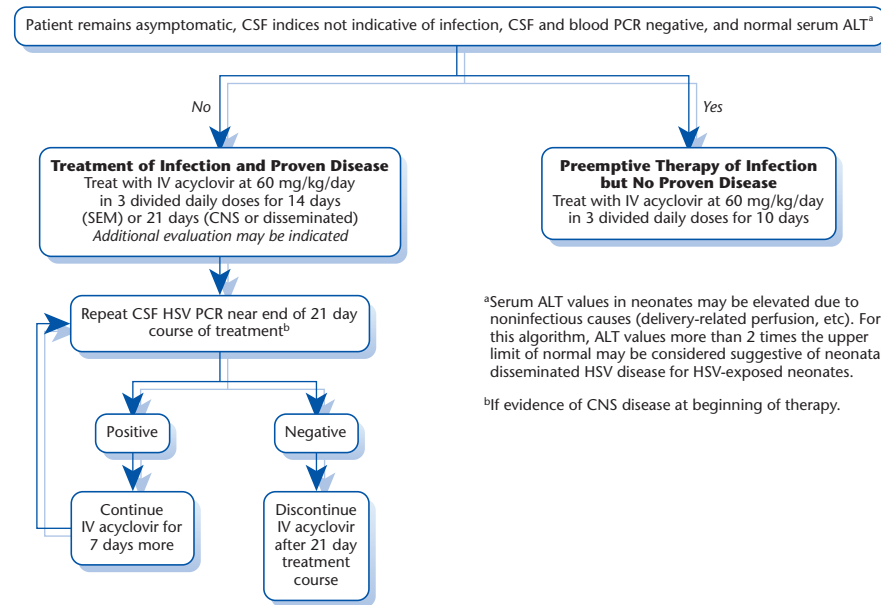
**Figure 102-1** Algorithm for the evaluation of asymptomatic neonates after vaginal or cesarean delivery to women with active genital herpes lesions. ALT, alanineaminotransferase; D/C, discontinue. (Reprinted from Kimberlin DW, Baley J; American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and Newborn. Guidance on management of asymptomatic neonates born to women with active genital herpes lesions. *Pediatrics*. 2013;131[2]:e635–e646.)

and dissemination (miliary TB), including meningitis. Because treatment of the infant with multiple drugs greatly improves outcome, making the correct diagnosis is imperative. Diagnosis is established by demonstrating acid-fast bacilli or isolating *M tuberculosis* from body fluids. The tuberculin skin test (TST) is initially negative and may take 1 to 3 months to become positive. A positive TST result in infants is a sentinel indicator for recent transmission. If the mother (or household member) has received antituberculosis therapy for less than 2 weeks before delivery, then the exposed newborn should be treated with isoniazid for 3 months after active TB disease is excluded. A TST is performed at that time, and therapy is discontinued if negative. Similar recommendations ought to be implemented in exposed infants in the nursery or neonatal intensive care unit (NICU).

Infants suspected of having congenital TB need to be isolated and appropriate infection control precautions undertaken. Because HIV infection represents the greatest risk factor for acquisition of TB, both mother and child should be tested for HIV. Separation of the infant from the mother (or household member) is necessary only if the mother has multidrug-resistant TB (or, inevitably in the future, extensively drug-resistant TB) or if noncompliance is expected.

### Varicella-Zoster Virus

The only herpesvirus that can also be transmitted without person-to-person contact is varicella-zoster virus (VZV). With current vaccination programs in the United States, susceptibility rates of pregnant women are low, and congenital infection with VZV



**Figure 102-2** Algorithm (continued) for the evaluation of asymptomatic neonates after vaginal or cesarean delivery to women with active genital herpes lesions. ALT, alanineaminotransferase; D/C, discontinue. (Reprinted from Kimberlin DW, Baley J; American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and Newborn. Guidance on management of asymptomatic neonates born to women with active genital herpes lesions. *Pediatrics*. 2013;131[2]:e635–e646.)

(nervous system stigmata, malformed extremities), which affects 5% of exposed infants, is extremely rare. Perinatal VZV infection is associated with a high death rate if maternal disease develops within 5 days before or 2 days after delivery. Progressive pneumonitis is characteristic of perinatal disease. Postexposure prophylaxis is available and effective.

## NEONATAL SEPSIS

Most common bacterial pathogens that cause neonatal sepsis are acquired perinatally.

### Group B *Streptococcus*

Group B *Streptococcus* (GBS) was the leading cause of neonatal infections in the 1970s and 1980s, with case fatality rates of 20% to 50%. The implementation of preventive intrapartum antibiotic prophylaxis (IAP) since the 1990s has reduced early-onset disease incidence by 85% to a rate of approximately 25 cases per 100,000 live births, with case fatality rates of 7%, except in preterm infants (<37 weeks' gestation), among whom the fatality rate approaches 25%.

GBS colonizes the genitourinary or gastrointestinal tract (or both) of women. Carriage rates are higher in black women (up to 40% vs 15%). GBS can be transmitted in utero (which may result in stillbirth), at delivery, or postnatally. It is classified as early-onset (before the first week of life with 90% manifesting within 24 hours) or late-onset disease (between 1 week and 90 days of life). The incidence ratio of early-onset to late-onset disease in the era of IAP has dropped from 3:1 to 1:1. In the neonate, early disease manifests with bacteremia, sepsis, pneumonia, and meningitis (<10% of cases). Late-onset disease presents as meningitis (35% of cases), occult bacteremia, and focal infections such as osteomyelitis or arthritis, facial cellulitis,

submandibular cellulitis, or cellulitis-adenitis in other regions. Evaluation for CNS involvement is indicated in the cellulitis-adenitis syndrome.

Since 2002, revised guidelines from the CDC, AAP, and American College of Obstetrics and Gynecology recommend universal rectogenital culture-based screening of pregnant women at 35 to 37 weeks' gestation. Pregnant carriers should receive intravenous penicillin or ampicillin intrapartum (oral antibiotics are ineffective) at least 4 hours before delivery to allow appropriate distribution to amniotic fluid and genital secretions. If GBS status is unknown at the time of delivery, intrapartum antibiotics should be administered in the presence of 1 or more of the following: preterm labor less than 37 weeks, temperature more than 100.4°F (38°C) during labor (as an indicator for maternal chorioamnionitis), rupture of membranes (ROM) 18 or more hours before delivery, previous newborn with GBS disease, or GBS bacteruria during current pregnancy. IAP does not eliminate colonization in women, likely a reason for the unchanged rates of late-onset disease.

Culture remains the gold standard for diagnosis; real-time PCR analysis of samples taken from the ear, nose, or rectum, when standardized, may hasten the speed of diagnosis and avoid unnecessary treatment. Ampicillin and gentamicin are provided empirically for the treatment of GBS disease and substituted with penicillin once the organism is isolated from any sterile site. Duration of treatment for septicemia is 10 days, for meningitis 14 to 21 days.

Guidelines have been put forth for evaluation and management in situations considered high risk for neonatal early-onset sepsis (EOS) such as maternal chorioamnionitis and inadequate IAP. In circumstances where IAP is indicated but not adequately given, the 2010 CDC recommendations advocate for a

limited evaluation (complete blood count [CBC] and blood culture) without empiric antibiotic therapy treatment if the infant is 37 weeks or less gestation with no signs of sepsis, or if ROM is 18 hours or more. In 2012, the AAP Committee on Fetus and Newborn (COFN) published guidelines for EOS evaluation and prevention that advocated clinical observation in this setting for well-seeming infants with a normal physical examination born at 35 weeks' or more gestation. In these infants, a CBC at 6-12 hours without a blood culture is advocated as long as the infant continues to seem well. If the duration of membrane rupture is 18 hours or longer, COFN recommends hospital observation for 48 hours without further testing or cultures.

In 2010, the CDC recommended empiric antibiotics while awaiting limited evaluation results of blood culture and CBC for all infants whose mothers have intrapartum chorioamnionitis. Challenges in the accurate diagnosis of chorioamnionitis (maternal fever is frequently used as a surrogate) and in the use of this obstetric diagnosis to guide neonatal therapy are acknowledged. Recently, there are reports suggesting that the risk of EOS in infants born to women with chorioamnionitis is strongly dependent on gestational age, with risk as low as 0.5% to 1.25% for infants born at more than 35 weeks' gestation. These publications have prompted many centers to develop local adaptations of the recommendations in an effort to avoid unnecessary treatment of uninfected infants. Obstetric and neonatal interventions to prevent EOS are effective and should be continued, with periodic reexamination based on efficacy and cost-effectiveness data.

Healthy-seeming infants without evidence of bacterial infection should not receive broad-spectrum antimicrobial agents for more than 48 to 72 hours, including the well-seeming term infant whose mother was treated for chorioamnionitis and who has a negative blood culture even when the infant's laboratory results (CBC and/or C-reactive protein obtained at 6 to 12 hours of age) are abnormal. Reports based on serial examination, rather than risk factors or screening laboratory tests, are emerging as solid indicators of infection. Adoption of such approaches will require that frequent examinations be performed, particularly over the first 24 hours. Observation may occur at home after 24 hours if the infant is full-term and there is a knowledgeable observer and ready access to medical care.

So far, maternal GBS prophylaxis has not resulted in a greater likelihood of non-GBS infections, such as invasive *Escherichia coli* infections, in newborns except in VLBW infants. Meanwhile, ampicillin resistance has emerged among gram-negative pathogens; thorough evaluation and systematic monitoring for trends in various pathogen prevalence rates and resistance patterns in these infants are critical.

### **Escherichia coli**

*Escherichia coli* (*E coli*), a member of the gram-negative Enterobacteriaceae, which are prevalent in the maternal gastrointestinal and birth tracts, used to be the second-leading cause of neonatal bacteremia, sepsis, and meningitis. In the era of IAP for GBS, the incidence of *E coli* infections in overall neonatal

sepsis has equaled that of GBS. The incidence of *E coli* sepsis has increased in VLBW and premature infants. Transmission risk factors are the same as those for GBS. Many *E coli* strains isolated from neonates express capsular proteins and toxins that facilitate traversing the blood-brain barrier and attaching to brain endothelial cells. Meningitis is more likely when the level of bacteremia is high. The organism can be isolated from sterile sites, and treatment should be adjusted according to the sensitivities. Most *E coli* are ampicillin resistant, and third-generation cephalosporins should be included as empiric treatment of suspected gram-negative sepsis in newborns. Case fatality of *E coli* meningitis is 10% to 20%. CSF should be checked 48 to 72 hours after initiation of antibiotic therapy, and reexamined until sterility. Early head imaging should be utilized to ensure that ventricles communicate, and to assess for other complications such as ventriculitis or abscess. Minimum duration of treatment is 21 days.

Other strains cause epidemic diarrhea in newborn nurseries with listlessness, poor feeding, and watery, mucousy stools developing over 3 to 6 days. Endotoxemia, overgrowth of gram-negative bacilli in the absence of lysozyme (normally present in human milk), and many other factors have been implicated in the pathogenesis of necrotizing enterocolitis. No strategies for preventing gram-negative infections have been identified yet, and because of the diversity of neonatal pathogens, single-pathogen vaccines will have limited effect.

### **Listeria monocytogenes**

*Listeria monocytogenes* is a gram-positive rod that is acquired through ingestion of raw or unpasteurized milk or their products, soft cheeses, undercooked poultry or meat, including patés, or unwashed fruit or vegetables, and can colonize the vagina and rectum of pregnant women. Infection rates have declined in the past decade. It manifests as influenza-like illness 2 to 14 days before delivery in 65% of women, and clinical chorioamnionitis is common.

A nationally notifiable disease, it has characteristics similar to GBS disease. Early-onset sepsis is most likely acquired in utero and has a case fatality rate of about 25%; late-onset (after 1 week of age) meningitis is acquired at parturition and, less commonly, in the hospital environment. Treatment is with ampicillin and gentamicin.

### **Special Considerations for Infants Requiring Prolonged Hospitalization**

Infants in NICUs are at increased risk of developing diseases from several other organisms. Coagulase-negative staphylococci have been the most common cause of hospital-acquired infections in the NICU since the 1980s. *Staphylococcus aureus*, a skin colonizer, is implicated in various clinical entities and outbreaks. Enterococci are isolated in 10% to 15% of neonatal cases of sepsis in the NICU. The emergence of antibiotic resistance will dictate the challenges of therapy in these newborns. Multifaceted interventions that help ensure adherence with evidence-based infection-control practices and the judicious use of antibiotics are essential in controlling these potentially invasive pathogens.



### Candida Species

Invasive *Candida* infections (incidence 1%–15%) have been observed in recent years as a result of the larger numbers of surviving premature, VLBW babies with prolonged central vascular catheter use and prolonged use of broad-spectrum antibiotics. Death (11%–44%) or neurodevelopmental impairment (with and without documented meningitis) occur in young, VLBW infants who develop candidiasis. Other complications include indolent arthritis, osteomyelitis, and endocarditis. *Candida albicans* is the most common and most virulent colonizing species, but it can be treated with fluconazole and is less likely to display resistance during drug exposure. *Candida galbrata* and *Candida parapsilosis* act more as opportunists, but they are capable of developing resistance to azoles under pressure of drug exposure. Some NICUs have adopted prophylaxis with fluconazole to reduce colonization and subsequent invasive fungal infections. Universal prophylaxis with fluconazole may lead to emergence of resistant organisms and increases in the prevalence of non-*albicans* species. No conclusive data exist on changes in late morbidity and mortality rates with this regimen. Targeted short-course fluconazole to VLBW infants who are to receive broad-spectrum antibiotics for more than 3 days has been shown to be cost effective and may alleviate some of the previously mentioned concerns. In addition, newer antifungal agents are being evaluated in this age group.

### Respiratory Syncytial Virus

Premature infants, especially those with chronic lung disease, and certain groups of infants with serious medical conditions (acyanotic CHD requiring medication or surgery in the first year of life, infants with respiratory compromise or severe immunodeficiency), are at increased risk for severe respiratory infections caused by respiratory viruses such as respiratory syncytial virus (RSV) and influenza. Compared with healthy infants, they have prolonged and more severe complications from respiratory infections for the first year of life. Guidelines for prophylaxis against RSV with the monoclonal antibody palivizumab (Synagis) beginning before the onset of RSV season were last revised in 2014. Breakthrough infections occur in 2% to 3% of cases. Early detection with available rapid tests is crucial to optimize supportive care, thus preventing associated morbidity. Vaccinating those around newborns with the influenza vaccine is the only way to protect the infants from infection with influenza viruses.

### TOOLS FOR PRACTICE

#### Medical Decision Support

- *Congenital Syphilis—United States, 2003–2008* (article), Centers for Disease Control and Prevention ([www.cdc.gov/mmwr/preview/mmwrhtml/mm5914a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5914a1.htm))
- *Postvaccination Serologic Testing Results for Infants Aged ≤24 Months Exposed to Hepatitis B Virus at Birth: United States, 2008–2011* (article), Centers for Disease Control and Prevention ([www.cdc.gov/mmwr/preview/mmwrhtml/mm6138a4.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6138a4.htm))
- *Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings* (article), Centers for Disease Control and

Prevention ([www.cdc.gov/mmwr/preview/mmwrhtml/rr5514a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5514a1.htm))

- *The Epidemiology and Prevention of Congenital Cytomegalovirus Infection and Disease: Activities of the Centers for Disease Control and Prevention Workgroup* (article), *Journal of Women's Health*, Vol 15, Issue 3, 2006
- *The Prevention and Management of Congenital Syphilis: An Overview and Recommendations* (article), *Bulletin of the World Health Organization*, Vol 82, Issue 6, 2004
- *Trends in Perinatal Group B Streptococcal Disease—United States, 2000–2006* (article), Centers for Disease Control and Prevention ([www.cdc.gov/mmwr/preview/mmwrhtml/mm5805a2.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5805a2.htm))

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### Chapter 103

## THE NEWBORN WITH HEMATOLOGIC ABNORMALITIES

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Evaluating hematologic disorders in newborns is fundamentally different from evaluating hematologic disorders in older children because the developmental aspects of erythropoiesis and hemostasis are not complete at birth but rather continue throughout much of the first months of life.

### ANEMIA IN THE NEONATE

The fetal and neonatal erythrocyte differs from the adult erythrocyte with regard to life span, membrane structure, hemoglobin (Hb), and metabolic content. The life span of the erythrocyte in a healthy term infant is 60 to 80 days and in a preterm infant is 30 to 50 days.

This time span is significantly shorter than the 120 days of an adult red blood cell. At birth, the erythrocyte reflects the hypoxic environment of fetal life in which oxygen delivery is one-third that of an adult. This relative hypoxia leads to increased erythropoietin and active erythropoiesis evident by increased reticulocytes and nucleated red cells during the first few days of life. At birth, when lungs become the oxygen source, Hb saturation increases to 95%, erythropoietin levels fall, and erythropoiesis significantly decreases.

Hematologic values for the term and preterm newborn reflect the active nature of erythropoiesis in late fetal development during which Hb concentration rises slowly from approximately 14.5 g/dL at 28 weeks' gestation to 15.0 g/dL at 34 weeks to 16.8 g/dL at 40 weeks. The reticulocyte count is elevated for the first 3 days of life and drops to less than 1% by day 7 in the term newborn, whereas in the preterm newborn, the reticulocyte count is higher in cord blood and may remain elevated until day 7 of life.

The physiologic anemia of the term newborn is not a pathologic state but rather an adjustment to the state of excess capability of oxygen delivery relative to tissue needs at birth. The combination of a shortened neonatal red cell survival, decrease in erythropoiesis, and growth-related increase in blood volume leads to a progressive decrease in Hb concentration during the first 2 months of life. This physiologic nadir may occur from weeks 6 to 12 of life, when the Hb concentration is between 9.5 and 11.0 g/dL. Erythropoietin will then increase as sensors in the kidney and liver detect tissue hypoxia, and an increase in reticulocytes heralds an increase in Hb concentration, which rises to a mean of 12.5 g/dL.

Anemia in premature neonates, however, is not physiologic and is multifactorial in nature. Up to 50% of premature infants younger than 32 weeks' gestation will develop symptoms associated with anemia of prematurity. Symptoms may include respiratory difficulties (apnea, periodic breathing, tachypnea), poor feeding and weight gain difficulties, tachycardia, flow murmurs, and pallor. The erythropoietin response to anemia is suboptimal in the preterm infant in whom the liver is the source of erythropoietin and hepatic oxygen sensors may be less sensitive. The preterm infant's shortened red cell survival, expanding blood volume with rapid growth, and iatrogenic blood loss from frequent testing aggravate the effects of erythropoietin deficiency.

Infants weighing less than 1.2 kg will reach their Hb nadir at 4 to 8 weeks with a Hb concentration of 6.5 to 9.0 g/dL. Infants from 1.2 to 2.5 kg will reach a nadir between 5 and 10 weeks with a Hb concentration of 8.0 to 9.0 g/dL. Iron supplementation is recommended for all preterm infants, in the range of 4 to 6 mg/kg/day of elemental iron. Ensuring adequate nutritional intake of vitamin E, B<sub>12</sub>, and folate is also important. Anemia of prematurity typically resolves by 3 to 6 months of age. The Premature Infant in Need of Transfusion randomized clinical trial, published in 2006, demonstrated that transfusion to maintain a high hematocrit does not reduce mortality or

morbidity or improve long-term outcome for infants with anemia of prematurity.

### Approach to Anemia

Three broad classifications of anemia exist in the newborn, including blood loss, hemolysis, and decreased production. The medical history and physical examination may often reveal the cause of the anemia. The maternal history (ABO/Rh, infections, autoimmune disease), obstetrical history (gestation, delivery difficulties), and family history (anemia, jaundice, cholelithiasis, splenomegaly, transfusion history) may identify a cause. The age at presentation is important because a significant anemia detected within the first 24 hours of life is usually caused by blood loss or alloimmune hemolysis. Anemia detected after 24 hours of age points to hemolysis or internal hemorrhage. Anemia detected several weeks after birth may be physiologic or is compatible with Hb disorders or rare hypoplastic erythrocyte disorders. The physical examination of an infant with hemolysis may demonstrate icterus, hepatosplenomegaly, and stigmata of congenital infections. Infants with acute blood loss will exhibit hypovolemic shock, whereas those with chronic blood loss may have pallor without clinical distress or, if there is significant blood loss, may present in congestive heart failure and hydrops. The initial laboratory evaluation of anemia should include a complete blood count CBC, reticulocyte count, evaluation of the peripheral smear, and a direct antiglobulin test (DAT). The diagnosis of anemia should be based on reference ranges for the newborn and must take into account gestational and postnatal age. During the neonatal period, variation in normal hematologic values is higher than at any other time of life.

### Anemia Caused by Blood Loss

Hemorrhage may occur at any time during prenatal, perinatal, or postnatal life. Fetal hemorrhage is more commonly associated with fetal to maternal hemorrhage (FMH), which may occur in up to 8% of all pregnancies. The effects of FMH depend on the volume of hemorrhage and whether it is acute or chronic. Approximately 50 mL of fetal blood must be lost to produce significant anemia in a full-term infant and less for a preterm infant. Infants with chronic blood loss will exhibit pallor and anemia that can be mild normochromic, normocytic (Hb 9–12 g/dL), or hypochromic and microcytic (Hb 5–7 g/dL). Most forms are clinically stable and can be treated conservatively with iron supplementation for 3 months. Symptomatic infants (tachycardia, tachypnea, poor feeding) should be transfused with packed red blood cells. Acute blood loss, however, may result in hypovolemic shock. These infants may have a normal Hb concentration at birth, but anemia will be present hours later as the plasma volume re-expands. FMH may be diagnosed by the presence of fetal RBCs in the maternal circulation. This task can be accomplished by either the Kleihauer-Betke test, which involves examination of a stained maternal blood smear following differential acid elution of Hb A but not fetal Hb, or by flow cytometry techniques. These studies, however, may have negative results if ABO incompatibility exists between

mother and infant in which incompatible fetal red cells may be rapidly removed. Twin-to-twin transfusion (TTTS) may occur in monozygous twins and can result in significant anemia for 1 twin and polycythemia for the other. TTTS has a high rate of fetal mortality (approximately 63%). Hemorrhage occurs because of vascular anastomoses in monochorionic placentas, which allow transfer of blood from 1 twin to the other. Historically the diagnosis was made when there was a weight discordance of 15% to 20% and a hemoglobin difference of more than 5 g/dL between twins. However, because weight or hemoglobin differences are common in monochorionic twins, this definition has been abandoned. Ultrasound now can detect differences in amniotic fluid volume between twins when the donor twin has oligohydramnios and the recipient twin has polyhydramnios. Blood volume discrepancies can also be diagnosed prenatally by Doppler ultrasound velocities of the middle cerebral arteries when the donor twin has higher velocities.

Perinatal hemorrhage is associated with obstetric complications such as placenta previa, abruptio placenta, ruptured umbilical cord, and emergency cesarean section. Placenta previa occurs more commonly in women with a history of previous cesarean birth and increased parity. The incidence is approximately 1 in 3,000 deliveries, and the mortality is high in cases undetected before delivery (33%–100%). Placental abruption occurs when the placenta separates from the uterus. The incidence is 3 to 6 per 1,000 live births and increases with lower gestational age. Mortality is high, with death in 15% to 20% of cases with significant abruption (involvement of more than 50% of the placental surface). Cord rupture can occur from traction on a shortened or abnormal umbilical cord. Cord aneurysms, varices, and cysts can lead to a weakened cord.

Postnatal blood loss is commonly caused by fetal transfusion into the placenta at birth and by birth trauma. Fetoplacental hemorrhage occurs when the infant is held above the placenta at birth. Birth trauma can result in internal hemorrhage. Cephalohematoma and subgaleal hematomas can occur with vacuum- or forceps-assisted births. This diagnosis should be considered when a fluid collection occurs in dependent areas of the infant's head with signs of hypovolemia. Occult hemorrhages usually occur after 24 hours of life. Breech deliveries and infants with macrosomia may develop splenic, renal, or adrenal hemorrhage into the retroperitoneal space as a consequence of a difficult delivery.

### Hemolytic Anemia

Red cell hemolysis is a common cause of anemia in the newborn and has multiple causes. The neonatal red cell has intrinsic properties that lead to shortened survival. The normal neonatal erythrocyte has a less deformable membrane in the microcirculation and is more likely to be sequestered and removed by the reticuloendothelial system. Infants with mild hemolysis may have a blunted erythropoietic response and may not respond with reticulocytosis because of the excess oxygen-carrying capacity of blood. Thus hyperbilirubinemia may be the only symptom in mild anemia.

Severe hemolytic anemia will also be accompanied by an elevated reticulocyte count. Hemolytic anemias can be classified based on immune-mediated disorders, acquired disorders, and hereditary disorders of the erythrocyte.

### Alloimmune Hemolysis

Alloimmune hemolytic anemia, caused by maternal fetal blood group incompatibility (Rh[D] and ABO) is the most common cause of neonatal hemolytic anemia worldwide. The spectrum of alloimmune hemolysis can range from mild anemia and hyperbilirubinemia to severe anemia with hydrops fetalis. Antigens in the ABO, Rh, Kell, MN, Duffy, and Vel systems are expressed on the fetal red cell during the first trimester. The advent of immunoprophylaxis to prevent Rh(D) sensitization in 1968 dramatically decreased the incidence of alloimmune hemolysis. Nevertheless, Rh incompatibility is still a main cause of serious alloimmunization, although ABO incompatibility is far more prevalent. Cases of alloimmunization are detected by a positive DAT, which detects the presence of antibody on fetal red cells or in the plasma (indirect antiglobulin test). Eliminating alloimmunization as a cause of hemolytic anemia is important before testing for other etiologies.

**RH(D) HEMOLYTIC DISEASE.** Rh(D) hemolytic disease occurs in an Rh-negative mother and Rh-positive fetus when fetal red cells leak into the maternal circulation and sensitize the mother to the D antigen on the fetal red cell. The mother produces anti-D immunoglobulin G (IgG) antibody, which crosses into the fetal circulation, causing fetal red cell destruction. First pregnancies usually result in maternal sensitization without significant fetal hemolysis. However, subsequent pregnancies are more severely affected. A first pregnancy with significant neonatal Rh hemolytic disease usually indicates that the mother was previously exposed to Rh-positive red cells, through therapeutic abortion, ectopic pregnancy, or blood transfusion. Approximately 50% of Rh-sensitized pregnancies result in a newborn who requires transfusion postnatally; 9% of sensitized fetuses require intrauterine transfusion, and fetal death occurs in 1.5% of affected pregnancies. Concomitant ABO incompatibility decreases the risk for developing Rh alloimmune hemolysis. Rh-negative women who are not sensitized should receive Rh immune globulin at 28 weeks' gestation and then an additional dose at the birth of an Rh-positive infant. Infants with Rh incompatibility can develop a "late" anemia from ages 1 to 3 months, because of decreased endogenous erythropoietin production. The incidence of late anemia is higher in infants receiving intrauterine transfusions.

**ABO INCOMPATIBILITY.** Alloimmune hemolysis associated with ABO incompatibility occurs in group O mothers and infants with blood group A or B. ABO incompatibility occurs in 12% of pregnancies, but fewer than 1% are associated with significant hemolysis. First pregnancies can be affected, given that naturally occurring maternal anti-A IgG and anti-B IgG cross the placenta. The mild hemolysis of ABO incompatibility is, in part, related to the presence of A and B antigens on other tissues besides red cells.



Therefore other tissues aside from erythrocytes absorb the anti-A IgG and anti-B IgG that cross the placenta. The result of a DAT may be negative because of fewer type-specific antigens on the surface of the fetal red cell compared with adult red cells. The indirect antiglobulin test, however, is usually positive. The peripheral blood smear will show spherocytes, which are the result of reduced red cell surface area caused by the removal of antibody and membrane complexes by the reticulo-endothelial macrophages. Although hemolysis in ABO incompatibility is mild, infants with evidence of hemolysis need to be monitored in the first few days of life for hyperbilirubinemia and for anemia during their first 2 to 3 weeks of life.

**MINOR BLOOD GROUP INCOMPATIBILITY.** The prevalence of other blood group incompatibilities is increasing because of the successful prevention of Rh immune disease. Common incompatibilities occur with Rh (c and E), Kell, Duffy, and Kidd antigens. Kell incompatibilities can result in significant hemolysis and currently account for 22% of alloimmunization cases, surpassing anti-D, which occurs in 18.4% of cases. Because the Kell antigen is expressed on red blood cell precursors, the reticulocyte and nucleated red blood cell numbers in Kell antigen incompatibility is usually not as elevated as with Rh incompatibility.

### Acquired Hemolysis (Nonimmune)

**INFECTION.** Congenital infections (cytomegalovirus, toxoplasmosis, rubella, syphilis) may cause hemolysis, impaired erythropoiesis, and thrombocytopenia. Hepatosplenomegaly is usually present, and an active reticuloendothelial system may account for red cell sequestration. Bacterial infections (group B streptococcus, *Escherichia coli*) may also cause hemolysis, disseminated intravascular coagulation (DIC), and hemorrhage. Malaria should also be anticipated in endemic areas and in individuals traveling from these areas.

**MICROANGIOPATHIC HEMOLYSIS.** Hemolysis may occur when red cells interact with fibrin deposition in the microcirculation. The red cells are sheared and form fragments (schistocytes), which lose their deformability and hemolyze. The most common cause of microangiopathic hemolysis is DIC, which is most commonly associated with infection. Other causes of microangiopathic anemia include cavernous hemangiomas, arteriovenous malformations, renal artery stenosis or thrombosis, severe valvular stenosis, and coarctation of the aorta.

### Hereditary Hemolytic Anemia

Hereditary disorders of erythrocytes may cause hemolysis during the neonatal period. These disorders include membrane defects, enzyme deficiencies, and hemoglobinopathies.

**MEMBRANE DEFECTS.** Hereditary spherocytosis is an autosomal disease caused by mutations in genes for the membrane cytoskeleton proteins ( $\alpha$ - or  $\beta$ -spectrin, ankyrin, band 3). These proteins are important in vertical interactions that tie the membrane cytoskeleton to the lipid bilayer. Spherocytes present on a peripheral blood smear are characteristic of the disease. Spherocytes develop when loss of membrane

surface area occurs caused by microvesiculation of the lipid bilayer. The spherocyte loses flexibility and is entrapped in the microcirculation of the reticulo-endothelial system. Clinical variation is significant. Some patients are transfusion dependent, whereas others have reticulocytosis without anemia. Neonatal hemolysis or hyperbilirubinemia occurs in approximately one-half of patients. A family history will be present in approximately 75% of patients, reflecting autosomal dominant inheritance. Another 25% of patients with spherocytosis have no family history, and the disease may be the result of recessive inheritance or a new mutation. Given that spherocytes are prominent in ABO incompatibility as well, hereditary spherocytosis must be distinguished from ABO incompatibility.

Hereditary elliptocytosis is an autosomal dominant disorder of the membrane proteins, commonly  $\alpha$ - or  $\beta$ -spectrin or less often protein 4.1 or glycophorin C. The disease is clinically heterogeneous, and patients who are heterozygous have elliptical erythrocytes on peripheral smear but are not anemic. A transient hemolysis and poikilocytosis may occur in the newborn period in the heterozygous infant. However, patients who are homozygous or compound heterozygotes may have chronic hemolysis and splenomegaly. Hereditary pyropoikilocytosis is the severest variant and exhibits in the neonatal period with hemolysis that persists. The smear morphologic assay reveals spherocytes, poikilocytes, fragmented red cells, and an extreme microcytosis. The inheritance may be recessive with both parents asymptomatic, or it may be that one parent has hereditary elliptocytosis and the other is a silent carrier.

**ENZYME DISORDERS.** Red cell enzymopathies, with the exception of glucose-6-phosphate dehydrogenase (G6PD) deficiency, are rare. They can occur in the neonatal period with hemolytic anemia and hyperbilirubinemia. G6PD is an X-linked disorder affecting millions throughout the world, primarily in areas endemic for malaria. Hemolysis is, for the most part, episodic and occurs after exposure to infections or potent oxidants. G6PD is an enzyme of the hexose monophosphate shunt that is required to generate the antioxidant glutathione. The absence of glutathione leads to oxidant damage to the erythrocyte with denaturation of globin, which, in turn, damages the red cell membrane and results in red cell hemolysis. G6PD deficiency's clinical heterogeneity is dependent on race and gender. The G6PD A-minus variant results in decreased stability and occurs in individuals of African origin. Reticulocytes have normal enzyme activity; therefore affected patients with an elevated reticulocyte count may be misclassified as having normal G6PD activity. The disease is usually mild with a transient hemolysis primarily seen with infection. The Mediterranean and Asian variant, however, results in more severe hemolysis that may be fatal, especially on exposure to fava beans. The diagnosis is suggested by a nonimmune hemolytic anemia in association with infection or administration of oxidant drugs. In the African variant, the enzyme is present in young reticulocytes such that testing after a hemolytic episode, with the presence of elevated reticulocytes, may reveal normal G6PD activity. Neonatal jaundice is



a common presentation, and in parts of the Mediterranean and Southeast Asia, G6PD deficiency is the most common cause of kernicterus. Male infants with unexplained early jaundice and no evidence for ABO or Rh incompatibility should be screened for G6PD deficiency. Females may also have G6PD deficiency resulting from extreme X-chromosome inactivation in the heterozygote state, or alternatively may be homozygotes for the G6PD gene mutation.

**HEMOGLOBINOPATHIES.** Hemoglobins are developmentally regulated throughout gestation and do not complete the switch to adult Hb A until the first year of life. Hemoglobin consists of 2  $\alpha$ -like and 2  $\beta$ -like globin chains. The  $\alpha$ -like chains consist of  $\zeta$ -globin chains in embryonic life with a transition to adult  $\alpha$  chains by the end of the first trimester. The  $\beta$ -like chains consist of the embryonic  $\epsilon$  globin, which switches to the fetal  $\gamma$  globin in the first trimester. The switch from fetal  $\gamma$  chains to adult  $\beta$  chains starts in the first trimester and is completed during the first year of life. Thus  $\alpha$ - and  $\gamma$ -globin chains are vital to fetal Hb ( $\alpha_2\gamma_2$ ) production, which is the major Hb throughout fetal life. Mutations in the genes encoding  $\alpha$  and  $\gamma$  globins are the cause of Hb disorders that occur in the neonatal period. (See also Chapter 262, Hemoglobinopathies and Sickle Cell Disease.)

**THALASSEMIA.**  $\alpha$ -Thalassemia is a major cause of neonatal hemolytic anemia, hyperbilirubinemia, and hydrops fetalis in Southeast Asia. It is common in areas of the world where malaria is endemic. The molecular basis of  $\alpha$ -thalassemia is deletion of 1 or more of the 4  $\alpha$ -globin genes. Nondeletional forms of  $\alpha$ -thalassemia are known but are less common. Deletion mutants are classified as (1) silent carrier, in which 1 of the 4 genes is deleted or nonfunctional, and there are no clinical or hematologic sequelae; (2)  $\alpha$ -thalassemia trait, in which deletion or nonfunction (in *cis* or *trans*) of 2  $\alpha$  genes results in microcytosis without anemia; (3) Hb H disease (deletion or nonfunction of 3 of the 4 genes), which results in a chronic hemolytic anemia with microcytosis; and (4) homozygous  $\alpha$ -thalassemia (deletion of all 4  $\alpha$  genes), which results in fetal hydrops with severe anemia, hepatosplenomegaly, and usually fetal demise.  $\alpha$ -Thalassemia should be thought to exist in any infant with elevation of Hb Bart syndrome ( $\gamma_4$ ). Infants with the silent carrier or trait status are not symptomatic. Infants with Hb H disease, however, may have neonatal hemolytic anemia and hyperbilirubinemia when exposed to oxidant drugs or infections. Both Hb H and homozygous  $\alpha$ -thalassemia occur almost exclusively in infants of Asian descent who have *cis* gene deletions. Testing the parents of a child with Asian ancestry who has  $\alpha$ -thalassemia trait or Hb H disease is important because future pregnancies might be at risk for a fetus with homozygous  $\alpha$ -thalassemia.

$\beta$ -Thalassemia is common in Southeast Asia, Africa, the Mediterranean, and India. It is caused by point mutations or deletions of the adult  $\beta$ -globin gene, which, in the homozygous state, results in transfusion dependency.  $\beta$ -Thalassemia may be classified as  $\beta^0$  with no production of  $\beta$  globin or  $\beta^+$ , which results in decreased synthesis of normal  $\beta$ -globin protein. Neonates with homozygous  $\beta$ -thalassemia are not symptomatic at birth because fetal Hb ( $\alpha_2\gamma_2$ ) predominates during fetal

and neonatal life. However, by 3 months of age, the switch from fetal to adult  $\beta$  globin chain production is approximately 80% complete, and symptoms of anemia and hepatosplenomegaly will appear.

**HEMOGLOBIN E.** Hb E, common in Southeast Asia, is a structurally abnormal Hb caused by an amino acid substitution of lysine for glutamine at position 26 of the  $\beta$ -globin protein. The Hb E mutation also results in abnormal RNA splicing, which results in decreased synthesis as well, and is considered a thalassemic phenotype. Patients homozygous for Hb E have microcytosis but little or no anemia. Patients who are compound heterozygotes for Hb E and  $\beta^0$  thalassemia, however, are transfusion dependent.

**SICKLE CELL DISEASE.** The sickle hemoglobinopathies are  $\beta$ -globin chain disorders that, similar to  $\beta$ -thalassemia, are asymptomatic at birth. The sickle Hb variants are diagnosed in newborn screening programs by Hb electrophoresis as Hb SS (FS), Hb SC (FSC), Hb S $\beta^0$  thalassemia (FS), and Hb S $\beta^+$  thalassemia (FSA). Alternatively some screening programs use DNA diagnosis. Infants with a sickle hemoglobinopathy are protected during the first months of life by the presence of fetal Hb; therefore few symptoms occur before 6 months of age. (See Chapter 262, Hemoglobinopathies and Sickle Cell Disease, for complete discussion.)

### Hypoplastic Anemia

Hypoproliferative anemias caused by decreased erythrocyte production may occur in thalassemia syndromes, with decreased production of globin chains, blood loss resulting in iron deficiency, congenital infections (parvovirus, rubella, cytomegalovirus), and rare bone marrow failure syndromes. Diamond-Blackfan anemia (DBA) is a rare congenital hypoplastic anemia characterized by the absence of erythroid precursor cells in the bone marrow. The incidence is 2 to 7 per 1 million live births; 10% to 20% are familial, and mutations in 9 genes coding for ribosomal subunit proteins have been identified. Congenital malformations including growth retardation, skeletal anomalies, and renal anomalies are present in approximately 30% of individuals. Approximately 25% of patients will be diagnosed in the neonatal period, when DBA is suggested by a normochromic, macrocytic anemia with a reticulocytopenia. Treatment of DBA includes corticosteroids, which usually produce a remission, but chronic transfusion therapy has also been used. DBA should be distinguished from hypoproliferative anemia caused by maternally acquired parvovirus infection.

## HEMOSTATIC DISORDERS IN THE NEONATE

The diagnosis and management of hemostatic disorders in the newborn is challenging because the system is dynamic and coagulant protein and inhibitor concentrations are age dependent. The hemostatic system in the newborn is thromboprotective, with an overall decrease in thrombin generation. Although the concentrations of hemostatic proteins are related to gestational age, maturation is rapid, and by 6 months of age, adult values are attained in both term and preterm infants. The coagulant proteins that are

vitamin K dependent (FII, FVII, FIX, FX) are approximately 50% of adult levels at birth. The inhibitors of coagulation (antithrombin, heparin cofactor II, protein C, and protein S) are also 50% of adult values at birth. The normal values for prothrombin time (PT) and activated partial thromboplastin time (aPTT) are prolonged in newborns. Platelet counts and life span in the newborn are similar to adult values.

### Approach to the Newborn With Bleeding

Infants with clinically significant bleeding should be evaluated for a hemostatic disorder. Although acquired disorders predominate, hereditary deficiencies of coagulation proteins and inhibitors often present in early infancy. (See Chapter 230, Coagulation Disorders.)

Evaluation of the infant with a bleeding complication should include a medical history that queries familial bleeding problems, maternal illnesses (immune thrombocytopenia, infections), outcomes of previous pregnancies, obstetric problems at delivery, and documentation that vitamin K was given. The physical examination is important in determining whether bleeding is local or diffuse and if the infant has a healthy or sick appearance. Infants with hereditary deficiencies usually display ecchymosis or localized bleeding but seem healthy. However, ill infants with DIC have diffuse bleeding and petechial hemorrhage. Infants with isolated thrombocytopenia usually seem healthy and have petechiae or ecchymoses.

The initial laboratory evaluation should include a PT, aPTT, thrombin time, fibrinogen, and platelet count. Because the hemostatic system in newborns, especially premature infants, is physiologically immature, normal reference values for screening coagulation studies and factor assays will vary from adult normal values. These screening assays will direct selection of other studies, such as specific factor assays. The management of an infant with a hemostatic disorder depends on the defect identified. Replacement therapies may include specific factor concentrates, fresh-frozen plasma, cryoprecipitate, and platelet transfusions.

### Inherited Hemorrhagic Disorders

#### Hemophilia

Deficiencies of coagulation factors VIII and IX are called hemophilia A and hemophilia B, respectively. They are X-linked disorders, and a family history can be obtained in two-thirds of cases, but approximately one-third represent new mutations. The clinical presentation is that of neonatal bleeding in 40% to 70% of cases. The most common sites of bleeding are intracranial hemorrhage, cephalohematoma, umbilical stump bleeding, and circumcision. The aPTT is prolonged for age, and the specific FVIII or FIX factor assay will confirm the diagnosis. The treatment is recombinant factor-specific concentrates. (See Chapter 230, Coagulation Disorders.)

#### Other Hereditary Deficiencies

The most common hereditary coagulation disorder is von Willebrand disease, which occurs in up to 1% of the population. However, symptoms of this disorder do not usually appear in the newborn period because of elevation of von Willebrand factor proteins at birth.

Other, less common severe factor deficiencies (FV, FVII, FX, FXI, fibrinogen, and FXIII) may produce bleeding at birth.

### Acquired Hemorrhagic Disorders

#### Disseminated Intravascular Coagulation

Disseminated intravascular coagulation is a secondary process related to disease states in the neonate such as asphyxia, shock, infection, necrotizing enterocolitis, and respiratory distress syndrome. DIC results from activation of coagulation factors, generation of excess thrombin, and decreased generation of the antithrombotic proteins antithrombin, protein C, and protein S. The consumption of platelets and other coagulation factors leads to diffuse bleeding. DIC occurs in sick infants, and common bleeding manifestations include oozing from mucosal membranes and puncture sites, hematuria, bruising, and intracranial hemorrhage. Laboratory findings may include prolonged PT and aPTT, decreased fibrinogen, increased fibrin degradation products, and decreased platelets. The treatment of DIC involves treating the underlying causes, such as infection, and replacing depleted coagulation and antithrombotic factors with fresh-frozen plasma, cryoprecipitate, and platelets.

#### Vitamin K Deficiency

Infants are at greater risk for bleeding from vitamin K deficiency because of the physiologic decrease in vitamin K-dependent factors (factors II, VII, IX, X) at birth. The 3 clinical presentations of vitamin K deficiency are early, classic, and late.

The early form of vitamin K deficiency occurs in the first 24 hours of life and is linked to maternal medications that interfere with vitamin K stores or function, such as anticonvulsants and antibiotics (including those for tuberculosis). The classic form presents on days 2 to 7 of life in healthy breastfed term infants. This form occurs, in the absence of prophylactic vitamin K, in 0.25% to 1.7% of term infants. The late form manifests between 2 and 8 weeks of life and is primarily caused by disorders that result in malabsorption of vitamin K, such as biliary atresia and other hepatobiliary diseases. Infants thought to have vitamin K deficiency should receive parenteral vitamin K and fresh-frozen plasma for significant bleeding.

#### Liver Disease

The coagulopathies of liver disease in neonates are caused by failure of synthetic function of the liver in combination with a physiologic immaturity of the coagulation system. The common causes of liver disease in the newborn include viral hepatitis, hypoxia, total parenteral nutrition, biliary atresia, and inherited metabolic defects. Coagulopathies related to liver disease must be distinguished from DIC.

## THROMBOEMBOLIC DISEASE IN THE NEONATE

A significant increase has occurred in thromboembolic (TE) disorders in newborns because of improvement in tertiary care and the use of catheters, extracorporeal

membrane oxygenation circuits, and cardiopulmonary bypass, all of which provide thrombogenic surfaces. Approximately 50% of TEs in children occur during the neonatal period; the use of catheters is the major risk factor in 90% of TEs.

### Genetic Risk Factors

Hereditary risk factors for TE rarely contribute to neonatal thrombosis unless a significant acquired risk factor is also present. Testing for prothrombotic genetic risks should be reserved until an infant is at least 3 months of age because of the physiologic decrease in these factors (proteins C and S) at birth. Exceptions, however, would include infants with purpura fulminans, which is often a symptom of the rare homozygous or compound heterozygous state for proteins C and S or antithrombin deficiencies. Besides these antithrombotic proteins, other genetic risks include factor V Leiden, which results in resistance of activated protein C proteolysis of FVa. Factor V Leiden is the most common inherited risk factor and occurs in 5% of whites. Prothrombin gene mutation 20210 is another genetic risk factor and is associated with increase in prothrombin levels.

### Acquired Risks

The use of catheters, central venous lines, and umbilical lines is the most common risk factor for TE in newborns. Clinical signs of TE in central venous lines include loss of patency, limb swelling and discoloration, pulmonary embolism, chylothorax, and superior vena cava syndrome. Umbilical venous and arterial catheters induce clots in 1.7% to 30% of patients; however, most are asymptomatic. Arterial clots can result in ischemia and organ dysfunction and have resulted in limb-length discrepancy. The diagnosis of TE can be made by compression Doppler ultrasound, magnetic resonance venography, and computed tomographic scan. Therapy in newborns is not guided by clinical trials data but may include short-term anticoagulation, conventionally 6 weeks to 3 months of anticoagulation, or close monitoring.

### Renal Vein Thrombosis

Renal vein thrombosis (RVT) is the second most common TE in neonates and accounts for 10% of neonatal venous TE, with approximately one-half occurring in preterm infants. RVT usually causes hematuria, flank mass, and thrombocytopenia, and these are bilateral in approximately 20% of cases. The risk factors for RVT include asphyxia, congenital heart disease, polycythemia, dehydration, sepsis, and infants of diabetic mothers. In a small series, the prevalence of thrombophilia was higher in neonates with RVT. The long-term morbidity includes hypertension and decreased renal function. Use of anticoagulants should be considered for unilateral RVT extending into the inferior vena cava and patients with bilateral RVT.

### Neonatal Stroke

Approximately 25% of arterial ischemic stroke during childhood occurs in the neonatal period, commonly in

term infants. Seizures are the most common clinical presentation; approximately 50% of newborns with a seizure have an arterial infarct as reflected on magnetic resonance imaging. Acquired risk factors for arterial stroke include asphyxia, sepsis, congenital heart disease, dehydration, meningitis, and delivery complications. Outcomes reveal no sequelae in 30% to 50% of patients, and the remaining develop hemiplegia, seizures, cerebral palsy, and visual impairment. Anticoagulation or antiplatelet therapy is usually not recommended, except in cases of a cardioembolic source or recurrent events.

Sinovenous thrombosis (SVT) is less common than arterial stroke but commonly occurs in the newborn period. The major sites for SVT are the superior sagittal and transverse sinuses. The clinical presentation includes seizures, lethargy, and jitteriness. Physical examination may reveal a tense fontanel and dilated scalp veins. Acquired risk factors for SVT include asphyxia, dehydration, and sepsis. The diagnosis is made by magnetic resonance venography and Doppler ultrasound through the anterior fontanel. For neonates with SVT without intracranial hemorrhage, anticoagulation with low-molecular-weight heparin for 6 weeks to 3 months is recommended. For infants with significant hemorrhage, supportive care and monitoring of the thrombosis by neuroimaging and anticoagulation is recommended if thrombus extension is noted. Seventy percent of patients are neurologically normal at 2 years of age.

## PLATELET DISORDERS

### Thrombocytopenia

The platelet count in newborns is similar to levels in healthy adults. A platelet count lower than  $150 \times 10^9/L$  is classified as thrombocytopenia. The prevalence of thrombocytopenia in the healthy newborn is 0.7% to 4%, whereas in the sick newborn, it is 20% to 40%. Causes of thrombocytopenia include diseases associated with decreased production, increased destruction, and a combination of both.

### Decreased Production

Congenital thrombocytopenia is rare and can be seen with bone marrow diseases (amegakaryocytic thrombocytopenia, thrombocytopenia absent radii syndrome, congenital leukemia, metastatic neuroblastoma, osteopetrosis), immune disorders (Wiskott-Aldrich syndrome), neutrophil defects (Chédiak-Higashi syndrome), and giant platelet syndromes (Alport syndrome, Bernard-Soulier syndrome).

### Increased Destruction

The most common mechanism leading to thrombocytopenia is increased destruction. DIC often occurs with bacterial infections. A localized consumption of platelets is seen with asphyxia, RVT, necrotizing enterocolitis, maternal eclampsia, and the vascular lesion kaposiform hemangioendothelioma, which causes the consumptive coagulopathy Kasabach-Merritt syndrome. Immune-mediated mechanisms include both alloimmune and autoimmune and should be considered in otherwise

healthy infants with an isolated severe thrombocytopenia (platelets  $<50 \times 10^9/L$ ).

### Combination

Intrauterine infections (eg, toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex, HIV, parvovirus B19) may have neonatal thrombocytopenia, in addition to other stigmata. The mechanisms are multifactorial and include bone marrow suppression and consumption in the reticuloendothelial tissues.

### Approach to Neonatal Thrombocytopenia

The evaluation of a newborn with thrombocytopenia should include a review of the maternal history for infections, medications, immune disorders, previous affected pregnancies, or a family history of thrombocytopenia. Whether the newborn is sick or healthy is important, given that thrombocytopenia in most healthy newborns is caused by immune disorders. Thrombocytopenia within the first 72 hours of life is usually related to maternal or perinatal events, whereas the presentation after day 3 usually implies bacterial sepsis. The laboratory investigation should include a CBC with examination of the peripheral smear, a coagulation screen, and a platelet count on the mother.

Neonatal alloimmune thrombocytopenia (NAIT) occurs when the mother is sensitized to paternal antigens on the fetal platelet and produces an IgG that crosses the placenta and destroys fetal platelets. The incidence of NAIT is 0.18% of pregnancies. The first pregnancy can be affected because fetal platelets leak into the maternal circulation. The most common alloantigen in the white population is human platelet antigen (HPA)-1A (PLA1), which is the cause of 80% of NAIT. However, the actual risk for developing NAIT is also related to maternal human leukocyte antigen (HLA) type because the risk is 140-fold higher with HLA-D3 alloantigen. The clinical presentation is that of severe thrombocytopenia at birth, with intracranial hemorrhage occurring in 15% to 20% of patients. Therapy consists of transfusion of maternal platelets, if available, or intravenous  $\gamma$ -globulin. Alternatively, random donor platelets may be given. If there is no response to a random platelet transfusion, then HPA-1 or -5 negative platelets, or HPA-4 negative for mothers of Asian descent, may be given. The diagnosis can be confirmed by platelet antigen typing of the parents and maternal antibody testing.

Autoimmune thrombocytopenia in the neonate occurs with maternal autoimmune disorders such as immune thrombocytopenic purpura and is milder than alloimmune disorders. Approximately 15% to 45% of infants with maternal immune thrombocytopenic purpura will have thrombocytopenia. Therapies include intravenous immunoglobulin, steroids, and platelet transfusions.

## NEUTROPHIL DISORDERS IN THE NEONATE

Bacterial and fungal infections are major causes of morbidity and mortality in neonates, especially among very low-birth-weight infants for whom infection

rates are more than 40%. Neutrophil production and some neutrophil functions are immature in neonates. The neutrophil functions of phagocytosis and bactericidal activity are at normal adult levels in newborns. However, migration of neutrophils to chemotactic stimuli is impaired. The neutrophil storage pool is also smaller in neonates than in adults and results in a limited response to infectious challenges. The normal neutrophil count in term infants is 8,000 to 14,000/ $\mu L$ , peaking 12 to 24 hours after birth. By 72 hours, normal levels are 2,000 to 7,500/ $\mu L$ . Very low-birth-weight infants exhibit a wider range of neutrophil values, which may range from 2,000 to 14,000/ $\mu L$  12 hours after birth and fall to 1,000 to 7,500/ $\mu L$  at 48 hours.

### Neutropenia

Neutropenia in the neonate can be caused by increased destruction or decreased production. Increased destruction of neutrophils is most commonly associated with infections and less often with immune-mediated mechanisms such as alloimmune or autoimmune disorders.

*Alloimmune neutropenia* results from maternal transfer of IgG antibody directed against fetal neutrophil antigens. Maternal sensitization may occur at any time during gestation and, similar to alloimmune thrombocytopenia, can occur in the first pregnancy. The incidence is 0.5 to 2 per 1,000 live births. Commonly the neutropenia is detected in the first week of life when the neonate becomes febrile or develops an infection. Typically the neutrophil count is 100 to 200/ $\mu L$ , with otherwise normal values for white blood cell count, hemoglobin, and platelets. The clinical course varies, but most infants have infections of the umbilicus, skin, or respiratory tract. However, more serious infections, such as sepsis and meningitis, may occur. Treatment includes prompt administration of broad-spectrum antibiotics. Intravenous immunoglobulin has not produced consistent results and has a limited role in therapy. Recombinant granulocyte colony-stimulating factor (rG-CSF) has had more success in increasing neutrophil counts. Neutropenia typically has a mean duration of 11 weeks. Diagnosis is made by testing for antineutrophil antibodies in the infant and mother, and neutrophil antigen typing of the infant and both parents. Several neutrophil-specific antibodies have been identified, and the most common are directed against the neutrophil antigens NA1, NA2, NB1, and NC1.

*Autoimmune neutropenia* (AIN) in the neonate is seen when the mother has a diagnosis of AIN with maternal transfer of auto IgG neutrophil antibodies. Symptoms and treatment is similar to infants with alloimmune neutropenia.

Decreased production of neutrophils in neonates can be seen in infants of hypertensive mothers, in twin-to-twin transfusions, and in Rh hemolytic disease. In most cases, neutropenia is transient and may persist for about 5 to 8 days. Other causes of decreased production of neutrophils include rare genetic disorders such as severe congenital



neutropenia (SCN) and Shwachman-Diamond syndrome. SCN is a heterogeneous disease with autosomal dominant, recessive, and X-linked forms characterized by reduction in circulating neutrophils caused by a maturation arrest of bone marrow progenitor cells. Mutations are described in genes for neutrophil elastase (ELA2), granulocyte colony-stimulating factor receptor (CSF3R), HAX1 mitochondrial antiapoptotic protein, and the Wiskott-Aldrich syndrome protein (WASp). Most patients present with life-threatening infections during the first 6 months of life. Absolute blood neutrophil counts are usually less than 200/ $\mu$ L, and daily administration of rG-CSF results in neutrophil counts greater than 1,000/ $\mu$ L, although 10% of patients may be refractory to rG-CSF. There is concern over the use of rG-CSF therapy in patients with the CSF3R mutation because these patients are prone to develop myelodysplastic syndrome and acute myelogenous leukemia. Shwachman-Diamond syndrome is a rare bone marrow failure and cancer predisposition disorder affecting multiple organs. Mutations in the Shwachman-Diamond syndrome gene are found in most patients. Shwachman-Diamond syndrome is characterized by dwarfism, exocrine pancreatic insufficiency, metaphyseal chondrodysplasia, and neutropenia. In the newborn period, symptoms may include diarrhea, failure to thrive, eczema, otitis media, and pneumonia. Neutrophil counts range from 200 to 400/ $\mu$ L, and rG-CSF can increase neutrophil counts to a normal level.

#### Approach to Neutropenia in the Neonate

The evaluation of the newborn with neutropenia should include a thorough history with regard to a familial history of infections and neutropenia. The obstetric history should include queries for peripartum infection, maternal hypertension, medications associated with neutropenia, fetal distress, and asphyxia, especially for infants presenting in the early neonatal period. Infants with persistent neutropenia should be evaluated for alloimmune neutropenia by detection of antineutrophil antibodies in the infant and maternal blood, followed by parental neutrophil antigen typing when appropriate. Patients with negative neutrophil antibodies and persistent neutropenia, with absolute neutrophil count less than 500, should be evaluated for SCN and Shwachman-Diamond syndromes by bone marrow analysis and genetic testing.

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#### Chapter 104

### PRENATAL DRUG USE: NEONATAL EFFECTS AND THE DRUG WITHDRAWAL SYNDROME

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#### INTRODUCTION

Few barriers exist to the passage of most drugs across the placenta or to their biotransformation in the placenta, which can produce inactive or active drug metabolites. Maternal drug use during pregnancy increases the risk of complications such as stillbirths, meconium-stained amniotic fluid, premature rupture of the membranes, maternal hemorrhage (abruptio placenta or placenta previa), and fetal distress. Newborns exposed to drugs in utero experience greater morbidity and mortality compared to other neonates. Problems include a higher incidence of asphyxia, prematurity, low birth weight, infections (including sexually transmitted infectious diseases), pneumonia, congenital malformations, cerebral infarction, drug withdrawal, and acquired immunodeficiency syndrome. Long-term sequelae also have been reported, including delays in physical growth and cognitive development, sudden infant death syndrome, and learning disabilities. This chapter discusses complications of the infant who is antenatally exposed to drugs with emphasis on the neonatal abstinence syndrome.

In 2012, an estimated 23.9 million Americans ages 12 or older were current illicit drug users, meaning they had used an illicit drug during the month prior to the survey interview. This estimate represents 9.2% of the population ages 12 or older. Illicit drugs include marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants, and prescription psychotherapeutics (pain relievers, tranquilizers, stimulants, and sedatives) used nonmedically. Marijuana was the most commonly used illicit drug. Among pregnant women ages 15 to 44, 5.9% were current illicit drug users based on data averaged across 2011 and 2012. This was lower than the rate among women in this age group who were not pregnant (10.7%). The rate of current illicit drug use in the combined 2011–2012 data was 18.3% among pregnant women ages 15 to 17, 9.0% among pregnant women ages 18 to 25, and 3.4% among pregnant women ages 26 to 44. These rates were not significantly different from those in the combined 2009–2010 data. It should be noted that these statistics were obtained exclusively from maternal interviews and therefore may be subject to significant under-reporting of drug use. In one study, an estimate of drug use among pregnant women varied from 0.4% to 27% where drug use was detected by maternal history, urine toxicology, or both. When a more sensitive

method (meconium drug testing) was employed, a prevalence rate of 44% was found in contrast to 11% by maternal self-report.

### **PATHOPHYSIOLOGY**

Two major theories have emerged to explain the phenomenon of drug withdrawal: disuse hypersensitivity and alternative pathways. The theory of disuse hypersensitivity postulates that a drug may depress certain neural systems and render their targets hypersensitive to their usual stimuli, with an increase in binding sites for the drugs. When the depressant drug is removed, the withdrawal syndrome occurs, caused by rebound hypersensitivity of the affected targets. Morphine, for instance, has been shown to inhibit activation of non-adrenergic cells in the brainstem. Thus, chronic morphine exposure results in an increase in the number of brainstem adrenergic binding sites. When morphine is withdrawn, the abstinence syndrome occurs as a consequence of adrenergic hypersensitivity. The theory of alternate pathways states that a drug may depress a primary neural pathway, and as a result alternate pathways, normally of minor activity, become prominent in an attempt to compensate. When the drug is removed, both the primary and alternate pathways remain operative in an additive fashion and cause the withdrawal syndrome.

As tolerance or addiction to drugs develops in the pregnant woman, passive dependence on the drug also develops in her fetus. Withdrawal of the infant

from drugs may occur in utero or soon after birth. (See Box 104-1 for drugs that cause withdrawal.) In utero withdrawal manifests as an increase in fetal movement or activity, an increase in catecholamine levels in the amniotic fluid, or signs of fetal distress, such as meconium staining of the amniotic fluid or abnormal umbilical velocity waveform. It is not safe for the pregnant addict to undergo rapid or self detoxification, because this will lead to withdrawal in her fetus and its concomitant complications.

### **DRUGS ASSOCIATED WITH THE NEONATAL DRUG WITHDRAWAL SYNDROME**

Drug withdrawal in the mother and infant can occur secondary to use of or exposure to narcotics or non-narcotic hypnosedatives (Box 104-1). However, there is a significant difference in the susceptibility to addiction in the infant compared to the mother. Unlike with narcotics, the development of addiction in the mother to nonnarcotic hypnosedatives requires prolonged and continuous use of large doses, usually over months or years, particularly if the drugs are taken orally. On the other hand, addiction in the neonate to nonnarcotic hypnosedatives can occur even if the pregnant woman takes the drug at therapeutic dose during gestation. For instance, maternal use of phenobarbital for epilepsy may not cause addiction in the mother, but can induce passive addiction in her fetus. There are

#### **BOX 104-1 Drugs of Abuse in Pregnant Women**

##### **NARCOTICS OR OPIATES**

- Morphine
- Codeine
- Heroin
- Methadone
- Propoxyphene (Darvon)
- Pentazocine (Talwin)
- Meperidine (Demerol)
- Oxycodone (Percodan, Tylox, Vicodin, Percocet)
- Hydromorphone (Dilaudid)
- Fentanyl (Sublimaze, Actiq, Duragesic, Wildnil, Alfenta, Sufenta)
- Buprenorphine (Buprenex)
- Nalbuphine (Nubain)
- Butorphanol (Stadol)
- Tramadol

##### **NONNARCOTIC HYPNOSEDATIVES**

- Barbiturates
- Nonbarbiturate sedatives and tranquilizers
  - Bromides
  - Chloral hydrate
  - Benzodiazepines (diazepam, chlordiazepoxide, clorazepate, flurazepam, halazepam, prazepam,

clonazepam, lorazepam, quazepam, estazolam, alprazolam, oxazepam, temazepam, midazolam, triazolam)

- Ethchlorvynol (Placidyl)
- Glutethimide (Doriden)
- Alcohol (ethanol)

##### **STIMULANTS**

- Cocaine
- Amphetamines and congeners
- Nicotine
- Phencyclidine (PCP)
- Marijuana
- SSRIs—venlafaxine, sertraline, paroxetine

##### **INHALANT (VOLATILE SUBSTANCE) DRUGS**

- Paint solvents
- Lacquers
- Glues

##### **OTHERS**

- Baclofen
- Valproate

SSRIs, selective serotonin reuptake inhibitors

also some differences in the withdrawal of the infant from narcotics compared to nonnarcotics. The manifestations of withdrawal from nonnarcotics are often more intense and more commonly involve convulsion. Withdrawal from narcotics in the infant is also observed commonly within the first 3 postnatal days because of the short half-life of narcotics, except for methadone. In contrast, withdrawal from nonnarcotics (eg, phenobarbital) may occur 7 to 21 days after birth because of the slow clearance of the drug in the infant. Lastly, unlike narcotic addiction, neonatal addiction to nonnarcotic hypnotosedatives is often induced by the physician who is unaware that the therapeutic dose of the drug given to the mother is already addicting to her fetus.

The mother may also be addicted to any of a large number of central nervous system (CNS) stimulants. These include cocaine, amphetamines and their congeners, indolealkylamines (eg, LSD, psilocybin), phenylethylamines (mescaline, peyote), cannabinoids, inhalants (solvents and aerosols), and phencyclidines. Neonatal withdrawal from some of these drugs has been described, although it is possible that the manifestations regarded as withdrawal are actually toxic effects of the drug on the infant.

### Narcotics

The term “narcotics,” or “opiates,” refers to a family of natural or synthetic drugs that have morphine-like pharmacologic actions. These include morphine, codeine, heroin, methadone, propoxyphene (Darvon), pentazocine (Talwin), nalbuphine (Nubain), buprenorphine (Buprenex), butorphanol (Stadol), meperidine (Demerol), oxycodone (Percodan, Tylox, Vicodin, and Percocet), hydromorphone (Dilaudid), fentanyl (Immovar, Sublimaze), and tramadol. Extended use of narcotics, even in therapeutic doses, can lead to withdrawal in the infant. The use of methadone in pregnant women for the treatment of opiate addiction is also associated with an abstinence syndrome in their infants at birth, and its severity is related to the maternal dose, cord blood level of methadone, and concomitant use of heroin or benzodiazepines. Neonatal withdrawal from methadone is also more severe and prolonged compared to heroin, and seizures are more likely in affected neonates. The birth weight of infants whose mothers are on methadone is comparatively larger compared to those exposed to those heroin. Buprenorphine has been used as a substitute treatment for maternal heroin addiction and can also induce a neonatal withdrawal syndrome that is less prolonged in comparison to methadone, except if buprenorphine is combined with other drugs such as benzodiazepines. The severity of withdrawal from buprenorphine is also related to the maternal dose. The onset of withdrawal from methadone and buprenorphine can be delayed. Thus, prolonged observation is needed in these infants and includes making the mother aware of this possibility if the infant is discharged early.

There has been increasing use of opiates and sedatives in the treatment of infants, especially in the intensive care unit, because of increasing awareness of the adverse effects of pain experienced by neonates.

The drugs commonly used include fentanyl, morphine sulfate, and midazolam. Withdrawal consisting of shorter sleeping time and increased muscle tone has been observed in these infants when the drugs are abruptly discontinued. In one report, severe midazolam and opioid withdrawal resulted in transient myocardial ischemia which resolved once fentanyl and midazolam were reinstituted.

### Nonnarcotic Hypnotosedatives

#### Barbiturates

Although barbiturates have been used in clinical medicine for more than 50 years, their addiction potential was only recognized at a much later time. It may be the frequent association of barbiturate use with alcohol that masked the identification of the addicting potential of barbiturates. This phenomenon may be explained by the property of barbiturates to attenuate the symptoms of alcohol withdrawal.

Barbiturates are classified on the basis of their duration of action as ultrashort, intermediate, and long-acting.

The intermediate-acting barbiturates are abused most often; for example, secobarbital (Seconal), pentobarbital (Nembutal), amobarbital (Amytal) and butabarbital (Butisol). Abuse of the long-acting barbiturates (eg, phenobarbital) is not as common as abuse of the shorter-acting forms. However, phenobarbital is involved most often with nonnarcotic abstinence in the newborn because it has been used for insomnia, as an anticonvulsant, or for sedation in toxemia of pregnancy.

Passive acquisition by the fetus of physical dependence on barbiturates can occur after prolonged intrauterine exposure to the drug. Barbiturates readily cross the placenta and establish high levels in both maternal and cord blood. Relatively high levels of barbiturates have been found in the fetal brain, liver, and adrenals. The manifestations of barbiturate withdrawal in the neonate are similar, regardless of which barbiturate was used by the mother. However, the time of onset of withdrawal may differ. Withdrawal from intermediate-acting barbiturates occurs within a day after birth, and approximately 3 to 7 days after birth in the case of the long-acting barbiturates.

Barbiturates are metabolized principally by the liver, although a significant portion may be excreted unchanged by the kidney. In adults, for instance, up to 30% of the total dose of phenobarbital ingested is excreted in the urine in unchanged form. The half-life in infants of prenatally administered phenobarbital is almost twice that in the adult and varies inversely with the extent of the prenatal exposure to phenobarbital. The prolonged half-life of phenobarbital in the neonate is caused by a lower glomerular filtration rate and a decreased capacity of the neonatal liver to metabolize drugs.

Withdrawal from barbiturates can occur in infants even at therapeutic, nonaddicting maternal doses. Withdrawal from phenobarbital has been reported in an infant born to an epileptic mother receiving phenobarbital at a dose of 60 mg per day. An awareness of the possibility of late-onset withdrawal, especially after exposure to long-acting barbiturates, should alert

the physician to monitor these infants closely during the first 2 weeks of life.

### **Benzodiazepines**

**CHLORDIAZEPOXIDE.** Chlordiazepoxide is a long-acting benzodiazepine often used in the management of anxiety disorders, withdrawal symptoms from alcoholism, and preoperative anxiety. It has low toxicity and is safe for preanesthetic use during labor. There have been no reports of adverse effects with the occasional use of chlordiazepoxide in the second and third trimester. However, there are well-documented case reports of neonatal withdrawal syndrome among infants who were either chronically exposed to chlordiazepoxide in utero or exposed to small amounts intrapartum. In a set of twins born to a mother who used chlordiazepoxide at a dose of 20 mg/24 hr during the second and third trimesters of her pregnancy, withdrawal occurred on the 21st day of life and consisted of severe irritability and coarse tremors.

**LORAZEPAM.** Lorazepam, which has been used for pregnancy-induced hypertension, has also been used often during labor because of its prolonged amnestic action. Lorazepam and its metabolite do not cross the placenta as easily as other benzodiazepines. However, its elimination from the newborn is slow, taking up to 8 days in term babies and even longer in premature infants. Full-term infants whose mothers had received oral lorazepam were noted to have no complication apart from a slight delay in establishing feeding. In contrast, intravenous use of lorazepam for severe hypertension was associated with neonatal withdrawal and significantly low Apgar scores, hypothermia, poor suck, and depressed respiration that required ventilation.

### **Alcohol**

Ethanol has a depressant effect on the CNS. It is rapidly absorbed by diffusion in the mucosa of the stomach (20%) and intestines (80%). The absorption rate is not affected by pregnancy, but blood alcohol levels may be higher in pregnancy. Ethanol is usually cleared from the bloodstream within 1 hour in adults and 2 hours in newborns. Approximately 95% is metabolized by the liver and 5% eliminated by the kidneys and lungs. Ethanol is metabolized to acetaldehyde and then to acetate. Acetaldehyde is more toxic than ethanol itself.

Infants can undergo withdrawal from alcohol, but this often is mistaken for withdrawal from narcotics or other drugs. The withdrawal from ethanol occurs early (within the first 12 hours of life) because of its short half life and may manifest as abdominal distention, opisthotonos, convulsions, tremors, hypertonia, apnea, and cyanosis. Affected infants are irritable, sleep restlessly, and engage in exaggerated mouthing behavior.

### **Stimulants**

#### **Cocaine**

Data from controlled studies show devastating early effects of prenatal cocaine exposure. After controlling for confounders, at 40 weeks' (40<sup>0</sup>/<sub>7</sub>-40<sup>6</sup>/<sub>7</sub> weeks) gestation, cocaine exposure was estimated to be associated with growth deceleration and a decrease of 151 g, 0.71 cm, and 0.43 cm in birth weight, length, and head circumference, respectively. Neurobehavioral

abnormalities, such as tremulousness, irritability, hypertonicity, high-pitched cry, abnormal sleep pattern, and sometimes seizures, have been observed in infants who have been exposed prenatally to cocaine, and are similar to the manifestations of withdrawal from opiates. It is difficult to separate the overlapping effects of cocaine and opiate withdrawal because it is not uncommon for addicts to abuse both drugs. In general, the CNS manifestations in cocaine-exposed infants are significantly milder than those observed in narcotic withdrawal. Abnormalities in cardiorespiratory patterns (increased episodes of apnea, periodic breathing), EEG (bursts of sharp waves and spikes), and neonatal behavior as assessed by the Brazelton score (impairment of orientation, motor, and state regulation) have also been described. These abnormalities may be manifestations of the drug's stimulant effect rather than withdrawal.

### **Marijuana**

Marijuana is the most widely used illicit drug among women of childbearing age in the United States. Tetrahydrocannabinol (THC) is highly bound to the lipoprotein fraction in the blood. THC crosses the placenta within minutes of administration. The concentrations of THC in maternal and fetal sera essentially are identical.

Most studies do not show a significant effect of prenatal marijuana use on fetal growth or weight. There is an equivocal relationship between prenatal marijuana use and neurobehavioral outcome of the offspring. Prenatal marijuana exposure has been associated with increased fine tremors in the infant, accompanied by exaggerated and prolonged startles (both spontaneous and in response to mild stimuli), poorer visual but not auditory stimuli habituation, decreased ability to regulate state, and disrupted sleep patterns. Elevated serum norepinephrine levels have been observed among these infants. Other reports have found no altered neurobehavioral patterns in marijuana-exposed offspring.

### **Nicotine**

Nicotine is the compound considered primarily responsible for the stimulant effects of smoking. It is absorbed readily from the lungs, almost with the same efficiency as intravenous administration, and is distributed rapidly throughout the body. Nicotine is metabolized principally in the liver into its 2 principal metabolites, cotinine and 3' p-hydroxycotinine. These metabolites have been measured in meconium with the highest concentrations found in infants whose mothers were heavy smokers (>2 packs per day). Of interest, equivalent amounts of cotinine were found in meconium of infants whose mothers were passive smokers and those whose mothers who smoked 1 pack per day, which indicates the significant exposure from passive smoking.

Tobacco is used widely by women of childbearing age. About 1 in 6 pregnant women ages 15 to 44 (15.9%) had smoked cigarettes in the past month, based on combined 2011 and 2012 data. Several studies have investigated the effect of cigarette smoking during pregnancy on newborn behavior and later child development. Offspring of mothers who smoked



during pregnancy have been observed to perform less well on the Brazelton Neonatal Behavioral Assessment Score in such items such as habituating to sound or orienting to a voice, compared with offspring of nonsmoking mothers. Other studies indicate poorer performance with head turning and sucking, lower visual alertness, more crying, tremors, and startles, and increased lability of skin color. In a study of 27 nicotine-exposed and 29 unexposed full-term newborn infants, the tobacco-exposed infants were more excitable and hypertonic, required more handling, and showed more stress/abstinence signs, specifically in the CNS and gastrointestinal and visual areas. Dose-response relationships showed higher maternal salivary cotinine values related to more stress/abstinence signs among the tobacco-exposed infants. The findings suggest neurotoxic effects of prenatal tobacco exposure on newborn neurobehavior; the dose-response relationships could indicate neonatal withdrawal from nicotine. A prospective, 2-group parallel study on 17 consecutive newborns of heavy-smoking mothers and 16 newborns of non-smoking, unexposed mothers (controls) showed that Finnegan withdrawal scores were significantly higher in newborns of smokers than in control infants at days 1, 2, and 4. Significant correlations were observed between markers of nicotine exposure and severity of withdrawal scores.

### **Phencyclidine**

Phencyclidine (PCP) was first introduced as a dissociative anesthetic, but its clinical use was discontinued after reports of adverse effects that included agitation, confusion, delirium, and persistent hallucinations. It remains a popular drug of abuse because of its hallucinogenic and sedative effects. Phencyclidine has strong, centrally mediated effects in animals and humans, and influences many different neuronal systems. It inhibits the uptake and increases the release of monoamines in the brain, interacts with cholinergic and serotonergic systems, and antagonizes the neuronal stimulation caused by the excitatory amino acid N-methyl aspartate.

The prevalence of PCP abuse during pregnancy has not been firmly established because most reports are from urban areas and cannot be generalized nationally. In 1983, a study reported that 12% of a random sample of 200 newborns had measurable quantities of PCP in their cord blood.

Early case reports of PCP-exposed newborns showed abnormal neurobehavioral findings in the infants. These included irritability, tremors, hypertonicity, poor attention, bizarre eye movements, staring spells, hypertonic ankle reflexes, and depressed grasp and rooting reflexes. One of the most characteristic features in infants is a sudden and rapid change in level of consciousness, with lethargy alternating with irritability. The behavior of these newborns has been attributed to PCP intoxication, rather than to withdrawal.

### **Amphetamines**

The amphetamines are a group of chemically related sympathomimetic amines that have both CNS stimulant and peripheral actions. There is a strong abuse

potential because of their psychic effects, which include wakefulness, alertness, mood elevation, self-confidence, a reduced sense of fatigue, and often euphoria and elation.

Methamphetamine, the methylated derivative of amphetamine, is prepared through the reduction of ephedrine or pseudoephedrine. The ease of its synthesis, its availability and affordability, and a prolonged “high” have made it an increasingly popular drug of abuse. Ice, the smokable form of methamphetamine, is claimed to produce an intense euphoria.

An infant born to an amphetamine addict manifests with diaphoresis, episodes of agitation alternating with lassitude, miosis, and vomiting. Infants exposed to both cocaine and methamphetamine are described as having abnormal sleep patterns, tremors, poor feeding, hypertonia, sneezing, a high-pitched cry, frantic fist sucking, tachypnea, loose stools, fever, yawning, hyperreflexia, and excoriation of the buttocks because of irritation from the loose stools. A study of 134 mother-infant pairs whose mothers used methamphetamine during pregnancy were compared to 160 unexposed newborns. Exposure to methamphetamine throughout gestation was associated with decreased growth relative to infants exposed only for the first 2 trimesters. The incidence of withdrawal in infants in the methamphetamine group was 49%, but only 4% required pharmacologic treatment for their withdrawal. Bupropion, which is also called amfebutamone, is an amphetamine marketed to assist with smoking withdrawal and has been shown to be associated with a higher than expected frequency of neonatal cardiac malformations in infants born to women who have used the drug during pregnancy.

### **Antidepressants**

Since their introduction in 1988, the selective serotonin reuptake inhibitors (SSRIs) have become the drug class of choice to treat depression and selected other disorders of mood and behavior. Depression during pregnancy is common, with an estimated prevalence of about 7% to 13%. In a multisite study across the United States, the use of antidepressants during pregnancy was shown to have increased from 2% in 1996 to 7.6% in 2004 and 2005. SSRIs were the most commonly used antidepressants during pregnancy, with a prescription frequency of about 5.6%. Drug withdrawal syndrome associated with antidepressants, both tricyclic antidepressants and SSRIs, is well documented in adults. Newborns whose mothers are on tricyclic antidepressants may exhibit manifestations such as irritability, tachycardia, respiratory distress, sweating, and convulsions. Neonatal withdrawal syndrome associated with maternal SSRI use during pregnancy has been reported from the WHO database with a total of 93 cases identified. About 30% of infants exposed to SSRIs during the third trimester of pregnancy had a 3-fold increased risk of neonatal behavioral syndrome. This syndrome includes signs of toxicity or withdrawal from SSRIs. Possible mechanisms of action of neonatal SSRI syndrome can be attributed to cholinergic overdrive or dependence on the serotonin system. Paroxetine and fluoxetine are the most commonly reported SSRIs associated with neonatal SSRI syndrome. Paroxetine has a short half-life and a distinct

affinity to muscarinic receptors, and is a more potent inhibitor of norepinephrine reuptake than sertraline or citalopram. These aspects of paroxetine may render neonates with in utero SSRI exposure susceptible to withdrawal postnatally. Infants with withdrawal signs usually present within 2 days to 1 month with less than 2 weeks' duration in most cases. Withdrawal signs are characterized as alterations in sleep and changes in the gastrointestinal and central nervous systems. Fluoxetine is known to cross the placenta, and elevated drug levels in cord blood among newborns exposed prenatally have also been described. Late-gestation exposure to SSRIs with long half-life such as fluoxetine may be associated with neonatal toxicity syndrome. These infants present within a few hours after birth and clinically manifest with neurobehavioral and respiratory abnormalities. These effects include acrocyanosis, tachypnea, temperature instability, irritability, and hypoglycemia. Treatment of infants with SSRI syndrome includes placing the infant in a quiet environment with avoidance of overstimulation. The use of sedatives is uncommon.

### Inhalant (Volatile Substance) Abuse

Inhalants produce alcohol-like effects described as a "high," resulting in slurred speech, clumsy movements, dizziness, and euphoria. Lightheadedness and hallucinations/delusions can also occur. Inhalants are often the first drugs used by young children. In a survey conducted from 2002 to 2004, an average of 598,000 youths aged 12 to 17 reported each year that they had initiated inhalant use in the 12 months prior to being surveyed.<sup>95</sup> Youths aged 14 or 15 were more likely to be recent inhalant initiates (39.2%) than was the population as a whole (33.9%). The types of inhalants most often mentioned as having been used included glue, shoe polish, or toluene (30.3%); gasoline or lighter fluid (24.9%); nitrous oxide or "whippets" (24.9%); and spray paints (23.4%). Neonatal withdrawal from volatile substances has been described. The principal products abused are paint solvents, lacquer, and glue. Nail polish remover, lighter fluid, deodorant and hair sprays, whipped cream canisters, and cleaning fluids are all widely used inhalant sources. Toluene and other hydrocarbons may be present. A characteristic chemical odor in the neonate or mother is noted that can persist for several days because the lungs are a major route for excretion, and the highly lipophilic substances are excreted slowly. The typical manifestations in the infant include an excessive and high-pitched cry, sleeplessness, tremors, hypertonia, and poor feeding. Metabolic acidosis also has been described. Withdrawal occurs within the first 24 hours of life, and 2 different patterns are observed. The common form is transient and resolves spontaneously or after a single dose of sodium bicarbonate. The other type is more persistent, lasts for 1 to 2 weeks, and requires treatment with repeated doses of sodium bicarbonate or Shohl solution. The cause of the metabolic acidosis is not known, although it may be secondary to the acid load of toluene metabolite or from renal tubular acidosis.

### Other Drugs

Neonatal withdrawal consisting of seizures has been reported in infants born to mothers who have received

the antispasmodic baclofen during pregnancy. Neonatal hypoglycemia and withdrawal manifestations have also been reported with maternal use of valproate for epilepsy.

## ONSET AND DURATION OF NEONATAL DRUG WITHDRAWAL

The onset of withdrawal is common within the first 72 hours after birth, usually within the first 24 to 48 hours. In a few instances the onset may appear soon after birth, if the drug has a short half-life or if the mother already has begun to experience withdrawal while in labor. Withdrawal occurring after the first or second week has been observed with drugs that have a longer half-life, such as phenobarbital. Among narcotics, delayed manifestations of withdrawal, sometimes as late as 6 weeks, have been observed with methadone.

The onset and severity of withdrawal are affected by several factors including affected by a number of factors, among which are the amount of maternal drug use, timing of the last dose before delivery, use of anesthesia or analgesia in the mother during labor, maturity and nutrition of the infant, and metabolism and excretion of the drugs and their metabolites.

Neonatal withdrawal from narcotics can occur within the first 2 days of postnatal life, usually peaks by the third day, and subsides between the fifth and seventh day. On the other hand, withdrawal from methadone can occur after the first week of postnatal life. Manifestations include irritability, tremors, hypertonicity, sneezing, hiccups, and regurgitation. The duration of withdrawal is related to its severity; it is more prolonged in those with severe withdrawal. Infants treated for withdrawal also show a prolonged withdrawal period. Thus, drug treatment may ameliorate the manifestations of withdrawal but prolong its duration. It is important that the mother be made aware that her infant's symptoms of withdrawal may persist for weeks after discharge from the nursery. The uninformed mother also may misinterpret her infant's irritability as hunger and then overfeed, which can lead to diarrhea and vomiting. The mother also should be instructed on how to reduce the infant's discomfort by swaddling and cuddling. She should be reassured that signs of withdrawal will eventually subside. In most instances, the mother who is well informed can successfully cope with the situation. If drugs are used to treat the withdrawal, relapse may occur if treatment is discontinued abruptly. Although withdrawal manifestations diminish in intensity within the first week after birth, they do not disappear completely. The tremors and irritability may persist for as long as 8 to 16 weeks. Withdrawal from barbiturates, diazepam, chlorthalidone, and even methadone may occur weeks later.

## NEONATAL NARCOTIC WITHDRAWAL

The prototype of drug withdrawal in the neonate is withdrawal from narcotics. The manifestations are multisystemic and involve the CNS and respiratory, gastrointestinal, vasomotor, and cutaneous systems. (See Box 104-2.)

**BOX 104-2 Manifestations of Neonatal Abstinence Syndrome****CENTRAL NERVOUS SYSTEM SIGNS**

- Hyperactivity
- Hyperirritability—excess crying, high-pitched outcry
- Increased muscle tone
- Exaggerated reflexes
- Tremors
- Sneezing, hiccups, yawning
- Short, nonquiet sleep
- Fever

**RESPIRATORY SIGNS**

- Tachypnea
- Excess secretions

**GASTROINTESTINAL SIGNS**

- Disorganized, poor sucking
- Vomiting

- Drooling
- Sensitive gag
- Hyperphagia
- Diarrhea
- Abdominal cramps

**VASOMOTOR SIGNS**

- Stuffy nose
- Flushing
- Sweating
- Sudden, circumoral pallor

**CUTANEOUS SIGNS**

- Excoriated buttocks
- Facial scratches
- Pressure point abrasions

**Central Nervous System**

Neurologic signs predominate and appear early. Findings are those of CNS excitability, such as hyperactivity, irritability, tremors, and hypertonicity. Occasionally, fever may accompany these increased neuromuscular activities.

Hyperactivity manifests as nearly incessant movements of the extremities. When the infant is supine and unrestrained, movements assume a jerky, purposeless nature, apparently perpetuated by unchecked proprioceptive stimuli. When placed in the prone position, the infant's motor behavior becomes more organized. There are crawling movements, which may lead to the infant's displacement from the crib, abrasions or friction injuries to the knees and legs, and other motions such as chin lifting, side-to-side head movement, chest elevation, and hand-to-mouth activity. The latter usually quiets the infant, as does the use of pacifiers.

Hyperirritability manifests as an almost incessant shrill, high-pitched crying. The infant's tone is exaggerated, sometimes assuming an opisthotonic position, making the infant hard to hold. Tremors and myoclonic jerks are frequent and sometimes sustained. Unlike seizures, tremors can be abolished by restraint of the tremulous extremity. The reflexes of the infant, such as Moro, traction response, weight bearing, placing, stepping, crawling, and Landau, are exaggerated. The infant's response to sensory stimuli such as sound and light is disproportionately increased.

Electroencephalographic tracings on the addicted neonate may be abnormal and show high frequency dysynchronous activity suggesting CNS irritability. The prevalence of seizures is estimated to be between 5% and 21% in infants manifesting narcotic withdrawal.

In premature infants, neural hyperexcitability is more episodic than in term newborns. The neonates seem restless and overactive for short periods and

then lapse into periods of lethargy and inactivity. Sustained tremors usually are not seen in premature infants until they reach the gestational age when tone is present in the upper and lower extremities. Sweating, which is seen in the full-term infant, is also not observed in preterm infants.

The normal patterns of active and quiet sleep periods are disturbed in the infant experiencing withdrawal, with a significant decrease in sleep from the normal 3 to 4 hours to less than 1 hour. Infants addicted to heroin or methadone also have fewer periods of quiet sleep. Initially, these findings were thought to be related to withdrawal. However, because these abnormal sleep patterns persist beyond the period of withdrawal, they might be the result of the addiction process itself, rather than the general distress secondary to withdrawal, and may be secondary to the direct effects of chronic opiate exposure on the opiate receptors in the brain involved in sleep regulation.

**Cardiorespiratory Signs**

Abnormalities in ventilation have been described in infants withdrawing from narcotics, including longer and increased frequency of apneic episodes and periodic breathing. During withdrawal, these infants also may also exhibit tachypnea with concomitant respiratory alkalosis. In animals, exposure to morphine initially results in apnea or hypoventilation and later causes tachypnea. It is postulated that the dual action of morphine is secondary to the effects of the drug concentration and to the effects of the drug on 2 different sites involved in the control of respiration. After a bolus of morphine, its initial high concentration causes respiratory depression and apnea. As the drug is metabolized, the lower concentration is associated with stimulation of respiration, hence the tachypnea. Morphine is found to be inhibitory to the

respiratory neurons in the medulla and to the neurons located more rostrally that act to inhibit respiration.

Abnormal heart rate tracings associated with elevated serum creatine phosphokinase were noted to be significantly different in infants of drug-dependent mothers compared with unexposed infants. In addition, these changes were more intense among infants who had moderate to severe withdrawal. The elevated serum creatine phosphokinase is postulated secondary to the excess muscular activity of infants undergoing withdrawal.

Other physiologic alterations include elevated systolic blood pressure, an increase in plasma renin activity, and elevated catecholamine levels. In one report, these conditions persisted for 21 days after delivery, suggesting increased beta-adrenergic activity.

### Gastrointestinal Signs

The sucking of the infant withdrawing from narcotics is disorganized and poorly coordinated with swallowing. Both sucking rate and nutrient consumption are low. Often, milk drools around the corners of the infant's mouth. The infant seems incessantly hungry, and when feeding is unfulfilled it leads to mounting agitation, persistent crying, hyperactivity, and exhaustion. The poor nutrient intake and increased caloric expenditure from hyperactivity may occur and lead to significant weight loss. Vomiting and diarrhea also are often observed and may lead to dehydration, electrolyte imbalance, and excoriations around the buttocks.

### Vasomotor Signs

Significant vasomotor instability in a newborn experiencing withdrawal manifests as a stuffy nose, flushing, mottling, sweating, and episodes of sudden, circum-oral pallor.

### Cutaneous Signs

Newborns experiencing withdrawal may be hyperactive, and this may lead to facial scratches and abrasions on pressure points. Excoriations of the buttocks can occur if diarrhea is present.

## NEONATAL WITHDRAWAL FROM NONNARCOTIC DRUGS

Withdrawal from nonnarcotic drugs is similar to narcotic withdrawal except that convulsions are observed more often in the former. Infants born to mothers who have abused stimulants during pregnancy (eg, cocaine, amphetamines) also may manifest tremors, irritability, a high-pitched cry, and abnormal sleep patterns during the neonatal period. These are probably manifestations of drug effects rather than withdrawal.

### DIAGNOSIS

The diagnosis of drug withdrawal is based on signs and symptoms and the verification of fetal drug exposure. However, identifying drug exposure in an infant is not easy: there is significant under-reporting of maternal drug use because of fear of the consequences of such an admission. Even with maternal cooperation, information regarding the type and extent of drug use often is inaccurate. Similarly, many of the drugs to

which the fetus is exposed in utero do not produce immediate or recognizable effects. High-risk characteristics in the mother that should lead to the suspicion of drug abuse include little or no prenatal care, ethanol use, teenage pregnancy, history or presence of sexually transmitted infectious disease or hepatitis B, and abruptio placenta. A number of laboratory tests commonly are used to detect drug exposure in the infant. These include toxicologic analysis of the infant's urine, hair, and meconium. Urine screening can have a high false-negative rate because only the results for infants who have had recent exposure will be positive. Meconium testing is more likely to identify infants of drug-abusing mothers.

### DIFFERENTIAL DIAGNOSIS

Withdrawal from narcotic and nonnarcotic drugs needs to be distinguished from other entities such as hypoglycemia, hypocalcemia, hypomagnesemia, sepsis, meningitis, subarachnoid hemorrhage, infectious diarrhea, and intestinal obstruction. Blood chemistry, cerebrospinal fluid, radiographic studies, and cultures may be performed as indicated by the clinical circumstances.

Maternal use of phenothiazines (eg, chlorpromazine) may induce extrapyramidal dysfunctions in the newborn such as tremors, facial grimacing, increased muscle tone, cog-wheel rigidity, increased reflexes, and torticollis, all of which can resemble the withdrawal syndrome. The maternal medical history and identification of the drug's metabolites in the infant's serum or urine are necessary to establish the diagnosis.

## ASSESSMENT OF THE SEVERITY OF NEONATAL DRUG WITHDRAWAL

The manifestations of withdrawal can range in severity from none or mild to severe. It has been shown that neither the infant's gender, race, or Apgar score nor the mother's age, parity, or duration of heroin intake correlate with the severity of the infant's withdrawal. Likewise, control of the environment to reduce the amount of light or noise in the nursery does not improve the severity of withdrawal. Since adults undergoing withdrawal experience abdominal cramps, palpitation, nausea, and other discomforts, it can be speculated that the same discomforts also are experienced by the infant, which may abolish any potential benefits from stimuli (light or noise) reduction in the nursery. Although environmental control may not ameliorate the severity of withdrawal, a quiet and darker nursery, in general, is preferred. The severity of an infant's withdrawal from methadone correlates significantly with the methadone dose of the mother. Mothers taking higher doses of methadone are likely to have infants experiencing severe withdrawal. Neonatal withdrawal tends to be more intense if the mother was on 20 mg or more of methadone per day before delivery. The frequency of diarrhea and vomiting should be noted and the infant's weight checked at least every 8 hours. The temperature, heart rate, and respiratory rate should be taken every 4 hours. Laboratory examinations to detect serum electrolyte or pH imbalance should be performed as indicated.



The severity of the withdrawal can be assessed clinically by several scoring systems. The scoring system designed by Finnegan is an extensive evaluation that is particularly useful for research purposes in evaluating the severity of withdrawal as well as the response to treatment. However, the Finnegan scoring system contains 21 items to evaluate, including minor symptoms such as yawning, sneezing, sweating, and so on; because of the large number of items to be evaluated, the scores may not be filled out completely or uniformly. Likewise, the Finnegan assessment criteria do not include weight loss, which is an important manifestation of neonatal drug withdrawal. Using the Finnegan scoring system, treatment of the infant with medications is recommended, if the total score is greater than 8 for 3 consecutive times. This can be problematic since a total score of more than 8 may be achieved by the inclusion of minor signs of withdrawal such as yawning, mild tremors, sneezing, nasal stuffiness, and mottling, which per se do not warrant drug treatment. More stringent criteria should be adopted for pharmacologic treatment since once drugs are used, the infant stays in the hospital longer in order to control the withdrawal and to allow time for gradual weaning and prevent a rebound withdrawal. Thus, treatment of the infant with pharmacologic agents results in a prolonged hospital stay and longer separation of the mother from her infant (7–10 days). The latter adversely affects mother-infant bonding, which is already compromised by the maternal addiction problem. Child abuse has been one consequence of impaired mother-infant bonding. Furthermore, a prolonged hospital stay also increases hospital cost. Another system evaluates the infant's need for drug treatment and focuses on manifestations of withdrawal that are life threatening, such as irritability, tremors (convulsion), weight loss, vomiting, diarrhea, and tachypnea (Table 104-1). Measurement of infant movement with a motion detector has been used in research settings to objectively gauge the severity of withdrawal.

The effect of polydrug abuse on the severity of withdrawal is controversial. Abstinence scores of

infants whose mothers were on methadone and cocaine were similar to the scores of those infants whose mothers were on a high methadone dose. Similarly, multiple opiates did not alter the severity of withdrawal. However, higher abstinence scores have been reported in infants exposed to both cocaine and heroin compared to either drug alone. In 2 reports, no difference was observed in the severity of withdrawal in infants born to mothers who have used both cocaine and methadone or either singly, whereas in a third report, higher abstinence scores were noted in infants exposed to both drugs compared with those exposed to only one.

## SUPPORTIVE TREATMENT OF DRUG WITHDRAWAL

The care of the neonate with drug withdrawal is primarily supportive. This includes swaddling the infant, placing him or her in a prone position, and cuddling more often. Swaddling, particularly with the infant's extremities flexed and hands placed before its mouth, enhances the infant's hand-to-mouth facility, which is soothing. A similar soothing action can be achieved with a pacifier. Other measures include frequent small feedings of hypercaloric (24 cal/oz) formula to supply the additional caloric requirements, hydration, and observation of sleeping habits, temperature stability, weight loss, diarrhea, and change in clinical status that might suggest another disease process. Daily caloric intake should provide the 150 to 250 cal/kg required for proper growth in neonates exhibiting withdrawal.

## Pharmacologic Treatment of Drug Withdrawal

Only 25% of infants who exhibit withdrawal will need drug treatment. The remainder can be managed conservatively. The decision to use pharmacologic agents to treat withdrawal is based on the assessment of the severity of withdrawal. In the system of clinical assessment shown in Table 104-1, drugs are used to treat withdrawal if there is a moderate degree of vomiting,

**Table 104-1** Assessment of Clinical Severity for Neonatal Drug Withdrawal Syndrome

	MILD	MODERATE	SEVERE
Vomiting	Spitting up	Extensive vomiting for 3 successive feedings	Vomiting associated with imbalance of serum electrolytes
Diarrhea	Watery stools	Watery stools 5–6 times per day for 3 days; no electrolyte imbalance	Diarrhea associated with imbalance of serum electrolytes
Weight loss	<10% of birth weight	10%–15% of birth weight	>15% of birth weight
Irritability	Minimal	Marked but relieved by cuddling or feeding	Unrelieved by cuddling or feeding
Tremors or twitching	Mild tremors when stimulated	Marked tremors or twitching when stimulated	Convulsions
Tachypnea	60–80/minute	80–100/minute	>100/minute and associated with respiratory alkalosis

Treat with pharmacologic agents (see Table 104-2) if infant has:

1. Moderate vomiting, diarrhea, or weight loss

2. Any severe sign of withdrawal (eg, convulsion or severe vomiting, diarrhea, weight loss, irritability, tachypnea)

From Ostrea EM. Infants of drug-dependent mothers. In: Berg FD, Ingelfinger JR, Wald ER, eds. *Current Pediatric Therapy*. Vol. 14. Philadelphia: WB Saunders; 1993. Reprinted with permission.

diarrhea, or weight loss or any severe sign of withdrawal (convulsion, severe vomiting, diarrhea, weight loss, or irritability). The use of pharmacologic agents, as compared to supportive care only, seems to reduce the time to regain birth weight and the duration of supportive care, but increases the duration of hospital stay. The duration of treatment also is related to the severity of withdrawal, although the length of stay of infants in the nursery is not significantly different whether treatment is with methadone or morphine.

The drugs that are used to treat drug withdrawal in the infant are listed in Table 104-2. As a rule, drug selection should match the class of agent from which the infant is withdrawing. Thus, for narcotic withdrawal, narcotics are the drugs of choice, whereas for nonnarcotic withdrawal, nonnarcotic hypnotosedatives (eg, phenobarbital) are preferred. Combinations of opiate and nonopiate drugs have also been used. Improved neurobehavioral scores have been noted in infants treated for withdrawal with opiate and phenobarbital. Although the neurologic manifestations of narcotic withdrawal may be controlled successfully by a nonnarcotic agent, non-CNS manifestations of withdrawal (eg, diarrhea) are treated more effectively with narcotics.

Laudanum (tincture of opium) and methadone are the narcotics most commonly used to treat neonatal opiate withdrawal. The use of paregoric has been discouraged because of the potential toxic effects of some of its ingredients. Besides camphor, a potent CNS stimulant, paregoric contains isoquinolone derivatives (noscapine and papaverine), which are antispasmodics. It also contains a high concentration of ethanol (44% to 46%), a CNS depressant, and anise oil, which may cause habituation. Laudanum is the preferred drug for neonatal narcotic withdrawal. (Caution: Laudanum, USP is available only as a 10% solution that contains 1.0% morphine.) Laudanum must be first diluted 25-fold to a concentration of 0.04% to reduce its morphine content to equal the amount found in paregoric. At this dilution, the recommended initial dose of 0.04% laudanum is 0.1 mL/kg (0.04 mg/kg) with feedings every 4 hours. The dose may be increased by 2 drops/kg every 4 hours as needed to control withdrawal. After the infant has stabilized for 3 to 5 days, the dose may be slowly decreased without altering the frequency of administration. An abrupt decrease in dosage or discontinuance of the drug should be avoided because of the risk

of relapse. Lower peak doses of tincture of opiate and shorter dosing intervals have been associated with shorter hospital stays for infants with neonatal abstinence syndrome secondary to maternal methadone treatment. Oral morphine solution sulfate has been used in place of laudanum because of its more exact content of morphine. It is given as an oral solution at a dose of 0.03 to 0.1 mg/kg. The initial dose may be increased stepwise if withdrawal is not adequately controlled. If methadone is used, initial doses of 0.05 to 0.1 mg/kg may be given every 6 hours, with increases of 0.05 mg/kg until withdrawal signs are controlled. Thereafter, methadone may be given every 12 to 24 hours and discontinued after weaning to a daily dose of 0.05 mg/kg per day.

Neonatal abstinence syndrome can occur as well in infants who receive narcotics for analgesia or sedation (iatrogenic neonatal abstinence syndrome). The guidelines for effective weaning of infants from opioids are not well established. A suggested strategy is that all NICU patients who have received opioids for more than 3 to 5 days be systematically weaned from the opioid while being regularly evaluated for signs of withdrawal.

Nonnarcotic hypnotosedatives are used to treat neonatal withdrawal from nonnarcotic drugs (Table 104-2). The commonly used drugs are phenobarbital and chlorpromazine. Barbiturates can be used to treat withdrawal from nonbarbiturates (including alcohol) or vice versa. Although chlorpromazine is not a nonnarcotic hypnotosedative, its capacity to treat withdrawal may result from its ability to suppress REM sleep, which is exaggerated during withdrawal. However, the prolonged excretion time and many side effects of chlorpromazine, including cerebellar dysfunction, decreased seizure threshold, and hematologic problems, have limited its use in the treatment of withdrawal in the neonate. The Cochrane review does not recommend the use of chlorpromazine in the treatment of the neonatal abstinence syndrome owing to lack of randomized studies. Diazepam has not commonly been used because of reported side effects such as bradycardia, respiratory depression, and discoordinate sucking and swallowing. During the treatment of withdrawal, attention should also focus on the nutrition and fluid and electrolyte balance of the infant, particularly if vomiting, diarrhea, hyperpyrexia, and hyperhidrosis are present. Appropriate intravenous

**Table 104-2** Common Drugs for the Treatment of Neonatal Drug Withdrawal Syndrome

DRUGS	DOSAGE
<b>NARCOTICS</b>	
Laudanum (0.4 mg/mL morphine)	0.1 mL/kg (0.04 mg/kg) every 4 hours and may be increased by 0.1 mL/kg (0.04 mg/kg) every 4 hours to control withdrawal manifestations
Methadone	0.05–0.1 mg/kg every 6 hours, orally. Increase dose by 0.05 mg/kg until withdrawal signs are controlled.
<b>NONNARCOTICS</b>	
Phenobarbital	3–6 mg/kg/day in divided doses, every 6 hours, orally

fluids may be required to correct deficits or prevent the occurrence of imbalances.

The aim of treatment with drugs is to render the infant comfortable but not obtunded. Thus, the drug should be titrated, starting with the smallest recommended dose and increased accordingly, until the desired effect is achieved. Once the infant has been asymptomatic for 3 to 5 days, the drug can be slowly tapered in dose until completely discontinued. The total detoxification period can last for 2 to 3 weeks. After discontinuance of the drug, the infant should be observed for a day or 2 for possible recurrence of the withdrawal (rebound phenomenon). Once the infant is discharged from the nursery, the mother should be informed that some jitteriness and irritability may persist for as long as 8 to 16 weeks.

### Complications

The complications of neonatal drug withdrawal are related to the severity of the withdrawal. Biochemical aberrations in the serum electrolytes and pH and dehydration may occur after vomiting and diarrhea. Weight loss may be profound not only because of excess fluid losses, but also because of poor oral intake. Aspiration pneumonia may occur because of vomiting and incoordinate sucking and swallowing. Respiratory alkalosis can occur because of tachypnea. Convulsions may be present and are observed more often in withdrawal from nonnarcotic drugs. The use of naloxone in the delivery room is contraindicated in infants whose mothers are known to be opioid dependent. Administration of naloxone may result in neonatal seizures, because of abrupt drug withdrawal. In the absence of a specific history of opioid abuse, naloxone treatment remains a reasonable option in the delivery room management of a depressed infant whose mother has received a narcotic drug during labor. However, the physician should be prepared to treat withdrawal in the delivery room.

### Other Supportive Measures

The addicted woman has serious impediments to a successful mothering role. Similarly, the neurobehavioral abnormalities and withdrawal in her baby can prevent gratifying feedback, which is important in bonding. Thus, the mother and child should have early and repeated contacts. Social services and the appropriate child welfare authorities should be engaged to ensure that the necessary family supports and community resources are in place if the infant is discharged home with the mother. The infant's disposition is influenced by local community child welfare policies. Consideration is often given to whether the mother is in recovery, what drugs she is using, if she is enrolled in drug treatment, if she has resources, and whether the extent of her family or informed support network is sufficient. Staff personnel should also discuss with the mother her infant's condition and assure her that with control of withdrawal manifestations, the infant will begin to feed better and respond more positively to her.

If plans have been made to place the infant in a foster care home, then in the interim the infant will need

human contact and should receive stimulation through regular holding and cuddling by staff professionals.

### BREASTFEEDING

Most drugs taken by the mother will cross into her breastmilk. The concentration of illicit substance in the breast milk will depend on the amount and time of drug intake by the mother. There also is the danger of transmission of human immunodeficiency virus (HIV) through the breastmilk; thus, in the United States breastfeeding is not recommended in a mother who is HIV positive. In developing countries where infant malnutrition and contaminated water are equally, if not more, important problems, the risk of acquisition of HIV/AIDS has to be weighed against the benefits of breastfeeding. Seropositivity for hepatitis-B surface antigen or hepatitis C is not a contraindication to breastfeeding provided the infant is vaccinated and given hepatitis B immunoglobulin as soon as possible after delivery. For the infant whose mother has continued to use illicit substances throughout pregnancy, breastfeeding is probably unsafe. The American Academy of Pediatrics guidelines on breastfeeding in the mother who continues to use illicit drugs can be summarized as follows: Methadone is "usually compatible with breastfeeding"; benzodiazepines are of "unknown effect but may be harmful"; phenobarbitone has "significant effects documented—use with caution"; and amphetamines, cocaine, heroin, marijuana and phencyclidine are contraindicated because harmful effects have been documented in nursing infants.

For the woman who is in treatment for substance abuse and abstinent at the time of delivery, postpartum breastfeeding support, close monitoring of the mother for relapse and of the infant for adequate weight gain, and frank discussions concerning the risks posed by exposure to illicit substances through breastmilk are essential.

Methadone treatment in the mother is compatible with breastfeeding; no adverse effects have been reported in nursing infants when the mother is on a methadone dose of 20 mg per day or less. The concentration of methadone in breastmilk is low and does not correlate with maternal dose. Breastfed infants of women on methadone have lower Finnegan scores and reduced need for pharmacotherapy compared to their formula-fed counterparts. It is suggested that the mother take the dose of methadone after the evening feeding and supplement breastfeeding with a bottle at the next feeding.

### DECISIONS REGARDING THE INFANT'S CAREGIVER

The ability of the drug-addicted woman to provide adequate care for her infant has often been questioned. Frequently, these women are denied their rights and responsibility to care for their infants on the basis of an unstable home and lifestyle and emotional and psychological weakness. Current evidence suggests that this practice may be counterproductive. A study that determined the outcome of such infants on the basis of the type of caregiver showed that the outcome (growth, development, and frequency of

medical illnesses and child abuse) of infants cared for by their own mother with the help of a caregiver (either a husband or relative) was better than for those in foster care. Thus, with appropriate guidance and supervision and the presence of a supportive person, the addicted mother is capable of providing adequate care for her infant, particularly if she is highly motivated. Coordinated outpatient care of the infant also has been used to shorten the stay of the infant in the nursery. Although a high incidence of signs suggestive of child abuse (cigarette burns or hematoma) has been observed in infants born to drug-dependent mothers, these have occurred in situations where the infant was cared for exclusively by the mother, and very few occurred in infants whose mothers had help available. Thus, it is important that a support person be available at home to help the mother in the care of her infant and prevent child abuse or neglect. It is also important to understand, identify, and treat risk factors that could destabilize the home. This is particularly true of domestic violence, which is not only linked to higher rates of child abuse and neglect but can have a cumulative effect in regard to adverse childhood experiences that can cause long-term problems with the physical and mental health of children.

### **SOCIAL AND PROTECTIVE SERVICE REFERRAL AND FOLLOW-UP**

All infants of drug-dependent mothers should have a social service referral to assess the adequacy of parenting and care of the infant at home. The discharge of the infant to the mother's care, with the help of a support person, is the primary objective unless serious conditions dictate otherwise. The discharge of the infant to a person other than the mother (foster parent) or an agency should be attempted only when it is apparent that the infant will be neglected, poorly cared for, or abused. Most mothers hesitate to admit to the use of drugs during pregnancy because of fear that their infants will be taken away from them. They should be reassured otherwise; in fact, they should be encouraged to be responsible for the primary care of their infants. The social worker and physician also should advise the mother regarding the availability of medical and social services in the community, including substance abuse counseling, referrals for mental health, other supportive treatment, and family planning. Maternal initiation of drug treatment and supportive services in the perinatal period can have positive results, especially since the mother has the motivation of being a good parent to her newborn to help with compliance. There will be situations in which the mother is not willing or able to engage in the needed treatment or support services. Thus, it is equally important for the health care provider to work collaboratively with colleagues in child protection to optimize flow of accurate information to the social service agencies that will be working on behalf of the child for safety and permanency.

As part of child protection laws operative in many states, infants born to drug-dependent mothers are considered potentially abused and are required by law to be reported to a child protection agency after

birth. The agency usually requires a positive drug screen in the infant before any legal action can be taken against the mother. If necessary, confirmatory tests of positive drug test results should be done to validate the test results and avoid unnecessary referral to protective service. Thus, maternal admission of the use of illicit drugs during pregnancy is not sufficient to generate a child protection agency referral because the mother can subsequently deny her illicit drug use. Referral to a child protection agency is helpful when the intent is to ensure the adequacy of care of the infant at home. If a prenatal determination is made that the baby will be placed in foster care and the mother is informed about it, she may refrain from continuing prenatal care with her providers, choosing to deliver at another facility where she and her history are not known. This puts the mother (and baby) at higher risk for pregnancy-related complications and causes a greater risk of fetal death or morbidity.

### **LONG-TERM PROBLEMS**

The infant of the drug-dependent mother is at risk for long-term problems including child abuse, delays in physical, mental, and motor development, and learning disabilities. Drug-exposed newborns have increased neonatal mortality from sudden infant death syndrome, particularly low-birth-weight infants. The infant also is at risk for ongoing exposure to illicit drugs in the household as a result of accidental ingestion or passive exposure, particularly to smoked crack cocaine. Follow-up of these infants should be planned, not only to assess their medical well-being, but to ascertain the occurrence of such complications and initiate appropriate interventions.

Neurobehavioral problems in infants of drug-dependent mothers have been noted ranging from hyperactivity and impulsivity to poor sustained attention, which may or may not fulfill diagnostic criteria for attention-deficit/hyperactivity disorder (ADHD). Prenatal smoking and alcohol use are 2 of the most commonly studied agents linked to ADHD and ADHD-like symptoms. In a small cohort, opiate-exposed infants were significantly more likely to have neurodevelopmental impairment compared to healthy control infants when assessed at 18 months and 3 years of age. The findings of the Maternal Lifestyle Study group of the National Institutes of Health showed that opiate-exposed infants who were longitudinally followed at 1 and 3 years of age scored 3.8 Psychomotor Developmental Index points below the nonexposed group, but the difference was not statistically significant after controlling for covariates. Children with prenatal opiate exposure had smaller intracranial and brain volumes, including smaller cerebral cortex, amygdala, brainstem, cerebellar cortex, cerebellar white matter, and other regions of the brain.

With regard to cocaine, deficits in the quality of parent-child interactions have been noted in preschool-age children exposed prenatally. At 7 months, cocaine-exposed infants displayed higher arousal or reactivity and lower regulation during a procedure designed to arouse anger and frustration. Those exposed to cocaine responded with negative affect (anger and



sadness) more quickly as the level of stress increased. Sleep problems were also noted in 18-month- to 9-year-old children with prenatal drug exposure. During middle childhood, heavier prenatal cocaine exposure is associated with mild compromise of selective areas of neurocognitive development, specifically cognitive regulation. As part of the longitudinal maternal lifestyle study, prenatal cocaine exposure increased the likelihood of the children receiving individualized education programs, special education conditions, support services, special education classes, and speech and language services. The cocaine-exposed children also had 2.8 times greater risk of developing a learning disability by age 7 than non-cocaine-exposed children.

Neurocognitive testing showed that children with prenatal methamphetamine exposure scored lower on sustained attention, long-term spatial and verbal memory, and visual motor integration. Neuroimaging has produced reports of smaller striatum and hippocampus volumes and decreased numbers of dopamine D2 receptors and dopamine transporter density.

To optimize long-term outcomes in infants of drug-dependent mothers, early intervention services should be identified and enacted; this can positively affect outcomes for drug-exposed newborns at risk for developmental delay. Perinatal health care providers should work collaboratively to educate state legislators that identification of drug use alone is not adequate to cure the problem of addiction or to specifically identify parents who will abuse or neglect their children. It is essential to develop and utilize screening tools to identify parents at risk, fund evidence-based treatment for addiction, and link high-risk parents to effective educational programming to preserve families and make better use of state resources.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Alcohol Use and Pregnancy* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/ncbddd/fasd/documents/fas\\_alcoholuse.pdf](http://www.cdc.gov/ncbddd/fasd/documents/fas_alcoholuse.pdf))
- *Fetal Alcohol Spectrum Disorders* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/ncbddd/fasd/documents/fas.pdf](http://www.cdc.gov/ncbddd/fasd/documents/fas.pdf))

#### Medical Decision Support

- *Fetal Alcohol Spectrum Disorders* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/ncbddd/fas](http://www.cdc.gov/ncbddd/fas))
- *National Institute on Drug Abuse* (Web site), US Department of Health and Human Services, National Institutes of Health ([www.drugabuse.gov](http://www.drugabuse.gov))

### AAP POLICY

Hudak ML, Tan RC; American Academy of Pediatrics Committee on Drugs, Committee on Fetus and Newborn. Neonatal drug withdrawal. *Pediatrics*. 2012;129(2):e540–e560 ([pediatrics.aappublications.org/content/129/2/e540](http://pediatrics.aappublications.org/content/129/2/e540))

### SUGGESTED READINGS

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### Chapter 105

## TRANSIENT METABOLIC DISTURBANCES IN THE NEWBORN

Zuzanna Kubicka, MD; George A. Little, MD

At birth, placental function, including transport of glucose, calcium, phosphorus, and magnesium, is suddenly interrupted. Usually this process occurs uneventfully; however, pediatricians and other physicians must be aware of the physiologic mechanism of transition and possible problems that may occur clinically.

### GLUCOSE METABOLISM IN THE FETUS AND METABOLIC ADAPTATION AT BIRTH

Carbohydrate is transported to the fetus as *glucose* by transplacental facilitative diffusion across a concentration gradient. Glucose transport capacity increases with gestational age, with a portion used for placental metabolism. When placental function and fetal growth are normal, fetal glucose production is limited.

Glucose-sensing and insulin-secreting pathways are present in the human fetus as early as 14 to 18 weeks' gestation, but secretion of insulin in response to glucose is attenuated. During fetal development, pancreatic  $\beta$  cells mature, with biphasic insulin release developing after birth. When the fetus is subjected to reduced glucose supply, hypoglycemia and hypoinsulinemia may develop despite fetal glucose production.

Healthy, term neonates transition to the extrauterine environment without need for metabolic monitoring. Hepatic glycogen content increases with gestational age, and most deposition occurs toward the end of gestation.

Neonatal glucose requirements of approximately 5 to 8 mg/kg per minute, mostly for cerebral use, must be met endogenously when the placental glucose supply ceases. Immediately after birth, a 3- to 5-fold surge in glucagon and catecholamines takes

place, which initiates glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis. Endogenous growth hormone and cortisol facilitate the onset of gluconeogenesis within several hours, and insulin secretion and serum concentrations fall. Enzymatic systems for glycogen breakdown and gluconeogenesis must be in place, along with a supply of substrate in the form of fat and amino acids. Human milk has an important role in the induction of ketogenesis, which spares glucose for brain consumption and facilitates gluconeogenesis.

Preterm and some intrauterine growth-restricted neonates have transitional metabolic processes that are not fully developed, and less glycogen stores are available for glucose mobilization after birth. Glucose regulation problems also occur with a wide range of antepartum, intrapartum, and postnatal problems such as maternal diabetes, hypoxic stress, and sepsis.

### NEONATAL HYPOGLYCEMIA

In 2009 a National Institute of Child Health and Human Development Workshop on neonatal hypoglycemia focused on knowledge gaps and research needs for understanding and treating neonatal hypoglycemia. The goal of the workshop was to identify future research areas, including glucose metabolism in the brain, the definition of clinically significant hypoglycemia, and improved methods for plasma glucose monitoring and treatment. The definition, significance, and management of hypoglycemia persist as controversial issues in contemporary neonatal pediatrics.

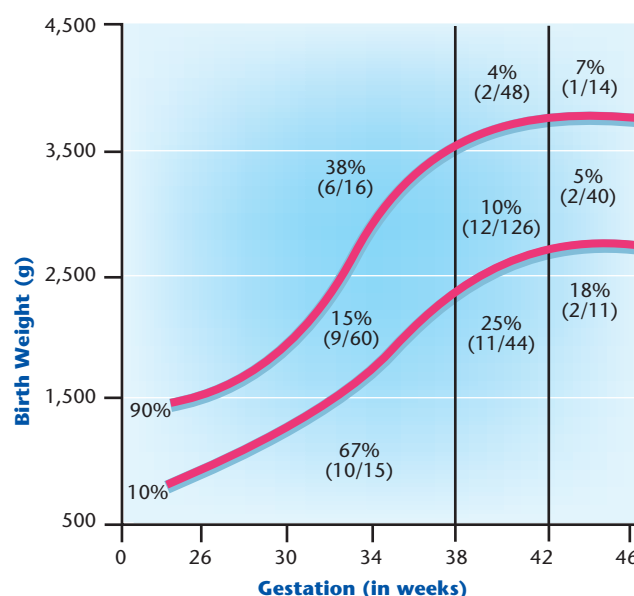
#### Definition

The definitive diagnosis of neonatal hypoglycemia must satisfy the Whipple triad: the presence of clinical manifestations; coincidence with reliable low plasma glucose concentrations; and resolution of manifestations once normoglycemia has been reestablished.

This definition does not include so-called *asymptomatic* hypoglycemia without clinical manifestations, even with very low plasma glucose concentrations (see further discussion in the Evaluation section). Controversy remains as to whether transient asymptomatic hypoglycemia causes sequelae.

Attempts have been made to identify a threshold blood glucose concentration below which a substantial likelihood of functional impairment exists. The evidence for a glucose level that causes irreversible neuronal injury remains poorly defined. Data from animal studies support the theory that sustained hypoglycemia is associated with neuronal necrosis. No prospective study in human infants has been conducted to determine such a threshold.

Neuropathology findings in symptomatic hypoglycemic infants are suggestive of widespread acute neuronal and glial injury for the most part in occipital lobes. The most consistent finding of neuroimaging studies on symptomatic hypoglycemic newborns is cortical and white matter occipital abnormalities. Current reports on term infants with symptomatic hypoglycemia extend the spectrum of magnetic resonance imaging (MRI) abnormalities to global white matter, deep nuclear gray matter, and cortical infarction. The early MRI abnormalities in this study were



**Figure 105-1** Incidence of hypoglycemia by birth weight, gestational age, and intrauterine growth. (From Lubchenco LO, Bard H. Incidence of hypoglycemia in newborn infants classified by birth weight and gestational age. *Pediatrics*. 1971;47:831–838.)

much more predictive for neurodevelopmental outcomes than severity or duration of hypoglycemia. This suggests that MRI may become a routine investigation for the neonate with symptomatic hypoglycemia.

Numerous textbooks and papers use the arbitrary plasma glucose level of 40 to 45 mg/dL or blood glucose value less than 35 mg/dL as a defining threshold for intervention, with the range as wide as 27 to 47 mg/dL.

An important point to remember is that a healthy term newborn exhibits an immediate postnatal fall in blood glucose concentration during the first 2 to 4 hours from values close to maternal levels to approximately 30 to 45 mg/dL (1.7–2.5 mmol/L).

#### Frequency

Overall incidence has been estimated to be 1 to 5 per 1,000 live births. The classic Lubchenco and Bard studies of neonatal hypoglycemia illustrate that intrauterine birth-weight/gestational-age status may serve as an indicator (Figure 105-1).

#### Differential Diagnosis

Table 105-1 presents a comprehensive list of causes of neonatal hypoglycemia. The information provided can be used to identify at-risk infants for whom routine monitoring of blood glucose is recommended. In clinical practice this will most commonly include small-for-gestational-age (SGA) infants, infants born to a diabetic mother (IDMs)/large-for-gestational-age (LGA) infants, and late-preterm infants 34 to 36 weeks' (34 $\frac{0}{7}$ –36 $\frac{6}{7}$ ) gestation.

Transient hypoglycemia usually resolves within 2 to 3 days. A requirement of more than 8 to 10 mg/kg per

**Table 105-1** Differential Diagnosis of Neonatal Hypoglycemia

ETIOLOGY	EXPLANATION	DURATION OF HYPOGLYCEMIA
Associated with maternal problems:	Hyperinsulinism and resulting inhibition of glycogenolysis, lipolysis, glyconeogenesis, and increased peripheral glucose utilization	Transient (<7 days' duration)
1. Diabetes in pregnancy, IDM	Decreased glucose supply	
2. Drug treatment: Oral hypoglycemic agents	Hyperinsulinism	
• Terbutaline	Unknown mechanism	
• Ritodrine	Possibly prevention of sympathetic stimulation of glycogenolysis, prevention of recovery from insulin induced, decreases in free fatty acid and glycerol	
• Propranolol	Hyperinsulinism	
3. Intrapartum administration of glucose		
Associated with neonatal problems:		
1. Perinatal hypoxia-ischemia	Higher glucose utilization or decreased production	Transient (<7 days' duration)
2. Infection	Hyperinsulinism, possibly increased number of pancreatic $\beta$ -cells	
3. Hypothermia		
4. Hyperviscosity		
5. Erythroblastosis fetalis, hydrops		
6. Iatrogenic:		
• Malpositioned umbilical artery catheter	Infusion of high glucose concentration into celiac, superior mesenteric artery; hyperinsulinism	
• Abrupt cessation of high glucose infusion	Hyperinsulinism	
• Exchange transfusion	Blood containing high glucose concentration, hyperinsulinism	
Intrauterine growth restriction, prematurity, inadequate caloric intake	Limited glycogen stores Altered insulin secretion Altered hormonal response to hypoglycemia	Transient (<7 days' duration)
Genetic disorders: Beckwith-Weidemann syndrome, Perlman syndrome, Sotos syndrome (rare), genetic forms of hyperinsulinism (dysfunction of pancreatic ATP-sensitive potassium channel), insulin-secreting tumors	Hyperinsulinism	Prolonged
Endocrine disorders: hypopituitarism, adrenal insufficiency, hypothalamic deficiency	Higher glucose utilization or decreased production	Prolonged
Inborn errors of metabolism, including fatty acid oxidation deficiency and congenital glycosylation disorders	Higher glucose utilization or decreased production	Prolonged

ATP, adenosine triphosphate; IDM, infant of diabetic mother.

Adapted from Cornblath M, Hawdon JM, Williams AF, et al. Controversies regarding definition of neonatal hypoglycemia: suggested operational thresholds. *Pediatrics*. 2000;105:1141–1145; McGowan JE. Neonatal hypoglycemia. *NeoReviews*. 1999;(July):e6–e15; Wilker RE. Hypoglycemia and hyperglycemia. In: Cloherty JP, Eichenwald EC, Stark AR, eds. *Manual of Neonatal Care*. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2012; Cornblath M, Schwartz R. Hypoglycemia in the neonate. *J Pediatr Endocrinol*. 1993;6:113–129.

minute suggests hyperinsulinism and is seen most commonly in the IDM. Persistence for more than 7 days or recurrence usually warrants subspecialty endocrine or metabolic evaluation.

## Evaluation

### Physical Examination

The typical clinical manifestations of hypoglycemia are summarized in Box 105-1. Birth-weight/gestation-age indicators previously discussed (see Figure 105-1), including their morphologic expressions (LGA, SGA, intrauterine growth restricted), must be considered.

An important point to realize is that the quiet or inactive newborn who is not exhibiting any of the listed symptoms may, in fact, be hypoglycemic. On the other hand these signs may occur with other common neonatal disorders, including sepsis, intracranial hemorrhage, or hypocalcemia. Infants exhibiting one

### BOX 105-1 Clinical Signs Associated With Hypoglycemia<sup>a</sup>

- Changes in behavior—irritability, lethargy
- Changes in neurologic status—hypotonia, limpness, tremor, jitteriness, seizures
- Cardiovascular signs—tachycardia, bradycardia
- Abnormal respiratory patterns—apnea, cyanotic spells, tachypnea, respiratory distress
- Feeding poorly, especially after feeding well
- Hypothermia

<sup>a</sup>Clinical signs should be alleviated with concomitant correction of plasma glucose levels.

Adapted from Cornblath M, Hawdon JM, Williams AF, et al. Controversies regarding definition of neonatal hypoglycemia: suggested operational thresholds. *Pediatrics*. 2000;105:1141–1145.

or more of these signs should have blood glucose screened.

### Laboratory Evaluation

Glucose reagent strips screen for low blood glucose concentration and provide a valuable estimate. Diagnosis depends on plasma glucose values. Whole-blood glucose levels are 10% to 15% lower than plasma glucose levels. Blood samples should be processed quickly because of possible glycolysis. False elevation can result from line sampling without preflushing.

Blood glucose concentrations reflect enteral feeds, reaching a peak by approximately 1 hour after feeding and a nadir just before the next feeding. Given that the purpose of blood glucose monitoring is to identify the lowest blood glucose level, prefeed measurement is recommended.

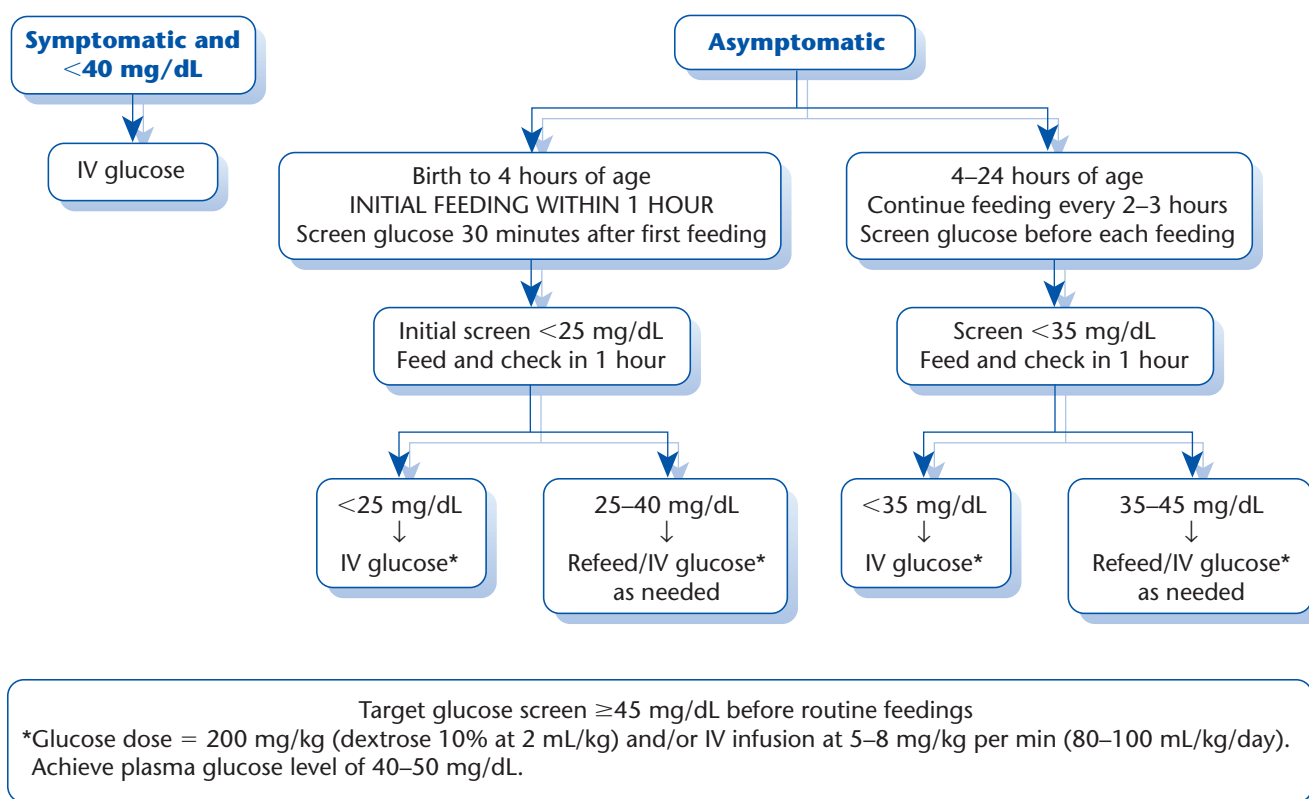
Continuous glucose monitoring in newborn babies at risk for hypoglycemia (<32 weeks' gestational age, IDM, SGA, LGA) has been recently investigated. The monitor, which provides 288 interstitial glucose concentration reading points per day, detected more episodes of low glucose concentration than intermittent blood glucose measurement and allows

measuring the duration, severity, and frequency of hypoglycemia in an individual baby. The sensor was well tolerated by patients, with single insertion providing up to 7 days of continuous reading. However, the physiologic importance of identifying previously undetected hypoglycemic episodes is unknown and could potentially lead to unnecessary treatment without changing the long-term outcomes. Further research is needed before adopting this method into clinical practice.

### Management

Pragmatic operational thresholds (blood glucose concentrations at which clinical interventions should be considered) for various clinical scenarios have been recently proposed.

Figure 105-2 provides a summary of management of neonatal hypoglycemia in various clinical scenarios in 2 time periods (birth to 4 hours and 4–24 hours), accounting for physiologic changes in glucose levels occurring over the first 12 hours after birth. For practicality, the management includes only the most common in clinical practice at-risk groups of infants (SGA, LGA, IDM, and late preterm).



Symptoms of hypoglycemia include: irritability, tremors, jitteriness, exaggerated Moro reflex, high-pitched cry, seizures, lethargy, floppiness, cyanosis, apnea, poor feeding.

**Figure 105-2** Screening and management of postnatal glucose homeostasis in late-preterm (LPT; 34–36<sup>6</sup>/<sub>7</sub> wk) and term small-for-gestational age (SGA) infants and infants who were born to mothers with diabetes (IDM)/large-for-gestational age (LGA) infants. LPT and SGA (screen, 0–24 hr), IDM and LGA >34 wk (screen, 0–12 hr). (From Adamkin D; Committee on Fetus and Newborn. Postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics*. 2011;127[3]:575–579.)



In large numbers of other maternal or neonatal conditions listed as at-risk for hypoglycemia (Table 105-1), clinical symptoms are common, and most infants are already being monitored for plasma glucose levels. However, the thresholds for clinical interventions should be similar in this group of infants.

### Term Newborn

Feeding is the main preventive strategy for healthy, term newborns without risk factors or clinical signs suggesting problems. Breastfed newborns demonstrate lower blood glucose and higher ketone body concentrations than those who are formula fed.

### Newborns With Abnormal Clinical Signs

Symptomatic newborns should have a glucose reagent strip screen while awaiting laboratory determination. If the plasma value is less than 40 mg/dL (2.2 mmol/L), then clinical intervention to increase the blood glucose concentration is indicated.

Enteral feeds may be continued or introduced when clinically appropriate, and parenteral treatment is not a reason to delay them. Gradual rather than rapid reductions in the rate of glucose infusion help maintain stability and avoid labile glucose concentrations.

### Asymptomatic Infants With Risk Factors for Compromised Metabolic Adaptation

Routine determination of plasma glucose concentration should be performed for infants considered at risk. At-risk infants should be fed by 1 hour of age and screened 30 minutes after feeding. If the initial plasma glucose concentration is less than 25 mg/dL (1.4 mmol/L) before 4 hours of age or less than 35 mg/dL (1.9 mmol/L) within 4 to 24 hours of age, the asymptomatic at-risk infant should be fed again, and plasma glucose should be checked 1 hour after refeeding. Subsequent plasma glucose lower than 25 mg/dL within the first 4 hours of life, or less than 35 mg/dL within 4 to 24 hours of age, should prompt intravenous glucose treatment.

The target glucose level before feedings should be greater than 45 mg/dL (2.5 mmol/L).

Glucose monitoring should continue until at least 12 hours of age for IDM/LGA patients if they maintain prefeeding plasma glucose concentration greater than 40 mg/dL. Late preterm and SGA infants require plasma glucose monitoring for at least 24 hours because they remain more vulnerable to hypoglycemia especially if adequate oral feedings are not yet well established.

Maintaining therapeutic levels in excess of 60 mg/dL (3.3 mmol/L) may be indicated for symptomatic infants with documented hyperinsulinemic hypoglycemia; however, it should not be the therapeutic goal for most newborns with transient or brief episodes of low plasma glucose concentrations.

Intravenous glucose treatment should consist of minibolus of D<sub>10</sub>W 2 mL/kg and/or intravenous infusion of D<sub>10</sub>W at 5 to 8 mg/kg per minute (80–100 mL/kg/day). Excessive intravenous glucose infusions should be avoided to minimize pancreatic stimulation.

### Preterm Infants

The same strategies and thresholds mentioned previously apply to preterm newborns. Intravenous glucose infusion is often necessary owing to risk factors for development of hypoglycemia, including poor glycogen stores and limited oral feeding ability. Most well-nourished but preterm infants require at least 6 to 8 mg/kg per minute of glucose initially.

## HYPERGLYCEMIA

### Definition

A whole-blood glucose level greater than 125 mg/dL or a plasma glucose level of greater than 145 mg/dL is considered to be outside normal limits by most authors.

### Differential Diagnosis

Common causes of hyperglycemia are presented in Table 105-2.

Although more common than hypoglycemia, a large portion of hyperglycemia occurs in low-birth-weight infants receiving parenteral glucose. Infusion rates higher than 6.6 mg/kg per minute in infants less than 1,100 g and

**Table 105-2** Differential Diagnosis of Neonatal Hyperglycemia

CAUSE	MECHANISM
Prematurity, very low birth weight (<1,500 g)	Variable insulin response to persistent endogenous glucose production; high catecholamine and other stress hormone levels
Sepsis	Decreased insulin release or decreased glucose utilization; elevation of stress hormones
Hypoxia	Increased glucose production or absent increased utilization
Surgical procedures	Increased release of stress hormones; administration of intravenous glucose
Drugs: steroids, caffeine, theophylline, phenytoin	Increased glycogenolysis or gluconeogenesis
	Increased insulin resistance
	Increased insulin resistance and decreased insulin release
Hyperosmolar formula (inappropriate formula dilution)	Increased glucose load
Rare endocrine disorders: transient neonatal diabetes mellitus, diabetes related to pancreatic lesions	Decreased insulin release

Derived from Wilker RE. Hypoglycemia and hyperglycemia. In: Cloherty JP, Eichenwald EC, Hansen AR, Stark AR, eds. *Manual of Neonatal Care*. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2012.

more than 6 mg/kg per minute in healthy, full-term newborns may cause iatrogenic hyperglycemia.

### Evaluation

#### Physical Examination

Clinical dehydration caused by osmotic diuresis is a serious complication of hyperglycemia; each 18-mg/dL rise in the blood glucose concentration increases serum osmolality by 1 mOsm/L and can contribute to hyperosmolality of more than 300 mOsm/L. Researchers have hypothesized that hyperglycemia, by increasing osmolality, causes the water to move from the intracellular to the extracellular compartment. This *contraction* of intracellular volume may be associated with risk for intracranial hemorrhage, particularly in the very low-birth-weight infant.

#### Laboratory Evaluation

In addition to blood determination for hyperglycemia, urine monitoring for glucosuria caused by exceeding renal tubular reabsorption capability of glucose may be helpful.

### Management

Prevention strategies and treatment of hyperglycemia are summarized in Box 105-2.

#### BOX 105-2 Prevention and Management of Neonatal Hyperglycemia

##### PREVENTION

- Avoid sudden changes in glucose concentration.
- Avoid glucose infusion rates  $>8$  mg/kg/min in premature and full-term infants.
- Use initially 5% glucose infusion concentration for infants  $<1,000$  g.
- Avoid using hypotonic fluids ( $<5\%$  dextrose).
- Start parenteral nutrition as soon as possible; some amino acids promote insulin secretion.
- Continue enteral feedings if not contraindicated because this promotes insulin secretion.

##### MANAGEMENT

- Decrease the glucose infusion to 4 to 6 mg/kg/min or by 2 mg/kg/min every 4 to 6 hr.
- If glucose level is persistent above 250 mg/dL despite all the measures to decrease the glucose intake, then consider insulin therapy.
- Continuous intravenous insulin infusion of 0.01 to 0.1 units/kg/hr (with close monitoring of plasma glucose levels, potassium levels).
- Subcutaneous insulin, 0.1 to 0.2 units/kg every 6 hr, is used most commonly in neonatal diabetes (with close monitoring of plasma glucose levels and potassium levels).

Adapted from Wilker RE. Hypoglycemia and hyperglycemia. In: Cloherty JP, Eichenwald EC, Stark AR, eds. *Manual of Neonatal Care*. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2012; Pildes RS. Hypoglycemia and hyperglycemia in tiny infants. *Clin Perinatol*. 1986;3:351–375.

## CALCIUM AND PHOSPHORUS METABOLISM IN THE FETUS AND METABOLIC ADAPTATION AT BIRTH

Active calcium and phosphorus transport to the fetus is necessary for fetal growth and increases through gestation to a peak in the third trimester. Premature newborns are therefore at risk for deficiency, which can worsen after birth as a result of renal losses and deficient intestinal absorption.

Neonatal serum calcium homeostasis is maintained by exogenous intake or absorption from bones, or by both processes. In the first day, serum calcium decreases (low intake and cessation of maternal-fetal transport), and ionized calcium reaches the lowest level of 1.10 to 1.36 mmol/L (4.4–5.4 mg/dL) at approximately 24 hours of age, rising slowly thereafter.

Fetal phosphorus concentration is higher than the maternal concentration. Postnatal absorption takes place primarily in the jejunum, with low excretion levels in the newborn. During the first day of life, neonatal serum phosphorus concentration increases before increased absorption, probably related to its release during breakdown of tissue glycogen. This increased phosphorus concentration also probably contributes to decreased calcium concentration.

Calcium is the most abundant mineral in the human body, with 99% contained in the bones. Eighty-five percent to 90% of phosphorus is found in the skeleton. Calcium-phosphorus serum concentration is tightly regulated by parathyroid hormone (PTH), vitamin D metabolites, and calcitonin.

### VITAMIN D SUPPLEMENTATION

The American Academy of Pediatrics (AAP) recommendation published in 2008 is to initiate vitamin D supplementation of 400 units daily beginning in the first few days of life in breastfed and partially breastfed infants as well as formula-fed infants consuming less than 1,000 mL/day. The new recommendations come from emerging data about higher rates of vitamin D deficiency during pregnancy, suggesting that the rates of deficiency among women in child-bearing ages are up to 12% and are even higher among blacks. There is also growing evidence that 400 units/day of vitamin D is sufficient to prevent rickets and maintain normal vitamin D level.

Furthermore, prematurely born infants are even more likely to be vitamin D deficient because of limited transplacental transport. Exclusive breastfeeding without adequate sun exposure and vitamin D supplementation is another risk factor for deficiency, with vitamin D content on average 22 units per 1,000 mL of breast milk.

## NEONATAL HYPOCALCEMIA

### Definition and Diagnosis

Calcium circulates in blood in 3 fractions: protein bound (40%–45%); complexed with anions such as lactate, citrate, and bicarbonate (5%–10%); and ionized (50%). The last of these fractions is the only physiologically active fraction. With low serum protein, the total

calcium may be decreased, whereas the ionized fraction remains within normal limits. With normal total calcium, the ionized fraction may be decreased by alkalosis, administration of bicarbonate, or chelating agents present in blood products.

Hypocalcemia in the term newborn is best defined as serum ionized calcium concentration of less than 1.1 mmol/L (4.4 mg/dL). (See later discussion under Laboratory Evaluation.)

### Differential Diagnosis

Common causes of neonatal hypocalcemia are summarized in Table 105-3.

### Evaluation

#### Physical Examination

Physiologically the clinical signs of hypocalcemia are related to increased cell membrane excitability because low serum calcium levels increase cellular permeability to sodium ions. Signs of neonatal hypocalcemia are

often nonspecific and may include jitteriness, hyperreflexia, increased tone, and generalized or focal seizures, as well as apnea and rarely laryngospasm. Occasionally the newborn may exhibit classic tetany and positive Chvostek and Trousseau signs. Electrocardiographic readings may be significant for prolonged QTc interval. These signs may also be present with other disorders, including hypoglycemia.

#### Laboratory Evaluation

Ionized calcium values of less than 1.1 mmol/L in full-term infants and less than 1.07 mmol/L (4.28 mg/dL) in preterm infants should be used as reference value for hypocalcemia. The traditional definition of total serum calcium less than 2 mmol/L (8 mg/dL) for full-term infants and less than 1.75 mmol/L (7 mg/dL) for preterm infants is of limited value and should be used only if ionized calcium values are not available.

Measuring magnesium levels in the setting of hypocalcemia is important because correction of low

**Table 105-3** Differential Diagnosis of Neonatal Hypocalcemia

#### EARLY HYPOCALCEMIA ( $\leq 4$ DAYS AFTER BIRTH)

#### MECHANISM

Prematurity, intrauterine growth restriction	Low stores in more premature infants, low intake, increased phosphorus load, increased calcitonin levels, transient hypoparathyroidism, end-organ resistance to vitamin D
Maternal diabetes	Maternal hypomagnesemia during pregnancy, hypoparathyroidism, hyperphosphatemia, abnormal vitamin D metabolism
Perinatal asphyxia	Decreased intake, increased phosphorus load, increased calcitonin concentration
Maternal anticonvulsants (phenobarbital and diphenylhydantoin)	Increase hepatic catabolism of vitamin D

#### LATE HYPOCALCEMIA ( $> 4$ DAYS AFTER BIRTH)

#### MECHANISM

Cow milk–based formulas (particularly undiluted cow milk or evaporated milk)	Hyperphosphatemia
Hypomagnesemia	Impaired parathyroid hormone (PTH) secretion and peripheral PTH action
Hypoparathyroidism:	
• Transient congenital	• Hypocalcemia and hyperphosphatemia, low PTH, with PTH improving spontaneously
• Secondary	• Maternal hyperparathyroidism with maternal or fetal hypercalcemia and subsequent neonatal hypoparathyroidism
• Congenital primary—parathyroid agenesis or part of DiGeorge sequence, PTH gene mutation	• Decreased PTH
Other causes:	
• Vitamin D deficiency (renal disease, hepatobiliary disease, malabsorption, maternal vitamin D deficiency)	• Decreased calcium absorption
• Alkalosis	• Decreased ionized calcium, decreased calcium reabsorption from bones
• Citrated blood transfusion	• Chelated ionized calcium
• Lipid infusions	• Enhanced calcium-albumin binding
• Phototherapy	• Possibly increased melatonin, which causes increased bone calcium uptake
• Furosemide, xanthenes	• Promotion of calciuresis

Derived from Rigo J, Mohamed WM, De Curtis M. Disorders of calcium, phosphorus and magnesium metabolism. In: Fanaroff AA, Martin RJ, eds. *Neonatal-Perinatal Medicine*. 9th ed. St Louis, MO: Mosby; 2011.

serum calcium might not be possible without correcting hypomagnesemia. Low serum calcium may also be associated with seizures, although it is not the cause.

### Management

Management is complicated by several factors. Most cases of neonatal hypocalcemia are asymptomatic and self-resolving by day 3 of life. Similar signs may coexist with other neonatal conditions. Asymptomatic hypocalcemia in a well newborn usually resolves spontaneously without specific treatment. With the serum calcium level below 6.5 mg/dL (usually the asymptomatic very low-birth-weight newborn), some authors recommend continuous calcium infusion with the dose of 5 mL/kg/day of 10% calcium gluconate.

The treatment of symptomatic hypocalcemia consists of administering calcium salts (Table 105-4, Figure 105-3). Symptoms that are unresponsive to calcium therapy may be the result of hypomagnesemia. (See later discussion of management of hypomagnesemia.)

Bradycardia may be a serious systemic complication of intravenous calcium administration. Possible local complications include umbilical arterial spasm with rapid administration, extravasations into soft tissues, and hepatic necrosis if umbilical venous catheter lodged in the branch of the portal catheter.

The management of late-onset hypocalcemia usually consists of treating the underlying disorder.

## NEONATAL HYPERCALCEMIA

### Definition

Serum ionized calcium concentration greater than 1.35 mmol/L (5.4 mg/dL) with or without a total serum calcium level greater than 2.75 mmol/L (11 mg/dL) is considered abnormal.

### Differential Diagnosis

Neonatal hypercalcemia is usually iatrogenic. Excessive administration of calcium or vitamin D<sub>3</sub> should be excluded before extensive investigation for other etiology such as maternal hypoparathyroidism, neonatal hyperparathyroidism, hypophosphatemia, or drug-induced hypercalcemia (thiazides).

**Table 105-4** Forms of Calcium Salts

FORM OF CALCIUM SALT	ELEMENTAL CALCIUM (mg/mL)
10% calcium gluconate	9.4
10% calcium chloride	27.2
Calcium glubionate syrup	23.6

Calcium gluconate administration is preferred over calcium chloride (may cause metabolic acidosis).

Derived from Rigo J, Mohamed WM, De Curtis M. Disorders of calcium, phosphorus and magnesium metabolism. In: Fanaroff AA, Martin RJ, eds. *Neonatal-Perinatal Medicine*. 9th ed. St Louis, MO: Mosby; 2011.

### Evaluation

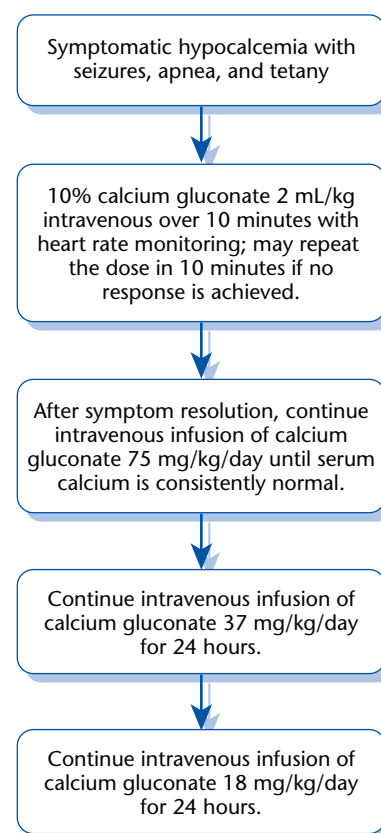
Newborns with hypercalcemia may be asymptomatic or have nonspecific signs, including poor feeding, constipation, polyuria, dehydration, decreased muscle tone, lethargy, and bradycardia. Long-term neonatal hypercalcemia may result in nephrocalcinosis.

### Management

The therapy of severe, symptomatic hypercalcemia in the acute phase should include intravenous fluid (normal saline) and furosemide administration to promote urinary calcium excretion, as well as removal of excessive calcium and vitamin D from the diet.

## MAGNESIUM METABOLISM IN THE FETUS AND METABOLIC ADAPTATION AT BIRTH

Most of maternal-fetal magnesium transfer occurs in the third trimester and involves active transport against a concentration gradient. Magnesium is found mostly in the skeleton and intracellular fluid, with only 1% present in the extracellular fluid, making assessment of stores difficult.



**Figure 105-3** Management of symptomatic hypocalcemia. (Derived from Rigo J, De Curtis M. Disorders of calcium, phosphorus and magnesium metabolism. In: Fanaroff AA, Martin RJ. *Neonatal-Perinatal Medicine*. 9th ed. St Louis, MO: Mosby; 2011.)



Magnesium is absorbed mainly in the small intestine; regulation of serum concentration is performed primarily by kidneys under PTH supervision. Increase in the serum magnesium will decrease PTH secretion and renal reabsorption, whereas decrease in magnesium concentration will lead to increased PTH release and decrease urinary excretion. Chronic magnesium deficiency, however, will reduce PTH secretion.

## HYPOMAGNESEMIA

### Definition

The normal serum magnesium value for the newborn is 0.66 to 1.15 mmol/L (1.6–2.8 mg/dL). Clinical symptoms usually do not develop until the serum magnesium level falls to less than 0.49 mmol/L (1.2 mg/dL). Measurement of active, ionized magnesium is usually not available; only total magnesium levels are routinely measured.

### Etiology

Table 105-5 summarizes the most common causes of neonatal hypomagnesemia.

### Evaluation

Hypomagnesemia in the neonatal period is usually transient and asymptomatic. However, in severe cases, hypomagnesemia can cause irritability, tremor, hyperexcitability, and intractable hypocalcemic seizures that are unresponsive to calcium and anticonvulsant therapy. Electrocardiographic data may show a prolonged QT interval.

Hypocalcemia can be explained by magnesium depletion and resulting hypoparathyroidism.

### Management

Management of hypomagnesemia consists of magnesium salt administration. The usual neonatal dose is 50% magnesium sulfate, 0.05 to 0.1 mL/kg (2.5–5 mg/kg of elemental magnesium) administered intramuscularly or by slow intravenous infusion over 15 to 20 minutes. The dose may be

repeated every 12 hours and eventually adjusted to oral preparations.

## HYPERMAGNESEMIA

### Definition

Hypermagnesemia is defined as a serum magnesium level higher than 1.15 mmol/L (2.8 mg/dL). Hypermagnesemia does not cause hypocalcemia in the neonatal period despite PTH suppression, possibly as a result of magnesium facilitating the bony release of calcium.

### Etiology

Hypermagnesemia in the neonatal period is always an iatrogenic event, commonly related to maternal magnesium sulfate administration for seizure prevention in preeclampsia or for tocolysis. Neonatal levels do not reach problematic values and return to normal within a few days as a result of urine excretion. Less common sources of excessive magnesium are magnesium-containing antacids or excessive magnesium in parenteral nutrition.

### Evaluation

The most common clinical manifestation of hypermagnesemia is hypotonia and depression at birth secondary to maternal administration of magnesium sulfate during obstetric management. Neurologic and respiratory depression may be evident on observation and examination.

### Management

Usual management consists of supportive treatment, including optimal hydration. Respiratory support may be required in extreme cases. With unusually severe central nervous system depression, exchange blood transfusion may be indicated to lower the serum magnesium level.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *These Tests Could Save Your Baby's Life—Newborn Screening Tests* (handout), Health Resources and

**Table 105-5**

**Differential Diagnosis of Neonatal Hypomagnesemia**

CAUSE	MECHANISM
Maternal diabetes	Maternal urinary losses of magnesium leading to neonatal magnesium depletion; blunted response to parathyroid hormone
Intrauterine growth restriction	Poor maternal supply or placental transfer
Hypoparathyroidism	Increased urinary losses
Malabsorption syndromes	Poor supply
Renal tubular defects: congenital or acquired (hypoxic ischemic syndrome, nephrotoxicity) or genetic defects of renal magnesium handling	Increased urinary losses
Defects of intestinal magnesium transport	Decreased absorption
Citrated blood transfusion	Complexing of citrate with ionized magnesium

Derived from Rigo J, Mohamed WM, De Curtis M. Disorders of calcium, phosphorus and magnesium metabolism. In: Fanaroff AA, Martin RJ, eds. *Neonatal-Perinatal Medicine*. 9th ed. St Louis, MO: Mosby; 2011.

Services Administration, US Department of Health and Human Services ([mchb.hrsa.gov/pregnancyandbeyond/newbornscreening/newborn\\_brochure.pdf](http://mchb.hrsa.gov/pregnancyandbeyond/newbornscreening/newborn_brochure.pdf))

- *Newborn Screening Disorders—What Parents Want to Know about Newborn Screening Disorders* (hand-out), Health Resources and Services Administration, US Department of Health and Human Services ([www.medicalhomeinfo.org/downloads/pdfs/Newbornscreeningdisorders.pdf](http://www.medicalhomeinfo.org/downloads/pdfs/Newbornscreeningdisorders.pdf))

### Medical Decision Support

- *Newborn Screening ACT Sheets and Confirmatory Algorithms* (screening tool), American College of Medical Genetics ([www.ncbi.nlm.nih.gov/books/NBK55827](http://www.ncbi.nlm.nih.gov/books/NBK55827))
- *Newborn Screening* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/ncbddd/pediatricgenetics/newborn\\_screening.html](http://www.cdc.gov/ncbddd/pediatricgenetics/newborn_screening.html))
- *The S.T.A.B.L.E. Program: Learner Manual*, 6th ed (book), Kristine A. Karlsen, PhD, APRN, NNP-BC ([www.aap.org/bookstore](http://www.aap.org/bookstore))
- *The S.T.A.B.L.E. Program: Learner Course Slides on DVD*, 6th ed (DVD), Kristine A. Karlsen, PhD, APRN, NNP-BC ([www.aap.org/bookstore](http://www.aap.org/bookstore))
- *The S.T.A.B.L.E. Program: Physical Exam and Gestational Age Assessment Slides*, 2nd ed (DVD), Kristine A. Karlsen, MSN, RNC, NNP ([www.aap.org/bookstore](http://www.aap.org/bookstore))
- *The S.T.A.B.L.E. Program: Quick Reference Bedside Card Set*, 4th ed (cards), Kristine A. Karlsen, PhD, APRN, NNP-BC ([www.aap.org/bookstore](http://www.aap.org/bookstore))
- *The S.T.A.B.L.E. Program: Blood Gas Interpretation Chart*, 3rd ed (chart), Kristine A. Karlsen, PhD, APRN, NNP-BC ([www.aap.org/bookstore](http://www.aap.org/bookstore))

### AAP POLICY

American Academy of Pediatrics Committee on Fetus and Newborn. Postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics*. 2011;127(3): 575–579 ([pediatrics.aappublications.org/content/127/3/575](http://pediatrics.aappublications.org/content/127/3/575))

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## Chapter 106

# SPECIFIC CONGENITAL METABOLIC DISEASES

Angel Rios, MD; Darius J. Adams, MD

When evaluating a neonate the challenge that confronts the physician is to determine if a medical problem is a transient phenomenon that can be easily treated or if the problem will evolve into a life-threatening condition. Neonates often exhibit nonspecific signs and symptoms that may be indicative of an array of disorders, including sepsis, delayed transition, congenital cardiac disease, endocrine disturbances, and inborn errors of metabolism.

Newborns with metabolic disease are typically healthy and asymptomatic at birth. In utero the fetus is protected by the placenta, which is responsible for removing metabolites and transferring substrates to meet fetal energy needs. Once the fetal nutrient supply is withdrawn with clamping of the umbilical cord at delivery the newborn must activate physiological mechanisms to support metabolism, remove all toxic metabolites, and maintain an endogenous energy supply. Although inborn errors of metabolism are individually rare—for example, the incidence of medium-chain acyl-CoA dehydrogenase deficiency is 1 in 10,000—collectively inborn errors of metabolism have an incidence of 1 in 800 to 1,000. Clinical suspicion should be aroused in an infant who initially seems well and then progressively deteriorates despite appropriate therapy of the presenting clinical signs. The onset of symptoms caused by an inborn error of metabolism may range from a few hours after birth to several weeks of age, depending on the underlying disorder.

## EVALUATING THE NEWBORN

### Initial Approach

A complete family history is a crucial and integral part of the initial evaluation. Key items to include in the history are listed in Box 106-1. The initial assessment must also include a thorough physical examination and review of the pregnancy history. Maternal prenatal history can be useful in diagnosing inborn errors of metabolism. A newborn with a fatty acid oxidation disorder can predispose the mother to developing acute fatty liver of pregnancy and HELLP syndrome (preeclampsia with hemolysis, elevated liver enzymes, and low platelet count).

### Physical Examination

A thorough physical examination can provide helpful clues in identifying the correct diagnosis. Table 106-1 lists some of the common physical findings associated with specific metabolic and endocrine disorders. Some of the disorders listed do not cause acute illness in the newborn period, but the described physical findings are present from birth, such as the coarse facies in a newborn with galactosialidosis. The presence of atypical

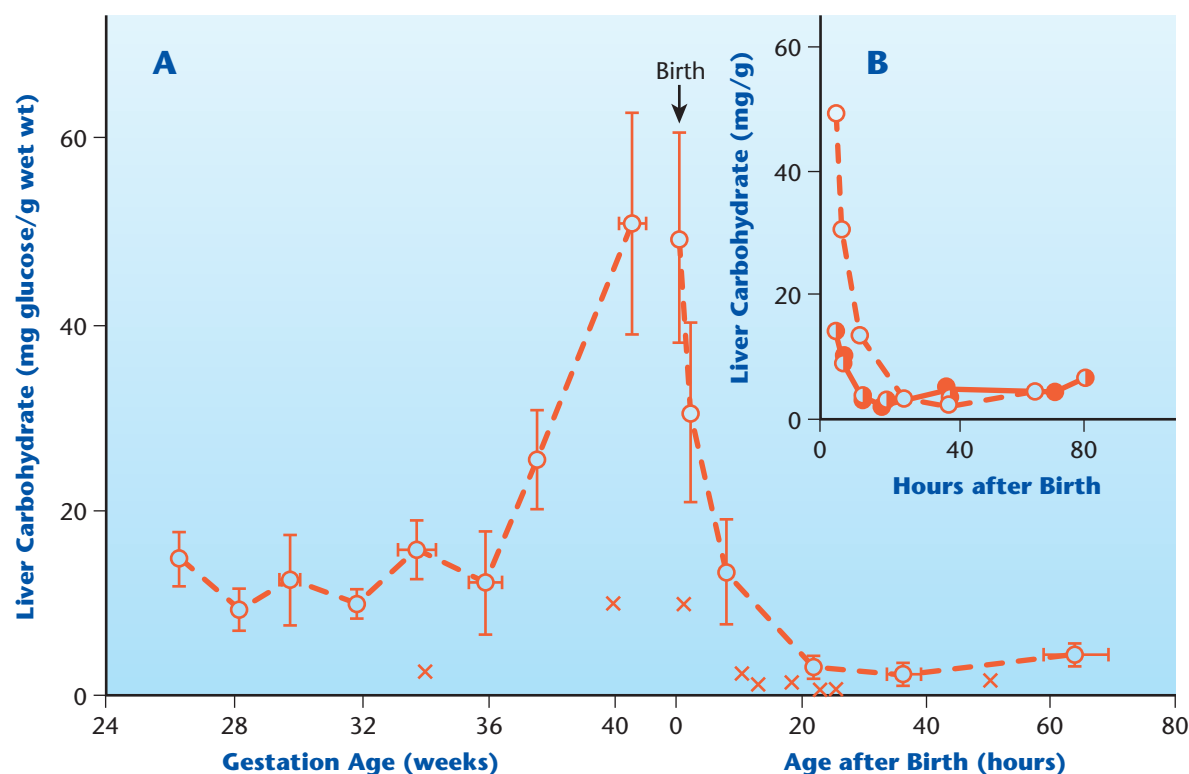
**BOX 106-1 Key Items in Family History**

- Prior unexplained death in sibling or siblings
- Age of death
- Presenting symptoms
- Seizures
- Encephalopathy
- Hypoglycemia
- Onset of symptoms
- Sex of siblings
- Pregnancy
- HELLP syndrome—disorders of fatty acid oxidation
- Acute fatty liver of pregnancy—disorders of fatty acid oxidation
- Parental consanguinity
- Unusual family illness
- Ethnic group with increased frequency of disorders
  - Ashkenazi Jews
  - African—sickle cell disease
  - Mediterranean—glucose-6-phosphate dehydrogenase
  - French Canadian—maple syrup urine disease
  - Old Order Mennonite population of Lancaster County, PA—maple syrup urine disease
- Hyperinsulinism-hyperammonemia syndrome
- Female carriers of ornithine transcarbamylase deficiency can become acutely ill during periods of stress, despite the X-linked pattern of inheritance for this disorder.

HELLP, Hemolysis, elevated liver function tests, and low platelets.

**Table 106-1** Physical Findings Associated With Metabolic and Endocrine Disorders in the Newborn Period

FINDING	PROBLEM	DISORDER
Odor	Maple Syrup	Maple syrup urine disease
	Sweaty feet	Isovaleric acidemia
		Glutaric acid type II
	Musty	Phenylketonuria
	Cat urine	Multiple carboxylase deficiency
General appearance	Cabbage	Tyrosinemia
	Mid-line defects	Smith-Lemli-Opitz syndrome
Dysmorphism	Coarse facies	Galactosialidosis
		Sialidosis
		Mucopolysaccharidosis type VII
		G <sub>M1</sub> gangliosidosis
Head	Macrocephaly	Glutaric acidemia type I
	Microcephaly	Canavan disease
	Alopecia	Cobalamin disease type C
		Multiple carboxylase deficiency
Eye	Cataracts	Galactosemia, Zellweger syndrome
	Dislocated lens	Homocystinuria
Heart	Cardiomyopathy	Electron transport-chain disorders
		Disorders of fatty acid oxidation
		Glycogen storage disease type III
		Glycogen storage disease type IV (occasional)
		Electron transport-chain disorders
Visceromegaly	Hepatomegaly	Glycogen storage disease, Wilson disease
		Galactosemia, $\alpha_1$ -antitrypsin
		Disorders of fatty acid oxidation
	Hepatosplenomegaly	Lysosomal storage disorders
Neurologic	Hypotonia	Electron transport chain disorders
	Seizures	Medium-chain, acyl-coenzyme A dehydrogenase deficiency
	Lethargy	Maple syrup urine disease, nonketotic hyperglycinemia
	Coma	Urea cycle defects
Genitourinary	Microphallus	Smith-Lemli-Opitz syndrome



Left-hand side of A shows concentration in the fetus during the last trimester (data from 15 fresh still-births and 32 babies <4 hr old); right-hand side shows the changes after birth in babies of >37 weeks' gestation (data from 40 babies). Vertical lines indicate S.E. of the means

○ Babies of normal birth weight for the period of gestation

× Individual babies of low birth weight for the period of gestation

Insert B compares the changes after birth in babies of >37 weeks' gestation (○) with those born at 30–37 weeks (◐) and <30 weeks (●); total number of infants, 188

**Figure 106-1** Liver glycogen before and after birth. (From Shelley HJ, Neligan GA. Neonatal hypoglycaemia. Br Med Bull. 1966;22[1]:34–39, with permission from Oxford University Press.)

physical findings should alert the physician to potential problems.

## HYPOGLYCEMIA IN NEWBORNS

Hypoglycemia is among the more common signs in newborns. The incidence of hypoglycemia in healthy newborn infants is estimated to be between 5% and 15%. Prenatally, glucose is an important substrate because it serves as the primary fuel source for both the placenta and fetus. Glucose is responsible for supplying approximately 80% of fetal energy requirements. Because of the absence of gluconeogenesis in the fetus, it must rely on maternal glucose. The importance of maternally transported glucose is exemplified in a study revealing that over 95% of fetal plasma glucose was derived from maternal plasma. In addition, 40% of the transported glucose in the fetus is either converted to glycogen in the liver and muscle or to lipid for storage. Liver glycogen storage increases throughout gestation, with the major contribution occurring during the third trimester. Figure 106-1 reveals the changes in fetal liver glycogen as shown by Shelley and Nelligan: fetal liver glycogen rises dramatically

after 36 weeks' gestation. By term, the liver glycogen stores are 2 to 3 times the adult levels. Postnatally, glycogenolysis is critical with glycogen levels decreasing rapidly over the first 24 hours of life.

The human placenta regulates the transfer of glucose to the fetus by facilitated diffusion. Glucose transport is achieved by the activity of the facilitated diffusion glucose transporter (GLUT) protein family. Table 106-2 lists the various GLUT isoforms and their location and function. The driving force for glucose transport is the gradient from the higher maternal glucose concentration in comparison to the fetal glucose concentration. The 3 primary GLUT transporter isoforms found in the placenta are GLUT-1, GLUT-3, and GLUT-4. Figure 106-2 shows the distribution of GLUT transporter isoforms in the human placenta. GLUT-1 is the primary glucose transporter in the human placenta. The GLUT-1 transporter is asymmetrically distributed in the syncytiotrophoblast, where there is a 3-fold higher expression on the maternal-facing microvillous membrane compared to the fetal-facing basal membrane (see Figure 106-2). The decreased expression of GLUT-1 in the basal membrane has led

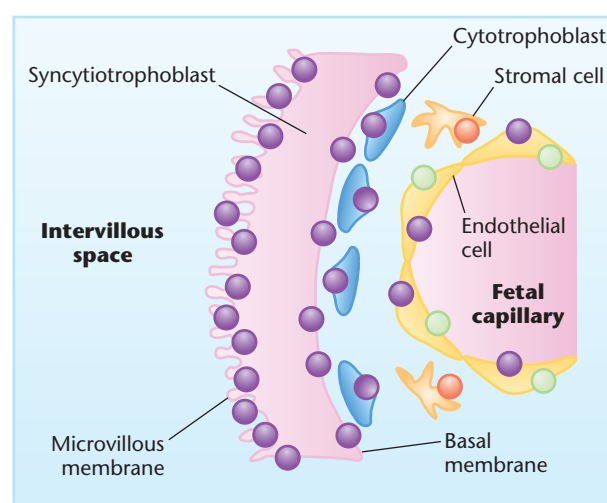


**Table 106-2** GLUT Facilitated-Diffusion Glucose Transporter Family

ISOFORM	LOCATION	FUNCTION(S)
GLUT1	Placenta, muscle, adipose tissue, brain, endothelium	Basal glucose transporter isoform for cellular metabolism and glucose transport
GLUT2	Pancreatic $\beta$ -cells, liver, small intestine, renal proximal tubule	High-capacity, low-affinity (high $K_m$ ) isoform. Acts as a glucose sensor and in transepithelial of glucose and fructose
GLUT3	Neural, small intestine	High-affinity (low $K_m$ ) isoform, possibly to act as a scavenger for cells with a high rate of glucose metabolism
GLUT4	Muscle, heart, adipose tissue	Insulin-responsive isoform; expressed only in insulin-responsive cells/tissues. Translocates to plasma membrane upon insulin stimulation
GLUT5	Small intestine, brain, muscle and adipose tissue	Fructose transporter
GLUT6	Ubiquitous	Pseudogene, nonfunctional

to the proposal that the basal membrane performs as the rate limiting step in transplacental glucose transfer from the mother to the fetus. GLUT-3 seems to be expressed in the vascular endothelium and has been recently discovered in the placental syncytial microvillous membrane. There is high expression of GLUT-3 early in pregnancy, decreasing as the fetus approaches term. This increase in GLUT-3 expression early in fetal life suggests higher glucose needs in fetal growth during early pregnancy. The distinct changes in the expression in GLUT-3 seem to be controlled by the placental production of CRH. GLUT-4 has only been identified in the stroma of the placental villous. The role of GLUT-4 is uncertain.

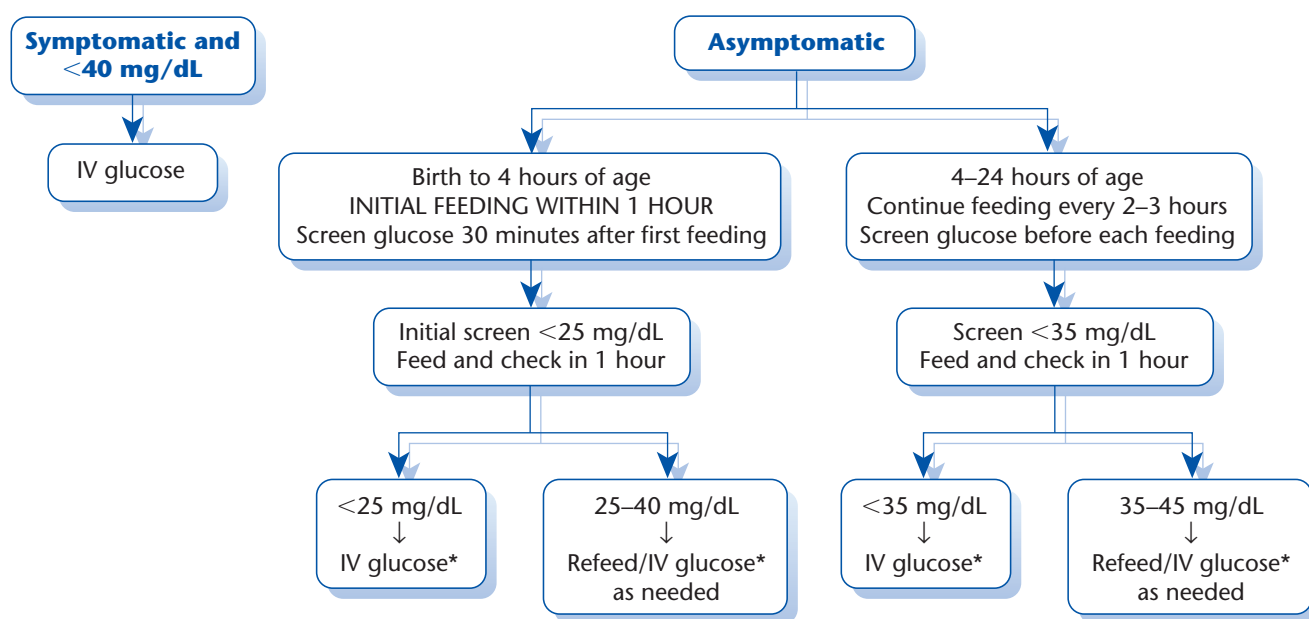
The fetal blood glucose level is approximately 70% of the maternal level. Hypoglycemia may be caused by many conditions that increase the infant's metabolic rate or may result from inadequate endogenous glycogen stores in infants born preterm or growth restricted. Box 106-2 lists signs and symptoms that may be present in the hypoglycemic newborn. There continues to be controversy about the degree of hypoglycemia that can cause neurologic damage. Although a number of studies using magnetic resonance imaging have described a wide spectrum of cerebral injury associated with hypoglycemia, such as bilateral loss of white/grey matter differentiation in the parietal occipital lobe, corticospinal tract injury, and damage to basal ganglia and thalamus, there are no evidence-based studies that directly associate neurologic damage with an absolute glucose concentration. Therefore, treatment of hypoglycemia remains to a great extent empiric. In 2011, the Committee on Fetus and Newborn of the American Academy of Pediatrics developed pragmatic screening and management guidelines for postnatal glucose homeostasis in "at-risk" newborn infants, a category including the late preterm (34<sup>0</sup>/<sub>7</sub> to 36<sup>6</sup>/<sub>7</sub> weeks' gestational age) and term small-for-gestational-age (SGA) infants, and infants of diabetic mothers (IDM)/large-for-gestational-age (LGA) infants. In a study enrolling 514 "high-risk" newborn infants, hypoglycemia occurred in 51% infants (hypoglycemia defined as a glucose level of <46 mg/dl [ $<2.6$  mmol/L]) with 19% developing severe hypoglycemia (defined as



**Figure 106-2** Distribution of GLUT isoforms in the human placenta, illustrating the syncytial asymmetry of GLUT1, the endothelial localization of GLUT3 and the stromal location of GLUT4. Cellular structures are not to scale and are separated to enable clear visualization. • GLUT1; • GLUT3; • GLUT4. (From Illsley NP. Glucose transporters in the human placenta. *Placenta* 2000;21[1]: 14–22, with permission from Elsevier.)

### BOX 106-2 Signs and Symptoms of Hypoglycemia

Cyanotic spells	Tremors
Apnea	Poor feeding
Respiratory distress	Hypotonia
Temperature instability	Tachypnea
Seizures	Tachycardia
Lethargy	Bradycardia
Irritability	Vomiting
Coma	



Target glucose screen  $\geq 45$  mg/dL before routine feedings

\*Glucose dose = 200 mg/kg (dextrose 10% at 2 mL/kg) and/or IV infusion at 5–8 mg/kg per min (80–100 mL/kg/day). Achieve plasma glucose level of 40–50 mg/dL.

Symptoms of hypoglycemia include: irritability, tremors, jitteriness, exaggerated Moro reflex, high-pitched cry, seizures, lethargy, floppiness, cyanosis, apnea, poor feeding.

**Figure 106-3** Screening for and management of postnatal glucose homeostasis in late-preterm (LPT 34 $\frac{0}{7}$ –36 $\frac{6}{7}$  weeks) and term small-for-gestational age (SGA) infants and infants who were born to mothers with diabetes (IDM)/large-for-gestational-age (LGA) infants. LPT and SGA (screen 0–24 hours), IDM and LGA  $\geq 34$  weeks (screen 0–12 hours). IV indicates intravenous. (From American Academy of Pediatrics Committee on Fetus and Newborn. Postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics*. 2011;127[3]:575–579.)

a glucose level of  $<40$  mg/dL). Eighty-one percent of infants developed hypoglycemia within the first 24 hours of life with a mean duration of 1.4 hours. This study reveals the vulnerability of developing hypoglycemia in this population of infants and the importance of close monitoring during the first 24 hours of life. Figure 106-3 describes the management approach in this high-risk population.

The physician should consider inborn errors of metabolism and endocrine abnormalities in the differential diagnosis of a newborn whose symptoms persist despite appropriate therapy. Prompt diagnosis and initiation of appropriate therapy are essential to prevent death and permanent neurologic damage.

In the initial hours after delivery the typical newborn does not have fully active gluconeogenic function and is consequently unable to use alanine, lactate, and glycerol efficiently for endogenous hepatic glucose production. Delay in the expression of phosphoenolpyruvate

carboxykinase (PEPCK), the rate-limiting step in the gluconeogenesis pathway, increases the susceptibility of the neonate to developing hypoglycemia. By 24 hours of age, PEPCK reaches adult values. Therefore, early, serial preprandial glucose monitoring in conjunction with the initiation of early feedings is important in the care of a newborn with risk factors for hypoglycemia. Other causes of hypoglycemia must be considered in neonates with persistent hypoglycemia beyond 24 hours of age, including severe refractory hypoglycemia and hypoglycemia not responding to enteral feeds, as well as newborns with persistent clinical signs as detailed in Box 106-2. Box 106-3 provides a list of factors that may contribute to neonatal hypoglycemia. Hypoglycemia caused by congenital hyperinsulinism occurs during the first few days of life, but cases occurring later in infancy and childhood have been reported. Hypoglycemia that occurs because of congenital hyperinsulinism is severe and persistent, requiring

**BOX 106-3 Etiologic Factors Contributing to Neonatal Hypoglycemia****PRENATAL CAUSES**

- Maternal diabetes
- Maternal drug administration
- Beta-sympathomimetics
- Intrapartum intravenous dextrose bolus
- Oral hypoglycemics
- Propylthiouracil
- Pregnancy-induced hypertension

**EXCESS UTILIZATION**

- Hyperinsulinism
- IDM
- LGA
- SGA
- Erythroblastosis
- Increased energy expenditure
- RDS
- Sepsis
- Seizures
- Drug withdrawals
- Hypothermia
- Increased work of breathing
- Inborn errors of metabolism
- Hypoxemia
- Ischemia
- Shock

- Hemorrhage
- Postexchange transfusion
- Hyperviscosity, polycythemia

**INADEQUATE PRODUCTION OR SUBSTRATE DELIVERY**

- Inadequate delivery of calories
- Delayed enteral or parenteral nutrition
- Transient developmental immaturity of critical metabolic pathways, reducing endogenous production of glucose or other substrates
- Endocrine disorders:
  - Hypothyroidism
  - Hypothalamic
  - Pituitary
- Abrupt cessation of hypertonic parenteral glucose
- Discordant twins
- Cerebral hemorrhage
- Perinatal asphyxia
- SGA
- Glucose transporter deficiency
- Suppressed gluconeogenesis, glycogenolysis, lipolysis, proteolysis and ketogenesis secondary elevated insulin levels (hyperinsulinism).

**IATROGENIC CAUSES**

- Malposition of umbilical catheter
- Cold stress

IDM, Infant of diabetic mother; LGA, large for gestational age; RDS, respiratory distress syndrome; SGA, small for gestational age. Modified from Cornblath M, Ichord R. Hypoglycemia in the neonate. *Semin Perinatol*. 2000;24(2):136–149, with permission from Elsevier.

**Table 106-3 Initial Management Steps to Consider to Treat Persistent, Severe Hypoglycemia**

Step 1	Obtain labs: glucose, growth hormone, insulin, and cortisol levels
Step 2	Give D10 2 ml/kg (200 mg/kg) IV push Increase IV infusion 10%–15%
Step 3	Repeat blood glucose
Repeat step 2 if hypoglycemia persists. Consider additional medical management if glucose infusion rate >15 mg/kg/min.	

large glucose infusion rates to maintain euglycemia. Glucose infusion rates greater than 15 mg/kg/min are often necessary. Endogenous hepatic glucose production and utilization rate in the healthy newborn is 4 to 6 mg/kg/min. Euglycemia can be maintained in the otherwise healthy newborn with a glucose infusion rate of 5 to 8 mg/kg/min. This circumstance is in stark contrast to the hyperinsulinism exhibited by infants of diabetic mothers and those who are growth restricted or experience perinatal asphyxia. The hyperinsulinism present in these conditions is transient. Transient

hyperinsulinism can also occur without any predisposing factors. Table 106-3 describes the recommended management steps if the hypoglycemic episode is refractory to initial treatment. Additional medical management may be required for glucose infusion rates >15 mg/kg/min.

The following formula can be used to determine the glucose infusion rate (GIR):

$$\text{GIR (mg/kg/min)} = \frac{\% \text{ dextrose} \times \text{infusion rate (ml/hr)}}{6 \times \text{weight (kg)}}$$

## APPROACH TO THE INFANT WITH PERSISTENT HYPOGLYCEMIA

Ascertaining the cause of persistent hypoglycemia requires an understanding of the adaptive processes involved in the response to hypoglycemia and application of a systematic approach in identifying any underlying metabolic problems.

Physicians often initially suspect sepsis in the infant who is hypoglycemic and seems ill; metabolic disorders may not be considered until the infant exhibits continued deterioration despite standard therapeutic measures or when laboratory results fail to support or confirm a diagnosis of infection. Furthermore, metabolic disorders may cause other systemic manifestations. An infant affected by galactosemia may develop *Escherichia coli* sepsis, whereas an infant with glycogen storage disease type Ib (glucose-6-phosphatase translocase deficiency) or organic aciduria may exhibit neutropenia, thus mimicking sepsis in the newborn in face of a metabolic disorder. A metabolic or endocrine disorder should be suspected when altered consciousness or seizures occur in conjunction with profound hypoglycemia requiring greater than 15 mg/kg/min glucose infusion rates or if hypoglycemia is not responding to standard therapy.

Hypoglycemia can occur at distinct times depending on the disorder and may also occur preprandially, postprandially, or during a period of fasting. The timing of the hypoglycemic episode can be a helpful clue to its underlying cause. Five processes are responsible for maintaining normal blood glucose levels during periods of fasting in the healthy newborn infant:

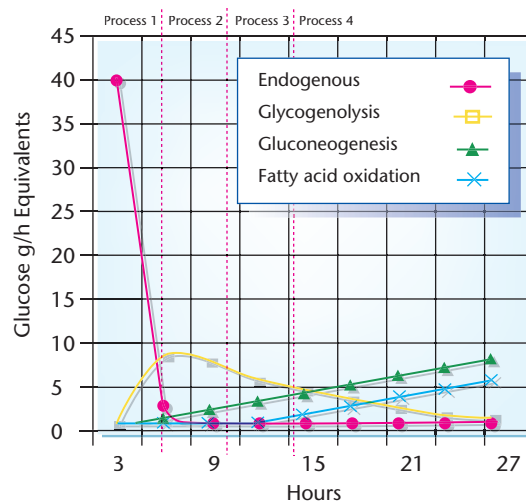
1. Glycogenolysis
2. Gluconeogenesis
3. Adipose tissue lipolysis
4. Fatty acid oxidation (to synthesize glucose and ketone bodies)
5. Endocrine system capable of integrating and modulating these first 4 processes during periods of fasting

Sufficient endogenous gluconeogenic substrates (amino acids, glycerol, and lactate) are required for these metabolic reactions. Glycogenolysis, gluconeogenesis, adipose tissue lipolysis, and fatty acid oxidation are temporally related. Figure 106-4 illustrates the relationships of these processes when prolonged starvation occurs during the newborn period. Once the endogenous supply of glucose is exhausted, glycogenolysis (process 2) takes over, usually after 4 hours. Gluconeogenesis (process 3) is activated, achieving peak activity after 12 hours of starvation. Fatty acid oxidation (process 4) begins to peak after 14 hours. Figure 106-5 reveals the relationship of the various processes after 24 hours.

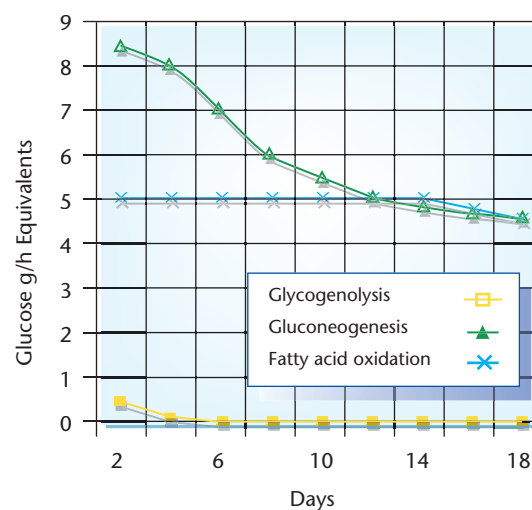
Infants with progressive clinical deterioration and a high clinical suspicion of inborn error of metabolism require prompt detection and intervention.

### Process 1: Gastrointestinal Absorption of Glucose

Glucose becomes available from gastrointestinal nutrient absorption immediately after feeding. Breast-feeding infants have a greater capacity to generate ketone bodies compared with formula-feeding neonates, suggesting that human milk augments ketogenesis in human neonates through as yet undescribed



**Figure 106-4** Glycogenolysis, gluconeogenesis, lipolysis, and fatty acid oxidation are temporally related. (Adapted from Ruderman NB, Aoki TT, Cahill GF Jr. *Gluconeogenesis and its disorders in man*. In: Hanson RW, Mehlman MA, eds. *Gluconeogenesis, Its Regulations in Mamalian Species*. New York: John Wiley & Sons, Inc; 1976: 518, with permission.)



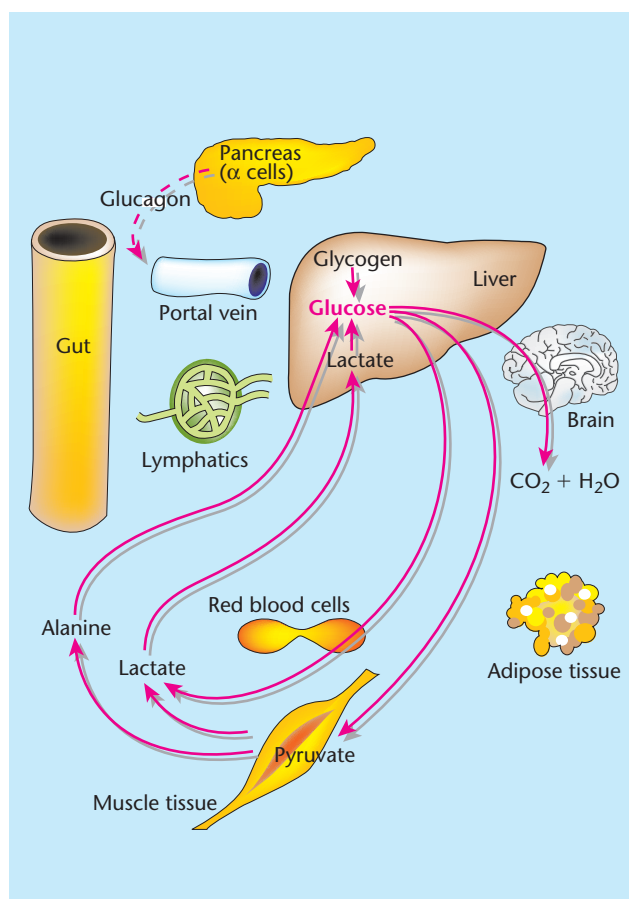
**Figure 106-5** The relationship of glycogenolysis, gluconeogenesis, and fatty acid oxidation after 24 hours and beyond.

pathways. Insulin and glucose levels are elevated, and glucagon is depressed as intestinal absorption of glucose takes place. Hypoglycemia occurring during this phase suggests hyperinsulinism. Excessive insulin secretion in response to an enteral feeding induces a hypoglycemic response. Consequently, hypoglycemia that is caused by hyperinsulinism is typically responsive to administration of glucagon and octreotide.

Figure 106-6 depicts how hepatic glycogenolysis preserves blood glucose homeostasis during process 1 (early fasting), a time in which gastrointestinal absorption of glucose is predominant.

Causes of neonatal hyperinsulinism are listed in Box 106-4. Although the underlying cause of hyperinsulinism varies, the basic problem is increased glucose





**Figure 106-6** Metabolic interrelationships of major tissues in early fasting state. (Adapted from Devlin TM, ed. Textbook of Biochemistry With Clinical Correlations. 7th ed. New York: John Wiley & Sons; 2011: 843. Reprinted by permission.)

#### BOX 106-4 Causes of Neonatal Hyperinsulinism

- Infant of diabetic mother
- Intrauterine growth restriction
- Perinatal asphyxia
- Congenital hyperinsulinism
- Beckwith-Wiedemann syndrome
- Hypopituitarism
- Rh isoimmunization

utilization resulting from excessive insulin secretion or, in the case of Beckwith-Wiedemann syndrome, excess tissue production of insulin-like growth factor-II. Some disorders have a genetic basis (Beckwith-Wiedemann syndrome, congenital hyperinsulinism), whereas others can be associated with adverse intrauterine events (intrauterine growth restriction, perinatal asphyxia). Infants of diabetic mothers, intrauterine growth-restricted infants, and infants who experience perinatal asphyxia typically receive parenteral glucose

infusions during the initial stabilization period. Congenital hyperinsulinism, Beckwith-Wiedemann syndrome, and hypopituitarism require more extensive treatment as an adjunct to high concentrations of infused glucose.

#### Infant of Diabetic Mother

Infants born to mothers with diabetes risk developing hypoglycemia as a result of fetal responses to chronic intrauterine hyperglycemia. As noted previously, glucose is transported from the maternal circulation to the fetus by facilitated diffusion. This process is driven by the concentration gradient between the maternal and fetal blood glucose. At birth the newborn's insulin secretion remains elevated while the maternal source of glucose abruptly ceases. The greatest risk for developing hypoglycemia in the IDM is in the first few hours after birth and may continue through the first 48 hours of life. The increased release of insulin results from an increased sensitivity of the  $\beta$ -cell to stimulation. An IDM will secrete more insulin in response to a given amount of glucose than an infant born to a mother without diabetes. The increase in  $\beta$ -cell sensitivity progressively diminishes over the first 7 to 10 days of age. An IDM can be macrosomic with significant adiposity because increased insulin levels in utero stimulate fetal growth. Therefore, all LGA infants should be monitored for hypoglycemia resulting from hyperinsulinism.

#### Congenital Hyperinsulinism

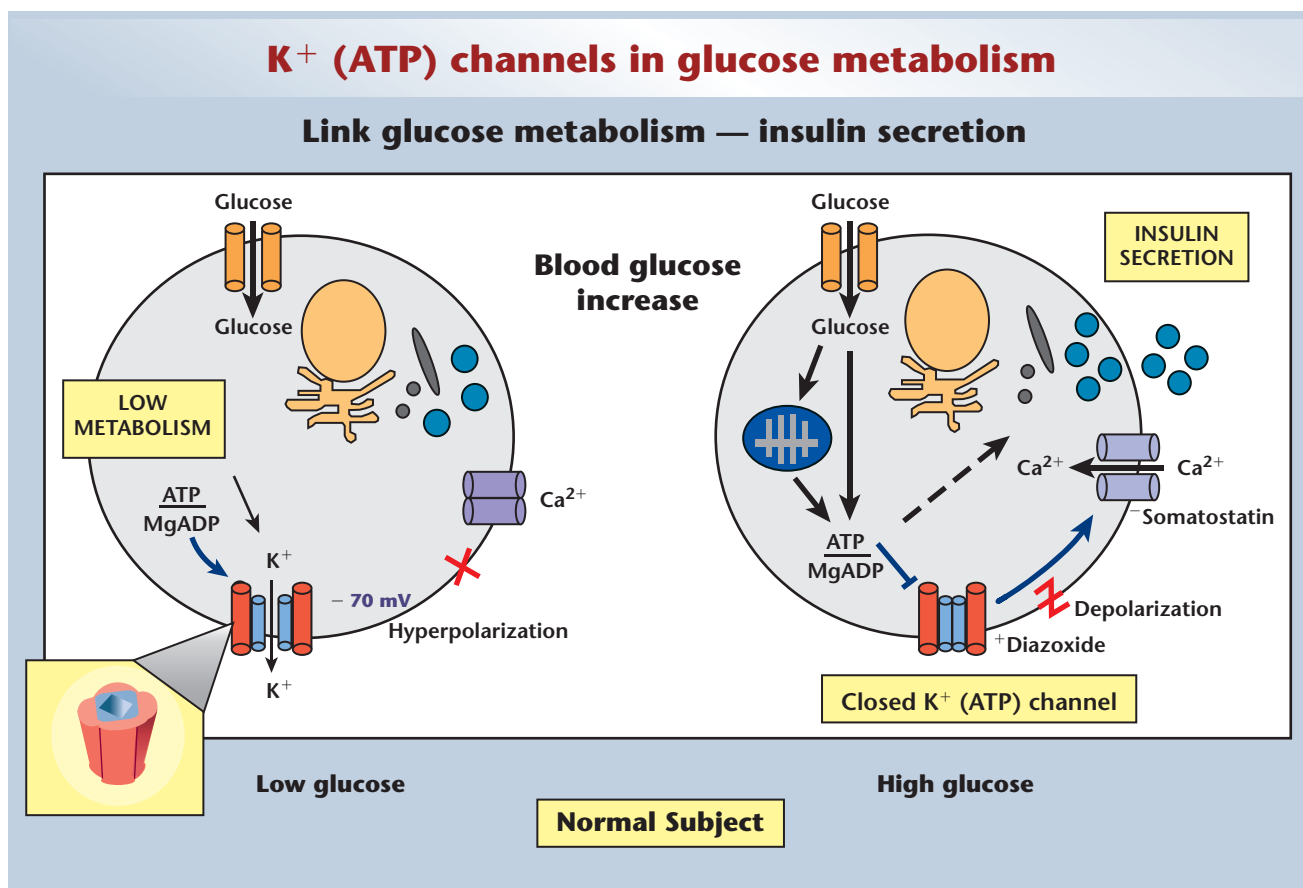
**PATHOPHYSIOLOGIC FEATURES.** Congenital hyperinsulinism is the most common cause of persistent hypoglycemia occurring in the neonatal period. The incidence varies from 1 in 3,000 live births in parts of the Middle East to 1 in 40,000 live births in parts of Europe. Congenital hyperinsulinism is characterized by recurrent and persistent fasting hypoglycemia caused by dysregulation of insulin secretion. Nesidioblastosis, which is a diffuse proliferation of pancreatic islet cells, was thought to be the cause of congenital hyperinsulinism. However, nesidioblastosis is a common pancreatic finding in normoglycemic newborns. The most common cause of congenital hyperinsulinism responsible for 40% to 45% of cases involves the ABCC8 and the KCNJ11 genes that are located on chromosome 11 and encode the SUR1 and KIR6.2 proteins. These proteins are subunits of the  $\beta$ -cell responsible for the adenosine triphosphate-sensitive potassium ( $K^+_{ATP}$ ) channels. In 5% to 10% of cases congenital hyperinsulinism occurs as a result of enzymatic or transcription anomalies secondary to gene mutations. The cause of the remaining cases remains unknown. Table 106-4 lists the genes responsible for congenital hyperinsulinism. The inheritance of congenital hyperinsulinism can occur with autosomal-recessive or -dominant mutations of the ABCC8 or KCNJ11 genes. Some infants with congenital hyperinsulinism inherit it as an autosomal-recessive trait. Figure 106-7 demonstrates the actions of the SUR1 and KIR6.2 in the pancreatic ( $\beta$ -cell secretion). The  $K^+_{ATP}$  channels are octameric complexes comprising 2 types of subunits—4 regulatory SUR1 (sulphonylurea receptors) surrounding 4 KIR6.2 (pore-forming inwardly rectifying potassium channels); see Figure 106-8. When there is a normal increase in blood glucose that results in an increase in intracellular ATP, the increase in

**Table 106-4** Summary of Congenital Hyperinsulinism Genes

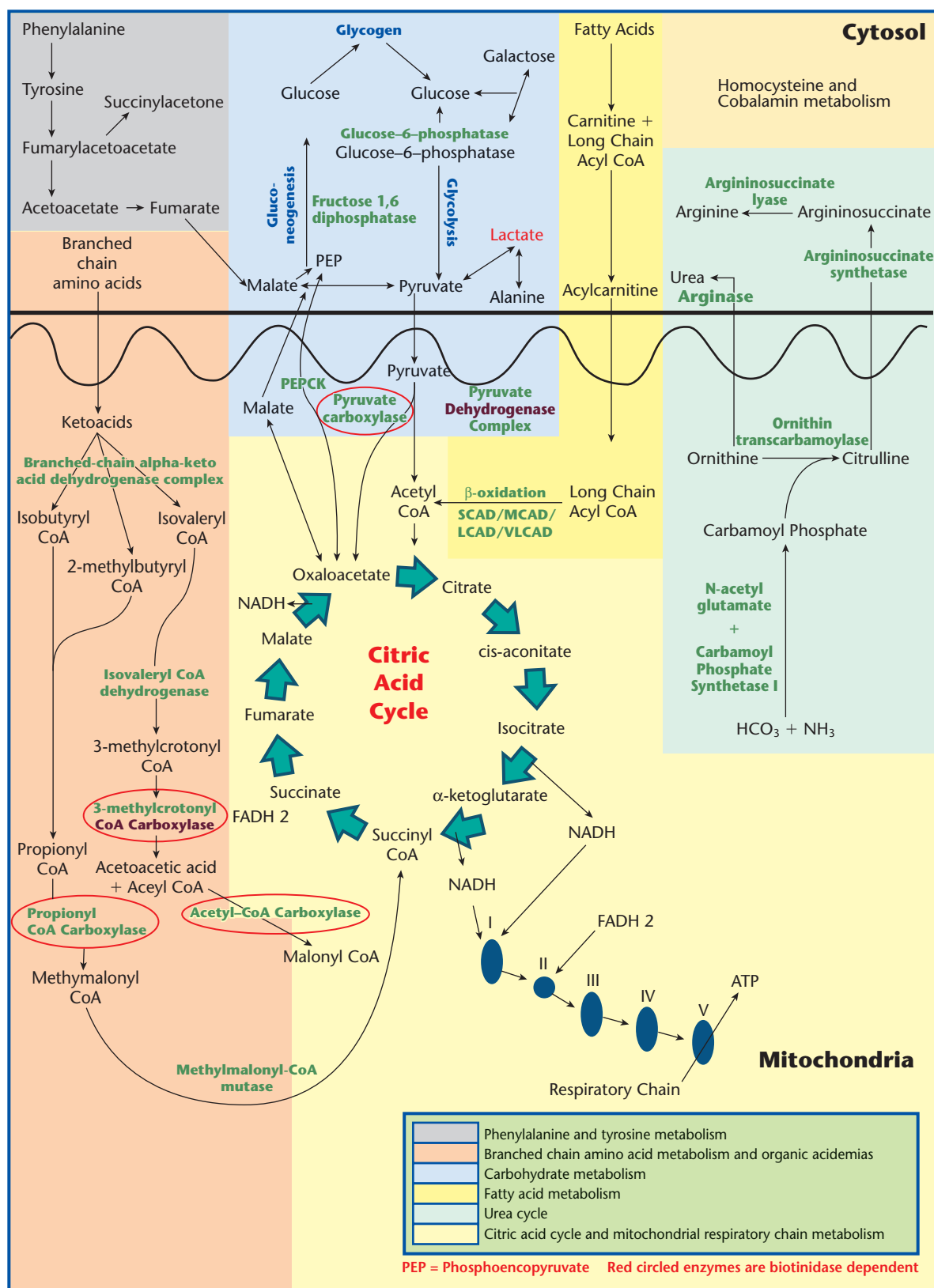
GENE	PROTEIN	INHERITANCE	DIAZOXIDE RESPONSE	PHENOTYPE	HISTOLOGY
<b>KATP CHANNEL</b>					
<i>ABCC8</i>	SUR 1	Rec	No	LBW	Focal/diffuse
		Dom	Usually		Diffuse
<i>KCNJ11</i>	Kir6.2	Rec	No	LBW	Focal/diffuse
<b>ENZYMES/TRANSPORTERS</b>					
<i>GCK</i>	GCK	Dom/Rec	Usually	LBW (MODY 2)	Diffuse
<i>GLUD1</i>	GDH	Dom/Rec	Yes	HI/HA	Diffuse
<i>HADH1</i>	SCHAD	Rec	Yes		Diffuse
<i>SLC16A1</i>	MCT1	Dom	Usually	EIHI	Diffuse
<i>UCP2</i>	UCP2	Dom	Yes		Diffuse
<b>TRANSCRIPTION FACTORS</b>					
<i>HNF4A</i>	HNF4A	Dom/Rec	Yes	LBW (MODY 1)	Diffuse
<i>HNF1A</i>	HNF1A	Dom	Yes	LBW (MODY 3)	Diffuse

*Dom*, dominant; *EIHI*, exercise-induced hyperinsulinism; *GCK*, glucokinase; *GDH*, glutamate dehydrogenase; *HADH*, hydroxy-acyl-CoA dehydrogenase; *HI/HA*, hyperinsulinism/hyperammonemia syndrome; *LBW*, large birth weight; *MCT1*, monocarboxylate transporter 1; *MODY*, maturity-onset diabetes of the young; *Rec*, recessive; *UCP2*, uncoupling protein 2.

From Dillon PA. Congenital hyperinsulinism. *Curr Opin Pediatr*. 2013;25:357, with permission.



**Figure 106-7** K<sup>+</sup>ATP channels in glucose metabolism. (From Flechtner I, Vaxillaire M, Cavé H, et al. Neonatal hyperglycemia and abnormal development of the pancreas. *Best Pract Res Clin Endocrinol Metab*. 2008;22(1):17–40, with permission from Elsevier.)



**Figure 106-8** Metabolic pathways involved in maintaining euglycemia: Phenylalanine and tyrosine metabolism; branched chain amino acid metabolism and organic acidemias; carbohydrate metabolism; fatty acid metabolism; urea cycle; and citric acid cycle and mitochondrial respiratory chain metabolism. FADH<sub>2</sub>, Flavin adenine dinucleotide; NADH, Nicotinamide adenine dinucleotide; PEP, phosphoenolpyruvate.

intracellular ATP inhibits the potassium efflux through the  $K^+_{ATP}$  channels. The closure of the potassium channels depolarizes the plasma membrane, which activates calcium channels increasing the intracellular calcium, resulting in the release of insulin via exocytosis. Each  $K^+_{ATP}$  channel contains at least 2 of these proteins. These mutations impair the function of the  $K^+_{ATP}$  channels and are inherited in an autosomal-recessive manner.

Hyperinsulinism-hyperammonemia syndrome is an autosomal-dominant condition that causes hypoglycemia. A serum ammonia level should be added to the diagnostic evaluation to determine this possibility. Hyperinsulinism-hyperammonemia syndrome is caused by mutations in the glutamate dehydrogenase gene.

**LABORATORY EVALUATION.** Laboratory findings include hyperinsulinemia in the presence of symptomatic hypoglycemia. Table 106-5 lists the blood and urine samples required when evaluating for persistent refractory hypoglycemia. These laboratory evaluations should be obtained prior to medical treatment of hypoglycemia. The unrestricted insulin release inhibits counterregulatory mechanisms. This inhibition will affect ketone body synthesis and lipolysis, resulting in a decrease in blood ketones and fatty acids. Gluconeogenesis is also inhibited. Newborns with congenital hyperinsulinism are at risk for brain damage resulting from hypoglycemia and lack of alternate fuels for brain metabolism. Serum cortisol response is blunted, and glucocorticoid administration does not correct the hypoglycemia. A definitive diagnosis of hyperinsulinism is made based on insulin and cortisol levels obtained during the acute hypoglycemic episode, but may be difficult in mild cases. The physician needs a high index of suspicion; otherwise, the diagnosis can easily be missed.

**TREATMENT STRATEGIES.** Adequate carbohydrate intake can be provided with intravenous glucose or enteral feeds, as described, and is critical to prevent brain injury. Correction of hypoglycemia may require glucose infusion rates greater than 15 mg/kg/min. A central line is required when administering glucose at concentrations greater than 12.5% dextrose because higher concentrations of intravenous glucose are particularly caustic to blood vessels. Table 106-6 provides a list of medications that may be used in the treatment of hypoglycemia. Surgery involving partial pancreatectomy or resection of localized adenomas is reserved for infants who fail to respond to medical management. Percutaneous transhepatic pancreatic venous blood sampling may be used to identify these “hot spots.”

Compared to the more invasive pancreatic blood sampling mentioned above, the use of fluorine-18-L-dihydroxyphenylalanine ( $^{18}F$ -Dopa PET) is gaining more popularity because it is less invasive and requires less ionizing radiation.  $^{18}F$ -Dopa PET takes advantage of the incorporation of DOPA by the  $\beta$ -cells, which is converted into dopamine by aromatic L-amino acid decarboxylase. In one study, the  $^{18}F$ -Dopa PET scan was shown to be useful in defining the extent of the lesion in two-thirds of cases; the authors recommend the need for intraoperative histologic confirmation.

**Diazoxide and Chlorothiazide.** Diazoxide and chlorothiazide together are the drugs of choice. Diazoxide is a ligand of the  $K^+_{ATP}$  channel, which binds to SUR1 and, in the presence of intracellular nucleotides, opens the channels. Chlorothiazide acts on the  $K^+_{ATP}$  channels but is also used to overcome the fluid retention caused by diazoxide.

**Glucagon.** Glucagon may be used in the acute management of hypoglycemia. Its onset of action is

**Table 106-5** Blood and Urine Samples Required During Hypoglycemia

BLOOD SPECIMEN	REQUIRED SAMPLE	NORMAL VALUES
Insulin	Serum	3–20 mcU/mL
Growth hormone	Heparinized serum/plasma	5–53 ng/mL
Cortisol	Heparinized serum/plasma	1–24 mcg/dL
Glucose	Serum	40–60 mg/dL
<b>ELECTROLYTES AND LIVER FUNCTION TEST RESULTS</b>		
Blood gas	Heparinized whole blood	7.26–7.45 pH
Ketones	Whole blood	0.1–1.5 mmol/L
Lactate	Whole blood	1.1–2.3 mmol/L
Ammonia	Whole blood	21–95 mmol/L
Free fatty acids	Whole blood	0.5–1.6 mmol/L
Uric acid	Serum	1.7–5.8 mg/dL
Acylcarnitine profile	Blood spots on Guthrie card	Laboratory dependent
Pyruvate	Whole blood	0.3–0.7 mg/dL
Alanine (plasma amino acids)	Serum	Age dependent
<b>URINE SPECIMEN</b>		
Ketones	—	Negative
Organic acids	—	Laboratory dependent
Reducing substances	—	Negative



10 to 15 minutes, and its effect is transient. Glucagon should only be used as an acute therapy in infants with adequate glycogen stores. Glucagon is not appropriate for use in small-for-gestational-age and low-birth-weight infants. Subcutaneous or intravenous administration of glucagon in a dose of 0.5 to 1.0 mg will stimulate mobilization of endogenous glycogen stores and result in an increase in blood glucose greater than 30 mg/dL.

**Octreotide.** Octreotide is an analogue of somatostatin that can be used in the acute and chronic treatment of hypoglycemia. As a somatostatin analogue, octreotide has an inhibitory effect on various hormones, including growth hormone (GH), thyroid-stimulating hormone (TSH), and adrenocorticotrophic hormone (ACTH). Octreotide is also used in the treatment of congenital hyperinsulinism. Octreotide's mechanisms of action include alteration in  $\beta$ -cell intracellular translocation of calcium and inhibition of insulin-containing granule exocytosis. Octreotide can decrease gallbladder contractility and bile secretion leading to hepatic dysfunction, steatorrhea, cholestasis, and cholelithiasis. Octreotide can also decrease splanchnic blood flow, potentially increasing the risk of necrotizing enterocolitis.

### Beckwith-Wiedemann Syndrome

Beckwith-Wiedemann syndrome is an imprinting disorder occurring in approximately 1 in 14,000 newborns. Approximately 85% of cases are sporadic,

inheritance is complex, and a familial autosomal-dominant form with a variable phenotype has been described. The critical chromosomal region responsible for Beckwith-Wiedemann syndrome is located at 11p15.5. Beckwith-Wiedemann syndrome occurs when paternal uniparental disomy is present (an imprinting defect in which the maternal allele is not expressed), with microdeletions involving the critical region, with contiguous gene duplications in the 11p15 region, or with *CDKN1C* mutations. Characteristic findings include macrosomia (defined as birth weight >4,000 g), an abdominal wall defect, and macroglossia. Other features include hemihypertrophy, indentations on the posterior rim of the ear's helix, and linear creases of the earlobe. Treatment of the hypoglycemia is as described previously, and the hypoglycemia tends to resolve over time. Long-term management includes monitoring alpha-fetoprotein levels and abdominal sonography to monitor for tumor development, that is, Wilms tumors. Figure 106-8 depicts the metabolic pathways involved in maintaining euglycemia.

In the following sections, specific metabolic pathways and their involvement in maintaining euglycemia are examined.

### Process 2: Glycogenolysis—Postabsorptive and Early Catabolism

Glycogenolysis occurs when glycogen stored in the liver is broken down after completion of intestinal carbohydrate absorption, approximately 3 to 4 hours

**Table 106-6** Additional Medical Management for Hypoglycemia Requiring a Glucose Infusion (>15–20 mg/kg/min)

MEDICATION	MECHANISM OF ACTION	ROUTE OF ADMINISTRATION	DOSE	SIDE EFFECTS
Glucagon	Increased glycogenolysis and gluconeogenesis	SC, IV, IM <b>Use only in acute management.</b>	0.025–0.3 mg/kg/dose repeat 20 min as needed (max dose 1 mg)	Nausea, vomiting Do not use in SGA or low-birth-weight infants.
Diazoxide	K <sup>+</sup> <sub>ATP</sub> channel agonist decreasing insulin secretion	IV, PO	2–5 mg/kg IV push 2–105 mg/kg every 8–12 hr	Hyponatremia and fluid retention, hypertrichosis, hypotension
Chlorothiazide	Unknown	PO IV not recommended in infants and children.	6 mo–2 yr: 10–20 mg/kg divided twice daily (max. 375 mg) 2–12 yr: 1 g divided twice daily >12 yr: 30–60 mg/kg divided two to three times daily (max. 2 g)	Hypotension, alopecia, photosensitivity, hyperuricemia
Octreotide	Inhibits insulin and GH	SC, IV	Start 2–10 mcg/kg/day every 6–8 hours. Increase up to 40 mcg/kg/day every 4–8 hours	Tachyphylaxis, diarrhea, constipation
Hydrocortisone	Decreased peripheral glucose utilization	IV, IM	5 mg/kg every 12 hours	Immunosuppression, growth delay, gastric irritation

GH, growth hormone; IM, intramuscular; IV, intravenous; SC, subcutaneous; SGA, small for gestational age; PO, oral.

postprandially. Liver glycogen stores are 50 to 75 g/kg of liver. During glycogenolysis, glucose-6-phosphate (G-6-P) is produced, releasing glucose by the action of glucose-6-phosphatase. Insulin levels return to basal levels, and increasing glucagon and epinephrine levels augment glycogenolysis. The brain, red blood cells, and renal medulla use glucose exclusively.

Hypoglycemia occurring during this phase is suggestive of an abnormality in glycogenesis. Muscle glycogen cannot be used by other tissues during this phase because muscle cells lack glucose-6-phosphatase. Box 106-5 lists the disorders of glycogenesis.

### **Glycogen Storage Disease Type I**

Glycogen storage disease type I (GSD I) has been classified as a disorder of gluconeogenesis because the enzyme glucose-6-phosphatase catalyzes the final common step in glycogenolysis and gluconeogenesis. The most common abnormalities found in GSD types Ia and Ib are hypoglycemia, lactic acidosis, hyperlipidemia, and hyperuricemia. GSD type Ia is secondary to a deficiency of glucose-6-phosphatase, whereas GSD Ib is caused by mutations in the glucose-6-phosphate translocase gene, responsible for the microsomal transport of glucose-6-phosphatase. The common end result of GSD types Ia and Ib is blockage of glucose release from the liver. The gene for glucose-6-phosphatase is located on chromosome 17q21. The gene for the glucose-6-phosphate transporter gene is located on chromosome 11q23. Inheritance is autosomal recessive for both forms of GSD. These enzymatic defects result in an excessive accumulation of both glycogen and fat in the liver. These 2 types of GSD are not clinically discernable; the major difference is that GSD Ib has an increased risk of infection and immunologic abnormalities. GSD Ib is associated with a decreased number of neutrophils and defective neutrophil and monocyte function, which increases the risk for infections. This circumstance is another example of a metabolic disease with an increased susceptibility to bacterial infection, thereby potentially masking the metabolic disorder. Definitive diagnosis is achieved by performing a liver biopsy along with enzyme analysis or by DNA analysis. As encountered in all disorders of glycogenesis, hypoglycemia becomes evident when exogenous glucose sources are depleted. Glucose-6-phosphatase has the combined effect of blocking glucose release from both the glycogenolytic and gluconeogenic pathways.

#### **BOX 106-5 Disorders of Glycogenesis**

- Glycogen storage disease type Ia (glucose-6-phosphatase deficiency, Von Gierke disease) and type Ib (glucose-6-phosphate translocase deficiency)
- Glycogen storage disease type III (debranching-enzyme deficiency)
- Glycogen synthase deficiency
- Mitochondrial respiratory-chain disorders

The goal of treatment is to prevent hypoglycemia-induced brain damage. Therapy consists of frequent feedings, initially by continuous nasogastric feedings and then by feeding uncooked cornstarch, particularly overnight. Uncooked cornstarch has the advantage of having a more protracted release of glucose than is available from cooked cornstarch; however, cornstarch use is limited to children older than 1 year. The dose of uncooked starch is 1.6 g/kg every 4 hours in patients between 1 and 2 years of age. Children unresponsive to cornstarch can be given continuous nasogastric infusion of glucose to prevent hypoglycemia. Fructose and galactose are restricted from the diet. Galactose and fructose must be converted to glucose-6-phosphate or to fructose-6-phosphate, respectively, before forming glucose. Because glucose-6-phosphatase is deficient, glucose-6-phosphate enters glycolysis, which results in a dramatic increase in lactate levels. Allopurinol is given to control the uric acid levels and prevent uric acid crystal accumulation. For patients with GSD type Ib, granulocyte colony-stimulating factor is used to prevent neutropenia and to decrease the severity of bacterial infections. Long-term outcomes in patients with GSD types Ia and Ib can be good if diagnosis occurs early and treatment is started promptly.

### **Glycogen Storage Disease Type III (Debranching-Enzyme Deficiency)**

GSD type III results from a deficiency of the debranching enzyme, amylo-1,6-glucosidase. The inheritance pattern is autosomal recessive. The gene for this debranching enzyme is located on chromosome 1p21. Debranching-enzyme deficiency results in an inability to degrade stored glycogen, thereby impairing the release of glucose from glycogen. Glucose production from gluconeogenesis remains unaffected. Some of the clinical features of GSD III are similar to those of GSD I. Hepatomegaly is present at birth as a result of glycogen accumulation, and improves gradually during the course of childhood. Although this disorder usually occurs in infancy, severe hypoglycemia can occur at birth and steadily improves with advancing age; thus GSD III differs dramatically from GSD I in this respect. Approximately 85% of patients exhibit liver and muscle (cardiac and skeletal) involvement (type IIIa). Myopathy is the major chronic morbidity associated with GSD type IIIa, while 15% of patients with GSD type IIIb have liver involvement without any associated muscle disturbance. GSD IIIa and IIIb are allelic disorders. Patients with IIIa have enzyme deficiency in both the liver and muscle, while patients with IIIb have enzyme deficiency limited to the liver. In comparison with GSD type I, concentrations of lactate and uric acid are normal. Unlike with GSD type I, no dietary restriction of fructose and glucose is required in these patients.

### **Differences Between GSD Type I and GSD Type III**

After a glucose challenge, lactate and uric acid levels are normal in GSD type III. Alanine levels are lower in

GSD III compared with GSD I, given that individuals with GSD III have increased gluconeogenesis and lower lactate levels. Therefore, the hypoglycemia in GSD III is usually not as severe as in GSD I. A robust response to a glucagon challenge is seen in patients with GSD III compared to those with GSD I after a short fast; however, this more robust response will decrease as the length of the fast increases.

Definitive diagnosis is made by confirming deficiency of amylo-1,6-glucosidase in leukocytes or from a liver, muscle, or skin biopsy. Prenatal diagnosis has been accomplished by amniocyte or chorionic villus sampling using enzyme activity analysis or immunoblot analysis. In comparison with GSD I, treatment of GSD III is easier to implement.

### **Glycogen Synthase Deficiency**

Glycogen synthase deficiency is a rare disorder that results in decreased synthesis of glycogen leading to decreased glycogen stores. Glycogen synthase deficiency is not a GSD because no accumulation of glycogen occurs. Glycogen synthase deficiency leads to ketotic hypoglycemia. Blood levels of lactate and alanine are low and no hyperlipidemia is present. Unlike GSD I and III, glycogen synthase deficiency can be observed clinically with a liver that is normal or slightly enlarged because of the decreased glycogen synthesis. Glucagon response after fasting hypoglycemia is usually reduced or absent, although it may be present in some affected infants. A minimal or absent response to glucagon suggests the diagnosis. Individuals with this condition also exhibit hyperglycemia and hyperlactatemia after feeding because of an inability to store excess glucose. Glycogen synthase is expressed only by the liver. The diagnosis is confirmed by liver enzymatic studies on a liver biopsy specimen.

### **Mitochondrial Respiratory-Chain Disorders**

Mitochondrial diseases involve the impairment of the oxidative phosphorylation (OXPHOS) system. The mitochondria's major goal is to provide the energy required for normal cellular function through the process of OXPHOS. The OXPHOS system consists of 5 multienzymatic complexes. These complexes are divided into 4 respiratory chain complexes (complex I, II, III, and IV) each existing independently in the mitochondrial inner membrane and ending at the adenosine triphosphate synthase (complex V) to form ATP, the molecule that supplies energy for cellular metabolism. Its synthesis is achieved by an electrochemical gradient. Any defect in the respiratory chain will affect mitochondrial respiration and energy production and cause neonatal decompensation consisting of clinical symptoms primarily involving organs with high energy demands. Respiratory-chain proteins are encoded by a large number of genes, resulting in several patterns of genetic inheritance that can cause mitochondrial disorders. Disorders of the respiratory chain can occur through spontaneous, autosomal-recessive, autosomal-dominant, X-linked, and maternally inherited mutations. Although these diseases can occur at virtually any age, the neonatal presentation can include hypoglycemia, apnea, seizures, lethargy, muscle atrophy, hypotonia, sideroblastic anemia,

lactic acidosis, coma, hepatomegaly with liver failure, and hypertrophic cardiomyopathies. Lactic acidosis is a common finding. Diagnosis is made by obtaining a muscle biopsy with mitochondrial enzyme analysis.

### **Process 3: Gluconeogenesis During Early or Intermediate Starvation**

Once hepatic glycogen stores are depleted, gluconeogenesis becomes the primary source for energy. Gluconeogenesis progressively replaces glycogen as the major source of glucose. Therefore, hypoglycemia during this phase suggests impaired gluconeogenesis. Gluconeogenesis typically begins after 12 to 16 hours of fasting once glycogen stores are depleted in the term infant. This process may occur more rapidly in preterm and stressed newborn infants. Gluconeogenesis uses amino acids, lactate, and glycerol to manufacture glucose. The most characteristic feature in newborns with defects of gluconeogenesis is hepatomegaly without evidence of liver insufficiency. Important substrates for gluconeogenesis are lactate, alanine, and oxaloacetate. A hallmark of the disorders of gluconeogenesis is elevation of alanine, pyruvate, and lactate levels. Both alanine and lactate are in equilibrium with pyruvate. Abnormalities in gluconeogenesis cause an increase in downstream metabolites such as pyruvate that causes elevations in lactate and alanine. During gluconeogenesis, the brain is not yet using ketone bodies significantly. Fatty acids used for lipolysis and glycerol production become essential when prolonged fasting occurs. Box 106-6 lists the disorders of gluconeogenesis.

### **Fructose-1,6-Diphosphatase Deficiency**

Fructose-1,6-diphosphatase deficiency is a disorder of gluconeogenesis rather than a defect in fructose metabolism. Fructose-1,6-diphosphatase deficiency is inherited in an autosomal-recessive manner. Newborns usually exhibit severe hypoglycemia and lactic acidosis during the first few days of life. These episodes are triggered by decreased oral intake. Clinical symptoms include apnea, tachycardia, hyperventilation, lethargy, and seizures. Fructose-1,6-diphosphatase deficiency has a direct effect on the formation of glucose involving gluconeogenic precursors. Hypoglycemia occurs because of the inability to make fructose-1-phosphate from fructose-1, 6-diphosphate. Fructose-1-phosphate is an important precursor to glucose formation. The enzyme deficiency results in a downstream increase in pyruvate, resulting in severe lactic acidosis. Laboratory analysis reveals increased levels of lactate, alanine, glycerol, and ketones. Definitive diagnosis is made by measuring fructose-1,6-diphosphatase activity in liver tissue. Because of the heterogeneity in

#### **BOX 106-6 Disorders of Gluconeogenesis**

- Fructose-1,6-diphosphatase deficiency
- Phosphoenolpyruvate-carboxykinase deficiency
- Pyruvate carboxylase deficiency

expression of this disorder, deficient leukocyte activity is diagnostic; however, normal leukocyte activity does not rule out fructose-1,6-diphosphate deficiency because a form of the disorder occurs with normal leukocyte activity and isolated liver enzyme deficiency. In this case a liver biopsy will be indicated.

Treatment of acute, severe episodes involves controlling hypoglycemia and acidosis through continuous intravenous glucose infusion and administration of sodium bicarbonate. Once the hypoglycemia and acidosis are corrected, maintenance therapy is directed at preventing prolonged periods of fasting. This task can be accomplished through continuous nasogastric feedings or intake of uncooked cornstarch after 1 year of age. Dietary restriction includes elimination of fructose, sucrose, glycerol, and sorbitol, which may precipitate an acute life-threatening event. Follow-up should include monitoring growth and development. With advancing age, issues with fasting will improve, which is thought to occur because of an increased capacity for the liver to store glycogen, lowering the need for gluconeogenesis.

#### **Phosphoenolpyruvate-Carboxykinase Deficiency**

Phosphoenolpyruvate-carboxykinase is an important target in the regulation of gluconeogenesis. PEPCK deficiency is a rare disorder that results from a defect localized to chromosome 20q13.31. PEPCK is active in mitochondria and the cytosol. The time of clinical presentation ranges from the neonatal period to early infancy. Affected infants exhibit hypoglycemia. Other clinical features include nonspecific symptoms such as lethargy, hypotonia, and failure to thrive. Systemic manifestations include hepatomegaly with hepatocellular damage, fatty liver, renal tubular acidosis, and fatty kidneys. PEPCK is involved in the conversion of oxaloacetate into phosphoenolpyruvate. Deficiency in PEPCK blocks the conversion of pyruvate, lactate, alanine, and the citric acid-cycle intermediates to glucose. Measuring PEPCK activity from freshly obtained liver biopsy samples is necessary to make the diagnosis. Because 2 isoforms of PEPCK can occur, one found in the mitochondria and the other in the cytosol, liver biopsy samples require fractionating to make the diagnosis. Initial treatment involves correction of hypoglycemia with intravenous glucose and sodium bicarbonate. Once stable, avoidance of fasting and use of nasogastric feeds or uncooked cornstarch after 1 year of age at bedtime are the mainstay of therapy. Unfortunately, the long-term prognosis is poor, with patients succumbing to hypoglycemia and neurologic injury.

#### **Pyruvate Carboxylase Deficiency**

Pyruvate carboxylase (PC) deficiency is an autosomal-recessive disorder. The PC gene is located on chromosome 11 and has 3 distinct clinical presentations: a severe neonatal form, a milder form occurring later with psychomotor retardation, and a benign form occurring with recurrent episodes of lactic acidosis and mild neurologic deficits. In the neonatal form, infants exhibit seizures, hypotonia, spasticity, renal tubular acidosis, and hepatic dysfunction. PC is responsible for the conversion of pyruvate and carbon dioxide to

oxaloacetate. PC is essential in supplying oxaloacetate to the citric acid cycle and thus in providing the necessary substrate for other metabolic pathways such as gluconeogenesis, lipogenesis, and glycerogenesis. Laboratory analysis reveals lactic acidosis, hypoglycemia, and increased ammonia, lysine, citrulline, and alanine levels. Hyperammonemia distinguishes PC deficiency from the other disorders of gluconeogenesis and should therefore be considered in any newborn infant with severe neurologic abnormalities. Diagnosis is made by measuring PC enzymatic activity in liver or skin tissue. Treatment revolves around addressing the lactic acidosis and hypoglycemia (see previous discussion). The hyperammonemia can be treated by providing an alternate source of 4-carbon intermediates (aspartate or citrate) as it replenishes oxaloacetate. The prognosis for infants presenting in the neonatal period is especially poor, with survival beyond 3 months of life rare.

### **Process 4: Fatty Acid Oxidation and Ketogenesis**

#### **Pathophysiologic Features**

Fatty acid oxidation (FAO) disorders include medium-chain acyl-coenzyme A (CoA) dehydrogenase deficiency (MCADD), which is the most common of these metabolic disorders. Through the  $\beta$ -oxidation pathway, fatty acids provide energy-yielding substrates during periods of fasting and stress. This process is typically initiated after fasting for more than 12 hours. Normal metabolism of endogenous fats begins with lipolysis; this process, in turn, releases free fatty acids, resulting in an increase in plasma concentration. Free fatty acids are then bound to albumin and transported to other tissues. Short- and medium-chain fatty acids cross the mitochondrial membrane without esterification, unlike long-chain fatty acids. After conversion of long-chain fatty acids to their CoA esters, they react with L-carnitine to form acylcarnitine esters. The fatty acylcarnitine complex is then transported across the mitochondrial membrane. Once transported inside the mitochondria, the fatty acid-acyl-CoA complex will undergo  $\beta$ -oxidation, which is an important source of energy for the body during times of prolonged fasting and metabolic stress.  $\beta$ -Oxidation involves successive shortening by 2 carbon atoms ultimately releasing the end product acetyl-CoA.

In the muscle, acetyl-CoA enters the citric cycle (ATP production). While in the liver, acetyl-CoA is used to synthesize the ketone bodies 3-hydroxybutyrate and acetoacetate. These ketones can then be used as a secondary fuel source for most tissues, particularly the brain. Inborn errors involving intramitochondrial FAO diminish the supply of nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FAD) available for mitochondrial oxidative phosphorylation, decreasing the formation of ATP. Therefore, disorders related to FAO may lead to multiorgan failure secondary to acute ATP deficiency. Clinical features of FAO disorders include hypotonia, cardiomyopathy, coma, and hepatomegaly (fatty liver). The clinical presentation may be confusing and misleading; for example, hyperammonemia may suggest Reye syndrome, and



unexpected death may be taken as sudden infant death syndrome. Many patients have a family history of sudden death in siblings during infancy. The classic presentation is hypoketotic hypoglycemia, indicating impairment in FAO. Patients can exhibit vomiting and lethargy, which occurs after fasting. Intercurrent illness can induce prolonged fasting, potentially unmasking a primary underlying disorder of FAO. Diagnosis can be delayed considerably, given that some patients reach adulthood before experiencing a prolonged fasting episode that induces symptoms. Some affected individuals remain asymptomatic for life. This great variability in the clinical presentation can prevent prompt diagnosis in some patients. Pregnancies complicated by either acute liver failure of pregnancy or HELLP syndrome have been associated with fetuses affected with disorders of FAO. The physician must be aware of these prenatal clues and consider all newborns delivered in mothers with acute liver failure of pregnancy or HELLP syndrome to be at risk for disorders of FAO. Box 106-7 lists the disorders of fatty acid oxidation.

Table 106-7 lists the distinguishing metabolic markers encountered with the fatty acid-oxidation disorders. These markers can be obtained by analysis of

acylcarnitine profiles in plasma, blood spots (Guthrie cards), and urine.

### Medium-Chain Acyl-CoA Dehydrogenase Deficiency

MCADD is the most common disorder in the FAO pathway. The estimated frequency is 1 in 5,000 to 10,000 live-born infants. MCADD testing is currently included on newborn metabolic screening panels in many states. It is an autosomal-recessive disorder, with the A985G mutations occurring with the highest frequency. The worldwide prevalence is shown in Table 106-8. MCADD produces hypoketotic hypoglycemia after a fasting period of 8 to 12 hours in neonates or potentially earlier if an acute intercurrent illness is present. The most common time for presentation of MCADD is after 3 months of age, when infants typically stop night feedings. Older children may need to be fasting for 18 to 24 hours before symptoms become evident.

The first step in treatment is focused on avoiding prolonged fasts. As noted previously, this is not usually an issue for newborns because they generally feed every 2 to 3 hours. As individuals with this condition get older, they generally tolerate longer fasting intervals. In neonates and infants, going longer than 6 hours without a feeding should be avoided. At 1 year of age, raw cornstarch may be instituted to supply a slow release source of glucose for up to 8 hours. This approach cannot be used in children younger than 1 year because of enzyme immaturity and inability to handle the osmotic load.

Plasma L-carnitine levels should be checked as soon as the diagnosis is suspected. Some individuals may have low plasma L-carnitine levels that require supplementation with oral carnitine. Low L-carnitine levels cause a progressive cardiomyopathy. Another function of L-carnitine is to remove short-chain and

### BOX 106-7 Disorders of Fatty Acid Oxidation

- Medium-chain acyl-coenzyme A (CoA) dehydrogenase deficiency
- Long-chain acyl-CoA dehydrogenase deficiency
- Very long-chain acyl-CoA dehydrogenase deficiency
- Short-chain acyl-CoA dehydrogenase deficiency

**Table 106-7** Fatty Acid Oxidation Disorders with Distinguishing Metabolic Markers

DISORDER	PLASMA ACYLCARNITINES	URINARY ACYLGLYCINES	URINARY ORGANIC ACIDS
VLCAD MCAD	Tetradecenoyl- Octanoyl- Decenoyl-	Hexanoyl- Suberyl- Phenylpropionyl- Butyryl-	
SCAD LCHAD	Butyryl- 3-Hydroxy-palmitoyl- 3-Hydroxy-oleoyl- 3-Hydroxy-linoleoyl-		Ethylmalonic 3-Hydroxydicarboxylic
DER ETF and ETF-DH	Dodecadienoyl- Butyryl- Isovaleryl- Glutaryl- Methylglutaryl-	Isovaleryl- Hexanoyl-	Ethylmalonic Glutaric Isovaleric 3-Hydroxy-3-methylglutaric

DER, 2,4-dienoyl-coenzyme A reductase; ETF, electron-transfer flavoprotein; ETF-DH, ETF dehydrogenase; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; MCAD, medium-chain acyl-coenzyme A dehydrogenase; SCAD, short-chain acyl-coenzyme A dehydrogenase; VLCAD, very-long-chain, acyl-coenzyme A dehydrogenase

From Stanley CA, Bennett JM, Mayatepek E. Disorders of mitochondrial fatty acid oxidation and related metabolic pathways. In: Fernandes J, Saudubray JM, van den Berghe G, Walter JH, eds. *Inborn Metabolic Diseases*. 4th ed. Heidelberg: Springer Science + Business Media; 2006:181, with permission.

**Table 106-8**      **Worldwide Frequency of the A985G Mutation**

LOCATION	FREQUENCY OF CARRIERS
Japan	Very low
Italy	1:333
Czech Republic	1:240
Turkey	1:216
Finland	1:191
Hungary	1:168
Spain	1:141
France	1:140
Normandy	1:118
Germany	1:116
United States	1:107
Denmark	1:101
Poland	1:98
Bulgaria	1:91
North Carolina (United States)	1:84
Belgium	1:77
Australia	1:71
United Kingdom	1:68–1:40
Holland	1:55

From Ozand PT. Hypoglycemia in association with various organic and amino acid disorders. *Semin Perinatol.* 2000;24(2):172–193, with permission from Elsevier.

medium-chain fatty acids from the mitochondria so as to maintain CoA levels. These fatty acids accumulate as a result of normal and abnormal FAO. This mechanism prevents the build-up in the mitochondria of short-chain and medium-chain fatty acids that may interfere with the energy production essential to the normal function of the cell. In individuals who have normal plasma L-carnitine levels, experts have recommended that L-carnitine not be given because it may result in increased stress on the FAO pathway by its function in assisting the transport of long-chain fatty acids into the mitochondria for oxidation. Box 106-8 lists other FAO defects and characteristic findings.

### Process 5: Disorders of Hormonal Regulation—Deficiency of Counterregulatory Hormones

When a newborn experiences hypoglycemia, a cascade of hormonal responses is activated to counter and restore blood glucose levels to normal. The first physiological response suppresses insulin secretion. This event is followed by an increase in counterregulatory hormones if hypoglycemia persists. The counterregulatory hormones are listed in Table 106-9.

These counterregulatory hormones stimulate glycogenolysis, gluconeogenesis, adipose tissue lipolysis, and hepatic ketogenesis. Some overlap in counterregulatory hormone effects occurs; thus if 1 system fails, partial compensation occurs by another hormone. Deficiencies in GH, glucagon, cortisol, and insulin-like growth factors may contribute

to hypoglycemia. Box 106-9 describes disorders of hormonal regulation.

### Pituitary Deficiency

Congenital pituitary deficiency is the second most common cause of persistent neonatal hypoglycemia, after congenital hyperinsulinism. Physical examination may range from a normal examination to identifying abnormalities involving midline defects such as single central incisor, optic nerve hypoplasia, and cleft lip or palate. Another physical finding is the presence of a microphallus and undescended testis in male newborns secondary to gonadotropin deficiency. Therefore the association of hypoglycemia and microphallus should alert the physician to the possibility of panhypopituitarism. Female newborns with gonadotropin deficiency have normal external genitalia because the development of the female external genitalia does not require the presence of gonadotropin-releasing hormone, luteinizing hormone, follicle-stimulating hormone, or ovarian hormones. The unopposed insulin secretion found with congenital pituitary deficiency can result in clinical findings similar to hyperinsulinism.

### Adrenal Deficiency

Adrenal insufficiency is rare cause of hypoglycemia in the newborn infant and occurs in cases of congenital adrenal hypoplasia or aplasia and adrenal hemorrhage. The resulting cortisol deficiency can be life threatening, making early recognition imperative.

### Non-Hypoglycemic Neonatal Onset Metabolic Disease

A variety of metabolic conditions exist that do not have hypoglycemia as a presenting symptom but will produce acidosis or hyperammonemia. Many of these conditions occur initially with feeding intolerance or irritability (or both) that can progress to increasing lethargy, seizures, and coma. If untreated, then the classic forms of these conditions cause severe neurologic devastation or death. Many of these metabolic conditions are now included on newborn screening programs in several states. However, screening results can take up to 7 days to return, and, in many of these conditions, onset of symptoms may begin at 3 days of life. Keeping these conditions in mind will allow the physician to intervene and minimize the effect on an affected neonate.

An important term to clarify in regard to treatment for some of these conditions is *natural protein*, which is a protein obtained from complete sources—that is, standard baby formulas or table foods.

**L-CARNITINE DEFICIENCY.** Carnitine deficiency is an autosomal-recessive disease localized to chromosome 5q31. Some individuals have low plasma L-carnitine levels that require supplementation with oral L-carnitine as a result of decreased enzyme activity necessary for carnitine uptake in the intestine and kidney. The reduction in L-carnitine will ultimately affect  $\beta$ -oxidation by limiting the entry of acyl-CoA esters into the mitochondria. Thus L-carnitine removes short-chain and medium-chain fatty acids from mitochondria to maintain CoA levels. These fatty acids

**BOX 106-8 Rare Fatty Acid Oxidation Defects**

The prevalences of these defects are unknown, although LCADD is likely the most common. The inheritance of these conditions is autosomal recessive: Short-chain acyl-coenzyme A (CoA) dehydrogenase deficiency (SCADD), long-chain acyl-CoA dehydrogenase deficiency (LCADD), trifunctional enzyme deficiency, long-chain hydroxyacyl-acyl-CoA dehydrogenase deficiency (LCHADD), very long-chain acyl CoA dehydrogenase deficiency (VLCADD)

**CLINICAL FINDINGS**

- Seizures
- Hypotonia
- Cardiomyopathy
- Sudden infant death syndrome

**LABORATORY FINDINGS**

- Hypoketotic hypoglycemia
- Abnormal liver function tests

**SPECIALTY BIOCHEMICAL TESTING**

- Organic acids have a typical profile
- Acylcarnitine profile
- Plasma amino acids are normal
- Enzyme testing is available but difficult

**ACUTE TREATMENT**

- Intravenous glucose
- Formula containing medium-chain triglycerides (medium-chain triglyceride oil)—Pregestimil
- Supportive care for cardiomyopathy

**Table 106-9 Hormonal Regulation of Fasting Metabolic Systems**

	<b>HEPATIC GLYCOGENOLYSIS</b>	<b>HEPATIC GLUCONEOGENESIS</b>	<b>MUSCLE PROTEOLYSIS</b>	<b>ADIPOSE TISSUE LIPOLYSIS</b>	<b>HEPATIC KETOGENESIS</b>
Insulin	Inhibits	Inhibits	Inhibits	Inhibits	Inhibits
Glucagon	Stimulates	—	—	—	Stimulates
Cortisol	—	Stimulates	Stimulates	—	—
Growth hormone	—	—	—	Stimulates	—
Epinephrine	Stimulates	Stimulates	—	Stimulates	Stimulates

Derived from Polin RA, Fox WW, Abman S. *Fetal and Neonatal Physiology*, 3rd ed. Philadelphia, PA: WB Saunders; 2003.

**BOX 106-9 Disorders of Hormonal Regulation**

- Panhypopituitarism (adrenocorticotrophic hormone deficiency)
- Growth hormone deficiency
- Adrenal deficiency (cortisol deficiency)

accumulate as a result of normal and abnormal FAO. This mechanism prevents the buildup in the mitochondria of short-chain and medium-chain fatty acids that may interfere with energy production essential to the normal function of the cell. In certain organic acidemias, L-carnitine will also bind the offending organic acid for removal, that is, propionic acid. As noted previously, in well individuals who have FAO disorders and normal plasma L-carnitine levels, experts have recommended that L-carnitine not be given because it may result in increased stress on the FAO pathway by its function in assisting the transport of long-chain fatty acids into the mitochondria for oxidation. Clinically low L-carnitine levels cause

a progressive cardiomyopathy, encephalopathy, and hypoketotic hypoglycemia.

Low levels of L-carnitine in serum and tissue are diagnostic.

Treatment with L-carnitine 100 to 200 mg/kg/day can result in a dramatic response. In severe cases peritoneal dialysis has been found to be a safe, effective, and easy way to remove excess offending metabolites in neonates and infants. Some debate has occurred over hemodialysis in neonates because of reports of poor outcomes; however, it has also been used successfully and with more efficient metabolite removal. Much can depend on the experience of persons who implement the hemodialysis in the neonatal setting.

Ammonul (sodium phenylacetate–sodium benzoate) is an intravenous plasma ammonia-binding solution that will lower ammonia levels.

**GALACTOSEMIA.** Galactosemia has a prevalence of 1 in 40,000 to 60,000 live births. Individuals with the classical form of galactosemia have a complete inability to metabolize galactose. Galactosemia is an autosomal-recessive condition. The primary defect in the classical form of galactosemia is deficiency of galactose-1-phosphate uridylyltransferase. Deficiency in this enzyme results in an accumulation of galactose-1-phosphate and galactose. In the newborn period, galactosemia

can be lethal within 2 weeks. Many states test for galactosemia as part of the newborn metabolic screening program. However, clinical signs generally emerge before the newborn screening results are available. Clinical features include jaundice, increased reducing substances in the urine, abnormalities in prothrombin time and partial thromboplastin time, and liver dysfunction. The primary cause of death at 1 to 2 weeks of age is *E coli* infection resulting from an affected infant's increased susceptibility to infection.

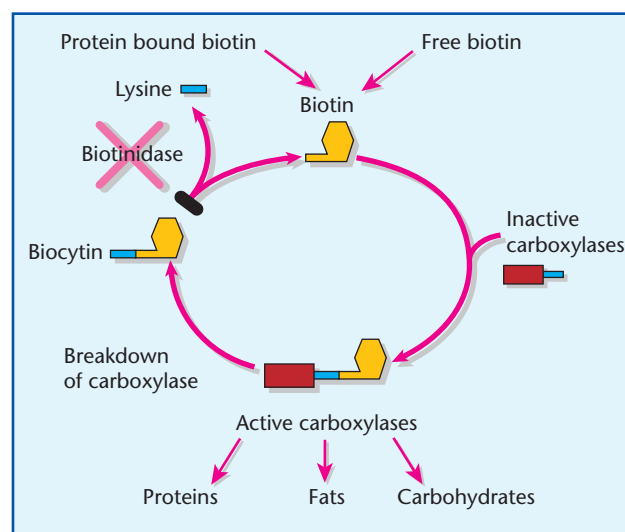
An important fact when considering a diagnosis of galactosemia is that urine-reducing substances will be markedly positive (4 or more urine-reducing substances) in the context of a normal screening using a glucose meter, which is specific for glucose. This circumstance should alert the physician to the fact that the infant is excreting a sugar other than glucose into the urine. Care must be taken in performing invasive procedures such as a lumbar puncture in a neonate because the associated hepatic dysfunction may cause a severe coagulopathy and bleeding. Despite the importance of evaluating the infant for possible meningitis, affected infants are at significant risk of intraspinal bleeding that may cause paralysis.

The risk of lethal *E coli* infection is high several days after birth because of increasing accumulation of abnormal metabolites. Once the galactose metabolites are lowered the risk of *E coli* infection is similar to that of the general neonatal population. In the past, authorities thought that tight control of galactose intake would prevent long-term sequelae. However, it is now apparent that older patients with galactosemia are at high risk for specific medical issues despite minimizing galactose intake. Long-term medical complications include speech delays, premature ovarian failure in women, and, in some individuals, onset of tremor and ataxia. These complications have been associated with the *Q188R* mutation, which results in complete absence of the galactose-1-phosphate uridylyltransferase enzyme.

The primary goal in management of neonates suspected of having or diagnosed with galactosemia is to minimize galactose intake. Because breast milk and standard cow milk-based infant formulas contain lactose, these feedings must be stopped. Lactose is a disaccharide that consists of glucose and galactose. Metabolism of lactose releases the galactose, resulting in elevations in galactose metabolites. Soy milk-based infant formulas do not have galactose and provide a safe alternative infant feeding. If a neonate has clinical manifestations of galactosemia, then a sepsis evaluation should be performed even after they are placed on a soy milk formula. Blood and urine cultures should be obtained, but a spinal tap should be avoided, given the risks noted previously, until results of coagulation studies confirm normal coagulation.

Long-term dietary management requires intensive nutritional counseling to avoid galactose-containing foods. The goal of the diet is to incorporate soy-based products and to avoid galactose-containing products. Individuals with galactosemia must remain on this diet for life.

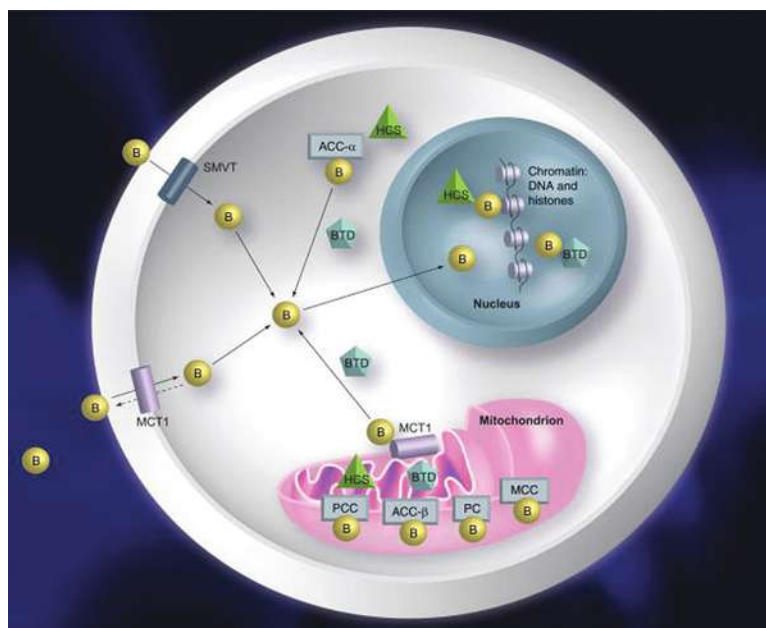
**FRUCTOSEMIA.** Fructosemia does not occur in the neonatal period but surfaces when sucrose, fructose, or fruits are introduced in the infant's diet.



**Figure 106-9** The biotin cycle has not yet been localized to a specific cellular compartment; therefore this cycle is not displayed on the master biochemical pathway figure.

**BIOTINIDASE DEFICIENCY.** Biotinidase deficiency is an autosomal-recessive condition with a prevalence of approximately 1 in 60,000. The gene for biotinidase is located on chromosome 3q25. Biotinidase is an enzyme involved in the generation and maintenance of biotin, an essential water-soluble vitamin. Figure 106-9 reveals how biotinidase is generated. Biotin is an essential cofactor that covalently binds to the  $\epsilon$ -amino group of a specific lysine residue to 5 carboxylases: pyruvate carboxylase, 3-methylcrotonyl-CoA carboxylase, propionyl-CoA carboxylase, and the 2 identified isoforms of acetyl-CoA carboxylases have been identified—acetyl-CoA carboxylase  $\alpha$  and acetyl-CoA carboxylase  $\beta$ . The functional activity is shown by the red-circled enzymes in Figure 106-8. Each biotin-dependent carboxylase has distinct roles involving amino acid synthesis, fatty acid biosynthesis/oxidation, and gluconeogenesis. Propionyl-CoA carboxylase and 3-methylcrotonyl-CoA carboxylase are important for protein metabolism; pyruvate carboxylase is localized in the mitochondria and is key for gluconeogenesis and acetyl CoA carboxylase  $\alpha$  is required for fatty acid synthesis while acetyl-CoA carboxylase  $\beta$  is required for fatty acid oxidation in the mitochondria. Figure 106-10 illustrates the role of biotinidase, the sodium-dependent multivitamin transporter and holocarboxylase synthetase in the homeostasis of biotin. Infants with biotinidase deficiency may become symptomatic within several days to several months after birth. The deficiency can occur acutely with seizures, vomiting, diarrhea, feeding difficulties, tachypnea from acidosis, and apnea. Laboratory findings may include hyperammonemia, ketolactic acidosis, and organic aciduria. If biotinidase deficiency is not detected early and treatment initiated, then late manifestations of biotinidase deficiency may cause hypotonia, ataxia, hearing loss, optic atrophy, alopecia, abnormalities in cellular immunity, basal ganglia





**Figure 106-10** Biotin and its homeostasis. (From Zemleni J, Hassan YI, Wijeratne SS. Biotin and biotinidase deficiency. *Expert Rev Endocrinol Metab.* 2008;3:715–724. Reprinted with permission of FUTURE DRUGS LTD.)

calcifications, intellectual disability, skin rash, and seborrheic dermatitis. Newborn screening for biotinidase deficiency is performed in most states.

Treatment involves large doses of biotin: 20 mg/day is usually sufficient for life. Biotin supplementation prevents all of the disease manifestations. In some cases, with neonatal onset, seizures may begin during the first few days of life, necessitating antiepileptogenic medication in addition to supplemental biotin. Usually, as the biotin takes effect, the seizure medication can be discontinued.

**ORGANIC ACIDEMIAS.** The organic acidemias are a set of conditions that tend to occur in a similar way and have similar treatments. Organic acids form from the breakdown of branched-chain amino acids, methionine, and threonine in most cases. In individuals with enzyme deficiencies, accumulation of intermediate metabolites can cause severe illness and death. Affected infants tend to exhibit severe acidosis within several days of life. The physician should identify the involved organic acids because treatment includes use of specialized, amino acid–modified (free) infant formulas once the infant is stabilized after acute therapies.

*Methylmalonic acidemia* has a prevalence of 1 in 40,000 to 50,000 live births. It is an autosomal-recessive condition that results from methylmalonyl-CoA mutase deficiency, or it may also result from a defect in cobalamin (vitamin B12) metabolism.

*Propionic acidemia* has a prevalence of 1 in 50,000 to 100,000 live births. It is an autosomal-recessive condition resulting from the deficiency of propionyl-CoA carboxylase, a biotin-dependent enzyme.

*Isovaleric acidemia* has an unknown prevalence. It is an autosomal-recessive condition that results from isovaleryl-CoA dehydrogenase deficiency. This enzyme is

involved in leucine metabolism; however, leucine is not elevated in these individuals because of an irreversible step before isovaleryl-CoA dehydrogenase.

Infants with methylmalonic acidemia and propionic acidemia usually exhibit poor feeding, irritability, respiratory difficulty with tachypnea and labored breathing, severe and repetitive vomiting, cerebral edema, and progression to coma and death over a period of days to weeks. Infants affected by isovaleric acidemia can exhibit the previously listed findings along with a strong *sweaty sock* odor. This sign may not be noticed if the neonate has been catheterized or if the urine is dilute.

**Evaluation.** Laboratory findings of infants with organic acidemias include metabolic acidosis on a blood gas sampling, leukopenia, thrombocytopenia, and ketosis. Hyperammonemia can be present in methylmalonic acidemia and propionic acidemia. Hyperammonemia is thought to be the result of secondary inhibition of the urea cycle by the abnormal metabolites generated. As a consequence, affected individuals may have normal blood urea nitrogen levels despite evidence of dehydration caused by a decreased ability to generate urea.

Diagnosis of an organic acidemia requires analysis of urine organic acid patterns. Characteristic excretion patterns are identifiable for various organic acidemias. Plasma amino acid analysis is significant for a marked elevation of glycine and is the reason for the categorization of methylmalonic acidemia and propionic acidemia as ketotic hyperglycinemias. In isovaleric acidemia, glycine is not elevated, which may be the result of the conjugation of isovaleryl metabolites to form isovalerylglycine. Elevations of valine, methionine, isoleucine, and threonine can be seen in methylmalonic acidemia and propionic acidemia.

**Treatment.** Treatment for methylmalonic acidemia and propionic acidemia involves therapy to lower the level of the elevated plasma organic acid. Beneficial therapies in the acute management of these conditions include dialysis to lower potentially elevated ammonia and the offending plasma organic acid, and L-carnitine in a dosage of 200 to 300 mg/kg/day to bind plasma organic acids and replenish L-carnitine. Natural protein intake should also be limited to 1.0 to 1.2 g/kg/day in the acute decompensation. Additionally, though not routinely available, treatments such as *metabolic* parenteral solutions that do not contain valine, methionine, isoleucine, and threonine and administration of intravenous sodium phenylacetate–sodium benzoate (Ammonul) to correct hyperammonemia may be helpful.

Treatment of isovaleric acidemia is as described for methylmalonic acidemia and propionic acidemia, with the following exceptions: Oral glycine is given at a dose of 500 mg/kg/day to bind isovaleryl metabolites, and parenteral solutions should not contain leucine.

Long-term treatment involves use of specialty commercial formulas to prevent buildup of the offending organic acid. Natural protein is typically maintained at 1.0 to 1.5 g/kg/day, with the remainder of protein and calories provided by the specialty formula.

**UREA-CYCLE DEFECTS.** Urea-cycle defects are a category of conditions that involve primary dysfunction of the urea cycle. Several enzyme deficiencies cause these conditions, and most are autosomal recessive. A notable exception is ornithine transcarbamylase (OTC) deficiency, an inherited X-linked trait that is the most common urea-cycle disorder. This inheritance pattern results in a more severe presentation in male patients, with female patients typically minimally affected, if at all. The prevalence of OTC deficiency is approximately 1 in 80,000 live births. Box 106-10 lists the diagnostic criteria for OTC deficiency.

The clinical presentation of urea-cycle disorders is similar to the presentation of other metabolic conditions. However, acidosis is usually not a presenting component of these conditions. Lactic acidosis may become prominent once the patient becomes critically ill. Presenting signs often include anorexia, irritability, lethargy, vomiting, somnolence, asterixis (rare), obtundation, coma, cerebral edema, and combativeness and disorientation (in older individuals). Death may occur if treatment is not rapid or effective. Laboratory findings of importance are hyperammonemia (usually >150 mcmol/L; can be as high

as 2,000–4,500 mcmol/L), low blood urea nitrogen, and respiratory alkalosis. Metabolic acidosis is *not* present unless the patient is in critical condition. Characteristic amino acid profiles confirm the specific urea-cycle defect.

Acute treatment of urea-cycle disorders involves dialysis to remove the ammonia, provision of calories by administration of 20% lipid solutions, infusions of intravenous sodium phenylacetate–sodium benzoate (Ammonul), and specially formulated formula once oral intake is possible. An infant with OTC deficiency requires infusions of arginine in doses of 200 mg/kg/day and intravenous glucose.

In certain cases, when no response or sluggish response to pharmacologic therapy occurs, the health care professional must consider hemodialysis.

Long-term urea-cycle defects are treated by providing formulas that contain essential amino acids along with natural protein at approximately 1.0 to 1.5 g/kg/day. Typically, affected infants require treatment with oral ammonia-binding agents such as sodium benzoate or Buphenyl to maintain plasma ammonia at an acceptable level. This treatment allows for maintenance of ammonia levels close to the normal range, in most cases, while the individual is well. However, affected patients remain susceptible to transient elevations of ammonia during illness even while on ammonia-binding agents. During episodes of illness, all protein should be stopped for 24 hours and a formula consisting of carbohydrates and fats administered. Protein is gradually reintroduced into the diet once the ammonia level declines. An important point to note is that protein must be given after 24 hours to prevent endogenous protein catabolism and further worsening of the hyperammonemia. If levels are dramatically elevated, then the acute management protocol described previously should be initiated. Depending on the severity of the condition, liver transplant should be considered, especially if the individual does not respond to medical management or requires frequent hospitalizations.

**TYROSINEMIA TYPE 1.** Tyrosinemia type 1 is inherited in an autosomal-recessive manner. Tyrosinemia type 1 results from a deficiency of fumarylacetoacetate hydrolase encoded by the FAH gene, which is the only gene responsible for the disease. Tyrosinemia type 1 has a prevalence of 1 in 1,800 in certain regions of Quebec and is estimated to be approximately 1 in 100,000 elsewhere. Tyrosine is usually metabolized to acetoacetate; however, in classical tyrosinemia type 1, fumarylacetoacetate hydrolase deficiency will result in excess succinylacetone. Succinylacetone is toxic and leads to the clinical findings in tyrosinemia type 1. Type 1 tyrosinemia is an acute-onset disorder that initially produces diffuse liver dysfunction, which without intervention progresses to liver failure and death. Other clinical manifestations include renal tubular dysfunction resulting in growth failure and rickets. This enzyme deficiency results in accumulation of metabolites that require metabolism via alternative pathways.

Acute management of tyrosinemia type 1 has been revolutionized recently with the development of nitisinone (Orfadin) (2-[2-nitro-4-trifluoro-methylbenzoyl]-1,3

#### **BOX 106-10 Ornithine Transcarbamylase Deficiency Diagnosis**

- Low plasma citrulline
- High plasma glutamine
- Ornithine transcarbamylase urine organic acids
- High urinary orotic acid
- Specific hepatic enzyme studies
- DNA analysis

cyclohexanedione). This medication inhibits enzyme function proximal to fumarylacetoacetate hydrolase, preventing the accumulation of fumarylacetoacetate and its conversion to succinylacetone which results in biochemically transforming tyrosinemia type 1 into tyrosinemia type 2. (The enzyme defect in tyrosinemia type 2 is a deficiency of hepatic cytosol tyrosine aminotransferase activity.) Treatment should be started immediately once the diagnosis of tyrosinemia type 1 is confirmed. Tyrosinemia type 2 is a milder form of tyrosinemia that results in cataract formation and skin findings without the hepatic involvement. However, even with administration of nitisinone, plasma tyrosine levels will require continued monitoring and control through dietary intervention to prevent the ocular and skin findings that are associated with tyrosinemia type 2.

Liver transplantation is reserved for patients presenting with severe liver failure that does not respond to nitisinone.

Several commercial formulas are available that do not contain tyrosine. These formulas can be used to control plasma tyrosine levels. Typically, natural protein is kept at 1.0 to 1.5 g/kg/day, with the remainder of protein and calorie requirements provided by the tyrosine-deficient formulas.

**PHENYLKETONURIA.** Phenylketonuria (PKU) does not exhibit acutely in the neonatal period; however, given that PKU is among the most common inborn errors of metabolism, with a prevalence of 1 in 10,000 to 15,000 live births, a brief mention is provided here. The primary defect is in phenylalanine hydroxylase activity, and it results in elevations in phenylalanine. Chronic phenylalanine elevations cause brain injury that may progress to severe intellectual disability if the condition is not treated.

Newborn screening for PKU does not differentiate between the classical form of PKU and rare forms that result from bipterin deficiency. The active form of bipterin, tetrahydrobiopterin, is a cofactor for phenylalanine hydroxylase. Up to 2% of affected individuals with hyperphenylalaninemia have a bipterin abnormality that disrupts neurotransmitter metabolism in addition to phenylalanine metabolism.

PKU was one of the first conditions that was screened for in newborns and was the model condition for dietary management of an inborn error of metabolism. Numerous commercial formulas and low-protein products are available to aid in maintaining plasma phenylalanine concentrations at an appropriate level.

Individuals with bipterin abnormalities do not typically respond to dietary manipulations alone, given that the cofactor deficiency also adversely affects neurotransmitter production. Bipterin deficiency is treated by replacing the precursors to the affected neurotransmitters, folinic acid in some cases, and providing the active form of the cofactor, tetrahydrobiopterin. For some affected patients, treatment with tetrahydrobiopterin may make additional therapy unnecessary. A growing body of evidence indicates that up to 10% of individuals with phenylalanine hydroxylase deficiency may be responsive to tetrahydrobiopterin.

**MAPLE SYRUP URINE DISEASE.** Maple syrup urine disease (MSUD) has an approximate prevalence of 1 in 120,000 to 500,000 live births. The highest incidence occurs in the Mennonite population in Pennsylvania, affecting approximately 1 in 176 newborns. MSUD is an autosomal-recessive condition; its primary defect is in the metabolism of the branched-chain amino acids, including isoleucine, leucine, and valine. The enzyme involved is branched-chain alpha-keto dehydrogenase complex. Acute clinical signs begin several days after birth when branched-chain amino acids accumulate as infants increase their feeding intake. Presenting signs include poor feeding, irritability, and stereotypical seizures characterized by bicycling motions of the arms and legs. In addition, the infant and the infant's urine have an odor of maple syrup. Lethargic infants rapidly progress to coma and death.

Therapy involves extracting the branched-chain amino acids from plasma, thereby reducing total body concentration of these amino acids. Dialysis is necessary to reduce the elevated amino acid levels rapidly in an affected neonate. Peritoneal dialysis has been shown to be safe and effective in lowering these amino acids; however, in severe cases, hemodialysis may be necessary. Once the leucine level is reduced to approximately 10 mg/dL, dialysis can be discontinued. Thereafter, the treatment goal is to maximize caloric intake to prevent catabolic breakdown of endogenous proteins, resulting in continued elevations of the branched-chain amino acids. Initially, 20% lipid solutions in a dose of 2 g/kg/day are administered in conjunction with 12.5% to 20% dextrose to prevent catabolism. Parenteral nutrition solutions without branched-chain amino acids are used to control branched-chain amino acid levels while enteral nutrition is implemented.

A thiamine (vitamin B1)-responsive form of MSUD has been identified. Thiamine supplementation corrects the enzyme deficiency, resulting in the ability to tolerate normal protein in normal amounts. Usually, 10 mg/day of thiamine will correct the hyperbranched-chain aminoaciduria without the need for dietary intervention.

In cases in which thiamine does not have any effect, several commercial formulas are available that do not contain the branched-chain amino acids, which can be used as a protein source. Additional calories can be provided by other specialty formulas that contain only fats and carbohydrates. As the branched-chain amino acids decline into the physiologic range, small amounts of natural protein are required in the form of a standard formula to prevent branched-chain amino acid deficiencies. Natural protein can be started at 1.0 to 1.25 g/kg/day and then adjusted to keep the branched-chain amino acid levels within normal range. The remainder of protein requirements, 2.5 to 3.0 g/kg/day, can be achieved with the specialty formula that lacks the branched-chain amino acids.

Long-term management of MSUD involves a low-protein diet, continued use of specialty formulas, and intensive monitoring of plasma isoleucine, valine, and leucine levels.

**HOMOCYSTINURIA.** Homocystinuria has a prevalence of approximately 1 in 200,000. It is an autosomal-recessive condition. Most newborn screening programs

test for plasma methionine concentrations to evaluate for the presence of the condition, given that methionine is elevated in individuals with homocystinuria. However, methionine can be elevated in a variety of conditions that cause liver disease, or it may occasionally be transiently elevated in the newborn. Cystathionine  $\beta$ -synthase is a critical enzyme in the metabolism of homocysteine. Deficiency of cystathionine  $\beta$ -synthase is the most common cause of homocystinuria. Cobalamin plays a critical role in the formation of cofactors for the metabolism of methylmalonic acid and homocysteine.

The acute findings in homocystinuria include thromboembolism and seizures. Homocysteine is an endothelial irritant that causes lesions resulting in intravascular clot formation. High concentrations of plasma homocysteine can lower seizure thresholds and may be noted as a presenting symptom. Untreated or inadequately treated patients develop intellectual disability and developmental delay, psychiatric disorders, ectopia lentis, scoliosis, and osteoporosis. Fifty percent of affected individuals die before the age of 25 years.

Approximately 50% of individuals are responsive to vitamin B6, a cofactor for cystathionine  $\beta$ -synthase. Individuals who respond to vitamin B6 do well and do not require further treatment. Nonresponders to vitamin B6 therapy must be maintained on a restricted methionine and cystine diet for life. Natural protein intake at 1.0 to 1.5 g/kg/day via a low-protein diet and formula are necessary. Betaine, a trimethylglycine, is formed through the oxidation of choline and has shown promising results in the management of individuals with homocystinuria. It converts homocysteine to methionine and permits reduction of the dietary restrictions. Experts recommend that methionine

levels be kept below 1,000  $\mu\text{mol/L}$  to prevent cerebral edema. Studies have not yet been conducted on neonates or infants to evaluate for safety of this therapy.

**COBALAMIN DISEASE.** Seven subtypes of cobalamin (Cbl) disorders, designated Cbl A through G, have been identified. This group of cobalamin disorders can cause elevations in methylmalonic acid only (Cbl A and B), a combination of methylmalonic acid and homocysteine elevations (Cbl C, D, and F), or homocysteine elevations only (Cbl E and G). These disorders result from abnormal Cbl (vitamin B<sub>12</sub>) metabolism or transport.

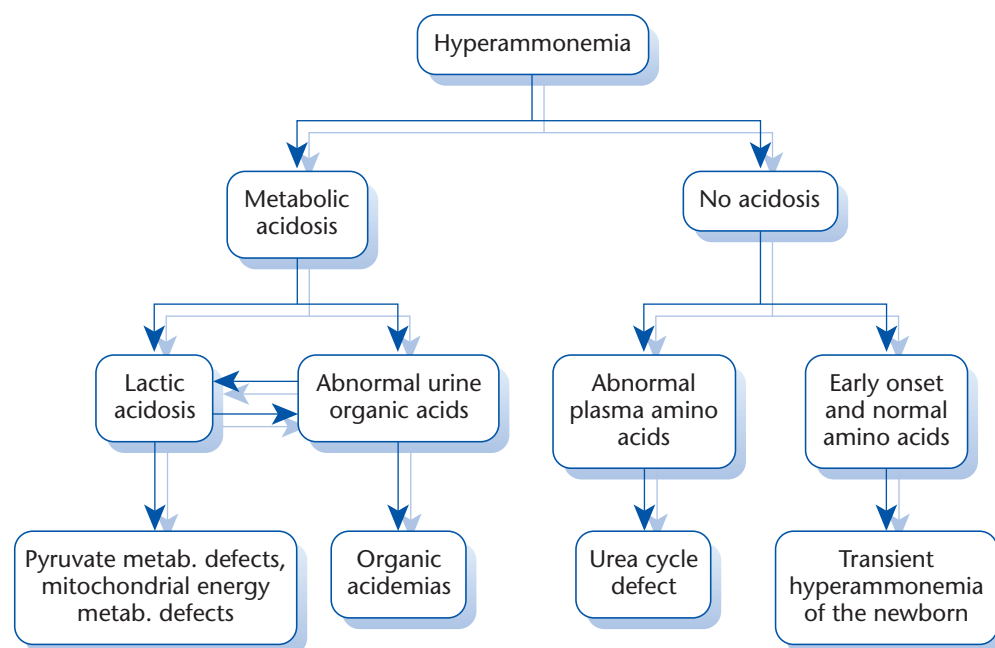
Administration of hydroxycobalamin, the active form of Cbl, corrects the biochemical abnormalities and usually allows for a complete recovery. Hydroxycobalamin is administered subcutaneously.

#### **PYRUVATE-DEHYDROGENASE COMPLEX DEFICIENCY.**

The pyruvate-dehydrogenase complex plays a critical role in metabolizing the product of glycolysis, pyruvate, to acetyl-CoA. Pyruvate-dehydrogenase complex deficiency is a mitochondrial disorder that can exhibit acutely in the neonatal period with a severe lactic acidosis. X-linked and autosomal-recessive forms have been identified. This condition is not currently screened for on state newborn metabolic testing; however, prompt intervention can minimize the effects of accumulating toxic metabolites.

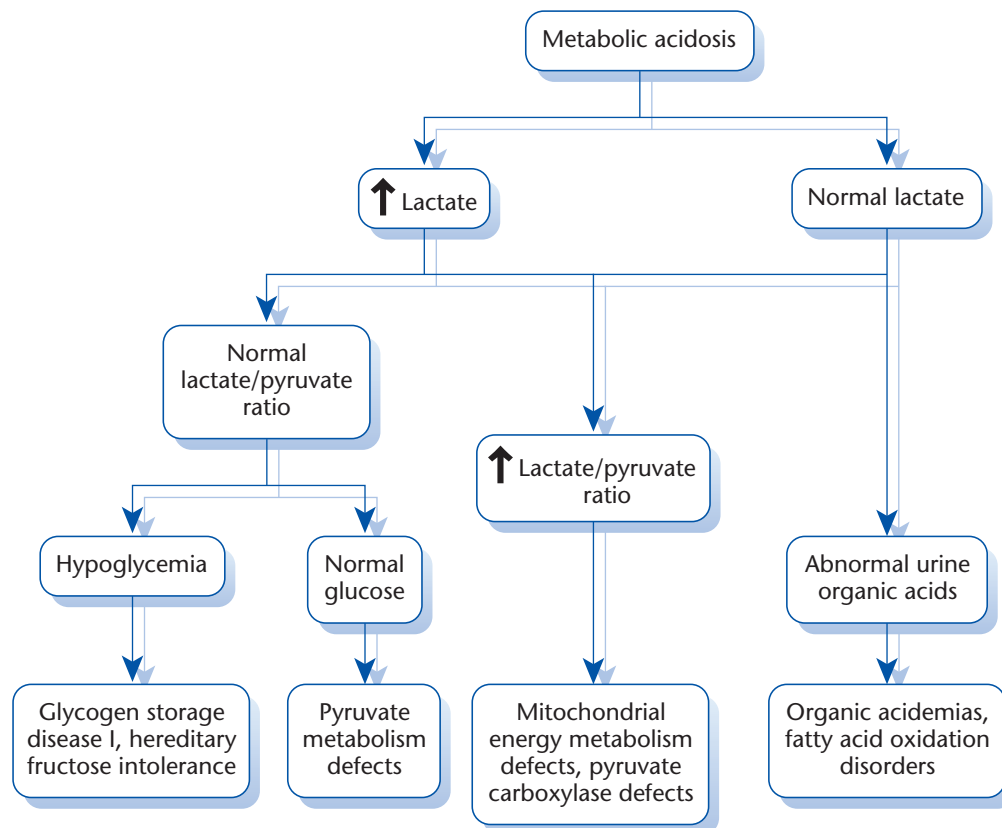
Minimizing carbohydrate and glucose intake lowers the levels of lactic acid. Formulas that are high in protein and fat are commercially available. Five-percent dextrose is tolerated well; however, higher glucose concentrations can cause increased lactate levels. As long as the lactate is controlled, these infants have a good chance of surviving the neonatal period.

The algorithms shown in Figure 106-11, Figure 106-12, and Figure 106-13 can assist the physician with inborn

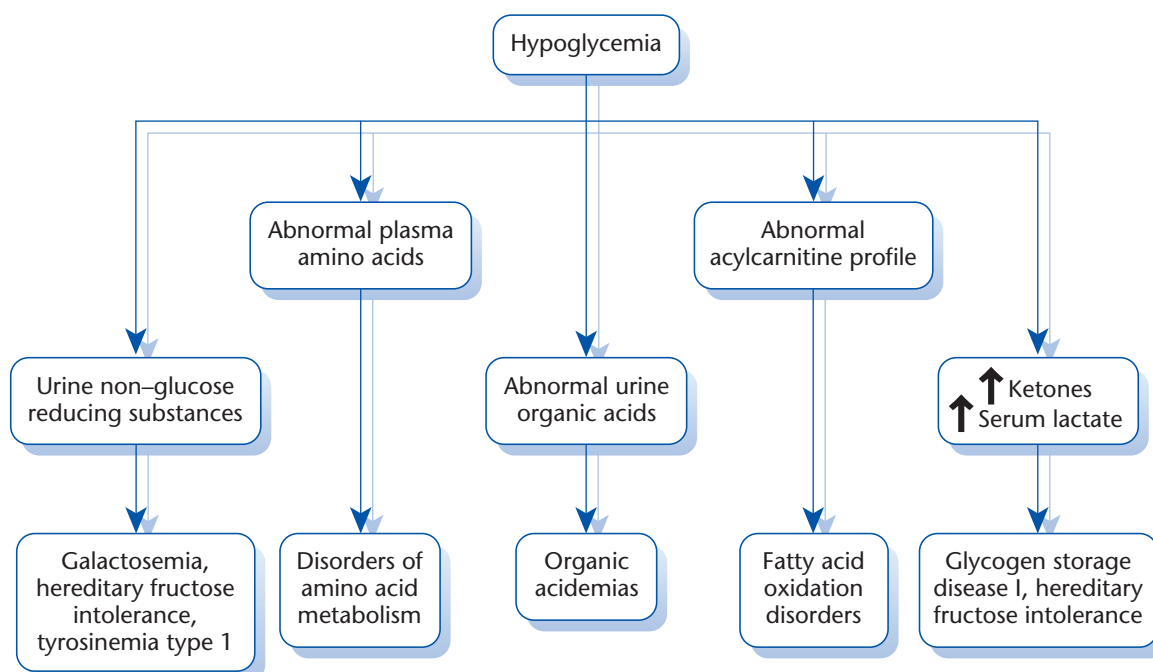


**Figure 106-11** Algorithm for evaluation of hyperammonemia





**Figure 106-12** Algorithm for evaluation of metabolic acidosis



**Figure 106-13** Algorithm for evaluation of hypoglycemia

errors of metabolism presenting with hyperammonemia, metabolic acidosis, and hypoglycemia.

Unfortunately, stressful situations will occur when a newborn infant suspected of having an inborn error of metabolism deteriorates rapidly with impending death before a definitive diagnosis is established. When the physician is presented with this clinical scenario it becomes imperative to establish a diagnosis. Doing so will help the family in 2 major ways: first, by bringing closure to the cause of their baby's death, and second, by providing valuable information for future pregnancies. Table 106-10 provides various samples that should be set aside for future testing. Keep in mind that enzyme activity diminishes rapidly. For proper perimortem sample analysis it is important that the samples are processed rapidly and efficiently with advanced notification of appropriate laboratories. This will ensure that errors in handling will not occur. Consultation with a geneticist is recommended to assist in the ordering and handling of the proper biochemical analysis.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *These Tests Could Save Your Baby's Life—Newborn Screening Tests* (handout), Health Resources and Services Administration, US Department of Health and Human Services ([www.medicalhomeinfo.org/downloads/pdfs/NewbornScreeningtests.pdf](http://www.medicalhomeinfo.org/downloads/pdfs/NewbornScreeningtests.pdf))
- *Newborn Screening Disorders—What Parents Want to Know About Newborn Screening Disorders* (handout), (brochure), Health Resources and Services Administration, US Department of Health and Human Services ([www.medicalhomeinfo.org/downloads/pdfs/Newbornscreeningdisorders.pdf](http://www.medicalhomeinfo.org/downloads/pdfs/Newbornscreeningdisorders.pdf))
- *Genetics Home Reference* (Web site), US National Library of Medicine

### Medical Decision Support

- *Newborn Screening ACT Sheets and Confirmatory Algorithms* (algorithm), American College of Medical Genetics ([www.ncbi.nlm.nih.gov/books/NBK55827](http://www.ncbi.nlm.nih.gov/books/NBK55827))
- *Newborn Screening* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/ncbddd/pediatricgenetics/newborn\\_screening.html](http://www.cdc.gov/ncbddd/pediatricgenetics/newborn_screening.html))
- *GeneReviews* (e-book), ([www.ncbi.nlm.nih.gov/books/NBK1116](http://www.ncbi.nlm.nih.gov/books/NBK1116))
- *GeneTests* (Web site), ([www.genetests.org](http://www.genetests.org))
- *Online Mendelian Inheritance in Man* (Web site), Johns Hopkins University ([omim.org](http://omim.org))

### SUGGESTED READINGS

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**Table 106-10** Perimortem Biochemical Samples Collected in a Dying Neonate Suspected With an Inborn Error of Metabolism

SAMPLES SET ASIDE FOR FUTURE TESTING	BIOCHEMICAL TESTS TO CONSIDER
Plasma (at least 5 mL) freeze $-20^{\circ}\text{C}$ Red cells (refrigerate $4^{\circ}\text{C}$ )  Green top tube 4 blood spots on Guthrie card Urine (10–20 mL) freeze $-20^{\circ}\text{C}$ Skin biopsy in sterile saline or in culture medium at room temperature (caution: preservatives and antiseptics are toxic to cell growth) <sup>a</sup>	Amino acid analysis, carnitine levels, acylcarnitine profile Electrolytes, growth hormone, cortisol, insulin level, lactate, ammonia Karyotype  Urinalysis, urine reducing substances, organic acid analysis
WITH PROPER CONSENT, PERIMORTEM SAMPLES	
Unfixed liver tissue immediately frozen at $-20^{\circ}\text{C}$ <sup>a</sup> Muscle biopsy immediately frozen below $-20^{\circ}\text{C}$ <sup>a</sup>	

<sup>a</sup>Use chlorhexidine to prepare skin; avoid betadine, which inhibits tissue growth.

## Chapter 107

THE NEWBORN WITH  
NEUROLOGIC FINDINGS

Oranee Sanmaneechai, MD; Aleksandra Djukic, MD, PhD

*If the infant is pushed slightly and bent forward a few minutes after birth, he will make his first steps. Nevertheless, the newborn is capricious and does not always walk to order. Well disposed at one moment, he is no longer so the next. The examiner is discouraged and gives up; then he tries a last time—the baby starts walking immediately, perfectly regularly and over a long distance.*

—ANDRE-THOMAS AND AUTGAERDEN (1966)

Neurologic examination of the neonate is a complex task; findings depend on age, behavioral stage, and position. Neuronal mechanisms of a newborn are inconsistent, with responses varying from moment to moment. Despite the objective difficulties, when the approach to the neurologically impaired neonate is well thought out and accommodates the individual baby, relevant and reliable information can be obtained (Box 107-1). A thorough knowledge and understanding of the normal development of the infant and young child is fundamental to anyone concerned with the care of children.

The main stages of brain development are illustrated in Figure 107-1. During and after the third trimester of pregnancy, at the time when the fetus becomes viable, all neurons have already migrated to their final destinations. The main developmental events during this period are the following: First, glial cells proliferate in the periventricular germinal zone, which is immature and therefore exquisitely vulnerable. Second, synaptogenesis allows neurons to talk to each other. Insufficiency of synaptic connections is partially the basis of difficulties in the

assessment. The relation between stimulus and response is often not consistent. Third, myelination develops, which will, when the child is older, enable faster and more reliable communication not only between neurons but also between the child and another person. Fourth, apoptosis, or the programmed elimination of neurons that are normally produced in excess, occurs.

A neonate's neurologic organization differs greatly from that of the older child. Initial assessment of the neonate should be based on the following fundamental principles: developmental stage of the infant, assessment adjusted to the expected level of maturity, and differential diagnosis focused on treatable conditions for which a delayed response caused by awaiting consultation with a specialist might alter the prognosis.

## EVALUATION

The goal of evaluation is not only to identify pathologic findings but also to assess the degree of neurologic maturity. This task can be accomplished by careful observation of the quality of spontaneous, endogenously generated movements of the neonate. A rapidly accumulating body of evidence has proved that the spontaneous motility of preterm and term infants, which is in continuity with fetal movements, is of great clinical significance. Spontaneous motility is an important indicator of brain dysfunction at an early age, and it tells us more about the young nervous system than reflex testing. Observation is the most important part of any examination. Expected findings vary with the infant's developmental maturity and may be influenced by in utero environmental conditions such as uteroplacental insufficiency and maternal drug or other exposures, or intrinsic fetal factors, such as brain maldevelopment. The examiner plays an active role in eliciting and quantifying both behavioral and motor responses. Items included in assessment of the preterm and full-term newborn are listed in Box 107-2. The ideal time for the examination is 2 to 3 hours after feeding, when the infant is in a period of quiet wakefulness. Except for lip, glabella, anal, and cremasteric reflexes, which can be elicited regardless of behavioral state, all other reflexes correlate with the level of alertness.

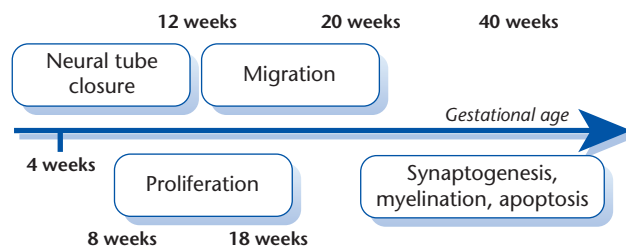
Developmentally, palmar grasp (weak) and Moro reflex (not full) first appear at 28 weeks' (28<sup>0</sup>/<sub>7</sub>–28<sup>6</sup>/<sub>7</sub> weeks)

**BOX 107-1** Neurologic Examination  
of the Neonate**OBSERVATION PERIOD**

- Observation of unprovoked, spontaneous activity
- Qualitative assessment
- Passive role of the examiner

**EXAMINATION PERIOD**

- Response to provoked external stimuli
- Quantitative approach
- Active role of examiner

**Figure 107-1** Main stages of brain development.

**BOX 107-2 Assessment of the Preterm and Full-Term Newborn****EXAMINATION OF THE HEAD**

- Fontanels
- Occipitofrontal (head) circumference
- Skull shape, deformations, and defects
- Evidence of trauma (cephalohematoma, subgaleal hemorrhage, skull depression or deformation, forceps or vacuum injury)

**HABITUATION**

- Light
- Sound

**MOVEMENTS AND TONE**

- Posture
- Arm and leg recoil and traction
- Popliteal angle
- Head control
- Head lag
- Ventral suspension
- Head raising in prone position
- Arm release in prone position

- Spontaneous body movements
- Tremors and startles
- Abnormal body movements

**REFLEXES**

- Deep tendon reflexes
- Palmar grasp
- Rooting
- Sucking
- Walking
- Moro reflex

**NEUROBEHAVIORAL**

- Eye appearance (pupillary light responses, position, movements)
- Auditory and visual orientation
- Alertness
- Defensive reactions
- Irritability
- Consolability

gestation. Deep tendon reflexes are already present at this time. Asymmetrical tonic neck reflex, stepping reflex, and stronger sucking can be recorded from 34 weeks. The healthy term baby has a strong grasp (the infant can be lifted off the bed), full Moro reflex, and placing reflex. The limbs are semiflexed, and the lower limbs are in slight adduction at the hips. When the child is prone, the head may be lifted off the surface and turned to the side. Visual fixation and tracking, which is still not smooth, are present.

**SEIZURES**

*Seizures* are clinical manifestations of temporary alterations in brain function that occur as a result of excessive synchronous neuronal electrical discharge. In the newborn, seizures represent an emergency for 2 main reasons: they indicate significant dysfunction or damage to the immature brain, and they can further interfere with the process of normal neurologic maturation.

The most important single determinant of prognosis in neonates with seizures is their cause. Immediate and thorough investigation for potentially treatable causes and early institution of cause-specific therapy may mitigate the development of long-term sequelae. The initial differential diagnosis is guided by 2 main questions: (1) Is the concerning event epileptic or nonepileptic? (2) If epileptic, then was it provoked? A detailed history and basic laboratory workup are often sufficient diagnostic tools with direct therapeutic implications.

Clinical suspicion that the event is a seizure should be based on the occurrence of paroxysmal, stereotypical, repetitive, and abnormal events. The signs of seizures in the neonate may be different from those in

older children and adults; this difference is the result of the immature state of the central nervous system (CNS) before the final cortical architecture, synaptic networks, and myelination have been attained.

Newborns rarely have well-organized, generalized tonic-clonic seizures; instead, their seizures are characterized by multifocality, asynchrony, disorganized pattern of propagation, and subtle oral-buccal, bicycling, stepping, pedaling, or ocular movements. However, none of the clinical characteristics is specific; based on the characteristics of movements only, events associated with gastroesophageal reflux or those during sleep are often clinically indistinguishable from seizures. Information about the setting in which they occur, reactivity to external stimuli, associated features, and electroencephalographic (EEG) characteristics is more specific.

Nonepileptic events may include jitteriness, characterized by rhythmical tremor as a dominant movement that can be stopped by restraint, is not accompanied by autonomic changes or ocular signs, and is especially sensitive to stimulus. Jitteriness may be caused by hypoglycemia, hypocalcemia, neonatal encephalopathy, or drug withdrawal, but in some cases the cause cannot be determined. Benign neonatal sleep myoclonus occurs only during sleep. The phenomenon disappears spontaneously, and the child's development is normal. Tonic fits associated with gastroesophageal reflux are linked to feeding. Hyperekplexia (familial startle syndrome) is characterized by abnormal response to unexpected stimuli associated with sustained tonic spasms or exaggerated startle with additional generalized hypertonia.

The main causes of epileptic seizures include hypoxia-ischemia, intracerebral hemorrhage, brain



**BOX 107-3 Main Categories of Neonatal Hypotonia****PERIPHERAL OR MOTOR UNIT HYPOTONIA**

- Muscle diseases (congenital myopathies, congenital muscular dystrophies, myotonic dystrophy)
- Neuromuscular junction diseases (transient neonatal myasthenia gravis, congenital myasthenic syndrome, infantile botulism)
- Peripheral nerve diseases (hereditary motor and sensory neuropathies)
- Anterior horn cell disease (spinal muscular atrophy)

**CENTRAL HYPOTONIA**

- Brain and spinal cord (acute injuries or congenital)
- Chromosomal disorders (Down syndrome, Prader-Willi syndrome, other genetic syndromes)

**METABOLIC OR ENDOCRINE DISORDERS**

- Metabolic disorders (amino acid, organic acid, lactic acid, glycogen storage disorder, mitochondrial disorders)
- Endocrine disorders (hypothyroidism)

infarction, metabolic disorders (ie, hypoglycemia, hypomagnesemia, hypocalcemia), infection, inborn error of metabolism, congenital malformation, genetic predisposition, neonatal abstinence syndrome from in utero drug exposure, and pyridoxine dependency. An important point to keep in mind is that several factors may contribute to the onset of seizures in a single infant. Because most neonatal seizures occur in a provoked setting, when the provocative factor is corrected, they are usually short lived.

Benign familial and nonfamilial neonatal seizures are neonatal epileptic syndromes defined by a favorable outcome. The classic phenotype of benign familial seizures is a neonate born after an uneventful pregnancy and delivery with onset of tonic-clonic seizures during the first 2 weeks of life, intact neurologic function between seizures, and a family history of seizures (autosomal-dominant inheritance). In the absence of family history and an identifiable cause, when seizures in an otherwise healthy neonate appear between 3 and 7 days of age (*fifth-day fits*), diagnosis of benign neonatal nonfamilial convulsions can be proposed. The interictal EEG pattern is either normal or moderately altered. Both syndromes can only be diagnosed after excluding provocative factors.

Early infantile epileptic encephalopathy and early myoclonic encephalopathy are severe neonatal epilepsies characterized by onset during the first days or weeks of life, severe seizures that do not respond to medication, a burst-suppression EEG pattern, and a poor prognosis.

In addition to the laboratory tests that should be performed urgently (determination of blood glucose, sodium, potassium, calcium, phosphorus, and magnesium levels; lumbar puncture), the workup includes EEG and imaging studies. Magnetic resonance imaging is preferable for detecting possible abnormal structural brain malformations and anomalies. The need for further, more extensive workup is determined by the results of the initial tests.

Clinical observations and the precise characterization of neonatal seizures form the basis for their rational evaluation and therapy. Treatment strategy and duration should be based on the cause and severity of seizures. Treatment based on the specific cause of seizures should always be considered first. The initial antiepileptic medications are phenobarbital followed

by phenytoin and diazepam. Duration of treatment depends on the etiology. It is short term for a provoked seizure or benign neonatal seizure. Medications are usually provided for 2 to 3 months. Long-term antiepileptic medication is needed for the severe epileptic syndromes or congenital cerebral malformations.

## DISORDERS OF MUSCLE TONE AND MOVEMENT

*Tone* refers to resistance of skeletal muscles to passive movement and also to muscle tension at rest. Tone deficiency, or *hypotonia*, is among the most common neurologic signs in the neonate. It can be caused by a dysfunction at any level of the nervous system, from the muscles to the cortex of the brain, and it can result from drugs administered to the mother (benzodiazepines) or from genetic or metabolic disorders (Box 107-3). Initial assessment that focuses on the presence or absence of reflexes, weakness, associated systemic signs, and dysmorphic features is helpful. Based on the combination of answers to these simple questions, planning of further workup and treatment can be approached.

In primary disorders of the muscle (congenital myopathy, congenital muscular dystrophy, myotonic dystrophy), neonates are hypotonic, weak, and typically areflexic.

Congenital myopathies are a group of primary muscle diseases with abnormalities of muscle structure or function. They present with hypotonia, weakness, and facial muscle weakness. Muscle biopsy can help to identify the presence of abnormal muscle structures such as central core, nemaline rod, and centronuclear. Genetic testing for many of these conditions is available.

Congenital muscular dystrophies present with muscle weakness, respiratory difficulty, and contractures, with variable involvement of the eyes, brain, and other tissues. Patients with these conditions have high creatine kinase and dystrophic muscle, with signs of muscle necrosis and regeneration on biopsy.

Myotonic dystrophy is an autosomal-dominant condition and a cause of neonatal hypotonia. Family history of myotonic dystrophy or maternal signs of disease such as myotonia are clues to diagnosis. The definite diagnosis can be made by genetic testing.

Testing should be done in the event of unexplained hypotonia because the disorder might not have been diagnosed yet in the family. These diseases are chronic, and the care in the neonatal period is supportive.

Neuromuscular junction disorders, including infant botulism and transient neonatal myasthenia gravis, are treatable but potentially life-threatening disorders. Therefore, the physician needs to recognize the symptoms of these conditions early.

Myasthenic infants are hypotonic and weak, although their deep tendon reflexes are present. Transient neonatal myasthenia gravis occurs in 10% to 15% of infants born to myasthenic mothers as a result of transplacental transfer of circulating acetylcholine receptor antibodies from the mother to the fetus. The severity of the mother's disease has no relationship to the severity of the neonate's disease. Symptoms typically appear within the first day of life with hypotonia, feeding difficulties, trouble breathing, feeble cry, facial weakness, and oculomotor problems. Diagnosis is confirmed by positive antibodies to acetylcholine receptor, repetitive nerve stimulation test, and clinical response to anticholinesterase medications. The condition is self-limited; it completely resolves within a few weeks and does not recur. Treatment is supportive, with anticholinesterase inhibitors.

Congenital myasthenic syndromes represent a heterogeneous group of nonautoimmune diseases caused by genetic defects that affect neuromuscular transmission. They are typically of autosomal-recessive inheritance. Response to anticholinesterase inhibitors is variable. A classification system of congenital myasthenic syndromes based on molecular genetics is established.

Botulism occurs when ingested spores of *Clostridium botulinum* colonize and grow in the infant's large intestine and produce botulinum neurotoxin. It causes constipation, weakness (notably of gag, cry, suck, and swallow), ptosis, autonomic (pupillary) abnormalities, loss of muscle tone, and difficulty breathing. Symptoms typically appear between 18 and 36 hours after the infant is infected by the bacteria and between 3 weeks and 6 months of life. A human-derived botulism antitoxin, intravenous botulism immunoglobulin, is a safe and effective treatment that has been licensed by the US Food and Drug Administration as Baby-BIG. Treatment should be provided as soon as possible because its efficacy may decrease over time as motor nerve intoxication proceeds.

Spinal muscular atrophy is among the most common neuromuscular disorders in childhood; it is progressive. Pathologically, spinal muscular atrophy is characterized by degeneration of anterior horn cells of the cord and of the bulbar motor nuclei. This disorder has autosomal-recessive inheritance. The affected infants are hypotonic, weak, and areflexic. They have trouble breathing as a result of weakness of their intercostal muscles, and they have feeding difficulty. Cognition and facial expression are normal. In spinal muscular atrophy type I, which has its onset before 6 months of age, the infant has no ability to sit and rarely survives beyond the first 2 years of life. A genetic blood test confirms diagnosis and should be performed early to guide the family appropriately.

In severely hypotonic infants with paraplegia and urinary retention, spinal cord injury should be

screened for with imaging studies in the appropriate clinical setting.

Genetic or syndromic conditions in a hypotonic infant are considered based on dysmorphic features, systemic signs, presence of deep tendon reflexes, and often absence of weakness. Neonatal hypotonia or floppiness at birth in an infant with weak cry and decreased activity are highly suggestive of Prader-Willi syndrome (PWS). This disorder occurs in 1 in 10,000 to 15,000 live births and should be considered in any neonate who exhibits generalized hypotonia. Infants with PWS often have a history of breech or other abnormal presentation, decreased or atypical fetal movement patterns, excessive sleepiness, poor sucking reflexes, and feeding difficulties in the newborn period. Profound hypotonia may lead to severe respiratory compromise. Other common features include a weak cry and genital hypoplasia (cryptorchidism, small penis, scrotal hypoplasia, small labia minora, and clitoral hypoplasia). PWS is caused by deletions on the paternal chromosome 15, uniparental disomy of the maternal chromosome 15, and, rarely, imprinting defects. Molecular genetic testing is required to confirm the diagnosis.

Some hypotonic infants have CNS disorders, and in these cases hypotonia is accompanied by other signs of CNS involvement, such as lethargy or seizures. Decrease in muscle tone is an immediate response to severe CNS injury. Increased tone is a delayed consequence. Therefore hypertonia, which is a common neurologic problem in children, is far less common in neonates. Acute CNS injury of any cause (vascular, metabolic, infectious) can cause a depression of nervous functions during the initial phase. Motor responsiveness improves, and an increase in tone develops over the course of weeks.

*Hypertonia* refers to increased resistance to passive movement and is caused by a lesion between the cerebral cortex and the anterior horn cells at the level of the spinal cord. The syndrome of upper motor-neuron dysfunction consists of increased muscle tone, weakness, and hyperreflexia.

Hypoxia-reperfusion injuries to the brain in both preterm and term infants are among the main causes of upper motor neuron syndrome. Interestingly, the same pathophysiologic event that causes similar long-term consequences also causes different types and patterns of cellular injury at different ages. Selective neuronal necrosis that is most prominent in the watershed areas is the pathologic substrate in the term neonate. Lesions in a periventricular distribution in the white matter are also caused by hypoxia and reperfusion in the preterm baby. Therefore, topographic distribution of the weakness and hypertonia varies according to the site, extent of injury, and age of the infant. These injuries typically develop in the form of either hemiplegia or quadriplegia in the term neonate and diplegia in the preterm neonate. One of the etiologies of static encephalopathy, spastic quadriplegia, or cerebral palsy is a neonatal hypoxic ischemic encephalopathy (HIE), an acute encephalopathy caused by cerebral ischemia and hypoxemia, which result from perinatal asphyxia. Clinical presentation of HIE includes encephalopathy, seizures, hypotonia, or hypertonia. Treatment of HIE is mainly supportive. Selective head cooling (by cool cap) is a novel and promising treatment approved by the US

Food and Drug Administration in January 2009 for treatment of the full-term infant with moderate to severe HIE. Selective brain hypothermia (temperature 34.5°C) during the period between 6 and 72 hours of age slows the metabolism and reduces energy requirements, acting through a neuroprotective effect. About 75% to 96% of infants with severe HIE have neurologic disabilities, including spastic quadriplegia, cognitive deficit, seizure, hearing loss, and death. Therapeutic hypothermia has been found to improve mortality and morbidity in these patients. Brain cooling is done in the hospital by a neonatologist using complex instruments, continuous monitoring, and close assessment of various organ systems, but not all hospitals in the United States have these facilities. Family physicians caring for future mothers specifically at risk to give birth to an infant with asphyxia should be aware of their regional brain cooling centers. Mothers at risk for having a newborn with severe HIE who might benefit from hypothermia treatment are those with chronic systemic disease resulting in uteroplacental insufficiency, placenta previa, or abruptio placenta. Prompt evaluation and immediate treatment are crucial to reduce morbidity and mortality and to facilitate optimal development of the infant.

Cerebrovascular accidents (ischemic or hemorrhagic) lead to focal brain lesions and focal, lateralized signs of upper motor dysfunction such as hemiparesis. Contrary to the acute and catastrophic presentation of stroke in older children and adults, many neonates follow a different clinical scenario. They have normal neonatal neurologic history and may remain asymptomatic during the first few months of life. Development of early hand preference during the first year of life or seizures (or both) is usually the first sign of their impairment. The pediatrician should initiate a thorough neurologic evaluation of these infants immediately. Most neonatal strokes are arterial in origin, but they can also result from sinovenous thrombosis, coagulation abnormalities, certain genetic mutations, perinatal complications, or cardiac anomalies. Neonates with stroke usually have more than 1 risk factor. The overall risk for recurrence is low.

Germinal matrix intraventricular hemorrhage and periventricular leukomalacia is the brain injury that occurs in premature infants. Its occurrence is inversely related to gestational age and birth weight. Primary injury and destruction of the glial precursors have a direct influence on the subsequent stages of brain maturation. Accelerated cell death of these reversibly injured neurons occurs through a variety of secondary injury mechanisms (excitotoxicity, oxidative stress, inflammation) and is a potential therapeutic target.

Feeding difficulties occur in a variety of clinical settings. They may be caused by encephalopathies of different causes; disorders of the anterior horn cell, neuromuscular junction, or muscles; congenital malformations (Möbius syndrome, Chiari malformation); focal posterior fossa tumors; or laryngeal paralysis. Congenital isolated pharyngeal dysfunction is a self-limited disorder that is diagnosed by exclusion; it can be severe and may persist for months.

Decreased arm movement and asymmetrical Moro reflex are commonly caused by *brachial plexus injury*. Risk factors for brachial plexus injury include large babies, shoulder dystocia, and breech delivery.

Erb palsy (cervical roots 5 and 6) is the most common form and exhibits with the arm being adducted, pronated, and internally rotated as a result of weakness of the shoulder abduction, elbow flexion, and supination. Grasp is usually present. Klumpke paralysis (C7, C8, T1) results in weakness of the hand muscles, absent grasp, and sometimes Horner syndrome. Total brachial plexus palsy involves both upper and lower roots. The site and type of nerve injury determine the prognosis. Most patients have the least severe form of nerve injury (neurapraxia) and recover spontaneously or with supportive physical therapy. Treatment includes occupational or physical therapy and is directed toward prevention of contractures. Avulsion, the most severe form of the injury, is rare. Surgical exploration should be considered in infants who do not experience sufficient recovery within 3 months.

## **INJURIES OF THE HEAD AND SKULL**

Caput succedaneum, cephalohematoma, and linear fractures are rarely associated with intracranial disease and are self-limited. *Ping-pong fracture* is a form of depressed skull fracture associated with inward buckling of the bone, often without a fracture line. It is rarely associated with intracranial injuries and can often be corrected by nonsurgical techniques (eg, vacuum extractor, breast pump).

Potentially dangerous and treatable conditions are growing skull fracture and subgaleal hemorrhage. Growing skull fractures result from tearing of the dura and trapping of arachnoid and brain tissue in the fracture. The pulsatile force of the brain during its maximal growth causes the fracture in the thin skull to enlarge. These fractures commonly produce a progressive, often pulsatile, scalp mass that appears some time after head trauma during infancy. Imaging is diagnostic. Surgery is required to repair the dural tear.

Subgaleal hemorrhage is a rare but potentially lethal condition found in newborns. It is caused by accumulation of the blood between the epicranial aponeurosis of the scalp and the periosteum. Because this space may hold a significant volume, subgaleal hemorrhage can lead to severe hypovolemia, which may result in death. The swelling, which appears as a fluctuant, boggy mass over the scalp, develops gradually 12 to 72 hours after delivery. Subgaleal hemorrhage is most often associated with vacuum extraction and forceps delivery. Treatment consists of prompt and aggressive prevention of hypovolemic shock and treatment of any associated coagulopathy.

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**Chapter 108****SURGICAL EMERGENCIES OF THE CHEST AND ABDOMEN IN THE NEWBORN**

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**INTRODUCTION**

Newborns often present with nonspecific gastrointestinal (GI) signs that can indicate either GI pathology or infection. Therefore, an understanding of the common presenting GI signs and their differential diagnoses, as well as diagnostic work-up and management, is essential when caring for neonates.

**GENERAL APPROACH TO A NEWBORN WITH SUSPECTED ABDOMINAL PATHOLOGY****History**

Since infants with GI pathology often present within the first few days after birth, the postnatal history is not always contributory. Valuable information can be obtained from the prenatal history and any antenatal testing that was performed. Specific attention should be paid to prenatal findings such as oligohydramnios or polyhydramnios which can indicate genitourinary or GI abnormalities. Results from prenatal ultrasound examinations are usually readily available and can guide the postnatal diagnostics and management. (See Chapter 97, Postnatal Assessment of Common Prenatal Sonographic Findings.)

Monitoring urine output and stooling patterns is routine during the first days of life; additionally, parents should be encouraged to monitor voids and stools even after the infant is discharged home. Feeding patterns and difficulties with oral intake should be evaluated, especially in infants presenting with symptoms such as emesis, abdominal distention or delayed passage of stool. It is also important to assess the infant for nonspecific signs such as activity level or presence of lethargy or temperature instability, whether the infant wakes for feedings, the quality of the infant's suck and muscle tone, and for signs of respiratory distress or pain. Although the presence of these symptoms/signs can suggest GI pathology, they are not specific for GI involvement and other conditions such as sepsis should be considered in the differential diagnosis and ruled out. These signs can also be indicative of thoracic- or otorhinolaryngology-related pathology.

**Physical Examination**

In addition to a general physical examination, special attention should be paid to assessment of the abdomen in newborns presenting with feeding intolerance, emesis, abdominal distention, GI bleeding, or delayed passage of stool. Specifically, the examination should start with inspection of the abdomen with the infant in the

supine position. In addition to noting generalized versus more focal distention, prominent abdominal veins, or discoloration and abnormalities of the umbilicus may be appreciated. Although nonspecific, the presence of hyperactive bowel sounds (indicative of acute obstruction) or absence of bowel sounds (indicative of ileus) can be helpful clues on auscultation. Unlike in older children, percussion is often not helpful in the neonatal period. Palpation should start from the lower quadrants so as not to miss the lower edges of the liver or spleen. Tenderness can be appreciated by carefully observing the infant during palpation. A soft, nontender abdomen can be reassuring but does not necessarily exclude pathology. The location and characteristics of masses should be noted. Inspection of the inguinal and perianal area and exterior genitalia, as well as a rectal examination, should also be performed.

**Common Presenting Symptoms**

The most common presenting symptoms observed in infants with abdominal pathology include feeding intolerance with or without emesis (Figure 108-1), abdominal distention (Figure 108-2), delayed passage of stool (Figure 108-3), and abdominal pain/discomfort (see Table 108-1 for a clinical tool to assess neonatal pain). (See also Chapter 124, Abdominal Distention, Chapter 125, Abdominal Pain, Chapter 206, Vomiting, and Chapter 257, Gastrointestinal Obstruction.)

In the following sections, some of the more common GI disorders that occur in neonates are described, including pathogenesis, clinical findings, diagnostic tests, and management.

**ESOPHAGEAL ATRESIA AND TRACHEOESOPHAGEAL FISTULA**

Esophageal atresia (EA; complete interruption in the continuity of the esophageal lumen) and tracheoesophageal fistula (TEF; fistulous connection between the proximal or distal esophagus and the airway) are common congenital anomalies occurring in 1 in 2,500 to 4,500 births. The most common form is EA with a distal TEF (88% of cases), where the upper esophagus ends in a blind pouch and the TEF is connected to the distal esophagus. Figure 108-4 depicts the various types of TEF.

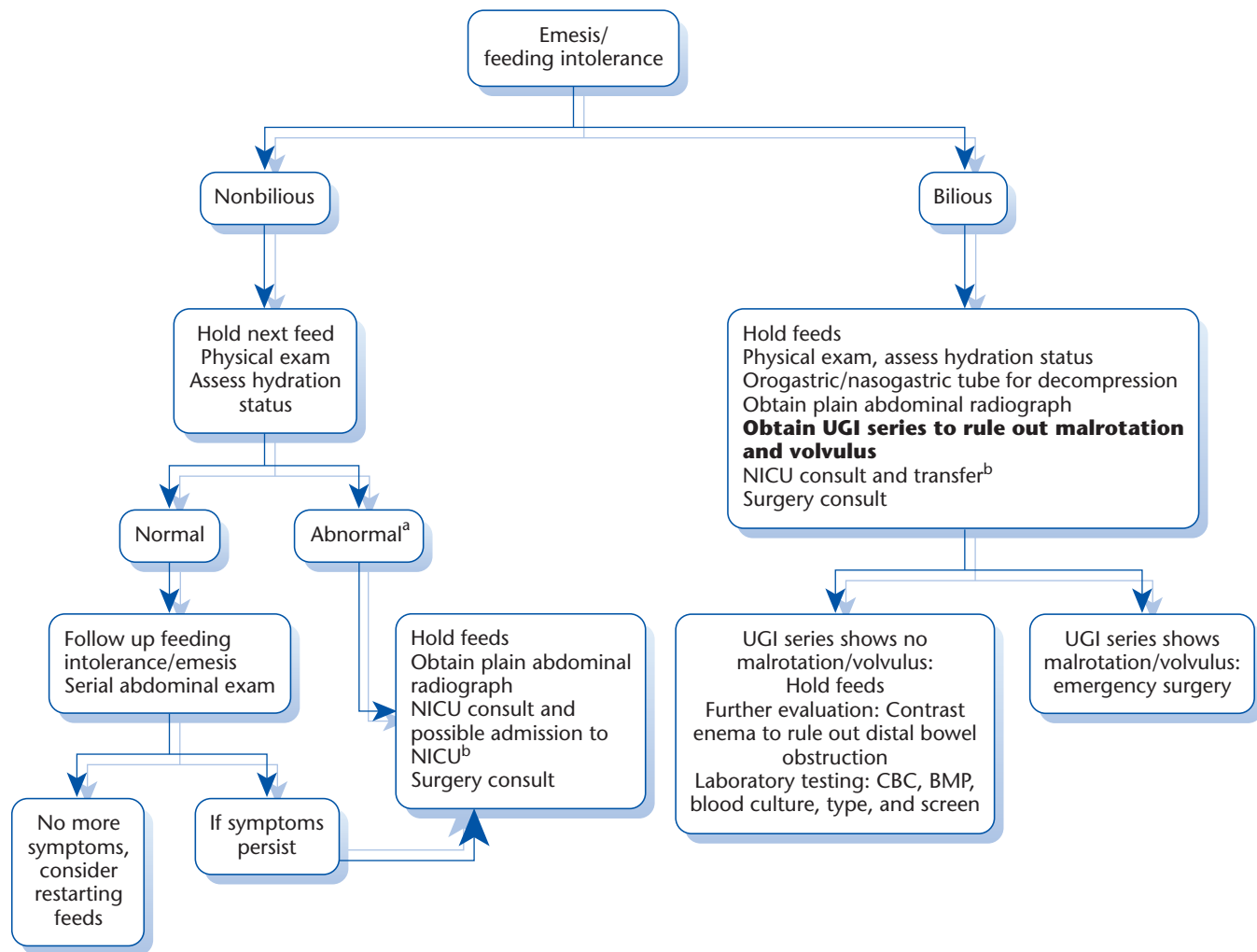
**Etiology and Genetics**

The etiology of EA and TEF is thought to be multifactorial, and most cases are sporadic and nonsyndromic. However, EA and TEF are often associated with other congenital anomalies including cardiac (35% of patients), genitourinary, GI, skeletal, and CNS defects. EA/TEF is commonly seen in patients with VACTERL association (*vertebral, anal, cardiac, tracheoesophageal, renal, and limb*), DiGeorge and Down syndrome, Pierre-Robin sequence, and CHARGE association (*coloboma, heart anomalies, atresia of the nasal choanae, retardation of growth and/or development, and genital and ear anomalies*).

**Diagnosis and Management**

The prenatal diagnosis of EA may be suggested by the presence of polyhydramnios and the absence of





**Figure 108-1** Management of infants with emesis and feeding intolerance. NICU, neonatal intensive care unit; UGI, upper gastrointestinal; CBC, complete blood count; BMP, basic metabolic panel.

<sup>a</sup>Abnormal exam: abdominal distention, abnormal bowel sounds, tenderness, abdominal wall edema or erythema, assess for inguinal hernia.

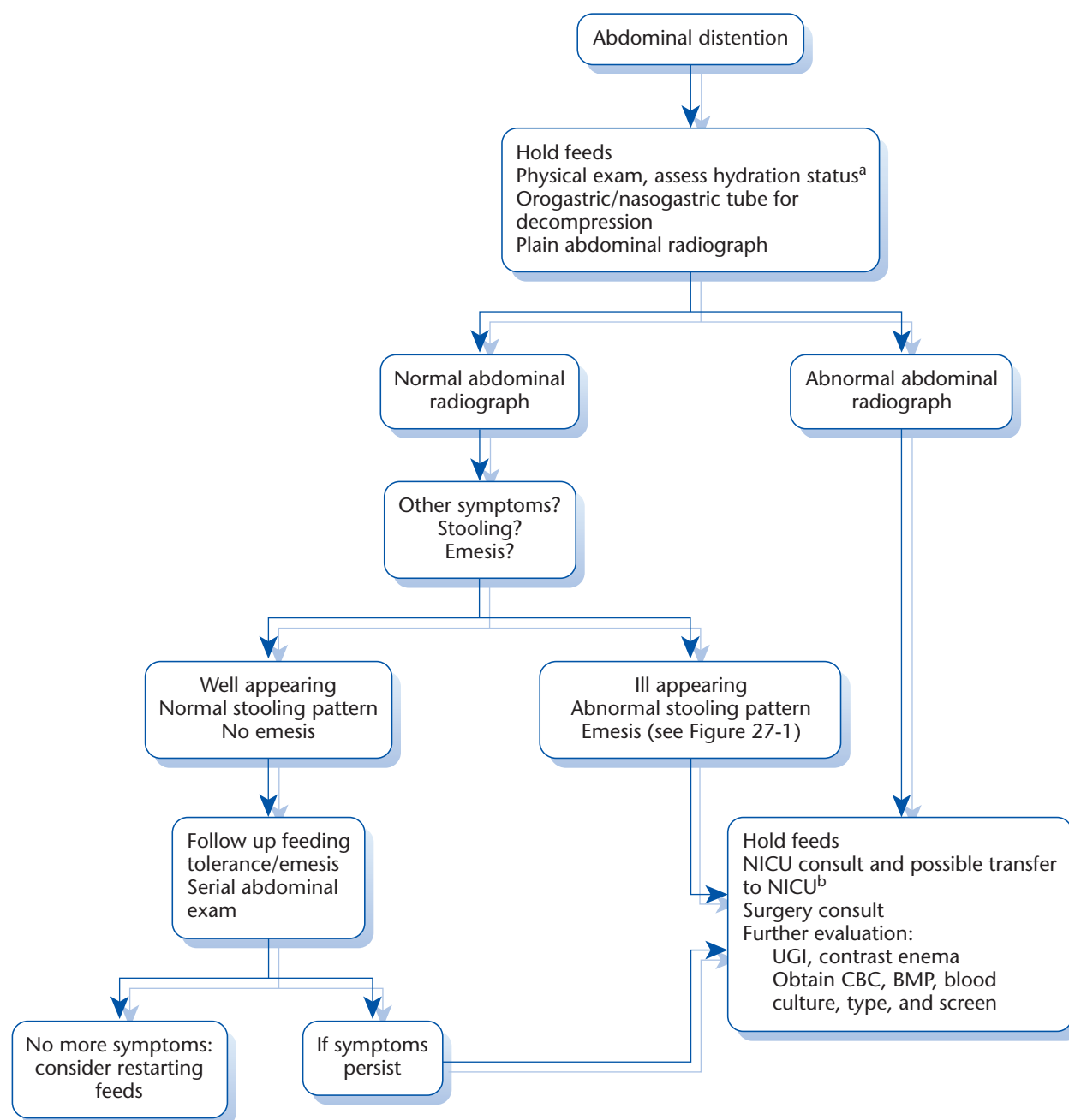
<sup>b</sup>If patient is at a facility with no pediatric surgery or neonatal/pediatric intensive care, consider early transfer to such a facility for further evaluation and management. If patient is ill-appearing, establish IV access and start IV fluids and antibiotics until transport can be arranged.

the stomach bubble on fetal ultrasound. However, most cases of EA and TEF are diagnosed in the newborn period. The typical presentation includes the presence of copious oropharyngeal secretions, feeding intolerance, reproducible choke and spit with every swallow, cyanosis, and respiratory distress. Children with isolated TEF without EA (“H-type” fistula) often present after the neonatal period with chronic respiratory difficulties such as paroxysms of coughing precipitated by feeding, gaseous distention of the GI tract, recurrent pneumonia, and bronchospasm.

The diagnosis is made by the careful passage of an 8-10 French nasogastric/orogastric tube, followed by radiographs of the chest and abdomen to ascertain tube position. Passage of the tube nasally can also help rule out choanal atresia. In patients with EA, the orogastric tube typically stops at 10 to 12 cm

(in the proximal esophageal pouch) (Figure 108-5 and Figure 108-6); the presence of a gas-filled stomach and intestine indicates the presence of a distal TEF (Figure 108-6).

Infants with EA or TEF should be evaluated for other congenital anomalies. Preoperative echocardiography is essential to define the anatomy of the aortic arch and its relation to the trachea and esophagus, as well as to diagnose any cardiac abnormalities that may be important predictors of morbidity and mortality. The newborn may experience significant respiratory distress caused by either marked abdominal distention that pushes the diaphragms up and limits respiratory excursions or aspiration of secretions and reflux of gastric contents into the lung through the fistula. A repleg/sump tube should be carefully placed into the proximal esophageal pouch



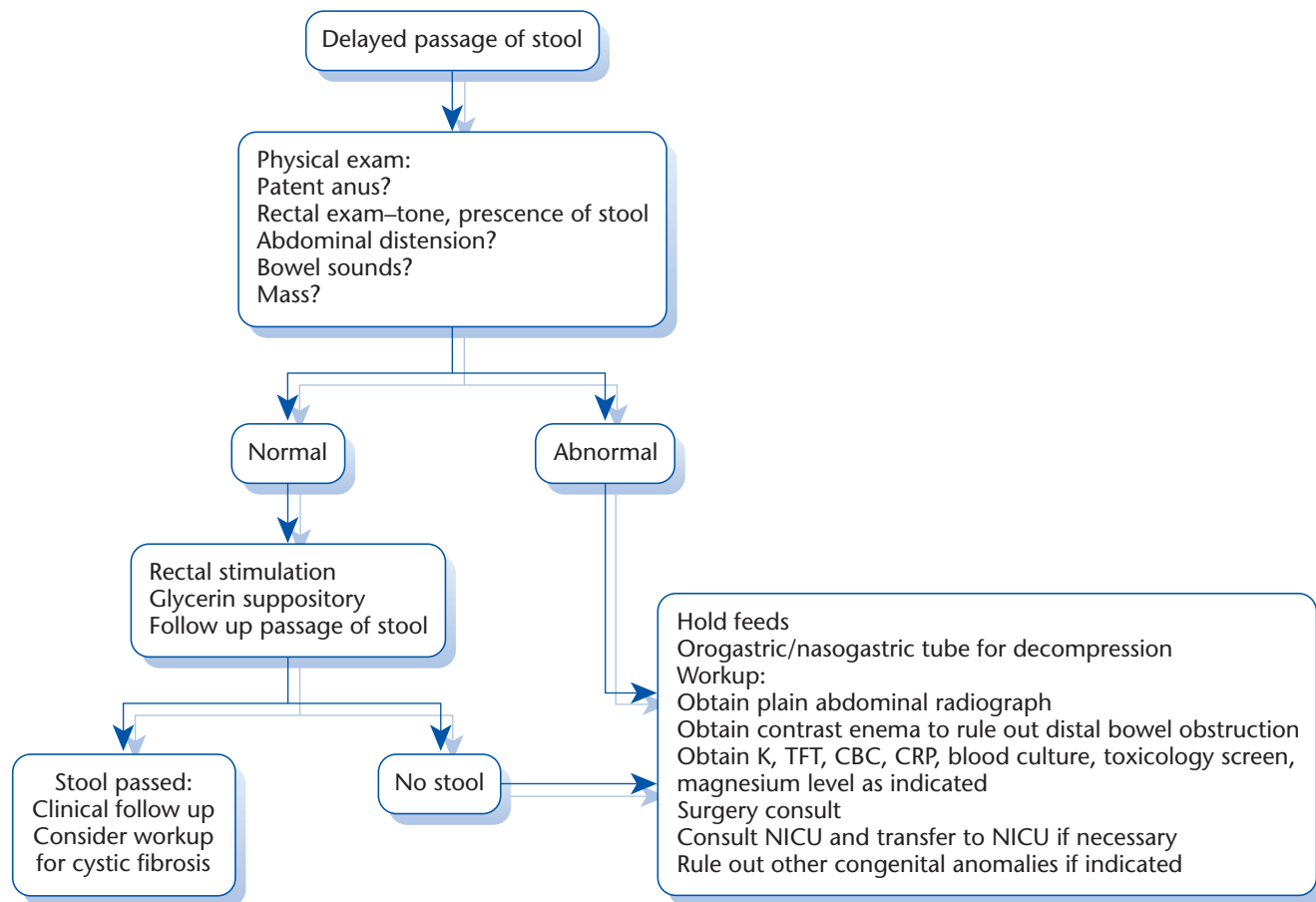
**Figure 108-2** Management of infants with abdominal distention. NICU, neonatal intensive care unit; UGI, upper gastrointestinal; CBC, complete blood count; BMP, basic metabolic panel.

<sup>a</sup>Abnormal exam: abdominal distention, abnormal bowel sounds, tenderness, abdominal wall edema, abdominal wall erythema, assess for inguinal hernia.

<sup>b</sup>If patient is currently at a facility with no pediatric surgery or neonatal or pediatric intensive care unit, consider early transfer to such a facility for further management. If patient is ill-appearing, establish IV access and start IV fluids and antibiotics until transport can be arranged.

and connected to suction (40 mm Hg). The head of the bed should be elevated to 45 degrees to avoid gastric reflux as much as possible. Preoperative intubation and use of continuous positive airway distending pressure (CPAP) should be avoided if possible as positive airway pressure can lead to significant gastric distention

via the TEF and can therefore compromise ventilation even further. If intubation becomes necessary, the endotracheal tube should be placed just proximal to the carina as most fistulas are located above the carina. Prophylactic antibiotic treatment should be considered in these patients.



**Figure 108-3** Management of infants with delayed passage of stool. *NICU*, neonatal intensive care unit; *CBC*, complete blood count; *K*, potassium; *TFT*, thyroid function panel; *CRP*, C-reactive protein. If patient is currently at a facility with no pediatric surgery or neonatal or pediatric intensive care unit, consider early transfer to such a facility for further management. If patient is ill-appearing, establish IV access and start IV fluids and antibiotics until transport can be arranged.

The operative repair of EA or TEF usually consists of division of the fistula and primary anastomosis of the distal and proximal esophageal pouches. In cases where the gap between the 2 ends is deemed too far apart for primary anastomosis, gastrostomy tube placement and delayed primary anastomosis at 8 to 12 weeks of age may be appropriate. In cases with “long-gap” atresia, either serial dynamic lengthening of the esophagus or replacement of the esophagus at a later age (3–4 months) is performed. At present, gastric transposition for esophageal replacement is preferred by many surgeons.

### Complications and Outcomes

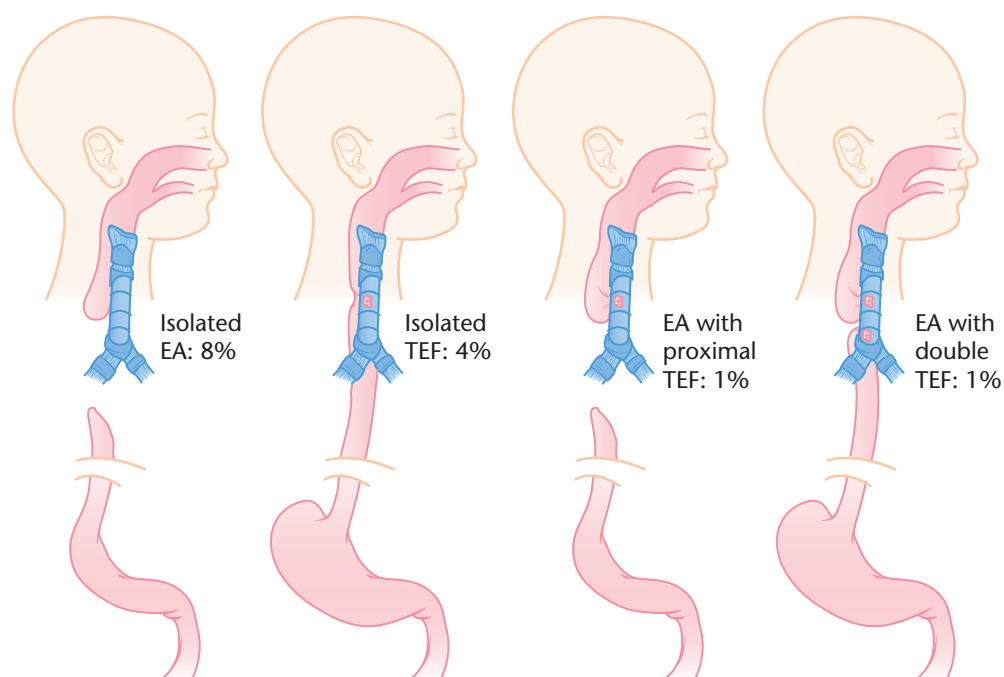
GI complications are common sequelae following EA or TEF repair. Anastomotic leaks complicate the early postoperative course in 10% of patients. Most are minor and seal spontaneously. Esophageal strictures develop in up to 40% of infants and should be considered in the differential diagnosis of children with history of EA or TEF who present with dysphagia, poor feeding, emesis, food aspiration, and recurrent aspiration pneumonitis. Most patients with strictures have good results with repeated dilation; the need for esophageal dilation

decreases with increasing age of the patient. Both anastomotic leak and gastroesophageal reflux disease (GERD) are related to the development of strictures. Abnormal peristalsis is found in almost all children with EA or TEF. Because of the intrinsic motor dysfunction of the esophagus, GERD is extremely common in patients with EA/TEF; long-standing and severe GERD can lead to subsequent development of esophagitis. Approximately half of children with GERD will respond to medical therapy; however, as many as 25% of patients eventually require surgical management of GERD (Nissen fundoplication). Recurrence of GERD after surgery occurs in up to 25% of children. Dysphagia related to dysmotility is common and can persist into adulthood. Children will often need to eat slowly, take plenty of fluids with meals, and avoid certain foods (such as meats and doughy baked goods). In severe cases, infants may present with failure to thrive, which can be a result of both dysphagia and GERD. Respiratory symptoms are almost as common as GI symptoms, especially in the first 3 years of life, and are important contributors to hospitalization and late mortality. Recurrent pneumonia, chronic cough, and bronchitis seem to decrease

**Table 108-1** Neonatal Pain, Agitation, and Sedation Scale (N-PASS)

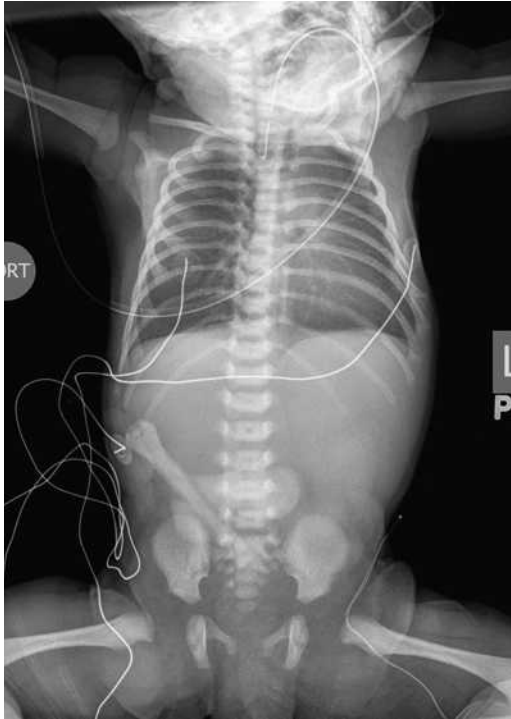
ASSESSMENT	SEDATION		SEDATION/ PAIN	PAIN/AGITATION	
Criteria	-2	-1	0/0	1	2
<b>Crying/ Irritability</b>	No cry with painful stimuli	Moans or cries minimally with painful stimuli	No sedation/ No pain signs	Irritable or crying at intervals Consolable	High-pitched or silent-continuous cry Inconsolable
<b>Behavior State</b>	No arousal to any stimuli No spontaneous movement	Arouses minimally to stimuli Little spontaneous movement	No sedation/ No pain signs	Restless, squirming Awakens frequently	Arching, kicking Constantly awake or arouses minimally/ no movement (not sedated)
<b>Facial Expression</b>	Mouth is lax No expression	Minimal expression with stimuli	No sedation/ No pain signs	Any pain expression intermittent	Any pain expression continual
<b>Extremities/ Tone</b>	No grasp reflex Flaccid tone	Weak grasp reflex ↓ muscle tone	No sedation/ No pain signs	Intermittent clenched toes, fists, or finger splay Body is not tense	Continual clenched toes, fists, or finger splay Body is tense
<b>Vital Signs: HR, RR, BP, SaO<sub>2</sub></b>	No variability with stimuli Hypoventilation or apnea	<10% variability from baseline with stimuli	No sedation/ No pain signs	↑ 10%–20% from baseline SaO <sub>2</sub> 76%–85% with stimulation—quick recovery	↑ 20% from baseline SaO <sub>2</sub> ≤75% with stimulation—slow recovery Out of sync with vent

From Hummel P. N-PASS—Neonatal pain, agitation and sedation scale. Available at: [www.n-pass.com/assessment\\_table.html](http://www.n-pass.com/assessment_table.html). Accessed March 17, 2014. Reprinted with permission.



**Figure 108-4** Different types of TEF. Type A: Esophageal atresia without TE fistula. Type B: Esophageal atresia with a fistulous connection between the proximal esophageal pouch and the trachea. Type C: Esophageal atresia with a fistula between the distal esophageal pouch and the trachea, blind proximal pouch (most common type). Type D: Esophageal atresia with a fistula between both the proximal and distal esophageal pouches and the trachea. Type E: H-type TE fistula (no esophageal atresia).





**Figure 108-5** Esophageal atresia without tracheoesophageal fistula. Note orogastric tube ending in esophageal pouch and absent bowel gas indicating no fistulous connection to the distal part of the esophagus.

over time, whereas the prevalence of wheezing remains fairly constant until early adulthood. Tracheomalacia, although often found on pathology specimens, seems to be clinically significant in only 10% of patients. If persistent and recurrent respiratory symptoms and choking/gagging with feeds occur, the recurrence of TEF should be considered and ruled out.

## CONGENITAL DIAPHRAGMATIC HERNIA

Congenital diaphragmatic hernia (CDH) is a condition where there is herniation of the abdominal viscera into the thoracic cavity through a defect in the diaphragm. It occurs in 1 in 2,200 to 4,000 live births and is often associated with other congenital malformations.

### Etiology and Pathophysiology

The diaphragm initially develops as a septum between the heart and liver, progresses posterolaterally, and closes at the left foramen of Bochdalek at approximately 8 to 10 weeks' gestation. Failure of closure of the pleuroperitoneal canals during embryonic development of the pleural and peritoneal cavities results in CDH. The defects in the diaphragm can be posterolateral or central, resulting in Bochdalek and Morgagni hernias, respectively. Approximately 85%



**Figure 108-6** Esophageal atresia with distal tracheoesophageal fistula. Note curled orogastric tube in proximal pouch and the presence of bowel gas.

of CDH are left sided; in these patients, there can be herniation of the small or large bowel and other solid intra-abdominal organs. Fourteen percent of CDH are right-sided; in these patients, the liver and a portion of the large bowel are present in the thoracic cavity. Bilateral CDH is rare, occurring in approximately 1% of cases, and is usually fatal. The incidence of associated congenital anomalies varies depending on the method of diagnosis and inclusion of autopsy cases/aborted fetuses. Anomalies described in patients with CDH include chromosomal anomalies (trisomy 13, 18, 21), Fryns syndrome, congenital heart disease (hypoplastic left heart syndrome, coarctation of the aorta, and tetralogy of Fallot), neural tube defects, and cleft palate.

The herniated abdominal contents result in compression of the developing lungs with subsequent development of pulmonary hypoplasia and hypertrophy of the pulmonary vascular smooth muscle cells. Both lungs are affected with the ipsilateral lung being more affected than the contralateral lung. The degree of pulmonary hypoplasia depends on the size of the defect, presence of liver in the thoracic cavity, and gestational age at which the hernia occurred. After birth, these changes interfere with gas exchange leading to respiratory failure and pulmonary hypertension.

### Diagnosis and Management

Approximately 50% to 60% of patients with CDH are diagnosed antenatally. The clinical presentation varies, with minimal respiratory symptoms in patients

with small hernias and severe respiratory failure in patients with large hernias and associated pulmonary hypoplasia or pulmonary hypertension. The abdomen may be scaphoid with poor air entry on auscultation. Heart sounds may be shifted to the right in patients with left-sided hernias. Chest radiography will reveal loops of bowel in the thoracic cavity (Figure 108-7). If the stomach is herniated into the thoracic cavity, the tip of the OG tube may be seen curling in the left side of the chest (Figure 108-8).

If antenatally diagnosed, patients with CDH should be delivered at a tertiary care center with a neonatal intensive care unit equipped with extracorporeal membrane oxygenation (ECMO) and pediatric surgical capabilities. If the diagnosis of CDH is known or suspected, infants should be intubated immediately after birth and an orogastric tube placed for gastric decompression. The use of face mask to provide positive pressure ventilation should be avoided. Gentle ventilation strategies with permissive hypercapnia should be adopted to minimize lung injury. High-frequency ventilation may be required in patients in whom acceptable blood gas parameters cannot be achieved with conventional modes of ventilation. ECMO is used as rescue therapy in cases of persistent or worsening hypoxemia and failure of ventilatory strategies. Routine use of surfactant is not recommended; however, it may be beneficial in preterm infants with respiratory distress syndrome. Although there may be short-term benefit from the selective use of inhaled nitric oxide (iNO) therapy, the routine use of iNO for all CDH infants is not supported by the available data. Surgical repair should preferably be

delayed until the patient is stable and pulmonary hypertension has resolved. Surgery involves reduction of the viscera and closure of the defect in the diaphragm. The approach is determined by the size of the defect, with large defects requiring a patch for closure and small defects being closed either primarily or with a patch.

### Complications and Outcomes

Antenatal diagnosis of CDH is associated with poor prognosis. Antenatal ultrasonographic and magnetic resonance imaging (MRI) findings associated with increased mortality include presence of the liver in the thorax, low lung-to-head ratio (LHR) and total fetal lung volume, small lung-to-thorax transverse area ratio, low gestational age at diagnosis, mediastinal shift, left heart hypoplasia, and stomach in the thorax. Postnatal factors associated with poor prognosis are low Apgar score at 5 minutes, the size of the diaphragmatic defect, low birth weight, right-sided defect, the need for ECMO, surgical repair performed while patient is on ECMO, and persistence of pulmonary hypertension beyond 3 to 4 weeks of age.

Survival of patients with isolated CDH is approximately 70% if ECMO is required and 90% if ECMO is not needed. Mortality and morbidity in CDH patients with other severe congenital anomalies is dependent, at least in part, on these associated abnormalities. Long-term complications include pulmonary hypertension, obstructive airway disease, and GERD with failure to thrive. Pulmonary hypoplasia and pulmonary hypertension predispose children with CDH



**Figure 108-7** Congenital diaphragmatic hernia. Note bowel loops in the left hemithorax with mediastinal shift to the right.



**Figure 108-8** Congenital diaphragmatic hernia. Note that the stomach bubble is in the left hemithorax with the tip of the orogastric tube coiled in the stomach.

to a high risk for hypoxemia, which may result in neurodevelopmental delays. Chest wall deformities and scoliosis may also be seen.

### INTESTINAL ATRESIA/STENOSIS

Intestinal atresia is the most common cause of congenital intestinal obstruction. Approximately one-third of bowel obstructions in the newborn period can be attributed to intestinal atresia, with an overall incidence of 1 in 2,700 births. Duodenal atresia and stenosis are slightly more common than jejunoileal atresia, whereas colonic atresias are rare.

#### Etiology and Genetics

Duodenal obstruction is thought to be caused by a failure of recanalization of the duodenal lumen from its solid cord stage, leading to either partial obstruction by an imperforate membrane or mucosal web or complete atresia. More than 50% of cases are associated with other congenital anomalies such as cardiac, GI (pancreatic anomalies, intestinal malrotation, esophageal atresia, Meckel diverticulum, or imperforate anus), central nervous, and renal anomalies. Approximately 30% of patients with duodenal atresia have Down syndrome (trisomy 21). Other associated genetic abnormalities include Feingold syndrome and a variant of the VACTERL association. In contrast, jejunoileal atresia is attributed to a vascular accident occurring later in gestation, resulting in an ischemic insult to the developing bowel. Some studies have shown an association between jejunoileal atresias and defects that may cause strangulating obstruction of the intestinal tract (eg, malrotation, volvulus, intussusception, internal hernias, and gastroschisis). Cystic fibrosis (CF) may be found more often in newborns with jejunoileal atresia. Association with other congenital malformations is rare.

#### Diagnosis and Management

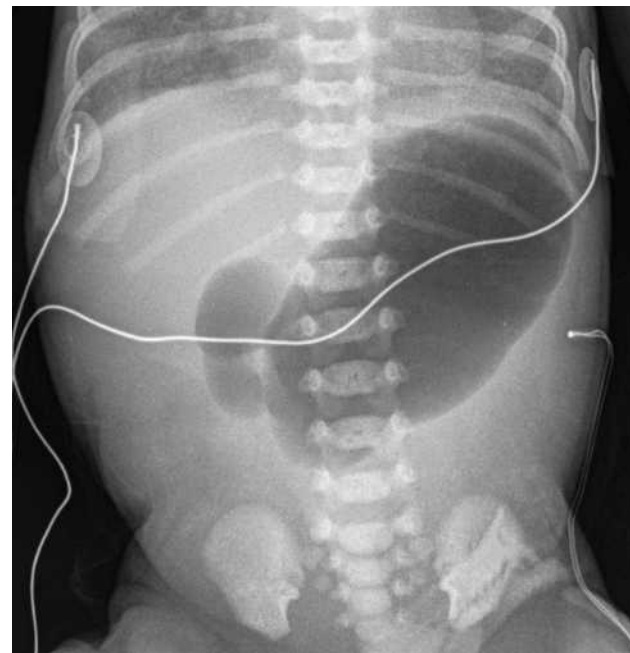
The prenatal diagnosis of intestinal atresia or stenosis is suggested by polyhydramnios. Duodenal obstruction is suggested by the findings of a dilated stomach and duodenum (double-bubble sign; Figure 108-9). Echogenic or dilated loops of bowel and abdominal cysts noted during fetal ultrasonography can indicate bowel obstruction. Despite improving prenatal ultrasound techniques, approximately two-thirds of newborns with intestinal atresias are diagnosed after birth.

The typical clinical presentation is a newborn infant with feeding intolerance, bilious emesis, abdominal distention (which is usually seen with distal small bowel obstruction/atresia rather than with proximal obstruction), and failure to pass meconium. If there is a suspicion of malrotation with or without volvulus, the patient should be considered to have a surgical emergency until proven otherwise. Neonatal and surgical consultation should be immediately obtained and the infant should be evaluated for transfer to a neonatal/pediatric intensive care unit for continuing care. A plain abdominal radiograph is the first step in evaluating such infants. The classic double-bubble sign

indicates duodenal atresia (Figure 108-10), whereas dilated loops of bowel with air-fluid levels indicate more distal obstruction such as jejunoileal obstruction (Figure 108-11). An upper-GI contrast study with small-bowel follow-through is useful to rule out malrotation or volvulus in cases with partial obstruction. Distal small-bowel obstructions are ruled out intraoperatively and a contrast enema is rarely required. Contrast enemas, when performed, may demonstrate microcolon and may help in ruling out rare colonic atresia or obstruction.



**Figure 108-9** Duodenal atresia. Note the double-bubble sign on the prenatal ultrasound. (Sonogram courtesy of Dr. Pe'er Dar, Montefiore Medical Center.)



**Figure 108-10** Duodenal atresia. Note the double-bubble sign with a large stomach bubble, smaller proximal duodenum, and no air in the distal bowel.





**Figure 108-11** Jejunal atresia. Note distended proximal bowel loops with no gas in the distal bowel.

A nasogastric tube should be placed to decompress the stomach and intestines, and fluid resuscitation and electrolyte management initiated. A blood gas may be obtained to check for evidence of metabolic or respiratory acidosis as this may provide information necessary for general management of these infants. In infants with duodenal atresia, a thorough evaluation for other congenital anomalies is important. In most infants, the workup can be completed after surgical repair with the exception of echocardiography to evaluate for congenital heart disease and, if considered urgent, abdominal ultrasound for evaluation of renal abnormalities. Genetic testing for Down syndrome in children with duodenal atresia should be obtained; workup for CF should be considered in infants with a diagnosis of jejunoileal atresia. Operative repair is most commonly performed with resection of the atretic segment and primary anastomosis. In some cases, temporary ostomy placement may be necessary, and in infants with multiple atresias, a staged approach may be required.

### Complications and Outcomes

The survival rate of patients with duodenal atresia is excellent (86%–90%) with early mortality (3%–5%) mostly related to coexisting congenital heart disease. Immediate postoperative complications include bowel obstruction, prolonged ileus, anastomotic leak, and wound infection. Late complications are reported to occur in 12% to 15% of patients, with an

associated 6% late mortality rate. Complications include megaduodenum with abnormal intestinal motility, blind loop syndrome, duodenogastric reflux and esophagitis, pancreatitis, cholecystitis, and cholelithiasis. Megaduodenum may present with poor weight gain, abdominal pain, and vomiting. It can be avoided or corrected with a tapering duodenoplasty. Blind loop syndrome occurs only in patients in whom a duodenojejunostomy was performed. GERD caused by dysmotility is common and may require either medical or surgical management. Patients with an annular pancreas have an increased tendency for late complications, often requiring a second operation. These patients should be monitored closely into adulthood as some of the complications (ie, peptic ulcer disease, gastric outlet and duodenal obstruction, pancreatitis, gastric cancer) manifest later in life.

Mortality rates for infants with jejunoileal atresia have decreased significantly, with survival approaching 100%. However, this does not include possible mortality related to short-bowel-syndrome (SBS) which is the most common and significant complication for patients with jejunoileal atresias. In most instances, infants are on total parenteral nutrition (TPN) for a short period of time only. In those who required more significant bowel resection and therefore greater loss of absorptive area, prolonged TPN dependence poses an additional risk for morbidity and mortality, including central line complications, sepsis, and TPN-related liver disease.

## MALROTATION AND MIDGUT VOLVULUS

In newborns who present with bilious vomiting, one of the most important diagnoses to exclude is malrotation with or without volvulus. Infants with volvulus constitute a surgical emergency and require prompt medical and surgical intervention. Up to 80% of affected patients are diagnosed during the neonatal period, with 50% presenting in the first week of life. If not recognized in a timely fashion, volvulus can lead to catastrophic loss of bowel with resultant lifelong disability, and even death.

### Embryology and Genetics

Normally, during fetal development the intestinal loop rotates counterclockwise around the superior mesenteric artery (SMA) and after returning into the abdominal cavity becomes firmly attached to the posterior abdominal wall, with the cecum positioned in the right lower quadrant and the duodenojejunal junction in the left upper quadrant. Malrotation results when the normal staged process of elongation, herniation with subsequent return to the abdomen, and finally fixation of the intestinal loop does not occur. Malrotation predisposes the infant to volvulus with strangulation of the intestines around the axis of the SMA; however, not all patients with malrotation experience this potentially life-threatening complication. There is a predominance of male patients who present during the newborn period; this gender



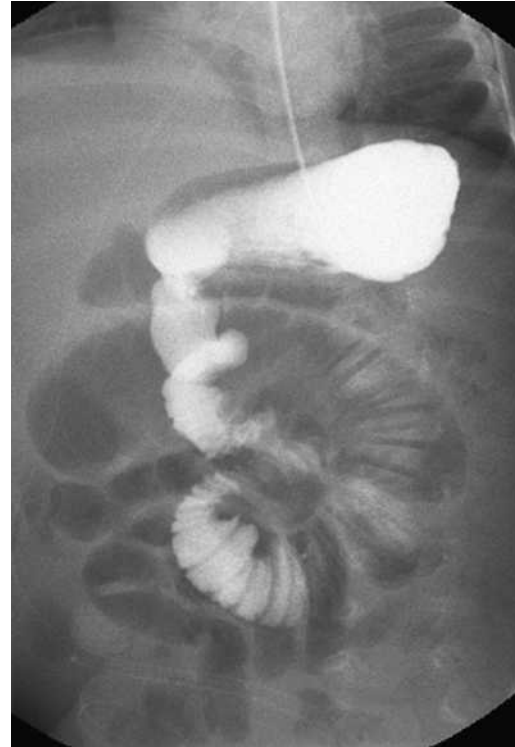
predilection is not observed in patients presenting after 1 year of age. Most children with malrotation do not have any predisposing syndrome or genetic susceptibility. Malrotation is often present in children with heterotaxia syndrome. Nonrotation is almost invariably present in children with CDH, omphalocele and gastroschisis. Other GI malformations that may be seen in patients with malrotation include atresias, Meckel diverticulum, intussusception, Hirschsprung disease (HD), GERD, gastric volvulus, persistent cloacae, and anomalies of the extrahepatic biliary system.

### Diagnosis and Management

With increasing accuracy of prenatal ultrasound, more cases of in utero volvulus or its sequelae are diagnosed antenatally; however, most infants are still identified after birth. The risk for midgut volvulus is highest in babies younger than 1 month. The most common presenting sign is bilious emesis, which should prompt an immediate evaluation for malrotation with or without volvulus. However, nonbilious emesis does not rule out malrotation and volvulus. Although bilious emesis is a general sign of intestinal obstruction, it can also be present in the absence of surgical pathology (up to 60%). The physical examination may be normal in up to 50% of the patients. Abdominal distention in the setting of malrotation and volvulus suggests the presence of ischemic bowel. There can be stooling abnormalities such as blood-stained (especially when strangulation of the intestines has occurred) and diarrheal stools. In cases where strangulation and necrosis of the bowel are advanced, the patient can present in shock, with abdominal distention and signs of peritonitis; these infants have a poor prognosis.

Plain abdominal radiographs in anterior-posterior and cross-table lateral position usually demonstrate a normal bowel gas pattern and are helpful in excluding other potential causes for bilious emesis such as intestinal obstruction/atresias. A normal bowel gas pattern on a plain radiograph, however, cannot exclude malrotation and volvulus. Signs of malrotation seen with an upper GI contrast study include incomplete obstruction of the duodenum, duodenojejunal flexure to the right of the expected location, proximal jejunal loops lying abnormally on the right side of the abdomen, and a high cecum seen with delayed follow-through films (Figure 108-12). Ultrasound with Doppler flow may be used to assess the position and relative relationship of the superior mesenteric vessels; reversal of the position of these vessels, the sonographic “whirlpool” sign, is highly sensitive for the diagnosis of midgut volvulus secondary to malrotation, but is not sufficiently accurate to exclude the diagnosis.

Management includes holding feeds, gastric decompression using a nasogastric or orogastric tube attached to continuous suction, and fluid resuscitation, as necessary. In addition to fluid resuscitation, prompt surgical intervention is indicated. The preferred surgical approach is the Ladd procedure, which consists of laparotomy with reduction of the midgut volvulus, if



**Figure 108-12** Upper gastrointestinal series in an infant with malrotation. Visualization of the position of the duodenum is key to assess for malrotation. The fourth portion of the duodenum should be seen to the left of the left spinal pedicle and should be near to the level of the pylorus. The main signs for malrotation are (1) abnormal position of the duodenojejunal junction, (2) spiral, “corkscrew,” or Z-shaped course of the distal duodenum and proximal jejunum, and (3) location of the proximal jejunum in the right abdomen.

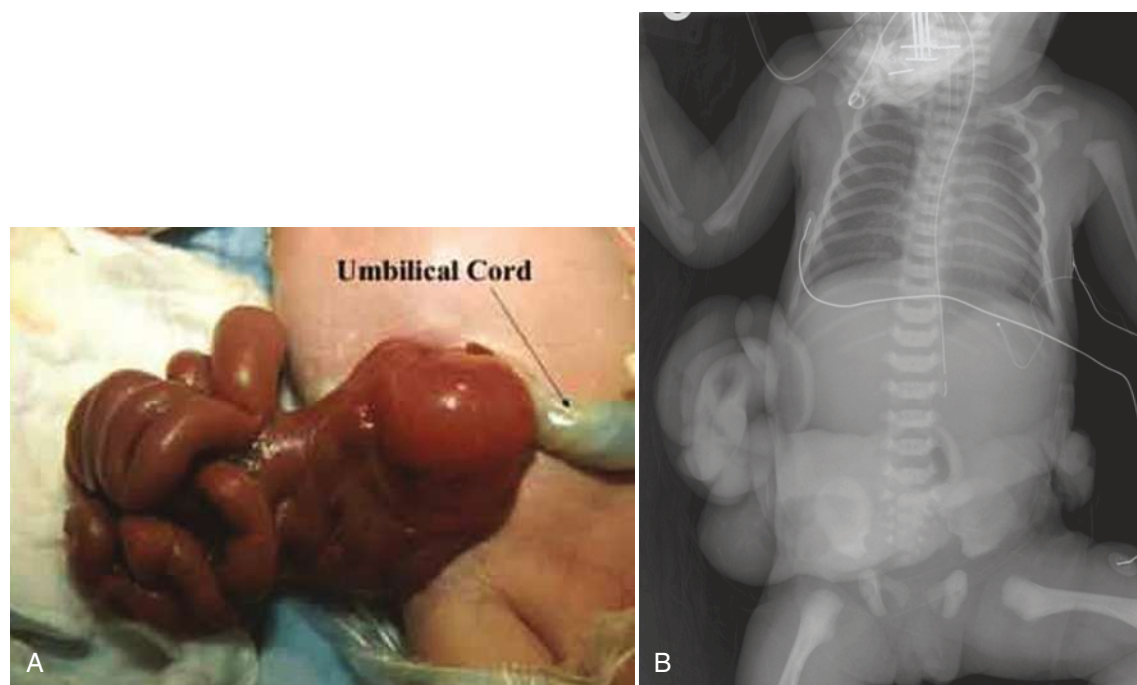
present, in a *clockwise* fashion; division of peritoneal Ladd bands obstructing the duodenum; repositioning the bowel in a nonrotated state with the cecum in the left upper quadrant; and appendectomy. In select cases, the surgery can be done laparoscopically.

### Complications and Outcomes

The most commonly experienced complications are adhesions and the subsequent development of bowel obstruction. Neonates are particularly susceptible to this complication and parents should be counseled regarding this possibility. Recurrent volvulus, although rare, is an important complication. The overall survival for children with malrotation with volvulus is over 80%; however, a significant number of children experience substantial morbidity as a result of bowel loss with short-gut syndrome and its associated complications.

### GASTROSCHISIS AND OMPHALOCELE

Gastroschisis and omphalocele are the most common defects of the anterior abdominal wall. Gastroschisis presents as a full thickness defect in the abdominal



**Figure 108-13** A, Infant with gastroschisis. B, Plain chest and abdominal radiograph of an infant with gastroschisis.

wall with prolapse of the intestine through the defect (Figure 108-13). There is no covering membrane, and the defect lies to the right side of an intact umbilical cord. The incidence is 0.3 to 4 per 10,000 live births with increasing numbers for unknown reasons. In omphalocele, the defect is midline and the prolapsed organs are always covered with a protective membrane consisting of amnion on the outer surface, peritoneum on the inner surface, and Wharton's jelly in between (Figure 108-14). Omphaloceles contain a variable amount of intestine, often parts of the liver, and occasionally other organs. The umbilical vessels insert into the membrane and not the abdominal wall. The incidence is 1.5 to 3 per 10,000 live births, and unlike gastroschisis, the incidence has remained stable.

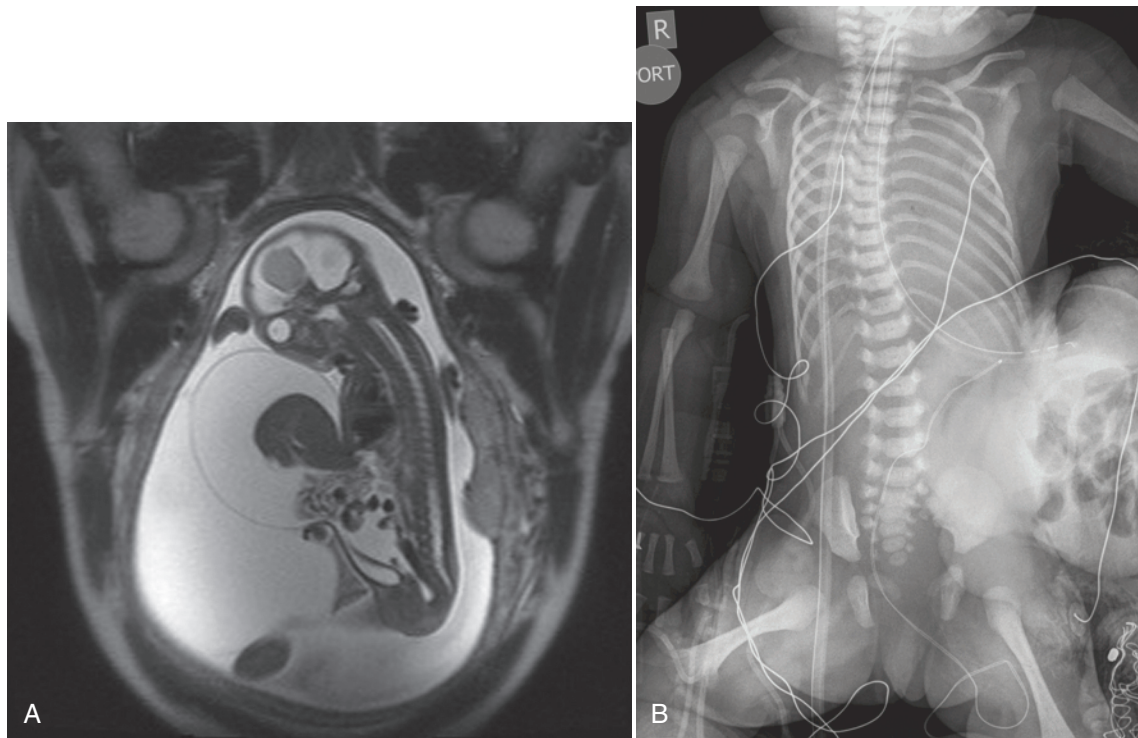
### Etiology and Genetics

Gastroschisis is considered to be the result of a vascular accident of the omphalomesenteric artery, a failure of mesoderm formation, rupture of the amnion around the umbilical ring with herniation of the midgut, or abnormal involution of the right umbilical vein with body wall weakening. Failure in the correct process of embryonic body wall folding is also hypothesized. There is no evident genetic cause seen in gastroschisis; however, young maternal age (<20 years old) has been strongly linked to it. Associated intestinal atresias occur in 6.9% to 28% of patients, most of them involving the GI tract, such as atresias and stenoses. These abnormalities are thought to be related to vascular compromise as well. In contrast, omphalocele is thought to be the result of herniation of the intestine and other abdominal organs into the umbilical cord without returning into the

abdominal cavity. It is associated with syndromes and chromosomal abnormalities in over 50% of cases, including Beckwith-Wiedemann syndrome (omphalocele, macroglossia, organomegaly, hypoglycemia and increased risk for childhood tumors such as Wilms tumor, neuroblastoma, and hepatoblastoma).

### Diagnosis and Management

Abdominal wall defects (AWD) are often detected during routine prenatal ultrasounds (Figure 108-14). The accuracy of the diagnosis may be affected by the timing of the fetal ultrasound, fetal positioning, or expertise of the ultrasonographer, therefore leading to undiagnosed and miscategorized defects. Both gastroschisis and omphalocele are associated with an increased risk of fetal growth restriction, premature delivery, and fetal death; therefore, careful obstetric follow-up with serial ultrasounds and other tests of fetal well-being are indicated. Maternal serum alpha-fetoprotein is usually elevated, with higher values in gastroschisis than omphalocele. Patients with AWD have a higher risk for intrauterine growth restriction, premature delivery, and fetal death. The expectant parents should be counseled by geneticists, pediatric surgeons, and neonatologists. It is important to prepare the parents for a prolonged neonatal intensive care unit stay as the newborn will need surgical intervention and is likely to have feeding intolerance, at least initially. Infants diagnosed prenatally should be delivered at a center where pediatric surgery is available immediately after birth. Although the timing of delivery of patients with gastroschisis is controversial, most infants can be delivered vaginally. There are no clear data supporting routine cesarean delivery, with the possible exception of giant omphaloceles.



**Figure 108-14** A, Prenatal ultrasound of an infant with a giant omphalocele. B, Plain chest and abdominal radiograph of an infant with omphalocele.

Regardless of the mode of delivery, the birth should be a coordinated event between the obstetricians and the neonatal and surgical providers. In the delivery room, a sterile field must be created on the infant warmer. Most physicians recommend the use of latex-free products in the care of these infants. In addition to the ABCs of newborn resuscitation, special care needs to be given to thermoregulation and management of the exposed bowel. The baby should be placed with the right side down in order to avoid kinking of the mesenteric pedicle, while the bowel is carefully stabilized and monitored for appearance. The exposed viscera and the lower half of the body are placed in a sterile transparent bowel bag, which is both easy and quick and allows for visualization of the defect and the exposed viscera. Alternatively, sterile gauze soaked in warm saline solution can be used to cover the defect, which is then carefully wrapped with sterile gauze around the body and eventually covered by either a sterile bowel bag or clear plastic wrap. Moist dressings alone without a covering plastic layer should be avoided as the newborn with gastroschisis has increased evaporative fluid and heat losses. When taking care of a patient with omphalocele, it is important to maintain the integrity of the sac. If the covering sac has ruptured, omphaloceles should be treated in a manner similar to gastroschisis.

Respiratory management can be difficult, especially if there is associated pulmonary hypoplasia or a significant cardiac lesion. Early intubation in the delivery room may be required as prolonged bag-mask ventilation or CPAP via mask should be avoided so as not to

distend the bowel. Irrespective of whether the infant requires respiratory support, a nasogastric tube should be inserted in order to prevent abdominal distention. Fluid and electrolyte management is challenging in patients with gastroschisis and ruptured omphaloceles since there are significant ongoing fluid losses that require volume resuscitation. Fluid requirements can range up to 2.5 times that of a healthy newborn. Initial resuscitation of these patients includes a 10 to 20 mL/kg bolus of normal saline or lactated Ringer solution in addition to maintenance IV fluids. Additional isotonic fluid should be administered, as needed, until urine output is established. Metabolic acidosis is common as a result of poor perfusion related to hypovolemia; therefore, acid-base balance should be monitored closely. Broad spectrum antibiotic coverage is also indicated in these patients.

For infants with gastroschisis, a common surgical approach is Silastic silo placement at the bedside which allows for covering of the defect and visual monitoring of bowel integrity. With appropriate fluid management and decompression of the intestines, the bowel wall edema decreases over time until the herniated intestine and other organs can be safely placed inside the abdominal cavity and closure of the abdominal defect can be attempted. A staged surgical approach may be necessary if the abdominal pressure is too high or in the presence of intestinal atresia.

If the sac of an omphalocele is intact, there is no urgency for surgical intervention. The infant can be stabilized and evaluated for associated anomalies. For smaller defects, primary closure with excision of membrane may



be possible. In the case of bigger defects, a common approach is topical application of sulfadiazine in order to allow for epithelialization of the membrane over weeks to months. Once associated problems have been addressed and enteral feeds established, the infant's care can be taught to the parents and continued on an outpatient basis. When the sac is sturdy enough to withstand external pressure, compression is done with elastic bandages while serially increasing the pressure until reduction of the abdominal contents is achieved and a ventral hernia repair can be performed, a process that may take 6 to 12 months.

### Complications and Outcomes

Outcomes for patients with gastroschisis depend mainly on the condition of the bowel at time of birth. Overall, the prognosis is excellent, with 90% to 95% survival rates. Mortality stems mainly from catastrophic bowel loss and sepsis. Infants often have prolonged hospitalizations (weeks to months), since feeding intolerance is a major problem, even with an otherwise intact bowel. GERD can be severe, and infants are at higher risk for developing necrotizing enterocolitis (in up to 20% of patients postoperatively). Long-term complications arise from short bowel syndrome, especially in infants who have associated intestinal atresia. However, even in infants with gastroschisis and intestinal atresia, most patients eventually do well after bowel rehabilitation and hyperalimentation. Outcomes for patients with omphalocele are greatly dependent on associated anomalies. Most of the mortality and morbidity is related to the associated anomalies rather than to the AWD itself. In isolated omphalocele without major cardiac defect and normal karyotype, survival rates between 75% and 95% have been reported. Pulmonary hypoplasia is a limiting factor to survival, especially in patients with giant omphalocele, who may have long-term ventilator dependency.

## ANORECTAL MALFORMATIONS (IMPERFORATE ANUS)

Anorectal malformations (ARM), a wide spectrum of diseases involving the distal anus, rectum, and the genitourinary tract, occur in 1 in 5,000 live births.

### Embryology and Genetics

Anorectal malformations are considered a complex malformation of the hindgut. Although the etiology remains unclear, it is likely to be multifactorial. Certain risk factors such as fever during pregnancy, being overweight, caffeine intake, cigarette smoking, and certain occupational exposures have been implicated in increasing the risk for ARM. There is a familial component to these malformations, with the risk for siblings approximately 1 in 100. Approximately 50% of patients have associated genitourinary malformations; additionally, ARMs are common in patients with syndromes such as VACTERL, trisomies, and OEIS (*omphalocele, exstrophy, imperforate anus, spinal defects*).

### Diagnosis and Management

ARMs are generally diagnosed in the nursery on the first physical examination when the patency and

correct position of the anal opening is assessed. Anal stenosis and anterior ectopic anus most likely represent imperforate anus with perineal fistula. If there is no opening or fistula visualized, there may be a low lesion with well-formed buttocks and a so-called "bucket handle" (midline skin bridge or thickened raphe). After 24 hours, a bluish or black discoloration in the area will likely indicate accumulation of meconium behind the lesion. In higher lesions, the buttocks and the perineal area may seem flat and there may be a prominent sacral dimple. Meconium passage may be noted through either the urethra (recto-urethral fistula is common in boys) or in the introitus anterior to the vaginal opening in female infants. Rectovaginal fistulas are exceedingly rare. In females, there may be a single perineal orifice consistent with cloaca. In addition, infants may present with delayed passage of meconium, emesis, and abdominal distention (which may be caused by accumulating meconium in the intestines, but may also be secondary to hydronephrosis or hydrocolpos).

The presence of other malformations should also be investigated. Tethered cord is present in approximately 25% of patients with anorectal malformations; a spinal ultrasound or MRI should therefore be obtained in all patients with this diagnosis. Abdominal sonography can be helpful, especially to evaluate the pelvic organs, kidneys, and bladder. Radiographs to exclude sacral anomalies and a voiding cystourethrogram should be performed.

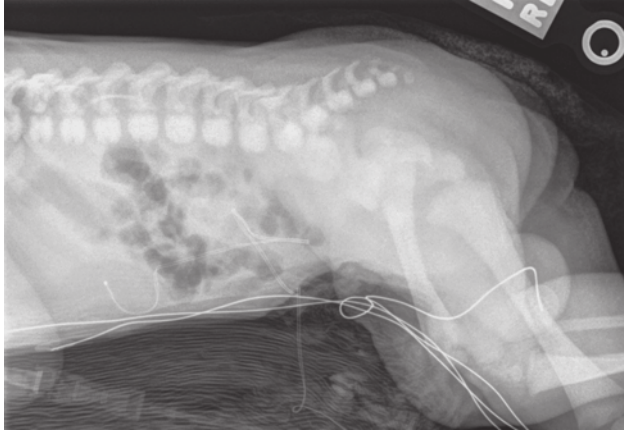
Initial management includes gastric decompression and intravenous fluid management. For male infants, a piece of gauze should be placed around the penis in order to filter any meconium particles in the urine. It is important to observe the infant for 16 to 24 hours prior to initiating diagnostic testing since meconium and air take time to fill the rectal area. In the small percentage of patients for whom clinical evidence does not delineate the likely anorectal anomaly, a cross-table lateral abdominal radiograph with the patient in prone position, obtained after 16 to 24 hours, can help show the air column in the distal rectum (Figure 108-15).

If there is evidence for a recto-urinary tract communication, male infants should undergo fecal diversion with colostomy. Definitive repair in the newborn period can be attempted; however, the risks for an adverse outcome are high since the exact position of the rectum is not known and there is a risk of injury to the adjacent structures. A primary repair is performed in female infants with a perianal fistula only; a colostomy is generally performed for other defects. A diverting colostomy helps avoid infections and wound dehiscence. The definitive repair, posterior sagittal anorectoplasty (PSARP), is usually performed at approximately 1 year of age in both male and female infants. More recently, a laparoscopic approach has been used in selected cases.

### Complications and Outcomes

The mortality in patients with anorectal malformations is low and is mainly related to other associated anomalies or chromosomal abnormalities. Postoperative complications such as colostomy prolapse,





**Figure 108-15** Imperforate anus. Cross table lateral radiograph in prone position shows absence of bowel gas beyond the S2 vertebra. (Radiograph and MRI images courtesy of Terry Levin, MD, Department of Radiology, Montefiore Medical Center.)

stricture, and stoma complications have decreased significantly, especially since the introduction of PSARP. Constipation is the most common functional disorder after repair for ARM, especially in low lesions, and is generally thought to be related to impaired gut motility. Proactive management of constipation is important and includes the use of laxatives, dietary manipulations, and enemas. Overflow incontinence can be an issue for these patients as well. True fecal incontinence and soiling is present in a smaller group of patients and is more common in patients with high lesions and sacral abnormalities. In most cases, these children require a bowel management regimen to achieve socially acceptable fecal continence. Urinary incontinence is mostly associated with sacral and neurologic abnormalities such as tethered cord. Before the introduction of PSARP, urinary problems were more common particularly in high lesions. Females with ARM have a high incidence of genital malformations, the most common being vaginal and uterine septation anomalies and vaginal agenesis. Vaginal scarring can interfere with sexual intercourse and childbirth in adult life.

### MECONIUM ILEUS AND MECONIUM PLUG SYNDROME

Meconium ileus (MI) and meconium plug syndrome (MPS) are associated with delayed passage of stool in the newborn. Most full-term infants will pass stool by 24 hours (97%), and almost every baby will have done so by 36 hours (99.8%) of age. There is generally no difference in the time to the first stool between formula and breastfed infants. Premature infants often take longer to pass their first stool. MI represents obstruction of the small bowel caused by accumulation of sticky and inspissated intraluminal meconium. In most cases, this results from intestinal and pancreatic dysfunction associated with CF. However, it is important to note that not all patients with MI have CF. It is

the third most common cause of neonatal small bowel obstruction. The simple form involves obstruction only, whereas *complicated* MI includes associated conditions such as volvulus, intestinal atresia, necrosis, perforation, and meconium peritonitis. On the other hand, MPS represents a transient large bowel obstruction which is relieved by passage of meconium plugs. MPS can be considered a presenting symptom rather than a diagnosis in itself as up to 38% of infants with MPS will eventually be diagnosed with HD. Patients with CF may also present with MPS. There is also an overlap with small left colon syndrome (SLCS), commonly seen in infants of diabetic mothers.

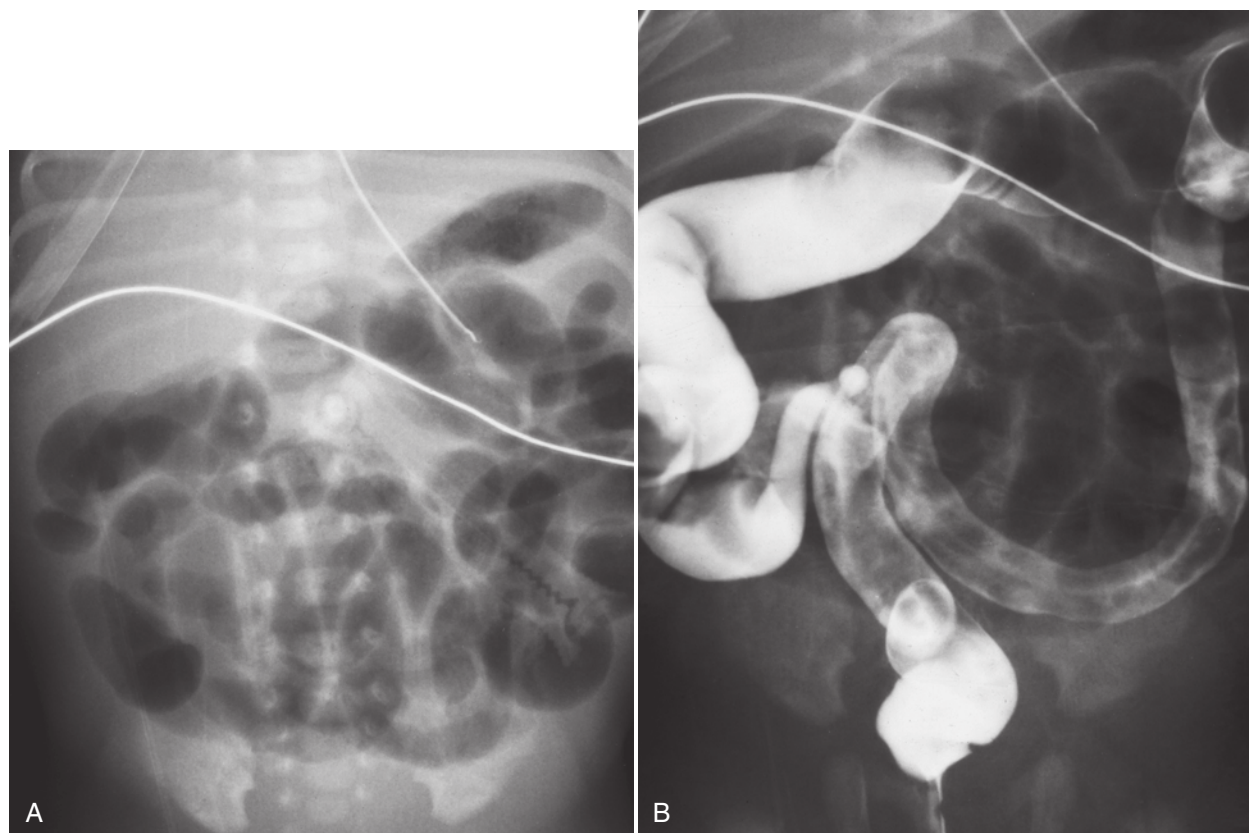
### Etiology and Genetics

In most cases, MI is the earliest presenting symptom of CF, an autosomal-recessive disease that occurs in approximately 1 in 2,500 live white births. Whites are estimated to be heterozygous carriers at a ratio of 1:20. A fetus with CF produces abnormal meconium marked by stool hyperviscosity as well as changes in the meconium contents. These characteristics result in adherence of meconium to the mucosal surface of the small bowel leading to obstruction. If the impaction is progressive, it can lead to complicated MI. In contrast, there are no known genetic causes of MPS; however, there is an association with HD and SLCS. The etiology for MPS is largely unknown but suspected to be related to transient decrease in intestinal motility.

### Diagnosis and Management

Prenatal ultrasound may show polyhydramnios, echogenicity of the bowel, and intra-abdominal calcifications in cases with meconium peritonitis. Parents may have been screened for CF during pregnancy, and a carrier state should raise the index of suspicion for MI. *Simple* MI and MPS have overlapping clinical presentations with the common presenting signs being abdominal distention, delayed passage of meconium (>24 hours), and bilious emesis. Sometimes, the impacted meconium can be palpated. In cases with severe abdominal distention, especially in complicated MI, the newborn may experience respiratory distress and seem ill. A rectal examination is important to evaluate anal tone and the presence of meconium in the rectal vault. Rectal stimulation during the examination may trigger the passage of meconium plugs in the case of MPS. Abdominal radiographs in MPS show nonspecific intestinal dilatation. In patients with MI, plain abdominal radiography may show signs of either small- or large-bowel obstruction depending on the location of the obstruction (Figure 108-16 and Figure 108-17).

The infant should first be evaluated for general appearance and hydration status, and feeds held. If the infant seems to be in no acute distress, rectal stimulation should be performed to see if passage of meconium can be triggered. A glycerin suppository may be helpful in some cases. After passage of meconium plugs, the subsequent stooling pattern should be monitored carefully. As there is an association with HD and in some reports also with CF, workup for both these conditions should be considered. Suction rectal



**Figure 108-16** A, Meconium plug syndrome with small left colon syndrome. B, Contrast enema demonstrating meconium plug syndrome with small left colon.

biopsy to rule out HD should be performed in patients with MPS.

If abdominal distention is present, the intestines should be decompressed with an orogastric tube. In an ill-appearing infant, vascular access should be established and intravenous fluids started. Hyperosmolar gastrografin enemas are considered the initial diagnostic procedure, and are often therapeutic in patients with MPS. Gastrografin enemas evacuate meconium in approximately 40% of patients with MI and are associated with a lower mortality rate than surgery alone. In patients with MI, if passage of meconium cannot be achieved with an enema, enterotomy and irrigation are likely needed. Complications such as atresia, perforation, and meconium peritonitis require immediate surgical intervention, including intestinal resection and intestinal anastomosis/ileostomy. Meconium ileus is the earliest manifestation of CF in 10% to 20% of patients, therefore it is important to rule out the disease once the immediate condition has been treated. The infant should be evaluated by a geneticist and referred to a CF center for testing.

### Complications and Outcomes

Patients with MPS will develop a normal stooling pattern once the meconium plugs have been evacuated. However, it is important for parents to watch for constipation. Hirschsprung disease should be ruled out by suction rectal biopsy and CF genetic testing

with arrangements at the time of discharge for appropriate follow-up primary pediatric and subspecialty care. Simple meconium ileus often resolves with an enema alone, and therefore few complications occur. In some instances, initial feeding intolerance and abnormal peristalsis may be present but these usually resolve with time. If operative management is required, postoperative complications include wound infections, ostomy-related problems, need for parenteral nutrition, and short-gut syndrome. Patients with CF require lifelong supplementation with pancreatic enzymes, appropriate nutritional support for adequate intestinal function, and pulmonary management. The care for patients with CF has improved significantly over the last decades, and therefore the quality of life and overall life expectancy have improved.

### SMALL LEFT COLON SYNDROME

Small left colon syndrome is a functional disorder of the lower colon that produces signs of intestinal obstruction in the neonatal period. The condition is associated most commonly with maternal gestational diabetes mellitus. The magnitude of the problem is difficult to estimate because most of the literature is comprised of case series or case reports.

### Etiopathology

The exact etiology underlying small left colon remains unclear. Davis reported the presence of an increased



**Figure 108-17** Meconium ileus.

number of small immature ganglionic cells in the myenteric plexus and suggested this hypercellularity was similar to that found in the colon of premature infants. Philippart proposed that humoral and autonomic nervous system changes, occurring in response to neonatal hypoglycemia, may contribute to the development of decreased intestinal motility. Glucagon release and sympatho-adrenal stimulation are typical responses to hypoglycemia as well as stress. Both glucagon and sympathetic stimulation are known to decrease intestinal motility. This theory also explains the occurrence of small left colon in the absence of diabetes mellitus. Other possible contributors to intestinal hypomotility include maternal medications used during the third trimester. This concept is supported by the report of cases of neonatal SLCS in infants born to mothers using psychotropic drugs with known anticholinergic effects and the recognized association between hypermagnesemia (in infants born to mothers treated with magnesium sulfate) and hypomotility conditions.

### Diagnosis and Management

Most infants with small left colon are born at or near term and are of normal birth weight. Most of these infants have a history of maternal diabetes mellitus. There may also be a history of other maternal comorbidities (usually eclampsia) which contribute to neonatal stress or the use of psychotropic medications like lithium. Affected infants usually present with delayed passage of meconium (>24 hours of



**Figure 108-18** Small left colon syndrome. Contrast enema shows an abrupt transition in the caliber of the small colon with a large caliber rectum.

life), bilious emesis or nasogastric aspirates, and progressive abdominal distention that may rarely progress to intestinal perforation. Plain radiographs of the abdomen reveal distal intestinal obstruction with air fluid levels. If there is no evidence of intestinal perforation on the plain radiograph, a contrast enema should be performed. Findings on contrast enema include dilation of proximal colon with abundant intraluminal meconium, an abrupt cone-shaped caliber transition at or just distal to the splenic flexure, and a constricted descending and sigmoid colon with a larger caliber rectum devoid of meconium (Figure 108-18). However, the radiographic findings in this condition can seem similar to HD; therefore, a rectal biopsy is warranted to look for aganglionosis. If meconium ileus is suspected, screening for CF should be performed.

Management should be directed toward appropriate fluid resuscitation, decompression of the abdomen to relieve symptoms of intestinal obstruction, and antibiotics if clinically warranted. For most patients with SLCS, the contrast enema is not only diagnostic but also therapeutic. Most infants pass meconium spontaneously after the procedure. Enteral feeds should be initiated cautiously after meconium passage. Surgery is generally not required for most cases; surgical intervention is reserved for patients with intestinal perforation or those with refractory intestinal obstruction.

### Complications and Outcomes

Most infants with small left colon do not require surgical intervention and advance to full enteral feedings fairly rapidly. Reports in literature indicate normalization of intestinal caliber within a few weeks in



numerous patients who have undergone follow-up examinations of their colon. However, a small number of patients experience delayed complications such as recurrent or refractory obstruction or delayed perforation. This necessitates monitoring of these infants closely during the first few weeks of life.

### HIRSCHSPRUNG DISEASE

Also known as congenital aganglionic megacolon, HD has an overall incidence of 1 in 4,000 live births and accounts for 20% to 25% of cases of neonatal bowel obstruction. The disease is 4 times more common in boys than in girls.

#### Embryology and Genetics

The cause of HD is an absence of enteric neurons within the myenteric and submucosal plexus of the rectum or colon. Although the rectosigmoid is most often involved, a variable length of the intestine can be affected. Approximately 8% of patients with HD have Down syndrome.

#### Diagnosis and Management

Nearly all children with HD are diagnosed within the first 2 years of life, with approximately one-half of the children being diagnosed before 1 year of age. The mean age at diagnosis has decreased to 2.6 months, chiefly because of vigilance on the part of physicians and early use of rectal biopsy to confirm the clinical diagnosis. A common presentation in the newborn period is failure to pass meconium during the first 36 to 48 hours of life, abdominal distention, and vomiting. Although such infants subsequently pass meconium, their bowel movements are sparse and irregular. Older infants and children present with chronic constipation (but rarely experience soiling and overflow incontinence) and may be malnourished. Enterocolitis is thought to be caused by bacterial proliferation as a result of stasis and typically presents with abdominal pain, fever, foul-smelling or bloody diarrhea, and vomiting. If not recognized early, enterocolitis can progress to sepsis, transmural intestinal necrosis, and perforation, and can be fatal.

Rectal examination may result in explosive expulsion of stool when the finger is removed. Plain abdominal radiographs show gas and stool in the colon but absence of stool and gas distal to the pelvic rim (Figure 108-19). Contrast enema may reveal a transition zone that separates the small- to normal-diameter aganglionic bowel from the dilated bowel above. However, a transition zone may not be recognizable in up to 25% of neonates with classic HD, in patients with ultrashort-segment HD, and in patients with total colonic aganglionosis in whom the transition zone is above the colon. The presence of contrast in the 24-hour delayed abdominal film also suggests HD. The definitive diagnosis of HD is made by demonstrating the absence of ganglion cells in the rectal biopsy tissue. Additionally, acetylcholinesterase staining of the rectal tissue identifies hypertrophy of extrinsic nerve trunks.

Initial management includes intravenous hydration, withholding enteral feeds, gastric decompression, and



**Figure 108-19** Hirschsprung disease. Plain abdominal radiograph shows dilated bowel loops with paucity of air in the rectum.

serial rectal irrigations to decompress the bowel and prevent the development of enterocolitis. Patients with enterocolitis should be treated with decompression of the rectum with a large catheter and with warm saline irrigations several times a day, volume resuscitation, and administration of broad-spectrum antibiotics. In otherwise healthy newborns with short-segment HD and a normal-caliber colon, a single-stage ileoanal pull-through procedure may be performed. In patients with associated enterocolitis or a significantly dilated colon, surgical management includes a staged procedure with placement of a diverting colostomy at the level of normal bowel, and rectal irrigations followed by rectal resection with a pull-through procedure once the bowel caliber is restored to normal. The ability to perform a single-stage pull-through procedure largely depends on the availability, experience, and capabilities of the staff pathologist because aganglionic intestine must not be in the pull-through segment.

#### Complications and Outcomes

Postoperative complications include intermittent fecal soiling and incontinence, anastomotic leak, stricture formation, intestinal obstruction, and enterocolitis. Most children achieve fecal continence; however, children with Down syndrome may be expected to have lower rates of fecal continence. Management of postoperative enterocolitis includes rectal irrigations several times a day and antibiotic therapy; in some cases, application of topical nitric oxide, posterior



myotomy/myomectomy, or injection of botulinum toxin may be warranted.

### SUMMARY

It is important for pediatricians to have a high index of suspicion and be familiar with a stepwise approach to the evaluation of neonates with GI symptoms. A complete physical examination and assessment of the patient's overall clinical condition should be followed by appropriate radiographic studies and blood tests. In cases with congenital anomalies, further evaluation of associated anomalies or syndromes is important. Early subspecialty involvement can save valuable time and expedite patient care. Discussions with the family regarding the immediate delivery room management (in cases of antenatal diagnosis) as well as long-term management and anticipated complications can help ease parental anxiety and concerns.

Lastly, for the pediatrician caring for older children, it is important to remember that some of these patients can have long-term consequences that may, at first glance, seem not to be directly related to the original disease.

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## SECTION FOUR

# Perinatal Care: Caring for the High-Risk Infant

### Chapter 109

## ASSESSMENT AND STABILIZATION AT DELIVERY

Joaquim M. B. Pinheiro, MD, MPH

Most neonates successfully meet the challenge presented by labor, the delivery process, and subsequent adaptation to the extrauterine environment. Birth is the riskiest stage of life because failure of postnatal transition can result in immediate physiologic instability, end-organ dysfunction, and disability or death. Approximately 10% of neonates require some resuscitative assistance during transition in the delivery room. In subgroups such as very low-birth-weight newborns, (<1,500 g), 90% require immediate respiratory support; although most of these neonates need only oxygen, approximately 6% receive advanced resuscitation, including chest compressions.

Prenatal history and intrapartum evaluation allow physicians to anticipate most newborns who will need resuscitation after delivery; still, unexpected complications are common. Immediate assistance aimed at ensuring stabilization and appropriate transition of the neonate must be available and effectively implemented, usually in the first few minutes of life. Thus, the American Academy of Pediatrics (AAP) and American College of Obstetrics and Gynecology (ACOG), in their *Guidelines for Perinatal Care*, recommend that “[a]t every delivery, there should be at least one individual whose primary responsibility is the newborn and who is capable of initiating resuscitation, including positive pressure ventilation (PPV) and chest compressions. . . . Either this individual or someone else who is immediately available should have the skills required to perform a complete resuscitation, including endotracheal intubation, establishment of vascular access, and the use of medications.”

A skilled resuscitator does not suffice to ensure an effective resuscitation. An integrated approach involving all perinatal staff is needed for immediate recognition of distressed neonates, communication among care providers, and rapid implementation of accepted resuscitation procedures. The Neonatal Resuscitation Program (NRP), jointly sponsored by the American Heart Association and the AAP, provides evidence-based guidelines and expert opinion on neonatal resuscitation. The guidelines include a curriculum for training and evaluating neonatal primary care physicians, individually and in teams, and practical tools to guide resuscitation. Because the NRP curriculum is now used to train most providers of neonatal resuscitation in the United

States and in many other countries, hospitals base their neonatal resuscitation procedures on principles espoused by the NRP, adapted to local resources. As a result, this chapter suggests practices generally aligned with those published by the NRP. Of particular note are NRP recommendations including delayed cord clamping in selected neonates, de-emphasis of color in favor of pulse oximetry to assess oxygenation, restriction of oxygen use during postnatal transition, and less aggressive suctioning of the airway in both meconium-stained and other newborns.

This chapter is intended for primary care physicians and other providers of neonatal primary care who may practice at hospitals without a tertiary care perinatal center. It focuses on practical evaluation and management of neonates who need assistance during transition in the delivery room setting. After briefly reviewing the physiologic basis of neonatal resuscitation, it outlines the necessary physical infrastructure, provider roles, and procedures for routine and contingency resuscitations. Routine care of neonates and evaluation of sick newborns after the delivery room transition are addressed in Chapter 110, Identifying the Newborn Who Requires Specialized Care; and Chapter 114, Follow-up Care of the Graduate From Neonatal Intensive Care.

### ANTICIPATING HIGH-RISK DELIVERIES

Prenatal anticipation of the need for neonatal resuscitation allows time for adequate preparation. Significant resuscitative interventions in the delivery room can be expected in very premature newborns (with gestational age <32 weeks [32%–32%]) and those with major congenital malformations.

Gestational age should be assessed before birth because obstetric criteria are more accurate for this purpose than a postnatal physical examination that uses a method such as the New Ballard Score. An accurate approximation of gestational age is particularly crucial in deliveries around the edge of viability, between 21 and 25 weeks of gestation. Because no official algorithm exists to ensure uniform determinations of gestational age by obstetricians, finding discrepant gestational ages on a maternal record is common. Primary care physicians should verify the obstetric estimation of gestational age, which is optimally based on the first day of the mother's last menstrual period, and confirmed by an early prenatal ultrasound. Proper advanced planning, which ranges from withholding resuscitation to advanced notification of a regional center's transport team, is contingent on obtaining reliable gestational age estimates.

**BOX 109-1 Factors That Increase the Likelihood of Neonatal Resuscitation****PREPARTUM PRESENTATION**

- Indicated preterm delivery<sup>a</sup>
- Magnesium sulfate<sup>a</sup>
- Maternal infection<sup>a</sup>
- Oligohydramnios<sup>a</sup>
- Hydrops fetalis<sup>a</sup>
- Major fetal malformations<sup>a</sup>
- Multiple gestation<sup>a</sup>
- Size-date discrepancy<sup>a</sup>
- Lung immaturity
- Premature rupture of membranes
- Postterm gestation (>42 weeks' gestation)
- Diminished fetal activity
- Polyhydramnios
- Fetal anemia
- Maternal hypertension
- Maternal diabetes
- Maternal drug abuse
- Acute maternal illnesses
- Recent vaginal bleeding
- Maternal adrenergic blockade
- No prenatal care

**INTRAPARTUM PRESENTATION**

- Preterm delivery<sup>a</sup>
- Chorioamnionitis<sup>a</sup>
- Meconium-stained amniotic fluid<sup>a</sup>
- Abnormal fetal heart rate<sup>a</sup>
- Emergency cesarean delivery<sup>a</sup>

- Placental abruption<sup>a</sup>
- Cord prolapse<sup>a</sup>
- Maternal narcotics <4 hours before delivery
- Abnormal presentation (breech, transverse)
- Placenta previa
- Cord compression
- Precipitous labor
- Prolonged labor
- Prolonged second stage of labor >2 hours
- Shoulder dystocia
- Uterine tetany
- Ruptured membranes >18 hours
- General anesthesia
- Maternal hypotension
- Forceps- or vacuum-aided delivery

**POSTPARTUM PRESENTATION**

- Severe respiratory distress<sup>a</sup>
- Drug-induced depression<sup>a</sup>
- Central nervous system injury<sup>a</sup>
- Central nervous system anomalies
- Spinal cord injury
- Airway obstruction
- Sepsis or infection
- Diaphragmatic hernia
- Pneumothorax
- Deformities
- Abdominal anomalies

<sup>a</sup>Most common and significant conditions.

Congenital malformations identified prenatally, whether necessitating neonatal surgery or potentially interfering with cardiorespiratory transition at birth, may require specialized resuscitative interventions in the delivery room.

Common intrapartum exposures such as maternal magnesium sulfate therapy and chorioamnionitis are usually identified well in advance of the delivery. However, meconium staining of the amniotic fluid and significant decelerations of the fetal heart rate are most often noted just before delivery. Review of the obstetric history is useful to identify these and other factors (Box 109-1) that may affect the newborn's need for resuscitation and early postnatal care.

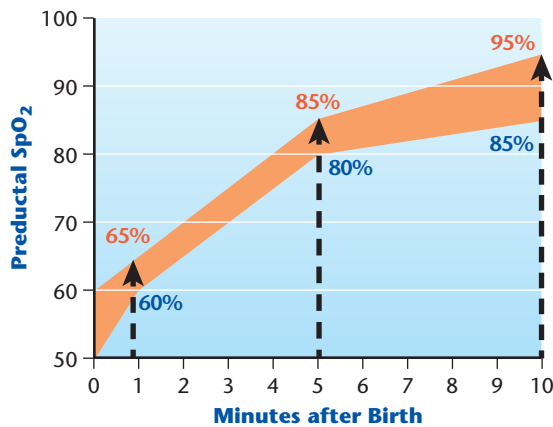
A continuum of risks is anticipated at delivery. Each institution should establish specific criteria delineating which deliveries require the presence of a separate team to care for the neonate, as well as the composition of such a team, according to level of risk. The traditional practice of calling a neonatal team to every cesarean delivery, initially justified by the use of general anesthesia in the mother and the frequent presence of fetal distress as the indication for urgent surgical delivery, is no longer sensible. Rates of cesarean section delivery now exceed 30% in the United States, with many

medically and socially elective surgical deliveries, prompted by prior cesarean deliveries or maternal choice. Given that the need for pediatric staff attendance at low-risk, elective cesarean deliveries is controversial, individual hospital obstetric and newborn service providers should consult with their risk management department to develop policies and programs that best serve their unique circumstances.

## ESSENTIAL TRANSITIONAL CARDIORESPIRATORY PHYSIOLOGY

The successful establishment of cardiorespiratory function in the newborn requires adequately grown and unobstructed conducting airways, gas-exchanging airways with sufficient surfactant and matching pulmonary vasculature, removal of fetal lung fluid, sustained breathing, and a rapid increase in pulmonary blood flow. These changes result in a gradual rise in preductal O<sub>2</sub> saturation (SpO<sub>2</sub>) from 65% to 90% over the first 10 postnatal minutes (Figure 109-1). Anatomic or functional derangements in 1 or more of these areas can result in cardiorespiratory insufficiency in the newborn. Although these functions may be approached by following the ABC (airway, breathing, circulation)





**Figure 109-1** Targeted preductal SpO<sub>2</sub> in the 10 minutes following birth, reflecting the ranges expected in normal neonates. Note the gradual rise in SpO<sub>2</sub> from 65% to 85%–95%. (Drawn from data in Kattwinkel J, Perlman JM, Aziz K, et al. Neonatal Resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Pediatrics. 2010;126:e1400–e1413.)

sequence commonly taught for resuscitation, each requires integration of respiratory, hemodynamic, neurologic, and other inputs.

A functional airway must be anatomically normal, externally straight and uncompressed, and unobstructed by intrinsic structures such as the tongue or vocal cords; its lumen must also be clear of extraneous matter (eg, amniotic fluid, meconium, blood, secretions). The initial postnatal breaths clear lung fluid from the airways and establish a gaseous functional respiratory capacity; normal tone of pharyngeal and laryngeal muscles sustains a patent upper airway. Thus, any condition that causes apnea, generalized hypotonia, or laryngospasm at birth will compromise the airway.

Box 109-2 lists common or typical causes of symptomatic airway obstruction in the immediate postnatal period. They are categorized according to whether they are extrinsic to the airway, intrinsic to airway structures, or the result of removable luminal fluids or particulates. The actual incidence of these conditions is unknown, and they may coexist (eg, mild laryngomalacia, nasal secretions, nasal mucosal edema). Iatrogenic causes are emphasized because they are common and mostly preventable. For example, airway obstruction can easily occur during bag-mask ventilation, through mandibular pressure from the mask or from impingement of the resuscitator's fourth and fifth fingers on submandibular tissue. Laryngospasm can be readily induced by mechanical stimulation of the hypopharynx or larynx with a suction catheter or laryngoscope.

In the newborn, initial breaths inflate and aerate the lungs and promote gas exchange. Each of these elements has independent and synergistic physiologic effects. Lung inflation decreases vagal tone, directly diminishing the apneic and bradycardic effects of vagal activity. Lung inflation and aeration each

### BOX 109-2 Common or Prototypical Causes of Airway Obstruction in the Newborn

#### EXTRINSIC

- Mandibular pressure from facemask<sup>a</sup>
- Submandibular pressure from resuscitator's fingers<sup>a</sup>
- Kinked upper airway (flexed or hyperextended)<sup>a</sup>
- Masses (eg, epulis)
- Vascular ring

#### INTRINSIC (PARIETAL)

- Hypotonic pharyngeal muscles, tongue
- Laryngospasm
- Nasal trauma, edema
- Airway malformations (Pierre Robin sequence, choanal atresia)
- Laryngomalacia
- Vocal cord paralysis

#### INTRALUMINAL

- Pharyngeal secretions (with or without meconium, blood)
- Nasal secretions
- Residual lung fluid
- Aspiration of upper airway fluid and suspended particles

<sup>a</sup>Most common and significant conditions.

decrease pulmonary vascular resistance, allowing the postnatal increase in pulmonary blood flow necessary for gas exchange; the latter is optimized by the inflation-induced stimulation of surfactant secretion. The subsequent increase in systemic oxygenation has additional vagolytic effects.

Significant intrapartum hypoxia and exposure to common medications such as magnesium sulfate and narcotics depress respiratory drive, producing hypopnea or apnea in the newly born. Common and archetypal causes of apnea in the delivery room are listed in Box 109-3. In most instances, the neonate exhibits primary apnea, which is induced by respiratory reflexes and is thus readily reversed. Secondary apnea is much less common because it reflects significant hypoxia-ischemia, with resulting metabolic dysfunction of the central respiratory apparatus. Protracted depression of the respiratory drive can also be the result of transplacental transfer of maternal medications with neuroinhibitory effect.

Hypoventilation may occur despite unobstructed conducting airways and normal or increased respiratory effort. Common or typical conditions causing hyperpneic respiratory failure include severe lung immaturity (respiratory distress syndrome), lung hypoplasia (diaphragmatic hernia, oligohydramnios), and external impediments to lung inflation (tension pneumothorax, large pleural effusions, thoracic hypoplasia).

### BOX 109-3 Common or Prototypical Causes of Apnea or Hypopnea in the Newborn

- Hypoxemia
- Reflexes elicited by trigeminal or ocular pressure, laryngeal stimulation
- Deflated lungs
- Airway obstruction
- Magnesium sulfate
- Recent intrapartum narcotics
- General anesthesia (rare)
- Hypoxia-ischemia

Circulatory adequacy depends on heart rate and stroke volume. Thus, cardiac output is compromised by bradycardia, acute hypovolemia, or both. In addition, an inadequate increase in pulmonary blood flow at birth will cause functional circulatory insufficiency with consequent hypoxemia. Rare anatomic defects such as transposition of the great vessels with intact ventricular septum can produce severe, persistent hypoxemia from birth. However, cardiovascular lesions that depend on patency of the ductus arteriosus for maintenance of pulmonary or systemic blood flow would not become symptomatic in the delivery room.

Common causes and clinical correlates of inadequate transition from fetal to newborn circulation are listed in Box 109-4. Acute hypovolemia is particularly difficult to diagnose because pallor and peripheral vasoconstriction commonly result from the catecholamine surge induced by fetal or neonatal distress (or both) and acidosis. However, when these symptoms occur in the setting of a tight nuchal cord, hypovolemia caused by significant fetoplacental transfusion should be suspected; this condition is likely underdiagnosed and occurs in approximately 3% of deliveries at term. Clamping of the umbilical cord early after birth interrupts the normal return of placental blood to the newborn, resulting in a blood volume deficit in excess of 20 mL/kg birth weight, which may be prevented by delaying cord clamping for 30 to 60 seconds (see section on delayed umbilical cord clamping).

Another typical transitional disorder is persistent pulmonary hypertension, with right-to-left shunt at the level of the foramen ovale and ductus arteriosus and with consequent systemic hypoxemia. The persistently increased pulmonary vascular resistance may result from a combination of inadequate lung inflation, alveolar hypoxia, hypoventilation, and acidosis; these complications may be superimposed on hypoplastic or hyperreactive pulmonary vasculature, and they may be exacerbated by hypothermia developing during resuscitation.

Thermoregulation is a fundamental but easily overlooked aspect of transition in neonates requiring cardiopulmonary resuscitation. Hypothermia can develop within minutes, and it adversely affects circulatory transition because it induces pulmonary vasoconstriction and increases oxygen consumption. Thus, efforts

### BOX 109-4 Common or Prototypical Causes of Inadequate Circulatory Transition in the Newborn

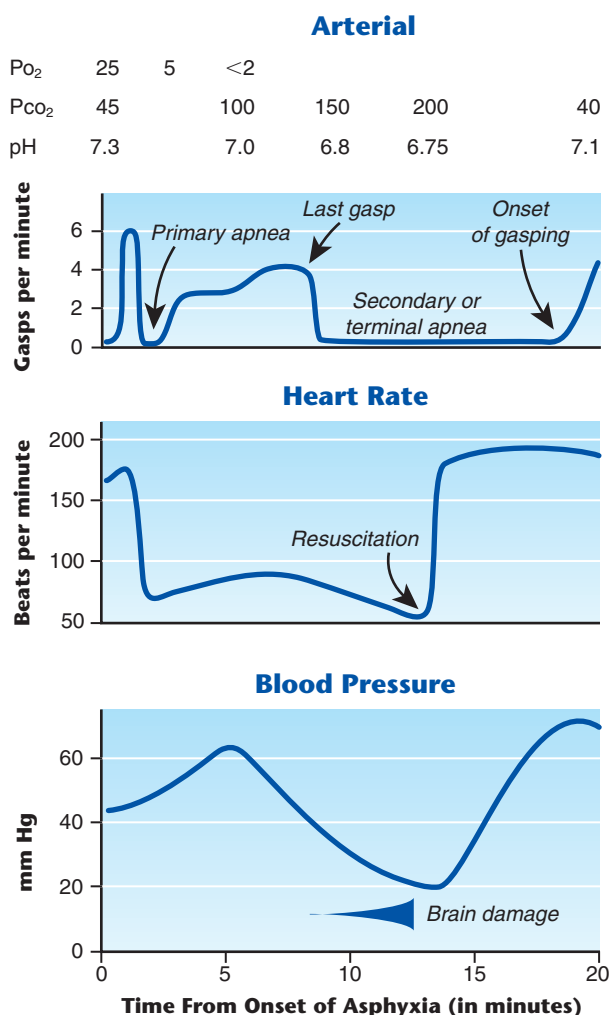
- Acute hypovolemia (nuchal cord, fetoplacental or fetomaternal transfusion, placental abruption, cord accidents, early cord clamping)
- Prolonged fetal bradycardia
- Persistent pulmonary hypertension (lung hypoplasia, fetal distress, meconium aspiration, asphyxia)
- Hypothermia
- Polycythemia
- Hydrops fetalis
- Transposition of the great vessels (with intact ventricular septum)
- Cardiomyopathy
- Pneumopericardium
- Tension pneumothorax

to maintain a neutral thermal environment and minimize heat losses should precede resuscitation and be sustained while performing other interventions (in mnemonic terms, T-ABC[D] [temperature, airway, breathing, circulation, drugs]).

## ACUTE FETAL HYPOXIA AND ASPHYXIA

Despite the myriad causes of cardiorespiratory insufficiency in the neonate, acute hypoxia that develops during or immediately after birth is a central feature of most transitional disorders. Sustained hypoxemia and ischemia result in asphyxia and ultimately death. Intermittent fetal hypoxia occurs normally with uterine contractions as a result of decreased uterine blood flow, umbilical cord compression, or both. Pathologic intrapartum hypoxia likely develops most often in susceptible human fetuses by repetitive cord compression and incomplete recovery between contractions.

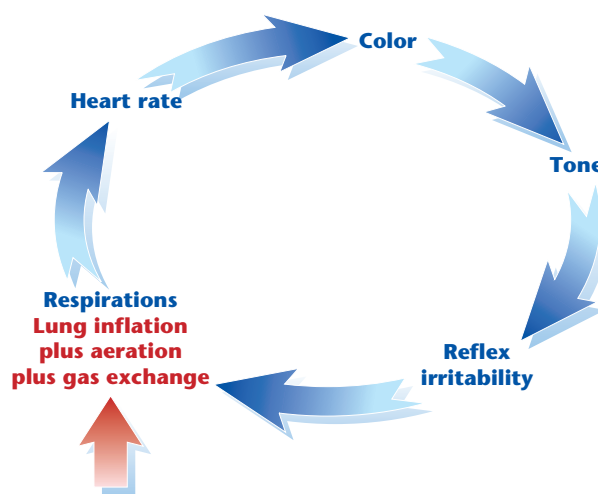
Much of the understanding of the physiology of asphyxia is extrapolated from Dawes' experiments with acute total asphyxia in a normal newborn rhesus monkey model. Figure 109-2 illustrates the progression of cardiorespiratory and neurologic dysfunction during acute asphyxia, produced by delivering the animal's head into a saline-filled bag and clamping the umbilical cord. The initial response to hypoxia is reflex (primary) apnea and bradycardia. Progressive mixed acidosis ensues and induces gasping, which ceases as the respiratory centers develop severe metabolic dysfunction; this stage is the phase of secondary (or terminal) apnea and bradycardia, during which neurologic responsiveness has been lost, and only artificial resuscitation can avert death. Permanent brain injury may develop during this stage. Resuscitation with PPV results in immediate recovery of the heart



**Figure 109-2** Sequence of cardiorespiratory and neurologic abnormalities during total acute asphyxia followed by positive pressure ventilation in newborn rhesus monkeys. (From Dawes GS. Fetal and Neonatal Physiology. Chicago, IL: Year Book Medical Publishers, Inc; 1968:149. Copyright 2008 Elsevier Ltd. Reprinted by permission.)

rate, return of blood pressure, and finally, the reappearance of gasping respirations.

The importance of reflex mechanisms in determining immediate cardiorespiratory responses in the newborn cannot be overemphasized. Natural and iatrogenic stimuli, including hypoxia, acidosis, lung deflation, trigeminal pressure, and secretions or mechanical irritation in the periglottic region act synergistically to induce laryngeal closure, central apnea, and bradycardia. These reflex responses are mediated through arterial chemoreceptors and vagal and somatosensory afferents. Conversely, simple lung inflation stimulates pulmonary stretch receptors, producing an immediate vagolytic effect while desensitizing laryngeal and carotid body reflexes and inducing further deep inspirations through the Head paradoxical reflex. Adequate lung inflation, whether spontaneous or assisted, is therefore paramount in restoring spontaneous cardiorespiratory and neurologic function in the depressed newborn.



**Figure 109-3** Recovery of clinical signs within the Apgar scoring system in response to assisted ventilation. Immediate responses are reflexive in nature; the cycle is sustained by oxygen transport and metabolism.

Cardiorespiratory depression in a newborn thus results from cardiorespiratory reflexes superimposed on and interacting with a continuum of hypoxia-ischemia. Rapid assessment of the severity of physiologic dysfunction in the individual baby is essential to apply appropriate resuscitative measures. In the clinical setting, practical evaluation methods must be used in place of invasive physiologic measurements. The Apgar scores were traditionally devised for this purpose, but they are no longer recommended as a guide to resuscitation, partly because evaluation of heart rate, respirations, tone, reflex irritability, and color cannot be done rapidly, reliably, and unobtrusively in emergency conditions. The NRP now recommends repeated assessment of the dyad of respirations and heart rate to guide further interventions in the delivery room, whereas pulse oximetry should replace color when evaluating SpO<sub>2</sub>. Nevertheless, Apgar scores are still routinely obtained to assess the condition of the newborn. Both the Apgar scoring system and the abbreviated NRP evaluation method can be fundamentally understood from the continuum of perinatal depression studied by Geoffrey Dawes in animal models and observed by Virginia Apgar in human newborns.

As shown in Figure 109-3, the 5 clinical signs in the Apgar scoring system can be considered as sequential steps in a cycle of oxygen transport and utilization. Individual signs are further linked through reflex mechanisms. Conditions that depress fetal cardiorespiratory or neurologic function in the immediate perinatal period will produce primary apnea and hypoventilation in the newly born. Failure of lung inflation, aeration, and oxygenation triggers a sequence of progressive dysfunction. The increased vagal tone causes reflex (*primary*) apnea and bradycardia. Consequent progressive hypoxia produces cyanosis and promotes gradual loss of neuromuscular function. Sustained hypoxia results in metabolic dysfunction in the muscular and central neurologic systems, culminating in secondary apnea and

concurrent unresponsiveness to stimuli. Asystole follows prolonged, severe hypoxia.

Figure 109-3 depicts the sequence of recovery of functions when effective resuscitation with positive pressure ventilation is applied before the onset of asystole. The vagolytic effect of lung inflation immediately increases heart rate. Peripheral oxygenation then visibly improves, and neuromuscular function gradually recovers, ultimately producing sustained respirations.

Understanding these intrinsic relationships within the Apgar system facilitates the assessment of depressed newborns independently of the attribution of numerical scores. The abbreviated evaluation scheme suggested by the NRP includes initial muscle tone followed by repeated rapid assessment of respirations and heart rate, then oxygenation through oximetry. The NRP method effectively uses the same basic functions as the Apgar system without the obtrusive scoring. Given the interdependence of the 5 clinical signs, isolated abnormalities in any measure should suggest specific causes directly affecting that sign and unrelated to hypoxia (eg, sustained bradycardia in a pink, vigorous newborn might indicate congenital heart block).

The concerns about hypoxia must be complemented by the understanding that even brief hyperoxia during or following resuscitation may exacerbate adverse neonatal outcomes.

## RESUSCITATION IN THE DELIVERY ROOM

### Withholding, Limiting, or Withdrawing Resuscitation

Resuscitation of the newborn is a medical intervention with variable effectiveness, benefits, and risks, which largely depend on the baby's underlying conditions and gestational age. In keeping with ethical principles, resuscitation should not be applied indiscriminately to all newborns with cardiorespiratory depression, particularly when the prognosis for survival is poor or when survival will likely be burdensome to the child. Because most delivery room resuscitations are expected, time is usually available to discuss the expected outcomes with the family. An evidence-based, family-centered valuation of the outcomes of resuscitation should guide clinical decision making in the delivery room. Ideally, the obstetric and pediatric physicians and the parents would reach a common understanding of the goals of resuscitation before the time of birth. Only then can the extent of interventions be tailored to the individual mother and baby—including the options of continuous fetal monitoring, cesarean delivery, and withholding or limiting resuscitation of the newborn.

Resuscitation and subsequent intensive care are indicated when survival is likely and risk for unacceptably severe morbidity is low.

Resuscitation is generally not indicated in babies with poor prognoses that entail early death or major morbidities in the rare long-term survivor. Newborns in this category may include those of confirmed gestational age less than 23 weeks or birth weight below 400 g, those with anencephaly, and

those with confirmed trisomy 13 or 18 or other known lethal anomaly. Comfort care and support of the family are always indicated.

Noninitiation of resuscitation is also appropriate at the parents' request for some infants with uncertain prognosis, including those with high probability of death or extreme morbidity. Newborns at 23 to 24 weeks' gestation typify a situation in which the parents' wishes for resuscitation should be ascertained, respected, and supported by physicians. To provide accurate information to parents, physicians must first attempt to minimize the uncertainty inherent in gestational age determinations, and consider additional prognostic factors such as gender, weight, antenatal glucocorticoid exposure, and multiple gestation. A calculator of expected outcomes in extremely preterm births is available online at [www.nichd.nih.gov/about/org/der/branches/ppb/programs/epbo/Pages/epbo\\_case.aspx](http://www.nichd.nih.gov/about/org/der/branches/ppb/programs/epbo/Pages/epbo_case.aspx). This approach is suggested by the NRP and supported by the AAP Committee on Fetus and Newborn and the Canadian Paediatric Society.

### Preparing for Resuscitation

To maximize the efficiency of stabilization during the initial, crucial 10 minutes after birth, the resuscitation team should be organized in advance, familiar with the available equipment, and informed about the prenatal factors relevant to accurate assessment of the individual newborn (Box 109-5).

Before or at arrival at the delivery site, the resuscitation team can rapidly assess the fetal condition by ascertaining gestational age, other major underlying diagnoses, and evidence of fetal distress. Next, the resuscitation equipment and medications can be checked and organized systematically by applying the T-ABC(D) mnemonic. Team leadership and additional roles should be defined, and additional support should be sought if needed. If time permits, a more detailed assessment of the fetal and maternal risk factors can then be undertaken. The pediatric team should assess and plan the resuscitation by communicating clearly with the obstetric staff and the family, among themselves, and with a tertiary care center if neonatal transport is anticipated.

By directly observing the last few minutes of the delivery, rather than waiting by the resuscitation table, the team leader can obtain useful information that is often not verbally communicated. This information may include the fetal heart rate pattern during the last contractions, presence or absence of meconium or blood in the mouth, a tight nuchal cord, the baby's facial response to suctioning or handling, and the tone immediately after expulsion. Awareness of these factors allows the resuscitator to stay a step ahead and quickly identify the hypovolemic baby after a fetoplacental transfusion or question the reported absence of heart rate in the newborn who had some flexor tone after expulsion, 40 seconds prior.

## INITIAL POSTNATAL EVALUATION AND INTERVENTION

The general flow of neonatal resuscitation, according to the NRP, is shown in Figure 109-4.



**BOX 109-5 Domains of Preparation for Delivery Room Resuscitation****ASSESSMENT OF THE FETUS**

- Gestational age
- Anticipated fetal pathologic abnormality
- Signs of fetal distress
- Fetal heart rate tracing
- Meconium
- Pregnancy history
- Course of labor
- Intrapartum medications
- Risk factors for infection
- Other (eg, major bleeding)

**RESUSCITATION EQUIPMENT****Thermoregulation**

- Warmer, towels, plastic wrap

**Airway**

- Suction (bulb syringe and wall), catheters, meconium aspirator

- Intubation equipment (functioning laryngoscope; endotracheal tubes)

- Laryngeal mask airway

**Breathing**

- Ventilation equipment, tubing, blended oxygen supply and pulse oximeter, carbon dioxide detector

**Circulation**

- Location of medications, catheters

**Drugs**

- Other medications, if needed (eg, surfactant)

**PERSONNEL ROLES**

- Airway manager
- Assistant to monitor heart rate
- Other assistants as needed

Cycles of assessment and consequent appropriate intervention are repeated at approximately 30-second intervals, following the ABC(D) sequence, while thermoregulation is maintained throughout. Subsequent care, from routine to postresuscitation stabilization, depends on the level of intervention needed during the initial resuscitation. This algorithm may be used to perform a quick initial assessment of a newborn. Three essential questions are asked, as listed in Box 109-6. The first question can be answered before delivery, and the last 2 within seconds after birth. For most newborns, the answer to these 3 questions is yes, and such newborns require only thermoregulatory support (warmth and drying), maintenance of an open and clear airway, and assessment of color to verify respiratory and circulatory efficacy. Such babies can remain with their mothers. The subsequent discussion applies to the few newborns who need assistance with transition.

Very premature newborns ( $\leq 28$  weeks' gestation) lose heat rapidly, and they often develop hypothermia despite standard thermoregulatory care. The delivery or resuscitation room temperature should be increased to 77°F to 79°F (25°C–26°C), if possible. Prewarmed, dry blankets diminish conductive heat losses. Most important, convective losses should be minimized by immediately covering the baby with a plastic barrier. This goal can be achieved by placing the baby in a clean, food-grade polyethylene bag. Alternatively, 2 sheets of nonadhesive Saran-type wrap (or another brand of polyvinylidene chloride film) can be used to wrap the head and the body below the neck, respectively. In some settings, using exothermic mattresses and a warmed incubator for transfer to the neonatal unit may also be helpful.

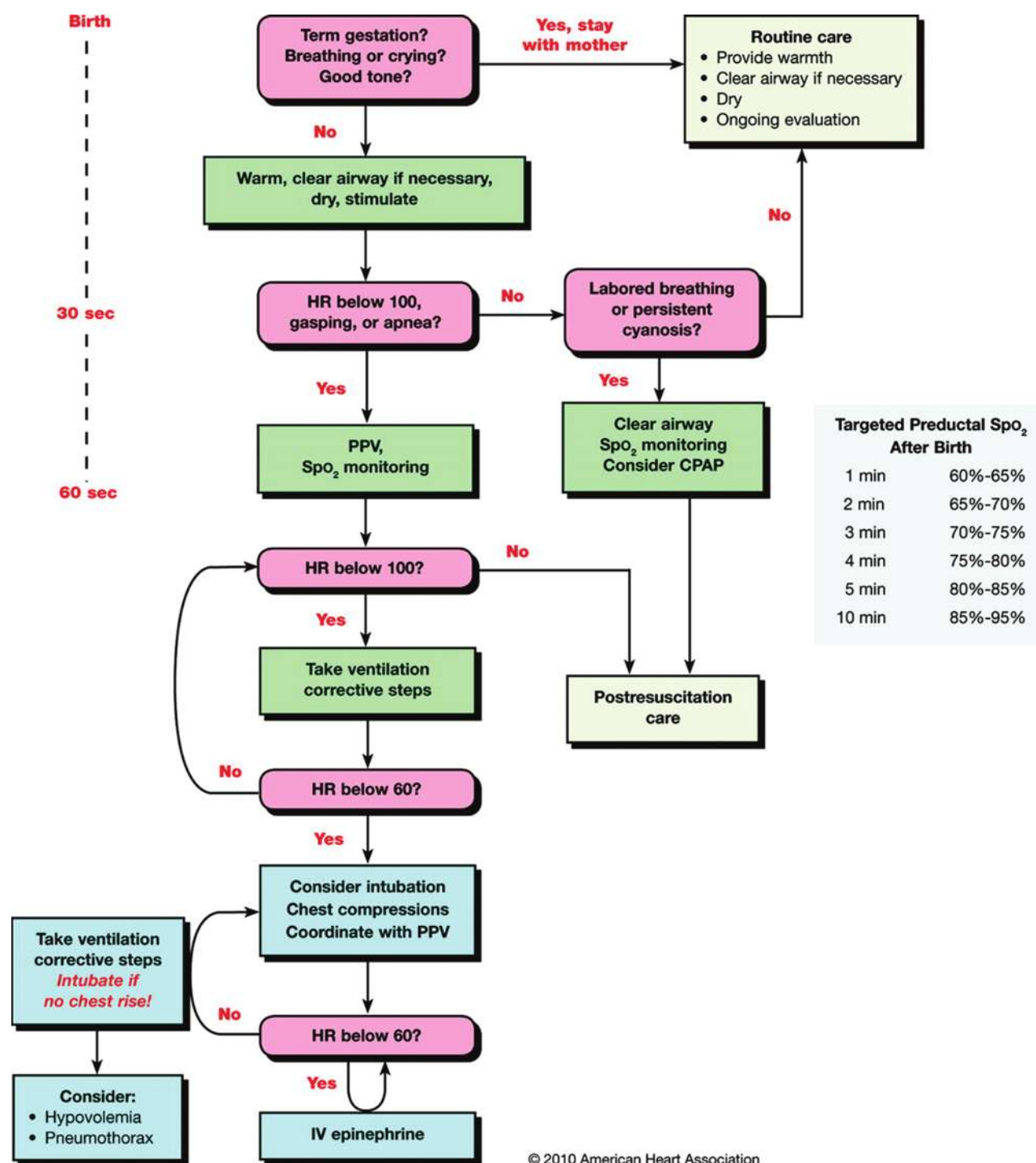
If the amniotic fluid contains meconium, blood, or infected matter, or if the newborn infant is not breathing

or exhibits hypotonia, then immediate airway management is needed while supporting thermoregulation.

The airway can be approached by external positioning and internal suctioning, in that order (see Box 109-2). External patency is ensured by positioning the head so that the neck is slightly extended, in the sniffing posture; the mandible should be lifted anteriorly. Internal airway patency is achieved by suctioning to remove obstructing matter (meconium, bloody or infected secretions) from the mouth first and then the nose. Routine suctioning of clear, non-obstructing secretions is unnecessary, and it can cause bradycardia.

Meconium or pus in the amniotic fluid is not an exception to the *airway before breathing* rule. Meconium-stained babies who are vigorous (as evidenced by strong respirations, normal muscle tone, and heart rate  $>100$  beats/minute) have already established an airway and effective breathing, so they need only observation and routine care with the mother. However, meconium-stained babies who are not vigorous (ie, they have suboptimal respirations, muscle tone, or heart rate) may benefit from tracheal intubation and direct suctioning, in addition to clearing of the oropharyngeal airway. Assistance with breathing, whether by stimulation or PPV, should not be given until suctioning has been performed. Suctioning of the airway before delivery of the head does not improve meconium aspiration syndrome or related outcomes in meconium-stained babies. Therefore, routine intrapartum suctioning of such babies by the obstetrician is no longer recommended. Previous practices, such as judging the thickness of the meconium and visualizing the cords to decide whether to intubate, are not supported by evidence.

Approximately 30 seconds after birth, most newborns have been provided with a patent airway, as well as some tactile stimulation through drying. Recurrent



**Figure 109-4** Chart describing general flow of neonatal resuscitation. Endotracheal intubation may be considered at several steps. (Reprinted from Kattwinkel J, Perlman JM, Aziz K, et al. Neonatal Resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Pediatrics. 2010;126:e1400-e1413. Available at: [pediatrics.aappublications.org/cgi/content/full/126/5/e1400](http://pediatrics.aappublications.org/cgi/content/full/126/5/e1400). Accessed February 24, 2014.)

#### BOX 109-6 Key Questions in Determining the Need for Resuscitation

Was the baby born after full-term gestation?  
Is the baby breathing or crying?

Does the baby have good muscle tone?

evaluation of the dyad of respirations and heart rate is then needed to decide whether resuscitative support should be escalated or abated, in a stepwise manner, at approximately 30-second intervals. An increase in heart rate is the most sensitive indicator of a positive response at each step. Color (or SpO<sub>2</sub>) is additionally used to evaluate oxygenation. Persistent cyanosis may suggest hypoxemia, but when oximetry readings are obtained, SpO<sub>2</sub> should be used because of the unreliability of color assessments.

Indications for immediate institution of PPV include apnea, gasping, or bradycardia (heart rate <100 beats/minute). Adequate inflation and ventilation of the lungs are by far the most essential aspect of resuscitation in the depressed newborn. During the first “golden minute,” the initial steps, reevaluation, and assistance with ventilation, if needed, should all be accomplished.

A higher threshold for oxygen supplementation is a key component of the current NRP recommendations. This is justified by recognition of the gradual transition towards normoxemia over 10 minutes in healthy newborns (Figure 109-1), evidence that resuscitation with air produces results equal or superior to those obtained by resuscitation with oxygen, and concerns with adverse effects of even brief hyperoxia in both term and preterm newborns. Therefore, a newborn who is breathing and has a normal heart rate, but who is cyanotic, should have SpO<sub>2</sub> monitoring and possibly receive respiratory assistance with

continuous positive airway pressure before supplemental oxygen is started.

Breathing support requires devices to assist and monitor ventilation, as well as equipment to deliver and monitor oxygen (Table 109-1). Assisted ventilation necessitates both a positive pressure generator such as a bag or T-piece ventilator and a mechanism to connect this device to the newborn’s airway (eg, facemask, endotracheal tube) (Table 109-2). PPV should begin with air in term neonates or blended oxygen titrated to attain SpO<sub>2</sub> in the time-appropriate target range in preterm neonates.

An additional team member will be needed and should be called for when beginning PPV.

Bag-mask ventilation, a critical skill in resuscitation, is often performed suboptimally. A tight seal between the mask and face is necessary to operate a flow-inflating bag or T-piece resuscitator. However, obstructing the airway by depressing the mandible with the facemask or inadvertently pressing with the free fingers on the submandibular area (see Box 109-2) must be avoided. Deliberately placing the middle and fourth fingers under the chin and the angle of the mandible, respectively, provides a jaw lift and keeps the airway open during ventilation (Figure 109-5).

Effective ventilation is signaled by a slight rise of the chest with each assisted breath, with a consequent rapid increase in heart rate; secondary signs include gradual improvement in oxygenation, return of muscle

**Table 109-1** Equipment for Oxygen Delivery and Monitoring

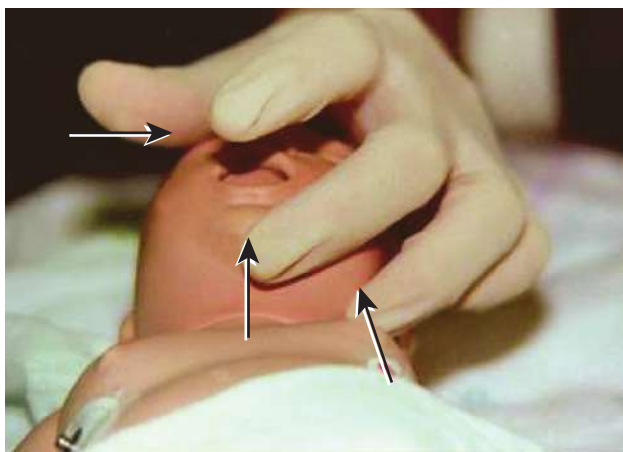
FUNCTION	DEVICE	COMMENT
Oxygenation monitoring	Pulse oximeter	Allow gradual rise in SpO <sub>2</sub> from 65% to 90% by 10 min of age. Avoid SpO <sub>2</sub> >95%
Adjustable FiO <sub>2</sub>	Oxygen blender	Avoid hyperoxia, particularly in very preterm neonates (<32 wk)
Air source	Wall outlet, tank	—
Oxygen source	Wall outlet, tank	—
Free-flow oxygen conduit	Tubing, mask, with or without bag	Cannot be delivered through a self-inflating bag and mask

FiO<sub>2</sub>, fraction of inspired oxygen; SpO<sub>2</sub>, oxygen saturation by pulse oximetry.

**Table 109-2** Equipment for Assisting and Monitoring Ventilation

FUNCTION	DEVICE	COMMENTS
Pressure generator	Flow-inflating or self-inflating bags, T-piece ventilators	Self-inflating bag can function without a gas source, but cannot deliver PEEP; others need compressed gas (wall outlet, tank) but can deliver PEEP or CPAP.
Pressure conduit into airway	Facemask, endotracheal tube, laryngeal mask airway	Assess appropriate size (and tube depth) before use.
Ventilation monitoring	Carbon dioxide detector; pressure manometer	Tidal volume monitoring would be ideal, but it is not commonly available.

CPAP, continuous positive airway pressure; PEEP, positive end-expiratory pressure.



**Figure 109-5** Positioning of hand to maintain open airway during bag-mask ventilation. The middle and fourth fingers are placed under the chin and the angle of the mandible, respectively, which lifts the jaw. Keeping these fingers on bony landmarks prevents inadvertent compression of submandibular tissue and airway obstruction. The first 2 fingers naturally accommodate the facemask.

tone, and spontaneous breathing. Assisted breaths should be given at a rate of 40 to 60 per minute, at the minimal peak inflation pressure necessary to effect a slight chest movement (most often 20–30 cm H<sub>2</sub>O). The NRP recommends starting PPV with room air or blended oxygen. If blended O<sub>2</sub> is not available, resuscitation should be initiated with air.

Bag-mask ventilation that is ineffective in achieving physiologic improvement should prompt reassessment of the airway (external or internal)-breathing sequence. The physician should reposition the baby's head, lift the jaw, reapply the facemask, check for secretions and suction as needed, increase inflation pressure, and check the bag. When bradycardia persists after 90 seconds of resuscitation, FiO<sub>2</sub> should be increased to 100% until the heart rate normalizes.

Persistently ineffective ventilation should prompt the use of a more reliable airway, either by endotracheal intubation or by insertion of a laryngeal mask airway. This is followed by ventilation and reassessment.

Modifying this sequence of interventions may be appropriate in some circumstances. For example, some very premature infants may benefit from prophylactic surfactant and early use of continuous positive airway pressure; avoidance of hyperoxia is particularly important in this population (Table 109-3).

Chest compressions are indicated when bradycardia (heart rate <60 beats/minute) persists despite effective PPV for 30 seconds. Because of the requirement for effective ventilation and reevaluation, compressions would rarely begin in the first postnatal minute. Chest compressions are preferably performed with the 2-thumb technique, with hands encircling the chest. Ventilation (with 100% oxygen) must remain adequate during chest compressions; thus, intubation is strongly recommended at this point. Chest compressions are carried out in 2-second cycles of 3 compressions followed by 1 breath,

coordinated as the compressor verbalizes “1-and-2-and-3-and-breathe-and . . .”; this technique results in 90 compressions and 30 breaths per minute.

Epinephrine is indicated if the heart rate remains below 60 beats/minute after about 60 seconds of coordinated ventilation and chest compressions. The NRP recommends administration of epinephrine intravenously (Table 109-3), through a shallow umbilical venous catheter, inserted to a depth of 3 or 4 cm. While vascular access is sought, epinephrine may be given once endotracheally at a higher dose (Table 109-3), with the understanding that its absorption from the airway is erratic and its effectiveness uncertain. Epinephrine doses may be repeated every 3 to 5 minutes. Reassessment of heart rate should occur at approximately 1-minute intervals, to minimize interruptions of ventilation and compressions.

### Extensive or Complicated Resuscitation

Because persistent cardiorespiratory depression most often results from ineffective resuscitative efforts, the mechanics of each basic step should be reassessed before further intervention.

The physician should recheck the airway (endotracheal tube position) (Table 109-4), the effectiveness of ventilation (exhaled CO<sub>2</sub>, chest movement, breath sounds), chest compressions, and epinephrine delivery and then consider the possibility of hypovolemia.

If the baby responds poorly to resuscitation and blood loss is suspected (eg, pallor, hypoperfusion, history of abruption placenta, tight nuchal cord with early cord clamping), then hypovolemia is likely. This circumstance is an indication for volume expansion with 1 or more doses of normal saline or lactated Ringer solution. Unmatched O-negative blood may be used immediately if anemia is suspected.

The efficacy and safety of sodium bicarbonate in neonatal resuscitation are uncertain, and its use during brief resuscitations is discouraged.

Naloxone should not be administered during the primary steps of resuscitation. Intrapartum exposure to narcotics causes central apnea, not direct cardiac and neuromuscular dysfunction. Thus naloxone is indicated only after PPV has restored a normal heart rate and color, if respiratory depression continues, and if a history of intrapartum narcotic administration within 4 hours of birth exists.

Continued failure of effective ventilation despite appropriate endotracheal tube placement should raise consideration of airway malformations (see Box 109-2) or inability to inflate the lungs as a result of pneumothorax or diaphragmatic hernia; obvious asymmetry of breath sounds and shifted or muffled cardiac sounds suggest the latter diagnoses. Poor response to resuscitation despite adequate ventilation may indicate primary circulatory insufficiency (see Box 109-4).

Suspected tension pneumothorax, or hydrothorax, in a newborn who responds poorly to resuscitation is an indication for emergency thoracentesis. An 18- or 20-gauge angiocatheter, rather than a butterfly needle, is safe for this purpose. The catheter should be inserted at the fourth intercostal space, anterior axillary line, to drain gas, or at the midaxillary line to drain fluid.



**Table 109-3** Medications for Neonatal Resuscitation in the Delivery Room

MEDICATION	DOSE	ROUTE	INDICATION
Epinephrine (1:10,000, ie, 0.1 mg/mL)	0.1 to 0.3 mL/kg	IV (preferred) A first, higher dose may be endotracheal	Bradycardia persisting after adequate ventilation and chest compressions. Endotracheal dose (0.3–1 mL/kg) optional, while establishing IV access
Volume expander (normal saline, lactated Ringer solution, or blood)	10 mL/kg	IV, slow	Poor response to resuscitation, and suspected blood loss, shock, pallor, hypoperfusion
<i>The medications below have a limited role in neonatal resuscitation; they are not recommended in the immediate delivery room setting.</i>			
Sodium bicarbonate (0.5 mEq/mL)	2 mEq/kg	IV, slow	Prolonged CPR unresponsive to adequate ventilation and other therapies
Naloxone	0.1 mg/kg	IV or IM only (not endotracheal)	After resuscitation (ie, heart rate and color normal), for intrapartum narcotic-induced respiratory depression

CPR, cardiopulmonary resuscitation; IM, intramuscular; IV, intravenous.

**Table 109-4** Endotracheal Tube Size and Depth for Neonates

GESTATIONAL AGE, WK	WEIGHT, G	TUBE INNER DIAMETER, mm	DEPTH OF INSERTION FROM UPPER LIP, cm
23–24	<600	2.5	5.5–6
25–28	600–1,000	2.5	6.5–7
28–34	1,000–2,000	3	7–8
34–38	2,000–3,000	3.5	8–9
39–42	3,000–5,000	3.5–4.0	9–10

### Newborns Unresponsive to Resuscitation

Asystole persisting after 10 minutes of adequate resuscitation, which may be beyond 10 minutes of life, indicates a very low probability of intact survival. Therefore, discontinuing resuscitation and instituting comfort care centered on the family's needs may be appropriate. This decision should be individualized, based on factors such as the underlying prognosis, the presumed causes and potential reversibility of the cardiorespiratory arrest, and the family's feelings regarding acceptable risk for morbidity. Persistent bradycardia unresponsive to adequate resuscitation in a newborn with obvious conditions associated with lung hypoplasia (eg, oligohydramnios sequence, Potter syndrome) would also justify discontinuing resuscitation efforts.

### Technical Considerations of Endotracheal Intubation

Intubation should not be viewed as a step in resuscitation but rather as a method that may be applied during any of the basic steps for distinct indications. It may be used to suction debris from the airway; to establish an artificial airway and enhance ventilation when bag-mask ventilation is ineffective, prolonged, or inadvisable (eg, diaphragmatic hernia, gastroschisis); or to administer drugs such as surfactant.

Experts suggest that a physician capable of performing endotracheal intubation be available at every delivery. In addition to appropriately sized endotracheal tubes, a laryngoscope with a No. 0 blade for a preterm newborn or a No. 1 blade for term newborns is essential. The following tips are intended to improve efficacy and safety of intubation.

Intubation of a main-stem bronchus is a common event that can result in ineffective ventilation and other serious complications. Thus, the physician should explicitly designate both endotracheal tube size and intended depth of insertion before attempting intubation. The depth of endotracheal tube insertion can be estimated from actual or expected weight, as noted in Table 109-4. Alternatively, Tochen's rule (6 + weight in kg = tip-to-lip depth in cm) is easy to memorize, although inaccurate in extremely preterm neonates. Appropriate endotracheal tube insertion depth should first be guided by visually placing the vocal cord mark on the tube at the level of the vocal cords; external depth at the lip should then be verified using the length (cm) marks on the tube, before assisted ventilation is initiated. At ventilation, confirmation of endotracheal tube placement in the trachea should rely primarily on finding an increasing heart rate and exhaled carbon dioxide by using a carbon dioxide detector. Other useful methods of verifying endotracheal tube placement, such as observing chest rise, condensation in the tube,

skin color, or auscultation of breath sounds, are less reliable. If the endotracheal tube is to remain in place after resuscitation, then a radiograph should be obtained to verify tube position.

The NRP now recognizes the laryngeal mask airway as an alternative device to assist ventilation in newborns of at least 34 weeks' gestation who cannot be effectively managed by bag-mask ventilated or endotracheal intubation. These devices are simple to use, but experience with their application in neonatal resuscitation is still limited.

### Special Considerations for Premature Newborns

Preterm babies, especially those who are very premature ( $\leq 28$  weeks' gestation), have special needs during and after resuscitation, as detailed previously and summarized in Table 109-5.

Physicians will note the new NRP emphasis on more strict management of oxygenation during neonatal resuscitation, particularly in preterm newborns. This action was prompted by preliminary clinical and laboratory evidence suggesting deleterious effects of even brief exposures to hyperoxia and equivalent effectiveness and resuscitation with room air or 100% oxygen. Present NRP guidelines do not indicate a specific initial  $\text{FiO}_2$  for assisting ventilation in very preterm newborns ( $< 32$  weeks), but 30% to 40%  $\text{FiO}_2$  is commonly used in practice. Using pulse oximetry monitoring and an oxygen blender during resuscitation, the physician can titrate  $\text{FiO}_2$  to increase  $\text{SpO}_2$  gradually toward 90% over 10 minutes.  $\text{FiO}_2$  should be decreased if oxygen saturations exceed 95%. In the presence of bradycardia, appropriate ventilation with 100% oxygen is indicated.

For full-term newborns, the NRP guidelines recommend administering initial PPV using room air, without

the immediate need for pulse oximetry monitoring. However, experts recognize that alternative approaches may be reasonable.

## POSTRESUSCITATION ASSESSMENT AND STABILIZATION

After initial stabilization, a more detailed assessment of the baby's condition and evaluation of relevant risk factors in the prenatal history (see Box 109-1) should be undertaken to guide further care.

Acute postresuscitation derangements in cardiorespiratory, neurologic, and metabolic function should be sought. Reexamining the ABCs is a simple strategy to ensure sustained adequate ventilation and perfusion in addition to thermoregulation. A malpositioned endotracheal tube, large pneumothorax, or acute hypovolemia after fetoplacental transfusion can cause further physiologic derangements. Frequent monitoring of vital signs is useful. However, blood pressure may remain normal despite insufficient systemic or pulmonary blood flow, which would be evident as peripheral hypoperfusion and hypoxemia, respectively. Newborns who were significantly depressed need to be evaluated for acute metabolic complications such as hypoglycemia or severe acidosis.

Preexisting conditions, such as maternal diabetes, fetal growth restriction, significant dysmorphisms found by obstetric ultrasound or during physical examination, and risk factors for sepsis, require specific diagnostic and therapeutic interventions shortly after birth.

Some congenital malformations require specific attention during stabilization. For example, relief of airway obstruction caused by Pierre Robin sequence can be accomplished by prone positioning and a nasopharyngeal airway.

**Table 109-5** Special Needs of Preterm Newborns During Resuscitation

SPECIAL FEATURE OF PRETERM NEWBORNS	ADJUSTMENT TO RESUSCITATION PROCEDURES
Thermoregulation: rapid heat loss	Avoid convective and evaporative losses. Use plastic wrap when infant is $\leq 28$ weeks' gestation.
Fragile skin, particularly at $< 25$ weeks' gestation	Avoid rubbing. Use protective barriers when taping or otherwise securing devices onto skin.
Diminished respiratory drive	Low threshold for supporting ventilation. Need physician skilled at intubation.
Likely surfactant deficiency	May benefit from prophylactic surfactant.
Lungs susceptible to immediate ventilatory injury	Provide continuous positive airway pressure or the minimal inflation pressures needed to support adequate ventilation and oxygenation.
Tissue vulnerability to hyperoxic injury	Use oxygen blender, pulse oximetry to attain $\text{SpO}_2$ between 85% and 95% by 10 minutes of age. Start resuscitation with an oxygen concentration $< 100\%$ (eg, 30%–40%).
Susceptibility to brain hemorrhage and/or ischemia	Avoid hyperventilation, hypocapnia, and rapid infusion of fluid boluses or hypertonic solutions.
Metabolic susceptibility to hypoglycemia	Monitor for hypoglycemia.
Susceptibility to infection	Assess risk for infection. Many preterm newborns $< 35$ weeks' gestation need an evaluation for sepsis immediately after birth, and possibly empirical antibiotic therapy, pending diagnostic tests.

$\text{SpO}_2$ , oxygen saturation by pulse oximetry.

Anomalies characterized by exposed internal organs, such as gastroschisis, meningocele or other neural tube defects, and cloacal exstrophy, necessitate protection from heat and fluid loss, contamination by environmental microorganisms, and traumatic or ischemic injury. Immediate enclosure in a sterile plastic bag safeguards tissues from evaporation and infection. Generally, the newborn should be positioned so as to optimize blood flow to the structures. This goal can be achieved by keeping pressure off the anomaly and by keeping arterial and venous supply to the lesion unobstructed; a newborn with a gastroschisis, for example, would best be stabilized in the right lateral decubitus position. Finally, the newborn should be protected from excessive, unnecessary examinations, and appropriate pain management should be provided if needed.

## UMBILICAL CORD BLOOD GAS ANALYSIS

Identifying newborns at risk for complications from intrapartum asphyxia is an issue of significant concern to obstetric and pediatric primary care physicians. The use of arterial umbilical cord acid-base status to define the degree of fetal acidemia that correlates with a high risk for neonatal complications has been the focus of ongoing research efforts. Umbilical arterial or venous blood gases or an early neonatal arterial base deficit (before administration of volume or bicarbonate [no longer recommended]) have been studied for their utility in delineating the degree of acidosis at the time of delivery. Umbilical arterial cord blood gas analysis provides the best information regarding fetal status, whereas umbilical venous cord blood reflects placental functioning most directly. When extensive delivery room resuscitation is necessary, an umbilical venous blood-gas analysis can also be obtained from the newborn immediately on insertion of the umbilical venous catheter.

Neonatal complications are associated with fetal metabolic acidosis, rather than respiratory acidosis; even brief cord compression will produce significant hypercarbia. Therefore, interpretation of umbilical cord pH should include consideration of both respiratory and metabolic components. Although umbilical arterial pH identifies an infant at potential risk for short-term neonatal morbidity, it does not distinguish the infant at risk for a poor long-term outcome. Among infants exhibiting severe hypoxic-ischemic encephalopathy,

fetal hypoxemia is found to be the cause in less than 25% of cases studied. Umbilical arterial pH is normal in 80% of infants experiencing perinatal compromise. Box 109-7 lists the causes of acidosis in infants.

At delivery, the mean umbilical arterial base deficit is 4 to 5 mmol/L. Lackman et al have reported on umbilical cord blood gases in relation to birth size (appropriateness of growth for gestational age) from a population of nearly 30,000 term infants born over a 10-year period (1990–1999) in Canada. The investigators found that the mean pH was  $7.26 \pm 0.07$  and the mean base deficit was  $4.7 \pm 2.9$  mmol/L in umbilical arterial cord blood specimens. Among infants with intrauterine growth restriction, the base deficit was  $5.3 \pm 3.1$ , whereas large-for-gestational-age babies exhibited base deficits of  $4.4 \pm 2.8$  mmol/L.

The degree of metabolic acidosis that determines the threshold for *potential* injury is defined as greater than 2 standard deviations from the mean (10–12 mmol/L) and is accepted as greater than 12 mmol/L. Base deficit levels exceeding 12 mmol/L occur in less than 2% of a normal obstetric population. Also important to note is that most newborns with a base deficit greater than 12 mmol/L do not demonstrate neurologic injury. Among symptomatic infants experiencing severe metabolic acidosis with base deficits greater than 16 mmol/L, most either die or have neurodevelopmental morbidities. In contrast to the symptomatic infant who requires resuscitation and has evidence of a significant metabolic acidosis, the approach to the baby who seems to be transitioning without difficulty but is found to have a base deficit greater than 12 mmol/L is less clear. At a minimum, in addition to a thorough physical assessment for signs of illness or transitional delay, a blood gas analysis should be obtained from the infant to ascertain the persistence of metabolic acidosis or other abnormality necessitating further evaluation or intervention. In the absence of significant hypoxemia or hypothermia, metabolic acidosis that is present at birth and persists is likely caused by circulatory insufficiency resulting most likely from hypovolemia.

The availability of umbilical cord blood gases will depend on the individual hospital policy. Although experts have argued that umbilical cord blood acid-base determination does not add to the evaluation of the vigorous term infant who is assessed to have normal Apgar scores, the medical-legal climate is such that some obstetric societies and hospitals in North

### BOX 109-7 Causes of Acidosis in Neonates

- Respiratory distress<sup>a</sup>
- Sepsis
- Hypovolemia<sup>a</sup>
- Hypothermia<sup>a</sup>
- Severe anemia<sup>a</sup>
- Low cardiac output (hypotension) with poor tissue perfusion
- Cardiac failure
- Perinatal asphyxia<sup>a</sup>
- Inborn errors of metabolism
- Renal bicarbonate losses

<sup>a</sup>These conditions are relevant during delivery room resuscitation.

America and Europe are recommending the routine surveillance of umbilical arterial cord blood gases for all births.

### DELAYED UMBILICAL CORD CLAMPING

Clamping of the umbilical cord shortly after birth is a historically recent practice that is challenged by substantial new evidence. Early cord clamping usually occurs by 15 seconds after birth, whereas the definition of delayed cord clamping has varied among studies, ranging from 30 seconds to 3 minutes after birth, or even to cessation of pulsations in the cord. Multiple studies have shown that early cord clamping interrupts the normal fetoplacental transfusion, resulting in a blood volume deficit of 15 to 20 mL/kg birth weight compared with newborns whose cord clamping was delayed. Systematic reviews have shown improved iron status in infancy after delayed cord clamping in term neonates. In preterm neonates with uncomplicated births, good-quality evidence reveals functional benefits of delayed cord clamping, including higher blood pressures during stabilization, the need for fewer blood transfusions, a lower incidence of intraventricular hemorrhage, and improved development in infancy; these benefits outweigh an increased need for phototherapy with delayed cord clamping. There is insufficient information to evaluate the risks and benefits of delayed cord clamping in the neonates who require resuscitation. Consequently, the NRP recommends delaying umbilical cord clamping for at least 1 minute in newborn infants who do not require resuscitation, while withholding specific recommendations on timing of cord clamping in babies requiring resuscitation. ACOG recently recommended delaying cord clamping in preterm infants, when feasible; this statement has been endorsed by the AAP. Practical consequences of these recommendations include the need for delaying the transfer of the baby between the obstetrician and the neonatal team, and minor alterations in umbilical cord blood gas values, if these are obtained. Recent studies suggest that active milking of the cord may accelerate placental transfusion and yield benefits similar to delayed cord clamping in preterm neonates. These interventions highlight the importance of coordination between the obstetric and neonatal teams in order to optimize outcomes for the neonate.

### DISPOSITION

Depending on the level of support provided to a newborn during resuscitation (see Figure 109-4), subsequent care may be routine or observational (more frequent evaluation in the delivery room or designated observation area), or it may involve postresuscitation care in a special care nursery.

The management of newborns with significant perinatal depression and those whose underlying conditions impart a risk for physiologic instability should be discussed with a neonatologist, and referral to a neonatal intensive care unit may be necessary. Technically challenging interventions such as surfactant administration in the delivery room or the initiation of therapeutic hypothermia should be planned in conjunction with the regional center. After delivery room resuscitation, therapeutic hypothermia should be considered for infants born at 36 weeks' gestation or later with an

umbilical arterial cord gas or arterial pH less than 7.0 or respiratory depression persisting for 10 minutes, because these infants are at risk for evolving hypoxic-ischemic encephalopathy.

### COMMUNICATION AND DOCUMENTATION

After resuscitation interventions, a discussion should take place with the parents, nursing staff, and obstetrician regarding assessment of the newborn and development of a postresuscitation plan of care.

Documentation of these activities is essential. This task is facilitated by the use of structured forms that help guide the flow of resuscitation while rapidly recording evaluations and interventions at appropriate time intervals and even the corresponding orders. Attribution of Apgar scores, whether performed concurrently by an observer or in retrospect, is more meaningful if the signs assessed are recorded together with concurrent interventions. An expanded Apgar score form has been proposed for this purpose.

### EVALUATION AND QUALITY IMPROVEMENT IN NEONATAL RESUSCITATION

Neonatal resuscitation is a critical activity amenable to perinatal quality assurance and quality improvement. The performance of both individual physician and the team can be improved by incorporating techniques such as simulation, team training, checklists, and habitual team briefing plus debriefing around actual resuscitations. Measures related to both the resuscitation process and immediate outcomes may be useful in characterizing the effectiveness, efficiency, and timeliness of resuscitative interventions, even if only in high-risk subgroups (eg, very-low-birth weight, meconium staining). The variables to be tracked should depend on the specific questions to be answered about each institution's neonatal stabilization procedures. However, a few measures reflect efficacy and safety in core processes; they may be particularly useful if they are easy to collect and if published benchmark data are available. For example, in newborns with very low or extremely low birth weight, record the proportion given chest compressions, epinephrine, or both; the time to first surfactant dose and admission temperature; in all newborns, note the number of intubation attempts and the proportion of endotracheal tubes.

Maintaining a highly effective recording system for neonatal resuscitation requires not only maintenance of infrastructure and recurrent training and updating of personnel, but also a planned, systematic evaluation of procedures in high-risk cases and sentinel events. Both intramural evaluations and external benchmarking in conjunction with the regional perinatal center are necessary elements of this process.

### TOOLS FOR PRACTICE

#### Medical Decision Support

- *Guidelines for Perinatal Care*, 7th ed (book), American Academy of Pediatrics and American College of Obstetricians and Gynecologists ([shop.aap.org](http://shop.aap.org))



- *Neonatal Resuscitation Program* (Web page), American Academy of Pediatrics ([www.aap.org/nrp](http://www.aap.org/nrp))
- *Textbook of Neonatal Resuscitation, 6th ed* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *NRP Instructor Manual* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *NRP Code Chart* (poster), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *NRP Pocket Card* (card), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *NRP Wall Chart* (poster), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *S.T.A.B.L.E. Program Learner Manual, 6th ed* (book) ([shop.aap.org](http://shop.aap.org))

### AAP POLICY

Centers for Disease Control and Prevention. Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC, 2010. *MMWR Recomm Rep*. 2010;59 (No. RR-10):1–32 (AAP endorsed) ([www.cdc.gov/mmwr/preview/mmwrhtml/rr5910a1.htm?s\\_cid=rr5910a1\\_w](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5910a1.htm?s_cid=rr5910a1_w))

American College of Obstetricians and Gynecologists Committee on Obstetric Practice. Committee opinion no. 543. Timing of umbilical cord clamping after birth. 2012 (AAP endorsed) ([www.acog.org/Resources\\_And\\_Publications/Committee\\_Opinions/Committee\\_on\\_Obstetric\\_Practice/Timing\\_of\\_Umbilical\\_Cord\\_Clamping\\_After\\_Birth](http://www.acog.org/Resources_And_Publications/Committee_Opinions/Committee_on_Obstetric_Practice/Timing_of_Umbilical_Cord_Clamping_After_Birth))

### SUGGESTED READINGS

- Goldsmith JP. Delivery room resuscitation of the newborn. In: Fanaroff AA, Martin RJ, Walsh MC, eds. *Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant*. 9th ed. St Louis, MO: CV Mosby; 2010
- Kattwinkel J, Perlman JM, Aziz K, et al. Neonatal Resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Pediatrics*. 2010;126:e1400–e1413
- Perlman JM, Wyllie J, Kattwinkel J, et al, on behalf of the Neonatal Resuscitation Chapter Collaborators. Neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation*. 2010;122(16 Suppl 2):S516–S538

## Chapter 110

# IDENTIFYING THE NEWBORN WHO REQUIRES SPECIALIZED CARE

Upender K. Munshi, MBBS, MD

Full-term newborn infants after a normal spontaneous vaginal delivery are usually assessed by the delivery room nurse, who may notify the primary care physician (PCP) if any abnormality of cardiorespiratory adaptation or any external malformations are observed. The PCP or nurse practitioner who attends a high-risk delivery will typically perform a brief assessment of the newborn after birth. After this initial assessment, a

decision is made whether the baby is stable enough to remain with the mother and continue to receive couplet care or if the infant requires specialized newborn care in a transitional, special care or neonatal intensive care unit (NICU).

## NEWBORNS TYPICALLY CARED FOR IN A NEONATAL INTENSIVE CARE UNIT

Most newborns who are referred to a NICU fall into 1 of 3 broad categories: infants who have a clear need for neonatal intensive or critical care; those with a possible need for NICU care, and; infants with a normal initial assessment but who have warning signs in their prenatal history/maternal lab results, postnatal examination findings, or newborn screening labs (Box 110-1).

### Clear Need for Neonatal Intensive Care Unit Care

The decision-making process for referral to a higher level of care is straightforward in this group. Referral to the NICU should be initiated immediately while the initial diagnostic and therapeutic measures commence.

### Possible Need for Neonatal Intensive Care Unit Care

For newborns who have borderline maturity, mildly abnormal physical findings, or borderline laboratory results, making the decision for referral to NICU will depend on the level of care and resources available at the place of birth. For level I hospitals with basic newborn care, it is a relatively easy decision to initiate transfer to the higher-level facility after consulting with the accepting neonatologist; however, for pediatricians and neonatologists covering level II or higher hospitals, referral to regional NICU may not be that easy a decision. In addition, some newborns exhibit grunting, flaring, and chest wall retractions within minutes after birth, which results in an early transfer to NICU. These transient respiratory symptoms frequently subside within first few hours, often during the transport itself, making such transfers from level II or higher hospitals to the regional NICU unnecessary.

These transfers cause parental anxiety and interruption in the newborn–parent bonding, particularly when it involves transfer to another hospital. Watchful observation in consultation with the regional NICU attending physician and communication of clinical or laboratory parameters for a reasonable amount of time is appropriate. This communication can avert an unnecessary NICU admission as well as prevent delay in NICU transfer of infants who need neonatal intensive care.

### Well-Seeming Infants and Neonatal Intensive Care Unit Care

For most infants who are vigorous and appear well at birth, no higher level care will be required. However, occasionally a baby in this group may have warning signs in the prenatal or postnatal history, subtle findings in the physical examination, or concerning laboratory results that need to be addressed.

### BOX 110-1 Broad Categories of Newborns for Neonatal Intensive Care Unit (NICU) Referral

Group 1: Clear need for NICU care (*Call NICU early; start appropriate diagnostic and therapeutic measures and arrange prompt transfer if the necessary neonatal level of care is not available on-site*)

- Very low-birth-weight infants <1,500 g, or gestation <34 weeks
- Moderate to severe respiratory distress at birth or any time afterward
- Sepsis syndrome: temperature or cardiorespiratory instability, lethargy, mottling of skin, respiratory distress
- Compromised cardiovascular function, central cyanosis, moderate to severe metabolic acidosis
- Hypoxic ischemic encephalopathy, neonatal seizures
- Severe hemolytic anemia, erythroblastosis fetalis, hydrops
- Life-threatening malformations such as gastroschisis, diaphragmatic hernia, prenatal diagnosis of duct-dependent congenital heart disease

Group 2: Possible need for NICU (*Communicate and discuss with regional NICU team if delivery occurs at a level I hospital*)

- Borderline maturity (34-37 weeks' gestation) and birth weight just below the acceptable limits for a community hospital (<2,000 g)
- Transitional issues, including mild to moderate respiratory distress within first hours after birth on low respiratory support
- Infant with vomiting or abdominal distention, non-passage of meconium >24 hours after birth
- Cord blood bilirubin more than 4 mg/dl, onset of jaundice during the first 24 hours, and rapidly rising serum bilirubin

Group 3: Infants with a normal initial assessment (*Review history, physical examination, and laboratory results. Watch for any warning signs*)

- Infants at risk for neonatal hypoglycemia (infant of diabetic mother, late preterm infant, small-for-gestational-age infant)
- Infants at risk for sepsis (maternal fever, prolonged rupture of membranes, chorioamnionitis, GBS positive mother with no or inadequate prophylaxis)
- Abnormal finding on prenatal sonography, such as suspected ovarian cyst, echogenic dilated bowel, hydronephrosis, ventriculomegaly
- Infant with borderline results of pulse oximetry screening for congenital heart disease

## REFERRAL FOR NEONATAL INTENSIVE CARE

The objective of this chapter is to present a systematic approach for the PCP to identify newborns in the 2 categories who may require admission to NICU for close monitoring and management. Early recognition of these conditions may help with timely referrals and avert complications resulting from delayed transfer of patients. In addition, factors other than the actual medical condition of the newborn may come into play while

### BOX 110-2 Initial Workup of an Ill-Seeming Newborn

- Vital signs, including 4-limb blood pressures
- Pulse oximeter oxygen saturation (SpO<sub>2</sub>), pre- and postductal
- Rapid point-of-care blood glucose testing using a glucose strip test (Dextrostix) or glucometer
- Blood cell counts: hematocrit and hemoglobin, white cell count with differential, platelet count
- Basic metabolic panel: serum glucose, electrolytes, calcium, urea nitrogen, creatinine
- Umbilical cord blood gases (pH and base deficit), if available
- Blood gas and chest radiograph, deferring if no respiratory distress
- Blood culture, deferring if low risk of infection
- If SpO<sub>2</sub> or arterial pressure of oxygen in room air is low (<90%), then observe the response to 100% oxygen (hyperoxia test)

If an inborn error of metabolism is suspected, blood should be sent for lactate, pyruvate, ammonia, plasma amino acid profile, carnitine, and acylcarnitine. Also test urine for organic acids and reducing substance. Keep extra samples of blood and urine for specific genetic tests and store at 68°F (20°C).

referrals of the newborn to other hospitals are made. These factors, not discussed in this chapter, may include training and competence of the PCP in the field of newborn medicine; the PCP's experience of an adverse outcome in a previous case; availability of around-the-clock, in-hospital physician coverage; time restrictions; financial implications of the commitment to ambulatory patient care; adequacy and comfort level of the nursing staff; and third-party payer characteristics.

To assess a newborn properly, the PCP must review the mother's medical, pregnancy, and intrapartum history and delivery course, including results of screening laboratory tests and any imaging studies. A newborn exhibiting signs of illness should have an initial workup (Box 110-2) that may facilitate early recognition of problems and more timely consultation with or referral to the NICU.

## COMMON CONDITIONS REQUIRING NEONATAL INTENSIVE CARE

### The Immature Infant

Increased morbidity and mortality in preterm infants is inversely proportional to the degree of gestational maturity. Every state health care system has attempted to classify newborn care facilities into levels of care so that the care provided by each hospital appropriately matches with the needs of infants of varying gestation and severity of illness, leading to the concept of regionalized perinatal care. In order to have uniform definitions of levels of care and standard nomenclature for health care providers and state public health care systems, the American Academy of Pediatrics (AAP) Committee on Fetus and Newborn (COFN) has provided guidelines and recommendations in their policy statement from 2012

**Table 110-1** Definitions, Capabilities, and Provider Types: Neonatal Levels of Care

LEVEL OF CARE	CAPABILITIES	PROVIDER TYPES <sup>a</sup>
Level I Well newborn nursery	<ul style="list-style-type: none"> <li>• Provide neonatal resuscitation at every delivery</li> <li>• Evaluate and provide postnatal care to stable term newborn infants</li> <li>• Stabilize and provide care for infants born at 35 to 37 weeks' gestation who remain physiologically stable</li> <li>• Stabilize newborn infants who are ill and those born at less than 35 weeks' gestation until transfer to a higher level of care</li> </ul>	Pediatricians, family physicians, physician assistants, pediatric or family nurse practitioners, and other advanced practice registered nurses
Level II Special care nursery	Level I capabilities plus: <ul style="list-style-type: none"> <li>• Provide care for infants born at 32 or more weeks' gestation and weighing 1,500 g or more who have physiologic immaturity or who are moderately ill with problems that are expected to resolve rapidly and are not anticipated to need subspecialty services on an urgent basis</li> <li>• Provide care for infants convalescing after intensive care</li> <li>• Provide mechanical ventilation for brief duration (&lt;24 hours) or continuous positive airway pressure or both</li> <li>• Stabilize infants born before 32 weeks' gestation and weighing less than 1,500 g until transfer to a neonatal intensive care facility</li> </ul>	Level I health care providers plus: Pediatric hospitalists, neonatologists, and neonatal nurse practitioners
Level III NICU	Level II capabilities plus: <ul style="list-style-type: none"> <li>• Provide sustained life support</li> <li>• Provide comprehensive care for infants born at less than 32 weeks' gestation and weighing less than 1,500 g and infants born at all gestational ages and birth weights with critical illness</li> <li>• Provide prompt and readily available access to a full range of pediatric medical subspecialists, pediatric surgical specialists, pediatric anesthesiologists, and pediatric ophthalmologists</li> <li>• Provide a full range of respiratory support that may include conventional or high-frequency ventilation and inhaled nitric oxide</li> <li>• Perform advanced imaging with interpretation on an urgent basis, including computed tomography, MRI, and echocardiography</li> </ul>	Level II health care providers plus: Pediatric medical subspecialists, <sup>b</sup> pediatric anesthesiologists, <sup>b</sup> pediatric surgeons, and pediatric ophthalmologists <sup>b</sup>
Level IV Regional NICU	Level III capabilities plus: <ul style="list-style-type: none"> <li>• Located within an institution with the capability to provide surgical repair of complex congenital or acquired conditions</li> <li>• Maintain a full range of pediatric medical subspecialists, pediatric surgical subspecialists, and pediatric anesthesiologists at the site</li> <li>• Facilitate transport and provide outreach education</li> </ul>	Level III health care providers plus: Pediatric surgical subspecialists

<sup>a</sup>Includes all providers with relevant experience, training, and demonstrated competence<sup>b</sup>At the site or at a closely related institution by prearranged consultation agreementFrom American Academy of Pediatrics Committee on Fetus and Newborn. Levels of neonatal care. *Pediatrics*. 2012;130(3):587–597.

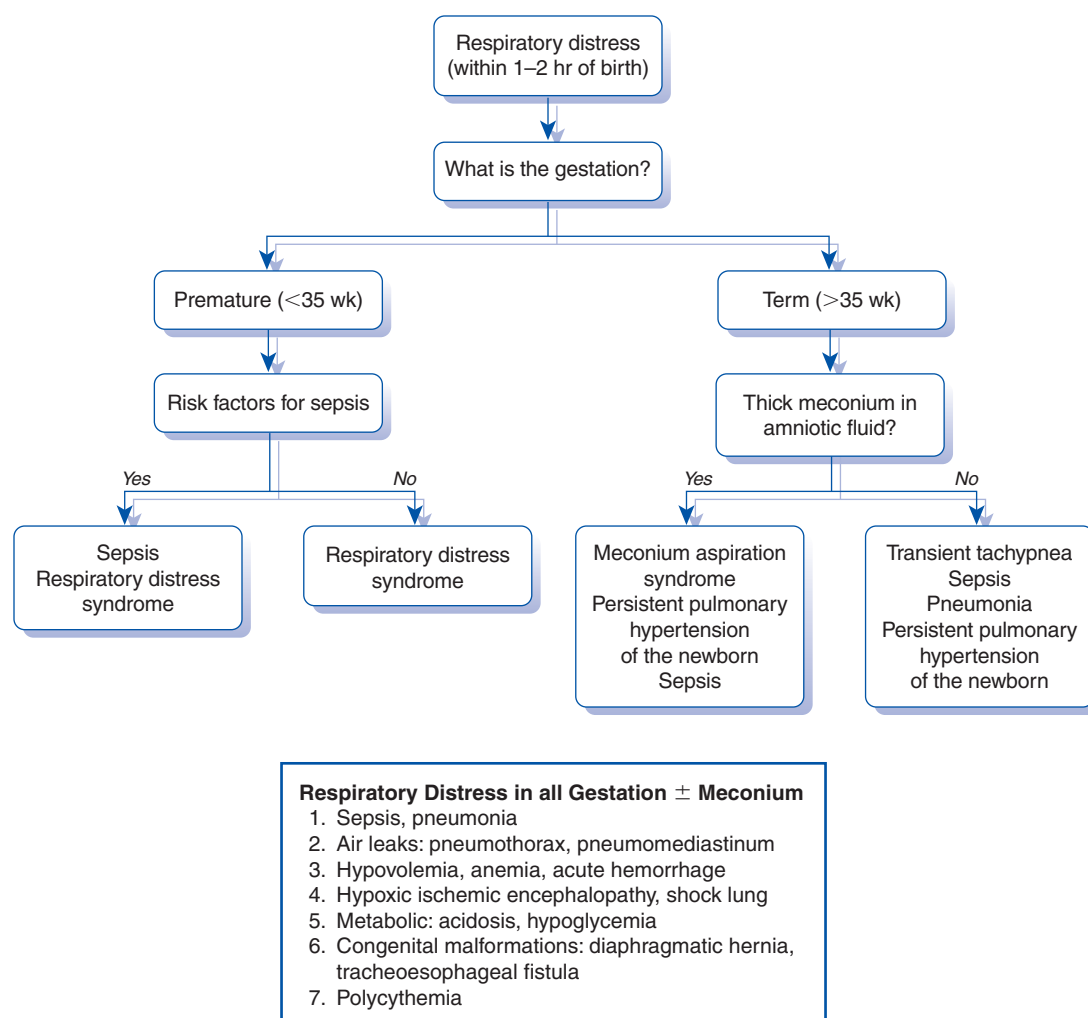
(Table 110-1). According to this statement, neonatal levels of care are provided at 4 levels: Level I (Well Newborn Nursery), Level II (Special Care Nursery), Level III (Neonatal Intensive Care Unit: NICU), and Level IV (Regional NICU), depending on capabilities and the provider type at each level.

Resources at level II and III hospitals may vary significantly; therefore, each hospital should have guidelines (conforming to AAP guidelines, respective state health department regulations, and their own available resources) for gestation and birth weight cutoffs

below which affected preterm or low-birth-weight infants should be referred for a higher level of care.

### Respiratory Distress

Common causes of respiratory distress within the first few hours of life are listed in Figure 110-1 (see also Chapter 100, Respiratory Distress and Breathing Disorders in the Newborn). Increased respiratory rate and work of breathing, as characterized by breathing rates of more than 60 breaths per minute, grunting, nasal flaring, and chest wall retractions, are the findings that



**Figure 110-1** Respiratory distress within the first few hours of life.

typically prompt evaluation and intervention. If these signs are accompanied by central cyanosis or the need for supplemental oxygen to maintain normal color or pulse oximeter saturations, then it may indicate an underlying disorder that requires immediate diagnostic and therapeutic intervention. Presence of these signs in a preterm newborn suggests respiratory distress syndrome caused by surfactant deficiency. Similar manifestation in a term or late preterm newborn may be the result of transient tachypnea of newborn (TTN) if the amniotic fluid is clear and the delivery is by cesarean. Respiratory distress that improves with each hour and resolves in approximately 24 hours is caused by TTN, whereas worsening or persisting respiratory distress beyond 24 hours rules out this diagnosis. Respiratory distress with presence of thick meconium-stained fluid points toward meconium aspiration syndrome, which is especially common in postterm infants who require resuscitation at delivery. These infants usually have meconium staining of nails and umbilical cord. Meconium aspiration syndrome is invariably associated with persistent pulmonary hypertension of newborn, which makes the respiratory failure worse and difficult to manage.

An infant exhibiting signs of respiratory distress persisting beyond the initial 20 to 30 minutes after delivery at level I (community) hospitals should be considered for transfer to a higher level of care. At level II (special care nursery), infants with mild to moderate respiratory distress diagnosed to be TTN after review of chest radiograph can be managed on continuous positive airway pressure (CPAP), with the regional NICU team consulted to follow up on the progress. Those infants who do not improve in 12 to 24 hours and continue to require an increasing fraction of inspired oxygen need to be transferred to a NICU. Neonates with respiratory distress resulting from causes other than TTN should be transferred to level III (NICU); see Box 110-1 depicting guidelines from the COFN statement. All other categories of respiratory distress needing invasive ventilatory support should result in transfer to a higher level of care.

### Sepsis Syndrome

Sepsis mimics most of the neonatal systemic disorders that affect newborns of all gestational ages, and its onset can span from the delivery room to anytime thereafter. Risk factors for neonatal sepsis, such as



maternal fever, chorioamnionitis, prolonged rupture of membranes, urinary tract infections, group B *Streptococcus* colonization, or a history of genital herpes, should be sought in the maternal history. In the delivery room, sepsis syndrome occurs mostly in the form of respiratory distress and cardiovascular instability in the form of tachycardia; pale, mottled skin; delayed capillary refill; and hypotension. Later onset is demonstrated by a change in the baby's baseline behavior, such as poor feeding, irritability, and lethargy, as well as temperature instability in a baby who had been having apparently normal activity and feeding pattern. Skin or mucous membrane lesions should be examined for the possibility of neonatal herpes; negative maternal history of genital herpes does not rule out neonatal herpes infection (see Chapter 102, The Newborn at Risk for Infection). Physicians need to recognize these changes early enough to initiate diagnostic (biochemical and hematologic studies, body fluid cultures) and therapeutic interventions (intravenous antibiotics) promptly, and physicians at level I and level II hospitals should simultaneously initiate referral to a higher level of care. Blood cell counts are often checked to find evidence for or against the diagnosis of neonatal sepsis; however, these results should be interpreted judiciously and not relied on as the sole factor for decision making. Neutropenia in the absence of pregnancy-induced hypertension or preeclampsia syndrome is worrisome, as is a marked left shift with ratio of immature neutrophils (band forms) to total neutrophils (bands plus segmented neutrophils) of 0.3 or more. Elevated C-reactive protein (CRP) as an acute phase reactant in response to infection supports the diagnosis of sepsis. Repeating CRP levels 24 to 48 hours after initiating empirical antibiotics may increase the negative predictive value of the test in ruling out sepsis. In a culture-proven or culture-negative presumed sepsis treated with antibiotics, declining CRP levels have been used to guide the duration of antimicrobial treatment. Use of other cytokines in diagnosis of sepsis like interleukin 6 (IL6) or interleukin 8 (IL8) are still investigational at this time. A combination of CRP and IL6 may provide additional accuracy for differentiation between septic and nonseptic newborn infants during the first 24 hours of suspected sepsis.

### **Infants at Risk for Hypoxic Ischemic Encephalopathy and Multiorgan Involvement**

Newborns with severe cardiorespiratory compromise at birth that requires sustained resuscitation, including intubation, positive pressure ventilation, chest compressions, or epinephrine, are potentially at risk for hypoxic ischemic encephalopathy. These infants should be carefully monitored and their clinical status discussed with the regional NICU team attending. The objective evidence of hypoxic ischemic encephalopathy is based on an umbilical arterial cord pH of less than 7.0, a 5-minute Apgar score of 3 or less, and abnormal neurologic examination (hyper- or hypotonia, irritability, seizures) and involvement of another major organ system. The other organ systems most commonly involved are kidneys, myocardium, lungs, and gastrointestinal tract.

Infants meeting the criteria for hypoxic ischemic encephalopathy should be considered for therapeutic

hypothermia (head cooling or generalized body cooling) (see Figure 110-2) and promptly arranged for transfer to NICU so that cooling is initiated within 6 hours of birth as per current standards. Because of the time constraint on initiating therapeutic hypothermia, within 6 hours, low cord pH of less than 7.0, metabolic acidosis of more than 16, negative base excess with prolonged delivery room resuscitation, and abnormal neurological examination are considered indications for starting head/body cooling since other major organ system dysfunction may not manifest fully within the first few hours. These infants also need ventilatory, metabolic, and nutritional support, as well as neurologic evaluation and seizure control.

Umbilical cord blood gases (UBCG) can help in ascertaining the type (chronic vs acute) and degree of fetal compromise in utero before the delivery. Carbon dioxide diffuses rapidly across the placenta whereas organic acids from metabolism are cleared relatively slowly; therefore, the presence of significant metabolic acidosis (base excess greater than  $-15$ ) is considered as evidence of significant compromise of fetal circulation and should be discussed with the referral NICU attending. After an aggressive resuscitation, newborns who do not strictly meet these criteria but who have abnormal neurologic examination findings or seizures should also be referred to a neonatal intensive care unit for further neurologic evaluation and monitoring.

### **Common Metabolic Derangements**

Common metabolic derangements with early onset (within day 1 or 2 of life) are hypoglycemia, metabolic acidosis, hypocalcemia, hypo- or hypernatremia, and hypo- or hyperkalemia.

Hypoglycemia is the most common metabolic derangement, mostly seen in large-for-gestational-age infants of diabetic mothers (IDM). This derangement is the result of hyperinsulinemia as in IDM infants or, because of depleted glycogen stores, in small-for-gestational-age (SGA) infants. These babies should be routinely monitored by rapid blood glucose strip test. Rarely, hypoglycemia can be the result of inborn error of carbohydrate metabolism (see Chapter 363, Hypoglycemia, and Chapter 106, Specific Congenital Metabolic Diseases). Hypocalcemia is a common problem sometimes seen in infants of diabetic mothers or in situations in which maternal hypercalcemia is present causing transient suppression of fetal parathyroid function. Occasionally, early persistent hypocalcemia may be a clue to DiGeorge syndrome. Early hyponatremia may reflect maternal fluid overload or neonatal fluid overload particularly after administering electrolyte-free, intravenous dextrose solution to newborns beyond the first day of life.

### **Cardiovascular Malformations**

Very few cardiac malformations manifest clinically in the delivery room, such as transposition of great vessels with intact septum, and total anomalous pulmonary venous return may present with respiratory distress and cyanosis at birth or within the first few hours of life. The most common manifestation of serious cardiac malformation coincides with the closure of the ductus

**A Gestational Age  $\geq 36$  weeks****B Physiologic criteria (either of 2)**

- pH  $\leq 7.0$  or base deficit  $\geq 16$  mmol/L  
[on cord blood gas or neonatal ( $<1$  hr old) blood gas]
- pH 7.01 to 7.15 or base deficit 10 to 15.9 mmol/L or no blood gas available.

And

1. Acute perinatal event (late or variable decels, cord prolapse or rupture, uterine rupture, maternal trauma / hemorrhage / cardiorespiratory arrest)
2. 10 minutes Apgar  $\leq 5$   
or  
assisted ventilation at birth—continued for at least 10 minutes

**C Neurologic criteria (either of 2)**

- Signs of moderate to severe encephalopathy on at least 3 of 6 categories; (see table)
- Presence of seizures

**Exclusion Criteria:**

- $>6$  hours old
- Major congenital anomaly
- Severe IUGR (birth weight  $\leq 1,800$  g)

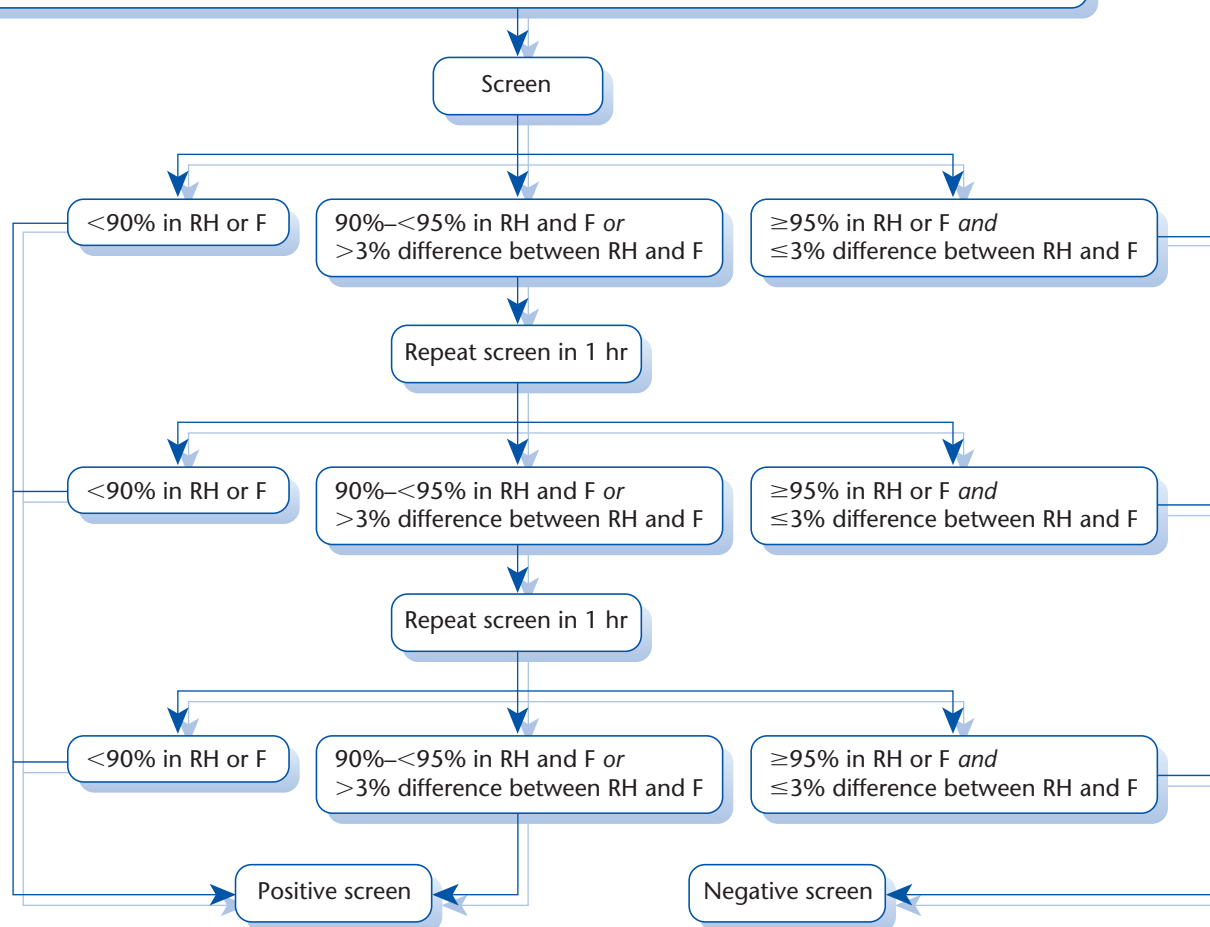
Criteria for Defining Moderate and Severe Encephalopathy		
Category	Moderate Encephalopathy	Severe Encephalopathy
Level of consciousness	Lethargic	Stupor or coma
Spontaneous activity	Decreased activity	No activity
Posture	Distal flexion, complete extension	Decerebrate
Tone	Hypotonia (focal or general)	Flaccid
<i>Primitive reflexes</i>		
Suck	Weak	Absent
Moro	Incomplete	Absent
<i>Autonomic system</i>		
Pupils	Constricted	Deviated, dilated or nonreactive to light
Heart rate	Bradycardia	Variable
Respiration	Periodic breathing	Apnea

**Figure 110-2** A standard checklist to determine eligibility for TH, which includes simplified examination findings to improve consistency among providers. IUGR, intrauterine growth restriction. (From Olsen SL, Dejonge M, Kline A, et al. Optimizing therapeutic hypothermia for neonatal encephalopathy. *Pediatrics*. 2013;131[2]:e591–e603.)

arteriosus (duct-dependent lesions), which occurs anywhere from the first 24 hours of life to the end of the first week of life. Symptoms from the remaining lesions appear later, as the pulmonary resistance continues to decline from 2 to 12 weeks. A normal physical examination and absence of murmur on the first day of life does not rule out congenital heart disease; approximately one-half of confirmed duct-dependent lesions are in infants whose initial physical examination was reported to be “normal.”

Although many congenital heart malformations are discovered by prenatal fetal ultrasounds that examine the 4-chamber view and major outflow tracts of the fetal heart, not all cases are picked up because of the technical demands of the skill of fetal echocardiography. Presence of a cardiac murmur often raises anxiety in the staff and parents because of the possibility of a congenital heart malformation. An audible murmur needs to be assessed: Does it have the characteristics of a clinically significant murmur, or is it an

Child in well-infant nursery at 24–48 hr of age or shortly before discharge if <24 hr of age



**Figure 110-3** The proposed pulse oximetry monitoring protocol based on results from the right hand (RH) and either foot (F). (From Kemper AR, Mahle WT, Martin GR, et al. Strategies for implementing screening for critical congenital heart disease. *Pediatrics*. 2011;128[5]:e1259–e1267.)

innocent one? Approximately one-half of the murmurs heard in the newborn period beyond the first day of life are innocent in nature. Innocent murmurs are short systolic in timing, have no diastolic component, have no ejection clicks, are less than grade 3/6 in intensity, and change intensity with posture change. Clinically significant murmurs, on the other hand, are louder (more than grade 3/6), are associated with palpable heave or thrill, may be holosystolic, may have a diastolic component, and may have ejection clicks. (See Chapter 101, The Newborn With a Heart Murmur or Cyanosis.)

An effort should be made to feel the femoral pulses on all newborns. If the pulses are difficult to feel, then blood pressure should be measured in both upper and lower limbs with an appropriate cuff size. Selecting an appropriate cuff size is important since an undersized cuff gives a higher reading and an oversized cuff underestimates the blood pressure. Cuff size is selected by measuring the circumference of the upper arm and following the manufacturer's recommendation. For example, Critikon neonatal blood pressure cuff size 1

is used for circumference of 3 to 6 cm, Size 2 for 4 to 8 cm, and Size 3 for 6 to 11 cm.

Presence of brachiofemoral delay in pulse or significant blood pressure difference in upper and lower limbs may point toward coarctation syndromes. A chest radiograph and electrocardiogram may be of some help. However, in the presence of a significant murmur, the referral NICU and the pediatric cardiology service should be contacted.

Pulse oximetry checking preductal saturation (right hand) and simultaneous post-ductal saturation (on either foot) beyond 24 hours or before discharge has been evaluated and recommended as routine screening for critical duct-dependent congenital heart malformations in newborn infants (Figure 110-3).

Sudden onset of poor feeding, cardiorespiratory compromise, metabolic acidosis, cyanosis, and no significant improvement in oxygenation while breathing 100% oxygen in a newborn beyond the first day of life should arouse suspicion of a duct-dependent cardiac malformation. Examples of duct-dependent lesions are hypoplastic left heart syndrome, left outflow tract

obstruction, coarctation of aorta, transposition of great vessels, tricuspid atresia, pulmonary stenosis, and atresia. Prostaglandin infusion may be initiated in consultation with the pediatric cardiology service as soon as possible. Other important differential diagnoses, such as sepsis or inborn error of metabolism, should be also kept in mind (Box 110-3).

### Abnormal Neurologic Signs

Neonatal seizure is the most common neurologic cause of referral to the NICU. Treatment should be based on reliable history from parents or from witness accounts by medical personnel. Seizures may need immediate attention for control, then clinical and diagnostic evaluation to find the cause. Neonatal seizures may be caused by perinatal hypoxia or ischemia, metabolic disturbances, intracranial hemorrhage or infarction, sepsis, or withdrawal syndrome, or they may be of the benign familial type. In the management of a clinical seizure, an important feature is to look for hypoglycemia before providing anticonvulsant therapy. Hypoglycemia should be assessed by a rapid blood glucose strip test. If hypoglycemia is present, the infant is treated with an intravenous glucose bolus first; if hypoglycemia is absent, then a loading dose of anticonvulsant is given. Other therapy will depend on the causative factor for the seizure. After the seizure is controlled, transfer should be initiated in consultation with the accepting NICU as further evaluation for the cause of seizure continues. (See Chapter 107, The Newborn With Neurologic Findings, and Chapter 327, Seizure Disorders)

Other neurologic causes for referral may include unexplained hypotonia (*floppy infant*), poor feeding, hypertonia, and exaggerated reflexes. The NICU team and pediatric neurology service should be consulted regarding whether the baby requires intensive care or whether the infant is feeding and stable enough to be followed up in the outpatient department.

### BOX 110-3 Well-Seeming Newborn With a Serious Underlying Disorder

- Neonatal sepsis (group B *Streptococcus* infection, *Escherichia coli* infection, herpes simplex virus infection) during incubation period
- Duct-dependent cardiovascular malformation (before ductus arteriosus starts closing)
- Gastrointestinal causes (small-bowel obstruction, malrotation, Hirschsprung disease) before feeding and abdominal distension
- Inborn errors of metabolism (before feeding and accumulation of offending metabolites)
- Congenital adrenal hyperplasia, particularly in boys (before any physiological stress)
- Congenital clotting disorders, particularly in boys (before circumcision)

### Congenital Anomalies

Life-threatening malformations that require early medical or surgical intervention, such as critical congenital heart defects, gastrointestinal atresias, gastroschisis, omphalocele, and diaphragmatic hernia, diagnosed by prenatal ultrasound, should preferably be delivered at a hospital with a NICU with the required subspecialty support. Presence of polyhydramnios or oligohydramnios on prenatal ultrasounds should alert the PCP to assess the affected infant for additional malformations. Polyhydramnios is associated with tracheoesophageal fistula and open neural tube defects, whereas oligohydramnios is associated with renal dysplasia, obstructive uropathy, and pulmonary hypoplasia. Occasionally, these infants are born in a community hospital without a prenatal diagnosis, or the mother experiences an unexpectedly rapid progression of labor before reaching a perinatal regional referral center. The PCP should contact the regional NICU team to optimize the pretransport stabilization.

### Dysmorphology

The most common dysmorphologies are trisomy 21, 18, and 13 phenotypes and their association with major organ system malformations. Other group associations include VACTERL (vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb anomalies) and CHARGE (coloboma, heart disease, atresia choanae, retardation of growth or development, genitourinary tract anomalies, and ear anomalies), in which the presence of 1 feature leads to the discovery of another. Facial dysmorphic features (eg, frontal prominence, depressed nasal bridge, palpebral fissure slants, micrognathia, ear anomalies, facial clefts) may be present as isolated findings, but a combination of these findings along with others found by systemic examination should be discussed with the NICU or a genetic service (or both) for diagnosis and management. These infants may or may not require NICU care, depending on the presence or absence of any associated serious systemic malformations.

### Hematologic Problems

Acute hemorrhage, hypovolemia, and anemia may be life threatening and should be addressed promptly. Although volume resuscitation and blood transfusion are contemplated, the referral process to the NICU should be initiated. Early onset jaundice and pallor (within 24 hours of life) signifying hemolysis should be assessed promptly, and the infant should be referred after consultation with the accepting NICU. A ruddy-appearing baby might have polycythemia, which is defined as a venous hematocrit level of 65% or more. It is commonly associated with IDM, diabetes, small-for-gestational-age babies, Down syndrome, delayed clamping, and milking of the umbilical cord, and should be discussed with the NICU team. The issue of polycythemia caused by delayed cord clamping is an area of controversy, since a 2013 Cochrane database systematic review did not find a difference in the incidence of polycythemia between the early and late cord clamping groups in the 5 trials reporting this outcome. Thrombocytopenia caused



by maternally acquired antibodies may occasionally be severe enough to cause life-threatening bleeding in newborns, and referral should be decided with the NICU team and in consultation with pediatric hematology service.

### Hyperbilirubinemia

Jaundice within the first 24 hours after birth, particularly when associated with significant anemia, is a cause for concern and should be discussed with the regional referral hospital NICU team. Exaggerated physiological jaundice and breastfeeding jaundice are common causes of neonatal readmission to the hospital and can be managed at level I or level II facilities or on the general pediatric unit. (See Chapter 99, Neonatal Jaundice, for information on the management of this condition.)

### Inborn Errors of Metabolism

Inborn errors of metabolism (IEMs) are rare disorders when considered individually, but when considered together are found in 1 in 1,500 births by some estimates. Carbohydrate metabolism-related disorders (eg, galactosemia) will produce hypoglycemia, hepatic dysfunction, and acidosis. Aminoacidopathies (phenylketonuria, tyrosinemia, maple syrup disease) produce acidosis, encephalopathy, and hepatic dysfunction. Lipid metabolism disorders are errors with fatty acids and organic acidemias, medium-chain acyl-coenzyme A dehydrogenase deficiency, propionic academia, and primary lactic acidosis. Poor feeding, faster breathing, respiratory alkalosis, and encephalopathy in absence of significant metabolic acidosis may point towards urea cycle disorders. (See Chapter 105, Transient Metabolic Disturbances in the Newborn; and Chapter 106, Specific Congenital Metabolic Diseases.)

In a stable newborn, IEMs are diagnosed either as part of the state screening program or by way of prenatal or postnatal diagnostic workup in response to a positive family history of a genetic disorder. In either case, the PCP should contact the designated screening program or the genetics service for guidance. In an ill-appearing newborn in whom IEMs are suspected (sudden deterioration after 1–2 days or of feeding and unexplained severe acidosis or hypoglycemia), a few general screening tests may be performed to arrive at a diagnosis pending the results of the genetic testing (see Box 110-2).

### Endocrine Conditions

The most common endocrine derangement is neonatal hypoglycemia caused by increased fetal insulin in IDMs. Congenital hypothyroidism, generally discovered by newborn screening, is the next most common disorder. Congenital adrenal hyperplasia is usually detected in newborn girls because virilization leads to ambiguous genitalia; boys with the same condition are not discovered unless the state-mandated newborn screening tests detect increased levels of 17-hydroxyprogesterone. Transient hypoparathyroidism may produce hypocalcemia, but it may occasionally be the earliest clue to DiGeorge syndrome.

### In Utero Drug Exposure and Neonatal Abstinence Syndrome

In recent years there has been a surge in infants diagnosed with neonatal abstinence syndrome (NAS) resulting from increased abuse of prescription narcotic drugs by pregnant women. Abuse of other substances such as marijuana, cocaine, alcohol, and tobacco continues at previous rates, and more often multiple substance use occurs. Drug withdrawal manifests as jitteriness, increased muscle tone, inconsolable crying, and (rarely) seizures. Maternal history and results of drug screening tests are helpful. Infants exposed to in utero drugs are closely monitored, for instance using the Finnegan scoring system (primarily used for narcotic withdrawal), and appropriate interventions planned in consultation with the NICU attending, depending on the severity of the infant's symptoms. Infants with persistently high Finnegan scores (>8) with no response to nonpharmacological interventions like swaddling and minimal stimulating environment may need to be treated with medications such as morphine, methadone, or phenobarbital. During initiation of opiate therapy, infants require cardiorespiratory monitoring.

## ASSESSMENT OF WELL-APPEARING INFANTS

In a well-appearing infant, some clinical clues may be present that lead to the suspicion or diagnosis of a problem. This will assist the physician with the decision about the need for consultation or immediate referral of the infant to a NICU. Few situations occur in which the newborn seems apparently well only to show signs of a serious disorder later (Box 110-4; see

### BOX 110-4 Common Diagnostic Categories for an Ill-Seeming Newborn (Beyond 12 to 24 Hours After Normal Cardiopulmonary Transition at Birth)

- Respiratory distress: neonatal sepsis, pneumonia
- Critical congenital heart disease: duct-dependent cardiac lesion
- Common metabolic derangements: hypoglycemia, hypocalcemia
- Inborn errors of metabolism: unexplained, severe, persistent metabolic acidosis or hypoglycemia
- Neurologic problems: neonatal seizures, hypertonia, hypotonia, apnea
- Surgical conditions: Intestinal atresias, malrotation, volvulus, Hirschsprung disease, meconium ileus, ovarian cysts
- Endocrinological: disorders of sexual development (congenital adrenal hyperplasia)
- Hematologic problems: hyperbilirubinemia, anemia, polycythemia, severe alloimmune thrombocytopenia, congenital clotting disorders
- Genitourinary problems: renal dysplasia, hydronephrosis, hypertension

also Box 110-3). The 2 most common conditions that start as an apparently well newborn at birth who remains stable for a several hours to a few days before rapidly becoming symptomatic are neonatal sepsis and duct-dependent congenital heart disease.

After initial assessment, consideration of the conditions listed in Box 110-4 and based on the available resources at the primary care facility, a determination should be made after consultation with regional NICU team regarding the ongoing evaluation and treatment required by the infant at an appropriate level of care. The first consideration is immediate stabilization of the infant including the initiation of necessary diagnostic studies. Consultation with a neonatologist prior to neonatal transfer facilitates care coordination and provides an opportunity for discussion about interim evaluation, treatment and pretransport preparation. At the same time, PCPs should explain to the parents the reasons for the infant's transfer to a neonatal unit providing a higher level of care and the presumptive diagnosis and interim treatment plan. The PCP serves an integral role as medical liaison and support for the parents, assisting them in deciphering information about

their infant's condition, evaluation and treatment plans and expected outcome.

## SUMMARY

History of maternal gestation, prenatal maternal laboratory results, prenatal ultrasound results, and complete physical examination of an ill-appearing newborn are essential to arrive at a provisional diagnosis. An initial basic workup adds to the process of diagnosis and decision-making (see Box 110-2). Occasionally an apparently well-appearing newborn may have a serious underlying condition, although in most cases a warning sign will be present in the history, physical examination, or laboratory results that may provide a clue and reason to pursue further evaluation (Box 110-5). For the PCP, communication with the accepting NICU attending physician and with the baby's parents is crucial to this entire process.

## TOOLS FOR PRACTICE

### Medical Decision Support

- *Guidelines for Perinatal Care*, 7th ed (book), American College of Obstetricians and Gynecologists and American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

### BOX 110-5 Warning Signs in an Apparently Well Term Baby

#### SEPSIS

- Increased difference of central to peripheral skin temperature of more than 1°C in a thermo-neutral environment
- Presence of skin or mucous membrane vesicles with inflamed base
- Complete blood cell count performed for risk factors shows neutropenia with left shift

#### CONGENITAL HEART DISEASE

- Positive pulse oximetry newborn screening
- Dysmorphic features: trisomy 21, 13, 18 syndromes, Turner syndrome
- Significant cardiac murmur
- Difference in femoral and brachial pulses or low blood pressure in lower limbs as compared with upper limbs
- Sudden onset of cardiorespiratory compromise in a previously well baby beyond the first day of life and no improvement in oxygenation while breathing 100% oxygen (hyperoxia test)

#### INBORN ERRORS OF METABOLISM

- Poor feeding after 1 or 2 days of initial normal feeding
- Unexplained metabolic acidosis, hypoglycemia
- Respiratory alkalosis, hyperammonemia
- Family history of inborn errors of metabolism or unexplained neonatal deaths

#### ENDOCRINE PROBLEMS

- Hypoglycemia: hyperinsulinism in large-for-date infants of diabetic mothers
- Hypoglycemia with microphallus: hypopituitarism, growth hormone deficiency

- Hypoglycemia, hypothermia, holoprosencephaly: panhypopituitarism
- Hypocalcemia with hyperphosphatemia: hypoparathyroidism
- Hyponatremia with hyperkalemia: ambiguous genitalia: congenital adrenal hyperplasia, adrenal insufficiency
- Hyperbilirubinemia, constipation, slow feeder: hypothyroidism
- Unexplained tachycardia with maternal history of Graves disease: hyperthyroidism

#### HEMATOLOGIC PROBLEMS

- Polycythemia: large ruddy-looking infant of diabetic mother or small for gestational age, chronically stressed baby caused by placental insufficiency, twin-twin transfusion
- Excessive bleeding from circumcision: clotting disorder, immune thrombocytopenia
- Jaundice within 24 hours with or without pallor: hemolytic disease

#### OTHER PROBLEMS

- Choking on attempts to feed or inability to pass orogastric or nasogastric tube, prenatal history of polyhydramnios: esophageal atresia or proximal bowel obstruction
- Bilious vomiting should raise concern about malrotation and midgut volvulus
- Inability to pass meconium after more than 24 hours with abdominal distension: mid or distal bowel obstruction, such as ileal atresia, left microcolon, cystic fibrosis, Hirschsprung disease
- Persisting jaundice with acholic stools: biliary atresia, cholestasis

- *Strategies for Implementing Screening for Critical Congenital Heart Disease* (article), *Pediatrics*, Vol 128, Issue 5, 2011
- *The S.T.A.B.L.E. Program: Learner Manual*, 6th ed (book), Kristine A. Karlsen, PhD, APRN, NNP-BC (shop.aap.org)

### AAP POLICY

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### SUGGESTED READINGS

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- Enns GM, Packman S. Diagnosing inborn errors of metabolism in the newborn. *NeoReviews*. 2001;2(8):e192–e199
- Shenvi A, Kapur J, Rasiah SV. Management of asymptomatic cardiac murmurs in term neonates. *Pediatric Cardiology*. 2013;34:1638–1646

low-birth-weight infants and term infants with known congenital anomalies are born in hospitals that are not designed to provide specialized care. In addition, some term infants will fail to transition or have unpredicted medical needs and require transport to a tertiary care center.

### STABILIZING INFANTS

Stabilizing a sick or premature infant before interfacility transport means first ensuring an adequate airway and then optimizing ventilation. The next most critical issue is evaluating and obtaining an effective blood circulating volume. After the airway, breathing, and circulation (ABCs) have been established, several other parameters that are crucial to maintaining neonatal stability should be addressed, including thermoregulation, glucose homeostasis, evaluation for sepsis and the efficacy of ongoing therapies, and family crisis support. Because dealing with a sick neonate is an infrequent occurrence for people working outside of neonatal intensive care units, the S.T.A.B.L.E. mnemonic was created by the developers of the S.T.A.B.L.E. course (www.stableprogram.org) to aid recall of these steps for managing the infant before transport. The mnemonic is as follows:

S = SUGAR and SAFE care  
 T = TEMPERATURE  
 A = AIRWAY  
 B = BLOOD PRESSURE  
 L = LABORATORY EVALUATION  
 E = EMOTIONAL SUPPORT

The remainder of this chapter will summarize the S.T.A.B.L.E. Program Learner Manual content and review each of these issues, in mnemonic order, as it applies to pretransport management.

### Sugar

Because the newborn infant is at risk for hypoglycemia, measuring serum glucose is imperative. Newborns have limited glycogen stores and since most glycogen is produced and stored during the third trimester, hypoglycemia is of particular importance for the premature infant. The sick newborn will have increased glucose utilization, and hyperinsulinemia may be present in the infant who is large for gestational age or the infant of a mother with diabetes. Other causes of increased glucose utilization include perinatal distress, respiratory distress, hypoxia, shock, hypothermia, sepsis, and cardiac disease. In conditions of normoxia, infants rely on aerobic metabolism, which is efficient in producing energy from glucose. However, during hypoxia, anaerobic metabolism occurs, which utilizes additional glucose to produce the same amount of energy. Inadequate glucose production occurs in premature infants and those who are small for gestational age. Some maternal medications potentiate infant hypoglycemia, including  $\beta$ -sympathomimetics,  $\beta$ -blockers, benzothiadiazine diuretics, and chlorpropamide. Infants with polycythemia or congenital hypopituitarism are also at risk for hypoglycemia.

## Chapter 111

# CARE OF THE SICK OR PREMATURE INFANT BEFORE TRANSPORT

Gina Marie Geis, MD; Karen S. Wood, MD

Organized neonatal transport programs emerged in the late 1970s when perinatal care shifted to regional centers. Regionalization of care promoted maternal-fetal transport and reduced the number of newborns requiring postnatal transport. In addition, regionalization resulted in improvements in perinatal mortality and neonatal morbidity as the percentage of very low-birth-weight infants delivered outside of tertiary care centers decreased. Sick or premature infants, however, continue to be delivered at institutions that are unable to provide for all of their medical needs. In some areas, organized regional perinatal care services have deteriorated. In all regions of the country, very

The goal range for serum glucose is 50 to 110 mg/dL (2.8–6.0 mmol/L). Hypoglycemia is traditionally defined as a serum glucose concentration of less than 40 mg/dL; however, to provide a buffer, 50 mg/dL is designated as the concentration at which to intervene for patients undergoing transport. In most instances, sick infants are not stable enough for oral feedings, and glucose administration will require placement of a peripheral intravenous catheter or umbilical venous catheter. The initial glucose infusion rate (GIR) should be 4 to 6 mg/kg/min; glucose can be delivered with 10% dextrose in water (D<sub>10</sub>W) at 80 mL/kg/day or in extremely low-birth-weight (<1,000 g) infants with D<sub>5</sub>W at 120 mL/kg/day. If the initial measured serum glucose concentration is less than 50 mg/dL, then a peripheral intravenous line should be inserted, with a GIR of 4 to 6 mg/kg/min and a 2 mL/kg D<sub>10</sub>W (200 mg/kg) glucose bolus given over 2 to 5 minutes. Higher-concentration glucose boluses are discouraged because of the rebound hypoglycemia that can follow. A repeat serum glucose measurement should be performed 15 to 30 minutes after the bolus. If subsequent glucose measurements continue to be less than 50 mg/dL, the physician must first ensure that the intravenous line is functioning and that a GIR of 4 to 6 mg/kg/min is being delivered, and then an additional 2 mL/kg D<sub>10</sub>W bolus should be given intravenously. As needed, 2 glucose boluses may be given before increasing the GIR, which should be done in increments of 2 mg/kg/min. The physician should continue to repeat the serum glucose measurements until 2 successive measurements are greater than 50 mg/dL. Infants with hyperinsulinemia may need a GIR twice the initial starting rate and may require an increased fluid rate or a central line to achieve this goal. The steps for managing serum glucose are outlined in Box 111-1.

### Temperature

A neutral thermal environment has an important effect on the well-being of a newborn. Although the

seminal work by Silverman demonstrated increased survival in a neutral thermal environment for premature infants only, in practice, this principle is used for all newborns. Oxygen consumption increases at temperatures above and below the neutral thermal range. Hypothermia is a significant predictor of neonatal morbidity and mortality, particularly in the transport literature. Studies have demonstrated that head cooling or whole-body hypothermia may have advantages for neurologic outcome in a subset of neonates who have suffered a hypoxic insult at birth. However, for the general neonatal population, normothermia is the goal. The normal core temperature range for an infant is 97.7°F to 99.5°F (36.5°C–37.5°C). Every effort should be made to prevent heat loss in the neonate because rewarming an infant who has become hypothermic can be difficult.

All infants are at risk for hypothermia. Groups at higher risk include preterm infants, particularly those weighing less than 1,500 g; infants who are small for gestational age; infants who are hypoxic or those who require a prolonged resuscitation; acutely ill infants with infectious, cardiac, endocrine, neurologic, or surgical issues (abdominal wall and neural tube defects); infants who are sedated or paralyzed; and infants with hypoglycemia. During the transition to extrauterine life, an infant can lose heat at rates up to 1.0°C/min. The recommended delivery room temperature range, therefore, is 77°F to 82.4°F (25°C–28°C).

Heat can be lost by a variety of mechanisms; however, by the law of thermodynamics, heat always flows from warm to cold. Conductive heat loss occurs when the infant comes in contact with a cooler object such as a mattress, scale, stethoscope, blanket, or care provider. Warming objects (not to exceed 40°C) that the infant contacts and providing insulators, such as hats, are good mechanisms to avoid conductive heat loss. Convective heat loss occurs from the skin surface to the surrounding air and is increased when the environmental air temperature is colder or when the air currents are higher. Careful attention to the environmental temperature, including use of a prewarmed isolette or nonobstruction of the overhead heat source on a radiant warmer, and avoiding drafts, including cold oxygen currents, can help eliminate convective heat loss. Infants weighing less than 1,500 g should be covered with polyethylene plastic from neck to feet to reduce convective heat loss until a humidified environment can be provided. Radiant heat loss occurs between solid surfaces not in contact with each other. The heat sink is usually a cold wall or window, although a cold radiant warmer or isolette can have the same effect. The infant should not be located close to a cold solid object, and thermal shades and covers should be used. Finally, heat can be lost through the mechanism of evaporation, which is a particular concern in the delivery room. Evaporative losses occur when moisture on the skin surface or in the respiratory tract is converted into vapor, with a concurrent cooling effect. This type of heat loss can be minimized by drying the infant after delivery or bathing. No infant should be bathed until a normal core temperature has been established and the infant is otherwise stable. Oxygen should

#### BOX 111-1 Serum Glucose Management

- Step 1: Make sure the neonate receives nothing by mouth.
- Step 2: Start IV glucose infusion at 4 to 6 mg/kg/min
- Step 3: Check serum glucose (Step 3 may precede Step 2)
- Step 4: If serum glucose is <50 mg/dL then:
  - a. Check IV infusion rate
  - b. Administer a bolus of 2 mL/kg D<sub>10</sub>W
  - c. Recheck serum glucose in 15 to 30 minutes
  - d. May proceed through Step 4 twice
- Step 5: If serum glucose is <50 mg/dL after 2 boluses, then:
  - a. Increase glucose infusion by 2 mg/kg/min
  - b. Recheck serum glucose in 15 to 30 minutes
  - c. Repeat Step 5 as needed
- Step 6: If serum glucose is >50 mg/dL, then recheck serum glucose in 30 to 60 minutes
- Step 7: If serum glucose is >50 mg/dL on 2 serial checks, then space glucose measurements to 1 to 3 hours

D<sub>10</sub>W, 10% dextrose in water; IV, intravenous.



be heated and humidified as soon as possible. Polyethylene plastic wrap covering the infant can also reduce evaporative heat loss.

Term infants have adaptive mechanisms in response to cold stress, including peripheral vasoconstriction, increased muscle activity and flexion, and brown adipose metabolism. These mechanisms require oxygen and glucose. Peripheral vasoconstriction prevents blood flow to and heat loss from the skin surface. Infants cannot shiver; however, muscle activity generates some heat, and flexion conserves the surface area from which heat can be lost. Brown adipose is metabolized in response to cold stress with norepinephrine release, creating nonshivering thermogenesis. Brown adipose is accumulated throughout gestation, predominantly during the third trimester, and has a unique capability for extraordinary energy production and subsequent heat production. Pulmonary vasoconstriction occurs in addition to peripheral vasoconstriction in response to norepinephrine release and can lead to persistent pulmonary hypertension. The cascade of problems that occur with hypothermia is demonstrated in Figure 111-1.

In the event of heat loss, rewarming must occur, though rapidly rewarming the patient can result in vasodilation and hypotension. Unfortunately, no studies exist to define rewarming rates that are too fast or

too slow. If the infant is rewarming in an isolette, then the air temperature should be set to 1.0°C to 1.5°C above the infant's core temperature; after equilibration, the air temperature should be increased by an additional 1.0°C to 1.5°C until the infant's core temperature is within the normal range. If the infant is being rewarmed with a radiant warmer, then overly aggressive rewarming should be avoided. The servo control should not be set to greater than or equal to 36.5°C unless the infant's temperature is within 1.5°C of this value. The neonate's response to rewarming should be monitored, and the speed of rewarming, depending on tolerance, should be adjusted.

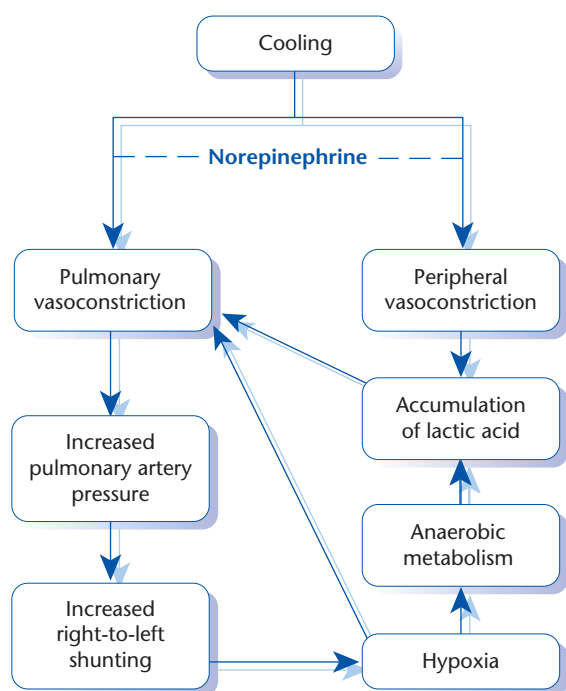
### Airway

Stabilizing the airway usually represents the most critical management dilemma in a pretransport newborn. The most common diagnosis requiring transport to a neonatal intensive care unit is respiratory distress. Respiratory failure can occur quickly but may be thwarted by early respiratory support, including correct airway positioning, supplemental oxygen therapy via hood or nasal cannula, continuous positive airway pressure (CPAP) via high-flow nasal cannula or CPAP device, or assisted ventilation through an endotracheal tube. The amount of support needed may change during the pretransport period, necessitating constant reevaluation of the patient's respiratory requirements. If adequate ventilation for the infant is not achieved, then other management strategies, including medications, will not be effective.

The normal respiratory rate for a newborn is 40 to 60 breaths per minute. Respiratory distress may manifest as apnea, poor air entry on auscultation, cyanosis, or increased work of breathing, such as tachypnea, retractions, grunting, or nasal flaring. The newborn can endure hypoxia for only a brief period, during which the infant relies on anaerobic metabolism, metabolizes large amounts of glucose, and produces significant quantities of lactic acid. If hypoxia continues, profound metabolic acidosis causes cellular dysfunction and cell death with organ injury. A postductal saturation measurement provides an estimation of oxygenation and is useful for continuous monitoring; however, an arterial blood gas test is the gold standard for assessing oxygenation, ventilation, and acid-base balance and can guide further management. A low partial pressure of carbon dioxide in arterial blood with tachypnea typically represents a nonpulmonary cause of respiratory distress, such as congenital heart disease, metabolic acidosis, or central nervous system dysfunction. A high partial pressure of carbon dioxide with tachypnea typically represents a pulmonary cause, such as pneumonia, meconium or amniotic fluid aspiration, pneumothorax, respiratory distress syndrome, airway obstruction, or pulmonary hypoplastic syndromes such as chest mass or congenital diaphragmatic hernia. A chest radiograph should be obtained to help diagnose the cause of respiratory distress and define the extent of disease. (See Chapter 100, Respiratory Distress and Breathing Disorders in the Newborn.)

Rarely does a term newborn require CPAP; therefore using the oxygen hood is usually the best technique to

### Cardiovascular Response to Cold Stress in the Critically Ill Newborn



**Figure 111-1** Cardiovascular response to hypothermia. (From Baumgart S. *Incubation of the human newborn infant*. In: Pomerance JJ, Richardson CJ, eds. *Neonatology for the Clinician*. Norwalk, CT: Appleton & Lange, 1993. Copyright McGraw-Hill Education. Used with permission.)

supply oxygen to nonventilated newborns. Unlike the nasal cannula, the hood allows measuring the amount of oxygen being supplied to the nares. In term infants, the use of high oxygen concentrations (fraction of inspired oxygen = 1.0) in the time frame for stabilization is permissible. Using a nasal cannula to provide oxygen therapy is common practice; however, this method also provides unnecessary CPAP, which increases the risk for air leak and is therefore not the best choice for term patients. If an insufficient amount of oxygen is being delivered via the hood or the patient's respiratory status is deteriorating, then the infant should be intubated and placed on assisted ventilation. The endotracheal tube size and placement depth are dictated by the infant's weight (Table 111-1). The initial ventilator settings should consider the patient's gestational age, weight, and disease process (Table 111-2).

In contrast, in preterm infants, judicious use of oxygen therapy must occur because of the known retinal and pulmonary toxicities of oxygen. Premature infants often need CPAP but little supplemental oxygen; therefore, the best initial device for them is CPAP or a nasal cannula with a flow meter and blender to deliver the minimal necessary oxygen concentration.

**Table 111-1** Endotracheal Tube Size and Placement Depth

WEIGHT (G)	TUBE SIZE (MM)	TUBE INSERTION DEPTH (CM)
<1,000	2.5	6.5–7.0
1,000–2,000	3.0	7–8
2,000–3,000	3.5	8–9
>3,000	3.5–4.0	>9

Adapted from Kattwinkel J. *Textbook of Neonatal Resuscitation*. 5th ed. Elk Grove Village, IL: American Academy of Pediatrics and American Heart Association; 2006.

Given that CPAP devices are not universally available, increasing flow rates with the nasal cannula can create CPAP. A flow rate not to exceed 2 L/min should be sufficient for newborn premature infants. For infants requiring more support, intubation and assisted ventilation should be provided (see Table 111-1 and Table 111-2). (See Chapter 109, Assessment and Stabilization at Delivery.)

Respiratory distress can result from parenchymal lung disease but can also be caused by airway obstruction. Obstruction can occur at any point in the airway: nose, mouth, jaw, larynx, trachea, or bronchi. Upper airway obstruction can produce the aforementioned signs of respiratory distress, as well as stridor. The character of the stridor can suggest the level of obstruction. (See Chapter 197, Stridor.) The diagnosis of choanal atresia can be excluded by the ability to pass a catheter through each nare. Patients with choanal atresia often need only an oral airway but may need intubation to bypass the obstruction. Nasal cannula and CPAP devices are ineffective in choanal atresia. Infants with Pierre Robin sequence have micrognathia, cleft palate, and airway obstruction from the posterior position of the tongue. These infants often improve with prone positioning, allowing the tongue to fall forward with gravity. An oral airway or a laryngeal mask airway, if available, may be effective. If these mechanisms fail, then an endotracheal tube can be passed through the nares to the pharynx and be used to supply humidified oxygen or CPAP. If all these mechanisms are ineffective, then endotracheal intubation should be performed. However, endotracheal intubation can be technically difficult because of the micrognathia.

Persistent pulmonary hypertension (PPHN) can occur with sustained elevation of pulmonary vascular resistance after birth and persistence of fetal circulation. Given that blood follows the path of least resistance, it is shunted from right to left, away from the lungs, through the ductus arteriosus or foramen ovale, resulting in hypoxemia. Idiopathic PPHN can occur, and PPHN can accompany hypothermia, sepsis, congenital

**Table 111-2** Suggestions for Initial Ventilator Support for Infants of Varying Weights

SETTINGS	VLBW (<1.5 KG)	LBW (1.5–2.5 KG)	TERM (>2.5 KG)
Rate (per minute)	30–45	20–40	20–40
Inspiratory time (in seconds)	0.30–0.35	0.30–0.35	0.35–0.40
Positive inspiratory pressure (PIP) (cm H <sub>2</sub> O)	16–22	18–24	20–28
Positive end expiratory pressure (PEEP) (cm H <sub>2</sub> O)	4–7	4–7	4–7

LBW, low birth weight; VLBW, very low birth weight.

Notes:

1. PEEP

- The amount of PEEP selected will be based on the infant's disease process and goals of therapy.
- A PEEP of 4 may be insufficient and may result in collapse of the alveoli.
- Excessive PEEP for the disease process and clinical situation may impair ventilation, lung perfusion, or venous return (return of deoxygenated blood to the right side of the heart).

- The amount of pressure required (PIP) will also vary depending on the infant's size, disease state, and response to ventilation. Start with pressure in the lower end of the range and adjust up or down as needed based on the infant's response to treatment, chest x-ray, blood gas, and physical examination.
- An inspiratory time greater than 0.5 seconds may result in air trapping and increase the risk for barotrauma and injury to the lung tissue.
- A chest x-ray and blood gas may be helpful to assess response to changes.

From Karlsen KA. *The S.T.A.B.L.E. Program. Post-resuscitation/Pre-transport Stabilization Care of Sick Infants. Guidelines for Neonatal Healthcare Providers: Learner Manual*. 6th ed. Salt Lake City, UT: S.T.A.B.L.E. Program; 2006. Used by permission.

heart disease, or birth depression. However, most cases of PPHN occur with a parenchymal lung disorder such as meconium aspiration, pulmonary hypoplasia, pneumonia, or respiratory distress syndrome. With prompt recognition and early management of PPHN, infants typically need far less support than those with delayed diagnosis.

PPHN should be considered in any infant with respiratory distress. Infants with PPHN will have tachypnea, cyanosis, and lability in oxygen saturations. The presence of PPHN is suggested by a preductal-to-postductal oxygen saturation difference greater than or equal to 10%. Some infants with PPHN will shunt only at the atrial level and will not display this preductal-to-postductal saturation difference but will have lower than normal oxygen saturations. The chest radiograph in infants with PPHN may demonstrate parenchymal lung disease or decreased vascular markings, as in idiopathic PPHN, as well as a heart size that is normal or slightly enlarged. PPHN is also suggested by a low partial pressure of oxygen on an arterial blood gas sample; however, congenital heart disease needs to be ruled out in these patients. Providing adequate oxygen and eliminating acidosis may significantly improve the partial pressure of oxygen in patients with PPHN but not in patients with congenital heart disease. Comparison of an arterial blood gas test in room air and a second arterial blood gas test after 30 minutes of 100% oxygen (fraction of inspired oxygen = 1.0) exposure is known as the hyperoxic challenge test. An improvement in the partial pressure of oxygen to 100 mm Hg or higher with the hyperoxic challenge test is suggestive of a pulmonary process over a structural cardiac disorder. Echocardiography is the gold standard for diagnosing congenital heart disease but is often unavailable in the pretransport setting. Prostaglandin E<sub>1</sub> should be considered for any infant not responding to conventional ventilatory strategies until the structural cardiac anatomy can be defined. Therapy for PPHN includes adequate ventilation and oxygenation (may require intubation), correction of acidosis or mild alkalosis, provision of sedation and analgesia, maintenance of adequate cardiac output via volume and inotropic support, elimination of hypothermia, correction of polycythemia but maintenance of a normal hematocrit, and correction of metabolic abnormalities, including hypoglycemia and hypocalcemia. After all of these therapies have been optimized, inhaled nitric oxide can be considered; extracorporeal membrane oxygenation should be contemplated only as a last therapeutic option.

Pneumothorax occurs often in neonates. In fact, based on radiographic surveys, spontaneous pneumothoraces occur in 1% to 2% of all live births and are a consequence of the high negative intrapleural pressures (40–100 cm of water) produced with initial respirations in a newborn. Despite a high frequency of occurrence, most pneumothoraces are asymptomatic. Parenchymal lung disease, resuscitation at birth with positive pressure ventilation, or assisted ventilation in the neonatal period increases the risk for a symptomatic pneumothorax. Surfactant replacement and ventilation using lower peak airway pressures (gentle ventilation) have decreased the

incidence of air leaks, particularly in the preterm population.

Pneumothorax can be the primary cause of respiratory distress, or it can arise as a complication of lung disease. Air accumulating in the pleural space can compress the lung, affect ventilation, and, in severe cases, restrict cardiac output. A pneumothorax should be suspected in any infant who undergoes a rapid deterioration of respiratory status, especially if an associated cardiovascular collapse occurs. However, smaller air leaks can produce an insidious change in vital signs. A pneumothorax can usually be diagnosed by an anterior-posterior view chest radiograph, although a lateral view is occasionally needed. With an unstable infant, as seen with a tension pneumothorax, there may not be time to wait for the radiograph, and in these cases transillumination of the chest can be used to diagnose the pneumothorax. Transillumination indicates a pneumothorax if the fiber-optic light on the chest wall demonstrates a degree of lucency in excess of the usual 2- to 3-cm halo around the probe tip. A completely collapsed lung can demonstrate a false-negative transillumination. The room should be dark, and the transilluminator light source needs to be bright. False-positive transillumination can occur with chest wall edema, subcutaneous air, pneumomediastinum, and severe pulmonary interstitial emphysema.

Asymptomatic infants with a small pneumothorax require only close observation. Infants with respiratory distress may benefit from oxygen therapy best delivered without positive pressure via an oxygen hood. Unstable infants will require evacuation of the pneumothorax with needle decompression or thoracostomy tube placement. The presence of parenchymal lung disease or ongoing positive pressure ventilation substantially increases the need for evacuation. Needle decompression is performed in the second intercostal space in the midclavicular line. The thoracostomy tube should be inserted in the fourth or fifth intercostal space at the midpoint of the anterior axillary to mid-axillary line for an anterior tube placement. If size 10 or 12 French thoracostomy tubes are not available and continuous evacuation of air leak is necessary, then a 23-gauge butterfly needle can be placed, as in needle decompression, and the end of the tubing submerged in sterile water for temporary drainage.

### Blood Pressure

Hypotension results in inadequate oxygen delivery to the tissues. In newborns, hypotension occurs secondary to hypovolemia, heart failure, sepsis, or a combination of these conditions. In the extremely low-birth-weight infant, adrenal insufficiency may be an isolated cause for hypotension. Delaying treatment of shock can lead to multisystem organ failure and death; therefore early identification is essential.

The normal range for blood pressure varies by gestational age, and the exact normal range remains controversial. It is a commonly used convention that the mean blood pressure should approximate gestational age. Given that low blood pressure is a late finding in cardiac collapse, early signs of compromise must be identified. The physical examination findings of hypotension include weak peripheral pulses,

cyanosis, poor perfusion (represented as a capillary refill time  $>3$  seconds), pallor, and mottled and cool skin. Cardiac output is a product of stroke volume and heart rate. Although older patients increase cardiac output by increasing stroke volume, the infant has a poorly compliant myocardium and therefore relies on increased heart rate to increase cardiac output. Infants with hypotension will initially demonstrate tachycardia but progress to bradycardia before arrest. Infants in shock will also demonstrate respiratory distress with increased work of breathing, tachypnea, apnea, and finally gasping as a sign of impending cardiac arrest. Urine output, particularly after the first 24 hours of life, can be used to approximate cardiac output.

The most common cause of hypotension is hypovolemia resulting from hemorrhage occurring during the intrapartum or postpartum period. However, sepsis, dehydration, pneumothorax, or pneumoperitoneum can impair ventricular filling and lead to hypovolemic hypotension. A second cause of hypotension is heart failure that results from asphyxia, hypoxia, metabolic acidosis, infection, severe metabolic and electrolyte disturbances, arrhythmias, or congenital heart disease. The final category of hypotension is that caused by sepsis, which typically produces distributive shock with the loss of vascular tone and accompanying capillary leak. Infants can have hypotension from any or a combination of these different causes, and each will have its own management plan.

Treatment for the infant in hypovolemic shock relies on volume resuscitation. Initially, volume expansion should use lactated Ringer solution or normal saline at 10 mL/kg. If the patient is anemic, then ideally, cross-matched packed red cells should be given. Infants should be reassessed for further volume replacement. Cardiogenic failure is best treated with inotropic agents such as dopamine, dobutamine, or epinephrine. The starting dose for dopamine or dobutamine is 5 mcg/kg/min and should be titrated to the desired mean blood pressure or effect. In septic shock, capillary leak and the ongoing third-space losses will require volume replacement, and the cardiac effects will require inotropic support. Requiring large amounts of volume replacement is not uncommon for infants in septic shock. Patients with cardiogenic and septic hypotension can have significant metabolic acidosis; however, the use of sodium bicarbonate is controversial and reserved for term infants who are well ventilated and have a pH of less than 7.15. The most effective therapy for these infants is to identify and treat the cause of the metabolic acidosis. Also important in the face of hypotension is maintaining adequate glucose, calcium, sodium, and potassium for optimal cardiac function. (See also Chapter 373, Shock.)

## LABORATORY EVALUATION

Before transport, the 4 laboratory specimens that are helpful to obtain are:

- Blood glucose
- Blood gas
- Complete blood count
- Blood culture

## Blood Glucose

The reader is referred to the Sugar section earlier in this chapter.

## Blood Gas

A blood gas test is essential because most patients referred to higher-level centers will have respiratory symptoms, and the acid-base balance gives valuable diagnostic information. An arterial blood gas test is preferred if the distinction between a cardiac disorder and a respiratory disease remains in question; however, a capillary blood gas level is often easier to obtain and is acceptable to assess pH and ventilation. The blood gas analysis helps define the infant's status and can be communicated to the consultant at the referral center to determine further management and urgency of transport.

The reader is referred to the Airway section earlier in this chapter.

## Blood Count and Blood Culture

The complete blood count and the blood culture are the essential components of an initial sepsis evaluation in a neonate. Because all neonates are immunodeficient, and because failure to treat a septic infant can be fatal, performing a sepsis evaluation in a symptomatic infant is critically important. The risk factors for neonatal sepsis include premature rupture of membranes, rupture of membranes more than 18 hours, maternal fever, recent maternal infection or illness, maternal urinary tract infection, maternal chorioamnionitis, maternal group B streptococcal colonization, fetal distress, perinatal asphyxia, low birth weight, male gender, and intrapartum or postpartum instrumentation. Clinical signs of sepsis can be subtle or dramatic and include respiratory distress, temperature instability, abnormal skin perfusion, abnormal heart rate, abnormal blood pressure, feeding disturbance, and neurologic dysfunction. Given the wide spectrum of presentation for sepsis and the fact that considerable overlap exists with other diagnoses, it is imperative to obtain blood work and initiate antibiotic therapy until infection is ruled out.

Causative agents for neonatal sepsis are not always bacterial. However, bacterial infections are more common in the neonate than in patients at any other stage in life, and bacteria are the organisms to which therapy should be targeted in the pretransport period. The most common infecting organisms include group B *Streptococcus*, *Escherichia coli*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and, less commonly, *Enterococcus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Listeria monocytogenes*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Enterobacter*, *Neisseria meningitidis*, and group A *Streptococcus*. A blood culture, preferably 1 mL in volume, collected from a carefully prepped site can identify the infectious agent. Obtaining the blood culture should precede antibiotic administration; however, antibiotic delivery should not be delayed if a culture cannot be obtained.

The complete blood count and differential may suggest sepsis if it reveals neutropenia, neutrophilia, immature neutrophils, thrombocytopenia, or



thrombophilia. Neutrophils are the critical component of defense against bacterial infections, and elevation of neutrophil counts can signal sepsis, although a diminished neutrophil count is much more ominous for neonatal sepsis. When neutrophils are depleted, the bone marrow produces more immature neutrophils. The diagnosis of sepsis should be entertained with neutropenia, especially an absolute neutrophil count below 1,800/mcL, or an immature to total neutrophil ratio above 0.15 in the first 24 hours of postnatal life. Thrombocytopenia may indicate sepsis. The normal range for the platelet count of a term infant is 310,000 ( $\pm$ 68,000)/mcL. Thrombocytopenia is defined as a platelet count less than 150,000/mcL. For term infants, the risk of bleeding is low until platelet counts drop below 30,000/mcL, and therefore platelet transfusions are rarely necessary in the pretransport period. An essential point to note is that the complete blood count is not diagnostic for sepsis. An infant with sepsis can have normal values in the complete blood count, and an infant without sepsis can have an abnormal complete blood count.

The suggested therapy for presumed early-onset neonatal sepsis consists of ampicillin and gentamicin. The ampicillin dose is 100 mg/kg/dose every 12 hours intravenously. This higher dose is used because meningitis is not easily excluded with an initial neonatal sepsis evaluation. Gentamicin should be dosed in accordance with the NeoFax guidelines, with dose ranges from 4 to 5 mg/kg/dose every 24 to 48 hours depending on postmenstrual and postnatal age. According to current NeoFax guidelines, neonates who are  $\leq$ 29 weeks postmenstrual age and between 0 and 7 postnatal days of age should be administered gentamicin 5 mg/kg/dose IV every 48 hours. For neonates who are 30-34 weeks postmenstrual age and between 0 and 7 postnatal days of age, gentamicin dosing should be 4.5 mg/kg/dose IV every 36 hours. For neonates  $\geq$ 35 weeks postmenstrual age and for all postnatal days of life, gentamicin dosing should be 4 mg/kg/dose IV every 24 hours. The antibiotic regimen is continued until sepsis is satisfactorily ruled out; this typically requires monitoring of the blood culture for a minimum of 48 hours.

Early-onset group B streptococcal (GBS) infection can occur in the first week of life as sepsis, pneumonia, meningitis, or any combination. The incidence of this infection has decreased in recent years with the implementation of maternal carrier screening and peripartum antibiotics. Neonates who demonstrate signs of sepsis at birth should have a blood culture obtained, and should be started on antibiotics. Given that premature infants have an increased risk of early-onset GBS disease compared with term infants, and because distinguishing GBS disease from respiratory distress syndrome is often difficult, these preterm infants more frequently deserve an initial sepsis evaluation.

## EMOTIONAL SUPPORT

An ill newborn requiring transfer to another hospital represents a significant and unexpected crisis for most parents. Feedback from parent support groups reveals

that for infants being transferred, while the needs of the neonate are being met, the needs of the parents often are not. Parents should be informed of the assessment and plan for their infant. This information often needs to be repeated because families may be in shock and not fully understand the information that is provided. In addition, maternal health status and peripartum medications received can affect a mother's ability to understand her infant's medical condition.

Families receiving catastrophic news undergo the stages of grief as outlined by Elisabeth Kübler-Ross in her book *On Death and Dying*: shock, denial, anger, bargaining, depression, testing, and acceptance. During the pretransport period, it is typical for families to be in the earliest stages, expressing shock and denial, finding it incomprehensible that what was supposed to be a happy, uncomplicated event has gone awry. However, individual family members transition through these stages at different speeds and sometimes in different orders. Consequently, the caretaking team needs to be capable of managing families in all stages of grief. A designated hospital staff member must be responsible for communicating directly with the family during the stabilization period and after departure of the infant. The parents should be encouraged to write questions down for the physician or transport team because forgetting questions is common when under stress.

The caretakers communicating with the family should identify the infant as personally as possible. Family members should be encouraged to touch their infant, take pictures, and when appropriate, obtain mementos such as footprints or a lock of hair. Any additional sources of support such as family members, friends, or members of the clergy should be identified and contacted. The assigned communicator should accompany the transport team to the mother's room and stay to hear the discussion with the family because questions will inevitably arise once the team leaves. Once the transport team departs with the neonate, the caretaking team should switch its focus from taking care of the infant to taking care of the parents. A helpful measure is to review with the family the information communicated by the transport team, such as the new caretakers for the infant, the plan of care at the receiving hospital, and directions to the receiving hospital. Also important is assessing the parents' response and coping mechanisms when the infant departs. Inquiring into the mother's plan to breastfeed and obtaining a breast pump (many insurance plans will provide mothers with a hospital-grade electric breast pump if the infant is hospitalized and unable to nurse) and encouraging her to proceed with breast milk expression can be useful. Offering to help the parents make subsequent contact with the center caring for their infant is appropriate.

Few parents anticipate that their term newborn will not be healthy, and families having preterm infants are ill prepared for birth, much less for coping with an infant requiring critical care. Providing families with information, an opportunity to talk and grieve, support in their time of crisis, and close personal follow-up is an essential and often overlooked portion of providing care in the pretransport stabilization period.

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## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *What Is a Neonatologist?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Neonatologist.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Neonatologist.aspx))
- *NICU Medical Team* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/baby/preemie/Pages/NICU-Medical-Team.aspx](http://www.healthychildren.org/English/ages-stages/baby/preemie/Pages/NICU-Medical-Team.aspx))

### Medical Decision Support

- *Guidelines for Air and Ground Transport of Neonatal and Pediatric Patients* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *The S.T.A.B.L.E. Program: Learner Manual*, 6th ed (book), Kristine A. Karlsen, PhD, APRN, NNP-BC ([shop.aap.org](http://shop.aap.org))
- *The S.T.A.B.L.E. Program: Learner/Provider Course Slides on DVD*, 6th ed (DVD-ROM), Kristine A. Karlsen, PhD, APRN, NNP-BC ([shop.aap.org](http://shop.aap.org))
- *The S.T.A.B.L.E. Program: Physical Exam and Gestational Age Assessment Slides DVD*, 2nd ed (DVD-ROM), Kristine A. Karlsen, PhD, APRN, NNP-BC ([shop.aap.org](http://shop.aap.org))
- *The S.T.A.B.L.E. Program: Quick Reference Bedside Card Set*, 4th ed (cards), Kristine A. Karlsen, PhD, APRN, NNP-BC ([shop.aap.org](http://shop.aap.org))
- *The S.T.A.B.L.E. Program: Blood Gas Interpretation Chart*, 3rd ed (chart), Kristine A. Karlsen, PhD, APRN, NNP-BC ([shop.aap.org](http://shop.aap.org))

## AAP POLICY

American Academy of Pediatrics Committee on Hospital Care and Institute for Patient- and Family-Centered Care. Patient- and family-centered care and the pediatrician's role. *Pediatrics*. 2012;129:394–404 ([pediatrics.aappublications.org/content/129/2/394](http://pediatrics.aappublications.org/content/129/2/394))

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## Chapter 112

# CONTINUING CARE OF THE INFANT AFTER TRANSFER FROM NEONATAL INTENSIVE CARE

Deborah E. Campbell, MD

The scope of continuing or convalescent hospital care for the infant returned to a community hospital after neonatal intensive care (*back transfer*) varies based on the child's underlying medical problems and ongoing health needs. In addition to maintaining bed availability within regional or tertiary neonatal intensive care units (NICUs), an important aspect of care for the infant who is back transferred is to foster the parent-infant relationship and bonding. It is well known that the separation imposed by the need to transport a sick newborn, often long distances, for tertiary care creates tremendous hardships for families. Parents' active involvement in their child's in-hospital care, preparation for their baby's discharge home, and post-hospital care are critical to facilitating the transition from hospital to home. Back transport to a community special care nursery (level II) or well newborn nursery (level I) can facilitate linking the child and family with follow-up systems within the community in which the child resides. (Table 112-1 describes levels of neonatal care.) Costs for care are often less than at the regional perinatal center or community level III NICU; a successful transfer also promotes a reciprocal relationship between the community hospital and tertiary center that fosters communication and collaboration.

The hospital to which the infant is returned ("back transported") and the timing of the return transfer depend on the individual patient's health care needs and the capability of the receiving hospital. Under certain circumstances within some integrated health care delivery networks or regionalized perinatal care networks, an infant may be transferred to a facility with a lower level of care that was not the birth hospital to complete treatment and preparation for discharge home. Infants transferred to level II units include extremely low-birth-weight infants needing convalescent care, infants with chronic lung disease of infancy, infants with feeding problems, infants receiving antibiotic therapy, and infants with nonacute surgical, neurosurgical, and subspecialty medical issues. Some infants may have stable or regressing retinopathy of prematurity (ROP) or apnea of prematurity (AOP) requiring infrequent or no stimulation. Infants

**Table 112-1** Definitions, Capabilities, and Provider Types: Neonatal Levels of Care

LEVEL OF CARE	CAPABILITIES	PROVIDER TYPES <sup>a</sup>
Level I Well newborn nursery	<ul style="list-style-type: none"> <li>• Provide neonatal resuscitation at every delivery</li> <li>• Evaluate and provide postnatal care to stable term newborn infants</li> <li>• Stabilize and provide care for infants born at 35 to 37 weeks' gestation who remain physiologically stable</li> <li>• Stabilize newborn infants who are ill and those born at less than 35 weeks' gestation until transfer to a higher level of care</li> </ul>	Pediatricians, family physicians, physician assistants, pediatric or family nurse practitioners, and other advanced practice registered nurses
Level II Special care nursery	Level I capabilities plus: <ul style="list-style-type: none"> <li>• Provide care for infants born at 32 or more weeks' gestation and weighing 1,500 g or more who have physiologic immaturity or who are moderately ill with problems that are expected to resolve rapidly and are not anticipated to need subspecialty services on an urgent basis</li> <li>• Provide care for infants convalescing after intensive care</li> <li>• Provide mechanical ventilation for brief duration (&lt;24 hours) or continuous positive airway pressure or both</li> <li>• Stabilize infants born before 32 weeks' gestation and weighing less than 1,500 g until transfer to a neonatal intensive care facility</li> </ul>	Level I health care providers plus: Pediatric hospitalists, neonatologists, and neonatal nurse practitioners
Level III NICU	Level II capabilities plus: <ul style="list-style-type: none"> <li>• Provide sustained life support</li> <li>• Provide comprehensive care for infants born at less than 32 weeks' gestation and weighing less than 1,500 g and infants born at all gestational ages and birth weights with critical illness</li> <li>• Provide prompt and readily available access to a full range of pediatric medical subspecialists, pediatric surgical specialists, pediatric anesthesiologists, and pediatric ophthalmologists</li> <li>• Provide a full range of respiratory support that may include conventional or high-frequency ventilation and inhaled nitric oxide</li> <li>• Perform advanced imaging with interpretation on an urgent basis, including computed tomography, MRI, and echocardiography</li> </ul>	Level II health care providers plus: Pediatric medical subspecialists, <sup>b</sup> pediatric anesthesiologists, <sup>b</sup> pediatric surgeons, and pediatric ophthalmologists <sup>b</sup>
Level IV Regional NICU	Level III capabilities plus: <ul style="list-style-type: none"> <li>• Located within an institution with the capability to provide surgical repair of complex congenital or acquired conditions</li> <li>• Maintain a full range of pediatric medical subspecialists, pediatric surgical subspecialists, and pediatric anesthesiologists at the site</li> <li>• Facilitate transport and provide outreach education</li> </ul>	Level III health care providers plus: Pediatric surgical subspecialists

<sup>a</sup>Includes all providers with relevant experience, training, and demonstrated competence<sup>b</sup>At the site or at a closely related institution by prearranged consultation agreementFrom American Academy of Pediatrics Committee on Fetus and Newborn. Levels of neonatal care. *Pediatrics*. 2012;130(3):587–597.

with life-limiting conditions may be transferred to a community hospital nearer to their homes and families for hospice (comfort) care. Box 112-1 provides a summary of the benefits of and requirements for return transfer.

The continuing care needs of the infant who is transferred back to a community level I or level II unit are determined by the infant's underlying medical condition and clinical course while in intensive care. As the infant progresses through the recovery period, the primary care physician should reassess the infant's ongoing medical care needs to determine the infant's readiness for discharge home or if transitional (rehabilitation) or chronic care is required. The decision whether the baby is able to be discharged home or will need chronic care is based on multiple factors, including the infant's ability to effectively feed and demonstrate adequate weight gain, the need for home

oxygen therapy and multiple medications, the need for intensive rehabilitation, the parents' receptivity and ability to care for the infant safely at home, and the availability of home health care services and public health nurse services within the community in which the child will reside. Key to all phases in this process is communication among the treating physicians and staff at the tertiary care center, the receiving primary care physician and the intermediate or primary care nursery staff, and the parents. The receiving physician should speak directly with a member of the treating medical personnel in addition to reviewing a detailed written summary about the infant's medical problems and hospital course. Box 112-2 provides information that should be contained in the transfer summary.

Common medical issues in the continuing care of infants returned to community care after a stay at a level III NICU are discussed in the following sections.

**BOX 112-1 Neonatal Return Transfer to the Community Setting****BENEFITS**

- Provides continuing and convalescent care in the child's home community
- Increases availability of tertiary care beds for other critically ill infants
- Increases opportunities for parent involvement in their infant's care, facilitates parent education, and fosters parent-infant interaction
- May lessen financial burden for the family and reduce health care costs overall
- Promotes communication and collaboration between community health care providers and tertiary care providers

**REQUIREMENTS**

- Infant is hemodynamically stable.
- Appropriate level of care is available closer to the infant's home.
- Individual patient care needs determine the level of continuing care required and the timing of the return transfer.
- Telephone consultation between the receiving health care professional and the perinatal center or community

neonatal intensive care unit staff to initiate the transfer process, prepare the receiving hospital regarding the infant's current medical needs, and develop a treatment plan for the infant.

- The referring center medical staff maintains responsibility for the infant during the transport.
- Parental consent authorizing transfer, treatment, and admission to the receiving center are typically obtained by the referring hospital staff.
- The parents should be encouraged to visit the receiving intermediate or primary care nursery.
- The transport team should communicate with the receiving center regarding the estimated time of arrival.
- On arrival at the receiving hospital the transport team should discuss with the receiving staff the infant's medical history, events during the transport, and the baby's current status and recommended treatment plan.
- A discharge summary from the sending hospital should accompany the infant.
- Periodic communication should be maintained between the referring and receiving hospital personnel.

**BOX 112-2 Information That Should Be Contained in the Transfer Summary**

- Summary of infant's clinical course in the tertiary care unit that reviews each of the infant's medical problems and complications, the treatments received, and ongoing health conditions
- Current medications, nutrition needs, and feeding regimen
- Results of completed diagnostic tests
- Pending test results
- Necessary follow-up testing, including retinopathy of prematurity checks, newborn metabolic and hearing screening, and neuroimaging
- Immunizations received, immunizations due

- Eligibility for and timing of palivizumab administration for the prevention of respiratory syncytial virus infection
- Needed subspecialty consultations and ongoing follow-up care
- Family assessment:
  - Parents' understanding of their infant's health issues
  - Parents' emotional responses and coping style in response to their infant's illness and ongoing health needs
  - Financial and social support resources
- Goals of continued hospital care

**ANEMIA**

Anemia unrelated to underlying hemolytic anemias and congenital red cell disorders is a common medical problem for preterm and sick neonates related to blood loss and decreased red blood cell (RBC) production (ineffective erythropoiesis). (See Chapter 103, The Newborn With Hematologic Abnormalities, for a detailed discussion of neonatal anemia.) Blood losses may be acute or chronic resulting from repeated blood sampling, hemorrhage, and procedure-associated loss. Nutritional deficiencies of protein, iron, folic acid, or vitamin B<sub>12</sub> lead to decreased erythropoiesis. Vitamin E deficiency, common in preterm infants, may lead to increased RBC destruction, particularly in infants receiving supplemental iron. Infection, both acquired

(bacterial or viral sepsis) and congenital (TORCH infections [toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex], parvovirus, HIV, and malaria), may lead to decreased erythrocyte production or increased red cell destruction.

*Anemia of prematurity* typically occurs in infants younger than 32 weeks' gestation and occurs between 2 and 4 months of age. It is the result of low RBC mass, shorter RBC survival, and increased requirements resulting from growth. Premature infants also exhibit more rapid and greater reduction in their hemoglobin levels than do full-term neonates, typically 7 to 8 g/dL. Nearly one-half of preterm infants younger than 32 weeks' gestation will exhibit symptoms from anemia of prematurity. Among very low-birth-weight



**BOX 112-3 Symptoms of Anemia of Prematurity**

- Tachypnea
- Tachycardia
- Bradycardia
- Periodic breathing, apnea, desaturations
- Poor weight gain, feeding difficulties
- Decreased activity
- Pallor
- Flow murmurs
- Metabolic acidosis

infants, 60% to 80% will receive at least 1 transfusion during their hospitalization, most within the first 2 to 4 weeks of life. The decision to transfuse an infant is often based on the infant's underlying health problems and the presence of signs (changes in cardiovascular and respiratory status, increased oxygen or ventilatory support requirements, deterioration in feeding efficiency, and declining weight gain). Box 112-3 lists the signs of anemia of prematurity.

**Transfusion**

Controversy exists in the approach to treating anemia in preterm infants, including a threshold for red cell transfusion, defining symptomatic anemia and the role of erythropoietin in the treatment of anemia of prematurity, and reducing the need for transfusion (Table 112-2). Guidelines from the American College of Pathologists detail thresholds for transfusion based on severity of illness and the degree of technologic support needed by the infant. The use of recombinant human erythropoietin (rHuEPO) to promote erythropoiesis remains controversial because studies have not demonstrated a significant reduction in the transfusion requirements during the first 2 weeks of life, when most transfusions occur in sick neonates. The use of poly packs to split a unit of packed RBCs into multiple aliquots has also reduced the number of donors to which a neonate is exposed. Therefore use of rHuEPO is individualized to selected cases (eg, infants with intrinsic renal disease or infants born to Jehovah's Witness or Rastafarian families who typically refuse blood products for their infants on a religious basis).

Sporadic reports since the 1980s have raised concerns about an association between RBC transfusions required after the first weeks of life and the development of necrotizing enterocolitis (NEC) in very preterm, very low-birth-weight infants. A temporal relationship among anemia, RBC transfusion, and an episode of NEC in up to one-third of transfused infants has been reported in several retrospective studies.

These infants are typically 3 weeks of age or older, were born at younger gestational ages (GAs), and developed symptoms within 48 to 72 hours of the transfusion. Although there are no data demonstrating a causal relationship, it is speculated that transfusion in these infants may cause an immunologic or ischemic

injury to the immature intestine or that the intestine of the preterm infant with clinically symptomatic anemia may be susceptible to injury because of poor tissue oxygenation. A recent case-controlled study noted a reduction in NEC following transfusion in preterm infants if feedings were withheld during the time of transfusion administration.

**Strategies to Prevent and Treat Anemia****Reduce Iatrogenic Blood Loss**

Reducing iatrogenic blood losses that are the result of blood sampling for laboratory testing is important to minimize the infant's transfusion needs. Point-of-care testing devices, validated for use with neonatal blood samples, are valuable tools in reducing blood loss. Unnecessary blood sampling should be avoided as well. Noninvasive monitoring (transcutaneous arterial oxygen saturation [SaO<sub>2</sub>]) is an additional tool that reduces the need for blood sampling. Experts no longer recommend that transfusions be performed to replace phlebotomy losses alone.

If a blood transfusion is required, then the volume of packed red blood cells infused is typically 10 to 15 mL/kg administered via a peripheral intravenous catheter over 2 to 3 hours. The American Association of Blood Banks *Standards for Blood Banks and Transfusion Services*, 29th edition, published in 2014, specifies the testing required for blood donated in the United States.

**Iron Supplementation**

Infants, whether full-term or preterm, require iron supplementation during the first year of life to prevent nutritional anemia. Iron supplementation should provide 2 to 3 mg/kg/day of elemental iron for breastfed infants and babies whose formula intake does not provide the required daily iron intake. Preterm infants need supplementation in the range of 4 to 4.5 mg/kg/day of elemental iron to prevent iron deficiency anemia. During the infant's hospitalization, iron supplementation will often be initiated when the enteral intake is at least 100 mL/kg/day (between 2 and 4 weeks of age). Infants who have required multiple transfusions may receive a significant iron load from the transfused blood. Monitoring of ferritin levels to determine the appropriate time to start iron therapy may be prudent in this circumstance. Vitamins providing nutritional doses of vitamin E (25 IU/day), folate, and vitamin B<sub>12</sub> should also be given daily to high-risk infants.

**APNEA, BRADYCARDIA, AND DESATURATION**

Apnea, bradycardia, and desaturations are common problems encountered in neonatal units. (Box 112-4 provides a list of definitions.) These symptoms may occur in isolation or together. The incidence and severity of apnea increases with decreasing GA. The need to treat neonatal apnea varies with GA and symptoms. AOP is experienced by more than 50% of premature infants and nearly 100% of babies weighing less than 1,000 g at birth. The relationship among apnea, bradycardia, and desaturation is complex and further complicated by the occurrence of 1 or more of these symptoms in relation to feeding or choking episodes.

**Table 112-2** Suggested Guidelines for Packed Red Blood Cell Transfusion in Neonates<sup>a</sup>

HEMATOCRIT, HEMOGLOBIN LEVEL	AMERICAN COLLEGE OF PATHOLOGY RECOMMENDATIONS
Hematocrit (Hct) <0.4 (40%) Hct ≤0.35 (35%) or hemoglobin (Hg) ≤12 g/dL (≤7.44 mmol/L)	Acute blood loss with shock Severe RDS requiring mechanical ventilation, $P_{aw} > 8$ cm H <sub>2</sub> O + $FiO_2 > 0.5$ OR Severe congenital heart disease with cyanosis or heart failure
Hct ≤0.3 (≤30%) or Hg ≤10 g/dL (≤6.2 mmol/L)	Moderate RDS + $FiO_2 > 0.35$ , or nasal cannula oxygen or ventilation with IMV and $P_{aw}$ 6–8 cm H <sub>2</sub> O
Hct ≤0.25 (≤25%) or Hg ≤8 g/dL (≤4.96 mmol/L)	Any of the following conditions: 1. Apnea and bradycardia ≥10 episodes/24 hr or ≥2 episodes requiring bag-mask ventilation 2. Sustained tachycardia >180 beats/min or sustained tachypnea >80 breaths/min over 24-hr period 3. Inadequate weight gain for 4 days with 100 kcal/kg/day (420 kJ/kg/day) caloric intake 4. Mild RDS with: 1. $FiO_2$ 0.25–0.3 2. Nasal cannula 125–250 mL/min 3. IMV or NCPAP with $P_{aw} \leq 20$
Hct ≤0.2 (≤20%) or Hg ≤7 g/dL (≤4.34 mmol/L) and reticulocyte count	Irrespective of the presence or absence of symptoms
HEMATOCRIT LEVEL	AMERICAN ASSOCIATION OF BLOOD BANKS GUIDELINES <sup>b</sup>
Hct <45%	ECMO
Hct <35%	Cyanotic congenital heart disease >35% supplemental O <sub>2</sub> CPAP/intermittent ventilation with MAP ≥6–8 cm H <sub>2</sub> O
Hct <30%	<35% supplemental O <sub>2</sub> O <sub>2</sub> by nasal cannula CPAP/intermittent ventilation with MAP <6 cm H <sub>2</sub> O Significant apnea, bradycardia, tachycardia, or tachypnea Poor weight gain
Hct <20%	Low reticulocyte count Symptomatic anemia

CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation;  $FiO_2$ , Fraction of inspired oxygen; IMV, intermittent mandatory ventilation; MAP, mean arterial pressure; NCPAP, nasal continuous positive airway pressure;  $P_{aw}$ , airway pressure; RDS, respiratory distress syndrome

<sup>a</sup>Hematocrit and hemoglobin level and clinical symptom criteria on which to base the transfusion decision

<sup>b</sup>Roseff SD, American Association of Blood Banks. *Pediatric Transfusion: A Physician's Handbook*. 2nd ed. Bethesda, MD: American Association of Blood Banks; 2006

**BOX 112-4** Definitions of Apnea, Bradycardia, and Desaturations

Apnea: Absence of breathing for 20 seconds or more, or more than 10 seconds if associated with bradycardia (heart rate <80 bpm) or desaturation ( $SpO_2$  <80%–85%)

Apnea classification:

- Central: cessation of chest wall movement (inspiration) caused by lack of central nervous system neural input (10%–25%)
- Obstructive: respiratory effort without nasal airflow (10%–20%)
- Mixed: combination of central and obstructive apneas (50%–70%)

Bradycardia: Age-related norms have been defined for infants based on postmenstrual and postnatal age

Significant bradycardia in infants less than 44 weeks postmenstrual age: less than 80 bpm for more than 15 seconds or less than 60 bpm for 5 seconds

Desaturation: Oxygen saturation less than 80%–85% for more than 4 seconds (normal range for full-term and preterm infants from birth to 28 days of age: 93%–100%; mean oxygen pressure 70–76 mm Hg during postnatal days of life 2–7)

- May accompany periodic breathing (respiratory pauses)
- May or may not occur in association with bradycardia

Periodic breathing: Episode of 3 or more successive respiratory pauses of 3 seconds or more in duration, each separated by 20 or more seconds of normal respiration

Periodic breathing is considered significant if it occurs during more than 5% of the quiet sleep time

Derived from Finer NN, Higgins R, Kattwinkel J, et al. Summary proceedings from the Apnea of Prematurity Group. *Pediatrics*. 2006;117(3):547–551; Ramanathan R, Corwin MJ, Hunt CE, et al, and the Collaboration Home Infant Monitoring Evaluation (CHIME) Study Group. *JAMA*. 2001;285(17):2199–2207.

The criteria used to define *clinically significant* apnea, bradycardia, and desaturation are controversial, presenting a challenge to the physician caring for preterm infants who exhibit these symptoms. Apnea in the larger preterm infant typically resolves by 34 to 36 weeks postmenstrual age (PMA), with over 90% of infants being apnea free by 37 weeks PMA. Among extremely low-birth-weight infants less than 28 weeks' gestation, apnea duration is longer, often not resolving until 40 to 43 weeks PMA.

Despite numerous studies, consensus as to the optimal SaO<sub>2</sub> range has not been achieved. Earlier study outcomes for infants born at less than 27 weeks' gestation have demonstrated improved survival rates and reduced morbidity (chronic lung disease, ROP) without an increase in cerebral palsy among infants who are maintained with SaO<sub>2</sub> in the range of 84% to 94%. The recent international, multicentered BOOST (Benefits of Oxygen Saturation Targeting) II and SUPPORT (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments) trials designed to evaluate the efficacy of tightly controlling oxygen saturation in extremely preterm infants less than 28 weeks' gestation have identified higher survival rates at 36 weeks PMA of infants born at less than 28 weeks of gestation and randomly assigned to oxygen saturation (SpO<sub>2</sub>) targets of 91% to 95% rather than 85% to 89% while breathing supplemental oxygen. A recent meta-analysis of the SUPPORT, BOOST and Canadian Oxygen (COT) trials demonstrated that more restrictive oxygen saturation SpO<sub>2</sub> targets of 85% to 89% versus 91% to 95%, though associated with lower rates of ROP and a slight trend toward reduced chronic lung disease, contributed to higher rates of death and necrotizing enterocolitis.

There are no data relating specific SaO<sub>2</sub> levels and the incidence or frequency of apnea. However, apnea frequency is increased in the presence of lower oxygen saturations. Until more definitive data are available, prudence suggests maintaining SaO<sub>2</sub> levels in the range of 90% to 94% (alarm limits 88%–96%) for infants at 32 weeks or less GA and between 92% and 97% for preterm infants 33 weeks or more GA (alarm limits 90%–98%).

Preterm infants with lung disease often have SpO<sub>2</sub> measurements less than 90% lasting less than 20 seconds. These episodes often occur during feedings and periods of wakefulness and sleep and are not associated with apnea, bradycardia, or cyanosis. Infants with chronic lung disease are more likely to have severe desaturations less than 80%. Episodes of prolonged desaturation (SpO<sub>2</sub> ≤80%) for more than 4 seconds are most often seen during periodic breathing or hypoventilation. Experts suggest that infants less than 34 weeks' gestation receive cardiorespiratory monitoring and pulse oximetry for apnea and bradycardia during their hospitalization. Desaturations or bradycardia occurring without apnea suggest airway obstruction (obstructive apnea).

### Evaluation of Apnea, Bradycardia, or Desaturation

Evaluation of the infant with apnea, bradycardia, or desaturations will vary with the frequency and severity of the infant's symptoms. Although primarily related to

the infant's underlying prematurity, other causes must be considered, including infection, anemia, hyperthermia (environmental overheating), seizures, necrotizing enterocolitis, metabolic abnormalities (hypoglycemia, acidosis, hyponatremia, hypocalcemia, inborn errors of metabolism), and patent ductus arteriosus or heart failure. Excessive neck flexion may also trigger apneic or bradycardic episodes. The use of sedation, analgesia, and other medications may contribute to respiratory depression and apneic episodes. Acute stress such as that experienced by preterm infants undergoing an eye examination for ROP or after multiple procedures occurring on the same day may contribute to fatigue and an increase in feeding intolerance or apnea, bradycardia, or desaturations in the hours after the procedure. Increased symptoms may be exhibited irrespective of whether the infant receives sedation before the procedure. Gastroesophageal reflux (GER), another common condition among preterm infants, is also thought to contribute to AOP. Although the 2 conditions often occur coincidentally, recent studies have failed to demonstrate a causal link between these 2 conditions in premature infants. Increased frequency of apnea, bradycardia, and desaturations has been observed in very preterm infants following primary immunization at 2 months chronologic age. Preterm infants at highest risk are those of younger GA and those with more medical complications and pre-existing apnea. The frequency of apnea is also more common when multiple vaccines are administered. Consequently, cardiorespiratory monitoring is recommended for a period of 48 hours following primary immunization of very preterm infants.

### Treatment of Apnea, Bradycardia, and Desaturation

Treatment of apnea, bradycardia, and desaturation will depend on the underlying cause or causes for the symptomatology. In addition to diagnosing and treating precipitating conditions, therapy may include the use of tactile stimulation, nasal cannula with air-oxygen flow, nasal continuous positive airway pressure (CPAP), methylxanthines, or mechanical ventilation alone or in combination.

### Medications

Aminophylline, theophylline, and caffeine are the methylxanthines most often used in the treatment of significant AOP (Box 112-5). Caffeine is considerably less toxic than theophylline and is the drug of choice for treating neonatal apnea. Treatment is deemed effective if the reduction in episodes of apnea is 50% or greater. The effectiveness and safety of caffeine treatment and lack of side effects have been confirmed in a 5-year, multicenter, multinational randomized clinical trial. An additional benefit of caffeine therapy is improved brain white matter development and motor outcome through 5 years of age among infants treated with caffeine. Signs of methylxanthine toxicity include tachycardia, gastrointestinal intolerance, and jitteriness or agitation. Medications can usually be discontinued when the preterm infant reaches 32 to 34 weeks PMA and has been apnea free for 7 to 10 days. Infants treated with caffeine require monitoring for 7 days because of caffeine's long half-life. The period of

### BOX 112-5 Methylxanthines Used to Treat Apnea of Prematurity

#### CAFFEINE

- Loading dose: 10 mg/kg IV or PO (20 mg/kg caffeine citrate)
- Maintenance dose: 2.5 mg/kg every 24 hr
- Therapeutic plasma level 8 to 20 mg/L
- Mean half-life is approximately 100 hours and remains prolonged until 37 to 38 weeks postmenstrual age; caffeine half-life decreases with maturity and postnatal age
- Infants with cholestasis have longer caffeine half-life caused by impaired hepatic metabolism
- Long-term administration associated with increased oxygen consumption and reduced weight gain

#### AMINOPHYLLINE OR THEOPHYLLINE

- Aminophylline is metabolized to theophylline (80% theophylline)
- Loading dose: 4 to 6 mg/kg IV or PO
- Maintenance dose: 6 mg/kg/day divided every 6, 8, or 12 hours IV or PO
- Therapeutic plasma level: 6 to 11 mg/L (theophylline)
- Plasma half-life 12 to 64 hours

IV, intravenous; PO, by mouth.

observation after discontinuation of theophylline is somewhat shorter, at 4 to 5 days.

### Noninvasive Ventilation

Noninvasive ventilation (NIV) has become a primary form of respiratory support for preterm and sick infants with respiratory illness including lung immaturity, retained fetal lung fluid (TTN), and apnea of prematurity. There are 2 forms of NIV commonly used: CPAP delivered either through a continuous-flow (continuous positive pressure across the respiratory cycle) device or through a variable-flow device with phasic ventilation (continuous positive pressure with the addition of periods of increased airway pressure [or breaths]), typically referred to as nasal intermittent positive pressure ventilation (NIPPV). NIV stabilizes the airways, alveoli, diaphragm, and chest wall; increases lung volumes; and decreases airway resistance and the work of breathing. NIV facilitates extubation from mechanical ventilation and results in less post-extubation failure (need for reintubation). It also has been shown to reduce the incidence and severity of apnea and bradycardia, reduce the risk of ventilator-associated pneumonia, and improve survival in infants weighing less than 1,500 g with respiratory distress syndrome (RDS). In combination with surfactant administration, NIV shortens the time on mechanical ventilation, thus causing less chronic lung disease. In 2014, the AAP published a policy statement on Respiratory Support for the Preterm Infant



**Figure 112-1** Premature infant on nasal continuous positive airway pressure.

at Birth. Care recommendations included that CPAP started at or soon after birth with subsequent selective surfactant administration may be considered as an alternative to routine intubation with prophylactic or early surfactant administration in preterm infants; and (2) that infants with RDS may vary markedly in the severity of the respiratory disease, maturity, and presence of other complications, and thus it is necessary to individualize patient care.

### Continuous Positive Airway Pressure

CPAP is a commonly used noninvasive respiratory support modality in the care of neonates with transitional difficulties and premature infants with RDS, chronic lung disease, and AOP. CPAP is provided through short binasal prongs (NCPAP), nasopharyngeal tube (NP-CPAP), or infant nasal mask (NM-CPAP) used in conjunction with a continuous flow source (underwater seal, bubble CPAP) or an infant or multipurpose ventilator equipped with a CPAP mode (Figure 112-1). These CPAP devices provide heated and humidified continuous or variable flow in order to increase an infant's functional residual capacity, improve lung compliance, and decrease airway resistance. The resultant increase in tidal volume reduces the infant's work of breathing and stabilizes minute ventilation. In addition, CPAP reduces pharyngeal and airway collapse, stabilizes chest wall musculature, and decreases chest wall inhibitory reflexes. CPAP is effective in mixed and obstructive apnea. Indications for CPAP use in infants include the presence of abnormalities on physical examination, inadequate arterial blood gases, poor lung expansion on chest radiograph, and conditions that are known to benefit from CPAP (Box 112-6, Box 112-7). The duration of CPAP therapy, typically applying 4- to 6-cm water ( $H_2O$ ) pressure, will depend on the reason for its use and the infant's stability as the CPAP is weaned to physiologic levels (3 cm  $H_2O$ ).

Complications associated with CPAP use include nasal irritation and nasal septal erosion, abdominal distention, and feeding intolerance. Barotrauma and



**BOX 112-6 Continuous Positive Airway Pressure Indications**

- Increased work of breathing; respiratory rate 30% above the normal for age
- Retractions, grunting, and nasal flaring
- Presence of cyanosis, pallor, and respiratory distress
- Inadequate arterial blood gas values; inability to maintain partial pressure of oxygen greater than 50 mm Hg with an  $\text{FiO}_2$  less than 0.25 and partial pressure of carbon dioxide higher than 50–55

$\text{FiO}_2$ , fraction of inspired oxygen.

**BOX 112-7 Conditions Benefiting From Continuous Positive Airway Pressure**

- Apnea of prematurity
- Atelectasis
- Pulmonary edema
- Respiratory distress syndrome
- Recent extubation
- Tracheomalacia or similar lower airway abnormality
- Transient tachypnea of the newborn

air leaks may also result if excessive pressure is applied or if an inappropriate CPAP device is used. Overdistention of alveoli will impair ventilation-perfusion ratios and lead to decreased oxygenation and carbon dioxide retention and may also reduce cardiac output and cause an air leak. Insufficient gas flow through the CPAP device creates a fluctuating baseline pressure that can increase the infant's work of breathing. Nasal prong obstruction may occur from accumulated secretions or bleeding after traumatic suctioning or nasal irritation. Humidification and gentle suctioning are important aspects of care for infants requiring CPAP to prevent nasal mucosal damage. Proper positioning of the CPAP prongs and correct nasal prong size are additional factors important to ensuring effective CPAP therapy. The infant's head position is also important because excessive head rotation or neck extension can lead to altered effective CPAP pressure. Maintaining a closed-mouth position is also important to ensuring that the infant is receiving the prescribed positive airway pressure and oxygen concentration. Studies have demonstrated that a 2.2-cm  $\text{H}_2\text{O}$  drop in CPAP pressure occurs from the CPAP prongs to the pharynx with the mouth closed. This pressure loss increased to 3.2 cm  $\text{H}_2\text{O}$  when the infant's mouth was open. Gastric and abdominal distention are common complications of CPAP therapy and may contribute to feeding tolerance problems or aspiration.

**High-Flow Nasal Cannula**

Heated, humidified, high-flow nasal cannula (HFNC) is another noninvasive respiratory support modality used in the management of preterm infants with lung disease. Some neonatologists also use HFNC as a treatment strategy in preterm infants with AOP. HFNC refers to the delivery of heated, humidified, and blended oxygen/air via small caliber nasal cannulae (NC) at flow rates of  $>1$  L/min. NC at flow rates as low as 1 to 2.5 L/min is associated with increased pharyngeal pressure and can deliver positive distending pressure in preterm neonates. HFNC is as effective as nasal CPAP in the management of AOP as well as RDS in infants 28 weeks or more GA. However, there is a potential for asynchrony in the infant's breathing that may cause respiratory fatigue over time. If used, frequent assessment of the infant's work of breathing is important. Although HFNC may be a less intensive intervention, infants receiving it should still be monitored (eg, with capillary blood gases or chest radiographs) as they would on CPAP. Laboratory studies evaluating the effect of HFNC flow rate, nasal cannula size, the percentage occlusion of the nares by different sized cannula, and the degree of mouth occlusion have demonstrated that airway pressure progressively increased with both increasing HFNC flow rate and nasal prong-to-nares ratio. In clinical studies of extremely low-birth-weight infants, HFNC has been shown to deliver high pharyngeal pressures. Thus, use of HFNC in infants less than 1,000 g is not recommended and remains controversial among infants between 1,001 and 1,500 g.

**BRONCHOPULMONARY DYSPLASIA (CHRONIC LUNG DISEASE)**

Bronchopulmonary dysplasia (BPD) develops in one-third of very low-birth-weight infants (rates of BPD vary with NICU care practices and approaches to ventilatory support) and is most common among infants less than 32 weeks' gestation. In addition to higher mortality rates, infants with BPD experience greater morbidity. Changes in clinical practice, particularly restriction in postnatal steroid usage caused by concerns about higher rates of cerebral palsy among infants receiving early postnatal corticosteroids, have resulted in increased numbers of very low-birth-weight infants surviving with BPD. (For detailed information on BPD, see Chapter 100, Respiratory Distress and Breathing Disorders in the Newborn.)

BPD is defined by oxygen dependence at specific periods after birth (28 days postnatal age or 36 weeks PMA) among infants with persistent lung disease and characteristic radiographic findings (Box 112-8). Characteristic BPD findings have changed over time as the disease, originally described in larger preterm infants with severe RDS who required treatment with mechanical ventilation with high pressures (tidal volumes) and high oxygen concentrations, has evolved to include more immature infants with mild to moderate lung disease who exhibit prolonged oxygen requirements. Currently, classic BPD, the form of chronic lung disease resulting from severe RDS and leading to

### BOX 112-8 Definitions of Bronchopulmonary Dysplasia (BPD)

- Oxygen (O<sub>2</sub>) requirement at 28 days of age
- O<sub>2</sub> requirement at 36 weeks postmenstrual age (PMA)
- O<sub>2</sub> or positive airway pressure requirement at 36 weeks PMA
- O<sub>2</sub> requirement at 36 weeks PMA with more than 28 days of oxygen therapy duration
- National Institutes of Child Health and Human Development (2001) severity-based definition of BPD for infants less than 32 weeks GA

**Mild BPD**—need for supplemental O<sub>2</sub> for 28 days or more but not at 36 weeks PMA or hospital discharge if the infant is less than 36 weeks PMA

**Moderate BPD**—need for supplemental O<sub>2</sub> for 28 days or more plus treatment with less than 30% O<sub>2</sub> at 36 weeks PMA

**Severe BPD**—need for O<sub>2</sub> for 28 days or more plus 30% or more O<sub>2</sub> and/or positive pressure at 36 weeks PMA

### BOX 112-9 Complications Associated With Bronchopulmonary Dysplasia

- Apnea
- Reactive airway disease
- Infection
- Feeding difficulties
- Gastroesophageal reflux
- Poor growth
- Poor bone mineralization (osteopenia, nutritional rickets)
- Electrolyte abnormalities
- Nephrocalcinosis
- Impaired cardiac function: pulmonary hypertension, cor pulmonale, left ventricular hypertrophy
- Systemic hypertension
- Poor cognitive and motor outcomes
- Retinopathy of prematurity

atelectasis, edema, fibrosis, smooth muscle disease, right-ventricular hypertrophy, and the need for prolonged ventilation, develops in fewer than 25% of babies with BPD. Most infants with BPD exhibit milder RDS signs of hazy lungs, minimal airway lesions, pulmonary edema, and disruption of lung growth and alveolarization, and require prolonged oxygen, CPAP therapy, or both. Complications associated with BPD are listed in Box 112-9.

## Oxygen Therapy

Oxygen therapy is an important component of BPD management. Oxygen may be delivered to convalescing infants through various devices: oxygen hood, nasal cannulae (high- and low-flow cannulae), CPAP devices, or conventional ventilators. Precise measurement of the oxygen concentration delivered to the infant is not as easily determined when a baby is on a nasal cannula or CPAP. The actual oxygen concentration received by the infant reflects a blend of the nasally inspired oxygen and ambient (room) air inhaled through the nose and mouth. The infant's minute ventilation and ratio of nose-to-mouth breathing also alter the effective fraction of inspired oxygen (FiO<sub>2</sub>) received. This consideration is important during the process of weaning an infant from supplemental oxygen therapy and in determining whether a need exists for home oxygen use. Approximately two-thirds of convalescing infants can be successfully weaned from supplemental oxygen when the infant's SpO<sub>2</sub> is greater than 96% and the FiO<sub>2</sub> is less than or equal to 0.23. A simplified formula for calculating the oxygen level delivered to the infant's hypopharynx has been devised that uses the infant's weight, nasal cannula flow, and FiO<sub>2</sub>:  $0.21 + (\text{flow} + \text{weight}) \times (F_{\text{NCO}_2} - 0.21)$ , where  $F_{\text{NCO}_2}$  is the FiO<sub>2</sub> set to be delivered via the nasal cannula.

Care must be taken when providing flow through a nasal cannula because positive distending pressure has been demonstrated in premature infants weighing less than 2,000 g when nasal cannula flow rates of 1 to 2 L/min are used. Nasal cannula prong diameter is another factor in the delivery of positive distending pressure because a 0.3-cm nasal cannula has been shown to deliver increased pressure as a function of the flow rate used. It is also important to recognize that the need for supplemental oxygen or air flow support (low-flow nasal cannula with FiO<sub>2</sub> 0.21) at 36 weeks PMA may be multifactorial, reflecting an interaction between abnormal lung tissue function caused by BPD and continuing immature respiratory control. Infants with significant chronic lung disease also may be particularly susceptible to developing periodic breathing when they become hypoxemic with even brief central apneas.

## Oxygen Saturation

Maintaining the arterial pressure of oxygen (PaO<sub>2</sub>) levels above 55 torr (mm Hg) is important for infants with chronic lung disease. Infants with BPD may exhibit increased oxygen requirements during nipple feeding and sleep if significant desaturations (SpO<sub>2</sub> <85%) occur during pulse oximetry. The issue of SpO<sub>2</sub> limits (oxygen targeting) is the focus of debate and ongoing study. Results from recent multicentered trials in the US, UK, and Australia on SpO<sub>2</sub> and its role in developmental outcome, as well as the incidence and severity of ROP and BPD in extremely premature babies, continue to be elucidated. The conundrum is that optimal oxygen thresholds to protect the developing eye may be harmful to the cardiovascular and respiratory function of the infant with BPD. Hypoxemia is detrimental to the baby with BPD because it leads to increased pulmonary vascular resistance, pulmonary vasoconstriction, impaired

right-ventricular performance, and peripheral oxygen delivery. Further chronic hypoxemia affects brain growth and weight gain.

When caring for a premature infant with BPD who is less than 35 weeks PMA, the SpO<sub>2</sub> range should be maintained between 90% and 95%. Tighter SpO<sub>2</sub> limits in the range of 92% to 94% are recommended but have been shown to be difficult for many nurseries to attain. An SpO<sub>2</sub> of 94% to 98% for infants with BPD who are more than 35 weeks PMA is recommended to reduce the risk of pulmonary hypertension. During sleep the SpO<sub>2</sub> should be kept above 93% because this level has been shown to improve sleep architecture. In the STOP-ROP study evaluating the efficacy of 2 supplemental oxygen strategies to prevent the development of threshold ROP in preterm infants with BPD, maintaining SpO<sub>2</sub> levels above 96% was shown to increase the risk for adverse pulmonary and cardiovascular outcomes and resulted in a longer duration of oxygen treatment, medication use (diuretics, methylxanthines, and steroids) and hospitalization. However, the infant with BPD and pulmonary hypertension requires adequate oxygen to reduce the pulmonary vascular resistance and avoid death. Current recommendations for these infants are to avoid SpO<sub>2</sub> less than 93% and maintain saturation pressure levels between 94% and 98%.

### Monitoring

In addition to impairing right-ventricular heart function, BPD is associated with other cardiovascular abnormalities: left-ventricular hypertrophy, systemic hypertension, and the development of bronchial and other systemic-pulmonary collateral vessels. Postnatal steroid use may also contribute to the development of transient left-ventricular hypertrophy. Pulse oximetry is an important tool used in the routine monitoring of infants with chronic lung disease while they remain in the hospital. Monitoring should occur through all of the infant's activities of daily living—while awake, during bathing and feeding, and during active and quiet sleep. Blood pressures should be monitored at least weekly, and periodic electrocardiograms should be obtained to evaluate the infant for right-ventricular hypertrophy. Infants requiring prolonged positive pressure and/or oxygen therapy or who have evidence of pulmonary hypertension should have serial echocardiography performed every 2 to 3 months.

### Medications

Medications used in the treatment of BPD include aerosolized beta-agonists, inhaled steroids, and diuretics (Box 112-10). The duration of medication use is predicated on the infant's clinical symptoms, tolerance of fluid volumes and growth, and continued dependence on oxygen or respiratory support. The effectiveness of bronchodilator therapy in preterm infants is unclear. Studies have demonstrated short-term improvement in respiratory function with treatment. However, long-term benefits in the treatment of BPD have not been conclusively demonstrated in randomized, controlled studies. For infants with worsening respiratory symptoms such as wheezing, increasing airway resistance, or worsening lung compliance, the

### BOX 112-10 Medications Used in the Treatment of Bronchopulmonary Dysplasia

#### DIURETICS

- Hydrochlorothiazide: 20 to 40 mg/kg/day in 2 divided doses every 12 hours
- Spironolactone: 2 to 4 mg/kg/day in 2 divided doses every 12 hours
- Furosemide: 2 to 4 mg/kg/dose every 12 to 24 hours
- Potassium chloride: 1 to 4 mEq/kg/day in 2 to 4 doses every 6 to 12 hour

#### BRONCHODILATORS

- Albuterol: 0.5 cc by nebulizer or inhaler every 6 to 12 hours
- Ipratropium: 0.5 cc by nebulizer or inhaler every 12 hours
- Levalbuterol: 0.62 mg respule by nebulizer

#### ANTI-INFLAMMATORY AND INFLAMMATORY DRUGS (inhaled steroids)

- Cromolyn: inhaler or nebulizer; takes 2 to 4 weeks for adequate trial
- Budesonide: 0.25 to 0.5 mg respule every 12 to 24 hours
- Fluticasone: 0.125 mg (1 puff) every 12 hours
- Betamethasone valerate
- Oral prednisone for serious exacerbations

physician should consider a closely monitored trial of albuterol and ipratropium. The preferred mode of drug delivery is through a metered-dose inhaler plus spacer rather than nebulizer or via hand-bag ventilation. Consultation with a neonatologist or pediatric pulmonary specialist can assist in implementing and monitoring the efficacy of respiratory management strategies.

## NUTRITION AND GROWTH

### Premature Infant

Continuing care of the recovering infant or growing premature baby includes optimizing the infant's growth and nutrition. Increased calories, protein, and mineral intake are needed to promote better linear growth and mineral accretion in the very preterm. The recommended caloric intake will vary with the infant's underlying medical issues and degree of prematurity. Caloric requirements for most infants will range from 100 to 120 kcal/kg/day to achieve an average daily weight gain of 20 to 30 g. For the preterm baby, weight gains of 15 to 25 g/day are more typical between 28 and 32 weeks of gestation. As infants recover, more of their caloric intake is available for tissue growth and weight gain. However, during periods of increased energy expenditure, such as when the infant is weaning from CPAP or oxygen, transitioning from isolette-bassinette conditions, learning to nipple feed, or experiencing an intercurrent illness, growth may slow or the infant may lose weight. Energy requirements for



infants with chronic lung disease have been shown to be 25% higher than for preterm infants without BPD. Consequently, infants with chronic lung disease require 120 to 160 kcal/kg/day. The caloric density of the feeding will depend on the infant's growth velocity, feeding efficiency, evidence of feeding fatigue, and ability to handle fluid volume.

The rate of weight gain and adequacy of growth are a significant concern in the care of the preterm infant because suboptimal growth will affect brain growth and cognitive outcomes; however, excessively rapid growth has the potential to predispose the infant to cardiovascular problems in adulthood. A common practice involves restricting the feeding volume until a weight plateau occurs before increasing the feeds. This factor is important in the growth delay experienced by many preterm infants. Common patterns of growth in preterm infants are listed in Box 112-11.

Achieving optimal postnatal growth is a challenge as growth lags considerably after birth among most very low-birth-weight infants. Figure 112-2 depicts an aggressive nutritional approach to prevent poor postnatal growth in very low-birth-weight infants. Nutrient intakes that meet current recommended daily intakes are difficult to achieve during early postnatal life. By the end of the first week, significant cumulative energy and protein deficits occur in preterm infants, irrespective of GA. Among the smallest infants, weight loss often exceeds 15% of their birth weight. Energy and protein deficits persist at 5 weeks of age; infants of 30 weeks' gestation or younger exhibit mean energy deficits of 813 kcal/kg and protein deficits of 23 g/kg. Among infants older than 30 weeks' gestation, comparable energy and protein deficits are evident at the end of the first week of life, although by 5 weeks of age these infants' energy and protein deficits are 382 kcal/kg and 13 g/kg, respectively. Evidence is increasing of long-term consequences for these children who remain shorter, weigh less, and have a greater risk of neurodevelopmental impairment than their normal-birth-weight full-term counterparts. As GA decreases, an incremental lag occurs in weight gain and growth velocity (Figure 112-3 and Figure 112-4). Infants with subnormal head circumferences at 8 months

corrected age have an increased risk of neurologic impairment, lower IQ, and poorer academic performance. Male infants are more likely at greatest risk for extrauterine growth restriction, require mechanical ventilation during the first day of life, need respiratory support at 28 days of age, develop necrotizing enterocolitis, and receive postnatal steroids.

The length of time required to regain birth weight is an important predictor of the overall rate of weight gain and of the likelihood that an infant will be below the 10th percentile at the time of hospital discharge. Early initiation of parenteral nutritional support and enteral feeding is critical. Trophic and minimal enteral feedings promote intestinal motility and bile secretion and induce lactase activity, reducing sepsis and cholestasis. Early aggressive nutrition regimens limit the degree of extrauterine growth restriction and improve the postnatal metabolic and nutritional status of the infant. Daily volume increments of 10 to 35 cc/kg/day have been shown to be safe. More rapid advancement of feedings (25–35 cc/kg/day) results in a shorter time to regain birth weight without an increase in the rate of necrotizing enterocolitis. After regaining birth weight, the weight gain goal for a preterm infant is 14 to 16 g/kg/day. Once the infants reach readiness for discharge, the weight gain goal is 20 to 30 g/day.

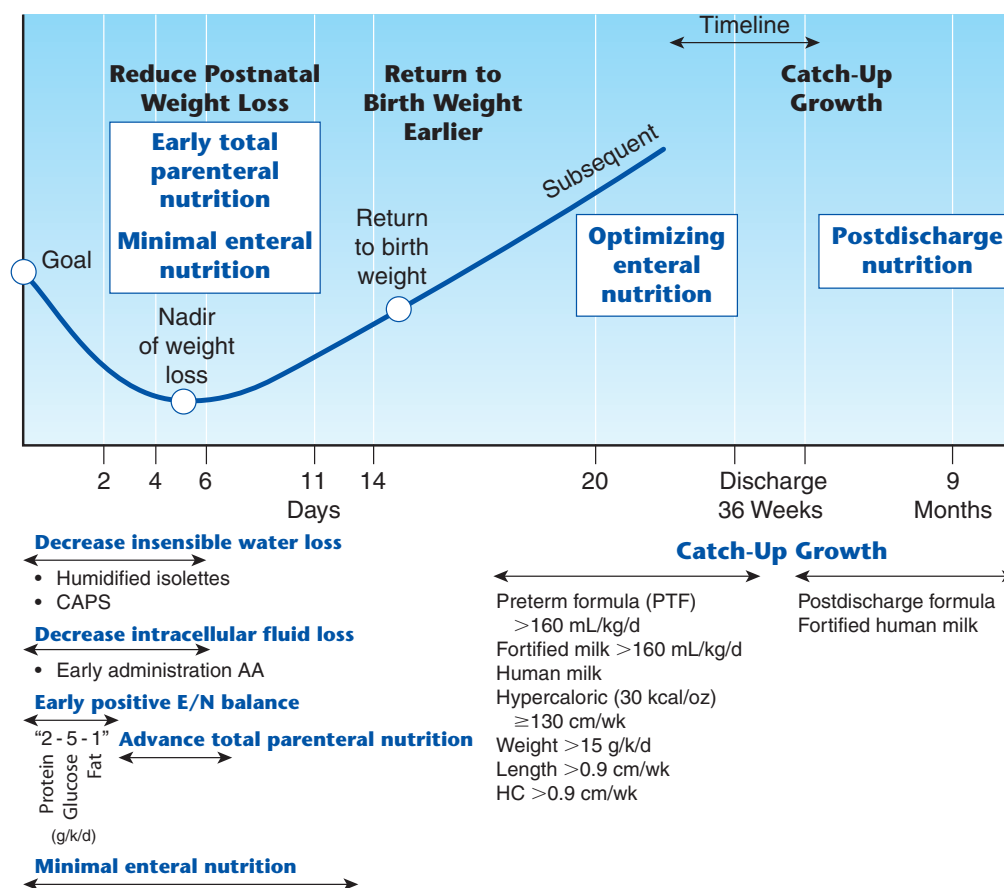
Just as inadequate growth is detrimental, excessive weight gain, rapid growth velocity, and growth patterns that alter the body's composition have harmful long-term cardiovascular and metabolic effects. The postnatal environment, nutrient energy sources, hormones, and factors that influence growth during the postnatal period differ from the intrauterine condition. After birth, fat becomes the primary fuel source for the neonate, in contrast to fetal dependence on glucose, lactate, and amino acids. Very preterm infants younger than 32 weeks' gestation also have decreased insulin sensitivity. The rate of postnatal weight gain in preterm infants is dependent on caloric intake, whereas brain growth and increasing length are influenced by the infant's protein intake. Fat accretion is increased postnatally in preterm infants who at term-postmenstrual age have a higher body fat content and more visceral fat than normal-birth-weight full-term infants. An important consideration in planning a nutritional support program for the recovering and growing low-birth-weight infant is recognizing that a pattern of rapid catch-up growth during the first 2 years of life and an observed increase in central fat distribution at 5 years of age in these children predispose them to cardiovascular disease and metabolic syndrome in later life.

Infants who are returned to community neonatal units for continuing and convalescent care will vary in their nutritional needs, as well as their mode of nutritional intake at the time of back transfer. Some infants may be on full enteral feeding, whereas others may be transitioning from parenteral nutrition (PN) to enteral feedings. Specific nutrient requirements will be influenced by the infant's underlying medical problems and degree of prematurity and whether the nutrient sources are from parenteral fluids, breast milk, or

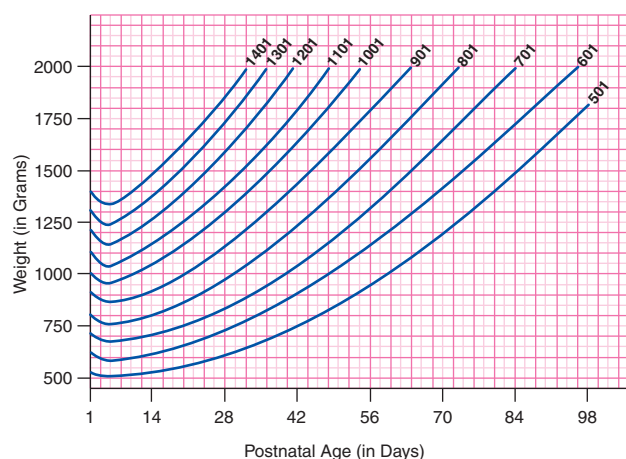
### **BOX 112-11** Convalescing Preterm Infant Growth Patterns

- Appropriate-for-gestational-age (AGA) infant at birth who at discharge has a body weight that is appropriate for the PMA (corrected age)
- AGA preterm infant at birth whose discharge weight is below the reference for the PMA (postnatal or extrauterine growth restriction)
- Small-for-gestational-age (SGA) infant who remains below the 10th percentile for PMA at the time of discharge
- SGA infant who exhibits early postnatal catch-up growth and whose weight at discharge is appropriate for postmenstrual age

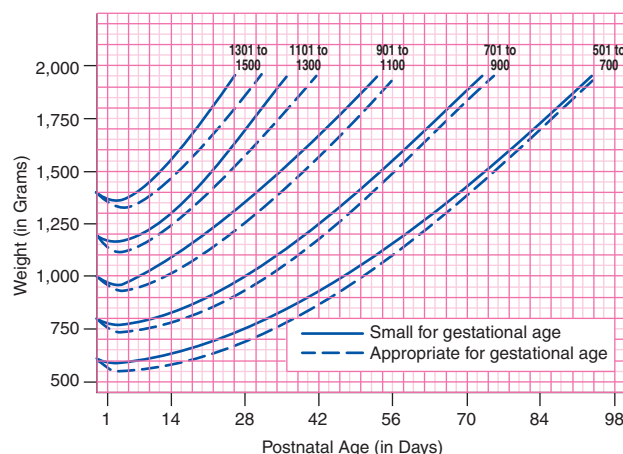




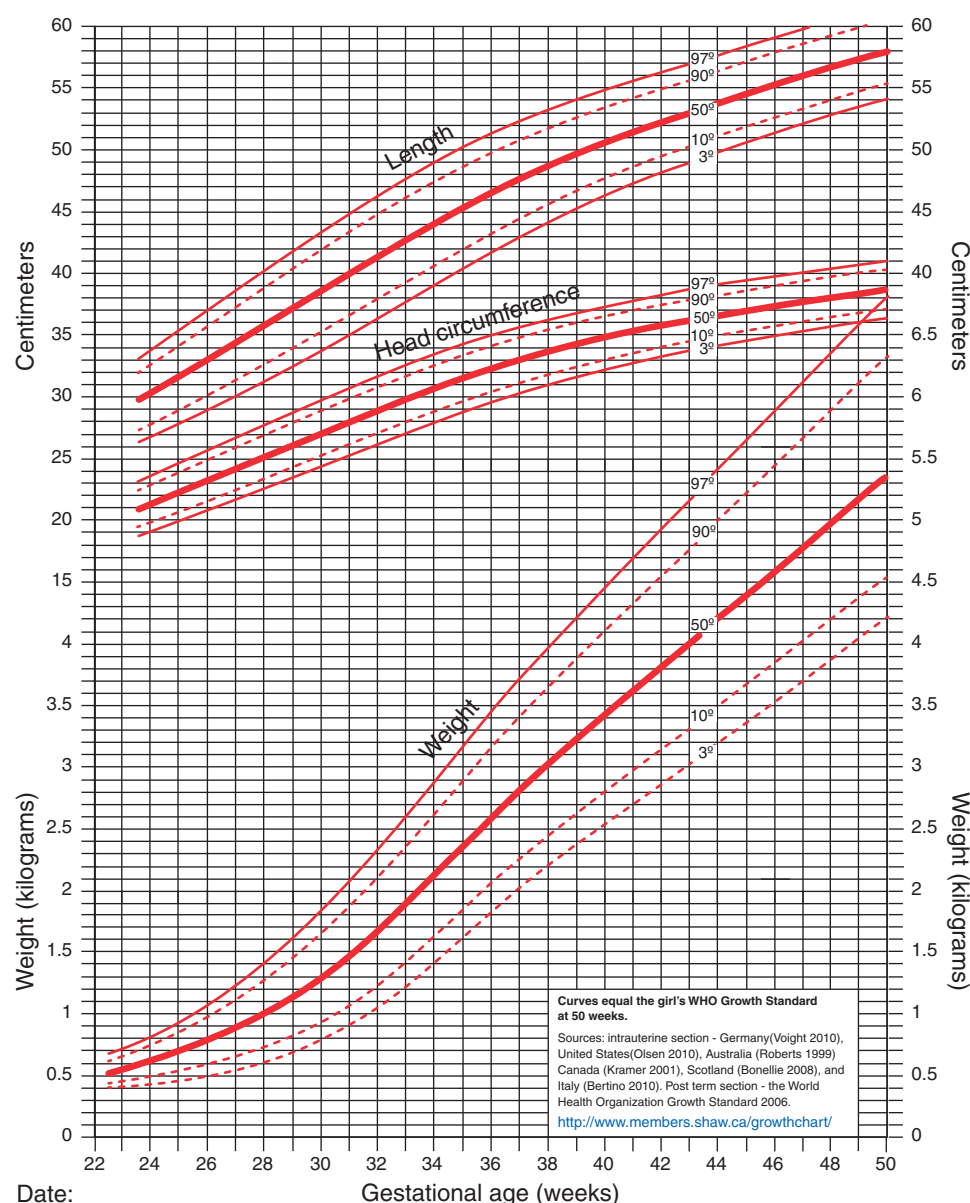
**Figure 112-2** Aggressive nutrition to prevent extrauterine growth restriction. (From Adamkin DH. Nutrition management of the very low-birth-weight infant I. Total parenteral nutrition and minimal enteral nutrition. *NeoReviews*. 2006;7:e602–e607.)



**Figure 112-3** Longitudinal growth of hospitalized very low-birth-weight infants. (From Ehrenkranz RA, Younes N, Lemons JA, et al. Longitudinal growth of hospitalized very low birth weight infants. *Pediatrics*. 1999;104:280–289.)



**Figure 112-4** Growth curves of appropriate-for-gestational-age and small-for-gestational-age, very low-birth-weight infants versus postnatal age (days). (From Ehrenkranz RA, Younes H, Lemons JA, et al. Longitudinal growth of hospitalized very low birth weight infants. *Pediatrics*. 1999;104:280–289.)



**Figure 112-5** Fetal-infant growth chart for preterm infants—girls (curves equal the female WHO Growth Standard at 50 weeks). (From Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr.* 2013;13:59. © Fenton and Kim; licensee BioMed Central Ltd. 2013. Available at: <http://bmcpediatr.biomedcentral.com/articles/10.1186/1471-2431-13-59>. Accessed January 28, 2016.)

infant formula. Use of standardized feeding protocols has been shown to optimize nutritional intake, promote weight gain, and reduce the risk of extrauterine growth restriction.

Weekly assessment of growth should include plotting the infant's weight, length and head circumference on one of the commonly used postnatal growth charts (Fenton growth charts, Figure 112-5 and Figure 112-6; or Olsen growth charts, Figure 112-7).

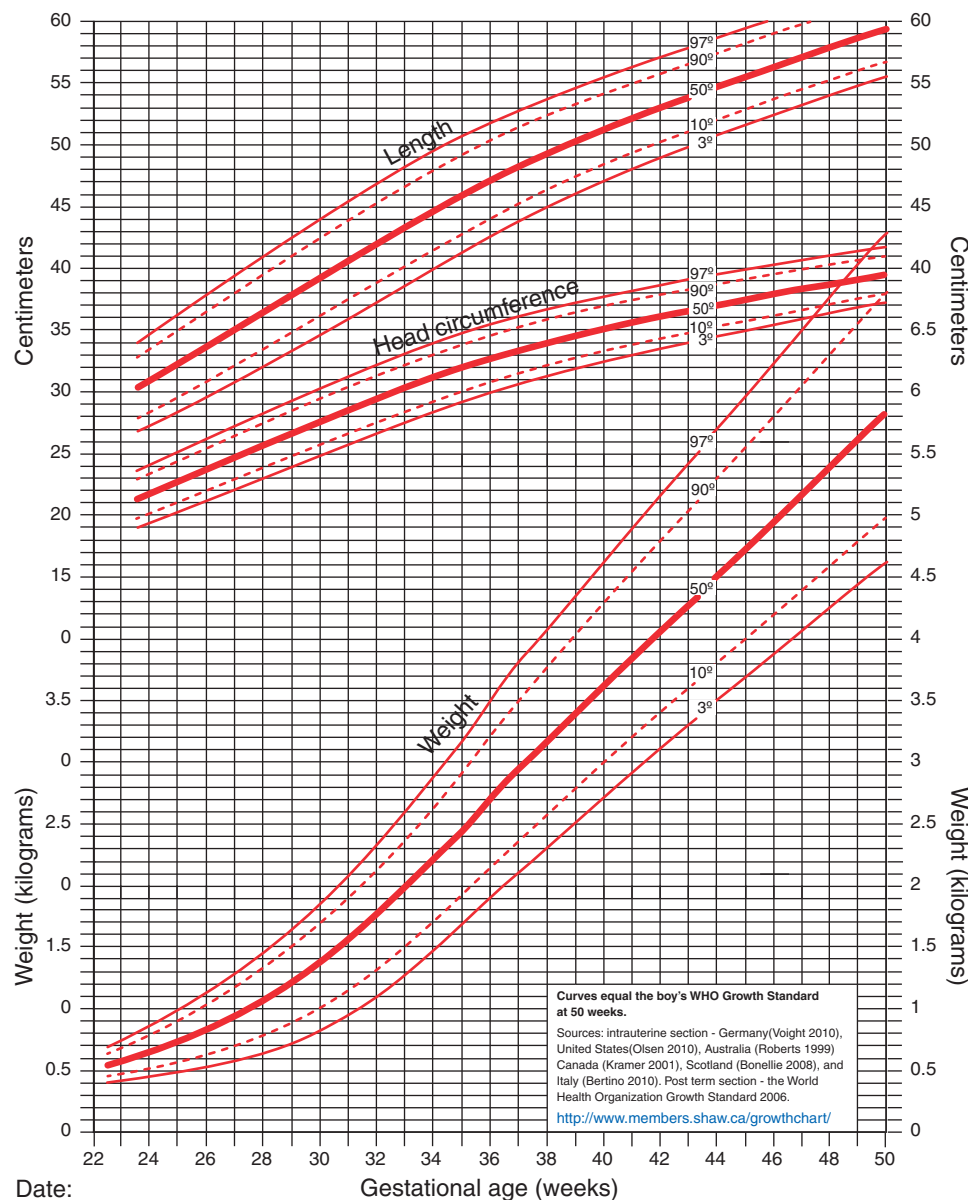
### Parenteral Nutrition

Parenteral nutrition solutions may be administered via peripheral or central intravenous lines. Table 112-3

and Table 112-4 list considerations in calculating PN solutions.

The ratio of calories to grams of nitrogen is important to promote optimal nitrogen utilization for protein synthesis and tissue growth. The optimal energy-to-protein ratio is 150 to 200 nonprotein cal to 1 g of nitrogen, or 22 kcal/g of protein. The total grams of amino acids per day are divided by the factor 6.25 to yield the grams of nitrogen per day: ratio = nonnitrogen calories ÷ grams of nitrogen.

Increased calories are needed during episodes of metabolic stress. Table 112-5 lists the effects of certain diseases on specific nutrient requirements.



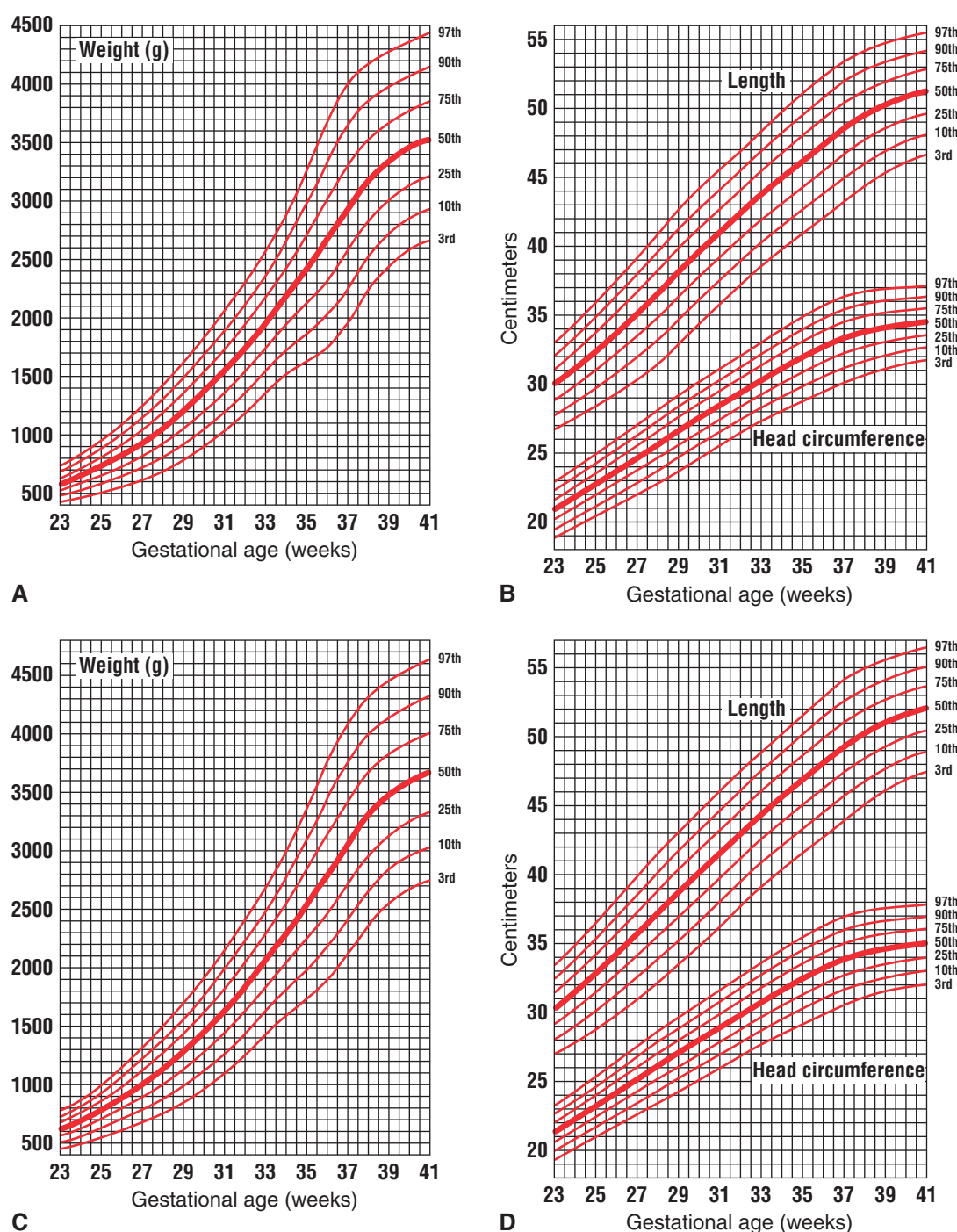
**Figure 112-6** Fetal-infant growth chart for preterm infants—boys (curves equal the male WHO Growth Standard at 50 weeks). (From Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr.* 2013;13:59. © Fenton and Kim; licensee BioMed Central Ltd. 2013. Available at: <http://bmcpediatr.biomedcentral.com/articles/10.1186/1471-2431-13-59>. Accessed January 28, 2016.)

In brief, nutritional requirements are altered as follows:

- + 12% for every degree fever
- + 20% to 30% for infants requiring surgery
- + 40% to 50% for septic infants
- + 50% to 100% for infants with long-term growth failure

Peripheral PN solutions cannot exceed 12.5% dextrose or 3.0% to 3.5% amino acid; maximal calcium concentration is also limited because of the risk of severe tissue injury in the event of extravasation. Each gram of protein provides 4 kcal. Potential risks associated with protein administration include acidosis,

elevated blood urea nitrogen, hyperammonemia, and cholestasis. Taurine and cysteine are considered conditional essential amino acids for neonates and should be added to PN solutions; particularly for very preterm (<32 weeks' GA)/very low-birth-weight (<1,500 g) infants. Dextrose yields 3.4 kcal/g and may be advanced to provide a maximal glucose infusion rate of 12 to 14 mg/kg/min. Complications associated with dextrose infusions include hyper or hypoglycemia, glycosuria and possible osmotic diuresis, and cholestasis or steatosis (or both) as a result of long-term high-caloric intake. Intravenous lipid solutions provide 10 kcal/g. A 20% soybean emulsion is commonly used



**Figure 112-7** Olsen growth chart. (From Olsen IE et al. *New intrauterine growth curves based on United States data*. *Pediatrics*. 2010;125:e214.)

because it is more efficiently cleared than the 10% solution and provides 2 kcal/mL. Lipid infusions are administered over a 20- to 24-hour period at rate of 0.12 to 0.15 g/kg/hour and should not exceed 60% of the total caloric intake. Triglyceride levels should be measured periodically and should be less than 200 mg/dL. Potential adverse effects from lipid infusions include hyperlipidemia, bilirubin displacement

from albumin-binding sites by free fatty acids, potential to interfere with pulmonary clearance in infants with chronic lung disease, lipid overload resulting in hepatic failure, and coagulopathy. The ratio of calcium to phosphorous in PN solutions is 1.3 to 1.7:1 by weight.

Additional additives to PN solutions include trace elements and vitamins. Trace elements contain zinc,



**Table 112-3** Parenteral Nutrition Macronutrient Components

NUTRITIONAL GOALS FOR PARENTERAL NUTRITION	NONPROTEIN CALORIES (KCAL/KG/DAY)	CARBOHYDRATE (MG/KG/MIN)	PROTEIN (G/KG/DAY)	PROTEIN (G/KG/DAY)
Basal metabolic need (prevents catabolism)	50–60	4–6 (glucose infusion rate)	1.0–1.5	0.6–1.0 (prevents essential fatty acid deficiency; 4%–5% total fat calories should be from linoleic acid and 1% from linolenic acid)
Positive balance (promotes growth)	80–100	8–10; gradually advance to max 12–13	2.7–3.5	3.0–3.5 (30%–55% of the total calories from fat)

**Table 112-4** Daily Total Parenteral Nutrition Intake

NUTRIENT	PRETERM INFANT	BIRTH TO 12 MONTHS
Fluid volume (cc/kg)	60–200	120–150
Protein (g/kg)	2.5–4.0	2.5–3.0
Energy (kcal/kg)	80–100	80–120
Carbohydrate (g/kg)	12–25	12–25
Lipid (g/kg)	0.5–3.0	0.5–3.0
Sodium (mEq/kg)	2–5	2–4
Potassium (mEq/kg)	2–3	2–3
Chlorine (mEq/kg)	2–5	2–4
Calcium (mg/kg) [mEq/kg]	50–90 [3–4]	40–60 [2–3]
Magnesium (mEq/kg)	35–70 [1–2]	30–50 [1–2]
Positive balance (promotes growth)	0.2–0.6	0.5–1.0

**Table 112-5** Effects of Neonatal Disease on Specific Nutrient Requirements

NUTRIENT	RESPIRATORY DISTRESS SYNDROME	BRONCHO-PULMONARY DYSPLASIA <sup>a</sup>	CYANOTIC CONGENITAL HEART DISEASE	CONGESTIVE HEART FAILURE	SEPSIS	INTRAUTERINE GROWTH RESTRICTION
Free water	↓	↓	↔	↓	↔	↑
Energy	↑	↑↑	↑	↑↑	↑	↑
Fat	↔	↑	↑	↑	↔	↑
Carbohydrate	↑	↓	↑	↑	↑	↑
Protein	↔	↑	↑	↑	↑↑	↑
Calcium	↔	↑ <sup>b,d</sup>	↑ <sup>b,c</sup>	↑ <sup>b,c,d</sup>	↔	↑
Iron	↔	↑ <sup>b</sup>	↑	↔	↓	↑
Vitamin A	↑ <sup>b</sup>	↑ <sup>b</sup>	↔	↔	↔	↔
Vitamin E	↔	↑	↔	↔	↔	↔

<sup>a</sup>From Huysman WA, de Ridder M, de Bruin N C, et al. Growth and body composition in preterm infants with bronchopulmonary dysplasia. *Arch Dis Child Fetal Neonat Ed.* 2003;88:46–51.

<sup>b</sup><1,500 g birth weight

<sup>c</sup>Postoperative

<sup>d</sup>Calciuric diuretics

manganese, copper, and chromium, and are typically initiated 2 to 3 weeks after birth if the infant does not have renal or liver dysfunction. During the first 2 weeks of life, zinc should be provided in a dose of 0.15 mL/kg/day (150 mcg/kg/day; 1-mg/mL concentration). Thereafter, preterm infants require an additional 300 mcg/kg/day, and full-term infants should receive 200 mcg/kg/day of zinc. Selenium is also essential for both preterm and full-term infants and should be given in a dose of 2 mcg/kg/day. Trace elements are discontinued from the PN solution if the infant develops cholestasis. Trace element requirements are adjusted to provide a total daily intake of 400 mcg/kg/day of zinc for the preterm infant (100–350 mcg/kg/day for full-term infants), 0.2 mcg/kg/day of chromium, and 2 mcg/kg/day of selenium. Pediatric vitamins, 2 mL/kg/day, are also added to PN solutions up to a maximum of 5 mL/day. Heparin is often added to PN solutions to be administered through a central line.

Biochemical monitoring for infants on established (maintenance) PN regimens typically includes evaluation of blood electrolytes, blood urea nitrogen, creatinine, and calcium 1 to 3 times per week. Liver function studies (albumin, total and direct bilirubin, alanine aminotransferase,  $\gamma$ -glutamyltransferase, alkaline phosphatase), phosphorus, magnesium, triglyceride level, and complete blood count, including differential and platelet count, are monitored weekly to biweekly while the infant is receiving PN. Growth should be assessed weekly, plotting the occipitofrontal circumference, weight, and length on standard postnatal growth charts (Figure 112-5, Figure 112-6, Figure 112-7).

The baby is weaned from PN as advancing enteral feeding intake is tolerated. Once the daily enteral intake exceeds 50 mL/kg/day the lipid infusion can be discontinued. Thereafter, PN is typically stopped when the infant's intake is 80 to 120 mL/kg/day. The wide range in total enteral fluid intake at which PN may be discontinued relates to a lack of consensus on the optimal duration of PN support and the need to individualize therapy based on a baby's specific energy and nutrient needs. Infants who develop cholestasis and continue to require prolonged PN therapy benefit from *cycling* (intermittent infusion) of the PN solution with lipid administration limited to 3 days/week. Intermittent PN infusion promotes a feeding-fasting cycle that decreases the severity of cholestasis. If this strategy is used, then close monitoring of the infant's glucose is necessary to avoid hypoglycemia.

### Enteral Nutrition

Enteral feeding regimens typically begin with expressed breast milk or preterm formula. Infants may be nipple fed if they are clinically stable, with respiratory rates less than 60 to 70 breaths/min, and they are 34 weeks' gestation or older. Infants between 32 and 34 weeks' gestation may be able to nipple feed but should be assessed to document their oromotor skills, state regulation, and evidence of a coordinated suck-swallow-breathing pattern. Bolus feeding rather than continuous feeding is preferred for the recovering neonate.

### Feeding Intolerance

A common concern relates to the significance of gastric residual volumes and the risk for necrotizing enterocolitis. The color or volume (or both) of aspirated gastric residuals are factors often considered in the decision whether to continue enteral feeding. Investigators have shown that the color of the gastric residual did not predict the risk for developing necrotizing enterocolitis. Maximal residual volumes of more than 3.5 mL or greater than 33% of the feed volume are suggested as the threshold for concern that requires clinical assessment of the infant. However, an important point to note is that gastric residuals must be considered in the context of the infant's clinical status, vital signs, abdominal examination, stool character, and stooling pattern.

Premature infants are predisposed to feeding intolerance because of functional dysmotility and immaturity of the gastrointestinal tract, particularly after prolonged periods of no oral intake. Lack of early enteral feeding disrupts the intestine's barrier functions, which leads to gut atrophy, loss of intestinal villi and malabsorption, bacterial translocation, and impaired immune function. The initiation of early small-volume minimal enteral or trophic feedings is beneficial in maintaining intestinal integrity and promoting gastrointestinal motility.

Erythromycin has been recommended by some investigators for infants who are unable to establish full enteral feeding within 2 to 3 weeks of age. It has prokinetic properties as a motilin agonist that stimulates gastric emptying and proximal small intestinal contractility. Data from several randomized clinical trials provide conflicting results about the efficacy of erythromycin in improving feeding tolerance. Comparison of these studies is difficult because each employed a different erythromycin dose (low vs antimicrobial), route (enteral vs intravenous), and mode (prophylactic or rescue) of treatment. A 2008 meta-analysis by Ng and colleagues examined 10 randomized studies and found insufficient evidence to recommend the use of erythromycin in low or high doses for preterm infants with or at risk of feeding intolerance. However, the meta-analysis did identify evidence that use of erythromycin at higher treatment doses (40–50 mg/kg/day) or in infants older than 32 weeks GA reported more positive effects in improving feeding intolerance without higher complication rates of necrotizing enterocolitis or sepsis.

Given concerns regarding erythromycin-induced hypertrophic pyloric stenosis and cardiac arrest, prophylactic treatment of preterm infants is not routinely recommended. If a trial of erythromycin is used to promote intestinal motility, then the oral route is preferred because of the risk of significant morbidity and mortality with intravenous administration. The optimal and safest dose of erythromycin is not known. However, exposure to antimicrobial doses for more than 14 days has been associated with the development of hypertrophic pyloric stenosis. A 2005 review by Patole et al summarizes the current understanding of the physiological gastrointestinal function and feeding intolerance in premature infants and the gastrointestinal effects of erythromycin. Currently, erythromycin can

be cautiously recommended only for a select subset of premature infants older than 32 weeks GA with a protracted course of feeding intolerance.

### **Human Milk and Preterm Infant Formula Use**

Human milk is the choice for feeding full-term and preterm infants. However, for the very low-birth-weight premature infant, human milk requires fortification to provide nutrient intakes comparable to intrauterine accretion rates. Human-milk feeding has been shown to result in improved neurodevelopmental and cognitive outcomes and visual acuity among premature infants in comparison with their formula-fed counterparts. Fresh milk is preferred when available. (See Chapter 88, Breastfeeding the Newborn.) Routine screening cultures for evidence of bacterial contamination or heat treatment of the mother's own milk has not been shown to be necessary or cost effective. If a mother's own milk is not immediately available, then use of pasteurized donor human milk, if available, may be considered. Pasteurized donor human milk maintains most of the properties of fresh human milk (immunoglobulins, growth and developmental hormones, enzymes, anti-inflammatory factors), is sterile, and reduces necrotizing enterocolitis while improving feeding tolerance. Studies have shown that healthy preterm infants born less than 30 weeks' gestation are able to tolerate milk volumes of 150 to 200 mL/kg/day without adverse effects. Human milk-fed, extremely low-birth-weight infants require approximately 180 mL/kg/day to achieve adequate growth, nutrient retention, and nutritional status.

The nutrient composition of human milk varies because of the individual properties of expressed milk and changes that occur during collection, storage, and use. The energy and protein content of expressed human milk varies, as does the fat content. Human milk is not homogeneous; as the milk stands, the fat content separates. Much of the variation in the energy content of milk used is the result of differences in or losses of fat in unfortified milk. Although concentrations of protein, sodium, and zinc decline during the period of lactation, the nutrient needs of premature infants remain higher than those of full-term infants, even after the preterm infant reaches term postmenstrual age. This circumstance results in the need to fortify expressed human milk to compensate for the inadequate nutrient supply. Mineral content of calcium and phosphorus varies less during lactation but remains too low with respect to the premature infant's nutrient needs. Low calcium and phosphorus intake causes physiological changes that result in poor bone mineralization that may have long-term effects on the preterm child's height. Nutrient availability of vitamin C, vitamin A, and riboflavin declines during collection, storage, and administration of expressed milk.

Human-milk fortification is typically started when the intake reaches 50 to 80 mL/kg/day. Additional caution is warranted for preterm infants who are significantly growth restricted at birth with evidence of absent or reversed end diastolic doppler flow on antenatal testing because of the risk for necrotizing enterocolitis in the population of infants. Fortification for this group of babies has been recommended to be delayed until the infant is tolerating at least 120 to 150 mL/kg/day unfortified

breast milk. Fortifiers typically provide 4 kcal/packet and are added to 25 mL of breast milk to achieve a caloric density of 80 kcal/dL (24 kcal/oz). Human milk fortifiers are available as a powder, an acidified liquid, and human milk-based products that support trophic feedings, pasteurized donor milk, and human milk fortifier to enrich breast milk feedings of the mother's own milk (Prolacta). Concerns about contamination and risk for sepsis from human milk mixed with powdered fortifier as well as insufficient protein intake from unmodified human milk have resulted in the development of liquid human milk fortifier and a hydrolyzed liquid protein fortifier. Additional calories may be required because poor weight gain (600–800 IU/L) and radiographic evidence of metabolic bone disease require increased calcium and phosphorus intake. Infants receiving more than 150 mL/kg/day of fortified human milk are at a greater risk for hypercalcemia and hyperphosphatemia and thus require closer monitoring of calcium and phosphorus levels. Preterm liquid formula may also be added to human milk to increase the caloric and nutrient intake.

*The Food and Drug Administration has issued a warning against the use of gum xanthum thickeners such as Simply Thick in preterm infant feedings, because this has been linked to an increased risk of necrotizing enterocolitis.*

Premature infant formulas are typically recommended for preterm infants weighing less than 1,800 g at birth or who are less than 34 weeks' gestation. Preterm formulas are cow milk-based, whey-predominant formulas that provide between 2.7 and 3.0 g of protein per 100 kcal. High-protein, higher-calorie preterm formulas that provide 3.3 g protein/100 kcal and 24 cal/oz are available for feeding growing low-birth-weight infants and premature infants who may need extra protein to help support growth. Studies have shown that the growth of hospitalized infants is related to protein intake. Extremely preterm infants, less than 28 weeks' gestation, have higher protein requirements than more moderate and later preterm infants. To meet the higher protein needs of this group of infants who are receiving expressed breast milk (their mother's milk or donor breast milk), liquid protein supplements are available. Fat calories are derived from long- and medium-chain triglycerides. A 30 cal/oz iron-fortified formula may be used for feeding growing low-birth-weight infants and premature infants with limited fluid intake because of the need for fluid restriction and/or higher caloric needs. This formula is also suitable for use as a human milk fortifier and/or a breast milk extender when mixed 1:1 with human milk. An important consideration when fortifying or modifying breast milk or an infant formula is assuring that the feeding is not hyperosmolar. The American Academy of Pediatrics (AAP) Committee on Nutrition recommends limiting the osmolality of nutrient dense feedings to less than 450 mOsm/L (see Table 112-6).

Formulas designed for preterm infants (Table 112-7) should be used instead of protein hydrolysate (Alimentum, Pregestimil, Nutramigen) or amino acid-based (Neocate, Elecare) formulas that are designed for full-term infants, unless a specific indication exists for use of one of these formulas (cholestasis, malabsorption, intestinal failure, or short-bowel syndrome). Soy

**Table 112-6** Osmolarity of Common Infant Formulas and Nutritional Supplements

FORMULA/SUPPLEMENT	CALORIES/FL OZ	OSMOLARITY, MOSM/L
Enfamil Premature 20	20	220
Enfamil Premature 24	24	260
Enfamil Premature 30	30	270
Enfa Care RTU	22	250
Pregestimil 20 RTU	20	260
Pregestimil 24 RTU	24	300
Similac Special Care 20	20	235
Similac Special Care 24	24	280
Similac Special Care HP 24	24	280
Similac Special Care 30	30	325
Neosure 22 RTU	22	250
Alimentum	20	370
Gerber Good Start Premature	20	229
Gerber Good Start Premature	24	275
Gerber Good Start Premature High Protein	24	299
Gerber Good Start Premature	30	341
Enfamil HMF	2 packets (7 cal)	17.5
Similac HMF	2 packets (7 cal)	45
Liquid Protein Fortifier (Abbott)	1 mL	~12
Enfamil Human Milk Fortifier Acidified Liquid	5 mL	36

protein-based formulas are not recommended for pre-term infants who weigh less than 1,800 g because their use results in reduced serum phosphorus levels that contribute to reduced bone mineral content. In addition, use of soy protein-based formulas leads to poorer growth (weight and length) and lower serum albumin levels and poses the potential for aluminum toxicity.

Routine iron supplementation should begin at 2 months postnatal age providing 2 to 4 mg/kg/day of iron. Infants with iron deficiency anemia require a higher iron intake of 4 to 6 mg/kg/day. Oral vitamin supplements are initiated after 2 weeks of age, typically once the preterm neonate is able to tolerate full enteral feedings. A summary of nutrient recommendations for preterm and term infants is found in Table 112-7.

### Infants With Chronic Lung Disease

Nutrition management of infants with chronic lung disease includes providing appropriate nutrient and caloric intake to meet the infant's increased energy and nutrient needs. Babies with chronic lung disease have reduced fat accretion, fat mass, growth, and muscle mass. Infants with BPD continue to exhibit slow or faltering growth during the first year of life. Medication use can alter energy requirements because methylxanthines will increase energy expenditure, and dexamethasone therapy has been associated with decreased weight gain. Infants with BPD require 15% to 25% more calories per day (140–150 kcal/kg/day) during the acute phases of their disease compared with their healthy peers. Protein intakes of 3.5 to 4.0 g/kg/day are considered adequate to meet the anabolic and tissue growth requirements. Diuretic use is common in the management of infants with BPD, with resultant

increased urinary losses of sodium, potassium, chloride, and calcium. Replacement of excess salt and mineral losses is often required. Close monitoring of the electrolyte and mineral balance is important to prevent complications related to nutrient depletion and poor growth. Inadequate mineral intake combined with diuretic use increases the risk for osteopenia and metabolic bone disease (nutritional rickets). This risk may be further increased by using hydrolyzed, elemental formulas or preterm formulas that are modified by the addition of carbohydrate or fat but contain insufficient calcium and phosphorus for bone mineralization.

### Infants With Complex Congenital Heart Disease

Similar to infants with chronic lung disease, the caloric requirements for infants with complex congenital heart disease may be as high as 150 mL/kg/day. Adequate weight gain and growth may be impeded by episodes of hypoxemia, tachypnea, and feeding fatigue that limit intake and increase energy expenditure. Gastroesophageal reflux and delayed gastric emptying further complicate appropriate nutritional management. Poor nutrition contributes to delayed wound healing, impaired immunity, and an increased risk for infection. Swallowing difficulties are a common complication after cardiac surgery in children. Prolonged intubation and injury to the recurrent laryngeal nerve resulting in vocal cord paralysis also contribute to feeding difficulty. Fiberoptic endoscopic evaluation of swallowing is a useful adjunct in the assessment of feeding in these babies in order to construct an appropriate feeding regimen (gavage vs nipple) and plan for oral-motor therapy. Refer to Chapter 116, Health and Developmental



**Table 112-7** Preterm Infant Fortifier, Formula, and Supplement Information

FORTIFIER, FORMULA, SUPPLEMENT	MANUFACTURER	MEASURING	PRECAUTIONS, COMMENTS
<b>FORTIFIERS</b>			
Human milk fortifier (provides increased protein, carbohydrate, fat, vitamins, minerals, and calories for the preterm infant; infants are rarely discharged on human milk fortifier)	—	—	<p>Not for use in preterm infants born more than 34 weeks' gestation, once a very low-birth-weight infant weighs &gt;2,500 g, or if the infant has an intake of more than 500 mL/day, given that human milk fortifier supplementation may exceed renal solute load</p> <p>Prolonged use associated with vitamin D toxicity and may supply several times RDA for vitamin A at intakes &gt;500 mL/day</p> <p>Not for postdischarge use with full-term infants or in cases of failure to thrive</p> <p>Infants are rarely discharged on human milk fortifier</p>
Similac human milk fortifier (powder)	Abbott Nutrition	<p>For 22 kcal/oz, use 1 packet and 50 mL of human milk</p> <p>For 24 kcal/oz, use 1 packet and 25 mL of human milk. Measure human milk first and add powder</p>	<p>Discontinue once the infant weighs 2,000 g (4.5 lb)</p>
Enfamil human milk fortifier (powder)	Mead Johnson	<p>For 22 kcal/oz, use 1 packet and 50 mL of human milk</p> <p>For 24 kcal/oz, use 1 packet and 25 mL of human milk. Measure human milk first and add powder</p>	<p>Infants are rarely discharged on human milk fortifier</p> <p>Discontinue once the infant weighs 2,000 g (4.5 lb)</p>
Similac Natural Care, Advance (liquid and ready-to-feed)	Abbott Nutrition	Provides 24 kcal/30 mL (0.8 kcal/mL); use in equal amounts with human milk for 22 kcal/oz	<p>Discontinue once the infant weighs 2,000 g (4.5 lb) if used as human milk fortifier</p> <p>May be continued to a weight of 3,600 g (8 lb) in preterm infants with inadequate weight gain</p>
Enfamil Human Milk Fortifier Acidified Liquid	Mead Johnson	<p>Provides 4 kcal/vials; add 1 vial to 25 mL HM (provides 24 cal/oz; raises the protein content to 4 g/100 cal)</p> <p>1 vial/50 mL HM will provide 22 cal/oz</p> <p>1 vial added to 25 mL BM increases human milk osmolality by +36 mosm</p>	<p>No increase in rates of NEC or sepsis in babies &lt;1,250 g bwt<sup>a</sup> Once prepared, fortified breast milk can spoil quickly. Either feed fortified human milk immediately or cover and store in refrigerator at 35–40°F (2–4°C) for no longer than 24 hours. Agitate before each use</p> <p><b>For bottle feeding:</b> Pour only the amount of fortified human milk to be fed into a feeding container and feed immediately. Do not use fortified human milk if it is unrefrigerated for more than a total of 2 hours. After feeding begins, use within 1 hour or discard</p> <p><b>For tube feeding:</b> Once fortified human milk is prepared, it can remain at room temperature for no longer than a total of 4 hours</p> <p>Discontinue once the infant weighs 2,000 g (4.5 lb) or is ready for discharge</p>

Continued

**Table 112-7** Preterm Infant Fortifier, Formula, and Supplement Information—cont'd

FORTIFIER, FORMULA, SUPPLEMENT	MANUFACTURER	MEASURING	PRECAUTIONS, COMMENTS
Prolacta	Prolacta Bioscience	Product available as 24 (Prolact+4), 26 (Prolact+6), 28 (Prolact+8) and 30 (Prolact+10) cal/oz concentrations Refer to Prolact+H <sup>2</sup> MF instructions for thawing, preparation and feeding ( <a href="http://www.prolacta.com/instructions-for-use/">www.prolacta.com/instructions-for-use/</a> )	Prolact+H <sup>2</sup> MF is the first and only commercially available human milk fortifier made from concentrated 100% human milk; these formulations are fortified with essential minerals and offer protein delivery up to 3.7 g/100 mL of fortified milk <sup>b</sup> and 24–30 cal/fl oz Use in infants <1,250 g bwt results in a significant reduction in NEC risk Minimal effect on osmolality—1 mL contributes ~12 mOsm/kg water per 100 mL feeding prepared Refrigerate fortifier after opening—use within 24 hours or discard
Liquid Protein Fortifier, extensively hydrolyzed protein	Abbott Nutrition	Can be added to human milk or infant formula 6 mL liquid protein fortifier adds 4 cal and 1 g protein	
<b>FORMULAS</b> (Provides increased protein, calcium, phosphorous, vitamins A and D. Can supplement or fortify human milk)	—	—	Contributes to improved growth and bone mineralization compared with preterm infants fed standard infant formulas Current recommendation is to use transitional formula until 9 months corrected age; some infants may benefit from continued use until 12 months corrected age Infants exhibiting rapid catch-up growth whose weight exceeds the 50% may be transitioned to standard infant formula or exclusive breastfeeding sooner
Similac NeoSure, Advance (powder and ready-to-feed)	Abbott Nutrition	<i>Formula:</i> For 22 kcal/oz (standard dilution), use 1 packed, level scoop and 60 mL water For 24 kcal/oz, use 3 packed, level scoops and 165 mL of water For 27 kcal/oz, use 5 packed, level scoops and 240 mL <i>Fortifier:</i> For 22 kcal/oz, use 1 tsp in 180 mL For 24 kcal/oz, use 1 tsp in 90 mL For 27 kcal/oz, use 2 tsp in 90 mL Measure water or human milk first, then add powder	Should not be used for calorie enhancement in growth-restricted infants whose gestational age is >34 weeks, birth weight >1,800 g
Enfamil EnfaCare (powder)	Mead Johnson	Same as for Similac NeoSure above	Should not be used for calorie enhancement in growth-restricted infants whose gestational age is >34 weeks

**Table 112-7** Preterm Infant Fortifier, Formula, and Supplement Information—cont'd

FORTIFIER, FORMULA, SUPPLEMENT	MANUFACTURER	MEASURING	PRECAUTIONS, COMMENTS
Similac Special Care 24 High Protein	Abbott Nutrition		24 cal/fl oz iron-fortified feeding for growing, low-birth-weight infants and premature infants who may need extra protein to help support growth Can be mixed with human milk or other preterm infant formulas for a variety of high-caloric, nutrient-dense formulas Not intended for feeding low-birth-weight infants after they reach a weight of 3,600 g (~8 lb)
Similac Special Care 30 with Iron	Abbott Nutrition	Available as ready-to-feed Can be mixed with other preterm infant formulas to achieve caloric densities of 26 and 28 cal/oz	Calcium and phosphorus ratio (1.8:1) Approximately 2 mg iron/kg body weight per day, when fed at 120 cal/kg/day Not intended for feeding low-birth-weight infants after they reach 3,600 g (~8 lb)
<b>SUPPLEMENTS</b>			
MCT oil	Mead Johnson/Novartis	Provides 8.8 kcal/mL; add 0.5 mL/oz of breast milk or formula	Can cause loose stools, steatorrhea; does not provide essential fatty acids
Safflower oil	—	Provides 8 kcal/mL	—
Microlipid emulsified safflower oil	Mead Johnson	Provides 4.5 kcal/mL	Contains long-chain fatty acids
Polycose glucose polymer (liquid or powder)	Abbott Nutrition	½ tsp of powder provides 4 kcal; 1 mL of liquid provides 2 kcal; 23 kcal/tbsp; add ½ tsp/oz of formula	Can cause diarrhea
Moducal	Mead Johnson	30 kcal/tbsp	
<b>SPECIALIZED FORMULAS NOT RECOMMENDED FOR ROUTINE USE</b>			
Soy-based formulas			Not recommended for infants with low birth weights Suboptimal carbohydrate and mineral absorption; results in less weight gain and linear growth, lower serum albumin and phosphorus levels, and higher alkaline phosphorus levels indicative of poorer bone mineralization No data to support the use of thickened formula in preterm infants with reflux after discharge
Enfamil AR (standard infant formula with added rice starch recommended for infant feeding of babies with gastroesophageal reflux)	Mead Johnson		
EleCare	Abbott Labs	1 scoop (9.4 g) added to 2 oz water provides 20 cal/oz	Amino acid–based infant formula with iron for use in infants with protein maldigestion, malabsorption, short-bowel syndrome, GI-tract dysfunction Fat blend contains 33% medium-chain triglycerides Does not contain milk protein, soy protein, fructose, galactose, lactose, or gluten
Pregestimil	Mead Johnson	1 packed scoop (8.9 g) added to 2 oz water provides 20 cal/oz	Hypoallergenic, lactose-free infant formula for babies with fat malabsorption problems
Neocate	Nutricia North America	1 scoop per oz water	55% fat as medium-chain triglycerides 100% free amino acids For use in infants with short bowel syndrome, multiple-food protein intolerance

Continued

**Table 112-7** Preterm Infant Fortifier, Formula, and Supplement Information—cont'd

FORTIFIER, FORMULA, SUPPLEMENT	MANUFACTURER	MEASURING	PRECAUTIONS, COMMENTS
Thickeners (rice cereal, carob)	—	A practice used by some physicians in the treatment of infants with symptomatic reflux or feeding problems assessed by a feeding therapist is to thicken infant formula with rice cereal	Thickening feedings is a common practice but is controversial. FDA warns against use of <i>Simply Thick</i> . Thickening human milk is often unsuccessful as the naturally occurring enzymes digest the thickener. Does not contain necessary vitamin and mineral content for the growing preterm infant. Some evidence that thickened feeds increase the duration of reflux episodes. For infants with feeding difficulties, thickened feedings may further exacerbate pre-existing feeding difficulties.

RDA, recommended daily allowance; FDA, Food and Drug Administration

<sup>a</sup>Moya F, Sisk PM, Walsh KR, Berseth CL. A new liquid human milk fortifier and linear growth in preterm infants. *Pediatrics*. 2012;130(4):e928–e935.

<sup>b</sup>Wojcik KY, Rechtman DJ, Lee ML, Montoya A, Medo ET. Macronutrient analysis of nation wide sample of donor breast milk. *J Am Diet Assoc*. 2009; 109(1): 137–140.

Adapted from *Nutrition Practice Care Guidelines for Preterm Infants in the Community (Revised August 2006)*, Child Development and Rehabilitation Center, Nutrition Services, Oregon Department of Human Services, Nutrition & Health Screening—WIC Program Oregon Pediatric Nutrition Practice Group.

Outcomes of Selected Medically Complex Neonates, for related information.

## GASTROESOPHAGEAL REFLUX AND GASTROESOPHAGEAL REFLUX DISEASE

GER, defined as the retrograde passage of gastric contents into the esophagus, occurs in approximately 50% of all young infants. Babies who exhibit symptoms or complications of GER (vomiting, poor weight gain, difficulty feeding, hematemesis, and airway symptoms such as chronic lung disease and airway inflammation, apnea, aspiration, and recurrent pneumonia) are classified as having gastroesophageal reflux disease (GERD), requiring evaluation and treatment. Therapy is empiric, with little evidence for efficacy of current treatment modalities. Pediatric clinical practice guidelines published in 2001 by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and endorsed by the AAP list the following points:

- A time-limited trial of medical therapy for infants with symptomatic GER should be provided.
- An up to 4-week trial of a hydrolyzed or amino acid formula in infants with vomiting that is suspected to be caused by cow-milk allergy should be considered.
- Thickened feedings reduce visible vomiting but do not improve reflux.
- Antireflux formulas are not appropriate for preterm infants.
- Ensure adequate caloric intake; increase caloric density if necessary.
- Prone positioning may be beneficial for select infants with significant symptoms; however, supine sleep position is associated with the lowest risk of sudden infant death syndrome, and is the position of preference while the infant is convalescing in the neonatal unit and after discharge home.

- Infants who are maintained in the prone position require continuous monitoring.

Joint evidence-based recommendations from NASPGHAN and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition published in 2009 provide a synthesis of the mechanisms involved in reflux and detail clinical practice approaches based on presenting symptomatology and complicating sequelae. This consensus practice guideline offers limited guidance regarding practice approaches for preterm and very young infants, although it does provide a review of the available evidence about pathogenesis and diagnostic and treatment modalities.

GER is common among preterm infants, who may exhibit 3 to 5 episodes of reflux per hour, and is related to physiological transient lower esophageal sphincter relaxation (TLESR). These episodes of TLESR occur in both asymptomatic and symptomatic infants and may be elicited by gastric distention that accompanies feeding and abdominothoracic straining that accompanies movement. Episodes of acid GER have been shown to occur frequently in healthy preterm infants and resolve in most preterm babies as they reach term postmenstrual age. Use of gavage feeding tubes is also associated with increased reflux symptoms. Clinical concerns about feeding intolerance and recurrent episodes of apnea, bradycardia, and desaturation lead to the frequent use of prokinetic agents and acid suppressant drugs. However, behaviors often interpreted as signs of reflux disease in the preterm infant are nonspecific and not predictive of esophagitis. In addition, although reflux episodes may be more common in infants with BPD, there is no evidence that GERD therapy affects the clinical course or outcome.

The frequency of feeding in young infants results in relatively brief periods of gastric pH less than 4; consequently, pH probe measurements may not be helpful in



diagnosing significant reflux in the preterm infant. Although a common concern is that GER may contribute to apnea, numerous studies have failed to document a link between the 2 events. Impedance studies have demonstrated retrograde reflux of air and fluid into the esophagus occurring in addition to episodes of acid reflux. Approximately 25% of reflux events are strongly acidic, with total esophageal exposure time to acid estimated to be 5%. Recent studies have not confirmed a temporal link between acid-based GER and AOP. As a result, medication use to treat reflux is not recommended as part of the management of episodic apnea, bradycardia, and desaturation in preterm infants. Other pharmacologic and medical approaches may be necessary to optimize growth, nutrition, and respiratory function. The challenge that arises in management of GER in the preterm infant is the lack of data on the efficacy of antireflux measures. Although metoclopramide has been shown to reduce reflux symptoms, its use is associated with adverse effects such as irritability, dystonic reactions, drowsiness, emesis, apnea, and involuntary muscle movements, as well as oculogyric crisis (involuntary upward conjugate gaze). Metoclopramide's action as a dopamine-receptor antagonist accounts for its promotility effects in the intestine and blockade of dopamine receptors in the brain, resulting in the central nervous system effects. Therefore, metoclopramide is not recommended in the management of reflux in preterm and young infants.

Symptomatic preterm infants with GERD often exhibit significant vomiting of more than 50% of the fed volume more than 3 to 4 times per day in conjunction with:

- Recurrent episodes of apnea, bradycardia, and desaturations associated with feeding
  - Signs of discomfort or distress during feeds (arching, crying)
  - Difficulty advancing feeding volume
  - Poor weight gain
- Management strategies include:
- Infant positioning in prone with slight elevation of the head of the bed (requires continuous monitoring)
  - Infant transitioned to supine sleep position 1 to 2 weeks before anticipated discharge home to lessen the risk for sudden infant death syndrome
  - Consideration of discontinuation of methylxanthines (caffeine or theophylline)
  - Symptoms of infant reflux are rarely so severe that breastfeeding should be discontinued
  - Breastfeeding infants with regurgitation and vomiting may benefit from a 2–3 week trial of withdrawal of cow's milk products, beef, soy, and eggs from the maternal diet

Acid suppression therapy, although not well studied in the preterm infant, may also be considered: histamine-2 ( $H_2$ ) blockers (ranitidine [1 mg/kg/dose every 12 hr], famotidine [1 mg/kg/day divided every 12 hr]) or proton pump inhibitors (omeprazole [1.0 mg/kg/day given once daily or divided every 12 hours] or lansoprazole [1.5 mg/kg/day given once daily or divided every 12 hours]). Care must be taken if  $H_2$ -blockers are used because therapy has been associated with higher rates of necrotizing enterocolitis in very low-birth-weight infants. Famotidine has been shown to decrease the

number of reflux episodes and crying time in infants between 1 and 11 months of age, but treatment was also associated with increased neurologic events, including increased irritability, anorexia, and somnolence. Orenstein et al determined in a multicentered randomized clinic trial that there was no difference in efficacy between lansoprazole and placebo for symptoms attributed to GERD in infants age 1 to 12 months. Severe adverse events, particularly lower respiratory tract infections, occurred more often with lansoprazole than with placebo. Consultation with a pediatric gastroenterologist may be considered. It is well recognized that pediatric subspecialists such as gastroenterologists and pulmonologists more frequently prescribe  $H_2$  blockers and PPI medications than their neonatologist colleagues. A recent review by Shakhnovich and colleagues suggests that for a subset of infants with acid reflux, PPI medications may be beneficial.

If a family history of allergy exists, then the physician should consider having the mother eliminate dairy from her diet if she is providing breast milk for the infant, or initiate a trial of an elemental (casein-hydrolyzate) formula such as Pregestimil, Alimentum, or Nutramigen. Neocate or EleCare (amino acid–based formulas) may be used for infants with severe milk intolerance. (For a full discussion of the management of GERD, see Chapter 255, Gastroesophageal Reflux Disease.)

## CHOLESTASIS

Parenteral nutrition–associated cholestasis (PNAC), or parenteral nutrition–associated liver disease (PNALD), is a complication seen among infants who have enteral feedings withheld for extended periods. At greatest risk are infants with intestinal immaturity or intrinsic gastrointestinal disease, sepsis, and hypoxemia, and babies who require prolonged PN. Among preterm infants, babies at less than 28 weeks' gestation and infants who are small for GA are at greater risk of developing PNAC. The time to full enteral feeding has been shown to be a significant predictor of PNAC; rates of PNAC are higher among infants with chronic lung disease (BPD). Toxicity has been associated with amino acids such as methionine; trace elements such as copper, chromium, and manganese; intravenous soy-derived lipid infusions (providing primarily omega-6 fatty acids), and excessive energy and dextrose intakes. Medications and nutrient deficiencies of taurine, cysteine, choline, fatty acids, and trace minerals have been associated with an increased incidence of cholestasis. Biochemical abnormalities include elevations in serum alkaline phosphatase, direct bilirubin, and transaminases. Direct bilirubin levels above 2 to 3 mg/dL warrant evaluation and intervention. Treatment strategies include small amounts (trophic) of enteral feedings, especially for infants who require PN for longer than 3 weeks because enteral feeding enhances gastric motility and bile flow. Trace minerals (copper and manganese) can be eliminated from PN once enteral feeding is initiated. Cycling of PN is also suggested for infants who may require long-term PN once they are more than 44 to 48 weeks PMA. Intravenous lipid emulsion infusions are typically reduced to 1 g/kg/day on alternating days or 2 to 3 times per week while the infant remains PN dependent. Cholagogues such as ursodeoxycholate (Ursodiol or Actigall, 10 mg/kg/dose

every 8–12 hours) are also used to treat cholestasis and are considered more efficacious than phenobarbital or amoxicillin. Discontinuation of PN and progression of enteral feedings result in a gradual improvement of cholestasis over weeks to months.

## OSTEOPENIA

Osteopenia of prematurity (OOP), also referred to as *nutritional rickets* or *metabolic bone disease of prematurity*, occurs frequently in very low-birth-weight infants who exhibit decreased bone mineral content because of inadequate mineral intake, prolonged PN use, and chronic diuretic therapy. Infants with enterostomies may also exhibit increased electrolyte and mineral losses from high ostomy output (Box 112-12). Medications commonly used in premature babies that result in calcium excretion and increase mineral needs include furosemide, xanthines, and dexamethasone. Anticonvulsants such as hydantoin and phenobarbital increase the turnover of vitamin D, leading to decreased serum levels of calcium and magnesium. Use of chronic thiazide diuretics also contributes to bone demineralization. Renal or liver disease increases the risk for osteopenia.

Mineral deficiencies are reported to occur in 30% to 50% of preterm infants who are fed either unfortified human milk or formulas designed for full-term infants. Infants born with very low birth weight or 28 weeks' gestation or less are at highest risk for OOP primarily as a result of inadequate phosphorus intake. Growing preterm infants who are fed human milk exclusively will not achieve bone mineral contents comparable to that attained through in utero accretion. Radiographs of the wrist and long bones reveal evidence of poor bone mineralization ("thinning"), with widening and cupping at the metaphyseal ends of the bones. Healing fractures may also be noted on routine radiographs involving the ribs and long bones. The risk for fractures is greatest between 6 and 12 weeks postnatal age; fractures occur in approximately 10% of very low-birth-weight infants and when alkaline phosphatase (APA) levels exceed 1,000 IU/L. Given that vitamin D deficiency is not a primary factor in OOP, supplemental vitamin D beyond nutritional requirements, 200 to 400 IU daily, is generally not needed unless serum 1, 25-OH vitamin D levels are low. Infants with cholestasis require additional vitamin D supplementation. Human milk should be fortified or the appropriate premature formula used. In the United States, fortification of human milk is recommended for very low-birth-weight preterm infants until a weight of 1,800 to 2,000 g is reached.

Routine monitoring of serum phosphorus and APA levels is helpful in detecting very low-birth-weight infants at risk for metabolic bone disease beginning at 4 to 6 weeks postnatal age and biweekly thereafter. Although serum calcium and APA levels are monitored in conjunction with serum phosphorus values, they are not useful markers of bone mineralization. In general, serum calcium remains within normal levels at the expense of bone loss. Alkaline phosphatase levels are elevated and serum phosphorus levels are lower in babies with osteopenia. Serum calcium levels are typically maintained within a normal range during osteopenia at the expense of bone mineralization. Serum APA levels greater than 800 to 1,000 IU/L in

### BOX 112-12 High-Risk Criteria for Rickets in Preterm Infants

- Born at <27 weeks' gestation
- Birth weight <1,000 g
- Long-term parenteral nutrition (eg, >4 to 5 weeks)
- Severe bronchopulmonary dysplasia with use of loop diuretics (eg, furosemide) and fluid restriction
- Long-term steroid use
- History of necrotizing enterocolitis
- Failure to tolerate formulas or human milk fortifiers with high mineral content

From Abrams S; American Academy of Pediatrics Committee on Nutrition. Clinical Report: Calcium and vitamin D requirements of enterally fed preterm infants. *Pediatrics*. 2013; 131(5):e1676–e1683.

conjunction with a serum phosphorus concentration less than 4.0 mg/dL (1.3 mmol/L) warrant radiographic evaluation of the wrist or knee for evidence of rickets or severe bone loss. Physical activity in the form of passive range of motion exercise has been shown to reduce bone mineral losses, increase bone strength, and promote growth in preterm infants. Among very preterm infants who do not develop rickets, clinical experience indicates that if the infant has serum alkaline phosphorus levels less than 400 to 800 IU/L and has achieved full feeds of human milk with a mineral-containing fortifier or a preterm infant formula, there is minimal, if any, risk of developing rickets, and measurement of APA can usually be stopped. Treatment strategies for the management of the preterm infant with nutritional rickets are summarized in Box 112-13.

In preparation for discharge, very low-birth-weight/very preterm infants typically transition from high mineral containing fortified human milk or preterm formula to unfortified human milk or a postdischarge preterm formula. This process often begins when the infant achieves a body weight of 1,800 to 2,000 g. Delaying the switch to transitional/post-discharge preterm formulas and continuing the use of formula designed for preterm infants or human milk fortifier should be considered for infants on fluid restriction, especially less than 150 mL/kg per day, or for infants with a prolonged course of parenteral nutrition and a persistent elevation of serum APA (ie, >800 IU/L). Use of formula designed for preterm infants would likely be safe until body weight of at least 3,000 g is reached. Extended use of preterm formulas beyond this time may result in excessive vitamin and mineral intake. The AAP Committee on Nutrition recommends that preterm infants who do not tolerate cow-milk protein or lactose-containing products continue biochemical monitoring for an extended period of time, and in some cases that the infants receive direct supplementation with added minerals. Amino acid-based, soy-based, and other specialized infant formulas generally have higher levels of minerals than do routine infant formulas, but the bioavailability of these minerals, especially in high-risk

### BOX 112-13 Management Approach for Enterally Fed Preterm Infants With Radiologic Evidence of Rickets

1. Maximize nutrient intake. Consider increasing human milk fortifier and/or feeding volume of preterm formula, as clinically indicated. If unable to tolerate human milk fortifier or preterm formula, then will likely need elemental minerals added as described below.
2. If no further increases in these can be made, add elemental calcium and phosphorus—usually beginning at 20 mg/kg per day of elemental calcium and 10–20 mg/kg/day elemental phosphorus and increasing, as tolerated, usually to a maximum of 70–80 mg/kg per day of elemental calcium and 40–50 mg/kg/day elemental phosphorus.
3. Evaluate cholestasis and vitamin D status. May consider measuring 25-OH-D concentration, targeting serum 25-OH-D concentration of >20 ng/mL (50 nmol/L).
4. Follow serum phosphorus concentration and serum APA weekly or biweekly.
5. Recheck radiographs for evidence of rickets at 5- to 6-week intervals until resolved.
6. Advise caregiving team to be cautious in handling of infant.
7. Limit use of steroids and furosemide, as clinically feasible.

From Abrams S; American Academy of Pediatrics Committee on Nutrition. Clinical Report: calcium and vitamin D requirements of enterally fed preterm infants. *Pediatrics*. 2013; 131(5):e1676–e1683.

infants such as those with a history of feeding intolerance or intestinal failure, is uncertain.

## TRANSITION TO ORAL FEEDING

Feeding disorders are common among infants, particularly babies who have been ill or who are preterm. The ability to nipple feed is an important developmental task that requires neurologic maturation, self-regulation, motor strength, and physiological stability. Successful nipple feeding requires coordination of nutritive sucking, swallowing, and breathing. Coordination of the tongue, pharynx, and upper trunk movements is necessary for an infant to swallow safely. The infant must also learn to protect the airway during feeding. In preterm infants this process is complicated by the occurrence of *deglutition apnea* episodes in which the infant stops breathing during successive swallows while feeding. This occurrence diminishes as the infant matures and as feeding skill improves.

Oral feeding is not initiated in preterm infants before 32 weeks of PMA mainly because the coordination of sucking, swallowing, and respiration is not established. Significant maturation of feeding behaviors occurs between 33 and 36 weeks PMA with more coordinated suck-swallow-respiration patterns; longer sucking bursts are noted by 37 weeks PMA. By 35 weeks' gestation, swallowing occurs typically at the end of inspiration. Consequently, swallowing less frequently interrupts respiration.

### BOX 112-14 Techniques to Support Development of Oral Feeding Skills

- Nonnutritive sucking, offering the infant a pacifier or the infant's fingers to suck and orally explore:
  - Accelerates transition from tube to oral feedings
  - Enhances weight gain and increases gastrointestinal motility
  - Improves the infant's behavioral state and organization
  - Does not fully reflect the oral feeding experience because swallowing is less and rhythmic sucking and breathing can more easily occur
- Provide tastes of breast milk or formula on the pacifier or infant's fingers; provides sensory stimulation before the introduction of nipple feeding
- Kangaroo care allowing the infant to nuzzle, lick, and suck at the mother's breast
- Use of slower or low-flow nipples to support the infant's swallowing; bolus size will increase as the infant's feeding skills mature and coordination improves
- Jaw, cheek, and/or chin support and proper positioning to sustain postural control
- Pacing:
  - Useful for infants who are not yet able to self-regulate their feeding or control successive swallows
  - Done by shifting the infant slightly forward every 3 to 5 sucks or the bottle tilted down to allow the milk to drain from the nipple and giving the infant a chance to breathe
- Demand or "infant-driven" feeding rather than a set feeding schedule, such as every 3 hours
- Some infants will require supplemental oxygen during nipple feeding to maintain adequate oxygenation and prevent desaturations and bradycardic episodes
- Assessment and monitoring of the infant's coordination of the suck-swallow-breathing sequence is necessary for timely identification of feeding difficulties

Infants who are less mature at birth, who experience complex medical courses with significant respiratory illness, or who require prolonged ventilation or oxygen therapy have greater difficulty establishing nipple feeds and take longer to master coordination of sucking, swallowing, and breathing than their healthy counterparts. Infants who have difficulty coordinating sucking, swallowing, and breathing quickly fatigue and lose motor tone. This situation contributes to desaturation, apnea, and bradycardia while feeding. For many of these infants, feeding difficulties continue after discharge from the neonatal unit and throughout infancy. These feeding behaviors lead to the development of feeding refusal in some infants. Sensorimotor interventions that combine sucking and swallowing exercises (oral + tactile/kinaesthetic stimulation) have been shown to improve oral feeding in very preterm infants.

Techniques helpful in supporting the development of oral feeding skills are listed in Box 112-14.

### BOX 112-15 Assessment of an Infant's Oral Feeding Ability

Assessment of an infant's oral feeding ability encompasses the following:

1. State regulation and response to tactile stimulation
2. Feeding position
3. Oral motor control
4. Physiological response to feeding episode
5. Coordination of suck-swallow-breathing sequence
  - a. Consider feeding evaluation by a speech pathologist or feeding therapist
  - b. Consider airway and feeding efficiency assessment with a modified barium swallow and fiberoptic endoscopic swallowing study to evaluate the vocal cords and swallowing and assess for evidence of aspiration
6. Caregiver–infant feeding interactions

The first attempts at oral feeding usually occur between 32 and 33 weeks' GA or PMA and exhibits a stable respiratory status. Infants are deemed to be successfully nipple feeding when they are able to complete feedings within 20 minutes. This goal may or may not be fully achieved by the time of the infant's discharge home. The choice of nipple used may facilitate or impede feeding efficiency. Some infants benefit from use of low- or variable-flow nipples to aid pacing during the feeding. Infants who are unable to achieve full nipple feeding may require a specialized program of intensive feeding therapy. A gastrostomy may also need to be placed if the infant is unable to gain adequate weight until sufficient oral feeding is attained. Signs that an infant may not be developmentally ready to initiate nipple feeding include falling asleep, not latching on, or exhibiting respiratory irregularity and loss of muscle tone when a bottle is placed in the mouth.

Assessing an infant's oral feeding ability requires evaluating multiple considerations (Box 112-15). The physician plays a critical role in promoting breastfeeding of the hospitalized infant (Box 112-16, Box 112-17).

## HEALTH MAINTENANCE

### Newborn Screening of the Critically Ill or Premature Infant

Newborn screening is an important component of acute and continuing care for the sick or preterm infant. Maternal medical conditions and treatments can affect newborn screening results. In addition, prematurity, low birth weight, illness, and treatments received by infants requiring neonatal intensive or specialized care can also alter newborn screening results. Most neonatal units have established protocols that specify the timing when newborn metabolic screening is conducted for babies requiring specialized neonatal or intensive care or transfer to another hospital. State health department newborn screening policies guide individual hospital

### BOX 112-16 Promotion of Breastfeeding in the Hospitalized Infant

- Discuss feeding options for the infant and the benefits of providing colostrum or human milk
- Provide mother with information or handouts on human milk expression and storage
- Work with nursery and postpartum staff to ensure that human milk expression is initiated in the first hours after delivery, employing both hand expression and use of an electric breast pump
- Provide referral to lactation consultant (hospital or community-based)
- Facilitate arrangements to rent or purchase a hospital-grade electric breast pump to support mother's goal of providing expressed human milk for her infant
- Most state Medicaid departments and WIC programs have guidelines that authorize payment for hospital-grade electric breast pumps for infants with the following conditions:
  - Prematurity
  - Neurologic disorders
  - Genetic abnormalities (Down syndrome)
  - Anatomic and mechanical malformations (cleft lip and palate)
  - Congenital malformations requiring surgery
  - Prolonged infant hospitalization
  - Conditions that prevent normal breastfeeding (respiratory compromise)
- Many insurers will include among subscriber benefits (these are plan specific) recommendations for electric breast pump authorization, such as prematurity, feeding difficulty caused by abnormal infant suck, or a hospitalized mother or infant

WIC, Special Supplemental Nutrition Program for Women, Infants, and Children.

practices. The timing of the first newborn screen is typically between 24 and 48 hours of age after the infant has established milk (human milk or formula) feeding. The infant who requires transfer to another facility, needs a blood transfusion, or is critically ill should have a newborn screening test obtained on the first day of life (<24 hours of age). A second screening test should be obtained between 48 and 72 hours of age. Infants who are less than 34 weeks' gestation or less than 2,000 g at birth require a repeat blood spot screen at 28 days of age. However, if the infant has a short NICU stay and few treatments, the third screening sample may not be necessary. Repeat screening is required on any infant with abnormal results on a first screen. Box 112-18 summarizes the advantages and disadvantages of screening at different points.

If an infant is transfused before obtaining the initial newborn screening test, then an additional specimen is necessary 2 to 3 months posttransfusion or when the blood cells tested are presumed to be the infant's and not reflect those of the donor. Earlier retesting may reflect donor hemoglobins and invalidate testing for galactosemia (red blood cells assayed



**BOX 112-17 Transition to Breastfeeding**

- Criteria to initiate *nonnutritive sucking time at the breast*
  - Begin at approximately 30 to 32 weeks gestational or postmenstrual age
  - Infant demonstrates ability to swallow own secretions
  - Stable outside incubator for more than 10 to 15 minutes
  - Able to tolerate kangaroo care (skin-to-skin contact)
  - Infant responses:
    - Mouth is at the breast; may or may not latch on or suck
    - May swallow once or twice
    - May fall asleep at the breast
  - Coordinate nonnutritive nursing attempts with infant hunger cues
- Reinforce importance of expressing breast milk every 3 hours (100 min/day)
- Initiation of nutritive sucking:
  - Infant displays consistent latch-on ability
  - Infant is able to feed for approximately 5 minutes
  - Supplementation with expressed human milk or formula after nursing episode:
    - Breastfeeds
    - Breastfeeds 5 to 10 minutes: gavage one-half enteral feeding volume
    - Breastfeeds more than 10 minutes: supplementation is not needed unless inadequate weight gain or signs of dehydration are exhibited
- Mother should continue to pump between and after feedings in order to maintain her milk volume as the infant's nursing skills strengthen.

for galactose-1-phosphate uridylyltransferase). Infants receiving PN, particularly preterm infants, may have elevated amino acids (eg, phenylalanine) resulting in positive screening results.

Current newborn screening recommendations include testing for cystic fibrosis. Testing algorithms rely on immunoreactive trypsinogen (IRT) or screening for cystic fibrosis transmembrane conductance regulator mutations. Newborn infants with meconium ileus are at risk for cystic fibrosis but may have low initial IRT test results (false negative). Consequently, all babies with meconium ileus require follow-up sweat tests. Infants experiencing severe perinatal distress or who have low Apgar scores may exhibit elevated IRT levels on testing (false positive). Follow-up testing is needed.

Premature infants often have abnormal newborn screening test results that are not the result of an underlying metabolic disorder. Preterm infants often have elevated 17-hydroxyprogesterone (17-OHP) and low thyroxine levels. The typically higher 17-OHP level in premature infants presents a difficulty in diagnosing congenital adrenal hyperplasia among this group of babies. Many states use weight-adjusted cutoff values to reduce the high false-positive rates seen with standard testing. Antenatal corticosteroid treatment does not seem to suppress 17-OHP levels. Transient hypothyroxinemia, with low thyroxine and normal

**BOX 112-18 Newborn Dried Blood Spot Screening****SCREEN UPON ADMISSION****Advantages:**

- Reliable for hemoglobinopathies (ie, sickle-cell anemia), galactosemia, and biotinidase deficiency
- Provides baseline amino acid and acylcarnitine levels
- May be more likely to detect fatty acid oxidation disorders caused by the infant's catabolic state
- Increases chance screening specimen will be drawn on every baby requiring neonatal specialized or intensive care

**Disadvantages:**

- Increased false positive and negative results for TSH (thyroid stimulating hormone)/17-OHP (17-hydroxyprogesterone) and IRT (immunoreactive trypsinogen, screens from CF, cystic fibrosis)
- Interpret abnormal results for CH, CAH, and CF with caution: many of these may normalize on a repeat screen

**SCREEN AT 48 TO 72 HOURS (IF FIRST ONE <24 HOURS)****Advantages:**

- Should be reliable for congenital hypothyroidism (CH, unless TSH primary), congenital adrenal hyperplasia (CAH), CF, and most aminoacidopathies (unless baby is receiving parenteral nutrition)
- 90% of first specimen abnormalities disappear

**Disadvantages:**

- Carnitine and fatty acid oxidation disorders may be masked if the infant is receiving adequate nutrition from parenteral nutrition
- Will not identify CH with delayed rise in TSH

**RESCREEN AT 28 DAYS OR UPON DISCHARGE (WHICHEVER OCCURS FIRST)**

Infants <34 weeks, gestation or <2,000 g

**Advantages:**

- For especially small premature babies, thyroid function may have matured to expected newborn levels
- May resolve (for most) any previous abnormal results such as multiple amino acids or carnitine elevations
- Especially beneficial for very low-birth-weight babies likely to have had more interventions that interfere with NBS results

**Disadvantages:**

- Cost of additional screening

thyroid-stimulating hormone levels, is common among sick preterm babies and is most often self-limited. Acute illness may further depress thyroid function and increase adrenal steroid production, contributing to persistent abnormalities on retesting. Preterm infants need to be monitored until normal test results are achieved. Infants with persistent abnormalities require assessment of thyroid function and may need treatment to reduce the risk of poor neurocognitive outcome related to hypothyroidism. Serial screening tests or diagnostic evaluation may be required based on local state health department requirements. Infants

with physical or metabolic signs suggestive of the condition should undergo an immediate evaluation for the suspected disorder.

### Cranial Ultrasonography Screening

In a preterm infant, limited cerebral autoregulation in association with vascular, cellular, and anatomic features of the developing brain result in vulnerability to hemorrhage and ischemic brain injury. Hemorrhagic lesions involve the germinal matrix (GM), and may extend into the ventricular system or be associated with parenchymal lesions in the brain. The GM involutes during the third trimester, by 34 to 36 weeks' PMA. Ischemic injury within the periventricular area is the injury pattern seen more commonly in less mature infants and is related to hypoperfusion and ischemia occurring along the end-zone regions of the long penetrating arteries that arise from the anterior, middle, and posterior cerebral arteries. Both hemorrhage and ischemic injury may occur coincidentally. White-matter injury may lead to nonhemorrhagic cerebral infarction, periventricular leukomalacia (PVL), or porencephaly. Ventriculomegaly (VM) may also occur because of loss of cerebral white matter in the absence of an intraventricular hemorrhage (IVH). Most IVH is evident by 3 days of age; 50% of hemorrhages occur within the initial hours following birth.

The American Academy of Neurology practice parameter on neuroimaging of the neonate recommends routine screening cranial ultrasonography in preterm infants between 7 and 14 days of age on all infants younger than 30 weeks' gestation. The initial study identifies IVH. The presence of cystic PVL within the first 2 weeks of age indicates an antenatal insult. A repeat study should be obtained between 36 and 40 weeks PMA to detect the presence of PVL and low-pressure VM. These 2 timeframes have been chosen as the most useful in terms of predicting long-term neurodevelopmental outcomes. However, from a clinical care perspective, diagnosing the GM hemorrhage or IVH early is often important. The Canadian Paediatric Society statement on routine screening cranial ultrasonography suggests that an earlier neurosonogram should be performed by the third day of life in infants with multiple early complications.

Follow-up studies should be obtained as clinically indicated. Because of the inverse relationship between brain injury and gestational age, an alternate approach has been suggested by Perlman and Rollins, who recommend an initial cranial sonogram between days 3 and 5 with 3 follow-up studies at 10 to 14 days of age, at 28 days of age, and before discharge for babies weighing less than 1,000 g at birth. The initial study at 3 to 5 days will identify 75% of hemorrhages in the extremely low-birth-weight preterm infant. The second ultrasound at 10 to 14 days of age will identify 84% of hemorrhages and detect early hydrocephalus and cyst formation. The 28-day scan identifies the presence of periventricular echogenicity and VM. The yield of these studies performed in more mature preterm infants decreases with increasing GA. Consequently the recommended periodicity for cranial ultrasonography screening in larger preterm infants is consistent with American Academy of Neurology

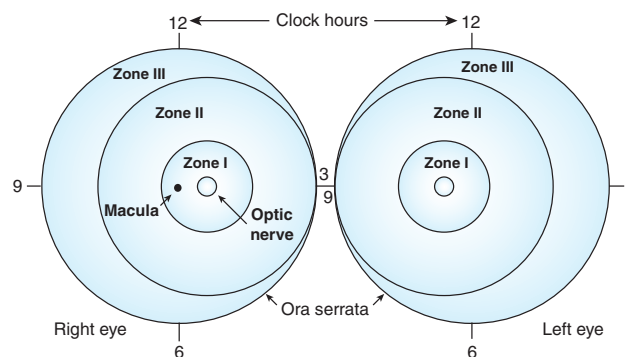
and the Canadian Paediatric Society guidelines. Although the American Academy of Neurology did not find sufficient evidence to recommend inclusion of conventional magnetic resonance imaging (MRI) of the brain at term postmenstrual age in addition to cranial sonography to assist in the prediction of neurodevelopmental outcome, recent research has increased understanding of the utility of this imaging technique in outcome prediction.

For full-term infants who exhibit neonatal encephalopathy with a history of birth trauma, low hematocrit, or coagulopathy, recommendations call for a noncontrast computed tomography (CT) scan to be performed. Infants whose CT scan is inconclusive should have an MRI performed between 2 and 8 days of age to assess the location and extent of the injury, information important in diagnosis and prognosis for the infant.

### Retinopathy of Prematurity Screening

ROP affects primarily premature infants weighing less than 1,500 g or who are born before 31 weeks' gestation. The incidence of ROP is inversely related to GA. ROP typically involves both eyes, is one of the most common causes of visual loss in childhood, and can lead to lifelong vision impairment and blindness. ROP is classified according to the severity of the changes in the developing blood vessels and the region of the retina into which these abnormal vessels have grown. The severity is referred to as the *stage* and the retinal regions as *zones* (Figure 112-8). Fifty percent of infants weighing 1,500 g or less at birth will develop some degree of ROP. For most preterm infants, ROP will regress as the infant matures. Approximately 10% of infants with ROP require medical treatment. Approximately 400 to 600 infants with ROP are classified as legally blind each year in the United States. Early treatment of severe ROP is important, producing significant reductions in unfavorable outcomes (retinal detachment, blindness, poor visual acuity).

Infants who are transferred back to the community hospital setting have been shown to be more likely to miss follow-up ophthalmologic care than infants remaining in tertiary care facilities. Infants not screened for ROP during their NICU hospitalization were more



**Figure 112-8** Retinopathy of prematurity is described by the examining ophthalmologist in terms of zones and stages, whereby the zone is the location of the retinopathy and the stage is the severity.

likely to miss follow-up care than infants assessed before hospital discharge. This tendency reinforces the need for communication between medical care providers and for written recommendations in transfer summaries that detail findings on the initial examinations (stage of ROP if present and zone to which the retina is vascularized) and specify the timing for subsequent follow-up evaluations.

The joint statement from the AAP, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus, and American Association of Certified Orthoptists entitled “Screening Examination of Premature Infants for Retinopathy of Prematurity” and the Canadian Paediatric Society policy statement “Retinopathy of Prematurity: Recommendations for Screening” provide guidelines for the timing of the initial and follow-up eye examinations and offer criteria to determine the need for treatment.

#### Who should be screened?

- Infants with a birth weight less than 1,500 g or who are 30 weeks’ gestation or younger
- Selected infants with a birth weight between 1,500 and 2,000 g or gestational age greater than 30 weeks who have experienced an unstable clinical course, including the need for cardiorespiratory support, or who are thought to be at high risk

Table 112-8 provides the appropriate timing of the first eye examination in these infants. The following schedule of follow-up examinations is recommended based on the examining ophthalmologist’s findings:

- **1-week or less follow-up for:**
  - Immature vascularization: zone I—no ROP
  - Immature retina extends into posterior zone II, near the boundary of zone I
  - Stage 1 or 2 ROP: zone I
  - Stage 3 ROP: zone II
  - Presence or suspected presence of aggressive posterior ROP
- **1- to 2-week follow-up for:**
  - Immature vascularization: posterior zone II
  - Stage 2 ROP: zone II
  - Regressing ROP: zone I

#### 2-week follow-up for:

- Stage 1 ROP: zone II
- Immature vascularization: zone II—no ROP
- Regressing ROP: zone II

#### 2- to 3-week follow-up for:

- Stage 1 or 2 ROP: zone III
- Regressing ROP: zone III

The presence of plus disease (dilated, tortuous posterior retinal blood vessels) in zones I or II suggests that peripheral ablation, rather than observation, is necessary. Treatment may also be initiated for any of the following retinal findings:

- Zone I ROP: any stage with plus disease
- Zone I ROP: stage 3 with no plus disease
- Zone II: stage 2 or 3 with plus disease

Treatment should generally be accomplished, when possible, within 72 hours of determination of treatable disease to minimize the risk of retinal detachment. The conclusion of acute retinal screening examinations should be based on age and retinal ophthalmoscopic findings (see Figure 112-8).

The following medications are used to dilate the infant’s eyes: amethocaine 1% (or benoxinate 0.4%), cyclopentolate 0.5% (Cyclogyl), and phenylephrine 2.5%. One drop of each preparation is instilled in each eye 30 minutes before the ophthalmologist’s arrival (ie, 0800 hr for a 0830-hr starting time) and repeated 10 minutes later. The eye drops are effective for up to 2 hours from the last installation. Infants with a darker iris may require a longer time and repeat drops for their pupils to dilate. A sucrose nipple can also be used for analgesia during the eye examination.

#### Immunizations

Diphtheria-tetanus-acellular pertussis (DTaP), inactivated polio vaccine (IPV), *Haemophilus influenza* type b conjugate (HiB), and pneumococcal conjugate vaccines are recommended. Current AAP recommendations include immunization of clinically stable premature and low-birth-weight infants at 2 months postnatal age. Vaccines should be preferentially administered in the anterolateral area of the thigh using a small needle.

**Table 112-8** Timing of First Eye Examination Based on Gestational Age at Birth

GESTATIONAL AGE AT BIRTH (IN WEEKS)	AGE AT INITIAL EXAMINATION (IN WEEKS)	
	POSTMENSTRUAL	CHRONOLOGIC
22 <sup>a</sup>	31	9
23 <sup>a</sup>	31	8
24	31	7
25	31	6
26	31	5
27	31	4
28	32	4
29 <sup>b</sup>	33	4
30 <sup>b</sup>	34	4
Older gestational age, high risk factors		4

<sup>a</sup>Guideline should be considered tentative rather than evidence-based for infants 22–23 weeks gestational age

<sup>b</sup>If necessary

From American Academy of Pediatrics Section on Ophthalmology, American Academy of Ophthalmology, American Association for Pediatrics Ophthalmology and Strabismus. Policy Statement: Screening Examination of Premature Infants for Retinopathy of Prematurity. *Pediatrics*. 2013;131:189–195.

The immune responses in preterm infants to diphtheria, pertussis, and polio antigens are similar to those seen with full-term babies. In contrast, the immunogenicity of HiB vaccine varies and is thought to be altered by the choice of conjugate protein, use of combination vaccine, and the infant's underlying medical condition. Antibody responses to vaccines in low-birth-weight and preterm infants are often less than those in term infants, though protective antibody levels are achieved. Reports of adverse side effects after immunization of sick preterm infants have noted an increase in the incidence of apnea and cardiorespiratory events after the first vaccinations. These events are most common among infants with preexisting apneas, bradycardias, and desaturations at the time of DTaP-IPV-HiB immunization, some of whom may require intervention. However, concerns about potential cardiorespiratory events should not preclude timely immunization. Infants at risk should be appropriately monitored after vaccination.

### **Hepatitis B Vaccine**

The timing of the initial hepatitis B vaccine administration in preterm and low-birth-weight infants is based on birth weight and maternal hepatitis B surface antigen (HBsAg) status, given that immunogenicity is poor in newborns weighing less than 2,000 g when hepatitis B vaccine is given at birth. Infants born weighing less than 2,000 g to HBsAg-negative mothers should receive hepatitis B vaccine at 30 days of age or at the time of hospital discharge if this occurs before 30 days. If the mother's hepatitis B status is not known at the time of delivery, then hepatitis B vaccine should be given within 12 hours of birth. Hepatitis B immune globulin should also be administered within 12 hours for newborns weighing less than 2,000 g and within 7 days if the newborn is greater than 2,000 g and the mother is confirmed HBsAg positive.

### **Influenza Vaccine**

Rarely, a chronically ill infant may require continued hospitalization at 6 months of age. The first of 2 doses of inactive influenza vaccine should be administered at 6 months postnatal age, particularly for infants with chronic lung disease. It is important to encourage families to immunize all household contacts and caregivers if the infant is less than 6 months of age. In 2009, New York State passed legislation requiring that hospitals with a NICU offer flu vaccine to the parents and anticipated caregivers of newborns currently in the NICU during the flu season.

### **Rotavirus Vaccine**

The AAP recommends routine immunization of infants with either RV1 (live, oral human attenuated rotavirus vaccine) or RV5 (live, oral human-bovine reassortant rotavirus vaccine). If RV5 is used, it should be administered orally in a 3-dose series at 2, 4, and 6 months of age. If RV1 is used, it should be given orally in a 2-dose series at 2 and 4 months of age. Rotavirus vaccine may be administered to infants with minor acute illness. Current recommendations include administration of

the first dose of rotavirus vaccine between 6 weeks and 14 weeks, 6 days of age.

Preterm infants should be immunized on the same schedule and with the same precautions as term infants if they are clinically stable and meet the age requirements for rotavirus vaccine (6 weeks to 14 weeks and 6 days of age for the first dose). Because vaccine strains of rotavirus are shed in the stools of immunized infants, preterm infants in NICUs or nurseries who are age-eligible and clinically stable may be immunized at the time of discharge. If an immunized preterm infant is readmitted to the NICU within 2 weeks after vaccine administration, contact precautions should be instituted and maintained for 2 to 3 weeks after vaccine administration.

### **In-Hospital Respiratory Syncytial Virus Prophylaxis With Palivizumab**

Respiratory syncytial virus (RSV) is responsible for a significant percentage of lower respiratory tract infections (bronchiolitis and pneumonia) in young children. Immune prophylaxis is recommended for high-risk very preterm infants, preterm babies <32 weeks, 0 days' gestation with chronic lung disease (defined as oxygen requirement for at least 28 days after birth), infants <12 months of age with hemodynamically significant respiratory compromise affecting the infant's ability to clear secretions, or infants <24 months of age with profound immunocompromise. The physician should be familiar with local and regional variations in the onset and duration of RSV activity because these variations will guide when RSV immune prophylaxis should be initiated. Data from the Centers for Disease Control and Prevention National Respiratory and Enteric Virus Surveillance System suggest that the annual seasonal peak for RSV infection begins in July in Florida, in the remainder of the South in October, and in the Northeast during November. Highest RSV activity is in October, late December, and early January in Florida, the remainder of the South, and in the Northeast, respectively. Seasonal duration varies across the US from 13 weeks in the New England States (HHS region 1) to 27 weeks in Florida (HHS region 4; however the seasonal duration in the other states comprising region 4 is 22 weeks).

Family-centered care is integral to the functioning of most neonatal units nationwide. Siblings, parents, and grandparents, as well as various health professionals, are in contact with vulnerable infants, thus posing frequent potential infectious exposures including to RSV. Consequently, some physicians have advocated RSV immune prophylaxis with palivizumab in preterm infants hospitalized during RSV season. Studies have demonstrated that extremely preterm infants younger than 29 weeks PMA are able to mount a protective immune response to 15 mg/kg of palivizumab. Seventy percent of infants studied were able to maintain protective palivizumab concentrations 2 weeks after the initial dose. Less than 25% of infants maintained protective concentrations at 4 weeks after administration. Mid-point concentrations (2 weeks after prophylaxis) were higher after second and third palivizumab doses among the hospitalized cohort of infants. These findings have



been confirmed by other investigators. Palivizumab prophylaxis is not recommended for prevention of RSV nosocomial disease.

### Positional Plagiocephaly

Positional or deformational plagiocephaly is common among sick and preterm infants or may result from positioning in a restrictive uterine environment. The calvarial bones of the cranium are more malleable in the preterm infant than in their healthy peers, increasing the infant's susceptibility to external molding forces. This circumstance results in unilateral flattening in the parieto-occipital region, with associated anterior advancement of the ipsilateral ear and anterior displacement (bossing) of the ipsilateral forehead. The head shape resembles a parallelogram. The weight of the infant's head and the child's overall decreased tone and strength are contributing factors as well. Preterm and sick infants, particularly those who require prolonged ventilatory support or who experience neurologic compromise, more often spend extended time with their heads in fixed positions that promote development of a long, narrow scaphocephalic-shaped head. For a full discussion of plagiocephaly, see Chapter 316, Positional Deformational Plagiocephaly.

## ASSESSMENT AND MANAGEMENT OF PAIN

Early repetitive pain experiences result in permanent changes in pain processing, neuroendocrine function, and development that contribute to abnormal pain thresholds, increased anxiety and stress disorders, and atypical behaviors that include exaggerated startle responses and hypervigilance. Attention should be paid to providing appropriate analgesia to alleviate procedural and postoperative pain. Several measures are available to facilitate assessment of neonatal pain. Among the commonly used measures are the Premature Infant Pain Profile (PIPP), Neonatal Infant Pain Score (NIPS), Neonatal Facial Coding System (NFCS), Neonatal Pain, Agitation and Sedation Scale (N-PASS), Cry, Requires Oxygen, Increased Vital Signs, Expression, Sleeplessness (CRIES), and COMFORT Scale.

## DEVELOPMENTALLY SUPPORTIVE CARE

Preterm and sick infants experience repetitive painful stimuli and prolonged stress, which has both short- and long-term physiological effects on the child. A developmentally supportive neonatal care environment that integrates noise and bright-light reduction, cycling of light exposure to mimic physiological diurnal variations, and grouping of care activities has demonstrated efficacy in supporting the neurodevelopment and self-regulation abilities of the sick and preterm infant. Benefits attributed to developmentally appropriate care include enhanced growth and behavioral outcomes, decreased need for respiratory support, and decreased length of hospitalization. Environmental modifications include

flexed positioning, use of containment to promote state regulation, gel and shape-retaining pillows to provide head support and reduce positional plagiocephaly, adjustable ambient lighting with the use of procedure lights, incubator covers, limiting decibel levels for continuous and transient sounds to less than 50 dB (maximum of 70 dB for transient sounds), and modifying handling and touch in synchrony with the infant's sleep-wake cycles and behavioral responses (cues). For comparison purposes, 45 dB corresponds to noise levels of normal living, talking, or background radio sound; 70 dB is equivalent to average roadway traffic or a vacuum cleaner or quiet hair dryer 1 m away from the ear.

Infants who are most sensitive to stimulation, particularly tactile contacts, are babies who are less mature (<32 weeks PMA), have chronic cardiorespiratory conditions (BPD, cardiac disease), and demonstrate physiological and behavioral disorganization. Parents should be encouraged to touch and hold their infant, providing tactile experiences appropriate to the baby's ability to tolerate stimulation and handling. Beneficial forms of stimulation for preterm and sick infants include nonnutritive sucking, kangaroo (skin-to-skin) care, and infant massage. Nonnutritive sucking provides comfort, facilitates state regulation, and enhances growth and development. Kangaroo care or skin-to-skin contact has demonstrated benefits, including enhanced physiological stability with fewer episodes of apnea and bradycardia, improved sleep-wake cycles, reduced infection, reduced hospital length of stay, and improved lactation and breastfeeding. Infant massage is also beneficial, but requires assessment of the infant's responses to tactile and kinesthetic stimulation (handling and position changes).

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Born Early (Preterm): At the Hospital* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Born Early (Preterm): Health Concerns* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)

### Medical Decision Support

- *Clinical Protocols* (guidelines), Academy of Breastfeeding Medicine ([www.bfmed.org/Resources/Protocols.aspx](http://www.bfmed.org/Resources/Protocols.aspx))
- *Cry, Requires Oxygen, Increased Vital Signs, Expression, Sleeplessness (CRIES) Instrument* (scale), Bildner J ([prc.coh.org/pdf/CRIES.pdf](http://prc.coh.org/pdf/CRIES.pdf))
- *Guidelines for Air and Ground Transport of Neonatal and Pediatric Patients* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Guidelines for Perinatal Care*, 7th ed (book), American Academy of Pediatrics and American College of Obstetricians and Gynecologists ([shop.aap.org](http://shop.aap.org))
- *National Respiratory and Enteric Virus Surveillance System (NREVSS)* (Web site) Centers for Disease Control and Prevention ([www.cdc.gov/surveillance/nrevss](http://www.cdc.gov/surveillance/nrevss))

- *Neonatal Facial Coding System* (scale), Centre for Evidence Based Physiotherapy ([www.cebp.nl/vault\\_public/filesystem/?ID=1425](http://www.cebp.nl/vault_public/filesystem/?ID=1425))
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- *Newborn Screening ACT Sheets and Confirmatory Algorithms*, American College of Medical Genetics ([www.ncbi.nlm.nih.gov/books/NBK55827](http://www.ncbi.nlm.nih.gov/books/NBK55827))
- *Nutritional Support of the Very Low Birth Weight Infant* (toolkit), California Perinatal Quality Care Collaborative ([www.cpqcc.org/quality\\_improvement/qi\\_toolkits/nutritional\\_support\\_of\\_the\\_vlbw\\_infant\\_rev\\_december\\_2008](http://www.cpqcc.org/quality_improvement/qi_toolkits/nutritional_support_of_the_vlbw_infant_rev_december_2008))
- *Online Low Flow Oxygen Calculator* (clinical calculator), Auckland District Health Board ([www.adhb.govt.nz/newborn/Guidelines/Respiratory/Oxygen/ActualO2.htm](http://www.adhb.govt.nz/newborn/Guidelines/Respiratory/Oxygen/ActualO2.htm))
- *Premature Infant Pain Profile (PIPP)* (scale), Centre for Evidence Based Physiotherapy ([www.cebp.nl/media/m347.pdf](http://www.cebp.nl/media/m347.pdf))

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## Chapter 113

# DISCHARGE PLANNING FOR THE HIGH-RISK NEWBORN REQUIRING INTENSIVE CARE

Christina Long, DO; Deborah E. Campbell, MD

## INTRODUCTION

One of the most important aspects of caring for a premature or sick infant is the preparation for the infant's discharge from the hospital. The most medically complex infants have often spent weeks or months in a neonatal intensive care unit (NICU) and require a broad array of medical and other services for their postdischarge health care, including primary pediatric care, subspecialty follow-up, home or public health nursing care, early intervention services, extensive care coordination, and family support.

Comprehensive discharge planning is as important as the medical care that the infant received in the NICU; it requires a team approach that includes the neonatologist, pediatric specialists, the infant's primary care physician, hospital nurses, social worker, lactation consultant, therapists, and most important, the infant's family. The family is central to the discharge planning process and vital to its success. Discharge planning is necessary not only for infants who will be discharged home with their families, but also for infants who may be transferred to a transitional or chronic-care facility, such as a children's rehabilitation center.

The transition from the NICU to home can be stressful for the neonate and the family. Preparing the family for a coordinated discharge, with adequate opportunities for parents to assimilate the staff's teaching and to ensure availability of the necessary resources, can help alleviate many of the fears parents have about taking home their premature or medically fragile infant. The infant's primary care physician is an integral member of the team as coordinator of the child's medical home and overseer of the infant's ongoing health and developmental care needs. The hospital-based medical team is responsible for engaging the primary care physician, and ensuring complete disclosure of the infant's medical information and the required follow-up care services. The neonatal team needs to ensure that the pediatrician is also fully informed about the family's material resources, as well as psychosocial and other support needs, so that the parents may properly care for and nurture their infant at home as well as handle their other family responsibilities.

Every neonatal or special care unit has basic criteria that must be met for the infant to be discharged from the acute-care setting. Most units require that an infant demonstrate a sustained pattern of weight gain with effective oral feeding by breast or bottle, be able to maintain a normal body temperature under ambient (thermoneutral) conditions, and maintain a stable cardiorespiratory status with resolution of

apnea, bradycardia, and desaturations. Additional criteria for discharge are evidence of active parental involvement and demonstrated parental ability to adhere to the child's prescribed care. Arranging for timely, appropriate medical follow-up after the infant's hospital discharge is another important aspect of the discharge planning process. Families in rural and other underserved communities may face particular challenges in accessing the needed specialized follow-up care their infants require, placing an additional burden on the family, discharging hospital, and primary care physician.

## FEEDING AND NUTRITION

### Discharge Criteria

Despite advances in nutritional support with attention to early aggressive nutrition, many low-birth-weight or chronically ill infants exhibit slow or inadequate postnatal growth; and among the smallest, least-mature infants, nearly universal growth failure is evident at discharge. The goal of postdischarge nutrition is to provide the necessary nutrients to optimize growth and bone mineralization and promote a pattern of weight gain and head growth that supports appropriate catch-up growth, yet prevents excessive or inappropriate weight-gain patterns that may predispose the infant to adverse health consequences, such as metabolic syndrome later in life. Infants at risk for poor growth include preterm, low-birth-weight, and severely growth-restricted infants, as well as babies born with anatomic abnormalities or neurologic disorders that interfere with effective oral feeding, limit nutrient utilization, or increase metabolic requirements that are not easily met through typical feeding regimens. Infants with complex nutritional needs include those with chronic lung disease, short bowel syndrome, cholestasis, and cardiac disease.

Individual hospitals and health systems have established criteria regarding the specific weight an infant must attain before discharge; many units aim for a weight of 1,800 to 2,000 g. Significant variation exists in the actual discharge weights of NICU infants, given that the infant's comorbidities often determine the timing of discharge, as does the availability of community resources to support the infant with continuing feeding issues and the infant's mode of enteral intake at discharge—oral or via a feeding tube (nasogastric or gastrostomy). Insurance coverage for the infant's post-hospital care may support an earlier discharge for the infant with home nursing care.

For infants with feeding difficulties, the neonatal team, in collaboration with a speech pathologist with feeding expertise, nutritionist, or lactation consultant, must devise a feeding plan with the parents that will support the infant's nutrition and weight gain and that is feasible for the family to implement. A feeding plan should include the type of feeding, amount of feeding, frequency and method of feeding, and any special instructions necessary. For example, some infants may require specialty formulas that require special preparation. The parents and primary care physician should understand the feeding regimen, the nutrition and weight-gain goals, and the parents need to demonstrate their ability to feed their infant appropriately.

During the course of the infant's hospitalization the baby's weight and other growth parameters, length, and head circumference should have been plotted on a standardized infant growth curve, such as the Fenton (Babson-Benda intrauterine and postnatal growth chart) or Olsen intrauterine growth curves that track growth of preterm infants from 22 to 50 weeks' gestation or the 2000 standard growth curves from the Centers for Disease Control and Prevention. The weight-gain goal at discharge and during the transition home is typically 20 to 30 g/day, with an intake of 100 to 120 kcal/kg/day and a volume intake of at least 180 mL/kg/day, unless a particular reason exists that an infant requires fluid restriction. Experts have recently recommended that a more appropriate weight-gain target to promote optimal growth should be 14 to 16 g/kg/day. Many recovering preterm infants without feeding or cardiorespiratory problems who are fed on demand, without volume restriction have daily intakes that range between 170 and 220 mL/kg/day. Preterm infants who are receiving exclusively expressed human milk may exhibit a reduced weight-gain pattern. However, if the infant is consuming more than 170 to 180 mL/kg/day of human milk, then growth patterns comparable to formula-fed preterm infants are seen. Acceptable weight gain for an infant receiving only human milk should also be 20 to 30 g/day. It is important to note that infants discharged home on calorie-dense, enriched feedings may consume smaller feeding volumes because of the earlier satiety induced by the enriched formula's higher fat content. Gastroesophageal reflux is a common problem among preterm and some term infants and may also limit feeding volume and weight gain.

The following aspects of the hospital feeding plan assessment inform a discharge feeding plan:

1. Type of feeding—unfortified or fortified human milk, formula, or a combination
  - Human milk fortifier is often discontinued when the infant reaches a weight of approximately 1,800 g.
  - 24 kcal/oz premature formula (Similac Special Care Formula or Enfamil Premature Formula) may be continued until the infant attains a weight of 1,850 to 2,400 g (4.0–5.5 lb).
  - Some states' Special Supplemental Nutrition Program for Women, Infants, and Children (WIC programs) will provide these formulas postdischarge until the infant reaches 3 to 4 months postnatal age (approximately term-corrected age).
  - 22 cal/oz transitional or postdischarge formula (Enfamil Enfacare or Similac Neosure) is started when the preterm infant achieves a weight of 1,850 to 2,400 g and is continued until optimal growth is achieved, nutritional deficiencies are corrected, or the infant reaches 6 to 9 months corrected age.
  - Sick preterm infants with birth weights between 1,500 and 1,850 g who have required parenteral nutrition and diuretics and are exhibiting suboptimal growth may also benefit from transitional or postdischarge formula if breastfeeding is not the chosen feeding method.



2. Volume of feedings—milk intake (in mL/kg/day) and volume per feeding if bottle fed
  - Goal is an intake of approximately 160 to 180 mL/kg/day.
  - Intakes of less than 160 mL/kg/day are suboptimal.
3. Method of feeding—breast, bottle, lactation aid, cup, tube feeding (oro- or nasogastric tube or gastrostomy tube) or a combination of methods
  - Feeding is suboptimal if the infant cannot consume all feeds orally because of fatigue or poor coordination.
  - Assess the adequacy of the infant's latch and suckling if breastfeeding.
  - Adequacy of growth—average daily weight gain and weekly rate of linear and head growth
  - Growth is deemed adequate when weight (>20 g/day), length (>1 cm/week), and head circumference (>0.5 cm/week) are within normal for corrected age or improving.
  - Growth is inadequate if the weight gain is less than 20 g/day or length gain is less than 0.5 cm/week.
4. Adequacy of nutrition—biochemical monitoring of nutritional status (blood urea nitrogen, phosphorus, and alkaline phosphatase) Oral multivitamin supplementation may be required for the infant who is breastfeeding or ingesting less than 32 oz of formula per day.
  - Until the infant is taking in at least 500 mL/day of formula, vitamin D in a dose of 400 IU/day should be provided.
  - Preterm infants who are exclusively breastfeeding should begin elemental iron supplementation at 2 months of age at a dose of 2 to 4 mg/kg/day.
  - Formula-feeding, preterm infants should receive an iron-fortified formula.

### Transitioning to Breastfeeding

Mothers who have been expressing milk during their infant's hospitalization should be assisted in transitioning to breastfeeding in advance of the infant's discharge. Clinical guidelines are available that offer information for use by both physicians and mothers. High-risk infants who have been receiving fortified feeds should be monitored at least 1 week on unfortified human milk to properly assess the adequacy of growth and nutrient intake. Infants with signs of persistent inadequate growth and nutritional deficiencies (low serum albumin and blood urea nitrogen levels, and elevated serum alkaline phosphatase) and infants who have difficulty completing their feedings will benefit from continued nutritional supplementation after discharge. Determining whether the infant can be fed on demand or needs to continue on a schedule is another important factor to ensure that infants with chronic conditions, feeding difficulties, and feeding fatigue achieve the desired intakes.

Optimally the goal is for the infant to breastfeed rather than for the mother to continue to express milk for administration by bottle. A common parental concern relates to the adequacy of the infant's intake once the mother is no longer able to monitor the baby's oral intake visually. Information and guidance are necessary to foster maternal confidence in her

ability to nourish her infant adequately without benefit of a volume measure. Pre- and postfeeding weights can be measured as a tool to assist mothers in assessing their infant's intake during a feeding. The mother should be counseled to continue expressing or pumping milk at least 3 times daily to maintain her milk supply as she is transitioning the baby for exclusive breastfeeding. Iron and multivitamin supplementation should be started once the infant is receiving unfortified human milk.

### Maintaining the Mother's Milk Supply

Mothers who are expressing milk for their hospitalized infant must often contend with a decreasing or insufficient milk supply during the infant's extended hospital stay. As an adjunct to increasing the frequency of breast pumping, some women use galactagogues, pharmacologic and herbal products, to boost their milk supply. The evidence to support use of these varied medications and herbal substances is limited, based on small studies. Domperidone and metoclopramide are the 2 most widely prescribed medications. Domperidone is not approved for marketing in the United States by the US Food and Drug Administration (FDA), but is available in Canada and other countries. Domperidone is also available from some compounding pharmacies in the US. Metoclopramide (Reglan) use is controversial. It has been shown to be effective in increasing and maintaining milk production in some women in a few small studies. Metoclopramide increases prolactin secretion and is typically prescribed in a dosage of 10-mg tablet taken orally, 3 to 4 times per day for 1 week, followed by a 1-week period during which the medication is tapered. Continuing kangaroo care after discharge is another technique that can improve milk production and encourage faster transition to breastfeeding. Some breastfeeding women prefer to use herbal products or natural foods to increase their milk supply. Herbs commonly used include fenugreek, goat's rue, milk thistle, anise, basil, blessed thistle, fennel seeds, and marshmallow. No standard dosing, preparation, or combinations of these substances exist, and they are not approved by the FDA. Fenugreek, a member of the pea family listed as generally safe by the FDA, may be consumed in capsules or as a tea; side effects are rare, but it can cause hypoglycemia. Goat's rue is recommended in several European countries; used alone, no side effects have been reported. Milk thistle is an herb that, according to the American Herbal Products Association, may be safely consumed during lactation. Mother's milk tea is a blend of plants used to increased milk supply; it is promoted as having no caffeine, and none of the ingredients have pharmacologic actions. Other herbal teas considered safe during lactation include chicory, orange spice, peppermint, raspberry, red bush (rooibos, hibiscus, sorrell) tea, and rose hips. Although the FDA does not approve the use of herbal medicines for lactation purposes, many have been proven safe. However, many herbs, particularly those containing alkaloids, are contraindicated in lactation, including aloe, buckthorn bark, buckthorn berry, cascara sagrada bark, coltsfoot leaf, senna leaf, peppermint oil, caraway oil, kava kava, petasites root, Indian



snakeroot, rhubarb root, senna leaf, Chinese ephedra (ma huang), and uva ursi.

### Special Considerations

If the infant does not gain appropriate weight with unfortified human milk, then 2 to 3 feedings of an enriched premature infant formula (prepared as 22–24 cal/oz; Special Care Formula or Enfamil Premature) or a transitional/postdischarge formula (prepared as 22–24 kcal/oz; Neosure or Enfacare) should be added to the infant's feeding regimen (Table 113-1 provides formula modifications). Several state WIC programs will provide premature infant formulas after hospital discharge if the preterm infant is younger than 90 days postnatal age. The infant should be monitored closely for improved growth. In general, human milk fortifier and preterm formulas typically used during the NICU hospitalization are not usually recommended after discharge because the nutrient content is greater than the infant's needs and because ensuring correct preparation can be difficult. Human milk fortifier is typically discontinued when an infant reaches approximately 36 weeks postmenstrual age and weighs 1,800 to 2,000 g. If suboptimal weight gain or growth continues, then additional supplementation should be provided, with an increase in the caloric density to 24 to 30 kcal/oz.

A similar feeding assessment and formula adjustment should be performed for the formula-feeding preterm infant.

During the hospital course, infants with cardiac, renal, pulmonary, and gastrointestinal disease may require increased calories. This requirement for special nutrition often continues after discharge. Such infants must be discharged home on an appropriate formula that provides adequate nutrition for their metabolic and growth needs. For example, infants with renal disease who are not breastfeeding often require a formula with a low solute load and low phosphorous content (Similac PM 60:40). Infants with a cleft lip and palate require a comprehensive feeding assessment to determine the extent of feeding difficulties and whether special nipples or an obturator are needed to facilitate oral feeding. Babies born with a cleft lip or palate can successfully breastfeed, although the infant may require an obturator if the cleft palate is large.

### Eligibility for the Special Supplemental Nutrition Program for Women, Infants, and Children

An important resource for neonates ready for discharge from the NICU is the WIC program. WIC is a federal-grant program administered by federal and state agencies in each of the 50 states, the District of Columbia, Native-American tribal organizations, and 5 territories that include Northern Mariana, American Samoa, Guam, Puerto Rico, and the Virgin Islands. The WIC program targets the low-income population with infants and children who are at nutritional risk. The program provides supplemental nutritious foods, nutrition education, screening, and referrals to other health, welfare, and social service centers. Applicants must meet all of the eligibility requirements, including categorical, residential, income, and nutritional risks.

Categorical eligibility includes pregnant women (during pregnancy and up to 6 weeks after birth), postpartum women (up to 6 months after the birth of the infant or the end of pregnancy), breastfeeding women (up to the infant's first birthday), infants (up to 1 year of age), and children (up to 5 years of age). Applicants must live in the state in which they apply and have an income at or below an income level or standard set by the state agency to which they apply. Applicants must be seen by a health professional who determines whether the applicant meets nutritional risk criteria. WIC-eligible patients should be referred for enrollment before hospital discharge.

### TEMPERATURE REGULATION

An infant's ability to maintain a normal body temperature is another important criterion used to determine readiness for hospital discharge. This is especially important for low-birth-weight infants and babies exhibiting poor growth caused by a prolonged illness, feeding difficulties, or feeding restrictions that limit fluid and caloric intake. Infants who have underlying neurologic dysfunction may also exhibit difficulty with temperature regulation. The infant who is ready for discharge should be able to maintain thermoneutrality when dressed in infant clothing and covered with a blanket. A normal body temperature in the range of 97.7°F to 99.5°F (36.5°C–37.5°C) with the infant in an open bassinet should be maintained for at least 24 hours. If any evidence of temperature instability exists, the infant should not be discharged. Infants at less than 34 weeks gestation are least likely to be able to maintain body temperature in an open bassinet, although more mature infants may also exhibit difficulty with temperature regulation because they are recovering from serious illness, have limited adipose stores, or have high energy expenditure associated with learning to feed or ongoing cardiorespiratory disease. Infants who are unable to maintain their body temperature under routine ambient environmental conditions should continue to be cared for in a heated isolette. An additional important factor to consider relates to the infant who exhibits a change in the ability to maintain body temperature without a change in the environmental conditions. Temperature instability is a nonspecific, although often present, sign suggestive of infection.

### RESPIRATORY

#### Home Oxygen Therapy and Pulse Oximetry

Some infants discharged from neonatal units will have residual lung disease requiring supplemental oxygen therapy at home. The decision regarding an infant's need for home oxygen therapy is often based on a combination of objective and subjective criteria. The infant's clinical care needs must be balanced with the parents' caregiving responsibilities at home and an assessment of the parents' ability or desire to have their infant home on oxygen. Some parents will prefer having their infant transition to a chronic-care or rehabilitative facility until the infant no longer requires oxygen. Other parents will undertake the challenge of

**Table 113-1**     **Formula Adjustments**

FORMULA	CALORIES DESIRED	MIXING INSTRUCTIONS (WATER)	FORMULA POWDER	FINAL VOLUME
Standard 20 cal/oz	22	5.5 oz	3 scoops	6 oz
	24	5 oz	3 scoops	10 oz
	26	3 oz	2 scoops	3.5 oz
	27	8.5 oz	6 scoops	10 oz
Similac Neosure 22 cal/oz	20	4.5 oz	2 scoops	5 oz
	24	5.5 oz	3 scoops	6 oz
	26	5 oz	3 scoops	5¾ oz
	27	8 oz	5 scoops	9 oz
Enfamil EnfaCare Lipil 22 cal/oz	20	4.5 oz	2 scoops	5 oz
	24	5.5 oz	3 scoops	6 oz
	26	5 oz	3 scoops	5.5 oz
	27	8 oz	5 scoops	9 oz
Neocate 20 cal/oz	20	3.5 oz	4 scoops	4 oz
	22	4 oz	4.5 scoops	4.5 oz
	24	5 oz	7 scoops	6 oz
	27	7 oz	5 scoops	8 oz
Pregestimil or Nutramigen 20 cal/oz	22	5.5 oz	3 scoops	6 oz
	24	5 oz	3 scoops	5.5 oz
	26	3 oz	2 scoops	3.5 oz
	27	7 oz	5 scoops	8 oz
Nutramigen liquid concentrate	22	11 oz	1 can concentrate	24 oz
	24	9 oz	1 can concentrate	22 oz
	26	7 oz	1 can concentrate	20 oz
	27	6 oz	1 can concentrate	19 oz
Human milk fortified with standard formula	22	4 oz HM	¾ Tsp	—
	24	3 oz HM	1 Tsp	—
	26	6 oz HM	1 scoop	—
	27	5.5 oz HM	1 scoop	—
Human milk fortified with Neosure	22	6 oz HM	1¼ Tsp	—
	24	6 oz HM	2½ Tsp	—
	26	5 oz HM	1 Tbsp	—
	27	6 oz HM	1 scoop	—
Human milk fortified with Enfamcare	22	6 oz HM	1 Tsp	—
	24	4 oz HM	1¼ Tsp	—
	26	5 oz HM	1 Tbsp	—
	27	3 oz HM	2 Tsp	—

combining parenting with medical caregiving to bring their baby home sooner. Additional considerations include availability of home health care support, local equipment vendors, and the expertise of the child's primary care physician who will be managing the infant's continuing respiratory care needs at home.

Controversy exists regarding specific guidelines for discharging infants on home oxygen therapy. The concentration of oxygen to be used, its duration, the need for cardiorespiratory monitoring versus pulse oximetry, and strategies for weaning the infant from oxygen are issues of debate. Consultation with pediatric pulmonary specialists who will participate in the infant's postdischarge medical care is an additional important aspect of discharge planning for these infants (see Box 113-1). Individual hospital policies delineate the specific criteria for home oxygen therapy.

Factors to consider when deciding on the necessity for home oxygen therapy include:

- The effect of supplemental oxygen on carbon dioxide retention should be considered before deciding on an oxygen flow.

- Most infants with chronic lung disease are not ready for discharge until their supplemental oxygen requirement is less than 0.5 L/min delivered through a nasal cannula.
- The safety of short-term disconnection from supplemental oxygen should be assessed before discharge.

Assessment of oxygenation during sleep with continuous overnight oximetry or polysomnography is recommended when weaning infants from supplemental oxygen. Discontinuation of oxygen therapy should be based on clinical assessments and documentation of adequate oxygenation in room air.

Preterm infants with residual or chronic lung disease often have brief arterial oxygen saturations less than 90% during feedings, periods of wakefulness, and sleep that are not associated with apnea, bradycardia, or cyanosis. Infants with chronic lung disease are also more likely to have severe oxygen desaturations less than 80%. Improved survival rates and reduced morbidity (chronic lung disease, retinopathy of prematurity) without an increase in cerebral palsy have been

**BOX 113-1 Discharge Criteria for Home Oxygen Therapy**

- Maintains oxygen saturations above 92%–93%
- Can cope with short periods without oxygen if the nasal cannula is removed or dislodged
- No apneic events for a predetermined period
- Immunizations up to date, and palivizumab prophylaxis as appropriate to the time of year for respiratory syncytial virus activity for the region where the child resides
- Parents and caregivers capable of caring for infant on home oxygen therapy
- Satisfactory home environment with a functioning telephone
- Satisfactory home environment with functioning electricity and adequate, functioning electrical outlets
- Home care visit completed (before discharge)
- Parents and caregivers trained on use of oxygen, equipment, and cardiopulmonary resuscitation
- Advice given for smoking cessation
- Advice given regarding avoidance of open-flame use in the presence of oxygen
- Parents or caregivers advised to travel with cylinders and inform their home and vehicle insurance companies
- Appropriate resources for parental help in place and emergency contact telephone numbers given to parents
- Communication with the primary care pediatrician completed (before discharge)

Derived from Balfour-Lynn I, Primhak R, Shaw B. Home oxygen therapy for children: who, how and when? *Thorax*. 2005;60:76–81.

observed among infants born less than 27 weeks' gestation who are maintained with oxygen saturations in the range of 84% to 94%. Desaturations or bradycardias that occur without apnea suggest airway obstruction. Although most neonatal units will not discharge a preterm infant until at least 34 weeks' postmenstrual age, if the decision is made to send such an infant home before 34 weeks' postmenstrual age, then the option of a brief period of home monitoring should be considered, given that episodes of prolonged desaturation for more than 4 seconds occur often during periodic breathing or hypoventilation. Infants who continue to exhibit cardiorespiratory instability with recurrent episodes of desaturation, apnea, or bradycardia requiring intervention should not be discharged from the hospital. The frequency of these episodes and the interventions required may be useful in determining the feasibility of the infant transitioning to a chronic-care facility versus remaining in an acute-care hospital.

Experts recommend that infants with residual lung disease and infants at risk for developing pulmonary hypertension be discharged on home oxygen therapy if they are unable to maintain their oxygen saturation above 93% while breathing ambient (room) air. Infants with chronic lung disease whose oxygen saturation is maintained above 93% on home oxygen with low-flow oxygen have been shown to have a reduced risk of sudden infant death, improved weight gain, lower pulmonary artery pressure and airway resistance, and fewer hypoxemic episodes. The goal for oxygen therapy is to maintain the oxygen saturation equal to or greater than 95% ( $\text{SpO}_2$  range 95%–98%). Oxygen, however, is not benign. Oxygen toxicity can occur in premature infants and contribute to ongoing lung injury, in addition to inhibiting lung healing.

Low-birth-weight infants, in particular very low-birth-weight (VLBW) infants, with severe bronchopulmonary dysplasia (BPD) exhibit significantly lower mean  $\text{SpO}_2$  levels during feeding at 2 to 6 months

corrected age. Infants with severe BPD have higher rates of growth delay (weight <10th percentile) during this period of time as well.

Infants with documented persistent apnea also require home monitoring. Some infants with persistent feeding difficulties may have increased oxygen or air-flow requirements to prevent desaturations during feeding. These infants typically have poor oromotor coordination and may have associated posterior pharyngeal dysfunction causing airway collapse. Provision of low-flow air or low concentrations of oxygen may be beneficial in preventing episodes of desaturations or bradycardia during feeding. A feeding assessment by a qualified speech pathologist with infant feeding expertise will facilitate making this diagnosis and deciding the need for supplemental flow or oxygen during feeding.

After requirements for discharge are met, the required home oxygen equipment (Box 113-2) must be ordered and delivered, and the parents and other caregivers properly trained in the equipment use. Another important decision is the type of home monitoring that is necessary for the infant—a cardiorespiratory monitor or a pulse oximeter. Pulse oximetry is a simple, noninvasive technique for measuring and monitoring arterial oxygenation saturation. However, no evidence has been found that pulse oximetry improves the outcome of babies on home oxygen therapy. Pulse oximetry is notable for frequent false alarms, especially when the infant is active. In addition, oxygen saturation is only 1 measurement of an infant's respiratory status. A sick infant may still maintain normal oxygen saturation while receiving oxygen despite changes in other physiological parameters. Therefore the issue of discharging an infant with pulse oximetry remains controversial, although it is helpful in the periodic assessment of the infant's status with measurement of the infant's oxygenation during activity (bathing, crying), sleep, feeding, and while in a vehicle safety seat or infant seat.

Most third-party insurers have policies guiding their approval process for home oxygen therapy and

### BOX 113-2 Equipment Required for Home Oxygen Therapy

- Oxygen concentrators are preferred with a back-up cylinder and portable cylinder for use during travel.
- Oxygen concentrators require 2 outlets.
- Low-flow meters must provide the appropriate flow range for infants and young children (many require <1 L/min of flow).
- Humidification system is required for some specific flow rates.
- Appropriately sized nasal prongs required, with face mask and extension tubing.
- Lightweight ambulatory equipment is required.
- Families must have functioning electricity and must be provided with documentation for the local electric company to prevent electricity disruption.
- An assessment should be made regarding the need for an emergency generator as a back-up electricity source.

Derived from Balfour-Lynn I, Primhak R, Shaw B. Home oxygen therapy for children: who, how and when? *Thorax*. 2005;60:76–81.

home monitoring for specific groups of high-risk infants. The hospital care managers will coordinate the initial insurance company approvals, but the pediatrician will need to become familiar with the specific insurer's guidelines regarding periods of coverage and authorizations required for continued equipment use at home. The neonatal team, in consultation with the pulmonary specialist, typically determines the concentration of inspired oxygen and equipment required by the infant at discharge and provides the home health care company, equipment vendor, and the family with specific instructions. The equipment vendors typically provide the family with detailed instruction on the equipment setup and use, and provide 24-hour access for technical support and equipment replacement in the event that a problem arises. No consensus exists about the optimal alarm settings required for home oxygen saturation monitoring, although, in general, typical alarm settings are heart rate greater than 200 beats/min and less than 80 beats/min and oxygen saturation less than 80%.

An infant who is discharged on home oxygen therapy requires close medical follow-up. The infant should also have a follow-up visit with a pulmonary specialist, if feasible. In communities where appointments for subspecialty care are not easily accessible for families, the pediatrician will need to have an identified pulmonary specialist with whom to consult on management issues.

### Supplemental Oxygen Requirements During Air Flight

An important, although uncommon, consideration is the potential need for supplemental oxygen during air flight for infants whose families plan air travel after discharge. Commercial air travel has been shown to decrease oxygenation in children. Experts recommend

that children, particularly infants with residual lung disease, undergo a preflight assessment of their response to a hypoxemic challenge to determine their need for in-flight oxygen therapy. If the pulse oximeter saturation decreases to less than 85% during the hypoxic challenge test, then supplemental in-flight oxygen is necessary. For infants with a history of respiratory disease, experts recommend that supplemental oxygen be provided if the pulse oximeter saturation is less than 90%. Most formerly preterm infants who are younger than 12 months corrected age at the time of the proposed air travel and not requiring oxygen supplementation in room air are felt to be at risk for hypoxemia during air flight. However, a recent publication by Bossley et al determined that former preterm infants babies without BPD who are at least 3 months corrected age do not seem to be a particularly at-risk group for air travel, and routine preflight testing is not indicated. It is notable that in this study, feeding babies in a low oxygen environment leads to a further fall in SpO<sub>2</sub>, which is significant but transient.

Infants at highest risk for in-flight hypoxia are younger than 3 months corrected age, irrespective of whether the infant has chronic lung disease. This risk exists even among infants who passed preflight hypoxia testing with SpO<sub>2</sub> levels higher than 85% while breathing an FiO<sub>2</sub> of 0.14 to 0.15. Prudence therefore suggests that if a preterm infant younger than 3 months corrected age must undertake air flight, the infant should be monitored in-flight with supplemental oxygen available if the SpO<sub>2</sub> falls below 85%.

### Home Ventilation

Improving survival rates among medically complex infants with severe cardiorespiratory disease, craniofacial anomalies, and neurologic abnormalities affecting respiratory control have resulted in a group of infants who require long-term ventilatory support and home ventilation. The discharge planning and care coordination of infants needing ventilator assistance at home requires extensive preparation and coordination before the child and family can safely move to a community setting. Before considering home ventilation, the infant must be medically stable, with stable ventilator settings for at least 1 week, and require an FiO<sub>2</sub> less than or equal to 0.4 (40% oxygen), have stable blood gases within the normal range for the infant's diagnosis, and have a secure airway with a mature tracheostomy that is healed (at least 1 week postoperative). The infant should not require intensive care (1-on-1) nursing or invasive monitoring.

The infant's parents must be committed to home ventilation, and adequate home health care personnel must be available, including the parent and at least 1 other person (parent or other family member or a registered or licensed practical nurse). Infants who are being discharged on home ventilation should have professional home nursing for at least 16 hours per day to support the safe transition of the infant from the hospital and ensure the parents' ongoing education and technical skills in managing the respiratory equipment. If other children or individuals with developmental disabilities are in the home, then an intensive assessment should occur as to the feasibility, safety, and appropriateness of the infant's discharge to the home.



The home environment needs to be evaluated by the equipment vendor and the home health care agency to ensure adequate space, electricity, and other utilities, and a safe home environment. The respiratory equipment vendor must ensure 24-hour access and in-home support. The local community emergency medical services providers (fire department and emergency medical system) should be made aware of the infant's home ventilation need. Local utility companies, including telephone and electric companies, need to be made aware of the child's technology dependence to ensure that services are not interrupted. Arrangements for routine and emergency transport of the infant for primary, specialty, and emergency care visits must be clearly detailed. Community resources must also be identified and linkages established to ensure that the infant and family receive appropriate medical, psychosocial, and early intervention services. Parent and other home caregiver education must include tracheostomy care and changing, airway suctioning, medication administration, manual ventilation and resuscitation, and recognition of changes in the infant's status—lethargy or agitation, cyanosis, respiratory distress, temperature instability (hyperthermia or hypothermia), and dehydration.

### Apnea, Bradycardia, and Desaturations

Apnea, bradycardia, and desaturation commonly occur in premature infants. A detailed discussion about the underlying pathophysiological mechanism is provided in Chapter 112, Continuing Care of the Infant After Transfer From Neonatal Intensive Care. The timing of discharge for a preterm infant with a history of apnea, bradycardia, and desaturation is controversial, as is the definition of when the infant can be deemed *medically stable* for discharge. Treatment of apnea, bradycardia, and desaturation depends on its underlying cause. The etiology of these signs further influences the decision regarding the appropriate time for discharge of an infant experiencing apnea, bradycardia, and desaturation. The standard practice is to delay the discharge of premature infants until they have achieved a set duration of days without any apnea, bradycardia, or desaturations.

No standard or universally accepted guidelines exist regarding the duration of this observation period or the effectiveness of delaying discharge. However, among the most immature infants, a period of observation that is too short may predispose a subset of infants to apparent life-threatening events at home. Apnea in the larger preterm infant resolves in most affected infants by 34 to 36 weeks postmenstrual age, with more than 90% of infants being apnea free by 37 weeks postmenstrual age. The duration of apnea is extended, often not resolving until 40 to 43 weeks postmenstrual age, among extremely low-birth-weight infants born at less than 28 weeks' gestation. Premature infants may also exhibit apnea as a developmental process; however, persistent apnea may also occur because of other factors, such as sepsis, temperature instability, sedation, gastroesophageal reflux, and physiological instability in response to positioning and handling. Each infant needs to be evaluated individually when determining the cause of the apnea and the possibility of discharge. Infants requiring treatment

with methylxanthines for apnea of prematurity should have medications discontinued when they reach 32 to 34 weeks postmenstrual age, and be apnea free for 7 to 10 days before discharge if home monitoring is not planned. Infants treated with caffeine require an extended period of observation of 7 days because of caffeine's long half-life; the period of observation after discontinuation of theophylline is somewhat shorter at 4 to 5 days.

Recommendations for the period of symptom-free days before hospital discharge for the infant who does not require home monitoring range from 3 to 8 days. Evidence suggests that continuing hospital care for preterm infants with significant apnea until cessation of apnea for a predetermined duration is a reasonable clinical practice. Infants who have been apnea free for 8 days or more are unlikely to have another apneic episode, unless other associated complications exist. In a survey of neonatal units, the margin of safety for infants with gestational age greater than or equal to 30 weeks between the last documented episode of apnea and hospital discharge was 5 to 7 days. Zupancic et al explored the economic implications of monitoring for resolution of apnea of prematurity for a fixed number of days before discharge home. Results of the economic modeling performed demonstrated a sharp decline in the utility or *value* for the cost of continuing hospital care as the duration of monitoring increased and decreasing cost effectiveness for infants who were born at higher gestational ages. Currently, no studies have established either the efficacy or the cost effectiveness of the various durations of monitoring.

### Predischarge Polysomnography (Event Monitoring)

Predischarge monitoring of infants with a history of apnea of prematurity using 12- to 24-hour pneumocardiogram recordings are a routine aspect of discharge planning in some hospitals. A pneumocardiogram is a diagnostic test that provides a continuous recording of heart rate and respirations that can detect periods of central apnea and periodic breathing. A 4-channel device also employs a nasal thermistor to detect airflow and a pulse oximeter to measure oxygen saturation through the activities occurring during the period of monitoring. The thermistor can help distinguish between central and obstructive apnea. Pneumocardiograms may be used as screening tests to determine which infants are at risk for life-threatening apnea; however, no evidence exists to support predischarge monitoring as predictive of life-threatening apnea or sudden infant death syndrome (SIDS). In addition, although such studies may reveal ongoing episodes of apnea, bradycardia, or desaturation, they reflect the events over a limited time frame and may not identify all infants at continuing risk. The infant being tested may not exhibit signs during the examination. Therefore no current guidelines have been formulated to recommend the routine use of pneumograms in infants with apnea; however, distinguishing the type of apnea that an infant experiences may be useful clinically.

### Home Apnea Monitoring

Apnea monitors were first introduced in the 1960s for managing apnea of prematurity in hospital settings.

Subsequently, home cardiorespiratory monitoring became widely used, with the hypothesis that SIDS might be prevented by monitoring for apnea. No scientific evidence has been found to support the premise that cardiorespiratory monitoring at home reduces the incidence of SIDS or that apnea is a precursor to SIDS. Apnea of prematurity does not predispose an infant to SIDS, although prematurity, itself, is a risk factor for SIDS. The efficacy of home cardiorespiratory monitoring for siblings of infants who died of SIDS has also not been proven. Given the lack of evidence that home cardiorespiratory monitoring has any effect on SIDS, prevention of SIDS is not an acceptable indication for home cardiorespiratory monitoring. Di Fiore et al concluded that infants referred for apnea monitoring studies because of persistent bedside monitor alarms had very infrequent apnea of at least 20 seconds' duration. A high frequency of desaturation and bradycardia was noted in response to short respiratory pauses when compared with infants with no persistent bedside monitor alarms. Some premature infants continue to experience recurrent apneic episodes despite evidence that they are otherwise ready for discharge because they have achieved full oral feeding and demonstrate appropriate temperature regulation. The decision to discharge a premature infant on home apnea monitoring is typically based on the infant experiencing *clinically significant cardiorespiratory events*. These events are defined as apnea greater than 20 seconds' duration, apnea of less than 20 seconds that is associated with bradycardia (heart rate [HR] less than 80 beats/min), a 33% drop in HR below the resting HR or a decline in the oxygen saturation below 85%, bradycardia with an HR less than 80 beats/min, or oxygen desaturation less than 80% for more than 5 seconds. Infants who have experienced apparent life-threatening events associated with apnea, color change, marked change in muscle tone with hypotonia or flaccidity, and choking and gagging should also be considered for home apnea monitoring. Home monitoring until 43 to 45 weeks postmenstrual age may offer an acceptable alternative to continued hospitalization if the parents are in agreement and if close coordination and follow-up care is provided by the pediatrician.

Home monitoring may be also medically necessary and justified for other infants with significant medical conditions. Infants who are technology dependent requiring home ventilation (continuous positive airway pressure or nasal bilevel positive airway pressure), who have a tracheostomy or require home oxygen therapy, or who have neurologic or craniofacial abnormalities that affect respiratory control or function are typically discharged with home monitoring. The AAP offers specific recommendations for home cardiorespiratory monitoring (Box 113-3). Parents and caregivers must learn that home cardiorespiratory monitoring does not guarantee avoidance of sudden death from an underlying cause.

If home monitoring is prescribed, then the parents and other caregivers must be trained in the correct application and operation of the monitor and in infant cardiopulmonary resuscitation (see Tools for Practice). The family should have 24-hour access to an equipment specialist from the home care supply vendor, as

### BOX 113-3 Home Cardiorespiratory Monitoring

- Home cardiorespiratory monitoring should not be prescribed to prevent SIDS.
- Monitoring may be warranted for premature infants who are at high risk of recurrent episodes of apnea, bradycardia, and hypoxemia after hospital discharge.
- Monitoring may be warranted for infants who are technology dependent (tracheostomy, continuous positive airway pressure), have unstable airways, have rare medical conditions affecting the regulation of breathing, or have symptomatic chronic lung disease.
- If monitor is prescribed, then monitor should be equipped with an event recorder.
- Parents should be advised that home monitoring does not prevent sudden, unexpected deaths in infants.
- Pediatricians should continue to promote proven practices that decrease the risk of SIDS—supine sleep position, safe sleeping environments, and elimination of exposure to tobacco smoke.

From American Academy of Pediatrics Committee on Fetus and Newborn. Apnea, sudden infant death syndrome, and home monitoring. *Pediatrics*. 2003;111:914-917.

well as medical support, should questions or problems arise with the equipment or its use. Most insurers have detailed policies that delineate eligibility requirements for the use of apnea monitors. Confirming with individual carriers whether the patient meets the criteria for an apnea monitor according to the insurance company may be necessary.

### Sleep Position

Guidance regarding safe infant sleep and sleep position is discussed in the section on Infant Safety.

### Vehicle Seat Safety

Preterm infants who have achieved readiness for hospital discharge are at an increased risk of respiratory compromise (desaturation, apnea, and bradycardia caused by poor postural tone, hypoventilation, and airway obstruction) when seated in standard vehicle seats. The AAP recommends that all premature infants born at less than 37 weeks gestation at birth be assessed for cardiorespiratory stability in their vehicle seat before discharge. Experts recommend that infants should have a vehicle seat challenge test performed several days before the infant's anticipated discharge date during which the infant is placed in the vehicle seat to be used by the family for 60 to 90 minutes of continuous monitoring. Careful attention must be given to smaller infants who require proper positioning to maintain head, neck, and trunk stability. The AAP has made specific recommendations for the positioning of preterm infants in vehicle safety seats (Box 113-4). In addition, the recommendation is that infants should not be left unsupervised in vehicle seats. Tremendous variation exists among neonatal units in the practice of predischarge vehicle seat testing, and among neonatal units where vehicle

### BOX 113-4 Recommendations for Positioning of Preterm Infants in Vehicle Safety Seats

- Use infant-only, rear-facing safety seats with 3- or 5-point harness systems.
- The vehicle safety seat should be semi-reclined to a 45-degree angle in the rear seat of the vehicle, ideally adjacent to an adult.
- Place the infant's buttocks and back firmly against the back of the vehicle safety seat to reduce slouching.
- The distance from the crotch strap to the seat back should be  $\leq 14$  cm and from the lower harness strap to the seat bottom should be  $\leq 25$  cm.
- Shoulder straps should be in the lowest slots until the infant's shoulders are above the slots.
- Place the retainer clip over the midpoint of the chest rather than on the abdomen or near the neck.
- The vehicle safety seat should not be placed in the front passenger seat of a vehicle with a passenger-side front air bag.
- The infant should not be left unattended in a vehicle safety seat.

Adapted from American Academy of Pediatrics Committee on Injury and Poison Prevention and Committee on Fetus and Newborn. Safe transportation of premature and low birth weight infants at hospital discharge. *Pediatrics*. 2009;123(5):1424–1429.

seat testing is conducted, variation in the indications for testing, duration of the observation period in the vehicle seat, and criteria for *passing* the challenge test exist.

Improper positioning of preterm infants, even infants born at 35 or 36 weeks' gestation, can cause respiratory compromise. Poor postural tone contributes to slouching that can cause neck flexion and airway obstruction. Consideration regarding delaying the discharge home to allow for continued growth and maturation should be given to infants who, despite proper positioning and modifying the seat with blanket rolls or inserts, exhibit desaturations or other signs of cardiorespiratory compromise during the vehicle seat test. Although the recommendation for vehicle seat testing exists, an evidence base is not currently available that confirms the clinical importance of desaturations, bradycardia, or apnea experienced by preterm infants who are classified as *failing* the challenge test or that passing a vehicle seat challenge will improve the outcome in preterm infants.

An alternative transportation device for infants is the vehicle bed. Vehicle beds allow the infant to travel reclining rather than positioned vertically in a vehicle seat. Vehicle beds have been suggested as being more appropriate for transportation of infants at risk for desaturation, apnea, or bradycardia when in a vehicle seat. Vehicle beds can be positioned so the infant is flat or inclined at 30 degrees. Vehicle beds have been recommended for infants with medical conditions requiring prone or supine position, such as premature infants, infants after repair of myelomeningocele, or infants who must lie prone to maintain an open airway (eg, those with Pierre Robin sequence). A recent

investigation by Salhab et al comparing car seat versus car bed for infant transportation found no significant difference in the incidence of apnea, bradycardia, or desaturation in very low-birth-weight infants. Each infant was tested in an infant car seat and a car bed. The reported incidence of 1 or more cardiorespiratory events was 15% and 19%, respectively. Infants with chronic lung disease were more likely to have a vehicle seat event, whereas infants with lower gestational age at birth were at greater risk for a vehicle bed event.

## IMMUNIZATIONS

### Routine Immunizations

Routine immunizations are required for all infants, including preterm and sick infants. Preterm and low-birth-weight infants are at greater risk of increased morbidity from vaccine-preventable diseases than term infants. Therefore gestational age and birth weight should not deter an infant from receiving immunizations on schedule, except with specific criteria for the hepatitis B vaccine. In addition, vaccine doses should not be decreased or altered for preterm or low-birth-weight infants. The anterolateral thigh is the preferred site for administering intramuscular vaccines to preterm and low-birth-weight infants.

If an infant is in the NICU at 2 months of age, then routine vaccines including diphtheria and tetanus toxoids, acellular pertussis, *Haemophilus influenzae* type B conjugate, inactivated polio vaccine, and pneumococcal conjugated vaccine (Prevnar) will have been administered according to the schedule and doses for full-term infants according to the AAP and the Centers for Disease Control and Prevention (CDC). The safety of these vaccines in preterm and low-birth-weight infants is comparable to that in full-term infants, with no increase in adverse reactions noted. Routine vaccinations should also be given at 4 and 6 months of age.

### Hepatitis B Vaccine

Hepatitis B vaccine is recommended for administration at birth or before discharge home from the hospital. Recommendations for administering the hepatitis B vaccine to preterm neonates depend on the maternal hepatitis B status. Infants born to hepatitis B surface antigen-positive mothers will have received monovalent hepatitis B vaccine and hepatitis B immune globulin within 12 hours after birth, regardless of birth weight or gestational age. If the infant's birth weight was less than 2,000 g, then this dose does not count toward the 3-dose hepatitis series. Three additional doses are required beginning at 1 month of age. In addition, these infants should be tested for anti-hepatitis B antibodies and hepatitis B surface antigen at 9 to 15 months of age after the immunization series has been completed.

Medically stable preterm infants and infants weighing less than 2,000 g demonstrate predictable hepatitis B-antibody response and should receive the first dose of monovalent hepatitis B vaccine at 30 days chronologic age, regardless of gestational age or birth weight. If hospital discharge occurs before 30 days, then the infant should be immunized before discharge. These infants should complete the 3-vaccine series, and follow-up



testing is not required. Medically stable infants who receive the vaccine at birth or at 30 days may receive a hepatitis B–containing combination vaccine beginning at 6 to 8 weeks of age, regardless of whether their weight is less or greater than 2,000 g.

### Respiratory Syncytial Virus Prophylaxis

Respiratory syncytial virus (RSV) is an important pathogen that causes lower respiratory tract infections in infants and young children. Premature infants may develop severe, fatal lower respiratory tract infections from RSV. Palivizumab should be given to infants and children younger than 24 months who were infants born at less than 32 weeks' gestation, infants with chronic lung disease, and infants with cardiovascular complications. Infants born from 32 to 35 weeks gestation may be considered for prophylaxis if 2 or more risk factors are present, including child care attendance, school-aged siblings, exposure to environmental air pollutant, congenital abnormalities of the airway, or severe neuromuscular disorders. Infants with chronic lung disease, hemodynamically significant congenital heart disease, or other serious conditions that compromise respiratory or immune function should also be scheduled to receive palivizumab monthly during the RSV season. Some hospital neonatal services provide a referral to the appropriate specialty pharmacy or community-based RSV-prevention program. The pediatrician must be familiar with immunoprophylaxis guidelines, local resources, and specific insurer and state Medicaid eligibility requirements to ensure that infants at risk receive treatment. Seasonal variation can be found in the timing of RSV infection geographically, with additional variation in regional peak infection rates. Palivizumab use should not interfere with the standard immunization schedule.

### Influenza Vaccine

Preterm and other medically fragile infants with chronic medical conditions are at high risk for complications and morbidities associated with the influenza virus infection. Plans for vaccine administration to the infant and family should be included in the discharge summary. If the infant is being discharged from the hospital during influenza season, then the child's parents and household contacts should be strongly encouraged to receive the influenza vaccine, particularly if the high-risk infant is younger than 6 months and is unable to be vaccinated.

### Rotavirus Vaccine

Rotavirus is the most common cause of severe gastroenteritis in infants and young children worldwide. In consideration of the potential risks for and benefits of vaccinating premature infants against rotavirus, the CDC Advisory Council on Immunization Practices (ACIP) has encouraged providers to immunize preterm infants born at less than 37 weeks' gestation between 6 and 12 weeks of age. Limited data suggest that preterm infants are at increased risk for hospitalization from viral gastroenteritis during their first year of life. The safety and efficacy of the rotavirus vaccine seems to be similar for premature and term infants, although relatively few preterm infants have been

evaluated in clinical trials. A theoretical concern exists that lower levels of maternal antibody to rotaviruses in very low-birth-weight premature infants have the potential to increase the risk for adverse vaccine reactions because the vaccine is administered as a live virus. Despite this caution, the ACIP supports vaccination of prematurely born infants if they are at least 6 weeks of age, are being or have been discharged from the hospital, and are clinically stable. The ACIP considers the benefits of vaccination of preterm infants against rotavirus to outweigh the theoretical risks. No safety or efficacy data are available regarding administration of rotavirus vaccine to immunocompromised infants. Rotavirus vaccine should also be deferred for 42 days after any administration of immune globulin.

### HEARING SCREENING

Universal newborn hearing screening has become the standard of care in the United States; currently more than 90% of newborn infants are screened before hospital discharge. The overall rate of permanent hearing loss at birth is 1 to 2 per 1,000 live births. The prevalence of hearing loss increases with a child's advancing age because of progressive losses caused by genetic, hereditary, and acquired conditions, as well as environmental exposures. Among healthy newborn infants the incidence of permanent childhood hearing loss is 0.9 in 1,000, in comparison with a prevalence of 9 to 13 per 1,000 or 5% to 10% of infants requiring neonatal intensive care. The cause of hearing loss in childhood is equally distributed among hereditary or genetic conditions and environmental hazards or acquired conditions.

Infants who are at risk from environmental and acquired causes include those born preterm, babies with persistent pulmonary hypertension (particularly if extracorporeal membrane oxygenation and inhaled nitric oxide are required), those with TORCH infections (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex) and bacterial meningitis, and infants with significant hyperbilirubinemia. Among infants who have experienced persistent pulmonary hypertension, 17% to 30% will develop progressive sensorineural hearing loss. As a group, high-risk neonates are 10 times more likely to experience sensorineural hearing loss. Hyperbilirubinemia, prematurity, exposure to ototoxic medications, hypoxia, and infection predispose infants to auditory neuropathy (AN) and auditory dys-synchrony (AD). Infants with AN-AD have abnormal sound transmission to the brain and will have normal otoacoustic emissions (cochlear function) but will have abnormal brainstem-evoked responses (response to sound and the auditory neural pathway). Preterm infants who are born at 23 to 28 weeks' gestation experience the highest rates of AN-AD and sensorineural hearing loss and have a higher prevalence rate for AN-AD compared with more mature infants. In addition, young-for-gestational-age and low-birth-weight preterm infants with AN-AD have increased exposure to potentially ototoxic medications, an increased incidence of bronchopulmonary dysplasia, and extended hospitalizations. Prolonged hospital courses are caused by their multiple medical



complications: intraventricular hemorrhage or periventricular leukomalacia, gastroesophageal reflux, retinopathy of prematurity, cholestasis, osteopenia, and anemia.

Newborns who require an extended period of neonatal intensive care, particularly those with additional risk factors, are at risk for delayed-onset or progressive hearing loss. In addition to a hearing screen before discharge, these newborns should receive audiologic monitoring every 6 months until 3 years of age, as recommended by the Joint Committee on Infant Hearing. The indicators are listed in Box 113-5. (See Chapter 26, Auditory Screening, for more information.) Discharge planning for infants in the NICU should include newborn hearing screening, preferably using a 2-stage screening approach, with the initial screen performed to assess the infant's auditory brainstem response. If the infant does not pass this test, then otoacoustic emission testing should be initiated. Infants may be tested as early as 30 weeks postmenstrual age, although the optimal time for the initial hearing screen is when the infant is at least 34 weeks postmenstrual age. Infants who are at risk must

be screened because infants requiring neonatal intensive care have been found to be more likely to miss predischarge screening for hearing loss. An important point to note is that mild (20–40 dB) and low (conductive)–to-middle frequency (500–2,000 Hz) hearing losses will not be identified by newborn hearing screening. Continued hearing surveillance and periodic hearing testing are necessary for infants at risk for delayed onset and progressive hearing loss. Infants who fail or miss NICU screening must have follow-up testing scheduled. Infants with known hereditary (genetic) or acquired conditions associated with a high risk for late onset or preprogressive hearing loss should be referred for a comprehensive medical and otologic evaluation.

## NEWBORN SCREENING

Newborn blood spot testing for a variety of metabolic, endocrine, and hematologic disorders is routine throughout the United States, the District of Columbia, Puerto Rico, US Virgin Islands, and Guam. Premature and sick neonates will often have serial testing performed during their NICU hospitalization based on established state protocols. In contrast to healthy newborns who have their newborn blood spot test obtained at 2 to 3 days of age, sick and preterm newborns have their initial newborn screening sample obtained during the first hours of life because of the need for blood product administration or early initiation of parenteral nutrition. The amino acid contained in parenteral nutrition solutions can cause elevations in various amino acids levels (eg, phenylalanine, tyrosine), leading to a false-positive test result. Blood transfusions can also result in elevation in the blood spot hemoglobin A level; this elevated level will be detected on the newborn screen in states that test for hemoglobinopathies. Therefore screening tests will need to be repeated 3 to 4 months after a transfusion.

State screening protocols require repeat blood spot screens at 1 to 2 weeks and at 1 month of age for infants requiring prolonged hospitalization. Infants transferred to another facility should have their screening test before transfer, and then coordinated follow-up between the medical care providers is required to ensure test results are known. Sick and extremely preterm infants often exhibit transient abnormalities in thyroid function that require monitoring to ensure that persistent thyroid dysfunction is not missed. Another common abnormality identified on the early newborn screening tests of premature infants are elevations in 17-hydroxyprogesterone (17-OHP) levels, suggestive of congenital adrenal hyperplasia. However, preterm infants often have high blood 17-OHP levels that decline as they mature. Weight-adjusted 17-OHP values may be used to reduce the incidence of false-positive results in premature neonates. Cystic fibrosis (CF) screening is included in the newborn screening panel in many states. The test process involves detection of immunoreactive trypsinogen (IRT) activity and cystic fibrosis transmembrane conductance regulator (CFTR) mutations.

Current mutation analysis encompasses the gene mutations common among white individuals but does not detect the mutations more typically occurring in black patients. IRT levels may be elevated,

### BOX 113-5 Risk Factors or Indicators for Infants With Delayed-Onset or Progressive Hearing Loss

1. Parental or caregiver concern regarding hearing, speech, language, or developmental delay
2. Family history of permanent childhood hearing loss
3. NICU stay more than 5 days, assisted ventilation more than 10 days, prolonged exposure to ototoxic medications (gentamicin and tobramycin) or loop diuretics (furosemide)
4. Postnatal infections associated with sensorineural hearing loss, including bacterial meningitis
5. In utero infections such as cytomegalovirus, herpes, rubella, syphilis, and toxoplasmosis
6. Neonatal indicators (eg, hyperbilirubinemia at a serum level requiring exchange transfusion, conditions requiring extracorporeal membrane oxygenation)
7. Stigmata or other findings associated with a syndrome known to include a sensorineural or conductive hearing loss or eustachian tube dysfunction
8. Syndromes associated with progressive hearing loss such as neurofibromatosis, osteopetrosis, and Usher syndrome
9. Neurodegenerative disorders
10. Head trauma
11. Recurrent or persistent otitis media for at least 3 months
12. Physical findings such as a white forelock associated with a syndrome known to include a sensorineural or permanent conductive hearing loss
13. Chemotherapy

NICU, neonatal intensive care unit.

From Joint Committee on Infant Hearing, et al. Year 2000 position statement: principles and guidelines for early hearing detection and intervention programs. *Pediatrics*. 2000;106(4):798–816; Joint Committee on Infant Hearing. Year 2007 position statement: principles and guidelines for early hearing detection and intervention programs. *Pediatrics*. 2007;120(4):898–921.

causing false-positive test results in many conditions, including perinatal distress and prematurity; levels may be low (false-negative test) in infants with meconium ileus. Infants with meconium ileus are at risk for CF and should have a follow-up sweat test, even if the newborn screen is negative. Infants with abnormal IRT levels or identified CFTR mutations require a postdischarge sweat chloride test. Any newborn with an abnormal blood spot screen should have a repeat test before hospital discharge. The need for postdischarge testing will be based on the hospital-based test results. These newborns should be monitored for any signs or symptoms of the diagnosed disorder until the repeat screening results are available. Physical or metabolic signs suggestive of the presence of a screened condition should prompt appropriate diagnostic testing for the suspected disorder immediately.

### RETINOPATHY OF PREMATURETY SCREENING

Conducting a thorough ophthalmologic evaluation and ensuring close follow-up care after hospital discharge are important aspects of eye care for extremely premature infants. Infants whose birth weight was less than 1,500 g or gestational age less than or equal to 30 weeks, and selected infants with a birth weight between 1,500 and 2,000 g or gestational age greater than 30 weeks who experienced an unstable clinical course, including the need for cardiorespiratory support or who are thought to be at high risk, require ophthalmologic evaluation for the presence of retinopathy of prematurity (ROP). If the infant is to be discharged or transferred from the NICU before the first ROP examination at 4 to 6 weeks postnatal age, then an eye examination should be scheduled. If concern exists about the family's ability to comply with the appointment or the availability of ophthalmologic examination at the transfer hospital, then consideration should be given to completing the initial examination performed before the infant is discharged. Communication with the pediatric ophthalmologist and family is

necessary to ensure coordination of follow-up eye care. Table 113-2 and Box 113-6 provide a summary of recommendations for continuing ophthalmologic care.

Some infants may experience adverse effects from the medications used to dilate the infant's eyes. Side effects include sweating, tearing, eye swelling,

#### BOX 113-6 Schedule of Follow-up Examinations for Retinopathy of Prematurity (ROP)<sup>a</sup>

##### 1-WEEK OR LESS FOLLOW-UP

- Immature vascularization in zone I (no ROP)
- Immature retina extends into posterior zone II, near the boundary of zone I
- Stage-1 or -2 ROP in zone I
- Stage-3 ROP in zone II
- Presence or suspected presence of aggressive posterior ROP

##### 1- TO 2-WEEK FOLLOW-UP

- Immature vascularization in posterior zone II
- Stage-2 ROP in zone II
- Unequivocally regressing ROP in zone I

##### 2-WEEK FOLLOW-UP

- Stage-1 ROP in zone II
- Immature vascularization in zone II; no ROP
- Regressing ROP in zone II

##### 2- TO 3-WEEK FOLLOW-UP

- Stage-1 or -2 ROP in zone III
- Regressing ROP in zone III

<sup>a</sup>Based on the examining ophthalmologist's findings. From American Academy of Pediatrics Section on Ophthalmology, et al. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics*. 2013;131(1):189–195.

**Table 113-2** Timing of First Eye Examination Based on Gestational Age at Birth

GESTATIONAL AGE AT BIRTH (IN WEEKS)	AGE AT INITIAL EXAMINATION (IN WEEKS)	
	POSTMENSTRUAL	CHRONOLOGIC
22 <sup>a</sup>	31	9
23 <sup>a</sup>	31	8
24	31	7
25	31	6
26	31	5
27	31	4
28	32	4
29	33	4
30	34	4
Older gestational age, high-risk factors <sup>b</sup>		4

<sup>a</sup>This guideline should be considered tentative rather than evidence-based for infants with a gestational age of 22 to 23 weeks because of the small number of survivors in these gestational-age categories.

<sup>b</sup>Consider timing based on severity of comorbidities.

From American Academy of Pediatrics. Policy statement: screening examination of premature infants for retinopathy of prematurity. *Pediatrics*. 2013;131:189–195.

arrhythmias, apnea and bradycardia, hypertension, and eye irritation. In addition, the examination may be uncomfortable and stressful for the infant. Consequently, medically fragile infants require close monitoring after the examination. Infants at risk for ROP are also at risk for other eye disorders: strabismus, amblyopia, and cataracts. Infants with suspected congenital infection should undergo an ophthalmologic examination before discharge. If this examination is not possible before discharge, then a follow-up appointment should be made as soon as possible after discharge.

## NEUROLOGIC EVALUATION

Premature and sick infants are at risk for brain abnormalities, including intraventricular hemorrhage, periventricular leukomalacia, perinatal stroke, hemorrhagic lesions from birth trauma, or encephalopathy, among other cerebral injuries. Both preterm and term neonates are vulnerable to hemorrhagic and ischemic injury. These abnormalities may lead to poor neurodevelopmental outcome. With advancing techniques in the area of ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI), information can be obtained that may help predict the infant's neurodevelopmental outcome.

Hemorrhagic brain lesions may involve the germinal matrix and the ventricles and extend into the brain parenchyma. Routine cranial ultrasonography is often performed in preterm infants and babies suspected of having intracranial abnormalities. Postdischarge neurosonography for ongoing surveillance of resolving hemorrhages, residual ventriculomegaly, or evolving periventricular leukomalacia or extraaxial fluid collections may be required. The American Academy of Neurology (AAN) recommends that routine cranial sonographic screening be performed between 7 to 14 days of age on all newborns less than 30 weeks postmenstrual age. A repeat scan should be performed between 36 and 40 weeks postmenstrual age to detect the presence of periventricular leukomalacia. Screening at these times can guide clinical care and inform predictions regarding the newborn's potential long-term neurodevelopmental outcome.

The AAN does not currently recommend that conventional MRI of the brain be performed on preterm infants with abnormal screening cranial ultrasounds because evidence as reviewed in 2002 was insufficient to support the utility of MRI in prediction of long-term outcome. However, recent studies suggest a role for MRI at term-postmenstrual age in predicting neurodevelopmental outcome.

Individual hospital policies guide the level of sedation—conscious sedation or general anesthesia—required for completion of the MRI so as to limit motion artifact caused by infant movement. In addition, hospital policies may vary if the infant is an inpatient or an outpatient. If sedation is used, then the infant should be monitored after the procedure for evidence of cardiorespiratory depression, apnea, bradycardia, or desaturations. If an MRI is to be performed before the infant's discharge, then it should be obtained a few days before the anticipated discharge if feasible.

For term newborns who experience birth trauma, neonatal encephalopathy or seizures or have evidence of a perinatal stroke or other brain injury, a noncontrast CT scan and MRI are typically performed early in the neonate's hospital care. Follow-up studies are often performed 2 to 3 weeks after birth to provide information about the evolution of the brain injury and about the infant's prognosis. Discharge planning for these newborns requires follow-up neurologic care and referral to early intervention for periodic developmental surveillance or therapeutic services based on the child's specific needs.

## SPECIALTY FOLLOW-UP CARE

Many infants who are ready for discharge from the NICU have experienced medical conditions requiring consultations with pediatric specialists. For example, infants with suspected (abnormal echocardiograms) or confirmed heart disease, neurologic injury or signs of neurologic dysfunction, renal dysfunction, or chronic lung disease, should have pediatric specialty follow-up appointments. Because of geographic variations, it may not be possible for parents to bring their infant for follow-up appointments with subspecialists. Often, the pediatrician must address these issues while consulting with the specialists. Some tertiary-care centers offer comprehensive neonatal or condition-specific follow-up programs (craniofacial center, spina bifida clinic) in which provide an opportunity for the infant to be assessed by a multidisciplinary team of specialists. Though coordinated, comprehensive care is optimal, insurers and state Medicaid guidelines may not provide reimbursement for multiple visits in a single day or specific components of the child's specialty care. This circumstance can present a challenge to both the family and pediatrician.

## LABORATORY STUDIES

Discharge planning of a patient from the NICU may include obtaining specific laboratory tests to provide a baseline for the infant's biochemical or hematologic status at the time of hospital discharge. Decisions about what studies are necessary should be based on the infant's specific medical issues. For example, an infant with anemia should have a recent complete blood count and reticulocyte count before discharge. If the patient will be discharged on medications that require periodic drug level monitoring, such as phenobarbital, then drug levels should be obtained before discharge to ensure appropriate medication dosing. If the infant is on medications that can cause electrolyte abnormalities, such as diuretics, then a basic metabolic profile should be obtained. The infant with residual renal or liver dysfunction or metabolic bone disease (osteopenia) should have the appropriate studies to establish the infant's biochemical status at the time of discharge. The infant with cholestasis should have a liver function profile drawn. A baby with osteopenia should have calcium, phosphorus, and alkaline phosphorus levels checked before discharge. If patients are receiving medications to treat these disorders, then the dosages may need to be adjusted before discharge. Information about the proposed timing for any follow-up testing, if required,

should be included in the infant's discharge recommendations.

## CIRCUMCISION

Parents of medically stable male infants may request a circumcision before hospital discharge (see Chapter 89, The Circumcision Decision). The procedure may be performed by various medical professionals, including neonatologists, pediatricians, pediatric surgeons, obstetricians, and urologists. Circumcising a very-preterm infant who may weigh less than 2,000 g at the time of discharge may present a challenge because of the infant's small size. The person performing the circumcision should be experienced with the procedure in the preterm infant. Prematurity is not a contraindication for circumcision; however, the infant should be clinically stable before circumcision. No weight criteria or requirement exists for a specific penile size for a premature infant to have a circumcision performed; however, most institutions will delay circumcision until an infant is ready for discharge. An important point to remember is that preterm infants undergoing a circumcision may exhibit cardiorespiratory compromise in response to pain and the stress of the procedure. Monitoring these infants for a brief period after the procedure may be necessary. As with any infant undergoing a circumcision, appropriate pain management should be provided.

## SOCIAL SERVICES AND CASE MANAGEMENT

Most hospitals have mechanisms to identify infants at social and environmental risk. Many neonatal units have established policies that offer the opportunity to or require that all families meet with a social worker. Social workers and case managers play an essential role in the care of any infant admitted to the NICU. They can assess the family constellation and family dynamics, identify risk factors that have the potential to influence the infant's care and family functioning, identify resource needs, and evaluate the adequacy of future home environment. Social workers also serve a vital role as advocates and support for all family members during the infant's NICU stay and can assist in assessing the mother for perinatal depression. They may also serve as liaisons between medical caregivers and community resources, such as child welfare agencies, that service at-risk children and families or community-based home health care programs. Social workers and care managers also assist in coordinating the discharge planning process, especially ordering equipment that the infant might need at home, such as an apnea monitor or oxygen-delivery system. The social worker can facilitate the preparation of paperwork that the parents might need.

## INSURANCE COVERAGE

### Third Party

On admission to the NICU, hospital personnel routinely verify insurance coverage for an infant and will assist the parents in obtaining necessary

coverage, depending on the child's medical needs and the specific terms of the existing insurance policy. In preparation for discharge, some important assessments include the scope of the infant's insurance coverage, and the scope of services covered for continuing outpatient and inpatient hospital care, primary pediatric, and subspecialty care, as well as coverage for durable medical equipment. Individual states have guidelines that determine Medicaid eligibility, physically handicapped children's program eligibility and requirements regarding potential exemptions from enrollment in Medicaid managed-care programs for children with special health care needs. Insurance carrier-driven policies may alter the infant's follow-up care because subspecialty follow-up may need to be with a different medical professional, based on physician insurance plan participation.

### Medicaid

Medicaid is the single largest insurer of children and is an important health resource, especially for children with special health care needs. Medicaid functions on the state and federal level. However, eligibility requirements, as recommended by the AAP, fall under federal legislation.

### Social Security

Many medically complex and extremely low-birth-weight infants are eligible to receive Supplemental Security Income in addition to Medicaid. Neonates born with birth weights less than 1,200 g or who have medical complications such as blindness, deafness, or cerebral palsy may be eligible for Supplemental Security Income. The Social Security Administration eligibility requirements are available at [www.ssa.gov](http://www.ssa.gov).

### Home Health or Public Health Nurse Visit

Infants who are ready to be discharged home from the NICU should have a home nursing visit scheduled, preferably within the first 2 days of discharge. Home nursing visits allow for a medical evaluation of the NICU graduate who is at home and in the care of the infant's parents or caregivers. Home nursing is also a resource that allows parents an opportunity for follow-up immediately after discharge. In addition, some infants may require a predischARGE home visit, which can provide the medical team with information on potential safety problems that the infant may encounter after discharge. For example, if electricity is not working in the home, an infant's health may then be compromised. A predischARGE home visit is important to assess the adequacy of the home environment and parental readiness for the infant's homecoming and can assist parents in their preparation for the infant's discharge. Individual hospital policies guide the specific discharge planning processes and define personnel roles and care-coordination responsibilities.

## PARENT EDUCATION

Ideally, parental involvement in the care of a sick infant should begin at the time of the infant's admission to the NICU. Parental participation is vital during the



NICU hospitalization and can aid the transition to home at the time of discharge. Parent involvement allows the parents the opportunity to gain an understanding of their infant's medical problems and become more comfortable with caring for and nurturing their infant. Ample time should be devoted to parent and other caregiver education.

## INFANT SAFETY

### Cardiopulmonary Resuscitation Training

Infants being discharged home from the NICU may be at continued risk for a health crisis and other apparent life-threatening events that may require cardiopulmonary resuscitation (CPR), such as apneas, bradycardias, and choking. Teaching parents and other caregivers the basic steps in CPR is a necessary part of discharge planning. A variety of tools are available to assist in CPR training, with personal training models available to teach parents and caregivers CPR, including videos or basic course instruction. Teaching materials are available from the American Heart Association. *Infant CPR Anytime* is a self-directed learning program that allows families and caregivers to learn core skills of infant CPR and choking prevention. The kit contains an infant manikin, practice video, sanitizing wipes, and reference guide ([www.aap.org/family/infantcpranytime.htm](http://www.aap.org/family/infantcpranytime.htm)). CPR teaching should be completed before the infant's discharge.

### Sleeping Position

Prone sleeping position is a risk factor that has been identified for SIDS, and importantly, can be modified. Parents of all infants should be educated about the risk factor of prone sleeping and SIDS. Not only the parents, but also all caregivers should be educated. Prone sleeping has been recognized as a major risk factor for SIDS, with odds ratios ranging from 1.7 to 12.9 in various studies.

Discussing sleeping position with parents before discharge is extremely important because many preterm infants are maintained in a prone position during the early stages of their NICU care. Parents and caregivers must be helped to understand that while the infant is hospitalized, the infant is on a cardiorespiratory monitor and under medical supervision. This positioning is often used as an adjunct to improve gastrointestinal reflux and other symptoms such as apnea in some infants and to facilitate development care and flexed positioning. Consequently, parents often believe that because the infant was placed prone in the NICU, this position is optimal for the infant or that the baby *became accustomed to that position* and is uncomfortable when placed supine. Preterm and low-birth-weight infants are at an increased risk for SIDS, and data suggest that the prone sleep position is a major factor in the incidence of SIDS in these patients. Bhat et al demonstrated that, compared with term infants, premature infants ready for discharge sleep with fewer arousals and more central apneas in the prone position. Apnea of prematurity does not increase the risk of SIDS for premature infants. Premature and low-birth-weight infants should be placed supine to sleep.

Parents should be encouraged to place their newborn infants in a crib or bassinette to sleep rather than leaving the baby in an infant seat or car bed. A recent controlled trial demonstrated that hypoxic events occurred more often among healthy full term infants allowed to remain in an infant/car seat or car bed for more than 90 minutes in comparison with placement in a crib. This raises additional concern for preterm infants and babies who have been sick or have residual cardiorespiratory or neuromuscular disease.

### Exposure to Secondhand Smoke

Many preterm and chronically ill infants have evidence of residual lung disease at the time of hospital discharge. Infants exposed to secondhand smoke from tobacco are at risk for medical conditions such as allergies, asthma, ear infections, pneumonia, permanent lung changes, SIDS, and learning disabilities. However, premature infants are especially at risk. Parents and family members should be counseled about smoking cessation long before an infant is ready for discharge. Educating the parents and providing them with resources for smoking cessation can aid them and sometimes motivate them to quit smoking. Different pharmacotherapies, nicotine replacement therapies, and behavioral-modification programs exist to help with smoking cessation. In addition, the Smoke-Free Home Project is a comprehensive, national effort to teach pediatricians methods to reduce children's secondhand smoke exposure through parental smoke cessation and harm reduction.

Mothers who are breastfeeding should be encouraged not to smoke and should be provided with information about smoking cessation and a referral to a smoking-cessation program. If they cannot stop smoking, then these mothers should be encouraged to reduce the number of cigarettes smoked and to switch to a low-nicotine cigarette. Mothers who continue to smoke should be instructed to breastfeed before smoking a cigarette and to delay nursing or to express milk after smoking. Despite their tobacco use, mothers who smoke should be encouraged to continue breastfeeding because the benefits to the infant outweigh potential risks. Breastfeeding mothers who desire to quit smoking may safely use the nicotine gum or nicotine transdermal patches. Safety in lactation has not been determined with nicotine gum; however, the gum exposes the infant only to nicotine and its metabolites and not the effects of smoking. Nicotine patches are designed to deliver a precise amount of nicotine transdermally over time. The infant is exposed to the effects of nicotine in the mother's milk. However, fewer effects occur than with smoking, and compared with other forms of nicotine therapies, the patch is more predictable.

### Preparation for Caregiving at Home: Rooming In

One technique to support parents also affords the family the opportunity to gain confidence in caring for their infant at home is rooming in with the infant for a defined period, during which time the parents assume all caregiving responsibilities. Support from the NICU

staff is immediately available for answering questions or solving problems.

## PRESCRIPTIONS AND MEDICATION ADMINISTRATION

Many infants will be discharged on multiple medications. Parents should have the medications filled before the infant's discharge, and they should be able to demonstrate their ability to administer the medications at the appropriate time and in the appropriate dose. Parents should be instructed to avoid adjusting or discontinuing medications on their own. Discussion should include assessment of the parents' understanding of the reason for each medication and what adverse effects, if any, to anticipate. Many NICUs have developed medication logs and care diaries as tools to help parents and caregivers keep track of their infant's treatments and other care. This tool can be helpful for infants on multiple medications, those with technology dependence, or those in families with multiple births.

## CHILD FIND AND EARLY INTERVENTION

Preterm infants and any full-term neonate who require neonatal intensive care may be at risk for developmental delays and disabilities. The Individuals with Disabilities Education Act requires all states to have a "comprehensive Child Find system" to ensure that all children in need of early intervention or special education services are located, identified, and referred. State-specific eligibility requirements vary, although all programs are guided by federal regulations. Some states have elected to serve children who are at risk of developmental disability, even if the actual diagnosis has not been made.

Examples of eligibility criteria for referral to the Child Find system portion of the early intervention program include the following:

- Infants born at less than 32 weeks' gestation or with birth weights less than 1,500 g
- Infants who spend 10 days or more in the NICU
- Infants with prenatal exposure to drugs of abuse
- Infants exposed prenatally to therapeutic drugs with known developmental implications (antineoplastic, anticonvulsant, and psychotropic drugs)
- Any infant at risk for a developmental delay

Infants who are also at risk for developmental delay may include infants with suspected hearing loss and infants with experienced meningitis, a birth injury, or head trauma. Many infants will automatically meet eligibility requirements. These requirements vary from state to state, however, and include infants with chromosomal abnormalities, genetic disorders, inborn errors of metabolism, disorders of the nervous system (neural tube defects), congenital infections, low birth weight (criteria vary by state), extreme prematurity (criteria vary by state), severe sensory impairment, HIV and severe infectious disease, toxic exposure, cerebral palsy, grade-III and grade-IV intraventricular hemorrhage, hydrocephalus, neuromuscular disorders, disorders of sense organs, brain injury, and technology dependency (tracheostomy).

## DISCHARGE SUMMARY AND FOLLOW-UP CARE

Follow-up care of the discharged NICU graduate is essential to the medical care of the neonate. The primary care physician should receive a detailed summary of the infant's hospital course and continuing care needs. Optimally, the NICU staff should communicate personally with the pediatrician to discuss and evaluate the salient issues for the child and family. Consideration should be given to allocating additional time for the initial primary care visit because the physician not only has to become familiar with the child's prior and current medical issues, but also has to ascertain from the parents how the first days at home have gone and what their particular concerns may be. Follow-up specialty appointments should also be scheduled before the infant's discharge. The timing of initial pediatric primary care appointment depends on individual patient medical problems. For high-risk infants the follow-up appointment should occur within a few days of NICU discharge. Parents should be given a copy of the infant's medical summary and a schedule of follow-up appointments at the time of discharge (Figure 113-1 and Figure 113-2).

### Discharge Summary

#### History of Present Illness:

Include pertinent maternal, pregnancy, and birth history; Apgar score; and admission assessment (infant's gestational age, weight, length, head circumference, and critical vital signs and laboratory results).

#### Neonatal Intensive Care Unit (NICU) Problems:

Include all of the problems the infant was diagnosed with during the admission, and indicate which problems are currently diagnoses.

#### NICU Course by Systems or Medical Problems:

Make sure to include a section for routine health care maintenance issues, such as immunizations, neurosonographic examinations, and newborn screening tests (newborn screen, retinopathy of prematurity, and hearing).

### Assessment

#### Discharge Plan and Follow-up Care:

Include appointment with primary care pediatrician, subspecialty appointments, pending laboratory or diagnostics tests, Child Find referral, and plan for discharge nutrition, medications, monitoring, and any ongoing treatments.

**Figure 113-1** Sample discharge summary format.

### Neonatal Intensive Care Unit Discharge Planning Checklist

Name: \_\_\_\_\_ Medical Record Number: \_\_\_\_\_

Category	Item	Check	Comment
General admission	Primary care physician	<input type="checkbox"/>	
	Maternal laboratory tests and blood type	<input type="checkbox"/>	
	Integrated medical delivery system (IMDS)	<input type="checkbox"/>	
	Medicaid or insurance for infant	<input type="checkbox"/>	
	Complete physical examination	<input type="checkbox"/>	
Home, placement	Discharge to rehabilitation center; send summary	<input type="checkbox"/>	
	Acute coronary syndrome (ACS) clearance, if necessary	<input type="checkbox"/>	
	Home care referral	<input type="checkbox"/>	
	Home nursing (if necessary)	<input type="checkbox"/>	
	Equipment needed for discharge (apnea monitor, pulse oximeter, oxygen)	<input type="checkbox"/>	
Tests, procedures	Feeding assessment; speech referral, if necessary	<input type="checkbox"/>	
	Child-Find or early interventions	<input type="checkbox"/>	
	Vaccinations	<input type="checkbox"/>	
	Synagis and referrals for prophylaxis	<input type="checkbox"/>	
	Circumcision	<input type="checkbox"/>	
	Head ultrasound	<input type="checkbox"/>	
	Retinopathy of prematurity	<input type="checkbox"/>	
	Hearing test: otoacoustic emissions (OAE) testing for all, and possible auditory brain-stem response (ABR), if criteria is met	<input type="checkbox"/>	
	Hip ultrasound: if abnormal examination and if female and breach	<input type="checkbox"/>	
	Vehicle seat challenge	<input type="checkbox"/>	
Parent education	General teaching for baby care (ie, bathing, feeding)	<input type="checkbox"/>	
	Medication administration	<input type="checkbox"/>	
	Cardiopulmonary resuscitation	<input type="checkbox"/>	
	Smoking-cessation plan, if necessary	<input type="checkbox"/>	
	Feeding plans: how to mix formula, instructions for feeding	<input type="checkbox"/>	
Final discharge disposition	Rooming in, if necessary	<input type="checkbox"/>	
	Medical clearance	<input type="checkbox"/>	
	Social work and ACS clearance	<input type="checkbox"/>	
	Prescription available to parents before discharge	<input type="checkbox"/>	
	Women, infants, children (WIC) program form and prescription for special formula	<input type="checkbox"/>	
	Discharge physical (including weight, length, head circumference, hips, hernias, red reflex)	<input type="checkbox"/>	
	Parent notification	<input type="checkbox"/>	
	Primary care provider appointment	<input type="checkbox"/>	
	Transfer of responsibility to provincial medical director (PMD)	<input type="checkbox"/>	
	All other appointments	<input type="checkbox"/>	

**Figure 113-2** Neonatal intensive care unit discharge planning checklist.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Infant CPR Anytime* (toolkit), American Heart Association ([shop.aap.org](http://shop.aap.org))
- *Preemies: The Essential Guide for Parents of Premature Babies*, 2nd ed (book), Dana Wechsler Linden et al, 2010
- *Toolkit for the Follow-Up Care of the Premature Infant* (Web site), MedImmune and National Initiative for Children's Healthcare Quality ([www.preemietoolkit.com/index.aspx](http://www.preemietoolkit.com/index.aspx))
- *Newborn Screening* (Web page), National Institutes of Health ([www.nlm.nih.gov/medlineplus/newborn-screening.html](http://www.nlm.nih.gov/medlineplus/newborn-screening.html))
- *Disorder Fact Sheets for Parents* (Web page), Screening, Technology and Research in Genetics (STAR-G) Project ([www.newbornscreening.info/index.html](http://www.newbornscreening.info/index.html))

### Medical Decision Support

- *California Perinatal Quality Care Collaborative* (Web site), ([www.cpqcc.org](http://www.cpqcc.org))
- *National Lung Health Education Program* (Web site), ([www.nlhep.org](http://www.nlhep.org))
- *Neonatal Resuscitation Program* (Web site), American Academy of Pediatrics ([www.aap.org/nrp](http://www.aap.org/nrp))
- *Toolkit for the Follow-Up Care of the Premature Infant* (Web site), MedImmune and National Initiative for Children's Healthcare Quality ([www.preemietoolkit.com/index.aspx](http://www.preemietoolkit.com/index.aspx))

## AAP POLICY

- American Academy of Pediatrics Committee on Fetus and Newborn. Hospital discharge of the high-risk neonate. *Pediatrics*. 2008;122(5):1119–1126. Reaffirmed May 2011 ([pediatrics.aappublications.org/content/122/5/1119](http://pediatrics.aappublications.org/content/122/5/1119))
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- American Academy of Pediatrics Committee on Fetus and Newborn, Section on Surgery, Section on Anesthesiology and Pain Medicine, Canadian Paediatric Society Fetus and Newborn Committee. Prevention and management of pain in the neonate: an update. *Pediatrics*. 2006;118(5):2231–2241. Reaffirmed May 2010 ([pediatrics.aappublications.org/content/118/5/2231](http://pediatrics.aappublications.org/content/118/5/2231))
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## Chapter 114

# FOLLOW-UP CARE OF THE GRADUATE FROM NEONATAL INTENSIVE CARE

Judy C. Bernbaum, MD

The scope of pediatric primary care for children who require neonatal intensive care will vary depending on the neonate's underlying medical problems and any sequelae that occur. Most infants who require specialized newborn care will need only routine pediatric primary care, with particular attention paid to periodic developmental surveillance of infants with risk factors for developmental delays and susceptibility to certain illnesses. However, among the most immature and sickest neonates, a comprehensive and coordinated approach to care is necessary that integrates



routine health care, medical and surgical subspecialty care, psychosocial and emotional support needs of the family, and periodic developmental screening—the latter to identify early intervention needs and appropriate resources.

Establishing a medical home for the neonatal intensive care unit (NICU) graduate encompasses the same principles that apply to creating a medical home for any child with special health care needs. Parents have become acclimated to a high-technology, fast-paced hospital environment and have come to rely on a particular set of health caregivers. When their infant is discharged from the hospital, parents must transition to a new physician for their child and a health care system that is complex and, at times, fragmented. Some parents will have felt supported during their infant's hospital experience and think they were true partners in their child's care. Other families will have felt disenfranchised, believing that they were not actively included in decision making about their child's care, or will be unhappy with their child's outcome, continuing health and developmental care needs, or uncertain future. Irrespective of their NICU experience, all parents have concerns about how their child will fare at home, their role as parents, and what the future will bring. Parents of technology-dependent infants must adapt to the challenges of negotiating a vast array of home health services, medical suppliers, and early intervention services that add further stressors on family time and functioning, parenting, and economic resources.

### IDENTIFYING INFANTS REQUIRING CLOSE FOLLOW-UP

There are well-defined risk groups of term and preterm infants who will require specialized follow-up care. Infants in these risk groups may be classified based on biologic risk, the need for specific interventions because of significant fetal or neonatal issues, or social-environmental factors that predispose the infant to adverse outcomes. The National Institute for Child Health and Human Development (NICHD), National Institute for Neurological Disorders and Stroke, and Centers for Disease Control and Prevention (CDC) have identified a subset of infants who are at higher risk for adverse developmental outcomes and who require close neurodevelopmental surveillance and follow-up. This group of babies includes extremely low-birth-weight infants ( $\leq 1,000$  g or  $\leq 28$  weeks' gestation) and infants whose neonatal course has been complicated by neurologic abnormalities such as seizures, intracranial hemorrhage/periventricular leukomalacia, or congenital malformations involving the central nervous system. Infants who experienced profound hypoglycemia, hyperbilirubinemia requiring exchange transfusion, or in utero substance exposure are additional important risk groups who require surveillance and periodic screening through 30 to 36 months of age. In addition, the American Academy of Pediatrics (AAP) recommends that infants who have required neonatal intensive care for longer than 5 days receive periodic neurodevelopmental screening within the primary care setting.

Although many tertiary care neonatal centers offer neonatal follow-up care for high-risk NICU graduates, funding for such programs is limited, and many families live far from existing programs. The AAP and the NICHD have published recommendations regarding the role of the primary care physician (PCP) in the follow-up care of high-risk infants, and the components of health and developmental surveillance that should be provided for high-risk, premature infants.

### PREPARING FOR DISCHARGE

In preparation for hospital discharge, some parents have the opportunity to meet or speak with the physician who will care for their child after the infant's hospital discharge. The PCP may have the opportunity to visit the child in the NICU or may, in some community settings, have assumed responsibility for the infant's care when the baby was transferred to a special care or level II NICU for continuing or convalescent care. In other communities, limited and fragmented care present a challenge for both the hospital team planning for the infant's discharge and the family members who must coordinate and schedule appointments and figure out transportation arrangements, juggling their other responsibilities to comply with their baby's health care requirements.

Comprehensive care programs, either community based or hospital based, have been shown to be effective in reducing life-threatening illness in high-risk infants. However, adherence to recommended follow-up medical care is more likely to be a challenge for families of the sickest infants, particularly when multiple medical appointments are necessary. McPherson and colleagues found that children who required 3 or more medical appointments after their discharge from a pediatric intensive care unit were more likely to miss appointments. Of note was the finding that, after hospital discharge, the children were more likely to complete a primary care visit than follow up with a specialist. Infants who have been transferred from tertiary care units to level I or II nurseries for continuing care are more likely to be readmitted to the hospital and fail to adhere to recommended follow-up care. In addition to a detailed written summary of the infant's hospital course that includes recommendations for the early follow-up subspecialty care needs of the infant, direct communication with the NICU staff can facilitate transfer of care and ensure that the PCP has a complete understanding of the infant's history and discharge plan. Identifying barriers that will interfere with the family's ability to comply with the child's recommended care is also important. This information will help assist the health professional in planning the visit length, given that allotting more than 1 new patient time slot may be necessary to properly assess the infant, address parental concerns about the transition home, adjust medications, plan follow-up appointments, and plan for and review equipment needs if the infant is technology dependent.

An important concern for parents bringing the medically fragile infant into a physician's office is the risk to the baby's health because of a possible exposure to individuals who are sick. Minimizing the time spent in the reception and waiting areas and having

the office staff attuned to the concerns of parents of children with special health care needs can increase parental confidence and satisfaction with the primary care experience. Families also need to know the practice's policies for contacting their child's physician during off hours and for emergencies, as well as which hospital emergency room or urgent care facility to use. Transportation requirements need to be discussed and arrangements made for ambulance or other transportation services as necessary to ensure that the child is able to keep appointments.

The degree of care coordination required of the PCP will vary by community, proximity to specialty care, and availability of high-risk follow-up programs for at-risk infants. Some infants will be enrolled in comprehensive follow-up programs that provide some elements of primary care, whereas other babies may be scheduled for periodic neurodevelopmental surveillance or may need to rely on their pediatric caregiver for these aspects of their care.

## MANAGEMENT ISSUES DURING PEDIATRIC CARE

The specific health care needs of an individual infant or child will be based on the complications or sequelae from their original illness or health condition. The child's and the family's needs will change over time as the child transitions through different health and developmental stages; thus, periodically eliciting the family's assessment of their need for information, resources, and support is important. Parents may be at a different transition point than the professionals involved in the child's care and may express needs that are different from what the physician perceives as necessary or important. Initially, the focus tends to be on ongoing medical concerns as well as infant and early childhood development. During middle childhood through adolescence and young adulthood, parental concerns are focused primarily on the child's academic achievement and school performance, behavior, and social skills. For some families, the child's health issues will continue to be problematic. These issues are discussed in detail in Chapter 115, Health and Developmental Outcomes of Very Preterm and Very Low-Birth-Weight Infants, and Chapter 116, Health and Developmental Outcomes of Selected Medically Complex Neonates.

Components of care for high-risk infants from infancy through adolescence are summarized in Table 114-1. The timing for specialized or more in-depth assessments has been recommended as follows: 3 to 4 and 6 to 8 months corrected age (age adjusted for the degree of prematurity [chronologic age minus the number of weeks born preterm]; corrected age is typically used through 24 months), 12 to 14 months corrected age, 18 to 24 months corrected age, 3 to 5 years chronologic age, and at-school age (8 to 10 years). Components of assessment during these visits should include growth, blood pressure and nutrition, neurologic assessment, gross and fine-motor development, language and communication, socioemotional behavior, health status, and health-related quality of life. Cognitive assessments, either comprehensive or limited

using screening or abbreviated intelligence tests, should be performed when the child is 12 and 24 months corrected age, 3 to 4 years of age, and at 6 and 8 years of age. In addition, a screen for autism spectrum disorders should be performed at 18 and 24 months corrected age. Results of standardized screening or comprehensive developmental testing provide important information that will guide referral for diagnostic or intervention services as needed.

## Transition Home Through the First Year of Life

During the initial transitional period from the hospital through the first 3 months at home, parents' primary concerns are typically focused on feeding, weight gain, elimination, sleep, and adaptation to the home environment (crying, state regulation, and social interaction). In addition, parents are worried about the child's risk for infection and other illnesses, having sufficient medical supplies if the infant is technology dependent, and managing multiple medical appointments and early intervention assessments. Common medical problems experienced by the highest-risk infants are listed in Box 114-1. Parents often report an increasing sense of isolation as family and friends return to their own routines and the parents no longer have day-to-day contact with, and support from, the NICU staff. Communication and partnership building with the child's PCP and subspecialists, as well as communication issues *between* parents and with their family and friends, can also present an important challenge. Often, the assistance provided by home health professionals is an added benefit for many families, especially those who have children with complex medical needs.

Establishing routines can be challenging for families because many preterm infants exhibit sleep problems during the early weeks at home. These problems can be related to immature sleep-awake cycles (day-night cycles), disruptions in sleep patterns caused by the need to administer medications, and heightened parental vigilance because of the infant's perceived vulnerability. The last of these issues can lead to the parent overresponding to the infant's nighttime behaviors, resulting in further sleep disruption. Residual neurologic immaturity and emerging muscle tone abnormalities can contribute to difficulty in caring for and calming the infant. Providing the family with strategies to help calm the infant and to support the infant's state regulation will ease the family's adaptation. Swaddling the infant, keeping the infant's arms and legs close to the body, avoiding sudden movements, and gradually introducing stimuli will support the infant's ability to adapt. Demonstrating the infant's abilities during a routine primary care visit can also provide the parents with valuable insights into their infant's capabilities and developmental needs. Remember, especially when discussing normal developmental milestones, to use their child's corrected age.

The first follow-up pediatric visit after NICU discharge should occur within 1 week of the initial hospital discharge. During the first years of life, infants who required neonatal intensive care have higher, though varying, rates of rehospitalization. Among the most

**Table 114-1****Components of Health and Developmental Surveillance for the Preterm and High-Risk Infant**

<b>TIME FRAME</b>	<b>IMPORTANT HEALTH AND NEURODEVELOPMENT SURVEILLANCE</b>
<b>INFANCY (CORRECTED AGE)</b>	
0–1 mo	<ul style="list-style-type: none"> <li>Follow-up results of neonatal metabolic screen if repeat testing was required at hospital discharge</li> <li>Review specialty follow-up appointments:               <ul style="list-style-type: none"> <li>Refer to pediatric audiologist for initial screening if hospital screening was not documented or to follow-up evaluation based on the initial screening or identified risk factors</li> <li>Refer to ophthalmology as indicated for follow-up of retinopathy of prematurity</li> </ul> </li> <li>Assess growth and nutrition; record on standard growth charts plotting parameters using corrected age</li> <li>Infants with chronic health conditions will need condition-specific assessments</li> <li>Review technologies use, adequacy of equipment function, parent comfort with use, home care support, and continuing need for the technology</li> </ul>
3–4 mo	<ul style="list-style-type: none"> <li>Evaluate family functioning, family stress, and parent-infant interaction</li> <li>Examine for strabismus; refer to pediatric ophthalmologist if present</li> <li>Examine for hip dysplasia; refer to pediatric orthopedist if hip laxity present</li> <li>Assess growth and nutrition; record on standard growth charts plotting parameters using corrected age</li> </ul>
4–6 mo	<ul style="list-style-type: none"> <li>Evaluate family functioning, family stress, and parent-infant interaction</li> <li>Refer for standardized movement, muscle tone, and movement quality assessment</li> <li>Assess growth and nutrition—record on standard growth charts plotting parameters using corrected age</li> </ul>
8–12 mo	<ul style="list-style-type: none"> <li>Evaluate family functioning, family stress, and parent-infant interaction</li> <li>Refer for developmental testing as indicated</li> <li>Refer for standardized movement assessment, assessment of muscle tone and movement quality</li> <li>Screen language, fine-motor adaptive, and personal-social skills</li> <li>Refer for ophthalmologic follow-up vision surveillance and audiologic follow-up, even if screening is normal before NICU discharge.</li> <li>Assess growth and nutrition; record on standard growth charts plotting parameters using corrected age</li> <li>Evaluate family functioning, family stress, and parent-infant interaction</li> </ul>
<b>EARLY CHILDHOOD (CORRECTED AGE)</b>	
15–18 mo	<ul style="list-style-type: none"> <li>Refer for standardized movement assessment</li> </ul>
18–36 mo	<ul style="list-style-type: none"> <li>Screen other areas of development and social interaction</li> <li>Refer for standardized assessment of speech and language skills</li> </ul>
36–48 mo	<ul style="list-style-type: none"> <li>Screen other areas of development and social interaction, including autism screening</li> <li>Refer for standardized assessment of cognition and social-adaptive skills</li> <li>Screen for school readiness</li> <li>Refer to ophthalmologist experienced with children for follow-up vision surveillance</li> </ul>
<b>MIDDLE CHILDHOOD</b>	
6–12 yr	<ul style="list-style-type: none"> <li>Review academic achievement and school performance, attention skills, behavior, peer relationships, self-esteem, and coping skills</li> <li>Review intercurrent or continuing health care issues</li> <li>Assess for hypertension and risk for insulin resistance and metabolic syndrome</li> <li>Refer for psychometric testing as indicated</li> <li>Refer for ophthalmologic follow-up at 9–12 years of age, particularly children with a history of retinopathy of prematurity, irrespective of the need for prior laser or cryotherapy</li> </ul>
<b>ADOLESCENCE</b>	
13–21 yr	<ul style="list-style-type: none"> <li>Review academic achievement and school performance, attention skills, behavior, peer relationships, self-esteem, and coping skills</li> <li>Review intercurrent or continuing health care issues</li> <li>Assess for hypertension and risk for insulin resistance and metabolic syndrome</li> <li>Refer for psychometric testing as indicated</li> </ul>

Adapted from Washington State Department of Health, Children with Special Health Care Needs Program. *Low Birth Weight Neonatal Intensive Care Unit Graduate: Critical Elements of Care*. Washington State Consensus Project. Revised 2002. Available at: [www.medicalhome.org/4download/cec.pdf](http://www.medicalhome.org/4download/cec.pdf). Accessed June 11, 2014.

**BOX 114-1 Continuing Health Problems**

- Anemia
- Apnea of prematurity
- Bone mineralization
  - Osteopenia
  - Rickets
  - Fractures
- Cholestasis
- Feeding difficulties, gastroesophageal reflux disease, oromotor issues
- Gallstones
- Growth
  - Incomplete catch-up growth
  - Slow weight gain
  - Poor or excessive head growth
- Hearing problems: progressive or late-onset hearing loss
- Hypertension
- Hypothyroidism
- Malabsorption, short bowel syndrome, enterostomy losses, constipation, dumping syndrome
- Nephrolithiasis
- Neurologic
  - Seizures
  - Hypertonia or hypotonia
  - Intraventricular hemorrhage
  - Periventricular leukomalacia
  - Developmental delay
- Ophthalmologic issues
  - Vision loss and impairment
  - Strabismus, myopia
  - Field defects, eye motility disorders
- Oral health
  - Enamel hypoplasia
  - Delayed tooth eruption
  - High arched palate
- Pain perception: hyposensitivity and hypersensitivity to painful stimuli
- Postanesthesia complications: apnea
- Respiratory
  - Chronic lung disease
  - Airway complications (subglottic stenosis, laryngo-tracheomalacia)
  - Respiratory infections
  - Increased susceptibility to respiratory syncytial virus
  - Cor pulmonale
  - Sudden death
  - Hypoxia
- Scars, hernias
- Seizures
- Sleep problems
- Sudden infant death syndrome
- Use of chronic technologies
  - Supplemental oxygen
  - Home ventilation
  - Nasogastric tube
  - Gastrostomy tube
  - Tracheostomy
  - Parenteral nutrition
  - Cardiorespiratory monitoring
  - Pulse oximetry

immature infants, 45% of very preterm infants are hospitalized 1 or more times, with nearly 50% of them having 2 or more hospitalizations in this period. The most common causes for hospitalization include respiratory illness, apparent life-threatening events, surgery (hernia repair, laser therapy for progressive retinopathy, enterostomy closure, ventriculoperitoneal shunt revision, placement of feeding tubes), and failure to gain weight.

From 3 months corrected age through 1 year of age, parent concerns continue to focus on the infant's feeding, weight gain, and catch-up growth, as well as the infant's general health. As infants mature, they exhibit improvements in state regulation and ability to handle stimulation and social interaction. Among very preterm or chronically ill young infants, these problems may be persistent. Transient muscle tone abnormalities are common during infancy among preterm infants and include high, low, or mixed tone. This may result in postural or movement difficulties that contribute to feeding or sleep problems, positional plagiocephaly, and quality of, delays in, and acquisition of age-appropriate milestones.

Emerging milestones, particularly motor skills, may be a concern as delays in development become more apparent to the parents, their families, or members of the community. Parents of infants who have experienced a neurologic injury (intraventricular hemorrhage, periventricular leukomalacia or hydrocephalus, neonatal encephalopathy, seizures, or microcephaly) will have ongoing concerns about the risk for cerebral palsy and other neurologic sequelae. The need for early intervention often needs to be addressed. Some families will experience continued erosion of their informal social network, further increasing their sense of isolation. Even parents who have strong family supports and well-established informal support networks will experience isolation. Parents often struggle with the inability of their family and friends to understand and empathize with the challenges and concerns the child and family are experiencing or the family's concerns and fears. When appropriate, encouraging families to participate in parent support groups, sponsored by either hospital or community programs, can be a valuable resource in providing support and guidance to families. Interacting with families who have gone



through similar experiences with their child allows them to share their experiences, verbalize frustrations, learn techniques for coping, and realize that their journey with their child is not unique.

### Toddler and Early Childhood Years

Parental concerns from age 1 to 3 typically focus on motor milestones, communication and language skills, and sensory issues. Generally, infants with motor problems continue to improve and, hopefully, make steady progress. Those with persistent abnormalities in muscle tone may be diagnosed with some form of cerebral palsy. Catch-up growth continues during this time. Infants not previously eligible for early intervention services may require referral for evaluation of speech-language or communication problems or persistent delays in other developmental domains that now meet specific state eligibility requirements. During the preschool years, social immaturity, attention difficulties, and hyperactivity occur in 10% to 20% of preterm and other high-risk children. Emerging learning difficulties will be evident in many children, some also with sensory problems. Social immaturity will be a continuing concern for others. Parents should be advised to observe for learning difficulties and seek early remedial assistance from preschool, nursery, or specialized child-care programs. Children should be screened for autism during this period of time, and a formal evaluation should be performed on those who fail the screening process, with appropriate interventions and referrals made for those diagnosed as being on the autism spectrum.

### Growth and Nutrition Management

Growth patterns of an infant who is born low birth weight, who is preterm, or who is ill at birth provide valuable information about the infant's health. Chronic illness, feeding difficulties, malabsorption, gastroesophageal reflux, increased metabolic and nutritional requirements with inadequate nutritional intake or excessive loss, and social-emotional problems can contribute to aberrant growth. Feeding difficulties may be related to poor oromotor skills, respiratory symptoms, fatigue, or reflux esophagitis. Abnormalities of growth associated with intrauterine growth restriction, genetic or chromosomal disorders, congenital infection, or other syndromes can be responsible for reduced growth potential that prevents expected catch-up growth. Growth measurements should be plotted on standard growth charts, correcting for the degree of prematurity until the child is 24 to 30 months corrected age (see section on catch-up growth). For preterm infants born weighing less than 1,500 g, the CDC National Center for Health Statistics recommends that health care providers

- Use the World Health Organization growth charts to monitor growth of infants and children ages 0 to 2 years in the United States, with the measurements plotted using the *corrected* rather than *chronologic* age
- Use CDC growth charts to monitor growth for children 2 years and older in the United States without the need for correction after 30 months of age

Caloric requirements for adequate growth vary, and feeding recommendations should be adjusted

depending on the trends seen when plotting weight on these charts. An excellent resource for guiding the physician through the nutritional needs of the growing preterm and high-risk infant can be found in the AAP *Pediatric Nutrition* handbook, 7th edition.

### Postdischarge Formula or Human Milk Feeding

Healthy preterm infants require 110 to 130 kcal/kg/day, whereas infants with chronic illness may need up to 150 kcal/kg/day to sustain adequate weight gain and growth. At the time of hospital discharge, most infants are gaining about 10 to 15 g/kg/day, comparable to intrauterine growth rates. However, infants who have been born very preterm or who experience serious illness often have residual caloric and nutritional deficits at the time of discharge; most of these infants leave the hospital with a weight below the expected mean for their gestational and postnatal age. Preterm infants also experience greater morbidity during their first year of life, including more hospitalizations and intercurrent illnesses, that can further affect their feeding and growth.

Tremendous variation often exists in infants' human milk or formula intake. Some infants will be feeding well, ingesting more than 200 mL/kg/day, whereas others are barely achieving intakes of 130 mL/kg/day. The caloric density of a feeding has been shown to influence an infant's intake because infants on lower-calorie (less calorie-dense) feedings will feed up to 20% more than an infant being fed a higher-calorie formula. Preterm infants continue to need higher than normal protein intake to replace deficits that accumulate after birth. Optimal postnatal nutrient intakes for preterm infants have not been fully determined. As a consequence, recommendations regarding target intakes for calcium and phosphorus vary. Recommended mineral intakes range from 100 to 160 mg/kg/day to 150 to 175 mg/kg/day of calcium and from 60 to 90 mg/kg/day to 90 to 105 mg/kg/day of phosphorus. At the time of discharge from the hospital, very low-birth-weight infants will often be provided higher intakes of minerals through the use of transitional formulas than are provided by human milk or formulas intended for term infants. When infants reach a body weight of more than 1,500 g and tolerate full enteral feeds, vitamin D intake should generally be approximately 400 IU/day. Infants with radiologic or biochemical evidence of rickets should have efforts made to maximize calcium and phosphorus intake by using available commercial products and, if needed, direct supplementation with these minerals. The heterogeneity in nutritional status among preterm infants and the differences in growth rates related to gestation, illness severity, and gender at the time of discharge present a challenge to determining an optimal feeding regimen. Special nutrient-enriched formulas are available for postdischarge use in North America and Europe that contain additional protein, minerals, and vitamins and provide 22 cal/oz (73 kcal/dL) and 1.8 g protein/dL. However, study results on the effectiveness of these nutrient-enriched formulas in optimizing growth and development have been mixed. When an infant is volume limited (inadequate intake; fluid restricted), formulas can be concentrated to provide

higher caloric density or supplements can be added to formula to increase caloric intake without substantially increasing volume of intake (see Box 114-2). If an infant is not meeting his or her expected weight gain, because of either feeding difficulties or inability to provide adequate caloric intake, referral to a specialist may be a consideration. Speech or occupational therapists often can address feeding difficulties, whereas a dietitian or nutritionist can help with adjusting the diet by making suggestions on the best way to provide adequate nutrition to result in more appropriate growth.

In a small randomized study of preterm infants less than 35 weeks' gestation who were fed either a nutrient-enriched infant formula or a term formula after hospital discharge, Lucas and colleagues found that the infants fed the enriched formula grew better and had better bone mineralization at 6 to 9 months corrected age. Similarly, Cooke and colleagues demonstrated increased protein intake and greater weight, length, head circumference, and lean and fat mass in preterm infants fed nutrient-enriched formula until 6 months corrected age. Comparison infants who received the nutrient-enriched formula only until they reached term gestation or who were fed a term formula exclusively did not demonstrate these results. Between term corrected age and 6 months corrected, both boys and girls exhibited greater growth when fed a nutrient-enriched formula. Carver and colleagues further refined the understanding of the benefits of feeding a nutrient-enriched formula, demonstrating better growth (weight, length, and head circumference) among infants under 1,250 g at birth (2.75 lb). In a larger randomized trial conducted by Lucas and associates, preterm infants fed a nutrient-enriched formula were heavier and longer at 9 and 18 months corrected age. The effects were greater for preterm boys. No difference in neurodevelopmental outcomes was noted. These benefits were not exhibited if the nutrient-enriched formula was discontinued before

the preterm infant had reached at least 6 months corrected age. Infants who received enriched formulas until term or 2 months corrected age did not demonstrate any benefit. In a separate study by Koo and Hockman, very low-birth-weight, very preterm infants were fed a standard term formula or an enriched preterm formula. Among the infants enrolled in this study, a growth advantage at 1 year of age was noted for infants who were fed the standard term formula. However, details about the volume of study milk and amounts of other nutritional intakes were not recorded for the study subjects. It is possible that the increased energy needs were met by consuming larger volumes of term formula compared with the amount needed by infants consuming preterm formula.

The duration of feeding is an important consideration because most studies point out that the use of nutrient-enriched postdischarge formulas until the preterm infant is 6 to 12 months corrected age promotes better growth.

Postdischarge enriched formulas should be considered for feeding preterm infants, particularly those weighing less than 1,250 g at birth and other preterm babies who exhibit suboptimal catch-up postnatal growth. If used, enriched formula should be continued until the infant is 9 to 12 months corrected age. Preterm infants, such as those with significant chronic lung disease (CLD), higher metabolic needs, or poor postdischarge growth (slowing growth velocity or growth failure), may require continued specialized formula use beyond 12 months corrected age (Box 114-2).

If a standard formula is used at any time during the first 12 months after discharge in a preterm infant, supplemental vitamins and additional iron should be provided. Vitamin supplementation is recommended with a liquid multivitamin until the infant's intake reaches 600 mL/day (20 oz/day). If a postdischarge enriched formula is fed, supplemental vitamins may

### BOX 114-2 Preparation of Higher Caloric Density Preterm Formulas

Preterm Discharge Formulas (Enfacare/Neosure/Good Start Nourish)

1. Wash bottle with soap and water.
2. Rinse it with clean, cool water.

To make 24-calorie/oz formula:

- Measure **11 ounces of water** in a clear measuring cup.
- Add **6 level scoops of powder**. Only use the scoop that comes in your can of formula.

To make 24-calorie HUMAN milk:

- Measure **3 oz of human milk** in a clear measuring cup.
- Add **1 level teaspoon** of preterm infant formula powder. Use a teaspoon that comes in a measuring spoon set.

To make 27-calorie/oz formula:

- Measure **8 ounces of water** in a clear measuring cup.
- Add **5 level scoops of powder**. Only use the scoop that comes in your can of formula.

To make 27-calorie/oz HUMAN milk;

- Measure **3 oz of human milk** in a clear measuring cup.
- Add **2 level teaspoons** of preterm infant formula powder. Use a teaspoon that comes in a measuring spoon set.
- 3. Mix very well and pour into bottle(s).
- 4. Feed immediately or cover and refrigerate.
- 5. Throw out unused mixture after 24 hours.
- 6. Throw out any milk that is still in the bottle 1 hour after a feeding.

Supplements if additional calories are needed

Microlipid: 4.5 kcal/mL

Duocal: 42 kcal/Tbsp

MCT oil: 7.6 kcal/mL

Dry baby cereal: 10 kcal/Tbsp

not be necessary for infants whose intake is more than 200 mL/kg/day. Information about the composition, usage guidelines, and preparation of available post-discharge formulas and nutritional supplements is found in Chapter 112, Continuing Care of the Infant After Transfer From Neonatal Intensive Care. For children older than 1 year who continue to exhibit inadequate growth and weight of less than the 5th percentile for corrected age, nutritional supplementation can be continued using 1 of several specialized, complete formulas that provide 30 kcal/oz.

### Supporting Breastfeeding

Supplementation of infants who successfully transition to exclusive breastfeeding and demonstrate adequate weight gain and growth is not usually necessary. (See Chapter 88, Breastfeeding the Newborn.) Studies comparing preterm infants fed unfortified human milk or standard term formula after hospital discharge demonstrated lower bone mineral content, lower serum phosphorus, and higher serum alkaline phosphatase compared with preterm formula-fed infants. These differences persisted through 12 months of age, but by age 2, human milk-fed infants had caught up to their preterm formula-fed peers. Preterm infants who are exclusively breastfeeding should receive vitamin D and iron supplementation. Adequacy of growth should be closely monitored, with consideration given to supplementation with an iron-fortified standard term or enriched postdischarge preterm formula if an infant is exhibiting a slowing growth velocity or developing signs of nutritional deficiency. The physician should confirm that the infant is not experiencing hypoxemia or increased work of breathing during feeding because this may be contributing to suboptimal weight gain.

A suggested strategy to support continued breastfeeding, if growth is noted to be suboptimal, is as follows:

- Supplement exclusive breastfeeding every 2 to 3 hours during the daytime with formula feeding in the evening and during the night.

Alternatively,

- Enriched preterm formula can be mixed with expressed milk to increase the caloric density and nutrient composition as described in Box 114-2.
- Consider referral to a lactation specialist who has experience with preterm infants.

Supplementation should be continued for at least 6 months, or longer if the infant's growth and nutritional assessment have not normalized within that period. The goal is to achieve growth within the 25% to 50% range for corrected age. Some infants with poor growth, higher metabolic requirements, or specific nutritional deficiencies may need to remain on calorie-dense and nutrient-enriched feedings until 9 to 12 months corrected age. Periodic measurement of serum phosphorus and alkaline phosphatase is also important, given that phosphorus levels under 4.5 mg/dL and an elevated alkaline phosphatase above 1,000 IU/mL may warrant further evaluation and supplementation.

### Tube Feedings

Infants with chronic health conditions or neurologic impairment may not be able to tolerate a portion or all of their enteral feedings by mouth. In addition, infants

with specific nutrient or fluid requirements may require supplementation by tube feeding to ensure an appropriate intake. If tube feedings are necessary, the caregiver should ensure that the infant has opportunities for nonnutritive sucking either by sucking on a pacifier or through partial oral feeding. Some infants may require only episodic supplemental tube feedings until their oromotor skills mature. These babies may be able to have their feedings supplemented using a nasogastric (NG) tube if the parents are comfortable inserting it. Consideration should be given to placement of a gastrostomy tube in infants who are anticipated to require a longer period without full oral feeding (>3–6 months) because there are potential side effects of long-term NG feeding. Long-term tube feeding may be required for infants with neurologic or cardiorespiratory compromise, dysfunctional feeding, or other chronic health conditions. Side effects that may occur with long-term NG feeding include chronic nasal-pharyngeal-esophageal irritation, development of oral aversion, exacerbation of underlying gastroesophageal reflux, serous otitis media, incorrect placement of tube upon insertion, irritation of facial skin where tube is being taped, and rarely, perforation of the esophagus, lung, or stomach.

Infants who have gastrostomy tubes can experience problems caused by leakage or irritation and local infection at the gastrostomy insertion (stoma) site. Leakage may develop because of enlargement of the stoma site or inadequate inflation of the balloon that helps to keep the tube snug against the gastric wall. The amount of water in the gastrostomy balloon should be checked periodically (every 2 weeks); the balloon of an infant should typically contain 3 to 5 mL of water; an older child's balloon should be inflated with 5 to 10 mL of water, but these do vary depending on the individual manufacturer. During feeding, the infant should be positioned upright or right side down. Irritation, bleeding, and localized infection at the stoma site are common problems. Bleeding and irritation may arise as granulation tissue forms in response to tube movement. Applying a topical steroid or, if unsuccessful, cauterizing any granulation tissue that develops around the stoma may also reduce leakage. Localized fungal infections are not uncommon and respond to topical antifungal therapy.

Local care includes gently cleansing with mild soap and water 2 to 3 times per day; ensuring that the gastrostomy balloon is properly inflated and snug against the gastric wall; ensuring appropriate treatment of granulation tissue; and administering topical, systemic, or both forms of treatment of local infection. Tube migration may occur with slippage of the gastrostomy tube tip into the pylorus or duodenum. Measuring the tube and ensuring the external disk is secure against the abdominal wall reduce this risk. Accidental removal is more likely to occur in small infants and during the early weeks after initial gastrostomy tube placement, before complete healing has taken place. Parents can be instructed on how to replace a balloon gastrostomy that is mature (>4 weeks). If the family is uncomfortable replacing the tube themselves, they may be instructed to bring the child to the emergency department or physician's office. Mature gastrostomy tubes that become dislodged should be replaced within 24 hours.

### **Strategies to Support Tube Feeding and Transition to Oral Feeding**

Infants who are tolerating partial oral feeding (at least 50%) can be fed by mouth during the day as much as tolerated and tube-fed the remainder at night using either bolus or continuous feeds. If the presence of the NG tube causes increased gagging, consider removing the tube during the daytime to encourage oral feeding. If the infant does not seem hungry for oral feedings, consider adjusting the feeding volume or feeding interval to allow hunger cues to develop, ensuring that the infant's total daily intake is sufficient to meet nutrient, energy, and fluid needs.

If continuous feeds are given overnight, stop feeding at least 2 hours before the infant awakens in the morning to allow time for hunger cues to develop by the first morning feeding. Gradually decrease the amounts given at night to support increased appetite during the daytime.

When the oral intake is near the total required, discontinue tube feedings on a trial basis and monitor for weight changes. Temporary plateau in weight or loss of up to 5% may be acceptable for 1 to 2 weeks if the infant remains hydrated, well nourished, and otherwise healthy. If the child has a gastrostomy tube, it can be removed after an adequate period of monitoring on full oral feedings (at least 1 month).

### **Infants With Short Bowel Syndrome or Intestinal Failure**

Increased survival among neonates developing intra-abdominal emergencies has resulted in a higher prevalence of infants with short bowel syndrome requiring long-term nutritional support. Short bowel syndrome results from surgical resection, congenital defect, or disease-associated malabsorption with resultant loss of fluid, electrolytes, protein, and micronutrients. The range of clinical problems necessitating extensive bowel resection includes necrotizing enterocolitis, bowel atresia, midgut volvulus caused by a malrotation, and congenital intestinal aganglionosis. The loss of a significant portion of the intestines' absorptive capability can contribute to intestinal dysfunction or intestinal failure. Loss of absorptive function in existing intestinal tissue can cause intestinal failure and can develop following intestinal obstruction, dysmotility, intestinal resection, congenital defect, or disease-induced malabsorption. Infants with gastroschisis and markedly thickened bowel at delivery are at risk for developing intestinal failure. Infants who lose their ileocecal valve during surgery are at additional risk because the ileocecal valve slows intestinal transit time and prevents reflux of intestinal contents and bacteria from the colon into the small intestine. Associated complications include malabsorption of vitamin B<sub>12</sub>, bile salt deconjugation, reduction in bile salt absorption, and impaired intestinal function.

Management of short bowel syndrome and intestinal failure includes minimizing fluid, electrolyte, and nutrient losses, with the goal of promoting growth and optimal nutrition and maximizing the process of bowel adaptation. Long-term parenteral nutrition (PN) support through a secure central catheter is often required for these infants. Intestinal failure-associated liver disease occurs in 40% to 60% of infants with short bowel syndrome. Milder liver dysfunction in the form of

PN-induced cholestasis is also common in infants, with preterm infants at higher risk than term babies (see previous section). Infants on long-term PN support require care from a multidisciplinary team that includes pediatric surgeons, pediatric gastroenterologists, nutritionists, clinical nurse specialists, and home care nurses to assist the parents in caring for their child. When enteral feedings are initiated, continuous feedings through a gastrostomy tube are often the preferred method for feeding. In cases in which the infant has a mucous fistula, refeeding of the effluent from the proximal enterostomy into a distal mucous fistula has been shown to improve weight gain and maintain electrolyte stability. Additional important aspects of the infant's nutrition and intestinal rehabilitation include provision of non-nutritive sucking, oral-motor therapy, and early oral feedings, if feasible.

### **Feeding Problems**

Feeding difficulties are most common during the neonatal period but can remain a problem for preterm infants, as well as for babies who are recovering from severe cardiorespiratory or chronic lung disease, infants with neurologic impairments, and those with craniofacial or gastrointestinal malformations that may interfere with normal feeding. Additional factors that can contribute to feeding difficulties include tracheostomy, gastroesophageal reflux, and repetitive noxious oral stimuli caused by oral suctioning, repeated intubations, nasogastric or orogastric tube placement, and air flow from nasal cannula or nasal continuous positive airway pressure, which may result in feeding aversions. (The process of transitioning to oral feeding is discussed in Chapter 112, Continuing Care of the Infant After Transfer From Neonatal Intensive Care.) Delayed feeding skills may develop in infants who exhibit immature sucking and swallowing patterns, babies who experience frequent or prolonged illness or who fail to transition to age-appropriate feeding methods, infants with gastroesophageal reflux, or infants who are fed inappropriately (such as when force-fed). Oral reflexes that facilitate normal feeding and protect the airway from aspiration may be hypoactive or hyperactive. Tongue thrusting and a hyperactive gag reflex can further interfere with effective feeding. Infants who develop oral hypersensitivity (tactile defensiveness) may be unable to tolerate any oral stimulation and refuse placement of a nipple or spoon in their mouth. Dysfunctional feeding skills may develop in infants with physical, structural, or neurologic deficits, as well as infants with severe reflux. Babies who do not receive appropriate oral stimulation during enteral or parenteral feeding are also at risk. Feeding dysfunction may also develop after a fundoplication or surgical repair of a tracheoesophageal fistula. The primary care physician must recognize and intervene when feeding difficulties become apparent, especially when a persistent plateau in weight gain or poor growth occurs.

Referral for a feeding evaluation with a feeding therapist or interdisciplinary team should be considered if the parents or caregivers are reporting that feeding is stressful or difficult and any of the following is persistent:

- Feedings that consistently take longer than 45 minutes
- Feeding more frequently than every 2.5 to 3 hours resulting from infant fatigue, food refusal or



avoidance behaviors, or difficulty achieving an adequate feeding volume

- Parent needing to enlarge or cut a nipple hole for the infant to suck human milk or nonthickened formula successfully from the nipple
- Parents reporting that the only way the infant will complete a bottle is during sleep
- Parents having difficulty interpreting or responding appropriately to the infant's cues
- Disrupted sleep associated with crying or a parental perception of the infant being in pain
- The infant exhibiting significant discomfort during or for 30 minutes after feeding, including
  - Arching, grimacing, grunting, leg stiffening
  - Multiple swallows, coughing, emesis
  - Significant loss of fluid during feeding, poor lip seal, wide jaw excursion

- Heavy breathing or nasal flaring
- The need for frequent rest periods or pacing during feeding

Among infants who are unable to orally feed because of oromotor coordination difficulties or aspiration risk, the goal of feeding therapy is to attempt to normalize oral sensorimotor development and to develop protective reflexes and oral motor skill. Oromotor difficulties and aspiration risk can be further evaluated with a modified barium swallow study, which may help to direct the approach taken by a feeding therapist. Infants with significant feeding issues who are otherwise typically developing remain at risk for later communication disorders involving expressive language. Box 114-3 outlines a series of anthropometric, clinical, feeding, and dietary “red flags” that should alert the physician to the need for

### BOX 114-3 Anthropometric, Clinical, Feeding, and Dietary “Red Flags” for High-Risk Infants

#### ANTHROPOMETRIC

- Weight for age or weight for length <5% on the standard CDC growth chart for corrected age
- Weight for age or weight for length >95%
- Slowing growth velocity, weight loss, or significant decline in percentiles, especially if decline in weight percentile precedes decline in length
- Poor weight gain for age, adjusted for prematurity up to 24 mo of age
  - Term (40 wk PMA) to 3 mos: <20 g/day (<5 oz/wk)
  - 3 to 6 mo: <15 g/day (<3.5 oz/wk)
  - 6 to 9 mo: <10 g/day (<2 oz/wk)
  - 9 to 12 mo: <7 g/day (<1.5 oz/wk)
  - 1 to 2 yr: <1 kg (2 lb)/6 mo
  - 2 to 5 yr: <0.7 kg (1.5 lb)/6 mo
- Disproportionate head growth
  - Term to 3 mo: <0.5 cm/wk
  - 3 to 6 mo: <0.25 cm/wk
  - Any time during infancy: >1.25 cm/wk

#### CLINICAL

- Vomiting
- Diarrhea
- Constipation
- Chronic health conditions
- Chronic medication use that can affect nutritional status

#### FEEDING

- Use of technology to support nutrition
  - Gastrostomy tube, nasogastric or jejunal tube feeding
  - Supplemental feeding systems or lactation aids
  - Home parenteral nutrition
- Parents have difficulty interpreting or responding appropriately to feeding cues

- Prolonged feeding duration, insufficient intake, or difficulty with feeding or food progression

#### INFANTS

- More than 30 min to complete a feeding
- Fussy or distressed during feeding
- Respiratory distress during feeding
- Difficult to wake for feeding
- Feeding fatigue
- Frequently gags, coughs, or chokes during feeding
- Refuses feeding or arches backward during feeding
- Limited intake
  - Fewer than 5 feedings/day or less than 24 oz/day
  - Older than 6 mo corrected age not yet starting spoon feeding (persistent tongue thrusting, oral sensitivity)

#### TODDLERS

- More than 45 min to complete a meal
- Inappropriate intake
  - Fewer than 4 feedings/day or less than 16 oz milk/day with no other sources of dietary dairy products
  - Older than 1 yr drinking more than 32 oz cow milk/day
  - Older than 1 yr not taking finger foods
- Limited dietary intake—exclusion of 1 or more food groups
- Mealtimes are frustrating for parent or child or both
- Inappropriate formula preparation or use
  - Low iron formula
  - Using enriched preterm formulas for nonrecommended purposes
  - Adding inappropriate supplements to infant formula or breast milk
  - Adding insufficient or excess water during infant formula preparation (overfeeding: more than 40 oz/day)

CDC, Centers for Disease Control and Prevention; IHDP, Infant Health and Development Program; PMA, postmenstrual age.

Adapted from Groh-Wargo S, Thompson M, Cox JH, eds. *Nutritional Care for High-Risk Newborns*. 3rd ed. Chicago, IL: Precept Press; 2000. Used by permission.

evaluation of the infant's feeding ability and appropriateness of the nutritional intake. Sample questions to assist the provider in assessing the infant's feeding proficiency are provided in Box 114-4.

Feeding an infant is normally a relaxing, nurturing act that plays a role in parent-infant bonding. In the presence of a feeding disorder, feedings may become a major source of stress, frustration, and anxiety for the infant, parent, and physician; thus, early recognition of these issues is essential.

### Management of Regurgitation

Regurgitation is common among infants and must be distinguished from the potentially more serious gastroesophageal reflux disease. Strategies for the management of infants with significant gastroesophageal reflux have been published by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and are summarized in Chapter 112, Continuing Care of the Infant After Transfer From Neonatal Intensive Care. (See also Chapter 255, Gastroesophageal Reflux Disease.) Techniques to manage the common effects of regurgitation are based on symptom reduction or symptom control. Infants who are vomiting as a result of overfeeding benefit from smaller, more frequent feedings. If the infant is not gaining adequate weight, increasing the caloric density of the infant's formula can promote weight gain without the need to increase the feeding volume. Reduction of air swallowing before or after feeding can be controlled by starting the feeding before the infant cries for a prolonged period. Use of an angled bottle or positioning the bottle so that the nipple is filled will reduce the amount of air swallowed. Proper positioning of the baby and cheek support are recommended to ensure that the infant grasps the nipple correctly and is able to maintain good lip closure on the nipple. Avoiding excessive stimulation during and after feeding is another effective strategy to limit vomiting. Prone positioning is no longer recommended unless

the infant is continuously monitored. Use of hyperosmolar formulas ( $\geq 27$  kcal/oz) or fat supplements should be avoided because these forms of caloric supplementation can delay gastric emptying.

### Constipation

Constipation is common in premature infants. Factors that contribute to difficulty with stooling include decreased abdominal muscle strength and intestinal motility, decreased free water intake from nutrient-dense feedings, an increased incidence of mechanical gastrointestinal dysfunction after episodes of necrotizing enterocolitis or other gastrointestinal complications, and an increased incidence of muscle tone abnormalities associated with preterm birth or significant illness. A thorough examination is also important to evaluate the infant for the presence of anterior anal displacement, an anatomic cause of constipation. Dietary manipulation to provide more fiber (non-rice-containing cereal, strained prunes or prune juice, pears or apricots, spinach) can be tried for infants older than 4 months corrected age who are tolerating complementary feedings. Milk of magnesia and osmotic laxatives such as a malt soup extract, polyethylene glycol, and lactulose can be considered in the treatment of uncomplicated constipation in older infants. Mineral oil should be avoided in children younger than 2 years or if the child has lung disease or swallowing problems because of the risk for aspiration. Consultation with a pediatric gastroenterologist should be considered for infants with persistent symptoms to rule out any anatomic abnormalities.

### Introduction of Solid Foods

Introduction of solid foods into the diet of the high-risk infant will depend on several factors, in particular the infant's readiness and ability to accept complementary foods by mouth. In general, introduction of solid foods can begin at 4 to 6 months corrected age, provided that the infant exhibits appropriate postural control of the head, neck, and trunk; decreased tongue thrusting; and an interest in feeding. Although some preterm infants with sucking difficulty may prefer feeding solids by spoon, others may exhibit difficulty tolerating the thickened texture of solid food or demonstrate aversive responses to the forms of oral tactile stimulation associated with spoon feeding. So as not to interfere with the adequacy of formula intake, a general rule of thumb to offer parents is to hold off on the introduction of solid foods until the infant is consuming between 28 and 32 ounces of formula per day. Recent studies have suggested that breastfed infants benefit most from introducing meats as the first solid food because they are rich in iron, which is diminishing during the second half of the first year. Meats are good sources of high-quality protein, iron, and zinc and provide greater nutritional value than cereals, fruits, or vegetables.

### Catch-up Growth

Most catch-up growth occurs during the first 2 to 3 years of life, with a significant growth spurt between 36 and 40 weeks postmenstrual age. As discussed in Chapter 115, Health and Developmental Outcomes of Very Preterm and Very Low-Birth-Weight Infants,

#### BOX 114-4 Sample Feeding Questions

- Is feeding your baby unusually stressful?
- How much time does it take to feed your baby?
- Is there any dribbling of milk down your baby's chin while he/she is feeding?
- What type of nipple are you using?
- Have you made any changes or modifications to the nipple or the baby's feeding routine since the baby has come home?
- Does the baby seem uncomfortable during or after the feeding? Does he/she cry or arch frequently? What about vomiting or spitting up?
- Does the baby suck a pacifier? If so, can he/she keep it in his/her mouth by himself/herself while sucking? (If not, this suggests low oromotor tone or oral tactile sensitivity or both.)

very low-birth-weight children often remain lighter, shorter, and with smaller head size through early to middle childhood.

Head growth is usually more rapid than weight gain and is often the first parameter to catch up. Rapid head growth must be distinguished from pathologic head growth caused by late-onset hydrocephalus and may require neuroimaging to ensure that progressive ventriculomegaly is not developing. Some infants exhibit head growth that crosses head circumference percentiles, but this growth should rarely exceed the 97th percentile. Often, increased extra-axial fluid (subarachnoid) can be a benign cause for this increase, noted as a head circumference greater than the 95th percentile between 3 and 12 months corrected age, which then plateaus rather than continuing to increase. However, in some cases this may not be benign and may be associated with an increased risk for future developmental delays. The head circumference should be measured at each visit during infancy. Cranial imaging is required if the rate of head growth is more than 1.25 cm/week or if any signs or symptoms are noted of increased intracranial pressure or changing neurologic status. Suboptimal brain growth, reflected in a head circumference declining more than 2 standard deviations below the mean, increases the infant's risk for developmental delays. Growth velocities for weight and length vary significantly, and an increase in weight may precede an increase in length. Growth velocity may fluctuate as the infant increases activity levels, experiences an intercurrent illness, or has feeding difficulty, worsening reflux symptoms, or changes in diet and caloric intake. Low weight for length or a decline in all growth parameters suggests inadequate nutritional intake. Obesity may also develop in infants who were preterm or who experienced poor weight gain while in the hospital. Parents become hypervigilant about feeding and food intake or may be unable to read their infant's cues, interpreting crying and fussiness as signs of hunger. Such issues can lead to overfeeding the infant.

### **Small-for-Gestational-Age Infants**

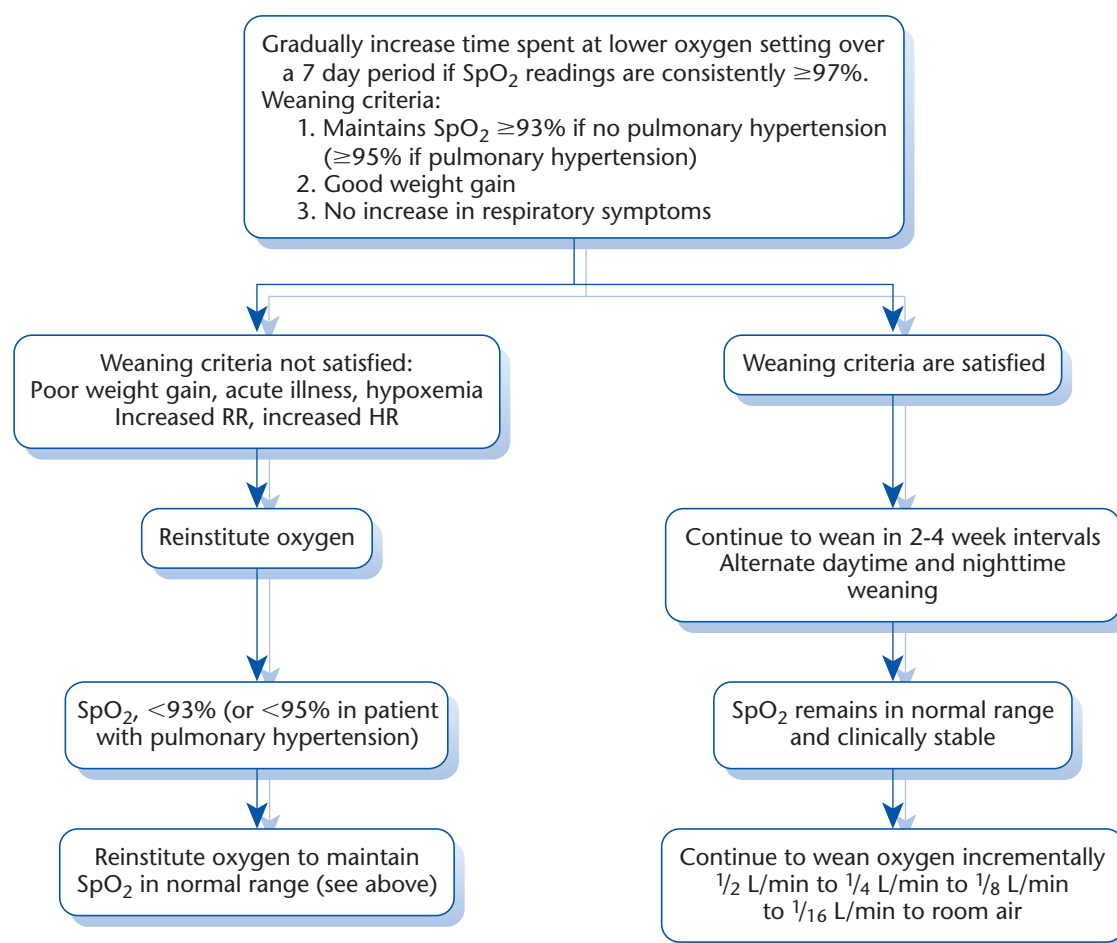
Growth potential for infants born small for gestational age (SGA) depends on the underlying cause of the fetal growth abnormality and is most likely to be limited for specific infants who are less than the 3rd percentile for gestational age at birth. Seventy percent to 80% of SGA children will exhibit catch-up growth during the first years of life. Investigations are ongoing about the potential benefits of hormonal therapy (growth hormone) for the 10% of SGA children who do not exhibit catch-up growth. In a 2007 consensus statement, the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society recommend that SGA children who do not demonstrate catch-up growth should be referred for early monitoring, evaluation for possible endocrine and metabolic disturbances, and neurodevelopmental assessment for potential delays warranting early intervention. Consideration of early therapy with growth hormone should be given to children between 2 and 4 years of age whose height remains more than 2.5 standard deviations below the mean for age.

### **Chronic Lung Disease**

Chronic lung disease (CLD), which includes bronchopulmonary dysplasia (BPD), is a significant health condition affecting many graduates of neonatal and pediatric critical care. BPD/CLD refers to unresolved lung disease following acute lung injury in the neonatal period. Discussion about pathogenesis, pathophysiologic features, and early management strategies can be found in Chapter 112, Continuing Care of the Infant After Transfer From Neonatal Intensive Care; Chapter 100, Respiratory Distress and Breathing Disorders in the Newborn; and Chapter 113, Discharge Planning for the High-Risk Newborn Requiring Intensive Care. Many infants continue to have symptoms after discharge home from the hospital and may episodically exhibit the following signs: tachypnea and tachycardia, paradoxical respirations (see-saw pattern during wakefulness), retractions, cough, wheezing, pallor or cyanosis, irritability or lethargy, poor feeding, and poor weight gain or weight loss. Additional conditions that can further exacerbate CLD symptoms include gastroesophageal reflux, upper airway obstruction caused by tracheomalacia, bronchomalacia, or subglottic stenosis; acute, intercurrent infections; high altitude for infants residing well above sea level; and poor compliance with home oxygen, bronchodilator, or diuretic therapy. Optimal management for the infant with CLD involves a combination of strategies aimed at optimizing the infant's nutrition, respiratory treatment (oxygen, medications), avoidance of infection or exposure to secondhand smoke, and parental education to support and optimize the child's care. Figure 114-1 provides a sample algorithm for weaning home oxygen therapy. Box 114-5 describes strategies to optimize the care of children with CLD.

If the infant is discharged home on diuretics, then the question arises as to when these medications can be weaned or when the infant can be permitted to outgrow the discharge medication dose. The diuretics can be weaned if the infant remains clinically well, exhibits adequate weight gain, has no evidence of respiratory distress, and has an improved lung examination. The lung fields should be clear to auscultation, with a heart rate and respiratory rate that remain in the normal range for the infant's age. The infant should not have any evidence of hepatomegaly (because of heart failure or lung hyperinflation), should be weaning from or stable on supplemental oxygen, and should have no signs of fluid retention.

Infants who have difficulty weaning from supplemental oxygen should be evaluated for adequacy of their caloric intake because their energy and nutrient needs may have increased. Medication doses should be reviewed and doses adjusted for weight gain. Consideration should also be given to adding medications depending on symptoms. Consultation with a pediatric pulmonary specialist can assist the PCP in optimizing the infant's respiratory care. The infant's history should be reviewed to determine whether new or worsening reflux symptoms or signs of aspiration are present. The infant's oxygen saturation should be checked in all activity states and the oxygen concentration adjusted to maintain the oxygen saturation at



**Figure 114-1** Weaning home oxygen therapy. *HR*, heart rate; *RR*, respiratory rate.

### BOX 114-5 Strategies to Optimize Care of Infants With Chronic Lung Disease

#### RESPIRATORY

- Oxygen saturation should be maintained higher than 92% to 93% for infants with bronchopulmonary dysplasia (but without pulmonary hypertension)
- During sleep, the oxygen saturation (measured using pulse oximetry) should be kept above 93% because this has been shown to improve sleep architecture
- Infants who have evidence of pulmonary hypertension should be maintained at a target range of 94% to 96%<sup>a</sup>
- Infants should be closely monitored for illness and acute or subtle signs of hypoxemia or bronchospasm
- May need to increase or reinstitute oxygen therapy
- May need to initiate or increase the frequency of bronchodilators or corticosteroids

#### MEDICATIONS

- Diuretics: try to wean off as soon as possible after discharge
- Hydrochlorothiazide: 20 to 40 mg/kg/day divided 2 to 3 times per day
- Spironolactone: 2 to 4 mg/kg/day divided every 12 hr (if needed to offset electrolyte imbalance)
- Potassium chloride: 1 to 4 mEq/kg/day divided every 6 to 12 hr (if electrolyte imbalance noted)
- Bronchodilators: used if there is a component of reversible airway obstruction and recurrent symptoms (tachypnea, cough, or wheeze); avoid chronic use
  - Albuterol: 0.5 to 2.5 mg (0.1–0.05 mL) by nebulizer or 90 to 180 mcg (1–2 puffs) by metered dose inhaler every 4 to 6 hr



**BOX 114-5 Strategies to Optimize Care of Infants With Chronic Lung Disease—cont'd**

- Ipratropium bromide: 250 to 500 mcg ( $\frac{1}{2}$ –1 vial) by nebulizer or 18 to 36 mcg (1–2 puffs) by inhaler 20 min before albuterol (if not stabilized on  $\beta$ -agonist alone).
- Levalbuterol: 0.62/3 mL to 1.25 mg/3 mL solution by nebulizer or 1 to 2 puffs inhaler (45 mcg/actuation) every 4 to 6 hr used in lieu of albuterol (if side effects noted from albuterol)
- Anti-inflammatory drugs
  - Inhaled nonsteroidal: cromolyn sodium: 20 mg (2 mL) by nebulizer or 1,600 mcg (2 puffs) TID (2–4 wk required for adequate trial)
  - Inhaled steroids (side effects minimized by use of a spacer device)
    - Budesonide: 0.25–0.5 mg every 12–24 hr
    - Fluticasone: 44 mcg/puff (1–2 puffs) every 12 hr up to 110 mcg/puff (1 puff BID)
    - Beclomethasone: 40 to 80 mcg/puff (1–2 puffs) every 12 hr
  - Oral prednisone for serious acute exacerbations: 2 mg/kg initial dose, then 1 mg/kg every 12 hr for 5 days (starting 12 hr after initial dose)

**PREVENTION OF INFECTION AND REACTIVE AIRWAYS DISEASE**

- Respiratory syncytial virus and influenza virus prophylaxis
  - Avoid secondhand smoke and vapor exposures: paint, kerosene, strong perfumes, aerosol sprays, incense, fireplace smoke, or soot
  - Limit exposure to crowds and large child-care settings
  - Hand washing

**OXYGEN THERAPY**

- Can be weaned to a lower oxygen concentration (lower flow rate) when oxygen saturations are routinely  $>97\%$  and when the infant exhibits: (see Figure 114–1)
  - No symptoms of respiratory distress or decreased stamina

- Sustained, adequate weight gain
- No recent intercurrent illnesses and improving overall health status
- The ability to maintain oxygen saturation at or above 95% after 30 to 40 min on the proposed lower oxygen setting without any increase in respiratory symptoms. Close monitoring for several days to assure stable oxygen saturations
- No compensatory tachypnea, tachycardia, pallor, cyanosis, or respiratory distress
- No change in activity level, endurance, or increase in irritability

**FEEDING AND NUTRITION**

- Provide adequate calories to promote a weight gain of 15 to 30 g/day; to realize catch-up growth, weight gain of 45 to 60 g/day may be necessary
  - Increased calorie requirements resulting from increased work of breathing and greater calorie consumption
  - Infants often need 120 to 150 kcal/kg/day
  - Use nutrient-dense feeding, providing 22 to 26 kcal/oz (increasing further by adding carbohydrate and/or fat supplements) with close monitoring of fluid and electrolyte status; for children older than 1 yr, there are nutritionally complete formulas that provide 30 kcal/oz
  - Infants with moderate to severe chronic lung disease may require fluid restriction; attention is needed to provide appropriate calories without giving an excessive solute load that can cause additional complications
  - Consider tube feeding to supplement oral feeding if inadequate weight gain occurs with oral feedings alone
  - Closely monitor the infant for signs of feeding difficulties and initiate early referral for feeding therapy if appropriate
- Infants with signs of gastroesophageal reflux disease should be treated aggressively

\*Abman SH. Monitoring cardiovascular function in infants with chronic lung disease of infancy and childhood. *Am J Respir Crit Care Med.* 2003; 168(3):356–396.

From Panitch H. Bronchopulmonary dysplasia. In: Libby RC, Imaizumi SO, eds. *Guidelines for Pediatric Home Health Care.* 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009:317–344.

or above 92% to 93%. The infant should be screened for significant anemia that may be contributing to symptoms. Additional testing can include a chest radiograph, an electrocardiogram, and possibly an echocardiogram to evaluate for worsening pulmonary disease (atelectasis or infiltrates) or cardiovascular sequelae (pulmonary hypertension, right ventricular heart failure/cor pulmonale) associated with progressive CLD. A blood test for B-type natriuretic peptide can be of additional benefit in assessing degree of right heart failure.

**Infants Discharged on Home Monitoring**

Home cardiorespiratory monitoring may be required for infants with persistent apnea or apparent life-threatening

events, those discharged home on supplemental oxygen or methylxanthines, and babies with chronic conditions or malformations that impair cardiorespiratory function. If home monitoring is prescribed, an event recorder monitor capable of data storage (memory) should be used. The parents and all caregivers of infants discharged on home monitoring should have CPR training as well as be educated on how to respond to alarms before discharge. Within 1 week after discharge, follow-up contact with staff from the home monitoring program should occur. Subsequent follow-up contacts are often within 2 to 4 weeks and may entail a visit to the apnea center or communication by phone. Depending on the reason for home monitoring, many physicians will discontinue monitoring after a symptom-free period of 4 to

6 weeks (best documented by a monitor download); some physicians will obtain a monitor download (performed at home) or refer the infant for a diagnostic sleep study to assess the infant for any evidence of central or obstructive events that warrant continued therapy, monitoring, or both. If the infant has an abnormal study 4 to 6 weeks after discharge, monitoring can be continued for an additional 4 to 6 weeks, followed by repeat testing for persistent abnormalities. If a preterm infant is discharged on a methylxanthine, such as caffeine, the medication may be discontinued when the infant reaches term gestation, provided that the baby is not having any symptoms or monitor alarms. A monitor recording or polysomnographic study should be obtained 7 to 14 days after discontinuing the medication. If the study is normal, then monitoring can be safely discontinued. If the study is abnormal, monitoring should be continued. The decision whether to reinstitute methylxanthine treatment is typically based on the severity of abnormalities documented on the recording.

### Outpatient Screening

Follow-up care for high-risk infants should include periodic screenings beyond the components of care that are routine for full-term infants based on the infant's chronic conditions and risk factors.

### Hearing Screening

Continued surveillance and periodic hearing testing are necessary for infants at risk for delayed-onset or progressive hearing loss. Infants who fail or miss NICU hearing screening must have follow-up testing scheduled. Infants with known hereditary (genetic) or acquired conditions associated with a high risk for hearing loss should be referred for medical evaluation and comprehensive audiologic and otologic evaluation. Factors to consider when determining the frequency of periodic hearing testing, beyond parental concern, include a family history of permanent hearing loss or a syndrome with associated hearing loss, the need for intensive care for more than 5 days or assisted ventilation longer than 10 days, and prolonged exposure to ototoxic medications (aminoglycosides such as gentamicin and tobramycin) or loop diuretics (furosemide). Infants who have recovered from postnatal infections associated with sensorineural hearing loss, including bacterial meningitis and in utero infections such as cytomegalovirus, herpes, rubella, syphilis, or toxoplasmosis, also require serial hearing testing. Babies treated for severe hyperbilirubinemia (those requiring an exchange transfusion) or who experience respiratory failure necessitating extracorporeal membrane oxygenation are also at high risk for progressive or late-onset hearing loss and should have follow-up hearing tests every 6 months until 3 years of age.

### Ophthalmologic Examinations

Follow-up of preterm infants with retinopathy of prematurity (ROP) should adhere to the screening and surveillance guidelines issued by the American Association of Pediatric Ophthalmology and Strabismus and the American Academy of Ophthalmology

in collaboration with the AAP. The frequency of surveillance is based on the examining ophthalmologist's findings. The Canadian Association of Pediatric Ophthalmology and the United Kingdom have similar guidelines regarding the timing of initial screening and subsequent surveillance. The risk for vision loss from ROP is low after the preterm infant has reached 45 weeks postmenstrual age without developing prethreshold or more severe ROP, if the infant's retina is vascularized into zone III without evidence of retinopathy in zone II, or if the retina is fully vascularized. At this point, serial ROP screening can be discontinued. However, periodic surveillance of visual acuity and other ocular morbidity should continue. Preterm infants should be examined by a pediatric ophthalmologist at 6 and 12 months corrected age, before school entry, and again at 9 to 12 years of age. Robaei and colleagues recently reported on visual morbidity affecting moderately preterm and low-birth-weight children who were born between 32 and 36 weeks' gestation, weighing between 1,500 and 2,499 g. Both groups of children were found to be at higher risk for development of amblyopia, strabismus, and decreased visual acuity. Low-birth-weight children were also more likely to exhibit anisometropia.

### Neurodevelopment and Behavior

Neurologic immaturity, sensory defensiveness, and transient muscle tone abnormalities can cause concern for families caring for preterm babies and infants recovering from serious illness. Strategies to support these infants' ability to tolerate stimulation and handling include using calming techniques, using containment positioning during holding and especially bathing, and cautioning parents against infant swing use because this causes sudden changes in movement patterns. Calming techniques consist of swaddling and containment (ie, holding the infant with arms and legs flexed close to the body). The infant should be swaddled or positioned using containment before being moved. Sudden movements should be avoided. Pacifiers can be helpful for infants who have an organized sucking response and are receptive to the pacifier. Family members must be made aware of the early developmental needs of the infant recovering from a very preterm or traumatic birth. Infant sleep should be protected to promote development and infant regulation. Recognizing and responding to the infant's neurodevelopmental cues can help the infant's adaptation to the environment and support the infant's increasing tolerance of handling and other forms of sensory stimulation. Parents benefit from guidance about their infant's ability to signal their needs through movement, facial expressions, and breathing patterns, and about how to interpret and respond to these behavioral cues. Some neonatal units have therapists or psychologists trained in the NIDCAP (Newborn Individualized Developmental Care and Assessment Program), an assessment performed with parent participation at the bedside that highlights the strengths and weaknesses of the infant. These sessions can help to teach parents about their child and make recommendations on

how to encourage continued developmental progress. During the early weeks and months after hospital discharge, preterm infants may be more irritable and less responsive to their environment and social interactions. They typically need more help in calming and learning to self-soothe. The primary goal of caregiving is to match the caregiver's responses to the infant's needs without being intrusive or overwhelming the infant. Consistent caregiver responses to the infant's cues help the infant learn to anticipate and expect a response. Exposure to electronics such as television and handheld devices should be avoided before 2 years corrected age.

As the infant matures and recovers, parents' concerns about infant vulnerability can affect their parenting skills and contribute to child behavior problems over time if they have difficulty with limit setting and discipline. Symptoms of posttraumatic stress disorder (PTSD) are increased for parents of NICU graduates, and the hypervigilance that is a hallmark of PTSD can contribute to parental overprotection. Overprotective behaviors can result in infant sleep disruption and interfere with normal infant exploration, which plays a key role in development. Parents will benefit from support and guidance about strategies to encourage appropriate infant development. Often, support can come from therapists within early intervention programs serving infants birth to age 3 years or interdisciplinary professionals associated with follow-up programs. Many families will consult baby books and multimedia resources and search the Internet for information and guidance about their infant's particular health issues and routine aspects in infant care. Parents should be reminded to adjust for their infant's prematurity when reading information about anticipated growth and development. Families will also benefit from assistance, available from their PCP, early intervention therapist, or interdisciplinary professional, with sorting through the myriad materials in press, in the media, and on the Internet to discern factual information.

### Family Adjustment

The stress of a preterm or sick newborn can have serious effects on parents and siblings, cause significant economic hardship, and lead to family disruption and dysfunction. Parents often feel isolated and experience a wide range of emotions ranging from euphoria to despair. Discord may develop between the parents, or between the parents and other family members or members of the infant's medical team. Each parent and family member has unique coping abilities, values, beliefs, and preferences. Grandparents, extended family members, and friends can be a source of emotional support and respite for the parents. The converse may also occur when parental perspectives and wishes differ from the values and beliefs of other family members or friends. Siblings may be or feel neglected and may exhibit behavioral changes caused by disruption in the family routine and associated parent distraction and distress. Child vulnerability (vulnerable child syndrome) is discussed in Chapter 115, Health and Developmental Outcomes of Very Preterm

and Very Low-Birth-Weight Infants, and Chapter 116, Health and Developmental Outcomes of Selected Medically Complex Neonates. All the typical concerns of parents of healthy infants are exaggerated when the child is born prematurely or with a birth defect, or has experienced significant neonatal illness. Parents should be encouraged to normalize their care routines for their preterm or recovering infant as much as possible. Having opportunities to connect with other families of similar children is helpful for families who have a premature or sick infant because they can gain insight and support from their shared experiences. A subset of parents of preterm infants will experience serious symptoms of anxiety, post-traumatic stress, or depression that extend well beyond the neonatal period. These symptoms are known to have a significant detrimental effect on parent-child relationships and child development. The likelihood of parents developing these more lasting mental health concerns is not necessarily directly related to the severity of the infant's medical course, and predisposing parental factors play a significant role in determining risk. In these cases, parents will benefit from psychological or psychiatric intervention. There are several mental health screening tools available for use in primary care. See [www.integration.samhsa.gov/clinical-practice/screening-tools](http://www.integration.samhsa.gov/clinical-practice/screening-tools) for a sample. Guidance on assisting families who are confronting an unfavorable diagnosis or chronic illness for their infant is found in Chapter 9, Partnering With Families in Hospital and Community Settings, and Chapter 67, Palliative Care and Bereavement.

If developmental concerns become apparent or persist beyond age 3 years, referral can be made for an evaluation in the federally mandated 3- to 5-year-old assessment programs that are administered by the county or school district of residence. Those caring for a child who is struggling in any developmental domain, including a physician, nurse, therapist, or family member, can ask for such an evaluation. Given the higher rates of learning disabilities, attention-deficit/hyperactivity disorder, emotional and behavioral disorders, and autism in this high-risk population, these evaluations can be quite helpful in identifying any problems that may need intervention well before official school age or put a parent's mind at rest if, in fact, the child is developing within the normal range for their age.

### ACKNOWLEDGMENT

This chapter's guidance on introduction of solid foods is adapted from Meek JY, ed. *New Mother's Guide to Breastfeeding*. 2nd ed. New York, NY: Bantam Books; 2011. Copyright © 2011 American Academy of Pediatrics.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *American Family Physician* (Web site), ([www.familydoctor.org](http://www.familydoctor.org))
- *Born Early (Preterm): At the Hospital* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Born Early (Preterm): Health Concerns* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

- *Cleft Palate Foundation* (Web site), ([www.cleftline.org](http://www.cleftline.org))
- *Cystic Fibrosis Foundation* (Web site), ([www.cff.org](http://www.cff.org))
- *March of Dimes* (Web site), ([www.marchofdimess.com](http://www.marchofdimess.com))
- *Mothers of Supertwins* (Web site), ([www.mostonline.org](http://www.mostonline.org))
- *National Down Syndrome Society* (Web site), ([www.ndss.org](http://www.ndss.org))
- *Multiples of America* (Web site), ([www.nomotc.org](http://www.nomotc.org))
- *Nemours Foundation: Kids Health* (Web site), ([www.kidshealth.org](http://www.kidshealth.org))
- *Parenting your Premature Baby & Child: The Emotional Journey* (book), Deborah L. Davis and Mara Tesler Stein, 2004
- *Preemie Milestones* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/baby/preemie/Pages/Preemie-Milestones.aspx](http://www.healthychildren.org/English/ages-stages/baby/preemie/Pages/Preemie-Milestones.aspx))
- *Support Organization for Trisomy* (Web site), ([www.trisomy.org](http://www.trisomy.org))
- *The Premature Baby Book* (book), William Sears et al, 2004

### Medical Decision Support

- *WHO Growth Charts* (charts), World Health Organization ([www.cdc.gov/growthcharts/who\\_charts.htm](http://www.cdc.gov/growthcharts/who_charts.htm))
- *Clinical Growth Charts* (charts), Centers for Disease Control and Prevention ([www.cdc.gov/growthcharts/clinical\\_charts.htm](http://www.cdc.gov/growthcharts/clinical_charts.htm))
- *Extremely Low Birth Weight NICU Graduate: Supplement to the Critical Elements of Care for the Low Birth Weight Neonatal Intensive Care Graduate (CEC-LBW)* (guideline), Washington State Medical Home ([medicalhome.org/4Download/cec/elbw.pdf](http://medicalhome.org/4Download/cec/elbw.pdf))
- *Guidelines for Perinatal Care*, 7th ed (book), American Academy of Pediatrics and American College of Obstetricians and Gynecologists ([shop.aap.org](http://shop.aap.org))

### AAP POLICY

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## SECTION FIVE

# Neonatal Outcomes

### Chapter 115

## HEALTH AND DEVELOPMENTAL OUTCOMES OF VERY PRETERM AND VERY LOW-BIRTH-WEIGHT INFANTS

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Approximately 10% to 15% of newborns require specialized neonatal care after their birth. The preterm and low-birth-weight (LBW) rates in the United States increased through 2006 and were reported as 12.8% and 8.6%, respectively. Since 2006, preterm and LBW rates have steadily declined in the United States to 11.6% and 8% respectively. In 2012, 3.4% of babies were born before 34 weeks' (34<sup>0</sup>/<sub>7</sub>–34<sup>6</sup>/<sub>7</sub> weeks) gestation and 8.1% were born 34 to 36 weeks' gestation. Most of the reduction in preterm and low-birthweight deliveries has been among infants born late preterm ( $\geq 34$  weeks' gestation) and in the rate of triplet and higher-order multiple births. Modest reductions in preterm birth rates have been seen among non-Hispanic black (11%), non-Hispanic white (10%), and Hispanic women (5%).

Innovations in prenatal diagnosis, fetal interventions, and neonatal intensive and surgical care have contributed to the survival of extremely premature babies and infants with malformations for which therapy was previously limited. Improved survival rates have led to increased numbers of infants and children with chronic health conditions and increased use of chronic and acute care resources. The need for neonatal intensive care after birth has long-term health-related quality-of-life (HRQL) implications. This need is particularly present for children born preterm. Rehospitalization rates for infants who have required neonatal intensive care are higher than for healthy term infants. Illness is typically less severe among late preterm infants (greater than 34 weeks' gestation) and babies who required fewer than 4 days of neonatal intensive care. As discussed in Chapter 90, Care of the Late Preterm Infant, babies born between 34 and 36 completed weeks of gestation are most likely to require rehospitalization for problems related to jaundice, feeding difficulties, dehydration, and suspected sepsis. Among infants younger than 32 weeks' gestation, the most common readmission diagnoses are sepsis, respiratory disease, gastroesophageal reflux or apparent life-threatening events, and hernia repair. Normal-birth-weight (NBW) infants who require neonatal intensive care, babies with congenital anomalies, and neonates with a low 5-minute Apgar score have

higher post-neonatal intensive care unit (NICU) health care utilization—physician visits, assistive technology use, and rehospitalization; over 30% of infants with malformations require rehospitalization during the first 6 months of life.

The primary causes of postneonatal deaths for infants between 28 and 365 days of age have remained stable over the last decade, although the number of infants dying during the postnatal period from a specific cause has changed. During 1985 and 1986, the most common causes for postneonatal death were sudden infant death, congenital conditions, prematurity-related conditions, and nonintentional injuries. The Centers for Disease Control and Prevention reported that the 5 leading causes of infant mortality during 2011 were congenital malformations (20%), disorders relating to short gestation and LBW (16%), sudden infant death syndrome (8%), maternal complications of pregnancy (6%), and unintentional injuries (4%). The frequencies of these causes of death also vary by geographic region in the US, as well as by race and Hispanic origin.

### HEALTH-RELATED OUTCOMES DURING INFANCY AND CHILDHOOD

Health-related outcomes and HRQL are important considerations when evaluating the consequences of neonatal illness and the cost effectiveness of care. Infancy and early childhood measures of quality of life and health status among newborns requiring neonatal intensive care reveal that preschool-aged children who required NICU care had poorer health status and HRQL than newborns who did not require NICU care. Among preterm children born at less than 32 weeks' gestation, parents report significantly lower HRQL, with problems affecting the lungs and stomach, feeding disorders and problems with motor functioning, communication problems, and anxiety. The range and severity of the developmental and health conditions experienced by these infants is influenced by the number of developmental domains affected. Among infants tracked prospectively who were born at less than 30 weeks' gestation, 17% had a single disability, whereas 44% exhibited multiple disabilities. Low birth weight, chronic lung disease (CLD), and evidence of disability at 2 years were associated with multiple impairments. Health outcomes and HRQL of preschool children born between 29 and 32 weeks' gestation have been shown to be quite similar to those of children born at less than 28 weeks' gestation, despite the fact that the children born earlier than 28 weeks' gestation typically are sicker than the later-arriving group of infants. In addition, children born at 28 to 32 weeks' gestation differ in both health and development in

comparison to children born at term. Among children with intellectual disability, the prevalence of birth defects is reported to be approximately 30% in population-based data, the percentage of intellectual disability varying with the specific organ system involved. Among moderately preterm infants, born at 32 to 33 weeks of gestation, poorer health, developmental, and school age performance outcomes than their full-term, NBW peers are also common. A comprehensive review of outcomes for all infants requiring neonatal special or intensive care is beyond the scope of this chapter. However, outcomes are reviewed for the broad categories of infants who require the greatest resource utilization while hospitalized.

### Respiratory Disease and Lung Function

Chronic lung disease of infancy encompasses a heterogeneous group of pulmonary disorders that originate in the perinatal period and produce airway and parenchymal inflammation leading to chronic airway obstruction, increased work of breathing, and airway hyperreactivity. Bronchopulmonary dysplasia (BPD) is one such condition that develops in response to the interplay of inciting factors: lung immaturity and surfactant deficiency in combination with barotrauma and stretch injury to the lung and oxygen toxicity from the therapies applied to treat the underlying disease. Extreme prematurity, the presence of intra-uterine inflammation (antenatal chorioamnionitis), and changes in alveolar development (fewer, but larger and more simplified alveoli caused by disruption alveolarization) resulting from early extrauterine lung growth further alter lung growth and development. More mature preterm and full-term infants requiring ventilator support are also potentially at risk for developing BPD and subsequently CLD of infancy. Conditions that can cause CLD of infancy include pneumonia or sepsis, meconium aspiration pneumonia, pulmonary hypoplasia, persistent pulmonary hypertension of the newborn, apnea and various congenital malformations involving the cardiorespiratory system (tracheoesophageal fistula, congenital diaphragmatic hernia, and congenital heart disease), and congenital neuromuscular disorders. (For further information, see Chapter 100, Respiratory Distress and Breathing Disorders in the Newborn.)

Children born very preterm experience more upper and lower respiratory illnesses and more episodes of recurrent wheezing throughout childhood and adolescence. In addition to higher rates of rehospitalization in the first year of life, very preterm children with and without BPD have higher healthcare utilization throughout childhood with higher rates of continued medication usage into adolescence and adulthood. Bronchopulmonary dysplasia with or without chronic oxygen dependency after NICU discharge predicts poorer neurodevelopmental outcomes at 36 months corrected age (age adjusted for the degree of prematurity).

Respiratory function studies performed at various times throughout childhood into young adulthood in preterm children who develop BPD demonstrate persistent reductions in airflow and higher airway

resistance. The more preterm the child or young adult was at the time of birth, the greater the airflow reductions involving primarily the smaller airways and air trapping; reductions in FEV1 (forced expiratory volume in 1 sec) are largest among individuals born at less than 26 weeks' gestation. FEV1 reduction is also present in children and adults born preterm who did not develop BPD in comparison with children and adults born at term. Increased airway reactivity is also a common finding, particularly among preterm young adults born earlier than 27 weeks' gestation. Despite these changes, most extremely low-birth-weight (ELBW) and extremely preterm survivors are asymptomatic and have pulmonary function and exercise capacity similar to those of adults born full term. Recent studies have also identified that adults born preterm have abnormal paradoxical ventilatory responses when they are exposed to hypoxic or hyperoxic environments. This has implications for individuals with concomitant sleep-disordered breathing (obstructive sleep apnea) and those individuals residing at high altitude.

### Child Vulnerability and Parental Adaptation to Preterm Birth

The experience of giving birth to an infant who has a prenatal diagnosis or requires neonatal intensive care is traumatic for families. A prolonged hospitalization, the diagnosis of a chronic health condition, being the medically fragile survivor of a complicated neonatal hospital course or multiple pregnancy, and, in some instances, even a non-life-threatening, self-limited condition such as hyperbilirubinemia or transient tachypnea of the newborn can predispose the child to *vulnerable child syndrome*. Parental reactions to their child's illness or perceived vulnerability can have long-term psychological consequences, with deleterious effects for the child and family. Among the observed parental responses can be excessive concerns about the child's health and development leading to hypervigilance, medical visits for minor symptoms, separation problems, difficulty with limit setting, sleep disorders, and underestimation of the child's abilities and potential. Parental stress can also lead to family dysfunction, increase the risk for child maltreatment (either of the child who is ill or of a sibling), and affect the parents' own health and well being.

The severity of the stress experienced by parents has been shown to correlate with later depressive symptoms and posttraumatic stress disorder (PTSD) among parents of high-risk infants. The prevalence of PTSD among parents of children with chronic illness is reported to be as high as 23%. Depressive symptoms may vary over time and by parent gender. Parents experiencing more depressive symptoms or parenting stress, or who have a weaker sense of coherence (control), report more behavioral and emotional problems in their very low-birth-weight (VLBW) children. Parents' information needs and reactions are also influenced by their history, expectations, coping strategies, and experiences. Concerns about long-term developmental outcomes and the need for information do not diminish over time. Carnevale and colleagues identified 6 themes among parents caring for a child with a

chronic illness and technology dependence that inform the information, resource, and support needs of families of high-risk, medically complex infants: confronting parental responsibility, seeking normalcy, conflicting social values, living in isolation, concern over the “voice” of the child, and questioning the “moral order,” or fairness, of life.

The perception of child vulnerability and heightened vigilance among parents of very preterm children and adolescents may be an important factor in the finding of lower rates of risk-taking behaviors, including alcohol, smoking and drug use, and early sexual activity among adolescents and young adults born preterm. This observation is consistent in single-center and population-based studies in the United States, Canada, Scandinavia, and Australia. Parental mental health and family functioning have also been shown to improve (normalize) over time.

## OVERVIEW OF SHORT- AND LONG-TERM OUTCOMES

### Prematurity

Outcomes data for preterm infants have focused principally on the VLBW or extremely preterm infant. The emphasis on babies born early or with a LBW is growing because of the increased understanding of the short- and long-term morbidities experienced by these children, as well as the effect on their cognitive and developmental performance. Male preterm children are reported to have more

behavioral problems and higher disability rates than female preterm children.

### Very Low-Birth-Weight, Extremely Preterm Infants

The National Institute of Child Health and Human Development (NICHD) Center for Research for Mothers and Children Neonatal Research Network has been prospectively collecting data regarding VLBW preterm infants and children since 1993. Survival rates for infants born during the 1990s between 23 and 32 weeks' gestation have increased. Table 115-1, Table 115-2, and Table 115-3 summarize the early outcomes data for this group of infants. Rates of low mental developmental assessment scores and neurodevelopmental impairment at 18 to 22 months of age declined in infants born in the late 1990s, and the improved outcomes correlated with antenatal steroid administration to promote fetal lung maturity. Among infants born weighing less than 1,500 g (3.3 lb), reports of survival and morbidity rates through the first 4 months of life have changed little since the mid-1990s. The survival rate for infants born from 1997 to 2002 with birth weights between 501 g (1.1 lb) and 1,500 g (3.3 lb) is 85%. Birth weight-specific survival for babies born during this period weighing 501 to 750 grams (1.10–1.65 lb) is 55%. The survival rate improved to 88% for infants weighing 751 to 1,000 g. For infants with birth weights in the weight groups 1,001 to 1,250 g (2.2–2.75 lb) and 1,251 to 1,500 g, survival is similar at 94% and 96%, respectively. Among infants

**Table 115-1** Neurodevelopmental Outcomes of Extremely Low-Birth-Weight Infants (1993–1998)

OUTCOME	22–26 WEEKS	27–32 WEEKS	P VALUE
Survival	61%	86%	.0001
Moderate or severe cerebral palsy	10%	6%	.0001
Mental developmental index <70	37%	23%	.0001
Psychomotor developmental index <70	26%	17%	.0001
Blind	1%	0.4%	.01
Hearing loss	1.8%	1.8%	NS
Neurodevelopmental impairment	45%	28%	.0001

NS, not significant.

From Vohr BR, Wright LL, Poole K, et al. Neurodevelopmental outcomes of extremely low birth weight infants. *Pediatrics*. 2005;116(3):635–643.

**Table 115-2** Outcomes at 18–22 Months' Corrected Age by Weight Quartile

OUTCOME (%)	QUARTILE 1	QUARTILE 4	P VALUE
Cerebral palsy	21	6	<.01
Abnormal neurodevelopment	30	14	<.01
Mental developmental index <70	39	21	<.01
Psychomotor developmental index <70	35	14	<.001
Head circumference <10%	31	22	.09
Rehospitalized	63	45	.01

Quartile 1, <25%; Quartile 4, >75%.

From Ehrenkrantz RA, Dusick AM, Vohr BR, et al. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. *Pediatrics*. 2006;117:1253–1261.

**Table 115-3** Factors Associated With Neurodevelopmental Morbidity in Infants With Normal Head Ultrasounds

FACTOR	CEREBRAL PALSY, OR	MENTAL DEVELOPMENTAL INDEX LESS THAN 70, OR
Male	1.8	2.0
Multiple birth	1.6	1.8
Low birth weight	1.3	1.2
Pneumothorax	2.3	—
Prolonged ventilation	1.2	—
Maternal race (black/Hispanic & other)	—	1.6/1.5
Maternal education	—	1.4
Public assistance	—	1.7

OR, odds ratio.

Adapted from Laptook AR, O'Shea M, Shankaran S, Bhaskar B, and the NICHD Neonatal Network. Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: prevalence and antecedents. *Pediatrics*. 2005;115(3):673–680.

born between 1993 and 1998, extremely preterm infants with gestational ages between 27 and 32 weeks showed a significant decline over time in the percentage with a mental developmental index (MDI) score of less than 70. In contrast, rates of cerebral palsy (CP) for all infants between 22 and 32 weeks remained stable, as did the percentage of infants with MDI scores less than 70 who were born at 22 to 26 weeks' gestation.

#### Factors Influencing Outcomes of Extremely Low-Birth-Weight Infants

Improvements in antenatal and postnatal care have contributed to a reduction in some sequelae. Survival without neonatal major morbidity (BPD, intraventricular hemorrhage [IVH], and necrotizing enterocolitis) has remained unchanged at 70%. A nearly 20% increase has been reported in the survival rate of VLBW infants born of a multiple gestation. Postnatal growth failure, common among immature and sick infants, has also decreased. Among the least mature infants weighing 501 g to 750 g, morbidity rates have increased since the mid-1990s. Only 20% of these infants are reported to be morbidity free. Babies born weighing 751 to 1,000 g fare somewhat better, with 33% exhibiting major neonatal morbidity; 55% of these infants are free of neonatal morbidities by 4 months of age. Similar differences are seen when the infants are grouped by gestational age (see Table 115-1). Neonatal nutrition and postnatal growth are additional factors that influence outcomes at 18 to 22 months of age, as summarized in Table 115-2. Adequacy of postnatal growth also influences school-aged outcomes; infants with postnatal growth problems exhibit poorer cognitive scores and academic achievement. Preterm infants who are small for gestational age (SGA) at birth but who demonstrate adequate postnatal growth do not exhibit deficits similar to those seen among appropriately grown preterm infants with poor postnatal growth. Providing human milk as part of the ELBW infant's nutritional regimen seems to have a protective effect on MDI measurements at 18 months corrected age. Every 10 mL of human milk fed was correlated

with a 0.5-point increase in the MDI score. Evidence indicates that all areas of brain growth, including the whole brain, cerebral and subcortical gray matter, and cerebral white matter, are affected. Regions of the brain that are most vulnerable are the sensorimotor cortex, premotor cortex, and mid-temporal cortex. Cerebral volume at 8 years of age is related to the child's gestational age, irrespective of evidence of chorioamnionitis at birth or the presence of ventriculomegaly or periventricular leukomalacia. High rates of learning and attention difficulties, as well as minor motor impairments, occur in children born very preterm. Experts have speculated that perinatal brain injury or postnatal nutritional deficiencies predispose these children to abnormal brain development, causing reduced caudate and hippocampal volumes. Reduced caudate volume is associated with low IQ. Memory deficits are seen among children with smaller hippocampal volume.

Among very preterm and VLBW children born after the year 2000, survival to hospital discharge has increased although morbidity and intact survival rates have remained essentially unchanged as illustrated in Table 115-4.

Figure 115-1 (Extremely PT Infant Survival to discharge without morbidity, 2003–2007, NICHD NRN) summarizes the morbidity-free survival rates among very preterm infants born in the US between 2003 and 2007.

When evaluating the outcomes for VLBW children, the 3 morbidities that seem to have the most significant effect on later outcomes are BPD, severe IVH (grade 3 to 4) or periventricular leukomalacia (PVL), and severe retinopathy of prematurity (ROP). The more severe the degree of BPD or CLD is, the greater the likelihood of CP or neurodevelopmental impairment. Infants who continue to require oxygen at 36 weeks' postmenstrual age have a 17% to 27% risk of CP and a 45% to 62% incidence of neurodevelopmental impairment. The need for prolonged ventilation greater than 90 days nearly triples the risk for CP from 28% to 80%. Each of the 3 risk factors (BPD, severe IVH or PVL, and severe ROP) independently correlates with a poor outcome;



**Table 115-4** Survival and Morbidity Rates at Discharge in Extremely Preterm Infants Born Between 2003 and 2007 in the US NICHD Neonatal Research Network

CHARACTERISTIC	22 WK	23 WK	24 WK	25 WK	26 WK	27 WK	28 WK	TOTAL
Birth weight (g), mean $\pm$ SD	511 $\pm$ 67	581 $\pm$ 92	651 $\pm$ 105	744 $\pm$ 135	854 $\pm$ 163	964 $\pm$ 189	1082 $\pm$ 206	836 $\pm$ 241
Multiple births (%)	28	30	25	21	22	25	28	25
Intrauterine growth restriction (%)	0	4	6	8	8	10	9	8
Delivery room resuscitation (%)	19	68	87	82	75	65	47	67
Survived (%)	6	26	55	72	84	88	92	72
Survived without morbidity (%)	0	8	9	20	34	44	57	37
Never intubated (%)	0	<1	<1	2	5	12	23	9
BPD at 36 wk PMA (%)	89	70	68	55	44	31	22	40
Severe BPD at 36 wk PMA (%)	56	39	37	26	17	13	8	18
Late onset sepsis (%)	58	62	55	46	35	27	20	36
Necrotizing enterocolitis (%)	5	12	15	13	9	10	8	11
ROP (%)	96	88	89	79	65	49	32	59
ROP requiring intervention (%)	50	40	35	17	8	4	2	12
Postnatal growth <10% at 36 wk PMA	92	91	85	83	79	76	73	79
No intraventricular hemorrhage (IVH) (%)	32	41	49	57	65	70	77	64
IVH, grade 1-2	26	18	20	17	16	15	14	16
IVH, grade 3-4	38	36	26	21	14	11	7	16
Ventriculomegaly, no IVH	4	3	3	3	2	2	1	2
Periventricular leucomalacia (PVL) within 28d	6	4	3	4	3	2	2	3
Patent ductus arteriosus	53	52	56	55	51	43	34	47

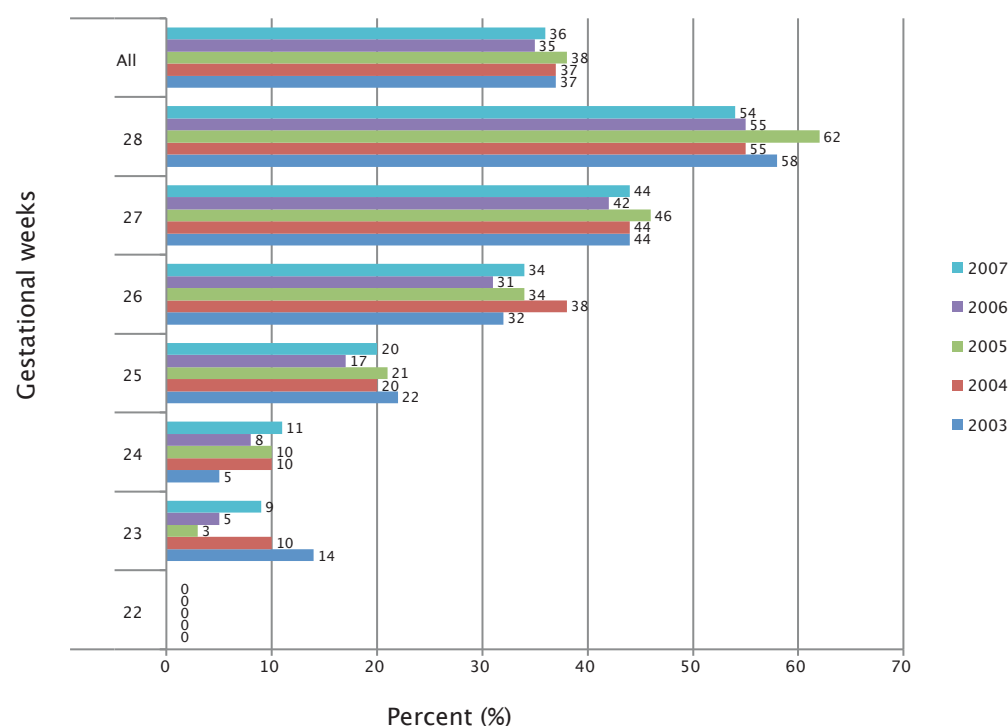
BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; PMA, postmenstrual age; PVL, periventricular leucomalacia; ROP, retinopathy of prematurity. Adapted from Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics*. 2010;126:443–456.

the presence of 2 or more of these risk factors significantly increases the likelihood of an adverse outcome that includes CP, cognitive delay, severe hearing impairment, and bilateral blindness.

Among ELBW infants, poor long-term outcome was present in 18% of children without BPD, brain injury, or severe ROP. In contrast, 88% of children with all 3 morbidities experienced a poor outcome. Important caveats to these findings are that not every infant who sustains a grade 3 or 4 IVH will develop CP, and, conversely, a normal neurosonogram (showing no evidence of IVH or PVL) does not always predict a good outcome. Among babies in the NICHD cohort who had normal head ultrasound examinations, 9.4% were diagnosed with CP, 25% had cognitive delay, and nearly 30% exhibited motor delays. Factors associated with neurodevelopmental impairment (CP or MDI score below 70) in babies with normal neurosonography are male gender, multiple birth, lower birth weight, pneumothorax, prolonged mechanical ventilation, maternal race and education, and poverty. (Table 115-3 summarizes the degree of risk associated with each of these factors.) Late-onset

sepsis has also been shown to negatively affect the outcome for ELBW neonates, increasing the risk for CP, low MDI, low psychomotor developmental index, and vision impairment. At 30 months' corrected age, the majority of unimpaired ELBW/extremely preterm children have cognitive scores toward the lower end of the normal distribution with mean MDI scores of 100 or less on the Bayley examination. Exposure to antenatal steroids is associated with a greater likelihood of an unimpaired outcome.

Regional and national differences have been reported in mortality and morbidity rates. European outcomes reported for infants born less than 1,000 g are notable for lower survival rates and increased rates of morbidity in comparison with outcomes for infants born in the United States during the 1990s, but demonstrate improved survival of infants born after 2005 who are 24 to 25 weeks' gestation. An important consideration when reviewing data from various countries is understanding the approach to perinatal and neonatal care delivery (including at what gestation and birth weight resuscitation is offered), the



**Figure 115-1** Extremely preterm infant survival to discharge without morbidity, 2003–2007. (Adapted from Schmidt B, Asztalus EV, Roberts RS, et al. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms. *JAMA*. 2003;289:1124–1129.)

scope of care available, the decision processes regarding termination of care, and whether the infants for whom outcomes are reported are population based or reflect only those infants admitted to the NICU.

### Neurodevelopmental and School-age Outcomes

Understanding the scope and evolution of neurodevelopmental outcomes requires surveillance through childhood into adulthood. Longitudinal outcomes that reflect the effect of current approaches to perinatal care take decades to elucidate. The earliest neurodevelopmental outcomes are typically reported between 18 and 22 months of age, with school-age outcomes, particularly at age 8 years, being the most predictive of future performance. Functional outcomes have recently been reported for several cohorts of preterm young adults who have been followed longitudinally in the United States, Canada, Europe, and Australia since their birth. Sequential follow-up is necessary as neurodevelopmental function has been shown to improve with time for many preterm, VLBW children. Evidence is increasing of neurodevelopmental recovery with improvement in functional outcomes and verbal and IQ testing with advancing age. Ment et al reported on full-scale, verbal, and performance IQ test scores for VLBW children with and without IVH between 3 and 8 years of age. Between 4.5 and 6 years of age, improvements in mean IQ scores were evident in both groups of VLBW children. By 8 years of age, the mean full-scale IQ score was reported to be 96 for VLBW children without a history of IVH and 94 for VLBW children with a prior IVH. Verbal IQ is

higher than performance IQ for both groups of children. Forty-five percent of the children monitored demonstrated at least a 10-point gain; 12.5% had a 5- to 9-point increase in their scores.

Behavioral and emotional outcomes have been reported by investigators in the United States, Canada, Europe, Australia, and New Zealand. The range of problems encountered include hyperactivity, conduct problems, emotional symptoms with both internalizing and externalizing behaviors, peer difficulties, attention problems, delinquent behavior, and social problems. Generally, a 1.5- to 3-fold increase is found in these problems in comparison with healthy children born at term gestation.

Developmental coordination disorders are also more common in preterm, LBW children. Developmental coordination difficulties correlated with behavior problems and poorer cognitive function and academic performance, and were more prevalent among EBLW and very preterm male children. Adaptive behavioral and externalizing problems were more often demonstrated. Of interest, preterm male children more often exhibit externalizing behaviors, whereas preterm girls demonstrate more internalizing behaviors.

Neuropsychological deficits are reported to be both global and specific in nature, with greater involvement in a range of educational areas involving attention, language, sensorimotor and visuospatial abilities, and verbal memory. An increased incidence of nonverbal learning disabilities, borderline cognitive function, and fine-motor problems has been reported; verbal cognitive skills typically exceed nonverbal abilities. Aspects of

functioning that are affected include visual-motor integration, visual perception, mathematics and spatial skills, and fine-motor speed. Beyond nonverbal learning difficulties, problems with verbal abstracting (inferences), reading comprehension, written output, and social skills are exhibited. Reading decoding has not been shown to be affected. These deficits are associated with problems in executive functioning—organization, planning, problem solving, and abstraction. Estimates of visual-perceptual and visual-motor integration problems range from 11% to 20%. Fine-motor difficulties are reported to occur in up to 70% of ELBW children. Speech and language impairments are common in children born preterm. Delays can be found in expressive language, receptive language processing, articulation, and phonological short-term memory (the capacity for holding a small amount of information in mind in an active, readily available state for a short period of time for easy retrieval). Although vocabulary and receptive language are within normal limits for LBW children, preterm children have more difficulty with more complex verbal processes such as understanding syntax, abstract verbal skills, verb production, and the length of phrases or sentences produced. Critical to academic and social success, these language difficulties are also significantly influenced by the child's environment and language experiences.

As a group, 50% to 70% of VLBW and ELBW children, respectively, require educational assistance in school. By middle childhood, ELBW children are 3 to 5 times more likely to have difficulties with reading, spelling, mathematics, or writing. Grade retention is reported for 23% to 39% of LBW children; up to one-third exhibit school problems, with particular difficulty in mathematics and reading. Fifteen percent to 28% continue to require special education. Over 50% of preterm children without any neurosensory impairment enrolled in a mainstream educational setting may require additional educational support. Common factors that influence outcomes include parent involvement, parent perspectives about and approaches to the child's limitations, maternal education and socioeconomic status, and access to services.

Longitudinal follow-up of ELBW children into late childhood and early adolescence (ages 10–14 years) continues to confirm residual effects of extreme prematurity. There is an increased trend toward depressive symptoms that is more prevalent among preterm children who have poorer family functioning, social risk factors, and the coexistence of a chronic medical condition. By 10 to 12 years of age, most (85%) extremely preterm children will be functioning in mainstream academic environments without significant adjustment problems. VLBW children with BPD experience more significant cognitive and academic impairments than VLBW children without CLD. Decreased functioning is present in the areas of cognition (intelligence), reading, mathematics, and gross-motor skills, with greater utilization of special educational services.

### **Chronic Conditions, Functional Limitations, and Special Health Care Needs**

Extremely low-birth-weight infants are affected by more chronic health conditions that contribute to

functional limitations and increase service and technology utilization. Hack et al reported that the health conditions most prevalent at 8 years of age are asthma, mild hearing impairment, visual disability, and CP. Blindness and hearing loss requiring hearing aids also occurred but were less common. These conditions correlated with school performance and academic deficiencies, including low IQ, limited academic skills, poor motor skills, and poor adaptive functioning. Farooqi et al confirmed these findings in their report on health and functional outcomes for a group of Swedish extremely immature preterm children tracked until 10 to 12 years of age.

Among preterm infants with CLD, over 50% exhibit airway reactivity. Postdischarge mortality can occur because these infants are at risk for sudden death. Lung function improves between 8 and 14 years of age, at which time rates of asthma are similar to NBW children, and lung function is within the normal range. Pulmonary function testing reveals lower airflow but no difference in lung volumes or air trapping, irrespective of whether the ELBW child had BPD.

An increased prevalence of tooth enamel defects affects both the primary and permanent teeth of preterm infants. Eruption of the first tooth in preterm girls has been reported to occur later than in preterm boys. However, by the age of 2 years, no significant delays in tooth maturation are observed between preterm and full-term children. Maturation of permanent teeth was also not noted to be delayed in the preterm children. The presence of palatal grooves and a high arched palate caused by prolonged intubation and orogastric tube placement can also affect oral health, feeding, and normal speech development.

### **Vision Function and Retinopathy of Prematurity**

Strabismus, myopia, and poor visual acuity are more common in preterm children. More than 33% of ELBW children require prescription glasses, compared with 10% of full-term children. Difficulties with visual-motor integration in middle childhood are strongly related to the presence of visual impairment. Mild ROP has not been shown to be correlated with decreased visual acuity at age 7 years. Stephenson et al reported on visual and cognitive outcomes in late childhood and early adolescence for a cohort of LBW children whose birth weights were less than 1,701 g. Among children aged 10 to 13 years with a history of ROP, 50% had an adverse ophthalmologic outcome, with myopia, strabismus, and reduction in visual acuity predominating. Additional visual abnormalities involved color vision and visual-field defects. Children between the ages of 10 and 13 years with a history of mild ROP (stages 1 and 2) did not experience adverse visual outcomes. When outcomes for children with and without treated severe ROP (threshold ROP) are evaluated, there is a 10-fold increase in the rate of functional limitations involving 4 or more of the following areas: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. Children with severe ROP showed a significant difference in the severity of functional limitations when sighted children are compared with blind or low-vision VLBW

children—6.4% versus 46.5%, respectively. A recent study explored the question of whether the visual problems experienced by preterm infants are the result of common associated morbidities, ROP, IVH or PVL, or premature exposure to extrauterine visual stimulation. At 5 to 7 months corrected age, preterm infants without evidence of ROP or neurologic abnormalities exhibit visual function that is not significantly different from that of healthy infants born full term.

### Growth

Preterm children are at risk for incomplete catch-up growth, largely because of postnatal growth deficiency that develops in the weeks to months after their early birth. Growth, weight gain, and nutrient accretion that parallel intrauterine accretion postnatally are not achieved by many LBW infants. Four growth patterns are seen among preterm and sick infants.

- The infant is appropriate for gestational age (AGA) at birth and continues to grow along a gestation-specific intrauterine growth curve
- The infant is AGA, but postnatal growth falls below the curve
- The infant is SGA at birth, but demonstrates catch-up growth
- The infant is born SGA and remains below the curve

Postnatal growth failure is common among preterm and LBW children born at less than 32 weeks' gestation and less than 1,500 g birth weight. The incidence of extrauterine growth restriction is common, reported at 28%, 34%, and 16% for weight, length, and head circumference, respectively. For each growth parameter, the incidence of extrauterine growth restriction increased with decreasing gestational age and birth weight and was influenced by the infant's illness severity. Poor physical growth is associated with suboptimal nutrition, poor feeding skills, prolonged hospitalization, chronic respiratory disease, and late-onset sepsis or infection. At 1 year of age, a significant percentage of these infants continue to demonstrate subnormal growth (<10%) for weight, length, and head circumference. The rate of neonatal hospital weight gain and head growth also influences growth and neurodevelopmental outcomes at 18 to 22 months of age. Poor postnatal growth, particularly head growth, has been correlated with residual suboptimal growth and neurodevelopmental impairment at 7 years of age.

Larger, more stable infants typically demonstrate catch-up growth during the first and second years of life. VLBW and ELBW children may not exhibit catch-up growth by the third year and, as a group, tend to remain permanently lighter and shorter than children born at full term. Doyle et al reported that weight measurements among VLBW children were 1 standard deviation below the mean for age at 2, 5, and 8 years of age, with catch-up achieved by 14 years of age. At 8 to 12 years of age, preterm children also have lower fat mass and body mass index than full-term children. Similar results have been reported by Farooqi et al on children born extremely preterm at 23 to 25 weeks' gestation. At 11 years of age, these ELBW children were significantly smaller on all growth parameters than their full-term counterparts, despite evidence of

catch-up growth beginning by 3 months' postnatal age. Of additional importance was the finding that among this group of children, catch-up head growth did not occur after 6 months of age.

### Cardiovascular Health

Preterm birth and very low birth weight are associated with an increased risk for later cardiovascular disease (CVD) that appears to be related to structural changes in the developing cardiovascular system that occur because of the early birth. Infants born preterm have systolic blood pressures that average 3 to 4 mm Hg (range 2.5–6) above the mean for their age. This elevation in systolic blood pressure is evident from mid- to late childhood and persists into adolescence and adulthood. Women born preterm appear to be at greater risk than preterm men. However, recent meta-analyses have not confirmed an association with a higher rate of metabolic disease among adults born preterm, although preterm adults do appear to have higher levels of plasma low-density lipoprotein, a risk factor for atherosclerosis and cardiovascular disease. Although children born preterm are reported to weigh slightly less and be slightly shorter than children born at term during childhood and adolescence, there are several reports of increased abdominal adiposity and higher BMI with more truncal fat among men who were born preterm. Affected individuals are also more likely to have abnormal lipid profiles. At present we do not have a full understanding of the mechanisms that predispose preterm adolescents and adults to this greater cardiovascular risk, but there is evidence that preterm and very low-birth-weight individuals have higher pulse pressures and alterations in carotid intimal thickness (a marker for atherosclerosis), contributing factors to CVD. Cardiac magnetic resonance imaging studies have determined that preterm individuals have increased left ventricular mass in adult life with evidence of functional and structural changes. These findings may be the manifestation of the effect of the need for the preterm infant to adapt to an extrauterine environment at a developmental stage in cardiac development that disrupts or disorders the normal developmental processes leading to the changes described and to the resultant increased cardiovascular risk.

### Pain Sensitivity

Long-term consequences occur as a result of repetitive painful and noxious stimuli during the neonatal period. Preterm children have lower-than-normal response thresholds to tactile stimulation and seem hypersensitive to pain. At 4 to 5 years of age, significantly increased somatization occurs. Repetitive pain leads to an altered pain system with decreased pain thresholds. At 8 to 10 years of age, ELBW children have similar perceptions of pain intensity, although they rate medical pain more intensely than psychological pain and ascribe higher intensity ratings to recreational pain. More preterm children report fatigue (13%) and anxiety (8%) than children who were born at term. Preterm adolescent girls exhibit greater pain sensitivity than preterm adolescent boys.

### Adolescence and Young Adulthood

Longitudinal outcomes data are being reported throughout the United States, Canada, Australia/New



Zealand, and Europe for groups of preterm children who are now adolescents and young adults. Assessing outcomes during adolescence has yielded interesting data about parental and adolescent perceptions regarding the preterm teenager's health, well being, and functional abilities. In recent years, numerous publications have reported on the adolescent and young adult outcomes for preterm and LBW children born during the late 1970s and early 1980s. Most of the reports detail outcomes for very preterm infants less than 32 weeks' gestation and VLBW infants. In the last decade, particular attention has been paid to the consequences of extreme prematurity and extremely low birth weight. Although concerns have been raised regarding the applicability of these outcomes to preterm and LBW children born today, comparison shows that

outcomes for children born in the late 1990s and early 2000s are similar to those reported for the older cohorts of preterm or LBW individuals. Continued reporting of the longitudinal consequence of early birth will further enhance physicians' ability to counsel families and develop appropriate surveillance programs for children born preterm. Overall, the transition to young adulthood is fairly comparable to young adults who were born with NBW and at full term. Three areas of difference are persistence of neurodevelopmental disability, lower educational achievement, and suboptimal growth despite catch-up growth. Table 115-5 and Box 115-1 summarize the data on young adult outcomes.

Longitudinal follow-up of growth among a group of VLBW infants at 2, 5, 8, and 14 years has been

**Table 115-5** Transition to Adulthood

OUTCOME	EXTREMELY LOW-BIRTH-WEIGHT GROUP (%)	COMPARISON NORMAL-BIRTH-WEIGHT GROUP (%)
Completed university education	5	14
Pursuing postsecondary education	32	33
Completed less than high school	15	11
Permanent employment	48	57
Unemployed <sup>a</sup>	26	15
Married or cohabiting	23	25
Living with parents	11	14
Visual problems <sup>b</sup>	64	37
Neurosensory impairment <sup>b</sup>	27	2

<sup>a</sup>Statistically significant,  $p = .02$ .

<sup>b</sup>Statistically significant,  $p < .0001$ .

Derived from Saigal S, Stoskopf B, Streiner D, et al. Transition of extremely low birth weight infants from adolescence to adulthood: comparison with normal birth weight controls. *JAMA*. 2006;295(6):667–675.

### BOX 115-1 Adult Outcomes for Preterm and Low-Birth-Weight Infants

#### INTELLIGENCE AND ACADEMIC ACHIEVEMENT

- Mean IQ: 81–98
- IQ <85: 19%–49%
- Completed high school or obtained a general education degree: 56%–85%
- Post-high school: 37%–38%

#### WORK STATUS

- Full-time employment: 48%
- Unemployed, not in school: 14%–26%

#### HEALTH STATUS

- Chronic illness or disability: 47%
- General health
  - Similar to term adults
  - Increased frequency of reactive airway disease or asthma
- Growth
  - Weight: below normal in infancy followed by catch-up growth

- Height: shorter relative to peers and mid-parental expected height
- Body mass index: normal as teen and young adult
- Head circumference: remains below normal
- Neurosensory
  - Impairment (cerebral palsy, blindness, deafness): 12%–28%
  - Vision problems: 37%
  - Retinal detachment: 4%–7%

#### SOCIAL BEHAVIOR

- Significantly less risk-taking behavior
  - Drug and alcohol use
  - Sexual activity
- Similar rates of conviction and incarceration
- Similar rates of independent living, marriage, cohabitation, and parenting

reported for a cohort of Australian youth born between 1977 and 1982. Pubertal development in these individuals was similar to that seen for full-term controls. These VLBW teenagers were significantly shorter and lighter, with smaller occipitofrontal head circumference measurements than their NBW counterparts. Children with birth weights less than 1,000 g had lower weight scores during childhood but not at 14 years when compared to children born weighing 1,000 to 1,499 g. Among this latter group, lower height scores were present only at 2 years of age. However, significantly lower head circumference measurements were noted on the serial assessments. Hellgren et al reported on a group of preterm Swedish youth at 15 years of age. Significant differences were found in visual acuity, stereo acuity, and astigmatism, as well as full-scale (85 vs 97) and performance (87 vs 99) IQ.

Preterm adolescents who had evidence of brain injury performed more poorly on all achievement tests than term adolescents. Nearly 50% of teens with brain injury had associated visual dysfunction, and 33% had learning disabilities. Visual dysfunction is related to white matter injury in preterm infants causing subnormal visual acuity complicated by perceptual and cognitive visual problems. Rogers et al found significant differences in motor performance in unimpaired ELBW preterm adolescents at 17 years of age, with decreased aerobic capacity, strength, endurance, flexibility, and activity level. The teens reported a more inactive lifestyle with less previous or current sports participation, poorer coordination, and more difficulty maintaining rhythm and cadence.

Parents report a high incidence of mental health problems in VLBW teens. They describe more social and attention problems and less social and school competence among VLBW boys than is seen among term adolescents. Parents also reported more internalizing behaviors (withdrawn, somatic complaints, anxious or depressed) and social and attention problems and less school competence in VLBW girls than is seen among term adolescents. Interestingly, teenage VLBW boys report that they are more active and have less psychological distress and fewer problems with attention than teens who were born full term. Teenage VLBW girls also describe externalizing behaviors, being less social with fewer thought and attention problems, and higher activity levels. Discrepancies exist between parent-reported problems and competencies and teen self-reports. Notably, teens who were SGA or girls self-reported more total problems and internalizing behaviors than NBW teens and boys. These results have been seen across several studies in the United States, Canada, and Europe. At 15 and 16 years of age, preterm teens do not rate their health status and HRQL differently than comparison group teens born at term, with the exception of reporting a higher level of cognitive difficulty (40.7% vs 25%). Teens who were born preterm exhibited wider variation in their functional abilities. Saigal and colleagues found that preterm teens described similar self-worth as full-term teens on most domains of self-esteem, although some gender effects regarding athletic competence and physical appearance were noted. Boys rated themselves more highly than girls. Among another

cohort of Canadian ELBW adolescents born between 1981 and 1986, lower than normal cognitive scores and academic skills were reported. ELBW teens reported lower than expected scholastic, athletic, job, and romantic competence. These teenagers viewed themselves as more likely to need help getting a job.

Evaluation at 12 to 16 years of age among a longitudinal cohort born in Ontario found that more of the ELBW teenagers had neurosensory impairments—28% versus 2% of term teenagers. These ELBW adolescents exhibited a higher incidence of visual problems (57% vs 21%), seizures (7% vs 1%), developmental delay (26% vs 1%), learning disabilities (34% vs 10%), and hyperactivity (9% vs 2%), as well as more use of specialists and community resources, than adolescents born at term. Teenagers who were born weighing less than 750 g were the most disadvantaged, with 58% requiring special educational assistance or grade retention (or both), as compared to 13% of the full-term controls, a 4.5-fold greater risk for the ELBW group. A difference of 13 to 18 points was found on psychometric testing. Developmental measures at 8 years of age have been shown in numerous studies to predict reduced academic performance.

Most very preterm and VLBW adolescents are educated in mainstream classroom settings, although a percentage of these students continue to require additional educational supports, and approximately 5% to 10% have severe motor or neurosensory impairments. Parents of these extremely preterm teens attending mainstream classes report an increased incidence of problems with physical health and family functioning, and the students' teachers rated these teens as slower than normal. Only 29% of the extremely preterm adolescents attending mainstream classes were without health issues compared to 49% of their term classmates; 100% of the extremely preterm teenagers in special education classes had health problems. Asthma, vision problems, learning disabilities, and behavioral problems were the most commonly reported. The psychological effect on parents of these teens' health issues was greatest for those whose children were in special education. Extreme prematurity affected both family functioning and family life. Teens' self-assessment of their own health did not differ from controls. In addition, no apparent difference was found in the onset of puberty in girls or boys. Similar rates of medication and tobacco use, but decreased alcohol and recreational drug use, were reported for mainstream and special education preterm students. Increased health service use was reported only among the special education preterm teens. When future plans were queried, a lower than normal proportion of the extremely preterm teens were planning to continue in school or attend vocational training, with additional planning for low-skilled types of employment.

### The Role of Early Intervention

Few data are available about the specific benefits of early intervention for very preterm and VLBW children. The Infant Health and Development Program is the only randomized clinical trial to evaluate the longitudinal effects of an intensive 36-month

early-intervention program for LBW infants and their parents. The study population was composed of 985 LBW preterm infants (a *light low-birth-weight* [LLBW] group at or below 2,000 g and a *heavy low-birth-weight* [HLBW] group weighing 2,001 to 2,500 g). Infants in these groups were randomized to receive routine follow-up care or to participate in an intensive home- and center-based group intervention that lasted 3 years. Major assessment points were at 3, 5, and 8 years of age. At 36 months corrected age, children in the intervention group had higher scores than children in the follow-up-only group on tests of receptive language, cognitive development, and visual-motor and spatial skills. The effects were the strongest for families with the greatest risk (ie, children whose parents had a high school education or less and who were of ethnic minority status). The intervention was found to be effective for the HLBW infants but not for the LLBW infants. McCarton et al found no overall significant differences between the intervention and follow-up groups. However, a subsample of the HLBW children who participated in the intervention group had higher scores on several cognitive tests (receptive vocabulary, mathematics, overall IQ) than the subsample of HLBW children in the follow-up group. The difference between the 2 groups at later ages was less than that seen at age 3; thus, the effects of the intervention program seemed to decline over time. Among the LLBW children in the intervention group, all of the earlier positive effects had disappeared by age 8. Reassessment of these individuals at age 18 revealed a continued 4-point achievement advantage for the HLBW group that remained stable over time. Intervention participants also exhibited fewer risky behaviors. Similar to the results seen at age 8, loss of intervention benefits was demonstrated in the LLBW group. The high school drop-out rate was lower than that reported for other groups of potentially high-risk students.

### Young Adulthood

Examination of young adult outcomes reveals findings similar to those from adolescent age-reported outcomes. In general, the findings related to growth, academic and employment achievement, personal satisfaction, and HRQL are comparable to the results seen during adolescence. In a report assessing 20-year-olds born with VLBW, fewer than expected graduated from high school (74% vs 83%). Furthermore, VLBW men are significantly less likely than expected to be enrolled in postsecondary education (30% vs 53%). Testing reveals lower than normal mean IQ scores (87 vs 92), lower than normal academic achievement scores, higher than normal rates of neurosensory impairments (10% vs 1%), and subnormal height (10% vs 5%). Less than expected alcohol and drug use was noted, with lower than expected rates of pregnancy in the young adults both with and without neurosensory impairment. When growth was evaluated, VLBW young women in this group were reported to catch up by 20 years of age, whereas VLBW young men remained significantly shorter and lighter than NBW young men. Predictors of growth attainment at 20 years included maternal education and height,

race, birth-weight z score, length of NICU stay, and chronic illness at 20 years of age. In contrast, another study reports that among VLBW adults (20 years), weight and height were not different from the general population and were consistent with parental height. Among this group of young adults, the mean body mass index was 24.0, and findings revealed that the VLBW adults were relatively heavy for their height.

Similar findings have been reported in Canada and Sweden. Assessment of the Ontario preterm young adults at 22 to 25 years revealed that 27% had residual neurosensory impairments yet had similar rates of graduation (82% vs 87%) and no significant differences in educational attainment (32% vs 33% postsecondary education), employment (48% vs 57%), independent living, marriage or cohabitation, or living with parents than the NBW controls. Lindstrom found that among 23- to 29-year-old preterm adults, 13.2% of individuals born between 24 and 28 weeks' gestation and 5.6% of individuals born between 29 and 32 weeks' gestation received economic aid because of handicap or chronic illness. Adults who were born between 33 and 37 weeks' gestation also exhibited significant risks for disability, accounting for 74% of the total disability associated with preterm birth in this population-based study. Preterm adults were also less likely than expected to complete postsecondary education and had a lower than average net income. These findings were further supported by a report from Lefebvre et al, who demonstrated that most preterm adults had a mean adult IQ that was in the normal range but more than 1 standard deviation below that of NBW controls. Again, school failure, IQ less than 85, and use of special educational assistance were more prevalent than normal among the preterm group.

Measurement of quality of life and social activities in preterm young adults continues to demonstrate less alcohol and illicit substance use than full-term controls, although the frequency of smoking and sexual activity was similar between groups. In the United Kingdom cohort on which Cooke reported, preterm young adults had more children; were shorter, less satisfied with their appearance, and more likely to use regular prescription medication; and had less higher education than their term counterparts. Employment rates were similar to the adults born at term. Hack et al, reporting on the Cleveland cohort of VLBW adults, determined that VLBW men exhibited fewer delinquent behaviors but showed no differences in internalizing, externalizing, or total behavior problems than NBW men. Parents continued to report significantly more than expected thought problems for their sons. VLBW women were more withdrawn and exhibited more internalizing behaviors (anxious or depressed) and fewer delinquent behaviors than NBW men; their parents reported significantly more than expected anxiety and depressive symptoms and attention problems. No differences in self-report of attention-deficit/hyperactivity disorder were noted. Allin et al assessed personality among adults who had been born before 33 weeks' gestation and found different personality characteristics in the very preterm group, with lower than expected scores on extraversion and higher than normal levels of neuroticism

among female participants. These results are similar to those reported by Hack: decreased risk-taking and antisocial behaviors, primarily among female participants, who reported less than expected recreational drug use and sexual activity. Saigal confirms these findings, noting that among the Ontario cohort, 27% of the ELBW adults tracked had residual neurosensory impairments (13-fold higher than NBW adults) and were more likely to have multiple impairments. No overall or gender difference was noted in current health status for physical or mental health and emotional state scores between the ELBW and NBW adults. However, VLBW adults did report increased rates of seizures (8% vs 2%; odds ratio 3.8), asthma in men (18% vs 3%; odds ratio 6.3), and recurrent bronchitis (6% vs 1%; odds ratio 8.5), and a higher than expected prevalence of chronic health conditions and functional limitations in the previous 6 months. Areas of functional impairment were broad, encompassing vision, hearing, dexterity, clumsiness, and learning disabilities. Higher than normal rates for use of antidepressant medications, prescription glasses, and home care services were noted. VLBW adults also demonstrated weaker handgrip strength and lower scores in physical self-efficacy, perceived physical ability, and physical self-confidence than NBW adults. An important yet unexpected finding was a 4% incidence of late retinal detachment, with an additional 6.6% of study participants found to have retinal tears. The 15-year outcome Cryotherapy for Retinopathy of Prematurity Cooperative Group trial for threshold ROP found late retinal detachment in 4.5% of treated eyes and 7.7% of untreated eyes.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *March of Dimes* (Web site), ([www.marchofdimess.com](http://www.marchofdimess.com))
- *HealthyChildren.org* (Web site), American Academy of Pediatrics ([www.healthychildren.org](http://www.healthychildren.org))
- *Medical Home Information for Families* (Web site), National Center for Medical Home Implementation ([www.medicalhomeinfo.org/for\\_families](http://www.medicalhomeinfo.org/for_families))
- *Family Voices* (Web site), ([www.familyvoices.org](http://www.familyvoices.org))
- *Build a Care Notebook for Your Child* (Web page), Seattle Children's, Center for Children With Special Needs ([cshcn.org/planning-record-keeping/care-notebook](http://cshcn.org/planning-record-keeping/care-notebook))

#### Medical Decision Support

- *National Center for Medical Home Implementation* (Web site), ([www.medicalhomeinfo.org](http://www.medicalhomeinfo.org))
- *Low Birth Weight Neonatal Intensive Care Unit Graduate: Critical Elements of Care* (guideline), Washington State Medical Home Partnerships Project ([www.medicalhome.org/4Download/cec/CEC.pdf](http://www.medicalhome.org/4Download/cec/CEC.pdf))
- *Extremely Low Birth Weight NICU Graduate Supplement* (guideline), Washington State Medical Home Partnerships Project ([www.medicalhome.org/4Download/cec/elbw.pdf](http://www.medicalhome.org/4Download/cec/elbw.pdf))
- *Cerebral Palsy: Critical Elements of Care* (guideline), Seattle Children's Hospital Center for Children With

Special Needs ([cshcn.org/sites/default/files/webfm/file/CriticalElementsofCare-CerebralPalsy.pdf](http://cshcn.org/sites/default/files/webfm/file/CriticalElementsofCare-CerebralPalsy.pdf))

- *Toolkit for the Follow-up Care of the Premature Infant* (toolkit), MedImmune/ National Initiative for Children's Healthcare Quality ([www.preemietoolkit.com/index.aspx](http://www.preemietoolkit.com/index.aspx))
- *Infant Measurement and Infant Outcomes Estimator Tools* (toolkit), NICHD Neonatal Research Network ([neonatal.rti.org/index.cfm?fuseaction=tools.main](http://neonatal.rti.org/index.cfm?fuseaction=tools.main))

### SUGGESTED READINGS

- Hack M, Schluchter M, Andreias L, et al. Change in prevalence of chronic conditions between childhood and adolescence among extremely low-birth-weight children. *JAMA*. 2011;306:394–401
- Long-term outcome for the tiniest or most immature babies (issue topic). *Semin Fetal Neonatal Med*. 2014;19(2):71
- Moore GP, Lemyre B, Barrowman N, Daboval T. Neurodevelopmental outcomes at 4–8 years of children born at 22–25 weeks' gestational age: a meta-analysis. *JAMA Pediatr*. 2013;167:964–974
- Vollsaeter M, Røksund OD, Eide GE, et al. Lung function after preterm birth: development from mid-childhood to adulthood. *Thorax*. 2013;68:767–776

### Chapter 116

## HEALTH AND DEVELOPMENTAL OUTCOMES OF SELECTED MEDICALLY COMPLEX NEONATES

Sarah Chambers, MD; Deborah E. Campbell, MD

Advances in neonatal and pediatric intensive care have contributed to increased survival among infants whose birth is complicated by prematurity, low birth weight, congenital disorders and birth defects, and maternal conditions affecting the newborn. Among all neonates, approximately 14% require specialized newborn care in a special or intensive care nursery. Fifty-one percent of infants requiring specialized neonatal care are born at term or postterm. The infant mortality rate has steadily declined over the past several decades. In recent years, the decline has continued but at a slower rate: from 6.61 infant deaths per 1,000 live births in 2008 to 6.39 infant deaths per 1,000 live births in 2010. Congenital malformations, deformations, and chromosomal abnormalities are the leading causes of infant deaths (20.8%). Congenital diseases of the heart are among the most common congenital malformations in infants and are commonly associated with chromosomal disorders. Congenital malformations, chromosomal disorders, and congenital heart disease become less significant causes of death in children and adolescents, contributing to 2.2% of deaths in children ages 1 to 9 years in 2009. The other top conditions that contribute to infant mortality are disorders related to short gestation and low birth weight, sudden infant death syndrome, maternal complications of pregnancy, and accidental injuries.



Approximately 22% of children have a chronic health condition that affects their well-being and causes functional limitations in their day-to-day activities. Nearly 9% of children have 2 or more chronic conditions affecting their health and abilities. The prevalence of children with special health care needs increased 18% between 2001 and 2010. The infants with the greatest continuing care needs are full-term and late preterm infants with acute illness, babies with congenital malformations (eg, neural tube defects; ear-nose-throat, cardiac, gastrointestinal, or genitourinary anomalies; and genetic syndromes), and premature infants who are physically healthy but immature and have long-term health and developmental problems caused by their preterm birth.

This chapter focuses on health and developmental outcomes for the growing population of infants and children, cared for by general pediatricians and family physicians, who are born with major congenital malformations of the heart, tracheobronchial tree, and diaphragm, and infants who require extracorporeal membrane oxygenation (ECMO) treatment for neonatal respiratory failure or therapeutic hypothermia (whole-body or brain cooling) to reduce the risk for brain injury caused by hypoxic-ischemic encephalopathy. Chapter 115, Health and Developmental Outcomes of Very Preterm and Very Low-Birth-Weight Infants, provides detailed information on the health and developmental outcomes for the low-birth-weight and preterm infant and child.

### PEDIATRIC PRIMARY CARE FOR THE INFANT WITH COMPLEX MEDICAL NEEDS

Central to the ongoing health and developmental care for infants and children with complex medical needs is the medical home. A medical home is an approach to providing comprehensive primary care. (For more information, see Chapter 6, Medical Home Collaborative Care, and [www.medicalhomeportal.org/medical-home](http://www.medicalhomeportal.org/medical-home).) In a medical home, a primary care physician (PCP) works in partnership with the family and patient to assure that the medical and nonmedical needs of the child are met. Through this partnership, the PCP can help the family and patient access and coordinate specialty care, educational services, out-of-home care, family support, and other public and private community services that are important to the overall health of the child and family. A medical home provides care that is “accessible, continuous, comprehensive, family centered, coordinated, compassionate, and culturally effective.” Within some medical communities and health systems, complex medical care programs are developing that serve the function of the medical home, providing the child and the family with an interdisciplinary team of professionals who provide, coordinate, and oversee the child’s health and developmental care needs in an integrated fashion. Transitions in care across the child’s life span and into adulthood require alignment of key components of the child’s health care with the adult health care system, which should be grounded in the Institute of Medicine principles of the patient-centered medical home. The

4 principles that support a seamless transition in care over the health care continuum are

- **Family-centered partnership:** trusting, collaborative, working partnership with families, respecting their diversity and recognizing that they are the constant in a child’s life
- **Community-based system:** family-centered, coordinated collaborations designed to promote the healthy development and well-being of children and their families
- **Transitions:** provision of high-quality, developmentally appropriate health care services that continue uninterrupted as the individual moves along and within systems of services and from adolescence to adulthood
- **Value:** a high-performance health care system that has appropriate financing to support and sustain medical homes that promote system-wide quality care with optimal health outcomes, family satisfaction, and cost efficiency

### IMPACT ON FAMILIES AND FAMILY FUNCTIONING

The birth of a critically ill infant, whether anticipated because of a prior prenatal diagnosis or unexpected in the event of an urgent delivery or the onset of neonatal illness after birth, causes significant emotional distress for families. Under these circumstances diagnosis and treatment often need to be completed quickly, limiting the time for detailed discussions with anxious parents and family. In most instances, the medical indication for treatment defines the moral obligation for treatment. Ethical problems may arise when treatment is only partially successful, long-term complications occur, and questions arise related to quality of life and the relative benefits and burdens of continued treatment. Physicians and families may struggle with decisions regarding withdrawing or withholding treatment. Tensions exist as well in regard to “trial of therapy” approaches to care, with parental fears of overtreatment or of being asked to end treatment if the infant does not respond. Physicians caring for the infant may fear potential litigation if they do not offer every available therapy. Shared decision making is optimal but complex because it requires a willingness to participate, yet individual parent and family goals for their infant may change over time, as may the parents’ level of involvement. Chapter 67, Palliative Care and Bereavement, and Chapter 117, Support for Families Whose Infant Is Sick or Dying, provide in-depth discussion about shared decision making, palliative care, and family bereavement through the continuum of a child’s illness and ongoing complex health care needs.

#### Decision Making

Shared decision making is a process with decisional responsibility based on parental preferences. This requires fully informing parents and providing them complete information about the risks and benefits of treatment as well as of forgoing treatment so that they may make informed, reasoned decisions. Shared decision making requires a reciprocal exchange of information. Physicians should communicate medical information objectively to

the parents; in return, parents should share information about their values and goals for their child and family. In shared decision making, the physician's role includes active participation, sharing in the decisional responsibility, and providing evidence-based recommendations that provide a basis for parental discussions and decisions. Parents exhibit varied decision-making preferences. Respecting a family's right to determine their level of participation in decision making is both legal and ethical. It has been suggested that for parents who choose a less active role in their child's medical decision making, an appropriate compromise is a combined approach that integrates consent to give physicians decisional discretion and assent for some of the actual medical decisions.

### Palliative Care Across the Continuum of Care

*Palliative care* (Box 116-1) is an approach that improves the quality of life of patients and families facing the problems associated with life-threatening illness, preventing and relieving suffering by means of early identification, assessment, and treatment of pain and other symptoms (physical, psychosocial, and spiritual). *Supportive care* is a component of palliative care that is applicable during the course of illness, in conjunction with other therapies that are intended to prolong life, for example, ECMO, peritoneal dialysis, repair of congenital heart disease (CHD), and other interventions. Supportive care includes investigations needed to better understand and manage distressing clinical complications. *End-of-life care* focuses on the specific preparations for an anticipated death and managing the end stage of a fatal medical condition. Nearly one-third of all child deaths between birth and 18 years of age occur in the neonatal period. Twenty-eight percent of childhood deaths occur because of prematurity and low birth weight, complications of pregnancy, abnormal placentation, CHD, respiratory distress, and congenital anomalies. Thus neonatal intensive care units (NICUs) bear most of the responsibility for care of these patients.

Care for the dying or severely ill neonate should include pain and symptom management, as well as psychosocial and spiritual support for the family.

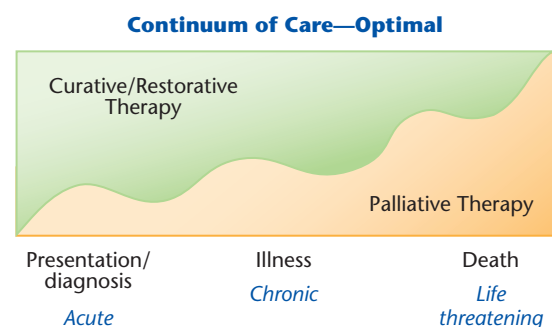
#### BOX 116-1 Palliative Care

- Provides relief from pain and other distressing symptoms
- Affirms life and regards dying as a normal process
- Intends neither to hasten nor postpone death
- Integrates the psychological and spiritual aspects of patient care
- Offers a support system to help patients live as actively as possible until death
- Offers a support system to help the family cope during the patient's illness and in bereavement
- Uses a team approach to address the needs of patients and their families, including bereavement counseling if indicated
- Will enhance quality of life and may also positively influence the course of illness

Attention to the quality of life and best interests of the child should be addressed as determined through culturally sensitive, family-centered, collaborative care decisions. Involved health care providers also require support because of the emotionally, physically, and intellectually challenging environment in which care is provided for neonates who remain unimproved despite maximal therapy. Instituting a palliative care protocol facilitates earlier identification of infants who may benefit from a more comprehensive plan of care, especially as it becomes evident that curative therapies have remained ineffective or are minimally effective. Transitioning from a curative-only to a palliative-supportive, end-of-life model of care encompasses family and staff impressions and assessments as well as communication and shared decision making. Additionally, palliative care principles can also be integrated into the care plan for all medically complex, high-risk neonates undergoing intensive care as well as the at-risk neonate in the delivery room, whether the focus is continuation of life-sustaining therapies or palliation and comfort until death occurs (see Figure 116-1).

### INFANTS WITH SIGNIFICANT CONGENITAL HEART DISEASE

Congenital heart disease is the most common severe congenital abnormality in the pediatric population. The incidence of CHD varies widely, depending on the definition and the methods reported. Table 116-1 provides a summary of the incidence of CHD. Estimates of the incidence of all CHD (including trivial, clinically irrelevant lesions such as tiny ventricular or atrial septal defects) are as high as 50 to 75 per 1,000 live births. However, the incidence of moderate to severe CHD is about 6 to 8 per 1,000 live births. This includes structural defects that require expert cardiac care and medical or surgical intervention, ranging from hypoplastic left heart syndrome and total anomalous pulmonary venous return to d-transposition of the great arteries (d-TGA) and tetralogy of Fallot, to a large ventricular septal defect or a large patent ductus arteriosus. Bicuspid aortic valve incidence, not included in this number, has a relatively high incidence of 10 to 20 per 1,000 live births and is clinically significant



**Figure 116-1** Palliative care and treatment of underlying disease are integrated throughout the course of a child's illness. (From Korones D. *Pediatric palliative care*. *Pediatr Rev*. 2007;28:e46–e56.)

because of the risk for developing valvular stenosis or incompetence over time. The diagnosis of moderate to severe CHD is often made prenatally, and a delivery and perinatal care plan can be made in advance by a multidisciplinary team including the obstetrician, pediatric cardiologist, neonatologist, cardiothoracic surgeon, and the family.

Medical therapies, catheter-based interventions, and surgical techniques for the treatment of congenital heart disease have advanced significantly in the past 60 years. In the current era, most structural cardiac abnormalities can be repaired or palliated. As a result, the number of adults with CHD has surpassed the number of children with CHD. At least 85% of patients who undergo surgical treatment of CHD now reach adulthood, and most deaths resulting from CHD occur after 20 years of age. This number includes not only patients with the most common forms of CHD affecting adults (eg, congenital valve defects, atrial and ventricular septal defects, and patent foramen ovale) but also many patients with severe complex CHD. These patients, who are now surviving into adulthood, are encountering long-term complications of open heart surgery (eg, arrhythmia or conduit obstruction after tetralogy of Fallot repair), single-ventricle palliation (Fontan procedure), or orthotopic heart transplantation.

The study of the long-term outcomes in patients with CHD has become a focus of attention and research in pediatric cardiology and has contributed to the emergence of a new subspecialty in adult CHD. Medical and surgical outcomes, such as arrhythmia, ventricular failure, and the need for reoperation, have been studied, but neurodevelopmental and social outcomes have also become a focus of attention as these patients have survived to become adult members of society.

### Prenatal Diagnosis and Outcome of Congenital Heart Disease

The prenatal diagnosis of CHD is improving but still a challenge. The reported detection rates for prenatal CHD vary widely, from 23% to 57% in published studies. Two of the more recent studies report rates at the

higher end of this range, from 47% to 57%. Furthermore, there is significant variability in the detection rates of individual cardiac lesions in different studies. Table 116-2 summarizes the reported detection rates from different population studies for overall detection of CHD and detection of individual cardiac lesions. Two studies from France and the Czech Republic have analyzed the change in detection rates over time and demonstrated that for most lesions, prenatal detection rates are significantly higher in the new millennium.

There is some debate within the pediatric cardiology community regarding whether prenatal diagnosis of CHD affects the outcome of live-born infants. It is widely acknowledged that fetal diagnosis of complex CHD allows for prenatal counseling and genetic testing if indicated and can include the option of pregnancy termination. However, if the pregnancy is continued, there is debate regarding whether a prenatal diagnosis contributes to improved outcomes. Theoretically, prenatal diagnosis allows for delivery at a tertiary care center and early initiation of treatment if indicated. However, many studies have reported conflicting data regarding the benefits (and adverse effects) of prenatal diagnosis. The outcomes studied have included short-term or long-term survival, surgical morbidity and mortality, and neurodevelopmental and quality-of-life outcomes. Much of the confusion results from the small number of patients in this population and the wide variation in disease severity between (and even among) cardiac lesions. Some studies have reported that patients with a prenatal diagnosis of moderate to severe CHD (eg, d-TGA) have a decreased risk for early mortality, but others have shown no difference in neonatal mortality, especially in patients requiring univentricular palliation, such as those with hypoplastic left heart syndrome (HLHS) or pulmonary atresia with intact ventricular septum. Although there is much debate regarding the effect of prenatal diagnosis of CHD on mortality, many studies have demonstrated an improvement in neonatal morbidity when CHD is diagnosed prenatally. These improvements include reduced early neurologic morbidity in HLHS, decreased use of preoperative mechanical ventilation, administration of antibiotics, cardiac catheterization, and emergency surgery, fewer cases of preoperative cardiac failure and closure of the ductus arteriosus, and a shorter duration of postoperative mechanical ventilation. Long-term follow-up has demonstrated less residual cardiac dysfunction and a longer freedom from catheter-based reintervention or repeat surgical intervention.

The effect of prenatal cardiac evaluation and diagnosis on the mother and on mother-infant bonding patterns has also been studied. Women referred for a fetal echocardiogram have been shown to have higher anxiety levels, especially when referred for an abnormal finding on obstetric ultrasound (vs a reason such as maternal diabetes mellitus). However, these women also self-reported that fetal and pregnancy testing was reassuring. Studies of parents whose fetus is diagnosed with serious CHD show that the parents experience a crisis period similar to the process of bereavement, in which they go through the stages of shock, denial, anger, depression, acceptance, and adjustment. A study

**Table 116-1** Incidence of Congenital Heart Disease Per 1,000 Live Births

ALL CONGENITAL HEART DISEASE	9.6
All cyanotic congenital heart disease	1.4
Ventricular septal defect	3.6
Atrial septal defect	0.9
Patent ductus arteriosus	0.8
Aortic coarctation	0.41
Hypoplastic left heart syndrome	0.27
Tetralogy of Fallot	0.42
Transposition of the great arteries	0.32
Atrioventricular septal defect	0.35
Bicuspid aortic valve	13.6

Adapted from Hoffman JIE, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol.* 2002;39:1890–1900, with permission from Elsevier.

**Table 116-2**      **Reported Prenatal Detection Rates of Congenital Heart Disease**

STUDY	EUROPE <sup>a</sup>	PARIS, FRANCE <sup>b</sup>	CZECH REPUBLIC <sup>c</sup>	SOUTH AUSTRALIA <sup>d</sup>	NORWAY <sup>e</sup>
Date	1990–1993	1983–1988	1995–2000	1986–2006 1986–1999    2000–2006	1991–2001
<b>Overall detection of congenital heart disease (%)</b>	39	23	47	28	57
<b>Hypoplastic left heart syndrome (%)</b>	55	32	89	31    96	61    60
<b>Transposition of the great arteries (%)</b>	21	13	73	6    26	15    59
<b>Atrioventricular septal defect (%)</b>	58	—	—	—    —	24    71
<b>Tetralogy of Fallot (%)</b>	49	20	70	9    37	25    43
<b>Aortic coarctation (%)</b>	4	0	42	3    20	44

<sup>a</sup>Grandjean H, Larroque D, Levi S. The performance of routine ultrasonographic screening of pregnancies in the Eurofetus Study. *Am J Obstet Gynecol.* 1999;181:446–454.

<sup>b</sup>Khoshnood B et al. Trends in prenatal diagnosis, pregnancy termination, and perinatal mortality of newborns with congenital heart disease in France, 1983–2000: a population-based evaluation. *Pediatrics.* 2005;115:95–101.

<sup>c</sup>Marek J et al. Prenatal ultrasound screening of congenital heart disease in an unselected national population: a 21-year experience. *Heart.* 2011;97:124–130.

<sup>d</sup>Khoo NS et al. Effectiveness of prenatal diagnosis of congenital heart defects in South Australia: a population analysis 1999–2003. *Aust N Z J Obstet Gynaecol.* 2008;48:559–563.

<sup>e</sup>Tegnander E et al. Prenatal detection of heart defects in a non-selected population of 30,149 fetuses—detection rates and outcome. *Ultrasound Obstet Gynecol.* 2006;27:252–265.

by Menahem and Grimwade has suggested that the prenatal diagnosis of serious CHD, coupled with effective prenatal counseling, may improve postnatal mother-child bonding in families that decide to continue the pregnancy. The authors postulate this may be a result of the mother having already experienced the grieving process for the loss of her previously anticipated healthy baby. There are fewer data on the effect of prenatal diagnosis of CHD on the father of the fetus. A postnatal study of father-infant attachment in infants requiring cardiac surgery before 3 months of age demonstrated normal mean scores on the Paternal Postnatal Attachment test but lower scores on the pleasure/interaction and affection/pride subscales of the test. Self-reports of the relationship by the fathers in this study vary, with some fathers reporting feeling closer to their infant and others reporting apprehension and reservation about getting too close to their infant. This is a field that merits further study in the prenatal setting. In summary, in addition to reducing the mortality and physiologic morbidity of congenital heart disease, prenatal diagnosis may improve the psychosocial environment for some patients.

### Perinatal and Surgical Outcomes

The overall survival rate of heart surgery for CHD is greater than 90% in most studies in the current era, and more than 95% in some reports. However, there are known groups of patients who are at higher risk for perinatal and perisurgical morbidity and mortality. For

example, although the outcomes after single-ventricle (Fontan) palliation have improved dramatically during the past 3 decades, the long-term survival remains between 80% and 90%. Patients with HLHS are at even higher risk; contemporary 5-year survival rates (including Fontan palliation) are 50% to 60% with expectations that 70% of infants born with HLHS will reach adulthood.

Perioperative factors have been identified that are significantly associated with outcomes following neonatal congenital heart surgery. For example, intraoperative and postoperative hyperglycemia has been associated with increased morbidity and mortality after pediatric cardiac surgery. A prospective, randomized study from Europe suggests that tight glycemic control in the intraoperative and postoperative period has a protective effect on the myocardium and reduces the body's inflammatory response and the need for vasoactive support. In the postoperative period, the amount of cardiovascular support required during the first 48 hours (measured by a vasoactive-inotrope score) is a good predictor of mortality and morbidity in young infants after cardiac surgery. Important predictors include duration of mechanical ventilation, time to negative fluid balance (diuresis), and length of stay in the intensive care unit. These perioperative factors have led to the development of prediction measures, such as the Aristotle Comprehensive Complexity Score or the Risk Adjustment for Congenital Heart Surgery (RACHS-1), that attempt to predict the risk for mortality and morbidity after congenital heart surgery.



Recent studies have reported an increased risk for neonatal death or other adverse outcomes for healthy infants without birth defects who were born at 37 to 38 weeks' (37%–38% weeks) gestation compared with those born at 40 weeks. In many centers, infants with complex CHD are electively delivered (often by induction of labor) between 37 and 40 weeks' gestational age, at a time when organ development is thought to be complete because this allows for a coordinated mobilization of expert teams in the delivery of care to a potentially critically ill neonate. However, a large study of patients with critical CHD demonstrated that babies born before 39 weeks' gestation have increased mortality compared with those born at 39 to 40 weeks. These infants also experience increased morbidities and resource use, including more days of mechanical ventilation and more days in intensive care. Interestingly, infants born after 40 weeks also experience increased mortality rates, suggesting that the ideal gestational age of delivery for patients with critical CHD may be 39 to 40 weeks' gestation.

#### **Role of Low Birth Weight and Preterm Birth**

It is well documented that infants with CHD are at higher risk for low birth weight (<2,500 g) than the normal population. Although these infants are not at increased risk for premature birth compared with the normal, non-CHD population, both low birth weight and prematurity are widely recognized as risk factors for morbidity and mortality associated with cardiac surgery. Neonates with a birth weight of less than 2,500 g have higher mortality and morbidity for cardiac surgery. Studies report 15% to 24% overall surgical mortality in critically ill low-birth-weight neonates and up to 28% mortality in infants undergoing a palliative surgery as opposed to a full repair. This raises the suggestion that primary repair may confer a survival benefit over palliation in this population. Common postsurgical morbidities include pulmonary complications (pneumonia, lobar atelectasis, pneumothorax), pulmonary hypertensive crisis, arrhythmia, renal insufficiency, seizure, and sepsis.

#### **Role of Associated Genetic Disorders and Extracardiac Malformations**

Another group known to have poorer outcomes after cardiac surgery includes those infants with associated genetic disorders or extracardiac malformations. There are known associations between certain genetic disorders and cardiac lesions, such as atrioventricular canal defects in trisomy 21, conotruncal defects (eg, transposition of the great vessels), and 22q11 deletion syndromes. Patients with genetic disorders and cardiac disease are thought to have increased morbidity and mortality associated with cardiac surgery compared to patients with a normal genetic complement. However, it must be remembered that corrective or palliative cardiac surgery in patients with genetic disorders such as trisomy 21 can also improve their long-term survival.

#### **General Long-term Health Outcomes**

As surgical techniques and postnatal care have improved, most patients with CHD now survive into

#### **BOX 116-2 Nutrition Goals**

- Weight gain goals are 20 to 30 g/day during the first 3 months of life; 18 to 20 g/day from 3 to 6 months of age.
- Infants and children with CHD have caloric needs 120% to 140% higher than the recommended daily allowance.
- Infant caloric requirements can be 130 to 170 kcal/kg/day to achieve adequate weight gain.

#### **BOX 116-3 Strategies for Nutritional Support**

- Consider the route of feeding: supplemental tube feedings can promote weight gain and reduce calorie expenditure.
- Adjust caloric density and target volume of enteral feedings.
- Closely monitor weight gain; use World Health Organization growth curves from birth to 24 months.
- Monitor and evaluate feeding behaviors.

adolescence and adulthood. However, for many patients, survival does not necessarily equal cure. Although some lesions, such as valvar pulmonary stenosis or a ventricular or atrial septal defect, may be completely repaired by surgical or catheter-based intervention, even these patients need to be followed by a cardiologist throughout their life. A stenotic pulmonary valve can restenose over time and require reintervention. There might be a residual ventricular septal defect, in which case the patient will require subacute bacterial endocarditis (SBE) prophylaxis for indicated procedures; or the patient may develop ventricular arrhythmias later in life if the surgical repair involved a ventriculotomy.

Infants born with more complex CHD often require lifelong medication, may require multiple reinterventions throughout their life, and may require more aggressive treatment for routine childhood illnesses (eg, viral upper respiratory tract infections) than healthy children. The PCP must carefully follow their somatic growth, developmental milestones, and general state of health in order to provide the best possible care of these complex patients (Box 116-2, Box 116-3, Box 116-4, Box 116-5). Furthermore, many of these patients have significant morbidities after cardiac surgery, such as feeding difficulties (sometimes requiring tube feeding), vocal cord abnormalities, respiratory abnormalities (including the need for tracheostomy in some patients), rhythm abnormalities, and the need for anticoagulation therapy. The PCP is pivotal in providing a stable medical home for these patients and collaborating with the family and multiple subspecialists to coordinate optimal care for the patient. Together, the PCP and subspecialists develop a care plan with the family that addresses the child's specific health and developmental needs and delineates which professional is responsible for managing each of the

**BOX 116-4 High-Calorie Formula**

- Concentrate formula to 24 cal/oz.
- If the patient is receiving human milk, carefully consider constituents added to ensure that adequate protein intake ( $>7\%$  total calories; 2–3 g/kg/day) is maintained while caloric density is boosted.
- Add modular nutrients to increase caloric density above 24 cal/oz:
  - CHO modulars: polycose, Moducal
  - Protein modulars: Beneprotein
  - Fat modulars: Microlipid, medium-chain triglyceride oil, vegetable oil

**BOX 116-5 PredischARGE Checklist: Feeding**

- Demonstrates 3 consecutive days of weight gain (using the same scale) of  $>10$  g per day
- Tolerates the planned home feeding regimen for 3 days with no change in emesis or stool patterns
- Parent/caregiver competence with feeding plan (parent teach-back and demonstration of necessary skills)
  - Formula preparation
  - Feeding regimen including feeding volumes, feeding techniques, tube feedings if needed, home weights, home feeding, and/or monitor logs
- Family has a clearly written feeding plan
  - If mother is breastfeeding, mother has information, lactation support, and supplies needed to breastfeed as well as express milk to sustain milk volume
  - If formula or combination (human and formula) feeding, specify formula type and concentration (cal/oz)
  - Feeding route, frequency, and volumes
  - Weight gain goals
- Family has identified where to get formula and supplies
  - Home health agency
  - Specialty pharmacy
  - Women, Infants, and Children (WIC) Nutritional Program
  - Family to provide
- Family has identified whom to contact for feeding issues and follow-up appointments; there is a need for clear identification of who will actively manage the infant's feeding and nutrition

specific facets of the child's health needs; for example, who will manage the child's nutritional needs to optimize growth.

**Nutrition**

Infants and children with CHD are at higher risk for poor nutrition and slow growth, especially those with

**BOX 116-6 Feeding Problems in Infants With Congenital Heart Disease**

- Lack of or poor coordination of sucking, swallowing, and breathing
- Inefficient suck (feeding fatigue, limited endurance)
- Gastroesophageal reflux disease
- Oral aversion
- Respiratory distress
- Aspiration

**BOX 116-7 Causes of Failure to Thrive in Infants With Congenital Heart Disease**

- Low caloric intake
- Heart failure
- Intercurrent illness, infection
- Gastrointestinal: reflux, malabsorption, obstruction

**BOX 116-8 Feeding and Nutrition "Red Flags"**

- Weight loss of  $>30$  g in 1 day
- Failure to gain 20 g in 3 days
- Intake  $<100$  mL/kg/day
- 2 episodes of vomiting in 24 hours
- Loose stools (change from baseline)

cyanotic CHD. Many of these patients require prolonged intensive care unit stays and prolonged endotracheal intubation in the perioperative period. Furthermore, cardiac surgery carries a risk for recurrent laryngeal nerve damage, which can increase the risk for aspiration or microaspiration with feeding. Studies have shown that up to 48% of infants who have undergone a Norwood procedure (first stage of surgery for HLHS involving reconstruction of the aortic arch using the main pulmonary artery and placement of an aortopulmonary shunt for pulmonary blood flow) have laryngopharyngeal dysfunction. It is well documented that neonates who have undergone surgery for CHD are at risk for feeding difficulties (Box 116-6) and poor weight gain (Box 116-7, Box 116-8).

Cardiopulmonary bypass (CPB), increased RACHS-1 score, and prolonged intubation have been identified as increasing the risk for feeding problems. Infants with comorbidities such as genetic syndromes are also at increased risk for poor feeding and poor growth. The PCP as well as the pediatric cardiologist, should

closely monitor the patient's weight gain and linear growth and adjust the caloric intake as needed. Some patients may require nasogastric or gastric tube feedings at home. This requires parental education and often coordination of home nursing services. Involvement of a nutritionist may be helpful if patients are underweight or overweight.

### Medications

Many children with CHD are on chronic medication. Classes of common long-term medications used in the treatment of these patients include diuretics, antiarrhythmics, anticoagulants, pulmonary vasodilators, afterload reducers, and inotropes. The PCP and the pediatric cardiologist should work together to ensure that the doses are appropriate for the patient's weight and to monitor for medication side effects. Furosemide, a common diuretic used in this population, can cause electrolyte abnormalities and loss of bone density with chronic use. Warfarin, used for anticoagulation in patients with mechanical valves, requires careful monitoring of therapeutic levels and increases the risk for bruising and bleeding. Dietary changes can significantly affect warfarin levels. Careful parent and caregiver education is imperative in patients who are taking this medication. Many antiarrhythmic medications can cause significant electrocardiographic changes (eg, prolonged QTc interval) and are themselves arrhythmogenic. Close monitoring of the patient's electrocardiogram is required, especially during initiation of treatment, and parents should be educated about the signs and symptoms of arrhythmia in infants and children.

### Infections

Children with CHD are at increased risk for morbidity from common childhood infections such as viral respiratory infections. Respiratory syncytial virus (RSV) is an example that has been well studied in this population. Children with hemodynamically significant CHD are more likely to require hospital admission, admission to the intensive care unit, and mechanical ventilation for RSV bronchiolitis than other children with RSV infection. Monthly prophylaxis with palivizumab during the RSV season (November through April) for the first 2 years of life significantly reduces the rate of hospitalization in patients with CHD and should be initiated for patients with significant CHD. PCPs should also ensure that patients with CHD are up to date on their immunizations, including yearly influenza vaccination. Furthermore, some children with CHD have coexisting conditions that lead to immunocompromise (eg, 22q11 deletion syndrome and asplenia in heterotaxy patients). The T-cell abnormalities in 22q11 deletion syndrome may be a contraindication to live virus vaccination; these patients should be referred to an immunologist before administration of these vaccines. Patients with heterotaxy syndrome and asplenia (anatomic or functional) are at increased risk for bacterial infection and should be prescribed prophylactic antibiotics.

Some patients with CHD are at high risk for SBE following dental procedures (or select other procedures)

and should receive antibiotic prophylaxis before these procedures. In 2008, the American Heart Association (AHA) revised its recommendations regarding the patients for whom prophylactic antibiotic therapy is indicated. These recommendations include patients with prosthetic valve material, a previous history of infectious endocarditis, unrepaired (or palliated) cyanotic CHD, cardiac surgery using a prosthetic device or material within 6 months, cardiac surgery with a residual high-velocity shunt, and heart transplantation with valvulopathy. PCPs and pediatric cardiologists should review whether a patient with congenital heart disease should receive SBE prophylaxis and educate the patients and other caregivers accordingly.

## NEURODEVELOPMENTAL ABNORMALITIES IN CHILDREN WITH CONGENITAL HEART DISEASE

It is widely acknowledged that children with CHD have an increased incidence of neurodevelopmental abnormalities compared with the general population. Abnormalities can range from profound brain damage and developmental delay to behavioral disorders such as attention-deficit/hyperactivity disorder and learning difficulty in school, and also include an increased risk for psychiatric disorders. The remarkable improvements in survival after infant cardiac surgery and the increasing numbers of children, adolescents, and adults with repaired CHD have led to an increased awareness and focus on understanding and trying to prevent these adverse neurodevelopmental outcomes. Although we do not have a full understanding of all the factors that contribute to neurodevelopmental abnormalities in patients with CHD, we know that it is multifactorial in origin, with sequelae related to factors including underlying genetic conditions, an increased incidence of preoperative central nervous system abnormalities possibly related to abnormal fetal cerebral blood flow, and postnatal factors such as operative risks, specific intraoperative effects of cardiopulmonary bypass (CPB), and deep hypothermic circulatory arrest, and factors related to the postoperative course.

### Genetic Factors

Although a detailed description of syndromic conditions that are associated with CHD and neurodevelopmental abnormalities is beyond the scope of this chapter, it is important to note that children with a chromosomal abnormality and CHD generally have a worse neurodevelopmental outcome than those with a normal karyotype. Additionally, some syndromes, such as trisomy 21 or 22q11 deletion, have known patterns of neurodevelopmental abnormalities. For example, patients with 22q11 deletion syndrome, which is associated with conotruncal abnormalities such as tetralogy of Fallot or d-TGA, have poor visual-spatial and mathematical skills, can have an IQ ranging from profound disability to an average IQ, and have an increased risk for psychiatric disorders, specifically schizophrenia and schizoid disorder.

With few exceptions, the recent literature suggests that genetic disorders, including trisomy 21, are not a significant risk factor for increased mortality associated with surgical repair of CHD. However, multiple studies have demonstrated that genetic disorders are associated with higher morbidity surrounding cardiac surgery, including increased length of stay, renal insufficiency, postoperative infections, and postoperative respiratory complications. There are few data, however, on neurodevelopmental outcomes specifically in patients with genetic disorders following cardiac surgery for CHD. Visootsak and colleagues published the first study to evaluate the developmental pattern in patients with trisomy 21 who had undergone complete atrioventricular valve repair compared with patients with trisomy 21 and a normal heart. In a small cross-sectional study, motor development was significantly impaired in patients who had cardiac surgery compared to those with a normal heart, but there was no statistically significant difference in cognitive or language abilities.

There may be a genetic component to neurodevelopmental abnormalities in patients with CHD who do not have a described genetic syndrome. A recent study demonstrated that the apolipoprotein E  $\epsilon$ 2 allele is associated with increased behavior problems, restricted behavior patterns, and impaired social interactions in preschool-age children with CHD requiring surgical treatment.

### Gender Differences

Boys have an increased incidence of some forms of CHD, such as HLHS, tetralogy of Fallot, and TGA. Studies on the cellular mechanisms of perinatal brain damage have demonstrated significant male-female differences. Male brains may be more sensitive to cell apoptosis after hypoxic-ischemic injury, whereas female brains may have increased risk for cell apoptosis after oxidative stress injury. Majnemer et al demonstrated that boys with CHD requiring early surgical repair are at increased risk for neuromotor impairments and activity limitations at school entry.

### Central Nervous System Abnormalities

Many newborns with CHD show evidence of neurologic abnormalities preoperatively, suggesting that there are prenatal and perinatal factors involved. Studies have demonstrated that more than 50% of babies with CHD have clinical evidence of neurologic abnormalities before heart surgery. The abnormalities include hypotonia and hypertonia, jitteriness, motor asymmetries, absent suck, poor state regulation, feeding difficulties, seizures, and abnormal somatosensory evoked potentials. Interestingly, these findings were not confined to patients with cyanotic heart disease. These abnormalities are present more commonly in patients with acyanotic heart disease, suggesting that hypoxemia may not be the underlying etiologic cause of the neurologic abnormalities in these patients. There is also radiologic and metabolic evidence of abnormal brain structure and function in neonates with CHD. Preoperative neuroimaging (with magnetic resonance imaging [MRI] or ultrasound) has demonstrated a high incidence of brain malformations (up to

40%–60% of studied infants), including agenesis or dysgenesis of the corpus callosum, holoprosencephaly, microcephaly, lissencephaly, Dandy-Walker malformation, and immature cortical mantle. Studies have reported microcephaly in up to 36% of neonates with CHD. There is also a high incidence of preoperative acquired neurologic injury in these patients, including cerebral atrophy, intraventricular hemorrhage, thromboembolism, infarct, periventricular leukomalacia, and gray matter injury.

Not only brain structure but also brain development is abnormal in patients with CHD. MRI and magnetic resonance spectroscopy studies have demonstrated that term newborns with CHD have levels of brain metabolites that suggest a 1-month delay in brain development. Studies assessing structural evidence of brain development by brain MRI have suggested a similar delay. Preoperative neurologic abnormalities have been significantly associated with long-term neurologic outcome.

Seizures are among the more common acute neurologic events in CHD patients. Preoperative seizures have been documented in neonates before heart surgery, and it is well known that acute postoperative seizures can occur after heart surgery at any age. Postnatal seizures have been reported in 15% to 20% of neonates after heart surgery, with one study demonstrating subgroups of neonates in whom seizures may occur in up to 50%. These subgroups include patients who underwent prolonged deep hypothermic arrest during surgery, patients with associated genetic abnormalities (eg, 22q11 deletion syndrome and trisomy 21), and patients with aortic arch obstruction. There is evidence that seizures in the neonate can indicate lasting physical injury, and the Boston circulatory arrest trial demonstrated that the presence of postoperative clinical seizures after repair of d-TGA was significantly associated with longer-term neurodevelopmental abnormalities and brain MRI abnormalities.

Theories on the etiology of neurodevelopmental abnormalities in patients with CHD include altered cerebral vascular resistance resulting from decreased cerebral blood oxygen content in d-TGA and decreased cerebral perfusion caused by retrograde perfusion of the aortic arch in HLHS. However, neurologic abnormalities are not limited to these lesions and occur in acyanotic and cyanotic CHD. Furthermore, structural brain abnormalities (primarily in the white matter) persist into adolescence. The search for the etiology of neurodevelopmental abnormalities in all patients with CHD is ongoing.

### Preoperative Risk Factors

Clinical risk factors associated with increased preoperative brain injury in newborns with CHD include lower gestational age and lower 5-minute Apgar score. Hemodynamic factors that have been associated with increased preoperative brain injury include decreased carbon dioxide reactivity and low baseline cerebral blood flow. Additionally, preoperative hypoxemia causes damage to the areas of the brain associated with executive functions. Preoperative hypoxemia, severe acidosis, and cardiocirculatory insufficiency have



been correlated with poor long-term neurodevelopmental outcomes.

Balloon atrial septostomy (BAS) is a procedure commonly performed in neonates with d-TGA to improve intracardiac mixing and systemic output in these patients preoperatively. Some studies have reported a significant association between BAS and stroke in these patients; however, other studies have reported that BAS is a confounding factor and that the brain injury is associated with oxygen delivery and time to surgery rather than with the BAS procedure itself.

### Intraoperative Factors

#### Cardiopulmonary Bypass

Cardiopulmonary bypass (CPB) is used in many congenital cardiac surgeries to allow for perfusion of vital organs with oxygenated blood by a mechanical pump circuit. Known neurologic risks of CPB include embolic complications and the activation of systemic inflammatory pathways. Some congenital cardiac surgeries require deep hypothermic circulatory arrest (DHCA) to completely drain the heart of blood and stop circulation through the body. This is achieved by cooling the patient to 60.8°F to 64.4°F (16°C–18°C). Some studies have demonstrated a correlation between the duration of DHCA and adverse neurologic outcome such as seizures and impaired motor function. A safe duration of DHCA has not been definitively demonstrated. Deep hypothermic circulatory arrest times longer than 45 to 60 minutes have been associated with mortality, neuromotor deficits, and global developmental delay. The Boston Circulatory Arrest Trial investigated the use of DHCA in neonates undergoing surgical repair of d-TGA. Infants undergoing DHCA for more than 40 minutes had an increased incidence of postoperative seizures compared to those with DHCA duration of less than 40 minutes. The incidence of postoperative seizures in patients with DHCA duration less than 40 minutes was not significantly different than in those patients undergoing regular CPB. Long-term neurodevelopmental follow-up of these patients showed that DHCA is associated with worse neurodevelopmental outcomes at 8 years of age than is hypothermic continuous low-flow bypass. However, other studies have found different results in other groups of patients. Fuller et al reported that in a cohort of patients with CHD without aortic arch obstruction, there was no significant association of DHCA with neurodevelopmental outcome at 4 years of age.

Surgical techniques are evolving to try to maximize neuroprotection in patients undergoing surgical repair for CHD. Hybrid strategies have been developed that avoid CPB in neonates with HLHS. Regional low-flow cerebral perfusion techniques allow brain perfusion without DHCA in aortic arch repairs, but a single-center comparison of the 2 techniques did not demonstrate an overall significant difference in primary endpoints of neurodevelopmental outcome (intelligence, reading, mathematics). Patients who underwent DHCA during repair of d-TGA had worse performance on motor function testing, visual-motor tracking, and phonologic awareness than patients

who underwent low-flow CPB; however, patients who underwent CPB had more impulsivity and worse behavior than those who underwent DHCA. Pediatric cardiothoracic surgeons, anesthesiologists, and perfusionists are continuing to explore new techniques that may continue to improve neuroprotection during CPB and DHCA.

### Anesthesia

There is emerging evidence linking neonatal and pediatric exposure to anesthesia with neurodevelopmental abnormalities. Animal models have demonstrated that exposing the developing brain to anesthetic agents causes neurotoxicity and abnormal neurobehavioral responses in adult animals. Flick et al demonstrated that, in humans, repeated anesthesia exposure before age 2 is an independent risk factor for the later development of learning disabilities. There are still limited data in humans, but this is a focus of research and scientific discussion.

### Postoperative Risk Factors

The postoperative neurologic risk in patients who have undergone surgical repair of CHD can be divided into the immediate and long-term postoperative periods. In the immediate postoperative period, hypotension and hypoxia are independent risk factors for periventricular leukomalacia. Evidence also suggests that the increasing complexity of the postoperative course (measured by length of intensive care unit stay and hospital stay) is associated with poorer tests of cognitive function and development.

Sick euthyroid syndrome is common after congenital heart surgery and is more marked in increasingly complex cases. In preterm infants, transiently low thyroid levels early in life are associated with poorer motor function, learning disabilities, and cerebral white matter damage. It is possible that postoperative thyroid abnormalities are a contributing factor to postoperative neurologic risk in CHD patients.

There are also long-term factors that place these children at increased risk for neurologic damage. Many patients who undergo congenital heart surgery during infancy or childhood require cardiac catheterization later in life. Although the risk associated with cardiac catheterization is generally lower than for CPB surgery, a 0.38% incidence of neurologic events (primarily seizure and stroke) in children undergoing cardiac catheterization has been described. If intravenous contrast is used for angiography, there is a risk for contrast toxicity, which is also associated with seizures. Children who have poor left ventricular function, arrhythmias, or prosthetic left-sided valves are at increased risk for the development of intracardiac thrombi, which can embolize to the brain. Furthermore, if there is a residual intracardiac communication such as an atrial septal defect or a Fontan fenestration, paradoxical emboli can cross from the systemic venous circulation to the brain. If patients with a prosthetic valve are managed with anticoagulation, over-anticoagulation can occur caused by dietary changes or medication interaction. This increases the risk for hemorrhagic stroke. Finally, CHD

is the most common predisposing cause of brain abscess, which can result from septic emboli in endocarditis.

### **Neurodevelopmental Outcome in Children With Congenital Heart Disease**

Children who have undergone surgical repair or palliation for CHD have lower scores on many aspects of neurodevelopmental and functional testing. As these children grow older, they have more difficulty in school as well as an increased risk for inattention and hyperactivity and psychiatric disorders. Although this is widely acknowledged in academic settings, a study from Canada suggested that the degree of functional limitation in day-to-day life is underestimated in the clinical (community) setting. Insufficient awareness of these developmental and educational limitations may lead to these children receiving fewer support services, such as occupational and speech therapy, than they truly require.

Although it is difficult to generalize across the heterogeneous population of infants who have had surgery for CHD, it has been well demonstrated that these children have significant impairments in many aspects of neurodevelopment compared with the general population. During infancy, patients commonly demonstrate global developmental delay, with more profound abnormalities in gross and fine motor skills. These deficits persist into childhood, with school-age patients demonstrating delays in adaptive, fine, and gross motor skills that manifest as difficulties with balance, coordination, and manual dexterity. These children also exhibit behavior problems such as inattention and shyness, in addition to poor visual-spatial skills, poor expressive language, IQ in the low-normal range, and poor socialization skills.

Parents of children with CHD report poorer school performance, more problems with grade retention, and more social, behavioral, and attention difficulties than children without CHD. Child self-reports were similar to children without CHD, with the exception that children with CHD reported increased depressive symptoms. A recent meta-analysis of the psychological and cognitive functioning of children and adolescents with CHD reported an increased risk for total internalizing behaviors and, to a lesser degree, externalizing problem behaviors, as well as poorer cognitive performance, that remained stable over time and age groups. Perceptual organizational and visual-spatial abilities were also impaired.

The heterogeneity of CHD has resulted in certain subsets of patients being studied in greater detail in regard to neurodevelopmental outcome. These include children with d-TGA and patients with single-ventricle physiology requiring Fontan palliation, especially those with HLHS.

#### ***d-Transposition of the Great Arteries***

The aforementioned Boston Circulatory Arrest Trial follows patients who have undergone an arterial switch procedure for d-TGA and has reported the neurodevelopmental outcomes for these patients at ages 1, 4, and 8 years (with the 16-year evaluation ongoing). At 1 year of age, patients undergoing DHCA

rather than low-flow CPB had lower motor development scores and more neurologic abnormalities such as seizures or abnormalities on examination. At 2.5 years of age, patients who underwent DHCA demonstrated slower expressive language development, and at 4 years of age they had lower fine and gross motor scores, more abnormalities in speech and language, and more oromotor apraxia. All patients (regardless of treatment group) demonstrated more neurodevelopmental abnormalities than healthy children and had mean full-scale IQ scores 0.5 standard deviation below the normal population mean. At age 8 years, the neurodevelopmental abilities of the entire group of children followed (regardless of treatment group) included decreased academic performance and poorer fine motor function, visual-spatial skills, and working memory. These children demonstrated poor executive function with difficulties in task planning and task completion, sustained attention, and more complex language and communication skills. Bellinger has proposed that some of the patterns of neurodevelopmental abnormalities seen in these patients can be understood as “theory of mind deficits” that are expressed as poor social cognition. These patients have difficulty describing their own emotional states as well as identifying other people’s feelings and emotions (“reading” people). This decreased ability to interpret social information may lead to difficulties in forming and maintaining social relationships and contribute to poor psychosocial functioning in general.

#### ***Single Ventricle (Including Hypoplastic Left Heart Syndrome)***

Children with HLHS are reported to have the highest risk for neurodevelopmental abnormalities of all patients with CHD. A recent review of HLHS describes a pattern of dysfunction in these patients that includes mild cognitive impairment, impaired social interactions, poor communication skills, inattention, impulsivity, and impaired executive function. Studies demonstrate low psychomotor development and low motor development scores in these patients at 1 and 2 years of age. With a change in surgical practice from the Blalock-Taussig shunt to the right ventricle-to-pulmonary artery shunt at one institution, there was an improvement in psychomotor development at 2 years of age. Risk factors for poor neurodevelopmental outcome include seizures and longer bypass time.

### **QUALITY OF LIFE IN CHILDREN WITH CONGENITAL HEART DISEASE**

The perceived health status of children after open heart surgery is generally comparable to that of the general population despite increased reporting of problems with learning, behavior, and socialization. However, when focusing on social and emotional functioning, parents of children with CHD describe their children as more withdrawn, having more social problems, and engaging in fewer activities compared with parents of children with an innocent murmur. Parents of children with CHD have a high risk for feeling distress and hopelessness. In mothers of infants with CHD, there is a correlation between the severity

of CHD in the child and maternal symptoms of depression and anxiety at 6 and 18 months postpartum. Fathers of infants undergoing surgery for CHD report conflicting reactions of joy, sadness/loss related to the illness, fear of the infant's vulnerability and possible death, and a drive to maintain control and be strong for others while undergoing intense emotions themselves. Studies suggest that, as with other serious childhood illnesses, severe CHD has a significant psychosocial effect on the family, with an underlying genetic disorder in the patient and poorer perceived social support being associated with increased familial effects in 1 study. The effects on the family are not limited to parents and the patient; Janus and Goldberg described effects on healthy siblings' behavior, demonstrating that the family's accommodation of the patient's illness seemed to increase the risk for behavioral problems in the sibling. Discussion of the psychosocial effects of having a child with CHD is important for the PCP to gain a full understanding of the effect on the whole family as well as to try to provide support services whenever possible.

Adult patients with CHD do not have significantly different quality-of-life scores from the general population, based on self-report questionnaires. However, these patients have a high rate of medical complications and psychosocial problems that may not be accounted for by the health-related quality of life measures studied. Many of these patients report decreased exercise intolerance and corresponding limitation of their activities. The psychosocial problems that are often encountered by this population include disability benefits, problems with life or health insurance, and concerns about having children. A single large Canadian center reported that adults with CHD report moderate to extreme concern about physical activity, insurance, assuming increased health responsibility, diet, mental health, and their mortality.

## EXTENDING CARE INTO ADULTHOOD

There are currently more than 1 million adults with CHD in the United States, and this number is rising exponentially. Fewer than half of these patients are seen by subspecialist providers in the recently emerged field of adult CHD. The AHA published a scientific statement on the best practices in managing the transition from adolescence to adulthood for patients with CHD that focuses on maintaining uninterrupted health care for these patients and optimizing their quality of life and life expectancy.

Recent guidelines recommend individualizing the transition process for each patient and starting to prepare the patient for transition to adult care during adolescence. The pediatrician and pediatric cardiologist should initiate discussions about risk-reducing behaviors, including the cardiac risks of illicit and prescription drug, alcohol, and tobacco use; nutrition counseling; and discussions about contraception with female patients. Pregnancy and delivery involve major hemodynamic changes in the female body and confer an increased risk to a woman with CHD. Furthermore, there is an increased risk for CHD in the fetus with a first-degree relative with CHD. The management of an adolescent with CHD should include counseling about

these risks during discussions of sexual health and contraception.

## SUMMARY

The diagnosis and treatment of congenital heart disease has made rapid advances over the last half-century. Many children born with complex CHD now survive into adulthood. An understanding of the morbidities associated with congenital cardiac surgery and the long-term outcomes of these diseases is important to provide a stable and comprehensive medical home for these often complex patients. Collaboration and cooperation with multiple medical subspecialists is often required to coordinate problems that may range from mild developmental delay to respiratory and feeding abnormalities requiring mechanical support, to ongoing cardiac abnormalities. Furthermore, referral to support services for possible neurodevelopmental difficulties and psychosocial and behavioral problems may be required, both for the patient and for members of the patient's family. For adolescents, the PCP should play a pivotal role in the transition to adult care and discussions about risk-reducing behaviors. The PCP, as the fulcrum of the medical home, is in a unique situation to ensure that comprehensive care is provided to these patients.

## INFANTS WITH MALFORMATIONS OF THE TRACHEOBRONCHIAL TREE AND DIAPHRAGM

### Tracheobronchomalacia

The term *malacia*, derived from the Greek *malakia*, means softness, and in medical terminology usually refers to cartilage or bone. Tracheobronchomalacia therefore is a softness or weakness of the cartilage in the trachea and bronchi. Clinically, tracheobronchomalacia usually manifests as expiratory stridor and cough caused by collapse of the airway lumen, especially during states in which the intrathoracic pressure is greater than the intraluminal pressure (eg, during a Valsalva maneuver). However, there are some cases of cervical or extrathoracic tracheobronchomalacia in which symptoms manifest during inspiration. Tracheobronchomalacia is the most common congenital anomaly of the trachea and is generally classified as primary (congenital) or secondary (acquired).

Primary tracheobronchomalacia can be further divided into isolated or syndromic etiologies. Isolated tracheobronchomalacia can be seen in otherwise healthy full-term infants but more commonly affects premature infants. It is thought to be caused by immaturity of the tracheobronchial cartilage, either because of preterm birth or because of structural (developmental) immaturity of the tracheal tissue. In term infants, the symptoms usually present during the first few weeks or months of life and often demonstrate improvement by 1 year of age as the airway smooth muscle increases the tone of the trachea. Tracheobronchomalacia is thought by some investigators to be part of the spectrum of bronchopulmonary dysplasia in preterm infants, with reported incidences of 25% to 86% in different series. Conditions associated with syndromic primary tracheobronchomalacia



include genetic abnormalities (eg, Down syndrome, 22q11 deletion syndrome, CHARGE syndrome, VACTERL association, mucopolysaccharidoses, Diamond-Blackfan syndrome, and Pierre Robin sequence), chondrodysplasias, tracheoesophageal fistula, and esophageal atresia.

Secondary tracheobronchomalacia is caused by degeneration of normal tracheal and bronchial cartilage. Tracheomalacia can result from prolonged ventilation, either from endotracheal intubation or from tracheostomy. Prolonged intubation is a common cause of secondary tracheomalacia, with increased airway pressure from mechanical ventilation and increased infection risk as additive insults to the tissue. This contributes to the risk for tracheomalacia in preterm infants requiring prolonged intubation as well as in infants and children requiring multiple intubations, prolonged intubation, or tracheostomy (eg, cardiac abnormalities requiring cardiac surgery, respiratory failure, or organ transplantation). Thus, premature infants, who often require endotracheal intubation, are at risk for both primary and secondary tracheobronchomalacia. Tracheostomy, as well as endotracheal intubation, is a risk factor for secondary tracheobronchomalacia with potential involvement of the stoma site, the cuff site, and the tube tip site. External compression of the airway is another common cause of secondary tracheobronchomalacia. This can be caused by a vascular abnormality such as a double aortic arch, a vascular ring, or an abnormal take-off of the innominate artery, or from left atrial enlargement as is seen in severe dilated cardiomyopathy. Other causes of external airway compression include mediastinal masses (eg, thymoma, ectopic thyroid, teratoma, bronchogenic cyst, and lymphoma), skeletal deformation (eg, scoliosis), and infection (eg, abscess).

Treatment of tracheobronchomalacia varies according to its etiology. As mentioned earlier, some forms of idiopathic tracheobronchomalacia resolve over the first 1 to 2 years of life as the tracheal smooth muscle gains tone and the tracheal cartilage strengthens. Symptomatic treatment during the first 2 years can include humidified oxygen, pulmonary toilet, and treatment of respiratory infections. In patients in whom the above measures are inadequate, continuous positive airway pressure can be an effective treatment that avoids the need for more invasive measures. However, in some patients, the disease is persistent or causes severe life-threatening episodes and therefore merits interventional therapy. Historically, the therapy for these patients has been tracheostomy and mechanical ventilation, but these treatments confer significant morbidity (eg, infection risk, recurrent bronchospasm, and difficult decannulation) as well as the inherent risk for worsening tracheomalacia. In recent years, however, new surgical techniques have been developed that show promise in the treatment of this disease. Aortopexy, in which the anterior aortic wall is sutured to the sternum, thus widening the anterior-posterior dimension of the tracheal lumen (because the anterior wall of the trachea is adherent to the posterior wall of the ascending aorta), has been demonstrated as an effective treatment for severe tracheomalacia. Internal tracheal and/or bronchial stents,

deployed by bronchoscopy, have also been developed and require a less interventional approach.

### Tracheoesophageal Fistula and Esophageal Atresia

Tracheoesophageal fistula (TEF) is a congenital connection between the tracheal tree and the esophagus (either proximal or distal). Esophageal atresia (EA) is a complete interruption of the esophagus with no connection of the esophagus with the stomach. TEF and EA can occur separately but often occur together and affect 1 in 2,400 to 4,500 people. EA and TEF are seen in combination with other congenital defects in 25% of patients, most commonly cardiac anomalies (35%), genitourinary anomalies (24%), other gastrointestinal anomalies (24%), skeletal anomalies (13%), and central nervous system anomalies (10%); when all the above defects occur together, this is termed the VACTERL association. Despite significant advances in the field of fetal medicine, the antenatal diagnosis of EA and TEF remains challenging, with only 10% to 40% of cases diagnosed on prenatal ultrasound. Neonates with EA and TEF have excessive oral secretions and feeding and respiratory difficulties. EA and TEF are treated with surgical repair and are commonly repaired during early infancy. However, EA with a distal TEF requires urgent neonatal surgery because of a high risk for aspiration pneumonitis. Some severe cases may require multiple procedures (eg, esophageal lengthening procedures) and delayed esophageal-gastric anastomosis. Surgical survival rates for low-risk patients with EA and TEF are excellent; however, survival rates decrease significantly in higher-risk populations. Prematurity, associated abnormalities (especially cardiac and chromosomal abnormalities), and prenatal diagnosis have been shown to have predictive value in overall outcome. Current surgical survival rates have been reported as 98% for patients with birth weight above 1,500 g and no major cardiac anomalies, 82% for patients with a birth weight of less than 1,500 g or a major cardiac anomaly, and 50% for patients with a birth weight of less than 1,500 g and a major cardiac anomaly. Surgical correction can be performed with an open or a thoracoscopic approach and is successful in most cases, but recurrence of the TEF occurs in about 9% of cases. In addition to surgical mortality risk, there are a number of morbidities that affect long-term outcome in patients with EA and TEF.

### Gastrointestinal Complications

Gastrointestinal complications are common in patients with EA and TEF. Dysphagia and gastroesophageal reflux are some of the more common complications in this population. Dysphagia with abnormal esophageal peristalsis is seen in up to 75% to 100% of children and young adults with EA and is reported to persist in 53% to 92% of adult patients. Abnormal esophageal peristalsis may cause failure to thrive or frequent aspiration because of poor feeding and can lead to esophageal obstruction requiring surgical intervention. Gastroesophageal reflux disease (GERD) occurs in 35% to 58% of children with EA and TEF and can lead



to esophageal strictures and frequent aspiration (which can lead to permanent lung damage). Many of these patients respond to medical antireflux therapy, but 13% to 25% of patients require Nissen fundoplication for treatment of GERD. Anastomotic leak is an early postoperative complication, reported in up to 17% of patients, that can have serious long-term consequences. Essentially all anastomotic leaks (95%) resolve either spontaneously or with pleural drainage, but esophageal stricture and even recurrence of the TEF can occur in 50% of cases. The rate of postoperative esophageal stricture varies in the literature from 6% to 40% of patients, and is more common after repair of an atretic gap greater than 2.5 cm and in patients with GERD. They often present with gastrointestinal symptoms, such as poor feeding and emesis, but can present with recurrent postaspiration pneumonia. The usual treatment for esophageal stricture involves repeated dilation.

### **Respiratory Complications**

Patients with EA and TEF have a high incidence of respiratory symptoms, including recurrent pneumonia, aspiration, chronic cough, and choking, gagging, and cyanosis with feeding. These patients often require hospitalizations because of respiratory disorders. Tracheomalacia is also a common respiratory finding in patients with EA and TEF, but it is clinically significant only in 10% to 20% of patients. In severe cases of tracheomalacia, tracheal collapse occurs during expiration and usually causes a hoarse cough, but it can sometimes result in life-threatening spells with apnea and cyanosis. Patients with these acute life-threatening spells can undergo surgical treatment with aortopexy to maintain patency of the tracheal lumen. Aspiration, tracheomalacia, sudden infant death syndrome, and reactive airway disease are reported as causes of death in 60% of late deaths in patients with EA and TEF.

### **Congenital Diaphragmatic Hernia**

Congenital diaphragmatic hernia (CDH) is a defect in the diaphragm that results in herniation of abdominal contents into the thorax. It occurs in approximately 1 in 2,400 to 3,000 live births and more commonly involves the left hemidiaphragm (75%–85%). Pulmonary hypoplasia of the ipsilateral lung is the usual associated finding, caused by the presence of abdominal organs in the thorax during fetal development. Malrotation of the intestine is also often present. CDH can occur in isolation or in association with other findings, such as omphalocele, CHD, trisomy 21, trisomies 13 and 18, Brachmann-de Lange syndrome, and Pallister-Killian syndrome (tetrasomy 21p mosaicism).

CDH was considered to be a surgical emergency in the newborn until the early 1990s and had an overall survival rate of approximately 50% to 55%. The treatment in that era was aggressive ventilation with hyperventilation and high peak pressures, with salvage measures such as ECMO and high-frequency oscillation ventilation (HFOV). However, survival was not improved by any of these measures, and it was not until the implementation of “lung preservation” or gentle ventilation strategies in the mid-1990s, with

changes to both resuscitation and ventilation techniques, that overall survival rates improved. This gentle ventilation approach includes allowing spontaneous breathing and permissive hypercapnia combined with elective surgical repair, and the avoidance of chest tube placement during repair. Survival rates in the current era are now higher than 70% to 80% and have been reported above 90% by some centers. Factors that are associated with increased mortality include severity of pulmonary hypertension at 1 month of life, birth weight and gestational age, and need for ECMO therapy. Newer techniques such as thoracoscopic repair of CDH and fetal interventions to correct CDH are ongoing but have not been conclusively demonstrated to be superior to conventional repair.

As has been seen with congenital heart disease, significant reductions in mortality rates spurred interest in investigating and minimizing the morbidities associated with the treatment. The survival of larger numbers of patients with CDH and the recognition of the multisystem morbidities seen in these patients has led to the development of multidisciplinary follow-up centers that follow standardized protocols for long-term evaluation and treatment.

### **Neurodevelopmental Morbidity**

Studies of children who survive repair of their CDH demonstrate anatomic neurologic abnormalities in 33% to 48% of patients, including periventricular leukomalacia and intracranial hemorrhage. Patients with repaired CDH also have functional neurodevelopmental abnormalities, such as neuromotor delay, hypotonia, and language delay. Risk factors for neurodevelopmental abnormalities at 2 years of age include right-sided CDH, ECMO therapy, intrathoracic liver, Gore-Tex patch repair (as opposed to direct repair), hypotonicity, and oxygen use at day of life 30. School-age CDH survivors (including children who did not require ECMO) demonstrate an increased incidence of learning disabilities compared with the normal population. Hearing loss, especially sensorineural, occurs in a large percentage of survivors of CDH, although the pathogenesis of the hearing loss is unknown.

### **Pulmonary Morbidity**

Although patients with CDH have abnormal pulmonary function tests at 1 year of age, the abnormalities normalize in most patients by 2 years of age. However, patients with CDH remain at risk for recurrent respiratory infections, asthma, restrictive lung disease, and pulmonary hypertension.

### **Gastrointestinal Morbidity**

Most patients with repaired CDH have documented GERD by pH probe and impedance testing, although only about half of patients report GERD symptoms. Risk factors for severe GERD include Gore-Tex patch repair, intrathoracic liver, HFOV, and ECMO support. Some patients have esophageal dysmotility as well as GERD and require treatment with promotility medication as well as antacid therapy. Studies have shown that GERD persists into adulthood in many survivors of CDH and confers an increased risk for the development of premalignant Barrett esophagus in these

patients. With this knowledge, some centers are aggressively treating GERD with surgical therapy such as gastric fundoplication at the time of CDH repair.

### **Musculoskeletal Morbidity**

Musculoskeletal abnormalities in patients with CDH repair include chest wall deformities (eg, pectus excavatum and pectus carinatum) and scoliosis. Centers have tried many different materials for patch repair of CDH, but no single material has been demonstrated to be markedly superior in preventing chest wall deformities or hernia recurrence.

## **NEONATES TREATED WITH ADVANCED THERAPIES FOR CARDIORESPIRATORY FAILURE OR SUSPECTED HYPOXIC ISCHEMIC ENCEPHALOPATHY**

### **Respiratory Failure in Term and Late Preterm Infants**

Severe respiratory failure can develop in full-term and late preterm infants born with CDH or because of persistent pulmonary hypertension of the newborn (PPHN). PPHN may develop in response to meconium aspiration syndrome; other primary pulmonary pathology such as primary pulmonary hypertension, pneumonia, and respiratory distress syndrome; or secondary to pulmonary air leak or sepsis. In addition to respiratory support that includes noninvasive and invasive ventilation, oxygen therapy, and inhaled nitric oxide to reverse the pulmonary hypertension, a small percentage of infants will require treatment with ECMO. Also referred to as extracorporeal life support, ECMO is a form of prolonged extracorporeal cardiopulmonary bypass used in patients with acute reversible respiratory or cardiac failure. ECMO involves (1) draining venous blood to allow (2) removal of CO<sub>2</sub> and (3) addition of O<sub>2</sub> through an artificial lung (bypass circuit) that then (4) returns warmed, oxygenated blood to the circulation, thus (5) allowing normal aerobic metabolism while the lung “rests” (Figure 116-2). There are 2 types of ECMO, venovenous and venoarterial. Absolute contraindications for treatment of neonatal

respiratory failure with ECMO include a lethal chromosomal disorder, irreversible brain damage, and grade III or greater intraventricular hemorrhage. Relative contraindications include irreversible organ damage (unless patient is considered to be an organ donor), weight less than 2 kg, and gestational (or postmenstrual) age younger than 34 weeks, because of the increased incidence of intracranial hemorrhage.

### **Morbidity and Mortality Associated With Extracorporeal Membrane Oxygenation**

Survival rates vary among infants based on the underlying cause of the cardiorespiratory failure. Data from the Extracorporeal Life Support (ELSO) Registry in Ann Arbor, Michigan, reveal that among neonates treated with ECMO because of respiratory failure, 85% survive ECMO treatment, but only 75% ultimately survive to hospital discharge or transfer to another care facility. The group of neonates treated with ECMO because of respiratory failure is quite heterogeneous. Patients treated with ECMO because of meconium aspiration syndrome, primary pulmonary hypertension, respiratory distress syndrome, pneumonia, or massive air leak recover in more than 80% of cases. This is in contrast to infants treated with ECMO because of CDH or sepsis. Survival in this group of babies is approximately 60%. Review of neonatal ECMO outcomes reported to the ELSO registry for infants treated between 2005 and 2010 revealed that 20% of the infants supported with ECMO had neurologic complications. Patient factors (gestational age and birth weight), pre-ECMO illness severity (metabolic acidosis), and use of venoarterial ECMO are associated with increased neurologic complications and mortality risk.

The United Kingdom Collaborative ECMO Trial reported survival rates and health and developmental outcomes at ages 1, 4, and 7 years for a group of infants with respiratory failure born between 1993 and 1995 who were treated with either conventional medical management or ECMO. Among children treated with ECMO who recovered, 70% were reported to have normal health and cognition at age 7 years. Areas of difficulty included spatial abilities (pattern construction and design recall), reading comprehension, fine motor skills, auditory processing, communication difficulties that can interfere with learning, and verbal and nonverbal memory. Neuromotor development was normal in 40% of ECMO-treated survivors and impaired in 40% of the group. Approximately 7% of these children were classified as having milder impairments on standardized testing. Behavioral problems were reported in 18% of ECMO-treated children. The subsequent health of ECMO-treated children was better than that of children treated with conventional medical therapy: 11% of ECMO-treated children reported wheezing in the preceding 12 months, and 25% used an inhaler in comparison with conventionally treated children, of whom one-third wheezed and 40% used an inhaler at age 7 years. Similar outcomes have been reported by investigators from the Netherlands: 20% of children exhibited a combination of motor, cognitive, and behavioral problems at age 5 years,



**Figure 116-2** Infant receiving extracorporeal membrane oxygenation.

whereas 12% demonstrated only isolated cognitive or behavioral problems.

An important sequela following ECMO treatment is sensorineural hearing loss (SNHL) that is progressive and often delayed in onset. Reported rates of SNHL vary between 3% and 42%. Permanent hearing loss (PHL) is highest among infants with CDH. One factor that contributes to development of PHL is therapy with ototoxic medications often used in the treatment of infants in severe respiratory failure. Duration of medication use and possibly also therapy with neuromuscular blockers contributes to PHL. In addition, clinical seizure activity before ECMO and the duration of ECMO therapy are significantly associated with SNHL.

### **Follow-up Health and Developmental Screening and Surveillance**

Recommended follow-up care for infants treated with ECMO who recover from severe neonatal respiratory failure includes enhanced surveillance and screening as detailed in Table 116-3.

### **Neonates Treated for Suspected Hypoxic Ischemic Encephalopathy**

Hypoxic ischemic encephalopathy (HIE) is an important cause of brain injury in the newborn and can result in lifelong health and neurodevelopmental consequences. Perinatal hypoxia may result in long-term neurologic complications varying from mild behavioral deficits to epilepsy, severe cognitive impairment, and cerebral palsy. HIE occurs in 1 to 6 infants per 1,000 live full-term births in developed countries; rates are higher in low- and medium-resource countries. Of affected newborns, 15% to 20% will die in the postnatal period, and an additional 20% to 35% will exhibit childhood disabilities, including cognitive impairments, visual motor or visual perceptive dysfunction, increased hyperactivity, cerebral palsy, and epilepsy. Later outcomes are related to disease severity (Table 116-4). Among infants who die before NICU discharge, death is often because of multisystem organ failure and redirection of care. Deaths of infants after hospital discharge are most commonly caused by complications from aspiration pneumonia and systemic infection. Survivors of HIE often experience significant feeding difficulties and growth problems during the early months after NICU discharge. Factors associated with subsequent cerebral palsy are listed in Box 116-9.

### **Pathogenesis**

The outcomes of HIE result in significant burdens for patients, families, and society. The neuropathologic features of perinatal HIE vary considerably with the gestational age of the infant, the nature of the insult, and treatments provided. The development of brain injury after a hypoxic ischemic insult is an evolving process that is initiated during the acute insult and extends into a reperfusion phase. The principal pathogenetic mechanism underlying neurologic damage in HIE resulting from hypoxemia or ischemia is deprivation of required brain glucose and oxygen supplies. This causes energy failure and initiates a cascade of

biochemical events leading to cell dysfunction and cell death. This initial injury is compounded by a subsequent reperfusion injury that often worsens brain damage.

### **Treatment Strategies**

Treatment during the immediate newborn period is primarily supportive. Therapy includes correction of hemodynamic and pulmonary disturbances (hypotension, metabolic acidosis, and maintenance of adequate ventilation), correction of metabolic abnormalities (glucose, calcium, magnesium, and electrolytes), treatment of seizures if present, and monitoring for other organ system dysfunction, such as acute kidney injury. Maintenance of adequate ventilation and perfusion is a central component of supportive care. Oxygen deprivation may lead to loss of normal cerebrovascular autoregulation with subsequent neuronal and white matter injury. The presence of seizures, typically beginning within the first hours after birth, may potentiate the underlying brain injury and predict a poor outcome of HIE. The incidence of seizures in neonates with moderate or severe HIE is reported to range from 22% to 64%.

A number of neuroprotective drugs (*N*-acetylcysteine, allopurinol, magnesium, glutamate receptor blockers, and erythropoietin) are being studied to evaluate their value in protecting neonates from the neurologic sequelae following a hypoxic ischemic insult. However, the most potent and promising intervention to prevent brain injury is mild hypothermia. Reducing the body temperature slightly [3.6°F to 7.2°F (3°C–5°C)] below the normal level, to 91.4°F to 95°F (33°C–35°C) (mild hypothermia), reduces cerebral injury, decreases brain energy utilization, reduces the size of infarcts, and ameliorates neuronal cell loss, preserving hippocampal structure. Neonatal therapeutic hypothermia may be achieved through the application of head (brain) cooling (Figure 116-3), or through whole-body cooling with placement of a hypothermia blanket under the infant. Hypothermia improves neurologic outcomes after moderate asphyxia. The beneficial effects of mild hypothermia occur at multiple sites in the cascade to cell death. Hypothermia should be initiated within 6 hours of birth before the onset of delayed energy failure in brain tissues.

Early initiation of hypothermia in infants improves survival and reduces the rate of disability of those survivors. Several clinical trials currently ongoing in the United States and Europe are investigating the efficacy of later initiation of mild hypothermia after 6 hours of age, and other studies are evaluating the effects of moderate hypothermia. During treatment with mild therapeutic hypothermia, neonates typically are also treated with sedatives, analgesics, antiepileptic drugs, and antibiotics as adjunctive therapy to selective brain or whole-body cooling. The benefits of antiepileptic medications are unclear, although Glass et al have reported improved outcomes among infants treated with phenobarbital in the presence of clinical seizures. There is evidence of delayed clearance of drugs administered to infants during hypothermia that are metabolized by cytochrome P-450 enzymes.

Table 116-3

## Recommendations for Enhanced Surveillance and Screening

	BEFORE DISCHARGE	1-3 MO AFTER BIRTH	4-6 MO AFTER BIRTH	9-12 MO AFTER BIRTH	15-18 MO AFTER BIRTH	ANNUAL THROUGH 16 YR
<b>Weight, length, head circumference</b>	X	X	X	X	X	X
<b>Chest radiograph</b>	X	If patched	If patched	If patched	If patched	If patched
<b>Pulmonary function testing</b>						
<b>Childhood immunizations</b>	As indicated throughout childhood	X	X	X	X	X
<b>RSV prophylaxis</b>	RSV season during the first 2 yr after birth if evidence of CLD	X	X	X	X	X (through 24 mo age if CLD present)
<b>Echocardiogram and cardiology follow-up</b>	X	If previously abnormal or if on supplemental O <sub>2</sub>	If previously abnormal or if on supplemental O <sub>2</sub>	If previously abnormal or if on supplemental O <sub>2</sub>	If previously abnormal or if on supplemental O <sub>2</sub>	If previously abnormal or if on supplemental O <sub>2</sub>
<b>Head CT or MRI</b>	If (1) abnormal finding on head ultrasound; (2) seizures/abnormal neurologic findings <sup>a</sup> ; or (3) ECMO or patch repair	As indicated	As indicated	As indicated	As indicated	As indicated
<b>Hearing evaluation</b>	Auditory evoked brain response and otoacoustic emissions screen	X	X	X	X	Every 6 mo until 3 yr, then annually until age 5 yr
<b>Developmental screening evaluation</b>	X	X	X	X	X	Annually until age 5 yr, repeat at age 8 yr
<b>Neurodevelopmental evaluation<sup>b</sup></b>	X	X	X	X	X	Annually until age 5 yr, repeat at age 8 yr
<b>Assessment of oral feeding problems</b>	X	X	X	X	X	If oral feeding problems
<b>UGI study, pH probe, and/or gastric scintiscan</b>	Consider for all patients	If symptoms	If symptoms	If symptoms	If symptoms	If symptoms
<b>Esophagoscopy</b>		If symptoms	If symptoms	If symptoms	If symptoms	If symptoms
<b>Scoliosis and chest wall deformity screening (PE, chest radiograph, and/or chest CT)</b>				or if abnormal gastrointestinal evaluations		X

CLD, chronic lung disease; CT, computed tomography; MRI, magnetic resonance imaging; PE, pulmonary embolism; RSV, respiratory syncytial virus; UGI, upper gastrointestinal.

<sup>a</sup>Muscle weakness, hypotonia, hypertonia, or other abnormal neurologic sign or symptom.

<sup>b</sup>The neurosensory tests performed and the frequency of surveillance among infants with CDH may differ because of variability in neurologic, developmental, and physical impairments. Follow-up should be tailored to each infant.

Adapted from American Academy of Pediatrics. Policy statement: post-discharge follow-up of infants with congenital diaphragmatic hernia. *Pediatrics*. 2008;121:627-632.



**Table 116-4** Outcomes of Neonatal Encephalopathy Caused by Hypoxic Ischemic Injury

Mild encephalopathy	No increased risk for motor or cognitive disability 15%–20% exhibit significant learning disabilities
Moderate encephalopathy	30%–50% exhibit serious sequelae 10%–20% exhibit minor disabilities Significant motor deficits Memory impairment Visual, motor, or visual perceptive dysfunction Increased hyperactivity Delayed school readiness
Severe encephalopathy	Increased risk for death (75% die), cerebral palsy, and IQ <70 70%–80% experience serious sequelae 10%–20% exhibit moderate to serious sequelae

Adapted from de Vries LS, Jongmans MJ. Long-term outcome after neonatal hypoxic-ischaemic encephalopathy. *Arch Dis Child Fetal Neonatal Ed.* 2010;95:F220–F224.

### BOX 116-9 Factors Associated With Later Cerebral Palsy

- Severe encephalopathy
- More than 1 neonatal seizure
- Need for phenytoin
- Abnormal neurologic findings at NICU discharge
- Antiepileptic medication at discharge



**Figure 116-3** Head cooling to reduce the risk for brain injury in a baby with hypoxic ischemic encephalopathy.

This may prolong the effects of specific therapies, including antiepileptic drugs.

### Patterns of Brain Injury

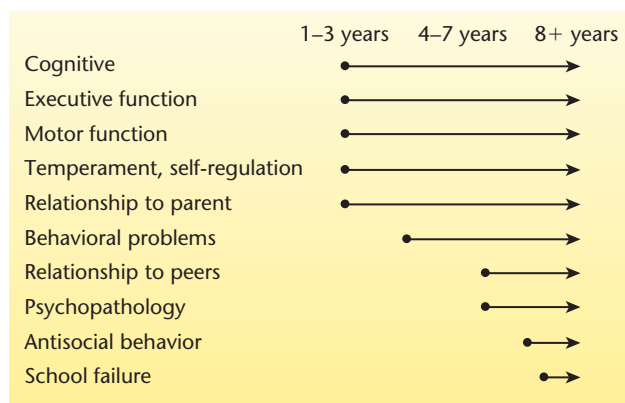
Predischarge evaluations typically include magnetic resonance and diffusion weighted imaging studies that assist in characterizing the timing and pattern of brain injury. Among infants born at term, 2 patterns of injury are predominant: basal ganglia-thalamus (BGT) injury pattern and the watershed-predominant injury pattern. BGT injury is caused by an acute event that results in near-total asphyxia. Children who suffer

from BGT injury often experience associated damage to the hippocampus and brainstem and exhibit more severe impairments than children who have watershed injuries. Watershed injuries occur after prolonged partial asphyxic episodes that compromise anterior middle and posterior middle cerebral artery blood flow, injuring the white matter and, in some instances, the overlying cerebral cortex. This injury pattern is also seen in infants whose neonatal course is complicated by hypotension, hypoglycemia, or infection. Although severe motor impairment is uncommon, children who experience a watershed injury often exhibit subnormal head growth, language delays, and behavioral problems. There is a third, less common, pattern of injury seen in late preterm and early term infants with HIE (and infants with milder encephalopathy) that involves small punctate lesions in the periventricular white matter similar to those seen in preterm infants with periventricular leukomalacia.

### Follow-up Developmental Assessments and Outcomes

Postdischarge follow-up care of infants who develop HIE requires longitudinal surveillance and assessment and early referral for intervention when delays or impairments are identified (Figure 116-4). Timely assessment of feeding, vision, and hearing and evaluation for the continued presence or late onset of seizures are essential. The infant exhibiting persistent feeding difficulties at discharge warrants early and frequent follow-up visits with careful monitoring of feeding intake, hydration status, and weight gain and growth. Early assessments between 4 and 8 months of age should focus on head growth, general health, and motor development. Initial assessments of cognitive abilities and language development should occur between 12 and 24 months of age. This facilitates early referral for early intervention because of emerging motor impairment, oral-motor dyspraxia, communication delays, and progressive or late-onset sensorineural hearing loss.

Periodic hearing testing is another important element of follow-up care: behavioral audiometry or brainstem auditory evoked response testing should optimally be performed every 6 months, until age 3 years. At a



**Figure 116-4** Timeline for assessments of neurodevelopmental outcomes. (From American Academy of Pediatrics. *Follow-up care of high-risk infants*. Pediatrics. 2004;114:1377-1397.)

minimum, follow-up hearing testing should occur at 8 to 10 months of age and between 24 and 30 months of age, with routine hearing health surveillance at each pediatric visit.

Follow-up evaluations between 2 and 4 years will assess the development of fine and gross motor function, whereas evaluations between 4 and 7 years of age assess cognitive function. Evaluation and testing between 7 and 9 years delineates learning disabilities and executive functioning, measures language and auditory processing, and assesses behavioral adaptation. Memory impairment, likely related to earlier hippocampal injury, is a common problem and includes difficulties in episodic memory (context-rich memory for events), difficulties with verbal learning and recall, and difficulties with visual recall. Semantic memory (context-free memory for facts) is less affected. School difficulties include problems with spelling, mathematics, reading, sentence repetition, and narrative memory (comprehension). Eighty percent of children with minor neurologic dysfunction and perceptual-motor difficulties have evidence of mild to moderate basal ganglia injury or more marked white matter brain lesions.

### Medicolegal Considerations

Litigation on behalf of a child with developmental delay or cerebral palsy assumed to have been caused by perinatal brain damage is a common reason for pediatric lawsuits. For pediatricians and family physicians, whether the treating physician in the delivery room or the admitting physician in the newborn or special care nursery, accurate medical record documentation is crucial. Emphasis should be placed on the use of consistent language by all disciplines. This enhances mutual understanding and reduces conflicts (inconsistencies) in the medical record. The pediatric care professionals should not characterize or evaluate (draw conclusions about) obstetric issues outside their area of clinical expertise. The source of information regarding the mother's health or medical condition should be

specifically cited in the infant's medical record, such as "The prenatal record indicates. . . ." Documentation should focus on objective information, including the neonate's findings on physical examination (description of the infant's condition), planned diagnostic studies based on the suspected diagnoses (eg, laboratory and imaging tests), and initiated or proposed treatments. Discussions with the family, including the issues discussed and any information and educational materials given that are germane to infant's care and treatments, should be documented in the medical record.

In general, the best practice is not to use terms or descriptions unless they are relevant to the infant's diagnosis, treatment, or care plan. Among terms to avoid are *perinatal asphyxia*, *intrapartum asphyxia*, *hypoxia*, *nonreassuring tracing*, *fetal distress*, *perinatal depression*, and *traumatic or difficult delivery*. There is a general recommendation that the term HIE should not be used before 1 to 3 weeks postdelivery and should only be used if there is MRI confirmation of a pattern of acquired brain lesions consistent with changes seen after hypoxic ischemic brain injury. Early MRI findings in infants with clinical signs suggestive of HIE performed when the infant is 3 to 5 days of age are helpful in providing information about the etiology (global hypoxia ischemia, focal arterial infarction [stroke]) of the brain injury.

### SUMMARY

With 1 in 5 children having a chronic health condition and nearly 1 in 12 being affected by 2 or more health conditions, pediatricians are increasingly overseeing the medical home for medically complex infants and children and working in partnership with subspecialty physicians, community professionals, and families. Survivors of advanced technologies (eg, ECMO, open heart surgery) require enhanced health and developmental surveillance throughout childhood and are prone to developmental, behavioral, and academic difficulties that are similar to those seen in early preterm infants.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Family Voices* (Web site), ([www.familyvoices.org](http://www.familyvoices.org))
- *How to Partner With Your Physician* (Web page), National Center for Medical Home Implementation ([www.medicalhomeinfo.org/for\\_families/partner\\_with\\_physician.aspx](http://www.medicalhomeinfo.org/for_families/partner_with_physician.aspx))

#### Medical Decision Support

- *Best practices in managing transition to adulthood for adolescents with congenital heart disease: the transition process and medical and psychosocial issues. A scientific statement from the American Heart Association* (article), *Circulation*, Vol 123, Issue 13, 2011
- *For Physicians & Professionals* (Web site), Medical Home Portal Project ([www.medicalhomeportal.org/clinical-practice](http://www.medicalhomeportal.org/clinical-practice))
- *Got Transition* (Web site), Center for Health Care Transition Improvement ([www.gottransition.org](http://www.gottransition.org))
- *Pediatric palliative care and hospice care commitments, guidelines, and recommendations* (article), *Pediatrics*, Vol 132, Issue 5, 2013

- *Postdischarge follow-up of infants with congenital diaphragmatic hernia* (article), *Pediatrics*, Vol 121, Issue 3, 2008

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### **SUGGESTED READINGS**

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Burstein DS, Jacobs JP, Li JS, et al. Care models and associated outcomes in congenital heart surgery. *Pediatrics*. 2011;127:e1482

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## SECTION SIX

# Supporting Families During Perinatal Illness and Death

### Chapter 117

## SUPPORT FOR FAMILIES WHOSE INFANT IS SICK OR DYING

Joseph A. Vitterito II, MD; Deborah E. Campbell, MD;  
George A. Little, MD

The greatest risk of dying is in the perinatal period. For expecting families, birth is usually a moment filled with surprise, joy, and some trepidation about the responsibility of caring for a new life. With the birth of a premature or sick infant, emotions become fraught with shock, sadness, and possibly anger and grief.

Premature births in the United States have risen to record levels. Since 1981, the year the government began separately reporting premature births, the rate has increased 30%. Additionally, the rates of low-birth-weight and multiple births have also increased, significantly contributing to morbidity and mortality in the newborn population (Table 117-1).

Neonatal diseases range from prematurity to such entities as respiratory distress, birth asphyxia, sepsis, and less commonly seen conditions such as hematologic or oncologic conditions such as severe anemia, neonatal thrombocytopenia, hemophilia, hemophagocytic lymphohistiocytosis, neuroblastoma, and infantile leukemia. Box 117-1 lists the 6 leading causes of infant morbidity based on common diagnoses of infants admitted for intensive care and 5 causes of infant mortality.

Full-term newborns account for up to 40% of neonatal intensive care unit (NICU) admissions. The remainder of advanced neonatal care is for premature infants. When a newborn requires more than general newborn care, the family will also require care beyond congratulatory support and anticipatory guidance.

### BOX 117-1 Common Causes of Infant Morbidity and Mortality

#### MORBIDITY

- Birth asphyxia
- Cardiac and other congenital anomalies
- Infection
- Prematurity
- Respiratory distress syndrome
- Seizures

#### MORTALITY

- Congenital malformations (20.8%)
- Prematurity and low birth weight (17.2%)
- Sudden infant death syndrome (7.2%)
- Maternal complications (6.6%)
- Accidents/unintentional injuries (4.6%)
- Placenta, cord, or membrane complications (4%)

From Hamilton BE, Hoyert DL, Martin JA, Strobino DM, Guyer B. Annual summary of vital statistics: 2010–2011. *Pediatrics*. 2013;131:548–558.

**Table 117-1** Percentage of Preterm, Low Birth Weight, and Multiple Births

CHARACTERISTIC	PERCENTAGE OF BIRTHS				
	1990	2003	2006	2010	2011
<b>BIRTH WEIGHT</b>					
Low (<2500 g)	7.0	7.9	8.26	8.15	8.1
Very low (<1500 g)	1.27	1.41	1.48	1.45	1.44
Preterm birth	10.62	12.3	12.8	11.99	11.72
Late preterm	7.30		9.15	8.49	8.28
Early preterm	3.32		3.66	3.50	3.44
<b>MULTIPLE BIRTHS (PER 1,000 LIVE BIRTHS)</b>					
Twins	22.6	31.5	32.2	33.1	
Higher order multiples	72.8	187.4	153.3	137.6	

From Hamilton BE, Hoyert DL, Martin JA, Strobino DM, Guyer B. Annual summary of vital statistics: 2010–2011. *Pediatrics*. 2013;131:548–558; Martin JA, Hamilton BE, Ventura SJ, et al. Births: final data for 2010. In: *National Vital Statistics Reports*, vol. 61, no. 1. Hyattsville, MD: National Center for Health Statistics; 2012.

## ROLE OF THE PRIMARY CARE PHYSICIAN

Whether providing direct care for a sick neonate, arranging for transfer to a tertiary care facility, or providing follow-up care, the primary care pediatrician (PCP) has important and unique responsibilities, especially for providing continuity in a medical home. To best support the infant and family, the PCP should be familiar with the guidelines in Box 117-2. The complete guidelines provide PCPs with specific suggestions related to initiating and coordinating acute and longitudinal care, counseling families, and, crucially, communicating with families. These combined precepts are the cornerstone for supporting families.

### Trust

Trust is the fundamental premise of an effective and dynamic professional relationship with families. Trust, in turn, facilitates communication. Transparency allows for a fluid dialogue. For the family members, informed consent establishes that the infant is, in fact, their baby.

### Communication

In the current medical model for advanced neonatal care, as in most fields of medicine, the specialist pediatrician often consults a subspecialist (ie, a neonatologist) for guidance in medical decision making. Decision making occurs with consideration of many factors and incorporates the fields of medicine, bioethics, medical sociology, and economics. In other words, physicians draw on medical education, expertise, and experience

to develop the best plan of care that suits each individual patient and family. A major part of decision making is guided by the art of medicine, which is the essence of care and decision making and which pediatricians and other physicians should consistently endeavor to refine throughout their careers. The family must be included fully and appropriately in decisions regarding their infant.

A difficulty lies with the temporal nature of information processing. In situations in which physicians may be apt to understand a disease process quickly or approach a clinical situation with volumes of clinical experience, families, with the exception of those familiar with the medical environment, are likely experiencing urgent and critical care of an infant for the first time. What a physician has learned to understand over years of training and experience, the family is struggling to comprehend instantaneously.

Communication requires sincere, forthright presentation. Shared decision making between parents or family decision makers and the infant's health care team is at the core of neonatal care, particularly when treatment outcomes are uncertain. Parents should ideally receive most information about their baby's condition from the medical team, as opposed to secondary sources. This will not only ensure that the parents/family decision makers have the appropriate information on which to base their decisions, but afford the health care team the opportunity to assist the family in articulating their beliefs, values, and preferences for their infant and family. Parents, family members, and physicians come to situations from various social and educational backgrounds. Although most families' members are not expecting to become medical experts, they deserve thorough explanations of their infant's condition and the reasoning behind decisions and care plans.

### Transparency

*Transparency* can be defined as requiring "the physician to engage in the typical patient-management thought process, only to do it out loud in language understandable to the patient." Two requirements further define this standard: providing full disclosure of the evidence and reasoning regarding proposed and alternative treatments, and encouraging and answering patient questions about proposed treatment, evidence, and reasoning.

These concepts are also applicable to delivering health care in the NICU setting. Some physicians may equate transparency with letting down a person's guard. This unfortunate view implies a defensive stance as a health care professional. Parents and physicians share the common goal of doing what is best for the infant. Without knowledge, neither party can make a decision. Without shared knowledge—that is, transparency—neither can collaborate in this decision-making process. This partnership with families forms the basis and goal of family-centered care.

### Shared Decision Making and Informed Consent

The concept of *informed consent* in pediatrics has a unique meaning. Although informed consent is generally defined as "the exercise of the patient's moral and

#### BOX 117-2 Role of Primary Care Physician (PCP) in the Management of High-Risk Newborn Infants

- Guideline 1—To make timely decisions, the PCP should be knowledgeable regarding problems that may occur in the perinatal period.
- Guideline 2—The PCP acts as an important communication link between the family and the personnel of the center providing critical care, whether or not they are both located in the same institution.
- Guideline 3—The PCP should have the expertise to assume responsibility for the acute, although less critical, care of the infant and stabilize the patient for transfer to a specialist or to specialized neonatal or NICU care.
- Guideline 4—The PCP should understand the need for proper continuity of care and be capable of providing it.
- Guideline 5—The PCP should share responsibility with the neonatologist for the development and delivery of effective services in the hospital and community for newborns.

From American Academy of Pediatrics Committee on Practice and Ambulatory Medicine and Committee on Fetus and Newborn. The role of the primary care pediatrician in the management of high-risk newborn infants. *Pediatrics*. 1996;98(4):786–788; American Academy of Pediatrics Committee on Fetus and Newborn. Clinical report: hospital discharge of the high-risk neonate. *Pediatrics*. 2008;122(5):1119–1126. Reaffirmed May 2011.

legal right to control over his or her bodily integrity," the infant patient is unable to comprehend information, exercise control, or make decisions. Although such a situation occurs with some adult patients, this inability is the state of any infant. Providing informed consent thus falls to the parents. Parents who are thrust into a new and overwhelming setting with a sick or premature infant for whom they can offer no immediate remedy may feel stripped of their rights to comfort and care for their infant. In this instance, parents must be assured of their role as part of the team and the pivotal part they have in the shared decision-making process for their infant.

In order to facilitate informed decision making on the part of the parents/legal guardians, physicians must whenever possible provide parents clear, complete, and understandable information regarding their infants' diagnoses and expected short-term and long-term outcomes. The informed consent process should offer best estimates for each potential outcome that are based on local outcome data, available assessment techniques, and the infant's condition at birth. Information regarding aspects of care that are considered experimental trials of therapy should be clearly stated to the family with discussion about the burdens and benefits of each option. Physicians should explain to the parents in clear language those medical interventions that are considered to be in the infant's best interests as well as discussing at what point they would feel uncomfortable with a nonintervention or intervention decision (depending on the infant's underlying condition and prognosis), and at what point they would seek to override parental decisions. To the degree possible, physicians should base their recommendations on published outcome data and take care to avoid a tendency to overestimate disability. It is important to note that health care professionals consistently underestimate and undervalue the quality of life for children, young adults, and their families who have experienced preterm birth or serious early childhood illness.

Physicians should provide parents with the level of information that the parents require to make the decision they think is most reasonable. When therapeutic options are perceived as having equivalent risks, or outcomes of therapy cannot be predicted, the physician should discuss all appropriate care options and offer an opinion as to the best course of action. Physicians should give their recommendation, diminishing any potential shift in responsibility to the infant's parents, thereby minimizing grief and guilt.

It is important to recognize that there are several factors that influence parental decision making. Some of these factors include the parents' reproductive history, which may involve experience of a previous preterm or high-risk infant birth, or the loss of 1 or more fetuses or babies in a multiple pregnancy. A prior history of pregnancy termination, the presence of other children from the current or previous parental relationships, prior history of infertility, miscarriage, stillbirth, or loss of a child or children all influence parental decisions and the focus of their concerns and beliefs. As a consequence, 1 or both parents may be initially more concerned about a baby's survival than his or her prognosis. Decision making may also

be affected by expectations of family life. If both the mother and the father are new to parenthood, they are less likely to have prior experience with childbirth or parental responsibilities. The parents may therefore have an idealized views of what to expect. If they have older children, parents might worry about the effect of having a new child who has disabilities. If they are already caring for a child with disabilities, they may wonder about their ability to adequately care for another child with a disability, or may think that they are fully cognizant of the breadth of care needs and can handle the additional responsibilities. They may feel obligated to take the welfare of their other children into account in decision making. Initially parental attention may be displaced towards the new child. Parents may wonder if they should involve their other children or extended family in caregiving that in some cases may entail a lifelong commitment.

The attitudes and experiences of parents and extended families towards pain, suffering, vulnerability, disability, and death, and the influence of spirituality, including religious beliefs, also influence parental decision making. The birth of a severely ill infant may undermine, strengthen, confuse, or clarify preconceived notions about family ties. Individual family members may be influenced if they have relatives or friends with disabling conditions. Parents and families oftentimes react in different ways at different points in their lives. Disagreement may occur within the family—for example, between parents, between parents and their immediate family, and between other family members. Broader social attitudes and expectations often come into play when family members find themselves directly involved in the diagnosis of a congenital or genetic disorder or decisions about withholding or withdrawing medical treatment for another family member. Issues related to maternal blame for the infant's condition, family shame at having a child with a serious illness or congenital condition, the potential for a child's marriageability, and the family's position within their community can add an additional layer of complexity to decision making and information sharing. In recent years, the Internet has contributed to a significant change in the way that people communicate and make decisions about health care. Social media provide many more opportunities for parents to seek other views and opinions on their child's condition. Families who have never met each other can communicate readily. Parents sometimes form support networks through which they may receive help or channel their experiences to assist others. Condition-specific advocacy groups may provide parents with a balanced perspective or one oriented toward a particular view. It is therefore important for the clinical team to be aware of the social media content available to families.

### **Decision Making When Parents and Physicians Disagree**

Making decisions in partnership between parents and professionals satisfies several important ethical considerations of procedural justice, personal and professional responsibility, and the well-being of those most closely involved. When parents' requests to initiate, continue, or withhold neonatal intensive care are

perceived as unreasonable, inappropriate, or clearly not in the infant's best interests, the physician has an obligation to protect the infant's well-being. This may include seeking review by an ethics committee or, if necessary as a last resort, referring to local child protective services or the courts for a case review. Court opinion is typically sought after all other options are exhausted and only when requested interventions are perceived as contrary to the infant's best interests. When consensus cannot be reached, parents and physicians both have the right to consult with the hospital ethics committee. Hospital ethics committees offer the benefits of a broader range of impartial decision makers who may act to protect infants from problematic decisions by physicians or parents. Their advice typically is limited to discussions about ongoing care, rather than emergent decisions about resuscitation.

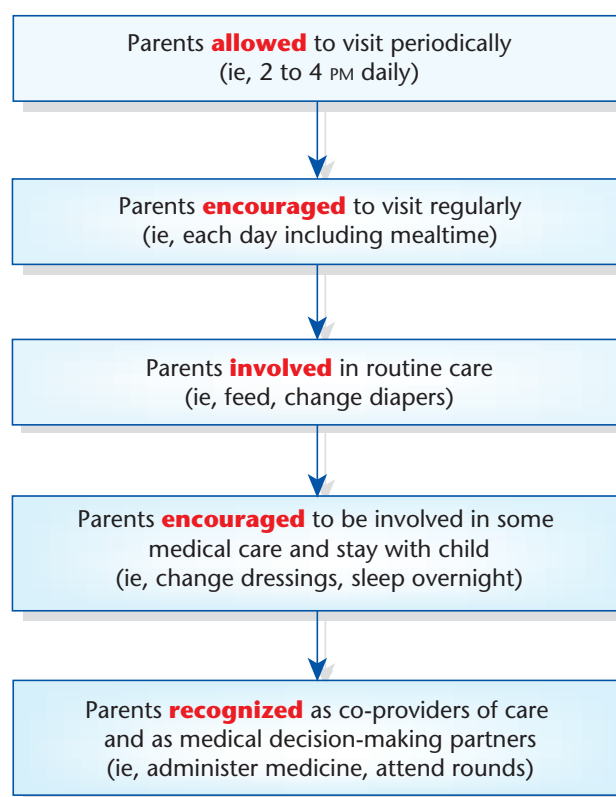
Unlike general hospital ethics committees whose members are unlikely to have extensive NICU experience, pediatric ethics committees in children's hospitals more commonly include members with expertise in neonatal medicine and the care of children with complex or disabling conditions and their families. Thus hospital ethics committees may have varying abilities to identify and weigh the benefits and burdens that parents consider in their decision making. When all agree that necessary life-sustaining treatment should be withheld from the infant, treatment should not be administered, and no civil or criminal liability should ensue. An important facet of a hospital ethics committee is the clinical ethics consultation that provides a framework for bioethics mediation. Mediation provides a process for families, and health care professionals, enmeshed in conflict as they wrestle with decisions about life and death, to articulate their beliefs, values, and preferences, and guides the physicians and caregivers in understanding and managing conflict while supporting the family's traditional and religious commitments and personal wishes. Bioethics mediation promotes balance—levels the playing field—to avoid putting some families, such as immigrants, the poor, or nonprofessionals, at a disadvantage. Mediation identifies individual interests, explores options, and helps craft a principled resolution—a consensus that identifies a plan aligned with accepted ethical principles, legal stipulations, and moral rules, and that charts a clear course of future intervention. It is also a valuable process for assisting parents and their extended families or support networks in working through internal disagreements regarding what is in the infant's best interest.

When parents refuse life-sustaining medical treatment that the physician or ethics committee feels is appropriate, the courts may appoint a *guardian ad litem* to represent the infant's best interests. The courts offer the benefits of witnesses, medical experts, a complete exposition of opposing views, and consistent reasoning across cases. However, the time required for due process is not well suited to resuscitation and intensive care proxy decision making. Court decisions involving nonintervention require clear and convincing evidence that withholding treatment is in the infant's best interests. Many courts override nonintervention decisions, restrict parental decision-making capacity, or constrain an individual's right to a natural death.

## FAMILY-CENTERED CARE

Transparency and communication are essential attributes of family-centered care. As neonatal, general, and inpatient pediatric practices aim to include family members in discussions and decision making, the concept of direct alliances with families has evolved from the paternalistic role of the physician and the permissive care role of the family. Parents and family members should be recognized as full partners and participants in care. The American Academy of Pediatrics (AAP) states that "health care providers should engage parents as co-providers and decision-making partners and seek to ensure that every encounter builds on the family's strengths, preserves their dignity, and enhances their confidence and competence." Physicians are sought for information, insight, and guidance, not for directives. In fact, all physicians involved in the care of the infant should actively seek parents' and guardians' observations and preferences for the care plan. Families should become directly involved in the general routine care of their infant, as would be done if they were at home; parents should change diapers, feed the baby, and check the infant's body temperature; parents should also record such events in the baby's bedside chart (Figure 117-1). In the neonatal realm, families may structure the day around feeding schedules or certain hospital activities, such as rounds. As they become more familiar with their infant, parents become skilled at recognizing subtle cues of illness or wellness.

The initiation of family-centered care and support optimally begins in the prenatal period. Whether the



**Figure 117-1** Evolution of hospital family-centered care.



family seeks the PCP for general counsel about the newborn period or the neonatologist for information about a high-risk pregnancy, a likely premature birth, or a suspected congenital defect, involvement should initiate the development of rapport and trust. Open, evidence-based conversation with family members that uses appropriate terminology and provides ample time for questions, comments, and expression of feelings is paramount to establishing this relationship. Parents are often interested in the basic pathophysiological features of the disease process, and clear, comprehensive explanations are important.

A multidisciplinary approach to the care of an infant and family is another vital component of support in the critical care setting. The core of family-centered care is “collaboration among patients, families, physicians, nurses, and other professionals for the planning, delivery, and evaluation of health care.” To deal with the potential reactive stages of shock, sadness, anger, and grief, teams need skills to elicit and take care of a family’s emotional and spiritual needs, as well as financial concerns, in an ongoing manner.

The core principles of family-centered care guide physicians as they assert themselves in developing compassionate collaborations with families and children. These concepts provide the backdrop in which supporting families, sharing information, and decision making can flourish (Box 117-3).

### BOX 117-3 Core Principles of Family-Centered Care

- Respect each child and the child’s family.
- Honor racial, ethnic, cultural, and socioeconomic diversity and its effect on the family’s experience and perception of care.
- Recognize and build on the strengths of each child and family, even in difficult and challenging situations.
- Support and facilitate choices for the child and family about approaches to care and support.
- Ensure flexibility in organizational policies, procedures, and provider practices so services can be tailored to the needs, beliefs, and cultural values of each child and family.
- Share honest and unbiased information with families on an ongoing basis and in ways they find useful and affirming.
- Provide and ensure formal and informal support (eg, family-to-family support) for the child and parents or guardians during pregnancy, childbirth, infancy, childhood, adolescence, and young adulthood.
- Collaborate with families at all levels of health care, in the care of the individual child, and in professional education, policy making, and program development.
- Empower each child and family to discover their own strengths, build confidence, and make choices and decisions about their health.

Adapted from American Academy of Pediatrics Committee on Hospital Care. Family-centered care and the pediatrician’s role. *Pediatrics*. 2003;112:691–697.

## NEONATAL INTENSIVE CARE UNIT ENVIRONMENT

Evidence of the importance of the environment where babies receive care has mounted. Physicians and leaders need to be proactive in designing and implementing environments that enhance recovery and long-term outcomes.

The *microenvironment* around the baby is extremely important. Physical stimuli such as sound and light affect babies in ways that remain incompletely understood, and such stimuli should be managed to prevent excesses. The *macroenvironment* within which family-centered care is provided affects physicians, families, and the infants. Physical and interpersonal considerations need to be addressed. Space and privacy for comfort, communication, and deliberation are important and subject to study, implementation, and evaluation. For example, single-patient rooms that allow family members to spend 24 hours a day with their neonate in the first or second week before discharge provide family members with the opportunity to care more expertly for their infant at home.

## SPECIAL SITUATIONS AND CHALLENGES

The care of a high-risk or premature infant presents PCPs with many unique situations and challenges. PCPs, acting in the patient’s best interest, should be prepared to incorporate the concepts of family-centered care and initiate the development of a supportive and nurturing environment.

### Consultation Before Birth

With the increasing number of extremely premature infants in NICUs, families are often facing decisions regarding the support of an infant born at the edge of viability. Although direct prenatal counseling will usually be done by obstetrical or neonatal physicians PCPs should possess basic knowledge of the data associated with survivability of, and morbidity associated with, extremely premature infants (Table 117-2, Table 117-3; see also Chapter 115, Health and Developmental Outcomes of Very Preterm and Very Low-Birth-Weight Infants). PCPs’ roles may be varied: they may initiate a consultation, offer additional support, clarify suggestions or evidence, and, in some cases, have direct involvement in resuscitation decisions and care.

Because of study limitations and the individuality of newborns, discussions focus not on absolutes, but rather on ranges of survival and quality of life. The AAP recommends the use of *nondirective* counseling while recognizing the role of direct suggestions in cases of extreme prematurity, congenital anomalies that result in a state incompatible with sustained life, or situations in which the benefits of treatment are outweighed by the associated burdens or consequences of intervention. Physicians and members of the care team must be familiar with evidence-based and local outcome data to be able to facilitate the most complete and accurate discussion.

For the family facing important decisions involving the possibility of poor pregnancy outcomes, the PCP

**Table 117-2** Survival to NICU Discharge for Extremely Premature Infants

WEEKS' GESTATION AT BIRTH (W)	RATE (%)					
	SURVIVAL TO NICU DISCHARGE, LITERATURE SURVEY			SURVIVAL TO DISCHARGE, VERMONT OXFORD, 2010–2012 <sup>d</sup>		
	NICHD OVERALL <sup>a</sup>	NICHD MORBIDITY-FREE <sup>a</sup>	SWEDEN (2004–2007) <sup>b</sup>	EPICURE (2006–2010) <sup>c</sup>	OVERALL	MORBIDITY-FREE
<23	6	0	10	0	7	<1
23 <sup>0</sup> / <sub>7</sub> to 23 <sup>6</sup> / <sub>7</sub>	26	8	52	20	37	4.5
24 <sup>0</sup> / <sub>7</sub> to 24 <sup>6</sup> / <sub>7</sub>	55	9	67	43.7	62	11
25 <sup>0</sup> / <sub>7</sub> to 25 <sup>6</sup> / <sub>7</sub>	72	20	81	67.2	76	21.5
26 <sup>0</sup> / <sub>7</sub> to 26 <sup>6</sup> / <sub>7</sub>	84	34	85	—	85	34

<sup>a</sup>Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics*. 2010;126:443–456

<sup>b</sup>EXPRESS Group; Fellman V, Hellström-Westas L, et al. One-year survival of extremely preterm infants after active perinatal care in Sweden. *JAMA*. 2009;301:2225–2233

<sup>c</sup>Seaton SE, King S, Manktelow BW, et al. Babies born at the threshold of viability: changes in survival and workload over 20 years. *Arch Dis Child Fetal Neonatal Ed*. 2013;98:F15–F20

<sup>d</sup>Vermont Oxford Network, accessed Nightingale Reports on 04-16-14 at URL: <https://nightingale.vtoxford.org/login.aspx?ReturnUrl%2fhome.aspx>.

<sup>e</sup>Serenius F, Källén K, Blennow M, Ewald U, Fellman V, et al. Neurodevelopmental outcome in extremely preterm infants at 2.5 years after active perinatal care in Sweden. *JAMA*. 2013;309:1810–1820

<sup>f</sup>Moore T, Hennessy EM, Myles J, Johnson SJ, Draper ES, et al. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies. *BMJ*. 2012;345:e7961

<sup>g</sup>Moore GP, Lemmyre B, Barrowman NJ, Daboval T. Neurodevelopmental outcomes at 4 to 8 years of children born at 22 to 25 weeks' gestational age: a meta-analysis. *JAMA Pediatr*. 2013;167:967–974

**Table 117-3** Neurologic Disability Rates for Extremely Premature Infants

WEEKS' GESTATION AT BIRTH (W)	RATE (%)		
	SEVERE NEUROLOGIC DISABILITY		
	SWEDEN <sup>a</sup> (2004–2006) AGE 2.5 YRS	EPICURE <sup>b</sup> (2006) AGE 3 YRS	META-ANALYSIS <sup>c</sup> AGE 4–8 YRS
<23	40	10	31
23 <sup>0</sup> / <sub>7</sub> to 23 <sup>6</sup> / <sub>7</sub>	21	29	17
24 <sup>0</sup> / <sub>7</sub> to 24 <sup>6</sup> / <sub>7</sub>	13	19	21
25 <sup>0</sup> / <sub>7</sub> to 25 <sup>6</sup> / <sub>7</sub>	10	16	14
26 <sup>0</sup> / <sub>7</sub> to 26 <sup>6</sup> / <sub>7</sub>	9.6	10	

<sup>a</sup>Serenius F, Källén K, Blennow M, Ewald U, Fellman V, et al. Neurodevelopmental outcome in extremely preterm infants at 2.5 years after active perinatal care in Sweden. *JAMA*. 2013;309:1810–1820

<sup>b</sup>Moore T, Hennessy EM, Myles J, Johnson SJ, Draper ES, et al. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies. *BMJ*. 2012;345:e7961

<sup>c</sup>Moore GP, Lemmyre B, Barrowman NJ, Daboval T. Neurodevelopmental outcomes at 4 to 8 years of children born at 22 to 25 weeks' gestational age: a meta-analysis. *JAMA Pediatr*. 2013;167:967–974

<sup>d</sup>Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics*. 2010;126:443–456

RATE (%)								
SEVERE NEUROLOGIC DISABILITY			MODERATE TO SEVERE NEUROLOGIC DISABILITY				NO TO MILD DISABILITY	
SWEDEN (2004– 2006) <sup>e</sup> AGE 2.5 YRS	EPICURE (2006) <sup>f</sup> AGE 3 YRS	META- ANALYSIS AGE 4–8 <sup>g</sup>	SWEDEN (2004– 2006) <sup>e</sup> AGE 2.5 YRS	EPICURE (2006) <sup>f</sup> AGE 3 YRS	META- ANALYSIS AGE 4–8 <sup>g</sup>	NICHD <sup>a</sup>	SWEDEN (2004– 2006) <sup>e</sup> AGE 2.5 YRS	EPICURE (2006) <sup>f</sup> AGE 3 YRS
40	10	31	20	42	43	13.5	40 (mild)	55
21	29	17	30	18	40		49	
13	19	21	21	33	28	25	67	69
10	16	14	17	12	24	—	73	75
9.6	10	—	7.2	10	—	—	83	80

RATE (%)						
MODERATE TO SEVERE NEUROLOGIC DISABILITY				NO TO MILD DISABILITY		
SWEDEN <sup>a</sup> (2004–2006) AGE 2.5 YRS	EPICURE <sup>b</sup> (2006) AGE 3 YRS	META-ANALYSIS <sup>c</sup> AGE 4–8 YRS	NICHD <sup>d</sup>	SWEDEN <sup>a</sup> (2004–2006) AGE 2.5 YRS	EPICURE <sup>b</sup> (2006) AGE 3 YRS	
20	42	43	13.5	40 (mild)	55	
30	18	40		49		
21	33	28	25	67	69	
17	12	24		73	75	
7.2	10			83	90	

should facilitate a discussion that encourages the parents to explore their perception of, and ability to care for, a child with chronic illness or disability. If the pregnancy is early in gestation, then the parents may be considering termination and may seek further information, counseling, or guidance from the PCP. Discussions may explore the effect of having a child at risk of extreme hardship or early death. Similarly, parents may be guided to examine the effect that the termination of a pregnancy may have on their lives. PCPs must have insight into their own beliefs and values related to issues such as quality and sanctity of life. If the discussion about termination of pregnancy or other issues progresses beyond their level of comfort, then a referral may be appropriate.

Professional relationships formed with families with a history of at-risk pregnancy may lead to future contact when planning for another pregnancy. Proactive preconception counseling for such families (ie, interconception care) is an important part of providing comprehensive care.

### Resuscitation and Stabilization

From a practical standpoint, physicians should provide parents with a description of the delivery and resuscitation experience, including who will be present and any anticipated procedures such as intubation or umbilical line placement. Ethical principles must be incorporated into these medical discussions. The Neonatal Resuscitation Program now includes a lesson in its *Ethics and Care at the End of Life* chapter specifically designed to guide physicians with decision making and support of families.

Physicians must be careful to avoid absolutes when discussing resuscitation options, explaining the possibility of modifying decisions based on the baby's condition at birth. Nonintervention decisions based on quality-of-life or best-interests considerations are made difficult by medical and ethical uncertainties. The care team should support parents' wishes to initiate or withhold care in cases of borderline survival or significant morbidity when the prognosis is uncertain. In cases in which the prognosis is known (eg, anencephaly or newborns born at <23 weeks' gestation), resuscitation is not indicated. Parents typically prefer more aggressive care than do neonatologists and nurses, but many parents defer to physicians' judgment and do not demand resuscitation for infants unlikely to survive but not certain to die. In instances where competent and informed parents request treatment of their infant whose outcome is uncertain or prognosis is poor, a trial of therapy should be initiated or the care transferred to another physician or hospital if the physicians caring for the expectant mother and fetus do not think they should intervene. If in the prenatal period a fetal condition is identified that necessitates palliative or comfort care, then the physician should explain options and elicit input from the family. In the event parents are not clear whether to initiate care, initial resuscitation and stabilization may provide an opportunity for further assessment, offering the family and care team more data for decision making.



**Figure 117-2** Rounds in a family-centered environment encourage participation by parents. Note the mother and father (providing expressed milk by tube feeding) joining a nurse and attending physician during presentation by a medical student.

### Rounds

Parent advocates and opinion leaders have long expressed the belief that parents should be involved in all activities in which their child is discussed. Daily rounds are the primary discussion and decision-making forum in most hospital services, including pediatrics and neonatology (Figure 117-2). This time also presents an opportunity for reciprocal information and teaching. A movement toward inclusion of parents in daily rounds has recently taken place, with recognized benefits of parent involvement and satisfaction with care.

## ANTICIPATORY GUIDANCE

### Adjustment to the Neonatal Intensive Care Unit Experience

As parents transition through the emotions and realities associated with the birth of a sick or premature infant, they not only learn to cope with the news, but also begin to adapt to the new challenge of life in the NICU environment. Physicians, recognizing parents' longitudinal adjustment pattern as they assimilate the role of being a parent inside the NICU, need to encourage parents to work to maintain their lives outside the hospital. This encouragement is especially important for parents with children or other family members at home. Physicians should point out to parents that leaving the hospital as needed is acceptable; indeed, maintaining a stable and healthy family unit may be crucial. This transition is difficult for families who expected their infant, once delivered, to come home shortly thereafter.

Families with seriously ill or extremely premature infants will experience many interactions with a variety of health professionals. Their reaction has been characterized as the *model of guarded alliance*. Parents progress through 3 stages when their infant has a prolonged hospital stay: naive trust, disenchantment, and guarded



alliance. The first stage, *naïve trust*, places emphasis on the physician. It recognizes the parents' reliance, for the care of their infant on professionals with whom they are likely unacquainted. Of utmost importance in this period is referring to the infant as a baby, using the baby's name, and encouraging family members to see the baby, despite any monitors, tubes, and wires.

*Disenchantment* occurs when the infant, after a period of relative stability, worsens or fails to improve rapidly. Families of stable infants (eg, those working on achieving adequate feeding and growth patterns) may also feel as though their needs are less important than select families with a more critical infant. *Guarded alliance* occurs as parents become more comfortable expressing needs and asking questions, mainly facilitated by the trust relationships they have formed with physicians. This alliance becomes the foundation for family-centered care. In recognizing these stages, health care professionals can help normalize the family life in the unit, helping members express and prioritize needs.

For many mothers, the postpartum period produces emotional, physical, and cognitive changes. PCPs must recognize that this time requires intervention and support. Parental development in the NICU environment evolves over time as they become more accustomed to their baby, the NICU culture, and their role in this unique environment. Assuring that parents and families perceive that there is a true continuum of care for the infant is a critical facet of establishing and sustaining trust between the family and health care team. The NICU setting typically includes care provided by a large cadre of neonatal nurses, nurse practitioners, physician assistants, and respiratory therapists, rotating neonatologists, social workers, pediatric trainees (fellows, residents, interns), and medical students. In addition, families of the sickest, most medically complex infants often also interact with pediatric subspecialist consultants and surgeons, dietitians, and a variety of therapists (feeding, occupational, physical, developmental specialists). This complex system of caregiving creates the potential for parental misinformation, miscommunication, and misunderstanding about their infant's condition, complications, and treatment plans as they speak with the myriad professionals involved in their child's day-to-day care. Especially at first, adjusting to having a child in the NICU and having fellows and attendings changing service frequently can exacerbate communication problems and leave families feeling as if "no one knows their baby."

The lack of a common language or clear treatment plan as information and plans are shared can be confusing to parents and engender distrust. Various strategies can be helpful in supporting families through this challenging time: (1) identifying a primary neonatologist for communications with the family; (2) routine family meetings to provide updates to the parents, review the infant's progress and care plan, and address any inconsistencies or concerns that the parents/family has; (3) periodic discussions among the treating physicians to ensure that all participants in the infant's care are fully aware of the infant's medical issues, treatment recommendations of other team members, and to formulate an integrated, comprehensive care

plan; and (4) establishing daily care goals that can be shared with all the caregivers and family as a means to minimizing miscommunications. Engaging the baby's identified primary care provider for post-NICU pediatric care is another effective strategy that can facilitate communication and understanding. Families who have an established relationship with a pediatric primary care professional typically look to that professional for information and guidance with interpreting medical information and deciding among treatment options. The pre-existing relationship with the family can ease communication for the whole team.

The mother's partner, be it the biological father or another person, may also experience difficulty coping with the birth of a sick or premature infant. This person may have the added burden of role confusion, identifying the person's own role with the traditionally mother-baby care dyad. Physicians can aid partners by including them as part of the care team and focusing on the family as a unit when addressing the parents.

Finally, physicians should never undermine the element of hope. This act may be inappropriately viewed as a form of denial or a coping mechanism; it may also have a deep spiritual basis. After respectfully acknowledging the parents' beliefs, the PCP can emphasize the known medical facts versus what is unknown and cannot be predicted.

### Fostering Bonding in the Neonatal Intensive Care Unit

*Bonding*, the process of psychological intimacy and attachment that occurs between parents and infants, is recognized as an important component of the developmental changes that occur in families. Visitation policies, rounds, and care regimens, such as those incorporating kangaroo care, must promote the interaction of family members with the infant. Kangaroo care is a method of holding a baby that involves skin-to-skin contact. The baby, who is naked except for a diaper and a piece of cloth covering his or her back (either a receiving blanket or the parent's clothing), is placed in an upright position against a parent's bare chest. This snuggling of the infant inside the pouch of their parent's shirt, much like a kangaroo's pouch, led to the creation of the term *kangaroo care*. There are physiological benefits to the neonate as well as to the parents. For mothers and fathers, it fosters improved bonding and feelings of closeness with the babies and creates for parents an increased sense of control and increased confidence that their babies are being cared for. This is important for any parent whose infant requires specialized neonatal care, but especially so for parents whose child is critically ill or dying. Despite the known benefits of kangaroo care, there may be infants too unstable to tolerate placement on their parent's chest. In those instances, parents can be encouraged to cradle their infant on the warmer or in the infant's isolette or to use containment techniques, such as cupping of 1 hand around the infant's head with the other hand on the infant's chest or cradling the legs. The caregiving team can provide reassurance to families and assist them in determining which techniques are

most comforting to the infant. Incorporating family members into caregiving while preserving and building their sense of responsibility can help develop the optimal environment for the bonded family structure and help maximize outcome potentials.

### Siblings

Explaining the hospitalization of a sick or premature infant to a young child may prove challenging for parents. PCPs should encourage sibling visitation when appropriate and should seek opportunities to talk with children as part of routine office visits.

Sibling visitation policies vary among NICUs. Actually seeing an infant who is sick or premature may help some children understand the necessity of their parents' frequent absence. Sometimes allowing a child to simply see the hospital, describing it as the place "where mommy and daddy go every day" or "where your baby brother is living right now," may help.

As is the case with introducing a new infant into the home, children may not easily adapt to the disruption in their usual routine, or they may view the situation as a threat to time with parents. Physicians can suggest that parents keep some usual routines such as bedtime intact, or that they specifically schedule time with the child for activities. For families with chronically hospitalized infants, providing the children at home with a calendar or schedule highlighting the times the parents will be at the hospital may be helpful.

### Grandparents and Other Important Support Individuals

The role of grandparents of a sick neonate is unique and often difficult. In the family constellation, grandmothers and grandfathers are simultaneously grandparents to the child and parents to the child's parents. The grandparents' own children are, at best, under stress and, if not physically sick themselves, are often dealing with a crisis for which they have relatively little life experience.

Grandparents need special consideration, as well as guidance and care, themselves. The natural inclination to parent may be difficult to subordinate when a grandchild is in crisis. PCPs and other members of the neonatal care team need to tend to the baby and reinforce the primacy of the parents' role. At the same time, health care professionals need to provide guidance to grandparents; they can often be recruited and guided to support and assist the new parents.

Many steps consistent with family-centered care can be taken to help parents and grandparents. For example, many neonatal units permit unlimited visiting for parents and others whom the parents approve. The suggestion that grandparents might be first on the list of people to visit freely is often appreciated by all. In addition, when and if special meetings and decisions have to be faced, parents often appreciate being asked whether they would like 1 or more grandparents to be present. It is important to recognize that for some families grandparents may not be the individuals on whom the parents most rely. Their most intimate and important supporters may be other family members, a close friend, or 1 of their other children. The clinical care-giving team needs to be sensitive to each family constellation and the individuals in their lives that they

value and rely on. With parental permission, these individuals should be integrated into the child's care and support team.

### Anger

Families with infants in the NICU setting experience high levels of emotional, financial, and physical stressors that may manifest as anger. Anger can be the result of distrust, unmet expectations, or fear, or it can be the result of inherent pre-existing psychosocial stressors or medical or psychiatric illness. Acknowledging the presence of anger is the first step in assuaging discontent. Addressing concerns in a calm, private environment will present an opportunity for the physician to discern the underlying source. This step includes listening completely to all of the thoughts and feelings of the parent(s) without any defensiveness or responses until the parent(s) is finished. Commonly, this anger may be the result of a lapse or misunderstanding in communication. Admitting fault and ensuring better attention to the matter at hand may help regain rapport with the family.

In cases in which anger or disruptive behavior is a product of the family's psychopathological characteristics, social service support or psychiatric services, or both, should be involved to help counsel the family members and provide support while the family endures the hospitalization of the infant. Although the health care team must continue to communicate transparently and involve the family fully in the care of their infant, team members may be hesitant about sharing too much information out of concern of angering the family and perhaps precipitating an outburst. These situations are challenging tests of physician skills. Situations such as this often benefit from private discussion outside of formal rounds within the unit. The use of regularly scheduled family meetings may foster a calmer environment for discussions. The use of a mediation process is another option that allows families and the medical team to work together, sharing the burden of difficult and end-of-life decision making. In bioethics mediation, a member of the hospital clinical ethics team serves as an impartial third-party helping the medical staff and the family reach consensus on a treatment plan (described earlier in the section titled *Shared Decision Making and Informed Consent*).

In instances of intense verbal exchanges or physical harm or threats to patients, visitors, or staff members, the first resort is the institution's security team and contact with risk-management members. Health care professionals who feel insecure may be compromised in their efforts to care for patients.

### Death of a Baby

When resuscitation of a newborn deliberately has not been initiated or has been unsuccessful, physicians must remain supportive, caring, and professional. Whether or not they have had an opportunity before delivery to meet the family or have been involved in the infant's care in the neonatal unit, physicians need to state clearly that the infant has died. An appropriate statement would be, "I'm sorry your daughter/son has died. I am very sorry for your loss," identifying the baby by name. If culturally acceptable and comfortable,

a physical gesture (lightly touching the parent's shoulder or offering a handshake) is appropriate.

In situations in which care was withdrawn or not initiated, or if the infant's condition has been recognized as life-limiting but the parents prefer to continue care until the baby's death, parents may prefer to hold the baby while the child dies. In this instance, physicians must ask parents their wishes. The emotional act of holding the baby who is in the last moments of life is an important time for many parents to bond with and comfort the infant, and process the event. However, some families may decline to see or hold the infant for personal or cultural reasons. In circumstances in which family members cannot be present at the time of withdrawal of support or death, a health care professional may hold the infant. Nonetheless, the family should be provided with some time alone, and PCPs should offer to call support persons (eg, other family members, spiritual counselor, chaplain, bereavement specialist) as needed.

Private space for the grieving family within the hospital is important and may mean closing off the immediate area surrounding the infant's bedside. In most NICUs, suites or private rooms are available for this purpose. Finally, physicians should be present with the family in the moments surrounding the time when care is withdrawn or when an infant dies. This time is when the family will need caregivers most—if not for questions, then for emotional support. Many hospitals will offer families a memory box that contains the baby's picture and/or the footprint or a lock of hair placed with a note from the hospital and information to help the parents and other family members through the grieving process. Some parents may not want to accept the memory box immediately after their child's death, but will contact the hospital at a later date. Therefore, the memory box or mementos of the baby's life should be kept in the event that parents ask for them later.

The actual place where a child dies is of great concern to some families. Parents sometimes prefer to have a baby die in a place perceived to be closer to nature than a hospital environment—perhaps a patch of grass outside the hospital, with staff discreetly nearby. A planned death of a baby at home is an appropriate alternative. Such deaths may be anticipated to happen soon or some days or weeks ahead. Babies with conditions such as trisomy 13 or 18 might be home for weeks or months before death. Babies with shorter anticipated life spans, including those on some form of life support, might, with collaboration of medical and nursing staff, go home for a short interval. Hospital staff and physician leadership providing compassionate support and careful planning are necessary to ensure a safe transition to the home environment. This provision includes anticipating not only medical issues, but also matters such as prior notification of community services (eg, emergency response teams). Coordination between hospital and community physicians is an important general principle and is essential in these situations.

## SUPPORT FOR THE FAMILY

Caring for the family becomes an integral component of the medical care and nurturing of the infant. Psychosocial, emotional, and spiritual support for the

family are necessary elements of care since focus on the infant's quality of life and best interests frame decision making for the baby. The principles of family-centered care are interwoven in the delivery of all facets of neonatal care. These principles form the basis for an open dialogue with families that is culturally sensitive, negotiated, and respectful of the strengths, values, and perspectives that the family brings to the discussion (Box 117-3).

The health care professional should recognize and validate the parents' role and the range of experiences, beliefs and expectations, strengths, and needs expressed by the family. Family constellation and individual beliefs, values, and expectations affect a parent's ability to weather and adapt to having a premature infant or sick child. For many individuals, no greater loss exists than the death, serious illness, or severe disability of a child. Siblings may also exhibit a variety of feelings and responses that further influence a family's functioning and needs (Box 117-4). For many parents, their acute responses may evolve to

### BOX 117-4 Factors That Influence a Child and Family's Adjustment to Death

- Sudden, unanticipated death (birth catastrophe, undiagnosed lethal birth defect, or newborn illness)
  - After a prolonged illness (extreme prematurity, complex medical condition unresponsive to interventions)
  - Prenatal diagnosis of lethal or incurable condition (trisomy 13, 18, other chromosomal disorders, Potter's syndrome)
  - Stillbirth or loss of 1 or more infants in a multiple gestation
- Physical and emotional functioning of the surviving adults
- Physical and emotional functioning of the surviving siblings: age and cognitive understanding of death
- Individual personality and temperament
- Pre-existing risk factors
  - Mental illness
  - Learning and social-behavioral problems
- Family structure, functioning, and relationships
  - Quality of prior family member relationships
- Concurrent life stressors
  - Finances
  - Living situations
  - Divorce, single parenting
  - Concurrent illness in other family members
- Availability of support services, resources, and interventions before, during, and after the death

From Capitolo KL. Evidence for healing interventions with perinatal bereavement. *MCN Am J Matern Child Nurs.* 2005;30(6):389-396; Limbo R, Kobler K. The tie that binds: relationships in perinatal bereavement. *MCN Am J Matern Child Nurs.* 2010;35(6):316-321, quiz 321-323; Kobler K, Limbo R. Making a case: creating a perinatal palliative care service using a perinatal bereavement program model. *J Perinatal Neonatal Nurs.* 2011;25(1):32-47, quiz 42-43; Yee W, Ross S. Communicating with parents of high-risk infants in neonatal intensive care. *Paediatr Child Health.* 2006;11(5):291-294.

**BOX 117-5 Strategies to Support Family Coping**

- Truth telling
  - Limits confusion, mistrust
  - Avoids unnecessary information
  - Avoids mixed messages
- Provide information simply and directly using correct words and language; euphemisms may cause more distress, although some cultures have specific preferences for acknowledging the deceased.
- Gain familiarity with cultural and religious beliefs and practices.
  - Families may have specific rituals and customs in response to serious illness or death.
  - Understand how to respond, tailor comforts, and what is within the realm of expected behavior.
  - Understand the role of religion or spirituality in family coping.
- Religion is a prime source of support and strength for many people when dealing with death or serious illness.
- Religious preferences may cause distress for individuals for whom faith has not played an important prior role or if the perceived religious tenets or proscriptions related to end-of-life decision making or withdrawal or withholding care are contrary to parental views.
- Reassure children that they are not to blame.
- Understand that children make comparisons.
  - Wishing for their life before the crisis occurred
  - Comparing their life to the lives of others
- Model appropriate responses.
  - Do not hide feelings and emotions; contain strong, dramatic feelings that might frighten, confuse younger children.
  - Find ways, if feasible, to involve children in the infant's routine while in the hospital or in funeral rituals.
  - Demystify events associated with illness, death, and burial.
- Encourage children to talk and ask questions.
  - What does the child think and feel?
  - Explore feelings about illness and death, and determine appropriateness of child's participation in the death process; visiting their dying sibling, the funeral, and burial, and sending the child away during this time.
  - Correct misinformation and misconceptions.
- Be attuned to and respond to child's own pace for sharing feelings.
  - Provide multiple opportunities for children to express their feelings; recognize that children go through developmental stages in their understanding of death.
  - Encourage expression of grief, collection of keepsakes, and sharing of memories.
  - Acknowledge and affirm children's expressions.
- Provide understanding, support, and extra guidance.
- Encourage families to seek support from other family members and friends and from the spiritual or faith community.

one of chronic or recurrent sorrow and sadness, irrespective of the child's clinical condition or level of health care need. Periods of anticipated developmental transitions or high-risk periods, such as an acute illness or the need for hospitalization or surgery, may result in the need for increased family support. Recognizing that the fears and concerns exhibited by some families may seem out of proportion to the severity of the infant's medical problems is also important. The meaning of their child's condition to the parents and family should be explored, as well as their concerns and prior experiences that may be influencing their responses.

### PERINATAL BEREAVEMENT

Parents confronting a perinatal or infant death often face common dilemmas, such as what is happening to their family; why family and friends do not understand; a sense of feeling out of balance, without boundaries or freedom; and a feeling of being atypical or different for their child and family. The grief parents experience lasts a lifetime, evolves over time, and is multifaceted. Gender differences are common in terms of the distress each parent feels. Over time, individual partner needs may change. Therefore the health care professional should recognize these differences so as to facilitate long-term adjustment for parents.

Emphasis on hope, empowerment, taking action, and parent-professional partnerships are important factors in the process of adapting and healing after a high-risk birth. Parents benefit from guidance and practical tools for their day-to-day living and decision making. The health care professional should assist the family in identifying and understanding their feelings of loss and helplessness, developing their parental identity, and managing relationships (Box 117-5). The professional must also recognize the complexities of changing expectations, parental control, death, dying, multiple births, and survival with poor, unexpected, or, in the case of multiple births, varying outcomes. If their child is critically ill, then parents must learn to cope with having to make life-and-death decisions, uncertainty regarding their infant's chance for survival, or the risk for long-term disability and understanding the realities of medical decision making when viable options may not exist (Box 117-6).

### PALLIATIVE CARE

Palliative care for neonates is an active, comprehensive approach to an infant's care and comfort and family support, from the time of diagnosis, throughout the infant's life, death, and beyond (Figure 117-3 and



**BOX 117-6 Four-Quadrant Decision-Making Tool—Approach to Collaborative Decision Making****QUADRANT 1: MEDICAL FACTS**

Infant's underlying diagnoses and opportunities for recovery

Goals of care—risks and benefits

Response to current treatments—complications

Infant's prognosis—likelihood for survival, recovery, long-term health conditions, and disability

Potential additional treatment and intervention options

**QUADRANT 2: PATIENT AND FAMILY PREFERENCES**

Parents' understanding of their child's medical problems and available treatment options

Parents' desires and goals for their child and family

1. Being involved in decisions

2. Desire for autonomy

3. Desire for privacy

4. Each specific treatment option

Parents' views about illness, death, and disability

**QUADRANT 3: QUALITY OF LIFE**

Infant's current quality of life

1. Components of life that give value and meaning to the family

2. Ability to experience and control pain and suffering

3. Ability to be comforted, interact, and engage with parents and other caregivers

Infant's anticipated quality of life if survival is possible/probable

1. Anticipated functional outcomes

2. Anticipated ability to engage with family and caregivers—experience, comfort, pleasure

3. Anticipated life expectancy

4. Chronic pain and suffering

Range of continued medical care and treatment needs and expected benefits

Herpes simplex virus

**QUADRANT 4: CONTEXTUAL ISSUES**

Parents' cultural and spiritual beliefs/values, philosophical and psychological factors that guide their decision making

1. Parents' views about withholding or withdrawing care—spiritual and faith-based influences should also be explored

2. Family constellation

Family and support network preferences that factor into parents' ability to make decisions Family resources and needs

Needs and opinions of professional caregivers

Legal issues:

1. State, local, and hospital procedural regulations that affect care options

2. Federal Child Abuse amendments that permit discontinuation of care in cases where there is irreversible coma, treatment prolongs dying, or treatment is considered inhumane

Usually associated with immunosuppression

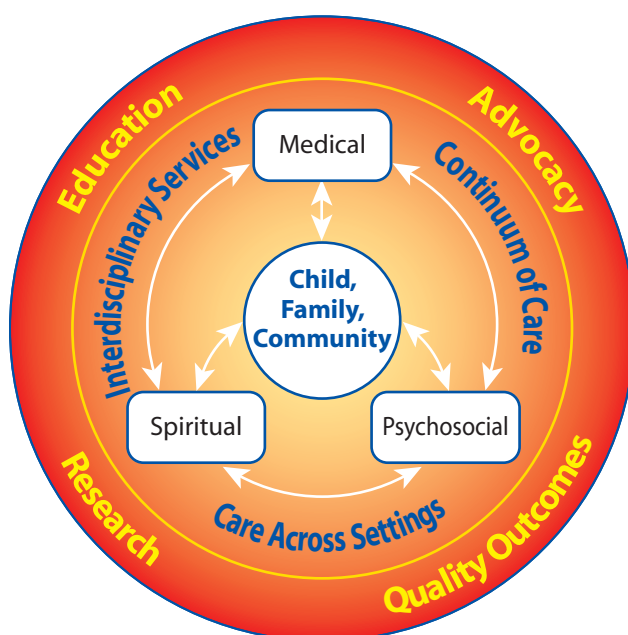
Adapted from Jonsen AR, Seigler M, Winslade WJ. *Clinical Ethics: A Practical Approach to Ethical Decisions in Clinical Medicine*. New York: McGraw-Hill; 1992; Seattle Washington Pediatric Palliative Care Project, Children's Hospital and Regional Medical Center, Seattle.

Figure 117-4). It embraces physical, emotional, social, and spiritual elements, and focuses on the enhancement of quality of life for the baby and support for the family. It includes symptom management, support for the caregivers, care at the end of life, and bereavement support. Palliative care can be introduced at any point: some neonates may require palliative care from birth, others only as their condition deteriorates. A key element of palliative care is supportive care, defined by the World Health Organization as a component of palliative care that is applicable during the course of illness, in conjunction with other therapies intended to prolong life. Supportive care includes those investigations needed to better understand and manage distressing clinical complications. Families may also vary as to whether they wish to pursue treatments aimed to cure or significantly prolong life.

When prenatal diagnosis involves identification of a life-limiting condition that will lead to an early perinatal death, hospice care should begin immediately. Perinatal hospice offers a caring, supportive program of services to families who choose not to terminate a pregnancy after a prenatal diagnosis or when the timing of the diagnosis does not allow for this option. Perinatal

hospice provides information and counseling to assist families in birth planning, anticipatory grieving, and preparing for what time they may have with their infant if the child is live born. Parents who choose perinatal hospice or comfort care for their infant wish to parent their baby for as long as possible. If the infant is born alive, provide care in the hospital (mother-baby unit or NICU) or at home that focuses on how the parents want the experience to be for them, their family, friends, and their baby. This includes the opportunity to be with their baby after death and to have any ritual and keepsake activities that are important to them. Local hospice services may be engaged to support care at home for infants with life-limiting conditions who are not expected to die immediately. Referrals may include social services, religious or spiritual services, and consultation with neonatology and maternal-fetal-medicine specialists.

Palliative care for the dying neonate includes supporting the family in finding meaning in their baby's life and death. Creating a physical environment that is family centered offers psychosocial and spiritual resources, and supports the family in decision making, advanced care planning, and the grieving process.



#### Interdisciplinary Services

Child-life specialists	Nurses
Community support	Pharmacy services
Counseling	Physicians
Durable medical supplies	Physical and occupational therapists
Expressive therapies	Speech therapy
Home health aides	Respite services

#### Care Across Setting

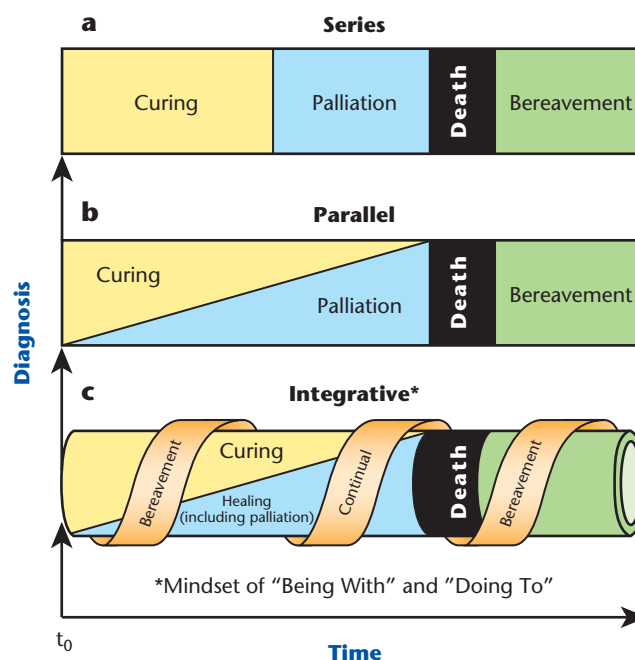
Family home
Alternative home (eg, foster care)
Inpatient hospice
Inpatient hospital
Long-term care nursing home

#### Continuum of Care

Time of diagnosis
Acute care
Chronic care
Terminal care
Bereavement

**Figure 117-3** Scope of pediatric palliative care. (From Carter BS. *Comfort care principles for the high risk newborn*. *NeoReviews*. 2004;5(11):e484. Data from the National Hospice & Palliative Care Organization: ChIPPS, 2001.)

Bereavement care begins with the infant's birth; bonding should be encouraged and families supported in their birth rituals and comfort care for their baby. Parents should be encouraged to name their infant, if this is an appropriate cultural practice for the family. The health care professional should provide the family with a private, quiet place to spend time with their dying infant and encourage them to hold, examine, and caress their infant. Families may wish to conduct cultural practices that celebrate, bid farewell, or offer protection to their infant during the dying process. Professionals may also assist families by providing resource listings that incorporate a range of media—texts, videotapes, electronic resources, and referrals to support groups—and offering information that responds to the spectrum of medical and educational information, emotional, and practical support needs of families. The professional needs to be aware of specific red flags



**Figure 117-4** Model of integrative neonatal care. (From Milstein J. *A paradigm of integrative care: healing with curing throughout life, "being with" and "doing to."* *J Perinatol*. 2005;25:563–568. Reprinted with permission from Macmillan Publishers Ltd.)

that should prompt referral of the parent for immediate medical or mental health care and assess the parent-child relationship for signs of inappropriate bonding and attachment, excessive perceived child vulnerability, and child abuse or neglect involving the infant or other children. Parents or caregivers who exhibit depressive symptoms or signs of mood disorder as well as parents who appear unable to grieve openly or whose grief is delayed or incomplete should also be referred for additional support and mental health care.

## CONCLUSION

When supporting a family with a sick or premature infant, the physician and other health care professionals must draw on a full complement of skills and resources. These situations test a physician's strength in conveying medical knowledge in a professional, clear, concise manner, while maintaining a calm, sincere, and compassionate persona. Patients, families, and health care professionals benefit from family-centered care ideals. Physicians can derive a sense of fulfillment and job satisfaction from recognizing that their efforts to help and support babies and families are effective.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Newborn Intensive Care: What Every Parent Needs to Know*, 3rd ed (book), American Academy of Pediatrics (shop.aap.org)

- *A Gift of Time: Continuing Your Pregnancy When Your Baby's Life Is Expected to Be Brief* (book), Johns Hopkins University Press ([perinatalhospice.org/A\\_Gift\\_of\\_Time.html](http://perinatalhospice.org/A_Gift_of_Time.html))

### Medical Decision Support

- *Guidelines for Perinatal Care*, 7th ed (book), American Academy of Pediatrics and American College of Obstetricians and Gynecologists ([shop.aap.org](http://shop.aap.org))
- *Neonatal Resuscitation: Instructor's Manual*, 6th ed (book), American Academy of Pediatrics and American Heart Association ([shop.aap.org](http://shop.aap.org))
- *Recommendations to Improve Preconception Health and Health Care—United States: A Report of the CDC/ATSDR Preconception Care Work Group and the Select Panel on Preconception Care* (article), Centers for Disease Control and Prevention ([www.cdc.gov/mmwr/preview/mmwrhtml/rr5506a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5506a1.htm))
- *Clinical Practice Guidelines for Quality Palliative Care*, 2nd ed (booklet), National Consensus Project for Quality Palliative Care ([www.nationalconsensusproject.org/guideline.pdf](http://www.nationalconsensusproject.org/guideline.pdf))
- *When Children Die: Improving Palliative and End-of-Life Care for Children and Their Families* (book), Field MJ, Behrman RE, eds, 2003
- *Precepts of Palliative Care for Children, Adolescents, and Their Families* (article), National Association of Neonatal Nurses ([www.aphon.org/files/public/last\\_acts\\_precepts.pdf](http://www.aphon.org/files/public/last_acts_precepts.pdf))
- *Children's Hospice International* (Web site), ([www.chionline.org](http://www.chionline.org))
- *Creation of a Neonatal End-of-Life Palliative Care Protocol* (article), *Journal of Perinatology*, Vol 22, Issue 3, 2002

### AAP POLICY

American Academy of Pediatrics Committee on Fetus and Newborn. Levels of neonatal care. *Pediatrics*. 2012; 130(3):587–597 ([pediatrics.aappublications.org/content/130/3/587](http://pediatrics.aappublications.org/content/130/3/587))

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American Academy of Pediatrics Committee on Bioethics and Committee on Hospital Care. Palliative care for children. *Pediatrics*. 2000;106(2):351–357. Reaffirmed June 2012 ([pediatrics.aappublications.org/content/106/2/351](http://pediatrics.aappublications.org/content/106/2/351))

### SUGGESTED READINGS

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Institute for Patient- and Family-Centered Care. Available at: [www.ipfcc.org](http://www.ipfcc.org)

Johnson K, Posner S, Biermann J, et al. Recommendations to improve preconception health and health care—United States. A report of the CDC/ATSDR Preconception Care Work Group and the Select Panel on Preconception Care. *MMWR Recomm Rep*. 2006;55:1–23

Munch S, Levick J. "I'm special too": promoting sibling adjustment in the neonatal intensive care unit. *Health Soc Work*. 2001;26:58–64

National Hospice and Palliative Care Organization, Children's Project on Palliative/Hospice Services (ChiPPS) <http://www.nhpco.org/resources/pediatric-hospice-and-palliative-care>







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## PART 5

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# Adolescence

- 118 Challenges of Health Care Delivery to Adolescents
- 119 Interviewing Adolescents
- 120 Counseling Parents of Adolescents
- 121 Adolescent Sexuality
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## Chapter 118

# CHALLENGES OF HEALTH CARE DELIVERY TO ADOLESCENTS

Richard E. Kreipe, MD

Several challenges threaten health care delivery to contemporary adolescents. Adolescence is a transitional stage between childhood and adulthood. Developmentally, adolescents share characteristics of both children and adults, often vacillating between extremes, depending on circumstances. Therefore, a health care system designed for younger individuals (who depend on their parents) or adults (who act autonomously) does not easily accommodate adolescents. The major health threats to adolescents are related to their behavior and their environments. The causes of mortality and morbidity for adolescents can be traced to modifiable behaviors more than to diseases. The US blueprint for the health of its citizens now includes Adolescent Health as a specific topic area. Focus areas include motor vehicle crashes, including those caused by drinking and driving; homicide; suicide; substance use including tobacco; sexually transmitted infections (STIs), including HIV; teen and unplanned pregnancies; obesity; and homelessness. Thus, primary health care for adolescents should focus on prevention in addition to diagnosis and management of illness. In this regard, *Healthy People 2020* includes several objectives emphasizing positive youth development such as increasing the proportion of adolescents who participate in extracurricular or out-of-school activities, who are connected to a parent or other positive adult caregiver, and who transition to self-sufficiency from foster care.

A growing body of knowledge focused on changing health-related behaviors in adolescents continues to emerge. However, the highly variable contexts of health care delivery, both the settings in which it occurs and the health care providers who render the care, represent another challenge. For example, ambulatory settings include private physician's offices, hospital clinics, school-based clinics, or private agencies. Adolescents also may receive care in free clinics that emphasize confidential services, whereas homeless youth may receive care from a mobile facility. Similarly, physicians providing these services can range from board-certified adolescent medicine physicians to youth workers. The wide variety of settings and health care providers, with little in the way of standardization or best-practice models, represents a major challenge to delivering consistently high-quality health care to adolescents. The Institute of Medicine concluded that "existing adolescent health care training across disciplines fails to address many of the health needs of adolescents." Another factor challenging adolescents is the system in which health care is delivered. Issues related to health insurance, time spent at visits, and other factors need to be addressed in a realistic manner. Although landmark health care

reform legislation is now in effect in the United States, with many positive features for adolescents, legal and practical challenges threaten many aspects of this important systems factor.

This chapter addresses each of these challenges and points to opportunities in these areas for improving health care delivered to adolescents. Improving the health of adolescents and young adults often requires strong advocacy and innovative methods. However, the challenges regarding health care delivery to adolescents are not insurmountable, if the emphasis is on the word *care*. As Peabody noted more than 70 years ago, the secret of patient care is in *caring* for the patient.

## DEVELOPMENTAL ISSUES RELATED TO HEALTH CARE DELIVERY TO ADOLESCENTS

### Puberty

Tanner observed that the only thing constant about adolescence is change. Within the realm of pubertal changes, a well-recognized sequence of events of sexual maturation exists for boys and for girls, but the timing of the onset and the velocity of the changes vary widely among individuals. Thus, healthy 12-year-old children can range from having no secondary sex characteristics to full sexual maturity. Girls are now experiencing the onset of breast development (thelarche) up to 2 years earlier than they were a generation ago. This factor is important because earlier-developing girls are at greater risk of engaging in high-risk health behaviors than those who develop later, and because girls who experience precocious sexual development may not be mature cognitively. Similarly, endogenous androgen levels (or exogenous anabolic agents) may account for some aggressive behaviors in boys. However, the psychosocial aspects of adolescence are not necessarily synchronous with each other, or with sexual maturation.

### Autonomy

The emergence of independence and autonomy, a hallmark of adolescence, also affects health care delivery. Adolescents who have not reached the age of majority (eighteenth birthday in most jurisdictions) have legal rights to seek health care without parental consent depending on several factors (Box 118-1). State laws vary on this issue, however, and thus it is important to be aware of applicable local laws.

Confidential health care tends to be sought most often for conditions that may be highly charged emotionally, such as reproductive health care. To the degree that an adolescent's right to confidential health care is honored, the adolescent's parents may feel excluded and think that their parental rights and responsibilities are being ignored. Health care providers, especially family practitioners, family nurse practitioners, and physician's assistants who provide primary care for both adolescents and adults in a family, may be caught in the middle of this conflict. Determining what is in the best interest of the adolescent

**BOX 118-1 Factors Permitting Health Care for Minors Without Parental Consent**

- Marriage
- Military service
- Bearing a child
- Living independently (emancipation)
- Reproductive care
- Mental health or substance abuse evaluation
- Life-threatening emergency care (until parents are contacted)
- Local laws governing legal status

may be difficult in such situations. A balanced approach, honoring the rights and needs of both adolescents and parents, is most productive. Nonadherence to treatment, especially for chronic illnesses such as diabetes, HIV infection, or cystic fibrosis, often emerges during adolescence as a manifestation of a struggle for autonomy. Adolescents may not want to be told what to do, or they may use the disease as a means of exerting control in conflict with parents.

**Cognition**

Nonadherence to a treatment regimen may be related to cognitive limitation because of the concrete, operational nature of adolescents' thinking. For example, a 15-year-old with pelvic inflammatory disease might be encouraged by a physician to complete a 14-day course of antibiotics to prevent infertility. After taking the medication for 2 days, she might stop treatment because she feels better. However, she might also interpret the warning about infertility after an insufficient course of treatment to mean that she no longer needs to use birth control. A better method to increase adherence would be to warn about the possibility of chronic pain or internal scarring if she does not complete treatment. These complications are concrete and immediate realities that may have greater meaning to the patient than warning about a possible future, abstract concept such as infertility. The delivery of health care to adolescents should take into consideration the cognitive functioning (including the literacy level) of each patient and adapt education and interventions accordingly.

**Identity**

Identity development, sometimes characterized as the "essence of adolescence," can present a challenge to professionals delivering health care to patients in this age group. As the major task of adolescence, identity development generally occurs in the context of peer groups, which can have either health-promoting or health-threatening, risky behaviors. The latter behaviors may predispose individuals to STIs, unintended pregnancy, violence, or substance abuse, and may also make obtaining the history extremely difficult. For example, if a girl has been forbidden by her parents to see her boyfriend, she may deny sexual activity with him; or if a boy is a member of an athletic

team known for drug use, he may not be willing to admit to substance use. Similarly, a boy experiencing emerging homosexuality may have numerous concerns related to this aspect of identity and behavior but not be able to address them unless specifically asked about sexual orientation by a physician. Thus, the developmental aspects of adolescence itself present significant challenges to the delivery of health care in several domains.

Not all identity developmental challenges represent barriers to the delivery of care, however. Normal adolescents focusing on their own identities may be very self-centered or egocentric. Instead of viewing this as a narcissistic shortcoming, the physician can use it to the patient's benefit by providing authoritative advice to help the adolescent to take control, rather than an authoritarian prescription of what must be done. Alternatively, adolescents may modify their physical appearance as a personal statement reflecting their identity. Multicolored hair, body piercings, tattoos, and clothes all relate to the emerging individual's sense of self (even if the person assumes an appearance that is remarkably similar to that of peers). For physicians, the challenge is to continue to respect the person, regardless of how unusual the adolescent may appear, and to identify the positive qualities and assets of each adolescent, as described by Ginsburg in a strength-based approach.

**MORBIDITY AND MORTALITY IN ADOLESCENTS**

As illustrated in Box 118-2, most mortality and morbidity in adolescents is generally related to behavior and potentially preventable.

An effective means of preventing many of these conditions, however, remains elusive. Because adolescents are generally healthy, adolescent health care should focus on behavior, knowledge, and attitudes, rather than on illness. The conditions affecting the health of adolescents are not readily preventable, may be resistant to treatment, or may require interventions that physicians are unable to provide. Therefore physicians need to involve other segments of society, such as social workers, educators, and law enforcement individuals, to assist in providing an environment that encourages healthy behaviors.

Given the nature of health problems facing adolescents, physicians may feel unprepared to address either the problems or the adolescents who contend with them. An analysis of a US national ambulatory dataset found that counseling regarding nutrition, exercise, STIs, or birth control was 2 to 3 times more likely at an acute visit than at a well visit, which is intended to include such counseling. Thus adolescent health care providers require a high degree of flexibility and willingness to use each encounter with adolescents as an opportunity to provide anticipatory guidance. Moreover, physicians benefit from training and experience related specifically to the care of adolescents. This training and experience is available through publications, continuing-education services, and programs by professional organizations such as the American Academy of Pediatrics ([www.aap.org](http://www.aap.org)),



### BOX 118-2 Major Causes of Mortality and Morbidity in Adolescents and Young Adults

#### **Mortality** (causes of 75% of deaths)

- Motor-vehicle crashes
- Homicide
- Suicide

#### **Morbidity**

- Mental health (depression, anxiety)
- Violence-related injuries
- STIs (including HIV)
- Unintended pregnancy and its complications
- Substance use/abuse
- Eating disorders and obesity

the Society for Adolescent Health and Medicine ([www.adolescenthealth.org](http://www.adolescenthealth.org)), and numerous universities that provide hands-on or distance-learning opportunities in adolescent health.

In response to the need for greater efforts at preventing morbidity and mortality among adolescents, different comprehensive preventive strategies have been developed, most notably the American Medical Association's *Guidelines for Adolescent Preventive Services* (GAPS) or the American Academy of Pediatrics and Maternal and Child Health Bureau *Bright Futures Guidelines* ([brightfutures.aap.org](http://brightfutures.aap.org)). These resources structure both initial and follow-up health supervision visits by providing paper forms that adolescents and parents complete and providing specific questions that physicians can use in assessment and management.

## CONTEXTS (SETTINGS AND PROVIDERS) OF HEALTH SERVICE DELIVERY TO ADOLESCENTS

### Outpatient Settings

As health care expands to include preventive adolescent services, the settings in which health services are delivered to adolescents have appropriately expanded beyond the physician's office or the hospital bed. A wide variety of service settings and an even wider variability of service providers are available. For example, within the category of private office, the physician might be a pediatrician, internist, or family physician, each of whom will have different training in adolescent health, ranging from an optional elective to a 3-year fellowship in adolescent medicine. In addition, nurse practitioners and physician's assistants often provide health care to adolescents, depending on the setting (eg, college- or institution-based care) and geographic location.

School-based clinics offer many advantages, most notably convenience, ready access, and the ability to minimize school absence. Because schools represent a focal point of youth activity, full-service schools that offer education, health services, after-school activities, and family services are attractive. This model has

special advantages for inner-city communities that may offer little in the way of quality health care or safe out-of-school activities to their residents. The challenge is to get the community invested in the program; this requires a commitment by school and community leaders to ensure the program succeeds. Many federally qualified community health centers (FQ-CHCs) provide excellent health care for underserved adolescents, both urban and rural, precisely because they require active engagement by the community that they serve.

Because of the public nature of schools, political controversy may surround school-based health services, especially those related to reproductive health care. For example, for sexually active adolescents, many health care professionals consider the consistent use of condoms as an important preventive measure. Some other groups argue, however, that providing condoms encourages sexual activity and subverts parental rights and authority. If condom distribution in schools is not allowed, it may be possible to inform students where free condoms are available. Health care providers can play an important role in their communities by advocating for sensible public health policies at local and state levels.

Multiple service settings can be seen as a challenge or as an opportunity. For example, homeless youth constitute a high-risk, underserved group with respect to health. Because their needs cannot be met in traditional medical settings, leaders in cities such as Seattle, Los Angeles, New York, Vancouver, and Toronto have established programs that include free clinics with late evening hours, linkages with community-based youth workers, mobile units providing information and services, telephone hotlines, job training, high school equivalency education, and referral to adolescent-friendly specialists. Similarly, obstetric or gynecologic services are often clustered in a clinic specifically for adolescents, but with adolescent obstetric services provided at different times than adolescent gynecologic services. This model recognizes the differences between pregnant teens and adults (eg, greater need for assistance with high school education, nutrition assistance, child care, and transportation) and the different obstetric and gynecologic needs of teens.

Regardless of the outpatient setting, several considerations need to be given to the needs of adolescents. If space allows, a waiting area with space that is adolescent oriented, apart from space for young children, is optimal. Contemporary posters, magazines, and patient-education materials should consistently focus on adolescents in a positive light. The American Academy of Pediatrics has several health brochures and pamphlets for adolescents ([www.healthychildren.org/english/ages-stages/teen/Pages/default.aspx](http://www.healthychildren.org/english/ages-stages/teen/Pages/default.aspx)). With respect to appointments, arranging clinic schedules at times when teens do not miss school and when only other adolescents are in the waiting room is optimal.

Perhaps the most important aspect of making an outpatient setting attractive to adolescents, however, is the attitude of the clerical and support staff toward adolescents. When adolescents perceive they are welcomed, a positive tone is set for their visit. If teens feel disrespected or disregarded, they may approach a

visit with a negative attitude or fail to keep appointments. In such circumstances, the skills and training of the physician are irrelevant because the staff made the physician inaccessible to the adolescent. Unfortunately, this response may occur for patients who are the most in need of care.

Researchers are developing interactive computer programs that obtain medical history and provide immediate feedback to the adolescent waiting for a scheduled appointment. The information is available to the physician during the visit. Such innovative technology can serve several purposes simultaneously: entertaining, educating, and keeping a medical record.

### Inpatient Settings

Most hospitals, even large, university-based facilities, do not have a separate inpatient unit for adolescents. Despite the advantages of creating an adolescent-oriented therapeutic environment and developing professional staff with expertise to work with adolescents on a dedicated adolescent unit, most institutions do not have the critical mass of specialists with experience (or interest) in adolescent health care nor an average census of adolescent patients to sustain such a unit. Thus, adolescents tend to be admitted to hospital units based on their age (to pediatrics) or their admitting diagnosis (eg, to orthopedics for a fractured femur or to psychiatry for depression). This tendency can result in additional challenges in delivering appropriate inpatient services. For example, in some hospitals the age limit for pediatrics is 16 years, resulting in middle adolescents being admitted to a unit where the average patient age is more than 60.

Hospitalizing adolescents on units based on their admitting diagnosis can present other challenges. For example, orthopedic units may be unprepared to address the psychosocial needs of a 15-year-old boy with attention-deficit/hyperactivity disorder who breaks his femur driving a car while intoxicated and without a license. He would benefit from the unit's staff understanding his need for concrete, concise, and clear explanations of any treatment planned and for consistent and reasonable limits on behavior in the hospital. This model enhances his sense of control over the environment in which he is rendered relatively vulnerable and addresses his need to express his feelings in socially acceptable and productive ways. Otherwise, the hospital unit staff may respond to typical behavior with escalating frustration or punitive restrictions.

Even when adolescents are admitted to a pediatric unit, they may not have their psychosocial needs met if they have chronic symptoms or undiagnosed conditions. If staff members do not understand the mental health needs of these adolescents, especially those with life-threatening conditions or somatic symptoms such as incapacitating headache or abdominal pain, opportunities to help the patient may be missed. For example, the "rule-out" approach, in which an adolescent is admitted for a battery of tests or procedures but is finally judged to have a psychosomatic condition because of a negative workup, is rarely of benefit. The biopsychosocial model recognizes the complex interplay among biological, psychological, and social

factors and includes mental health issues in both the differential diagnosis and the treatment planning for each adolescent patient.

Even if a hospital does not have a geographically distinct adolescent unit, several factors can improve adolescent inpatient services. First, having a recreation room where adolescents can congregate for social interaction and leisure activity, sufficiently far away from patient rooms that noise levels will not bother other patients, is advisable. A child-life professional on staff can ensure that developmentally appropriate activities are available and that the psychosocial needs of hospitalized adolescents (eg, keeping up with schoolwork) are identified. A daily schedule, particularly for anyone in the hospital for more than 3 days, provides structure and predictability and enhances the adolescent's sense of control. Regardless of the length of stay, a unit should have clear rules for adolescents regarding visitors, timing of various activities, temporarily leaving the unit, and schoolwork, among others. Emphasis should be on what the adolescent *may* do, rather than a series of rules on what *not* to do.

In the absence of a geographically distinct unit, cohorting adolescents together is best, rather than distributing them throughout a pediatric inpatient service. A close working relationship with 1 or more physicians who have subspecialty training in adolescent medicine provides important support in staff development and consultation services. Because pediatric residency in the United States includes a mandatory 1-month educational unit in adolescent medicine, most institutions have such a specialist, albeit often as a part-time faculty member. Mental health consultation should be readily available as well. Such consultation may be patient or staff oriented; that is, the mental health services are often requested not only to address diagnosis and treatment for the adolescent, but also to address staff concerns about their response to behavior and how an adolescent's behavior affects other patients and staff on the unit. Similarly, when a simple behavior modification program needs to be established for an adolescent inpatient, the hospital staff may need assistance in its development and implementation.

## HEALTH CARE SYSTEM AND THE DELIVERY OF SERVICES TO ADOLESCENTS

The National Adolescent and Young Adult Health Information Center (NAHIC) has proposed 5 recommendations to improve health for this population as it relates to the individual:

1. Ensure the delivery of high-quality services (by improving training in adolescent and young adult health; by improving workforce distribution to provide health care services; and coordinated support for adolescent and young adult health services)
2. Provide access to comprehensive health services (by ensuring appropriate services are readily available and by implementing strategies to overcome adolescent and young adult barriers to access)
3. Improve financial access to comprehensive health services (by improving existing health coverage and

by expanding coverage for adolescents and young adults beyond existing parameters)

4. Ensure the legal right to health care and confidentiality (by improving legal access to health services and by ensuring legal protection of confidential care)
5. Ensure that services are available, accessible, and appropriate.

In addition, the NAHIC described 5 crosscutting themes related to systems issues (Box 118-3) to improve adolescent health.

## PRACTICAL ISSUES IN PROVIDING ADOLESCENT HEALTH SERVICES

Much of the discussion about challenges to delivering health care to adolescents focuses on adolescents themselves rather than on health care providers. Some specific suggestions have been made in each of the preceding sections of this chapter to enhance services. Additional practical issues, however, deserve consideration (Box 118-4).

This section addresses these issues in the context of a traditional office visit, but the principles apply widely.

Ideally, children enter adolescence having been in the care of a physician who will provide care across

the transition from childhood to adulthood. In anticipation of the emergence of puberty, physicians often advise parents of children around age 8 or 9 about starting to provide the child with some time alone with the physician around the age of 10 years. This policy can be framed in the context of preparing the adolescent to take increasing responsibility for his or her own health (paralleling the increasing responsibility in other domains, such as school and work). At the next visit, the parent can be reminded of the physician's desire to talk to the child alone, usually at the end of the visit.

### Confidentiality

As adolescents progress developmentally, an increasing need for, and right to, confidential care should be honored. This is best addressed at the outset of the visit, and framed in terms of privacy; in most instances it needs to be addressed only once. Two points regarding confidentiality deserve emphasis. First, the ethical principle supporting confidentiality is respect for the person, not keeping secrets from parents. Second, absolute confidentiality should never be offered. A physician might say to the adolescent in the presence of the parent or parents, "It is important for my adolescent patients to have private time with me because by the time they get to be 18 years old, they can see me completely on their own. To help you prepare for that, you will have time at each visit when we talk alone. What we talk about will be between us, unless I think that you or others are in danger—like if you were seriously thinking about hurting yourself. I would only do what I think is in your best interest and I will not go behind your back; but most things we talk about will remain private." Parents are usually comfortable with this policy. If they are not, then there may be a problem with trust in their relationship, which itself might be a focus for intervention.

The electronic medical record (EMR) is a work-in-progress that holds much promise for improving communication, but also presents many challenges with respect to providing confidential health care. Potential threats to privacy include parents accessing information available electronically regarding their adolescent's sexual activity, because this information might be divulged to a physician if the adolescent is aware of possible disclosure to parents. In addition, parents receiving a health insurance "explanation of benefits" (EOB) that includes charges for their daughter's pelvic examination, testing for STIs, and a pregnancy test—all conducted appropriately as part of a confidential and responsible health care visit—could have significant repercussions.

### Private Time With Patients

A question commonly asked by physicians is, "How do I get the parent to leave the room?" A useful technique is to get some background history from the accompanying parent or parents, then give the adolescent an examination gown while saying, "Please put on this gown so that I can do your physical examination. Your mom and dad and I will step out to give you some privacy." Then, after shepherding the parents out of the room, the physician asks if either parent has any

#### BOX 118-3 Improving Adolescent Health Care Systems Issues

- Prioritize the health and well-being of adolescents on a national level
- Coordinate care and reduce fragmentation to maximize existing resources at the local, state, and federal levels
- Use resources effectively, with joint collaborative efforts, and additional sustainable funding to address gaps in adolescent health
- Focus programmatic efforts on primary prevention and early intervention that is substantiated by rigorous research
- Increase the role of families and other meaningful adults who play a critical role in the lives of young people as they transition to adulthood

#### BOX 118-4 Physician Factors Related to Adolescent Health Services Delivery

- Training and experience in providing health care to adolescents and young adults
- Structure and format of the adolescent visit
- Billing and financial considerations
- Referrals
- Transition of youth with chronic illness to adult providers and systems

concerns. This approach gives the parents an opportunity to mention concerns privately. The parents can then be asked to have a seat in the waiting room while the adolescent is examined privately. Again, most parents accept this approach readily. Parents who refuse to leave the room may have trust problems with their adolescent or with the physician; the issue is to avoid having parents feel that they are being “kicked out” of the room. The physical examination is a fairly low-yield procedure in an asymptomatic adolescent, but the adolescent and parents often expect it to be performed. Because adolescents may be sensitive about having a physical examination, it can be less threatening and more efficient to link the history and physical examination. That is, while examining the musculoskeletal system briefly, the physician can ask about physical activity and sports; while listening to the lungs and heart, the physician can ask about issues such as smoking and family history. For example, after listening to the lungs with a stethoscope, the physician can ask “Does anyone you live with smoke?”, leaving the differentiation regarding tobacco or other drugs ambiguous in order to open a discussion about any positive response. As the physician prepares to listen to the heart, he or she can ask “Do you know if anyone in your family has a heart problem?” Depending on the response, the physical examination could be suspended to talk about relevant issues and possibly provide feedback and health education. This approach allows items in the HEADSSS (Home, Education/Employment, Activities, Drugs, Sexuality, Suicide/Depression/Self-image/Safety) psychosocial screening tool to be added at various times in the session in a more conversational manner.

Most physicians allow at least 30 minutes for follow-up adolescent visits, and more for an initial visit. Using structured survey forms, such as *GAPS* or *Bright Futures*, greatly facilitates data gathering, but the information contained in such formats needs to be reviewed before the adolescent leaves the office. The adolescent must know what is going to happen at the visit, how much time has been allotted, and that additional visits may be necessary if all concerns cannot be addressed at once. Electronic screening tools are under development, but most are proprietary.

### Financial Considerations

Billing issues need to be discussed openly and early in the delivery of services to adolescents. Although many adolescents are without health care insurance, in the United States the federal Affordable Care Act promises increased access to care for adolescents and young adults up to 26 years old. Adolescents who are living in poverty or are members of racial or ethnic minority groups are more likely to be uninsured.

Billing appropriately for services is necessary to avoid viewing the adolescent as a source of lost revenue. For patients who do have health insurance, some insurance companies or managed care organizations allow for confidential billing. Alternatively, services can be provided under a broad ICD-10 generic time-based code (such as 99215) when the medical decision-making is of high complexity. For example, a pelvic examination might be recorded in

the chart but not be noted on the bill. The fees for counseling sessions should reflect the time spent. In addition, parents may be willing to pay for bills that do not have a detailed list of services, reassured that their adolescent is acting responsibly toward health maintenance. Adolescents who prefer to pay out of pocket generally need an installment plan but are often more than willing to pay for services with their own money. Finally, patients who cannot pay for services can be referred to free clinics, if they are available locally.

### Specialty Referral

The referral of an adolescent to a subspecialist is most likely to represent a challenge when the subspecialist is a mental health care provider. Adolescents tend to interpret the referral to a psychiatrist, psychologist, social worker, or counselor as an indication that they are “crazy.” To minimize resistance, the physician should let the adolescent know the reason for the referral (“I am concerned that you seem to be feeling very sad, at times hopeless, and recently thinking that life’s not worth living”), to frame the referral in terms of bringing the consultant onto the treatment team (“I want to call on Dr. Smith. He’s a psychiatrist who helps me to help my patients who are feeling the way you are”), and to plan a follow-up so that the referral does not evoke feelings of rejection or abandonment (“I want to schedule a visit in 2 weeks, after you had a chance to talk to him. I want to make sure that things are improving. You also know you can call me if you feel like you’re going to hurt yourself before you see him”).

Patients with chronic conditions, previously fatal during childhood or adolescence, are now living into adulthood. As a result, an increasing awareness exists of the need for the transition from pediatric to adult health care. The transition of care needs to be anticipated and a plan made for this process. This transition of care should occur early in the patient’s life. Hearing from a pediatrician the statement, “and when Jenny gets to be an older adolescent or young adult, we will need to make sure that the physician who will be assuming care for her knows about her cystic fibrosis” is interpreted by parents as positive because it reflects an expectation that she will live to adulthood. Combined training in medicine and pediatrics prepares physicians especially well for the care of such patients, given that no need exists for transfer of care as the patient grows out of the pediatric age group. Physicians with such training are especially well prepared to address the needs of adolescents with complex medical and surgical problems as they progress toward adulthood.

### CONCLUSION

Although caring for adolescents can be challenging, following the principles outlined here enables the physician to provide sensitive, effective care for a group of patients who are often desperately in need of sound health care, thus providing a great service to these patients and a sense of satisfaction for the physician.



## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Clinical Preventive Services (“CPS”) for Adolescents* (handout), National Adolescent and Young Adult Health Information Center ([nahic.ucsf.edu/wp-content/uploads/2013/10/AMCHP-Handout-Clinical-Prev-Serv.pdf](http://nahic.ucsf.edu/wp-content/uploads/2013/10/AMCHP-Handout-Clinical-Prev-Serv.pdf))
- *For Today’s Teen: A Message from your Pediatrician* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Helping Teens Stay Healthy and Safe: Health Care, Birth Control, and Confidential Services* (brochure), Center for Adolescent Health and the Law ([www.cahl.org/helping-teens-stay-healthy-and-safe-health-care-birth-control-and-confidential-services-2007](http://www.cahl.org/helping-teens-stay-healthy-and-safe-health-care-birth-control-and-confidential-services-2007))
- *Stages of Adolescence* (fact sheet), American Academy of Pediatrics ([healthychildren.org/English/ages-stages/teen/Pages/Stages-of-Adolescence.aspx](http://healthychildren.org/English/ages-stages/teen/Pages/Stages-of-Adolescence.aspx))
- *Tips for Parents of Adolescents* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *What Is an Adolescent Health Specialist?* (fact sheet), American Academy of Pediatrics ([healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-an-Adolescent-Health-Specialist.aspx](http://healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-an-Adolescent-Health-Specialist.aspx))

### Medical Decision Support

- *Implementing Mental Health Priorities in Practice* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/implementing\\_mental\\_health\\_priorities\\_in\\_practice.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/implementing_mental_health_priorities_in_practice.aspx))
- *Improving the Health of Adolescents & Young Adults* (report), Centers for Disease Control and Prevention ([nahic.ucsf.edu/wp-content/uploads/2011/11/Complete2010Guide.pdf](http://nahic.ucsf.edu/wp-content/uploads/2011/11/Complete2010Guide.pdf))
- *Pediatric Intake Form*, Bright Futures ([www.brightfutures.org/mentalhealth/pdf/professionals/ped\\_intake\\_form.pdf](http://www.brightfutures.org/mentalhealth/pdf/professionals/ped_intake_form.pdf))
- *Young Adult Clinical Preventive Screening Guidelines*, National Adolescent and Young Adult Health Information Center ([nahic.ucsf.edu/yaguidelines](http://nahic.ucsf.edu/yaguidelines))

## SUGGESTED READINGS

- Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Adolescent and School Health; Health Resources and Services Administration, Maternal and Child Health Bureau, Office of Adolescent Health; National Adolescent Health Information Center, University of California, San Francisco. *Improving the Health of Adolescents & Young Adults: A Guide for States and Communities*. Atlanta, GA: Centers for Disease Control and Prevention; 2004. Available at: <http://nahic.ucsf.edu/wp-content/uploads/2011/11/Complete2010Guide.pdf>. Accessed January 7, 2016
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## Chapter 119

# INTERVIEWING ADOLESCENTS

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The skill of interviewing is tested in the practice of adolescent medicine because the relationship between the adolescent patient and the adult in a position of authority changes rapidly and is often fragile. Good interviewing requires establishing a relationship that enhances communication between the interacting parties. The information most relevant and useful to both people emerges when the relationship promotes communication and respect. Conversely, even skillfully formulated questions do not yield useful information if the interaction between the conversing parties is tense, rushed, hostile, or judgmental.

## WHOM TO INTERVIEW

During adolescence, a transition from dependence to independence should be made by the teenager and facilitated by the parents. In early adolescence, the parents are still largely responsible for their teen’s health care, although by late adolescence, these patients are often managing their own medical needs completely. These changes occur over a relatively brief period; therefore, the physician is faced with assessing the stage of transition toward independence each time the adolescent patient is seen. Whom to interview should be decided in the context of this transition, and the following factors need to be considered.

## ADOLESCENT’S DEVELOPMENTAL LEVEL

Nothing is more upsetting to adolescents than feeling that they are being treated as younger children. This perception is a particular problem in early adolescence, when a teen’s lack of sexual maturation can cause insensitive adults to underestimate the youth’s psychological age. Adolescent patients are often sensitive to the atmosphere of the primary care professional’s office that emphasizes the interests of the young child. Therefore the physician should arrange the office waiting room with a section that contains reading material and decor appropriate for adolescent patients. At least 1 examining room should be equipped and decorated with the adolescent patient in mind. The hospital ward should also have a section furnished and decorated specifically for adolescent patients, and an interviewing room to be used exclusively for teens should be available.

The need for privacy during the interview is never more important than in the practice of adolescent medicine. If the adolescent thinks that the conversation will be interrupted or overheard, then important information may not be revealed. Privacy may be particularly difficult to find on the hospital ward or in the emergency department, but every effort should be made to achieve it.

The interview room should be arranged with the physician, the patient, and the parents seated at the same level, at comfortable conversational distances, and without desks between the professional and the other person or persons to whom the professional is speaking. The few moments needed to rearrange the furniture to meet these requirements are well spent.

### ESTABLISHING RAPPORT

Establishing rapport with an adolescent can be difficult; therefore, the physician should take a genuine interest in the adolescent from the beginning of the interview. Establishing a collaborative partnership with the adolescent patient is important to building trust and setting the stage for developing an effective therapeutic relationship. Greeting the adolescent patient before greeting the parent or guardian is best. Asking the patient to introduce the others in the room can be helpful. The adolescent is then given the message that the primary focus is on the adolescent and that he or she is the expert about the other people in the room. Also helpful is to chat informally with the adolescent patient briefly before the interview begins, being careful to gear the conversation to the appropriate developmental level for that patient. To accomplish this task, the physician should know enough about normal adolescent development to judge the appropriateness of this preinterview conversation. This initial conversation with the adolescent patient can help establish rapport and possibly relieve anxiety the patient may have about the visit.

### PARENTS' ROLE

Although creating an environment in which the adolescent feels comfortable is essential, the physician should not ignore the importance of the parents' role. In early and middle adolescence, the parents' input is critical for a thorough evaluation because adolescents may have limited insight about themselves or inadequate perspective on the timing and importance of symptoms. Adolescents may not be familiar with their own perinatal and birth history, developmental history, previous illnesses, hospitalizations, surgeries, allergies, medications, immunizations, and family history. A portion of the interview conducted with the parent present may help elicit important health history information while giving the adolescent the opportunity to hear and learn about these important aspects of his or her own medical history. Interviewing the patient and parent together initially also gives insight into family dynamics and interaction.

Confidentiality issues should be addressed with both the adolescent patient and the parents before sensitive topics are discussed. The physician should also explain that the adolescent will be interviewed alone for part of the medical history and that the

adolescent may have the physical examination conducted without the parents to ensure confidentiality. Confidentiality and the limits of confidentiality based on state laws or physician comfort should be made clear to the adolescent and the family. The physician should be aware of the particular state's laws regarding the adolescent's rights to confidential evaluation, and these rights must be respected. State-specific guidelines are available from the American Medical Association and the National Center for Adolescent Health and Law. For more information on confidentiality laws by state, see *State Minor Consent Laws: A Summary*, available from the Center for Adolescent Health and Law, or visit their Web site at [www.cahl.org](http://www.cahl.org).

Although adolescents' independence should be encouraged and time should always be set aside for the adolescent to see the physician alone, the appropriate role of the parents should not be ignored. Because of adolescents' possible limited perspective and their need for emotional and financial support, the physician would be wise in most cases to encourage younger adolescents to involve their parents in their medical decision making. When parents are involved, allowing them time to discuss their concerns *without* their child present may also be helpful because they may be reluctant to discuss some concerns in front of their child, such as parental conflict or mental health issues.

### PHYSICIAN NEUTRALITY

If significant disagreements exist between an adolescent and his or her parents, then the physician must avoid the appearance of taking sides on these issues. This task can best be accomplished by interviewing the adolescent and parents together and concentrating on understanding and clarifying their disagreements, thus conveying an appropriately neutral attitude about the conflict. The following vignette illustrates this technique. The evaluation was initiated by the parents, who were concerned that their 15-year-old son had behavioral problems.

Mr. Jones: We think his choice of friends leaves a lot to be desired.

Jim: What's the matter with my friends?

Mr. Jones: Most of them have no ambition. They don't care about school and spend their time just hanging around.

Jim: It's just that we're not like you. You don't care about anything except work. At least my friends know how to have fun.

Physician: Jim, you think your father devotes too much time to work.

Jim: Yeah.

Physician: And, Mr. Jones, you wish Jim were more ambitious and that he would pick friends who are ambitious too.

Mr. Jones: Yes. I worry that Jim isn't going to succeed.

Jim (to his father): I'll succeed in my own way.

Physician: What are your ideas about success, Jim?

In this interaction, the physician has facilitated communication between the father and son by using

reflections and open-ended questions without stating an opinion that would seem to commit to either person's point of view. A review of these issues before the interview helps the physician make a reasonable decision about whom to interview first; no rigid rules apply. The choice depends on the age of the adolescent patient, the person who initiates the contact, and whether conflict exists between the adolescent and parents regarding the problem.

## INTERVIEWING TECHNIQUE

The key to good interviewing is building a trusting relationship among the physician, patient, and parents. This can be accomplished if the physician makes an effort to understand how the adolescent patient perceives the problem and relationships with important people in his or her life. Most health professionals would say that they attempt to understand their patients. However, physicians can often become involved in their own agenda of asking questions and obtaining answers to specific medical questions, and thus miss important clues about their patients' feelings and perspectives. The following vignette illustrates the insensitivity that results when medical issues are pursued vigorously and when the physician becomes more interested in the answers than in establishing a therapeutic relationship. The patient is a 16-year-old girl who has diabetes.

Physician: How much insulin do you take?

Sarah: 16 units of NPH and 4 units of regular each morning.

Physician: Do you test your urine?

Sarah: Yeah.

Physician: How often?

Sarah: Every morning and in the late afternoon, when my mother doesn't bug me.

Physician: Do you ever spill sugar?

Sarah: Sometimes; not too often.

Physician: How much? 1 plus, 2 plus?

Sarah: Just 1 plus a couple of times a week. Mom's always asking me that, but I tell her to leave me alone.

Physician: Do you ever have insulin reactions?

Sarah: Not for a long time.

Physician: How's school?

The casual observer can sense the physician's urgency to "fill in the blanks" of the medical history and that a rushed demanding of information is taking place, illustrated by the series of closed-ended questions asked of the patient without eliciting more elaboration. In the process, this physician has failed to pick up the clues of the mother-daughter conflict. The physician completed the agenda and then turned to a question about the adolescent's life that will probably be perceived by the patient as a mechanical question because the physician did not *hear* the previous comments.

Report can be better established by using techniques to further open communication based on motivational interviewing. These strategies include using open-ended questions, affirmations, reflections, and summaries (the mnemonic is *OARS*). Open-ended questions encourage adolescents to voice their

thoughts or concerns and avoid the feeling of being interrogated by numerous closed-ended questions asked in a row. Affirmations are statements of appreciation of patient strengths or past efforts. Some affirmations show support for patients' sharing information, such as, "I really appreciate that you are able to share that information with me" and "That sounds like a really difficult time for you. I'm impressed that you have taken care of yourself so well." Reflections indicate to adolescents that their perspective is being understood. They can be a simple restatement of what the adolescent has said, or they can be made more complex by extending the meaning of the words or emotions that the adolescent has used. Summaries are often helpful to clarify the problem and pull together the discussion, and they can often help encourage the adolescent to make additional comments.

One strategy to identify salient sources of affirmations is to ask every adolescent to tell the physician about a special attribute by saying "Tell me something about yourself that is special or unique." Explore this fully with open-ended questions and reflections and document this in the chart. The "special attribute" may be as simple as being on the honor roll, excelling at track, helping a parent care for younger siblings, volunteering in the community, or, for an adolescent patient with special health care needs, having academic success in some area. Giving back this information in the form of an affirmation both establishes rapport by helping adolescents feel they are appreciated by the physician and helps adolescents feel good about themselves.

Several problems can arise during the adolescent interview. Adolescents may disclose sensitive issues that they do not feel comfortable sharing with their parents. When this occurs, the physician should help the adolescent identify, when possible, other trusted adults in the adolescent's life (eg, family member, coach, or teacher) who can support the adolescent and be a sounding board for the adolescent to discuss these issues. Rarely, parents may ask for confidential information about their son or daughter, such as whether or not they are using drugs or having sex, or they may request a drug test without their adolescent's knowledge. These issues can be addressed by first having discussions with parents and adolescents about confidentiality early at the first adolescent visit and, when the request for confidential information arises later, to reiterate the limits of confidentiality and when this can and cannot be breached. Often the sharing of confidential information or performing of a drug test can be negotiated with the adolescent who will agree to limited sharing of some information or will agree to a drug test in order to "get the parents off my back" without needing to breach confidentiality and injure the therapeutic relationship between the physician and the adolescent.

Techniques that promote the acquisition of useful information fall into 2 main categories: listening skills and facilitative responses (see interviewing techniques in Chapter 46, Effective Communication Strategies; and Chapter 13, Pediatric History: Assessing the Child). Component aspects of these techniques, discussed briefly in the next 2 sections, are outlined in Box 119-1.



**BOX 119-1 Interview Techniques**

- Listening skills
- Clarification of meaning
- Verbal asides
- Nonverbal communication
- Facilitative responses
- Repetition and review
- Acknowledgment of feelings
- Periods of silence

**Listening Skills**

Unless physicians pay attention to the meaning of words, they often think that they understand the patient's perspective when they really do not. Every time patients use words that are abstract or unclear, physicians should ask for clarification by using open-ended questions or reflections. Skilled interviewers continually ask themselves if they understand what has just been said. In the following vignette, the importance of this technique is illustrated. The patient is a 15-year-old boy who has problems with school.

Nurse Practitioner: Your parents seem concerned about how you are doing in school. What do you think?

Dave: Sometimes I think I'm a wreck.

NP: A wreck?

Dave: Yeah, you know, like I'm a mess.

NP: I don't know, Dave. What does that feel like?

Dave: Like I get these funny feelings, and I think I'm falling apart.

NP: Tell me about one of these funny feelings.

Dave: Well ... sometimes it's like my fingers are growing really big, or small. It's weird.

NP: You mean like parts of your body are changing size?

Dave: Yeah.

NP: What else?

Dave: Sometimes I feel like I'm walking just a little off the ground, like I am floating.

If the nurse practitioner did not pursue the meaning of Dave's words, she might have been left with the vague statement that Dave thinks he is a *wreck*, which many people would assume means that he thinks he is a failure. Instead, the physician now has evidence that Dave is experiencing somatic symptoms of anxiety or psychotic thinking and can pursue the source of these feelings.

Verbal asides are parenthetical statements that often reveal the patient's true feelings but that are stated as though they are unimportant. They usually reflect the adolescent's ambivalence about exposing real feelings. The patient with diabetes described earlier, who said that she tested her urine twice a day "when my mother doesn't bug me," is giving a verbal aside. Statements about her mother constitute unsolicited and important information. Physicians often focus

only on the solicited information and therefore fail to hear such asides. All that is usually required to facilitate further communication is to echo the phrase back to the patient in a simple or complex reflection followed by an open-ended question such as, "It sounds like you are annoyed at your mom. What do you mean when you said she bugs you? Tell me more about that."

Nonverbal communication consists of body movements and facial expressions that reveal a person's feelings. A physician who is preoccupied with asking the right questions, accumulating the answers, and documenting them on the record will miss these important clues. The skilled interviewer learns to divide attention between the words that are being said and the body language of the person being interviewed. Because body language usually is outside the patient's awareness, commenting immediately on such observations may be premature, which may impart discomfort or anxiety on the patient. Part of the art of interviewing is to sense when such comments may be useful. A good rule to remember is that when body language reveals something that the person seems to be trying to hide, it should be left alone. For example, a person's clenched fists may indicate tension when the patient's words suggest calm. However, when a facial expression suggests an inner thought or feeling, then commenting is often useful by using a reflection of emotion. The patient may say something funny, for example, and then seem sad. In this instance, saying something such as, "It looks as if that thought suddenly made you feel sad" is often helpful.

**Facilitative Responses**

The person who is talking usually feels good when the listener can synthesize what the speaker has just said into a summary that reflects the speaker's thoughts accurately. If, for example, the patient has had difficulty finding the right words to describe symptoms and the physician then restates these symptoms briefly and accurately, then the patient realizes that the professional heard what the patient has been experiencing. People like to be understood, and this type of repetition and review using summaries greatly facilitates further communication.

An important component of repetition and review is the acknowledgment of feelings, as well as the recognition of facts and meaning. In many instances, patients make a series of statements that are really meant to build a case for the underlying feelings they are experiencing. If the physician can hear and then acknowledge these feelings with a reflection of emotion or meaning, then the relationship may be significantly enhanced. The following segment of an interview illustrates this interaction. The patient is a 13-year-old girl brought in by her parents because of acting-out behavior.

Physician: Your parents are upset over some of the things you have done. What do you think?

Jen: They really bug me. Last week, Mom wouldn't let me go to the mall with my friends. She said that we were too young to go by ourselves; but all of my friends' parents let them go. Then, a couple of nights



ago, I wanted to stay at Katie's house for dinner, and Dad made me come home. He said that it's getting too dark at night. You'd think I was a baby!

Physician: You don't feel that your parents trust you.

Jen: I know they don't trust me. It makes me feel like doing whatever I want, since they don't trust me anyway.

Physician: It makes you angry that they don't give you more freedom.

Another important facilitative response is the carefully timed use of silences, or pauses. This tactic is particularly important when the patient has difficulty with self-expression. Physicians are usually highly verbal people and respond to such patients by asking more and more questions. When a question has been asked and the response is not immediate, the interviewer should look closely for cues that the patient is processing the question. If the patient seems to be thinking about the answer, then the physician should pause to allow a response. Further statements might include facilitative responses, such as, "What thoughts are you having?" or "It's hard, sometimes, to find the right words." Such replies tend to encourage the response. Similarly, the periods of silence should not be so long that the patient is made to feel uncomfortable. In psychiatric interviews, long silences are sometimes used purposefully; however, this approach would be too threatening for most medical interviews, especially with younger adolescents. Instead, the suggested approach is to allow time for the person whose verbal responses are slow.

## APPROACHING THE SENSITIVE ISSUES OF DRUGS, SEX, AND EMOTIONAL PROBLEMS

Vital issues in adolescent medicine include a healthy response to emerging sexuality and avoidance of addiction to drugs or alcohol. Physicians should address these issues from the perspective of prevention. This approach requires inquiring about these topics throughout the period of adolescent development. However, adolescents and physicians often feel uncomfortable with these issues. Questions about sexual activity, the use of drugs and alcohol, and the possibility of serious emotional problems often seem intrusive and embarrassing. Reassuring the adolescent again about confidentiality is important at this stage of the medical interview. In addition, a useful way to begin the discussion is to explain to the adolescent why these questions are being asked—for example, "I am asking you these questions to help me find out if there is anything that may be putting your health at risk and to tell me what kind of exam and tests I should do."

A tool for assessing the psychosocial history in adolescents is known by the acronym HEEADSSS, used to address issues of home, education or employment, eating, activities in the peer group, drugs, sexuality, suicide or depression, and safety. The HEEADSSS assessment was developed in 1972, refined in 1988, and then updated in 2004. Examples of HEEADSSS questions are summarized in Table 119-1.

Providing an anonymous questionnaire for the adolescent to fill out is another method to help facilitate questioning on more sensitive issues. Such questionnaires usually begin with questions that are medical, such as questions about the adolescent's perception of his or her own weight, skin condition, and development of secondary sexual characteristics. Such questionnaires should include a review of systems with questions about the major organ systems, psychiatric issues, and general complaints such as fatigue and change in appetite. Questions may then move to more sensitive areas such as sexual orientation and activity, use of alcohol and drugs, and exposure to violence and abuse. Questions should also address mental health problems such as feelings of depression, suicidal thoughts, and symptoms of anxiety. The questionnaire should also ask about school performance, including possible problems with teachers or peers. The physician can then use the questionnaire to address issues that are pertinent to the adolescent at the visit. For example, if the adolescent indicates sexual activity is occurring, then the physician can address issues of preventing pregnancy and sexually transmitted infections. If the patient is not sexually active, then the physician can emphasize making informed choices about abstinence and sexual activity in the future. However, a questionnaire should not be a substitute for addressing these issues in person and conducting a thorough history. The questionnaire can be a helpful tool to open up conversation; but questions unanswered or answered as no problem should be addressed during the interview, because problems may be revealed that the adolescent was uncomfortable writing down, especially related to sexuality, substance use, sexual or physical abuse, and mental illness.

When addressing the issue of sexuality with adolescents, care must be taken to avoid making assumptions regarding their sexual orientation. Such assumptions may dissuade adolescents from discussing important medical problems related to their sexual health. The use of gender-neutral terms such as *partner* can keep communication open for discussion of same-gendered attractions. One way of opening a conversation about sexual orientation is to ask, "Many people have sexual experiences with members of the same sex at some point in their lives. Have you had any experiences with other men [women]?" This question can be followed up with questioning regarding whether adolescents consider themselves attracted to men, women, or both, or if they are unsure. The physician should recognize that people who have sex with those of the same gender may not consider themselves to be homosexual. In addition, the physician should be aware that a person's sexual orientation may change throughout the person's life and that adolescents can go through periods of confusion in which they may be unsure or questioning of their sexual orientation. For further information on this subject, refer to Chapter 76, Lesbian, Gay, and Bisexual Youth.

Another helpful approach, especially in addressing issues of drug and alcohol use, is to precede any direct questions about such use with indirect normative statements about the possible use of such substances

Table 119-1	The HEEADSSS Interview
TOPIC	SAMPLE QUESTIONS
Home	<ul style="list-style-type: none"> <li>• Who lives with you at home?</li> <li>• Where do you live? Do you live in a house or apartment? Tell me about your living situation.</li> <li>• Do you share a room or have your own?</li> <li>• Do any new people live in your home?</li> <li>• How are your relationships with parents, siblings, other important relatives?</li> <li>• What are the rules like at home?</li> <li>□ Have you ever been homeless or in shelter care?</li> </ul>
Education	<ul style="list-style-type: none"> <li>□ Have you ever been in foster care or a residential group home?</li> <li>• What school do you go to? What is your grade level?</li> <li>• Are you in gifted, regular, or special education classes?</li> <li>• How do you do in school in terms of grades?</li> <li>• What are your best and worst subjects?</li> <li>• In the last year, how many days of school have you missed? Why?</li> <li>□ Have you ever had to repeat a year of school? Why?</li> <li>□ Have you ever been suspended? Why?</li> <li>▲ What are your educational goals?</li> <li>▲ How connected do you feel to your school? Do you feel as if you belong?</li> <li>▲ Which adults at school do you feel you could talk to about something important?</li> </ul>
Employment	<ul style="list-style-type: none"> <li>• Do you work after school?</li> <li>• What type of work do you do?</li> <li>• How many hours a week do you work?</li> <li>• What are your future career goals? What do you want to do when you grow up in terms of a job?</li> </ul>
Eating	<ul style="list-style-type: none"> <li>□ Do you have any home chores? Do you get an allowance?</li> <li>• How do you feel about your weight? Do you want to weigh more or less or stay the same?</li> <li>• What do you think your ideal or perfect weight should be?</li> <li>• How many meals and snacks do you eat per day?</li> <li>• Tell me what you would eat in a typical day.</li> <li>□ Do you ever skip meals? Why? How often?</li> <li>□ How do you control your weight? With exercise, vomiting, diuretics, laxatives?</li> <li>□ How often do you have a bowel movement? Do you have any problems with your bowel movements?</li> </ul>
Activities	<ul style="list-style-type: none"> <li>▲ What would it be like if you gained (lost) 10 pounds?</li> <li>• How do you like to spend your free time? What do you like to do for fun? What do you particularly excel at?</li> <li>□ What hobbies, clubs, or church or school activities do you have?</li> <li>• What sports do you play, and how many hours a week?</li> <li>□ How many hours of television per week do you watch? How many hours a week are you on the computer (sedentary)?</li> </ul>
Drugs	<ul style="list-style-type: none"> <li>• How much time do you spend with social media such as Facebook and text messaging?</li> <li>• How many of the people with whom you hang out smoke cigarettes, drink alcohol, or use drugs?</li> <li>• How do drinking, smoking, and drugs fit in with your life?</li> <li>• Do you smoke or chew tobacco?</li> <li>• Do you drink alcohol? What kind? Beer, wine, wine coolers, hard liquor?</li> <li>• How often do you use tobacco, alcohol, or drugs? How much and how often?</li> <li>□ Have you ever blacked out or passed out?</li> <li>□ Have you ever done anything you regretted while drunk or high?</li> <li>□ When do you most often use alcohol or drugs? Socially? Alone? Time of day? Day of week?</li> <li>□ How do you feel about cutting back or quitting?</li> <li>• What other drugs have you used or tried? Marijuana, inhalants, cocaine or crack, heroin, pills, LSD, ecstasy, crystal meth, or other drugs?</li> <li>• Do you use anabolic steroids?</li> <li>▲ Have you ever received drug treatment or counseling?</li> <li>▲ How do you support your alcohol or drug use? Have you ever had any arrests?</li> </ul>

**Table 119-1**     **The HEEADSSS Interview—cont'd**

TOPIC	SAMPLE QUESTIONS
Depression and suicidality	<ul style="list-style-type: none"> <li>• How do you usually feel: happy, sad, or a bit of both?</li> <li>• What makes you feel stressed?</li> <li>• What do you do to relieve stress? How do you cope?</li> <li>• Have you ever thought about trying to hurt or kill yourself?</li> <li>□ Have you ever tried to hurt or kill yourself? What did you do? Whom did you tell?</li> <li>□ Have you ever gotten counseling or therapy?</li> </ul>
Sexuality	<ul style="list-style-type: none"> <li>▲ Have you ever been in a psychiatric hospital? Why? How long did you stay?</li> </ul> <p>For female adolescents:</p> <ul style="list-style-type: none"> <li>• How old were you when you started your menstrual periods?</li> <li>• How often do you have a period?</li> <li>• How long are your periods, and how heavy is your flow?</li> <li>• Do you have menstrual cramps?</li> <li>• How often do you miss school because of cramps?</li> </ul> <p>For all adolescents:</p> <ul style="list-style-type: none"> <li>□ When you think of people to whom you are attracted, are they guys, girls, both, neither, or are you not sure? How comfortable are you with your feelings?</li> <li>□ When you think of yourself as a person, do you think of yourself as male, female, neither, or both? How comfortable are you with your feelings of who you are, in terms of gender, on the inside?</li> <li>• Have you ever had the kind of sex in which [add specific type of contact: penis in vagina, mouth on penis, mouth on vagina, penis in rectum, etc]?</li> <li>• How old were you when you first [describe sexual contact]?</li> <li>• How often do you have pain during sexual intercourse or other sexual activities?</li> <li>• How satisfied are you with how often you have sexual relations, and with what you do with your sexual partner?</li> <li>□ Do you have any problems becoming aroused, getting an erection, getting lubricated (wet), or having an orgasm?</li> <li>□ Have you ever been pregnant or gotten someone pregnant? What concerns do you have about being able to get pregnant or get someone else pregnant?</li> <li>□ What have you used in the past to prevent pregnancy? What are you using now? For methods that you stopped, why did you stop them?</li> <li>□ How many people have you had sexual relationships with in your lifetime? What about the last 3 months?</li> <li>□ Have you ever had a sexually transmitted infection such as gonorrhea, <i>Chlamydia</i>, trichomonas, herpes, or warts? What concerns do you have about sexually transmitted infections?</li> <li>□ Have you ever exchanged sex for drugs, money, food, or a place to stay?</li> <li>□ Have you ever sent nude or partially nude pictures of yourself or someone else via cellphone or over the Internet?</li> </ul>
Safety	<ul style="list-style-type: none"> <li>• Have you ever been forced to have sex or been touched in a sexual way against your will? By whom, and is this still going on?</li> <li>• In what ways does that experience affect your day-to-day life?</li> <li>• In what ways does that experience affect your sexual relationships now?</li> <li>• How often do you wear protective sports gear when you play sports?</li> <li>• Have you ever been a victim of violence in your home, neighborhood, or school?</li> <li>• Have you ever been bullied in your neighborhood, school, or anywhere else in your life?</li> <li>• Do you have access to weapons? Is there a gun in your home?</li> <li>□ Do you ever ride in a stolen car, in a car with a drunk driver, in a car late at night?</li> <li>□ Do you use a cell phone or text while you are driving? If so, how often?</li> <li>□ Do you use sunscreen when in the sun?</li> </ul>
Spirituality	<ul style="list-style-type: none"> <li>• What do you consider to be your religion?</li> <li>▲ How often do you participate in religious activities?</li> <li>▲ How important are your spiritual beliefs in your day-to-day life?</li> <li>• How do your beliefs influence your health and attitudes about drug and alcohol use, sex, and contraception?</li> </ul>

• = essential questions   □ = as time permits   ▲ = when situation requires

by others. The following vignette illustrates this approach. The patient is a 15-year-old boy.

Nurse Practitioner: Sometimes kids your age try alcohol, like beer, wine, or mixed drinks, when they're at parties or hanging out together. Have you ever had anything with alcohol?

Justin: Yeah, like, a couple of times.

NP: What was it like?

Justin: Once I was with a friend who was driving and I thought he was, like, kind of crazy. I was really afraid he might get us in an accident.

NP: Was there anything you felt you could do to protect yourself?

Justin: Well, no, but I sure wish there was.

NP: How about yourself? Did you ever feel you drank too much?

Justin: Well, yeah, once I woke up the next day and I couldn't remember anything that happened.

These responses would probably not have been forthcoming had the nurse practitioner asked directly, "Do you drink alcohol or take drugs?" The indirect approach is face saving and is therefore likely to yield more truthful information. The nurse practitioner can now offer more targeted advice. The importance of possible drug or alcohol abuse has also led to screening questionnaires that may be helpful in a population of adolescents at particularly high risk for abuse. Such questionnaires usually assume some alcohol or drug use and are designed to measure the severity of that use and indicate when a referral might be needed. One such method of assessing the severity of drug and alcohol use is the CRAFFT questions outlined in Box 119-2.

## SUMMARY

The interviewing techniques described provide some suggestions for the physician who provides care to adolescents. Effective interviewing requires practice.

### BOX 119-2 CRAFFT Questions

C - Have you ever ridden in a **CAR** driven by someone (including yourself) who was "high" or had been using alcohol or drugs?

R - Do you ever use alcohol or drugs to **RELAX**, feel better about yourself, or fit in?

A - Do you ever use alcohol/drugs while you are by yourself, or **ALONE**?

F - Do you ever **FORGET** things you did while using alcohol or drugs?

F - Do your **FAMILY** or **FRIENDS** ever tell you that you should cut down on your drinking or drug use?

T - Have you gotten into **TROUBLE** while you were using alcohol or drugs?

Two or more YES answers on the CRAFFT suggest a serious problem and need further assessment.

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However, the skill is well worth learning because it leads to the completion of better medical and psychosocial histories and improved patient compliance. The result is improved health care for adolescents and their families.

*The authors acknowledge the substantive contributions of Esther Wender and Susan Coupey in authoring the previous versions of this chapter.*

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Helping Teens Stay Healthy and Safe: Health Care, Birth Control, and Confidential Services* (brochure), Center for Adolescent Health and the Law ([www.cahl.org/helping-teens-stay-healthy-and-safe-health-care-birth-control-and-confidential-services-2007](http://www.cahl.org/helping-teens-stay-healthy-and-safe-health-care-birth-control-and-confidential-services-2007))
- *For Today's Teen: A Message From Your Pediatrician* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Teen* (Web page), American Academy of Pediatrics ([www.healthychildren.org/english/ages-stages/teen/Pages/default.aspx](http://www.healthychildren.org/english/ages-stages/teen/Pages/default.aspx))
- *What Is an Adolescent Health Specialist?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-an-Adolescent-Health-Specialist.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-an-Adolescent-Health-Specialist.aspx))
- *Information for Teens: What You Need to Know About Privacy* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/teen/Pages/Information-for-Teens-What-You-Need-to-Know-About-Privacy.aspx](http://www.healthychildren.org/English/ages-stages/teen/Pages/Information-for-Teens-What-You-Need-to-Know-About-Privacy.aspx))

### Medical Decision Support

- *HEADSS Guide* (booklet), BC Children's Hospital ([www.bcchildrens.ca/nr/rdonlyres/6e51b8a4-8b88-4d4f-a7d9-13cb9f46e1d6/11051/headss20assessment20guide1.pdf](http://www.bcchildrens.ca/nr/rdonlyres/6e51b8a4-8b88-4d4f-a7d9-13cb9f46e1d6/11051/headss20assessment20guide1.pdf))
- *Sample HEADSSS Questions (Long Form)* (questionnaire), Minnesota Department of Health ([www.health.state.mn.us/youth/providers/headsslong.html](http://www.health.state.mn.us/youth/providers/headsslong.html))
- *Pediatric Intake Form*, Bright Futures ([www.brightfutures.org/mentalhealth/pdf/professionals/ped\\_intake\\_form.pdf](http://www.brightfutures.org/mentalhealth/pdf/professionals/ped_intake_form.pdf))
- *The CRAFFT Screening Tool* (questionnaire), Center for Adolescent Substance Abuse Research ([www.ceasar-boston.org/CRAFFT/index.php](http://www.ceasar-boston.org/CRAFFT/index.php))
- *Implementing Mental Health Priorities in Practice* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/implementing\\_mental\\_health\\_priorities\\_in\\_practice.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/implementing_mental_health_priorities_in_practice.aspx))

## AAP POLICY

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## Chapter 120

# COUNSELING PARENTS OF ADOLESCENTS

Jonathan D. Klein, MD, MPH

Adolescence is characterized by dramatic, often uneven, integration of developmental changes into the daily lives of young people. Teenagers simultaneously experience changing body image, mood swings, burgeoning sexuality, intense need for peer acceptance, increasing independence from family, expectations to achieve, pressure to “act maturely,” and fragile egos. At the conclusion of adolescent development, the emerging young adult is expected to comprehend the nuances of complex issues, arrive at decisions, have developed an ethical and moral value system, prepare for a chosen field of work, and be capable of intimacy. These tasks begin and are realized within family units. Parents often view their pediatrician as a person from whom to seek advice about both physiologic and behavioral issues. The pediatrician’s ongoing relationship with families allows ample opportunity to provide anticipatory guidance and to support parents as their children enter and move through adolescence.

Autonomy and independence evolve over the adolescent years, usually progressing from and within an environment of continuous connectedness to parents and family. This process rarely leads to adolescents achieving independence through a sudden break with their parents; rather, the process is a gradual redefinition of relationships eventually leading to a state of adult interdependence. The adolescent years are one phase of this developmental continuum, as young people continually renegotiate their place within their families. Experimentation and risk-taking behaviors are often perceived negatively, as something to be avoided. Nonetheless, some risks, such as those faced by athletes, performers, or peer leaders, have positive development effects, enhancing self-esteem and leading to competence and mastery. Most adolescents need to experience the tension created by experimenting with ideas and lifestyles that contrast with those of their family. However, during this time of *trying on* diverse personalities, the adolescent also needs to know that return to the safety and refuge of the family is assured.

A parent or guardian’s greatest challenge is to maintain the delicate balance between fostering their adolescent’s independent behavior and supporting the adolescent’s need for trust and security within their family. The tension created by adolescents’ experimentation with ideas and behaviors can be a source of conflict and emotional distress to both parents and young people. Parents may feel a loss of control provoked by the young person’s independent behavior; and adolescents may experience discomfort from feelings of loss of childhood security, as the young person struggles to cope with greater freedom and responsibility. This emotional conflict and pain are often unrecognized and unarticulated; yet these issues underlie many common confrontations between parents and adolescents. Helping parents understand the developmental basis for this conflict may reduce their frustration, as does acknowledging and empathizing with parents about the emotional separation, which may be more painful for them than it is for their adolescent.

## PARENTING GOALS

Pediatricians can help parents navigate their children’s adolescence, beginning with providing parents information about the physical, cognitive, and psychosocial developmental tasks of adolescence and with helping parents realize that adolescent development is a variable process. Parenting styles may be described as authoritarian, authoritative, permissive, or uninvolved. *Authoritarian* parents are demanding and directive, expecting their orders to be obeyed without explanation. *Authoritative* parents are both demanding and responsive, monitoring and communicating standards for children’s conduct and expecting their children to learn self-regulation of behavior. *Permissive* parents do not require or expect mature behavior and generally avoid confrontation. *Uninvolved* parents are neither responsive nor demanding, and they may be neglectful. Although both authoritarian and authoritative parenting styles have been shown to lead to equally good social and vocational outcomes, the former style is often associated with much greater conflict and turmoil for all family members. Parents

should be encouraged to set clear expectations for their adolescents; however, parents should also be encouraged to communicate with their adolescents with 2 major goals. The first goal is to promote communication and resolution of conflict through mutual respect. Parents should maintain the adolescent's trust in the family by speaking respectfully to their child and ensuring that their child speaks respectfully to them. The second goal for parents is to be able to tolerate the adolescent's expression of differing views. When parents can demonstrate this ability and are able to avoid being provoked, the teenager's perception of parental support is heightened, and the adolescent's ego is nurtured. In this way, parents become leaders in a process in which collaboration and mutuality are affirmed, and the ultimate goal of interdependent adult partnership can be achieved.

## PARENT-ADOLESCENT COMMUNICATION

Open communication is probably the most important skill for parents to develop and maintain with their maturing child (Box 120-1). Adolescents need a trusted sounding board, and, as facilitators, parents should listen more than speak. When parents lecture, adolescents shut down. The axiom *actions speak louder than words* makes a more useful parental motto than *do as I say, not as I do*. This latter philosophy seems hypocritical, often diminishing the adolescent's respect for the parent. Such a situation may result in angry confrontations and weakens the parent-teen relationship.

Adolescents' need for parental affection and acceptance, plus their not yet fully developed sense of self, makes them vulnerable to perceived injustices, put-downs, and negative innuendos. Parents gain immeasurably when they respond to their adolescents' feelings with empathetic rather than intellectual responses. For example, during the teen years, peer relationships are characterized by intense emotions consistent with adolescents' egocentricity. Should a break occur in a heretofore close friendship, then the wise parent demonstrates support by empathizing with their child's hurt feelings. Statements such as, "I'm sorry that you are in such pain," "I can imagine how bad you might be feeling," or "It seems that your friend has really hurt you; do you want to talk about it?" express empathy and allow for continued discussion. Sometimes in an attempt to *make it better*, parents tend to minimize the adolescent's pain, perceiving it as "only" a short-lived adolescent

drama. They respond with statements such as, "You'll find other friends," or "Don't worry; you're young and have your whole life ahead of you." Rather than finding this approach helpful, the adolescent may feel misunderstood and may cut off communication, saying, "You just don't understand!"

If the parent did not approve of the friend, then the end of the relationship may be a source of relief for the parent. Telling a teenager to "forget about it" may represent the parent's wish, rather than the teen's. The ultimate negative scenario is a parent who adds, "I told you so!" Thoughtful parents refrain from statements that belittle the adolescent. In fact, adolescents feel devastated when berated by a parent, despite attempts to defend themselves against the hurt by false bravado or an "I don't care!" response. When parents empathize with their teenagers' emotional intensity and allow their youngsters to express emotions without restraint or embarrassment, adolescents are comforted and feel supported. This approach reinforces open communication with parents and minimizes the need for adolescents to act out their angry or hurt feelings.

Parents also have an obligation to clarify expectations, responsibilities, and privileges. However, these decisions are not made in a vacuum, and the parents of adolescents should allow teens to participate as a member of the contractual, decision-making team. The success of a contract between 2 parties requires that each person express *without dissent* what the other person wants. Also important is that both sides *gain something* from the outcome. Win-lose outcomes breed discontent and nonadherence by the person who perceives no gain. These guidelines can be useful when thinking about interactions between parents and adolescents. Open communication and decision making founded on mutual respect are skills that are best learned within a family and ensure a win-win outcome.

The consequences of breaking a contract should be discussed by all involved family members. Few parents have difficulty grounding their adolescent for nonadherence to an agreement, but many have difficulty acknowledging that they, themselves, have failed to abide by an agreement. As an example of this situation, consider a family in which the parents conceded that they nagged their daughter about not spending enough time on school work, fearing her academic failure. The parents agreed with their physician's counsel that they respect the adolescent's privacy and give her responsibility for her school work. A contract was signed by the pediatrician (as mediator), parents, and the adolescent. The terms included the adolescent's decision about the time to set aside for study and the parents' agreement to permit her to experience her decision and to avoid questioning her. If the adolescent's grades declined, then she would be grounded; if the parents continued to nag, then they agreed to be grounded, too.

### BOX 120-1 Dos and Don'ts of Parent-Adolescent Communication

- Listen more, speak less.
- Respond empathetically rather than intellectually.
- Resist saying "I told you so!"
- Clarify expectations.
- Discuss consequences.
- Allow adolescents to participate in decision-making.

## ASSESSING THE PARENT-ADOLESCENT RELATIONSHIP

Pediatricians can assess how families are coping with their adolescents' development by asking parents how parent-teen decision making is handled. Curfews and rules are good issues to discuss with parents because they are a frequent source of conflict, and also

because setting rules and expectations for safe and responsible behavior helps adolescents maintain healthy behaviors and avoid risky behaviors. Curfew decisions include safety issues (which are and should be subject to parental authority) and the issues of adolescent choice of friends and social functions (decisions which are within the adolescent's jurisdiction); thus, they are ideal for discussion of learning about shared decision making and negotiating choices. Physicians should explore whether parents are able to have open discussions with their adolescent about the young person's plans. Do the parents routinely ask about the location of the social function and travel plans? Do they easily agree on curfews with which everyone is reasonably satisfied? In the event of a disagreement, how are compromises negotiated? (See Box 120-2.) Parents should try to avoid arbitrarily rigid limits. An example of the type of statement best avoided is, "I have decided that you are to be home no later than midnight." Such unilateral decisions usually end in angry, unresolvable confrontations. Sometimes the rigidity of the curfew time is confounded by the parents' feelings about the adolescent's choice of friends or activities.

Not infrequently, parental disapproval of an adolescent's friends or activities may be the *expressed* reason for parental inflexibility about the teen's curfew. However, the *underlying* cause for concern may have more to do with the parents' fear that their adolescent might engage in unsafe sexual activity or substance use. The pediatrician might ask the parents whether they and their adolescent have been able to share their views about alcohol and drug use or about sexual activity and relationships and, if so, whether the discussion resulted in mutual understanding. The pediatrician can suggest to both parent and teen that such discussions should take place to make sure that parents have made their values and expectations clear and to encourage communication about responsible behavior and safe decision making.

Parents may also feel anxious because they fear adverse outcomes from their adolescent's behavioral choices. In particular, parents may be afraid that such behavior will become permanent or will threaten the teen's opportunity to mature into a responsible, productive adult. Knowing that extremes of adolescent behavior are generally transient and that most adolescents mature into adults whose lifestyles, values, and mores are similar to those of their families may reassure parents. However, rigid parental control may lead to greater adolescent rebellion. The adolescent's perception of parental acceptance, interest, warmth, and respect is associated positively with the adolescent's self-esteem. Nevertheless, parents should

be supported in their efforts to protect adolescents from injuries and dangerous behavior that may occur during experimental ventures.

Parents should be advised to avoid abdicating their authority. Parental limit-setting is strongly associated with less risky behavior by adolescents. Thus, parents need to be encouraged to maintain confidence in their authority to negotiate limits, particularly when true issues of safety are involved. For example, at a routine visit, in response to a question about how things were going, a mother reported that her 14-year-old son thought he no longer needed a parent. The boy silently rolled his eyes. When each person was given an opportunity to explain, the mother focused on her son's defiant behavior after they denied his request for an extended curfew to join a friend's birthday party at a downtown urban center. The pediatrician encouraged the mother to explain her main objection. She cited her fear for their son's safety, given the lateness of his planned return. At this statement, the boy blurted out: "Why didn't you just say that!" The parents' perceived loss of control undermined their authority; as a result, their son's immaturity became the focus of the confrontation. In this instance, the pediatrician facilitated a reframing of the problem to highlight the safety issues, on which both the parents and the son agreed.

## MANAGEMENT OF PARENT-ADOLESCENT CONFLICT

Some families are intuitively or purposefully flexible and reasonable, and others are able to achieve this with their pediatricians' counsel. However, some families require the intervention of a mental health professional. For example, some parents resist understanding adolescent development and have difficulty acknowledging the mutuality of parent-adolescent interactions. Instead, they chronically respond to the adolescent's point of view with "Yes . . . but," followed by a litany of the adolescent's misdeeds. Other parents are themselves immature and needy and may thus rely inappropriately on the adolescent for nurturing and support. The unmet needs of such adolescents may result in chronic acting-out behaviors, which may include poor school performance, loss of friends, somatic complaints, and, in some situations, depression or suicide attempts. For serious adjustment issues and depressive symptoms, referral to and support by mental health professionals is essential. For less serious adjustment issues, some pediatricians may choose to manage these patients by meeting with the parents to assess their willingness and capacity to understand the developmental and family communication issues and to manage change within the family. (See Chapter 46, Effective Communication Strategies.) If parents are refractory to counseling after 1 or 2 meetings, the pediatrician will be in a better position to make an appropriate mental health referral than he or she would have been at the initial visit. (See Chapter 61, Psychosocial Therapies.)

Pediatricians who counsel parents and adolescents about developing mutually satisfying working relationships can make a significant difference in these families' lives. By enhancing parents' knowledge and increasing their coping abilities, pediatricians can help parents provide a safe harbor for their adolescent

### BOX 120-2 Guidance for Parents

- P**articipate as partners with the adolescent.
- A**cknowledge your parental authority.
- R**espect each other's differences.
- E**ncourage open communication.
- N**egotiate win-win agreements.
- T**olerate the adolescent's separateness.



patients; they can also help promote appropriate development of responsibility and autonomy, as teenagers mature into adults.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Family Conflicts* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/family-dynamics/Pages/Parenting-Conflicts.aspx](http://www.healthychildren.org/English/family-life/family-dynamics/Pages/Parenting-Conflicts.aspx))
- *Teen* (Web page), American Academy of Pediatrics ([www.healthychildren.org/english/ages-stages/teen/Pages/default.aspx](http://www.healthychildren.org/english/ages-stages/teen/Pages/default.aspx))
- *What Is an Adolescent Health Specialist?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-an-Adolescent-Health-Specialist.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-an-Adolescent-Health-Specialist.aspx))
- *Information for Teens: What you Need to Know about Privacy* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/teen/Pages/Information-for-Teens-What-You-Need-to-Know-About-Privacy.aspx](http://www.healthychildren.org/English/ages-stages/teen/Pages/Information-for-Teens-What-You-Need-to-Know-About-Privacy.aspx))

#### Medical Decision Support

- *Implementing Mental Health Priorities in Practice* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/implementing\\_mental\\_health\\_priorities\\_in\\_practice.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/implementing_mental_health_priorities_in_practice.aspx))

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## Chapter 121 ADOLESCENT SEXUALITY

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Adolescent sexuality and sexual behavior are best viewed within the context of overall adolescent development. Sexuality is a multidimensional construct and includes ethical, psychological, biologic, functional, and cultural dimensions. The overt expression of sexuality

depends on the biopsychosocial environment in which the individual exists. Biologic changes at puberty prime the adolescent brain and body for reproduction, and individual and family psychodynamics influence sexual behavior. The larger sociocultural environment sets the norms for sexual behaviors and controls them through its institutions, including religious organizations, schools, government, and the media. As adolescents experiment with sexual expression, they inevitably make errors of judgment. Most such errors are minor, but many have significant health consequences.

Pediatricians and other physicians are in an ideal position to provide longitudinal sexual health care to children and adolescents as part of preventive care and to help adolescent patients maintain their sexual health (Box 121-1). Traditionally, monitoring pubertal changes and providing anticipatory guidance to adolescents and their parents regarding timing of the growth spurt or onset of menstruation have been viewed as appropriate tasks for pediatricians. However, with initiation of sexual intercourse at younger ages, pediatricians caring for teens should also be able to provide preventive care related to sexual behavior, including contraceptive counseling and prescription, screening for sexually transmitted infections (STIs), and counseling related to issues of sexual orientation and abuse. In addition, because of a high prevalence of health problems stemming from sexual behavior in the adolescent age group, pediatricians must be able to diagnose and manage conditions such as pregnancy, STIs, sexual dysfunction, and sexual victimization. As part of health maintenance, physicians can play an active role in a young adolescent's perception of healthy sexuality. The physician's role is not limited to providing direct care—schools and other community organizations can often benefit from

### BOX 121-1 Adolescent Sexuality: Role of the Pediatrician

#### ANTICIPATORY GUIDANCE

- Pubertal development
- Postponing coitus
- Safer sex practices
- Family planning
- Sexual victimization
- Genetic counseling
- Development of sexuality

#### PREVENTIVE CARE

- Screening for sexually transmitted infections (STIs)
- Prescribing contraceptives
- Providing psychological support (sexual orientation and abuse)

#### DIAGNOSIS, TREATMENT, AND REFERRAL

- STIs
- Pregnancy
- Sexual dysfunction
- Sexual victimization



the expertise of team members, who may help design sexuality education classes, pregnancy prevention programs, or HIV and AIDS prevention initiatives. This expanded societal role gives pediatricians a broader influence on adolescent sexuality than is possible within the patient-physician-family relationship.

## PUBERTAL DEVELOPMENT AND SEXUALITY

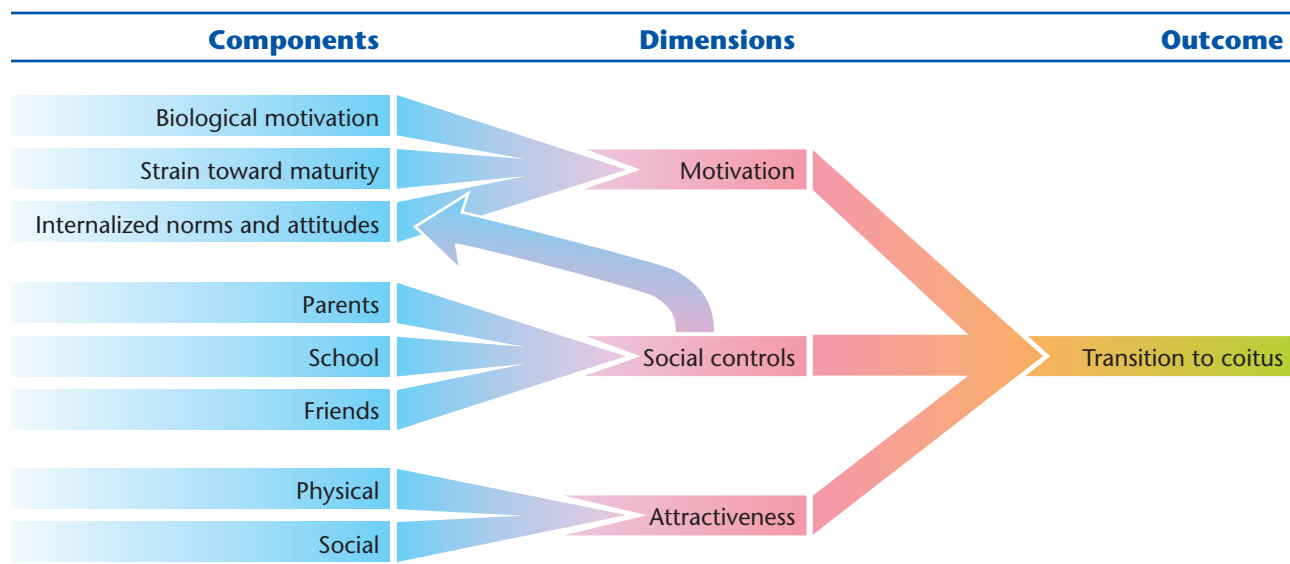
In the United States, most girls enter puberty at age 9 or 10 years, reach menarche on average at 12½ years, and achieve full fertility by age 15 or 16 years. On average, black girls reach each stage of puberty 9 months earlier than white girls. Boys begin pubertal development somewhat later than girls, at age 11 or 12 years, produce sperm (spermarche) and have their first ejaculation on average at age 13 or 14, and achieve full fertility at approximately age 16 years. Thus, by middle adolescence, most boys and girls have completed the biologic developmental requirements for reproduction.

Puberty is accompanied by a surge of hormones in both sexes. Androgenic hormones are primarily responsible for sexual motivation (libido) and pubic and axillary hair growth in both boys and girls and for the increase in muscle mass and skeletal growth in boys. Estrogenic hormones are important for skeletal growth in both sexes and for breast and uterine development and body fat redistribution in girls. (See Chapter 185, Puberty: Normal and Abnormal.) Sex hormones have a direct effect on the brain, and as their levels increase during puberty the adolescent's sexual interest is stimulated. Most adolescents report their first experience of sexual attraction occurred between ages 10 and 12, with the first sexual fantasy occurring several months to a year later. Changes in the adolescent's outward appearance signals to others in

the environment the individual's readiness for sexual intercourse (Figure 121-1). Hence girls who are early developers are at risk for early initiation of intercourse.

Social factors can either facilitate or inhibit sexual expression. Researchers who propose a biopsychosocial model have identified individual attributes correlated with adolescent sexual behavior, such as testosterone levels, physical maturation, and temperament and personality, as well as social influences such as religiosity and friends' behaviors. Differences by race and ethnicity are found for some adolescent sexual behaviors. Black and Hispanic adolescents are more likely to report early initiation of sexual intercourse than are white adolescents, and boys report sexual intercourse at an earlier age than girls. Postponing sexual initiation in girls is also associated with later pubertal development (menarche at age 13 years or later), higher parental education, 2-parent families, careful parental supervision, good communication with mother, and high educational aspirations. Sociocultural influences are less well understood for male coital behavior, and few studies have looked at factors that are associated with postponing sexual initiation in boys.

Intervention trials have shown the importance of sexual education in middle schools to prevent early initiation of sexual intercourse. A program developed by Howard and McCabe entitled *Postponing Sexual Involvement: Educational Series for Young Teens* was used with all eighth grade students in 24 Atlanta city schools and was evaluated in the mid-1980s. The evaluation found that the program was helpful to both boys and girls. By the end of the ninth grade, boys who had not had sexual intercourse before they participated in the program were significantly more likely to postpone sexual involvement than were similar boys who had not participated. The results indicate that boys do respond to educational intervention aimed at helping them control their sexual behavior. However, in this



**Figure 121-1** Conceptual model of transition to coitus in adolescence. (Modified from Udry JR. *Hormonal and social determinants of adolescent sexual initiation*. In: Bancroft J, Reisch JM, eds. *Adolescence and Puberty*. The Kinsey Institute Series. Vol. 3. New York, NY: Oxford University Press; 1990. Reproduced with permission from The Kinsey Institute for Research in Sex, Gender, and Reproduction.)

study 44% of the eighth grade boys (ages 13 and 14 years) had already initiated sexual intercourse before the program was given, and these sexually experienced boys did not benefit from the intervention. Tortolero and colleagues conducted a randomized controlled trial using a sexual education program focusing on HIV, STI, and pregnancy prevention that was taught at 5 of 10 urban middle schools in Texas, while the other 5 schools received standard health education that varied by school. The authors found that compared with schools with standard health education, the schools with the sexual education program had an overall lower prevalence of sexual initiation by ninth grade (23% vs 30%). However, girls in the schools with the sexual education program showed a significantly lower risk for initiating sexual activity (adjusted risk ratio = 1.42), whereas boys' risk for sexual initiation was not different between the intervention and control schools.

## ADOLESCENT SEXUAL BEHAVIOR

### Definitions

*Gender identity* refers to an individual's innate sense of being male or female and develops in early childhood. *Gender role* is influenced by societal and cultural norms and refers to the outward expression of the individual's sense of maleness or femaleness to the outside world. *Sexual orientation* refers to an individual's pattern of physical and emotional arousal toward others. *Sexual behavior* refers to the actual sexual acts in which an individual engages. During adolescence, sexual orientation and sexual behavior are not necessarily congruent.

### Prevalence of Sexual Intercourse

In most developed countries most youth become sexually active during their teenage years. At least 70% of

adolescents have had intercourse by the age of 19 years. Even though the mean age at which adolescents become sexually active does not vary significantly among European countries and the United States, European adolescents are less likely to have sex before age 15 years, more likely to use contraceptives, and have substantially lower pregnancy rates. However, US adolescents are waiting longer to have sex now than they did in the recent past. In 1995, 19% of girls and 21% of boys became sexually active before the age of 15 years. However, by 2006–2008 only 11% of girls and 14% of boys reported becoming sexually active before age 15 years. In addition, the use of contraceptives at first sexual intercourse has increased from 76% in 2000–2004 to 84% in 2005–2008.

Large changes in adolescent sexual behavior have occurred since the 1960s and continue to evolve. Several high-quality longitudinal data sets link sexual behavior to demographic characteristics in adolescents in the United States. These data include the National Survey of Family Growth for Females, the National Survey of Adolescent Males, the Youth Risk Behavior Survey (YRBS), and the National Longitudinal Survey of Adolescent Health (Add Health). Although findings vary somewhat among individual studies, the trends are consistent. From 1991 to 2001, as measured by the YRBS, the proportion of male and female high school students in the United States reporting any sexual intercourse fell from 54% to 46%, with the greatest drop seen among white adolescent males. From 2001 to 2013, the proportion of students reporting sexual intercourse has been unchanged at 47%. Data from the 2013 YRBS survey of US high school students are summarized in Table 121-1.

Sexual behaviors among adolescents who have made the transition to sexual intercourse have also

**Table 121-1 Sexual Behaviors Among High School Students in the United States, 2013**

INFORMATION SURVEYED	ALL (%)	BOYS (%)	GIRLS (%)
<b>EVER SEXUALLY ACTIVE</b>			
Students who have ever had sexual intercourse	46.8	47.5	46
<b>RACE-ETHNICITY</b>			
White	43.7	42.2	45.3
Black	60.6	68.4	53.4
Hispanic	49.2	51.7	46.9
<b>GRADE</b>			
Ninth grade	30	32	28.1
Twelfth grade	64.1	65.4	62.8
Students who had first sexual intercourse before age 13 years	5.6	8.3	3.1
Students who have ever been physically forced to have sexual intercourse	7.3	4.2	10.5
<b>CURRENTLY SEXUALLY ACTIVE</b>			
Students who have had sexual intercourse within the previous 3 months	34	32.7	35.2
<b>HIGH-RISK SEXUAL BEHAVIORS</b>			
Students who have had 4 or more lifetime sexual partners	15	16.8	13.2
Currently active students who used drugs or alcohol at last intercourse	22.4	25.9	19.3
<b>HEALTHY BEHAVIORS</b>			
Currently active students who used a condom at last intercourse	59.1	65.8	53.1
Students who were ever tested for HIV	12.9	11.2	14.6

Data from Kann L, Kinchen S, Shanklin SL, et al. Youth risk behavior surveillance—United States, 2013. *MMWR Surveill Summ*. 2014;63(Suppl 4):1–168.

been studied. Of adolescents who are sexually active, most practice serial monogamy; that is, they have only 1 sexual partner at a time. Nevertheless, boys and girls who begin having intercourse in early or middle adolescence will often accumulate 3 to 5 different sexual partners before they leave their teens. We do not know what percentage of young people have intercourse once or twice and then stop the behavior for months or years. Some studies indicate that younger adolescents who are unlikely to be living with a sexual partner have intercourse infrequently. For example, sexually active, 15-year-old boys report an average of nearly 8 months of the year without a sexual partner.

### Noncoital Sexual Behaviors

Recent studies indicate that noncoital sexual behaviors are practiced with increasing frequency among adolescents. In 2008, Add Health found that by the age of 18 years, more than two-thirds of US adolescents have engaged in vaginal or oral-genital sexual activity, but only about half reported both, and about 1 in 10 adolescents reported anal intercourse. In addition, one-third of the adolescents who initiated sexual intercourse initiated oral-genital and vaginal intercourse within a 1-year period, suggesting that oral-genital intercourse did not postpone initiation of vaginal intercourse for most adolescents.

In a longitudinal survey conducted in 2005 of almost 600 ninth graders in California, 20% reported having had oral sex compared with 14% reporting vaginal sex; and 32% of students intended to have oral sex in the next 6 months, whereas 26% planned to have vaginal sex. In addition, these ninth graders perceived oral sex as having significantly less risk than vaginal sex on health, social, and emotional consequences. However, oral sex has also been associated with high-risk behaviors. Prinstein and colleagues reported that adolescents who were engaged in oral sex alone had more sexual encounters, had more partners, and were less likely to use condoms compared with adolescents engaging in vaginal intercourse alone.

### Masturbation

Masturbation is a common sexual behavior in adolescents. Smith and colleagues surveyed 15- to 18-year-old Australian adolescents and found that 59% of boys and 43% of girls reported having masturbated. In a 2009 study conducted in the United States, Robbins and associates reported masturbation rates as high as 74% in males and 48% in females, and other studies show rates as high as 90% to 94% in males and 50% to 60% in females. Despite high prevalence of the behavior, masturbation is still given little attention in research, clinical settings, and sexuality education curricula.

### Homosexual Behavior

Historically, homosexual behavior was often overlooked in studies of adolescent sexuality, but current research more often documents trends in homosexual and bisexual behaviors among adolescents. Only in the past few decades have any studies of large representative populations tackled the issue of sexual orientation in adolescence. (See Chapter 76, Lesbian,

Gay, and Bisexual Youth.) Data from the 2008 National Survey of Family Growth indicated that 3% of males and 8% of females aged 18 to 19 years identify themselves as homosexual or bisexual. The 2001–2002 Add Health study found that 5% to 13% of students in grades 7 through 12 reported some degree of same-sex romantic attraction and 1% to 3% reported same-sex behaviors. In addition, of the students identifying themselves as “mostly heterosexual,” almost 6% of males and 15% females reported bisexual behavior. The 2013 YRBS found similar rates of US high school students identifying themselves as gay or lesbian (1% to 3%) and bisexual (3% to 5%).

In the past, girls were thought to develop a homosexual identity at an older age than boys, often not until young adulthood or later. In a study of 100 bisexual and lesbian young women (ages 16–23 years), who were followed for 10 years, Diamond and colleagues found that homosexual female behaviors varied over time in a nonlinear fashion; some of the young women experienced what the authors termed “an abrupt emergence of novel erotic feelings and experiences,” whereas others reported “periodic episodes of reorganization in sexual identity.” The authors found that women were more likely to report bisexual attractions than to report exclusive same-sex attractions; to show a greater capacity for change in same-sex attraction over time and across situations; and to ascribe a role for choice and circumstance in their same-sex sexuality.

### Adolescent Sexuality and the Media

Adolescents seek and receive a great deal of information about sexual behavior and sexuality from media, whether actively going to Web sites for answers to questions or passively watching sexualized programs on TV. In the United States, 95% of adolescents regularly “go online,” and 71% use more than one social networking site (SNS). The Media Practice Model suggests that the “media diet” chosen by adolescents is a reflection not only of who they think they are but also who they want to be. Studies show that social media use may have a significant effect on the social and sexual well-being of adolescents. Multiple studies found a significant relationship between viewing sex in the media and adolescent sexual behavior (including early sexual debut) as well as influence on youths’ attitudes and beliefs about sex and sexuality. Online disinhibition may lead to divulging private information more readily than in a face-to-face interaction. In addition, daring and high-risk behaviors may lead to more “likes” by the audience, thus perpetuating such behavior. In a cross-sectional study, 54% of SNS profiles were found to contain 1 or more references to a high-risk behavior such as sexual activity, substance abuse, or violence. Self-exploitative behaviors such as creation and distribution of explicit or inappropriate materials, photos, comments, and suggestions may also occur on Internet sites.

Other adolescents may participate in “sexting,” which refers to the sending, receiving, or forwarding of sexually explicit messages, photographs, images, or videos through the Internet, by cell phone,

or another digital device. In a longitudinal study, Temple and colleagues reported that 28% of their subjects had received a “sext” and 57% had been asked to send a sext. In addition, sexting increased the likelihood of high-risk sexual behaviors in female adolescents.

Despite these real concerns, digital media have afforded opportunities for the breakdown of geographic boundaries in health promotion, especially sexuality education. Web-based interventions can be tailored to the cognitive developmental stage of the target audience and can reach underserved youth more easily, especially when it comes to dissemination of sensitive information that adolescents may not feel comfortable discussing in face-to-face interactions. In a review summarizing the effectiveness of digital media-based sexual health interventions in adolescents, Guse and colleagues reported a positive attitude of adolescents toward Web-based interventions. From studies utilizing SNSs to prevent the decline of condom use among adolescents to investigators using SNSs to provide accurate and age-appropriate STI information, educators are working to take advantage of SNS popularity in adolescents. Thus, despite the potential negative consequences of digital media, SNSs can serve as valuable tools for adolescent care providers and educators. Continuing challenges include providing accurate, relevant information and ensuring confidentiality for youth.

## HEALTH CONSEQUENCES OF ADOLESCENT SEXUAL BEHAVIOR

### Sexually Transmitted Infections

Adolescents represent one-fourth of the sexually active population but account for nearly half (9.1 million) of the 18.9 million new cases of STIs each year. Young people who begin to have sexual intercourse in early or middle adolescence are more likely to develop an STI than those who postpone intercourse until later adolescence or adulthood. This is due both to anatomic and behavioral factors. Cervical ectopy, a normal feature of the anatomy of the cervix in adolescent girls, increases the risk for acquisition of STIs. For young adolescents, romantic relationships may last only a few days or weeks, and younger sexually active teens may accumulate several different sexual partners by the time they reach adulthood. Thus they are more likely to be exposed to STIs than are their peers who wait until they are older to initiate sexual intercourse and whose relationships usually last months or years. In addition, asymptomatic STIs are prevalent in both boys and girls and contribute to the spread of infections. Because of the many barriers adolescents face in obtaining routine STI screening and gynecologic care, asymptomatic infections are likely to go undetected and untreated unless or until they become symptomatic. Newer nucleic acid amplification tests that can be performed on urine specimens and do not require genital examination should help with the detection and control of asymptomatic infections.

Some STIs are associated with a high rate of permanent damage to the reproductive tract, especially for

girls. For example, salpingitis or pelvic inflammatory disease caused by *Chlamydia trachomatis* is the leading cause of acquired infertility in women. Chlamydia infection remains the most common reportable STI in the United States. The Centers for Disease Control and Prevention national surveillance data show an increase in chlamydia rates since the late 1980s, thought largely to be because of enhanced screening efforts and the availability of more sensitive testing modalities. Adolescent girls aged 15 to 19 years have the highest age-specific rate of infection, with more than 3,000 cases per 100,000. There are also racial disparities in chlamydia infection rates, with black adolescents having 6 times higher rates than white adolescents. Similar disparities exist with gonorrhea rates. For example, black adolescent males have a rate of gonorrhea that is 36 times higher than white male adolescents.

Human papillomavirus (HPV), the most common STI in adolescents, can cause cancer of the cervix, vulva, anus, penis, and oral cavity as well as genital warts; studies of adolescents report that up to one-third of sexually active girls are infected with this virus, although most are completely asymptomatic. In 2006, the American Academy of Pediatrics recommended routine vaccination with the quadrivalent HPV vaccine for all adolescent girls. In 2011, the recommendation was revised to include both male and female adolescents aged 11 to 26 years. Despite these recommendations, rates of vaccination in the United States continue to be low. In a sample of US adolescent females (ages 14-17 years) 50% of those surveyed initiated HPV vaccination and only 38% completed the vaccine series. Common factors associated with non-vaccination included parental concerns with vaccine safety and health care providers not recommending the vaccine. Data from Australia, where the vaccination rate of adolescent girls has been very high for several years, already show a reduced rate of HPV infection, and there is every expectation that with longer follow-up, a reduced rate of HPV-related cancers will be documented.

Human immunodeficiency virus infection continues to occur among adolescents, especially those in certain subgroups of the population. Factors found to be significantly associated with HIV seropositivity in adolescents include early age at sexual initiation, having older sex partners, having been sexually abused, engaging in survival sex, having sex under the influence of drugs or alcohol, using multiple drugs, having sex with casual partners, having had an STI, and engaging in male homosexual relationships.

### Unintended Pregnancy

Unintended pregnancy is one of the most socially significant issues related to adolescent sexual activity. Adolescent mothers are more likely to drop out of school, face unemployment, live in poverty, and rely on public assistance than are their peers who do not have children. The children of adolescent mothers have more health and social problems than children of adult women as well. In the United States, from 2000 to 2008, among women younger than 20 years of age, pregnancy rates declined by 19% and birth rates declined by 16%.



The Alan Guttmacher Institute reported that in 2008, for every 1,000 women aged 15 to 19 years, there were 68 pregnancies, 40 births, and 18 abortions. Part of the reduction in teen pregnancy rates in the United States can be explained by increased condom use. As shown in Table 121-1, almost 60% of sexually active high school students in 2013 used a condom at last intercourse, and this is a significant increase from the 46% using condoms in 1991. Despite the significant decline in US teen pregnancy rates from the 1990s to 2000s, the rate in the United States is still very high (68 per 1,000) compared with other developed countries such as Canada (28 per 1,000) and Sweden (31 per 1,000). The primary reasons for the high teenage pregnancy rate in the United States include less overall contraceptive use and less use of the most effective contraceptives, that is, hormonal methods. Other reasons include negative societal attitudes toward teenage sex, restricted access to reproductive health services, and ambivalence toward contraception.

### Depression and Suicide

Depression is quite common in the adolescent population, as are suicide ideation and attempts, and sexuality issues are often linked to these mental health problems. In community samples, the 6-month prevalence of depressive disorders in adolescents is 5% to 6%, with the lifetime prevalence reaching 15% to 20%. Depression is the leading risk factor for youth suicide. According to the 2011 YRBS, nationwide almost 16% of high school students had seriously considered suicide in the previous year, and 8% had made an attempt. Forced sexual activity is a risk factor for suicide, and 7% of students surveyed in the 2013 YRBS reported being physically forced to have sex (Table 121-1). In both genders, having sex before age 13, injection drug use, and being forced to have sex are associated with suicidality. Adolescents who identify themselves as gay, lesbian, or bisexual are also at high risk for suicide. In a sample of more than 2,000 high school students in San Francisco, the students who identified themselves as homosexual or bisexual had a 3.6 times greater risk for suicide attempts in the past year compared with their heterosexual peers.

### Sexual Victimization

Sexual abuse should always be considered a possibility when an adolescent has very early onset of sexual activity. Both adolescent boys and girls who have been victims of forced sex, either as young children by an adult perpetrator or as adolescents, have higher rates of health risk behaviors and mental health problems. Prevalence rates of child and adolescent sexual abuse vary in the literature depending on the definition of abuse. A telephone survey conducted in 1995 of a national household probability sample of more than 4,000 adolescents aged 12 to 17 years using a very clear and explicit definition of sexual abuse found 8% of adolescents reported being victims of sexual abuse. The survey found that a prior history of sexual abuse correlated significantly with young age at onset of voluntary sexual intercourse, unintended pregnancy, suicide attempts, drug and alcohol abuse, eating

disorders, and violence. Girls who have been sexually abused are twice as likely as those not abused to have had intercourse by age 15 years and 3 times more likely to have been pregnant. Thus it is important to explore the possibility of sexual abuse when an adolescent has very early onset of sexual intercourse or has multiple behavioral problems.

An often-overlooked subset of adolescent victims of sexual abuse are those involved in sex trafficking. Sex trafficking is defined as the recruitment, harboring, transportation, provision, or obtaining of a person for the purpose of a commercial sex act. Seventy percent of women involved in prostitution were introduced into the commercial sex industry before age 18 years. The average age at which children are being lured into commercial sex exploitation is between 11 and 14 years. The first US national level data on human trafficking became available in 2008. The US Department of Justice found that from 2008 to 2010, 40% of more than 2,500 cases of human trafficking in the United States involved minors. Adolescents from any socioeconomic background and any ethnic or racial group can become a victim of sex trafficking. However, poverty, isolation, drug addiction, violence in the family, school failures, a history of childhood sexual abuse, family dysfunction, or criminal behavior make adolescents both emotionally and economically vulnerable.

### Sexual Dysfunction

Sexual dysfunction is an area not well studied in adolescence, although the prevalence in both boys and girls is probably quite high. Clinical reports indicate that many sexually active adolescent girls do not enjoy sexual intercourse and have never reached orgasm. Reasons for engaging in the behavior have more to do with intimacy and closeness to the partner than with personal sexual gratification. Occasionally a girl who is anxious and unsure about sexual activity or who has previously been abused develops vaginismus. Large numbers of adolescent boys are thought to have premature ejaculation, but they rarely complain of the problem. Erectile dysfunction does occur in adolescence, often as a result of “performance anxiety” and other psychogenic causes. Heavy alcohol or marijuana use can be responsible for erectile dysfunction and should be explored in the medical history. Prescription medications (eg, antihypertensives, antipsychotics, and antidepressants) often are implicated in erectile dysfunction in men and anorgasmia in women. Other drugs that cause sexual dysfunction and that may be taken by adolescents are cimetidine, ranitidine, sulfasalazine, and some anticonvulsants.

## ADOLESCENT SEXUALITY AND THE PATIENT-PHYSICIAN-PARENT RELATIONSHIP

Even though sexual feelings and behaviors are of great concern to adolescents and their families and adverse effects of sexual behavior are common in this age group, most patients and parents will avoid introducing the subject at the health care visit. Pediatricians can set the stage for frank, honest discussions of

feelings and behaviors that often are embarrassing, shameful, and psychologically painful.

All physicians should pay particular attention to privacy for both adolescent patients and parents. In general, the medical interview with the adolescent should take place in private. Studies show that giving assurance of confidentiality increases the number of adolescents willing to return for future visits. Every physician should be aware of the individual state laws that exist regarding diagnosis and management of STIs, contraception, and termination of pregnancy. To give optimal care to adolescents, physicians should be open, honest, interested, concerned, and supportive and should tailor their communication style to the developmental and functional level of the adolescent. Asking questions that do not make assumptions or presuppose certain behaviors is important, given that adolescents are more likely to disclose closely guarded information when interviewed in this way. For example, if the pediatrician assumes that everyone is heterosexual and asks girls if they have a boyfriend and boys if they have a girlfriend, adolescents who are questioning their sexual orientation or who know they are homosexual will be unlikely to offer this information. If, on the other hand, the question pertains to sexual attraction to women, men, or both men and women or includes a gender-neutral term, such as sexual partner, then the adolescent is more likely to share information. Similarly, asking open-ended questions in the context of peer behavior is more likely to yield important information. Questions can begin with “Most adolescents at this age are interested in exploring . . .” or “Are you aware of anyone in your class who is involved in . . .”.

Some adolescents who have been abused are afraid to disclose painful secrets because they have not yet developed a secure, trusting relationship with the physician. The physician should understand this factor, should avoid pushing too hard and too soon for disclosure, and should explore the topic in more depth at a later visit when the relationship has had a chance to develop.

Negotiating confidentiality between adolescents and parents around sexual issues is a delicate area for the patient-physician-parent relationship. When a problem is diagnosed the specifics of what will be disclosed to parents need to be discussed in advance with the patient. For the physician to lie to parents would be unprofessional and set a bad example. However, disclosing all of the details of the situation is usually unnecessary. For example, a 16-year-old girl being seen for her annual health supervision visit reveals that she has recently become sexually active. She reports that she has had 2 partners in the last 8 months. She complains of a slight vaginal discharge. The physician discovers mucopurulent cervicitis during a pelvic examination and prescribes appropriate antibiotics. What should the mother be told? Most adolescents would agree to allow the physician to tell the mother that a pelvic examination was performed and an infection was noted that is easily treated with antibiotics. The physician can tell the adolescent beforehand that if the mother asks directly whether the infection is sexually transmitted, she will be told

that information about her daughter's sexuality is kept in confidence. However, the adolescent patient should know that the physician will encourage a dialogue between mother and daughter about sexual behavior. The physician must resist acting as a go-between in the mother-daughter relationship and should emphasize the necessity of direct communication between parent and child. At the same time, it is important to help parents communicate clearly to their adolescents about sexual issues because this may have the added benefit of making teenagers less likely to rely on peers for advice and less likely to conform to peer norms. It is the physician's role to help parents develop the skills to communicate effectively with their teenage children. Studies have shown that parent-child connectedness and clear communication about sexual issues have been associated with delay of sexual initiation.

An integral part of caring for adolescents is providing developmentally and functionally appropriate anticipatory guidance. An important point to remember is that the early adolescent still retains concrete thinking. Given the increased awareness of physical changes, these factors need to be addressed and explored during this stage. If the adolescent is not sexually active, then the adolescent should be encouraged to postpone coitus to a later stage. In middle adolescence an increase in risk-taking behaviors often occurs. Counseling at this stage should focus on safer sex practices and contraception as well as on postponing intercourse. Anticipatory guidance should also include a discussion of signs and symptoms of STIs and the need for regular screening. By late adolescence, patients should be encouraged and empowered to negotiate the health care system and make decisions regarding their reproductive health. Pregnant adolescents should be offered options counseling in a safe, nonjudgmental, and trusted environment.

## SUMMARY

Providing health care related to adolescent sexuality is one of the more difficult tasks of the primary care physician. It requires in-depth knowledge of pubertal and psychosexual development, familiarity with the norms of adolescent sexual behavior, knowledge of pertinent gynecologic and urologic medicine, and superior communication skills. Adolescents are in great need of this type of care and are very appreciative when it is done well; most adolescents want to be sexually healthy and eventually to have children and raise healthy families themselves.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Cervical Cancer—Basic Facts on Screening and the Pap Test* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/cancer/cervical/pdf/cc\\_basic.pdf](http://www.cdc.gov/cancer/cervical/pdf/cc_basic.pdf))
- *Contraception* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/reproductivehealth/UnintendedPregnancy/Contraception.htm](http://www.cdc.gov/reproductivehealth/UnintendedPregnancy/Contraception.htm))
- *Deciding to Wait* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

- *Emergency Contraception* (fact sheet), American Academy of Pediatrics (pediatrics.aappublications.org/content/130/6/1174)
- *For Today's Teens: A Message From Your Pediatrician* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Helping Teens Stay Healthy and Safe: Health Care, Birth Control, and Confidential Services* (brochure), Center for Adolescent Health and the Law (www.cahl.org/helping-teens-stay-healthy-and-safe-health-care-birth-control-and-confidential-services-2007)
- *Information for Teens: What you Need to Know About Privacy* (Web page), American Academy of Pediatrics (www.healthychildren.org/English/ages-stages/teen/Pages/Information-for-Teens-What-You-Need-to-Know-About-Privacy.aspx)
- *Making Healthy Decisions About Sex* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *National Emergency Contraception Hotline* (800-NOT-2-LATE)
- *The Pelvic Exam* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *What Is an Adolescent Health Specialist?* (fact sheet), American Academy of Pediatrics (www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-an-Adolescent-Health-Specialist.aspx)

### Medical Decision Support

- *Improving the Health of Adolescents & Young Adults* (handout), US Department of Health and Human Services (nahic.ucsf.edu/wp-content/uploads/2011/11/Complete2010Guide.pdf)
- *Pediatric Intake Form* (questionnaire), Bright Futures (www.brightfutures.org/mentalhealth/pdf/professionals/ped\_intake\_form.pdf)

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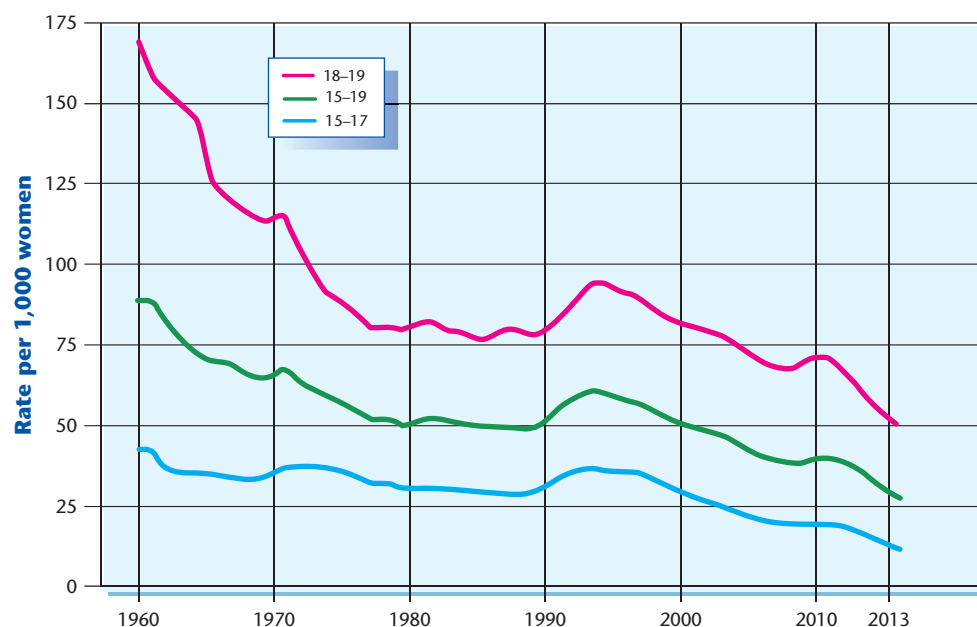
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## Chapter 122

# ADOLESCENT PREGNANCY AND PARENTHOOD

Dianne S. Elfenbein, MD; Marianne E. Felice, MD

Teenage pregnancy and parenthood are a national concern. They frequently result in societal, economic, and educational disadvantages for teen mothers and their babies. Likelihood of teen pregnancy is influenced by many factors: individual goals, societal pressure, family values, pubertal timing, age at first intercourse, risk-taking behaviors, and knowledge of contraceptive choices, among others. Although the United States has higher rates of births to teen mothers than most other industrialized nations, these figures have decreased since the late 1950s (Figure 122-1). Declines in teen birth rates have been accompanied by decreases in rates of pregnancy, induced abortion, and fetal loss.



**Figure 122-1** Birth rates for teenagers aged 15 to 19 years, by age group: United States, 1960–2013. (From Martin JA, Hamilton BE, Osterman MJK, et al. *Births: final data for 2013*. Natl Vital Stat Rep. 2015;64(1).)

From 1991 to 2013, decreases occurred in the teen birth rates of all racial and ethnic groups, with the greatest decrease for non-Hispanic black teens (67%) and Asian/Pacific Islanders (68%). Birth rates for non-Hispanic white teens dropped 57%, and rates among Hispanic teens dropped 60%. The future will tell if this trend continues.

The decrease in the rates of adolescent pregnancies and births seems to be the result of several factors, including delayed initiation of sexual activity, increased use of contraception (eg, condoms) at first coitus, and a greater efficacy of contraceptive methods. All hormonal methods remove the act of pregnancy prevention from the act of sexual intercourse and are more effective than barrier methods, spermicides, or methods based on the periodicity of the menstrual cycle. Methods such as injectable or implantable contraception and newer hormonal delivery systems such as patches and intravaginal rings do not require the need to take a pill every day, which may be difficult for young women who may not have regular life routines. Implants and intrauterine devices have been recommended as preferred contraception for teens by the American Academy of Pediatrics and the American College of Obstetrics and Gynecology.

### CHARACTERISTICS OF TEEN PARENTS

Teens growing up in conditions of poverty are known to be at the highest risk for early pregnancy. In addition, pregnancy rates differ for young women of different racial and ethnic groups; marked changes in the rates of each group have occurred over the past 40 years. Data from 2013 indicate that Hispanic teens aged 15 to 19 years have the highest birth rates of their age group (41.7 live births per 1,000), in contrast

to non-Hispanic black teens (39.0) and non-Hispanic white teens (18.6) or Asian/Pacific Islanders (8.7). More than two-thirds of all births in the age range of 15 to 19 years were to 18- to 19-year-old women. Numerically, births to women younger than 15 years represent a small proportion of overall births; however, in this age group, black mothers have consistently had the highest rate. Birth rates also vary geographically, with the highest rates of teen pregnancy in Arkansas (43.5) and New Mexico (43.3) and the lowest rate in Massachusetts (12.1) in 2013. Geographic rates generally reflect the racial, ethnic, and socioeconomic status of those living in the area.

Early childbearing is associated with educational disadvantages. Girls who become pregnant as teens are educationally behind their peers before the pregnancy, and girls with intellectual disability seem to be at particularly high risk for pregnancy. In addition, the educational aspirations of girls who bear children seem to be lower than those of their peers; such teens do not regard early pregnancy and parenting as undesirable life options. Other associations with pregnancy in teens include risk-taking behaviors; early initiation of sexual activity; family history of adolescent pregnancy in the mother or in siblings; and adverse childhood experiences such as abuse, exposure to violence, substance abuse, mental illness, criminal household member, and divorced or separated parents.

Fathers of infants born to teen mothers have the same backgrounds and many of the same characteristics as their partners, although many of the men are older and are legally adults. In most instances, male sexual partners are approximately 3 years older than their female partners, whatever their ages. In some racial and ethnic groups, the age difference between fathers and their teen partners may be greater than



average. Each state has its own definition of statutory rape, and some pregnancies clearly fit into this official category, although most teen mothers view their sexual activity as voluntary and consensual. The younger the pregnant teen, the greater the likelihood that the pregnancy is a result of either forced sex or statutory rape (perpetrators could be family members, caretakers, friends, dating partners, or strangers). In general, the men who father the infants of teen women are frequently from disadvantaged socioeconomic classes, are often educationally behind their peers, are more likely to have legal difficulties, are more likely to use illegal substances, and are more likely to acquire a sexually transmitted infection than age-matched peers. If they work, these men usually have lower-paying jobs than their age-matched peers. Many of these young men have mothers or sisters who were pregnant as adolescents. It also seems that having a teen father predisposes to becoming a teen father. These characteristics may not apply to young men whose pregnant partners choose to terminate their pregnancies.

## EVALUATION

### Physical Examination

Pregnant teenagers may not seek care for the classic symptoms of pregnancy, such as a missed menstrual period, morning nausea, and breast tenderness. Instead, teens may seek care for other physical complaints, some of which are entirely unrelated to pregnancy (eg, sore throat). Physicians who care for young women of childbearing age must always consider pregnancy, regardless of the symptoms the teen exhibits. The last menstrual period should be routinely determined and recorded at every office visit for a teenage girl, then noted by the nurse or other nonphysician before seeing the patient. The validity of the stated last menstrual period should be questioned if any clinical suspicion of pregnancy exists, and a urine or serum pregnancy test should be performed.

Pregnancy should always be considered in a young woman who has secondary amenorrhea. Other symptoms that suggest pregnancy are fatigue, nausea (particularly nausea that is relieved by eating), dizziness or syncope, urinary frequency, weight gain, breast tenderness or enlargement, and abdominal tenderness or enlargement.

Pelvic and breast examinations may be performed to confirm the diagnosis. Breast fullness and tenderness may be noted. Uterine enlargement varies with the gestational age of the pregnancy (Box 122-1). In addition, the physician may note cervical softening and cyanosis during the pelvic examination during early pregnancy. A pregnancy test should be performed in these cases.

### Laboratory Evaluation

Currently available urine pregnancy tests, most of which use enzyme-linked immunosorbent assay techniques and monoclonal antibodies to human chorionic gonadotropin (hCG), are sensitive and are able to detect pregnancy as early as 3 to 3.5 weeks after the last menstrual period (1–1.5 weeks after ovulation in a

### BOX 122-1 Uterine Changes With Pregnancy

- 4 weeks: Cervical softening and cyanosis is noted.
- 8 weeks: Uterus is the size of an orange.
- 12 weeks: Uterus is grapefruit sized and palpable suprapubically.
- 20 weeks: Uterus is at the umbilicus.

woman with 28-day cycles), although they are more accurate at 4 to 4.5 weeks because the low level of hCG seen during the first week of gestation is at the lower level of detection and may be missed. These tests are easy to perform in an office setting. Serum hCG determination can be performed if any question exists of urine tampering, inaccurate urinary hCG, spontaneous or threatened abortion, or ectopic pregnancy.

### Imaging Studies

If the dating of the pregnancy is in question, or suspicion of an abnormal pregnancy exists, then a pelvic ultrasound may be useful. Pelvic ultrasound performed transabdominally can detect a gestational sac as early as 5 to 6 weeks after the last menstrual period. If the ultrasound is performed transvaginally, then a gestational sac may be determined as early as 4 to 5 weeks' gestation.

## MANAGEMENT

Once a teen pregnancy has been confirmed, several complicated issues need to be addressed with the patient. To address these issues appropriately, physicians must be familiar with the pertinent laws of the state in which they are practicing, with their local school system's policies in dealing with pregnant teens and teen parents, and with local medical, financial, and social resources. Prenatal care may be provided by a teen-friendly physician, by a publicly funded clinic (some of which have extra expertise in caring for teens), or by a university clinic. It is important for the pediatrician to help the teen choose an obstetric provider who will provide the most supportive environment locally and financially possible. Many teens will need additional educational, social, and financial supports for optimal care during the pregnancy and during childrearing. Box 122-2 lists the ways a primary care physician can help the pregnant teenager.

The teen must first be privately informed of her pregnancy. Her reaction will depend on several factors—whether the pregnancy was suspected or not suspected, wanted or unwanted, planned or unplanned. Next, a determination must be made as to whether informing the patient's parents and the father of the child will cause any difficulties, and then the patient must be helped to address the difficulties. The age of the father of the baby and the teen's relationship to the father should always be asked to determine whether the physician should inform local authorities of abuse or statutory rape (see Chapter 371, Rape, for

**BOX 122-2 How a Primary Care Physician Can Help a Pregnant Teenager**

- Help the teenager think through her options for the pregnancy.
- Facilitate an appointment for prenatal care.
- Help the teen's parents cope with the pregnancy.
- Facilitate the teen's return to school.

more information). In addition, the patient should be helped to understand the social, emotional, educational, and financial implications of the pregnancy. Addressing all of these issues may require referral of the patient to an outside counselor such as a social worker skilled in these issues, or several office visits for a patient with few other resources.

All patients should be presented with the options legally available to them: abortion, adoption, or parenthood. Some pregnant teens will decide that they are not ready to parent, and they may decide to terminate the pregnancy or to make a plan for adoption. Physicians who have moral or religious objections to discussing these issues should refer their patients to other physicians who can support the possible patient choices. Patient coercion of any kind in this matter is not appropriate professional behavior. Primary care physicians should refer patients who choose termination to the appropriate local resources. Patients who choose adoption should be referred to agencies that have policies in place to safeguard the rights of the pregnant mother, her infant, the father of the baby, and the prospective parents. Teens who choose to terminate the pregnancy and those who opt for adoption may continue to need emotional support from their primary care physician or their counselor, just as the young mother who decides to parent will.

Although the social aspects of the pregnancy are addressed, and although the patient is awaiting her first obstetric visit with a physician who is knowledgeable about and accepting of teenage pregnancy, the primary care physician must be sure that the young mother has no disorders that might constitute a risk to herself or her unborn child and that she can appropriately care for herself during her pregnancy. In addition, the risk for violence to the young mother should be determined. Baseline height, weight, and blood pressure should be obtained. Screening for human immunodeficiency virus, syphilis, chlamydia, gonorrhea, bacterial vaginosis, and *Trichomonas* should be carried out, and treatment should be initiated as appropriate. The adolescent should be counseled about proper nutrition and rest; she should also be encouraged to avoid exposure to tobacco, alcohol, and drugs, including both drugs of abuse and excessive over-the-counter medications. Any medications taken for chronic illnesses should be reviewed for teratogenic potential. Prenatal vitamins should be prescribed. Tdap and influenza vaccines should be provided as recommended by the American Academy of Pediatrics Committee on Infectious Diseases in the *Red Book*.

**OUTCOMES**

Pregnancy outcomes in teens include not only the physical outcomes to mother and child but also the social, educational, emotional, and financial outcomes for everyone affected by the pregnancy. An abundance of information exists regarding infants' and mothers' health, but the lives of the infant's father, grandparents, and other family members will also be affected.

The physical outcomes of pregnancies in teenagers are generally good. However, very young mothers are at increased risk for toxemia of pregnancy, maternal anemia, infant death, prematurity, and low-birth-weight infants. Many of these effects seem to be ameliorated by early prenatal care and appropriate maternal weight gain. Although poor outcomes are influenced by the lower socioeconomic status of the adolescent mother, age itself may be a moderating factor as well. Adolescent mothers generally do well in labor and recover easily from the effects of childbirth.

Other risk factors exist for the adolescent mother. One short-term concern is violence. Pregnant teens seem to be at increased risk for becoming victims of family or intimate partner violence. Another short-term concern is depression; postpartum adolescents seem to be at higher risk than their adult counterparts, although this may be ameliorated by the presence of social supports from the teen's mother and from the father of the infant. Women who become pregnant during adolescence also seem to have a higher than normal long-term risk for depression and other emotional difficulties. In addition, although most women who become pregnant as teenagers eventually complete their high school education, they continue to remain educationally behind their age-matched peers; many of their peers elect participation in post-high school training, and teen mothers are less likely to do so. Only two-thirds of teen mothers receive their GED or high school diploma by age 22, compared with 94% of those who did not give birth as teens. Mothers who live with the father of their infant or who do not return to school to complete their education are most likely to have a repeat pregnancy soon after the first. The second pregnancy is more likely to end in elective termination than the first. If it does not, then the mother frequently enters into prenatal care later than she did with her first infant, and the second infant is at greater risk for low birth weight. The second infant is also at greater risk for death by homicide, with the mother's current boyfriend (not the infant's father) being the most common perpetrator. Marriages formed in response to pregnancy generally fail with time, leaving the young mother with children and few resources for their support. These issues clearly produce significant financial implications for the young mother, her children, and society. Clinics specializing in the care of pregnant adolescents have been shown to improve the outcomes of pregnancy, reduce premature delivery, and reduce subsequent teenage pregnancies.

For the child born to a teen mother, the long- and short-term effects of the mother's lower educational status, lower financial status, developmental immaturity, emotional stress, and adverse environment are

### BOX 122-3 How a Primary Care Physician Can Help a Teen Mother and Her Infant

- Teach the teen mother normal child development.
- Help the teen mother use positive parenting.
- Discuss ways to improve infant safety.
- Watch closely for postpartum depression.
- Encourage contraceptive use.
- Teach the infant's grandmother modern childrearing concepts.
- Help the father feel welcome at well-baby visits.
- Encourage the young mother to continue her education.
- Refer the family to support services as needed.
- Watch for behavioral and school problems in the child.

significant. Many adolescent mothers seem to lack knowledge of normal infant behavior, misinterpreting infant behavior as indicating that their child is more capable than is the case. They also seem to offer less infant stimulation than older mothers and to use harsher methods of discipline. The higher than normal rate of postpartum depression in teen mothers may influence maternal-child bonding and the amount of energy that the developmentally immature mother is able to put into guiding and teaching her infant. Infants of teenage mothers also seem to have an increased risk for abuse and neglect, although this seems to be related to family stress, socioeconomic circumstances, and the presence of a new boyfriend in the mother's life. Children born to teen mothers seem to have a higher than normal incidence of early behavior problems and to be less secure in their maternal-child bond than their peers. They also have higher rates of school failure, legal difficulties, and adolescent parenthood than their age-matched peers. The children of adult women who are prior teen mothers seem to be at excessive risk for poverty, death, poor educational outcomes, and involvement with state-sponsored family services programs. Some of the problems teen mothers encounter with parenthood can be addressed by providing social supports such as visiting nurses on a regular basis. Box 122-3 lists ways to help a teen mother.

## PREVENTION

Physicians can facilitate pregnancy prevention by routinely providing education about risks and prevention methods to all pubertal patients. Many teens who become pregnant seem not to have understood their actual risk at the time of conception. However, prevention seems to require more than education and readily available contraception. Facilitating parent-child discussions about sexuality and childbearing may also be an effective strategy, as may teaching negotiation skills for pregnancy prevention. Community programs, particularly those that foster positive youth development, may be an effective adjunct.

Effective programs need to identify specific youth at greatest risk—school dropouts, risk takers, delinquents—and concentrate their efforts on these individuals. Much has been learned about the prevention of adolescent pregnancy in the past 40 years, and clearly no sole program is appropriate for all communities or for all teens and their families. However, some characteristics are common to most successful programs. These characteristics include:

1. A focus on specific behavioral goals
2. A program based on theoretical approaches
3. Delivering clear messages about sexual activity and contraceptive use
4. Providing basic information about risks associated with teen sexual activity
5. Addressing social pressure to have sex
6. Providing activities to practice communication and refusal skills
7. Incorporating multiple teaching methods
8. Tailoring the program to participants' age, culture, and level of sexual experience
9. Providing an appropriate length of time to cover all the activities
10. Providing appropriate training for teachers or peer leaders who are involved in the program

Programs to reduce repeat births (secondary prevention) need a different emphasis than the programs for primary prevention (preventing the first birth). Successful secondary prevention programs require effective personnel who maintain close, sustained relationships with teen mothers with an emphasis on school completion and family planning. Regardless of the type of program developed for secondary prevention, physicians should always remember that the pregnant teenager is an adolescent who happens to be pregnant, not a pregnant woman who happens to be an adolescent.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Contraception* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/reproductivehealth/UnintendedPregnancy/Contraception.htm](http://www.cdc.gov/reproductivehealth/UnintendedPregnancy/Contraception.htm))
- *Deciding to Wait* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Helping Teens Stay Healthy and Safe: Health Care, Birth Control, and Confidential Services* (handout), Center for Adolescent Health and the Law ([www.cahl.org/helping-teens-stay-healthy-and-safe-health-care-birth-control-and-confidential-services-2007](http://www.cahl.org/helping-teens-stay-healthy-and-safe-health-care-birth-control-and-confidential-services-2007))
- *Information for Teens: What You Need to Know About Privacy* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/teen/Pages/Information-for-Teens-What-You-Need-to-Know-About-Privacy.aspx](http://www.healthychildren.org/English/ages-stages/teen/Pages/Information-for-Teens-What-You-Need-to-Know-About-Privacy.aspx))
- *Making Healthy Decisions About Sex: Important Information For Teens* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *The Pelvic Exam* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Tips for Parents of Adolescents* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))



**Community Advocacy and Coordination**

- *Adolescent Health Topics: Reproductive Health* (Web page), US Department of Health and Human Services ([www.hhs.gov/ash/oah/adolescent-health-topics/reproductive-health](http://www.hhs.gov/ash/oah/adolescent-health-topics/reproductive-health))

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**Chapter 123****CONTRACEPTION AND ABORTION**

Eric Schaff, MD

In 2009, the number of 15- to 19-year-old female adolescents in the United States was approximately 10 million, of which approximately 750,000 became pregnant; one-half of these pregnancies resulted in births, one-third resulted in abortions, and the remaining were failed pregnancies. Although the rate of unintended pregnancies in the United States continues to decline slowly, it is higher than that in most developed countries. In 2013, the total teen pregnancy births dropped an additional 10% from 2012, to 273,000, the

lowest level reported to date. An estimated one-third of teens will experience a pregnancy by age 20. The Healthy People 2020 Objectives established by the US Department of Health and Human Services include the goal of reducing adolescent pregnancies by increasing the percent of females or their partners who used contraception at their most recent intercourse to 92% (up from 83% from 2010 findings).

An unintended pregnancy can have significant medical, social, and financial consequences for an unprepared teen, her family, and the community. The American Academy of Pediatrics, American College of Obstetrics and Gynecology, and American Medical Association's *Guidelines for Adolescent Preventive Services* have recommendations for physicians caring for teens that include routine screening for sexual activity, support for sexual abstinence, the need for contraception, and the importance of counseling about the risks of unintended pregnancy or a sexually transmitted infection (STI). The National Campaign to Prevent Teenage Pregnancy in "No Easy Answers: Research Findings on Programs to Reduce Teen Pregnancy" found that no single strategy reduces teen pregnancy rates significantly. Approaches should target both abstinent and sexually active youth.

Physicians are particularly attuned to preventive public health measures that decrease morbidity and decrease costs. Physicians play an important role in preventing unintended pregnancies by ensuring access to contraceptive methods and emergency contraception for sexually active teens. Physicians, knowing that most older teens do become sexually active at some point, should encourage normal, healthy sexual development by assessing an adolescent's readiness to become involved in relationships that may lead to sexual activity. Teenagers who wish to wait and abstain from sex need encouragement and reassurance, emphasizing that abstinence is normal, is prevalent, and prevents both pregnancy and STIs. Youths who desire to become sexually active or who are already sexually active should be encouraged to use contraception, to know their partner's and their own STI screening status, and to limit the number of sexual contacts. In querying youth, the physician can better assess and address the context of the adolescent's sexual relationships (healthy or not) and provide appropriate counseling and services. Physicians should also be aware that intimate partner violence is, unfortunately, common in adolescents and may be either physical, emotional, or sexual. Because intimate partner violence may have profound effects on contraception behavior and risk for acquiring an STI, physicians should screen for safe relationships.

The rights of teens to receive different types of health care without parental consent vary widely among states. These situations include emergency medical care, reproductive health services, the emancipated minor, and the mature minor. To be emancipated, an adolescent must generally be of a state-defined minimal age (often 16 years), live apart from her parents, and be economically self-sufficient. Emancipation includes teens who are married, parenting, or serving in the military.



Although parental involvement in minors' reproductive decisions may be helpful and is ideally desirable, some adolescents will not seek services if they are required to inform their parents. Under the federal Health Insurance Portability and Accountability Act, physicians must follow state guidelines for confidentiality and may require the consent of the adolescent before releasing information to anyone, including her parents.

The benefits of contraceptive services typically outweigh any medical risks. The long-acting intrauterine device (IUD) and the 3-year progestin subdermal implant rod are gaining increasing favor, and the 3-month progesterone injection continues to be popular. Condoms continue to be a mainstay for STI prevention. More emergency contraceptive options are emerging.

Significant advances have been made in early abortion services. Detection of early pregnancy has been simplified by inexpensive home and office pregnancy tests that are positive 4 weeks after the last menstrual period. Earlier and more accurate pregnancy dating starting about 5 weeks from the last menstrual period is now possible through vaginal probe sonography. Earlier and safer abortion procedures are now available with the medical abortion pill mifepristone, and with suction abortion.

This chapter provides information basic to the physician's task of providing reproductive health care to teenagers.

## CONTRACEPTION

Two methods are used to describe the effectiveness of contraception to prevent pregnancy: typical use rate and perfect use rate. Typical use rate refers to the effectiveness of a method when used by the average woman (ie, not using the method correctly or every time). Perfect use rate refers to the ability of the method to prevent pregnancy when the method is used perfectly (ie, according to manufacturer's directions and every time required).

In general, all contraceptive methods are highly effective when used correctly, and, in all healthy women, their benefits far outweigh their health risks. When considering a contraceptive method, the short- and long-term medical risks and financial costs should also be compared with the risks and costs associated with not using the method, that is, an unintended pregnancy.

In the past, a physical examination that included breast and pelvic examinations was accepted practice before prescribing hormonal contraception. These examinations have not been found to affect prescribing and may be feared and avoided by teens, thereby being a barrier to highly effective contraceptive methods. Expert medical opinion has shifted away from requiring a general examination that includes breast and pelvic examinations before initiating hormonal contraception. Of note, breast cancer is rare in women younger than 30 years of age. The US Preventive Services Task Force recommends breast cancer screening with mammography, with or without clinical breast examination, starting at age 40.

Unrelated to contraception, sexually active female teens should be screened yearly for chlamydia and, if the community prevalence is high, both females and

males should be screened for gonorrhea. A significant advance, especially for pediatric practices that are not prepared for pelvic examinations or male penile cultures, is the screening for chlamydia and gonorrhea by urine testing.

Cervical cancer screening with either Papanicolaou tests or liquid cytologic assessment should also not be directly tied to hormonal contraceptive provision. Current cervical screening guidelines recommend starting at age 21 because most cervical dysplasia reverts back to normal, aggressive treatment can have negative consequences, and progression takes years.

## Hormonal Methods

Hormonal methods of contraception involve using either combined synthetic estrogen and progestin (combined oral contraceptive pills, transdermal patch, and vaginal ring) or progestin-only products (progesterone-only pills, 3-month injection, 3-year subdermal implant, and 3- and 5-year progestin IUD). Although progesterones are sufficient and necessary for contraception, estrogens help to regulate the menstrual cycle. As a group, these methods have many features in common that include their mechanism of action, effectiveness, advantages, disadvantages, and side effects. To a varying degree, these methods prevent pregnancy by 3 main mechanisms: suppressing luteinizing and follicle-stimulating hormones, thereby inhibiting ovulation; thickening cervical mucus, making it less penetrable by sperm; and altering the endometrium, making it less receptive to implantation of a fertilized ovum. When hormonal methods begin within 5 days of the onset of a normal menses, ovulation is usually suppressed, thereby preventing pregnancy. When used correctly, these methods are 99% effective in preventing pregnancy, and ovulation returns quickly when stopped (except for intramuscular progesterone, which often delays ovulation beyond 3 months).

While using combined hormonal contraception, menses are usually regular, shorter in duration, sometimes absent, and avoided altogether for convenience by skipping the hormone-free time period between active ingredients. These methods are also associated with less dysmenorrhea, acne, benign fibrocystic breast disease, pelvic inflammatory disease (because of thickened cervical mucus that blocks ascending infection), and ovarian and endometrial cancer. Women who use an oral contraceptive pill (OCP) for as little as 6 to 12 months experienced a 40% reduction in the risk for ovarian cancer, and long-term OCP users (>10 years) experienced an 80% reduction. No evidence has been found that OCPs increase mortality from breast cancer, even with prolonged use.

Before prescribing estrogen-containing hormonal contraception, the physician should be certain that there are no contraindications to their use, which are very few. In general, healthy teens are excellent candidates for hormonal contraceptives. A summary of the recommendations by the World Health Organization for prescribing estrogen-containing hormonal contraception is noted in Box 123-1. Combined hormonal contraception can safely be provided based on a negative medical history for contraindications and a blood pressure measurement within normal limits.

### BOX 123-1 World Health Organization Contraindications and Precautions for Prescribing Estrogen-Related Hormonal Contraception

#### NO CONTRAINDICATIONS

- Mild headaches
- Benign breast disease
- Obesity
- Pelvic inflammatory disease
- Thyroid disorders
- Epilepsy
- Iron-deficiency anemia
- Use of antibiotics
- Dysmenorrhea
- Endometriosis
- HIV
- Viral hepatitis carrier
- Irregular menstrual bleeding
- History of ectopic pregnancy
- History of gestational diabetes
- Family history of breast cancer
- Gestational trophoblastic disease (benign or malignant)
- Benign ovarian tumors

#### CAUTION ADVISED

- Hyperlipidemia
- Less than 21 days postpartum
- Breastfeeding from 6 weeks to 6 months postpartum using medications that affect liver enzymes (eg, rifampin, griseofulvin, phenytoin, carbamazepine, barbiturates, primidone)
- Undergoing major surgery with prolonged immobilization
- Unexplained vaginal bleeding

#### CONTRAINDICATIONS

- Pregnancy
- Hypertension
- Certain heart and liver diseases
- Diabetes mellitus when either longstanding or with end-organ involvement
- History of thromboembolic disease or stroke
- Migraine headaches with focal, neurologic symptoms
- Less than 6 weeks postpartum and breastfeeding

To improve access to care and adherence with contraception, pediatricians need to ensure confidentiality. They must also assess their patient's understanding of the benefits, risks, and alternatives of the chosen method; their concerns about becoming pregnant; and their motivation to use the method selected. Counseling and handouts are key to supporting teens dealing with or anticipating minor side effects, such as breakthrough vaginal bleeding, nausea, headaches, bloating, mood changes, and irritability, all of which are likely to resolve after several menstrual cycles. Many of these side effects may be unrelated to contraception but rather the usual stresses in a teen's life. Weight gain caused by an increase in appetite

while on hormonal contraception can be countered by good eating habits and regular exercise. Persistent mood changes or depression will require stopping the hormonal method for further evaluation. Although effective at preventing pregnancy, these methods do not protect against STIs, and therefore the use of condoms must always be encouraged for teens at risk for STIs.

### Combined Estrogen/Progestin Methods

**ORAL CONTRACEPTIVES.** Oral contraceptive pills are one of the most popular methods of birth control used by young women. Unfortunately, adherence continues to be a concern, and more than one-half of teens will discontinue their OCP during the first year of use.

All low-dose combination pills consist of only a single estrogen, ethinyl estradiol, with the dose ranging from 10 to 35 mcg/day, and one of many different synthetic progestins derived from estranes, gonanes, or an unclassified group. Estranes were marketed first and consist of norethindrone or compounds that convert to norethindrone. Gonanes consist of norgestrel, levonorgestrel, norgestimate, and desogestrel. The latter 2 agents are newer and have the advantage of being potent progestins but producing fewer androgenic side effects. Norgestimate and desogestrel also increase high-density lipoprotein, which is protective against atherosclerosis, and have a slightly longer half-life that makes vaginal spotting and pregnancy less likely if a woman forgets to take her daily pill. An unclassified progestin is drospirenone derived from spironolactone and has antimineralocorticoid properties with fewer premenstrual bloating symptoms and mild antiandrogenic activity. There is no difference in effectiveness in pregnancy prevention among the different OCPs.

The disadvantages of OCPs include the need for daily use, theoretical decreased effectiveness caused by some antibiotics (eg, rifampin, doxycycline) and antiseizure medications (eg, phenobarbital and phenytoin), and increased risk for rare venous thromboembolic disease.

The risk for venous thromboembolism for healthy teenagers not using hormonal contraception is very low, approximately 3 per 100,000 women. The risk increases to 7 to 10 per 100,000 when using combined oral contraceptives. To decrease the risk, the doses of synthetic estrogens have decreased significantly since the original pill formulations. The risk should be compared with the greater risk for thromboembolism in pregnancy. Some confusion exists in attempting to quantify the exact risk attributed to different birth control pills because these adverse events are rare and the studies are not randomized but postmarket observations. Newer methods may seem to have higher risk for thromboembolism than older methods because of a bias to prescribe the newest and lowest-dose oral contraceptives to women not tolerating older OCPs and women at possible higher risk for medical complications.

Considerable flexibility exists regarding which brand of OCP to prescribe. Most commonly, a 28-day-cycle pack (21 days of active hormones and 7 days of placebo) is used. Despite claims by manufacturers, clinical differences among brands of low-dose pills are minimal

regardless of whether the hormones are fixed (monophasic) or varied (biphasic or triphasic) throughout the month. The lowest dose estrogen pills may not provide the best cycle control and mid cycle spotting may occur which, in turn, may decrease compliance. Physicians can choose any one of the following strategies in prescribing oral contraceptives: an inexpensive generic brand, a low-estrogen preparation containing 10 to 25 mcg of ethinyl estradiol, a 30- to 35-mcg pill that has less intermenstrual spotting, an older progestin with low androgenicity such as norethindrone, or a new-generation progestin that has a longer half-life but also low androgenic effects (norgestimate or drospirenone). Pills containing desogestrel have a small increased risk (1.5 to 2.7 times) for venous thromboembolism.

To improve adherence, the physician should prescribe a sufficient number of packs to prevent running out of pills. The first few months should serve to identify any health concerns or problems the teen may identify in taking the pills. After this initial prescription, 12-month supplies can be prescribed to increase adherence.

OCPs can be started on day 5 after the start of menses, on the Sunday after menstrual bleeding starts (Sunday start), or by the “quick-start” method. Quick-start allows hormonal methods to be started on any day if the physician is reasonably certain that the teenager is not pregnant; for example, she has not had sex since her last normal menses or has been using another birth control method correctly and every time. For quick-start, if more than 5 days have elapsed since the menses started, then the teenager needs to abstain from sex or use additional contraceptive protection such as condoms for the next 7 days. These 3 options ensure that the teen is not pregnant and should suppress ovulation during the first cycle (except for the quick-start method).

The pill should be taken at the same time each day. Taking it before bedtime allows for the peak concentration of the hormones to occur during sleep, thereby masking some symptoms such as nausea. If 1 pill is forgotten (particularly during the first 7 days that are needed to suppress ovulation), then it should be taken as soon as it is remembered. If 2 or 3 pills are missed, and if there was no unprotected intercourse in the last 5 days, then the teenager should take 2 active pills all at once, use back-up method for the next 7 days, and finish the pill pack by taking 1 pill daily. If there was unprotected intercourse in the last 5 days, then the teenager should be instructed to use emergency contraception today, restart the active pills the next day, and use a back-up method for 7 days. If 4 pills are missed, and if there was no unprotected intercourse in the last 5 days, the teenager should use a back-up method for the next 7 days and finish the pill pack by taking 1 pill daily, skip the 7 placebo pills, and immediately start the next pack. If there was unprotected intercourse in the last 5 days, she should use emergency contraception today, restart the active pills the next day, skip the 7 placebo pills, immediately start the next pack, and use a back-up method for 7 days. Withdrawal bleeding is common 2 or 3 days after the last pill is taken.

If mild side effects do not resolve after several cycles of a particular OCP, then the brand can be changed to another containing a different amount of estrogen or a different progestin. If menstruation does not occur, the pills should be continued and a pregnancy test obtained for reassurance and to detect the rare pregnancy.

Use of extended-cycle oral contraceptives of 84 days or continuous-cycle of 365 days of active pills reduces the number of menses from 13 to only 4 or 1 per year. All of the combined estrogen/progesterone methods can become extended-cycle by avoiding the week of placebo or no medication for 2 out of 3 cycles. Theoretically, a chance ovulation is less likely to occur because follicles have less chance of maturing during the pill-free week when on monthly OCPs. Extended-cycle products may be of benefit for teens who prefer to have fewer menses or who have a history of menorrhagia, menstrual migraine, difficulty with regulating other long-term medications affected by the changes of hormones during the pill-free week, and endometriosis. Breakthrough bleeding may be encountered.

**TRANSDERMAL PATCH AND VAGINAL RING.** Newer methods that change the route of administration of hormones and do not require daily use show improved adherence and higher typical use effectiveness rates. These methods include the weekly transdermal patch and the monthly vaginal contraceptive ring.

The transdermal patch (Ortho Evra) has the advantage of once-weekly application. This product contains 0.75 mg ethinyl estradiol and 6 mg norelgestromin, the active metabolite of norgestimate. The patch is worn weekly for 3 consecutive weeks; the fourth week is patch free, allowing for withdrawal bleeding. The patch may be applied to the abdomen, buttocks, upper outer arm, or upper torso (excluding breasts). Clinical trials suggest that the transdermal patch is less effective in women weighing more than 198 lb (90 kg). The average serum concentration of ethinyl estradiol (area under the curve) is approximately 60% higher than oral contraceptives, although the clinical significance and risk for thromboembolic disease are unknown. The patch must be adherent to the skin and cannot be off for more than 24 hours. If these conditions do not hold, a back-up method should be used for that week until another patch is applied.

The vaginal ring (NuvaRing) is a combination of 2.7 mg ethinyl estradiol and 11.7 mg etonogestrel that delivers a daily dose of 15 mcg and 0.12 mg, respectively. The ring consists of a flexible plastic ring of ethylene vinyl acetate and is available in one size (2 inches in diameter and 1/8-inch thick). Because the ring is “one size fits all,” it requires no specific placement techniques. The ring should be placed in the vagina within the first 5 days of the menstrual cycle and remain in place for 3 consecutive weeks. It is then removed and discarded. A new ring is inserted after 7 days, allowing for withdrawal bleeding. If the user and her partner prefer, the ring may be removed for intercourse as long as it is replaced within 2 to 3 hours. However, if the ring is left out for more than 3 hours, then she can reinsert the ring but must either abstain from sex or use a condom for the next 7 days.



### Progestin-Only Methods

The progestin-only methods (progestin-only oral contraceptives, 3-month injectable depo-medroxyprogesterone acetate, 3-year subdermal rod implant, and progestin-IUD) are not associated with venous thromboembolic events. Therefore, these methods are indicated for women with a contraindication to estrogen or preferred because of their inherent properties. These methods are associated with more irregular vaginal bleeding than combined hormonal methods.

#### PROGESTIN-ONLY ORAL CONTRACEPTIVES.

Progestin-only OCPs, also known as mini-pills, contain a low dose of a progestin (norethindrone). They have the same mechanism of action as combined estrogen/progestin pills. They are taken for 28 days with no break between packs and need to be taken at the same time each day.

#### THREE-MONTH DEPO-MEDROXYPROGESTERONE ACETATE INJECTION.

A highly effective and popular method is the 3-month injectable progestin, depo-medroxyprogesterone acetate (DMPA; Depo-Provera) injection. As many as 10% to 15% of teens report using DMPA. Each 150-mg injection provides 12 weeks of effective contraceptive protection plus an additional 2-week grace period (for a total of 14 weeks). It requires vigorous shaking to suspend all the particles and is given deep intramuscularly in either the deltoid or upper outer quadrant of the gluteal muscle. The site should not be massaged because the rate of absorption and metabolism may be increased, thereby decreasing effectiveness. A generic product is available that reduces the cost. DMPA is also known to stimulate appetite and can lead to weight gain if calories are increased.

A new route of medroxyprogesterone acetate is subcutaneous administration, the same used for insulin injections. This 104-mg dose can be given at home if the teen or a support person can be taught how to give the injection, thereby avoiding an office visit.

The advantages of the progesterone-only injection include long-acting protection; avoidance of estrogen and its risk for venous thromboembolism; lack of interference with breastfeeding; possible reduction in both the incidence of seizures and the painful hemolytic crisis of teens with sickle cell disease; continued contraceptive effectiveness when using antibiotics or antiseizure medicines; and thinning of the endometrium, causing amenorrhea in up to 50% of women after the first year and an even higher percentage of women thereafter. The disadvantages of this injection include the need for repeated injections every 3 months; a hypoestrogen state that causes a reversible decrease in bone density, though significantly less than pregnancy; and a delay in clearance of DMPA for as long as 12 months, resulting in reduced fertility after discontinuation. Decreased bone mineral density has been shown to be reversible and should not be a reason to discontinue use.

Irregular or prolonged bleeding while on DMPA is common in the first year. Managing side effects is important in supporting continued use of injectable progesterone. Vaginal bleeding can be managed by offering 14 to 28 days of conjugated estrogen 0.625 mg, estradiol 1 mg, or a cycle of combined OCPs.

**THREE-YEAR SUBDERMAL ROD IMPLANT.** A subdermal implantable hormonal contraceptive (Implanon) is highly effective at providing low-dose, continuous contraception for up to 3 years. It involves only the progesterone etonogestrel within a rod of ethylene vinyl acetate. (Both components are also used with the vaginal ring.) Etonogestrel is the active metabolite of desogestrel, a progestin in oral contraceptives. With training, insertion and removal under local anesthesia with 1% lidocaine are easy skills to learn.

The advantages of the implantable rod include its long-acting protection; avoidance of estrogen and therefore venous thromboembolic disease; low dose of progestin, allowing for continuous endogenous estrogen production and thereby not affecting bone demineralization; and quick reversibility. The major disadvantages of this method include the unpredictability of menstrual patterns, the cost, and the need for a minor procedure.

**THREE- AND FIVE-YEAR PROGESTIN INTRAUTERINE DEVICE.** See the section on intrauterine devices.

### Emergency Contraception

An emergency contraception pill (ECP) prevents pregnancy after unprotected intercourse and may also be referred to as a *postcoital* or *morning-after* pill. They consist of a single dose of 1.5 mg of the oral progestin levonorgestrel. An alternative, older method is possible by taking an equivalent dose of levonorgestrel or norgestrel from 4 or 5 combined low-dose pills and repeating 12 hours later.

ECPs are indicated when other methods fail, when no contraception is used, or when rape occurs. They are available over the counter for women aged 17 years and older. One strategy to increase access to an ECP for sexually active teens younger than 17 years is to give them a prescription in anticipation of unprotected intercourse.

ECPs reduce the risk for pregnancy by about 88%. For example, if 100 women have unprotected intercourse in the second or third week of their cycle, 8 will become pregnant without ECPs, but 1 will become pregnant using progestin-only ECPs, an 88% reduction. If a current pregnancy is possible, then a pregnancy test should be performed before taking ECPs, though taking them has not been known to harm an established pregnancy. A nationwide hotline (800-NOT-2-LATE) and Web site ([ec.princeton.edu](http://ec.princeton.edu)) are available to increase public awareness of emergency contraception.

High-dose levonorgestrel (Plan B One Step or generic) should be taken as soon as possible after unprotected intercourse for greatest effectiveness, but can be used up to 5 days later. Nausea and, rarely, vomiting can occur and may require anti-nausea treatment. Breast tenderness, irregular bleeding, fluid retention, and headaches rarely occur. For ongoing contraception, hormonal contraceptives can be started on the first Sunday after the onset of the next menstrual period or the same day as the ECP (quick-start method) with 7 days of condom use. If the next menses is delayed, then the teen should be instructed to return for a pregnancy test.



A progesterone agonist/antagonist (Ella) is approved by the US Food and Drug Administration for emergency contraception within 5 days of unprotected intercourse.

## Barrier Methods

### Condoms

Throughout the world, condom use has increased significantly because of social marketing campaigns addressing the human immunodeficiency virus (HIV) epidemic. Latex condoms work by containing the ejaculate and are effective in pregnancy prevention and in reducing the spread of all STIs, including HIV. Making condoms readily available increases their use. Even if teens prefer a hormonal birth control as their primary method for preventing pregnancy, they should be encouraged to use condoms if they are at risk for STIs.

Condoms are inexpensive, available over the counter, a means to involve the male in sharing responsibility for contraception, lubricated for comfort, associated with minimal side effects, and simple to use. The disadvantages of condoms are the diminished genital sensation noted by some individuals and the lack of 100% protection against STIs.

Lubricated (but not nonoxynol-9) latex condoms offer the best protection. Condoms should be placed on the erect penis before sex. To prevent condom breakage, condoms should not be stored in warm places (eg, a wallet) for long periods, lubricated with oil-based lubricants such as Vaseline, or reused. Polyurethane condoms, an alternative, are more expensive, but are stronger and thinner than latex condoms, odorless, and compatible with oil-based lubricants.

To prevent accidental spillage, teens should be instructed that the condom be removed shortly after ejaculation while holding the rim of the condom on the base of the penis. If spillage occurs or a condom breaks, then the penis and vagina should be washed with soap and water, spermicide used, and ECPs taken.

### Diaphragm and Female Condom

The diaphragm is a thin, rubber, 6.5- to 8-cm dome that is inserted into the vagina. It covers the cervix and blocks sperm from entering. It must be used with spermicidal contraceptive jelly, which has the active ingredient nonoxynol-9. When used correctly and consistently, the diaphragm's effectiveness can be quite high, although the typical use failure rate ranges from 6% to 16%. It also offers some protection from STIs and has minimal side effects. A diaphragm is a reasonable choice for a motivated teen who has contraindications or wants to avoid taking contraceptive hormones. The disadvantages of the diaphragm include the skill needed for placement, the need to leave it in place 6 hours after intercourse, the need for a second application of spermicidal jelly if intercourse is repeated after 6 hours, and the slight increase in vaginitis and urinary tract infections. Disadvantages for the physician include keeping a set of diaphragm rings for sizing and learning and maintaining the skill to fit a diaphragm when the requests are likely to be few.

The female condom is readily available without a prescription but is not widely used because of its high cost. It is made from polyurethane with 2 flexible polyurethane rings. One ring is placed inside the vagina to cover the cervix, similar to a diaphragm; the 2nd open ring remains on the outside of the perineum to protect against STIs. The female condom should not be used at the same time as latex condoms, nor should it be reused.

### Spermicidals: Vaginal Foam, Vaginal Sponge, and Vaginal Suppository

Vaginal foam, sponges, and suppositories contain nonoxynol-9, which has in vitro and in vivo protective properties against some STIs. These methods are relatively simple, effective, and inexpensive and can be obtained without a prescription. Spermicidals are important complementary methods when they are used with condoms, intercourse is infrequent, and they are used as a back-up method for other birth control methods.

The vaginal sponge, which is moistened with water before use, can be inserted several hours before intercourse and remains effective for 24 hours. Suppositories must be in the vagina at least 10 to 15 minutes before intercourse to allow them to dissolve.

### Natural Family Planning

Natural family planning methods identify the most fertile time during the menstrual cycle in order to avoid sexual intercourse. Methods include charting of menstrual cycles on the calendar to determine likely ovulation about 14 days before the next menses, recording basal body temperatures to document the rise of at least 0.4°C after ovulation, and monitoring the thinning of cervical mucus to detect when ovulation occurs. Advantages include the lack of side effects, acceptance by women opposed to hormonal and barrier methods, knowledge gained about reproductive physiology, and its practicality when barriers exist to accessing other methods. Disadvantages for teenagers include their irregular menstrual cycles, which make predicting ovulation difficult, the high degree of motivation required for effective use, and a 20% typical failure (pregnancy) rate.

### Intrauterine Device

There are 2 basic types of plastic IUDs available in the United States: one with a copper wire wrapping (Para-Gard) that lasts for 10 years and two containing the progestin levonorgestrel with either 52 mg that lasts for 5 years or a slightly smaller one with 13.5 mg that last for 3 years and being promoted for nulliparous women. Both types have a typical and perfect use rate of approximately 99% in preventing pregnancy. Once in place, the IUD requires no effort for continued effectiveness and has no additional costs. The mechanism of action is not clear but likely involves either causing a sterile inflammatory process of the endometrium, making it unsuitable for implantation of a fertilized egg; copper's toxic effects on enzymes that inhibit sperm migration; or additional atrophic endometrial changes from the progestin-containing IUD that also reduces menstrual bleeding. The IUD is indicated for

teens interested in highly effective, nonhormonal, long-term, and reversible contraception. It is also an appropriate choice for teens having difficulty with complying with other birth control methods or those who have serious medical conditions that would be worsened with a pregnancy.

The IUD has previously not been offered to teens because of the concern it might lead to fallopian tube scarring and infertility. Recent evidence-based studies have demonstrated the safety of IUDs for all age groups with recommendations that the benefits outweigh the risk. The IUD's monofilament strings do not interfere with protective properties of cervical mucus and the progestin-containing IUD thickens the cervical mucus and decreases menstrual flow or amenorrhea, all mechanisms that decrease the risk for pelvic inflammatory disease. A current or high risk for an STI is still a contraindication. Condoms are recommended for STI protection. Compared with other countries, the prevalence of IUD use in the United States is low, mainly because of its high initial costs.

The copper IUD allows for regular menstrual cycles, which can be heavier. Insertion can be easier during the menstrual cycle or after an abortion or pregnancy. Nulliparous women have a slightly higher rate of expulsion.

## ABORTION

More than one-third of pregnant teens in the United States choose abortion. The earlier the abortion is performed, the safer it is. Unfortunately, teens are more likely than older women to delay an abortion. The reasons cited most often by teens for choosing an abortion are how a baby will negatively affect their lives, financial concerns, and feeling that they are not mature enough to have a child.

Most young teenagers involve their parents in these decisions. Some states require parental consent or notification for a minor to obtain an abortion. In these states, a minor who does not want to involve her parents must be able to obtain a judicial or administrative bypass.

### Suction Curettage

Surgical (suction) abortion is greater than 99% effective and has an excellent safety record of approximately 1 death per 1 million early first-trimester procedures. Women receive local anesthesia and may have the choice of additional medication to relieve pain or anxiety by mouth or IV sedation. Unfortunately, mortality rates remain high in developing countries where a need exists for safe, legal, and accessible abortion services.

Rare complications of abortion can include excessive bleeding, infection, perforation of the uterus, and adverse anesthetic events. A prophylactic antibiotic is recommended following the procedure.

### Medical Abortion

Mifepristone (Mifeprex, formerly known as RU 486, the *French abortion pill*), available in more than 2 dozen countries since 1988, was approved in the United States in 2000. Mifepristone blocks the action of progesterone,

which causes the pregnancy to separate from the endometrium and sensitizes the uterus to the uterotonic effects of a synthetic prostaglandin. The second required medication, misoprostol, is the synthetic prostaglandin given 1 to 2 days later, which causes the uterus to contract and the pregnancy to be expelled. The prescribing physician must be able to confirm that the gestational age is no greater than 7 weeks, to make sure it is not an ectopic pregnancy, and to perform or refer for a surgical abortion if needed. Because of the high cost of mifepristone, evidence-based regimens in the United States have been developed that use a lower dose of mifepristone, require a higher dose of misoprostol taken either buccally or vaginally, and are effective up to 9 weeks of pregnancy, depending on the regimen. A prophylactic antibiotic is often recommended, as with suction abortion.

Approximately 2% to 5% of women will need an aspiration curettage for a continuing pregnancy or persistent or heavy bleeding.

The major advantages of a medical abortion include its early use in pregnancy; avoidance of a surgical procedure; and perception of being more natural, less invasive, and private. Disadvantages of medical abortion include the length of time involved from initiation to final confirmation; potential side effects of nausea, vomiting, and diarrhea from misoprostol; cramping; unexpected heavy or persistent bleeding requiring suction curettage; continuing pregnancies requiring suction curettage in less than 1% of women; and the serious infections from *Clostridium* species (*C. sordellii*) that have a mortality rate of approximately 1 per 100,000 medical abortions, found at a similar rate as a spontaneous miscarriage.

## SUMMARY

Teens need to be encouraged to develop healthy relationships, regardless of whether they elect to be sexually active or not. Physicians should offer encouragement to those who choose abstinence, as well as identify those who are ready to become or already are sexually active, and help them make informed decisions about pregnancy prevention and STI protection. Current contraceptive methods are highly effective and safe. Hormonal methods have important noncontraceptive benefits such as regulated menses, reduced dysmenorrhea, and reduced risks for endometrial and ovarian cancer. Easy access to emergency contraception is an important back-up method to reduce unintended pregnancies and can be prescribed in advance at pediatric visits or is available over the counter for those older than 16 years of age. Early abortion should be readily available with minimal obstacles because of its safety over delayed abortions. Mifepristone is an important alternative to suction abortion for teens fearful of a surgical procedure. Pediatricians continue to play an important role in supporting the reproductive health care needs of their teen patients.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Cervical Cancer—Basic Facts on Screening and the Pap Test* (fact sheet), Centers for Disease Control

- and Prevention ([www.cdc.gov/cancer/cervical/pdf/cc\\_basic.pdf](http://www.cdc.gov/cancer/cervical/pdf/cc_basic.pdf))
- *Condom Fact Sheet In Brief* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/condomeffectiveness/brief.html](http://www.cdc.gov/condomeffectiveness/brief.html))
  - *Contraception* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/reproductivehealth/UnintendedPregnancy/Contraception.htm](http://www.cdc.gov/reproductivehealth/UnintendedPregnancy/Contraception.htm))
  - *Deciding to Wait* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
  - *Effective Birth Control for Sexually Active Teens* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/teen/dating-sex/Pages/Birth-Control-for-Sexually-Active-Teens.aspx](http://www.healthychildren.org/English/ages-stages/teen/dating-sex/Pages/Birth-Control-for-Sexually-Active-Teens.aspx))
  - *Emergency Contraception* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/teen/dating-sex/Pages/Emergency-Contraception.aspx](http://www.healthychildren.org/English/ages-stages/teen/dating-sex/Pages/Emergency-Contraception.aspx))
  - *Helping Teens Stay Healthy and Safe: Health Care, Birth Control, and Confidential Services* (brochure), Center for Adolescent Health and the Law ([www.cahl.org/helping-teens-stay-healthy-and-safe-health-care-birth-control-and-confidential-services-2007](http://www.cahl.org/helping-teens-stay-healthy-and-safe-health-care-birth-control-and-confidential-services-2007))
  - *Info for Teens* (Web page), Planned Parenthood ([www.plannedparenthood.org/teens](http://www.plannedparenthood.org/teens))
  - *Information for Teens: What you Need to Know about Privacy* (web page), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/teen/Pages/Information-for-Teens-What-You-Need-to-Know-About-Privacy.aspx](http://www.healthychildren.org/English/ages-stages/teen/Pages/Information-for-Teens-What-You-Need-to-Know-About-Privacy.aspx))
  - *Making Healthy Decisions About Sex: Important Information For Teens* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
  - *National Emergency Contraception Hotline* (800-NOT-2-LATE)
  - *The Pelvic Exam* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
  - *What Is an Adolescent Health Specialist?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-an-Adolescent-Health-Specialist.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-an-Adolescent-Health-Specialist.aspx))

### AAP POLICY

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## PART 6

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# Presenting Signs and Symptoms

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## Chapter 124

# ABDOMINAL DISTENTION

Peter F. Belamarich, MD

Abdominal distention can be a challenging clinical problem. There are no statistical definitions of distention available to pediatricians; therefore, determining what is likely to be pathological distention takes experience that includes many examinations of children of various ages in illness and in health.

Establishing the precise cause of abdominal distention in childhood from the history and physical examination alone can be also be difficult. The number of possible diagnoses is very large, and the most likely diagnoses vary greatly with the age of the child. Furthermore, not all distention is pathological. Healthy infants may have variable degrees of abdominal distention caused by aerophagia, and healthy toddlers may have a potbelly resulting from a combination of lumbar lordosis and relative hypotonia of the abdominal rectus muscles. The nonpathological distention often seen in infants and toddlers may exceed the mild distention seen with an intraabdominal malignancy. Therefore, a careful systematic approach should be used whenever concerns about abdominal distention are raised. The assessment of distention invites us to combine a systematic diagnostic thinking process and the art of physical diagnosis to minimize tests, radiation, discomfort, and expense.

## APPROACH TO THE CHILD WITH ABDOMINAL DISTENTION

### History

The history should establish the tempo of the obstruction, the presence or absence of gastrointestinal (GI) symptoms, pain, and constitutional symptoms.

Symptoms of GI obstruction (vomiting, pain, constipation, delayed passage of meconium at birth) or malabsorption (failure to thrive, diarrhea or greasy, bulky, malodorous stools) should be sought.

Although pain is present in most cases, an episode of acutely painful distention is a surgical emergency until proved otherwise. Painless distention raises the question of ascites, progressive organomegaly, tumors, and cysts, as well as abdominal hypotonia.

The presence of fever, weight loss, failure to thrive, anorexia, fatigue, irritability, or bone pain should be sought because these symptoms may suggest a malignancy; however, their absence does not exclude one.

See Table 124-1 for a list of symptoms that suggest specific causes of distention.

Medication use, including herbal and alternative therapies, should be reviewed, with particular attention to laxative dependence as a clue to Hirschsprung disease or another organic cause of constipation and to the use of agents that can cause GI ileus and constipation.

Travel history should be covered to explore the possibility of geographically specific causes of distention, such as ascariasis, which in many parts of the world is a common cause of GI obstruction.

Given the vast differential diagnosis, the past medical history should be comprehensive. Conditions that predispose children to an intraabdominal malignancy include the WAGR syndrome (Wilms tumor, aniridia, genitourinary abnormalities, and mental retardation) and Denys-Drash syndrome, which are associated with increased risk for Wilms tumor, and Beckwith-Wiedemann syndrome, which puts affected children at increased risk for Wilms tumor, hepatoblastoma, and adrenal carcinoma. Children with trisomies, DNA fragility syndromes, and immunodeficient states are at risk for lymphoma and leukemia. A history of abdominal surgery suggests the possibility of intestinal adhesions causing obstruction. Behavioral and psychiatric disorders should raise the question of a bezoar.

The family history should include questions about cystic fibrosis (meconium ileus), polycystic kidney disease, metabolic diseases, and whether any history exists of fetal demise or early neonatal death that might indicate an unrecognized metabolic disease, some of which produce hepatomegaly, splenomegaly, and congenital ascites.

In newborns, additional clues may be found in the pregnancy history: oligohydramnios suggests distal

**Table 124-1** Symptoms That Suggest Causes of Abdominal Distention

SYMPTOM	CAUSE
Fever	Peritonitis
Diffuse severe pain	Obstruction, peritonitis, pancreatitis
Constitutional symptoms—weight loss	Malignancy
Perception of a mass	Malignancy
Bilious or pernicious vomiting	GI obstruction, ruptured ectopic pregnancy
Progressive, asymptomatic distention	Malignancy, ascites
Malodorous stools	Malabsorption
Amenorrhea	Imperforate hymen
Weakness	Rickets

urinary obstruction, whereas polyhydramnios is seen with upper GI obstruction.

For infants and toddlers with otherwise asymptomatic distention, a diet history may suggest that the child is at risk for rickets. One must be careful to differentiate a parent's concern about the potbelly appearance of a toddler from more ominous reports of progressive or marked distention or the perception of a mass.

In female adolescents, the possibility of a pregnancy mandates that a confidential history of sexual activity be obtained. A history of amenorrhea despite advanced puberty raises the question of imperforate hymen with hematocolpos.

### Physical Examination

The value of an unhurried, calm, reassuring, and gentle approach to the anxious younger child with an abdominal problem cannot be overstated. Having the child's parents model the examination, using the child's doll or toy to demonstrate what will happen, is key to achieving this. To this end, sometimes the examination table must be forgone in favor of lying the child down across the parent's lap. The abdominal examination of an unwilling, anxious child who is struggling and crying is uniformly unsatisfying and nondiagnostic.

The profile of the abdomen should be inspected with the child in a supine position, noting whether the distention is generalized (maximum at the umbilicus) or localized. Box 124-1 presents commonly encountered causes for focal abdominal distention and common masses. The pattern and prominence of the

abdominal veins should be noted. Prominent superficial veins on the abdomen may indicate portal hypertension or obstruction to the systemic venous return. The abdomen should be auscultated for hyperactive bowel sounds (malabsorption, acute obstruction), rushes (incomplete obstruction), and absence of sounds (paralytic ileus), as well as for bruits (vascular malformation).

Percussion can be used to differentiate diffuse from the more focal epigastric tympani and to identify shifting dullness in older children.

Gentle palpation should begin from the lower quadrants and progress upward so that the inferior edge of the liver and spleen are appreciated (massive hepatomegaly may be missed if the liver is compressible and the liver's edge is near the child's pelvis). The abdomen should be assessed for focal or generalized tenderness. Involuntary guarding noted on gentle palpation is a sensitive sign of peritoneal inflammation; assessment of rebound tenderness in young children is vulnerable to false-positive results.

When an abdominal mass is appreciated, the examiner should note its location and whether it is painful, is mobile (intraabdominal) or nonmobile (retroperitoneal, malignant), moves with respiration (liver and spleen), is cystic or solid or malleable (fecal masses), is smooth or nodular, and whether it crosses the midline (often seen with neuroblastoma). Ballottement—"throwing" the kidney anteriorly with a finger in the costovertebral angle while palpating the surface of the abdomen with the other hand—can help elicit masses in the flank that cannot be appreciated with simple palpation.

#### BOX 124-1 Causes of Focal Abdominal Distention or Mass

##### EPIGASTRIUM

- Duodenal atresia
- Pyloric stenosis
- Malrotation
- Gastric duplication
- Bezoar

##### FLANK

- Wilms tumor
- Hydronephrosis
- Multicystic kidney
- Polycystic kidney
- Neuroblastoma
- Renal vein thrombosis
- Adrenal hemorrhage

##### RIGHT UPPER QUADRANT

- Choledochal cyst
- Hepatomegaly
- Hepatic tumors
- Hydrops of the gallbladder

##### LEFT UPPER QUADRANT

- Splenomegaly
- Splenic cyst

##### RIGHT LOWER QUADRANT

- Ovarian mass
- Intussusception
- Appendiceal abscess
- Crohn disease
- Fecal mass

##### LEFT LOWER QUADRANT

- Ovarian mass
- Fecal mass

##### HYPOGASTRIUM

- Hydrometrocolpos
- Hematocolpos
- Fecal mass
- Presacral teratoma
- Obstructed bladder
- Urachal cyst



Although rectal examination is often avoided, properly done it can add considerable information to the evaluation of children who have constipation, anal stenosis, Hirschsprung disease, and pelvic masses.

Infants who have ascites have bilateral bulging flanks in the supine position; in older children, the examiner may be able to elicit shifting dullness by percussion or appreciate a fluid wave. An acquired umbilical hernia may indicate massive ascites.

In female patients, a genital examination is necessary to exclude imperforate hymen with hydrometrocolpos or, in adolescents, hematocolpos and pregnancy. In both sexes, lower genitourinary tract malformation raises the question of upper genitourinary tract malformation.

Examination of the inguinal region and the scrotum in males for an inguinal hernia is always warranted with gaseous distention or symptoms of obstruction. Scrotal edema may accompany ascites caused by hypoalbuminemia.

Finally, an assessment of muscular tone and a search for the signs of rickets are warranted in all children whose distention remains unexplained.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis can be narrowed further based on whether the child has a tympanitic abdomen or prominent GI symptoms, a palpable mass, organomegaly, ascites, or hypotonia of the abdominal wall (Table 124-2). Causes of hepatomegaly and splenomegaly are reviewed separately in Chapters 162 and 196, respectively.

Life-threatening causes of abdominal distention are presented in Box 124-2.

## Tympanitic Abdomen in Newborns and Neonates

Tympanitic abdominal distention may occur in healthy infants, in infants who have systemic conditions, and in newborns who have congenital causes of intestinal obstruction.

Some healthy infants experience transient mild distention because of air swallowing with crying or feeding. This distention is variable, greatest after feeding or fussing, and absent at other times. Vomiting is

### BOX 124-2 Life-Threatening Causes of Abdominal Distention

- Sepsis
- Peritonitis (GI perforation, infected ascites, primary bacterial, chemical)
- Intraabdominal bleeding
- Liver, spleen, or GI laceration or hematoma
- Severe pancreatitis
- Splenic sequestration crisis
- Acute renal failure
- Acute liver failure
- Ruptured ectopic pregnancy
- Severe electrolyte disturbances or toxicological etiologies leading to ileus

**Table 124-2** Differential Diagnosis of Abdominal Distention Based on Physical Examination Findings

PHYSICAL SIGN	POSSIBLE CAUSES
Tympanitic abdomen	GI ileus GI obstruction Peritonitis Malabsorption Aerophagia Pneumoperitoneum
Palpable mass	Renal tumor or hydronephrosis Adrenal, sympathetic chain tumor Hepatomegaly or hepatic tumor GI duplication Mesenteric, omental cyst Ovarian cyst or tumor, hematocolpos Splenic or lymphatic enlargement or tumor
Ascites	Hypoalbuminemia from nephrosis, protein-losing enteropathy Hepatic cirrhosis, liver failure Heart failure Urinary ascites from a ruptured urinary tract Chylous ascites—congenital, traumatic, postoperative
Abdominal wall hypotonia	Generalized hypotonia Rickets Hypothyroidism
Signs of peritonitis	GI perforation Bacterial peritonitis Chemical peritonitis—leak of bile or pancreatic fluid

absent, and the stooling pattern and physical examination are normal.

In the ill newborn, many systemic conditions cause a paralytic intestinal ileus characterized by quiet, non-tender abdominal distention: sepsis, pneumonia, birth asphyxia, hypothyroidism, and electrolyte imbalance. In premature infants, necrotizing enterocolitis (NEC) should be considered.

Congenital causes of proximal GI obstruction causing distention in newborns include intestinal atresias, annular pancreas, and abnormalities of intestinal rotation and fixation. The most common proximal GI obstruction is duodenal atresia, characterized by polyhydramnios in 50% of patients and the onset of bilious vomiting in the first hours of life in conjunction with focal epigastric distention (Figure 124-1). Upright plain radiographs are diagnostic of duodenal obstruction when they demonstrate the double-bubble sign. Because malrotation is present in up to 19% of patients who have intrinsic duodenal obstruction, a barium enema should establish normal intestinal rotation in infants whose surgery is deferred.

Upper abdominal distention is a common, although not universal, finding in newborns and infants who have symptomatic intestinal malrotation, most of whom have bilious vomiting in the first 4 weeks of life. Plain radiographs may demonstrate a distended stomach or duodenal distention with a paucity of gas distally, or the radiographs may appear normal. Therefore, clinical suspicion even in the face of a normal plain radiograph warrants an upper GI series.

Congenital causes of lower intestinal obstruction include distal intestinal atresias, meconium ileus, Hirschsprung disease, small left colon syndrome, and anorectal malformations. Newborns who have lower intestinal obstruction typically develop generalized tympanitic distention over the course of 24 to 48 hours, with bilious vomiting and failure to pass meconium. Although an imperforate anus or an incarcerated hernia will be apparent on physical examination, differentiation of the remaining causes of lower intestinal obstruction involves radiographic evaluation.

Marked tympanitic abdominal distention can be a manifestation of pneumoperitoneum, which is demonstrated by upright and cross-table lateral abdominal radiographs revealing free air within the peritoneum. When pneumoperitoneum is associated with peritonitis, intestinal perforation is likely, and the causes

include NEC, volvulus, an intestinal obstruction causing perforation, appendicitis, and spontaneous perforations. In infants on a respirator, pneumoperitoneum may occur without peritonitis as a complication of pneumomediastinum.

### Tympanitic Abdomen Beyond the Neonatal Period

Beyond the neonatal period, the causes of a tympanitic abdomen include intestinal ileus, mechanical obstruction, pneumoperitoneum, and malabsorption.

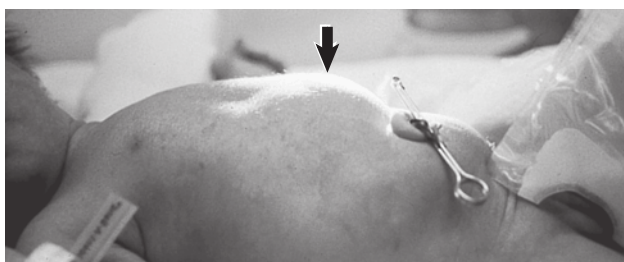
Children with paralytic ileus have a clinical picture similar to that seen with distal mechanical bowel obstruction; however, bowel sounds are diminished or absent, and plain radiographs demonstrate air throughout the GI tract. Common precipitants include abdominal surgery, peritonitis, trauma, shock, sepsis, hypokalemia, and anesthesia, as well as numerous medications.

GI obstruction causing a tympanitic abdomen beyond the neonatal period can be either a late presentation of a congenital problem or an acquired condition, including an intraluminal obstruction such as pyloric stenosis, intussusception, a bezoar, meconium ileus equivalent, intestinal polyps, ascariasis, or an intrinsic tumor. Extraluminal obstructions include postoperative adhesions, an appendiceal abscess, a Meckel diverticulum, and extrinsic compression by abdominal or pelvic masses.

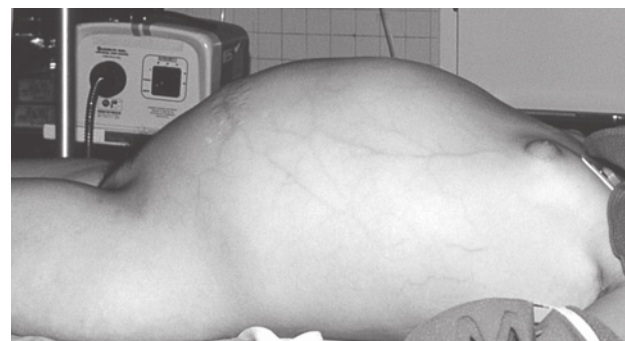
Tympanitic distention occurs in conjunction with the fat malabsorption syndromes, cystic fibrosis, and celiac disease. These conditions are characterized by steatorrhea and variable degrees of malnutrition and suboptimal growth. Although idiopathic constipation is extremely common throughout childhood and impaction can cause abdominal distention (Figure 124-2), marked distention or recurrent distention should not be attributed to functional constipation (see Chapter 134, Constipation).

### Abdominal Masses in Newborns and Neonates

Two-thirds of abdominal masses in neonates originate from the kidney or the urinary tract. Renal masses are



**Figure 124-1** Newborn infant with duodenal atresia and upper abdominal distention.



**Figure 124-2** Thirteen-year-old girl with severe fecal impaction.

retroperitoneal, nonmobile, and appreciated either in the flank or on deep abdominal palpation. Cystic masses predominate and have a slightly compressible quality. A multicystic kidney is the single most common neonatal flank mass. It can be appreciated on physical examination as a soft mass with a slightly irregular contour. The next most frequently encountered renal mass is caused by hydronephrosis. A smooth unilateral flank mass in an otherwise well newborn is usually from a ureteropelvic junction obstruction. Posterior urethral valves, a common cause of bilateral hydronephrosis and hydroureters in male infants, may present as bilateral flank masses or a palpable bladder. Newborns who have autosomal recessive polycystic kidney disease may have palpable bilateral firm flank masses, oliguria, hematuria, and hypertension. The most common renal tumor encountered in newborns is a mesoblastic nephroma, a tumor that can cause massive unilateral nephromegaly.

Renal vein thrombosis is a rare but important cause of a smooth flank mass and hematuria, which develop concurrently in an ill newborn after an episode of asphyxia, sepsis, or dehydration or in an infant whose mother has diabetes.

Of the remaining one third of neonatal abdominal masses that arise outside the urinary tract, neuroblastoma, GI duplications, hydrometrocolpos, and ovarian cysts account for a large proportion.

When a newborn has a palpable flank mass after a traumatic or breech delivery, the possibility of an adrenal hemorrhage should be considered, as should hepatic and splenic hematomas.

Female newborns may have a lower abdominal or pelvic mass from hydrometrocolpos. An imperforate hymen will be evident on the genital examination as a bulging round membrane within the introitus. A rectal examination can be diagnostic for the presence of a dilated vagina in higher obstructions.

Although rare, a significant number of benign epithelial cysts may arise in the neonatal period, including choledochal cysts (right upper quadrant), splenic cysts (left upper quadrant), mesenteric cysts (midabdominal, mobile in the transverse plane), and urachal cysts (hypogastrium). Retroperitoneal cysts include abdominal lymphangiomas and pancreatic cysts.

### Abdominal Masses Beyond the Neonatal Period

The differential diagnosis of masses in infants and older children includes late presentations of congenital masses, malignancies, fecal masses, bezoars, and pancreatic pseudocysts. Of the congenital masses, GI duplications, mesenteric cysts, and choledochal cysts may enlarge slowly and become apparent in later infancy or childhood. Similarly, an adolescent who has an imperforate hymen or vaginal septum may not become symptomatic with hematocolpos until the onset of cyclical uterine bleeding.

The abdomen is the site of origin of Wilms tumor, hepatic tumors, ovarian tumors, about 70% of neuroblastomas, and 30% of non-Hodgkin lymphomas. Neuroblastoma, Wilms tumor, and hepatoblastoma may produce an asymptomatic abdominal distention or mass that is noted by the parent during bathing or

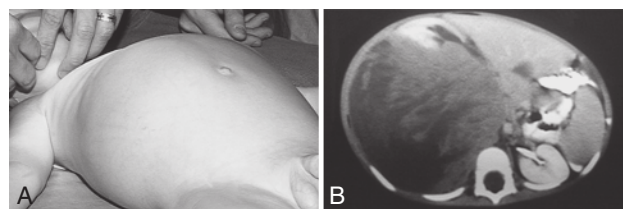
dressing the child or by the physician on routine physical examination. Wilms tumor tends to occur in older infants and toddlers, with a peak incidence in 2- to 5-year-old children (Figure 124-3). Hepatoblastoma, the most common primary hepatic malignancy in childhood, is also overwhelmingly discovered as an asymptomatic abdominal mass, with a median age at diagnosis of 12 months. In the second decade, tumors detected as an abdominal mass are predominantly ovarian (Figure 124-4) or non-Hodgkin lymphoma.

Fecal masses are extremely common in childhood and adolescence and may be found in the right lower quadrant (when a redundant sigmoid colon loops to the right), in the hypogastrium, or in the left lower quadrant. They are mobile, nontender, and malleable. Reexamination after laxative therapy should confirm that the masses are no longer present.

Bezoars, which are intragastric concretions of indigestible material, can cause a large array of GI complications, including upper abdominal discomfort and a large mass. Most commonly, they result from the ingestion of hair.

### Ascites

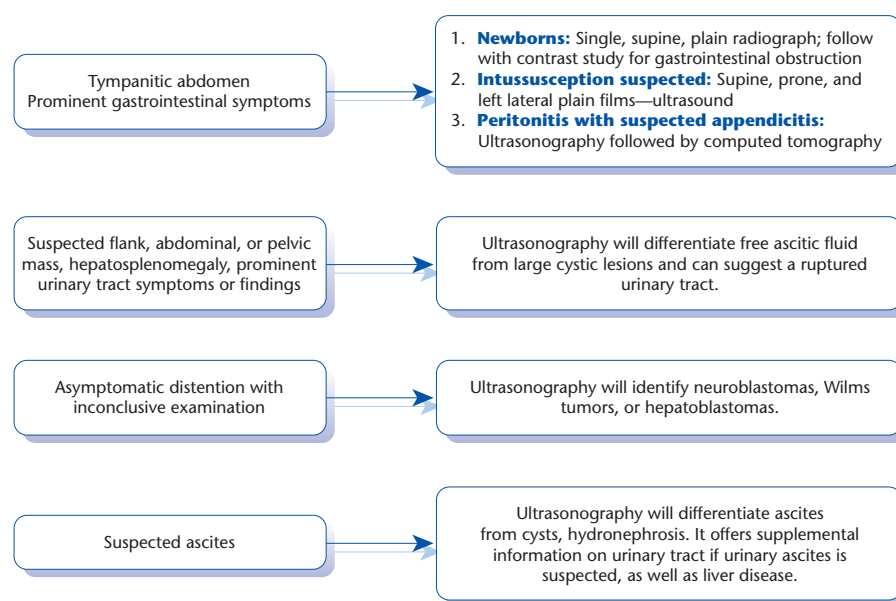
The newborn with ascites has a distended, nontympanic abdomen with bulging and dullness in the flanks, findings that may be mimicked by a massively dilated bladder, a severely hydronephrotic kidney, or a large ovarian cyst. In the newborn, ascites results most



**Figure 124-3** A, Abdominal distention from a right-sided Wilms tumor. B, Computed tomographic scan of tumor.



**Figure 124-4** Lower abdominal distention caused by ovarian teratoma.



**Figure 124-5** Initial radiographic approach to abdominal distention in infants and children.

often from a perforation within an obstructed urinary tract; in boys, posterior urethral valves are a common precipitant.

Beyond the neonatal period, ascites occurs most commonly as a consequence of nephrotic syndrome. It is also commonly seen in chronic liver disease with cirrhosis and portal hypertension, and in congestive heart failure.

Chylous ascites is a rare condition that occurs when lymphatic fluid leaks directly into the peritoneum because of a malformation or perforation of the intestinal lymphatics. The diagnosis is made by paracentesis.

### Abdominal Wall Hypotonia

Abdominal distention is frequently encountered in healthy infants and may also be seen in infants with a variety of neuromuscular conditions that produce generalized hypotonia. Hypothyroidism and rickets can cause abdominal distention to develop insidiously.

### Radiographic Approach

Although the history and physical examination sometimes provide the diagnosis, many children who have abdominal distention require radiographic imaging. The choice of initial imaging modality is dictated by clinical suspicion, primary findings on physical examination, and locally available resources and expertise.

Given that a single abdominal computed tomography (CT) scan can deliver the same radiation dose as 250 chest radiographs, the judicious and informed use of CT scanning for the evaluation of children with abdominal distention is encouraged.

Therefore, consulting with the radiologist is helpful. Some general guidelines for choosing an initial radiologic study are presented in Figure 124-5.

*The author wishes to thank Kenneth Kenigsberg, MD, for providing the photographs used in this chapter.*

### WHEN TO ADMIT

Abdominal distention in the presence of:

- Refractory vomiting, dehydration
- Peritonitis
- Toxic or septic appearance
- Moderate or severe pain that is undiagnosed or not well controlled
- Mass suspicious for malignancy
- Urgently needed surgical or radiologic procedures

### TOOLS FOR PRACTICE

#### Medical Decision Support

- *Evaluation and treatment of constipation in infants and children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition* (guideline), North American Society for Pediatric Gastroenterology, Hepatology and Nutrition ([www.naspghan.org/user-assets/Documents/pdf/PositionPapers/constipation.guideline.2006.pdf](http://www.naspghan.org/user-assets/Documents/pdf/PositionPapers/constipation.guideline.2006.pdf))
- *North American Society for Pediatric Gastroenterology, Hepatology and Nutrition* (Web site), ([www.naspghan.org](http://www.naspghan.org))

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## Chapter 125 ABDOMINAL PAIN

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John F. Thompson, MD

Abdominal pain is one of the most common symptoms in children and adolescents and is estimated to account for approximately 5% of unscheduled office visits. Acute abdominal pain may require medical or surgical intervention to prevent disability or even death. The precise number of children who experience acute abdominal pain is unknown, but acute appendicitis is the most common abdominal emergency in the pediatric population, with an estimated 81,000 appendectomies performed in the United States annually. More commonly, abdominal pain is a recurrent symptom not associated with physical disability or mortality.

Abdominal pain is determined by several different factors, including the provocation itself, the type of receptor involved, the organization of the neural pathways from the site of injury to the central nervous system, and complex communication between transmission, understanding, and reaction to pain. Abdominal pain is transmitted through distinct types of afferent nerve fibers. These result in the perception of 3 different types of abdominal pain: visceral, parietal, and referred pain.

The principal mechanical signal to which visceral nociceptors are sensitive is stretch, and visceral pain is transmitted by nonmyelinated nerves that are found in muscle, mesentery, peritoneum, and viscera. Pain from abdominal viscera tends to be burning, dull, diffuse, crampy, poorly localized, more gradual in onset, and long in duration. Abdominal organs convey sensation to both sides of the spinal cord; therefore, visceral pain is usually perceived to be in the midline. The area involved may be contingent on the organ affected.

For example, lower esophageal, gastric, and duodenal pain tends to be felt in the epigastrium. Small intestinal distention may be periumbilical or in the hypogastrium. Colonic pain may be felt in the lower abdomen. Innervation of most viscera is multisegmental, and because there are fewer nerve endings in the viscera than in more sensitive organs such as the skin, visceral pain is not well localized. Secondary effects such as sweating, restlessness, nausea, vomiting, perspiration, and pallor often accompany visceral pain. The patient may shift position in an attempt to relieve the distress.

Parietal pain is mediated by myelinated nerve receptors that are distributed principally to skin and muscle. These pain receptors respond to tearing or inflammation. Pain is perceived as sharp, sudden, and well-localized such as that which follows an acute injury. Parietal pain occurring from injurious stimulation of the parietal peritoneum is more powerful and more precisely localized than visceral pain. In acute appendicitis, early vague periumbilical visceral pain is followed by the localized parietal pain at McBurney point that is produced by inflammatory involvement of the parietal peritoneum. Parietal pain is typically heightened by movement. Reflexive responses, such as abdominal rigidity and involuntary guarding, are facilitated by spinal reflex arcs that contain parietal pain pathways.

Referred pain results from the interplay between visceral and parietal pain. It is felt in regions distant from the diseased organ and results when visceral and somatic neurons from different areas meet at second-order neurons in the same spinal segment as nerve fibers from cutaneous dermatomes. Examples of this type of pain include referred right scapular pain secondary to acute cholecystitis and mid-back pain from acute pancreatitis.

Functional abdominal pain (FAP), the most common cause of chronic abdominal pain in the pediatric population, was first characterized by Apley and Naish as pain that occurs at least 3 times over a period of 3 or more months severely enough to affect daily activities in children older than 3 years. The prevalence of FAP is estimated to be between 0.3% and 19%, although in large studies the prevalence is far lower, 0.3% to 8%. One reason for the broad range may be the lack of uniformity of criteria for making the diagnosis of FAP: its definitions may be too broad and may include other functional gastrointestinal disorders, such as functional dyspepsia.

A multidimensional measurement of FAP has been created, which, according to the Rome III criteria, must include episodic or continuous abdominal pain, insufficient criteria for other functional gastrointestinal disorders, and absence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms. The experience of the pain must occur once a week for at least 2 months. Regardless, no consensus exists on an exact definition. Some trends have been noted, such as a higher prevalence of FAP in girls. The highest prevalence occurs in children between 4 and 6 years of age and in early adolescence. Studies have also demonstrated associations between FAP and the child's family dynamics (eg, children

living in a single-parent household are more likely to experience chronic abdominal pain), psychological comorbidity such as anxiety, and socioeconomic environment (eg, children living in low-income, low-educated-worker families are more likely to experience pain).

Criteria have been established to categorize FAP. Initially, the Rome I criteria, later updated as Rome II, improved the definition of functional gastrointestinal disorders. Although this classification system can help categorize patients so that appropriate treatment options can be considered, not all children can be clearly placed in these categories. Some authorities have argued against using the classification in children, with one major reason being that the most common location of FAP is periumbilical pain, which is not in the Rome II criteria. Twenty-seven percent of children with abdominal pain do not meet Rome II criteria overall.

Pediatric gastroenterologists have identified and developed similar criteria for childhood functional disorders, including FAP. These criteria—the Rome III Criteria for Functional Bowel Disorders Associated With Abdominal Pain or Discomfort in Children—are based on symptom classification. Four classes were identified, including functional dyspepsia, irritable bowel syndrome, childhood functional abdominal pain as defined above (with a subgroup of children having childhood functional abdominal pain syndrome), and abdominal migraine. The usefulness of the Rome III criteria still needs to be established.

As difficult as characterizing different types of FAP is assessing the effectiveness of various treatments. Significant inconsistencies exist in the methodologic approaches currently used to assess pain. The influence of age and developmental maturation, individual differences (eg, temperament, coping patterns), family interactions, and community and cultural contexts may influence the expression of FAP, and these areas have not been addressed in the assessment of pain. To attend to some of these issues, a multidimensional analytic approach has been developed to assess the primary outcome in clinical trials.

In light of suboptimal classification and assessment tools, a symptom-based differential diagnosis with an emphasis on identifying the warning signals for organic disease is currently the most useful approach to patient care. Pediatricians and other physicians must recognize that chronic abdominal pain can lead to significant dysfunction and disability, with school absences, repeated visits to health care professionals, and secondary psychological problems if assessment and initiation of treatment are either ignored or delayed.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of acute abdominal pain can be subdivided into 3 broad categories: conditions that require immediate surgical intervention (Box 125-1), conditions that may be managed medically at first but may require surgical involvement (Box 125-2), and conditions that can be managed medically (Box 125-3). The differential diagnosis of acute abdominal pain based on age is provided in Box 125-4. The differential diagnosis of chronic or recurrent abdominal pain include those functional entities defined in the Rome III criteria as well as nonfunctional entities as shown in Box 125-5.

### BOX 125-1 Differential Diagnosis of Acute Surgical Abdomen

- Closed loop intestinal obstruction
- Volvulus (gastric, midgut, sigmoid)
- Incarcerated hernia (inguinal, internal, external)
- High-grade bowel obstruction
- Nonreducible intussusception
- Malrotation with Ladd bands
- Ovarian torsion
- Testicular torsion
- Acute appendicitis
- Perforated viscus with diffuse peritonitis or toxicity
- Ruptured tumor
- Ectopic pregnancy

### BOX 125-2 Differential Diagnosis of Acute Abdominal Pain That May Require a Combined Surgical and Medical Approach

- Partial small bowel obstruction
- Postsurgical adhesions
- Crohn disease
- Lymphoma
- Periappendiceal abscess
- Abdominal abscess
- Cholecystitis
- Gallbladder hydrops
- Pancreatitis
- Pancreatic pseudocyst
- Toxic megacolon or typhlitis

Entities that may require combined surgical and medical management are primarily associated with the gastrointestinal lumen as well as its associated organs (see Box 125-2) and can include postsurgical complications such as abdominal abscess or pancreatitis.

The concept of *referred pain* is especially relevant when discussing acute abdominal pain in children. A complete history may provide crucial information that suggests the abdominal pain may originate outside the abdomen. For example, a 3-year-old who has pneumonia may have inflammatory irritation of the diaphragm, resulting in acute abdominal pain as the presenting complaint. In addition, perihepatitis (Fitz-Hugh-Curtis syndrome) can produce acute abdominal pain, and the physician should be sensitive to an adolescent girl's possible reluctance to spontaneously disclose a history of sexual intercourse. The differential diagnoses of medical entities, including those that are extraabdominal or systemic, are listed in Box 125-3.

### BOX 125-3 Differential Diagnosis of Acute Abdominal Pain That May Require Medical Management

- |  |  |
|--|--|
| <ul style="list-style-type: none"> <li>• Upper respiratory infection, pharyngitis</li> <li>• Viral gastroenteritis (mesenteric adenitis)</li> <li>• Pneumonia</li> <li>• Partial bowel obstruction</li> <li>• Paralytic ileus</li> <li>• Fecal impaction</li> <li>• Meconium ileus equivalent in cystic fibrosis</li> <li>• Bacterial enterocolitis</li> <li>• Acute gastritis or peptic ulcer</li> <li>• Acute constipation</li> <li>• Flare of functional abdominal pain</li> <li>• Acute hepatitis</li> <li>• Perihepatitis (Fitz-Hugh–Curtis syndrome)</li> <li>• Inflammatory bowel disease (Crohn disease and ulcerative colitis)</li> </ul> | <ul style="list-style-type: none"> <li>• Henoch-Schönlein purpura</li> <li>• Hemolytic uremic syndrome</li> <li>• Collagen vascular disease</li> <li>• Hereditary angioedema</li> <li>• Pyelonephritis</li> <li>• Renal calculi</li> <li>• Pelvic inflammatory disease</li> <li>• Sickle cell crisis</li> <li>• Diabetic ketoacidosis</li> <li>• Dysmenorrhea</li> <li>• Mittelschmerz</li> <li>• Poisoning</li> <li>• Porphyria</li> <li>• Intestinal gas pain</li> </ul> |
|--|--|

### BOX 125-4 Main Causes of Acute Abdominal Pain by Age

- |   |  |
|---|--|
| <p><b>NEONATE</b></p> <ul style="list-style-type: none"> <li>• Necrotizing enterocolitis</li> <li>• Spontaneous gastric perforation</li> <li>• Hirschsprung disease</li> <li>• Meconium ileus</li> <li>• Intestinal atresia or stenosis</li> <li>• Peritonitis owing to gastroschisis or ruptured omphalocele</li> <li>• Traumatic perforation of viscus (difficult birth)</li> </ul> <p><b>INFANT (&lt;2 YEARS)</b></p> <ul style="list-style-type: none"> <li>• Colic (&lt;3 months)</li> <li>• Acute gastroenteritis or viral syndrome</li> <li>• Traumatic perforation of viscus (child abuse)</li> <li>• Intussusception</li> <li>• Incarcerated hernia</li> <li>• Volvulus (malrotation)</li> <li>• Sickling syndromes</li> </ul> | <p><b>SCHOOL AGE (2–13 YEARS)</b></p> <ul style="list-style-type: none"> <li>• Acute gastroenteritis or viral syndrome</li> <li>• Urinary tract infection</li> <li>• Appendicitis</li> <li>• Trauma</li> <li>• Constipation</li> <li>• Pneumonia</li> <li>• Sickling syndromes</li> </ul> <p><b>ADOLESCENT</b></p> <ul style="list-style-type: none"> <li>• Acute gastroenteritis or viral syndrome</li> <li>• Urinary tract infection</li> <li>• Appendicitis</li> <li>• Trauma</li> <li>• Constipation</li> <li>• Pelvic inflammatory disease</li> <li>• Pneumonia</li> <li>• Mittelschmerz</li> </ul> |
|---|--|

Box 125-4 lists some of the major diagnostic considerations for acute abdominal pain in children by age. Although diagnostic considerations overlap for each age group, the child's age and physiologic development can help the physician focus the differential diagnosis. For example, Hirschsprung disease should be considered more likely in an infant in the first weeks of life; Mittelschmerz should most certainly be in the differential diagnosis for an adolescent girl.

The cause of chronic abdominal pain in an adolescent female merits particular attention as it may be gynecologic, resulting from dysmenorrhea, endometriosis, pelvic inflammatory disease, or ovarian abnormalities.

Dysmenorrhea is common among adolescent females: up to 90% report symptoms when surveyed, but only 40% have told their physician about the pain. Dysmenorrhea is categorized into primary and secondary dysmenorrhea, depending on whether there is underlying pelvic pathology. Symptoms usually begin 6 to 12 months after menarche. Patients complain of lower abdominal pain that is crampy, spasmodic, stabbing, or dull. The pain typically occurs during menstruation but can begin a day or 2 before the onset of menses. Other symptoms can include nausea, vomiting, and diarrhea (see Chapter 141, Dysmenorrhea). Adolescents with endometriosis can present with cyclic abdominal pain,

**BOX 125-5 Main Causes of Chronic Abdominal Pain by System****GI TRACT**

- Gastroesophageal reflux disease
- *Helicobacter pylori* gastritis
- Peptic ulcer
- Esophagitis
- Lactose intolerance
- Celiac disease
- Parasitic infection (*Giardia*, *Blastocystis hominis*)
- Inflammatory bowel disease
- Meckel diverticulum
- Malrotation with intermittent volvulus
- Chronic appendicitis
- Constipation

**GALLBLADDER, LIVER, AND PANCREAS**

- Cholelithiasis
- Choledochal cyst
- Hepatitis

- Liver abscess
- Recurrent pancreatitis

**GENITOURINARY TRACT**

- Hydronephrosis
- Urinary tract infection
- Urolithiasis
- Dysmenorrhea
- Pelvic inflammatory disease
- Mittelschmerz

**MISCELLANEOUS**

- Familial Mediterranean fever
- Malignancies
- Sickle cell crisis
- Lead poisoning
- Vasculitis (especially Henoch-Schönlein purpura)
- Angioneurotic edema
- Acute intermittent porphyria

nausea, diarrhea, and constipation in addition to typical symptoms of dysmenorrhea. The pain may be severe enough for patients to miss school, visit their pediatrician, or go to an emergency department for medical care. Sexually active adolescents can have lower abdominal pain from pelvic inflammatory disease and may even have fever and vomiting depending on the severity of the infection. Ovarian abnormalities that may cause pain include ovarian cysts, ruptured ovarian cysts, ovarian torsion, and Mittelschmerz.

Constipation is a frequent cause of abdominal pain and should be considered when a child presents with chronic abdominal pain. Three percent of general pediatric outpatient visits and 25% of pediatric gastroenterology consultations are related to possible dysfunction of defecation. The stool history may be unreliable, and an abdominal radiograph may not be helpful, but serious consideration should be given to empirical treatment with a stool softener (see Chapter 134, Constipation).

**EVALUATION****History**

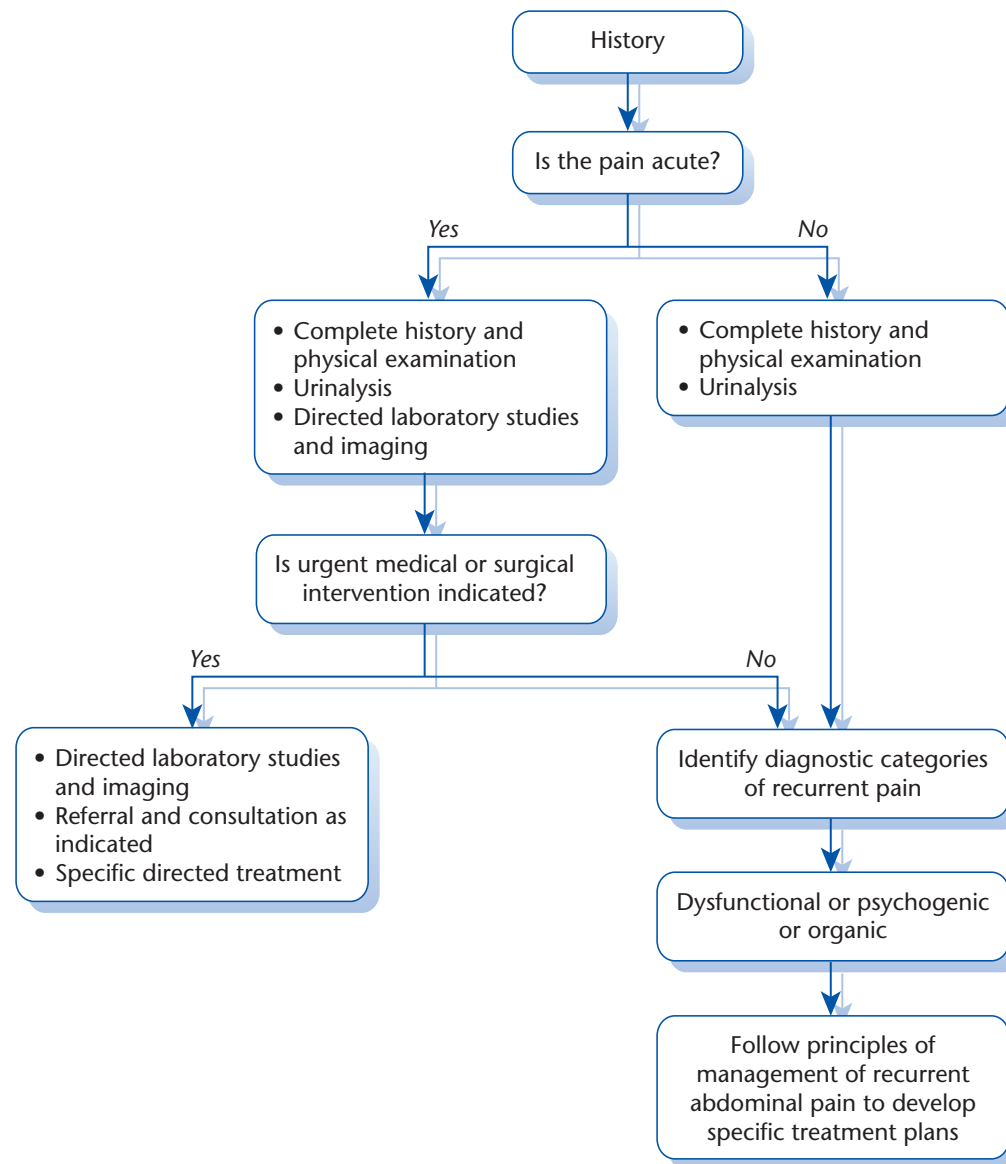
The approach to the evaluation of abdominal pain begins with a complete history and a thorough physical examination. The findings should direct the use of selected laboratory studies that are based on a reasonable differential diagnosis and will permit a clear therapeutic strategy to be created. Figure 125-1 summarizes the evaluation of the child or adolescent who has abdominal pain. The history alone accounts for most of the data the physician uses in making a diagnosis.

A systematic history should elicit information about the location, onset, and severity of the pain, alleviating

and precipitating factors, and associated symptoms. The timing of the onset and changes in the intensity, location, and quality of pain over time are essential factors in determining its cause. For children or adolescents who have recurring abdominal pain, information about the timing of the onset of the pain in relation to other events (eg, mealtime, school days), as well as the duration of each episode and the frequency of recurrence, is helpful. The effect of abdominal pain on school, work, sleep, and mood should be assessed. Additional information about family (inherited disorders, concurrent illnesses, chronic pain disorders), medical history (prior surgery, chronic medication, faltering growth), and environmental or behavioral factors (recent changes in family or school, travel, unusual food) should also be obtained. In adolescents, additional history should include menstrual history in females, sexual history, drug and alcohol use, and screening for depression. The timing of abdominal pain in relation to menses must be considered.

One must keep in mind that pain frequency, severity, location, presence or absence of associated symptoms, and effects on lifestyle cannot be used to distinguish between an organic or a functional cause for chronic abdominal pain. Nonetheless, children with FAP are more likely than children without FAP to have headache, joint pain, anorexia, vomiting, nausea, excessive gas, and altered bowel symptoms. The presence of alarming symptoms or signs suggests a higher probability or prevalence of organic disease and may justify performing diagnostic tests and referring the child to a subspecialist. Alarm symptoms or signs include, but are not limited to, involuntary weight loss, deceleration of linear growth, gastrointestinal blood loss, significant vomiting, chronic severe diarrhea, persistent right upper or right lower quadrant pain,





**Figure 125-1** Evaluation of child or adolescent who has abdominal pain.

unexplained fever, and family history of inflammatory bowel disease (see When to Refer). No single test can diagnose FAP. In patients with FAP a component of pain can be visceral hyperanalgesia, which provides a physiologic explanation of symptoms in children who have distinct functional gastrointestinal disorders.

The physician should help the family understand the importance of the history during the assessment. Both the parents and the patient should be interviewed. Patients must feel comfortable in discussing their own symptoms and concerns, even if these are different from those expressed by the parents. Confidentiality should be addressed with the adolescent patient when the parent is not present. Obtaining a history from the patient without the parents is therefore often useful; similarly, the parents may want to relate some of their concerns without the child being

present. Important diagnostic information can be missed if the pediatrician does not give the child and parents the opportunity to provide separate histories.

In addition to the presence of specific symptoms and positive history, negative aspects of the history can provide important information to narrow the differential diagnosis. For example, the absence of dysuria in an older child or adolescent would make the diagnosis of urinary tract infection unlikely.

### Physical Examination

Specific findings on the physical examination of children with FAP have rarely been described. The presence of tenderness on abdominal palpation has been reported to be characteristic of children with recurrent episodes of abdominal pain without evidence of organic disease, but most children's physical

examination will be normal. A normal examination and the absence of alarm signals point toward a functional diagnosis for abdominal pain. A complete physical examination, however, including a careful external examination of the urethral orifice and vaginal orifice as well as a rectal examination, should always be part of an initial assessment of abdominal pain. The history of the presenting symptoms will alert the pediatrician to consider more specific aspects of the physical examination.

### Laboratory Evaluation

Laboratory and diagnostic studies performed without any medical indications are generally not helpful and may actually hinder the therapeutic suggestions made by the pediatrician in FAP. The common pitfall of over-testing occurs when the physician responds to the parents' initial request to rule everything out by performing a battery of laboratory or radiographic studies. Maintaining a systematic approach to FAP will not only minimize the use of expensive, unnecessary laboratory studies but will also decrease recurrent emergency visits and, most important, prevent a delay in beginning effective treatment.

Dysfunctional and psychogenic causes account for most diagnoses of FAP, with organic causes identified in only approximately 5% to 8% of cases. However, diagnostic testing is indicated when alarm signals or abnormal physical findings suggest the possibility of an organic disorder. Tests to consider are listed in Box 125-6. When the history and physical examination indicate a dysfunctional or psychogenic cause, urinalysis could suffice as the initial laboratory study, but suggested screening laboratory tests are listed in the table below.

Laboratory and other diagnostic studies such as urinalysis (particularly in female patients of childbearing age), stool, or genital tract cultures; serum chemistries or erythrocyte sedimentation rate; radiographic studies (eg, barium swallow, upper or lower

gastrointestinal series, gallbladder series); and abdominal or pelvic ultrasound or computed tomographic scans should be directed to evaluate specific concerns identified in the history and physical examination. For example, when pancreatitis is suspected, laboratory investigations should include amylase and lipase. When indicated, abdominal and pelvic ultrasound provides a safe, noninvasive way to assess bowel and pelvic organ structures and help clarify the need for urgent surgical intervention (eg, intussusception, ovarian torsion, kidney abscess). In general, the physician should consider the least invasive procedures first, keeping in mind the cost of special studies in terms of pain, discomfort, and time.

Common laboratory tests (complete blood cell count, erythrocyte sedimentation rate, comprehensive metabolic panel, urinalysis, stool parasite analysis) are not helpful in distinguishing between organic and functional abdominal pain. The coexistence of abdominal pain and an abnormal test result does not necessarily indicate a cause-and-effect relationship. For example, eliminating dietary lactose as the treatment for patients with demonstrable lactose malabsorption does not necessarily result in the resolution of abdominal pain. Children found to have *Helicobacter pylori* infection are not more likely to have abdominal pain than children without *H pylori*.

### Imaging Studies

Ultrasound of the abdomen or pelvis is not useful in the absence of alarm symptoms. When atypical symptoms are present, such as jaundice, urinary symptoms, back or flank pain, vomiting, or abnormal findings at physical examination, abdominal and pelvic ultrasound is more likely than not to detect an abnormality. Endoscopy with biopsy in the absence of alarm symptoms similarly fails to reveal organic disease. Insufficient evidence exists to suggest that the use of esophageal pH monitoring in the absence of alarm symptoms results in finding organic disease. In patients who experience recurrent vomiting, an upper gastrointestinal series should be considered to define potential anatomic abnormalities such as gastric outlet disorder or malrotation. The choice of radiologic test should be guided by the differential diagnosis generated by the history and the physical examination.

### TREATMENT

The treatment of abdominal pain that results from an organic process should be pursued according to accepted practice guidelines for that condition. The treatment of FAP should be approached as a biopsychosocial phenomenon. FAP is still real pain. However, the response to pain can be subjective and understood through life experience. The treatment may therefore be a combination of psychotherapy, pharmacology, dietary, or alternative medicine techniques. It must always begin with educating the child and parent about the cause of the pain and the treatment plan. This approach not only improves the adherence to the treatment plan but also has been shown to affect the outcome. Treatment response may be influenced by whether the parents perceive the pain to have an organic cause. Similarly, children of parents

#### BOX 125-6 Suggested Screening Laboratory Tests

##### ALL PATIENTS

- Complete blood count with differential
- Erythrocyte sedimentation rate
- Comprehensive metabolic panel
- Stool hemocult

##### DIARRHEA

- Stool ova and parasite
- *Giardia* enzyme-linked immunosorbent assay
- *Clostridium difficile* toxin or PCR
- Celiac panel
- Lactose or fructose breath test
- Dyspepsia
- *Helicobacter pylori* stool antigen testin

who are open to a psychiatric consultation are more likely than not to report less pain.

## MANAGEMENT

A discussion of FAP as a real entity that is a product of an alteration in the brain-gut axis makes understanding the cause of the pain easier for parents. A good analogy is that of a migraine: no specific test exists to confirm the diagnosis, but stress and other inciting events may trigger a headache. When explained this way, parents may be better able to understand that the current thinking of autonomic dysfunction and visceral hypersensitivity as causes of the child's recurrent FAP does not mean that the pain is purely in the child's head or solely the effect of an undiagnosed physical ailment. Equally important is to inform the parents that the goal of therapy is not so much to arrive at a diagnosis, but rather to be able to have the child resume the lifestyle that preceded the onset of the abdominal pain, including school attendance, sleep patterns, and appetite.

## Psychosocial Treatment

Several different psychological strategies have been tried in a variety of conditions associated with functional pain, including treatment aimed at individuals or parent-child couples in one-to-one contacts with a therapist, group-based interventions, or a mixture of individual and group treatment. Psychological treatments, principally relaxation and cognitive-behavioral therapy, are effective in reducing the severity and frequency of chronic headache in children and adolescents. However, no evidence has been found for the effectiveness of psychological therapies in attenuating pain in conditions other than headache.

Cognitive-behavioral therapy that combines operant elements and stress management may provide an effective treatment for FAP, however. Cognitive-behavioral therapy results in short-term improvement, with more than one-half of patients experiencing freedom from pain. The child's coping skills and the parent's caregiving strategies predict the effectiveness of treatment. Disengagement and involuntary engagement are correlated with increased anxiety, depression, and somatic symptoms. Anxiety as a comorbidity has also been associated with FAP, and therefore psychological therapy may be used as a strategy in treating FAP.

Alternative medical techniques for the treatment of functional gastrointestinal disorders, including FAP of childhood, are becoming more common. Specific mind-body techniques include various breathing techniques, guided imagery, progressive muscle relaxation, biofeedback, hypnosis, cognitive-behavioral training, and music therapy. Of those techniques, guided imagery, relaxation, biofeedback, and hypnosis have shown the most promise in treating FAP of childhood. Reported improvement in the pain, fewer school absences, better engagement in social activities, and fewer visits to the physician's office may result from guided imagery and progressive relaxation techniques taught over approximately 4 office visits. Such techniques are easy to learn and teach and are office friendly, even with children.

## Medication

Many drugs have been used in the attempt to treat FAP in childhood, including famotidine, pizotifen, and peppermint oil. Peppermint oil in the form of a pH-dependent, enteric-coated capsule has been shown in evidence-based studies to be helpful in alleviating abdominal pain. Other commonly used medications are anticholinergics, antiemetics, antidepressants, and simethicone, but they have not yet been adequately studied. Citalopram, a selective serotonin reuptake inhibitor, has been used to treat FAP, with improvement of abdominal pain, anxiety, depression, and functional impairment. Amitriptyline has also been shown to reduce pain, depressive symptoms, and somatization in children with FAP and irritable bowel syndrome.

Probiotics have been used to treat alterations in gut flora in ulcerative colitis and antibiotic-associated diarrhea, but there is little evidence to support their use in FAP. Only one study has shown that the probiotic VSL#3 improves abdominal pain as well as bloating, gassiness, discomfort, and quality of life in patients with irritable bowel symptoms. Other studies suggest that *Lactobacillus GG* does not relieve abdominal pain but can decrease its frequency and reduce bloating.

## Dietary Interventions

Dietary manipulation has been used to treat the pain in functional disorders. Common dietary interventions include a high-fiber diet, avoidance of lactose, an oligoantigenic diet, and a low-oxalate diet in abdominal migraine. A high-fiber diet may be helpful primarily in constipated children, to substitute for nutrient-poor, high-fat, and high-calorie diets. Avoidance of high-fructose corn syrup and glucose-based drinks and of sugar-free gum and candy may improve symptoms. Sorbitol, the sugar substitute in gum and candy, can cause bloating, cramping, abdominal pain, and diarrhea. Dietary manipulation is easily understood by parents and children and can empower the family.

## CONCLUSION

The causes of abdominal pain range from acute, life-threatening disease to chronic, functional conditions. Regardless of the cause, the consequences of abdominal pain can be far reaching and can affect not only the emotional and psychological well-being of the child but also the social and economic dynamics of the family. The need to diagnose and treat emergent conditions quickly must be balanced with unnecessary testing when a functional cause seems likely. In the case of functional conditions, a caring approach that educates and reassures the patient and parents is essential for good adherence and an effective therapeutic relationship.

## WHEN TO REFER

- Involuntary weight loss
- Deceleration of linear growth
- Gastrointestinal blood loss

- Significant vomiting
- Chronic severe diarrhea
- Persistent right upper or right lower quadrant pain
- Unexplained fever
- Family history of inflammatory bowel disease
- Extraintestinal symptoms
- History of psychiatric disorder
- Abnormal test results
- Anemia or low mean corpuscular volume
- Peripheral eosinophilia
- Increased erythrocyte sedimentation rate
- Increased transaminases
- Increased blood urea nitrogen or creatinine
- Hypoalbuminemia
- Low complement-4 protein

### WHEN TO ADMIT

Hospitalization is seldom indicated for patients with FAP; in fact, some studies suggest that placing patients with FAP in the hospital may lead to worse outcome. Some patients do experience relief of symptoms during hospitalization. However, no data suggest that the natural history of the pain is affected. Hospitalization does not help the fundamental goals of environmental modification and will likely reinforce pain behavior. Hospitalization is required in the following circumstances:

- Surgical or medical emergency as determined by diagnostic or therapeutic intervention
- Inability to tolerate enteral nutrition
- Inability to maintain hydration
- Diagnosis that requires observation to evaluate the progress or natural history of the illness

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Abdominal Pain* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/tips-tools/Symptom-Checker/Pages/Abdominal-Pain.aspx](http://www.healthychildren.org/English/tips-tools/Symptom-Checker/Pages/Abdominal-Pain.aspx))
- *Abdominal Pain in Children* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/abdominal/Pages/Abdominal-Pain-in-Children.aspx](http://www.healthychildren.org/English/health-issues/conditions/abdominal/Pages/Abdominal-Pain-in-Children.aspx))
- *Abdominal Pain in Infants* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/abdominal/Pages/Abdominal-Pains-in-Infants.aspx](http://www.healthychildren.org/English/health-issues/conditions/abdominal/Pages/Abdominal-Pains-in-Infants.aspx))

#### Medical Decision Support

- *Pediatric Nutrition Handbook*, 7th ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

### AAP POLICY

American Academy of Pediatrics Subcommittee on Chronic Abdominal Pain. Chronic abdominal pain in children. *Pediatrics*. 2005;115(3):812–815 ([pediatrics.aappublications.org/content/115/3/812](http://pediatrics.aappublications.org/content/115/3/812))

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### Chapter 126

## ALOPECIA AND HAIR SHAFT ANOMALIES

Nancy K. Barnett, MD

Hair matters. It does not serve an essential function, inasmuch as people can live without it. Nevertheless, the symbolism over the ages, from Samson to John Lennon, and the emotional investment people have in their hair make any of its abnormalities a matter of concern. This anxiety is particularly so with alopecia: loss of hair is a disturbing event.

### INTRODUCTION

A sequence of events makes up the life of a single hair, from active growth over 2 to 6 years, a busy period known as the *anagen phase*, to passivity, a resting period of about 3 months, known as the *telogen phase*. As many as 15% of scalp hairs may be in the telogen phase at any specific time. These hairs are soon lost in the constant turnover of scalp hair, a continuous shedding that is hardly apparent to a casual observer. Surprisingly, about 50% of the hair must be shed for loss to be noticeable. Normally, up to 100 hairs are lost from the scalp daily, and 200 are lost with shampooing.

Hair loss may increase to as much as 60% during a period known as a *telogen effluvium*. During such a period, the situation is similar to that of animals, which shed seasonally. In humans, this change in the normal anagen-to-telogen ratio may occur after a period of stress, such as a prolonged fever, a pregnancy, or a severe illness. It may occur in either gender and results in a diffuse, nonpatterned and nonscarring loss of hair. The diagnosis of telogen effluvium can be confirmed simply by plucking a group of hairs and examining them microscopically (see Evaluation, later in this chapter). Notably, plucking these hairs does not hurt because they are in the resting phase, with the number of resting hairs increased well beyond the usual 10% to 15%.

Excessive hair loss is a matter deserving careful attention. A precise, pointed history and physical examination are necessary. Determining whether an alopecia is scarring or nonscarring is important. The pediatrician must not limit the examination



simply to the site of hair loss. The whole body and all its hair-bearing parts must be observed and hairs themselves examined microscopically. Under the light microscope, the normality of the individual hair and the ratio of anagen to telogen hairs can be judged. The pediatrician may need to consult with a dermatologist.

Lanugo, the first hair made by hair follicles in utero, feels silky and covers the entire body of the fetus. It is most often shed in utero, to be replaced by hair that begins to grow on the scalp in the third trimester; continues to grow after birth, and is lost a few months after birth in a normal process that results in temporary near-baldness. In many instances, parents are concerned with the thinning or with a more markedly localized area of loss, usually over the occiput, once thought to be the result of the pressure of the head as the infant lies in the crib. Finally, however, the lost early hair is gradually replaced by new hair, which has more of a “feel” to it; thicker, usually darker, and more stable, it grows longer before loss and does not shed quite so readily.

The constant ebb and flow of growth and shedding and the extreme activity of the hair follicle put it at great risk when exposed to antimetabolites and mitotic inhibitors. When a child loses scalp hair rather suddenly, the physician should be concerned with the possibility of a toxic event. Children treated with antimetabolites for a malignancy suffer hair loss because of the damage done by the drugs during the anagen phase, resulting in an anagen effluvium. Occasionally, similar hair loss is caused by accidental poisoning, as with rat poison that contains thallium or coumarin. In most instances, over a period of several months, new hairs will replace lost hairs, unless the exposure to the toxic element is chronic.

The prognosis for the return of hair depends in large part on elimination of the toxic stimulus and on whether the loss is accompanied by scarring. Loss with scarring (eg, from iatrogenic scalp injury during delivery or from a burn) is permanent. Additionally, hair will not grow at the site of most nevi and hemangiomas. In children, alopecia of both known and unknown causes usually occurs without scarring, as in alopecia areata (spotty loss of scalp hair); alopecia totalis (loss of all scalp hair); alopecia universalis (loss of all scalp and body hair); drug-induced, postfebrile, and postpartum alopecias; and alopecias associated with an endocrinopathy (hypothyroidism, hyperthyroidism, or hypoparathyroidism) or a nutritional deficiency (vitamins A, B, and C, or kwashiorkor).

When scarring is present, as with a kerion associated with tinea capitis, keloid formation, or discoid lupus erythematosus, little hope exists for hair recovery.

## EVALUATION

Appropriate diagnosis requires microscopic differentiation of the hair and its root in both the anagen and the telogen stages. Anagen hairs have fat, healthy follicle bulbs and an attached emerging long terminal hair, whereas telogen hairs have a small bulb and an attached hair resulting in a club-shaped appearance. Deformities of the hair shaft can be seen, particularly

with aminoacidopathies and in a variety of rare syndromes, including Menkes kinky hair syndrome. The physician can differentiate microscopically monilethrix (usually an inherited, autosomal dominant disorder in which the diameter of the hair shaft varies) from pili torti (a disorder in which the hair is twisted on its long axis).

## DIFFERENTIAL DIAGNOSIS

A variety of congenital and hereditary disorders can produce hair loss, either total or less obvious with thinning (Table 126-1). True congenital alopecia is rare and may be inherited as an isolated autosomal recessive trait or as one feature of a significant hereditary disorder. Hairs may be thin or poorly anchored to the scalp or have a variety of shaft abnormalities. The pediatrician must look for signs of ectodermal dysplasia, and thus consider radiographic exploration for skeletal defects (as with cartilage-hair hypoplasia, congenital ectodermal dysplasia, or orofaciocigital syndrome), as well as for evidence of inherited metabolic or endocrine disorders such as phenylketonuria, homocystinuria, and congenital hypothyroidism. Children with serious chromosomal defects (eg, de Lange syndrome or trisomy 13 syndrome) usually provide a surfeit of signs and symptoms beyond simple loss of hair.

## Hair Shaft Anomalies

Anomalies of the hair usually result in a stubbly growth of broken hair rather than true alopecia. Ectodermal defects, brittle fingernails, or perhaps cataracts and tooth anomalies may accompany hair shaft anomalies. Fragile hair with resultant breakage (trichorrhexis) and stubble can be seen in a variety of rare conditions. Trichorrhexis nodosa is a familial condition in which the hair is fragile without other associated findings. Children with argininosuccinic aciduria, a rare inborn error of metabolism, have stubbly hair and show evidence of severe intellectual disability in the first year of life.

The texture of hair may be helpful in finding the source of difficulty. In an infant who has hypothyroidism, the hair may be coarse, brittle, and without luster; with progeria and cartilage-hair hypoplasia syndrome, it may be fine and even silky. In all these circumstances, the hair may break off, and apparent baldness increases. Whenever the hair is abnormal, it becomes weakened, fragile, and fractured, and it may be lost or unevenly shortened, often resulting in a stubbly, ragged alopecia. Given that a variety of abnormalities (congenital, traumatic, or endocrine) can lead to such fragility and loss, referral to a dermatologist is appropriate so that a specific diagnosis can be pursued.

## Loose Anagen Syndrome

Loose anagen syndrome is characterized by hairs that are quite easily and painlessly pulled from the scalp. Generally, but not always, affected children are blond female preschoolers between 2 and 5 years of age. Their hair appears sparse. The individual hairs are not fragile. On examination, they have misshapen anagen bulbs with a cuffed cuticle and no external root sheath.

**Table 126-1 Distinguishing Characteristics of Alopecia**

CONDITION	PATTERN OF LOSS	PULLED-HAIR CHARACTERISTICS AS EXHIBITED WITH LIGHT MICROSCOPY
<b>NONSCARRING WITH HAIR SHAFT ABNORMALITIES</b>		
Trichorrhexis nodosa	Fragile, short hair with grayish-white nodules	Nodes along hair shaft similar to interlocking broom or brush ends
Monilethrix	Fragile, short, stubble-like growth	Variable shaft thickness gives beaded appearance with internodal breakage
Pili torti	Fragile, short, light-colored hair appears spangled as a result of light reflection	Irregularly spaced twists along the shaft appear flattened
<b>NONSCARRING WITHOUT HAIR SHAFT ABNORMALITIES</b>		
Alopecia areata	Sharply demarcated, round, nearly bald patches appearing suddenly	Exclamation-point hairs from periphery of patches with poorly pigmented shaft and tapered attenuated bulb
Androgenetic alopecia	Thinned scalp hair in common male baldness pattern or diffuse thinning with retained frontal hair in the female	Increased telogen-to-anagen ratio Biopsy shows miniaturized anagen bulbs
Trichotillomania	Irregularly shaped areas of thinned stubble of varying lengths	Normal cuticle, shaft, and anagen bulb of varying lengths
Traumatic alopecia	Bizarre patterns conforming to site and method of injury (eg, head trauma, braiding)	Normal cuticle, shaft, and anagen bulb of varied lengths
Telogen effluvium	Diffuse thinning with easy epilation from all areas of scalp	More than 25% of pulled hairs are telogen club hairs with no pigment
Anagen effluvium	Significant thinning	Tapered anagen bulbs
Loose anagen syndrome	Slight diffuse or patchy thinning	Anagen hairs have misshapen pigmented bulbs with ruffled cuticle
<b>POTENTIALLY SCARRING WITHOUT HAIR SHAFT ABNORMALITIES</b>		
Tinea capitis and kerion	Varied, ranging from round, minimally inflamed alopecic area with slight seborrheic scale to the boggy, tender, often pustular, severely inflamed kerion	Potassium hydroxide preparation of broken hairs (black-dot hairs) reveals clusters of chains of arthrospores around or in hair shaft and bulb
Lupus erythematosus	Discoid, well-demarcated erythematous plaques with scale, plugging of follicles, and atrophy or thinning as a result of broken, fragile hair with acute flares (lupus hair)	Not applicable if scarred Short, broken (frayed) anagen hairs

Hairs are not firmly anchored because of an inner root sheath defect.

Typically, the child's hair is said to be slow growing, seldom requiring cutting. The hair over the occiput often is matted and sticky. The condition may wane with time, although adult-onset cases have been reported. The hair grows thicker and longer, and its pigmentation increases. Nonetheless, even in adulthood, it may pull out easily and painlessly. A hereditary factor may be involved, but most cases are sporadic. The diagnosis can be made from the history and examination, the painless *pull test* (when hair is growing normally, it usually hurts to pull it), and light microscopy to view the recovered hairs. Management is limited to reassurance.

### Trichorrhexis Nodosa

Trichorrhexis nodosa is a common abnormality of the hair shaft that becomes obvious under the light microscope, where the *nodes* resemble the effect observed when the ends of 2 brushes are pushed together. Most

often congenital, trichorrhexis nodosa results in breakage of hair and short stubble over the scalp; it may also be a genetic predisposition in some black patients, who experience hair breakage over large areas of the scalp and whose hair will not grow beyond a relatively short length. Trichorrhexis nodosa is usually accompanied by a history of hair straightening or repeated vigorous brushing and combing. Avoiding this kind of steady abuse and using a more gentle cosmetic approach can result in some gradual improvement. White and Asian individuals can experience the same difficulty, probably without congenital or familial relationship, and the breakage occurs most often at the distal end of the hair. White specks marking the nodes may appear after some physical and chemical injuries. Here again, a gentle approach and elimination of any noxious exposure are appropriate.

### Monilethrix

Monilethrix (beaded hair syndrome) is a condition in which scalp hairs have regularly spaced differences in

their circumference, suggesting a chain of beads. The cause is unknown but probably genetic, and no treatment is known. Although some degree of recovery may occur spontaneously, particularly after puberty or during pregnancy, this period is a long time to wait, inasmuch as hair breakage becomes obvious during infancy. Variable expressivity was noted in 3 kindreds in whom monilethrix was mapped to the type II keratin gene cluster at chromosome 12q13. Occasionally, associated problems (cataracts, brittle nails, faulty teeth) are suggestive of a more widespread ectodermal defect.

### Pili Torti

Pili torti simply means *twisted hair*, which indeed is the way this hair appears under the microscope. The color is “off,” and the hair is coarse and lusterless. It is as though straight and curly hair were competing for a place in the same strand. In cross-section, a straight hair appears round, and a curly hair appears oval. In pili torti, both configurations may be seen in a single strand, an abnormality that can be an important clue to Menkes kinky hair syndrome, an X-linked disease characterized by low serum copper, progressive cerebral degeneration with hypotonia and often with seizures, arterial degeneration, and osteoporotic bones.

### Alopecia Areata

Alopecia areata, most often seen as an acute problem, results in a sudden and total loss of hair in sharply circumscribed, round areas, often several centimeters in diameter, usually on the scalp, but possibly anywhere on the body where hair is found (Figure 126-1). Hairs at the periphery of an area are plucked easily and may be particularly colorless and thin. *Exclamation-point hairs* (broken hairs with a narrow bulb) may appear throughout the patch, which is sometimes salmon colored as a manifestation of the presumed inflammation seen histologically around the hair follicle. The fingernails may be pitted, possibly indicating a more extensive ectodermal problem.

Just a few patches of loss may be found, or a total absence of body hair (alopecia universalis) may occur, including eyebrows and eyelashes. The more extensive the loss and the younger the child, the less likelihood there is of a full recovery. The prognosis is best when the loss is less widespread and only 1 or 2 patches are present. Although the cause is unknown, some suggestion has been made of a T-cell-mediated autoimmune process against the anagen hair follicle, explaining recent interest in T-cell “biologics” as therapy, but thus far they have not been helpful. Occasionally, autoimmune antibodies are identified in patients who have alopecia areata when no other clinical evidence exists of autoimmune disease. An increased incidence of alopecia areata also occurs in persons who have acute autoimmune thyroid disease and vitiligo. The association with multiple genes suggests a susceptibility to alopecia areata, which manifests with various environmental factors.

About one-third of patients who have alopecia areata will regrow hair spontaneously in 6 months; for another one-third, hair will regrow within 5 years. For



**Figure 126-1** This 30-year-old man developed slow, expanding hair loss on the scalp 1 month earlier. Although a potassium hydroxide preparation was supposedly positive, he did not improve on topical ciclopirox shampoo and oral itraconazole. At a subsequent visit 1 month later, several new patches were noted, and the diagnosis was changed to alopecia areata. (Reprinted with permission from DermAtlas.org. Courtesy of Manoj Ram, MD.)

the remaining one-third, treatment is needed to stimulate hair growth.

Cortisone creams applied topically have been used with some success. In the older, more cooperative child, direct injection of corticosteroid into the scalp or eyebrow hair follicles can be effective, but the process is painful. The primary care pediatrician should seriously question the appropriateness of this procedure, carefully assessing the effect of the disease and of the treatment on the child, and should refer the patient to a dermatologist for consideration of this intervention. Excimer laser has shown some success even in children as young as 6 years of age with patchy alopecia areata.

Large areas (>50% scalp hair loss) that require steroid infiltration present obvious difficulty. Oral steroid therapy has the risk for serious complications but is occasionally used. Minoxidil 5% solution can be used twice daily as an adjunct to topical steroids for small, stubborn areas of alopecia. Latanoprost, a prostaglandin analog used to treat glaucoma, was noted by chance to promote the growth of eyelashes and is now commercially available; it and several newer agonists have had mixed results thus far in attempts to treat eyebrow and eyelash alopecia areata. There is no guarantee that if hair regrows in response to therapy it will persist, especially once treatment is stopped.



For extensive alopecia, some irritants (dinitrochlorobenzene immunotherapy and tars such as short-contact anthralin) and psoralen with ultraviolet A light (known as *PUVA therapy*) have been used. These agents should be used only in children older than 12 years and only by a knowledgeable dermatologist in controlled circumstances.

An oddity of alopecia areata is that when hair does regrow, it may initially be white. Eventually color returns, and casual observers cannot identify the formerly affected area.

The efficacy of treatment is difficult to assess because of the waxing-and-waning nature of alopecia areata. The National Alopecia Areata Foundation ([www.naaf.org](http://www.naaf.org)) offers education and support to families, and sponsors an annual children's camp. In counseling patients and their families, primary care pediatricians should remind them that the disease is nonscarring and that there is always the potential for full regrowth. Also, it is hoped that further elucidation of the genetics of alopecia areata will lead to more targeted therapies in the future.

### Telogen Effluvium

Telogen effluvium, the diffuse loss of hair in the telogen phase of growth, may be difficult to distinguish from diffuse alopecia areata. Actually the most common form of hair loss in children, telogen effluvium is what occurs in most infants at 6 to 8 weeks of age, probably as a result of the stress of birth, and it is the type of hair loss that can follow the stress of a febrile illness, surgery, or trauma. Presumably, the stress causes a synchronization of the hair follicles so that many of them reach the telogen phase simultaneously, reversing the normal 4:1 ratio of anagen to telogen. This is evident on the hair pull/pluck test, when the hairs of diffuse alopecia areata appear as dystrophic anagen rather than telogen hairs. Telogen effluvium is generally reversible.

### Androgenetic Alopecia

Androgenetic alopecia is a genetically determined loss of hair that begins most often with a receding hairline and some thinning over the vertex. It occurs most often in men but can happen to women. The fullest expression is most common in the mature adult, but pediatricians are confronted with the problem in 15% of adolescents older than 14 years. Hairs from affected follicles do not epilate easily on pulling, but they are shorter and finer as a result of normal pubertal androgen increase. No therapy is reliably effective, although topical minoxidil twice daily and hair transplant micrografts may help some individuals. Finasteride can be tried after 18 years of age with male patients but is contraindicated in female patients because of the possibility of genital defects in exposed male fetuses if a pregnancy occurs.

### Trichotillomania

Some children have a compulsive need to pull out their hair or even their eyebrows or eyelashes. Although not always of emotional significance, trichotillomania may provide a major clue to an underlying



**Figure 126-2** Trichotillomania in a 7-year-old boy.

psychosocial problem. The hair loss often appears in large, patchy, ill-defined patterns. The family structure and the interaction with siblings and parents and with friends at home and at school should be explored in an effort to find stressors. Consulting a psychiatrist should also be considered. The primary care pediatrician can paint the attacked areas with petroleum jelly in an attempt to frustrate the habit; however, without attention to the possibility of an underlying emotional issue, this approach is quite obviously temporary. Both imipramine and fluoxetine have been used successfully to control trichotillomania in some children.

The hair lost is that which is most accessible to the probing hand. In some cases, enough is pulled to simulate alopecia areata (Figure 126-2). The patient who eats hair may accumulate it in the stomach and create a trichobezoar (hairball), which may ultimately lead to acute intestinal obstruction or, most often, to the complaint of abdominal pain. A trichobezoar may be palpable as an abdominal mass and is demonstrable on a radiograph. Referral for either endoscopic or surgical removal is indicated.

### Traumatic Alopecia

Hair is fragile. It should be handled gently and without physical or chemical assault. In children, hair is probably best left alone, except for simple washing, combing, and cutting.

Constant teasing or straightening with heat or chemicals may seriously damage hair. Some hairstyles, particularly with barrettes, ponytails, braids, or cornrows, cause constant and prolonged traction, especially along the hairline. The hair may then fall out, accompanied by redness and inflammation, even with pustular involvement of the follicles. Generally, simply discontinuing the stress will help. In childhood, the hair will almost always return, although the regrowth can be slow. Injured hair follicles, whether from trichotillomania or simple traction, do not heal quickly, often taking 3 months or longer to return to an anagen phase.

### Tinea Capitis

Whenever a child has patches of alopecia or stubbly hair growth, even in the absence of crusting, scaling,





**Figure 126-3** A young boy admitted for asthma therapy was incidentally noted to have a scalp lesion. The scaling and focal alopecia suggested the diagnosis of tinea capitis. The child was successfully treated with griseofulvin.

redness, or other inflammatory signs, the physician should consider the possibility of tinea capitis, along with seborrheic dermatitis, atopic dermatitis, or psoriasis (Figure 126-3). Certainly, seborrhea and atopy are more common in children than fungal scalp infection; but particularly when alopecia is accompanied by local adenopathy, tinea capitis should be in the differential diagnosis. Obviously, if crusting, scaling, or redness is present, then the likelihood of alopecia areata is diminished because inflammation is not a symptom of that condition. In any event, the practitioner should perform a mycologic examination, looking particularly for the usual fungus, *Trichophyton tonsurans*. Clinically, the lesions tend to be more elevated than in other forms of tinea and may be characterized by black dots. In rare cases, the endothrix fungi *Microsporum canis* and *Microsporum audouinii* can invade the hair shaft and cause breakage and stubble. *M canis* tends to cause much more inflammation than does *M audouinii*. Endothrix fungal infections, but not *T tonsurans*, can produce a greenish fluorescence under Wood light in a darkened room.

On occasion, particularly with *M canis* or after treatment with an irritant, the affected area may become secondarily infected and seriously inflamed, requiring treatment with an antibiotic. Kerion, a delayed hypersensitivity reaction to the fungus, may develop, and if it is unchecked, the resultant scarring interferes with the regrowth of hair (Figure 126-4). Early diagnosis and treatment are therefore helpful.

Topical antifungal agents do not provide adequate treatment because the fungus is deep in the follicle. Oral griseofulvin had been the standard of care, but the usual course of 2 to 3 months of therapy may present difficulties with adherence in a young child. Several newer agents have the appeal of offering a



**Figure 126-4** A 2½-year-old boy with a kerion caused by chronic, progressive tinea capitis.

shorter course, despite their expense. The fungicidal drug terbinafine seems effective for tinea capitis when given for 6 weeks and is currently approved for children 4 years and older for this use by the US Food and Drug Administration; neither itraconazole nor fluconazole is approved, but they may be similarly safe for short courses in children. These agents certainly provide alternatives if griseofulvin therapy fails or is not tolerated, but they have not proved effective for *Microsporum tinea capitis*. Liquid itraconazole has been associated with diarrhea in children and with pancreatic adenocarcinoma in laboratory animals and should be avoided. Liver function should be tested if antifungal medications are used for longer than 12 weeks and at the start of therapy if any suggestion of preexisting liver disease exists. Oral prednisone tapered over 10 days may help rapidly decrease the tenderness and inflammation of a kerion and prevent a widespread id reaction. (For medication dosage information, consult the American Academy of Pediatrics *Red Book*.)

### Acrodermatitis Enteropathica

Acrodermatitis enteropathica, an autosomal-recessive disorder characterized by abnormal zinc absorption, has several important cutaneous manifestations, simulating, at times, psoriasis, epidermolysis bullosa, pyoderma, or candidiasis. Zinc deficiency can result in abdominal pain and diarrhea, as well as a wispy alopecia and dystrophic development of the fingernails, suggesting widespread ectodermal involvement. Oral zinc sulfate is the treatment of choice.

### Discoid and Systemic Lupus Erythematosus

Discoid lupus erythematosus can be disfiguring to the scalp and, with scarring, can cause a permanent loss of hair (Figure 126-5). Early treatment with topical or intralesional steroids may prevent scarring. Systemic



**Figure 126-5** This 43-year-old woman had an 11-year history of slowly progressive red scaly plaques with central scarring and hair loss in sun-exposed areas. A biopsy showed changes typical of discoid lupus. She was otherwise well and complained of itching of her feet where she had new lesions. She also had some asymptomatic erosions on the tongue and buccal mucosa. (Reprinted with permission from DermAtlas.org. Courtesy of Kosman Sadek Zikry, MD.)

lupus erythematosus can also cause alopecia, and the scalp itself can be erythematous; however, the loss of hair is generally temporary and does not involve the scarring characteristic of discoid disease.

## MANAGEMENT

Treatment for alopecia depends, of course, on the cause. Physicians are accustomed to seeing children who are being treated with antimetabolites wearing baseball caps or bandannas to hide their full or partial baldness from anagen arrest. A noticeable loss of hair from any cause may be disturbing to both patient and parent; therefore, the suggestion that the child wear a baseball cap or other concealing adornment may be appropriate. Even a hairpiece can be designed for a child. These steps serve in the interim while physicians attempt potentially helpful treatments or wait expectantly in circumstances in which their role is diagnostic and supportive. The possibility that hair will not fully regrow must be considered when loss follows high fever (telogen effluvium) or chronic toxicity (anagen effluvium); is accompanied by scarring; or occurs in the areas of nevi, aplasia cutis, or persistent hemangiomas. The pediatrician must talk this through with the child who is old enough and with the parents as well, exploring the emotional reaction and discomfort and, if recovery of hair is questionable, working with them to achieve an emotional balance consistent with reality and to adopt suitable coping mechanisms. In most instances, this goal is achievable, and the pediatrician should not back away from trying. The physician, sometimes frustrated by the lack of a practical, successful management regimen, should not forget

the value of a willing, listening ear. Plastic surgery expertise should be sought for consideration of hair transplants and scalp reduction (for scarred areas) when possible.

## WHEN TO REFER

- Rapid, diffuse hair loss
- Chronic, progressive, localized, or diffuse hair loss without regrowth
- Scarring alopecia
- Inability to grow hair as a result of breakage, loss, or abnormal texture of hair
- Appearance of scalp mass or plaque affecting localized hair loss

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- National Alopecia Areata Foundation (Web site), ([www.naaf.org](http://www.naaf.org))
- Teens—Alopecia Areata Fact Sheet (fact sheet), National Alopecia Areata Foundation ([www.naaf.org/kids/teen-facts.asp](http://www.naaf.org/kids/teen-facts.asp))
- Locks of Love (Web site), ([www.locksoflove.org](http://www.locksoflove.org))

### Medical Decision Support

- *Pediatric Dermatology: A Quick Reference Guide* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

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## Chapter 127 AMENORRHEA

Maria Trent, MD, MPH; Alain Joffe, MD, MPH

Amenorrhea is a common clinical complaint; its frequency varies based on the gynecologic age of the young woman (the number of months or years elapsed since menarche). For example, in a study of high school adolescent girls, the rates of girls who missed 3 consecutive menstrual periods in a single year were 12.5% in the first year after menarche and 5.4% after 7 postmenarchal years. Traditionally, amenorrhea has been classified as being either primary or secondary. Primary amenorrhea is defined as the failure to initiate

**BOX 127-1 Major Causes of Amenorrhea in Adolescent Girls by Organ System****CENTRAL NERVOUS SYSTEM**

- Familial-physiologic delay
- Systemic illness
- Developmental defects (eg, Kallmann syndrome)
- Laurence-Moon-Bardet-Biedl syndrome
- Prader-Willi syndrome
- Infiltrative disease
- Head trauma
- Sheehan syndrome (postpartum necrosis)
- Primary empty sella syndrome
- Irradiation
- Surgery
- Depression
- Drugs (eg, hormonal contraception, cocaine, phenothiazines)
- Psychological stressors
- Eating disorders (eg, anorexia nervosa)
- High-level athletic training with low weight for height (eg, female athlete triad)
- Psychosocial stress
- Central nervous system tumor (eg, prolactinoma)

**THYROID**

- Hyperthyroidism
- Hypothyroidism

**ADRENAL**

- Addison disease
- Cushing syndrome
- Late-onset congenital adrenal hyperplasia (21-hydroxylase deficiency)
- Tumor

**OVARIES**

- Gonadal dysgenesis
- Premature ovarian failure
- Radiation or chemotherapy
- Ovarian removal or destruction
- Polycystic ovary syndrome
- Tumor

**UTERUS**

- Pregnancy
- Uterine synechiae
- Congenital abnormalities (müllerian agenesis, androgen insensitivity)

**VAGINA, CERVIX, HYMEN**

- Agenesis
- Imperforate hymen
- Transverse septum

menstruation, whereas secondary amenorrhea refers to cessation of menses in an adolescent who has previously menstruated. Although some value can be found in knowing whether the absence of menses results from a disruption or lack of initiation, this distinction is of limited clinical utility because many diseases and clinical states cause both primary and secondary amenorrhea.

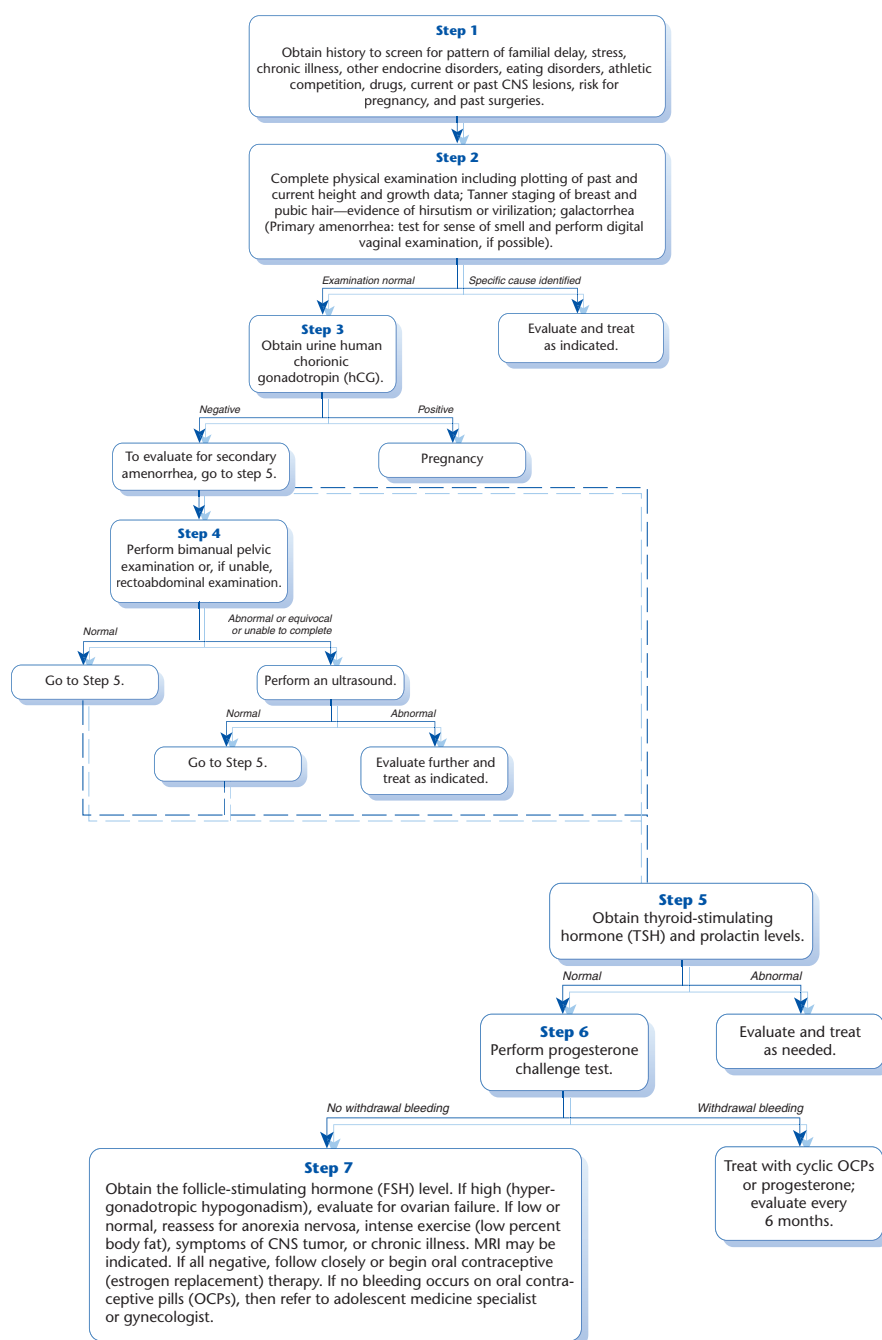
The mean age of menarche among girls in the United States has decreased slightly in recent years. In 1973, the average age of menarche was 12.76 years among participants in the National Health Examination Survey (NHES). Recent analyses using the combination of the NHES and National Health and Nutrition Examination Surveys (NHANES) have documented that the current average age of menarche in the United States is 12.54 years, with some variation by race or ethnicity. Further analyses from the NHANES data demonstrated that 90% of girls will have menstruated by age 13.75 years and that fewer than 10% menstruate before 11 years of age.

Amenorrhea is a symptom, not a disease, and has a variety of causes. The differential diagnosis for the patient with amenorrhea includes maturational (constitutional) factors, disorders of the central nervous system (CNS), adrenal and ovarian disease, congenital abnormalities of the reproductive tract (primary amenorrhea), thyroid disease, nutritional disorders, systemic illness, and pregnancy. Therefore, a thoughtful,

systematic approach to the patient who has a menstrual disorder usually identifies the cause. The major causes of amenorrhea are listed in Box 127-1.

Menstruation usually begins about 2 years after breast budding; however, the interval between these events can be as short as 6 months or as long as 4 years. Given this broad range of individual variation in the onset of puberty and menarche, the physician first must assess pubertal status, noting breast and pubic hair development. An evaluation is warranted if:

1. No signs of secondary sexual development are present by 14 years of age. In this instance, the evaluation should include an assessment for delayed puberty. (See Chapter 185, Puberty: Normal and Abnormal.)
2. Menarche has not occurred by 16 years of age even if the patient has experienced development of secondary sexual characteristics and growth has been normal.
3. Menarche has not occurred and the patient has been at Tanner stage 5 for at least 1 year or has had breast development for 4 years.
4. Three consecutive menstrual cycles are absent in a patient with signs of an eating disorder.
5. The patient has previously menstruated but has had amenorrhea for more than 6 months.
6. The patient has not had menses and has symptoms or stigmata of another disease process such as Turner syndrome.



**Figure 127-1** Evaluation of patients who have amenorrhea in whom secondary sex characteristics are present.

7. The patient has had menstrual cycles, has missed one period, and has had unprotected sexual intercourse in the interim. In this instance, the patient should be evaluated for pregnancy.

Gynecologic age is important when evaluating an adolescent who seems to have secondary amenorrhea. After the onset of menarche, many teenagers will menstruate sporadically; regular monthly cycles often are not established until 1 to 2 years after menarche. Clearly, the abrupt cessation of menstruation in a

teenager who has established regular cycles is of greater concern than the absence of menses for 3 to 4 months in a teenager who has a gynecologic age of 6 months to 1 year. The point at which the physician elects to pursue an evaluation depends on the anxiety of the patient and her family, the possibility of pregnancy, and the likelihood that a potentially serious disease is responsible for the amenorrhea. For a general approach to the evaluation of amenorrhea, see Figure 127-1.



## HISTORY

The history and physical examination are critical elements in the diagnostic approach. Although the adolescent should always be interviewed alone during the visit, many adolescent girls may have difficulty with the details of their own medical and family medical histories, making maternal involvement during the visit extremely useful. Mothers are able to provide detailed medical histories for their daughters from infancy to the present, the details of their own menstrual and medical histories, and usually that of first-degree female relatives. Finally, mothers are often acutely aware of behavioral factors within the home, such as a daughter's menstrual patterns, symptoms associated with menstrual cycles, consumption of pads or tampons, dietary and exercise patterns, stressors on the family and children, and the subtle development of physical features such as weight gain, acne, or hirsutism. Detailed discussions of personal lifestyle factors such as sexual activity should be conducted without the parent present. Use of the HEADDSS assessment (home situation, educational status of the patient, activities, diet, drug use, suicidality or depression, and sexuality or sexual behavior) facilitates this portion of the interview.

The hypothalamic-pituitary-ovarian axis of the adolescent is more sensitive to physical and psychological stress than is that of the adult woman. Stress, emotional upset, fever accompanying viral illness, and changes in weight or environment (eg, going away to college) all can induce amenorrhea. Comments about weight or body image may be a clue to anorexia nervosa. The history also should include questions about drug or medication use, including any forms of hormonal contraception that the patient may be using. Most women who develop amenorrhea while using combined estrogen-progesterone contraceptive methods resume menstruation within 6 months of discontinuing their use. Pregnancy should be the primary consideration in patients who have a history of sexual intercourse. Unfortunately, denial of sexual activity does not exclude pregnancy, inasmuch as many teenagers are reluctant to admit to something they believe will be met with condemnation from adults. Sudden cessation of menstruation is more likely to indicate pregnancy or stress as a cause, whereas a gradual cessation suggests polycystic ovary disease or premature ovarian failure. A history of uterine surgery or abortion raises the possibility of uterine synechiae. Given that many women are involved in sports, questions about exercise patterns or participation in athletics (frequency, duration, intensity) are essential. The physician must be sure to seek clues to any of the endocrine abnormalities (eg, galactorrhea), a history of past CNS insults (eg, meningitis), or symptoms of an intracranial tumor. The age at which the patient's mother and sisters first menstruated is also helpful information because such a pattern may be familial. Finally, chronic diseases such as inflammatory bowel disease or renal failure may be subtle in their early presentation; hence, questions aimed at uncovering these illnesses must be included in the review of systems.

## PHYSICAL EXAMINATION

Plotting of previous growth data (both height and weight) is essential. A short girl who has amenorrhea should prompt a search for the other physical characteristics of Turner syndrome. Diagnostic criteria for anorexia nervosa include loss of weight or failure to gain the weight expected with pubertal development. A complete physical examination, which in most cases will include a pelvic examination, should be performed. Obesity or excessive thinness can result in amenorrhea. Abnormalities of the visual field, smell, or other cranial nerve function; papilledema; or disturbances of reflexes suggest a CNS tumor. Hirsutism, a receding hairline, excessive acne, moon facies, striae, enlarged thyroid, or buffalo hump suggests an endocrine disorder. A webbed neck, short stature, or widely spaced nipples suggest Turner syndrome. Nipple discharge may indicate elevated prolactin levels, and lack of or scant pubic hair in a girl who has Tanner stages 3 to 4 breast development suggests androgen insensitivity syndrome.

A pelvic examination is essential to ensure the presence of normal internal and external female genitalia. An imperforate hymen or transverse vaginal septum prevents menstrual blood from escaping. If the hymenal opening is patent, then the examination should proceed to determine the presence of a normal vagina, cervix, and uterus. If the hymenal opening is very small, then the cervix and uterus can be palpated by means of a bimanual rectoabdominal examination. The size of the clitoris should be noted because clitoromegaly indicates the presence of excess androgens (eg, partial 21-hydroxylase deficiency). In the few cases in which a pelvic or rectoabdominal examination cannot be performed to determine the presence or absence of a uterus, an ultrasound may be necessary.

Although a pink vaginal mucosa indicates the presence of some degree of estrogenization, the patient's estrogen status can be assessed using a progesterone challenge, vaginal maturation index, or measurement of serum estradiol levels. The progesterone challenge is particularly useful because a positive result indicates an estrogen-primed uterus. The progesterone challenge is conducted by administering 10 mg of medroxyprogesterone acetate for 5 to 10 days. Any spotting or bleeding in the week afterward is considered a positive test. Some experts in the field recommend measuring follicle-stimulating hormone (FSH) levels before performing a progesterone challenge because some women who have hypergonadotropic amenorrhea will have a withdrawal bleed. A vaginal maturation index is performed by collecting cells from the upper lateral sidewall of the vaginal wall using a moistened cotton-tipped applicator, rolled on a glass slide, and fixed using the same technique in Papanicolaou smear preparation. Cytologic assessment will determine the number of parabasal, superficial, and intermediate cells present. Samples can be scored using Meisel's modified scoring system to interpret results in terms of estrogen and pubertal status.

## LABORATORY TESTS

For the girl with primary amenorrhea who has an unremarkable history, review of systems, and general physical examination, and no evidence of vaginal outlet obstruction, the next step is to determine, either by pelvic examination, ultrasound, or both, whether a uterus is present. If not, then karyotyping and serum testosterone levels should be determined to screen for müllerian agenesis or androgen insensitivity syndrome. If a uterus is present, then an evaluation comparable to that for secondary amenorrhea should be pursued.

Patients with primary or secondary amenorrhea who have a history of sexual activity should first be screened for pregnancy using a urine pregnancy test. If negative, then initial laboratory evaluation includes FSH, prolactin, and thyroid-stimulating hormone. Low or normal FSH levels are usually associated with physiologic delay, hypothalamic and pituitary causes of amenorrhea, and chronic illnesses. Elevated levels of FSH indicate ovarian failure. Follow-up testing in patients with elevated FSH levels should include karyotyping and screening for autoimmune endocrinopathies. Patients with amenorrhea and clinical evidence of androgen excess most likely have polycystic ovary syndrome (PCOS) or, less commonly, late-onset congenital adrenal hyperplasia (21-hydroxylase deficiency). Additional useful laboratory tests to assess for PCOS and other disorders associated with androgen excess include serum testosterone (total and free) and dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S). Measurement of the first morning 17-hydroxyprogesterone levels is also indicated for patients with elevations in DHEA-S to further assess for late-onset congenital adrenal hyperplasia. If the patient has evidence of virilization (eg, clitoromegaly), or if the androgens are elevated in the tumor range, then adrenal and ovarian imaging are indicated, depending on the source of androgens. Isolated elevations of testosterone are suggestive of ovarian origin, whereas DHEA-S is suggestive of adrenal origin. (See also Chapter 164, Hirsutism, Hypertrichosis, and Precocious Sexual Hair Development.)

Imaging is indicated for other specific presentations of amenorrhea. Pelvic sonography is indicated if abnormalities are noted on bimanual examination or if bimanual examination is not possible. Magnetic resonance imaging of the pelvis is indicated for patients with possible congenital abnormalities. Dual-energy radiograph absorptiometry bone density evaluations should be obtained in girls with hypogonadotropic amenorrhea, given the association with low bone mineral density. Hypogonadotropic amenorrhea is commonly seen in patients with restrictive eating disorders, athletic amenorrhea, and ovarian failure.

## MANAGEMENT

Definitive recommendations for treatment of secondary amenorrhea depend on the underlying cause. When adolescent girls initiate puberty late, but progression through puberty seems normal and the findings of a thorough history and physical examination are also normal, the patient can be reassured that she

should anticipate menarche 2 to 3 years after the initiation of puberty. This probability is particularly true when family history suggests late menarche in first-degree female relatives. Regularly scheduled follow-up visits until menarche occurs are warranted. Any halt in development or absence of menarche by age 16 years merits an evaluation.

In patients with secondary amenorrhea and normal estrogen levels, medroxyprogesterone 5 to 10 mg for 12 to 14 days can be used every 1 to 3 months to stimulate withdrawal bleeding. For sexually active patients and patients with PCOS, treatment with combined contraceptives is indicated. Patients with PCOS may also benefit from additional medications to address underlying metabolic abnormalities or clinical findings associated with androgen excess (hirsutism and acne). In patients with low levels of estrogen, normalizing weight for height is important by addressing disordered eating and intensity of athletic training.

Although many pediatric practices provide gynecologic care, patients who cannot receive a thorough gynecologic assessment in the pediatrician's office should be referred to an adolescent medicine specialist or pediatric gynecologist for evaluation. Adolescent medicine physicians may be particularly well suited to address other developmental or endocrinologic issues that may also be present. Patients who have evidence of complicated endocrine disease; evidence of a CNS, adrenal, or androgen tumor; genetic disorder; eating disorder; or structural abnormality should also be referred to the appropriate specialty team for further evaluation and management.

## WHEN TO REFER

- The amenorrhea appears secondary to a chronic illness that the pediatrician is unable to manage
- The pediatrician feels uncomfortable performing a pelvic examination
- Long-term hormonal therapy is required
- The patient has an eating disorder
- Evidence exists of anatomic or chromosomal abnormality
- Evidence exists of a complicated endocrine disorder
- Evidence exists of a CNS, adrenal, or ovarian tumor
- The patient is pregnant and the pediatrician is unwilling or unable to provide comprehensive options counseling or referral for all options

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## Chapter 128

# ANEMIA AND PALLOR

Alicia K. McFarren, MD; Adam S. Levy, MD

## INTRODUCTION

Anemia is a laboratory finding reflecting a decrease in red blood cell (RBC) mass below an age-appropriate normative value. Anemia may be associated with pallor, but it is more likely a silent symptom and detected only on routine screening studies. Pallor and anemia are not diagnoses; rather, they are signs and symptoms of an underlying disease process requiring a thorough evaluation by the primary care physician.

## DEFINITIONS AND CLINICAL MANIFESTATIONS

### Pallor

Pallor, derived from the Latin *pallere*, meaning “to be pale,” is a clinical sign associated with a variety of systemic illnesses resulting in a decrease in the amount of

oxygenated hemoglobin visible through the superficial and translucent layers of the skin and mucosa. Accurate assessment of pallor may be hindered by fluorescent lighting, dark skin color, jaundice, or cyanosis. Although a common finding in children with moderate to severe anemia, pallor does not necessarily indicate a low hemoglobin level. Sepsis may cause pallor resulting from a decrease in peripheral perfusion. Vasoconstriction from exposure to cold or febrile illnesses may also lead to pallor. Disorders that lead to an accumulation of fluid in the interstitium such as heart failure, hypoproteinemia, or myxedema can also result in pallor.

### Anemia

Anemia can be defined as a reduction in RBC number, RBC mass (hematocrit), or hemoglobin concentration. For each value, the lower limit of the normal range is defined as 2 standard deviations from the mean for age and gender (Table 128-1). Normal ranges for hemoglobin and hematocrit vary with age and gender. Racial differences exist as well. Black children on average have normal hemoglobin values that are approximately 0.5 g/dL lower than white and Asian children.

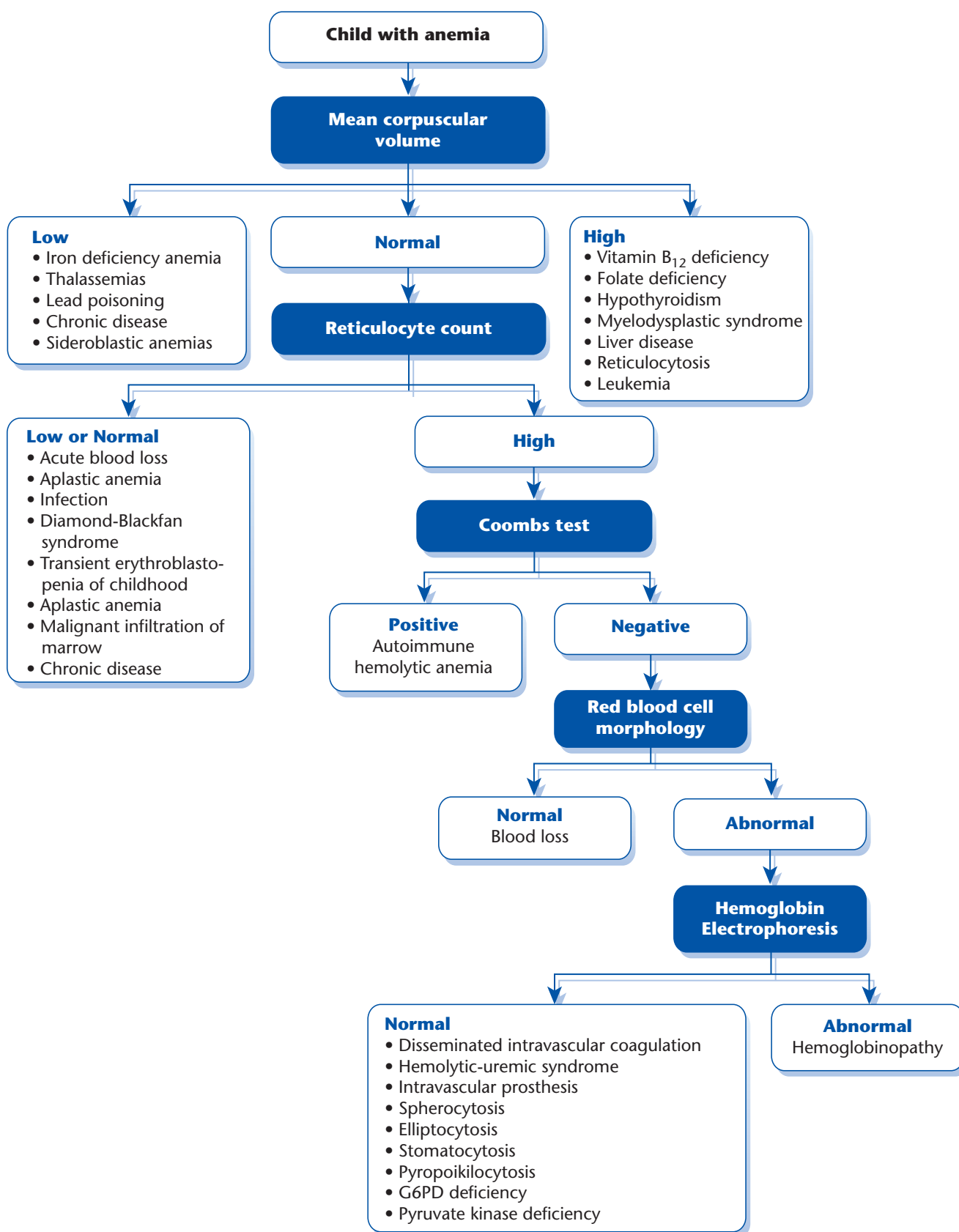
## CLASSIFICATION AND DIFFERENTIAL DIAGNOSIS

Anemias can be systematically evaluated based on RBC size (mean corpuscular volume [MCV]). Normal MCV values vary with age, but microcytic anemias generally have an MCV less than 70 fL, normocytic anemias have an MCV of 72 to 90 fL, and macrocytic anemias have an MCV of greater than 90 fL. Subclassification of anemias as microcytic, normocytic, and macrocytic will greatly reduce the differential diagnosis and limit the number of laboratory tests needed to attain the diagnosis. Figures 128-1 and 128-2 contain guidelines for a diagnostic approach to children and newborns with anemia. Box 128-1 lists the differential diagnoses of specific pathologic RBC features.

**Table 128-1** Mean Values for Hemoglobin, Hematocrit, and Mean Corpuscular Volume

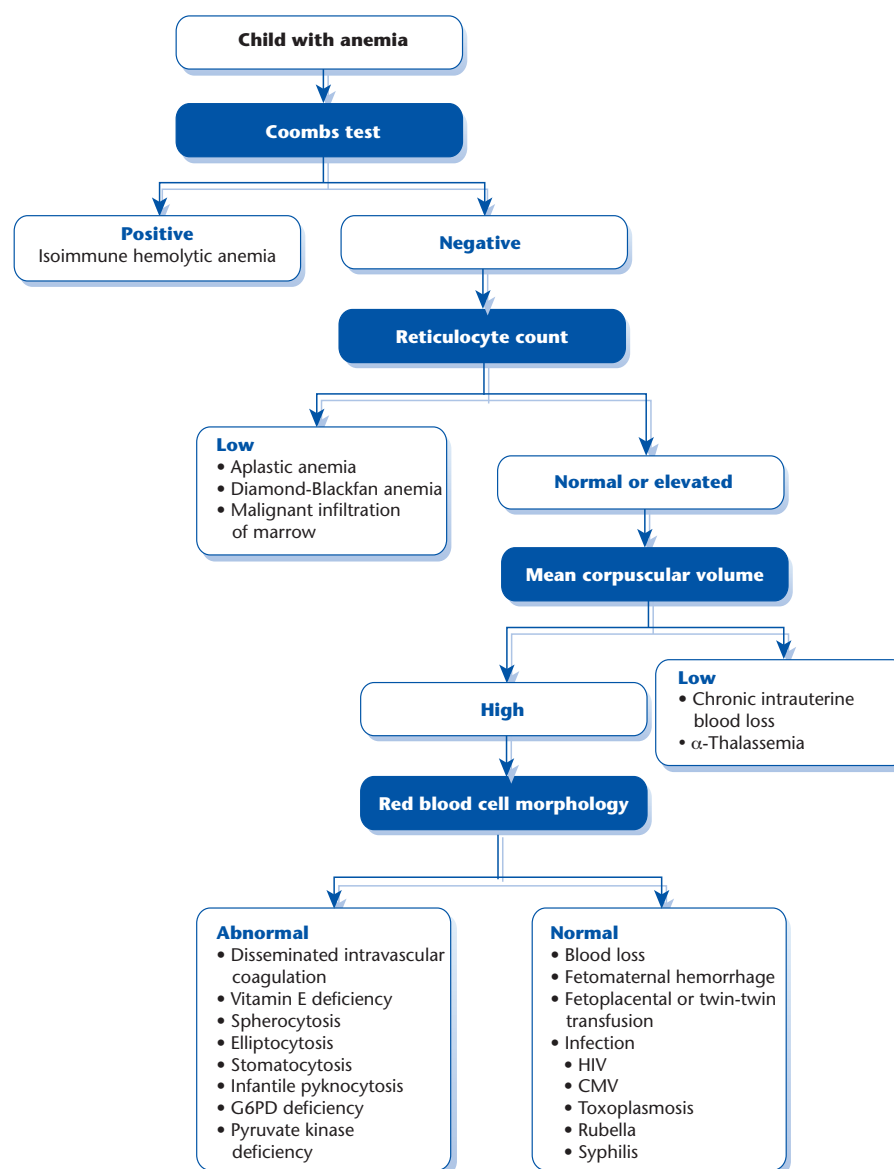
AGE	HEMOGLOBIN (g/dL)	HEMATOCRIT (%)	MCV (fL)
Cord blood	15.3	49	112
1 day	19.0	61	119
1 wk	17.9	56	118
1 mo	17.3	54	112
2 mo	10.7	33	100
3 mo	11.3	33	88
6 mo–2 yr	12.5	37	77
2–4 yr	12.5	38	79
5–7 yr	13	39	81
8–11 yr	13.5	40	83
12- to 14-year-old girls	13.5	41	85
12- to 14-year-old boys	14	43	84
15- to 17-year-old girls	14	41	87
15- to 17-year-old boys	15	46	86

Modified from Nathan DG, Orkin SH. A diagnostic approach to the anemic patient. In: *Nathan and Oski's Hematology of Infancy and Childhood*. 5th ed. Philadelphia, PA: WB Saunders; 1998. Copyright © 1998, Elsevier, with permission.



**Figure 128-1** Diagnostic approach to anemia in childhood based on red blood cell mean corpuscular volume. G6PD, glucose-6-phosphate dehydrogenase. (Derived from Nathan DC, Oski F. Hematology of Infancy and Childhood. 3rd ed. Philadelphia, PA: WB Saunders; 1987.)





**Figure 128-2** Diagnostic approach to anemia in the newborn. CMV, cytomegalovirus; G6PD, glucose-6-phosphate dehydrogenase; HIV, human immunodeficiency virus. (Derived from Nathan DC, Oski F. Hematology of Infancy and Childhood. 3rd ed. Philadelphia, PA: WB Saunders; 1987.)

### Microcytic Anemia

The differential diagnosis of a microcytic anemia is listed in Table 128-2, and the main causes are reviewed in detail here.

### Iron Deficiency

Iron deficiency is the most common cause of anemia in the United States. Iron deficiency may be attributed to poor iron intake, poor iron absorption, or blood loss. Full-term neonates are born with sufficient iron stores to last for the first 6 months of life. Iron deficiency is rare during this period. The incidence of iron deficiency anemia peaks at age 12 to 24 months and then

again in adolescence. The peak in childhood corresponds to the transition of children from human milk or iron-containing formulas to whole milk. Iron deficiency in adolescents is typically related to a poor dietary intake of iron, as well significant blood and iron loss in adolescent girls with menstrual bleeding.

In children of all ages, occult blood loss must be considered as a source for iron loss leading to deficiency. Blood loss may be acute, chronic, or intermittent. A thorough history should be obtained to rule out melena, hematochezia, tarry stools, and bloody or coffee-ground emesis. Stool guaiac tests for occult blood should be performed at several different times

**BOX 128-1 Differential Diagnosis of Specific Pathologic Red Blood Cell Features<sup>a</sup>****TARGET CELLS**

(Surface-to-volume ratio increased)

- Thalassemia
- Hemoglobinopathies
- Hemoglobin E disease
- Hyposplenism or postsplenectomy
- Hepatic disease
- Severe iron deficiency anemia
- Abetaproteinemia
- Lecithin or cholesterol acyltransferase deficiency

**SPHEROCYTES**

(Hyperdense cells with a decrease in surface-to-volume ratio and an increased mean corpuscular hemoglobin concentration)

- Hereditary spherocytosis
- Hemolytic anemia (autoimmune, ABO incompatibility, water dilution)
- Microangiopathic hemolytic anemia
- Hemoglobin SS disease
- Hypersplenism
- Burns
- After RBC transfusions
- Pyruvate kinase deficiency

**ACANTHOCYTES (SPUR CELLS)**

(Cells with 10–15 spicules that are typically irregular in length, spacing, and width; cells usually smaller than normal RBCs)

- Disseminated intravascular coagulation
- Microangiopathic hemolytic anemia
- Hyposplenism or postsplenectomy
- Hepatic disease
- Hypothyroidism
- Vitamin E deficiency
- Abetalipoproteinemia
- Malabsorption

**ECHINOCYTES (BURR CELLS)**

(Cells with 10–30 spicules that are typically of comparable size and distributed evenly)

- Dehydration
- Renal disease
- Hepatic disease
- Pyruvate kinase deficiency
- Peptic ulcer disease
- After RBC transfusion

**PYKNOCYTES**

(Hyperchromic RBCs with a decreased volume and distorted shape)

- Similar to acanthocytes and echinocytes

**BLISTER CELLS**

(Contain a clear area in RBCs that contains no hemoglobin)

- Hemoglobin SS disease
- G6PD deficiency
- Pulmonary emboli

**BASOPHILIC STIPPLING**

(Retention of RNA resulting in fine blue inclusions in the cytoplasm)

- Iron deficiency anemia
- Lead poisoning
- Hemolytic anemias
- Pyrimidine 5'-nucleotidase deficiency

**ELLIPTOCYTES**

(Elliptical-shaped cells)

- Hereditary elliptocytosis
- Iron deficiency anemia
- Thalassemia
- Hemoglobin SS disease
- Sepsis
- Megaloblastic anemia
- Malaria
- Leukoerythroblastic reaction

**TEARDROP CELLS**

(Microcytic and hypochromic cells that are in the shape of a teardrop)

- Normal finding in newborns
- Thalassemia
- Myeloproliferative diseases
- Leukoerythroblastic reaction

**SCHISTOCYTES**

(RBC fragments that result from trauma)

- Disseminated intravascular coagulation
- Hemolytic anemia and microangiopathic hemolytic anemia
- Kasabach-Merritt syndrome
- Purpura fulminans
- Hemolytic-uremic syndrome
- Uremia, glomerular nephritis, acute tubular necrosis
- Cirrhosis of the liver
- Malignant hypertension
- Thrombosis
- Thrombotic thrombocytopenia purpura
- Amyloidosis
- Chronic relapsing schistocytic hemolytic anemia
- Burns
- Connective tissue disorders

**BOX 128-1 Differential Diagnosis of Specific Pathologic Red Blood Cell Features<sup>a</sup>****STOMATOCYTE**

(Area of central pallor is more slit-like than round)

- Present in small numbers in normal individuals
- Stomatocytosis (hereditary)
- Thalassemia

**NUCLEATED RED BLOOD CELLS**

(Normal on a peripheral blood smear in the first week of life only)

- Normal newborns
- Significant bone marrow stimulation

- Congenital infections
- Hyposplenism or postsplenectomy
- Leukoerythroblastic reaction, particularly with severe infections and leukemias or metastatic tumors in the bone marrow
- Megaloblastic anemia
- Dyserythropoietic anemias

<sup>a</sup>Frequently, normal blood smears will contain abnormal-appearing RBCs that are simply an artifact of trauma during the blood draw or ex vivo processing of the blood.

*G6PD*, glucose-6-phosphate dehydrogenase; *RBC*, red blood cell.

Modified from Nathan DG, Orkin SH. A diagnostic approach to the anemic patient. In: *Nathan and Orkin's Hematology of Infancy and Childhood*. 5th ed. Philadelphia, PA: WB Saunders; 1998.

**Table 128-2 Classification of Anemia in Childhood**

<b>MICROCYTIC</b>	<b>NORMOCYTIC</b>	<b>MACROCYTIC</b>
Iron deficiency anemia	Infection	Megaloblastic anemias from B <sub>12</sub> or folate deficiency
Lead poisoning	Acute blood loss	Reticulocytosis
Copper deficiency	Renal disease	Postsplenectomy
Malnutrition	Connective tissue disorder	Myelodysplastic syndrome
Chronic disease	Hepatic disease	Aplastic anemia
Thalassemia	Hemolysis	Fanconi anemia
Hemoglobin E trait	Hypersplenism	Diamond-Blackfan syndrome
Sideroblastic anemia	Malignancy	Pearson syndrome
Atransferrinemia	Aplastic anemia	Dyskeratosis congenita
Inborn errors of metabolism	Dyserythropoietic anemia	Paroxysmal nocturnal hemoglobinuria
	Drugs	Down syndrome
		Hypothyroidism
		Hepatic disease, jaundice
		Drugs (eg, phenytoin, methotrexate)

to capture any intermittent bleeding. Common causes of gastrointestinal bleeding include gastric and duodenal ulcers, Meckel diverticulum, polyps, hemorrhoids, and gastritis. Signs and symptoms of inflammatory bowel disease should also be considered in the history and physical examination. Patients with iron deficiency anemia have symptoms similar to those in other forms of anemia, including pica as a craving for ice.

When iron deficiency is sufficient to cause anemia, other abnormalities may be seen on routine laboratory testing. In addition to being microcytic, the RBCs will be hypochromic, with target cells and elliptocyte forms visible on the peripheral blood smear. These features and a low reticulocyte count are sufficient to make the diagnosis of iron deficiency anemia. In many instances, further testing is not necessary but may be helpful in some settings. Serum iron and ferritin levels are low, whereas the total iron-binding capacity is

elevated. Many children also have an elevated platelet count.

When a primary care physician is treating a child with hypochromic, microcytic anemia found on a routine screening blood cell count, and a history of poor iron intake or excessive milk intake is elicited, a reasonable approach would be to give a trial of supplemental iron (6 mg/kg of elemental iron per day divided into 2 or more doses) rather than to draw additional blood for biochemical analysis. The reticulocyte count should increase within 5 to 7 days once therapy is initiated. Assuming the dietary deficiency is corrected, supplemental iron should continue for 2 to 3 months after the hemoglobin concentration has normalized to replenish iron stores fully. For patients with a hypochromic microcytic anemia who do not seem to be at risk based on diet alone, and for those who do not respond to supplemental iron, additional testing is required. Iron deficiency, although common, is still

abnormal, and the etiology of the deficiency should be clearly defined.

### Thalassemias

The thalassemias are a heterogeneous group of disorders of hemoglobin production. The  $\alpha$ -thalassemias have deficient production of the  $\alpha$  chain, and the  $\beta$ -thalassemias have deficient production of the  $\beta$  chain. In either case, the excess of one chain relative to the other results in precipitation and destruction of the RBCs.

**$\beta$ -THALASSEMIA.** Thalassemia minor (or thalassemia trait) is common among black patients and results from a mutation of 1 of the 2 genes on chromosome 11 encoding for the  $\beta$ -chain. When only 1 gene is affected, a mild decrease in  $\beta$ -chain production occurs, resulting in a mild anemia. Patients with thalassemia trait frequently have a hypochromic, microcytic anemia found on a routine complete blood count, similar to patients with iron deficiency anemia. Target cells are also common to both diseases. However, patients with thalassemia trait usually have an increase in the number of RBCs, whereas patients with iron deficiency commonly have a decrease in RBC number. A hemoglobin electrophoresis may also be helpful in diagnosing thalassemia trait. Both the hemoglobin F and hemoglobin A<sub>2</sub> levels are commonly elevated. Although treatment is not necessary, diagnosing thalassemia trait is important so that appropriate genetic counseling may be offered to patients and families.

**THALASSEMIA MAJOR.** Thalassemia major (Cooley anemia) results from defects in both  $\beta$ -globin genes and manifests as a severe hemolytic anemia. Marked compensatory erythropoiesis causing expansion of the medullary space results in a prominence of the cheeks and frontal bossing. Long-term transfusion therapy is required for these patients, and immediate referral to a hematologist is necessary.

**$\alpha$ -THALASSEMIA.** Each chromosome 16 contains 2 identical genes (4 genes total) for the  $\alpha$  chain. Abnormalities in these genes, most commonly seen in blacks and Asians, result in  $\alpha$ -thalassemia. When 1 gene is affected, the patient will be asymptomatic, with little or no abnormality on routine testing.  $\alpha$ -Thalassemia trait is the result of a mutation in 2 genes. Patients with  $\alpha$ -thalassemia trait are also asymptomatic. They have laboratory findings similar to patients with  $\alpha$ -thalassemia trait or iron deficiency (microcytic, hypochromic) anemia. However, unlike  $\alpha$ -thalassemia trait, the anemia is usually less severe, and the hemoglobin electrophoresis is normal. The diagnosis is based on the findings of a microcytic, hypochromic mild anemia in patients of Asian or black descent with a normal electrophoresis and no evidence of iron deficiency. Molecular genetic testing of *HBA1* and *HBA2* detects deletions in about 90% and point mutations in about 10% of affected individuals. For purposes of genetic counseling, the typical Asian genotype, with both abnormal genes on the same chromosome, is of more concern than the usual genotype in black patients, with 1 abnormal gene on each chromosome 16. When 3 of the 4 genes are affected, hemoglobin H disease is the result. Patients

with hemoglobin H disease may be asymptomatic but on laboratory testing show a moderate to severe anemia (hemoglobin, 7–10 g/dL). The anemia is microcytic and hypochromic, with RBC fragments visible on review of the peripheral blood smear. A hemoglobin electrophoresis shows 5% to 30% hemoglobin H (hemoglobin consisting of 4  $\beta$  chains). In the newborn period, hemoglobin Barts may be detected, which consist of 4 gamma chains. With mutations in all 4 genes, no normal hemoglobin is made, and unless the diagnosis is made prenatally to allow for intrauterine transfusions, the fetus will die with hydrops fetalis.

### Lead Poisoning

Any measurable lead in the plasma is abnormal, but clinically significant lead poisoning occurs at lead levels higher than 10 mcg/dL, and levels higher than 5 mcg/dL deserve attention. In most instances, lead poisoning is diagnosed on routine screening tests. The anemia in lead poisoning is microcytic and hypochromic, similar to iron deficiency. However, intense basophilic stippling of the RBCs may also be observed. Lead inhibits the insertion of iron into the protoporphyrin ring, thus inactivating heme synthesis and leading to an accumulation of free erythrocyte protoporphyrin, the levels of which can be elevated in both iron deficiency and lead poisoning.

### Chronic Inflammation

Chronic illness may be associated with anemia, likely the result both of decreased production and shortened RBC survival. Iron flow from the reticuloendothelial cells to the erythroblasts may also be diminished, resulting in a hypochromic, microcytic anemia. Anemia of chronic disease can be associated with malignancies, autoimmune diseases, renal failure, and chronic infections. Frequently, RBCs in chronic disease are normocytic and normochromic, but microcytic and hypochromic anemias are seen as well. The hemoglobin typically is in the range of 7 to 10 g/dL with a normal to low reticulocyte count.

### Sideroblastic Anemias

The sideroblastic anemias, caused by the retention of iron in the mitochondria of immature erythrocytes, are rare forms of anemia in childhood. Acquired sideroblastic anemia is a disease primarily of adulthood, whereas inherited forms of the disease occur in childhood.

### Normocytic Anemia

Normocytic anemia is defined as a decreased circulating RBC mass with an MCV in the appropriate range for age. As noted previously, the distinction of age-appropriate normative values is well established and important to consider lest the physician misinterpret a child's results and pursue an unnecessary evaluation (see Table 128-1).

The differential diagnosis of normocytic anemia (see Table 128-2) is broad and can be divided into primary hematologic disorders or systemic disorders with secondary anemia. Primary hematologic causes of normocytic anemia include early iron deficiency



anemia, aplastic anemia and other bone marrow failure syndromes, and hemolytic anemias (most commonly sickle cell disease). Systemic disorders with secondary normocytic anemia include anemia of chronic disease, systemic infection, acute blood loss, renal failure, and other disorders. The physician can also classify normocytic anemia as a disorder of decreased RBC production or increased RBC destruction. Whichever way is chosen to develop a diagnostic algorithm, approaching the diagnosis of anemia in a structured way that can consistently consider the broad range of diagnostic possibilities is useful.

### **Primary Hematologic Causes of Normocytic Anemia**

For many patients, the diagnosis of anemia is made on routine screening. Iron deficiency anemia is the most common cause of nutritional anemia in childhood discovered by routine screening. Although the classic indices for iron deficiency anemia include a low MCV and a high red cell distribution width, early iron deficiency anemia may appear as a normocytic anemia. A reticulocyte count will be lower than expected for a patient with anemia because RBC production will be decreased. Iron studies should corroborate the diagnosis of iron deficiency anemia, but a trial of supplemental iron should be both diagnostic and therapeutic.

Aplastic anemia and bone marrow failure syndromes can result in normocytic anemia as a result of decreased RBC production. Examples include congenital or acquired aplastic anemia, transient erythroblastopenia of childhood, pure red cell aplasia (Diamond-Blackfan anemia), and viral infections (eg, parvovirus, Epstein-Barr virus).

Bone marrow infiltration from a malignant process (either leukemia or metastatic solid tumors) can result in decreased RBC production and cause a normocytic anemia. Again, the reticulocyte count will be lower than expected for the degree of anemia. Abnormalities in the white blood cell count and platelet count may also be noted. Immature cells may be noted on review of a peripheral blood smear. Evidence of hemolysis and increased RBC turnover should be absent.

Hemolytic anemias result from RBC membrane defects (eg, hereditary spherocytosis, elliptocytosis), enzyme defects (eg, glucose-6-phosphate dehydrogenase [G6PD] deficiency, pyruvate kinase deficiency), hemoglobin defects (eg, sickle cell disease, thalassemias), and autoimmune hemolytic anemias. In general, the hemolytic anemias are characterized by an elevated reticulocyte count and evidence of increased RBC destruction (elevated serum bilirubin level). A patient with a personal or a family history of early cholecystectomy or intermittent jaundice may suggest a familial hemolytic anemia. Obtaining the complete blood count results of immediate family members may help confirm the diagnosis. Although routine newborn screening will identify patients with sickle cell disease born in the United States, children born in areas without routine screening may well have their sickle cell disease diagnosed later in life.

Rarely, normocytic anemia may result from a combination of a microcytic anemia (iron deficiency) and a

macrocytic anemia (folate deficiency). The MCV is a mean and, as such, 2 populations of RBCs may average out to a normal MCV.

### **Systemic Causes of Normocytic Anemia**

Acute blood loss will result in a normocytic anemia. Patients with chronic blood loss (eg, gastrointestinal bleeding) will likely become iron deficient and develop a microcytic anemia. However, in the early stage of the process, the patient will have normocytic RBCs. Testing the stool for occult blood is indicated in the evaluation.

Anemia of chronic disease is a poorly understood but well-recognized cause of normocytic anemia in children and adults. Anemia of chronic disease can be associated with a variety of illnesses, including rheumatologic conditions, systemic infections, endocrine dysfunction, liver failure, lung disease, and renal disease.

### **Evaluation of Normocytic Anemia**

In general, normocytic anemias that are nonresponsive to supplemental iron and not clearly associated with a systemic illness warrant referral to a pediatric hematologist. A reticulocyte count and review of the peripheral blood smear are indicated for every child with normocytic anemia referred to a hematologist. The smear may help identify morphologic features to aid in the diagnosis (eg, spherocytosis, sickle cells) or reveal evidence of hemolysis (schistocytes, RBC fragments).

The percentage reticulocyte count must be considered within the context of the patient's hemoglobin level and hematocrit. A high percentage reticulocyte count is expected in a child who can mount an appropriate response to anemia. An apparently normal reticulocyte percentage (1.1%–3.5%) in a child with severe anemia is actually relatively lower than it should be to compensate for the anemia. For this reason, the reticulocyte index is a useful calculation: the reticulocyte count multiplied by the ratio represented by the patient's hematocrit divided by the normal hematocrit.

A relatively low reticulocyte count (<1%) suggests decreased RBC production. The primary care physician must then consider aplastic anemia, malignancy, transient erythroblastopenia of childhood, and other causes of bone marrow suppression. A bone marrow aspirate and biopsy are rarely indicated but must be considered to rule out malignancy, especially when more than a single blood cell line is abnormal.

An elevated reticulocyte count suggests that the bone marrow is compensating for blood loss either from hemolysis or from hemorrhage. Causes of blood loss must be considered. Patients with an elevated reticulocyte count and an elevated bilirubin level likely have ongoing hemolysis. A positive Coombs test (direct antiglobulin test) suggests an autoimmune hemolytic anemia. Without evidence of an autoimmune process, hemoglobinopathies (sickle cell disease and variants and thalassemias) must be evaluated by hemoglobin electrophoresis.

Other specialized assays may define specific RBC disorders that result in hemolysis. G6PD deficiency,

which is X-linked, is the most common enzyme defect in males. Many variants have been found, and the assay may be falsely negative in patients with a high reticulocyte count immediately after a hemolytic crisis. Families need to be educated regarding the triggers for hemolysis in G6PD deficiency, including a variety of medications, infections, exposure to mothballs, and, for some variants, fava beans (favism). A positive osmotic fragility test helps confirm the diagnosis of hereditary spherocytosis and should be considered in patients with RBC morphology consistent with the diagnosis.

### Macrocytic Anemias

Macrocytic anemias in childhood are extremely rare and are typically the result of deficiencies in folate or vitamin B<sub>12</sub>. Folate deficiency can be associated with inborn errors of metabolism, poor dietary intake, increased utilization in patients with hemolytic anemias, malabsorption, and drugs that inhibit folate metabolism (methotrexate). Vitamin B<sub>12</sub> deficiency may be caused by inborn errors of metabolism, poor dietary intake, and malabsorption. In cases of significant deficiencies, these anemias can be quite severe, with an MCV between 100 and 140 fL. In addition to normochromic macrocytic RBCs, hypersegmented neutrophils may be visible on the peripheral blood smear. Serum folate and B<sub>12</sub> levels may help confirm the diagnosis, but the underlying cause of the vitamin deficiency must be determined.

A macrocytic anemia in a child is always concerning for an underlying disorder in bone marrow production. Myelodysplasia, early aplasia, and leukemia may all manifest as macrocytosis with or without anemia. In the absence of a clear B<sub>12</sub> or folate deficiency, a referral to a hematologist is warranted for assessment of macrocytosis to rule out myelodysplasia or malignancy.

### Anemia of the Newborn

The differential diagnosis of anemia in a newborn is distinctly different from that in older children. Peripartum hemorrhage and maternal factors, such as alloantibodies, are important in deciphering neonatal anemias. Iron deficiency in the newborn period is quite rare. Anemias with similar origins may also be displayed differently in infants and children.

Table 128-1 lists the normal hematologic parameters for infants and children. Hematologic parameters in children evolve over the first couple of months of life. Typically, a normal hemoglobin level in a term newborn is approximately 19 g/dL. The hemoglobin concentration falls gradually to a nadir of 10 to 11 g/dL by 8 to 12 weeks of age. This nadir, termed *physiologic anemia of the newborn*, is more pronounced in preterm infants with nadirs as low as 7 to 8 g/dL. Despite the low nadir, transfusions are necessary only if the anemia is uncompensated, although early supplementation with iron is usually indicated.

When considering the differential diagnosis of anemia in newborns, classifying the cause of the anemia into 1 of 3 broad groups is helpful: (1) blood loss, (2) hemolysis, or (3) decreased production. Blood loss

may occur at any time during a pregnancy. Common causes include fetomaternal transfusion, twin-to-twin transfusion, placental abruption, placenta previa, and internal hemorrhage (eg, intraventricular hemorrhage, cephalohematoma, caput succedaneum). The Betke-Kleihauer test detects the presence of fetal RBCs in the mother. Fetal cells can be detected in the circulation of 50% of pregnancies; however, rarely is the hemorrhage significant enough to cause anemia in the newborn. Mothers who are blood type O with infants who are not type O may have a false-negative Betke-Kleihauer test result.

At least 15% of monochorionic twins develop significant twin-to-twin transfusions, with differences in hemoglobin concentrations of 5 g/dL or more. At birth, the donor twin typically is smaller and may have pallor, oligohydramnios, and even shock. Polycythemia, polyhydramnios, and congestive heart failure may be present at birth in the recipient twin.

The clinical manifestation of neonatal anemia from blood loss is dependent on the severity and rapidity of the blood loss. Infants with chronic blood loss throughout pregnancy may have pallor and microcytic, hypochromic anemia but appear otherwise well and hemodynamically stable. Infants with acute blood loss may have pallor, tachypnea, tachycardia, hypotension, and decreased tone. A normocytic, normochromic anemia with a reticulocytosis is detectable soon after birth.

The most common cause of hemolytic anemia in the newborn is isoimmune hemolytic anemia caused by an incompatibility in maternal and fetal RBC antigens, including Rh, ABO, and minor blood groups. Mothers who are Rh negative may become immunized against the Rh antigen when pregnant with an Rh-positive fetus. During subsequent pregnancies, if the fetus is Rh positive, then maternal anti-Rh antibodies will readily cross the placenta and destroy the Rh-positive RBCs in the fetus. In utero and perinatal hemolysis may be rapid and severe, resulting in life-threatening hemolysis and hyperbilirubinemia. However, with the prenatal administration of Rh immune globulin to Rh-negative mothers, life-threatening Rh incompatibility is rare today. In cases of hemolytic anemia from ABO or minor blood group antigen incompatibility, the mechanism of immunization and hemolysis is similar to Rh incompatibility, but the hemolysis is rarely severe. Hemolytic anemia in the newborn may also occur as a result of maternal drug use and neonatal infections, including bacterial sepsis, cytomegalovirus, toxoplasmosis, herpes, and rubella. Microangiopathic hemolysis may occur in infants with thrombi, disseminated intravascular coagulation, and Kasabach-Merritt syndrome (multiple cavernous hemangiomas).

Hemolysis from hemoglobinopathies rarely causes symptomatic anemia in newborns. Anemia from  $\beta$  chain defects (eg, sickle cell disease,  $\beta$ -thalassemias) may not appear until later in infancy when the hemoglobin concentration is more dependent on  $\beta$ -chain production.  $\alpha$ -Thalassemia major will manifest as erythroblastosis fetalis in the newborn period. RBC membrane and enzyme defects may be apparent at birth but more commonly appear later in the newborn period.

RBC production deficiencies are rare in the newborn period and are typically the result of infection or drugs. Diamond-Blackfan anemia is a rare congenital pure RBC precursor aplasia. However, affected patients are typically not anemic until 3 to 12 months of age. Congenital leukemias and osteopetrosis may also result in deficient RBC production but are also typically associated with disorders in the other cell lines and are extremely rare.

## EVALUATION

Anemia is frequently identified in the first or second year of life and in adolescence on routine screening performed by primary care physicians. By using information obtained from a thorough history and physical examination, as well as results of routine laboratory studies, most causes of anemia can be accurately diagnosed in the primary care physician's office. Diseases leading to anemia and pallor in infants and children are listed in Table 128-2, Figure 128-1, and Figure 128-2.

## History

Many children with anemia are asymptomatic and have their condition diagnosed only on routine screening evaluations. Nonetheless, a thorough history may help identify patients most at risk for developing anemia, as well as help identify the cause of an existing anemia. Demographic factors such as age, gender, and ethnicity will identify risk groups for specific types of anemia. Toddlers and adolescent girls account for most cases of iron deficiency anemia. Blacks are at greatest risk for sickle cell anemia, whereas the thalassemias occur primarily in patients of Mediterranean and Southeast Asian descent. A diet history is crucial in identifying children most likely to develop iron deficiency anemia. Sulfa drugs can produce a hemolytic anemia in patients with G6PD deficiency. Many common acute bacterial and viral infections

may result in a mild anemia from decreased RBC production or increased RBC destruction, or both. Anemias resulting from such infections are typically short-lived but are commonly the cause of abnormalities identified on routine screening. Acute or chronic blood loss (or both) should be considered in all patients with anemia. Common sites of blood loss in otherwise asymptomatic patients include the gastrointestinal tract for all patients and the genitourinary tract for female patients. Anemia may be the benign manifestation of an underlying systemic disease such as autoimmune disorders and may be associated with signs of systemic illness (fevers, weight loss, among other signs). Finally, a family history may help guide the workup for a patient with anemia. In addition to a family history of hemoglobinopathies, a history of jaundice during systemic illnesses, cholecystectomy at a young age, or splenectomy may suggest a hereditary hemolytic anemia. Historical factors worthy of note in evaluating an anemic patient are listed in Table 128-3.

## Physical Examination

Infants and toddlers may experience fatigue, irritability, pallor, increased periods of sleep, poor feeding, and failure to thrive. Older children and adolescents may experience fatigue, pallor, exercise intolerance, dizziness, headaches, shortness of breath, or palpitations. However, most mild to moderate anemias in childhood are asymptomatic because they develop slowly over time, and patients are usually well compensated. In fact, seeing a child for a routine physical examination only to find out later that routine laboratory studies reveal anemia is not uncommon.

Pallor is the classic physical examination finding suggestive of anemia but is rare in mild anemias and frequently only seen reliably with hemoglobin concentrations less than 8 g/dL. Pallor may be more easily identified in the nail beds, mucosa, conjunctiva, and

**Table 128-3** Pertinent Historical Factors in the Diagnosis of Childhood Anemia

Age	Nutritional anemias are rare in infancy in term infants but are more common in infants born preterm, as well as in school-aged children and adolescents. Significant anemia diagnosed in the first 6 months of life in a term infant is most likely a congenital anemia.
Gender	G6PD is an X-linked disorder.
Race and ethnicity	Hemoglobin S and C are more common among patients of African descent. $\alpha$ -Thalassemias are most common in patients of African or Asian ancestry. $\beta$ -Thalassemia syndromes are more common in patients from the Mediterranean.
Nutrition	Sources of iron, folate, B <sub>12</sub> , and vitamin E should be documented. A history of pica suggests iron deficiency.
Medications	Phenytoin and methotrexate can induce a megaloblastic anemia. Oxidants can induce hemolytic anemias.
Family history	Document a history of anemia, jaundice, gallstones, cholecystitis, splenomegaly, splenectomy, or hemolytic crisis, which may suggest an inherited hemolytic anemia.
Infection	Infections may induce hemolysis or red blood cell hypoplasia or aplasia (parvovirus B19), whereas hepatitis may induce aplastic anemia.
Gastrointestinal	The gastrointestinal tract is a common source of blood loss. Nutritional deficiencies may result from malabsorption syndromes.

G6PD, glucose-6-phosphate dehydrogenase.

Modified from Nathan DG, Orkin SH. A diagnostic approach to the anemic patient. In: *Nathan and Orkin's Hematology of Infancy and Childhood*. 5th Ed. Philadelphia, PA: WB Saunders; 1998. Copyright © 1998, Elsevier, with permission.

palmar creases than in a cursory examination of the skin. Splenomegaly, scleral icterus, and jaundice in the setting of anemia are highly suggestive of a hemolytic process. In chronic hemolytic anemia such as thalassemia, frontal bossing and maxillary prominence are indicative of the marrow expansion necessary to keep pace with ongoing hemolysis. Leukemia or lymphoma may manifest as an anemia associated with focal lymphadenopathy and hepatosplenomegaly. Regardless of the cause of the anemia, a mild to moderate decrease in RBC mass may result in a pulmonary valve flow murmur, whereas more severe anemias may be associated with signs and symptoms of congestive heart failure. Compensated anemia usually refers to anemia associated with sufficient cardiovascular compensation to preserve normal oxygen delivery to tissues. Patients in whom the anemia develops or persists over a long period may have hemoglobin concentrations less than 6 g/dL but no signs or symptoms of anemia other than pallor. Cardiac stroke volume is increased, allowing patients to maintain normal oxygen delivery to tissues with normal or near-normal heart rates. Patients who lose blood more rapidly, from hemolysis or hemorrhage, may not have time for compensatory mechanisms to maintain tissue perfusion and oxygenation. Tachycardia is an early sign, followed by orthostasis, headache, dizziness, and hypotension, all of which are reasons to hospitalize a patient with anemia.

### Laboratory Findings

In addition to a determination of the hemoglobin level and hematocrit, which may be done exclusively in some practice settings, RBC morphology and reticulocyte count should be assessed. Anemias may be classified by RBC size as determined by the MCV and by RBC production as determined by the reticulocyte count. An elevated reticulocyte count implies bone marrow compensation for chronic blood loss or hemolysis, whereas a low reticulocyte count may suggest impaired RBC production or acute blood loss. Although not necessary in the initial diagnosis of all patients with anemia, iron studies may be performed and erythrocyte sedimentation rate, serum bilirubin, and serum lactate dehydrogenase levels may be assessed easily in most practice settings and may provide clues to the cause of the anemia. The mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) are generally of minimal value in the classification and diagnosis of an anemia. Changes in the MCH typically parallel changes in the MCV. The MCHC is a measure of RBC hydration status. Higher MCHC values ( $>35$  g/dL) are seen in dehydrated red cells associated with spherocytosis, and low MCHC values may be seen in iron deficiency.

### TREATMENT

Treatment of a compensated anemia will be dictated by the cause of the anemia. Patients with uncompensated anemia should be admitted to the hospital for observation and possible transfusion. Effective treatment of the anemia is best accomplished by treating

the underlying disorder. A substantial number of patients with a microcytic anemia or a normocytic anemia have early iron deficiency anemia, and a course of supplemental iron is appropriate. However, for patients with anemia that is nonresponsive to nutritional supplements and not clearly related to a systemic illness, referral to a pediatric hematologist is warranted. Referral to a pediatric oncologist is also warranted for management of most macrocytic anemias that are not related to nutritional deficiencies. Specific treatment will be predicated on the underlying hematologic disorder.

### WHEN TO REFER

- Hemoglobin level less than 8 g/dL or hematocrit less than 25%
- Anemia of unknown origin
- Anemia is associated with disorder in white blood cells or platelets
- Diagnosis of hemoglobinopathy or RBC membrane defect is suspected or confirmed

### WHEN TO ADMIT

- Profound anemia (hemoglobin level  $<5$ )
- Uncompensated anemia or anemia associated with a rapidly dropping hemoglobin level
- Anemia in an ill child

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Anemia and Your Young Child* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Iron and Iron Deficiency* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/nccdpdp/dnpa/nutrition/nutrition\\_for\\_everyone/iron\\_deficiency/index.htm](http://www.cdc.gov/nccdpdp/dnpa/nutrition/nutrition_for_everyone/iron_deficiency/index.htm))

#### Medical Decision Support

- *Pediatric Nutrition Handbook*, 7th ed (book), American Academy of Pediatrics (shop.aap.org), pp 403–417

### SUGGESTED READINGS

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## Chapter 129

# ANXIETY

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### INTRODUCTION

Symptoms of anxiety affect many children, including a large number whose symptoms do not rise to the level of a disorder. At some stages and in some circumstances, a certain level of anxiety is developmentally appropriate (eg, stranger anxiety in late infancy or anxiety in anticipation of a painful medical procedure). However, from 6% to 20% of youth will meet diagnostic criteria for an anxiety disorder at some time during childhood, with approximately half experiencing impairment of daily functioning. Anxiety disorders (generalized anxiety disorder, panic disorder, separation anxiety disorder, agoraphobia, social phobia, post-traumatic stress disorder [PTSD], obsessive-compulsive disorder [OCD], specific phobias; see Table 129-1) are among the most common mental health disorders in children and adolescents. Anxiety disorders often occur concomitantly with chronic medical conditions—affecting children's use of medical resources through frequent emergency department visits and hospitalizations—and with other psychiatric disorders, especially depression. Anxious children often have an anxious or a depressed parent.

The guidance in this chapter applies to the care of children presenting with symptoms of anxiety in pediatric clinical settings. Though, as noted above, there are several distinct forms of anxiety disorders, they often co-occur, sharing core symptoms and approaches to initial treatment. Thus the pediatrician may want to start building competence in this area by learning about anxiety problems in general before trying to further differentiate the various disorders.

The following guidance is based on the work of the World Health Organization, whose recommendations may be updated annually. The most up-to-date information can be found at [www.who.int](http://www.who.int).

### FINDINGS SUGGESTING ANXIETY

Symptoms of anxiety vary by age. Children may experience developmentally normal fears; they may have fears that are exaggerated or persistent beyond norms for their age; and they may have fears and associated reactions or panic attacks that impair their functioning at school, at home, or with peers. Box 129-1 provides a summary of the symptoms and clinical findings that suggest anxiety. These may be elicited from either parents or youth. Parents and youth often disagree on the severity of anxiety symptoms; however, agreement is much better if the discussion is about whether there are symptoms at all, regardless of severity or effect on function. Agreement at this level may facilitate further discussion of how to approach the problem.

**Table 129-1** General Overview of Anxiety and Anxiety-Related Disorders

TYPE	DESCRIPTION
<b>ANXIETY</b>	
Generalized anxiety disorder	Excessive anxiety and worry about a number of events or activities. Children tend to worry excessively about their competence or the quality of their performance at school or in sporting events.
Panic disorder	Recurrent, unexpected, abrupt surge of intense fear or discomfort that reaches a peak within minutes and includes symptoms such as sweating, trembling, palpitations, and dizziness.
Separation anxiety disorder	Developmentally inappropriate and excessive fear or anxiety concerning separation from those to whom the individual is attached.
Agoraphobia	Marked fear or anxiety in using public transportation, being in open or enclosed spaces, standing in line or being in a crowd, or being outside of the home alone.
Social phobia	Marked fear or anxiety about 1 or more social situations in which the individual is exposed to possible scrutiny by others. In children, the anxiety must occur in peer settings and not just during interactions with adults.
Specific phobias	Marked fear or anxiety about a specific object or situation (eg, insects, heights, storms, needles, airplanes, loud sounds, costumed characters). In children, the fear or anxiety may be expressed by crying, tantrums, freezing, or clinging.
<b>OBSESSIVE-COMPULSIVE DISORDERS</b>	
Obsessive-compulsive disorder (OCD)	Presence of obsessions or compulsions. Obsessions are recurrent and persistent thoughts, urges, or images that are experienced as intrusive and unwanted. Compulsions are repetitive behaviors or mental acts that an individual is driven to perform, often in response to an obsession or rigidly applied rules.
<b>TRAUMA- AND STRESSOR-RELATED DISORDERS</b>	
Post-traumatic stress disorder (PTSD)	Development of characteristic symptoms following exposure to actual or threatened death, serious injury, or sexual violence.

Derived from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association; 2013.

**BOX 129-1 Symptoms and Clinical Findings Suggesting Anxiety**

- Normal fears (eg, strangers, dark, separation, new social situations, unfamiliar animals or objects, public speaking) are exaggerated or persistent.
- Fears are keeping child from developmentally appropriate experiences (eg, school refusal, extreme shyness or clinging, refusal to sleep alone).
- Tantrum, tearfulness, acting-out behavior, or another display of distress occurs when child is asked to engage in feared activity.
- Child worries about harm coming to self or loved ones or fears something bad is going to happen.
- Behavior changes following a traumatic experience, such as abuse, witness to violence, loss of a loved one, or medical trauma, as follows:
  - **Infants and toddlers:** Crying, clinging, change in sleep or eating habits, regression to earlier behavior (eg, bed-wetting, thumb-sucking), repetitive play or talk
  - **3- to 5-year-olds:** Separation fears, clinging, tantrums, fighting, crying, withdrawal, regression to earlier behavior (eg, bed-wetting, thumb-sucking), sleep difficulty
  - **6- to 9-year-olds:** Anger, fighting, bullying, irritability, fluctuating moods, fear of separation or of being alone, fear that traumatic events will recur, withdrawal, regression to earlier behavior, physical complaints (eg, stomachaches, headaches), school problems (eg, avoidance, academic difficulty, difficulty concentrating)
- **10- to 12-year-olds:** Crying, aggression, irritability, bullying, resentment, sadness, social withdrawal, fears that traumatic events will recur, suppressed emotions or avoidance of situations or discussions that evoke memories of the traumatic event, sleep disturbance, concern about physical health of self or others, academic problems or decline related to lack of attention
- **13- to 18-year-olds:** Numbing, reexperiencing, avoidance of feelings (or situations or discussions that evoke memories of the traumatic event), resentment, loss of trust or optimism about future, depression, withdrawal, mood swings, irritability, anxiety, anger, exaggerated euphoria, acting out, substance use, fear of similar events, appetite and sleep changes, physical complaints, academic decline, school refusal
- Somatic features accompany worries: palpitations, stomachaches, headaches, breathlessness, difficulty getting to sleep, nausea, feeling wobbly (“jelly legs”), butterflies.
- *Panic attacks* occur in response to feared objects or situations, or happen spontaneously. These are unexpected and repeated periods of intense fear, dread, or discomfort along with symptoms such as racing heart-beat, shortness of breath, dizziness, light-headedness, feeling smothered, trembling, sense of unreality, or fear of dying, losing control, or losing one’s mind. Panic attacks often develop without warning and last minutes to hours.

**TOOLS TO ASSIST WITH IDENTIFICATION**

Because many children do not spontaneously disclose their symptoms, standardized psychosocial screening instruments may be used to identify children with symptoms of anxiety. Several instruments have versions to collect information directly from the youth or from parents or teachers. Table 129-2 provides an overview of general psychosocial screening tools available in the public domain, along with results suggesting that anxiety may be present. Use of additional instruments, such as the Spence Children’s Anxiety Scale or Screen for Child Anxiety Related Disorders 2 (SCARED), can help to confirm findings of the initial screening; and use of a functional assessment tool, such as the Strengths & Difficulties Questionnaires (SDQ) or Columbia Impairment Scale (CIS), will assist in determining whether the child is significantly impaired by the symptoms. Use of a tool to assess the effect of the child’s problem on other members of the family may also be helpful; the Caregiver Strain Questionnaire (CGSQ) is an example.

It is important to differentiate the use of these tools as screening instruments at routine visits from their use to refine concerns that have already been raised. When used as screening tools, they tend to have relatively low sensitivity and positive predictive value.

That is, positive results need further discussion to understand the meaning of the result, and negative results may not be reassuring if the parent or youth are truly concerned. When used to follow up on existing concerns, results still need discussion with families, but are more likely to be a fair indicator of the nature and severity of the child’s problems.

**ASSESSMENT**

Assessment begins by differentiating the child’s symptoms from normal behavior. Some children have a temperament that is, from the outset, marked by having more difficulty with change and wariness of new situations or individuals. Recognizing that these are longstanding traits can help parents promote active coping skills and avoid misinterpreting the child’s behavior as oppositional. Anxiety is a universal experience, and it can occur predictably at particular stages of life or in particular situations. When anxiety persists outside of these stages and situations, or when its severity is disruptive, further assessment and treatment may be warranted. Some stages in which particular anxieties may normally emerge include the following:

- **8 to 9 months:** Peak of stranger anxiety.
- **Toddlers and early school age:** Development of separation anxiety (fear of new people, places, or

**Table 129-2** General Psychosocial Screening/Results Suggesting Anxiety

SCREENING INSTRUMENT	SCORE SUGGESTING ANXIETY
Pediatric Symptom Checklist (PSC)-35	<ul style="list-style-type: none"> <li>• Total score <math>\geq 24</math> for children 5 years and younger.</li> <li>• <math>\geq 28</math> for those 6–16 years.</li> <li>• <math>\geq 30</math> for those 17 years and older.</li> </ul> AND <ul style="list-style-type: none"> <li>• Further discussion of items related to anxiety confirms a concern in that area.</li> </ul>
PSC-17	<ul style="list-style-type: none"> <li>• Internalizing subscale is <math>\geq 5</math>.</li> </ul> AND <ul style="list-style-type: none"> <li>• Further discussion of items related to anxiety confirms a concern in that area.</li> </ul>
Strengths & Difficulties Questionnaire (SDQ)	<ul style="list-style-type: none"> <li>• Total symptom score of <math>&gt; 19</math>.</li> <li>• Emotional symptom score of 7–10 (see instructions at <a href="http://www.sdqinfo.com">www.sdqinfo.com</a>).</li> <li>• Impact scale score of 1 (medium impairment) or <math>\geq 2</math> (high impairment).</li> </ul> AND <ul style="list-style-type: none"> <li>• Further discussion of items related to anxiety confirms a concern in that area.</li> </ul>

being away from trusted caregivers), usually ends by age 2 to 3 years. Depending on their temperament, toddlers and young children may have greater or lesser tolerance of changes to routine or expectations or of novel experiences (which can include new clothing, foods). Fears of the dark (or of unseen monsters) are common and exacerbated by other stresses and exposure to frightening media.

- **5 to 8 years:** During this period, many children experience an increase in worry about harm to parents or attachment figures. Worries may be triggered by illness or death in family members, by the child's own illness, or by world events.
- **School-aged children of any age:** Many children experience anxiety and distress at the time of high-stakes testing, as well as initial reluctance to socialize in new situations.
- **Adolescence:** Previously resolved anxiety issues often occur again in early adolescence, sometimes associated with concerns about appearance, new social situations, and school performance.

Children with anxiety disorders have fear and distress that interferes with functioning in response to everyday situations. Verbal older children and adolescents are usually able to describe their fears ("worries" may be a more understandable concept), but evaluating reports of younger children's anxiety may be challenging, especially if the parent giving information is also anxious; therefore, it is important to communicate directly with children about these symptoms and to observe or get the child's report of physiologic symptoms (eg, increased heart rate, shortness of breath, numbness, tingling). Sometimes children will display anxiety through repetitive play that acts out their concerns—crashing toy cars or having violent or tragic things happen to dolls—or through drawings that they make in response to simple requests to "draw something." Bad behavior can also be a masked presentation of anxiety. Children and youth at any age may become irritable or oppositional in the face of situations—imminent or anticipated—that they fear. Depression or bereavement may mimic or co-occur

with anxiety, so at least some exploration of other emotional symptoms and of current stressors is always warranted. When children and youth of any age are anxious, it is always important to ask about stressors in the family environment—serious illness (including anxiety and depression) in a family member, economic problems, or marital discord.

Anxiety, like depression, also may occur in multiple family members. When children are found to be anxious, it is not unusual to find that one or more close family members are anxious as well. Helping parents manage their own anxiety can be very important, especially, as discussed in the following text, when trying to use modelling as a form of treatment. Table 129-3 provides a summary of these conditions.

Children with anxiety sometimes have panic attacks, which are episodes of autonomic arousal that occur suddenly, often (but not always) cued by thoughts of a feared situation. People experiencing panic attacks usually report sudden onset of shortness of breath, palpitations, trembling, diaphoresis, and often a feeling of faintness, dread, or impending doom. The attacks usually subside by themselves over the course of several minutes, but it is not unusual, especially among teenagers, for some of the symptoms to be prolonged and result in a call for emergency medical assistance. Differentiating panic attacks from hypoglycemia, asthma exacerbations, or cardiac conditions may in itself help with their treatment; often they will improve as other aspects of anxiety are treated. As noted in the following text, they can sometimes be suppressed with medication if their frequency is causing disability, which can facilitate treatment of the underlying anxiety problem.

Treatment for anxiety generally involves identifying the specific situations in which it is triggered and helping individuals learn how to reduce anxious feelings when they occur and gradually become tolerant of the triggers to the point where anxious responses are either no longer evoked or remain manageable. Treatment is usually tailored to the specific triggering situation, often through carefully supported increasing

**Table 129-3** Conditions That May Mimic or Co-occur With Anxiety

CONDITION	RATIONAL
Learning problems or disabilities	If symptoms of anxiety are associated with problems of school attendance or performance, the child may be experiencing academic difficulties. (See Chapter 172, Learning Difficulty, for more information.)
Somatic complaints	Anxious children may present with a variety of somatic complaints (eg, gastrointestinal symptoms, headaches, chest pain). These may elicit medical workups if they are not recognized. Conversely, acute or chronic medical conditions or pain syndromes may cause anxiety.
Depression	This can be very difficult to distinguish from anxiety. Depression coexists in half or more of anxious children. Marked sleep disturbance, disturbed appetite, low mood, or tearfulness in the absence of direct anxiety provocation could indicate that a child is depressed.
Bereavement	Most children will experience the death of a family member or friend sometime in their childhood. Other losses may also trigger grief responses—separation or divorce of parents, relocation, change of school, deployment of a parent in military service, breakup with a girlfriend or boyfriend, or remarriage of a parent. Such losses are traumatic. They may result in feelings of insecurity and anxiety immediately following the loss or exacerbate existing anxiety. Furthermore, they may make the child more susceptible to impaired functioning at the time of subsequent losses.
Autism spectrum disorders including pervasive developmental disorder and Asperger syndrome	Children who have these difficulties also have problems with social relatedness (eg, poor eye contact, preference for solitary activities), language (often stilted), and range of interest (persistent and intense interest in a particular activity or subject). They often will have very rigid expectations for routine or parent promises and become anxious or angry if these expectations are not met.
Exposure to adverse childhood experiences (ACE)	Children who have experienced or witnessed trauma, violence, a natural disaster, separation from a parent, parental divorce or separation, parental substance use, neglect, or physical, emotional, or sexual abuse are at high risk of developing emotional difficulties such as adjustment disorder or PTSD. Determination of the temporal relationship between the trauma and onset of anxiety symptoms is essential. Denial of trauma symptoms does not mean trauma did not occur; questions about ACE should be repeated as a trusting relationship is established.
Psychosis	Symptoms associated with psychosis, such as hallucinations or delusions, may occur in children with PTSD. They may also occur infrequently with adolescent onset of bipolar disorder and are features of schizophrenia, which may also have its onset in adolescence. The teen may manifest fear without disclosing the hallucinations or delusions.
Physical illness	Medical issues that can mimic or provoke anxiety symptoms include thyroid disease, hypoglycemia, side effects of medications (eg, bronchodilators), and endocrine tumors (pheochromocytoma). Drug or alcohol withdrawal is a consideration for teens (the latter potentially a medical emergency).
Selective mutism	Consider this if a child who has had normal language development suddenly stops talking in certain situations (most often in school and to adults outside the home). This can be confused with children making a language transition (eg, a child raised speaking Spanish who is suddenly placed in an English-speaking class.)

exposure to the trigger coupled with practice of a variety of cognitive, somatic, and social coping strategies. Treatment of OCD and PTSD involves these same treatment elements, but differs in that the etiology of the disorders takes on a role in treatment (whereas in the treatment of other anxiety disorders there is less emphasis on how the problem began and more on how to get it to remit). For OCD, the fact that obsessions and compulsions develop without particular triggers (though they can be worsened by other stresses) plays an important role in children's and family's understanding of the condition. For PTSD, linking what may be nonspecific symptoms to a particular past trauma can be an important part of treatment.

- **Consider OCD in the presence of marked rituals or compulsive behaviors.** Most children have

phases of ritualized behavior that usually can be distinguished from OCD by the degree of distress caused if a ritual is interrupted. Individuals with OCD usually report—or after discussion will admit—that the symptoms have a major effect on how they plan their activities or interact with others, and that attempts to stop the thoughts or actions have been difficult to carry out or even contemplate. School-aged children and adolescents will often—once the symptoms can be openly discussed—admit being aware that there is something objectively out of proportion about their concerns, even though they remain difficult to resist. The most common concerns center on contamination—fears of touching things that may be dirty, or the need to repetitively wash or bathe. Other common difficulties are the need to check that something has been done (usually



related to security—doors locked, stove turned off) or a need to have one's personal possessions in a particular order or place.

- **Consider PTSD if the onset of anxiety was preceded by an extremely distressing experience**, such as witnessing violence, losing a loved one, undergoing medical trauma, or experiencing sexual or physical abuse. Parents may be unaware of exposures to trauma, such as bullying at school or in the community, and there may be major traumas in the family (eg, serious illness in a parent, pending divorce) that are similarly not discussed or disclosed; consequently, clinicians may need to interview children and parents separately to elicit a complete history. It is important to note that the triggering circumstances need only be traumatic in the eye of the child. Most antecedents have in common situations in which the child felt that there was risk to her life, or that of someone close to her. The 3 hallmark symptoms of anxiety in the wake of trauma are *re-experiencing* (often repetitive play in young children), *avoidance* of memories or situations that recall the trauma, and *hypervigilance* (eg, increased worry about safety, startling or anxiousness at unexpected sounds or events). Avoidance can also take the form of changing the subject or acting inappropriately when subjects related to trauma are brought up in conversation. Children most at risk for developing PTSD following trauma or loss are those with preexisting mental health conditions, those whose caregivers are experiencing emotional difficulties, those facing preexisting or consequent family life stressors, such as divorce or loss of job, those with previous loss or trauma experiences, those repeatedly exposed to media coverage of traumatic events, and those with a limited support network. Clinicians can provide the child with a safe and comfortable environment to express her feelings and allow the child to control the interview, taking breaks or discontinuing as needed. Even children with limited symptoms of PTSD after a trauma can benefit from treatment.

## PLAN OF CARE FOR CHILDREN WITH ANXIETY

The care of a child experiencing anxiety can begin in the primary care setting from the time symptoms are recognized, even if the child's symptoms do not rise to the level of a disorder and regardless of whether referral to a mental health specialist is ultimately part of the care plan. Both children and parents may, by temperament, be more or less socially outgoing and more or less open to new or unexpected experiences. Helping parents appreciate their own areas of comfort and discomfort, and how these may differ from those of their child, can be a first step toward treatment. Regardless of parent or child temperament, parents can be helped to learn ways to help their child gain better emotional regulation.

### Engage Child and Family in Care

Without engagement, most families will not seek or persist in care. The process may require multiple primary care visits.

Reinforce strengths of the child and family (eg, good relationships with at least 1 parent or important adult, prosocial peers, concerned or caring family, help-seeking, connection to positive organizations) as a method of engagement, and identify any barriers to addressing the problem (eg, stigma, family conflict, resistance to treatment). Use "common factors" techniques to build trust and optimism, reach agreement on incremental next steps, develop a plan of care, and collaboratively determine the role of the primary care physician. Regardless of other roles, the primary care physician can encourage a positive view of treatment on the part of the child and family.

Remember that it is in many ways normal for people with anxiety problems to initially resist their treatment. This is because most people cope with anxiety through avoidance, and initiating treatment means that one has to start thinking about the situations that trigger the anxious feelings.

### Provide Psychoeducation

Tell the family a little bit about anxiety; much of the material discussed previously in this chapter could be useful. Emphasize that anxiety is a normal human emotion, that anxiety problems are very common, and that they can be addressed. For some children and families, it can be helpful to talk about variations in temperament or personal style that make some people more or less anxious in new situations or more or less responsive to threats. Again, acknowledge that these are traits we are born with and not to be ashamed of. The clinician can also say that anxiety has nothing to do with bravery or accomplishment, noting that many famous performers and athletes experience serious degrees of "stage fright" and yet, with support and encouragement, have become very successful (usually by working hard to prepare themselves). It can be helpful to point out that one can very much enjoy and be good at things but still experience anxiety when having to do them in front of others or in particularly high-stakes circumstances.

### Encourage Healthy Habits

Encourage exercise, outdoor play, balanced and consistent diet, sleep (critically important to mental health), special time with parents, frequent acknowledgment of the child's strengths, and open communication with a trusted adult about worries. Children, particularly younger ones, should be shielded from certain types of media, such as the news, when there are violent or disturbing images or stories. Likewise, TV shows, even some cartoons, may contribute to a child's feeling anxious. For preteens and teens, media messages about body image and social media may contribute to or exacerbate anxiety.

### Reduce Stress

Consider the child's social environment (eg, family social history, parental depression screening, results of any family assessment tools administered, reports from child care or school). Questions to raise might include the following:

- *Is an external problem causing the child to be anxious* (eg, bullying at school, academic difficulties,

disruption at home)? Take steps to address the problem.

- *Is the child exposed to frightening electronic media?* Sometimes this results from unsupervised access to television or Internet content, but it may also occur during shared family activities (eg, movies, TV, video games) when parents or other family members underestimate or fail to recognize how frightened the child has become. Limiting these exposures, and providing reassuring explanations if they occur, can be an important part of reducing anxiety, especially among younger children.
- *Is the child's worry about a parent's welfare legitimate because of a serious illness, domestic violence, or parent impairment?* Address environmental issues, enlisting the help of school personnel or social services as appropriate to the situation.
- *Is the parent anxious or depressed or impaired because of substance abuse? Has the parent experienced trauma or loss?* Anxious children very often have an anxious or a depressed parent. Advise parents to minimize their own displays of fear or worry when the child is present. A referral to adult mental health services might also be appropriate.

### Offer Initial Intervention(s) to Address the Anxiety Symptoms

The strategies described in the following text are common elements of evidence-based psychosocial interventions for anxiety disorders. They are applicable to the care of children with mild or emerging anxiety symptoms and to those with impairing symptoms that do not rise to the level of a disorder. They can also be used as initial primary care management of children with anxiety disorders and while readying children for referral or awaiting access to specialty care. Medications can be helpful, especially to speed suppression of panic and OCD symptoms or when very time-limited and severe stressors need to be faced, but, in the absence of psychosocial treatments, symptoms may recur as the medications are discontinued. Interpreting the results of a medication trial can also be problematic, because the severity of anxiety problems is often cyclic. Families may seek care as symptoms are peaking. If medication is started at this point, it often cannot be determined if the condition improved on its own or responded to medication. Thus, starting with a carefully administered psychosocial treatment plan may be a reasonable first step until the severity and natural history of the anxiety concerns are better understood.

*Guide parents in managing the child's fears.* Help the parents to identify their child's fear(s) and reach consensus with the child and family on the goal of reducing symptoms and on a way to do it. This could include teaching the child and parent cognitive behavioral strategies to improve coping skills at times when the child feels anxious. Examples of these skills include deep breathing, muscle relaxation, positive self-talk, thought stopping, and thinking of a safe place. The child and family may also benefit from reading

material or a Web course, as appropriate to their literacy level.

*Gradually increase exposure.* One of the best validated approaches to anxiety and phobias is to gradually increase the child's exposure to feared objects or experiences. The eventual goal is to master rather than avoid feared things. To do this, the parent might start out with brief exposure to the feared object or activity and gradually lengthen the exposure. First, help the child imagine or talk about the feared object or activity or look at pictures; then learn to tolerate a short exposure with support from the parent; proceed to tolerate a longer exposure in a group or with the parent or another coach; and, finally, tolerate the feared activity alone (when that is appropriate) but with a chance to get help if needed. During these trials, parents need to stay as calm and confident as possible; if they become distressed, it will be a cue for the child to become distressed.

*Manage school phobia.* For some children who are vulnerable to anxiety, it is necessary to return the child promptly to the anxiety-producing situation. School phobia is an example. For the child who is afraid at school or resists going to school, rule out bullying, trauma, learning difficulties, and medical conditions that may be contributing to stress and fear. Also, the primary care physician can partner with school personnel to manage the child's return to school and gently, but firmly, insist that the child attend school, in addition to providing positive feedback and calm support. If absence becomes prolonged or parents are reluctant to support the child's return, referral to a mental health specialist will be necessary.

If anxiety is secondary to environmental stress, support the parents' efforts to protect the child, buffer stress, and help the child master his anxiety. Help the child to rename the fear (ie, "annoying worry") and assist the child to become the boss of the worry. It is also helpful to reward brave behavior (see Table 129-4).

**Table 129-4**

### Tips for Reward System

#### REWARD SYSTEMS FOR BRAVE BEHAVIOR

#### GUIDELINES FOR USE

Small rewards  
Star charts

- Include positive feedback.
- Focus on only 1 or 2 behaviors at a time.
- Have 1 star chart per behavior.
- Negotiate rules for the star chart (eg, sleeping in own bed for 1 night = 1 star; 4 stars = trip to the pool).
- Ignore mistakes and failures; do not even mark them on the star chart.
- Continue awarding stars when they are earned.

*Attend to overall parenting style.* Children can become anxious if parents are inconsistent about rules and expectations. Determine whether there are catastrophic consequences for failure (“I know Dad will get angry if I bring home a bad grade....”). Explore the child’s sense of responsibility for the family’s stresses (“I know that the only reason Mom and Dad work hard is so I can go to a better school, so I’m afraid that if don’t do well....”).

*Treat panic attacks.* Early treatment, including psychosocial and psychopharmacologic therapy, is useful and may prevent progression to agoraphobia and other problems such as depression and substance abuse. When children are aware of the triggers for their attacks, developing alternative responses to those triggers can diminish the frequency of attacks. When attacks appear without apparent triggers, referral for pharmacologic treatment may be most effective.

Links for further information regarding the treatment of anxiety symptoms are provided in Tools for Practice at the end of this chapter.

### Provide Resources

Helpful handouts and publications are included in Tools for Practice: Engaging Patient and Family at the end of this chapter. Provide the family with contact numbers and resources in case of emergency.

### Monitor the Child’s Progress Toward Therapeutic Goals

Child care, preschool, or school reports can be helpful in monitoring progress. Screening instruments that gather information from multiple reporters (youth, parent, teacher), such as the SDQ, can be helpful in monitoring progress with symptoms and functioning.

It is important for the primary care physician to work with the family to understand that it is not uncommon for treatment to be successful for a period of time and then seem to lose effectiveness. This can happen when there are new stresses or demands, or when, after a period of success, there has been a letup on treatment. If troubleshooting existing treatment and ways of dealing with new stresses does not help get function back to baseline, new treatments or new diagnoses need to be considered. In particular, as school demands increase, learning issues may need to be considered even if they were not seen as contributing problems in the past.

### Involve Specialist(s)

Involve specialist(s) if the child does not respond to initial interventions or if the following clinical circumstances exist:

- Child has severe functional impairments at school, at home, or with peers—for example, if anxiety threatens to interfere with academic progress or other developmentally important goals.
- Multiple symptoms of anxiety occur in many domains of life (eg, fearful of new situations, reluctant to do things in public, trouble separating, worries a lot).

- The child or parent is very distressed by the symptom(s).
- There are co-occurring behavior problems. (The combination of shyness, anxiety, and behavior problems is thought to be particularly risky for future behavior problems of a more serious nature.)
- The anxiety was preceded by serious trauma or symptoms suggesting PTSD.
- The child seems to have panic disorder or OCD, both of which require specialized treatment.
- The anxiety occurs in a child with an autism spectrum disorder. Anxiety about both normal childhood issues (weather, animals), as well as the orderliness and predictability of daily routines, is relatively common among higher functioning children who display autism spectrum symptoms, including stereotyped interests and poor social perceptions and skills.

*When specialty care is needed, ensure that it is evidence-informed and assist the family in accessing it.* A variety of evidence-based and evidence-informed psychosocial interventions, and some pharmacologic interventions, are available for the treatment of anxiety disorders in children and adolescents. Ideally, those referred for care in the mental health specialty system would have access to the safest and most effective treatments. Table 129-5 provides a summary of these interventions. Youth referred for mental health specialty care complete the referral process only 61% of the time, and a significantly smaller number persist in care. Approaches to improving the referral process include making sure that the family is ready for this step in care, has some idea of what the specialty care will involve, and understands what the primary care physician’s ongoing role may be. If the specialty appointment is not likely to occur shortly, the physician can work with them on a plan to manage the problem as well as possible in the meantime.

Note that not all evidence-based interventions may be available in every community. If a particular intervention is not available, this becomes an opportunity to collaborate with others in the community to advocate on behalf of children. Increasingly, states offer both telepsychiatry services and consultation/referral support “warmlines” that help physicians provide initial treatment and locate resources. The availability of the latter form of help is tracked at [www.nncpap.org](http://www.nncpap.org).

*Reach agreement on respective roles in the child’s care.* If the child is referred to mental health specialty care for an anxiety disorder, the physician may be responsible for initiating medication or adjusting doses; monitoring response to treatment; monitoring adverse effects; engaging and encouraging the child and family’s positive view of treatment; and coordinating care provided by parents, school, medical home, and specialists. In fact, the child may improve just knowing that the physician is involved and interested. Resources available to help clinicians in these roles are provided in Tools for Practice: Medical Decision Support.

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## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *How to Ease Your Child's Separation Anxiety* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/toddler/Pages/Soothing-Your-Childs-Separation-Anxiety.aspx](http://www.healthychildren.org/English/ages-stages/toddler/Pages/Soothing-Your-Childs-Separation-Anxiety.aspx))
- *Tips for Parenting the Anxious Child* (handout), American Academy of Pediatrics ([www.brightfutures.org/mentalhealth/pdf/families/mc/tips.pdf](http://www.brightfutures.org/mentalhealth/pdf/families/mc/tips.pdf))
- *Helping Your Anxious Child: A Step-by-Step Guide for Parents*, 2nd ed (book), New Harbinger Publications
- *Feelings Need Check-ups Too* (toolkit), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Children-and-Disasters/Pages/Feelings-Need-Checkups-Too-Toolkit.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Children-and-Disasters/Pages/Feelings-Need-Checkups-Too-Toolkit.aspx))

### Medical Decision Support

- *Pediatric Symptom Checklist* (screen), Massachusetts General Hospital ([www.massgeneral.org/psychiatry/services/psc\\_home.aspx](http://www.massgeneral.org/psychiatry/services/psc_home.aspx))
- *Strengths & Difficulties Questionnaires* (screen), Youth in Mind, Ltd ([www.sdqinfo.com](http://www.sdqinfo.com))

- *Spence Children's Anxiety Scale* (scale), Susan H. Spence, PhD ([www.scaswebsite.com](http://www.scaswebsite.com))
- *Screen for Child Anxiety Related Disorders* (screen), University of Pittsburgh (child version: [www.psychiatry.pitt.edu/sites/default/files/Documents/assessments/SCARED%20Child.pdf](http://www.psychiatry.pitt.edu/sites/default/files/Documents/assessments/SCARED%20Child.pdf); parent version: [www.psychiatry.pitt.edu/sites/default/files/Documents/assessments/SCARED%20Parent.pdf](http://www.psychiatry.pitt.edu/sites/default/files/Documents/assessments/SCARED%20Parent.pdf))

## SUGGESTED READINGS

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- Merikangas KR. Vulnerability factors for anxiety disorders in children and adolescents. *Child Adolesc Psychiatr Clin N Am*. 2005;14:649–679, vii

**Table 129-5** Psychosocial and Psychopharmacologic Treatments for Anxiety (as of November 2014)<sup>a</sup>

PSYCHOSOCIAL TREATMENTS		
CLUSTER AREA	LEVEL 1 (BEST SUPPORT)	LEVEL 2 (GOOD SUPPORT)
Anxious or avoidant behaviors <sup>b</sup>	<ul style="list-style-type: none"> <li>• Cognitive behavior therapy (CBT)</li> <li>• CBT and medication</li> <li>• CBT with parents (includes parent and child, focusing on the child's concerns)</li> <li>• Education</li> <li>• Exposure</li> <li>• Modeling</li> </ul>	<ul style="list-style-type: none"> <li>• Assertiveness training</li> <li>• Attention</li> <li>• CBT for child and parent (child and parent receive CBT separately, focusing on each of their concerns)</li> <li>• Cultural storytelling</li> <li>• Family psychoeducation</li> <li>• Hypnosis</li> <li>• Relaxation</li> <li>• Stress inoculation</li> <li>• Exposure</li> <li>• Eye movement desensitization and reprocessing</li> </ul>
Traumatic stress <sup>b</sup>	<ul style="list-style-type: none"> <li>• CBT</li> <li>• CBT with parents (includes the parent as well as the child, focusing on the child's concerns)</li> </ul>	<ul style="list-style-type: none"> <li>• Eye movement desensitization and reprocessing</li> </ul>
US FOOD AND DRUG ADMINISTRATION–APPROVED PSYCHOPHARMACOLOGIC INTERVENTIONS <sup>c</sup>		
DIAGNOSTIC AREA	PSYCHOPHARMACOLOGIC INTERVENTION	
Anxiety disorders	Currently (as of November 2014), the only psychopharmacologic interventions approved by the US Food and Drug Administration are selective serotonin reuptake inhibitors (SSRIs) (sertraline, fluvoxamine) and clomipramine for the treatment of obsessive-compulsive disorder (OCD). Currently, no psychopharmacologic interventions have been approved for other anxiety disorders, although a number of randomly controlled clinical trials suggest their efficacy and safety.	

<sup>a</sup>For AAP policy, please visit [pediatrics.aappublications.org/site/aappolicy](http://pediatrics.aappublications.org/site/aappolicy).

<sup>b</sup>Excerpted from PracticeWise Evidence-Based Child and Adolescent Psychosocial Interventions. Reprinted with permission from PracticeWise. For updates and an explanation of PracticeWise determination of evidence level, please visit [www.aap.org/mentalhealth](http://www.aap.org/mentalhealth).

<sup>c</sup>For up-to-date information about Food and Drug Administration (FDA)-approved interventions, go to [www.fda.gov/ScienceResearch/SpecialTopics/Pediatric-TherapeuticsResearch/default.htm](http://www.fda.gov/ScienceResearch/SpecialTopics/Pediatric-TherapeuticsResearch/default.htm).



## Chapter 130

# ATAXIA

Philip Overby, MD

Ataxia derives from the Greek—*a* (without), *taxia* (order) and means a “lack of order.” Broadly, ataxia encompasses disorders in which there is an absence of coordinated movements, often involving gait. Although ataxia can certainly be chronic, as a presenting symptom in pediatrics it is almost always acute. For the treating physician, the list of its potential causes can be daunting (see Box 130-1), in part because ataxia can be caused by dysfunction at any level of the motor system from brain to muscle. Diagnostically, the goal is to localize the ataxia to the level of dysfunction.

## EVALUATION

### History

Practically, the initial approach to the child with acute ataxia should focus on the serious causes of ataxia. Once these have been excluded clinically, more common as well as treatable causes can be considered. Life-threatening conditions fall into 4 broad categories: infection or inflammation, neoplasm, stroke, and ingestion. Although the initial history should be

directed foremost at identifying serious causes of acute ataxia, in most cases, the causes of acute ataxia are self-limited and benign. One retrospective study of 40 pediatric cases found that 80% could be attributed to acute cerebellitis, toxic ingestion, and Guillain-Barré syndrome (GBS). Note that although it certainly is a common cause of acute ataxia in children, ingestion in this discussion is included among the more serious causes because missing the diagnosis can be life threatening.

The history should explore evidence of recent or current infection: fever, rash, respiratory symptoms, or vomiting. Questions about possible toxic exposures in the home, such as medications, alcohol, or illicit drugs, are essential. The possibility of trauma, observed or unobserved, should be explored with all caregivers and children who might be aware of it.

Associated symptoms can further guide the history. Although acute cerebellitis is characterized by preservation of alertness, a change in mental status is concerning and can signal a systemic process. Considerations include toxic ingestion, infection, or mechanical compression of the brainstem by a tumor or abscess. Headaches, recurrent vomiting, visual loss or diplopia, and worsening of symptoms when supine can be signs of elevated intracranial pressure (ICP) from hydrocephalus in the setting of posterior fossa masses. It should be noted, however, that these findings can be late or even intermittent, and their absence does not exclude elevated ICP.

### BOX 130-1 Causes of Acute Ataxia in Childhood

#### INFECTIOUS/IMMUNE-MEDIATED CEREBELLAR DISORDERS

- Acute cerebellar ataxia<sup>a</sup>
- Acute demyelinating encephalomyelitis<sup>a</sup>
- Systemic infections
- Brainstem encephalitis
- Multiple sclerosis

#### MASS LESIONS

- Tumors
- Vascular lesions
- Abscesses

#### HYDROCEPHALUS

#### TRAUMA

- Cerebellar contusion or hemorrhage
- Posterior fossa hematoma
- Postconcussion syndrome
- Vertebrobasilar dissection

#### STROKE

- Vertebrobasilar dissection or thromboembolism
- Cerebellar hemorrhage

#### PARANEOPLASTIC DISORDERS

- Opsoclonus-myoclonus syndrome

#### SENSORY ATAXIA

- Guillain-Barré syndrome
- Miller-Fisher syndrome

#### PARETIC ATAXIA

- Upper motoneuron
- Lesions of frontal lobe, corticospinal pathways
- Lower motoneuron
- Spinal cord: transverse myelitis, vascular lesions, cord compression
- Peripheral nerve: Guillain-Barré syndrome, Miller Fisher syndrome, tick paralysis

#### OTHER NEUROLOGIC DISORDERS

- Inborn errors of metabolism (see Box 130-2)<sup>a</sup>
- Basilar migraine, benign paroxysmal vertigo
- Nonconvulsive seizures
- Central pontine myelinolysis
- Wernicke encephalopathy

#### FUNCTIONAL ATAXIA

<sup>a</sup>Most common.

From Ryan MM, Engle EC. Topical review: acute ataxia in childhood. *J Child Neurol.* 2003;18:309–316, with permission from SAGE Publications.

Recent and abrupt onset of symptoms is more suggestive of a vascular, toxic, or infectious cause. Tumors and immune-mediated processes are typically more subacute in their progression. The exception is tumors that hemorrhage. If a patient with a known brain tumor has an acute change in mental status, or acute ataxia, he or she should be evaluated for hemorrhage acutely with a head CT. If hemorrhage is present, neurosurgery should be contacted immediately. Prior similar episodes are suggestive of chronic conditions such as migraine, or even seizures. Recurrent episodes are also potentially suggestive of metabolic processes (see Box 130-2).

### Physical Examination

Life-threatening causes of acute ataxia typically originate in the central nervous system. They tend to involve the posterior fossa or brainstem. In particular, symptoms are referable to 3 sources: cranial nerves, the pyramidal tracts, and the cerebellum. Moreover, the involvement of brainstem and cerebellar structures typically results in abnormalities both on history and physical examination. As such, a normal neurologic examination, carefully performed, is a pertinent negative.

The physical examination begins with vital signs. Fever suggests infection. Autonomic changes can be seen in the setting of acute stroke, elevated ICP, or peripheral processes such as GBS. The examination can be challenging because the child may be uncooperative. Given this, the examination should move from the

least to the most invasive. General observations (Does the child appear ill or uncomfortable? Is she agitated or careful not to move?) are valuable. The somatic examination should explore for evidence of meningismus: neck stiffness as well as photophobia and discomfort with movement. Next, attention should be given to the child's mental status. Behavioral changes, decreased alertness, inattention, or dysarthria can all be clues to elevated ICP, brainstem compression, or cranial neuropathies that may affect eye movements. If possible, fundi should be inspected for papilledema. The presence or absence of associated findings to suggest elevated ICP, such as restriction of upward gaze or lateral eye movements, should also be noted.

Cerebellar hemisphere dysfunction is often associated with a wide-based gait. Attempts to stand with feet close together can result in swaying from side to side with eyes open or closed. Unilateral weakness or pyramidal tract dysfunction manifests as asymmetries in arm or leg use. Subtle gait difficulties can be elicited with tandem walking. Sensory ataxia can be elicited by asking the child to stand still with feet together and eyes closed, the "Romberg test," which examines the dorsal columns. A positive test is one in which swaying or a frank fall occurs.

### Differential Diagnosis—Serious Disorders

#### Acute Stroke

In the absence of trauma, hemorrhagic stroke (intracerebral hemorrhage, or ICH) in children most commonly

### BOX 130-2 Causes of Episodic or Intermittent Ataxia in Childhood

#### RECURRENCE OF ACUTE CEREBELLAR ATAXIA<sup>a</sup>

##### MIGRAINE OR MIGRAINE EQUIVALENTS

- Basilar migraine<sup>a</sup>
- Benign paroxysmal vertigo
- Benign paroxysmal torticollis of infancy
- Alternating hemiplegia of childhood

##### METABOLIC DISORDERS

- Mitochondrial disorders
  - Pyruvate decarboxylase deficiency
  - Pyruvate dehydrogenase deficiency
  - Leigh disease
- Amino acidopathies
  - Maple syrup urine disease, intermittent form
  - Hartnup disease
  - $\gamma$ -Glutamylcysteine synthetase deficiency
- Urea cycle disorders
  - Carbamoyl phosphate synthetase type 1 deficiency
  - Ornithine transcarbamylase deficiency
  - Citrullinemia
  - Arginosuccinic aciduria

- Organic acidopathies
  - Holocarboxylase deficiency
  - Biotinidase deficiency
  - Isovaleric acidemia
- Carnitine acetyltransferase deficiency

##### RECURRENT GENETIC ATAXIAS

- Episodic ataxia type 1 (paroxysmal ataxia with myokymia)
- Episodic ataxia type 2 (acetazolamide responsive)
- Episodic ataxia types 3 and 4
- Episodic ataxia with paroxysmal dystonia
- CAPOS syndrome (cerebellar ataxia, areflexia, pes cavus, optic atrophy, sensorineural hearing loss)

##### NONCONVULSIVE SEIZURES

##### DRUG INGESTION<sup>a</sup>

##### PAROXYSMAL TONIC UPGAZE OF CHILDHOOD

##### COGAN SYNDROME

<sup>a</sup>Most common.

From Ryan MM, Engle EC. Topical review: acute ataxia in childhood. *J Child Neurol*. 2003;18:309–316, with permission from SAGE Publications.

results from an arteriovenous malformation (AVM). Emergent neurologic and neurosurgical evaluation is critical. Associated symptoms of ICH include headache, seizure, or visual loss. Decompression of a posterior fossa hemorrhage can be life saving. Hemorrhagic stroke will be apparent on head computed tomography. Ischemic stroke of the posterior circulation is rare in children but can be seen in the setting of vertebral dissection—often from trauma.

### **Acute Disseminated Encephalomyelitis**

Acute disseminated encephalomyelitis (ADEM) is an acute demyelinating event that is typically most severe at onset. It is an immune-mediated encephalitis often occurring in the context of viral or postviral infections. The white matter of the brain and spinal cord are preferentially affected. Typically, ADEM follows a prodrome of fever, vomiting, headache, and malaise. The neurologic features are broad: unilateral or bilateral pyramidal signs (60%–95%), acute hemiplegia (76%), ataxia (18%–65%), cranial nerve palsies (22%–45%), visual loss from optic neuritis (7%–23%), seizures (13%–35%), and spinal cord involvement (24%). Ultimate outcome does not seem to be affected by immunologic therapy, which can, however, hasten recovery.

### **Tumor**

Childhood brain tumors occur most frequently in the posterior fossa. The most common tumors are medulloblastoma, brainstem glioma, ependymoma, and cystic astrocytoma. There are 3 potential areas of involvement: cranial nerves, pyramidal tracts, and the cerebellum. Although symptoms may be reported to have developed over the course of days, a careful history typically reveals subtle signs of weakness and coordination difficulties lasting weeks to months. Signs from obstruction of cerebrospinal fluid (CSF) flow are common, and children younger than 2 years typically present with increasing head circumference. In older children, symptoms such as headaches and ataxia are more common. The average time from symptom onset to diagnosis is 7 months. Although less common than brain tumors, spinal tumors can also present with ataxia. Depending on the spinal level, signs of weakness or sensory loss referable to the lower or upper extremities with preservation of reflexes will be present. In addition, paraneoplastic presentation of tumors (eg, opsoclonus-myoclonus syndrome) at times need to be considered in the differential diagnosis of ataxia.

### **Cerebellitis**

Acute cerebellitis, also known as acute cerebellar ataxia, is a common, typically benign infectious or parainfectious phenomenon. It typically occurs in preschool- and school-aged children. Generally, the acute ataxia is most prominent on awakening and improves over the course of hours to days. Rarely, however, fulminant cerebellitis occurs. Unlike its more benign form, fulminant cerebellitis progresses from its onset to the development of encephalopathy, with

hydrocephalus caused by obstruction of the fourth ventricle. Outcomes can be favorable with aggressive management.

### **Trauma**

Life-threatening conditions to consider in the setting of trauma are hemorrhagic stroke and ischemic stroke from vertebrobasilar artery dissection. In the absence of more diffuse injury causing associated encephalopathy, it is unusual for trauma to present with isolated ataxia. The important exception to this rule is vertebral artery dissection, which represents 7% to 20% of pediatric ischemic strokes. The vertebral arteries supply the posterior circulation. Presenting signs and symptoms are referable to the posterior fossa: ataxia, vertigo, vomiting, diplopia, and head and neck pain. Although these symptoms are common and nonspecific, 88% of patients in a 2005 review had focal neurologic deficits. Fifty percent of children in the same study had a history of trauma.

### **Toxic Ingestion**

Ingestion of a toxin represents a major cause of ataxia in children, accounting for up to 32.5% of cases. Ingestion associated with ataxia includes antihistamines, alcohol, anticonvulsants (especially phenytoin and carbamazepine), piperazine, diphenylhydantoin, barbiturates, carbon monoxide, organic solvents, and bromides. Accidental ingestion occurs in young children. Adolescents can also present after ingestion in attempts to self-harm. Symptoms of ingestion can be nonspecific. Indeed, when symptoms do not fit well into a clinical syndrome, ingestion should become a concern. When considering toxic ingestion, it is also important to evaluate for other evidence of metabolic aberrations, such as hypoglycemia, hyponatremia, and hyperammonemia.

### **Common Causes of Ataxia**

#### **Sensory or Motor Ataxia Caused by Guillain-Barré Syndrome**

Studies of the incidence of GBS in children younger than 16 years old, most of which have been performed in Europe and North America, suggest rates between 0.4 and 1.4 per 100,000. Although the typical presentation of symmetrical weakness is well known, an acute progressive ataxia is another presentation of GBS seen particularly in young children. Important early clues include distal paresthesias or numbness. Younger children may present with prominent symptoms of leg pain, agitation, or vomiting, and meningeal signs may be present on examination. Reflexes are depressed or absent. Lumbar puncture typically demonstrates dissociation between cells and protein, with elevated protein and borderline-to-normal WBC counts. The CSF may be normal on initial presentation.

Three disorders need to be considered in the setting of suspected GBS. First, transverse myelitis (TM) can also present with limb weakness, back pain, and depressed reflexes. Sustained sphincter dysfunction and

a sensory level distinguish TM from GBS. Second, tick paralysis can also present with pure motor weakness and absent reflexes. Particularly in the late spring or summer if careful inspection reveals a tick, its removal is typically curative. Oculomotor paralysis can be a clue and can appear similar to the Miller Fisher variant of GBS, characterized by ataxia, oculomotor palsies, and absent deep tendon reflexes. Finally, brainstem encephalitis can also mimic the Miller Fisher variant of GBS.

### **Acute Cerebellar Ataxia**

Acute cerebellar ataxia (ACA) occurs most commonly in children younger than 5 years old but can occur at any age. It has been associated with a variety of infections but is usually the result of postinfectious demyelination rather than direct infection. The presentation is characterized by maximal deficits at onset, and often on awakening. Pancerebellar dysfunction can result in truncal ataxia, with the consequent inability to sit or stand without assistance. Head titubation, nystagmus, and dysmetria are sometimes present. Mental status is normal. Full recovery is typical but can take as long as 3 to 6 months. There is no evidence that immune therapy such as steroids alters the outcome of ACA.

### **Migraine**

Vertigo as the primary or sole manifestation of migraine occurs with very young children and teenaged girls. Children younger than 4 years can have the abrupt onset of unsteadiness lasting seconds to minutes. More commonly, adolescents describe repeated bouts of isolated vertigo, or headache and vertigo. In both cases, there is usually a family history of migraine and a propensity to motion sickness in the context of a normal neurologic examination.

### **Labyrinthitis**

The clinical symptoms of labyrinthitis are superficially similar to ACA: acute onset of ataxia and nystagmus. However, children with acute labyrinthitis generally appear more ill, have prominent vomiting, and hold themselves still to minimize exacerbation of symptoms. This condition frequently occurs in clusters of exposed individuals, most frequently in spring and early summer, supporting an infectious (likely viral) cause. In particular, the vestibular nerve is inflamed.

### **Laboratory Evaluation**

A thorough history and physical examination often make laboratory testing unnecessary. At a minimum, however, urine toxicology should be considered. If there is a high clinical suspicion, blood and urine samples should be held with the intention of sending targeted analysis following consultation with poison control.

Lumbar puncture should be considered in the setting of suspected infectious or inflammatory processes. Normal white blood cell count or a mild pleocytosis is typical in ACA. More significant pleocytosis or low glucose raises the concern for bacterial meningitis or

encephalitis, and an expanded evaluation for viral (especially herpes simplex virus) and bacterial causes is warranted.

### **Imaging**

Imaging of the brain is indicated in the presence of a focal neurologic examination, or with the inability to perform a reliable neurologic examination in the presence of illness or sedation. Imaging in the absence of these indications is low yield. Acutely, head CT is effective for evaluating for hemorrhage or hydrocephalus. However, magnetic resonance imaging of the brain both spares the child radiation and provides more sensitive visualization of the brain parenchyma. Additional studies with contrast are indicated if there is concern for infection and inflammation or tumor. Imaging of the vasculature with magnetic resonance angiography or magnetic resonance venography is useful when stroke is a consideration. Neurologic consultation should typically be obtained before ordering imaging to optimize the study, and before considering conventional cerebral angiography or computed tomographic angiography.

## **MANAGEMENT**

### **Treatment Approach**

Treatment is directed at the underlying diagnosis. Initial attention to vital signs in the ill child is crucial. Posterior fossa hemorrhage requires urgent neurosurgical consultation. Ischemic stroke requires neurologic consultation and admission to a pediatric critical care unit for further management. In the case of ADEM, immune modulating therapy such as steroids, intravenous immunoglobulin (IVIG), or plasma exchange (PLEX) can be considered: treatment can hasten recovery, but does not appear to alter ultimate outcome. A 2004 study of vestibular neuritis in adults found that vestibular function was improved in patients treated with methylprednisolone but not valacyclovir.

Infectious processes, such as cerebellar abscess or brainstem encephalitis, are treated initially with broad antimicrobial therapy (including ampicillin for *Listeria* in the case of brainstem encephalitis) as well as antiviral therapy (acyclovir for herpes simplex virus) until the causative agent is identified. Brain tumors require neurologic, oncologic, and neurosurgical consultation.

GBS requires admission for monitoring of vital signs and respiratory function. Respiratory function can worsen from presentation, and initial monitoring in the PICU for 24 to 48 hours should be considered. Treatment with IVIG or PLEX speeds recovery, and IVIG is favored because it is less invasive. IVIG should not be used in patients who are immunoglobulin A deficient.

### **Ongoing Care**

Long-term treatment is not typically required for the common causes of pediatric acute ataxia. However, follow-up 2 to 4 weeks after discharge to monitor recovery is reasonable. Prognosis and management



are linked to diagnosis. If persistent or permanent dysfunction results, physical therapy and adaptive devices should be coordinated. Aside from ingestion, few of the causes of ataxia are preventable. In most cases, the outcome is a good one. In patients requiring admission, early recognition leading to early admission and treatment may improve outcomes.

### TOOLS FOR PRACTICE

#### Medical Decision Support

- *Intravenous Immunoglobulin for Gullain-Barré Syndrome* (article), *Cochrane Database of Systematic Reviews*, Issue 16, Article No CD002063, 2010

### SUGGESTED READINGS

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## Chapter 131 BACK PAIN

Joel S. Brenner, MD, MPH; David V. Smith, MD

### DEFINITION

The back encompasses the region from the upper thoracic vertebra (T1) and shoulder girdle to the sacrum and surrounding musculature. The patient who complains of pain in this region may have difficulty localizing the source of the pain and describe it simply as deep pain, or the patient may localize pain to a specific muscle group or vertebral body. Allowing patients to define in their own words the nature, location, and duration of the pain is an important first step in arriving at a clinical diagnosis. If parents, coaches, or peers are available during the interview, they can be valuable to confirm or elaborate on the patient's symptoms. One should keep in mind that young children and adolescents may minimize pain out of imagined fears of diagnostic or therapeutic procedures. Functional disability such as interference with sports, play,

or school may prompt more urgent diagnostic evaluation and treatment.

### EPIDEMIOLOGY

Population-based data on back pain in children are limited, and estimates of prevalence vary considerably depending on sample size and method used. At the least, most studies have consistently shown that the prevalence of back pain increases with age. In nonclinical populations, the prevalence is less than 10% in preteens, progressing to nearly 50% of 18- to 20-year-olds reporting at least one episode of low-back pain. Clearly, most people who experience such pain do not seek medical care. In preadolescent children, back pain is not only unusual but also likely to indicate serious underlying illness when severe or persistent enough to prompt a medical visit. One 6-year study in a tertiary orthopedic setting found that back pain constituted fewer than 2% of referrals in children ages 15 years or younger, but that roughly 50% of these children had serious underlying diseases. From early adolescence onward, back pain becomes more common as a presenting complaint but is more likely to be a benign condition related to acute injury or repetitive stress. The physician presented with a child or adolescent complaining of back pain should use a careful history and physical examination to guide any further laboratory or radiologic evaluation. Overall, they should be aware of the relatively higher risk for serious underlying disease in younger children, even without specific physical findings.

### DIFFERENTIAL DIAGNOSIS

#### Infants

From infancy through the third or fourth year of life, the patient is not capable of localizing or complaining of pain in the back. Unexplained fever or toxicity, along with refusal to walk or stand, may be the presenting signs of diskitis. Other pathologies localized to the back to consider include leukemia, lymphoma, pyelonephritis, vaso-occlusive crisis, or vertebral osteomyelitis in a child who has sickle cell disease, or accidental or nonaccidental trauma.

#### Children

As children mature and become more capable of communicating and localizing symptoms, a specific history of the duration, quality, associated symptoms, and radiation of back pain becomes possible. Back pain before adolescence remains an uncommon presenting complaint and should prompt thorough evaluation. Only after a thorough diagnostic evaluation should the physician consider the diagnosis of muscular or ligamentous strain as a cause of back pain in younger children. The differential diagnosis of back pain in this age group is broad and includes acute leukemia, lymphoma, and primary vertebral tumors, such as Ewing sarcoma, aneurysmal bone cyst, benign osteoblastoma, and osteoid osteomas. Other etiologies include diskitis, an unusual if not rare condition that is most common in children younger than 10

**Table 131-1**     **Differential Diagnosis of Back Pain**

INFANTS	CHILDREN	ADOLESCENTS
Diskitis Leukemia, lymphoma Vaso-occlusive crisis Osteomyelitis Trauma	Diskitis Tethered cord Osteomyelitis Ankylosing spondylitis Vaso-occlusive crisis Leukemia, lymphoma Ewing sarcoma Osteoid osteoma Spinal tuberculosis	<b>Acute</b> Muscle, ligament strain Lumbar disk disease Apophyseal ring fractures Sciatica Piriformis syndrome Osteomyelitis Epidural abscess Spinal tuberculosis <b>Chronic</b> Spondylolysis Spondylolisthesis Scheuermann kyphosis Facet, vertebral dysfunction Sacroiliac dysfunction Lumbar disk disease Spinal stenosis Spondyloarthropathy Tumor or malignancy Soft tissue strain Functional (nonorganic)

years (mean age, about 6 years). Diskitis is an inflammatory process presumed to be a bacterial infection in the intervertebral disk space. Vertebral osteomyelitis usually affects school-aged children and teenagers and presents as severe back pain and systemic symptoms. A family history of rheumatoid disease should prompt consideration of ankylosing spondylitis. In the presence of sickle cell disease, a vaso-occlusive crisis is a strong consideration. Back pain on walking may be the only sign of a tethered cord. An underlying leg-length discrepancy of any cause may result in chronic or recurrent low-back pain from musculoligamentous strain.

### Adolescents

Classifying the causes of back pain in adolescents as acute or chronic is helpful (Table 131-1). In adolescent patients, a diagnostic consideration of acute back pain caused by muscular or ligamentous strain is reasonable. Other causes of acute back pain include lumbar disk disease, apophyseal ring fractures, vertebral osteomyelitis, epidural abscess, and sciatica caused by piriformis syndrome. The adolescent who has chronic pain (>3 weeks) may still have a strain, but stronger consideration should be given at this point to spondylolysis or spondylolisthesis, which are the most common identifiable causes of low-back pain in this age group. The most frequent cause of spondylolysis is a stress fracture of the pars interarticularis (posterior arch) of the spine, thought to be acquired through repetitive extension loading. Athletes who participate in gymnastics, dance, cheerleading, football, and diving are at highest

risk. For example, ballet dancers, as a group, as well as football players (offensive lineman), have great flexibility but may be predisposed to lumbar lordosis by postural demands and relatively weak core musculature, possibly making them prone to spondylolysis and disk disease. Individuals with benign hypermobility syndromes may also be at risk. Less commonly, spondylolysis can be an asymptomatic congenital deformity. Spondylolisthesis is the anterior movement of one vertebral body on top of another, usually L5 on S1, as a result of bilateral spondylolysis.

Chronic low-back pain, especially in adolescent athletes or others who have cumulative trauma, may indicate lumbar disk disease. Other chronic causes of back pain in this age group include Scheuermann kyphosis, facet or vertebral dysfunction, sacroiliac dysfunction, spinal stenosis, the spondyloarthropathies (ie, ankylosing spondylitis, psoriatic arthritis, Reiter syndrome, arthritis of inflammatory bowel disease that with the exception of psoriatic arthritis can be classified as enthesitis-related juvenile idiopathic arthritis), and tumor or malignancy. Chronic back pain can also be a disorder of the soft tissues of the back, postulated to be caused by a combination of repetitive strain, genetic predisposition, and environmental factors. Assessing for discrepancy in leg lengths and for tight hamstrings is advisable because both alter the dynamic stress put on the muscles and ligaments of the low back. Modifiable contributing factors may include prolonged seated posture, forward bending of the spine while sitting at a desk for long periods, or carrying an excessively heavy backpack (>10%–20% of body weight).

## PSYCHOSOCIAL CONSIDERATIONS

Although malingering or the use of pain symptoms for secondary gain may be relatively common in adults, it should not be a strong consideration in the diagnosis of back pain in children or adolescents. Back pain is not as common a somatoform symptom among adolescents as is headache, abdominal pain, or chest pain. If a thorough diagnostic evaluation of chronic back pain in an adolescent is unrevealing and the usual management involving exercise and stretching is not beneficial, then a psychosocial or nonorganic cause should be considered. The Waddell test, a series of 5 questions, may be used to help determine whether significant psychological stress is associated with chronic low-back pain.

If 3 or more of the following 5 criteria are present, then the test is considered positive:

1. Inappropriate tenderness that is superficial or wide-spread
2. Pain on pressing the top of the head or on passive rotation of shoulders and pelvis
3. Distraction signs such as inconsistent performance between straight-leg raising in the seated and the supine positions
4. Strength and sensory loss patterns that do not fit with accepted neuroanatomy
5. Overreaction during the physical examination

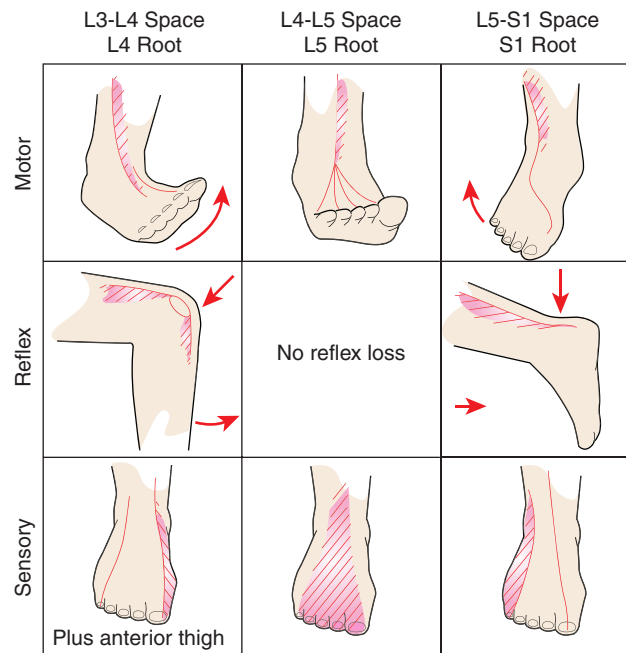
## EVALUATION

### Infants, Children, and Adolescents

The age of the patient is a critical factor in the diagnostic evaluation, with the extent and urgency of evaluation usually being greater for preadolescent patients. The duration of symptoms is an additional factor because chronic pain, even in adolescent patients, is uncommon and may indicate structural or serious underlying disease. The evaluation of acute or chronic back pain should always include motor, sensory, and reflex examination to help differentiate any nerve root involvement (Figure 131-1).

Chronic pain should prompt a diagnostic evaluation possibly to include rectal examination for sphincter tone loss, radiographs of the spine (anteroposterior, lateral, and oblique views), uric acid, lactate dehydrogenase, white blood count, sedimentation rate, C-reactive protein, and urinalysis and urine culture. Infants, young children, or adolescents who have fever and back pain must be considered as having an infectious, inflammatory, or neoplastic process until proved otherwise. Diagnoses that should be considered include diskitis, vertebral osteomyelitis, ankylosing spondylitis, pyelonephritis, vaso-occlusive crisis in a patient who has sickle cell anemia, acute lymphoblastic leukemia, Ewing sarcoma, and Hodgkin lymphoma. Spinal tuberculosis (Pott disease) is rare but should be considered when back pain is accompanied by low-grade fever.

A child with diskitis is typically uncomfortable in an upright posture, may refuse to walk, or may have pain when bending forward. Even in the absence of fever, a child who refuses to walk, particularly a preschooler, should be evaluated promptly for diskitis. Typically,



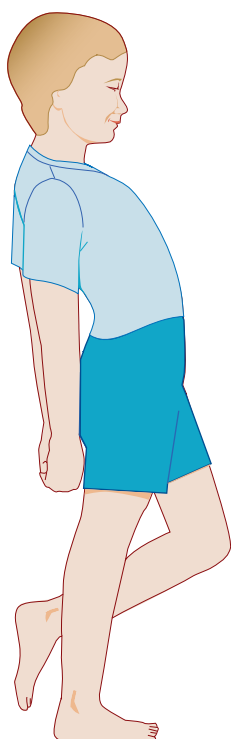
**Figure 131-1** Sensory, motor, reflex grid. (From Lewis RC. Primary Care Orthopedics. New York: Churchill Livingstone; 1988, with permission from Elsevier.)

diskitis is associated with an elevated erythrocyte sedimentation rate and a high white blood cell count; plain radiographs of the spine may show narrowing of the disk space. In a recent review, 76% of children with diskitis had changes evident on plain radiographs; however, plain radiographs are often negative in the first 2 to 3 weeks of the disease. If a second imaging test is needed, magnetic resonance imaging (MRI) is generally thought to be sensitive in identifying diskitis.

Weight loss, bone pain in other locations, bruising, organomegaly, or adenopathy should prompt aggressive diagnostic evaluation for malignancies such as leukemia, lymphoma, or sarcomas. Especially in the presence of fever or other systemic signs and symptoms, acute leukemia and lymphoma are serious concerns and must be ruled out.

A child with nocturnal back pain, even if relieved by nonprescription analgesics, should be evaluated for osteoid osteoma or osteoblastoma with a bone scan if plain radiographs are normal. Primary vertebral tumors almost always are visible on plain radiographs, but computed tomography (CT) or MRI may be needed.

Fever accompanied by back pain should prompt an aggressive diagnostic evaluation and orthopedic surgery consultation because aspiration and culture to evaluate for possible vertebral osteomyelitis should be considered. Dysuria, urinary urgency, or urinary frequency, especially if accompanied by fever, warrants consideration of pyelonephritis.



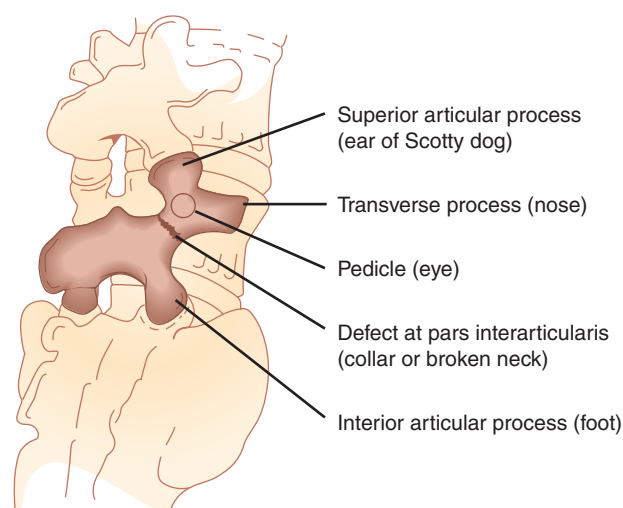
**Figure 131-2** One-leg hyperextension test (stork test).

Idiopathic scoliosis usually does not cause back pain in children. Scoliosis with pain should raise concern about an alternative cause, including malignancy in the region of the spine or a benign osteoid osteoma.

### Adolescents

Muscular or ligamentous strain begins to become common during adolescence. The typical presentation is low-back pain of 3 weeks' or less duration, with or without recollection of an acute injury, that is exacerbated by postural changes or specific movements. Associated signs and symptoms such as neurologic deficits of the lower extremities; limited straight-leg raising; sciatic pain; bowel, bladder, or sexual dysfunction; fever; weight loss; adenopathy; urinary urgency or frequency; scoliosis; or marfanoid habitus should be absent. The pain is exacerbated by lifting, stooping, and exercising. Radiologic studies are not needed if muscular or ligamentous strain is thought to exist. However, very localized tenderness in the spine after an injury (eg, motor vehicle crash, athletic trauma) warrants radiologic evaluation for compression fracture. Plain radiographs (anteroposterior and lateral) should be ordered initially.

Low-back pain associated with excessive lordotic curvature, especially in an athlete subjected to repetitive extension loading (eg, gymnasts, football linemen), may indicate spondylolysis or spondylolisthesis. Spondylolysis may be unilateral or bilateral and is



**Figure 131-3** Scotty dog with a collar. (From Smith JA, Hu SS. Management of spondylolysis and spondylolisthesis in the pediatric and adolescent population. *Orthop Clin North Am.* 1999;30(3):487–499, ix, with permission from Elsevier.)

most common at L5. Symptoms of spondylolysis are not usually acute; it more commonly exhibits as a gradual worsening of back pain on extension, usually in an athlete during the growth spurt or after intense training. Pain can be reproduced reliably by having the patient hyperextend the back while standing on one leg (the stork test) (Figure 131-2). The sensitivity of the stork test is modest, however, and a negative stork test should not be relied on to rule out an active spondylolysis. The patient usually has no pain with flexion, rotation, or lateral bending of the back. Hamstring tightness is a common associated finding. Plain radiographs of the lumbar spine should be ordered (anteroposterior, lateral, oblique views). The *Scotty dog with a collar* is visualized on the oblique radiographs (Figure 131-3). Normal plain radiographs alone do not rule out spondylolysis. One study reported that oblique views detected only 32% of spondylolyses detected on CT. A single-photon emission computed tomography (SPECT) scan should be ordered if the diagnosis is highly suggested. A positive plain radiograph with a negative SPECT scan is indicative of a nonmetabolically active spondylolysis that may not be the cause of the patient's back pain. Back pain on extension with normal plain radiographs and SPECT scan is usually from facet or vertebral dysfunction.

Spondylolisthesis may be accompanied on physical examination not only by excess lumbar lordosis but also by the sensation of a shelf at the base of the lordotic curvature, where the lower of the 2 affected vertebrae has held its position while the upper vertebral body slipped forward. The anterior slippage is diagnosed and staged for treatment purposes on the lateral plain radiographs. In rare cases, radiographs will reveal congenital absence of a lumbosacral articular process.





**Figure 131-4** Slump test. (From Reider B. *The Orthopedic Physical Examination*. Philadelphia, PA: WB Saunders; 1999, with permission.)

Accompanying neurologic symptoms, including radicular pain down the leg, numbness or tingling, bowel or bladder problems, erectile dysfunction, or loss of sphincter tone on rectal examination, may indicate lumbar disk herniation or other nerve compression and should prompt an urgent evaluation and referral. Symptoms are typically worsened by mechanical strain, as with lifting or coughing. A positive straight-leg raise test or a *slump test* (Figure 131-4) is highly suggestive of nerve root compression. Using cervical flexion to accentuate the patient's symptoms during straight-leg raising may add to the test's sensitivity. Any reproduction of the patient's usual symptoms during testing before 60 degrees of hip flexion, or marked asymmetry in symptoms, should be considered a positive test. Pain after 60 degrees or limited to the posterior thigh is more likely caused by hamstring tightness.

A spondyloarthropathy should be suspected when there is limited lumbar flexion (modified Schober test), tenderness at entheses (particularly the Achilles-calcaneal entheses, the origin or insertion of the plantar fascia, or the base of the fifth metatarsal), pain in the sacroiliac (SI) area with flexion-abduction and external rotation (an abnormal FABER test), or tenderness over the SI joints. MRI with gadolinium of the SI joints and ultrasonography of the entheses can confirm local inflammation. The presence of HLA-B27 antigen is not diagnostic because it is present in 10% to 30% of individuals of European ancestry.

Scheuermann disease, or butterfly's back, typically exhibits in an adolescent, particularly a competitive swimmer, with thoracic back pain after exercise or late in the day. Patients have rigid thoracic kyphosis on examination and pain worsened by forward flexion. It must be differentiated from postural kyphosis, which is commonly seen in adolescents. Postural kyphosis is a flexible kyphosis that disappears on forward flexion and conscious postural straightening. Scheuermann disease is confirmed by anterior wedging of 5 degrees or greater in 3 or more contiguous vertebrae shown on lateral plain spine radiographs. Oblique radiographs also should be obtained because spondylolysis is associated with Scheuermann disease.

Stigmata of Marfan syndrome include joint hyperextensibility, pectus excavatum, pes planus, dislocated lenses, hernias, arachnodactyly, and scoliosis. The scoliosis may result from a dural ectasia or widening of the subarachnoid space in the lumbar area, which has been associated with low-back pain in adolescents and young adults. Patients who have Marfan syndrome are also at increased risk for spondylolysis.

## MANAGEMENT

Pain that is acute and lasting fewer than 3 weeks, especially with a history of musculoskeletal injury, may be managed expectantly in many cases, whereas more chronic pain in a child or adolescent demands further

investigation. When back pain results from an underlying disorder, treatment of the pain itself should be undertaken in addition to treatment of the primary condition.

### Infants

Treatment for diskitis is variable, depending on its cause. Most experts recommend parenteral followed by oral antibiotic administration, if evidence of bacterial infection exists, and relative rest to promote pain control. Staphylococcal infection is the most common cause of vertebral osteomyelitis and should be treated with antibiotics, rest, and a prompt orthopedic surgery consultation.

### Children

Treatment for diskitis and osteomyelitis in children is the same as that for infants. Management of patients with ankylosing spondylitis is best coordinated by a pediatric rheumatologist, who will often use anti-inflammatory medications with physical and occupational therapy. Treatment of vaso-occlusive crisis entails pain management, hydration, and physical therapy. Leukemia, lymphoma, and Ewing sarcoma should be managed by a pediatric oncologist. Pain from osteoid osteoma is typically relieved with nonsteroidal anti-inflammatory agents, and patients should be referred to a pediatric orthopedic surgeon for possible excision or ablation.

### Adolescents

When the adolescent exhibits back pain acutely after an injury that is thought to be a muscular or ligamentous strain, the PRICEMMMS mnemonic (protection, relative rest, ice, compression, elevation, medication, motion, modalities, strength) should be used. Bed rest, which has been shown to delay recovery, should be discouraged. Continuous-frequency ultrasound and massage are often helpful. Pain-free activity may be resumed gradually, and low-back and hamstring flexibility, as well as the strengthening of the core musculature (abdominal area, hip, and back) with an exercise ball, Yoga, or Pilates exercises, should be emphasized.

Evidence indicates that full sit-ups with the feet fixed and the knees bent, by using hip flexors rather than abdominal muscles, increase intervertebral disk pressure and should be discouraged. The goal of abdominal muscle strengthening is to reduce pelvic tilt and its accompanying tendency toward lordosis and low-back strain. Because decreased strength and endurance of spinal extensor muscles is associated with low-back pain, extensor exercises such as raising the torso and head off the floor or exercise ball while lying prone are recommended. These same exercises, and stretching after warming the muscles by gentle exercise or moist heat, are recommended for chronic low-back pain of muscular origin. Proper posture should also be taught, and backpack weights should not exceed 10% to 20% of the person's body weight. Acupuncture may be a useful adjunct for chronic back pain. If a leg-length discrepancy is discovered, a heel lift as well as physical

therapy to reduce any accompanying flexion contractures at the knee and hip and genu valgus could be of benefit.

The treatment of spondylolysis is controversial and may best be managed by a pediatric sports medicine specialist or orthopedic surgeon. All regimens include the initial cessation of extension-loading activities while providing symptomatic relief and physical therapy that promotes abdominal strengthening and hamstring stretching (the Williams program). Thoracolumbar bracing to prevent extension has been shown to be helpful in some studies; however, others showed no difference in outcomes with or without the use of a brace. Some experts advocate restricting extension activities without a brace. When bracing is implemented, it can be used for up to 6 months or until the patient is pain free with extension. Bone stimulators have been used as adjunctive therapy.

Treatment of the spondyloarthropathic conditions involves anti-inflammatory and immunomodulatory therapies along with physical therapy, and the patient should be referred to a pediatric rheumatologist. Treatment for Scheuermann disease is usually conservative, including physical therapy with strengthening and stretching exercises, avoiding painful activities, and analgesic medication if needed. Thoracolumbar bracing and surgery may be indicated if kyphosis is more than 60 degrees. Patients should be referred to an orthopedic surgeon (pediatric or spinal) for failure of conservative management, intractable pain, or progression of the kyphotic deformity.

Referral to a mental health professional may not be necessary for functional or nonorganic back pain. If the family has a high degree of trust with the physician, then a sensitive evaluation of family and social factors may be an effective first step. In these cases, the physician should not assume that the pain is feigned but rather consider it as a very real physical symptom rooted in psychological or emotional distress. At the very least, chronic pain and its accompanying disability can, of itself, lead to psychological distress, which should be addressed openly by the physician.

### WHEN TO REFER

- Abnormality of posture or gait
- Neurologic findings
- Persistent pain in a preteen
- Pain unrelated to activity or on awakening from sleep
- Functional disability (decreased play or sports activity)
- Diagnosis and evaluation are outside of the primary care physician's scope of expertise

### WHEN TO ADMIT

- Whenever a prompt and thorough outpatient diagnostic assessment cannot be completed for a child who has back pain and associated fever or neurologic findings

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Backpack Safety* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/safety-prevention/at-play/Pages/Backpack-Safety.aspx](http://www.healthychildren.org/English/safety-prevention/at-play/Pages/Backpack-Safety.aspx))
- *Sports Shorts: Lower Back Pain in Athletes* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/injuries-emergencies/sports-injuries/Pages/Lower-Back-Pain-in-Athletes.aspx](http://www.healthychildren.org/English/health-issues/injuries-emergencies/sports-injuries/Pages/Lower-Back-Pain-in-Athletes.aspx))

### Medical Decision Support

- *Care of the Young Athlete*, 2nd ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Essentials of Musculoskeletal Care*, 3rd ed (book), American Academy of Orthopaedic Surgeons and American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

## AAP POLICY

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## Chapter 132

# CARDIAC ARRHYTHMIAS

J. Peter Harris, MD

Arrhythmias in young people are common and may occur as a result of normal rhythm variations, premature beats, atrial or ventricular tachyarrhythmias, or conduction defects. They can occur at any age, and their clinical implications range from benign to lethal. Newer diagnostic modalities such as event recorders to capture infrequent episodes have enhanced our ability to detect arrhythmias. Empirical therapy without arrhythmia identification does not meet the

current standard of practice. A 12-lead electrocardiogram (ECG) should always be obtained when an arrhythmia is suspected, because electrophysiologic alterations may be quite subtle and not always identified on a rhythm strip. A thorough family history is required, with particular emphasis on sudden and premature death, syncope, seizures, and recurrent arrhythmias.

Infants with arrhythmias may have nonspecific signs and symptoms such as fatigue, malaise, poor feeding, nausea, and pallor. Older children tend to exhibit more specific symptoms such as palpitations (the disquieting awareness of the person's own heartbeat), lightheadedness, syncope, visceral chest pain, and dyspnea.

Premature beats and supraventricular tachyarrhythmias in infancy may be noted incidentally on a visit for other reasons, but, more commonly, infants with supraventricular tachycardia (SVT) present with signs and symptoms of congestive heart failure: tachypnea, dyspnea, truncal diaphoresis, diminished pulses, pallor, hepatomegaly, and poor feeding. Older children and adolescents are able to verbalize discomfort, including palpitations, chest pain, dyspnea, and nausea, with various forms of SVT. Ventricular tachyarrhythmias often compromise cardiac output to a greater degree than SVT and have more overt signs of congestive failure, chest pain, syncope, dyspnea, and palpitations. Myocardial dysfunction is usually related to increased oxygen demand owing to the tachycardia, inadequate time for ventricular filling, ischemia from insufficient time for diastolic coronary perfusion, and loss of atrioventricular synchrony. Infants and children with moderate or severe bradycardia from advanced second-degree and complete heart block also display signs and symptoms of inadequate cardiac output, including fatigue, reduced exercise capacity, pallor, presyncope, and syncope.

## APPROACH TO ARRHYTHMIAS

As a part of the systematic approach to ECG interpretation, the cardiac rhythm should be analyzed in an organized fashion. The answers to the following 4 questions will define most arrhythmias:

1. Is the rhythm fast or slow?
2. Is the rhythm regular or irregular?
3. Are the QRS complexes narrow or wide?
4. What is the relationship between the P waves and the QRS complexes?

## NORMAL RHYTHM VARIATIONS

Recognizing normal rhythm variations allays patient and parental anxiety and avoids unnecessary investigations and interventions. For instance, sinus arrhythmia (phasic respiratory variations of sinus rate with inspiratory acceleration and expiratory slowing) is common in childhood; so too is wandering atrial pacemaker, usually noted with slower heart rates and characterized by different P-wave morphologies. These rhythm variations are related to alterations in vagal tone.



A wide range of heart rates is present in the young. Sinus tachycardia has been documented at rates of 230 to 250 beats per minute during infancy, but a rate in excess of 200 beats per minute in a teenager who is not involved in maximal exertion would be abnormal. Sinus bradycardia is a sinus rate below what is expected for a patient's age. A sinus rate below 100 beats per minute in an awake neonate would be abnormal, but during sleep, rates down to 80 beats per minute are commonly observed on ECG monitoring. Brief dips into the 60- to 80-beats-per-minute range are also observed in sleeping neonates during normal, vagally induced episodes of junctional rhythm that arise from either the atrioventricular node or the bundle of His and that are characterized by a narrow QRS without a preceding P wave. A highly conditioned adolescent endurance athlete may have a resting heart rate of 40 beats per minute or less. Table 132-1

**Table 132-1** Bradycardia by Age and Stat

AGE	HEART RATE
<b>SURFACE ELECTROCARDIOGRAM</b>	
Neonates and infants	<100 beat/min, awake
Children to 3 years	<100 beats/min
Children 3–9 years	<60 beats/min
Adolescents 9–16 years	<50 beats/min
Adolescents >16 years	<40 beats/min
<b>AMBULATORY (HOLTER) MONITORING</b>	
Neonates and infants	<60 beats/min, sleeping; 80 beats/min, awake, quiet
Children 2–6 years	<60 beats/min
Children 7–11 years	<45 beats/min
Adolescents >11 years	<40 beats/min
Athletes	<30 beats/min

provides guidelines for the diagnosis of sinus bradycardia on the surface ECG and during ambulatory monitoring.

## PREMATURE BEATS

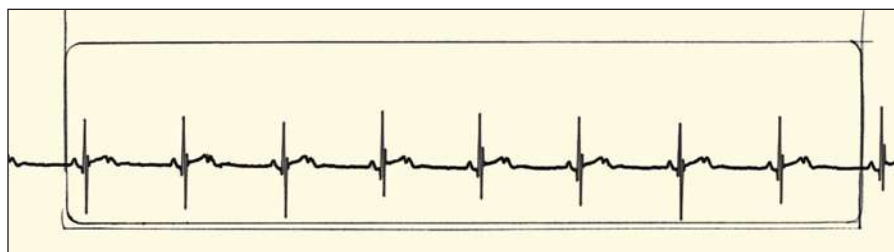
Premature beats are common, but usually benign, arrhythmias and may arise in the atria, the atrioventricular junction, or the ventricles. By definition, premature beats are early and thus are distinguished from escape or late beats occurring when higher pacemaker cells fail to produce an impulse at the expected interval. Two premature beats in a row constitute a couplet. If every second or third beat is a premature impulse, then a bigeminal or trigeminal rhythm is present.

### Atrial Premature Contractions

Atrial premature contractions (APCs) are characterized by premature P waves with an axis and morphology that are different from the sinus P waves. If an APC occurs when one of the bundle branches is refractory, then the premature beat will be conducted down the other bundle branch, resulting in an aberrant APC with a QRS morphology wider and different from sinus QRS complexes (Figure 132-1). If both bundle branches are refractory, then the APC will not be conducted to the ventricles (blocked APC) but may reset the sinus node with a resultant pause greater than the previous RR interval. If every other beat is a blocked APC (blocked atrial bigeminy) in a newborn infant who is dependent on an adequate heart rate for normal cardiac output, then slowing of the heart rate sufficient to alter feeding and arousal time may be present. T waves are usually smoothly inscribed, and consistent sharp deflections in the T waves may represent P waves (Figure 132-2). APCs usually occur with normally conducted QRS complexes; but if wide beats



**Figure 132-1** Atrial premature contractions (arrows) with normal and aberrant conduction.



**Figure 132-2** Every other beat is a blocked atrial premature contraction (blocked atrial bigeminy) represented by a consistent sharp deflection in the T waves.



are also noted, then the apparently prolonged QRS beats are likely to be aberrant APCs because premature atrial and ventricular contractions rarely occur together, especially in the newborn period.

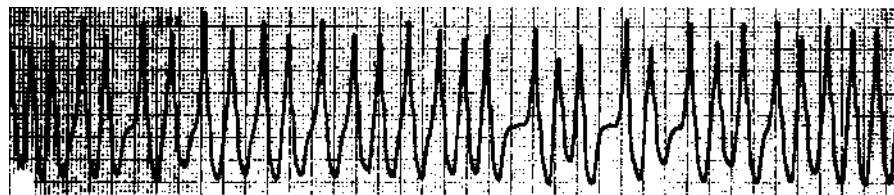
The incidence of APCs is 50% to 75% in children on Holter monitoring. Most are benign and require no therapy; however, there are occasional associations with myocarditis, atrial stretch, sympathomimetic or other stimulant drugs, intracardiac catheters, and electrolyte disturbances. They are most often without an obvious incitant and are usually not recognized by the child or adolescent. If suppressive therapy is required, then either digoxin or propranolol is suitable.

### Premature Ventricular Contractions

Premature ventricular contractions (PVCs) are less common than APCs but may be present on Holter monitoring in up to 25% of healthy infants, children, and adolescents. PVCs are characterized by a QRS morphology that is different from sinus QRS beats, occur before the next expected sinus beat, and are not preceded by a premature P wave. The QRS duration may be only slightly prolonged. Uniform PVCs have similar morphology to one another, and multiform PVCs have diverse morphology. The designations *unifocal* and *multifocal* are no longer used, because the form of PVCs is now known not to correlate reliably with focus of origin. If a PVC occurs late, at the beginning of the next expected sinus beat, then it will produce a hybrid or fusion beat derived, in part, from the normal conduction pathways and, in part, from the PVC. Fusion beats have a morphology that is intermediate between the sinus QRS and PVC.

Although most PVCs are observed in healthy children and adolescents, PVCs can occur in patients with underlying heart disease, such as myocarditis, hypertrophic and dilated cardiomyopathies, and ventricular dysfunction in congenital cardiac malformations. The new appearance of PVCs in the setting of a febrile illness should raise the question of myocarditis. Other causes include sympathomimetic and street stimulant drugs, electrolyte imbalances, and intraventricular catheters. A 12-lead ECG should always be obtained to assess the premature beat morphology and to look for chamber enlargement but also to calculate the corrected QT interval.

$$QTc = \frac{QT \text{ interval (seconds)}}{\sqrt{\text{Preceding RR interval (seconds)}}}$$



**Figure 132-3** Antegrade conduction over an accessory pathway during atrial fibrillation in a 15-year-old boy with syncope. The short RR intervals represent rapid conduction over the accessory connection and a risk for ventricular fibrillation.

PVCs are considered benign if no evidence of heart disease exists, the QTc is normal ( $\leq 0.44$  second), the family history is not adverse (no sudden premature deaths or cardiac arrests, important arrhythmias, or cardiomyopathies), and the PVCs are uniform in appearance and are either suppressed or not aggravated with exercise. Conversely, the presence of any of these risk factors should prompt referral for further investigation. Because underlying heart disease may be subtle, an echocardiogram to assess cardiac structure and function is usually obtained in referred patients.

Benign PVCs do not require treatment or curtailment of exercise, even if a bigeminal rhythm is present. However, if frequent benign PVCs persist, then cardiology surveillance should be arranged to detect the unusual situation of arrhythmia-induced ventricular dilation or dysfunction, especially if the ectopy burden constitutes more than 5% of the total beats on a 24-hour ambulatory electrocardiogram. PVCs that are not clearly benign require the expertise of a pediatric cardiologist to determine whether there is a need for therapy. Ventricular couplets are assessed in the same manner, but triplets represent ventricular tachycardia and are discussed later in this chapter.

### SUPRAVENTRICULAR TACHYCARDIA

Supraventricular tachycardia (SVT) is common in the young, affecting as many as 1 in 250 children. More than 90% of pediatric SVT is reentrant in nature, involving 2 distinct atrioventricular pathways with differing conduction characteristics and unidirectional block in one pathway. An APC may initiate SVT by entering the unblocked pathway, activating the ventricle, and then re-entering the atrium retrograde through the blocked pathway, completing the reentrant circuit. Most re-entrant SVT in infants and children results from an accessory pathway, but the incidence of atrioventricular nodal reentry increases during adolescence with further development of the atrioventricular node. Wolff-Parkinson-White (WPW) syndrome is present if the ECG demonstrates pregrade conduction through the accessory pathway in sinus rhythm as a short PR interval, delta wave, and wide QRS. The prevalence of WPW syndrome in the general population is 0.15%, but in many affected individuals, no SVT occurs. Patients with asymptomatic WPW syndrome carry a small (0.05%–0.5% per year) but definite risk for sudden death related to rapid antegrade conduction down the accessory pathway if atrial fibrillation occurs (see Figure 132-3).

WPW syndrome (with tachycardia) may be inherited in an autosomal-dominant fashion, and for these individuals the risk for sudden death is substantially increased. Automatic atrial tachycardias account for less than 10% of SVTs in children and tend to be incessant with a variable rate dependent on autonomic tone.

About 50% of patients with SVT present with tachycardia during the first 4 months of life, and 60% of this group will have recurrences, particularly if WPW syndrome is present. Although potentially still inducible at an electrophysiologic study, more than 90% will be free of clinical episodes of tachycardia at 1 year of age. However, as many as one-third of children who have a history of SVT in early infancy and clinical resolution by 1 year of age may have a recurrence at a mean age of 8 years. SVT presenting for the first time in a child 5 years or older implies a likelihood of recurrent episodes of tachycardia as high as 75% to 80%. SVT is usually initiated by an APC or sinus tachycardia in early infancy, but in childhood and adolescence, PVCs and sinus pauses with junctional escape beats are additional initiators. Most children with SVT have a structurally normal heart, but if WPW syndrome is present, there is a somewhat higher incidence of cardiac defects such as hypertrophic cardiomyopathy, Ebstein malformation, or levotransposition of the great vessels.

## PRESENTATION OF SVT

During infancy, SVT may be detected incidentally on a routine examination; more commonly, however, young infants exhibit varying degrees of congestive heart failure related to the rate and duration of tachycardia and the presence of associated heart disease. As a general rule, 25% of infants develop congestive heart failure after tachycardia for 24 hours, and 50% have heart failure after SVT for 48 hours. Often, a history of poor feeding and pallor over several days is present, culminating in respiratory distress. Children older than 5 years are usually able to communicate their distress soon after the onset of SVT—hence the relative rarity of congestive heart failure caused by SVT in older children. The duration of SVT in children and adolescents ranges from a few seconds to several hours. Palpitations are the only symptom in some children; others have lightheadedness, chest discomfort, pallor, diaphoresis, and nausea. SVT-induced syncope is rare. In infancy, the heart rate with SVT may range from 230 to 300 beats per minute but is usually between 260 and 280 beats per minute, in contrast to older patients who typically have rates between 180 and 240 beats per minute. The QRS complexes are usually narrow but may be transiently wide at initiation as a consequence of aberrancy (Figure 132-4). A 12-lead ECG may reveal sharp deflections in the T waves, representing retrograde conduction from the ventricles to the atria through an accessory pathway (Figure 132-5).

## MANAGEMENT OF SVT

If cardiogenic shock is present with SVT, then direct current synchronized cardioversion should be performed; otherwise, adenosine can be administered

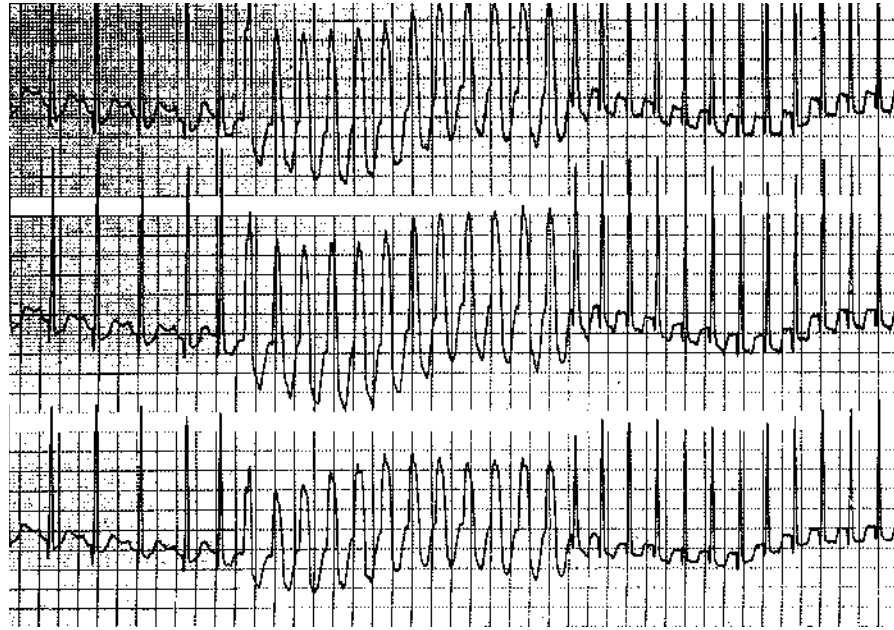
through an intravenous bolus of 100 mcg/kg, followed by a second doubled dose if the first dose is ineffective. Adenosine always should be administered with ECG monitoring to detect the rare conversion to a more malignant arrhythmia. If adenosine is ineffective, or if SVT quickly recurs, cardiology consultation is advised. In this circumstance, an infusion of procainamide can be administered to infants and young children after appropriate loading, with a subsequent repeat trial of adenosine. Alternatively, amiodarone (5 mg/kg) may be administered intravenously over 20 to 60 minutes, followed by a repeat bolus if conversion is not achieved with the first dose. In general, in children younger than 1 year, intravenous verapamil and propranolol are contraindicated.

After conversion to a sinus rhythm is achieved, a 12-lead ECG should be repeated to look for evidence of pre-excitation. If WPW syndrome is present, suppressive therapy with propranolol is appropriate. Digoxin and verapamil should be avoided in children with WPW because either medication may shorten the antegrade refractory period of the accessory pathway, allowing more rapid conduction to the ventricles, a potentially fatal scenario if atrial fibrillation develops. If pre-excitation is not present, either digoxin or propranolol has been used with success to prevent recurrences. Many cardiologists currently avoid the use of digoxin because of concerns about unproven efficacy and its potential for toxicity. Beta blockers are not universally effective either and may aggravate congestive heart failure, sick sinus syndrome, or bronchospasm. Other possible medical therapies include flecainide, sotalol, or amiodarone, all of which require hospitalization for drug initiation because of possible proarrhythmic effect. Infants who have SVT are usually treated for 6 to 12 months and then observed in view of the risk for later recurrence. Because of the higher risk for complications, including the prospect that the resultant myocardial scar may grow with the patient and become a subsequent nidus for malignant and often drug-refractory arrhythmias, ablations are not commonly recommended in the first 2 years of life. If surgery for a cardiac defect is contemplated and episodes of SVT have occurred, then preoperative assessment and ablation should be considered to reduce arrhythmia-related postoperative morbidity and mortality.

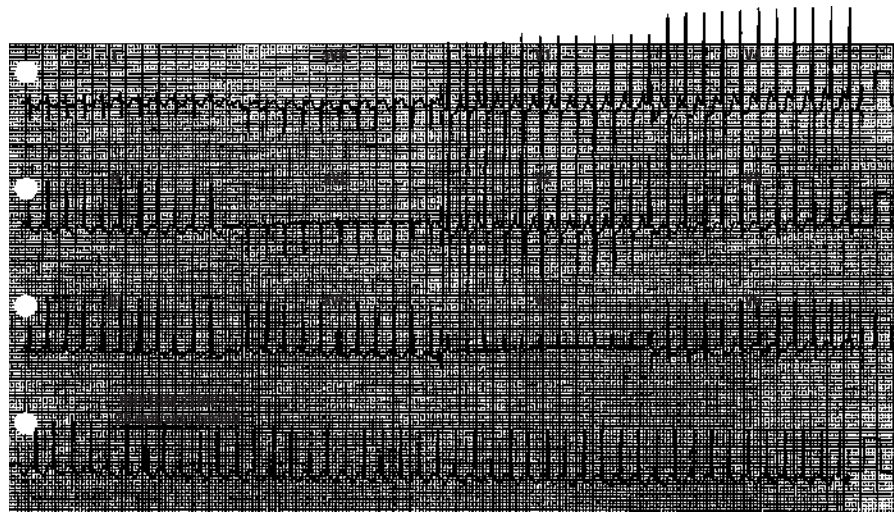
Depending on the frequency and ease of conversion of episodes, older children and adolescents have 3 therapeutic choices:

1. No therapy other than self-conversion through a supine Valsalva maneuver or headstand
2. Drug therapy, although the duration, adherence issues, and cost of this approach need to be addressed with the family
3. Radiofrequency ablation, currently at least 90% successful but with a chance of a later recurrence

Automatic ectopic tachycardias in childhood are often incessant and relatively drug resistant, with the eventual possible outcome of a tachycardia-induced cardiomyopathy if conversion is not achieved. However,



**Figure 132-4** Transient aberrant conduction at the onset of supraventricular tachycardia during an exercise test in a 14-year-old adolescent. The QRS duration then returns to normal.



**Figure 132-5** Twelve-lead electrocardiogram (ECG) of supraventricular tachycardia in a 2-week-old infant. Consistent sharp deflections in the T waves are present in lead III, indicating retrograde atrial activation via an accessory pathway. A repeat ECG after conversion to sinus rhythm did not reveal any pre-excitation; therefore, a concealed accessory pathway is present. Note also the ST depression in the lateral precordial leads, indicating an element of myocardial ischemia.

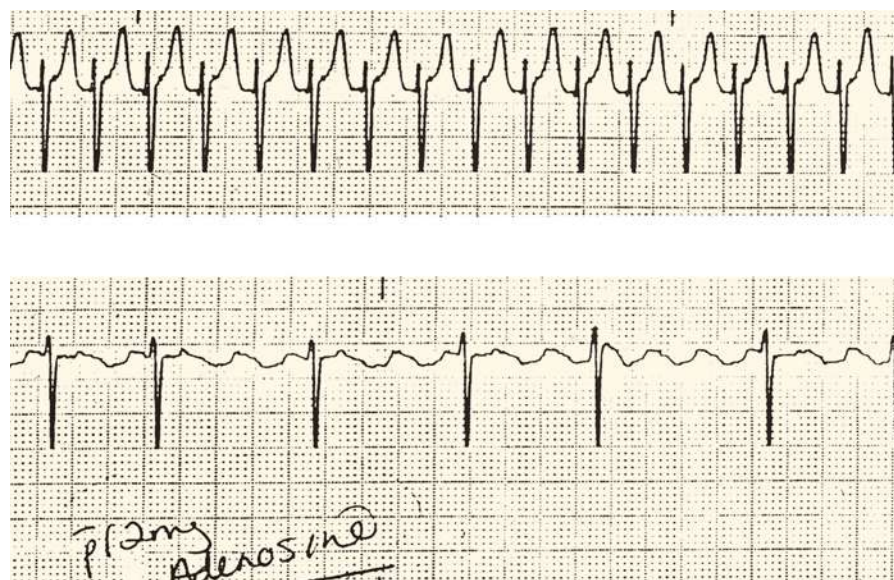
spontaneous resolution may occur, especially in patients younger than 3 years.

### ATRIAL FLUTTER

Atrial flutter, a primary atrial re-entrant tachycardia, is seen in a bimodal distribution in newborns and in older children, the latter usually with cardiomyopathies and after repair of complex congenital heart malformations.

In the newborn, the characteristic rapid sawtooth pattern with inverted P waves in the inferior limb leads is found with an atrial rate typically between 350 and 500 beats per minute and variable, commonly 2:1, atrioventricular block, resulting in a mean ventricular rate typically about 200 beats per minute. If the onset is in utero, then hydrops fetalis may develop. After birth, congestive heart failure tends to be less severe than in SVT. Structural cardiac problems are uncommon.





**Figure 132-6** Intra-atrial re-entrant tachycardia before and immediately after adenosine treatment in a 12-year-old boy after a Mustard repair of transposition of the great arteries in infancy. Adenosine produces high-grade AV block revealing but not converting the underlying IART.

Spontaneous conversion may occur within a few hours of birth. Although most require electrical cardioversion, chronic pharmacotherapy is usually unnecessary because recurrences are rare.

Although the typical form of atrial flutter may be seen in older children and adolescents, more common in this age group is a different variety called intra-atrial re-entrant tachycardia (IART), characterized by a slower atrial rate and distinct P waves separated by isoelectric periods. IART is usually seen after repair of complex congenital cardiac lesions (Figure 132-6). Management is often difficult, but if conversion to and maintenance of a sinus rhythm cannot be achieved, morbidity is substantial, with a 4- to 5-fold increase in the risk for sudden death. If an inappropriately rapid heart rate of 100 to 140 beats per minute is noted in an older child after repair of congenital heart defect, a 12-lead ECG should be obtained to look for IART, even if the surgical repair is in the remote past.

### ATRIAL FIBRILLATION

Atrial fibrillation, an irregular tachycardia with variable atrioventricular conduction, is much less common than the other forms of SVT and is seen in older patients with structural heart disease, cardiomyopathies, and alcohol binges. However, the incidence of idiopathic and paroxysmal atrial fibrillation in adolescence may be underestimated. If pre-excitation (WPW syndrome) is present and the accessory pathway is capable of rapid antegrade conduction, atrial fibrillation may conduct quickly to the ventricles, with a resultant decrease in cardiac output, syncope, and the potential for ventricular fibrillation and sudden death (see Figure 132-3).

### VENTRICULAR TACHYCARDIA

Ventricular tachycardia (VT) is defined as 3 or more repetitive excitations arising from the ventricles with a rate more than 120 beats per minute or 25% faster than the sinus rate. The QRS complexes are different from the sinus QRS complexes and are typically wide, except in young infants in whom minimal QRS prolongation (0.08–0.09 second) may be seen. VT may be extremely rapid, up to 500 beats per minute, and slightly irregular because of intermittent sinus capture beats. The differential diagnosis includes SVT with persistent aberrancy (see Figure 132-4) and SVT with antegrade conduction across an accessory pathway (see Figure 132-3), both of which are relatively uncommon. Safety dictates that all wide QRS tachycardias be considered VT until proved otherwise. The presence of similar but isolated PVCs and fusion beats in sinus rhythm assists in establishing the diagnosis, but VT is confirmed by the presence of atrioventricular dissociation (Figure 132-7).

VT in the newborn and young infant is rare, and when it is drug resistant and incessant, a ventricular tumor may be present. Mitochondrial fatty acid  $\beta$ -oxidation disorders can also cause VT in neonates. Predisposing factors in older children and adolescents include myocarditis, repaired and unrepaired congenital cardiac lesions, cardiomyopathies, long QT syndrome, catecholamine- or exercise-induced VT, marked electrolyte imbalances, and use of street drugs (eg, cocaine). In general, VT is a marker for myocardial disease.

Acute management depends on the patient's clinical status, which is determined by the rate and duration of VT and the presence of structural cardiac lesions or





**Figure 132-7** Ventricular tachycardia: wide QRS tachycardia with atrioventricular dissociation.

prior myocardial dysfunction. Hemodynamic compromise dictates electrical cardioversion with 1 to 2 watt-seconds/kg. If reasonable clinical stability is present, then intravenous amiodarone, procainamide, magnesium, or lidocaine can be administered.

Chronic suppressive therapy is predicated on the risk for recurrence, the morbidity and mortality of the type of VT, and the risk-to-benefit ratio of treatment. Beta blockers, sotalol, and amiodarone are commonly used to prevent VT recurrences. Other treatments include implantation of an automatic cardioverter-defibrillator and VT ablation. In contrast to classic VT, accelerated ventricular rhythm is characterized by a rate of 120 beats per minute, or less than 25% faster than the basic sinus rate. Accelerated ventricular rhythm is benign when it occurs in an otherwise normal heart.

## CONDUCTION ABNORMALITIES

First-degree atrioventricular block is a prolongation of the PR interval beyond the upper limit of normal for age, with all impulses conducted. It may be seen in patients who have congenital cardiac malformations (especially atrioventricular septal defects), electrolyte disorders, rheumatic fever, myocarditis, and congenital muscular disorders. Patients receiving antiarrhythmic agents frequently exhibit first-degree atrioventricular block, which is usually benign in most settings.

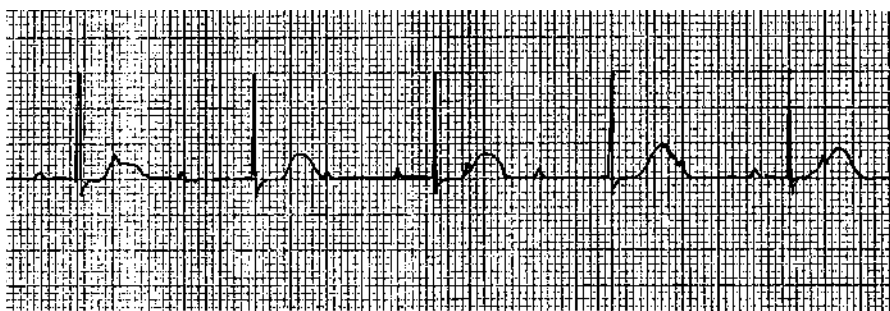
Mobitz type I second-degree atrioventricular block, also known as *Wenckebach block*, is a progressive prolongation of the PR interval until a dropped ventricular beat (nonconducted P wave) occurs. It is a normal finding in healthy children during sleep and in highly conditioned athletes at rest, circumstances that are associated with a predominance of vagal tone. In general, this entity, when it occurs without exertional symptoms or syncope, is benign.

On the other hand, Mobitz type II second-degree atrioventricular block is characterized by intermittent loss of atrioventricular conduction without preceding lengthening of the PR interval. Because the site of Mobitz type II block is more distally located in the bundle of His (in contrast to type I, in which the site of block is in the atrioventricular node), there is greater risk for progression to complete atrioventricular block. The presence of type II block implies an abnormal conduction system with greater risk for associated

symptoms and threatening complications, so referral to a cardiologist is appropriate for ongoing medical surveillance and evaluation for potential pacemaker implantation.

Complete atrioventricular block (CAVB), in which no atrial impulses are conducted to the ventricles, occurs in 1 of 10,000 to 20,000 live-born infants and may be acquired or congenital. Acquired block is usually a consequence of conduction system injury at the time of repair of congenital cardiac malformations but can also be seen in myocarditis, including Lyme disease, and with ingestion of beta blockers, clonidine, opioids, and sedatives. About 50% of newborns who have complete congenital atrioventricular block (CCAVB) have underlying complex congenital heart malformations, particularly levotransposition of the great vessels and complex atrioventricular septal defects. Even with permanent pacing, the mortality rate of CCAVB in the setting of structural heart disease is high (>75%). The other 50% of neonates with CCAVB have immune-mediated block associated with the passage in utero of immunoglobulin G SS-A/Ro and SS-B/La antibodies from the mother who has overt or occult autoimmune disease. When the fetus is exposed to these maternal antibodies, particularly to high levels ( $\geq 100$  U/mL) of maternal anti-Ro antibodies between 15 and 24 weeks of gestation, there may be fibrotic replacement of atrioventricular nodal tissue with consequent second-degree block or CAVB (Figure 132-8). Fewer than 5% of infants born to mothers who have autoimmune disease develop CCAVB. Infants without CCAVB born to anti-Ro/SS-A-positive mothers with autoimmune disease may have QT prolongation and sinus bradycardia. If a mother bears a child who has CCAVB, the risk in future pregnancies is 15%. An immune-mediated myocarditis may also occur in fetuses exposed to maternal anti-Ro and anti-La antibodies, with possible development of a postnatal dilated cardiomyopathy (endocardial fibroelastosis).

Risk factors for fetal, neonatal, or late death with CCAVB include fetal hydrops, premature birth, the presence of complex structural heart disease, a prolonged QT interval seen in up to 25% of affected patients, congestive heart failure, ventricular ectopy, atrioventricular valve insufficiency, and a low or decreasing ventricular rate (55 beats per minute or less in a neonate). In view of the risk for mortality, early



**Figure 132-8** Complete congenital atrioventricular block in a newborn infant whose mother has Sjögren syndrome. The atrial rate is 150 beat/min, and the ventricular rate is 60 beats/min. The QRS duration is normal.

pacemaker implantation is advised if any of these risk factors or signs of an inadequate cardiac output is present. An infusion of isoproterenol can be administered, if necessary, to increase the heart rate while awaiting pacemaker therapy but should not delay implantation. In patients who do not require pacemaker implantation in early infancy, pacing usually becomes necessary in adolescence.

### SUDDEN CARDIAC DEATH

Sudden cardiac death, a rare but devastating event in the young, strikes approximately 1 in 100,000 children and teenagers, with the highest incidence in mid-adolescence. In decreasing order of frequency, predisposing factors include the following:

1. Repaired complex congenital heart malformations
2. Cardiomyopathies
3. Myocarditis
4. Congenital coronary artery anomalies (especially origin of the left main coronary artery from the right sinus of Valsalva)
5. Primary arrhythmias such as long QT syndrome (LQTS), WPW syndrome, and catecholamine-sensitive polymorphic VT

LQTS is a familial, clinically and genetically heterogeneous ion channel cardiac disorder that prolongs repolarization and may cause syncope, seizures, and sudden death as a consequence of polymorphic VT (torsades de pointes). The autosomal-dominant Romano-Ward subcategory, which accounts for 95% of patients with LQTS, is related to a heterozygotic mutation on chromosomes 11, 7, 3, 4, or 21. The remaining 5% are characterized by homozygotic mutations on chromosome 11 leading to the autosomal-recessive Jervell and Lange-Nielsen (JLN) syndrome, which is characterized by marked prolongation of the corrected QT intervals and congenital deafness. Patients with JLN syndrome have a greater degree of QTc prolongation and a substantially higher incidence of sudden death compared with patients with the much more common Romano-Ward variant. Potassium-channel function is affected by mutations on chromosomes 11, 7, 4, and 21, whereas the sodium channel is perturbed as a consequence of mutations on chromosome 3.

The incidence of LQTS is estimated at 1 in 2,500 individuals, with no gender predisposition, but the incidence may be underestimated because of incomplete genetic ascertainment. The annual mortality rate after onset of symptoms in untreated young patients is 1% to 5%, with a nearly 10% risk for sudden death as the initial symptom. The cumulative probability of a cardiac event (predominantly syncope) occurring in patients who are genotyped LQT1, 2, and 3 by 15 years of age ranges between 10% for patients with LQT3 and 69% for those with LQT1. LQTS has been identified as a rare cause of the sudden infant death syndrome. The highest risk for sudden death occurs in patients with a history of syncope and a QTc of more than 500 milliseconds. Syncope, atypical seizures, or cardiac arrest usually occur during exertion or emotional stress, except for long QT3 subtype events, in which symptoms predominantly occur at rest. Other than bradycardia, the physical examination is usually normal. LQTS is defined by a corrected QT interval in excess of 460 milliseconds, with a borderline QTc defined by an interval of 440 to 460 milliseconds. In general, the longer the QTc, the greater the risk for polymorphic VT. The differential diagnosis of QTc prolongation also includes electrolyte abnormalities such as hypokalemia, hypocalcemia, and hypomagnesemia. Myocardial ischemia or injury, acute central nervous system events, and cardiomyopathies may be associated with mild QTc prolongation. Cisapride, imipramine, pentamidine, and intravenous erythromycin may also prolong the QT interval. Management of LQTS includes beta-blocker therapy, restriction from competitive sports, avoidance of sympathomimetics and drugs capable of prolonging the QTc, and avoidance and rapid correction of electrolyte abnormalities. More invasive management is often necessary, including pacing, left stellate ganglionectomy, and implantation of an internal cardiac defibrillator. Gene-specific therapy with potassium channel opening agents and sodium channel blockers is on the horizon.

Beyond infancy, 25% of sudden cardiac deaths in the young occur during exercise; most occurrences are electrical in nature, with ventricular fibrillation as

the final common pathway. Athletic risk may be stratified by asking 2 critical questions in pre-sports clearance evaluations: (1) Has the patient ever passed out, had visceral chest pain, or experienced symptomatic palpitations during strenuous exercise? (2) Has any family member died suddenly and unexpectedly before the age of 35 years? An affirmative answer to either question should prompt a referral to a cardiologist before participation in competitive sports. For any child or adolescent who collapses suddenly with no discernible cardiac output, rapid resuscitation including early defibrillation is mandated. Automatic external defibrillators that are available in some school systems have already begun to decrease the incidence of sudden cardiac death in the young.

### WHEN TO REFER

- Arrhythmias associated with presyncope, syncope, chest pain, or a sense of doom
- Arrhythmias associated with repaired or unrepaired congenital heart disease or cardiomyopathies
- Family history of premature (<35 years) sudden cardiac death
- Persistent or repetitive bradycardias or tachycardias
- Premature ventricular beats that increase with exercise
- Asymptomatic WPW syndrome

### WHEN TO ADMIT

- Arrhythmias associated with congestive heart failure, syncope, or low cardiac output
- Symptomatic high-grade atrioventricular block
- Difficult-to-control SVT, atrial flutter
- VT
- Heart disease with syncope, aborted sudden death

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Irregular Heartbeat (Arrhythmia)* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/heart/Pages/Irregular-Heartbeat-Arrhythmia.aspx](http://www.healthychildren.org/English/health-issues/conditions/heart/Pages/Irregular-Heartbeat-Arrhythmia.aspx))
- *Sudden Cardiac Death* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/injuries-emergencies/sports-injuries/Pages/Sudden-Cardiac-Death.aspx](http://www.healthychildren.org/English/health-issues/injuries-emergencies/sports-injuries/Pages/Sudden-Cardiac-Death.aspx))

#### Medical Decision Support

- *Preparticipation Physical Evaluation*, 4th ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Preparticipation Physical Evaluation Forms* (questionnaire), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Watch, Learn and Live (Arrhythmias)* (interactive media), American Heart Association ([watchlearnlive.heart.org/CVML\\_Player.php?moduleSelect=arrhyt](http://watchlearnlive.heart.org/CVML_Player.php?moduleSelect=arrhyt))

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## Chapter 133 CHEST PAIN

Scott A. Schroeder, MD

Although chest pain from cardiac disease in children is extremely rare, few symptoms result in more fear and anxiety in children and their parents. Undiagnosed cardiac disease causes chest pain in less than 5% of patients, and if children with preexisting heart disease are excluded, then cardiac abnormalities are found in less than 1% of patients. Although chest pain from cardiac disease occurs in a few children, much of the pediatrician's evaluation and teaching will be focused on convincing families that the heart is normal. If the care of a child with chest pain is managed inappropriately, then grief, anxiety, restriction of activities, and distrust by the family may result. However, a thorough history and physical examination will usually uncover the cause of the chest pain and will almost always allow the physician to state emphatically that the chest pain in this case is certainly not from heart disease.

### DIFFERENTIAL DIAGNOSIS

Of children and adolescents with chest pain, by far the largest number have musculoskeletal chest wall



trauma or other conditions identified as the source of the pain. Pulmonary diseases—pneumonia, asthma, pneumothorax, and cough itself—account for approximately one-fifth of cases, and the rest are the result of hyperventilation or psychiatric causes, gastrointestinal disorders, and, finally, cardiac disease. Approximately 15% of cases remain idiopathic. However, most studies on the causes of chest pain in children originate in pediatric emergency departments and pediatric cardiology clinics, and therefore these studies have not rigorously looked for the presence of esophageal disorders or reactive airway disease, both of which have been shown to be common in children with idiopathic chest pain.

## **PATHOPHYSIOLOGIC FEATURES OF CHEST PAIN**

Because numerous organ systems are within the thorax, and because of the confusing overlap of sensory inputs from the various tissues in the chest, a systematic approach to the thorax is essential to determine the source of the child's pain. Pain from the chest wall and the supporting musculoskeletal structures is transmitted from these inflamed or irritated tissues to the central nervous system through the primary sensory afferents that terminate in the dorsal root ganglia. Spinal neurons then transmit the sensation from the inflamed chest wall tissues to the brain, where it is perceived as a sharp, localized pain. This feature is why chest wall pain (eg, from costochondritis or trauma) is sharp, localized, and easily reproduced on palpation.

Spinal neurons that receive input from the organs within the thorax also receive sensory input from the thoracic dermatomes. This overlap of sensory input leads to the phenomenon of *referred pain*, which often makes the evaluation of chest pain challenging. Diffuse, poorly localized chest pain can originate from any of the organs within the thorax. Inflammation of the structures that pass through the mediastinum results in pain over dermatomes T1 to T4, from the retroclavicular to the retrosternal regions. Pain over dermatomes T5 to T8, especially in the xiphoid area, suggests lower chest wall or diaphragmatic irritation or even intra-abdominal disease. Because both the intercostal nerves and the phrenic nerve innervate the diaphragm, peripheral diaphragmatic irritation causes pain in the lower anterior chest or epigastric regions, and central diaphragmatic inflammation results in ipsilateral shoulder pain because of its innervation by the phrenic nerve. The pericardium, positioned on the central diaphragm, has pleural connections and is innervated by the phrenic, vagus, and recurrent laryngeal nerves. Therefore, when the pericardium is inflamed or infected, sharp substernal pain can occur. The pain of pericarditis may be limited to the sternal and precordial areas; however, if the left lobe of the diaphragm is irritated, then pain will be referred to the ipsilateral shoulder or neck. Pleural pain results from distention or inflammation of the pleura that can occur during the course of pneumonia, pneumothorax, or empyema. Pain from pleural inflammation is

aggravated by respiratory movements. The pain is characterized as well localized and sharp, exaggerated by coughing or deep inspiration. The pain associated with a pneumothorax can be pleuritic in nature, or it can be referred to the ipsilateral shoulder. Pleurodynia is a specific cause of pleuritic chest pain heralded by fever and associated with coxsackievirus B; an idea of its intensity comes from its apt nickname as “the devil’s grip.”

The pain associated with esophageal disorders can seem indistinguishable from that associated with myocardial ischemia because the sensory afferents from the esophagus are through the cardiac and esophageal plexi as well as the sympathetic trunk. Within the lungs, sensory input exists only from the larger airways and parietal pleura; thus, the pain arising from pulmonary parenchymal disease results from inflammation of or traction on contiguous structures.

## **EVALUATION**

### **History**

Because pathognomonic findings are rare on physical examination in the evaluation of a child with chest pain, a detailed history will help focus the differential diagnosis, develop a logical intervention, and allow the child and family to voice their concerns. A meticulous history should address the nature of the pain as well as the child's response to the pain. If possible, children should describe the pain in their own words, and they should be asked what they think is causing the pain. Along with a description of the location, duration, radiation, and quality of the pain, the pediatrician should elicit any associated signs and symptoms, as well as any aggravating and alleviating factors, and attempt to uncover the family history and dynamics. To many adolescents, chest pain is synonymous with heart disease; therefore, this issue should be addressed, and if no cardiac cause is discovered, then the physician should unequivocally state to the adolescent and the family that the heart is normal.

Pain that occurs with exercise points toward either a cardiac or a respiratory cause. If the pain awakens the child from sleep, then the cause might be respiratory, cardiac, musculoskeletal, or gastroesophageal, but it is never psychological. When the pain is poorly localized or is associated with recurrent somatic complaints or family or school stress, and when a family history of chest pain can be found, a psychogenic source of the pain is likely. Conversely, deep, poorly localized pain that radiates to the neck or shoulders is characteristic of visceral pain. Superficial sharp pain that is exacerbated by lifting or movements of the torso suggests musculoskeletal pain.

Peripheral pain that increases with inspiratory efforts originates from pleural inflammation. Questions regarding trauma to the chest wall should always be asked, and even if the trauma occurred 1 to 3 months before the pain, it should not be discounted because the pain might represent a posttraumatic pericardial effusion. Sharp pain that decreases when the child



leans forward is characteristic of pericardial inflammation. Children with a family history of Marfan or Turner syndromes, as well as those with a history of Kawasaki disease or congenital heart disease, warrant referral to a pediatric cardiologist.

Even if the history is highly suggestive of the cause for the chest pain, the pediatrician should be careful and thorough because the potential exists for 2 different causes of the pain. Children with asthma can also have gastroesophageal reflux. Children with sickle cell disease who develop acute chest syndrome may have chest pain as a result of medication-induced gastritis, vaso-occlusive crisis, or asthma.

### Laboratory Evaluation

Laboratory tests are usually not helpful in establishing a specific diagnosis; therefore, a thorough history and physical examination should guide the physician in ordering tests. In most cases, chest radiographs and electrocardiographs will only confirm what is suspected clinically. If a child has a fever, acute onset of chest pain, and an abnormal cardiac examination suggestive of pericarditis, then a chest radiograph and electrocardiogram are indicated. If a child has fever, tachypnea, chest pain, and decreased breath sounds over a segment of the lungs, then a chest radiograph is appropriate to determine whether a pneumothorax, a pneumonia, a pleural effusion, or other pulmonary disease is present. If the pain occurs with exercise, then exercise testing or spirometry may help uncover underlying asthma or exercise-induced bronchospasm. One cause of idiopathic chest pain may be an esophageal disorder. Signs and symptoms of children with chest pain who warrant hospitalization or specialty evaluation are listed in Box 133-1.

## SPECIFIC CAUSES OF CHEST PAIN IN CHILDREN

### Musculoskeletal and Chest Wall Conditions

After a determination has been made that the child is in no distress, inspection of the thorax will determine the presence of bruising, swelling over joints, splinting, signs of trauma, or an abnormal breathing pattern. Palpation and percussion are extremely important to localize and reproduce the pain because disturbances in the chest wall are the most common diagnoses in children with chest pain. Each rib cartilage should be palpated with only one finger or with the child's finger because palpation with 2 or more digits may cause splinting and will not recreate the pain. Reproduction of point tenderness at the origin of the spontaneous pain is the strongest evidence favoring the diagnosis of chest wall disease. Pain from the thoracic cage that can be elicited by movements of the torso or by flexion of the arms is highly suggestive of a musculoskeletal chest wall injury. The pain of costochondritis causes tenderness over the affected costochondral or costosternal junctions and can occur at rest or with movement. Adolescents with gynecomastia or breast pain may experience chest pain that is easily discernible on inspection and palpation of the developing breast tissue. No laboratory testing is

### BOX 133-1 Signs and Symptoms That Accompany Chest Pain and Warrant Referral or Hospitalization

#### SIGNS

- History of Kawasaki disease, Turner syndrome, Marfan syndrome, sickle cell disease, or cystic fibrosis
- Recent elective abortion, calf pain, oral contraceptive use
- Family history of hypertrophic obstructive cardiomyopathy or unexplained syncope
- Pica
- Foreign body aspiration
- Conversion disorder
- Cyanosis or toxic appearance
- Murmur that increases with Valsalva maneuver
- Pleural or pericardial friction rub
- Pulsus paradoxus
- Cardiac clicks, thrills, gallop, or third heart sound

#### SYMPTOMS

- Syncope
- Fevers, chills, weight loss, malaise, anorexia
- Respiratory distress
- Chest pain with exercise
- Palpitation or tachycardia

needed if any of these conditions is identified as a cause of the chest pain. Table 133-1 lists common, uncommon, and rare causes of chest pain and their associated signs and symptoms.

### Pulmonary Conditions

Children with asthma may have chest pain from excessive coughing and overuse of their intercostal muscles. Having pain alone as a manifestation of asthma is unusual for a child; usually, nocturnal cough, adventitious breath sounds, abnormal pulmonary function tests, or other signs of atopic diseases can exist.

A variety of other diseases of the airways, pleurae, and parenchyma can cause substernal or pleuritic chest pain. Pneumonia, asthma, exercise-induced bronchospasm, pleural effusions, and air in the pleural space can cause pain, but the chest pain is never the sole sign of the underlying disease process. A child with a parapneumonic effusion will classically have fever, tachypnea, tachycardia, a pleural friction rub or crackles (or both) on auscultation, and dullness to percussion in addition to the pleuritic chest pain that intensifies with inspiration.

Exercise-induced chest pain or chest tightness that resolves with the cessation of the exercise or the administration of bronchodilators may be a manifestation of cardiac disease but is more commonly related to exercise-induced bronchospasm. Exercise testing, cold air challenge, or a therapeutic trial of bronchodilators can confirm the diagnosis of exercise-induced

**Table 133-1** Common, Uncommon, and Rare Causes of Chest Pain and Associated Signs and Symptoms

CAUSE OF CHEST PAIN	SIGNS AND SYMPTOMS
<b>MUSCULOSKELETAL</b>	
Costochondritis (common)	Localized, superficial, reproducible pain over rib cartilage
Exercise, overuse, muscle strain (common)	Reproducible pain with use of involved muscle group
Protracted coughing or vomiting (common)	Intercostal muscle tenderness
Trauma	Localized pain; pain with movement of involved areas
Stitch (common)	Sharp, crampy costal pain that occurs with running
Precordial catch (uncommon)	Transient, stabbing pain at left sternal border; relieved by forced inspiration
<b>PULMONARY</b>	
Asthma (common)	Associated with cough, shortness of breath, wheezing, abnormal pulmonary function tests; relief with inhaled anti-inflammatory drugs or bronchodilators
Exercise-induced bronchospasm (common)	Abnormal exercise tests; improvement with bronchodilators
Pneumonia (common)	Crackles, fever, cough
Pleural effusion (uncommon)	Pleural rub, fever, decreased breath sounds
Pneumothorax (uncommon)	Sudden pain, referred shoulder pain, dyspnea, hyperresonance and/or absent or reduced breath sounds on affected side
Pulmonary embolus (rare)	Contraceptive use or recent abortion, pleuritic pain
<b>GASTROINTESTINAL</b>	
Esophagitis (common)	Retrosternal pain; relief with antacids
Gastroesophageal reflux (common)	Retrosternal burning pain; worse after eating and when reclining; relief with antacids
<b>CARDIAC</b>	
Hypertrophic cardiomyopathy (rare)	Syncope, family history, systolic ejection murmur
Pericarditis (rare)	Associated fever with acute onset of pain; pain increases with movement; narrow pulse pressure, distant heart sounds; alleviated by leaning forward
Myocarditis (rare)	Precedent viral illness, anorexia, shortness of breath, third heart sound or gallop, cardiomegaly
<b>NONORGANIC</b>	
Psychogenic (common)	Normal physical examination, trouble sleeping, family or school problems, life stresses, family history of chest pain, other somatic complaints
Hyperventilation (common)	Associated light-headedness, paresthesias, underlying anxiety

or cold air-induced bronchospasm. Treatment with bronchodilators will help these children participate in sports and allow them to lead normal, active lives.

Spontaneous pneumothorax can occur in teenagers with chronic illnesses such as cystic fibrosis, asthma, and Marfan syndrome, but it can also occur in healthy teenagers. A child with cystic fibrosis who experiences chest pain should be assumed to have a pneumothorax until proven otherwise. Dyspnea, shoulder pain, and tachypnea are often observed in addition to the chest pain in a typically tall, thin adolescent who develops a spontaneous pneumothorax.

### Gastrointestinal Conditions

Acid reflux to the esophagus can mimic the pain of angina and can cause both acute and chronic chest pain. Pain that originates from the esophagus or stomach is described as an uncomfortable, gnawing substernal burning sensation. The pain can last for hours, and it intensifies after meals and on reclining. Any inflammation of the esophagus, abnormalities of peristalsis, esophageal foreign body, or trauma can cause

chest pain. The most common gastrointestinal cause of chest pain is esophagitis. However, because the clinical presentation of esophagitis can be nonspecific, children with idiopathic chest pain may benefit from a trial of antacids or H<sub>2</sub>-receptor antagonists before embarking on an exhaustive evaluation.

### Cardiac Conditions

The least likely but most worrisome causes of chest pain in children are cardiac disorders that cause myocardial ischemia. Cardiac disease in children rarely produces isolated chest pain and is always associated with other findings at evaluation. Sudden death from cardiac disease in children is caused by a small subgroup of disorders: abnormalities of the myocardium or coronary vessels, specific congenital heart lesions, arrhythmias, and conduction disorders. Signs and symptoms that identify children with these disorders and warrant cardiology evaluation include exertional nonrespiratory dyspnea, syncope, and palpitations. A pediatric cardiologist should also see children with chest pain and a family history of sudden death.

A child with chest pain from myocarditis or pericarditis usually appears ill, with fever, dyspnea, changes in the pain associated with the respiratory cycle, and abnormal auscultatory findings. In most instances, the echoviruses, especially coxsackievirus B, are identified as the culprit responsible for myocarditis. Pericarditis can result from either an infectious agent or an autoimmune process.

Aortic stenosis and idiopathic hypertrophic cardiomyopathy, which are the most important lesions that cause left ventricular outflow obstruction, can cause chest pain as a result of the heart's inability to increase the cardiac output with exercise. These disorders cause syncope and chest pain with exertion. Mild aortic stenosis does not cause chest pain.

Chest pain may be, but is not usually, the primary complaint of children with arrhythmias unless they perceive the palpitations as painful. More commonly, older children complain of light-headedness or dizziness along with the palpitations. The arrhythmia can usually be detected on auscultation and confirmed by resting electrocardiogram. If the palpitations or chest pain occur infrequently or are not associated with exercise, then referral to a pediatric cardiologist is indicated for Holter monitoring.

Although mitral valve prolapse (MVP) is commonly thought to cause chest pain in adolescents, most children with MVP are asymptomatic. Chest pain has been found to be no more common in teenagers with MVP than it is in those without MVP.

Findings on auscultation that point to a cardiac source of pain include clicks, rubs, and systolic murmurs. A murmur can be worrisome if it increases in intensity with the Valsalva maneuver or any other procedure that expands the degree of left ventricular outlet obstruction. A third heart sound or gallop is heard in myocarditis and congestive heart failure. Pleural friction rubs, wheezes, tachypnea, and crackles suggest a pulmonary cause. Conversely, hyperventilation associated with light-headedness, paresthesias, dizziness, and a high level of stress or anxiety suggests a hyperventilation syndrome.

### Idiopathic Causes

Especially among adolescents, as many as 39% of patients complaining of chest pain will not have a readily identifiable cause. Children with chronic chest pain, no history of respiratory or cardiac disease, and a normal physical examination are unlikely to have a serious cause for their pain. For teenagers, a careful explanation of the pathophysiologic features in concrete terms is a fundamental part of their therapeutic regimen. Several studies of children with idiopathic chest pain have shown that most of them have no further pain 1 to 2 years after their initial evaluation.

### Psychogenic Chest Pain

A child with a long history of chest pain, other recurrent somatic problems, school or sleep problems, a family history of chest pain, or any combination of these factors may have a psychogenic cause for the pain. If a psychogenic cause is entertained, then the

diagnosis should not be made by exclusion of organic disease; rather, the diagnosis should be based on positive psychiatric evidence. As with any somatic illness, if the family or the child is able to articulate a relationship between the chest pain and stress or emotional upheaval, then the diagnosis will be easier for them to comprehend and accept. Emotional causes for chest pain seem to be more common in adolescents than in children younger than 12 years. Hyperventilation can be associated with the chest wall syndrome but is more commonly seen in teenagers with underlying anxiety. The diagnosis is usually made by history alone because the child may need to hyperventilate for 20 minutes to reproduce the pain.

Almost all children with hyperventilation syndrome have associated paresthesias, carpopedal spasm, and light-headedness. For a child with an acute episode of hyperventilation, the treatment is to have the child breathe into a paper bag to relieve the hypocapnia. Resolution of the chronic problem is based on techniques to allow the children to understand the nature of their anxiety and allow them to regain control of their emotional state. The treatment of other forms of psychogenic chest pain should be focused on the family's comprehension of the cause of the pain and reassurance that no long-term sequelae exist, all while acknowledging that the pain is real. For children with more significant psychiatric problems, referral to a psychiatrist may be necessary.

### When to Admit

Rarely will a child with chest pain need to be hospitalized because, for the most part, chest pain is usually benign, self-limited, and not associated with severe intrathoracic illness. Box 133-1 provides guidance for when to refer and when to admit. However, children with the following should be hospitalized:

- Myocarditis
- Pericarditis
- Empyema
- Pneumothorax
- Significant thoracic trauma
- Acute chest syndrome
- Esophageal foreign bodies
- Coronary artery anomalies or other cardiac lesions
- Myocardial ischemia
- Chest pain and palpitations
- Cyanosis
- Distress

### SUGGESTED READINGS

Thull-Freedman J. Of 3700 children thought to have non-cardiac chest pain at initial paediatric cardiology clinic evaluation, none suffered cardiac death over a median of 4 years follow-up. *Evid Based Med.* 2012;17(6): 190-191

## Chapter 134

# CONSTIPATION

Peter F. Belamarich, MD

The term *constipation*, which denotes both a symptom and a chronic condition, refers to the infrequent elimination of large or hard stools that may cause pain on defecation. In childhood, constipation that is not caused by another condition is known as idiopathic or functional constipation. Given that constipation encompasses both objective and subjective complaints that vary by age, it has defied a comprehensive standard definition. Several consensus groups have developed definitions of constipation; however, none of these definitions seems entirely satisfactory to all. One expert consensus definition of constipation is presented in Box 134-1.

Constipation is a common symptom among children in the industrialized world. In parental surveys, 16% to 37% of toddlers are reported to suffer from it. Functional constipation presents a challenge to the pediatrician, as suggested by the observation that the evaluation and treatment of constipation occupies 25% of all referrals to pediatric gastroenterologic services, although these children rarely require an invasive procedure. To pediatricians caring for chronically constipated children, treatment failure raises the question of Hirschsprung disease. Among referral populations, more than 90% of childhood constipation is functional; ultimately, 50% to 90% of these children are cured.

The approach to constipated children used by gastroenterologists is well within the scope of the primary care pediatric practice. The focus of this chapter is on identifying and treating children who have functional constipation. An evidence-based guideline, endorsed by the American Academy of Pediatrics, has been published on evaluating and treating constipation.

### BOX 134-1 Definition of Constipation

Constipation is a symptom defined by the occurrence of any of the following, independent of stool frequency:

- Passage of hard, scybalous, pebble-like, or cylindrical cracked stools
- Straining or painful defecation
- Passage of large stools that may clog the toilet
- Stool frequency less than 3 per week, unless the child is breastfed

Adapted from Hyams J, Colletti R, Faure C, et al. Functional gastrointestinal disorders: Working Group Report of the First World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr.* 2002;35 (Suppl 2):S110.

## PATHOPHYSIOLOGIC MECHANISM OF FUNCTIONAL CONSTIPATION

### Normal Colonic Function

The role of the colon is to reclaim water from the liquid ileal effluent. This task is accomplished, in part, by a motility pattern that includes focal circular contractions, which impede the progress of the luminal contents while solutes and water are absorbed. Subsequently, forward progress of the relatively dehydrated fecal stream is achieved by coordinated contractile waves, which propel the bolus of stool to the next colonic segment and ultimately to the rectum. The final elimination of stool is controlled by defecation, a coordinated sequence of neuromuscular events with both reflexive and conscious components. Control of defecation, continence, is a critically important social achievement in early childhood. At rest, continence is maintained by the involuntary resting tonic contraction of the smooth muscle cuff of the internal anal sphincter and by the posterior turn of the anal canal in relation to the anterior angulation of the rectal vault. This angle is modulated by the puborectalis sling muscle, which loops posteriorly around the anorectal junction and is anchored anteriorly on the pubic bone.

When stool arrives in the rectal ampulla, causing distention of the rectal walls, a reflexive relaxation of the internal anal sphincter occurs, which lowers the pressure of the anal canal and allows the stool bolus to descend to the anal canal, a phenomenon known as the rectoanal inhibitory reflex. Control of defecation then occurs by the voluntary (and learned) deliberate contraction of the striated muscle of the external sphincter and puborectalis sling muscles, which increase the pressure in the anal canal and make the exiting angle more acute. Conversely, a Valsalva maneuver, in combination with relaxation of the external anal sphincter and the puborectalis sling, permits defecation to proceed. Normal stool frequency decreases from about 4 stools per day in infancy to 1.2 stools per day at 4 years old.

### Factors in Functional Constipation

The pathophysiologic basis of functional constipation is not clear. It may be the final common pathway for a number of underlying distinct conditions: a disorder of the dynamics of defecation; a problem with rectal sensation; or a disorder of colonic transit, leading to impacted, overly desiccated stool in the colon. Functional constipation can also arise solely from a behavioral aversion to or learned problems with the process of defecation.

Stool withholding, the act of voluntarily deferring defecation to avoid pain, significantly contributes to the chronicity of constipation in childhood independently of the primary cause.

### Stool Withholding

In practical terms, several commonly recognized clinical scenarios can result in constipation, including painful anal fissures, perianal streptococcal cellulitis,



traumatic toilet-training experiences, and transient periods of dehydration, illness, or immobility. Stool withholding likely figures prominently in the perpetuation of constipation when pain or an aversive experience is the primary insult. Withholding behavior in the toddler or child is strongly self-reinforcing. The child is avoiding painful bowel movements, which makes the stool harder and more painful to pass. Parents who focus with great concern on the withholding crisis, often believing that the child is valiantly trying to defecate rather than to withhold, also reinforce stool withholding unwittingly. Toddlers love the worried attention of their parents! The lack of privacy commonly found in some school lavatories can engender withholding by older children. Anorectal manometric studies have documented abnormalities in the dynamics of defecation in a large series of chronically constipated children, the most common being a paradoxical contraction of the external anal sphincter and the puborectalis sling in response to the rectoanal inhibitory reflex.

This commonly identified abnormality is known variously as rectoanal pelvic floor dyssynergia, abnormal defecation dynamics, and anismus. Most experts consider dyssynergia a learned phenomenon. For a large proportion of chronically constipated children, painful defecation and withholding antedate the clinical presentation of constipation by 1 to 5 years. In a significant subset of children who experience persistent constipation, withholding becomes entrenched and particularly difficult to unlearn. In fact, initial enthusiasm over manometrically based biofeedback training was based on its potential to help patients identify and unlearn this withholding behavior. However, controlled studies have not documented greater improvements in the outcome for patients who have undergone biofeedback training than for those given a standard treatment regimen.

### Sensory Abnormalities

Another common manometric abnormality found in chronically constipated children is known as megarectum. As the name implies, the rectum is dilated with a chronic impaction, a finding associated with an increase in the sensory threshold to minimal rectal distention, as well as an increase in the minimal volume required to initiate the urge to defecate. These sensory abnormalities persist for several years in some patients after successful treatment, suggesting that ongoing sensory abnormalities contribute to relapses and perhaps to the initial pathogenesis of constipation in some children.

### Slow Transit

Constipation from abnormally slow transit of the fecal stream through the colon occurs predominantly in young women but can occur in children. Whether slowed colonic transit is the primary problem or is secondary to distal difficulties with defecation is unclear. Slow-transit constipation in children is not easily differentiated clinically from normal-transit constipation. A unique therapeutic approach to slow-transit constipation has not emerged.

### Dietary Factors

Whether dietary factors alone cause constipation is unclear. In infancy, human milk is highly protective. Despite broad agreement that dietary fiber has an important role in promoting a regular bowel habit, very little literature and no prospective studies support this belief. A case-control study has documented decreased fiber intake as a risk factor for childhood constipation; however, substantial overlap exists in the fiber intake between cases and controls. Nonetheless, many physicians have remarked that, in infancy, the transition from human milk or formula to whole cow's milk, or periods of excess protein intake such as occur in toddlers with excessive whole cow's milk consumption, are associated with constipation. The tenacious and harmful myth that iron-containing formula causes constipation has been disproved many times.

### DIFFERENTIAL DIAGNOSIS

The differential diagnosis of chronic childhood constipation includes many conditions (Box 134-2). Despite the large number of possible diagnoses, at least 90% of affected children have functional constipation.

Frequently, the foremost consideration in the differential diagnosis of chronic constipation is Hirschsprung disease. The most common basis for this concern is treatment failure, an appropriate concern in early infancy when functional constipation is unusual and easily treatable. However, treatment failure in the toddler and the school-aged child more often reflects the complexity and duration of intervention required to treat functional constipation adequately than a missed diagnosis of Hirschsprung disease. Fortunately, several findings in the history are useful in the process of ruling out Hirschsprung disease. Perhaps most useful is that almost all children with functional constipation withhold stool in response to the rectoanal inhibitory reflex, whereas this reflex is absent with Hirschsprung disease. Simply stated, stool withholding behaviors are a historical finding that almost always rule out Hirschsprung disease. Conversely, Hirschsprung disease should be considered in any child with refractory constipation who has had any of the following:

1. Failure to pass meconium in the first 24 hours of life.
2. Onset of constipation before 3 months of age.
3. Symptoms of intestinal obstruction at any time (distention, emesis).
4. Lifelong dependence on laxatives, enemas, or mechanical manipulation to initiate defecation.
5. History of enterocolitis in early infancy (sometimes misdiagnosed as gastroenteritis).
6. Constipation in children with syndromes associated with Hirschsprung disease (eg, trisomy 21, Waardenburg-Shah, congenital central hypoventilation).
7. Failure to thrive or growth faltering. See Table 134-1 for a summary of features that distinguish Hirschsprung disease from functional constipation.

Other conditions that specifically affect the neuromuscular function of the colon include the

**BOX 134-2 Differential Diagnosis of Constipation in Childhood****FUNCTIONAL CONSTIPATION**

- Disorders of intestinal neuromuscular function

**ANAL AND RECTAL DISORDERS**

- Anal fissure
- Anterior ectopic anus
- Anal stenosis
- Anorectal malformations
- Rectal duplication
- Anal trauma (abuse)
- Pelvic tumor (presacral teratoma, ganglioneuroma, ovarian cyst, hemocolpos)

**NEUROLOGIC—NEUROMUSCULAR**

- Hirschsprung disease
- Pseudoobstruction syndromes
- Spinal cord lesions
- Spinal dysraphism, including spina bifida
- Cerebral palsy
- Neuromuscular diseases with hypotonia

**METABOLIC AND ENDOCRINE**

- Hypothyroidism
- Diabetes insipidus

- Hypercalcemia

- Hypokalemia

**MEDICATION AND TOXIN RELATED**

- Antihistamines
- Anticholinergics
- Anticonvulsants
- Opioids
- Bismuth, aluminum hydroxide
- Tricyclic antidepressants
- Iron preparations (not iron-fortified formulas)
- Plumbism
- Infant botulism

**MISCELLANEOUS**

- Celiac disease
- Cystic fibrosis
- Cow milk allergy
- Scleroderma
- Systemic lupus erythematosus

**Table 134-1 Comparison of Hirschsprung Disease to Functional Constipation**

CHARACTERISTIC	HIRSCHSPRUNG DISEASE	FUNCTIONAL CONSTIPATION
Prevalence	~1 in 6,000 births	1.5% of 7-year-old boys
Failure to pass meconium <24 hr	58%–94%	~5%
Constipation in first 3 mo	90%	Rare
Symptoms or signs of obstruction	Common	Absent
Abdominal distention	Common	Mild or absent
Stool size	Narrow, ribbon-like	Intermittent large-caliber stools
General appearance	Chronically ill	Well
Stool-withholding behavior	Rare	Extremely common
Soiling	Unusual	Common
Stool in ampulla	Unusual	Common
Plain radiographs	Empty rectum	Dilated enlarged rectum
Rectal manometry	Rectoanal reflex absent	Rectoanal reflex present
Typical barium enema	Distal spasm, proximal dilatation	Diffusely dilated colon and rectum

pseudoobstruction syndromes, which are characterized by intermittent episodes of functional intestinal obstruction. Furthermore, a large percentage of children who have generalized neuromuscular disabilities (eg, cerebral palsy, muscular dystrophy, generalized hypotonia) have refractory constipation that is frequently multifactorial and difficult to treat.

Anorectal disorders producing constipation include anal fissures, anal stenosis, anterior ectopic anus, and extrinsic masses that partially obstruct the rectum. Fissures may induce a self-perpetuating cycle of

withholding and worsening of constipation that causes reinjury. Congenital anal stenosis is characterized by straining during the production of small-caliber stools; it is frequently diagnosed during infancy. The anal canal is noted to be narrow and not distensible during digital examination. Occasionally, chronic constipation is caused by a subtle anorectal malformation known as anterior ectopic anus, in which the anal orifice is misplaced anteriorly so that the stool bolus must turn anteriorly at the perineum to exit. The parents may report seeing a perineal bulge

when the infant attempts to defecate. Surgical reconstruction may be necessary in children who fail to improve with medical therapy. In rare cases, constipation is a manifestation of an intermittent or partial extrinsic obstruction of the rectum by a rectal duplication cyst or by a pelvic mass such as a neuroblastoma, presacral teratoma, or ovarian tumor.

Spinal cord lesions affecting the second, third, and fourth sacral nerves are associated with both sensory and motor deficits affecting defecation. Trauma to the sacral cord, intraspinal and extraspinal tumors, and congenital malformations that can alter the spinal cord function should be suspected when constipation is accompanied by abnormalities in bladder function or gait, or when there are visible abnormalities or palpable findings over the lumbosacral spine, including hair tufts, dimples, pigmentary abnormalities, or a deviated gluteal cleft.

Metabolic and endocrine disorders associated with constipation include hypothyroidism, hypercalcemia, diabetes insipidus, hypokalemia, and plumbism. These conditions generally do not manifest with chronic constipation as a sole symptom.

Both cystic fibrosis and celiac disease can cause constipation. Physicians should be alert to these possibilities in children with poor growth in weight or height, recurrent respiratory complaints, anemia, or hypoproteinemia.

Many medications and toxins are reported to cause constipation (see Box 134-2).

Recently, 2 reports have linked constipation to cow milk protein allergy. In a study of a referral population of 65 children who had treatment-resistant chronic constipation, 44 had a positive therapeutic response to the substitution of soy milk for cow milk. Questions remain, however, about the generalizability of these findings to the primary care setting.

Box 134-3 presents a diagnostic approach for children thought to have an organic cause of their constipation.

## COMMON PRESENTATIONS OF FUNCTIONAL CONSTIPATION

### Infancy

Particularly in the first 6 months of life, parental notions of what constitutes constipation may be incorrect. Breastfed infants may have a mushy stool as infrequently as once a week. In the otherwise healthy infant, this situation does not deserve the label constipation and requires no intervention. In general, stool consistency rather than frequency is the critical determinant of constipation in the infant. Parents also worry about infants who strain or grunt excessively (often turning deep red) in the course of producing a soft stool of normal caliber. Manometric studies have documented the presence of a functioning rectoanal inhibitory reflex at birth, and infants exhibiting this behavior are likely attempting, unsuccessfully, to coordinate the voluntary with the involuntary components of defecation.

The truly constipated infant, who does require treatment, typically displays a pattern of straining associated with either the production of a desiccated

### BOX 134-3 Studies in Children With Constipation

- For growth failure, failure to thrive, short stature
  - Thyroid function tests
  - Celiac panel
  - Sweat test
  - Hirschsprung disease
- For delayed passage of meconium
  - Anorectal manometry
  - Rectal suction biopsy
  - Unprepared contrast enema
  - Sweat test
- For hair tufts, lipomas or hemangiomas overlying the lumbosacral spine and for abnormalities of gait, urination, absence of anal wink or cremaster reflex
  - Consider imaging the lumbosacral spinal cord (ultrasound, magnetic resonance imaging)
- For refractory constipation
  - Thyroid function tests
  - Serum calcium
  - Potassium
  - Lead
  - Celiac panel
  - Sweat test

Routine studies of children who are thought to have functional constipation are not recommended.

plug of stool followed by loose stool or by the production of a consistently desiccated stool that has a pebbly consistency.

### Toddlers

Although parents of toddlers are usually aware of when their child is constipated, they frequently do not recognize stool withholding. During the act of withholding, the child may hide quietly, clinging to an inanimate object, while squeezing the buttocks together. Numerous variations of stool-withholding behavior exist, including crouching, dancing or walking on tip-toes, and crying out in anticipation of the pain. Not infrequently, these episodes are misinterpreted by the parents as valiant attempts to defecate, and they generate great concern. Eliciting a history of stool withholding is critical for both diagnostic and therapeutic purposes.

### Childhood

Once the child has attained privacy in the bathroom, parents are not likely to be involved in the toilet routine, and constipation becomes occult. The child often goes to the bathroom with a regular or increased frequency but during defecation passes only a small, hard piece of desiccated stool. Not infrequently, the child emerges from the bathroom not terribly bothered. The parent inquires, "Did you go?" The child answers, "Yes." Thus both parties are happy. This stooling pattern, known as incomplete evacuation, is

**BOX 134-4 Findings That Support the Diagnosis of Functional Constipation**

- Onset after infancy
- Presence of stool-withholding behavior
- Absence of red flags
- Episodic passage of large-caliber stools

common in school-age children and is punctuated episodically by the passage of massive bowel movements. Many children do not seem very bothered by their constipation and are brought in by their parents not for the constipation itself but rather for associated phenomena, such as soiling, recurrent abdominal pain, blood streaks seen on the stool, excessive flatus, or anorexia. Finally, pelvic floor dyssynergia seen in children with stool withholding can affect urinary voiding dynamics, predisposing some to enuresis or urinary tract infection. Box 134-4 lists features that support the diagnosis of functional constipation.

**EVALUATION**

Functional constipation frequently can be diagnosed by history, physical examination, and therapeutic response to a comprehensive treatment regimen. The history should incorporate the frequency, consistency, and caliber of the stools that the child passes, as well as the age of the child at the onset of constipation. The newborn history should specifically establish whether the child passed meconium in the first day of life. A history of the child's toilet-training experience and whether traumatic toileting experiences occurred is critical in toddlers and preschool-aged children. The diet history can establish whether the onset of constipation occurred concurrently with the transition to cow milk or with periods of high protein intake (excessive cow whole milk consumption).

Common complications of constipation should be assessed: fissures, bleeding, abdominal pain, anorexia, enuresis, and urinary tract infection. A history of distention and vomiting is explored because they are not caused by functional constipation. Eliciting a history suggesting stool withholding is critical because it strongly supports the diagnosis of functional constipation and should be addressed in the therapeutic plan. Details of prior evaluations and treatments should be explored, including over-the-counter medicines, home remedies, alternative therapies, and culturally specific therapies that can be incorporated in the treatment plan, if they pose no harm.

Specific questions should address the differential diagnosis. Symptoms of Hirschsprung disease, as well as endocrine, metabolic, and neurologic disease, should be sought. The possibility of an occult spinal process affecting the sacral nerves can be addressed by inquiring about any changes in the urinary voiding

pattern (urinary stream or urinary continence) or in the child's gait. The family history covers heritable conditions in the differential diagnosis and a family history of functional constipation, which has been shown to have a heritable component. A developmental history may also be important.

On physical examination, the child's growth parameters, including recent growth velocity, should be normal. The child should appear well and not wasted or malnourished. The abdomen should not be distended, and the examination should establish the presence or absence of a fecal impaction in the lower quadrants or in the hypogastric area. The external examination of the perineal area is performed to establish normal placement of the anal orifice and to look for evidence of soiling, fissures, skin tags, and a normal anal wink in response to touch.

When a rectal examination can be done with the child's cooperation, it should be part of the evaluation. In most children who have functional constipation, desiccated stool is found in the rectal vault on rectal examination. For older children who have long-standing constipation and a megarectum, chronic rectal distention may efface the internal sphincter along the rectal wall, making the anal canal feel foreshortened. Children who soil from chronic constipation with a megarectum have only a sensory disorder; thus, the tone of the internal sphincter should be normal. The examiner should be alert during the digital examination for the rare situation in which an extrinsic mass is compressing the rectum. A patulous anus is indicative of a neurologic lesion or of sexual abuse involving the anus. Especially in infants, an empty rectum on digital examination raises the possibility of Hirschsprung disease, particularly in conjunction with an explosive gush of stool on withdrawal or a hard, impacted mass palpated in the pelvis or lower abdomen. Impactions in infancy are unusual and may indicate Hirschsprung disease. In the older child who has functional constipation, an empty rectum may be found occasionally if the child has just defecated. Nonetheless, the possibility of Hirschsprung disease should be considered carefully.

The evaluation should continue with an examination of the spine, looking for a dimple, hair tuft, or palpable vertebral deformity (signs of spina bifida occulta), and from this evaluation to a thorough neurologic examination that explicitly assesses the tone, strength, symmetry, and reflexes of the lower extremities and to an analysis of the patient's gait.

Routine laboratory tests are not indicated in evaluating for functional constipation. In addition, a recent systematic review has shown that plain abdominal radiographs do not have significant diagnostic value. Nonetheless, plain radiographs of the abdomen can be used selectively for confirmation that an abdominal mass appreciated on physical examination is indeed a fecal impaction.

Children thought to have Hirschsprung disease should be discussed with a consulting surgeon and radiologist to decide on the choice of initial diagnostic testing, keeping in mind that rectal biopsy is the gold standard. Box 134-5 presents red flags in constipation.



**BOX 134-5 Red Flags in Childhood Constipation**

- Failure to thrive, weight loss, poor growth
- Vomiting
- Abdominal distention
- Persistent anal fissures, perianal disease
- Persistent blood in stool or guaiac-positive stool
- Delayed passage of meconium
- Weak urinary stream, diurnal enuresis

**TREATMENT**

Treatment of constipation involves laxatives, parental education, diet, and behavioral modification. Consideration must be given to the age of the patient and the duration of symptoms. Whereas transient constipation of several days' duration typically can be managed with 1 to a few days of laxative use and dietary change, most patients who have functional constipation are affected for weeks to months before coming to attention and require a phased approach and months of treatment. Successful treatment of functional constipation in older children may even require 1 to 2 years of laxative therapy. Ultimately, the goals of treatment are to establish a pattern of soft bowel movements at a regular frequency (at least 3 per week), to wean the child from pharmacotherapy, and to have the child and family manage the problem on their own with diet and behavioral modification.

**Treatment of Infants**

Before they are introduced to infant food, constipated infants can be treated by the addition to the diet of undigestible, osmotically active carbohydrates: either dark corn syrup or malt soup extract can be added to the formula in a dose of 2 to 6 teaspoons divided in several bottles per day. Once juice and infant food are introduced, apple or prune juice and fruits can be added to the diet. Infant glycerin suppositories can be used at the beginning of therapy to remove a desiccated rectal plug but should not be the mainstay of therapy because infants can become behaviorally conditioned to depend on rectal stimulation to initiate defecation. Infants should not receive mineral oil because of the risk for pneumonia from aspiration. Externally visible anal fissures should be treated with petroleum jelly. Two studies have established the efficacy of polyethylene glycol (PEG) in infants. Infants whose constipation is refractory to these measures should be referred to a pediatric gastroenterologist.

**Treatment in Toddlers and Older Children**

The treatment of established constipation is divided into 3 phases: (1) education and disimpaction, (2) maintenance, and (3) weaning. This method has been adopted widely by pediatric gastroenterologists and advocated in published guidelines.

**Education**

The treatment of constipation begins with parental education regarding the pathogenesis of constipation. Particular focus is given to the concept that, once established, constipation frequently engenders withholding, which is self-perpetuating. Toddlers, in particular, require several months of laxative treatment that produces soft stools before they abandon this behavior. Parents should be instructed to ignore stool withholding events as they would a temper tantrum. At times when the child is not withholding, parents should talk directly to toddlers and engage them in the therapeutic program: "I want you to push the poo-poo out of your body; don't hold it in. That's how you will get better, and it will stop hurting!"

Physicians should address the widely held misconceptions that long-term laxative use in childhood is not safe or engenders laxative dependence. This fear, compounded by a general reluctance to medicate children for what is widely perceived as a transient problem, almost always leads to premature discontinuation of therapy. In fact, innumerable studies have established that nonstimulant laxatives such as mineral oil, milk of magnesia, PEG, and lactulose do not result in dependence. On the other hand, experts discourage the prolonged use of stimulant laxatives (Senna, Bisacodyl), but the limited use of Senna, an anthraquinone-stimulant laxative, is acceptable.

**Disimpaction**

Treatment begins with disimpaction in the toddler or child who has had months to years of symptoms or an impaction on examination. For children attending school, disimpaction treatment (Table 134-2) should be deferred until the weekend; in the interim, the child can be treated with mineral oil to lubricate the impacted stool. Enemas once a day for 3 to 6 days are simple and effective and, with some important caveats, are safe. Dose guidelines should be followed, and the child should be brought to medical attention in the rare event of failure to stool following an enema. Sodium phosphate enemas are contraindicated in children who weigh less than 10 kg, in those who have any cardiac or renal impairment or electrolyte disorders, and in those who may have any form of intestinal obstruction. In 4- to 11-year-old children, a comparison of daily oral PEG for 6 days versus daily enemas for 6 days showed equal efficacy in resolving fecal impactions. The choice of enemas versus the oral route should be made with the child and family's input.

The goal of disimpaction is to remove all the hard-formed stools throughout the colon. A follow-up telephone call after 2 to 3 days can ascertain whether the child is still passing hard stools. Any questions about whether the disimpaction phase of treatment is complete should prompt a revisit for an abdominal and rectal examination or an abdominal radiograph. Last, children who have extremely hard or treatment-resistant impactions can be admitted for nasogastric administration of a PEG solution or surgical disimpaction. Failure to achieve a thorough disimpaction, a

**Table 134-2** Regimens for Older Toddlers and Children Who Have Chronic Constipation<sup>a</sup>**LAXATIVE DOSAGES****DISIMPACTION****Enema**Hypertonic sodium phosphate<sup>a,b</sup>

3 mL/kg/dose, once daily via rectum for 3–6 days, maximum 135 mL

Mineral oil

30–60 mL, once daily via rectum for 1–6 days

**Oral**

Polyethylene glycol, electrolyte free

1.5 g/kg/day, maximum 100 g for 3–6 days

Mineral oil

30 mL/year of age to maximum 8 oz twice daily for 3 days

Polyethylene glycol with electrolytes

10–40 mL/kg/hr, via nasogastric tube (maximum 2 L/hr) until stool effluent clear

**MAINTENANCE**

Polyethylene glycol, electrolyte free powder

0.8–1.5 g/kg/day

Mineral oil

1–3 mL/kg/day

Milk of magnesia

1–3 mL/kg/day

Lactulose 10 g/15 mL

1–2 mL/kg/day

Senna syrup 218 mg/5 mL<sup>b</sup>

10–20 mg/kg/dose po qhs

<sup>a</sup>Not recommended for children younger than 2 years of age.<sup>b</sup>See maximum doses in the *Physicians' Desk Reference*.

common therapeutic mistake, undermines successful treatment because laxatives given in maintenance doses do not penetrate or remove the impaction. For the same reason, fiber is withheld during the disimpaction phase of treatment.

**Maintenance**

The maintenance phase of treatment follows disimpaction and should incorporate laxative use and dietary and behavioral advice. Maintenance doses of laxatives are listed in Table 134-2. Telephone follow-up within 2 to 3 days of starting therapy is essential so that the laxative can be titrated to a dose that induces a daily soft bowel movement. Results of a Cochrane review support both PEG and mineral oil as superior to other agents for the treatment of constipation. If mineral oil is used, then it should not be prescribed to children younger than 2 years or to children who are at risk for pulmonary aspiration. PEG has gained wide use for the treatment of functional constipation. PEG, an osmotic laxative, is a polymer of ethylene glycol that is not absorbed or fermented by colonic bacteria. One appeal of PEG is that it is a fairly tasteless, water-soluble powder that can be disguised when mixed into a child's drink. Pediatric studies of PEG have established clinical tolerance, effective dose, and the absence of unanticipated or serious adverse effects in small groups of study subjects.

A recent systematic review of nonpharmacologic therapies for childhood constipation concluded that apart from an increase in fiber intake, other therapies such as an increase in fluid intake, the addition of probiotics/prebiotics to the diet, an increase in physical activity, and yoga are not studied to the point at which they can be offered as evidence-based recommendations. These therapies deserve further study because they may be beneficial and are associated

with little harm. The addition of dietary fiber is a widely advocated adjunct to the treatment of childhood constipation, and a recent randomized controlled trial has shown benefits of a fiber supplement when prescribed with a laxative. Alternatively, dietary changes that increase the child's fiber intake can be made and include the introduction of whole-grain breads and cereals and increasing the child's fruit and vegetable intake.

Simple behavioral advice has been a mainstay of treatment recommendations. For toddlers, the focus is on replacing stool-withholding behavior with deliberate attempts to defecate. Toilet-training efforts are deferred until the child stops withholding. For older children, a behavioral modification program of sitting on the toilet for 5 to 10 minutes after meals to capitalize on the gastrocolic reflex is recommended, with success rewarded by the use of a star-chart system: the child should be rewarded for the targeted behavior (sitting). The physician is responsible for titrating the laxative dose to achieve the desired effect (a soft bowel movement every day), which requires an active partnership with the child and parents, who need to report to the physician frequently. Referral to a child behavior specialist or psychiatrist is warranted when toileting is the focus of a power struggle or when a significant mental health problem complicates the treatment regimen.

**Weaning From Maintenance Therapy**

Weaning, as opposed to abrupt cessation, of laxative therapy is the next phase of treatment. Successful weaning can occur following 6 to 12 weeks of maintenance treatment in some toddlers but may not be possible for 6 to 12 months in older children. Typically, the daily laxative dose is decreased to 75%, 50%, and 25% of the initial dose over successive months, or the full dose is given every second day for

### BOX 134-6 Common Reasons for Treatment Failure of Functional Constipation

- Reliance on dietary advice alone
- Inadequate disimpaction
- Failure to escalate laxative dose to achieve 1 to 2 soft stools per day
- Failure to address widely held notion that laxatives are addictive, leading to premature discontinuation
- Relying on dietary fiber alone

6 to 8 weeks and then every third day for another 6 to 8 weeks. Efforts to increase the child's fiber intake and to comply with the behavioral program are redoubled during weaning. Older school-aged children are encouraged to practice self-monitoring of the frequency and adequacy of their bowel movements, and a rescue plan for an enema, a suppository, or a dose of stimulant laxative must be in place for a transient relapse (no stool for longer than 3 days) that may occur during weaning. The inability to wean from laxatives after 12 months of therapy is not uncommon in functional constipation but may reasonably justify referral to a pediatric gastroenterologist. Box 134-6 presents common reasons for treatment failure of functional constipation. Remaining optimistic and involved at this point is important because improvement beyond 12 months of therapy is well documented.

#### WHEN TO REFER

- Abnormal studies
- Findings that are inconsistent with functional constipation (growth failure, distention, vomiting, bleeding)
- Significant behavioral, emotional, and parenting problems complicating treatment
- Refractory to comprehensive treatment regimen

#### WHEN TO ADMIT

- Constipation associated with obstruction or enterocolitis
- Failure of disimpaction as an outpatient

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Constipation and Your Child* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Constipation* (Web page), American Academy of Pediatrics (www.healthychildren.org/English/health-issues/conditions/abdominal/Pages/Constipation.aspx)
- *Everyone Poops* (book), Kane/Miller Book Publishers
- *Guide to Toilet Training* (book), American Academy of Pediatrics (shop.aap.org)

- *Toilet Training* (Web page), American Academy of Pediatrics (www.healthychildren.org/English/ages-stages/toddler/toilet-training/Pages/default.aspx)
- *Toilet Training* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)

#### Medical Decision Support

- *Constipation in Infants and Children: Evaluation and Treatment* (guideline), *Journal of Pediatric Gastroenterology and Nutrition*, Vol 43, Issue 3, 2006

### AAP POLICY

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## Chapter 135 COUGH

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### INTRODUCTION

Cough is among the most common complaints of children. Although generally resulting from acute viral infections and therefore self-limited, cough may be the harbinger of a more serious problem. Because cough can be exceedingly disruptive to the child and family, it can lead to significant anxiety for all involved parties. Allaying this anxiety through appropriate diagnosis and management is of prime importance to the primary care physician.

### PATHOPHYSIOLOGIC FEATURES

Cough can be described as a forceful exhalation. Its primary purpose is to facilitate the removal of inhaled irritants and secretions from the airway. The cough reflex can be triggered by stimulation of the cough receptors located at all levels of the respiratory tract, beginning at the sinus level and extending caudally throughout the respiratory tree and ending at the terminal bronchi. It also includes the auricular branch of the vagus nerve (Arnold nerve), which carries afferent impulses from the concha of the ear and posterior portion of the external auditory canal. Impulses from

these cough receptors travel through the cranial nerve afferent pathway to the medullary cough center. The reflexive efferent response of this activation causes the coordinated activity of glottic closure and diaphragmatic, chest wall, abdominal, and pelvic floor contraction, resulting in cough.

The cough sequence can be divided into 3 classic phases. The first phase, termed the inspiratory phase, results in a deep inspiration ending in glottic closure. During the short second phase, termed the compressive phase, intrathoracic pressure increases as a result of coordinated contraction of the expiratory muscles. With the expiratory third phase, the glottis opens rapidly, leading to the sudden, sometimes explosive, release of the pent-up intrathoracic air (ie, cough). Coupled with this third phase, secretions and irritants are expelled from the airway. Incomplete or inefficient removal of these materials will result in recurrence of the cough sequence, as will ongoing irritation or inflammation.

## CLASSIFICATION

Many classification schemes for cough have been developed over the years, and each has its benefits and limitations. Ultimately, any useful classification scheme must help in planning an efficient and successful evaluation and management plan. When classifying cough, 2 basic questions need to be addressed. First is whether the cough is acute or chronic (>4 weeks' duration), with chronic cough likely requiring a more extensive evaluation plan. The second question is whether the cough is triggered by upper, lower, or combined airway pathology (although the effect of the upper airway on the etiology of cough is somewhat controversial), and whether it is specific or nonspecific. This is not always apparent, especially in younger children, but is critical to determine to minimize unnecessary testing, treatment, or both.

## DIFFERENTIAL DIAGNOSIS

In considering a functional differential diagnosis, the physician should try to answer the above 2 questions on the initial assessment. In this regard, the character of the cough can sometimes be helpful, with *croupy*, *throaty*, and *honking (foghorn)* coughs being more likely to originate in the upper airway. However, young children with asthma (clearly a disease of the lower airways) may initially exhibit a croupy cough, presumably from the physiologic narrowing of the subglottic space in children younger than 4 years.

At the other extreme, although a productive cough with expectoration of sputum is classically associated with lower airway inflammation (eg, pneumonia, asthma), children with severe chronic sinusitis (a disease of the upper airway) will often cough and expectorate or swallow thick sputum, which may at times even be tinged with blood. Therefore, cough character, although helpful, should not limit the differential diagnosis. A variety of qualities attributed to cough character have been described that can be useful starting points in the evaluation of cough, including paroxysmal for pertussis; staccato for *Chlamydia* infection; barking for laryngotracheal infection; throat

clearing for postnasal secretions; and honking for habit cough syndrome. History and pattern of illness progression are crucial for putting these cough qualities into perspective. For example, cough that occurs only during the daytime, increases with attention, and does not limit or change with physical activity is more likely habit cough syndrome. However, such a cough can also indicate tracheal pathology if it does not possess all of these characteristics. In contrast, if the cough clearly increases with activity and limits the child from participating in desired physical activities, then asthma is a likely diagnosis. Night cough is frequently seen with asthma; however, when nasal symptoms are present it could also suggest allergy or sinusitis (or both) as triggers; cough during feeding suggests swallowing dysfunction or tracheoesophageal fistula with aspiration; and cough after feeding with spitting up, retching, or arching of the back suggests gastroesophageal (GE) reflux.

Age of onset is also an important feature in planning a workup. Chronic or recurrent cough that begins in early infancy, especially in children younger than 3 months, suggests a congenital or anatomic origin and clearly requires a more aggressive evaluation. These children are also at risk for protracted bacterial bronchitis, although the effect of this entity is still being delineated. Similarly, an aggressive approach should be considered when cough begins relatively suddenly, especially in toddlers, since this might suggest foreign-body aspiration. In both of these scenarios visualization of the airway using bronchoscopy should be considered early in the evaluation process. Cough beginning at more than 6 months of age may suggest airways hyperreactivity, and a therapeutic trial of treatment with a  $\beta$ -2 agonist may be a reasonable first step. Cough beginning relatively suddenly in adolescents, especially at times of psychosocial stress, might indicate a psychogenic origin.

Classifying cough in this way, using key historical information, can provide a useful starting point in developing a differential diagnosis. Studies have shown that an organized approach to the assessment and management of cough can greatly improve diagnostic and treatment success.

## EVALUATION

### History

#### Personal and Family History

The history from a patient complaining of cough should begin with an accurate description of the cough, with a focus on the pattern and progression of symptoms. The duration of cough; the frequency of discrete cough episodes; quiet periods between cough (daily cough vs days or weeks between cough episodes); and the quality, timing, and triggers of the cough are all important pieces of information to help make an accurate diagnosis. Associated fever suggests a respiratory tract infection; cough worsening with exercise suggests asthma; and night cough in the absence of any other daytime symptomatology may suggest a postnasal drip, as with allergy or sinusitis. Past history is also important. Previous episodes, especially with a recurrent pattern of spring and fall



seasonal variation, may suggest allergy, and chronic cough with poor weight gain suggests a more severe systemic illness such as cystic fibrosis or an immune deficiency. Family history can be especially helpful with more chronic symptoms. A family history of allergies, atopy or asthma makes these diagnoses far more likely in the child with chronic or recurrent cough, given that a history of asthma or atopy in first-degree relatives confers a 2- to 4-fold increase in risk of asthma in the child. Similarly, a family history of early childhood death related to infection makes an immune deficiency more likely.

### Neonatal History

Neonatal history is similarly important because pre-term infants are more likely than full-term infants to have persistent airways hyperreactivity, laryngotracheomalacia, and GE reflux. Infants with poor Apgar scores, perinatal hypoxia, or a difficult postnatal course may have central nervous system sequelae and therefore have suck or swallow dysfunction, increasing the risk of aspiration. Finally, associated congenital abnormalities (eg, diaphragmatic hernia) may result in pulmonary hypoplasia, leading to chronic respiratory dysfunction and recurrent pneumonia.

### Environmental History

Environmental history is also important in determining the source of cough. Children who live in households with smokers have significantly more respiratory infections and asthma symptoms than children not exposed to secondhand smoke. Exposure to molds from household water leaks, decaying garbage, vegetation or ineffective cleaning of bathroom tile; dust mites from mattresses, pillows, stuffed animals, or forced air heating systems; and roaches, mice, and household pets all increase the risk of allergy and asthma symptoms. Exposure to other children through school, child care, babysitters, or school-aged siblings all make recurrent respiratory tract infections far more common. Even thirdhand smoke, residual chemicals from tobacco use which remain on surfaces such as walls, clothing, and even hair, may play a role in chronic cough.

### Physical Examination

The physical examination plays a critical role in pinpointing the trigger for the cough and identifying signs of a more serious underlying or chronic condition. A nasal speculum examination can help determine the color and quality of the nasal mucosa, as well as the presence or absence of nasal secretions. Inflamed nasal mucosa, coupled with thick secretions, suggests rhinitis; when the symptoms have been prolonged, sinusitis can be considered. Associated maxillary, ethmoid or frontal sinus tenderness and pharyngeal drip with a cobblestone appearance (lymphoid hyperplasia) further support the diagnosis of sinusitis. Halitosis may also be present. In contrast, pale, boggy, swollen nasal mucosa makes allergic rhinitis more likely. Associated atopic symptoms, such as eczema, further support this diagnosis. Other features of the pharyngeal examination can also be helpful. Chronic pharyngeal inflammation, in the absence of

other signs of acute infection, suggests GE reflux. Oral mucosal ulcerations or thrush suggests an immune deficiency. When pertussis is a consideration, cough paroxysms triggered by a tongue depressor support the diagnosis. Signs of an acute infectious process, such as fever, adenopathy, pharyngitis, or rash, are important to appreciate but do not necessarily rule out a predisposing condition, especially when the pattern of illness suggests chronicity or frequent recurrence. A thorough assessment of other body systems is important in judging whether a more global workup is necessary. Growth failure, poor developmental milestone achievement, clubbing, heart murmurs, hepatosplenomegaly, and chronic lymphadenopathy are all potential clues to a more severe underlying process.

A thorough examination of the respiratory system is critical in making an accurate diagnosis. Stridor and inspiratory rhonchi or wheeze suggest upper and large central airway disease, whereas rales, expiratory rhonchi, and wheeze are indicative of lower or distal airway inflammation. Similarly, a change in the quality of air exchange can be an early finding in asthma and other diseases of airways obstruction.

An accurate lower airway examination depends on the cooperation of the patient. Wheeze and distal airway sounds can be masked by a patient's vocalization or crying. Similarly, force of airflow insufficient to uncover milder changes may mask both inspiratory and expiratory findings in infants and children who do not take deep breaths on command. Every effort should be made to place the child at ease during the examination. Game playing, such as blowing on a feather or blowing up a balloon, can be helpful. In younger children and infants, the examiner can mimic a forced expiratory maneuver by firmly but gently compressing the anteroposterior chest wall inward once the child has begun voluntary exhalation. This approach will frequently uncover milder degrees of wheezing previously not appreciated with passive breathing. The examiner should allow the child to begin exhalation passively before performing this maneuver to ensure that the glottis is relaxed and the procedure proceeds safely and effectively.

### Laboratory Evaluation

#### Hematologic Tests

Acute cough rarely needs extensive laboratory assessment. A detailed history and physical examination are usually sufficient to reach an accurate presumptive diagnosis, and response to empiric therapy will confirm this assessment. In cases where this approach does not lead to a resolution of symptoms, or when the cough is either recurrent or chronic, an organized approach using a standardized algorithm has proven to be very helpful in identifying the cause and optimizing treatment, thereby shortening the duration of cough. A complete blood cell count (CBC) with differential may help distinguish a bacterial from a viral cause if infection is suspected. However, localized infections such as sinusitis are not always accompanied by an elevated white blood cell count with a shift to the left. The total eosinophil count on the CBC may be an important clue to atopy. Similarly, an elevated IgE level or positive nasal smear for eosinophils would

further corroborate the diagnosis of allergy and suggest the possibility of asthma. Although increased polymorphonuclear leukocytes on a nasal smear may suggest rhinosinusitis, the result is difficult to quantify, and the test may be misleading. Ultimately, if sinusitis is suspected, empiric therapy should be initiated based on history and physical examination, and response to therapy should be monitored. Advanced imaging techniques (computed tomography) can be considered in complicated cases.

### **Gastroesophageal Tests**

When aspiration or GE reflux (although the effect of GE reflux as a trigger for cough has not been clearly proven) is a consideration, a barium swallow (modified for aspiration and standard for GE reflux) may be useful. Although barium swallow is of limited use in diagnosing GE reflux (approximately 40% false negative), looking for anatomic causes related to esophageal abnormalities such as partial obstruction, tracheoesophageal fistulae, and vascular rings, is important in infants. Monitoring with a pH probe is the gold standard for diagnosing GE reflux; however, many experts suggest a period of empiric therapy if reflux is suggested by history and physical examination findings, with the pH probe being reserved for patients in whom primary empiric treatment fails.

### **Pulmonary Function Tests**

Early use of pulmonary function testing can be very helpful in making the distinction between upper and lower airways disease and differentiating obstructive from restrictive changes. Children must be old enough to exhale fully and inhale forcefully on command, and the test should be reproducible to ensure accuracy and reliability of results.

Flattening of the inspiratory portion of the flow-volume loop suggest upper airway obstruction, whereas changes in the ratio of the forced expiratory volume in the first 1 second to the forced vital capacity of the lungs ( $FEV_1/FVC$ ) or the forced midexpiratory flow rate over the middle half of the FVC ( $FEF_{25\%-75\%}$ ) indicate airways obstruction consistent with distal disease. Reversibility of these changes (20% improvement) with a  $\beta$ -2 agonist confirms the diagnosis of asthma and leads to effective therapy.

In younger children, 3 to 6 years old, impulse oscillometry may be used to assess airways resistance and response to bronchodilators. This can be helpful in children too young to perform formal spirometry. Infant pulmonary function testing can be used in even younger ages; however, the results are less reliable and require a high level of expertise to be performed accurately.

### **Other Tests**

Chest radiograph is important when cough is chronic and no clear diagnosis is evident on first assessment. Other tests, such as the sweat test, tuberculin skin test, immunologic studies, and alpha-1 antitrypsin levels (although these patients characteristically present with lung disease in the third or fourth decade of life), can all be useful in the proper clinical setting. Bronchoscopy can be useful to diagnose

abnormalities of both the upper and lower airways and should be considered in patients with chronic symptoms not responsive to empiric treatment. It is especially helpful in confirming the diagnosis of protracted purulent bronchitis and directing appropriate antimicrobial therapy. Furthermore, it is the test of choice when a foreign body or chronic aspiration are considered likely. In cases in which an upper airways origin is likely, flexible bronchoscopy (vs laryngoscopy) is still preferred to make the definitive diagnosis since lesions below the vocal cords up to the thoracic inlet can still be the cause of upper airway symptomatology.

## **TREATMENT**

Once the history and physical examination have led to an initial assessment, the fact that cough is a symptom of an underlying condition should be discussed with the patient and family. Treatment of the underlying disorder (if necessary) should always be the prime focus. Empiric therapy, based on primary assessment, can be a reasonable starting point. Judicious use of laboratory testing, as previously discussed, can be helpful in confirming the diagnosis and allaying parental anxiety. Furthermore, in some conditions, cough is an important component of the body's natural response to the primary illness, and suppressing the cough in the absence of effective therapy of the primary disorder may actually worsen the problem.

Treatment of the underlying disorders causing cough is discussed in other sections of this book; this chapter is limited to a review of medications used to treat cough itself. The decision to use a cough medicine as an adjunct to the treatment of the primary disease is left to the primary care physician and family. When cough is limiting or otherwise debilitating the patient, symptomatic treatment may be attempted; however numerous studies question whether over-the-counter cough preparations offer any significant clinical benefit. In addition these cough and cold medications should not be given to children younger than 4 years because serious and potentially life-threatening side effects can occur from their use. Finally, several studies have shown that honey may be beneficial in children older than 2 years of age.

### **Expectorants**

Expectorants such as guaifenesin (formerly known as glyceryl guaiacolate) may be used in an attempt to make secretions more fluid and reduce sputum thickness, however the effectiveness of this treatment has been called into question. This therapeutic approach may be useful when drainage of secretions is important, as with sinusitis. Because expectorants work by increasing the fluid content of secretions, water is probably the most effective expectorant. Saline nose sprays can make secretions more fluid and easily cleared by the patient and systemic hydration, but not overhydration, should always be optimized. Despite widespread use, expectorants have not been shown to decrease cough in children. Other older expectorants, such as potassium iodide and ammonium chloride, are no longer prescribed to children because of their adverse effects when used at effective doses.

### Mucolytic Agents

Acetylcysteine was previously used as a mucolytic agent to help liquefy thick secretions, especially in diseases such as cystic fibrosis; however, its propensity for inducing airway reactivity and inflammation has lately made it less popular.

### Cough Suppressants

Cough suppressants, which can be divided into peripheral and centrally acting agents, can be effective in transiently decreasing cough severity and frequency. Peripheral agents include demulcents (eg, throat lozenges), which soothe the throat, and topical anesthetics, which can be sprayed or swallowed. Topical agents block the cough receptors, but their effects are short-lived because oral secretions rapidly wash them away. Centrally acting cough suppressants, including both narcotic and nonnarcotic medications, suppress the cough reflex at the brain stem level. The narcotic agent most commonly used in children is codeine. Although it has been shown to be effective in adults, studies on its safety and efficacy in children are lacking. Furthermore, data from adults should not be extrapolated to children, particularly those younger than 2 years, because the metabolic pathway for clearance of codeine is immature in infants. In older children, codeine should still be avoided and only used in extreme cases and with very clear instructions because of the unpredictable and potentially dangerous variation of its metabolism in the pediatric population. Other agents, such as hydrocodone, have no demonstrated advantage and pose a greater risk of dependency. Dextromethorphan (the dextro-isomer of codeine) is the most commonly used nonnarcotic antitussive; and despite data from adults, evidence of efficacy for children is lacking.

### Decongestants

Decongestants such as pseudoephedrine can be used either topically or systemically to decrease nasal mucosal swelling. Decongestants can also facilitate sinus drainage by decreasing sinus ostia obstruction, and may work well in combination with expectorants to optimize treatment of chronic sinusitis. Care should be taken in the use of these agents because they have been shown to lead to tachyarrhythmias in individuals who use them in excess. In addition, these agents have not been studied in children and should be avoided in children younger than 2 years. Multiple reviews of the data from children between 2 and 6 years old also show lack of efficacy combined with a risk of side effects in this age group. It is therefore recommended that these agents not be used in children younger than 6 years.

### Antihistamines

Antihistamines, which can be helpful in the treatment of cough triggered by allergy, have minimal effect when cough is the result of viral or bacterial infection and may actually be detrimental because they can increase the thickness of secretions. First-generation H<sub>1</sub>-receptor antagonists may decrease nasal drip by exerting an anticholinergic effect. Additionally,

diphenhydramine may have a modest direct effect on the medullary cough center. The clinical benefits of these agents are unclear.

### WHEN TO REFER

- Cough persists despite adequate therapy of primary disease
- Cough thought to be from hyperreactive airways is not easily reversible with  $\beta$ -2 agonist
- Cough recurs more frequently than every 6 to 8 weeks
- Cough associated with failure to thrive
- Cough associated with other systemic illness

### WHEN TO ADMIT

- Patient has respiratory distress
- Infant is unable to feed
- Cough is associated with bacterial pneumonia not responsive to oral antibiotic trial

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Cover Your Cough* (flyers and posters), Centers for Disease Control and Prevention ([www.cdc.gov/flu/protect/covercough.htm](http://www.cdc.gov/flu/protect/covercough.htm))

#### Medical Decision Support

- *Managing Cough as a Defense Mechanism and as a Symptom: A Consensus Panel Report of the American College of Chest Physicians* (article), *Chest*, Vol 142, Issue 2, 1998 ([journal.publications.chestnet.org/article.aspx?articleid=1073794](http://journal.publications.chestnet.org/article.aspx?articleid=1073794))
- *A Cough Algorithm for Chronic Cough in Children: A Multicenter, Randomized Controlled Study* (article), *Pediatrics*, Vol 131, Issue 5, 2013 ([pediatrics.aappublications.org/content/131/5/e1576](http://pediatrics.aappublications.org/content/131/5/e1576))

### AAP POLICY

- American Academy of Pediatrics Committee on Drugs. Use of codeine- and dextromethorphan-containing cough remedies in children. *Pediatrics*. 1997;99(6):918–920. Reaffirmed October 2006 ([pediatrics.aappublications.org/content/99/6/918](http://pediatrics.aappublications.org/content/99/6/918))
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## Chapter 136 CYANOSIS

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### INTRODUCTION

Cyanosis is a bluish purple appearance of the skin or mucous membranes usually caused by an increased concentration of deoxygenated (unsaturated or reduced) hemoglobin (Hgb). While occasionally a benign finding, as in a healthy newborn with acrocyanosis or when observed in the lips and fingers of a child who has been in the cold ocean, acute cyanosis often indicates a significant reduction in oxygen concentration and may signify a life-threatening event. The presence or history of cyanosis requires careful evaluation.

Cyanosis occurs in all ages and may be the result of congenital or acquired disorders of the respiratory or cardiovascular systems. In the neonatal period, persistent pulmonary hypertension of the newborn (PPHN) and congenital heart disease are common causes of cyanosis, while respiratory disorders are the most common cause of life-threatening cyanosis in older children.

Observed most easily in the nail beds, the lips, mucous membranes of the mouth, the ears, the conjunctivae, and the tip of the nose, cyanosis is especially visible in buccal mucosa and beneath the tongue. At these locations, capillary beds are close to the surface and arterial and venous blood are seen together. Cyanosis can be present peripherally, centrally on the head and trunk, and also differentially with only lower parts of the body affected. The location where cyanosis is observed can help in determining the cause.

Cyanosis is made worse by vasoconstriction, so a patient should be examined in a warm environment. The perception of cyanosis depends on the quality of ambient lighting and by an examiner's ability to perceive subtle shades of blue.

To most observers, cyanosis becomes visible when the concentration of deoxygenated Hgb approaches 3 to 5 g/dL, but some reports suggest that the threshold for detecting cyanosis may be as low as 1.5 g/dL. The appearance of cyanosis is related to the absolute concentration of deoxygenated Hgb rather than to a specific oxyhemoglobin saturation (SaO<sub>2</sub>). Cyanosis in a patient with a Hgb concentration of 15 g/dL will be apparent at an arterial SaO<sub>2</sub> somewhere between 70% and 80%: 5 g/dL of Hgb is desaturated at 70% arterial saturation, and 3 g/dL is desaturated at 80% saturation. The higher the patient's Hgb concentration, the

more readily cyanosis becomes evident. For example, 5 g/dL represents one-half of the Hgb in a child with 10 g/dL but only one-third in a patient with 15 g/dL of Hgb. Thus, as Hgb concentration falls, cyanosis becomes apparent only at lower oxyhemoglobin saturations. Because Hgb concentration varies in both healthy and ill children and throughout life, cyanosis appears at different degrees of desaturation in different children and at different times.

Whereas patients becoming progressively more anemic do not manifest cyanosis until their oxygen saturations have fallen substantially, a patient who is polycythemic with a Hgb concentration of 20 g/dL, for example, might manifest cyanosis when 92% saturated (1.5 g/dL desaturated Hgb) and certainly when 75% saturated (5 g/dL desaturated Hgb). It is important to remember that in an anemic patient, a severe degree of oxygen desaturation can occur without cyanosis. Although cyanosis is always a concern, the absence of cyanosis is not necessarily reassuring in a patient with respiratory distress.

The arterial Hgb oxygen saturation measured with a pulse oximeter is referred to as SpO<sub>2</sub> to distinguish it from a saturation measurement obtained from an arterial blood gas (ABG), which is referred to as SaO<sub>2</sub>. SpO<sub>2</sub> and SaO<sub>2</sub> are often used interchangeably and are usually almost identical in the absence of significant amounts of carbon monoxide, methemoglobinemia, elevated bilirubin levels, or very poor perfusion. A pulse oximeter measures SaO<sub>2</sub> directly and permits the recognition of decreasing degrees of SaO<sub>2</sub> before cyanosis becomes visible. Screening newborns using pulse oximetry detects degrees of Hgb desaturation indicative of congenital heart disease that may not be obvious on examination.

In an ABG sampling, the pH, PCO<sub>2</sub>, PO<sub>2</sub>, and SaO<sub>2</sub> are determined in addition to other values. Depending on the type of ABG analyzer, the SaO<sub>2</sub> is measured directly in a process called co-oximetry or is calculated based on the pH, PCO<sub>2</sub>, PO<sub>2</sub>, and oxyhemoglobin dissociation curve.

### CENTRAL AND PERIPHERAL CYANOSIS

Cyanosis is described as being *central* or *peripheral* in origin. Central cyanosis occurs when the origin of desaturation is either an oxygenation defect of the lungs or the result of addition of venous blood to arterial blood from shunts or mixing lesions in the heart. In central cyanosis, the arterial blood leaving the heart is desaturated. Peripheral cyanosis occurs when blood leaves the heart and lungs fully saturated, but, from either excessive tissue oxygen extraction or sluggish blood flow in tissue beds (including some, such as the nail beds or lips, that are visible), the venous blood becomes desaturated to the extent that cyanosis becomes evident. Whether cyanosis is central or peripheral is a function of the physiologic dysfunction rather than where the cyanosis is evident on physical examination.

*Acrocyanosis* refers to bluish color in the hands and feet and around the mouth (circumoral cyanosis). The mucous membranes generally remain pink. A form of peripheral cyanosis that usually reflects benign vasomotor changes in the affected extremities, acrocyanosis



does not indicate pathology unless cardiac output is extremely low, resulting in severe venous desaturation from increased oxygen extraction.

In the newborn, acrocyanosis is a striking example of cyanosis arising from intense peripheral vasoconstriction and variable perfusion in the extremities compared with the central circulation. It is seen in well babies and resolves within the first few days of life.

Acrocyanosis may also occur in infants when they cry, regurgitate, vomit, cough, or hold their breath. This finding is often very alarming to the caregiver who witnesses the event, and it requires careful questioning and observation to differentiate it from serious underlying pathology (eg, seizure, apneic episode, cardiac arrhythmia, congenital heart defect). The child with acrocyanosis typically does not have major changes in mental status during the event and appears well on physical examination.

Moderate cold exposure slows the transit time of blood through capillary beds and allows for increased unloading of oxygen from the blood to the tissues in infants and young children, leading to cyanosis, especially in the lips and perioral region. This form of acrocyanosis rapidly resolves with warming of the patient.

## OXYGEN CONTENT, DELIVERY, AND TRANSPORT

Because deoxygenated Hgb has a dark blue to purplish color, the higher the concentration of desaturated Hgb, the bluer the blood and the more cyanotic the patient appears. Hgb desaturation and hence cyanosis result from disorders of oxygen uptake, transport, and utilization.

In an intact postnatal circulation, venous blood with a saturation of approximately 75% travels via the pulmonary artery to the pulmonary capillary bed where it becomes fully saturated upon exposure to oxygen from the alveolus across the alveolar capillary membrane. Fully oxygenated blood returns to the left atrium via the pulmonary veins and from there moves through the left ventricle to the aorta.

Oxygen in the blood is either bound to Hgb or dissolved in plasma. The amount bound to Hgb is reflected by the oxyhemoglobin saturation, and the amount dissolved in plasma is measured by the  $\text{PaO}_2$ . The role of oxyhemoglobin saturation on the oxygen content of blood is described by the equation

$$\text{CaO}_2 = [\text{Hgb}] \times \text{SaO}_2 \times 1.36 \text{ mL/g} + 0.003 \times \text{PaO}_2$$

where  $\text{CaO}_2$  is the oxygen content,  $[\text{Hgb}]$  is the concentration of hemoglobin in g/dL,  $\text{SaO}_2$  is the oxyhemoglobin saturation, 1.36 mL/g is the binding capacity for oxygen in mL/g of Hgb, and  $\text{PaO}_2$  is the tension of dissolved (unbound) oxygen in the plasma. Approximately 97% of the oxygen in blood is bound to Hgb, leaving only a small amount unbound and dissolved in blood. Delivery of oxygen to the tissues is a function of the flow of blood produced by the systemic ventricle of the heart (cardiac output) and the oxygen content of the blood.

In a normal circulation, beyond the neonatal period, arterial blood with an oxyhemoglobin saturation of

95% to 98% flows to capillary beds throughout the body, where in the course of traversing the tissue beds approximately 25% of the Hgb-bound oxygen molecules are offloaded to the tissues. This is known as oxygen consumption or utilization. The end-capillary oxyhemoglobin saturation is, on average, about 25% less than at entrance to a capillary bed. Some tissues will extract more oxygen and some may extract less. The 25% difference in oxygen content between arterial and venous blood is relatively conserved as long as cardiac output is adequate to meet tissue oxygen demands. In tissue beds with reduced cardiac output (blood flow), a higher proportion of oxygen is drawn from Hgb, resulting in greater than 25% extraction.

Hypoxemia is the term used to describe decreased oxygen tension ( $\text{PaO}_2$ ) and saturation ( $\text{SaO}_2$ ) of arterial blood. Hypoxia is the state that occurs when inadequate oxygen is delivered to tissues with resultant decreased function and a transition to anaerobic respiration.

With oxygenated arterial blood appearing red and deoxygenated venous blood usually appearing dark red or bluish, the color of a capillary bed becomes a function of the relative amounts of arterial and venous blood present in the bed. The more deoxygenated Hgb present, the bluer (cyanosed) the capillary bed appears to be. When cardiac output to a tissue falls below normal, more than 25% of oxygen may be extracted from each Hgb molecule to meet the metabolic requirements of the tissue. This increased off-loading will result in a decrease in oxyhemoglobin saturation for the end capillary blood and an increase in the arterial to venous oxygen content difference, thus making cyanosis more prominent. As the oxyhemoglobin saturation of the end capillary blood decreases, cyanosis becomes obvious.

In circumstances in which the Hgb of the arterial blood entering a capillary bed is not fully saturated with oxygen, venous blood leaving the capillary bed will be desaturated to an even greater degree and the capillary beds will look even more cyanotic. For example, if arterial blood enters a capillary bed with an oxyhemoglobin saturation of 85%, the resultant venous blood may have an oxyhemoglobin saturation of 60% after the off-loading of 25% of oxygen molecules. Thus, the blood in the capillary bed will look cyanotic. The preservation of an arterial to venous oxygen content difference of approximately 25% is used as a surrogate indicator of adequate cardiac output and tissue oxygen delivery. In the presence of adequate cardiac output and an appropriate Hgb concentration, adequate tissue oxygen delivery can occur even in the presence of significantly desaturated or cyanotic arterial blood.

## PULMONARY MECHANISMS OF CYANOSIS

The Hgb desaturation of central cyanosis can result from pathology of the airways, lungs, heart, or Hgb itself. Normally, Hgb is close to 100% saturated with oxygen when it leaves the alveolar capillary unit and slightly less than 100% when it leaves the left ventricle—there is a normal, very small amount of

venous blood shunted to the blood entering the left side of the heart from the lungs. With pulmonary disease, a disturbance of alveolar gas exchange may result in desaturated blood entering the pulmonary veins and left atrium. The desaturation of pulmonary venous blood is a key factor distinguishing desaturation caused by pulmonary disease from desaturation caused by congenital heart disease. In congenital heart disease, pulmonary venous blood is usually fully saturated even when systemic saturations may be very low. Five pathophysiologic mechanisms explain why blood does not become fully oxygenated as it travels through the pulmonary alveolar capillary beds. These 5 mechanisms of hypoxemia are mismatching of alveolar ventilation to perfusion, intrapulmonary shunt, hypoventilation, diffusion block, and breathing hypoxic gas mixtures.

In patients with parenchymal lung disease such as pneumonia, ventilation-perfusion (V/Q) mismatch is the most important mechanism for hypoxemia. For blood to become fully oxygenated, the flow of blood to an alveolar-capillary unit must match the ventilation in the unit. V/Q mismatching occurs when the relationship of alveolar ventilation to capillary bed perfusion is not appropriately balanced. The matching of ventilation to perfusion is along a continuum. At 1 extreme are alveolar capillary units that are ventilated but not perfused; these are described as having dead space ventilation ( $V/Q = \infty$ ). At the other extreme are lung units that are perfused but not ventilated ( $V/Q = 0$ ); these are described as intrapulmonary shunt, occurring when blood travels through the lungs from the right side of the heart to the left without being exposed to aerated alveoli. Between the 2 extremes is a continuous range of V/Q ratios that, overall, result in a normal ABG. In lung diseases such as acute respiratory distress syndrome, pneumonia, bronchiolitis, pulmonary edema, and asthma, most hypoxemia is the result of V/Q mismatching with only a small component from intrapulmonary shunt.

Hypoventilation occurs in patients with neurologic, traumatic, pharmacologic, or chemical suppression of respiratory drive, as well as with suffocation. A patient who develops apnea or acute upper airway obstruction caused by a foreign body will become profoundly hypoxemic and very rapidly become cyanotic. Cyanosis associated with viral laryngotracheobronchitis (croup) or pertussis (whooping cough) are examples of hypoventilation-induced hypoxemia. Any acquired or congenital abnormality of the airway that obstructs airflow can potentially cause significant hypoventilation and result in hypoxemia to the extent that cyanosis becomes apparent.

Breathing hypoxic gas mixtures occurs when victims are trapped in a hypoxic environment such as a closed-space fire or when exposed to high concentrations of gases such as methane and helium that are not in themselves toxic but induce hypoxia by displacing breathable oxygen. Another example of breathing hypoxic gas is the effect of altitude on barometric pressure. At higher altitudes, the barometric pressure, and hence the amount of oxygen available to breathe, is lower: arterial  $PaO_2$  and  $SaO_2$  thus fall in proportion to the decrease in barometric pressure.

Diffusion block occurs when the interstitial space between the pulmonary capillary and the alveolus becomes so thickened or damaged that oxygen cannot move from the alveolus to the capillary. Diffusion block is seen with pulmonary fibrosis.

The  $SaO_2$  of arterial blood depends on the effectiveness of oxygen transfer at the alveolar level but is also affected by the shunting of venous blood into the systemic arterial system through the heart or lungs. The addition of desaturated venous blood to oxygenated blood is called *venous admixture* and is the mechanism behind intrapulmonary shunt. The resultant saturation of the arterial blood is proportional to the amount and saturation of the combined blood volumes. It is the  $SaO_2$  and oxygen content of the blood volumes that are being combined that influence the resultant saturation, not the  $PaO_2$ . Breathing 100% oxygen for a prolonged time can partially correct desaturation resulting from alveolar hypoventilation, diffusion block, or V/Q mismatching, but does not correct hypoxemia resulting from intrapulmonary shunt.

## PULMONARY VERSUS CARDIAC CYANOSIS

Distinguishing whether a sick newborn or child is cyanotic for pulmonary or cardiac reasons is challenging. Cyanotic heart disease may mimic respiratory disease and vice versa. Tachypnea, retractions, nasal flaring, and grunting point toward a pulmonary cause of cyanosis. Patients with anatomic cardiac lesions as the cause of cyanosis are generally somewhat distressed from a respiratory standpoint but to a somewhat lesser extent than found with purely respiratory disease. In cyanosis from PPHN, there may be a history of a difficult delivery, meconium-stained amniotic fluid, meconium aspiration, perinatal sepsis, asphyxia, and low Apgar scores. Because there is often a component of meconium aspiration pneumonia, these newborns demonstrate severe respiratory distress.

Pulse oximetry should be obtained immediately with any suggestion of cyanosis. A hyperoxia test (see following text) may help distinguish hypoxemia for respiratory reasons, such as pneumonia or neonatal respiratory distress syndrome, from hypoxemia caused by congenital heart disease or PPHN. Early in life, the  $PaO_2$  may increase to greater than 100 mm Hg in infants with forms of cyanotic heart disease with high pulmonary blood flow such as total anomalous pulmonary venous return (TAPVR). If there is an inadequate rise in  $PaO_2$  or oxygen saturation from a hyperoxia test, echocardiography should be performed immediately to ascertain the presence or absence of a congenital heart lesion. In general, echocardiography should be performed to assess for the possible presence of congenital cyanotic heart disease (CCHD) whenever hypoxemia is not responsive to supplemental oxygen or mechanical ventilatory support.

## CYANOSIS WITH PULMONARY DISEASE

Lower airway diseases, such as viral bronchiolitis, pneumonia, and status asthmaticus, can cause cyanosis from V/Q mismatching and small degrees of intrapulmonary shunt. Bronchiolitis, most often caused by

respiratory syncytial virus (RSV), is a common disease process affecting infants in winter months. The airways become edematous and infiltrated with inflammatory cells, ultimately obstructing the lumens. In addition to signs and symptoms of respiratory distress such as tachypnea, retractions, grunting, and nasal flaring, RSV bronchiolitis is also associated with apnea that can induce deep cyanosis by hypoventilation.

Pertussis caused by *Bordetella pertussis* or *parapertussis* is often associated with cyanosis. In the paroxysmal phase, coughing paroxysms without an intervening breath can result in deep visible cyanosis. As the illness progresses over time, patients can turn blue after only a few coughs.

Upper airway obstruction presents with inspiratory symptoms often manifested as stridor, a harsh, sometimes high-pitched sound produced by vibration of upper airway structures upon inspiration. An infant with significant upper airway obstruction and stridor often demonstrates substernal retractions. Worrisome symptoms are change in voice, muffling or hoarseness, and difficulty in swallowing and handling secretions.

Croup, usually from infection with the parainfluenza virus, is the most common cause of stridor in children. Less common inciting agents include influenza, adenovirus, measles, and RSV. Croup usually occurs in children aged 6 months to 3 years. The pathophysiology involves endothelial damage, mucous production, loss of ciliary function, and edema of the subglottic region. Infants present with a history of a preceding upper respiratory infection, low-grade fever, characteristic barking cough, and inspiratory stridor. Airway radiographs may reveal subglottic narrowing.

Epiglottitis is a life-threatening bacterial infection of the epiglottis and supraglottic structures, usually caused by *Haemophilus influenzae*. Patients present with high fever, toxic appearance, and stridor. The incidence of epiglottitis has decreased significantly since the introduction of the *Haemophilus influenzae* vaccine.

Aspiration of foreign bodies is relatively common and can cause severe respiratory distress and cyanosis when an object is lodged in the trachea. Foreign body aspiration should be suspected in an afebrile infant with acute onset of coughing, choking, stridor, or wheezing. Many foreign bodies are not radiopaque, and physicians should thus have a high index of suspicion regardless of radiographic findings.

Laryngomalacia, choanal atresia or stenosis, subglottic stenosis, tracheomalacia, bacterial tracheitis, and obstructive sleep apnea are other causes of airway obstruction that may present with cyanosis.

## CYANOSIS WITH HEART DISEASE

Pediatric heart disease of several different types can result in cyanosis. CCHD results in cyanosis either from mixing of venous blood with arterial blood through intra- and extracardiac shunts or from insufficient pulmonary blood flow.

Heart disease that causes pulmonary venous congestion can result in cyanosis by leading to pulmonary edema, which forms when increased left atrial pressure

is transmitted back to the pulmonary veins and further back to the pulmonary capillary bed. Increased pressure on the venous side of the pulmonary capillary bed results in transudation of fluid from the capillary to the interstitium and from there to the alveoli. The presence of edema fluid in the alveoli overwhelms the pulmonary lymphatics, deactivates pulmonary surfactant, and results in alveolar flooding and collapse. The resulting ventilation perfusion mismatching and intrapulmonary shunt can cause severe hypoxemia and even cyanosis. Diseases that can cause cyanosis by this mechanism include mitral stenosis and mitral regurgitation. With severe systolic and diastolic dysfunction of the left ventricle, such as may result from acute myocarditis, elevated left atrial pressure can lead to the formation of pulmonary edema as described above. In dilated cardiomyopathy, the left heart can dilate to the point that the mitral valve no longer effectively separates the left atrium from the left ventricle and, with each systole, there is retrograde flow of blood into the left atrium and pulmonary veins, leading to pulmonary edema. A similar effect occurs when the mitral valve leaflets are damaged by rheumatic heart disease.

A typically noncyanotic heart lesion such as a ventricular septal defect (VSD) can result in cyanosis with the development of Eisenmenger syndrome. With a VSD, blood flows from the left ventricle to the right ventricle because of the lower resistance of the pulmonary vascular system. There is no cyanosis. However, if the VSD is unrestrictive to flow and the lesion is not corrected over time, the extra volume of blood eventually induces hypertrophic changes in smooth muscles of the pulmonary arteries with a resultant increase in pulmonary vascular resistance. The pulmonary vascular resistance may become so high that the shunt reverses direction, with blood moving in a right-to-left direction through the VSD. This results in venous blood mixing with arterial blood in the left ventricle and the development of severe desaturation and cyanosis. Fortunately, with early repair of VSDs, Eisenmenger syndrome is seen very rarely. It may be seen, however, in parts of the world where access to repair of congenital heart lesions is not readily available.

## Congenital Cyanotic Heart Disease

Cyanosis in VSD and heart failure as described above is rare; but cyanotic heart disease always results in significant cyanosis. An infant with CCHD typically develops cyanosis in the first few hours of life. Initially, cyanosis may be noticeable with crying or feeding and generally without evidence of respiratory distress. In these lesions, a patent ductus arteriosus (PDA) serves either as a means to deliver blood from the aorta to the pulmonary artery so it can be oxygenated in the lungs (left-to-right shunt) or as a means of maintaining systemic blood flow (right-to-left shunt). In many cases, patients with cyanotic heart disease either deteriorate hemodynamically or become progressively more cyanotic as the PDA closes.

The lesions of CCHD can be placed into different groups. One group, consisting of tetralogy of Fallot (TOF), pulmonary atresia, tricuspid atresia, pulmonic stenosis, and Ebstein anomaly, creates cyanosis by



obstructing pulmonary blood flow with resultant shunting of blood from the right to left side of the circulation. In dextro-transposition of the great arteries (d-TGA) and TAPVR, on the other hand, pulmonary blood flow may be normal or increased, but pulmonary venous return is anatomically separated from the systemic arterial circulation. In truncus arteriosus and double outlet right ventricle (DORV), there is mixing of arterial and venous blood with consequent cyanosis. Another group of lesions includes the left-sided obstructive lesions of hypoplastic left heart syndrome (HLHS), critical coarctation of the aorta and interrupted aortic arch that produce desaturation because of dependence on right-to-left shunting through a PDA to maintain systemic perfusion.

Simultaneous upper and lower extremity pulse oximetry measurements can be diagnostic. An  $\text{SaO}_2$  that is higher in the right arm than in the umbilical artery or lower extremities indicates that venous blood has been added to the aorta at the level of the ductus arteriosus and is known as *differential cyanosis*. With d-TGA in the presence of pulmonary hypertension or coarctation of the aorta, the saturation in the right arm is less than in the lower extremities because oxygenated blood is added to desaturated blood at the level of the PDA; this is called *reverse differential cyanosis*.

If the patient is not at a facility where echocardiography can be performed, immediate transport should be arranged to such a center. Stabilization should include initiation of an infusion of prostaglandin E1 (PGE1) at a dose of 0.05 mcg/kg/min if there is any suspicion of ductal dependent heart disease. PGE1 dilates the ductus arteriosus to provide adequate pulmonary or systemic blood flow. In that the benefits of prostaglandin are lifesaving and the drawbacks minimal, the threshold should be very low for initiating PGE1 therapy until ductal dependent heart disease is ruled out. The PGE1 infusion can be increased to a dose of 0.15 mcg/kg/min if no improvement in saturation and pulses is seen soon after initiation. It is appropriate to administer PGE1 to any infant in whom the diagnosis of CCHD is strongly suspected, even before a complete evaluation is performed. Potential side effects of PGE1 include apnea, jitteriness, seizures, and peripheral vasodilation with hypotension, as well as an increased risk of infection. Fluid administration may be necessary if vasodilation leads to hypotension, and respiratory support including intubation may be required if significant apnea occurs.

### Abnormalities of the Right Ventricular Outflow Tract

Tetralogy of Fallot, the most common congenital heart lesion that can cause cyanosis, consists of VSD, pulmonic stenosis, right ventricular hypertrophy, and an overriding aorta. On examination, the systolic murmur of pulmonic stenosis might be appreciated. Chest radiographs reveal normal cardiac size, with a rounded, uplifted apex and concavity at the site of the pulmonary artery, a “boot-shaped” heart. There is diminished pulmonary vasculature. Electrocardiogram demonstrates right axis deviation and right ventricular hypertrophy.

With TOF, the degree of cyanosis depends on the severity of the right ventricular outflow tract obstruction. With more severe pulmonic stenosis, right ventricular pressure increases and blood is shunted across the septal defect from the right to the left ventricle, bypassing the lungs. In infants with mild obstruction, symptoms of heart failure from the large VSD are likely to predominate. Other infants may have severe cyanosis on closure of the ductus arteriosus. “Tet spells” may occur with vigorous crying or dehydration: affected infants initially become hyperpneic and restless as cyanosis increases; the murmur of pulmonic stenosis softens and then disappears as pulmonary blood flow decreases; and the spell may precipitate a syncopal episode. Treatment for an acute tet spell includes putting the patient in a knee-to-chest position to increase systemic vascular resistance and administering supplemental oxygen, sedation, and a beta blocker. Ultimately, only surgical repair can provide consistent pulmonary blood flow.

Pulmonary atresia with a VSD is a more severe form of TOF that presents with severe cyanosis shortly after birth. With atresia, the prominent murmur of pulmonic stenosis characteristic of TOF is absent. If there is sufficient pulmonary blood flow from collateral vessels from the descending aorta (identified by a continuous murmur heard over the back), the patient may not require treatment with PGE1.

Neonates with pulmonary atresia and an intact ventricular septum have severe cyanosis that progresses as the ductus arteriosus closes. Patency of the ductus arteriosus is necessary for pulmonary blood flow in this lesion.

### Abnormalities of the Tricuspid Valve

With tricuspid atresia, the only outlet for blood from the right atrium is a patent foramen ovale, through which blood travels from the right to the left atrium and then to the left ventricle. From the left ventricle, blood flows via an unrestrictive VSD to the right ventricle and from there to the pulmonary artery. Tricuspid atresia may be associated with normally related or transposed great arteries. Saturation, degree of cyanosis, and blood flow depends on the relationship of the great arteries, the size of the VSD, and the presence or absence of pulmonic stenosis. If pulmonary blood flow is unobstructed, patients may have tachypnea and heart failure with minimal to no cyanosis. Physical examination is significant for an increased left ventricular impulse as opposed to other cyanotic heart diseases with an increased right ventricular impulse. A murmur may or may not be present depending upon restriction of blood flow through the VSD (a holosystolic murmur at the left lower sternal border) and the semilunar valves (a systolic ejection murmur).

Ebstein anomaly of the tricuspid valve involves the downward displacement of the valve leaflets into the right ventricular cavity. The severity of the disease is dependent on the degree of displacement and the ability of the remaining portion of the right ventricle to generate sufficient force to pump blood into the pulmonary arteries. Newborns may have massive cardiomegaly on chest radiograph, marked cyanosis, a holosystolic murmur with a gallop rhythm, hydrops,



and pulmonary artery hypoplasia. Infants with severe disease require PGE1 to maintain pulmonary blood flow until pulmonary vascular resistance has fallen and adequacy of the right ventricle and pulmonary valve can be assessed.

### Transposition of the Great Arteries

Transposition of the great arteries (TGA) is the most common cardiac lesion in neonates with cyanosis, with a male predominance. Neonates with TGA show severe cyanosis immediately after birth. There are 2 separate parallel circulations with oxygenated blood continuously circulating through the lungs and deoxygenated venous blood becoming increasingly deoxygenated as it flows through the systemic arterial circulation. Left untreated, affected neonates progress from cyanosis to tissue hypoxia, acidosis, and death. Unlike neonates with other cyanotic congenital heart lesions, these neonates have a normal volume of blood passing through the pulmonary bed. However, because their circulation is separated in parallel, neonates with TGA have very little effective pulmonary blood flow (deoxygenated blood from the systemic circulation reaching the pulmonary vascular bed) and little effective systemic blood flow (oxygenated blood that perfuses the systemic bed). The degree of mixing between the separate circulations depends on the number and size of the anatomic connections. Blood may shunt at the atrial, ventricular (if a VSD is present), or ductal level. The typical neonate with TGA and an intact ventricular septum becomes progressively more hypoxemic as the ductus arteriosus closes. Frequently, these neonates are given PGE1 until the atrial communication through the foramen ovale can be enlarged by balloon atrial septostomy performed in the cardiac catheterization laboratory or at the bedside. Clinically, the neonate with TGA is likely to appear cyanotic but otherwise healthy, with a weight appropriate for gestational age. Reverse differential cyanosis is rare but is indicative of TGA and a PDA with an associated aortic arch anomaly or pulmonary hypertension. In a neonate with TGA and an intact intraventricular septum, the chest radiograph may show a narrowed superior mediastinum with an egg-shaped cardiac silhouette (egg on a string), mild cardiomegaly, and increased pulmonary vascular markings. Surgical repair, typically by arterial switch operation, is often undertaken in the first week of life.

Truncus arteriosus is an uncommon lesion characterized by a single arterial trunk that originates from the heart and supplies the systemic, pulmonary, and coronary circulations. A large VSD is usually present, which allows total mixing of the 2 circulations. The degree of cyanosis depends on the amount of pulmonary blood flow, which is determined by the pulmonary vascular resistance and any concurrent pulmonic stenosis. Radiographs usually show cardiomegaly.

With TAPVR, pulmonary veins drain ectopically into the systemic venous circuit and ultimately into the right atrium, resulting in complete mixing of oxygenated and deoxygenated blood. The site of connection can be supracardiac, infracardiac, or cardiac. Maximal cyanosis occurs in neonates with an infradiaphragmatic connection, with pulmonary venous obstruction,

and with a small atrial communication. Auscultation of the heart may not reveal any murmurs. Chest radiographs help by demonstrating pulmonary congestion in the absence of an enlarged cardiac silhouette.

### Critical Left-Sided Obstructive Heart Lesions

Newborns with critical obstructive cardiac lesions, such as critical coarctation of the aorta, interrupted aortic arch, and HLHS, often look pale and poorly perfused and may demonstrate abnormalities in regional oxygen saturation on pulse oximetry. Hypoperfusion from insufficient flow of blood into the systemic circulation results in hypotension and, with inadequate delivery of oxygen to the tissues, progressive metabolic acidosis. With ductal-dependent systemic circulation, as the ductus arteriosus starts to close, the affected patient clinically deteriorates. With HLHS, the diminished size and function of the mitral valve, left ventricle, aortic valve, and aortic arch result in a severely diminished systemic circulation that is dependent on a widely patent ductus arteriosus to supply blood to the body. In HLHS, not only are structures distal to the ductal insertion into the aorta dependent on the ductal flow, but, given the absence of forward blood flow through the aortic valve, the coronary arteries and the right arm are also dependent on the ductus via retrograde blood flow. Closure of the ductus with HLHS often results in rapid cardiac arrest and death.

In HLHS, the  $\text{SaO}_2$  reflects mixing at the atrial level. Venous blood returning from the systemic veins mixes in the right atrium with oxygenated blood coming from the left atrium via an atrial septal defect. This mixed blood then travels through the right ventricle to the pulmonary artery and from there to the lungs and to the systemic circulation via the PDA. The measurement of  $\text{SaO}_2$  becomes crucial in this circumstance of trying to balance 2 parallel circulations. In other words, blood in the pulmonary artery of patients with HLHS can flow either into the low-resistance pulmonary vasculature or into the high-resistance systemic vasculature. An ideal saturation in this situation is about 75%, representing an approximate balance of blood flow into the lungs and into the systemic vasculature. An acute rise in saturation could represent a preponderance of blood flow into the lungs to the detriment of systemic flow, resulting in acidosis and signs of systemic hypoperfusion despite the higher  $\text{SaO}_2$ .

## CYANOSIS WITH DYSHEMOGLOBINEMIAS

Dysfunctional Hgb that is unable to bind and deliver oxygen adequately is another cause of central cyanosis. Methemoglobinemia occurs when the iron in heme is in the 3+ oxidation state and cannot bind oxygen. Most often, methemoglobinemia results from the presence of an oxidizing substance that changes Hgb  $\text{Fe}^{2+}$  to  $\text{Fe}^{3+}$ , combined with the deactivation of the usual process for reducing methemoglobin back to Hgb. The only accurate method of determining the concentration of methemoglobin is through co-oximetry.

With carbon monoxide poisoning, significant tissue hypoxia can result from the increased affinity of Hgb for carbon monoxide compared to oxygen. However, cyanosis is not usually apparent. Direct determination of oxyhemoglobin and carboxyhemoglobin saturation by means of co-oximetry can reveal the true  $\text{SaO}_2$ . Standard pulse oximeters do not accurately measure  $\text{SaO}_2$  in the presence of carbon monoxide, but special pulse oximeters are now available to determine carboxyhemoglobin saturation.

Cyanide binds to the iron of cytochrome a3, not Hgb. Thus, cyanide poisoning does not directly cause cyanosis, but results in significant tissue hypoxia from the inhibition of oxidative phosphorylation. Even with Hgb 100% saturated, a person with cyanide poisoning is not able to use the oxygen that tissues draw from the blood. At the point when sufficient tissue hypoxia makes the muscles of respiration dysfunctional, cyanosis results from hypoventilation.

### MISCELLANEOUS CAUSES OF CYANOSIS

Occasionally, children with significant gastroesophageal reflux will have paroxysmal acrocyanosis (especially perioral cyanosis) in association with brief episodes of limpness, stereotypical positioning or tonic clonic motions suggestive of a seizure, or apnea. This constellation of features is called Sandifer syndrome and often responds to treatment of the gastroesophageal reflux.

Prolonged generalized seizures are often associated with impaired respiration and can result in cyanosis if respiration ceases for a prolonged period.

Neuromuscular disorders causing weakness of respiratory muscles, such as spinal muscular atrophy, botulism, congenital myopathies, or metabolic disorders, can result in hypoventilation followed by collapse of lung units that combine to result in hypoxemia that, if severe enough can, manifest as cyanosis.

In cyanotic breath-holding spells children present with a history of crying, typically followed by sudden breath-holding in forced expiration with apnea and cyanosis. These features may progress to limpness and loss of consciousness. Cyanosis can appear faster than anticipated with simple breath-holding, and the loss of tone is often striking. As the child resumes normal breathing, the cyanosis resolves. Cyanotic breath-holding spells most commonly occur around 1 year of age with a range of 6 months to 4 years. Up to 15% of cases may have an initial episode before the age of 6 months.

### CYANOSIS IN THE NEWBORN

Acrocyanosis of the hands and feet is common in the first 6 to 24 hours of life and is usually of little significance in an otherwise well newborn. Central cyanosis persisting beyond the first few minutes of life may indicate inadequate oxygen delivery and necessitates further evaluation. Newborns can have cyanosis over the lower half of the body in the presence of right-to-left shunting across a PDA. Newborns with persistent cyanosis or hypoxemia despite oxygen administration may have CCHD, primary lung disease, or pulmonary artery hypertension.

In utero, the fetus is markedly cyanotic because the placental circulation provides blood with an  $\text{SaO}_2$  ranging from only 50% to 65% ( $\text{PaO}_2$  18–25 mm Hg). Even at this low saturation, oxygen delivery in the fetus is adequate for growth and development because of a high concentration of Hgb and the presence of fetal Hgb (Hgb F), which binds oxygen with a greater affinity than Hgb A. In utero, there is only minimal blood flow through the pulmonary artery into the lungs; instead, blood is shunted via the ductus arteriosus, the patent foramen ovale, and other anatomic channels from the right heart to the systemic circulation. At birth, with separation from the placenta and a rapid drop in pulmonary vascular resistance, blood flows from the right ventricle through the pulmonary artery and into the pulmonary capillary beds, where it is exposed to oxygen in the air. Within the first few breaths, the lungs become an extremely efficient gas exchange organ resulting in  $\text{SaO}_2$  levels sufficient for the newborn to transition from cyanotic to centrally pink. In a healthy neonate, oxygen saturations continue to rise slowly over the initial few minutes of extrauterine life. The postductal oxygen saturations are usually lower than the preductal saturations for as long as 15 minutes, indicating persistence of elevated pulmonary vascular resistance with resultant mixing of venous blood in the aorta at the level of the ductus arteriosus. In the absence of a substantial pulmonary or cardiac defect, the arterial saturation continues to rise, and simultaneously, the channels that shunt blood from right to left in utero will close. By 24 hours of age, an Hgb oxygen saturation of less than 95% in the lower extremities is abnormal and warrants further investigation.

In the period following birth, the persistence of Hgb F, with its higher affinity for oxygen, results in a leftward shift of the oxyhemoglobin dissociation curve so that cyanosis is observed only at lower oxygen tensions: 32 to 42 mm Hg, corresponding to saturations of 75% to 85%. Thus, in the presence of Hgb F, a greater degree of hypoxemia is required for cyanosis to be visible.

The best method for assessing cyanosis in a newborn is to look at the tongue. If central cyanosis persists for more than a few minutes after birth, a search for the cause should be undertaken. Comparing arterial blood saturation proximal to and distal to the entrance of the ductus arteriosus into the aorta is helpful in determining the origin of cyanosis in a newborn. In the presence of right-to-left shunting of blood through a PDA, blood in the aorta at the level of the ductal entry and more distally (left arm and lower extremities) is relatively desaturated from the admixture of venous blood entering the aorta via the PDA. In contrast, blood in the aorta proximal to the level of the PDA (right arm) will be more fully saturated because of a greater contribution of well-oxygenated blood that has returned to the left atrium and left ventricle via the pulmonary veins.

### Hyperoxia Test

In the presence of cyanosis, oxyhemoglobin desaturation, or low  $\text{PaO}_2$ , a hyperoxia test should be performed in a newborn to determine if the problem is

with pulmonary oxygenation, from an anatomic shunting of blood through the PDA, or an intracardiac lesion. In pulmonary causes of cyanosis or hypoxemia, there should be a significant increase in  $\text{SaO}_2$  and  $\text{PaO}_2$  with administration of 100% oxygen. A  $\text{PaO}_2$  of less than 100 mm Hg in an enriched-oxygen environment is a strong indicator of CCHD or PPHN, and an echocardiogram should be obtained to evaluate for congenital heart disease. With a heart lesion in which some pulmonary blood flow is present, there can be a significant increase in  $\text{PaO}_2$  or  $\text{SaO}_2$  during a hyperoxia test. A  $\text{PaO}_2$  greater than 250 mm Hg makes cyanotic heart disease unlikely, but a  $\text{PaO}_2$  of 100 to 250 mm Hg does not completely rule out CCHD and warrants further investigation. When performing a hyperoxia test, simultaneous determinations of preductal and postductal  $\text{SaO}_2$  or  $\text{PaO}_2$  should be made to delineate the presence of a right-to-left ductal shunt or other shunting pattern. If desaturation is present, and especially if there is not a significant improvement in saturation with administration of 100% oxygen, the consultation of a neonatologist or pediatric cardiologist should be sought.

### Persistent Pulmonary Hypertension of the Newborn

In PPHN, high residual pulmonary vascular resistance reduces pulmonary artery blood flow to the lungs with concomitant persistence of shunting from the right to the left side of the circulation through the ductus arteriosus and foramen ovale. This is known as persistence of fetal circulation, and the oxygen content of blood in the left atrium is decreased as a result of mixing desaturated venous blood that has crossed the foramen ovale with whatever oxygenated blood has managed to traverse the pulmonary capillary bed. The blood leaving the left ventricle becomes further desaturated when mixed with blood entering the aorta through the ductus arteriosus, having bypassed gas exchange in the lungs. With blood distal to the ductal entrance to the aorta being more desaturated than the preductal blood, the oxyhemoglobin saturation measured by pulse oximetry or ABG in the right arm may be higher than in the left arm or legs; this is known as differential oxyhemoglobin saturation or differential cyanosis.

### Newborn Screening for Congenital Cyanotic Heart Disease

Current recommendations by the American Academy of Pediatrics state that newborns should be screened by pulse oximetry prior to discharge from the newborn nursery to ascertain the possible presence of CCHD that otherwise might be missed. Studies have shown that by 24 hours of life, an oxyhemoglobin saturation of less than 95% is not normal and supportive of a cyanotic or mixing cardiac lesion. A newborn should have oxyhemoglobin saturation measured in the right arm and in 1 leg at 24 hours of life, and if there is a gradient in saturation or if the saturation is 95% or lower, an echocardiogram should be obtained prior to discharge.

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## Chapter 137 DEPRESSION

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Symptoms of depression affect many children, including a large number whose symptoms do not rise to the level of a disorder. It is estimated that in the United States up to 3% of children younger than 13 years and up to 6% of adolescents experience depression at any given time. Estimates of lifetime prevalence of major depressive disorder (MDD) are significantly higher at up to 20%.

Depression may remit on its own or after treatment but recur spontaneously at times of developmental transitions or with new stressors (both positive and negative). Depression is among the mental health problems associated with suicidal ideation, suicide attempts, and completed suicide. Other associated problems include negative effects on school performance, early pregnancy, and impairment of function in the work, social, and family environments. Risk factors for the development of depression among children and adolescents include family history (heritability is approximately 40%), adverse childhood experiences, temperament/neuroticism, and the existence of a major nonmood disorder or a chronic or disabling medical condition. Children who seem depressed may have relatives who have also



experienced depression or other mental disorders. Finding such a history may reinforce the need to thoroughly evaluate concerns about the child, especially if there is a family history of suicide. Knowing that there are other family members who have experienced the same problems can increase empathy for the child's problems and may well provide role models for successful treatment.

There is some evidence that either initial onset or recurrence of depression may be preventable. Nurturing care during the critical first years of life, warm and confiding family relationships, learning active coping strategies for predictable stressors, promoting a sense of self-efficacy through learning to work through problems, and trying to maintain regular patterns of sleep and exercise may all be protective. If parents have mental health problems (especially depression), helping children understand and cope with changing parental mood and behavior may help prevent children themselves becoming depressed. If a child or youth has received treatment for depression, continuing treatment beyond the early stages of recovery is associated with a reduced risk of relapse or recurrence.

The guidance in this chapter applies to the care of children presenting with undifferentiated depression in pediatric clinical settings. It is based on the work of the World Health Organization, whose recommendations may be updated annually. The most up-to-date information can be found at [www.who.int](http://www.who.int).

## FINDINGS SUGGESTING DEPRESSION

Though depression may come on without an apparent trigger, even among those who seem highly successful and privileged, it can often develop after 1 or more stresses or losses, or in conjunction with prolonged anxiety. Most children and adolescents will experience an event that induces sadness, such as breakup with a friend, the death of a loved one or pet, or other losses resulting from life changes such as a move, a family member's military deployment, or parents' separation. A sadness experience of greater intensity or duration than is typical for the child's peers is a cause for concern and may indicate depression. Symptoms of depression vary. A summary of the symptoms and clinical findings that suggest depression can be found in Box 137-1. For those familiar with the symptoms of depression in adults, it is important to remember that, among children, irritability may be a more prominent symptom than sadness. In some cases, withdrawal from usual activities or decreased interaction with friends and family may be the only obvious sign, possibly coupled with a change in appetite, sleep, or level of energy. Symptoms may be elicited from either parents or youth, but ideally from both. Children and youth may be better able to report on feelings that do not result in behavior change that is obvious to others; on the other hand, children and youth may not be aware of how their appearance or behavior has changed in ways that are apparent to others. Ideally, reports should be obtained from both youth and parents if there is a suspicion of depression.

### BOX 137-1 Symptoms and Clinical Findings Suggesting Depression

#### INDICATIONS FROM HISTORY FROM YOUTH OR PARENT

- Low or sad mood present most days
- Loss of interest in school or other activities present most days
- Loss of pleasure in activities formerly enjoyed (When is last time he/you had fun?)
- Suicidal thoughts or acts
- Irritability (especially in adolescents)
- Academic difficulties
- Withdrawal from friends and family
- Physical symptoms such as headaches, abdominal pain, trouble sleeping, fatigue, or poor control of a chronic illness
- Hopelessness
- Poor concentration
- Poor or excessive sleep for developmental stage
- Weight loss (or failure to gain weight normally) or excessive weight gain
- Low self-esteem
- Loss of energy
- Agitation or slowing of movement or speech

#### RISK FACTORS FOR INCREASED SUSCEPTIBILITY

- Adverse childhood experiences (eg, mother experienced postpartum depression)
- Prior trauma or bereavement
- Family breakdown
- Shy personality
- Peer relationship problems
- Breakup of a relationship; setback or disappointment

## TOOLS TO ASSIST WITH IDENTIFICATION

Since many children do not spontaneously disclose their symptoms, standardized psychosocial screening instruments may be used to identify children with symptoms of depression. Several instruments have versions to collect information from the youth, parents, and teachers. Table 137-1 provides examples of general psychosocial screening results suggesting that a child may be depressed. Additional instruments such as the Patient Health Questionnaire for Adolescents (PHQ-A) or PHQ-A Depression Screen, Beck Depression Inventory-Primary Care (also known as Fast Screen), or the Modified Patient Health Questionnaire-9 (PHQ-9) can also be used to screen adolescents for depression or to help confirm findings of a general psychosocial screening.

It is important to differentiate the use of these tools as screening instruments at routine visits versus their use to refine concerns that have already been raised. When used as screening tools, they tend to have



**Table 137-1** General Psychosocial Screening/Results Suggesting Depression

SCREENING INSTRUMENT	SCORE SUGGESTING DEPRESSION
Pediatric Symptom Checklist (PSC)-35	<ul style="list-style-type: none"> <li>• Total score <math>\geq 24</math> for children 5 years and younger.</li> <li>• <math>\geq 28</math> for those 6–16 years.</li> <li>• <math>\geq 30</math> for those 17 years and older.</li> </ul> AND <ul style="list-style-type: none"> <li>• Further discussion of items related to depressive symptoms confirms a concern in that area.</li> </ul>
PSC-17	<ul style="list-style-type: none"> <li>• Internalizing subscale is <math>\geq 5</math>.</li> </ul> AND <ul style="list-style-type: none"> <li>• Further discussion of items related to depressive symptoms confirms a concern in that area.</li> </ul>
Strengths & Difficulties Questionnaire (SDQ)	<ul style="list-style-type: none"> <li>• Total symptom score of <math>&gt;19</math>.</li> <li>• Emotional symptom score of 7–10 (see instructions at <a href="http://www.sdqinfo.com">www.sdqinfo.com</a>).</li> <li>• Impact scale (back of form) score of 1 (medium impairment) or <math>\geq 2</math> (high impairment).</li> </ul> AND <ul style="list-style-type: none"> <li>• Further discussion of items related to depression confirms a concern in that area.</li> </ul>

relatively low sensitivity and positive predictive value. That is, positive results need further discussion to understand the meaning of the result, and negative results may not be reassuring if the parent or youth are truly concerned. When used to follow up on existing concerns, results still need discussion with families, but are more likely to be a fair indicator of the nature and severity of the child's problems. The use of a functional assessment tool such as the Strengths & Difficulties Questionnaire (SDQ) or Columbia Impairment Scale (CIS) will assist the clinician in determining whether the child's functioning is significantly impaired by the symptoms. Use of a tool to assess the impact of the child's problem on other members of the family may also be helpful; the Caregiver Strain Questionnaire (CGSQ) is one example.

## ASSESSMENT

Assessment begins by differentiating the child's symptoms from normal behavior. All children may be sad or irritable at times, but, for some children, these symptoms limit their adaptability to normal peer and family situations, interfere with learning, or precipitate suicidal thoughts. Of particular concern is major depressive disorder (MDD); *DSM-5* criteria for MDD are summarized in Box 137-2.

There are also some conditions that may mimic or co-occur with depression. Table 137-2 provides a summary of these conditions.

For a child with symptoms of depression, the psychosocial assessment process always includes determination of suicide risk, as described in Box 137-3.

## PLAN OF CARE FOR YOUTH WITH DEPRESSION

Suicidal intent is an emergency requiring immediate treatment and close supervision of the youth at all times. The care of a youth experiencing depression can begin in the primary care setting from the time symptoms are recognized, even if the youth's symptoms do not rise to the level of a disorder and

regardless of whether referral to a mental health specialist is ultimately part of the care plan.

### Engage Youth and Family in Care

Without engagement, most families will not seek or persist in care. The process may require multiple primary care visits.

Reinforce strengths of the youth and family (eg, good relationships with at least 1 parent or important adult, prosocial peers, concerned or caring family, help-seeking, connection to positive organizations) as a method of engagement and identify any barriers to addressing the problem (eg, stigma, family conflict, resistance to treatment). Use "common factors" techniques to build trust and optimism, reach agreement on incremental next steps, develop a plan of care, and collaboratively determine the role of the primary care physician. Regardless of other roles, the primary care physician can encourage a positive view of treatment on the part of the youth and family.

### Provide Psychoeducation

Depression is very common and not the result of lack of coping ability or personal strength. There is often a family history of the condition; talking about this may reduce stigma and increase empathy and a willingness to seek care, but may also be met with resistance. To assist family members in understanding the disorder, additional points to highlight include that the youth is not making the symptoms up, what looks like laziness or crossness can be symptoms of depression, and the hopelessness of depression is a symptom, not an accurate reflection of reality. However, this negative view of the world and of future possibilities can be hard to penetrate. In addition, the clinician can emphasize that treatment works, though it can take several weeks for improvement, and the affected individual is often the last person to recognize that it has taken place.

Families should be encouraged to address risk factors for maintenance of depression and for the risk of suicidal acts. Weapons should ideally be removed

**BOX 137-2 Criteria for Major Depressive Episode (DSM-5)**

- A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least 1 of the symptoms is either depressed mood or loss of interest or pleasure. **Note:** Do not include symptoms that are clearly attributable to another medical condition.
1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad, empty, hopeless) or observation made by others (eg, seems tearful). **Note:** In children and adolescents, can be irritable mood.
  2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
  3. Significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gain.
  4. Insomnia or hypersomnia nearly every day.
  5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
  6. Fatigue or loss of energy nearly every day.
  7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
  8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
  9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
- B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- C. The episode is not attributable to the physiologic effects of a substance or to another medical condition. **Note:** Criteria A–C represent a major depressive episode.
- Note:** Responses to a significant loss (eg, bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite and weight loss as noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss.
- D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
- E. There has never been a manic episode or a hypomanic episode. **Note:** This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the psychological effects of another medical condition.

From American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Publishing; 2013, with permission.

from the home or secured, and a careful survey should be made for potentially lethal medications or household chemicals including pesticides. Suicidal and depressive thoughts can be spread through social networks and, increasingly, through social media. Electronic communication has been found, paradoxically, to promote isolation at the same time as it seems to be increasing connectedness. Though not often easy, parents can be helped to both monitor and limit the use of e-mail, texts, and social media posts until the child has recovered.

The clinician may also, at this point, talk about how there is a variety of treatments for depression including various forms of psychosocial care, and, for teens, medications. It may be useful to ask about what the teen and family have thought of or heard about treatment; in that way, the clinician can discover if they are anxious that the discussion is leading to a suggestion they would not be willing to accept.

### Encourage Healthy Habits

Encourage exercise, outdoor play, healthy diet, sleep, limiting screen time, 1-on-1 time with parents, praise

for positive behavior, and acknowledgment of the youth's strengths. Caring for oneself can be presented honestly as therapeutic. One can "prescribe pleasure" by telling youth and families that caring for oneself, including engaging in activities that previously were pleasurable, is not weakness but rather an important part of self-care, just as athletes need to rest or stretch in addition to testing their limits in workouts.

### Reduce Stress

Consider the youth's social environment (eg, family social history, parental depression screening, results of any family assessment tools administered, reports from child care or school). Questions to raise might include the following:

- *Are there grief and loss issues in the youth or other family members?* Grief and loss are virtually universal childhood experiences. Children vary widely in their reactions to these events, depending on their developmental level, temperament, prior state of mental health, coping mechanisms, parental responses, and support system. Also helpful can be supportive counseling; explaining to children and adolescents what

**Table 137-2** Conditions That May Mimic or Co-occur With Depression

CONDITION	RATIONALE
Sleep deprivation	Sleep problems can cause irritability and labile mood; conversely, depression may contribute to difficulty sleeping.
Somatic complaints	Depressed children may present with a variety of somatic complaints (eg, gastrointestinal symptoms, headaches, chest pain). Conversely, acute or chronic medical conditions or pain syndromes may cause depression.
Learning problems or disabilities	If symptoms of depression are associated with problems of school performance, the child may be experiencing learning difficulties. See Chapter 172, Learning Difficulty, to explore this possibility.
Exposure to adverse childhood experiences (ACE)	Children who have experienced or witnessed trauma, violence, a natural disaster, separation from a parent, parental divorce or separation, parental substance use, neglect, or physical, emotional, or sexual abuse are at high risk of developing emotional difficulties such as adjustment disorder, post-traumatic stress disorder (PTSD), and depression. Denial of trauma symptoms does not mean trauma did not occur; questions about ACE should be repeated as a trusting relationship is established. See also Chapter 129, Anxiety.
Maltreatment	Children who have experienced neglect or physical, emotional, or sexual abuse are at high risk of developing emotional difficulties such as depression; this possibility should always be considered.
Anxiety	Depression often co-occurs with anxiety. See Chapter 129, Anxiety.
Bereavement	Most children will experience the death of a family member or friend sometime in their childhood. Other losses may also trigger grief responses—separation or divorce of parents, relocation, change of school, deployment of a parent in military service, breakup with a girlfriend or boyfriend, or remarriage of parent. Such losses are traumatic. They may result in feelings of sadness, despair, insecurity, or anxiety immediately following the loss and, in some instances, more persistent anxiety or mood symptoms or disorders. Furthermore, they may make the child more susceptible to impaired functioning at the time of subsequent losses. See also the discussion of PTSD in Chapter 129, Anxiety.
Physical illness and medication side effects	Medical issues that can mimic or provoke symptoms of depression include hypothyroidism, lupus, chronic fatigue syndrome, diabetes, and anemia. Children with any chronic medical condition are more likely to experience depression than their peers (and depression may contribute to poor management of the condition). Medications commonly used in adolescence can be associated with depression (eg, acne preparations, oral contraceptives, interferon, corticosteroids).
Substance use	Children with symptoms of depression may self-medicate with alcohol, nicotine, or other drugs. Conversely, children using substances may manifest depression and deteriorating school performance. See Chapter 198, Substance Use: Initial Approach in Primary Care.
Conduct or oppositional disorders	Oppositional children may manifest depressive symptoms. Children with conduct problems are at higher risk for suicide. See Chapter 139, Disruptive Behavior and Aggression.
Psychosis	Depression can be complicated by problems with thinking that go beyond the distortions or hopelessness of low mood. These problems include delusions (ie, strongly held and usually odd false beliefs about others, one's body, or one's self), paranoia (ie, strongly felt and unjustified concerns that others are following or intend harm), or hallucinations (ie, seeing or hearing things that others don't hear or see). Individuals often don't volunteer that they are having these sorts of thoughts; asking is important if the person's interactions seem unusual. (Do you ever feel your eyes or ears play tricks on you?)
Bipolar disorder	Adults and older adolescents with bipolar disorder may have markedly varying low mood (depression) or high mood (mania), cycling over weeks or months. Diagnosis of bipolar disorder in children remains controversial. It may be considered in children who cycle through low and high moods very rapidly and in children with explosive or destructive tantrums, dangerous or hypersexual behavior, aggression, irritability, bossiness with adults, driven creativity (sometimes depicting graphic violence), excessive talking, separation anxiety, chronic depression, sleep disturbance, delusions, hallucinations, psychosis, and talk of homicide or suicide. See also Chapter 168, Inattention and Impulsivity, Chapter 139, Disruptive Behavior and Aggression, and Chapter 129, Anxiety.

they might reasonably expect; inviting them to participate in the funeral or other ceremonies to the level they feel comfortable; active listening while allowing the child or adolescent to express his or her grief; providing guidance about the grief process; and identifying and addressing feelings of guilt. When a parent is also grieving, children and adolescents may need time alone with the clinician because they may be reluctant to increase parental sadness. Providing

follow-up to see how the child and family are coping with a loss can help gauge how the family is doing and provide opportunities to assess for more serious reactions such as complicated bereavement, depression, or PTSD. Providing referral to community resources may also be helpful. The effects of profound losses, such as the death of a sibling or parent during childhood or removal from parents, last a lifetime. The clinician will need to view all future physical

**BOX 137-3 Determining Suicide Risk**

*Are there others in the family (present or past generations) who have had depression or bipolar disorder or who have attempted suicide?* Teens and parents may need opportunities to answer these questions confidentially because this is information that is not always shared among family members. Positive responses—especially a family history of suicide—increase concern. Other risk factors include substance use, a model among peers or famous individuals known to the youth, or a recent traumatic or shameful episode. A past attempt by the youth is the single strongest risk factor for future attempts and may warrant mental health referral for the current episode if the youth is not in ongoing care.

The severity of suicidal thoughts can be assessed with several questions (eg, Bright Futures, page 276) and tools (eg, SAD PERSONS; GLAD-PC). Examples include the following:

- “Have you ever felt bad enough that you wished you were dead?”
- “Have you had any thoughts about wanting to kill yourself?”
- “Have you ever tried to hurt or kill yourself or come close to hurting or killing yourself?”

- “Do you have a plan?”
- “Do you have a way to carry out your plan?”

One way of approaching suicidality is to think of your inquiry as a staged process. A significant minority of adolescents have transient suicidal thoughts or what psychiatrists call “passive death wishes”—thoughts that perhaps death would be a way out of problems or stresses but without thinking of a way to harm themselves. Absent the risk factors discussed above, these youth likely need exploration of stressors and assessment for depression or other mental health problems. A smaller group will have thought about ways of harming themselves but without a concrete plan or making any preparations. Again, absent past attempts, ongoing stressors, or substance use, these youth need support and further evaluation but are not at high risk of harming themselves. Youth with plans for harming themselves (no matter what the likelihood of success) or who have gathered or identified the means (ropes, medications, knives or other weapons) are at high risk of harming themselves. They require both a short-term plan for safety and an urgent mental health evaluation. For more information, see Chapter 191, Self-harm.

and mental health issues in the family through the prism of this loss. Overlooking such experiences and failing to follow up on the child and family’s progress after a traumatic event are lost opportunities to connect with the child and family around important mental health issues.

- *Is the youth or family experiencing unusual stress?* The family can work to try to reduce stresses and increase support for the youth. This may involve reasonable and short-term changes in demands and responsibilities, including negotiating extensions for assignments or other ways of reducing stress at school; it can also include seeking help for others in the family who are distressed. If a parent is grieving a loss or manifesting symptoms of depression, it is particularly important that the parent address his or her own needs and find additional support for the youth and other family members.
- *Are there weapons or medications in the house?* Guns should be removed from the home; other weapons, medications (including over-the-counter preparations and acetaminophen), and alcohol should be removed from the home, destroyed, or secured. In farm communities, there may be toxic products (such as insecticides or fertilizers) that may need to be secured. Depressed individuals should be dissuaded from operating dangerous machinery or engaging in other activities that require care and normal risk aversion to avoid injury.

### **Offer Initial Intervention(s) to Address the Depression Symptoms**

The strategies described in the following text are common elements of evidence-based psychosocial

interventions for depression in children and adolescents. They are applicable to the care of children with mild or emerging depressive symptoms and to those with impairing symptoms that do not rise to the level of a disorder. They can also be used as initial management of children with a depressive disorder while readying them for or awaiting access to specialty care.

*Help the youth to develop cognitive and coping skills.* Find agreement with the youth and family on a description of the problem. Many negative thoughts can be empathetically challenged and looked at from another perspective. Helpful metaphors include, “Long journeys start with a single step” and “The glass is half full, not half empty.” Relaxation techniques and visualization (eg, practicing relaxation cued by a pleasant memory, imagining being in a pleasant place) can be helpful for sleep and for anxiety-provoking situations. The clinician can also ask the youth what he or she does to feel better or relax and, if appropriate, prescribe more of that (*behavioral activation*). Encourage a focus on strengths rather than weaknesses and doing more of what the youth is good at. Distraction is also good therapy—if the youth is ruminating on a particular stressor, give permission to think about or engage with something else.

*Help the youth to develop problem-solving skills.* Determine what small achievable act would help the youth feel that he is on the way to overcoming his problems. Suggest that the youth list difficulties, prioritize them, and concentrate efforts on one issue at a time. Avoid downplaying social crises that are important to the young person even if, from an adult perspective, they seem trivial. Instead, offer to help the young person evaluate the options as he sees



them, seeking, if there is an opening, permission to offer alternatives that may not have been raised.

**Rehearse behavior and social skills.** Reactions to particular situations or people often seem to trigger or maintain low mood. If these can be identified, assist the youth in developing and practicing means of avoidance or alternative responses. Practice doing things and thinking thoughts that improve mood.

**Create a safety and emergency plan.** Developed in partnership with the family, a treatment plan includes a listing of telephone numbers to call in the event of a sudden increase in distress. This listing should be specific to the child's community and circumstances (eg, the number for a suicide or depression hotline, on-call telephone number for the practice, or area mental health crisis response team contact information). The family should also be instructed to proactively remove lethal means and monitor for suicide risk factors such as increased agitation, stressors, loss of rational thinking, expressed wishes to die, previous attempts, and comorbid conduct disorder or aggressive outbursts.

### Provide Resources

Helpful handouts and Web sites are included in Tools for Practice: Engaging Patient and Family at the end of this chapter. Provide the family with contact numbers and resources in case of emergency.

### Monitor the Youth's Progress Toward Therapeutic Goals

Child care, preschool, or school reports can be helpful in monitoring progress. Screening instruments that gather information from multiple reporters (youth, parent, teacher), such as the SDQ and PSC, can be helpful in monitoring progress with symptoms and functioning.

It is important for the clinician to work with the family to understand that it is not uncommon for treatment to be successful for a period and then seem to lose effectiveness. This can happen when there are new stresses or demands, or when, after a period of success, there has been a letup on treatment. If troubleshooting existing treatment and ways of dealing with new stresses does not help get function back to baseline, new treatments, or new diagnoses, need to be considered. In particular, as school demands increase, learning issues may need to be considered even if they were not seen as contributing problems in the past.

### Involve Specialist(s)

Involve specialist(s) if the youth does not respond to initial interventions or if indicated by the following clinical circumstances:

- A preadolescent child manifests depression or suicidal ideation.
- An adolescent with depressive symptoms has made a prior suicide attempt, developed a plan (especially with means available), or known a friend or acquaintance who has committed suicide.
- An adolescent's functioning is significantly impaired.

- Symptoms are threatening the achievement of developmentally important goals (eg, attending school or spending time with friends).
- The adolescent has mental health comorbidities such as substance use or odd behavior suggestive of an emerging psychotic disorder.
- The adolescent also has symptoms of bipolar disorder—elevated (often more driven rather than positive) mood and energy associated with irritability and behavior that seems audacious for his or her age (grandiosity).
- Depressive symptoms were preceded by serious trauma.

For youth with a diagnosis of moderate to severe MDD, data indicate superior efficacy of a combination of cognitive behavior therapy (CBT) and a selective serotonin reuptake inhibitor (SSRI) compared with either CBT alone (which may not be sufficiently helpful for these more severe cases) or an SSRI alone. Thus, youth with MDD would ideally receive treatment from a licensed therapist with training in CBT (see following text).

*When specialty care is needed, ensure that it is evidence-informed and assist the family in accessing it.* A variety of evidence-based and evidence-informed psychosocial interventions, and some pharmacologic interventions, are available for the treatment of depressive disorders in children and adolescents. Ideally, those referred for care in the mental health specialty system would have access to the safest and most effective treatments. Table 137-3 provides a summary of these interventions. Youth referred for mental health specialty care complete the referral process only 61% of the time, and a significantly smaller number persist in care. Approaches to improving the referral process include making sure that the family is ready for this step in care, that they have some idea of what the specialty care will involve, and that they understand what the physician's ongoing role may be. If the specialty appointment is not likely to occur shortly, the physician can work with the child and family on a plan to manage the problem as well as possible in the meantime.

*Reach agreement on respective roles in the youth's care.* If the youth is referred to mental health specialty care for a depressive disorder, his or her primary care physician may be responsible for initiating medication or adjusting doses; monitoring response to treatment; monitoring adverse effects; engaging and encouraging the youth's and family's positive view of treatment; and coordinating care provided by parents, school, medical home, and specialists. In fact, the youth may improve just knowing that the clinician is involved and interested. Resources available to help clinicians in these roles are provided in Tools for Practice: Medical Decision Support.

Note that not all evidence-based interventions may be available in every community. If a particular intervention is not available, this becomes an opportunity to collaborate with others in the community to advocate on behalf of children. Increasingly, states offer both telepsychiatry services and consultation/referral support "warmlines" that help physicians provide initial treatment and locate resources. The availability of the latter form of help is tracked at [www.nncpap.org](http://www.nncpap.org).

**Table 137-3** Psychosocial and Psychopharmacologic Treatments for Depression (as of November 2014)<sup>a</sup>

PSYCHOSOCIAL TREATMENTS		
CLUSTER AREA	LEVEL 1 (BEST SUPPORT)	LEVEL 2 (GOOD SUPPORT)
Depressive or withdrawn behaviors <sup>b</sup>	<ul style="list-style-type: none"> <li>• Cognitive behavior therapy (CBT)</li> <li>• CBT and medication</li> <li>• CBT with parents (includes parent and child, focusing on the child's concerns)</li> <li>• Family therapy</li> </ul>	<ul style="list-style-type: none"> <li>• Client-centered therapy</li> <li>• Cognitive behavioral psychoeducation</li> <li>• Expressive writing/journaling/diary</li> <li>• Interpersonal therapy</li> <li>• Relaxation</li> </ul>
Suicidality <sup>b</sup>	None	<ul style="list-style-type: none"> <li>• Attachment therapy</li> <li>• Counselors care</li> <li>• Counselors care and support training</li> <li>• Interpersonal therapy</li> <li>• Multisystemic therapy</li> <li>• Psychodynamic therapy</li> <li>• Social support</li> </ul>
US FOOD AND DRUG ADMINISTRATION-APPROVED PSYCHOPHARMACOLOGIC INTERVENTIONS <sup>c</sup>		
DIAGNOSTIC AREA	PSYCHOPHARMACOLOGIC INTERVENTION	
Major depressive disorder (MDD)	Selective serotonin reuptake inhibitor (SSRI) (fluoxetine and escitalopram are currently the only drugs approved by the FDA for treating MDD among youth). There are data that indicate superior efficacy of combination CBT and SSRI versus CBT or SSRI alone.	

<sup>a</sup>For AAP policy, please visit [pediatrics.aappublications.org/site/aappolicy](http://pediatrics.aappublications.org/site/aappolicy).

<sup>b</sup>Excerpted from PracticeWise Evidence-Based Child and Adolescent Psychosocial Interventions. Reprinted with permission from PracticeWise. For updates and an explanation of PracticeWise determination of evidence level, please visit [www.aap.org/mentalhealth](http://www.aap.org/mentalhealth).

<sup>c</sup>For up-to-date information about Food and Drug Administration (FDA)-approved interventions, go to [www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/default.htm](http://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/default.htm).

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## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Childhood Depression: What Parents Can Do to Help* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/emotional-problems/Pages/Childhood-Depression-What-Parents-Can-Do-To-Help.aspx](http://www.healthychildren.org/English/health-issues/conditions/emotional-problems/Pages/Childhood-Depression-What-Parents-Can-Do-To-Help.aspx))
- *Help Stop Teenage Suicide* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/emotional-problems/Pages/Help-Stop-Teen-Suicide.aspx](http://www.healthychildren.org/English/health-issues/conditions/emotional-problems/Pages/Help-Stop-Teen-Suicide.aspx))
- *Teen Suicide, Mood Disorder, and Depression* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Ten Things Parents Can Do to Prevent Suicide* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/emotional-problems/Pages/Ten-Things-Parents-Can-Do-to-Prevent-Suicide.aspx](http://www.healthychildren.org/English/health-issues/conditions/emotional-problems/Pages/Ten-Things-Parents-Can-Do-to-Prevent-Suicide.aspx))

### Medical Decision Support

- *Patient Health Questionnaire (PHQ) Screeners* (screen), Pfizer, Inc ([www.phqscreener.com](http://www.phqscreener.com))

- *Pediatric Symptom Checklist* (screen), Massachusetts General Hospital ([www.massgeneral.org/psychiatry/services/psc\\_forms.aspx](http://www.massgeneral.org/psychiatry/services/psc_forms.aspx))
- *Strengths & Difficulties Questionnaire* (screen), Youth in Mind, Ltd ([www.sdqinfo.com](http://www.sdqinfo.com))

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## Chapter 138

## DIARRHEA AND STEATORRHEA

Martin H. Ulshen, MD

Diarrhea, similar to vomiting, is a common symptom in young children, especially during infancy. Loosely defined, diarrhea is characterized by an increase in the frequency and water content of stools. Normal daily stool volume varies with the size of the child. Adults and older children have a normal daily stool weight up to 250 g (consisting of 60%–85% water); infants weighing fewer than 10 kg can have about 5 g/kg/day of stool. An intermediate range of 50 to 75 g/day is an appropriate approximation for the preschool-aged child. In infancy, the frequency and quality of normal stools depend very much on diet.

During the first weeks of life, breastfed infants commonly have up to 8 loose stools per day, which, at times, may contain mucus. These stools frequently follow feedings, as a result of the *gastrocolic reflex*, and do not constitute diarrhea. Infants receiving cow milk or soy formula usually have firmer and somewhat less frequent stools. After the first few weeks of life, normal breastfed infants tend to have less frequent stools, occasionally even less than once a week, although the stools remain soft. Commonly, the stool of the nursing infant becomes firm when solids or cow milk is introduced into the diet.

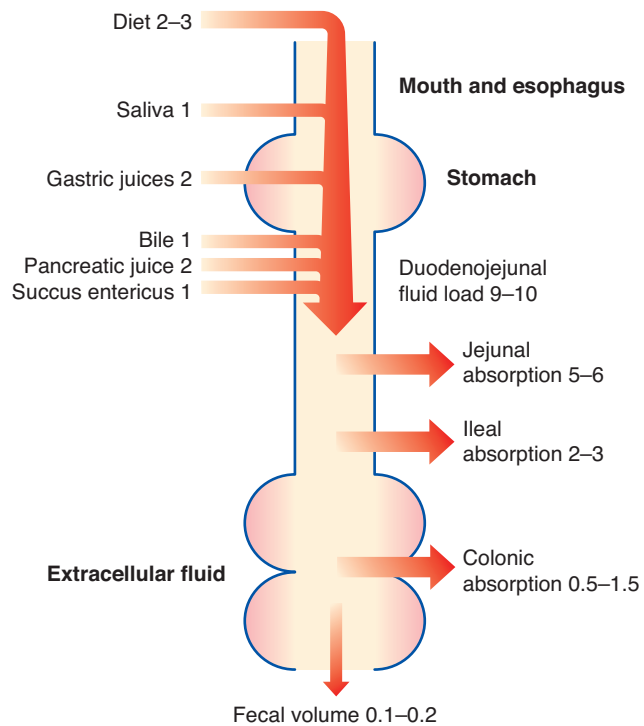
Steatorrhea signifies an excess of fat in the stool and is a symptom of malabsorption. However, disorders associated with malabsorption, such as gluten-sensitive enteropathy, do not always produce steatorrhea. Stools that contain an increased quantity of fat can be greasy, bulky, and foul smelling; however, with mild steatorrhea, the stool may appear normal. The stool can be evaluated quickly for fat content by using light microscopy with Sudan staining (known as qualitative analysis for stool fat). Fat excretion can be measured more precisely by quantitative chemical analysis of a 72-hour collection of stool. A record of the diet is kept during this period, and fat intake is calculated. The percentage of the ingested fat that is absorbed is called the *coefficient of absorption*.

$$\frac{\text{Fat Intake} - \text{Fat Output}}{\text{Fat Intake}} \times 100$$

Absorption of fat by infants varies with the type of fat that is fed and with the maturity of the infant. A healthy premature infant may absorb as little as 65% to 75% of dietary fat, but this amount improves to 90% in the term infant. Furthermore, neonates absorb vegetable fat much more efficiently than butterfat but human milk fat best of all. Children and adults typically absorb at least 95% of the fat in a normal diet.

## PATHOPHYSIOLOGIC FACTORS

Advances in the understanding of the pathophysiologic mechanism of diarrhea allow a more rational approach to diagnosis and treatment. Normally, the



**Figure 138-1** Ingestion, secretion, and absorption of water in the gastrointestinal tract of an adult. Numbers refer to liters of water.

gastrointestinal tract processes a large volume of fluid (Figure 138-1 lists adult data). An infant can rapidly become fluid depleted from diarrhea when such large gastrointestinal fluid shifts take place each day. Under normal circumstances, about 90% of fluid absorption takes place in the small bowel. However, the colon has a reserve capacity for fluid absorption that must be overcome before diarrhea results. In adults, the colon can reabsorb as much as 2 L of ileal fluid daily without diarrhea occurring.

Movement of water across the gastrointestinal tract mucosa is passive, following osmotic gradients created by electrolytes and other osmotically active solutes such as glucose and amino acids. Nutrients are absorbed by active transport, facilitated transport, or passive diffusion; some solutes first require digestion to simpler compounds. The flux of electrolytes across the mucosa is bidirectional. The net result of absorption and secretion of these osmotically active solutes is net water retention or loss in the stool. In this sense, diarrhea can be considered the result of either malabsorption or net secretion of osmotically active substances.

Many nutrients, including glucose and most amino acids, are absorbed by active, carrier-mediated transport, which is coupled with sodium transport. The osmotic gradient created promotes the absorption of water. Movement of water, in turn, also carries small solutes such as sodium and chloride. This process is known as *solvent drag* and appears to be an important route for sodium absorption during normal digestion. These mechanisms of sodium movement associated

with carrier-mediated nonelectrolyte transport are important to preserve normal fluid and electrolyte balance during some episodes of diarrhea (see discussion on oral rehydration).

Active absorption of chloride in exchange for bicarbonate takes place in the ileum and colon. Potassium moves passively along electrochemical gradients in the small intestine, but both active absorption and secretion of potassium occur in the colon. The permeability of the intestinal mucosa to passive fluid and electrolyte movement is high in the duodenum and proximal jejunum and decreases distally to the ileum and colon, which are poorly permeable. This feature allows the proximal intestinal contents to equilibrate rapidly with the isotonic extracellular fluid and facilitates the rapid absorption of water and small solutes by diffusion (ie, solvent drag). Conversely, the ileum and colon are poorly permeable and are able to absorb water and sodium against high electrochemical gradients.

The pathophysiologic mechanisms for diarrhea fall into 4 basic groups: osmotic diarrhea, diarrhea resulting from secretion or altered absorption of electrolytes, exudative diarrhea, and diarrhea resulting from abnormal intestinal motility. Each mechanism has unique clinical characteristics and requires a different therapeutic approach. Therefore, for the physician considering an individual patient who has diarrhea, this framework provides a rational approach for both diagnosis and treatment. Frequently, more than one mechanism of diarrhea will be involved in an episode of diarrhea, but this variation will be apparent in the evaluation.

### Osmotic Diarrhea

The ingestion of a poorly absorbable, osmotically active substance and its presence in the bowel lumen create an osmotic gradient that encourages movement of water into the lumen and subsequently into the stool. Electrolyte losses increase because electrolytes will follow water into the lumen through solvent drag and will tend not to be reabsorbed because of unfavorable electrochemical gradients.

Two main groups of poorly absorbed solutes exist, the ingestion of which result in osmotic diarrhea. The first group includes normal dietary components that may be malabsorbed either transiently or permanently. For example, disaccharides are usually hydrolyzed to monosaccharides before they are absorbed. If a mucosal disaccharidase (eg, lactase) is deficient, then the disaccharide (in this case lactose) will be malabsorbed and will represent an osmotic load that will produce diarrhea. Similarly, monosaccharides may, at times, be poorly absorbed. Medium-chain triglycerides are also osmotically active and may lead occasionally to diarrhea when ingested in high concentration, such as when infants who have compromised mucosal function are given an elemental formula containing medium-chain triglycerides. Malabsorption of long-chain triglycerides (LCTs) does not lead to osmotic diarrhea because LCTs are large hydrophobic molecules and therefore have little osmotic activity. Malabsorption of LCTs, however, may lead to secretory diarrhea, as described later in this chapter. In addition, any osmotically active solute may produce diarrhea in healthy

persons if given in quantities great enough to surpass the intestinal capacity for absorption. Thus some infants whose bowel function is normal will not tolerate the high osmolality of an elemental formula, especially if it is undiluted. Similarly, older children may develop functional gastrointestinal symptoms, including diarrhea, from ingesting large amounts of fructose in fruits and juices. Patients who have decreased mucosal surface area may have decreased functional capacity and resultant osmotic diarrhea, a problem seen in infants after small bowel resection. Protein malabsorption does not appear to be associated with diarrhea, except in the rare instance of congenital trypsinogen or enterokinase deficiency. For example, Hartnup syndrome, with its malabsorption of primary amino acids, is not associated with diarrhea.

The second group of poorly absorbed solutes includes substances that are transported in limited amounts, even by healthy individuals. This group includes magnesium, phosphates, and sulfates. Because these ions invariably lead to diarrhea when given in large enough quantities, they are used as cathartics. The introduction of lactulose in the treatment of hepatic encephalopathy takes advantage of its being a nondigestible disaccharide that leads to acidification of colonic contents by bacterial fermentation of nonabsorbed sugar. Its side effect is diarrhea. In fact, lactulose has become a popular alternative for the treatment of constipation. Sorbitol, an artificial sweetener, causes osmotic diarrhea when ingested in large quantities.

The key characteristic of an osmotic diarrhea is its association with the ingestion of the offending solute. When a patient who has an osmotic diarrhea is given no oral or enteral feeding, the diarrhea will stop dramatically within 24 hours or less. If the agent is reintroduced, as in a lactose tolerance test, the diarrhea will reappear. The diarrhea is of a moderate volume compared with that in secretory diarrhea. The sodium and potassium ion concentrations in the stool fluid are useful in establishing a diagnosis. As ileal and colonic sodium absorption continue to function against a concentration gradient, stool sodium concentration will be lower than it is in the plasma. Normally, the electrolyte concentration in the stool is roughly twice its combined sodium and potassium concentration. When this number is much less than the total stool osmolality (usually about 290 mOsm/kg), osmotically active nonelectrolytes must be in the stool, and osmotic diarrhea is present. An osmotic gap of more than 50 mOsm/kg indicates osmotic diarrhea. In some instances, the physician may be able to find the osmotic component in the stool, such as a reducing substance in lactose malabsorption.

### Diarrhea Secondary to Secretion or Altered Electrolyte Absorption (Secretory Diarrhea)

Under normal circumstances, opposing active and passive secretory and absorptive processes result in normal luminal electrolyte and water content. Secretory diarrhea occurs when a physiologic electrolyte secretory process is pathologically stimulated. Under such circumstances, a net increase in luminal electrolytes and, subsequently, a secondary increase in water occur. In addition, an associated decrease in absorptive



processes may occur. The electrolytes that have been implicated are sodium, chloride, and perhaps bicarbonate. Diarrhea also may result from a decrease in active electrolyte absorption in the absence of any change in secretory function. Distinguishing increased electrolyte secretion from decreased absorption is clinically difficult; the results are similar.

The prototype for a secretory diarrhea is cholera. Cholera enterotoxin increases intestinal secretion of chloride and inhibits the absorption of sodium by stimulating surface epithelial adenylate cyclase, leading to an increase in cellular levels of cyclic 3'5'-adenosine monophosphate. The intestinal mucosa appears normal during cholera infection, without evidence of cell necrosis, inflammation, or local bacterial invasion; and other cell absorptive functions remain normal. The normal absorption of glucose provides a route for secondary sodium absorption; as a result, oral glucose- and electrolyte-containing solutions have gained wide use in the management of cholera. A growing number of infectious agents may be associated with secretory diarrhea. Toxigenic *Escherichia coli* produces at least 2 enterotoxins that activate adenylate cyclase or guanylate cyclase. Infantile diarrhea resulting from enterotoxigenic *E coli* is well known. Other bacteria that have been associated with stimulation of intestinal secretion are strains of *Shigella*, *Salmonella*, *Yersinia*, *Klebsiella*, *Clostridium perfringens*, *Staphylococcus aureus*, and *Pseudomonas* species. Experimental work with viral enteritis suggests that this diarrhea has a significant secretory component. With rotavirus infection, secretion is the result of viral enterotoxin and only secondarily of damage to villous epithelial cells in the small intestine and repopulation of the villi with immature crypt cells.

Noninfectious causes of secretory diarrhea exist as well. Malabsorbed bile acids and long-chain fats have been shown to stimulate a colonic secretory diarrhea. Certain prostaglandins have been shown to activate adenylate cyclase and produce intestinal secretion in experimental models. Because prostaglandins are released during inflammation, researchers have hypothesized that diarrhea associated with certain inflammatory states may be caused by these hormones. This hypothesis is a particularly appealing way to explain the small bowel secretion that may take place with chronic inflammatory bowel disease. Prostaglandins have also been suggested as possible mediators for the activation of adenylate cyclase by *Salmonella* organisms in the absence of an enterotoxin. Secretory diarrhea may occur in association with increased levels of certain gastrointestinal hormones, most notably vasoactive intestinal polypeptide (VIP).

Isolated decrease of electrolyte absorption is much less frequent. The best-known example, although extremely rare, is congenital chloride-losing diarrhea. This autosomal recessive abnormality results from the apparent lack of normal, active chloride absorption by the distal small intestine. Great quantities of chloride are lost in the stool and lead to diarrhea from birth onward. A metabolic alkalosis results, in contrast to other causes of diarrhea.

The stool in secretory diarrheas tends to be watery and large in volume. Unlike osmotic diarrhea, secretory

diarrhea persists despite discontinuing oral intake. The stool electrolyte concentration (ie, twice the sum of the sodium and potassium concentrations) is about equal to the stool water osmolality because no significant osmotic nonelectrolyte component is present.

### Exudative Diarrhea

A break in the integrity of the mucosal surface of the intestine can result in water and electrolyte loss, driven by hydrostatic pressure in blood vessels and lymphatics. The exudate contains mucus, protein, and blood cells. Examples include infectious, allergic, or ulcerative colitis.

### Motility Diarrhea

The intestine has a cyclical, orderly pattern of motility. Increased, decreased, or disordered movement can lead to diarrhea. Rapid intestinal transit often occurs in association with osmotic and secretory diarrheas. Increased intraluminal volume has been implicated in stimulating increased peristaltic action. Increased motility may cause diarrhea by allowing less time for the contact of intraluminal contents with absorptive surfaces. When bowel function is compromised, as with short bowel syndrome, the time of contact with the limited functioning surface may be a crucial factor. In irritable bowel syndrome, disordered motility may also play a role. Slowed transit and severely disordered motility lead to intraluminal stasis. In the normal bowel, steady, progressive movement of chyme is one of the mechanisms that prevents the development of bacterial overgrowth, whereas stasis encourages overgrowth. Certain bacteria deconjugate bile acids in the upper small bowel and produce fat malabsorption. In addition, bacterial proteases may damage the small bowel surface. Stasis may result from an anatomic obstruction, as well as from functional motor disorders. Disordered motility frequently is an associated factor in chronic inflammatory bowel disease. Stools associated with motility diarrhea, except those secondary to fatty acid malabsorption, tend to be small in volume. The response to feeding is variable, and the gastrocolic reflex may be heightened. Patients who have chronic inflammatory bowel disease may find that meals stimulate intestinal activity, resulting in postprandial abdominal cramps and bowel movements.

## ACUTE DIARRHEA

Acute diarrhea is common in children, is transient and usually self-limited, and is caused most often by infection. In the United States, children in the first few years of life average 1 or 2 episodes per year. For most diarrheal infections, the incidence is greatest before 4 years of age. The role of the physician is to rule out causes that require specific treatment, to advise parents in supportive management, and to provide follow-up for possible complications. Box 138-1 lists some of the more frequent causes of acute diarrhea categorized by the usual presentation with or without gross blood in the stool. Transmission of diarrheal organisms is commonly by food, water, person-to-person spread, or exposure to animals at home, fairs, and petting zoos. Child care centers are likely sites for the spread

**BOX 138-1 Causes of Acute Diarrhea****USUALLY WITHOUT BLOOD IN STOOL**

- Viral enteritis rotavirus, orbivirus, noroviruses, other caliciviruses, enteric adenovirus, astrovirus, sapoviruses
- Enterotoxin *E coli*, *Klebsiella* organisms, cholera, *C perfringens*, *Staphylococcus* organisms, *Bacillus cereus*, and *Vibrio* species
- Parasitic *Giardia*, *Cryptosporidium*, *Cyclospora*, *Dientamoeba fragilis*, and *Blastocystis hominis* organisms
- Extraintestinal infection otitis media and urinary tract infection
- Antibiotic-induced and *C difficile* toxin (without pseudomembranous colitis)

**COMMONLY ASSOCIATED WITH BLOOD IN STOOL**

- Bacterial *Shigella*, *Salmonella*, and *Campylobacter* organisms, *Yersinia enterocolitica*, invasive *E coli*, gonococcus (venereal spread), enteroadherent *E coli*, enteroaggregative *E coli*, *Aeromonas hydrophilia*, and *Plesiomonas shigelloides*
- Cytomegalovirus (especially in immunocompromised individuals)
- Amebic dysentery, *Trichuris trichiura* (whipworm)
- Hemolytic uremic syndrome (enterohemorrhagic *E coli*—*E coli* O157:H7 and other Shiga toxin-producing *E coli*)
- Henoch-Schönlein purpura
- Pseudomembranous enterocolitis (*C difficile* toxin)
- Ulcerative or granulomatous colitis (acute presentation)
- Necrotizing enterocolitis (neonates)

of enteric pathogens. Pathogens that have been associated with epidemics include *Giardia lamblia*, rotavirus, *Norovirus*, *Shigella*, *Campylobacter*, *Cryptosporidium*, and *C difficile* organisms.

**Neonatal Diarrhea**

Neonates with acute diarrhea must be considered differently from older infants and children because of both lower tolerance to the associated fluid shifts and the greater likelihood of severe infection or of a congenital anomaly. In addition, signs of necrotizing enterocolitis, including gastric retention (frequently bilious), distention, and occult or bright red blood in the stool, should raise concern. Although this disease usually occurs in premature infants, it also has been reported in full-term infants. The presence of pneumatosis intestinalis, gas in the portal vein, or free intraperitoneal gas seen on abdominal radiographs supports this diagnosis. Epidemics of diarrhea associated with rotavirus, enteropathogenic *E coli*, salmonellae, and other organisms, including *Klebsiella* organisms, have been reported in nurseries. If the onset of diarrhea is associated with initial feedings, then the physician should consider congenital digestive defects, especially sugar intolerance. Hirschsprung disease may produce acute diarrhea and enterocolitis

in the neonatal period and should be considered, especially in the infant who has not passed meconium in the first 24 hours. Bloody diarrhea that results from cow milk or soy protein intolerance may develop as early as the first few days of life. Resolution and exacerbation on removal and reintroduction of cow milk or soy formula, as well as an atopic family history, are clues to the diagnosis.

**Differential Diagnosis in the Older Infant and Child**

Most episodes of acute diarrhea are transient and benign. On the initial visit, the physician must evaluate the course in terms of both possible causes and the status of hydration. The diarrhea is usually the result of viral enteritis, typically occurring with low-grade fever, vomiting, and frequent watery stools. Generally, the stools are without blood or white blood cells. Enterotoxin-producing organisms (eg, toxigenic *E coli*) are associated with watery stools and are without evidence of mucosal invasion (no high fever or blood in the stool). *G lamblia* produces watery diarrhea associated with intestinal gas and crampy abdominal pain. Diarrhea in association with extraintestinal infections, most notably otitis media and pyelonephritis, has been called *parenteral diarrhea*; its mechanism is obscure. An associated viral enteritis may occur in some cases of otitis media. Certain antibiotics, especially ampicillin, have been associated with transient diarrhea. Less common but of greater danger is antibiotic-associated pseudomembranous colitis, which may occur acutely or as a more chronic illness of 1 or 2 months' duration. *C difficile* toxin, the cause of most cases of pseudomembranous colitis, may also be associated with chronic childhood diarrhea in the absence of colitis.

The presence of blood in the stool, especially with symptoms of colonic involvement (tenesmus, urgency, and crampy lower abdominal pain), should make the physician think of infection with *Campylobacter*, *Shigella*, or *Salmonella* organisms or with *C difficile* toxin-associated pseudomembranous colitis. The symptoms of dysentery may be less striking with *Salmonella*. When the *Shigella* is an enterotoxin-producing organism, watery diarrhea may actually precede the onset of dysentery.

Patients who have *Shigella* organisms tend to appear severely ill and may have meningismus or seizures. The stools tend to be foul smelling. Up to 40% of individuals who have Guillain-Barré syndrome have evidence of a *Campylobacter* infection occurring before the onset of neurologic symptoms. *Yersinia enterocolitis* also may be associated with blood in the stool, but *Yersinia* appears to be incriminated less commonly as an etiologic agent in the United States. *E coli* can produce diarrhea by several pathogenic mechanisms; the enteroadherent, enteroinvasive, enterohemorrhagic, and enteroaggregative forms can all be associated with blood in the stool. Hemolytic uremic syndrome is the result largely of enterohemorrhagic *E coli* (especially Shiga toxin-producing *E coli* O157:H7) and less commonly *Shigella* infections.

Amebiasis is unusual in the United States, but *Entamoeba histolytica* can produce a picture of acute colitis. Causes of bloody diarrhea that are not obviously

infectious include intussusception and immune deficiencies. Chronic inflammatory bowel disease can produce an initial episode of acute dysentery, although the history may reveal previous episodes; arthralgia or growth failure may have preceded the diarrhea. A history of recent similar diarrheal illness in family members or friends suggests an infectious diarrhea.

Food-borne spread of organisms or toxins is an important cause of acute diarrheal illness. Improperly prepared poultry and eggs are the major source for both campylobacteriosis and salmonellosis, and the major source for *E coli* O157:H7 infection is ground beef. Preventive measures include safe food-handling practices, pasteurization of in-shell eggs, and irradiation of ground meat and raw poultry. Explosive diarrhea after ingesting seafood is likely from infection with *Vibrio* species. Outbreaks of norovirus have occurred on cruises ships as well as college campuses. The most common pathogens causing food-borne illness are listed in Box 138-2.

### Evaluation

At the initial evaluation (Box 138-3), the physician should establish the quantity of the diarrhea, the child's ability to maintain oral intake, and the presence of associated vomiting. On physical examination, the state of hydration should be estimated. The presence of tears and saliva is usually evidence of adequate hydration, but the most reliable reassurance comes from a normal heart rate and a brisk capillary refill. A simple guideline to hydration is that the absence of tears and the presence of a dry mouth suggest 5% dehydration; the addition of sunken eyes, sunken fontanelle, and poor skin turgor suggests 10% dehydration. Shock indicates at least 15% dehydration. In the presence of hypernatremia, the state of dehydration is typically more severe than suggested on physical examination inasmuch as extracellular fluid volume tends to be preserved at the expense of intracellular volume. A recorded weight is essential; it can be compared with previous weights and will also be available to reevaluate the state of hydration during the illness. Information about the frequency and quantity of urination is important. A history of good urine output is reassuring. Parents may underestimate or overestimate urine output (frequency and volume), especially when urine becomes mixed with liquid stool.

A stool culture should be obtained if blood or leukocytes are noted in the stool and the child is severely ill. Examination of the stool for leukocytes is helpful in establishing the presence of colitis. In the presence of both infectious and noninfectious colitis, white blood cells (WBCs) are usually found in high numbers, frequently in sheets. Polymorphonuclear leukocytes usually account for at least 60% to 80% of the cells; the presence of only occasional cells is considered a negative finding. The absence of WBCs in grossly bloody diarrheal stool occurs with enterohemorrhagic *E coli* infection but should also direct attention to entities such as intussusception and Meckel diverticulum when these diagnoses seem clinically appropriate. Amebic colitis also may not be associated with WBCs in the stool, although the trophozoites and numerous red blood cells may be visible on a saline wet mount

### BOX 138-2 Top 5 Pathogens Causing Domestically Acquired Food-Borne Illnesses (CDC 2011 Estimates)<sup>a</sup>

- *Norovirus*
- *Salmonella*, nontyphoidal
- *C perfringens*
- *Campylobacter* species
- *S aureus*

<sup>a</sup>The top five pathogens from among 31 pathogens known by the Centers for Disease Control and Prevention (CDC) to cause food-borne illness. However, unspecified agents account for 80% of the annual number of food-borne illnesses estimated by the CDC.<sup>21,22</sup>

### BOX 138-3 Evaluation of Acute Diarrhea

#### HISTORY

1. Length of illness
2. Characterization of stools: frequency, looseness (watery versus mushy), and presence of gross blood
3. Oral intake: diet, quantity of fluids and solids taken
4. Presence of vomiting
5. Associated symptoms: fever, rash, and arthralgia
6. Urine output: frequency and qualitative amount
7. Possible exposure to diarrheal illness

#### PHYSICAL EXAMINATION

1. Hydration status: weight (stable or loss), heart rate, capillary refill, mucosa (moist or dry), saliva and tears (present or absent), skin turgor (normal or poor), eyeballs and fontanelle (normal or sunken), and vital signs
2. Alertness
3. Infant: vigor of suck

#### LABORATORY (PERFORMED AS INDICATED)

1. Stool evaluation: test for viral etiology when available, culture, ova and parasites, smear for white blood cells, *C difficile* toxin assay, occult blood, and reducing substances
2. Complete blood count
3. If hydration status is in question: blood urea nitrogen (BUN) and serum electrolyte levels
4. Urinalysis
5. If child is lethargic or has had a seizure, culture for sepsis: measure the BUN and serum electrolyte and glucose levels and examine and culture the cerebrospinal fluid

preparation of the stool. Invasive bacterial diarrhea frequently is associated with a peripheral blood leukocytosis.

### Treatment

The cornerstone of treatment in acute gastroenteritis is good fluid and electrolyte management (Box 138-4).

**BOX 138-4 Fluid and Electrolyte Management of Acute Diarrhea**

- A. General rules for management of acute diarrhea
1. Oral rehydration therapy with glucose-electrolyte solution (oral rehydration solution [ORS]) is the preferred treatment of fluid and electrolyte loss, except as noted below. These solutions generally contain 25 g/L glucose (or  $\geq 30$  g/L rice starch), 45–90 mEq/L sodium, 20–25 mEq/L potassium, and 30 mEq/L bicarbonate. The higher sodium concentration is appropriate for rehydration; the lower concentration is usually adequate for rehydration with mild diarrhea and is appropriate for maintenance.
  2. Moderate to high stool output should be replaced with ORS at 10 mL/kg/stool, if losses cannot be estimated. Losses from emesis should be replaced with ORS at 2 mL/kg/episode of emesis or replace estimated losses.
  3. The use of ORS is labor intensive. If a caregiver is not available to give small amounts of fluid frequently, then intravenous therapy may be necessary. If the child is not severely dehydrated, then oral rehydration may be completed at home with close follow-up. Otherwise, intravenous fluids should include replacement of deficit, ongoing losses, and maintenance fluids. Addition of intravenous potassium should wait until urine output is established.
  4. ORS therapy is effective for hypernatremic dehydration, as well as hyponatremic and isotonic dehydration.
  5. Age-appropriate feedings should be continued during acute diarrhea, except as noted below. Formula should be offered full strength. Diet may be better tolerated if fatty foods and foods high in simple sugars (eg, undiluted juices and soft drinks) are avoided.
  6. Breastfeeding should be continued when possible.
  7. Lactose-free diet is generally unnecessary. If stools worsen on reintroduction of lactose (human milk, cow milk, or lactose-containing formula), then lactose intolerance should be considered. If stools become acid and contain reducing substances, then lactose intolerance is likely.
- B. No dehydration
1. Continue age-appropriate feeding (see A.5, A.6).
  2. Use ORS only to replace excessive stool output (see A.2).
- C. Mild-to-moderate dehydration (3%–9% of body weight)
1. Correct dehydration with 50–100 mL/kg ORS over 3–4 hours, and replace continuing losses from stool and emesis with additional ORS (see A.2). See section E for special considerations for vomiting.
  2. Reevaluate hydration and replacement of losses at least every 1–2 hours. This process may require medical supervision (emergency department, hospital outpatient unit, or physician's office).
3. Once dehydration is corrected, begin feeding (see A.5, A.6) and continue to correct losses as above.
- D. Severe dehydration (at least 10%)
1. Resuscitate with intravenous or intraosseous normal saline or lactated Ringer's solution 20 mL/kg of body weight over 1 hour. Monitor vital signs closely. Repeat until pulse and state of consciousness return to normal. Larger volumes and shorter periods of administration may be required. Delay giving intravenous potassium until urine output is established.
  2. Determine serum electrolyte levels.
  3. Lack of response to initial resuscitation suggests an underlying problem such as septic shock, toxic shock syndrome, myocarditis, cardiomyopathy, or pericarditis. Persistently poor urine output may be a sign of hemolytic uremic syndrome.
  4. ORS may be initiated when the child's condition has stabilized and mental status is satisfactory. An intravenous line should be maintained until no longer needed. See section E for special considerations for vomiting.
  5. Feeding may be restarted when rehydration is complete (see A.1, A.2).
- E. Special considerations
1. Vomiting
    - a. Vomiting occurs commonly during acute gastroenteritis.
    - b. Children who are dehydrated and vomit usually tolerate ORS.
    - c. Intractable, severe vomiting, unconsciousness, and ileus are contraindications to ORS treatment.
    - d. ORS should be started at 5 mL every 1–2 minutes.
    - e. Vomiting usually decreases as dehydration improves; larger amounts can be given at less frequent intervals.
    - f. Nasogastric tube can be used for continuous ORS infusion for persistent vomiting or feeding refusal secondary to mouth ulcers (do not use in comatose child or one who has ileus or intestinal obstruction).
    - g. Intravenous fluids should be used if ORS treatment is unsuccessful.
  2. Refusal to take ORS
    - a. Children who are not dehydrated may not take ORS because of the salty taste. However, dehydrated children generally take it well.
    - b. Giving ORS in small amounts at first allows the child to become accustomed to the taste.
    - c. ORS can be frozen in ice-pop form.

Modified from American Academy of Pediatrics Provisional Committee on Quality Improvement, Subcommittee on Acute Gastroenteritis. Practice parameter: the management of acute gastroenteritis in young children. *Pediatrics*. 1996;97:424–435; and King CK, Glass R, Bresee JS, et al. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR*. 2003;52:1–16.



Commercial oral hydration solutions provide more sodium and lower carbohydrate concentration than traditional clear liquids. Human milk contains low concentrations of sodium (6–7 mEq/L); therefore, a supplemental rehydration solution should be used when diarrhea is persistent or severe.

Electrolyte content in diarrheal stool varies widely, with the highest concentrations occurring in secretory diarrheas such as cholera. Fecal sodium levels may range from 40 to 100 mEq/L and may occasionally be as high as 150 mEq/L. In rotavirus diarrhea, fecal sodium concentration is typically 20 to 40 mEq/L.

Viruses cause at least 40% to 50% of acute diarrheal illnesses in childhood. Rotavirus is becoming less common with the widespread use of vaccine; other viruses, in descending frequency, are noroviruses, astroviruses, and enteric adenoviruses. Viral enteritis has been shown to result in a transient, patchy, mucosal lesion of the small intestine, which may be associated with temporary lactose and fat malabsorption. Decreased mucosal lactase levels may be seen. In experimental viral diarrhea in piglets, intestinal glucose-stimulated absorption of sodium, and therefore water, is impaired. Rotavirus produces an enterotoxin (known as NSP4), which is of much greater importance in the production of diarrhea than virus-induced mucosal damage. Abnormal glucose absorption has also been observed in infants who have rotavirus enteritis. Nevertheless, secretion can be converted to net absorption in most children by providing oral glucose electrolyte solution because of the patchy nature of the lesion in viral gastroenteritis.

Oral rehydration solutions have been used safely and successfully to treat acute diarrhea with dehydration. Infants who have diarrhea are usually able to drink large volumes of salty-tasting liquids ad libitum appropriate for the stool output. Episodes of diarrhea in previously healthy, well-nourished children are often mild; nevertheless, the use of oral rehydration solutions to replace diarrheal loss is encouraged in infants. Liquids can be offered ad libitum, although smaller volumes per feeding may be tolerated better when diarrhea is associated with vomiting. Guidelines for rehydration are described in Box 138-4. The most recent World Health Organization recommendation is for a lower-osmolarity (245 mOsm/L) solution for rehydration (containing 75 mEq/L sodium and 75 mmol/L glucose). The contents of commercially available rehydration solutions have evolved with advances in the understanding of optimal absorption during oral rehydration; thus, the physician should consult current manufacturer specifications before choosing a product. Continuing regular feedings with supplemental oral rehydration solution is generally tolerated and thought to lead to quicker recovery. Vomiting is usually not a contraindication to oral rehydration.

Oral rehydration appears to be associated with shorter hospitalization and lower medical costs. Infants who have hypernatremic dehydration have fewer problems with seizures during oral rehydration compared with intravenous rehydration. Oral rehydration therapy, however, requires the constant

presence of a caretaker, although this individual need not have previous medical experience. The use of starches, amino acids, and probiotics in oral maintenance or rehydration solution to improve sodium and water absorption has been considered.

Indications for medications in the treatment of acute gastroenteritis in infants and children are limited. As already noted, the key mechanisms involved are intestinal secretion and transient malabsorption; physiologically, no apparent rationale exists for medications that slow gut motility (diphenoxylate, loperamide, and anticholinergics). In fact, pooling of fluid in the intestinal lumen after treatment may give a false impression that the diarrhea has improved. Slowing intestinal transit with drugs may allow greater mucosal contact with pathogens and thereby allow for local mucosal invasion. Bismuth subsalicylate, which may decrease the duration of diarrhea, has been shown to be a safe adjunct to oral rehydration but is not used routinely. Antibiotics are useful in specific situations: *Shigella* dysentery, *Yersinia* or *Campylobacter* gastroenteritis, pseudomembranous colitis, *Salmonella* infections in infants younger than 6 months, and *Salmonella* infections in older patients who have enteric fever, typhoid fever, or complications of bacteremia. *Campylobacter* gastroenteritis must be identified very early for antibiotics to shorten the illness. For the individual patient, the presence of an *E coli* serotype previously labeled enteropathogenic correlates poorly with the presence of diarrhea and is not alone an indication for antibiotic treatment. *Lactobacillus* or other probiotics may be useful to prevent infectious diarrhea but are probably not effective as treatment.

Most episodes of gastroenteritis are self-limited and of short duration. Symptoms of rotavirus enteritis typically last 4 to 10 days. However, prolonged secretion of rotavirus in stool (up to 8 weeks) has been demonstrated in association with severe gastroenteritis in immunocompetent children. The current approach to treatment is to restart the previous full-strength formula and solids early after the onset of diarrhea. If diarrhea recurs on the introduction of lactose-containing formula, then the child may have transient lactose intolerance. In this situation, a lactose-free formula should be offered. (The sugar in this formula can be either sucrose or a glucose polymer.) Sugar malabsorption (see Malabsorption Syndromes) can be identified by the determination of reducing substance in the stool. (Sucrose must be hydrolyzed first with hydrochloric acid.) Transient lactose intolerance usually lasts only a week or less but can, at times, persist for months. If the degree of dehydration is 5% or greater, then use of oral rehydration solution should be instituted, if possible, in the manner presented in Box 138-4. For severe dehydration or shock, rapid intravenous administration of 10 to 20 mL/kg of isotonic fluid or colloid is required initially and may need to be repeated early. Hyponatremia and hypernatremia must be corrected slowly to prevent complications of the central nervous system. Oral solutions are better tolerated and result in fewer central nervous system complications than intravenous solutions in infants who have hypernatremia. Potassium should not be

added to intravenous fluids until adequate urine output is established. Urine specific gravity may be misleading inasmuch as kidney-concentrating ability may be poor as a result of reduced renal urea or whole-body potassium. Inability to acidify the urine during acute diarrhea occurs commonly in infants despite the presence of metabolic acidosis. This finding is thought to be caused by sodium deficiency and the resulting inadequate delivery of sodium to the distal nephron.

## CHRONIC DIARRHEA

Although chronic diarrhea occurs in children of all ages, it is most frequent and often most challenging to diagnose in infants. Both healthy and ill infants can develop diarrhea in response to a variety of stresses. The younger the infant is, the more likely he or she will be to enter the cycle of diarrhea and secondary malnutrition that leads to further diarrhea, malnutrition, and susceptibility to infection (known as protracted diarrhea of infancy). Many of the causes of chronic diarrhea may appear at any time during childhood. Certain diseases, however, occur more commonly in infancy; others are more likely to begin in later childhood. Dividing the causes of diarrhea between infancy and older childhood is arbitrary because the groups overlap, but this method is a helpful guide in initiating the evaluation of the child who has chronic diarrhea (Box 138-5).

### Infants

The physician confronted with an infant who is reported to have chronic diarrhea must decide first whether the stool pattern is abnormal. A nursing mother who has not been forewarned may become concerned about the appearance and frequency of her child's transitional stools. The infant's weight gain and healthy appearance, combined with an explanation about stools of breastfed infants, should dispel these concerns.

In the latter half of the first year and in the second year, the most common cause for persistent diarrhea is chronic nonspecific diarrhea (also called *toddler's diarrhea*). Affected infants and toddlers have intermittent loose stools for no apparent reason. In many instances, the stools occur early in the day and typically not overnight. These children appear healthy and are thriving according to weight and length growth curves, unless inappropriate treatment with clear fluids has led to caloric deprivation. This condition represents a stool pattern rather than a pathologic state and requires minimal or no laboratory evaluation. Symptoms may begin initially after an apparent acute enteritis (postinfectious irritable bowel).

Treatment may include restricting the frequency of feedings, whether liquids or solids, in an effort to decrease stimulation of the gastrocolic reflex (in the toddler, 3 meals and a bedtime snack with nothing by mouth in between); restricting the volumes of fluids ingested when excessive; avoiding excessive intake of juices; and reassuring the parents of the benign nature of this entity. A high-fat diet may be helpful in some children, although probably is of less importance.

## BOX 138-5 Causes of Chronic Diarrhea

### COMMON CAUSES

- Chronic enteric infection: *Salmonella* organisms; *Yersinia enterocolitica*; *Campylobacter*, *Giardia*, *Cryptosporidium*, and *Cyclospora* organisms; *C difficile* toxin; enteroadherent *E coli*; rotavirus (in immunodeficient patients); cytomegalovirus; adenovirus; and HIV
- Food allergy
- Chronic nonspecific diarrhea (toddler's diarrhea, irritable colon of childhood); postinfectious irritable bowel
- Disaccharide intolerance
- Chronic constipation with overflow diarrhea
- Cystic fibrosis
- Celiac disease (gluten-sensitive enteropathy)
- Inflammatory bowel disease: Crohn disease and ulcerative colitis
- Hirschsprung disease
- Immunodeficiency states
- Monosaccharide intolerance
- Eosinophilic (allergic) gastroenteritis
- Short bowel syndrome
- Urinary tract infection
- Postenteritis bile acid malabsorption
- Factitious causes

### LESS COMMON CAUSES

- Autoimmune enteropathy
- Hormonal: adrenal insufficiency and hyperthyroidism
- Vasoactive intestinal polypeptide-secreting tumor
- Neural crest tumor and carcinoid
- Intestinal lymphangiectasia
- Acrodermatitis enteropathica
- Intestinal stricture or blind loop
- Pancreatic insufficiency with neutropenia
- Trypsinogen or enterokinase deficiency
- Congenital chloride-losing diarrhea
- Congenital sodium-secretory diarrhea
- Abetalipoproteinemia
- Microvillus inclusion disease
- Tufting disease
- Immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX)
- Intestinal pseudoobstruction
- Ileal bile salt receptor defect
- Congenital disorders of glycosylation

Cholestyramine (2 g by mouth 1 to 3 times daily) is also effective at times; however, the duration of use should be restricted because of the potential for interference with fat-soluble vitamin absorption. In any event, this condition is self-limited and typically resolves by 3.5 years of age. The only danger is that well-intentioned parents may restrict oral intake to clear liquids repeatedly in an effort to treat the child; this action may result in poor weight gain. Bile acid

malabsorption is an occasional sequela of gastroenteritis that can produce persistent, watery diarrhea. This condition also will respond to cholestyramine therapy.

### **Protracted Diarrhea of Infancy**

The syndrome of protracted diarrhea of infancy is poorly understood, probably representing the final pathway for multiple causes, including gastrointestinal infections and, perhaps, food intolerances. This condition is defined somewhat arbitrarily as occurring in infants younger than 3 months and persisting for more than 2 weeks. Historically, this syndrome, previously called intractable diarrhea of infancy, has been associated with a high mortality from irreversible diarrhea and related malnutrition. However, the outcome has improved markedly with the advent of elemental diets and total parenteral nutrition. Now, intractable diarrhea is rare and related to more specific causes, such as microvillus inclusion disease.

Generally, malnutrition develops and, in concert with the protracted diarrhea, leads to alteration of gastrointestinal flora sometimes associated with bacterial overgrowth of the small intestine. Altered mucosal function of the small intestine and transient pancreatic insufficiency may occur with malnutrition and protracted diarrhea. Bile salts may be deconjugated as a result of bacterial overgrowth. In many instances, the initiating cause of protracted diarrhea is not found; it may likely be no longer present when the diarrhea has become chronic. The small bowel biopsy specimen may show patchy villous shortening with a decreased villus-to-crypt ratio and marked inflammation, as well as a damaged surface epithelium. However, the results of the small bowel biopsy also may be normal. Similarly, a rectal biopsy specimen may show evidence of inflammation, including crypt abscesses, or it may be normal. The presence or absence of these biopsy findings may not correlate with the severity of the clinical syndrome. Affected infants are severely malnourished and have low serum protein and hemoglobin levels. In many instances, they have had repeated treatment with oral clear liquids and peripheral intravenous fluids, all of which provide inadequate nutrient intake.

When evaluating a young infant who has protracted diarrhea, the physician must rule out causes that require urgent treatment while correcting hydration and nutrition. Rehydration is similar to the treatment of acute diarrhea, although estimating the level of dehydration accurately is difficult in the presence of malnutrition, and initial oral therapy is less likely to be successful. Stool output should be measured. If the urine is collected in a urine bag, then diapers can be weighed before and after stools to give an accurate measure of stool output. Urine specific gravity and volume may be deceptive because of poor concentration by the kidneys in the presence of malnutrition and total-body hypokalemia. The infant should be weighed at least daily.

Infection should be ruled out as a cause of diarrhea early in the evaluation. Several stools should be collected for culture, for examination for parasites, and for *C. difficile* toxin assay when indicated; blood and

urine cultures should also be ordered. Consideration of Hirschsprung disease with enterocolitis is important because infants who have this disorder are prone to perforation of the colon unless a decompression colostomy is performed. In such infants, eliciting a history of early obstipation and of the absence of stools in the first 24 hours of life is usually possible. In Hirschsprung disease, a flat plate radiograph of the abdomen may show a dilated colon with absence of air in the rectum. Toxic megacolon may also be seen in infectious colitis or in chronic inflammatory bowel disease in infancy. Air-fluid levels throughout the bowel are common in infants who have gastroenteritis, and this sign is not helpful in defining a cause. A barium enema under low pressure in the unprepared patient may show the narrow distal segment of rectum; however, this finding may not be present in neonates, and evaluation for ganglion cells on rectal biopsy is often necessary. The transition zone of Hirschsprung disease may be more obvious on a delayed radiograph (24–48 hours after the barium enema).

For a child who has chronic diarrhea and has been fed recently, the presence of reducing substance or an acid stool pH (<5.3) suggests carbohydrate malabsorption. The stool pH is not a good measure of the effect of diarrhea on total-body acid-base balance. If stool concentration of sodium and potassium minus chloride is greater than the plasma bicarbonate, then the infant is losing bicarbonate. WBCs or gross blood in the stool usually indicates colonic inflammation; occult blood in the stool suggests loss of blood across the mucosa anywhere in the gastrointestinal tract.

Nutritional rehabilitation should begin at once. The best choices are either enteral alimentation with an elemental or modular formula or total parenteral nutrition (TPN), peripheral or central. In many instances, enteral nutrition is tolerated best by the continuous-drip method, and recovery may be more rapid when enteral alimentation is used. Nevertheless, unsuccessful attempts at enteral feeding necessitate initiation of TPN therapy in some infants. Initial treatment with TPN and a gradually increasing, continuous enteral drip is a good approach to patients who do not tolerate elemental diet alone. Elemental formulas are composed of predigested components in fixed proportions; modular formulas allow the physician to vary the components. Stool output and weight gain may be measured to assess the infant's response.

During the treatment, further workup, including an upper gastrointestinal series with small bowel radiograph, barium enema, small bowel biopsy, proctoscopy, the measurement of sweat electrolytes, and other specific tests to rule out the entities noted later in this chapter, should be conducted as indicated. If disaccharidase levels are abnormal on small bowel biopsy, then disaccharides should be avoided.

### **Malabsorption Syndromes**

Infants and children who have malabsorption syndromes typically have diarrhea, steatorrhea, growth failure, or a combination of these conditions. Celiac

disease and cystic fibrosis are the most common chronic disorders that cause malabsorption in children in the United States. Steatorrhea is much more striking with cystic fibrosis, resulting from pancreatic insufficiency and secondary maldigestion. Infants with cystic fibrosis who nurse or are fed soy formula, but not cow milk formula, may exhibit protein malabsorption in the first months of life.

Although cystic fibrosis is thought of primarily as a respiratory disease, some infants and children have malabsorption and little history of respiratory symptoms; these patients typically have voracious appetites. The diagnosis must be confirmed by sweat electrolyte studies or genetic testing. Other diseases much less common than cystic fibrosis may be associated with prominent steatorrhea in early infancy, including congenital pancreatic insufficiency with cyclic neutropenia (Shwachman-Diamond syndrome), intestinal lymphangiectasia, and abetalipoproteinemia. Transient steatorrhea may follow an acute enteritis. Measurement of stool pancreatic elastase level is a useful screening test for pancreatic insufficiency.

Celiac disease (gluten-sensitive enteropathy) is now appreciated to be a much more frequent disorder than previously recognized. Presentation may occur at any age, and the manifestations may be subtle. In infancy, celiac disease becomes apparent within 1 to several months after the introduction of gluten-containing products (wheat, rye, barley) into the diet. The classic symptoms in an infant with celiac disease are irritability, loose stools, poor appetite, and poor weight gain. Vomiting may occur as well. In older children, features such as growth retardation or iron deficiency anemia may be more striking than diarrhea. In many patients, steatorrhea is not present, and results of absorptive studies such as the D-xylose tolerance test may be normal. Gluten-free dietary trials and antigliadin antibody studies may be misleading. The presence of endomysial antibody (EMA), tissue transglutaminase (tTG), or deamidated gliadin peptide (DGP) antibody in the serum is a much more reliable predictor of celiac disease. tTG has been identified as the antigen recognized by endomysial antibody. In individuals with total serum immunoglobulin A (IgA) deficiency, assay for tTG IgA, EMA, or DGP IgA is unreliable. A tTG or DGP IgG level can be measured. A diagnosis of celiac disease should be confirmed by small bowel biopsy. In the past, the diagnosis was often reconfirmed by a challenge with gluten and a repeat biopsy. Currently available antibody studies make this strategy unnecessary. Measuring endomysial IgA or tTG antibody may be useful in assessing the adequacy of a gluten-free diet or evaluating adherence to diet. *Giardia* infection can produce small bowel malabsorption that mimics celiac disease.

Carbohydrate (monosaccharide or disaccharide) intolerance may be primary or more commonly secondary to other gastrointestinal disorders. The congenital form of lactase deficiency is much less common than congenital sucrase-isomaltase deficiency, which typically appears after introduction of sucrose into the diet in solids. In carbohydrate intolerance, the extent of symptoms varies directly with the quantity of the offending sugar in the diet. Similarly, the age at

presentation varies with the age at which the sugar is introduced into the diet. Infants who have congenital sucrase-isomaltase deficiency may have diarrhea when fed formula containing glucose polymers as well. The diagnosis can be established by conducting standard sugar tolerance tests, measuring hydrogen excretion in the breath, or assaying the enzymes present in tissue obtained by a small bowel biopsy. Examination of the stool for reducing sugars is an imprecise screening test for stool carbohydrate content. A stool pH less than 5.3 is suggestive of carbohydrate malabsorption, whereas a stool pH more than 5.6 is evidence against this diagnosis. Sorbitol, a sugar substitute, as well as fructose, may produce diarrhea when ingested in large amounts, and both are present in fruits. Oral enzyme supplements are available for both lactase and sucrase deficiency.

The congenital deficiency of trypsinogen, the zymogen precursor of the pancreatic protease trypsin, has been reported to be a very rare cause of congenital diarrhea. The absence of trypsin in the stool suggests the diagnosis (in the absence of cystic fibrosis and congenital pancreatic insufficiency), but evaluation of the pancreatic proteases in the duodenal aspirate is necessary to confirm this impression. Congenital deficiency of enterokinase, the intestinal enzyme that activates trypsinogen to trypsin, appears in a similar fashion to that of congenital trypsinogen deficiency but is reversed with very small amounts of pancreatic replacement.

A recently described congenital, autosomal recessive disorder of chronic malabsorption and diarrhea has been characterized by a lack of intestinal enteroendocrine cells. This disorder is associated with a mutation of a gene (*NEUROG3*) expressing a protein required for endocrine cell development in the pancreas and intestine. Individuals with this disorder have been identified to develop glucose intolerance as well.

### Infection

Acute bacterial or viral enteritis may be an important initiator of protracted diarrhea in infancy. If the initial infection is no longer present at the time of evaluation for chronic diarrhea, then this association will be difficult to prove. Infections at distant sites, especially urinary tract infections, have also been implicated as a cause of chronic diarrhea in infancy. A urinalysis and urine culture should be obtained routinely in the evaluation of children who have chronic diarrhea. *Salmonella* enteritis is commonly associated with a chronic asymptomatic carrier state, especially in infancy. *Salmonella* infection, however, may also be associated with persistent diarrhea in infants. *Y enterocolitica* enteritis has been associated with a chronic relapsing diarrhea, although not commonly in the United States; however, the microbiology laboratory must look specifically for this organism, or it will be missed. *Campylobacter* enteritis also may have a protracted course. Persistence of either rotavirus or enteric adenovirus excretion has been identified in immunocompromised individuals; rarely, rotavirus may be present in the stool of an immunocompetent child for a prolonged period after a severe gastroenteritis. *Candida* has been described as



a rare cause of persistent diarrhea in immunocompetent individuals. However, the incidental finding of *Candida* is so common that the physician must be cautious before identifying it as the cause of diarrhea. A dramatic response to treatment for *Candida* would support this diagnosis.

### Parasites

The principal parasite that causes diarrhea in the United States is *G lamblia*, which may be associated with watery diarrhea and crampy abdominal pain and may occur in epidemic form. Stool testing for *Giardia* antigen is sensitive and has improved the ability to diagnose giardiasis. Evaluation of duodenal fluid aspirate or a small bowel biopsy is rarely necessary. Diarrhea from *Cryptosporidium* occurs in immunocompetent individuals and also can be recognized by stool antigen assay. *Cyclospora* has been introduced into the United States on contaminated fruits. *B hominis* and *D fragilis* may cause persistent diarrhea. Amebic dysentery may be indistinguishable from the colitis of inflammatory bowel disease and must be considered along with bacterial colitis before a diagnosis of inflammatory bowel disease can be made.

### Hirschsprung Disease

Hirschsprung disease is a congenital abnormality involving the submucosal and myenteric plexuses of the colon (rarely involving the small intestine) and accounts for about 25% of intestinal obstructions in newborns. Affected neonates almost invariably fail to pass meconium early and have persistent obstipation and recurrent abdominal distention. These features may be overlooked, however, and the infants may subsequently have chronic diarrhea. The diarrhea is secondary to enterocolitis, which can be a surgical emergency that demands rapid diagnosis and treatment. A barium enema in the neonate may reveal false-negative findings. Anorectal manometric examination may be helpful, but an adequate rectal biopsy specimen showing absence of ganglion cells and presence of nerve fiber hypertrophy confirms the diagnosis. Calretinin staining is useful as well. Properly performed, suction biopsy of the rectum is highly reliable.

### Food Allergy

Dietary protein hypersensitivity occurs in 6% to 8% of children during the first 5 years of life and most commonly is a hypersensitivity to cow milk protein. Food allergy is present in about 4% of the adult population. In 85% of children who have dietary protein intolerance, the symptoms resolve by 3 years of age. This entity should be considered when an infant who has chronic diarrhea has any of the following manifestations:

- Occult or gross blood in the stool (colitis)
- Protein-losing enteropathy
- Peripheral eosinophilia
- Other extraintestinal manifestations of allergy such as eczema, hives, or asthma

Continued or recurrent manifestations when the infant is fed a soy formula diet (free of cow milk) do not rule out the diagnosis, inasmuch as 30% to 50% of

children who have cow milk protein intolerance will also be intolerant to soy protein. Typically, symptoms improve when the feeding is changed to a protein hydrolysate formula, although the response to specific protein hydrolysate formulas may not be equivalent. Occasionally, an amino acid formula will be necessary.

Most food allergic reactions are IgE mediated and include immediate gastrointestinal hypersensitivity, with nausea, abdominal pain, and vomiting within 1 to 2 hours and diarrhea in 2 to 6 hours. Implicated food proteins include milk, egg, peanut, soy, cereal, and fish. Eosinophilic (allergic) gastroenteropathy is considered a mixed IgE-mediated and non-IgE-mediated disorder. It is characterized by infiltration of the stomach and intestine with eosinophils and often a peripheral eosinophilia. Symptoms include vomiting, abdominal pain, growth failure, and diarrhea (often with gross blood). Eosinophilic gastroenteropathy may respond to elimination diet, but corticosteroid treatment may be necessary. Non-IgE-mediated hypersensitivity food protein-induced enterocolitis syndrome (FPIES), which occurs most commonly in the first year of life but can occur at any age. Diet-induced proctitis causes gross blood in stool and often diarrhea in the first few days to months of life. Symptoms usually resolve within 72 hours with removal of the offending food allergen. Bloody diarrhea can develop in some infants while they are nursing; resolution may occur when cow milk is removed from the mother's diet or when a protein hydrolysate formula is substituted for nursing, suggesting an allergic basis.

### Short Bowel Syndrome

Short bowel syndrome is associated with congenital anomaly of the small intestine or follows extensive resection of the small intestine, resulting in chronic malabsorption and diarrhea. It begins most commonly in the newborn period in association with necrotizing enterocolitis or a congenital anomaly such as gastroschisis, intestinal atresia, or malrotation with secondary midgut volvulus. Recovery may be prolonged, requiring the use of TPN for the first several years of life. The factors that appear to contribute to persistence of symptoms in neonates include the cause, decreased intestinal absorptive surface, altered intestinal motility, intraluminal bacterial overgrowth (with secondary deconjugation of bile salts and hydroxylation of fatty acids), malabsorption of bile salts secondary to terminal ileal resection, and disaccharidase deficiency. Among neonates, infants with necrotizing enterocolitis or gastroschisis tend to have a more prolonged course than those with other causes of short bowel. In infants, symptoms of colitis may occur during the initiation of enteral feedings. Later in life, volvulus, trauma, and Crohn disease are the most common causes of short bowel syndrome.

### Intestinal Lymphangiectasia

Intestinal lymphangiectasia is a syndrome of dilated intestinal lymphatic vessels and is associated with protein-losing enteropathy, steatorrhea, lymphocytopenia, and chronic diarrhea. As a result of the bowel

protein loss, affected children may have hypogammaglobulinemia and hypoalbuminemia, usually with peripheral edema. Primary intestinal lymphangiectasia appears to be a developmental anomaly of unknown origin and is frequently associated with lymphatic abnormalities of the extremities. Secondary lymphangiectasia may result from chronic volvulus secondary to malrotation with malfixation of the bowel, constrictive pericarditis, tumor, lymphatic malformation, elevated right atrial pressure associated with the Fontan procedure for congenital heart disease, or any other factor that leads to obstruction of intestinal lymphatic flow. The diagnosis is suggested by a history of chronic diarrhea and poor growth and the presence of peripheral edema, hypoalbuminemia, hypogammaglobulinemia, and lymphocytopenia. The last 2 abnormalities may lead to a decreased immune defense and an increased risk for infections. A radiologic small bowel follow-through study may show generalized thickening of the intestinal folds. The diagnosis is confirmed by the presence of characteristically dilated lymphatics on a small bowel biopsy specimen. The treatment includes the dietary use of medium-chain triglycerides and avoidance of long-chain fat. Protection from and early treatment of infection also are important.

#### **Acrodermatitis Enteropathica**

Acrodermatitis enteropathica is a rare autosomal recessive disease that typically appears when breastfed infants are weaned. The infant has chronic diarrhea, intermittent vomiting, and an intractable erythematous, raw, and crusty rash, which is most prominent in the perianal and perioral regions but may be seen on the extremities. Alopecia is characteristically present, and conjunctivitis and dystrophic changes of the nails may occur. Infants who have acrodermatitis enteropathica are usually irritable and unhappy. The disorder is associated with a zinc deficiency (perhaps secondary to malabsorption) and responds dramatically to zinc salts given orally. A mutation of a gene that encodes a zinc-transporter protein has been identified in this condition. Nutritional zinc deficiency (eg, TPN without zinc supplementation or cystic fibrosis) may produce a syndrome similar to acrodermatitis enteropathica.

#### **Factitious Diarrhea**

Factitious diarrhea is undoubtedly more common than pediatricians recognize. Screening a stool specimen for laxative abuse is reasonable when an infant has persistent diarrhea that does not seem to fit any known pattern. Surreptitious administration of laxative to an infant is a symptom of the caregiver's psychosocial dysfunction; problems in other areas often become apparent during the social history. Frequently, a parent is a medically knowledgeable person (eg, nurse, laboratory technician) and often seems to prefer staying in the hospital to being at home. These parents are usually helpful to the nursing staff, often to the degree of excessive involvement in the nursing care, and are commonly described by the nurses as caring and concerned parents. The pediatrician may note that the parent seems to encourage invasive

diagnostic studies and treatment even beyond the medical plan and does not show an appropriate degree of hesitancy. A stool osmolality well below 290 mOsm/L can only occur by surreptitious dilution of stool with water. Another form of factitious diarrhea occurs among teenage girls who take laxatives surreptitiously to lose weight.

#### **Hormone-Related Diarrhea**

Adrenal insufficiency caused by either adrenogenital syndrome or adrenal hemorrhage may be associated with significant diarrhea, as may congenital thyrotoxicosis. VIP-secreting tumors of the pancreas have been reported as a rare cause of diarrhea in adults and an even rarer cause in children.

Ganglioneuroma and ganglioneuroblastoma have been associated with chronic secretory diarrhea. The tumors are usually abdominal but have also been reported in the mediastinum. Although these tumors are catecholamine secreting, prostaglandins or VIP may be the mediator of the diarrhea. A workup of the infant who has persistent, undiagnosed, secretory diarrhea should include urinary catecholamine studies, prostaglandin and VIP levels, and computed tomography scans of chest and abdomen. Even when the results of these studies are negative, the physician must strongly consider further studies if severe secretory diarrhea persists. When a tumor is found and is completely excised, the diarrhea usually resolves abruptly.

#### **Immune Disorders**

Immunodeficiency should be considered in any child who has chronic diarrhea. AIDS has become a major cause of immunodeficiency in childhood, and its first manifestation may be diarrhea. Several mechanisms of diarrhea have been described in infants and children who have AIDS. In addition to the organisms the physician usually considers in individuals who have persistent diarrhea (especially *Giardia*), cytomegalovirus, *Mycobacterium avium-intracellulare*, *Cryptosporidium parvum*, *Isospora belli*, and *Enterocytozoon bieneusi* must also be considered. Astrovirus, calicivirus, and adenovirus have been associated with diarrhea in HIV-infected individuals and may be more important than rotavirus as agents of AIDS diarrhea. HIV may be a primary pathogen in the bowel of these patients as well. Lactose intolerance occurs commonly in individuals who have AIDS, presumably occurring as a result of injury to small bowel mucosa. Pancreatic insufficiency with steatorrhea also has been noted in these patients.

The 2 major inborn disorders of immunity associated with diarrhea in early infancy are severe combined immunodeficiency and Wiskott-Aldrich syndrome. The most common primary disorder seen in later childhood is late-onset, variable hypogammaglobulinemia. Pure T-cell abnormalities (DiGeorge syndrome and other T-cell deficiencies) are also associated with diarrhea. Patients with selective IgA deficiency have an increased risk for celiac disease. Measurement of immunoglobulin levels should be a routine part of the workup of any patient who has chronic diarrhea. If

the diagnosis remains unclear, then a T-cell evaluation should be conducted. Chronic parasitic, adenovirus, or rotavirus infection can be seen with immunodeficiencies. Diarrhea in association with granulomas of the intestinal tract has been noted in chronic granulomatous disease of childhood. These children may have perianal fistulas or gastric outlet obstruction; the disorder may initially be mistaken for Crohn disease.

The physician must consider the full range of enteric infections associated with immunosuppression in children who have received organ transplants. Diarrhea may also be the presentation of tacrolimus toxicity or of lymphoproliferative disease. In bone marrow transplant recipients, graft-versus-host disease is a common cause of diarrhea as well.

### **Autoimmune Enteropathy**

Autoimmune enteropathy is a poorly understood disorder, with chronic diarrhea beginning in the first year of life, and is often associated with failure to thrive. Intestinal biopsies demonstrate villous atrophy and increased T-cell infiltrate in the lamina propria. Serum antienterocyte antibodies are identified in at least 50% of these patients. Extraintestinal autoimmune disorders (eg, diabetes mellitus, arthritis, thrombocytopenia, hemolytic anemia) are common and help make the diagnosis. Celiac disease, food allergy, and gastrointestinal infection must be ruled out. Treatment is immunosuppressive therapy, and a response confirms the diagnosis.

### **IPEX Syndrome**

Immune dysregulation, polyendocrinopathy, enteropathy, and X-linked inheritance (IPEX) syndrome exhibits a presentation similar to autoimmune enteropathy and similar biopsy findings. This disorder is the result of a mutation in the *FOXP3* gene.

### **Idiopathic Intestinal Pseudoobstruction**

Idiopathic intestinal pseudoobstruction constitutes a group of rare disorders characterized by widespread gastrointestinal dysmotility. When this syndrome occurs in early infancy, vomiting and diarrhea are often major components. Diarrhea may alternate with constipation. In older children, the presentation is frequently more insidious; a long history of constipation may precede the onset of diarrhea. Persons who have this syndrome usually have intermittent or constant abdominal distention. The syndrome is characterized by the radiographic findings of bowel dilation with disordered motility; urinary bladder dysfunction is also often present. These disorders, which can be sporadic or transmitted in an autosomal dominant fashion, can result from a visceral myopathy or neuropathy or from a combination of both. Bacterial overgrowth is an important cause of diarrhea in this disorder.

### **Microvillus Inclusion Disease**

Microvillus inclusion disease (familial enteropathy) is a rare disorder that is present from birth and causes

severe intractable secretory diarrhea with malabsorption. It is the most common cause of intractable diarrhea in the neonatal period. Affected infants have small bowel villous atrophy in the absence of crypt hyperplasia. The villous surface epithelial cells lack a normal brush border, and on electron microscopic examination, the microvilli are absent or severely abnormal. The defective enterocytes and colonocytes contain intracytoplasmic inclusions, which, in turn, contain the components of the brush border. Microvillus inclusions are not found in every enterocyte. Fecal sodium and chloride concentrations are similar to those found in serum. Several families have been identified with more than 1 child with this disorder.

### **Tufting Enteropathy**

In contrast to microvillus inclusion disease, symptoms of tufting enteropathy are not present at birth. Affected infants develop chronic watery diarrhea in the first few months of life. The name derives from a typical light microscopic *tufted* configuration of the small bowel mucosal epithelium.

### **Congenital Disorders of Electrolyte Absorption**

Congenital chloride-losing diarrhea and congenital sodium-secretory diarrhea are very rare, autosomal recessive disorders associated with maternal polyhydramnios. The small bowel mucosa is histologically normal, and absorption of other nutrients is normal. Infants with congenital chloride-losing diarrhea have persistent diarrhea resulting from absence of the normal ileal mechanism for active absorption of chloride in exchange for bicarbonate. They have acidic stools and a chronic metabolic alkalosis instead of the metabolic acidosis usually seen in chronic diarrhea. Stool chloride concentration is high, usually exceeding the sum of concentrations of sodium and potassium. The stool chloride of children who have this disorder may be in the range of 100 to 150 mEq/L, although it may be 30 to 100 mEq/L in infants. (Adult stool chloride is normally <20 mEq/L.) Although no satisfactory treatment exists, support with oral fluids and potassium chloride is recommended. Congenital sodium diarrhea is also a rare cause of watery diarrhea from birth. However, these infants are acidotic, and stool chloride concentration is not excessive. The disorder is the result of defective mucosal  $\text{Na}^+/\text{H}^+$  exchange in the small and large bowel.

### **Congenital Disorders of Glycosylation**

Congenital disorders of glycosylation exhibit in the first year of life, often with multisystem dysfunction. In addition to hepatic, neurologic, cardiac, and optic manifestations, they can be associated with chronic diarrhea or severe protein-losing enteropathy, or both. Diagnosis is suggested if levels of serum glycoproteins such as haptoglobin and transferrin are low. Screening for this diagnosis has been performed with serum transferrin isoelectric focusing.



### Infant of a Drug-Addicted Mother

Diarrhea may be a prominent manifestation of neonatal drug abstinence syndrome, and this diagnosis should be entertained in newborns who have persistent diarrhea, especially when other symptoms of neonatal drug withdrawal are present.

### Older Children

A pediatrician will see fewer older children with chronic diarrhea than they will infants, but older children are more likely to have chronic diarrhea associated with significant underlying disease compared with toddler's diarrhea in young children. As in infancy, the association of poor growth, weight loss, or other systemic manifestations suggests a serious organic cause. Older children may deny symptoms, and the true effect of the disorder may not be immediately apparent. Clues may include subtle changes in personality, diminished sense of well-being, or loss of appetite. Children may hesitate to talk about their stooling pattern, and the degree of deviation from the norm may become apparent only after improvement occurs following initiation of appropriate therapy.

Causes of diarrhea differ somewhat after infancy, although many of the causes seen in infancy, even congenital anomalies, may exhibit first in childhood and therefore must still be considered. Factors that determine the age at diagnosis include variability of presentation of signs and symptoms, parental expectations of normality, and the index of suspicion of the physician who is consulted. However, certain diseases, including inflammatory bowel disease and chronic constipation with encopresis, are much more likely to be seen in childhood than in infancy. Symptoms of celiac disease may begin at any age, and the high occurrence rate of celiac disease is now recognized. Cystic fibrosis may be associated with only mild manifestations in infancy and may be overlooked until frequent, bulky, foul-smelling stools become intolerable at home. AIDS is seen in older children, as well as in infants.

### Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) similar to that occurring in adults may be seen in children and adolescents. Stools may alternate from diarrhea to constipation. In addition, the patient may have recurrent, crampy, abdominal pain. Late-onset lactose intolerance and fructose or sorbitol ingestion are important to rule out as causes of symptoms that may mimic IBS. Symptoms of inflammatory bowel disease or celiac disease may also be mistaken at first for IBS. Standard treatment includes increased fiber in the diet and anticholinergics; the tricyclic antidepressants can be used for diarrhea-predominant IBS, under experienced supervision.

### Inflammatory Bowel Disease

The manifestations and presentation of Crohn disease and ulcerative colitis are so variable that these diseases should be considered whenever the physician

sees an older child who has chronic diarrhea. Systemic evidence of inflammation (fever, weight loss, and leukocytosis), abdominal pain, blood in the stool (gross or occult), perianal disease, anemia, or extraintestinal manifestations (arthralgia, arthritis, or erythema nodosum) are helpful in suggesting this diagnosis. Growth failure can occur with or precede other symptoms. An elevated sedimentation rate also is a clue; however, normal sedimentation rates may occur in as many as 50% of patients who have inflammatory bowel disease. Thrombocytosis and elevated C-reactive protein, both acute phase reactants, have been associated with inflammatory bowel disease as well and may be present in the absence of an elevated sedimentation rate. Suggestive signs and symptoms require evaluation, including a complete blood count, platelet count, erythrocyte sedimentation rate, serum protein levels, and possibly a stool assay for calprotectin. One would then consider imaging the small bowel by conventional contrast radiographs, computed tomography scan of the abdomen and pelvis, or MR enterography, as well as endoscopic examination of the upper gastrointestinal tract and colon with biopsy. Capsule endoscopy is useful when, despite negative radiographic and colonoscopic evaluation, a strong suggestion of small bowel Crohn disease is present. Serum antibody screening studies for IBD may be helpful in identifying the need for further evaluation for Crohn disease or ulcerative colitis, but may be misleading. Management of inflammatory bowel disease includes an array of medical, nutritional, and surgical measures.

### Chronic Constipation

Chronic constipation with overflow incontinence may be mistaken for diarrhea. A thorough history and physical examination, including a rectal examination, should make the diagnosis apparent. A large amount of stool may be palpable in the abdomen, but a hard mass of stool is usually found in the rectal ampulla. This presentation is treated in the usual fashion of chronic constipation (as noted in Chapter 134, Constipation).

#### WHEN TO REFER

- Persistent diarrhea when the workup for routine infectious causes is negative
- Steatorrhea
- Diarrhea or steatorrhea (or both), causing weight loss or failure to thrive
- Diarrhea associated with fevers, chronic anemia, or abdominal pain without an obvious explanation
- When inflammatory bowel disease is a consideration

#### WHEN TO ADMIT

- Acute or chronic diarrhea with mild to moderate dehydration that cannot be managed successfully with outpatient rehydration solution



- Dehydration greater than 10% of body weight
- Diarrhea with intractable vomiting
- Severe electrolyte imbalance, including hypernatremic dehydration or serum potassium level less than 3 mEq/L
- Laboratory evidence suggesting hemolytic uremic syndrome
- Chronic diarrhea or steatorrhea (or both) with persistent signs of malnutrition that is unresolved with outpatient management
- Severe manifestations of inflammatory bowel disease, unresponsive to routine outpatient treatment

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Chronic Diarrhea* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/healthywater/hygiene/disease/chronic\\_diarrhea.html](http://www.cdc.gov/healthywater/hygiene/disease/chronic_diarrhea.html))
- *Common Childhood Infections* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Cryptosporidium Infection* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/parasites/crypto/index.html](http://www.cdc.gov/parasites/crypto/index.html))
- *Diarrhea* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/abdominal/Pages/Diarrhea.aspx](http://www.healthychildren.org/English/health-issues/conditions/abdominal/Pages/Diarrhea.aspx))
- *Diarrhea and Dehydration* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *E coli (Escherichia coli)* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/ecoli](http://www.cdc.gov/ecoli))
- *Entamoeba coli* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/parasites/nonpathprotozoa/index.html](http://www.cdc.gov/parasites/nonpathprotozoa/index.html))
- *Healthy Pets Healthy People—Salmonella from Pocket Pets* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/healthypets/pets/pocket-pets/salmonella.html](http://www.cdc.gov/healthypets/pets/pocket-pets/salmonella.html))
- *Healthy Pets Healthy People—Turtles Kept as Pets* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/healthypets/pets/reptiles/turtles.html](http://www.cdc.gov/healthypets/pets/reptiles/turtles.html))
- *Healthy Swimming/Recreational Water* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/healthywater/swimming](http://www.cdc.gov/healthywater/swimming))
- *Norovirus* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/norovirus/about/index.html](http://www.cdc.gov/norovirus/about/index.html))
- *Parasites—Giardia* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/parasites/giardia/index.html](http://www.cdc.gov/parasites/giardia/index.html))
- *Rotavirus* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Salmonella serotype Enteritidis* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/nczved/divisions/dfbmd/diseases/salmonella\\_enteritidis](http://www.cdc.gov/nczved/divisions/dfbmd/diseases/salmonella_enteritidis))
- *Salmonella* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/salmonella](http://www.cdc.gov/salmonella))
- *Shigellosis* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/shigella](http://www.cdc.gov/shigella))

#### Medical Decision Support

- *Cryptosporidium* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/dpdx/cryptosporidiosis/index.html](http://www.cdc.gov/dpdx/cryptosporidiosis/index.html))
- *Diarrheagenic Escherichia coli (non-Shiga toxin-producing E coli)* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/ncidod/dbmd/diseaseinfo/diarrecoli\\_t.htm](http://www.cdc.gov/ncidod/dbmd/diseaseinfo/diarrecoli_t.htm))
- *Giardiasis* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/dpdx/giardiasis/index.html](http://www.cdc.gov/dpdx/giardiasis/index.html))
- *Managing Acute Gastroenteritis Among Children* (guideline), Centers for Disease Control and Prevention ([www.cdc.gov/mmwr/PDF/RR/RR5216.pdf](http://www.cdc.gov/mmwr/PDF/RR/RR5216.pdf))
- *Norovirus* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/norovirus/hcp/index.html](http://www.cdc.gov/norovirus/hcp/index.html))
- *Practice Guidelines for Management of Infectious Diarrhea* (guideline), Infectious Diseases Society of America ([www.idsociety.org/Organ\\_System/#Diarrhea](http://www.idsociety.org/Organ_System/#Diarrhea))
- *Rotavirus* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/rotavirus](http://www.cdc.gov/rotavirus))

### AAP POLICY

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### SUGGESTED READINGS

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- Centers for Disease Control and Prevention. Diagnosis and management of foodborne illnesses: a primer for physicians and other healthcare professionals. *MMWR*. 2004;53:1–33
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## Chapter 139

**DISRUPTIVE BEHAVIOR  
AND AGGRESSION***Lawrence S. Wissow, MD, MPH*

Disruptive and aggressive behaviors are common among children from toddlerhood through adolescence. They may be transient, influenced by temperament and environmental factors, or they may be persistent, rising to the level of oppositional-defiant disorder (ODD) or conduct disorder (CD) and causing significant impairment in the child's and family's functioning. ODD affects 1% to 16% of children, depending on the population studied; CD affects 1.5% to 3.4%. Male-to-female ratio varies with age and diagnosis from 3.2:1 to 5:1. Some children progress from ODD to CD. They can be extremely challenging to manage and, if untreated, experience an increased risk of school failure, difficulty with legal authorities, substance abuse, and ultimately underemployment as adults. Those who go on to develop CD may be dangerous to themselves and others and, in some instances, require emergent treatment. All children manifesting disruptive or aggressive behaviors require intervention, education, support from parents and teachers, and careful monitoring.

There is accumulating evidence that some behavior problems can be prevented. Effective strategies include population-based interventions, supporting parents' mood and reducing exposure to stresses, helping parents learn to both read and help modulate infant emotions, and helping parents learn ways to stimulate and have positive interactions with their infants and

young children. As children get older, clinicians can offer anticipatory guidance about predictable parenting issues, written or online parenting materials, and referrals to parenting workshops. The Centers for Disease Control and Prevention ([www.cdc.gov/ncbddd/childdevelopment/positiveparenting/index.html](http://www.cdc.gov/ncbddd/childdevelopment/positiveparenting/index.html)) offers colorful public-domain materials for children and youth of a wide range of ages and a new "Essentials" series of video modules for parents of children 2 to 4 years of age. The American Academy of Pediatrics (AAP) has published guidelines for effective discipline.

The following guidance is based on the work of the World Health Organization (WHO), whose recommendations may be updated annually. The most up-to-date information can be found at [www.who.int](http://www.who.int).

**FINDINGS SUGGESTING DISRUPTIVE  
BEHAVIOR OR AGGRESSION**

Manifestations of disruptive behavior and aggression vary by age. In younger children, they include tantrums, defiance, fighting, and bullying. In older children and adolescents, they may include serious law breaking such as stealing, damage to property, or assault. A summary of the symptoms and clinical findings that suggest disruptive behavior and aggression can be found in Box 139-1. These may be elicited from parents, teachers, others familiar with the child, or the children or youth themselves. Children, youth, and even parents may minimize problems, and parents and teachers may be unaware of conduct problems that happen when the child is out of their direct supervision. Thus, tactful but persistent discussion and comparing notes among observers may be required to get a full picture of the child's behavioral issues.

**BOX 139-1 Symptoms and Clinical Findings Suggesting Disruptive Behavior and Aggression****INDICATIONS OF DISRUPTIVE BEHAVIOR  
AND AGGRESSION**

- In younger children, marked tantrums, defiance, fighting, and bullying.
- In older children and adolescents, serious law breaking such as stealing, damage to property, or assault.
- Repetitive, persistent, excessive aggression or defiance; behaviors out of keeping with the child's development level, norms of peer group behavior, and cultural context indicating a disorder rather than a phase or transitional disruption.
- Aggression may be impulsive and associated with intense emotional states, or it may be predatory and premeditated. It is important to distinguish which pattern of aggression the child is showing.

**BEHAVIORS CHARACTERISTIC OF OPPOSITIONAL-  
DEFIANT DISORDER (ODD)**

- Symptoms may be confined only to school, home, or the community.
- Angry outbursts.

- Loss of temper.
- Refusal to obey commands and rules.
- Destructiveness.
- Hitting.
- Intentional annoyance of others, but without the presence of serious lawbreaking.

**BEHAVIORS CHARACTERISTIC OF CONDUCT  
DISORDER**

- Vandalism.
- Cruelty to people and animals (including sexual and physical violence).
- Bullying.
- Lying.
- Stealing.
- Truancy.
- Drug and alcohol misuse.
- Criminal acts.
- All the features of ODD.

## TOOLS TO ASSIST WITH IDENTIFICATION

Because some children and parents do not spontaneously disclose their symptoms to their primary care clinician standardized psychosocial screening instruments may be used to identify children with symptoms of disruptive behavior or aggression. Several instruments have versions to collect information from youth, parents, and teachers. Table 139-1 provides examples of general psychosocial screening results suggesting that a child has disruptive behavior or aggression. Use of additional instruments, such as the Vanderbilt ADHD Rating Scale (developed for children 6–12 years of age) and the Modified Overt Aggression Scale (MOAS) (developed for adults, but sometimes used with adolescents), can help confirm findings of the initial screening; and the use of a functional assessment tool, such as the Strengths & Difficulties Questionnaire (SDQ) or Columbia Impairment Scale (CIS), will help the clinician determine whether the child is significantly impaired by the symptoms. For adolescents, consider assessing the extent of substance use. Use of a tool to assess the effect of the child's problem on other members of the family may also be helpful; the Caregiver Strain Questionnaire (CGSQ) is one example of such a tool. All of these instruments require

consideration of their results in the context of other clinical information obtained in the process of discussing the results with the child/youth and family members.

## ASSESSMENT

Assessment begins by differentiating the child's symptoms from normal behavior. All children are defiant at times, and it is a normal part of adolescence to, at times, do or at least consider doing the opposite of what one is told. A problem or disorder may be present if the behaviors interfere with family life, school, or peer relationships, or put the child or others in danger. Children with disruptive behavior or aggression tend to exhibit repetitive and excessive aggression or defiance out of keeping with developmental and social norms. The behaviors persist, rather than appearing briefly as part of adaptation to a new situation or developmental period. Aggression may be impulsive and associated with intense emotional states, or may be predatory and premeditated. It is important to distinguish which pattern of aggression the child is showing.

Some conditions, such as depression (with prominent irritability), attention-deficit/hyperactivity (ADHD), or sleep deprivation, can mimic or co-occur with

**Table 139-1** General Psychosocial Screening/Results Suggesting Disruptive Behavior and Aggression

SCREENING INSTRUMENT	SCORE
Pediatric Symptom Checklist (PSC)-35	<ul style="list-style-type: none"> <li>• Total score <math>\geq 24</math> for children 5 years and younger.</li> <li>• <math>\geq 28</math> for those 6–16 years.</li> <li>• <math>\geq 30</math> for those 17 years and older.</li> </ul> <p>AND</p> <ul style="list-style-type: none"> <li>• Further discussion of items related to disruptive behavior and aggression confirms a concern in that area.</li> </ul>
PSC-17	<ul style="list-style-type: none"> <li>• Externalizing subscale is <math>\geq 7</math>.</li> </ul> <p>AND</p> <ul style="list-style-type: none"> <li>• Further discussion of items related to disruptive behavior and aggression confirms a concern in that area.</li> </ul>
Strengths & Difficulties Questionnaire (SDQ)	<ul style="list-style-type: none"> <li>• Total symptom score of <math>&gt; 19</math>.</li> <li>• Conduct problem score of 5–10 (see instructions at <a href="http://www.sdqinfo.com">www.sdqinfo.com</a>).</li> <li>• Impact scale (back of form) score of 1 (medium impairment) or <math>\geq 2</math> (high impairment).</li> </ul> <p>AND</p> <ul style="list-style-type: none"> <li>• Further discussion of items related to disruptive behavior and aggression confirms a concern in that area.</li> </ul>
Ages & Stages Questionnaires: Social-Emotional (ASQ:SE) Early Childhood Screening Assessment	<ul style="list-style-type: none"> <li>• Cutoff score varies by age-specific questionnaire.</li> </ul> <p>AND</p> <ul style="list-style-type: none"> <li>• Total score of <math>\geq 18</math>.</li> <li>• Thorough emotional and behavioral history, family history, and close follow-up.</li> <li>• Regardless of the total score, any items with a "+" circled should be explored further. These "+"s correlate with a child's emotional or behavioral problems, although, in some cases, parental reassurance is all that is necessary.</li> </ul> <p>Parent score</p> <ul style="list-style-type: none"> <li>• A score of 1 or 2 on questions 39 and 40 identify depression in adult primary care settings.</li> <li>• Scores <math>&gt; 0</math> on items 37 and 38 should be further investigated for maternal distress.</li> </ul>

lesser degrees of disruptive behavior and aggression. Substance abuse may play a role in both minor and more severe forms of behavior problems. Having witnessed or experienced trauma, or currently living in a stressful or an anxiety-provoking situation may also provoke disruptive behavior. Table 139-2 summarizes these conditions.

In addition, perceptions of the child's symptoms may vary among caregivers or as a particular caregiver's circumstances change. A child whose behavior is perfectly acceptable in one setting may be seen as problematic in another where there are greater dangers or constraints, or where a caregiver may be experiencing other stressors. Recognizing the

**Table 139-2**

### Conditions That May Mimic or Co-occur With Disruptive Behavior and Aggression

CONDITION	RATIONALE
ADHD	This is a common comorbidity. Association of ODD and ADHD confers a poorer prognosis and children tend to be more aggressive, have more behavior problems that are more persistent, suffer peer rejection at higher levels, and have more significant academic underachievement. See also Chapter 168, Inattention and Impulsivity.
Sleep deprivation	Sleep problems can cause irritability and contribute to outbursts of anger and poor impulse control.
Learning problems or disabilities	Unidentified learning difficulties can contribute to frustration and oppositionality. If disruptive or aggressive behavior is associated with problems of school performance, the child may have a learning disability. See Chapter 172, Learning Difficulty, to explore this possibility.
Developmental problems	Children with overall intellectual or social limitations may experience frustration and poor impulse control.
Exposure to adverse childhood experiences (ACE)	Children who have experienced or witnessed trauma, violence, a natural disaster, separation from a parent, parental divorce or separation, parental substance use, neglect, or physical, emotional, or sexual abuse are at high risk of developing emotional difficulties such as adjustment disorder or post-traumatic stress disorder (PTSD) and may manifest outbursts of disruptive or aggressive behavior; this possibility should always be borne in mind because PTSD requires specific trauma-focused interventions. The clinician should tactfully explore the possibility that harsh physical or emotional punishment is related to the child's behavior problem or that tensions might escalate to that point. Denial of trauma symptoms does not mean trauma did not occur; questions about ACE should be repeated as a trusting relationship is established. See Chapter 129, Anxiety.
Bereavement	Most children will experience the death of a family member or friend sometime in their childhood. Other losses may also trigger grief responses—separation or divorce of parents, relocation, change of school, deployment of a parent in military service, breakup with a girlfriend or boyfriend, or remarriage of parent. Such losses are traumatic. They may result in feelings of sadness, despair, insecurity, anger, or anxiety immediately following the loss and in some instances, more persistent anxiety or mood problems, including PTSD or depression. In some children, such losses trigger aggressive or disruptive behavior. See also Chapter 137, Depression.
Anxiety	Many children with disruptive or aggressive behaviors have anxiety. When faced with demands that make them anxious, they use oppositional behavior to manage their anxiety or avoid the expectations that triggered their anxiety. See Chapter 129, Anxiety.
Depression or bipolar disorder	Marked sleep disturbance, disturbed appetite, irritability, low mood, or tearfulness could indicate that a child is depressed. Symptoms of depression rapidly alternating with cycles of agitation may suggest bipolar mood disorder. Common symptoms of pediatric bipolar disorder include explosive or destructive tantrums, dangerous or hypersexual behavior, aggression, irritability, bossiness with adults, driven creativity (sometimes depicting graphic violence), excessive talking, separation anxiety, chronic depression, sleep disturbance, delusions, hallucinations, psychosis, and talk of homicide or suicide. <sup>a</sup>
Substance use	All children exhibiting disruptive or aggressive behavior should be screened for substance use and abuse because drug effects or withdrawal from drugs may cause irritability and reduced self-control.
Autism spectrum disorders	Children with this developmental pattern also have problems with social relatedness (eg, poor eye contact, preference for solitary activities), language (often stilted), and range of interest (persistent and intense interest in a particular activity or subject). They often will have very rigid expectations for routine or parent promises and become anxious or angry if these expectations are not met.

ADHD, attention-deficit/hyperactivity disorder; ODD, oppositional-defiant disorder.

<sup>a</sup>About pediatric bipolar disorder: a guide for families. Child & Adolescent Bipolar Foundation Web site. [www.bpkids.org/site/PageServer?pagenameln\\_about](http://www.bpkids.org/site/PageServer?pagenameln_about). Accessed November 24, 2014



influence of context can be therapeutic by itself and can lead to development of a more holistic approach to intervention engaging the child, the primary caregiver, and others who support them.

## PLAN OF CARE FOR CHILDREN WITH DISRUPTIVE BEHAVIOR OR AGGRESSION

Suicidal or homicidal intent is an emergency requiring immediate treatment and close supervision of the youth at all times. Other emergencies may involve parents who feel that they can no longer tolerate the child's behavior, parents who have considered expelling the child from the home or feel that they could harm the child, or situations in which the child's behavior is related to past or ongoing trauma. Community social service agencies often have crisis services that may be of help in these situations and that can provide either respite care or emergency in-home intervention.

The care of a child exhibiting disruptive behavior or aggression can begin in the primary care setting from the time symptoms are recognized, even if the child's symptoms do not rise to the level of a disorder or if referral to a mental health specialist is ultimately part of the care plan.

### Engage Child and Family in Care

Without engagement, most families will not seek or persist in care. The process may require multiple primary care visits.

Reinforce strengths of the child and family (eg, good relationships with at least 1 parent or important adult, prosocial peers, concerned or caring family, help-seeking, connection to positive organizations) as a method of engagement, and identify any barriers to addressing the problem (eg, stigma, family conflict, resistance to treatment). Use "common factors" techniques to build trust and optimism, reach agreement on incremental next steps, develop a plan of care, and collaboratively determine the role of the primary care physician.

Regardless of other roles, the primary care physician can encourage a positive view of treatment on the part of the youth and family. To do this, the physician will likely have to manage visits in which strong negative emotions are expressed. Parents and youth may accuse each other of instigating problems, or make derogatory remarks about each other. Either party may express hopelessness about improving the situation, and youth, in particular, may refuse to speak or otherwise collaborate in care. Techniques for making the best of these encounters include avoiding taking sides, acknowledging the legitimacy of feelings, acknowledging the frequency with which these problems occur, reminding that strong feelings often occur when people care about each other, and offering to have separate conversations with youth and parents so as to give both a chance to be fully heard.

### Provide Psychoeducation

Families can be assured that behavior problems are common and something for which the clinician is

well-prepared to offer help. By the time families seek help, they are often discouraged and both angry and fearful of being criticized. Clinicians can help by emphasizing the great variation among children's temperament and personality, families' constantly evolving circumstances and stressors, and how these factors can combine to form challenges for any parent. Psychoeducation can often be tailored to a given situation by asking parents what they think are the causes of the child's behavior problems. Clinicians can acknowledge the validity of these beliefs and, to the extent necessary, begin to sketch out a range of other possible contributing factors that can be explored as treatment progresses. Usually, what parents are hoping to hear is a combination of reassurances that the behavior will improve over time and concrete plans that will work toward improvement in the short term.

### Encourage Healthy Habits

Encourage exercise, outdoor play, balanced and consistent diet, sleep (critically important to mental health), avoidance of exposure to frightening or violent media, limits on cell phone use and on TV and video games, positive and consistent (not punitive) experiences with parents, praise for good behavior, and reinforcement of strengths. This advice may extend to the parent; if the parent thinks that his ability to carry out normal activities is restricted by the child's behavior, it may be appropriate to see if there are ways the parent can feel more free to do routine or enjoyable activities.

### Reduce Stress

Consider the environment (eg, family social history, parental depression screening, results of any family assessment tools administered, reports from child care or school). Questions to raise might include the following:

- *Is stress on the parent(s) from causes other than the child leading to parental irritability or low mood, drinking, or greater demands for the child to behave? Are there ways for parents to get more support for themselves? Explore parents' readiness to seek and accept help.*
- *Do inconsistencies or differing beliefs about parenting among caregivers (eg, parents, grandparents) undermine attempts to create rules, limits, or consequences? Can caregivers agree on priority behavioral problems and how to address them? Explore conflicts; seek agreement on common beliefs and achievable steps to help the child.*
- *Are nonacademic issues such as the presence of bullying contributing to the behavior? Are there other social or behavioral challenges in school? Collect information directly from the school to explore these issues.*

If problems are mainly or exclusively at school, parents should request that the school assess the child for special educational needs and develop a plan to monitor behavior while at school. Primary care clinicians can often provide support in these situations by communicating to the school the degree to which the parents are actively engaged in finding help for their child's problems.

### Offer Initial Intervention(s)

The strategies described in the following text are common elements of evidence-based and evidence-informed psychosocial interventions for disruptive behavior and aggression. They are applicable to the care of children with mild or emerging problems with disruptive behavior and aggression and to the care of those with impairing symptoms that do not rise to the level of a disorder. They can also be used as initial primary care management of children with CD or ODD while readying them for referral or awaiting access to specialty care.

*Promote daily positive joint activities between parents and the child or teen.* The clinician can counsel parents to reinforce compliant, pro-social behavior using parental attention (“Catch ‘em being good” [Ed Christopher-son]). In addition, parents can encourage, praise, and reward specific, agreed-upon, and desired (target) behaviors. If appropriate, they can be monitored with a chart. Parents can negotiate rewards with the child. Change target behaviors every 2 to 6 weeks; change rewards more frequently. The choice of target behaviors and the time intervals for rewards should be developmentally appropriate. Parents can be encouraged to focus discipline on priority areas. Some minor unwanted behaviors can be ignored; often they will stop as the main focus of child-parent conflict improves. What is most important is that parents find a way to reduce the overall negative tone of interaction and find as many “successes” as possible about which to comment.

*Encourage parents to focus on prevention.* There are several ways for parents to do this. They can reduce positive reinforcement of disruptive behavior by not responding to negative bids for attention and by not engaging in discussion with the child when delivering a request or consequence. In contrast, when children seek attention in a prosocial way, parents should make every attempt to respond positively, even if the response is brief. When possible, parents can try to reorganize the child’s day to avoid situations in which the child cannot control himself. Examples include asking a neighbor to look after the child while the parent goes shopping, ensuring that activities are available for long car journeys or other potentially boring activities, and arranging activities in separate rooms for siblings who are prone to fight. In addition, parents can monitor the whereabouts of adolescents by telephoning the parents of friends whom they say they are visiting. All children appreciate age-appropriate advance notice of what will be expected of them and opportunities to make choices about how to meet those expectations.

Parents also can determine ways to limit contact with friends who have behavior problems and promote contact with friends who are a positive influence. If parents suspect the child’s behavior may be caused or exacerbated by a learning problem, they can request that the school evaluate the child for learning problems.

*Encourage parents to be calm and consistent.* The clinician can suggest the following strategies to parents:

- Set clear house rules and give short, specific commands about the desired behavior, not prohibitions

about undesired behavior (eg, “Please walk slowly,” rather than “Don’t run”).

- Prioritize issues and target only a few key behaviors until things improve. Within these areas of behavior, make initial targets easily achievable.
- Provide consistent and calm consequences for misbehavior. Consequences should not be drastic or, in the case of young children, go on for so long that the child is likely to forget what he or she originally did wrong. “Time out” should be brief (the rule of thumb for preschoolers is 1 minute per year of age); consequences for older children can involve brief loss of privileges or parental attention. Ideally, these punishments are mirrored by inverse responses for good behavior, especially more parental attention.
- Find a way for children to make reparation for a negative behavior (eg, doing something nice for a sibling they have struck, cleaning up a mess they made while in a tantrum), followed by praise.
- When enforcing a rule, avoid getting into arguments or explanations, because this merely provides additional attention for the misbehavior; defer negotiations until periods of calm.
- If the behavior is taking place in public, quietly advise the child or youth that the problem has been noted but, if possible, defer a response until home or in a less public place.
- Consider parenting classes.
- See also the suggestions in Chapter 168, Inattention and Impulsivity, including Strategies for Working Constructively With a Child’s School and Guidelines for Homework Battles.

*Create a safety and emergency plan.* When behavior problems are severe or involve threats of violence or running away, a care plan should be developed jointly with family, including a listing of telephone numbers to call for emergencies. This listing can include hotlines, the on-call telephone number for the practice, or area mental health crisis response team contact information, according to community protocol. The clinician should also instruct the family to proactively remove weapons from the home and monitor for situations that trigger outbursts.

### Provide Resources

Offer the child and parents educational resources to assist them with self-management. Helpful handouts, publications, and Web sites are included in Tools for Practice: Engaging Patient and Family. Provide the family with contact numbers and resources in case of an emergency.

### Monitor the Child’s Progress Toward Therapeutic Goals

Child care, preschool, or school reports can be helpful in monitoring progress. Screening instruments that gather information from multiple reporters (youth, parent, teacher), such as the SDQ and PSC, can be helpful in monitoring progress with symptoms and functioning.

It is important for the clinician to help the family understand that it is not uncommon for treatment to

**Table 139-3** Evidence-based Parenting Programs

CLUSTER AREA	PARENTING PROGRAM
For disruptive behavioral problems	<ul style="list-style-type: none"> <li>• The Incredible Years (<a href="http://www.incredibleyears.com">www.incredibleyears.com</a>)</li> <li>• Triple P Positive Parenting Program (<a href="http://www.triplep.net">www.triplep.net</a>)</li> <li>• Parent-Child Interaction Therapy (<a href="http://www.pcit.org">www.pcit.org</a>)</li> <li>• “Helping the Noncompliant Child” parent training program (<a href="http://www.strengtheningfamilies.org/html/programs_1999/02_HNCC.html">www.strengtheningfamilies.org/html/programs_1999/02_HNCC.html</a>)</li> <li>• Nurse-Family Partnership (<a href="http://www.nursefamilypartnership.org">www.nursefamilypartnership.org</a>)</li> </ul>
For high-risk pregnant women (First-time mother, refer before 28 weeks’ gestation.)	
For children in foster care	<ul style="list-style-type: none"> <li>• Attachment and Biobehavioral Catch-up (<a href="http://www.infantcaregiverproject.com">www.infantcaregiverproject.com</a>)</li> <li>• Multidimensional Treatment Foster Care Program for Preschoolers (<a href="http://www.uoregon.edu/~snaplab/SNAP/Projects.html">www.uoregon.edu/~snaplab/SNAP/Projects.html</a>)</li> <li>• Parent Child Interaction Therapy (<a href="http://www.pcit.org">www.pcit.org</a>)</li> </ul>
For parent-child relationship disturbances and high-risk parenting situations	<ul style="list-style-type: none"> <li>• Circle of Security (<a href="http://www.circleofsecurity.net">www.circleofsecurity.net</a>)</li> <li>• Promoting First Relationships (<a href="http://www.pfrprogram.org">www.pfrprogram.org</a>)</li> <li>• Parents as Teachers (<a href="http://www.parentsasteachers.org">www.parentsasteachers.org</a>)</li> <li>• Child Parent Psychotherapy (<a href="http://childtrauma.ucsf.edu/resources-0">childtrauma.ucsf.edu/resources-0</a>)</li> </ul>
For children exposed to trauma, including sexual abuse or domestic violence	<ul style="list-style-type: none"> <li>• Child Parent Psychotherapy</li> <li>• Trauma-focused cognitive behavioral therapy (<a href="http://tfcbt.musc.edu">tfcbt.musc.edu</a>)</li> </ul>

be successful for a period and then seem to lose effectiveness. This can happen when there are new stresses or demands, or when, after a period of success, there has been a letup on treatment. If trouble-shooting existing treatment and ways of dealing with new stresses does not help get function back to baseline, new treatments, or new diagnoses, need to be considered. In particular, as school demands increase, learning issues may need to be considered even if they were not seen as contributing problems in the past.

### Involve Specialist(s)

Consider involving specialist(s) if the child does not respond to initial interventions or if indicated by the following clinical circumstances:

- Child is younger than 5 years and problems go beyond what is expected developmentally.
- Family is not able to maintain a calm, consistent, or safe environment.
- Child’s behaviors are injurious to other children or animals.
- Child has comorbid depression.
- Child is experiencing severe dysfunction in any domain.
- Child has comorbid anxiety. (The combination of shyness, anxiety, and behavior problems is thought to be particularly risky for future behavior problems of a more serious nature.)
- An adolescent has co-occurring problems with substance use.
- Problems at school are interfering with academic achievement or relationships.
- Child or adolescent is involved with legal authorities. (This situation requires coordination with probation officers and understanding the terms of probation; simply reminding the adolescent and

family of the consequences of violating probation can help promote participation in treatment or changes to lifestyle.)

*When specialty care is needed, ensure that it is evidence-informed and assist the family in accessing it.* A variety of evidence-based and evidence-informed interventions are available for the treatment of emotional problems in young children and for CD and ODD in school-aged children and adolescents. Ideally, those referred for care in the mental health specialty system would have access to the safest and most effective treatments. Table 139-3 lists programs targeting young children and their families. Table 139-4 provides a summary of interventions for children and adolescents.

Approaches to improving the referral process include making sure that the family is ready for this step in care, that they have some idea of what the specialty care will involve, and that they understand what the clinician’s ongoing role may be. If the specialty appointment is not likely to occur in the near future, the clinician can work with parents on a plan to manage the problem as well as possible in the meantime.

Note that not all evidence-based interventions may be available in every community. If a particular intervention is not available, this becomes an opportunity to collaborate with others in the community to advocate on behalf of children. Increasingly, states offer both telepsychiatry services and consultation/referral support “warmlines” that help physicians provide initial treatment and locate resources. The availability of the latter form of help is tracked at [www.nncpap.org](http://www.nncpap.org).

*Reach agreement on respective roles in the child’s care.* If the child is referred to mental health specialty care, the primary care physician may be responsible

**Table 139-4****Psychosocial and Psychopharmacologic Treatments for Disruptive Behavior and Aggression (as of November 2014)<sup>a</sup>**

PSYCHOSOCIAL TREATMENTS		
CLUSTER AREA	LEVEL 1 (BEST SUPPORT)	LEVEL 2 (GOOD SUPPORT)
Delinquency and disruptive behavior <sup>b</sup>	<ul style="list-style-type: none"> <li>• Anger control</li> <li>• Assertiveness training</li> <li>• Cognitive behavior therapy (CBT)</li> <li>• Contingency management</li> <li>• Multisystemic therapy</li> <li>• Parent management training</li> <li>• Parent management training and problem solving</li> <li>• Social skills</li> </ul>	<ul style="list-style-type: none"> <li>• CBT and teacher training</li> <li>• Communication skills</li> <li>• Functional family therapy</li> <li>• Parent management training and CBT</li> <li>• Parent management training and classroom management</li> <li>• Problem solving</li> <li>• Rational emotive therapy</li> <li>• Relaxation</li> <li>• Self-control training</li> <li>• Therapeutic foster care</li> <li>• Transactional analysis</li> </ul>
US FOOD AND DRUG ADMINISTRATION-APPROVED PSYCHOPHARMACOLOGIC INTERVENTIONS <sup>c</sup>		
DIAGNOSTIC AREA	PSYCHOPHARMACOLOGIC INTERVENTION	
Aggression	The US Food and Drug Administration (FDA) has no approved indications for aggression in children and adolescents apart from irritability-associated aggression in children with autism. In other populations, recent federally supported evidence-based reviews suggest efficacy for some psychotherapeutic agents.	

<sup>a</sup>For AAP policy, please visit [pediatrics.aappublications.org/site/aappolicy](http://pediatrics.aappublications.org/site/aappolicy).

<sup>b</sup>Excerpted from PracticeWise Evidence-Based Child and Adolescent Psychosocial Interventions. Reprinted with permission from PracticeWise. For updates and an explanation of PracticeWise determination of evidence level, please visit [www.aap.org/mentalhealth](http://www.aap.org/mentalhealth).

<sup>c</sup>For up-to-date information about Food and Drug Administration (FDA)-approved interventions, go to [www.fda.gov/ScienceResearch/SpecialTopics/Pediatric-TherapeuticsResearch/default.htm](http://www.fda.gov/ScienceResearch/SpecialTopics/Pediatric-TherapeuticsResearch/default.htm).

for monitoring response to treatment through use of parent and teacher reports and communication with referral sources or agencies involved in care; engaging and encouraging a positive view of treatment; coordinating care provided by parents, school, medical home, and specialists; and observing for comorbidities. Resources available to help clinicians in this role are provided at the end of this chapter in Tools for Practice: Medical Decision Support.

## ACKNOWLEDGMENT

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## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Everybody Gets Mad: Helping Your Child Cope With Conflict* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/healthy-living/emotional-wellness/Pages/Everybody-Gets-Mad-Helping-Your-Child-Cope-with-Conflict.aspx](http://www.healthychildren.org/English/healthy-living/emotional-wellness/Pages/Everybody-Gets-Mad-Helping-Your-Child-Cope-with-Conflict.aspx))
- *Parents' Roles in Teaching Respect* (handout), Bobbi Conner ([www.brightfutures.org/mentalhealth/pdf/families/mc/parent\\_role.pdf](http://www.brightfutures.org/mentalhealth/pdf/families/mc/parent_role.pdf))
- *Play Nicely* (video), Monroe Carell Jr Children's Hospital at Vanderbilt ([www.playnicely.org](http://www.playnicely.org))

### Medical Decision Support

- *Pediatric Symptom Checklist* (screen), Massachusetts General Hospital ([www.massgeneral.org/psychiatry/services/psc\\_forms.aspx](http://www.massgeneral.org/psychiatry/services/psc_forms.aspx))
- *Strengths & Difficulties Questionnaires* (screen), Youth in Mind, Ltd ([www.sdqinfo.com](http://www.sdqinfo.com))
- *NICHQ Vanderbilt Assessment Scale* (scale), National Institute for Children's Health Quality ([www.nichq.org/childrens-health/adhd/resources/vanderbilt-assessment-scales](http://www.nichq.org/childrens-health/adhd/resources/vanderbilt-assessment-scales))
- *Modified Overt Aggression (MOAS) Scale* (scale) <https://depts.washington.edu/dbpeds/Screening%20Tools/ScreeningTools.html>
- *Practice Parameter for the Assessment and Treatment of Children and Adolescents With Oppositional Defiant Disorder* (article), *Journal of the American Academy of Child and Adolescent Psychiatry*, Vol 46, Issue 1, 2007 ([www.aacap.org/App\\_Themes/AACAP/docs/practice\\_parameters/jaacap\\_adhd\\_2007.pdf](http://www.aacap.org/App_Themes/AACAP/docs/practice_parameters/jaacap_adhd_2007.pdf))
- *Treatment of Maladaptive Aggression in Youth: CERT Guidelines I. Engagement, Assessment, and Management* (article), *Pediatrics*, Vol 129, Issue 6; 2012 ([pediatrics.aappublications.org/content/129/6/e1562](http://pediatrics.aappublications.org/content/129/6/e1562))
- *Treatment of Maladaptive Aggression in Youth: CERT Guidelines II. Treatments and Ongoing Management* (article), *Pediatrics*, Vol 129, Issue 6, 2012 ([pediatrics.aappublications.org/content/129/6/e1577](http://pediatrics.aappublications.org/content/129/6/e1577))



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## Chapter 140 DIZZINESS AND VERTIGO

Ruby F. Rivera, MD; Catherine R. Sellinger, MD

*Dizziness* and *vertigo*, although often used interchangeably, refer to very different symptoms that have very different clinical implications. Distinguishing these symptoms in young children may be especially difficult because much of the distinction depends on the patient's account of the history.

### DIZZINESS

#### Definition

Dizziness, a relatively common complaint in childhood and adolescence, is “an imprecise term commonly used by patients in an attempt to describe various peculiar subjective symptoms such as faintness, giddiness, light-headedness, or unsteadiness.” Patients who have simple dizziness do not describe the room spinning around them, and they do not have nystagmus.

#### Causes of Dizziness

Dizziness is commonly seen as a symptom of presyncope in children and adolescents with fever, dehydration, orthostatic hypotension, and vasovagal syncope. It is also commonly associated with anemia, either from acute or chronic blood loss or from a congenital condition such as sickle cell disease. Any heart disease or dysrhythmia that reduces cardiac output can cause dizziness; so too can hypertension. Hypoglycemia, which may be associated with altered mental status or seizures, can first manifest as dizziness. Hyperthyroidism, hypothyroidism, and Addison disease can also cause dizziness. In female adolescents, pregnancy should be considered in the differential diagnosis of dizziness. Ocular disorders such as refractive errors, astigmatism, amblyopia, and strabismus can cause dizziness. Dizziness is often a symptom of anxiety and as part of panic attacks. Dizziness may also be caused by medications

that affect the ear, such as aminoglycosides, phenytoin, loop diuretics, and nonsteroidal anti-inflammatory drugs. An algorithm to aid in narrowing the differential diagnosis of dizziness is shown in Figure 140-1.

When young children cannot describe dizziness or vertigo, observers tend to apply these terms to a child who is unsteady while standing. Disequilibrium in this age group may reflect acute cerebellar problems, such as postviral acute cerebellar ataxia and posterior fossa tumors. In adolescents, particularly girls, ataxia as part of multiple sclerosis may be described as dizziness. Another common cause of disequilibrium in young children is middle-ear disease. Several studies have shown deterioration in vestibular balance and motor function in children with middle-ear effusion. If not self-limited, symptoms usually resolve after placement of tympanostomy tubes.

## VERTIGO

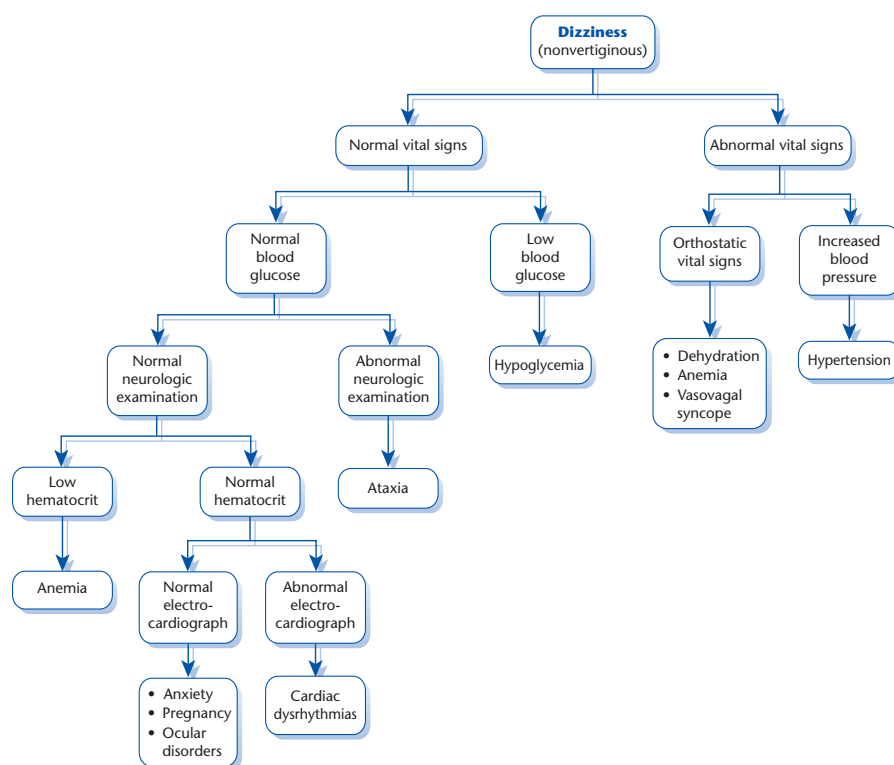
#### Definition

Vertigo is “a sensation of spinning or whirling motion. Vertigo implies a definite sensation of rotation of the subject or of objects about the subject in any plane.” True vertigo almost always is accompanied by nystagmus, at least at the time of the episode. Thus the primary care physician should ask observers about the presence of nystagmus and should ask them to watch for it in future episodes.

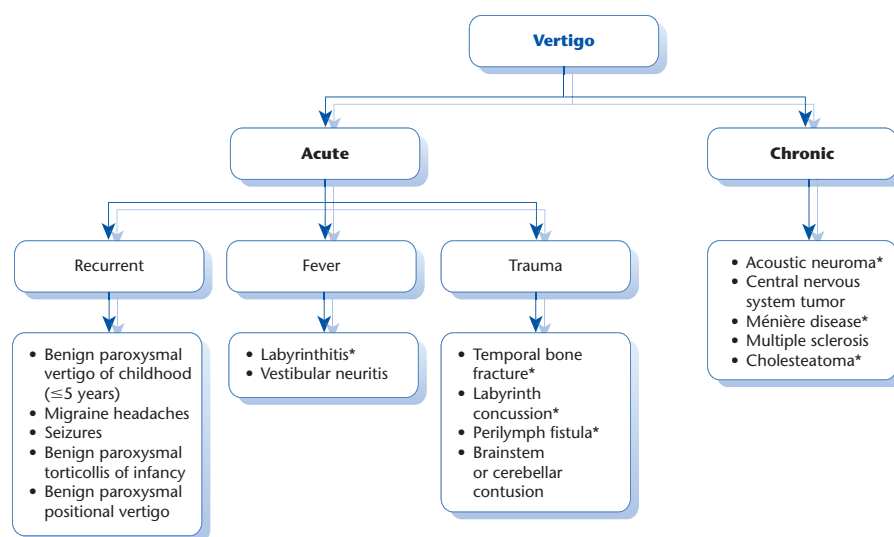
#### Causes of Vertigo

The causes of vertigo can be differentiated based on 3 elements in the history: whether the vertigo is acute or chronic, whether episodes are recurrent, and whether it is accompanied by hearing loss. The causes of vertigo in children vary greatly from those in adults. Acute episodic vertigo is the most common type encountered by pediatricians and is usually not accompanied by hearing loss (Figure 140-2).

The most common causes of acute episodic vertigo are migraine headaches and related syndromes. Benign paroxysmal torticollis of infancy is thought to be a migraine variant that begins in infancy and generally resolves spontaneously by 2 to 3 years of age. It is characterized by episodes of recurrent head tilt, which may last for hours or days and is often associated with vomiting, agitation, pallor, and ataxia. Benign paroxysmal vertigo of childhood is also considered a migraine variant and is typically seen in children younger than 5 years. These children have the sudden onset of extreme unsteadiness and inability to stand, usually with nystagmus and sometimes with vomiting. The episodes last seconds to minutes. In many cases, the family has a history of migraine headaches, and many of these patients develop more typical migraine headaches in later life. Older children and adolescents may have episodic vertigo as a result of basilar artery migraines. Affected patients often have scintillating scotomas or visual obscuration, oral paresthesias, tinnitus, and occasionally drop attacks with or without loss of consciousness. These early symptoms are commonly



**Figure 140-1** Algorithm for the differential diagnosis of dizziness.



**Figure 140-2** Algorithm for the differential diagnosis of vertigo. Asterisk denotes an associated hearing loss.

but not always followed by a pounding headache. Other causes of acute recurrent vertigo include seizures, perilymph fistula, and benign paroxysmal positional vertigo. Seizures that are associated with vertigo are followed by an alteration or loss of consciousness. A perilymph fistula is an abnormal

connection between the inner- and middle-ear spaces. Although some fistulas are congenital, most are acquired from trauma, such as direct penetrating trauma, head trauma, or barotrauma. Flying, diving, coughing, sneezing, or any type of excessive strain or exertion may tear the oval or round window,

causing a sudden onset of vertigo associated with hearing loss. Benign paroxysmal positional vertigo (BPPV), although extremely common in adults, is rare in children. BPPV is believed to be caused by otoconia (debris or *ear rocks*) that have been deposited in a sensitive location in the semicircular canal. Acute episodes of severe vertigo are precipitated by a change of head position and are associated with nystagmus, nausea, and vomiting. The Epley and Semont maneuvers attempt to relocate the otoconia into a less-sensitive location. (A helpful Web site that illustrates these maneuvers is [www.dizziness-and-balance.com/disorders/bppv/bppv.html](http://www.dizziness-and-balance.com/disorders/bppv/bppv.html)). Vestibular neuritis exhibits similar symptoms to BPPV and, although uncommon in children, should be considered if vertigo is preceded by a viral infection. Neither BPPV nor vestibular neuritis is associated with hearing loss.

Vertigo with hearing loss in childhood is usually associated with severe otitis media leading to labyrinthitis. Affected patients are acutely uncomfortable, both from ear pain and from severe vertigo, usually with nausea, vomiting, and nystagmus. Less common causes of hearing loss with vertigo in children include head trauma or ear trauma. Ménière disease, consisting of vertigo, fluctuating hearing loss, pressure in the ear, and tinnitus, is rare in young children, usually occurring after 11 years of age.

Chronic persistent vertigo, especially if accompanied by neurologic signs, is usually indicative of central nervous system disease, including tumors, acoustic neuromas (seen in neurofibromatosis type II), and demyelinating and degenerative disorders.

## EVALUATION OF DIZZINESS AND VERTIGO

### History

Most episodes of dizziness and vertigo can be diagnosed on history and physical examination. Useful information, which may lead to a particular diagnosis, is listed in Table 140-1.

### Physical Examination

On physical examination, the physician should document orthostatic vital signs, look for evidence of anemia or dehydration, and pay particular attention to the head, neck, cardiac, and neurologic findings. The Dix-Hallpike maneuver (Nylan-Barany test) can help localize the source of nystagmus or vertigo. To provoke an episode, the child is moved rapidly from a sitting to supine position with the head 45 degrees below the edge of the table and turned 45 degrees to 1 side. The ear that is facing the floor when the nystagmus is elicited is the affected side. Nystagmus that resolves when the child fixates on an object is suggestive of a peripheral or vestibular disease, as opposed to persistent nystagmus, which is seen in central nervous system disorders.

The ears are examined for vesicles of herpes zoster (Ramsay-Hunt syndrome); a distorted tympanic membrane may be seen with otitis media, cholesteatoma, and perilymph fistula. Two useful maneuvers that may

**Table 140-1**

### Differential Diagnoses of Dizziness and Vertigo

INFORMATION	POSSIBLE DIAGNOSES
<b>FAMILY HISTORY</b>	
Neurofibromatosis	Acoustic neuroma
Seizure disorder	Seizure
Migraines	Benign paroxysmal torticollis of infancy
	Benign paroxysmal vertigo of childhood
	Migraine
	Dysrhythmias
Unexplained syncope or sudden cardiac death	
Anxiety, panic disorders	Anxiety
<b>MEDICATION HISTORY</b>	
Aminoglycosides, loop diuretics, phenytoin, nonsteroidal anti-inflammatory drugs, chemotherapeutic agents, quinine	Ototoxicity
	Intoxication
<b>MEDICAL HISTORY</b>	
Acute or chronic blood loss	Anemia
Palpitations or chest pain	Dysrhythmias
	Anxiety, panic disorder
Recent life stressor	Anxiety
Last menstrual period	Pregnancy
Motion sickness	Benign paroxysmal vertigo of childhood
	Migraine
	Vestibular neuritis
Recent upper respiratory infection	
Fever	Otitis media
	Labyrinthitis
Ear trauma, barotrauma	Perilymph fistula
Headache	Migraine
	CNS disease
Head trauma	Temporal bone fracture
	Labyrinth or brainstem concussion
	Cerebellar contusion
	Perilymph fistula
Neurologic deficits	CNS tumor
	Multiple sclerosis
Hearing loss	Cholesteatoma
	Acoustic neuroma
	Temporal bone fracture
	Perilymph fistula
	Labyrinth concussion
	Labyrinthitis
	Ramsay-Hunt syndrome (herpes zoster oticus)
	Ménière disease
Triggered by change in head position	Benign paroxysmal positional vertigo
	Perilymph fistula
	Vestibular neuritis
	Acute labyrinthitis
Loss of consciousness or altered mental status	Seizure
	Dysrhythmia
	Vasovagal syncope
	CNS disease
	Hypoglycemia

CNS, central nervous system.

help in the diagnosis of perilymph fistula are applying pressure to the tragus to occlude the external auditory canal and pneumatic otoscopy; these may induce nystagmus or vertigo and transiently worsen a hearing loss.

### Laboratory Testing and Imaging

With a limited role in the evaluation of dizziness and vertigo, laboratory tests such as complete blood count, metabolic panel, thyroid function tests, electrocardiogram, electroencephalogram, and magnetic resonance imaging should be guided by the history and physical examination. In adolescent girls, a pregnancy test should also be considered. Formal audiometry and electronystagmography may be warranted for the evaluation of vertigo.

## MANAGEMENT OF DIZZINESS AND VERTIGO

For patients who have presyncopal or orthostatic dizziness, reassurance and instructions about adequate hydration, about care when arising suddenly, and about the necessity of putting the head lower than the heart when symptoms occur generally suffice for patient management. For patients in whom dizziness is part of a panic attack or a marker of significant stress, further history should be obtained, including any suicidal ideation, and referral for counseling considered.

Treatment for migrainous vertigo and its related syndromes should be symptomatic and targeted to the treatment of migraines (see Chapter 157, Headache).

Vestibular suppressants such as diazepam, meclizine (for children >12 years), and dimenhydrinate may be used to relieve the symptoms of vertigo and nausea. Antibiotics are required for treating labyrinthitis. Treatment for postinfectious vestibular neuritis is symptomatic and supportive, but evidence suggests that prednisone may be helpful.

### WHEN TO REFER

- Acute ataxia
- A clear history of vertigo, especially with other neurologic signs, or after head trauma or barotrauma
- Suspected perilymph fistula or cholesteatoma
- Suspected seizure
- Complicated migraine

### WHEN TO ADMIT

- Bacterial or suppurative labyrinthitis
- Head trauma with temporal bone fracture
- Space-occupying lesions
- Potential life-threatening cardiac dysrhythmias
- Labile hypertension

## TOOLS FOR PRACTICE

### Medical Decision Support

- BPPV: *Benign Paroxysmal Positional Vertigo* (Web page), Timothy C. Hain, MD ([www.dizziness-and-balance.com/disorders/bppv/bppv.html](http://www.dizziness-and-balance.com/disorders/bppv/bppv.html))

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## Chapter 141

# DYSMENORRHEA

Linda M. Dinerman, MD, PC

Dysmenorrhea, or painful menstruation, is a syndrome characterized by varying degrees of crampy, lower abdominal pain and other symptoms such as nausea, vomiting, urinary frequency, low back pain, diarrhea, fatigue, thigh pain, nervousness, dizziness, sweating, and headache. The pain typically begins just after menses and lasts for about 1 to 2 days, but it can also begin 1 to 2 days before the onset of menses and can last up to 4 days into menstruation. Cramps may be more severe among teenagers who smoke. At least 40% to 60% of adolescent girls suffer some degree of discomfort during menstruation, with about 15% reporting severe symptoms and 14% reporting that they frequently miss school as a result of menstrual symptoms. Most affected teenage girls have primary dysmenorrhea not associated with pelvic or other pathologic conditions; however, causes of secondary dysmenorrhea always should be considered when the patient is evaluated.

## PRIMARY DYSMENORRHEA

Increased amounts of prostaglandins  $E_2$  and  $F_{2\alpha}$  in the endometrium of women with dysmenorrhea lead to smooth muscle contractions along with other symptoms such as vomiting and diarrhea. This biologic explanation correlates with the clinical observation that women who have anovulatory cycles usually do not have dysmenorrhea. Adolescent girls typically develop dysmenorrhea 1 to 2 years after menarche, correlating with the onset of ovulatory cycles.

The incidence of dysmenorrhea increases with gynecologic age (as does the number of ovulatory cycles), with up to 31% of girls reporting dysmenorrhea in their first year of menses and 78% in their fifth year. The increase in prostaglandin synthesis may be related to changes in serum progesterone levels not seen in anovulatory women. Additional confirmation comes from the dramatic response women experience with use of either prostaglandin synthetase inhibitors or oral contraceptives, which



inhibit ovulation. Increased levels of prostaglandin activity are associated with increased uterine tone and high-amplitude myometrial contractions, both of which result in reduced uterine blood flow and pain.

The assessment of a teenager with dysmenorrhea should include the following:

- Complete menstrual history
- Timing of cramps or pain
- Missed school or other activities
- Ability to participate in social events
- Presence of nausea, vomiting, diarrhea, dizziness, or other symptoms
- Medications used, including doses
- Factors that improve or worsen symptoms
- Family history of dysmenorrhea or endometriosis

In some cases, dysmenorrhea may be the presenting complaint when the true agenda is otherwise. For example: Is the patient reluctant to attend school? Does the patient have a history of physical or sexual abuse? Does the patient have significant psychosocial problems? Is the teen secretly sexually active, and is this a way for her to obtain oral contraceptives for the purpose of contraception?

A careful history usually excludes most pathologic causes of dysmenorrhea. Physicians differ in their opinions regarding what examination is necessary to evaluate a patient with dysmenorrhea. In general, for a non-sexually active teenager who has mild to moderate menstrual cramps relieved by nonsteroidal anti-inflammatory drugs (NSAIDs), only an external genital examination to rule out hymenal abnormalities is indicated. Some physicians would also initiate oral contraceptive pills for a few cycles before performing a pelvic examination if the dysmenorrhea is unresponsive to NSAIDs. For any sexually active teenager or, in the opinion of some experts, for one who is having significant pain that is unresponsive to NSAIDs, a thorough pelvic examination is necessary. In sexually active teenagers, evaluation for sexually transmitted infections and pregnancy should be included. If a pelvic examination is not possible, then a rectoabdominal examination will provide some useful information about the presence of masses or adnexal tenderness. A pelvic ultrasound may be useful in defining uterine and vaginal abnormalities associated with obstruction but is not helpful in the detection of pelvic or abdominal adhesions or endometriosis.

Although treatment of primary dysmenorrhea is likely to include drug therapy, the physician also should take the valuable opportunity to teach the patient about her body. Many teenagers do not understand the physiologic mechanisms of menstruation fully or may have inaccurate beliefs that have been passed on from mother to daughter.

Although teenagers who have very mild discomfort benefit from almost any analgesic, prostaglandin synthetase inhibitors in the form of NSAIDs are the treatment of choice for most young women with dysmenorrhea. Doses, both in terms of amount and timing, vary from patient to patient. Establishing not only prior use of specific medications but also doses is important, given that most patients use them in

subtherapeutic amounts. Some need medication only for part or all of the first day of menstruation; others require medication for up to 4 days or more. Ibuprofen (200–800 mg every 6–8 hours) is highly effective for dysmenorrhea, as is naproxen sodium (550 mg immediately and then 275 mg every 6–8 hours). Mefenamic acid, an NSAID that blocks the effect of prostaglandin at the end-organ level and inhibits its production, can be used in a dose of 500 mg administered immediately, followed by 250 mg every 6 hours. Celecoxib, a cyclooxygenase inhibitor, in a dose of 200 mg every 12 hours, has been shown to be effective; however, intestinal bleeding and cardiovascular events have limited its use. In 1 study, 57% of adolescents used medications less often than the maximal daily frequency; thus, advising patients of the range of correct doses is important. These medications are most effective if started at the first sign of menstrual bleeding; women who experience significant nausea with menses may benefit from starting treatment at the earliest symptom of menses, even before bleeding occurs. If the adolescent fails to respond to 1 type of NSAID (eg, ibuprofen), then another (eg, naproxen sodium) should be tried because variability is noted in response to different NSAIDs. Between 70% and 80% of girls will respond to one NSAID or another. The patient should be reevaluated after 2 to 3 menstrual cycles to determine effectiveness of the treatment.

Some patients (perhaps as many as 20% to 30%) will not respond to these measures. In these young women, a trial of oral contraceptive pills (OCPs) used in the same way as for contraception usually provides relief. OCPs work by suppressing ovulation and decreasing endometrial prostaglandin production. Patients should be told that 2 to 3 cycles may elapse before contraceptives exert their maximal effect. If the patient is sexually active, then oral contraceptives are continued on a routine basis; for the non-sexually active teenager, therapy can be reassessed at 6- to 12-month intervals.

Low dose OCPs significantly decrease the symptoms of dysmenorrhea in adult women and adolescents. After 3 cycles, adult patients using OCPs with 20 mcg of ethinyl estradiol and 150 mcg of desogestrel and adolescent patients using OCPs with 20 mcg of ethinyl estradiol and 100 mcg of levonorgestrel experienced significant relief of dysmenorrhea compared with those using placebo.

In a study of adolescent girls using the patch (Ortho Evra) for contraception, dysmenorrhea decreased in 39%, increased in 11%, and resulted in no change in 50%. Depot-medroxyprogesterone acetate (Depo-Provera, DMPA) is also used to prevent ovulation and menstrual flow when OCPs are not tolerated or estrogen is contraindicated. An extended oral contraceptive regimen in which OCPs are taken for up to 12 consecutive weeks followed by 1 hormone-free week is another treatment approach. Continuous OCPs have also been well accepted and shown to be effective in eliminating menses, thereby reducing dysmenorrhea. DMPA and extended oral contraceptive regimens decrease

dysmenorrhea, and they decrease the frequency of menses.

The efficacy of other treatments is still unproved. Some experts believe that heat, pelvic exercise, general exercise, biofeedback, relaxation therapy, massage, vitamin E, or various herbal remedies are effective; other authorities remain skeptical of these alternatives. Magnesium has been shown to be beneficial in some studies. To the extent that smoking exacerbates dysmenorrhea, it provides yet another reason for physicians to urge their patients to stop smoking. The adolescent with dysmenorrhea should be encouraged to exercise, eat a well-balanced diet, decrease stress, and decrease caffeine consumption.

Women who fail to respond to any of these measures should be referred to an adolescent medicine specialist or gynecologist for evaluation; they probably have secondary rather than primary dysmenorrhea.

## SECONDARY DYSMENORRHEA

Causes of secondary dysmenorrhea, such as pelvic inflammatory disease (PID), endometriosis, and conditions arising in a variety of other organ systems, can usually be excluded by a careful history and physical examination. Underlying pathologic conditions should be anticipated in a young woman whose pain begins after 20 years of age, who has a history of surgery related to the genitourinary or gastrointestinal tract, or who has pain that is dull and constant rather than crampy.

Endometriosis is the presence of functional endometrial glands and stroma outside the normal anatomic location in the uterus. Patients who have endometriosis will have failed therapy with NSAIDs and oral contraceptives, and their pain may be acyclic rather than cyclic. Menstrual bleeding may be irregular, gastrointestinal symptoms may be present, and a family history of endometriosis can often be elicited. Endometriosis also may be associated with dyspareunia, tenesmus, and rectal pain. Some studies of teenagers with chronic pelvic pain show 25% to 38% of those undergoing laparoscopy have endometriosis. In yet other studies, 52% to 73% of teenagers with chronic pelvic pain have evidence of endometrial implants. PID can cause dysmenorrhea acutely, and women often develop chronic pelvic pain as a consequence of PID. Even with assurances of confidentiality, some young women may still not admit to sexual activity. Hence, physicians must maintain a high index of probability if other historical and physical examination findings suggest PID. Teenagers who have a history of genital tract surgery, including abortion, may have outflow tract obstruction. A variety of müllerian anomalies with incomplete obstruction of the outflow tract also produce dysmenorrhea. Depending on the type of obstruction, a pelvic mass may be palpable. Endometrial polyps or fibroids are rare in women younger than 20 years but should be anticipated if the menstrual bleeding is heavy, prolonged, or associated with the passage of clots. Whether these entities alone cause dysmenorrhea is unclear.

A pelvic examination that reveals cervical motion tenderness, or adnexal tenderness, or masses strongly suggests PID. If the cervical os is stenotic or the

cervix or uterus feels atretic or abnormally shaped, then outflow obstruction is possible (eg, a uterus with a blind horn). Among adult women, physical findings such as small fixed nodules in the rectovaginal septum or cul de sac or fixation of the uterus indicated by the sensation of pain on stretching of the uterosacral ligaments suggest endometriosis. However, most adolescents generally have normal examinations; hence, endometriosis can be extremely difficult to detect on clinical grounds alone. If a secondary cause of dysmenorrhea is thought to be present, then consultation with an adolescent medicine specialist or gynecologist is warranted. Ultrasound examination of the uterus will rule out uterine anomalies but cannot exclude endometriosis. Confirmation of endometriosis requires laparoscopy. Because the lesions of endometriosis in adolescents may differ from the typical lesions seen in adults, a gynecologist who is experienced in evaluating adolescents should perform this procedure. Endometriosis may be difficult to manage, and women who have this condition are at increased risk for infertility.

PID should be treated according to standard antibiotic regimens. Follow-up is critical because young women, once infected, are at risk for further episodes of PID as well as for chronic pelvic pain, ectopic pregnancy, and infertility.

### WHEN TO REFER

- For dysmenorrhea, referral might be appropriate if
- Physician feels uncomfortable prescribing OCPs for the treatment of primary dysmenorrhea
- Patient fails to respond to NSAIDs and OCPs
- Clinical presentation or course suggests that the patient has secondary rather than primary dysmenorrhea
- Patient is sexually active and the physician feels uncomfortable performing a pelvic examination

### WHEN TO ADMIT

If the cause of the dysmenorrhea is determined to be PID, some physicians would recommend hospitalization of all adolescents for treatment. Others recommend hospitalization under certain but not all circumstances.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Center for Young Women's Health* (Web site), ([www.youngwomenshealth.org](http://www.youngwomenshealth.org))
- *Menstrual Disorders* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/genitourinary-tract/Pages/Menstrual-Disorders.aspx](http://www.healthychildren.org/English/health-issues/conditions/genitourinary-tract/Pages/Menstrual-Disorders.aspx))

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## Chapter 142 DYSPHAGIA

Mohammad F. El-Baba, MD

Feeding and swallowing disorders are common complaints in children. Dysphagia is defined as difficulty swallowing, which derives from the Greek root, *dys*, meaning “difficulty,” and *phagia*, meaning “to eat.” It is not synonymous with the term *odynophagia*, which refers to painful swallowing.

### NORMAL DEVELOPMENT OF SWALLOWING

A sucking reflex, present as early as 18 weeks’ gestation, is initially disorganized but becomes more organized and efficient for feeding by 34 to 36 weeks’ gestation. For the term newborn the suck is mature and efficient for liquid feedings. During early infancy, the infant develops a more rapid suck rate and higher suck pressure. Tongue movements are differentiated and become more coordinated, preparing the infant for pureed food by 5 to 6 months of age. After this stage, sensory experience with food increases, and oral motor skills expand to handle more textured food. The gag reflex decreases to allow swallowing of an increasing amount of food with more texture. By age 2 years, chewing and tongue movements become more proficient.

### NORMAL PHASES OF SWALLOWING

Swallowing is divided into 3 phases: oral, pharyngeal, and esophageal. These phases allow the food and liquid to move from mouth to stomach efficiently and safely. In the oral phase, the food is mixed with saliva and chewed if needed. A single bolus of food is collected between the roof of the mouth and tongue. The bolus is propelled to the posterior of the tongue and then to the pharynx. In infants and young children, the suckling swallow allows the liquid to fall from the mouth into the pharynx.

The pharyngeal phase is the actual reflexive swallow stimulated by the presence of food on the posterior tongue. During this phase the soft palate rises to keep the food from the nasal passage. The larynx moves up and forward, closing the glottis. The vocal cords come together, the epiglottis closes over the airway, and respirations cease. Food is propelled further by contraction of the pharyngeal muscles and relaxation of the upper esophageal sphincter.

During the esophageal phase, esophageal peristalsis moves the food down the esophagus into the stomach through the relaxed lower esophageal sphincter. The lower esophageal sphincter then returns to the closed tonic state to prevent regurgitation of gastric contents.

### CAUSES OF DYSPHAGIA

Any anatomic or functional disorder in the well-coordinated act of swallowing can result in dysphagia,

which can be for liquids, solids, or both. In general, mechanical or obstructive factors result in dysphagia for solids. Dysphagia for liquids is more pronounced in patients with neurologic disorders. The causes of dysphagia in children are widespread and include congenital, inflammatory, infectious, systemic, neoplastic, and traumatic reasons (Box 142-1).

Infants born before term or with a birth weight below the tenth percentile for gestational age are at increased risk for developing dysphagia and feeding difficulties. Improved survival of infants born prematurely has contributed to the increased incidence of dysphagia in children.

Central nervous system impairment and developmental delay are common causes of dysphagia in infants and children. Almost all children with severe cerebral palsy are reported to suffer from some degree of dysphagia, and about 70% of children with severe traumatic brain injury present with dysphagia during the acute phase of care. Children with gastroesophageal reflux disease often experience some feeding problems and food refusal. Reflux can lead to nausea, vomiting, and esophagitis, all of which may cause feeding to be perceived as an aversive experience. Eosinophilic esophagitis has become a recognized entity that causes dysphagia in adults and children, and it should be considered in the differential diagnosis of children with unexplained oral aversion, feeding difficulties, and poor weight gain.

Prolonged tube feeding in infancy or childhood can lead to long-term feeding difficulties. Several factors are implicated in such difficulties and include age at which oral feeding commences, underlying medical conditions, exposure to taste and textures during sensitive periods, aversive experiences, and different methods of delivering tube feeds.

Infants and young children occasionally exhibit transient feeding difficulties such as selective eating, exceedingly slow eating, and tantrums. Some children without apparent risk factors show deviating feeding behaviors such as food refusal, aversion to feeding, low food intake, excessive gagging, and vomiting even before food is presented. Nonorganic feeding disorders are usually transient, but in 3% to 10% become persistent and carry the risk of inadequate growth. Early intervention and a multidisciplinary approach are crucial in the management of this group of children.

### CLINICAL MANIFESTATION

Feeding disorders are commonly seen in early childhood. Minor feeding problems are reported in 25% to 35% of healthy young children, with major feeding disorders observed in 40% to 70% of infants born prematurely or children with chronic medical problems. Affected infants or children commonly exhibit feeding difficulties, food refusal, failure to thrive, or sensation of food stuck in the throat or chest. These children may also have drooling, difficulty initiating swallowing, change in dietary habits, aversions to certain food textures, and unexplained weight loss.

**BOX 142-1 Causes of Dysphagia in Children**

- Prematurity
- Congenital abnormalities
  - Congenital anomalies of the nasal and oral cavity
    - Cleft lip or palate
    - Choanal atresia or stenosis
    - Craniofacial anomalies (Crouzon syndrome, Apert syndrome, Möbius sequence, Pierre Robin sequence, Treacher Collins syndrome)
    - Congenital nasal masses (dermoids, encephaloceles)
  - Congenital anomalies of the larynx, trachea, and esophagus
    - Laryngomalacia
    - Laryngeal clefts
    - Laryngeal stenosis and webs
    - Vocal cord paralysis
    - Tracheoesophageal fistula
    - Esophageal atresia
    - Esophageal duplication
- Vascular rings
  - Double aortic arch
  - Right aortic arch with left ligamentum from a descending aorta
  - Innominate artery tracheal compression
- Infectious causes
  - Acute pharyngitis or tonsillitis
  - Peritonsillar and retropharyngeal abscesses
  - Epiglottitis
  - Esophagitis (cytomegalovirus, herpesvirus, *Candida albicans*)
- Inflammatory causes
  - Esophagitis secondary to gastroesophageal reflux disease
  - Eosinophilic esophagitis
- Neurologic or neuromuscular disorders
  - Hypoxic-ischemic encephalopathy
  - Head trauma
  - Cerebral palsy
  - Congenital malformations (Arnold-Chiari malformation, absent corpus callosum)
  - Degenerative diseases of white and gray matter
  - Brainstem tumors
  - Syringomyelia
  - Infantile spinal muscular atrophy (Werdnig-Hoffmann disease)
  - Diseases of neuromuscular junction
    - Myasthenia gravis
    - Guillain-Barré syndrome
    - Botulism
- Muscular
  - Congenital myopathies
  - Mitochondrial diseases
  - Glycogen storage diseases
  - Congenital muscular dystrophy and myotonic dystrophy
- Traumatic
  - External trauma
  - Intubation injury
- Neoplastic
  - Hemangioma
  - Lymphangioma
- Miscellaneous
  - Foreign-body aspiration
  - Caustic ingestion
  - Motor dysfunction of esophagus (achalasia)
  - Epidermolysis bullosa

Some children may experience change in voice, recurrent coughing, or noisy breathing during feeding. Oropharyngeal dysphagia should be considered in young children with recurrent aspiration or unexplained respiratory symptoms. Respiratory symptoms that result from dysphagia vary and may be associated with coughing, chronic congestion, recurrent choking, acute life-threatening events, recurrent pneumonias, and chronic lung disease. The different symptoms of dysphagia in infants and children are summarized in Box 142-2.

**EVALUATION****History and Physical Examination**

A complete history and thorough physical examination of the child with dysphagia usually leads to the diagnosis and guides the selection of further diagnostic tests. Emphasis should be placed on birth history, neurodevelopmental history, and medical comorbidities.

Detailed feeding history should include the type of current diet, texture, route of administration, meal duration, and specific food aversion or aversions. General examination should document any orofacial malformation. The combination of micrognathia and glossoptosis seen in Pierre Robin sequence may cause feeding difficulty in an infant. Cleft lip and palate, including submucous cleft, are important causes of dysphagia. Newborns with choanal stenosis may experience difficulty feeding because of the obligate nasal breathing in the first few months of life. Neurologic examination should include assessment of muscle tone and strength and evaluation of cranial nerve function.

A clinical feeding evaluation should be performed by an experienced occupational therapist or speech pathologist. This clinical evaluation includes assessment of posture, positioning, oral structure and function, patient motivation, and interaction between the infant and feeder. A variety of foods, different



**BOX 142-2 Symptoms of Dysphagia in Infants and Children****ORAL PHASE**

- Failure to initiate or maintain sucking
- Prolonged feeding time
- Drooling

**ORAL HYPERSENSITIVITY**

- Exaggerated gag reflex
- Difficulty making the transition to textured foods
- Sensitivity to touch in and around mouth

**ORAL HYPOSENSITIVITY**

- Retaining food in the mouth
- Increased drooling

**PHARYNGEAL PHASE**

- Coughing
- Choking
- Noisy breathing during feeding
- Nasopharyngeal reflux

**ESOPHAGEAL PHASE**

- Spitting up or vomiting
- Irritability or arching during feeding
- Preference for liquid food
- Sensation of food stuck in the throat

positions, and adaptive utensils may be used during the examination. Specific symptoms observed during feeding can help identify the underlying disorder. Gagging, coughing, or emesis is usually present in infants with a structural or neurologic disorder. Repeated swallowing after feeding, fussiness, crying, or regurgitation are usually noted in infants with gastroesophageal reflux disease and require further investigation.

**Laboratory Evaluation**

A complete blood count can be useful as a screening test for infectious or inflammatory conditions. Serum protein and albumen are useful for nutritional assessment. Chromosomal karyotyping, metabolic analysis, or specific DNA tests may be required for a specific diagnosis as directed by physical and neurologic examination. Electromyography, nerve conduction studies, and muscle biopsy may be needed in infants with suspected neuromuscular disorders.

**Imaging Studies**

Chest radiography is indicated in patients with suspected pneumonia or chronic lung disease. Persistent pulmonary infiltrates on chest radiograph may be better elucidated by high-resolution chest computed tomography (HRCT). Computed tomography or magnetic resonance imaging of the brain may be especially

helpful in patients with suspected central nervous system injury or structural abnormalities.

**Diagnostic Studies*****Upper Gastrointestinal Barium Study***

Barium radiography plays a role in evaluating esophageal dysphagia. It is valuable in assessing anatomic or structural abnormalities, such as strictures, fistulas, masses, or intestinal rotational anomalies. Barium studies are usually more sensitive than endoscopy in the evaluation of patients suspected to have achalasia or vascular ring. In most cases, vascular rings appear as a persistent indentation of the esophagus.

***Videofluorographic Swallowing Study***

The videofluorographic swallowing study (VFSS), also known as the modified barium study, is considered the gold standard for assessment of the oral and pharyngeal stages of swallowing and allows the physician to determine the risk of aspiration. Conducted jointly by a radiologist and a dysphagia-trained speech pathologist or occupational therapist, the VFSS provides evidence of all categories of oropharyngeal swallowing dysfunction, which include inability or excessive delay in initiation of pharyngeal swallowing, aspiration of food, nasopharyngeal regurgitation, and residue of food within the pharyngeal cavity after swallowing.

During this study the child will drink or eat foods mixed with barium while radiographic images are observed and recorded. Patients' difficulties with different food textures can be identified and compatible diets planned. The definitive finding of aspiration will permit the physician to make suggestions to avoid the offending consistency, usually thin liquids. Furthermore, the study allows for testing of the efficacy of compensatory dietary modifications, postures, and swallowing maneuvers so that the observed dysfunction can be corrected. Its disadvantages are those of exposure to ionizing radiation, hence a time limit on the study duration and a need for patient cooperation. Dose limiting techniques, such as pulsed fluoroscopy and tight coning, will be effective in eliminating unnecessary radiation.

***Fiberoptic Endoscopic Evaluation of Swallowing***

In fiberoptic endoscopic evaluation of swallowing (FEES) a fiberoptic endoscope is introduced into the nose and advanced into the laryngopharyngeal area, permitting observation of the pharyngeal phase of swallowing. A swallowing assessment is performed with liquids and a variety of textures, if developmentally appropriate. Typically, dye is added to the food to provide better visualization and to determine residual pooling of food versus saliva. The feeding parameters evaluated in this study are laryngeal penetration and aspiration. FEES, combined with laryngopharyngeal sensory testing, has shown that patients with a higher laryngopharyngeal sensory threshold are more likely to experience laryngeal

penetration and aspiration during a feeding assessment. The ability to initiate airway closure with stimulation demonstrates airway protection. FEES and sensory testing may be particularly valuable for the evaluation of swallowing safety in children who refuse to ingest adequate amounts of barium to perform VFSS.

### **Esophagogastroduodenoscopy**

Endoscopy is suggested for most patients with dysphagia of esophageal origin to establish or confirm a diagnosis, to seek evidence of esophagitis, and, when appropriate, to implement therapy. It is particularly useful in evaluating patients suspected of having strictures, webs, mucosal inflammatory lesions, or specific infections. Endoscopic and histologic features are required for the diagnosis of eosinophilic esophagitis. A normal appearance of the esophagus during endoscopy does not exclude histopathological esophagitis; subtle mucosal changes such as erythema and pallor may be observed in the absence of esophagitis. During endoscopy, esophageal biopsy should be performed to detect microscopic esophagitis and to exclude causes of esophagitis other than gastroesophageal reflux.

### **Esophageal Manometry**

Esophageal manometry, the standard test for disorders of esophageal motility, is especially useful in establishing a diagnosis of achalasia and for detecting esophageal motor abnormalities associated with autoimmune diseases.

### **Esophageal pH Probe Study**

Esophageal pH monitoring, a valid and reliable measure of acid reflux, is useful to establish the presence of abnormal acid reflux, to determine whether a temporal association exists between acid reflux and frequently occurring symptoms, and to assess the adequacy of therapy in patients who do not respond to treatment with acid suppression. Most centers are currently replacing pH monitoring with combined multiple intraluminal impedance (MII) and pH monitoring. This test detects acid and nonacid reflux episodes. It is superior to pH monitoring alone for evaluation of the temporal relation between symptoms and GER.

### **Scintigraphy**

Scintigraphy is useful in the evaluation of gastric emptying and can also demonstrate episodes of aspiration detected during a 1-hour study or on images obtained up to 24 hours after the test feeding is administered. The role of scintigraphy in diagnosing gastroesophageal reflux disease in infants and children is unclear.

## **MANAGEMENT**

Management of children with dysphagia often involves a multidisciplinary approach, the aims of which are to identify and characterize dysphagia and identify the underlying cause whenever possible. Special emphasis should be placed on detection of treatable

conditions, which include surgically or endoscopically treatable structural abnormalities, inflammatory conditions (eg, reflux esophagitis, eosinophilic esophagitis), specific infections, and underlying systemic conditions.

The goals of managing dysphagia are to reduce aspiration, improve the ability to eat and swallow, and optimize nutritional status. Feeding therapy for infants and children may include the strategies described below.

### **Normalization of Posture and Tone**

Head and trunk control are crucial to the development of oral motor skills. Children with neurologic abnormalities frequently have poor head control and poor trunk stability. Occupational and physical therapy can be used to improve head control, neck and trunk tone, and posture as a basis for improved oral motor function.

### **Adaptation of Food and Feeding Equipment**

Food and feeding equipment may be adapted by changing the attributes of food and liquids, such as bolus volume, consistency, temperature, and taste. Adjustments in feeding schedule may be beneficial for children receiving continuous tube feeds with supplemental food orally. The feeds can be changed gradually to bolus feeds to stimulate the child's appetite. The rate of feeding should be paced to allow sufficient time to swallow before giving another bite. In addition, the bottle or utensils may be changed according to the child's needs.

### **Oral Motor Therapy**

Oral motor therapy is focused on improving the oral phase of feeding and may include stimulation with stroking, stretching, brushing, icing, tapping, and vibrating areas of the face and mouth.

### **Nutritional Support**

Management of dysphagia must focus on meeting the child's nutritional needs for adequate growth. When a patient is unable to achieve adequate nutrition and hydration by mouth, supplemental feedings through a nasogastric tube or a percutaneous endoscopic gastrostomy may be necessary. The presence of a feeding tube is not a contraindication for therapy. Many children with feeding disorders have neurologic or anatomic abnormalities that cannot be corrected, making oral feeding difficult or unsafe.

## **MANAGEMENT OF ASSOCIATED DISORDERS**

Associated disorders, such as gastroesophageal reflux disease, eosinophilic esophagitis, and chronic lung disease, may also need to be specifically managed. Application of synchronized neuromuscular electrical stimulation to cervical swallowing muscles (VitaStim therapy) has been shown to improve oral intake and help restore normal swallowing mechanism in adults, but empirical data are lacking to support its use in children.

**WHEN TO REFER**

A referral to a pediatric dysphagia center, if available, provides the most complete method to establish a diagnosis and render a management plan. Members of the team vary from center to center and usually include a gastroenterologist, otolaryngologist, pulmonologist, physical medicine and rehabilitation specialist, surgeon, occupational therapist, and pediatric dietitian. Referral is warranted

- When symptoms are persistent
- When the cause of dysphagia is unclear
- On evidence of aspiration

**WHEN TO ADMIT**

- Severe feeding difficulties
- Malnutrition
- Failure to thrive
- Dehydration
- Aspiration

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## Chapter 143

### DYSPNEA

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Dyspnea is the uncomfortable feeling of not being able to satisfy *air hunger*. Patients may complain of not being able to catch their breath or of a suffocating feeling. As with any subjective complaint, the diagnosis of dyspnea and its cause in an infant or young child can be problematic. Therefore, to evaluate fully a child in respiratory distress, the pediatrician must be familiar with the pathophysiologic features, signs, and common causes of dyspnea. With the aid of the medical history, physical examination, and appropriate laboratory tests, the condition can be diagnosed and therapy initiated.

**PATHOPHYSIOLOGIC FEATURES**

Dyspnea is seen most commonly with exercise because of the increased work of breathing necessary to keep up with the body's increased metabolic demands. The sensation is probably transmitted from stretch receptors in the chest wall muscles to the central nervous system (CNS). Chemoreceptors play a role, sensing changes in arterial pH, oxygen, and carbon dioxide concentrations, as well as chest wall proprioceptors, lung stretch receptors, and mechanoreceptors in the heart, skeletal muscles, and upper airway. The transmission is processed in the CNS, causing the individual to experience the sensation of dyspnea. With exercise, the person who has dyspnea is aware of an increased ventilatory effort. Under these circumstances, the dyspnea is relieved after the exercise ceases and the pH and oxygen and carbon dioxide levels return to normal. Dyspnea also occurs when ventilation or gas exchange is compromised.

To satisfy their oxygen needs, children who have dyspnea must increase their minute ventilation ( $\dot{V}_E$ ), working harder to do so. In normal breathing, respiratory muscles work only during inspiration, and the diaphragm does most of the work. The work of inspiration is the sum of the work necessary to overcome the elastic forces of the lung, the tissue viscosity of the lung and chest wall, and airway resistance. When any of these factors is increased (eg, elastic force and tissue viscosity in restrictive pulmonary disease, resistance in obstructive airway disease), the work of inspiration must increase to maintain adequate  $\dot{V}_E$ . The accessory muscles of inspiration (the sternocleidomastoid, anterior serratus, and external intercostal muscles) are recruited to accomplish this task. Contraction of these muscles causes forceful expansion of the thorax, resulting in an unusually large negative intrathoracic pressure. This negative pressure draws in the soft tissues of the chest wall and creates 1 of the classic signs of dyspnea, retractions, which may be seen in the suprasternal, infrasternal, intercostal, subcostal, and supraclavicular areas. An alternative way to maintain an adequate  $\dot{V}_E$  is to increase the rate of breathing; hence the second classic sign of dyspnea, tachypnea. Nasal flaring and grunting are other signs during respiration.

Little energy is expended during normal expiration. Relaxation of the diaphragm, elastic recoil of the lungs and chest wall, and compression of the lungs by the intra-abdominal organs force air from the lungs. In obstructive airway disease the force generated by these processes may not be great enough to effect adequate expiration. With tachypnea the elastic recoil may not be fast enough to allow adequate exhalation between breaths. In either instance the accessory muscles of expiration are used. The abdominal recti muscles contract and force the abdominal contents against the diaphragm to compress the lungs, and the internal intercostal muscles contract to pull the ribs downward and create a positive intrathoracic pressure to force the air from the lungs. The contractions of these muscles



provide the most important expiratory sign of dyspnea.

Although dyspnea is a respiratory symptom, it may be caused by primary disorders in other body systems. Cardiac, hematologic, metabolic, circulatory, and psychogenic causes must be considered in the differential diagnosis of dyspnea. The child's age is also important, because the frequency of some disorders may vary with age.

### History

The history begins with a complete description of the dyspnea. The patient or parent should be asked whether the onset was sudden (eg, inhaled foreign body, lung collapse) or evolved over several hours (eg, asthma, diabetic ketoacidosis). The patient should also be asked about the duration of the illness, the frequency of attacks of dyspnea, and whether a trigger or event is apparent that is temporally related to the onset of dyspnea. An attempt should be made to quantify the severity of the dyspnea. This task may be accomplished by asking to what degree daily activities are restricted by shortness of breath. However, given that dyspnea is a subjective sensation, its perceived severity can be affected by the patient's anxiety level, previous experiences, perceived control over the symptom, perceived consequences of the symptom, and available coping resources. The chronic use of medications such as inhaled corticosteroids and  $\beta_2$ -agonists has also been shown to have an effect on the patient's perception of dyspnea. Therefore, whenever possible, objective measures as discussed here should be obtained.

An inquiry should be made as to whether the dyspnea is affected by the patient's position. With unilateral lung disease, dyspnea may get worse when the patient lies with the affected lung down. Dyspnea that worsens with recumbency is often caused by left-ventricular failure, obstructive airway disease, or muscle weakness. Dyspnea in the upright position relieved by lying down usually is caused by intracardiac, vascular, or parenchymal lung shunts.

The patient should also be asked about associated symptoms such as cough, wheezing, sputum production, and pleuritic pain. In addition, a history of other known illnesses, allergies, illnesses in the family, medication, and environmental exposure must be obtained.

### Clinical Evaluation

A thorough physical examination is always indicated, with special attention paid to the aforementioned systems. The most useful laboratory tests are the complete blood count and peripheral blood smear, arterial blood gas measurement, and radiographic studies of the airways and lungs. Measurement of arterial oxygen saturation by pulse oximetry is invaluable for its capacity to assess oxygenation status quickly and non-invasively. Pulmonary function tests are helpful but may not be immediately available for evaluation of an acutely ill patient.

## ETIOLOGY AND CLINICAL PRESENTATION

### Pulmonary Disease

Pulmonary disease that causes dyspnea can be classified as obstructive, restrictive, or vascular.

#### Obstructive Pulmonary Disease

Obstructive disease is characterized by narrowing of airways that can be caused by intraluminal objects (mucus, foreign bodies, or tumor), intramural factors (smooth-muscle contraction, edema, or bronchomalacia), or extramural compression (tumor or lymph nodes). The narrowing increases both airway resistance and turbulent flow in the airways. If a fixed obstruction is present, then affected areas of the lungs will become atelectatic. With a ball valve-type obstruction (ie, air can get into the lungs but not out), air is trapped, and affected areas become hyperinflated. In either case, an imbalance occurs between pulmonary ventilation and perfusion, and oxygen exchange is adversely affected. All of these processes force the patient to work harder to maintain adequate ventilation; dyspnea ensues.

During normal respiration, inspiration and expiration are of equal length. With a fixed degree of obstruction, both processes are equally prolonged. If the obstruction varies and is extrathoracic (ie, above the vocal cords), then inspiration is affected more because the negative intra-airway pressure during inspiration tends to collapse the extrathoracic airway. The characteristic sign of such an obstruction is inspiratory stridor (see Chapter 197, Stridor).

If the obstruction varies and affects the intrathoracic airways, then expiration is prolonged because the positive intrathoracic pressure tends to collapse these airways during expiration. If larger airways are involved, then rhonchi are present. Airflow across an obstruction in smaller airways generates wheezing.

A paradoxical pulse and cyanosis are sensitive, but nonspecific, signs of severe obstruction. Patients who have chronic obstructive disease may be barrel chested and have signs of chronic hypoxia such as clubbing. Children who have a systemic disease, such as cystic fibrosis, will also show the extrapulmonary manifestations of this disease. The common causes of obstructive airway disease in childhood are shown in Box 143-1. Obstruction in the nose or nasopharynx should not be overlooked, especially in infants who are obligatory nasal breathers.

Blood gas values may be normal with mild obstructive disease. As the disease progresses, hypoxemia is the first sign of abnormality. Hypocapnia, initially seen as a reflection of increased VE, is replaced by hypercapnia as the maldistribution of ventilation and perfusion increases. The patient then tires, and respiratory failure occurs.

The chest radiograph may reveal whether the cause of the obstruction is inside or outside the airway. In many instances, hyperinflation with an increased anteroposterior chest diameter and flattened diaphragm are seen. Atelectasis may appear with a fixed



### BOX 143-1 Causes of Obstructive Pulmonary Disease

#### NEWBORNS

- Choanal atresia or stenosis
- Dermoid cyst
- Encephalocele
- Nasolacrimal duct cyst
- Hemangioma
- Vocal cord paralysis
- Pierre Robin sequence
- Ankyloglossia (tongue tie)
- Pertussis
- Tracheal stenosis (postintubation)

#### INFANTS

- Foreign body
- Vascular ring
- Tracheal web
- Bronchiolitis
- Asthma
- Cystic fibrosis
- Bronchomalacia
- Pyogenic thyroid
- Accessory thyroid

#### CHILDREN AND ADOLESCENTS

- Foreign body (airway or esophagus)
- Asthma

- Adenopathy
  - Lymphoma
  - Systemic lupus erythematosus
  - Tuberculosis
  - Sarcoidosis
- Croup
- Epiglottitis
- Retropharyngeal abscess
- Enlarged tonsils or adenoids
- Cystic fibrosis
- Anaphylaxis
- Laryngeal tumor
- Vocal cord tumor
- Tracheal tumors
- Mediastinal tumors
- Vocal cord polyp
- Laryngeal trauma
- Supraglottitis
- Diphtheria
- Bacterial tracheitis
- Ingestion of caustic substance
- Crack cocaine
- Trauma
- Environmental or occupational inhaled toxin exposure

obstruction. Fluoroscopic examination or inspiratory and expiratory radiographs may be useful in localizing a ball valve-type obstruction. However, an important point to remember is that many foreign bodies are radiolucent and will not be seen on radiographic examination. If a radiolucent foreign body is suspected, then laryngoscopy, bronchoscopy, or even esophagoscopy may be required.

#### Restrictive Pulmonary Disease

The cardinal features of restrictive pulmonary disease are a reduction in lung volume and pulmonary compliance secondary to pathologic changes in the lung parenchyma or the pleura, deformities of the chest wall, or neuromuscular disease. Decreased volume necessitates an increase in respiratory rate to maintain a normal  $\dot{V}_E$ . The work of breathing must be increased to overcome the reduced compliance. Because breathing rapidly with small tidal volumes is more energy efficient than breathing slowly and attempting to

expand the chest against great restrictive forces, children who have restrictive diseases characteristically have rapid, shallow respirations. The common pediatric causes of restrictive pulmonary disease are listed in Box 143-2.

Observation of the child often reveals skeletal and neuromuscular causes. Pleural and parenchymal diseases are detected best by palpation, percussion, and auscultation of the chest. Tactile fremitus can demonstrate pulmonary consolidation or pleural effusion. Careful percussion reveals effusions, consolidation, and abnormal diaphragmatic excursion. Auscultation can reveal rales characteristic of alveolar disease and changes in whispered pectoriloquy and egophony.

The complete blood count may be helpful in diagnosing an infectious cause. Arterial blood gases have a characteristic pattern of hypoxemia and hypocapnia. The chest radiograph is useful because it can demonstrate decreased lung volume, pleural thickening and effusions, increased interstitial markings, parenchymal consolidation, skeletal deformities, and abnormal movement of the diaphragm.

#### Vascular Pulmonary Disease

Vascular lung disease is characterized by a decrease in the size of the pulmonary vascular bed. In the neonate, this disease often results from persistent pulmonary hypertension of the newborn. Microthrombi have also been reported in the lungs of infants who are in severe respiratory distress. In older children, the most common cause of vascular pulmonary disease is intimal hyperplasia after persistent left-to-right shunting and resultant pulmonary hypertension. The size of the pulmonary vascular bed can also be reduced by obstruction caused by thromboembolic disease, obliteration (eg, vasculitis), or destruction, as in emphysema. The reduced blood flow through the lungs results in arterial hypoxemia and hypercapnia, which, in turn, lead to the symptoms and signs of dyspnea.

In addition to the common signs of dyspnea, the child who has vascular lung disease may have signs of pulmonary edema and pleural effusion. Systemic signs of right-sided heart failure caused by pulmonary hypertension or left-sided heart failure that was the cause of the pulmonary hypertension may be present. The cardiac findings observed with pulmonary hypertension are an accentuated  $P_2$ , paradoxical splitting of second heart sound, a third heart sound, a pulmonary ejection click, and a right-ventricular heave.

An electrocardiogram is helpful in the diagnosis of right-ventricular hypertrophy. A chest radiograph may reveal increased right ventricular size, enlargement of the pulmonary artery silhouette, decreased pulmonary blood flow in advanced disease, or increased flow early in the course of disease, with a left-to-right shunt.

#### Exercise-Induced Dyspnea

As described earlier, dyspnea is a normal sensation felt during exercise, especially for children with a sedentary lifestyle and poor cardiovascular conditioning. However, if the dyspnea is severe, occurs after only

**BOX 143-2 Causes of Restrictive Pulmonary Disease****NEWBORNS**

- Hyaline membrane disease
- Hypoplastic lungs
- Pulmonary agenesis
- Eventration of the diaphragm
- Meconium aspiration
- Pneumonia (group B streptococci or gram-negative organisms)
- Diaphragmatic paralysis
- Osteogenesis imperfecta
- Central nervous system depression
  - Hypoxia
  - Congenital
  - Maternal drugs
- Congenital myasthenia gravis
- Aspiration
- Pulmonary edema
  - Septicemia
  - Congenital heart disease

**INFANTS**

- Pneumonia
  - Bacterial
  - Viral
  - Aspiration
- Bronchopulmonary dysplasia
- Wilson-Mikity syndrome
- Hamman-Rich syndrome
- Pulmonary edema
- Infantile botulism
- Congenital lobar emphysema

**CHILDREN AND ADOLESCENTS**

- Skeletal
  - Kyphoscoliosis
  - Ankylosing spondylitis
  - Pectus excavatum
  - Crush chest injury
- Parenchymal
  - Pneumonia

- Hypersensitivity pneumonitis
- Systemic lupus erythematosus
- Scleroderma
- Fibrosis
- Toxin inhalation
- Granulomatous disease
- Drugs (eg, antineoplastic agents, narcotics)
- Carcinoma
- Fat embolus
- Pneumothorax
- Pneumomediastinum
- Smoke inhalation
- Pulmonary infarction
- Pulmonary edema
  - Congestive heart failure
  - Sepsis
  - Intracranial disease
  - Croup
  - Epiglottitis
- Neuromuscular
  - Cord transection
  - Myasthenia gravis
  - Muscular dystrophy
  - Multiple sclerosis
  - Guillain-Barré syndrome
  - Pickwickian syndrome
  - Toxins
- Pleural effusion
  - Pneumonia
  - Malignancy
  - Cardiac disease
  - Hepatic disease
  - Renal disease
  - Rheumatologic disease
- Hypoproteinemia
- Renal failure
- Tumor
- Pulmonary infarction

minimal exertion, or is troublesome to the patient, then investigations into the cause of exercise-induced dyspnea (EID) are warranted.

Asthma is the most common cause of pathologic EID. However, when other signs and symptoms of asthma are absent, or when pretreatment with beta-agonistic medications does not prevent EID, then other causes must be considered. These causes include vocal cord dysfunction, exercise-induced laryngomalacia, exercise-induced hyperventilation, restrictive airway disease caused by skeletal abnormalities such as scoliosis and pectus deformities, and cardiac arrhythmias that occur only during exercise.

**Cardiac Disease**

Dyspnea occurs with cardiac disease when insufficient blood is pumped to the lungs as a result of congenital structural anomalies in the heart, pump failure (myocarditis or cardiomyopathy), restrictive pericarditis, arrhythmia, or, as already described, secondary pulmonary hypertension. Heart disease must be considered in all dyspneic newborns and older children who have a history of congenital heart disease. In the neonate, pulmonary disease can often be differentiated from cyanotic heart disease through a hyperoxia test. The nature of the cardiac defect can be delineated with the help of a thorough cardiac examination, an electrocardiogram, a chest radiograph, and an echocardiogram.

A trivial respiratory infection in a healthy child may cause severe respiratory insufficiency in a child who has cardiopulmonary disease. Indeed, the mortality of infants who have respiratory syncytial viral pneumonia and congenital heart disease has been shown to exceed significantly the mortality of children who have normal hearts.

### Hematologic Disease

If the oxygen-carrying capacity of the blood is reduced sufficiently, then tissue hypoxia ensues. The resultant drop in arterial pH signals the CNS and stimulates the onset of dyspnea. Severe anemia, whether chronic or acute, congenital or acquired, can cause dyspnea. The oxygen-carrying capacity can also be lowered when the hemoglobin's ability to bind oxygen is reduced, seen most commonly with carbon monoxide poisoning but also with cyanide poisoning and methemoglobinemia. In any of these cases the child will not be cyanotic. The blue color of cyanosis is caused by at least a 5-g/dL reduction of oxygenated hemoglobin in the blood. Such a concentration of reduced hemoglobin is not found in anemia uncomplicated by other diseases or in the other conditions cited. Conversely, an infant with polycythemia whose blood is hyperviscous may have dyspnea from poor perfusion. Because such an infant has an increased hemoglobin concentration and more oxygen is removed from the hemoglobin as a result of decreased flow, the child may be cyanotic (having more than 5 g/dL unsaturated hemoglobin) and not hypoxic. An extreme elevation of leukocyte or platelet counts can also cause blood hyperviscosity and dyspnea.

Children with anemia, even though they may have tissue hypoxia and be dyspneic, are usually not hypoxemic; that is, the arterial oxygen tension measured by blood gas analysis is in the normal range.

### Metabolic Disease

Disorders that increase the body's rate of metabolism and therefore oxygen consumption can cause dyspnea. Examples are hyperthyroidism and fever. Metabolic disorders associated with an increased production of hydrogen ion and carbon dioxide cause a dyspnea-like breathing pattern to help rid the body of the carbon dioxide. The classic example is Kussmaul breathing with diabetic ketoacidosis. Aspirin poisoning can be characterized similarly. In addition, children who have various muscle enzyme deficiencies, especially those affecting the mitochondria, may have dyspnea as a result of their increased acid production and decreased work tolerance. In chronic renal failure the kidney's inability to remove acid from the blood adequately is the underlying cause of dyspnea. The history, physical examination, and appropriate laboratory tests should facilitate the proper diagnosis of these diseases.

If oxygen cannot reach the tissues, then the body responds with dyspnea, cardiovascular collapse, and shock.

### Obesity

Dyspnea, especially with exertion, is a common complaint of obese children because their metabolic

requirement for a given amount of work is increased. In addition, the diaphragm of an obese child must move against increased abdominal pressure, and the chest wall is heavier; thus, more energy must be expended to maintain  $\dot{V}_E$ .

Asthma does not seem to play an important role as a cause of dyspnea in obese individuals. Although obesity is a risk factor for self-reported asthma, bronchodilator use, and dyspnea on exertion, obese individuals have a lower risk of objective airway obstruction as compared with persons who are not obese.

Treatment of dyspnea in obesity should include dietary regulation and an exercise program graded to keep pace with the child's level of exercise tolerance.

### Pregnancy

Dyspnea is normal during pregnancy and occurs during the first or second trimester. Seventy-six percent of women complain of dyspnea by the 31st week of gestation. The sensation reflects a subjective awareness of the hyperventilation normally present during pregnancy.

The normal dyspnea of pregnancy can be differentiated easily from dyspnea arising from heart or lung disease. The woman who has dyspnea of pregnancy has no other symptoms of cardiac or pulmonary disease. Furthermore, dyspnea of pregnancy begins early and plateaus or improves as term approaches, while dyspnea resulting from heart disease begins during the second half of pregnancy and is worst during the seventh month. Finally, dyspnea of pregnancy is rarely severe, rarely occurs at rest, and does not interfere with the activities of daily life.

### Intravenous Drug Use

Several causes of dyspnea must be considered in patients with a history of intravenous drug use. Heroin can cause bronchospasm that responds to bronchodilator medications. In addition, heroin and other opioids may precipitate pulmonary edema. Therapies consist of oxygen, diuretics, and naloxone.

Infections also may cause dyspnea in intravenous drug users. The most common infection is community-acquired pneumonia. However, opportunistic pulmonary infections, tuberculosis, and bacterial endocarditis with associated septic pulmonary emboli or heart failure must be considered.

Finally, talc granulomatosis, which can lead to chronic mild to moderate dyspnea, must be considered. It is caused by intravenous injection of dissolved opioid tablets, with deposition of foreign bodies in the pulmonary vasculature and granuloma formation.

### Psychogenic Cause

Stress or hysteria may cause dyspnea. A complete history and thorough physical examination are keys to the diagnosis. Affected patients are tachypneic and complain of air *hunger*. When dyspnea is caused by pulmonary or cardiac conditions, the shortness of breath worsens with increasing activity and improves with rest. However, the dyspnea associated with hysteria does not improve with rest and may worsen. Affected patients also often complain of chest pain and sigh more frequently than normal. Contrary to previous belief, tetany is an uncommon accompaniment of hysterical dyspnea.

Findings on physical examination are usually normal. However, stress-induced paradoxical adduction of the vocal cords during inspiration has been reported. Patients with this disorder may have either stridor or wheezing. In this instance the diagnosis of hysterical dyspnea is one of exclusion, and it can be made only after pathological lesions in the airways and lungs have been ruled out.

In most instances, the only laboratory abnormality found with hysteria-induced dyspnea is a diminished arterial carbon dioxide tension.

Treatment consists of calm reassurance and, occasionally, mild sedation. If the condition is chronic, then interventions to reduce stress and gain insight into the cause of the dyspnea, such as psychotherapy and hypnosis, may be required. When paradoxical vocal cord motion is the cause, the patient should also be taught laryngeal relaxation techniques.

## MANAGEMENT

Severe acute dyspnea is a medical emergency. If not treated promptly, a child who has dyspnea may then progress rapidly to respiratory failure and death. First, the adequacy of the airway must be assessed. Foreign bodies must be removed and anatomic obstructions bypassed with endotracheal intubation or, in rare cases, tracheotomy. Bronchospasm, when present, should be treated with beta-agonistic drugs.

Subsequently, the efficacy of the child's ventilation must be evaluated. Normally, breathing uses 2% to 3% of the total body energy expenditure. When the work of breathing is increased during dyspnea, this amount may rise to 30% or more. Such a degree of energy expenditure cannot be continued indefinitely, and the child tires. Even after an obstruction is removed, the child may still be unable to effect adequate ventilation. In this instance, or in the case of neuromuscular disease, the child requires either noninvasive positive pressure ventilation or intubation and mechanical ventilation.

Once ventilation is established, the cardiovascular system's ability to deliver oxygen to the tissues must be appraised by evaluating the heart, peripheral circulation, intravascular volume status, and the blood's oxygen-carrying capacity. Therapy with vasopressors, fluids, blood transfusions, or diuretics should be initiated when indicated. Although not all children who have dyspnea require supplemental oxygen, every child should have oxygen administered until the cause of the dyspnea is known. Once the patient's condition has stabilized, the search for the underlying cause of the dyspnea should progress urgently, but calmly. At this point, a detailed history can be elicited, a full physical examination performed, and a chest radiograph and appropriate blood tests obtained. When the diagnosis is made, specific therapy can be initiated.

When dyspnea is caused by a chronic illness, no satisfactory therapy may be available to treat the underlying disease. However, simply relieving the dyspnea can significantly improve the child's functional ability and quality of life. Several modalities can be used to treat the symptom of dyspnea in a chronically ill child. Sedatives

and narcotics reduce  $\dot{V}_E$  and thereby diminish the intensity of the breathless feeling. These medications are usually administered orally or by injection. However, they also may be effective when delivered by nebulization. Beta-agonists may blunt the perception of dyspnea without affecting ventilation. Theophylline may improve diaphragmatic contractility. Continuous supplemental oxygen reduces ventilatory drive. Noninvasive positive pressure ventilation is useful in assisting fatigued or dysfunctional respiratory muscles and in keeping small airways open. Children who have chronic obstructive pulmonary disease may be taught to breathe through pursed lips, reducing respiratory rate, increasing tidal volume, and diminishing the sensation of dyspnea. Hypnosis has proved useful in some patients, and others have reported a decrease in dyspnea when seated next to an open window or a blowing fan.

Exercise and proper nutrition are helpful in maintaining or increasing inspiratory muscle mass and thereby reducing the perceived magnitude of dyspnea. Finally, because dyspnea is a subjective complaint, the psychological contribution to its perceived severity is significant. The child's emotional state, behavior, and personality must be monitored because psychosocial intervention may be indicated.

### WHEN TO REFER

- Chronic pulmonary disease
- Congenital or acquired heart disease
- Metabolic disease
- Conditions requiring endoscopy or surgical procedures

### WHEN TO ADMIT

- Respiratory failure
- Impending respiratory failure
- Hypoxia while breathing room air

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## Chapter 144

### DYSURIA

Beatrice Goilav, MD; Frederick J. Kaskel, MD, PhD

Dysuria is any discomfort with urination but particularly refers to pain or burning during urination. Generally stemming from irritation of the bladder or urethra, it is a commonly reported sensation that affects men, women, and children alike. Although dysuria can be caused by any condition associated with inflammation, irritation, or obstruction of the urinary tract, in children and adolescents it most commonly accompanies urinary tract infections (UTIs), urethritis, and chemical or traumatic irritation. Identifying the underlying cause of dysuria requires a detailed history, a careful physical examination, and a focused laboratory evaluation as needed.

### HISTORY

The younger the child, the less precise is the complaint of painful urination. Other symptoms, such as pruritus or pain in the genital or perineal area, may be more noticeable while the child is voiding and not distracted. Although dysuria may be the only complaint, it is more often accompanied by associated symptoms. Regardless of the child's age, dividing the associated symptoms into either specific urinary symptoms or nonspecific symptoms is helpful. Symptoms specific to the urinary tract include hematuria, discharge, malodorous urine, frequency, urgency, refusal to void, new-onset nocturnal enuresis, and daytime incontinence. The physician should inquire about exposure to detergents, perfumed soaps, bubble baths, or ointments and about the type of underwear fabric, any of which can irritate the mucosal lining of the urethra or bladder. A thorough history of the timing of toilet training, last occurrence of daytime accidents, nocturnal enuresis, withholding maneuvers, and constipation can help elucidate a diagnosis of dysfunctional elimination syndrome. The lack of a history of trauma may not be accurate because children often do not recall it or, in the case of masturbation or sexual abuse, may deliberately deny it. To judge the possibility of a sexually transmitted infection, adolescents should be asked about sexual activity and safety practices. A family history of nephrolithiasis should focus attention on hypercalciuria as a cause for dysuria, and a more detailed dietary history should be elicited, including intake of salt, dairy products, and vitamins.

Symptoms outside the urinary tract, such as conjunctival injection, oral and genital ulcers, arthralgia, or a generalized rash, could suggest a systemic inflammatory condition, such as Stevens-Johnson syndrome, Reiter syndrome, or Behçet disease. A history of fever suggests an infectious condition such as pyelonephritis, appendicitis, or pelvic inflammatory disease.

### PHYSICAL EXAMINATION

The presence of a fever (body temperature  $>101.3^{\circ}\text{F}$  [ $38.5^{\circ}\text{C}$ ]) can indicate inflammation or an upper UTI such as pyelonephritis; cystitis and urethritis of any cause do not usually produce significant fever. Inspection of the skin may reveal vesicles with varicella or herpes simplex, or target lesions with Stevens-Johnson syndrome, which can be accompanied by conjunctival inflammation and oral lesions. Arthritis, particularly of the knee joint, in an adolescent should raise suspicion of Reiter syndrome.

In children of any age presenting with dysuria and a history of voiding dysfunction, particularly when accompanied by a history of chronic constipation, an occult spina bifida should be excluded by careful examination of the lower back looking for midline defects, such as a sacral cyst, a fistula, or a tuft of hair. The neurologic examination should include careful evaluation of the lower extremities for strength and reflexes, and, when suspicion is raised, the bulbocavernosus reflex should be evaluated as well.

Special attention should also be paid to the abdominal examination, which may reveal a flank or suprapubic mass, suggestive of urethral obstruction. Costovertebral tenderness suggests pyelonephritis, and suprapubic tenderness often accompanies cystitis.

On inspection of the genital area, the examiner should evaluate for discharge; if present, its character should be noted. In female patients, clear discharge may be a normal finding, whereas an odorless, cottage cheese-like appearance suggests an infection with *Candida* spp. A greenish discharge, suggestive of gonorrhea, should raise the possibility of pelvic inflammatory disease if accompanied by lower abdominal tenderness. Any discharge in male patients should be considered abnormal. Scratch marks around the mucosal area in females may suggest contact dermatitis or chemical irritation. Examination should include looking for labial adhesions and a urethral prolapse, which appears as a red circumferential protrusion of the mucosa from the urethral orifice. Attention should be paid to whether or not the male patient is circumcised; if not, note whether the foreskin is age-appropriately retractable. The location and the size of the meatus should be examined for hypospadias or stenosis.

### DIFFERENTIAL DIAGNOSIS

Dysuria can be caused by any inflammation, irritation, or obstruction of the bladder or urethra, but most often it is a symptom of a common disorder of childhood and adolescence, such as a UTI, urethritis, or a chemical or traumatic injury. Table 144-1 lists infectious and noninfectious causes of dysuria. Figures 144-1 and 144-2 depict a simplified algorithm allowing the physician to establish quickly whether the cause of dysuria is infectious/inflammatory or rather chemical/mechanical in male and female patients.

**Table 144-1****Infectious and Noninfectious Causes of Dysuria**

INFECTIOUS	NONINFECTIOUS
Pyelonephritis	Dysfunctional voiding
Cystitis	Chemical irritants
Urethritis	Trauma
Vulvovaginitis	Meatal stenosis
Balanitis and balanoposthitis	Labial adhesions
Pelvic inflammatory disease	Urethral strictures
	Urethral prolapse
	Hypercalciuria

**Common Conditions****Urinary Tract Infection**

UTIs are the most common cause of dysuria in children. The localization of the infection within the urinary tract may be challenging in young children because they tend to develop systemic symptoms such as fever, vomiting, and diarrhea even in the absence of pyelonephritis. Older children, who are likely to mount a fever with pyelonephritis rather than cystitis, can report suprapubic pain with cystitis or flank and costovertebral tenderness with pyelonephritis. All children younger than 2 years and boys of all ages should be evaluated for congenital anatomic abnormalities, such as vesicoureteral reflux, after the first UTI.

**Urethritis**

Urethritis can present with dysuria accompanied by discharge or blood spotting on the child's underwear. Causes of urethritis include infection, trauma, chemical irritation, and foreign body. Infectious causes in children are uncommon. Patients suspected of having infectious urethritis should have a urethral smear and urine culture included as part of their laboratory evaluation. Sexually transmitted infections are the major cause of urethritis in adults and adolescents. The finding of *Neisseria gonorrhea* or *Chlamydia trachomatis* in a child should prompt immediate investigation to rule out sexual abuse.

**Irritants/Trauma**

Irritants such as soap, bubble baths, and laundry detergents cause mild erythema at most. Localized trauma can result from foreign bodies, masturbation, voluntary sexual activity, or sexual abuse. Bicycle accidents and other traumas usually generate more extensive injuries than isolated genitourinary lesions.

**Meatal Stenosis**

Meatal stenosis occurs relatively commonly in boys after circumcision. Typically, the urinary stream is deflected upward, and the boy has difficulty aiming. It may be accompanied by dysuria, increased frequency, and delayed bladder emptying. Consultation with a pediatric urologist is warranted.

**Dysfunctional Voiding**

Dysfunctional voiding can result from neuropathic or non-neuropathic voiding disorders. Neuropathic voiding is associated with conditions affecting the innervation of the muscles involved in coordinated micturition. Non-neuropathic voiding dysfunction encompasses all other causes of lack of coordination between the bladder, the bladder outlet, and the pelvic floor muscles. If the patient is also constipated, then the condition is referred to as *dysfunctional elimination syndrome*, which is an important cause of idiopathic urethritis in childhood; the history should focus on timing of completion of toilet training, episodes of bed wetting, and daytime incontinence.

**Uncommon Conditions****Labial Adhesions**

Labial adhesions occur in prepubertal girls and are generally asymptomatic unless they cause secondary infections. The treatment is separation of the adhesion and topical estrogens to prevent readhesion.

**Urethral Strictures**

Urethral strictures in children can be congenital or acquired. Congenital strictures are rare. Acquired strictures occur after instrumentation, trauma, or processes accompanied by inflammation with production of an exudate and secondary sclerosis. The child presents with dysuria, infection, or a weak urinary stream. The diagnosis is made by voiding cystourethrogram or cystoscopy.

**Urethral Prolapse**

Urethral prolapse is the complete protrusion of the urethral mucosa beyond the meatus in girls. Although it is rare in the general population, there is an association with young age, black race or Hispanic ethnicity, and low socioeconomic status. The cause is unclear. Patients present with dysuria, gross hematuria, or blood spotting on the underwear. Treatment includes sitz baths, antibiotics, topical estrogens, or surgical repair. Left untreated, the prolapsed mucosa can become necrotic.

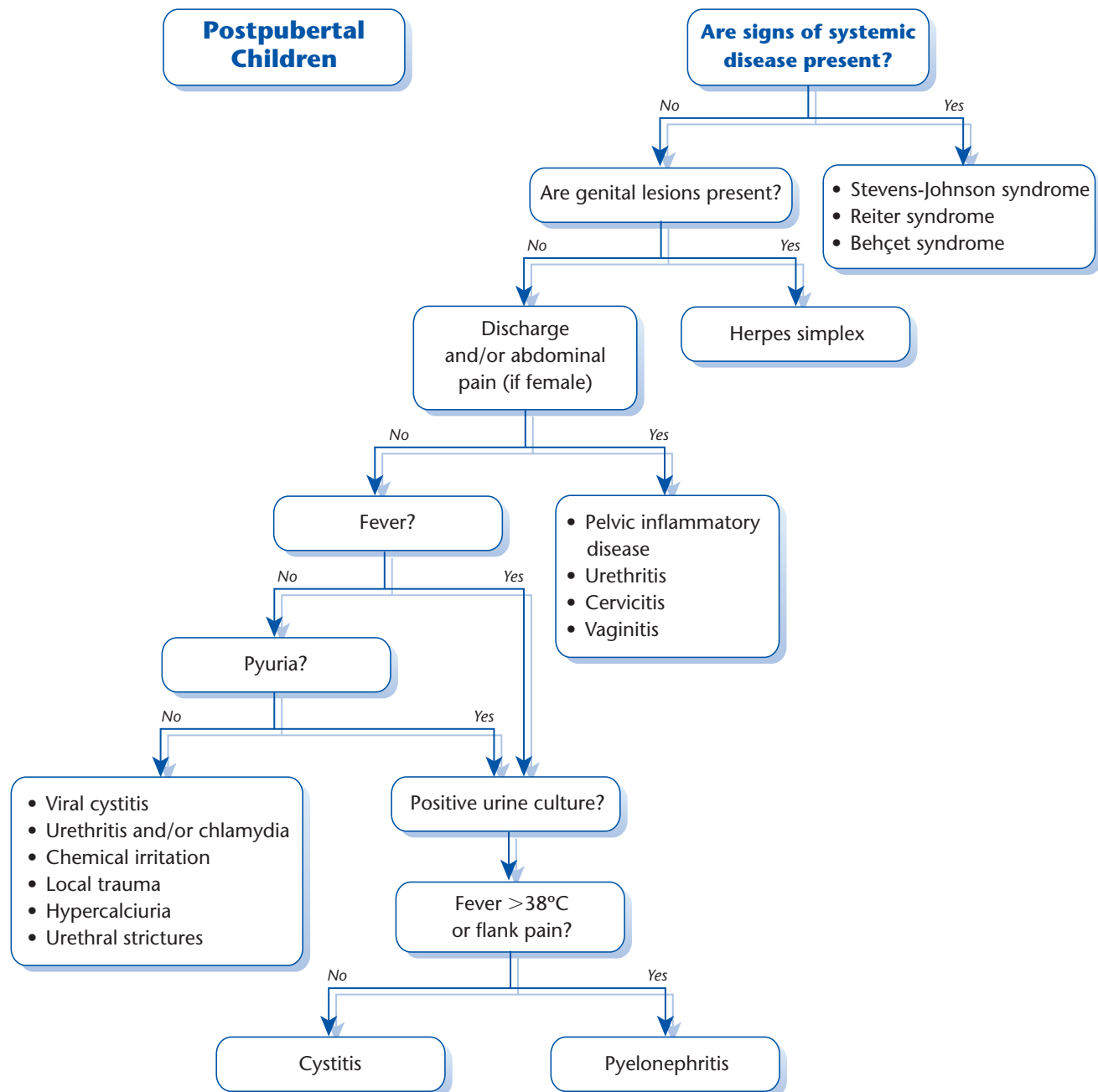
**Pelvic Inflammatory Disease**

Pelvic inflammatory disease primarily affects sexually active adolescent females, but should raise suspicion of sexual abuse in prepubertal girls. It presents with abdominal pain.

**Vulvovaginitis**

Vulvovaginitis, a rare cause of dysuria, more commonly presents with erythema of the vaginal mucosa and may be associated with discharge, which varies from clear to white to green, and may be odorless or foul smelling.

It occurs most often in sexually active adolescents, and sexually transmitted pathogens are the main cause. In prepubertal girls, the cause is often not apparent, but poor hygiene or allergies may play a role. Pathogens include local flora, such as group A streptococcus, or anaerobic bacteria, with concomitant decrease in the concentration of *Lactobacillus* spp. *Candida* spp.

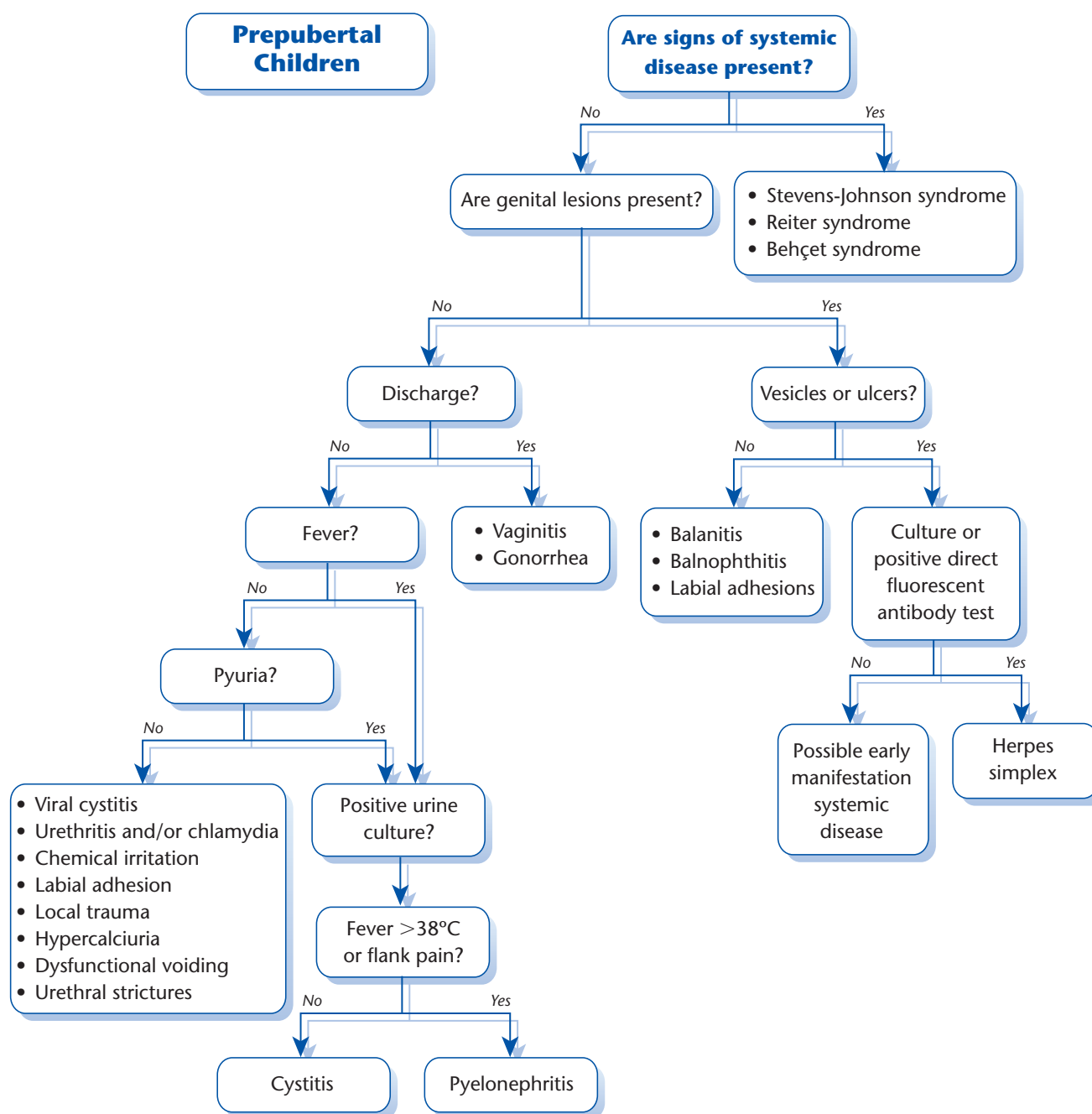


**Figure 144-1** Algorithmic approach to dysuria in postpubertal males and females. (Adapted with permission from Fleisher GR. Evaluation of dysuria in children. In: Bassow DS (ed); UpToDate, Waltham MA. Copyright © 2013 UpToDate, Inc. Available at: [www.uptodate.com](http://www.uptodate.com).)

are commonly encountered in the setting of recent antibiotic treatment or diabetes mellitus. Herpes simplex infection can present with erythema alone; the absence of vesicles or ulcerative lesions does not rule it out. When erythema of the vaginal mucosa is observed, a Gram stain and culture, KOH, and a wet prep should be sent. Any vaginal discharge should be sent for pH testing. Screening for herpes simplex should be considered.

### **Balanitis and Balanoposthitis**

Inflammation of the glans penis (balanitis) or both the glans and prepuce (balanoposthitis) occurs almost exclusively in young, uncircumcised boys with phimosis. Infection from entrapped smegma under the foreskin may result from trauma, allergies, or poor hygiene. Treatment consists of warm soaks as well as oral or local antibiotics. Topical steroids may alleviate the inflammation associated with balanitis from contact dermatitis.



**Figure 144-2** Algorithmic approach to dysuria in prepubertal males and females. (Adapted with permission from Fleisher GR. Evaluation of dysuria in children. In: Bassow DS (ed); UpToDate, Waltham MA. Copyright © 2013 UpToDate, Inc. Available at: [www.uptodate.com](http://www.uptodate.com).)

### Hypercalciuria and Urolithiasis

Urolithiasis rarely presents with dysuria, but rather is seen with flank pain and often with gross hematuria. Hypercalciuria, however, commonly manifests as dysuria caused by irritation of the uroepithelium by calcium-oxalate crystals. Patients typically have frequency, urgency, gross or microscopic hematuria, and dysuria. Examination of the urinary sediment may reveal crystals along with eumorphic red blood cells. The family history may be positive for urolithiasis.

### WHEN TO REFER

- Voiding dysfunction
- Nephrolithiasis
- Girl younger than 2 years with a UTI for the first time
- Boy of any age with a UTI or meatal stenosis
- Genitourinary tract anomalies



**WHEN TO ADMIT**

- Systemic inflammatory or infectious cause of dysuria
- Suspicion of sexual abuse

**TOOLS FOR PRACTICE****Engaging Patient and Family**

- *What Is a Pediatric Urologist?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Urologist.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Urologist.aspx))

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## Chapter 145

### EDEMA

Paul A. Levy, MD

At birth, as much as 70% of the newborn's body weight is water. This decreases to approximately 60% of total body weight in older children. For adolescent and adult males, total body water is even lower, with only about 55% to 60% of their body weight being made up of water, and total body water is lowest in adolescent and adult females, who have only about 50% of their body weight contributed by water. The body water is distributed into several compartments. Intracellular water represents two-thirds of the total volume. The remaining one-third is considered extracellular and is distributed between the vascular

compartment (25%) and the interstitial spaces between the cells (75%). The distribution of water in these various body compartments is tightly controlled. Failure of this control can result in the accumulation of extra fluid in the interstitium, which is *edema*.

**PATHOPHYSIOLOGIC FEATURES**

Water movement across a semipermeable membrane (osmosis) is governed by the number of particles (osmolarity) on either side of the membrane. Water moves to establish equilibrium between the 2 compartments. In blood vessels, such as capillaries, the osmolarity is generated, in part, by the electrolytes in plasma; however, because the concentrations of electrolytes in plasma and the interstitium are relatively equal, the osmotic force is largely determined by charged protein molecules, with albumin being the most predominant. The plasma proteins are referred to as *colloids*, and the osmotic force they generate is the *colloid osmotic pressure*, or *oncotic pressure*. Movement of fluid across a capillary wall is controlled by a combination of oncotic pressure, hydrostatic pressure, and the permeability of the capillary wall. The capillary oncotic pressure draws fluid into the capillary; the interstitial oncotic pressure draws capillary fluid out. The capillary hydrostatic pressure, which is related to blood pressure, is highest at the arteriole end of the capillary and drops off as blood moves toward the venule. The capillary hydrostatic force pushes fluid into the interstitium. Interestingly, systemic (arterial) hypertension does not result in edema because arteriolar sphincters protect the capillary bed from increased blood pressure. The interstitial hydrostatic pressure is related to the pressure of the fluid in the interstitium, which depends on the lymphatic drainage, the amount of fluid present in the interstitium, and the compliance of the tissue. This force counteracts the capillary hydrostatic pressure and pushes fluid back into the capillaries. Finally, the permeability of the capillary wall contributes to the leakage of fluid into the interstitium.

In normal circumstances, the interplay of these forces results in fluid exiting the capillaries at the arteriolar end and entering the capillaries at the venule end. Approximately 90% of fluid that leaves the capillaries is reabsorbed before reaching the venule. The lymphatic system returns the remaining 10%, along with its associated proteins, to the circulation.

**CAUSES OF EDEMA**

Fluid distribution between the intravascular compartment and the interstitial compartment results from the interplay of oncotic pressure, hydrostatic pressure, and capillary membrane permeability. Disruption of these forces can result in edema, but sodium concentration is usually the ultimate controller of this fluid movement (Box 145-1).

**Change in Capillary Membrane Permeability**

An increase in capillary membrane permeability is often the result of cytokines released from inflammation. Infections and burns tend to cause localized

### **BOX 145-1 Causes of Edema (Systemic or Localized as Noted)**

#### **INCREASED CAPILLARY PERMEABILITY**

- Inflammation (localized or systemic edema)
- Burns (localized edema)
- Trauma (localized edema)
- Allergic reaction (localized or systemic edema)

#### **DECREASED CAPILLARY ONCOTIC PRESSURE**

- Protein loss (nephrotic syndrome, congenital lymphangectasia, inflammatory bowel disease)
- Decreased synthesis (cirrhosis, malabsorption, malnutrition)

#### **INCREASED CAPILLARY HYDROSTATIC PRESSURE**

- Systemic venous hypertension
  - Heart failure (myocarditis, cardiomyopathy, ischemic heart disease)
  - Constrictive pericarditis
  - Note: right-sided failure results in peripheral edema, left-sided failure results in pulmonary edema.
  - Cirrhosis/liver failure
  - High output failure [anemia (ABO and Rh incompatibility), arteriovenous fistulas, hyperthyroidism]
- Localized venous hypertension (localized edema)
  - Deep vein thrombosis, compression of venous return (localized edema)

#### **INCREASED PLASMA VOLUME**

- Heart failure
- Renal failure

#### **LYMPHATIC OBSTRUCTION AND INCREASED INTERSTITIAL ONCOTIC PRESSURE**

- Lymphedema, leakage of protein into the interstitium.

edema. An allergic reaction may cause more generalized edema. Hereditary angioedema can cause localized edema of the gastrointestinal tract and larynx. Trauma causes local edema.

### **Decreased Capillary Oncotic Pressure**

A decrease in the capillary oncotic pressure can be caused by decreased levels of protein, usually of albumin in the blood. Decreased synthesis of albumin occurs in cirrhosis or as a result of malnutrition or intestinal malabsorption. Protein loss by the kidneys in nephrotic syndrome may also contribute to edema. Albumin levels below 2 mg/dL are usually associated with generalized edema. The mechanism of edema formation with decreased oncotic pressure results in extravasation of fluid into the interstitium, but it also results in poor kidney perfusion, which activates renin-aldosterone secretion and results in increased sodium reabsorption and fluid retention. This fluid may then leak into the interstitium because of the decreased oncotic pressure, compounding the edema.

### **Increased Capillary Hydrostatic Pressure**

#### **Systemic Venous Hypertension**

Systemic venous hypertension can be the result of heart failure (from cardiomyopathy, tricuspid valvular disease, or ischemic heart disease), constrictive pericarditis, or cirrhosis. In addition, high output failure (from anemia, hyperthyroidism, or arteriovenous fistulas) also leads to systemic venous hypertension. All of these conditions lead to increased capillary hydrostatic pressure and result in edema from increased extravasation of fluid into the interstitium. Left-ventricular heart failure results in pulmonary edema; right-ventricular heart failure results in venous congestion, hepatomegaly, and peripheral edema.

#### **Localized Venous Hypertension**

Localized edema may result from increased venous pressure with deep vein thrombosis or from compression of the inferior vena cava or iliac vein by a tumor. The increased venous pressure raises the capillary hydrostatic pressure.

#### **Increased Plasma Volume**

Glomerular nephritis increases plasma volume resulting from sodium retention. Renal failure can increase plasma volume from an inability to secrete sodium and water. Heart failure and liver disease (cirrhosis) result in decreased effective volume, which increases sodium reabsorption in the kidney by activation of the renin-angiotensin-aldosterone system. Sympathetic nervous stimulation can also result in increased sodium reabsorption in the kidney.

### **Increased Interstitial Hydrostatic Pressure**

Increased interstitial hydrostatic pressure, although rare, may result from lymphatic obstruction by a tumor or large lymph nodes, from damage to the lymphatic system by radiation or surgery, or from parasitic infections such as filariasis.

## **EVALUATION**

### **History**

A detailed history must be obtained to discover the cause of the edema. The time course of the edema—whether its onset is recent or chronic—is particularly important. If chronic, then the parents and child may report weight gain, tight clothing, or snug-fitting shoes, findings they may have attributed to the growth of the child. The history of a recent illness, such as pharyngitis, is important for the diagnosis of glomerulonephritis. In addition to the edema, other systemic complaints may be present, including shortness of breath, tachypnea, or cough, which may indicate the presence of heart failure and pulmonary edema. Ascites, a form of localized edema, is seen with liver failure or cirrhosis and with some congenital liver malformations. The child's nutritional status should be assessed, because malnutrition may result in hypoalbuminemia, which can, in turn, result in edema.

### Physical Examination

Edema may be generalized or localized. If localized, then it may be easily apparent when it affects an extremity (deep vein thrombosis, cellulitis, burn). If generalized, it may be more occult (pulmonary edema from left-ventricular heart failure, ascites from liver disease). Physical examination should begin with close observation of the vital signs. Tachypnea may indicate pulmonary edema. Increased blood pressure may be present in glomerulonephritis and renal failure. Fever and localized edema may be present with cellulitis.

Periorbital edema is generally found with nephrotic syndrome and glomerulonephritis. Crackles or rales may indicate the presence of pulmonary edema. A gallop may indicate heart failure. Abdominal distention, shifting dullness, or a fluid wave may be present with ascites. Generalized edema may include scrotal or labial edema. Findings related to generalized edema may depend on whether the patient has been lying down (sacral edema) or standing (feet and lower legs). Chronic edema may result in bedsores. A distinction may be made between pitting and nonpitting edema. Nonpitting edema is often the result of lymphedema, whereas pitting edema is the result of increased membrane permeability, increased hydrostatic pressure, or decreased oncotic pressure.

### Laboratory Evaluation

Initial testing may include a urinalysis, complete blood count, electrolytes with blood urea nitrogen and creatinine, liver function tests with albumin, lipid studies and cholesterol, and thyroid function tests. The results of this initial evaluation may suggest further testing. Elevated blood urea nitrogen may suggest chronic renal injury. A renal ultrasound may be warranted to look for hydronephrosis because of congenital anomalies. With proteinuria, C3, C4 and antinuclear antibody (ANA) may be indicated. If heart failure is suspected, an electrocardiogram and chest radiograph can be obtained. Testing for fecal fat is appropriate if intestinal malabsorption is suspected, and  $\alpha_1$ -antitrypsin may be helpful for diagnosing protein-losing enteropathy. With angioedema, whether hereditary or acquired, levels of C1 esterase inhibitor are low.

## INTERPRETATION OF TESTS

### Hematologic Abnormalities

Severe anemia can result in edema, especially in a newborn. The anemia can be the result of hemolysis from ABO blood type or Rh incompatibility or from glucose-6-phosphate dehydrogenase deficiency. High-output cardiac failure leads to increased capillary hydrostatic pressure, resulting in edema.

### Renal Disease

The presence of proteinuria with low serum albumin is highly suggestive of nephrotic syndrome. If red cell casts and hematuria (especially cola-colored urine) are present, then glomerulonephritis may be the cause of the edema. C3 levels may be needed to help distinguish between the types of glomerulonephritis. Low C3 suggests poststreptococcal glomerular nephritis

(PSGN) or membranoproliferative glomerular nephritis (MPGN). PSGN usually has improving C3 levels after several weeks. For nephrotic syndrome, low C3 with low C4 and a positive ANA suggest lupus nephritis. If uremia is present, a renal ultrasound may be indicated to look for dysplastic kidneys or hydronephrosis resulting from posterior urethral valves or other anatomic abnormalities. Children with undiagnosed reflux nephropathy may have severe hydronephrosis and renal failure.

### Liver Disease

Hypoalbuminemia without proteinuria suggests either a synthesis defect found with chronic liver disease or a protein-losing enteropathy. Prothrombin time, which is a good marker of the liver's ability to synthesize protein, should be assessed when hypoalbuminemia is present without proteinuria. Liver function tests may also provide helpful information. Analysis of stool  $\alpha_1$ -antitrypsin will help diagnose protein-losing enteropathy.

### Venous Thrombosis

If venous thrombosis is suspected, a Doppler ultrasound examination should be performed to assess the blood flow in the area that may be affected by the thrombosis. Clotting studies should then be conducted, especially if no predisposing factor, such as an indwelling catheter, is present.

### Enteropathy

The presence of increased fat in fecal matter strongly suggests intestinal malabsorption. Determining which intestinal disorder (cystic fibrosis, inflammatory bowel disease, milk protein allergy, enterokinase deficiency, celiac disease, or intestinal lymphangiectasia) may be the cause of the hypoalbuminemia requires further testing and consultation with a gastroenterologist.

## MANAGEMENT

Initial management involves determining whether the patient should be admitted to the hospital. Many causes of edema require admission. Patients with signs of respiratory distress that result from edema of the airway, heart failure with pulmonary edema, and tachypnea should be admitted. Renal causes, such as previously undiagnosed renal failure, acute glomerulonephritis, or nephrotic syndrome, may also require admission. Oliguria from renal failure or poor renal perfusion should result in emergent admission. Edema that results from cirrhosis may require admission if the cirrhosis had been unrecognized or if respiratory distress resulting from the ascites is present. Localized edema that results from venous thrombosis or lymphatic obstruction requires admission to assess and treat the underlying cause. Further management depends on the underlying cause of the edema.

### Anemia

Severe anemia may need to be treated with transfusion. A hematologist should be consulted if the cause of the anemia is not readily apparent.

### Renal Disease

Most patients with renal disease benefit from a low-sodium diet. Fluid restriction may help, but it should be used cautiously on an individual-patient basis in consultation with a nephrologist. Diuretics may also be needed but should be used cautiously. If plasma volume is decreased, then fluid expansion with colloid followed by diuretics may be necessary.

### Liver Disease

A low-sodium diet is generally helpful if ascites is present. Diuretics, especially spironolactone, may also be beneficial. When possible, treating the underlying cause of the ascites is critical.

### Heart Disease

Treating heart failure may require inotropic medications such as digoxin or dobutamine. An angiotensin-converting enzyme inhibitor may help with afterload reduction. If congenital heart disease is causing the heart failure, then surgical repair of the underlying structural lesion is the ultimate treatment.

### Venous Thrombosis

When a venous thrombosis is present, anticoagulation therapy may be indicated. Consultation with a hematologist and possibly a vascular surgeon may be necessary. In the absence of an obvious predisposing factor, investigation for an underlying coagulopathy is appropriate.

### Enteropathy

Treatment depends on the cause of the enteropathy. A gastroenterologist should be consulted.

### Myxedema

Generally, myxedema is found with hypothyroidism and responds to treatment with thyroid hormone replacement.

## SUMMARY

Edema is the accumulation of fluid in the interstitial tissues resulting from disruption of the forces that control normal fluid movement out of and into capillaries and may be the result of many different disease states. The underlying cause is generally apparent, although sometimes subtle. Intervention may initially need to be supportive, but once a patient is stable, efforts to treat the underlying cause of the edema should be pursued, often with the help of a specialist.

### WHEN TO REFER

Many disorders that cause edema may require the assistance of a specialist. A referral to a specialist should be considered if evidence exists of

- Liver disease (ie, ascites)
- Renal disease (glomerulonephritis, nephrotic syndrome)
- Anemia
- Protein-losing enteropathy or increased fecal fat with malabsorption and secondary hypoalbuminemia
- Heart failure

### WHEN TO ADMIT

Many of the causes of edema are serious medical problems that often require admission. This approach may initially be for support. Once a diagnosis is established and the patient is stable, further treatment usually continues on an outpatient basis with the assistance of a specialist. Signs of any of the following may require admission:

- Respiratory distress
- Heart failure
- Tachypnea
- Renal failure
- Acute glomerulonephritis or nephrotic syndrome
- Oliguria from renal failure
- Edema caused by previously unrecognized cirrhosis
- Localized edema that results from venous thrombosis or lymphatic obstruction
- Anemia severe enough to require a transfusion

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## Chapter 146 EPISTAXIS

Miriam Schechter, MD; David M. Stevens, MD

Epistaxis, from the Greek *epistazō*, to bleed at the nose (from *epi*, on, + *stazō*, to fall in drops) is defined as acute bleeding from the nostril, nasal cavity, or nasopharynx. A nosebleed is a relatively common and usually self-limited occurrence in childhood; however, when profuse or recurrent, it can be extremely distressing to children and parents and can at times be a sign of a more serious condition.

### EPIDEMIOLOGIC FACTORS

The incidence of epistaxis has a bimodal distribution with peaks in children younger than 10 years and in adults older than 50 years. It is more common in boys and men than it is in girls and women. From 5% to 14% of Americans have a nosebleed each year, and approximately 10% of them seek care from a physician. Although common in children, epistaxis is rare before the age of 2 years, peaks between the ages of 3 and 8 years, and is uncommon after puberty. Nosebleeds also are more common in children living in dry



climates and occur more often in winter months. Approximately 30% of children from birth to age 5, 56% of children aged 6 to 10, and 64% of children aged 11 to 15 have had at least 1 nosebleed in their lifetime. In a study of the epidemiology of epistaxis in US emergency departments from 1992 to 2001, approximately 1 in 200 emergency department visits were for epistaxis. Peaks were found in children younger than 10 years and in older adults between the ages of 70 and 79. A higher proportion of emergency department visits occurred during the winter months, and 83% of cases were from atraumatic causes.

## DEFINITIONS AND ANATOMIC FEATURES

Nosebleeds are usually classified as anterior or posterior based on the location of the vessels that are the source of the bleed. The blood supply to the nose originates in both the internal and the external carotid arteries (Figure 146-1). The ophthalmic branch of the internal carotid gives off the anterior and posterior ethmoid arteries, which supply the superior nasal septum and the lateral nasal wall. The internal maxillary and facial arteries, which are branches of the external carotid, further divide to supply the nose. The internal maxillary artery splits into the sphenopalatine artery, the posterior nasal artery, and the greater palatine artery, and the facial artery gives off the superior labial artery. The branches of the sphenopalatine provide blood flow to the turbinates laterally and the anterior and posterior septum, the greater palatine supplies the anterior septum, and the superior labial artery supplies the anterior nose and anterior nasal septum.

The anastomoses of vessels in the anterior 2 to 3 cm of the nasal septum, just 0.5 cm from the tip of the nose, also known as Little area, make up Kiesselbach plexus, the primary source of anterior nosebleeds. The delicate vessels that comprise Kiesselbach plexus include the septal branches of the anterior ethmoid, sphenopalatine, greater palatine, and superior labial arteries. These vessels are superficial because the nasal mucosa is

closely adherent to the perichondrium and periosteum. Posterior bleeds usually originate in Woodruff plexus, a convergence of the sphenopalatine, posterior nasal, and ascending pharyngeal arteries, located over the posterior middle turbinate. Specifically, the sphenopalatine is the most frequent source of posterior epistaxis.

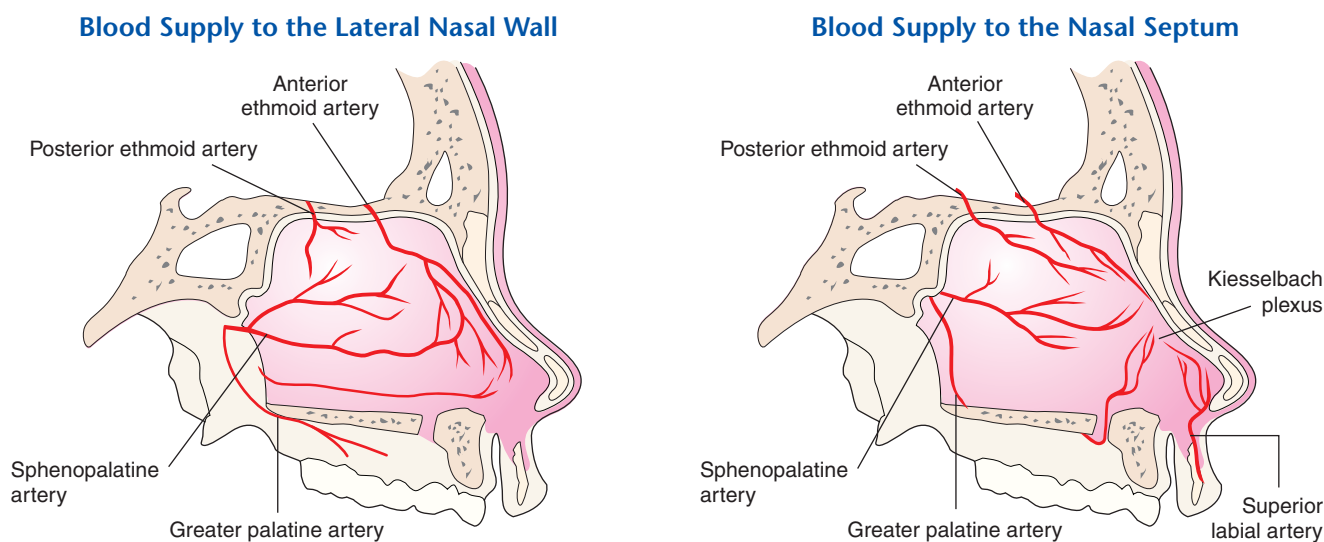
Anterior bleeds are by far the most common type, accounting for greater than 90% of epistaxis in children. The rich vasculature under the thin mucosa in the area most exposed to trauma and dry air makes Kiesselbach plexus the most vulnerable to bleeding. During anterior epistaxis, almost all the blood exits anteriorly through the nares. However, with posterior epistaxis, most of the blood flows into the nasopharynx and mouth, making the degree of bleeding difficult to assess. Anterior bleeds are therefore much easier to visualize and easier to control than posterior bleeds, which are generally much more profuse and are more likely to lead to hemodynamic instability.

## DIFFERENTIAL DIAGNOSIS

The causes of epistaxis can be categorized into local and systemic causes (Box 146-1). More than 1 factor often plays a role in the bleeding.

Trauma from nose picking or nose rubbing accounts for most cases in children, particularly in association with inflammation from infection or allergy. Epistaxis from blunt external trauma is generally acute and self-limiting, but could result from child abuse in very young children. Trauma from a foreign body is an occasional cause in toddlers, often resulting in unilateral bleeding accompanied by foul-smelling or bloody discharge.

Upper respiratory infection and allergic rhinitis are commonly associated with childhood epistaxis. The resultant rhinorrhea leads to digital manipulation or forceful sneezing and nose blowing, and the vascular congestion and mucosal irritation promote easy injury to the blood vessels of the anterior septum. Positive allergy skin tests and recurrent epistaxis are associated in children.



**Figure 146-1** Blood supply to the nose (septum and lateral wall).

**BOX 146-1 Causes of Epistaxis in Children****LOCAL**

- Trauma
  - Nose picking or rubbing
  - Blunt trauma or facial fractures
  - Foreign body
- Inflammation
  - Upper respiratory infection
  - Allergic rhinitis
- Dry air
- Neoplasms
  - Benign
    - Polyps
    - Hemangiomas
    - Juvenile nasopharyngeal angiofibroma
  - Malignant
    - Nasopharyngeal carcinoma
    - Rhabdomyosarcoma
- Nasal septal deviation
- Intranasal drugs
  - Steroids
  - Cocaine

**SYSTEMIC**

- Bleeding disorders
  - Thrombocytopenia
    - Immune thrombocytopenic purpura
    - Leukemia
  - Platelet dysfunction
    - Bernard-Soulier syndrome
    - Aspirin; nonsteroidal anti-inflammatory drugs
  - Coagulopathies
    - von Willebrand disease
    - Hemophilias
    - Liver disease
- Vascular abnormalities
  - Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome)

Exposure to low environmental humidity, especially in winter months, has clearly been associated with an increased frequency of nosebleeds. A deviated nasal septum can contribute to recurrent epistaxis by causing a change in normal airflow, leading to mucosal drying and irritation. Colonization with *Staphylococcus aureus* leading to chronic inflammation and neovascularization may contribute to recurrent episodes.

Neoplasms (benign or malignant) are uncommon causes of epistaxis in children but should be considered in certain circumstances. Polyps in children are usually associated with cystic fibrosis. Juvenile nasopharyngeal angiofibroma is a benign vascular tumor originating in the lateral nasopharynx that occurs only in male adolescents because of its hormonal sensitivity. Although unilateral progressive obstruction or discharge

are clues to this diagnosis, recurrent epistaxis is the most frequent presenting complaint in these patients. Rhabdomyosarcoma of the nasal cavity or nasopharynx is a rare malignant cause of severe episodic epistaxis and may be associated with signs of eustachian tube dysfunction such as unilateral middle ear effusion. Nasal hemangioma is also a rare cause of epistaxis but should be considered in infants. Nasopharyngeal carcinoma is an extremely uncommon but serious disease in children; epistaxis is the presenting complaint in approximately 50% of cases, although it is nearly always accompanied by a neck mass or neck pain.

Systemic causes of epistaxis should be considered whenever nosebleeds are recurrent or persistent in the absence of any obvious local cause. Hematologic disorders include platelet disorders and coagulation defects and may be either congenital or acquired. Thrombocytopenia as a cause of epistaxis is almost always accompanied by petechiae or ecchymoses. The most common cause of isolated thrombocytopenia in otherwise healthy children is immune thrombocytopenic purpura, which presents as acute mucosal hemorrhage, often epistaxis, in approximately 30% of patients, although the bleeding is rarely severe. By contrast, epistaxis rarely is the first symptom of leukemia, but this diagnosis should be considered in an ill-appearing child with epistaxis, especially with fever, pallor, lymphadenopathy, or hepatosplenomegaly. Thrombocytopenia can also be an adverse reaction to a variety of medications, including anticonvulsants such as carbamazepine and chemotherapeutic agents.

Platelet dysfunction from aspirin or nonsteroidal anti-inflammatory drugs can also predispose the individual to epistaxis. Bernard-Soulier syndrome, a disorder of platelet adhesion, is an occasional diagnosis in children evaluated for isolated epistaxis. Primary coagulation defects may result in persistent and long-standing epistaxis; a positive family history is often present. Up to one-third of children with isolated recurrent epistaxis have a diagnosable coagulopathy. Von Willebrand disease (vWD) is the most commonly identified inherited coagulopathy. In fact, 60% of patients with vWD suffer from recurrent epistaxis; other mucosal bleeding (eg, menorrhagia or postsurgical or postdental extraction) is also a common complaint in older children and adolescents. Much less common are the hemophilias, which in mild cases may cause isolated epistaxis (factors VII, VIII, IX or XI deficiency).

Acquired coagulopathies are a rare cause of epistaxis in children, unlike adults, but include various liver diseases (eg, chronic active hepatitis) with consequent depletion of clotting factors. In addition, an acquired form of vWD has been described in children receiving valproic acid.

Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome) is an autosomal-dominant disorder of blood vessel walls characterized by the progressive development of cutaneous and mucosal telangiectasias. More than 90% of affected patients have recurrent and progressively worsening epistaxis, presenting at a mean age of 12 years, although gastrointestinal bleeding and pulmonary arteriovenous malformations also occasionally occur in childhood. Primary isolated hypertension has not been clearly

associated with epistaxis in children, except in the context of renal failure. Finally, 1 recent study has shown a significant association between migraine headaches and recurrent epistaxis, suggesting a common pathogenesis.

## EVALUATION

The evaluation of children with epistaxis should begin with a careful history and physical examination. The season and associated environmental conditions should be noted. The degree of chronicity may suggest an inherited systemic cause. Unilaterality may suggest a local anatomic cause. A history of nose picking or blunt trauma should be sought. One-half of children treated in an emergency room for intranasal foreign body admitted placing the object in the nose; therefore young children should be questioned. A family history of bleeding symptoms or diagnosed disorder is useful in identifying children with a bleeding diathesis.

Associated symptoms should be sought. Unilateral progressive obstruction suggests a mass. The presence and character of any associated rhinorrhea should be noted. Clear, watery rhinorrhea with associated sneezing suggests allergic rhinitis, and mucoid discharge with cough suggests upper respiratory infection. Unilateral foul smelling discharge in a young child may indicate a retained foreign body. A history of petechiae or easy bruising or other mucosal bleeding (eg, menorrhagia, postsurgical) may point to a bleeding disorder. Associated fever or pallor may suggest leukemia. A history of medication use, particularly of aspirin or nonsteroidal anti-inflammatory drugs, should be sought.

The physical examination should include a blood pressure and pulse if the history suggests significant acute or chronic blood loss. A careful examination of the nose should include an attempt to identify the source of any active bleeding (see Management later in this chapter) and to note any discharge, obstructing mass, or foreign body. The skin should be checked for petechiae or unusual location or number of ecchymoses. The neck should be examined for the presence of a mass. If the child is ill, a full examination, including a search for lymphadenopathy and hepatosplenomegaly, should be performed.

The need for and extent of laboratory testing should be guided by the history and physical examination. Frequent and prolonged episodes may warrant ruling out anemia caused by blood loss. Persistent or recurrent epistaxis in the absence of an obvious cause may warrant testing to search for an underlying pathologic condition. A complete blood cell count (CBC) is always indicated in the presence of petechiae or unusual ecchymoses to rule out thrombocytopenia. In an ill child with pallor, fever, lymphadenopathy, or hepatosplenomegaly, a CBC will help rule out leukemia.

The frequency, duration, amount, age at onset, and site of epistaxis have been used in an epistaxis scoring system (Table 146-1) to determine which patients should be evaluated for an underlying bleeding disorder. Use of another pediatric bleeding questionnaire revealed that epistaxis of long duration, lacking seasonal correlation, and requiring medical intervention to stop was

**Table 146-1 Epistaxis Scoring System**

COMPONENT	SCORE <sup>a</sup>
<b>FREQUENCY</b>	
5–15/yr	0
16–25/yr	1
>25/yr	2
<b>DURATION</b>	
<5 min	0
5–10 min	1
>10 min	2
<b>AMOUNT<sup>b</sup></b>	
<15 mL	0
15–30 mL	1
>30 mL	2
<b>EPISTAXIS HISTORY AND AGE<sup>c</sup></b>	
33%	0
33%–67%	1
>67%	2
<b>SITE</b>	
Unilateral	0
Bilateral	2

<sup>a</sup>Mild, 0–6; severe, 7–10.

<sup>b</sup>Estimation of average blood loss per episode, based on fractions or multiples of teaspoons, tablespoons, or cups.

<sup>c</sup>Proportion of the child's life that nosebleeds had been recurrent (>5/yr). From Katsanis E, Luke K, Hsu E, et al. Prevalence and significance of mild bleeding disorders in children with recurrent epistaxis. *J Pediatr*. 1988;113:73–76. Copyright © 1988, Elsevier, with permission.

significantly associated with vWD. This is especially true if the child has bled excessively following circumcision, dental extraction, or with menses. Age younger than 1 year or the need for cauterization have been suggested as reasons to perform an evaluation. Prothrombin time and partial thromboplastin time are useful as initial screening tests. However, given that these results may be within the normal range in some patients with vWD, further evaluation with von Willebrand factor studies may be necessary. If this relatively common coagulopathy is being considered or a platelet dysfunction disorder is suspected, then referring the patient to a hematologist may be prudent.

Rarely, imaging studies are indicated, but plain films can rule out an associated fracture of the facial bones in the setting of blunt trauma. In children younger than 2 years, a child abuse evaluation for inflicted trauma may be warranted. If a mass is thought to be present, then a computed tomography scan or referral to an otolaryngologist should be made.

## MANAGEMENT

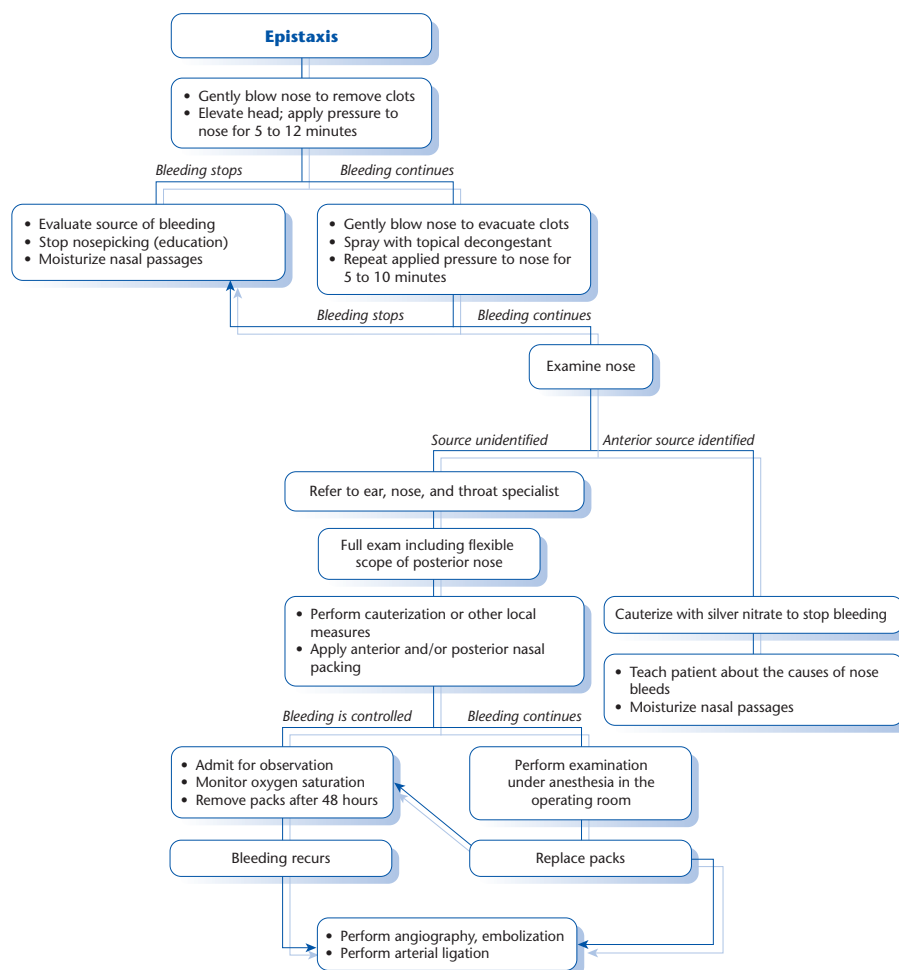
Management of nosebleeds can be divided into 3 general phases. The initial first aid measures that often are performed at home should also be the first line of treatment on presentation to the physician. Next is the acute management of persistent bleeding, which may be initiated by a pediatrician in an office or emergency department but may have to be continued by an

otolaryngologist if initial measures are unsuccessful. This phase may involve medical or surgical intervention, or both (Figure 146-2). Finally, long-term preventive treatment of recurrent epistaxis is necessary, including evaluation and treatment of underlying causes. Although most episodes of epistaxis in childhood are self-limited, they create parental concern and anxiety, and pediatricians must therefore be aware of the treatment options.

Many physicians and patients are unaware of the proper spot for applying direct pressure to the nose to stop a nosebleed. Given that most bleeds originate anteriorly, in Little's area, the first step is to apply pressure to the alar nasi using the first and second fingers. Pressure should be held by pinching the nostrils without interruption for 5 to 10 minutes. The child should sit up with the head bent forward slightly, to minimize blood dripping posteriorly and being swallowed, which can cause nausea and hematemeses. Some physicians suggest placement of ice packs to the forehead, bridge of the nose, nape of the neck, or upper lip to promote vasoconstriction, although only theory supports this practice.

In the health care setting, initial treatment measures should occur simultaneously with assessment and history taking. Basic equipment should be readied (Box 146-2). Most anterior nosebleeds in children will stop after basic first aid. However, if bleeding persists, then additional measures are available. As in any acute situation, an initial CAB (Circulation, Airway, Breathing) assessment should be made. Evaluation for major hemorrhage includes evaluating for tachycardia, hypotension, and orthostasis. Although uncommon in children, airway compromise or hemodynamic instability (or both) requires emergency management.

A history should quickly be obtained (see discussion under Evaluation earlier in this chapter) and an attempt made to locate the source of bleeding. The bleeding has often stopped by the time medical attention is sought. The child should be asked to blow out all clots. If this is not possible, then blood in the nose can be suctioned out. To try to visualize the source of bleeding, 1 of the following 3 tools could be used: a flashlight, while applying gentle upward pressure to the nasal tip; an otoscope with speculum; or a headlight and nasal speculum. Because the anterior septum



**Figure 146-2** Treatment of epistaxis. (From Rudolph AM, Rudolph CD, Hostetter MK, et al, eds. Rudolph's Pediatrics. 21st ed. New York, NY: McGraw-Hill; 2003. Reprinted by permission of The McGraw-Hill Companies, Inc.)



is the most common location of epistaxis in children, this area should be inspected first. Anterior bleeds on the septum, or lateral wall, should be evident by active bleeding, clots, crusts, ulcerations, or prominent blood vessels. If an anterior source is not found and a posterior bleed is thought to exist, then an otolaryngologist should be consulted immediately because posterior bleeds are usually profuse and difficult to stop. Luckily, posterior bleeds are rare in children. If an anterior bleed has not ceased with application of pressure alone, then topical vasoconstrictors (Box 146-2) can be applied with a cotton pledget to shrink the nasal mucosa to improve visualization and possibly to slow down or even stop the bleeding. Use of topical thrombin may also help promote hemostasis. Pressure, again by pinching, should be applied for another 5 to 10 minutes.

The next step to attempt to stop persistent hemorrhage is chemical cauterization, with silver nitrate on applicator sticks. First, local anesthesia should be administered (Box 146-2) with a cotton pledget for 5 minutes to reduce the discomfort of cauterization.

### **BOX 146-2 Equipment Used in the Initial Management of Anterior Epistaxis**

#### **EXAMINATION**

- Flashlight *or*
- Otoscope with speculum *or*
- Headlight and nasal speculum
- Suction

#### **TOPICAL VASOCONSTRICTION**

- Oxymetazoline 0.05% (Afrin) *or*
- Phenylephrine 0.25%, 0.5% (Neo-Synephrine) *or*
- Epinephrine 1:1,000 *or*
- Cocaine solution 3%–5%

#### **TOPICAL ANESTHESIA**

- Lidocaine 4% *or*
- Cocaine solution 3%–5% *or*
- Ethyl chloride

#### **HEMOSTASIS**

- Silver nitrate sticks
- Vaseline strip gauze
- Oxycellulose sponges (Surgicel) *or*
- Gelatin sponges (Gelfoam) *or*
- Nasal tampons/expandable nasal pack (Merocel, RhinoRocket)

#### **ADDITIONAL ITEMS**

- Antibiotic ointment or cream (Naseptin; note: contains peanut oil)
- Cotton pledgets, gauze
- Gown, gloves, mask

After inserting and opening a nasal speculum, using adequate lighting, the silver nitrate is applied to the bleeding point and can be rolled over the site for 5 to 10 seconds. The procedure may have to be repeated 2 to 3 times to achieve hemostasis. Silver nitrate does not work well in pools of blood; therefore, suction may be necessary to keep the area dry. A gray eschar will form at the cautery site. Excess silver nitrate should be removed with cotton or gauze to minimize dispersion by nasal secretions and resulting injury to intact mucosa. Caution should be used to avoid cauterizing too large or too deep an area and to avoid cauterizing both sides of the septum because these measures can lead to septal perforation. After cauterization, the physician should prescribe antibiotic cream or ointment to apply to the area twice a day for 5 days to prevent crusting and infection. Hydration with saline or ointment should continue until healing is complete, in approximately 1 to 3 weeks. Nasal trauma and forceful nose blowing should be avoided during this time. Otolaryngologists may use electrocautery as another hemostatic measure. This type of thermal cautery, however, cannot be performed with topical anesthesia alone.

If an anterior bleed persists despite direct pressure or nasal cautery, then anterior nasal packing may be required. This task can be accomplished with antibiotic impregnated petroleum jelly gauze, which is layered into the anterior nose and provides a tight pack. However, packing is uncomfortable and may require procedural sedation, requires subsequent removal (usually after 2 to 3 days), and can cause additional mucosal injury. Oxycellulose or gelatin sponges are absorbable and do not require later extraction. Although they do not apply a great deal of pressure to the bleeding site, these types of packing are usually adequate for most nosebleeds. Commercially available nasal tampons made of a dehydrated polyvinyl polymer sponge can also be used. The tampons are inserted dry and then expand with blood or added saline partially to fill the nasal cavity. These products come in many sizes and can be cut to fit a child's nasal cavity. They must be removed, usually after 3 to 5 days, and have a tendency to adhere to the nasal lining.

All types of packing and sponges should be impregnated or coated with antibiotic ointment to prevent toxic shock syndrome, which is a reported complication of anterior and posterior nasal packing. Although no clear evidence exists to prove that prophylactic antibiotics reduce the incidence of serious infection, studies have shown that they reduce gram-negative bacterial growth, and common practice is to prescribe them for any patient with nasal packing. Antibiotics, such as amoxicillin-clavulanate, may also help prevent sinusitis that can result from stasis of nasal secretions when packing is in place.

Identification of the source of a posterior bleed must be done by an otolaryngologist using a flexible fiberoptic nasopharyngoscope; sedation may be required for younger patients. In addition to locating a superior or posterior bleeding site, endoscopic visualization may also reveal causes such as foreign bodies, tumors, or sinusitis. In older, more cooperative patients, a rigid endoscope may be used. Cauterization

of a posterior bleeding site can be performed under general anesthesia. Posterior packing can be done with gauze or even urinary catheter balloons. Other types of packing include premade nasal tampons or balloons. All patients requiring posterior packing need sedation and must be admitted to the hospital and monitored in an intensive care unit for airway obstruction and respiratory compromise. More invasive measures such as arterial embolization for refractory bleeds and arterial ligation for recurrent epistaxis are rarely indicated in children.

Once the acute episode of epistaxis has resolved, attention can be focused on looking for predisposing factors or causes and respective preventive strategies or specific management. If a dry environment is present, then the use of normal saline nasal spray helps to humidify the nasal cavity. The spray should be used 4 to 5 times a day. A humidifier in the home may also be useful. The increased moisture helps prevent the accumulation of crusts, which are often the impetus for nose-picking, and keeps scabs soft, allowing them to stay in place longer and thus promoting healing of underlying mucosal injury. Local trauma should be minimized by discouraging nose-picking, forceful rubbing, or blowing of the nose. Fingernails can be trimmed as well. Parents should be educated about the home management of an acute nosebleed; they should pinch the nasal tip for 5 to 10 minutes with the child sitting up, leaning slightly forward.

If allergic rhinitis is a factor in epistaxis, then appropriate testing and medical management is indicated, including treatment with oral antihistamines or inhaled topical nasal steroids. For sinusitis, oral antibiotics are prescribed. If a bleeding disorder is thought to exist, then laboratory workup (see discussion under Evaluation earlier in this chapter) or referral to a hematologist is warranted. Otolaryngologists treat other uncommon lesions and conditions. For example, they will cauterize granulomas, monitor hemangiomas, and excise juvenile nasopharyngeal angiofibromas after hormonal therapy and embolization. Patients with hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome) are now treated with argon laser therapy along with septal dermoplasty.

A common challenge for physicians is the management of recurrent nosebleeds. A recent Cochrane review of the literature on interventions for recurrent idiopathic epistaxis in children exposed the lack of evidence for current treatments of this problem. The condition was defined as repeated nasal bleeding in patients younger than 16 years without identifiable cause. Consensus does not exist on the frequency or severity of the episodes of epistaxis that warrant medical intervention. However, common interventions for less severe cases include cautery with silver nitrate, application of antibiotic nasal creams, instillation of nasal saline spray, or coating the interior nose with ointments such as petroleum jelly. Less commonly advocated topical agents include oxymetazoline, desmopressin, antifibrinolytics, and, most recently, fibrin sealants. On review of the few studies that have been done, no single treatment (neomycin-chlorhexidine antiseptic cream, silver nitrate cautery, petroleum jelly) was found to be superior to another or to no treatment

at all. No serious adverse effects were experienced, although silver nitrate cauterization caused pain in children despite topical anesthesia. One small study suggested that cautery combined with antibiotic cream is more effective than cream alone. Also, if cautery is used, 75% silver nitrate has been shown to be more effective in the short term (but not long term) and caused less pain for the children than 95%. High-quality studies, with longer follow-up, are needed to ascertain which, if any, of these remedies for recurrent epistaxis in children are most optimal.

Nosebleeds occur commonly in children. Although quite upsetting and worrisome to parents, most epistaxis in childhood is anterior, is controlled by simple first aid measures, and results from benign causes. Epistaxis is therefore usually treated on an outpatient basis by general pediatricians. An understanding of all potential causes and acute and long-term management of nosebleeds will assist the pediatrician in appropriate treatment of this condition.

### WHEN TO REFER

#### Ear, Nose, and Throat

##### *Urgent Referral*

- Profuse, uncontrollable bleeding
- Inability to locate source of bleed
- Posterior bleeding
- Assistance with anterior packing
- Recurrence of bleed after initial emergency department measures

##### *Nonurgent Referral*

- Removal of anterior packing
- Recurrent epistaxis
- Evaluation for structural lesions (ie, granulomas, tumors, polyps)
- Treatment of specific lesions

#### Hematology

- Abnormal CBC or coagulation laboratory profile
- Severe, persistent, or recurrent bleeding
- Bleeding from more than 1 site, based on history or physical examination
- Bleeding that required blood transfusion or iron therapy
- Family history of coagulopathy

### WHEN TO ADMIT

- Hemodynamic instability on presentation
- Posterior nasal packing in place

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Chronic Nosebleeds: What To Do* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/ear-nose-throat/Pages/Chronic-Nosebleeds-What-To-Do.aspx](http://www.healthychildren.org/English/health-issues/conditions/ear-nose-throat/Pages/Chronic-Nosebleeds-What-To-Do.aspx))

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## Chapter 147 EXTREMITY PAIN

Michael G. Burke, MD, MBA; David C. Hanson, MD

### DEFINITION OF TERMS

Extremity pain is a common complaint in primary care pediatric practice. Up to 16% of school-aged children report at least 1 episode of activity-limiting extremity pain annually. Among surveyed 8- to 18-year-old Norwegian children, 38.9% of girls and 46.6% of boys reported lower extremity pain during the 3 months prior to survey, while 13.9% of girls and 18.4% of boys reported arm pain. In a 9-year, 6-point, longitudinal survey, British researchers found that 56.6% of caregivers of 5- to 13-year-olds reported that their child often experienced extremity pain at the time of at least 1 survey. Over the 9-year course of the study, caregivers reporting extremity pain in their child increased from 15.1% for 5-year-olds to 32.5% for 13-year-olds. There is some evidence that extremity pain is more common in obese children than in controls. Overall, approximately 6% of pediatric office visits are related to extremity pain. Fortunately, most of these visits involve pain caused by minor trauma, overuse syndromes, and normal skeletal growth variants. Occasionally, however, limb pain is the presenting complaint of a systemic illness, a neoplasm, an infectious process, a nutritional derangement, a specific orthopedic disorder, or a rheumatologic disease. The challenge for the physician is to determine when the pain is significant without exposing the child to excessive diagnostic studies and without delaying treatment or referral. For the most part, this determination is based on the history and physical examination alone.

### EVALUATION

#### History

A thorough history from patients and parents often reveals the cause of extremity pain in children. Pain described as aching or cramping is likely to be muscular in origin. Bone pain is often described as deep and nerve pain as burning, tingling, or numbness. Referred pain is common in children; thus, although usually helpful, the location of pain may be deceiving. Migrating extremity pain is less likely to occur after

trauma and is more typical of systemic illnesses such as leukemia, acute rheumatic fever, disseminated gonorrhea, and arthralgia or arthritis associated with inflammatory bowel disease. The mode of onset, variability, duration, and frequency of pain also help in determining its cause. Activities associated with worsening or relief of pain can also lead to a diagnosis. Similarly, color change associated with extremity pain may indicate inflammation (faint red), infection (intense red), or autonomic dysfunction (pallor, cyanosis, and erythema). Stiffness, especially with clinical evidence of arthritis not associated with trauma, should prompt concern about a rheumatologic process.

A history specific to trauma associated with extremity pain can be helpful. Trauma accompanied by an audible pop or snap is more likely the result of a dislocation, sprain, or fracture. Mild trauma that leads to a fracture might indicate some previous defect in the bone, as with a pathological fracture. If the physical findings of trauma are greater than would be expected from the history, then physical abuse must be considered.

The child's general health history completes the picture of extremity pain. For example, the differential diagnosis changes with age. Toxic synovitis of the hip is a common diagnosis in a child younger than 10 years; a slipped capital femoral epiphysis is more likely in an overweight adolescent.

As a screen for systemic disease, all systems should be reviewed briefly. Particular attention should be paid to a history of fever, recent weight loss, sweating, rashes, and gastrointestinal symptoms. A history of recent medications is important and might reveal a serum sickness–like illness. Even a short course of systemic steroids can cause aseptic necrosis of the hip or can result in demineralization of bone. Immunizations, particularly for rubella, may cause joint or extremity pain, and a history of exposure to viral illness might explain myalgia or arthralgia. Specifically, both parvovirus and hepatitis B can cause significant arthralgia.

The patient's family history may reveal a tendency toward autoimmune disease or recent exposure to infectious diseases. The family history is particularly helpful in identifying hemoglobinopathies. A family history of sickle cell anemia in a 6- to 24-month-old child whose hands and feet are painfully swollen may lead to the diagnosis of hand-foot syndrome and previously undiagnosed sickle cell disease. A sickle cell pain crisis must always be considered in a black child or a child of Mediterranean origin who has a painful extremity. Human leukocyte antigen B27 is associated with reactive arthritis (formerly called Reiter syndrome), psoriatic arthritis, inflammatory bowel disease, and ankylosing spondylitis, and has been described in association with enthesitis-related arthritis (inflammation of tendons, ligaments, or fascia at their attachments to bone). Joint hypermobility syndrome and fibromyalgia also can be familial.

Extremity pain may be a symptom of a functional disorder and can serve as an entry to the physician's office. One large group of pediatric rheumatologists has estimated that 11% of their new patients suffer from psychosomatic musculoskeletal pain. In cases of



functional pain, the history may be either quite dramatic or highly understated. Pain in a nonanatomic distribution or that disturbs only unpleasant activities (waxing on school days and waning on weekends) should raise suspicion of a functional disorder. Eliciting a history of recent events at home, recent school performance, and other social history can be essential to determining the diagnosis.

### Physical Examination

A brief general physical examination is worthwhile even if the history points to extremity pain from minor local trauma. Abnormalities in blood pressure, heart rate, or growth pattern can reveal an endocrine cause. An elevated resting heart rate is associated with rheumatic fever. Pallor, fever, lymphadenopathy, or organomegaly may be clues to systemic disease. A rash may be particularly helpful. Dermatomyositis occurs with muscle pain and proximal weakness associated with a vasculitic rash on the extensor surfaces of knuckles, knees, and elbows (Gottron papules). Palpable purpura and extremity pain are associated with Henoch-Schönlein purpura. A photosensitive rash in a child who has limb pain might point to systemic lupus erythematosus, dermatomyositis, or parvovirus infection. Nail pitting is associated with psoriasis.

In a child with unexplained extremity pain, a thorough eye examination by an ophthalmologist may detect uveitis, sometimes associated with juvenile idiopathic arthritis. Photophobia, eye injection, or pain with accommodation associated with extremity pain warrants a consultation with a rheumatologist and ophthalmologist. A complete physical examination can reveal generalized joint laxity and hyperextensibility, differentiating benign hypermobility syndrome from a focal ligament injury. In benign hypermobility syndrome (Ehlers-Danlos syndrome type III), the joint laxity allows chronic hyperextension, which can cause pain, typically in weight-bearing joints. The pain often is worse in the evening. Dancing and gymnastics may exacerbate arthralgia, as can any other joint-impacting activity.

Claudication is a rare cause of extremity pain in children. However, in popliteal artery entrapment syndrome, vascular calf pain that radiates to the foot is associated with an anomalous popliteal artery or anomalous placement of the gastrocnemius muscle. The pain begins with activity, sometimes more with walking than with running. This syndrome is suggested if normal pedal pulses are lost with simultaneous knee extension and foot plantar flexion.

Because referred pain is common in children, the physical examination should include areas proximal and distal to the site of the complaint. A slipped capital femoral epiphysis and Legg-Calvé-Perthes disease, both of which affect the hip, can produce knee or thigh pain, whereas an abscess of the psoas muscle may cause hip pain. Appendicitis and other intra-abdominal processes and diskitis can also cause pain that is referred to a lower extremity.

Examination of a painful extremity should include assessment of peripheral vascular status, muscle strength, soft-tissue swelling, and skeletal injury.

Disruption of joint integrity may be shown by demonstration of abnormal range of motion of the joint with passive movement. Peripheral vascular status is assessed by palpating the pulses and determining the capillary refill time distal to the pain. Skin color and warmth, tenderness to palpation, and the extent of passive and active range of motion should all be assessed. Swelling, warmth, and erythema over a joint are signs of arthritis. Point tenderness over a bone raises suspicion of a fracture. Point tenderness in the absence of a clear history of trauma may indicate osteomyelitis. Comparing the opposite limb is helpful when assessing swelling, muscle wasting, or joint mobility. Observing the patient's gait or use of the painful limb when the patient is unaware of the observation helps in diagnosing a functional process. Isolated distal weakness is likely to be of neurologic origin, whereas proximal weakness is most likely from muscular disease. Finally, with chronic extremity pain, serial examinations of the patient over the course of weeks can be the key to diagnosis.

### Laboratory Examination

Laboratory studies are unnecessary for most extremity pain. However, if the history and physical examination do not lead to a definitive diagnosis, if they raise suspicion of a systemic or an infectious disease, or if the pain persists longer than anticipated, then screening laboratory tests are in order. A basic evaluation should include a complete blood cell count (CBC), a sedimentation rate, a C-reactive protein, and a sickle cell preparation or hemoglobin electrophoresis when indicated. Appropriate serologies should be considered if features of the physical examination are consistent with rheumatologic disease. An elevated sedimentation rate raises suspicion of an infectious or inflammatory disorder or, occasionally, of a neoplasm. A CBC may reveal anemia or may suggest an infectious disease. With leukemia, the white blood cell (WBC) count varies, but immature forms may be present in the differential WBC count or thrombocytopenia may be present. A creatine phosphokinase determination is occasionally indicated if muscular pain or weakness is suspected.

### Imaging

Radiologic studies are often unnecessary in evaluating limb pain. However, because of the plasticity of children's bones, traumatic injury that would ordinarily cause only a sprain in an adult is more likely to result in a greenstick or buckle fracture in a child. The presence of point tenderness or gross deformity in an extremity or pain on motion of the involved limb increases the likelihood of fracture. In an effort to minimize the use of radiographic studies after traumatic injury to the knee and ankle, The Ottawa Criteria have been developed for use in adults. These criteria have also now been validated for use in children older than 5 years (Box 147-1). When no clear history of trauma is revealed, when symptoms persist, and when associated systemic complaints are present, radiographs can help identify bony tumors, pathological fractures, some metabolic defects, and a significant number of orthopedic conditions.



### BOX 147-1 Indication for Plain Radiograph Evaluation After Trauma Using the Ottawa Ankle and Knee Rules

Radiograph of the knee is indicated after trauma if<sup>a</sup>

- Age older than 55 years
- Isolated tenderness of patella
- Tenderness at the head of the fibula
- Inability to flex the knee to 90 degrees
- Inability to bear weight both immediately and at medical evaluation

Radiograph of the ankle is indicated after trauma in cases of<sup>b</sup>

- Pain in the malleolar zone and (1) tenderness of the tip of the medial malleolus or bone tenderness of the distal 6 cm of posterior tibia, OR (2) tenderness of the tip of the lateral malleolus or bone tenderness of the distal 6 cm of the posterior fibula, OR (3) inability to bear weight immediately after injury and at the time of medical evaluation.

Radiograph of the foot is indicated after trauma in cases of

- Pain in the midfoot zone and (1) tenderness at the base of the fifth metatarsal, OR (2) tenderness at the navicular bone, OR (3) inability to bear weight immediately after injury and at the time of medical evaluation.

<sup>a</sup>Dowling S, Spooner CH, Liang Y, et al. Accuracy of Ottawa Ankle Rules to exclude fractures of the ankle and midfoot in children: a meta-analysis. *Acad Emerg Med.* 2009;16(4):277–287

<sup>b</sup>Vijayasankar D, Boyle AA, Atkinson P. Can the Ottawa knee rule be applied to children? A systematic review and meta-analysis of observational studies. *Emerg Med J.* 2009;26(3):250–253

A bone scan is a useful diagnostic tool in evaluating limb pain and should be considered when a stress fracture, osteomyelitis, or malignancy is suspected. Bone scans are more sensitive than plain-film radiography for establishing these diagnoses. Increasingly, magnetic resonance imaging (MRI) is being used as a replacement for bone scans in the diagnosis of osteomyelitis. The combined use of T1, T2, and short-tau inversion-recovery images effectively rules out osteomyelitis, with a negative predictive value approaching 100%. MRI offers the additional advantage of excellent visualization of soft-tissue and joint disease. There may still be a role for bone scan in the evaluation for osteomyelitis when need for sedation is a concern and when the area of potential involvement cannot be adequately narrowed based on physical examination.

### Differential Diagnosis

The differential diagnosis of extremity pain is extremely broad (Box 147-2). However, most limb pain is benign, requires no intervention, and is self-limited. Characteristic patterns of pain and associated signs and symptoms signal the presence of certain diseases and conditions. A discussion of some of these disorders follows.

### Growing Pains

Growing pains are a time-honored pediatric disorder. They are intermittent, deep extremity pains that affect the lower more often than the upper extremities. The pain is nearly always bilateral, rarely involves the joints, and is almost universally worse at night, lasts fewer than 2 hours, and resolves completely in the morning. Despite their name, growing pains do not

### BOX 147-2 Extremity Pain in Childhood: Differential Diagnosis

#### IMMUNE-MEDIATED ORIGIN

- Dermatomyositis
- Familial Mediterranean fever
- Guillain-Barré syndrome
- Henoch-Schönlein purpura
- Inflammatory bowel disease
- Juvenile idiopathic arthritis
- Kawasaki disease
- Mixed connective-tissue disease
- Polyarteritis nodosa
- Rheumatic fever
- Scleroderma
- Serum sickness
- Systemic lupus erythematosus

#### CONGENITAL ORIGIN

- Caffey disease
- Hemophilia
- Hypermobility syndrome (Ehlers-Danlos syndrome type III)

- Mucopolidosis
- Mucopolysaccharidosis
- Osteogenesis imperfecta
- Popliteal artery entrapment syndrome
- Sickle cell anemia, thalassemia

#### ENDOCRINE ORIGIN

- Hypercortisolism
- Hyperparathyroidism
- Hypothyroidism

#### IDIOPATHIC ORIGIN

- Fibromyalgia
- Growing pains
- Restless leg syndrome
- Sarcoidosis

#### INFECTIOUS ORIGIN

##### *Bacterial*

- Arthralgia or myalgia associated with streptococcal infection
- Diskitis, spinal epidural abscess

*Continued*

**BOX 147-2 Extremity Pain in Childhood: Differential Diagnosis—cont'd**

- Gonorrhea
- Osteomyelitis
- Pyogenic myositis
- Septic arthritis
- Enteric disease
- Meningococcal disease
- Syphilis: periostitis
- Tuberculosis

**Viral**

- Myalgia, arthralgia
- Myositis
- Toxic synovitis

**Other**

- Histoplasmosis
- Immunization reaction
- Trichinosis

**METABOLIC ORIGIN**

- Carnitine palmityltransferase deficiency
- Fabry disease
- McArdle syndrome
- Phosphofructokinase deficiency

**NEOPLASTIC ORIGIN**

- Langerhans cell histiocytosis
- Leukemia
- Lymphoma
- Neuroblastoma
  - Chondrosarcoma
  - Ewing sarcoma
  - Osteoblastoma (benign)
  - Osteogenic sarcoma
  - Osteoid osteoma (benign)
- Tumors of soft tissue
  - Fibrosarcoma
  - Rhabdomyosarcoma
  - Synovial cell sarcoma
- Tumors of the spinal cord
- Tumors of bone

**NUTRITIONAL ORIGIN**

- Gout
- Hypercholesterolemia

- Hypervitaminosis A
- Osteoporosis
- Rickets (vitamin D deficiency)
- Scurvy (vitamin C deficiency)

**ORTHOPEDIC ORIGIN**

- Chondromalacia patellae
- Freiberg disease
- Inflexible flat feet, tarsal coalition
- Kohler disease
- Legg-Calvé-Perthes disease
- Osgood-Schlatter disease
- Osteochondritis dissecans
- Osteogenesis imperfecta
- Pathological fracture
- Sever disease
- Slipped capital femoral epiphysis

**PSYCHOSOCIAL ORIGIN**

- Behavior disorders
- Psychogenic pain
- Reflex neurovascular dystrophy
- School phobia

**TRAUMA OR OVERUSE**

- Compartment syndrome
- Fracture
- Myohematoma
- Myositis ossificans
- Nerve compression syndrome
  - Carpal tunnel syndrome
  - Cervical nerve root entrapment
- Other peripheral nerve root compression
- Physical abuse
- Shin splint
- Sprain
- Stress fracture
- Subluxed radial head
- Thoracic outlet syndrome

occur most frequently during periods of rapid growth. Instead, their onset is described at 3 to 5 or 8 to 12 years of age. For many children growing pains resolve in 12 to 24 months; however, they may persist into adolescence. In a 5-year follow-up of 35 children with growing pains, half had resolution of the condition and nearly all had improvement.

The cause of growing pains remains unclear. However, headache and abdominal pain, often associated with emotional illnesses, also have accompanied

growing pains. In the 5-year follow-up study, only children with persistent growing pains had lower pain thresholds than controls.

The diagnosis of growing pains is significant for its lack of associated physical signs. Thus, any abnormal finding on physical examination should provoke a search for another cause. Similarly, radiographs and the results of screening laboratory tests usually prove normal. Treatment involves heat, massage, and analgesics.

## Sprains

A sprain is a physical disruption of a ligament. In children, sprains occur less commonly than in adults because a child's open epiphyseal plate or plastic bony cortex tends to give way more easily than does a ligament. Therefore, Salter-Harris fractures and buckle fractures should be considered when the history indicates a sprain and when physical examination reveals tenderness on palpation or pain on stretching the ligament. Joint stability should also be assessed. Sprains can be graded according to the degree of associated ligament disruption. A mild, microscopic tear that results in no laxity of the involved joint is a grade I sprain. Grade II sprains involve macroscopic but incomplete ligament tears. Joint laxity is greater, but less than a 5-mm movement differential exists between the sprained and the contralateral joint. Grade III sprains result in more than 5 mm of increased mobility of the affected joint. The primary care physician can treat grade I sprains by icing and wrapping the involved joint to minimize swelling. Early range of motion exercises should be encouraged, with a gradual return to activity. The recurrence of pain indicates too rapid a return to a given level of activity. Grade II and grade III sprains should generally be referred to an orthopedist or sports medicine physician for immobilization and consideration of surgical repair of torn ligaments.

## Overuse Syndromes

Overuse injuries have become more common as organized sports for children have become popular nationwide and as the competitive level of some sports activities has increased. Localized, gradually increasing, and persistent extremity pain that worsens with weight bearing, exercise, and activity, but that diminishes with rest, can indicate a stress fracture. Stress fractures are rare in children younger than 12 years. They most commonly affect the second metatarsal, the proximal tibia, or the fibula. A radiograph may show normal findings, and although a bone scan or an MRI can help establish the diagnosis they are not routinely indicated because treatment consists mostly of rest and nonsteroidal anti-inflammatory agents. Casting or splinting is occasionally necessary.

*Little League elbow* is an overuse injury caused by the repetitive motion of pitching a baseball; this motion compresses the radial aspect of the elbow and stretches the ulnar aspect. The result is painful inflammation of the epicondyles. The range of joint motion also may be diminished. Fragments of bone splintered into the joint may cause the joint to catch or lock. Treatment consists of resting the arm by avoiding the repetitive movement. A change in pitching technique may reduce recurrences. To prevent this problem, some Little League systems limit both the number of innings a child may pitch in a game and the age at which certain pitches can be thrown.

Shin splints are also caused by overuse. The term originally referred to pain along the posteromedial aspect of the tibia as a result of irritation at the origin of the posterior tibial muscle. Shin splints now refer to any of a series of painful overuse syndromes of the lower portion of the leg, including irritation of the

posterior or anterior tibial muscle, inflammation of the interosseous membrane located between the tibia and fibula, and both anterior and posterior compartment syndromes. All of these abnormalities can cause pain in the lower legs. The condition, which is exacerbated by running and jumping, occurs most commonly at the beginning of a training season. Although the pain occurs initially after activity, it may occur during or before activity as the syndrome progresses. On examination, tenderness may be felt over the posteromedial aspect of the tibia, over the proximal portion of the posterior tibia, or over the anterior tibia. Differential diagnosis includes Osgood-Schlatter disease with pain localized to the tibial tuberosity. Treatment of shin splints involves rest, application of ice, and anti-inflammatory agents. For runners, training on a softer surface or with better-quality running shoes may help.

## Subluxation of the Radial Head

Nursemaid's elbow is a common injury in toddlers. The injury usually follows sudden, forceful traction of the hand or forearm, which pulls the immature radial head briefly from the cuff formed by the annular ligament. Release of the force allows the radius to trap the ligament against the capitellum. A verbal patient usually localizes the pain to the elbow or, occasionally, to the wrist. More often, the child refuses to use the extremity and holds the arm with the elbow flexed, the forearm close to the chest, and the hand in pronation. The diagnosis is usually made by history alone. If the history is unclear, or if attempts to reduce the subluxation are unsuccessful, then radiographs may be obtained to rule out a fracture. Radiographic findings in subluxation of the radial head usually are negative. The physician can reduce the subluxation by using 1 hand to supinate the patient's forearm quickly while simultaneously exerting traction on the forearm and using the thumb of the other hand to create pressure over the patient's radial head. This maneuver is completed by placing the elbow through full extension and flexion while maintaining pressure over the radial head. Alternatively, the child's forearm can be fully pronated instead of supinated, and then either fully extended or flexed. With either maneuver, normal use of the extremity usually returns within 30 minutes. The rapid recovery is dramatic and rewarding to the parents and the physician. A prompt return to normal use of the affected arm may not occur if the subluxation has been present for some time because of swelling of the ligament. In such instances, the affected arm should be placed in a simple sling and positioned across the upper portion of the abdomen for 12 to 24 hours. Referral to an orthopedist is rarely required.

## Slipped Capital Femoral Epiphysis

A slipped capital femoral epiphysis is caused by a sudden or gradual dislocation of the head of the femur from its neck and shaft at the level of the upper epiphyseal plate. The characteristic pain occurs in the affected hip or the medial aspect of the ipsilateral knee. The displacement may be sudden, in which case the pain is usually severe and associated with the inability to bear weight. Gradual displacement is associated with slowly increasing, dull pain. This condition

typically affects sedentary, obese adolescent boys. The physical examination may reveal diminished abduction and internal rotation of the hip. The diagnosis is made radiographically. Management involves surgical placement of a pin through the femoral head and the epiphysis to prevent further slippage. Avascular necrosis of the femoral head is a common complication, even with early recognition and treatment.

### Toxic Synovitis

Toxic synovitis, a self-limited inflammation of the hip joint, commonly occurs in children younger than age 10 years. The cause is unknown; however, because it often occurs within 2 weeks after an upper respiratory infection, a postviral inflammatory process is suspected. Typical presentation is that of a child who refuses to walk because of apparent pain in the hip. The hip is held in flexion, abduction, and external rotation. Findings may include a slight elevation in the WBC count and the sedimentation rate, a frustrating development for the physician, who hopes to rule out septic arthritis. A C-reactive protein of less than 1 mg/dL has been shown to have an 87% negative predictive value for septic arthritis. This study may offer reassurance. However, persistent concern for septic arthritis may lead to consultation with an orthopedist. Treatment of toxic synovitis consists of bed rest, usually for fewer than 4 days. In rare instances, avascular necrosis of the femoral head may be a late complication.

### Osteochondroses

Osteochondroses include a group of disorders in which degeneration or aseptic necrosis of bone and overlying cartilage occurs at an ossification center and is followed by recalcification. The disorders vary in name and presentation according to their locations.

Legg-Calvé-Perthes disease, or osteochondrosis of the femoral head, results from compromise of the tenuous vascular supply to the area. The condition may be idiopathic or may result from a slipped capital femoral epiphysis, trauma, steroid use, sickle cell crisis, or congenital dislocation of the hip. Toxic synovitis also is associated with subsequent Legg-Calvé-Perthes disease, but not commonly. After compromise of the vascular supply, the bone underlying the articular surface of the head of the femur becomes necrotic. Collapse of the necrotic bone flattens the femoral head and causes a poor fit with the acetabulum, even after new bone is formed. The pain associated with Legg-Calvé-Perthes disease, which results from necrosis of the involved bone, is often referred to the medial aspect of the ipsilateral knee. A limp may be the presenting complaint. In many instances, an early diagnosis eludes the physician because radiographic findings may be normal or show only swelling of the joint's capsule. A bone scan may demonstrate diminished blood flow to the femoral head compared with the contralateral hip. Later, radiographs may show areas of bone resorption, irregular widening of the epiphysis, or dense new bone formation. The goal of therapy is to prevent flattening of the femoral head as it undergoes new bone formation by keeping the hip abducted so that the head of the femur is held well inside the rounded portion of the acetabulum. Either bracing or

an osteotomy may accomplish this task; both require referral to an orthopedic surgeon.

Two similar processes can affect the knee joint. Osteochondritis dissecans involves degeneration of bone and cartilage at the articular surface of the knee, particularly at the lateral aspect of the medial condyle of the femur. Knee pain, crepitus, or a sensation of instability or locking caused by loose bone and cartilage fragments in the joint can result. Chondromalacia patellae occurs because of a painful softening or breakdown of the inner surface of the patella. The pain is localized to the knee and increases with activities that require prolonged knee bending and even with prolonged sitting. The pain is described as grinding and can sometimes be elicited by applying pressure over the patella. Moving the patella from side to side over the knee joint may cause crepitus and apprehension. Treatment is usually limited to pain relief and reassurance that, in time, the condition will resolve. Exercise to strengthen the medial quadriceps muscles and to stretch the hamstrings may promote better alignment of the patella with the knee and thereby diminish the pain. Rarely, in severe cases, the patella may have to be realigned surgically. Osteochondrosis of the growth plate of the calcaneus (Sever disease) can produce heel pain that worsens with activity. This usually mild process requires only rest, nonsteroidal anti-inflammatory agents, and padding of the heel to relieve the pain. Avascular necrosis and osteochondrosis of the tarsal navicular bone (Kohler disease) and of the head of the second metatarsal (Freiberg disease) can cause foot pain. Treatment usually requires only pain medication and rest.

Osgood-Schlatter disease is a painful degeneration of the tibial tubercle at the site of insertion of the quadriceps ligament. It is characterized by painful swelling of the anterior aspect of the tibial tubercle, usually occurring during adolescence. The degree of swelling may be alarming, and the area is tender to palpation. Pain is exacerbated by activity that involves increased use of the quadriceps muscles. The process is self-limited and resolves toward the end of adolescence when the epiphysis at the insertion site closes and the bone becomes stronger than the inserted ligament. Until it resolves, the condition is treated with rest, analgesics, and, occasionally, supportive patellar knee straps. In rare cases, casting or surgical attachment of the quadriceps ligament is required.

### Osteomyelitis

Osteomyelitis is a local infection of bone, usually involving 1 of the long bones. The highest incidence is in children 3 to 12 years of age. Although infection often occurs by hematogenous seeding, it can be caused by direct entry after local trauma. In both children and adults, the most commonly isolated organism is *Staphylococcus aureus*. Improved diagnostic testing has allowed identification of *Kingella kingae* as 1 of the primary pathogens of osteomyelitis (and septic arthritis) in children younger than 6 years. Effective vaccination for *Haemophilus influenzae* type b has made this pathogen a rare cause of osteomyelitis in immunized children. Other organisms, including *Salmonella* species and group A streptococci also infect the bone.



Group B *Streptococcus* is more likely the cause of infection in newborns. Osteomyelitis caused by *Salmonella* tends to occur more often in children who have sickle cell anemia than in other children. In assessing trauma from a puncture wound to the foot, especially through a sneaker, *Pseudomonas aeruginosa* must be considered. In addition, tuberculous osteomyelitis still occurs and may become more common with the resurgence of tuberculosis.

Osteomyelitis can produce extremity pain alone or extremity pain with signs of a systemic infectious disease (fever, irritability, septic appearance). In the absence of systemic signs, distinguishing between osteomyelitis and a traumatic cause of the pain is often difficult. A period of 2 weeks or longer may be required for radiographic evidence of osteomyelitis to develop. A bone scan is usually, but not always, diagnostic. In rare cases, a reduction in perfusion caused by pressure from the exudative process may result in false-negative scans. MRI is now the preferred test for confirming this diagnosis. In addition, the WBC count and sedimentation rate are often elevated in osteomyelitis. The effectiveness of treatment can be monitored by repeating tests of the sedimentation rate or the C-reactive protein.

### Neoplasms

Although neoplasm is not commonly the cause of limb pain, the possibility of a tumor is a common concern for parents of children who have this complaint. Even if rare, benign and malignant bone tumors and systemic malignancies can cause limb pain.

Osteoid osteoma is a benign prostaglandin-secreting bone tumor that occurs most often in adolescents and usually involves a femur, tibia, or lumbar vertebral body. Pain, the presenting complaint, is initially dull and increases in intensity to deep and boring. The pain is more intense at night and with weight bearing. Radiographic findings of sclerotic bone around a lucent center are diagnostic of this condition; tomograms are sometimes required for confirmation. Surgical excision is curative.

Systemic neoplasms in which extremity pain occurs include leukemia and metastatic neuroblastoma. Childhood leukemia is an uncommon cause of extremity pain. However, up to one-third of children who have acute lymphocytic leukemia have bone pain at the time of diagnosis, and in one-fourth of children, joint or bone pain is a significant presenting complaint. Unrelenting, increasing pain that worsens at night or with rest and that is not relieved by analgesics, heat, or massage may indicate the presence of a metastatic bone tumor. Systemic signs (weight loss, pallor, lymphadenopathy, hepatosplenomegaly, or fever) may accompany the pain. In leukemia, examination of the extremity may reveal strikingly little to account for the degree of pain. Radiographic studies of the extremities may show lucent leukemic lines in the subepiphyseal area.

Primary malignant tumors of bone may cause severe unilateral pain, with swelling and tenderness at the tumor site. The possibility of this diagnosis supports the use of radiographic studies when unilateral limb pain is not explained adequately by a

history of trauma and when pain from trauma does not resolve as expected. The peak incidence of both osteogenic sarcoma and the less common Ewing sarcoma occurs in late childhood and during adolescence. The radiograph of an osteogenic sarcoma may reveal a tumor in the metaphysis with the presence of both radiolucent and radiopaque areas. The characteristic sunburst results from extension of calcification into the overlying soft tissue. Although periosteal elevation may be present, it is not diagnostic of the disease.

### WHEN TO REFER

- Surgical procedure or subspecialist required for definitive treatment (eg, suspected anterior cruciate ligament tear, Ewing sarcoma, other associated conditions)
- Surgical procedure or subspecialist required for diagnostic evaluation (eg, suspected septic arthritis, juvenile idiopathic arthritis, systemic lupus erythematosus, other associated conditions)
- Extremity pain part of multisystemic signs and symptoms (eg, Fabry disease, Crohn disease, other associated conditions)

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Growing Pains Are Normal Most of the Time* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/orthopedic/Pages/Growing-Pains-Are-Normal-Most-Of-The-Time.aspx](http://www.healthychildren.org/English/health-issues/conditions/orthopedic/Pages/Growing-Pains-Are-Normal-Most-Of-The-Time.aspx))
- *Ankle Sprain Treatment* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/injuries-emergencies/sports-injuries/Pages/Ankle-Sprain-Treatment.aspx](http://www.healthychildren.org/English/health-issues/injuries-emergencies/sports-injuries/Pages/Ankle-Sprain-Treatment.aspx))
- *Nursemaid's Elbow* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/orthopedic/Pages/Nursemaids-Elbow.aspx](http://www.healthychildren.org/English/health-issues/conditions/orthopedic/Pages/Nursemaids-Elbow.aspx))

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## Chapter 148

# FACIAL DYSMORPHISM

Robert W. Marion, MD; Joy Samanich, MD

*"It is my business to know things. Perhaps I have trained myself to see what others overlook."*

SHERLOCK HOLMES, "A CASE OF IDENTITY"

If someone were searching for a role model for the field of dysmorphology, the study of the recognition of patterns of congenital malformations and dysmorphic features that characterize particular syndromes, Sir Arthur Conan Doyle's famous detective, Sherlock Holmes, would be an excellent candidate. Like Holmes, the dysmorphologist, who is a subspecialist within the field of medical genetics, searches for clues when evaluating a patient: sometimes facts become available from a carefully obtained history; sometimes facial features that are in plain sight can lead to a diagnosis; and, similar to a detective solving a crime, the dysmorphologist attempts to assemble these bits of information into a single, unifying diagnosis. These clues may be obvious, or they may be so subtle that other physicians simply overlook them. Their diagnostic significance and the information they may provide about the developmental timing of a congenital anomaly, however, may prove invaluable.

## DEFINITIONS

Defined as clinically significant abnormalities in form or function, congenital *malformations* result from localized, *intrinsic* defects in morphogenesis that occur in embryonic or early fetal life. These defects, which include clefting of the lip or palate, congenital heart disease such as tetralogy of Fallot, and multicystic kidney disease, may result from an unknown cause, but increasingly can be traced to mutations in or deletions of single developmental genes. Malformations usually require surgical intervention.

*Deformations* differ from malformations in that they arise from environmental forces acting on *normal tissue primordia*. For example, a fetus reared in a uterus in which a large fibroid is present may have limited space for the limbs to go through their normal range of motion; limitation of motion of the limbs leads to congenital contractures, a condition known as *arthrogryposis multiplex congenita*. Deformations occur later than malformations, usually after the first trimester of pregnancy is completed, and they often resolve with minimal therapy.

A malformation such as a cleft lip or cleft palate or a deformation such as clubfoot deformity (Figure 148-1) may occur as an isolated feature or, in instances in which multiple malformations occur together, may be part of a *malformation sequence*, a *syndrome*, or an *association*.

When a single malformation causes secondary effects on other structures later in development, a

malformation sequence will result. For instance, in the Pierre Robin malformation sequence, the primary malformation, failure of the growth of the mandible during the first weeks of gestation, results in micrognathia (small jaw); because of the insufficient size of the jaw, the tongue, which is normal in size, is forced into an unusual position; the abnormally placed tongue blocks the fusion of the palatal shelves that normally come together in the midline, thus producing a U-shaped cleft of the palate; after delivery, the normal-sized tongue in the smaller-than-normal oral cavity leads to airway obstruction and obstructive apnea, a potentially life-threatening complication. Thus, 3 anomalies result from the single malformation.

In clinical genetics, a syndrome is defined as a group of malformations that occur together and are caused by a clearly identifiable causative agent. This agent may be a single gene mutation; such is the case in Marfan syndrome in which a mutation in the *FBN1* gene on chromosome 15 leads to abnormally formed fibrillin, an important component of the myofibrillar array of connective tissue. The result is a characteristic set of abnormalities of the skeletal, cardiovascular, and ophthalmologic systems. Single gene mutations account for approximately 7.5% of all multiple malformation syndromes. A second cause of a syndrome can be a chromosomal abnormality, as in Down syndrome, in which an extra copy of chromosome 21 leads to craniofacial dysmorphic features, developmental disabilities, cardiac anomalies, and other abnormalities. Approximately 6% of infants with multiple malformation syndromes have a chromosomal abnormality. A third underlying cause of a syndrome can be a teratogenic agent—a drug, chemical, or environmental toxin that causes damage to the developing embryo or fetus. One example is valproic acid, an anticonvulsant that when given to a woman during the first trimester of pregnancy leads to spina bifida, a characteristic facial appearance, limb defects, and other anomalies in exposed embryos. Teratogens account



**Figure 148-1** Club feet. (From Hoyme HE. Assessing dysmorphology in primary care. In: Saul RA, ed. Medical Genetics in Pediatric Practice. Elk Grove Village, IL: American Academy of Pediatrics; 2013:135–174.)

for approximately 6% of cases of infants with multiple malformation syndromes. Finally, a syndrome can result from unknown factors, as is the case with septo-optic dysplasia, which is characterized by midline brain abnormalities, optic nerve hypoplasia and pituitary endocrine dysfunction. Though a small number of patients (<1%) with septo-optic dysplasia have a mutation in the *HESX1* gene, most individuals with this condition have no identifiable underlying cause.

Associations differ from syndromes in that no single underlying cause has been identified to explain a recognizable pattern of anomalies that occur together more than would be expected by chance alone. One example is the VACTERL association (vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb anomalies). Because no single unifying cause that explains this condition has been identified, it is considered an association. When the cause of an association becomes known, the disorder is recategorized as a syndrome. This change recently happened with the CHARGE association (coloboma, heart disease, atresia choanae, retardation of growth or development, genitourinary tract anomalies, and ear anomalies) when, in 2004, this entity was found to be related to mutations in the *CHD7* gene on chromosome 8. Identification of mutations in this gene in patients with this condition allowed CHARGE association to become CHARGE syndrome.

Between 2% and 5% of newborns are found during the neonatal period to have 1 or more congenital malformations. This percentage increases at 1 year of age to between 7% and 8% because some malformations, such as congenital heart disease and renal anomalies, may remain clinically silent during the newborn period only to display later in life. In approximately one-half of children with congenital malformations, only a single malformation is identifiable; in the other half, multiple malformations are present.

## APPROACH TO THE CHILD WITH DYSMORPHIC FEATURES

The birth of a child with dysmorphic features is a difficult and unsettling experience for the family, the

physician, and the medical staff. In many instances, recognition of any problem in an infant will lead to a crisis for the family; the physician caring for the infant and the family may easily panic in such a situation. Therefore, establishing a standardized routine in a format that can routinely be followed when the physician is faced with such a situation is helpful for the evaluation of the child with dysmorphic features. This routine should include taking the history, including a 3-generational family history, and performing a careful physical examination. Following these steps, specific diagnostic laboratory tests can be ordered to confirm a diagnosis (Box 148-1).

When approaching a child with dysmorphic features, physicians must be sensitive about the terminology used to describe the infant. The terms *funny-looking kid* and *funny-looking face* are derogatory, justifiably arouse parental indignation, and should be avoided at all times. In discussing dysmorphic features with parents or describing them in written or verbal communication with colleagues, the physician should describe the abnormal features as clearly and concisely as possible.

### History

In taking the history, the following questions about the pregnancy should be asked:

1. *What was the birth weight?* A lower-than-expected birth weight can be associated with a chromosomal anomaly or exposure to a teratogen. Babies who are large for gestational age may be infants of diabetic mothers or have an overgrowth syndrome, such as Beckwith-Wiedemann syndrome. Infants who are accurate for gestational age may have a single gene mutation, a multifactorial condition, or, most likely, no genetic disease at all.
2. *Was the baby full term, premature, or postmature?* This information is especially important when evaluating an older child with developmental disabilities. Complications of extreme prematurity may be responsible for the patient's problems. Postmaturity is associated with some chromosome anomalies (such as trisomy 18) and anencephaly.
3. *Was the baby born by vaginal or cesarean delivery? If the latter, what was the indication?* These questions are helpful in evaluating the newborn with dysmorphic features and in older children with developmental disabilities. Cesarean delivery may be performed because of fetal distress, a risk factor for developmental disability caused by oxygen deprivation. Furthermore, babies born from breech presentation are approximately 4 times more likely than infants born from vertex presentation to have congenital malformations.
4. *How old were the parents at the time of the child's delivery?* Advanced maternal age is associated with an increased risk of nondisjunction leading to trisomies, such as Down syndrome (trisomy 21), whereas advanced paternal age may be associated with an increased risk of a new mutation leading to an autosomal dominant trait, such as achondroplasia.
5. *Did the pregnancy have complications? Does the mother have underlying medical problems? Does*

### BOX 148-1 Evaluation of the Individual Who Has Facial Dysmorphism

- Review the pregnancy and medical history.
- Review the family history.
- Evaluate growth of the individual in height, weight, and head circumference.
- Evaluate the craniofacial region for dysmorphic features, and describe any such features that are found.
- Describe any other dysmorphic somatic features.
- Define the development of the individual.
- Develop a differential diagnosis and consider appropriate laboratory tests.
- Discuss the findings with the family and, if appropriate, offer genetic counseling.



she take any medications? Did she smoke cigarettes, drink alcohol, or take any drugs? Exposure of the embryo to teratogens—medications, or environmental agents known to cause birth defects—is a significant cause of congenital malformations.

6. *When did the mother feel quickening? Were fetal movements active?* Quickening, which normally occurs between 16 and 20 weeks' gestation, is delayed in hypotonic fetuses, who also have movements during fetal life that are not as vigorous as those of a fetus with normal muscle tone. Additionally, a mother's report of persistent hiccups in an infant found to have neonatal seizures suggests a prenatal onset of the condition.
7. *Was the amount of amniotic fluid normal?* An increased amount of amniotic fluid is associated with intestinal obstruction or a central nervous system anomaly that leads to poor swallowing, whereas a decreased amount of fluid may point to a renal or urinary tract abnormality that leads to failure to produce urine or a chronic amniotic fluid leak.

A 3-generation pedigree should be constructed, searching for similar and dissimilar abnormalities in first- and second-degree relatives; a history of pregnancy or neonatal losses should also be documented.

### Physical Examination

In the process of evaluating the child with dysmorphic features, the physical examination is the most important element. Whenever possible, the patient should be examined using a standardized approach, described in the following sections.

#### Growth

The height (length), weight, and head circumference should be carefully measured and plotted on appropriate growth curves. Growth that is appropriate for age may be consistent with the presence of a single gene disorder, a multifactorially inherited condition, or, most commonly, no genetic disease. Small size or growth restriction may be secondary to a chromosomal abnormality, a skeletal dysplasia such as achondroplasia, or exposure to toxic or teratogenic agents. Larger-than-expected size suggests an overgrowth syndrome (eg, Soto or Beckwith-Weidemann

syndromes) or, if in the newborn period, of maternal diabetes.

#### Proportions

Do the limbs look appropriate for the head and trunk? If not, then are the limbs too short (implying the presence of a short-limbed bone dysplasia such as achondroplasia)? A trunk and head that are too small for the extremities may suggest a disorder affecting the vertebrae, such as spondyloepiphyseal dysplasia.

#### Craniofacial Features

Careful examination of the craniofacies is crucial for the diagnosis of many congenital malformation syndromes. Often, a careful observer can make a diagnosis simply by looking at the child's face.

In assessing the face, head shape and facial features should be systematically observed.

**HEAD SHAPE.** In the newborn period, molding may cause the head to be misshapen, the result of a late prenatal deformational process (see previous discussion). The examiner will need to allow a few days for the deformation to resolve before assessing the shape. The head should then be described using the following terms:

- *Normocephaly* describes a normal head shape.
- *Dolichocephaly* or *scaphocephaly* describes a long, thin head.
- *Brachycephaly* describes a head that is narrow in the anteroposterior diameter and broad laterally.
- *Plagiocephaly* describes a head that is asymmetric or lopsided.

**FACIAL FEATURES.** A dysmorphic face may be appropriate in relation to the family's physiognomy, or it may indicate a particular syndrome. The child who has a large head who also has a parent with a large head does not prompt as much concern as the large-headed child whose parents have normal-size heads. Thus, the examiner must evaluate dysmorphic facial features in light of the child's genetic background. (Table 148-1 lists examples of genetic causes of facial malformation.)

In evaluating the face, the examiner should first note the symmetry. Facial asymmetry may result from a deformation related to intrauterine or extrauterine positioning or a malformation of 1 side of the face, as

**Table 148-1** Examples of Genetic Causes of Facial Malformation<sup>a</sup>

CAUSE	EXAMPLE	FACIAL DYSMORPHISM
Chromosomal	Down syndrome (trisomy 21)	Midface hypoplasia, upward obliquity of palpebral fissures, epicanthal folds, flat nasal bridge, anteversion of nares
Autosomal dominant	Treacher Collins syndrome	Dysplastic ears, maxillary hypoplasia
Autosomal recessive	Hurler syndrome	Corneal clouding, coarse facies
Teratogenic: intrauterine infection	Congenital rubella	Cataracts
Drug induced	Fetal alcohol syndrome	Smooth philtrum (Figure 148-2), small eyes

<sup>a</sup>Smith's *Recognizable Patterns of Human Malformation* is the most valuable resource for this purpose; it also is helpful in determining if a particular condition is genetically based.



is the case with *hemifacial microsomia* (also known as Goldenhar syndrome or *oculoauriculovertebral syndrome*).

For purposes of evaluation, the face should be divided into 4 regions, each of which should be evaluated separately.

1. The *forehead* extends from the anterior hairline to the eyebrows.
2. The *midface* encompasses the region from the eyebrows to the upper lip and laterally from the outer canthus of each eye to the outer commissure of the lips.
3. The *malar region* extends on either side from the upper portion of the ear to the midface.
4. The *mandible* extends from lower ear to lower ear and including the lower lip.

By analyzing each of these 4 regions and determining which is typical and which is not, a clear description of the child's dysmorphic features can be made.

The forehead may show overt prominence (as is the case with *achondroplasia*) or deficiency (often described as a *sloping* appearance, which occurs in children with primary microcephaly).

Hypoplasia of the midface is a common component of many syndromes, including Down syndrome and fetal alcohol syndrome. Evaluating the midface involves careful assessment, first by measurement and then through plotting those measurements on appropriate growth curves, of both the distance between the eyes

(inner and outer canthal distances) and pupils (interpupillary distance). Such assessment may confirm the impression of hypotelorism (eyes that are too close together), suggestive of a defect in midline brain formation (holoprosencephaly); or hypertelorism (eyes that are too far apart), suggestive of a syndrome such as *Opitz syndrome* (ocular hypertelorism, tracheal and esophageal anomalies, and hypospadias). The length of the palpebral fissure should be noted and plotted on the appropriate growth chart; palpebral fissures may be short in fetal alcohol syndrome or excessively long in Kabuki syndrome (short stature, intellectual disability, long palpebral fissures with eversion of lateral portion of lower lid).

Other features of the eyes should be noted. The obliquity (slant) of the palpebral fissures may be upward (as in Down syndrome [Figure 148-3]) or downward (as in Treacher Collins syndrome [Figure 148-4] or Noonan syndrome [Figure 148-5]). The presence of epicanthal folds—flaps of skin covering the inner canthus of the eye, usually associated with flattening of the nasal bridge—may indicate Down syndrome or fetal alcohol syndrome.

Features of the nose—especially the nasal bridge, which can be flattened in Down syndrome or prominent as in velocardiofacial syndrome—should be noted. Are the nares oriented normally, or are they tipped back (a condition known as anteversion)? Is the body of the nose normal, or is it deficient?



**Figure 148-2** Smooth philtrum, characteristic of fetal alcohol syndrome. (From Hoyme HE. *Assessing dysmorphism in primary care*. In: Saul RA, ed. *Medical Genetics in Pediatric Practice*. Elk Grove Village, IL: American Academy of Pediatrics; 2013:135–174. Courtesy of Greenwood Genetic Center, Greenwood, SC.)



**Figure 148-3** Upslanted palpebral fissures, characteristic of Down syndrome. (From Hoyme HE. *Assessing dysmorphism in primary care*. In: Saul RA, ed. *Medical Genetics in Pediatric Practice*. Elk Grove Village, IL: American Academy of Pediatrics; 2013:135–174. Courtesy of Greenwood Genetic Center, Greenwood, SC.)



**Figure 148-4** Treacher Collins syndrome. (Courtesy of Marilyn Jones, MD)



**Figure 148-5** Downslanted palpebral fissures, characteristic of Noonan syndrome. (From Hoyme HE. *Assessing dysmorphology in primary care*. In: Saul RA, ed. *Medical Genetics in Pediatric Practice*. Elk Grove Village, IL: American Academy of Pediatrics; 2013:135–174. Courtesy of Greenwood Genetic Center, Greenwood, SC.)

In evaluating the malar region, the ears should be checked for size (measured and plotted on growth charts that record length for age), shape (noting abnormal folding or flattening of the helices), position (ears are described as low set if the top of the ear is below a line drawn from the outer canthus to the occiput) and orientation (posterior rotation is present



**Figure 148-6** Webbed neck, characteristic of Turner syndrome. (From Hoyme HE. *Assessing dysmorphology in primary care*. In: Saul RA, ed. *Medical Genetics in Pediatric Practice*. Elk Grove Village, IL: American Academy of Pediatrics; 2013:135–174. Courtesy of Lynne Bird, MD.)

when the ear seems to be turned toward the rear of the head). Ears may be low set because they are small (or microtic) or because of a malformation of the mandibular region.

Finally, the examiner should evaluate the mandibular region, the area encompassing the lower portions of each ear and including the lower jaw. In most newborns, the chin is retruded (slightly set back behind the vertical line extending from the forehead to the philtrum). If the mandible itself is small, then it is described as micrognathic, whereas an unusually prominent mandible is described as prognathic. Significant micrognathia is seen in the Pierre Robin malformation sequence.

#### Remainder of the Body

Once facial dysmorphic features have been detected, the primary care physician must conduct a thorough examination looking for additional unusual findings. Again, findings may point to a specific diagnosis.

**NECK.** Examination of the neck may reveal webbing, a feature common in Turner (Figure 148-6) and Noonan syndromes, or shortening, as is occasionally seen in some skeletal dysplasias and in conditions in which anomalies of the cervical spine occur, such as Klippel-Feil syndrome. The position of the posterior hairline should also be evaluated, and the size of the thyroid gland should be assessed.

**TRUNK.** The chest should be examined for shape (a shieldlike chest is found in Noonan and Turner syndromes) and symmetry (hypoplasia of the pectoralis major and minor muscles, leading to asymmetry, is a feature of the Poland malformation sequence). A pectus deformity of the chest (either pectus excavatum

or pectus carinatum) is usually an isolated finding but is a cardinal feature of Marfan syndrome. Scoliosis, also usually an isolated feature, is often seen in individuals with Marfan syndrome, as well as in several other disorders.

**EXTREMITIES.** Anomalies of the extremities are common in many congenital malformation syndromes. All joints should be examined for range of motion. The presence of single or multiple joint contractures suggests either intrinsic neuromuscular dysfunction, as in the case of some forms of muscular dystrophy, or external deforming forces that limited motion of the joint in utero. Radioulnar synostosis, an inability to pronate or supinate the elbow, occurs in fetal alcohol syndrome and in some X chromosome aneuploidy syndromes (such as 48, XXXX and 48, XXXY syndromes).

Next, the hands should be examined. Polydactyly (the presence of extra digits) occurs in isolation as an autosomal dominant trait in up to 1% of all newborns, but can also be seen as part of a malformation syndrome such as trisomy 13. Oligodactyly (a deficiency in the number of digits) is seen in Fanconi syndrome (growth restriction, aplastic anemia, development of leukemia or lymphoma and associated heart, renal and limb defects, including radial aplasia and thumb malformation or aplasia), in which it is generally part of a more severe limb reduction defect, or secondary to intrauterine amputation that may occur with *amniotic band disruption sequence* (Figure 148-7). Syndactyly (a joining of 2 or more digits) is also common to several syndromes, including Smith-Lemli-Opitz syndrome.

Dermatoglyphics, especially the palmar crease pattern, are also important to note. A transverse palmar crease (Figure 148-8), indicative of hypotonia during early fetal life, is seen in approximately 50% of children with Down syndrome (and 10% of individuals in the general population). A characteristic palmar crease pattern is also seen in fetal alcohol syndrome.

**GENITALIA.** Genitalia should be examined for abnormalities in structure. In male infants, if the penis seems short, then it should be measured and plotted on an appropriate growth chart. Ambiguous genitalia can be associated with endocrinologic disorders such as congenital adrenal hyperplasia (female infants have masculinized external genitalia, but male genitalis may be unaffected), chromosomal disorders such as Turner syndrome mosaicism, or part of a multiple malformation disorder such as Smith-Lemli-Opitz syndrome. Although hypospadias, which occurs in 1 in 300 male newborns, is a common congenital malformation that often occurs as an isolated defect, if it is associated with other anomalies, then the possibility of a syndrome is strong.

### Laboratory Evaluation

Following completion of the medical history, family history, and physical examination, the dysmorphologist takes the clues that have been gathered and attempts to solve the puzzle by assembling them into a diagnosis. The differential diagnosis is made up of conditions that feature some or all of the clues. Once this list has been assembled, a series of laboratory and



**Figure 148-7** Amniotic bands. (From Hoyme HE. *Assessing dysmorphism in primary care*. In: Saul RA, ed. *Medical Genetics in Pediatric Practice*. Elk Grove Village, IL: American Academy of Pediatrics; 2013:135–174.)



**Figure 148-8** Single palmar crease. (From Hoyme HE. *Assessing dysmorphism in primary care*. In: Saul RA, ed. *Medical Genetics in Pediatric Practice*. Elk Grove Village, IL: American Academy of Pediatrics; 2013:135–174. Courtesy of Lynne Bird, MD.)

imaging tests can be performed in an attempt to arrive at a definitive diagnosis. Typical tests used by the dysmorphologist are outlined here.

Chromosomal microarray analysis (CMA), should be routinely ordered for children with

- Multiple congenital anomalies
- The involvement of 1 major organ system and 2 or more dysmorphic features
- The presence of intellectual disability
- The presence of an autism spectrum disorder

Chromosome analysis (karyotype) will identify conditions caused by too much chromosomal material



(ie, trisomies) or those with too little chromosomal material (ie, monosomies). However, karyotype will only identify large abnormalities. Chromosomal microarray uses DNA technology to identify smaller partial trisomies or monosomies than can be seen by karyotype, making it about 4 to 5 times more sensitive. This technique compares the amount of DNA from the patient to that of a control, looking for changes in the number of DNA copies. It is able to look for copy number changes throughout the genome. CMA will not identify balanced rearrangements such as translocations or inversions, so if this is suspected, karyotype should be ordered.

Fluorescent in situ hybridization (FISH) uses DNA technology to identify specific regions of the genome that are either missing or duplicated. FISH uses a DNA probe that is complementary to a specific region of the genome. After a fluorescent marker is attached to this probe, it is incubated with chromosomal DNA from the patient. If the sequence is present in the patient, then the probe will hybridize, its presence announced by the appearance of the bound fluorescent marker.

A FISH study is requested when a syndrome with a known chromosomal defect is suspected. Such disorders as velocardiofacial syndrome (deletion of *22q11.2*), Prader-Willi syndrome (deletion of *15q11.2*), Angelman syndrome (deletion of *15q11.2*), and Beckwith-Wiedemann syndrome (duplication of *11p15.2*) are included in this group. It may also be used to confirm findings of a CMA.

In a growing number of disorders, *direct DNA* analysis can be performed to identify specific mutations known to cause disease. Because the list of these disorders increases every day, using Web-based resources for the most recent information is necessary. An extremely helpful Web site is [www.genetests.org](http://www.genetests.org). Frequently updated, Genetests provides information about the availability of testing for specific conditions and identifies laboratories performing the testing. Newer technologies, termed next-generation sequencing, are emerging that perform DNA analysis of multiple genes in a single test. These emerging techniques, including whole exome sequencing and whole genome sequencing, will allow for better diagnosis of disorders caused by multiple genes, and the identification of genes for disease in which the cause remains elusive.

Radiologic imaging plays an important role in the evaluation of children with dysmorphic features. Individuals found to have multiple external malformations should have a thorough evaluation to search for the presence of internal malformations. Testing might include ultrasound evaluations of the head and abdomen, the latter area to look for anomalies in the kidney, bladder, liver, and spleen. Skeletal radiographs should be taken if concern exists about a possible skeletal dysplasia. The presence of a heart murmur should trigger a cardiology consultation, and an electrocardiogram and echocardiogram may be indicated. Magnetic resonance imaging may be indicated in children with neurologic abnormalities or spinal defects. The presence of craniosynostosis indicates the need for a 3-dimensionally reconstructed computed tomographic scan of the head.

## DIAGNOSIS

Although the presence of characteristic findings may sometimes make the definitive diagnosis of a malformation syndrome simple, in most cases no specific diagnosis is immediately evident. Some constellations of findings are rare, and finding a match may prove difficult. In many cases, all laboratory tests are normal, and confirmation relies on subjective findings. Clinical geneticists have attempted to resolve this difficulty by developing scoring systems, cross-referenced tables of anomalies that help in developing a differential diagnosis, and even computerized diagnostic programs.

An accurate diagnosis is important for 3 reasons as follows:

1. It offers the family an explanation of why their child was born with congenital anomalies. This information may help allay feelings of guilt, given that parents often believe that they are responsible for their child's problem.
2. The natural history of many disorders is well described; as such, a diagnosis allows the physician to anticipate medical problems associated with a particular syndrome and to perform appropriate screening. A diagnosis may also provide reassurance that other medical problems are no more likely to occur than they might with other children who do not have the diagnosis.
3. It permits accurate recurrence risk for future progeny; only after a diagnosis is confirmed can genetic counseling and, eventually, preimplantation genetic diagnosis or prenatal diagnostic testing be performed.

Once a definitive diagnosis has been made, the dysmorphologist must meet with the family in person to explain the condition and the prognosis. Such meetings are often difficult, since this is the moment that the news is first delivered to the parents and the full effect of the child's condition is realized. A sufficient amount of time should be allotted for this meeting because families may have many questions, and each question should be answered in a thoughtful and considerate way. It is also often helpful to include social support professionals as participants in these meetings; genetic counselors, social workers and psychologists can help the family accept the news and begin moving on with the next phase of their lives.

The diagnosis also enables the physician to provide the family with educational materials about their child's condition. Additionally, many condition-specific support groups exist and the physician can provide the family with information about such groups in their area. These groups offer social and emotional assistance for the family of a child with a newly diagnosed genetic disorder. The Internet has become an important source for parents seeking information about their child's condition, but care should be exercised because information on the Internet is not always subject to editorial control, and some of the information may be inaccurate, or at times misleading or inappropriate. Physicians should try to screen Web sites before they suggest them to the family. Some recommendations of Web sites can be found in the Tools for Practice section at the end of this chapter.



## SUMMARY

The physician confronted with a patient who has dysmorphic facial features must decide whether the patient or family will benefit from a thorough evaluation or referral. The most important task initially is to determine whether the features are consistent with the individual's genetic background or whether they represent an abnormal phenotype. Through systematic gathering of information, the physician should attempt to establish an etiologic diagnosis and then convey the implications (including genetic counseling) to the appropriate family members.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Congenital Abnormalities* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/developmental-disabilities/Pages/Congenital-Abnormalities.aspx](http://www.healthychildren.org/English/health-issues/conditions/developmental-disabilities/Pages/Congenital-Abnormalities.aspx))

### Medical Decision Support

- *Genetests* (Web site), ([www.genetests.org](http://www.genetests.org))
- *Genetic Alliance* (Web site), ([www.geneticalliance.org](http://www.geneticalliance.org))
- *Management of Genetic Syndromes*, 3rd ed (book), John Wiley & Sons
- *March of Dimes* (Web site), ([www.marchofdimes.com](http://www.marchofdimes.com))
- *National Organization for Rare Diseases* (Web site), ([www.rarediseases.org](http://www.rarediseases.org))
- *Online Mendelian Inheritance in Man* (Web site), National Center for Biotechnology Information ([www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM))
- *Smith's Recognizable Patterns of Human Malformations*, 6th ed (book), Elsevier

## SUGGESTED READINGS

- Hennakam RCM, Krantz ID, Allanson JE. *Gorlin's Syndromes of the Head and Neck*. 5th ed. New York, NY: Oxford University Press; 2010
- Jones KL. *Smith's Recognizable Patterns of Human Malformation*. 6th ed. Philadelphia, PA: WB Saunders; 2005

## Chapter 149

# FAILURE TO THRIVE: PEDIATRIC UNDERNUTRITION

Andrew D. Racine, MD, PhD

The unfortunate term *failure to thrive* has burdened generations of physicians and their patients as an unenlightening phrase that combines a heterogeneous group of infants and young children with nothing more in common than a growth pattern irreconcilable with a predetermined standard for age. Abnormalities ranging from congestive heart failure to psychosocial deprivation can eventually lead to the same place, called failure to thrive. To find a child in such a location, however, tells us little about the

direction from which he or she strayed to come to our attention. Moreover, the term failure to thrive is as pejorative as it is devoid of content; thus, recent scholarship has favored phrases such as *pediatric undernutrition*, as used in the *Bright Futures in Practice* literature, or *weight faltering*, as adopted by our British colleagues.

Given the diversity of potential causes, evaluation and management of a child who fails to gain weight adequately represent a formidable challenge that requires of the physician:

- A determination to listen attentively and examine thoroughly, given that no adequate substitute has yet been found for a complete history and physical examination
- A broad familiarity with the many pathophysiologic sequences that can give rise to this condition
- An understanding of healthy infant behavior and development to identify aberrancies that may threaten weight gain at different ages
- A capacity to gather and synthesize information about the physical, psychological, emotional, familial, and social contexts of the patient's presentation
- A willingness to work with a team of other medical professionals to evaluate and manage the child
- The patience to persevere for as long as required to establish adequate weight gain

## DEFINITION

A diagnosis generally signals the culmination of a process of evaluation. By contrast, the diagnosis of failure to thrive merely serves to *initiate* the evaluation of a patient who has an abnormal pattern of weight gain. Deviation from normal weight gain has been defined conventionally by reference to age-adjusted nationally standardized norms of weight and rate of weight gain. Infants or young children who either fall below a given weight-for-age or weight-for-height percentile, or whose rate of weight gain has declined across 2 major percentiles (ie, 90th, 75th, 50th, 25th, 10th, or 5th) invite close scrutiny. The Social Security Administration, for example, defines failure to thrive as a fall in weight to below the third percentile or to less than 75% of the median weight-for-height or weight-for-age percentile in children younger than 2 years.

Static measurements of a child's weight-for-age or weight-for-height percentile that document a child's *size* should be distinguished from repeated measurements over time that record a child's *growth*. A deviation from the norm in size may or may not, depending on the clinical circumstances, indicate an abnormality of growth.

A clinical entity defined by reference to statistical norms merits some additional comment. First, although an occasional child may have obvious signs of severe malnutrition at the initial examination, a single observation of weight in a child is generally insufficient to make any diagnosis. The concern here, for the most part, is with children who exhibit abnormal patterns of weight gain over time.

Second, although the aim is to identify children whose weight or weight gain is abnormal, some

children will fall into the extreme tails of the standard distributions, be it 10%, 5%, or 3%, of any cohort. The farther out on the curve we observe any individual child, however, the more likely the child is to be truly abnormal with respect to weight-for-age or weight-for-height percentile.

Third, the national reference charts for children's anthropometric measurements are constructed by using serial cross-sections of children, not longitudinal observations of cohorts as they grow. Therefore, the rate at which a child gains weight individually will differ from tracks across collections of different children at different ages that appear on these charts. Over time, children's weights generally regress toward the mean, with heavier infants gaining weight at slower rates than lighter infants. To account for this pattern, British researchers developed weight charts from a cohort of 3,418 full-term infants from Newcastle based on standard deviations of weight changes over time. These charts have wider percentile channels at upper weights and narrower channels at lower weights.

Finally, statistical descriptions must not be allowed to obscure the salient feature common to most children who fail to gain weight adequately: they suffer from malnutrition and are therefore at risk for its attendant consequences. When acute malnutrition results in decreased weight-for-age percentile, the condition is referred to as *wasting*. If caloric deprivation is prolonged, it will eventually affect the child's linear growth, at which point the child is said to be *stunted*. Abnormalities in linear growth not accompanied by wasting (the child who has short stature alone) are not the subject of failure to thrive.

One common set of criteria defines failure to thrive in children younger than 2 years as

- Weight consistently less than 80% of the median for age, or
- Weight on more than 1 occasion falling below the third percentile for age, or
- Weight that has fallen across 2 major percentiles on growth charts

Until 2006, the instruments most commonly used to track children's height, weight, and head circumference were growth charts published by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) based on data collected on children in the United States between the years 1963 and 1994. These data reflected the actual growth of infants and children from a fairly homogeneous population with respect to its racial composition and also depicted the weights of a population most of whose members were formula fed.

In response to these and other shortcomings, in 2006 an expert panel with representatives from the CDC, the National Institutes of Health, and the American Academy of Pediatrics recommended adoption of the international growth charts for children 0 to 24 months of age released that year by the World Health Organization (WHO). The data used to compile these charts were collected between 1997 and 2003 from six sites around the world. These charts are described as representing *standards*, meaning that they capture "... the growth of healthy children in optimal conditions," rather than the reference charts from the

NCHS that they were designed to replace, which described "... how certain children grew in a particular place and time." The expert panel recommended continued use of the older NCHS charts for children 24 to 59 months, where discrepancies between the NCHS and WHO charts were felt to be negligible.

Common cutoff values used to identify children in need of more intense scrutiny differ between the NCHS charts and the WHO charts. The accepted value used with the NCHS charts is the 5th percentile, whereas the recommendation based on the WHO charts suggests concentrating on infants who fall below the 2.3rd percentile. Thus, although the older NCHS reference charts could have been anticipated to identify as many as 10% of children seen in outpatient settings and 3% to 5% of hospital admissions, those fulfilling equivalent criteria using the WHO cutoffs are likely to be less numerous. Children who exhibit weights from 61% to 75% of the median for age on the new charts are fewer still but require intensive outpatient monitoring. When a child's weight falls below 60% of the median for age on the new charts, the associated morbidity is severe and warrants inpatient hospitalization. Children from lower socioeconomic backgrounds may be at heightened risk for malnutrition and consequent wasting.

## HEALTHY WEIGHT GAIN IN INFANTS

Both the NCHS and the WHO growth charts have received widespread application as tools for plotting the growth patterns of healthy infants and children. The ease of their use makes them ideal screening instruments, but, as with all screening tools, their sensitivity and specificity are limited. They do not, for example, take into account parental size or the presence of pre-existing chromosomal abnormalities, leading some researchers to argue for the use of standards that control for mean parental height or the presence of certain genetic conditions such as trisomy 21. The *Bright Futures* publication on nutrition provides references for growth charts based on specific disorders.

Recent studies examined the rate at which infants gain weight and how regression to the mean reflects the tendency of some heavier infants to gain weight more slowly and some lighter infants to gain weight more quickly over time. The mean weight of a newborn is approximately 3.25 kg ( $\pm 0.9$  kg.). Many infants lose between 6% and 10% of this weight in the first week as they undergo the normal diuresis associated with adaptation to the extrauterine environment. Birth weight usually is regained by the age of 10 days. Because a newborn's weight at birth predominantly reflects the influence of maternal characteristics and the intrauterine environment, it is an imperfect reflection of genetic growth potential. By 4 to 8 weeks of age, however, much catch-up growth in babies born "light for dates" has already occurred; thus, an infant's weight at this time seems to be a more reliable predictor than birth weight or weight at 12 months. In general, infants can be expected to gain a mean of 30 g ( $\pm 15$  g) a day during the first 3 months of life. Infants will usually triple their birth weight by 1 year of age, at which time the mean daily weight gain has declined to approximately 10 g ( $\pm 3$  g). Characteristics

of maternal and child feeding behaviors may have important influence on the rate of weight gain in the first year of life among subpopulations of infants with feeding difficulties.

## **PATHOGENESIS**

Infants and children grow in the presence of adequate amounts of 4 fundamental constituents: oxygen, substrate, hormones, and love. Deficiency of any one or a combination of these impedes normal weight gain. Oxygen deprivation at the tissue level from causes as diverse as congestive heart failure, chronic lung disease, or anemia will result in poor weight gain. Inadequate calories, protein, or micronutrients either from environmental deprivation, malabsorption, or inability to metabolize them at the tissue level also inhibit normal weight gain. Deficiencies in growth hormone, insulin-like growth factors, glucocorticoids, thyroid hormone, and other regulators of growth can result in failure to thrive. Finally, infants or children severely deprived of affection will often not grow despite what appears to be normal caloric intake. Chronic disease from many causes will interrupt normal weight gain through the induction of anorexia, malabsorption, increased metabolic needs, and the elaboration of inflammatory mediators, including tumor necrosis factor. Children with chromosomal or other genetic abnormalities, although they may exhibit idiosyncratic growth patterns specific to their particular condition, will also attain their full growth potential only in the presence of these critical ingredients.

In the past, patients with inadequate weight gain were classified as a minority whose difficulty stemmed from a readily identifiable *organic* cause, and a majority whose problem was categorized as *nonorganic*. Other researchers emphasized the overlapping nature of these distinctions and have suggested a third, or *mixed*, category of failure to thrive. More recent approaches have tended to depart from the organic–nonorganic dichotomy in recognition of the somewhat arbitrary nature of this distinction.

A more useful categorization of infants and children who have inadequate weight gain acknowledges an imbalance between the energy needs of the organism that does not grow and the energy at its disposition. The largest share of energy consumed, about 55% to 60%, is devoted to maintaining a basal metabolic rate. An additional 5% to 10% of energy is lost in urine and stool, 5% is accounted for by specific dynamic action, 15% is used for normal physical activity above basal metabolic functions, and 15% is directed toward growth. To provide for all these functions, infants need approximately 100 to 110 kcal/kg/day.

An imbalance between energy needs and energy supplies can arise either from increases in the former or deficiencies in the latter. Box 149-1 lists conditions that increase the energy needs of the organism. Energy needs increase either with increases in the intensity of energy expenditure or decreases in the efficiency of energy use. Conditions that increase the intensity of energy expenditure include chronic heart disease, chronic lung disease, chronic anemia, chronic infection, certain endocrine abnormalities, malignancy, and intoxications. The efficiency of energy

### **BOX 149-1 That Increase Energy Needs**

#### **INCREASED INTENSITY OF ENERGY UTILIZATION**

- Chronic heart disease (congenital or acquired)
- Chronic lung disease (bronchopulmonary dysplasia, cystic fibrosis, pulmonary lymphangiectasis)
- Chronic anemia (hemoglobinopathies, enzyme deficiencies, membrane abnormalities)
- Chronic infection (urinary tract infections, respiratory infections, tuberculosis)
- Endocrine abnormalities (hyperthyroidism)
- Malignancy (neuroblastoma, ganglioneuroma)

#### **DRUGS OR TOXINS OR DECREASED EFFICIENCY OF ENERGY UTILIZATION**

- Chronic infection
- Chronic renal disease
- Hepatic insufficiency (cirrhosis)
- Metabolic disease (disorders of amino acid or carbohydrate metabolism, idiopathic hypercalcemia of infancy)
- Hormonal disturbances (hypopituitarism, hypoparathyroidism, chronic adrenocortical insufficiency, diabetes insipidus, hypothyroidism)
- Genetic conditions (Down syndrome, de Lange syndrome, cri du chat syndrome, Smith-Lemli-Opitz syndrome, familial dysautonomia)
- Micronutrient deficiencies (iron, zinc, carnitine)

utilization can be compromised by chronic infection, chronic renal disease, hepatic insufficiency, inborn errors of metabolism, hormonal abnormalities, certain genetic syndromes, and deficiencies of various micronutrients, including iron, zinc, and carnitine.

Conditions leading to deficiency in energy supply are listed in Box 149-2. These conditions originate because calories are either withheld from or improperly presented to the child because they are refused, vomited, not ingested, or not absorbed.

In the category of caloric deprivation, nutritional deprivation in utero that may result in permanent growth restriction must be included. After delivery, a newborn may not receive sufficient calories because of parenting difficulties ranging from unfamiliarity with proper preparation of infant formula or appropriate breastfeeding techniques, to psychosocial dysfunction, to maternal depression, and even to frank abuse or neglect. Other conditions that fall into this category include economic deprivation, unsound parental beliefs regarding nutrition, and subtle central nervous system abnormalities in the child causing him or her to be a difficult feeder.

Food refusal in children, beginning even in infancy, can result from many causes, including pain (from reflux esophagitis), psychosocial adjustment disorders from emotional deprivation, anorexia from chronic infection or intoxication, and structural abnormalities resulting in dysphagia. Structural malformations of the nose or oropharynx, such as cleft palate, choanal



**BOX 149-2 Conditions That Result in Deficient Energy Supply**

- Calories withheld
- In utero conditions
- Formula preparation mistakes
- Breastfeeding difficulties
- Parent–child psychosocial dysfunction
- Maternal depression
- Intentional abuse or neglect
- Poverty
- Unsound parental beliefs regarding nutrition
- Feeding difficulties
- Calories not properly ingested or digested
- Oral pain caused by dental disease
- Anorexia (reflux esophagitis, emotional deprivation, chronic infection, dysphagia)
- Structural abnormalities of the oropharynx or nasopharynx (cleft palate, choanal atresia, Treacher Collins syndrome, Pierre Robin syndrome, laryngeal web)
- Structural abnormalities of the gastrointestinal tract (stenosis or atresia of the esophagus or duodenum, tracheoesophageal fistula, vascular ring, strictures, achalasia, malrotation, antral web, pyloric stenosis)
- Neuromuscular disorders (cerebral palsy, hydrocephalus, myopathies)
- Conditions leading to excessive dyspnea (congestive heart failure, chronic lung disease)
- Vomiting and rumination
- Malabsorption
- Small bowel disease (celiac disease, inflammatory bowel disease, disaccharide malabsorption, intestinal lymphangiectasia, jejunal atresia, duplication cysts, chronic parasitic infections)
- Pancreatic disease (cystic fibrosis, Shwachman-Diamond syndrome, chronic pancreatitis)
- Liver disease (cirrhosis, intrahepatic cholestatic syndromes, biliary atresia)

atresia, or Treacher Collins syndrome, can lead to an inability to ingest nutrients properly, as can muscular weakness, cerebral palsy or other central nervous system abnormalities, and diseases that give rise to excessive dyspnea.

Vomiting caused by structural abnormalities of the gastrointestinal tract, increased intracranial pressure from any source, chronic acidosis, rumination, and gastroesophageal reflux may all impede growth through caloric deprivation.

The principal organ of nutrient absorption is the small bowel. Malabsorption can occur from gross structural abnormalities, inflammatory conditions, infectious agents, or disorders of organs that elaborate enzymes essential for digestion.

In consideration of these potential causes for inadequate weight gain, 2 cardinal principles should be emphasized. First, most cases encountered in ambulatory practice will result from inadequate caloric intake,

with most of these originating in a disturbance in the parent–child feeding behavior. At one time, maternal mental health disorders were thought to account for the majority of these cases. The particular issue of maternal depression as a risk factor for failure to gain weight in infancy has received wide attention in the literature. Although case-control studies have indicated a possible association between these 2 conditions, more definitive population-based cohort studies have failed to confirm this finding. Recent analysis dissected a more subtle web of causation. The term *transactional model* allows for the complex interplay of social conditions, family interactions, and individual psychodynamics in creating feeding abnormalities. The salient feature that distinguishes infants in this category who do not gain weight at the same rate as their peers is that they take in foods with less total energy.

Second, a thorough history and physical examination is the surest route to diagnosis for the residual minority of cases not caused by caloric insufficiency. If the cause of the problem is not made clear by history and physical examination, then laboratory investigation is unlikely to reveal it.

## EVALUATION

Prompt evaluation of infants and children who do not gain weight as expected is important. The history and physical examination should be directed toward certain areas (see later discussion), and in cases in which psychosocial features predominate, most laboratory tests may be unnecessary.

## HISTORY

### Initial Approach

Every evaluation of an infant or child who is not gaining weight must begin with a thorough history. Although the history and physical examination will usually be conducted in the office, a home visit affords the pediatrician an opportunity to observe the family interaction around feeding in the context in which it normally occurs. A history of the present illness should assemble all data available from previous anthropometric measurements of the patient, including weight, height, and head circumference. Premature infants should have their measurements corrected for gestational age until 18 months of age for head circumference, 24 months of age for weight, and 40 months of age for height. The physician should begin by asking the principal caregivers how they think the baby is doing and what they believe is the problem. Knowledge of a parent's frame of mind may propel further evaluation toward or away from difficulty in parent–child interaction, including child neglect, as a potential explanation for a child's lack of weight gain.

### Feeding

A thorough feeding history is essential. Is the baby bottle fed or breastfed? How often does the child breastfeed, and for how long? Does the mother feel as though the child is sucking well, and does the baby appear satiated after he or she feeds? If bottle fed, how in detail is the formula prepared and by whom? What



is the baby's sleep pattern, and how many ounces will the baby take in a 24-hour period? Does the infant wet 6 to 8 diapers a day? Consider observing a feeding, which can be done while taking the history.

For older children, when were solids introduced? Does the parent find the child to be a *picky eater* or difficult to interest in food? Does the child drink excessive amounts of juice during the day, substituting for more calorie-rich nutrients? What are meal times like at home? Where does the child eat, and with whom? Are distractions, such as television or video games, present during meals? Is food being used for discipline or in battles over control? A 24-hour dietary recall of a typical day can often help quantify the caloric intake of the patient. If this information proves difficult to elicit, then the parents can be sent home with a nutritional diary to fill out prospectively and bring in at the next visit.

### Vomiting

The physician should inquire about any vomiting or spitting up, being sure to explore frequency, volume, and presence of blood or bile in the emesis. Gastric outlet obstructions (pyloric stenosis, antral web) often result in the generation of significant propulsive forces leading to projectile vomiting, whereas gastroesophageal reflux often results in less dramatic patterns of regurgitation. An obstruction distal to the ligament of Treitz will generally produce bilious vomiting, a symptom that must be taken with utmost seriousness in infancy because it may indicate the presence of a malrotation and midgut volvulus.

### Stools

The pattern and frequency of stooling must not be overlooked in the history of present illness. The child who has liquid stools may have a small-bowel pathologic condition, and bulky, foul-smelling stools may result from fat malabsorption. If mucus or blood is in the stools, an inflammatory condition may be present.

### Medical History

Additional information should be obtained as part of the medical history, beginning with the parents' attitudes regarding their decision to have a baby and what their experience with the pregnancy was like. Did the mother gain a reasonable amount of weight? Did she experience any illnesses during her pregnancy? Hypertension or preeclampsia will result in an infant who is small for gestational age; gestational diabetes may produce an infant with macrosomia who fails to gain weight because of postnatal cardiac complications.

The physician should ask about specific toxic exposures in utero, particularly to tobacco, marijuana, and alcohol. Tobacco may result in a small baby who rapidly catches up in weight with her peers, whereas marijuana and alcohol exert an influence on growth that may be sustained throughout childhood. Recording the child's gestational age at birth, any unusual complications of the labor and delivery, and the presence of malformations or other obvious deformities will complete this portion of the history.

### Family History

A family history should document the growth patterns of siblings; record the occurrence of fetal loss or infant deaths; review the presence in the family of immune deficiencies, neurologic disorders, or metabolic derangements; and highlight any unexplained growth deficiencies in close relatives. These findings may provide clues to the cause of the growth abnormality in the child. The results of recent comprehensive longitudinal studies from England emphasize the extent to which mean parental height and parity overwhelm the influence of traditional markers of socioeconomic deprivation that includes parental education or occupational status on the weight gain of young infants.

### Social History

The social history should focus on the availability of social supports for the parents, the existence of economic or legal circumstances that threaten the stability of the family, the nature of the relationship between the parents, and the presence of affective disorders, particularly depression, in either the mother or father. Is there substance abuse in the home, either of alcohol or drugs? Any recent disruptive events in the family's life should be explored to determine what effect they may have had on the parents' ability to care for the patient. Has there been any involvement of the family with child protective services? Finally, at this point, the physician may uncover unrealistic expectations that parents harbor regarding feeding patterns, dietary fads, or behavior in infancy, all of which provide clues to why feeding this infant developed into such a challenge.

## PHYSICAL EXAMINATION

Repeated anthropometric measurements over time constitute the most important component of the physical evaluation of children who are not gaining weight. On the initial examination, the physician should begin with observing the child's general relatedness to the parents and the examiner. Does the child appear listless, easily distractible, or irritable? Can he or she be engaged to make eye contact or to play with an age-appropriate toy? With the child completely undressed, a notation should be made of any evidence of wasting, of the presence and distribution of normal subcutaneous body fat, of muscle mass and tone, and of the presence of dysmorphic features. These observations will serve to set the stage for more detailed examination.

Particular attention should be paid to organ systems that may reflect evidence of malnutrition. The mucous membranes, hair, nails, and skin develop abnormalities in the presence of vitamin, protein, fat, and micronutrient deficiencies. The head, eyes, ears, nose, and throat may reveal conditions ranging from open fontanelles of hypothyroidism or craniotabes of nutritional rickets to the blurred disk margins of increased intracranial pressure in a child who has chronic emesis or a submucosal cleft of the hard palate in an infant who feeds poorly. Examination of the mouth may reveal extensive dental disease or a dental abscess that can be causing severe pain on oral intake.

The thyroid should be palpated gently and then auscultated for evidence of hyperthyroidism. Examination of the heart and lungs, with observation, palpation, and particularly auscultation, may reveal wheezing, rales, or heart murmurs suggestive of chronic conditions, which often result in substantial energy expenditures that outstrip the supply of nutrients available to the infant. Examination of the digits for clubbing in the older child should not be neglected. A thorough abdominal examination will identify organomegaly associated with tumor, infection, or storage disease. Intestinal distention can be associated with carbohydrate malabsorption from various causes. The neurologic examination may suggest explanations for an infant's inability to ingest adequate calories: disorders of mentation, cranial nerve abnormalities, generalized weakness, or spasticity should be carefully sought.

With infants who are not gaining weight, it can be very informative to observe a feeding. Does the parent make meaningful eye contact with the child and burp the baby appropriately? If there is any question about the adequacy of the baby's swallowing, an assessment by a speech therapist for the efficiency and safety of the swallow can be helpful.

## LABORATORY EVALUATION

In the absence of evidence from the history or physical examination indicating the need for specific laboratory testing, expectations of the yield of laboratory investigation should be modest. When charts of 185 patients who were hospitalized for failure to thrive at the Children's Hospital of Buffalo were reviewed, only 1.4% of the laboratory studies performed were found to be of diagnostic value. A similar review of 122 infants who were hospitalized at the Boston Children's Hospital revealed that a mean of 40 laboratory tests were ordered, but only 0.8% revealed an abnormality that contributed to a diagnosis.

If the cause of a child's failure to gain weight adequately remains uncertain after careful history and physical examination, then a limited number of screening studies might be considered, including a complete blood count, a blood pH, serum electrolytes, blood urea nitrogen and creatinine, a urinalysis and urine culture, and an examination of the stool for reducing substances, pH, occult blood, and ova and parasites. More extensive testing for malabsorption, endocrine disorders, occult infection, malignancy, and cardiac, pulmonary, or renal abnormalities should be done only when historical or physical examination evidence of these diagnoses is present.

## THERAPY AND FOLLOW-UP

The therapeutic approach to children failing to gain weight adequately must be tailored to the individual needs of the family and the child. For infants and children in whom a specific diagnosis was identified, therapy should be directed toward the underlying disease or condition. A disturbance in the parent-child interaction will more often be recognized as the cause of the patient's inability to gain weight. Children exhibiting food avoidance behaviors may respond well

to interventions that involve differential rewards aimed at extinguishing problematic interactions. Regardless of the underlying cause, the family should be approached nonjudgmentally, and the severity of the child's condition should dictate the initial approach to therapy.

## Mild to Moderate Undernutrition

The pediatrician, with consultation from a nutritionist, can manage infants and children exhibiting mild degrees of malnutrition (greater than 80% of ideal body weight for age) as outpatients, with occasional consultation from subspecialist colleagues. Patients who have evidence of more severe caloric deprivation will require the involvement of a multidisciplinary team, including the pediatrician, nutritionist, mental health or behavioral therapist, and social worker. Hospitalization may be necessary for a subset of these patients whose malnutrition is combined with or results from another significant medical condition. Home visitation using professionals has been demonstrated to be a useful intervention in select circumstances. Others, however, have achieved less success in generating improved weight gain with this intervention despite its other notable benefits. Child protective services must be alerted about any child thought to be the victim of neglect.

The goals of management must focus on nutritional rehabilitation, parental education, and behavioral intervention. Attempts to overfeed malnourished infants at the outset of therapy should be avoided because initially they may exhibit some degree of anorexia, and refeeding that is too vigorous may induce malabsorption and diarrhea. The refeeding regimen should be calculated to provide about 10% to 15% of calories from protein, 50% to 60% from carbohydrate, and 30% to 40% from fat.

A typical 3-phase regimen may begin with provision of 100% of daily age-adjusted energy and protein requirements based on the child's weight on day 1.

If this phase is well tolerated, in phase 2 intake is then increased to provide adequate nutrition to achieve catch-up growth. Multiplying the age-adjusted energy requirements (kcal/kg/day) by the ratio of the child's ideal body weight for height divided by the child's actual body weight at presentation will generate a reasonable estimate of the nutritional requirements for this stage. The same calculation can be made for protein requirements (Box 149-3). In most instances, the energy and protein requirements for these phases of infant refeeding can be accomplished with the use of a routine infant formula modified to increase its caloric density. Mixing 13 oz of concentrated formula with 10 oz of water rather than 13 oz of water will create a formula that is 24 cal/oz, as will mixing 3 scoops of powdered formula with 5 ounces of water. Alternatively, the use of carbohydrate in the form of glucose polymers or fat in the form of medium-chain triglycerides will add calories while avoiding the complications of overhydration. For older children, the repertoire of caloric supplements will include a wide variety of solid foods as well.

In the third, or consolidation, phase of nutritional rehabilitation, a varied diet is offered ad libitum as the

**BOX 149-3 Sample Rehabilitation Schedule for Undernutrition**

Scenario: A 6-month-old boy with poor weight gain is referred for nutritional rehabilitation. He currently weighs 5.5 kg and is 67 cm in length. The 50th percentile weight for this length is 7.7 kg, putting

the infant at 71% of the ideal body weight for height.

Normal adjustment catch-up requirements include the following:

	REQUIREMENT		FACTOR		REQUIREMENT
Calorie supplementation	100 kcal/kg/day	×	7.7 / 5.5	=	140 kcal/kg/day
Protein supplementation	2 g/kg/day	×	7.7 / 5.5	=	2.8 g/kg/day

Adding a multivitamin with iron to this child's regimen would be advisable.

child gradually approaches ideal body weight. Multivitamin and iron supplementation should be part of every refeeding regimen for undernourished children.

Initiation of nutritional rehabilitation is an ideal time to engage the parents in an educational program that focuses on family interactions, psychological vulnerabilities, and social needs. Emphasis should be placed on appropriate nutritional information, and concrete suggestions should be offered about how to structure mealtime at home to minimize distractions in a relaxed social environment that encourages good eating habits. For families in need, access to community resources such as the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) and the Supplemental Nutrition Assistance Program (SNAP, formerly food stamps) must be facilitated. Pediatricians should be prepared to advocate vigorously for patients in need of supplemental nutrition or special infant formulas when families experience difficulties in obtaining these products.

### Severe Undernutrition

Children who are less than 60% of ideal body weight for height should be hospitalized, as should any less severely undernourished child who fails to respond to appropriate outpatient management with adequate weight gain. They should be cared for by a multidisciplinary team of nutritionists, social workers, pediatricians, and pediatric subspecialists, with attention to avoiding the refeeding syndrome with its attendant morbidity. The nutritional rehabilitation of these children will be more prolonged and may entail a period of tube feedings in addition to oral supplements. In cases in which the gastrointestinal tract is temporarily inaccessible, parenteral feedings with central venous access may be necessary. The laboratory evaluation of these patients will also need to be more intensive, with appropriate surveillance of potential electrolyte disturbances that can accompany initial refeeding if it is pursued too aggressively.

### Follow-up

Once identified, poor weight gain in infancy should be followed up assiduously. Initial weekly visits for infants may be necessary to reassure the parents and physician that the therapy undertaken is having the

desired effects. Studies of hospitalized children demonstrate that those younger than 6 months, when provided with adequate calories, begin to gain weight in a few days. Older children may take longer than their younger counterparts before sustained weight gain is established. Ongoing developmental, behavioral, and social evaluations must be incorporated into any plan for follow-up. Abnormalities in these domains need to be monitored closely because they are frequently present in patients who gain weight poorly. Moreover, the lingering effects of calorie, protein, and micronutrient deprivation may show themselves in developmental and behavioral abnormalities, particularly in families in which the mothers exhibit affective disorders.

### PROGNOSIS

Outcomes for children who have abnormal weight gain patterns in infancy and childhood should be predicted cautiously in view of the variety of conditions that may give rise to this clinical picture and the lack of high quality data on which reasonable predictions might be sustained. A systematic review of 13 long-term longitudinal studies of children with failure to thrive lamented these methodologic challenges but concluded that the growth and neurocognitive outcomes in these children probably do not differ substantially from their unaffected peers. A less sanguine view was taken by an extensive review of the literature conducted by the Agency for Healthcare Research and Quality, which concluded that children with failure to thrive in infancy are likely to suffer immunologic, behavioral, cognitive, and psychomotor developmental deficits that persist despite interventions. Such disparate findings suggest that most children in the mild category will experience brisk nutritional rehabilitation and, with adequate follow-up, will do quite well. More severely affected children, depending on the cause of their condition, may require more prolonged or repetitive interventions and may be left with residual cognitive, behavioral, and educational consequences of their malnutrition. There is some evidence that intense interventions, including weekly home visitation programs, can, at least in controlled circumstances, attenuate the anthropometric deficiencies that might otherwise result from

significant undernutrition in infancy. In light of these findings, all children who exhibit faltering weight gain during infancy and childhood absolutely must receive early comprehensive evaluation and prompt treatment.

### WHEN TO REFER

- Diagnosis is made of a chronic disease pertaining to a subspecialty such as cardiology, pulmonary medicine, nephrology, gastroenterology, or endocrinology
- Psychosocial family dynamic indicates a need for psychiatric intervention for either or both parents
- Nutritional rehabilitation warrants the attention of a nutritionist
- Provider is concerned about intentional starvation or neglect, a referral to Child Protective Services must be made

### WHEN TO ADMIT

- Any child with a weight less than 60% of ideal body weight
- Any child who, despite appropriate outpatient management, continues to fail to gain weight at an acceptable rate
- Any child who presents with signs of marasmus or severe protein malnutrition (kwashiorkor)
- Any child for whom the provider believes a period of close, continuous monitoring would be helpful

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Childhood Nutrition* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/healthy-living/nutrition/Pages/Childhood-Nutrition.aspx](http://www.healthychildren.org/English/healthy-living/nutrition/Pages/Childhood-Nutrition.aspx))
- *Making Sure Your Child Is Eating Enough* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/healthy-living/nutrition/Pages/Making-Sure-Your-Child-is-Eating-Enough.aspx](http://www.healthychildren.org/English/healthy-living/nutrition/Pages/Making-Sure-Your-Child-is-Eating-Enough.aspx))

### Medical Decision Support

- *Growth Charts—Girls* (chart), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Growth Charts—Boys* (chart), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Growth Charts—Interactive Tutorials* (Web site), Centers for Disease Control and Prevention ([www.cdc.gov/growthcharts](http://www.cdc.gov/growthcharts))

## AAP POLICY

Block RW, Krebs NF; American Academy of Pediatrics Committee on Child Abuse and Neglect and Committee on Nutrition. Failure to thrive as a manifestation of child neglect. *Pediatrics*. 2005;116:1234–1237. Reaffirmed May 2009 ([pediatrics.aappublications.org/content/116/5/1234](http://pediatrics.aappublications.org/content/116/5/1234))

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## Chapter 150 FAMILY DYSFUNCTION

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## INTRODUCTION

Theories of child development have long recognized that children in modern Western cultures require approximately 2 decades of life to achieve the self-sufficiency necessary for separation from their families. Because of this relatively prolonged dependency and because adverse childhood experiences negatively affect the developing brain and long-term health outcomes, the functioning of the family is of utmost importance for optimal development and well-being of the child.

Complex sociocultural changes continue to redefine the family, with fewer “traditional” households that historically have consisted of 2 married biologic parents located near extended family members for support. Single, divorced, remarried, same-gender, foster, and adoptive parents are commonplace. Children may also experience multiple, changing parental figures if grandparents assume their care or if biologic parents move on to new partners. Many children have half-, step-, or foster siblings. Particularly in times of economic hardship, families may move in together or experience frequent changes in composition.

In the case of separation or divorce, children often live between 2 different households. Children may also be separated from a caregiver for prolonged periods because of parental employment, illness, or incarceration. The mobility of Western society has resulted in the geographic isolation of many nuclear families from extended family support. Oftentimes, nonrelatives assume the roles of extended family members.

Many children have a family that changes dramatically over time. As a result, family may be defined less by composition and more by functional relationships. In fact, the American Academy of Family Physicians (AAFP) states, “The family is a group of individuals with a continuing legal, genetic and/or emotional relationship.” The AAFP additionally asserts, “Society



relies on the family group to provide for the economic and protective needs of individuals, especially children and the elderly.” When children are involved, the most important function of the family is to provide a safe and caring environment in which the child can grow and develop into a healthy adult.

## FAMILY CHARACTERISTICS

Families function in complex and multifaceted ways, with family members tending to assume various roles that interplay. Changes in the functioning of an individual member affect the family unit, and changes in the family unit affect the individual members and their interactive roles. As a result, a variety of internal and external factors may influence the functioning of a family, and some families are more adaptable and resilient than others.

Healthy families have well-defined roles (ie, parent or child). Members freely ask for and provide attention, but boundaries are respected. Rules tend to be explicit and remain consistent, but with some flexibility to adapt to the individual. Communication is encouraged, and emotional expression is accepted. Security in relationships allows individuals to explore their own interests, and individuation is encouraged. As individual members grow and develop, the family as a unit adapts, also experiencing ongoing intrinsic growth and development over time, which is a sign of health.

All families experience misunderstandings, conflicts, and stressors at some time. Stressors may be internal (eg, illness, change in composition) or external (eg, financial insecurity, relocation). Healthy families cope with difficulties and maintain a sense of connectedness, which fosters a sense of security, self-worth, and competence in their children.

## PARENT CHARACTERISTICS

For the child, the most critical characteristic of a healthy family is an adult who functions as caregiver. In fact, the most important contributory factor regarding children’s resilience is the presence in their lives of at least 1 consistent, caring adult. This adult not only addresses safety and basic needs, but also shares an emotional connection with the child, conveying the sense that she has intrinsic value and is loved.

When 2 (or more) caregivers are involved, the relationship between them is exceptionally important. A supportive and flexible partnership fosters good parenting. Even those with very different backgrounds, knowledge, and attitudes can provide a consistent and united approach without undermining each other.

Specific parental practices do not have to be perfect. Although some are more intuitive than others, people with a variety of abilities, personal backgrounds, and personality types can be good parents. However, there are certain characteristics of maturity that are necessary for optimal caregiving—the ability to care for oneself, a sense of self-worth, the ability to emotionally connect with another person, a sense of responsibility, and a degree of selflessness. Healthy parents do not desire a child to fix something in their own lives or relationships.

Parenting styles depend on many factors, including the parent’s emotional health, experience in their own family of origin, and experience in the parental role, as well as the influence of or compromise with other adults assuming a co-parenting role, culture, and socioeconomic factors. Some traits are more enduring, but parenting styles may be dynamic because of these changeable influences. The needs and temperament of a particular child may also result in variations in parenting. Conversely, children may vary in their response to parenting styles because of their developmental stage, temperament, and degree of resilience.

A parent who can maintain a healthy caregiver role helps the child develop a sense of self-worth and competence, learn to maintain appropriate interpersonal relationships, and plan for her independent future.

## Effects of Parenting Styles

Certain parenting styles are characteristic of healthy families. A caring yet authoritative parent will be attentive to the child and responsive to his needs, yet set consistent and developmentally appropriate expectations. Emphasis is placed on the parent-child relationship and communication, and discipline is provided in a constructive fashion that fosters the child’s learning and self-control. Growing up in a context of guided yet growing autonomy, these children demonstrate more academic mastery, social and moral maturity, self-regulation, and sense of self-worth as they reach adulthood.

Conversely, some parenting styles may have less favorable outcomes. Authoritarian parents satisfy their own need for control by granting little autonomy while also remaining less interpersonally involved with the child. Expectations for behavior give poor consideration to the needs or developmental abilities of the child, who learns over time that approval and affection may be conditional and unpredictable. Consequently, these children typically have poor self-esteem, are withdrawn and anxious, lack in resourcefulness, and are easily frustrated. They reach adulthood with much less mastery, and often exhibit dependent or aggressive behaviors as adults. Not only are these children at high risk for maltreatment, but they are also at high risk for perpetuating the cycle of maltreatment when they have children of their own.

Alternatively, parents may relinquish their authoritative parental role if they are distracted by their own needs or insecure in their parent-child relationship. The resultant permissiveness, whether arising through inattentiveness or overindulgence, grants the child developmentally inappropriate autonomy, adversely affecting their ability to delay gratification and work to meet their own needs. These children enter adulthood with less academic and interpersonal mastery, resulting in less self-control and more demanding and disruptive social behavior.

Parents may also be relatively uninvolved, either from their own emotional detachment or from being overwhelmed by the stressors of their own lives. In the extreme form, this may present as true neglect, and the child may have developmental delays in a variety of areas, including interpersonal attachment. Growing up with little support or discipline, these

children often reach adulthood with little emotional, academic, or interpersonal mastery, demonstrating poor self-esteem and antisocial behaviors.

## **FAMILY DYSFUNCTION**

Difficult life circumstances may stress family functioning. If these circumstances are short-lived or less severe, healthier families adjust and persevere in their developmental tasks. When families become overwhelmed, composition is unstable, individual members are emotionally unhealthy, roles and boundaries are blurred, or communication is impaired, families may function in variations of chronically maladaptive patterns. When a parent figure fails to maintain a healthy parent role, the child's emotional health and development suffer, with potentially lifelong consequences.

Dysfunction can be subtle or severe. However, consequences of these problems affect almost all aspects of a child's life, including relationships, emotions, behavior, learning, the acquisition of coping skills, and psychological development. Instead of developing a sense of self-worth and competence, the child incorporates self-doubt and insecurity. The child has difficulty developing trust and the balanced give-and-take of healthy relationships. In severe cases, chronic disappointment and frustration lead to hopelessness and limited expectations for the future.

## **PATTERNS OF DYSFUNCTION**

Parental dysfunction typically exists in certain core areas. The parent who lacks the desire or ability to emotionally connect with and appreciate the child causes the child to feel devalued and unlovable, undermining the development of healthy attachment. The insecure parent may be overcontrolling in an effort to demonstrate his or her authority, be permissive in an attempt to ensure the child's love, prioritize a partner over caring for the child, or use the child to meet her own needs. The parent who cannot consistently care for him/herself cannot consistently care for the child, resulting in the child's feeling insecure and frustrated. In severe cases, the roles may become reversed, with the child becoming parentified. These characteristics may manifest themselves in many circumstances, but are especially predictable in certain patterns.

### **Uninvolved Parent**

The uninvolved or "inaccessible" parent may be preoccupied with his career, relationships, or community status. As our culture continues to change, even very committed parents may fall into routines that allow less time for their children. They may become caregivers for their own parents or seek new educational or employment opportunities. Families may easily become overscheduled, being "together" disproportionately in a social context rather than as a family unit. In addition, technology frequently replaces, rather than enhances, true interpersonal interaction and communication.

### **Over-involved Parent**

Conversely, parents may become over-involved for multiple reasons. Commonly, parents attempt to

relieve their own youth through their children's activities and status, and may allow little individuation or have unhealthy expectations. Additionally, societal factors have resulted in an extreme focus on achievement, and many children grow up in a culture of extreme competition. Even the possibility of failure may be perceived as an unbearable threat to self-worth, despite the fact that optimal development depends on the child's learning by trial and error. Less secure parents may become overprotective and try to lessen either the risks or the consequences for their children. As a result, the child tends to become less self-reliant, have unrealistically entitled expectations for life independent of the family, blame others rather than learn personal responsibility, paradoxically develop a decreased sense of competency, and consider self-worth to be conditional rather than intrinsic.

### **Divided Loyalties**

When power struggles exist in the family, the child may be put in the middle of the conflict. This is especially true in cases of divorce, in which the parents or extended family members may harbor a great deal of unresolved hurt and animosity. The child, now especially vulnerable and insecure as the family restructures, may be considered a trophy, used as a conduit of information, or forced to choose sides. Children tend to blame themselves for the parents' divorce, and often learn to consider love and relationships as conditional. Frequently, they live with unresolved grief. If parents cannot model appropriate conflict resolution, children often become bullies or victims of bullying.

### **Blurred Roles or Boundaries**

If a parent becomes vulnerable (ie, from illness, addiction, financial insecurity, loss of a relationship, or interpersonal violence), the child also becomes vulnerable. Not only has the child lost a degree of support, but the child often takes on a degree of worry about the parent. If stigma is associated with parental impairment (ie, addiction or mental illness), the child may receive little information or guidance to deal with their confusion, fear, and shame over the parent's circumstances. Many children are unable to develop close relationships because of feelings of loneliness and helplessness.

Blurred parent-child roles or boundaries may occur in a variety of circumstances. When a parent is significantly impaired or when a child loses a parent through death or divorce, the child may become parentified, taking on tasks, concerns, and family roles more appropriately associated with an adult caregiver. This typically results in a tremendous amount of stress and can interfere with his or her developmental tasks.

## **PRESENTATIONS IN THE PRIMARY CARE SETTING**

Physicians caring for children should be mindful of family functioning as it affects the well-being of the children both physically and emotionally. This is

especially true in the setting of the medical home, where a physician with an ongoing relationship with the child and family coordinates continuity of care. The American Academy of Pediatrics (AAP) Task Force on Mental Health has recommended that children's health supervision visits routinely include psychosocial screening of the family, as well as the child. However, any encounter provides an opportunity for assessment and intervention as indicated.

Family dysfunction may present in a wide variety of ways in the primary care setting. The appropriateness of physical care is typically more obvious, as the physician assesses safety, growth and development, general health, and medical care. The family who has trouble keeping appointments or completing treatment may be showing signs that the parent is overwhelmed or that there are other barriers to care.

The child in a struggling family often develops signs of stress, which may manifest physically (eg, frequent somatic complaints) or emotionally (eg, mood or behavior changes). Changes in sleep, appetite, energy, motivation, self-care, school achievement, recreational pursuits, or social interactions are cause for some degree of further exploration. Often, parents are unaware of the child's internal distress until external behavior problems (eg, irritability, aggression, school failure, drug use, self-injury) arise.

When family disturbance is severe, maltreatment may occur. Pediatricians and other physicians receive formal training in the detection of child abuse and neglect, and are uniformly considered to be mandated reporters for child welfare agencies. However, families (including the victim) often conceal abuse or neglect, necessitating a high index of suspicion. Chronic maltreatment, especially sexual abuse, may only be detected by specific investigation.

The growing tendency of families to use emergency departments and urgent care centers in addition to (or instead of) a medical home setting (or even the practice of seeing more than 1 physician within a clinic) undermines continuity of care, and may also mask the degree of dysfunction. The use of multiple physicians should alert the physician to increase vigilance. Appropriate documentation is vital, and forms for release of information facilitate communication among treating physicians.

## THE PHYSICIAN'S ROLE

Family dynamics are complicated, and patterns of interaction can become quite ingrained. However, support for families can have a profound, positive, and enduring effect for children and those in their lives. For the primary care physician, attention to family functioning is inextricably linked to practice, providing many opportunities for supporting the development of healthy families as well as for addressing problems as they may arise.

Indeed, the physician-family relationship provides a unique opportunity for positive influence. Families are built on relationships, and the physician supports the family by first developing a therapeutic alliance with the child and caregiver. In this important position, the physician affirms intrinsic dignity and

self-worth by modeling healthy, respectful interactions with each.

The preventive aspect of primary care integrates routine anticipatory guidance. This helps parents understand their children, guides them through appropriate caregiving practices, and promotes healthy aspects of family development. Over time, the physician gains understanding of differences in personalities, expectations, and the culture of parenting within the family. This allows further customization of care, with recognition of strengths and anticipation of needed support.

In addition to office visits, most physicians provide supplemental educational material and refer families to parenting classes as available. Some physicians incorporate group checkups or classes of their own to facilitate discussion, involve extended family members, and engender parent-to-parent support. When family problems are apparent, the physician may build on the above practices, remaining constructive and supportive.

The timing of well-child visits correlates with the transitional challenges of various developmental stages. Additional visits may be indicated for circumstances that challenge family members, such as the occurrence of night terrors or the experience of divorce. An up-to-date social history is invaluable.

The physician who is sensitive to parental development may prevent problems that arise from misinterpretation ("My baby cries because he doesn't like me"), unrealistic expectations ("He should be toilet-trained by now"), parental self-doubt ("I feel so guilty going back to work"), discipline ("He just needs a good spanking"), and cultural issues ("My father thinks we spoil her").

The need for anticipatory guidance remains dynamic, even as the child matures and seems to be more self-sufficient. Each child is unique, and may challenge a parent in ways a sibling did not. A new parental influence or attitude may be introduced (such as through a remarriage/new partner, more contact with a grandparent, or a new child care or classroom setting). Misinterpretation by a caregiver may become quite problematic (even to the point of maltreatment) if a child is labeled "oppositional," "bossy," "mean," "moody," or "lazy," especially if there is little consideration of the factors that may overwhelm the child and keep him from successfully adapting to the demands of his daily tasks. What seems to be "nothing" to an adult may mean much more to a child.

Many factors that influence parenting behavior may not be readily apparent, even to the parents themselves. A particular age or situation may present a special challenge to a parent who similarly struggled (ie, a mother who was assaulted, or a father who became overdependent on athletic competition for a sense of self-worth).

Typically, family roles are learned in the family of origin. However, rapid cultural changes may result in much different family structures, needs, dynamics, and practices. Commonly, struggles within the family of origin resurface when the now grown child begins a family of her own. Even in the best of circumstances,

there is some degree of differing opinion in regard to parental practices. Clearly, the physician who monitors family development and provides appropriate intervention provides a tremendous support to parental efficacy, child development and sense of self-worth, and overall family health.

For any clinical encounter, the interpersonal interaction is of great importance. However, it is even more so for a family that is struggling. The physician may be among the few consistent supports for the family. Although families typically place trust in the physician who cares for their child, this should not be taken for granted. In fact, there are many cultural stereotypes (ie, industry influence, overuse of medications) that may cause a family to be wary of their physician or treatment recommendations. One should always listen carefully to what the family is truly communicating and confirm shared understanding of the purpose of the visit.

Even if the child is the family member considered to need help, parents may be quite frustrated or ashamed of their perceived failure, and subsequently quite sensitive to any implied criticism. The physician should remain nonjudgmental, acknowledging the parents' care for their child and expressing the desire to problem-solve with them. The physician can both model respectful interactions and constructively guide interactions between family members during the office presentation.

Typically, several techniques are employed. Emotional effect is acknowledged. ("That must have been quite upsetting.") Expectations are clarified. ("We won't use that type of language.") Communication is fostered. ("I feel that we pay attention to each other better if the cell phone is put away.") Positive actions are encouraged. ("I like the way that you followed through with the consequences.") Education is provided.

It is important to have the appropriate family members present and to ensure that each has a chance to be heard. Even if the physician disagrees with a statement or considers an emotion to be unwarranted, it is important to acknowledge an understanding of the perspective being communicated. Disagreement between any participants should be made transparent, with the goal of seeking a common point of agreement upon which to proceed. Problem-solving should be as concrete, achievable, and action-centered as possible. The "next steps" should be agreed upon and documented as specifically as possible ("We will turn off the computer an hour before bedtime.") It is important to acknowledge family strengths, efforts, and successes.

Physician-family interaction may range from a longer, prescheduled, and defined "family meeting" to a few minutes of conversation during a well-child or an acute-care visit. If the allotted time does not seem to be sufficient to the task, this should be acknowledged, with agreement on the acute priority of the day. In this fashion, the physician can accommodate a variety of methods to work with families while still working within the schedule constraints of a clinical practice. By the end of a particular encounter, however, one

should always try to understand the situation as clearly as is feasible, ensure safety, have an agreed-upon plan for the "next steps," and have scheduled follow-up.

Physicians vary a great deal in regard to personality, style of practice, experience, training, abilities, and motivation to work with families. This is especially true when working in challenging situations. Many already feel overtaxed by time constraints, documentation, and other work-related demands. Subsequently, it can be quite daunting to address additional levels of complexity when working with patients and their families. However, techniques can be customized across a variety of practice settings, presenting situations, and professional skill levels.

It is critical for the physician to understand, define, and communicate their own role. Caregivers by nature, physicians may have varied emotional responses to the patients and families in their care. Although families can be a source of joy, they may also engender sadness or other emotions that may not be as transparent. Professionals may feel frustrated with families who do not facilitate care or who challenge their skill level. They may feel anxious in sensitive or disagreeable situations, or feel dislike or anger towards certain patients or family members. They may be even more vulnerable to distress or countertransference in circumstances that resonate with their own life experiences. Often, the needs of the family seem insurmountable or can only be met with resources far outside of the physician's scope of practice. Subsequently, the effective physician needs a certain degree of self-reflection to provide insight into her own emotions and behaviors, and must acknowledge tendencies for minimization or avoidance, maintain appropriate boundaries, develop reasonable expectations for her work, and determine the need for additional resources and support.

As adult learners, physicians monitor their own "practice gaps" and seek information accordingly. A variety of resources is available to enhance the knowledge and skills that facilitate working with families. In addition to the traditional written resources, organizational toolkits, workshops, and mentoring opportunities support the incorporation of knowledge and skills into clinical practice.

Physicians will be most effective if they also use educational and community resources for both children and the adults. There are many books, support groups, and Internet resources for common problems (eg, divorce, bereavement, alcoholism, violence). Families with significant and chronic dysfunction will typically benefit from the specific ongoing guidance of family therapy, and the physician should be aware of local mental health resources. When referral to additional physicians is warranted, personal attention to family engagement will greatly facilitate follow-through with the recommendation.

The AAP Task Force on Mental Health has recommended that physicians develop "common factors" communication skills to elicit an accurate understanding, identify and address any barriers to the care and



follow-up of identified problems, and build a therapeutic alliance with the child and family. Such skills have been shown to be readily acquired by experienced physicians and effective across a wide range of psychosocial problems presenting commonly in the primary care setting.

## CONCLUSION

Family dynamics are complex and vulnerable to a variety of influences. Pediatric practice, however, provides a unique and powerful opportunity to guide not only the development of healthy children, but the development of healthy families as well. By understanding both adaptive and maladaptive patterns of behavior, the primary care physician can prevent problems, detect issues as they emerge, and intervene at early stages. By honing communication skills, using professional resources, and identifying community services, the physician can offer support, provide appropriate materials, and coordinate referrals for more specialized care. This results in profound benefits for children and their families, with the potential to affect generations to come.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Connected Kids (Violence Prevention)* (handouts), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

### Medical Decision Support

- *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* (toolkit), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Promoting Mental Health* (guideline), American Academy of Pediatrics ([brightfutures.aap.org/3rd\\_Edition\\_Guidelines\\_and\\_Pocket\\_Guide.html](http://brightfutures.aap.org/3rd_Edition_Guidelines_and_Pocket_Guide.html))
- *The Resilience Project* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Medical-Home-for-Children-and-Adolescents-Exposed-to-Violence/Pages/Medical-Home-for-Children-and-Adolescents-Exposed-to-Violence.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Medical-Home-for-Children-and-Adolescents-Exposed-to-Violence/Pages/Medical-Home-for-Children-and-Adolescents-Exposed-to-Violence.aspx))

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## Chapter 151

# FATIGUE AND WEAKNESS

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## DEFINITIONS

Fatigue and weakness are ubiquitous complaints that may or may not be related to medical diagnoses but are used commonly in medical and colloquial language. Both terms are difficult to define. To add to the confusion, both patients and physicians often use the 2 concepts interchangeably. Moreover, adolescents and children often use other terms to describe their perceptions of somatic weakness and fatigue. Fatigue, in fact, is very different from true body weakness. Therefore, defining the 2 terms carefully is important, although the definitions must be modified for each age group.

*Fatigue* involves extreme and unusual tiredness, decreased physical performance, and an excessive need for rest. It often is accompanied by feelings of sleepiness, weariness, irritability, lassitude, boredom, and decreased efficiency. *Weakness*, in contrast, refers to diminished body or muscle strength, either the inability to generate force or maintain force (stamina), or both. True weakness can be identified only by demonstration of abnormal neurologic or muscular function based on history, physical examination, or laboratory techniques. Practically speaking, a history of weakness, on further questioning, will often suggest hypotonia in infants and will be expressed in older children as trouble running or keeping up in gym class, clumsiness, or lack of agility.

## ETIOLOGY

### Fatigue

Fatigue may be a normal result of any physical or mental work in which energy expenditure exceeds the restorative processes. The temporary fatigue that follows intense exercise involves several complex mechanisms, including increased central inhibition mediated by group III and IV muscle afferents along with a decrease in muscle spindle facilitation and suboptimal cortical output. At the level of the muscle cell, fatigue results from a reduction in adenosine triphosphate caused by high utilization rates, as well as a depletion of glycogen. Normal fatigue also follows activities such as cramming for examinations and occurs with food or sleep deprivation. In all of these instances, the degree of fatigue, even when prolonged, is usually appropriate for the amount of physical or mental exertion expended.

On the other hand, fatigue may be a pathologic state with an organic or psychological foundation. The lassitude associated with somatic illness, often with definable physical or laboratory abnormalities, is well known. Fatigue has also been shown to have a strong correlation with the psychiatric diagnoses of depression and anxiety disorder. Any acute illness or trauma

may be accompanied by fatigue, but only prolonged fatigue is usually noteworthy.

### Weakness

True weakness in a child should always be a cause of concern. Weakness is the result of a derangement of neuromuscular function at one of several levels, including the cerebral hemispheres, cerebellum, spinal cord, anterior horn cells, peripheral nerves, myoneuronal junction, or muscle.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of prolonged fatigue is listed in Box 151-1. Box 151-2 lists some of the differential diagnoses for weakness in children.

### Fatigue in Infants

The term *fatigue* is rarely pertinent for infants. However, parents sometimes report that their infant tires easily during feedings or seems droopy. Infants who are in heart failure often appear to tire easily and sweat excessively with feedings. Infants who have other serious conditions, including severe anemia and hypothyroidism, may also be described by their parents as being listless.

### Fatigue During Childhood

Children complain only infrequently of feeling fatigued. Remarkably, even with chronic organic diseases, the child does not express fatigue itself verbally. Rather, concerned parents usually report that the child appears fatigued. Parents commonly make such statements as, "He has no energy," "She lies around all the time," "She seems bored and droopy," "He's sleeping a lot of the time," "She has no pep," "He drags around," or "I can't get her to do a thing." On questioning, younger children occasionally express a sense of lassitude and fatigue to their pediatrician. Much of the difficulty in the middle years of childhood (before adolescence), however, is children's inability to put into words what they feel. Fatigue, therefore, is usually exhibited in terms of a child's physical activity and performance in school, sports, and other organized activities. The younger the child, the more likely that the expressed or observed fatigue has a pathologic basis.

### Recurrent or Chronic Infection

The most common problem associated with fatigue in children is recurrent or chronic infection. Otitis media, sinusitis, and tonsillitis of a recurrent and smoldering nature are often overlooked for their systemic effects, among which fatigue may be prominent. Often mistakenly considered insignificant, upper respiratory tract allergies may cause impressive fatigue, irritability, and mild depression in children and adolescents.

### Endocrine Disorders

Of the common endocrine disorders, only hypothyroidism is likely to be associated with fatigue. Certainly, a child with hypothyroidism whose rate of growth has fallen off may exhibit increasing fatigue and lassitude, at first subtle, as the only symptoms. Thyrotoxicosis, in contrast, is uncommon in young

## BOX 151-1 Disorders Commonly Associated With Prolonged Fatigue in Different Age Groups

### INFANCY

- Cyanotic heart disease
- Congestive heart disease
- Severe anemia
- Hypothyroidism

### CHILDHOOD

- Chronic upper respiratory tract infections
- Otitis media and sinusitis
- Tonsillitis
- Chronic asthma
- Chronic allergies
- Hepatitis
- Rheumatic fever
- Disseminated malignancy
- AIDS
- Immunologic disorders
- Chronic renal disease
- Obstructive sleep apnea

### ADOLESCENCE

- *Mycoplasma* and other viral pneumonia
- Infectious mononucleosis
- Hepatitis
- Juvenile idiopathic arthritis
- Systemic lupus erythematosus
- Diabetes mellitus types 1 and 2
- Malignancy
- Inflammatory bowel disease
- Addison disease
- Drug abuse, including alcoholism
- Chronic pulmonary disease
- Juvenile primary fibromyalgia
- Obstructive sleep apnea
- Narcolepsy
- Depression
- Severe obesity

## BOX 151-2 Differential Diagnosis of Weakness and Hypotonia

- Down syndrome
- Spinal muscular atrophy
- Muscular dystrophies
- Congenital hypothyroidism
- Botulism
- Myasthenia gravis
- Guillain-Barré syndrome
- Juvenile dermatomyositis
- Polymyositis

children but occasionally produces isolated fatigue in adolescents.

### Diabetes Mellitus

Although any metabolic disorder can cause fatigue, only diabetes mellitus occurs with enough frequency

to merit consideration. Fatigue almost always accompanies the initial or uncontrolled diabetic state.

### **Inflammatory Diseases**

Inflammatory diseases, especially juvenile idiopathic arthritis and other rheumatologic disorders, appear frequently in pediatric practice, and many children have significant fatigue, out of proportion to their musculoskeletal complaints. Lyme arthritis is a notable example.

### **Pulmonary Disease**

Cyanotic heart disease and chronic advanced pulmonary disease, as seen with cystic fibrosis, are commonly associated with marked fatigue; in these cases, however, the underlying disease is usually readily evident before the fatigue becomes severe. The pediatrician may occasionally see an older child for the first time who has severe fatigue caused by a previously undiagnosed hypoxic disorder.

### **Anemia**

Overall, the condition thought to be present most often as a cause of fatigue in both children and adults is anemia—usually, incorrectly so. Although fatigue is often ascribed to mild or moderate anemia, from whatever source, symptoms are usually not seen in children until the hemoglobin level falls to 6 or 7 g/dL; if red blood cell counts decrease gradually, then even lower hemoglobin levels may ensue without clinically evident symptoms. Irritability and attention problems may be present with mild to moderate iron deficiency anemia, but fatigue is usually not a common feature. Younger children especially seem to tolerate incredibly low hemoglobin levels with no symptoms at all.

### **Malignancy**

Malignancy, particularly leukemia or lymphoma, occasionally develops insidiously, with fatigue as the major symptom. Although always feared, these diseases are seen infrequently in pediatric office practice.

### **Emotional Disorders**

Many children who come to the pediatrician with unexplained chronic fatigue are found to have an emotionally related disorder. Before adolescence, the complaint usually centers on the parents' concern about a child's reduced activity level. A younger child will be noted to prefer sedentary activities—to "lie around the house a lot," appear tired, lack energy, and shrink from social contacts. These traits may have been longstanding, but a comment from grandparents or a teacher may arouse parental anxiety, precipitating the first visit to the pediatrician.

At this point, the family is often convinced that the child has a serious organic disease. Further evaluation, however, usually reveals that the child is performing very satisfactorily but not up to the family's excessive expectations. The child may be withdrawing because of failure to compete with an exceptional sibling or because of real or imagined failure in school. In other cases, a child may feel a lack of well-being because of parental discord. Similarly, lack of parental

involvement with a child may lead to lassitude and boredom. Stress and anxiety in children often result in either hyperactivity or withdrawal, and the more common withdrawal reaction may express itself as chronic fatigue.

Most children experience transient periods of lassitude or fatigue, but such instances are brief and usually self-limited. At the opposite extreme is the child whose chronic fatigue is a sign of true psychiatric depression. In this case, as in the adolescent, the more protracted and severe the periods of withdrawal, the more likely that depression and fatigue are caused by a pathologic process.

### **Fatigue in Adolescents**

Complaints of chronic fatigue are encountered most often in adolescents. The normal swings in adolescent moods, from excessive exuberance to fatigue, are usually of more concern to parents and teachers than they are to the patient. In many instances, the adolescent may disagree vehemently with the parents' view and not share their concern. Adolescents, however, also initiate visits to their pediatrician because they feel fatigue. Parents may be unable or may refuse to recognize the adolescent's symptoms. Whereas a younger child who has a profound medical illness often does not experience fatigue, even minor illnesses often precipitate prolonged fatigue in adolescents.

### **Viral Illnesses**

*Mycoplasma pneumoniae* infection, often low grade and without fever, produces progressive fatigue. In addition, prolonged viral and parasitic illnesses (eg, infectious mononucleosis, hepatitis, cytomegalovirus infection, toxoplasmosis) commonly produce fatigue, especially in adolescents.

### **Infectious Mononucleosis**

The terms *chronic infectious mononucleosis* and *chronic fatigue syndrome* have become popular with both physicians and the media. This attention has led to misuse of these terms, as well as, undoubtedly, mild mass hysteria among young adults and adolescents who now are convinced they have one of these disorders. Most adults and many infants and children have been infected with the Epstein-Barr virus (EBV). The clinical manifestations in proved cases are extremely variable; some patients remain symptom free, whereas clinical, hematologic, and serologic findings support the diagnosis of infectious mononucleosis in others. The symptoms of infectious mononucleosis usually resolve in several weeks, but an occasional patient may have an atypical or a more prolonged course in which the initial clinical findings either persist or are intermittent over a period of months or, in rare cases, years. These unusual but documented cases of chronic infectious mononucleosis typically include complaints of chronic fatigue. Another much smaller group of patients has been described as having a serious, sometimes lethal, illness associated with EBV infection. These patients usually do not exhibit the classic findings of infectious mononucleosis; their conditions are often proved to be either acquired or genetically determined immunologic abnormalities.



### Other Conditions

Always unpredictable and often insidious in its onset, inflammatory bowel disease may arouse concern initially with unexplained fatigue and a loss of sense of well-being. Although eventually accompanied by fever, abdominal symptoms, or abnormal stools, this disorder can continue for months, with fatigue as the only major symptom. The possibility of Addison disease should be considered in children or adolescents who have unexplained fatigue and associated weakness, anorexia, nausea, vomiting, or weight loss. Of more current importance in older children and adolescents are alcoholism and drug abuse—causes of chronic fatigue that are easily overlooked.

### Emotional Disorders

By far, adolescents are the patients who most commonly complain of fatigue. Pediatricians can expect to see a generous number of adolescents who characteristically appear each spring complaining of fatigue or lassitude and lack of energy and seem mildly depressed. This disorder usually appears during periods of greatest school-related stress, such as before examinations. Although the patient may have a fever, usually caused by infection (eg, infectious mononucleosis, influenza), the cause of fatigue is usually emotionally based.

In many instances, the adolescent collapses with fatigue after intense and exuberant activity involving schoolwork, extracurricular activity, sports, or social events. These individuals may also be short on sleep, have unhealthy eating habits, and complain of an additional variety of hypochondriacal symptoms. Burnout and fatigue are particularly common in overachieving high school and college students during late adolescence. The emotional reaction may actually be precipitated by a physical illness, particularly an infection. Most of these patients have normal findings on physical examinations and routine laboratory tests.

### Chronic Fatigue Syndrome

Since 1985, adolescents, adults, and, occasionally, children have been described as having a disorder referred to as *chronic fatigue syndrome* (CFS), which most commonly involves persistent or relapsing severe fatigue, fever, headache, sore throat, tender lymphadenitis, nausea or vomiting, myalgia, arthralgia, and abdominal pain. Neurocognitive complaints, such as an inability to concentrate, sleep disturbances, episodic confusion and memory problems, depression, anxiety, and irritability, are also especially common in CFS.

The neurocognitive complaints are the most difficult to evaluate in CFS because of the extreme difference in emotional perception from person to person. Furthermore, careful physical examinations by experienced physicians often fail to document any physical abnormalities, and extensive laboratory evaluations usually produce normal results. In addition, much of the difficulty surrounding both the diagnosis and the search for a cause of CFS is attributable to confusion about the use of the terms *chronic fatigue* and *chronic fatigue syndrome*. Consequently, in 1994, the Centers for Disease Control and Prevention (CDC) formulated

strict criteria for the case definition of CFS. Unfortunately, these criteria were based mainly on observations of adult populations and may not be completely pertinent to children and adolescents.

Nevertheless, the CDC criteria for CFS stipulate that the debilitating fatigue must last at least 6 months in addition to the presence of 4 or more symptoms (such as muscle pain, tender lymphadenopathy, headaches, arthralgia, pharyngitis, impaired memory or concentration, low-grade fever, postexertional malaise, and sleep disturbances). Although the CDC criteria exclude most past or current major psychiatric disorders, they allow some comorbid psychiatric symptoms, such as anxiety and nonmelancholic depression. This allowance can be problematic because both anxiety and depression have an independent and well-established relationship with fatigue.

Chronic fatigue syndrome quickly became a popular diagnosis. The syndrome was initially attributed to infection with the EBV, although few patients had documented physical findings or hematologic abnormalities consistent with the diagnosis of infectious mononucleosis. In addition, most patients had no serologic evidence of active EBV infection. Recently, however, a better understanding of the natural course of EBV antibody activity in healthy individuals months and years after an initial illness with infectious mononucleosis indicates that healthy patients who had mononucleosis years earlier could not be differentiated from fatigued patients who currently had the disease.

Until recently, the diagnosis of CFS in children and adolescents was based on adult criteria. However, children with the illness may exhibit a different symptomatology than adults with CFS. In 2006, the International Association of Chronic Fatigue Syndrome published a Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Pediatric Case Definition. The main difference from the adult diagnostic criteria for CFS is a 3-month requirement for fatigue and other symptoms. Although few longitudinal data are available, the prognosis for pediatric patients with CFS is better than that for adults. Although symptoms may persist for months or several years, most children and adolescents with CFS have a good outcome, with approximately one-half reporting complete recovery.

### Weakness

Infants with weakness are often brought to their pediatrician with a complaint of being floppy. A floppy infant is usually one who has hypotonia caused by a neuromuscular disorder. (See Chapter 167, Hypotonia.) In the newborn period, some of these patients may assume a *frog-leg* position. Chromosomal anomalies such as Down syndrome, congenital hypothyroidism, and the infantile form of spinal muscular atrophy (Werdnig-Hoffmann disease) are some of the more common causes of hypotonia in infancy. Infant botulism from ingesting *Clostridium botulinum* spores in honey can cause infants to appear floppy with a weak cry caused by muscle weakness, loss of head control, lethargy, inability to feed, and constipation.

Older children and adolescents who have weakness experience difficulty walking, running, and participating in athletic activities. Myasthenia gravis and



Guillain-Barré syndrome (postinfectious polyneuropathy) are perhaps the 2 most common causes of weakness in this age group. A distinguishing clinical feature is that, in myasthenia gravis, deep tendon reflexes may be diminished but are rarely absent, whereas Guillain-Barré syndrome is remarkable for bilateral, symmetrically absent tendon stretch reflexes. Other causes of weakness in the older child include the muscular dystrophies, the juvenile form of spinal muscular atrophy, dermatomyositis, and polymyositis.

## EVALUATION

### Relevant History

Although the patient who is chronically fatigued may first appear to have an insignificant problem, great care must be taken to rule out underlying medical illness, to return the child to a state of well-being, and to relieve parental concerns. The pediatrician must remember that either the child or the parents are worried about the child's fatigue. Because family members may disagree about the significance of the symptoms, adequate time and concern are needed to evaluate the history. The symptoms of chronic fatigue cannot be dismissed casually over the telephone or with a quick office visit.

Because most patients who come to the physician complaining of fatigue have emotionally based problems, a careful history, with information from both child and parents (taken separately when appropriate), often helps narrow the differential diagnosis. An accurate assessment of sleep patterns, presence or absence of snoring, nocturnal awakenings, and daily exercise activities is essential. Discrepancies between the child's and the parents' observations soon become evident, and the diagnosis of emotionally related fatigue emerges in most cases based on the history alone. The information derived from a longstanding physician-patient relationship contributes enormously to reducing tensions during the evaluation. Although fatigue may be the only symptom, further questioning almost always uncovers other symptoms of somatic disease. Chronic fatigue, in the absence of other physical symptoms, is usually emotionally based. Other associated complaints are somnolence, depression, anxiety, boredom, decreased activity, and inappropriate affect. In many instances, emotional stress or some disruption in the patient's life is part of the history.

### Physical Examination

A physical examination, thoroughly performed, may be the only measure necessary and may reassure the anxious child or parent. The child's affect and appearance are most revealing. The impression that the child appears well invariably proves to be an accurate measure of the child's health. The condition of the adolescent, in contrast, may be more difficult to interpret. Although the physical examination may be benign, adolescents may be slovenly, uncommunicative, depressed, and unable to express their feelings; thus, at first, adolescents sometimes appear to be physically ill.

In all age groups, a search should be made for sites of chronic latent infection: adenopathy, enlargement

or tenderness of the liver and spleen, and abdominal masses. Careful palpation for an enlarged or tender thyroid gland is essential. Mild scleral icterus and petechiae are easy to overlook. Similarly, a patient's pallor (a common finding, especially after long winters indoors) may evade even the most experienced physician. On the other hand, the characteristic facies of the chronically allergic child and signs such as clubbing and cyanosis are obvious. Examination of the oropharynx may reveal hyperpigmentation of gums and buccal mucosa, which may be present in Addison disease.

An assessment of the plotted height and weight should be an essential part of every routine health visit. Failure of a child to progress along the expected growth parameters should draw the physician's attention to the possibility of an underlying systemic process affecting growth and causing unexplained fatigue. A normal linear growth velocity decreases the possibility of chronic cardiac, pulmonary, gastrointestinal, or renal disorders in children or adolescents who are excessively tired. An underlying endocrinopathy, such as hypothyroidism or Cushing syndrome, may cause fatigue in association with poor growth velocity and obesity. Poor weight gain over time may be a subtle manifestation of inflammatory bowel disease in adolescents with unexplained fatigue.

### Laboratory Testing and Imaging

A limited, well-selected group of laboratory tests should be performed on most patients who are chronically fatigued. These results will reassure the family, the patient, and the pediatrician and will usually erase any lingering doubt about the diagnosis.

### Other Diagnostic Tests

The laboratory evaluation should initially include a complete blood count with red blood cell indices, thyroid and liver function tests, a throat culture, and a stool examination for blood. The cold agglutinin test is often valuable as a simple initial screening test for a *Mycoplasma* species infection. Radiograms are rarely necessary and should be discouraged. Critical evaluation of data collected from the history, physical examination, and laboratory tests should enable the physician to detect quickly any organic causes of fatigue. Prolonged fever, however low grade, must always be viewed as significant and may suggest infection, inflammatory disease, or malignancy. Pallor points to the possibility of anemia or hypothyroidism. Hypertrophied tonsils or snoring and disturbed sleep might direct investigation toward a sleep study to evaluate airway competence during sleep and motor activity during sleep, and toward electroencephalogram tracings. In adolescence, a multiple sleep latency study may be considered in teens with fatigue and somnolence for early detection of narcolepsy.

### Viral Disease

Cervical adenopathy, even a single enlarged node in the absence of other findings, can be a clue to the diagnosis of infectious mononucleosis. In fact, in the autumn and early winter of each year, every physician begins to look for patients who have infectious mononucleosis.

However, infectious mononucleosis is a protean illness, and the physical examination results are sometimes normal. Children and adolescents who have infectious mononucleosis may have no fever or signs of toxicity but may exhibit major fatigue. Furthermore, results of the heterophile antibody test for infectious mononucleosis may be negative in many young children and infants and in approximately 10% of older children and adolescents who have the disease. The reliability of EBV antibody testing has improved to the point at which the diagnosis of acute, active infectious mononucleosis can be confirmed. During the evaluation of chronic fatigue, EBV antibody titers can usually differentiate long-past infection from recent and active infection, thus eliminating EBV infection and infectious mononucleosis as causes for the fatigue and permitting a search for other likely neuropsychiatric causes. Toxoplasmosis and cytomegalovirus infections may mimic mononucleosis closely; these infections produce significant fatigue but with only minimal cervical adenopathy and fever. Positive results of a fluorescent antibody test for toxoplasmosis or cytomegalovirus with negative results of a heterophile antibody test will confirm the diagnosis. Similarly, fatigued children may have hepatitis and may be anicteric (or only slightly icteric), with little or no hepatic tenderness or enlargement. Other common viral infections, especially during convalescence, can cause a prolonged fatigue syndrome accompanied by depression.

### **Chronic Fatigue Syndrome**

The diagnosis of CFS should be restricted to patients who meet ME/CFS pediatric case definition criteria, including the new onset of persistent or relapsing fatigue lasting at least 3 months with no prior history of such fatigue and the exclusion of other clinical conditions that might produce similar symptoms. In addition, the children must have the concurrent occurrence of the classic ME/CFS symptoms, which must have persisted or recurred in the past 3 months of illness (symptoms may predate the reported onset of fatigue).

### **Autoimmune Disease**

Children who have an autoimmune disease may have fatigue with little else at first. Mild articular or periarticular inflammation may be missed on examination. The emphasis must be on careful observation of subtle or minimal physical findings because children usually do not display fulminant findings initially. Children with inflammatory bowel disease, arthritis, or an arthritis-like illness, and some patients with a malignancy (monocytic leukemia, in particular), may have especially prolonged symptoms, including fatigue, without any physical findings whatsoever.

### **Thyroid Disease**

An enlarged, tender thyroid gland and fatigue may indicate thyroiditis with emerging hypothyroidism. However, the thyroid is often palpable and full in healthy adolescents. In any event, chronic fatigue from thyroid disease can usually be ruled out quickly with a thyroid-stimulating hormone and free thyroxine (free T<sub>4</sub>) tests. Some patients who have hypothyroidism

also demonstrate mild to moderate anemia, and those who have active thyroiditis may have an elevated sedimentation rate.

### **Anemia**

To be acceptable as an explanation for fatigue, the diagnosis of pure anemia requires marked reduction of hemoglobin. Red blood cell indices and a reticulocyte count will characterize the anemia and the probable cause. Anemia accompanied by thrombocytopenia, however, suggests leukemia or aplastic anemia. The white blood cell count may be normal in infectious mononucleosis or hepatitis, but lymphocytosis with atypical lymphocytes will most likely be present in the former. The heterophile antibody screening test (the *mono test*) is diagnostic in most such circumstances.

### **Screening and Other Diagnostic Tests**

The erythrocyte sedimentation rate is the most valuable screening test for inflammatory diseases of all varieties. A normal sedimentation rate is usually reassuring in ruling out autoimmune disease, inflammatory bowel disease, chronic smoldering infections, and disseminated malignancies. An elevated sedimentation rate requires further investigation. A routine urinalysis almost always reveals diabetes, and most patients who have chronic renal failure have abnormal urinalyses, as well as significant anemia. In these patients, the subsequent measurement of blood glucose in diabetes and of creatinine or blood urea nitrogen in renal disease can confirm these diagnoses. Hyperkalemia, hyponatremia, and hypoglycemia are useful diagnostic features of Addison disease, with the adrenocorticotrophic hormone stimulation test being the most definitive diagnostic test.

### **Weakness**

The evaluation of a patient who has weakness may include chromosomal studies, muscle enzyme assays, nerve conduction studies, electromyography, edrophonium (Tensilon) challenge, muscle biopsy, and a lumbar puncture, depending on the suspected diagnosis. Consultation with a pediatric neurologist is often required.

## **MANAGEMENT**

After significant organic disease is ruled out in most patients, further management requires meaningful communication among the pediatrician, the patient, and the parents. In younger children, the variability in performance and behavior of healthy children must be put into perspective. Again, appropriate parental expectations must be emphasized. In addition, the child's and the family's daily schedule should be reviewed. A chaotic lifestyle that is frantic, with poorly structured activity and inadequate sleep patterns, is often revealed. Occasionally, true psychiatric depression is discovered, which calls for referral to a psychiatrist.

Older children and adolescents benefit from personal, warm attention. The value of a continuous relationship with a single physician becomes self-evident. An understanding, thorough session with the patient's

pediatrician usually streamlines the evaluation and eliminates the need for excessive testing. Conversation after the physical examination should attempt to reassure children or adolescents about their basic health, reiterate the common and normal occurrence of fatigue, examine the daily routine and stresses on patients, and suggest modifications of patients' lifestyle and approaches to life's situations. This period is a time for respectful give and take. Attempting to establish the probable cause of the fatigue is the physician's responsibility before the patient is referred to a specialist. If emotional fatigue is thought to exist, then the adolescent, in particular, must be comfortable with the conclusion that organic diseases were ruled out. The patient then must be made aware of the emotional basis for the fatigue; if psychiatric referral is needed, then the reasons must be made clear. A knowledgeable pediatrician will be reassuring but firm in approaching the child or adolescent who needs referral. Fortunately, such a referral usually is not necessary.

### WHEN TO REFER

- Unexplained weight loss
- Hypotonia in infants
- Suspected major affective disorder
- Suspected malignancy

### WHEN TO ADMIT

- Severe depression or suicidal ideation
- Need for evaluation of neuromuscular disorders such as spinal muscular atrophy, Guillain-Barré syndrome, and myasthenia gravis

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Building Resilience in Children and Teens*, 3rd ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Helping Children Handle Stress* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/healthy-living/emotional-wellness/Pages/Helping-Children-Handle-Stress.aspx](http://www.healthychildren.org/English/healthy-living/emotional-wellness/Pages/Helping-Children-Handle-Stress.aspx))
- *Helping Teens Handle Stress* (audio), American Academy of Pediatrics ([www.healthychildren.org/English/healthy-living/emotional-wellness/Pages/Helping-Teens-Handle-Stress.aspx](http://www.healthychildren.org/English/healthy-living/emotional-wellness/Pages/Helping-Teens-Handle-Stress.aspx))
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- *Stress Management & Coping: Core to Resilience* (video), American Academy of Pediatrics ([www.healthychildren.org/English/healthy-living/emotional-wellness/Pages/Stress-Management-Coping-Core-to-Resilience-Video.aspx](http://www.healthychildren.org/English/healthy-living/emotional-wellness/Pages/Stress-Management-Coping-Core-to-Resilience-Video.aspx))

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## Chapter 152 FEVER

Élise W. van der Jagt, MD, MPH

For centuries, fever has been associated with illness. As many as 30% of all patients seen by primary care physicians and more than 5 million emergency department visits each year have fever as their principal complaint, making it among the most common reasons children are taken to a physician. Add to this the numerous telephone calls about fever that physicians receive day and night, and it becomes evident that the proper evaluation and management of fever is a basic and necessary skill for everyone caring for children.

Even though physicians have long dealt with this common clinical sign, its mechanism, meaning, and management have remained sufficiently unclear and controversial that research on these matters continues. Although advances in neurochemistry and neurophysiology have improved the understanding of the pathophysiology of fever, clinical investigators continue to search for practical knowledge that will enhance the care of the febrile patient. Availability of such information can simplify the challenging role of the physician, who must evaluate a child quickly and effectively, arrive at a diagnosis, institute appropriate therapy, and both educate and support the parents and child during the entire process. The extent to which physicians accomplish these goals depends on their knowledge of the mechanisms of disease, the various clinical manifestations of disease, and their awareness of the social context in which the disease occurs.

## DEFINITION

The word *fever* is derived from the Latin *fovere*, meaning *to warm*, and commonly means an increase in body temperature. Although this general definition is acceptable in common parlance, fever is described more accurately as an adaptive response of thermoregulation. It must be differentiated from hyperthermia, an increased body temperature resulting from conditions that overwhelm the normal process of thermoregulation.

Normal rectal body temperature ranges between 97°F and 100°F (36.1°C and 37.8°C), although, on rare



occasions, it may be as low as 95.5°F (35.3°C) or as high as 101°F (38.3°C). The *normal* temperature of 98.6°F (37°C) was derived from an 1868 study of more than 1 million axillary temperatures taken in adults. This value may have no relevance for children, not only because adults were studied, but also because axillary and rectal temperatures correlate poorly. Young children seem to have higher body temperatures than adults, with temperatures slightly higher than 37.8°C occurring commonly in those younger than 2 years. The upper limits of the normal range for a rectal temperature are 100.4°F (38°C) for newborns younger than 1 month, 100.6°F (38.1°C) in 1-month-olds, and 100.8°F (38.2°C) in 2-month-olds. A total of 6.5% of well infants less than 3 months old have been reported to have rectal temperature of 100.4°F (38°C). Nevertheless, because it is unknown which of these infants have these relatively high “normal” temperatures, it is safest to consider 100.4°F (38°C) as an abnormal temperature (fever) in this age group. Lowest body temperatures occur between 2 am and 6 am, and the highest ones occur between 5 pm and 7 pm, a diurnal variation that persists even during a febrile illness.

Because a range of normal body temperatures exists, it may be helpful in some instances to know a child’s usual body temperature so that an abnormal increase can be recognized more easily. The extent to which body temperature is increased above normal may help determine the presence and significance of fever. This circumstance may be true especially in young infants, in whom even a mild fever may be associated with serious disease. Although the variability and range of normal temperatures in children have made it difficult to define fever precisely and consistently, a consensus panel of experts has recommended that the lower limit of fever be defined as a rectal temperature of 100.4°F (38°C). This definition has become standard and is used both clinically and in research studies about fever.

## SIGNS AND SYMPTOMS ASSOCIATED WITH FEVER

The behavior of humans and animals is remarkably similar when fever is present. When the set point in the hypothalamus is increased, patients attempt to adjust the environment to keep their bodies at this higher temperature. Young children usually seek close contact with a warm person (generally a parent), wish to be covered by a blanket, sit near a warm stove or register, and refuse cold liquids or foods. Although children may be quite comfortable at this higher body temperature, they interact less with others, have a decreased ability to concentrate, substitute quieter activities for energetic ones, and become less communicative except to indicate discomfort and distress. This adaptive withdrawal is often accompanied by loss of appetite and complaint of headache.

Such a combination of behavioral symptoms is a familiar indicator of illness to most parents and usually results first in placing the hand on the forehead, then measuring the temperature with a thermometer.

Unfortunately, parents may not recognize the onset of fever in the younger child because the alterations in behavior are fewer and subtler. In a small infant, irritability and loss of appetite may be the sole evidence of fever and disease. If a parent is not familiar with these subtle cues, then recognition of serious illness may be significantly delayed.

In addition to the behavioral changes that may accompany fever, the general physical examination may reveal a pronounced hypermetabolic state. The child may have flushed cheeks, have an unusual sparkle in the eyes (likely from pupillary dilatation), and be either sleepy and lethargic or exceptionally alert and excited (particularly 5- to 10-year-olds). With rare exception, the pulse is increased by approximately 10 to 15 beats per 1°C of fever, and the respiratory rate is increased. (If the pulse rate is less than expected for the degree of fever, then typhoid fever, tularemia, mycoplasma infection, or factitious fever should be considered.) The skin may feel hot and dry (“burning up with fever”), although the distal extremities may be cold and pale (vasoconstricted), obscuring an extremely high core body temperature. Most children are not particularly uncomfortable, but some may shiver or sweat, mechanisms by which the body increases or decreases temperature. Sweating may be so severe that dehydration occurs, particularly if the intake of fluids has been poor. Thus, a dry mouth and lips may result not only from rapid mouth breathing, but also from dehydration. Finally, irritability of the central nervous system may increase, resulting in a febrile seizure.

The aforementioned signs and symptoms may be less obvious in a small infant. Shivering does not occur in the first few months of life, and diaphoresis is seen less often than in the older child. Because irritability and pallor may be the only suggestions of illness, a careful measurement of the temperature should be taken if the parent mentions these signs.

## PRESENTATION

A febrile child may come to the attention of a primary care physician in several ways. Probably the most dramatic and frightening manifestation of fever in a child is the sudden occurrence of a seizure. A generalized tonic or tonic-clonic seizure, usually lasting less than 15 minutes and occurring within 24 hours of the onset of fever, may begin without warning. Most parents are not aware that a fever is present and often feel guilty for not having noted it. The primary care physician may be called immediately after the seizure has occurred or after the child has been transported to the emergency room. There the child is likely to be postictal and have a rectal temperature of 102°F to 104°F (39°C–40°C). A thorough assessment of the patient is indicated because a seizure may be the first sign of meningitis or encephalitis.

Although some experts have suggested that every patient who has a first febrile seizure should routinely undergo a lumbar puncture (LP), the American Academy of Pediatrics (AAP) recommends an approach that takes the age and immunization status of the child into consideration. The younger the child is, the more difficult it is to diagnose meningitis clinically



(eg, meningismus, Kernig sign, Brudzinski sign), and strong consideration should be given to performing an LP. In infants younger than 6 months, an LP should be strongly considered because clinical signs of meningitis may be absent. In children between 6 and 12 months of age, when clinical manifestations of meningitis still may be subtle, an LP should be considered if the infant has not received the recommended immunizations for *Haemophilus influenzae* and *Streptococcus pneumoniae* or immunization status is unknown. Infants who have received the 3 *H influenzae* and *S pneumoniae* immunizations are unlikely to develop meningitis from these organisms. In children older than 12 months, an LP is not routinely warranted except in the presence of signs and symptoms suggestive of meningitis or other intracranial infection. Because antibiotic treatment can mask meningitis, an LP should also be considered in a child with a fever and a seizure who has received antibiotics. Reexamination of the child after the convulsive episode may also help determine whether an examination of the cerebrospinal fluid is needed.

More commonly, a patient with fever is first examined when the fever has been present for longer than 24 hours and is associated either with nonspecific symptoms or with symptoms referable to a particular organ system. Inasmuch as many evaluations of febrile children take place over the telephone (the first contact with the physician), the physician must be able to take an accurate and pertinent history. Of particular significance are the age of the patient (the younger the child is, the more thorough the evaluation will need to be), any associated signs and symptoms, exposure to illness in the family or community, history of recent immunizations, and a history of any recurrent infections (eg, urinary tract infections [UTIs], streptococcal infections, otitis media). The time of year also should be considered, because certain viral illnesses are more prevalent at particular times of the year. For example, respiratory syncytial virus (RSV) and influenza virus infections are more common during the winter, parainfluenza virus infections (the most common cause of croup) are more common during the spring and especially in the fall, and enterovirus infections occur primarily during the summer. In addition, questions should be asked about the duration and height of the fever. A low-grade fever that has been present for many days usually does not need to be evaluated as urgently as a temperature of 106°F (41°C) that has been present for a few hours. The former is more likely to indicate a chronic or benign illness; the latter is more likely to be a potentially rapidly progressive infectious disease. Unfortunately, the height of the fever is often not very reliable in distinguishing viral from bacterial illness or even serious from nonserious disease. Young infants especially may not have much of a fever or even be hypothermic during a serious infection.

A visit or telephone call for minimal fever and little evidence of disease should prompt a thorough assessment of the psychosocial factors that may be contributing to parental concern. Is the main concern about something else—a hidden agenda? Is the caregiver

anxious about the fever because of lack of knowledge about its significance? Has the caregiver had a previous traumatic experience with disease, resulting in excessive anxiety? Might the patient be a vulnerable child? Is this family dysfunctional, in which minor illness either cannot be dealt with or is used as a means to meet other needs? Answers to these questions and others may clarify the situation.

## DIFFERENTIAL DIAGNOSIS

Because many conditions may cause fever, an extensive discussion about each condition is beyond the scope of this chapter. However, classifying conditions associated with fever into broad categories is useful (see Box 152-1). In addition to specific etiologies, dehydration, excessive muscle activity, autonomic dysfunction, and heat exposure all may cause hyperthermia.

Although any disease in these categories may cause fever at any age, some diseases are more likely to occur at some ages than at others. Autoimmune disease and inflammatory bowel disease, for example, are unusual in infants but become progressively more common with increasing age. Similarly, febrile immunization reactions are much more common during the first year of life when most immunizations are administered.

Infections affecting the respiratory and gastrointestinal tracts account for most fevers in all age groups. Most of these infections have a viral origin (eg, enteroviruses, influenza virus, parainfluenza virus, RSV, adenovirus, rhinovirus, rotavirus) and are generally self-limited. Knowledge of the seasonality of these viruses promotes correct and efficient diagnoses. In addition, knowledge of the typical physical findings in these infections and their course may help distinguish them from bacterial diseases. For example, high fever, irritability, posterior cervical adenopathy, and painful vesicles on the gums and tongue are characteristic of herpes gingivostomatitis. Failure to examine the tongue and gums may result in an unnecessary workup in search of a possible bacterial infection. On the other hand, assuming that a high fever in a 2-month-old infant is from roseola (exanthem subitum) would be erroneous because this

### BOX 152-1 Differential Diagnosis of Fever

- Infection
- Autoimmune disease
- Neoplastic disease
- Metabolic disease (eg, hyperthyroidism)
- Chronic inflammatory disease
- Hematologic disease (eg, sickle cell disease, transfusion reaction)
- Drug fever and immunization reaction
- Poisoning (eg, aspirin, atropine)
- Central nervous system abnormalities
- Factitious fever

infection (human herpesvirus type 6) usually does not occur at such an early age.

## EVALUATION

Failure to evaluate the fever further might result in missing a serious bacterial infection. Although viral infections may cause significant morbidity and mortality, the more aggressive course and serious outcomes of bacterial infections make early diagnosis especially important, particularly because effective antibiotic treatment is usually available. Bacterial infections may be especially devastating in younger children who are relatively immunocompromised because of their immature immune systems. An infection that remains localized in the older child may disseminate rapidly in the infant and toddler, particularly to the blood (bacteremia), the lungs (pneumonia), the meninges (meningitis), the bones (osteomyelitis), and the joints (arthritis). Because these infections may be seriously debilitating or even fatal if not recognized, the physician must be able to differentiate bacterial infections from the more benign viral infections.

At greatest risk are those children who present with fever or hypothermia and have severe sepsis or septic shock, because the mortality, although better than in adults, is still as high as 8% to 12%. These children typically have a constellation of symptoms and signs collectively called systemic inflammatory response syndrome (SIRS), along with evidence of organ dysfunction. The Worldwide Pediatric Surviving Sepsis Campaign has standardized (by consensus of experts) the definitions of SIRS, sepsis, severe sepsis and septic shock as outlined in Table 152-1, Table 152-2, and Table 152-3.

Early recognition and aggressive, goal-directed therapy can decrease mortality significantly. This means that careful clinical and laboratory assessment is necessary to identify patients, give antibiotics within an hour, and provide early and rapid fluid administration (eg, 20 mL/kg boluses of crystalloid given over 5–10 minutes), along with early use of inotropic agents as appropriate to normalize the patient's physiology. Both the International Surviving Sepsis Guidelines for pediatric patients and the American Heart Association's Pediatric Advanced Life Support Sepsis algorithm provide guidance to the management of these patients.

The younger the child is, the more difficult it is to recognize bacterial infection. Complaints cannot be verbalized, and physical signs and symptoms are more subtle and easily missed unless a high index of suspicion is maintained. Serious bacterial disease is especially difficult to diagnose in children with no obvious focus of infection. For this reason, many attempts have been made during the last 30 years to identify children in whom fever is a sign of a serious bacterial infection, particularly pneumococcal disease and infections caused by *Haemophilus influenzae* type b (Hib). Children between birth and 36 months of age have been of special interest because fever is most common in this age group, and they may be difficult to assess, particularly during the first 3 to 6 months of

**Table 152-1** Systemic Inflammatory Response Syndrome Criteria

SIGN	AGE	VALUE
Temperature	All ages	<36°C or >38.5°C
Heart rate (bpm)	0 days–1 mo	<100 or >180
	1 mo–1 yr	<90 or >180
	2–5 yr	>140
	6–12 yr	>130
	13–18 yr	>110
Respiratory rate (rpm)	0 days–1 wk	>50
	1 wk–1 mo	>40
	1 mo–1 yr	>34
	2–5 yr	>22
	6–12 yr	>18
White blood cell count ( $\times 10^3/\text{mm}^3$ )	13–18 yr	>14
	0 days–1 wk	>34
	1 wk–1 mo	>19.5 or <5
	1 mo–1 yr	>17.5 or <5
	2–5 yr	>15.5 or <6
	6–12 yr	>13.5 or <4.5
	13–18 yr	>11 or <4.5
	all ages	>10% bands (immature WBC)

WBC, white blood cell.

From Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6(1):2–8, with permission from Wolters Kluwer Health.

life. Efforts to improve the ability to diagnose a serious bacterial infection have focused on 3 areas: data from the history and physical examination, laboratory data, and response to antipyretics. Of the 3 areas, the response to antipyretics has been shown most clearly to be unhelpful in distinguishing between patients who have a serious bacterial infection and those who have a more benign viral infection. Children who have a serious infection respond to antipyretics no differently from those whose illness is less significant. In fact, some children who have viral illnesses do not defervesce either.

Many studies have attempted to delineate the precise combination of clinical or laboratory variables that might identify the febrile child at risk for serious disease. Defined clinical observational scales (eg, Yale Observation Scale, Young Infant Observation Scale, Severity Index) are not sufficiently discriminatory and predictive to be used alone. Laboratory studies continue to be necessary as well.

During the early 1990s, specific practice guidelines were published to facilitate the initial management of febrile infants and children without an obvious source of infection. Although these guidelines remain controversial, as many as one-third of primary care physicians found them to be helpful and changed the way they evaluated young children with fever. Nevertheless, each patient continues to require individual assessment, with application of the recommendations as

**Table 152-2** Sepsis-Related Definitions

Systemic inflammatory response syndrome (SIRS)	The presence of at least 2 of the following SIRS criteria, 1 of which must be an abnormal white blood cell (WBC) count or abnormal temperature: (1) temperature abnormality; (2) tachycardia/bradycardia; (3) increased respiratory rate; (4) abnormal WBC count.
Sepsis	SIRS + evidence or suspicion of infection.
Severe sepsis	Sepsis + (cardiovascular dysfunction OR acute respiratory distress syndrome OR 2 other organ dysfunctions [see Table 152-3]).
Septic shock	Severe sepsis + cardiovascular dysfunction as defined in the organ dysfunction.
Refractory shock	<i>Fluid Refractory:</i> Cardiovascular dysfunction persists in spite of >60 mL/kg of fluid over 1 hr. <i>Catecholamine Refractory:</i> Cardiovascular dysfunction persists in spite of >10 mcg/kg/min of dopamine and/or need for epinephrine/norepinephrine.

**Table 152-3** Severe Sepsis—Organ Dysfunctions

Cardiovascular	Despite >40 mL/kg fluid in an hour, there is systolic hypotension OR need for vasoactive drugs to keep BP within normal limits OR 2 of the following: capillary refill >5 sec; unexplained metabolic acidosis (base deficit >5 meq/dL); oliguria (<0.5 mL/kg/hr urine); lactate >2× upper limit of normal; >3 degrees between peripheral and core temperature.
Respiratory	Any of the following: $P_{aO_2}/F_{iO_2}$ <300 in absence of cyanotic heart disease or pre-existing lung disease; >50% $F_{iO_2}$ to maintain $O_2$ sat >92%; $P_{CO_2}$ >65 or >20 mm Hg over baseline; need for nonelective mechanical or noninvasive ventilation.
Neurologic	Glasgow Coma Scale ≤11 or an acute change in Glasgow Coma Scale with decrease of ≥3 from baseline.
Hematologic	Platelets <80,000 or >50% decrease from previous 3-day baseline OR INR >2.
Hepatic	Total bilirubin ≥4 mg/dL OR ALT >2× upper limit of normal.
Renal	Serum creatinine ≥2× upper limit of normal or 2× baseline.

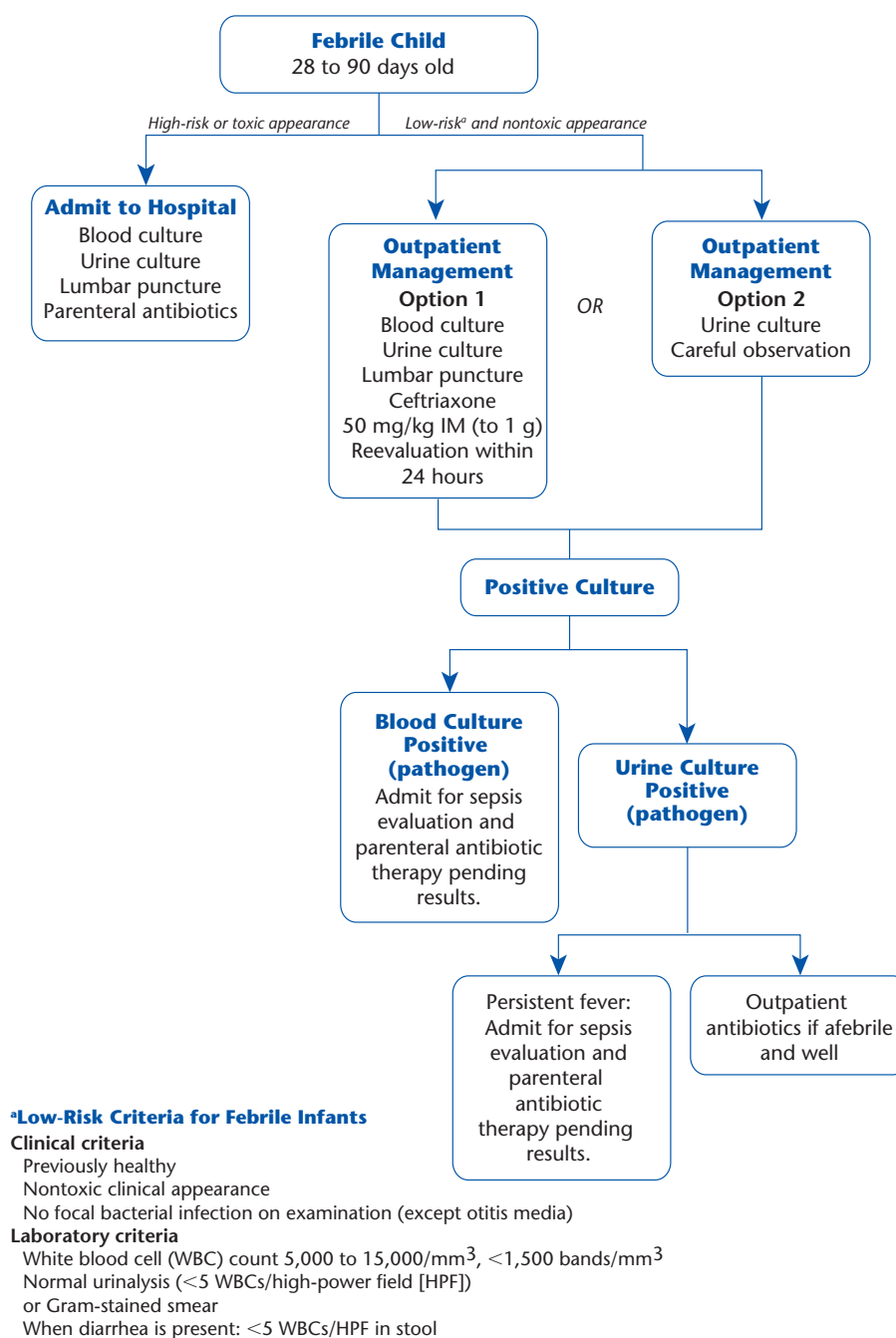
ALT, alanine aminotransferase; BP, blood pressure;  $F_{iO_2}$ , inspired fraction of oxygen; Hg, mercury; INR, international normalization ratio;  $P_{aO_2}$ , partial pressure of oxygen in arterial blood;  $P_{CO_2}$ , partial pressure of carbon dioxide.

appropriate to the individual context of the patient. Considerations of the inconvenience, discomfort, and cost of laboratory testing and the increasing resistance to antibiotics in the community must be weighed carefully against the risk of missing a serious bacterial infection, with its subsequent morbidity and mortality. Therefore, physicians must make the best decisions possible in an environment of incomplete certainty about the presence of serious disease. Parents need to be part of these discussions, and adequate follow-up of all patients is crucial, no matter what is decided in the initial visit.

Although the early practice guidelines were helpful during the 1990s, they were formulated before the introduction in 2001 of the heptavalent pneumococcal vaccine for infants. This vaccine provides protection against pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, and is administered at 2, 4, and 6 months and between 12 and 15 months of age. With the introduction of the vaccine, a decline of 60% to 80% in pneumococcal disease occurred in children younger than 24 months. In 2010, a more comprehensive pneumococcal vaccine was introduced, covering 13 serotypes including serotype 19A, with similar recommendations for administering it 4 times in the first 15 months. Because occult pneumococcal bacteremia and other pneumococcal

infections made up most of the serious bacterial infections in young children with high fever (>102°F [>39°C]), the use of this vaccine greatly lowered the incidence of serious bacterial infections in children at greatest risk—those between 2 to 3 months and 3 years of age. A similar effect occurred when the Hib vaccine was introduced in the 1980s, nearly eliminating Hib meningitis, epiglottitis, and bacteremia. Given the marked decrease in pneumococcal and Hib serious bacterial infections, the likelihood of a serious bacterial infection when high fever (>102°F [>39°C]) is present in infants and toddlers is now even smaller, and a fairly limited assessment may be more suitable at this time. In addition, with an increased ability to diagnose specific viral illnesses (RSV, influenza, enterovirus) by rapid diagnostic testing with polymerase chain reaction (PCR) methodology, and the increased use of inflammatory markers more typically associated with bacterial infections (procalcitonin, C-reactive protein), the likelihood of missing a serious bacterial infection is even lower. Thus, even the revised, updated practice guidelines of 2000 are no longer as useful as they once were (figures 152-1 and 152-2).

Fever during the first 4 days of life has been associated with a high incidence of bacterial disease. A temperature above 98.6°F (37°C) occurs in 1% of all

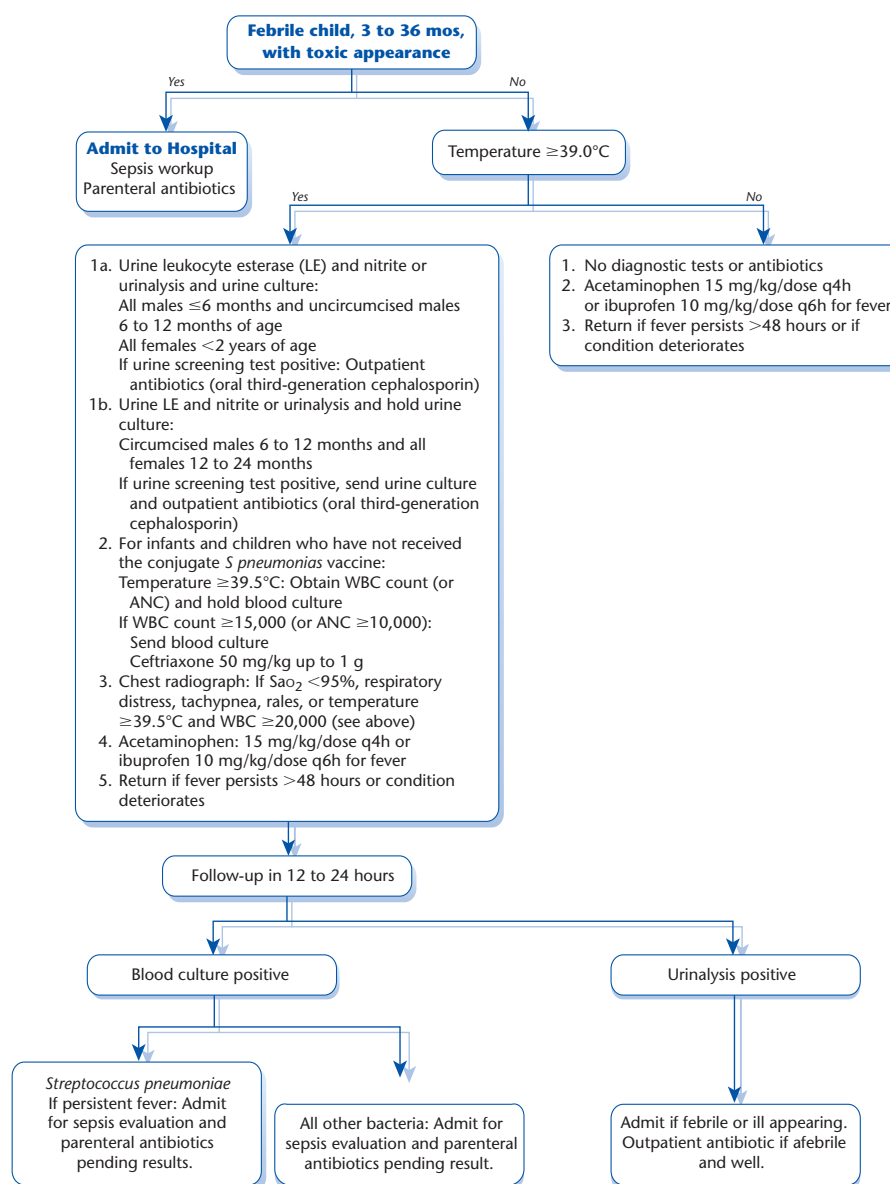


**Figure 152-1** Algorithm for the management of a previously healthy infant 28 to 90 days of age with fever without source at least 100.4°F (38°C). (From Baraff LJ. Management of fever without source in infants and children. Ann Emerg Med. 2000;36:602–614. Copyright © 2000, Elsevier, with permission.)

newborns; of these children, 10% have a bacterial infection, usually caused by group B streptococcal or gram-negative enteric pathogens. A full workup is indicated in these children, including a complete blood count and differential count, a urine analysis, and cultures of the blood, urine, and cerebrospinal fluid (CSF); antibiotics (usually intravenous ampicillin and gentamicin, or ampicillin and cefotaxime) should be administered until the results of cultures are known.

Similarly, neonates up to 28 days of age with fever have a significant risk of a bacterial infection (approximately 12% in some studies). Pneumococcal infection is uncommon; *Escherichia coli* (*E coli*), group B *Streptococcus*, and other enteric pathogens are more usual; *E coli* is by far the most common and *Listeria monocytogenes* has become very uncommon. Urinary tract infection (UTI) and occult bacteremias are the most common types of infection;





**Figure 152-2** Algorithm for the management of a previously healthy child 91 days to 36 months of age with fever without source. (From Baraff LJ. Management of fever without source in infants and children. Ann Emerg Med. 2000;36:602–614. Copyright © 2000, Elsevier, with permission.)

however, with group B *Streptococcus* infection, the risk of accompanying meningitis is as high as 39%. Low-risk criteria, such as the Rochester criteria, may not be consistently reliable to differentiate young patients with serious bacterial infection from those who have more benign disease. Although some studies have demonstrated only a 0.2% incidence of bacteremia or meningitis in neonates satisfying the low-risk criteria, others have found that up to 6% of neonates who satisfy low-risk criteria have a serious bacterial infection. Of note, neonates with RSV infection do not have a lower incidence of serious bacterial infection when they have fever but these are typically UTIs and not meningitis or

bacteremia. Concomitant UTIs are especially common, occurring in 5% to 7% of patients. In addition to bacterial infection, herpes simplex virus (HSV1/HSV2) infection, especially meningoencephalitis, should be considered in any neonate who has risk factors for HSV infection (maternal primary HSV infection, prolonged rupture of membranes, fetal scalp electrode use) or clinical evidence (temperature elevation/depression or instability, seizures, lethargy, skin/oral/ocular vesicles, CSF pleocytosis, or hemorrhage). Acyclovir is the treatment of choice while awaiting an HSV PCR test on spinal fluid/blood/surface cultures to confirm the diagnosis.

Fever of 100.4°F (38°C) or higher in infants between 28 and 60 days of age is associated with a 5% to 10% incidence of serious bacterial infection. Unfortunately, neither height of fever nor apparent degree of toxicity has been a reliable predictor by itself of bacteremia or serious bacterial infection. Instead of using a single predictor, a combination of clinical and laboratory criteria seems to be more useful in identifying infants who are at low risk for having a bacterial infection. The most well known of these combinations are the Rochester criteria (Table 152-4). The infants must satisfy all of the following conditions: previously healthy (as defined in Table 152-4), no clinical signs of toxicity (in some studies defined by an infant observation score of  $\leq 10$ ), no focal bacterial infection found at physical examination, a white blood cell (WBC) count between 5,000 and 15,000 cells/mm<sup>3</sup> with 1,500 bands or fewer, a normal urinalysis ( $\leq 5$  WBCs per high-power field [HPF] with few or no bacteria found in centrifuged urine and a Gram-stained smear of stool demonstrating fewer than 5 WBCs/HPF if diarrhea is present. If cerebrospinal fluid is obtained, then the cell count should be 8 WBCs/HPF or fewer. One- to 2-month-old infants who satisfy these criteria have only a 1.1% probability of having a serious bacterial infection, and a 0.5% probability of having meningitis.

Because of the difficulty in determining solely by the degree of fever whether an infant younger than 3 months is at a low or high risk for bacterial disease (septicemia has occurred even in infants who have low-grade fevers), evaluation should be prompt and thorough whenever a fever of at least 100.4°F (38°C) exists, paying particular attention to obtaining the data necessary for classifying the child as low or high risk. Such a comprehensive evaluation should generally include a complete physical examination, total and differential WBC count, urinalysis and urine culture, a Gram-stained smear of stool if diarrhea is present, blood culture, and possibly examination and culture of cerebrospinal fluid. A urine culture is especially important because UTIs are the most common bacterial infections in this age group, even in the absence of pyuria.

If the infant seems nontoxic and meets the low-risk criteria, then examination and culture of the cerebrospinal fluid and blood might reasonably be avoided as long as good observation and follow-up can be made within 24 hours and antibiotics are not administered. If antibiotics are to be administered, then a full workup, including blood and cerebrospinal fluid cultures, should always be performed.

After obtaining a thorough history, including queries about illness of a similar nature in other family members and queries about whether the child has been immunized with the Hib and pneumococcal vaccines, the physician should assess the child for toxicity. If the child seems toxic (eg, lethargic or irritable, noninteractive, poor perfusion), then hospitalization should be considered along with further diagnostic tests to assess for serious bacterial infection. If the child does not seem toxic, a WBC count should be considered; if this count is greater than 15,000/mm<sup>3</sup>

**Table 152-4**      **Rochester Criteria**

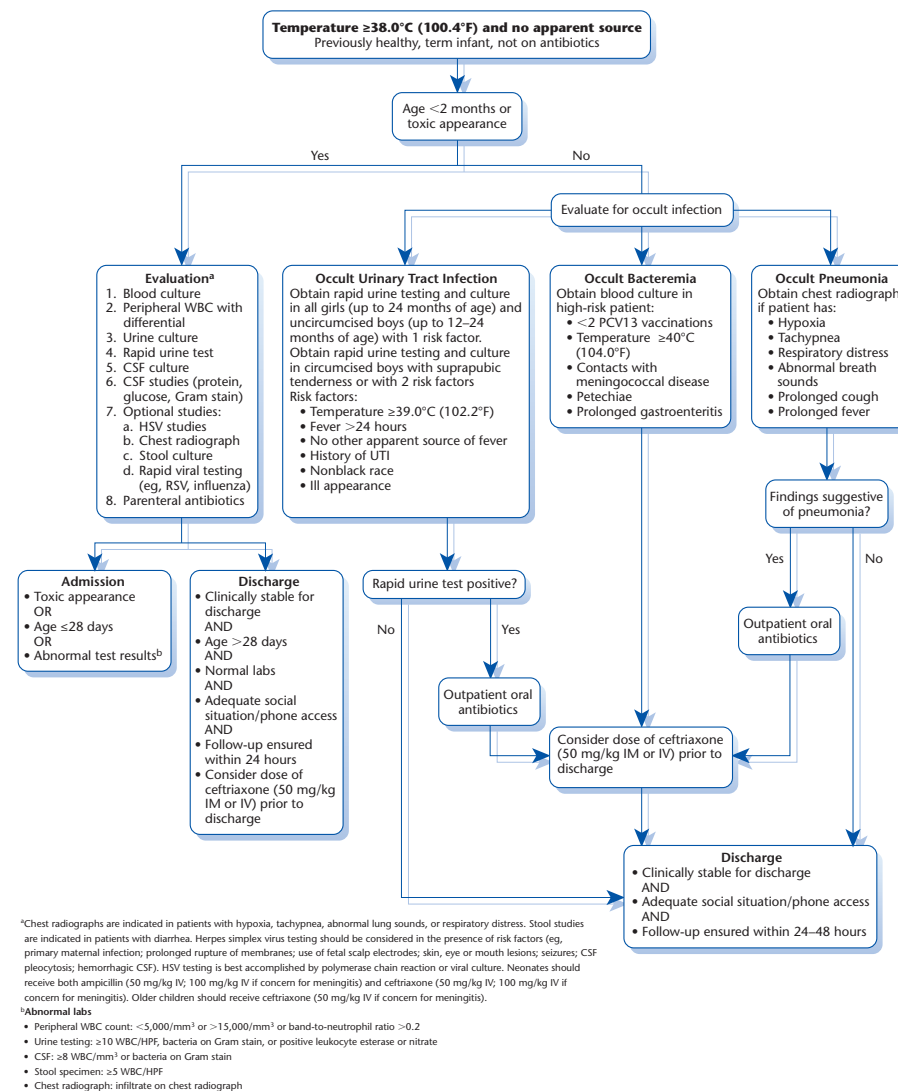
- 1 Infant seems generally well.
- 2 Infant has been previously healthy.  
Born at term ( $\geq 37$  weeks' gestation).  
Did not receive perinatal antimicrobial therapy.  
Was not treated for unexplained hyperbilirubinemia.  
Had not received and was not receiving antimicrobial agents.  
Had not been previously hospitalized.  
Was not hospitalized longer than mother.
- 3 No evidence of skin, soft tissue, bone, joint, or ear infection.
- 4 Laboratory values:  
Peripheral blood white blood cell (WBC) count 5.0 to  $15.0 \times 10^{11}$  cells/L (5,000 to 15,000/mm<sup>3</sup>).  
Absolute band form count  $\leq 1.5 \times 10^{11}$  cells/L ( $\leq 1,500$ /mm<sup>3</sup>).  
 $\leq 10$  WBC per high-power field ( $\times 40$ ) on microscopic examination of a spun urine sediment.  
 $\leq 5$  WBC per high-power field ( $\times 40$ ) on microscopic examination of a stool smear (only for infants with diarrhea).

From Jaskiewicz JA, McCarthy CA, Richardson AC, et al; Febrile Infant Collaborative Study Groups. Febrile infants at low risk for serious bacterial infection—an appraisal of the Rochester criteria and implications for management. *Pediatrics*. 1994;94:390–396.

then a blood culture should be considered. In the pre-pneumococcal vaccine era, children with WBC counts  $>15,000/\text{mm}^3$  were 5 times as likely to experience bacteremia as those who had WBC counts  $<15,000$ . In addition, an absolute neutrophil count of at least 10,000/mm<sup>3</sup> correlated with an increased (8.2%) risk of pneumococcal bacteremia. Practically, obtaining the WBC and blood culture at the same time is easiest, with the blood sent for culture only if the WBC count warrants doing so. Procalcitonin and C-reactive protein blood levels might have better sensitivity and specificity than the WBC count in predicting serious bacterial infection, but findings from various studies still vary widely with respect to the best cutoff levels to use.

Given the lower incidence of pneumococcal disease now, avoiding blood tests altogether might be more cost-effective and reasonable as long as the child has received at least 3 doses of the Hib and pneumococcal vaccines, does not seem toxic, has no obvious focus of infection, and has reliable physicians with excellent follow-up capabilities.

Approximately 5% to 8% of children in the 3- to 36-month-old age group who have an undifferentiated febrile illness have a UTI. Two groups of patients in this age group are especially at risk. Female infants with temperatures greater than 39°C (102.2°F) have a UTI incidence of 16% to 17%. Uncircumcised boys in the first 12 months of life have an 8- to 9-fold higher rate of UTI than circumcised boys. Because of the high rate of UTIs in this age group, a urine culture is suggested for febrile boys younger than 6 months of age. A urinalysis alone is generally not adequate as a screening tool to determine which child should have a



**Figure 152-3** Fever without apparent source in children 0 to 24 months old. (From Ishimine P. Risk stratification and management of the febrile young child. Emerg Med Clin N Am. 2013;31:601–626. Copyright © 2013, Elsevier, with permission.)

urine culture; 20% of children who have a UTI have a normal urinalysis, including a negative test for urinary nitrites or leukocyte esterase. However, a more recent study suggests that the urine dipstick may be an adequate screen for ruling out a UTI, with a negative predictive value of over 98%. A chest radiograph is generally necessary only if clinical symptoms or signs suggest pneumonia (eg, cough, tachypnea, dyspnea, rales, decreased breath sounds, dullness to percussion). However, at least 1 study has suggested that up to 20% of children with fever of at least  $102.2^{\circ}\text{F}$  ( $39^{\circ}\text{C}$ ) and a WBC count of more than  $20,000/\text{mm}^3$  have pneumonia by chest radiograph, even in the absence of respiratory symptoms and signs.

If one considers all of the above, it is obvious that one must attempt to predict the risk of a serious bacterial infection in different age groups and circumstances. The advent of immunizations directed to

serious bacterial pathogens with a subsequent decline in serious illness caused by these agents, and the possibilities of diagnosing viral infection very early, even in the emergency room, make it imperative that a balanced approach be taken in diagnostic testing, hospitalization, and treatment. One way of doing this has been outlined by Ishimine and is shown in Figure 152-3.

A further consideration in the approach to a febrile infant or child in the first 3 years of life is the increased availability of rapid diagnostic viral testing. Rapid tests are now available for influenza A and B, RSV, and enterovirus. Although sensitivity and specificity vary with individual tests, a positive test may be helpful in decreasing the number of other tests that need to be performed to rule out a bacterial infection. Including neonates younger than 28 days, the rate of serious bacterial infections in febrile patients is lower if they

are infected with influenza and RSV. When this rate of infection is coupled with a generally lower incidence of serious pneumococcal and *H influenzae* infections because of the advent of vaccines given at a young age, a reasonable strategy might be to use positive viral tests as a way to reduce blood and urine tests in vaccinated children older than 2 to 3 months who do not seem toxic.

Children older than 3 years are more likely to have signs and symptoms consistent with a recognizable illness. If they have nonspecific symptoms, an urgent consultation with a physician is probably unnecessary; however, regardless of age, all febrile children with localized signs and symptoms, such as swollen joints, meningismus, labored respirations, chest pain, dysuria, petechiae, alteration of consciousness, and severe abdominal pain, should be examined immediately. Moreover, any child with fever or hypothermia who satisfies the criteria for SIRS should be immediately evaluated.

Although many febrile children do not have signs and symptoms pointing to an obvious cause, a complete physical examination may reveal important clues to the origin of the fever. Because most infections involve the respiratory tract, this area must be examined carefully. In all instances, the tympanic membranes should be examined for otitis media, the pharynx for pharyngitis, the nose for the discharge of sinusitis or a viral upper respiratory tract infection, and the lungs for evidence of pneumonia or bronchiolitis. Conjunctivitis may be a clue to adenovirus, influenza or RSV infection, conjunctivitis-otitis syndrome, or Kawasaki disease.

The skin is no less important and may demonstrate typical viral exanthems, such as those associated with rubella, roseola, or chickenpox, or it may show the erythema marginatum of rheumatic fever or the rose spots of typhoid fever.

Generalized lymphadenopathy often occurs with viral illnesses, such as infectious mononucleosis, hepatitis, or cytomegalovirus infection, but it also may be a clue to the diagnosis of leukemia or lymphoma. Localized enlargement of lymph nodes should prompt a search for a skin infection or for a tumor. Isolated cervical lymphadenopathy may be associated with tuberculosis infection or cat scratch disease (*Bartonella* infection).

The musculoskeletal system must be examined with care. Localized bone tenderness may suggest osteomyelitis, and a restricted range of motion in a warm joint may suggest arthritis. Although the latter finding may occur in many different diseases, a meticulous examination of the heart is always indicated to detect the carditis of rheumatic fever or infective endocarditis. The spine should be palpated for any evidence of diskitis, and any costovertebral angle tenderness should prompt an examination of the urine for evidence of a UTI.

Although uncommon, factitious fever is a final consideration and a well-described entity. Children as young as 8 years have been known to increase the thermometer reading artificially by rubbing the mercury thermometer bulb on the sheets or by exposing it to warm liquids. Clues at physical examination include

a pulse that is not correlated with the increase in temperature, inability to document fever when it is measured rectally, and an absence of sweating during defervescence. Investigation of psychosocial disturbances within the family is usually necessary.

## SUMMARY

Although fever may be associated with serious illness, treatment of the fever itself is much less crucial than the evaluation and treatment of the illness causing the fever. Health care professionals are responsible for educating parents about the proper management of their febrile children, emphasizing their role in the observation for signs and symptoms that are more likely to be associated with serious disease. Fever as a harbinger of severe sepsis is especially important and both physicians and parents need to be educated on how to differentiate patients who are septic from those who have a more benign illness. Fever is but a single sign that should be evaluated in the total context of the care of the patient.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Fever and Your Child* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *How to Take a Child's Temperature* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/fever/Pages/How-to-Take-a-Childs-Temperature.aspx](http://www.healthychildren.org/English/health-issues/conditions/fever/Pages/How-to-Take-a-Childs-Temperature.aspx))
- *Medications Used to Treat Fever* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/fever/Pages/Medications-Used-to-Treat-Fever.aspx](http://www.healthychildren.org/English/health-issues/conditions/fever/Pages/Medications-Used-to-Treat-Fever.aspx))

## AAP POLICY

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## Chapter 153

## FEVER OF UNKNOWN ORIGIN

Élise W. van der Jagt, MD, MPH

Fever without a discernible cause poses several difficulties for the physician. Since fever suggests disease, the inability to identify its cause can create anxiety for the family and the physician, undermine the physician's credibility, and affect patient rapport. The longer the fever persists, the more concerned parents are and the higher their level of anxiety. A fever of only a few days' duration, not associated with any localizing signs or symptoms, usually does not even come to a physician's attention unless the child also appears ill. Fever that continues beyond 5 to 7 days, or that occurs repeatedly, almost always will prompt a medical consultation. This discussion focuses on these prolonged fevers including their evaluation and management.

## DEFINITION

In 1961, Petersdorf proposed the classic definition for a fever of unknown origin (FUO): fever that is higher than 38.3°C (101°F) on several occasions, that is present for more than 3 weeks, and that has a cause that is still unexplained after 1 week of evaluation in the hospital. Since then, researchers have suggested that these criteria are inappropriate for immunocompromised patients and that the third criterion—evaluation—be changed either to reflect the increased emphasis on ambulatory assessment (unexplained fever after 3 days of in-hospital evaluation or 3 ambulatory visits) or to make the evaluation more quantitative by requiring specific tests that should have been performed before applying the label of FUO. The latter definition is more acceptable to most primary care physicians, who usually don't wish to delay evaluation for 3 weeks or require a week of hospitalization. In children, an FUO has been defined as a daily rectal temperature greater than 38.3°C (101°F), lasting for at least 2 weeks, the cause of which has not been determined by simple diagnostic tests, including a complete history and thorough physical examination. Some experts suggest that 1 of the 2 weeks of fever should be documented in the hospital.

Careful and precise documentation of fever is necessary before using the label of FUO. A thorough awareness of the range of normal core body temperature for age, with its diurnal variation, may help to exclude patients who are actually not febrile but, instead, have a high normal body temperature. The physician should teach the parents how to take a rectal temperature and define a day of fever as a 24-hour period in which a temperature greater than 38.3°C (101°F) occurs at least once. All medications taken, the activities in which the child has participated, and the environmental temperature during this time should be recorded because each of these may affect body temperature.

Although much importance has been attached to fever patterns in the past (ie, remittent, intermittent, sustained), detailing them may not be useful because they are rarely diagnostic of a specific disease. Nevertheless, some inflammatory diseases do have recognizable fever patterns (eg, double quotidian fever of systemic idiopathic juvenile arthritis). In addition, it should be carefully determined if even 1 or 2 days of normal temperature have been interspersed between days of fever: children with this pattern may have a series of rapidly sequenced brief febrile illnesses, which are masquerading as a single febrile illness. Careful documentation of fever should also help exclude the so-called *pseudo-FUO* or factitious fever. Children who have a pseudo-FUO not only do not have a true fever if their body temperature is measured accurately and consistently (sometimes this needs to be done under hospital supervision), but also exhibit a specific and recognizable constellation of findings that is often diagnostic (Box 153-1). In addition to the inability to corroborate fever, and in the setting of a completely normal physical examination, the parents may relate a previous serious illness and their concerns about its possible recurrence or lasting effect on the child (vulnerable child syndrome). Their child may have missed an excessive amount of school, given the general degree of illness described; school absence is often prompted by the presence of fatigue, abdominal pain, and headache in the morning—symptoms that are conspicuously absent during the rest of the day. Others have noted a similar pattern of findings and called it *deconditioning syndrome*, which occurs after an acute, easily definable febrile illness and usually occurs in children who are older than 12 years. The syndrome includes significant fatigue, sedentary habits, absence of depression, and a normal neurologic and musculoskeletal exam. Treatment is directed towards

**BOX 153-1 Characteristics of the Child Who Has Pseudo-Fever of Unknown Origin**

- Absence of documented, persistent fever
- Lack of objective, abnormal physical findings
- History of significant or near-fatal illness
- Parental fear of malignant or crippling disease
- Frequent environmental exposure to illness
- Absence of persistent weight loss
- Normal erythrocyte sedimentation rate and platelet count
- Many missed school days because of subjective morning complaints
- Discordance of fever and pulse rate
- Medical or paramedical family background
- One or more of mild self-limited diseases, behavioral problems, parents who have misconceptions concerning health and disease, or families under stress

From Kleiman MB. The complaint of persistent fever. *Pediatr Clin North Am.* 1982;29(1):201–208. Copyright © 1982, Elsevier, with permission.

**BOX 153-2 Causes of Fever of Unknown Origin in Children****INFECTIOUS DISEASES****Bacterial**

- Bacterial endocarditis
- Bartonellosis
- Brucellosis
- Chlamydia
  - Lymphogranuloma venereum
  - Psittacosis
- Dental infections
- Ehrlichiosis
- Leptospirosis
- Liver abscess
- Lyme disease (*Borrelia burgdorferi*)
- Mastoiditis (chronic)
- Osteomyelitis
- Mycoplasma infections
- Pelvic abscess
- Perinephric abscess
- Pyelonephritis
- Salmonellosis
- Sinusitis
- Subdiaphragmatic abscess
- Tuberculosis
- Tularemia

**Viral**

- Cytomegalovirus
- Epstein-Barr virus (infectious mononucleosis)
- Hepatitis viruses
- Human immunodeficiency virus
- Rickettsial diseases
  - Q fever
  - Rocky Mountain spotted fever

**Fungal**

- Blastomycosis (nonpulmonary)
- Histoplasmosis (disseminated)

**Parasitic**

- Malaria
- Toxoplasmosis
- Visceral larva migrans
- Visceral leishmaniasis

**AUTOIMMUNE DISEASES**

- Polyarteritis nodosa
- Sarcoidosis
- Systemic idiopathic juvenile arthritis
- Systemic lupus erythematosus

**MALIGNANCIES**

- Hodgkin disease
- Leukemia
- Lymphoma
- Neuroblastoma
- Pheochromocytoma

**PERIODIC FEVER SYNDROMES**

- Cyclic neutropenia
- Familial Mediterranean fever
- Hyperimmunoglobulinemia D and periodic fever syndrome (HIDS)
- Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA)
- Tumor necrosis factor receptor–associated periodic syndrome (TRAPS)
- Other periodic fever syndromes

**MISCELLANEOUS CAUSES**

- Colitis, granulomatous
- Colitis, ulcerative
- Diabetes insipidus—central
- Diabetes insipidus—nephrogenic
- Drug fever
- Ectodermal dysplasia
- Familial dysautonomia
- Hemophagocytic lymphohistiocytosis
- Infantile cortical hyperostosis
- Kawasaki disease
- Kikuchi-Fujimoto disease
- Münchausen by proxy
- Pancreatitis
- Pseudo-fever (factitious fever)
- Serum sickness
- Thyrotoxicosis

Modified from Feigin RD, Cherry JD. *Textbook of Pediatric Infectious Diseases*. 5th ed. Philadelphia, PA: WB Saunders; 2004. Copyright © 2004, Elsevier, with permission.

establishing required physical activity in a graduated way while acknowledging that fatigue is present.

Another category of FUO is periodic fever. Instead of a single episode of prolonged fever, affected children have shorter episodes of fever that recur in a regular (periodic) fashion, accompanied by a predictable constellation of symptoms. Patients with this pattern of fever are said to have *periodic fever syndrome*. Many of these periodic fevers are now known to be

genetically based and can be diagnosed by sophisticated genetic testing. Unfortunately, the most common periodic fever (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy [PFAPA]) is not known to be genetic.

**DIFFERENTIAL DIAGNOSIS**

Box 153-2 lists the common causes of FUO in children. The causes are subdivided into 5 main categories:

**Table 153-1** Diagnoses of Prolonged Fever in Children

DIAGNOSIS	AGE		TOTAL
	<6 YEARS	≥6 YEARS	
INFECTION			
Viral	14 (27%)	7 (15%)	21
Nonviral	20 (38%)	11 (23%)	31
OTHER			
Collagen	4 (8%)	16 (33%)	20
Malignancy	4 (8%)	2 (4%)	6
Miscellaneous	7 (13%)	3 (6%)	10
No diagnosis	3 (6%)	9 (19%)	12
Total	52	48	100

From Pizzo PA, Lovejoy FH, Smith DH. Prolonged fever in children: review of 100 cases. *Pediatrics*. 1975;55(4):468–473.

(1) infectious diseases—bacterial/viral/fungal/parasitic, (2) autoimmune diseases, (3) malignancies, (4) periodic fever syndromes, and (5) miscellaneous. This list suggests that most FUOs eventually are found to be caused by common pediatric illnesses that are either self-limited or treatable.

An infectious illness is the most common cause for an FUO in children, comprising between 40% and 60% of the reported cases; the second most common cause is autoimmune disease, comprising between 7% and 20% of the cases. Children younger than 6 years are most likely to have an FUO from an infection; autoimmune diseases become more common after 6 years, although infection remains the most frequent cause of FUO overall (Table 153-1).

Although most infections that present themselves as an FUO are atypical or incomplete manifestations of common infectious diseases, less common infections should also be considered. Epstein-Barr virus is the most common infectious cause of FUO, followed by osteomyelitis and bartonellosis. The advent of serologic testing (indirect immunofluorescent antibodies) for Epstein-Barr virus and *Bartonella* infections has made these diagnoses easier to make. Although bartonellosis (caused by *Bartonella henselae*) usually presents as classic cat-scratch disease, it may also manifest as atypical cat-scratch disease, producing prolonged fever and hepatosplenic abscesses, lymphadenopathy, or central nervous system disease. Thus, when exposure to kittens and cats can be documented, serologic testing for *Bartonella* should be obtained; if positive, an abdominal ultrasound should be considered. Tick-borne diseases should also be considered, especially in areas of the United States where ticks are plentiful. These diseases include Lyme disease, tularemia, tick-borne relapsing fever and ehrlichiosis. Osteomyelitis, particularly of the axial skeleton (intervertebral disk space and vertebral body) and the pelvis, should also be a consideration, especially in young children who are more difficult to examine.

Another interesting syndrome likely initiated by a variety of viruses, and first described in 1972 in adults, is Kikuchi-Fujimoto disease or histiocytic necrotizing lymphadenitis, which is most common in the Far East. Kim recently described a series of 40 children, noting that 90% of them had fever ( $>37.5^{\circ}\text{C}$ ) lasting for a mean of 18 days with tender unilateral cervical lymphadenitis ( $<3$  cm, often multiple). Leukopenia was present in 45%, elevated LDH ( $>500$  U/L) in 88%, and ANA was weakly positive in 30% of patients in whom it was measured. All patients completely recovered.

The appearance during the 1980s and the subsequent increased incidence of HIV infection and acquired immunodeficiency syndrome (AIDS) should encourage primary care physicians to look for characteristic physical signs and symptoms, as well as known risk factors, including parental intravenous drug abuse, parental sexual contact with individuals who may be HIV positive, an HIV-positive mother, and hemophilia requiring transfusion of blood products. Fortunately, in the United States, hemophilia poses less of a risk, since screening for HIV is very sensitive and more synthetic factors are also being used. In addition, infant screening for HIV is also occurring now. Fever is not usually the sole manifestation of HIV infection. However, HIV infection should be strongly considered and the appropriate laboratory tests performed if the fever has been present for more than 2 months and is associated with 1 or more of the following:

- Failure to thrive or a weight loss of more than 10% from baseline
- Hepatomegaly
- Splenomegaly
- Generalized lymphadenopathy (lymph nodes measuring at least 0.5 cm in 2 or more sites, with bilateral site involvement counting as 1 site)
- Parotitis
- Persistent or recurrent diarrhea

Of the autoimmune diseases, systemic-onset juvenile idiopathic arthritis (formerly known as systemic juvenile rheumatoid arthritis) is the most common. Fever is almost always associated with this illness, and it frequently precedes the joint manifestations by weeks or months. The typical double quotidian fever (2 fever spikes in 24 hours with a normal temperature in between) is a helpful clue to this diagnosis. Other common autoimmune diseases that should be considered are lupus erythematosus and chronic regional enteritis. These latter conditions are more common in children older than 6 years.

Malignancy, the diagnosis that provokes the most anxiety, is present in only a small percentage of patients in most studies (1.5%–6%). This is in significant contrast to adults with FUO, of whom between 7% and 16% have a neoplastic process. The most common malignancy in children is leukemia, although solid tumors such as lymphoma, neuroblastoma, hypernephroma, pheochromocytoma and hepatoma have been reported to present as FUO. The exact reason for fever in these diseases is unclear but seems to be related to various endogenous pyrogens such as interleukin-1, interleukin-6 and other cytokines produced by the neoplastic cells. A

large variety of miscellaneous diseases may cause prolonged fevers (see Box 153-2). However, a clear diagnosis is never obtained in 25% to 67% of patients who have persistent fever. These fevers are the genuine FUOs. Most of these patients seem to do well, and the fever eventually disappears after months or even years.

Some patients have fevers that do not satisfy the classic definition of FUO. Instead, they have recurrent fevers that are associated with a well-defined constellation of symptoms each time. The most common of these periodic fever syndromes is PFAPA. This nonhereditary autoinflammatory syndrome has its onset before the age of 3 years, is associated with a sudden fever to 39°C to 40°C (102°F–104°F) lasting 3 to 5 days. Also present are anorexia, mild oral ulcerations with pharyngitis, cervical lymphadenopathy, an increased white blood cell count, and an increased erythrocyte sedimentation rate (ESR). This constellation of symptoms returns every 3 to 6 weeks. A single dose of corticosteroids may quickly resolve the symptoms of individual episodes. In the longest follow-up study available, the average time until resolution of symptoms was 6.3 years, but some patients still had symptoms 18 years later. Removal of adenoids/tonsils has been associated with resolution but it is not always effective.

Other periodic fever syndromes include cyclic neutropenia, familial Mediterranean fever, hyperimmunoglobulinemia D and periodic fever syndrome (HIDS, or mevalonate kinase deficiency), and tumor necrosis factor receptor-associated periodic syndrome (TRAPS). These syndromes are found in various populations around the world and are associated with known gene mutations. The primary care physician should therefore know the patient's race, ethnicity, and country of origin because these factors may provide clues to a specific periodic fever syndrome.

## EVALUATION

### History

Whether the child has a true FUO or a pseudo-FUO cannot be determined without a precise history and thorough physical examination, with the physician paying close attention to behavioral, social, familial, and environmental factors. Information regarding travel, patient residence if outside the United States, animal exposure, frequency of exposure to other persons who have common febrile illnesses, previous illness, hospitalizations, medications, family history of disease, race and ethnicity, and the precise course of the exhibiting symptoms must be obtained methodically and efficiently. Meticulous documentation of dates is especially important. To this end, having the family record on a calendar both the daily time and height of the fever, along with associated symptoms, is usually helpful.

For children older than 11 to 12 years, a separate interview should be conducted alone with the child to obtain the child's perspective on the illness and to elicit information that may be difficult to express in the presence of parents. School, peer relationships, family

functioning, and sexual identity and activity should be explored.

### Physical Examination

A full physical examination must be performed. Rectal temperature, respiratory rate, heart rate, and blood pressure measurements should be obtained. Any discrepancy between heart rate and temperature may imply factitious fever. A thorough examination of the respiratory tract is indicated. Inspection of the tongue and gums for aphthous ulcers, pharynx for hyperemia and exudate, the tympanic membranes for chronic otitis media, and the nose for a purulent nasal discharge, and auscultation of the chest for localized wheezing are all important. In the older child, an examination of the teeth to exclude dental caries and periodontal disease should be included. A new cardiac murmur may be a clue to rheumatic fever or infective endocarditis. A careful abdominal exam may demonstrate an enlarged and/or tender liver, splenomegaly, generalized tenderness, or a mass. Lymphadenopathy, especially if generalized, may suggest a viral infection, such as infectious mononucleosis, cytomegalovirus infection, toxoplasmosis, or HIV infection, but could also suggest leukemia. If lymphadenopathy is limited to the cervical areas, the physician should consider periodic fever syndrome, Kawasaki disease, Kikuchi-Fujimoto disease, and cat-scratch disease. Joints must be examined meticulously for swelling, restricted range of motion, and tenderness. Skin rashes may suggest a viral disease, a tick-borne disease, infectious mononucleosis, or an autoimmune disease such as juvenile idiopathic arthritis. The absence of sweating and the presence of a smooth tongue are consistent with familial dysautonomia, a rare genetic disorder of thermoregulation. Finally, a rectal examination in the older child and a stool guaiac test are imperative; finding pararectal lymphadenopathy may suggest a pelvic infection, and a positive stool guaiac test may be consistent with inflammatory bowel disease.

### Laboratory Evaluation

If the history and physical examination disclose no specific findings and growth is normal, then only simple diagnostic tests are indicated. Routine blood counts and urinalyses have not been shown to be particularly useful, although no one advocates their elimination from the workup. A purified protein derivative tuberculin skin test or interferon-gamma release assay (IGRA) should be done to detect tuberculosis. Negative blood, urine, and throat cultures exclude infections of these areas. One should be careful to recognize that if there is a group A strep positive throat culture without symptoms or physical findings of pharyngitis, one should assume that the throat is colonized with group A strep and this is not the etiology of the fever.

Probably the most useful laboratory tests are the ESR, C-reactive protein (CRP), albumin-globulin ratio, LDH, and uric acid. If the ESR is more than 30, the CRP is elevated, or the albumin-globulin ratio is inverted, then a higher probability of serious disease



exists, particularly an autoimmune vascular disease or a malignancy. Significantly elevated LDH and uric acid suggest tissue breakdown often associated with lymphoproliferative disease or other malignancy. A significantly elevated ferritin is usually present in hemophagocytic lymphohistiocytosis (HLH) and juvenile arthritis with macrophage activation syndrome, but affected children are usually very ill and clearly require hospitalization. Further evaluation should be vigorously pursued.

The remainder of the evaluation should be individualized based on historical and clinical findings. Because infectious causes are the most common, pursuing specific serologic tests for such diseases as hepatitis A and B, Epstein-Barr virus infection (infectious mononucleosis), bartonellosis, toxoplasmosis, and cytomegalovirus infection are reasonable. A radioactive gallium (or other isotope) scan may be useful in detecting occult abscesses and infections, although this scan has been found to be less helpful in children than in adults. Total body computed tomographic scans may help find tumors; however, if the abdomen is of primary concern, an abdominal ultrasound may detect significant abnormalities and would avoid the significant radiation associated with computed tomography. Radiologic studies of the sinuses, the gastrointestinal tract, and the chest all may be appropriate in certain individuals but should not be routine. A bone marrow examination may occasionally help in the diagnosis of tuberculosis, leukemia, metastatic cancer, or fungal infections, but should be considered only in children who have either a clinical or laboratory finding suggestive of malignancy or who are immunocompromised. More recently, with the advent of sophisticated imaging technology, a F-FDG PET or PET/CT scan has been found especially helpful in diagnosing systemic-onset idiopathic juvenile arthritis, obviating further workup. The PET scans demonstrate areas where there is high glucose consumption, typically areas of tumor or inflammation. Further evaluation of the benefit of these types of scans is necessary.

If the ESR, CRP, albumin-globulin ratio, LDH, and uric acid are normal and no signs and symptoms are present that are specific to a particular disease, little can be gained from any of the tests previously mentioned. Observation and periodic evaluation are the only measures that are required while the physician remains alert for the occurrence of new symptoms or signs that might lead the investigation in a specific direction. Fortunately, most FUOs for which a cause cannot be found resolve over time.

Since it is likely that the parents and patient will be anxious about an undiagnosable problem, the primary care physician must be ready to provide all family members with a clear explanation of the evaluative process, any normal results, and reassurance. Referrals to pediatric infectious disease specialists, rheumatologists, specialized diagnosticians, or any combination of these professionals may occasionally be necessary for additional assistance in determining a diagnosis. However, over-referral may accentuate the anxiety of the family.

## SUMMARY

The evaluation of the child who has FUO must be individualized and depends on a careful assessment of the history, the physical examination, and the social context of the child. An initial and often repeated meticulous examination of all these factors is the physician's responsibility and is the first stage of managing the patient. Whether hospitalization is part of this approach ultimately depends on the amount of parental anxiety, the necessity to document fever, and the need for diagnostic tests that cannot be done on an outpatient basis. A minimal number of diagnostic tests is usually sufficient to rule out serious disease that requires aggressive intervention and/or treatment by specific subspecialists.

Frequent assessment of children with persistent FUO is necessary so that subtle clues for diagnoses are not missed, diagnostic testing is timed carefully, and the family continues to maintain confidence in the physician. In the absence of any alarming symptoms, physical findings, or results of diagnostic tests, it is important to emphasize to families and the patient (where appropriate) that even though the fever may last for weeks or months, children with FUOs generally do well.

## WHEN TO ADMIT

Consider admission for the following patients:

- Patients in whom the accuracy of reported temperature is unclear or questionable; temperatures must be taken by hospital staff or under their direct supervision.
- Patients who need multiple tests, many of which require procedural sedation. Coordinating these tests together over a period of 24 to 48 hours may be more efficient than performing them individually as an outpatient.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Fever* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Fever* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/fever/Pages/default.aspx](http://www.healthychildren.org/English/health-issues/conditions/fever/Pages/default.aspx))
- *Fever and Your Child* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

### Medical Decision Support

- *Red Book: 2015 Report of the Committee on Infectious Diseases*, 30th ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

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## Chapter 154

## FOOT AND LEG PROBLEMS

Benjamin Weintraub, MD

## INTRODUCTION

Parents frequently come to the physician with concerns about their children's feet and legs, such as "my son is pigeon-toed," or "my daughter is knock-kneed." In most cases, these findings are purely normal developmental stages seen in the growth of the lower extremities. For example, it is entirely normal for a toddler just starting to walk to be "bowlegged" or "pigeon-toed," or for a 3-year-old to have "knock-knees." However, it may be pathologic for a 10-year-old to have significant genu valgus (knock-knees) or a 5-year-old to have severe genu varum (bowed legs). The physician, then, needs to understand the normal changes seen during growth and development to judge properly when a finding is pathologic and requires further evaluation, treatment, and referral to a specialist.

## NATURAL GROWTH OF LOWER EXTREMITIES

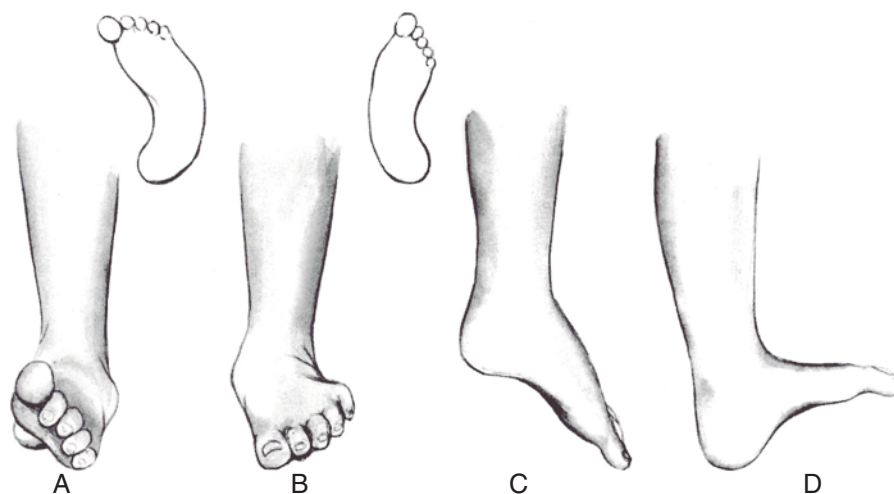
During the course of gestation, the lower extremities of the fetus undergo vast changes. Lower limb buds develop at 4 weeks' gestation. During week 6, the lower limbs begin to flex toward the parasagittal plane, and then proceed to rotate medially so that the knee points cranially and the great toe is brought to the midline. By term, 80% of babies are in the classic fetal position with knees and hips flexed, hips externally rotated, and ankles plantar-flexed and internally rotated. This tightly packaged position conveniently helps drive the femoral head into the acetabulum,

thereby aiding in the development of the hip socket. It also leads to a number of transient conditions that self-resolve over time but until then may cause significant parental anxiety: pigeon toeing and bow legs, or more precisely, internal tibial torsion, metatarsus adductus, and medial femoral anteversion.

Of the remaining 20% not in the usual fetal position, most are in a position with hips and knees flexed, ankles dorsiflexed, and legs and feet externally rotated, which can lead to external tibial torsion, calcaneovalgus feet, and out-toeing.

After birth, the first of these "packaging defects" to self-correct is metatarsus adductus. This medial deviation of the forefoot usually either self-resolves or can be corrected by 1 year of age with simple stretching. Tibial bowing is next to resolve by about age 2 to 4 years. Bowing is usually followed by the appearance of an increasingly knock-kneed or genu valgus stance from 3 to 5 years of age. By the end of the first decade of life, tibial torsion goes from a mean of 5 degrees medial torsion to 10 degrees lateral torsion, and femoral anteversion decreases from about 40 degrees at birth to about 10 degrees. The result is a lateral rotation of the lower extremity during growth and a gradual decline in the degree of genu valgus until the normal adult stance of minimal genu valgum is reached at maturity (Figure 154-1).

Most functional deformities of the legs and feet are self-correcting in time through this normal developmental progression of the lower extremities. In the past, many of these rotational and positional deformities were treated with stretching, bracing, and even casting. However, studies of these functional deformities comparing treated versus untreated paired-control groups have demonstrated the relative ineffectiveness of treatment for these conditions. Therefore, most physicians choose watchful waiting for these conditions because children naturally grow out of them. A more detailed discussion of these conditions follows.



**Figure 154-1** Positional deformities of the foot and ankle. A, Varus. B, Valgus. C, Equinus. D, Talipes calcaneus.

## ORTHOPEDIC TERMINOLOGY

Orthopedists use a standard terminology to describe positional and structural variations of the lower extremities. In general, the joint that is primarily involved in the condition constitutes the first word; the subsequent word or words relate to the positioning of the extremity relative to the midline of the body. For example, coxa vara is a condition of the hip (coxa) that results in a deviation of the leg toward the midline (varus position). The orthopedic terms in Box 154-1 have special reference to abnormalities of the feet and legs.

## ROTATIONAL DEFORMITIES

### In-toeing and Out-toeing

Rotational deformities of the lower extremities are the most common cause of in-toeing and out-toeing. With in-toeing (pigeon toe), the foot turns inward more than expected during walking or running relative to the line of progression; with out-toeing, the foot turns outward more than expected. Parents, seeing either in-toeing or out-toeing, often become concerned that some intervention is needed. In most cases, these deformities are physiologic, related to normal growth and development, and the appropriate intervention is reassurance.

### BOX 154-1 Glossary of Terms That Refer to Foot and Leg Abnormalities

- *Abduction*: deviation away from the midline of the body
- *Adduction*: deviation toward the midline of the body
- *Cavus*: medial longitudinal arch of the foot elevated
- *Equinus*: foot plantar-flexed, placing the toes below the level of the heel
- *Pes*: the foot
- *Planus*: medial longitudinal arch of the foot flattened
- *Talipes*: congenital deformity describing a foot that is twisted out of shape or position
- *Talipes calcaneus*: a deformity of the foot in which the foot is dorsiflexed
- *Torsion*: excessive or abnormal twisting along the long axis
  - *Internal torsion*: excessive or abnormal inward twisting
  - *External torsion*: excessive or abnormal outward twisting
- *Varus*: medial or inward deviation of the distal segment of an extremity relative to the proximal (previous) segment
- *Valgus*: lateral or outward deviation of the distal segment of an extremity relative to the proximal (previous) segment
- *Version*: physiologic or normal twisting along the long axis
  - *Inversion*: physiologic or normal twist inward
  - *Eversion*: physiologic or normal twist outward
  - *Anteversión*: physiologic or normal twist forward
  - *Retroversion*: physiologic or normal twist backward

In-toeing and out-toeing may be seen at all ages and are caused by a variety of conditions affecting the feet, ankles, legs, knees, and hips. In general, with in-toeing, if the child's patellae are rotated inward (kissing knees) while walking, then the underlying problem will be found above the knee—most commonly femoral anteversion. If the patellae face straight forward, then the underlying problem is likely below the knee—most commonly medial tibial torsion or metatarsus adductus. Less common causes of in-toeing include talipes equinovarus, metatarsus varus, and spasticity of the internal rotator muscles of the hip, as seen in cerebral palsy.

Excessive out-toeing, less common than in-toeing, may be seen with excessive external tibial torsion and femoral retroversion, or with posterior maldirection of the acetabulum, rigid flat feet, and flaccid paralysis of the internal rotator muscles of the hip. Most adults have a mild degree of physiologic out-toeing when standing and walking.

Parents can be reassured that most cases of in-toeing and out-toeing will resolve spontaneously as the lower extremities finish growing. Although in-toeing or out-toeing may reflect a variety of underlying orthopedic diseases, no evidence has been found to suggest that uncorrected in-toeing or out-toeing of normal developmental origin leads to any functional disabilities.

An orthopedic or neurologic evaluation should be made for any child with severe in-toeing or out-toeing, or for an unsteady gait (especially while running) that causes stumbling. A referral may also be advised if a child's condition does not follow the expected physiologic progression with growth.

## Metatarsus Adductus and Deformities of the Forefoot

### Clinical Conditions

Deformities of the forefoot are among the earliest causes of in-toeing noted by parents. The most common and generally benign cause is *metatarsus adductus* (Figure 154-2), a condition in which the only finding is a flexible adduction of the metatarsals at the tarsometatarsal joints. The incidence of metatarsus adductus is generally reported to be approximately 1 in 1,000 live births, but in some studies it is reported to be as high as 1 in 100. There is a slightly higher incidence in the left foot than the right, and 50% to 60% of cases occur bilaterally.

The differential diagnosis of metatarsus adductus includes the uncommon conditions talipes varus, metatarsus varus, and clubfoot. *Talipes varus* (Figure 154-3) is a condition in which the entire foot is inverted and the forefoot is adducted. In *metatarsus varus* (Figure 154-4), the forefoot is inverted and adducted while the hindfoot and heel are in the normal position. Talipes varus and metatarsus varus have been considered lesser degrees of clubfoot and are fixed deformities of the foot that require early treatment.

## Evaluation

### Relevant History

Although its exact cause has not been established, metatarsus adductus is widely considered a packaging defect. There may be a history of oligohydramnios,

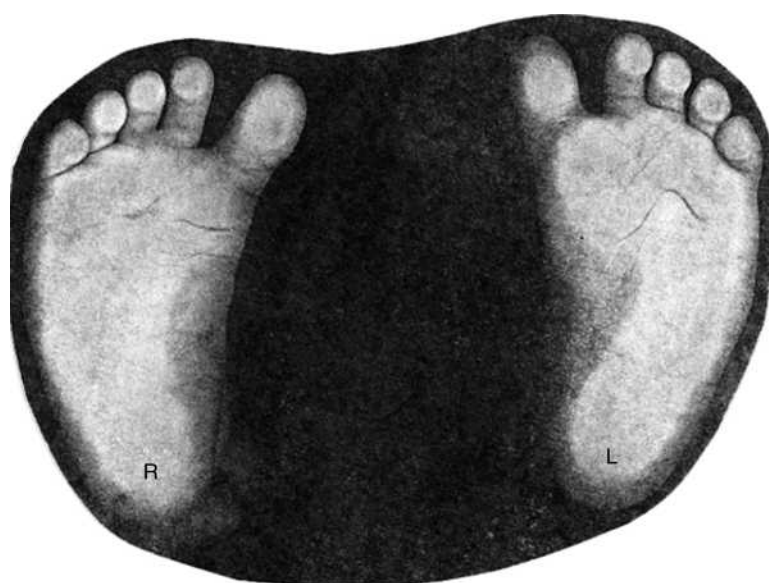
uterine fibroids, multiple gestation, or other cause of a crowded intrauterine environment; but such a history is not necessary for making the diagnosis. Metatarsus adductus was previously thought to be associated with developmental hip dysplasia. However, more recent studies do not support the association, and an ultrasound of the hips is no longer required as part of the workup of metatarsus adductus.

### Physical Examination

Metatarsus adductus is graded by both the degree of adduction and the flexibility of the deformity. The severity of adduction is graded by the heel bisector

method. Normally, a line bisecting the heel and sole longitudinally lines up approximately with the second toe. In mild metatarsus adductus, the heel bisector line falls through the third toe, whereas in severe metatarsus adductus, the line falls between the fourth and fifth toes. The heel bisector line can be assessed directly on the child's foot, or the child may be stood up on a photocopy machine to take a photograph of the soles of the feet. A bisector line can then be drawn on the photocopy. An advantage of this method is that it allows for easy tracking of the condition over time.

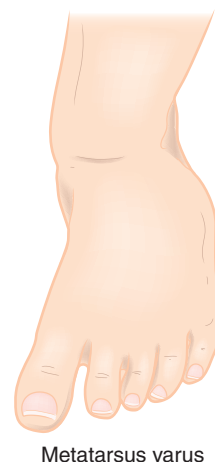
Next, flexibility of the forefoot should be assessed by holding the heel and abducting the forefoot. With a



**Figure 154-2** Photocopy of the feet of a 9-month-old infant with bilateral metatarsus adductus. (From Greene WB. *Metatarsus adductus and skewfoot*. Instr Course Lect. 1994;43:161–177. Reproduced with permission from American Academy of Orthopaedic Surgeons.)



**Figure 154-3** Talipes varus. The entire foot is twisted inward on its longitudinal axis, and the forefoot is adducted.



**Figure 154-4** Bilateral metatarsus varus. The forefoot is inverted and adducted, and the lateral border of the foot is convex. The hindfoot is in a neutral position.



flexible foot, the second toe can be easily brought in line with or even past the heel bisector line. If the foot is not flexible, then the defect is more consistent with metatarsus varus or talipes varus, and referral should be made to an orthopedist.

### Imaging

Radiographic examination is necessary only when there is limited flexibility of the forefoot to evaluate for talipes varus and metatarsus varus.

### Management

Metatarsus adductus is a functional deformity and requires minimal if any treatment because most cases correct spontaneously during the first year of life. Parents may be instructed to perform simple stretching exercises of the child's foot. The parent holds the heel in place and puts gentle pressure on the medial side of the foot with the other hand, stretching the midfoot and bringing the foot into normal or even slightly overcorrected position. This stretch can be held for several seconds and repeated 5 to 10 times with each diaper change. About 85% to 90% of cases will resolve by 8 to 12 months of age with this simple management. If some improvement is not seen by 6 months of age, referral to a specialist should be made. Most of these refractory cases can be treated successfully with serial casting. Whether through spontaneous resolution or with treatment, nearly all cases of metatarsus adductus resolve without any long-term complications.

Talipes varus and metatarsus varus are fixed deformities of the foot that require early referral and treatment. Treatment consists of serial casting, long-leg splints that abduct the forefoot, or both. Abduction stretching exercises and outflare shoes may be used as an adjunct to cast treatment but should not be relied on as the only therapy. The sooner therapy is initiated, the better the outcome.

### Tibial Torsion

#### Natural History and Presentation

*Tibial torsion* is the rotation of the tibia on its longitudinal axis. Most infants are born with internal tibial torsion resulting from normal growth and the classic fetal position in utero. This turning inward results in mild in-toeing at birth for many infants. The average tibial torsion in infancy is  $-5$  degrees (5 degrees of internal tibial torsion). An increased degree of internal tibial torsion is a common cause of in-toeing in toddlers up to age 3 or 4 years. As the child grows, the tibia externally rotates until a mild degree of external tibial torsion is reached in later childhood. Adults have an average external tibial torsion of  $+15$  to  $+25$  degrees, which accounts for the standard mild out-toeing position seen in adulthood. There is no evidence that patients with unresolved internal tibial torsion experience any increased incidence of knee pain, arthritis, or other conditions later in life. External tibial torsion in early childhood is much less common. It may be idiopathic, or it can be seen with calcaneovalgus foot deformities, as compensation for persistent severe femoral anteversion, or associated with tight iliotibial bands. As the tibia normally undergoes external rotation during growth, external

tibial torsion may actually worsen over time rather than improve.

Pathologic degrees of internal and external tibial torsion are rare and may occur with other significant deformities of the hips or lower extremities, or as a result of improperly applied casts or braces.

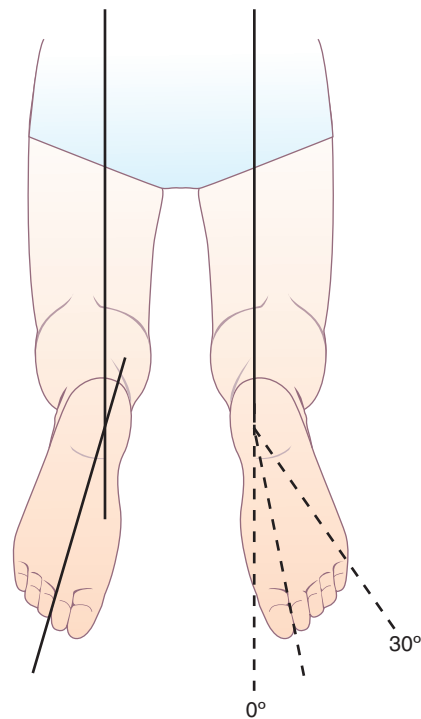
### Evaluation

#### Physical Examination

The easiest way to assess tibial rotation is to measure the thigh-foot angle, which is the axis of the foot relative to the axis of the thigh (see Figures 154-5 and 154-6). The infant or child should be placed prone on the abdomen with the knees together and bent to 90 degrees and the ankles in neutral position. The acute angle made between the axis of the femur and the heel bisector is the thigh-foot angle. An internal or negative angle indicates internal rotation; an external or positive angle indicates external rotation. The normal thigh-foot angle at birth ranges widely from  $-35$  degrees to  $+40$  degrees, with a mean of  $-5$  degrees. Thigh-foot angles of  $+10$  degrees and  $+15$  to  $+25$  degrees are the average seen in older children and adults, respectively.

### Imaging

Although studies have shown computed tomography scanning to be an excellent method for measuring the exact degree of tibial torsion, imaging is not required in most cases: physical examination is generally sufficient.



**Figure 154-5** Thigh-foot angle: normal range. (From Alexander JJ. *The Foot: Examination and Diagnosis*. New York, NY: Churchill Livingstone; 1990. Copyright © 1990, Elsevier, with permission.)

## Management

In the past, various forms of bracing, such as Denis Browne splints, were used to treat internal tibial torsion. However, because it is now understood that this condition resolves on its own over time, treatment of primary internal tibial torsion is no longer recommended. Even toddlers who may occasionally trip over their toes as a result of increased internal tibial torsion generally do not need treatment and outgrow the condition by age 6 years. The mainstay of treatment is parental reassurance and education about the natural growth and development of the legs. In very rare cases, when severe residual internal tibial torsion is affecting function, derotational osteotomies may be required. Surgery should be delayed until at least 8 to 10 years of age to ensure that the issue does not self-correct. Surgery may also be required for the rare case of significant external tibial torsion that interferes with function.

## Femoral Anteversion

*Femoral anteversion* is the increased internal rotation or twisting of the femoral neck anteriorly relative to the femoral condyles; *femoral retroversion* is the extreme twisting of the femoral neck posteriorly relative to the femoral condyles. Femoral anteversion is greatest at birth (about 40 degrees) and gradually declines to adult values of 10 to 15 degrees by age 8 years. Femoral anteversion is the most common cause of in-toeing seen in preschool-aged children. Conversely, femoral retroversion is an uncommon condition that results in an out-toeing gait. New

onset of femoral retroversion may occur in older children in the setting of slipped capital femoral epiphysis (SCFE).

## Natural History and Presentation

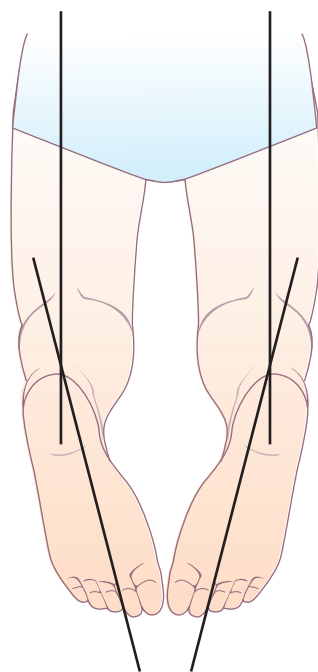
In utero and postnatal positioning of the legs and hips produces stresses that are thought to bring about these rotational deformities of the femoral neck. The true incidence of excessive anteversion and retroversion is not known. However, femoral anteversion is much more common and occurs twice as frequently in girls as in boys.

## Evaluation

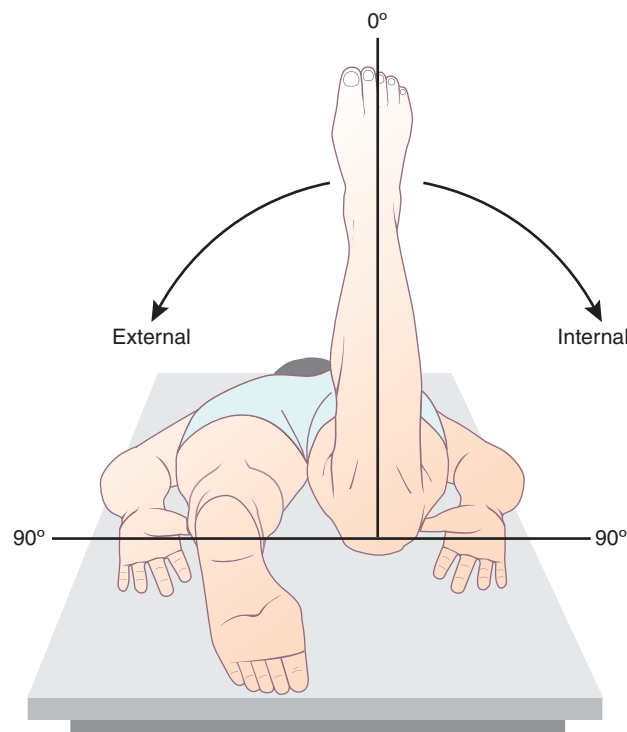
### Physical Examination

Parents of a child with femoral anteversion may express concerns about kissing knees, in-toeing, or a clumsy gait, or they may note that the child will not or cannot sit in the modified lotus position but rather prefers to “W” sit.

The best manner in which to assess for femoral anteversion or retroversion is to place the child in the prone position with the knees flexed to 90 degrees. To measure hip rotation, the lower leg is used as a pointer, and the legs are rotated through the axis of the hip joint (Figures 154-7 and 154-8). Normally the examiner should be able to move the hip through approximately 50 degrees of internal and 40 degrees of external rotation. With excessive femoral anteversion, there will be



**Figure 154-6** Bilateral internal tibial torsion. (From Alexander LJ. *The Foot: Examination and Diagnosis*. New York, NY: Churchill Livingstone; 1990. Copyright © 1990, Elsevier, with permission.)



**Figure 154-7** Starting position for measuring hip rotation with the hip extended while the child is in the prone position. (Reprinted with permission from Joint Motion Method of Measuring and Recording. Rosemont, IL: American Academy of Orthopedic Surgeons; 1965.)

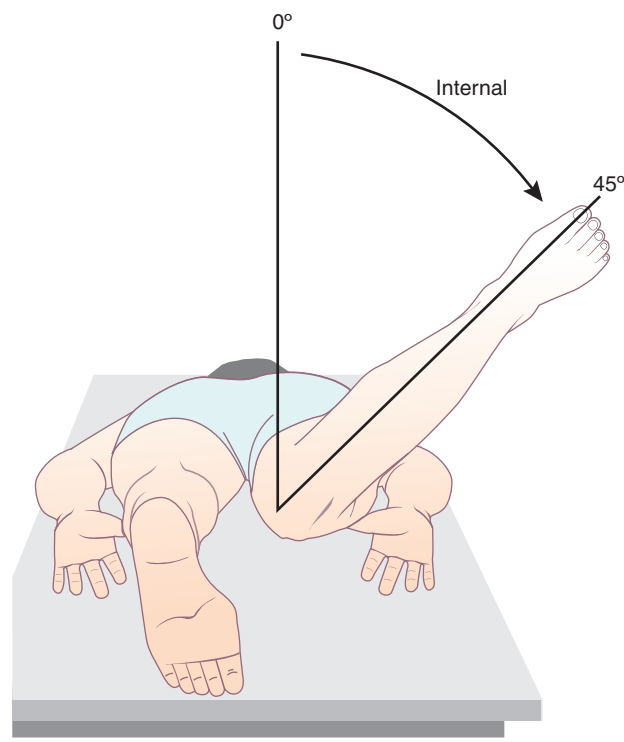
increased internal rotation of the hip of at least 60 to 65 and sometimes as much as 80 to 90 degrees, along with a decrease in external rotation to less than 20 degrees. With excessive femoral retroversion, there will be increased external rotation and decreased internal rotation. Until 1 or 2 years of age, the clinical measurement of hip rotation using this method is limited by the physiologic tightness of the hip joint capsule.

### Imaging

Imaging is only required with severe femoral anteversion. New-onset, severe, or worsening femoral retroversion, however, can be associated with SCFE or other hip disorders, and radiographs should be obtained.

### Management

Most femoral torsion deformities correct themselves by 7 years of age. Children with pronounced femoral anteversion often are noted to sit in a “W” position with the child’s bottom firmly planted between the feet. It is unclear if this sitting position contributes to the development of femoral anteversion, or if children with preexisting femoral anteversion find this position to be more comfortable. Parents who feel the need to intervene can encourage their child to sit in a modified lotus or Indian-style position, while discouraging sitting in the “W” position. They should be informed that these interventions are more anecdotal than evidence based. The use of splints is contraindicated, and corrective shoes are of no value.



**Figure 154-8** Internal rotation. (Reprinted with permission from Joint Motion Method of Measuring and Recording. Rosemont, IL: American Academy of Orthopedic Surgeons; 1965.)

An orthopedist should be consulted if the femoral anteversion does not follow the typical pattern of improvement with growth, if it is associated with difficulty walking or running, or if significant asymmetry of the anteversion exists between the 2 legs. Orthopedic treatment may consist of the use of a bivalve lower trunk and leg cast during sleeping hours or, in rare cases, a derotation osteotomy of the middle or lower femoral shaft. It remains unclear whether untreated excessive femoral anteversion contributes to early degenerative changes and osteoarthritis of the hip. Stronger evidence indicates that persistent excessive femoral retroversion may be associated with degenerative changes, and therefore referral to an orthopedist may be warranted. With femoral retroversion, immediate referral should be made if radiographs reveal SCFE.

## PATHOLOGIC BOWED LEGS AND KNOCK-KNEES

Genu varum (bowed legs) is an angular deformity at the knee with the tibia adducted (varus) in relation to the femur. Genu valgum (knock-knees) is characterized by alignment of the knee with the tibia abducted (valgus) in relation to the femur. These conditions are generally part of the normal growth and development of the lower extremities. Bowed legs, normal at birth, start to correct once children begin to walk and are usually fully resolved by 2 to 3 years of age. Children then become increasingly knock-kneed by age 3 to 4 years, with ultimate resolution over the next several years.

### Differential Diagnosis

Although bowed legs and knock-knees are normal at various stages of growth and development, extremes of either of these conditions, unilateral presentation, or their persistence beyond the normal time of resolution may indicate an underlying pathology. Extreme degrees of physiologic bowing of the legs may occur in the young child, and although even this usually resolves over time without treatment, a basic evaluation should be performed to ensure there is no underlying pathology (Figure 154-9).

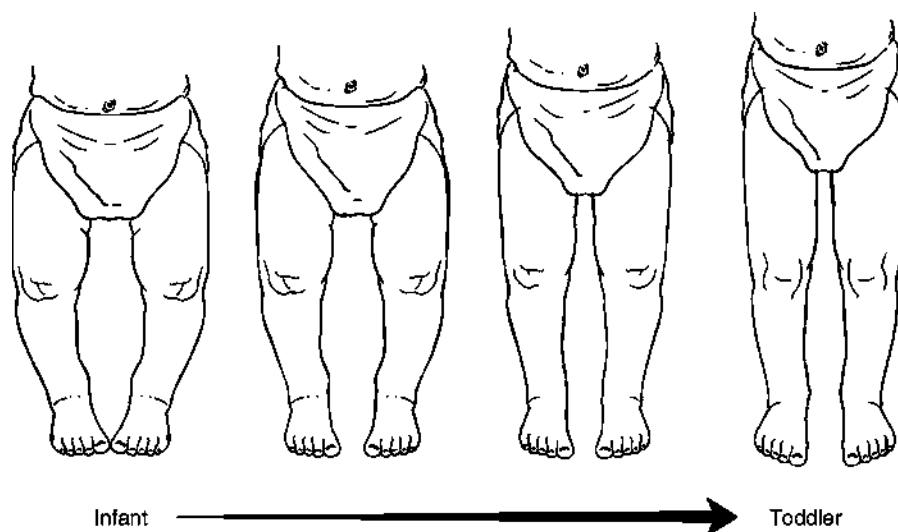
Genu varum (bowed legs), when extreme, unilateral, or persistent, may result from a variety of conditions, including rickets, chondroplasia, osteogenesis imperfecta, osteochondritis, neuromuscular disorders, or Blount disease. In addition, trauma, infection, or tumor involving the medial proximal epiphysis of the tibia can result in genu varum.

Genu valgum (knock-knees) is often associated with pronation and is more frequently seen in the overweight child. Causes of severe bilateral genu valgum include rickets, renal osteodystrophy, and skeletal dysplasia. Unilateral genu valgum may be a result of trauma, infection, or tumors involving the lateral proximal epiphysis of the tibia (Figure 154-10).

### Evaluation

#### Pertinent History

When evaluating severe or abnormal genu varum or valgus, a family history of metabolic, renal, or skeletal



**Figure 154-9** Normal progression from bowlegs of infancy through slow evolution to a physiologic valgus angle of about  $12^\circ$  at 3 years of age. (From Gómez JE. *Growth and maturation*. In: Harris SA, Anderson SJ, eds. *Care of the Young Athlete*. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2010:18)



**Figure 154-10** Clinical photograph of boy referred for evaluation of “knock-knees.” The patient was considered to be within normal limits. (From Greene WB. *Genu varum and genu valgum in children*. Instr Course Lect. 1994;43:151–159. Reproduced with permission from American Academy of Orthopaedic Surgeons.)

diseases should be elicited, along with any history of prior trauma, endocrine, metabolic, or bone abnormalities.

#### Physical Examination

The best way to track the progression of genu varum is to lay the patient down supine, place the ankles

together, and measure the distance between the knees. This distance can be followed over time and can be used as a simple way to demonstrate to a parent that the issue is self-resolving. Similarly, the degree of genu valgum can be tracked by measuring the distance between the medial malleoli when the child is standing with the knees together.

#### Imaging

With extreme or unilateral genu valgum or genu varum, radiographic examination should be obtained to exclude rickets, chondroplasia, osteogenesis imperfecta, osteochondritis, Blount disease, injury to the proximal epiphysis of the tibia, or other pathologic process. Additional targeted laboratory evaluation for underlying metabolic conditions may also be indicated.

#### Management

Simple observation and reassurance are all that are required for physiologic genu varum and genu valgum because these conditions spontaneously correct 99% of the time. When identified, underlying causes of extreme varus or valgum deformities must be effectively treated to improve angulation. Treatment of severe bowing or knocking of the knees caused by underlying disease is determined by the nature of the condition and may include wedge osteotomy, epiphyseal stapling, or nutritional, hormonal therapy. Treatment of mild cases of Blount disease may be attempted with bracing; more severe cases often require surgery.

### CLUBFOOT

#### General

*Clubfoot* or *talipes equinovarus* is a pathologic condition in which the foot and ankle are rigidly inverted, adducted, and plantar-flexed, resulting in a clubbing appearance (Figure 154-11). Clubfoot can easily be





**Figure 154-11** Bilateral congenital clubfoot seen in a newborn. (From Sarwark JF, ed. *Essentials of Musculoskeletal Care*. 4th ed. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2010. Reproduced with permission.)



**Figure 154-12** Clinical photograph of a calcaneovalgus foot in a neonate. (From Sarwark JF, ed. *Essentials of Musculoskeletal Care*. 4th ed. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2010. Reproduced with permission.)

distinguished from benign packaging deformities of the foot that frequently occur in newborns; whereas functional deformities can be placed into normal physiologic position and usually even overcorrected, clubfoot is a rigid deformity that cannot be placed into normal alignment.

The differential diagnosis of clubfoot includes severe metatarsus adductus, talipes varus and metatarsus varus, and *calcaneovalgus* foot, which is characterized by eversion of the heel and forefoot, abduction of the forefoot, and dorsiflexion of the entire foot (Figure 154-12). Calcaneovalgus foot generally resolves in time with stretching exercises.

### Evaluation

#### Relevant History

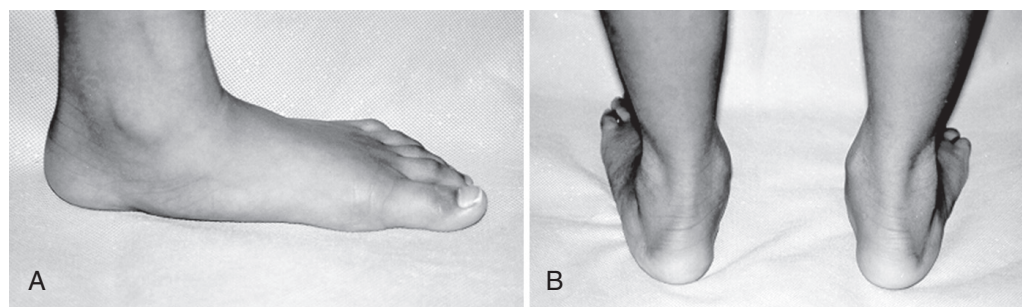
The cause of congenital clubfoot is unknown. Although it can be associated with conditions such as spina bifida, trisomy 18, or congenital constriction band syndrome, clubfoot occurs as an isolated deformity in otherwise normal newborns in 80% of cases. Inheritance of idiopathic clubfoot seems to be multifactorial, and a specific genetic cause has not yet been

identified. The incidence of clubfoot is approximately 1 in every 1,000 live births. It occurs bilaterally in 50% of cases and affects boys twice as frequently as girls. There is a 3% to 4% risk for recurrence in a family if a prior sibling had clubfoot. When a parent and sibling are affected, future children have upward of a 25% risk. Clubfoot can also develop later in life as a result of neuromuscular conditions such as arthrogryposis and meningomyelocele, and even as a neurologic complication of Wilson disease.

### Physical Examination

Four main components combine to form the defective foot and ankle of a clubfoot: significant and uncorrectable plantar flexion of the ankle; heel and hindfoot adduction; high arch (cavus) at the midfoot; and severe adduction of the forefoot. All combined, the result is a rigidly plantar-flexed, medially rotated, and twisted foot and ankle that cannot be passively manipulated into a normal foot position.

When clubfoot is present, an evaluation for associated neurologic, muscular, or other skeletal anomalies should be performed.



**Figure 154-13** Medial (A) and posterior (B) views of flatfoot. (From Sarwark JF, ed. *Essentials of Musculoskeletal Care*. 4th ed. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2010. Reproduced with permission.)

### Imaging

Although radiographic examination is not generally required for diagnosis, it is useful to delineate the pathologic findings and guide management.

### Management

For pediatricians, treatment of clubfoot entails early and immediate referral to a pediatric orthopedist for either serial casting or surgery. Some institutions report extremely high success rates with serial casting beginning in the first weeks of life and continuing through several months of age. Rates of recurrence vary after correction by manipulation alone. Recurrence after casting is most common within the first 2 to 3 years but may still happen as late as 5 to 7 years of age. Surgical correction (tenotomy, muscle transplantation, and arthrodesis) may be required in severe cases, when conservative management fails, or as a result of recurrence when the child is older. Recurrence is much less likely after surgical correction, although functional outcomes are not necessarily improved compared with more conservative measures. Even with successful treatment, the affected foot is generally smaller and less mobile than a normal foot. Early initiation of therapy increases the success rate of manipulative or conservative management and therefore decreases the need for surgical intervention.

## FLATFOOT

*Pes planus*, or flatfoot, is a very common condition in childhood characterized by the loss or absence of the medial longitudinal arch when weight bearing. It is associated with a pronated gait and stance, eversion of the calcaneus and valgus position of the heel, and prominence of the medial talar head. The condition is best divided into 2 main categories: flexible flatfoot and rigid flatfoot. There is significant disagreement about the clinical importance of flexible flatfoot, if any, and its treatment. Rigid flatfoot is more likely to be clinically significant and to require treatment, although disagreement exists about this condition as well.

### Flexible Flatfoot

Infants are born with flat feet. The normal medial longitudinal arch does not begin forming until about 3 years of age and continues to develop for several years. The prevalence of flexible flatfoot in one study was shown to decrease on average from 54% at

3 years to 24% by 6 years of age. Boys seem twice as likely as girls to have flatfoot at 6 years of age. Overweight and obesity also increase the risk for flexible flatfoot. By adulthood, the prevalence of flatfoot is closer to 10% to 20%.

Prevailing opinion in the past was that flatfoot was a cause of foot, leg, and back pain, and that it interfered with physical activity. This, however, is now not so clear. Some studies suggest that people with flatfoot walk more slowly and have decreased physical performance, whereas other studies, one involving military recruits and one involving teenagers, showed neither disadvantages in performance nor increased injury rates with flatfoot. In short, there remains a lack of general consensus on the clinical significance of this condition.

### Physical Examination

The diagnosis of flexible flatfoot is made clinically; imaging is not required. The patient's foot should be examined while he or she is standing. If flatfoot is present, the examiner will notice a collapse of the medial longitudinal arch and ankle pronation with valgus heel position (Figure 154-13). When viewed from behind, the Achilles tendon is noted to bend medially before arcing back laterally toward the everted calcaneus. To be certain that the condition is flexible, the examiner should have the patient stand on tiptoe: in flexible flatfoot, the medial longitudinal arch of the foot will return; with rigid flatfoot, the sole remains flat.

### Treatment

Treatment of flexible flatfoot remains controversial. If flatfoot is not causing any problems, no treatment is needed beyond parental reassurance. In cases in which the condition seems to be contributing to pain and discomfort or impairing function, flatfoot can be managed conservatively with arch support inserts. If the condition is associated with tight Achilles tendons, stretching may be a beneficial part of treatment.

### Rigid Flatfoot

Unlike flexible flatfoot, rigid flatfoot is more likely to represent a pathologic condition. It can result from tarsal coalition (fusion of 1 or more of the tarsal bones) or vertical talus. Two types of tarsal coalitions have been identified: *calcaneonavicular coalition*,

which involves the calcaneus and the navicular bones; and *talocalcaneal coalition*, in which the calcaneus is coalesced to the talus. Congenital rigid flatfoot occurs in approximately 1% of the population and frequently is bilateral. Rigid flatfoot may also be acquired from trauma, infection, an arthritic process, or neuromuscular disease. In these cases, the condition may be progressive, and any underlying condition should be treated as part of the management of the rigid flatfoot.

### Physical Examination

Examination of a rigid flatfoot reveals a foot with a stiff, flattened arch in both weight-bearing and non-weight-bearing positions. There is no return of a normal arch when standing on tiptoe. This condition is generally associated with a significant degree of ankle pronation. Vertical talus and accessory tarsonavicular can usually be detected in the newborn by the presence of a bony prominence on the medial and plantar aspects of the foot, with limitation of plantar flexion and inversion of the forefoot.

Tarsal coalitions are not usually detected until late childhood or adolescence, when the initially fibrous or cartilaginous bar connecting the hindfoot bones becomes ossified, producing pain with walking and an inability to invert the foot. The foot is held in a pronated position with eversion of the forefoot. The peroneal tendons stand out prominently when attempts are made to invert the foot. Calcaneonavicular coalition tends to develop between 9 and 13 years of age, whereas talocalcaneal coalition develops later, typically at 13 to 16 years of age.

### Imaging

Radiographs may be useful in identifying the exact cause of rigid flatfoot in a patient.

### Treatment

Treatment in most cases of rigid flatfoot is with orthopedic shoes. Surgical correction is required only for accessory tarsonavicular or tarsal coalition if symptoms cannot be relieved through conservative means (only about 10% of cases) and is usually performed in adulthood. Vertical talus usually requires surgical correction early in infancy.

## PES CAVUS

Pes cavus (cavus foot deformity) is an equinus deformity of the forefoot relative to the hindfoot, producing a very high medial longitudinal arch (Figure 154-14). It is referred to as clawfoot when associated with flexion deformities of the toes. The primary pathologic condition is neuromuscular rather than bony, with weakness or paralysis of the intrinsic muscles of the foot and its dorsiflexors leading to the deformity over time. Pes cavus is not seen at birth. Depending on the underlying neuromuscular disease, it usually does not develop until late childhood or adulthood. Pes cavus may be seen in muscular dystrophy, peripheral neuropathies, and diseases of the spinal cord, brainstem, and cerebral cortex. Cerebral palsy, meningomyelocele, poliomyelitis, Charcot-Marie-Tooth disease, and



**Figure 154-14** Clinical photograph demonstrating pes cavus. (From Sarwark JF, ed. *Essentials of Musculoskeletal Care*. 4th ed. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2010. Reproduced with permission.)

Friedreich ataxia are some neurologic conditions that may produce pes cavus as a late manifestation.

### Evaluation

#### Pertinent History

Because pes cavus is not seen at birth but rather develops over time, parents may say they have begun finding it difficult to fit shoes on their child's feet, or they may note that the foot is different in appearance. A review of symptoms may reveal problems with bowel or bladder control consistent with spinal cord pathology. There may be a family history of pes cavus because many of the conditions producing this deformity are inherited.

### Physical Examination

A high-arched foot is the main finding in this condition. Pes cavus takes 1 of 2 forms: cavovarus, in which the calcaneus is inverted with tightness of the heel cord; or calcaneocavus, in which a high arch with normal heel alignment is present, usually from weakness of the calf muscles resulting in increased ankle dorsiflexion and increased plantar flexion of the forefoot.

### Imaging

Radiographic examination may be necessary if surgical management is being considered.

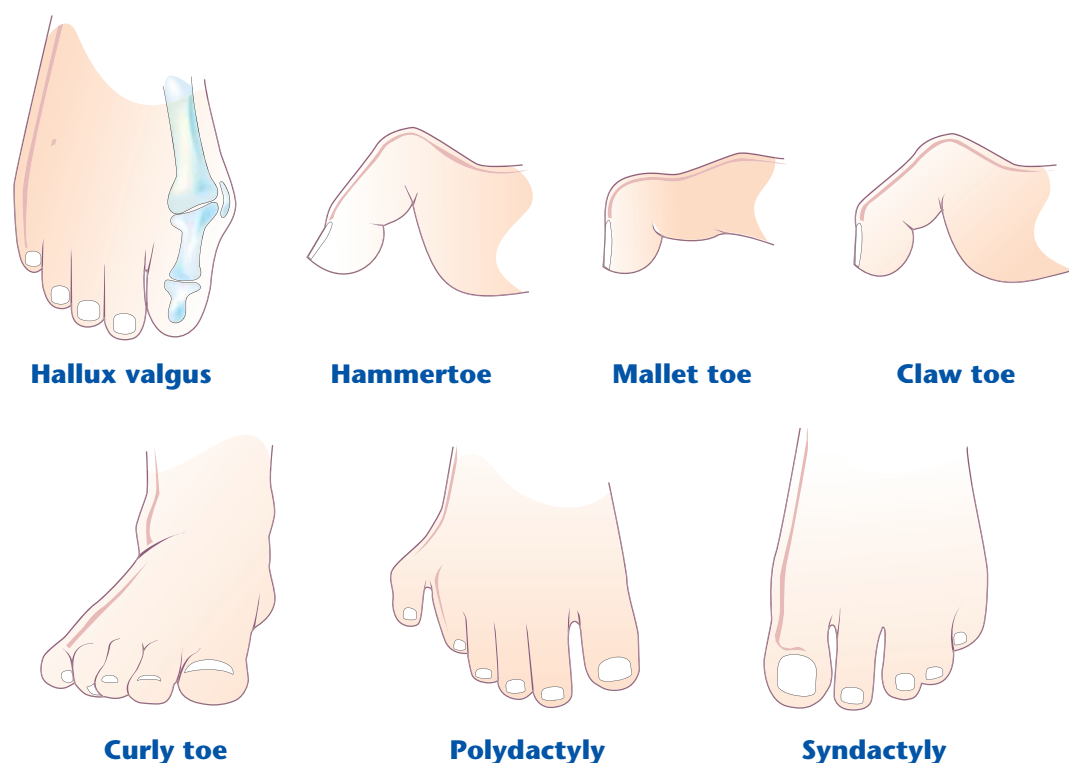
### Management

Early treatment includes exercises designed to strengthen the affected muscles and application of metatarsal pads to the innersoles of the shoes or metatarsal bars to the outer soles. Surgical correction of the fixed deformities may be required if contractures develop.

## TOE DEFORMITIES

### Hallux Valgus

Hallux valgus is a common problem in which the great toe is deviated laterally and the first metatarsal bone is



**Figure 154-15** Common toe anomalies.

deviated medially, causing a prominence to form on the medial aspect of the first metatarsophalangeal (MTP) joint (Figure 154-15). The condition is more common in females than males, and most cases are asymptomatic and do not require treatment other than counseling to wear shoes with adequate toe room and to avoid high heels. Persistent irritation of the overlying bursa from rubbing against a shoe can lead to inflammation and a painful bunion. Frequently, some degree of ankle pronation and flat foot is associated with hallux valgus, in which case a shoe insert may help prevent progression. In severe cases, surgical correction may be necessary.

### Hammertoe

Hammertoe describes a contracture of the proximal interphalangeal joint (PIP) in the second, third, fourth, or fifth toe (Figure 154-15). In an infant, hammertoe is usually hereditary; in an older child, it usually results from ill-fitting shoes. Most cases of hammertoe are mild, cause no pain, and can be left alone. Parents should make sure that the child has roomy shoes that allow the toes to stretch. More severe cases can cause pain, corns (an area of thickened skin overlying an area of pressure on the toes), inflammation, and worsening contractures. In severe cases, surgical correction may be needed.

### Mallet Toe

Mallet toe occurs less frequently than hammertoe. It is a chronic flexion deformity of the distal interphalangeal joint (DIP) (Figure 154-15) that causes pressure on the

tip of the toe resulting in callouses or nail deformities. It usually occurs at the second digit but may affect the third to fifth toes as well. Generally caused by improperly fitting shoes, it may also be idiopathic or congenital, result from trauma, or rarely result from a neuromuscular problem. Most cases of mallet toe are mild, flexible, and need no treatment. When a corn develops over the deformity, shaving and padding will help. In the more severe cases, surgical correction can be performed.

### Claw Toe

Claw toe involves all joints of the toe—fixed hyperextension of the MTP joints and flexion contractures at both the PIP and DIP joints (Figure 154-15). Claw toe is a rare condition but usually occurs in conjunction with a cavus foot, is present in neuromuscular diseases such as Charcot-Marie-Tooth disease, and can occur in inflammatory conditions such as rheumatoid arthritis.

### Curly Toe

In a child with a curly toe, the fourth or fifth toe is usually flexed downward and twisted underneath the adjacent toe (Figure 154-15). Curly toe is quite common in infancy and childhood. If curly toe does not cause symptoms, no treatment is needed. When the condition is severe and causes irritation with shoe wear, surgical transfer of the toe flexor can correct the problem.

### Polydactyly

Polydactyly, the presence of an extra digit (Figure 154-15), may exist as an isolated finding or as part of a more extensive syndrome of congenital anomalies (5% of



cases) such as trisomy 13, trisomy 21, or Ellis-van Creveld syndrome. There is a family history of polydactyly of the toes in 30% of cases, and 50% of cases occur bilaterally. In 80% of cases, the extra digit occurs postaxially. If the extra toe is not causing problems with walking and shoe wear, no treatment is needed. However, the extra toe usually does cause difficulty and is cosmetically unacceptable for most families. In these cases, surgical excision of fully formed digits is generally performed after 9 to 12 months of age, whereas vestigial digits can be removed by suture ligation at birth.

### Syndactyly

Syndactyly, the presence of webbed digits (toes) (Figure 154-15), may exist as an isolated finding or, in rare cases, as part of a more extensive syndrome of congenital anomalies. A family history of the same anomaly is often found. Syndactyly is quite common and rarely causes problems. The interconnection between 2 or more toes can vary from thin skin that partially connects the digits to a bony attachment (synostosis) between parts of the phalanges. Unlike with fingers where surgical separation is needed to obtain finer hand functions, syndactyly in the toes does not necessitate treatment.

### Bunionette (Tailor Bunion)

Whereas a bunion forms on the great toe in association with hallux valgus, the less common bunionette occurs at the fifth MTP joint. When a bunionette develops, the bursa over the lateral aspect of the fifth MTP joint becomes prominent, inflamed, and painful. When padding does not help relieve the discomfort of a bunionette, surgical correction is needed.

## TOE-WALKING

Walking on the toes or the ball of the foot is a variation of normal gait often seen between 10 and 18 months of age as toddlers begin to walk. This variation usually progresses to a toe-heel gait and eventually to the normal heel-toe gait pattern several months later. By parental report, as many as 25% of children continue to exhibit some degree of toe-walking later in development.

### Differential Diagnosis

Bilateral toe-walking beyond 2 years of age may be idiopathic or habitual toe-walking, but the differential diagnosis includes spastic diplegia, tethered cord, and diastematomyelia, muscular dystrophy, and other neuromuscular diseases. Unilateral toe-walking may be caused by spastic hemiplegia, a congenitally short Achilles tendon, a shortened limb, a dislocated hip, or significant tibial bowing on the affected side. Children with idiopathic toe-walking are able to place their feet flat on the ground and even have normal dorsiflexion. However, they prefer to use a toe-walking gait. In rare, extreme cases, this can lead to Achilles contractures and an equinus deformity.

### Evaluation

#### Pertinent History

A full history should be obtained, including birth history, developmental history and milestones, and history

of stooling and bladder control to help find cases with underlying pathology. Children with idiopathic or habitual toe-walking exhibit otherwise normal development, whereas those with a spastic diplegia usually exhibit delays in attaining gross motor skills and walking.

### Physical Examination

A thorough examination is required to rule out underlying conditions. The legs should be examined for evidence of any leg-length discrepancies, joint abnormalities, or limitation in range of motion. A neuromuscular examination should be performed to evaluate for spasticity or abnormal bulk, tone, or sensation that could indicate cerebral palsy, muscular dystrophy, tethered cord, or other neuromuscular disorders. In males, look for hypertrophy of the calf muscles and Gower sign as part of the examination for Duchenne muscular dystrophy. Children with simple idiopathic or habitual toe-walking will have normal neurologic and musculoskeletal examinations.

### Imaging

Radiographic examination is not indicated in most cases of toe-walking. Neuroimaging or other testing may be necessary if the toe-walking is acquired (develops after a period of normal gait) or underlying pathology is suggested by history or examination.

### Management

The only treatment generally required for idiopathic toe-walking is parental reassurance. However, in the child with idiopathic toe-walking beyond 2 to 3 years of age, stretching exercises or a dorsiflexion-assist ankle-foot orthosis may be of benefit. Older children who have developed mild Achilles tendon contractures from toe-walking may require serial casting. If any underlying pathologic cause of toe-walking is found, then treatment for the specific disorder should be initiated. Additional stretching and bracing, the use of ankle-foot orthoses, or casting may also be required for these children.

## SHOES

The foot grows to conform to the shape of the shoe. Improperly fitted or manufactured shoes may be the primary cause of acquired foot deformities and problems. Shoes that do not fit properly can deform an otherwise normal foot, resulting in hammertoes, hallux valgus, bunionettes, corns, and, ultimately, the need for surgery.

### Functions of Shoes

Parents often ask the physician when their child should begin wearing shoes and what kind of shoe should be worn. The shoe has 2 functions, the most important of which is protecting the feet from trauma and extreme temperatures. The second function of the shoe is to provide style. Older children will often sacrifice comfort for style despite parental or medical advice to the contrary.

Support to the foot and ankle is not a function of the shoe except when a pathologic condition is present. Athletes in all sports that place the feet and ankles under severe strain wear low shoes that have soft uppers. Ski boots are worn not to support the foot and ankle

but to make them one with the ski, to ensure response to movements originating in the knee and lower leg. Babies and toddlers usually wear ankle-high shoes, not to provide support to the foot and ankle but to make removing the shoes more difficult for the child.

Style is the only reason for a baby to wear shoes at all until the child begins walking outdoors or is taken out in cold weather. Some babies may gain a certain degree of stability from hard-sole shoes when beginning to stand, but this circumstance has not been shown to enhance learning to walk. In fact, shoes that are rigid prevent foot motion and may diminish the development of the intrinsic musculature of the feet. Properly fitting shoes that have flexible, smooth soles and soft uppers should be recommended. They need not be expensive. Toddlers can go barefoot in a protected environment such as indoors. Sneakers are perfectly adequate for summer wear and for winter indoor wear for older children, but toddlers may stumble in sneakers, which can stick to the floor during the stance and step-off phases of the toe-heel gait that typifies this age group.

### Fitting Shoes

Determining the proper fitting of shoes involves no great science. Given that the foot widens while standing and through the day, these measurements should be made later in the day with the child standing. Both feet should be measured so that the shoes can be fitted to the larger foot. The counter should hug the heel snugly; the length should allow a fingerbreadth ( $\frac{1}{2}$  inch) between the tip of the great toe and the top of the toe box. The foot should fit snugly into the widest part of the shoe; the width should not crowd the ball of the foot and should allow the toes to extend without wrinkling the upper. While still in the store, parents should have the child walk in the shoes to ensure comfort. The shoes should not be expected to stretch to fit. If shoes do not fit, they should not be purchased. Shoes in good condition can be handed down to a younger sibling.

The frequency with which shoes should be changed depends on the rate of growth of the feet, the quality of the shoes, and the degree of their use. Parents are usually able to tell when shoes become too small (or rather, feet become too large) without professional advice. The toes will be felt to press against the toe box, and getting the shoes on or having the child keep them on will be increasingly difficult.

### WHEN TO REFER

- In-toeing and out-toeing
- Severe in-toeing
- Unsteady gait (especially while running) that causes stumbling
- Condition that does not follow the expected physiologic progression with growth
- Metatarsus adductus and metatarsus varus
- Forefoot with limited flexibility
- Condition that appears to be progressing or is not improving with growth
- Tibial torsion
- Extreme rotation (especially when associated with difficulty walking or running)

- Significant asymmetry
- Sudden proximal tibial deviation
- Condition that does not follow the typical pattern of improvement with growth
- Femoral anteversion
- Extreme rotation (especially when associated with difficulty walking or running)
- Significant asymmetry of the femoral anteversion
- Condition that does not follow the typical pattern of improvement with growth
- New-onset femoral retroversion
- Bowed legs and knock-knees
- Severe, asymmetrical, or unilateral genu varum or genu valgus
- Condition that does not follow the expected physiologic progression with growth
- Clubfoot
- Immediate referral to an orthopedist on diagnosis of clubfoot
- Flatfoot
- Presence of a rigid flatfoot
- Symptoms not relieved through conservative management
- Pes cavus
- Referral for evaluation by a neurologist, physiatrist, or orthopedist, individually or in collaboration
- Toe anomalies
- Referral to a podiatrist or orthopedist if the anomaly leads to pain, uncomfortable shoe wear, or ambulation, and if these symptoms do not respond to conservative management
- Toe-walking
- Persists beyond 3 to 4 years of age
- Abnormal neuromuscular examination
- Leg-length discrepancy of  $>1$  cm or other significant physical abnormality on examination

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Flat Feet and Fallen Arches* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/orthopedic/Pages/Flat-Feet-Fallen-Arches.aspx](http://www.healthychildren.org/English/health-issues/conditions/orthopedic/Pages/Flat-Feet-Fallen-Arches.aspx))
- *Shoes: Finding the Right Fit* (fact sheet), American Academy of Orthopaedic Surgeons ([orthoinfo.aaos.org/topic.cfm?topic=A00143&return\\_link=0](http://orthoinfo.aaos.org/topic.cfm?topic=A00143&return_link=0))

#### Medical Decision Support

- *Essentials of Musculoskeletal Care*, 4th ed (book), American Academy of Orthopaedic Surgeons and American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Wheeless' Textbook of Orthopaedics* (book), Duke Orthopaedics ([www.wheelessonline.com](http://www.wheelessonline.com))
- *Children* (Web page), American Academy of Orthopaedic Surgeons ([orthoinfo.aaos.org/menus/children.cfm](http://orthoinfo.aaos.org/menus/children.cfm))
- *National Library of Medicine and the National Institutes of Health: Medline Plus* (Web site), ([medlineplus.gov](http://medlineplus.gov))
- *Orthoseek* (Web site), ([www.orthoseek.com](http://www.orthoseek.com))
- *Pediatric Orthopaedic Society of North America* (Web site), ([www.posna.org](http://www.posna.org))

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## Chapter 155

# GASTROINTESTINAL HEMORRHAGE

Jeffrey R. Avner, MD

Most causes of gastrointestinal (GI) bleeding in children, unlike in adults, are relatively benign and involve small amounts of blood loss. Although rare, some GI lesions may cause severe bleeding and lead to life-threatening conditions. In addition, GI bleeding may be a symptom of systemic illness or serious underlying chronic disease.

Evaluation of GI bleeding must be systematic. The age of the child, the history, the physical examination, and associated symptoms help focus the workup and allow the physician to identify the source of the bleeding in most cases. Endoscopy and new radiologic techniques are particularly useful for diagnosis and management of many conditions.

Bleeding can occur at any point along the length of the GI tract, from the mouth to the anus. Multiple folds, coils, and villous borders of the GI mucosa provide a large surface area for secretion of enzymes and absorption of water and nutrients. A large vascular supply to the GI tract accounts for an appreciable fraction of the cardiac output, especially after meals. Bleeding may be arterial, venous, or both. Although most bleeds are slow and involve oozing from the mucosal surface, massive bleeding can result from lesions involving high-pressure arteries or a large, engorged venous plexus.

Acute GI bleeding may occur with or without symptoms and can originate in either the upper or the lower GI tract. Chronic bleeding is usually slow and intermittent and may be identified only by occult blood in the stool. The slow nature of these bleeds allows the body ample time to compensate and preserve cardiac output. Signs of chronic bleeding include compensatory tachycardia, iron deficiency anemia, fatigue, pallor, or change in stool color.

**DEFINITION OF TERMS**

It is helpful to divide GI bleeding as originating from either the *upper* GI tract (proximal to the ligament of Treitz) or the *lower* GI tract (distal to the ligament of Treitz). In addition, a variety of terms describe specific characteristics of GI bleeding that may also give clues to the nature, location, and duration of the bleeding.

Hematemesis is bloody vomitus, which usually represents bleeding proximal to the ligament of Treitz. Blood that is altered by gastric acid becomes dark and coffee ground-like in appearance. Bleeding that has little or no contact with gastric acid will be bright red. GI bleeding that occurs proximal to the ileocecal valve and is passed rectally will usually appear as melena: black, tarry, sticky stools that result from the denaturing of hemoglobin by intestinal bacteria and enzymes. Hematochezia (red, bloody stool passed rectally) usually results from distal GI bleeding. Blood is usually mixed with the stool or passed just before or just after defecation. Occasionally, rapid bleeding from an upper GI source combined with the cathartic action of blood can speed transit time and cause hematochezia. Specific types of hematochezia include maroon-colored stools, seen with significant bleeding usually from the distal small bowel, and currant-jelly stools, indicative of intestinal vascular congestion and hyperemia.

**DIFFERENTIAL DIAGNOSIS****Identification of True Bleeding**

Red color appearing in the stool is often assumed to be blood. However, many other substances cause change in stool color. Foods that contain a high concentration of red pigments, such as tomatoes, cranberries, beets, and red fruit juices and gelatin (Jell-O), can cause red stools. Similarly, red-colored medications such as acetaminophen and amoxicillin can be passed in the stools, especially if diarrhea is present. Spinach, licorice, iron, and bismuth (Pepto-Bismol) often lead to dark, black stools, which can be confused with true melena. In infants, *Serratia marcescens* can cause *red diaper syndrome* as a result of the formation of red pigment in soiled diapers stored for longer than 1 day.

Several biochemical tests are available to detect blood in the stool. The most common test, the stool guaiac, uses the peroxidase activity of hemoglobin to catalyze a color change on a test card or paper strip. This highly sensitive test is able to identify even trace amounts of blood. Foods that have peroxidase activity may cause false-positive results if eaten within 3 days of testing: red meat, liver, processed meats, and raw fruits and vegetables, especially melon, turnip, radishes, and horseradish. High vitamin C intake interferes with the peroxidase reaction and can cause false-negative results. Similarly, outdated guaiac cards and prolonged storage may affect the accuracy of the test. Stool guaiac cards are not accurate for testing emesis for the presence of blood because gastric acid can affect the reaction that causes the color change. Therefore, heme testing of emesis should be done with guaiac cards that use a buffered stabilized hydrogen peroxide solution (eg, Gastrocult).

**Nongastrointestinal Source of Bleeding**

Although blood is present in the GI tract, the bleeding may originate from a peripheral source. The most common example of this phenomenon occurs in the newborn period. The infant may swallow maternal blood either during delivery or when breastfeeding if



the mother has bleeding nipples. The Apt-Downey test is helpful in differentiating maternal blood from infant blood. One part of the bloody stool (or gastric aspirate) is mixed with 5 parts of water to lyse the red blood cells. After the mixture is centrifuged, 1 mL of 0.2 normal sodium hydroxide is added to the supernatant hemoglobin solution. After 2 minutes, fetal hemoglobin, which resists the alkaline reduction, remains pink, whereas maternal hemoglobin turns yellow-brown. Melena contains denatured hemoglobin and therefore cannot be used for the Apt-Downey test.

Swallowed blood by a child is usually the result of nosebleeds or bleeding mouth lesions. These nasopharyngeal bleeds can mimic hematemesis or melena. Although rare in children, pulmonary hemorrhage may exhibit acutely as hematemesis or more chronically as melena and anemia. Vaginal bleeding in a newborn with estrogen withdrawal may be mistaken for rectal bleeding. In the menstruating teenager, vaginal blood may affect the accuracy of stool guaiac testing. The possibility of blood being added to the stool by a caregiver suggests Münchausen syndrome by proxy.

### Age at Presentation

#### Newborn

GI bleeding in newborns usually appears as rectal bleeding or blood suctioned from the stomach during routine postnatal care. In many instances, no lesion is readily discernible, and the bleeding resolves spontaneously and permanently. Common causes of GI bleeding in the first 24 hours of life include maternal blood swallowed during delivery and local trauma after nasogastric suctioning. Hemorrhagic disease of the newborn as a result of inherited deficits of coagulation factors or delay in administration of postnatal vitamin K occasionally produces GI bleeding, although it is more common for these disorders to show as diffuse bleeding from venipuncture sites.

Premature infants and newborns who have low Apgar scores are at increased risk for having gastric ulcerations and erosions that can bleed. These lesions are rarely primary, usually resulting from asphyxia associated with a difficult delivery, a cardiac lesion, or sepsis. The diagnosis is made by radiograph or upper GI endoscopy. Newborns who have persistent or severe gastroesophageal reflux can develop esophagitis. Although esophageal bleeding is upper GI bleeding, hematemesis is rare. Rather, the slow bleeding is occult and exhibits more commonly with signs of anemia or guaiac-positive stools. Because a barium swallow has poor sensitivity, pH probe manometry and esophagoscopy are better tests for identifying gastroesophageal reflux. Treatment usually involves histamine-2 ( $H_2$ ) receptor blockers.

Newborns with necrotizing enterocolitis (NEC) usually have a sudden onset of bilious vomiting, abdominal distention, lethargy, and lower GI bleeding. These symptoms usually occur after the first feeding but may be delayed for a few weeks. NEC is most common in premature infants but can occasionally occur in stressed full-term infants. Up to 5% of neonates in intensive care units develop NEC, and the overall mortality rate may be as high as 30%. Complications of NEC

include sepsis and shock. The diagnosis is confirmed by the presence of pneumatosis intestinalis on abdominal radiograph, but this finding is variable. These neonates remain hospitalized for bowel rest and intravenous antibiotics, and they occasionally need surgical intervention.

Intrinsic structural lesions of the GI tract are also a serious cause of lower GI bleeding in the newborn. Intestinal duplication, a tubular structure lined with normal GI mucosa adjacent to the true intestine, can be present anywhere along the GI tract. Duplications can cause lower GI bleeding, either acute or chronic, along with abdominal distention and vomiting. The diagnosis is confirmed by radiograph, computed tomography (CT) scan, or ultrasound. Unrepaired duplications may lead to obstruction, volvulus, or perforation. A volvulus or malrotation of the GI tract should be suspected in any infant who has abdominal pain, bilious vomiting, and melena. However, because these symptoms and signs are often unreliable, the diagnosis should be considered in any newborn who vomits and has guaiac-positive stools. An abdominal radiograph may show loops of small bowel overriding the liver shadow, with paucity of air in the GI tract distal to the volvulus. An upper GI series, barium enema, or both are sometimes needed to confirm the diagnosis. Midgut volvulus may also be diagnosed on CT scan or ultrasound by noting duodenal dilation, fixed midline bowel, and the wrapping of the bowel and the superior mesenteric vein around the superior mesenteric artery (whirlpool sign). Immediate surgical repair is necessary. Vascular malformations can occur anywhere along the GI tract and produce slow or diffuse lower GI bleeding. The bleeding is usually painless, and the color of the blood in the stool will vary depending on the level of the lesion. Vascular malformations may be associated with cutaneous hemangiomas or cardiac defects.

Milk or soy protein allergy can begin as early as the first week of life and exhibit as severe diarrhea, gross blood in the stool, abdominal distention, and vomiting. Older infants may have occult lower GI bleeding and mucus in the stool. The diagnosis is made by clinical response to withdrawal and rechallenge with the offending protein. Infectious enteritis, although rare in the newborn, may appear later in the first month of life. In very young infants, bacterial gastroenteritis, especially that caused by *Salmonella* spp, can cause bloody diarrhea with or without fever; 8% to 13% of infants may have associated bacteremia. Bright-red blood streaks on the surface of the stool suggest an anal fissure. Often associated with hard stools, anal fissures are the most common cause of rectal bleeding. Visual inspection of the anus usually confirms the diagnosis. Medications, such as indomethacin and dexamethasone, can cause mucosal erosion and GI bleeding.

#### Infants and Young Children

Upper GI bleeding in a young child is usually caused by mucosal lesions in the esophagus and the stomach. Infectious esophagitis is usually viral, but fungi can be the cause of disease in immunocompromised children. As infants become more mobile and dexterous, they



are at higher risk for foreign body and toxic ingestions. Coins and small toys, when lodged in the esophagus, can cause drooling, vomiting, and chest pain. Persistent or unrecognized esophageal foreign bodies lead to edema and erosion of the esophagus and may cause hematemesis. Caustic ingestion severe enough to burn the esophageal mucosa can also result in painful swallowing, drooling, oral burns, and hematemesis. Children who have forceful or prolonged vomiting may develop a rent at the gastroesophageal junction known as a Mallory-Weiss tear. The emesis becomes streaked with bright-red blood and may develop into coffee-ground emesis if the tear persists. Although the bleeding is minor and usually resolves spontaneously, an H<sub>2</sub>-blocker may be needed to prevent continued irritation by stomach acid.

Gastroesophageal varices can occur at any age but usually occur in children younger than 8 years. Variceal bleeding can range from slow, persistent oozing to acute massive hematemesis. Physical examination usually reveals signs of portal hypertension, such as enlarged liver or spleen, or both. Most cases result from the cavernous transformation of the extrahepatic portion of the portal vein, which has been associated with umbilical vessel catheterization, omphalitis, or neonatal conditions associated with hypoxia, prolonged jaundice, or sepsis. Intrahepatic causes of cirrhosis, leading to portal hypertension that may first show during childhood, include Wilson disease (>6 years of age),  $\alpha_1$ -antitrypsin deficiency, biliary cirrhosis, and metabolic, infectious, or anatomic forms of chronic liver disease. These chronic liver diseases also may be associated with coagulopathy and thrombocytopenia from the hypersplenism that usually accompanies them. If the cause of the portal hypertension is extrahepatic, then the bleeding may be tolerated remarkably well, in contrast to that in patients who have cirrhotic liver disease, in whom rapid hepatic decompensation may occur. Fortunately, most variceal bleeding stops spontaneously, but the incidence of rebleeding is high. Endoscopy confirms the diagnosis.

Juvenile polyps are the most common cause of lower GI bleeding, reaching a peak incidence in children aged 3 to 7 years. Typically, polyps are located in the colon and are simple, solitary, benign hamartomatous lesions that may irritate the GI tract and cause intermittent, painless, bright-red rectal bleeding. Many of these polyps will autoamputate if left alone and are passed with the stool. Because most polyps are located within 25 cm of the anus, they can often be identified by digital examination, air-contrast barium enema, or sigmoidoscopy and can be removed with snare electrocautery.

Adenomatous polyps may produce rectal bleeding as early as infancy, but they are managed differently from juvenile polyps. Juvenile polyps are benign inflammatory lesions that do not cause later complications. Adenomatous polyps, conversely, are premalignant tumors, which may transform into a malignancy over an average period of 10 years. Familial polyposis and Gardner syndrome are associated with adenomatous polyps. Juvenile polyposis coli (JPC) is suggested by the presence of 5 to 10 juvenile polyps; 10 or more polyps is considered diagnostic. JPC, which occurs in about 10% of patients who have colonic polyps, is

associated with anemia, right-colon polyps, and adenomas.

Meckel diverticulum, a remnant of the omphalomesenteric duct found within 2 feet of the ileocecal valve, is present in up to 2% of the population. The acid secreted by ectopic gastric mucosa, which is usually present in diverticula that bleed, causes peptic ulceration of the ileal mucosa. Meckel diverticulum typically occurs in children younger than 3 years and causes painless, maroon- or red-colored lower GI bleeding. Typically, the bleeding is severe enough to cause the hemoglobin level to fall to about 8 g/dL. Diagnosis is made by technetium-99 scan, which identifies the ectopic gastric mucosa. This test is fairly sensitive but only during active bleeding; thus, a repeat scan is sometimes necessary when the suspicion is high. Treatment requires surgical excision.

Intussusception, the telescoping of an intestinal segment, is seen typically in children 6 to 24 months of age. The occurrence is often idiopathic and usually involves invagination of the distal ileum through the ileocecal valve into the colon. Older children who have intussusception and those who have multiple recurrences may have pathologic lesions that serve as lead points (Meckel diverticulum, polyp, and tumor). The classic presentation begins with intermittent, severe, crampy abdominal pain, with vomiting following shortly thereafter. As the intussusception progresses, lethargy or paradoxical irritability develops. Guaiac-positive stools are seen as the bowel becomes ischemic and may progress to the passage of red bloody mucus, classically referred to as *currant-jelly stools*. The use of screening ultrasound has decreased unnecessary enemas for clinically suspected intussusception. Diagnosis can be confirmed on ultrasound by identification of the layering of intestinal mucosa as a *bull's-eye* or *coiled-spring* lesion. Confirmation of diagnosis, followed by hydrostatic reduction with barium or air enema, is successful in about 70% to 80% of cases, even in those with symptoms for more than 24 hours. Complications include intestinal perforation, peritonitis, and significant bleeding.

Lymphonodular hyperplasia on the mucosa of the terminal ileum or colon may cause painless, blood-streaked stools. Lymphonodular hyperplasia is usually seen in children younger than 6 years and may be associated with food allergy. Diagnosis is made by endoscopic examination and histologic confirmation.

Symptoms associated with infectious enterocolitis range from mild diarrhea to fever, abdominal cramping, and watery or mucoid stools (or both forms) with or without blood. *Salmonella*, *Shigella*, *Yersinia*, and *Campylobacter* spp are the most common bacterial causes of bloody diarrhea. Pseudomembranous colitis, caused by *Clostridium difficile*, also causes fever, diarrhea, abdominal cramping, and bloody stools. In many instances, a history of recent hospitalization and antimicrobial therapy exists, but the onset of symptoms can be delayed for weeks. A variety of parasites, such as *Entamoeba histolytica* and *Trichuris trichiura*, can cause bloody diarrhea.

Systemic disease, in particular vasculitis, may be accompanied by bloody stools. The constellation of arthritis, hematuria, purpura, intestinal cramping, and bloody stools suggests Henoch-Schönlein purpura

(HSP). Children with HSP are at increased risk for intussusception, or they may have severe GI bleeding. Hemolytic uremic syndrome (HUS) often has a prodrome of hemorrhagic colitis caused by Shiga toxin-producing *Escherichia coli* with a serotype O157:H7. The classic triad of HUS includes thrombocytopenia, hemolytic anemia, and renal disease. Milk protein allergy, anal fissures, and congenital anatomic anomalies of the GI tract can also occur in this age group.

### Older Children and Adolescents

Peptic ulcer disease can occur at any age but is more common in older children and adolescents. Symptoms usually begin with epigastric or periumbilical pain accompanied by nausea. GI bleeding is evident in about 50% of children either as hematemesis or as melena. *Helicobacter pylori*, bacteria found in the gastric mucous layer or adherent to the epithelial lining of the stomach, has been causally associated with ulcers. *H. pylori* infection is diagnosed by culture of biopsy specimens from the stomach and duodenum. Serologic tests, which measure specific *H. pylori* immunoglobulin G antibodies, are often unreliable and, therefore, should be reserved for children with endoscopically diagnosed, or radiographically definitive, duodenal or gastric ulcers. Treatment, when indicated, consists of a 7- to 14-day course of any of a variety of antibiotic regimens together with a proton pump inhibitor.

Hemangiomas and other vascular lesions, such as hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome), must be considered in the evaluation for painless rectal bleeding. Its most common form is the larger cavernous hemangioma, either polypoid or diffuse, extending several centimeters through the submucosa of the small or large intestine. The large bowel, specifically the rectum, is the area usually involved in the diffuse type. Cutaneous vascular malformations are often present but may require scrupulous searching to detect. Selective arteriography or digital subtraction angiography may aid in demonstrating the abnormal vessels if they are not visible on direct inspection.

Inflammatory bowel disease may appear in the adolescent age group as episodes of bloody diarrhea, cramping, and tenesmus. The course may be atypical in children, making the diagnosis difficult. Growth failure, weight loss, or anemia with evidence of recurrent bouts of GI bleeding should alert the physician to the diagnosis, which colonoscopy and biopsy usually confirm.

## EVALUATION OF PATIENTS WHO HAVE GASTROINTESTINAL BLEEDING

When evaluating a patient who has GI blood loss, the physician should keep 2 goals in mind. First, the severity of the blood loss must be assessed quickly to expedite appropriate resuscitative measures. Second, the physician must consider the most likely causes so that problems requiring immediate surgery can be separated from those requiring medical evaluation and management. The workup is based on the patient's age and history, the clinical appearance, and the physician's familiarity with the patient. A list of lesions commonly associated with GI bleeding is provided in Box 155-1.

### Relevant History

A detailed history may help the physician determine the location and duration of the bleeding. Particular attention should be paid to the color of the stool and emesis and whether a change has occurred in the preceding days or weeks. Massive amounts of red blood from the mouth or rectum are readily apparent to the parent and the patient. However, the importance of maroon or tarry stools as a sign of GI bleeding may not be appreciated unless the physician asks.

Antecedent symptoms are also a key to identifying many diseases. Vomiting that progresses from bile stained to bloody is seen with intestinal obstruction (volvulus, intussusception, NEC) or with Mallory-Weiss tears. Bloody diarrhea may accompany infectious enteritis, food allergy, and inflammatory bowel disease, or it may precede HUS. Painless lower GI bleeding, if substantial, is seen with Meckel diverticulum or GI vascular anomalies, whereas a smaller amount of painless bleeding suggests polyps or lymphonodular hyperplasia. Fever is common in infectious or inflammatory disorders. Arthritis and rash are seen with HSP. Abdominal pain, fever, and weight loss suggest inflammatory bowel disease. Lower rectal disorders, such as hemorrhoids or anal fissures, produce blood-streaked stools and painful defecation. Young children who have upper GI bleeding should be questioned about foreign body or caustic ingestion. Medication use, especially of aspirin, nonsteroidal anti-inflammatory drugs, steroids, and tetracycline, is a frequent cause of gastritis. A family history of polyps, bleeding disorders, or GI diseases is important. Neonatal history should focus on risk factors for NEC or varices, including umbilical vein catheters, liver disease, and birth asphyxia. Sexual activity or abuse involving anal penetration should alert the physician to anal and rectal trauma.

### Physical Examination

The physical examination should be complete and systematic because clues to the diagnosis may be present in any organ system. The general appearance and vital signs can be helpful in determining the duration of bleeding. Slow, chronic bleeding allows time for physiologic changes such as tachycardia, orthostasis, and decreased pulse pressure. Children may initially appear comfortable but tired and have some degree of pallor. Patients who have acute, rapid bleeds may be in various stages of shock depending on the amount of blood loss. The nose and mouth should be examined for bleeding lesions or burns. The abdominal examination should evaluate for tenderness, bowel sounds, masses, and hepatosplenomegaly. The physician must also look for signs of chronic liver disease, such as the presence of telangiectasias, jaundice, hepatosplenomegaly, and a prominent abdominal venous pattern. With lower GI bleeding, a thorough rectal examination should be performed, with special attention paid to the perianal region, observing for skin tags, abscesses, fissures, bleeding points, or much less commonly, hemorrhoids; the character of the stool; and the presence of occult blood by guaiac testing. Palpation for polyps and pelvic masses must be part of the rectal examination. Eczema may be associated with food allergy. Finally,

**BOX 155-1 Causes of Gastrointestinal Bleeding****NEWBORNS****Upper GI Bleeding**

- Hemorrhagic disease of the newborn
- Gastritis
- Stress ulcer
- Esophagitis

**Lower GI Bleeding**

- Necrotizing enterocolitis
- Duplication
- Volvulus, malrotation
- Vascular malformations
- Milk allergy
- Infectious enteritis
- Anal fissure

**INFANTS AND YOUNG CHILDREN****Upper GI Bleeding**

- Nasopharyngeal bleeding
- Esophagitis
- Acid reflux
- Viral, fungal, caustic sources
- Esophageal foreign body
- Mallory-Weiss tear
- Gastroesophageal varices
- Gastritis

**Lower GI Bleeding**

- Juvenile polyps
- Meckel diverticulum
- Intussusception

- Infectious enterocolitis
- Pseudomembranous colitis
- Vasculitis (HSP, HUS)
- Milk allergy
- Lymphonodular hyperplasia
- Anal fissure or trauma (abuse)
- Duplication
- Vascular malformation

**OLDER CHILDREN AND ADOLESCENTS****Upper GI Bleeding**

- Nasopharyngeal bleeding
- Esophagitis
- Mallory-Weiss tear
- Gastroesophageal varices
- Gastritis
- Aspirin, NSAIDs
- *Helicobacter pylori*
- Peptic ulcer disease

**Lower GI Bleeding**

- Polyps
- Infectious enterocolitis
- Inflammatory bowel disease
- Vasculitis
- Vascular malformation
- Meckel diverticulum
- Hemorrhoids
- Anal fissure

GI, gastrointestinal; HSP, Henoch-Schönlein purpura; HUS, hemolytic uremic syndrome; NSAIDs, nonsteroidal anti-inflammatory drugs.

skin lesions such as purpura and petechiae suggest a bleeding disorder, HSP, or HUS.

**Laboratory Testing**

In the setting of GI bleeding, laboratory testing should focus on determining the amount and duration of the bleeding, assessing for coagulopathy, and evaluating for other laboratory abnormalities that may be associated with the underlying disease process. Hemoglobin determination can help assess the level of blood loss, with the caveat that acute bleeding may not lower the hemoglobin level until some intravascular equilibration takes place. An elevated white blood cell count may occur in infectious colitis. Coagulation studies should be obtained, including prothrombin and partial prothrombin times, as well as the platelet count. The prothrombin time may be elevated as a sign of a bleeding disorder or as a result of abnormalities in liver synthetic function. Liver function tests are useful in evaluating suspected liver disease. Serum chemistries can be used to assess renal function, although an elevation in the blood urea nitrogen may result from increased intestinal absorption of

blood with longstanding upper GI bleeding. Any patient with significant bleeding or a low hemoglobin level should have blood sent immediately for blood type and screen in the event of the need for blood transfusion. If bloody diarrhea is present, a stool specimen should be sent for culture and, if appropriate, ova and parasites.

**Imaging**

Most children with GI bleeding require some type of imaging study to locate the source of the bleeding or confirm a suspected diagnosis. The type of study will depend on the age of the child, clinical presentation, and possible diagnosis. Plain radiographic films are generally nonspecific and usually require additional imaging to confirm a diagnosis. Two-view (flat and upright) abdominal radiographs may show signs of intestinal obstruction such as air-fluid levels and dilated bowel loops. Some specific radiographic findings include pneumatosis intestinalis in NEC and intestinal obstruction with absence of gas in the right colon in intussusception. Barium studies can be used to identify intestinal foreign bodies, polyps, lymphonodular hyperplasia, and

inflammatory bowel disease, although, in many cases, endoscopy remains the procedure of choice for diagnosis. Color Doppler ultrasound is becoming increasingly useful as a diagnostic aid in both intussusception and malrotation, but its usefulness depends on the skill of the operator. CT scans are occasionally helpful in defining related anatomic features if the child is hemodynamically stable and either cooperative or sedated. Nuclear medicine imaging studies (Meckel scan, radioactively labeled colloid or red blood cells) or direct angiography can often identify the source of an acute, ongoing bleed.

Wireless capsule endoscopy (WCE) is a relatively new technical innovation used for evaluation of the small intestine, primarily in adult patients but now with increasing frequency in pediatrics. As in adults, a common use of WCE in children is for evaluation of obscure gastrointestinal bleeding. In one recent study, more than 50% of children had the source of obscure bleeding identified with WCE, including ulcerative jejunitis, polyps, angiodysplasia, blue rubber bleb nevus syndrome, and Meckel diverticulum. Some of the limitations of WCE use in pediatrics include the size of the standard capsule that needs to be swallowed and the risk for capsule retention in strictured areas of the small bowel (more common in Crohn disease). However, several studies show that WCE is a practical and safe technique, even in children as young as 2 years.

## MANAGEMENT

For a child who has acute massive GI bleeding, the approach must be the same as that in any other emergency. The physician must approach the patient with an efficient, rational plan in mind that will allow obtaining the pertinent historical information, performing a brief but adequate examination, stabilizing the patient clinically, arriving at a working diagnosis, and instituting appropriate therapy or consultations. Massive upper GI bleeding may lead to vomiting, aspiration, and airway obstruction that requires stabilization of the airway with endotracheal intubation. Administration of oxygen is always indicated. Evaluation of peripheral perfusion, quality of pulses, and capillary refill time assesses the adequacy of circulation. In children, the initial response to hypovolemic shock is tachycardia. In acute bleeds, adequate blood pressure may be maintained with blood loss of up to 30% without replacement.

Tachycardia and capillary refill time are essential criteria in determining the nature of the resuscitation required. Skin turgor and the color of the mucous membranes also should be noted. If signs of shock are present (eg, orthostasis or frank hypotension, tachycardia, poorly perfused extremities, pale mucous membranes, altered mental status), then at least 1 (preferably 2) large-bore intravenous catheters should be placed. Initial laboratory studies include complete blood count, hematocrit, reticulocyte count, coagulation times, electrolytes, blood urea nitrogen, creatinine, liver function tests, and blood typing and cross-matching. If percutaneous venous access is not obtained within a few minutes, then an intraosseous line should be placed, and 20 mL/kg of normal saline should be given rapidly to reexpand the vascular

volume. This fluid bolus may need to be repeated several times. Additional fluid should be given as needed to allow equilibration of these solutions with the extravascular space. With more than 30% to 40% acute blood loss, packed red blood cells should be given as soon as possible.

An appropriately sized nasogastric (NG) tube, preferably of the vented sump type, helps determine the source of bleeding and helps estimate the volume of ongoing blood loss. The tube should be left in place and attached either to low-pressure continuous suction, if vented, or to intermittent suction, if nonvented. The only instance in which NG tube placement may aggravate bleeding is in a patient who has varices. Nonetheless, even in this case, an NG tube may be required to quantitate blood loss adequately.

Controlling the bleeding and determining the specific diagnosis are the next steps in management. If the NG aspirate contains blood, or if the patient has hematemesis, then saline irrigation may be instituted in an attempt to decrease mucosal blood flow and thereby stop profuse bleeding. Although the efficacy of lavage in decreasing and controlling gastric bleeding has not been demonstrated conclusively, it allows easier assessment of the rate of bleeding and helps in removing clotted blood. At the same time, prolonged lavage (>10 minutes) may not allow fibrin clots to form at the bleeding site. Saline at room temperature should be used because irrigation with water can lead to hyponatremia, and iced or cold fluid may cause hypothermia. The saline is instilled through an NG tube and is withdrawn after 3 to 5 minutes. Aspirate returns that do not clear in 10 minutes suggest continued GI bleeding and should prompt additional evaluation.

If the bleeding ceases, then gastroduodenoscopy should be performed to demonstrate the bleeding source and to determine the type of lesion present. Upper GI fiberoptic endoscopy can establish the diagnosis in 75% to 90% of patients. If the bleeding is massive and cannot be controlled with saline lavage, then adequate visualization is not likely to be achieved with the fiberoptic endoscope. If the bleeding is not immediately life-threatening, then arteriography, which can demonstrate bleeding that occurs at a rate of 1.0 mL/min or more, should be considered. More sensitive than arteriography, and less invasive, a sulfur-colloid isotopic study can demonstrate active bleeding at rates as low as 0.1 mL/min. This method demonstrates active bleeding by using a tracer with a very short half-life. In small infants, a large uptake of the isotope by the liver may mask the right upper quadrant. An additional isotopic method of determining the bleeding site consists of injecting the patient with technetium-99 pertechnetate-labeled red blood cells. These labeled cells may remain in the circulation for more than a day and allow repeated imaging to locate the site of intermittent bleeding.

If the lesion is one of mucosal erosion or inflammation, then antacid therapy with or without the concomitant use of an H<sub>2</sub>-blocker may be instituted. For bleeding ulcers, intravenous therapy with a proton pump inhibitor reduces the risk for ulcer rebleeding but does not appear to influence the overall mortality rate. If the bleeding source is variceal, then the cause



of the lesions must be determined, with appropriate treatment of the underlying disease. In particular, liver or portal venous disease should be sought. Clotting factors and platelets should be replaced as indicated.

Variceal bleeding requires special mention because of the many settings in which varices may be seen. The treatment of variceal bleeding in children has evolved over the past 2 decades. Use of balloon tamponade with a Sengstaken-Blakemore tube (an NG tube with additional lumina for a gastric balloon and an esophageal balloon in which the gastric balloon is inflated and traction is applied so that the balloon abuts the gastroesophageal junction and tamponades the variceal bleeding) was effective in controlling most cases of bleeding but had a high incidence of complications. This treatment has been replaced, in most cases, with the use of vasoactive drugs and endoscopy. Previously, the major medical therapy included the use of intravenous vasopressin as a mesenteric vasoconstrictor to reduce portal blood flow and thus decrease variceal pressure. Octreotide, a synthetic peptide similar in properties to somatostatin, decreases splanchnic blood flow, which thereby decreases portal pressure, has less effect on systemic blood flow and is associated with fewer side effects than vasopressin. Pediatric studies (with no control groups) have shown octreotide to be 50% to 63% effective in controlling acute variceal bleeding. Initially, a 1-mcg/kg (maximum of 50-mcg) bolus is infused, preferably through a central or intraosseous line, followed by an infusion of 1 mcg/kg/hr, which may be increased by 1 mcg/kg/hr up to 4 mcg/kg/hr.

Endoscopy is the preferred intervention for variceal bleeding because it can provide both diagnosis and therapy. The most commonly used techniques are endoscopic injection sclerotherapy (EIS), which uses an injection of a sclerosing solution into the varices, and endoscopic variceal band ligation (EVL), in which elastic bands are placed around the varices in the distal esophagus. Endoscopy has been found to be 80% to 100% effective in controlling variceal bleeding. In a randomized controlled trial in 49 children, EVL achieved variceal eradication faster than EIS, with a lower rebleeding rate and fewer complications. Endoclips are a newer technique used in severe GI bleeding; metal devices, applied to the GI mucosa through a flexible endoscope, are used to compress the tissue around a bleeding vessel. In all cases, endoscopy should be performed by an experienced gastroenterologist, with the availability of general anesthesia and endotracheal intubation, if necessary, especially when performed in small children.

Studies in adults and experience in pediatrics, although limited to date, suggest that octreotide should be used as the initial treatment for bleeding varices, followed by endoscopic therapy, either EVL or EIS. If the bleeding continues despite vasoactive and endoscopic therapies, then balloon tamponade can be attempted.

Evaluation for lower GI bleeding differs in several aspects from that for upper GI bleeding. The abdomen, perineum, and rectum are thoroughly examined. Stool must be analyzed for the presence of blood and, when appropriate, for enteric pathogens and for ova and parasites. If diarrhea is present, then the stool

should be examined microscopically for polymorphonuclear leukocytes and mucus, both of which are evidence of bacterial infection. Digital rectal examination should follow in an attempt to discover the presence of anal fissures, rectal polyps, or hemorrhoids. Sigmoidoscopy may be necessary for children who have persistent rectal bleeding to identify polyps or mucosal lesions. The presence of blood originating from above the reach of the sigmoidoscope indicates the need to proceed with other diagnostic studies.

Several different imaging studies are used to evaluate persistent lower GI bleeding. An upright and supine view of the abdomen will reveal signs of obstruction or calcifications. For severe, life-threatening bleeds, angiography can be both diagnostic and therapeutic, depending on the ability to embolize the bleeding vessels. Because angiography has limited sensitivity in detecting slow or past bleeding, it is best performed when bleeding is active.

Children with persistent, active bleeding who are clinically stable should have a radionuclide scan, which identifies accumulation of an isotope at the bleeding site. With a sulfur-colloid isotopic scan, the isotope is extracted rapidly so that background radioactivity is low. Although high-contrast resolution can be found around the bleeding site, it is effective only for identifying rapid bleeding. An isotope-labeled red blood cell infusion has a lower contrast ratio but is better at detecting slower or intermittent bleeds than a sulfur-colloid isotopic scan. A Meckel scan uses technetium-99 pertechnetate, which is secreted by ectopic gastric mucosa, to identify the diverticulum. If the rate of bleeding does not permit the time necessary to perform these studies, then vasopressin or octreotide may be administered parenterally in an attempt to control the bleeding and to stabilize the patient. Air-contrast barium studies or endoscopy can identify sources of more chronic, low-grade bleeding. However, a barium enema or an upper GI series with small bowel follow-through should be the last study performed because they each make the further use of arteriography, isotope scans, and endoscopy impossible for several days thereafter. In cases in which the intestine is compromised vascularly, or when the rate of bleeding is excessive and uncontrollable by more conservative methods, prompt surgical intervention is required. Fortunately, however, conservative measures control most acute episodes of GI bleeding relatively easily; patients who eventually require surgical intervention can usually undergo elective surgery at a later time.

#### WHEN TO REFER

- Upper GI bleed
- Lower GI bleed that is of moderate amount, persistent, or intermittent

#### WHEN TO ADMIT

- Any nontrivial upper GI bleeding, such as that associated with active bleeding, moderate amount of blood, anemia, and abdominal pain
- Significant lower GI bleeding

- Hemodynamic instability
- Anemia (hematocrit)
- Severe abdominal pain
- Associated systemic symptoms (eg, HUS, inflammatory bowel disease)
- Altered mental status or lethargy
- Suggestion of surgical etiology (eg, Meckel diverticulum, intussusception, volvulus)

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## Chapter 156

# GENDER EXPRESSION AND IDENTITY ISSUES

Robert J. Bidwell, MD

Throughout history and across many cultures, children and adolescents have, through their gender expression and gender identity, transcended cultural expectations about the meaning of being a girl or a boy. In some times and places, as these children and youths grew into adulthood, they became respected and even revered members of their societies. In others, including the current culture in many parts of the United States, they have been seen as legitimate targets of discrimination and persecution. Issues related to gender expression and gender identity are highly controversial, and the understanding of them is evolving based on increased research and societal changes. In 2013, the American Academy of Pediatrics (AAP) issued a policy statement and accompanying technical report on office-based care of lesbian, gay, bisexual, transgender and questioning (LGBTQ) youth. These give physicians the basic understanding and skills to work in a respectful and relevant manner with children and youths facing issues related to sexual orientation and gender identity. A similar position paper has been issued by the Society for Adolescent Health and Medicine. While sexual orientation (whom one is attracted to) is distinct from gender identity (one’s inner sense of

being female, male, or another gender), in practice these 2 concepts are often interrelated, as the following section will explain.

### DEFINITIONS

Gender is a complex concept that is still not well understood. Researchers and theorists have attempted to study and explain various aspects of gender to improve their understanding of this important part of being human. *Gender role* represents a set of behaviors, attitudes, and interests that a society or culture believes are typically female or male. A child internalizes these cultural gender role expectations by the age of 3 to 5 years. *Gender expression* refers to how an individual signifies gender in terms of dress, speech, interests, and other outward signs. When a child displays behaviors, attitudes, or interests outside the cultural norm for the child’s biologic (genetic or anatomic) sex, it is referred to as *gender nonconforming* or *gender variant* expression. More recent terms include *gender creative* and *gender expansive* expression. For example, boys with gender nonconforming behavior may prefer playing house to playing football, enjoy dressing up in their mothers’ clothes or trying on their makeup, prefer long hair, and be more stereotypically feminine in their mannerisms and speech, as determined by a particular culture. Girls with gender nonconforming behavior may avoid wearing clothes that are culturally more associated with girls, enjoy more physically aggressive play with boys, prefer short hair, and have more stereotypically masculine mannerisms.

In contrast, *gender identity* refers to a person’s deepest inner sense of being female or male (or even something other than female or male) and is often established early in childhood. For most individuals, gender identity is congruent with biologic or birth-assigned sex. For some, it is not. Although their bodies seem to tell them and the world around them that they are female or male, their inner identity is either of the opposite gender or a sense of gender separate from female or male. These individuals are referred to as *transgender*.

Gender identity is distinct from *sexual orientation*, which refers to an individual’s affectional, romantic, or sexual attraction to others of the same sex (homosexual), opposite sex (heterosexual), or both sexes (bisexual).

*Transgender* also is used sometimes as a broader umbrella term encompassing those who do not conform to cultural norms of being female or male. This group includes individuals whose gender identity is incongruent with their biologic gender and who may seek to change their bodies to make them more consistent with their inner sense of gender. These individuals are sometimes referred to as *transsexual*, but more commonly are referred to as transgender in the narrower sense of the term as described above. Transgender in its broader sense recently has been referred to as the *trans\* spectrum*. In addition to those who experience an incongruence between their bodies and their inner gender identity, the trans\* spectrum also includes those who cross culturally defined gender boundaries, including crossdressers (transvestites),

drag kings and queens, and persons who perceive themselves to be of both genders (bigender), all genders (pangender) or no gender (agender). It also includes those who may refer to themselves as *genderfluid* or *genderqueer*, or who are routinely gender nonconforming in terms of their attitudes, interests, and behaviors. The term *transgender* is not used in referring to prepubertal children with gender dysphoria or gender nonconforming behavior.

In this chapter, *transgender* is used in its narrower sense, referring to gender identity. Transgender individuals often refer to themselves as *trans*, *trans\**, *TG*, or *T*. Many transgender people, but not all, experience significant *gender dysphoria*, a persistent discomfort with the gender assigned to them at birth and the societal gender role expectations that accompany it. These dysphoric feelings often begin in early childhood and increase with the appearance of unwanted physical changes at puberty. Many transgender individuals gradually let go of the need to conform to societal expectations attached to their birth-assigned gender and increasingly present themselves to the world in a manner consistent with their gender identity. This process is known as *transition*. The transition process may be facilitated medically by pubertal suppression, cross-gender hormonal treatment, and/or gender-affirmation surgery (also referred to as sex-reassignment surgery or SRS). However, it not only is a physical process but also takes place on psychological, social, and spiritual levels. The terms *male-to-female* (MTF) and *female-to-male* (FTM) transgender are used to describe the direction of transition from biologic gender to actual gender identity. An FTM transgender person is often referred to as a *trans-man* and an MTF person as a *trans-woman*.

Most gender nonconforming children and youths do not experience gender dysphoria nor do they have gender identities that differ from their birth-assigned sex. The prevalence of gender nonconformity in children and youth is uncertain, although studies have shown that gender nonconforming behavior is common. Persistent gender nonconforming behavior or expressed wishes to be another gender are less common. In a 2011 population-based survey of middle school students in San Francisco, when given a choice of identifying themselves as male, female, or transgender, 1.3 percent chose the latter response. The World Professional Association for Transgender Health (WPATH) estimates that the prevalence of MTF transgender identity is 1 in 11,900 to 1 in 45,000 individuals and of FTM transgender identity is 1 in 30,400 to 1 in 200,000. Some believe that these estimates are low because they are based on individuals seeking hormonal and surgical transition services: some transgender individuals do not have access to or do not want sex-reassignment services and so are not represented in the data.

One of the most controversial issues related to gender expression and gender identity during childhood and adolescence is whether gender nonconformity and transgenderism are causes for concern. Do they represent a pathologic abnormality, or are they simply part of the continuum of normal human

expression and identity? Similar debates occurred around homosexuality until it was officially removed from the American Psychiatric Association's list of mental disorders in 1973. Although controversial, until 2013 transgenderism (in the narrower sense) and transsexualism were represented in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* under the diagnostic category of *gender identity disorder (GID)*. Based on the work of the DSM-5 Workgroup on Sexual and Gender Identity Disorders, the APA fifth edition (*DSM-5*) introduced several important changes in terminology and diagnostic criteria related to gender identity, with separate criteria for children and for adolescents and adults. The diagnostic category of GID was replaced by the less stigmatizing designation *gender dysphoria*. The controversy surrounding these diagnoses is well documented. The diagnostic criteria for both childhood and adolescent/adult gender dysphoria require a marked difference between an individual's experienced or expressed gender and the gender assigned at birth. For a diagnosis of gender dysphoria to be made, this gender incongruence must have persisted for at least 6 months and resulted in significant distress or impairment in social, school, occupational, or other important areas of functioning.

At a basic level, the move from GID to gender dysphoria emphasizes that no longer is cross-gender *identity* considered disordered. Instead, it is the distress related to having a cross-gender identity, which is often caused in significant measure by growing up and living in a nonaccepting, often aggressively hostile societal environment. Much of the controversy arising from the creation of both GID and gender dysphoria as DSM diagnostic categories is the observation that any gender-nonconforming child or adolescent raised in a society that enforces a binary view of gender will predictably experience some degree of discomfort or distress related to gender expression and identity. Given the overt discrimination and violence that have occurred against transgender individuals in the United States, distress or impairment in social and other areas of functioning is not surprising. Evidence suggests that transgender individuals growing up in more accepting societies experience less discomfort and distress related to their gender identity and gender expression.

Several developmental trajectories have been described for children with GID, which presumably are relevant for those now diagnosed with gender dysphoria. The diagnostic rubric of gender dysphoria is too recent to be reflected in a substantial body of literature. The studies on which these proposed trajectories are based are small and inconclusive. Taken as a whole, however, they suggest that many children diagnosed with GID (and more recently gender dysphoria) eventually self-identify as gay or bisexual as adolescents or adults and no longer experience gender dysphoria. A smaller percentage later self-identify as heterosexual and also experience no gender dysphoria. A small but significant percentage continue to experience discomfort with their biologic sex and self-identify as transgender.



## ETIOLOGY

Considerable controversy exists around possible causes for the development of persistent gender nonconforming expression, cross-gender identity, and gender dysphoria, which are related yet distinct phenomena. Theories proposed have suggested psychosocial, biologic, and genetic factors, or varying combinations thereof. However, research data are very limited, often narrowly focused, and sometimes contradictory. Therefore, to date there are no scientifically supported explanations for how gender nonconforming expression, gender identity, or gender dysphoria arise. Nevertheless, among all theories offered, those suggesting a biologic or genetic basis for cross-gender expression and identity are gathering the most robust scientific interest and support. Recent reviews have documented what little is known and how much still needs to be learned about the origins of gender identity and expression and the developmental trajectories experienced by gender nonconforming and gender dysphoric children and youths.

Psychosocial theories seeking to explain gender nonconforming expression and gender dysphoria often focus on familial, and particularly parental, psychopathology, and aberrant parenting practices that may interact with biologic factors and predispose a child to gender dysphoria. Zucker, for example, posits that some children may experience subtle biologically or genetically related prenatal events affecting areas of the brain that lead to gender nonconforming behavior or personality traits. This may in turn interact with parenting styles or psychopathology that encourages persistent gender nonconforming behaviors and possibly the development of gender dysphoria. Much of the controversy around such theories, in addition to a lack of robust scientific evidence to support them, is that many feel they are similar to earlier theories related to the origins of homosexuality, later discredited, that saw aberrant parenting and familial psychopathology as probable etiologies. This is especially relevant because research demonstrates that most gender dysphoric children and many gender nonconforming children later to come to recognize a lesbian, gay, or bisexual orientation in adolescence or adulthood. Psychosocial theories are no longer generally accepted as primary causal explanations for variances in gender expression and identity, while their role in informing the treatment approach to gender dysphoria remains highly controversial. Some have suggested that a more likely route to gender dysphoria for some children is growing up in a home and community that pathologizes their gender expression and identity, although this theory, like all others, lacks robust research support at this time.

Most recent scientific attention has focused on possible biologic, genetic, and neurologic explanations for gender nonconforming expression, cross-gender identity, and gender dysphoria. No clear unequivocal biologic markers for these have been identified, but early limited findings are intriguing and invite further research. One area of inquiry has examined the possible influence of prenatal maternal androgens on those areas of the developing fetal brain associated with sexual dimorphism. There is some evidence that prenatal

androgen exposure may predispose an individual to male gender identity, but not always; among 46, XY intersex children exposed to increased androgens prenatally but raised as girls, only 40% to 50% developed male gender identity. Also, MTF transgender individuals with presumed normal male prenatal levels of androgen exposure override this influence and develop a female gender identity. Recent studies examining 46, XX individuals exposed to higher levels of prenatal androgens demonstrated marked masculine gender expression but no evidence of male gender identity or gender dysphoria. In this area of inquiry, data suggest that for some gender nonconforming and transgender individuals, prenatal exposure to androgens may be influential, but it seems not to be applicable to the broader transgender community.

Recent research provides incomplete but increasing evidence for a genetic component to gender nonconformity and cross-gender identity. Hare and colleagues have identified an association between longer androgen receptor (AR) gene polymorphism and MTF transsexualism, perhaps caused by inhibition of the ability of testosterone to masculinize the fetal brain. A similar gene anomaly has been associated with FTM transsexualism. Familial and twin studies have documented increased occurrence of gender nonconforming expression and cross-gender identity within families and between twins, providing further evidence of a possible genetic component to the development of cross-gender identity and expression.

Another focus of biomedical inquiry has been comparison studies of transgender and nontransgender individuals looking at sex-related anatomic dimorphism in terms of brain structure and functioning. Differences have been reported, but most of these studies have not been replicated and therefore the significance of their findings is uncertain. However, documenting brain differences between transgender and nontransgender individuals would suggest a possible neurologic component to the development of cross-gender identity, at least for some individuals.

Given the complexity of gender as a concept, and the diverse ways in which it is experienced and expressed within a population, continuing research may find that the origins of gender expression and identity are multifactorial, with genetics, biology, and environment each playing a role in varying combinations and degrees of influence. Since gender nonconformity and cross-gender identity do not appear in the *DSM-5*, and therefore may be considered part of the normal spectrum of human experience, perhaps the most valuable research will be that which examines the factors contributing to gender dysphoria among children and adolescents. With this increased understanding, physicians and other providers will be better able to prevent the onset of dysphoria or to ameliorate its effects in the child where it already exists.

## ADVERSE EFFECTS

Due in large part to the experience of societal stigma and ostracism, gender nonconforming and transgender youths may be at high risk on many fronts, as outlined in the paragraphs that follow. Nevertheless, there are reasons for immense optimism because



these young people are coming of age on the cusp of enormous and positive societal change. This change is marked by an increased understanding and celebration of the diversity of gender expression and identity and an awareness of how this diversity can enrich families, schools, workplaces, and the broader community. In many parts of the United States, primary care physicians (PCPs) have begun to recognize the amazing creativity and resilience of these youths as they navigate changing societal currents. They have met parents who love their children unconditionally and who confidently and passionately work to make the world a safer, more accepting place for them. They have joined with educators, social workers, mental health professionals, and others to create empowering transgender youth programs, including youth leadership workshops, mentorship programs, music/poetry/art events, speakers' panels, and many others. Such programs help develop important life skills but just as importantly validate the rightful place of gender nonconforming and transgender youth among other happy, healthy, and hopeful young people. These exciting changes have not yet arrived in many parts of the United States, but they are on the horizon. The risks described below are still very real for many children and youths. But it is important to recognize that they are an aberration, a result of living in the presence of stigma and ostracism. They are not part of the natural history of being gender nonconforming or transgender.

In those communities where the societal change described above has not yet arrived, transgender youths often experience a profound isolation that intensifies their feelings of confusion and distress. They and most people in their lives, including parents, teachers, counselors, clergy, and physicians, often know little about gender identity or what it means to be transgender. In many instances, gender identity is confused with sexual orientation, a much different concept. Many PCPs and counselors were trained at a time when gender nonconforming behaviors and transgender identity were seen as aberrant or pathologic, and some continue to conduct their practices accordingly. Many transgender youths have few adult role models or mentors for support or validation, and many know no other transgender youth. When transgender youths have little access to accurate information, supportive counselors, or physicians, and when they have no opportunity for healthy interactions with transgender peers and adults, the negative messages that surround them in their daily lives go unchallenged. Although this continues to be true in many communities across the United States, over the past decade there have been major advances in increasing the understanding of families, health and social service providers, educators, and others about the importance of recognizing, validating, and empowering gender nonconforming and transgender youths. PCPs have often been at the forefront of the movement to increase public awareness, developing creative programs for youths and their families, and providing needed advocacy on their behalf. With the growing love and support of families and communities, many gender nonconforming and transgender

youths no longer struggle under the burden of stigma and ostracism.

For those many children and youths who grow up in families and communities still untouched by this societal change, the most harmful reality they face is society's disapproval of who they are and how they present themselves to the world. Social stigma, and the violence and discrimination it engenders, permeate their daily lives. It makes completing the expected developmental tasks of childhood and adolescence related to identity and self-esteem enormously difficult. Many of these children and youths are viewed by their families with shame and disgust. They are often forced to change their behaviors and renounce their declared inner sense of gender. Many of them are taken to therapists for the express purpose of changing their gender expression or identity. Many transgender adolescents and adults recall being ridiculed, ostracized, or beaten for being true to who they were, including within their own families. Many gender nonconforming and transgender youths drop out of school and run away or are thrown out of their homes; some seek survival on the streets; many contemplate or attempt suicide. As a result, many end up in the child welfare or juvenile justice systems. The harassment and abuse against gender nonconforming and transgender young people often continue in these settings, perpetrated both by other youths and by staff members. Fortunately, state judiciaries across the country as well as organizations such as the Child Welfare League of America and the Equity Project, with the active involvement of pediatricians and other advocates, have developed training, model policies, and other tools to meet the needs of transgender youths in out-of-home care and address the societal antecedents that bring them into these systems.

Schools often are especially dangerous places for gender nonconforming children and transgender youths. Many of them experience daily verbal, physical, and sexual harassment on the playground and in the classroom. In many instances, this harassment is not addressed by teachers, counselors, or other school staff, or it is dealt with by blaming the victim. Sometimes, disapproving teachers and other school staff members engage in harassing behaviors themselves. Many schools have no specific policies prohibiting harassment or bullying based on gender identity or expression, even though these, along with sexual orientation, are among the most common targets of harassment on school campuses. An increasing number of school systems, however, are adopting rigorous anti-bullying programs and antiharassment policies that specifically include harassment based on gender identity and expression. Many have included transgender issues in regular teacher trainings and have worked with national organizations such as the Gay, Lesbian and Straight Education Network (GLSEN) to ensure that school campuses are safe places for transgender students. Many school systems have encouraged the establishment of gay-straight alliances in schools to support LGBT students and their friends. Many schools also routinely invite PCPs to join in the development of individualized education programs (IEPs) and participate in other discussions related to

addressing the needs of individual gender nonconforming and transgender students.

Societal stigma also may be reflected in the daily discrimination experienced by some children and youths. Children may be admonished for playing with toys or displaying interests that are considered inappropriate for their presumed gender. They are told by what names they will be called and by what pronouns they will be referred to, in spite of their protests that these names and pronouns do not reflect who they really are. Their genitalia rather than their inner identity as female or male are referenced in assigning them to bathrooms, lockers, physical education classes, athletic teams, graduation ceremonies, and other school activities in which gender is still considered relevant. School dress codes often limit transgender students' ability to wear clothes that are consistent with their gender identity. Many PCPs have begun to work with individual schools on behalf of their gender nonconforming and transgender patients, advocating policies and accommodations that ensure safety, respect, and validation for their patients in the school setting.

As transgender youths grow older, they begin to experience broader societal forms of discrimination. Their driver's licenses and other forms of identification, as well as their school, employment, and health records, usually reflect their biologic sex rather than their gender identity. Because fear, embarrassment, and potential humiliation accompany the presentation of these documents to others, many transgender adolescents may avoid applying for school or a job or accessing health care. Transgender individuals have been denied access to educational opportunities, community programs, social services, and health care simply because of their gender identity. Fortunately, each year more states and municipalities enact laws and ordinances that prohibit discrimination based on gender identity and expression in the areas of housing, employment, public accommodations, and health care, providing transgender individuals, including adolescents, legal recourse when faced with discrimination. In addition, LGBT communities have made great strides in recognizing that LGBT social and health services should be as welcoming and accessible to transgender individuals as they are to members of the lesbian, gay and bisexual communities.

The risks described above are not inherent in being a gender nonconforming child or transgender youth. They are the common experience of any young person who is stigmatized, fearful, and alone. The genuine distress experienced by some children diagnosed with GID (and presumably gender dysphoria) and some transgender youths over the perceived dissonance between their biologic sex and gender identity should not be dismissed or minimized. Nevertheless, evidence from other cultures and the experience of many counselors and physicians suggest that when provided love, support, and validation, these young people thrive and can expect to grow into happy, healthy, and productive adults. Perhaps the most important role that PCPs can play in the lives of gender nonconforming children and transgender youths is to go beyond the confines of their offices and engage with schools, social service agencies, faith communities, and others

to ensure that these young people grow up in safe and nurturing environments.

## EVALUATION

The AAP, the American Academy of Child and Adolescent Psychiatry, and the Society for Adolescent Health and Medicine have each issued official guidelines related to providing supportive care to children and adolescents facing issues of gender identity and gender expression. In addition, several resources are available to PCPs on providing culturally sensitive and relevant care to gender nonconforming children and transgender adolescents and adults.

PCPs should not presume the sexual orientation or gender identity of any patient. Children with gender nonconforming behaviors, many of whom will later identify as LGB, have often learned or have been pressured to change their behaviors, particularly in public settings such as schools and health clinics. Many transgender youths will also hide their true gender identity. Even when asked in a sensitive and nonjudgmental manner about their inner feelings of being female, male, or another gender, they often will deny these feelings because they are fearful of PCP disapproval, uncertain about confidentiality, or still confused about the meaning of their emerging feelings. Perhaps one of the greatest barriers to appropriate health care for gender nonconforming and gender dysphoric children and transgender youth is physicians' assumption that they have no patients in their practices who are dealing with issues of gender identity and expression. Another mistaken assumption is that significant gender nonconforming behavior in childhood accurately predicts sexual orientation. Although some children with persistent gender nonconforming behaviors will later identify as LGB, many will not. Few PCPs may consider that some may also later identify as transgender. Many transgender youths are thought by their PCPs, and sometimes by themselves, to be LGB. However, the distinction between sexual orientation and gender identity is important for the provision of care because the different issues related to each require different responses from a PCP. In addition, transgender identity does not predict sexual orientation. Transgender youths may be gay, lesbian, heterosexual, or bisexual. For example, an MTF-transgender adolescent who is attracted to boys may be considered a heterosexual trans-woman, if she so considers herself. Some, however, may describe themselves as "gay," either because it feels like the appropriate term to them or because it is easier for others to understand.

The goal of PCPs is not to identify every child with gender nonconforming behaviors or transgender identity; instead, it is to create a safe and accepting clinical setting where children, adolescents, and their families know they can discuss any topic of concern, including gender identity and expression, without discomfort or disapproval on the part of the physician. Some patients and parents do not know that PCPs may have expertise in discussing issues of sexual and gender development. Specific messages can be provided through clinic posters and brochures informing patients that these issues are appropriate topics of discussion. The most important signal that

these topics are a natural part of pediatric practice is in the PCP's own history taking and anticipatory guidance, in which issues of child and adolescent sexuality and gender should be routinely discussed.

After patients have identified themselves as transgender, the PCP should create an accepting and supportive clinical environment by using pronouns consistent with their patients' gender identity and asking by what name they would like to be called by clinic staff. Although medical records must retain the patient's legal name, the notice "Also Known As [preferred name]" can be added to the front of the chart, and all clinic staff members should use this name in personal encounters with the patient. Patients should use either a unisex restroom or a restroom consistent with their gender identity while in the clinic. As with all adolescents, transgender patients should be seen alone for at least part of each visit and their confidentiality should be respected. An adolescent patient's gender identity should not be revealed to parents without the patient's permission. Patients should also be asked how they would like their gender identity recorded in the chart, if at all, because medical records containing confidential information are sometimes accessible to parents.

PCPs should reflect on their own feelings about gender nonconforming behaviors and gender identity issues. As products of their own society, many physicians may initially approach these issues with discomfort or disapproval. However, such an approach to gender nonconforming children or transgender youths will diminish the PCP's ability to care for these patients. Most transgender patients have had profoundly negative experiences with the health care system. In the past, these patients have been labeled as disordered and were often treated accordingly. Transgender patients report how staff in clinical settings often display fear or open disapproval of them or joke about them, even within hearing of the patient. At times, these patients have been refused medical care. PCPs who receive little training about transgender health issues often do not understand the transgender adolescent's unique life experiences and needs. Most PCPs are unfamiliar with community resources that might help their transgender patients. Most health insurance companies refuse to pay for transition treatments, including hormone therapy, surgery, and the laboratory studies needed to monitor treatment. Fortunately, this refusal of payment for necessary, even lifesaving, care is slowly beginning to change.

PCPs are in a position of power relative to their transgender patients. As gatekeepers, PCPs decide who does or does not receive transition treatments. Many, often through disapproval or lack of knowledge, have barred transgender patients from passing through that gate, preventing them from receiving necessary transition treatment and care. PCPs must understand the history of tension between the transgender and medical communities. PCPs can improve this strained relationship by listening carefully and respectfully to their patients' life stories and expressions of need and by providing care that addresses these needs in a compassionate, comprehensive, and timely manner.

## History

Gender and sexuality are important parts of a child's life. At each well-child visit, beginning in early childhood, the PCP should ask parents how they think their child is developing compared with other children. Parents and child should be asked how the child is getting along with siblings and peers. Does their child seem happy? Is the child teased or harassed by other children, and over what issues? All parents should be asked if they have any concerns over their child's sexual development or gender expression. Many parents who have such concerns are hesitant to bring them up on their own but are often relieved when the PCP does so. If a child with gender nonconforming behavior is happy and safe from teasing and parents have no concerns about these behaviors, no reason exists for the PCP to question further. However, as a child grows older and has more social contacts beyond the family, issues will likely arise related to being gender nonconforming or transgender in a society that is often nonaccepting. PCPs should remain attuned to this likelihood and reopen the door to discussion of these issues in future visits.

If parents express concerns about their child's gender expression or gender identity, then the PCP should ask what they have noticed or heard from the child and what their concerns or fears might be. Parents' concerns are often related to their own embarrassment because of their child's behavior; they may also fear for their child's safety in a nonaccepting world. Many of them fear that their child's behavior or verbal expressions of wanting to be the opposite gender signal an eventual lesbian or gay sexual orientation or transgender identity. PCPs may gently question gender nonconforming children if they feel safe from teasing at home and school and about their feelings of being more like a girl, a boy, or another gender inside. Care must be taken to avoid conveying the message that anything is wrong with the child because of the child's gender nonconformity. In addition to the well-child visit, any visit suggesting an unhappy child or a child in distress should lead the PCP to consider discussing issues of gender nonconforming expression and gender identity with the parents and child.

Transgender adolescents may come to the PCP's office either because of parental concerns or through school or child welfare agency referral. Transgender youths may also seek care themselves, often to discuss issues of safety and acceptance at home or school or concerns about sexually transmitted infections (STIs), or to request hormone treatment. However, many transgender patients see their PCPs not through referrals or acute care visits but rather in the context of routine well-teen evaluations. Many transgender patients hide any evidence of their inner gender identity; others are presumed, perhaps even by themselves, to be lesbian or gay. PCPs should initiate discussion of sexuality and gender with all adolescents at each well-teen visit. Although many PCPs routinely discuss sexual activity and safer sex practices, fewer discuss sexual orientation, and almost none of them address gender identity. However, as noted earlier, most transgender adolescents face significant confusion and distress related to their gender identity and major risks

from growing up in an often nonaccepting world. PCPs must be willing to open the door to discussion of gender in order to reduce the turmoil and dangers that these youths face.

The PCP can begin to approach the issue of gender identity in the broader context of obtaining a HEADSSS (home, education, activities, drugs, sexuality, suicide, and safety) interview. This approach will provide a sense of how things are going in various aspects of an adolescent's life, recognizing that many transgender youths face serious issues in each of these areas. Throughout this conversation, it is essential that the PCP use non-heterosexist, gender-neutral language, reflecting that no assumptions are being made about a youth's sexual orientation or gender identity, or that of family members or friends. To address gender identity within a broader sexual history, the PCP might say, "Sexuality and sexual feelings can be confusing sometimes. During puberty, bodies change in lots of different ways. Sexual feelings are changing as well. Some of my patients are not sure if they are attracted to guys or girls or maybe both; and some of my patients even wonder if they're more like a girl or a boy inside. All of this is completely normal but can be really confusing. So I'm wondering what it's been like for you." After asking about attractions (sexual orientation), the PCP can simply ask, "And how about inside? Do you feel more like a girl or a boy or maybe something else?" For the patient who is not dealing with gender identity issues, these questions may seem odd. This can be addressed by a simple statement such as, "These are questions I ask all my patients, and for some, they're really important." For transgender youths, the questions may be life saving. Even if they decide not to acknowledge their gender identity concerns at the current visit, they have learned that someone is available with whom they can talk when the time is right. If youths do acknowledge cross-gender feelings, the PCP can ask whether they have defined themselves in terms of gender. Some may refer to themselves as transgender while others may self-define as pansexual, pangender, bigender, genderfluid, genderqueer, or another designation. Some may refer to themselves as gay or lesbian. It is appropriate to ask each teen what their particular self-designation means to them. This demonstrates respect on the part of the PCP and can foster a sense of empowerment in the youth.

If adolescents acknowledge a transgender, pangender, or other-gendered identity, the PCP should thank them for their trust in sharing this important and personal part of who they are. As a demonstration of understanding and respect, the PCP should then ask about preferred name and pronouns and use these through the remainder of the interview and subsequent visits. Patients should be reassured that the discussion of gender identity will remain confidential unless they give permission to share it with others or unless a risk of danger to someone exists. It is essential to ask, at an appropriate time in the interview, "Do you have any periods of feeling very sad? How long do they last? Have you ever had feelings of wanting to hurt yourself or kill yourself? Have you ever actually tried to do this?" If the PCP is not comfortable with the depth of interviewing suggested in the following

paragraphs, she or he has a responsibility to refer the adolescent to someone else who can have this conversation.

The subsequent history may then focus on the adolescent's path to recognizing their transgender identity. When were they first aware of feeling more like a girl, a boy, or another gender? What was this experience like? How comfortable are they with their transgender identity now? What do they know about gender identity and what it means to be transgender? What are their hopes and dreams for the future? Do they see their futures as enhanced or limited by being transgender? The history may focus on the adolescent in the context of the world around them. Have they told others (family, peers, teachers, or counselors) about their inner feelings of gender? Have these people responded in a supportive or negative way? Have they been bullied, harassed, scolded, ridiculed, or teased because of their gender identity? With whom do they spend time, and what kinds of things do they do together? Have they met other transgender adolescents or adults? Have they been in relationships, and have these relationships been healthy ones? Have they been sexually active, and do they use safer-sex practices? How have they met their sexual and romantic partners? Have they ever been pregnant, impregnated anyone, or had an STI? How many different sexual partners have they had, and what have been their genders? Have they ever been touched sexually or forced to have sex without their permission?

Understanding that transgender youths often are subjected to harassment and rejection at home and school, the PCP should ask about their treatment in these settings and whether they have ever run away from home or dropped out of school. Have they needed to sell their bodies, deal drugs, or engage in other illegal activities to survive on the streets? Have they been involved with the child welfare or juvenile justice systems, and how have they been treated within them? Have they ever used drugs or contemplated suicide? How do they believe their physical health has been, and do they have any health needs they believe are not being addressed? What do they know about gender transitions and is that something they have thought about? Have they actually begun the transition process? Have they begun to cross-dress? Have they begun puberty blockers or cross-gender hormone therapy, and, if so, where have they obtained their treatment? Have they injected silicone? Have they thought about gender affirmation surgery (sex-reassignment surgery) or other transition-related procedures in the future?

Other questions to consider include, "What have you found on the internet or in various forms of media about transgender people?"; "Do you know any transgender or LGB people?"; and "Who do you have as supports?" Because eating disorders are common among sexual minorities and especially among transgender populations where malnutrition can suppress pubertal progression, it is also important to ask, "Do you restrict your diet, binge and then purge, or use laxatives or make yourself vomit?"

Not all of these questions need to be addressed at the first visit. Follow-up visits should be made to



address these issues on an ongoing basis. The PCP should be aware that the history, beyond providing specific information about the experience and needs of a transgender adolescent, is an opportunity for the PCP to interact with the patient in a comfortable, respectful, and caring manner that validates who the adolescent is as a human being. Many transgender adolescents have never experienced such acceptance before, and providing it is among the most fundamentally important things a PCP can do.

### Physical Examination

The physical examination of children with gender nonconforming behaviors or who express the desire to be other than their anatomic gender is the same as that for other children. A complete examination, including the genitals, should be a routine part of every well-child visit. On occasion, the PCP may observe a child wearing clothes or exhibiting behaviors or interests that are more typical of another gender. These behaviors or interests may or may not relate to the child's gender identity.

Similarly, the content of the physical examination of transgender adolescents does not differ significantly from that of other adolescents. It should be guided by a comprehensive and accurate health history, including sexual and other risk behaviors. The PCP should remember that transgender youths may be heterosexually, homosexually, or bisexually active or not sexually active at all. Many transgender youths hide all public expressions of their gender identity. Some may have already begun the transition process and come to clinic displaying dress, hairstyles, makeup, and mannerisms usually associated with another gender but consistent with their gender identity. Occasionally, transgender patients may wear non-gender-defining street clothes but underwear appropriate for their gender identity. If patients have begun pubertal suppression, they will generally remain at Tanner Stage 2 or 3 and depending on the duration of suppression may eventually show delay in pubertal development relative to their peers. If patients have already begun transition hormone treatment, they may show evidence of breast development (MTF), appearance of facial hair (FTM), and other expected changes of estrogen and testosterone treatment.

PCPs should understand and respect the significant discomfort that many transgender youths have related to their pubertal changes, such as development of facial hair, deepening of the voice, breast development, and menstrual periods, which feel alien to their gender identity. Some MTF-transgender adolescents may tuck their genitals, placing their penis and testes between their legs so they are less visible. Some FTM-transgender youths may wear chest binders or baggy tops to make their breasts less visible. Some may also wear a "packer," which is padding or a phallic-shaped object worn in the front of the underwear or pants to give the appearance of having a penis.

In preparing for the examination, the PCP should discuss the rationale for suggesting the parts of the examination that might be particularly uncomfortable for a transgender adolescent, especially the breast and genital examinations. PCPs should explain that their

intention is to make the examination as comfortable as possible for the patient and to elicit the patient's guidance in how best to accomplish this task. The patient should be informed that they have a right to refuse any part of the examination. The PCP should ask transgender patients what words they would like used in referring to various body parts—for example, *genitals* instead of *penis* or *vagina*. An FTM-transgender patient may prefer the term *chest* rather than *breast*. MTF-transgender patients should be treated the same as other female patients, and FTM-transgender patients like other male patients in conducting the examination. Conducting all comprehensive physical examinations of MTF- and FTM-transgender patients with the patient in a gown and draped appropriately to minimize exposure is best. At the same time, acknowledging that the patient's anatomic features may suggest gender-specific evaluation such as breast, testicular, or pelvic examinations is appropriate. For example, suggesting a pelvic examination for an FTM adolescent with unexplained vaginal discharge or bleeding might be appropriate. Most transgender patients will agree to the suggested examination if the medical rationale is presented in a factual and respectful manner, inviting the patient's questions and input on how to make the examination as comfortable as possible. All aspects of the physical examination should be for the purpose of medical necessity, not to satisfy physician curiosity about possible genital or breast changes related to hormonal or surgical transition therapy. As for all adolescents, a chaperone should be present during a breast, genital or anorectal examination. The gender of the chaperone should be based on patient preference.

### Laboratory Evaluation

The child with gender nonconforming behaviors who has an unremarkable history and normal physical examination requires no special laboratory evaluation. Laboratory evaluation of transgender adolescents should be based on an accurate and comprehensive history, including sexual and other risk behaviors, and physical examination, not on gender identity. Several clinical guidelines provide information on the appropriate laboratory evaluation and monitoring of those patients who elect to begin hormonal transition therapy.

## MANAGEMENT

The goal of care in working with gender nonconforming children and transgender youths is to promote optimal physical, developmental, emotional, and social well-being. The challenge faced by PCPs is to achieve this goal within a context of nonacceptance and stigmatization by many people in society. In this sense, gender nonconforming children and transgender youths have life experiences and needs that are similar to those of LGB youths.

Another challenge faced by PCPs is how to advise and support families of gender nonconforming and gender dysphoric children and youths when there is a considerable lack of professional consensus on appropriate treatment approaches and goals in these age groups. Because there has been insufficient research

in these and related areas, treatment approaches and goals rely in large part on “expert opinion” rather than scientific data. This has allowed a number of different treatment approaches to be proposed, particularly for preadolescent children, that are sometimes based on differing philosophical foundations but very little science. This lack of evidence-based best practice standards can present a dilemma for PCPs and families in trying to decide which of the varying approaches best meets the needs of a particular child. Fortunately, a 2012 issue of the *Journal of Homosexuality* was dedicated to assisting PCPs and parents by offering a comprehensive review of what is known and what has yet to be learned about gender nonconformity and gender dysphoria in childhood, as well as various treatment approaches and their specified goals. It also provided detailed descriptions of a number of well-established clinical programs and identified areas of consensus and disagreement among them. Ethical implications of the various approaches also were discussed. Since most PCPs work in communities without specialized child and adolescent gender clinics, it is imperative that PCPs become familiar with these issues, understand where they themselves stand philosophically on the continuum of treatment approaches, and be willing to reach out to experts at nationally recognized child and adolescent gender centers for consultation as the need arises.

Although relatively little is known about gender nonconformity, cross-gender identity, and gender dysphoria in childhood, the area that is best understood is the likely developmental trajectories of children with gender dysphoria. It also serves as an excellent example of how robust, reproducible research data can result in a greater degree of consensus around certain aspects of treatment approach. We now know, for example, that the dysphoria of most younger children with gender dysphoria does not persist into adolescence. These children are referred to as *desisters*, and their dysphoria usually disappears in later childhood at about age 7 to 9 years. Research has shown that most desisters will go on to self-identify as lesbian or gay during adolescence, and a small percentage will identify as heterosexual. Children with gender dysphoria that persists into adolescence are referred to as *persisters*, and most eventually identify in adolescence and adulthood as transgender. At this point, there is no way to accurately predict which children will end up desisting or persisting in their gender dysphoria. Another unknown is whether treatment aimed at promoting a child’s desistance is effective, or more importantly, ethical. This is among the more disputed aspects related to the treatment of gender nonconforming expression, cross-gender identity, and gender dysphoria in preadolescent childhood. While there is some controversy related to the treatment of transgender adolescents in terms of timing and length of various transition treatments, most clinical experts support medical transition treatments in adolescence and adulthood, such as pubertal suppression, hormone therapy, and eventual gender affirmation surgery. This is because research has shown that most transgender adolescents have a gender identity that will persist into adulthood. Furthermore, there is a robust body of evidence that

demonstrates that transition treatments are safe and lead to significant improvements in physical and emotional well-being. There is no similar body of research definitively supporting a single treatment approach over another in addressing gender dysphoria and gender nonconformity in preadolescent children, thus leading to the confusing and sometimes contradictory choices facing PCPs and the parents and children they are trying their best to support.

Despite controversy, several shared themes can be found across most treatment programs for preadolescent gender dysphoric and gender nonconforming children. Since research findings related to persistence and desistance among children are well-accepted, with an understanding that most gender dysphoric children will be desisters and no longer gender dysphoric as they move into adolescence, it is generally agreed that the appropriate approach is to provide support and counseling to parents and children, but not to provide medical transition treatment in childhood. There is also a widely held view that social transition in terms of living full-time as a child of another gender or use of name and pronouns consistent with inner gender identity should probably be deferred until adolescence. Since so many preadolescent gender dysphoric children eventually desist, many feel that encouraging them to transition socially and then later “de-transition” might cause unnecessary trauma to the child, although there are no research data to support this. Another area of general agreement is that, ideally, support and counseling should be provided to gender dysphoric children and their families by a multidisciplinary team consisting of the PCP, a psychiatrist or other mental health professional, and a social worker. These professionals can be valuable additions to the treatment plan in exploring a child’s or youth’s sense of gender identity, social and academic functioning, family relationships, cultural expectations, and self-esteem. They can help assess and support parents through the process of acceptance and, it is hoped, eventual celebration of their child. They also can address parental fears, concerns, and misconceptions, which likely will change in nature as a child grows older and moves into adolescence. Most treatment programs emphasize that their goal is not to prevent homosexuality or cross-gender identity. Instead, the stated goal for most is to prevent or ameliorate gender dysphoria, recognizing that not all children with cross-gender identity are gender dysphoric.

Despite these common themes among most programs, there are also significant and often controversial differences regarding what “support and counseling” actually mean among varying programs. These often reflect underlying philosophical differences and varying understandings of gender nonconformity and gender identity, their etiologies, and the degree to which they are felt to reflect possible underlying pathology or simply another way of “being” in the world. At one end of the spectrum are programs that are prepared to focus on perceived psychopathology in a child, a parent, or family dynamics that either cause gender nonconforming expression or

cross-gender identity and dysphoria or allow them to persist. Treatment often involves trying to help a child “work through” his or her cross-gender identity with the goal of decreasing gender dysphoria, even if it means engaging in efforts to decrease a child’s desire to be another gender. Parents are asked to put limits on their child’s cross-gender behaviors and to create more opportunities for their child to have interactions with temperamentally compatible same-sex peers, feeling that these kinds of interactions help solidify a child’s appropriate sense of gender consistent with natal sex, and perhaps counteract pathologic influences contributing to the creation or persistence of cross-gender identity. At the other end of the spectrum are those professionals who believe the appropriate approach is to validate and celebrate the unique gender identity of each child, respecting the child’s right to express their gender as they wish, while keeping them safe in an often nonaccepting and hostile world. Most programs working with gender nonconforming and gender dysphoric children fall somewhere in the middle of the spectrum. They tend not to focus on looking for sources of psychopathology as factors contributing to a child’s gender identity or gender dysphoria. Most feel that a good measure of the dysphoria experienced by children and youths comes from the negative responses of family, peers, and community to their cross-gender identity and expression. Therefore, a significant part of providing support to a child is to determine how safe and supportive that child’s environment is and to work with extended families, schools, places of worship, and other settings to ensure that a child is safe and validated in all areas of his or her life. Parents are provided information about gender dysphoria and its possible developmental trajectories, as well as the understanding, skills, and resources to support their child effectively, no matter what their gender identity or sexual orientation might eventually be. Most physicians take a “watchful waiting” approach toward the child, allowing the child to express their gender, although sometimes suggesting certain limits (for example, being allowed to cross-dress at home but not when they go to school). As a child approaches adolescence they are especially watchful for evidence that a child’s gender dysphoria, if present, may persist or desist. If it looks like it may persist then discussions with parents and child about possible future choices related to transition take place (for example, the initiation of pubertal suppression early in puberty). If it seems that the child’s gender dysphoria may desist, then there are other discussions to be had, including considering the possibility that a child may later recognize a lesbian or gay identity, and providing family and child supportive resources in preparation for this possibility.

When faced with such a diverse and often contentious array of opinion and practice, what is a PCP to do when a family arrives in their clinic expressing concerns about their young child’s gender nonconforming behaviors, expressed cross-gender identity, or gender dysphoria? First, it is important to be familiar with the areas of consensus and controversy outlined above. Secondly, it is important to keep in mind

the replacement of the GID diagnosis with gender dysphoria in the *DSM-5*. This means that gender nonconforming expression and cross-gender identity per se are now considered part of the normal spectrum of human diversity. Discomfort and distress over gender should be the focus of concern, and the goal of treatment is to prevent or ameliorate that distress, whether its origins are within a person’s psyche, in their environment, or perhaps both. It is important to remember that the goal of treatment is not to prevent homosexuality, and most physicians would agree that it is also not to change a child’s expressed gender identity. PCPs should be aware of and willing to access local and national resources that can support them in the provision of informed care to these children and youths and their families. If possible, it is very helpful to bring together a multidisciplinary team as described above, to support both the patient and the patient’s family over time, from childhood through adolescence and possibly into adulthood.

It is important to be open with parents about the varying approaches to working with gender nonconforming and gender dysphoric children, and about their underlying assumptions and goals. It is also important for PCPs to let parents know where they are on the spectrum of professional opinion about the appropriate treatment approach to these children and their families. PCPs or other team members should open the opportunity for a discussion of parental concerns, fears, and degree of comfort related to their child’s gender identity and expression. They should also be asked what their hopes and expectations around treatment might be. Parents should be informed clearly that the goals of treatment are to prevent or diminish a child’s distress around gender, but not to change their gender identity or sexual orientation. Often parents fear that their child might someday be lesbian or gay, and may or may not have thought about the possibility of their child being transgender. The PCP should gently remind parents that any child might be gay, lesbian, bisexual or transgender, and let them know of the medical profession’s position that all these possibilities are considered normal developmental outcomes, while recognizing that not all segments of society yet agree. The PCP should also share, in lay terms, what is known about the developmental trajectories of children experiencing gender dysphoria—that in adolescence many do come to realize their lesbian or gay identities, while a much smaller number are transgender. Over time, as a child gets older, this issue should be revisited, offering parents an opportunity to share their thoughts or concerns and allowing the PCP to correct misconceptions and connect parents, children, and youths to supportive resources.

Above all, PCPs should remind parents of the importance of expressing their unconditional love for their child and refraining from comments or actions that demonstrate disapproval of their child’s gender expression or identity. The Family Acceptance Project at San Francisco University has conducted research demonstrating the important role that parents play keeping their lesbian, gay, bisexual, and transgender children healthy and safe through the provision of acceptance and love. The PCP should share this understanding with

all families, and provide them the skills and resources to accept and support their children no matter what their gender identity or sexual orientation might be.

The following sections continue the discussion by focusing on how PCPs can recognize and address the needs of transgender adolescents.

### Physical Well-being

Gender nonconforming children and transgender youths face the same health issues as other young people. The health care they receive should be based on a comprehensive history, physical examination, and evaluative studies, not on their gender expression or identity. Nevertheless, the PCP should recognize that these children and youths often grow up in hostile environments that may have a negative effect on their physical well-being. Among these negative effects are the physical sequelae of substance use, poor nutrition caused by homelessness or disordered eating, unprotected sexual behaviors, self-harm, injuries from physical and sexual victimization, and hormonal or surgical transition treatments accessed outside of health care settings.

### Developmental, Social, and Emotional Well-being

In most ways, children with gender nonconforming expression and transgender youths are exactly the same as their peers. They have the same needs for protection, nurturance, and love and the same hopes and dreams for the future. They grow up in the same families and communities and attend the same schools and places of worship. Similar to other children, they face the fundamental task of achieving a sense of identity that integrates all aspects of who they are, including their sexual orientation and gender identity. This integration of sexual and gender identity, accompanied by a growing sense of comfort with that identity, is essential for the optimal health and well-being of each child and adolescent.

However, the experience of growing up as a child with gender nonconforming expression or as a transgender youth is different in several important ways. Unlike their peers, these young people face an often lonely and sometimes frightening journey of self-discovery, attempting to understand 2 of the most fundamental aspects of who they are as human beings—their gender identity and their sexual orientation. Some of these children will recognize, often at a young age, that their inner sense of being female, male, or another gender differs from the gender that was assigned to them at birth. Some children and adolescents accommodate themselves to this growing awareness. Most, however, experience significant confusion and distress, wondering what their feelings mean and uncertain of who they are. Growing up in a society that believes that a person is either male or female and that gender expression and identity must strictly reflect biologic sex undoubtedly intensifies their sense that something inside them has gone wrong. Many of these individuals become filled with an overwhelming mix of confusion, shame, anger, self-hatred, and despair. It is important to remember that most gender-dysphoric children eventually self-identify as lesbian, gay, or bisexual and no longer experience

gender dysphoria as adolescents. Being lesbian, gay, or bisexual in an often-disapproving society may bring its own distinct set of developmental challenges.

The PCP's role as educator and counselor is as important as that of medical physician in caring for gender nonconforming children, transgender youths, and their families. The PCP should avoid assumptions based on stereotypes and listen carefully to understand each patient's unique experience and needs. In general, the counseling of nonconforming and transgender youths will address 6 areas: (1) self-acceptance and validation of gender expression and identity, (2) safety, (3) connectedness to supportive others, (4) self-disclosure or *coming out*, (5) healthy relationships and sexual decision making, and (6) optimism for the future. Addressing each of these areas is essential in ensuring their healthy development. These should be addressed over time and not all at an initial presentation or single visit.

### Self-acceptance and Validation

The PCP can play an important role in countering the effects of disapproval and the pathologizing of gender nonconforming expression and identity. For the gender nonconforming child, the PCP should state that although being different in this society can be painful, the child's gender nonconforming behavior can be healthy for that child. For transgender youths, the PCP should acknowledge the controversy around the use of gender dysphoria as a diagnostic category. PCPs should present being transgender as part of the tapestry of normal human identity and clarify that the primary issue of concern is distress that can often come from having a transgender identity in a society that is unaccepting. This validating reassurance of healthiness and normalcy is perhaps the most powerful statement a PCP can make to gender nonconforming children and transgender youths and their families.

A growing number of older gender nonconforming children and transgender adolescents know a significant amount about gender, gender identity, and gender expression. Many have done extensive research on the Internet, accessing YouTube videos and Web sites that are easily searchable, or connecting with other gender nonconforming and transgender youth on social media. Others, however, continue to be very isolated and know little or nothing about the nature and meaning of their emerging sense of identity. Therefore, the PCP should conduct an initial inquiry into what the youth knows and has seen or read, and focus on correcting misconceptions, providing validation, and supporting empowerment. Gender nonconforming children can be reassured that many ways exist of being a boy or a girl and that their way is one of these many ways. They can also be told that some children feel more like a girl inside and some more like a boy, or perhaps another gender, and that however they feel in terms of gender identity is all right. Transgender youths should be provided information on sexual orientation, gender identity, and what it means to be transgender. Some of these adolescents may go through a period of confusion, not knowing whether they are gay, lesbian, bisexual, straight, transgender, or a combination of these. The PCP should inform the



adolescent that such uncertainty is normal and that over time they will have a clearer understanding of who they are. The PCP may also provide brochures to adolescents facing issues of gender identity or refer them to supportive Web sites.

Ethnic and other minority youths who are transgender may have an especially difficult time. The PCP should discuss these issues with their patients openly and connect them to appropriate supportive resources within their communities and online.

### **Safety**

Because gender nonconforming children and transgender youths endure higher rates of physical and sexual assault, harassment, discrimination, and social rejection, PCPs should ask gender nonconforming children and transgender youths about their safety in their home, school, place of worship, and broader community. If harassment or other harmful treatment is acknowledged, then the PCP should work with the youth and family to identify and implement appropriate strategies to end the violence. Many of these children and youths feel shame and are afraid to advocate for their own safety. They may think they deserve the harm inflicted on them, or they may simply accept that this is the way the world is. The PCP should tell children and adolescents that they do not deserve such treatment and that they should expect and demand safety and respect from everyone in their lives and in all settings. Because gender nonconforming children and transgender youths have so few advocates, the PCP should offer to join with them in approaching every venue in which they experience violence, including the home and school, to work out a plan to end violence immediately and completely. Parents, PCPs, teachers, and others should also work together to ensure that schools and other community organizations create and implement policies and practices that ensure respectful treatment and appropriate accommodations for these children. The state of Massachusetts, for example, has developed a detailed policy statement about the responsibilities of schools to accept and support gender nonconforming and transgender students, which can serve as a model for other states. (See Tools for Practice at the end of this chapter.) Many states also have specifically designated offices, often within state departments of education, to combat bullying and harassment, including that specifically based on gender identity and expression. If necessary, the PCP should call on the state child welfare services office or advocacy organizations such as the American Civil Liberties Union to join in the effort to keep these young people safe.

### **Isolation**

Because gender nonconforming children and transgender youths experience profound isolation and loneliness, their physical and emotional health may be compromised. PCPs should address the issue of isolation by giving accurate information about gender expression and gender identity. They should provide supportive and reassuring counseling, or they should refer the child or adolescent to colleagues who have the time, comfort, and expertise to

provide them accepting and supportive care and counseling. PCPs should connect these children and youths to local community resources such as support groups and other youth programs. Children, youths, and families who do not have access to local programs should be informed about national organizations and Web sites created specifically for gender nonconforming children, transgender youths, and their families (see Tools for Practice). PCPs can also point out positive gender nonconforming and transgender role models in the community or nationally. In certain circumstances, it is appropriate for transgender PCPs to present themselves as role models to transgender youths and their families.

### **Self-disclosure and Coming Out**

Transgender adolescents often reach a point in their development at which they feel a strong urge to disclose their gender identity to others. Transgender youths often have a history of gender nonconforming expression as children. Therefore others may have already assumed or sensed that they may be transgender or lesbian or gay. Some transgender youths, however, successfully conceal their gender identity, either by adapting their gender expression to fit societal expectations consistent with their biologic sex or by labeling themselves or allowing others to perceive them as gay or lesbian. The process of disclosure to family and friends is often emotional and traumatic. Transgender youths who disclose their gender identity (come out) risk condemnation and rejection by family and peers. Therefore, coming out should be considered carefully, weighing the risks and benefits. It is sometimes suggested that if an adolescent expects a negative response from parents, then the adolescent should wait to disclose until legally and financially independent. However, many adolescents think that continuing to live a lie is intolerable and harmful to their self-esteem, and they come out earlier. A PCP should never reveal an adolescent's gender identity to parents without permission unless imminent risk of harm exists. A PCP can play an important role in the process of disclosure by helping adolescents decide whether they are ready to come out to family or friends and helping them choose an appropriate time, place, and approach for disclosure. PCPs who feel they do not have the skills to provide such counseling effectively should refer to or collaborate with a therapist who can guide the teen and support the family through the coming out process.

### **Relationships and Sexual Decision Making**

Most transgender youths have difficulty in meeting other transgender adolescents to establish friendships and share mutual support. PCPs should help connect transgender youths to local LGBT teen support groups and LGBT-supportive programs in the community, if they exist. This task can be accomplished ethically without parental notification. PCPs can suggest national telephone hotlines or Web sites where transgender youths can receive accurate information and supportive counseling and can communicate with other transgender youths (see Tools for Practice). If these options are not available, then the PCP can serve

as a supportive and reassuring lifeline until the adolescent is old enough to become independent and possibly move away to attend school or work in a community more accepting of transgender people.

Transgender adolescents may be heterosexual, homosexual, or bisexual in their attractions and behaviors. Given the prevailing societal disapproval of transgender individuals, however, many transgender youths are afraid to reveal their gender identity to those with whom they might be interested in establishing a relationship. Therefore, some transgender youths find that their only options for exploring emotional and physical intimacy are through anonymous sexual encounters on the streets, in parks, or through Internet hookups. In addition to being potentially dangerous, these encounters are often accompanied by feelings of shame and degradation, which are harmful to an adolescent's sense of identity and self-worth. That many transgender youths are eager to engage in the typical courting practices of adolescence, which normally take place in safer and more affirming circumstances, is evidenced in the great popularity of LGBT youth proms and other social gatherings in a growing number of communities across the United States.

Transgender youths who are in relationships face many of the same questions as their nontransgender peers: "Am I in love?" "What do I want from a relationship?" "Do I really want to be in this relationship?" "How do I know if this is a good relationship?" "How do I get out of this relationship?" In addition, transgender youths face the exceedingly difficult questions of how and when to tell their potential boyfriend or girlfriend about their gender identity. A transgender-supportive PCP or therapist can help adolescents reflect on and find answers to these questions.

As with other adolescents, many transgender youths know little about sexuality and how to make healthy sexual choices. Abstinence is always the appropriate option for adolescents who do not feel ready for a sexual relationship. Transgender adolescents should understand that when they are ready for a sexual relationship, they can expect to lead healthy and fulfilling sexual lives. All adolescents who have decided they are ready for a sexual relationship should be advised to limit their number of sexual partners and avoid mixing sex and alcohol or drugs so as to reduce their risk for infection, trauma, and sexual assault. Transgender youths, like other adolescents and depending on the sexual behaviors they engage in, are at risk for unplanned pregnancy and should be counseled on contraception. Not only could pregnancy lead to medical risks but it often can be extremely psychologically traumatizing to a gender nonconforming or transgender youth. Safer sex practices related to oral, vaginal, and anal sex should be reviewed in detail. Transgender youths should also be aware that *no* always means *no* in negotiating sex, and any forced or coerced sexual experience represents sexual assault.

### **Optimism for the Future**

PCPs should not only focus on the risks that transgender youths face, but also identify specific strengths that have allowed them to survive and sometimes thrive in the face of an often hostile environment. They should also challenge the belief of many transgender

adolescents that their futures will be significantly limited by their gender identity. Although some communities are more accepting of transgender people than others, many transgender adults lead happy, healthy, and productive lives. Although growing up transgender is often challenging, the future should be seen as hopeful and exciting.

### **TRANSITION CARE**

Transition represents the emotional, psychological, social, physical, and legal processes transgender persons experience to assume a body and gender role consistent with their gender identity. The transition process often begins in childhood and continues through adolescence into adulthood. Pubertal suppression, hormone therapy, and surgery are often the final medical steps in this process. PCPs play an essential role in facilitating the patient's transition from female to male, male to female, or perhaps to another gender. They often have known their gender nonconforming and gender dysphoric patients since early childhood. As puberty approaches and it seems that gender dysphoria may persist into adolescence, they are in an advantageous position to provide patient and parents with detailed and accurate information about the nature and timing of transition, its limitations and benefits, and the choices that lie ahead. It is also important to share with families that, just as there is significant controversy around the understanding and management of gender dysphoria and gender variance in childhood, there is also controversy around certain aspects of the provision of medical transition care from early puberty through adolescence. This understanding is essential in order for patients and parents to give informed consent to treatment. At the same time, it is imperative for the PCP to be clear about where she or he stands within the spectrum of opinion on the medical management of transition, including pubertal suppression, hormonal treatment, and gender-affirmation surgery.

The PCP has an important role in helping patients and families identify possible natural transition points for initiating hormone therapy, such as when a patient is changing schools (for example, from middle school to high school) or a family is planning to move to a new home and neighborhood. Whether or not such transition points are identified, it is important that the PCP work with school personnel before transition begins, educating them about what it means to be transgender and the social and psychological benefits of transition. The potential risk of harassment by other students or by school staff should also be addressed. In order to ensure both respectful treatment and safety in the school setting, the PCP should advocate for the development of an IEP or other formal assurance that the transgender student's preferred name and pronouns will be used in all school settings, both inside and outside the classroom and whether the student is present or not, and that appropriate restrooms and changing rooms are identified and accessible.

In addition to facilitating and monitoring social and psychological aspects of transition, PCPs are playing an increasingly central role in the initiation and management of physical transition, including both pubertal suppression and hormonal therapy.

Many PCPs still feel they do not have the training, experience, or time to do so effectively. Therefore, they refer their patients with significant gender nonconformity or gender dysphoria to gender specialists and other colleagues whom they feel have greater expertise in assessing gender issues and providing transgender care. At the same time, they retain their role as PCP and provider of a medical home. Many larger communities have endocrinologists and adolescent medicine, family practice, and internal medicine physicians, as well as mental health physicians, who are experienced in providing medical care and counseling to gender dysphoric youths considering transition. Such physicians often can be located through local LGBT community centers or national organizations such as the Gay and Lesbian Medical Association. Many PCPs, however, practice in smaller communities with few or no physicians with such expertise. These physicians should reach out to regional or other gender experts, through telemedicine and other means, to request their guidance in the evaluation and management of children and youths experiencing significant gender nonconformity or gender dysphoria. Thus, through necessity, many PCPs have become experts on transgender care. They recognize that for most gender dysphoric youths entering puberty, the provision of transition-related treatments such as pubertal suppression and hormonal therapy (outlined below) is not elective but instead represents a standard of care, with the early institution of treatment predicting optimal improvement in both physical and psychological well-being.

Guidelines are available to help PCPs and other physicians facilitate the transition process. WPATH in 2011 published the seventh edition of *Standards of Care for Transsexual, Transgender, and Gender Non-conforming People*, which is considered to be among the most authoritative guides to providing medical and mental health transition counseling, treatment, and support. The Endocrine Society also has developed detailed clinical practice guidelines on hormonal transition treatment for transgender adolescents and adults. In addition, several health centers experienced in providing comprehensive transgender health care have developed their own clinical guidelines. These latter guidelines often approach transgender care based on an informed-consent model, which is premised on a belief in the ability of patients (and if a minor, their parents as well) to determine their own transition path if provided complete and unbiased information about transition choices and their benefits and limitations. This model differs markedly from the traditional approach to transition care, including those represented in earlier versions of the WPATH standards of care, which presented a very prescriptive and linear path to transition. Under these earlier standards, transition was presided over by medical and mental health gatekeepers who could decide who was eligible for transition treatments, as well as the nature, sequence, and timing of those treatments. The latest edition of the WPATH standards of care differs significantly from previous versions. It is much more patient centered and allows for a flexible approach in which recommendations related to transition care may be modified on a case-by-case basis in order to

address a patient's specific needs and circumstances. The ultimate goal of the current WPATH standards of care is to reduce gender dysphoria and maximize physical and psychological well-being. It explicitly emphasizes that efforts to change an individual's gender identity or expression are considered unethical.

Regarding physical interventions for adolescents considering transition, WPATH suggests an approach consisting of 3 stages: (1) fully reversible interventions, using gonadotropin-releasing hormone (GnRH) analogs in early puberty to suppress estrogen and testosterone production, thereby delaying the progression of puberty; (2) partially reversible interventions, consisting of hormone therapy to masculinize or feminize the body; and (3) irreversible interventions such as gender-affirmation surgery, generally occurring in adulthood. WPATH advocates a staged approach in order to allow the adolescent and parents time to adjust to one stage before moving on to the next. The involvement of a multidisciplinary team to support the adolescent and family through the significant changes of physical, psychological, and social transition is highly recommended, with the understanding that the role of each team member is to facilitate the process of timely transition and not to stand as a gatekeeper obstructing the path to receiving appropriate care, as has occurred in the past.

Despite WPATH's staged model of transition care, it is important to recognize that the path of transition is not the same for everyone. Some individuals are satisfied to live their lives consistent with their gender identity in a social sense but have no urge to initiate hormone therapy or undergo surgery. Others seek hormone treatment but feel that surgical alteration of their bodies is unnecessary. Still others may choose partial surgical gender reassignment; for example, many FTM transgender individuals choose mastectomy but not genital reconstruction. In addition, the transition process is not necessarily a linear one. Some individuals move back and forth between feelings of being more feminine or masculine and may present themselves differently to the world at different times in terms of gender role and expression. This fluidity of identity should be expected and supported by the PCP.

### Pubertal Suppression

Pubertal suppression has become the standard of care for children entering puberty with persistent gender dysphoria, and it is advocated by both WPATH and the Endocrine Society. Puberty is suppressed through the administration of GnRH analogs, very similar to the treatment of precocious puberty in younger children. Pubertal suppression as treatment for gender dysphoria represents an off-label use of this medication. GnRH analogs suppress the secretion of luteinizing hormone (LH) from the pituitary, resulting in suppressed levels of testosterone and estrogen, thereby postponing the development of secondary sexual characteristics. One proposed benefit of pubertal suppression is that it allows an adolescent additional time to better understand his or her gender identity and with increasing maturity be able to make more informed decisions about whether to proceed with gender transition or not. A second benefit is that pubertal

suppression can prevent or postpone the emotional trauma that can accompany the development of secondary sexual characteristics reflecting natal sex for most transgender youths, resulting in decreased gender dysphoria. A third benefit is that pubertal suppression prevents the development of secondary sexual characteristics that often makes later physical transition much more difficult. Hormonal therapy is much more effective in bringing about desired physical changes if the undesired pubertal changes reflecting natal sex have not taken place. Suppression of unwanted pubertal changes may also decrease the need for more invasive interventions later, such as breast surgery, electrolysis, and tracheal shaving.

For a child experiencing persistent or emerging gender dysphoria, pubertal suppression should be initiated when the first signs of puberty appear (which may occur as early as age 9). Suppression should continue until the adolescent is able to confidently specify his or her gender identity. If an adolescent decides that his or her gender identity is consistent with natal sex, pubertal suppression is ended and puberty allowed to proceed. The hormonal influences of suppression are completely reversible with no compromise to subsequent pubertal development. If an adolescent confirms a transgender identity, pubertal suppression is ended and cross-gender hormonal treatment is begun.

During pubertal suppression, the involvement of a supportive pediatric endocrinologist is recommended. Research on the use of GnRH analogs suggests the possibility of decreased bone mineral density in some patients during suppression treatment. However, current research suggests that children who have been on suppressive therapy catch up on bone growth once they progress through puberty or are started on cross-gender hormone therapy. Suppression therapy may also lead to irregular menses in biologic females, particularly if started later in pubertal development. An endocrinologist can help address these issues and can monitor attainment of gender-appropriate height, making appropriate adjustments to treatment as necessary. The few potential risks of suppression treatment must be weighed against the growing body of research documenting the positive outcomes on physical and psychological well-being resulting from the use of pubertal suppression in the management of gender dysphoric youth in early puberty and adolescence.

Gender dysphoric youths whose natal sex is male should be informed, along with their parents, that pubertal suppression could result in insufficient penile tissue if later penile-inversion vaginoplasty is desired. However, skin grafts and colonic tissue may be used instead. PCPs should also have detailed discussions with patients and their parents about the effects of both pubertal suppression and cross-gender hormone therapy on future fertility. Youths who receive only pubertal suppression treatment should progress to full fertility once pubertal suppression is discontinued and pubertal development resumes. Those who move from pubertal suppression directly to cross-gender hormone treatment likely will experience some degree of impaired fertility. Some patients may choose to have a hormone-free interval between pubertal suppression and the initiation of cross-hormone therapy in order to permit

collection of sperm and oocytes for cryopreservation. Others have interrupted cross-gender hormone therapy later in life for the same purpose. The important thing is that this essential conversation take place, and that patients and their families are made aware of fertility experts that they may turn to for further consultation. Finally, families should be informed that pubertal suppression treatment is expensive and may not be covered by some insurance plans, although this likely will change as such treatment increasingly is recognized as a standard of care.

The primary controversy related to pubertal suppression therapy relates to when it should be started. Gender specialists agree that for children who have long-standing or emerging intense gender dysphoria at the onset of puberty, pubertal suppression should be initiated early. While some guidelines suggest beginning therapy at Tanner Stage 2 or 3, many advocate beginning treatment with the first physical or hormonal evidence of puberty, early in Tanner Stage 2.

### Hormone Therapy

The offering of hormonal therapy, like pubertal suppression, represents a standard of care for adolescents experiencing gender dysphoria. A number of protocols are available that address the evaluation and hormonal treatment of transgender adolescents. There is uniform agreement across protocols on the appropriateness of hormonal treatment for transgender adolescents, supported by research showing the significant benefits of hormonal transition in terms of both physical and psychological well-being. Certain aspects of these protocols, however, continue to be quite controversial. The most significant among these reflects a debate among physicians about the appropriate age for initiating hormonal therapy. Historically, the age of 16 was most often cited, accompanied by a belief that a 16-year-old would be better able than a younger adolescent to make informed, mature decisions around treatment that could lead to irreversible physical changes. In fact, age 16 was initially recommended solely because the age of majority in the Netherlands, where most early treatment protocols were developed, was 16, and represented the age at which adolescents in that country could consent to their own care. The latest edition of WPATH's standards of care as well as the recommendations of others working in the field of transgender health allow for flexibility in determining the age of hormonal treatment initiation, advising that such decisions should be made on a case-by-case basis, with age 16 set only as a guideline and with allowances made for earlier initiation. In fact, many families and children seek care much earlier than age 16, and many centers initiate hormone therapy much earlier than 16 and sometimes as young as age 12. These centers see no reason to delay treatment unnecessarily, because the trauma of experiencing puberty reflecting natal sex or being told to wait for years in a suspended peripubertal state as peers continue to develop, is significant, and may even be life threatening. PCPs should discuss these issues openly with families and youths, considering the question, "For this particular child, what is the rationale for suppressing puberty for 3 to 5 years? Does this child in fact display uncertainty regarding his or her gender identity that dictates waiting



this long to end suppressive treatment or initiate hormonal therapy?”

While many centers operate under a belief that mental health support is an essential component of transition, it should not delay or become a barrier to accessing appropriate and timely treatment. WPATH's standards of care state directly that “refusing timely medical interventions for adolescents might prolong gender dysphoria and contribute to an appearance that could provoke abuse and stigmatization. As the level of gender-related abuse is strongly associated with the degree of psychiatric distress during adolescence... withholding puberty suppression and subsequent feminizing and masculinizing hormone therapy is not a neutral option for adolescents.”

### **Male-to-Female Hormone Treatment**

Estrogen is the mainstay of MTF-transgender hormone therapy. For adolescents, most physicians prescribe estrogen sublingually or transdermally, to avoid first-pass metabolism. Protocols also cite oral and injectable forms as options. For transgender individuals, many of the “side effects” of estrogen therapy are in fact desirable effects. Expected changes include breast development, softening of skin, increase in subcutaneous fat and its redistribution to the thighs and buttocks, diminished body hair, fewer erections, and testicular atrophy. Patients may also experience decreased libido, weight gain, and emotional changes. Some of these changes may be irreversible, continuing even after possible discontinuation of treatment. Fertility will be impaired while on estrogen therapy and possibly even if estrogen treatment is discontinued. This should be discussed openly with patients and their parents, as should the option of cryopreservation of sperm if desired. Estrogen treatment is generally safe in adolescents. Although PCPs should be aware of the precautions generally noted for estrogen therapy, including the possibility of blood clots in high-risk populations such as smokers, medical contraindications to estrogen treatment in adolescents are rare. Antiandrogens, such as spironolactone, finasteride, and GnRH analogs, are routinely added to the regimen to suppress the action of endogenous testosterone, augment breast development, and soften facial and body hair. Gonadectomy serves a similar purpose although generally is not considered until age 18 or older as part of gender affirmation surgery.

### **Female-to-Male Hormone Treatment**

The FTM transition is facilitated through the use of testosterone administered through injection, patch, or topical gel. Testosterone treatment is generally safe in adolescents. Among the potentially desirable “side effects” of testosterone treatment for these patients are increased facial and body hair, clitoral enlargement, vagina atrophy, cessation of menses, male pattern baldness, deepening of voice, decreased fat mass, increased muscle mass and strength, a more masculine body shape, increased weight, more prominent veins, coarser skin, and mild breast atrophy. Patients may also notice increased acne, mood changes, and increased libido. Some of these changes may be irreversible. Fertility will likely be impaired during testosterone treatment, although it may return if treatment is interrupted. PCPs

should discuss this openly with patients and their families, and should also discuss options for cryopreservation of oocytes before treatment is begun.

### **Other Treatments**

Some transgender individuals will seek other treatments to facilitate physical and psychosocial transition to their appropriate gender. Often these treatments will occur after the adolescent years, partly because these procedures are expensive and not yet covered by many insurance plans. Because many of these treatments involve irreversible changes, most protocols recommend deferring them until at least age 18, especially those that represent gender affirmation surgery. MTF-transgender individuals may seek reconstructive surgery, including penectomy, orchiectomy, vaginoplasty, clitoroplasty, vulvoplasty, breast and gluteal augmentation, tracheal shaving, and facial reconstruction. Electrolysis or other hair-removal procedures may be sought. Silicone injections also may be sought to obtain a more feminine body contour. FTM-transgender individuals may seek chest reconstruction surgery, hysterectomy, oophorectomy, phalloplasty, and other genital reconstruction. Both MTF and FTM individuals may seek voice therapy and professional guidance in how to present themselves as male, female or another gender through body language, facial expression, gait, posture, and mannerisms. Although these surgical, cosmetic, and other procedures often take place after adolescence, discussing these options and their benefits and limitations and making appropriate referrals should be part of the PCP's anticipatory guidance of transgender youths.

## **PARENTS**

Parents who come to recognize their child's gender nonconforming behavior or transgender identity may experience a variety of emotions: confusion, fear, sadness, concern, embarrassment, guilt, anger, or disgust, but also acceptance and celebration. These feelings should be discussed openly and with compassion. Many parents fear for their child's safety and happiness. Many of them fear that their child may eventually self-identify as lesbian or gay. In many instances these concerns and fears are not raised on visits to the PCP or are referred to only indirectly (“My son is a sensitive child,” or “My daughter is definitely a tomboy”). The PCP should be sensitive to any cues of parental worry about gender nonconformity and ask parents simply, “Do you have any concerns about your child's behaviors?” or even better, “Have you had any concerns that your son's [daughter's] behaviors or interests are more feminine [masculine] than other children's his [her] age?” Most concerned parents, although perhaps embarrassed, are relieved to have such a discussion. The PCP's primary role in working with parents is to help them understand and celebrate their gender nonconforming child and support them in their efforts to keep their child happy, healthy, and safe.

Parents should be referred to Web sites, books, brochures, and media resources geared to parents of gender nonconforming children.

Parents should be assured that with love, validation, and support their children should grow up to be happy, healthy, and productive adults, no matter what their gender expression, gender identity, or sexual

### **BOX 156-1 Children's National Medical Center Outreach Program Guidelines for Parents of Gender-variant and Transgender Youth**

- Love your child for who your child is. Love, acceptance, understanding, and support are especially important when peers and society are often intolerant of difference.
- Question traditional assumptions about gender roles and sexual orientation. Do not allow societal expectations to come between you and your child.
- Create a safe space for your child, allowing your child always to be who the child is, especially in the child's own home.
- Seek out socially accepted activities (sports, arts, hobbies) that respect your child's interests while helping your child fit in socially.
- Validate your child and your child's interests, supporting the idea that more than one way exists to be a girl or boy. Speak openly and calmly about gender variance with your child. Talk about these subjects in positive terms, and listen as your child expresses feelings of being different.
- Seek out supportive resources (books, videos, Web sites, support groups) for parents, families, and children.
- Talk about gender variance with other significant people in your child's life, including siblings, extended family members, babysitters, and family friends.
- Prepare your child to deal with bullying. Let your child know that he/she does not deserve to be hurt. Be aware of behaviors that suggest bullying may be occurring, such as school refusal, crying excessively, or complaining of aches and pains.
- Be your child's advocate. Expect and insist on acceptance, respect, and safety wherever your child is. Parents may need to educate school staff and others about the special experience and needs of gender-variant children.

### **BOX 156-2 Children's National Medical Center Pitfalls to Avoid as Parents of Gender-variant and Transgender Youth**

- Avoid finding fault. No blame exists. Your child's gender variance came from within, not from you as parents. Blame will get in the way of enjoying your child.
- Do not pressure your child to change, because this will cause much pain and harm.
- Do not blame the victim. Do not accept bullying as *just the way things are*. No one has the right to torment or criticize others because they are different.

orientation might be. The National Children's Medical Center has developed guidelines to help parents in their provision of support for their children.

Box 156-1 lists ways parents can support their child, and Box 156-2 lists pitfalls parents should try to avoid.

## **ADVOCACY**

Because of their expertise and position of respect, PCPs are in an advantageous position to advocate on behalf of children with gender nonconforming behaviors, transgender youths, and their families. PCPs should encourage parents, siblings, and extended family to accept and love these young people unconditionally. The PCP should also be willing to meet with school personnel, child and youth welfare program staff, and others to share information about gender nonconformity and transgenderism. Because schools are a major part of a child's or adolescent's life, and because they are often the site where significant harassment and bullying of gender nonconforming and transgender youths take place, it is especially important that PCPs

provide advocacy at all levels of local educational systems. This includes advocacy for the adoption of antiharassment policies specifically addressing harassment based on gender identity and expression as well as sexual orientation. It also includes advocating for mandated training of teacher and social service providers and policies that ensure that transgender youths are safe and treated respectfully, such as through the use of preferred names and pronouns, designation of appropriate bathrooms and changing rooms, and allowing a student to participate in graduation ceremonies and other activities based on gender identity rather than natal sex.

For PCPs seeking to advocate for societal change, encouraging the development and implementation of policies, procedures, and programs that recognize and respect the individuality of these children and youths and address their special needs for validation and safety is essential. The PCP may also provide testimony at official meetings and hearings on proposals to add gender identity and expression to laws and school policies prohibiting discrimination, bullying, and harassment. The PCP may also advocate for the inclusion of meaningful medical school, residency training, and continuing medical education curricula on the life experience and health needs of children with gender nonconforming behaviors and transgender individuals and how to meet these needs in a respectful and effective manner. Finally, the PCP should encourage professional organizations to develop policy statements and clinical guidelines to support them in their work with these young people and their families.

## **WHEN TO REFER**

Refer to a child behavioral, adolescent, or gender specialist whenever a child or adolescent

- Shows significant gender nonconforming behaviors, particularly if they are concerning to

parents or have resulted in rejection or mistreatment by family members, peers, or others. Ideally, referral will be made before possible dysphoria arises.

- Shows signs or symptoms of gender dysphoria, including expression of dissatisfaction or distress related to their birth-assigned gender or insistence that they are of another gender.
- Refer to a child and adolescent psychiatrist or other mental health professional whenever a child or adolescent.
- Experiences persistent or recurrent depressed or anxious mood that interferes with function.
- Has acute or recurrent suicidal ideation or self-injury.
- Evidences isolation from peers or family members.
- Engages in substance use or other high-risk behaviors.

It should be noted that referrals for therapy to change an adolescent's gender identity or expression are considered unethical.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *FORGE* (Web page), FORGE ([forge-forward.org](http://forge-forward.org))
- *Guidance for Massachusetts Public Schools: Creating a Safe and Supportive School Environment* (article), Massachusetts Department of Elementary and Secondary Education ([www.doe.mass.edu/ssce/genderidentity.pdf](http://www.doe.mass.edu/ssce/genderidentity.pdf))
- *TransYouth Family Allies* (Web page), ([www.imatyfa.org](http://www.imatyfa.org))

### Engaging Patient and Family

- *Camp Aranu'tiq* (Web site), Harbor Camps, Inc. ([www.camparanutiq.org](http://www.camparanutiq.org))
- *Family Acceptance Project* (Web site), Marian Wright Edelman Institute, San Francisco State University ([familyproject.sfsu.edu](http://familyproject.sfsu.edu))
- *Get Support* (Web page), Parents, Families, and Friends of Lesbians and Gays (PFLAG) ([community.pflag.org/staff/transgender](http://community.pflag.org/staff/transgender))
- *I Think I Might Be Transgender, Now What Do I Do?* (booklet), Youth Resource ([www.advocatesforyouth.org/component/content/article/731-i-think-i-might-be-transgender-now-what-do-i-do](http://www.advocatesforyouth.org/component/content/article/731-i-think-i-might-be-transgender-now-what-do-i-do))
- *If You Are Concerned About Your Child's Gender Behaviors: A Guide for Parents* (booklet), Children's National Medical Center: Outreach Program for Children with Gender-Variant Behaviors and Their Families ([childrensnational.org/~media/cnhs-site/files/departments/gender-and-sexuality-development-program/gvparentbrochure.ashx?la=en](http://childrensnational.org/~media/cnhs-site/files/departments/gender-and-sexuality-development-program/gvparentbrochure.ashx?la=en))
- *Legal Resources* (Web page), Trans Youth Equality Foundation ([www.transyouthequality.org/legal-resources](http://www.transyouthequality.org/legal-resources))
- *Resources: Parenting and Family* (Web page), Gender Spectrum ([www.genderspectrum.org/resources/parenting-and-family-2/#more-432](http://www.genderspectrum.org/resources/parenting-and-family-2/#more-432))
- *Resources: Teens* (Web page), Gender Spectrum ([www.genderspectrum.org/resources/teens-2/#more-428](http://www.genderspectrum.org/resources/teens-2/#more-428))

- *The Transgender Child: A Handbook for Families and Professionals* (book), Cleis Press
- *The Trevor Project* (Web site), ([www.thetrevorproject.org](http://www.thetrevorproject.org))
- *Transparenthood* (blog), ([www.transparenthood.net](http://www.transparenthood.net))
- *Youth and Education* (Web page), Trans Youth Equality Foundation ([www.transyouthequality.org/youth-and-education](http://www.transyouthequality.org/youth-and-education))

### Medical Decision Support

- *Guidelines for Care of Lesbian, Gay, Bisexual, and Transgender Patients (guideline)*, Gay and Lesbian Medical Association ([glma.org/\\_data/n\\_0001/resources/live/GLMA%20guidelines%202006%20FINAL.pdf](http://glma.org/_data/n_0001/resources/live/GLMA%20guidelines%202006%20FINAL.pdf))
- *Patient Health Questionnaire (PHQ) Screeners* (screen), Pfizer Inc. ([www.phqscreener.com](http://www.phqscreener.com))
- *Pediatric Symptom Checklist* (screen), Massachusetts General Hospital ([www.massgeneral.org/psychiatry/services/psc\\_forms.aspx](http://www.massgeneral.org/psychiatry/services/psc_forms.aspx))
- *Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People* (article), International Journal of Transgenderism, Vol 13, 2011 ([www.wpath.org/uploaded\\_files/140/files/IJT%20SOC,%20V7.pdf](http://www.wpath.org/uploaded_files/140/files/IJT%20SOC,%20V7.pdf))
- *Strengths & Difficulties Questionnaires* (screen), Youth in Mind, Ltd. ([www.sdqinfo.com](http://www.sdqinfo.com))
- *Transgender Persons* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/lgbthealth/transgender.htm](http://www.cdc.gov/lgbthealth/transgender.htm))

## AAP POLICY

- American Academy of Pediatrics Committee on Adolescence. Sexual orientation and adolescents. *Pediatrics*. 2004;113(6):1827–1832 ([pediatrics.aappublications.org/content/113/6/1827](http://pediatrics.aappublications.org/content/113/6/1827))
- American Academy of Pediatrics Committee on Adolescence. Office-based care for lesbian, gay, bisexual, transgender, and questioning youth. *Pediatrics*. 2013;132(1):198–203 ([pediatrics.aappublications.org/content/132/1/198](http://pediatrics.aappublications.org/content/132/1/198))

## SUGGESTED READINGS

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- Makadon H, Mayer K, Potter J, et al (eds.). *The Fenway Guide to Lesbian, Gay, Bisexual and Transgender Health*. Philadelphia, PA: The American College of Physicians; 2008
- Mallon GP, DeCrescenzo T: Transgender children and youth: a child welfare practice perspective. *Child Welfare*. 2006; 85(2):215–241
- Ryan C. *Helping Families Support Their Lesbian, Gay, Bisexual and Transgender (LGBT) Children*. Washington, DC: National Center for Cultural Competence, Georgetown University Center for Child and Human Development; 2009
- Spack NP, Edwards-Leeper L, Feldman HA, et al. Children and adolescents with gender identity disorder referred to a pediatric medical center. *Pediatrics*. 2012;129(3): 418–425

## Chapter 157

# HEADACHE

Jack Gladstein, MD

For a pediatrician, a chief complaint of headache can be daunting. Although the outcome is most often benign, the worry of both the parent and the clinician centers on the fear of missing a tumor or other serious condition. Given the constraints of time in a busy office, an efficient but caring approach will allay the anxiety of both the family and the physician.

### CLINICAL APPROACH

#### Part 1: Establish the Right Pattern

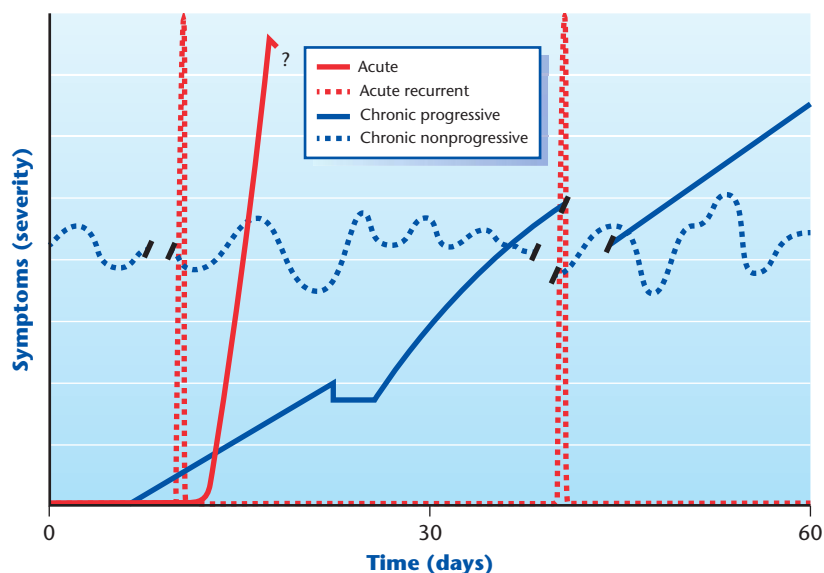
All headaches in the pediatric age group fall into 4 patterns as described by Rothner (see Figure 157-1). The most common pattern is called *acute and recurrent*, characterized by periods of normalcy between attacks. Severe attacks accompanied by autonomic symptoms (nausea/vomiting, photophobia and/or phonophobia) ensure the diagnosis of migraine. Milder attacks are called *tension type* headaches. The migraine patient may also have milder tension type headaches, and because these headaches still respond to triptans the distinction in a migraine patient is basically irrelevant. Children who *never* get autonomic symptoms but have this pattern have pure tension type headache, and do not respond to triptan medications. In children, location of the headache is less important diagnostically than in adults. Ninety percent of migraine in the pediatric age group is bilateral. Pain can be under the eyes or even in the neck area. If the pattern is still acute and recurrent, and there are

autonomic symptoms, the diagnosis is migraine. Most children and teens have migraine without aura. Children who have migraine with aura often describe wavy lines at the periphery of their vision.

In the context of headache, a *simple acute headache* is less of a diagnostic dilemma. It can be caused by meningitis, encephalitis, systemic viral or bacterial infection. Subarachnoid hemorrhage features a severe headache that gets to full force instantly. Patients describe feelings of being shot or punched in the head. There can sometimes be accompanying fever or neck stiffness. The speed of headache onset is what is important here.

The pattern of *chronic progressive headache*, where symptoms get worse and worse over weeks, should alert the physician that a tumor or other serious pathology looms. Pain is often worse in the morning and gets a little better as the day goes on. Systemic or neurologic signs and symptoms further add to the worry. Posterior fossa tumors are often accompanied by wobbly gait. Frontal tumors may present with unilateral weakness. Tumors of the pituitary area manifest with changes in visual acuity or problems with growth; adolescent girls may have secondary amenorrhea.

*Chronic nonprogressive headache* either evolves from a previous headache pattern or presents without previous headache history. In *transformed* or *chronic migraine* there is a history of prior acute intermittent headache accompanied by autonomic symptoms. Over time, the pain has become almost daily, with intermittent spikes in headache resembling bad migraine. In *chronic tension type headache* (CTTH), there is a history of episodic tension type headaches. With no history of migraine attacks, triptans have no role in this condition. In *new daily persistent headaches* (NDPH), the daily headache comes out of nowhere, often after a viral syndrome or mild head trauma. Whereas TM or CTTH responds well to a multidisciplinary approach, NDPH is more of a



**Figure 157-1** All headaches fit in this diagram. The severity of the headache is on the Y axis, and time measured in days is on the X axis. (From Rothner AD. *The evaluation of headaches in children and adolescents*. Semin Pediatr Neurol. 1995;2(2): 109–119, with permission from Elsevier.)



troublesome problem, often puzzling even the most experienced headache specialist. Patients with the chronic nonprogressive pattern of headache require imaging because there is no return to normalcy between attacks.

### Part 2: Establish Disability With 2 Questions

Since an acute headache is not, from the point of view of headache, a diagnostic dilemma, and chronic progressive headaches warrant timely evaluation for serious intracranial pathology, the issue most commonly facing the physician is how to proceed artfully and efficiently to manage most patients who come to attention with headaches. For both intermittent migraine and chronic daily headache the first priority is to assess how disabled the child is, using as measures *absenteeism* and *presenteeism*. Absenteeism refers to the number of days missed from school, work or after-school activities. Presenteeism refers to days when, although present, the child cannot learn or fully participate because of headaches. Worsening of school grades can result either from the child being absent or, if present, having performance adversely affected by headache. The more disabled the child is, the heavier the required intervention.

Having properly categorized the headache from the initial history, decided whether or not serious underlying pathology is a consideration, and assessed how disabling the headaches are for the child's normal functioning, the physician can next fill in details, including family history of headache, medications tried, comorbidities, "stuff" going on at home, triggers, level of stress, and sleep and eating patterns. This information will set the table for the assessment to be shared with the family at the end of the visit, when it is important to reinforce healthy habits for headache prevention. At this point, if worry level has dropped, it is a good time to say something like, "nothing so far makes me worried about a brain tumor."

### Part 3: Physical Examination

With the physical examination, the physician should look particularly for arrest of growth, puberty, or menstruation. Examination of the skin should be thorough, looking for lesions suggestive of a neurocutaneous disorder such as neurofibromatosis. The neurologic examination should include looking for abnormalities of the optic discs, impaired extraocular movements, visual field defects, evidence of ataxia on gait and rapid nose-to-finger movement, and asymmetric reflexes. When the history has already established a pattern of headaches that does not raise concern about serious underlying illness, the physical examination offers the opportunity for the physician to reinforce how reassuring are the benign findings: "With something serious, like a brain tumor, we would expect this part of the examination to be abnormal." If all is normal, a summary statement is appropriate to reassure that nothing in the history or physical examination raises concern about a tumor or anything else serious.

### Part 4: Imaging

Children and adolescents with a history consistent with migraine, who have a normal neurologic examination,

do not need magnetic resonance imaging (MRI). Patients with either systemic symptoms (arrested growth, puberty, or menstruation), abnormal neurologic features on history or physical examination, abrupt onset of severe headache, or a change in pattern to a more chronic headache, should have an MRI.

### Part 5: Management

The following sections will discuss the principles for treatment of migraine and chronic daily headache (see Figure 157-2).

#### Migraine Principles

**PRINCIPLE 1: PATIENTS WITH MIGRAINE HAVE A MORE SENSITIVE BRAIN.** Children with migraine are more sensitive to internal and external triggers than children without headaches. Therefore, migraine sufferers must not miss meals, must sleep at regular intervals, must exercise regularly, and must learn to manage their stress. When alerted, children are adept at figuring out what causes their headaches, often making it possible to modify or eliminate their identified triggers. Some strategies may include having a snack at school, cutting out some extracurricular activities, or assessing for an undiagnosed learning disability.

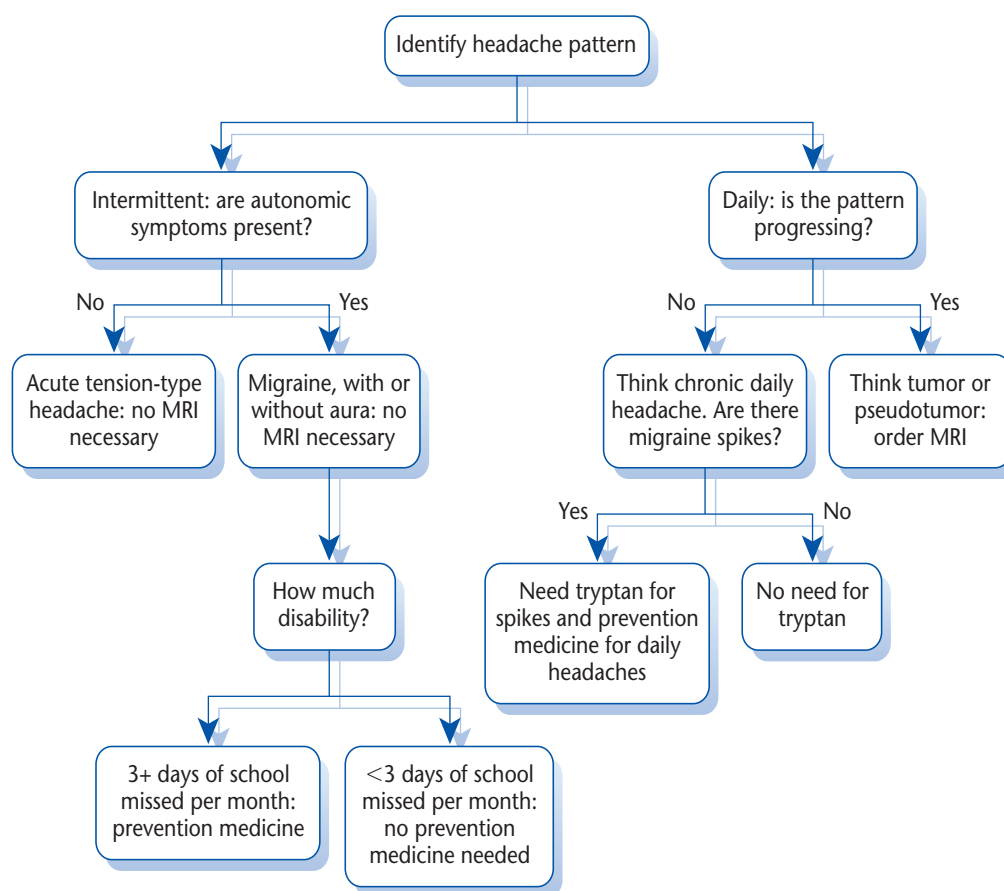
**PRINCIPLE 2: TREAT ATTACKS AT FIRST TWINGE.** With bee sting allergy, one does not wait until anaphylaxis sets in before seeking treatment. Similarly with migraine, medications work best the earlier they are given. Once a migraine is full blown, medication that previously was effective often will not work.

**PRINCIPLE 3: TREAT ATTACKS WITH HIGH DOSES OF ORAL MEDICATION.** A migraine starts a few hours before the patient notices. In particular, the stomach has delayed emptying. Therefore by the time headache is apparent, acute medication should be given in sufficient dose to ensure that a reasonable amount passes through the gastroparetic stomach. For most patients attacks are episodic, so there is no harm if high doses of the medication are used to treat a migraine attack.

**PRINCIPLE 4: DON'T WAIT UNTIL YOU ARE SURE IT IS A MIGRAINE.** Children with migraines who have a tension type headache still respond to triptans; so treating at the first twinge, even if that results in a few headaches being overtreated, offers more benefit than risk. The alternative, waiting too long and compromising the effectiveness of treatment, is far worse.

**PRINCIPLE 5: INVOLVE TEACHER AND NURSE.** Children are in school for a large portion of their lives. If a migraine strikes during the school day, the "alarm bell" should go off for that child, and the teacher and nurse should know to respond with treatment immediately.

**PRINCIPLE 6: TRIPTANS ARE OK.** Once principles 1 to 5 have been addressed, the child with migraines should go home with a plan to include healthy lifestyle changes, urgings to treat early, an explanatory letter to the school with authorization to treat, and a prescription for medication. Only a few triptans (sumatriptan nasal spray and eletriptan tabs) have thus far received FDA approval for use in children. Although studies have demonstrated excellent efficacy, they have not been able to prove benefit over placebo (see Table 157-1 and Table 157-2). Triptans are safe,



**Figure 157-2** Algorithm for pediatric headache.

**Table 157-1** Short-acting Triptans

TRIPTAN	TABLET (mg)	MELT (mg)	NASAL (mg)	SUBCUTANEOUS (mg)
Almotriptan	6.25; 12.5	—	—	—
Eletriptan	20; 40	—	—	—
Rizatriptan	5; 10	5; 10	—	—
Sumatriptan	25; 50; 100	—	5; 20	4; 6
Zolmitriptan	2.5; 5	2.5; 5	5	—

**Table 157-2** Longer Acting and Combination Triptans

TRIPTAN	TABLET (mg)	MELT (mg)	NASAL (mg)	SUBCUTANEOUS (mg)
Frovatriptan	2.5	—	—	—
Naratriptan	1; 2.5	—	—	—
Sumatriptan/Naproxen	85/500	—	—	—

Frovatriptan and naratriptan have longer half-lives than other triptans and may be used for menstrual migraine prophylaxis, or for migraine recurrence.

with no negative outcomes in any of the studies, and are available in low doses for preschool and school-aged children, and for adolescents.

**PRINCIPLE 7: WHO NEEDS PROPHYLAXIS?** A follow-up visit should be scheduled within 2 to 6 weeks to evaluate whether or not progress has been made. At

the follow up, if absenteeism and presenteeism have not diminished to an acceptable level despite the initial interventions described above, the child should receive either a nonpharmacologic or pharmacologic long-term treatment plan. Since they require substantial practice and a large time commitment, nonpharmacologic

**BOX 157-1 Dose Ranges of Preventive Medications**

- Amitriptyline 10–75 mg qhs
- Cyproheptadine 2–18 mg qd
- Divalproex sodium 125–500 mg tid
- Gabapentin 300–1,200 mg tid
- Propranolol 40–120 mg tid
- Topiramate 25–200 mg bid
- Verapamil 80–240 mg tid

*bid*, twice daily; *qd*, every day; *qhs*, every night at bedtime; *tid*, 3 times per day.

treatments work well only for patients invested in their recovery. Relaxation techniques, biofeedback, cognitive behavior therapy, and acupuncture can all be effective. The appropriate strategy is to try to treat comorbidities while avoiding medications that will make other conditions worse. Obese patients should use topiramate and avoid valproate, amitriptyline, and cyproheptadine. A patient with an eating disorder should avoid topiramate. A child with a sleep disorder may benefit from amitriptyline, while for patients with seizures either topiramate, gabapentin, or valproate may be appropriate. With hypertension, either propranolol or verapamil might be effective. Propranolol should not be prescribed for a child with depression. Whichever medication is selected, begin slowly and gradually increase the dose until either therapeutic effect is reached or side effects ensue (see Box 157-1). In the absence of side effects, the medication should be given time to become effective before deciding to change.

**PRINCIPLE 8: WHEN TO REFER.** A primary care physician should be able to prescribe medication, and recommend lifestyle changes and a prevention modality. If improvement is not reported, then referral to a headache specialist is indicated.

### Chronic Daily Headache Principles

#### PRINCIPLE 1: RULE OUT INTRACRANIAL PATHOLOGY.

Unlike migraine, which does not require neuroimaging, chronic daily headache does. Because migraine is so common, with an estimated yearly prevalence of 10% to 25% (at least among adults), many people diagnosed with brain tumors will have also had migraines. The change in the pattern of the headaches to daily chronic is what necessitates the MRI. Computed tomography scanning is not adequate because it does not delineate the posterior fossa well enough.

**PRINCIPLE 2: IDENTIFY PATTERN: TRANSFORMED MIGRAINE VS CHRONIC TENSION TYPE HEADACHE VS NEW DAILY PERSISTENT HEADACHE.** Transformed or chronic migraine will still have migraine spikes with autonomic symptoms, and these will respond to triptans. Sufferers of CTTH do not have migraine, and will not respond to triptans. Patients with NDPH may or may not have migraine spikes: if present, use triptans; if not, then no.

**PRINCIPLE 3: REMOVE ACUTE MEDICATIONS OVERUSED ON A DAILY BASIS.** Overuse of analgesics

can itself lead to headaches. Stopping an overused medication can be done “cold turkey” or gradually over a month or so. If an analgesic is removed acutely, the physician should provide comfort measures, knowing that the headache will get worse for a few days. Such comfort measures might include intranasal dihydroergotamine, or a long-acting drug like frovatriptan or naratriptan. Families should be told to begin the transition over a weekend, preferably a long one, to avoid unnecessary absence from school. If the medication is tapered gently over a month, the patient and family must be warned there will be spikes in headache activity during the withdrawal.

**PRINCIPLE 4: START OR REINFORCE HEALTHY HEADACHE HABITS.**

**PRINCIPLE 5: STAY IN SCHOOL.** Try to avoid health related home schooling, which will only make it harder to reintegrate once the child is better. School attendance forces the child to get up early and have a daily routine. Sleep patterns are easier to regulate, and tendencies towards isolation and depression are lowered.

**PRINCIPLE 6: START A NONPHARMACOLOGIC AND/ORPHARMACOLOGICINTERVENTION.** Someone with daily headache needs an intensive approach, as described in migraine Principle 7.

**PRINCIPLE 7: WATCH OUT FOR UNDETECTED DEPRESSION OR ANXIETY.** Consider referral for counseling as part of the comprehensive approach to the child with chronic headache.

**PRINCIPLE 8: WHEN TO REFER.** Ideally, all children and adolescents with chronic daily headache should be seen by a specialist. Many communities do not have an expert in pediatric headache, or even a pediatric neurologist with an interest in chronic headache. In such a setting, the principles listed above can guide the initiation of treatment, with a timely follow up in a month or so to confirm that progress has been made. If not, then referral is necessary. The primary care physician should also be familiar with local community mental health resources, as well as acupuncturists, physical therapists, and therapists with expertise in biofeedback and relaxation training.

### PROGNOSIS

Short-term studies show great improvement for both episodic and chronic headache with appropriate treatment. However there are no long-term studies tracking either childhood migraine or chronic daily headache cohorts over a long period of time. The goal of the pediatrician should be to prevent chronic headaches by treating migraine early and effectively.

### SUMMARY

This approach allows the physician to diagnose, assess, and treat headache effectively while addressing the concerns of the child and family. Identifying benign patterns of headache reassures the family and the physician, whereas identifying a worrisome pattern directs the child with a potentially serious condition to a diagnostic MRI. Promoting healthy headache activities, identifying comorbidities, and assessing the degree of disability will guide the prescription of acute or chronic medications and nonpharmacologic interventions. The pediatrician can properly manage most

patients with headache, but referral to a specialist is indicated when improvement is not seen after these measures have been implemented.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Headaches* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/head-neck-nervous-system/Pages/Headaches.aspx](http://www.healthychildren.org/English/health-issues/conditions/head-neck-nervous-system/Pages/Headaches.aspx))

#### Medical Decision Support

- *Complementary and Conventional Medicine Use Among Youth With Recurrent Headaches* (article), Bethell C, et al, *Pediatrics*, Vol 132, Issue 5
- *CT Scan Utilization Patterns in Pediatric Patients With Recurrent Headache* (article), DeVries A, et al, *Pediatrics*, Vol 132, Issue 1
- *Incidence and Risk Factors of Chronic Daily Headache in Young Adolescents: A School Cohort Study* (article), *Pediatrics*, Vol 132, Issue 1

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## Chapter 158 HEARING LOSS

Anne Marie Tharpe, PhD; Douglas P. Sladen, PhD, CCC-A;  
Ann Rothpletz, PhD, CCC-A

Pediatricians are usually the first health care practitioners approached by parents when they have concerns about their child's hearing, and in the course of a typical practice a pediatrician will encounter approximately a dozen children with severe-to-profound hearing loss. Although when the hearing loss is severe parents become concerned about their child's hearing rather early (at approximately 6 months of age), milder degrees of hearing loss typically do not generate concern until the child reaches school age. As such, it is imperative that pediatricians recognize the signs, symptoms, and

risk factors for hearing loss in children and become aware of appropriate referral paths. It is also important to note that despite the widespread implementation of newborn hearing screening, such programs are designed to identify moderate and greater degrees of hearing loss, not mild degrees of loss. Therefore, even a child who passed a hearing screening in the newborn period might still have hearing loss that was missed by or acquired after the screening. This chapter addresses permanent hearing loss in children, not transient losses that often accompany otitis media.

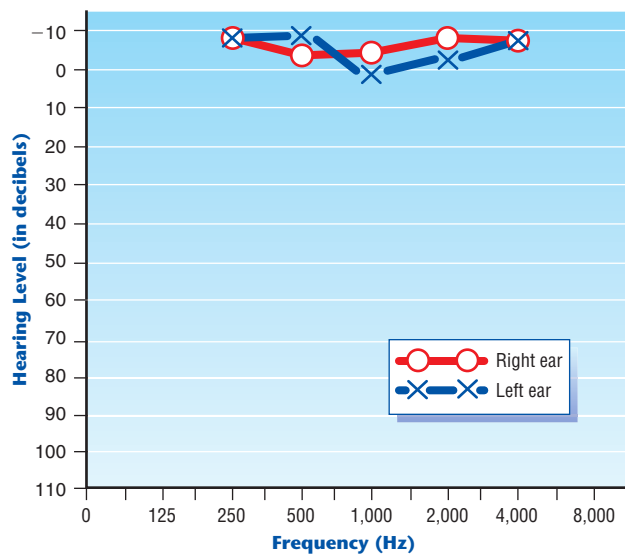
### DEMOGRAPHICS

Rubella and meningitis were once leading causes of severe-to-profound hearing loss in children; but the advent of vaccines for these disorders has virtually eliminated hearing loss caused by congenital rubella and dramatically reduced hearing loss resulting from meningitis. Genetic mutations are now the most common cause of congenital hearing loss, accounting for 50% to 60% of all cases. Consequently, severe-to-profound hearing losses are not as common as they once were, and milder degrees of hearing loss are more prevalent.

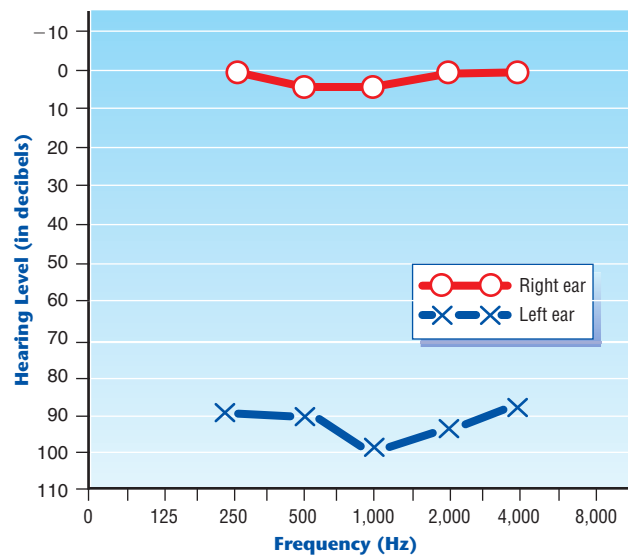
Although the prevalence of severe bilateral hearing loss in newborns is estimated to be 1 per 1,000, estimates for mild or minimal losses approach 1 per 20 in school-aged children. In the neonatal intensive care unit (NICU), estimates of hearing loss range from 20 to 40 per 1,000. Minimal hearing loss is defined as thresholds greater than 25 dB HL at 2 or more frequencies above 2,000 Hz, pure tone average between 15 and 25 dB HL bilaterally, or unilateral hearing loss of any degree. This increase in reported prevalence from the newborn period to school age is the result, in part, of not including minimal and mild losses as targets of newborn hearing screening, as well as the addition of losses that progress or are acquired later in childhood (eg, meningitis).

Figure 158-1 is the audiogram of a child with normal hearing sensitivity in both ears such that all the speech sounds fall within the range of audibility. Two of the more typical patterns of minimal-to-mild hearing loss are demonstrated in Figure 158-2 and Figure 158-3. Figure 158-2 is the audiogram of a child with normal hearing sensitivity for all frequencies through 1,000 Hz but a high-frequency hearing loss, a pattern typical with ototoxic drug use or perinatal anoxia. Although this child would be expected to develop speech and language in a timely manner, distortions or omissions of the high-frequency consonant sounds of speech are expected. Parents may report that the child has difficulty hearing in the presence of background noise but seems to have little difficulty in quiet settings. The hearing loss depicted in Figure 158-3 is a profound unilateral loss of the left ear that is not typically identified until a child enters school unless the child receives a hearing screening in the newborn period. A child with unilateral hearing loss may reach age-appropriate speech and language milestones but experience difficulty hearing in the presence of background noise. In addition, children with unilateral

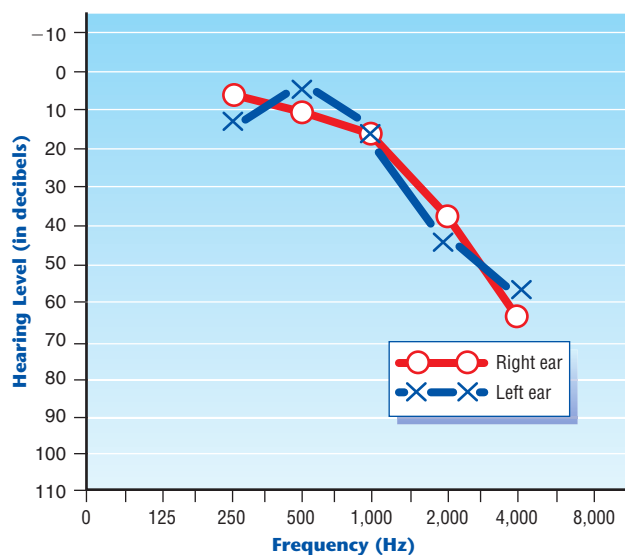




**Figure 158-1** An audiogram reflecting normal hearing sensitivity in both ears.



**Figure 158-3** An audiogram reflecting a profound hearing loss of the left ear.



**Figure 158-2** An audiogram reflecting a high-frequency hearing loss bilaterally.

hearing loss typically demonstrate difficulty localizing sound sources.

Although these patterns of hearing loss are termed *mild* or *minimal*, building evidence suggests that their effect is far from benign. School-aged children who have minimal and mild losses have been found to experience greater academic, communicative, social, and emotional difficulty than normally hearing children. In fact, approximately 35% of children with minimal hearing losses fail at least 1 grade in school compared to an overall failure rate of approximately 3%.

## ASSOCIATED SIGNS AND SYMPTOMS

The Joint Committee on Infant Hearing (JCIH) has published a list of risk factors that provides an excellent starting place when attempting to identify hearing loss in children. However, approximately 35% to 50% of children with hearing loss will not have any known risk factors, making a complete history and keen observation accompanied by hearing screening essential if hearing loss is to be identified early. Although most congenital hearing loss is hereditary, a negative family history is common: 80% of inherited hearing loss results from autosomal-recessive transmission, 18% from autosomal-dominant transmission, and approximately 2% from X-linked recessive transmission. Furthermore, even children with dominantly inherited hearing loss may have families who demonstrate incomplete penetrance. Evidence of the gene expression can be highly variable. In addition, most children with inherited hearing loss are nonsyndromic, providing no additional clues and potentially limiting the pediatrician's level of suspicion. However, 20% of children with congenital sensory hearing loss have an associated syndrome (eg, Alport syndrome, Waardenburg syndrome) or progressive loss (eg, Usher syndrome). Children with Down syndrome are at high risk for conductive hearing loss, as well as a higher-than-average risk for sensory loss.

Infants in the NICU may also be at increased risk for neural conduction or auditory brainstem dysfunction, including auditory neuropathy/dyssynchrony, a disorder characterized by a unique constellation of behavioral and physiologic auditory test results. Children with auditory neuropathy/dyssynchrony have normal outer cochlear hair cell function, but dyssynchronous signal firing at the level of the VIIIth cranial nerve. They exhibit a range of sensitivity from normal hearing to profound hearing loss and poor speech perception ability (often worse than would be expected based

on the degree of hearing loss). Infants who receive intensive neonatal care are at increased risk for auditory neuropathy/dyssynchrony, as are children with a family history of childhood hearing loss and infants with hyperbilirubinemia. However, some children with auditory neuropathy/dyssynchrony have no history of these risk factors. Currently, neither the prevalence of auditory neuropathy/dyssynchrony in newborns nor the natural history of the disorder is clearly understood, and treatment options are not well defined. Many children with auditory neuropathy/dyssynchrony do not benefit from the use of hearing aids but do benefit from cochlear implantation. Audiologic and medical monitoring of infants at risk for auditory neuropathy/dyssynchrony is recommended.

The significant speech and language delays associated with severe to profound childhood hearing loss are typically obvious to parents and physicians; but because identification of milder degrees of hearing loss may prove more elusive, children who exhibit behavioral, social, or academic difficulties should be screened for hearing loss in addition to those with speech and language delays or disorders. Some of the concerns expressed commonly by parents of children with milder forms of hearing loss are included in Table 158-1.

### IDENTIFICATION APPROACHES

The 2007 position statement of the JCIH recommended that identification of and intervention for congenital hearing loss in children should follow a 1-3-6 rule. That is, all infants should have access to hearing screening no later than 1 month of age, confirmation of hearing loss by 3 months of age, and early intervention services no later than 6 months of age. The recommendations of the JCIH are widely accepted, although significant concerns remain with follow-up. A significant percentage of infants who fail the screening do not return for follow-up testing.

According to the Centers for Disease Control and Prevention, only 70% of infants with hearing loss receive appropriate diagnostic testing by 3 months of age and only 56% receive intervention prior to 6 months of age. The pediatrician plays an important role in the identification of childhood hearing loss for several reasons. First, many infants lost to follow up can be recaptured when they are seen in pediatricians' offices for well- or sick-baby visits. Second, even if infants have passed a hearing screening at birth, many children with hearing loss acquire their deficits after the newborn period. Finally, the JCIH recommends that universal newborn hearing screening programs target permanent, bilateral, or unilateral hearing loss averaging 40 dB or greater, a target level that will necessarily miss some minimal and mild hearing loss. The obvious implication is that, even for children who have passed their newborn hearing screenings, pediatricians should be vigilant in monitoring hearing status and, with any suspicion of hearing loss by parents or others, should arrange for hearing assessments by audiologists experienced in working with children.

When an infant or child fails a hearing, speech, or language screening measure in the pediatrician's office, referral for a full audiologic evaluation is recommended. Unfortunately, at least 1 study suggested that more than half of children who failed hearing screenings in primary care practices did not receive rescreenings or referrals for further testing. Audiologists with pediatric experience can define the degree of hearing loss and distinguish among conductive, sensory, and neural types of loss in children of all chronologic ages and developmental levels. Evaluation of hearing in infants and young children consists of a combination of physiologic and behavioral measures. For infants younger than approximately 6 months, testing is typically limited to physiologic measures because their behavioral

**Table 158-1** Explanations for Parental Concerns Regarding Their Child's Hearing Acuity

PARENTAL COMMENTS	EXPLANATIONS
"He can hear me when he wants to hear me. Sometimes he just ignores me."	Children who have mild hearing losses may have little or no difficulty listening in quiet settings. However, if background noise is present they may have more difficulty.
"When I call her, she has to look around for me. She never seems to know where I am in the house."	Children who have unilateral hearing loss often have difficulty localizing a sound source.
"When we are in crowds, I have to call his name several times before he responds."	Children who have high-frequency or other mild hearing losses often have difficulty hearing in the presence of background noise.
"My child is exhausted when she comes home from school."	Children who have minimal or mild hearing loss may be fatigued by the effort exerted to listen throughout the day.
"His speech is very difficult to understand. I don't think it's his hearing, because he always responds when I call him."	Children who have high-frequency hearing loss may have poor speech production because they are unable to hear high-frequency speech sounds (consonants) even though they can hear low- and mid-frequency sounds clearly.
"My child is doing poorly in school, but I know she understands the material because we go over her homework at night."	Children who have minimal hearing loss may have difficulty hearing in school settings because of the background noise. When working at home in a 1-on-1 situation, they may demonstrate no hearing difficulties because the acoustic conditions are good.

responses are not yet reliable enough for defining the extent of hearing loss.

## MANAGEMENT

The early identification of hearing loss in children is of little value if timely intervention does not follow. Many children have conductive and sensorineural hearing losses that are not amenable to medical treatment. For these children, several options remain, the most familiar being traditional hearing aids, which are devices designed to pick up sounds in the child's environment and convert them to electrical signals that are amplified, filtered, and converted back to acoustic signals by a receiver. For children in noisy settings (eg, child care centers, classrooms), frequency-modulated (FM) systems can be used alone or in combination with hearing aids. These systems use a microphone worn by the teacher to amplify only the teacher's voice while minimizing the interfering background noise. The signal is transmitted to the child via an FM signal, which is received by a hearing aid or loudspeaker.

Most children who have hearing loss benefit from some form of amplification. However, in cases of severe-to-profound hearing loss, conventional amplification might not be enough. An alternative to traditional hearing aids for these children is the cochlear implant, a surgically implanted device with electrodes that are coiled into the cochlea to stimulate the auditory nerve with electrical current. Although cochlear implants do not restore normal hearing and children vary markedly in the benefits they derive from the implant, most experience at least an awareness of sound, and some reach a high level of speech recognition, enabling the development of normal speech and language skills. Children are eligible for cochlear implants at age 1 year, although some exceptions for earlier implantation can be made. Children who receive their cochlear implants at an early age (ie, prior to 3 years of age) tend to benefit more from the implant than children who receive their implants at older ages. All children who have cochlear implants are considered at risk for pneumococcal meningitis. Pediatricians should ensure these children are up to date on the pneumococcal vaccine recommendations. All vaccines should be administered at least 2 weeks or more prior to cochlear implant surgery.

As the gatekeepers for children's health care, pediatricians are responsible for recognizing the signs and symptoms of hearing loss in their young patients. Only through the vigilance of pediatricians and other health care practitioners will the age of identification of hearing loss in children be lowered, thus avoiding delays in intervention.

For infants with permanent hearing loss, communication with the state's coordinator for early hearing detection and intervention should ensure that the child and family are enrolled in appropriate early intervention services as soon as possible following identification of hearing loss. Such services can include speech-language and communication intervention, behavioral therapy, and family counseling or support. The pediatrician should also ensure that the child has received a thorough medical evaluation to determine the cause of the hearing loss, including a genetics consultation. Furthermore, because

of the high incidence of vision problems in children with hearing loss, a referral for ophthalmologic evaluation may be warranted. Children with permanent hearing loss are especially vulnerable to the effects of otitis media with effusion because additional hearing loss secondary to the effusion can negatively affect the audibility of speech through hearing aids. Accordingly, pediatricians must closely monitor and manage children who have persistent otitis media with effusion. Finally, approximately 30% to 40% of children with hearing loss have additional disabilities. Therefore periodic developmental screening and surveillance, as recommended by the JCIH, is an integral part of the management of these children.

## WHEN TO REFER

The 2007 position statement of the JCIH lists risk indicators for delayed-onset hearing loss. In addition to any babies who do not pass their newborn hearing screenings, children whose medical history includes 1 or more of the following indicators should be referred for audiologic testing:

- Caregiver concerns regarding hearing, speech, language, or developmental delay
- Family history of permanent childhood hearing loss
- Neonatal intensive care of more than 5 days or any of the following regardless of length of stay: ECMO, assisted ventilation, exposure to ototoxic medications (gentimycin and tobramycin) or loop diuretics (furosemide), hyperbilirubinemia that requires exchange transfusion
- In utero infections, such as CMV, herpes, rubella, syphilis, and toxoplasmosis
- Craniofacial anomalies, including those that involve the pinna, ear canal, ear tags, ear pits, and temporal bone anomalies
- Physical findings such as white forelock that are associated with a syndrome known to include a sensorineural or permanent conductive hearing loss
- Syndromes associated with hearing loss or progressive or late-onset hearing loss such as neurofibromatosis, osteopetrosis, and Usher syndrome; other frequently identified syndromes include Waardenburg, Alport, Pendred, and Jervell and Lange-Nielson
- Neurodegenerative disorders such as Hunter syndrome, or sensory motor neuropathies such as Friedreich ataxia and Charcot-Marie-Tooth syndrome
- Culture-positive postnatal infections associated with sensorineural hearing loss, including confirmed bacterial and viral meningitis
- Head trauma, especially basal skull/temporal bone fractures that require hospitalization
- Chemotherapy

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Your Baby Needs Another Hearing Test* (handout), Maternal Child Health Bureau, Health Resources and Services Administration and American Academy of

Pediatrics ([www.medicalhomeinfo.org/downloads/pdfs/Anotherhearingtest.pdf](http://www.medicalhomeinfo.org/downloads/pdfs/Anotherhearingtest.pdf))

### Medical Decision Support

- *Hearing Loss in Children* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/ncbddd/hearingloss/index.html](http://www.cdc.gov/ncbddd/hearingloss/index.html))
- *Hearing Loss in Children: Information About Early Hearing Detection and Intervention (EHDI) State Programs* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/ncbddd/hearingloss/ehdi-programs.html](http://www.cdc.gov/ncbddd/hearingloss/ehdi-programs.html))
- *NIDCD Fact Sheet: When a Newborn Doesn't Pass the Hearing Screening* (fact sheet), National Institute on Deafness and Other Communication Disorders ([www.medicalhomeinfo.org/downloads/pdfs/NIDCDFactSheetHowMedicalandOtherProfessionals.pdf](http://www.medicalhomeinfo.org/downloads/pdfs/NIDCDFactSheetHowMedicalandOtherProfessionals.pdf))

### AAP POLICY

American Academy of Pediatrics Joint Committee on Infant Hearing. Year 2007 position statement: principles and guidelines for early hearing detection and intervention programs. *Pediatrics*. 2007;120(4):898–921 ([pediatrics.aappublications.org/content/120/4/898](http://pediatrics.aappublications.org/content/120/4/898))

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Centers for Disease Control and Prevention. Early hearing detection and intervention among infants – Hearing screening and follow-up survey, United States, 2005–2006 and 2009–2010. *MMWR Surveill Summ*. 2014;63(Suppl 2):20–26

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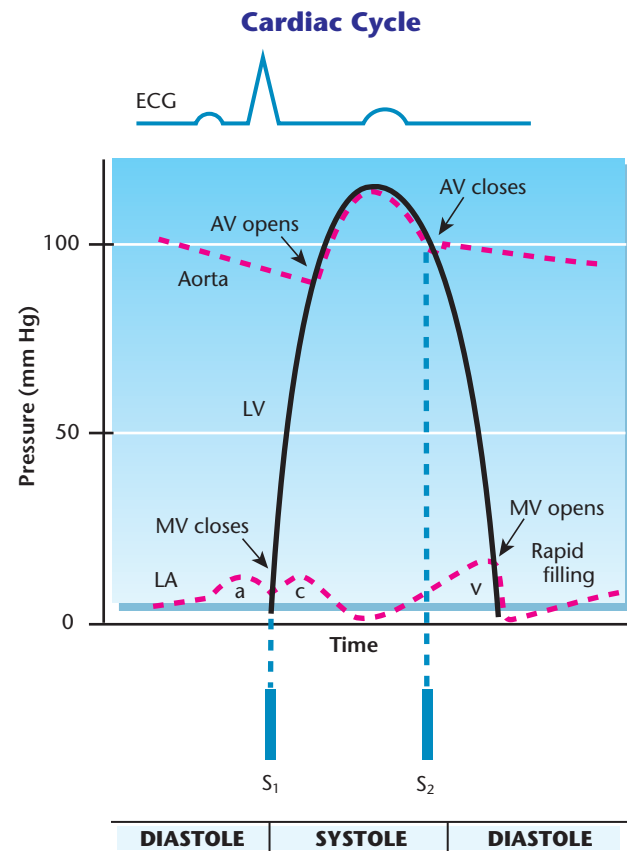
## Chapter 159 HEART MURMURS

Christine Tracy, MD; Christine A. Walsh, MD

A heart murmur is a common finding during the physical examination of children. However, few children with heart murmurs have structural cardiac disease. The challenge for the pediatrician lies in distinguishing innocent murmurs from those that indicate a cardiac abnormality.

### CARDIAC CYCLE AND ASSOCIATED HEART SOUNDS

The pediatrician needs to understand the events of the cardiac cycle and its associated heart sounds when determining the significance of a heart murmur. Heart



**Figure 159-1** Pressure time relationships of the left-sided heart chambers are illustrated during the normal cardiac cycle. AV, aortic valve; ECG, electrocardiogram; LA, left atrium; LV, left ventricle; mm Hg, millimeters of mercury; MV, mitral valve; S<sub>1</sub>, first heart sound; S<sub>2</sub>, second heart sound. (From Lilly LS. *Pathophysiology of Heart Disease*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003. Used by permission.)

sounds are directly related to the hemodynamic events of systole and diastole (Figure 159-1).

The first heart sound (S<sub>1</sub>) is related to the closure of the mitral and tricuspid valves at the end of diastole, when the ventricles are completely filled. The ventricles then undergo a period of isovolumic contraction, followed by opening of the aortic and pulmonary valves. Rapid systolic ejection ensues, followed by a phase of reduced ejection later in systole.

The second heart sound (S<sub>2</sub>) is created by the closure of the aortic and pulmonary valves at the end of systole. The first component of S<sub>2</sub> is created by the closure of the aortic valve (A<sub>2</sub>), and the second component of S<sub>2</sub> is created by the closure of the pulmonary valve (P<sub>2</sub>). During inspiration, P<sub>2</sub> occurs after A<sub>2</sub>, generating an audibly split S<sub>2</sub> (A<sub>2</sub>-P<sub>2</sub>). During exhalation, the closures of the aortic and pulmonary valves are nearly coincident, creating a single S<sub>2</sub>. Abnormal splitting of S<sub>2</sub> can be a clue to structural heart disease, but splitting of S<sub>2</sub> can be difficult to appreciate in infants or children with accelerated heart rates.

Wide splitting of S<sub>2</sub> is associated with prolonged ejection from the right ventricle, as occurs with conditions such as an atrial septal defect (ASD), in which S<sub>2</sub>



is widely split and fixed. A narrowly split  $S_2$  is associated with pulmonary hypertension, in which closure of the pulmonary valve is early, or aortic stenosis, when closure of the aortic valve is delayed. Failure of  $S_2$  to split at all can be the result of simultaneous closure of the aortic and pulmonary valves during all phases of the respiratory cycle, found with conditions that result in high pulmonary artery pressure. A single  $S_2$  can also be associated with certain congenital cardiac anomalies, such as truncus arteriosus and tetralogy of Fallot, or with a single ventricle after the bidirectional Glenn shunt or the Fontan operation.

Third and fourth heart sounds may also be appreciated during physical examination. The third heart sound ( $S_3$ ) is heard early in diastole, during the initial phase of passive rapid ventricular filling. It is a low-frequency sound that can be best heard at the left lower sternal border or at the apex. An apical  $S_3$  can frequently be heard in healthy children, particularly in competitive athletes. Usually pathologic, the fourth heart sound ( $S_4$ ) is also a low-frequency sound but is heard late in diastole, just before  $S_1$ . It results from rapid filling of the ventricle caused by atrial contraction. An  $S_4$  gallop is associated with decreased ventricular compliance (as is seen in cardiomyopathy) and congestive heart failure. Auscultation of an  $S_4$  gallop warrants an evaluation by a pediatric cardiologist.

Clicks may also be audible during the cardiac cycle. Ejection clicks are heard in systole; the timing of the click in the cardiac cycle helps elucidate the cause. An early systolic click, heard just after  $S_1$ , is associated with semilunar valve stenosis (aortic stenosis or pulmonary stenosis) or dilation of the great arteries (the aorta or pulmonary artery). Aortic valve clicks, best heard at the apex or right upper sternal border, do not vary in intensity with respiration. Pulmonary valve clicks increase in intensity with exhalation, and they are best heard along the left sternal border. A midsystolic apical click is heard with mitral valve prolapse and may be accompanied by a late systolic murmur.

## CARDIAC ANATOMY

In evaluating a child with a heart murmur, the physician must understand the anatomy of the heart and its position in the chest. The location of the heart murmur on the chest wall can serve as an important tool in deciding whether the murmur is innocent or pathologic. Figure 159-2 demonstrates the location of the valves of the heart in relation to their position on the chest wall.

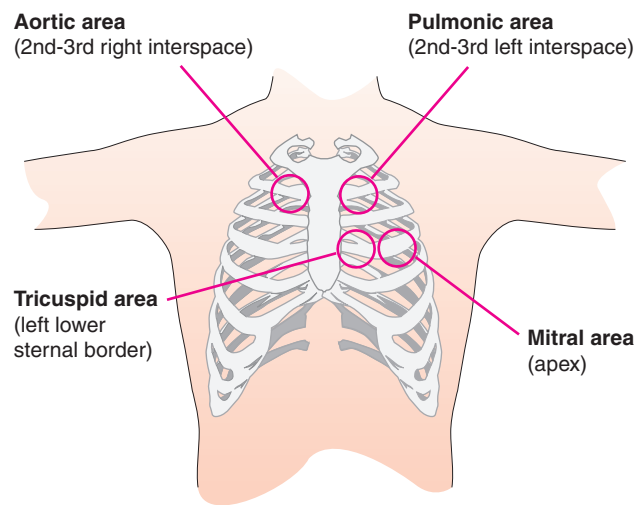
## PATIENT EVALUATION

### History

A complete and accurate history is one of the most important aspects of evaluating a cardiac murmur in children because the clinical context in which the murmur occurs provides clues to the cause of a heart murmur. The history should include the patient's chief complaints and medical history, including the birth history and family history (Box 159-1).

### Physical Examination

Evaluation of a cardiac murmur involves much more than auscultation of the heart. A complete physical



**Figure 159-2** Areas of cardiac auscultation are governed by the location of the heart valves in relation to their position on the chest wall. (From Lilly LS. *Pathophysiology of Heart Disease*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003. Used by permission.)

examination in the child or adolescent with a heart murmur is needed to put the murmur in perspective. Pertinent aspects of the physical examination in a patient with a heart murmur are outlined in Table 159-1.

## CARDIAC EVALUATION

A detailed cardiac examination includes thorough inspection, palpation, and auscultation.

### Inspection

Inspection begins with a general assessment of appearance, nutritional status, genetic abnormalities, color, and comfort. The chest wall should then be inspected for abnormalities, including deformities such as a pectus excavatum, asymmetry, and surgical scars.

### Palpation

Palpation should include more than the chest, beginning with the extremities to assess perfusion, pulses, capillary refill, and temperature. The precordium is then palpated to identify the point of maximal impulse (PMI) and to detect thrills. Under normal conditions, the PMI represents the activity of the left ventricle and is palpated in the left fourth or fifth intercostal space in the midclavicular line. Activity of the right ventricle is appreciated in the fourth to fifth intercostal space along the left lower sternal border. Abnormal intensity or location of the PMI or of the right ventricle's activity is suggestive of a cardiac anomaly. Thrills can be palpated in the suprasternal notch (suggesting aortic valve disease or coarctation of the aorta), along the left upper sternal border (suggesting pulmonary valve disease), along the right upper sternal border (suggesting aortic valve disease), or along the left lower sternal border (in association with ventricular septal defects [VSDs]). A thrill is an abnormal finding and warrants referral to a pediatric cardiologist.

**BOX 159-1 Raised Index of Suspicion for Cardiac Disease****PATIENT HISTORY**

- Poor weight gain or difficulty feeding
- Frequent respiratory difficulties or respiratory distress
- Cyanosis
- Exercise intolerance
- Chest pain with exercise
- Unexplained syncope (especially syncope resulting in injury)
- Concurrent syndromic disorder or genetic disease
- Concurrent metabolic disorder or storage disease
- Sickle cell anemia or blood dyscrasias resulting in anemia
- History of cardiotoxic chemotherapy
- Concurrent human immunodeficiency virus disease
- Hypertension

**BIRTH HISTORY**

- Maternal diabetes
- Maternal TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex) infections during pregnancy

- Multiple gestation pregnancy
- In vitro fertilization pregnancy
- Maternal drug use (either legal or illicit), known teratogens
- Abnormal amniocentesis
- Abnormal fetal ultrasound
- Maternal history of congenital heart disease

**FAMILY HISTORY**

- Congenital heart disease
- Sudden cardiac death or unexplained death in young people
- Hypertrophic cardiomyopathy
- Infantile Marfan syndrome

**Table 159-1 Physical Examination to Evaluate a Heart Murmur**

SITE	FINDING
Vital signs	Temperature, heart rate, respiratory rate, height, weight Blood pressures in the right arm, left arm, leg Pulse oximetry on room air (right hand and either foot if infant)
General	Cyanosis, pallor, dysmorphic features, overall distress Breathing pattern: retractions, grunting, nasal flaring
Head and neck	Jugular venous distention Thyromegaly, thyroid nodules
Chest	Chest wall deformity, asymmetry, surgical scars Lung aeration Rales, rhonchi, wheezes, stridor
Cardiac	Inspection Palpation Auscultation
Abdominal	Liver span Tenderness Distention, ascites
Extremities	Perfusion: capillary refill, temperature, quality of pulses Clubbing, cyanosis, edema Arachnodactyly, joint laxity (Marfan syndrome) Increased arm span, upper-to-lower body ratio (Marfan syndrome)

**Auscultation**

A systematic approach to auscultation of the heart ensures that each major anatomic area of the heart is heard in systole and diastole. The major areas of auscultation on the precordium are the apex, the left lower sternal border, the left mid or upper sternal border, and the right upper sternal border. These areas correspond to each atrioventricular and semilunar valve, as well as the outflow tracts of the right and left ventricles (see Figure 159-2). The physician should also auscultate the left and right infraclavicular areas, the axillae, and the back. Auscultation for systolic or continuous blood flow noises (bruits) should be performed over the liver and fontanelle. A bruit suggests an arteriovenous malformation. The patient should be examined in the supine, sitting, and left lateral decubitus positions. Other postural maneuvers, such as squatting or standing, or performing a Valsalva maneuver, may be useful during auscultation. Auscultation includes an assessment of  $S_1$  and  $S_2$ , including the nature of the splitting of  $S_2$ . Noting any  $S_3$  and  $S_4$ , murmurs, clicks, and rubs completes the auscultation.

**EVALUATION OF HEART MURMUR**

A heart murmur is usually the result of turbulent blood flow. Random fluctuations in velocity and pressure during blood flow result in vibration of the surrounding tissue, which is auscultated as a murmur. A complete description of a heart murmur includes its intensity, timing, location, radiation, and quality.

**Intensity**

Murmur intensity is graded on a scale of I to VI for murmurs in systole (Table 159-2). Some cardiologists use a scale of I to IV for murmurs in diastole (Table 159-3). The

Table 159-2 Intensity of Systolic Murmurs	
GRADE	DESCRIPTION
I	Barely audible
II	Soft, but easily audible
III	Moderately loud without a thrill
IV	Moderately loud with a thrill
V	Loud with a thrill, heard with stethoscope partly on the chest
VI	Loud with a thrill, heard with stethoscope off the chest

Table 159-3 Intensity of Diastolic Murmurs	
GRADE	DESCRIPTION
I	Barely audible
II	Soft, but immediately heard
III	Easily heard
IV	Very loud

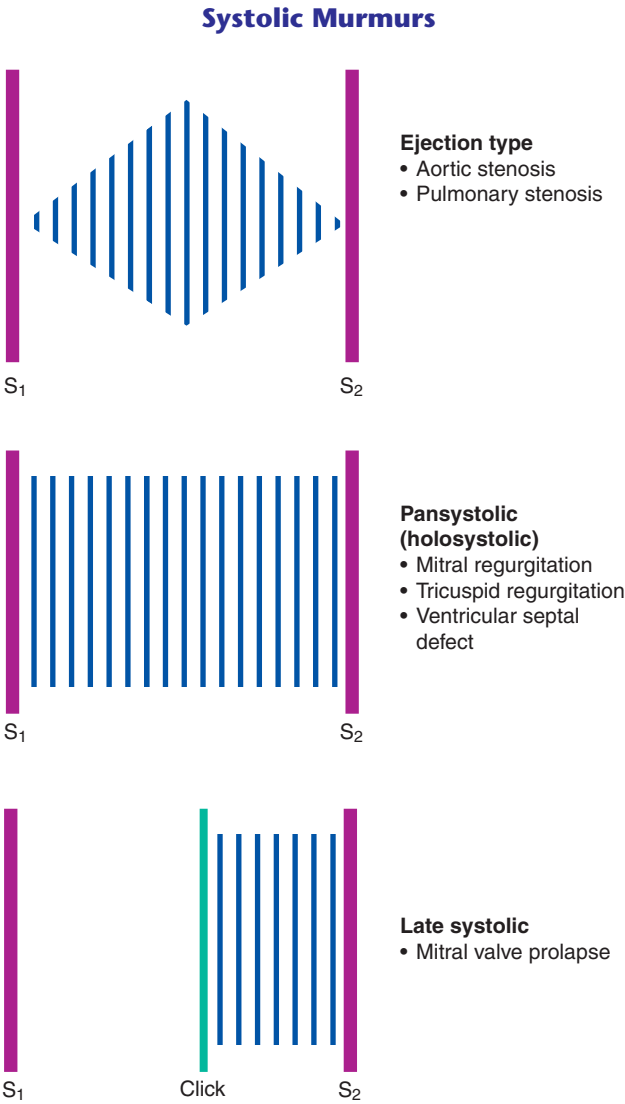
intensity of a murmur does not necessarily reflect the severity of the abnormality. For example, a small VSD may have a very loud murmur, but critical aortic stenosis may have a very soft murmur if cardiac output is low.

Timing

Timing refers to the point in the cardiac cycle at which the murmur is heard. Murmurs are described as being systolic, diastolic, or continuous.

Systolic murmurs occur between atrioventricular valve closure (S<sub>1</sub>) and semilunar valve closure (S<sub>2</sub>). Systolic murmurs are further divided into ejection (crescendo-decrescendo) murmurs, holosystolic (pansystolic) murmurs, and late systolic murmurs (Figure 159-3).

Ejection murmurs, which may be innocent or pathologic, begin shortly after S<sub>1</sub>, peak in intensity, and then end at or before S<sub>2</sub>. All innocent systolic ejection murmurs are grade I to III. Pathologic ejection murmurs can be of any intensity. They may result from obstructed blood flow across a semilunar valve (aortic or pulmonary stenosis), in which case an ejection click may usher in the murmur. Other pathologic ejection murmurs without associated clicks arise from excessive volume crossing a normal semilunar valve (ASD). Holosystolic murmurs start with S<sub>1</sub> and continue to S<sub>2</sub> at the same level of intensity, sometimes obscuring S<sub>2</sub>. These murmurs result from movement of blood from a higher-pressure chamber to a lower-pressure chamber, such as with a VSD or mitral regurgitation. Late systolic murmurs are associated with mitral valve prolapse and resultant mitral regurgitation; they are classically preceded by a mid- or late-systolic click.

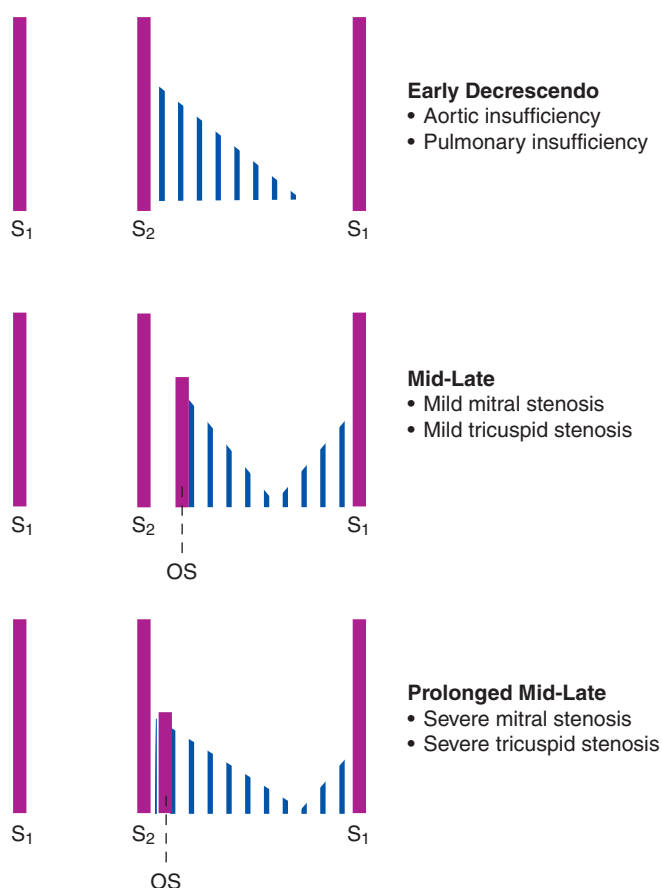


**Figure 159-3** Classification of systolic murmurs. S<sub>1</sub>, first heart sound; S<sub>2</sub>, second heart sound. (From Lilly LS. Pathophysiology of Heart Disease. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003. Used by permission.)

Diastolic murmurs occur between semilunar valve closure (S<sub>2</sub>) and atrioventricular valve closure (S<sub>1</sub>); they are further divided into early-, mid-, and late-diastolic murmurs (Figure 159-4). Diastolic murmurs are all pathologic and require referral to a pediatric cardiologist. Early-diastolic murmurs begin immediately after S<sub>2</sub> and are decrescendo in nature; they become less audible as the ventricle fills. Aortic insufficiency and pulmonary insufficiency are heard in early diastole. Mid-diastolic murmurs occur during rapid ventricular filling. Murmurs of mild mitral and tricuspid stenosis are heard in mid diastole. Late-diastolic (presystolic) murmurs occur near the end of diastole, during atrial contraction. Severe mitral stenosis or tricuspid stenosis murmurs increase in late diastole.

Continuous murmurs extend across portions of systole and diastole. They are almost always vascular in

### Diastolic Murmurs



**Figure 159-4** Classification of diastolic murmurs. OS, opening snap; S1, first heart sound; S2, second heart sound. (From Lilly LS. *Pathophysiology of Heart Disease*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003. Used by permission.)

origin and are caused by aortopulmonary (eg, patent ductus arteriosus) or arteriovenous (eg, arteriovenous malformation) connections, turbulent flow in collateral arteries (eg, coarctation of the aorta), turbulent flow in veins (eg, venous hum), or a surgical shunt. With the exception of the innocent venous hum (Table 159-4), continuous murmurs are pathologic. They tend to wax and wane in intensity through the cardiac cycle, often diminishing in late diastole (Figure 159-5). A somewhat different auscultatory phenomenon from the continuous murmur, the to-and-fro murmur describes an ejection murmur heard in systole, coupled to a decrescendo murmur early in diastole. Combined aortic stenosis and aortic insufficiency or combined pulmonary stenosis and pulmonary insufficiency produces to-and-fro murmurs.

#### Location and Radiation

Location refers to the area where the murmur is heard the best. Radiation means the murmur is also audible with unexpected intensity at some distance from its location. As seen in Figure 159-2, location helps

narrow the differential diagnosis of the murmur. Radiation of the murmur can also be very helpful diagnostically. For example, murmurs that radiate to the neck tend to be of aortic or left ventricular outflow tract origin, whereas a murmur heard best at the left upper sternal border with radiation to the axillae and back is more likely to be pulmonary in origin.

#### Quality and Behavior With Maneuvers

Quality refers to the pitch and nature of a murmur. Pitch is generally described as either high or low. High-pitched murmurs occur when the pressure differential involved is large. For example, aortic insufficiency is a high-pitched murmur. Low-pitched murmurs occur when a lower pressure differential is involved. Pulmonary insufficiency is a low-pitched murmur. Systolic murmurs are described as harsh, blowing, musical, or vibratory. Diastolic murmurs are described as blowing, rumbling, crescendo, or decrescendo.

Postural maneuvers are useful in distinguishing among different types of murmurs. Innocent murmurs tend to become louder when the patient moves from an upright to a supine position. Placing the patient in the left lateral decubitus position increases the murmur of mitral stenosis. A Valsalva maneuver, by decreasing venous return, makes the murmur of aortic stenosis softer; however, it makes the murmur of hypertrophic obstructive cardiomyopathy louder. Valsalva maneuver also decreases the murmurs associated with a VSD and mitral regurgitation and can nearly eliminate innocent Still murmurs (Table 159-4). Squatting increases venous return and makes the murmur of hypertrophic obstructive cardiomyopathy softer. Standing up after squatting can accentuate the murmur or click of mitral valve prolapse by moving the murmur and click closer to S1. Recumbent positioning and/or turning the head can eliminate the innocent continuous murmur of a venous hum.

### CONCLUSION

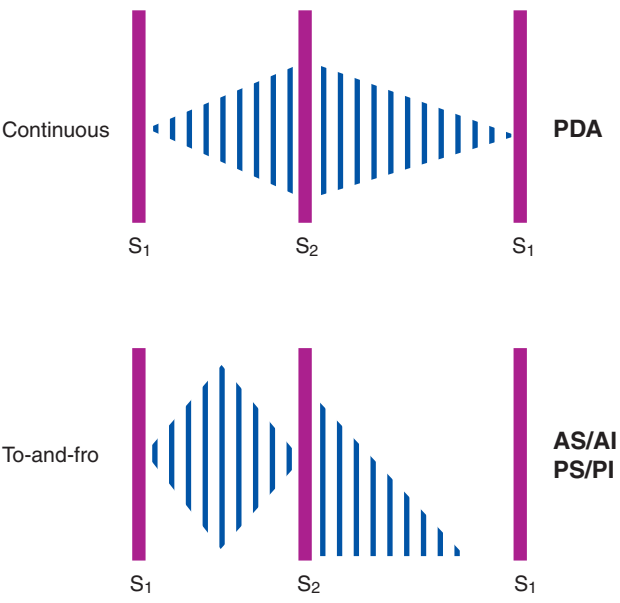
Pediatricians commonly evaluate childhood murmurs. Most murmurs in children and adolescents are innocent. They do not reflect cardiac disease, and they do not require referral to a pediatric cardiologist, prophylaxis against endocarditis, or exercise restriction. Innocent murmurs are generally short systolic murmurs and are less than grade IV. They are often low pitched, vibratory, or musical; are best heard in the supine position; and often diminish when the patient is upright or during a Valsalva maneuver. Most innocent murmurs can be recognized with confidence based on the clinical history and careful physical examination. Further evaluation is required for any murmur for which suspicion persists that it may be pathologic.

#### WHEN TO REFER

- Patient, maternal, or family history raising index of suspicion for heart disease
- All diastolic murmurs
- Continuous murmurs, except venous hum
- All systolic murmurs grade IV or higher



MURMUR	INTENSITY	TIMING	LOCATION	QUALITY
Still	I–III/VI	Early–mid systolic	LM–LLSB or apex	Vibratory, musical
Pulmonary	I–III/VI	Early–mid systolic	LUSB	Low pitched, ejection
Venous hum	I–III/VI	Continuous	Right (rarely left) infra- or supraclavicular	Low pitched, disappears with head turn, supine position, jugular compression



**Figure 159-5** Continuous murmur versus to-and-fro murmur. AS/AI, aortic stenosis and aortic insufficiency; PDA, patent ductus arteriosus; PS/PI, pulmonary stenosis and pulmonary insufficiency; S1, first heart sound; S2, second heart sound. (From Lilly LS. *Pathophysiology of Heart Disease*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003. Used by permission.)

- All systolic murmurs not clearly fitting the pattern of innocent murmur
- Auscultation of an S4 gallop
- A thrill is an abnormal finding and warrants referral to a cardiologist
- Cyanosis, clubbing
- Higher blood pressure in one or both arms than a leg
- Congestive heart failure—rales, respiratory distress, hepatomegaly, edema
- Abnormal electrocardiogram
- Symptoms that suggest reactive airway disease that do not improve with appropriate medical therapy

TOOLS FOR PRACTICE

Engaging Patient and Family

- *Heart Murmurs* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/heart/Pages/Heart-Murmur.aspx](http://www.healthychildren.org/English/health-issues/conditions/heart/Pages/Heart-Murmur.aspx))

Medical Decision Support

- American Heart Association (Web site), ([www.americanheart.org](http://www.americanheart.org))

SUGGESTED READINGS

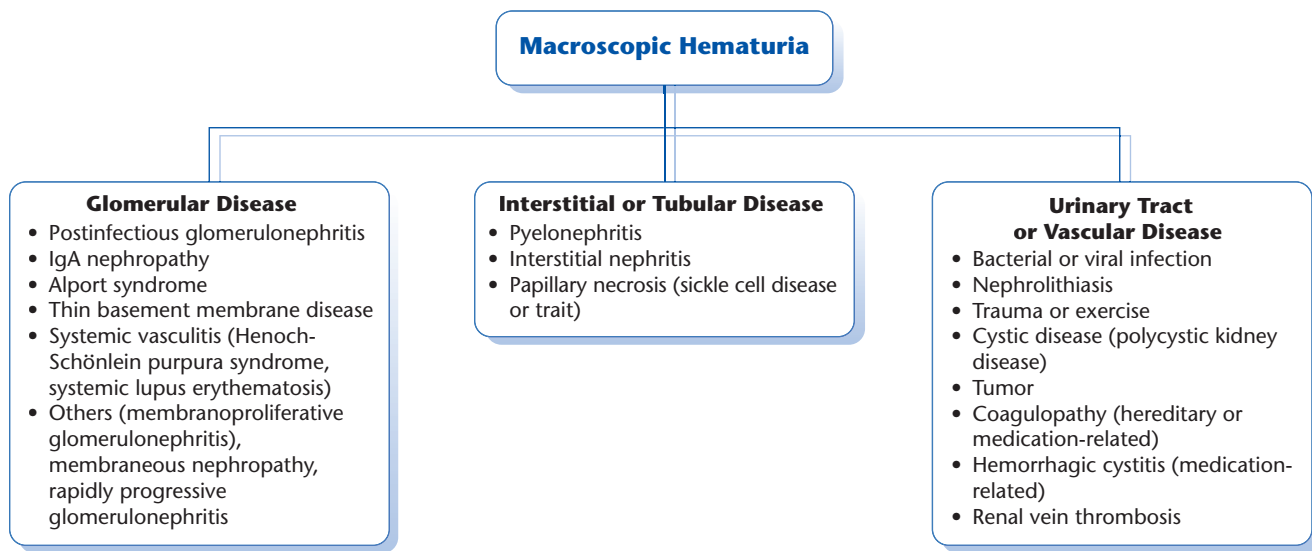
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Chapter 160  
HEMATURIA

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Hematuria may manifest as a dramatic change in the color of a child's urine, with the appearance of blood on a diaper or underwear, or as a finding on a urinalysis. Red or brown (cola-colored) urine with red blood cells (RBCs) seen on microscopy is typical of macroscopic (or gross) hematuria. In general, urologic causes of gross hematuria often present with red or pink urine, while glomerular hematuria presents with brown-, tea-, or cola-colored urine. In a retrospective study of children presenting to a pediatric emergency department, gross hematuria had an incidence of 1.3 per 1,000 visits. Microscopic hematuria (defined as >5 RBCs per high power field seen on microscopy of centrifuged urine) is more common. On routine screening urinalysis, studies suggest up to 32 per 1,000 girls and 14 per 1,000 boys will have microscopic hematuria. The American Academy of Pediatrics (AAP) currently does not recommend routine screening urinalyses in asymptomatic children.

The most likely causes of macroscopic and microscopic hematuria differ (Figure 160-1 and Box 160-1). Macroscopic hematuria may originate from any component of the genitourinary tract, and the differential diagnosis, in addition to infection, includes glomerular, interstitial, and tubular diseases and bleeding from trauma, stones, or coagulopathy. Many of the causes of macroscopic hematuria, such as infection, nephrolithiasis, and glomerulonephritis, may also present with microscopic hematuria. Overall, the



**Figure 160-1** Differential diagnosis of macroscopic hematuria in children.

### BOX 160-1 Causes of Microscopic Hematuria

- Transient
- Thin basement membrane disease
- Idiopathic hypercalciuria
- Immunoglobulin A (IgA) nephropathy or Alport syndrome
- Sickle cell anemia or trait
- Trauma or exercise
- Postinfectious glomerulonephritis
- Nephrolithiasis
- Other glomerular disease or glomerulonephritis
  - Focal and segmental glomerulosclerosis
  - Henoch-Schönlein purpura syndrome
  - Systemic lupus erythematosus
  - Membranoproliferative glomerulonephritis
  - Membranous glomerulonephritis
- Congenital abnormality
  - Ureteropelvic junction obstruction
  - Cystic disease
- Pyelonephritis or infection
- Vascular malformation
- Drugs or toxins

most common causes of asymptomatic isolated microscopic hematuria are thin basement membrane disease, idiopathic hypercalciuria, immunoglobulin A (IgA) nephropathy, and sickle cell disease or trait.

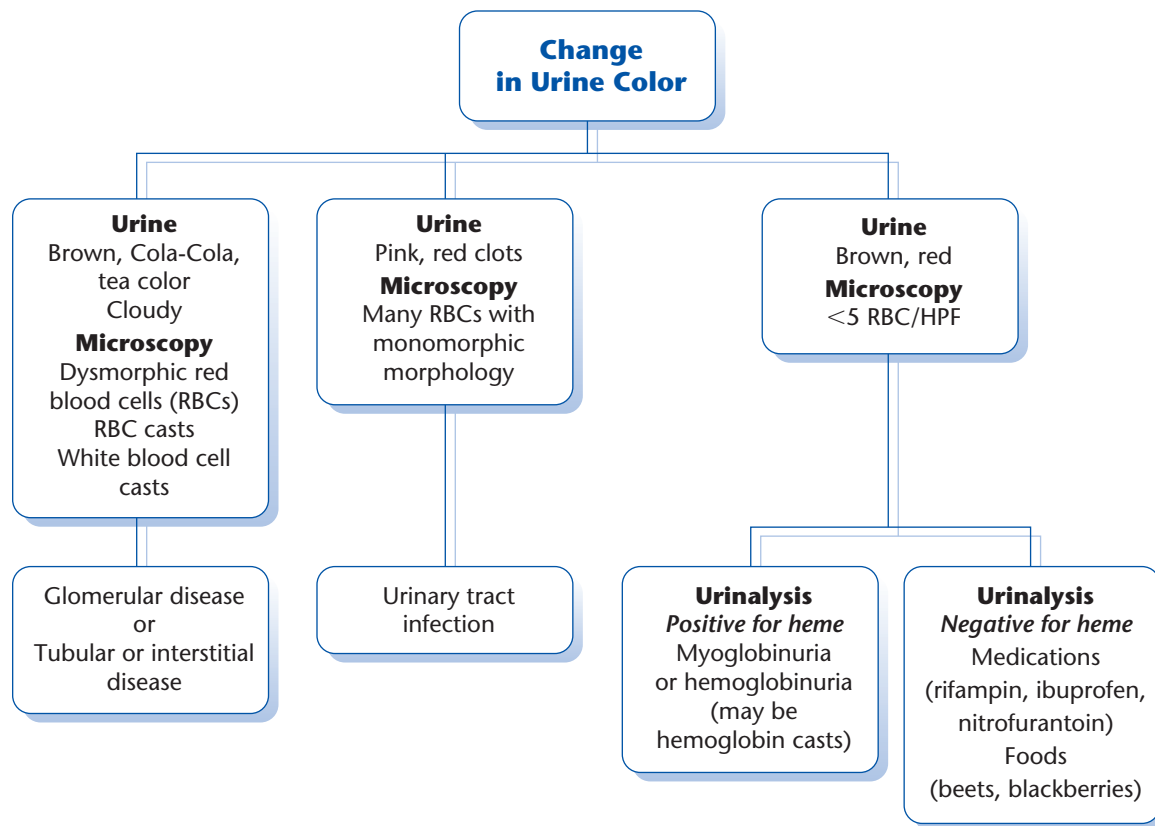
## MACROSCOPIC HEMATURIA

The first and most important step in evaluating macroscopic hematuria is obtaining a detailed description of the urine (Figure 160-2). Renal or glomerular causes of hematuria result in tea- or cola-colored urine, as

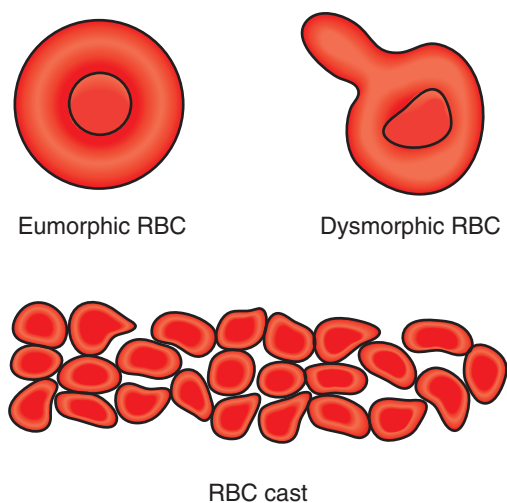
opposed to hematuria of lower-tract origin, which causes red or pink urine. In addition to color, highly turbid urine may indicate the presence of cells and suggests glomerular disease or infection. Blood clots suggest urinary tract bleeding. The timing of the bleeding may be helpful (eg, if it occurs only with the onset of micturation, then the source of the bleeding is likely to be in the lower urinary tract).

Associated signs and symptoms from a detailed history and physical examination will dictate laboratory and radiologic evaluation. Important historical elements include associated urinary symptoms, such as dysuria, frequency, urgency, or enuresis. A decrease in urine output should prompt particular concern and rapid evaluation and treatment. A review of systems should include associated symptoms of abdominal pain or colic, upper respiratory infection symptoms, swelling of extremities, or blurry vision or headaches suggestive of hypertension. The history should be explored for prior episodes of hematuria, preceding infections (either documented group A streptococcal throat infection or a history of sore throat or skin infection), history of trauma, or other illnesses, such as the presence of sickle cell trait or disease. Systemic illnesses may be suggested by a history of fever, malaise, weight loss, alopecia, rash, or joint pains, which may be seen in rheumatologic disease. The age of the patient is an important factor to consider—certain causes of hematuria, such as renal vein thrombosis and tumors, are more common in infants. Important points on the family history include other family members with hematuria, kidney or rheumatologic disease, and any history of deafness, which may occur with Alport syndrome.

A thorough physical examination should include measurement of blood pressure, abdominal or costovertebral angle tenderness, a search for evidence of local trauma to the genitourinary tract, inspection and palpation for periorbital, genital, or extremity edema, and examination of the skin for rashes. Hematuria in association with edema and hypertension suggests glomerulonephritis.



**Figure 160-2** Evaluation for macroscopic hematuria begins with the examination of the urine.



**Figure 160-3** Urinary findings in hematuria

Laboratory evaluation begins with a urinalysis with microscopic examination of a fresh-spun urine sample to confirm the presence of red blood cells. Dysmorphic red blood cells and red blood cell casts are pathognomonic of hematuria of glomerular origin (see Figure 160-3). If the urine dipstick is positive for blood and fewer than 5 red blood cells are found on microscopy, then the diagnosis is hemoglobinuria or

myoglobinuria rather than hematuria. Several drugs, including rifampin, ibuprofen, and nitrofurantoin, as well as foods such as beets and blackberries, can discolor urine to give it the appearance of hematuria, but urinalysis will be negative for blood. The presence of calcium, uric acid, or cystine crystals in the urine is suggestive of nephrolithiasis. Identification of white blood cell casts on microscopy or leukocyte esterase or nitrate positivity on urine dipstick point to infectious causes of hematuria.

Further evaluation is determined by the most likely cause of the blood in the urine. For example, a workup for suspected glomerular hematuria might include evaluation of serum electrolytes, blood urea nitrogen, creatinine, calcium, and phosphorus to assess renal function and liver function tests if there is a nephrotic component. Antinuclear antibody test, complement studies (C3, C4, and total complement), streptozyme (deoxyribonuclease B) and streptolysin O antibody titers may help determine the etiology of a glomerulonephritis. Throat culture or rapid testing for group A  $\beta$ -hemolytic streptococci is indicated with a history of sore throat. A urine culture should be performed on all patients with urinary symptoms or on infants, because infection is a common cause of hematuria. Proteinuria on urinalysis should be further evaluated with a first-morning void for protein-to-creatinine ratio. In patients with suspected nonglomerular macroscopic hematuria, a renal-bladder sonogram is indicated to evaluate for cystic disease, congenital obstruction,

tumors (including Wilms tumor), nephrolithiasis, or parenchymal renal disease. A renal doppler study is needed to evaluate for suspected vascular thrombosis, renal infarcts, or renal artery stenosis.

Evaluation of glomerular hematuria may be continued as an outpatient or inpatient. Indications for admission include decreased urine output, hypertension, azotemia, or renal insufficiency. Renal biopsy is absolutely indicated in cases of hematuria with nephrotic syndrome, recurrent hematuria, azotemia, or renal insufficiency. Renal biopsy may be considered if a family history of hematuria exists or if the history or laboratory evaluation is suggestive of rheumatologic disease, such as systemic lupus erythematosus.

Management of glomerular disease will depend on the cause of the glomerulonephritis. The most common glomerulonephritis is postinfectious, an entity characterized by a prodromal infection (often a streptococcal skin or throat infection but also viral infections, such as varicella, cytomegalovirus, Epstein-Barr virus, hepatitis B and C, and parasitic infections such as toxoplasmosis) between 1 and 6 weeks before the onset of hematuria. Other causes of acute postinfectious glomerulonephritis include ventriculoperitoneal shunt infections (shunt nephritis) and acute or subacute endocarditis. Low complement (C3) and elevated streptolysin O antibodies are characteristic of post-streptococcal glomerulonephritis. Post-streptococcal glomerulonephritis is typically self-limited with a good prognosis for long-term renal function. Admission may be required for renal insufficiency, oliguria, or acute hypertension (the latter requiring aggressive management with fluid and salt restriction and antihypertensive medications).

Other types of glomerulonephritis often require management by a nephrologist. The most common chronic glomerulonephritis worldwide is IgA nephropathy, although it is more often diagnosed in adults than children. IgA nephropathy characteristically results in persistent microhematuria with intermittent episodes of gross hematuria associated with upper respiratory infections. Long-term outcome is variable, with 20% to

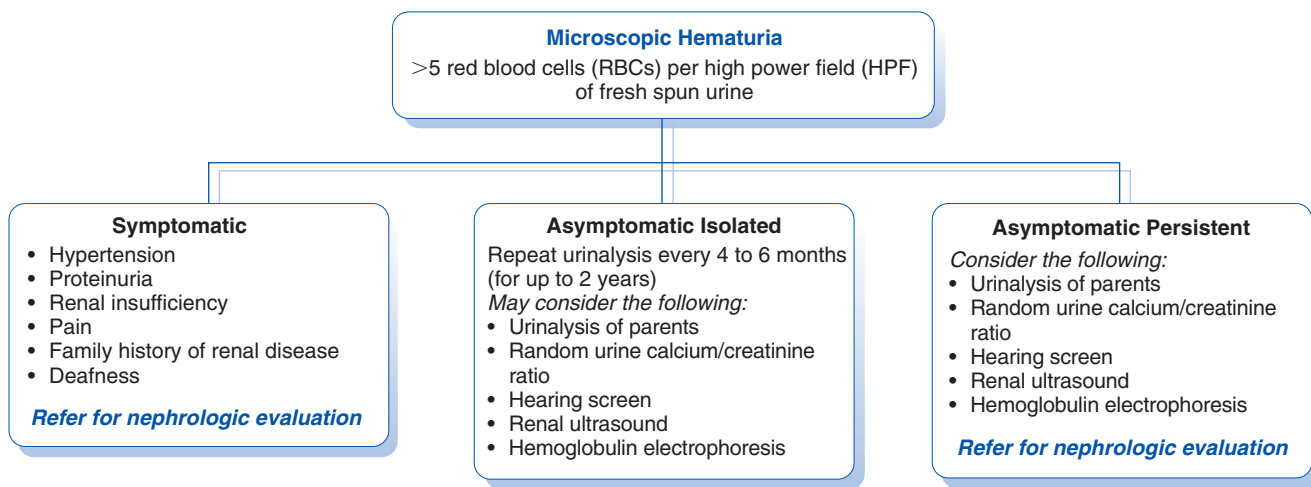
40% of children progressing to end-stage kidney disease. Proteinuria and hypertension are poor prognostic indicators. Henoch-Schönlein purpura (HSP), a common systemic vasculitis in children, is often associated with crampy abdominal pain, arthralgia, and palpable purpura, and can produce glomerulonephritis with hematuria.

Management of nonglomerular hematuria depends on the cause. Further imaging with computed tomography may be indicated. Patients with sickle-cell disease and macroscopic hematuria from papillary necrosis may require admission for intravenous hydration. Trauma, tumors, cystic disease, congenital obstruction, hemorrhagic cystitis, and lower urinary tract bleeding often require urologic evaluation, which may include direct visualization by cystoscopy. Children with nephrolithiasis benefit from both nephrologic and urologic evaluation.

## MICROSCOPIC HEMATURIA

The evaluation of microscopic hematuria involves a thorough history and physical examination. A family history of deafness or kidney disease and the presence of hypertension, proteinuria, or edema should prompt referral to a pediatric nephrologist for further evaluation. In the absence of any other signs and symptoms, microhematuria is often benign and, in many cases, resolves spontaneously (transient hematuria). Therefore, in an asymptomatic, normotensive child with isolated microhematuria, repeating a urinalysis on 1 or more occasions is often prudent before further evaluation. School-aged children may be observed in excess of 2 years before more extensive testing is undertaken. Figure 160-4 shows a proposed algorithm for the evaluation of microscopic hematuria. Significant proteinuria or the occurrence of gross hematuria should prompt referral to a pediatric nephrologist.

Hereditary nephritis includes a spectrum of familial hematuria that ranges from benign thin basement membrane nephropathy (TBMN) to progressive Alport syndrome. TBMN is a common cause of persistent microhematuria. TBMN is characterized by painless



**Figure 160-4** Evaluation of microscopic hematuria.



microscopic hematuria with minimal proteinuria and normal renal function. Renal biopsy reveals uniform thinning of the glomerular basement membrane. TBMN is also called thin basement membrane disease, hereditary hematuria, benign familial hematuria, and benign hereditary nephritis. Because it is transmitted in an autosomal-dominant fashion, a family history of microscopic hematuria without symptomatic renal disease, or an asymptomatic parent testing positive for hematuria, suggests the diagnosis of TBMN. The overall prevalence is estimated at 1% to 10% of the population. It is more common in females than in males and has been diagnosed in children as young as 1 year of age. Between 5% and 22% of affected individuals will have an episode of gross hematuria associated with an infection or exercise. No evidence has been found to support treatment of TBMN, which is typically nonprogressive. However, affected children should be monitored for with a yearly urinalysis and blood pressure check throughout their lives, because they are at higher risk of hypertension, proteinuria, and renal insufficiency in later adulthood.

Another common cause of microscopic hematuria is hypercalciuria, defined as a urine calcium-to-creatinine ratio of greater than 0.21 or more than 4 mg/kg/day of excreted calcium on a 24-hour urine collection. Children with hematuria and underlying hypercalciuria are at risk for nephrolithiasis, with the risk seeming to be greater in older children, in children with gross rather than microscopic hematuria, and when there is a family history of stone formation.

Significant proteinuria or the occurrence of gross hematuria should prompt referral to a pediatric nephrologist.

### BLOOD ON A DIAPER OR UNDERWEAR

Blood on a diaper or underwear most commonly occurs with trauma to or manipulation of the genital area. Localized irritation of the meatus in boys is the most frequent cause and responds to treatment with petroleum jelly and reassurance to the parent without further evaluation. Sexual abuse is on the differential diagnosis. Nonurethral sources of bleeding, such as perineal or vaginal bleeding, should be considered. Again, a urinalysis is useful to confirm that hematuria is the source of the discoloration. “Red diaper syndrome” can result from infection with *Serratia marcescens* (deposits of reddish pigment), or uric acid crystals (reddish/brown or pink crystals) that can be found in the normal or dehydrated newborn.

### CONCLUSION

Key points for the primary care physician include the following:

- Gross hematuria is a common sign of glomerular and urologic disease.
- Hematuria of glomerular origin presents with tea- or cola-colored urine.
- Hematuria arising from the urinary tract is usually red-pink, with or without clots.
- Red blood cell casts are the hallmark of hematuria of glomerular origin.
- Proteinuria is a more important prognostic finding than gross hematuria.

- Every child with gross hematuria should have a renal ultrasound to rule out nephrolithiasis, tumor, or urologic abnormalities, such as cystic disease and obstructive uropathy.
- Gross hematuria rarely is a cause of anemia.
- Most children with isolated microscopic hematuria do not have a serious or treatable cause for the hematuria and do not require an extensive workup.
- Hematuria of glomerular origin is typically painless.

### WHEN TO REFER

- Macroscopic hematuria
- Hematuria associated with pain
- Persistent microscopic hematuria, especially with associated proteinuria, hypertension, hearing loss, or family history of renal disease or deafness

### WHEN TO ADMIT

- When hematuria (with or without proteinuria) is associated with the following:
  - Severe abdominal or flank pain
  - Congestive heart failure or fluid overload indicative of oliguria or anuria
  - Hypertension
  - Renal insufficiency
  - Anasarca (generalized edema)

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Blood in Urine (Hematuria)* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/genitourinary-tract/Pages/Blood-in-Urine-Hematuria.aspx](http://www.healthychildren.org/English/health-issues/conditions/genitourinary-tract/Pages/Blood-in-Urine-Hematuria.aspx))
- *Proteinuria* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/genitourinary-tract/Pages/Proteinuria.aspx](http://www.healthychildren.org/English/health-issues/conditions/genitourinary-tract/Pages/Proteinuria.aspx))

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## Chapter 161

# HEMOPTYSIS

Scott A. Schroeder, MD

*Hemoptysis*, the spitting or coughing of blood that originates within the thorax, can vary from flecks of blood in the sputum to massive, life-threatening bleeding that can lead to respiratory distress or death. Unlike in adults, for whom more than 100 different causes of hemoptysis have been described, hemoptysis is a rare occurrence in children; it is most commonly associated with previously diagnosed congenital heart disease or cystic fibrosis (CF), although other causes include infectious respiratory illnesses and, rarely, neoplasms. Acute hemoptysis, respiratory failure, and cyanosis may be the result of exposure to mold growing in water-damaged homes or to environmental tobacco smoke. Affected children need to be hospitalized and placed on mechanical ventilation.

Four important considerations should be kept in mind when evaluating children who have hemoptysis. First, it is necessary to determine whether the bleeding requires an emergency resuscitative effort. Second, what seems to be hemoptysis may actually be bleeding from the upper airway or gastrointestinal tract; thus, the source of the bleeding should be established. Third, children without chronic diseases who develop hemoptysis with associated symptoms of a lower respiratory tract infection usually have mild, self-limited bleeding that requires no specific treatment other than management of the underlying acute illness. Fourth, the management of hemoptysis that arises from a localized site differs from that which causes a diffuse alveolar hemorrhage, because the latter may be the presenting sign of an underlying immunologic or rheumatologic disorder.

## **PATHOGENESIS**

Hemoptysis can result from the disruption of either arm of the dual pulmonary vascular system or from damage to the alveolar endothelial junction. The low-pressure, high-capacitance pulmonary arterial system accepts the entire cardiac output from the right ventricle and carries blood to be oxygenated at the pulmonary capillaries before returning the oxygenated blood to the left atrium through the pulmonary veins. Although the pulmonary arteries travel alongside the bronchial tree, they interact with the airways only at the level of the terminal bronchioles. The second arm of the blood supply within the lungs is the high-pressure bronchial system. The bronchial arteries originate from the aorta or, less commonly, the intercostal arteries, and they receive only 1% to 2% of the cardiac output. The bronchial arteries enter the lungs at the hilum, and as they branch with the bronchi they anastomose and penetrate the bronchial mucosa, forming an extensive submucosal plexus. The high-flow, low-pressure pulmonary capillary bed allows the exchange of gases between the

alveoli and the capillaries to occur with little risk for hemorrhage in the normal state.

Localized hemoptysis, in most cases, is the result of bleeding from the high-pressure bronchial circulation in inflamed airways. The pulmonary circulation is rarely to blame for hemoptysis except in necrotic infarcts and from pulmonary arterial aneurysms in tubercular cavities. Both of these conditions are extremely rare in children. Inflammation within the lungs, pulmonary vascular obstruction, and neoplasia can all cause an increase in the bronchial circulation. In chronic inflammatory conditions, such as bronchiectasis, the cardiac output to the bronchial circulation can triple, and bronchopulmonary anastomoses are increased, thereby increasing the potential for erosion of vessels in the presence of superimposed infection. The pathogenesis of disease states with diffuse pulmonary hemorrhage—for example, necrotizing granulomatous vasculitis—is not entirely understood, but the bleeding into the alveoli seems to result from neutrophil-mediated injury to pulmonary capillaries with interstitial and air-space fibrosis from the chronic hemorrhage.

## **ETIOLOGY**

### **Hemoptysis in Children Without a Preexisting Medical Condition**

In children who do not have a preexisting medical condition, the most common causes of hemoptysis are acute infections of the tracheobronchial tree, acute infectious pneumonias, and the aspiration of a foreign body. A child with a pneumococcal pneumonia who is old enough to expectorate is classically febrile, seems ill, and has a cough that is productive of rusty sputum. Certain other bacterial and viral lower respiratory tract infections can cause hemoptysis; in these cases, the hemoptysis usually occurs early in the course of the illness, is self-limited, and consists of only blood-tinged sputum. Globally, tuberculosis, echinococcus, and paragonimiasis are probably the most common causes of hemoptysis in children (Table 161-1).

After acute infectious processes, the most common cause of hemoptysis in a previously healthy child is the aspiration of a foreign body. In many children who aspirate foreign bodies, the initial choking episode is not observed or not remembered. A bout of paroxysmal coughing may occur after the initial event, but as the cough receptors in the bronchi or trachea adapt, the coughing will stop. Over time, and depending on the location and composition of the foreign object, subsequent inflammation will occur, which may result in airway obstruction, with wheezing or recurrent pneumonitis. If neovascularization of granulation tissue in the airways occurs, or if bronchiectasis develops, then hemoptysis can occur weeks to months after the initial event. Only 40% of children with a foreign-body aspiration will exhibit the classic triad of wheezing, cough, and decreased breath sounds distal to the site of obstruction. The chest radiograph will be normal in 25% of children with bronchial foreign bodies and in more than 50% of children with tracheal foreign bodies.

Because only 10% of aspirated foreign bodies are radiopaque, a normal chest radiograph does not

**Table 161-1** Common, Less Common, and Uncommon Causes of Hemoptysis

POPULATION	CAUSE	DIAGNOSTIC CLUES
Common causes in children who have no preexisting medical problems	Pneumonia	Usually rusty-colored sputum early in the course of the illness
	Foreign-body aspiration	Needs a high index of suspicion; may have a normal chest radiograph; localized wheezing that does not respond to medical therapy
Less common causes in children who have no preexisting medical problems	Pulmonary tuberculosis	Usually with systemic manifestations, such as anorexia and weight loss; may have negative purified protein derivative test
	Autoimmune disorders	Diffuse pulmonary hemorrhage, often with weight loss or other systems involved, including the kidneys and joints
	Congenital malformations	Symptoms depend on the nature of the lesion; may be associated with massive hemoptysis or respiratory distress in newborns
Rare causes in children who have no preexisting medical problems	Primary pulmonary neoplasms	Primary pulmonary cancers reported in fewer than 500 children; usually present with cough and recurrent pneumonitis
	Pulmonary embolism	Associated with pleuritic pain, cough, and dyspnea; oral contraceptive use; recent abortion; trauma to lower extremities
	Parasitic lung infections	Travel to endemic areas or sheep-raising areas; peripheral eosinophilia
	Arteriovenous malformations	Recurrent epistaxis, a positive family history for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome), or cutaneous telangiectasia
	Idiopathic pulmonary hemosiderosis	Cough, wheezing, iron-deficiency anemia, and diffuse pulmonary hemorrhage on chest radiograph
Common causes in children who have a preexisting medical problem	Catamenial hemoptysis	Hemoptysis occurs with onset of menses
	Factitious hemoptysis	Form of Münchhausen syndrome
	Bronchiectasis	Blood-tinged sputum, clubbing, signs of increasing airway inflammation
	Congenital heart lesions	Seen with Eisenmenger complex and pulmonary venous congestion
Less common causes in children who have a preexisting medical problem	Sickle cell anemia	Hemoptysis associated with acute chest syndrome or pulmonary infarction
	Aspergillosis	Seen in association with CF or asthma; peripheral eosinophilia and fungi seen on Gram stain of sputum

CF, cystic fibrosis.

preclude aspiration. Inspiratory and expiratory films, decubitus films, and fluoroscopy may be necessary to confirm the diagnosis. If the evidence for aspiration is definitive, then referral for rigid bronchoscopy to a pediatric surgeon or otolaryngologist experienced in retrieving foreign bodies is indicated. If the diagnosis is uncertain, then referral to a pediatric pulmonologist or other physician skilled in the use of the fiberoptic bronchoscopy is appropriate to determine whether a foreign body is present.

### Diffuse Pulmonary Hemorrhage

Children with acute hemoptysis, cough, wheezing, or crackles, diffuse patchy infiltrates on chest radiograph, and bronchoscopic evidence of blood in all lobes or hemosiderin-laden macrophages should be assumed to have diffuse pulmonary hemorrhage or hemosiderosis. The 4 categories of diffuse hemorrhage syndromes that occur in children are those associated with antglomerular basement membrane

antibodies in serum or tissue (eg, Goodpasture syndrome), those associated with an autoimmune-mediated disease (eg, systemic lupus erythematosus), those without any immunologic abnormalities but associated with antibodies to cow's milk, and idiopathic pulmonary hemosiderosis (IPH). All of these conditions are exceedingly rare.

*Goodpasture syndrome*, which occurs most commonly in men in their second and third decades, is characterized by diffuse pulmonary hemorrhage, antglomerular basement membrane antibodies in serum or tissue, and glomerulonephritis. The autoimmune diseases, which are more common in girls and women, rarely produce hemoptysis alone; more commonly, systemic manifestations occur, including fever, weight loss, malaise, anorexia, amenorrhea, rashes, or hypertension, as well as hemoptysis. Treatment for the pulmonary hemorrhage in these disorders should be directed at the underlying disease process.

In *Heiner syndrome*, or pulmonary hemosiderosis associated with cow milk allergy, infants and children exhibit failure to thrive, vomiting, gastrointestinal bleeding, and upper respiratory tract congestion, in addition to hemoptysis. Although the mechanism whereby the milk causes the multisystem damage is unclear, elimination of milk from the diet results in a dramatic improvement in the children.

In IPH, no evidence for an immune-mediated mechanism is found. Most children with IPH are diagnosed before the age of 7 years or after the age of 16 years. They usually have respiratory distress, bilateral alveolar infiltrates, and iron-deficiency anemia. The treatment of the acute exacerbations of IPH includes the use of high-dose oral or intravenous corticosteroids, as well as supportive care for the acute bleeding into the lungs. Controversy exists regarding the need for chronic immunosuppressive therapy, but most physicians caring for children with IPH use azathioprine, chloroquine, or cyclophosphamide to help maintain normal lung function and prevent further episodes of hemoptysis.

### Primary Pulmonary Neoplasms

Unlike in adults, primary pulmonary neoplasms are extremely rare in children, especially immunocompetent children. Fewer than 5% of tumors reported in the literature were associated with hemoptysis. The most common presentations of primary pulmonary neoplasms in children are fever, cough, and pleural pain.

### Hemoptysis in Children With a Preexisting Medical Condition

The most common chronic disease associated with hemoptysis is CF. Hemoptysis in CF, which usually begins in the second or third decade of life, can range from the production of blood-tinged sputum with excessive coughing to massive bleeding. Mild hemoptysis can be treated with conservative medical therapy, which includes bed rest, intravenous or oral antibiotics, withholding of chest physiotherapy, and administration of vitamin K. Massive hemoptysis has an annual incidence of 1% among patients with CF and carries a high mortality rate. Massive or recurrent hemoptysis in CF and other diseases is now treated with bronchial artery embolization. Despite a moderately high rate of recurrent bleeding, embolization can relieve symptoms for a significant period. A team composed of a pulmonologist, thoracic surgeon, and interventional radiologist should evaluate these patients before bronchial artery embolization.

Although the number of children with bronchiectasis has declined because of the decline of tuberculosis and the use of effective vaccines against measles and pertussis, children with immunodeficiencies, recurrent aspiration, and ciliary dyskinesias may develop bronchiectasis and have episodes of hemoptysis. In most cases, a history of a chronic, productive cough with purulent sputum and changes on the lung examination precede the hemoptysis. The diagnosis is made by high-resolution chest tomography, and management is similar to that of CF.

Hemoptysis is a well-recognized complication of congenital heart disease but is becoming an uncommon

problem because of advances in corrective cardiac surgery. Hemoptysis in primary or secondary pulmonary hypertension occurs as a result of thromboembolic events. In right ventricular outflow obstruction with increased bronchial arterial circulation, hemorrhage from enlarged and tortuous bronchial arteries can produce hemoptysis. Pulmonary vascular obstructive disease can lead to hemoptysis because of pulmonary hypertension, as well as to thrombosis. These vascular changes take years to develop and are usually first observed in adolescents.

### EVALUATION

As with any potential emergency, the first question to be answered about hemoptysis is, "Is it life threatening?" Because the expectoration of blood understandably arouses anxiety and fear, and because the blood can be mixed with saliva or phlegm and swallowed or aspirated, accurately determining the amount of blood is often difficult for children and their parents. In adults, the quantity of expectorated blood does not correlate with the seriousness of the underlying disease. In children, the gravity of the hemoptysis is determined more by the child's clinical status and ability to keep the airway clear than by the amount of blood expectorated. The greatest danger to a child with hemoptysis is not exsanguination but rather asphyxiation from aspirated blood. The management of the child with life-threatening hemoptysis is beyond the scope of this chapter. However, if the child has evidence of cardiorespiratory distress, hypotension, orthostatic changes, poor perfusion, pallor, tachypnea, tachycardia, mental status changes, arterial hypoxemia, or hypercarbia, then the stabilization and evaluation of the child should occur simultaneously in a pediatric intensive care unit.

Before summoning the bronchoscopist, echocardiographer, and interventional radiologist and scheduling pulmonary arteriography and radionuclide scanning, the primary care physician must ascertain whether the source of bleeding is indeed within the thorax. Thorough inspection of the oropharynx and nasal passages may identify an upper airway source of bleeding. Infants and young children with hemoptysis may not cough up blood but instead swallow the blood and vomit it later. Therefore, in infants, distinguishing hematemesis from hemoptysis is difficult. Examination of the blood-stained secretions may help differentiate the bleeding site so that it can be established whether the bleeding is from the respiratory tract or not. Table 161-2 describes how to differentiate hemoptysis from bleeding from other sources.

### History

As is the case for any sign or symptom with many possible causes, a detailed history of both pulmonary and nonpulmonary symptoms will often allow a tentative diagnosis to be made. The presumptive diagnosis can then be proved or disproved by the findings of specific laboratory tests and procedures. For a child or adolescent without any preexisting medical condition who displays a first episode of hemoptysis, the most common causes are acute infections of the tracheobronchial tree, pneumonias, and foreign-body aspirations.



**Table 161-2** Differentiation of Hemoptysis From Hematemesis and Upper Airway Hemorrhage<sup>a</sup>

CHARACTERISTIC	HEMOPTYSIS	HEMATEMESIS AND UPPER AIRWAY HEMORRHAGE
pH	Alkaline	Acidic
Color	Bright red	Dark red or brown
Consistency	Clotted, liquid, or frothy	Coffee ground
Symptoms	Cough	Nausea and vomiting
Gram stain	Macrophages	Food particles and epithelial cells

<sup>a</sup>Younger children and infants may swallow blood that originates from the lungs, which may seem to have a nonpulmonary source of bleeding.

Hemoptysis can be the presenting symptom for an autoimmune disorder or other immunologic abnormality, although this circumstance is rare. Travel to or from developing countries and areas that raise sheep may necessitate evaluation for mycobacterial, mycotic, or parasitic lung infections. Recurrent pneumonitis, sinus infections, and chronic sputum production may be indicative of bronchiectasis from CF, foreign-body aspiration, ciliary dyskinesias, or other chronic lung diseases. Other aspects of the history that will help focus the evaluation include recent trauma, easy bruising, changes in urine color, weight loss, arthralgias, previous heart disease or surgery, medication use, substance abuse, family history of bleeding disorders, surgical procedures, pica, fever, pleuritic chest pain, menstrual irregularities, and asthma not responsive to appropriate medical therapy. In adolescents with unusual or perplexing symptoms and normal findings at evaluation, factitious hemoptysis and Münchausen syndrome should also be considered. Factitious hemoptysis has been reported in children who underwent numerous invasive procedures, and, ultimately, the determination was made that these children were biting their oral mucosa to simulate hemoptysis.

### Physical Examination

Physical examination begins with a determination of the vital signs to decide the rapidity at which the examination should be conducted. A thorough inspection of the nasal passages and oropharynx is conducted to rule out a nonpulmonary cause of the hemoptysis. As the examination proceeds caudally, certain findings on inspection and auscultation may suggest a specific diagnosis. Cutaneous telangiectases with a murmur or bruit over the lung fields suggest hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Clubbing with or without adventitial breath sounds suggests bronchiectasis. A saddle nose and stridor suggestive of subglottic stenosis are often seen in patients with necrotizing granulomatous vasculitis. A pleuritic rub, acute pleuritic chest pain, and a history of oral contraceptive use or recent abortion suggest a pulmonary embolic event or other pleural-based lesion. Localized homophonous wheezing over a major airway or decreased breath sounds, with or without a cough, suggest an intraluminal obstruction such as an aspirated foreign body. Evidence of trauma to the thorax may be subtle and not always obvious. Thirty percent of children who experience major trauma to

other organ systems will be found to have thoracic trauma as well. Examination of the heart may provide evidence of pulmonary hypertension or a new murmur. Lymphadenopathy and hepatosplenomegaly should raise the possibility of a lymphoproliferative disease with an associated bleeding diathesis.

### Laboratory Evaluation

Numerous laboratory tests may be helpful, but they should be focused depending on the history and physical examination. If the patient has a compromised airway, then arterial blood gas measurement may help in the decision of how quickly the intensive care unit needs to be called. Urinalysis or specific serologic markers will help determine if the child has an immunologic disease that involves the basement membranes of both the kidneys and the lungs. A complete blood count with an eosinophil count may help differentiate a bacterial from a parasitic pneumonia. Although clotting studies are routinely ordered, they will invariably be normal because bleeding disorders do not generally cause spontaneous hemoptysis. Although skin tests for mycobacteria should always be performed, other skin tests, or serologic testing for fungi or other infectious agents, should be guided by clinical acumen. If sputum is produced or bronchoscopy is performed, then these pulmonary fluids should be cultured for bacteria, fungi, ova, parasites, and mycobacteria and stained for the presence of hemosiderin-laden macrophages. If warranted, early-morning gastric aspirates can be cultured and stained for microorganisms and macrophages.

### Imaging Studies

The history and physical examination should allow a tentative diagnosis and help decide what imaging studies or procedures need to be undertaken to make a definitive diagnosis. If the child is stable, then a chest radiograph should be obtained. Any abnormality on a chest film should be considered as a potential source for the hemoptysis, but a normal radiograph does not exclude the thorax as the source of bleeding. In approximately one-third of children with hemoptysis, the initial chest radiographic examination will reveal nothing abnormal. Findings on the chest film that help focus the evaluation include hilar adenopathy, an air-fluid level in an abscess, a mass, a cavitary lesion, mediastinal widening, or alveolar infiltrates. Alveolar infiltrates in a child with hemoptysis are a

common finding with autoimmune diseases that involve the lungs. Thickening of the bronchial walls with ring shadows and tramlines suggests bronchiectasis. If a foreign body is suspected to be the cause, then inspiratory and expiratory films or left and right lateral decubitus films may help localize the foreign body. If the foreign body is present and causes obstruction of an airway, then the side of the thorax that does not deflate normally on expiration or when dependent is the side with the foreign body. If the foreign body is embedded within the mucosa of the airway, or if only partial obstruction is present, then the standard chest radiograph may be normal.

The next imaging studies depend on the presumptive diagnosis because not every child with hemoptysis needs special radiographic studies. If the chest radiograph is normal or does not add any information to that obtained from the history and physical examination, then computed tomography (CT) or high-resolution computed tomography (HRCT) may be contributive. CT is effective for detecting parenchymal disease, and HRCT has replaced bronchography for diagnosing bronchiectasis. CT can identify airway abnormalities, elucidate abnormalities seen on chest radiographs, define mediastinal structures, and help categorize congenital pulmonary malformations and pulmonary vasculitis syndromes. CT may also serve as a road map for subsequent bronchoscopy.

Magnetic resonance imaging (MRI) is useful in looking for congenital vascular malformations and for the differentiation of structures within the mediastinum and hilum. Perhaps in the future MRI will supplant CT in the evaluation of hemoptysis, but for now the advantages of MRI do not outweigh its disadvantages, especially if excessive respiratory motion is present or the child's condition is unstable.

### Bronchoscopy

The timing and need for bronchoscopy, either rigid or flexible, depend on the stability of the child's condition and the suspected cause of the hemoptysis. Not every child with hemoptysis needs to undergo bronchoscopy; research indicates that hemoptysis is rarely the primary indication for bronchoscopy. If a child has rapid and complete resolution of hemoptysis after medical therapy, then bronchoscopy need not be performed. Indications for bronchoscopy include a diagnosis that is in question, massive hemoptysis, or an incomplete response to therapy.

No studies have compared the use of fiberoptic versus rigid bronchoscopy for evaluating hemoptysis in either adults or children. Both instruments can be used to administer therapeutic agents to the airways, sample bronchial fluids, and take biopsy samples. With the rigid bronchoscope, bronchoscopists have complete airway control: they can suction through a larger channel, sample suspicious lesions, and insert packing material to tamponade the bleeding. The rigid bronchoscope is the preferred instrument for removing foreign bodies from the airway. On the other hand, fiberoptic bronchoscopy does not require the use of general anesthesia; the scope is usually passed transnasally (so that the upper airways can also be examined), and it can be easily maneuvered into the

upper lobes and more distal airways. If a child with hemoptysis needs bronchoscopy, then fiberoptic bronchoscopy may be used for the initial evaluation. If an anatomic lesion or foreign body is discovered, then rigid bronchoscopy will be needed.

## HEMOPTYSIS IN THE NEWBORN PERIOD

Neonates who have a variety of congenital defects can develop localized hemoptysis and diffuse pulmonary hemorrhage in the newborn period. Arteriovenous malformations, extralobar sequestration, or hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome) can exhibit in the nursery as respiratory distress or mild to massive hemoptysis. All of these vascular malformations cause bleeding as a result of the abnormal connections between the bronchial and pulmonary circulations. The diagnosis of these lesions is made by CT scan with contrast, and children with these defects need to be hospitalized in a center that has a pediatric surgeon and an interventional radiologist.

Diffuse pulmonary hemorrhage is not an uncommon occurrence in infants of very low birth weight. The more premature the infant, the higher is the likelihood of hemorrhage. The pathogenesis of the diffuse bleeding is thought to be from effects of barotrauma on an immature pulmonary capillary endothelium. The risk for pulmonary hemorrhage increases slightly with the administration of exogenous surfactant therapy. Many nonpulmonary conditions have also been associated with diffuse hemorrhage in premature newborns, including central nervous system insults and coagulation and metabolic defects.

### WHEN TO ADMIT

- Evidence of hemodynamic instability
- Mental status changes
- High suspicion of tuberculosis
- Known heart disease
- Chronic lung disease (eg, CF, ciliary dyskinesias, immunodeficiencies)
- High suspicion of pulmonary neoplasm
- Sickle cell anemia, vaso-occlusive crisis, or acute chest syndrome
- Inability to protect airway
- Risk for pulmonary embolism
- Lung abscess
- Children younger than 1 year
- Foreign-body aspiration
- Pulmonary hypertension

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## Chapter 162

# HEPATOMEGALY

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### DEFINITIONS AND CLINICAL MANIFESTATIONS

Hepatomegaly is an enlargement of the liver resulting from an increase in the number or size of cells and structures within the liver. Although hepatomegaly usually manifests clinically as a palpable liver, not all palpable livers result from hepatomegaly. In healthy children, the liver edge may be palpable up to 2 cm below the right costal margin at the midclavicular line. Clinical estimation of the liver span has a much stronger correlation with hepatomegaly than does reporting the liver projection below the costal margin as a single indicator of liver size. The liver span is the distance between the upper and lower margins of the liver at the right midclavicular line. The upper margin should be determined by percussion and the lower edge by either percussion or palpation. Liver span has a curvilinear relation to age, height, weight, and body surface area. Studies have demonstrated no consistent sex differences in liver size. A normal liver span ranges from 5.9 cm ( $\pm 0.8$  cm) in the first week of life to 6.5 to 8 cm by 15 years of age. The upper edge of liver dullness is usually at the level of the fifth rib in the right midclavicular line. Radiographic assessment of liver size can be a helpful adjunct to the clinical examination. Ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and sulfur colloid scintigraphy have all been demonstrated to measure liver size reliably.

### DIFFERENTIAL DIAGNOSIS

The differential diagnoses of a palpable liver and hepatomegaly are presented in Box 162-1.

#### Palpable Liver Without Hepatomegaly

Several intrathoracic conditions may push the right hemidiaphragm down and thereby result in a palpable liver. For example, asthma, bronchiolitis, and pneumonitis may produce a palpable liver through hyperinflation of the lungs. Tension pneumothorax usually has other accompanying clinical features, including dyspnea, tachycardia, tracheal deviation, and hypotension. Congenital diaphragmatic hernias often manifest in the neonatal period with a scaphoid abdomen and the presence of bowel sounds in the chest. Other thoracic space-occupying lesions also can displace the diaphragm.

Abdominal sepsis with a subdiaphragmatic abscess may push the liver caudally. Riedel lobe is an occasional tongue-like process extending downward from the right lobe of the liver lateral to the gallbladder. A palpable liver without hepatomegaly also may be a normal variant.

#### Palpable Liver With Hepatomegaly

##### Inflammatory Disorders

Inflammatory liver disorders frequently manifest clinically with jaundice and a liver that is firm and tender to palpation. Viral hepatitis (including hepatitis A, B, C, D, and E) may be fulminant or insidious in onset. Hepatitis A may be anicteric in 50% of infected children younger than 4 years and in more than 80% of children younger than 2 years. Bacterial sepsis may result in hepatomegaly as part of a generalized process or a localized liver abscess. Toxic hepatitis may result from exposure to a variety of therapeutic and other chemical agents. Idiopathic neonatal hepatitis occurs with direct hyperbilirubinemia and may be difficult to distinguish clinically from congenital biliary atresia without a liver biopsy. Idiopathic neonatal hepatitis is characterized by marked infiltration with inflammatory cells in contrast to bile duct proliferation found in biliary atresia. Giant cell transformation is found in both conditions. In rare instances, autoimmune diseases such as systemic lupus erythematosus and sarcoidosis may involve the liver, leading to a hepatitis with hepatomegaly.

##### Infiltrative Disorders

Primary or metastatic neoplasia may infiltrate the liver and is often associated with other clinical findings. Malignant hepatic tumors manifest clinically with a hard, palpable liver. Benign tumors include large hemangiomas, which occasionally lead to a platelet consumption coagulopathy (Kasabach-Merritt syndrome) as a result of excessive trapping and destruction of platelets within the vascular bed. Clinically, a bruit may be heard over the liver in patients who have hemangiomas and arteriovenous shunts.

##### Storage Disorders

Several genetic enzyme defects result in excessive accumulation of metabolites in the liver. These conditions produce a smooth, distended liver. Many of these syndromes are also associated with other clinical features besides hepatomegaly. Fat and glycogen accumulation are well-known causes of hepatomegaly. Less frequently, copper accumulation results in Indian childhood cirrhosis or Wilson disease. Indian childhood cirrhosis, caused by genetic and environmental factors, produces jaundice and hepatomegaly predominantly in middle-income, rural Hindu children, but it also has been described in other parts of the world. Its onset is at approximately 1 to 3 years of age, usually with rapid evolution to cirrhosis and hepatic failure if left untreated. This disorder was previously thought to be uniformly fatal, but chelation therapy has shown promising results. Wilson disease, an autosomal recessive inherited disorder of copper metabolism, occurs with hepatomegaly in young children but does not generally manifest clinically until after 5 years of age. Children older than 10 years often have neuropsychiatric symptoms; they may also have hemolytic anemia.  $\alpha_1$ -Antitrypsin deficiency may occur with hepatomegaly, icterus, and acholic stools in the first week of life. Signs of chronic liver disease and portal hypertension are seen in older children.

### BOX 162-1 Differential Diagnosis of a Palpable Liver Without Hepatomegaly and With Hepatomegaly

#### PALPABLE LIVER WITHOUT HEPATOMEGALY

- Downward displacement of right hemidiaphragm
  - Hyperinflated lung (eg, asthma, bronchiolitis, pneumonitis)
  - Tension pneumothorax
  - Congenital diaphragmatic hernia
  - Thoracic tumors
- Subdiaphragmatic lesions (eg, abscess)
- Normal variant
- Aberrant lobe of liver (Riedel lobe)

#### PALPABLE LIVER WITH HEPATOMEGALY

- Inflammatory disorders
  - Viral hepatitis
  - Bacterial hepatitis (eg, abscess, sepsis)
  - Toxic hepatitis (eg, drugs)
  - Neonatal hepatitis
  - Autoimmune hepatitis (eg, systemic lupus erythematosus, sarcoidosis)
- Infiltrative disorders
  - Primary tumors
    - Hepatoblastoma
    - Hepatocellular carcinoma
    - Hemangioma
    - Focal nodular hyperplasia
  - Metastatic tumors
    - Lymphoma
    - Leukemia
    - Neuroblastoma
    - Wilms tumor
    - Histiocytosis
- Storage disorders
  - Fat accumulation
    - Obesity
    - Malnutrition
  - Reye syndrome
  - Cystic fibrosis
  - Diabetes mellitus
  - Lipid infusion
  - Metabolic liver disease
  - Lipidoses (eg, Niemann-Pick, Gaucher, Wolman diseases)
  - Glycogen excess
    - Glycogen storage diseases
    - Infant of mother who has diabetes
    - Beckwith-Wiedemann syndrome
    - Total parenteral nutrition
  - Copper accumulation
    - Indian childhood cirrhosis
    - Wilson disease
  - Miscellaneous
    - $\alpha_1$ -Antitrypsin deficiency
    - Hypervitaminosis A
- Vascular congestion
  - Suprahepatic
    - Congestive heart failure
    - Cardiac tamponade
    - Constrictive pericarditis
  - Intrahepatic
    - Hepatic vein thrombosis (Budd-Chiari syndrome)
    - Hepatic vein web
    - Vascular malformations
      - Cavernous hemangioma
      - Capillary hemangioma
      - Hemangioendothelioma
- Biliary obstruction
  - Congenital biliary atresia
  - Congenital hepatic fibrosis
  - Caroli disease

Excessive ingestion and accumulation of vitamin A can also result in hepatomegaly.

#### Vascular Congestion

Congestive heart failure, cardiac tamponade, and constrictive pericarditis all lead to impaired cardiac filling and pressure backup into the inferior vena cava and portal vein, all of which produce a smooth, distended, and tender liver. Other signs of cardiac decompensation, including dyspnea, cough, chest pain, and tachycardia, are usually present.

Budd-Chiari syndrome may be caused by a thrombus, mass, or web occluding the inferior vena cava or the hepatic veins and tributaries, resulting in an enlarged liver.

Vascular malformations produce hepatomegaly through several mechanisms, including hemorrhage

into the liver or high-output cardiac failure with secondary vascular congestion, or through the size of the malformation itself.

#### Biliary Obstruction

Biliary atresia occurs in approximately 1 of 8,000 births and is the most frequent reason for liver transplantation in children. The bile duct atresia may be extrahepatic, intrahepatic, or a combination thereof. The presence of jaundice, hepatomegaly, and acholic stools beginning during the first months of life in otherwise healthy-appearing infants is characteristic. Extrahepatic atresia can be corrected surgically, and intrahepatic atresia can be treated using the hepatoportoenterostomy procedure of Kasai. Nevertheless, many patients develop cirrhosis and portal hypertension requiring liver transplantation.



Congenital hepatic fibrosis is an autosomal recessive disorder that occurs in childhood with hepatosplenomegaly, portal hypertension, and bleeding esophageal varices. Up to 75% of affected children have associated renal disease. Histologic analysis reveals diffuse periportal and peribulbar fibrosis. Caroli disease is a congenital saccular dilation of intrahepatic bile ducts that is inherited in an autosomal recessive fashion. Symptoms are usually those of acute cholangitis manifesting in late childhood or young adulthood, with fever, icterus, abdominal pain, and a large, tender liver.

## EVALUATION

### Relevant History and Physical Examination

History and physical examination remain the cornerstone of establishing a prompt diagnosis in patients with hepatomegaly. A thorough history that explores not only gastrointestinal symptoms but also pulmonary and cardiac manifestations will often point in the right diagnostic direction. Physical examination of the liver should include an assessment of its size, consistency, texture, and tenderness. In addition, the liver should be auscultated with a stethoscope.

A firm and tender liver suggests an acute inflammatory disorder; a hard liver is often neoplastic. A smooth and exquisitely tender liver is found in conditions that cause vascular distention. Bruits are heard in arteriovenous malformations. Although a palpable liver may be a normal variant, the concomitant physical finding of an enlarged spleen usually suggests significant disease.

### Laboratory Testing and Imaging

Laboratory investigations should be directed at the suspected diagnosis. Liver function studies are usually necessary. The imaging study used most widely is ultrasonography, which is inexpensive, portable, reliable, and quickly obtainable in most settings. Liver masses detected on ultrasonography may be defined further by CT scanning or sulfur colloid scintigraphy. Hepatic angiography may be indicated in the evaluation of suspected vascular tumors. In patients with probable metabolic or genetic disorders, a percutaneous liver biopsy may be necessary to establish a diagnosis. In addition, the definitive diagnosis of a liver abscess can be made by ultrasound or CT-guided percutaneous liver aspiration.

## MANAGEMENT

Treatment should be aimed at the underlying disease entity. Patients with inflammatory hepatitis require supportive care; those who have bacterial infections should receive appropriate antimicrobials. Surgical excision is the definitive treatment for liver tumors. Chemotherapy may be a helpful adjunct in reducing tumor size either preoperatively or postoperatively.

The treatment of metabolic-genetic disorders includes dietary modifications and chelation therapy. Frequent small feedings of a high-protein, complex-carbohydrate diet, including continuous nighttime feeding via gastrostomy tubes, have been used successfully in managing glycogen storage disorders. Early treatment with D-penicillamine can prevent the progression of Wilson disease. In many cases, the

use of zinc acetate has been approved by the US Food and Drug Administration (FDA) for maintenance therapy of patients with Wilson disease, even if presymptomatic.

Exciting new developments have provided optimism for some disease entities for which no treatments were available in the past. For example, a synthetic enzyme, imiglucerase, has been highly effective in the treatment of Gaucher disease. Other recombinant glucocerebrosidases, recently approved by the FDA or pending approval, include vela-glucerase alpha (Shire HGT, Cambridge, MA, USA) and taliglucerase alpha (Protalix Biotherapeutics, Carmiel, Israel; Pfizer, NY, USA). Both successfully completed phase III trials and were proved safe and clinically efficient in the treatment of Gaucher disease. Although Indian childhood cirrhosis was previously thought to be uniformly fatal, chelation therapy with D-penicillamine has been shown to reduce mortality significantly if administered early in the disease.

### WHEN TO REFER

- Hepatomegaly with concomitant splenomegaly
- Palpation of a hard liver
- Hepatomegaly with distended abdominal veins
- Audible bruit over the liver
- Suspicion of malignancy

### WHEN TO ADMIT

- Liver failure
- Impending liver failure

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## Chapter 163

# HIGH BLOOD PRESSURE

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Hypertension is a well-established cause of substantial morbidity and mortality in adults, particularly in the later years of life. However, recent population-based studies have shown that during the past decade, mean blood pressure (BP) has

increased among children and adolescents. Furthermore, recent longitudinal cohort studies have revealed that elevated BP in childhood often continues into adulthood, predicting hypertension in young adulthood, and other studies have documented the familial nature of essential hypertension.

Even mild to moderate elevations of BP in children almost certainly warrant close attention, lifestyle modifications, and possibly therapy. Mild and moderate levels of hypertension in childhood are generally not associated with marked symptoms, but routine screening will identify a fair number of children who have either primary or secondary hypertension. Definitive therapy can decrease later morbidity. All pediatricians should be familiar with the basic aspects of hypertension in children, including the diagnosis of normal and abnormal BP, the causes of high BP, and the treatment options.

## DEFINITION OF HIGH BLOOD PRESSURE IN CHILDREN

The fourth report by the National Heart, Lung, and Blood Institute Task Force on Blood Pressure Control in Children based operational definitions of high BP in children on a combination of values found in healthy children, clinical experience, and consensus among leaders in the field. In children

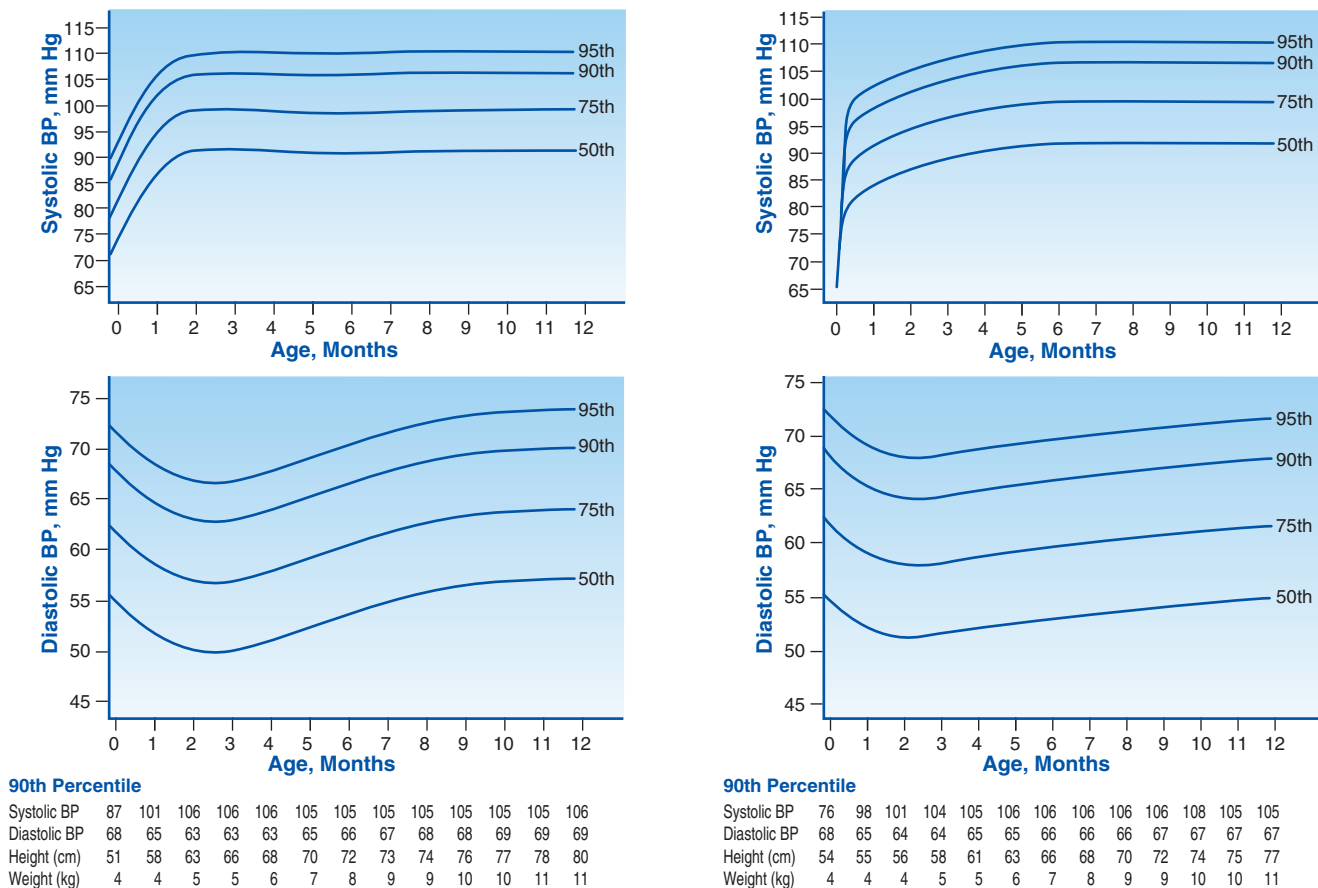
and adolescents, hypertension is defined as an elevated BP that persists on repeated measurements at the 95th percentile or greater for age, height, and sex in a healthy population. Stage 1 hypertension is defined as systolic and diastolic blood pressures that range from about the 95th percentile to 5 mm Hg above the 99th percentile, and stage 2 hypertension refers to systolic and diastolic blood pressures that are 5 mm Hg above the 99th percentile for age, height, and gender. High-normal or prehypertensive BP is defined as a BP between the 90th and 95th percentiles (normal systolic and diastolic BPs are less than the 90th percentile). Severe hypertension (with the risk of end-organ injury) is defined as BP greater than the 99th percentile.

Body size is the single most important determinant of BP in children and adolescents; thus, using accurate height percentiles is critical for correctly estimating BP percentiles (Figure 163-1 and Tables 163-1 and 163-2).

## FACTORS INFLUENCING BLOOD PRESSURE IN CHILDREN

### Age

BP tends to increase throughout the first 2 decades of life. The average systolic BP on the first day of life is 70 mm Hg, and it increases steadily for the next 2 months.



**Figure 163-1** Age-, sex-, height-, and weight-specific percentiles of systolic and diastolic blood pressure in boys (*left*) and girls (*right*) from birth to 12 months of age.

Table 163-1		Blood Pressure and Height Percentiles for Boys by Age														
		SYSTOLIC BP (MM HG)							DIASTOLIC BP (MM HG)							
AGE (YR)	BP PERCENTILE <sup>a</sup>	PERCENTILE OF HEIGHT							PERCENTILE OF HEIGHT							
		5	10	25	50	75	90	95	5	10	25	50	75	90	95	
1	50	80	81	83	85	87	88	89	34	35	36	37	38	39	39	
	90	94	95	97	99	100	102	103	49	50	51	52	53	53	54	
	95	98	99	101	103	104	106	106	54	54	55	56	57	58	58	
	99	105	106	108	110	112	113	114	61	62	63	64	65	66	66	
2	50	84	85	87	88	90	92	92	39	40	41	42	43	44	44	
	90	97	99	100	102	104	105	106	54	55	56	57	58	58	59	
	95	101	102	104	106	108	109	110	59	59	60	61	62	63	63	
	99	109	110	111	113	115	117	117	66	67	68	69	70	71	71	
3	50	86	87	89	91	93	94	95	44	44	45	46	47	48	48	
	90	100	101	103	105	107	108	109	59	59	60	61	62	63	63	
	95	104	105	107	109	110	112	113	63	63	64	65	66	67	67	
	99	111	112	114	116	118	119	120	71	71	72	73	74	75	75	
4	50	88	89	91	93	95	96	97	47	48	49	50	51	51	52	
	90	102	103	105	107	109	110	111	62	63	64	65	66	66	67	
	95	106	107	109	111	112	114	115	66	67	68	69	70	71	71	
	99	113	114	116	118	120	121	122	74	75	76	77	78	78	79	
5	50	90	91	93	95	96	98	98	50	51	52	53	54	55	55	
	90	104	105	106	108	110	111	112	65	66	67	68	69	69	70	
	95	108	109	110	112	114	115	116	69	70	71	72	73	74	74	
	99	115	116	118	120	121	123	123	77	78	79	80	81	81	82	
6	50	91	92	94	96	98	99	100	53	53	54	55	56	57	57	
	90	105	106	108	110	111	113	113	68	68	69	70	71	72	72	
	95	109	110	112	114	115	117	117	72	72	73	74	75	76	76	
	99	116	117	119	121	123	124	125	80	80	81	82	83	84	84	
7	50	92	94	95	97	99	100	101	55	55	56	57	58	59	59	
	90	106	107	109	111	113	114	115	70	70	71	72	73	74	74	
	95	110	111	113	115	117	118	119	74	74	75	76	77	78	78	
	99	117	118	120	122	124	125	126	82	82	83	84	85	86	86	
8	50	94	95	97	99	100	102	102	56	57	58	59	60	61	61	
	90	107	109	110	112	114	115	116	71	72	72	73	74	75	76	
	95	111	112	114	116	118	119	120	75	76	77	78	79	80	80	
	99	119	120	122	123	125	127	127	83	84	85	86	87	87	88	
9	50	95	96	98	100	102	103	104	57	58	59	60	61	61	62	
	90	109	110	112	114	115	117	118	72	73	74	75	76	76	77	
	95	113	114	116	118	119	121	121	76	77	78	79	80	81	81	
	99	120	121	123	125	127	128	129	84	85	86	87	88	88	89	
10	50	97	98	100	102	103	105	106	58	59	60	61	61	62	63	
	90	111	112	114	115	117	119	119	73	73	74	75	76	77	78	
	95	115	116	117	119	121	122	123	77	78	79	80	81	81	82	
	99	122	123	125	127	128	130	130	85	86	86	88	88	89	90	

Continued

**Table 163-1** Blood Pressure and Height Percentiles for Boys by Age—cont'd

SYSTOLIC BP (MM HG)					DIASTOLIC BP (MM HG)										
AGE (YR)	BP PERCENTILE <sup>a</sup>	PERCENTILE OF HEIGHT					PERCENTILE OF HEIGHT								
		5	10	25	50	75	90	95	5	10	25	50	75	90	95
11	50	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP, blood pressure.

<sup>a</sup>The 90th, 95th, and 99th percentiles are 1.28, 1.645, and 2.326 standard deviations, respectively, above the mean.From National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114(2):555–572.



Blood Pressure and Height Percentiles for Girls by Age																
			SYSTOLIC BP (MM HG)							DIASTOLIC BP (MM HG)						
AGE (YR)	BP PERCENTILE <sup>a</sup>		PERCENTILE OF HEIGHT							PERCENTILE OF HEIGHT						
			5	10	25	50	75	90	95	5	10	25	50	75	90	95
6		99	114	114	116	117	118	120	120	78	78	79	79	80	81	81
		50	91	92	93	94	96	97	98	54	54	55	56	56	57	58
		90	104	105	106	108	109	110	111	68	68	69	70	70	71	72
		95	108	109	110	111	113	114	115	72	72	73	74	74	75	76
7		99	115	116	117	119	120	121	122	80	80	80	81	82	83	83
		50	93	93	95	96	97	99	99	55	56	56	57	58	58	59
		90	106	107	108	109	111	112	113	69	70	70	71	72	72	73
		95	110	111	112	113	115	116	116	73	74	74	75	76	76	77
8		99	117	118	119	120	122	123	124	81	81	82	82	83	84	84
		50	95	95	96	98	99	100	101	57	57	57	58	59	60	60
		90	108	109	110	111	113	114	114	71	71	71	72	73	74	74
		95	112	112	114	115	116	118	118	75	75	75	76	77	78	78
9		99	119	120	121	122	123	125	125	82	82	83	83	84	85	86
		50	96	97	98	100	101	102	103	58	58	58	59	60	61	61
		90	110	110	112	113	114	116	116	72	72	72	73	74	75	75
		95	114	114	115	117	118	119	120	76	76	76	77	78	79	79
10		99	121	121	123	124	125	127	127	83	83	84	84	85	86	87
		50	98	99	100	102	103	104	105	59	59	59	60	61	62	62
		90	112	112	114	115	116	118	118	73	73	73	74	75	76	76
		95	116	116	117	119	120	121	122	77	77	77	78	79	80	80
11		99	123	123	125	126	127	129	129	84	84	85	86	86	87	88
		50	100	101	102	103	105	106	107	60	60	60	61	62	63	63
		90	114	114	116	117	118	119	120	74	74	74	75	76	77	77
		95	118	118	119	121	122	123	124	78	78	78	79	80	81	81
12		99	125	125	126	128	129	130	131	85	85	86	87	87	88	89
		50	102	103	104	105	107	108	109	61	61	61	62	63	64	64
		90	116	116	117	119	120	121	122	75	75	75	76	77	78	78
		95	119	120	121	123	124	125	126	79	79	79	80	81	82	82
13		99	127	127	128	130	131	132	133	86	86	87	88	88	89	90
		50	104	105	106	107	109	110	110	62	62	62	63	64	65	65
		90	117	118	119	121	122	123	124	76	76	76	77	78	79	79
		95	121	122	123	124	126	127	128	80	80	80	81	82	83	83
14		99	128	129	130	132	133	134	135	87	87	88	89	89	90	91
		50	106	106	107	109	110	111	112	63	63	63	64	65	66	66
		90	119	120	121	122	124	125	125	77	77	77	78	79	80	80
		95	123	123	125	126	127	129	129	81	81	81	82	83	84	84
15		99	130	131	132	133	135	136	136	88	88	89	90	90	91	92
		50	107	108	109	110	111	113	113	64	64	64	65	66	67	67
		90	120	121	122	123	125	126	127	78	78	78	79	80	81	81
		95	124	125	126	127	129	130	131	82	82	82	83	84	85	85

Continued

**Table 163-2** Blood Pressure and Height Percentiles for Girls by Age—cont'd

SYSTOLIC BP (MM HG)										DIASTOLIC BP (MM HG)									
AGE (YR)		BP PERCENTILE <sup>a</sup>	PERCENTILE OF HEIGHT							PERCENTILE OF HEIGHT									
			5	10	25	50	75	90	95	5	10	25	50	75	90	95			
16	99	131	132	133	134	136	137	138	89	89	90	91	91	92	93				
	50	108	108	110	111	112	114	114	64	64	65	66	66	67	68				
	90	121	122	123	124	126	127	128	78	78	79	80	81	81	82				
	95	125	126	127	128	130	131	132	82	82	83	84	85	85	86				
	99	132	133	134	135	137	138	139	90	90	90	91	92	93	93				
17	50	108	109	110	111	113	114	115	64	65	65	66	67	67	68				
	90	122	122	123	125	126	127	128	78	79	79	80	81	81	82				
	95	125	126	127	129	130	131	132	82	83	83	84	85	85	86				
	99	133	133	134	136	137	138	139	90	90	91	91	92	93	93				

BP, blood pressure.

<sup>a</sup>The 90th, 95th, and 99th percentiles are 1.28, 1.645, and 2.326 standard deviations, respectively, above the mean.From National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114(2):555–572.

It then tends to remain stable until 1 year of age, when it increases until adulthood. Diastolic BP increases slowly for the first week and then declines until 3 months of age. It then increases gradually until 1 year of age, when it returns to the level found in the first week. It again remains steady for the first 5 to 6 years, after which it begins to increase, along with systolic BP. Children tend to maintain the same BP percentile rank relative to their peers as they grow, a pattern that continues through adolescence, supporting the idea that primary hypertension begins in childhood. Normative data have been derived in premature infants in whom the average systolic BP is lower and increases with gestational age.

### Body Size

Body size is a major influence on BP in children. As in adults, the relationship between BP and weight in the teenage years is particularly prominent. Height is also related independently to BP at all ages. However, chronic hypertension is becoming increasingly common in adolescents, primarily because of increases in the prevalence of overweight and obesity. During the past 3 decades, obesity rates have more than doubled for children ages 2 to 5 and 12 to 19 years, and the rates have more than tripled among children ages 6 to 11 years. Presently in the United States, 9 million children older than 6 years are considered obese, with a body mass index (BMI) above the 95th percentile.

### Metabolic Syndrome

Childhood obesity has been associated with a cluster of risk factors for cardiometabolic disease characterized by combinations of insulin resistance, dyslipidemia, and hypertension, which some have termed metabolic syndrome. In turn, this syndrome is associated with the onset of type 2 diabetes and long-term atherosclerotic cardiovascular complications in both childhood and adulthood. Although metabolic syndrome is not currently well-defined, it is increasingly being recognized as a serious complication of childhood obesity. Analysis of the 1999–2006 National Health and Nutrition Examination Surveys found that nearly 1 million US adolescents (about 4% of the total) aged 12 to 19 years have metabolic syndrome; among 8- to 11-year-olds, national prevalence estimates of the syndrome's components ranged from 2% to 9%; and among overweight adolescents, the prevalence of the syndrome is nearly 30%. In addition, obstructive sleep apnea, an independent risk factor for resistant hypertension, is increasingly common in obese children.

Identifying and treating children and adolescents at the earliest stages of chronic disease should be the goal of clinical practice, yet no clear guidelines have been developed for determining the risk for metabolic syndrome or appropriate thresholds for risk factors.

### Ethnicity

In the United States, mean BP in adults differs among racial and ethnic groups. Non-Hispanic black adults have the highest prevalence and incidence of hypertension. However, the age at which BP begins to differ across racial and ethnic groups is unclear. According to the National Heart, Lung, and Blood Institute Growth and Health Study, among other reports, BP is

significantly higher for black girls than for white girls. The prevalence of primary hypertension in black adolescents is higher than that in their nonblack counterparts at lower ranges of BMI. In addition, Mexican American children have a higher mean-adjusted BP than do non-Hispanic white children. In many instances, a higher BMI explains the difference in BP between different ethnic groups. The increase in BMI in children in the United States has accounted for some of the increase in BP; however, other factors such as race contribute to higher BP levels.

### Genetics

Children from families with a history of hypertension tend to have higher BPs than do children from families without such a history, a relationship that generally supports the accepted conclusion that genes influence BP levels. Other cardiovascular risk factors among parents, including disorders of lipid and glucose metabolism, hyperuricemia, poor nutrition, passive smoking, and physical inactivity, are also significantly correlated with the cardiovascular risk factors of their children.

## CAUSES OF HIGH BLOOD PRESSURE IN CHILDREN

### Primary Hypertension

Primary hypertension (previously termed essential hypertension), long known to be the most common cause of hypertension in adults, used to be relatively uncommon in younger children. However, primary hypertension is now occurring more often in children, especially in adolescents. One recent study reported that about half of all children ( $N = 159$ ) seen in a hypertension clinic, albeit a selected population, had primary hypertension, leading to the conclusion that the prevalence of primary hypertension in children is increasing. However, the findings of a tertiary care sample may not generalize to the rest of the population. In this study, the diagnosis of primary hypertension occurred in the presence of obesity (56%) and a positive family history of hypertension (86%).

### Secondary Hypertension

Secondary hypertension is more common in children than in adults, and in most children, hypertension will be secondary to renal or renovascular causes (see Boxes 163-1 and 163-2).

Severe hypertension can occur in neonates and has been reported in 3% of premature infants. Hypertensive neonates often have evidence of congestive heart failure, respiratory distress, feeding difficulties, irritability, lethargy, coma, or seizures. In almost all cases, the hypertension is renal or renovascular in origin, most commonly from renal artery thrombi related to umbilical vessel catheterization.

Another common cause of high BP, especially from birth through the first year of life, is coarctation of the aorta. Medical therapy for the hypertension is usually effective, and the long-term prognosis is surprisingly good. High BP can also occur in infants who have bronchopulmonary dysplasia, patent ductus arteriosus, and increased intracranial pressure. Hypertension has been described in neonates undergoing

**BOX 163-1 Common Causes of Secondary Hypertension in Neonates and Infants**

- Renal artery thrombosis after umbilical artery catheterization
- Coarctation of the aorta
- Congenital renal parenchymal or structural disease
- Renal artery stenosis

**BOX 163-2 Common Causes of Secondary Hypertension in Children and Adolescents**

- Renal disease
- Renal artery stenosis
- Coarctation of the aorta
- Obstructive sleep apnea
- Prolonged treatment with steroids
- Amphetamines
- Mineralocorticoid excess
- Hyperthyroidism
- Pheochromocytoma
- Hypercalcemia
- Neurofibromatosis
- Neurogenic tumors
- Increased intracranial pressure
- Immobilization-induced essential hypertension

extracorporeal membrane oxygenation, possibly caused by volume overload.

Renal parenchymal disease remains the most frequent cause of hypertension in older children and adolescents, accounting for 60% to 80% of cases. Hypertension is evident at the initial diagnosis in almost 80% of all cases of acute poststreptococcal glomerulonephritis, and of those who are normotensive at diagnosis, nearly half will experience hypertension for a brief period during their illness. Hypertension is also associated with other forms of immune complex glomerulonephritis. It can be seen in membranoproliferative glomerulonephritis, systemic lupus erythematosus, diffuse proliferative glomerulonephritis, and immunoglobulin A nephropathy. Hemolytic uremic syndrome also is associated with hypertension, in proportion to the degree of arteriolar thrombosis. Nephrotic syndrome rarely leads to severe hypertension in children unless it is a manifestation of more serious renal disease. Reflux nephropathy, with 5% to 30% of affected children having high BP, is an important cause of hypertension. Hypertension also occurs with polycystic kidney disease and Wilms tumor, but is less common with other renal structural malformations.

Coarctation of the aorta is the most common nonrenal cause of hypertension in childhood, accounting

for 5% to 15% of cases. Hypertension can also occur immediately after repair of the coarctation and for years thereafter. The risk for postoperative hypertension seems to be lower if the lesion is repaired before 5 years of age. Renal artery stenosis, caused by fibromuscular dysplasia, Takayasu arteritis, Williams syndrome, or neurofibromatosis, constitutes 5% to 10% of childhood hypertension and may have marked symptoms caused by end-organ damage (congestive heart failure, left ventricular hypertrophy, retinal changes, and renal impairment).

Endocrinopathies must be considered as potential causes of hypertension in children. The problem may be endogenous, arising from conditions such as hyperthyroidism, hypercalcemia, adrenal cortical hyperplasia, or increased catecholamine production caused by a pheochromocytoma. The problem can also be exogenous, arising from ingestion or abuse of glucocorticoids or other steroids. Because of its association with high BP, the use of oral contraceptives should always be considered as a possible cause of hypertension in adolescent girls.

Various drugs can also be associated with hypertension, particularly sympathomimetics (cocaine, amphetamines, phenylephrine, and pseudoephedrine), and their use should be investigated in older children. Other drugs that can raise BP include nonsteroidal anti-inflammatory drugs, erythropoietin, and cyclosporine.

## MEASURING BLOOD PRESSURE IN CHILDREN

Appropriate BP measurement techniques are important because false-positive readings are more likely when proper care is not taken. All children older than 3 years should have their BP measured. However, certain high-risk groups should have their BP measured before age 3 years (see Box 163-3).

BP should be taken with children and adolescents seated, and with infants supine. In addition, to obtain the most accurate measurements, the child should not have recently ingested stimulant drugs or food and should sit quietly for 5 minutes before the measurement, with his or her back supported and feet on the floor. The BP should preferably be measured in the right arm for consistency and comparison with standard tables. The right arm should be supported, with the elbow at the level of the heart.

An appropriately sized BP cuff should be used to take the measurement. The width of the cuff's bladder must be at least 40% of the circumference at the midpoint of the upper arm, and its length sufficient to cover at least 80% of the circumference of the arm.

The cuff should be inflated to at least 30 mm Hg above the expected systolic BP, although too high a pressure in young children or infants may cause agitation. The stethoscope or Doppler crystal should be placed lightly over the brachial artery in the antecubital fossa, with the elbow remaining at the level of the heart.

Systolic BP is defined as the pressure at the onset of the first Korotkoff sound, and diastolic BP as the pressure at the fifth Korotkoff sound or at the disappearance



### BOX 163-3 Conditions Under Which Children Younger Than 3 Years Should Have Their BP Measured

- Prematurity, very low birth weight, history of neonatal hypertension or other neonatal complications requiring intensive care
- Congenital heart disease (repaired or nonrepaired)
- Recurrent urinary tract infections, hematuria, or proteinuria
- Renal disease or urologic malformations
- Family history of congenital renal disease
- Family history of moderate to severe hypertension
- Solid-organ transplantation
- Malignancy or bone marrow transplantation
- Treatment with drugs known to increase BP
- Other systemic illnesses associated with hypertension (eg, neurofibromatosis, tuberous sclerosis)
- Evidence of elevated intracranial pressure

Adapted from National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114(2):555–572.

or muffling of Korotkoff sounds. In some children, Korotkoff sounds can be heard until cuff pressure drops to 0 mm Hg. Measurements can be repeated with less pressure on the head of the stethoscope. If the fifth Korotkoff sound continues to identify very low pressures, the fourth sound can be recorded instead. BP should be measured twice at each visit, and the average systolic and average diastolic pressures should be recorded.

Automated BP devices can provide serial, noninvasive BP measurements in newborns and infants, in whom auscultation is difficult, and in the intensive care unit, where frequent BP measurements are needed. Automated measurements seem to correlate well with intraarterial readings. These devices are relatively simple to use, and they minimize observer bias and terminal digit preference. However, their reliability in the physician's office is less clear because they require frequent calibration and because reference standards have not been established. These devices may overestimate BP and the incidence of hypertension. Elevated BP obtained on automated devices should be confirmed by auscultation. Thus, in general, auscultation is the recommended method of measuring BP in children.

Ambulatory monitoring has recently been used to help establish the diagnosis of hypertension and to track diurnal variations of BP in older children. The monitors are worn on the arm for 24 hours and measure BP regularly throughout the day and night. Ambulatory monitoring is helpful specifically in evaluating white-coat hypertension, the risk for hypertensive end-organ injury, and efficacy of treatment and drug resistance, and to diagnose masked hypertension and hypotension that may occur with the use of antihypertensive drugs. In addition, ambulatory monitoring can be used to evaluate BP patterns in conditions such as episodic hypertension, chronic kidney disease, diabetes,

and autonomic dysfunction. BP typically decreases by more than 10% during sleep, and the absence of this decrease is strongly associated with masked hypertension and end-organ damage. Systolic and diastolic BPs above the 95th percentile for age, sex, and height in more than 25% of ambulatory measurements are considered abnormal and require treatment. However, ambulatory BP monitoring of children and adolescents should only be used and interpreted by persons experienced in treating pediatric hypertension.

## MECHANISMS OF BLOOD PRESSURE REGULATION

A complete discussion of the complex balance between hormonal and physical factors that regulate BP is beyond the scope of this chapter. Instead, the more important concepts are summarized here.

BP is the product of cardiac output and systemic resistance; therefore, anything that affects heart rate, stroke volume, blood volume, or peripheral resistance will alter BP. Peripheral resistance is affected not only by physical changes but also by the actions of various hormones on a given vascular bed. Angiotensin II, the major end product of the renin-angiotensin system, exerts the most hormonal control over BP. As a potent vasoconstrictor, it increases intravascular volume and is closely related to renal blood flow. Renin, the enzyme that stimulates the production of angiotensin II, is itself stimulated by volume depletion, hypotension, and salt depletion and is inhibited by volume expansion and salt loading. Several other hormonal systems also affect renin release, such as circulating catecholamines, glucagon, and adrenocorticotrophic and parathyroid hormones. Angiotensin II provides feedback that inhibits renin release; mineralocorticoids and antidiuretic hormone do the same.

Drugs can also affect renin release. Vasodilators and diuretics stimulate renin release, whereas mineralocorticoids and beta blockers inhibit it. Other hormonal systems also help regulate BP. Catecholamine secretion increases BP, and in the presence of a pheochromocytoma or neuroblastoma, it can cause severe hypertension. Mineralocorticoids and glucocorticoids affect BP, and adrenal hypertrophy and tumors may lead to severe hypertension. Also, obesity is characterized by increased sympathetic nervous activity and insulin resistance, which result in sodium retention and in increased levels of renin, angiotensin II, and aldosterone.

## DIAGNOSTIC EVALUATION

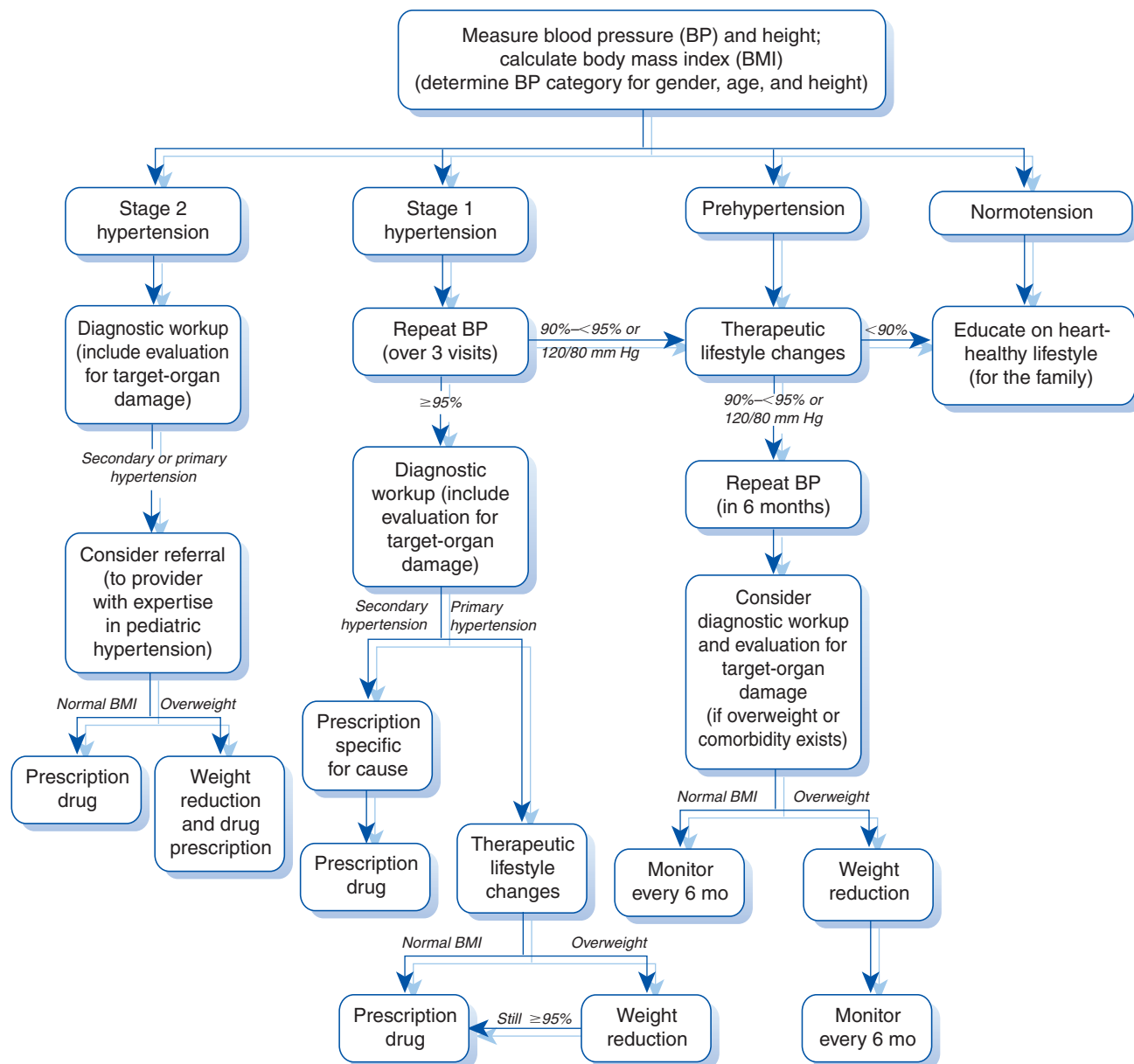
The first step in evaluating a child believed to have hypertension is to conduct a thorough history and physical examination. The medical history should include questions regarding all cardiovascular risk factors, symptoms suggestive of secondary hypertension, and possible target organ damage. In particular, attention should be paid to any history suggesting the recent onset of renal disease or of chronic urinary tract infections. In adolescents, the use of exogenous steroids, oral contraceptives, illicit drugs, tobacco, or alcohol should be specifically determined. A history of prematurity, patent ductus arteriosus, or bronchopulmonary

dysplasia and a positive family history, including age of onset of essential hypertension, systemic disease, or endocrinopathy, may help direct further evaluations. A systems review that includes the details of diet, salt intake, and exercise will be helpful in eliciting reports of symptoms associated with specific diseases that can cause hypertension.

Critical in the physical examination is the careful measurement of BP, as described earlier, with special attention to using an appropriately sized cuff and good technique. BP should be measured in all 4 extremities, and the radial, brachial, and, most important, femoral pulses should be assessed. To identify any abnormalities, a complete examination should include an examination of the optic fundi; calculation of

BMI (weight in kilograms divided by the square of height in meters); auscultation for carotid, abdominal, and femoral bruits; palpation of the thyroid gland; a thorough examination of the heart and lungs; examination of the abdomen for enlarged kidneys, masses, and abnormal aortic pulsation; palpation of the legs for edema and pulses; cutaneous examination for lesions associated with hypertension such as café au lait spots; and a neurologic assessment. These findings will further direct evaluation, which should be a stepwise investigation tailored to the age of the child and to the specific findings. For example, decreased femoral pulses may indicate coarctation of the aorta.

Hypertension can be diagnosed and managed with an algorithm (Figure 163-2). Ideally, BP values should



**Figure 163-2** Algorithm for diagnosing high blood pressure in children. (Modified from National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114[2]:555–572.)

be an average of at least 2 separate measurements or, even better, of measurements obtained on three separate occasions. All children should be screened for possible renal dysfunction by obtaining a urinalysis, complete blood count, serum urea nitrogen, creatinine, and serum electrolyte evaluation that includes glucose. A renal ultrasound may also be appropriate. If the family history is positive for essential hypertension, then a lipid profile that includes high- and low-density lipoprotein cholesterol and triglycerides will help assess cardiovascular risk (see Box 163-4).

If hypertension is severe and the initial diagnostic tests are inconclusive, or if BP remains elevated after initial treatment, more intensive investigations are indicated. If a renal cause is suspected, further imaging of the genitourinary system may be necessary. A stepwise, age-appropriate approach is suggested for evaluation for renovascular hypertension. In the neonate, color Doppler ultrasound of the aorta and renal vessels is a relatively simple, safe, noninvasive, and quick way of detecting aortic, renal venous, and arterial thrombi. This can be performed in conjunction with a renal ultrasound, which is necessary to look for congenital and parenchymal abnormalities. Additional diagnostic tools such as measurement of resistive indices and peak systolic velocities in the renal arteries increase sensitivity and specificity for diagnosing renal artery stenosis.

#### **BOX 163-4 Diagnostic Tests for Hypertension and Its Consequences**

##### **DIAGNOSTIC TESTS**

- Urinalysis
- Complete blood cell count with platelets and blood smear
- Serum electrolytes, blood urea nitrogen, creatinine, calcium, phosphorus, albumin
- Antinuclear antibody, serum C3 complement
- Plasma renin and aldosterone
- Renal ultrasound with Doppler study of renal vessels
- Urinary metanephrine, norepinephrine, and epinephrine
- Thyroid function tests
- Urine toxicology

##### **TESTS FOR END-ORGAN DAMAGE**

- Chest radiograph
- Electrocardiogram
- Echocardiogram
- Ophthalmologic examination

##### **ASSESSMENT OF ASSOCIATED RISK FACTORS**

- Serum lipid profile
- Fasting insulin and glucose
- Serum uric acid

A negative Doppler study, however, does not exclude renovascular hypertension. Nuclear scintigraphy with angiotensin-converting enzyme (ACE) inhibition has moderate sensitivity and specificity. It can be useful to evaluate differential renal function and predict renal functional deterioration with the use of ACE inhibitors.

Technical advances in recent years have improved the quality of images with high-resolution contrast-enhanced computed tomographic (CT) angiography, which can give 3-dimensional views of the renal arteries. The disadvantage is the exposure to radiation. Magnetic resonance angiography with gadolinium is also an alternative but requires sedation or general anesthesia and may not provide adequate spatial resolution compared with CT angiography. Both imaging modalities could still miss stenotic lesions of the renal arteries in small children. The gold standard for diagnosis of renovascular hypertension is digital subtraction angiography in which the visualization of blood vessels is enhanced by digitally subtracting images of background structures.

Plasma renin activity can be used to screen for renovascular hypertension and mineralocorticoid disease. Thyroid function or serum catecholamine tests may be helpful if hyperthyroidism or pheochromocytoma is suspected.

Cardiac evaluation is an important part of the examination. In addition to a thorough physical examination that includes feeling the femoral pulse, electrocardiography and echocardiography may identify coarctation of the aorta and will provide information about left ventricular mass. Left ventricular hypertrophy is the most prominent evidence of target-organ damage. Thus, in children with established hypertension, left ventricular mass should be assessed at diagnosis and periodically thereafter. Formal stress testing can help assess normal and abnormal BP responses to exercise, which might be especially informative in young athletes. Ambulatory BP measurements can help detect hypertension and determine the amount of time each day that BP is elevated.

#### **THERAPY FOR HIGH BLOOD PRESSURE**

The justification for treating children who have marked hypertension comes from the results of adult trials showing that reducing BP has positive effects on cardiovascular status and reduces the risk for target-organ damage. Pediatric studies showing beneficial effects on cardiovascular status are few.

Therapeutic lifestyle changes are generally recommended for children with mild or moderate hypertension. Initiating a low-salt or no-added-salt diet is reasonable because many patients will be salt sensitive. In addition, the intake of fresh vegetables, fruits, fiber, and low-fat dairy products should be increased.

Body size is a major determinant of BP, and weight loss is often associated with reduced systolic and diastolic pressures. Maintaining a normal weight in childhood reduces the likelihood of high BP in adulthood. Weight loss also is associated with decreased BP sensitivity to salt and decreases in other risk factors, such as dyslipidemia and insulin resistance.

Exercise as an adjunct to weight loss often reduces BP even more than weight loss alone. Increasing regular physical activity and decreasing sedentary activities are important in preventing hypertension in childhood and adolescence. Lifestyle modifications are recommended for all stages of hypertension because exercise reduces BP in all individuals regardless of body mass index. When children and adolescents do not respond to lifestyle modifications or have conditions such as stage 2 systemic hypertension, secondary hypertension, or established hypertensive target-organ damage, medications are indicated. Because the long-term effects of antihypertensive therapy in children are not well studied, a definite

indication for drug therapy is needed before starting treatment (see Table 163-3).

All classes of antihypertensive drugs lower BP in children; therefore, the choice of therapy depends on the underlying etiology. It is useful to determine whether hypertension is renin mediated or non-renin mediated. Volume-dependent hypertension as seen in poststreptococcal glomerulonephritis is responsive to diuretics. Diuretics are not desirable in active athletes because of the risk for hypovolemia and hypokalemia. ACE inhibitors and receptor blockers are useful in proteinuric renal disease for controlling hypertension, reducing proteinuria, and slowing progression of kidney disease. They have to be used

**Table 163-3** Antihypertensive Drugs Commonly Used to Manage Chronic Hypertension in Children

DRUG	INITIAL DOSE (mg/kg/day)	MAXIMAL DOSE	INTERVAL (TIMES/DAY)
<b>ACE INHIBITORS</b>			
Benazepril <sup>a</sup>	0.2	40 mg	1
Captopril <sup>b</sup>	0.15–0.5	6 mg/kg/day	3–4
Enalapril <sup>b</sup>	0.08–0.5	40 mg	1–2
Fosinopril <sup>a</sup>	0.1–0.6	40 mg	1
Lisinopril <sup>a</sup>	0.07	40 mg	1
<b>ANGIOTENSIN RECEPTOR BLOCKERS</b>			
Irbesartan <sup>a</sup>			
6–12 yr	2	75–150 mg	1–2
≥13 yr	2	150–300 mg	1–2
Losartan	0.7	100 mg	1–2
Candesartan	0.05–0.4	32 mg	1–2
Valsartan	1.3	160 mg	1
<b>ALPHA AND BETA BLOCKERS</b>			
Labetalol	1–4	1,200 mg	2
Atenolol	0.5–1.2	100 mg	1
Bisoprolol/HCTZ <sup>a</sup>	2.5/6.25 mg/day	10/6.25 mg	1
Metoprolol	1–2	200 mg	1–2
Propranolol	1–4	640 mg	2–4
<b>CALCIUM CHANNEL BLOCKERS</b>			
Amlodipine	0.1–0.6	20 mg	1–2
Felodipine <sup>a</sup>	2.5 mg/day	10 mg	1
Isradipine	0.15–0.2/dose	20 mg	2–4
Extended-release nifedipine	0.25–0.5	120 mg	1
<b>CENTRAL ALPHA-AGONIST</b>			
Clonidine (≥12 yr)	0.05–0.2 mg/day	2.4 mg	2–4
<b>DIURETICS</b>			
HCTZ	1–4	200 mg	1–2
Furosemide	0.5–2	6 mg/kg/dose	2–4
Spironolactone	1–3.3	200 mg	2–4
Amiloride	0.4–0.625	20 mg	1
<b>VASODILATORS</b>			
Hydralazine	0.75–1	200 mg	2–4
Minoxidil	0.1–0.5 mg/kg/dose	20 mg	2

ACE, angiotensin-converting enzyme; HCTZ, hydrochlorothiazide.

<sup>a</sup>Not recommended before age 6 years.

<sup>b</sup>The lowest effective dose of these drugs is used in neonates because it can cause acute deterioration in renal function.



with caution in female adolescents because of the risk for ACE inhibitor fetopathy. Beta blockers and calcium channel blockers can be used in children with hypertension and migraine. Beta blockers should not be used in active athletes because they decrease cardiac contractility, heart rate, and maximum oxygen uptake.

The noncardioselective beta blockers can cause hypoglycemia after intense exercise. They can be problematic for patients who have reactive airway disease or diabetes. Angiotensin blockers and calcium channel blockers have the least adverse effects in the physically active adolescent.

The basic medication strategy is to start with a single drug and assess the response. Additional drugs should be added one at a time, always attempting to target a different mechanism. In primary hypertension, the drug of first choice is usually an ACE inhibitor or a calcium channel blocker. The  $\alpha$ -agonists are generally considered to be second-line drugs. For children who have chronic primary hypertension but no hypertensive target-organ damage, the goal of drug therapy should be to reduce BP to below the 95th percentile for sex, age, and height. For children with chronic renal disease, diabetes, or hypertensive target-organ damage, the goal of therapy should be to reduce BP to below the 90th percentile for sex,

age, and height. Patients with stage 1 hypertension can be monitored every 3 to 6 months. Patients with stage 2 hypertension should be monitored more closely depending on the degree of control. Hypertension should be treated judiciously in patients with elevated intracranial pressure.

Note that ACE inhibitors and angiotensin receptor blockers are teratogenic. Avoidance of pregnancy is suggested in sexually active females.

### ATHLETIC PARTICIPATION BY CHILDREN WITH HYPERTENSION

Children should be encouraged to participate in non-competitive physical activity because regular aerobic exercise reduces both systolic and diastolic BP. Dynamic exercise greatly increases systolic BP and decreases diastolic BP, whereas isometric exercise increases both. Children with stage 2 hypertension need to be cautious about participating in competitive sports with highly static components (see Figure 163-3 and Table 163-4).

The dynamic component is the estimated percentage of maximal oxygen uptake ( $\text{max O}_2$ ). Higher uptake increases cardiac output. The static component is the percentage of maximal voluntary contraction. Higher contractions increase blood pressure.

Increasing Static Component ↑	III. High ( $>50\%$ MVC)	Bobsledding/luge, <sup>a,b</sup> field events (throwing), gymnastics, <sup>a,b</sup> martial arts, <sup>a</sup> sailing, sport climbing, water skiing, <sup>a,b</sup> weight lifting, <sup>a,b</sup>	Body building, <sup>a,b</sup> downhill skiing, <sup>a,b</sup> skateboarding, <sup>a,b</sup> snowboarding, <sup>a,b</sup> wrestling <sup>a,b</sup>	Boxing, <sup>a,c</sup> canoeing/kayaking, cycling, <sup>a,b</sup> decathlon, rowing, speed-skating, <sup>a,b</sup> triathlon <sup>a,b</sup>
	II. Moderate ( $20\%–50\%$ MVC)	Archery, auto racing, <sup>a,b</sup> diving, <sup>a,b</sup> equestrian, <sup>a,b</sup> motorcycling <sup>a,b</sup>	American football, <sup>a</sup> field events (jumping), figure skating, <sup>a</sup> rodeoing, <sup>a,b</sup> rugby, <sup>a</sup> running (sprint), surfing, <sup>a,b</sup> synchronized swimming <sup>b</sup>	Basketball, <sup>a</sup> ice hockey, <sup>a</sup> cross-country skiing (skating technique), lacrosse, <sup>a</sup> running (middle distance), swimming, team handball
	I. Low ( $<20\%$ MVC)	Billiards, bowling, cricket, <sup>d</sup> curling, golf, riflery	Baseball/softball, <sup>a</sup> fencing, table tennis, volleyball	Badminton, cross-country skiing (classic technique), field hockey, <sup>a</sup> orienteering, race walking, racquetball/squash, running (long distance), soccer, <sup>a</sup> tennis
		A. Low ( $<40\%$ $\text{max O}_2$ )	B. Moderate ( $40\%–70\%$ $\text{max O}_2$ )	C. High ( $>70\%$ $\text{max O}_2$ )
		Increasing Dynamic Component →		

**Figure 163-3** Classification of sports. This classification is based on peak static and dynamic components achieved during competition. It should be noted, however, that higher values may be reached during training. The increasing dynamic component is defined in terms of the estimated percent of maximal oxygen uptake ( $\text{max O}_2$ ) achieved and results in an increasing cardiac output. The increasing static component is related to the estimated percent of maximal voluntary contraction (MVC) reached and results in an increasing blood pressure load. The lowest total cardiovascular demands (cardiac output and blood pressure) are shown in **green** and the highest in **red**. **Blue, yellow, and orange** depict low moderate, moderate, and high moderate total cardiovascular demands. <sup>a</sup>Danger of bodily collision. <sup>b</sup>Increased risk if syncope occurs. <sup>c</sup>Participation is not recommended by the American Academy of Pediatrics. <sup>d</sup>The American Academy of Pediatrics classifies cricket as a low-static, moderate dynamic sport. (Adapted with permission from Mitchell JH, Haskell W, Snell P, et al. Task force 8: classification of sports. *J Am Coll Cardiol*. 2005;45(8):1364–1367.)

## HYPERTENSIVE EMERGENCY AND URGENCY

A hypertensive emergency or malignant hypertension is defined as a sudden elevation in blood pressure posing an immediate threat to the integrity of the cardiovascular system, kidneys, or central nervous system. Permanent neurologic damage, blindness, and chronic renal failure are some of the long-term consequences of malignant hypertension. Hypertensive emergency or crisis may occur in individuals previously not known to have hypertension or in those known to have chronic hypertension or kidney disease. Initial treatment should focus on reducing BP to alleviate acute symptoms, not necessarily to make the patient normotensive. Hypertensive emergencies should be treated with an intravenous antihypertensive medication that can steadily reduce BP, decreasing the pressure by no more than 25% over the first 8 hours and then gradually reducing it to normal over the next 24 to 48 hours (see Table 163-5). In contrast, hypertensive urgency is severe hypertension with no acute (or minimal) end-organ damage. It produces less serious symptoms, such as severe headache or vomiting. Urgencies can be treated by either intravenous or oral antihypertensives.

## CONCLUSION

Evidence of a link between the onset of hypertension in childhood and adult morbidity and mortality from end-organ damage is increasing. As pediatricians become more aware of the importance of monitoring BP in childhood and diagnosing hypertension earlier, they have the opportunity to decrease its long-term adverse cardiovascular effects. Even small reductions in BP can improve the health of children and their cardiovascular status later in life. Of equal

importance for physicians is the need to educate parents and children about the health dangers of obesity because this condition has become increasingly prevalent.

### WHEN TO REFER

- Stage 1 hypertension
- Stage 2 hypertension
- Specific conditions requiring referral
- Symptomatic essential hypertension
- Secondary hypertension
- Hypertension with diabetes
- Evidence of target-organ damage (left ventricular hypertrophy)
- Neonatal hypertension

### WHEN TO ADMIT

- Hypertensive emergencies (associated with manifestations in other organs)
- Hypertensive urgencies (severe BP elevation without other organ involvement)
- Acute glomerular diseases
- Poststreptococcal glomerulonephritis
- Hemolytic uremic syndrome
- Renal artery stenosis
- Fibromuscular dysplasia
- Previous umbilical artery catheter
- Neurofibromatosis
- Pheochromocytoma
- Coarctation of aorta
- Noncompliance with current antihypertensive medication
- Cocaine toxicity
- Dialysis patients with excessive volume expansion

**Table 163-4** Exercise Guidelines for Adolescents With Hypertension, by Intervention or Evaluation

	INTERVENTION	EXERCISE
Prehypertension	Daily physical activity Well-balanced diet Weight management Caffeine, drugs, tobacco, and stimulant use to be reviewed BP check every 6 months	No restriction Can participate in competitive athletic sports Encourage aerobic exercises
Stage 1 hypertension	Evaluation for end-organ damage Lifestyle modifications as with prehypertension	No restriction Can participate in competitive athletic sports if no end-organ damage Encourage aerobic exercises
Stage 2 hypertension	Evaluation for end-organ damage Evaluation by medical specialist Lifestyle modifications as with prehypertension Pharmacologic treatment	Restriction from high static sports Eligibility for competitive sports depends on extent of cardiac disease Encourage aerobic exercises, with intensity determined by extent of cardiac disease

**Table 163-5** Drugs Used to Treat Hypertensive Emergencies and Hypertensive Urgencies

HYPERTENSIVE EMERGENCY	ROUTE	DOSE	ADVERSE EFFECTS
Sodium nitroprusside	IV	0.5–8 mcg/kg/min	Thiocyanate toxicity with decreased renal function
Nicardipine	IV	1–3 mcg/kg/min	Headache; increased intracranial pressure
Labetalol	IV: infusion-bolus	0.25–3 mg/kg/hr; 0.2–1 mg/kg/dose Maximum, 40 mg/dose	Use with caution in hyperkalemia and congestive heart failure
Fenoldopam	IV	0.2–1.2 mcg/kg/min	Tachycardia; increased intracranial pressure
Enalaprilat	IV	0.005–0.01 mg/kg/dose	Acute renal failure and hyperkalemia
Hydralazine	IV	0.1–0.6 mg/kg/dose q4–6hr	Tachycardia, flushing, lupus-like syndrome
Nifedipine	Sublingual	0.1–0.25 mg/kg/dose Maximum 10 mg	Precipitous drop in blood pressure; tachycardia; headache
Esmolol	IV	Bolus 100–500 mcg over 1 min; 25–100 mcg/kg/min; can increase to 500 mcg/kg/min	Can cause congestive heart failure, bradycardia, and bronchospasm; contraindicated in cocaine toxicity
Clevidipine	IV	0.5–3.5 mcg/kg/min	Contraindicated in lipid disorders, egg and soy allergy
Phentolamine	IV	0.1–0.2 mg/kg/dose; not to exceed 5 mg/dose (0.05–0.1 mg/kg/dose for treatment of hypertension during surgery)	Orthostatic hypotension, tachycardia, gastrointestinal disturbances
<b>HYPERTENSIVE URGENCY</b>			
Furosemide	IV/PO	1–2 mg/kg/dose	Electrolyte disturbances
Clonidine	PO	0.05–0.3 mg	Rebound hypertension; sedation
Minoxidil	PO	0.1–0.2 mg/kg/dose Maximum 10 mg	Pericardial effusion

IV, intravenous; PO, by mouth.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *High Blood Pressure in Children* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/heart/Pages/High-Blood-Pressure-in-Children.aspx](http://www.healthychildren.org/English/health-issues/conditions/heart/Pages/High-Blood-Pressure-in-Children.aspx))

### Medical Decision Support

- *The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood pressure in Children and Adolescents* (Web page), National Heart, Lung, and Blood Institute ([www.nhlbi.nih.gov/files/docs/resources/heart/hbp\\_ped.pdf](http://www.nhlbi.nih.gov/files/docs/resources/heart/hbp_ped.pdf))

## AAP POLICY

National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114(2):555–576 (AAP endorsed) ([pediatrics.aappublications.org/content/114/Supplement\\_2/555](http://pediatrics.aappublications.org/content/114/Supplement_2/555))

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## Chapter 164

HIRSUTISM, HYPERTRICHOSIS,  
AND PRECOCIOUS SEXUAL  
HAIR DEVELOPMENT

Genna W. Klein, MD; Mariam Gangat, MD

## INTRODUCTION

The extent, distribution, and character of body hair depend on age, sex, ethnicity, and genetics. When evaluating a child or adolescent for the presence of body hair, understanding the history, physiology of the hair follicle, and hair development is essential in determining if the appearance of hair warrants immediate investigation, expectant management, or reassurance.

## BACKGROUND

## Definitions

*Hirsutism* is the presence of excessive terminal hair in androgen dependent and male pattern areas (especially in females). *Hypertrichosis* is excess hair growth, not limited to androgen-sensitive areas, and can be generalized or localized.

*Virilization* (or masculinization) is a result of (usually pathologic) androgen overproduction, with signs including clitoral or phallic enlargement, masculine body habitus, and deepening of the voice. *Pubarche* and *adrenarche*, although at times used interchangeably, more precisely refer to the onset of sexual hair noted on clinical examination and the biochemical rise of adrenal androgens, respectively. *Hyperandrogenism* is the presence of elevated androgens, manifested either clinically by hirsutism, virilization, acne, male-patterned baldness, or biochemically with elevated androgen levels.

## The Hair Follicle

The human body is covered by 5 million hair follicles. The only areas free of hair are the lips, palms, and soles. There are 3 main types of human hair, which are present at different times and at different locations in the human life cycle: lanugo, vellus, and terminal hair types. Lanugo hair sheds during fetal life, and is followed postnatally by vellus hair. Vellus hair (fine, short, and usually lightly pigmented or nonpigmented), is normally seen over the face and arms of children. Terminal hair (thicker, longer and pigmented), is normally found on the scalp, eyebrows, and eyelashes from the time of birth. Hair growth involves 3 asynchronous cycles: growth (anagen phase), rapid involution (catagen phase), and resting (telogen phase). The anagen phase comprises 8% to 85% of the cycle and determines the length and diameter of hair.

Androgens are the primary hormones involved in hair growth, regulating the prolongation of the anagen phase and transformation of vellus to terminal hairs. This occurs first during puberty in androgen-sensitive areas. Paradoxically, the same androgens

cause miniaturization or the transformation of terminal hair to vellus hair on specific areas of the scalp in genetically susceptible individuals, causing male-pattern alopecia (Figure 164-1).

The primary androgen affecting hair growth is testosterone. In normal pubertal females, up to 50% of testosterone production is from the ovaries and adrenal glands. The remainder is derived from peripheral conversion of weaker androgens to testosterone in adipose tissue and skin. Most of the testosterone in the circulation is bound to albumin (lower affinity) or sex hormone binding globulin (SHBG) (higher affinity); SHBG is therefore the primary regulator of free testosterone activity. Within hair follicles, type II 5 $\alpha$ -reductase regulates the conversion of testosterone to dihydrotestosterone (DHT), a more potent androgen because of its higher affinity for the nuclear androgen receptor.

INITIAL EVALUATION OF HAIR  
GROWTH

The evaluation of a patient with complaints of excess hair begins with a careful history and physical examination with specific points relevant to the chief complaint (Box 164-1).

In a preadolescent child, the chief complaint is usually that of body hair or odor. In an adolescent patient, the primary complaint depends on sex. Females typically complain of menstrual irregularities or dermatological manifestations of hyperandrogenism, including severe acne, hirsutism, or androgenic alopecia. Adolescent males come to attention much less frequently unless virilization is rapidly progressive or clinical signs such as alopecia or acne are excessive.

## HYPERTRICHOSIS

## Presentation

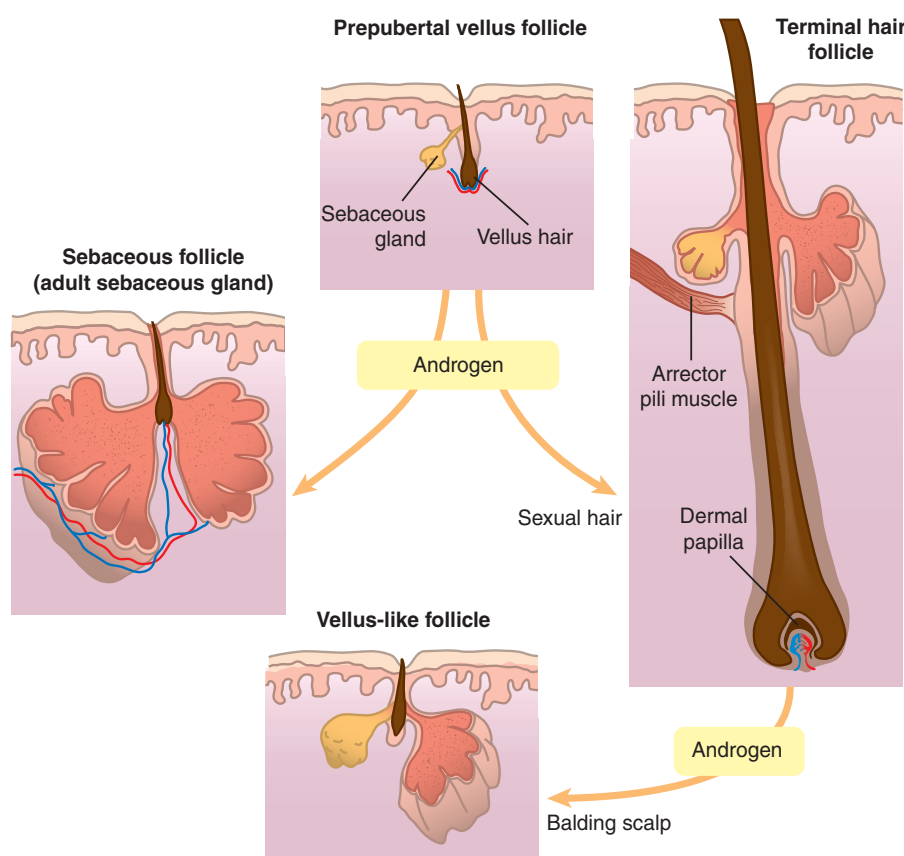
The initial task on examination is to differentiate between true sexual hair and hypertrichosis. The former will be dark, coarse, terminal hair that is limited to androgen-dependent regions, while hypertrichosis refers to excess hair growth relative to persons of the same age, sex, and ethnicity but excluding androgen-induced hair growth. If true sexual hair is abnormally present, androgen levels should be measured and, if elevated, the source of hyperandrogenism should be investigated (see Hyperandrogenism).

## Classification

Hypertrichosis is described based on type of hair (lanugo, vellus, or terminal), age of onset (congenital or acquired), distribution (generalized or circumscribed), and location (forehead, ear, neck, back). Although hypertrichosis is uncommon in children, there are many causes and associated conditions, some of which are listed in Box 164-2.

Classification of the different forms of congenital generalized hypertrichosis is difficult given its rarity and overlap of features. For example, *universal congenital hypertrichosis* is often used interchangeably with *Ambras syndrome*, characterized by extremely long vellus hair growth over the entire body (except





**Figure 164-1** Depending on location and androgen level, the prepubertal vellus hair follicle is transformed into a terminal hair follicle or adult sebaceous hair follicle. Scalp terminal hair follicles under androgen exposure can transform back to a vellus type hair follicle. (Reprinted with permission from Rosenfield RL. *Hirsutism*. N Engl J Med. 2005;353:2578–2588.)

palms, soles, and mucosae). Other experts think that Ambras syndrome is a separate entity. A careful examination with attention to the hair type and distribution is critical in classification. The mode of inheritance in most cases is autosomal dominant, although families with apparent X-linked transmission have been described. In a separate form, *congenital hypertrichosis lanuginosa*, affected infants present at birth with generalized homogeneous lanugo hair, which progressively sheds over the first year of life. The mode of inheritance is autosomal dominant although sporadic cases have been reported.

While the above types are rare, an interesting more common form of hypertrichosis is *prepubertal hypertrichosis*, in which the hair is noted at birth and progresses, with a predilection for (terminal) hair growth on the forehead, eyebrows, upper back, and upper limbs. Circumscribed forms of hypertrichosis also exist. An example of such is *lumbosacral hypertrichosis*, which, if seen on the newborn examination, should prompt an expeditious evaluation for an occult spinal dysraphism. Of note, hypertrichosis can be an early manifestation of pubarche, so the prepubertal patient should be observed for progression of the hair development specific to androgen-dependent areas.

### Treatment

Hypertrichosis can be a source of embarrassment for affected children and adolescents. Patients should be counseled that different treatment options are favored for different ages, types of hair, and body locations, but that all treatments have their limitations, pros, and cons. Treatments can be divided into different categories: physical cosmetic interventions (bleaching, waxing, plucking, trimming, shaving, chemical depilatories, electrolysis); light sources and lasers (of which there are different types); and pharmacological treatment. Further discussion on treatment modalities can be found in the discussion on *hirsutism* below. It is important to consider, however, that since hypertrichosis is androgen independent, antiandrogen therapies are not indicated for its treatment.

### HYPERANDROGENISM

When the history and physical examination are consistent with increased production of androgens, hormonal levels should be drawn to help determine the source. Causes can be broadly divided into the location of hormone production: adrenal, gonadal, tumor,

### BOX 164-1 Essential Elements in the History and Physical Examination for Complaint of Excess Hair

#### HISTORY

- General
  - Current age
  - Ethnicity
  - History of weight change
  - Height acceleration
- Hair Growth Description
  - Age of onset
  - Progression of hair growth
  - Location/distribution of hair
- Presence of Other Premature/Abnormal Pubertal Features (Body Odor, Irregular Menses)
- Medical Problems
  - Neurologic conditions
  - Developmental history
- Medications
  - Exposure to exogenous sources of androgens
- Birth History
  - Birth weight/length
  - Perinatal problems
- Family History
  - Maternal polycystic ovary syndrome (PCOS)

- Early infant demise
- Hirsute or infertile female relatives

#### PHYSICAL EXAMINATION

- General
  - Blood pressure
  - Anthropometric measurements
  - Dysmorphology
  - Masculinization
- Skin
  - Acne, oily skin
  - Café au lait spots, striae
- Hair
  - Type (lanugo, vellus, terminal)
  - Amount/severity
  - Location/pattern (androgen-dependent areas vs generalized)
- Thyroid enlargement
- Puberty
  - Tanner stage pubic hair
  - Females: breast Tanner staging, areolar hair, clitoromegaly, vaginal mucosa (estrogenization)
  - Males: testicular volume, phallic enlargement

### BOX 164-2 Causes of Hypertrichosis and Associated Conditions

#### CONGENITAL/GENETIC DISORDERS

- Congenital hypertrichosis lanuginosa
- Universal congenital hypertrichosis/Ambras syndrome
- Mucopolysaccharidosis
- Cornelia de Lange syndrome
- Trisomy 18
- Fetal hydantoin syndrome
- Fetal alcohol syndrome

#### SYSTEMIC ILLNESS

- Anorexia nervosa
- Hypothyroidism
- Malnutrition
- Malignancies

#### MEDICATIONS

- Corticosteroids
- Diazoxide
- Phenytoin
- Cyclosporine
- Streptomycin
- Minoxidil

or exogenous. Exogenous sources include androgenic medications and anabolic steroids.

#### Adrenal Hyperandrogenism

##### Adrenal Anatomy and Adrenarche

The adrenal cortex comprises 3 zones, each responsible for a different hormone pathway. The zona glomerulosa synthesizes aldosterone under regulation of the renin-angiotensin system. The zona fasciculata (glucocorticoid synthesis) and the zona reticularis (androgen synthesis) are regulated by the hypothalamic-pituitary-adrenal (HPA) axis. Corticotropin-releasing hormone (CRH) from the hypothalamus stimulates secretion of adrenocorticotrophic hormone (ACTH) from the pituitary gland, which in turn stimulates the adrenal gland. *Adrenarche* is characterized by the maturation of the zona reticularis, leading to increased androgen production and the appearance of pubic hair (*pubarche*). The main androgens derived from the adrenal glands are dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), androstenedione, and testosterone. Adrenarche has a role in sexual maturation; however, it occurs independently from gonadotropin-dependent puberty.

##### Premature Adrenarche

*Premature adrenarche* refers to the earlier than normal timing of this process: before age 8 years in girls and age 9 in boys. However, there is racial and ethnic

variation in the age at which puberty begins in normal children. Premature adrenarche is seen more commonly in females and black children. It has also been associated with fetal growth restriction, as seen in small for gestational age (SGA) babies and in prematurity. The concept of fetal programming and the association of pre- and post-natal weight gain with premature adrenarche, the development of obesity, metabolic syndrome, and PCOS offers attractive, yet incompletely understood mechanisms whereby nutritional, hormonal (GH-IGF system and insulin, for example) and epigenetic phenomena might link early processes with subsequent disease.

#### **PRESENTATION AND DIFFERENTIAL DIAGNOSES.**

These children usually present with pubic hair, initially noted perianally in girls and at the base of the penis in boys. Associated findings can include axillary hair and odor, oily skin, or mild acne. Signs of virilization are absent. Transient height acceleration and advancement of bone age may be present; however, final adult height is usually unaffected in cases in which the premature adrenarche is deemed benign (once other causes of premature hair development are excluded). Exposure to an exogenous hormone or drug must be ruled out because premature adrenarche caused by exogenous sources is reversible with removal of the source. Examples of exogenous causes include a family member who is using a testosterone gel without taking proper precautions for close contacts. Of more concern, premature adrenarche may be the first sign of a serious underlying disorder such as an androgen-secreting adrenal tumor or congenital adrenal hyperplasia (CAH). In these conditions, signs of virilization can be present and the bone age is significantly advanced.

**CONGENITAL ADRENAL HYPERPLASIA.** Congenital adrenal hyperplasia represents a group of autosomal recessive disorders involving a deficiency in 1 of the enzymes in adrenal steroid synthesis, leading to impaired cortisol production and increased ACTH production. Shunting of precursors proximal to the enzymatic block results in increased androgen production. The disease manifestations vary clinically and biochemically with each specific enzyme deficiency. The most common cause is 21-hydroxylase deficiency (mutations in the CYP21B gene located on chromosome 6) leading to decreased aldosterone and cortisol and increased production of androstenedione and testosterone. Although the classic form is usually diagnosed in infancy with salt-wasting in boys and ambiguous genitalia plus salt wasting in girls, a *non-classic 21-hydroxylase deficiency* typically presents later in life, with premature adrenarche, hirsutism, or menstrual abnormalities.

#### **Evaluation and Treatment**

If the findings are consistent with sexual hair development (with or without axillary hair, axillary odor, or acne) without any rapid progression, signs of virilization, or signs of true puberty (testicular enlargement in boys and breast development in girls), close follow-up is recommended. Baseline adrenal hormone levels (DHEA, DHEAS, androstenedione, testosterone, 17-hydroxyprogesterone) as well as a bone age

(radiograph of left hand and wrist) may be performed. In children with premature adrenarche, androgen levels are in the early-pubertal range and the bone age is usually within 2 standard deviations of chronological age.

If progression of pubic hair is rapid, signs of virilization are present, or there is moderate elevation of androgen levels or advancement of bone age, an ACTH stimulation test is warranted to rule out non-classical (or late-onset) CAH. Markedly elevated androgen levels or significant advancement of bone age suggests an androgen-producing adrenal or gonadal tumor. If a tumor is suspected, ultrasound or MRI for localization is necessary. Further, if there are signs of true pubertal development, other baseline or stimulation tests to evaluate the hypothalamic-pituitary-gonadal (HPG) axis as well as hypothalamic-pituitary imaging may be necessary. The evaluation and treatment of true precocious puberty will be discussed briefly below and in Chapter 185, Puberty: Normal and Abnormal.

Once a careful evaluation excludes these other conditions, reassurance and continued follow-up of growth and pubertal progression is necessary to make sure that the initial complaints and investigations do not herald a more serious condition. No specific medical treatment is indicated for premature adrenarche. Although premature adrenarche has been characterized as a benign condition (with many sources referring to it as *benign premature adrenarche*), studies in girls have shown associations with conditions such as PCOS and metabolic syndrome. Obesity and acanthosis nigricans are more common in patients with premature adrenarche. Offspring of women with PCOS are at higher risk for premature adrenarche, and brothers of women with PCOS have been found to have higher levels of DHEAS than brothers of unaffected women, suggesting a common cause or risk factor. These findings also lend support to a role for both adrenal and ovarian hyperandrogenism in PCOS, as opposed to it being merely an ovarian process (see section on PCOS). Although these associations among pre- and postnatal growth patterns, obesity, adrenarche, hyperandrogenism, metabolic derangements, and PCOS phenotypes have led to numerous hypotheses regarding common underlying hormonal mechanisms, a single cause remains elusive.

#### **Gonadal Hyperandrogenism**

The differential diagnosis of premature pubarche is age-dependent and may be the presenting sign of a more serious underlying endocrinopathy.

#### **Precocious Puberty**

Precocious puberty can be generally divided into gonadotropin-dependent or gonadotropin-independent precocity.

*Gonadotropin-dependent*, also referred to as *central* or *true* precocious puberty, results from abnormalities of the central nervous system that disrupt the balance between inhibitory and stimulatory factors. These abnormalities include congenital malformations, tumors, and acquired causes such as trauma, infection, surgery, radiation, or chemotherapy. A unique congenital

malformation is hypothalamic hamartoma, which is ectopically located neural tissue containing gonadotropin-releasing hormone (GnRH) secretory neurons. For most affected females, no specific cause of central precocious puberty can be identified, and precocity is therefore classified as idiopathic. GnRH agonists are the mainstay of treatment for central precocious puberty. The increased potency and continuous stimulation desensitizes the pituitary to stimulation from endogenous GnRH, thus halting further progression of puberty.

*Gonadotropin-independent* precocious puberty can be caused by gonadal tumors, McCune-Albright syndrome, and in males by familial testotoxicosis—a disorder caused by a missense mutation of the luteinizing hormone (LH) receptor. Peripheral precocious puberty can induce maturation of the HPG axis, and secondarily lead to true central precocity.

### Infancy

In the neonatal period, there is activation of the HPG axis, leading to androgen production. Peak testosterone production between 1 to 3 months of age coupled with a transient increase in the sensitivity of sexual hair follicles is thought to cause the appearance of pubic hair in the first few months of life. The pubic hair tends to occur in atypical locations—on the mons pubis in girls and on the scrotum in boys; it generally regresses spontaneously.

### Young Child

While generally not the presenting sign of normal central puberty, sexual hair can precede the initial signs of true puberty in up to 20% of normal boys and girls. Therefore, *premature adrenarche* may be the presenting sign of *premature central precocious puberty* (CPP), defined as occurring before age 8 years in girls and 9 years in boys. Chapter 185, Puberty: Normal and Abnormal, reviews pubertal development in normal and abnormal states. Briefly, puberty is the process of physical changes leading to sexual maturity, reproductive capability, and completion of skeletal growth. The process is initiated by *gonadarche* or reactivation of the HPG axis. The HPG axis is regulated by central inhibitory and stimulatory neurotransmitters, as well as peripheral factors such as nutrition and body mass composition. Increased pulsatile release of GnRH from the arcuate nucleus of the hypothalamus acts on the pituitary to stimulate LH and follicle-stimulating hormone (FSH) production. In females, LH acts on the ovarian theca cells and stimulates androgen production. Testosterone diffuses to the nearby granulosa cells where FSH stimulates aromatase conversion of testosterone to estrogen. In males, LH acts on the Leydig cells to stimulate testosterone production while FSH acts on the Sertoli cells to initiate and maintain spermatogenesis.

In girls, breast bud development (*thelarche*) is typically the initial physical change in puberty, which is then followed by the appearance of pubic hair. Height acceleration or growth spurt occurs early in girls, always preceding menarche. In boys, testicular enlargement (>3 mL in volume) is generally the first sign of puberty, followed by penile enlargement, and

development of pubic hair. The growth spurt occurs later in boys. A careful physical examination at the time of initial consultation, as well as continued follow-up for the development of other pubertal signs is crucial in determining if the child has isolated adrenarche or the evolution of CPP.

### Adolescent Female

In the adolescent female presenting with signs of hyperandrogenism, the differential diagnosis includes PCOS, idiopathic hirsutism, nonclassical CAH, exogenous exposure, or tumor. The diagnostics of the latter 3 conditions have been discussed previously.

**POLYCYSTIC OVARY SYNDROME.** Polycystic ovary syndrome (PCOS) was first described by Stein and Leventhal in 1935. It is the most common endocrine disorder affecting adolescent females and women of childbearing age. Although a single cause continues to elude scientists, much has been discovered regarding contributing factors and comorbidities. The diagnostic criteria have been adjusted and remain variable given different expert panel consensus statements. This, as well as imprecision with androgen assays, has made determination of true prevalence difficult. Most endocrinologists accept menstrual irregularities as the symptom of anovulation, combined with either biochemical or clinical evidence of ovarian hyperandrogenism as the pillars of diagnosis of PCOS. Although polycystic ovaries can support the diagnosis of PCOS, their absence does not rule out the diagnosis. As with the workup of the younger child for premature pubarche, it is imperative to exclude other causes of hyperandrogenism, such as exogenous exposure, tumor, and congenital adrenal hyperplasia, among others, prior to diagnosing a patient with PCOS. Further, other endocrinopathies can masquerade as PCOS, such as severe hypothyroidism and hypercortisolism.

PCOS in adolescence can manifest differently than in adult women. Whereas the chief complaint bringing the adult woman to medical attention may be menstrual irregularity or infertility, adolescent females might be more troubled by excess hair, acne, male-pattern alopecia, or menstrual irregularities, including even primary amenorrhea in some. Further, adolescent females with menstrual irregularities or weight gain and acne might be falsely led to believe that these findings are merely physiologic changes associated with pubertal development. This can lead to a delay in medical attention, evaluation, and treatment, as well as a negative effect on self-esteem.

PCOS is likely a polygenic, multifactorial condition. Multiple associated symptoms and biochemical derangements have been regarded as common to most females with PCOS. While obesity and insulin resistance, for example, play a role in many patients, there are lean women with PCOS as well. Fetal origins of PCOS have been studied, with attention to exposures in utero and the subsequent development of insulin resistance and hyperandrogenism, as in the child with premature adrenarche. Further, children born SGA have an increased risk for PCOS. Ovarian hyperandrogenism is a feature in PCOS, with the contribution of adrenal hyperandrogenism as well. The ovarian



theca cells produce weak androgens in response to stimulation by LH by the pituitary gland. In nonpathological states, the granulosa cells, under control of FSH, aromatize the androgens to estrogens. In PCOS an imbalance of LH/FSH leads to a decreased ability to aromatize excess androgen, and failure of the establishment of a dominant follicle, thus resulting in anovulation.

Although insulin resistance is a fundamental component of PCOS, it is unknown whether it causes, exacerbates, or functions as a marker for the condition. Females with PCOS are more insulin resistant than weight-matched females without PCOS. Whereas the liver, muscle, and adipose tissues are resistant to insulin in predisposed hosts, the ovary and adrenal glands maintain sensitivity to insulin. This results in enhanced ovarian hyperandrogenemia. Hyperinsulinism also decreases the level of sex hormone binding globulin (SHBG), which in turn increases the level of available free testosterone.

The manifestation of PCOS is variable across ages and ethnicities, and even within the individual. As mentioned, menstrual irregularities implying anovulation and clinical or biochemical hyperandrogenism are cardinal features. It is important to note that some girls and women with menstrual irregularity do ovulate, and conversely, some girls and women who bleed regularly are not experiencing ovulatory cycles. Most often, however, the presentation related to menses is oligomenorrhea or secondary amenorrhea, although primary amenorrhea and dysfunctional uterine bleeding are possible complaints as well.

The evaluation of a female suspected of having PCOS begins with a careful history and physical examination. Family history of hormonal disorders, infertility, hirsutism, or unexplained newborn demise (unrecognized congenital adrenal hyperplasia with adrenal crisis) should be explored. A complete past medical history, including birth data (for SGA), medications, and exposures is important, along with the timing of puberty and menstrual history. The presence of other findings related to the differential diagnosis of menstrual irregularities should be sought: disordered eating, large weight fluctuations, pregnancy, symptoms of thyroid disease, galactorrhea, and so on. The tempo of physical changes, including menstrual irregularities, and dermatological or other manifestations of hyperandrogenemia, if present, is crucial to determine if the process is gradual as opposed to sudden and rapidly progressive. The latter is more consistent with an exposure or an androgen-secreting tumor, and may be accompanied by more significant signs of virilization, including voice deepening and clitoromegaly, which are only rarely seen in PCOS.

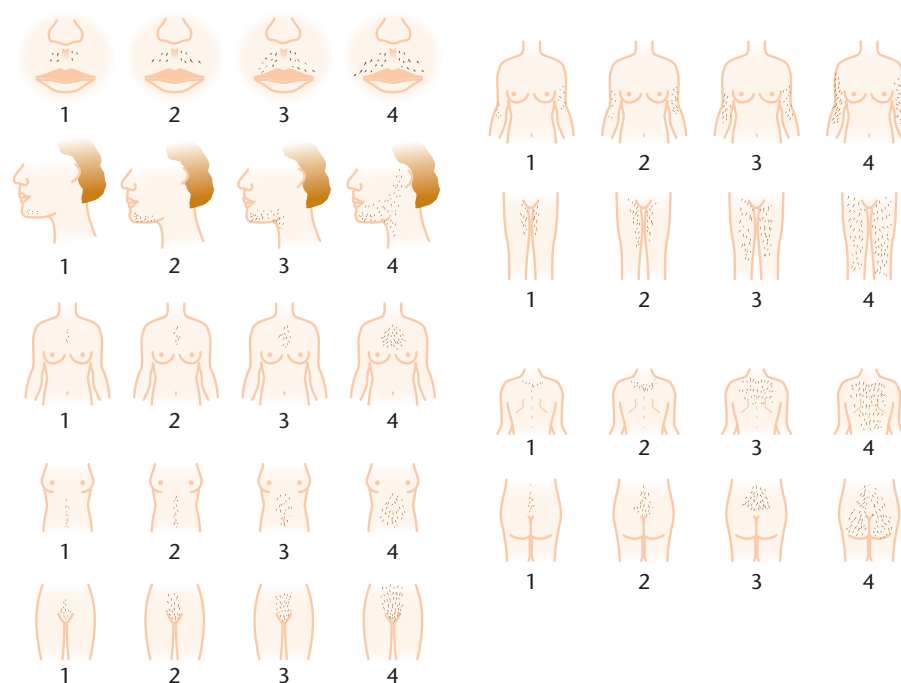
A complete physical examination is warranted to evaluate a female with menstrual irregularities, including a blood pressure check, body mass index measurement, careful inspection of optic discs for papilledema, skin for acanthosis nigricans, palpation of the thyroid, and breast examination for galactorrhea. Furthermore, specific attention should be given to the dermatological signs of hyperandrogenism, including acne (severity, location, extent), alopecia, and hirsutism. The modified Ferriman-Gallwey score is a widely

accepted method of quantifying hirsutism. This system estimates the amount of terminal hair in 9 areas: upper lip, chin, arms, thighs, chest, and upper and lower abdomen and back. Each area is assigned a score of 0 (absent) to 4 (extensive hair growth visible); therefore, the total score can range from 0 to 36. A score of 8 or greater indicates hirsutism; 8 to 15 indicates moderate hirsutism and greater than 15 indicates severe hirsutism (Figure 164-2).

Although widely used, this system has several limitations including the subjective nature of the assessment, inability to account for focal hirsutism, and lack of population based data that take into account racial and ethnic differences in body hair. Examination of the genitalia for clitoromegaly as well as the presence of estrogenized vaginal mucosa also should be done.

The laboratory evaluation of a woman suspected of having PCOS will be driven by the physician's index of suspicion and whether a previous workup for menstrual irregularities has been performed. If the patient has not been evaluated in the past, the full complement of studies may include a complete blood count and metabolic profile, LH, FSH, prolactin, thyroid function tests, pregnancy test, estradiol, and chromosomal analysis. Free testosterone is the single most helpful test in the diagnosis of PCOS. Alternatively, a total testosterone test with SHBG level can be done. Testosterone assays have been notorious for lack of standardization and precision, especially in the lower concentrations that are expected in women. Tandem mass spectrometry is available through commercial laboratories, and should be used if possible. DHEAS and androstenedione levels are often elevated in females with PCOS as well. Insulin resistance with hyperinsulinism is seen in many patients with PCOS, more commonly when the patient is obese. Because PCOS is associated with metabolic syndrome, affected females should be screened for glucose abnormalities. Appropriate evaluations could include a hemoglobin A1c, fasting glucose, and a 2-hour oral glucose tolerance test, along with fasting lipid panel and complete metabolic profile. The increased risk of obstructive sleep apnea in women with PCOS has been attributed to hyperandrogenism, rather than to obesity alone.

**IDIOPATHIC HIRSUTISM.** Idiopathic hirsutism is a diagnosis of exclusion, defined as hirsutism with regular ovulation and normal androgen levels. Many mechanisms have been implicated, including minor ovarian or adrenal functional hyperandrogenism, increased peripheral conversion of testosterone to DHT, or abnormalities in the androgen receptor leading to increased sensitivity of hair follicles to normal androgen levels. A careful history, including a complete menstrual history as well as details of the onset and progression of the hair growth, and physical examination are important to exclude other diagnoses. Of note, menstrual regularity does not preclude an anovulatory state. Thus it is recommended to obtain an early-morning free testosterone level in the following patients: women with moderate or severe hirsutism, women with hirsutism of any degree with sudden onset or rapid progression, or women with accompanying signs or symptoms suggesting malignancy or PCOS.



**Figure 164-2** Modified Ferriman-Gallwey (F-G) hirsutism scoring system. The F-G score should be used during clinical examination of a woman with hirsutism. (Reprinted with permission from Yildiz BO, Bolour S, Woods K, Moore A, Azziz R. Visually scoring hirsutism. *Hum Reprod Update*. 2009;16[1]:51–64.)

### Treatment

Treatment options for hirsutism can be divided into pharmacological therapy and cosmetic management. Education about reasonable expectations is crucial: the effects of pharmacological therapy do not become evident before 6 to 12 months of treatment because of the long duration of the anagen phase of the hair cycle. The choice of treatment depends on patient preference, the extent to which the area of hirsutism is amenable to cosmetic hair removal, and cost of treatment.

In PCOS, there are 4 levels of treatment: restoration of menstrual regularity; treatment of hirsutism, which is typically the most distressing symptom of androgen excess in adolescents; treatment of obesity and metabolic abnormalities if they exist; and improvement of psychological impairment that may be associated with any of the above.

The first line of pharmacological treatment for both idiopathic hirsutism and hirsutism in PCOS is oral contraceptive pills (OCPs), which inhibit ovarian androgen biosynthesis in 2 ways: suppression of gonadotropin secretion and increased hepatic SHBG production (thereby decreasing free androgen concentrations). OCPs usually combine a synthetic estrogen and progestin. Products that contain low-androgenic progestins, such as drospirenone or norgestimate, should be used. In addition to decreasing hirsutism, OCPs regulate menstrual cycles and protect the endometrium which is beneficial in PCOS. Side effects include breast tenderness, gastrointestinal discomfort, and worsening of headaches in a patient with migraines. The most

serious side effect is the risk of venous thromboembolism, which is increased in women older than 35, with a history of cigarette smoking, and with a personal or family history of a clotting disorder. A careful assessment of these risks is warranted. Drospirenone has been implicated in imparting an even higher risk of thromboembolism than other progestins, but it is not clear if that risk is clinically significant. The long-term effect of OCPs on metabolic risks (lipid abnormalities and glucose tolerance) have not been closely studied, and should be kept in mind when choosing a regimen.

If hirsutism persists after 6 months of treatment with an OCP, or if the use of an OCP is contraindicated or not desired, an antiandrogen can be used. In women of child-bearing potential, antiandrogen medications should not be used without adequate birth control measures because feminization of the male fetus can theoretically occur. Spironolactone, the most widely prescribed antiandrogen, is also an aldosterone antagonist and so should not be used in patients with renal failure, hyperkalemia or in conjunction with other medications that cause hyperkalemia. Spironolactone is a competitive inhibitor of the androgen receptor and also inhibits 5 $\alpha$ -reductase activity, thus demonstrating properties of both flutamide and finasteride, other antiandrogens which have been used in the treatment of hirsutism. A study comparing these 3 agents demonstrated similar efficacies in the treatment of hirsutism after 6 months. The long-term use of pharmacological therapy for hirsutism in adolescent females has not been studied.

Cosmetic forms of hair removal include both temporary and permanent methods. Temporary treatments include hair removal from the skin surface (depilation) and those that extract hairs from above the bulb (epilation). Depilation methods include shaving and the use of chemical depilatory agents. Shaving is the least expensive method. Contrary to common belief, shaving does not increase the diameter of the hair follicle or affect the rate of hair growth; however, shaving can cause irritation and folliculitis. Depilatory agents dissolve hair by reducing the disulfide bonds and peptides of hair keratin at the skin surface. They can cause irritant dermatitis. Bleaching, although not a method of hair removal, can camouflage dark hair. Epilation methods include plucking and waxing. Plucking can be painful and time-consuming, making it useful only in small areas such as the face.

Electrolysis and photoepilation are methods of permanent hair reduction, not removal. Electrolysis involves placing a fine needle in the hair follicle and applying an electrical current. Because each follicle is treated individually, the process is time-consuming and difficult if large areas need treatment. Photoepilation uses lasers and other light sources such as IPL to damage hair follicles without damaging the surrounding tissues. It is most effective in patients with light skin complexion and dark hair. Although hair follicles are destroyed, vellus hair follicles can remain, and in patients with hyperandrogenism these follicles can convert to terminal hair resulting in hair regrowth. Photoepilation requires multiple treatments, is expensive, and can cause dyspigmentation and scarring.

Eflornithine hydrochloride cream, which has been approved for the treatment of facial hirsutism, irreversibly inhibits ornithine decarboxylase (ODC) in hair follicles. Essential in hair growth, ODC catalyzes the synthesis of polyamines, small cationic molecules that play a role in cell proliferation in hair follicle development and growth. The cream can be added to photoepilation therapy for a more rapid initial response.

In adolescents with PCOS who have abnormalities of glucose or significant hyperinsulinism, treatment should be aimed at managing metabolic abnormalities in conjunction with the above measures. Dietary and exercise changes should be the first-line treatment for obesity and dyslipidemia. Although these measures can be extremely challenging, it should be emphasized to the patient that as little as a 5% to 10% weight loss can have significant clinical outcomes, including improvement in biochemical hyperandrogenism, menstrual regularity, and glycemic profiles. Lifestyle changes with small achievable goals should be set. The current evidence suggests that multiple dietary strategies can be successful as long as they are nutritionally adequate and can be sustained. Goals for exercise should focus on overall health improvement, not weight loss.

Glucophage, a biguanide insulin sensitizing agent, is the single oral antihyperglycemic drug approved for use in children as young as 10 years of age. It inhibits hepatic glucose production and increases insulin sensitivity in peripheral tissues. The common side effects of nausea and diarrhea can be minimized by starting

at a low dose, titrating upward as tolerated, and taking it with meals. Long-term treatment with glucophage has been associated with malabsorption of B<sub>12</sub>. The most serious, although rare, complication is lactic acidosis. Glucophage is contraindicated with renal or hepatic impairment, severe congestive heart failure, or a history of alcohol abuse. It is used along with OCPs in the treatment of PCOS, especially in patients with diabetes or impaired glucose tolerance. In patients in whom OCPs are contraindicated or not desired, glucophage has been used as monotherapy.

Although the treatment of infertility is not a common issue in adolescence, the implication of PCOS on future fertility should be discussed with affected young women. At the time when fertility is desired, referral to a reproductive endocrinologist is appropriate.

## SUMMARY

Abnormal or excessive hair development is a common presenting complaint in the pediatric population. A thorough history and physical examination will guide further evaluation and separate benign conditions from more serious pathology. Premature adrenarche and PCOS may be manifestations of the same disease process, which may have origins in fetal life.

### WHEN TO REFER

- Signs of adrenarche (pubic hair, axillary hair, and/or odor) prior to age 8 in girls and 9 in boys
- Signs of virilization (clitoromegaly, masculine body habitus) in girls at any age
- Signs of virilization (penile enlargement, deepening of the voice) in boys prior to age 9 or rapid virilization at any age
- Signs of puberty in girls (breast development, menarche) prior to age 8
- Signs of puberty in boys (testicular enlargement) prior to age 9
- Symptoms of PCOS (hirsutism, menstrual irregularities) in girls
- Metabolic syndrome (obesity, hypertension, insulin resistance or type 2 diabetes mellitus, dyslipidemia)

### WHEN TO ADMIT

- Hypertension secondary to suspected mineralocorticoid excess (congenital adrenal tumor [CAH]–C-11 hydroxylase deficiency)
- Central nervous system (CNS) symptoms (headaches, visual changes) secondary to CNS lesions
- Severe abdominal and/or pelvic pain secondary to suspected mass
- Marked hyperglycemia requiring insulin treatment

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Puberty—Ready or Not, Expect Some Changes* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)

- *What Is a Pediatric Endocrinologist?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/pages/What-is-a-Pediatric-Endocrinologist.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/pages/What-is-a-Pediatric-Endocrinologist.aspx))

### AAP POLICY

American Academy of Pediatrics Committee on Adolescence, American College of Obstetricians and Gynecologists, Committee on Adolescent Health Care. Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. *Pediatrics*. 2006;118(5):2245–2250 ([pediatrics.aappublications.org/content/118/5/2245](http://pediatrics.aappublications.org/content/118/5/2245))

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## Chapter 165 HOARSENESS

Sanjay R. Parikh, MD

### DEFINITIONS

Normal voice production requires the ability to generate subglottic air pressure during expiration, adduction of the vocal folds (previously called cords), reliable vocal fold mucosal wave production, and exit of air through the upper airway. Hoarseness is a symptom of vocal dysfunction that describes a breathy, harsh, coarse, strained, or raspy voice. In children, hoarseness can be used to describe both the quality of the voice and the quality of the cry. Causes vary by age group and can be attributed to infectious, anatomic, traumatic, inflammatory, neoplastic, neurologic, and iatrogenic sources. The prevalence of childhood hoarseness has been estimated as 6% to 7%. Hoarseness and stridor may occur distinctly or sometimes concurrently. Hoarseness should be discerned from stridor, which is a sign of turbulent airflow caused by obstructive lesions within the upper airway. See Chapter 197, Stridor, for a detailed discussion.

### DIFFERENTIAL DIAGNOSIS

Forming a differential diagnosis (Box 165-1, Box 165-2) for the hoarse child depends on the quality of hoarseness, progression of symptoms, related infection, history of surgery or trauma, and associated respiratory distress. The age of the patient at the onset of hoarseness is a useful way to organize the potential causes.

#### Neonate and Infant

Hoarseness that occurs at birth or shortly thereafter is most often attributable to congenital, traumatic or iatrogenic, neoplastic, or inflammatory sources. In this subgroup of prelingual patients, hoarseness often refers to a weak or breathy cry.

Vocal fold paralysis in the neonate is a well-known cause of hoarseness and stridor. Bilateral vocal fold paralysis, which is usually congenital, often causes respiratory distress and stridor, whereas unilateral vocal fold paralysis is more likely to exhibit initially as hoarseness or dysphagia. Central nervous system (CNS) disease such as the Arnold-Chiari malformation must be ruled out in cases of bilateral vocal fold paralysis. A weak or breathy cry in a neonate after thoracic or cervical surgery should alert the physician to the possibility of recurrent laryngeal nerve injury as a source of iatrogenic vocal fold paralysis. Additionally, traumatic intubation can cause arytenoid cartilage dislocation, with subsequent vocal fold immobility and hoarseness.

Congenital laryngeal webs form as a result of failure of the larynx to canalize fully during embryologic development. Webs may occur exclusively with hoarseness, but they may be associated with aphonia, stridor, and respiratory distress. Laryngeal webs vary from thin slips of tissue between the anterior areas of the vocal folds to complete laryngeal atresia, which is incompatible with life unless recognized immediately. Atresia or near-total atresia has been referred to as congenital high airway obstruction syndrome. Laryngeal saccular cysts are characterized by symptoms of airway obstruction and dysphagia. Saccular cysts are filled with mucinous fluid and arise as a result of an abnormal dilation of the saccule of the larynx secondary to secretory outflow obstruction.

Posterior laryngeal clefts are an uncommon laryngeal anomaly that result in an abnormal opening in the posterior larynx. Clefts can simply involve the posterior laryngeal commissure, but may extend through the cricoid inferiorly through the tracheoesophageal septum. Symptoms depend on the extent of the cleft; at birth, clefts typically cause aspiration, stridor, respiratory distress, and weak cry.

Subglottic hemangiomas classically occur between the first and sixth month of life, with varying degrees of respiratory distress, stridor, cough, dysphagia, and hoarseness. The natural history of hemangiomas is that of proliferation followed by involution. Subglottic hemangiomas can be unilateral, bilateral, or circumferential, and are more common in girls than in boys. Cutaneous hemangiomas of the head and neck are found concurrently in approximately 50% of cases of subglottic hemangioma.

A relationship may exist between pediatric and adult laryngeal disease and reflux. Whereas



**BOX 165-1 Differential Diagnosis of Pediatric Hoarseness by Category****CONGENITAL**

- Laryngeal anomalies
  - Laryngomalacia
  - Glottic webs
  - Subglottic stenosis
  - Laryngeal cleft
- Cystic lesions
  - Laryngocele
  - Saccular cyst
  - Thyroglossal duct cyst
  - Cervical bronchogenic cyst
- Angiomas
  - Lymphatic malformation
  - Hemangioma
  - Arteriovenous malformation
- Cri du chat syndrome

**NEUROGENIC (CONGENITAL AND ACQUIRED)**

- Supranuclear (eg, hydrocephalus)
- Nuclear (Arnold-Chiari malformation, Guillain-Barré syndrome)
- Peripheral (eg, myasthenia gravis, cardiovascular anomalies, recurrent laryngeal nerve trauma)
- Psychogenic hoarseness

**VOCAL FOLD ABUSE**

- Vocal fold nodules
- Vocal fold polyps

**NEOPLASIA**

- Papilloma
- Squamous cell carcinoma

**PHYSICAL VOICE CHANGE OF PUBERTY****INFLAMMATORY**

- Infectious
  - Viral laryngopharyngitis (upper respiratory tract infection)

- Viral laryngotracheitis (croup)
- Bacterial supraglottitis (epiglottitis)
- Rare infections: (*Candida*, diphtheria, tuberculosis, leprosy)
- Noninfectious
  - Laryngopharyngeal reflux
  - Allergic laryngitis
  - Foreign body
  - Angioedema
  - Rheumatoid arthritis
  - Relapsing polychondritis
  - Chemical irritation (smoking, second-hand smoke, toxic fumes, inhaled medications)

**TRAUMATIC**

- Hematoma
- Laryngeal cartilage fracture
- Impacted foreign body
- Postintubation
  - Arytenoid dislocation
  - Fold avulsion
  - Granuloma
  - Acquired glottic web
  - Subglottic stenosis
- Recurrent laryngeal nerve injury
  - Thyroidectomy
  - Tracheotomy
  - Cardiac surgery
  - Tracheoesophageal fistula repair
  - Tracheal resection
  - Penetrating neck wound

Adapted with permission from Friedberg J, El-Hakim H. Hoarseness. In: Bluestone CD, Stool SE, Kenna MA, eds. *Pediatric Otolaryngology*. 4th ed. Philadelphia, PA: WB Saunders; 2003.

gastroesophageal reflux (GER) refers to the backflow of stomach contents into the esophagus, laryngopharyngeal reflux (LPR) refers to the backflow of stomach contents into the throat, or laryngopharynx. Gastroesophageal reflux disease commonly produces emesis, dysphagia, sleep disturbance, and failure to thrive. The association among GER, LPR, and various neonatal laryngeal disorders such as hoarseness, posterior laryngitis, and silent aspiration, however, is an area of intense study that remains complicated and controversial.

**Older Child**

Older children and adolescents are subject to many of the same sources of hoarseness as adults. Infectious,

inflammatory, traumatic, and neoplastic conditions such as laryngitis, LPR, vocal nodules, and respiratory papillomata are the leading causes of hoarseness among older children.

Hoarseness of childhood from infectious disorders such as infective laryngitis, supraglottitis, and laryngotracheobronchitis rarely present a diagnostic challenge; however, concern over the airway should always take precedence. For example, hoarse voice may be an early indicator of the impending airway compromise seen in epiglottitis.

Although debate continues as to the specific role of LPR in the development of laryngeal lesions and hoarseness in children, infrequent reflux events have

### BOX 165-2 Differential Diagnosis of Pediatric Hoarseness by Age

#### 0 TO 6 MONTHS

- Traumatic intubation
- Iatrogenic: surgical
- Neurogenic: central or peripheral
- Neoplastic: hemangioma
- Congenital: web, cleft, cyst

#### 6 MONTHS TO 5 YEARS

- Traumatic: foreign bodies, intubation
- Infectious: URI
- Neoplastic: papillomas
- Behavioral, traumatic: nodules
- Inflammatory: allergy, LPR

#### 5 TO 13 YEARS

- Behavioral, traumatic: nodules
- Infectious: URI
- Inflammatory: allergy, LPR
- Neoplastic

#### 13 TO 18 YEARS

- Infectious: URI
- Inflammatory: allergy, LPR
- Behavioral, traumatic:
  - Male: mutational or transitional voice
  - Female: nodules
- Functional: muscle tension dysphonia

LPR, laryngopharyngeal reflux; URI, upper respiratory infection. Adapted and modified with permission from Smith ME, Gray SD. Voice. In: Bluestone CD, Stool SE, Kenna MA, eds. *Pediatric Otolaryngology*. 4th ed. Philadelphia, with permission PA: WB Saunders; 2003.

been shown to cause hoarseness in adults. LPR has also been found in association with pediatric laryngeal manifestations such as vocal fold nodules, posterior laryngitis, false vocal fold edema, vocal fold granulomas, functional voice disorders, and hoarseness. In addition, animal studies have shown that subglottic stenosis results when gastric acid is applied to the subglottic mucosa of dogs.

Vocal nodules arise from phonotrauma or voice abuse and are more common in boys than in girls. Symptoms may fluctuate based on aggravation by vocal abuse and respiratory tract infections. Sudden worsening of symptoms is sometimes seen when polyps swell from internal hemorrhage with excessive vocal trauma. Children with vocal nodules may share symptoms with other members of the immediate family who have similar vocal traits.

Airway trauma is also a potential cause of hoarseness in the older child and adolescent. Sources include blunt or penetrating injuries and intubation trauma.

Hoarseness of a progressive and unrelenting nature suggests a possible neoplastic cause. Ninety-eight

percent of pediatric laryngeal neoplasms are benign, and recurrent respiratory papillomatosis (RRP) is by far the most common lesion. RRP may be found on upper aerodigestive tract mucosal surfaces other than that of the larynx and have a characteristic cluster-of-grapes appearance. RRP may, however, be indistinguishable from the rare but ominous laryngeal squamous cell carcinoma of childhood.

Hoarseness in the adolescent years may also be of behavioral or psychogenic etiology. Mutational voice disorder occurs in male adolescents and results in hoarseness and high pitch during the stress of physiologic pubertal voice change. Paradoxical vocal fold dysfunction (seen more often in girls) is a disorder of psychogenic origin often misdiagnosed as asthma, which can produce episodic stridor or hoarseness.

## EVALUATION

### Relevant History

A thorough history is an essential part of the investigation of hoarseness. The age of the child is a critical factor in the development of an appropriate differential diagnosis, as is information on the quality of the voice with speech or crying, exacerbating or alleviating factors, and associated symptoms. Neurologic and congenital fixed anatomic lesions typically occur at birth, whereas inflammatory, neoplastic, traumatic, or iatrogenic causes of hoarseness occur later. The onset and course of dysphonia should be considered. Intermittent dysphonia may be related to infectious or inflammatory causes such as laryngitis, whereas persistent dysphonia may suggest a fixed anatomic lesion. A progressive, unremitting hoarse voice may suggest an enlarging neoplasm.

A review of medical and surgical history is also helpful. Patients with hoarseness who have symptoms such as regurgitation or vomiting, feeding difficulties, throat clearing, foreign body sensation, and cough may have underlying reflux.

Stridor that accompanies hoarseness should be investigated and treated expeditiously, because turbulent airflow resulting from airway obstruction may be life threatening.

### Physical Examination

A thorough physical examination, including a complete head and neck examination, should be part of the evaluation of pediatric hoarseness. Inspection of cranial nerve function and for craniofacial anomalies may reveal the underlying cause of a patient's hoarseness. Cutaneous head and neck hemangiomas, for example, may suggest a potential laryngeal hemangioma. Signs of aspiration during deglutition may be suggestive of sensorimotor causes of dysphonia such as vocal fold paralysis.

### Laryngoscopy

An essential part of the otolaryngologic physical examination is visualization of the larynx. Flexible nasopharyngolaryngoscopy, indirect mirror laryngoscopy, and rigid videostroboscopy are all methods for visualizing

the larynx that can provide useful, if not diagnostic, clues as to the source of a patient's hoarseness.

Indirect laryngoscopy using a mirror can be performed on cooperative children and can allow the physician to visualize gross disease and inflammatory changes in the larynx. This technique has largely been replaced by flexible fiberoptic nasopharyngolaryngoscopy, which provides clear views of laryngeal anatomy and function. Flexible endoscopy can be performed on virtually all age groups, although toddlers and patients who are developmentally delayed pose the greatest challenge to the examiner. Topical anesthesia can be used with topical decongestants to facilitate the examination. The flexible endoscope is gently passed through the nose or mouth. Examination in a nonmonitored setting, however, is not advisable if the patient has a tenuous airway or severe congenital cardiac anomalies.

Videostroboscopy uses a rigid, angled telescope placed gently into the oropharynx for dynamic examination of laryngeal anatomy and function. Examination requires a cooperative child. Videostroboscopy uses rapidly pulsed light to examine the vibratory characteristics of the vocal fold mucosa. Examinations are recorded on video to allow for repeated assessments viewed at different speeds to enhance visualization of the vibratory quality of the laryngeal mucosa. Vocal nodules or other lesions on the surface of the vocal fold will dampen the mucosal wave.

### Imaging

The role of diagnostic imaging in the workup of the hoarse child is of prime importance when the physician suspects CNS disease, external compression, malignancy, or external trauma.

Chest and neck plain-film radiographs may demonstrate mediastinal masses, cardiovascular anomalies, or abnormalities in the air column, suggesting possible infectious or obstructive diseases.

Computed tomography and virtual bronchoscopy are excellent methods for specifically defining the caliber of the airway and for delineating the site and extent of pathologic changes in airway caliber. Indications for laryngeal or neck computed tomography include congenital cysts, solid neoplasms, and external trauma.

Magnetic resonance imaging is helpful when suspicion exists of CNS disease such as the Arnold-Chiari malformation, and when evaluating possible airway hemangiomas or vascular malformations.

### Reflux Testing

Symptomatic or overt GER and LPR in the hoarse child may not necessitate expensive or invasive diagnostic studies. In the absence of identifiable disease in the hoarse child, however, investigation into LPR may be warranted. Although consensus on the role of LPR as it relates to various otolaryngologic manifestations is lacking, at least 1 study has used pH monitoring to suggest an association between pediatric reflux and hoarse voice in a cohort of children. Several diagnostic modalities exist for the workup of LPR, including pH monitoring, impedance testing, nuclear medicine

scintiscan, barium esophagoscopy, and direct laryngoscopy with or without biopsy.

Ambulatory 24-hour single-electrode pH monitoring remains the gold standard for the diagnosis of GER in infants and children. The double-electrode pH probe, with distal esophageal and pharyngeal electrodes, however, is thought to be the best method for diagnosing LPR and the otolaryngologic manifestations of GER.

Although pH-monitoring studies remain the gold standard for diagnosis of GER and LPR, they do not detect episodes of nonacidic reflux. Multichannel intraluminal impedance monitoring and nuclear medicine scintigraphy can measure both acidic and nonacidic episodes of reflux, which may play a role in such serious events as apnea, apparent life-threatening events, aspiration, and sleep disturbance. Nuclear medicine scintiscans have specificity between 83% and 100%, but they have been shown to be only 15% to 59% sensitive and lack a standardized technique, limiting the usefulness of comparisons between studies. Impedance monitoring evaluates the pH-independent change in intraluminal electrical resistance that occurs with the movement (antegrade or retrograde) of a bolus of food, liquid, or gas within the esophagus. This technique may be a reliable tool for evaluating the association between GER-related symptoms and nonacidic reflux events, and it may ultimately replace pH monitoring as the standard tool for detecting LPR in infants and children.

Barium esophagram has variable sensitivity and specificity for the diagnosis of LPR. It is useful mainly for detecting anatomic abnormalities such as hiatal hernia.

Laryngoscopy with biopsy may be the most specific test for LPR, but at least 1 study has failed to show a correlation between laryngoscopy and upper pH probe findings with significant laryngeal histopathologic inflammatory findings.

## MANAGEMENT

### Congenital Lesions

Management of hoarse voice resulting from unilateral or bilateral vocal fold paralysis is usually secondary to stabilization of the airway and management of dysphagia and aspiration. Tracheotomy is sometimes required in patients with bilateral vocal fold paralysis, but conservative management in select patients has been advocated. However, patients with congenital or acquired unilateral vocal fold paralysis often recover normal vocal quality by spontaneous resolution of the paralysis or by compensatory movement of the unaffected fold over time. Recovery has been noted up to 11 years after paralysis. In cases of persistent unilateral fold paralysis with persistent hoarseness, the treatment of choice remains speech therapy, although reports have surfaced of successful surgical vocal fold medialization techniques in the children.

Laryngeal webs are managed surgically, either endoscopically or via more extensive open laryngotracheal reconstruction techniques. The type of operation

depends primarily on the location and extent of the lesion, with thin webs being more amenable to endoscopic management.

Saccular cysts of the larynx are often managed endoscopically with excellent results via aspiration and marsupialization by sharp dissection or with the carbon dioxide (CO<sub>2</sub>) laser. Cyst recurrence, however, is well documented following endoscopic management, and open resection of the cyst may be necessary in these cases.

Posterior laryngeal clefts vary greatly in their extent and symptoms. Extensive or symptomatic clefts must be repaired as early as possible. Although endoscopic repair is possible in small clefts limited to the larynx and upper trachea, more extensive open techniques are used for larger clefts. Tracheotomy may also be placed in cases in which staged reconstruction of the cleft is necessary, and a gastrostomy tube is often needed to limit aspiration and protect the operative site following surgical repair of the cleft.

### Neoplasia

Subglottic hemangioma is a complicated airway anomaly without a universally accepted treatment. Numerous management options exist, including close observation, systemic or intralesional steroids, laser ablation, open surgical excision, and tracheotomy.

Recurrent respiratory papillomatosis associated with human papilloma virus (HPV), represents another airway tumor with a large number of accepted primary and adjuvant therapeutic modalities. CO<sub>2</sub> laser excision was developed as a treatment for RRP in the 1970s and remains a popular method for removing laryngeal papilloma, although it is associated with potentially severe sequelae such as airway fire, scarring, chronic laryngeal edema with airway compromise, vocal fold scarring, and poor voice. Nonlaser therapies such as cold dissection and powered débridement have also been used successfully for excision of RRP with comparable outcomes. Several adjuvant therapies, such as intralesional cidofovir,  $\alpha$ -interferon, indole-3-carbinol, bevacizumab, and heat-shock protein E7, have been used with varying degrees of efficacy and safety. There is hope that with the introduction of HPV vaccines there may be a future generational shift in the reduction of RRP.

### Inflammation and Infection

Behavioral and lifestyle modifications; pharmacotherapy using H<sub>2</sub> antagonists, proton-pump inhibitors, prokinetic agents, and antacids; and surgical therapy with fundoplication are acceptable for the management of GER and LPR in infants and children.

Viral laryngitis and laryngotracheobronchitis are generally treated conservatively, but they may require airway protection or intravenous steroids in severe cases. Bacterial infections such as epiglottitis and membranous laryngotracheobronchitis, though now rare, necessitate early airway protection and intravenous antibiotics directed against *Staphylococcus aureus* and *Haemophilus influenzae*, unless culture results direct differently.

### Trauma

The management of vocal fold nodules resulting from phonotrauma primarily relies on behavioral modification and speech therapy aimed at maximizing vocal hygiene. Only in rare circumstances is surgical excision indicated, because failure to correct the underlying voice misuse is likely to result in nodule recurrence.

Arytenoid dislocation resulting from intubation trauma can be adequately treated if recognized and reduced early under anesthesia with microlaryngoscopy.

Blunt laryngeal trauma resulting in hoarseness necessitates close observation and may require the use of systemic corticosteroids and tracheotomy in cases of severe laryngeal injury and edema. In adolescents with laryngeal fracture, open reduction and fixation may be required.

For patients with hoarseness related to iatrogenic unilateral vocal fold immobility, injection or external vocal fold medialization have been showed to be effective. Recurrent laryngeal nerve reinnervation procedures are also emerging as promising therapeutic options for long-term improvement.

## SUMMARY

Most cases of pediatric hoarseness result from benign, reversible, and self-limited disease; however, some causes of hoarseness are progressive, malignant, and potentially life-threatening. Thorough evaluation, precise diagnosis, and appropriate intervention are therefore essential.

### WHEN TO REFER

- Recognized cardiac, esophageal, or neurologic disease
- Progressive hoarseness
- Presence of cutaneous hemangioma
- Hoarseness after external trauma or uneventful intubation
- Poor speech intelligibility or psychosocial sequelae
- Hoarseness that has been present since birth

### WHEN TO ADMIT

- Presence of respiratory distress, stridor, tachypnea, or tachycardia
- Hoarseness following external trauma

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Hoarseness* (fact sheet), American Academy of Otolaryngology—Head and Neck Surgery ([www.entnet.org/content/hoarseness](http://www.entnet.org/content/hoarseness))

### Medical Decision Support

- *Clinical Practice Guideline: Hoarseness (Dysphonia)* (guideline), American Academy of Otolaryngology—Head and Neck Surgery ([www.entnet.org/content/clinical-practice-guideline-hoarseness-dysphonia](http://www.entnet.org/content/clinical-practice-guideline-hoarseness-dysphonia))



## SUGGESTED READINGS

Parikh SR, ed. *Pediatric Otolaryngology—Head and Neck Surgery: Clinical Reference Guide*. San Diego, CA: Plural Publishing; 2014

Schwartz SR, Cohen SM, Dailey SH, et al. Clinical practice guideline: hoarseness (dysphonia). *Otolaryngol Head Neck Surg*. 2009;141(3 Suppl 2):S1–S31

## Chapter 166 HYPERHIDROSIS

Nancy K. Barnett, MD

When excessive (beyond the norm for thermoregulation) localized sweating occurs in childhood, the child or the family usually expresses concern because the sweating is either odiferous or so intense that it interferes with hand functions (eg, holding a pencil) or foot functions. Axillary hyperhidrosis usually becomes more of a problem in adolescence because of the embarrassment of the sweat ring on clothing and the odor associated with bacterial degradation of apocrine sweat. The apocrine glands are stimulated at puberty by androgenic hormones. Palmar and plantar hyperhidrosis caused by eccrine sweat production may occur at any age. Eccrine sweat glands controlling thermoregulation are most numerous on the palms, soles, and axillae.

Palmoplantar hyperhidrosis is thought to be stimulated by anxiety, whereas axillary hyperhidrosis is probably stimulated by both heat and emotion. Both stop during sleep. Researchers have postulated that emotions and the temperature of the blood perfusing the hypothalamus stimulate the secretion of the hormones that regulate the autonomic nervous system's control of perspiration such that cholinergic sympathetic fibers hyperstimulate eccrine and apoeccrine sweat glands.

## EVALUATION

Excessive sweating that is not limited to the palms, soles, and axillae may be caused by and indicate a systemic disorder, such as infection, hypoglycemia, drug withdrawal, lymphoma, thyrotoxicosis, pheochromocytoma, or Riley-Day syndrome. These disorders should be considered in the presence of generalized increased perspiring.

## MANAGEMENT

Systemic anticholinergic agents may block acetylcholine, the sympathetic innervation terminal neurotransmitter to eccrine glands, and help hyperhidrosis, but the side effects of cholinergic blockage preclude their long-term use. The application of prescription 20% aluminum chloride (eg, Drysol) every other day has been an effective treatment for palmar sweating. Plantar hyperhidrosis also responds to aluminum salts, and absorbent powders (eg, Zeasorb) are used more

easily here than on the palms. Some authors report successful control of palmar and plantar hyperhidrosis with tap-water iontophoresis.

Palmar and plantar hyperhidrosis can be controlled by inhibiting sweat production with subepidermal injections of botulinum A toxin, which purportedly blocks the presynaptic acetylcholine release and is effective for as long as 12 months. Patients as young as 14 years have been treated in this manner, but temporary or, rarely, permanent muscle and nerve injury from the injections limits the toxin's usefulness in these locations.

For bromhidrosis (malodorous hyperhidrosis) of the soles, cleansing frequently with drying deodorant soaps and applying topical antibiotics (erythromycin or clindamycin) may help. The patient should go barefoot whenever possible.

Axillary hyperhidrosis is troublesome because continual sweating makes maintaining an effective antiperspirant in contact with the axillary skin difficult. One approach is to apply prescription 20% solution of aluminum chloride in anhydrous ethanol to the axillary vault. A problematic side effect of this treatment can be an irritant contact dermatitis, uncomfortable enough to require hydrocortisone cream for relief of inflammation. For individuals who have axillary hyperhidrosis and bromhidrosis, frequent clothing changes may be necessary, as may the use of topical antibiotics and deodorant powders. Propranolol and anxiolytics are options to reduce emotional stress.

Successful axillary sweat gland chemodenervation with intradermal botulinum toxin injections is being increasingly used and is an approved indication for the toxin. In extreme cases, when these measures fail and the patient is desperate for relief, local axillary skin can be excised or glands removed by less scarring curettage or liposuction techniques with reasonable expectation of success. Because of its attendant complications, ganglion sympathectomy cannot be recommended for most patients who have axillary hyperhidrosis. Hyperhidrosis is often life altering, and data exist to support management, even with significant measures like axillary suction curettage, because it improves quality of life.

Management of primary palmoplantar and axillary hyperhidrosis may have the secondary benefit of decreasing the significant risk for associated infections such as warts, dermatophytosis, and pitted keratolysis as well as eczematous dermatitis, which can coexist.

## WHEN TO REFER

- Hyperhidrosis that interferes with the function of a body part (eg, hand so slippery wet that the child cannot hold a pencil)
- Generalized excessive sweating
- Socially isolating hyperhidrosis as a result of odor or excessive drenching of clothing

## SUGGESTED READING

Jacobs AA, Desai A, Markus R. Don't sweat hyperhidrosis: a review of current treatment. *Cosmetic Dermatol*. 2005;18:725–731

## Chapter 167

# HYPOTONIA

Alfred J. Spiro, MD

Hypotonia indicates diminished resistance to passive movement around the range of motion of a joint. The commonly used term *floppy* refers to hypotonia, or weakness, or both. No readily administered, accurate test exists to quantify hypotonicity. Furthermore, tone, especially in a young infant, may vary greatly during the day or even during the examination. Hypotonia is not a diagnosis in itself; however, the origin of a neonate's floppiness may be obvious in, for example, overwhelming sepsis, meningitis, or marked hyperbilirubinemia. Central nervous system (CNS) abnormalities are commonly associated with hypotonia. Generally, central hypotonia involves diminished tone without appreciably diminished strength coupled with preserved or hyperactive deep tendon reflexes. In disorders of the motor unit (lesions of the anterior horn cell, peripheral nerve, myoneural junction, or muscle), strength is usually diminished, and tone may be reduced as a result. Hypotonia that is not associated with a motor unit disorder is more common than hypotonia caused by an underlying motor unit disorder. Testing of strength in infants and young children is difficult, even for experienced examiners; it can usually be done by observation of how strong a baby's kicking and pushing are, for example, or by functional testing.

## HYPOTONIA NOT CAUSED BY MOTOR UNIT DISORDERS

Disorders virtually anywhere in the brain may be associated with hypotonia. Global developmental delay is a common, but not universal, accompanying feature, as is microcephaly. Magnetic resonance imaging (MRI) of the brain may be helpful in documenting the lesion in some cases. In many instances, a specific diagnosis cannot be made. As infants who have hypotonicity get older, the abnormal tone may evolve into spasticity and the diagnosis of spastic quadriplegia, spastic diplegia, or other form of cerebral palsy becomes evident. A common misconception is that cerebral palsy is caused by obstetrical trauma; in most instances, the cause of cerebral palsy remains unknown. Nevertheless, a review of birth records, drug administration, and factors surrounding prematurity is indicated. On examination, deep-tendon reflexes are usually but not always hyperactive. Abnormalities of tone in patients with cerebral palsy are usually global; that is, both proximal and distal. Treatment of various types of cerebral palsy is supportive and symptomatic and usually requires a multidisciplinary team effort.

Several genetic syndromes, Down syndrome among the most common, are associated with hypotonia; the diagnosis can be made on clinical grounds and with appropriate genetic studies. Newborns and young infants with Prader-Willi syndrome may be extremely hypotonic and demonstrate a diminished level of consciousness. As these babies get older, tone may

improve, and they may become obese. They have characteristic almond-shaped eyes, short stature, and some degree of intellectual disability and hypogonadism; some have severe eating disorders and scoliosis, but these features are usually not present until school age. The clinical features coupled with analysis showing a deletion in the chromosome 15q11-13 region can generally establish the diagnosis.

Several of the Ehlers-Danlos syndromes may simulate hypotonicity, but the major feature of this group of connective tissue disorders is hyperlaxity of joints. Weakness is not a prominent feature.

Hypothyroidism and other metabolic disorders may be accompanied by hypotonia. Neonatal screening generally includes a test for hypothyroidism. If the diagnosis is not obvious on physical examination, then appropriate thyroid function studies can be done.

## HYPOTONIA CAUSED BY MOTOR UNIT DISORDERS

### History

In taking the history, the primary care physician should note whether hypotonia was present at birth or was recognized later. Parents of first children may have no basis for comparison and may not recognize an abnormality. Occasionally, photographs or family videos can be extremely useful in revealing abnormalities denied or not noted by parents. Breech presentation is common in babies who are subsequently diagnosed as having a motor unit disorder, but the reason for this has not been established. Congenital hip dislocation may be present in children who have central core disease, a congenital myopathy.

Thorough questioning can usually determine whether the hypotonia is improving or worsening or if weakness is periodic, as observed in hyperkalemic periodic paralysis (a rare autosomal-dominant disorder with onset usually in infancy or early childhood). The distribution of weakness, whether it is predominantly proximal, distal, or global, can also be identified with questions such as whether the baby or child moves the fingers and toes better than the large muscles of the pelvic and shoulder girdles. Details of the child's developmental milestones also can provide a clue to the nature of the lesion. For example, language development is normal in infantile progressive spinal muscular atrophy (SMA) and impaired in myotonic dystrophy.

Facial muscle weakness, observed in some congenital myopathies, can be considered if the parents state that the child sleeps with the eyelids partially open. Extraocular muscles, in addition to facial muscles, are abnormal in myotubular myopathy. Acquired autoimmune myasthenia gravis and myasthenic syndromes can occur in young children and may cause ptosis, extraocular muscle weakness, and, in some cases, generalized weakness and respiratory distress. Less severely affected patients may have only limited abnormal findings at the time of examination. Family videos taken at the times of the patient's maximal clinical involvement can be useful to document signs not seen in the examining room. Physicians should inquire about swallowing and sucking difficulties.

Details of the family history can be helpful because many of the motor unit disorders are genetic. The

presence of consanguinity suggests an autosomal-recessive entity. Examining parents and siblings can sometimes be revealing because some genetic disorders may be expressed quite subtly in family members and often are overlooked. Facial muscle weakness is a common example; patients do not seek medical attention if they cannot puff up their cheeks, whistle, or squeeze their eyelids closed completely, all features seen in certain congenital myopathies or facioscapulo-humeral muscular dystrophy. If early-onset myotonic dystrophy type 1 is thought to exist, then the child's mother and other family members should be examined for myotonia (slowed relaxation after a voluntary or induced muscle contraction) because neither percussion nor electrical myotonia is observed in infants or very young children.

### Physical Examination

The physician should conduct a thorough search for systemic disorders. Dysmorphic features such as high-arched palate and dental malocclusion are observed in some congenital myopathies, such as nemaline myopathy. An enlarged heart and congestive heart failure are observed in glycogen storage disease caused by acid maltase deficiency. Clubfoot deformity is commonly seen in the infantile form of myotonic dystrophy. Joint abnormalities and scoliosis are common in several motor unit disorders.

A striking paucity of spontaneous movement is observed in infantile progressive SMA; paradoxical respiration, in which the chest wall moves inward during inspiration instead of expanding, is also observed often.

In infants and in children younger than 5 years, manual muscle testing generally cannot be accomplished reliably, making observation of spontaneous movement and functional testing, such as the ability to hold the head erect, sit, roll over, and stand, and walk on heels and toes, mandatory. Assessing cranial nerve function should emphasize identifying facial and extraocular muscle weakness, as well as fasciculation and atrophy of the tongue. Fasciculation of the tongue, observed in infantile progressive SMA, should be assessed with the tongue not protruded and with the child not crying. Tremulousness of the outstretched fingers (minipolymyoclonus) is seen almost exclusively in SMA with a protracted course and in some hereditary sensorimotor neuropathies. Generally, deep-tendon reflexes are reduced or absent in motor unit disorders but preserved in most cases of myasthenia gravis. With hypotonia of central origin, reflexes are preserved or hyperactive; however, many exceptions to this rule can be found. The presence or absence of extensor plantar responses is also often difficult to assess in young children; these responses may normally be present at up to a year or more of age.

### Laboratory Studies

Laboratory studies include blood testing, neurophysiologic evaluation, and histologic examination of muscle. Laboratory studies should be goal directed and performed in an orderly manner. Serum muscle enzyme levels, particularly creatine kinase, are always markedly elevated in Duchenne and Becker muscular dystrophy but are not always increased in congenital myopathies. They are generally normal or only

minimally increased in spinal muscular atrophy. DNA studies for diagnostic purposes are readily available in many commercial and research laboratories (see Gene Tests or OMIM in the Tools for Practice section at the end of this chapter) for several motor unit disorders, including infantile progressive SMA, myotonic dystrophy, various hereditary sensorimotor neuropathies, selected mitochondrial myopathies, and Duchenne and Becker muscular dystrophy. When these disorders are thought to exist on clinical grounds, an appropriate DNA study may be all that is needed to document the diagnosis. Thus, a child who has classic infantile progressive SMA can be spared many painful studies when the DNA study is conclusive. Other noninvasive studies, such as computed tomography, MRI, or sonographic imaging of muscles, can assess muscle mass accurately; in the presence of very small muscles, imaging is indicated if a muscle biopsy is contemplated. Electromyographic studies can be useful in the diagnosis of motor unit disorders, but because of the pain involved and the need for sedation in some cases, they should be used with discretion when DNA studies are not helpful. Nerve conduction studies can be extremely useful in distinguishing the various types of peripheral neuropathies seen in infants and children. Repetitive stimulation studies are very helpful in diagnosing disorders of the myoneural junction, including infantile botulism, but testing can be quite painful. Physicians who are experienced in the particular technical and other problems encountered in this age group should perform all electrodiagnostic studies in young children.

Muscle biopsies, performed either with a special needle or surgically, are most useful in myopathies such as congenital myopathies, congenital muscular dystrophy, metabolic myopathies, and mitochondrial disorders. Many specialized analytical studies are available when needed. In virtually all instances when a biopsy is performed, sections should be taken for histochemical, biochemical, ultrastructural, and genetic studies, although not all of these studies are used in every case.

### Selected Motor Unit Disorders

#### *Anterior Horn Cell Disease*

Given the near elimination of paralytic poliomyelitis in the United States, the various types of infantile progressive SMA constitute the major disease in this category. Eponyms have been applied to these disorders, including Werdnig-Hoffmann disease, but these terms may be misleading and confusing. Now, a much more useful operational classification of SMA (Table 167-1) is commonly used.

In all types of infantile progressive SMA, cognition is normal, as are extraocular muscles. Weakness and muscle wasting are proximal more than distal and are more pronounced in the legs than in the arms. Fasciculation of the tongue and minipolymyoclonus (in types I and II, respectively) are observed often, and areflexia and normal sensation are the rule. Joint contractures and scoliosis may develop, especially in type II. All forms are autosomal recessive, with the responsible gene having been located at 5q11-q13. A deletion of the survival motor neuron gene has been identified in most patients, making this situation useful for diagnostic purposes and for prenatal diagnosis. Recent advances



**Table 167-1 Spinal Muscular Atrophy**

TYPE	AGE OF ONSET	COURSE
I	Birth to 6 mo	Never sits independently, even when placed; progressive; demise <2 y
II	6–18 mo	Sits independently when placed; life expectancy into the 20s or later
III	>18 mo	Weakness after having learned to walk; normal life expectancy

in understanding the molecular basis of this disorder have made phenotype-genotype correlation possible. Treatment generally is supportive and includes physical therapy and, when needed, respiratory and nutritional support and genetic counseling. Scoliosis is common in type II and must be addressed appropriately with a body jacket, molded back support, or surgery. Most children who have type II can use a motorized wheelchair at approximately 2 to 3 years of age. Life expectancy in type II can be well into adulthood.

### Peripheral Nerve Disorders

Peripheral nerve disorders are rare in infancy and very early childhood. Hypomyelinating neuropathy can produce severe weakness, hypotonia, and areflexia in a neonate or young infant. The diagnosis can be anticipated when extremely abnormal nerve conduction studies are encountered and can be confirmed with DNA studies or with a nerve biopsy. Hereditary sensorimotor neuropathies, with the many variants of Charcot-Marie-Tooth disease, are the most common cause of childhood peripheral nerve disorders and may cause both gait abnormalities from weakness of the anterior tibialis muscles and deformities of the foot. Ankle jerks are often diminished or absent, but all reflexes may be preserved in the early phases of peripheral neuropathies. Nerve conduction studies can be extremely useful in separating axonal from demyelinating neuropathies. DNA studies can be diagnostic in selected hereditary neuropathies, especially the demyelinating and the X-linked varieties. Treatment addresses symptoms; some children who have foot drop may require bracing.

Several CNS disorders may have a demyelinating form of peripheral nerve involvement in addition to abnormalities in the cerebral white matter; these include metachromatic leukodystrophy, Krabbe disease, and adrenoleukodystrophy.

### Myoneural Junction Disorders

Several disorders of the myoneural junction affect children and infants: passively acquired autoimmune myasthenia gravis, also known as transient neonatal myasthenia; acquired autoimmune myasthenia gravis, also known as juvenile or childhood myasthenia; nonautoimmune myasthenic syndromes, also known as congenital myasthenia gravis; and infantile botulism.

Passively acquired autoimmune myasthenia gravis occurs in approximately 20% of infants born to mothers who have myasthenia gravis. All newborns of seropositive mothers have acetylcholine receptor

antibodies, but only a small portion are symptomatic, most mildly, but some more severely, with hypotonia, a weak cry, swallowing and sucking difficulty, facial diaphoresis, respiratory distress, external ophthalmoparesis, and ptosis. The diagnosis can be made quickly when, after administering intravenous edrophonium, the abnormal findings subside. When the newborns are symptomatic, pyridostigmine can be given orally until symptoms are no longer present. The dose is then tapered, usually over a period of 1 to 2 weeks. These infants do not have clinical features of myasthenia gravis after the initial involvement. If weakness does not occur by 1 week of age, then it is highly unlikely to develop.

Major features of acquired autoimmune myasthenia include fatigability and fluctuating weakness of extraocular, facial, and lingual muscles, and, in some instances, mild or severe generalized weakness and hypotonicity of the limbs. An acute fulminating onset may be encountered in young children. The diagnosis can be made by using the edrophonium test and confirmed with the acetylcholine receptor antibody test, although the latter is not necessarily positive in milder cases and is less useful in children than in older individuals. Electrodiagnostic studies can be used in selected instances in children but are generally less useful than in adults. The mediastinum should be radiographed to assess thymic size, and thyroid function studies should be obtained to exclude associated hypo- or hyperthyroidism. Treatment includes judicious use of anticholinesterase drugs and, when needed, immunosuppressive treatment, intravenous gamma globulin, corticosteroids, and thymectomy.

Nonautoimmune myasthenic syndromes may be associated with ocular, bulbar, or respiratory involvement and, in some instances, with progressive weakness and hypotonicity. Some disorders may be genetic; patients are seronegative. Specialized electrodiagnostic and ultrastructural studies are required to establish an exact diagnosis, which is important in selecting appropriate therapy. For the moment, genetic studies for diagnosis are available only within a research setting. Some patients respond to anticholinesterase inhibitors or corticosteroids; others require diaminopyridine or other specific medications.

Infantile botulism is characterized by onset at an average age of slightly more than 3 months that produces weakness and hypotonia, poor feeding, constipation, and diminished activity. The onset may be rapid, developing over 2 to 3 days. The diagnosis is confirmed when the toxin is documented in the stool or when the organism is isolated from culture, but repetitive stimulation studies can be extremely useful in establishing the diagnosis quickly. Treatment is supportive; specific immune globulin may prove to be therapeutic.

### Myopathies

Myopathies constitute a diverse group of genetic, inflammatory, and metabolic disorders that involve muscle and, in many cases, other organ systems, including the brain and heart. Inflammatory myopathies (dermatomyositis) are seen only rarely in very young children and generally produce subacute weakness, not hypotonia. Patients with Duchenne muscular dystrophy (among the most common muscular disorders) do not have hypotonia in infancy. In the infantile form



of myotonic dystrophy–type 1 hypotonia can be severe at birth. Obtundation, difficulty with sucking and swallowing, weakness of facial muscles, clubfeet, and areflexia may be present. Myotonia will not be present either clinically or electrically until patients are older than 5 years. A neonate who survives will gain strength and tone and will eventually walk. Until strength and tone improve, assisted ventilation and gastrostomy tube feedings are often needed. Myotonic dystrophy–type 1 is an autosomal-dominant disorder; however, when it occurs in the neonatal period, it is virtually always the mother who transmitted the gene. She should be examined for the characteristic features of the disease, which include reflex and percussion myotonia, weakness of the neck flexor muscles, smallness of the sternocleidomastoid muscles, weakness of the wrist extensors and anterior tibialis muscles and facial muscles, and, often, intellectual disability. For children who first exhibit myotonic dystrophy beyond infancy, either parent may have transmitted the gene, which is located on 19q13. DNA studies can be done to document the diagnosis and predict the prognosis. This condition is an expanded trinucleotide repeat disorder, with correlation between the severity and the number of repeats. Family members should be provided with genetic counseling, given that prenatal diagnosis is available. Treatment is supportive.

Several congenital myopathies have been identified and are generally diagnosed on muscle biopsy by their characteristic morphologic mechanism. These myopathies, typified by nemaline myopathy, are often hereditary and are associated with varying degrees of hypotonia and weakness and sometimes with respiratory and sucking problems early in life. Some have rather characteristic clinical features. For example, in X-linked myotubular myopathy of very early onset, the extraocular and facial muscles are weak, in addition to generalized hypotonia and weakness. Central core disease is associated with congenital hip dislocation and a propensity for malignant hyperpyrexia. In some congenital myopathies, the gene location has been identified, but DNA testing is not yet available for establishing the diagnosis.

The congenital muscular dystrophies comprise a diverse group of diseases in which varying degrees of weakness and hypotonia are present early in life. Muscle biopsy shows characteristic, but not specific, pathologic findings, and more refined studies are required. The serum muscle enzymes (creatine kinase) are generally elevated, and, in some forms of this disorder, merosin is absent on the biopsy specimen. The merosin-deficient type of congenital muscular dystrophy is often associated with intellectual disability, seizures, and white matter brain abnormalities. In Japan, Fukuyama-type congenital muscular dystrophy is common and is also associated with severe CNS abnormalities.

Facioscapulohumeral muscular dystrophy usually occurs in older children but, at times, will produce severe facial weakness in early childhood. Although sometimes sporadic, most cases are autosomal-dominant and parents of affected children should be examined for involvement that may be very mild and go unnoticed, such as facial muscular weakness, scapular winging, and a round-shouldered stance. This

disease is genetically linked to high-frequency hearing deficits. Treatment is symptomatic, and it is appropriate to offer genetic counseling. DNA studies are available to document the diagnosis when this disorder is thought to exist, making electrodiagnostic testing and muscle biopsy unnecessary.

Glycogen storage disease caused by deficient acid maltase, in addition to its neuromuscular manifestations (hypotonia and weakness), is associated with a markedly enlarged heart and congestive heart failure. The diagnosis can be made readily by specific blood tests. Enzyme replacement therapy has recently become available; without this treatment, the prognosis is dismal. This condition is an autosomal-recessive disorder with the responsible gene located at 17q23.

An increasing number of mitochondrial encephalomyopathies are being reported that have varying CNS and muscle involvement. Lactic acidemia is common, but specialized genetic and other studies on muscle mitochondria are needed to provide a specific diagnosis if DNA studies are unrevealing. Treatment addresses symptoms.

Congenital hypotonia with favorable outcome or benign congenital hypotonia is a retrospective diagnosis used to denote infants who have hypotonia of early onset with a benign course. This relatively unclear disorder is often associated with joint hyperlaxity, sometimes also noted in parents or other relatives. In many instances, by 5 years of age, the children are indistinguishable from other children their age.

### WHEN TO REFER

- Persistent lack of normal motor development
- Regression of motor development
- Sudden or precipitous worsening of tone or strength
- Swallowing dysfunction
- New onset of neurologic signs

### TOOLS FOR PRACTICE

#### Medical Decision Support

- *Online Mendelian Inheritance in Man* (online database), Johns Hopkins University (omim.org)
- *Gene Tests* (Web site), (www.genetests.org)
- *Core Signs of Weakness* (videos), National Task Force for Early Identification of Childhood Neuromuscular Disorders (www.childmuscleweakness.org/index.php/videos)
- *Motor Delays: Early Identification and Referral* (article), *Pediatrics*, Vol 131, Issue 6, 2013 (pediatrics.aappublications.org/content/131/6/e2016)

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## Chapter 168

**INATTENTION AND IMPULSIVITY***Lawrence S. Wissow, MD, MPH***INTRODUCTION**

Symptoms of inattention and impulsivity affect many children, including a large number whose symptoms do not rise to the level of a disorder. Attention-deficit/hyperactivity disorder (ADHD) occurs in about 8% of children and youth, who experience significant impairment in their functioning as a result of their symptoms. As part of their condition, individuals with ADHD often have deficits in social skills, impairing their abilities to function well in school and social settings. ADHD is frequently comorbid with learning difficulties, and the 2 conditions can mimic each other in school or during cognitive tasks outside of school (including time devoted to doing homework). Thus, ADHD can result in significant adverse consequences. Follow-up studies have found that children with ADHD, particularly those untreated, are at greater risk for school failure, underemployment, difficulty with legal authorities, substance abuse, and morbidity from risky behaviors including motor vehicle crashes and sexually transmitted infections.

The guidance in this chapter applies to the care of children presenting with undifferentiated symptoms of inattention and impulsivity in pediatric clinical settings.

This chapter is based on the work of the World Health Organization, whose recommendations may be updated annually. The most up-to-date information can be found at [www.who.int](http://www.who.int).

**FINDINGS SUGGESTING INATTENTION AND IMPULSIVITY**

Inattention and impulsivity occur commonly during childhood. When these symptoms occur more persistently and to a greater degree than is seen in a child's peers, there may be cause for concern. Often, the child's teacher is the first to observe the symptoms or to encourage medical attention for them. A summary of the symptoms and clinical findings that suggest inattention and impulsivity can be found in Box 168-1. These symptoms may be elicited from parents, teachers, or youth. Because observers often disagree about behavioral and emotional symptoms, collecting information from all 3 sources can be helpful, and the process of reconciling differences can itself be therapeutic.

**TOOLS TO ASSIST WITH IDENTIFICATION**

Since many children do not spontaneously disclose their symptoms, standardized wide-range psychosocial screening instruments may be used to identify children with emotional and behavioral difficulties that may include symptoms of inattention and impulsivity. Diagnostic criteria for ADHD require presence of symptoms in more than 1 setting; therefore, collateral reports from the school or child care center, as well as the

**BOX 168-1 Indications in History From Youth or Parent**

- Excitability, impatience, angry outbursts (more than is seen in peers)
- Wandering attention (greater than is seen in peers)
- Difficulties with behavior at home and in the classroom
- Academic difficulties
- Parents and teachers presuming diagnosis of ADHD or seeking diagnosis of ADHD

parent(s), are critical elements in the identification process. Several instruments have versions to collect information from the youth, parents, and teachers. Table 168-1 provides an overview of general psychosocial screening tools available in the public domain, along with results raising concerns in the areas of inattention and impulsivity. Use of additional instruments, such as the Vanderbilt ADHD Rating Scales, can then help to confirm findings of the initial screening, corroborate a concern raised by a teacher or parent, and serve as a benchmark to track treatment progress. Use of a functional assessment tool such as the Impact Supplement of the Strengths and Difficulties Questionnaire (SDQ) or the Columbia Impairment Scale (CIS) will assist in determining whether the child is significantly impaired by the symptoms. Use of a tool to assess the effect of the child's problem on other members of the family may also be helpful; the Caregiver Strain Questionnaire (CGSQ) is an example of such a tool.

**ASSESSMENT**

Assessment begins by differentiating the child's symptoms from normal behavior. All children may be inattentive or impulsive at times, but, for some children, inattention and impulsivity limit their adaptability to normal peer and family situations and interfere with learning. Inattention and impulsivity are typical characteristics of preschool children, but extremes of these behaviors warrant further evaluation (eg, concern that the behavior is harming family or peer relationships, interfering with learning, or putting the child at risk for expulsion from child care or school because of behavior). Boisterousness or dreaminess can be normal behavior patterns in older children. Children with limited social experiences and those whose environment is relatively less structured may seem impulsive and inattentive compared to their peers, especially when entering highly structured situations such as a classroom or organized group activities.

Table 168-2 provides a summary of conditions, such as hearing or vision problems, receptive and expressive language problems, learning disorders, and sleep deprivation, which may mimic or co-occur with inattention and impulsivity problems.

**PLAN OF CARE FOR CHILDREN WITH INATTENTION AND IMPULSIVITY**

The care of a child experiencing symptoms of inattention and impulsivity can begin in the primary care

**Table 168-1** General Psychosocial Screening/Results Suggesting Inattention and Impulsivity

SCREENING INSTRUMENT	SCORE
Pediatric Symptom Checklist (PSC)-35	<ul style="list-style-type: none"> <li>• Total score <math>\geq 24</math> for children 5 years and younger.</li> <li>• <math>\geq 28</math> for those 6–16 years.</li> <li>• <math>\geq 30</math> for those 17 years and older.</li> </ul> AND <ul style="list-style-type: none"> <li>• Further discussion of items related to attention and impulse control confirms a concern in that area.</li> </ul>
PSC-17	<ul style="list-style-type: none"> <li>• Attention subscale is <math>\geq 7</math>.</li> </ul> AND <ul style="list-style-type: none"> <li>• Further discussion of items related to attention and impulse control confirms a concern in that area.</li> </ul>
Strengths and Difficulties Questionnaire (SDQ)	<ul style="list-style-type: none"> <li>• Total symptom score of <math>&gt;19</math>.</li> <li>• Hyperactivity scale score of 7–10 (see instructions at <a href="http://www.sdqinfo.com">www.sdqinfo.com</a>).</li> <li>• Impact scale (back of form) score of 1 (medium impairment) or <math>\geq 2</math> (high impairment).</li> </ul> AND <ul style="list-style-type: none"> <li>• Further discussion of items related to attention and impulse control confirms a concern in that area.</li> </ul>

setting from the time symptoms are recognized, even if the child's symptoms do not rise to the level of a disorder or referral to a mental health specialist is ultimately part of the care plan.

### Engage Child and Family in Care

Without engagement, most families will not seek or persist in care. The process may require multiple primary care visits.

Reinforce strengths of the child and family (eg, good relationships with at least 1 parent or important adult, prosocial peers, concerned or caring family, help-seeking, connection to positive organizations) as a method of engagement, and identify any barriers to addressing the problem (eg, stigma, family conflict, resistance to treatment). Use “common factors” techniques to build trust and optimism, reach agreement on incremental next steps, develop a plan of care, and collaboratively determine the role of the primary care physician. A key step is to reach agreement that there is a reason to consider intervention, and, ideally, that there are concrete problems that the family would like to see addressed. Regardless of other roles, the primary care physician can encourage a positive view of treatment on the part of the child and family.

### Offer Psychoeducation About ADHD, the Differential Diagnosis, and the Process of Arriving at a Diagnosis

Parents have likely heard about ADHD from other sources; their knowledge and concerns about the conditions may vary widely. They may have worries about being coerced into labeling their child with the condition by demands from the pediatrician or schools. The clinician can ask about what they know and what questions they may have. She can explain the process of making a provisional diagnosis and investigating alternatives, including language and learning problems, anxiety, and normal variation in development and temperament. Perhaps most importantly, the clinician can assure parents that she will not be jumping to a diagnosis, but rather will work with them to collect relevant information, make a plan of treatment,

and then reevaluate the situation as time goes on. At some point, parents will also want to know more about the natural history of the condition and the implications it may have for their child's future. It is reasonable to say that these sorts of problems are common and highly amenable to treatment of various kinds, and, while sometimes persistent, tend to be more easily managed as the child gets older.

### Encourage Healthy Habits

Regular exercise and outdoor play are beneficial to all children and may be particularly helpful to inattentive and impulsive children. These children may also benefit from participation in structured sports activities, which offer exercise as well as the opportunity to build social skills such as taking turns, following rules, and handling success and disappointment. Also important are regular sleep habits, special time with parents, praise for good behavior, and reinforcement of the child's strengths. Limiting media exposure may be particularly important for these children. Television programs, movies, and computer games can be overstimulating; long hours in these activities can produce irritability. Unrestricted access to a television or computer, especially in the child's bedroom, can contribute to loss of sleep, failure to do homework, and the risk of seeing programming that contributes to increased activity.

### Reduce Stress

Consider the child's social environment (eg, family social history, parental depression screening, results of any family assessment tools administered, reports from child care or school). Symptoms of inattention and hyperactivity will generally worsen in stressful settings. The physician can guide parents in providing a safe, structured environment and coach parents in working constructively with the child's school. The physician can also address stresses on family members—if they have problems with mood or irritability, they will have more difficulty adapting to and moderating the child's behavior.

### Offer Initial Intervention(s)

The strategies described in the following text are common elements of evidence-based and evidence-informed

**Table 168-2** Conditions That May Mimic or Co-occur With Inattention and Impulsivity

CONDITION	RATIONALE
Hearing or vision problems Sleep deprivation	All children who seem inattentive should be screened for sensory deficits.  Sleep problems can cause inattention and irritability. Attention-deficit/hyperactivity disorder (ADHD) may contribute to difficulty sleeping.
ADHD	Diagnosis requires that a child have a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development. These patterns are characterized as 6 or more symptoms of inattention (eg, careless with detail; fails to sustain attention; seems not to listen; does not finish instructed tasks; poor self-organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; and seems forgetful) or hyperactivity [eg, fidgets; leaves seat when should be seated; runs or climbs excessively and inappropriately; noisy in play; persistent motor activity unmodified by social context (but this is seen less in teens); talks excessively; blurts out answers before question completed; fails to wait turn; and interrupts others' conversation or games] for at least 6 months. Further features necessary to make this diagnosis include the following: <ul style="list-style-type: none"> <li>• These symptoms were present prior to age 12 years.</li> <li>• These symptoms are present in at least 2 types of settings (eg, home and school).</li> <li>• The symptoms cause significant distress or impaired functioning.</li> <li>• The symptoms are not better explained by another psychiatric disorder.</li> </ul>
Learning problems or disabilities	If symptoms of inattention and impulsivity are associated with problems of school performance, the child may be experiencing learning difficulties. See Chapter 172, Learning Difficulty, to explore this possibility.
Developmental problems	Children with overall intellectual or social limitations may seem less able to control their impulses and to focus and maintain their attention than their age-mates.
Language impairment or disorder	Children with receptive or expressive language impairment may be frustrated and inattentive at least in part because of difficulty understanding what others say or being able to express themselves. Similar problems can arise when children are learning a new language and cannot yet fully function at the level of their peers or teachers.
Depression	May co-occur with ADHD. Marked sleep disturbance, disturbed appetite, low mood, or tearfulness could indicate that a child is depressed as well as having attention difficulties. See Chapter 137, Depression.
Exposure to adverse childhood experiences (ACE)	Children who have experienced or witnessed trauma; violence; a natural disaster; separation from a parent; parental divorce or separation; parental substance use; neglect; or physical, emotional, or sexual abuse are at high risk of developing symptoms suggesting inattention and impulsivity. These symptoms may mask or be expressions of emotional difficulties such as adjustment disorder or posttraumatic stress disorder (PTSD). Some symptoms of PTSD may resemble symptoms of ADHD (eg, hypervigilance may mimic hyperactivity, or dissociation may mimic inattention). These children may also manifest other forms of anxiety. Inquiring about previous trauma in a confidential setting is important. See Chapter 129, Anxiety.
Anxiety	Anxious children may experience difficulty concentrating. See Chapter 129, Anxiety.
Bereavement	Most children will experience the death of a family member or friend sometime in their childhood. Other losses may also trigger grief responses—separation or divorce of parents, relocation, change of school, deployment of a parent in military service, breakup with a girlfriend or boyfriend, or remarriage of parent. Such losses are traumatic. They may result in such symptoms as sadness, anxiety, difficulty concentrating, poor impulse control, or academic decline immediately following the loss and, in some instances, more persistently. See also Chapter 137, Depression and the discussion of PTSD in Chapter 129, Anxiety.
Physical illness	Medical issues that can mimic or provoke symptoms of inattention and impulsivity include thyroid disease, hypoglycemia, hyperglycemia, side effects of medications (eg, bronchodilators), and endocrine tumors (eg, rarely pheochromocytoma).
Substance use	Children with symptoms of inattention and impulsivity may self-medicate with alcohol, nicotine, or other drugs. Conversely, children using substances may manifest inattention, impulsivity, and deteriorating school performance.
Conduct or oppositional disorders	See Chapter 139, Disruptive Behavior and Aggression, to differentiate these symptoms from problems of inattention and impulsivity and ADHD.
Tourette syndrome	Children with repetitive movements (tics) should be identified. In children with Tourette syndrome, ADHD symptoms may precede onset of tics. Stimulant medication may worsen tics. It is important to tailor treatment to the child's most pressing symptoms before deciding the risks and benefits of using stimulants in children with both problems.

Derived from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association; 2013



psychosocial interventions for management of children's behavior. They are applicable to the care of children with mild or emerging symptoms of inattention and impulsivity and to those with impairing symptoms that do not rise to the level of a disorder. They can also be used along with other specific interventions for ADHD.

*Guide parents in managing the child's behavior.* Good practices include the following:

- **Tangible rewards:** Rewards or privileges contingent on performance of routine tasks (eg, TV or computer time contingent on attaining a realistic goal). These rewards are most effective when coupled with a system for helping the child be aware of his or her own level of functioning, including charts that monitor events such as completion of homework without a reminder, staying "on-task" in school for a prearranged time before taking a break, carrying out chores at home before being asked.
- **Parent praise:** Conscious effort by parent to identify and comment on positive aspects of child's behavior (eg, compliment child, especially when desired action is spontaneous).
- **Parent monitoring:** Use of some systematic means to rate the child's burden of specific ADHD symptoms and overall social, emotional, and academic function (eg, weekly use of Vanderbilt scales or a customized checklist, often with simultaneous teacher ratings). Monitoring helps the parent advocate for the child and can help take pressure off the child by giving short-term, objective measures of progress.
- **Time-out:** Avoiding reinforcement of undesired behavior through arguing or allowing the behavior to continue (eg, child is required to sit without attention or activity for a brief period as a consequence for an undesired behavior).
- **Commands/limit setting:** Use of clear, simple commands that ideally give the child a warning of impending expected behavior, an opportunity to perform it, a warning of consequences for nonperformance, and a consistent consequence (eg, "You can do 1 more puzzle and then we have to go...now it's time to go...if you don't put the puzzle away now, you can't chose the music we listen to in the car.>").

*If there are battles over homework, offer guidelines.* Box 168-2 provides suggestions for parents to consider in addressing homework issues.

*If child meets diagnostic criteria for ADHD, consider specific therapy.* The course of treatment depends on the child's age and should be noted in the overall care plan.

For preschool-aged children (4–5 years of age), evidence-based, parent- or teacher-administered behavior therapy is considered the first line of treatment. Use of medications may be considered—ideally with specialist consultation—if behavioral treatment does not provide sufficient improvement or if evidence-based treatment is not available.

For elementary school-aged children (6–11 years of age), US Food and Drug Administration–approved medications for ADHD and/or evidence-based parent- and/or teacher-administered behavior therapy is considered first-line treatment for ADHD, preferably both. The evidence is particularly strong for stimulant medications and sufficient but less strong for atomoxetine, extended-release guanfacine, and extended-release clonidine (in that order).

### BOX 168-2 Strategies for Working Constructively With a Child's School

- Obtain consent for the clinician to exchange information with the child's teacher.
- Establish constructive 3-way (parent, teacher, pediatrician) communication with the school.
- Ask if testing has been requested and taken place to detect special educational needs.
- Monitor academic progress, helping to reinforce successes and identify particular subjects or educational settings where more support is needed.
- Advocate for appropriate classroom strategies.
  - Have the child sit at the front of the class.
  - If possible, engage the child in active learning, (eg, have the child go to the blackboard to write answers to questions).
  - Give extra time to stay organized (eg, write down assignments, make sure that all needed materials are taken home or gathered for a project, have the child repeat back what he or she is to do).
  - Break longer assignments into shorter pieces (also helpful for homework).
  - Coordinate reports of behavior with home—consider a daily report card of behavior and subsequent rewards or consequences.

For adolescents (12–18 years of age), Food and Drug Administration–approved medications for ADHD with the assent of the adolescent along with behavior therapy are considered treatment for ADHD.

### Provide Resources

Families may find support and resources from organizations such as Children and Adults With Attention-Deficit/Hyperactivity Disorder ([www.chadd.org](http://www.chadd.org)). Helpful publications are included in Tools for Practice: Engaging Patient and Family at the end of this chapter. Provide the family with contact numbers and resources in case of emergency.

### Monitor the Child's Progress Toward Therapeutic Goals

Child care, preschool, or school reports can be helpful in monitoring progress. The Vanderbilt scales (parent and teacher), SDQ (parent, teacher), and Pediatric Symptom Checklist (PSC) can be helpful in monitoring progress with symptoms and functioning. Both medications and behavioral treatments need careful titration to achieve their desired effects without the development of side effects. The need for higher-than-recommended doses of medication could be a sign of difficulties with adherence or a need to switch to a different medication. Behavioral treatments can be difficult to implement and maintain. Physicians can work with families to adapt behavioral suggestions to family circumstances and to explore barriers to other aspects of treatment, including effective engagement with schools.

It is important for the clinician to help the family understand that it is not uncommon for treatment to

### BOX 168-3 American Academy of Pediatrics Recommendations for Treatment of Attention-deficit/Hyperactivity Disorder

- Recommendations for treatment of children and youth with ADHD vary depending on the patient's age.
  - For *preschool-aged children (4–5 years of age)*, the primary care clinician should prescribe evidence-based parent- and/or teacher-administered behavior therapy as the first line of treatment (quality of evidence A/strong recommendation) and may prescribe methylphenidate if the behavior interventions do not provide significant improvement and there is moderate-to-severe continuing disturbance in the child's function. In areas in which evidence-based behavioral treatments are not available, the clinician needs to weigh the risks of starting medication at an early age against the harm of delaying diagnosis and treatment (quality of evidence B/recommendation).
  - For *elementary school-aged children (6–11 years of age)*, the primary care clinician should prescribe FDA-approved medications for ADHD (quality of evidence A/strong recommendation) and/or evidence-based parent- and/or teacher-administered behavior therapy as treatment for ADHD, preferably both (quality of evidence B/strong recommendation). The evidence is particularly strong for stimulant medications and sufficient but less strong for atomoxetine, extended-release guanfacine, and extended-release clonidine (in that order) (quality of evidence A/strong recommendation). The school environment, program, or placement is a part of any treatment plan.
  - For *adolescents (12–18 years of age)*, the primary care clinician should prescribe FDA-approved medications for ADHD with the assent of the adolescent (quality of evidence A/strong recommendation) and may prescribe behavior therapy as treatment for ADHD (quality of evidence C/recommendation), preferably both.
- Primary care clinicians should titrate doses of medication for ADHD to achieve maximum benefit with minimum adverse effects (quality of evidence B/strong recommendation).

For more information, see American Academy of Pediatrics Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2011;128(5):1007–1022 ([pediatrics.aappublications.org/content/128/5/1007](http://pediatrics.aappublications.org/content/128/5/1007)).

Adapted from *Caring for Children With ADHD: A Resource Toolkit for Clinicians*. Copyright 2011 American Academy of Pediatrics.

be successful for a period and then seem to lose effectiveness. This can happen when there are new stresses or demands, or when, after a period of success, there has been a letup on treatment. If modifying existing treatment and exploring ways of dealing with new stresses do not help get function back to baseline, then new treatments, or new diagnoses, need to be considered. In particular, as school demands increase, learning issues may need to be considered even if they were not seen as contributing problems in the past.

#### Involve Specialist(s)

*Involve specialist(s) if the child does not respond to initial interventions or if the following clinical circumstances exist:*

- Child has severe functional impairment.
- Child has severely disruptive behavior or aggression.
- Child has comorbid depression or posttraumatic stress disorder, or if problems with mood, behavior, and development seem more prominent than difficulties with attention or impulsivity.
- Symptoms are threatening school performance or the achievement of other developmentally important goals (eg, developing and sustaining friendships).
- The child or parent is very distressed by the symptom(s).
- There are co-occurring behavior problems. (The combination of shyness, anxiety, and behavior problems is thought to be particularly risky for future behavior problems of a more serious nature.)
- The child's symptoms were preceded by serious trauma.
- The child has ADHD and contraindications to stimulants or marked side effects with stimulants.
- The child's problems are occurring in the context of other family emotional or behavioral problems that

have not been alleviated with primary care interventions.

*When specialty care is needed, ensure that it is evidence-informed and assist the family in accessing it.* Pharmacologic interventions and a number of evidence-based and evidence-informed psychosocial interventions are available for the treatment of ADHD in children and adolescents. Ideally, those referred for care in the mental health specialty system would have access to the safest and most effective treatments. Box 168-3 provides a summary of these interventions. Youth referred for mental health specialty care complete the referral process only 61% of the time, and a significantly smaller number persist in care.

Note that not all evidence-based interventions may be available in every community. If a particular intervention is not available, this becomes an opportunity to collaborate with others in the community to advocate on behalf of children. Increasingly, states offer both telepsychiatry services and consultation/referral support “warmlines” that help physicians provide initial treatment and locate resources. The availability of the latter form of help is tracked at the National Network of Child Psychiatry Access Programs ([www.nncpap.org](http://www.nncpap.org)).

*Reach agreement on respective roles in the child's care.* If the child is referred to mental health specialty care, the physician may be responsible for initiating medication or adjusting doses; monitoring response to treatment; monitoring adverse effects; engaging and encouraging the child's and family's positive view of treatment; and coordinating care provided by parents, school, medical home, and specialists. In fact, the child may improve just knowing that the clinician is involved and interested. Resources available to help clinicians in these roles are provided in Tools for Practice: Medical Decision Support.

## ACKNOWLEDGMENT

The author and editor wish to acknowledge the contributions of Linda Paul, MPH, manager of the AAP Mental Health Leadership Work Group.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *ADHD: What Every Parent Needs to Know* (book), Reiff MI, American Academy of Pediatrics (shop.aap.org)
- *Addressing ADD Naturally* (book), Xlibris Corporation, 2010

### Medical Decision Support

- *Caring for Children with ADHD: A Resource Toolkit for Clinicians* (toolkit), American Academy of Pediatrics (shop.aap.org)
- *NICHQ Vanderbilt Assessment Scale* (scale), National Institute for Children's Health Quality (www.nichq.org/childrens-health/adhd/resources/vanderbilt-assessment-scales)
- *Pediatric Symptom Checklist* (screen), Massachusetts General Hospital (www.massgeneral.org/psychiatry/services/psc\_forms.aspx)
- *Strengths & Difficulties Questionnaire* (screen), Youth in Mind, Ltd. (www.sdqinfo.com)

## AAP POLICY

American Academy of Pediatrics Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2011;128(5):1007–1022 (pediatrics.aappublications.org/content/128/5/1007)

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- Huey SJ, Polo AJ. Evidence-based psychosocial treatments for ethnic minority youth. *J Clin Child Adolesc Psychol*. 2008;37(1):262–301
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## Chapter 169

# IRRITABILITY AND FUSSINESS

Diana King, MD; Waseem Hafeez, MBBS

Irritability, “a condition in which a person, organ, or a part responds excessively to a stimulus,” is a common complaint in children, especially in neonates and infants. Although experienced physicians can recognize irritability in a child, a concise definition is difficult because some subjectivity exists in the use of the term. Although it is not a quantifiable symptom, irritability includes episodes of crying or fussiness despite attempts at comforting the infant. While it is not a

symptom of any specific illness, most parents recognize that something might be wrong with the child even though other symptoms may not yet exist.

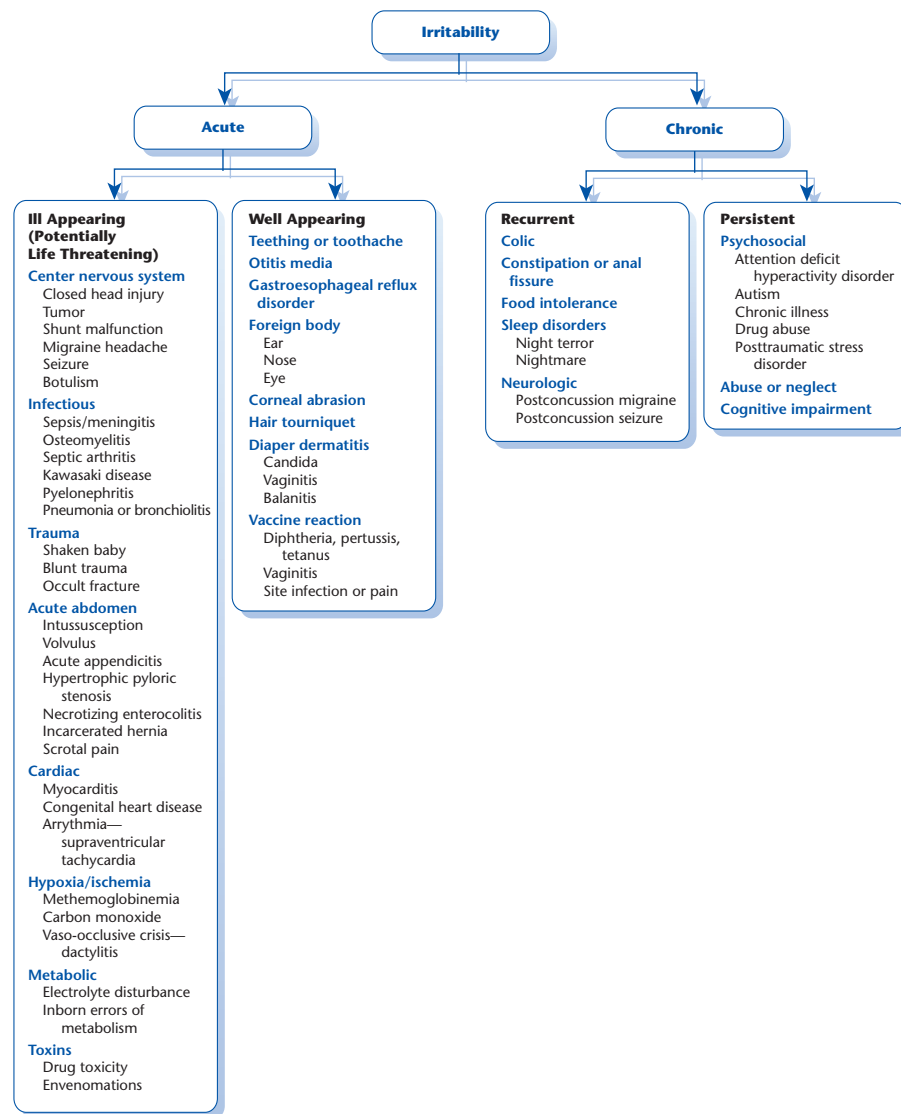
Irritability results from lack of vital nutrients (eg, oxygen, glucose), the presence of noxious stimuli (eg, pain, toxins), or an emotional state (eg, anger, frustration). It may have different causes and manifestations in infants, children, and adolescents. Whereas older children and adolescents may offer explanations that help clarify their complaint, an infant or preverbal child is unable to provide such information. Acute irritability may be associated with life-threatening illnesses requiring urgent intervention and stabilization before a search for the cause begins. A parent who seeks care for an infant who is fussier than usual may arrive with the child in shock, in respiratory distress, or having a seizure. An organized approach to the differential diagnosis minimizes unnecessary testing. If the child does not have an immediately life-threatening condition, then a complete history and thorough physical examination are the first steps in the evaluation of irritability and, in many cases, will reveal the cause of the symptom. Many common infectious, traumatic, toxic, allergic, and inflammatory conditions can be diagnosed by history and physical examination alone. Laboratory or radiologic procedures may confirm a clinical suspicion. An algorithm to differentiate some life-threatening conditions from less serious causes of irritability is presented in Figure 169-1.

## ACUTE IRRITABILITY IN THE ILL-APPEARING CHILD

### Central Nervous System

Children younger than 2 years have a high risk for significant brain injury after both accidental and non-accidental traumatic brain injury (TBI). In data collected between 2002 and 2006, the National Center for Injury Prevention and Control found that children aged 0 to 4 years had the highest rate of TBI-related emergency department visits (1,256 per 100,000 population), with falls, motor vehicle crash, and inflicted trauma as the leading causes. The incidence of intracranial injury was 13% in infants 0 to 2 months of age, 6% in infants 3 to 11 months of age, and 2% in infants 12 months or older. The American Academy of Pediatrics has recommended guidelines for evaluation and management of head injury in this age group. A history of a fall from the bed, infant-walker, stairs, or bicycle can often be obtained. To determine the need for computed tomography scan in clinically important TBI, prediction rules have been identified which include in children younger than 2 years abnormal mental status, loss of consciousness, scalp hematoma except frontal, palpable skull fracture, severe mechanism of injury, and not acting normally according to the parents. In addition to these findings, the prediction rule for children aged 2 years and older also includes vomiting, severe headache, and signs of basilar skull fracture.

A special concern is for children who sustain concussions from sports-related injuries. The American Academy of Neurology defines concussion as “a



**Figure 169-1** Algorithm for evaluation of the irritable infant.

trauma-induced alteration in mental status that may or may not involve loss of consciousness.” The term *post-concussive syndrome* refers to the constellation of acute symptoms, which can be somatic (headache, dizziness, blurriness), emotional (irritability, anxiety), and cognitive (concentration and memory difficulties). The term *second impact syndrome* has been proposed for an athlete who has sustained a concussion, sustains a second head injury before symptoms associated with the first have fully cleared, and is at risk for a catastrophic outcome such as permanent disability or death. To manage these injuries, a concussion grading scale has been developed with return-to-play guidelines that include physical and cognitive rest and rehabilitation.

Increased intracranial pressure (ICP) from a brain tumor may produce acute irritability and altered behavior without the usual preceding symptoms such as headache or loss of coordination and ataxia. Primary

brain tumors in the posterior fossa are the most common solid malignancies in infants and children younger than 7 years. In young children, the diagnosis of a brain tumor may be delayed because their symptoms are subtle (headache, irritability, or drowsiness) or similar to those of more common illnesses, such as gastrointestinal disorders (vomiting). Hydrocephalus, another cause of raised ICP, often occurs in infancy with irritability, vomiting, a tense or bulging fontanel, and an increasing head circumference that crosses percentile lines. Older children usually complain of headaches. Neuroimaging shows congenital malformation (myelomeningocele, Chiari syndrome, Dandy Walker malformation, aqueductal stenosis, arteriovenous malformation) or germinal matrix intraventricular hemorrhage of prematurity. Hydrocephalus is treated by the introduction of ventriculoperitoneal shunts to reduce the ICP. The ventriculoperitoneal shunt may become obstructed or infected, or it may malfunction,



causing overdrainage or underdrainage, initially causing irritability, headache, vomiting, or lethargy.

Undiagnosed migraine headache may manifest itself in the preverbal child with irritability. Headaches attributable to migraine occur in 8% to 12% of children younger than 3 years. There seems to be an association of infantile colic with excessive crying and irritability with later diagnosis of migraine. Children with seizures, especially unwitnessed, may seem irritable during an aura or the postictal phase. Neonatal seizures, more commonly seen in preterm infants than term infants, may have only subtle symptoms such as ocular or pedaling movements, lip smacking, or apnea. Nonconvulsive status epilepticus, which includes absence and partial complex seizures, is a relatively rare cause of abnormal behavior resulting from continuous or intermittent seizure activity in the absence of any motor component. The hallmark of nonconvulsive status epilepticus is a diagnostic electroencephalogram associated with irritability and a change in behavior or mental status.

Infant botulism, most commonly foodborne, may initially cause difficulty in feeding, irritability, lethargy, weak cry, and constipation. As the disease progresses, drooling, dysphagia, loss of head control, respiratory distress, and flaccid paralysis may occur from progressive bulbar involvement.

### Infections

The primary care physician should suspect a bacterial infection in a child with fever and irritability. Infants with meningitis may have irritability, lethargy, and poor feeding. If the fontanel is still open, then it may be bulging. Lumbar puncture is diagnostic, and treatment with intravenous antibiotics should not be delayed. The introduction of vaccines against *Haemophilus influenzae* type B and *Streptococcus pneumoniae* has changed the epidemiology of bacterial meningitis in children. Infants younger than 3 months of age are most commonly infected with Group B streptococci and gram-negative bacilli. Encephalitis from herpes simplex virus should also be considered. In children older than 3 months, the most common pathogens are *Streptococcus pneumoniae* and *Neisseria meningitidis*.

Irritability and decreased movement of a limb should raise concern for osteomyelitis. Swelling and erythema of the soft tissue overlying the bone may exist, often with a history of preceding trauma. Joint pain, fever, irritability, and a limp should raise concern for septic arthritis. Examination will reveal erythema, swelling, or warmth over the affected joint, with restricted movement. With septic arthritis of the hip, swelling and redness may not be visible, and the pain may be referred to the knee. Blood should be analyzed for culture, complete blood count, and C-reactive protein to help establish a diagnosis. An orthopedist should be consulted for possible surgical drainage.

Irritability is one of the most common associated symptoms in children with Kawasaki disease. The principal clinical manifestations of this systemic vasculitis are fever, rash, conjunctival injection, erythema of lips and mouth, cervical adenopathy, and changes in the extremities. Bacteremia and urinary tract

infections can also produce irritability, along with fever in an ill-appearing infant.

### Trauma

A systematic search for injuries should be performed on any child with a history of trauma. Inflicted injuries are more difficult to diagnose because the signs may be subtle and the history is often misleading. Abusive head trauma is the leading cause of traumatic death in children younger than 2 years. The rotational forces sustained during shaking cause movement of the brain within the subdural space and tearing of the bridging veins, resulting in subdural hematoma. The shearing forces can also cause diffuse axonal injury. Clinical signs of abusive head trauma may be poor feeding, vomiting, lethargy, or irritability. More severe central nervous system dysfunction can result in death.

In infants and young children, the pressure of the lap belt of a restraint system in a motor vehicle crash or other blunt abdominal trauma can lead to intra-abdominal bleeding, initially displayed as irritability from tissue hypoperfusion and pain. Many traumatic causes of irritability that are not life threatening may be apparent on initial physical examination and include fractures and dislocations.

### Acute Abdomen

Intussusception is seen most often between the ages of 3 months and 5 years, with a peak incidence at 6 to 11 months. The child seems colicky, cries, and may draw the knees toward the chest; this episode may last a few minutes and then subside. The child often looks better between episodes, but the irritability gradually increases and vomiting becomes more frequent and sometimes bilious. Mandeville et al found the classic triad of intermittent colicky abdominal pain, vomiting, and bloody stools was present in more than 65% of patients; and in patients younger than 12 months, irritability was an important clinical predictor.

Appendicitis is the most common condition requiring emergency surgery in children. Abdominal pain in a young child may first manifest as irritability, before the appearance of nausea, vomiting, fever, and right lower quadrant tenderness. Perforation rates for appendicitis are higher in children than in adults (30%–65%), and, given that the omentum is less developed in children, perforations are less likely to be walled off or localized.

Hypertrophic pyloric stenosis may become symptomatic as early as the first week of life and as late as the fifth month. Symptoms begin with nonbilious vomiting after feeding, and as the disease progresses the vomiting becomes projectile. The baby may initially seem normal, but hunger makes the infant irritable, and signs of dehydration eventually become apparent. The finding of an olive shaped mass in the right upper quadrant of the abdomen is diagnostic, and confirmed by ultrasound.

Malrotation with midgut volvulus peaks during the first month of life but can occur any time in childhood. The neonate will be irritable initially; as the bowel becomes obstructed and necrotic, bilious vomiting and shock may result from perforation.

Necrotizing enterocolitis is typically seen in premature infants in their first few weeks of life. It may rarely be seen in full term infants, within the first 2 weeks after birth, particularly with a stressor such as infection or anoxic event. Infants are ill appearing, irritable, and lethargic, with distended abdomen and bloody stools. Abdominal plain-film finding of pneumatosis intestinalis, caused by gas in the submucosal intestinal wall, is diagnostic of necrotizing enterocolitis with ultrasound becoming increasingly used to make the diagnosis while avoiding radiation. Because of a high mortality rate, management includes early surgical consultation and aggressive fluid resuscitation, bowel rest, and broad-spectrum antibiotic coverage.

Sixty percent of incarcerated inguinal hernias occur during the first year of life, especially in infants born preterm, with symptoms of irritability, vomiting, and pain in the groin and abdomen. A testicular examination is imperative in all male patients with irritability or abdominal pain. On examination a nonfluctuant tender mass is present in the inguinal region and may extend down into the scrotum. With the onset of ischemia of the involved bowel the pain becomes more intense and localized to the scrotum, and the infant may have bilious vomiting with the presence of bloody stools. An attempt should be made to reduce the incarcerated hernia manually by gentle compression. Sedation or analgesia, elevation of the lower torso, and an ice pack may be helpful. If reduction is unsuccessful or the child shows signs of small bowel obstruction, then operative reduction of the incarcerated hernia should be performed. Irritability with scrotal pain may also result from epididymitis, torsion of the testis, or torsion of the appendix testis.

### Cardiac System

Acute myocarditis can be a challenging diagnosis to make because the clinical presentation can vary. The diagnosis should be considered in an irritable child with resting tachycardia and respiratory symptoms. An electrocardiogram may reveal sinus tachycardia, ventricular hypertrophy, and ST and T wave changes. Low voltage QRS complexes, or an abnormal QRS axis, may be present. Chest radiograph may reveal cardiomegaly, pulmonary edema, or pleural effusion. Elevated C-reactive protein, serum troponin, and aspartate aminotransferase levels will support the diagnosis, and an echocardiogram will show reduced ventricular function. Cardiac magnetic resonance is a noninvasive method to confirm the diagnosis, but the gold standard is an endomyocardial biopsy. The presence of immune complexes indicates an immune-mediated process, and immunosuppressive therapy may be indicated. Treatment includes inotropic support, diuretics, and afterload reducers in a critical care setting.

Anomalous left coronary artery originating from the pulmonary artery (ALCAPA) is a congenital abnormality that can present in early infancy with irritability, poor feeding, and difficulty breathing. The electrocardiogram may reveal abnormal Q waves in leads  $V_4$ - $V_6$ , I and aVL, or an abnormal R wave progression.

An infant with supraventricular tachycardia may present with irritability, poor feeding, vomiting, cyanosis,

or pallor. Physical examination will reveal a rapid, regular rhythm; electrocardiogram is diagnostic.

### Hypoxic or Ischemic Events

Carbon monoxide (CO) poisoning and methemoglobinemia cause irritability by producing hypoxia. CO binds to hemoglobin with an affinity more than 200 times that of oxygen, whereas methemoglobin is unable to bind to oxygen. Both actions result in a leftward shift of the oxygen-hemoglobin dissociation curve and decreased oxygen delivery to the tissues. A history of smoke inhalation and exposure to an indoor gas stove or to automobile exhaust fumes may not be forthcoming without prompting. Early findings with CO poisoning are similar to influenza-like symptoms of headache, irritability, and dizziness, whereas prolonged exposure may result in altered mental status. Arterial measurement of carboxyhemoglobin is diagnostic.

Methemoglobinemia in infancy may be either hereditary or related to hypoxic events, medication use (sulfonamides, topical anesthetics, metoclopramide), products containing nitrites and nitrates (contaminated well water or foods with naturally occurring nitrates such as spinach, green beans, carrots, and squash), or to diarrhea, probably from the nitrite-forming bacteria in the gut. Hereditary methemoglobinemia is usually mild, whereas the acquired disease can be life threatening. The hallmarks of methemoglobinemia are characteristic blue-gray cyanosis that is not improved with oxygen despite normal arterial oxygen tension and chocolate brown appearance of arterial blood. Pulse oximetry will not be reliable as high levels of methemoglobin will tend to cause a pulse oximeter reading of about 85% regardless of the true level of oxygen saturation. Treatment of the patient begins with 100% supplemental oxygen by non-rebreather mask and aggressive supportive care. In CO poisoning, hyperbaric oxygen therapy may be indicated in certain clinical conditions; methylene blue is an effective treatment for methemoglobinemia.

In children with sickle cell anemia, ischemia may cause painful vaso-occlusive crisis. The first presentation in infants and younger children is usually irritability and dactylitis (painful swelling of the hands and feet) as a result of vascular stasis and ischemia. Treatment includes analgesia, hydration, and rest.

### Metabolic System

Hypoglycemia, hypo- or hyponatremia, hypo- or hypercalcemia, hypomagnesemia, and inborn errors of metabolism can all cause irritability. Hypoglycemia is defined as a glucose level of 40 mg/dL or less and can be a primary process or caused by sepsis, ingestion, or cardiac or respiratory failure. Rapid detection and treatment of hypoglycemia can prevent irreversible neurologic damage. Hyponatremia can result from gastrointestinal losses or water intoxication, whereas hyponatremia is seen with diarrhea in which the water losses exceed salt loss, when replacement fluid has too high a sodium content, or with improper preparation of infant formula. Hypocalcemia in the newborn period may cause irritability, poor feeding, and lethargy; later in infancy and during childhood, hypocalcemia is seen with rickets. Hypercalcemia is a rare

electrolyte disturbance resulting from hyperparathyroidism, vitamin D intoxication, or idiopathic causes. Hypomagnesemia is found with hypocalcemia.

The inborn errors of metabolism that cause irritability are those in which a toxic intermediate accumulates. Organic and aminoacidemias and urea cycle disorders result in metabolic acidosis or hyperammonemia. They are symptomatic in the first few weeks of life, with vomiting, poor feeding, irritability, and lethargy. When a milder degree of enzyme dysfunction is present, clinical disease may be triggered by a bacterial or viral illness.

### Toxins and Drugs

Life-threatening intoxication may result from heavy metals such as lead and mercury, drugs of abuse such as cocaine and alcohol, envenomation by scorpions and snakes, overdoses of or idiosyncratic reactions to medications, and contact with agricultural, industrial, or household chemicals. Thorough questioning about recent use of lawn chemicals, pesticides, and cleaning products may be the only clues to these factors as a cause of irritability because many of these chemicals will not be detected by standard toxicologic screenings of blood and urine. Prescribed or over-the-counter medications such as beta-agonists, antiepileptics, decongestants, antihistamines, antitussives, and various cold preparations may cause irritability even when used as directed and certainly when overused. Cocaine, alcohol, phencyclidine hydrochloride, inhalants, and other drugs of abuse are known to cause irritability. Infants and children may be exposed to these substances by passive means transplacentally, by ingestion of breast milk, or by inhalation. They may accidentally ingest alcohol, cigarettes, or other substances left within reach. A positive history may be difficult to elicit, and a toxicologic screen may not always be helpful; thus a strong index of suspicion is needed. Substance use or withdrawal should be considered in the differential diagnosis of any adolescent with chronic persistent irritability. In rare instances, intentional poisoning may be the cause of a child's distress.

### Malignancy

Many physicians remember at least 1 child who has had complaints of irritability and intermittent fever in whom leukemia with bone pain was diagnosed. Malignancies of all sorts may have a component of irritability among their symptoms and must be considered carefully when no other diagnosis is forthcoming.

## ACUTE IRRITABILITY IN THE WELL-APPEARING CHILD

Irritability in infants has been attributed to a variety of causes of pain or discomfort that may become obvious during the evaluation. Dental caries and teething may cause an infant to be fussy or irritable. In addition to irritability, teething may be accompanied by loose stools but not fever. Cold teething rings may provide some relief, but numbing gels with benzocaine are less helpful and may be harmful as they have been associated with methemoglobinemia.

Acute otitis media is a common cause of irritability, with or without fever, in children younger than 2 years and in those attending child care. Also common, particularly in the first year of life, is gastroesophageal reflux, which may be asymptomatic or reveal itself with postprandial irritability, recurrent vomiting, and inadequate weight gain.

Other sources of irritability and nonspecific crying episodes may be related to a foreign body in the ear or nose, a corneal abrasion, hair wrapped around a digit or penis, diaper rash, nonspecific vaginitis, balanitis, insect and spider bites or stings, and pain from the site of a vaccination. A thorough head-to-toe examination, including special attention to the eyes, ears, digits, and genitalia, is essential to establish a diagnosis.

A foreign body in the ear or nose, if present for a prolonged period, results in foul-smelling discharge. If visible, the object may be removed with forceps, by gentle irrigation, or by suction; otherwise removal should be done under sedation or general anesthesia. Disk batteries need to be removed emergently because they may leak and can cause tissue destruction. An insect in the ear canal can make a child very irritable and may be removed after first killing the insect with mineral oil or lidocaine.

Foreign bodies under the eyelid, inward turned eyelashes, or a baby scratching the eyes may cause corneal abrasion. The child may be irritable, with increased tearing, conjunctival injection, and photophobia. Diagnosis is made by Wood lamp examination after instillation of fluorescein into the eye. A foreign body may be removed by a moistened cotton-tipped applicator or by irrigation.

A hair tourniquet around a child's digit or genitals can cause irritability and pain. A thorough examination in the creases of the digits is essential because prolonged constricting bands may compromise distal circulation.

In some instances the source of a child's irritability will be found only on thorough examination of the genitalia, which may reveal evidence of vaginitis, balanitis, or an anal fissure. Diaper dermatitis, common after a diarrheal illness, with *Candida* infection or as an allergic reaction to the diaper material, is another potential cause of irritability in infants.

Infants can certainly be irritable after the administration of a vaccine, with local erythema, swelling, and tenderness at the injection site. Persistent, inconsolable crying lasting 3 hours or more within 48 hours of receiving whole-cell pertussis DTP vaccine have been reported but is significantly lower with the newer acellular-pertussis DTaP vaccine.

## CHRONIC IRRITABILITY

Chronic irritability may be recurrent or persistent in a child and challenges both the parents' and the physician's skills. Psychosocial causes may top the list, but toxic, neurologic, metabolic, and miscellaneous causes must be considered and are shown in Figure 169-1. Irritability as a chronic feature of a child's behavior may indicate significant problems with familial relationships and the ability to master the environment. Infants may be irritable because of parental-infant temperament mismatches, maternal depression, or

stress within the family from, for example, the birth of a new child. Abuse and neglect of a child may provoke irritable behavior or outbursts. An older child or adolescent who has a psychiatric condition such as depression, psychosis, autism, posttraumatic stress disorder, or substance abuse may be described as irritable by parents and others. The investigation and treatment of irritability in these situations may require a multidisciplinary and long-term approach.

### Chronic Recurrent Irritability

Colic is characterized by paroxysms of irritability or crying that begin and resolve without apparent cause in infants younger than 5 months of age. Criteria for the diagnosis are episodes of crying lasting 3 or more hours per day, occurring 3 or more days per week for at least 1 week. Colic typically peaks at 6 weeks and abates by 3 to 4 months. The physical examination is normal, and growth and development are not affected.

Constipation in the older infant or child, another common cause of recurrent irritability, is associated with inadequate fluid intake, low-fiber diet, dietary changes, and toilet training. The passage of large, hard stools can result in anal fissures, which make the situation worse as the child becomes even more reluctant to defecate because of the pain.

Food allergy affects approximately 6% to 8% of infants and young children and approximately 3.5% to 4% of adults. The most common food allergens include cow's milk, eggs, peanuts, wheat, and shellfish. Milk protein allergy is usually seen in the first few months of life: children are irritable and have blood-streaked stools, although they are otherwise healthy. Treatment involves switching to hypoallergenic formulas derived from cow's milk then gradually advancing to an unrestricted diet by 9 to 12 months of age.

Night terrors, typically occurring between 2 and 4 years of age during nonrapid eye movement sleep, usually begin with sudden and prolonged periods of inconsolable crying and end spontaneously, with the child rapidly returning to sleep. A nightmare occurs during rapid eye movement sleep, characterized by a frightening dream, which fully awakens the child, and return to sleep is delayed. Vivid recollection of the dream occurs, appropriate to the child's developmental and maturational stage. (See Chapter 194, Sleep Disturbances, Nonspecific.)

Neurologic disorders, such as brain tumors, migraine headaches, seizures, and postconcussion syndrome, are causes of chronic or recurrent irritability among older children and adolescents. Postconcussion syndrome is particularly distressing to families because the head injury may have occurred months or years before and may even have seemed minor, yet the irritability and behavior changes may be a persistent and major complaint.

### Chronic Persistent Irritability

#### Psychosocial Disorders

Attention-deficit/hyperactivity disorder is the most commonly diagnosed biological-behavioral disorder of childhood, occurring in approximately 8% to 10% of school-aged children. The children may have coexisting

externalizing disorders (conduct disorder and oppositional defiant disorder) and internalizing disorders (depression and anxiety disorders). A common presentation in infants and young children may be irritability from frustration as a result of family and peer relationships, propensity to accidental injury, and difficulty with academic work.

Autism spectrum disorder usually first manifests itself in children younger than 3 years. Early symptoms include irritability, deficits in verbal and social interaction, repetitive behaviors, failure to participate within groups, and hours spent in solitary play.

Children with a chronic condition face stressors beyond their illness itself, such as altered physical development and appearance, high absenteeism, and inability of their peer groups to accept their disease. The investigation and treatment of irritability in this context may require a multidisciplinary and long-term approach.

### Children With Cognitive Impairments

Children with severe intellectual disabilities are unable to verbalize what they are experiencing and are left to endure pain more often than healthy children. Although their caregivers are usually adept at reading their child's body language and behaviors to know when the child is in pain, the parent is not always able to identify the specific cause. These children are likely to experience pain from the same sources as unimpaired children (teething, sore throat, headache, minor trauma) but are also at risk for additional sources of pain and discomfort. Muscle spasms, gastroesophageal reflux, constipation, and urinary tract infections are frequent causes of irritability. In children with spastic quadriplegia, pathologic fractures often occur as a result of decreased bone density, limb rigidity, and joint contractures. Children with intellectual disabilities often require treatment for seizures, respiratory conditions, and constipation with drugs that have a high incidence of behavioral side effects (irritability, aggression, and hyperactivity).

A wide variety of chronic disorders have irritability as a prominent or sole component. Hormonal effects associated with adolescence in both boys and girls can cause moodiness and irritability.

## SUMMARY

Irritability has a variety of causes and can be indicative of life-threatening or relatively trivial or transient disorders, which is why it elicits a high degree of concern. In an ill-appearing infant or child the initial task is stabilization followed by a thorough search for a cause. In a well-appearing infant or child an organized approach is needed to determine the source of the irritability. A complete history and thorough physical examination can most often determine the cause. In puzzling cases, serial examinations and staged laboratory investigations may be necessary.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Prevent Shaken Baby Syndrome* (handout), American Academy of Pediatrics (patiented. solutions.aap.org)



- *Returning to Learning Following a Concussion* (article), *Pediatrics*, Vol 132, Issue 5, 2013 (pediatrics.aappublications.org/content/132/5/948)

### Medical Decision Support

- *Guidelines for Pediatric Concussion* (guideline), Ontario Neurotrauma Foundation (onf.org/documents/guidelines-for-pediatric-concussion)

### AAP POLICY

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## Chapter 170 JAUNDICE

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*Jaundice* is a yellowish discoloration of the skin, sclerae, and mucous membranes resulting from deposition of the bile pigment bilirubin. The presence of jaundice on clinical examination indicates *hyperbilirubinemia*, which is defined as a total serum bilirubin greater than 1.5 mg/dL. In general, jaundice becomes evident at serum bilirubin concentrations greater than 3 mg/dL in older children and greater than 5 mg/dL in newborns.

Hyperbilirubinemia is typically characterized by the fraction of bilirubin that is increased, unconjugated (indirect), or conjugated (direct). Elevation of either of these fractions results in jaundice. Conjugated hyperbilirubinemia refers to a direct bilirubin greater than 2 mg/dL or greater than 20% of the total bilirubin

concentration. The presence of conjugated hyperbilirubinemia suggests hepatobiliary tract conditions.

### BILIRUBIN METABOLISM

To identify the cause of jaundice, the pediatrician or other physician must be familiar with the normal metabolism of bilirubin, which is the end product of heme degradation. Heme is produced from the breakdown of hemoglobin (70%–80%) and other hemoproteins (20%–30%). The conversion from heme to bilirubin follows a 2-step process that occurs mainly in the reticuloendothelial cells of the spleen, liver, and bone marrow. Heme is converted to biliverdin by the microsomal enzyme heme oxygenase and then to bilirubin by the cytosolic enzyme biliverdin reductase. This unconjugated bilirubin is a hydrophobic compound that is tightly bound to serum albumin and is transported to the liver for conjugation and clearance.

The metabolism of bilirubin follows 4 distinct steps: (1) The bilirubin is taken up across the sinusoidal (basolateral) membrane of the hepatocyte by a membrane receptor carrier. (2) Once inside the hepatocyte, the bilirubin binds to cytosolic glutathione S-transferase, historically known as ligandin. It is then conjugated with glucuronic acid by the enzyme bilirubin UDP-glucuronosyl transferase (BUGT) in the endoplasmic reticulum to form bilirubin monoglucuronides and diglucuronides. (3) Water-soluble bilirubin glucuronides are excreted into the bile through the apical canalicular membrane. This process is mediated by adenosine triphosphate-dependent transporters. Almost all the bilirubin in adult human bile is of the conjugated form, with bilirubin monoglucuronides accounting for 15% and diglucuronides accounting for 85%. In contrast, neonates have a higher concentration of bilirubin monoglucuronides in their bile because of a lower BUGT activity. The monoglucuronides are easily deconjugated and reabsorbed in the intestine. (4) The excreted bilirubin is further metabolized by bacterial flora to form urobilinoids, which are then eliminated in the feces, thus preventing the intestinal absorption of bilirubin.

Bilirubin glucuronides can also be deconjugated by bacteria or tissue  $\beta$ -glucuronidase in the intestine and then reabsorbed in the terminal ileum, a process known as *enterohepatic circulation*. Newborns are at high risk for bilirubin absorption from the intestine because of the high concentration of bilirubin monoglucuronides in their bile, the lack of intestinal bacterial flora to efficiently produce urobilinoids, and the high content of bilirubin and  $\beta$ -glucuronidase in meconium. Conditions that delay the passage of meconium can result in neonatal hyperbilirubinemia.

### SERUM BILIRUBIN

Serum bilirubin is conventionally measured by spectrophotometry based on the Van den Bergh (diazotization) reaction. Conjugated (direct) bilirubin reacts rapidly and unconjugated (indirect) bilirubin reacts slowly with diazo reagents. Indirect bilirubin is calculated as the difference between the total bilirubin and the direct bilirubin fraction. Although the terms *direct* and *conjugated* bilirubin are used interchangeably, direct

bilirubin actually consists of 2 components: conjugated bilirubin and  $\delta$ -bilirubin. In hepatobiliary obstruction, bilirubin glucuronides are not excreted properly from the hepatocyte into the bile. Under these circumstances, bilirubin glucuronides can reflux back into the systemic circulation and covalently bind to albumin. This conjugated bilirubin-albumin compound is known as  $\delta$ -bilirubin. Methods such as high-performance liquid chromatography can measure  $\delta$ -bilirubin as well as  $\alpha$ -,  $\beta$ -, and  $\gamma$ -bilirubin that corresponds to the unconjugated, monoconjugated, and diconjugated forms, respectively. Because of the long half-life of albumin,  $\delta$ -bilirubin accounts for the prolonged direct hyperbilirubinemia occasionally observed after restoration of normal bile flow.

## DIFFERENTIAL DIAGNOSIS

When discussing the differential diagnosis in a patient with jaundice, one should first categorize hyperbilirubinemia as either unconjugated or conjugated. It is helpful then to discuss each category separately in 2 different age groups: (1) newborns and young infants (infants <6 months), and (2) older infants (infants >6 months) and children. In general, unconjugated hyperbilirubinemia is common in neonates but relatively rare thereafter. Neonatal unconjugated hyperbilirubinemia is usually transient and benign, but marked increases of bilirubin can be toxic to the central nervous system. On the other hand, conjugated hyperbilirubinemia is always pathologic. When present in young infants, it is often related to primary hepatobiliary disorders, systemic or metabolic diseases, or genetic defects in bilirubin and bile acid metabolism or transport. In older children, viral hepatitis and drug- or toxin-induced liver damage are more prevalent.

## JAUNDICE IN NEWBORNS AND YOUNG INFANTS

A brief list of the causes of jaundice in newborns and young infants is presented in Box 170-1.

### Unconjugated Hyperbilirubinemia

The transition from intrauterine to extrauterine life is commonly associated with hyperbilirubinemia. Newborns have a total bilirubin level greater than the adults' normal limit of 1.5 mg/dL. More than half of newborns develop clinical jaundice in the first week of life, with most of them having unconjugated hyperbilirubinemia.

#### Increased Production of Bilirubin

Nonphysiologic jaundice should always be considered part of the differential diagnosis in neonatal jaundice. When evaluating patients with jaundice, factors such as early onset, rapid progression, and persistence of jaundice beyond 2 weeks of life always suggest a pathologic cause. In most instances, pathologic unconjugated hyperbilirubinemia results from either excessive production or abnormal hepatic clearance of bilirubin.

Hemolysis is the most common cause of excessive bilirubin production in neonates and is usually

### BOX 170-1 Differential Diagnosis of Jaundice in Newborns and Young Infants<sup>a</sup>

#### UNCONJUGATED HYPERBILIRUBINEMIA

##### Increased production of bilirubin

- Hemolysis (ABO-Rh incompatibility, erythrocyte defects, erythrocyte enzyme defects, disseminated intravascular coagulopathy)
- Polycythemia
- Cephalohematoma resorption

##### Decreased hepatocellular uptake or conjugation

- Prematurity
- Congenital hypothyroidism
- Physiologic jaundice of the newborn
- Breast milk jaundice
- Drug toxicity
- Gilbert syndrome, Crigler-Najjar syndrome

#### CONJUGATED HYPERBILIRUBINEMIA

##### Liver diseases

- Acute liver damage (ischemia, hypoxia, acidosis)
- Infection (sepsis, TORCH [toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex])
- Viral or other hepatitis
- Parenteral nutrition associated liver disease
- Metabolic liver disease (galactosemia, neonatal hemochromatosis,  $\alpha_1$ -antitrypsin deficiency, tyrosinemia, mitochondrial defects)
- Hormones and drugs

##### Obstruction of biliary system

- Congenital anomalies (biliary atresia, choledochal cyst)

##### Defects of bilirubin metabolism or transport

- Progressive familial intrahepatic cholestasis
- Dubin-Johnson syndrome, Rotor syndrome

<sup>a</sup>Young infants defined as infants younger than 6 months.

observed within the first 24 hours of life. Hemolysis is often seen in association with maternal-fetal blood type incompatibility. ABO and Rh incompatibility are the 2 most common types leading to hemolytic disease of the newborn. ABO incompatibility occurs in approximately 15% of all pregnancies but results in hemolytic disease in only 3% of newborns, with less than 0.1% of infants needing exchange transfusion. Hemolysis caused by ABO incompatibility is usually seen in newborns with blood type A or B born to blood type O mothers. Laboratory findings include a weakly positive direct Coombs test, high reticulocyte count, spherocytes on blood smear, and high levels of unconjugated bilirubin. Hemolytic disease in Rh incompatibility usually develops when an Rh-negative mother has become sensitized after exposure to Rh-positive fetal blood during a previous pregnancy. Rh incompatibility is less common and usually more severe than ABO incompatibility. In the United States, the

prevalence of the Rh-negative genotype is approximately 15% in whites, 5% in blacks, and less than 1% in Asians. Rh incompatibility occurs in approximately 1.06 per 1,000 live births. Affected infants usually develop jaundice in the first hours of life. Anemia and hepatosplenomegaly are common features. In severe cases, fetal hydrops from intrauterine hemolysis may be present at birth. Laboratory findings include a positive direct Coombs test, high reticulocyte count, anemia, and high unconjugated bilirubin levels. The prophylactic use of RhoGAM (anti-D gammaglobulin) in Rh-negative mothers has greatly decreased the incidence of this type of hemolytic disease of the newborn.

Other causes of hemolysis leading to unconjugated hyperbilirubinemia in the neonate include hemoglobinopathies such as  $\alpha$ -thalassemia, red blood cell enzyme defects, and neonatal polycythemia.  $\alpha$ -Thalassemia should be suspected in newborns with jaundice and a moderate hypochromic, microcytic, hemolytic anemia. Erythrocyte enzyme defects such as glucose-6-phosphate dehydrogenase (G6PD) or pyruvate kinase deficiency may cause hemolysis at any age. Neonatal polycythemia can cause an increase in bilirubin production as a result of an absolute increase in red blood cell mass. Unconjugated hyperbilirubinemia occurs in 2% to 22% of newborns with polycythemia. Cephalohematomas also can lead to an increased bilirubin production from rapid breakdown of red blood cells in the extravascular space.

#### Decreased Hepatocellular Uptake or Conjugation of Bilirubin

Drugs such as aspirin, cephalosporins, and sulfonamides can impair bilirubin transport by altering bilirubin-albumin binding. Rifampin has been demonstrated to competitively inhibit hepatocellular uptake of bilirubin. Unconjugated hyperbilirubinemia is associated with a decreased BUGT activity in conditions such as physiologic jaundice of the newborn and breast milk jaundice, and with a delayed maturation of BUGT in hypothyroidism.

Crigler-Najjar and Gilbert syndromes are 2 types of familial unconjugated hyperbilirubinemia caused by several mutations in the gene encoding for BUGT. *Crigler-Najjar syndrome* is a rare familial form of unconjugated hyperbilirubinemia caused by mutations in the gene encoding BUGT1, leading to either absent (type 1) or decreased (type 2) BUGT activity. Crigler-Najjar syndrome type 1 is an autosomal recessive disease, which presents with severe nonhemolytic jaundice in the first hours of life. Crigler-Najjar syndrome type 2 is an autosomal dominant disease. Jaundice is usually less severe in type 2 and may improve with phenobarbital treatment. *Gilbert syndrome* is rarely diagnosed in this age group, and is further discussed in the Jaundice in Older Infants and Children section.

#### Conjugated Hyperbilirubinemia

Conjugated hyperbilirubinemia, also known as *cholestatic jaundice*, is always pathologic. It can occur as a result of impaired bile formation by the hepatocyte or from obstruction to bile flow through the intrahepatic

or extrahepatic biliary system. Conditions associated with conjugated hyperbilirubinemia include primary hepatobiliary disorders, genetic or metabolic diseases, systemic infections, and drug toxicity. *Neonatal cholestasis* refers to infants younger than 3 months who have cholestatic jaundice regardless of the cause. With the availability of new diagnostic techniques, the number of patients with an identified specific cause has increased.

#### Systemic Illnesses

Congenital TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex) infections have been associated with conjugated hyperbilirubinemia. Infants with TORCH infections often have a low birth weight, hepatosplenomegaly, and cutaneous manifestations, as well as ophthalmologic and central nervous system involvement. Common laboratory findings include anemia, thrombocytopenia, increased transaminases, and cholestasis. Other infections, such as HIV and hepatitis B and C, may also be associated with conjugated hyperbilirubinemia in newborns or young infants. However, these infections have decreased with improved prenatal screening.

Patients with sepsis may develop jaundice and hepatocellular dysfunction. The most frequent bacterial organisms associated with conjugated hyperbilirubinemia in neonates are *Escherichia coli*, *Streptococcus* group B, and *Listeria monocytogenes*. Conjugated hyperbilirubinemia may also develop in newborns and young infants with urinary tract infections.

Critically ill patients, including young infants with no previous underlying liver disease, may develop jaundice with other signs of hepatic dysfunction, such as increased transaminases. Conditions such as cardiopulmonary arrest, shock, and severe metabolic acidosis may cause an acute ischemic insult to the liver resulting in hepatocyte necrosis. Affected patients will have a marked increase in serum transaminase levels and direct hyperbilirubinemia developing within 24 to 48 hours after the insult. In most cases, the liver function will normalize once the initial insult is corrected; rarely, patients may develop acute liver failure.

Liver disease associated with parenteral nutrition (PN) is often seen in patients who receive PN for more than 2 weeks. There is growing literature suggesting that soybean-based lipid emulsions are the major factor accounting for PN-associated liver disease. Recent data have demonstrated that using lipid emulsions based on fish oil can reverse or prevent PN cholestasis. Similar results have been achieved by limiting the soybean-based lipid emulsions to 1 g/kg/day or less.

#### Metabolic Disorders

Metabolic liver diseases usually manifest during early infancy and should always be considered in the differential diagnosis in a newborn or young infant with cholestasis, especially when associated with hypoglycemia, hyperammonemia, or lactic acidosis.

*Galactosemia* is an inborn error of galactose metabolism inherited as an autosomal recessive trait, with an estimated occurrence of 1 in 60,000. The classic transferase-deficiency galactosemia can affect multiple organs, including the liver, kidneys, brain,



eyes, intestines, and gonads. The hepatocellular damage in galactosemia is caused by accumulation of toxic metabolites of galactose-1-phosphate and galactitol in the liver. The clinical presentation varies from mild liver disease to fulminant liver failure in the neonatal period. Patients often have vomiting, diarrhea, and poor feeding. They can also present with *E coli* sepsis. Jaundice can also be found in patients with other inborn errors of carbohydrate metabolism, such as hereditary fructose intolerance and certain types of glycogen storage diseases. In these conditions, the onset of symptoms rarely occurs during early infancy.

*Neonatal hemochromatosis* is a rare and severe liver disease in newborns. The typical pathologic finding is excessive iron deposition in extrahepatic sites. It has been recently hypothesized that this condition is caused by maternal alloimmunity directed at the fetal liver. Infants with neonatal hemochromatosis usually experience intrauterine growth restriction and are born prematurely. In most cases, signs and symptoms of acute liver failure are present at birth or develop soon thereafter. The clinical presentation includes hypoglycemia, cholestatic jaundice, hypoalbuminemia, and profound coagulopathy. Transaminases can be slightly increased or even normal. Typical laboratory findings include increased ferritin and transferrin saturation and a relatively low transferrin level. Neonatal hemochromatosis should be strongly considered in all newborns with acute liver failure. Diagnosis can be aided by punch biopsy of the lip mucosa; the tissue sample is analyzed for iron deposition in the salivary glands. New treatment modalities include the use of intravenous immunoglobulin and exchange transfusions.

$\alpha_1$ -Antitrypsin deficiency is a relatively common genetic disorder, with the homozygous *PiZZ* genotype found in 1 in 1,600 to 2,000 live births. Only 10% of patients with  $\alpha_1$ -antitrypsin deficiency will develop signs and symptoms of liver disease. This disorder typically manifests in the first few months of life with jaundice, although the onset of liver disease can occur later in life. Liver injury results from the hepatotoxic effect of retained mutant  $\alpha_1$  *ATZZ* molecules in the endoplasmic reticulum of the hepatocyte.

*Tyrosinemia type 1*, also known as *hepatorenal tyrosinemia*, is a rare disorder that affects multiple organs, including the liver, kidneys, and peripheral nerves. The deficiency of fumarylacetoacetate hydrolase, an enzyme involved in tyrosine degradation, results in tissue accumulation of tyrosine and other intermediate metabolites. Clinical findings range from severe liver disease or acute liver failure in early infancy to chronic liver disease in older children. The striking laboratory finding is a markedly increased  $\alpha$ -fetoprotein level. Patients with this condition may develop hepatocellular carcinoma early in life. The presence of succinylacetone in urine or blood is pathognomonic for tyrosinemia. Early diagnosis is important because specific medical therapy will improve quality of life and delay disease progression.

Primary mitochondrial hepatopathies are caused by a variety of defects, including mitochondrial DNA depletion, respiratory chain defects, fatty acid oxidation defects, and mitochondrial membrane enzyme defects.

In addition to having signs and symptoms of liver disease, affected patients have neuromuscular problems. Marked lactic acidosis is a relatively common feature. Symptoms usually develop within the first few months of life.

### Obstructive Jaundice

*Extrahepatic biliary atresia* (EHBA) is an idiopathic, destructive, inflammatory process of both the extrahepatic and intrahepatic bile ducts. Affected infants typically develop jaundice and acholic stools at around 2 weeks of age; however, in early stages, the stools may still have bile pigment. Infants with cholestatic jaundice need prompt referral and evaluation for EHBA because the prognosis can be improved by early diagnosis and timely surgery. Abdominal sonography is a useful screening tool. The absence of gallbladder or the appearance of a *triangular cord sign* at the hilar region is suggestive of EHBA. However, the presence of a gallbladder on sonography does not exclude this condition. Abdominal sonography can also exclude other causes of cholestasis, such as choledochal cysts, gallstones, or biliary sludge. Liver biopsy is usually performed when evaluating patients with suspected EHBA, although the histologic findings are not always conclusive. The diagnosis is confirmed at the time of endoscopic retrograde cholangiopancreatography (ERCP) with cholangiogram or intraoperative cholangiogram. Once the diagnosis is made, a hepatoportoenterostomy or Kasai procedure is then performed in an effort to reestablish bile flow.

*Choledochal cysts* are rare congenital anomalies of the biliary tract characterized by varying degrees of cystic dilation of the biliary tree. Choledochal cysts may be detected at any age; 18% of cases are diagnosed during the first year of life. The classic presentation of jaundice, abdominal pain, and right epigastric mass is rarely observed in infants and young children.

*Alagille syndrome*, also known as *arteriohepatic dysplasia*, is inherited as an autosomal dominant condition with variable penetrance. It is characterized by paucity of the intrahepatic bile ducts, peripheral pulmonary stenosis, butterfly vertebrae, posterior embryotoxon, and peculiar facies. Jaundice and pruritus are often present as the main clinical features during infancy. Mutations in the Jagged 1 (*JAG1*) gene are identified in most patients. The diagnosis is confirmed by genetic testing.

### Isolated Bile Acid Metabolism Defects

Progressive familial intrahepatic cholestasis (PFIC) has been identified as a distinct group of conditions involving intrahepatic cholestasis from bile acid transport defects leading to impairment of bile excretion. Three distinct gene mutations have been identified, accounting for the 3 major subtypes of this condition, including *PFIC1*, *PFIC2*, and *PFIC3*. Genetic testing is available to detect these mutations. Affected patients often develop jaundice in the first few months of life. In addition, they may also have severe pruritus, growth failure, fat-soluble vitamin deficiency, abnormal coagulation profile, and increased serum bile acids. The disease usually progresses to cirrhosis and liver failure early in life.



## JAUNDICE IN OLDER INFANTS AND CHILDREN

A brief list of the differential diagnosis of jaundice in older infants and children is presented in Box 170-2. In this age group, jaundice is an unusual sign and may suggest a serious clinical condition.

### Unconjugated Hyperbilirubinemia

Unconjugated hyperbilirubinemia is seen in older infants and children usually associated with underlying hemolytic diseases such as sickle cell anemia, G6PD deficiency, or hereditary spherocytosis. Mild unconjugated hyperbilirubinemia may also result from nonhemolytic conditions such as *Gilbert syndrome*, a benign disorder that affects 7% of the general population. It is inherited as an autosomal dominant trait, although an autosomal recessive pattern has been described. An insertional mutation of the *UGT1A1* gene results in a reduced level of expression of the gene. Jaundice does not typically develop until after puberty and is usually seen during prolonged fasting or in association with acute viral illnesses. Patients usually have mild indirect hyperbilirubinemia with otherwise normal liver tests and no evidence of ongoing hemolysis.

### Conjugated Hyperbilirubinemia

#### Liver Disease

Jaundice can develop as a result of acute or chronic viral hepatitis, autoimmune hepatitis, and drug- or toxin-induced hepatic injury. Metabolic liver diseases are much less common in older children, with the exception of Wilson disease. Infiltrative malignancies can also cause jaundice at any age. The incidence of acute viral hepatitis A has decreased in the United States with the use of vaccination. Children younger than 5 years with acute hepatitis A infection tend to be anicteric. The disease rarely causes fulminant liver failure. Hepatitis E infection has been increasingly recognized recently and has a clinical course similar to that of hepatitis A. Hepatitis B or C infection is usually anicteric and chronic in children. Other viruses, such as Epstein-Barr virus, cytomegalovirus, adenovirus, and enterovirus, can also cause acute hepatitis, although jaundice is not always present.

*Autoimmune hepatitis* (AIH) is a progressive inflammatory condition of the liver of unknown etiology, which can progress to cirrhosis if not promptly diagnosed and treated. AIH should always be considered in the differential diagnosis in a patient with increased transaminases. Jaundice is present in more than one-half of patients with AIH. Hyperglobulinemia is often evident, and autoantibodies such as antinuclear antibody, anti-smooth muscle antibody, and anti-liver-kidney microsomal antibody may be positive or negative. A positive liver-kidney microsomal antibody categorizes the disease as AIH type 2, which may have a more fulminant course and can present as acute liver failure. AIH type 1 is more common, with onset likely before adolescence.

*Drug-induced liver injury* is initially suspected based on circumstantial evidence. It can be classified into 3 types—(1) hepatic, (2) cholestatic, or (3) mixed hepatic-cholestatic—according to different clinical features.

### BOX 170-2 Differential Diagnosis of Jaundice in Older Infants<sup>a</sup> and Children

#### UNCONJUGATED HYPERBILIRUBINEMIA

- Hemolysis: erythrocyte defects, erythrocyte enzyme defect (glucose-6-phosphate dehydrogenase), disseminated intravascular coagulopathy
- Gilbert syndrome

#### CONJUGATED HYPERBILIRUBINEMIA

##### Liver disease

- Viral hepatitis (hepatitis A, B, C, E)
- Hepatitis caused by other viruses (herpes simplex virus, Epstein-Barr virus, cytomegalovirus)
- Toxins and drugs (ethanol, acetaminophen, isoniazid, phenytoin)
- Autoimmune hepatitis
- Metabolic liver disease ( $\alpha_1$ -antitrypsin deficiency, tyrosinemia, Wilson disease, mitochondrial defects)
- Nonalcoholic fatty liver disease
- Acute liver damage: ischemia, hypoxia, acidosis
- Parenteral nutrition–associated liver disease
- Pregnancy related (acute fatty liver of pregnancy, preeclampsia)
- Malignancy

##### Obstruction of the biliary system

- Choledochal cyst
- Cholelithiasis or choledocholithiasis
- Cholecystitis
- Diseases of the bile ducts (primary sclerosing cholangitis, AIDS cholangiopathy)

##### Bilirubin metabolism or transport defects

- Progressive familial intrahepatic cholestasis
- Dubin-Johnson syndrome, Rotor syndrome

<sup>a</sup>Older infants defined as infants older than 6 months.

Cholestasis is more prominent when damage to bile duct epithelial cells occurs, resulting in an impaired bile flow. Cholestatic jaundice can be caused by many different drugs, including estrogen or oral contraceptive pills, erythromycin, cyclosporine, and haloperidol. Acetaminophen overdose can cause acute hepatitis with zone 3 hepatocyte necrosis. Most cases of drug-induced liver damage spontaneously resolve once the drug responsible for the injury is withdrawn.

*Wilson disease* is an autosomal recessive disorder of human copper metabolism, with clinical onset usually after 5 years of age. Mutations in the *ATP7B* gene lead to impaired biliary excretion of copper, which results in a progressive accumulation of copper in the liver and subsequently in other organs and tissues. Hemolytic anemia, Kayser-Fleischer rings in the eyes, and neuropsychiatric symptoms are classic features of the disease. Copper deposition in the liver can result in acute or chronic hepatitis, cirrhosis, or even fulminant liver failure with severe cholestatic jaundice.

### Biliary Obstruction

*Cholelithiasis* is the most common cause of biliary obstruction in children and is often associated with obesity, dyslipidemia, or an underlying hemolytic disease. Children usually present with vomiting and right upper quadrant abdominal pain, with or without jaundice. Primary sclerosing cholangitis is characterized by stenosis, dilation, and fibrosis involving the intrahepatic or extrahepatic biliary tree, or both. It is the most common form of chronic liver disease in children with inflammatory bowel disease. Cholestatic jaundice is seen in less than one-half of affected patients.

### Hepatic Bilirubin Transport Defects

Dubin-Johnson syndrome and Rotor syndrome are both inherited as autosomal recessive disorders. Dubin-Johnson syndrome is caused by mutations in the canalicular transporter gene, which result in an impaired secretion of conjugated bilirubin, whereas Rotor syndrome involves an impaired intracellular storage capacity of the liver for binding anions. In both syndromes, conjugated hyperbilirubinemia is present without abnormalities in other liver tests. The striking characteristic in Dubin-Johnson syndrome is a brown to black discoloration of the liver, which results from pigment deposition in the lysosomes. The liver histology is otherwise normal in both syndromes.

## EVALUATION

### History

A detailed history is essential when evaluating a patient with jaundice because the information obtained may help to identify the cause. Special attention should be paid to the presence of signs and symptoms, such as a viral prodrome, abdominal pain or distention, acholic stools, dark urine, or pruritus. In neonates, the prenatal and birth history may help identify potential risk factors. In older children, the patient's age at the time of onset of jaundice, associated signs and symptoms, and exposure to hepatotoxic agents are of paramount importance. A detailed family history should include information about the presence of persistent jaundice, chronic liver diseases, hemolysis, and metabolic diseases. Distinguishing among acute and chronic liver diseases, intrahepatic processes and extrahepatic biliary tract obstruction, or primary liver diseases and systemic diseases is the major goal at the time of the initial evaluation. This approach may guide the physician in selecting appropriate laboratory tests and imaging studies that can lead to a definitive diagnosis.

### Physical Examination

In general, patients with jaundice from unconjugated hyperbilirubinemia have bright-yellow skin, whereas patients with jaundice from conjugated hyperbilirubinemia have dark green-yellow skin. Patients should undergo a complete physical examination with special focus on general appearance, growth, and development; signs of cardiovascular dysfunction; neurologic signs; and organomegaly. The size and the character of the liver should be carefully determined. The newborn or infant liver is a large organ relative to body

size. In newborns, the mean liver span is 5.9 cm along the midclavicular line, calculated by measuring the distance between the percussed upper and palpated lower liver edges. The healthy infant's liver may be palpable and is typically less than 2 cm below the right costal margin. The consistency and character of the liver edge may help determine the nature of underlying liver disease. An enlarged liver resulting from an acute intrahepatic process is usually tender but soft. A cirrhotic liver may have a hard and irregular edge; however, its edge is not always palpable.

A thorough abdominal examination should be performed to identify the presence of an enlarged spleen or any other abdominal masses, areas of tenderness, and ascites, as well as the abdominal cutaneous venous pattern. The tip of the spleen can normally be palpated below the left costal margin in newborns and infants. Splenomegaly in a patient with underlying liver disease implies portal hypertension, especially in the presence of ascites and a prominent abdominal cutaneous venous pattern. Other physical findings may indicate a particular cause, such as xanthomas in primary biliary cirrhosis, Kayser-Fleischer rings in Wilson disease, and characteristic facial features and posterior embryotoxon in Alagille syndrome.

### Laboratory Tests

Initial laboratory studies include a complete blood cell count (CBC), liver tests, and a coagulation profile. Isolated hyperbilirubinemia with otherwise normal liver tests suggests the possibility of hemolytic disease or bilirubin metabolism defects. A CBC is useful in detecting hemolysis, indicated by the presence of anemia with fragmented red blood cells (schistocytes) and increased reticulocytes on the smear. Thrombocytopenia is typically seen in patients with portal hypertension and hypersplenism.

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels are the most frequently used markers of hepatocellular injury. ALT is a more specific indicator of hepatocyte injury because AST also increases with hemolysis and myocardial or skeletal muscle injury. In general, a marked increase in AST and ALT occurs in severe viral hepatitis, acute toxin- or drug-induced hepatic necrosis, or ischemia. A mild increase of AST and ALT is seen in nonalcoholic fatty liver disease, chronic viral hepatitis, and drug toxicity. Declining AST and ALT levels usually indicate hepatocyte recovery. However, in the course of fulminant liver failure, if seen in association with a worsening liver synthetic function, falling AST and ALT levels may be an ominous sign of massive hepatic necrosis, with few viable hepatocytes remaining to further release these enzymes. AST and ALT levels are less useful in patients with chronic end-stage liver disease because they can be normal or only slightly increased in the presence of marked fibrosis of the liver.

Alkaline phosphatase and  $\gamma$ -glutamyltransferase (GGT) are useful markers for intrahepatic and extrahepatic cholestasis. In most hepatobiliary diseases, both alkaline phosphatase and GGT are increased. However, in progressive familial intrahepatic cholestasis (types 1 and 2), a normal or low GGT is

observed in the presence of a high alkaline phosphatase. Isolated increase of alkaline phosphatase may be seen in patients with nonhepatobiliary diseases such as bone disorders. Normal GGT values in newborns may be 5 to 8 times greater than those in adults.

Prothrombin time (PT) and albumin are used to evaluate hepatic synthetic function. An abnormal PT results from an impaired hepatic synthesis of coagulation factors I, II, V, VII, and X or deficiency of vitamin K (or both). Parenteral administration of vitamin K generally normalizes a prolonged PT in patients with vitamin K deficiency associated with cholestatic jaundice, but not in patients with hepatocellular disease. In acute liver injury, a markedly increased PT suggests the possibility of fulminant liver failure. Hypoalbuminemia may be seen in patients with acute and chronic liver diseases. In the early stages of acute liver injury, the serum albumin may not be a reliable indicator of hepatic synthetic function because it has a long half-life of approximately 21 days.

Based on the clinical information obtained and results of the initial laboratory tests, further evaluation including imaging studies may be warranted, including blood and urine cultures, viral serologic studies, toxin and drug screen, autoimmune markers,  $\alpha_1$ -antitrypsin phenotype, ceruloplasmin, urine succinyl acetone, and serum bile acids. In newborns or young infants with jaundice and abnormal liver tests, TORCH titers should also be obtained.

### Imaging Studies

Ultrasonography is the most useful initial imaging modality in the assessment of the intrahepatic and extrahepatic biliary system in patients with jaundice. This noninvasive study may help identify abnormalities such as biliary atresia, choledochal cyst, hepatic cystic lesions, and cholelithiasis. Computed tomographic scans may be preferred when general anatomic information of the hepatobiliary system is desired or a noncystic hepatic lesion is suspected. Nuclear scintigraphy is a useful study when considering the diagnosis of acute cholecystitis or chronic acalculous cholecystitis. Magnetic resonance cholangiopancreatography (MRCP) is a noninvasive study that identifies abnormalities of the intrahepatic and extrahepatic biliary system. ERCP provides similar information to that of the MRCP, but it allows the possibility of therapeutic interventions such as sphincterotomy, biliary stone extraction, or stent placement.

Liver biopsy provides information on the histology and architecture of the liver and has become an invaluable diagnostic tool in the evaluation of patients with liver disease; it is also helpful in assessing disease progression. Liver biopsy is most commonly performed in patients with persistently abnormal liver tests, especially when conventional laboratory and imaging studies do not lead to a specific diagnosis. The use of liver biopsy in the diagnosis of acute liver injury is limited because of the nonspecific histologic changes commonly found.

### MANAGEMENT

The treatment of newborns with unconjugated hyperbilirubinemia is based on the revised guideline

published by the American Academy of Pediatrics. This guideline provides a framework for detecting neonatal hyperbilirubinemia and preventing kernicterus in term and near-term newborn infants. It also emphasizes the importance of a systematic assessment of the risks of severe hyperbilirubinemia, close follow-up, and prompt intervention when necessary.

The management of patients with direct hyperbilirubinemia should focus on correcting the underlying cause, optimizing nutrition, and controlling pruritus. Malabsorption of fat and fat-soluble vitamins is commonly seen in patients with cholestasis because they have an impaired bile secretion. Unlike long-chain triglycerides, which require bile acid micelles for solubilization, medium-chain triglycerides (MCTs) are relatively water soluble and directly absorbed into the portal system. Therefore, a diet high in MCTs should be used to promote growth in children with chronic cholestasis. Formulas with a relatively high MCT concentration are often used in patients with cholestasis. Supplementation of fat-soluble vitamins A, D, E, and K is essential. Serum vitamin levels should be routinely followed to monitor adequate supplementation.

In the attempt to control cholestasis-associated pruritus, several different therapeutic agents have been used with very little success. Ursodeoxycholic acid has been shown to lower serum bile acid levels by increasing bile flow. Other agents, such as cholestyramine, a bile acid-binding resin, and rifampin, an antibiotic used in the treatment of tuberculosis, have also been used.

Liver transplantation in children is now an accepted therapy for many life-threatening liver diseases. Current survival rates for children after liver transplantation are 90% at 1 year and 85% at 3 years. EHBA is the most common indication for liver transplantation in children; other indications include  $\alpha_1$ -antitrypsin deficiency, fulminant liver failure, chronic hepatitis, metabolic liver disease, and cirrhosis of unknown origin. Early referral and transfer to a liver transplantation center are important to assure a good outcome.

#### WHEN TO REFER

- Unexplained jaundice
- Direct hyperbilirubinemia at any age
- Persistence of abnormal liver tests
- Hepatomegaly or splenomegaly

#### WHEN TO ADMIT

- Jaundice in an ill patient
- Feeding intolerance and dehydration
- Inpatient management of underlying conditions
- Impending acute liver failure

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Jaundice* (fact sheet), American Academy of Pediatrics ([healthychildren.org/English/ages-stages/baby/Pages/Jaundice.aspx](http://healthychildren.org/English/ages-stages/baby/Pages/Jaundice.aspx))
- *Jaundice and Your Newborn* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))



**Medical Decision Support**

- *BilliTool* (interactive tool), Tony Burgos, MD, et al (bilitool.org)
- *Jaundice/Kernicterus* (Web page), Centers for Disease Control and Prevention (www.cdc.gov/ncbddd/jaundice/index.html)

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## Chapter 171

### JOINT PAIN

David M. Siegel, MD, MPH; Bethany Marston, MD

Pediatricians are often faced with clinical situations involving musculoskeletal aches and pains, and within this group of symptoms lies the subset of joint pain. In fact, 1 of every 6 to 10 pediatric outpatient visits includes a musculoskeletal complaint. Discomfort in a joint can result from a wide variety of causes, and the possibilities must be considered to allow appropriate evaluation and management. A systematic approach to patients who experience pain or swelling in 1 or more joints helps physicians arrive at an accurate diagnosis and course of therapy.

**DEFINITIONS**

Joint pain, or arthralgia, is the subjective experience of pain referable to a bony articulation. In a young child, this might be inferred from the patient's refusal to move an extremity. The term *arthralgia* should only be used if the discomfort originates in the joint itself; it is important to distinguish arthralgia from myalgia, or muscle pain, and from other types of pain that may involve the limbs but not the joints. The term *arthritis* should be used only when there is evidence of inflammation in the joint; findings of swelling, tenderness, warmth, or erythema should be demonstrable, along with pain with motion. In the joint, inflammation is also accompanied by stiffness or loss of motion. *Arthropathy* is a term that can be used to describe any disease of a joint, regardless of its cause.

**ETIOLOGY**

Inflammatory causes of musculoskeletal pain are typically subacute or chronic, and are characterized by swelling, loss of motion, and a subjective sense of stiffness that is often prolonged after periods of inactivity. A relatively rapid onset of joint symptoms in the setting of fever, rash, lymphadenopathy, or other systemic complaints should raise concern for an infectious process or a systemic inflammatory disease. Traumatic causes of musculoskeletal pain can typically be identified by the sudden onset of symptoms following a fall, a blow, or other injury. Repetitive stress injuries, hypermobility arthralgias, and other mechanical noninflammatory syndromes can be subacute or chronic in onset, but are characterized by exacerbation of pain and stiffness after activity or at the end of a vigorous day, rather than upon awakening or after periods of inactivity.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of joint pain should begin by determining whether the disease is inflammatory or noninflammatory. Inflammatory joint disease can result from rheumatic or nonrheumatic causes. Noninflammatory diseases may result from trauma, repetitive stress, congenital or developmental anomalies, or other mechanical causes.

**Rheumatic Diseases**

The most common rheumatic disease of childhood is juvenile idiopathic arthritis (JIA), previously referred to as *juvenile rheumatoid arthritis*, which occurs in up to 1 in 1,000 children worldwide. Onset can be from the second year of life through late adolescence. The oligoarticular subtype is characterized by involvement of 4 or fewer joints, typically large joints with asymmetric distribution. This subtype has a good long-term prognosis, but can cause growth abnormalities, and especially in patients with a positive antinuclear antibody it carries an increased risk of eye involvement with iridocyclitis. When more than 4 joints are involved, JIA is subtyped as polyarticular, and this form is more likely to involve small as well as larger joints. A subset of patients with polyarticular JIA have serum IgM rheumatoid factor and typically more symmetric joint disease. Systemic onset juvenile arthritis



(sometimes called *Still disease*) is marked by high, spiking fevers; an evanescent, salmon-pink, maculopapular rash; lymph node, spleen, and liver enlargement; anemia; leukocytosis; and other laboratory evidence of pronounced inflammation. Arthritis may not be present at the onset of systemic findings, but should be present for 6 weeks or longer to establish the diagnosis of any form of JIA. Evaluation and management of JIA depends on the subtype present.

Juvenile forms of ankylosing spondylitis or spondyloarthropathy can start with involvement in the large joints of the lower extremities or in the entheses (insertion of a tendon or ligament into a bone); at onset, there may be no axial disease. Small joint involvement is often asymmetric when present, and dactylitis (sausage digits) can occur if several joints and intervening soft tissues in a single finger or toe are swollen. The classic presentation of ankylosing spondylitis includes sacroiliac involvement in late adolescence, and further axial disease can progress in adulthood. Severe disease leads to the radiographic finding of *bamboo spine*, which is caused by diffuse paravertebral fusions resulting in very limited back and neck movement. The human leukocyte antigen (HLA)-B27 is seen in about 90% of patients with ankylosing spondylitis. Spondylarthropathies are more common in boys than girls, unlike many other forms of juvenile arthritis. A similar pattern of asymmetric large joint and sacroiliac disease can be seen in patients with inflammatory bowel disease. Children with psoriasis, or with a first degree relative with psoriasis, may also have a similar presentation, with a predisposition for large joints, sacroiliac disease, and occasionally dactylitis.

Several other systemic inflammatory diseases may cause or be associated with arthritis. Systemic lupus erythematosus, more common in girls than boys and infrequently seen before adolescence, is a multisystem disease that can involve almost any organ in the body. Arthralgias and sometimes arthritis are not uncommon, and may be the presenting symptom. Juvenile dermatomyositis is characterized more by skin rashes and muscle inflammation and weakness than joint disease, but can also be accompanied by joint pain or swelling in some cases. Sjögren syndrome, scleroderma, and mixed connective tissue disease are other connective tissue diseases occasionally seen in children that can cause joint symptoms. Systemic autoimmune inflammatory syndromes, often referred to as *periodic fever syndromes*, including familial Mediterranean fever, tumor necrosis factor receptor-associated periodic syndrome, hyperimmunoglobulin D syndrome, and cryopyrinopathies, are genetic diseases that may be associated with arthritis in addition to recurrent fevers. Kawasaki disease and Henoch-Schönlein purpura, along with other types of vasculitis, are also systemic inflammatory diseases that can cause arthritis. Many other inflammatory conditions cause arthritis in adults, including sarcoidosis and crystalline arthritis, but these are quite rare in children.

### Infectious and Postinfectious Arthritis

Acute bacterial infection of the joint, or *septic arthritis*, is foremost among this group and represents a medical

emergency. The usual manifestation is the rapid onset of pain in a joint, typically accompanied by fever. The joint itself is red, warm, swollen, and exquisitely tender to palpation or with movement. This clinical situation demands immediate arthrocentesis for diagnosis and therapy. Analysis of the fluid for appearance (opaque), viscosity (usually low), mucin clot (friable), cell count ( $>100,000$  white blood cells/mm<sup>3</sup> with at least 80% polymorphonuclear cells), glucose (usually low, much less than serum), and protein (high) helps establish the diagnosis. Most important, a portion of the fluid must be Gram stained to assess for bacterial organisms. Cultures can direct definitive antimicrobial therapy. In the past, for a child younger than 4 years, *Haemophilus influenzae* was the most commonly responsible organism; but with the institution of regular immunization, these bacteria are no longer a major consideration in septic arthritis. *Staphylococcus aureus* and *Streptococcus* species now are more likely to be the causative organisms. In addition to joint fluid cultures, blood cultures may also yield growth of the organism, occasionally in the absence of a positive joint fluid culture.

*Osteomyelitis* is an acute infection of the bone. However, when one of the long bones next to a joint (eg, the distal femur and knee) is infected, the patient may describe pain in the joint, and a sterile effusion may even be present. Although unusual, the bacterial infection can directly invade the adjacent joint space from the bone, particularly in young children.

Systemic bacterial infections, notably those caused by *Neisseria meningitidis* and *Neisseria gonorrhoeae*, also can produce arthritis, although the organism is usually not isolated from the joint in these cases. After joint aspiration and establishment of at least a strong suspicion of a purulent arthritis, the child should be hospitalized and appropriate intravenous antibiotic therapy initiated. Prompt, aggressive therapy usually brings about recovery without adverse side effects, although some foci, such as the hip joint, can remain persistent problems. Because of the tenuous blood supply to the femoral capital epiphysis, purulent arthritis of the hip can lead to chronic problems despite timely intervention.

Diskitis, a disorder characterized by back pain and tenderness over the spinous process contiguous to the involved disk space, causes joint pain, sometimes with low-grade fever, but often with none. *Staphylococcus aureus* has been isolated from the blood and disk space in some instances, but often no culture-proven cause can be found. The presentation can involve sensory and motor complications resulting from nerve root impingement, and an epidural abscess must be considered in the differential diagnosis.

*Borrelia burgdorferi* is a tick-borne spirochete responsible for Lyme disease. The syndrome, which was first described in Old Lyme, Connecticut, is characterized by an initial tick bite that often (but not always) causes a large, circular, spreading, erythematous lesion known as *erythema migrans*. Meningoencephalitis, neuritis, and carditis also may occur. The arthritis occurs later in the course as recurrent attacks of inflammation of the large joints (85%–90% of cases involve the knee), with each recurrence usually lasting

no more than 1 or 2 weeks. Occasionally, symptoms may persist for several months, and chronic, persistent arthritis of the knee has been reported. A short course of high-dose amoxicillin therapy seems to shorten the course of the rash and perhaps attenuates the arthritis, and nonsteroidal anti-inflammatory drug (NSAID) therapy relieves the symptoms. Specific antibiotic regimens are suggested for different stages of disease and ages of patients. Although a vaccine against *B burgdorferi* was developed and distributed, it was taken off the market in 2002 and is no longer available.

In addition to bacteria, other infectious organisms can cause joint disease. Viruses, including rubella, mumps, varicella, parvovirus, adenovirus, the Epstein-Barr virus, and HIV, all can affect synovial tissue. Manifestations of the viral syndrome (rash, fever, mucous membrane involvement) usually precede joint involvement. Infectious hepatitis, on the other hand, can cause arthritis before overt hepatic involvement. Rubella immunization is associated with arthralgia and arthritis in as many as 3% of children who receive the vaccine, although rarely, if ever, with any sequelae. Other less common infections that can involve the joints include brucellosis, leptospirosis, tularemia, Rocky Mountain spotted fever, and rat-bite fever. Mycobacteria can cause arthritis, as can various fungal agents, particularly in immunocompromised individuals.

Reactive arthritis, previously referred to as *Reiter syndrome*—a triad of urethritis, conjunctivitis, and arthritis—may appear in children and adolescents. In children, it is often triggered by an episode of enteritis. Reactive arthritis is more common in boys than in girls, and making the diagnosis depends on excluding direct infectious causes of the inflammation. The arthritis predominantly occurs in large joints; again, it is often but not exclusively associated with the HLA-B27 class 1 major histocompatibility locus. The disorder is treated initially with anti-inflammatory drugs. Most children recover within a few months, although some follow a more chronic and relapsing course and can progress to ankylosing spondylitis. Transient synovitis of the hip, previously called *toxic synovitis*, also can cause arthralgia, arthritis, or both. This generally occurs in preschool or young school-aged children, and has a good prognosis. Etiology is unclear, but it may be viral or postviral in nature.

Acute rheumatic fever is less common than it once was, but is still an important consideration in a child with the acute onset of arthritis or arthralgia. This follows an infection with group A streptococcus, usually pharyngitis, usually and typically by about 2 or 3 weeks. Diagnosis is made using the Jones criteria, which include migratory arthritis or arthralgias as well as fever, carditis, rash (erythema marginatum), central nervous system involvement, subcutaneous nodules, elevated acute phase reactants and prolonged PR interval. A distinct condition called *poststreptococcal reactive arthritis* may occur after a streptococcal infection, in the absence of other findings. The arthritis may be more severe, and this may occur sooner after the preceding illness than is the case with rheumatic fever.

### Noninflammatory Causes of Joint Pain

Trauma causing fractures, dislocations, cartilage, ligamentous, or tendon injury, or other soft tissue damage are common in children and can cause joint pain, depending on the location of the injury. A careful history can usually provide information about the mechanism of the event. Physical abuse (non-accidental trauma) should be considered whenever signs of trauma are evident, and accidents that represent neglect on the part of parents or guardians need to be recognized and pursued. Any suspicious history or circumstance demands complete investigation.

Other more chronic mechanical stressors can lead to subacute arthralgia. Patellofemoral pain syndrome, also called *chondromalacia patellae*, is a common cause of anterior knee pain in children and adolescents, and is often bilateral. Knee pain is usually related to activity, and the child may report symptoms of “locking” with prolonged sitting, or “giving way” with extended standing. Exercises that strengthen the quadriceps femoris and adductor muscles can produce marked improvement. Repetitive activities can lead to chronic tendonitis or bursitis in periarticular areas, and are common in athletes, dancers, musicians, and other children who practice or perform repetitive movements. Stress fractures are uncommon in children but should be considered in an athlete with chronic bone or joint pain. Some injuries are specific to a developmental stage, such as Osgood-Schlatter disease, Sever disease, and other forms of apophysitis. These occur only in skeletally immature individuals who have either a repetitive or acute injury to the apophysis, which is a secondary ossification center to which a tendon attaches, and which is the weakest point of the biomechanical unit. These are treated by activity modification, rehabilitation, and analgesia as needed. Slipped capital femoral epiphysis is another condition seen only in skeletally immature children, in which the capital femoral epiphysis is displaced from the femoral neck. This may manifest as hip or sometimes thigh or knee pain, and is seen typically in overweight adolescents, and is diagnosed by imaging.

Some children experience arthralgias in the lower extremities, termed *growing pains*, which tend to be worse at night. These are not associated with warmth, swelling, or limitation of movement of the affected joints. Imaging will be normal. These children rarely have pain in the mornings, and have normal daytime activities. Symptoms can often be alleviated with a bedtime dose of NSAID or acetaminophen. Children with hypermobility syndrome often have a similar pattern of pain, worse after activity and improved by rest. Children with this disorder have increased joint laxity, and can be diagnosed by the presence of at least 3 of the following signs: hyperflexion of the wrist, bringing the thumb in contact with the volar surface of the forearm; hyperextension of the fingers to parallel with the forearm; hyperextension of the elbow to at least  $-10$  degrees; hyperextension of the knee to at least  $-10$  degrees; and hyperflexion of the spine such that with forward flexion, the palms can be placed flat on the ground with the feet together and without flexing the knees. Some genetic disorders of connective tissue, including Marfan syndrome and

Ehlers-Danlos syndrome, can cause pronounced hypermobility.

In an adolescent with chronic diffuse pain and fatigue without evidence of rheumatic disease on examination or laboratory studies, juvenile primary fibromyalgia syndrome should be considered. Multiple sets of diagnostic criteria have been published, but these generally include widespread pain for several months, presence of specific tender points on examination, and the presence of severe fatigue and nonrestorative sleep. These children often also have headaches, depression or anxiety, a sense of cognitive impairment, numbness or tingling or stiffness in the limbs, irritable bowel symptoms, or other complaints. Treatment should be multidisciplinary, and should include patient and family education, exercise, and psychological interventions such as cognitive behavioral therapy. Some patients benefit from medications including non-narcotic analgesics, low-dose tricyclic antidepressants, other antidepressants, and  $\gamma$ -aminobutyric acid agonists such as gabapentin or pregabalin.

Children who present with localized limb pain, sometimes after an injury but out of proportion to examination findings, may have complex regional pain syndrome (CRPS). The affected area should also demonstrate some evidence of autonomic dysfunction such as localized edema, increased sweating, or change in temperature or color. As with juvenile fibromyalgia, onset is most common in adolescent girls, and concurrent sleep disruption and psychological conditions are also common. Treatment consists of aggressive physical and occupational therapy, psychological and behavioral therapies, and sometimes pharmacotherapy or localized interventions such as nerve blocks.

### Other Causes

Hematologic disorders that have articular manifestations include hemophilia and sickle cell disease. In the latter disorder, the hand-foot syndrome type of vaso-occlusive crisis is a common initial presentation in children between 1 and 4 years of age.

Bone pain can also occur in patients with osteoid osteomas, which are benign bone tumors most often seen in older children and teens. Pigmented villonodular synovitis is a benign neoplasm of the synovium which can present with joint pain and swelling. Leukemia is the most common malignant condition to present with bone or joint pain, although lymphoma, neuroblastoma, and Ewing and other sarcomas can also cause these symptoms.

### EVALUATION

A complete history is indispensable in the initial assessment of a child with joint pain. The physical examination can then substantiate or alleviate suspicions raised during the interview. Distinguishing among arthritis, arthralgia, periarticular pain, and myalgia is essential. Further testing, including appropriate imaging, can confirm or further clarify the nature of bony or soft tissue abnormalities suspected based on the history and examination findings. In

some cases, the diagnosis can be reinforced by laboratory testing. Markers of inflammation, including erythrocyte sedimentation rate, C-reactive protein, and others, are often abnormal in inflammatory conditions. In some cases, appropriate specific tests or cultures can confirm a specific rheumatic or infectious diagnosis.

### TREATMENT

Management of joint pain that is secondary to an inflammatory arthritis focuses on subduing inflammation and preserving normal range of motion, strength, and function. NSAIDs are often used as initial therapy. In patients with oligoarticular disease, especially those with a single persistently active joint, intraarticular corticosteroids can be effective. Systemic corticosteroids occasionally have a place in therapy of other JIA subtypes, although they are used much less often than in the past, and with a goal of limited duration. Methotrexate has come to play a central role in the medical management of children with JIA and some other inflammatory conditions who require therapy beyond NSAIDs. Other immunomodulatory agents, such as sulfasalazine, leflunomide, and hydroxychloroquine may also be used in some patients. Many patients who have resistant joint inflammation or high-risk phenotypes benefit from biologic agents, including antitumor necrosis factor alpha agents, IL-1 or IL-6 antagonists, and others.

Any child with a bacterial infection of the joint space or bone should be promptly identified and treated with intravenous antibiotics. Other infectious causes of arthritis may also require treatment, such as those caused by Lyme disease or *Neisseria* infection. Others, such as parvovirus, will generally resolve spontaneously, so treatment is supportive.

In patients with joint pain resulting from trauma, therapy includes rest, ice, NSAIDs, or other analgesics, though any unstable injury should be promptly evaluated by an orthopedist to determine the need for external or surgical stabilization. There may also be a role for surgical treatment of longstanding joint damage resulting from chronic or severe inflammatory arthritis or mechanical derangements, and sometimes surgical interventions are necessary for establishing a clear diagnosis, as in synovial biopsy for atypical infections or bone biopsy for osteomyelitis.

After arriving at a diagnosis and plan of therapy, the physician must also offer management for the psychological aspects of joint disease. In children with ongoing joint problems, issues related to chronic pediatric disease must be addressed. The child may be unable to keep up with peers in physical activity and may be faced with having to make many health care visits, resulting in school absences. Many physicians think that environmental stress, in addition to the stress caused by the disease, can exacerbate various chronic conditions, and such may occur in children with JIA.

Children faced with hospitalization for an acute problem, such as septic arthritis, are exposed to all the complications of being taken out of their family and school environment, as well as having to deal with an



institutional setting. Children with ongoing joint disease, even those with only a mild disability, should be provided with the services of a specialized social worker, counselor, or psychologist. Family resources (both emotional and financial) need to be assessed and support provided when needed. Discussion groups or support groups composed of these children and their families can be helpful because they offer an opportunity to compare experiences and coping mechanisms. Attention to the physical dimension alone does not provide adequate care in these diseases. A functionally minor disability can cause major problems of body image and feelings of lack of independence that must be dealt with appropriately. As with other chronic physical disorders of childhood and adolescence, long-term psychosocial sequelae also may develop.

### WHEN TO REFER

- Orthopaedics
  - Fracture
  - Ligamentous or cartilage injury to joint
  - Continuous pain in a joint with deformity
- Rheumatology
  - Suspicion of juvenile arthritis or other rheumatologic disorder
- Infectious diseases
  - Septic arthritis
  - Lyme disease; other spirochetal infection
  - Osteomyelitis
- Hematology
  - Sickle cell disease
  - Hemophilia
- Gastroenterology
  - Joint symptoms associated with inflammatory bowel disease
- Occupational or physical therapy
  - Joint disease complicated by contractures, weakness, poor function
  - Hypermobility syndrome
  - Pain amplification syndromes (eg, fibromyalgia, CRPS)
- Mental health
  - Suspicion of somatization or conversion disorder

### WHEN TO ADMIT

- Fracture requiring open fixation or traction
- Systemic onset juvenile arthritis with macrophage activation syndrome
- Septic arthritis
- Osteomyelitis
- Severe sickle cell pain crisis
- Admit to rehabilitation if inadequate response to outpatient occupational or physical therapy

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *What is a Pediatric Rheumatologist?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Rheumatologist.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Rheumatologist.aspx))

#### Medical Decision Support

- *Red Book: 2015 Report of the Committee on Infectious Diseases*, 30th ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

### SUGGESTED READINGS

- Lowe RM, Hashkes PJ. Growing pains: a noninflammatory pain syndrome of early childhood. *Nat Clin Pract Rheumatol*. 2008;4:542-549
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## Chapter 172

## LEARNING DIFFICULTY

Barbara L. Frankowski, MD, MPH

### BACKGROUND AND SIGNIFICANCE

Learning difficulties can occur at any age and for a variety of reasons. They invariably cause frustration for the child or adolescent, which can lead to or compound behavior problems and emotional distress. The effects of learning difficulties, whatever their cause, can be profound, with economic and emotional consequences far into adult life. Children who do not receive timely intervention are at risk not only for academic failure, but also for the psychosocial morbidities that accompany limited academic achievement, such as substance abuse and juvenile delinquency. Some children with learning difficulties are among the 7% of US 15- through 24-year-olds who drop out of school, leading to chronic unemployment, poverty, and higher risk of health problems throughout adulthood. The drop-out rate is higher among minority populations of black non-Hispanics (8%) and Hispanics (22.5%) than white children. Clearly, learning difficulties are an important concern for primary care physicians providing services to children and adolescents.

### PRIMARY CARE PHYSICIAN'S ROLE

It is the primary care physician's role to recognize that a child is experiencing difficulty in learning, to help the family sort out the cause of the child's learning difficulties, to identify referral sources for psychological and educational assessment, to ensure that the child receives the educational resources he or she needs and is entitled to, to address any medical or mental health problems that may be associated with the child's learning difficulties, and to guide the family in advocating and providing a supportive environment for the child.



## RECOGNITION OF CHILDREN WITH LEARNING DIFFICULTIES

The primary care physician has opportunities at routine health supervision visits to elicit parental concerns, to monitor children's developmental progress and functioning, and to screen for developmental delays and symptoms of social and emotional problems. The physician may also receive referrals from childcare or school personnel who have observed that the child has difficulty learning compared with his or her peers or is experiencing behavioral problems in the classroom. There may be a family history of learning problems, compounding concerns about the child's progress in learning. Box 172-1 and Table 172-1 for signs and symptoms that a child is experiencing learning difficulties.

### BOX 172-1 Symptoms and Clinical Findings Suggesting Learning Difficulties

#### INDICATIONS FROM YOUTH'S OR PARENT'S HISTORY

- Child has experienced a delay in language development or has difficulty understanding language despite normal hearing and vision.
- Child has difficulty following directions.
- Child has difficulty learning letters, numbers, and colors.
- Child has struggled to read, grasp math concepts, or write in comparison with her peers.
- Letter reversals (b/d), inversions (m/w), transpositions (felt/left), substitutions (house/home), or confusion of arithmetic signs persist past peers.
- Child avoids reading aloud, writing, or homework.
- Child or parent is frustrated with the child's academic performance.
- Parent perceives child is "lazy" in school.
- Child is perceived as an "underachiever."
- Classroom behavior or inattention has become a problem.
- Other family members have experienced learning difficulties or did not complete high school.

**Table 172-1** Findings Suggesting Learning Difficulty

#### MEASUREMENT SCORE

End-of-grade test scores or achievement test scores	Percentiles are low ( $\leq 15\%$ ) or markedly scattered, or the child is performing considerably less well than would be expected for his or her intelligence.
Report cards	Grades are low or markedly scattered.
Intelligence tests	Percentiles are within the normal range or significantly higher than measures of academic achievement.

## CAUSES OF LEARNING DIFFICULTIES

### Lack of School Readiness

Some young children experience difficulties in learning because they are not yet ready for the school experience, socially, emotionally, or physically; because they do not have language and literacy skills comparable with their peers; or because their family or culture does not value their education. Box 172-2 outlines the specific traits a child should ideally possess in order to be ready for school, and Box 172-3 identifies key family and community supports for preparing a child for school.

Finally, many schools are not prepared to educate children with the full range of abilities and disabilities. Measurement of children's readiness for kindergarten should be used to assess the effectiveness of community-based programs and to prepare schools to meet the child's ongoing needs, rather than to exclude or delay children from their formal educational experience. Box 172-4 highlights key elements of schools that are ready for children.

### BOX 172-2 Traits for School Readiness

- Physical well-being and motor development: good health status and alertness; any physical disabilities identified and accommodated
- Social and emotional development: turn-taking, cooperation, empathy, and the ability to express his or her own emotions
- Approaches to learning: enthusiasm, curiosity, family and cultural values supportive of learning
- Language development: skills in understanding and speaking the language spoken in the classroom; adequate vocabulary and other literacy skills, including print awareness, story sense, and writing and drawing processes
- General knowledge and cognition: sound-letter association, awareness of spatial relations, and number concepts

### BOX 172-3 Preparing the Child for School: Key Elements

- At least a high school education or equivalent for parents
- High-quality prenatal health care for the mother
- Optimal nutrition for mother and child
- Comprehensive health care for the child
- Daily physical activity
- Daily time with parent in learning activities (eg, reading, conversation, family meals)
- Access to high-quality preschool for children in impoverished environments
- Access to programs for children and parents who speak English as a second language

### BOX 172-4 Preparing the School for the Child: Key Elements

- High-quality preschools for children in impoverished environments
- Programs and teacher training for children of all ability levels
- Preschool screening of children aimed at measuring the outcome of their preschool programs and at identifying and addressing students' needs (not at excluding children or delaying their school entry)

### Medical, Mental Health, and Developmental Problems

Learning difficulties may also be caused by cognitive limitations, a language or learning disorder; vision or hearing impairment; behavioral and emotional problems; a chronic disease that affects the child's concentration, interpersonal relationships, or school attendance; sleep deprivation; or medication affecting concentration or alertness. See Table 172-2 for a listing of problems that can cause or co-occur with learning difficulties.

### Learning Disabilities

Rarely diagnosed before a child enters school, learning disabilities (LDs) represent a broad array of specific learning challenges that significantly impede a child's ability to perform at the expected grade level. They generally occur in the context of normal sensory functioning and otherwise normal cognitive capabilities and, by definition, are not the result of a primary emotional disorder or lack of opportunity (although frustration and low self-esteem associated with LDs may contribute to development of problems such as anxiety, depression, or oppositionality). Learning disabilities are clearly familial, with genetics contributing substantially to a child's risk. It is estimated that between 5% and 17.5% of individuals meet diagnostic criteria for LDs and approximately 2 million US schoolchildren aged 6 to 11 years are affected. Eighty percent of those identified have dyslexia or a reading disorder.

### ASSESSMENT OF CHILDREN WITH LEARNING DIFFICULTIES

Assessment begins by differentiating the child's symptoms from normal behavior. Children learn at different rates. Typically developing children younger than 7 years may reverse and transpose letters and experience some frustration with new learning tasks, particularly if the child has had limited preschool experience or other children in the classroom have had more exposure to formal school experiences. Many children will have 1 or more of the symptoms in Box 172-1 from time to time. Children who have missed school for an illness, changed schools, or experienced a significant loss may experience transient problems with school functioning. Some parents have unrealistic expectations, based on their own learning experiences or that of older siblings or children of friends.

It is important to explore sources of stress in the family, school, or community, as any of these can cause inattentiveness and distraction in the child.

A full physical and psychosocial assessment of the child will serve to identify conditions that can cause or co-occur with learning difficulties (Table 172-2).

Two categories of medical risk deserve special attention: prematurity and cyanotic congenital heart disease. Premature infants are at significantly higher risk for global developmental delays and for LDs. In particular, children born at less than 32 weeks' gestation or who experience perinatal and postnatal complications such as prolonged ventilation, intracranial hemorrhage, sepsis, seizures, prolonged acidosis, or hypoglycemia are at higher risk for neurodevelopmental sequelae. Similarly, children surviving severe congenital cardiac anomalies are at high risk for LDs. Several genetic disorders have been linked to risk for various forms of LD. In particular, children with Klinefelter syndrome, Turner syndrome, velocardiofacial syndrome, and spina bifida with shunted hydrocephalus have all been shown to be at significant risk for LDs. When 1 of these risk factors is identified, the physician should have a low threshold to refer for psychological and educational assessment.

Adolescents who present with learning difficulties are a particular challenge for the primary care physician. An adolescent who has been progressing normally with academics may suddenly develop learning difficulties. It is possible that the adolescent may have a mild learning disability for which he or she has compensated in lower grades, but which is now causing difficulty in meeting the more rigorous demands of middle or high school. Together or separately, the adolescent may have mild attentional problems that have not required any special intervention up until this point. However, it is also possible that the adolescent has other problems causing or contributing to learning difficulties, such as inadequate amounts of sleep, poor nutrition, inadequate physical activity, anxiety, depression, or substance abuse. The adolescent could also, or alternatively, be struggling with issues of sexual orientation or bullying that cause stress in the school environment. It is important to consider all these possibilities when assessing an adolescent with learning difficulties.

To further the assessment of any child or adolescent with learning difficulties, the physician can communicate with school personnel (eg, guidance counselor, classroom teacher, school psychologist) to request data and observations such as the following:

- **Intelligence testing:** School personnel may be willing to administer a cognitive screening test or, if there are apparent discrepancies between intelligence and academic achievement, a full battery of psychological tests.
- **Achievement testing:** School personnel can provide a screening test or reports of achievement or end-of-grade tests.
- **Full psychoeducational evaluation:** School psychologist or community psychologist may provide, by referral.
- **School placement and special services.**
- **Individualized Educational Program (IEP) or 504 plan,** if in place.

**Table 172-2** Conditions That May Cause Poor School Performance or Co-occur With Learning Difficulties

CONDITION	RATIONALE
Hearing or vision problems Sleep deprivation	All children who are experiencing learning difficulties should be screened for sensory deficits. Sleep problems can cause inattention and irritability and contribute to poor school performance; conversely, poor school performance and homework struggles may contribute to difficulty sleeping.
Developmental problems	Children with overall intellectual or social limitations will learn more slowly than their age-mates. Children with low achievement and low intellectual levels often have the same problems as children with learning disabilities.
Attention-deficit/hyperactivity disorder (ADHD)	Children who are inattentive or impulsive may manifest poor academic performance. They may have problems with getting the work completed and turned in, rather than skill deficits. Conversely, children experiencing academic difficulties may seem restless and inattentive. See Chapter 168, Inattention and Impulsivity.
Exposure to adverse childhood experiences (ACE)	Children who have experienced or witnessed trauma, violence, a natural disaster, separation from a parent, parental divorce or separation, parental substance use, neglect, or physical, emotional, or sexual abuse are at high risk of developing emotional difficulties such as adjustment disorder or post-traumatic stress disorder (PTSD). Children with PTSD can manifest poor concentration, memory problems, school refusal, and academic decline. These children may also manifest other forms of anxiety. Physicians may want to consider speaking separately and confidentially with the youth and parents to explore this possibility. Parents are often unaware of exposures that children may have had at school or in the community. There may be major traumas in the family (eg, serious illness in a parent, maltreatment of the child, death or incarceration of a loved one) that are similarly not discussed or disclosed. The 3 hallmark symptom clusters of PTSD are reexperiencing, avoidance of memories or situations that recall the trauma, and hypervigilance (ie, increased worry about safety, startling or anxiousness at unexpected sounds or events). See also Chapter 129, Anxiety.
Anxiety	Anxious children may experience difficulty concentrating and perform poorly on tests. See Chapter 129, Anxiety.
Bereavement	Most children will experience the death of a family member or friend sometime in their childhood. Other losses may also trigger grief responses—separation or divorce of parents, relocation, change of school, deployment of a parent in military service, breakup with a girlfriend or boyfriend, or remarriage of parent. Such losses are traumatic. They may result in such symptoms as sadness, anxiety, difficulty concentrating, poor impulse control, or academic decline immediately following the loss and in some instances, more persistently. See also Chapter 137, Depression, and the discussion of PTSD in Chapter 129, Anxiety.
Depression	Depression may cause a decline in school performance, result from poor school performance, or simply coexist with learning disabilities. Marked sleep disturbance, disturbed appetite, low mood, or tearfulness could indicate that a child (or more commonly, an adolescent) is depressed. See Chapter 137, Depression.
Physical illness	Medical issues that may have an effect on school performance include all illnesses that may interfere with the child's attendance. Some illnesses (or symptoms caused by the illnesses) can affect attention in the classroom (eg, hypo- or hyperthyroidism, neurologic disorders, post-traumatic brain injury, undiagnosed diabetes), as can side effects of medications such as bronchodilators or anticonvulsants.
Substance use	Children frustrated with their school performance may use substances such as alcohol, nicotine, or other drugs to alleviate their frustrations, or self-medicate with caffeine or cocaine. Conversely, children using substances may manifest inattention, impulsivity, and deteriorating school performance. See Chapter 198, Substance Use: Initial Approach in Primary Care.
Conduct or oppositional disorders	These disorders may cause poor academic performance, and frustration with poor academic performance can exacerbate conduct or oppositional problems. See Chapter 139, Disruptive Behavior and Aggression.
Autism spectrum disorders including high-functioning autism, which was formerly known as pervasive development disorder, and Asperger syndrome	Children who have these difficulties also have problems with social relatedness (eg, poor eye contact, preference for solitary activities, language [often stilted], and range of interests [persistent and intense interest in a particular activity or subject]). They often will have very rigid expectations for routine and become anxious or angry if these expectations are not met. As such, these children may manifest difficulties in the classroom and many of the symptoms associated with learning disorders.

- **History of academic progress, behavior and discipline, and peer interactions.**

Use of additional instruments such as the Vanderbilt ADHD Rating Scale (see Tools for Practice) and general psychosocial screens [Pediatric Symptom Checklist (PSC)-35, PSC-17, Strengths and Difficulties Questionnaire (SDQ)] can be used to identify children who may have psychosocial problems contributing to their learning difficulties.

## PLAN OF CARE FOR CHILDREN WITH LEARNING DIFFICULTIES

The care of a child experiencing learning difficulties can begin in the primary care setting from the time symptoms are recognized, even if the child's problems do not rise to the level of a disorder or referral to the school or to a mental health specialist is ultimately part of the care plan.

### Engage Child and Family in Care

Without engagement, most families will not seek or persist in care. The process may require multiple primary care visits.

Reinforce strengths of the youth and family as a method of engagement and identify any barriers to addressing the problem (eg, stigma, family conflict, resistance to academic testing or special education). Use "common factors" techniques to build trust and optimism, reach agreement on incremental next steps, develop a plan of care, and collaboratively determine the role of the primary care physician. Regardless of other roles, the primary care physician can encourage a positive view of treatment on the part of the youth and family.

### Encourage Healthy Habits

Encourage exercise, outdoor play, balanced and consistent diet, sleep (critically important to mental health), avoidance of exposure to frightening or violent media, limitation of screen time to less than 1 to 2 hours per day, special time with parents, acknowledgment of child's strengths, and special efforts to support the child and help him or her to feel competent, special, positive, and appreciated.

### Reduce Stress

Consider the child's social environment (eg, family social history, parental depression screening, results of any family assessment tools administered, reports from child care or school). Questions to raise might include the following:

*Is the parent punitive or critical?* If parents' psychosocial problems are affecting their relationship with the child, explore their readiness to address these problems as part of helping their child. Encourage praise for their child's efforts. Urge parents to avoid comparisons with siblings or peers and to keep up the child's self-esteem. Urge parents to nurture the child's nonacademic gifts, such as art or music, and encourage participation in extracurricular activities that provide social experiences uncomplicated by academic performance and competition (eg, scouts, faith-based youth group, boys' or girls' club).

## BOX 172-5 Guidelines for Homework Battles

- Establish a routine (not waiting until evening to get started).
- Identify another student your child can call to clarify homework assignments.
- Limit distractions (eg, TV, computer, phone).
- Assist child in dividing assignments into small, manageable segments (especially important for long-range assignments and large projects).
- Assist child in getting started (eg, read directions together, watch child complete first items).
- Monitor without taking over.
- Praise good effort and completion of tasks.
- Do not insist on perfection.
- Offer incentives ("When you've finished, we can . . .").
- Help child study for tests.
- Do not force child to spend excessive time on homework; write a note to the teacher if the child put forth good effort but was not able to complete it.
- If child fails to turn in completed work, develop a system with the teacher to collect it on arrival.
- If unable to provide homework supervision and assistance, or if homework battles are adversely affecting the parent-child relationship, ask the teacher for help finding a tutor.

*Are there battles over homework?* Advise parents that the child is not lazy. Provide guidance about helping with homework (and requesting modified assignments, as appropriate). See Box 172-5 on Guidelines for Homework Battles.

*Is the child exposed to criticism or teasing at school? Is the child's teacher supportive and patient?* Provide strategies for communication between school personnel and home; coach them to praise progress and effort, not just outcomes, and to address teasing or bullying.

*Are school authorities proceeding with assessment in accordance with the child's rights?* Inform parents about the child's rights under the Individuals with Disabilities Education Act (IDEA) and Section 504 of the Rehabilitation Act. It is important to obtain information about how these 2 acts are specifically implemented in your state and school districts. If a child has a learning disability, he or she qualifies for specialized educational services, and IDEA requires that the school develop an Individual Education Plan (IEP). The IEP documents the child's current level of functioning, establishes goals, and delineates the services needed to meet those goals in the least restrictive environment possible. The parent is entitled to meet with school personnel to review and approve the IEP. If the child does not qualify for specialized educational services but has minor challenges that can be helped by minor classroom modifications (eg, preferential seating, homework modifications), the school may develop a 504 plan for the child. If the parent is dissatisfied with



the school's response to the child's needs, there is an appeal process within the school system.

If the school is not adequately addressing the child's needs, the physician may offer referral to a community mental health professional such as a psychologist or developmental-behavioral pediatrician, or an educational tutor. Results of this assessment may provide support for the parent's advocacy efforts in the school system or may guide the family in developing tutorial assistance for the child.

Whatever interventions are planned, it is important to acknowledge and reinforce protective factors (eg, good relationships with at least 1 parent or important adult, pro-social peers, concerned or caring family, help-seeking, and connection to positive organization[s]).

### Offer Initial Interventions

The strategies described below are applicable to the care of children with mild or emerging learning difficulties, as well as diagnosed learning disorders. They can also be used as initial primary care management of children with learning difficulties while readying children for further assessment or educational services or awaiting access to evaluation and treatment.

*Address comorbid conditions.*

*If there are battles over homework, offer guidelines to parents.* Box 172-5 provides guidelines for parents to address homework battles.

### Provide Resources

Families may find the National Center for Learning Disabilities ([www.ncl.org](http://www.ncl.org)) a helpful source for information and support. Parents with questions about special education law may wish to consult a dedicated resource like Wrightslaw ([www.wrightslaw.com](http://www.wrightslaw.com)). Helpful brochures, publications, and Web sites are included in Tools for Practice: Engaging Patient and Family.

### Monitor the Child's Progress Toward Educational Goals

School reports can be helpful in monitoring progress. Screening instruments that gather information from multiple reporters (youth, parent, teacher), such as the SDQ, can be helpful in monitoring progress with symptoms and functioning.

### Involve Specialist(s)

*Involve education or mental health specialist(s) if child does not respond to initial interventions or if indicated by the following clinical circumstances:*

- The child or parent is very distressed by the symptom(s).
- There are co-occurring behavior problems not responsive to primary care management.
- School evaluation is incomplete or untimely.
- Parent's relationship with school is adversarial.
- Child and family have conflicts not responsive to primary care management.
- Parent is very negative toward child or unresponsive to primary care guidance.

*Consider seeing a geneticist for a diagnostic genetic workup if there are persistent concerns that interventions are not producing results.*

*Reach agreement on respective roles in the child's care.* The primary care physician may be responsible for advising the family about the child's rights under IDEA; reducing stresses on the child while awaiting further assessment and treatment; engaging and encouraging the child's positive view of his or her evaluation and specialized instruction; monitoring academic progress; observing for and addressing any comorbidities; and coordinating care provided by parents, school, medical home, and specialists. Resources available to help physicians in this role are provided in Tools for Practice. The primary care physician may also review with the family whether the child's school interventions are evidence-based ones, or refer to a developmental-behavioral pediatrician who is more knowledgeable in this area.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Individualized Education Program (IEP) Meeting Checklist* (handout), American Academy of Pediatrics ([www.brightfutures.org/mentalhealth/pdf/families/mc/iep.pdf](http://www.brightfutures.org/mentalhealth/pdf/families/mc/iep.pdf))
- *Learning Disabilities: What Parents Need to Know* (handout), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/learning-disabilities/Pages/Learning-Disabilities-What-Parents-Need-To-Know.aspx](http://www.healthychildren.org/English/health-issues/conditions/learning-disabilities/Pages/Learning-Disabilities-What-Parents-Need-To-Know.aspx))
- *Reading for Children: Grades 1–6* (handout), American Academy of Pediatrics ([www.brightfutures.org/mentalhealth/pdf/families/mc/grades.pdf](http://www.brightfutures.org/mentalhealth/pdf/families/mc/grades.pdf))
- *Your Child's Mental Health: When to Seek Help and Where to Get Help* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

### Medical Decision Support

- *The LD Navigator* (Web site), National Center for Learning Disabilities ([ldnavigator.ncl.org](http://ldnavigator.ncl.org))
- *Practice Parameters* (Web page), American Academy of Child & Adolescent Psychiatry ([www.aacap.org/cs/root/member\\_information/practice\\_information/practice\\_parameters/practice\\_parameters](http://www.aacap.org/cs/root/member_information/practice_information/practice_parameters/practice_parameters))
- *Vanderbilt ADHD Rating Scale* (scale), ([www.brightfutures.org/mentalhealth/pdf/professionals/bridges/adhd.pdf](http://www.brightfutures.org/mentalhealth/pdf/professionals/bridges/adhd.pdf))

## AAP POLICY

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## SUGGESTED READINGS

American Academy of Pediatrics Section on Ophthalmology, Council on Children with Disabilities, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus, American Association of Certified Orthoptists. Joint statement—Learning disabilities, dyslexia, and vision. *Pediatrics*. 2009;124:837–844

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## Chapter 173 LIMP

Ginger Janow, MD; Norman T. Ilowite, MD

Limp is a common presenting complaint in both pediatric primary care offices and emergency departments. While the most common cause of limp is trauma, there are many other etiologies, ranging in severity from benign to life-threatening. Limp is defined as an abnormal gait pattern. Distinguishing a limp in a young child can be particularly challenging as the mature gait cycle does not fully develop until after 7 years of age.

## DIFFERENTIAL DIAGNOSIS

### General

The differential diagnosis of a limp is broad, and is best considered as 7 categories: trauma, vascular, infectious, malignancy or tumor, skeletal anomalies, inflammatory diseases, and neuromuscular disorders.

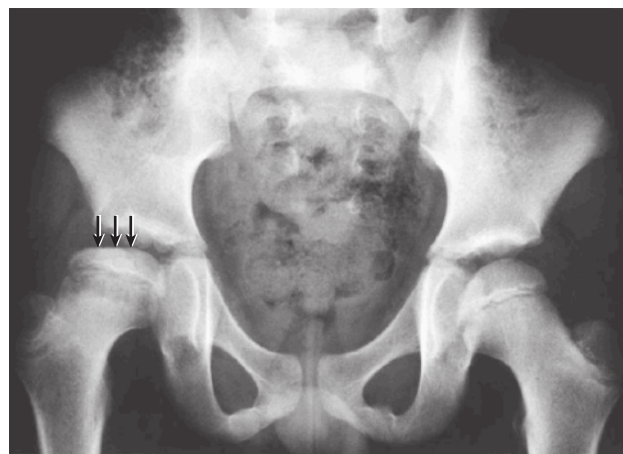
### Trauma

The most common cause of limp is trauma. If the history and physical examination suggest a fracture, ligament damage, or tendon damage, the patient should be referred to an orthopedist. Otherwise, rest, ice, compression, elevation, and analgesics are the mainstays of therapy. Radiographic evaluation should be guided by the history and physical examination.

### Vascular

**Legg-Calvé-Perthes disease** is characterized by avascular necrosis of the femoral head. Most often seen in the 5- to 10-year-old age group, it is more common in boys than girls. Patients generally present with groin or referred knee pain and an antalgic limp, with increased pain on activity. On examination, they generally have pain and limitation upon internal hip rotation. Early in the course, plain radiographs may be normal or may show increased density of the femoral head on the affected side, but later will show subchondral lucency, and ultimately, collapse and destruction of the femoral epiphysis (Figure 173-1). Once the diagnosis is suspected, pediatric orthopedics should be consulted for further workup and management.

**Osteochondritis dissecans** is the result of ischemia of the subchondral bone and can occur in multiple joints, although the knee is the most common. It generally occurs in adolescents, and most often presents with knee pain, swelling, and the sensation of the knee giving way. On physical examination, there is often joint swelling and pain on motion. Plain radiographs



**Figure 173-1** AP pelvis in an 8-year-old boy with right hip pain and limp. Right femoral head epiphysis shows loss of height and mixed sclerotic and lytic appearance (arrows) of Legg-Calvé-Perthes disease. (From Barkin RM, Barkin SZ, Barkin AZ. *The limping child*. *J Emerg Med*. 2000;18[3]:331–339. Copyright © 2000, Elsevier, with permission.)

reveal a radiolucent zone separating the osteochondral fragment from the rest of the bone.

### Infectious

**Septic arthritis**, or infection within the joint space, is among the most emergent causes of a limp, requiring rapid identification and treatment to avoid long-term damage and disability. The 2 peaks in incidence are in the toddler years and in adolescence. In most cases, the onset of pain is rapid and is accompanied by a fever and refusal to bear weight. On physical examination, the joint is generally swollen, warm, tender, and extremely painful with range of motion. If a septic joint is suspected, laboratory evaluation should include evaluation of synovial fluid (with Gram stain, culture, and cell count), blood culture, complete blood count (CBC), sedimentation rate (ESR) and C-reactive protein (CRP). Plain radiographs may reveal a joint effusion. An ESR of less than 20 mm/hr or a normal CRP lowers the likelihood of a serious infectious cause but does not exclude the diagnosis of skeletal infection. Etiologic agents are isolated in the blood or synovial fluid in 34% to 82% of cases. Synovial fluid generally reveals an elevated white blood cell count with increased segmented neutrophils (Table 173-1).

In the toddler age group, the most common organisms are *Staphylococcus aureus*, *Kingella kingae*, and in young infants. *Haemophilus influenzae* type b (Hib) previously accounted for 70% of cases of septic arthritis in children from 2 months to 2 years of age, but this pathogen has been virtually eradicated following universal Hib vaccine implementation. Group B *streptococcus* is the most common cause of invasive bacterial infection in infants less than 2 months of age, and both bone and joint infection can occur. In the adolescent age group, *S aureus* is still the most common pathogen, but gonococcal arthritis should be considered in the sexually active teen. If septic arthritis is suspected, orthopedics should be consulted for joint aspiration and drainage should be promptly performed in cases of hip or shoulder infection. Gram stain and culture, when positive, should guide antibiotic management.

**Osteomyelitis** is most common in the toddler age group but can be seen in all age groups, and is usually caused by the same organisms responsible for septic arthritis. The pathogenesis of infection is generally hematogenous seeding, but osteomyelitis may follow penetrating trauma or deep contiguous infection as may occur with decubitus ulcers. Involvement of long bones is most common; femur or tibia are the 2 most common sites reported. Patients often present with fever, pain in the affected extremity and limp, and may report preceding trauma. Physical examination findings are dependent upon the location of the infection, but point tenderness over the bony metaphysis is highly suggestive of osteomyelitis in the child with limp. Plain radiographs are often negative upon presentation, but generally show abnormalities 10 to 21 days after onset. Magnetic resonance imaging (MRI) scan may be diagnostic and should be used to guide surgical drainage if subperiosteal abscess is suspected. Laboratory evaluation is similar to that for septic arthritis. An orthopedist must be involved in the management, and input from an infectious diseases specialist is often helpful in the choice of antibiotic treatment. *S aureus* is far and away the most common pathogen associated with hematogenous osteomyelitis in children. *Pseudomonas aeruginosa* is a notable pathogen following nail puncture wounds involving the foot. Of note, children with sickle cell disease are especially at risk for osteomyelitis, and *Salmonella* is more often the responsible agent than *Staphylococcus*.

**Diskitis**, a relatively rare infection of the disk space, is most common in toddlers. Patients usually have a limp, or refuse to walk, sit, or perform any motion that requires range of motion of the affected region of the spine. Physical examination reveals pain over the involved disc space and decreased range of motion of the spine. The child generally does not seem ill or febrile, but may have increased inflammatory markers. The causative organism is usually *Staphylococcus aureus*, and treatment includes antibiotics and rest.

**Table 173-1** Characteristics of Synovial Fluid

GROUP AND CONDITION	COLOR AND CLARITY	VISCOSITY	WBC COUNT	PMN (%)
<b>NONINFLAMMATORY</b>				
Normal	Yellow and clear	Very high	<200	<25
Traumatic arthritis	Xanthochromic and turbid	High	<2,000	<25
Osteoarthritis	Yellow and clear	High	1,000	<25
<b>INFLAMMATORY</b>				
Systemic lupus erythematosus	Yellow and clear	Normal	5,000	10
Rheumatic fever	Yellow and cloudy	↓	5,000	10–50
Chronic arthritis	Yellow and cloudy	↓	15,000–20,000	75
Reactive arthritis	Yellow and opaque	↓	20,000	80
<b>PYOGENIC</b>				
Tuberculosis arthritis	Yellow-white and cloudy	↓	25,000	50–60
Septic arthritis	Serosanguineous and turbid	↓	50,000–300,000	>75

From Petty RE, Cassidy JT. Chronic arthritis in childhood. In: Cassidy JT, Laxer RM, Petty RE, Lindsley CB. *Textbook of Pediatric Rheumatology*. 6th ed. Philadelphia, PA: Elsevier Saunders; 2011, with permission.



### Malignancy or Tumor

**Leukemia** presents with musculoskeletal pain in 15% to 30% of cases, and is most common in the 2- to 5-year-old age group. The limp is usually accompanied by systemic symptoms, including fever, pallor, and fatigue. History will often reveal pain that wakes the patient from sleep and is generally out of proportion to findings on clinical examination. On physical examination, the child may have frank arthritis, bone tenderness, or bone pain. Laboratory evaluation will often show an abnormally high or low WBC count with anemia and thrombocytopenia. Thrombocytopenia and night waking can help differentiate malignancy from systemic juvenile idiopathic arthritis, which can also manifest as joint pain with systemic symptoms. Plain radiographs may reveal leukemic lines, which appear as metaphyseal sclerotic bands, and osteopenia.

**Osteosarcoma** is a malignant tumor seen primarily in adolescents. Patients often report night waking with pain and have tenderness at the affected site. Plain films generally show an abnormality in the bone, most often in the metaphyses of long bones. Once osteosarcoma is suspected, the patient should be immediately referred to a pediatric oncologist.

**Osteoid osteoma** is a benign tumor seen throughout childhood and adolescence. Patients typically have localized pain that is worse in the evenings and responds dramatically to nonsteroidal anti-inflammatory drugs. If left untreated, the tumor can cause asymmetric limb growth. Plain radiographs typically reveal cortical thickening and sclerosis with a less than 1 cm radiolucent nidus (Figure 173-2). However, the nidus is not visible on plain radiographs in 15% of cases. Therefore, if the index of suspicion is high, computed tomography (CT), MRI, or bone scan should be pursued to establish the diagnosis.



**Figure 173-2** Osteoid osteoma. Views of the midshaft of the femur demonstrate a dense sclerotic lesion with cortical thickening containing a small oval lucent nidus (arrow). (From Eisenberg RL. *An Atlas of Differential Diagnosis*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003. Copyright © 2003 Lippincott Williams & Wilkins.)

### Skeletal Anomalies

**Congenital hip dysplasia** is most commonly diagnosed in infancy but can manifest as a delay in walking or as an abnormal gait in the toddler age group. On physical examination, there is typically decreased abduction and extension of the affected hip with 1-sided toe walking to compensate for an apparent leg-length discrepancy. Beyond infancy, the anomaly is visible on standing radiograph (Figure 173-3). In the newborn period an ultrasound is generally diagnostic. Treatment after the newborn period generally requires surgical intervention, and referral to a pediatric orthopedist is necessary.

**Discoid meniscus** is a condition most commonly seen in school-aged children, in which the lateral meniscus is discoid rather than crescent-shaped. Patients often report pain with activity. On physical examination, the physician may notice swelling of the knee or the inability to fully extend the knee, as well as tenderness along the lateral joint line. Plain radiographs are normal and MRI is required for diagnosis.

**Tarsal coalition**, or abnormal ossification between the talus or navicular and calcaneus, generally occurs in adolescents and is often associated with foot pain. The physical examination reveals a stiff, flat foot in eversion with contracture of the peroneal muscles. Tarsal coalition can often be diagnosed on oblique radiographs of the ankle joint; however, if the plain radiograph is negative but there is a high index of suspicion, CT may be diagnostic. Management initially involves rest but may involve surgery in severe cases.

**Slipped capital femoral epiphysis (SCFE)** most commonly occurs in the 10 to 16 year age group and is more common in black than Hispanic children, and more common in Hispanic than white children.



**Figure 173-3** AP pelvis in a 14-month-old girl with an abnormal gait and difficulty walking. The left proximal femur is displaced superolaterally. The white arrow shows a small capital femoral epiphysis. The black arrow shows a steep acetabular roof. The patient had previously unrecognized developmental dysplasia of the left hip. Contrast in the bladder is from a voiding cystourethrogram. (From Barkin RM, Barkin SZ, Barkin AZ. *The limping child*. J Emerg Med. 2000;18[3]:331-339. Copyright © 2000, Elsevier, with permission.)



Obese adolescent males have a higher rate of SCFE as do children with hypothyroidism, low growth hormone level, pituitary tumors, craniopharyngioma, Down syndrome, renal osteodystrophy, and adiposogenital syndrome. It occurs when the femoral epiphysis slides posteriorly, resulting in limited internal rotation of the hip. Symptom onset can be acute or insidious with weeks to months of intermittent vague symptoms before the patient seeks medical attention. Plain radiographs in the frog-leg position are generally diagnostic (Figure 173-4). Patients suspected of having SCFE should be referred to a pediatric orthopedist for surgical management.

### Inflammatory Diseases

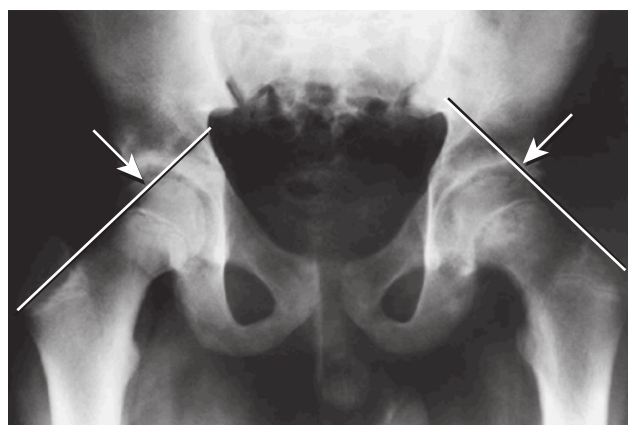
**Juvenile idiopathic arthritis (JIA)** is the general term used to describe arthritis lasting for greater than 6 weeks in a child 16 years or younger with no known cause. The specific subtype of JIA is determined by the number of joints and specific joints involved, associated systemic symptoms, and HLA-B27 positivity. The age of onset varies by subtype. Symptoms at onset include joint pain and swelling, limp, morning preponderance of pain, and morning stiffness. With systemic JIA, patients may also report fever and rash. Physical examination reveals arthritis in 1 or more joints, most often the knee. Arthritis manifests as swelling, limitation of motion, warmth, with pain on motion and/or tenderness. If present, leg-length discrepancy and muscle atrophy of the affected extremity suggest a chronic process. Laboratory evaluation should be performed to rule out other causes of arthritis and to assess inflammatory markers. Lyme serology (only in those from or who visited endemic areas), antistreptolysin O titer, and parvovirus should be sent in the appropriate clinical setting as well as a CBC, ESR, and CRP. Once the diagnosis of JIA is made, additional laboratory tests including rheumatoid factor, anticyclic citrullinated peptide antibody, antinuclear antibody,

and HLA-B27 typing can help clarify subtype. Plain radiographs may reveal a joint effusion or joint-space narrowing and erosions, but are often normal. If JIA is suspected, the patient should be referred to a pediatric rheumatologist for further workup and treatment.

**Systemic lupus erythematosus** is a chronic autoimmune disease affecting multiple organs associated with antinuclear antibodies. It is more common in black, Asian, and Hispanic females. One of the many symptoms associated with lupus is a nonerosive arthritis which can present with a limp. If there are other symptoms of lupus present and the index of suspicion is high, laboratory workup should include an antinuclear antibody, CBC, and a urinalysis, as well as the work up mentioned above to rule out infectious causes of arthritis. If lupus is suspected, the patient should be referred to a pediatric rheumatologist for further workup and treatment.

**Transient synovitis** most often presents as hip arthritis in children between the ages of 3 and 8 years. It may be preceded by a viral infection. It is generally less symptomatic than septic arthritis, without associated fever, and inflammatory markers may be normal or only mildly elevated. Transient synovitis generally lasts for 7 to 10 days. The patient often presents with a limp but is not ill-appearing. Physical examination commonly reveals pain on motion of the hip with mild limitation. Treatment generally includes rest and nonsteroidal anti-inflammatory medication, and symptoms generally resolve spontaneously.

**Juvenile dermatomyositis (JDM)** is a chronic autoimmune inflammatory myopathy and vasculopathy typically presenting with a heliotrope rash, Gottron papules (violet-colored inflammatory lesions over the knuckles) and proximal muscle weakness. Arthritis can also occur. Laboratory evaluation reveals elevated muscle enzymes, and noncontrast fat-suppressed MRI shows proximal muscle edema. Patients suspected of having JDM should be referred to a pediatric rheumatologist.



**Figure 173-4** AP pelvis in a 13-year-old boy complaining of left hip pain and limp. A Klein line is drawn along the superolateral cortex of the femoral neck. The arrow shows posteromedial slippage of the left femoral epiphysis and widening of the physis, consistent with SCFE. (From Barkin RM, Barkin SZ, Barkin AZ. *The limping child*. J Emerg Med. 2000;18[3]:331–339. Copyright © 2000, Elsevier, with permission.)

### Neuromuscular Disorders

**Cerebral Palsy (CP)**, a nonprogressive motor disorder that develops in the first 3 years of life, is the most common neurologic cause of limp in a child. The disease itself is highly variable. Physical examination may reveal spasticity of the knee or ankle joint with hyperreflexia and clonus. Patients with CP often benefit from evaluation by a pediatric neurologist and a pediatric physiatrist.

**Muscular dystrophy (MD)**, most often the X-linked Duchenne type, typically affects children between the ages of 2 and 5 years and often first manifests as delayed ambulation. The patient may demonstrate toe walking and a positive Gower sign (inability to rise from the floor without leaning on his legs with his hands), as well as proximal muscle weakness. On laboratory examination, the serum creatine phosphokinase is elevated. Patients suspected of having MD should be referred to a pediatric neurologist.

## EVALUATION

### History

The history is crucial in narrowing the differential diagnosis of a limp. The physician should first rule out

any known trauma. If the mechanism of injury described by the parent or child does not correlate with the physical findings, nonaccidental trauma should be considered. Careful details regarding the duration of symptoms, exact location (asking the child to point with 1 finger may be helpful), acuity of onset, time of day of symptoms, quality of pain, and severity are often important for making a diagnosis.

**Duration:** An acute-onset limp is more likely to result from a mechanical problem, specific hip disorder, or a transient infectious process. Limp that lasts for longer than 6 weeks is more consistent with chronic causes such as JIA or malignancy.

**Location:** While asking for a specific location of the pain is important, consider that some pain in the lower extremity is referred. Hip pathology is generally reported as groin pain, but can also be referred to the knee. Pain over the greater trochanter is less likely from pathology of the hip itself and may represent inflammation of the trochanteric bursa (rare in children) or enthesitis. Pain specific to the shaft of the bone outside the setting of trauma is more concerning for malignancy or focal lesions and less consistent with joint pathology.

**Timing of symptoms:** Limp that occurs in the morning and resolves as the day goes on is characteristic of inflammatory joint pain, as seen in arthritis. Pain or limp that worsens with activity is more likely to be from biomechanical factors secondary to trauma or overuse. Unilateral pain that wakes the child at night is worrisome for malignancy or osteoid osteoma.

**Severity:** Pain that is severe or limits activity or function is concerning.

**Systemic symptoms:** Fever or weight loss is more suggestive of an infectious, oncologic, or inflammatory cause. Rash may give helpful clues to the diagnosis, as in the case of Lyme arthritis, parvovirus-associated

arthritis, Henoch-Schönlein purpura, or systemic-onset JIA.

### Physical Examination

The extent and focus of the physical examination should be tailored to the individual based on the history obtained. If any indication of systemic illness exists, then a complete examination should be conducted. In the absence of systemic signs, most of the examination can be directed toward the back and lower extremities. Complaints of thigh or knee pain may be referred from a hip process and require thorough evaluation of the hip joint. Particularly with younger children, a great deal of useful information may be gained by opportunistic observation of the child before entering the examination room or when engaged in other activities.

### Gait Examination

A normal, mature, synchronous gait consists of a stance phase (weight-bearing phase), which begins with the heel-strike and plantar-flexion and ends with toe-off. This leads into the swing phase which starts with toe-off and finishes with heel-strike. This phase requires forward rotation, pelvic tilt, and lumbar spine stability to ensure a coordinated gait. Determining the phase of gait affected can help elucidate the cause (Table 173-2).

### Joints and Musculoskeletal Examination

General inspection of the lower extremities for evidence of skin breakdown, ecchymosis, erythema, or swelling may help localize the problem, using the non-affected limb for comparison. A side-to-side disparity in leg length or muscle bulk suggests chronicity. Leg length can be measured from the anterior superior iliac spine to the distal end of the ipsilateral medial malleolus. Palpation of the extremity along all surfaces can also help localize focal pathology.

**Table 173-2** Gait Abnormalities and Associated Pathology

TYPE OF GAIT ABNORMALITY	CAUSE	DESCRIPTION	ASSOCIATED PATHOLOGY
Antalgic	Pain on weight bearing	Shortened stance on affected leg with shortened swing phase on contralateral side	Soft-tissue or skeletal trauma, chondromalacia patellae, arthritis, osteomyelitis, inguinal lymphadenitis, abdominal infection, Legg-Calvé-Perthes disease, slipped capital femoral epiphysis, bone neoplasia, rickets, tarsal coalitions
Vaulting	Joint pain or muscle weakness	Straight-legged walking (locking of knee causes the child to “vault” over leg)	Arthritis, skeletal dysplasias, congenital short femur, neurologic and neuromuscular disease, soft-tissue infection (dependent on affected joint/site)
Steppage	Peroneal nerve injury or weakness of the tibialis anterior muscle	Foot drop	Congenital talipes equinovarus, chronic pain syndromes
Trendelenburg	Hip abductor weakness or hip joint instability	Hip girdle drops on affected side, trunk moves over affected side to maintain balance	Hip arthritis, myositis, osteomyelitis, soft-tissue infection, abdominal infection (including psoas abscess, appendicitis, peritonitis), Legg-Calvé-Perthes disease, slipped capital femoral epiphysis, developmental dysplasia of the hip, neurologic disease, dermatomyositis and neuromuscular disease

Each joint of the lower extremity should be evaluated independently for evidence of trauma or inflammation. Range of motion, size and contour should be symmetric, emphasizing the importance of side-to-side comparison. If joint involvement is suspected, the joints of the upper extremities and spine should be fully evaluated as well.

### **Sacroiliac (SI) joint**

The sacroiliac joint is where the sacrum attaches to the ilium. On physical examination, the joint can be palpated directly under the dimples of Venus. The Gaenslen maneuver, in which the patient hangs 1 leg off the table and pulls the opposite knee towards the chest, is a test for inflammation of the sacroiliac joint (Figure 173-5). The test is considered positive if the patient has pain in the buttock opposite the knee that is being held. The SI joint is often involved in 1 of the subtypes of JIA, enthesitis-related JIA; alternatively, insidious infection of the SI joint can occur.

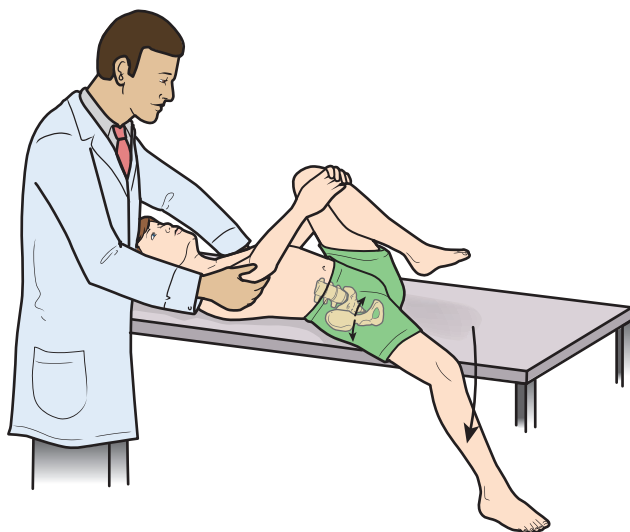
### **Hip joint**

Children with hip pathology tend to hold the joint in a flexed, abducted, and externally rotated position, taking pressure off of the joint. The hip joint can be isolated on physical examination using a maneuver called the logroll. The examiner places a hand on the mid-thigh and mid-shin of the patient and gently rolls the hip internally and externally, taking care not to simultaneously manipulate the knee joint.

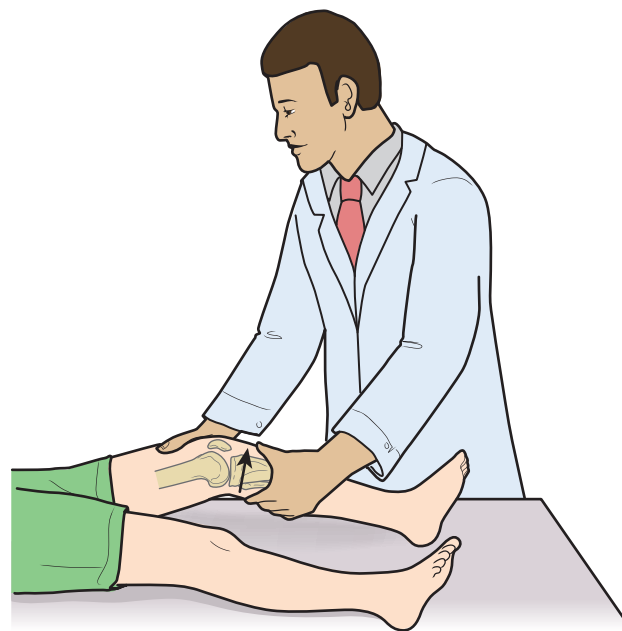
### **Knee joint**

The knee should be compared to the contralateral knee to assess for swelling, which often manifests as a loss of bony landmarks. The knee should be assessed for warmth and tenderness, as well as pain on motion or limitation of motion with either flexion or extension. Patellofemoral syndrome (formerly known as chondromalacia patella) can be assessed with the patellar inhibition test, whereby the examiner applies pressure to the

patellar tendon proximal to the patella, and asks the patient to tense the quadriceps muscles. If this reproduces the patient's pain, it is considered a positive test. Anterior cruciate ligamentous (ACL) injury can be assessed using the anterior drawer test: with the patient lying flat and the knee bent at 90 degrees, the examiner pulls the calf forward. If the tibial excursion is greater than normal, the test is considered positive and is suggestive of loss of ACL integrity. A Lachman maneuver is an appropriate substitute to evaluate the integrity of the ACL: the knee is placed at 30 degrees of flexion, and while the femur is stabilized with 1 of the examiner's hands the tibia is pulled anteriorly with the other hand (Figure 173-6). If there is no clear end point of anterior movement, or absence of a "clunk," the test is considered positive. The posterior drawer test is used to assess for injury to the posterior cruciate ligament (PCL), and is performed similarly to the anterior drawer test, but the shin is pushed posteriorly; excessive posterior movement is suggestive of PCL injury. Injury to the lateral collateral ligament (LCL) and medial collateral ligament (MCL) can be assessed by placing the patient flat on the back with the knee held at 30 degrees of flexion; the shin is shifted from side to side to test the integrity of the LCL (varus stress) and MCL (valgus stress). To assess for meniscal injuries, first palpate over the joint line for tenderness. The McMurray test examines the integrity of the medial and lateral menisci. To test the medial meniscus, the patient lies in the supine position with the knee in full flexion; with 1 hand, the examiner stabilizes the joint, applying pressure to the lateral aspect of the joint providing valgus stress, while with the opposite hand the examiner holds the heel of the patient and laterally rotates the tibia while extending the knee. To assess lateral meniscal



**Figure 173-5** Pain with this maneuver is indicative of pathology within the sacroiliac joint.



**Figure 173-6** With one hand stabilizing the femur, the proximal tibia is moved forward with the other hand. The absence of a distinct endpoint of forward tibial movement is suggestive of ACL injury.

integrity, the medial meniscus is stabilized by 1 hand while the tibia is rotated medially and the knee is extended by the other hand. If the patient has pain or the examiner feels a snap or click, the test is positive.

### Ankle

The ankle is comprised of 2 joints, the tibiotalar joint and the subtalar joint. The tibiotalar joint is responsible for dorsiflexion and plantar flexion, and the subtalar joint is responsible for inversion and eversion. Pain over the Achilles tendon or at the sites of attachment of the plantar fascia may be suggestive of a tendonitis, or in the setting of chronic pain, may be associated with enthesitis related to JIA.

### General Examination

On initial examination, the most important determination is whether or not the patient is ill-appearing, as this may be associated with more urgent problems such as a septic joint or a systemic disease. The patient should be assessed for any rashes or lesions suggestive of specific disorders. A thorough neurologic assessment should be performed, including an evaluation of muscle strength and function, sensation, and reflexes.

### Laboratory Testing

In cases of known trauma, blood testing is often not necessary. A CBC and measure of acute phase reactants are useful if inflammatory or infectious causes are suspected (see Differential Diagnosis for specific laboratory abnormalities by disease). If a septic joint is likely, joint aspiration should be performed and blood cultures should be obtained prior to initiation of antibiotics. Antinuclear antibody (ANA) testing in the absence of objective evidence of arthritis is not necessary unless there are additional clinical findings suggestive of autoimmune disease (vasculitic/malar rash, palatal ulcers, hair loss, serositis, renal or CNS disease). In the setting of chronic arthritis, the ANA is useful to delineate risk of developing uveitis, but it is not diagnostic. Approximately 20% of healthy children have a positive ANA without any underlying disease. If arthritis is seen on physical examination and the history is suggestive of the associated diseases, Lyme titers, gonococcal cultures, parvovirus IgG and IgM, anti-DNAse B and antistreptolysin O titers may be warranted.

### Imaging

#### Radiographs

Plain-film radiographs remain an important tool in the evaluation of limp, particularly in diagnosing fractures, hip disease, spinal abnormalities, and foot disease (eg, tarsal coalition). Obtaining at least 2 views of the affected area is essential; with suspected hip disease, the 2 views should be the anteroposterior (AP) and frog-leg lateral (Lauenstein) views of the pelvis. Diagnosis-specific radiographic findings are reviewed in the Differential Diagnosis section.

#### Ultrasound

Ultrasound can be used to assess musculoskeletal pathology. Joint effusions, synovial thickening, and increased blood flow seen by power Doppler are suggestive of underlying inflammation. While the cause of inflammation cannot be determined by this method, it

may be a useful adjuvant to the history and physical examination.

### Bone Scintigraphy

Bone scintigraphy measures the uptake of technetium-99m, which is increased at sites of high bone turnover. It is therefore most useful in the diagnosis of osteomyelitis, diskitis, stress fractures, osteoid osteomas, Legg-Calvé-Perthes disease, and neoplasm, especially if the location of the pathology is difficult to identify. However, MRI is often preferred to bone scintigraphy to spare children radiation exposure and to provide more specific information.

### Computed Tomography

Computed tomography is most useful for evaluating bony pathology, including tarsal coalition, spondylolisthesis, spondylolysis, or osteoid osteoma. However, it exposes the patient to a high dose of radiation and its use should therefore be limited to situations where other imaging modalities are inadequate or unavailable.

### Magnetic Resonance Imaging

Magnetic resonance imaging offers information about bone formation and inflammation as well as soft tissues without exposing the child to radiation, and is therefore the imaging modality of choice for clarifying difficult diagnoses. In cases of arthritis, osteomyelitis, diskitis, stress fractures, osteoid osteomas, Legg-Calvé-Perthes disease, and neoplasm, MRI is often crucial to diagnosis.

## WHEN TO REFER

Limp is a common presenting complaint in pediatric emergency departments and primary care offices. History and physical examination are crucial to diagnosing the cause of a limp, and imaging is an important adjuvant to the physical examination. There are very few emergent causes of limp, but they do occur, and suspicion of any of the following causes does warrant referral:

- Septic joint
- Malignancy
- Surgical cause (eg, appendicitis, psoas abscess)
- Serious fracture

Once these emergent causes of limp have been excluded, if the workup is negative, an observation period of 1 to 2 weeks may be appropriate. Following the observation period, if the diagnosis is still unclear, referral to an orthopedist, rheumatologist, or neurologist may be necessary depending on the clinical scenario.

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## Chapter 174

# LOSS OF APPETITE

Nancy McGreal, MD; Martin H. Ulshen, MD

Loss of appetite (anorexia) is a common symptom in children. Acute illness in childhood is often associated with transient loss of appetite. Prolonged loss of appetite associated with poor weight gain or loss of weight usually signifies a serious chronic illness, either organic or psychogenic.

## PATHOPHYSIOLOGIC FEATURES

The mechanisms that regulate hunger and satiety are complex and redundant, remaining incompletely understood. Appetite is regulated by multiple nuclei and signaling pathways in the hypothalamus, now known to be much more complex than the previously described *satiety center* in the ventromedial hypothalamus and the *feeding center* in the lateral hypothalamus. The hypothalamus detects peripheral signals, including gut hormones and blood-borne nutrients. Vagal nerve afferents from the gastrointestinal (GI) tract and hepatoportal region terminate in the brainstem, and information is conveyed to the hypothalamus. Both appetite-stimulating and appetite-suppressing neuropeptides are secreted in the hypothalamus. Central control of appetite is influenced by anticipation of a pleasurable meal, visual and taste sensations, ambient temperature, and changes in blood levels of glucose or other nutrients, as well as by limbic signals from higher central nervous system (CNS) regions. Initiators of satiety include vagal input from gastric distention, cholecystokinin from the intestine and CNS, and other humoral factors, including insulin, glucagon-like peptide-1, pancreatic polypeptides, and endorphins. Each individual may have a set point for body fat content. Deviations may cause alterations in diet intake, a process apparently mediated by the interaction of the hormones leptin, produced in adipose cells, and ghrelin, produced by endocrine cells in the stomach and GI tract, with receptors in the hypothalamus. Leptin suppresses and ghrelin stimulates appetite. Changes in the levels of these hormones influence the release of CNS neuropeptides, including neuropeptide Y, melanocyte-stimulating hormone, and the orexins.

Cytokines are key mediators of the appetite suppression that occurs with acute and chronic illnesses. Interleukin-1 $\beta$ , interleukin-6, and tumor necrosis factor- $\alpha$ , for example, have been shown to induce anorexia by acting directly on the hypothalamus. Effects on the peripheral nervous system and on hormone levels occur as well.

## DIFFERENTIAL DIAGNOSIS

When considering anorexia, the physician must first separate complaints based on unrealistic parental dietary expectations from justified parental concern over a child's diminished nutritional intake. In the

former situation, the child is typically growing well and appropriately thriving. Although significant GI disease commonly leads to poor appetite, anorexia may be the result of disease that is distant from the bowel. In the newborn period, poor oral intake by an infant who is developmentally capable of feeding may be the first indication of a major disorder, such as sepsis, meningitis, urinary tract infection, congenital viral infection, a GI anomaly, CNS disease, renal failure, or an inborn error of metabolism.

During infancy, a wide spectrum of causes can account for inadequate caloric intake. An acute infectious disease is a common cause of transient anorexia in infants. If no obvious explanation exists for poor feeding, then the pediatrician should always consider the possibility of an oral disease (eg, thrush), gastroesophageal reflux disease, eosinophilic esophagitis, renal tubular acidosis, dietary protein intolerance, or a neurologic disorder. Occasionally, an infant will lack interest in feeding from the first days of life but in every other respect will appear normal; such an infant may well need enteral feeding supplementation. Emotional deprivation is a common cause of failure to thrive; a thorough social history is essential to the evaluation. Early observation of parent-infant interaction in the hospital, including feeding techniques, may be helpful. An infant who has not received oral feedings for a prolonged period because of medical problems (eg, esophageal disease, short bowel syndrome) may not be interested when feedings are introduced by mouth. The mother and infant may require training (typically provided by an occupational therapist, physical therapist, or speech pathologist) and gradual advancement of an oral diet.

Box 174-1 presents a list of causes of loss of appetite that are applicable to both infants and children. Generally, the best approach to anorexia is to treat the underlying condition.

## EVALUATION

In formula-fed infants, a state of chronically inadequate caloric intake can be identified objectively by computing the total calories ingested, most of which come from formula, and comparing this total with the estimated caloric requirements for weight. Such computation is more difficult with breastfed infants, although intake may be established by weighing the infant before and after feedings. If the nursing infant has a reduced intake, the physician must establish whether maternal milk production is inadequate or the infant is too weak or disinterested to nurse.

In older children and adolescents, an adequate evaluation of nutritional intake requires careful calorie counts. If the possibility of malabsorption is a concern, a calorie count and 72-hour stool collection for fat analysis may be ordered. Separating children who have poor appetites from children who do not eat for fear of worsening their symptoms is important from the outset. Children with abdominal pain from chronic inflammatory bowel disease or chronic constipation may not eat because doing so increases their pain. Similarly, children with chronic diarrhea may find that eating less leads to less frequent stooling. These

**BOX 174-1 Causes of Decreased Appetite in Infants and Children****ORGANIC DISEASE**

- Infections (acute or chronic)
- Neurologic causes
  - Cerebral palsy
  - Congenital degenerative disease (eg, neurodegenerative disorders, spinomuscular atrophy, muscular dystrophy)
  - Hypothalamic lesion
  - Increased intracranial pressure, including a brain tumor
  - Static encephalopathy
- GI causes
  - Oral or esophageal lesions (eg, thrush, herpes simplex, dental caries, ankyloglossia)
  - Gastroesophageal reflux
  - Eosinophilic esophagitis
  - Dietary protein intolerance
  - Bowel obstruction (especially with gastric or intestinal distention)
  - Inflammatory bowel disease
  - Celiac disease
  - Constipation
  - Esophageal motility disorder (eg, cricopharyngeal dysfunction, achalasia, connective tissue disorder)
- Cardiac causes
  - Congestive heart failure or cyanotic heart disease
- Metabolic causes
  - Renal failure, renal tubular acidosis, or both

- Liver failure
- Inborn errors of metabolism
- Lead poisoning
- Nutritional causes
  - Marasmus
  - Iron deficiency
  - Zinc deficiency
- Drugs
  - Morphine
  - Digitalis
  - Antimetabolites
  - Methylphenidate
  - Amphetamines
  - Topiramate
- Prolonged restriction of oral feedings, beginning in the neonatal period
- Tumor
- Chronic febrile conditions (eg, rheumatoid arthritis, rheumatic fever)

**PSYCHOLOGICAL FACTORS**

- Anxiety, fear, depression, mania (limbic influence on the hypothalamus)
- Avoidance of symptoms associated with meals (abdominal pain, nausea, diarrhea, bloating, urgency, dumping syndrome)
- Anorexia nervosa
- Excessive weight loss and food aversion in athletes, simulating anorexia nervosa

children may actually not have anorexia, and treatment aimed at improving the other symptoms may result in rapid improvement in oral intake.

**TREATMENT**

Enlisting the help of a dietitian to plan diets can be useful for maximizing nutritional intake in older children. Nutritional supplements may be indicated, either high-calorie milkshakes or commercial high-calorie supplements. Several medications, including cyproheptadine and megestrol acetate, have been shown to stimulate appetite. Although cyproheptadine does not seem to affect appetite in all children treated, when successful, the response is dramatic. Megestrol acetate, a progesterone derivative, has been administered for cancer-related anorexia, primarily in adults. Its potential side effects on the endocrine system include adrenal insufficiency. Weight gained with megestrol acetate may be, to a large extent, from increased fat mass. Eicosapentanoic acid, an omega-3 fatty acid, has been evaluated in the treatment of adult and pediatric cancer-associated anorexia with equivocal results. In some disorders, such as congenital heart disease, initial nasogastric or

nasoduodenal infusion of nutrients may be necessary to promote growth. If prolonged supplementation proves necessary, a gastrostomy tube can be placed. Parenteral nutrition may be indicated in specific situations. However, expertise with this modality and close supervision are required, and caretakers need special training if the parenteral nutrition is to be provided at home. Refeeding after severe malnutrition requires careful consideration of potential cardiac and metabolic complications.

**WHEN TO REFER**

- Loss of appetite without an obvious explanation, especially in association with weight loss or failure to thrive
- Anorexia nervosa

**WHEN TO ADMIT**

- Weight loss or lack of weight gain that is unresponsive to outpatient management
- Requirement to initiate enteral or parenteral feeding because of inadequate oral intake

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## Chapter 175 LYMPHADENOPATHY

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Caroline Breese Hall, MD†

Enlargement of 1 or more lymph nodes is a common finding in childhood. Lymphadenopathy may be defined as any lymph node enlargement; all lymph nodes that are palpable are technically considered enlarged. However, nodes in the cervical chain, occipital, and inguinal areas drain regions that are commonly infected in childhood and are often mildly enlarged (<1 cm in diameter) in children who are otherwise healthy.

The clinically relevant problems in assessing lymphadenopathy are whether any lymph node or lymph node aggregate or chain is abnormal and requires further assessment; if abnormal, whether the nodes are benign, primarily inflammatory, or malignant; and what the appropriate evaluation, diagnosis, and management should be.

### CHARACTERISTICS OF LYMPH NODE ENLARGEMENT

#### Components of the Lymphatic System

The lymphatic system includes not only lymph nodes but also the spleen, thymus, tonsils, Waldeyer ring, appendix, and Peyer patches in the intestine. Potentially palpable lymph node groups and their drainage areas are listed in Table 175-1. The location of the lymphatics of the head and neck and lymph node drainage are shown in Figure 175-1 and may serve as a guide to palpation of these superficial nodes.

#### Lymph Node Features

Abnormalities of the palpable lymph nodes are assessed by noting the node's size, location, mobility, tenderness, erythema (inflammatory reaction), and consistency and whether it is matted. Nodes smaller than 1 cm are often found in the cervical chain and in the femoral areas. They are often somewhat larger in the inguinal areas. Similarly, nodes smaller than 0.5 cm may be palpated in the occipital, postauricular (mastoid), and axillary chains. Small occipital and

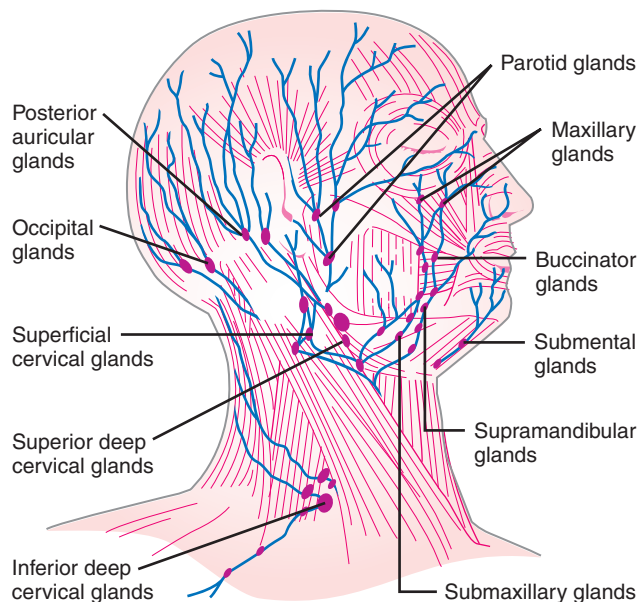
**Table 175-1**

### Correlations Between Lymph Node Locations and Disease Origin

#### LYMPH NODE GROUPS

#### AREA OF DRAINAGE

Occipital	Posterior scalp, neck
Anterior auricular, parotid	Lateral pinna, frontotemporal, eyelids
Posterior auricular	Mastoid area and pinna
Superior (anterior) cervical	Posterior scalp and neck, tongue, pharynx, larynx
Inferior (posterior) cervical	Posterior scalp, neck, pectorals, and arm
Submental	Apex of tongue and lower lip
Submaxillary	Tongue, buccal cavity, lips, and cheek
Supraclavicular	<i>Right:</i> Inferior neck and mediastinum <i>Left:</i> Inferior neck, mediastinum, and upper abdomen
Mediastinal, hilar	<i>Anterior:</i> Thymus, pericardium <i>Posterior:</i> Esophagus, pericardium, liver surface <i>Hilar:</i> Lungs
Axillary	Greater part of arm and shoulder; superficial, anterior, and lateral thoracic and upper abdominal wall
Epitrochlear	Hand, forearm, and elbow
Abdominal	Abdominal organs to various mesenteric nodes and to retroperitoneal nodes
Inguinal, femoral	Leg and genitalia



**Figure 175-1** Lymph nodes and lymphatics of the head and neck. The nodes in the region below the mandible are designated *submaxillary*. (Reproduced from *Anatomy of the Human Body* by Henry Gray, 20th edition, with permission from Bartleby.com, Inc.)

†Deceased

Table 175-2		Prevalence of Lymphadenopathy by Age									
PALPABLE NODES											
		OCCIPITAL		POSTAURICULAR		SUBMANDIBULAR		CERVICAL		NO PALPABLE NODES	
AGE	NUMBER OF PATIENTS	NUMBER	(%)	NUMBER	(%)	NUMBER	(%)	NUMBER	(%)	NUMBER	(%)
0–6 mo	52	17	(32)	7	(13)	1	(2)	1	(2)	32	(62)
7–12 mo	31	8	(26)	4	(13)	1	(3)	8	(26)	16	(52)
13–23 mo	39	4	(10)	3	(7)	7	(18)	11	(28)	20	(52)
2 years	35	3	(8)	2	(6)	7	(20)	16	(45)	11	(32)
3 years	27	2	(7)	0	(0)	7	(26)	9	(33)	11	(41)
4 years	20	0	(0)	0	(0)	5	(25)	11	(55)	7	(35)
5 years	19	0	(0)	1	(5)	4	(21)	12	(63)	5	(26)
Total	223	34	(15)	17	(8)	32	(14)	68	(30)	102	(45)

Reproduced with permission from Herzog LW. Prevalence of lymphadenopathy of the head and neck in infants and children. *Clin Pediatr*. 1983;22:485–487.



postauricular nodes are common in infants but not older children, whereas cervical and inguinal nodes are common after age 2 years. The distribution by age is shown in Table 175-2. In the submental or submaxillary regions, intraoral or facial infections may enlarge the nodes to more than 1 cm. However, finding lymph nodes of any size in the supraclavicular or epitrochlear areas is unusual. Thus, lymph nodes of the same size observed in 2 different regions may have markedly different implications. For example, a 1-cm node in the cervical region of a 5-year-old child is very likely benign, whereas a 1-cm supraclavicular node requires a biopsy because it is unlikely to result from superficial inflammatory disease and may reflect intrathoracic or intraabdominal malignancy. Noninflammatory nodes greater than 2 to 2.5 cm require biopsy.

Fluctuance and signs of inflammation surrounding a group of enlarged lymph nodes are helpful in reaching a diagnosis, particularly if an infectious source is found distal to the node area. These findings strongly suggest an infectious, primarily bacterial cause (Table 175-3), usually requiring systemic antibiotic therapy. If no inflammation is found, the consistency is firm, and the nodes are not mobile, then an underlying malignancy may be present, such as a lymphoma, sarcoma, or neuroblastoma. Hard, fixed nodes are seen more often in adults who have metastatic carcinoma. The nodes of Hodgkin disease and lymphoma are more matted than hard, although nodes associated with neuroblastoma, rhabdomyosarcoma, and other childhood malignancies may mimic the findings in adults.

**Table 175-3** Entities Associated With Lymphadenopathy<sup>a</sup>

	GENERALIZED	CERVICAL	OTHER REGIONAL
<b>INFECTIONS</b>			
<b>Viral</b>			
Respiratory viruses (adenoviruses, picornaviruses, respiratory syncytial virus [RSV], parainfluenza, influenza, coronaviruses)		1–3+	
Epstein-Barr virus (EBV)	2–3+	3+	+
Cytomegalovirus (CMV)	2+	2+	
Primary human herpesvirus type 6 (HHV-6)		+	2–3+ (postoccipital)
Parvovirus B19	1–2+		2+
Human immunodeficiency virus (HIV)	2–3+	+	+
Rubella	2+	3+	+
Rubeola	1–2+	3+	
Varicella zoster	1–2+	+	+
Herpes simplex virus (HSV)		3+	1–2+ (genital infection)
HHV-8	2–3+	2–3+	+
Hepatitis A	+	2+	
<b>Bacterial</b>			
<i>Staphylococcus aureus</i>		3+	2–3+
<i>Streptococcus pyogenes</i>	+	3+	2–3+
<i>Bartonella henselae</i> (cat-scratch disease)	+		2–3+
<i>Bartonella bacilliformis</i> (Oroya fever, verruga peruana)	3+	3+	3+
<i>Yersinia enterocolitica</i>	+		3+
<i>Salmonella typhi</i>	2–3+		2+
Tularemia	+	3+	2+
Brucellosis	2–3+	+	+
Dental, gingival infections		2–3+	2–3+
Postanginal sepsis ( <i>Fusobacterium</i> )		2–3+	
<i>Mycobacterium tuberculosis</i>	+	2–3+	2–3+
Atypical mycobacteria		2–3+	2–3+
Syphilis	2–3+	+	+
Lyme disease			+
Leptospirosis	3+	+	+
<b>Rickettsia/Chlamydia</b>			
Lymphogranuloma venereum			3+
Ehrlichiosis	2–3+		
<i>Rickettsia tsutsugamushi</i>	3+	2–3+	3+
<b>Protozoan</b>			
Toxoplasmosis	+	3+	+
Malaria	+		
<b>Parasitic</b> ( <i>Toxocara canis</i> , <i>Toxocara cati</i> , <i>Baylisascaris procyonis</i> , <i>Trichinella spiralis</i> , <i>filarialis</i> )			
	1–2+	+	1–2+

Continued

**Table 175-3** Entities Associated With Lymphadenopathy<sup>a</sup>—cont'd

	GENERALIZED	CERVICAL	OTHER REGIONAL
Myiasis		+	1–2+
<b>Fungal</b>			
Histoplasmosis	1–3+	+	1–2+
Coccidioidomycosis	1–3+	+	1–2+
Tinea capitis			2–3+
<b>IMMUNIZATIONS</b>			
Viral	+		+
Typhoid	+		+
Bacille Calmette-Guérin (BCG)			1–3+
<b>NEOPLASTIC</b>			
Leukemia	1–2+		
Lymphoma	1–3+	2–3+	2–3+
Hodgkin disease		2–3+	2–3+
Metastatic, solid tumors (neuroblastoma, Wilms tumor, Ewing sarcoma, rhabdomyosarcoma)	1–2+		1–2+
<b>HISTIOCYTOSES</b>			
Langerhans cell histiocytosis		1–3+	
Malignant histiocytosis		1–2+	1–2+
Sinus histiocytosis (Rosai-Dorfman disease)		3+	
Hemophagocytic syndromes	1–2+	2+	
<b>IMMUNOLOGIC</b>			
Deficiency syndromes	1–2+	1–2+	2–3+
Autoimmune lymphoproliferative syndrome (ALPS)	2–3+		
Serum sickness	2+	+	+
Ommen syndrome	1–2+	+	+
Juvenile idiopathic arthritis	1–2+	+	+
Atopic disease, eczema	2–3+	2+	2–3+
Castleman disease	1–3+	3+	2–3+
<b>MEDICATIONS (Phenytoin and others)</b>	1–2+		
<b>STORAGE DISEASES (Gaucher disease, Niemann-Pick disease)</b>	2–3+		1–3+
<b>GRANULOCYTE DEFECTS</b>			
Chronic granulomatous disease	+	1–2+	2–3+
Leukocyte adhesion deficiencies		1–3+	1–3+
Chédiak-Higashi anomaly		1–3+	1–3+
<b>OTHER</b>			
Kawasaki disease		2–3+	
Hemoglobinopathic conditions	+	1–2+	
Hemophilia with HIV	2–3+	+	+
Sarcoidosis	2–3+	+	1–2+
Gianotti-Crosti syndrome	3+	+	+
Necrotizing lymphadenitis (Kikuchi-Fujimoto disease)	+	2–3+	2–3+
Insect bites		+	+
Kimura disease		2–3+	1–2+
Addison disease	1–2+		
Hyperthyroidism	1–3+		

<sup>a</sup>Numbers represent relative prominence and incidence of lymphadenopathy.

## DIFFERENTIAL DIAGNOSIS

The major differential diagnostic categories for enlarged lymph nodes include infectious (inflammatory), neoplastic, immunologic, storage, and other diseases. Table 175-3 provides a summary of the common and unusual conditions associated with lymphadenopathy.

### Infections

Infectious problems may be localized or systemic. If localized, the primary site of infection draining to the

involved lymph node area should be identified (see Table 175-1). Lymph nodes enlarge most often in reaction to a localized or generalized infection, but a node can itself become intrinsically infected, resulting in lymphadenitis.

The common pyogenic bacteria (*Staphylococcus aureus* and *Streptococcus pyogenes*), atypical mycobacteria, and *Bartonella henselae* (cat-scratch disease) are most likely to cause localized adenopathy. Generalized adenopathy or regional adenopathy associated

with adenopathy elsewhere is more likely caused by infections from viruses, spirochetes, or, sometimes, *Toxoplasma* spp. *Mycobacterium tuberculosis* may produce localized or multiple sites of adenitis. Fungal infections, such as histoplasmosis, occasionally cause generalized lymphadenopathy when disseminated, but most fungal infections, if associated with adenopathy at all, produce regional enlargement.

### Neoplastic Diseases

Primary neoplastic diseases are the other major consideration in both localized and generalized adenopathy. Included in this category are lymphomas, leukemia, histiocytosis, and metastases from solid tumors such as neuroblastoma, Wilms tumor, Ewing sarcoma, and rhabdomyosarcoma. If a mediastinal mass is identified, then the diagnostic considerations vary with the anatomic location within the mediastinum (Box 175-1).

### Immunologic and Inflammatory Diseases

Generalized lymphadenopathy also may be associated with chronic inflammatory conditions, such as juvenile idiopathic arthritis, other autoimmune diseases, and sarcoidosis; with reactions to certain drugs, such as phenytoin and isoniazid; or with serum sickness.

#### BOX 175-1 Anatomic Locations of Mediastinal Masses

##### ANTERIOR MEDIASTINUM

- Lymphoma
- Thymoma
- Malignant germ cell tumor
- Benign teratoma
- Substernal goiter
- Thymic hyperplasia
- Thymic cyst
- Mesenchymal tumors

##### MIDDLE MEDIASTINUM

- Lymphoma
- Tuberculosis
- Sarcoidosis
- Histoplasmosis
- Castleman disease
- Bronchogenic cyst
- Sarcoma

##### POSTERIOR MEDIASTINUM

- Neuroblastoma
- Ganglioneuroma
- Neurofibroma
- Primitive neuroectodermal tumor
- Sarcoma
- Germ cell tumor
- Schwannoma
- Duplication cyst

Unusual causes, such as hyperthyroidism and Addison disease, also should be included in the differential diagnosis of generalized adenopathy.

### ASSESSMENT

The evaluation of lymphadenopathy is summarized in Table 175-4 and discussed in detail below.

#### History, Physical Examination, and Chest Imaging

The history and physical examination may reveal a source of a localized infection, such as a dental abscess, mastoiditis, scalp infection, insect bite, or cat scratch. Alternatively, systemic diseases, such as infectious mononucleosis, juvenile idiopathic arthritis, and infection with the human immunodeficiency virus, may be suggested by other characteristic historical and physical findings. The physical examination should include all the palpable nodes (see Table 175-1). Furthermore, assessment of enlarged lymph nodes that have no obvious inflammatory explanation requires a chest radiograph or computed tomography (CT) scan to determine whether enlarged mediastinal or hilar nodes are present. The chest radiograph is the study most commonly omitted in evaluating patients who have lymphadenopathy; the identification of mediastinal or hilar adenopathy would preclude trials of antibiotics, which often delay a diagnostic biopsy.

#### Imaging

The abdominal lymph nodes, including retroperitoneal, periportal, and celiac nodes, as well as the nodes of the splenic hilum, are difficult to evaluate without sophisticated imaging techniques. The spleen, which is primarily lymphoid tissue, may be enlarged in infectious, immunologic, and neoplastic disorders and may be delineated by ultrasound or CT examination. Abdominal and pelvic lymph nodes may be visualized by ultrasonography or may require techniques such as CT and magnetic resonance imaging. The sensitivity and specificity of methods to define chest (mediastinal or hilar) lymphadenopathy are variable. In one study of patients thought to have tuberculosis, the chest radiograph was 67% sensitive and 59% specific compared with spiral chest CT with contrast. Newer techniques include positron emission tomography and scintigraphy.

#### Complete Blood Cell Count and Acute Phase Reactants

A complete blood cell count may reveal the reactive lymphocytes of infectious mononucleosis or a granulocytosis with a shift to the left, suggesting systemic bacterial infection. Bicytopenia (eg, anemia, granulocytopenia, thrombocytopenia) would be a red flag that a hematologic malignancy, such as leukemia or lymphoma, or a metastatic disease involving the bone marrow, such as neuroblastoma, may underlie the lymphadenopathy. The finding of nucleated erythrocytes and immature granulocytes (leukoerythroblastic blood picture) on the blood film is an ominous sign suggesting bone marrow irritation, with premature release of blood cell precursors. This finding may be seen in metastatic diseases such as neuroblastoma

Table 175-4 Evaluation of Lymphadenopathy	
<b>HISTORY</b>	Exposures (animals, foods, travel) Medications Weight loss Fevers Night sweats Bone pain
<b>PHYSICAL EXAMINATION</b>	Palpable node areas Tonsils Spleen and liver
<b>IMAGING</b>	Chest radiograph Ultrasound—abdomen and pelvis Possibly computed tomography, magnetic resonance imaging, nucleotide or positron emission tomographic scanning
<b>LABORATORY</b>	<p><b>Neoplasia</b></p> <p>CBC with differential count and blood smear Sedimentation rate, C-reactive protein Uric acid, phosphate, lactate dehydrogenase Catecholamines, vanillylmandelic acid, homovanillic acid</p> <p><b>Infections (common)</b></p> <p><b>General</b></p> <p>CBC with differential count Sedimentation rate, C-reactive protein Gram stain of exudate</p> <p><b>Specific</b></p> <p>Viral, respiratory Epstein-Barr virus (EBV) Cytomegalovirus (CMV) Human immunodeficiency virus (HIV) Cat-scratch disease</p> <p>Bacterial <i>Staphylococcus aureus</i> Anaerobes <i>Streptococcus</i> (group A) Mycobacteria (purified protein derivative [PPD] or interferon-<math>\gamma</math> release assay [IGRA]) Atypical mycobacteria (PPD)</p> <p><b>Autoimmune</b></p> <p>Antinuclear antibody Anti-double-stranded DNA Serum ferritin</p>
<b>SURGERY</b>	<p><b>Biopsy<sup>a</sup></b></p> <p>Histology, cytochemistry, flow cytometry, DNA studies, chromosomes</p> <p><b>Needle aspiration</b></p> <p>Reserved for surgically inaccessible nodes Requires skilled cytopathologist</p>

CBC, complete blood count.

<sup>a</sup>Requires the availability of pediatric pathology.

and rhabdomyosarcoma, with immunologic vasculitis and with granulomas (mycobacteria) in the marrow. Isolated leukopenia and neutropenia may also be seen with viral infections or severe bacterial infections (particularly in infants). Other studies may be useful in assessing lymphadenopathy, including C-reactive protein and erythrocyte sedimentation rate, that detect a systemic inflammatory reaction and may reflect infection, vasculitis, or neoplasm.

### Infectious Evaluation

The diagnostic workup of potential infectious lymphadenopathy is diverse and depends on the history, the

patient's age, the location of the nodes (whether cervical, localized, or generalized), and the signs of inflammation accompanying the adenopathy. The cause of acute, inflamed, and localized adenopathy is often infectious and likely to be bacterial. A purified protein derivative or interferon- $\gamma$  release assay is indicated when tuberculosis is a possibility. Material should be obtained for culture and histologic or pathologic examination when possible, particularly in patients who do not respond to initial therapy. In children who have acute cervical adenitis, needle aspiration of an acutely inflamed, sometimes fluctuant, node demonstrates the infecting organism in two-thirds or more of



cases. In certain cases, a biopsy may be required. If tuberculosis or atypical mycobacterial infection is thought to be present (eg, young children with subacute lymphadenopathy in the submandibular or submental regions), then needle aspiration should be avoided to prevent spread of the infection; excisional biopsy is required. The material obtained from biopsy or aspiration should be cultured aerobically and anaerobically and examined histologically, including special stains such as that for cat-scratch disease (Warthin-Starry silver stain). Specific diagnosis by serologic assessment, antigen detection, polymerase chain reaction, and culture is available for most of the common agents causing lymphadenopathy in children (most prominently serology for *B. Henselae* [cat-scratch disease]). The erythrocyte sedimentation rate or the C-reactive protein may be useful in assessing underlying inflammation, but both may be elevated in immunologic and neoplastic diseases as well.

After initial evaluation by history, physical examination, chest radiograph, and preliminary laboratory studies, the physician may not yet have an obvious explanation for the node enlargement. If a bacterial source for localized adenopathy (eg, pharyngitis, cervical nodes) is suggested, then a limited course of 7 to 10 days of antibiotic therapy may be tried. However, if the nodes have not regressed significantly, then prompt further evaluation is necessary. At this time, a chest radiograph should be obtained if it has not already been performed. Hilar or mediastinal adenopathy requires prompt assessment of neoplastic or granulomatous causes. Even in the absence of mediastinal or hilar adenopathy, prompt biopsy of significantly enlarged, unexplained lymph nodes should permit institution of appropriate therapy.

### Biopsy

Biopsy of significant adenopathy should be performed early if no evidence of infection or other cause exists and particularly if mediastinal or hilar nodes are enlarged. The biopsy should encompass the central mass of the enlarged nodes so that a misdiagnosis of reactive inflammation in adjacent nodes can be avoided. This circumstance is particularly common in Hodgkin disease, in which an adjacent smaller lymph node may be more accessible and technically easier to biopsy but may not demonstrate the presence of Reed-Sternberg cells. Fine-needle aspiration is not recommended for biopsy of superficial, accessible nodes, although it might be useful for intrathoracic nodes to avoid thoracotomy. Appropriate expertise is required for interpretation, and negative findings are not definitive. For subacute, submandibular, or submental lymphadenopathy in which atypical mycobacteria are suspected, complete excisional biopsy provides both diagnosis and therapy.

Mediastinal adenopathy may be associated with airway or vascular obstruction (superior vena cava syndrome), presenting a critical risk if anesthesia or sedation is administered and a major dilemma in establishing a diagnosis.

Any biopsy should be performed at a medical center that specializes in the care of children so that all appropriate touch preparations, cultures, special cytochemical

or immunologic stains, flow cytometry, and biochemical, cytogenetic, and DNA studies are obtained. The pathology of Hodgkin disease, lymphoma, and other similar round-cell tumors may be difficult to establish and requires the assessment of a pediatric pathologist who has experience in these diseases. Immunophenotyping, cytogenetic analysis, molecular studies of gene rearrangement, and electron microscopy may be required for precise diagnosis. These studies, in conjunction with the histopathologic assessment, are central to the assessment and subsequent management, which may involve complex treatment with surgery, radiation, chemotherapy, or immunotherapy.

## TREATMENT

### Infectious Diseases (Details of Treatment—See Specific Organism)

Therapy of lymphadenitis depends on determining its cause or the most likely cause. Acute adenitis, particularly of the cervical area in young children, is frequently associated with infection from group A  $\beta$ -hemolytic streptococci or *Staphylococcus aureus*. The latter is particularly likely in adenitis that progresses to fluctuance. In the neonate and rarely in older children, group B streptococci may cause localized adenitis with or without cellulitis. In children beyond the neonatal period who have acute localized adenitis, particularly cervical adenitis, therapy should be initiated with an antibiotic directed at group A streptococci and penicillinase-producing strains of *S aureus* (eg, amoxicillin-clavulanic acid or cephalexin). Recently, infections with community-acquired methicillin-resistant *S aureus* in some areas have increased dramatically in children with skin and localized infections. In such circumstances, treatment should include an antibiotic to cover methicillin-resistant *S aureus* (eg, clindamycin or trimethoprim-sulfamethoxazole). For most patients, oral therapy is adequate.

The usual course of therapy is 10 to 14 days, but therapy should be continued for at least 5 days after the signs of acute inflammation have subsided. For patients who have suppurative adenitis from these organisms, drainage is not only diagnostic (by culturing the exudate obtained), but also therapeutic. A few patients may not respond to oral therapy, even with a drug to which the organism is sensitive. Parenteral antibiotic therapy then is required.

If an anaerobic infection is thought to be present, then therapy depends, in part, on the location of the adenitis, the type of organism, and the severity of the illness. Most anaerobic infections of the cervical and submental areas are serious infections associated with mouth flora, requiring inpatient therapy with clindamycin or metronidazole, possibly in combination with third-generation cephalosporins.

Both *M tuberculosis* and atypical mycobacteria can cause adenitis, with the latter being more frequent in children. Differentiating these may be difficult but is important because many strains of atypical mycobacteria are resistant to the usual antitubercular chemotherapy, and excisional biopsy may be required. If tubercular infection is thought to be present, then appropriate therapy for *M tuberculosis* should be initiated while awaiting

identification and sensitivities of the organism. Adenitis that is thought to be tubercular should not be incised or drained.

Cat-scratch adenitis is usually self-limited and generally requires no specific therapy. The discovery of *Bartonella* species, especially *B. henselae*, as the prime cause of cat-scratch disease has raised the possibility for specific antibiotic therapy, and some antibiotics alone or combined, including azithromycin, rifampin, and doxycycline, may be of clinical benefit. If nodes become markedly enlarged, tender, and fluctuant, then aspiration may help relieve symptoms; incision and drainage, however, should be avoided.

For the unusual case of severe primary herpes simplex virus infection with localized adenitis, treatment with oral acyclovir has shortened the clinical course.

### Neoplastic Disease

The treatment of neoplastic diseases today is, in most instances, oriented toward cure, with the effectiveness of therapy for lymphocytic and myelocytic leukemia, lymphomas, and Wilms and other tumors having improved markedly. The specific treatment of childhood cancer often involves combinations of chemotherapy, radiation therapy, and surgery, all of which depend on the individual diagnosis and are beyond the scope of this presentation. However, prompt, accurate diagnosis is essential for instituting specific treatment and optimal care of these patients.

#### WHEN TO REFER

- History and physical examination do not suggest an infectious cause.
- Potentially infectious nodes have not responded to a course of antibiotics.
- Supraclavicular, mediastinal, or hilar adenopathy is present.
- A biopsy is considered; biopsies should be performed only at a center specializing in the care of children.

#### WHEN TO ADMIT

- Biopsy requires hospitalization—for example, supraclavicular, mediastinal, or hilar biopsy.
- Biopsy results require inpatient treatment or further evaluation.
- An infection requires intravenous therapy.

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## Chapter 176 MACROCEPHALY

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### DEFINITION

Macrocephaly is defined as a head circumference of more than 2 standard deviations above the mean (about the 97th percentile) based on age and gender. Head circumference values should be plotted in appropriate head circumference charts (see Chapter 178, Microcephaly), such as the Centers for Disease Control and Prevention (CDC) growth charts (for children 0–3 years). For children older than 3 years, the Nellhaus charts had been used previously, although new age- and sex-appropriate US charts were published in 2010.

### DIFFERENTIAL DIAGNOSES

Head size is influenced by the different components that make up the cranial cavity. Among the causes of a large head in children are hydrocephalus, an enlarged brain (*megalecephaly*), a thickened skull, and space-occupying lesions. These conditions are not mutually exclusive, and some children may have more than 1 underlying factor (Box 176-1).

#### Hydrocephalus

Hydrocephalus, an enlargement of the ventricular system, may be congenital or acquired. The clinical presentation is influenced by the age of onset and the underlying condition causing the hydrocephalus. An enlarging head circumference is the most obvious finding in an infant whose cranial sutures have not fused. In the older child whose sutures have fused, significant head enlargement does not occur, but other signs and symptoms of increased intracranial pressure, such as headaches, vomiting, and papilledema, may occur.

Conventionally, hydrocephalus has been classified as either communicating or noncommunicating, depending on whether the connection between the ventricular system and the subarachnoid space is intact. Communicating hydrocephalus results from either the impaired absorption of cerebrospinal fluid by the arachnoid villi (from meningeal irritation caused by meningitis, trauma, or malignant infiltration) or less commonly with overproduction of cerebrospinal fluid from a choroid plexus papilloma. Noncommunicating or obstructive hydrocephalus is marked by enlargement of the ventricular system proximal to the site of an obstruction. The obstruction may be an anatomic defect, such as aqueductal stenosis, or the result of a tumor, infection, or infiltrate. In many cases, however, the classification of hydrocephalus as either communicating or noncommunicating may not be clear-cut; common causes of hydrocephalus, such as intraventricular hemorrhage and intrauterine infections, may lead to both communicating and noncommunicating hydrocephalus.

**BOX 176-1 Causes of Macrocephaly****HYDROCEPHALUS**

- Intraventricular hemorrhage
- Meningomyelocele
- Dandy Walker malformation
- Aqueductal stenosis
- Malignancy
- Intrauterine infections
- Meningitis
- Space-occupying lesions
- Benign accumulation of extracranial fluid

**MEGALENCEPHALY*****Megalencephaly—metabolic***

- Mucopolysaccharidoses
- Leukodystrophies
  - Canavan disease
  - Alexander disease
- Glutaric aciduria

***Megalencephaly—anatomic***

- Overgrowth syndromes
- Neurocutaneous syndromes
- Achondroplasia
- Autism
- Fragile X syndrome
- Various other genetic syndromes

***Megalencephaly—idiopathic (benign)*****SKULL THICKENING AND SKULL ABNORMALITIES**

- Thalassemia
- Cleidocranial dysostosis and other skeletal disorders

**SPACE-OCCUPYING LESIONS**

- Vascular malformations
- Intracranial tumors
- Subdural effusion
- Subdural hematoma

Intraventricular hemorrhage occurs in about 15% of premature infants with birth weight less than 1,500 g. The severity of hemorrhage is graded as follows:

- Grade I: subependymal hemorrhage
- Grade II: intraventricular hemorrhage without ventricular dilation
- Grade III: intraventricular hemorrhage with ventricular dilation
- Grade IV: intraventricular and intraparenchymal hemorrhage

Although subtle changes in head circumference may be present, macrocephaly is not always evident in an infant with intraventricular hemorrhage. Grade III and IV hemorrhages are associated with poorer neurodevelopmental outcomes than grades I and II, with an estimated 35% and 90% of affected children, respectively, showing neurologic sequelae.

Hydrocephalus with Chiari type II defect is present in 80% of children with myelomeningocele. Macrocephaly is commonly the first manifestation of the Dandy Walker malformation, a cystic dilation of the fourth ventricle, with hypoplasia of the cerebellar vermis and a variety of other cranial malformations. Head size may be normal at birth, but acceleration in head growth is noted in most children by 1 year of age, sometimes with prominence of the posterior part of the skull.

Congenital aqueductal stenosis, which may occur sporadically or be transmitted by X-linked inheritance, causes severe hydrocephalus that may complicate labor and delivery with cephalopelvic disproportion and lead to signs and symptoms of increased intracranial pressure after birth.

A condition characterized by a benign accumulation of extracranial fluid, probably subarachnoid, is identified in many children with macrocephaly who have an unremarkable neurologic examination. The exact nature of the extracranial collection has not been clearly established, leading to problems with nomenclature; the condition is variously referred to, whether accurately or inaccurately, as benign macrocephaly, external hydrocephalus, benign extracerebral fluid collections, benign subdural collections, and benign enlargement of the subarachnoid space. Neuroimaging reveals an extracerebral fluid collection most evident in the prefrontal area and, in some cases, mild nonprogressive dilation of the ventricular system. The size of the brain is normal. Affected children may have normal or large head circumferences at birth. In the succeeding months, the head circumference grows to greater than the 98th percentile and then generally parallels the normal growth curves. The large head size is an isolated feature, and the affected child has an otherwise normal neurologic examination and age-appropriate development, although transient early developmental delays, especially in the first year of life, may be observed. The condition seems to be self-limited, with normalization of computed tomography scan findings usually by 2½ years of age. The relationship of this condition to benign megalencephaly, wherein the brain is large but no extracranial fluid accumulation is present in a child who is also neurologically intact, has not been established and is not fully understood. More recently, an association with subdural hematoma in infancy has been suggested.

**Megalencephaly**

Another common cause of macrocephaly is an enlargement of the brain. Traditionally, megalencephaly is classified as metabolic or anatomic. In metabolic megalencephaly, enlargement of the brain is caused by an inborn error of metabolism that leads to the abnormal deposition of some substrate in the brain. The head circumference is usually normal at birth and then enlarges and may cross percentiles over time. It coincides with significant developmental delays and psychomotor regression. Most of these inborn errors are autosomal recessive disorders. The mucopolysaccharidoses, leukodystrophies such as Canavan disease and Alexander disease, are examples of metabolic conditions causing macrocephaly.



In Hurler syndrome, the most severe form of mucopolysaccharidosis resulting from a deficiency of  $\alpha$ -L-iduronidase, an enlarging head may be noted to cross percentiles during infancy. Coarse facial features, frontal bossing, and corneal clouding are characteristic findings of the syndrome. In the infantile form of Canavan disease, a leukodystrophy that predominantly affects Ashkenazi Jews from a deficiency of aspartoacylase, macrocephaly is associated with irritability, poor visual fixation, head lag, and motor delay, which are noted in the first few months of life. Alexander disease is a rare, mostly sporadic condition characterized by abundant accumulation of glial fibrillary acidic protein in Rosenthal fibers. Affected infants exhibit macrocephaly, seizures, spasticity, and developmental regression.

In anatomic megalencephaly, the large head size is usually present at birth and is often associated with neurodevelopmental impairment. The brain is abnormally large because of an increase in the size and number of its cells. The Online Mendelian Inheritance in Man (OMIM) provides a comprehensive list of syndromes associated with macrocephaly and megalencephaly. In overgrowth syndromes, macrocephaly is usually present at birth as part of a generalized increase in body size. An example is Sotos syndrome, which is associated with facial dysmorphism, neurodevelopmental deficits such as poor coordination and cognitive and behavioral problems, and macrocephaly that may result from a combination of megalencephaly, ventricular enlargement, and midline anomalies. It has been reported that about 90% of clinical cases of Sotos syndrome have mutations or deletions involving the *NSD1* gene in chromosome 5q35. Neurocutaneous syndromes such as neurofibromatosis, tuberous sclerosis, and hypomelanosis of Ito are associated with megalencephaly in addition to characteristic skin findings, intracranial conditions, and neurodevelopmental problems. In achondroplasia, megalencephaly is present in a child with short stature, shortened proximal arms and legs (rhizomelia), and dysmorphic facial features. Affected individuals usually have normal intelligence but are at risk for hydrocephalus, obstructive sleep apnea or central apnea, and spine and joint problems. Compared with the general population, a disproportionately large number of autistic children have enlarged head circumferences. The pattern of brain growth in some autistic children seems to be abnormal, with acceleration of head growth in early childhood, hyperplasia in cerebral gray matter and cerebral and cerebellar white matter, and a slight decrease in brain volume during adolescence. Whether this acceleration in head growth in early childhood relates to the behavioral and developmental features of autism remains unclear. Mutations in the phosphatase and tensin homolog (*PTEN*) gene, which have been associated with a spectrum of disorders with a predisposition to hamartomas and certain cancers such as Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, and Proteus syndrome, have been identified in some autistic children with severe macrocephaly. Fragile X syndrome is associated with a constellation of physical findings, including macrocephaly, a longish face with

prominent ears, joint hyperextensibility, and enlarged testes. A family history on the mother's side of intellectual disability, developmental and behavioral problems, and autistic behaviors suggests the possibility of this X-linked disorder.

A child with a large head who has no significant collection of extraventricular or intraventricular fluid, a normal neurologic examination and developmental history, no signs of raised intracranial pressure, and a family history of large head sizes in normal adults can be considered to have benign or idiopathic megalencephaly. Although these individuals have been thought to develop normally, recent evidence suggests they may exhibit mild neurodevelopmental dysfunction such as incoordination and visual-motor weaknesses.

### Other Causes of Macrocephaly

Thickening of the skull is a rare cause of macrocephaly. Children with a hemolytic anemia, such as  $\beta$ -thalassemia, may exhibit frontal bossing attributable to extracranial hematopoiesis in their skull bones. Cleidocranial dysostosis is an autosomal disorder of abnormal bone formation characterized by delayed closure of fontanelles, widening of the head circumference, and other skeletal abnormalities. Space-occupying lesions, such as an arteriovenous malformation or a brain tumor, may also produce macrocephaly. Although usually asymptomatic, subdural effusion is a complication of bacterial meningitis that may produce an enlarging head circumference, bulging anterior fontanelle, and signs of increased intracranial pressure in infants. Subdural hematoma may present with macrocephaly in infants but is usually associated with other symptoms as well.

## EVALUATION

### Relevant History

A review of previously measured head circumferences can ascertain whether a child has had any change in the pattern or percentiles of head circumference over time. A large head circumference at birth presupposes a cause of prenatal origin, necessitates a detailed prenatal history, and may indicate anatomic megalencephaly. Conditions that may cause congenital macrocephaly include X-linked aqueductal stenosis and the overgrowth syndromes. An abnormally enlarging head postnatally in a child with neurodevelopmental problems is a clue to an acquired condition, such as acquired hydrocephalus or a possible metabolic disorder. The history should explore delays in the developmental milestones; regression in motor, language, and social skills; seizures; and signs of increased intracranial pressure such as lethargy, vomiting, and behavioral changes. A family history of any genetic, neurologic, and developmental condition may be a red flag for similar disorders, whereas a history of otherwise normal parents and siblings with large heads can be reassuring.

### Physical Examination

The physical examination of the child with macrocephaly should focus on the specific issues listed in Box 176-2.



### BOX 176-2 Physical Examination of a Child with Macrocephaly

- Accurate measurement of the head circumference and assessment of the pattern of head growth
- Inspection and palpation of the skull
- Comparison of the head circumference with other growth parameters
- Presence or absence of dysmorphic features
- Presence or absence of congenital abnormalities involving other organ systems
- Thorough neurologic and developmental assessment, including a check for signs of increased intracranial pressure
- Skin examination using Wood lamp

Monitoring of head size must be performed periodically during health care maintenance visits. In the presence of a rapid enlargement in head circumference, more frequent monitoring, at the very least, is necessary. Measurements should be plotted on the appropriate head circumference charts. A disproportionately enlarged head in relation to height and weight may indicate a primary neurologic disorder. Measuring the size of the fontanelles and palpating sutures are important. Significant hydrocephalus in infants may produce a bulging anterior fontanelle and separation of cranial sutures, which are uncommon in anatomic megalencephaly. A vein of Galen arteriovenous malformation may produce a cranial bruit on auscultation. Because macrocephaly is a feature of many genetic syndromes, dysmorphic features and other organ involvement should be noted. Examination of the skin may reveal café au lait spots, axillary freckling, ash-leaf spots, and a whorled pattern of pigmentation that may indicate a neurocutaneous disorder. Careful neurologic examination is critical and may reveal abnormalities in muscle tone and posture, asymmetries, persistence of primitive reflexes, and hyperreflexia. Developmental assessment may reveal cognitive impairment, autistic features, learning disabilities, or behavioral difficulties. It is also important to measure the head circumference of the parents and make note of any dysmorphic features they may have.

#### Laboratory Testing

Metabolic testing is available to identify many of the storage diseases and is recommended in a child exhibiting developmental regression. Genetic testing should be done as appropriate for the clinical assessment.

#### Imaging

Neuroimaging is the procedure of choice in evaluating macrocephaly. For infants with open fontanelles, head ultrasound is useful in identifying intraventricular hemorrhage, hydrocephalus, and intracranial tumors. This procedure is especially useful in

infants because it eliminates the need for sedation. Computed tomography can identify hydrocephalus, intracranial calcifications, and hemorrhages. Magnetic resonance imaging (MRI) is most informative, especially in identifying gray and white matter disease (eg, leukodystrophy), migration defects, hydrocephalus, and posterior fossa lesions. MRI is also helpful in studying the subtleties in subdural and subarachnoid hemorrhages. Consultation with a neurologist or radiologist may be helpful in deciding which procedure would be most appropriate. MRI is generally not indicated in patients with autism and macrocephaly unless there are other concerns not explained by autism (eg, focal neurologic findings, cranial nerve dysfunction, severe headache). A skeletal survey may reveal bone age abnormalities in the overgrowth syndromes and radiologic abnormalities that may be present in the mucopolysaccharidoses, bone dysplasias, or trauma.

#### Management

The management of macrocephaly depends on its cause. Shunting procedures are the treatment of choice for significant and progressive hydrocephalus; however, shunt infection, obstruction, and malfunction are not rare and continue to be challenges in the care of these children. In premature infants, the risk for complications is even greater; medical management with pharmacologic agents (carbonic anhydrase inhibitors or other diuretics) and serial lumbar punctures may be used as initial therapy. Medical management is also used in asymptomatic or minimally symptomatic patients with slowly progressive hydrocephalus. For Dandy Walker cysts, shunting has been recommended to drain the hydrocephalus or the posterior fossa cyst, or both. Children in whom inborn errors of metabolism are suspected should be referred for genetic evaluation, treatment, and counseling. Although the treatment for these conditions is mainly supportive and symptomatic, bone marrow transplantation and enzyme replacement therapy are promising interventions for certain disorders. Although no specific treatment is available for anatomic megalencephaly, pediatricians should be aware of the association with developmental and cognitive problems, which warrant early intervention and special education services. The presence of subdural hematoma requires further evaluation (eg, skeletal survey, retinal examination) and may include referral to a child abuse expert. Serial measurement of the head circumference and clinical assessments are generally all that are needed for benign accumulation of extracranial fluid and idiopathic megalencephaly.

#### WHEN TO REFER

- Head circumference of more than 2 standard deviations above the mean (especially 3 standard deviations above the mean)
- Head circumference that is crossing percentiles or rapidly growing
- Dysmorphic features
- Abnormal neurologic examination

- Regression in developmental skills or significant developmental delay
- Suspected child abuse

### WHEN TO ADMIT

- Signs of increased intracranial pressure or mental status change
- Shunt infection or malfunction

### TOOLS FOR PRACTICE

#### Medical Decision Support

- *Growth Charts (charts)*, Centers for Disease Control and Prevention ([www.cdc.gov/growthcharts](http://www.cdc.gov/growthcharts))
- *CDC Growth Charts: United States* (article), National Center for Health Statistics ([www.cdc.gov/nchs/data/ad/ad314.pdf](http://www.cdc.gov/nchs/data/ad/ad314.pdf))
- *Online Mendelian Inheritance in Man* (online database), Johns Hopkins University ([omim.org](http://omim.org))
- *United States head circumference growth reference charts: birth to 21 years* (article), *The Journal of Pediatrics*, Vol 156, Issue 6, 2010 ([www.jpeds.com/article/S0022-3476%2810%2900020-X/abstract](http://www.jpeds.com/article/S0022-3476%2810%2900020-X/abstract))

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## Chapter 177

# MEDICALLY UNEXPLAINED SYMPTOMS

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### BACKGROUND

Medically unexplained symptoms (MUS) can present significant challenges and frustrations to the children affected by them, their families, and the physicians involved in their care. While medically unexplained physical symptoms are often associated with mental health issues, children with MUS often present in primary care and general medical settings rather than the mental health setting. Patients with MUS often present for multiple office visits and are at risk for potentially dangerous and unnecessary evaluations, laboratory tests, and procedures. Patients and families may be frustrated and confused by the physician's

judgment that "nothing is wrong" despite continued pain and impairment. MUS are thus an important entity for physicians to recognize to help facilitate accurate assessment and intervention.

Historically, physicians have been trained in the biomedical model that explains the presence of physical symptoms with a diagnosis based on the presence of pathology consistent with a specific disease. In this model, unexplained symptoms may not be presumed to be real, or may be considered representative of a mental disorder. This dichotomous approach, termed *dualism*, distinguishes between physical and mental disorders by virtue of whether there is evidence of a biomedical explanation. It is increasingly being recognized that such dualistic thinking is inadequate to address the entity of MUS. Using this model, physicians may complicate care, or even put patients at risk, in an attempt to avoid "missing" explanatory physical disease. Families and patients may feel stigmatized, misunderstood, and lacking in an explanation for their symptoms.

Our current understanding of pain suggests that it is an unpleasant sensory and emotional experience representative of physiologic changes and tissue damage. This suggests that pain is a derivative of demonstrable tissue pathology, yet pain can also be experienced subjectively in the absence of demonstrable pathology. Similarly, the level of pain experienced in association with a given degree of tissue damage may also vary. Rather than focusing on false dichotomies between physical and psychological health, it is preferable to recognize the connection between psychology and physiology. The term *somatization* is used to reflect the experience of the individual, including his subjective experience, distress, and desire to seek medical care, in the setting of MUS.

### EPIDEMIOLOGY

Medically unexplained symptoms are often encountered across childhood and adolescence, with pain and fatigue being especially common in all age groups. It is also important to remember that the presence of 1 type of MUS typically predicts the presence of other MUS. In preschool children, abdominal pain is a common manifestation. Among children and adolescents, headache and abdominal pain are the most prevalent symptoms, though other types of pain, such as limb and chest pain, are often reported. Fatigue is a particularly common complaint in teens. Other symptoms include urinary, cardiovascular, rheumatologic, and gastrointestinal complaints. MUS suggesting neurologic or sensory impairment, often referred to as "conversion" symptoms, are relatively unusual in community settings yet more common in specialty settings. A study of teens in the Ontario Child Health Study suggested a prevalence of recurrent somatic symptoms in the primary care setting of 4% for boys and 11% for girls. Other studies report that between 2% and 20% of children in primary care present with MUS. Boys and girls may have different clinical presentations, with some studies suggesting that girls report more somatic symptoms than boys and more frequently report symptoms of headache or abdominal pain than boys, particularly with increasing age into adolescence. All types of MUS

can be associated with significant impairment for patients and their families. This includes missed school days, increased health care utilization, distress, patient suffering, limitation of activities, impaired peer interactions, and significant effect on family functioning.

The precise etiology of MUS is unknown. Certain associations and risk factors have been identified (Box 177-1). In general, children with emotional and behavioral problems are more likely to experience MUS than otherwise healthy children. In a primary care sample, children identified as somatizers had a higher frequency of emotional/behavioral problems, including internalizing symptoms such as worrying, fear of new situations, and problems with separation. Children with diagnosed mental health disorders such as anxiety, depression, and disruptive behavior disorders have also been found to exhibit more somatic symptoms, including headache, abdominal pain, and musculoskeletal pain.

## CLASSIFICATION

Definitions for conditions characterized by chronic pain and physical suffering are detailed in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*, under the category of Somatic Symptom and Related Disorders. This category replaces that of Somatoform Disorders in *DSM-IV*. These disorders are characterized by pain or other somatic symptoms in association with impairment in functioning and significant individual distress. Somatic Symptom Disorder (SSD) is the diagnosis applied in the presence of distressing or impairing somatic symptoms along with excessive, maladaptive, or disproportionate thoughts or feelings about the physical symptoms. See Table 177-1 for additional disorders in this category, including Illness Anxiety Disorder, which replaces hypochondriasis, Conversion Disorder, and Psychological Factors Affecting Medical Condition.

### BOX 177-1 Risk Factors for the Development of Medically Unexplained Symptoms

- Genetics
- Modeling
- Physical illness
- School stressors
- Family stressors
- High-achieving families
- Parental overprotection
- Secondary gain<sup>a</sup>
- Impaired or limited coping mechanisms
- Difficulty identifying/expressing feelings
- Difficulty with transitions
- Psychiatric comorbidity
- Trauma

<sup>a</sup>Secondary gain refers to the social and familial reinforcement of the symptom.

Derived from Ibeziako P, Bujoreanu S. Approach to psychosomatic illness in adolescents. *Curr Opin Pediatr*. 2011;23:384–389.

Factitious Disorder, defined by the intentional falsification of symptoms with the apparent goal of achieving behavioral and social benefits associated with the sick role, is now included in this category as well. Historically, these disorders were considered when a medical explanation could not be found, although, in many cases, it can be difficult and counterproductive to fully exclude an exhaustive list of potential medical conditions. In *DSM-5*, the key component of these disorders is the presence of somatic symptoms and the way they are interpreted by the patient, rather than solely by the lack of medical explanation. Children with these disorders experience significant impairment across 1 or several domains, including relationships with peers or parents, school functioning, and participation in extracurricular activities. Table 177-1 describes the categories of somatic symptom and related disorders according to *DSM-5*, with the same criteria applied to both adults and children.

When considering the presence of a somatic disorder, it is important to assess for physical disorders that may be causing or contributing to the child's symptoms. However, the physician is cautioned to avoid unnecessary testing once it can be reasonably assumed that a medical disorder has been excluded, which can present a challenge for physicians. It is recommended that somatic disorders be included in the differential diagnosis rather than relegated to a diagnosis of exclusion. Other conditions to include in the differential diagnosis of MUS include Psychological Factors Affecting Other Medical Conditions, which describes the presence of psychological factors and symptoms associated with an underlying medical condition. Conditions such as anxiety and depression may also result in pain and fatigue and thus should be considered the primary diagnosis in those circumstances.

## ASSESSMENT

An empathetic and collaborative approach is recommended when considering MUS. Children affected by MUS and their families may be frustrated by frequent office visits, multiple laboratory tests, and being told that “nothing is wrong” despite patient suffering. While the approach to each child should be individualized, general principles can help guide successful assessment. Important aspects to consider during the assessment process are presented in Box 177-2. MUS should be approached just as any other symptom in the pediatric history, with a review of symptom characteristics including duration, frequency, intensity, and moderating factors. Special attention should be paid to environmental stressors, opportunities for secondary gain, and emotional factors such as anxiety, depression, or other psychological symptoms.

In addition to a careful history, standardized tools can be helpful in the assessment process. The Children's Somatization Inventory (CSI) can be used to assess for the presence of multiple somatic symptoms. It has been revised to a 24-item questionnaire that includes parent and child (age  $\geq 7$ ) versions and is available in the public domain. The Functional Disability Inventory is a 15-item questionnaire with parent and child (age  $\geq 8$ ) versions that can be used to assess health status across multiple domains.

**Table 177-1** Classification of Somatic Symptom and Related Disorders

DISORDER	DESCRIPTION
Somatic Symptom Disorder	<ul style="list-style-type: none"> <li>• Presence of <math>\geq 1</math> somatic symptoms that are distressing or result in significant disruption of daily life.</li> <li>• Excessive thoughts, feelings, or behaviors related to the somatic symptoms.</li> </ul>
Illness Anxiety Disorder	<ul style="list-style-type: none"> <li>• Symptoms must be persistent (usually <math>&gt;6</math> months).</li> <li>• Preoccupation with having a serious illness (<math>\geq 6</math> months).</li> <li>• If a medical condition or strong family history is present, worry is out of proportion to the likelihood of severe illness; somatic symptoms, if present, are mild.</li> <li>• High degree of anxiety about one's health.</li> <li>• Excessive engagement in health-related behavior or avoidance of necessary health care.</li> </ul>
Conversion Disorder	<ul style="list-style-type: none"> <li>• Presence of <math>\geq 1</math> symptoms of altered voluntary motor or sensory function that result in significant distress or impairment.</li> <li>• Evaluation suggests that symptoms are incompatible with recognized medical conditions.</li> </ul>
Psychological Factors Affecting Other Medical Conditions	<ul style="list-style-type: none"> <li>• Presence of psychological or behavioral factors that result in delayed recovery or added health risk, interfere with treatment, or escalate the need for medical treatment.</li> </ul>
Factitious Disorder (Imposed on Self or Imposed on Another)	<ul style="list-style-type: none"> <li>• An underlying medical condition must be present.</li> <li>• Intentional falsification of physical or psychological signs or symptoms or infliction of injury.</li> <li>• Deceptive behavior is present.</li> </ul>
Other Specified Somatic Symptom and Related Disorder	<ul style="list-style-type: none"> <li>• Presence of somatic symptoms that cause significant distress or impairment but do not meet full criteria for another category of somatic symptom and related disorders.</li> <li>• May be used when symptoms are brief (eg, 6 months) or just below the diagnostic criteria.</li> </ul>
Unspecified Somatic Symptom and Related Disorder	<ul style="list-style-type: none"> <li>• Presence of somatic symptoms that cause significant distress or impairment but do not meet full criteria for another category of somatic symptom and related disorders.</li> <li>• Used only in unusual situations when there is insufficient information to make a more specific diagnosis.</li> </ul>

Derived from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association; 2013.

### **BOX 177-2** Important Principles in the Assessment of Children With Medically Unexplained Symptoms

- Acknowledge symptoms, patient experience, and family concerns.
- Review past evaluations and treatment.
- Investigate fears related to symptoms.
- Remain alert to unrecognized medical diagnosis.
- Avoid unnecessary tests.
- Avoid diagnosis by exclusion.
- Understand symptom timing, context, and characteristics.

Adapted from Campo JV, Fritz G. A management model for pediatric somatization. *Psychosomatics*. 2001;42:467–476.

## **MANAGEMENT**

Collaborative care in the management of MUS requires communicating diagnostic impressions to the family in a clear and honest manner. Families may benefit from a discussion of the interplay between physiologic and emotional factors, with reassurance that the absence of diagnosable medical disease does not minimize the child's suffering or negate the reality of the problem. Physicians should be mindful of the stigma associated with mental health conditions and avoid the mind-body dualism that may characterize MUS as being "all in your head." The use of placebo and other forms of deception in attempts to achieve diagnosis or reduce symptoms is discouraged.

Once diagnostic impressions are communicated and questions are discussed, the physician must then attempt to shift the family's focus from the cause of symptoms to improving the child's functioning and reducing suffering. The physician should facilitate the



**Table 177-2** Interventions for Children With Somatic Disorders

INTERVENTION	CHARACTERISTICS
Cognitive behavioral therapy	May involve a combination of <ul style="list-style-type: none"> <li>• Cognitive restructuring (eg, “I realize I have some pain today, but I can still go for a walk with my friends.”)</li> <li>• Relaxation</li> <li>• Graded exposure to unpleasant experiences<sup>a</sup></li> </ul>
Rehabilitative approach	Focus on coping and improving health status
Behavioral intervention	Approaches include <ul style="list-style-type: none"> <li>• Reinforcement of healthy behaviors</li> <li>• Minimization of secondary gain</li> </ul>
Self-management	Possible techniques include mindfulness, hypnosis, imagery, and relaxation.
Family intervention	Involves work with the family system that may inadvertently reinforce the sick role
Maximal treatment of psychiatric comorbidities	Important to consider given the high prevalence of mental health conditions in children with medically unexplained symptoms
Medication management	Should be considered for <ul style="list-style-type: none"> <li>• The treatment of underlying mental health conditions</li> <li>• Somatic symptoms that accompany mental health conditions</li> </ul>

<sup>a</sup>Masia Warner C, Reigada LC, Fisher PH, et al. CBT for anxiety and associated somatic complaints in pediatric medical settings: an open pilot study. *J Clin Psychol Med Settings*. 2009;16(2):169–177.

Derived from Dell ML, Campo JV. Somatoform disorders in children and adolescents. *Psychiatr Clin North Am*. 2011;34:643–660.

development of a treatment plan that addresses physical pain, stress reduction, and reduction of stigma while fostering hope that the child will improve. Goals should be developed collaboratively and should be meaningful to the child and family. In many cases, treatment will involve an interprofessional approach involving medical, mental health, and allied health disciplines. Clear communication across disciplines is essential.

A number of interventions have been proposed for the treatment of somatic disorders, and thus MUS (Table 177-2). Treatments may be delivered independently or in combination, although medication is rarely successful if used without supportive therapies.

A substantial portion of the child’s treatment may occur outside the realm of primary care. In these circumstances, an important role for the pediatrician is one of care coordination, hope, and support. Pediatricians may be especially helpful in recognizing MUS as a possibility and making timely referrals to mental health professionals as indicated. In situations where symptoms are less intense or impairing, primary care management may be appropriate. In either case, pediatricians can play a key role in supporting families through the assessment and treatment process, which includes conveying an understanding that their concerns will be taken seriously and addressing parental anxiety, if present. Physicians in underserved areas may find themselves providing more direct care given challenges related to mental health and specialty care access. The psychiatric literature contains excellent resources for pediatricians who are interested in the assessment and initial management of MUS. In addition, a number of states are implementing psychiatric consultation resources for physicians that can provide guidance, education,

and, in some cases, facilitated referrals provided by Child and Adolescent Psychiatry. More information about these programs can be accessed through the National Network of Child Psychiatry Access Programs. Pediatricians should also be aware of their own frustration, as somatic disorders may present significant challenges in the primary care setting. Seeking advice and support from colleagues and specialists can be helpful in alleviating this frustration.

## PROGNOSIS

In general, the prognosis for children presenting with MUS is favorable, but proper symptom recognition and intervention are essential. An association has been documented between MUS in children and subsequent anxiety or depression in adulthood, as well as between anxiety and depression in childhood and subsequent impairing somatic symptoms in adulthood. Further studies will be needed to determine if identification and intervention in childhood can mitigate the development of lifelong symptoms. Meanwhile, it is clear that pediatricians play a key role in the initial management of the child with MUS, as well as in family support and care coordination. This type of approach can reduce child and family frustration, lead to improved outcomes, and be a rewarding experience for the physician who is able to help guide families through this complex process.

## TOOLS FOR PRACTICE

### Medical Decision Support

- *Pediatric Symptom Checklist* (screen), Massachusetts General Hospital ([www.massgeneral.org/psychiatry/services/psc\\_forms.aspx](http://www.massgeneral.org/psychiatry/services/psc_forms.aspx))

- *Strengths & Difficulties Questionnaires* (screen), Youth in Mind, Ltd ([www.sdqinfo.com](http://www.sdqinfo.com))
- *Functional Disability Inventory* (screen), [www.commondataelements.ninds.nih.gov/Doc/NOC/Functional\\_Disability\\_Inventory\\_Parent\\_Form\\_NOC\\_Request.pdf](http://www.commondataelements.ninds.nih.gov/Doc/NOC/Functional_Disability_Inventory_Parent_Form_NOC_Request.pdf)

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## Chapter 178 MICROCEPHALY

Oscar H. Purugganan, MD, MPH

### DEFINITION OF TERMS

Microcephaly refers to a head size that is 2 standard deviations below the mean (about the third percentile) based on age and gender. In itself, microcephaly means a small head; *micrencephaly* is the accurate term for a small brain. Because the forces of brain growth generally determine ultimate cranium size, a small brain leads to a small head. Without further brain growth, secondary closure of the sutures of the skull will ensue before the expected time, which should be differentiated from *craniosynostosis* in which primary and premature closure of sutures occurs with a normally growing brain.

### MEASUREMENT AND USE OF GROWTH CHARTS

Measuring the head circumference is an important element of the pediatric physical examination and should be performed at each well-child visit, especially in the first 3 years of life. Accurate measurements are critical and should be plotted on standardized charts. In the United States, the Centers for Disease Control and Prevention (CDC) released the latest growth charts in 2000. These charts, which include head circumference charts, were based on 5 national health surveys from 1963 to 1994 and have been updated from the 1977 growth charts. A new feature of these updated charts is the inclusion of curves for 3rd and 97th percentiles, which are important cutoffs in the measurements of head circumference. The World Health Organization (WHO) released new international growth charts for children up to 5 years of age in 2006. These charts represent growth standards derived from healthy children growing under optimal conditions from 6 sites worldwide. Their applicability in various clinical settings (including the US) and their potential effect on clinical practice are currently being investigated. Head circumferences of children

older than 3 years have traditionally been plotted on the growth curves developed by Nellhaus; newer US-normed head circumference charts from birth to 21 years were published in 2010. Charts are available for special populations with disturbances in growth, such as Down syndrome, Williams syndrome, achondroplasia, and very low birth weight.

Head circumference is measured by using a flexible, nonstretchable tape, running along the head above the supraorbital ridges and across the most prominent part of the occiput. This measurement is known as the occipitofrontal circumference and has been shown to correlate with brain volume. More instructive than a single measurement is a series of measurements over time, which can identify head circumferences that may be crossing percentiles while still falling within the normal range. Brain growth is maximal during the last few weeks of gestation to the first 2 years of life. Boys average a slightly larger head size than girls; the average head size at birth for boys in the United States is about 36 centimeters, and for girls about 35 centimeters.

### DIFFERENTIAL DIAGNOSIS

Microcephaly is a physical finding and not a diagnosis. A multitude of conditions exist that can lead to a small brain. These conditions can be either genetic or environmental (see Box 178-1). They can be syndromic or nonsyndromic.

Clinically, a useful approach to the evaluation of microcephaly is to determine whether the small head circumference is noted at birth (congenital microcephaly) or whether the head circumference does not grow as expected after birth (acquired microcephaly).

Congenital microcephaly (noted at birth) can be either from genetic or environmental causes.

Genetic microcephaly is almost always present at birth; Rett syndrome (see below) is a notable exception. In these conditions, the brain structure may be either normal or abnormal.

In microcephaly vera, or true microcephaly, the brain is very small, usually 3 standard deviations below the mean, but the brain architecture is grossly normal. Patients almost always have intellectual disability (ID) but have an otherwise unremarkable neurologic examination. A sloping forehead and prominent ears are usually the only dysmorphic features. Transmission is mainly autosomal recessive, although autosomal-dominant and X-linked forms also exist. Three genes that cause microcephaly vera have been identified: microcephalin (*MCPH*), abnormal spindle in microcephaly (*ASPM*), and deoxynucleotide carrier (*DNC*) protein, which is implicated in Amish microcephaly.

More common than microcephaly vera is a microcephalic child who has severe neurologic impairment such as seizures, spasticity, and global developmental delays. Neuroimaging may identify abnormal brain architecture such as defective prosencephalization (eg, holoprosencephaly), migration disorders (eg, lissencephaly, schizencephaly, pachygyri, polymicrogyri, heterotopias), and midline defects (eg, agenesis of corpus callosum).

Microcephaly may be associated with other clinical findings that collectively represent a genetic syndrome. Miller-Dieker syndrome, which is caused by a

**BOX 178-1 Causes of Microcephaly****GENETIC CAUSES**

- Microcephaly vera (isolated microcephaly with grossly normal brain architecture)
- Microcephaly with abnormal brain architecture (eg, lissencephaly, polymicrogyria)
- Genetic syndromes
  - Miller-Dieker lissencephaly
  - Seckel syndrome
  - Rubinstein-Taybi syndrome
  - Trisomy 21 syndrome
  - Trisomy 13 syndrome
  - de Lange syndrome
  - Rett syndrome
- Metabolic disorders
  - Aminoacidopathies
  - Mitochondrial
- Asymptomatic familial

**ENVIRONMENTAL CAUSES**

- Teratogens
  - Alcohol
  - Maternal phenylketonuria
  - Intrauterine irradiation
  - Other teratogenic drugs (eg, hydantoin)
- Intrauterine infections
- Maternal health problems
- Hypoxic-ischemic encephalopathy
- Traumatic brain injury
- Meningitis
- Malnutrition

deletion on the short arm of chromosome 17, is characterized by a small, smooth brain or lissencephaly (the most extreme of migration defects), facial dysmorphism, and severe ID. In Seckel syndrome, a rare autosomal-recessive disorder that has been mapped to loci in chromosomes 3 and 18, central nervous system (CNS) anomalies that suggest an underlying neuronal migration disorder are present together with growth retardation, intellectual disability, and a *bird-headed* facial appearance. Children with Rubinstein-Taybi syndrome have microcephaly, significant developmental problems, facial abnormalities, and broad thumbs and toes. Microdeletions of the cyclic adenosine monophosphate response element-binding protein gene on chromosome 16 have been implicated in this disorder. Trisomies account for some cases of microcephaly. A classic example is Down syndrome (trisomy 21 syndrome) in which microcephaly is part of the characteristic phenotype that includes distinct facial features, congenital heart anomalies, and growth retardation. In de Lange syndrome, affected children have growth retardation, microcephaly, hirsutism, and unusual facial features such as synophrys and low anterior hairline. Most cases are sporadic, but an autosomal dominant inheritance has been suggested.

*Smith's Recognizable Patterns of Human Malformation* and the online reference Online Mendelian Inheritance in Man (OMIM) provide comprehensive lists of conditions that are associated with abnormalities in head size.

Based on the definition of microcephaly, it follows that about 2.5% of all children would be classified as microcephalic, and, most certainly, some of these children will be neurologically normal, especially those with head sizes immediately below 2 standard deviations from the mean (head circumference  $>3$  standard deviations below the mean is almost always associated with some degree of neurologic impairment). In individuals with isolated microcephaly who are neurologically intact and have normal intelligence, measuring the head circumferences of the parents and siblings is important. A family history of small head size in the context of normal development and neurologic examination describes asymptomatic familial microcephaly.

Prenatal environmental factors may also lead to congenital microcephaly. A small head circumference at birth often reflects a condition of early prenatal origin. Intrauterine infections such as cytomegalovirus, toxoplasmosis, and rubella have been implicated in the development of microcephaly, and may also produce intrauterine growth retardation, hepatosplenomegaly, cardiac defects, retinopathy, cataracts, and hearing loss. Prenatal toxins that may lead to microcephaly in the newborn are alcohol, drugs of abuse such as cocaine, and irradiation. These environmental insults affect other organ systems as well, and microcephaly may be observed as a part of a syndrome. Prenatal exposure to alcohol may lead to intrauterine growth retardation, including microcephaly, facial features such as small palpebral fissures, smooth philtrum and thin upper lip, heart and eye defects, and behavioral and cognitive deficits, in a spectrum of disorders that range from alcohol-related neurodevelopmental disorder to fetal alcohol syndrome (FAS). Untreated maternal phenylketonuria and hyperphenylalaninemia produce findings very similar to those of FAS: microcephaly (the most consistent finding), ID, facial dysmorphism, and cardiac defects.

Head size that is not increasing as expected is a clue to an acquired microcephaly (also called postnatal-onset microcephaly), and investigation as to possible environmental and genetic causes should be initiated. Microcephaly from these causes is usually apparent by 2 years of age. A recent study classified 5 causal groups for acquired microcephaly: idiopathic, or no identifiable cause; familial; syndromic, with associated anomalies; symptomatic, following a pathogenic event; and mixed.

A genetic cause of microcephaly that does not usually present at birth is Rett syndrome, a condition exhibited almost exclusively in girls that is associated with a deceleration in head growth toward the second year of life leading to microcephaly, developmental regression, autistic features, and unusual hand mannerisms (hand-wringing and hand-washing movements). This genetic disorder has been mapped to the X chromosome and linked to a deletion of the *MeCP2* gene. Most cases are sporadic. Genetic causes also include metabolic disorders that may lead to a

deceleration of head growth in the first year of life; these conditions should be considered, especially if there is a history of parental consanguinity, episodic symptoms such as vomiting and encephalopathy, and developmental regression.

Severe perinatal asphyxia is an important environmental cause of acquired microcephaly. The asphyxiated newborn has a normal head circumference at birth, but head growth decelerates, and microcephaly and suboptimal head growth may be observed by 12 months of age, although acquired microcephaly can sometimes be detected as early as 6 weeks of age in infants who have had severe asphyxia. These children go on to develop significant neuromotor and cognitive deficits. Other environmental causes of acquired microcephaly are meningitis, malnutrition, traumatic brain injury, and abusive head trauma.

With multiple suture craniosynostosis, primarily a problem of the skull rather than the brain, the head circumference may be small at birth, or head growth may abruptly cease during infancy. The shape of the skull is asymmetrical, and evidence exists of bony ridging in the area of the fused sutures. Signs of increased intracranial pressure may be present. These characteristics clearly differentiate the microcephaly associated with craniosynostosis from *micrencephaly* in which the small head is round, symmetrical, smooth, and devoid of bony ridging in the area of the sutures. Premature closure of sutures may be an isolated feature or a part of a syndrome. Single-suture synostoses are not likely to cause microcephaly.

## EVALUATION

### Relevant History

Congenital microcephaly necessitates a thorough review of the prenatal history. Any potential exposure to toxins must be explored, such as the use of alcohol or other drugs of abuse. Poor maternal health during the pregnancy, intrauterine infections, and conditions causing placental insufficiency contribute to a suboptimal uterine environment that may lead to congenital microcephaly and intrauterine growth retardation. So, too, do psychosocial factors, as marked by lack of prenatal care and low levels of maternal education. A pedigree analysis can help identify a family history of genetic syndromes, miscarriages, or microcephaly. Taking note of the head sizes of the parents and siblings is an important component of the evaluation. A review of systems may identify medical problems such as feeding difficulties, seizures, and previous infections such as meningitis. The history should also include a chronology of developmental milestones, as well as a description of the child's current function and behavior, with close attention to possible developmental regression.

### Physical Examination

The physical examination of the microcephalic child should focus on the following:

1. Accurate measurement of the head circumference and assessment of the pattern of head growth and the onset of microcephaly if previous measurements are available

2. Inspection and palpation of the skull, looking for asymmetry and bony ridging
3. Comparison of the head circumference with other growth parameters
4. Presence or absence of dysmorphic features
5. Presence or absence of congenital abnormalities involving other organ systems
6. Careful examination of the skin
7. Careful neurologic and developmental assessment

Accurate measurement and plotting on appropriate charts are critical (see earlier discussion). Head circumference of premature infants is adjusted for the degree of prematurity until about 2 years of age. For infants with birth weight of less than 1,000 g, corrected age is often used until 3 years or when growth has caught up based on normal growth curves. Inspection and palpation of the skull may reveal an asymmetrical skull and face and bony ridging that are suggestive of craniosynostosis, the presence of which leads the pediatrician to a different approach in evaluation and management. A head circumference that is disproportionately small in relation to the child's weight and height is a likely indicator of a CNS condition. When microcephaly is part of generalized growth retardation, or when it is associated with dysmorphic facial features and multiple-organ system involvement, the search for conditions that may have a more systemic effect on the child should be investigated, such as chromosomal disorders, intrauterine infections, or exposure to toxins. Children with congenital microcephaly seem to have a higher frequency of major malformations when compared with normocephalic infants. Examination of the skin may reveal the rash of an intrauterine infection. A thorough neurologic examination should assess for asymmetries, abnormalities in muscle tone, posture, strength, and reflexes. A developmental assessment may reveal generalized psychomotor retardation and motor delays, as well as speech/language and cognitive impairments.

### Laboratory Testing

The laboratory evaluation should be guided by the differential diagnoses. Children who are thought to have intrauterine infections must be tested for prenatal infections (toxoplasmosis, rubella, cytomegalovirus, syphilis, human immunodeficiency virus, herpes) and have ophthalmologic and audiologic evaluations. A microcephalic newborn with other congenital anomalies and atypical facial features should have a genetic consultation and evaluation. Genetic testing is available for many disorders, including chromosomal disorders, Miller-Dieker syndrome, and Rett syndrome. For children with microcephaly and dysmorphic features, the availability of array comparative genomic hybridization (aCGH) testing has enhanced the likelihood of a genetic diagnosis. Metabolic testing is usually not recommended in the evaluation of an asymptomatic newborn with microcephaly; however, it should be considered in cases of postnatal-onset microcephaly, especially with a history of parental consanguinity, episodic symptoms, or developmental delays or regression.

### Imaging

In the evaluation of a child with microcephaly, several neuroimaging modalities are available to identify



abnormalities in brain structure. The yield is significantly higher in cases of severe microcephaly (>3 standard deviations below the mean) compared with mild microcephaly (2–3 standard deviations below the mean). Magnetic resonance imaging (MRI) is most suitable for identifying gray and white matter disease and migration defects such as lissencephaly, pachygyria, and polymicrogyria. However, MRI is limited in its ability to study bone and calcifications. Computed tomography is useful to identify intracranial calcifications that may result from intrauterine infections, the skull abnormalities seen with premature fusion of cranial sutures, and ventricular system abnormalities. In infants with open fontanelles, ultrasonography of the head can be helpful in delineating cranial abnormalities. A skull radiograph can demonstrate intracranial calcifications and the characteristic bone findings in craniosynostosis but cannot detect abnormalities in brain structure. Consultation with a neuroradiologist may be helpful in determining which procedure, if any, is appropriate for a given child.

Practice parameters for the evaluation of the child with microcephaly have been developed by the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society.

## MANAGEMENT

The management of microcephaly is largely symptomatic and preventive. Appropriate prenatal care, maternal education and nutrition, avoidance of teratogenic substances, screening for intrauterine infections, and management of maternal health conditions may minimize the number of preventable cases of microcephaly. Because many children with microcephaly may have other medical issues (eg, cerebral palsy, seizures, ophthalmologic disorders), the pediatrician should monitor for these conditions and initiate the provision of interventions as needed. Children with microcephaly require close follow-up for developmental issues and can benefit from early intervention and special education services as needed. Genetic counseling must be offered to parents who have offspring with genetic disorders. Children suspected to have craniosynostosis require neurosurgical consultation.

### WHEN TO REFER

- Consider for head circumference of more than 2 standard deviations below the mean (especially >3 standard deviations)
- Head circumference deceleration or poor head growth
- Dysmorphic features
- Abnormal neurologic examination and development
- Regression in motor, language, and social skills
- Seizures
- Suspected craniosynostosis

### WHEN TO ADMIT

- Signs of increased intracranial pressure
- Mental status change

## TOOLS FOR PRACTICE

### Medical Decision Support

- *Growth Charts*, Centers for Disease Control and Prevention ([www.cdc.gov/growthcharts](http://www.cdc.gov/growthcharts))
- *Online Mendelian Inheritance in Man* (online database), Johns Hopkins University ([omim.org](http://omim.org))
- *United States Head Circumference Growth Reference Charts: Birth to 21 Years* (article), *Journal of Pediatrics*, Vol 156, Issue 6, 2010

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## Chapter 179

# NONCONVULSIVE PERIODIC DISORDERS

Sarah M. Roddy, MD

A variety of paroxysmal nonepileptic disorders occur in children. These disorders have a wide range of clinical features that mimic seizures, and distinguishing them from seizures is important so that the child is not treated inappropriately with anticonvulsants. A thorough history is often all that is needed to make the diagnosis, although a few patients may require a more extensive evaluation.

## BREATH-HOLDING SPELLS

Breath-holding spells, or infantile syncope, occur in approximately 5% of children. Most children who have breath-holding spells begin having episodes between 6 and 18 months of age, although spells may begin in the first few weeks of life. The frequency of episodes ranges from once a year to several times daily. The history of the episode and the surrounding events is the most important part of the evaluation of a child who has such spells. Because the familial incidence of breath-holding spells is high, the parents should be questioned about episodes in other family members.

Two types of breath-holding spells occur: cyanotic and pallid. The cyanotic type is more common than the pallid form and is usually precipitated by frustration or anger. During such spells, children cry vigorously and then hold their breath in expiration. Apnea

is followed by cyanosis, with opisthotonic posturing and loss of consciousness. Recovery is usually quick, with return of respiration and consciousness within 1 minute. Evaluation of children who have severe cyanotic breath-holding spells has shown an underlying autonomic system dysregulation that may contribute to the pathophysiologic features of the episodes. Pallid breath-holding episodes are usually provoked by sudden fright or minor injuries, especially falling and hitting the occiput. The child gasps or cries briefly and then abruptly becomes quiet, loses consciousness, has pallor, and becomes limp. The child may then develop clonic jerks. Pallid breath-holding spells are a vasovagal phenomenon. The precipitating event induces a vagally mediated asystole, leading to cerebral ischemia. Ocular compression during simultaneous electroencephalographic and electrocardiographic tracing in children who have pallid breath-holding spells has shown asystole with flattening of the electroencephalogram without electrical seizure activity. The clonic jerks are caused by cerebral hypoxia rather than by epileptiform discharges from the brain.

The prognosis for children who have either type of breath-holding is excellent; most outgrow the episodes by school age. Children who have pallid breath-holding spells may later develop syncope. Treatment is directed mainly at reassuring the family of the benign nature of the episodes. The pediatrician or other physician should emphasize that the episodes are not seizures and that they do not lead to intellectual disability or epilepsy. Because cyanotic episodes are often precipitated by temper tantrums, anger, and frustration, advice about behavior management may be helpful. Anemia has been described as a contributing factor in breath-holding spells, and treating it may reduce the incidence of the episodes. Atropine is effective for pallid breath-holding episodes, but its use is rarely warranted. Anticonvulsants should not be used because they are not effective in treating either type of breath-holding spell (see Chapter 201, Temper Tantrums and Breath-holding Spells).

## SYNCOPE

Syncope, or fainting, is an acute and transient loss of consciousness caused by reduced cerebral perfusion. Episodes are relatively common, particularly among teenagers. Postural hypotension, which may occur after a sudden change from a sitting or reclining position to a standing position, can precipitate an episode. Emotional upset, fright, and overheating are also common provoking stimuli. Cardiac disorders, including arrhythmias, aortic stenosis, and severe cyanotic heart disease, may cause syncope by reducing cardiac output and causing cerebral hypoxia. In rare cases, episodes of syncope have been reported with swallowing, coughing, urinating, and defecating.

Patients have presyncopal symptoms that may include light-headedness, anxiety, sweating, nausea, generalized numbness, and visual changes described as constriction or darkening of vision. Observers notice marked pallor and clammy skin. These symptoms are followed by loss of consciousness and slumping to the floor. Once the patient is recumbent and cerebral perfusion is restored, consciousness returns within a

few seconds. If the patient is held with the head above the body and cerebral perfusion is not restored, clonic movements may occur. As with pallid breath-holding spells, these movements occur as a result of cerebral ischemia rather than epileptiform discharges from the brain. Patients are not disoriented or confused after an episode of syncope, although they may be tired.

The history is important in diagnosing syncope and should include a description of the event by the patient and an observer. Although laboratory evaluation is seldom needed, if atypical elements are involved, such as absence of a precipitating factor or confusion after the episode, an electroencephalogram or a cardiac evaluation, including Holter monitoring, may be appropriate. Evaluation with tilt-table testing can be helpful for children who have unexplained syncope. Treatment consists of teaching the patient and family about managing an episode. Because patients have presyncopal symptoms, they should be instructed to sit or lie down as soon as the symptoms begin, thereby preventing progression to loss of consciousness. If the patient loses consciousness, the parent should place the child in a recumbent position with the head lower than the trunk. Parents often pick up a child who has fainted; they should be cautioned against this action because they may prolong the period of unconsciousness (see Chapter 200, Syncope, for a more detailed discussion of syncope and its causes).

## BENIGN PAROXYSMAL VERTIGO

Benign paroxysmal vertigo of childhood is a disorder characterized by brief attacks of vertigo. Symptoms usually appear within the first 3 or 4 years of life, although they may begin later. Episodes are characterized by abrupt onset, with the child appearing fearful and unable to maintain normal posture and gait. The child may seek support and clutch the parent or abruptly sit down or fall. In severe cases, the child may be limp and incapable of using the extremities. Pallor and diaphoresis are usually apparent, and vomiting and nystagmus sometimes occur. An episode typically lasts less than 30 seconds or, in rare cases, a few minutes. A brief period of postural instability may follow the episode; but within a few minutes, the instability resolves. Consciousness is not altered during the episode, and only rarely does the child feel sleepy after it. The frequency of episodes varies from as many as several weekly to 1 episode every few months. Audiograms are normal. Oculovestibular testing with cold-water calorics is difficult to perform in young children, and results vary. When properly done, testing shows no abnormalities in vestibular function. The results of radiographic studies of the temporal bone and electroencephalographic recordings are also normal. Included in the differential diagnosis of vertigo in childhood are brainstem lesions, posterior fossa tumors, and epilepsy. The history and physical examination usually differentiate benign paroxysmal vertigo from these more serious disorders. In most cases, no treatment is necessary, and anticonvulsants are not effective. Antihistamines such as dimenhydrinate have been used in some patients who have frequent episodes, with an apparent reduction in the number of episodes. Because the frequency of attacks varies,

assessing the effect of therapy accurately is difficult. Attacks of vertigo usually stop spontaneously over a period of a few years. Some children with benign paroxysmal vertigo later develop migraine headaches (see Chapter 140, Dizziness and Vertigo).

### SHUDDERING ATTACKS

Shuddering or shivering episodes are a benign movement disorder that probably occurs in many children at one time or another. The episodes are brief and characterized by paroxysmal rapid tremors involving primarily the head and arms. Some episodes may involve flexion of the head, elbow, trunk, and knees, with adduction of the elbows and knees. Consciousness is not altered during the episodes. The frequency varies, with some children having more than 100 episodes daily. Emotional factors, including excitement, fear, anger, and frustration, may precipitate episodes. Shuddering episodes may start as early as a few months of age or not until later in childhood. The number of episodes usually declines gradually. The pathophysiologic mechanism of the episodes is unclear, although the attacks have been postulated to be an expression of an essential tremor. Electroencephalographic monitoring has shown that the episodes are not epileptiform in nature. In most cases, no treatment is necessary. If episodes are severe and interfere with activities, treatment with propranolol may be helpful. Anticonvulsants are ineffective and should not be used.

### BENIGN NEONATAL SLEEP MYOCLONUS

Sudden brief jerks of the extremities are normal in children and adults when falling asleep. Sleep-related myoclonus in neonates is called *benign neonatal sleep myoclonus*. The myoclonic jerks begin in the first month of life, often within the first day, and are present only during sleep, disappearing when the infant awakens. The jerking movements may start in one extremity and then progress to involve the other extremities, or they may begin bilaterally. The upper extremities are involved more often than the lower extremities. Jerks occur every 2 to 3 seconds for several minutes, although they have been reported to last up to 12 hours. Rocking the crib and repetitive sounds may provoke the myoclonus. Development is normal, and no neurologic deficits are present. Electroencephalographic results are normal, with no epileptiform discharges associated with the myoclonus. The major differential diagnosis of neonatal sleep myoclonus is a seizure disorder. A history of episodes only during sleep and a normal electroencephalogram help differentiate this benign disorder from seizures. The myoclonus usually diminishes gradually during the first 6 months of life, although it has rarely lasted until 3 years. No treatment is necessary. The infants do not subsequently develop epilepsy or cognitive delay.

### NIGHT TERRORS

Night terrors or sleep terrors are a sleep disorder with some features that mimic partial complex seizures. They occur in up to 6% of children, with a peak incidence in late preschool-aged and early school-aged children. Affected children often have a family history

of either night terrors or another sleep disorder. The episodes usually occur during the first 2 hours after falling asleep. The child sits up in bed abruptly and screams or talks unintelligibly. If the child's eyes are open, they have a glazed look. During the episode, the child appears to be hallucinating and does not respond to the parents. Tachycardia and diaphoresis result from activation of the sympathetic nervous system. In some cases, the child may sleepwalk. Night terrors usually last approximately 10 minutes, with the child then relaxing and abruptly falling back to sleep. On awakening, the child does not remember the episode. Night terrors are caused by a rapid partial arousal from deep, slow-wave sleep. Febrile illness and sleep deprivation may trigger night terrors.

Electroencephalography does not show seizure activity during the episodes. It is important to differentiate night terrors from nightmares, which occur later in the sleep cycle, during rapid eye movement (REM) sleep, and are associated with easy arousal and recall of the content, or at least the occurrence, of the nightmare. Night terrors usually occur less often as the child gets older, although episodes may continue into adolescence and adulthood. The nature of the episodes should be explained to the parents. Although parents tend to try to wake and reassure the child, they should be told that the child is not aware of their presence, and attempts to awaken the child are not helpful and may increase agitation. If the child is sleep deprived, parents should take steps to increase the amount of sleep the child is getting. If night terrors persist despite adequate sleep, a sleep study may be needed to evaluate for obstructive sleep apnea, which can trigger night terrors. In most cases, no medication is indicated. However, if episodes are frequent or severe, a benzodiazepine, imipramine, or L-5-hydroxytryptophan may be helpful.

### NARCOLEPSY

Narcolepsy is a sleep-wake disorder characterized by excessive and inappropriate periods of sleep during the day. The daytime sleepiness interrupts activities and does not diminish in response to adequate amounts of sleep at night. Naps may last from a few minutes to longer than an hour. In addition to the excessive daytime sleep, patients often have cataplexy, sleep paralysis, and hypnagogic hallucinations. Cataplexy is a transient partial or complete loss of tone, often triggered by an emotional reaction such as laughter or fright. The individual does not lose consciousness. Sleep paralysis occurs as the patient falls asleep or awakens and is characterized by the inability to move or speak. Hypnagogic hallucinations occur while falling asleep, can be auditory or visual, and may be very frightening to a child.

The estimated prevalence of narcolepsy is 0.02% to 0.05%. Onset usually occurs in the second decade, although it has been reported in toddlers. Sleep studies in patients who have narcolepsy show extremely short sleep onset latency. In narcolepsy, REM sleep occurs within 15 minutes of sleep onset; in healthy patients, 90 minutes of non-REM sleep precede the first REM period. A strong association exists between narcolepsy and the human leukocyte class II

antigen DQB1\*0602. Human leukocyte antigen typing may be helpful but is not diagnostic. The hypocretin peptides that are important for maintaining wakefulness may be absent on cerebrospinal fluid studies, especially in cases involving cataplexy. Sleep studies are important in diagnosing narcolepsy. Included in the differential diagnosis of excessive daytime sleepiness are chronic illness, sleep apnea, hypothyroidism, depression, and seizures.

Narcolepsy is a lifelong condition, but central nervous system stimulants such as methylphenidate and modafinil help reduce the frequency of naps. Tricyclic medications such as imipramine are used to treat cataplexy and the other associated symptoms.

### WHEN TO REFER

- Diagnosis cannot be made by history and physical examination
- Need exists for subspecialty expertise

### WHEN TO ADMIT

- Child needs video electroencephalographic monitoring to evaluate an episode

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## Chapter 180

# ODOR (UNUSUAL URINE AND BODY)

Erik Langenau, DO, MS

Unusual odors in children may be a chief complaint, symptom, or sign. The odors may emanate from the breath, urine, skin, sputum, vomitus, stool, or vagina, and they can provide helpful clues in the diagnosis of many specific conditions.

### DEFINITION OF TERMS

Although unusual odors can be caused by many different conditions, bromhidrosis and halitosis require careful attention.

Bromhidrosis, a condition in which sweat is malodorous and offensive, is caused by decomposition of products from the apocrine, eccrine, and sebaceous glands. Apocrine bromhidrosis, which begins after

puberty with a characteristic acrid or sweaty odor, results from a combination of short-chain fatty acids, ammonia, androgenic steroids, hexanoic acid, and saturated ketones and indoles. Eccrine bromhidrosis results from bacterial interaction with moist keratin and is caused by hyperhidrosis, obesity, intertrigo, and diabetes mellitus; it is aggravated by hot weather and occurs primarily in the soles, palms, and intertriginous areas.

Halitosis is an offensive odor emanating from the mouth or air-filled cavities such as the nose, sinuses, or pharynx; it may be physiologic or pathologic, with numerous causes, such as xerostomia (dry mouth), periodontitis, sinusitis, tonsillitis, or gastroesophageal reflux.

### EVALUATION OF UNUSUAL ODORS

The differential diagnosis of unusual odors is extensive and includes numerous systemic, metabolic, toxic, and infectious diseases. The physician may inquire about the presence or absence of an odor when evaluating a child with a particular infection, dermatologic condition, metabolic disease, or ingestion. After a thorough history and physical examination is conducted, the differential diagnosis of an unusual odor can become more focused.

### Chief Complaint

If an unusual body odor is the chief complaint, a thorough history of the present illness helps narrow the differential diagnosis. Relevant questions may include the following:

- When did you first notice the odor?
- What does it smell like?
- Does it smell like anything familiar?
- What is the quality?
- What is the intensity?
- Does it seem to come from a certain part of the body?
- Does bathing or cleaning make it better?
- Are there any other associated symptoms, such as vomiting, weight loss, lethargy?
- Do other members of the family have similar odors?
- Do any family members have metabolic or infectious diseases?
- Have you seen any insertion of a foreign body in the nose, ear, anus, or vagina?
- Has your child taken any oral or topical medications, vitamins, herbal supplements, or toxins?
- How has the odor affected the child and family?

### Physical Examination

In assessing an odor, the examiner should note the character of the odor, determine the patient's age (and stage of pubertal development), check for any other signs or symptoms during a complete examination with the child unclothed, and attempt to localize the odor to a particular body site.

In a routine medical encounter, an odor may be the first observation when the patient enters the examining room. Odors are often difficult to describe because of insufficient standards for classifying, qualifying, quantifying, and teaching about them. Historically and practically, odors have been compared with others



for which physicians have common experience, and odor strength is characterized by such adjectives as strong or faint. In addition, individuals differ in their ability to detect at least some odors and in their assessments of whether certain odors are offensive. Gas-liquid chromatography and enhanced odor classification systems now allow more precise identification of odors. Artificial nose technology, which can sense a wide range of volatile chemicals and be trained in pattern recognition, may soon become a tool to supplement the physician's own nose. Artificial noses or bioelectronic noses have already been used to detect diseases such as tuberculosis, urinary tract infections, *Helicobacter pylori* infection, gastroesophageal reflux disease, bacterial vaginosis, diabetes, and a number of cancers.

If a patient reports an intermittent unusual odor that is never detected by others, then the possibility of temporal lobe epilepsy with olfactory manifestations should be entertained. On the other hand, if the physician notices a clearly offensive body odor, but the patient or parent does not, then anosmia should be considered. Causes of impaired olfaction may include various endocrinopathies such as Kallmann syndrome, diabetes, Turner syndrome, and hypothyroidism; neuropsychiatric conditions such as schizophrenia; infections such as rhinitis and sinusitis; autoimmune diseases such as Sjögren syndrome, granulomatosis with polyangiitis (formerly known as Wegener granulomatosis) and multiple sclerosis; or medications including metronidazole, tetracycline, captopril, and amphetamines.

Physicians should also be aware that odor recognition involves complicated molecular and genetic mechanisms. Sex, age, and genetic variation may lead to differences in abilities and thresholds for detecting odors. Physicians and patients may therefore vary in their ability to detect certain odors.

## DIFFERENTIAL DIAGNOSIS OF UNUSUAL ODORS

An array of odors can be associated with the human body and clothing, and subtle differences in odor can be found among people as well. Therefore the first task may be to decide whether a particular odor truly is peculiar and whether it emanates from the body. The odor may be simply a normal body odor that draws attention because of its intensity or because the complainant is unusually sensitive to or concerned about it.

### Normal Body Odor

Normal body odors derive from secretions of the sweat and apocrine glands, vagina, cervix, respiratory tract, urine, feces, breath, and flatus. Odor may be produced or modified by the action of normal or abnormal microbial flora.

In Western culture, people often minimize body odors by frequently changing their clothing, bathing, and using deodorants, antiperspirants, mouthwashes, douches, or scents applied to the skin. If one of these artificial odors is too strong, then the physician may wonder what the patient is trying to hide. On the other

hand, if a patient does not practice these customs, then the physician may detect an odor that is offensive and then must decide why the patient is not complying with social expectations.

Body odor changes with puberty, and a characteristic adult odor may prompt a child (or the child's parents) to seek medical attention.

### Axillary Odor

Axillary odor, which varies in intensity from person to person, is often the strongest odor associated with adolescents and adults. Its pungency has long been attributed to the action of aerobic diphtheroids on apocrine secretions. Recent work has identified odor-binding proteins that originate in the apocrine glands. The most abundant of the smelly compounds may be (E)-3-methyl-2-hexenoic acid. Bacterial decomposition of androsterone is another possible cause of axillary odor. Axillary hair seems to retain or spread odor.

Some adolescents and adults have axillary odor that is unusually strong, a condition called osmidrosis axillae or axillary apocrine bromhidrosis. The odor emanates from the apocrine glands. Possible explanations include specific features of apocrine androgen metabolism, bacterial alteration of sweat, and abnormally large and numerous apocrine glands. A variety of topical interventions, as well as surgical excisions, have been used to treat this condition.

### Vaginal Odor

The odor of postpubertal vaginal secretions varies among individuals and with the menstrual cycle. Vulvar secretions, vaginal wall transudates, exfoliated cells, cervical mucus, fluids from the endometrium and uterine tubes, and metabolic products of the vaginal microflora all contribute. Some people characterize the resulting odor as unpleasant, even in the absence of vaginitis. Odor during menses is usually rated as the most offensive. Some individuals may be concerned about these normal odors. The rotten fish smell of the vaginal discharge associated with bacterial vaginosis is caused by trimethylamine.

### Mouth Odor

The odor of a healthy mouth is assumed to be inoffensive in childhood; however, *bad breath* is not uncommon, even in an otherwise well child. Halitosis in the absence of disease is thought to be caused by volatile sulfur compounds (hydrogen sulfide and methyl mercaptan), which are formed when the oral flora metabolize proteins that are found in the saliva or adhering to the teeth, tongue, or gums. Halitosis is exacerbated by infrequent eating and drinking, which ordinarily have a flushing action. Acutely, halitosis may accompany a variety of childhood respiratory tract and gastrointestinal infections. Persistent halitosis should prompt evaluation for dental or gingival disease, a nasal foreign body, lung disease, or gastroesophageal reflux.

Simple oral hygiene can temporarily modify mouth odor. Brushing the teeth and the dorsoposterior surface of the tongue and then rinsing with water or a mouthwash may well reduce both the concentrations of volatile sulfur compounds and the offensive odor.

### Foot Odor

Eccrine bromhidrosis, tinea pedis (athlete's foot), and pitted keratolysis have been associated with increased foot odor. Each of these conditions may be exacerbated by occlusive footwear (eg, boots) and a hot, humid climate. The odor from eccrine bromhidrosis of the feet is thought to result from the breakdown of keratin and lipids by diphtheroids; fatty acid metabolites may be the agents responsible for the odor. Pitted keratolysis (plantar keratolysis puncta) is characterized by white plaques and shallow pits on the plantar surface. Various gram-positive bacteria and dermatophytes have been identified in affected patients. The odor is thought to be related to the breakdown products (such as thiols and thioesters) of these microorganisms within the stratum corneum. Conditions associated with foot odor may respond to a combination of moisture control, topical antibiotics, and antifungal agents.

### Metabolic Abnormalities

Certain metabolic defects are associated with an unusual odor of the urine, sweat, and other body fluids because of accumulation of odoriferous metabolic precursors or byproducts. These metabolic disorders and associated odors are listed in Table 180-1. Metabolic disorders should be suspected if an infant has an unusual body odor, especially if the patient is ill appearing, malnourished, or ketotic. Recognizing the odor in a compatible clinical situation may lead to early diagnosis, and prompt treatment may prevent progressive brain damage or death. A specialist in metabolic diseases should be consulted, and an appropriate diet should be started while a more

thorough metabolic evaluation is being completed. The odor itself may lead to embarrassment, low self-esteem, and psychosocial problems. In some conditions, dietary manipulation may reduce the malodor as well as other symptoms.

### Foreign Bodies

Retention of a foreign body in an orifice may lead to a focal foul smell. Retained foreign bodies within the vagina (eg, tampons, diaphragms), auditory canals, and nostrils are common causes of local foul odor. A retained foreign body may also be related to a generalized body odor because odoriferous substances are absorbed and secreted in sweat. Nasal foreign bodies are the most commonly associated with this condition.

### Inhalation, Poisoning, and Ingestion

When inhalation or ingestion of a toxic substance is suspected, odor may provide a clue to the substance involved. Common associations are listed in Table 180-2. When puzzled, the physician should consult a poison control center.

Penicillin and cephalosporins give the urine a medicinal or musty smell. Topical benzoyl peroxide has been implicated in at least 1 case of persistent body odor. Thiourea compounds give the breath a sweet smell, resembling that of decaying vegetables. Newborns have smelled spicy when their mothers ate particular curries before labor.

### Other Diseases

Odor may suggest either the presence of an infection (Table 180-3) or other acquired medical conditions (Table 180-4).

**Table 180-1** Metabolic Abnormalities Associated With Unusual Odor

DISEASE	DESCRIPTION OF ODOR	CLINICAL FEATURES	METABOLIC DEFECT
3-hydroxy-3-methylglutaryl-CoA lyase deficiency	Cat urine	Malaise, hypoglycemia, hepatomegaly, transaminitis, mild acidosis	3-hydroxy-3-methylglutaryl-CoA lyase
Glutaric aciduria type II (multiple acyl-CoA dehydrogenase deficiency)	Sweaty feet, acrid, stale	Hypoglycemia, hypotonia, hepatomegaly, respiratory distress, death	Electron transfer flavoprotein (ETF) or ETF:ubiquinone oxidoreductase (ETF:QO)
Hawkinsinuria	Swimming pool	Failure to thrive, hepatomegaly, anemia, irritability	4-hydroxyphenylpyruvate dioxygenase
Hypermethioninemia	Boiled cabbage	Usually asymptomatic. Some develop intellectual disability, dystonia.	Methionine adenosyltransferase
Isovaleric acidemia	Sweaty feet, acrid	Acidosis, vomiting, dehydration, coma, mild-to-moderate intellectual disability, aversion to protein foods	Isovaleric acid CoA dehydrogenase
Ketoacidosis	Fruity, acetone-like, decomposing apples	Vomiting, dehydration, altered mental status, lethargy	Ketoacidosis (eg, from starvation or insulin deficiency)
Maple syrup urine disease	Maple syrup, burnt sugar, curry, malt, caramel, fenugreek beans	Severe form: feeding difficulty, vomiting, lethargy, acidosis, seizures, coma leading to death in first months of life	Mitochondrial branched-chain alpha-keto dehydrogenase complex

**Table 180-1** Metabolic Abnormalities Associated With Unusual Odor—cont'd

DISEASE	DESCRIPTION OF ODOR	CLINICAL FEATURES	METABOLIC DEFECT
		Intermediate form: mild acidosis, intellectual disability, developmental delay, ophthalmoplegia Intermittent form: episodic ataxia and lethargy that may progress to coma Thiamine-responsive form: respond to supplementation E3-deficient form: variable expression	
Multiple carboxylase deficiency	Tomcat urine	Failure to thrive, hypotonia, vomiting, seizures, rash	Holocarboxylase synthetase
Oasthouse urine disease (methionine malabsorption syndrome; Smith-Strang disease)	Dried celery, malt, hops, yeast, beer	Diarrhea, intellectual disability, spasticity, attacks of hyperpnea, fever, edema	Kidney and intestinal transport of methionine, branched-chain amino acids, tyrosine, and phenylalanine
Phenylketonuria	Musty; similar to a mouse, horse, wolf, or barn	Vomiting, progressive mental retardation, microcephaly, eczema, decreasing pigmentation, seizures, spasticity	Phenylalanine hydroxylase
Trimethylaminuria (fish odor syndrome)	Dead or rotting fish	Usually asymptomatic with isolated finding. Fish odor of urine and body.	Trimethylamine oxidase
Tyrosinemia	Boiled cabbage, rancid butter	Liver failure, death	Fumarylacetoacetate hydrolase deficiency

Data derived from multiple sources.

**Table 180-2** Inhalations, Poisonings, and Ingestions Associated With Recognizable Odors

ODOR	SITE	SUBSTANCE IMPLICATED
Bitter almond	Breath	Cyanide (chokecherry, apricot pits), jetberry bush
Burned rope	Breath	Marijuana
Camphor	Breath	Naphthalene (mothballs)
Carrots	Breath	Water hemlock (cicutoxin)
Coal gas	Breath	Coal gas (associated with odorless but toxic carbon monoxide)
Disinfectant	Breath	Phenol, creosote
Fishy	Breath	Zinc or aluminum phosphide
Fruity, acetone or decomposing apples	Breath	Lacquer, salicylates, chloroform
Fruity, alcohol	Breath	Alcohol (ethanol, isopropyl alcohol), phenol, acetone, amyl nitrites ( <i>poppers</i> )
Fruity, pearlike	Breath	Chloral hydrate, paraldehyde
Garlic	Breath, vomitus, stool	Arsenic
Glue	Breath, vomitus	Phosphorus, tellurium, parathion, malathion, dimethyl sulfoxide, selenium
Hydrocarbon	Breath, vomitus	Toluene, solvents ( <i>huffing</i> )
Medicinal, musty	Urine	Hydrocarbons
Metallic	Breath	Penicillins, cephalosporins
	Stool	Iodine
	Vomitus	Arsenic
Rotten eggs	Breath	Arsenic, phosphorus
Severe bad breath	Breath	Hydrogen sulfide mercaptans, disulfiram, dimethyl sulfate, N-acetylcysteine
Shoe polish	Breath	Amphetamines
Stale tobacco	Breath	Nitrobenzene
Sulfides or amines	Skin	Nicotine
Violets	Urine, vomitus	War gases
Wintergreen	Breath	Turpentine
		Methyl salicylate

Data derived from multiple sources.

**Table 180-3**      **Odor as a Clue to Infection**

INFECTION	ODOR
<b><i>Respiratory and Ear, Nose, and Throat Infections</i></b>	
Candidiasis	Sweet, fruity
Diphtheria	Sweet
Intranasal foreign body	Foul and putrid
Lung abscess, empyema, bronchiectasis, fetid bronchitis	Foul, putrid breath or sputum
<i>Pseudomonas</i> infection, otitis externa	Foul cerumen
Rubella	Fresh-plucked feathers
Trench mouth, tonsillitis, gingivitis	Severe halitosis
Tuberculous lymphadenitis (scrofula)	Stale beer
Typhoid fever	Fresh-baked brown bread
Yellow fever	Butcher shop
<b><i>Skin Infections</i></b>	
<i>Candida</i> (skin)	Heavily sweet
Decubitus ulcer	Foul
Diphtheria (skin)	Sweet
Erythroderma	Rancid
Hidradenitis suppurativa	Lingering, pungent
Pitted keratolysis (gram-positive bacteria and dermatophytes)	Cheesy, sweaty, rotten smell from feet
<i>Pseudomonas</i> skin infection (burns)	Musty, fruity, grapelike, wet corn tortillas
Syphilis (condyloma latum)	Foul
Tinea capitis	Mousy, mouse urine–like
<b><i>Genitourinary Infections</i></b>	
Bacterial vaginosis	Amine, fishy vaginal discharge
Genital warts (condyloma acuminatum)	Foul
Urinary tract infection with urea-splitting bacteria	Ammoniacal urine
Vaginal foreign body, vaginitis	Foul vaginal discharge
<b><i>Gastrointestinal Infections</i></b>	
Rotavirus gastroenteritis	Full
Shigellosis	Rancid stool
<b><i>Neurologic Infections</i></b>	
<i>Cryptococcus</i> meningitis	Alcohol smell to cerebrospinal fluid
<b><i>Miscellaneous Infections</i></b>	
Chorioamnionitis	Foul-smelling amniotic fluid
<b><i>Infectious Etiologic Agents</i></b>	
Anaerobic bacteria	Foul-smelling wound, rotten apples
<i>Candida</i> infection	Sweet, fruity, beer odor in peritoneal dialysate
<i>Clostridium</i> gas gangrene	Rotten apples
Proteolytic bacteria	Pus that smells similar to feces or overripe cheese
<i>Proteus</i> infection	Mousy
<i>Pseudomonas aeruginosa</i>	Musty, fruity, grapelike, wet corn tortillas

Data derived from multiple sources.

**Table 180-4**      **Other Conditions Associated With Specific Odors**

DISEASE	ODOR
<b><i>Systemic Diseases</i></b>	
Hepatic failure	Breath: musty fish, raw liver, feces, rotten eggs, or newly mown clover ( <i>Fetor hepaticus</i> ) (caused by mercaptans such as dimethyl sulfide)
Ketoacidosis (diabetes or starvation)	Breath: fruity, acetone-like, decomposing apples (caused by ketones)
Uremia	Urine: fishy (caused by dimethylamine and trimethylamine) Breath: ammoniac (caused by ammonia)
<b><i>Vitamin Deficiencies</i></b>	
Pellagra (niacin deficiency)	Sour or musty bread
Scurvy (vitamin C deficiency)	Putrid
<b><i>Dermatologic Conditions</i></b>	
Psoriasis (pustular)	Skin: heavy
Skin diseases with protein breakdown (pemphigus)	Skin: foul, unpleasant



**Table 180-4** Other Conditions Associated With Specific Odors—cont'd

DISEASE	ODOR
<b>Gastrointestinal Conditions</b>	
Malabsorption	Feces: foul
Melena (gastrointestinal bleeding)	Feces: foul
<b>Surgical Conditions</b>	
Esophageal diverticulum	Breath: feculent, foul
<b>Surgical Conditions cont'd</b>	
Intestinal obstruction	Breath: feculent, foul Vomitus: feculent
Nasal foreign body	Skin and nasal cavity: fetid, putrid
Peritonitis	Vomitus: fecal
Portacaval shunt, portal vein thrombosis	Breath: sweet
<b>Miscellaneous</b>	
Acute tubular necrosis	Urine: stale water
Trans-3-methyl-2-hexanoic acid, which may or may not be elevated in patients with schizophrenia	Sweat and skin: unpleasant, pungent, heavy

Data derived from multiple sources.

## SUMMARY

Once an odor is identified and evaluated, a proper diagnostic and treatment plan can begin. Identification of odors can be impeded by poor association between odors and names and failure to retrieve the name of an odor. Physicians can be trained to improve their sense of odor recognition with the aid of educational materials (study guides), simulations with volatile samples on rounds, surgical simulators, and sniffing bar test tubes.

Odor is imprecise. Not surprisingly, with many other diagnostic aids at hand, today's physicians have minimized olfactory cues. However, odor should not be neglected; it may be the patient's primary concern, causing severe psychosocial distress. Odor identification may provide diagnostic clues that may aid in the detection and treatment of an underlying disease process.

*The author would like to acknowledge the valuable contribution of Modena H. Wilson, MD, MPH, to this chapter.*

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## Chapter 181 PETECHIAE AND PURPURA

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## INTRODUCTION

Petechiae and purpura result from a wide variety of underlying disorders and may occur at any age.

Petechiae are small (1–3 mm), red, nonblanching macular lesions caused by intradermal capillary bleeding (Figure 181-1). Purpura are larger, typically raised lesions resulting from bleeding within the skin (Figures 181-2 and 181-3). Purpura can vary somewhat in color based on the age of the lesion as the blood within the skin is metabolized and fades. Similar to petechiae, purpura do not blanch and may occur anywhere on the body.

## EVALUATION

The evaluation of a patient with petechiae or purpura begins with a complete history that can readily eliminate most disorders from the differential diagnosis. Special attention must be paid to recent trauma, bleeding history, medication use, and symptoms consistent with infection, malignancy, and autoimmune, vasculitic, connective tissue, or rheumatologic disorders. Physical examination should determine whether the skin findings are isolated or evidence that a more generalized process is present. Particular physical findings to evaluate include hepatosplenomegaly, lymphadenopathy, arthritis, arthralgias, or findings that are consistent with an acute viral syndrome. The history and physical examination will dictate the appropriate laboratory evaluations, but at a minimum, a complete blood count with platelets and differential count, as well as assessing prothrombin time and partial thromboplastin time, are typically indicated. Likely diagnoses are detailed here, and the complete evaluation indicated will be discussed.

## DIFFERENTIAL DIAGNOSIS—GENERAL CONSIDERATIONS

Neither petechiae nor purpura are pathognomonic of a specific disorder. The physician must entertain a broad differential diagnosis and consider disorders of hemostasis as well as infection, autoimmune disorders, trauma, malignancy, and other rare causes (eg, vasculitis, connective tissue disorders). The age at



**Figure 181-1** Cutaneous petechiae on the shins and ankles: nonblanching, erythematous macules, often less than 3 mm in size.



**Figure 181-3** Palpable purpura of the lower extremity: erythematous, nonblanching papules that often measure more than 3 mm in size.



**Figure 181-2** Occasional petechiae on the face and large, bullous hemorrhages on the buccal mucosa.

presentation, overall appearance, and the extent of the lesions may help define the underlying pathophysiologic mechanism. For example, scant petechiae on the face of a well-seeming newborn would not be particularly concerning after a vaginal delivery because these lesions are likely caused by the trauma of passing through the birth canal. However, a newborn with diffuse petechiae warrants further evaluation. If the child seems ill, then sepsis must be strongly considered; if

the child seems well, then a platelet disorder should be considered. Thus, petechiae and purpura must be evaluated in the overall context of the patient, severity and extent of the lesions, and history and age of the patient.

With petechiae or purpura, the possibility of a hemostatic defect is always a concern. For isolated petechiae, the physician must consider a primary platelet disorder (ie, low platelet number, platelet dysfunction). Purpura may result from a platelet disorder or other coagulation defect, which can be classified as primary or as a secondary phenomenon from an underlying disease. Platelet disorders can also be classified into disorders of platelet production, disorders of platelet survival (destruction), or disorders of platelet function. In the case of connective tissue disorders, easy bruising is not secondary to a hemostatic defect, but rather is caused by the fragility of the capillaries and the perivascular connective tissues. As such, easy bruising and bleeding may be characteristic manifestations of disorders unrelated to the commonly considered clotting and platelet disorders. In general, however, when presented with a patient with petechiae and purpura, the physician must consider thrombocytopenia as the proximate cause.

The normal platelet count is between 150,000 and 450,000/mm. Patients with a platelet count greater than 80,000 will be hemostatically normal as long as platelet function is not altered. With a platelet count between 50,000 and 80,000, increased bleeding with trauma is likely, but spontaneous bleeding would be unusual. Between 20,000 and 50,000, a mild bleeding diathesis is expected. With a count of less than 20,000, spontaneous mucosal bleeding can occur, and a count of less than 10,000 is concerning for spontaneous severe bleeding.

### Infectious Causes of Petechiae and Purpura

The mechanism by which a variety of viruses cause thrombocytopenia is not clear and may involve decreased platelet production or immune-mediated

destruction. Live virus vaccinations, notably varicella and measles, can cause moderate thrombocytopenia. Cytomegalovirus has been implicated in thrombocytopenia, but treatment of cytomegalovirus has not affected the outcome of patients monitored for chronic thrombocytopenia. Parvovirus has been associated both with isolated thrombocytopenia and with pancytopenia. Dengue fever and other viral hemorrhagic fevers are known to cause thrombocytopenia, and patients may develop petechiae and purpura as a result. Rickettsial diseases such as Rocky Mountain spotted fever may produce a petechial rash. Alterations of the endothelial lining of blood vessels cause thrombi formation and platelet destruction. Thrombocytopenia and disseminated intravascular coagulation (DIC) may develop. Malaria can also cause either mild or profound thrombocytopenia through mechanisms that are not well defined. HIV has been associated with thrombocytopenia resulting from bone marrow suppression (ie, poor production) and immune-mediated destruction.

Platelet consumption is common in children with bacteremia and sepsis even before frank DIC has developed. In an ill-appearing child with petechiae or purpura, infectious causes must be considered and appropriate antibiotics administered based on likely pathogens. Bacterial meningitis in particular must be considered for the febrile ill child with petechiae or purpura.

Purpura fulminans has been associated with viral infections, as well as *Streptococcus* and *Meningococcus* species. Microscopic thromboses in arterioles result in purpura and infarction and bleeding within the skin and subcutaneous tissue. These lesions may coalesce and become necrotic, and patients typically develop full DIC.

### Disorders of Platelet Production: Malignancy and Bone Marrow Failure Syndrome

Although most patients with petechiae or purpura have a benign process, perhaps the greatest concern for the physician and parents is malignancy. As such the history must rule out the classic signs and symptoms of malignancy, including fevers, night sweats, weight loss, lymphadenopathy or other masses, pallor, malaise, bone pain, and anorexia. Of course, many of these symptoms overlap with those seen in infectious and autoimmune processes; thus the physical examination will help the physician greatly. Petechiae or purpura in the setting of hepatosplenomegaly or impressive lymphadenopathy would put leukemia high on the differential diagnosis. Other marrow-infiltrating malignancies must also be considered. If the history or physical examination is consistent with a malignancy, then in addition to a complete blood count and screening coagulation studies, a comprehensive metabolic panel, liver function tests, lactate dehydrogenase, and uric acid should be immediately obtained. A manual differential count of the peripheral blood should be performed as well. An important point to note is that the absence of leukemic blasts on a peripheral blood smear does *not* rule out leukemia. The diagnosis of leukemia can be made if peripheral blasts are present; however, having few or no peripheral blasts

seen on routine microscopy is not uncommon for patients with leukemia.

Isolated profound thrombocytopenia is not likely to result from a malignancy; however, when more than 1 cell line on a blood count is abnormal, a bone marrow process must be considered. Laboratory findings consistent with malignancy include elevated lactate dehydrogenase, and an elevated uric acid and abnormal serum electrolytes may result from tumor lysis even before therapy is started. A chest radiograph should be obtained immediately because patients may have occult but massive mediastinal lymphadenopathy.

Petechiae and purpura may be the presenting signs in patients with bone marrow failure secondary to nonmalignant processes. Abnormal hematopoiesis usually causes alteration of more than 1 cell line or all cell lines (pancytopenia). Bone marrow failure may occur secondary to infectious processes (viral, bacterial with sepsis), medication use (notably a variety of antibiotics and anticonvulsants), profound nutritional deficits, or rare bone marrow failure syndromes (eg, Fanconi anemia, myelodysplastic disease, Wiskott-Aldrich syndrome). Bone marrow aspiration and biopsy are usually indicated to rule out malignancy and define the abnormal hematopoiesis.

### Disorders of Platelet Function: Primary Platelet Disorders

Petechiae and purpura may result from a primary platelet disorder, either qualitative or quantitative. The qualitative disorders result from platelet dysfunction; that is, the absolute platelet number is normal, but the platelets lose normal hemostatic function. In most instances, platelet dysfunction is acquired and results from medication use. The classic example is aspirin, which causes the irreversible inhibition of cyclooxygenase within platelets. Other causes of acquired platelet dysfunction include uremia and liver disease, although the mechanisms of poor platelet function in these settings are not clear.

Although von Willebrand disease is not a primary platelet disorder, patients commonly present with painless mucocutaneous bleeding. For this reason it should be considered in patients who have petechiae and purpura with a normal platelet count and no other obvious systemic disease. Von Willebrand disease is the most common bleeding disorder and affects approximately 1% of the population. It results from a qualitative or quantitative deficiency of von Willebrand factor, a protein required for platelet adhesion. Coagulation screening along with factor VIII and von Willebrand factor assays can establish the diagnosis.

A variety of platelet function disorders can be considered in patients with a normal to near-normal platelet number but who are bleeding and have petechiae or purpura. These disorders, which are rare, can be diagnosed by a hematologist with specialized platelet aggregation studies or morphologic study of platelets. Such disorders include Glanzmann thrombasthenia, Hermansky-Pudlak syndrome, and Chédiak-Higashi syndrome. Bernard-Soulier syndrome, an inherited platelet disorder, is characterized by variable thrombocytopenia and large defective platelets.



### Disorders of Platelet Survival (Destruction)

Isolated thrombocytopenia in an otherwise well child may lead to petechiae or purpura as the chief complaint. Idiopathic (or immune) thrombocytopenic purpura is a diagnosis of exclusion that produces profound isolated thrombocytopenia and petechiae or purpura but few other findings on physical examination. The laboratory workup should be normal except for thrombocytopenia. No other blood cell line is affected, and microscopic review of the blood reveals platelets that are too few in number but large in size, indicating that they are young. Idiopathic thrombocytopenic purpura is a disorder in which the platelet lifespan is reduced to minutes or hours rather than the normal several days. The incidence is highest in children between 2 and 8 years of age. Although physicians performed bone marrow aspirates in the past to rule out malignancy or other bone marrow failure syndromes, most now think that the diagnosis can be made clinically, and bone marrow studies are rarely indicated.

Typically, one-third of the total body platelet mass is sequestered within the spleen at any time. Whatever the cause of increased spleen size, mild thrombocytopenia may result. Common causes of hypersplenism include liver disease, a variety of infections (including Epstein-Barr virus and malaria, among others), and metabolic diseases (eg, Gaucher disease). Hypersplenism alone does not typically cause platelet counts below 50,000. Alternative explanations should be considered for patients with moderate-severe thrombocytopenia.

Henoch-Schönlein purpura is an autoimmune vasculitic disorder that often presents with palpable purpura. The classic distribution of purpura is on the buttocks and legs, but purpura may be more disseminated. Laboratory evaluations fail to reveal an identifiable coagulopathy, nor is there a defect in the quality or quantity of their platelets. The etiology of the palpable purpura is thought to be secondary to the vasculitis resulting in inflammation and weakening of the vessel walls. Other findings in Henoch-Schönlein purpura may include arthritis, arthralgias, abdominal pain, and renal impairment.

Hemolytic uremic syndrome (HUS) produces a constellation of findings, including thrombocytopenia, hemolytic anemia, and renal failure, and has been associated with a variety of infections, most notably *Escherichia coli* O157:H7.

Thrombotic thrombocytopenic purpura (TTP) shares some clinical features with HUS but is a distinct syndrome related to either inherited or acquired loss of function in the ADAMTS13 protease that cleaves von Willebrand factor. TTP, rarely seen in children, is characterized by purpura, thrombocytopenia, DIC, hemolytic anemia, thrombotic strokes, and elevated lactate dehydrogenase.

Giant vascular malformations may cause intravascular destruction of platelets. Kasabach-Merritt syndrome is the classic example of a giant hemangioma causing severe thrombocytopenia secondary to platelet destruction. These lesions are generally readily apparent; however, multiple smaller vascular malformations that are more difficult to define may

cause platelet destruction as well. Although laboratory evaluation often fails to reveal a coagulopathy, thrombocytopenia or altered hemostasis may be associated with rare vascular disorders and connective tissue syndromes such as the hereditary telangiectasias, Ehlers-Danlos syndrome, Marfan syndrome, and osteogenesis imperfecta.

### SUMMARY

Petechiae and purpura may result from a variety of mechanisms requiring the physician to obtain a complete history and perform a thorough physical examination. Both primary hematologic disorders and systemic disorders are in the differential diagnosis. Prompt referral to a pediatric hematologist may be indicated to rule out malignancy or help manage altered hemostasis.

#### WHEN TO REFER

- Platelet count less than 100,000/mm<sup>3</sup>
- Diffuse petechiae or purpura
- Focal petechiae or purpura not clearly associated with trauma
- Evidence of more than 1 cell line abnormality on complete blood count

#### WHEN TO ADMIT

- Patient with toxic appearance
- Moderate to severe bleeding
- Concern for poor adherence

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## Chapter 182 POLYURIA

Ryan S. Miller, MD; Samuel M. Libber, MD; Leslie Plotnick, MD

Polyuria, or excessive urinary volume, is a symptom common to many pediatric disorders. It may be defined clinically as urine production of more than 2 L/m<sup>2</sup>/24 hours or functionally as inappropriately high urine output relative to circulating volume and osmolality (Table 182-1). Although polyuria is often associated with polydipsia, frequent urination, and nocturia, these features may occur with normal urine output. Differentiating polyuria from other conditions depends on total urine output. In situations in which



**Table 182-1** Normal Urine Volume

AGE RANGE	DAILY OUTPUT (24 hr)
Newborn	150 mL/kg
Infant	110 mL/kg
Older child	40 mL/kg

the exact daily urinary volume is unknown, a detailed history of fluid intake and urinary habits may help delineate the primary symptom.

With an older child, the parent may perceive an increase in fluid intake to be more prominent than polyuria. However, infants with polyuria, because they do not have independent access to fluids, are more likely to fall into negative water balance, with weight loss, dehydration, and electrolyte disturbances. Chronic or recurrent electrolyte disturbances in unrecognized diabetes insipidus (DI) may result in growth failure and central nervous system (CNS) injury.

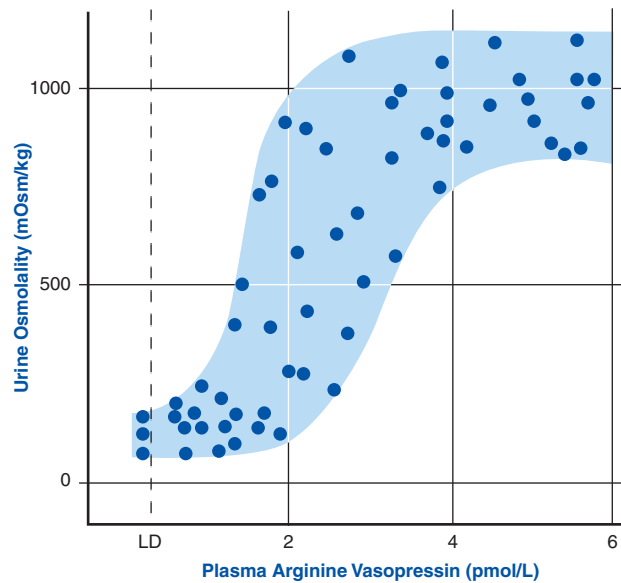
### **PATHOPHYSIOLOGIC FEATURES**

Normal serum osmolality and water balance are maintained primarily by release of arginine vasopressin (antidiuretic hormone [ADH]), thirst, and kidney function. Serum osmolality is tightly regulated—an increase in osmolality as small as 1% stimulates measurable release of vasopressin from the posterior pituitary. Vasopressin binds the V2 receptor of the renal tubules, resulting in insertion of aquaporin-2 protein at the apical surface of cortical cells and allowing water to enter the cell. Under normal conditions, plasma osmolality is maintained within a narrow range—about 285 to 290 mOsm/kg. Vasopressin levels rise as plasma osmolality increases above this range. However, maximal antidiuresis is reached at a plasma vasopressin concentration of 4 pmol/L, at which point urine cannot be further concentrated (Figure 182-1).

Vasopressin alone cannot restore fluid balance and osmolality; fluid replenishment is also required. Small increases in osmolality have been shown experimentally to stimulate thirst by increasing the concentration of solutes such as sodium chloride and sucrose (solutes that do not readily cross nerve cell membranes). This action results in intracellular dehydration, activating osmoreceptors in the brain that initiate neural mechanisms and resulting in generation of thirst. The osmolality at which thirst is experienced is likely higher than the point at which vasopressin production rises.

### **DIFFERENTIAL DIAGNOSIS**

Polyuria can be caused by any one of several conditions that play a role in water balance, each of which leads to the excretion of large volumes of dilute urine. Disorders of water balance fall into 4 major categories: central DI, nephrogenic DI, excessive fluid intake, and osmotic diuresis. DI is characterized by polyuria, polydipsia, dilute urine, dehydration, and hypernatremia. Central DI results from a deficiency in vasopressin secretion, whereas nephrogenic DI is the result of



**Figure 182-1** Relation between urine osmolality and plasma arginine vasopressin under various states of hydration. The stippled area is the normal reference range. LD represents the limit of detection of the assay (0.3 pmol/L). (From Baylis PH, Cheetham T. *Diabetes insipidus*. Arch Dis Child. 1998;79(1):84–89, with permission.)

reduced renal sensitivity to circulating vasopressin. Polyuria can also be a manifestation of excessive persistent fluid intake (primary polydipsia) or osmotic (solute) diuresis, as in uncontrolled diabetes mellitus (DM). In reaching a diagnosis in a patient who has polyuria, the physician must consider the systems involved in maintaining normal serum osmolality and water balance (Box 182-1).

### **Central Diabetes Insipidus**

Central or neurogenic DI is a condition in which secretion of vasopressin by the posterior lobe of the pituitary gland is inadequate to maintain normal serum osmolality, resulting in diuresis of varying degrees of severity. Of the known causes of central DI, nearly one-half of all cases result from a primary brain tumor, and about 18% are from histiocytosis or infiltrative processes. About 25% of cases are considered idiopathic. Familial vasopressin deficiency, also known as familial neurohypophyseal diabetes insipidus (FNHDI), is typically an autosomal dominant disorder and is rare, accounting for about 5% of all cases of DI. Although many mutations have been reported in the arginine vasopressin (AVP) gene, most cases involve mutations in the gene for neurophysin II (NP<sub>II</sub>), the carrier protein for AVP. In FNHDI, symptoms typically do not appear until 5 to 10 years of age. The syndrome consisting of DI, DM, optic atrophy, and deafness (DIDMOAD syndrome) typically presents in early childhood. Vasopressin deficiency is associated with certain congenital malformations (eg, septo-optic dysplasia, holoprosencephaly) and can result from CNS injury or tumor resection. After head trauma or surgery, patients may have a period of antidiuresis

### BOX 182-1 Differential Diagnosis of Polyuria in Childhood

1. Neurogenic vasopressin deficiency
  - a. Familial
  - b. Idiopathic
  - c. Congenital malformations (septo-optic dysplasia, holoprosencephaly, encephalocele)
  - d. Acquired
    - i. Head trauma
    - ii. Vascular event (thrombosis or hemorrhage)
    - iii. Postinfection (meningitis, encephalitis, congenital cytomegalovirus, toxoplasmosis)
    - iv. Tumor (craniopharyngioma, germinoma, optic glioma)
    - v. Systemic infiltrative diseases (histiocytosis, syphilis, tuberculosis, sarcoidosis)
    - vi. Inflammatory (lymphocytic hypophysitis)
    - vii. Guillain-Barré syndrome
    - viii. Autoimmune disorders
2. Renal vasopressin insensitivity
  - a. Familial nephrogenic diabetes insipidus
    - i. V2 receptor gene defect (X-linked)
    - ii. Aquaporin-2 gene defect (autosomal recessive)
  - b. Acquired
    - i. Postobstructive
    - ii. Drug-induced (lithium, amphotericin B)
    - iii. Associated with systemic disease (sickle cell disease, sarcoidosis, amyloidosis)
    - iv. Metabolic (hypercalcemia, hypokalemia)
3. Other renal disorders
  - a. Renal tubular defects (cystinosis, distal renal tubular acidosis, Bartter syndrome, renal Fanconi syndrome, ARC syndrome)
  - b. Nephronophthisis
4. Excessive fluid intake
  - a. Primary polydipsia
  - b. Water intoxication
5. Osmotic diuresis
  - a. Diet-induced
  - b. Drug-induced
  - c. Diabetes mellitus (type 1 or 2)

ARC, arthrogryposis, renal tubular dysfunction, and cholestasis.

after transient polyuria, followed by persistent central DI (triple-phase response).

In recent years, fewer cases of DI have been diagnosed as idiopathic, and a higher proportion have been diagnosed as occurring secondary to CNS infection or intracranial birth defects. Autoantibodies to hypothalamic vasopressin cells have been detected in some children previously thought to have idiopathic DI. Interestingly, about 50% of the patients who have histiocytosis also have vasopressin cell autoantibodies. In adolescents with acquired lymphocytic or granulomatous hypophysitis, hyperprolactinemia and

other anterior pituitary dysfunction may accompany the DI. The physician must search diligently for an underlying lesion that may not be evident at the initial evaluation.

### Nephrogenic Diabetes Insipidus

Renal disorders, both congenital and acquired, may be associated with polyuria because of a complete or partial inability of the renal tubule to concentrate urine despite normal or elevated circulating levels of vasopressin. Inherited forms of nephrogenic DI are rare, and symptoms of profound polyuria—vomiting, fever, failure to thrive, and hypernatremic dehydration—typically occur within the first weeks of life. Breastfed infants may show signs later than those who are bottle fed because of the lower osmotic load in human milk. The condition can be associated with damage to the CNS or even death if the infant develops recurrent hypernatremic dehydration. Older children and adults may be able to adjust their oral fluid intake to maintain serum osmolality. Mutations in the vasopressin V2 receptors of the distal convoluted tubule and collecting duct have been reported in affected members of kindreds with nephrogenic DI. A rare form of autosomal recessive nephrogenic DI has been described in patients with mutations in the gene for the water-channel protein aquaporin-2.

Besides the hereditary form of nephrogenic DI, the physician must consider other renal tubular defects in which vasopressin resistance has been observed. Patients who have cystinosis, distal renal tubular acidosis, renal Fanconi syndrome, or Bartter syndrome may have polyuria. An association between nephrogenic DI and the syndrome consisting of arthrogryposis, renal tubular dysfunction, and cholestasis (ARC syndrome) has been recognized; affected children are prone to severe growth impairment, as well as to intellectual disability and deafness. Structural abnormalities of the kidney leading to polyuria include congenital abnormalities such as renal dysplasia, familial juvenile nephronophthisis–medullary cystic disease, and oligomeganephronia, as well as acquired lesions caused by chronic pyelonephritis or obstructive uropathy.

In a systematic review of causes of nephrogenic DI, the most frequently reported risk factors for reversible vasopressin insensitivity were lithium, antibiotics, antifungals, antineoplastic agents, and antivirals. Longer duration of treatment with lithium correlated with increased risk for irreversible DI. Metabolic disturbances can also result in reversible vasopressin resistance. Hypercalcemia and hypokalemia each may be associated with a nephropathy in which tubular ability to conserve water is lost. Certain systemic disorders, such as sickle cell disease, sarcoidosis, and amyloidosis, also may cause renal tubular dysfunction and result in polyuria.

### Excess Water Intake

Polyuria is sometimes a consequence rather than a cause of excessive fluid intake. The ailment has a gradual onset, unlike the more abrupt onset typical of central DI. Primary polydipsia is a rare cause of polyuria in childhood. In primary polydipsia, excess fluid

intake can alter the renal medullary concentration gradient, leading to a relatively hypo-osmolar state. Primary polydipsia is diagnosed after excluding other possible causes of excessive water intake. However, as recently demonstrated in a child who was found to have a mutation in the *AVP* gene, an individual with evolving central DI can have a normal water deprivation test early in the disease course.

The term *psychogenic polydipsia* has been used to characterize excessive water drinking in institutionalized psychiatric patients and is most commonly associated with schizophrenia. Although some investigators believe this disorder is caused by a primary psychiatric disturbance, a study of adult patients with polydipsia and hyponatremia showed evidence of a defect in water excretion, osmoregulation of water intake, and vasopressin secretion. Although typical antipsychotic drugs such as haloperidol have been associated with worsening of polydipsia, clozapine has been reported to significantly reduce excessive water intake in limited studies.

### Osmotic Diuresis

Some patients have polyuria with renal water loss resulting from an osmotic diuresis. Glycosuria is frequently found to be the cause of sudden onset of polyuria in children with uncontrolled DM. In both type 1 and type 2 DM, diminished carbohydrate use results in hyperglycemia and glycosuria. When present in the urine at high concentrations, glucose acts as an osmotic diuretic, resulting in polyuria. Chronic hyperglycemia may also cause a form of partial nephrogenic DI. Osmotic diuresis may also be provoked by mannitol, radiologic contrast agents, or high-protein feedings (in which urea acts as the osmotic agent), or after the relief of bilateral urinary tract obstruction. Treatment with large volumes of dextrose-containing intravenous fluids can also result in hyperglycemia and polyuria. In contrast, renal glycosuria is characterized by a defect in renal tubular reabsorption of glucose, resulting in glycosuria without hyperglycemia or polyuria.

## EVALUATION

A detailed history often reveals the cause of polyuria. Age at onset, pattern of fluid intake, and rate of onset of polyuria are informative. A thorough feeding history can help identify infants who have water intoxication. New onset of nocturia is often the first manifestation of loss of concentrating ability. Young children with DI can have irritability as a result of hypernatremia and dehydration. Family history is important, given that familial forms of both central and nephrogenic DI exist. In most cases of familial nephrogenic DI, severe polyuria occurs within the first weeks of life. Growth failure is a feature common to both nephrogenic and central DI.

A 24-hour measurement of fluid intake and output is helpful to confirm polyuria before ordering laboratory tests. Urine specific gravity on a first-voided morning specimen is helpful but can be affected by the presence of glycosuria, proteinuria, or radicontrast material. Both types of DI and primary polydipsia result in relatively dilute urine. Patients with disorders resulting in renal tubular damage, such as sickle cell

disease, are more likely to have isosthenuria with specific gravities in the neighborhood of 1.010. Urinalysis with microscopy performed on a first-voided morning specimen also provides valuable information. Protein, casts, or formed blood elements in the urine suggest a renal disorder. Glycosuria with ketonuria strongly suggests DM. Other baseline studies include serum electrolytes, glucose, urea, phosphate, creatinine, calcium, osmolality, liver function tests, and complete blood count (Table 182-2).

Urine osmolality is best interpreted with a concomitant serum sample. A hyperosmolar state would suggest vasopressin deficiency or insensitivity, provided that the serum glucose concentration is normal. Low serum osmolality with hyponatremia suggests either primary polydipsia or water intoxication as the most likely diagnosis. Serum sodium level is usually normal in DI as long as free access to fluids exists and the thirst mechanism is intact. Hypernatremia is commonly seen in infants with DI or when a central lesion exists that also impairs thirst. Blood chemistries will detect causes of nephrogenic DI, such as hypercalcemia and renal impairment.

In polyuric children with low urine specific gravity and no glycosuria, the next step in evaluation is referral to a specialist for a formal water deprivation test to determine whether a defect exists in vasopressin production or renal responsiveness. In the case of patients with very low urine osmolality who are strongly suspected of having nephrogenic DI, the response to exogenous ADH can be determined without the need for prior fluid deprivation. Water deprivation testing should be undertaken with great caution in younger children and should not be performed in newborns. Because of the possibility of volume depletion, the study should be carried out during the day when supervision is optimum and should follow a 24-hour period of free access to fluids.

At baseline, the physician should record vital signs and weight and obtain blood and urine for osmolality, urine specific gravity, serum sodium concentration, serum urea nitrogen level, and hematocrit. Blood should also be obtained at the beginning and conclusion of fluid deprivation to determine plasma ADH levels, which may be helpful if the response to the water deprivation test is equivocal. Fluid intake is restricted for up to 8 hours, during which time the patient must be supervised closely to avoid surreptitious drinking. The patient should be weighed and have vital signs recorded every 2 hours for the first 4 hours, then hourly. Blood and urine should be collected after 4 hours, then every 2 hours for osmolality, serum sodium, and urine specific gravity measurements. The test should be terminated when 1 of the following endpoints is reached: (1) the patient has lost 5% or more of body weight, (2) urine specific gravity is greater than 1.020, (3) urine osmolality exceeds 600 mOsm/kg, (4) plasma osmolality exceeds 300 mOsm/kg, or (5) serum sodium exceeds 147 mEq/L. At the conclusion of the test, weight and vital signs should be recorded and blood and urine collected for osmolality, serum sodium, and urine specific gravity.

In healthy children, and in most children with primary polydipsia, the weight remains constant,

**Table 182-2** Interpretation of Baseline Values

CLINICAL SITUATION	SERUM SODIUM (mEq/L)	SERUM OSMOLALITY (mOsm/kg)	URINE OSMOLALITY	PLASMA VASOPRESSIN
Normal	135–145	280–290	50–1200	Normal
Central diabetes insipidus	Normal or elevated	Normal or elevated	<200	Low
Nephrogenic diabetes insipidus	Normal or elevated	Normal or elevated	<300	Normal or elevated
Primary polydipsia	Low normal	Normal or low	<200	Low

Adapted from Saborio P, Tipton G, Chan J. Diabetes insipidus. *Pediatr Rev.* 2000;21:122–129.

the urine specific gravity rises, and the urine volume decreases. Concentrating ability is frequently impaired in primary polydipsia, resulting in a maximal urine osmolality of 500 to 600 mOsm/kg, compared with greater than 800 mOsm/kg in healthy individuals. This difference likely results from a reduction in the osmotic gradient across the distal renal tubule, with reduced renal sensitivity to vasopressin (Table 182-3).

In the setting of continued diuresis, dehydration, weight loss, and hyperosmolality, the physician should suspect a diagnosis of DI. A small rise in urine osmolality may occur in both forms of DI from either partial vasopressin deficiency (central) or partial vasopressin resistance (nephrogenic). Administration of exogenous ADH may help differentiate between the 2 disorders (see Table 182-3). In an older child, the test can be performed after a water deprivation test or at a subsequent visit. Extreme caution is required when performing this test on infants or small children because of the danger of fluid overload and hyponatremia. The patient is given free access to water after administration of desmopressin acetate (DDAVP), a synthetic derivative of vasopressin. Subsequently, intake, output, and urine specific gravity are recorded every 30 to 60 minutes.

In a patient with complete vasopressin deficiency, the urine output will fall, and urine osmolality will increase significantly. Distinguishing between patients with partial central DI and primary polydipsia may be difficult. Individuals with partial DI may have an exaggerated response to the submaximal rise in vasopressin induced by fluid deprivation. Urine may be maximally concentrated when plasma osmolality is greater than 295 mOsm/kg. In this situation, there may be no further response to administration of exogenous ADH, a pattern suggestive of primary polydipsia. Patients who have primary polydipsia will have an increase in urine osmolality but no response to exogenous ADH because endogenous release is intact. Patients with complete nephrogenic DI do not increase urine osmolality in response to exogenous ADH administration. In patients with partial nephrogenic DI, urine osmolality may increase but will still be significantly lower than 300 mOsm/kg. In contrast, patients with partial vasopressin deficiency typically achieve a urine osmolality greater than 300 mOsm/kg after fluid deprivation.

Patients with vasopressin deficiency are best referred to an endocrinologist or neurologist so that the cause of the DI can be determined. A full investigation of other pituitary functions, visual-field examination, and magnetic resonance imaging of the brain will likely be the next steps in evaluation. Patients should be allowed free access to fluids, and their serum and urine osmolality should be monitored closely. When a diagnosis of central DI has been made, studies must be undertaken to ascertain the cause. Although many cases are idiopathic, a thorough evaluation for an underlying organic lesion must be conducted. The tumor markers human chorionic gonadotropin and  $\alpha$ -fetoprotein should be measured, and magnetic resonance imaging of the pituitary and hypothalamus should be performed to assess for pituitary masses, craniopharyngioma, pinealoma, or pituitary stalk abnormalities. Up to 70% of patients with central DI will lose the normal hyperintense signal of the posterior pituitary.

## MANAGEMENT

Management of polyuria depends largely on the underlying diagnosis and must be individualized carefully. In most cases, the results are gratifying, but patients are often found to have a chronic disease that requires close, long-term surveillance.

In a severely ill patient with central DI, aqueous vasopressin (0.1–0.2 U/kg) may be given subcutaneously every 4 to 6 hours. Vasopressin may also be given by continuous intravenous infusion. Reported starting doses vary from 0.5 to 4.6 mU/kg/hr; these doses should be increased or decreased as needed. Vasopressin is a potent vasoconstrictor and may cause tissue ischemia and severe lactic acidosis, particularly at high infusion rates. Once the child's condition has stabilized, management consists of desmopressin acetate, which can be administered orally in tablet form or instilled intranasally and should be given at the lowest dose that produces antidiuretic effect. When given intranasally, the total daily dose may range from 5 mcg in infants to 40 mcg in older children divided into 2 or 3 doses as needed. Children receiving dose multiples of 10 mcg may use the nasal spray; those receiving smaller or intermediate doses must use the rhinal tube. Desmopressin may also be administered effectively and safely orally. Therapeutic doses of oral desmopressin are generally 15 to 20 times larger than intranasal doses, and greater variability exists in the



**Table 182-3** Interpretation of Water Deprivation Test and Vasopressin Administration

CLINICAL SITUATION	PLASMA VASOPRESSIN	URINE OSMOLALITY	URINE SPECIFIC GRAVITY AFTER VASOPRESSIN
Normal	Increased	>800	Increased
Central diabetes insipidus	Low	<300	Increased
Nephrogenic diabetes insipidus	High	<200	Unchanged
Primary polydipsia	Unchanged	500–600	Unchanged or increased

Adapted from Saborio P, Tipton G, Chan J. Diabetes insipidus. *Pediatr Rev.* 2000;21:122–129.

effective dose. Consequently, response to treatment must be monitored closely if changing route of administration.

Treatment of small children and infants with central DI can be difficult, with rapid changes in serum osmolality potentially leading to complications. The parents must carefully monitor fluid intake and output in the younger child. Because young infants are exclusively fed liquids and have high fluid requirements, the addition of vasopressin can greatly increase the risk for severe hyponatremia. These children are best managed with fluid therapy alone. Small doses of desmopressin may be required if adequate fluid intake is difficult to maintain or if caloric intake is inadequate because of excessive fluid consumption. The risk for hyponatremia can be reduced by allowing escape from the antidiuretic effect for 1 hour before the next dose. A child with adipsia or hypodipsia is best managed by fixing the desmopressin dose and fluid intake. Daily weights and frequent sodium levels are useful in assessing fluid status at home.

In patients who have primary polydipsia, after a neurogenic lesion or gene mutation has been ruled out, medical therapy is not indicated. Psychiatric evaluation, however, may be useful in addressing the origin of the polydipsia.

Patients who have structural renal diseases leading to polyuria should be referred to a pediatric nephrologist. Children with nephrogenic DI should be allowed free access to fluids; parents of infants who have this disorder need to offer frequent water feedings to allow their infants to maintain osmotic homeostasis. A low-salt diet has been helpful in reducing urine output; thiazide diuretics can reduce polyuria further by reducing the amount of urine delivered to the distal tubule. Indomethacin and amiloride, when given concurrently with a thiazide, have each been found effective at reducing urine output.

Osmotic diuresis induced by drugs or diet generally is self-limited. In DM, polyuria secondary to hyperglycemia and glycosuria resolves with treatment of the underlying condition.

### WHEN TO REFER

- Hypotonic polyuria (confirmed by 24-hour urine and urine osmolality <300 mOsm). Perform water deprivation test.
- Polyuria after neurosurgery
- Polyuria and polydipsia secondary to DM

### WHEN TO ADMIT

- Polyuria and dehydration
- Diabetic ketoacidosis
- Severe hyponatremia
- Suspected diabetes insipidus in an infant
- Hyponatremia with MRI or neurologic findings suggestive of a brain tumor

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## Chapter 183 PROTEINURIA

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In adults, *proteinuria* is defined as a urinary protein excretion exceeding 150 mg/day. In children, protein excretion exceeding 4 mg/m<sup>2</sup>/hour is considered abnormal. Proteinuria may indicate the presence of renal injury and predict progressive renal disease; in adults, proteinuria is also an established independent risk factor for cardiovascular disease. Large losses of protein through the urine lead to hypercholesterolemia and hypertriglyceridemia, both of which, if sustained for a long time, increase cardiovascular mortality. Medications that reduce proteinuria provide important long-term benefits for adult patients with chronic kidney disease and this beneficial effect has been extrapolated to children.

## PATHOPHYSIOLOGIC FEATURES

Under physiologic conditions, the glomerular filtration barrier, composed of podocytes and vascular endothelium separated by the glomerular basement membrane, limits the passage of macromolecules from blood into urine based on both molecular size and electrical charge. The size barrier for filtration consists of pores with a diameter of approximately 40 Å in the slit diaphragm located between foot processes that is similar or smaller than the size of albumin (69 kDa). In addition, the glomerular capillary wall contains heparan sulfate and proteoglycans, which are negatively charged and thus repel macromolecules with the same electrical charge, such as albumin. Most inflammatory glomerular diseases lead to morphologic alteration of the size barrier and loss of negative charges, leading to proteinuria. Another factor that affects protein movement across glomerular capillary walls is glomerular hemodynamics (ie, glomerular plasma flow rate, hydrostatic and oncotic forces). A reduction in the number of functioning nephrons leads to hyperfiltration in the remaining nephrons and to proteinuria.

Low-molecular-weight proteins, such as  $\beta_2$ -microglobulin, retinol-binding protein, and  $\beta_1$ -microglobulin, are freely filtered through the glomerulus and are subsequently reabsorbed by the proximal tubule. Tubular injury results in impaired ability to reabsorb these proteins and their loss in the urine. Some proteins, such as the Tamm-Horsfall mucoprotein (uromodulin), a major constituent of urinary casts, are formed by the cells of the thick ascending loop of Henle.

## LABORATORY EVALUATION OF PROTEINURIA

The diagnosis of proteinuria depends on laboratory assessment of the level of protein in the urine. The 3 ways urine is tested are the dipstick test, assessment of a timed urine sample, and assessment of the urine protein-creatinine (P/Cr) ratio from an untimed urine sample.

### Dipstick Test

The most commonly performed urine screening method for protein is the dipstick test. Tetrabromophenol on the reagent strip reacts with the amino group of the protein and changes the color of the strip. The test reports findings as negative, trace, and 1+ (30 mg/dL), 2+ (100 mg/dL), 3+ (300 mg/dL), and 4+ (2,000 mg/dL).

The dipstick test primarily detects albumin and is less sensitive to low-molecular-weight proteins and  $\beta$ -globulins. Because the test measures the concentration of protein, false-negative results may occur with highly dilute urine. Conversely, false-positive results may occur with concentrated urine. Generally, a result of 1+ or more in a specimen with a specific gravity of less than 1.015 indicates abnormal protein loss.

The detection of protein depends on pH: extremely alkaline urine may yield a false-positive reading. Other causes of false-positive readings are prolonged immersion of the strip; hematuria, pyuria, or bacteriuria; presence of detergents and contaminating antiseptics, such as chlorhexidine and benzalkonium chloride;

presence of antibiotics, such as penicillins, cephalosporins, sulfonamides, and tolbutamide; or presence of radiographic contrast materials. An alternative office procedure to measure urinary protein is precipitation with sulfosalicylic acid. This measurement is a more accurate estimate of the total urinary proteins, including those of low molecular weight. False-positive results can occur in the previously mentioned conditions.

A positive dipstick result should be confirmed by urinalysis, and urine P/Cr ratio preferably performed on the first urine voided in the morning.

### Timed Urine Sample

The traditional and most accurate way of quantifying urinary protein excretion is to measure protein in a timed sample collected over a 24-hour period. The patient is instructed to void right after waking in the morning. This first urine is discarded, and all subsequent urines are collected. The last urine sample added to the collection should be 24 hours after the first one.

In adults, a protein excretion of less than 150 mg in 24 hours is considered normal. In children, an excretion rate of less than 4 mg/m<sup>2</sup>/hour is considered normal, 4 to 40 mg/m<sup>2</sup>/hour is abnormal, and more than 40 mg/m<sup>2</sup>/hour is considered nephrotic-range proteinuria. The adequacy of the sample can be determined by measuring the creatinine excretion in the sample. Steady-state daily creatinine excretion is 20 mg/kg/day in children from 1 to 12 years of age and 22 to 25 mg/kg in older children, and may be lower in females or children with reduced muscle mass. However, this method is cumbersome, can be impractical in children, and is fraught with error from under- and over-collection.

### Urine Protein-Creatinine Ratio

Measurement of the P/Cr ratio in an untimed (spot) urine sample offers a reliable method for classification of proteinuria. This method is easier than a 24-hour urine collection. Studies in adults and children have shown a strong correlation between untimed urine P/Cr ratio and 24-hour urine collection. A ratio of more than 3.5:1 indicates nephrotic-range proteinuria, and ratios of less than 0.2:1 in patients aged 2 and older and less than 0.5:1 in children aged between 6 and 24 months are considered normal.

## PREVALENCE

Finding proteinuria in a single urine specimen in children and adolescents is relatively common. However, the presence of persistent and not orthostatic proteinuria, also called *fixed proteinuria*, on repeat testing indicates renal disease until proven otherwise. The prevalence of proteinuria, both fixed and orthostatic, is generally between 5% and 15%. Prevalence of orthostatic proteinuria seems to rise with age, peaking in adolescence, with subsequent decline and a nadir in adulthood. For boys, prevalence peaks at age 16 years; for girls, the peak is at 13 years.

## ETIOLOGY

The basic evaluation of proteinuria should address the following issues: pathologic or nonpathological cause; presence or absence of symptoms; amount of protein

loss; presence or absence of associated findings, such as hematuria, hypertension, azotemia; and other urinary or systemic abnormalities.

### Nonpathologic Proteinuria

*Nonpathologic proteinuria* results from the adjustment of the kidney to extraneous physiologic conditions (ie, growth, exercise, fever, systemic illness). The level of proteinuria is generally less than 1 g/day and is not associated with edema.

#### Postural or Orthostatic Proteinuria

*Orthostatic proteinuria* accounts for 60% of all cases of asymptomatic proteinuria in children, with a higher incidence in adolescents. Children with this condition have normal urinary protein excretion in the supine position but spill abnormal amounts of protein in the upright position. The proteinuria decreases to normal range or disappears when they have been recumbent for a few hours, as in overnight sleep. These children are asymptomatic; proteinuria is usually found on a routine urinalysis. The cause of orthostatic proteinuria is unknown. It has been postulated that orthostatic proteinuria might result from higher than normal release of norepinephrine and angiotensin II upon standing, or transient compression of the left renal vein in the fork between the superior mesenteric artery and the aorta (renal nutcracker). Edema, hypertension, and hematuria are absent, and creatinine clearance and complements are normal. Renal ultrasound and histopathologic tests are also normal, although these tests are not usually performed in the evaluation process.

Children with asymptomatic proteinuria should be assessed for postural (orthostatic) proteinuria. The standard method is to collect a first-morning urine and if it is negative for protein on the dipstick, or if the measured P/Cr ratio is less than 0.2:1, the patient has orthostatic proteinuria. The more formal (although not currently used) orthostatic test for postural proteinuria includes 2 separate collections, one in the supine position and the other in the upright position. At bedtime, the child goes to bed immediately after voiding (the urine is discarded). The child is then allowed to sleep. All urine passed during the night, including the first specimen voided the next morning, is collected in a jar (specimen 1), and the time of the first-morning voiding is recorded. Then the child goes about daily activities but collects all urine in a second jar (specimen 2) for approximately the next 12 hours. This collection is the upright collection, which ends at bedtime, when the time is again recorded. In patients with orthostatic proteinuria, the sample obtained in the supine position will be free of protein or will contain a normal amount of protein; however, the sample obtained in upright position will contain an abnormal amount of protein. Children with orthostatic proteinuria generally excrete less than 1 g of protein in 24 hours.

The diagnosis of postural proteinuria can also be made by assessing the first-morning urine. If this sample has no protein, or if it has a P/Cr ratio less than 0.2:1, then a presumptive diagnosis of orthostatic

proteinuria can be made. Long-term follow-up studies in adults have documented the benign nature of orthostatic proteinuria, although rare cases of glomerulosclerosis have been identified later in life in patients who were initially found to have proteinuria with an orthostatic component. Therefore, long-term follow-up of children is necessary unless the proteinuria resolves. Signs to anticipate include appearance of hematuria, hypertension, increase in serum creatinine concentration, or proteinuria exceeding 1 g/day.

#### Transient Proteinuria

As many as 30% to 50% of children with proteinuria may have *transient, nonfixed proteinuria*. It can accompany fever, exercise, stress, dehydration, congestive heart failure, or seizures. Transient proteinuria may be found in children having a temperature of 38.3°C or higher. It usually does not exceed 2+ on the dipstick test and resolves when the fever abates.

Proteinuria associated with vigorous exercise rarely exceeds 2+ on the dipstick test. Transient proteinuria seems to be related to intensity of exercise rather than duration. It may be explained by an increased glomerular filtration barrier permeability and a partial inhibition of tubular reabsorption of protein. The effect of exercise increases with age. Transient proteinuria is considered benign if proteinuria resolves after 48 hours of rest.

### Pathologic Proteinuria

#### Persistent or Fixed Asymptomatic Proteinuria

Patients with a positive dipstick test (1+ or greater) should undergo a more accurate test, such as P/Cr ratio or a quantitative measurement of protein excretion. Orthostatic proteinuria should be excluded by repeat measurements on a first-morning void if the initial sample was taken at random. In the absence of other abnormalities, patients with 2 or more positive semiquantitative or quantitative tests, 1 to 2 weeks apart, are diagnosed as having fixed proteinuria. The prevalence in school-aged children may be as high as 6%. Various causes are listed in Table 183-1.

*Pathologic proteinuria* can be classified as either glomerular or tubular. Glomerular proteinuria, which is the more common of the 2 forms, is associated with increased permeability of glomerular filtration barrier. Glomerular proteinuria may be selective (plasma proteins with molecular weights up to and including albumin), as in minimal change disease, or nonselective (albumin and large-molecular-weight proteins, such as immunoglobulin G), as in most forms of glomerulonephritis. *Tubular proteinuria* results from decreased tubular protein reabsorption that results from tubular dysfunction (see Table 183-1).

#### Symptomatic Proteinuria

Symptomatic proteinuria associated with gravity-dependent edema, hypoalbuminemia, and hyperlipidemia is defined as a nephrotic syndrome. However, some children with nephrotic-range proteinuria and hypoalbuminemia remain completely asymptomatic. Edema in nephrotic syndrome results from multiple factors acting in concert, including increased distal nephron sodium reabsorption, increased capillary

**Table 183-1**      **Classification of Pathologic Proteinuria**

<b>GLOMERULAR</b>	<b>TUBULAR</b>
<b>NEPHROTIC SYNDROME</b> Idiopathic Minimal change Mesangial proliferation Focal segmental glomerulosclerosis Membranous nephropathy  <b>GLOMERULONEPHRITIS</b> Postinfectious Immunoglobulin A nephropathy Membranoproliferative glomerulonephritis <b>SYSTEMIC DISEASE</b> <b>SYSTEMIC LUPUS ERYTHEMATOSUS</b> <b>VASCULITIS</b> <b>TUMOR</b> <b>SUBACUTE BACTERIAL ENDOCARDITIS</b> <b>INFECTION (HIV, HEPATITIS)</b> <b>DRUGS OR TOXINS</b> <b>OBESITY</b> <b>OTHER</b>	<b>GENETIC</b> Polycystic kidney disease Cystinosis Wilson disease Lowe syndrome Galactosemia Renal tubular acidosis Dent disease  <b>ACQUIRED</b> Interstitial nephritis Acute tubular necrosis Heavy metal poisoning Drugs or toxins

permeability, and low plasma oncotic pressure associated with hypoalbuminemic states.

Proteinuria may be associated with other abnormalities, including hematuria, hypertension, and azotemia, as seen in glomerulonephritis. Patients with a combination of nephritis and nephrotic syndrome pose a clinical challenge even to the most experienced nephrologist.

## EVALUATION

### History

The first step in evaluating a child with proteinuria is obtaining a thorough history. History should include questions about recent illnesses, fever, rash, and arthralgias; change in urine output and color; symptoms of chronic disease (eg, weight loss, fatigue); and duration and severity of symptoms. History of urinary tract infections and family history of urinary reflux, hypertension, and deafness are important.

### Physical Examination

Physical examination should include measurements of growth parameters, blood pressure, and identification of edema, ascites, and pallor, as well as documentation of the presence or absence of any joint or skin lesions.

### Laboratory Evaluation

The presence of proteinuria should be confirmed by a urine P/Cr ratio on a first-morning urine sample. Once confirmed, fixed proteinuria should be quantified by a 24-hour urine collection for measurement of protein and creatinine (to determine adequacy of the sample). Serum electrolytes, blood urea nitrogen, and creatinine help determine the level of kidney function. Serum albumin, cholesterol, and triglycerides guide

the determination of the severity of metabolic changes that occur as a result of urine protein loss. Complement levels, anti-streptolysin O titers, hepatitis serologic testing, and HIV testing may be indicated based on the child's history. Renal ultrasound may be performed to assess for structural abnormalities. The patient should be referred to a pediatric nephrologist if any abnormalities are found during the initial workup. Some of the other warning signs of proteinuria are listed in Box 183-1.

The steps in evaluating proteinuria are illustrated in Figure 183-1.

Asymptomatic children with proteinuria should be tested to determine its etiology.

Assessment of total protein is appropriate in children to identify both albuminuria and low-molecular-weight proteinuria. Patients with a positive dipstick test of 1+ or greater should undergo confirmation by assessment of the P/Cr ratio within 3 months. Under most circumstances, first-morning spot urine protein and creatinine samples should be used to detect and monitor proteinuria in children.

Orthostatic proteinuria must be excluded by measuring P/Cr ratio in a first-morning urine sample. Patients with 2 or more positive first-morning P/Cr tests, obtained at 1- to 2-week intervals, should be diagnosed as having persistent or fixed proteinuria. Monitoring proteinuria in patients with chronic kidney disease should be performed by quantitative methods.

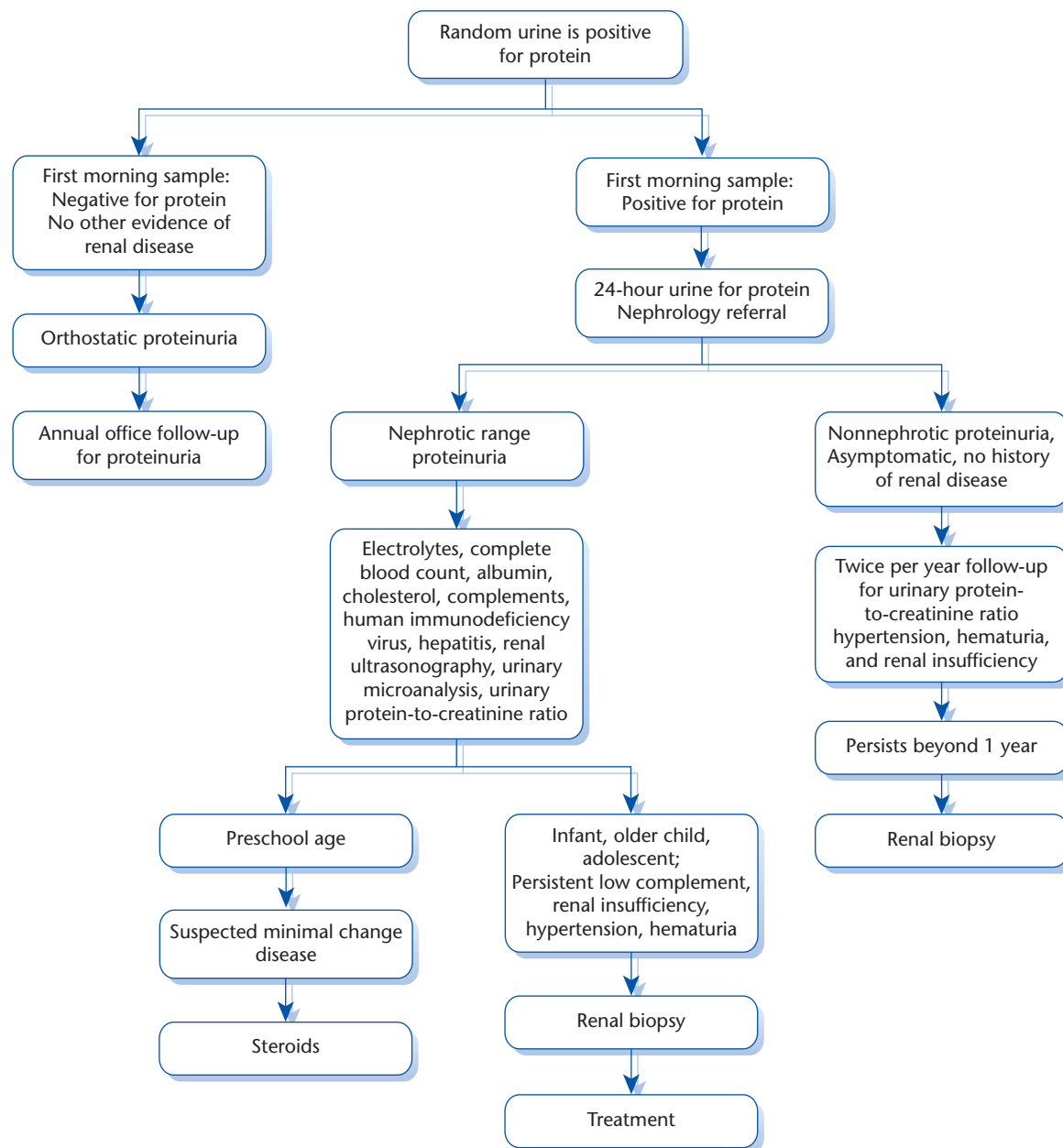
## MANAGEMENT

If orthostatic proteinuria is diagnosed, the child should be monitored with annual office visits and check of first-morning urine P/Cr ratio. Renal biopsy should be considered in certain situations with persistent proteinuria (see Box 183-2).



**BOX 183-1 Warning Signs of Proteinuria**

- Persistent, fixed, nonorthostatic proteinuria
- Proteinuria associated with other urinary abnormalities, such as hematuria, or urinary casts
- Proteinuria associated with renal insufficiency, anemia, or hypertension
- Family history of renal disease, kidney stones, dialysis, deafness, or autoimmune conditions
- Proteinuria associated with comorbidities such as prematurity, congenital anomalies of other organ systems, hypertension, diabetes, and obesity

**Figure 183-1** Diagnostic approach in a patient with proteinuria.

**BOX 183-2 Indications for Renal Biopsy in Persistent Proteinuria**

- Fixed, asymptomatic, isolated proteinuria >1 g/day
- Persistent hematuria and cellular casts
- Renal insufficiency
- Persistently low complement levels
- Hypertension
- Systemic symptoms such as recurrent rashes, joint pains, or fever
- Systemic lupus erythematosus
- Family history of kidney disease or autoimmune disease
- Corticosteroid-resistant nephrotic syndrome

If isolated fixed proteinuria less than 1 g/day is detected (urine P/Cr ratio), restrictions on the child's lifestyle and physical activity are not necessary. Children with proteinuria should receive the recommended daily allowance of protein for their age.

**WHEN TO REFER**

- Persistent, fixed, nonorthostatic proteinuria
- Proteinuria associated with other urinary abnormalities, such as hematuria
- Proteinuria associated with renal insufficiency, anemia, or hypertension
- Family history of renal disease, deafness, or autoimmune condition
- Proteinuria associated with comorbidities such as prematurity, congenital anomalies of other organ systems, hypertension, diabetes, and obesity

**WHEN TO ADMIT**

- Anasarca resistant to outpatient management
- Proteinuria associated with significant renal insufficiency
- Proteinuria associated with significant hypertension

**TOOLS FOR PRACTICE****Engaging Patient and Family**

- *Proteinuria* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/genitourinary-tract/Pages/Proteinuria.aspx](http://www.healthychildren.org/English/health-issues/conditions/genitourinary-tract/Pages/Proteinuria.aspx))
- *Proteinuria* (fact sheet), National Kidney and Urologic Diseases Information Clearinghouse, National Institute of Diabetes and Digestive and Kidney Diseases, and National Institutes of Health ([kidney.niddk.nih.gov/KUDiseases/pubs/proteinuria/index.aspx](http://kidney.niddk.nih.gov/KUDiseases/pubs/proteinuria/index.aspx))

**Medical Decision Support**

- *Pathologic Proteinuria Calculator* (interactive tool), ([www.metrohealthresearch.org/schelling](http://www.metrohealthresearch.org/schelling))

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**Chapter 184  
PRURITUS**

Nancy K. Barnett, MD

Pruritus, or itch, is the subjective perception of a cutaneous disturbance that is relieved by scratching or rubbing. It is usually not brought to the primary care physician's attention unless it is generalized, chronic, or associated with an eruption. In such instances, however, pruritus must be treated with great respect because severe itching can be incapacitating. In addition, scratching or rubbing the itch can produce extensive disfigurement in the form of linear excoriations or lichenified plaques and can predispose the patient to cutaneous infections. Constant scratching can even cause social isolation because, at times, people view the child with pruritus as being contagious or unclean.

**DEFINITION OF TERMS**

Because itch is a subjective sensation, objective evaluation to delineate its pathophysiologic characteristics has been difficult. However, current thinking implicates nonspecific itch receptors. Thought to be free, fine nerve endings at the dermoepidermal junction, these receptors transmit the pruritic sensation along dedicated, slow-conduction velocity, unmyelinated C fibers. The exact mediators and their release triggers are unknown. Mast cell histamine has elicited itch fairly consistently in experimental settings and appears to be active in human disease, as may be other local mediators such as substance P and interleukin. Other experimental triggers that have produced itch are physical pressure, heat, and electric shock. Researchers believe that the nerve impulses from the intraepithelial histamine-sensitive, unmyelinated C fibers ascend to the lamina I in the dorsal

horn of the spinal cord and travel along the contralateral spinothalamic tract to the thalamus. They are then transferred to multiple areas of the cortex and are interpreted as itch. A subsequent desire to scratch arises in the cortex. The dorsolateral prefrontal cortex and contralateral caudate nucleus and putamen areas in atopic patients and the anterior cingulate cortex have been identified as activated when histamine-induced itch and scratch are traced. In contrast, the primary motor and sensorimotor cortices and superior parietal lobe are activated in healthy controls. Itch is not a mild form of pain; the pathways are different, and aspirin alone does not relieve itch.

Certain circumstances alter the interpretation of the degree of pruritus. For example, the itch threshold in and around areas of active dermatitis can be lowered by psychic stress, decreased skin hydration, or increased skin temperature, and during the night. Pain can inhibit the itch sensation, and scratching can stimulate pain receptors.

## DIFFERENTIAL DIAGNOSIS

In children, local cutaneous disease rather than systemic disease is by far the most common cause of generalized pruritus. Pruritogenic itch arising in the skin is the focus of this chapter, and discussing neuropathic, neurogenic, and psychogenic itch is beyond the scope. The major differential diagnoses of generalized pruritus with skin lesions in children are infestation (scabies, pediculosis, insect bites, and papular urticaria), atopic dermatitis, miliaria, contact dermatitis, and acute or chronic urticaria.

Children may also itch with cutaneous diseases such as psoriasis, lichen planus, and linear immunoglobulin A bullous disease of childhood. These children should be referred to a dermatologist for evaluation and management, as should a child with pruritus who is otherwise healthy and does not have bites, eczema, heat rash, contact dermatitis, or hives. The child who has pruritus, from whatever cause, is at risk for psychological damage, infection secondary to impetiginization, and scarification.

Systemic causes of itch in the child who has pruritus but no skin lesions are hyperthyroidism and hypothyroidism, leukemia or lymphoma, chronic renal failure, obstructive biliary disease, and xerosis (generalized dry skin).

## EVALUATION AND MANAGEMENT

Most of the common cutaneous diseases associated with generalized pruritus can be diagnosed based on a thorough history and physical examination. The answers to the following questions may help diagnose infestation of one sort or another and direct therapy toward topical steroids, long clothes, and repellents:

Are any individual pruritic papules found with a central punctum?

If so, are they on exposed or nonexposed areas?

Does anyone else in the family have similar lesions? A family history of allergy, asthma, or eczema

in a child who has a chronic eczematous dermatitis over extensor surfaces in infancy and flexural areas in childhood suggests atopic dermatitis. Hydration and emollients will reduce the pruritus and should be the mainstay of therapy, although mid- and low-potency topical steroids for inflammation, antibiotics for secondary infection, and cool compresses may also be required to bring the scratch-itch cycle under control. Short courses (<8 weeks) of topical immunomodulators such as tacrolimus and pimecrolimus may be helpful in relieving atopic itch on facial skin and thin areas such as the axillae, but these medications should not be prescribed as chronic therapy. A tolerable (nonsoporific) dose of an antihistamine may relieve itch and should be given about 1 hour before bedtime because the itch threshold is lower at night than it is during the daytime. Hydroxyzine seems to be the most effective agent. Data conflict about the use of nonsedating antihistamines for controlling itch. Pinpoint crystalline or erythematous papules in areas of occlusion and sweating—that is, miliaria crystallina and miliaria rubra (heat rash)—can be controlled by simple measures such as applying dusting powders, avoiding tight clothing, and reducing exposure to high ambient temperatures.

In most instances, contact dermatitis is readily recognizable because of a linear array of papulovesicular erythematous lesions and sharp borders that conform to the shape of the contactant.

Acute urticaria, usually from exposure to a drug or other ingestant, produces intensely pruritic, erythematous, and edematous plaques and papules. Thorough historical and environmental sleuthing may reveal the cause of a contact allergic or contact irritant dermatitis, but the cause of 90% of acute urticaria cases remains a mystery. If the patient has not used any new drug or food, and if the hives persist despite regular use of antihistamines for several days, then a reasonable course of action would be to obtain a throat culture and a complete blood count with differential and to screen for mycoplasmal disease and infectious mononucleosis to rule out occult streptococcal, mycoplasmal, and viral infections. On rare occasions, a skin biopsy may be helpful. Physical urticarias should demonstrate dermatographism, which can be a helpful diagnostic tool.

For the child who has pruritus with no primary skin disorder, a complete blood count with differential count, complete chemistry panel, thyroid function tests (thyroid-stimulating hormone/free T<sub>4</sub>), urinalysis, and chest radiograph should be obtained to assess for possible systemic causes, especially before suggesting a psychogenic cause for the itching.

To relieve itching and prevent scarring (both mental and physical), the scratch-itch cycle must be broken. Itching provokes scratching, and when the scratching stops, the itching returns. To control itching, the following steps can be helpful:

- Keep the patient's fingernails short to prevent damage from scratching.
- Keep the child fully clothed except when applying medications.

- Apply bland emollient creams frequently, especially after bathing. Overwashing, especially without sealing in the water with an occlusive cream, may dry out the skin and worsen itch. A home humidifier may increase the relative humidity in the air and lessen dry skin itch.
- Apply cool compresses to relieve intense pruritus and to remove crusts and debris.
- Apply topical steroids for short periods (generally <2 weeks) to control inflammation.
- Increase the dose of antihistamine until the scratching stops or marked drowsiness occurs, and then reduce the dose to a level that controls the scratching but does not cause drowsiness.
- Advise the family to avoid stress, heat, and irritants (eg, wool, pet danders).
- See the patient frequently to provide support.
- If the child is old enough to understand, explain why these methods are being used.

Topical capsaicin, menthol, phenol, doxepin, and pramoxine may be indicated for localized use in some cases, but the potential for contact irritation and systemic absorption limits their prolonged or widespread use. Referral to the dermatologist is generally indicated in such a circumstance. Ultraviolet B light therapy may be helpful for generalized pruritus such as occurs in biliary cirrhosis or severe chronic atopic dermatitis. Chronic localized and intractable itch may respond to neurologic “sensor resetting,” in which the brain is fooled into believing the affected area is normal by mirror treatment, because we have come to understand that the sensation of itch results more from central perception than local reception.

### WHEN TO REFER

- Pruritus with uncommon disease (eg, psoriasis, bullae)
- Chronic pruritus without cutaneous disease to evaluate for systemic cause
- Pruritus uncontrolled by usual topical steroids and antihistamines

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *What Is a Pediatric Dermatologist?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Dermatologist.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Dermatologist.aspx))

#### Medical Decision Support

- *Pediatric Dermatology: A Quick Reference Guide* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Dermatology Course Series—Skin Infections* (online course), American Academy of Pediatrics ([pedialink.aap.org](http://pedialink.aap.org))

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### Chapter 185

## PUBERTY: NORMAL AND ABNORMAL

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Disorders of pubertal development constitute one of the most frequent referrals to pediatric endocrinology clinics. In many cases, no endocrine problem is found. A referral may be avoided by a careful evaluation, including family history, and a few simple laboratory procedures. The availability of pediatric endocrinology consultation and the pediatrician or other physician's level of comfort in diagnosing and treating disorders of puberty heavily influence the decision to refer.

### NORMAL PUBERTY

During puberty, a series of complex hormonal changes takes place. The hypothalamus secretes pulses of gonadotropin-releasing hormone (GnRH), which stimulates pituitary gonadotropin production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Concomitantly, the previously very sensitive hypothalamic-pituitary-gonadal feedback loop becomes less sensitive to the negative effect of gonadal steroids. As a result, gonadotropin levels rise, stimulating the secretion of greater amounts of sex steroids, either testosterone or estradiol, depending on the gender of the child, leading to the physical changes of puberty. This process is called *gonadarche*. The hypothalamic-pituitary-gonadal axis is active during fetal life and infancy until it enters an inactive state during the prepubertal years. Genetic factors determine 50% to 80% of the variation in pubertal timing. Environmental influences also play a role, particularly nutritional status. It has also been suggested that environmental chemicals capable of disrupting endocrine activity may affect pubertal timing. Leptin, which is secreted by adipocytes and regulates appetite and metabolism through the hypothalamus, is thought to play a permissive role in regulating the timing of puberty. Adrenarche is a separate process that refers to an increase in the secretion of adrenal androgens during puberty and is associated with the development of pubic hair, axillary hair, body odor, and acne. The mechanism that triggers the maturation of the adrenal cortex at puberty remains poorly understood.

In most girls, puberty begins between 8 and 13 years of age, with breast development (thelarche) usually the first sign. Menarche follows the onset of breast development by approximately 2 years. A growth spurt accompanies the changes, usually peaking before menarche. The range of normal variation, however, is quite wide, and differences have been reported between ethnic groups. A secular trend toward earlier puberty has taken place: the most recent data from the National Health and Nutrition Examination Survey (NHANES) 1992–2002 show a decline in the overall average age at menarche to 12.34 years (12.06 years, 12.52 years, and 12.09 years in non-Hispanic black



girls, non-Hispanic white girls, and Mexican American girls, respectively). Although an association exists between earlier sexual maturation in girls and increasing levels of adiposity, it remains unclear from existing data whether this relationship is causal. The average age at menarche declined by 2.3 months between NHANES III (1988–1994) and NHANES 1999–2002. Significantly, NHANES 1999–2002 had more girls with body mass index greater than the 85th or 95th percentile and had a different racial and ethnic composition. Although the overall age at menarche decreased, the changes within racial and ethnic groups was much smaller, indicating that the overall decrease in age at menarche may be because of changes in the population distribution of race and ethnicity and relative weight.

The mean ages for onset of breast development according to NHANES III data were 10.25, 11.05, and 10.70 years in non-Hispanic black girls, non-Hispanic white girls, and Mexican American girls, respectively. Similarly, the mean ages for onset of sexual hair in girls were 10.25, 10.96, and 11.17 years. A recent multicenter study suggests that there continues to be a modest decrease in mean age of breast development, especially in black and Hispanic girls.

In most boys, puberty begins between 9 and 14 years of age. Testicular enlargement is usually the first sign of puberty. NHANES III data found the mean ages of genital development in boys to be 10.79, 11.08, and 11.09 years for non-Hispanic black boys, non-Hispanic white boys, and Mexican American boys, respectively. Similarly, the mean ages for onset of sexual hair were 11.48, 11.81, and 12.20 years. Peak height velocity for boys is typically 2 years later than it is for girls and usually occurs during mid to late puberty (see Table 185-1 for summary of pubertal milestones by age).

The time of puberty is one of profound change, both physical and psychological. Problems of sexual identity, body image, adolescent independence, and peer acceptance are frequent. Because the ranges of age of normal puberty are wide, children of similar chronologic age may have markedly different physical maturity. When pubertal development is precocious or delayed, many of these problems are compounded.

## GYNECOMASTIA

Pubertal gynecomastia occurs in approximately 40% of healthy boys and usually resolves within 2 years. Clinical presentation may include breast tenderness and asymmetry. The mean age of occurrence is between 14 and 15.5 years and usually occurs after Tanner stage 3. Pubertal gynecomastia is thought to result from an increase in the ratio of estrogen to androgen. Treatment in most cases is reassurance; however, gynecomastia that does not resolve after 2 years or that develops rapidly may require a referral. Initial screening blood work includes levels of testosterone, estradiol, LH, FSH, prolactin, and a  $\beta$ -human chorionic gonadotropin as well as liver function tests. Medical therapy with clomiphene (antiestrogen), tamoxifen (estrogen antagonist), testolactone (peripheral aromatase inhibitor), and danazol (synthetic derivative of testosterone) has been reported to be successful; however, no randomized controlled trials have been conducted. Surgical intervention remains the mainstay of treatment. Whereas most pubertal gynecomastia is benign, pathologic causes include Klinefelter syndrome, partial androgen insensitivity syndrome, hyperprolactinemia, liver disorders, adrenal carcinoma, biosynthetic defects in testosterone production, androgen receptor defects, increased activity of peripheral aromatase, and certain drugs. Drugs that have an estrogen-like effect (diethylstilbestrol, oral contraceptive pills, digitalis, estrogen-containing cosmetics), that increase estrogen formation (gonadotropins, clomiphene), or that inhibit testosterone action (ketoconazole, spironolactone, cimetidine, isoniazid, methyldopa, captopril, tricyclic antidepressants, diazepam, marijuana, phenothiazines) have been associated with gynecomastia.

## DELAYED PUBERTY

Few matters are of greater concern to the adolescent than remaining short in stature or sexually underdeveloped. Delayed development demands the immediate attention of the physician.

Puberty is considered delayed in girls who have no breast development by 13 years of age or in boys who have no testicular enlargement by 14 years of age. In

**Table 185-1** Onset of Pubertal Milestones (Years)<sup>a,b</sup>

	NON-HISPANIC WHITES	NON-HISPANIC BLACKS	MEXICAN AMERICANS
<b>GIRLS</b>			
Thelarche	11.05 (9.7) <sup>c</sup>	10.25 (8.8) <sup>c</sup>	10.7 (9.3) <sup>c</sup>
Sexual hair development	10.96	10.25	11.17
Menarche	12.52	12.06	12.09
<b>BOYS</b>			
Testicular enlargement	11.08	10.79	11.09
Sexual hair development	11.81	11.48	12.20

<sup>a</sup>Note: All ages are expressed as means.

<sup>b</sup>From National Health and Nutrition Examination Survey III (1988–1994) and National Health and Nutrition Examination Survey (1999–2002).

<sup>c</sup>Biro FM, Greenspan LC, Galvez MP, et al. Onset of breast development in a longitudinal cohort. *Pediatrics*. 2013;132:1019–1027

girls, a delay of longer than 4 to 5 years from onset of puberty to menarche is also cause for concern. Similarly, maturation arrest in boys warrants evaluation.

Constitutional delay, a slow maturation with appropriate hormonal levels and delayed bone age, accounts for most cases of delayed pubertal development. This problem is identified more frequently in boys than in girls, perhaps because of general societal and peer group reaction to short and sexually underdeveloped boys. The delay is frequently familial. In many instances, early signs of puberty are found on thorough examination, which permits the physician to reassure the child and the parents. Affected children should be followed closely. The presence of chronic systemic diseases that can lead to delayed puberty may be difficult to differentiate from constitutional delay as a cause for the delay.

The remainder of the differential diagnosis of delayed development relates to failure at either the hypothalamic-pituitary level, shown by low serum gonadotropins (hypogonadotropic hypogonadism), or

the gonadal level, shown by elevated gonadotropins (hypergonadotropic hypogonadism). Either of these conditions may result from genetic disorders or acquired illnesses (see Box 185-1). The workup of the patient is directed toward identifying the specific cause. Common initial screening tests are shown in Box 185-2 and include a thorough history, physical examination, and assessment of growth velocity. A bone age assessment is often helpful. For delayed development to be the result of an undiagnosed systemic illness is relatively uncommon, but if the history or physical examination suggests a systemic illness, then specific screening may include a complete blood count, electrolytes, renal and liver function tests, erythrocyte sedimentation rate and C-reactive protein, inflammatory bowel disease panel, and celiac disease panel. A screen for endocrinopathies should include thyroid-stimulating hormone and thyroid hormone levels, gonadotropins (LH, FSH), testosterone, estradiol, and insulin-like growth factor I. Other tests that a specialist may order include insulin-like growth

### BOX 185-1 Causes of Delayed Puberty

1. Constitutional delay
2. Deficiency of gonadotropin-releasing hormone secretion by the hypothalamus
  - a. Genetic and molecular causes
    - i. Isolated deficiency
    - ii. Kallmann syndrome
    - iii. Laurence-Moon-Bardet-Biedl syndrome
    - iv. Prader-Willi syndrome
  - b. Acquired causes
    - i. Infection
    - ii. Neoplasm
    - iii. Infiltrative disease
    - iv. Trauma
3. Deficiency of gonadotropin secretion by the pituitary
  - a. Genetic
    - i. Panhypopituitarism (including transcription factor mutations in *PROT1*, *HESX1*, and *LHX3*)
    - ii. Isolated deficiency
    - iii. Fertile eunuch (normal follicle-stimulating hormone, low luteinizing hormone)
    - iv. Leptin or leptin-receptor deficiency
  - b. Acquired
    - i. Infection
    - ii. Tumor
    - iii. Excess prolactin secretion, adenoma
    - iv. Trauma
4. Gonadal disorders
  - a. Genetic and molecular
    - i. Turner syndrome (45,X or structural X abnormalities or mosaicism)
    - ii. Klinefelter syndrome (47,XXY)
    - iii. Noonan syndrome
  - iv. Syndromes of complete androgen insensitivity (no sexual hair)
  - v. del Castillo syndrome (Sertoli cells only)
  - vi. Pure gonadal dysgenesis
  - vii. Myotonic dystrophy
  - viii. Receptor mutations
  - b. Acquired
    - i. Infections
      - (1) Gonorrhea (male)
      - (2) Virus (mumps, coxsackie)
      - (3) Tuberculosis (male)
    - ii. After radiation or chemotherapy
    - iii. Mechanical causes
      - (1) Torsion
      - (2) Surgery
      - (3) Congenital anorchia (vanishing testes syndrome)
      - (4) Autoimmune
5. Adrenal and gonadal steroid enzyme deficiencies
6. Excessive exercise, malnutrition
7. Chronic systemic diseases
  - a. Congenital heart disease
  - b. Chronic pulmonary disease
  - c. Inflammatory bowel disease, celiac disease
  - d. Chronic renal failure and renal tubular acidosis
  - e. Hypothyroidism
  - f. Poorly controlled diabetes mellitus
  - g. Sickle cell anemia, thalassemia
  - h. Collagen-vascular disease
  - i. Anorexia nervosa
  - j. HIV infection

factor-binding protein 3, prolactin, karyotype, brain magnetic resonance imaging (MRI), pelvic ultrasound, and GnRH testing assessing for signs of central puberty.

Treatment should be directed toward the cause of the delayed development. If sex steroid secretion is deficient as a result of either gonadal failure or gonadotropin deficiency, then treatment focuses on replacing the appropriate sex steroid. In constitutional delay, waiting may be the best course. In boys, however, a short course of low-dose injectable testosterone (eg, 50–100 mg monthly for 4 doses) may be indicated if the delayed development is affecting the boy's psychological well-being. In girls, cosmetic treatment, such as the use of a padded bra, is helpful. Estrogen therapy is necessary only occasionally. In patients who have GnRH or gonadotropin deficiency, fertility may be induced with GnRH or gonadotropin therapy. In any case, strong psychological support must be provided to the adolescent and sometimes to the family. If the problem is difficult diagnostically, or if hormonal therapy is desired, then referral should be made to a pediatric endocrinologist.

## PRECOCIOUS PUBERTY

Classically, precocious puberty is the appearance of secondary sexual characteristics before 8 years of age

in girls and 9 years in boys. But a substantial number of girls, 27.2% of black girls and 6.7% of white girls, have breast or sexual hair development by 7 years of age. As a result of these data, the Drug and Therapeutics and Executive Committees of the Pediatric Endocrine Society published recommendations proposing that the age cutoff for precocious puberty should be decreased to 7 years in white girls and 6 years in black girls unless the tempo of puberty is abnormal, the bone age is advanced more than 2 years, the predicted height is less than 150 cm (59 inches), focal neurologic deficits are present, headaches are present, or the family's or the child's emotional state is affected adversely. These recommendations are controversial, and although extensive evaluation in 6- to 8-year-old girls is usually not revealing of pathologic abnormality, each child must be considered individually.

Early stimulation of the hypothalamic-pituitary axis, with resultant gonadotropin secretion and sex steroid secretion, is termed *central precocious puberty*. Sex steroid secretion that is independent of pituitary gonadotropin secretion may be termed *peripheral* or *pseudoprecocious puberty*. Box 185-3 lists the causes of these 2 conditions. Precocity may be isosexual (appropriate for phenotype) or heterosexual (appropriate for opposite gender phenotype) and is significantly more common in girls than it is in boys. Box 185-4 lists the causes of heterosexual precocious puberty. In girls, idiopathic precocious puberty is the single most common diagnosis and accounts for 85% of central precocious puberty, whereas 60% of precocious puberty in boys has a pathologic cause. Girls adopted from developing countries may be at particular risk

### BOX 185-2 Evaluation for Delayed Puberty

#### INITIAL SCREENING TESTS (AS INDICATED)

- Thorough history, physical examination, and calculation of growth velocity
  - Bone age
  - Luteinizing hormone, follicle-stimulating hormone
  - Testosterone or estrogen, depending on gender
  - Thyroid-stimulating hormone, thyroid hormone
- If systemic disease is thought to exist*
- Complete blood count
  - Erythrocyte sedimentation rate, C-reactive protein
  - Comprehensive panel (electrolytes; renal and liver function tests)
  - Insulin-like growth factor I, insulin-like growth factor-binding protein 3
  - Urinalysis
  - Celiac disease panel (antiendomysial immunoglobulin A [IgA] antibody or tissue transglutaminase IgA and total IgA levels)
  - Inflammatory bowel disease panel
  - Prolactin

#### OTHER TESTS (IF INDICATED)

- Karyotype
- Brain magnetic resonance imaging
- Pelvic ultrasound
- Gonadotropin-releasing hormone (GnRH) or GnRH analog stimulation test

### BOX 185-3 Causes of Isosexual Precocious Puberty

1. Central (with pituitary gonadotropin secretion)
  - a. Idiopathic
  - b. Central nervous system abnormalities
    - i. Congenital anomalies (hydrocephalus)
    - ii. Tumors (hypothalamic, pineal, other)
    - iii. Hamartoma
    - iv. Postinflammatory condition
    - v. Trauma
    - vi. Syndromes
      - (1) Neurofibromatosis
      - (2) Tuberous sclerosis
  - c. Hypothyroidism (severe)
2. Peripheral
  - a. Exogenous sex steroids
  - b. Gonadal tumors or cysts
  - c. Adrenal hyperplasia or tumor
  - d. Ectopic gonadotropin-secreting tumors (chorioepithelioma, hepatoblastoma, teratoma)
  - e. Familial Leydig cell hyperplasia, receptor mutation
  - f. McCune-Albright syndrome, G-protein mutation

### BOX 185-4 Causes of Heterosexual Precocious Puberty

1. Girls
  - a. Congenital adrenal hyperplasia
  - b. Androgen-secreting tumors
    - i. Adrenal
    - ii. Ovarian
    - iii. Teratoma
  - c. Exogenous androgens
2. Boys
  - a. Estrogen-producing tumors
    - i. Adrenal
    - ii. Teratoma
    - iii. Hepatoma
    - iv. Testicular
  - b. Exogenous estrogens
  - c. Increased peripheral conversion of androgens to estrogens

for precocious puberty. Internationally adopted girls have shown a trend toward early and rapidly progressing puberty that may be related to the increased metabolic activity exhibited if catch-up growth occurs after adoption. Precocious puberty can significantly reduce adult height and can, in some cases, have an adverse effect on a child's and a family's emotional state.

### VARIATIONS OF PUBERTY

Two entities not requiring treatment are isolated premature breast development (thelarche) and isolated premature development of sexual hair (adrenarche). Premature thelarche occurs in girls between 6 months and 3 years of age. Breast development is usually moderate, often regresses, and is seen without other signs of precocious puberty. Specifically, estrogen or gonadotropin levels do not increase significantly, and statural and skeletal maturation accelerate only mildly, if at all. Premature thelarche does not progress to complete precocious puberty. Premature adrenarche usually occurs between 5 and 7 to 8 years of age. The development of sexual hair is frequently accompanied by a mild growth spurt (with slight bone age advancement) and signs of increased adrenal androgens (increased levels of plasma dehydroepiandrosterone and its sulfate to the early pubertal range). In girls, signs of increased estrogen secretion are not seen. An abnormal androgen source such as a tumor or late-onset congenital adrenal hyperplasia must be excluded. Premature adrenarche may occur in children with neurologic problems. In some girls, premature adrenarche may be a marker for future polycystic ovarian syndrome.

With both premature thelarche and premature adrenarche, careful follow-up physical examinations are necessary to be sure they do not represent the early stages of complete sexual precocity.

### BOX 185-5 Evaluation for Precocious Puberty

#### INITIAL SCREENING TESTS

- Thorough history, physical examination, and calculation of growth velocity
- Bone age
- Luteinizing hormone, follicle-stimulating hormone
- Estradiol, testosterone
- Dehydroepiandrosterone sulfate
- 17-Hydroxyprogesterone
- Thyroid-stimulating hormone, thyroid hormone

#### SECONDARY TESTS (IF INDICATED)

- Pelvic ultrasound
- Brain magnetic resonance imaging
- Serum  $\beta$ -human chorionic gonadotropin
- Gonadotropin-releasing hormone (GnRH) or GnRH

### Isosexual Precocious Puberty

Evaluation and treatment of precocious puberty are a matter for a pediatric endocrinologist. The diagnosis of isosexual precocious puberty is based on the physical examination and laboratory evidence of sex steroid secretion. Common initial tests (Box 185-5) include evaluation of growth velocity, bone age, LH, FSH, and estradiol or testosterone. Additional testing might include dehydroepiandrosterone sulfate, 17-hydroxyprogesterone, thyroid-stimulating hormone, and thyroid hormone levels. The hormone levels should be drawn as close to 8:00 am as possible to coincide with normal early-morning hormone level peaks. Other tests may include a pelvic ultrasound, brain MRI,  $\beta$ -human chorionic gonadotropin, GnRH stimulation test, or adrenocorticotrophic hormone stimulation test assessing for congenital adrenal hyperplasia. Measurement of serum gonadotropin levels before and after an injection of GnRH usually distinguishes central from peripheral precocious puberty. With central precocious puberty, further workup focuses on a search for the cause of the gonadotropin secretion. The diagnosis of idiopathic central precocious puberty can be made only after the search for a pathologic cause is negative. Although onset is at an early age, the tempo and pattern of pubertal progression are normal in idiopathic central precocity. With peripheral precocious puberty, the workup is designed to identify the source of sex steroid, remembering that exogenous sources (eg, contraceptive pills, topical androgen creams or gels) are easily available. In boys, physical examination of the testes is particularly useful in the differential diagnosis. If both testes are of pubertal size, then the patient has gonadotropin-stimulated precocious puberty; if 1 testis is enlarged, then a testicular tumor may be present; if both testes are small, then the androgens are either exogenous or of adrenal origin.

Treatment of isosexual precocity centers on suppression or removal of the underlying cause. Idiopathic



central precocious puberty is treated with GnRH analogs, which lead to pituitary desensitization and a reduction in gonadotropin secretion to prepubertal levels. Several GnRH analogs are available in intramuscular (depot), subcutaneous, and intranasal forms. Depot leuprolide is used most commonly in the United States and is usually given every 3 to 4 weeks, although longer-acting forms, which may be given every 12 weeks, are available. This treatment has been used for years, is effective, and has minimal side effects. A long-acting analog is also available as an implant (histrelin acetate) and is equally effective. For gonadotropin-independent precocious puberty, testosterone and other aromatase inhibitors (anastrozole, letrozole), spironolactone (androgen-receptor inhibitor), and ketoconazole (steroidogenesis inhibitor) may be used. McCune-Albright syndrome is an unusual syndrome of irregular café au lait spots, polyostotic fibrous dysplasia, and precocious puberty caused by a somatic mutation that can lead to constitutive activation of various glands, including the thyroid, parathyroid, adrenal, and gonad. Tamoxifen (estrogen-receptor inhibitor) has recently been shown to be an effective treatment for McCune-Albright syndrome.

### Heterosexual Precocious Puberty

Heterosexual precocious puberty is uncommon (see Box 185-4 for a list of causes). Exogenous sex steroids, including topical preparations, must be considered. The diagnostic workup centers on the search for a sex steroid-producing tumor. These patients should be referred to a pediatric endocrinologist. Treatment is aimed at removal of the sex hormone source (exogenous or tumor) or suppression with glucocorticoid replacement therapy (congenital adrenal hyperplasia).

### SUMMARY

In most cases of delayed or precocious sexual development, a thorough history and physical examination and a few basic laboratory tests identify patients who are likely to have a pathologic cause requiring referral to a pediatric endocrinologist. (See Chapter 164, Hirsutism, Hypertrichosis, and Precocious Sexual Hair Development, for further discussion of various forms of precocious sexual development.)

In all cases, along with physical care, psychological care and support are extremely important, particularly when medical therapy is only partially satisfactory.

### WHEN TO REFER

For delayed puberty

- No breast development in girls by 13 years of age
- No menarche 4 to 5 years after the onset of breast development or by 15 to 16 years of age in girls
- No testicular enlargement in boys by 14 years of age
- Maturation arrest
- Hormonal abnormalities identified by initial screening tests (see Box 185-2)
- Parental or physician discomfort

For precocious puberty

- Signs of puberty before 6 to 8 years of age in girls (see text)
- Signs of puberty before age 9 in boys
- Rapidly progressive puberty (eg, stage 3 breast when first noted)
- Heterosexual precocious puberty
- Hormonal abnormalities identified by initial screening tests (see Box 185-5)
- Parental or physician discomfort

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Puberty* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/gradeschool/puberty/Pages/default.aspx](http://www.healthychildren.org/English/ages-stages/gradeschool/puberty/Pages/default.aspx))
- *Puberty—Ready or Not, Expect Some Big Changes* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *What Is a Pediatric Endocrinologist?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/pages/What-is-a-Pediatric-Endocrinologist.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/pages/What-is-a-Pediatric-Endocrinologist.aspx))

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## Chapter 186 RASH

Daniel Krowchuk, MD

Skin complaints are common in pediatrics. Surveys indicate that 10% to 20% of visits by children to outpatient facilities are associated with a dermatologic problem; it may be the primary reason for the visit, a secondary concern, or an incidental finding during physical examination. Because of the volume of skin-related problems, physicians caring for children must gain some skill in recognizing and managing the most common cutaneous disorders.

Dermatology is a visual discipline. With experience, pediatricians and other physicians can recognize most

of the common problems affecting the skin, including the subtle variations in presentation. For uncommon problems, an atlas, text, consultant, or other resource can be used to aid in identification. As in most medical specialties, an organized approach to the problem is helpful in leading to the correct diagnosis.

The approach to diagnosing skin problems in children is best based on the morphology of the patient's lesions. An appropriate history and accurate description of what is seen can usually overcome any obstacle to diagnosis.

## HISTORY

Although the diagnosis of skin lesions relies heavily on physical examination and the recognition of types of lesions, as with any problem, an appropriate, problem-oriented history is the first step in diagnosis. Some questions that may be useful and their rationale are presented in the following sections.

### History of the Present Illness

*How long have you had the rash? Has it gotten better or worse? Has it occurred in the past?* Conditions such as atopic dermatitis are chronic and recurrent, whereas others such as viral exanthems (eg, erythema infectiosum) are acute and self-limited.

*Are there associated symptoms?* A generalized erythematous macular eruption associated with fever, nasal congestion, and cough suggests the presence of a viral exanthem. Fever, petechiae, and purpura in an ill-appearing child may indicate a serious bacterial infection such as meningococcemia. Atopic or contact dermatitis and scabies characteristically produce pruritus.

*Are any medications being taken?* The onset of wheals in a child receiving an oral antibiotic might represent urticaria as a manifestation of drug allergy. Lithium can worsen acne, and minocycline may cause hyperpigmentation. Topical therapies also may be relevant to the patient's problem. Neomycin (used in certain topical antibiotic preparations), diphenhydramine (used to reduce pruritus), and certain anesthetics (used to reduce pain or pruritus), when applied topically, may induce a contact dermatitis.

*Are there factors that worsen or precipitate the rash?* The malar rash of systemic lupus erythematosus is worsened by sun exposure. For many children who have atopic dermatitis, reduced humidity during colder months is associated with an exacerbation of disease.

*What treatment has been tried, and what was its effect?* Knowing which therapies have been employed, if they were used appropriately, and if they were effective is helpful. Treatment for head lice infestation, for example, may fail if the product is applied incorrectly or if it is left on the scalp for an insufficient period. In addition, repeating a therapy is unwise if it was used correctly but proved ineffective.

### Family History

*Is there a family history of skin disease or other health problems?* Children who have atopic dermatitis often have a family history of atopic disease, including atopic dermatitis, allergic rhinitis, or asthma. If a child

is found to have multiple café au lait macules and a diagnosis of neurofibromatosis type 1 is being considered, determining whether the patient has any affected first-degree relatives is vital. Whether other family members are similarly affected is relevant when cutaneous infections or infestations are suspected. Impetigo, tinea capitis, scabies, and head lice are frequently transmitted within families.

### Social History

For adolescents, in particular, a social history may be relevant.

*Do you work after school?* Occupational exposure to greases or oils (eg, in a fast-food restaurant or car repair shop) may worsen acne.

*Have you ever been involved in a sexual relationship?* A confidential sexual history may be important. Secondary syphilis and disseminated gonococcal infection, as examples, have cutaneous manifestations, and sexual contact can lead to the transmission of molluscum contagiosum or scabies and infestation with pubic lice.

## PHYSICAL EXAMINATION

Recognizing and describing skin lesions accurately is essential to diagnosis. The first step is to identify the primary lesion, defined as the earliest lesion and the one most characteristic of the disease. Primary lesions, described later, include macules, papules, vesicles, and pustules, among others. Next, noting the distribution, arrangement, and color of primary lesions, along with any secondary change, such as crusting or scaling, is important.

### Types of Primary Lesions

Primary lesions may be flat, elevated, or depressed. Flat lesions include macules and patches. A *macule* is a small, circumscribed area of color change without elevation or depression. An example is a café au lait macule (Figure 186-1). Although specific criteria for size are lacking, a *patch* is a large macule (Figure 186-2). Elevated lesions may be solid or fluid filled. Solid lesions include *papules* (<0.5 cm in diameter), *nodules* (≥0.5 cm in diameter), *wheals* (pink, rounded, or flat-topped elevations caused by edema in the skin), and *plaques* (plateau-shaped structures often formed by the coalescence of papules) (Figure 186-3, Figure 186-4, Figure 186-5, and Figure 186-6). Elevated fluid-filled lesions are *vesicles* (<0.5 cm in diameter and filled with serous fluid), *bullae* (≥0.5 cm in diameter and filled with serous fluid), *pustules* (<0.5 cm in diameter and filled with purulent material), and *cysts* (≥0.5 cm in diameter that represent sacs containing fluid or semisolid material) (Figure 186-7, Figure 186-8, and Figure 186-9). A depressed lesion may be an *erosion* (a superficial loss of epidermis with a moist base) or an *ulcer* (a deeper lesion extending into or below the dermis) (Figure 186-10).

### Distribution

Given that certain disorders have unique patterns of distribution, noting the parts of the body involved may provide an important clue to diagnosis. For example, seborrheic dermatitis commonly involves not



**Figure 186-1** Café au lait macules in a patient who has neurofibromatosis type 1.



**Figure 186-2** A port-wine stain is an example of an erythematous patch.

only the scalp but also the eyebrows and nasolabial folds. Psoriasis also affects the scalp, but lesions are often seen in areas that are traumatized, such as the elbows and knees. Acne is limited to the face, back, and chest, sites of the highest concentrations of pilosebaceous follicles.

### Arrangement

Lesions may appear in lines (eg, vesicles in contact dermatitis from poison ivy), be grouped or clustered (eg, vesicles in herpes simplex virus infection), follow



**Figure 186-3** Neonatal acne is composed of erythematous papules and papulopustules.



**Figure 186-4** Nodules representing neurofibromas in a patient who has neurofibromatosis type 1.

a dermatome (eg, vesicles in herpes zoster), or form an annulus or ring (eg, papules in granuloma annulare or a patch in erythema migrans) (Figure 186-11, Figure 186-12, Figure 186-13, and Figure 186-14).





**Figure 186-5** Pink wheals in a patient who has urticaria.



**Figure 186-6** Scaling plaques, plateau-like lesions, are observed in psoriasis.

### Color

Although the color of a lesion may be obvious, descriptive terms that can be helpful include *skin colored*, *erythematous* (pink or red), *hyperpigmented* (tan, brown, or black), *hypopigmented* (the amount of pigment is decreased but not entirely absent), *depigmented* (all pigment is absent, as occurs in vitiligo), or *violaceous*. When erythematous lesions are observed, the examiner should note whether they blanch. The red color in skin depends on hemoglobin within red blood cells. If the red cells are within vessels (as occurs in urticaria, for example), compression of the skin forces the cells into deeper vessels, and blanching



**Figure 186-7** Vesicles, as seen here in varicella, are filled with clear or serous fluid.



**Figure 186-8** Bullae, filled with clear fluid, are observed in chronic bullous disease of childhood.

occurs. However, if the cells are outside vessels, as occurs in forms of vasculitis, blanching will not occur; nonblanching lesions are termed *petechiae*, *purpura*, and *ecchymoses*.

### Secondary Changes

Secondary changes are alterations in the skin that may accompany primary lesions. These changes, too, can be valuable in differential diagnosis. *Crusting* represents dried fluid; it is commonly seen after the rupture of vesicles or bullae, as occurs with the honey-colored crust of impetigo. In contrast, *scaling*

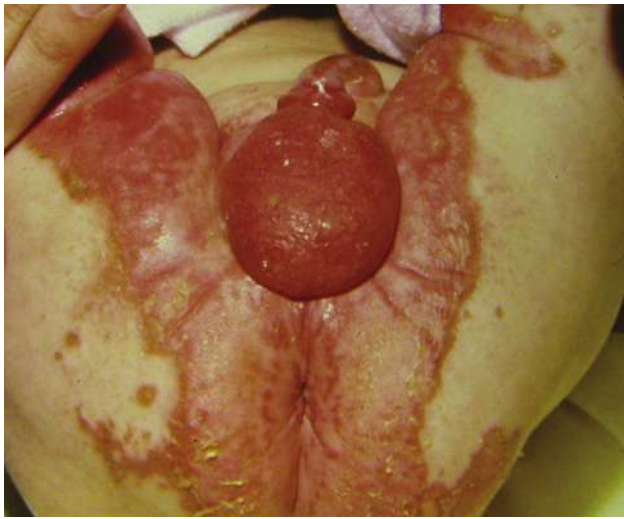




**Figure 186-9** Pustules are filled with purulent material. This patient has folliculitis.



**Figure 186-12** Grouped vesicles are characteristic of herpes simplex virus infection on the skin.



**Figure 186-10** Erosions, as seen in this infant who has acrodermatitis enteropathica, represent a superficial loss of epidermis.



**Figure 186-13** Herpes zoster is characterized by grouped vesicles on erythematous bases distributed along a dermatome.



**Figure 186-11** A linear arrangement of papules or vesicle often occurs in contact dermatitis caused by poison ivy.

represents epidermal fragments that are characteristic of several disorders, among which are fungal infections (eg, tinea corporis) and psoriasis. *Atrophy* is an area of surface depression from absence of the dermis or subcutaneous fat. Atrophic skin often appears thin and wrinkled. *Lichenification* is a thickening of the skin that results from chronic rubbing or scratching (as occurs in atopic dermatitis, for example); as a result, skin markings (ie, creases) appear more prominent.

## DIAGNOSIS

Once the primary lesions are identified, along with their distribution, arrangement, color, and secondary changes, these observations should be formulated into 1 or 2 sentences. For example, “Located on the extensor surfaces of the extremities are erythematous,



**Figure 186-14** An annulus (ie, ring-shaped lesion) is typical of tinea corporis.

scaling papules, and plaques. Scaling of the scalp and pitting of the nails are evident.” Such formulations assist in differential diagnosis. Identifying scaling papules and plaques, as in the previous example, places the patient’s condition into the category of papulosquamous (elevated and scaling) diseases and eliminates countless other disorders from consideration. In children, the most common papulosquamous disorders are chronic atopic or contact dermatitis, tinea corporis, and pityriasis rosea; less common conditions are psoriasis, secondary syphilis, lichen planus, dermatomyositis, and lupus erythematosus. Given the location of the lesions on extensor surfaces and involvement of the scalp and nails, psoriasis becomes a primary consideration.

Boxes 186-1 and Box 186-2 assist in differential diagnosis based on the morphology of lesions. Notably, however, these tables are not exhaustive; rather, they list the most commonly encountered disorders and a few less common ones to consider. Formulating a dermatologic differential diagnosis rests not only on the primary lesion but also on other information, such as the distribution, arrangement, and color of lesions and the presence of any secondary change. When the patient’s physical findings do not immediately make

### BOX 186-1 Differential Diagnosis of Rashes in Neonates

#### ELEVATED LESIONS

##### *Papules*

##### **Common**

- Erythematous
  - Erythema toxicum
  - Miliaria rubra
  - Acne
  - Candidiasis
  - Scabies
- White
  - Milia
- Yellow
  - Sebaceous gland hypertrophy
- Skin colored
  - Epidermal nevus
  - Skin tags

##### **Uncommon**

- Yellow
  - Juvenile xanthogranuloma
- Yellow/tan
  - Mastocytosis

##### *Nodules*

##### **Common**

- Erythematous
  - Hemangioma

##### **Uncommon**

- Skin colored
  - Condylomata acuminata
  - Dermoid cyst

- Yellow

- Mastocytosis

##### *Plaques*

##### **Common**

- Skin colored or yellow
  - Nevus sebaceus
- Skin colored
  - Epidermal nevus

##### *Vesicles or bullae*

##### **Common**

- Erythema toxicum
- Miliaria crystallina
- Sucking blisters
- Bullous impetigo
- Herpes simplex virus infection

##### **Uncommon**

- Incontinentia pigmenti
- Aplasia cutis congenita
- Varicella
- Epidermolysis bullosa
- Epidermolytic ichthyosis

##### *Pustules*

##### **Common**

- Erythema toxicum
- Transient neonatal pustular melanosis
- Miliaria pustulosa
- Herpes simplex virus infection
- Folliculitis

**BOX 186-1 Differential Diagnosis of Rashes in Neonates—cont'd**

- Acne
- Candidiasis
- Scabies

**Uncommon**

- Acropustulosis of infancy

**FLAT LESIONS****Macules****Common**

- Hypopigmented
  - Prehemangioma
  - Postinflammatory hypopigmentation
- Hyperpigmented
  - Transient neonatal pustular melanosis
  - Café au lait macule
  - Postinflammatory hyperpigmentation
  - Congenital melanocytic nevus

**Uncommon**

- Hypopigmented
  - Ash leaf macule

**Patches****Common**

- Erythematous
  - Salmon patch (nevus simplex)
  - Hemangioma (early)
  - Port-wine stain
  - Atopic dermatitis

- Seborrheic dermatitis
- Diaper dermatitis (irritant or seborrheic)
- Hyperpigmented
  - Dermal melanosis
  - Lentigo

**Uncommon**

- Erythematous
  - Acrodermatitis enteropathica
- Hyperpigmented
  - Pigment mosaicism
- Hypopigmented
  - Pigment mosaicism
  - Nevus depigmentosus

**DEPRESSED LESIONS****Erosions****Common**

- Bullous impetigo (after bullae rupture)
- Neonatal herpes simplex virus infection (after vesicles rupture)
- Staphylococcal scalded skin syndrome

**Uncommon**

- Aplasia cutis congenita
- Acrodermatitis enteropathica
- Epidermolysis bullosa
- Epidermolytic ichthyosis

**BOX 186-2 Differential Diagnosis of Rashes in Older Infants, Children, and Adolescents****ELEVATED LESIONS****Papules Without Scaling****Common**

- Erythematous
  - Viral exanthems (Many exanthems have a papular as well as macular component.)
  - Scarlet fever
  - Insect bites
  - Scabies
  - Urticaria
  - Papular urticaria
  - Acne
  - Early lesions of guttate psoriasis
  - Erythema multiforme
- Skin colored
  - Keratosis pilaris
  - Molluscum contagiosum
  - Flat warts
- Hyperpigmented
  - Nevus (intra-dermal)

**Uncommon**

- Yellow/tan
  - Mastocytosis

**Plaques Without Scaling****Common**

- Skin colored
  - Nevus sebaceus
  - Epidermal nevus
- Hyperpigmented
  - Congenital melanocytic nevus

**Papules or Plaques With Scaling (Papulosquamous Diseases)****Common**

- Tinea corporis
- Pityriasis rosea
- Chronic atopic or contact dermatitis
- Psoriasis

**Uncommon**

- Dermatomyositis
- Lupus erythematosus
- Lichen planus

Continued

**BOX 186-2 Differential Diagnosis of Rashes in Older Infants, Children, and Adolescents—cont'd****Nodules****Common**

- Erythematous
  - Pyogenic granuloma
- Skin colored
  - Wart
  - Callus
  - Corn
  - Epidermal cyst
  - Granuloma annulare

**Uncommon**

- Erythematous
  - Angiofibroma (ie, adenoma sebaceum)
- Skin colored
  - Neurofibroma
- Yellow/tan
  - Mastocytosis

**Vesicles or Bullae****Common**

- Contact dermatitis
- Bullous impetigo
- Varicella
- Herpes simplex virus infection
- Hand-foot-and-mouth disease
- Erythema multiforme

**Uncommon**

- Polymorphous light eruption
- Linear immunoglobulin A dermatosis

**Pustules****Common**

- Folliculitis
- Scabies
- Acne
- Periorificial dermatitis

**Uncommon**

- Associated with systemic bacterial infection (eg, disseminated gonococcal infection)

**FLAT LESIONS****Macules****Common**

- Erythematous
  - Viral exanthems
  - Drug eruptions
- Hypopigmented
  - Pityriasis alba (postinflammatory hypopigmentation)
  - Tinea versicolor
  - Vitiligo
  - Halo nevus

- Hyperpigmented
  - Freckles
  - Postinflammatory hyperpigmentation
  - Tinea versicolor
  - Café au lait macules
  - Melanocytic nevus

**Uncommon**

- Hypopigmented
  - Lichen sclerosus et atrophicus
  - Scleroderma
  - Ash leaf macule
  - Piebaldism

**Patches****Common**

- Erythematous
  - Salmon patch (nevus simplex)
  - Port-wine stain
  - Atopic dermatitis
- Hyperpigmented
  - Dermal melanosis
  - Becker nevus
  - Lentigo

**Uncommon**

- Erythematous
  - Toxic shock syndrome (diffuse macular [“sunburn-like”] erythema)
- Hyperpigmented
  - Pigment mosaicism
  - Incontinentia pigmenti

**DEPRESSED LESIONS****Erosions****Common**

- Bullous impetigo (after bullae rupture)
- Herpes simplex virus infection (after vesicles rupture)
- Staphylococcal scalded skin syndrome

**Uncommon**

- Epidermolysis bullosa

**HAIR LOSS****Congenital**

- Localized
  - Nevus sebaceus
  - Epidermal nevus
  - Aplasia cutis congenita
- Diffuse
  - Hair shaft abnormalities
  - Hypothyroidism



**BOX 186-2 Differential Diagnosis of Rashes in Older Infants, Children, and Adolescents—cont'd****Acquired**

## • Localized

- Friction alopecia
- Tinea capitis
- Traction alopecia
- Trichotillomania
- Alopecia areata
- Psoriasis

- Secondary syphilis
- Scleroderma
- Diffuse
  - Telogen effluvium
  - Chemotherapy
  - Hypothyroidism
  - Acrodermatitis enteropathica

the diagnosis clear, a textbook or atlas of dermatology, consultant, or other resource can provide assistance.

**SUGGESTED READINGS**

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## Chapter 187

# RECURRENT INFECTIONS

David L. Goldman, MD

Pediatric primary care physicians frequently encounter children who have recurrent infections, most of whom are otherwise healthy. Reassuring the parents of these children that no underlying abnormality exists is particularly important. Much less commonly, recurrent infections are a sign of an underlying, possibly immunologic, disorder. Early identification of these children is critical because prompt intervention can decrease morbidity and mortality.

## NORMAL PATTERN OF INFECTIONS IN CHILDHOOD

Generally, healthy children experience 6 to 8 upper respiratory tract infections per year in the first few years of life. However, up to 15 infections per year can still be within the normal range. The high frequency of infections in the first years of life results from the relative immunologic immaturity of young children and their frequent exposure to respiratory pathogens. Factors such as attendance in child care and exposure to secondhand smoke may increase the number of infections.

In the healthy host, these infections are self-limited, occur more frequently in the winter than in other seasons, and are associated with periods of wellness in between illnesses. Growth and development are normal. Considering that the average duration of a viral illness is 7 to 10 days, typically, a toddler may be sick for up to 100 days or almost one-third of the year.

## INFECTIONS ASSOCIATED WITH AN UNDERLYING IMMUNE DISORDER

Occasionally, a pediatrician will encounter a child who has a history of infections that number above the normal range. Certain patterns of infections should alert the physician to the possibility of an underlying immunodeficiency. One such pattern is an increased frequency of common infections. Although an immunocompetent child can experience a single serious bacterial infection such as pneumonia, meningitis, or osteomyelitis, repeated serious bacterial infections should alert the pediatrician to the possibility of an underlying disorder. Immunodeficiency may also cause a common infection to manifest uncommonly, with increased severity, prolonged duration, or failure to respond to appropriate treatment. Varicella, a typically benign infection in healthy, immunocompetent children, can cause overwhelming infections in children who have leukemia, and prolonged illness in children who have acquired immunodeficiency syndrome (AIDS). Immunodeficiency may also be suggested by a common infection exhibiting at an uncommon age. Thrush or candidal diaper dermatitis in children older than 1 year suggests a defect in T-cell immunity. Alternatively, immunodeficiency may produce an infection with an opportunistic pathogen (ie, *Pneumocystis jiroveci*, *Cryptococcus neoformans*). Rarely, immunodeficiency may become apparent as an infection after the administration of a live virus vaccine.

## NONIMMUNOLOGIC DISORDERS ASSOCIATED WITH ENHANCED SUSCEPTIBILITY TO INFECTIONS

Host defense against microbial pathogens involves anatomic, physiologic, and inflammatory barriers. Defects in any of these systems can lead to recurrent infections. In general, recurrent bacterial infections at

the same anatomic site that are not associated with other infections or other signs of an underlying syndrome should suggest the possibility of an anatomic defect that may be either congenital or acquired. This circumstance is true especially of children who have urinary tract infections and otitis media. About 62% of children younger than 1 year have more than 1 episode of otitis media, and 17% have 3 or more episodes. The increased susceptibility of young children to otitis media results from an age-related dysfunction of the eustachian tubes and is rarely associated with underlying immunodeficiency. Anatomic defects leading to recurrent infections may also occur in other organ systems. Recurrent meningitis may occur as the result of an occult cerebral spinal fluid leak. Recurrent pneumonia may result from various nonimmunologic causes such as alteration of the normal barrier as a result of foreign body aspiration, tracheoesophageal fistula, or gastroesophageal reflux. Impaired function of mucociliary transport, as seen in cystic fibrosis and immotile cilia syndromes, also leads to recurrent pneumonia. Besides anatomic defects, recurrent or unusual infections can also occur as a result of alteration in the normal microbial flora associated with antibiotic use (eg, *Clostridium difficile* colitis) and circulatory disorders such as venostasis.

Certain types of infection may be associated with recurrent disease in the absence of recognized immunodeficiency. Recurrent soft tissue and skin infections with *Staphylococcus aureus* and colitis with *C difficile* fit this pattern, in which recurrence is thought to result primarily from bacterial characteristics that lead to persistence despite antimicrobial therapy. Treatment is therefore directed at eliminating underlying infection.

Allergic conditions may be confused with recurrent infections. Allergic rhinitis may be misdiagnosed as recurrent upper respiratory tract infection, and asthma may be misdiagnosed as recurrent pneumonia. When repeated episodes of pneumonia are the sole presentation of recurrent infection, the physician should consider the possibility of reactive airway disease, which can produce recurrent respiratory symptoms in association with pulmonary infiltrates.

SECONDARY IMMUNODEFICIENCIES

Abnormalities of the immune system may be categorized as either primary or secondary. Secondary immunodeficiencies, more common than primary, are

either acquired or a consequence of a nonimmunologic process, including infection, malignancy, medication (ie, cytotoxic, immunosuppressive), malnutrition, splenic dysfunction, and metabolic disorders (Table 187-1). Improvements in medical care have led to an increase in the number of children with secondary immunodeficiencies, including those with organ transplants, rheumatologic diseases, and malignancies. New therapies have also led to new risk factors for unusual infections. For example, anticytokine therapies such as antitumor necrosis factor- $\alpha$  for rheumatoid diseases and Crohn disease have been associated with an increased susceptibility to tuberculosis and histoplasmosis. Similarly, the implantation of foreign materials (ie, heart valves, catheters) is associated with an increased risk for infection. Improved postnatal care has led to improved survival of premature neonates, who exhibit a variety of immune deficits that put them at increased risk for infection.

The spleen serves as a filter to remove infectious agents from the circulation and as a site for maturation of the immune response. Splenic dysfunction and its associated immunodeficiency can result from a variety of disorders, including congenital absence, surgical removal, hemoglobinopathies, and infiltrative diseases. Affected patients typically experience increased susceptibility to bacterial pathogens, especially encapsulated organisms.

Human immunodeficiency virus (HIV) infection, which produces a combined deficiency in both humoral and cellular immunity (AIDS) and is an important cause of secondary immunodeficiency, may be acquired congenitally or horizontally. Children infected with HIV can develop symptoms related to a variety of infection types (ie, opportunistic, recurrent, atypical), depending on the immune status of the child. Older children, who acquire HIV infection horizontally, may develop a primary syndrome in association with the HIV infection itself, which is clinically similar to other viral illnesses (ie, influenza, infectious mononucleosis). Recent advances in HIV therapy have helped decrease the morbidity and mortality associated with this disease, making early recognition and prompt intervention essential for optimal management. Other viral infections may impair the immune response in more subtle ways. For example, preceding influenza infection is readily recognized as a risk factor for superinfection with bacterial pneumonia.

Table 187-1      Secondary Immunodeficiencies

CAUSE	DISEASE
Infection	HIV; congenital rubella
Malignancy	Leukemia; lymphoma
Metabolic	Uremia; malnutrition; protein-losing enteropathy; diabetes; galactosemia
Chromosomal	Down syndrome; Bloom syndrome
Medications	Corticosteroids; chemotherapy; antirejection medication
Splenic dysfunction	Splenectomy; sickle cell disease; congenital asplenia

HIV, human immunodeficiency virus.

Malnutrition, resulting from protein, mineral, or vitamin deficiency, is an extremely important cause of secondary immunodeficiency in many areas of the world and has been linked to increased susceptibility to a variety of infections, including measles, pneumocystis, and tuberculosis.

PRIMARY IMMUNODEFICIENCY

Primary immunodeficiencies, far less common than secondary, are caused by intrinsic defects in the immune system that are genetically determined. Excluding selective immunoglobulin A (IgA) deficiency, primary immunodeficiencies occur at an incidence of 1 in 10,000 births. Because many of these syndromes are X-linked, boys are affected more commonly than girls. Most children who have primary immunodeficiencies are symptomatic within the first few years of life, with several exceptions, including common variable immunodeficiency and deficiencies of the terminal complement components. Primary immunodeficiencies may involve the innate or adaptive immune system and are classified by the specific component of the immune system that is affected (eg, humoral, cellular, complement, and phagocytic). As our understanding of immunity and genetics has grown, there has been increased recognition of primary immune deficiency states, including defects in the innate (eg, toll-like and dectin receptors) and cellular (eg, helper T cells subtype 17 [Th17]) immune responses. There has also been improved understanding of the basis of immunodeficiency for certain syndromes. For example, defects in the Th17 immune response are now recognized to contribute to the immunodeficiency associated with hyper-IgE syndrome. Defects in various arms of the immune system are associated with enhanced susceptibility to infections by particular types of pathogens (see later). Hence, the type of infecting pathogen may be useful in guiding the evaluation of a child with a suspected immunodeficiency. Associated clinical findings, which can be nonspecific or syndrome specific, may also suggest a primary immunodeficiency. A child who has serious recurrent infections will often experience growth failure. However, other physical, historical, and laboratory findings associated with primary immunodeficiency syndromes can be found (Table 187-2). The specific timing of infections may also serve as an important clue to the nature of

immunodeficiency. For example, antibody deficiency states are not generally recognized within the first few months of life because of the presence of maternal antibody. In contrast, severe combined immunodeficiency, complete DiGeorge syndrome, congenital neutropenia, and leukocyte adhesion defect typically present with infections early in life.

Defects in Humoral Immunity

Defects in humoral immunity, the antibody-mediated arm of the immune system, represent 50% to 70% of symptomatic primary immunodeficiencies. The defects occur at various stages of B-cell development and result in a wide variety of clinical presentations. Syndromes range in severity from a total absence of mature B cells to an isotype deficiency to a defective antibody response against polysaccharide antigens (Table 187-3). Given the protective effects of maternally acquired antibody, even the most severely affected children (eg, those who have a total absence of antibody production) do not become symptomatic until after the first few months of life. Children who have defects in the humoral immune system are characteristically susceptible to recurrent sinopulmonary infections with encapsulated bacteria, including *Streptococcus pneumonia* and *Haemophilus influenzae*. X-linked agammaglobulinemia (Bruton agammaglobulinemia), one of the first primary immunodeficiencies to be described, is associated with a complete absence of mature B cells. Affected children have poor lymph tissue development, and a physical examination may reveal the absence of lymph nodes and tonsils. Although these children are generally not more susceptible to viral illnesses, they may experience severe or persistent enterovirus and rotavirus infections. Oral vaccination with live attenuated polio (no longer available in the United States) should be avoided because of the risk for vaccine-associated disease. Persistent *Campylobacter* species infections also may occur. Children who have defects in humoral immunity are also predisposed to autoimmune disorders, such as dermatomyositis and asymmetrical arthritis. Chronic lung disease may also occur. Treatment for antibody deficiency disorders depends on the type of disorder. Lifelong replacement therapy with intravenous immunoglobulin (IVIG) is indicated for X-linked agammaglobulinemia.

Table 187-2 Signs Associated With Primary Immunodeficiencies	
SIGN	ASSOCIATED SYNDROME
Intractable diarrhea and malabsorption	SCID; XLA; CVID
Rheumatologic conditions	CVID; IgA deficiency; XLA
Hepatosplenomegaly, lymphadenopathy	Hyper-IgM syndrome
Absence of lymph tissue	XLA
Thrombocytopenia	Wiskott-Aldrich syndrome
Eczema	Wiskott-Aldrich syndrome; chronic granulomatous disease; Job syndrome
Oculocutaneous albinism	Chédiak-Higashi syndrome

CVID, common variable immunodeficiency; SCID, severe combined immunodeficiency; XLA, X-linked agammaglobulinemia.

**Table 187-3** Humoral Immunodeficiencies

SYNDROME	CLINICAL FEATURES	ASSOCIATED FEATURES
X-linked agammaglobulinemia	Susceptibility to encapsulated bacterial pathogens Sinopulmonary and gastrointestinal infections, sepsis, meningitis Enhanced susceptibility to enterovirus and rotavirus Symptomatic polio infection following live polio vaccination	Asymmetrical arthritis; dermatomyositis; malabsorption; absence of tonsils, adenoids, and lymph nodes
Transient hypogammaglobulinemia of infancy	Recurrent sinopulmonary infections; generally improves by 3–4 yr	May develop IgA deficiency
Hyper-IgM syndrome	X-linked Recurrent bacterial infections including encapsulated pathogens Infections associated with T-cell defects (eg, <i>Pneumocystis carinii</i> ) also seen	Low levels of IgG, IgA, and IgE Neutropenia, thrombocytopenia; T-cell defects
Common variable immunodeficiency	Sinopulmonary infections Bronchiectasis Giardiasis	Most common in second and third decade Noncaseating granulomas; malabsorption; autoimmune disease
IgA deficiency	Very common (1 in 400 individuals) but usually asymptomatic Recurrent pulmonary infections leading to bronchiectasis	Systemic lupus erythematosus; rheumatoid arthritis; chronic diarrhea Allergic reactions to gammaglobulin preparations IgG subclass deficiency in some
Specific antibody deficiency with normal immunoglobulins	Recurrent bacterial infections of the respiratory tract	
IgG subclass deficiency	Normal immunoglobulin levels but with impaired antibody responses to polysaccharide antigens Clinical significance not well delineated	

### Combined Defects in Cellular and Humoral Immunity

Combined defects in cellular immunity and humoral immunity make up the second largest group of primary immunodeficiencies. Isolated defects in cellular immunity, which is mediated primarily by T lymphocytes, with preserved antibody function are very uncommon because T cells play a critical role in B-cell function and development. A deficiency in the production and response to T-cell cytokines such as interferon- $\gamma$  is a rare exception. Most children with defects in T-cell immunity have associated defects in antibody immunity. In addition to bacterial infections, affected children are characteristically more susceptible to fungal, mycobacterial, and viral infections. These children may experience recurrent or persistent candidiasis (or both) in the form of thrush and diaper candidiasis. Common viral infections of childhood (eg, varicella) may cause severe or recurrent disease in affected children. Table 187-4 lists some of the more common combined immunodeficiency syndromes.

Severe combined immunodeficiency (SCID) is the prototypical combined immunodeficiency syndrome and actually represents a collection of diseases. A variety of defects may result in SCID, including those affecting the following systems: cytokine receptors, signaling pathways, enzymes of the nucleotide salvage pathway, and major histocompatibility complex. In the first few months of life, children with SCID typically experience

intractable diarrhea, failure to thrive, recurrent candidiasis, and *P jiroveci* pneumonia. Definitive therapy depends on the type of SCID and may involve bone marrow transplantation or enzyme or gene therapy.

Wiskott-Aldrich syndrome is an X-linked disorder associated with the triad of thrombocytopenia, eczema, and recurrent infections. This disorder is thought to be related to a deficiency in T-cell activation. Affected infants often experience bleeding in the first few years of life. These children may have low IgM levels but normal IgG levels.

Ataxia-telangiectasia is an autosomal recessive disorder that produces progressive ataxia, conjunctival telangiectasias, decreased IgA levels, and altered T-cell function. Children with ataxia-telangiectasia may have thymic hypoplasia, insulin resistance, or gonadal atrophy and are at increased risk for hematologic malignancies.

### Defects in Phagocytic Immunity

The phagocytic arm of the immune response includes neutrophils and monocytes. Phagocytes form the first line of defense against many pathogens and are considered part of the nonspecific immune response. Defects in phagocytic immunity range from the absence of a particular cell type (ie, congenital neutropenia, cyclical neutropenia) to defects in chemotaxis (leukocyte adhesion disorder) to defects in effector function (chronic granulomatous disease) (Table 187-5).



**Table 187-4** Combined Immunodeficiencies

SYNDROME	CLINICAL FEATURES	ASSOCIATED FEATURES
DiGeorge syndrome	Clinically variable	Hypocalcemia; hypoparathyroidism; congenital heart disease; abnormal facies
Severe combined immunodeficiency (SCID)	Increased viral and fungal infections Both B-cell and T-cell deficiencies present Includes a variety of disorders that have multiple modes of inheritance Presents early in life (within first 3 mo of age) with recurrent or severe infections with all types of pathogens	Failure to thrive; diarrhea Most common (50%) form is X-linked Thymic hypoplasia Cartilage-hair hypoplasia with certain forms of SCID At increased risk for graft-versus-host disease with red blood cell transfusions
Ataxia telangiectasia	Recurrent sinopulmonary infections	Truncal ataxia; mental retardation; thymic hypoplasia; telangiectasia of skin and conjunctiva; glucose intolerance; increased risk for malignancy
Wiskott-Aldrich syndrome	Recurrent sinopulmonary infections	Eczema; thrombocytopenia; increased risk for malignancy

**Table 187-5** Phagocytic Immunodeficiencies

SYNDROME	CLINICAL FEATURES	ASSOCIATED FEATURES
Chronic granulomatous disease (CGD)	Often X-linked Recurrent infection of skin, lungs, liver, lymph nodes, and bone Infections with catalase-positive organisms ( <i>Staphylococci</i> spp, <i>Escherichia coli</i> , <i>Aspergillus fumigatus</i> , and <i>Candida albicans</i> )	Eczema; lymphadenopathy; hepatosplenomegaly
Chédiak-Higashi syndrome	Autosomal recessive Recurrent pyogenic infections with organisms similar to those seen in CGD	Ocular albinism; lymphoreticular malignancies Neutrophils have abnormally large granules
Job syndrome	Recurrent sinopulmonary infections and skin abscesses	Eczema; red hair; coarse facies; high IgE levels
Leukocyte adhesion defect	Autosomal recessive Recurrent bacterial infections and necrotic skin lesions	Leukocytosis with absence of neutrophils at infection site Severe gingivitis with early loss of teeth Delayed separation of umbilical cord

Affected children typically experience recurrent skin infections and abscesses in addition to sinopulmonary infections. Children with defects in phagocytic oxidative burst (ie, chronic granulomatous disease) are particularly susceptible to infections caused by organisms (*Staphylococcus*, *Nocardia*, and *Aspergillus* species) that are catalase positive and thus able to degrade hydrogen peroxide. Other clinical features associated with defects in phagocytic immunity include poor wound healing, delayed umbilical cord separation, gingivitis, and eczema.

### Defects in the Complement System

Complement acts to lyse target cells and, as an opsonin, promotes the phagocytosis of microbial pathogens. Defects in the complement system are the least common among the primary immunodeficiencies. Congenital deficiencies in the late or terminal components of the complement system (C5, C6, C7, C8, and C9) are inherited as autosomal recessive traits and

result in recurrent neisserial infections. In contrast to many of the primary immunodeficiencies, terminal complement deficiencies tend to manifest in older children and in adolescents, typically with recurrent meningococcal infection (meningitis or meningococcemia) or gonococcal arthritis. Deficiency in the C3 component results in an increased susceptibility to encapsulated bacterial pathogens and may be difficult to distinguish from antibody deficiencies except that it tends to occur at an earlier age, within the first few months of life.

## EVALUATION OF THE CHILD WITH POSSIBLE PRIMARY IMMUNODEFICIENCY

### History

An evaluation for a primary immunodeficiency should be performed after nonimmunologic and secondary

**Table 187-6 Laboratory Examination**

IMMUNODEFICIENCY	SCREENING TESTS	GENERAL COMMENTS
Humoral (B cell)	Serum immunoglobulin levels (IgG, IgM, IgA)	Antibody levels must be interpreted with respect to age-appropriate values. High or low levels can be significant. Specific antibody responses must be interpreted in the context of vaccine history.
Cellular (T cell)	Antibody titers against protein (diphtheria, tetanus toxoid) and polysaccharide ( <i>Haemophilus</i> , <i>Pneumococcus</i> spp) antigens Lymphocyte count, anergy testing, lymphoproliferative assays	
Phagocytic (macrophage or neutrophil)	Complete blood count IgE level Nitroblue tetrazolium (NBT) test, flow cytometric respiratory burst assay	Total lymphocyte count is obtained by multiplying total white blood cell count by the percentage of lymphocytes. Value <1,500 mCL is considered lymphopenia. Anergy testing not reliable for children <1 yr. Abnormal neutrophil structure may be present.
Complement	CH <sub>50</sub> assay	IgE level elevated in Job syndrome.  Screening assay for components of classic complement pathway. May not be sensitive for limited deficiencies in individual complement components.

immunodeficiency syndromes have been considered. A complete history should be obtained for all children being evaluated for recurrent infections, including a history of risk factors for HIV infection (either personal for adolescents or parental when congenital transmission is a possibility): drug use, prostitution, blood-product transfusion, multiple sexual partners, or history of sexually transmitted infection and homosexual behavior. Particular attention should be paid to documenting the characteristics of previous infections, including the types of pathogens and infections, duration of illnesses, and need for hospitalizations. Because many of the primary immunodeficiencies are hereditary, a detailed family history is important. A complete review of systems should be obtained, with attention paid to known associated features of immunodeficiency syndromes, including failure to thrive. The immunization history is important because failure to make protective antibodies in response to immunizations can be indicative of immunodeficiency.

### Physical Examination

A complete physical examination should be performed. Many children who have immunodeficiency appear chronically ill. Growth parameters (height, weight, and head circumference percentiles) should be obtained to determine the presence of failure to thrive. Physical signs that may indicate underlying immunodeficiency include absence of tonsils and the presence of generalized lymphadenopathy and hepatosplenomegaly. Skin lesions (eczema, abscesses, and seborrhea) and mucous membrane involvement (telangiectasia, mucositis) are observed with some immunologic disorders. Signs of recurrent infection (eg, dull, retracted tympanic membranes) and evidence of ongoing infection (eg, thrush) may be present. Specific

signs associated with a particular immunodeficiency syndrome, such as oculocutaneous albinism in Chédiak-Higashi syndrome, may be present.

### Laboratory Evaluation and Referral

Laboratory evaluation for a child who is thought to have an immunodeficiency should be guided by the type of infections the child is experiencing. Initial screening tests usually include complete blood count and differential, serum immunoglobulin levels (IgG, IgA, and IgM), and lymphocyte count. Most primary immunodeficiency syndromes will be associated with abnormal serum immunoglobulin levels. HIV testing should be strongly considered, as indicated by the history and physical findings. In an area that has a high prevalence of HIV infection, testing should be considered even if no obvious risk factor can be identified. Other tests of humoral immunity include B-cell number, antibody levels to various antigens, and IgG subclass determinations. Tests of cellular immunity include delayed-type hypersensitivity (ie, mumps, *Trichophyton* species infection, tetanus toxoid), T-cell enumeration, and lymphoproliferative responses. Table 187-6 lists the initial screening tests to be considered for each component of the immune system. Antibody and T-cell studies must be analyzed in the context of age-adjusted normal values and may be affected by acute illnesses. Likewise, delayed-type hypersensitivity responses are unreliable in children younger than 1 year. Radiologic studies are used primarily in the diagnosis or management of associated infections, although the absence of a thymic shadow can be indicative of DiGeorge syndrome or SCID. Regardless of the results of initial screening tests, referral to a specialist, either immunologist or infectious diseases expert, should be considered for children who have signs and symptoms suggestive of immunodeficiency (Box 187-1).

**BOX 187-1 Reasons for Referral for Suspected Immunodeficiency**

- Recurrent serious (ie, sepsis, pneumonia, meningitis) bacterial infection
- Serious bacterial infection in the context of failure to thrive
- Infection with an opportunistic pathogen (ie, *Pneumocystis*, *Cryptococcus* spp infection)
- Vaccine-associated infection
- Unusual age for infection (ie, early zoster, late thrush)
- Unusual severity or chronicity for a given infection
- Family history of immunodeficiency

**Treatment**

Treatment of primary immunodeficiency is condition specific. Patients with humoral and combined immunodeficiencies may benefit from the administration of IVIG as replacement therapy. The initial regimen is 300 to 400 mg/kg every 3 to 4 weeks and should be adjusted based on the patient's response. The trough concentration of antibody should be at least 500 mg/dL. Replacement IVIG is not indicated for all types of humoral deficiency. Furthermore, patients with IgA deficiency may develop anaphylaxis to certain brands of IVIG that contain small amounts of IgA. Other therapies include bone marrow transplantation (SCID, Wiskott-Aldrich, DiGeorge syndrome), enzyme replacement (certain forms of SCID), and cytokine therapy (interleukin-2 deficiency). Recently, interferon- $\gamma$  treatment has been demonstrated to decrease the number of infections in patients with chronic granulomatous disease. The genetic basis for many of the primary immunodeficiencies is now known, and prenatal screening is increasingly available.

Pending a complete immunologic evaluation, children who are thought to have immunodeficiency syndromes should not receive live attenuated vaccines, such as varicella and measles, to avoid the possibility of vaccine-associated infection. Vaccine recommendations for specific immunodeficiencies can be found in the American Academy of Pediatrics *Red Book: Report of the Committee on Infectious Diseases*. Blood transfusion, when needed, should be with cytomegalovirus-negative, irradiated cells to prevent the possibility of cytomegalovirus infection and graft-versus-host disease.

**TOOLS FOR PRACTICE****Engaging Patient and Family**

- *Recurrent Infections* (fact sheet), Riley Hospital for Children at Indiana University Health ([iuhealth.org/riley/pediatric-allergy-and-asthma/recurrent-infections](http://iuhealth.org/riley/pediatric-allergy-and-asthma/recurrent-infections))
- *Primary Immunodeficiency Disease* (Web page), American Academy of Allergy, Asthma, and Immunology ([www.aaaai.org/conditions-and-treatments/primary-immunodeficiency-disease.aspx](http://www.aaaai.org/conditions-and-treatments/primary-immunodeficiency-disease.aspx))

**Medical Decision Support**

- *About Primary Immunodeficiencies* (Web page), The Immune Deficiency Foundation ([primaryimmune.org/about-primary-immunodeficiencies](http://primaryimmune.org/about-primary-immunodeficiencies))

**SUGGESTED READINGS**

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**Chapter 188****RED EYE/PINK EYE**

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Red eye in children can be difficult to diagnose and manage because, as a physical finding, it has many possible causes, variable presentations, and severity ranging from asymptomatic to vision threatening. The most common causes of a red eye in a child are infectious (bacterial, viral, or parasitic); inflammatory; allergic; traumatic, from a foreign body and corneal abrasion; or related to an underlying systemic cause. In general, red eye associated with pain, photophobia, or blurry vision indicates a serious ocular disease and should be considered for referral.

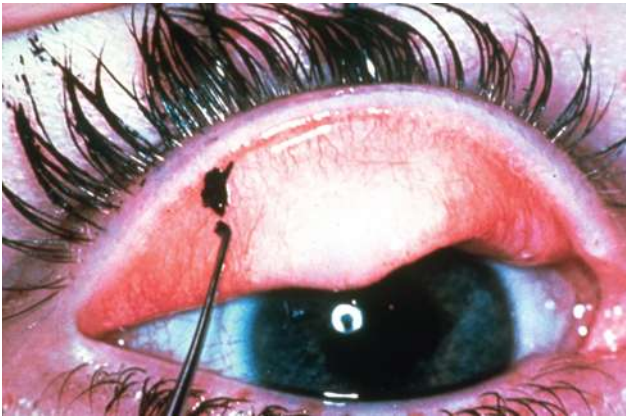
The first step in determining the cause of a child's red eye is identifying the location of the redness and swelling: is it isolated to the eyelid itself, or does it involve the conjunctiva, either diffusely, or focally around the cornea (ciliary flush, Figure 188-1)? The location provides clues to the underlying problem, which helps direct the history taking and organize the differential diagnosis. (See Table 188-1.)

**HISTORY**

A detailed history should be obtained, with specific attention paid to the onset and progression of the redness, prior episodes of redness, possible trauma or injury, prior ocular surgery, use of contact lenses, and personal contact with similarly affected individuals. In young children, the history of trauma or chemical injury can be difficult to obtain, so this possibility needs



**Figure 188-1** Ciliary flush.



**Figure 188-2** Foreign body in the conjunctiva.

Table 188-1	Causes of Red Eye by Location of Redness
Eyelid	Preseptal cellulitis Orbital cellulitis Eyelid tumors Allergic dermatitis Chalazia and hordeola Blepharitis
Conjunctiva	Trauma Viral Bacterial Chemical Allergic Vernal Phlyctenulosis Subconjunctival hemorrhage Papilloma
Cornea	Abrasion Corneal infection: bacterial, viral, fungal, or parasitic
Intraocular	Foreign body Iritis, uveitis Hyphema
Focal inflammation over involved area	Scleritis Episcleritis Ocular myositis



**Figure 188-3** Corneal abrasion.

to be considered on examination. Symptoms including itching, pain, photophobia, visual disturbance, tearing, mucous discharge, nasal discharge, and fevers should be elicited. In cases in which both eyes are affected, the sequence and timing of symptom onset are important to know: did both eyes become red initially, or was one affected before the other?

**PHYSICAL EXAMINATION**

If possible, assessing visual acuity should be the first step of any eye examination. In small children, the ability to fixate on and follow a toy is often all that can be gathered about their vision. Careful examination of ocular structures with a penlight should be next.

Starting with the lids, look for redness, crusting, clogged meibomian glands, redness at the lid margin, and thickening of the lid margin. Next, moving inward toward the eye, examine the conjunctiva, including everting the lids and looking for a foreign body (Figure 188-2). To look under the upper lid, place a cotton-tipped swab on the outside of the upper lid 1 cm above the lash line and gently evert the lid over the cotton swab. (This technique is demonstrated at [www.nlm.nih.gov/medlineplus/ency/imagepages/19662.htm](http://www.nlm.nih.gov/medlineplus/ency/imagepages/19662.htm).) Then, determine whether the conjunctival redness is diffuse or sectoral. Fine follicles in the conjunctiva overlying the lid indicate a viral infection, whereas edema suggests allergic conjunctivitis. The cornea should then be evaluated for opacities, foreign bodies, and disruption of the light reflex. The use of fluorescein and a cobalt blue light can highlight any corneal abrasions (Figure 188-3). Next, examine the pupils: check for size, shape, and reactivity. A mid-dilated pupil would suggest iritis. An irregular pupil may suggest trauma and possible intraocular foreign body. Beyond the eye, attention should be paid to



preauricular lymph nodes (viral conjunctivitis), stiff or tender joints (juvenile idiopathic arthritis, or JIA).

## DIFFERENTIAL DIAGNOSIS AND MANAGEMENT

### Eyelid Abnormalities

#### Preseptal and Orbital Cellulitis

Signs of preseptal cellulitis include tenderness, conjunctival swelling, and redness. As the name suggests, preseptal cellulitis (Figure 188-4) occurs anterior to the orbital septum, and therefore has *no* associated double vision, decreased vision, proptosis (eyeball pushed forward), limited motility, or pain with eye movement. These signs would indicate a more severe condition with orbital involvement. Common causes of preseptal cellulitis in children are trauma (laceration, insect bite, or puncture wound) or adjacent infections (sinusitis, herpetic dermatitis, infected chalazion, or dacryocystitis—an infected tear drainage duct) (Figure 188-5). For patients with mild to moderate preseptal cellulitis, laboratory evaluation is not usually needed. For highly febrile patients or severe preseptal cellulitis, a complete blood cell count (CBC) and blood culture should be considered. A computed tomography (CT) scan with contrast of the orbits and sinuses provides details related to bony structures or radiopaque foreign bodies and should be performed in cases of significant trauma or suspected foreign body, sinus disease, suspected orbital involvement, or abscess formation.

Signs of orbital cellulitis may include tenderness, conjunctival swelling and redness, double vision, decreased vision, proptosis, limited motility (Figure 188-6), pain with eye movement, fever, and in severe cases, pupillary involvement. The most common cause of orbital cellulitis in children is concomitant sinus disease with penetration through the thin bones of the orbital walls; but it can also result from dental infection, hematogenous spread, or orbital trauma. In cases of suspected orbital cellulitis, vital signs, mental status, neck flexibility, and facial sensation should be evaluated. Laboratory evaluation should include a CBC and blood culture. Computed tomography scanning of the orbits and sinuses with and without contrast should be performed to evaluate for foreign bodies, sinus disease, and abscess formation. Orbital tumors such as neuroblastoma, rhabdomyosarcoma, and lymphangioma can masquerade as orbital cellulitis. For better delineation of soft tissue details, and particularly if the physician also suspects an intracranial complication, magnetic resonance imaging may be needed. Admission for broad-spectrum intravenous antibiotics and possible surgical drainage is mandatory.

#### Eyelid Tumors

Capillary hemangiomas (Figure 188-7) and the port wine stain of Sturge-Weber syndrome can cause redness and swelling of the lid. In these conditions, which progress slowly over months, the visual axis can become obstructed leading to amblyopia—affected patients should be referred to an ophthalmologist for evaluation.



**Figure 188-4** Preseptal cellulitis.



**Figure 188-5** Dacryocystitis.



**Figure 188-6** Orbital cellulitis.

### Allergic Reactions

Contact dermatitis (Figure 188-8), insect bites, or bee stings can mimic preseptal cellulitis but can be differentiated by the significant itching, limited pain, and boggy rather than tense edema. Treatment options



**Figure 188-7** Capillary hemangioma.



**Figure 188-9** Chalazion.



**Figure 188-8** Contact dermatitis.

include oral antihistamines, topical or oral steroids, and cool compresses.

### **Hordeola and Chalazia**

Hordeola, commonly known as styes, and chalazia are localized inflammatory reactions to blocked oil glands (meibomian glands) in the eyelid margin. These lesions have focal areas of tense, firm, and often painful swelling with visible concretions in the oil glands near the areas of swelling (Figure 188-9). Treatment includes hot compresses with light massage and an antibiotic ointment (erythromycin, bacitracin) applied to the eyelash margin twice daily. If there is no resolution in 4 to 6 weeks, or if there is significant worsening, patients should be referred for evaluation of possible surgical drainage.

### **Blepharitis**

Blepharitis is a common, chronic inflammation and redness of the eyelid margin with blockage of the meibomian glands and associated crusting of the lashes. It is treated with lid scrubs using nonirritating products such as baby wash or baby shampoo to remove crusting, warm soaks to help drain the meibomian glands, and antibiotic ointment to the lids to reduce the bacterial load on the skin.

### **Trauma**

Trauma to the eye often leads to edema and ecchymosis of the eyelids, making examination difficult. The lids may be so tense that a lid speculum may be needed to open them, if the physician is comfortable using this instrument. If the eyelids cannot be opened with effort, a retrobulbar hemorrhage should be suspected, and emergent ophthalmologic consult should be obtained. Avoid putting any pressure on the eye until it is confirmed that the globe is intact.

### **Conjunctival Abnormalities**

Conjunctival redness can be either focal or diffuse, and the differential diagnosis includes viral or bacterial infection, chemical exposure, an allergic reaction, subconjunctival hemorrhage, a viral papilloma, or Kawasaki disease. For an overview of distinguishing characteristics among causes of conjunctivitis, see Table 188-2. Rarely, nondraining conjunctivitis can be caused by leptospirosis, tularemia, or toxin-mediated staphylococcal or streptococcal disease.

### **Viral Conjunctivitis**

The most common cause of conjunctivitis is a viral infection. Viral conjunctivitis is often highly contagious. Adenovirus is the most common viral pathogen. Rarely, herpes simplex virus (HSV) can cause conjunctivitis, but there are often typical HSV satellite lesions on the skin near the eye. Corneal involvement may also occur with HSV and is often accompanied by photophobia and more intense pain. (See Herpetic Keratitis.) Spreading through the copious watery discharge of an infected individual from eye to hand to eye, viral conjunctivitis quite commonly affects entire households or sports teams. In addition to itching, burning, or gritty sensation that typically starts in 1 eye and involves the fellow eye 2 to 5 days later, patients often complain of watery discharge, rhinorrhea, and sore throat. Patients can sometimes recall a recent exposure to a sick contact or someone with a red eye. There is often preauricular lymphadenopathy, and the conjunctiva will often have follicles, or bumps of lymphoid aggregates best seen with



**Table 188-2** Differentiating Types of Conjunctivitis

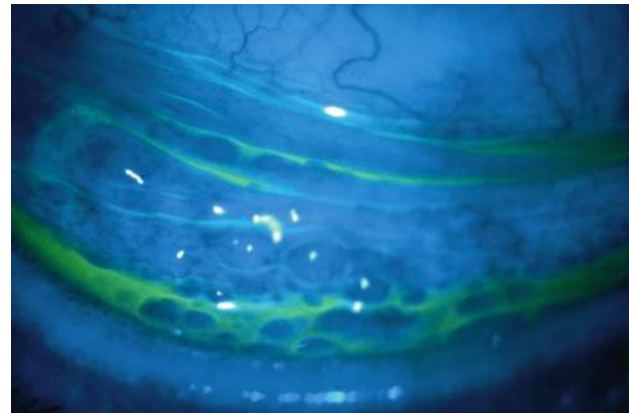
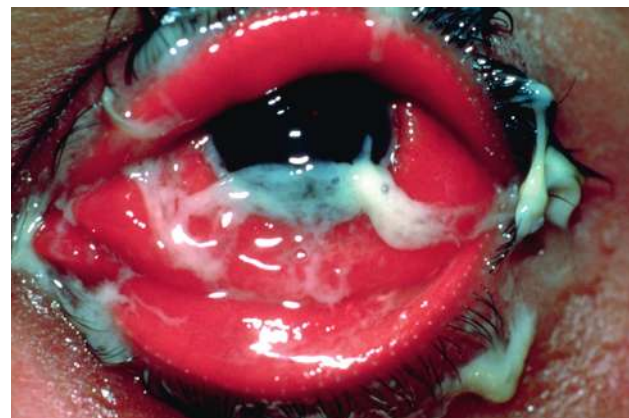
	BACTERIAL	VIRAL	ALLERGIC	PROBABLE REFERRAL
<b>Presentation</b>	Unilateral or bilateral	Usually unilateral, then spreads to other eye	Usually bilateral; can be unilateral	
<b>Season</b>	Common in winter	Spring or fall	Spring or fall	
<b>Onset</b>	Concurrent with otitis media	Concurrent systemic viral infection	Acute or chronic	
<b>Symptoms</b>	Crusting on eyelashes Gluey or sticky eyelids ± fever	Tearing Eye irritation ± fever	Itching Swelling of lids Conjunctival edema	Light sensitivity Pain Blurred vision
<b>Discharge type</b>	Purulent, thick, yellow/green	Serous or mucoid	Stringy, whitish, ropey, if any	
<b>Patient type</b>	Younger children Contact lens wearer	Any age	>2 yr	Red eye for ≥2 wk
<b>Examination findings</b>	Papules on conjunctiva	Follicles on palpebral conjunctiva Frequent preauricular nodes	Conjunctival edema and injection	

fluorescein (Figure 188-10). Severe cases sometimes have pseudomembranes of fibrin that cause scant bleeding when removed with cotton tips, as well as corneal subepithelial infiltrates, aggregates of immune cells. These signs occur 1 to 2 weeks after onset of symptoms and warrant referral to an ophthalmologist. Treatment is supportive, with a focus on minimizing contagion. Patients and parents should be instructed to wash their hands often and not share towels or bed linens. In the absence of systemic signs of illness such as fever, children with conjunctivitis should not be removed from school unless they are unable to participate in activities, the care of their classmates would be compromised by their need for special attention, or their exclusion has been recommended by a physician or department of health. In group care settings, if 2 or more children are infected with conjunctivitis at the same time, it is appropriate to seek the advice of a health care provider or department of health.

For nonspecific viral conjunctivitis or adenovirus, chilled preservative-free artificial tears 4 to 8 times a day and cool compresses several times a day are recommended for symptomatic relief. Currently, topical ganciclovir ophthalmic gel is being used off-label to treat adenoviral infections, as recent small case studies have shown its effectiveness. HSV conjunctivitis should be referred to an ophthalmologist for a more complete examination and antiviral therapy because it can be a vision-threatening infection.

### Bacterial Conjunctivitis

Compared with viral conjunctivitis, bacterial conjunctivitis is less common and often has a purulent rather than a watery discharge (Figure 188-11) and less of a follicular reaction. Cultures are not routinely performed. Common bacteria include *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. Topical antibiotic treatment

**Figure 188-10** Viral conjunctivitis.**Figure 188-11** Bacterial conjunctivitis.

is often successful, either with drops (trimethoprim-polymyxin B, moxifloxacin, or gentamicin 4 times a day for 7 to 10 days), or with an ointment (bacitracin-polymyxin B or erythromycin 4 times a day for 5 to 7 days). A fluoroquinolone gel (besifloxacin) is also approved for use, twice daily for 7 days.

In neonates with conjunctivitis, bacterial infection must be ruled out. With a hyperacute onset and copious discharge, gonococcus should be the first consideration because it can perforate a healthy cornea within 24 hours. Gonorrheal infection usually manifests 3 to 4 days after birth. Chlamydial infection can cause pneumonia as well as conjunctivitis and usually occurs within the first month of life. Cultures should be taken with special media. Presumptive treatment pending culture results involves intravenous ceftriaxone for *Neisseria gonorrhoeae* and oral erythromycin for chlamydia. Erythromycin has been associated with infantile hypertrophic pyloric stenosis (IHPS) when administered to infants younger than 6 weeks. Because the risk for IHPS after azithromycin has not been established and at least some evidence suggests it may be lower, some physicians prefer it in place of erythromycin, which the American Academy of Pediatrics continues to recommend. An ophthalmology consultation should be considered.

Of note, nasolacrimal duct obstruction, like bacterial conjunctivitis, can produce mucopurulent drainage, but the conjunctiva typically remains white and noninflamed. Pressure over the nasolacrimal sac, inferior to the medial canthus, will cause reflux of watery mucoid discharge.

In teenagers, bacterial conjunctivitis can represent a sexually transmitted disease, either gonorrhea or chlamydia. Gonorrhea typically produces hyperacute conjunctivitis with copious purulent discharge. Cultures should be taken, and the patient and sexual partners should be treated systemically for gonorrhea, usually with ceftriaxone. Chlamydia usually causes a chronic conjunctivitis with scant discharge and beefy inflamed conjunctiva. It should be suspected when topical antibiotics fail to improve a bacterial conjunctivitis. Treatment of patient and contacts is with oral azithromycin or doxycycline; however, the latter should be avoided in children younger than 8 years because of potential permanent staining of teeth.

### Chemical Conjunctivitis

Exposure to a chemical irritant can produce rapid conjunctival inflammation. For children who have gotten a household chemical into an eye, the most important treatment is immediate and copious irrigation with the nearest source of water. When the child is brought to medical attention, the pH of the conjunctival surface should be checked (basic solutions penetrate deeper and cause more damage than acids), and irrigation should not be discontinued until the pH remains 7.0 for several minutes after an interruption. If there are areas of white clear conjunctiva or corneal clouding, which suggest necrosis, the child should be urgently referred to an ophthalmologist for aggressive treatment. In most cases, however, artificial tears and topical antibiotic eyedrops are sufficient.

### Allergic Conjunctivitis

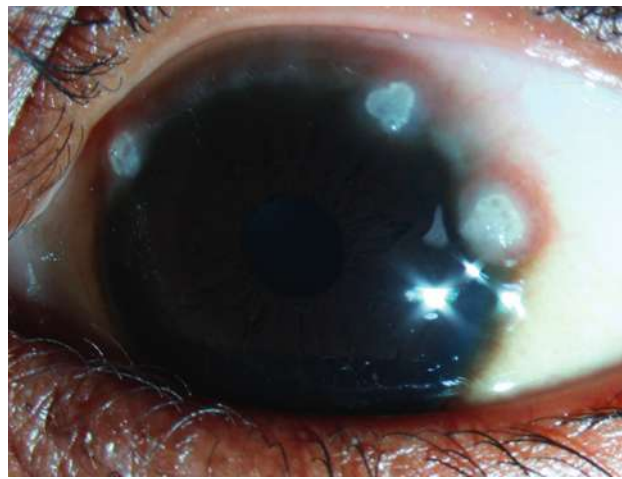
Allergic conjunctivitis may be acute or chronic, but it is almost always associated with itching. Discharge may be clear, with some mucus, or stringy and white. Conjunctival edema with associated redness may appear as an intensely swollen eye (Figure 188-12). Treatment of allergic conjunctivitis includes cool compresses, topical antihistamines and mast cell stabilizers, oral antihistamines, topical steroids, and rarely oral steroids.

Vernal conjunctivitis is a subset of allergic conjunctivitis that occurs most often in the springtime every year in young boys with a family history of allergies. On examination, there is often a ring of swollen, gelatinous conjunctiva with or without whitish-yellow deposits, and papillae are common on the tarsal conjunctiva (Figure 188-13).

Phlyctenulosis, another subset of allergic conjunctivitis, is a delayed hypersensitivity reaction that is often bilateral and results in a white, raised lesion on either



**Figure 188-12** Allergic conjunctivitis.



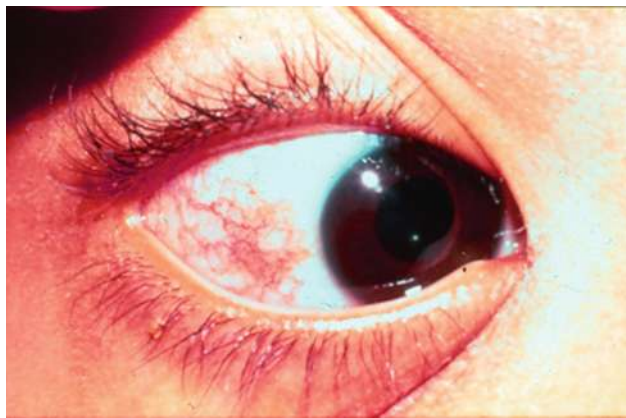
**Figure 188-13** Vernal conjunctivitis.



the conjunctiva or peripheral cornea, with dilated blood vessels at its borders (Figure 188-14). The most common precipitant is exposure to staphylococci, but it can also be associated with tuberculosis or histoplasmosis, so in cases without signs of blepharitis, a test for tuberculosis and a chest radiograph are warranted. Treatment is the same as for blepharitis, with the addition of interventions to treat the allergic component. Patients with significant irritation may require topical steroids and should be referred.

### **Subconjunctival Hemorrhage**

Subconjunctival hemorrhage is easily diagnosed by its often strikingly large patch of bright red on an otherwise white conjunctiva, usually in an asymptomatic patient (Figure 188-15). It can occur after a vaginal delivery, with Valsalva maneuver, with use of antiplatelet medications, from a severe cough as with pertussis, or from trauma. Nonaccidental trauma should be considered in atypical cases. When there are recurrent subconjunctival hemorrhages, a bleeding disorder or blood dyscrasia should be considered. No treatment is needed for a subconjunctival hemorrhage,



**Figure 188-14** Phlyctenule.

which will resolve over 2 to 3 weeks. It is worth counseling patients and parents that, as with most ecchymoses, the lesion may expand slightly and change colors as it resolves.

### **Conjunctival Papilloma**

Commonly a benign, self-limited lesion caused by human papillomavirus 6 or 11, a conjunctival papilloma is a fleshy nodule with a sunburst vascular pattern (Figure 188-16). For large, multiple, recurrent, or cosmetically disturbing lesions, treatment options include cryotherapy, surgical excision, and oral cimetidine.

### **Kawasaki Disease**

The bilateral nonexudative conjunctivitis of Kawasaki disease, an acute vasculitis, is associated with fever, mucosal erythema, rash, cervical lymphadenopathy, and the potential for coronary artery aneurysms. The conjunctivitis is usually self-limited and can be treated with artificial tears.

### **Corneal Abnormalities**

#### **Corneal Abrasion/Foreign Body**

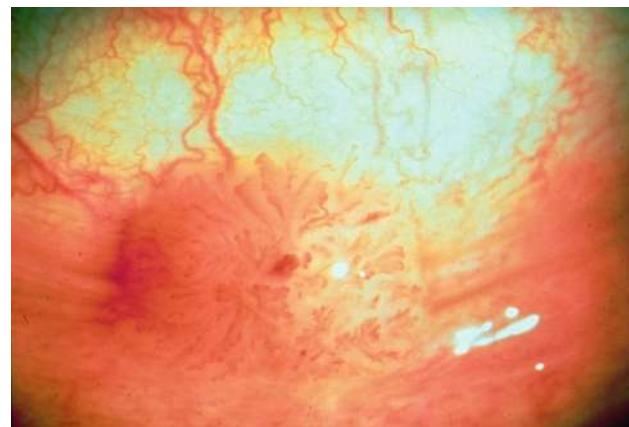
Corneal abrasions classically have a very painful presentation, and the patient will complain of a foreign body sensation, tearing, and often photophobia. Patients often recall a sudden onset after being hit or scratched in the eye. Examination is often difficult, but instillation of anesthetic drops, such as proparacaine 0.5%, facilitates examination. The corneal abrasion is easily identified with a Wood lamp and fluorescein. In patients with a corneal abrasion, a foreign body should be suspected, and the undersurface of the eyelids should be examined. A corneal foreign body (Figure 188-17) can be removed with a moist cotton-tipped applicator if superficial, but deeper ones should be referred to an ophthalmologist.

#### **Corneal Ulcer**

Bacterial, fungal, viral, or parasitic organisms can cause ulceration, a sight-threatening condition that requires urgent ophthalmologic evaluation if there is corneal opacity, decreased vision, or ocular pain



**Figure 188-15** Subconjunctival hemorrhage.



**Figure 188-16** Conjunctival papilloma.



**Figure 188-17** Corneal foreign body.

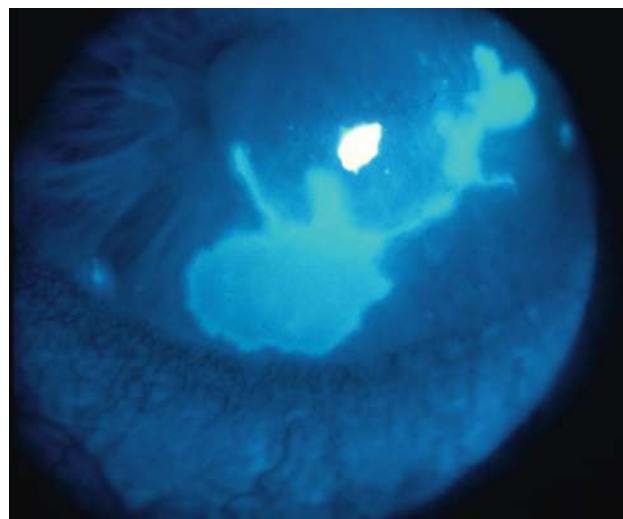


**Figure 188-18** Corneal ulcer.

(Figure 188-18). Because contact lenses are a significant cause of corneal infections, an ophthalmologist should evaluate patients who develop a red eye and wear contact lenses.

### **Herpetic Keratitis**

Both HSV and varicella-zoster virus (VZV) can infect the eye. Whereas VZV typically spreads to the eye from the face or eyelid, HSV can infect the cornea directly. Examination of the cornea with fluorescein reveals a dendritic branching epithelial defect (Figure 188-19). If herpes is suspected, an ophthalmologic evaluation is urgently warranted to evaluate for intraocular involvement and intraocular pressure elevation. Treatment of both HSV and VZV involves either oral antivirals (acyclovir, valacyclovir) or topical antiviral eyedrops (trifluridine) or gel (gancyclovir). If patients with a history of herpetic keratitis develop red eye, they should be seen by an ophthalmologist because recurrence is common. Corneal HSV disease often causes corneal scarring, which can be sight threatening.



**Figure 188-19** Herpetic keratitis.

### **Intraocular Abnormalities**

Corneal and ciliary flush (Figure 188-1) is a violaceous, extreme engorgement of vessels at the corneal limbus that indicates involvement of deeper ocular structures. A patient with this finding should always be referred to an ophthalmologist. The differential diagnosis includes corneal infection, iritis, uveitis, and hyphema.

### **Iritis/Uveitis**

Iritis and uveitis are inflammatory disorders within the eye often associated with sarcoidosis, HSV, syphilis, tuberculosis, lupus, or autoimmune arthritides—including JIA and the HLA-B27–positive spondyloarthropathies. Affected patients complain of photophobia, pain, and blurred vision and usually have ciliary flush and a mid-dilated pupil. In patients with a first episode of unilateral iritis, no workup is indicated because it will have an unidentified cause. However, in the case of recurrent or bilateral disease, or if the medical history suggests a systemic disorder, an underlying cause should be sought and treated. The laboratory workup includes antinuclear antibody, erythrocyte sedimentation rate, serum uric acid level, antineutrophil cytoplasmic antibody, rapid plasma reagin, and fluorescent treponemal antibody absorption. In children with JIA, frequent screening for uveitis is critical because the inflammation is commonly asymptomatic with few external findings and if left untreated can lead to blindness. Young patients with pauciarticular JIA should be evaluated every 3 months for 7 years. Treatment includes topical and/or oral steroids to control the disease and cycloplegia to prevent iris adhesions and reduce photophobia. In the event of long-term steroid use, intraocular pressure should be monitored.

### **Hyphema**

A hyphema is blood collected in the anterior chamber of the eye, which is located behind the cornea and in front of the lens (Figure 188-20). In children it is almost



**Figure 188-20** Hyphema.

exclusively a result of trauma, but in the absence of trauma, tumors and coagulopathies should be suspected. Affected patients should be referred to an ophthalmologist because treatment includes monitoring of intraocular pressure, cycloplegia to prevent iris movement and adhesions, topical steroids to decrease inflammation, and reduced patient activity to prevent a rebleed.

#### Other Inflammatory Conditions

Scleritis, episcleritis, and ocular myositis are rare inflammatory conditions that cause a focal conjunctival redness. Episcleritis and scleritis can be distinguished because episcleritis has minimal discomfort, in sharp contrast to the severe pain of scleritis. The inflammation of myositis is seen overlying the affected extraocular muscle, and often patients develop a head tilt to avoid using the sore muscle. The workup for these conditions is the same as for recurrent iritis. Treatment of episcleritis includes oral nonsteroidal anti-inflammatory drugs (NSAIDs, eg, ibuprofen) alone or accompanied by topical steroids. For scleritis and ocular myositis, ophthalmologic consultation should be obtained: treatment typically begins with NSAIDs; but if there is no improvement, systemic steroids with possible steroid-sparing immunosuppressive agents should be used.

In conclusion, the pediatrician can successfully perform the diagnosis and management of the red eye in children when attention is paid to the history, location of redness, and ocular structures involved. Accurate diagnosis allows for appropriate treatment and the proper timing of referrals.

#### SUGGESTED READINGS

- Bradford C, ed. *Basic Ophthalmology*. 8th ed. San Francisco, CA: American Academy of Ophthalmology; 2004.
- Ehlers JP, Shah CP. *The Wills Eye Manual: Office and Emergency Room Diagnosis and Treatment of Eye Disease*. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2008.

#### Chapter 189

### SCHOOL ABSENTEEISM AND SCHOOL REFUSAL

Ronald V. Marino, DO, MPH

A major developmental task of childhood is separating from the family and accepting the functional demands of society. One of the most obvious indicators that this process may not be proceeding normally is lack of attendance at school. Assessing a child's school attendance and functioning in the context of biopsychosocial health supervision is the responsibility of child health professionals.

Nonattendance may be the consequence of a variety of underlying causes. *Absenteeism* is generally considered to be parentally sanctioned nonattendance, most commonly attributed to medical illness. *Truancy* is nonattendance without parental consent, in which the time allegedly spent at school is often spent engaging in antisocial behaviors or rebelling against authority. *School refusal* is characterized by inappropriate fear about leaving home, inappropriate fear of school, or both.

#### ABSENTEEISM

Excessive absenteeism is important to health care professionals because it is an excellent marker for both physical and mental health problems (Box 189-1). It also is negatively correlated with social adjustment and academic performance. In fact, excessive absenteeism and failure to read at the appropriate level in the third grade are the 2 strongest predictors of subsequent dropping out of school. According to the National Center for Education Statistics for 2005, 19% of fourth-graders and 20% of eighth-graders missed at least 3 days of school in the past month. More specifically, 7% of fourth-graders and 7% of eighth-graders missed at least 5 days of school in the past month. National surveys indicate that healthy children average 4 or 5 absences a school year, whereas children who have a chronic disease typically are absent at least twice as often. Educators think that missing more than 10 days in a 90-day semester results in difficulty staying at grade level.

Acute physical health problems are given as the reason for nonattendance 75% of the time. However, the variability in absenteeism among children who have the same medical condition suggests that individual and family responses to the physical condition are more important than the actual condition in determining attendance. The decision not to attend school reflects subtle and complex relationships among the physical, social, and psychological states of the student, family, and community. Individual rates of absenteeism tend to be stable for a given child and also for a given school district.

The health conditions most commonly associated with nonattendance include upper respiratory tract infections, headaches, abdominal distress, menstrual cramps, and sleep disorders. Parental characteristics associated with excessive absenteeism include lower



### BOX 189-1 Chronic School Absence: Differential Diagnosis

- School refusal
- Parental overresponse to minor illnesses
- Chronic physical disease with poor adaptation
- Learning disability with poor adaptation
- Untreated mental health issues (eg, anxiety, depression)
- Bullying
- Truancy
- Substance abuse
- Psychosis
- Teenage pregnancy
- Family dysfunction (including violence and abuse)

socioeconomic class, cigarette smoking, chronic parental illness (including mental illness), lower educational expectations, and vulnerable child syndrome. A plethora of nonmedical conditions, including transportation difficulties, illness of other family members, religious holidays, family vacations, inclement weather, and professional appointments, are also reasons children miss school. Chronically ill children typically miss more school than their healthy peers. This tendency may result from a wide variety of causes, including acute exacerbations of the underlying condition, health care visits, side effects of medications, and parental misconceptions about the child's ability to attend school. Healthy adjustment by the child and family to the chronic condition minimizes the potential effect of the increase in school days missed. A significant increase in absenteeism over baseline is always a warning sign. Exploring the reasons why a particular child seeks to avoid school is the physician's responsibility. Sudden changes in school attendance may be the first concrete symptom of family dysfunction, mental illness, physical deterioration of the student or a family member, alcohol or drug abuse, or school refusal.

## SCHOOL REFUSAL

Difficulties attending school despite caretakers' support have been a problem for children, families, schools, and physicians since the early 20th century. Initial views of school refusal focused on truancy and its link to delinquency. In 1932, Broadwin focused attention on the frequent role of anxiety in attendance difficulties, and, in 1939, Patridge labeled this clinical condition *psychoneurotic truancy*. Johnson et al introduced the term *school phobia* in 1941, stressing that the child's anxiety about separating from mother was displaced to fear of attending school. This view was strengthened further in the 1950s, when Estes et al concluded that school phobia was a variant of separation anxiety.

This view and nomenclature persisted until the late 1970s, when the term *school refusal* was introduced.

The term has descriptive merits that recognize the heterogeneity of the underlying disorders. These disorders include, but are not limited to, major depression, simple and social phobia, or separation anxiety disorder. Criteria for making this diagnosis include severe difficulty in attending school or refusal to attend school, severe emotional upset when attempting to go to school, absence of significant antisocial disorders, and staying at home with the parent's knowledge.

A variety of physical symptoms often accompany the child's request to not attend school. Symptoms can be quite impressive to parents and may emulate organic medical problems.

## Prevalence

The prevalence of school refusal varies widely and has been estimated to be between 0.4% and 18%. The incidence of school refusal has 2 peaks—the first is associated with entering primary school (4–6 years), and the second is at the age of 11 to 12 years, a time of change from elementary to intermediate school, as well as the onset of early adolescence. The American Academy of Pediatrics estimates that 5% of elementary school children and 2% of junior high students experience this disorder. The symptoms of school refusal are associated with several psychiatric disorders. In an outpatient sample of referred children, 22% had separation anxiety disorder, 11% had generalized anxiety disorder, 8% had oppositional defiant disorder, and 5% had major depressive disorder. Of note is that 20% to 30% of school-refusing children do not qualify for any specific psychiatric diagnosis.

## Child-Related Factors

Children who have school refusal usually have at least average intelligence and academic achievement. Cultural norms encourage girls to admit fear and discourage boys from doing the same. The actual incidence of school refusal is nearly identical between the sexes. Younger children report more fear of being scolded or of performing before a group, whereas older children seem to be more intimidated by tests and the possibility of failure. Vague somatic symptoms, typically offered as a rationale for nonattendance, may belie the underlying anxiety that is frequently present. Symptoms may amplify in response to parental pressure to attend and/or excel in school. Overdependency or concern about the well-being of a parent is also a common underlying dynamic. Serious or chronic illness in the parent may lead to school refusal. Depression has often been noted, as have panic disorder and agoraphobia. Because there are reports of suicide among school refusers, any reference to this possibility must be addressed seriously.

## Family Factors

The family context is always a major factor because marital conflict or constricted communication patterns are often found in families with school refusers. The child's presence at home as a result of physical illness may provide a cohesive force to an otherwise unstable marital relationship. Families of youths with



school refusal behavior are often marked by poverty, poor cohesion and considerable conflict, enmeshment, isolation and detachment.

Common patterns of communication in families in which school refusal occurs have been described: Both parents are overly concerned and solicitous of the child's medical problem; 1 parent, typically the mother, is overprotective and concerned, whereas the other overtly disagrees; and 1 parent, typically the mother, is overinvolved in caring for the child's every need, whereas the other parent is emotionally absent. Because children are reared in many diverse family situations, physicians must remain open and attentive to family structure and dynamics in order to develop an effective treatment plan.

### School Environment Factors

The role of the school environment in school refusal has received little attention. Institutional factors such as changing classrooms or lack of privacy in the school bathroom have been associated with fear of school. The physical environment may include uncomfortable temperatures, mold, or allergens, which predispose to illness or student discomfort. Humiliation caused by an insensitive teacher may also be a precipitating stressor in the onset of clinical symptoms. Temperamental mismatch among teacher, student, and parents may serve a maintaining role.

Bullying and social humiliation are increasing in frequency and victims often develop somatic symptoms as a coping mechanism. The increased use of social media has created a new and potentially dangerous phenomenon in cyber bullying. Cyber bullying is defined as willful and repeated harm inflicted through the use of computers, cell phones, and other electronic devices. More than 20% of 4,400 randomly selected 11- to 18-year-olds indicated they had been subjected to cyber bullying at some point in their lives. In 2005, 24% of students aged 12 to 18 years reported gangs at their schools; this was more common among urban (36%) than suburban (21%) or rural (16%) schools. In addition, 28% of students aged 12 to 18 years were reportedly bullied at school in the past 6 months. Most said bullying occurred 1 to 2 times in 6 months, but 25% were bullied 1 to 2 times per month, 11% were bullied 1 to 2 times per week, and 8% were reportedly bullied almost daily. Both traditional and cyber bullying have been implicated as sources of severe emotional distress among victims, even leading to suicide. Violence in secondary schools provides children a seemingly appropriate reason for refusing to attend school. Twenty-six percent of junior and senior high school students have been assaulted on school grounds, 20% of students admitted bringing a knife or gun to school, and 10% admitted not going to school because of fear of violence. Media attention to school violence may further accelerates a child's anxiety and school refusal. Clearly, school-associated stressors are emerging as a concern in understanding and treating school refusal.

### Associated Stressors

While exploring factors related to the child, parent, family, and school environment, the physician must

also search for a precipitating event or stress that may have tipped the balance in causing a child to refuse to attend school. Illness or injury of a family member or of the child may be the initial reason for nonattendance. Similarly, the death of a relative or close friend may precipitate the refusal. Moving to a new home, community, or school also may contribute to refusal. The longer a child has been out of school, the more difficult and stressful returning can become.

### Clinical Management

In 1958, Eisenberg stated, "[I]t is essential that the paralyzing force of the school phobia on the child's whole life be recognized. The symptom itself serves to isolate him from normal experience and makes further psychological growth almost impossible. If we do no more than check this central symptom, we have nonetheless done a great deal." The foundations of any clinical treatment plan are rapport, trust, and respect. The initial interview should serve not only as a means of gathering data, but also as the start of a therapeutic alliance. Physicians should use a sensitive, holistic approach to data gathering, because the history-taking technique provides the first opportunity for creating a healing rapport. Factors related to the child, parents, family, and school environment must be investigated when exploring school maladaptation. An open mind that recognizes the unique and complex interactions of temperament, stressful life events, family systems function, learning style, parental medical or psychiatric conditions, and school system variables will be helpful in solving this problem. The child must understand that involving a physician in treatment reflects the seriousness of the symptoms and marks a turning point in changing the avoidant behavior.

Organic disease should be ruled out through a thorough history and physical examination, coupled with judicious laboratory evaluation. Time spent in conducting a thorough medical examination communicates the physician's sincere acceptance of the child's symptoms as being real. Parents are better able to confront the lack of organic disease when a physician who is completely familiar with the child's history and physical examination discusses the subject with them. A biopsychosocial approach from the outset also aids family acceptance of psychiatric concerns. The laboratory should be used in a symptom-specific, noninvasive, cost-effective manner consistent with ruling out possible organic disease. Additionally, addressing the potential contributions of parental disorders or specific environmental problems will be helpful in formulating a treatment plan.

The parents, physician, and school personnel must all agree that returning to school as quickly as possible is the immediate goal of treatment. Allowing the child to stay home while awaiting laboratory data results or using home tutors only delays the inevitable and makes the return to school more difficult. A specific plan must be developed to respond to clinical symptoms. Objective criteria for school absence, such as a measured fever, should be consistently used in modifying performance expectations, both at home and in school. Parents in doubt should seek the guidance of the child's physician regarding the significance of acute symptoms

before keeping the child home. In addition, the significant attachment figures in the child's life must make it clear they will adhere to the therapeutic program consistently and persistently. In most cases of school refusal, especially in the elementary years, the aforementioned program, carried out by the primary care pediatrician, is curative. Other treatment modalities, typically used by a mental health professional, include desensitization, psychotherapy, hypnotherapy, cognitive restructuring, and behavior modification. A variety of psychopharmacologic agents have been used to manage anxiety- or depression-based school refusal. Selective serotonin reuptake inhibitors (SSRIs) predominate the scant literature and have been found to be useful in some individuals. Concerns about a possible relationship between SSRIs and risk of suicide in children and adolescents have reduced the number of primary care physicians willing to prescribe these medications. Children who are recalcitrant to behavioral interventions may require referral to a mental health specialist. Suggested criteria for mental health referral are listed in Box 189-2.

Mental health professionals typically employ cognitive behavioral therapy with or without SSRIs. Severe cases may require inpatient treatment.

### Prognosis

Most children who refuse to attend school quickly overcome the difficulty with appropriate clinical management. Intermittent relapses associated with stress or new separation experiences, such as camp or sleepovers, occur in approximately 5% of children. Children who require psychiatric management do not fare as well. Most published series in the psychiatric literature reveal significant cohorts of patients requiring ongoing therapy and having persistent difficulties in emancipating themselves from their family. Phobias, depression, and anxiety are more common in adults who have a history of childhood school refusal. Table 189-1 lists long-term sequelae in children with school refusal.

### Prevention

Anticipatory guidance is an excellent means of primary prevention, and allows the primary care physician to advise parents on developmentally appropriate separation guidelines. For example, by the time an infant is 6 months of age, the parents should be able to spend some evenings out alone. By 1 year of age, peer contact should be encouraged. Toddlers should experience babysitters while awake. By age 3 years, the child should experience being away from home without a parent, such as in a playgroup or at a neighbor's home. Age 4 years is a good time to consider preschool for the child. Such guidance can be shared in the context of routine health supervision. Parents should also be discouraged from keeping children home because of minor illness, and physicians must avoid unnecessary medical restrictions.

Preventing vulnerable child syndrome is also important when caring for ill children. This disorder arises when parents think that their child's life has been threatened significantly, and it results in separation

### BOX 189-2 Criteria for Mental Health Referral

- Unresponsive to management
- Out of school for 2 months
- Onset in adolescence
- Psychosis
- Depression
- Panic reactions
- Parental inability to cooperate with treatment plan

**Table 189-1**

### Long-term Sequelae in Children With School Refusal

OUTCOME	PREVALENCE
Interrupted compulsory school	18%
Did not complete high school	45%
Adult psychiatric outpatient care	43%
Adult psychiatric inpatient care	6%
Criminal offense	6%
Still living with parents after 20-year follow-up	14%
Married at 20-year follow-up	41%

From Fremont WD. School refusal in children and adolescents. *Am Fam Physician*. 2003;68(8):1555–1560. Data from Bernstein GA, Hektner JM, Borchardt CM, McMillan MH. Treatment of school refusal: one-year follow-up. *J Am Acad Child Adolesc Psychiatry*. 2001;40(2):206–213; Flakierska-Praquin N, Lindström M, Gillberg C. School phobia with separation anxiety disorder: a comparative 20- to 29-year follow-up study of 35 school refusers. *Compr Psychiatry*. 1997;38(1):17–22.

difficulties, overprotection, bodily concerns, and underachievement in school. Parents need to be informed about the true significance and prognosis of any medical difficulty the child has experienced. Physicians have a responsibility to avoid creating iatrogenic misconceptions about a child's health. They can accomplish this task by using everyday language as much as possible, rather than medical jargon, and by demystifying anxiety associated with insignificant findings, such as a functional murmur. Parents need to be reassured that children who have recovered fully from an acute illness are at no increased risk for future illness. By inquiring about children's school attendance and promoting healthy parenting styles, primary care physicians can help prevent school refusal.

### TRUANCY AND DROPPING OUT

Truancy is a good predictor of dropping out at a later date. Many schools in inner cities report daily absence rates above 20%, with most of this thought to be the result of truancy; an equal or greater percentage of inner-city school children never finish high school. Truancy is a serious social problem that can have lifelong consequences. Unemployment or underemployment, criminal behavior, marital problems, and

chronic social maladjustment are often seen in children with truancy or children who drop out. These same long-term outcomes have been identified in groups of children who have learning disabilities. One risk factor for truancy is learning disability and its associated school failure.

Truancy also has been noted among children who have a history of having been sexually abused. Other risk factors are low socioeconomic status, conduct disorder, gang membership, substance abuse, cigarette smoking, and family discord. Early recognition of children at risk should prompt immediate intervention to promote optimal adjustment. Mobilization of resources in the school, community, and family is critical to help prevent progression from truancy to dropping out. Creative programs to foster school attendance and success have been conducted with variable results. An emerging new truancy variant is the child who goes to school or its immediate environment but does not attend class. This child is participating in the social aspects of the school community but is shunning the academics. Medical physicians can assume an advocacy role in guiding and supporting therapeutic interventions in the educational and social welfare arenas.

## CONCLUSION

Absenteeism is a symptom that has multiple causes. Because success in school is often the foundation for continuing success in life, health care professionals must devote thoughtful attention to understanding and treating absentees. Using a biopsychosocial model and mobilizing multidisciplinary resources are the keys to clinical success.

## TOOLS FOR PRACTICE

### Medical Decision Support

- *AAP Council on School Health* (Web page), American Academy of Pediatrics ([www.schoolhealth.org](http://www.schoolhealth.org))
- *Adolescent and School Health* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/HealthyYouth](http://www.cdc.gov/HealthyYouth))
- *Managing Infectious Diseases in Child Care and Schools* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *School Health: Policy & Practice*, 6th ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

## AAP POLICY

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## Chapter 190

# SCROTAL SWELLING AND PAIN

Lane S. Palmer, MD

Scrotal swelling can be particularly frightening for boys and their families, and because the differential diagnosis includes conditions that demand emergent treatment, it poses a challenge to pediatricians. A helpful organizing strategy during evaluation is to classify the scrotal swelling as either painful or painless and as acute or chronic (Box 190-1). Rapid and accurate evaluation of a boy with scrotal swelling depends on a thorough history and a physical examination of the genital area and abdomen that includes both inspection and palpation. Laboratory tests may be helpful but are not usually decisive, whereas imaging studies can be helpful in confirming a diagnosis and guiding management.

**BOX 190-1 Causes of Scrotal Swelling****ACUTE, PAINFUL SCROTAL SWELLING**

- Torsion of spermatic cord
- Torsion of appendix, testis, epididymis
- Acute epididymitis, orchitis
- Mumps orchitis
- Henoch-Schönlein purpura
- Trauma
- Insect bite
- Thrombosis of spermatic vein
- Fat necrosis
- Hernia
- Folliculitis
- Dermatitis, acute

**PAINLESS SCROTAL SWELLING**

- Tumor
- Idiopathic scrotal edema
- Hydrocele
- Henoch-Schönlein purpura
- Hernia

**CHRONIC SCROTAL SWELLING**

- Hydrocele
- Hernia
- Varicocele
- Spermatocele
- Sebaceous cyst
- Tumor

**EVALUATION OF THE CHILD WITH SCROTAL SWELLING**

The history should be taken from both the child (when possible) and the parent. The physician must determine whether the swelling or pain is a single event or recurrent and whether it is acute or chronic. The exact timing of the onset of symptoms is vital, particularly in the presence of acute pain and swelling. The nature of the pain must be determined: sharp, dull, constant, intermittent, constant with intermittent increases in intensity, or associated with nausea or vomiting. The location of the pain needs to be ascertained (ie, in the scrotum, specifically the testis; radiation into the abdomen or from the abdomen into the scrotum; laterality of the swelling and pain). Associated factors such as activity or positions that alleviate or aggravate the pain and swelling should be elicited. The nature of the swelling is important: specifically, whether the swelling changes in size during the course of a single day or whether it is constant or, in general, increasing or decreasing with time. Other important considerations include recent trauma, sexual activity, use of medications, the presence of rashes, weight loss, and nausea and vomiting.

The physical examination should include the abdomen, groin, and scrotum. Palpation of the abdomen and groin is important in determining whether an intraabdominal process is extending into the scrotum. Inspection of the scrotum should look for laterality of the process, scrotal erythema, and orientation of the testis, whereas palpation will determine the presence and symmetry of cremasteric reflexes, testicular position, tenderness, localization of the swelling to the intrascrotal contents, or the presence of proximal extension into the cord.

In general, laboratory tests are of limited value. The white blood cell count may be elevated in the setting of infection. Urinalysis may be helpful in distinguishing orchitis from torsion of the spermatic cord or testicular appendage when white blood cells or nitrites are present.

Imaging studies can be useful in differentiating among possible diagnoses. Ultrasound of the scrotum can be used to determine whether the scrotal swelling is fluid filled or solid, arising from the abdomen extending into the groin, limited to the scrotum, or arising from the testis or spermatic cord structures. Ultrasound with Doppler can assess the flow of blood into the testis, helping to differentiate torsion of the testis from an inflammatory process. Nuclear scintigraphy using technetium-99m pertechnetate is another way to evaluate blood flow to the testis; absence of flow results in a cold spot and suggests torsion, whereas inflammation results in increased flow to the same area. Nuclear scanning is less limited by the user variability associated with ultrasound and does not require placing a probe over a tender area. However, the study uses ionizing radiation and takes longer to perform than ultrasound, thus limiting its utility when time is of the essence. The sensitivity and specificity of the 2 modalities are similar.

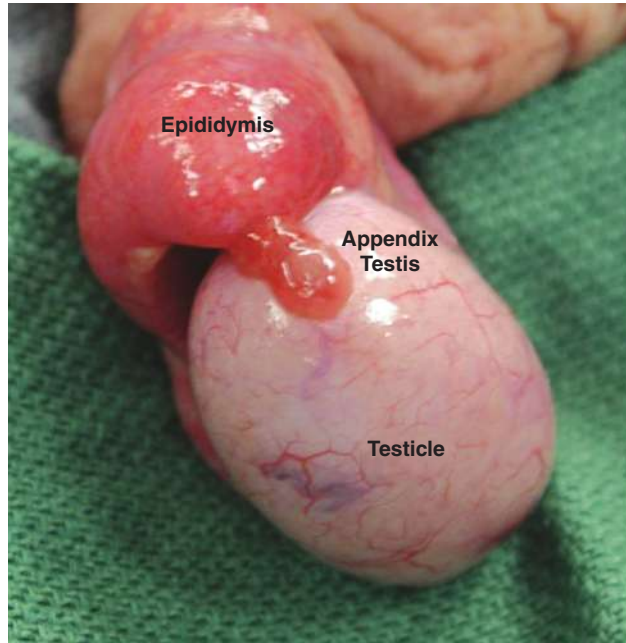
**ACUTE SCROTAL SWELLING WITH PAIN**

The sudden onset of scrotal swelling and pain can be a surgical emergency and therefore warrants urgent evaluation and management. The primary clinical entities that constitute this constellation of signs and symptoms include torsion of the testicle, torsion of the testicular appendages, and epididymitis-orchitis (Figure 190-1).

**Torsion of the Testicle**

Testicular torsion is the twisting of the spermatic cord, with resulting compromise of the blood supply to the testis. This compromise and the risk it poses for testicular loss makes torsion a surgical emergency. In the neonate, the torsion occurs on the cord above the insertion of the tunica vaginalis (ie, extravaginal torsion). In the adolescent, the *bell clapper deformity* leads to torsion on the cord within the confines of the tunica vaginalis (ie, intravaginal torsion). Torsion of the spermatic cord first causes venous congestion, which is followed by compromise of arterial blood flow. Spermatogenesis may be compromised after 4 to 6 hours of ischemia. Similarly, testicular salvage is time dependent, with universal loss of the testis after





**Figure 190-1** Structures of the scrotum.

24 hours of torsion. A familial tendency has been described, and although the mode of inheritance remains ill-defined, 1 family with 3 generations has been identified. In addition, there may be some seasonal variation in the presentation of acute testicular torsion with a predilection for the colder months, although this has not been true in all series.

### **Incidence**

Testicular torsion occurs in 1 in 4,000 boys. Although a peak in incidence occurs in the neonatal period, testicular torsion more commonly occurs between the ages of 12 and 18 years. Nevertheless, testicular torsion should not be excluded from the differential diagnosis of acute scrotal swelling and pain based on age.

### **Evaluation**

The history typically describes acute onset of constant, severe scrotal pain aggravated by physical activity and sometimes alleviated by being still. If periods of acute respite from the pain occur, then intermittent torsion and detorsion should be considered. Nausea and vomiting may occur. The patient may have a history of incidental antecedent scrotal trauma, but the onset of pain usually occurs during periods of rest or sleep. Characteristic findings on physical examination include scrotal erythema and swelling of the involved hemiscrotum. Further inspection may reveal a higher-than-normal position of the testis within the scrotum and may also demonstrate a horizontal rather than the normal vertical orientation of the testicle. Evaluation of the cremasteric reflex should begin on the contralateral side, along with palpation of the apparently unaffected testis to confirm normal size and position. Unilateral loss of the cremasteric reflex on the side of the swelling and pain highly correlates with the



**Figure 190-2** Intraoperative photograph of nonsalvageable testis after prolonged period of pain.

presence of torsion. The testis should then be palpated despite the pain the maneuver may cause to help differentiate torsion from epididymitis. With torsion, exquisite pain is elicited on palpation from the testis, as well as from the epididymis and distal spermatic cord. In some instances, the actual point of torsion of the spermatic cord can be palpated. An associated hydrocele may be palpated and confirmed by transillumination. A tense or large hydrocele often makes the examination difficult. Urinalysis is unremarkable, and although the white blood cell count may be mildly elevated, it is not discriminating. Imaging by nuclear scintigraphy or Doppler ultrasound should be performed if the diagnosis of testicular torsion is in question, but only when it will not unduly delay surgical exploration if a torsion exists, adding to the risk for testicular loss. The absence of blood flow on Doppler and the presence of heterogeneous parenchyma are indicative of a “missed torsion” and a nonsalvageable testis.

### **Treatment**

Surgical intervention is not only indicated when testicular torsion is strongly suspected, but also should be considered in equivocal cases when torsion cannot be convincingly excluded. The likelihood of salvaging the testis, the goal of surgical exploration, is highest when surgery occurs shortly after the onset of pain; the chance for a successful outcome dissipates rapidly with time (Figure 190-2). With surgery, the affected testis is explored first, and when torsion is present, the cord is detorsed. The contralateral testis, which may have the same anatomic defect, is explored and fixed in place to avert a future metachronous torsion. The affected gonad is then reinspected and the possibility of salvage determined. If the testis can be saved, then it is fixed in the scrotum. Subsequent atrophy may still

result because of the vascular insult, and fertility may be compromised as well.

When testicular torsion is diagnosed, manual detorsion can be attempted while surgery is being arranged. The testis is twisted either clockwise or counterclockwise. When twisting in 1 direction has not succeeded, an attempt in the opposite direction can be made. When the procedure is successful, the return of blood flow to the testis provides rapid relief from pain. If manual detorsion can be accomplished preoperatively, then the surgical intervention to tack down the testes can be performed electively.

### Neonatal Testicular Torsion

Neonatal testicular torsion can exhibit at delivery as a nontender hard scrotal mass. Salvage in these cases is rare, and emergent exploration is futile. At exploration, the contralateral testis should be anchored and the nonviable testis removed. Although neonatal torsion can occur after delivery, this is very uncommon and then is more typical of torsion in the older patient, with a greater potential for salvage if intervention is rapid.

### Torsion of the Appendix Testis

#### Evaluation

Torsion of the appendix testis or appendix epididymis may lead to a clinical picture similar to that of the more consequential and urgent torsion of the spermatic cord. The appendix testis is a vestige of the Müllerian duct system and hangs from the anterior surface of the testis where it meets the head of the epididymis. When it torses, inflammation and swelling of the testis and epididymis ensues, causing testicular pain and scrotal erythema. The onset of pain and swelling is commonly acute but can be progressive, usually occurring during periods of rest. The pain can be severe, but nausea and vomiting are less common than with testicular torsion. The physical examination may demonstrate hemiscrotal erythema and swelling. The *blue dot sign*, with the necrotic appendage visible through the scrotal skin, can help make the diagnosis. A normal cremasteric reflex is present bilaterally, and the testis is normally positioned within the scrotum. Testicular discomfort, if present, is typically mild, but point tenderness may be elicited from the uppermost pole of the testis near the head of the epididymis—the location of the appendages. On palpation, the examiner may feel a 3- to 5-mm tender indurated mass on the upper pole. In some cases, the inflammatory process resulting from torsion of the appendage can lead to physical findings that make differentiating from true spermatic cord torsion impossible. In these cases, imaging may be helpful because either scrotal Doppler ultrasound or nuclear scintigraphy will demonstrate normal or increased flow to the ipsilateral testis.

#### Treatment

The management of the torted appendage is nonsurgical. The patient should rest and use nonsteroidal pain relievers and cold compresses for several days to reduce the inflammation, swelling, and pain. Surgical intervention is indicated only when the diagnosis of

acute testicular torsion cannot be excluded. In these cases, the infarcted appendage is removed at surgical exploration.

### Acute Epididymitis-Orchitis

#### Evaluation

Acute inflammation of the epididymis or testis occurs in both young and older boys. Uncommon in the younger child, it usually results from an anomaly of the urinary tract, either congenital or acquired, which can often be identified by renal and bladder sonography. Renal duplications and posterior urethral valves are among the more common anomalies. Traditionally, a voiding cystourethrogram has been a routine part of the evaluation, but its yield is low with a normal ultrasound and a sterile urine. In children who perform intermittent catheterization, epididymo-orchitis can occur from the retrograde passage of bacteria back from the ejaculatory ducts at the level of the prostate to the testis and epididymis.

In the older child and adolescent, the history and physical examination may help distinguish epididymitis or orchitis from testicular torsion or appendix torsion, but this is not always the case. The history can reveal an acute or more protracted onset of pain. The patient may have fever or dysuria. Epididymal inflammation may arise after scrotal trauma. In the adolescent patient, a history of sexual activity or a urethral discharge helps guide antibiotic treatment. The physical examination reveals scrotal erythema and swelling and an intact cremasteric reflex. Palpation during the early phase of the inflammatory process demonstrates tenderness limited to the epididymis, whereas in the later phase, the tenderness and inflammation include both the epididymis and testis, and the distinction between the 2 structures may be difficult to appreciate. The Prehn sign (relief of pain with testicular elevation) may be positive.

Laboratory and radiologic imaging are useful in these cases. Urinalysis may prove positive for white blood cells and nitrite but is often unremarkable among adolescents. The white blood cell count is usually elevated. Ultrasound and nuclear scintigraphy studies demonstrate either normal symmetrical blood flow or increased blood flow to an enlarged epididymis or testis.

#### Treatment

Management of epididymo-orchitis requires antibiotic therapy that is based on the results of the urine culture and sensitivities. In the sexually active adolescent, the choice of antibiotic coverage must also include coverage of gonococcal and nongonococcal sexually transmitted infections. Additionally, anti-inflammatory agents, scrotal elevation, and rest should be prescribed.

### Other Causes of Acute Swelling and Pain of the Scrotum

#### Henoch-Schönlein Purpura

Henoch-Schönlein purpura is a systemic vasculitis that can cause abdominal pain, joint pain, renal disease, and bleeding from the gastrointestinal tract

and may involve the scrotal wall in a minority of cases. The onset may be insidious or acute, producing a variable degree of erythema and edema. In more severe cases, the process may involve the testis and epididymis, mimicking testicular torsion. The presence of concurrent Henoch-Schönlein purpura and testicular torsion has been reported; therefore, if torsion is a consideration, then imaging with either Doppler ultrasound or nuclear scintigraphy is indicated to evaluate testicular blood flow. Surgical exploration may be needed in equivocal cases.

### Focal Fat Necrosis

Focal fat necrosis can result in scrotal pain and swelling, usually after trauma, in an obese boy. The examination demonstrates pain and swelling limited to the scrotum and not the testis; however, the examination can be limited by the discomfort and the degree of obesity. If properly diagnosed, then management consists of rest and anti-inflammatory agents. When spermatic cord torsion cannot be excluded clinically, either an imaging study or immediate surgical exploration is indicated.

### Trauma

Injuries can vary from zipper entrapment of scrotal skin to more severe blunt or straddle trauma affecting the scrotal contents. The history can be definitive. The physical examination must include both hemiscrotums and the surrounding structures (penis, perineum), assessing for swelling, ecchymosis, and bleeding. Palpation may be limited by the degree of swelling or blood within the scrotum. The tenderness may be limited to the testis or the epididymis, depending on the extent of the trauma. Scrotal ultrasound can document the integrity of the testis and of the tunica albuginea and the adequacy of blood flow. Testicular or spermatic cord contusions are managed symptomatically, whereas testicular rupture may require surgical exploration, evacuation of the hematoma, debridement, and repair (when possible); however, a nonsurgical approach has been reported.

### Mumps Orchitis

Mumps orchitis can occur at any age but is more common among adolescents. Rarely occurring in isolation, the pain and swelling usually occur within 1 week

after parotitis. The physical examination demonstrates a tender testis. Treatment is symptomatic. Infertility may occur when mumps orchitis results in atrophy of both testicles.

### Scrotal Skin Disease

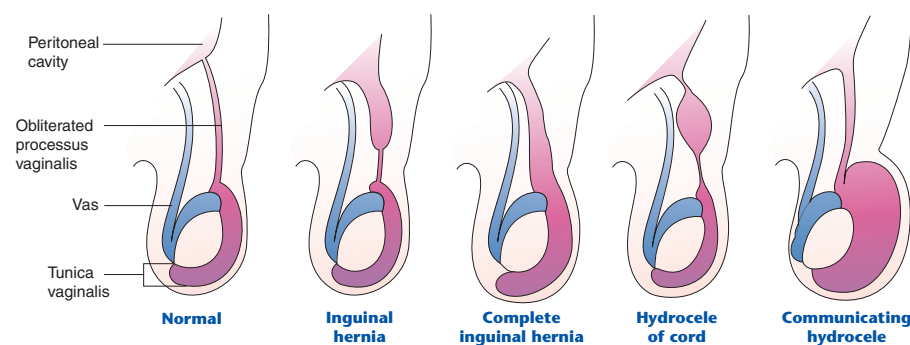
Insect bites, folliculitis, and allergic dermatitis may cause erythema and edema of the scrotal wall. The history may be of limited utility. The examination reveals redness and edema limited to the scrotum, with a normal testicle and spermatic cord. Idiopathic scrotal edema affects children younger than 14 years, with acute erythema, edema, and mild scrotal wall tenderness, sparing the testis and cord. The process resolves spontaneously. The management includes rest and scrotal elevation.

## SCROTAL SWELLING WITHOUT PAIN

### Inguinal Hernias and Hydroceles

Hernias and hydroceles, the most common causes of scrotal swelling, fall along a continuum (Figure 190-3). They are more common in premature infants and are predominately right sided. Most inguinal hernias and hydroceles are caused by persistent patency of the processus vaginalis (PPV), a peritoneal evagination that accompanies the testis during its abdominal-scrotal descent. The layers of the processus vaginalis condense late in gestation or early postnatally. Obliteration of the processus vaginalis only around the testis leads to an indirect inguinal hernia with the protrusion of fluid (or other contents) through the internal ring to the end of the pouch and potentially to the scrotum. A communicating hydrocele occurs when fluid travels through a PPV into the tunica vaginalis around the testis. A scrotal hydrocele occurs after complete obliteration proximally with patency distally. Hydroceles of the cord occur when the processus vaginalis obliterates proximally and distally, leaving a patent area in the midportion with retained fluid.

Inguinal hernias and hydroceles may be asymptomatic or may have a spectrum of symptoms. A hernia can occur at any age as an inguinal swelling extending toward and potentially reaching the scrotum. The swelling expands with increases in intraabdominal pressure (eg, crying, bowel movements, coughing, exercise). The parent or child will often report the



**Figure 190-3** Diagram of the continuum of hernia and hydrocele.



swelling to be smallest in the morning and greatest later in the day. When omentum is in the hernia sac, the likelihood of spontaneous reduction is low, and periods of discomfort can occur. An incarcerated hernia can produce pain, fever, nausea, vomiting, and irritability. A hydrocele is usually an asymptomatic bulge in the scrotum. In many instances, whether the hydrocele is acute or whether the scrotum has been chronically enlarged is unclear. The patient may have a history of trauma to the scrotum that stimulates the production of serous fluid. When the scrotum changes sizes during the day, the physician should suspect a communicating hydrocele.

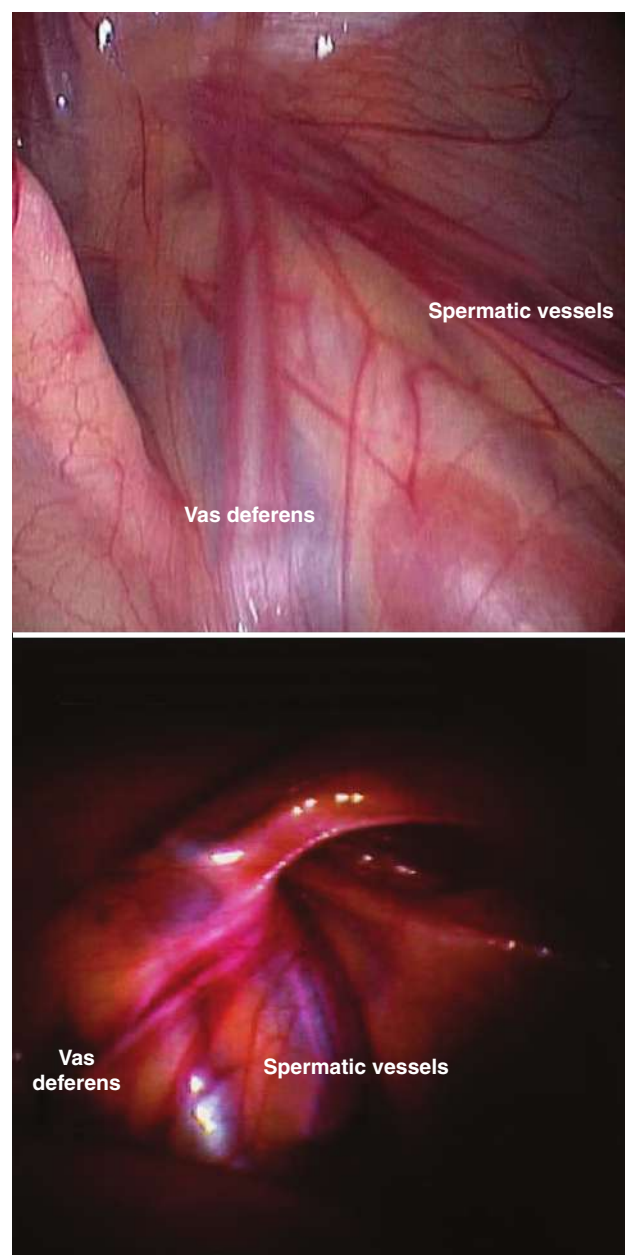
### Evaluation

The physical examination is often sufficient to distinguish among these entities. The examiner should feel for the testis first and keep it in mind during the rest of the examination so as to avoid confusing it with the contents of an incarcerated hernia. A bulge in the inguinal region with fluid that can be gently reduced back into the abdomen is diagnostic of an inguinal hernia. In the cooperative child who can increase his intraabdominal pressure, this procedure may be repeatedly demonstrated particularly with the child standing. When the fluid is limited to the testis and the spermatic cord can be palpated above the fluid, a hydrocele is present. The presence of a thickened spermatic cord or a *silk stocking sign* (the feel of the layers of the processus vaginalis being rubbed against each other) is suggestive of a PPV or a hernia, which is helpful in distinguishing a scrotal hydrocele from a communicating hydrocele. Hydroceles transilluminate, but so can the incarcerated bowel of an infant. A hydrocele of the spermatic cord feels distinct from the testis and is round or ovoid, possibly mimicking the presence of an additional testis. Hydroceles, whether communicating, scrotal, or of the cord, are rarely associated with tenderness on palpation.

Ultrasound can be useful to delineate the scrotal contents, especially when a large or tense hydrocele limits the physical examination, and to determine the cystic or solid nature of a tense scrotal mass (eg, hydrocele, tumor) or spermatic cord mass (eg, hydrocele of the cord, paratesticular tumor). Laboratory tests are useful only in cases of incarcerated inguinal hernias, with an elevated white blood cell count and possible acidosis.

### Treatment

Inguinal hernias and communicating hydroceles should be repaired on diagnosis to prevent incarceration. The risk for incarceration increases with time and is more likely in the young child or infant. Communicating hydroceles should also be repaired on diagnosis to avert progression. Surgery is performed inguinally, during which the sac is isolated from the cord structures and ligated at the level of the internal ring. The likelihood of a PPV on the contralateral side is highest in younger children, and the need for contralateral exploration remains controversial. However, diagnostic laparoscopy through the isolated ipsilateral sac allows visualization of the contralateral ring (Figure 190-4). If the internal ring is open, then



**Figure 190-4** Laparoscopic appearance of a closed (*top*) and an open (*bottom*) internal inguinal ring. The ring appears at junction of the vas deferens and the internal spermatic vessels.

contralateral surgical correction proceeds. Most hydroceles resolve spontaneously by 1 year and should be repaired if they persist beyond this age. However, if the hydrocele is painful, tense, and large, then surgery should proceed sooner. In younger children, the surgical approach is inguinal; in older boys and adolescents, a scrotal approach is appropriate.

### Tumors

Testicular tumors are uncommon in children, accounting for 1% to 2% of all solid tumors, but occur in all



age groups. Fortunately, about 74% of prepubertal testis tumors are benign. Tumors are usually displayed as a hard, painless (or a vague, heavy-feeling) mass in the testicle detected by the child, parent, or examining physician. On palpation, the mass is harder than the substance of the testis, but this distinction may be difficult to discern. The mass may bulge from the surface of the testis. Tumors do not transilluminate. Scrotal ultrasound is used to delineate the mass and in some cases help to assess whether the mass is likely to be benign (anechoic). Preoperative tumor markers ( $\alpha$ -fetoprotein [AFP],  $\beta$ -human chorionic gonadotropin) should be drawn and used for postoperative monitoring. AFP cannot be used effectively as a tumor marker until it is no longer produced at about 8 months of age. Staging depends on serum markers, computed tomography (CT) imaging of the retroperitoneum and chest, and pathology. The surgical approach depends on the nature of the mass. All cases are approached through an inguinal incision in case the mass is malignant. Mature teratoma, the most common testis tumor among prepubertal males, is benign and is managed by testis-sparing surgery. Immature teratoma has also been successfully managed without removing the testis. Yolk sac tumor is the second most common tumor and presents with elevated AFP levels (recall caveat above). Radical orchiectomy is curative in more than 90% of cases (stage 1); platinum-based chemotherapy and possible retroperitoneal lymph node dissection may be needed for higher stage disease. Boys with Leydig cell tumors present with a solid testis mass and precocious puberty and can be treated with tumor enucleation. Gonadoblastoma occurs in dysgenetic gonads of children with disorders of sexual differentiation carrying a Y chromosome.

### Varicoceles

Varicoceles, which are dilations of the spermatic veins or pampiniform plexus, are present in 15% of male adolescents and adults and may have a negative impact on fertility. The dilated veins are usually asymptomatic and are detected either by the patient or by the physician during routine physical examination, usually between 10 and 15 years of age. On occasion, the patient may report some heaviness or a *dragging* feeling in the scrotum. A predilection for the left side exists, reflecting the anatomy of the left gonadal vein entering the left renal vein at a right angle. The right gonadal vein enters the vena cava directly at an angle, precluding reflux of venous blood. The presence of bilateral or right-sided varicoceles warrants an abdominal and pelvic ultrasound or CT scan to evaluate for a possible mass occluding venous return. Physical examination should be performed with the patient in the supine and standing positions; the varicocele is usually decompressed in the supine position and present in the standing position. Inspection may reveal the classic *bag of worms* of dilated veins (grade 3 of 3). In other cases, increased blood pooling in the veins can be prompted by a Valsalva maneuver (grade 2 of 3). Less commonly, a varicocele is detected only by ultrasound (grade 1 of 3). Testicular size, most accurately assessed by ultrasound, should be measured; a significant loss of testicular volume is one indication for

surgery. Other indications for repair include abnormal semen analysis (older adolescent patients), very large varicoceles, and pain. Corrective measures include open surgery, laparoscopic surgery, or radiologic ablative techniques—all aimed at occluding direct venous return through the internal spermatic vein to improve the likelihood of normal fertility. In most cases, the testis will subsequently increase in size to equal that of the contralateral testis.

### Spermatoceles and Epididymal Cysts

Spermatoceles and epididymal cysts represent sperm-filled cystic lesions attached to the upper pole of the testis. They are separate from the testis and can be transilluminated. Painless and round, they usually remain stable in size but can sometimes enlarge. Management consists typically of observation, but surgery may be indicated when pain or significant enlargement is present. Postoperative scarring can obstruct the epididymal ductal system and lead to infertility.

#### WHEN TO REFER

- Acute painful scrotal swelling
- Acute hydrocele
- Hernia
- Scrotal trauma
- Cellulitis of scrotum
- Varicocele
- Testicular mass
- Paratesticular mass

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Hydroceles and Inguinal Hernias* (fact sheet), American Urological Association ([www.urologyhealth.org/urology/index.cfm?article=129](http://www.urologyhealth.org/urology/index.cfm?article=129))
- *Neonatal Testicular Torsion* (fact sheet), American Urological Association ([www.urologyhealth.org/urology/index.cfm?article=7](http://www.urologyhealth.org/urology/index.cfm?article=7))
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## Chapter 191

# SELF-HARM

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## FOUNDATIONS OF SELF-INJURY

Self-injury in children and youth may be grouped into 2 classifications: self-injury with intent to die (suicidal behaviors) and self-injury without intent to die (nonsuicidal self-injurious behaviors). Two of the best-known behaviors within the nonsuicidal classification are *nonsuicidal self-injury* (NSSI), occurring in typically developing children and youth, and *self-injurious behavior* (SIB), most common among children and youth with intellectual and developmental disabilities. Although cases of NSSI are seen more commonly than SIB in clinical practice, SIB is generally the more severe behavior. However, both forms of self-injury pose significant challenges to pediatricians. The chapter describes the independent and converging characteristics and features of each of these presentations of self-injury.

### Definition and Types of Self-injury

Nonsuicidal self-injury refers to the deliberate destruction of one's own body tissue, occurring without suicidal intent and for purposes not socially sanctioned. Thus, NSSI excludes piercings and tattoos. Most commonly, NSSI includes superficial to moderate self-cutting, burning, scratching, and bruising. NSSI occurs among typically developing children and adolescents. This behavior is often engaged in repetitively over long periods of time, with increasing severity, and has been found to be a significant risk factor for future suicidal behaviors. Furthermore, these self-inflicted injuries can result in medical complications, infection, or permanent scarring. Historically, this behavior has also been referred to as *self-mutilation*, *self-harm*, and *parasuicide*. The definition of NSSI excludes extreme forms of body mutilation (eg, amputation, enucleation) seen in patients with psychosis, as well as stereotypical self-injury seen among individuals with intellectual and developmental disabilities (IDD).

SIB among children and youth with IDD shares a similar definition with NSSI. SIB is defined as physical acts directed to one's own body that result in or produce tissue damage, or have the possibility of producing tissue damage if left unchecked. However, the most common forms of SIB are different from those of NSSI, and may include head banging, biting, scratching, pinching, and rubbing. Chronic SIB poses tremendous challenges for affected individuals and their families. Indeed, SIB is among the most disturbing and serious of all behaviors exhibited by children with IDD, because it has profound implications for a child's health and quality of life. SIB often leads to increased risk for institutionalization and social stigmatization, and decreased opportunities to learn.

### Epidemiology

The onset of NSSI most commonly occurs in early adolescence (12–14 years), although it is increasingly common for this behavior to occur among prepubertal children. Research has found that between 14% and 20% of adolescents in community samples report having engaged in NSSI at least once during their lifetime. Studies of mental health issues in college students have reported comparable lifetime prevalence estimates, suggesting that rates of NSSI are similar from adolescence to young adulthood. Currently, there has been no research investigating the prevalence of NSSI among prepubertal children in the general population; however, there is a clear indication from retrospective reports of self-injurers, as well as anecdotal reports (eg, physicians, school professionals) that NSSI does occur among children. In contrast to studies conducted with community samples, lifetime prevalence estimates of NSSI among clinical adolescent samples are substantially higher, with rates ranging from 60% to 80%.

Interestingly, while research has found NSSI rates to be much higher among females in clinical settings, the same pattern is not consistently found in community samples. Some studies have found a female predominance in the behavior, while others conclude that there may be little or no gender difference in occurrence of NSSI. In a review of the literature of NSSI among adolescents, Heath and colleagues found that studies reporting gender differences have included overdose and medication abuse, which have been found to be largely female behaviors. Investigations that are limited to cutting, burning, self-hitting to bruise, and other forms of tissue damage have failed to find a gender difference. Thus, it is important to avoid the assumption that NSSI is a predominantly female behavior in community practice, even though girls are more likely to be seen in clinical settings.

Findings regarding age of onset and gender patterns for SIB are notably different from those for NSSI. SIB occurs at all levels of IDD across the lifespan, with greater frequency typically reported among children with more severe intellectual impairments. The specific age of onset is typically unknown, but reports documenting SIB have included children as young as 18 months. Epidemiologic estimates vary depending on study design and participant characteristics, but it is estimated that approximately 20% of individuals with IDD living in large aggregate care facilities exhibit some form of self-injury. Unlike NSSI, there are clear gender differences in occurrence of SIB, with males overrepresented by a ratio of approximately 4 to 1. There have been no studies directly addressing ethnic differences in the prevalence of NSSI or SIB among children with IDD.

### Etiology and Function

For many years, self-injury occurring outside of the IDD population was believed to be indicative of severe psychiatric disorders, particularly borderline personality disorder (BPD). However, emerging research has shown that NSSI is not limited to individuals with BPD. Research has revealed that this behavior serves

a number of different functions. These may be understood as falling into 2 broad categories: functions that serve an internal or automatic purpose (eg, to elicit a calm feeling or eliminate tension) or functions that serve an external or social purpose (eg, as a form of communication or to elicit a response). For most individuals who engage in NSSI, emotion regulation difficulties are at the root of this behavior. These youth experience their intense negative emotions as intolerable and use NSSI to gain relief.

Although use of NSSI to regulate internal states or emotions has received the most support in the literature, for a minority of youth it seems that social factors may also play a role in this behavior. It has been suggested that in these cases NSSI serves as a form of communication to parents and peers when alternative forms of communication are perceived as being ineffective. Thus, for typically developing youth, the primary function of the behavior is to obtain relief from an internal state or experience. In contrast, as discussed below, SIB among children and youth with IDD is most often found to serve an environmental or social function (eg, to gain attention from others or to escape from task demands); however, it is recognized that an automatic function may also be involved in many cases (eg, to attain relief from pain caused by an underlying medical condition).

Advances in behavioral assessment technology have led to remarkable progress in identifying environmental and biologic variables underlying SIB. While the etiology of SIB may be related to an undiagnosed painful medical condition in some cases, the specific etiology of SIB is unknown in most cases. Little is known about the behavioral or biologic mechanisms influencing the early development of SIB in young children with IDD. Communication impairment associated with IDD is a primary risk factor, as is the overall severity of the intellectual impairment.

### Co-occurring Disorders

Research on co-occurrence is crucial for knowing how to assess and treat youth who engage in different forms of self-injury. For example, because the underlying functions of NSSI are similar to those of other mental health issues, it is necessary to be aware of which conditions tend to occur with NSSI and how to effectively assess and monitor them. Some of the most commonly co-occurring disorders include mood disorder, anxiety disorder, impulse control/conduct problems, uncontrolled anger, BPD, alcohol or substance abuse, eating disorders, and suicidality.

Similarly, a number of IDD-related syndromes tend to occur with SIB. The most common of these include Lesch-Nyhan syndrome, fragile X syndrome, Cornelia deLange syndrome, Prader-Willi syndrome, and Rett syndrome. Whether there are mechanisms specific to any single genetic disorder and the expression of SIB is unclear but unlikely.

## EVALUATION

Diagnostic and treatment approaches to NSSI and SIB differ substantially. NSSI is largely hidden and may

range in severity or treatment needs; therefore, much of the focus for the physician is on early risk assessment and referral to appropriate treatment. In contrast, SIB necessitates an initial ruling out of a possible underlying medical condition followed by the need for a full behavioral evaluation by a behavior analyst certified by the Behavior Analyst Certification Board (BACB.com). Interestingly, despite the obvious differences between the diagnostic approaches to NSSI and SIB, both share the difficulty of preconceived notions regarding the behavior (based on common misconceptions) and the lack of consideration of both internal and external functions. For clarity, the following section is divided into separate, brief reviews of NSSI and SIB.

### Nonsuicidal Self-injury Signs and Symptoms

A particularly challenging aspect of NSSI among children and youth is that it is a largely hidden behavior. Most youth engaging in the behavior make great efforts to keep the behavior secret, perhaps revealing only to friends or peers in online communities. Despite the child's reluctance to reveal the behavior, physical examination of the child will reveal fresh injuries, scars, burns, or unexplained bruises that are clearly indicative of NSSI. Some individuals will limit themselves to pin or razor blade scratching that they may explain as "cat scratches." Awareness of NSSI in typically developing youth ensures that physicians are cautious in their interpretation of signs of injury (eg, bruising, burning, or cutting) as signs of physical abuse (intentional harm by another).

One of the most significant obstacles to identification of NSSI by physicians is a lack of awareness of this behavior. It is widely thought that self-injury is largely a female behavior and limited to self-cutting; thus, NSSI is often overlooked in males or when other methods of injury are involved. Rather than understanding the underlying emotion regulation or "coping" function, physicians who encounter cases of NSSI often misidentify it as a suicide attempt or physical abuse, or assume that there are underlying disorders (eg, BPD, eating disorders). Additionally, physicians must recognize the high rate of occurrence for NSSI in youth and that the behavior is not limited to specific social cliques (eg, "emos" or "goths").

### Diagnostic Approach

Of particular importance is the need to distinguish between NSSI and suicidal behaviors. In the past, researchers have often failed to distinguish between self-injury with and without suicidal intent. However, suicide attempts and NSSI are distinct behaviors and should be understood, managed, and treated differently. Suicide attempts are behaviors that may or may not result in injury, for which there is intent to die. In contrast, NSSI is a behavior in which immediate tissue damage is present, but for which there is no intent to die. In essence, suicidal behaviors express a wish to stop living, whereas NSSI is reported by the youth as an attempt to feel better without any conscious desire to die. Nevertheless, these behaviors are not mutually



exclusive, and some youth engage in both, albeit at different times and with different intents. Therefore, it is important to evaluate for both suicidal and nonsuicidal self-injury.

### **Risk Assessment and Effective Referral**

A key role of the pediatrician is to complete a risk assessment to determine the current risk level and make appropriate referrals. Assessment includes evaluation of risk for suicide, physical injury, and the presence of other co-occurring risk factors. In determining risk-level status, the physician must recognize that there is no simple formula for determining whether a youth is at high or low risk. Nevertheless, if there is increased risk for suicide or physical injury, or if there are significant mental health concerns, then the risk-level status of the patient increases. Despite the extensive list of factors contributing to risk stratification, many patients who self-injure remain in the low-risk category. These patients may have mild, nonclinical levels of depression, anxiety, negative body image, or self-derogation and may seem to be functioning extremely well academically, socially, and within their home environment. Despite this apparent positive presentation, research has found that engaging in NSSI (even if only a few times) indicates problematic emotional regulation and a need for intervention to develop more adaptive coping strategies. Furthermore, it is known that risk level for suicide by individuals who engage in NSSI is substantial and subject to change over time; thus, regular reassessment is essential.

### **Self-injurious Behavior**

#### **Signs and Symptoms**

The physician should be aware that SIB injuries can have pattern-mark appearances and can be mistaken for physical abuse. Children with developmental disabilities, however, may be at higher risk for abuse or neglect. Careful history, risk assessment, and physical examination are warranted.

Presence of SIB often includes biting of the hands, arms, or lips; banging the head on solid surfaces; hitting the head or face with a closed fist or open palm; eye-poking; or scratching, picking, pinching, or rubbing skin. Mild, moderate, or permanent tissue damage and disfigurement, possibly life threatening, can occur if SIB is left untreated.

#### **Diagnostic Approach**

Behavioral evaluation of SIB is predicated on 3 empirically based assumptions: (1) SIB is functional, learned behavior (ie, a function, in part, of its circumstances and consequences); (2) the momentary likelihood of SIB is influenced by antecedent stimulus conditions (ie, it occurs more often in the presence of certain people, places, materials, demand contexts, and biological states than in others); (3) intervention linked to function (ie, related to antecedents and consequences) rather than form alone will result in superior, clinically significant outcomes. Behavioral evaluations require effort, time, and trained staff to administer and interpret, but lead to effective interventions more quickly than alternatives not based on behavioral function.

### **Functional Assessment and Analysis of Behavior**

Physicians who eliminate the possibility of underlying medical conditions and determine that SIB warrants evaluation should refer the patient to a board-certified behavior analyst (BCBA). State-by-state and provincial listings of BCBAs are available. Two broad categories of clinical evaluation procedures are available: functional assessment and functional analysis. Both types of evaluations are designed to generate information about environmental antecedents to, and contingent consequences of, behavior that can be directly linked to interventions. Functional assessments generate descriptive accounts of contextual and antecedent precursors to behavior as well as outcomes produced by behavior. The functional assessment interview is typically administered face to face, and it can be completed in approximately 1 hour (shorter or longer depending on the complexity of the behavior and level of information desired). The Questions About Behavioral Function, Functional Analysis Screening Tool, and Motivation Assessment Scale are more time-efficient survey forms that can be completed by caregivers at home or school. It is best practice to corroborate any interview and survey information with observations of the behavior, because these instruments have been found to generate different hypotheses about the function of SIB than observational accounts such as experimental functional analysis. Nevertheless, strong hypotheses of the function of SIB can be generated by these types of descriptive functional assessments and effective interventions can be developed based on those hypotheses.

Experimental functional analysis involves systematic manipulation of the antecedents to, and consequences for, SIB, and direct observation of the effects of these consequences. Typically, children are evaluated in clinical settings and the occurrence of SIB is compared across test and control conditions to determine whether SIB is sensitive to social consequences. The usual consequences evaluated are possible positive and negative reinforcers in the form of attention from others, escape from task demands, access to tangible items, or other preferred situations. When the presentations of antecedent and consequence stimuli are arranged systematically in a single-subject experimental design, causal claims between SIB and its consequences can be made. Experimental functional analysis requires highly trained professionals to administer and interpret (and is therefore more costly), but the tradeoff is confirmation of the environment-behavior relationship responsible for the maintenance of SIB, resulting in more prompt implementation of the proper intervention.

### **MANAGEMENT AND TREATMENT**

Effective treatment of NSSI begins with appropriate assessment. This includes a full history of the behavior, including age of onset; incidence over time; and specific aspects of the behavior over time, including the history of method(s), frequency, location(s), number of injuries per episode, and medical severity of injuries. These variables may change with time,



indicating an overall profile of increasing severity or a pattern of waxing and waning reflective of periods of stress. Currently, the only treatment approach for NSSI that has some empirical support (including randomized controlled trials) is dialectical behavior therapy (DBT) which has been found to be effective both with adults and adolescents. However, none of these studies used community samples of youth engaging only in NSSI; rather, this approach has been found to be effective with individuals with severe NSSI and co-occurring suicidal behaviors. DBT focuses on specific treatment goals arranged in a hierarchy of importance as follows: (a) decreasing life-threatening and NSSI behaviors; (b) eliminating behaviors that interfere with therapy; (c) decreasing behaviors that interfere with quality of life (eg, substance abuse, high-risk sex); and (d) skills training in mindfulness, distress tolerance, emotion regulation, and interpersonal effectiveness to help manage psychological distress. This approach is intensive and demanding of resources, requiring a therapist trained in DBT. Although DBT has been referred to as the “gold standard” of treatment, less intensive treatment approaches that incorporate the key elements of mindfulness, distress tolerance, emotion regulation, and interpersonal skills to some degree may be effective with community samples of youth who engage in NSSI. Regardless, at a minimum the physician working with the youth must be aware of the elements of DBT.

A child with IDD presenting with SIB should be evaluated for any possible illness or the likelihood of an acute or chronic condition that may be painful. Treating the underlying medical condition may lead to reduced SIB. For behavioral assessment, referral to a qualified specialist (eg, BCBA) is recommended. The evidence for SIB treatment based on behavioral evaluation is large and growing. Best practice calls for linking behavioral evaluation results directly to intervention strategies that include modifications to the antecedent environment in order to limit the presence of variables known to be associated with the onset of self-injury, and approaches to decreasing self-injury that emphasize reinforcement of desired behavior and de-emphasize the use of punishment. Specifics of any treatment regimen should be individualized with respect to the patient’s preferences, strengths, needs, and scope of SIB, as well as consideration of the caregivers’ preferences, strengths, capacities, and available family and community supports. Studies of neurobiologic factors associated with SIB have identified a role for opioidergic, dopaminergic, and serotonergic systems in the pathophysiology of SIB. These findings are in line with the results of a growing body of controlled psychopharmacologic studies demonstrating that SIB can be reduced to different degrees by agents that have actions in these neurochemical systems. One main difficulty to date is that it is not clear who will respond to what medication under what circumstances.

### Ongoing Care

The main consideration in the ongoing care of patients who have engaged in NSSI is the need for regular follow-up and suicide risk assessment. Although

many individuals will stop and not resume the behavior (exact numbers are unclear at this time), some youth will relapse and show a sharp escalation in severity following a stressor. While the prognosis is excellent for most youth who engage in NSSI at a low or moderate severity level, as a group they remain at significantly greater risk for suicide. Similarly, while tremendous advances have been made in the past 3 decades in our understanding and treatment of SIB, there is little evidence that the scientific community has effectively reduced the long-term burden of SIB on families and society. Prevalence estimates continue to suggest approximately 20% of people with IDD exhibit SIB, suggesting an ongoing need for intensive intervention with an emphasis on sustainability by incumbent supports.

### Self-injury Similarities and Differences

In summary, self-injury is generally understood to be a completely different phenomenon in typically vs atypically developing children and youth. While there are many differences in presentation and treatment approaches, these behaviors can be understood as possibly serving either an automatic or social function in both populations. Furthermore, it is essential in both instances to evaluate for the underlying functions in order to understand the reinforcers of these behaviors. Treatment for NSSI and SIB requires a detailed analysis and understanding of what is reinforcing the behavior and ultimately trying to interrupt this reinforcement chain. Effectively disrupting the response-reinforcer contingency depends, in part, on recognizing that self-injury elicits reactions from individuals in the patient’s or individual’s environment, which can create a complex situation (ie, it is a natural response on the part of a physician to want to react and stop an individual from harming himself). Documentation and clear communication to share information about any planned intervention is essential to effective outcomes.

#### WHEN TO REFER

##### NSSI

- Following initial risk assessment
- Emotional regulation difficulties or poor coping strategies

#### WHEN TO ADMIT

##### NSSI

- Threat of suicide
- Serious physical injury
- Underlying psychiatric conditions

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *S.A.F.E. Alternatives* (Web site), ([www.selfinjury.com](http://www.selfinjury.com))
- *Self-injury Outreach and Support* (Web site), ([sioutreach.org](http://sioutreach.org))

**Medical Decision Support**

- *Certificant Registry* (Web page), Behavior Analyst Certification Board ([www.bacb.com/index.php?page=100155](http://www.bacb.com/index.php?page=100155))
- *Five Things to Know About Non-Suicidal Self-Injury* (article), *Canadian Medical Association Journal*, Vol 185, Issue 6, 2013
- *Self-Injury Trauma (SIT) Scale: A Method for Quantifying Surface Tissue Damage Caused by Self-Injurious Behavior* (article), *Journal of Applied Behavior Analysis*, Vol 23, Issue 1, 1990
- *Pediatric Symptom Checklist* (screen), Massachusetts General Hospital ([www.massgeneral.org/psychiatry/services/psc\\_forms.aspx](http://www.massgeneral.org/psychiatry/services/psc_forms.aspx))
- *Strengths & Difficulties Questionnaire* (screen), Youth in Mind, Ltd. ([www.sdqinfo.com](http://www.sdqinfo.com))

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## Chapter 192

# SELF-STIMULATING BEHAVIORS

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Repetitive and self-stimulating behaviors, such as head banging, head rolling, rocking, thumb sucking, and masturbation, as well as habits such as hair pulling and nail biting, are of concern to both parents and pediatricians. Research has suggested that commonalities exist among repetitive behaviors, sometimes classified as *stereotypies*, and that they represent an interaction of the stage of neuromotor development with environmental influences (eg, restrictive car seats and cribs) and are a homeostatic mechanism that serves to regulate stimulation from the environment. Many of these behaviors, such as head banging, head rolling, and rocking, typically appear before 12 months of age, peak soon thereafter, and subsequently decline rapidly. Thumb sucking (25%) and nail biting (23%) are the most common behaviors described in preschool children, with only 4% developing motor stereotypies. Young children practice self-stimulation through

thumb sucking and genital play, with a peak at age 2½ years. In general, most of these behaviors are self-limited to the preschool period and are usually viewed as normal, common, and expected behaviors. These habits generally do not signify psychological maladjustment. They often require little intervention other than reassuring the parents and suggesting adequate interaction with their child.

**HEAD BANGING AND ROCKING**

*Head banging* consists of rhythmic movements of the head against a solid object, such as the crib mattress or headboard, and is often associated with rocking the head and the entire body. It is observed most commonly at bedtime or at times of fatigue or stress and may vary in duration from several minutes to hours. Head banging often continues even when the child is asleep. The age of onset shows wide variability, but the behavior is witnessed most commonly during the preschool years. The reported incidence of head-banging or rocking behavior varies between 3% and 20%, with a male-to-female ratio of approximately 3:1. Occasionally a family history of such behavior can be found, but only 20% of siblings of children who rock exhibit similar or other rhythmic pattern disturbances.

Various theories have been developed to understand these self-limited but often disturbing behaviors. Rocking is thought to be a soothing, pleasurable experience that every infant encounters in utero and that most infants encounter from the neonatal period onward. The pleasure from movement is repeated throughout life, from being rocked in the mother's arms during early childhood, for example, to jumping rope and playing on swings in childhood, to dancing in adulthood. Individual constitutional patterns in childhood account for a wide variability in the amount of stimulation any particular child may require. However, in certain children, such as those who are hearing or sight impaired, emotionally disturbed, or severely intellectually disabled, marked rhythmic movements are commonly found. In these cases the movements may represent a compensatory reaction for a lack of stimuli or the inability to integrate stimuli. Head banging in children with severe disabilities can be a form of functional communication. For example, a child may increase head banging to receive parental attention or to avoid task demands. In addition, the child who has no disability but who is inactive because of physical illness generally shows a need for motor release that is often characterized by bed rocking or other rhythmic body movements, which generally disappear once normal mobility is restored.

Physical and neurologic examinations show these children to be predominantly within normal limits, and electroencephalogram studies are not indicated because the findings are generally not helpful. These behaviors seem to be linked to maturational patterns and correlate closely with teething and other transitions of growth and development, perhaps as a mechanism for increasing or reducing arousal and maintaining homeostasis. Even though psychosocial growth and development are apparently not disturbed

in these children and studies indicate no connection between rocking behavior and parental divorce or separation, the question of inadequate stimulation for the child should be raised, and the presence of family turmoil and stress should be investigated.

Treatment is generally directed toward assuring the parents that head banging cannot cause brain injury and that the child will show no adverse neurologic effects in later life; children who engage in head-banging behavior usually grow up as typical, coordinated children. Securing the crib to prevent rolling may help during the limited rocking behavior, but crib bumpers are not recommended because of concerns of suffocation, strangulation, or entrapment. Sedation in the form of diphenhydramine may prove effective, but psychotropic medication is generally unnecessary and is thus discouraged. Parents should not visit the child frequently at night, because doing so could reinforce what may become an attention-seeking behavior. Rarely, if ever, do fractures of the skull or cerebral hemorrhages result from head banging in typically developing children, but soft-tissue swelling and scalp contusions have been reported. Intracranial injuries and retinal detachment have been reported in children with autism and severe intellectual disabilities, and a protective helmet may be advised in severe cases. Consultation with a child psychiatrist or psychologist is indicated if the head-banging or rocking behavior persists beyond 3 years of age. For children who show a lack of social interaction or a preoccupation with themselves or with self-stimulatory behavior, consultation is indicated.

### THUMB SUCKING AND NAIL BITING

Thumb sucking occurs almost universally in infancy but varies among cultures. Infants may place virtually every object they encounter in their mouth unless parents, for safety reasons, restrict the object choice.

The pleasurable sensations associated with the double tactile experience of sucking and being sucked and the feelings of security and comfort that these experiences evoke tend to reinforce this behavior. Many families substitute artificial pacifiers as a more socially acceptable means of oral pleasure, and children themselves often spontaneously suck a security blanket, a doll, or a stuffed animal. Thumb sucking usually occurs during times of stress or boredom and at bedtime. Young children may suck their thumb to help themselves fall asleep. Social and family pressures generally limit thumb sucking to the preschool years. However, the habit may persist into adolescence. Approximately 25% to 40% of American children engage in finger sucking during the preschool years and 10% to 20% continue beyond 6 years of age.

Nail biting is an extension or permutation of the habit of thumb sucking. Some experts consider this behavior a form of more overt self-aggression; others would define nail biting simply as a variation of thumb sucking because this behavior is also seen typically during times of stress. An estimated 25% of preschoolers and 33% of children ages 7 to 10 years bite their nails. Adolescent rates of nail biting are as high as 45%. Thus nail biting, in contrast to thumb sucking, often continues throughout development, but

decreases to adult rates of 10%. Gender differences do not appear until adolescence when the incidence of nail biting is greater for males. A family history exists in most cases, but this habit is so common that such an apparent association may be of no significance. Children from higher socioeconomic groups and higher levels of parental education seem to demonstrate oral habits more often, but no clear correlation has been found with the number of children in the family, birth order, type of feeding, or feeding schedule.

Thumb sucking, nail biting, and cuticle biting or picking may be harmful to dentition and increase the risk of dental malocclusion and the incidence of digital cutaneous infections. There is a higher probability of malocclusion if thumb sucking continues after the eruption of permanent teeth. In addition, thumb sucking that persists into school age can bring on teasing from peers and criticism from teachers and family, leaving the child with decreased self-esteem and increased psychological distress.

Clarifying with parents the nature of these habits is important, as is encouraging them to avoid punishing or shaming the child for them. An underlying cause of tension should always be investigated, but simple behavioral therapy (based on positive reinforcement) is often sufficient to alleviate the habit. The parents should be advised to avoid punishment, threats, or anger. Encouragement in the place of restrictions is helpful in engaging children in their own program to decrease or eliminate the behavior.

Bitter-tasting commercial preparations applied to the fingers may be used as a reminder for the child, but these preparations are generally inadequate unless supplemented by consistent positive reinforcement. The choice of reinforcement reward should be the child's and might take the form of extra television privileges, dessert, or other special treats. A combination of aversive taste treatment and a reward system seems to be effective in treating chronic thumb sucking. Weekly visits to the physician for the first month of treatment are important to reinforce the change in behavior. Hypnosis is another treatment that is often successful and poses no danger; psychotropic medications, on the other hand, are of little value. If these habits are linked to other signs of emotional distress or if there is excessive nail biting and cuticle picking, referral to a specialist in behavioral disorders is warranted to investigate other mental health issues such as anxiety or a body-focused repetitive behavior disorder.

### MASTURBATION

Childhood masturbation is almost universal and often causes great parental concern. Genital exploration and touch typically begin around 2 months of age and evolve into masturbatory activities that peak at 4 to 5 years of age and again in adolescence. Such activity may vary from direct manual genital stimulation to movements of the thighs against each other. Rhythmic swaying or thrusting motions of the child while straddling a hobby horse, pillow, stuffed animal, or other objects also are common methods of masturbation. Infants and children are capable of a physiologic orgasmic response similar to that experienced by the



adult, except for the absence of ejaculation in the male child, as demonstrated by the common practice in Europe in the late 1800s of masturbating an irritable child to induce relaxation and sleep. Occasionally, this orgasmic response has been incorrectly thought to represent a convulsive or movement disorder in infants and children leading to unnecessary and expensive neurological workup. Masturbatory activity is generally initiated as a response to the learned pleasure associated with touching of the genitalia that is first experienced in infancy during normal body exploration. Masturbation will continue as a lifelong pleasurable experience unless suppressed by parents or other adults.

The physician needs to educate parents about healthy childhood sexual development. Physicians should counsel parents on masturbatory practices and emphasize that masturbation is a normal, harmless, and healthy practice that helps the child to derive pleasure from the child's own body. Many parents may have received negative messages as children about their sexual development, and this has led them to view typical sexual behaviors as problematic. Myths must be dispelled concerning the belief that masturbation is a definitive sign of sexual abuse, that it may cause intellectual disability, physical deformity, blindness, poor physical and mental health, facial pimples, hair on the palms of the hand, homosexuality, and sexual perversions. Parents should be aware that masturbation occurs almost universally in children and should be encouraged to avoid punishing or shaming their child for a normal behavior. Negative parental reactions will not reduce the frequency of masturbation, but can lead to feelings of guilt and shame in children. If parents observe masturbatory activity in their child, they may want to suggest to the child the inappropriateness of manipulating their genitalia in public places or in front of others and inform the child that certain practices, such as using the toilet and masturbating, are best carried out in private.

Because local genital irritation, *Candida* infection, or pinworms in rare cases may cause a child to repeatedly touch their genitals, a physical examination helps to exclude such possibilities. Compulsive, overt masturbation among children and adolescents may lead to social ridicule and condemnation, or it may signify a deeper emotional problem. Consultation with a specialist in behavioral disorders of children and adolescents is indicated if the physician suspects that the masturbatory activity is excessive, compulsive, or not easily redirectable or may indicate the presence of a more complicated, troublesome emotional problem. Any masturbatory actions that involve self-harm or are coercive of other children are concerning and warrant additional evaluation and consultation.

The pediatrician should be aware that even with the current societal trends toward sexual openness and enlightenment, myths and feelings concerning masturbation often are deep seated and persistent. Thus, counseling and advice given by the pediatrician may be met with covert or overt resistance by parents or school authorities. The pediatrician should be well

prepared to educate persons responsible for the growth and development of children.

## HAIR PULLING AND TWISTING

Recurrent hair pulling and twisting (*trichotillomania*) is a form of self-stimulating behavior that often indicates the presence of psychological stress. The scalp is the most common area affected; eyebrows and eyelashes are the next most likely sites. The obvious cosmetic damage often results in ridicule by peers and shame for the child. The formation of a hairball, or *trichobezoar*, in the stomach if the child ingests the hair is a serious problem that often results in hospitalization for surgical removal of the accumulated matted hair. This behavior has been reported across all age groups and has a bimodal onset with peaks in the preschool years and in early adolescence (ages 11–13 years). Onset in very early childhood shows no gender bias; however, this behavior becomes more common in females with increasing age. The *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, groups trichotillomania with the obsessive-compulsive and related disorders because it is a recurrent, body-focused, repetitive behavior. Two types of trichotillomania have been described in clinical practice, both of which can coexist in the same individual. In the *focused* type, which is associated with tension before and relief after the hair is pulled, time is set aside to pull the hair. In the second, *automatic* type, the patient is generally unaware of the behavior during the hair pulling or twisting itself and often recognizes the action as senseless and undesirable.

Treatment is usually indicated and behavioral and cognitive behavioral therapy should be used as first-line treatment. Local irritation from a dermatologic condition is rarely the cause of this disorder, but the possibility should be investigated. Referral to a mental health professional is often warranted to investigate possible underlying causes of tension, anxiety, depression, or obsessive-compulsive disorder. Psychotherapy may be required in many of these cases. Research does not support the use of selective serotonin reuptake inhibitors (SSRIs) to treat trichotillomania, but SSRIs can treat comorbid anxiety in children and adolescents. Although studies of the treatment of adult trichotillomania showed significant benefit using N-acetylcysteine (NAC), research had not supported the benefit of NAC for the treatment of children.

## SPECIAL PROBLEMS IN CHILDREN WITH SEVERE MENTAL HEALTH DISORDERS

A broad spectrum of self-stimulating behaviors may be seen in children with developmental disabilities and severe mental health disorders. The behaviors, including body twirling or spinning and hand or arm flapping, are often seen in cases of infantile autism or childhood schizophrenia. Excessive rocking behavior is common in severely intellectually disabled and emotionally disturbed children. In addition, severe self-mutilating behaviors, such as compulsive self-biting,



severe head banging, and skin gouging, may be seen in these disorders and are characteristic of certain metabolic or genetic disorders, such as Lesch-Nyhan syndrome and Cornelia de Lange syndrome. Patients who have Prader-Willi syndrome often demonstrate severe skin picking.

These behaviors are part of a symptom complex in a severe disorder, in contrast to the generally isolated behaviors in typically developing children. The cause is generally linked to the basic disorder and may also reflect the lack, or disordered integration, of sensory stimuli. As previously mentioned, these behaviors can be reinforced by parental/adult reactions and often serve a communication function, eg, the child increases the self-stimulating behavior to receive attention and avoid unpleasant tasks.

All of these cases require treatment for the basic disorder and generally demand special behavioral treatment beyond the scope and expertise of the primary care physician. When the behavior is severe, institutionalization is often required, and methods of treatment include the application of aversive behavior modification techniques; the use of arm and neck restraints, head helmets, and psychotropic medications; and the institution of psychotherapeutic behavioral programs.

### WHEN TO REFER

- Persistence of head banging or rocking beyond the age of 3 years
- Preoccupation with self-stimulating behavior to the point that it interferes with healthy social and emotional interaction
- Presence of accompanying symptoms such as decreased socialization or other behavioral problems
- Causing tissue damage

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Common Childhood Habits* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/family-dynamics/communication-discipline/Pages/Common-Childhood-Habits.aspx](http://www.healthychildren.org/English/family-life/family-dynamics/communication-discipline/Pages/Common-Childhood-Habits.aspx))
- *Thumbsucking* (audio) American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/baby/crying-colic/Pages/Thumbsucking.aspx](http://www.healthychildren.org/English/ages-stages/baby/crying-colic/Pages/Thumbsucking.aspx))
- *Pacifiers and Thumb Sucking* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/baby/crying-colic/Pages/Pacifiers-and-Thumb-Sucking.aspx](http://www.healthychildren.org/English/ages-stages/baby/crying-colic/Pages/Pacifiers-and-Thumb-Sucking.aspx))

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## Chapter 193 SHORT STATURE

Paul Kaplowitz, MD, PhD

The accepted medical definition of when a child is too short is often at variance with the point at which parents worry about their child's growth. Parents may be concerned when a child is among the shortest in the class or when a younger sibling starts to catch up to the child in question, even if the child's height clearly falls within the normal range. Statistically speaking, the normal range encompasses 2 standard deviations above and below the mean, or approximately between the 97th and the 3rd percentiles. The third percentile may be difficult for primary care physicians (PCPs) to appreciate, given that the lowest curve on many growth charts is the fifth percentile. Furthermore, a single point on a growth chart often will not define whether a somewhat short child has a worrisome growth pattern; therefore, previous growth data should be plotted whenever available, and any suggestion of growth deceleration should be carefully reviewed. An additional complication is that in boys between the ages of 12 and 14 years, growth charts show an upward inflection in height as boys start their growth spurts; thus, a somewhat short boy who is prepubertal will seem to fall further behind, even though he is continuing to grow at a normal rate. The growth charts published by Tanner and Davis in 1985 make this point clear because they have a separate line for short, late-maturing boys and girls.

### DIFFERENTIAL DIAGNOSIS

Constitutional growth delay (CGD) and familial short stature (FSS) are the 2 most common causes of short stature. In the Utah Growth Study, which, through school screening, identified 555 children who were below the third percentile and growing at less than 5 cm per year; 81% of these children had CGD, FSS, or a combination of the 2 conditions. In CGD, children are healthy and growing below but parallel to the third percentile line. Birth weight is normal, but between 6 and 24 months linear growth and weight track downward to the third percentile or below; after age 3, children follow their own curve parallel to the low end of the growth chart. Children with CGD typically have a delayed onset of puberty and growth spurt and usually end up with heights in the lower half of the normal range. A characteristic finding is that the child has a bone age that is delayed by 2 or more years.

Familial short stature is quite easy to recognize when the child is healthy, growing at a normal rate below the third percentile, and 1 or both of the parents are quite short. Unlike CGD, children with FSS tend to have puberty at a normal age and achieve an adult height within 2 to 3 inches of their adult target height, which can be calculated by averaging the heights of the parents and adding 2.5 inches if the child is a boy and subtracting 2.5 inches if a girl. Some children may have features of both CGD and FSS.

### Short Stature Associated With Syndromes and With Being Born Small for Gestational Age

Short stature associated with a syndrome should be considered when a very short child has a dysmorphic appearance, particularly if born small for gestational age (SGA) (eg, birth weight of  $\geq 2,500$  g at term).

Turner syndrome should be a consideration in any girl whose height is well below the third percentile, but certain features make the diagnosis more likely. Lymphedema in the newborn period or frequent ear infections well past 2 years of age are common. The most common physical findings include a narrow, high-arched palate, cubitus valgus (a large angle at the elbow when the arms are stretched out), and upturned fingernails. The classic webbed neck is seen in only 40%. Approximately 15% have congenital heart disease, usually coarctation of the aorta. Mean birth weight is 2,785 g; thus, many patients are not born SGA.

Many less common syndromes exist in which dysmorphic features are associated with short stature. In Russell-Silver syndrome, the most characteristic features are a history of being born SGA and having a triangular face with a down-turned mouth. Noonan syndrome may be suggested by the finding of pulmonary stenosis and facial features that include a flat nasal bridge, hypertelorism, and ptosis.

Short stature associated with SGA is diagnosed when a child born SGA fails to catch up to the normal range in height by 2 years of age. Many of these children have no dysmorphic features, and no defined cause can be found for their intrauterine growth restriction.

### Chronic Illness and Nutritional Disorders

A chronic illness or nutritional disorder should be considered in short children whose weight is further below the curve than their height (or whose body mass index is below the 10th percentile for age).

Inadequate calories, rarely a result of poverty in the United States because high-calorie foods are inexpensive, is sometimes seen in the setting of a child who is on a self-imposed or parent-imposed restrictive diet to avoid gaining weight or to lower cholesterol levels. The extreme example of this situation is anorexia nervosa.

Inflammatory bowel disease, though rarely the cause of undiagnosed short stature, may be suspected in a child whose growth has been normal but then shows a marked falloff in both height and weight, particularly in the presence of gastrointestinal (GI) symptoms such as abdominal pain, early satiety, and blood in the stool. Growth attenuation may start when GI symptoms are relatively mild or even before they become apparent.

Celiac disease, or gluten enteropathy, is a common cause of short stature in Europe (up to 8% in some studies), although its frequency in the United States seems to be much lower. Abdominal pain, distension, and loose stools may suggest the diagnosis, but most short children with celiac disease have few if any GI symptoms.

Renal disease can cause short stature, but only rarely is it diagnosed solely because of an abnormal

growth curve. Renal tubular acidosis and chronic renal failure are the 2 renal conditions that can cause growth failure and that can be ruled out by appropriate screening tests.

### Poor Growth Associated With Medications

Children treated with stimulant medications for attention-deficit disorder may have growth attenuation starting either at the time the medications are begun or between 9 and 12 years of age. One recent study, which included younger patients with a mean age of 4.4 years, found a 20% reduction in height velocity and a 50% reduction in weight gain in treated children. Although the common belief asserts that decreased appetite is responsible for the slow growth, many of these children are not underweight, and the explanation for their slow linear growth is still unknown.

Chronic glucocorticoid therapy is another cause of short stature, mostly seen in children with such conditions as rheumatoid arthritis and inflammatory bowel disease treated with daily oral prednisone. The effect on the growth of children treated long-term with inhaled corticosteroids for asthma is clearly much less than for systemic glucocorticoids, although monitoring of linear growth may occasionally detect evidence of growth suppression.

### Endocrine Disorders

The Utah Growth Study reported that less than 5% of short, slowly growing children had a defined endocrine disorder. A major clue that an endocrine cause may exist is that height is often more affected than weight.

Growth hormone (GH) deficiency is not a common cause of short stature. In the Utah Growth Study the incidence in school aged children was estimated at 1:3,480. A 2004 study from Belgium, which considered all children diagnosed with GH deficiency between 1985 and 2001, estimated the incidence at 1:5,600. The diagnosis should be suspected in children who are well below the third percentile in height and falling further below over time. One suggestive physical finding is an increase in subcutaneous fat that is greater in the trunk area than elsewhere. Most cases are congenital; birth weight is usually normal but a falloff in growth occurs starting late in the first or in the second year of life. In the much less common acquired cases, a period of normal growth is followed by deceleration; central nervous system symptoms such as severe recurrent headaches may be part of the clinical picture. Once a diagnosis of acquired GH deficiency is established, the endocrinologist will order brain imaging to look for a tumor in the area of the pituitary gland. Milder or partial forms of GH deficiency are difficult to distinguish from CGD and FSS based on growth pattern, physical findings, and laboratory tests. The apparently higher frequency of GH deficiency in recent years is, in large part, because GH testing done in the United States has many false-positive results, and many normally growing children fail the test using the accepted cutoff of 10 ng/mL.

Acquired hypothyroidism, when severe, can cause slowing of growth or even complete growth arrest.

Other symptoms, including fatigue and cold intolerance, are often present, and most children will have a goiter. Acquired hypothyroidism needs to be excluded as a possibility in any child with documented growth deceleration, even if height is still above the third percentile.

Although iatrogenic Cushing syndrome is not uncommon, true endogenous Cushing syndrome is extremely rare. Rapid weight gain in the trunk, rather than generalized in distribution, accompanied by a slowing of linear growth are the key findings. Moon facies and purple abdominal striae are often seen, as well as increased skin pigmentation.

### Idiopathic Short Stature

*Idiopathic short stature* (ISS) is a term used to describe moderately to severely short children who do not meet the criteria for CGD and FSS (eg, they often have a subnormal rate of growth); and in whom no cause for their poor growth is found after extensive testing. Studies have shown that most children with ISS respond to a variable degree to GH and see a modest average improvement in adult height. The US Food and Drug Administration (FDA) in 2003 approved GH for children at or below the first percentile with an anticipated adult height (based on bone age) below the normal range. However, some insurance companies refuse to cover GH to treat ISS, arguing that no medical condition causing the growth problem exists and that treatment is cosmetic.

## EVALUATION

### History

The most helpful information in evaluating the short child is the growth curve. If the growth rate has been normal for the previous 2 or more years, then the child most likely has CGD or FSS and is unlikely to have a defined, treatable cause. A single height point that falls off the established curve is often a measurement error and should be rechecked. A history of stimulant medications or glucocorticoid use might be a key piece of information. Many children with chronic growth-limiting illnesses have a decreased energy level and may have a poor appetite, although many short, healthy children are also described as picky eaters. An abnormal stool history should make the PCP think of malabsorption, celiac disease, or inflammatory bowel disease.

Heights of parents and grandparents and growth percentiles of siblings should be reviewed because they may suggest FSS in a healthy child who is short but growing at a normal rate. Approximately two-thirds of children with CGD have a family history of a parent who was a late maturer (eg, mother's menarche after age 14 or a father who continued to grow after high school).

### Physical Examination

Most short children do not have any physical findings that point to a specific diagnosis. A child with decreased subcutaneous fat stores and weight more affected than height may simply not be getting enough calories or may have bowel disease or another chronic

illness. Conversely, a short child who is relatively pudgy (particularly if excess rippled fat is present over the trunk) may have GH deficiency. Dysmorphic features may provide a clue to a syndrome associated with short stature. In girls, the PCP should look for, among other things, a high-arched palate, cubitus valgus, and fingernails that bend upward, which may point to a diagnosis of Turner syndrome. An enlarged thyroid may be the only clue that a short child has hypothyroidism. Pubertal staging should be done on any short child who is 10 years or older. A short, healthy 14-year-old boy (or, less often, a short, healthy 13-year-old girl) who is still prepubertal is most likely to have a diagnosis of CGD. A child who has a flattened growth curve at 13 to 16 years of age and who, by examination, is found to be in the late stages of puberty has completed or has nearly completed growing, and nothing can be done to increase the individual's adult height.

### Laboratory Evaluation

Primary care physicians should resist the temptation to order multiple laboratory tests for a child who is only mildly short (at or above the third percentile) and whose growth rate seems to be normal. In this situation, a clinically significant abnormal test result that will explain why the child is short is rarely found. Most growth specialists prefer either to order a very few tests on such children or to perform no tests at all, particularly if everything points to a diagnosis of CGD or FSS.

Ordering screening tests in advance of a visit with a specialist might be appropriate if the child's height is well below the third percentile or if growth deceleration that cannot be explained by medication is well-documented. However, the specialist can order any needed test at the first consultation.

Insulin-like growth factor 1 (IGF-1) is still the best screening test if GH deficiency is suspected, although many children with CGD have IGF-1 levels that are borderline low for age. IGF-binding protein 3 has not lived up to its initial promise as a better screening test for GH deficiency than IGF-1, and it is not worth ordering routinely. A random GH level is of no value because of the pulsatile nature of GH secretion.

Thyroid testing should be limited to free thyroxine (T4) and thyroid-stimulating hormone (TSH) assessment, which will identify both primary and secondary hypothyroidism. Triiodothyronine (T3), T3 uptake, and thyroid antibodies are not helpful as screening tests for short children. A borderline increased TSH (in the 5.5- to 10-mcU/mL range) with a normal free T4 is usually a normal variation and will not explain poor growth.

Complete blood count and erythrocyte sedimentation rate are mainly useful in the occasional child in whom inflammatory bowel disease is suspected. A microcytic anemia may be a clue to occult GI blood loss. Either tissue transglutaminase immunoglobulin A (IgA) antibody or antiendomysial antibody are good tests to screen for celiac disease. Antigliadin IgG and IgA are much less specific and are not worth the extra cost.



A comprehensive metabolic profile will rule out electrolyte disturbances, kidney disease, and liver disease, all of which are rare causes of short stature.

### Imaging Studies

The only radiographic examination that should be considered is the bone age film, which is not a very useful diagnostic test because most children who are short for any reason (aside from genetic short stature) will have a bone age delay of a year or more. The clinician may order a bone age film in a child over 7 to make a height prediction when either CGD or FSS is suspected.

## MANAGEMENT

Healthy children who are at or above the third percentile and growing at a normal rate need not be referred to a specialist because the chances of finding a treatable cause for their short stature are small. If the parents insist on seeing a specialist, then they should be told that the child will not likely need or be eligible for coverage of GH therapy. Such children should have their growth carefully measured and plotted at each visit to make sure they are not dropping below the third percentile in height. A few children report having poor self-esteem because they are shorter than most of their peers, and they may be subjected to teasing or bullying; referral to a psychologist may be more helpful than to an endocrinologist.

Infants or children who are maintaining linear growth at or above the third percentile but whose weight is consistently below or has recently fallen below the third percentile almost never have an endocrine problem. If weight gain is slow but fairly consistent in a thin child, this may be a normal variation; parents may say that they were thin at the same age. If weight gain is persistently poor or there is weight loss, then referral to a GI or nutrition specialist should be considered.

The child who is still in the normal range but who is crossing percentiles may present a dilemma. Between 6 and 24 months, such percentile shifts in height and weight are common, especially in patients with CGD, and a stable growth curve is usually established between 2 and 3 years of age; therefore referral may be deferred if the child is healthy. If the child crosses 1 percentile channel (eg, from the 25th to the 10th percentile) over 3 or more years, and if the history and examination reveal nothing abnormal, then a cause will not likely be found. Children who cross more than 1 percentile channel in a period of less than 3 years have a greater chance of having a definable cause for their short stature. The most common cause of this growth pattern is the use of stimulant medication in children with attention-deficit disorder.

Parents of children who are short enough to be referred can be told that screening tests and a period of observation are needed before any decision can be made regarding the possible need for GH therapy. Such children are best referred between the ages of 3 and 6; children who are pubertal or on the verge of puberty are usually too old to derive much benefit from GH therapy.

## WHEN TO REFER

- Any child whose height is below the third percentile, particularly if the height is falling further below the normal range over time. Children who are below the first percentile have an even better chance of qualifying for GH therapy because they are more likely to have true GH deficiency; and if they do not have GH deficiency, then they may still meet the FDA criteria for GH treatment for ISS.
- A child with a history of intrauterine growth retardation who was born SGA and who has not caught up to the normal range by age 2 years or older. The FDA has approved the use of GH in such children without the need for GH testing. A dysmorphic child with a history of intrauterine growth retardation should also be referred to a geneticist to try to make a specific diagnosis.
- A child who is within the normal range in height but has experienced a drop-off in linear growth of more than 1 percentile channel over a period of less than 3 years, or who has shown documented growth arrest for a year.
- A child with short stature who has not started puberty by age 14. This situation occurs mostly in boys with CGD; and in many cases, when the boy is anxious to start his growth spurt sooner rather than later, treating such boys with a brief course of testosterone injections is appropriate.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *The Short Child: A Parents' Guide to the Causes, Consequences, and Treatment of Growth Problems* (book), Warner Wellness Books

### Medical Decision Support

- *Clinical Longitudinal Standards for Height and Height Velocity for North American Children* (article), *The Journal of Pediatrics*, Volume 107, Issue 3, 1985
- *Utah Growth Study: Growth Standards and the Prevalence of Growth Hormone Deficiency* (article), *The Journal of Pediatrics*, Volume 125, Issue 1, 1994

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## Chapter 194

**SLEEP DISTURBANCES  
(NONSPECIFIC)**

Mark L. Splaingard, MD; Anne May, MD

Sleep is necessary for human development and well-being, yet it has unique vulnerabilities in childhood that can manifest, for example, as central congenital hypoventilation syndrome or the inability of most primary school-aged children to awaken to very loud noises such as fire alarms during slow-wave sleep. Estimates of prevalence in children vary most widely for behavioral sleep problems like insomnia, as opposed to organic sleep problems like obstructive sleep apnea (OSA), with interesting cultural and ethnic variations. Underreporting by parents and underdiagnosis by primary care physicians have been issues, with sleep problems conservatively estimated to occur in approximately 25% of healthy children younger than 5 years and in up to 80% of children with special needs. Because many sleep difficulties can be managed successfully in the primary care setting, pediatricians are ideally positioned to anticipate, recognize, and treat most sleep problems and to refer children to a specialist when appropriate. Successful management of pediatric sleep problems often results in improved sleep and daytime function for all members of the household.

A strong subjective component can be found for many pediatric sleep problems, as in the typical case of the toddler with night awakenings who wants to get in the parental bed:

- The parents in family A do not consider this desire as a problem. Both parents are good sleepers and do not care if their child sleeps in their bed.
- The parents in family B believe strongly that the child does not belong in their bed and that their bedroom is the only place they have to themselves.
- The mother in family C lives with her own mother and is raising two children. They live in a small apartment in which the two children share a bed.
- The parents in family D own a bed-and-breakfast business and live on the premises. They do not want their child in their bed but cannot afford to have a crying child wake the guests.
- The parents in family E have let their child into their bed in the past, but another infant is due in 3 months, and they would like their child to transition to spending the night in her own bed.

These examples illustrate the variety of responses to a common sleep issue in the young child. All of these families have caring parents and normally developing toddlers. Some of the parents regard the behavior as a sleep problem, whereas others do not. The parents in family B are more likely to consult a pediatrician about the child's sleep than the parents in family A.

Some sleep problems such as OSA are more likely to be acknowledged as problems by most families, although perceptions may vary. A hearing-impaired parent may not complain of a child's snoring. A parent who is a light sleeper is more likely to take note of a

child's sleep disruptions than a parent who is a sound sleeper. Parents frequently consult pediatricians about sleep issues, and the pediatrician should recognize the range of sleep problems and the variability in parental perception of these problems.

**DEVELOPMENT OF SLEEP**

The development of physiologic sleep patterns is predictable (Table 194-1). It begins in utero; by 28 weeks gestational age, rapid eye movement (REM), or active sleep, can be discerned via fetal ultrasound. Non-rapid eye movement (NREM), or quiet sleep, appears at 32 weeks gestational age. At term, newborns have discrete sleep cycles, lasting 50 to 60 minutes, with awakenings every 2 to 6 hours. These sleep cycles are composed of alternating periods of equal amounts of quiet and active sleep. Quiet sleep is characterized by body stillness, regular respirations, and normal muscle tone. During active sleep, the infant has decreased muscle tone with frequent body movements, including eye movements and irregular respirations. The total daily amount of reported sleep at 1 month of age ranges widely from 9 to 19 hours, with an average of 14 hours (Table 194-2).

By 4 months of age, mature sleep stages begin to emerge, and day-night sleep patterns are well consolidated. Infants have their longest sleep periods at night and 3- to 4-hour periods of wakefulness during the day. By 6 months, circadian rhythms begin to display activity similar to rhythms in adults and are well established by 1 year of age. By 3 years of age, the child reaches an adult pattern of sleep, with each discrete cycle of NREM and REM sleep lasting 70 to 100 minutes.

At the beginning of the night, a child progresses rapidly through stage N1 and stage N2 sleep and enters slow-wave sleep (stage N3) for much of the first third of the night. During slow-wave sleep, the child is difficult to awaken. (Many parents will recognize this period as the time of night that they can vacuum or listen to loud music without waking the child.) Subsequent sleep cycles have decreased amounts of slow-wave sleep and increased amounts of stage N2 sleep and REM sleep. Dreaming takes place mainly during REM sleep. REM episodes become longer and more intense later in the sleep period; thus, children are more likely to complain of bad dreams during the last portion of the night. In addition, sleep-disordered breathing (SDB) is likely to be most prominent during REM sleep. This tendency is important to recognize, given that this time of night is when parents are least likely to be awake and watching the sleep patterns of their children.

The amount of sleep that children need varies by age, but most children in the early school years need at least 10 hours of sleep (see Table 194-1). Children who are sleep deprived are sometimes sleepy but are more often irritable, inattentive, or hyperactive. Adolescents need sleep as much as younger children do, but they are less likely to get as much sleep as they need.

Humans have internal clocks that operate on a cycle of approximately 24 hours. These 24-hour cycles, known as *circadian rhythms*, are controlled by the

**Table 194-1** Sleep Developmental Milestones

GESTATIONAL AGE (WK)	SLEEP PATTERNS
10	Spontaneous fetal movements are identified.
24	Neither quiet nor active sleep can be identified between 24 and 26 weeks. Early premature (24–27 weeks) neonates have atypical sleep state characteristic of active and quiet sleep.
28	Active sleep is identified by 28 to 30 weeks by eye, body, and irregular respiratory movements. Chin tone does not become tonic before 36 weeks. Rhythmic cycling period of activity and quiescence is identified between 28 and 32 weeks.
30	Typical sleep states begin to emerge at 30 weeks.
32	Tracé alternant pattern associated with quiet sleep appears at 32 to 34 weeks. Occipital predominance of delta activity is striking at 31 to 32 weeks. At 32 weeks, EEG differences among wakefulness, active sleep, and quiet sleep develop.
34	Active sleep is 60% of TST.
37	Sleep organization at 37 weeks similar to term newborn.
40	Sleep onset through active/REM (REM within 15 minutes of sleep onset). Three distinct sleep states in term newborn: (1) REM (active), (2) NREM (quiet), and (3) indeterminate. Newborn sleeps 16 to 17 of 24 hours. Active sleep 50% of TST in term infant. Newborn sleep cycle is 50 to 60 minutes (range, 30–70 minutes), 58% active, and 39% quiet. Periodic breathing is noted, particularly in active sleep.
46	Tracé alternant present in quiet sleep in normal infants is not seen after 46 weeks.
48	Sleep spindles appear. Premature infants show spindle development approximately 4 weeks in advance of full term. Periodic breathing becomes rare after 48 weeks.
3 months	NREM sleep stages begin to appear. By 3 months, sleep-onset REM is no longer present. By 3 months, 60% of sleep is quiet sleep, and 40% is active sleep. Lack of sleep spindles after 3 months is associated with hypothyroidism.
4 months	Sleep shifts to nighttime <i>settling</i> by 12 to 16 weeks. Slow-wave sleep recognized at 3 to 4 months. Adult sleep stages at 4 to 5 months. Infant asleep 14 to 15 hours a day by 4 months. By 16 weeks, sustained wake periods are as long as 3 to 4 hours.
6 months	By 6 months, 90% of infants have more NREM sleep than REM sleep.
8 months	REM sleep occupies 30% of TST. Total sleep duration is 13 to 14 hours a day by 6 to 8 months of age.

EEG, electroencephalogram; NREM, non-rapid eye movement; REM, rapid eye movement; TST, total sleep time.

**Table 194-2** Average Sleep by Age

AGE	TOTAL SLEEP DURATION (hr)	2%–98%	MEAN DAYTIME SLEEP DURATION (hr)	DAYTIME NAPPING CHILDREN (%)
1 mo	14	9–19	5.5	100
3 mo	14	10–18.5	5.0	100
6 mo	14.2	10.4–18.1	3.4	100
9 mo	13.9	10.5–17.4	2.8	100
12 mo	13.9	11.4–16.5	2.4	100
18 mo	13.6	11.1–16	2.0	96
2 yr	13.2	10.8–15.6	1.8	87
3 yr	12.5	10.3–14.8	1.7	50
4 yr	11.8	9.7–14.0	1.5	35
5 yr	11.4	9.5–13.3	0	8
6 yr	11.0	9.3–12.6	0	5
7 yr	10.6	9.2–12.1	0	1
8 yr	10.4	9.0–11.7	0	0
9 yr	10.1	8.8–11.4	0	0
10 yr	9.9	8.6–11.1	0	0
11 yr	9.6	8.3–10.9	0	0
12 yr	9.3	8.0–10.7	0	0
13 yr	9.0	7.7–10.4	0	0
14 yr	8.7	7.3–10.1	0	0
15 yr	8.4	7.0–9.9	0	0
16 yr	8.1	6.6–9.6	0	0

Adapted from Iglowstein I, Jenni OG, Molinari L, Largo RH. Sleep duration from infancy to adolescence: reference values and generational trends. *Pediatrics*. 2003;111(2):302–307.

hypothalamic suprachiasmatic nucleus. Most people have cycles that are not exactly 24 hours in length, and external time cues help reinforce the 24-hour schedule. The time cues are known as *zeitgebers* (German for *time givers*). The most powerful cue is exposure to bright light; other cues include social interaction, food, and exercise. Circadian rhythms are usually synchronized or *entrained* with light–dark cycles. Infants develop these circadian rhythms over the first few months of life, with rhythmic secretion of melatonin by 12 weeks in term infants. Circadian rhythm sleep disorders occur when a person’s sleep is of normal duration but occurs at a time that does not allow adequate sleep in the context of the person’s life. For example, an adolescent who is unable to fall asleep until 4:00 am and cannot wake before noon is said to have a circadian rhythm disorder (sleep-phase delay) and is likely to have problems functioning in a usual school environment. If, however, a person with the same sleep-phase delay works at night, then the sleep-phase delay is not considered a disorder.

SLEEP EVALUATION

Children rarely complain of sleeping problems. A parent or other caregiver usually initiates the diagnostic evaluation. The most common complaints are the child’s inability to fall asleep or remain asleep, daytime sleepiness, and abnormal behaviors during sleep (snoring, gasping, or yelling). In sorting out a concern about sleep, history is the major initial diagnostic tool.

Questionnaires for general screening or for evaluating sleep complaints may be helpful in gathering data in busy practices. One simple, 5-item pediatric sleep screening instrument is BEARS (Bedtime problems, Excessive daytime sleepiness, Awakenings at night, Regularity and duration of sleep, and Snoring). The key areas explored on the BEARS parent questionnaire can lead to further open-ended questions by the practitioner to determine the level of parental concern (or to elicit maladaptive patterns if no concern is expressed) and to help formulate a differential diagnosis (Table 194-3). Having the parents keep a sleep chart is helpful (Figure 194-1); it may demonstrate a consistent

Table 194-3      Questions to Clarify Sleep Problems

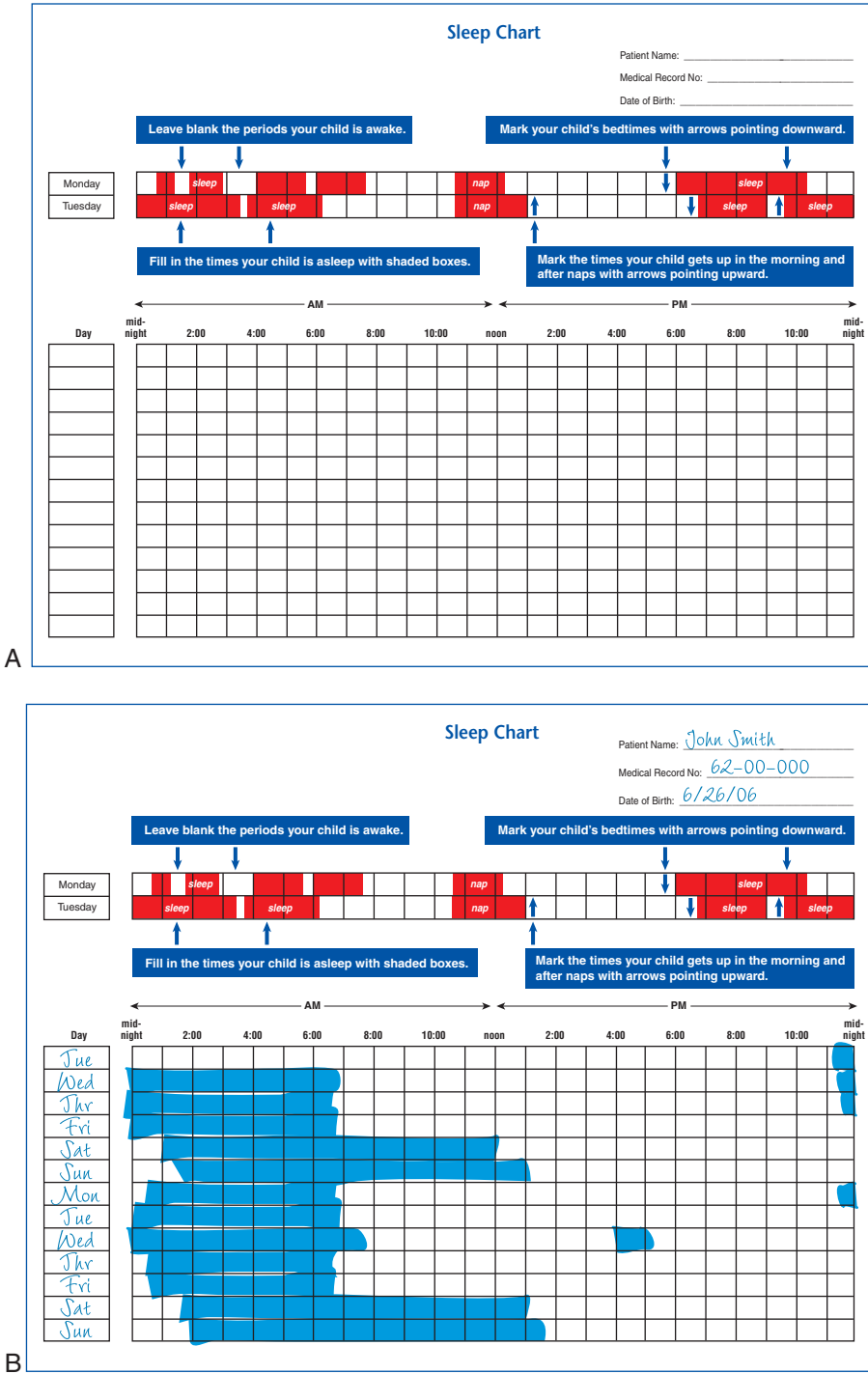
QUESTIONS	TO CLARIFY
<b>TO THE PARENTS</b>	
Do you have any concerns about the child’s sleeping?	Problem versus disorder
How do you think the child is sleeping compared with other children of similar age?	Traumas or stress
When and how did the child’s sleep problems start?	Secondary gain
Did other changes in the child’s life occur around this time?	Traumas or stress
• What methods have you tried to solve this problem?	
• What ideas have you had about solving this problem?	
• What have others told you about this problem?	
What is the atmosphere in the room where the child sleeps with regard to temperature, darkness, noise, presence of siblings, and type of bed?	Environmental sleep disorder
When is the last time the child eats before falling asleep?	Inadequate sleep hygiene
	Sleep-onset association disorder
Does the child consume any caffeine or nicotine in the evening?	Insomnia caused by substance or drug effects
What is the child doing just before bedtime?	Inadequate sleep hygiene
	Limit-setting disorder
	Bedtime resistance
What routines do you use to put the child to bed?	Inadequate sleep hygiene
	Limit-setting disorder
	Bedtime resistance
What exactly do you do at bedtime?	Sleep-association disorder
How does the child act at bedtime?	Bedtime resistance
Where and with whom does the child sleep?	Sleep-association disorder
What does your spouse or partner think about this arrangement?	Family conflict
Who else has something to say about the child’s sleeping?	Family conflict
Is the child already asleep when you put him or her in the crib or bed?	Sleep-association disorder
What time is the child put in bed?	Limit-setting disorder
	Inadequate sleep hygiene
	Circadian disorders
What time is the child asleep?	Limit-setting disorder
	Inadequate sleep hygiene
	Circadian disorders
Does the child do anything unusual during sleep?	Sleep-disordered breathing
Snoring, gasping, apnea?	

Continued

**Table 194-3** Questions to Clarify Sleep Problems—cont'd

QUESTIONS	TO CLARIFY
<b>TO THE PARENTS</b>	
Leg kicking, thrashing?	Periodic limb movements, restless leg syndrome
Bed wetting?	Nocturnal enuresis
Shaking, screaming?	Nocturnal seizures
	Parasomnias
What times does the child wake up?	Night feeders
	Sleep-association disorder
How does the child appear, or what does he or she do after waking?	Parasomnias
	Developmental night waking
	Trained night feeders
	Seizures
What works to resettle the child?	Sleep-association disorder
	Trained night waking
	Trained night feeding
	Gastroesophageal reflux
How is that process for you?	Secondary gain
Does the child snore or seem to stop breathing during the night?	Sleep-related breathing disorder
What time is the child up for the day?	Circadian disorders
	Mood disorders
Is the schedule the same on weekends, or does the child sleep in?	Limit-setting disorder or sleep-phase delay
How does the child wake up in the morning?	Circadian disorder or sleep-phase delay
When you wake the child, does he or she seem rested and cheerful?	Circadian disorder or sleep-phase delay
	Inadequate sleep
What time does the child eat in the morning?	Circadian disorder or sleep-phase advance
	Limit-setting disorder
If older than 3 years, does the child remember what happened during the night?	Parasomnia (not remembered)
	Nightmares (remembered)
	Panic attacks (remembered)
Does the child fall asleep during the day? If so, then when, where, and for how long?	Circadian disorders
How is the child settled for naps?	Idiopathic hypersomnia or narcolepsy
	Sleep-association disorder
Does the child sleep differently at other people's houses? If so, then how?	Limit-setting disorder
	Sleep-association disorder
Has the child ever been given any medications for sleep?	Limit-setting disorder
	Insomnia caused by a psychiatric or behavioral condition
What was the medication? How did it work?	
Has anyone in the family ever had sleep problems? Did either of you have sleep problems as kids?	Genetic factors (short or long sleeper)
<b>TO THE CHILD</b>	
What do you think about before you go to sleep?	Anxiety or mood disorder
	Limit-setting disorder
How do you feel when you wake up in the night?	Nightmares
	Disorders of arousal
	Anxiety or mood disorders
Do you still feel sleepy in the morning?	Inadequate sleep
	Circadian disorder or sleep-phase delay
How do you feel about this sleeping problem?	Anxiety
	Secondary gain
What do you think your parents should do about this?	Secondary gain
How are your concentration and grades at school?	Sleep-related breathing disorder
	Sleep-phase delay
	Periodic limb movements disorder
	Narcolepsy
	Idiopathic hypersomnia





**Figure 194-1** A, Sleep log. B, Sleep log showing sleep-phase delay.

pattern, which may improve with the use of sleep hygiene principles (Box 194-1). A general medical, developmental, and mental health history assessment should include any medications, herbal products, drugs, alcohol, or tobacco use. Given that many sleep disorders have a strong familial component, a history of parental sleep issues may be helpful.

Parental perceptions and differences of opinion about sleep often are critical in problem-solving efforts. Co-sleeping (one or both parents sharing a bed with one or more children) serves as a good example of this point. Co-sleeping is a common practice in many cultures and households. When it is agreeable to both parents, co-sleeping is not associated with

**BOX 194-1 Sleep Hygiene Principles**

General principles of sleep hygiene apply at any age, but specifics may vary with the child's age.

1. Establish a good sleep environment that is dark, quiet, and comfortable and has a steady, slightly cool temperature. Sleep should be in the same place for night and naps as much as possible. The bed or crib should be used as a place for sleep and not as play area or playpen while awake.
2. Establish a soothing bedtime routine that involves friendly interaction between the parent and the child. This routine may include a snack and then tooth brushing, use of the toilet, and then story, prayer, or talking time with children in their own bed. The parent should leave the room while the child is still awake.
3. Infants should be fed in a parent's arms and placed in the crib without a breast or a bottle in their mouth. Avoid excessive feeding close to bedtime to reduce the need to void during the night.
4. The child should be put to bed when moderately tired to reduce bedtime resistance.
5. For children whom the parents would like to have sleep in their own crib, teach them the skill of falling asleep on their own by avoiding pacifiers or body contact with the parent as they drift to sleep (self-soothing). This method enables children to go back to sleep on their own after waking during the night.
6. Avoid changing the routine because of demands or tantrums at bedtime, which can quickly develop into a pattern.
7. No television, computer, or any electronic screens should be in the child's room because research shows that video screens will prolong sleep onset and delay bedtime. It is advisable to enforce an electronic curfew for older children and adolescents to facilitate preparation for sleep without distraction and also prevent further use during the night without parental supervision.
8. Try to keep a consistent schedule for bedtime, naps, and morning wake up, which will help the child maintain regular circadian rhythms. Naps should not be taken too close to bedtime.
9. Remember that television programs and movies may be frightening or stimulating. Arguments between parents or other family members may also be distressing. Try to keep the household atmosphere calm in the evening.
10. Keep track of activities that seem to lead to sleeping problems. If active play or video games lead to problems, then stop them 1 or 2 hours before bedtime. Caffeine and nicotine can disrupt sleep. Avoid caffeine at least 6 hours before bedtime.

greater-than-average behavioral or emotional problems in the child. If, however, co-sleeping is a source of discord between parents or reflects a parent's inability to manage the child's behavioral bedtime problems, then it should be addressed as a sleep problem. When co-sleeping is planned, parents should agree on the desired duration. The pediatrician may help the parents by telling them that this arrangement is easier to change before 6 months of age (if an end is intended during infancy). Bed sharing with infants remains controversial particularly with mothers who smoke and when the infant is younger than 11 weeks.

Parental mental health needs to be screened in assessing sleep difficulties because the emotional stability of parents may affect both the perception of problems in children and the ability to carry out a treatment plan. Histories from babysitters or relatives who observe the child's sleep may be diagnostic, especially when problems seen at home are not seen in these settings. The family may provide audiotapes or videotapes that may be helpful.

The history is often diagnostic, but some patients need an overnight sleep study for further assessment. An overnight sleep study or polysomnogram consists of the following:

- Electroencephalogram (EEG) to identify sleep stages

- Electromyelogram of chin activity to help identify decreased tone during REM sleep
- Leg electromyogram to measure leg movements
- Electrooculogram to identify eye movements seen in REM sleep
- Electrocardiogram to monitor cardiac rate and rhythm
- Nasal and oral thermistors to measure airflow
- Thoracic and abdominal belts to measure chest and abdominal movements during breathing (helpful in demonstrating increased or decreased respiratory effort)
- Pulse oximetry to measure oxygen saturation
- End-tidal carbon dioxide monitoring to indirectly measure hypoventilation

All of these measurements provide clinically useful information about sleep stages, sleep disruption, respiratory status during all sleep stages, leg movements, and changes in cardiac rate and rhythm during sleep. The sleep study also provides a picture of the relationship of sleep-related measurements. For instance, OSA may cause arousals, cardiac deceleration, and oxygen desaturation; these findings may be mild during NREM sleep but profound during REM sleep.

Overnight sleep studies are attended by a sleep technologist who attaches monitoring sensors and adjusts them during the night. The technologist also

provides observations about the child's sleep that may be invaluable in making an accurate diagnosis.

Extended-montage video electromyograms may be incorporated into the polysomnogram to diagnose nocturnal seizures. Haplotyping, karyotyping, or fluorescent in situ hybridization studies can be helpful for diagnosing some of the genetic conditions associated with sleep disorders such as congenital central hypoventilation syndrome, Rett syndrome, Smith-Magenis syndrome, and Prader-Willi syndrome.

## CLASSIFICATION OF SLEEP DISTURBANCES

Sleep disturbances in children can be categorized according to the *International Classification of Sleep Disorders*, second edition.

- Behavioral insomnia of children
- Sleep-related breathing disorders
- Circadian rhythm disorders
- Parasomnias
- Sleep-related movement disorders
- Hypersomnias

## MATURATIONAL OR BEHAVIORAL ISSUES

### Day-Night Reversals

The earliest parental complaint about sleep is often day-night reversal, occurring around 2 weeks of age. This problem is predictable because consolidated nocturnal sleep has not yet developed. Parental concerns provide the pediatrician a valuable opportunity to assess parental coping skills and help parents understand the normal unfolding of the child's physiologic regulation. Day-night reversals can be shifted by establishing a general bedtime, keeping the lights off or low, and keeping handling and interaction to a minimum during nighttime feedings. In the morning, lights should be bright and social interaction encouraged. Lack of sleep at this age is unusual and should alert the clinician to medical problems, especially if associated with irritability.

### Delayed Settling

Another common problem is a delay in the much desired milestone of sleeping through the night. One definition of settling or sleeping through the night is 5 hours of continuous sleep after midnight for 4 consecutive weeks. Unrealistic parental expectations for sleeping through the night are common, and pediatricians need to carefully address misperceptions about how well a child should sleep. Anders observed that 44% of parents of 2-month-olds reported that their child slept throughout the night when, in fact, actual recording on time-lapse videotape showed that only 15% actually slept throughout the night without awakening.

The issue of sleeping through the night may have important ramifications for the breastfeeding infant. Despite the widely recognized and undisputed advantages of human milk for infants, the duration of

lactation in the United States is still well below the recommended goal of 50% at 6 months in all ethnic groups. The perceptions of normal maternal and infant sleep patterns may be an important factor in failure to sustain lactation. Although breastfed infants are typically assumed to feed more frequently and have shorter meal intervals than bottle-fed infants, widely disparate differences in sleep patterns, crying, fussiness, and colic behavior between breastfed and bottle-fed infants have been reported. The perception that breastfed infants typically *settle* at an older age than bottle-fed infants and awaken more frequently at night is quoted in the popular press as an *advantage* of formula feeding. As a corollary, a mother's need for an uninterrupted night's sleep may inadvertently promote the early cessation of breastfeeding.

In fact, breastfeeding need not be associated with increased night waking by 12 weeks of age; both breastfed and bottle-fed infants can respond to behavioral interventions aimed at increasing sleep time during the night. Additional evidence is emerging that continuing lactation can actually increase maternal slow-wave (restorative) sleep because of increased circulating prolactin levels. The circadian rhythm of tryptophan secretion in mother's milk may help promote nocturnal infant sleep and is being mimicked by investigation of varying amounts of tryptophan in day-night formulas.

Infants who appear to have a low threshold of sensitivity by temperamental disposition also tend to settle later. Premature infants tend to settle around the time expected for their gestational age, although variability is greater than among full-term infants. Delays in central nervous system (CNS) maturation often are associated with delays in settling. Infants with frank neurologic impairments may not only be delayed in settling but also have other medical issues that need to be addressed to allow settling to occur.

### Sleep-Onset Associations

Infants and children develop habits of falling asleep in accustomed circumstances, such as in a bed, in a parent's arms, or while being fed. These sleep-onset associations may begin in the first 2 months of life and are one of several behavioral causes for insufficient sleep outlined in Table 194-4. Sleep-onset association may be viewed as a problem by the family when a child older than 6 months needs prolonged parental assistance to fall asleep at the beginning of the night and after each nocturnal arousal. This pattern is a conditioned response, and the child is unable to fall asleep unless the conditions allowing sleep onset are recreated. Parents may complain that their own sleep is severely disrupted because they need to help the infant resettle several times each night. Treatment is straightforward—the child learns to make the transition from wake to sleep without expecting a parent's participation. Parents should be advised to place the infant while still awake into the crib for both night and naps starting by 48 weeks postgestational age. A helpful tactic is for the infant's bedding to have the mother's scent for comfort. If a problematic sleep-onset association has already developed, then parents may

**Table 194-4** Causes of Insufficient Sleep in Children

	PREVALENCE	TREATMENT
<b>BEHAVIORAL</b>		
Sleep-onset association disorder	30%–40%	Education, extinction strategy
Limit-setting disorder		Education, family counseling
Adjustment disorder		Education, family counseling
Chronic sleep deprivation	Common	Education in sleep hygiene
Early school starting times		Education; advocacy (petition school boards and legislature for later school start times)
Parent work schedule		Education
Social activities		Education
Idiopathic insomnia (diagnosis of exclusion; often made retrospectively)	Unknown	Good sleep hygiene; hypnotics under investigation
Circadian rhythm disorder		Education, morning light therapy
Delayed sleep phase		Advance sleep phase
Sleep entrainment		Intense sensory clues; regular or strict daily schedule; melatonin
Hypothalamic tumor		Intense sensory clues; regular or strict daily schedule; melatonin
Blindness		Intense sensory clues; regular or strict daily schedule; melatonin
Mental retardation		Intense sensory clues; regular or strict daily schedule; melatonin

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need to institute a graduated extinction program (see below) to help infants older than 6 months learn to fall asleep on their own over several weeks.

Although graduated extinction is a very effective treatment, parental distress is a common issue during the initial portions of employing an extinction strategy. Warning parents what to expect and addressing fears about harming or creating a sense of abandonment in the child may alleviate some parental concern. Successful treatment will require consistency, and it is important that all nighttime caregivers are able to implement the extinction technique. If the parents are uncertain that they will be able to consistently implement extinction strategy, it may be advisable to delay treatment until that is possible. Parents should be educated that the extinction process may take longer if the disruptive sleep pattern becomes more well-established as the child becomes older.

### Limit-Setting Disorder

Bedtime routines should take 30 minutes or less. Consistently longer bedtime routines may reflect parental difficulty in setting limits. Prolonged bedtime routines are often associated with multiple curtain calls for stories, hugs, water, and trips to the toilet. Toddlers and preschool children no longer sleeping in a crib may reappear after being put to bed, thus prolonging the routine. These curtain calls are unintentionally reinforced by the parental attention needed to return the child to bed, even if done with obvious displeasure.

The best management of prolonged bedtime routines is prevention through reasonable daily schedules, assurance of adequate special individual time with each parent every day, and careful limit setting. This approach reduces the child's separation anxiety as well as parental guilt. The bedtime routine should be limited to a defined set of activities or length of

time. Parents may then either notify the child that they will not respond to further requests, or say "only one more" and adhere to this declaration. Parents should be warned to avoid responding to the excuses that will likely ensue. Having the parent promise to check the child frequently can also be reassuring. Bedtime should occur when the child is tired to enhance his or her tendency to fall asleep. Naps should not occur close to bedtime.

Positive reinforcement may enhance limit setting. Children who stay in bed without calling out may be motivated by simple rewards with stickers in the morning or an extra story the following night. Parents may need coaching on limit setting or referral to a psychologist if discipline is a major problem, or they may benefit from marital counseling if significant discord exists regarding family life.

### Bedtime Fears

Preschool and early school-aged children often have bedtime fears, which are often generated by stresses such as separation from parents, aggressive peers, sibling birth, or the death of a grandparent. Exposure to frightening movies or video games can also contribute. The child's fears should be acknowledged, and he or she should be reassured that the parents will keep him or her safe. A ritual of the adult *spraying for monsters* may be helpful. Having the child help the parent buy a special flashlight to check out the room at night provides a sense of mastery. Older children benefit from relaxation exercises accompanied by empowerment stories. A nightlight may be helpful.

### Primary Insomnia

Primary insomnia can be seen in normal children but is generally transient and is a diagnosis of exclusion.



### BOX 194-2 Symptoms and Signs of Inadequate Amount of Sleep

1. Excessive daytime sleepiness (rare in young children)
2. Hyperactivity–impaired attention
3. Poor school performance–impaired concentration, vigilance
4. Behavior problems–bad mood, irritability
5. Obesity–possible link to inadequate sleep
6. Failure to thrive

It must last at least 1 month, interfere significantly with functioning or cause significant distress, and not be part of another medical, sleep, or mental disorder. The symptoms and signs of inadequate sleep are listed in Box 194-2.

Medication for primary insomnia in healthy children is controversial, but medications such as diphenhydramine, clonidine, and melatonin have been used in pediatric insomnia. Indiscriminate medication use can mislead physicians and families about the causes of insomnia and ignore the behavioral management needed.

A disruptive sleeping environment may cause either sleep onset or sleep maintenance insomnia. Excessive noise or light, uncomfortable bedding, excessive room temperature, interference of pets, or outside noises are commonly found. Treatment is simply to eliminate or correct the environmental condition or distraction.

### Other Difficulties Falling Asleep

Dyssomnia, the term for insomnia that does not meet disorder criteria, occurs mainly in preschool-aged and older children. This problem includes environmental sleep disorder caused commonly by noise, pets, and temperature extremes. Revising the household routine to allow quiet for adequate sleep is necessary to resolve this dilemma (Table 194-5).

### Awakenings From Sleep

Waking at night occurs in more than 80% of children and, of course, in infants who still need to feed. Night waking is only problematic when the child cannot return to sleep on his or her own. As many as 20% of 2-year-olds, 14% of 3-year-olds, and 6.5% of 5- to 12-year-olds have problematic night awakenings. Common causes and treatment of sleep fragmentation and disrupted sleep continuity are outlined in Table 194-5.

### Sleep-Onset Association Disorder

**TRAINED NIGHT FEEDING.** In Western industrialized societies, between 60% and 70% of either breastfed or bottle-fed infants are reported to be settling or sleeping through the night by 12 weeks of age without any specific behavioral interventions. Nonetheless, some infants older than 6 months who wake up during the night are immediately fed to encourage their return to

sleep. Their sleep cycle may be changed by the introduction of food to produce an arousal—basically, learned hunger—and they will consume a full feeding during the night. Trained night feeding should generally not be diagnosed before 6 months postterm because of the frequent need for a feeding during the night in younger or premature infants. Infants who learned to sleep through the night and subsequently begin waking during the night and seem genuinely hungry are probably ready for solids (if they are older than 4 to 6 months) or need increased volumes or number of feeds during the day and evening if they are formula fed. Breastfed infants may respond better to more frequent evening feedings (cluster feeding) of smaller but richer (higher lipid content) human milk.

Trained night feeding can be prevented by teaching parents ways to recognize when an infant is fussy because of hunger and when fussiness arises from other causes, such as boredom. Parents should not automatically feed a fussy infant unless the infant appears hungry. Parents who go to their infants older than 4 months at the first sound of stirring should also be encouraged to allow their infants the opportunity to return to sleep without intervention. Expectations of the appropriate need for a late (eg, 10:00 pm) feeding should be clarified. Daytime feeding intervals can be adjusted gradually and any sleep associations retrained simultaneously. If night feedings are an established pattern, then the formula-fed infant can be fed 1 oz less each night. This tactic will usually help resolve trained night feeding in approximately 1 week.

**TRAINED NIGHT WAKING.** Waking at night without requiring a feeding in the infant between 4 and 8 months of age is called *trained night waking*. This pattern often begins when the infant is ill or subjected to travel or some other change in routine, but the pattern may persist because the child gets a secondary reward from the parent's attention. One parent may believe that quieting the infant quickly is necessary to avoid disturbing other family members or neighbors. In some instances, parents who have little time to spend with the child during the day enjoy this time with the child and reinforce the night waking by playing with him or her. Trained night waking is also increasingly common in infants who have difficult temperaments.

Management of trained night waking that causes persistent family disruption requires management of the precipitant stress and, ideally, collaboration with the spouse or neighbors to tolerate some crying during the treatment. Bedtime routines need to be established, perhaps with bedding or infant clothing with a maternal scent, and the infant should be put into bed awake. Daytime naps should be limited to 2 hours to consolidate the longest sleep period at night. When awakening during the night, the infant should be allowed 1 to 2 minutes of crying before being checked, but not fed, and then checked every 2 to 5 minutes in most circumstances. The infant may be touched but not picked up, rocked, or cuddled. For success, this approach may require the more involved parent to take a shower, turn up music, or find some other distraction. Brief sedation with diphenhydramine for the

**Table 194-5** Causes of Sleep Fragmentation in Children

	PREVALENCE	TREATMENT
Behavioral	30%–40% of persons with sleep fragmentation	
Sleep-onset association		Education
<b>PARASOMNIAS</b>		
Sleep terrors		Education, good sleep hygiene, medication (rarely)
Sleep talking		Education, good sleep hygiene
Somnambulism		Education, good sleep hygiene, review safety issues
Confusional arousals		Education, good sleep hygiene
<b>SLEEP-RELATED BREATHING DISORDER</b>		
Sleep apnea	2%	Adenotonsillectomy, nasal CPAP
Upper airway resistance syndrome	Unknown	Adenotonsillectomy, nasal CPAP
<b>OTHER MEDICAL</b>		
Asthma		Medical management
Cystic fibrosis		Medical management
Gastroesophageal reflux		Medical management
Nocturnal seizure		Anticonvulsants
Periodic leg movements of sleep	3.9%–10% of adults; 2% of children; 20% of children with attention-deficit/hyperactivity disorder	Iron replacement therapy; dopamine agonists; gabapentin
<b>ENVIRONMENT</b>		
Co-sleeping, noise, pets		Education, safety issues

CPAP, continuous positive airway pressure.

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infant should rarely be needed to help modify this habit if the graded extinction techniques described previously are strictly applied.

**DEVELOPMENTAL NIGHT WAKING.** Although most infants are sleeping through the night by 6 months of age, many begin awakening again around 8 to 10 months of age. This new behavior, called *developmental night waking*, corresponds to several coincident developmental processes, including increased mobility, fear reactions to strangers, and object permanence (ability to remember and seek something or someone, like a parent, that is out of sight).

The best management is advising parents at the 6-month well visit to expect a recurrence of night waking. Because of differences in cultures, not all parents will see this circumstance as a problem. For parents who do, they should be advised to wait a few minutes before going to the infant but to avoid feeding or other reinforcement. If waking is already established, then the parents should have the contributing developmental forces explained and be advised to create a bedtime routine, including a transitional object and a dim nightlight. When the infant awakens, he or she should be given at least 2 minutes to self-soothe, with some fussing tolerated as part of the process. If fussing continues, then one parent can go to reassure the child briefly, without touching or feeding, and settle down within sight to sleep the rest of the night without talking to the child. The child often becomes enraged instead of fearful, which is more tolerable to the

parent, who can see that the child is safe. Some parents are more comfortable than others with this plan. For children who are no longer constrained to a crib, the parent must prevent body contact with the child by giving him or her the alternative that the parent will leave the room to avoid establishing a sleep association. Further interactions should be brief and minimally interactive. Eventually, the child will no longer require the parent's presence to return to sleep after nocturnal awakenings.

### **Sleep-Related Breathing Disorder**

The pediatrician is often confronted with the problem of what to do with the child who snores. Snoring is common; OSA is less common.

Young children with SDB are usually not obese, unlike typical adult patients. Some groups of children are at particularly high risk for SDB, including those with craniofacial anomalies, chromosomal syndromes, and neuromuscular disorders. Children with Down syndrome, Prader-Willi syndrome, cleft palate, achondroplasia, muscular dystrophy, cerebral palsy, and other underlying disorders should be routinely screened for sleep problems. Although children with Down syndrome, for instance, typically have learning difficulties, treatment of SDB may result in improved daytime performance.

While many children with obstructive SDB improve after adenotonsillectomy, those with either obesity or asthma are more likely not to have complete resolution

of symptoms. On occasion, nasal continuous positive airway pressure (CPAP) or even tracheostomy may be required.

The question of whether all children should have sleep studies before undergoing adenotonsillectomy is controversial. However, certain groups of children are clearly at higher risk for perioperative complications and may warrant polysomnograms as part of a preoperative evaluation, especially if outpatient surgery is being contemplated. Children younger than 3 years, children with morbid obesity or chromosomal or craniofacial anomalies, children with underlying neuromuscular disorders, and those with other underlying medical conditions that make them higher-risk surgical patients should be considered for preoperative polysomnograms.

### **Circadian Rhythm Sleep Disorder**

The most common circadian rhythm disorder causing insomnia is a sleep-phase delay that is commonly seen in adolescents. Because the natural circadian cycle is approximately 24.5 hours, some individuals are vulnerable to shifting sleep cycles by approximately 30 minutes a day. This shift often results in difficulty waking in time for school in the morning. Morning battles with parents about waking for school are common. Phase-delayed adolescents often sleep very late on weekends and vacations and then find falling asleep at a reasonable bedtime even more difficult. Changing adolescent sleep-phase delay is very difficult and requires intense commitment and active participation of the adolescent and parents with the use of bright light exposure in the morning and consistent wake times all 7 days of the week.

Some children who are deprived of normal circadian stimuli develop circadian rhythm disorders. Because zeitgebers that entrain normal circadian rhythm include light (especially sunlight that may be 100,000 lux), exercise, social activities, and eating, the fact that a child with cerebral palsy who is blind, wheelchair dependent, and fed by gastrostomy tube has difficulty with a varying sleep time is not surprising.

Other children have circadian rhythm problems that reflect a chaotic home life. Some families do not adhere to predictable routines, allowing children to set their own schedules, resulting in seemingly bizarre sleep patterns. A circadian rhythm disorder may be differentiated from an oppositional disorder by the child's behavior pattern. A child with a circadian rhythm disorder may not resist going to bed but is unable to fall asleep. In the morning, the child is difficult to arouse and does not feel rested.

A sleep-phase advance usually occurs in infants or toddlers who fall asleep early (7:00 pm) but then awaken early in the morning (3:00 am). Different types of circadian shift can be adjusted by simultaneously shifting naps, bedtime, waking time, and meals to a desired schedule that matches the child's total daily sleep needs.

In difficult cases, the child can wear an actigraph, a small portable device similar to a large wristwatch, for several weeks. The device senses physical motion by means of an accelerometer and stores the information. Actigraphy provides a graphic illustration of a child's

sleep-wake schedule and can be a useful, noninvasive method for assessing specific sleep disorders such as insomnia, excessive daytime sleepiness, and circadian rhythm disorders (Figure 194-2).

### **Parasomnias (Partial Arousal Disorders)**

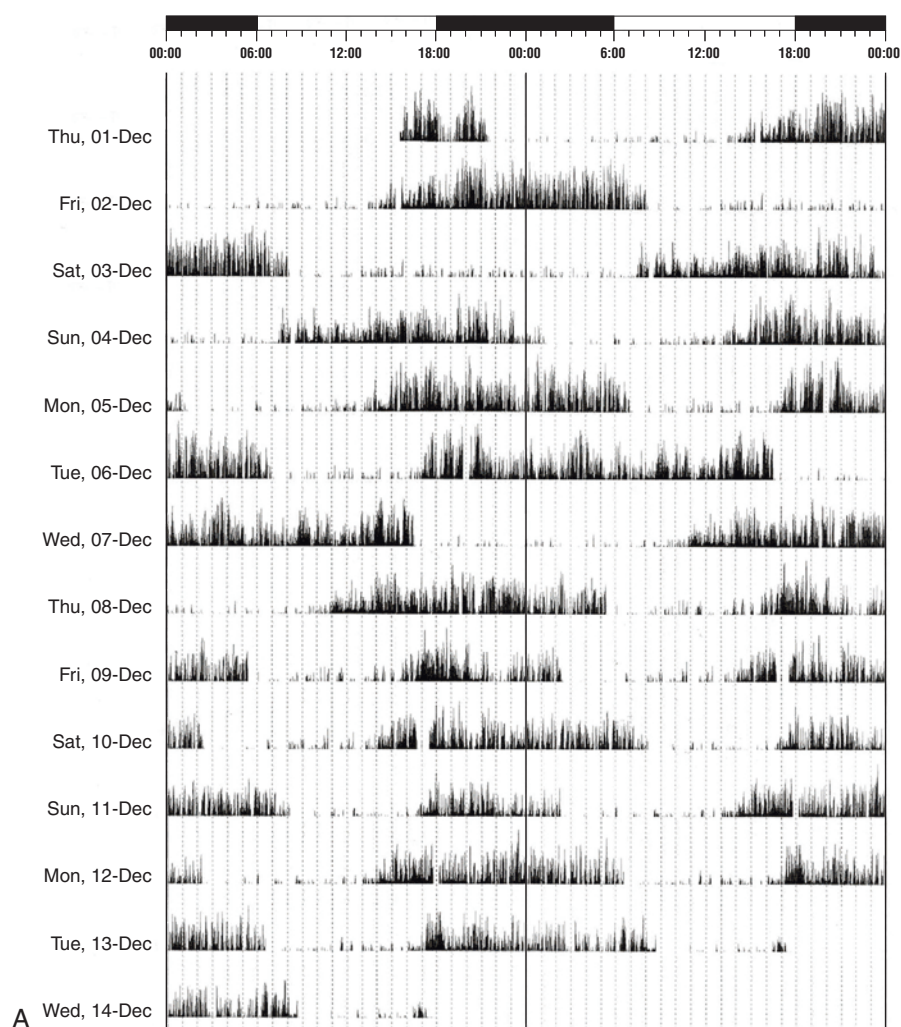
Parasomnias are unusual behaviors or experiences that occur during sleep or the transition between sleep and wake. Parasomnias associated with partial arousal from slow-wave sleep are common in children. They include confusional arousals, sleep terrors, and sleepwalking disorder (somnambulism). All of these episodes occur during arousal from slow-wave sleep, usually in the first third of the night. The child appears confused or frightened and is unresponsive to parental intervention. The child is not fully awake and does not remember the event in the morning.

Symptoms most often begin in childhood and resolve spontaneously, occasionally persisting into adulthood (0.5%). Diagnosis is based on the timing of these symptoms (generally during the first third of the night), the typical presentation, and the child's lack of recall of the events when awake the next morning (morning amnesia). A strong familial component exists, and history often reveals that one or both parents had similar behaviors as children.

**CONFUSIONAL AROUSALS.** Young children may experience partial arousals from slow-wave sleep, during which they sit up, mumble, and may appear awake; they seem confused and nonresponsive to parental questions. The prevalence of confusional arousals was 17% between ages 3 and 13 years in one study. Children may sometimes thrash about and respond combatively to parental attempts to intervene. Confusional arousals usually occur in the first third of the night, but a child may occasionally have multiple arousals, extending into the second half of the night, generally decreasing in intensity. Confusional arousals are most common when children are overtired or ill. Management includes reassurance that the episodes are generally benign, minimal intervention during episodes, and removal of potential safety hazards from the child's bedroom. Treating disorders that may fragment sleep such as OSA and restless leg syndrome can be helpful. In severe cases, a few weeks of a benzodiazepine, such as lorazepam, at bedtime may interrupt the sequence by reducing slow-wave sleep. However, rebound occurs with discontinuation of the medication, often with an increasing number of events. A sleep study may help to confirm the diagnosis and detect precipitating events such as OSA or nocturnal seizures in severe or atypical cases.

**SLEEP TERRORS.** Sleep terrors are partial awakenings from slow-wave sleep characterized by physiologic arousal including pallor, sweating, pupillary dilation, piloerection, and tachycardia. The child may sit up and scream and may appear terrified. The child may thrash or run and is not responsive to attempted parental comforting. The child does not remember the event in the morning. Sleep terrors occur in 3% of children, usually starting between 18 months and 5 years. These episodes do not reflect emotional disturbance, although, as with all NREM parasomnias, occurrence is increased with illness,





**Figure 194-2** Ten-year-old child with Down syndrome and nighttime G-tube feeding after brain injury. A, Random sleeping pattern with the child frequently awake at night.

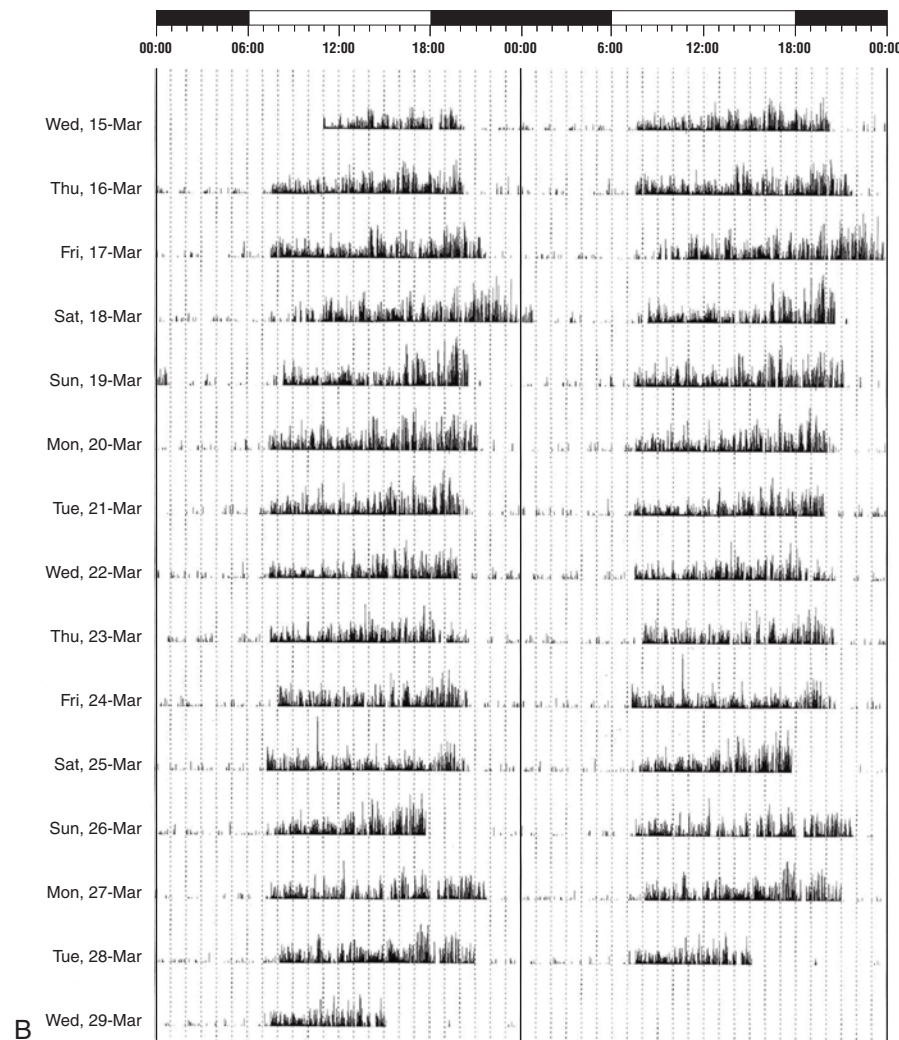
stress, or sleep deprivation. A family history of sleep terrors, enuresis, somnambulism, or sleep talking is often present. Sleep terrors may be precipitated by fatigue, stress, a full bladder, or loud noises. They tend to occur in bouts for several weeks and then disappear only to recur several weeks later. Parents need reassurance about the benign nature of sleep terrors and their tendency to resolve in approximately 95% of children by 8 years of age. The bladder should be emptied routinely before bedtime, and the environment should be kept dark and quiet. The bouts may occasionally be interrupted by waking the child 15 minutes before the expected episode, generally occurring approximately 1 hour into sleep each night for approximately a week. A 30- to 60-minute afternoon nap can also reduce the depth and amount of stage IV sleep and may decrease the number of episodes. Treatment with benzodiazepines can reduce the frequency of these events by altering slow-wave sleep, but episodes may recur when the child is weaned or when tolerance occurs. An investigation for nocturnal

seizures with full EEG as part of a sleep study is indicated in intractable cases or those that have their onset in adolescence.

#### **SLEEPWALKING DISORDER (SOMNAMBULISM).**

Approximately 15% of children sleepwalk at some time. Between 1% and 6% have 1 to 4 episodes per week, mostly between ages 4 and 12 years. Sleepwalking, as with other disorders of arousal, occurs mainly during slow-wave stage N3 sleep, generally in the initial 120 minutes of sleep. During sleepwalking, children are difficult to arouse, are uncoordinated, and tend to wander in illogical places, often urinating outside the toilet. Chronic sleepwalkers need to be carefully safeguarded so that they do not injure themselves. Door and window alarms and locks may be necessary. Amnesia of the event in the morning is common. Sleepwalking can usually be differentiated by history (regular timing, same movements) or videotapes from dissociative states or seizures; however, occasionally, extended EEG as part of a sleep study may be necessary.





**Figure 194-2, cont'd** B, Stabilized sleeping pattern using nighttime melatonin and morning phototherapy, and stopping G-tube feedings at night.

### Nightmare Disorder

Nightmares are an extremely common parasomnia occurring during REM sleep and are most common in the last third of the sleep period. The dream content often is recalled as frightening and reflects daytime stresses. Although children clearly dream by 14 months of age, nightmares are most common between 3 and 6 years, occurring in 10% to 50% of children. At these ages, children have the verbal skills to describe dreams. They also have vivid imaginations and fears.

Nightmares are uniformly part of posttraumatic stress disorder; they may increase after withdrawal of REM-suppressing substances such as alcohol and antidepressants.

A child who wakes from a frightening dream should be comforted, keeping the intervention brief to avoid secondary gain. The same concerns listed for bedtime fears should be addressed when nightmares are frequent. Children who have chronic nightmares have been shown to improve with targeted relaxation

exercises and stories in which the child masters a situation. Children can prepare to have good dreams through rehearsal and imaging at bedtime. Severe nightmares may respond to bedtime medications, although counseling is mandatory if the condition is of a severity to warrant medication.

### Violent Behavior During Sleep

An REM behavior disorder (RBD) has been described in which normal REM atonia does not occur. Dream content can be physically acted out, sometimes in violent ways. RBD is very rare in healthy children but has been seen in autistic children or in association with neurologic disorders. A clue to diagnosis is that abnormal behaviors occur during the last third of the night, unlike NREM motor parasomnias, which typically occur during slow-wave sleep during the first third of the sleep period. Diagnosis requires a sleep study and neuroimaging studies. Treatment with

clonazepam has been beneficial in autistic children and is the most common treatment in adults.

### Other Parasomnias

Bruxism is grinding the teeth during sleep and has been reported in more than 50% of children, with a mean age of onset of 10.5 years. No longitudinal studies demonstrating the natural history of bruxism have been conducted, but dental evidence of bruxism can be identified in 10% to 20% of the general population. Bruxism can also be caused by dental malocclusion or neurologic or psychiatric conditions. Tooth guards can protect the teeth and reduce potential damage to the temporomandibular joint. If stress or anxiety is a trigger, then relaxation exercises at bedtime may be helpful.

## SLEEP-RELATED MOVEMENT DISORDERS

### Restless Legs Syndrome and Periodic Limb Movements of Sleep

Restless legs syndrome occurs in about 2% of children between 8 and 17 years of age. It is characterized by uncomfortable sensations in the legs, which are worse at rest (“like worms crawling under my skin”). These sensations are present in the evening, are associated with the need to move, and are temporarily relieved by movement. They are sometimes confused with growing pains. They may interfere with the child’s ability to fall asleep. A strong familial component exists. Periodic limb movements of sleep are repetitive, brief leg twitches, occurring more than 5 times per hour in children. Leg movements or jerks may occur with resumption of a breath after a central apnea or with a loud snort or snore at the termination of an obstructive apnea. They may cause arousals, fragmenting the continuity of sleep and leading to a complaint of sleep maintenance insomnia. Although the two syndromes are not identical, many patients

experience both. In children, limb movements may be exacerbated by iron deficiency or the use of antidepressant medication. They are more common in children with attention-deficit/hyperactivity disorder (ADHD). Treatment may include iron supplements, clonidine, gabapentin, or dopaminergic agents, depending on the age of the child.

### Sleep–Wake Transition Disorder

Rhythmic movements while falling asleep are common in infants and toddlers. Rhythmic movement disorders include head banging and body rocking. Some rhythmic activity at bedtime occurs in more than half of 9-month-olds, decreasing to one-third at 18 months, and to less than one-fourth at 2 years of age. Head banging is typically monotonous, occurring 60 to 80 times per minute, usually for less than 15 minutes. Usually benign, head banging may occasionally be caused by CNS injury, headache, inner ear abnormality, sensory deprivation (including visual or hearing impairment), neglect, or abuse. Children of intense temperament are especially likely to bang. Although head banging usually does not cause brain injury, it can be traumatic if the bed is unstable or if safety precautions are not taken in the environment. The condition may be reduced by kinesthetic stimulation during the evening and holding the child as part of the bedtime routine. Sleep restriction (ie, limiting the time the child lies in bed before falling asleep) and mild sedation have been shown to be helpful in difficult cases. Parents often need reassurance of the generally benign nature of these behaviors.

## HYPERSOMNIA

Excessive daytime sleepiness (EDS) can be caused by insufficient sleep (see Table 194-4), fragmented sleep (see Table 194-5), or increased sleep drive (Table 194-6). Although some sleepy children appear to have difficulty remaining awake, many sleepy children may exhibit hyperactivity, restlessness, poor concentration,

**Table 194-6** Excessive Sleepiness in Children—Causes of Increased Sleep Drive

DIAGNOSIS	PREVALENCE	TREATMENT
Narcolepsy	0.2%	Stimulant medication, attention to sleep hygiene, treatment of coexisting sleep problems (periodic limb movement disorder, obstructive apnea)
<b>TEMPORARY HYPERSOMNOLENCE</b>		
Acute medical illness		None specifically
Illicit drug use		
Medications		
<b>RECURRENT HYPERSOMNOLENCE</b>		
Depression	Common	Antidepressants
Kleine-Levin syndrome	Rare	Lithium; carbamazepine; monitor serum levels for both drugs
Menstruation related	Rare	Oral contraceptives
<b>IDIOPATHIC HYPERSOMNOLENCE</b>		
		Stimulant medication

Reprinted from Givan DC. The sleepy child. *Pediatr Clin North Am*. 2004;51:15–31. Copyright 2004, with permission from Elsevier.

impulsivity, aggressiveness, or irritability. Sleepiness needs to be differentiated from weakness or fatigue. The major sleep disorders causing primary hypersomnia in children are narcolepsy and idiopathic hypersomnia.

### Narcolepsy

Narcolepsy is a potentially disabling syndrome of irresistible daytime sleep attacks, abnormally fast transitions to REM sleep from awake, and disrupted nighttime sleep. It occurs in 0.04% of whites and 0.07% of blacks. As many as one-third of adults with narcolepsy report onset of symptoms before 15 years of age, but diagnosis is frequently delayed at least a decade. Loss of muscle tone with emotions while awake (cataplexy), inability to move for a few seconds to minutes on awakening (sleep paralysis), and visual aura or dream states while falling asleep (hypnagogic hallucinations), along with EDS, make up the complete narcolepsy tetrad seen in 30% of affected persons. Approximately 90% of patients with narcolepsy with cataplexy are positive for HLA DQB1\*0602. Narcolepsy is seen in children, but peak age of onset of symptoms is 15 to 25 years. Cataplexy—brief episodes of bilateral muscle weakness, usually associated with laughter or strong emotion, that may result in falling, head bobbing, or jaw sagging—is highly specific to narcolepsy but may not be seen in more than 50% of cases. Diagnosis of narcolepsy without documented cataplexy can be made by overnight polysomnography showing absence of other sleep diagnoses and a multiple sleep latency test (5 nap opportunities, separated by 2 hours, immediately following the overnight sleep study) showing rapid sleep onset periods (mean, <8 minutes) with at least 2 naps containing REM sleep. Differential diagnosis includes hydrocephalus, postviral infection (mononucleosis), previous CNS trauma, or idiopathic hypersomnia. Absence of HLA DQB1\*0602 does not exclude the diagnosis of narcolepsy, especially without cataplexy. Given that 20% of the general population is positive for HLA DQB1\*0602, this test is not specific for possible narcolepsy patients with EDS. Recent research shows that narcolepsy with cataplexy results from the loss of approximately 70,000 hypothalamic neurons producing the neuropeptide hypocretin.

Narcolepsy treatment may include the use of stimulants such as modafinil or methylphenidate to address excessive daytime sleepiness, antidepressants such as venlafaxine to control cataplexy, regular adequate sleep, 2 to 3 planned 30-minute daytime naps, and timing of activities at optimal hours of alertness. Education of the patient, family members, and school personnel is important. Support for handling the difficulties of this lifelong chronic condition is such that referral to a pediatric sleep disorders center is indicated, but often primary care physicians may be required to monitor compliance with medications for participation in activities such as sports, school testing, and driving.

### Idiopathic Hypersomnia

Idiopathic hypersomnia is a disorder of constant and severe EDS, despite adequate nocturnal sleep.

Idiopathic hypersomnia is, by definition, a diagnosis of exclusion. A complete evaluation for other causes of hypersomnia must be undertaken, including neurologic disorders (hydrocephalus or CNS tumors), primary sleep disorders (OSA), mood disorders, chronic fatigue syndrome, and medical disorders (acute and chronic infections including mononucleosis, metabolic disorders, or muscle diseases). Although the mean sleep latency is short in idiopathic hypersomnia, similar to narcolepsy, affected patients do not have the 2 sleep-onset REM periods that characterize narcolepsy. Treatment of idiopathic hypersomnia includes attention to sleep hygiene issues, use of stimulant medications, and thorough review of safety issues such as driving or operating machinery.

## SLEEP DISORDERS ASSOCIATED WITH PSYCHIATRIC OR BEHAVIORAL DISORDERS

Although sleep problems may occur in association with almost any mental health disorder (Table 194-7), mood disorders are among the most common. Depression may cause sleep-onset insomnia, although this condition is less common in young children than in other age groups. The early-morning waking of depressed adults is not usually seen before puberty and only rarely among adolescents, for whom hypersomnia is a more common complaint than insomnia. The sleep problems that are intrinsic to depression are complicated by intrusive thoughts or worries that may interfere with sleep maintenance. Treatments of sleeping problems in depressed children may include cognitive behavioral therapy and antidepressants.

Children with bipolar disorder may have a dramatically reduced need for sleep (<4 hours a day) during the manic phase. Anxiety and panic disorders may result in difficulties falling asleep because of specific or nonspecific fears, as well as difficulties returning to sleep if aroused during the night. Children who have been abused have frequent sleep problems, including nightmares, increased activity during sleep, and sleep-onset and sleep-maintenance insomnia.

Personality disorders in adolescence have been associated with sleep-onset insomnia. Psychoses may include troubling intrusive thoughts, especially at night.

Insomnia or hypersomnia caused by substance abuse should be considered in sleep disorders in older children and adolescents. Alcohol can induce sleep, but it causes sleep fragmentation in the latter portion of the night. When alcohol is metabolized (1 beer, 5 oz of wine, or 1 oz of liquor per hour), sympathetic tone increases, leading to abrupt arousals and sleep maintenance insomnia. Withdrawal from chronic alcohol abuse may cause severe insomnia. Stimulants such as cocaine and amphetamines can cause severe insomnia. Some antidepressants such as fluoxetine may cause insomnia, whereas others such as tricyclics, trazodone, or mirtazapine may cause EDS. Antidepressants may eliminate REM atonia, thus precipitating RBD. Atypical antipsychotics such as aripiprazole may cause stimulation, whereas others such as olanzapine cause sedation.



**Table 194-7 Behavioral and Psychiatric Disorders Associated With Sleep Problems in Children**

DIAGNOSIS	SLEEP PROBLEMS
Depression	Sleep-onset or maintenance insomnia seen in 50% Early morning awakenings EDS seen in 25% Sleep complaints are the most prevalent symptoms of major depression in adolescents
Bipolar disorder	Decreased need for sleep without fatigue Insomnia
Seasonal affective disorder	Prevalence 3%–4% in children with EDS, fatigue in winter
Anxiety disorder	Increased night awakenings, nighttime fears Increased sleep-onset insomnia, bedtime problems Increased EDS
Obsessive compulsive disorder	Decreased total sleep time
Autism, pervasive developmental disorder	Sleep-onset insomnia, difficulty settling at night, prolonged and frequent nocturnal awakenings Shortened duration of sleep Irregular sleep–wake pattern Parasomnia (including rapid eye movement behavioral disorder)
Attention-deficit/hyperactivity disorder	Sleep-onset or maintenance insomnia Nocturnal waking, obstructive sleep apnea, excessive periodic limb movements

EDS, excessive daytime sleepiness.

Derived from Ivananko A, Crabtree VM, Gozal D. Sleep in children with psychiatric disorders. *Pediatr Clin North Am.* 2004;51:51–68.

## DEVELOPMENTAL DISORDERS

Learning disabilities are associated with increased rates of sleep disturbance, including night waking and trouble falling asleep. Half of these sleep difficulties persist for more than 3 years. Systematic review of the literature suggests that children with ADHD have higher daytime sleepiness, more movements during sleep, and higher apnea-hypopnea indexes compared with controls. Reported sleep problems also include trouble settling to sleep and multiple awakenings from sleep. Medications used to treat ADHD may prolong sleep-onset latency. Clonidine at bedtime has been found to be effective in improving the sleep of 85% of these children when behavioral measures failed.

Many children with autism have serious sleep problems, with difficulties falling asleep, waking in the night, and early-morning waking. Children with autism frequently have insomnia that may benefit from behavioral interventions, melatonin, or medications. Asperger syndrome has been associated with insomnia and RBD. Children who have Tourette syndrome have increased parasomnias.

## SLEEP DISORDERS ASSOCIATED WITH MEDICAL PROBLEMS

Sleep problems are seen in a variety of medical conditions (Table 194-8).

### Neurologic Disorders

Any CNS impairment can result in dysregulation of the sleep cycle. As many as 85% of children who have major developmental disabilities may experience chronic sleep problems. Behavioral sleep problems in these children can be improved by establishing a

bedtime routine and putting the child to bed when sleep onset is likely to occur quickly. If the child has persistent difficulty falling asleep, then establishing a new pattern may be helpful by delaying the usual bedtime for 30 minutes and then removing the child from bed if sleep does not occur in 15 to 20 minutes. After removing the child from bed, the parent should keep him or her awake for 30 minutes. This procedure is repeated until the child falls asleep within 15 minutes of being put in bed. Wake-up time is kept constant. Daytime naps are not allowed for children older than 4 years.

Other factors such as timing of medications, need for repositioning during the night, pain, nighttime feedings, and caregiver anxiety can contribute to sleep problems in the neurologically impaired child. Melatonin at bedtime has been shown to be helpful in some children who have CNS problems or blindness as the cause of their sleep disturbance. Melatonin should be used cautiously in children with seizure disorders.

Kleine-Levin syndrome, a rare disorder with episodes of severe daytime sleepiness, hyperphagia, and hypersexuality lasting hours to weeks, may be seen in adolescence. Tumors of the third ventricle or posterior hypothalamus may also cause daytime sleepiness. Brainstem lesions or Chiari malformation type II, which are common in children with myelomeningocele, can cause severe central apnea or vocal cord paralysis causing obstructive apnea.

### Sleep-Related Epilepsy

Approximately 20% of epileptic patients have seizures only during sleep, most often at the time of sleep–wake transitions. Seizures occurring during the night may disrupt sleep by causing multiple awakenings.



**Table 194-8** Medical Disorders Associated With Sleep Problems in Childhood

DIAGNOSIS	SLEEP PROBLEMS
Asthma	Circadian variation in <ul style="list-style-type: none"> <li>• Peak expiratory flow (nadir at 4:00 am)</li> <li>• Cutaneous immediate hypersensitivity to house dust allergen</li> <li>• Airway inflammation</li> </ul> Sleep-related changes <ul style="list-style-type: none"> <li>• Decrease in lung volumes and increase airway resistance</li> <li>• Increase airway resistance and decrease intrapulmonary blood volume</li> <li>• Decrease mucociliary clearance</li> <li>• Nocturnal gastroesophageal reflux</li> </ul> Frequent nocturnal awakenings and decrease stage 4 sleep
Cystic fibrosis	OSA can be common in children <7 years. Nocturnal oxygen desaturation in children >7 years <ul style="list-style-type: none"> <li>• Hypoventilation, especially in REM sleep caused by de-recruitment of ventilatory muscles</li> <li>• Ventilation-perfusion mismatch caused by decreased functional residual capacity</li> <li>• Occurs more frequently with forced expiratory volume &lt;65% or resting oxygen saturation while sitting &lt;94%</li> </ul>
Craniofacial abnormalities (Pierre Robin sequence, Goldenhar syndrome, Down syndrome, Treacher Collins syndrome, velocardiofacial syndrome, cleft lip and palate)	Upper airway obstruction Nocturnal hypoventilation
Gastroesophageal reflux	Increased night awakening and pain Delayed sleep onset May result in nocturnal stridor, cough, and wheezing
Down syndrome	Upper airway obstruction with OSA in 30%–60% Decreased REM sleep associated with low IQ
Sickle cell disease	Episodic and continuous nocturnal hypoxemia in 40% of children caused by either OSA or primary lung disease
Obesity	OSA <ul style="list-style-type: none"> <li>• Obesity hypoventilation syndrome: Hypercapnia, hypoxemia, and daytime somnolence.</li> <li>• 95% of children with Prader-Willi syndrome have excessive daytime sleepiness.</li> </ul>
Scoliosis or congenital neuromuscular disorder (Duchenne muscular dystrophy, spinal muscular atrophy)	Nocturnal hypoventilation Nocturnal hypoxemia—excessive daytime sleepiness, morning headaches OSA Restless sleep Frequent awakenings
Traumatic brain injuries	Sleep-onset and maintenance insomnia Excessive daytime sleepiness Dreaming disturbances Nocturnal hypoventilation
Spina bifida	Obstructive, central, or mixed apnea Nocturnal hypoventilation may cause severe excessive daytime sleepiness

OSA, obstructive sleep apnea; REM, rapid eye movement.

Derived from Bandla H, Splaingard M. Sleep problems in children with common medical disorders. *Pediatr Clin North Am.* 2004;51:203–227.

The possibility of a seizure disorder should be considered in adolescents with new-onset parasomnias. Atypical seizures may produce EDS.

### Sleep-Related Headaches

Most headaches occurring during sleep occur during REM sleep. Cluster headaches are more frequent at night than in the daytime and often disrupt sleep. Headaches on awakening are unusual; the child should be evaluated carefully for the presence of increased intracranial pressure or hypercapnia caused by hypoventilation (eg, Duchenne muscular dystrophy).

### Degenerative Disorders

Degenerative brain disorders result in frequent awakenings, difficulty falling asleep, early-morning waking, sleep deprivation, and daytime sleepiness.

### Other Medical Disorders

Any condition causing pain at night, such as juvenile idiopathic arthritis, can result in disrupted sleep. Eczema that causes associated scratching results in frequent awakenings. Painful menstrual cramps may also disrupt sleep.

### Sleep-Related Asthma

Asthma episodes are increased during sleep, presumably because the neuroendocrine regulators of respiration are sensitive to diurnal regulation. Children who have sleep-related asthma have fragmented sleep and may develop anxiety associated with breathing discomfort. This disruption may lead to bedtime resistance and insufficient nocturnal sleep, leading to problems outlined in Box 194-2. In one study of children with asthma, 34% awakened at least once a week, and 5% awakened every night from asthma symptoms. Daytime sequelae were common, with 59% reporting daytime sleepiness and 51% reporting difficulty with concentration. These complaints all improved with successful asthma management.

### Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) may produce sleep problems in a variety of ways. The reflux can be painful, resulting in night waking and crying. Reflux has also been associated with both central and obstructive apnea and with apparent life-threatening events in infants and young children. The diagnosis of GERD may not always be obvious, owing to lack of usual signs, including excessive spitting up, reswallowing motions, increased fussiness, refusal of feedings, and failure to thrive. Esophagoscopy, assessing for esophageal erosions, may be needed to determine the cause of nighttime pain. Failure to be consoled while being held can be a clue that the child is suffering pain. Holding the child upright reduces the amount of acid in the esophagus and may comfort a child with reflux. See Chapter 206, Vomiting, for further discussion of gastroesophageal reflux.

#### WHEN TO REFER

- If the physician is unable to relieve a sleep disturbance after working with the family over the course of 6 weeks, then assistance may be needed either from a sleep specialist or from a family therapist or psychologist. The physician should always consider, and generally respect, a family that really does not care to change a sleeping situation that would seem to be a sleep disturbance to others. Children with chronic, physically based sleep disorders, such as narcolepsy and SDB requiring CPAP, benefit from referral to a sleep disorders center for treatment and group support.
- Alternative therapies have been devised by many cultures to restore the essential health-giving function of sleep. Herbal remedies such as chamomile and other soothing teas are common. Any treatment that involves scheduled rest and mental preparation for sleep would be expected to result in improvement.

#### WHEN TO ADMIT

- Primary sleep disturbances rarely require hospitalization, other than the overnight stay needed for a sleep study. Exceptions may include severe SDB with life-threatening oxygen desaturations,

arrhythmias, or cor pulmonale. Hospitalization may be needed for some of the underlying disorders, such as CNS tumors or serious depression that may initially present symptoms of a sleep disorder. Admission for video EEG monitoring of movements during sleep that suggest seizures may be required.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Fostering Comfortable Sleep Patterns in Infancy* (fact sheet), Bright Futures ([www.brightfutures.org/mentalhealth/pdf/families/in/sleep\\_patterns.pdf](http://www.brightfutures.org/mentalhealth/pdf/families/in/sleep_patterns.pdf))
- *Sleep: What Every Parent Needs to Know*, 2nd ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Sleep (Baby 0–12 mos.)* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/baby/sleep/Pages/default.aspx](http://www.healthychildren.org/English/ages-stages/baby/sleep/Pages/default.aspx))
- *Sleep Apnea and Your Child* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Sleep Problems in Children* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Parenting Tips for Better Sleep* (fact sheet), American Academy of Pediatrics ([www2.aap.org/sections/dbpeds/pdf/sleeptips.pdf](http://www2.aap.org/sections/dbpeds/pdf/sleeptips.pdf))

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**Chapter 195****SPEECH AND LANGUAGE CONCERNS***Maris Rosenberg, MD; Nancy Tarshis, MA, MS***INTRODUCTION**

Speech and language delay, arguably the most common developmental concern parents have about their young children, occurs with an estimated prevalence of 2% to 19%. The delay can occur alone, or signal the presence of other developmental disorders such as intellectual disability, autistic spectrum disorders, or hearing impairment. In keeping with the recommendations of the American Academy of Pediatrics (AAP), the pediatrician should perform developmental surveillance and screening to identify children at risk, refer for appropriate evaluation, and implement intervention as early as possible. Speech and language impairments have academic, social, and behavioral implications, and appropriate intervention can maximize a child's outcome.

Parents commonly focus on their child's verbal communication and consult the pediatrician when there are concerns. A working knowledge of risk factors for communication delays, normal speech and language milestones, and red flags for language delays and associated developmental problems is essential in providing appropriate pediatric primary care.

**LANGUAGE DEVELOPMENT**

Language, as the primary vehicle for communication, is a socially shared code or conventional system for representing concepts through an arbitrary set of rule-governed symbols (speech sounds/phonemes) and symbol combinations. A social tool through which we share ideas and rules of behavior and develop our attachments to people and places, language is a rule-governed yet generative system that permits speakers to create an endless number of meaningful utterances to communicate thoughts, feelings, information, and ideas.

A summary of typically acquired speech and language milestones is presented in Table 195-1.

**RISK FACTORS FOR LANGUAGE DELAYS**

Risk factors for language delays are similar to those for developmental disorders in general. In a review for the US Preventive Services Task Force, the most common risk factors reported were a family history of speech and language delay, male gender, and perinatal factors. Other, less commonly reported risk factors included educational level of the parents, childhood illness, and family size. A careful history eliciting any prenatal, perinatal, or postnatal adverse events and a detailed family history focusing on developmental disorders, academic achievement, and social functioning are essential in determining which children are at greater risk. Environmental factors clearly play a role in determining language development. Children who live in disadvantaged environments with less language

**Table 195-1      Developmental Milestones**

AGE	DEVELOPMENTAL MILESTONES
0–6 mo	Cooing Babbling Differentiated cries
6–9 mo	Canonical babbling (reduplicated babbling, eg, “bababa”) Response to name Comprehension of familiar words in context
9–15 mo	First words Directed point (initially with hand, then with 1 finger)
18–24 mo	Uses own name 2-word sentences (by 24 mo) Knows 5 body parts
24–30 mo	Pretend play with familiar objects 3-word sentences Points to action words in pictures Answers simple, concrete “wh-” questions (eg, who, what)
30–36 mo	Uses 50+ words Names most familiar things and pictures Begins to recognize same and different Helps tell a familiar story Uses descriptive words (adjectives) Uses 200–1,000 words
3–4 yr	Speech is nearly all intelligible to any listener. Comprehends 1,000 words Points to common objects by function Responds to commands involving 2 actions Uses at least 800 words Responds to simple “how” questions Asks “what” and “who” questions Uses plurals and verb tense markers Talks about events out of the here and now
4–5 yr	Understands most of what is said to him or her Tells a personal story with a beginning, middle, and end Can listen and answer questions about a story Speech is fully intelligible. Can recognize and produce rhymes

stimulation and greater psychosocial stress are at greater risk for language delay than children from more advantaged backgrounds.

Table 195-2 states the red flags in language and play that may signal the existence of a language or other developmental disorder.

**ROLE OF THE PRIMARY CARE PHYSICIAN: SURVEILLANCE AND SCREENING**

Performing developmental surveillance at all health maintenance visits implies eliciting parental concerns, acknowledging risk and protective factors, performing longitudinal observations, and keeping an accurate, ongoing record.

The use of standardized general developmental screening instruments is recommended at ages 9, 18,

**Table 195-2** Red Flags in Language and Play

AGE	WARNING SIGNS AND RED FLAGS
0–12 mo: play	<ul style="list-style-type: none"> <li>Restricted repertoire of skills</li> <li>Does not follow objects that fall</li> <li>Little purposeful play</li> <li>Reduced or absent imitation</li> <li>Reduced object permanence</li> <li>No interactive games</li> </ul>
0–12 mo: sensory motor	<ul style="list-style-type: none"> <li>Does not reach or swat at objects</li> <li>Overly reactive to stimuli</li> <li>Extreme irritability</li> </ul>
0–12 mo: socioemotional	<ul style="list-style-type: none"> <li>Overly clingy</li> <li>No apparent attachments</li> <li>No awareness of danger</li> <li>Difficulty modulating emotions</li> <li>Reduced range of affect</li> </ul>
0–12 mo: speech and language	<ul style="list-style-type: none"> <li>Difficulty sucking and feeding</li> <li>Averts gaze</li> <li>Fails to make a variety of sounds</li> <li>Fails to respond to name</li> <li>Undifferentiated crying</li> </ul>
12–24 mo: play	<ul style="list-style-type: none"> <li>No container play</li> <li>No early problem solving</li> <li>Does not go to adults for help</li> <li>Very rigid play</li> <li>Focuses on irrelevant parts of toys such as wheels of car</li> <li>Does not include adults in play; prefers to play alone</li> <li>No interest in playing symbolically</li> <li>No spontaneous pretend play</li> <li>Restricted range of interests</li> <li>No early problem solving</li> </ul>
12–24 mo: socioemotional	<ul style="list-style-type: none"> <li>Short attention span</li> <li>Does not seek to engage with others</li> <li>Tunes out</li> <li>Avoids eye contact</li> </ul>
12–24 mo: speech and language	<ul style="list-style-type: none"> <li>No specific <i>mama</i> or <i>dada</i></li> <li>Does not point</li> <li>Cannot follow simple directives without gesture</li> <li>Reduced vocabulary</li> <li>No word combinations</li> </ul>
24–36 mo: play	<ul style="list-style-type: none"> <li>Little or no symbolic play</li> <li>Not able to sequence events in play</li> <li>Not interested in playing with peers</li> <li>Restricted range of skills and interests</li> <li>Lines up toys rather than playing with them</li> </ul>
24–36 mo: speech and language	<ul style="list-style-type: none"> <li>Avoids eye contact</li> <li>Reduced communicative intent</li> <li>Difficulty following directions</li> <li>Lack of verbal expression</li> <li>Reduced reciprocity and turn taking</li> <li>Talking better than listening</li> <li>Poor conversation skills</li> </ul>
3–4 yr: play	<ul style="list-style-type: none"> <li>Cannot take turns or play cooperatively with peers (prefers solitary play)</li> <li>Little interest in toys</li> <li>Insists on sameness in routine</li> <li>No idea how to approach new skills or toys</li> <li>Cannot use blocks to build simple structures</li> </ul>
3–4 yr: language	<ul style="list-style-type: none"> <li>Does not engage in back-and-forth communication for purely social reasons</li> <li>Does not talk about what communicative partners are talking about</li> <li>Uses language that is repetitive or recycled from other contexts</li> </ul>



**Table 195-2** Red Flags in Language and Play—cont'd

AGE	WARNING SIGNS AND RED FLAGS
4–5 yr: play	Cannot follow simple rules in play Prefers solitary play Insists on sameness in play Reacts strongly to change Does not engage in symbolic or imaginative play Does not integrate other children in play
4–5 yr: language	Weak ability to hold a conversation Cannot tell a personal narrative Difficulty with sequencing information Uses language that is repetitive or recycled from other contexts

and 30 months or whenever concerns arise in the course of surveillance. In addition, the recommendation for screening for autistic spectrum disorders at 18 and 24 months allows additional insight into the development of communication and social skills. After a systematic review in 2006, the US Preventive Services Task Force concluded that there is no single screening instrument that serves as a gold standard for screening specifically for language disorders, and there were no universally agreed-on recommendations for age or interval for speech and language screening. However, it is generally agreed that use of standardized screening instruments can assist the pediatrician in assessing a young child's general development and making decisions as to whether referral for further evaluation by developmental specialists would be appropriate. Screening instruments vary in format and applicability to particular populations. Table 195-3 provides a partial list of both general and language-specific screening instruments that can be used in the primary care setting. The resource provided by the AAP Developmental Screening task force lists additional tools.

## LANGUAGE DISORDERS

A language disorder as defined by the American Speech and Hearing Association can be classified as any disturbance to an individual's ability to develop and produce spoken or written language. This encompasses both the ability to comprehend and the ability to express language at an age-appropriate level. Language disorders, both developmental and acquired, represent a heterogeneous set of difficulties that range from mild to severe. Children with receptive language deficits have difficulty comprehending language. Of note, a receptive deficit is rarely seen in isolation, and in typical development, comprehension precedes expression of new and more mature language forms. Difficulty with comprehension manifests as reduced understanding of conversation and problems both with following directions and interpreting the intentions of others. Receptive language generally develops in advance of expressive language, except in very rare circumstances (eg, hydrocephalus, severe language processing disorder, and in autism spectrum disorders). Children with expressive language deficits have problems using language to express their most basic wants and needs as well as more sophisticated

thoughts, feelings, and intentions. They may have a hard time putting words into sentences; sentences may be simple and short with confused syntax or verb tense errors, or there may be difficulty finding the right words. A child's vocabulary might be below the level of other children the same age; or the child might use words and phrases repetitively or pick up scripts from videos, commercials, and television. Language impairment might also become apparent as a deficit in stringing sentences together to tell a cohesive story or personal narrative.

A language disorder can be characterized by deficits in the form (comprehension and expression of linguistic rules and syntax), the content (vocabulary and semantics), or the use (discourse pragmatics) of language. Difficulty acquiring and using the rules applicable to the sounds, words, phrases, and sentences or the surface features of what is being said constitutes a deficit in the *form* of language. For children with disorders of *content*, speaking may come easily, but often what they have to say lacks substance. Their discourse is missing the essential ingredients such as objects, events, relations between people, and cultural references that give meaning to the utterance. Pragmatic deficits result in weakness in language *use*, in managing and understanding the why, when, and where aspects of discourse. Children with this difficulty have a hard time selecting and maintaining topics, taking turns in conversation, choosing their style of speech to match the listener or context, using intonation to signal intention, and understanding the non-verbal aspects of language such as proximity, body posture, facial expression, and flexible gaze shifting.

Language-based learning disabilities present as problems with reading, spelling, or writing in addition to the aforementioned oral language deficits. Typically, children with such disabilities have trouble expressing ideas, finding words, learning new vocabulary, comprehending questions, following directions, and retaining written material. They struggle learning the alphabet, spelling rules, multiplication tables, and other rote-memorized information, all of which make it difficult to achieve academically.

## SPEECH DISORDERS

Speech disorders manifest as articulation errors past the age of expectation. *Articulation* is the movement of

**Table 195-3** General and Language-Specific Screening Instruments

TOOL	TIME FOR ADMINISTRATION	AGE RANGE	TYPE OF TOOL	LANGUAGES AVAILABLE	FOR FURTHER INFORMATION
Ages & Stages Questionnaires	10–15 min	4–60 mo	Parent-completed General developmental screen	English, Spanish, French, Korean	Paul H. Brookes Publishing: <a href="http://www.brookespublishing.com">www.brookespublishing.com</a>
Batelle Development Inventory Screen	10–30 min	0–95 mo	Direct-administration General developmental screen	English, Spanish	Riverside Publishing Co. <a href="http://www.riverpub.com">www.riverpub.com</a>
Brigance Screens II	10–15 min	0–90 mo	Direct-administration General developmental screen	English, Spanish	Curriculum Associates, Inc. <a href="http://www.curriculumassociates.com">www.curriculumassociates.com</a>
Denver Developmental II	10–20 min	0–72 mo	Direct-administration General developmental screen	English, Spanish	Denver Developmental Materials <a href="http://www.denverii.com">www.denverii.com</a>
Parents' Evaluation of Developmental Status (PEDS, PEDS-DM)	2–10 min	0–96 mo	Parent-completed General developmental screen	English, Spanish, and multiple other languages	Ellsworth & Vandermeer Press, LLC <a href="http://www.pedstest.com">www.pedstest.com</a>
Capute Scales (CAT/Clams)	15–20 min	3–36 mo	Direct-administration CLAMS specific for language	English, Spanish, Russian	Paul H. Brookes Publishing: <a href="http://www.brookespublishing.com">www.brookespublishing.com</a>
Early Language Milestone Scales	1–10 min	0–36 mo	Direct-administration Language screen	English	Pro-ed Inc: <a href="http://www.proedinc.com">www.proedinc.com</a>
Language Development Survey	10 min	18–35 mo	Parent-completed Language screen	English, Spanish	ASEBA <a href="http://www.aseba.org">www.aseba.org</a>
Communication and Symbolic Behavior Scales Developmental Profile (CSBS-DP) Infant-Toddler Checklist	5–10 min	6–24 mo	Parent-completed Language screen	English	Paul H. Brookes Publishing: <a href="http://www.brookespublishing.com">www.brookespublishing.com</a>
Modified Checklist for Autism in Toddlers (M-CHAT)	2–3 min	16–30 mo	Parent-completed Autism screen followed by questionnaire for positive items	Multiple languages	Available free from First Signs: <a href="https://www.firstsigns.org/downloads/m-chat.PDF">https://www.firstsigns.org/downloads/m-chat.PDF</a>

the speech mechanism (palate, lips, tongue, jaw, larynx) to create sound. *Phonology* is the rule system that governs how speech sounds interact with one another. A child with a lisp has a problem with articulation; a child who substitutes all K sounds with T (“otay” for okay) has a phonological problem. For pediatricians, knowing when to refer for evaluation is key. As a guideline, a 2-year-old should be 50% intelligible, a 3-year-old 75%, and a 4-year-old fully intelligible to a stranger, not just family and familiar adults.

A child might present with speech problems for several reasons. Some errors are developmental and will resolve in time, and others will need intervention. Some errors are related to the architecture of the mouth, and others are rule-based errors (phonologic). If the errors persist, or the child expresses frustration, an evaluation is in order. When a child makes errors

that are inconsistent, a motor speech disorder should be suspected. Apraxia is a motor speech disorder caused by a difficulty planning and executing speech sounds that cannot be attributed to muscle weakness or paralysis. Key characteristics include limited repertoire of vowels and vowel errors. The error patterns are typically highly variable, with unusual and idiosyncratic error patterns. Errors increase with the length and complexity of utterances, such as in multisyllabic or phonetically challenging words. If apraxia is suspected, a child should be evaluated as soon as possible because the earlier intervention begins, the better the outcome. *Stuttering* or *dysfluency* is a speech disorder characterized by breaks in fluency that can affect sounds, syllables, or words. In young children there can be a period of normal dysfluency between 2 and 4 years of age. The decision to refer for

evaluation should be based on how long dysfluency has persisted, whether there is a family history, the type of repetitions, and secondary behaviors. Indications for evaluation include dysfluency that persists for more than 6 months, family history of stuttering, awareness of difficulty, or anxiety or frustration related to speaking. In addition, if breaks in fluency are partial words, single sounds, silent or accompanied by any secondary or atypical behaviors, or if the balance of dysfluent speech to fluent speech is more than 10% of the overall communication, evaluation should be initiated.

## DIFFERENTIAL DIAGNOSIS

Delays in speech and language milestones are often the first indication of the presence of a developmental disorder. Hearing loss is an important consideration in any child who exhibits delayed acquisition of language milestones or unclear or atypical patterns of speech. Careful history and observation may suggest accompanying delays in other domains indicating more global involvement, as in intellectual disability. Subtle delays in communication can be apparent even before verbal communication is questioned. The phenomenon of joint attention, as evidenced by gaze sharing or pointing, can be documented as early as 8 to 10 months of age. The absence of joint attention should alert the physician to the possibility of an autism spectrum disorder. In the absence of the above conditions, *specific language impairment* (SLI), refers to the developmental disorders affecting primarily receptive, expressive, or mixed receptive-expressive language impairments, whereas *phonologic disorders* refer to conditions affecting the clarity of speech.

## THERAPEUTIC CONSIDERATIONS: WHAT THE PEDIATRICIAN NEEDS TO KNOW

Once a speech and language delay is suspected, referral for diagnostic evaluation is critical to determine the extent of impairment, characterize the nature of the disability, and suggest strategies for intervention. Referral for early intervention evaluation for children from birth to age 3 years, or to the Department of Education for children 3 years and older, offers a means of evaluation within a mandated time frame and services based on the evaluation results. Ideally, this evaluation is conducted by a multidisciplinary team, on which the speech and language pathologist (SLP) plays a key role. The SLP will gather information regarding communication across a variety of contexts. He or she will evaluate the child's ability to comprehend directions, stories, and other communication as well as vocabulary, grammar, and syntax and use of language for a variety of purposes. In certain circumstances, based on the presenting problems, speech sound development, literacy skills, writing, reading comprehension, and fluency will also be evaluated. This assessment should contain informal components such as pretend play in young children and conversation and storytelling in older children. Formal testing with standardized instruments can corroborate and

elucidate informal findings and should always be considered.

The pediatrician should order a formal hearing test to be done by an audiologist. Speech and language therapy should not be delayed pending definitive audiologic evaluation, however, because it may take months for an uncooperative child to have a hearing test completed. A formal hearing test should be ordered as part of the multidisciplinary evaluation, and hearing status should be followed according to recommendations of the audiologist as therapy progresses.

Any child with significant exposure to a second language or dialect is considered bilingually-exposed. Regardless of the type of exposure, simultaneous or sequential, such a child must be evaluated in both languages to determine the presence or absence of language impairment. Many children who are bilingually exposed may go through a short period of language loss, especially if recently exposed to a new language. There may be a delay in mastering some grammatical aspects of both languages, and vocabulary may be judged to be insufficient if words in both languages are not considered. Such children should be assessed by a qualified *bilingual* SLP. If a language impairment is documented in a bilingually exposed child, it is important to determine the dominant language when initiating therapy.

## PROGNOSIS

Based on their presentation and degree of severity, language disorders may resolve with intervention by the time a child enters the early school years. More often, they persist to some degree for the lifetime of the individual. Children identified with speech and language delays in toddler and preschool years are known to be at special risk for behavioral difficulties and for problems with socializing. The association between communication difficulties and externalizing disorders (attention deficit/hyperactivity disorder, oppositional defiant disorder) and internalizing disorders (anxiety disorders, depression) has also been described. The link between early language and later learning problems is also well documented. Children identified with communication impairments at age 4 to 5 years are likely to have significantly more difficulty in reading, writing, and overall academic achievement at ages 7 to 9 years. In addition, these children have more difficulty with peer relationships and less satisfaction with school than their peers.

A multitude of factors determine the outcome of children with speech and language impairments. Important considerations include nonverbal intelligence, type and degree of language disability, and response to intervention. Preschool-aged children with primarily expressive phonologic impairments tend to have a lower risk for later reading problems than those who demonstrate difficulty with phonologic awareness (eg, rhyming, letter-sound association). It is generally agreed that children with language problems that persist until kindergarten entry have a high risk for continuing problems throughout the school years. Parents should be counseled that providing a language-rich environment, stressing verbal interaction and literacy,

is recommended, in addition to specific therapy, to mediate the effects of a language delay (eg, the Reach Out and Read program, [www.reachoutandread.org](http://www.reachoutandread.org)).

## CONCLUSION

Speech and language delays are common and are readily detected in the context of the developmental surveillance and screening that are part of primary pediatric care. These delays may be associated with impairments limited to the domains of speech and language or may signal the presence of conditions such as hearing impairment, intellectual disability, or autistic spectrum disorders. Using the knowledge of risk factors and attention to “red flags” suggesting these disorders is the first step to referral for appropriate evaluation and interventions to minimize associated difficulties with learning, behavior, and socialization.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *American Speech-Language Hearing Association* (Web site), American Speech-Language Association ([www.asha.org](http://www.asha.org))
- *Is Your Toddler Communicating With You?* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Language Delay* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/toddler/Pages/Language-Delay.aspx](http://www.healthychildren.org/English/ages-stages/toddler/Pages/Language-Delay.aspx))
- *Language Development: 1 Year Olds* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/toddler/Pages/Language-Development-1-Year-Olds.aspx](http://www.healthychildren.org/English/ages-stages/toddler/Pages/Language-Development-1-Year-Olds.aspx))
- *Language Development: 2 Year Olds* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/toddler/Pages/Language-Development-2-Year-Olds.aspx](http://www.healthychildren.org/English/ages-stages/toddler/Pages/Language-Development-2-Year-Olds.aspx))
- *Learn the Signs. Act Early.* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/ncbddd/actearly/index.html](http://www.cdc.gov/ncbddd/actearly/index.html))

## AAP POLICY

American Academy of Pediatrics Council on Children with Disabilities, Section on Developmental and Behavioral Pediatrics, Bright Futures Steering Committee, Medical Home Initiatives for Children With Special Needs Project Advisory Committee. Identifying infants and young children with developmental disorders in the medical home: an algorithm for developmental surveillance and screening. *Pediatrics*. 2006;118(1):405–420. Reaffirmed December 2009 ([pediatrics.aappublications.org/content/118/1/405](http://pediatrics.aappublications.org/content/118/1/405))

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## Chapter 196 SPLENOmegaly

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*Splenomegaly* is an enlargement of the spleen resulting from abnormalities of its lymphoid, reticuloendothelial, or vascular components. Although splenomegaly is often considered to be an ominous clinical finding, certain normal variants have been found. In children, as a result of the thinness of the abdominal musculature, a palpable spleen is commonly encountered. Thus a soft spleen is normally palpable in 15% to 30% of neonates. By 1 year of age, 10% of healthy children have a palpable spleen. Even after 10 years of age, 1% of children have a palpable spleen.

Wide interobserver variability exists in the ability to appreciate an enlarged spleen on examination; this variability is not generally associated with clinical experience. The spleen moves downward with inspiration and enlarges diagonally across the midline toward the right iliac fossa.

An enlarged spleen may extend into the pelvis; thus, when examining a child with suspected splenomegaly, the physician should start palpating in the right lower quadrant and move across the abdomen toward the left upper quadrant. As the spleen enlarges, it replaces the tympany of the stomach and colon with the dullness of a solid organ. Percussion cannot confirm splenic enlargement, but it can raise suspicion of it. If tympany is prominent, especially laterally, then splenomegaly is not likely. In addition, a change from tympany to dullness on inspiration when percussing at the lower interspace in the left anterior axillary line suggests splenic enlargement.

Spleen size is conventionally recorded as “centimeters below the costal margin” in the midclavicular and anterior axillary lines. Measuring this span with a rigid ruler gives the most reproducible measurement.

Spleen length is correlated with age, height, weight, and body surface area in a nonlinear fashion, similar to the liver. No sex-based differences in spleen size have been found. Imaging of the spleen with ultrasonography, high-frequency ultrasonography, radioactive (technetium-99m) sulfur colloid scintigraphy, computed tomography (CT), or magnetic resonance imaging (MRI) can be an important adjunct to the physical examination in defining pathologic changes



in this organ. Contrast-enhanced sonography is a novel technique that allows real-time assessment of the spleen.

## DIFFERENTIAL DIAGNOSIS

When assessing a child with splenomegaly, the major splenic functions should be kept in mind: its hematopoietic, phagocytic, and immunologic roles and its role as a reservoir for blood-borne elements. The spleen is a major hematopoietic organ during fetal life. However, it is capable of resuming extramedullary hematopoiesis in children and adults with bone marrow failure. The spleen removes the senescent and abnormal red blood cells, as well as particulate material, from the blood. A major lymphoreticular organ that acts as a filter for infectious organisms in the blood, the spleen also acts as a site of immunoglobulin M and properdin production. Finally, the spleen acts as a reservoir for platelets, reticulocytes, and plasma proteins, especially factor VIII. Because the spleen has so many functions, splenomegaly may be caused by systemic infections, by an increase in normal splenic process (as seen in hemolytic anemia), by infiltration of storage diseases or malignancies, by congestion from splenic or portal vein obstruction, or by inflammatory diseases. The spleen is the organ most commonly injured following blunt abdominal trauma. Engorgement caused by splenic trauma with subcapsular hemorrhage may manifest as an enlarged, tender spleen. The differential diagnosis of splenomegaly is provided in Box 196-1.

## Infections

In infectious processes, splenomegaly results from hypertrophy of lymphatic and reticuloendothelial elements. Viral infections are the most common causes of splenomegaly in children. The splenic enlargement is usually transient and mild to moderate in severity. Infectious mononucleosis from Epstein-Barr virus, cytomegalovirus, and HIV infections leads to a greater degree of splenic enlargement. Specifically, splenomegaly occurs in 50% to 75% of cases of infectious mononucleosis. Subacute bacterial endocarditis, tuberculosis, and other chronic bacterial infections may cause splenic enlargement. Septicemia from meningococcus or pneumococcus may also be associated with splenomegaly. Malaria and visceral leishmaniasis are common causes of splenomegaly in areas endemic for these diseases. Progressive disseminated histoplasmosis can occur in healthy children younger than 2 years who have been exposed to fungus in endemic areas of the eastern and central United States (Mississippi, Ohio, and Missouri River valleys). Early manifestations of this disease include fever, failure to thrive, and hepatosplenomegaly.

## Hematologic Disorders

Splenomegaly associated with hemolytic states, such as membranopathies, hemoglobinopathies, and autoimmune hemolytic anemia, results from engorgement of the splenic sinusoids by abnormal red blood cells, as well as by increased phagocytic activity (work hypertrophy) of the reticuloendothelial elements. Splenic

### BOX 196-1 Differential Diagnosis of Splenomegaly

#### INFECTIONS

- Viral: Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus (HIV)
- Bacterial: acute bacterial infections, subacute bacterial endocarditis, congenital syphilis, tuberculosis
- Parasitic: malaria, toxoplasmosis, leishmaniasis
- Fungal: candidiasis, histoplasmosis, coccidioidomycosis

#### HEMATOLOGIC DISORDERS

##### *Hemolytic Anemias—Congenital and Acquired*

- Red cell membrane defects: hereditary spherocytosis, hereditary elliptocytosis
- Red cell hemoglobin defects: sickle cell disease and related syndromes, thalassemia
- Red cell enzyme defects: glucose-6-phosphate dehydrogenase deficiency, pyruvate kinase deficiency, etc
- Autoimmune hemolytic anemia

##### *Extramedullary Hematopoiesis*

- Thalassemia major, osteopetrosis, myelofibrosis

#### INFILTRATIVE DISORDERS

- Leukemias
- Lymphomas

- Lipidoses
- Mucopolysaccharidosis
- Langerhans cell histiocytosis

#### CONGESTIVE SPLENOMEGALY

- Portal vein thrombosis
- Hepatic cirrhosis
- Congestive heart failure
- Hepatic portal or splenic vein obstruction

#### INFLAMMATORY DISEASES

- Systemic lupus erythematosus (SLE)
- Juvenile idiopathic arthritis (JIA)
- Serum sickness
- Sarcoidosis
- Immune thrombocytopenias and neutropenias

#### PRIMARY SPLENIC DISORDERS

- Splenoptosis (wandering spleen)
- Cysts
- Hemangiomas and lymphangiomas
- Subcapsular hemorrhage
- Accessory spleen

enlargement as a result of extramedullary hematopoiesis occurs in diseases associated with increased demand on the bone marrow for cell production (thalassemia major). Measurement of the spleen's size and recording the result are an essential part of every physical examination in children with sickle cell disease. It is important to have this baseline information because a rapidly enlarging spleen with a falling hematocrit, pallor, dyspnea, weakness, and left-sided abdominal pain suggests the diagnosis of acute splenic sequestration crisis—a leading cause of death in children with sickle cell anemia and a medical emergency that requires prompt recognition and treatment.

### **Infiltrative Disorders**

The spleen is commonly enlarged in untreated leukemias and lymphomas, including Hodgkin disease. Malignant infiltration of the spleen often produces a massively enlarged, firm spleen that crosses the midline of the body. In the lipidoses and mucopolysaccharidoses, the phagocytic reticuloendothelial elements of the spleen accumulate large amounts of lipid and mucopolysaccharide, respectively. In Langerhans cell histiocytosis, the spleen is infiltrated by histiocytes.

### **Congestive Splenomegaly (Banti Syndrome)**

Splenomegaly may occur from obstruction of the hepatic, portal, or splenic veins. The most common causes include portal vein thrombosis, hepatic cirrhosis, and congestive heart failure. Umbilical vein catheterization or septic omphalitis in neonates may also result in obliteration of these vessels. Congestive splenomegaly is the most common cause of hypersplenism (the term used to describe patients with splenomegaly, peripheral blood cytopenias from excessive splenic function, and increased bone marrow production of the affected blood cells).

### **Inflammatory Diseases**

Splenomegaly seen in inflammatory diseases such as systemic lupus erythematosus (SLE), juvenile idiopathic arthritis (JIA), sarcoidosis, and serum sickness is the result of increased numbers of reticuloendothelial cells that remove antibody-coated cells and proteins. Lymphoid hyperplasia may occur as a result of accelerated antibody production in the spleen.

### **Primary Splenic Disorders**

Splenoptosis, or wandering spleen, is a congenital fusion anomaly of dorsal mesogastrium that results in a spleen of normal size that moves freely within the peritoneal cavity. A patient with splenoptosis usually has an asymptomatic abdominal mass. Splenic cysts may mimic splenomegaly. Two types of splenic cysts have been identified: those that are congenital (epidermoid) and those that are acquired (pseudocyst) from trauma or infarction. Cysts are generally asymptomatic and are confirmed by radiologic studies. Abdominal trauma may cause subcapsular hemorrhage of the spleen that results in abdominal pain and splenomegaly. Accessory spleens, which are found in 15% of individuals, may also mimic splenomegaly.

## **EVALUATION**

### **History**

The cause of splenomegaly can be determined by history and physical examination in addition to laboratory tests and, if necessary, radiographic studies. A thorough history, including travel and family history, may provide valuable clues to the possible cause of splenomegaly. In a child with a history of a fever, pharyngitis, malaise, and splenomegaly, a viral cause (Epstein-Barr virus, cytomegalovirus) should be considered. Malaria or histoplasmosis may be the cause if the patient has recently traveled to areas endemic for these diseases. In the patient with fever, night sweats, malaise, weight loss, rash, arthralgia, and bone pain, an underlying inflammatory, infectious, or malignant process should be suspected. A newborn with unexplained jaundice and a family history of anemia, jaundice, splenomegaly, or splenectomy most likely has a congenital hemolytic anemia. A history of umbilical vein catheterization or omphalitis in the neonatal period may suggest a diagnosis of portal vein thrombosis.

### **Physical Examination**

The normal palpable spleen is soft, smooth, and nontender and is less than 1 to 2 cm below the left costal margin. A pathologically enlarged spleen is usually firm, has an abnormal surface, and is often associated with signs and symptoms of an underlying disease. An enlarged spleen may be tender if it has enlarged quickly (splenic sequestration, splenic trauma with subcapsular hemorrhage). When portal hypertension causes splenomegaly, dilation of the superficial abdominal veins can be noted at physical examination. Findings of a rash, arthritis, mucosal ulcerations, and splenomegaly may suggest an autoimmune disorder. Although a palpable spleen may be a normal variant, the concomitant finding of hepatomegaly is usually pathologic and should prompt further investigation.

### **Laboratory Evaluation**

The initial laboratory testing of a child with splenomegaly should include a complete blood count with a white blood cell differential, reticulocyte count, and examination of the peripheral blood smear. Further laboratory investigations should be directed at the suspected diagnosis, as indicated by the history, physical examination, and the results of the initial laboratory tests.

### **Imaging Studies**

Radiologic confirmation of a mass in the left upper quadrant should be performed if any question exists about the nature of the mass. Retroperitoneal tumors such as neuroblastoma and Wilms tumor may be mistaken for an enlarged spleen. Ultrasonography is used to quantify splenic enlargement and to differentiate the spleen from other left-upper-quadrant abdominal masses. CT scanning has been used to evaluate splenic trauma and focal splenic pathology. Contrast-enhanced ultrasonography is a novel technique used to detect bleeding sites and hematomas in splenic

trauma. MRI of the spleen can further clarify abnormalities in size and shape and can define parenchymal disease. Technetium-99m sulfur colloid scan is used to assess splenic function.

## TREATMENT

Treatment of splenomegaly should be aimed at the underlying disease entity. Patients who have bacterial infections should receive appropriate antimicrobial therapy. Viral causes of splenomegaly generally respond to supportive care. With splenomegaly from infectious mononucleosis, patients should refrain from contact or collision sports until the illness has completely resolved clinically and the spleen has returned to a normal size, generally at least 4 weeks from the onset of illness. Some experts suggest a sonographic evaluation of spleen size to help decide when the patient can resume full athletic activity.

Splenectomy may be indicated to help control or stage some diseases that cause splenomegaly. Such diseases include hereditary spherocytosis, autoimmune thrombocytopenia or hemolysis, and lymphoma (Hodgkin lymphoma). Splenectomy may also be indicated for the treatment of chronic, severe hypersplenism. Laparoscopic splenectomy is being performed more commonly in children and has been found to be a safe procedure, with a shorter hospital stay, compared with open splenectomy. During the past decade, partial splenectomy has become a viable therapeutic alternative to total splenectomy. Removal of up to 90% of the enlarged spleen usually provides relief from splenomegaly while retaining sufficient splenic tissue for immune competence. Partial splenectomy has been used successfully in children with hereditary spherocytosis, nonparasitic splenic cysts, sickle cell disease, and thalassemia. All children without spleens are at risk for fulminant bacteremia, sometimes referred to as overwhelming postsplenectomy infection (OPSI), particularly from *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and *Neisseria meningitidis*, and should receive needed immunizations at least 2 weeks before surgery if possible. Twice-daily penicillin prophylaxis against pneumococcal infections (in addition to immunization) is recommended for these children if they are younger than 5 years and for at least 1 year after splenectomy. Some experts continue prophylaxis throughout childhood and into adulthood for particularly high-risk patients with asplenia.

### WHEN TO REFER

- Splenomegaly with concomitant adenopathy or hepatomegaly
- Palpation of a hard spleen
- Suspicion of malignancy or other infiltrative disorders
- Evidence of hemolytic anemias

### WHEN TO ADMIT

- Splenic sequestration in sickle cell disease
- Injury to the spleen from abdominal trauma

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## Chapter 197 STRIDOR

Alfin G. Vicencio, MD; John P. Bent, MD

## DEFINITION

Stridor is typically a high-pitched, monophonic noise caused by turbulent airflow through a partially obstructed extrathoracic airway, heard predominantly on inspiration. Although obstruction of large intrathoracic airways (ie, main-stem bronchi, mid and distal trachea) can produce a similar noise on expiration, these lesions are more thoroughly covered in Chapter 208, Wheezing, and will not be discussed here.

During the normal respiratory cycle, rhythmic expansion and contraction of the thorax leads to dynamic changes in thoracic pressures, allowing air to flow into and out of the lungs. (For a schematic representation, see Figure 208-1, Chapter 208, Wheezing.) During expiration the volume of the thoracic cavity decreases, creating positive pressures within the thorax. Airways located within the thorax are directly subjected to these positive pressures and thus are more prone to obstruction during expiration, leading to turbulent airflow and wheezing. On inspiration the thoracic cavity expands, resulting in negative intrathoracic pressures and improved patency of intrathoracic airways. However, because the intraluminal airway pressure drops to allow inflow of air, and because the extrathoracic airways (nose, nasopharynx, oropharynx, and larynx) may collapse from transmitted negative intrathoracic pressures, this portion of the airway is susceptible to obstruction, and thus stridor, during inspiration.

Because the extrathoracic airways extend from the nose to the proximal trachea, high-pitched laryngeal stridor must be differentiated from other abnormal inspiratory noises, such as stertor, a noisy, rumbling-type noise similar to snoring, which can be heard with partial airway obstruction in the oropharynx or nasopharynx. Accurately recognizing stridor will facilitate the ensuing diagnostic tests, given that the offending

lesion is likely to be in or around the glottic region, a relatively focused anatomic area.

## DIFFERENTIAL DIAGNOSIS

Because stridor reflects obstruction of a large centralized airway and can range in severity from mild to life-threatening, ensuring airway patency should precede the generation of a differential diagnosis. For the child who has signs of severe respiratory compromise—distressed appearance, severe retractions, nasal flaring, pallor or cyanosis, altered mental status—initial measures should focus on maintaining the airway and, if possible, relieving the obstruction. Only personnel skilled at airway management should attempt intubation, if required, and such a procedure should be performed in as controlled a setting as possible. In select situations for which medical intubation might prove difficult (ie, suspected epiglottitis in a patient with high fever, drooling, and severe respiratory distress), surgical support should be present before airway manipulation in the event that tracheostomy is required. Luckily, most cases of stridor that the general pediatrician encounters can be approached with a succinct, focused history and physical examination followed by directed diagnostic tests.

The most common causes of stridor in the pediatric age group, laryngomalacia and viral croup, can be easily recognized by the experienced physician after obtaining a focused history and physical examination (see Evaluation). However, because the differential diagnosis of stridor is extensive and includes anything that obstructs the extrathoracic airway, a major challenge for the pediatrician is identifying select patients who have less common causes of obstruction and thus require specific diagnostic tests and different management (Table 197-1). For example, laryngomalacia, vocal cord dysfunction, subglottic stenosis, laryngeal papillomatosis, glottic cysts, laryngeal webs, subglottic hemangiomas, foreign bodies, retropharyngeal abscesses, and laryngeal fractures can all compromise the extrathoracic airway and cause stridor. In most cases a careful stepwise evaluation by the astute pediatrician will lead to the correct diagnosis.

## EVALUATION

### History

Once airway patency has been ensured, a focused history should be elicited. Age of initial presentation and a description of the events surrounding the onset of symptoms can provide important clues to the underlying

**Table 197-1** Causes of Stridor

	HISTORY	OBJECTIVE FINDINGS
Laryngomalacia	<ul style="list-style-type: none"> <li>• Develops in the first few months of life</li> <li>• Present mostly when agitated or crying</li> </ul>	<ul style="list-style-type: none"> <li>• Predominantly inspiratory</li> <li>• May be positional</li> <li>• Obstruction of glottic space by collapsing supraglottic structures on laryngoscopy</li> </ul>
Viral croup	<ul style="list-style-type: none"> <li>• Preceded by upper respiratory tract infection symptoms and fever</li> <li>• No stridor between episodes</li> <li>• May have history of similar episodes in past</li> </ul>	<ul style="list-style-type: none"> <li>• Predominantly inspiratory</li> <li>• No change with position</li> </ul>
Subglottic stenosis	<ul style="list-style-type: none"> <li>• Develops after intubation or manipulation of airway</li> <li>• May be continuous</li> </ul>	<ul style="list-style-type: none"> <li>• Predominantly inspiratory but often biphasic</li> <li>• Flat inspiratory and expiratory loop on spirometry</li> <li>• Subglottic narrowing on neck radiograph and direct laryngoscopy</li> </ul>
Foreign body	<ul style="list-style-type: none"> <li>• Sudden onset</li> <li>• May have a history of choking</li> </ul>	<ul style="list-style-type: none"> <li>• Predominantly inspiratory if obstruction is extrathoracic</li> <li>• Foreign body may be visualized on radiograph if radiopaque</li> </ul>
Retropharyngeal abscess	<ul style="list-style-type: none"> <li>• Fever</li> <li>• Difficulty swallowing</li> </ul>	<ul style="list-style-type: none"> <li>• Often present with stertor</li> <li>• May have drooling</li> <li>• Retropharyngeal mass on lateral neck radiograph</li> </ul>
Hemangioma	<ul style="list-style-type: none"> <li>• Worsening stridor</li> <li>• History of cutaneous hemangiomas</li> </ul>	<ul style="list-style-type: none"> <li>• May have cutaneous hemangiomas</li> <li>• Subglottic obstruction on neck radiograph</li> <li>• Hemangioma seen on direct laryngoscopy</li> </ul>
Bilateral vocal cord paralysis	<ul style="list-style-type: none"> <li>• History of injury to both recurrent laryngeal nerves</li> <li>• Arnold-Chiari malformation or increased intracranial pressure</li> </ul>	<ul style="list-style-type: none"> <li>• No movement of vocal cords during laryngoscopy</li> </ul>
Vocal cord cyst	<ul style="list-style-type: none"> <li>• Hoarse voice</li> <li>• Chronic irritation to vocal cords or airway instrumentation</li> </ul>	<ul style="list-style-type: none"> <li>• Cysts visible on laryngoscopy</li> </ul>
Laryngeal papillomatosis	<ul style="list-style-type: none"> <li>• Maternal history of human papillomavirus infection</li> <li>• Hoarse voice</li> <li>• Can develop in the first several years of life</li> </ul>	<ul style="list-style-type: none"> <li>• Papillomas visible on laryngoscopy</li> </ul>
Laryngeal web	<ul style="list-style-type: none"> <li>• Develops shortly after birth (congenital)</li> <li>• Develops after airway instrumentation (acquired)</li> </ul>	<ul style="list-style-type: none"> <li>• Web visualized on laryngoscopy</li> </ul>



diagnosis. A commonly encountered patient is one whose stridor is preceded by fever, upper respiratory symptoms, and a *barky* or *seal-like* cough. This history, which may include repeated and similar episodes in the past, is consistent with viral croup and is easily recognized by an experienced pediatrician. Stridor beginning in the first few weeks of life that is present only during specific phases of alertness such as eating, sleeping, or excitement suggests congenital laryngomalacia as the underlying cause. Indeed, laryngomalacia is the most common cause of congenital stridor in infancy. In comparison, continuous stridor that begins soon after birth might suggest a congenital and fixed lesion such as a laryngeal web or, particularly in an infant with cutaneous hemangioma, subglottic hemangioma (obstruction associated with subglottic hemangiomas typically is mild at birth and worsens over the first 6 months of life).

Stridor that develops shortly after a prolonged intubation likely results from subglottic stenosis or granulation tissue and is often seen in premature infants who required mechanical ventilation during the neonatal period. A less common but important patient to recognize is one with a history of Arnold-Chiari malformation or hydrocephalus. Because increasing intracranial pressure can result in bilateral vocal cord paralysis, such patients should receive appropriate and emergent care to prevent brainstem herniation. Similarly, a stridulous toddler with a history of choking or placing small objects in the mouth should be evaluated for the presence of a foreign body. Recurrent respiratory papillomatosis is also usually associated with stridor or hoarseness 2 to 3 years after birth, although the infection is acquired through vertical transmission in the birth canal from maternal cervical human papillomavirus infection.

In addition to their onset, the chronicity and progression of symptoms can help identify the underlying cause and can be particularly helpful for patients with presumed laryngomalacia or viral croup who do not follow the expected clinical course. Stridor caused by laryngomalacia is typically intermittent and worsens over the first several months of life. As the child becomes older, such episodes become less severe and less frequent. Indeed, for most patients with laryngomalacia, symptoms will completely resolve by the first birthday. Similarly, the likelihood of developing stridor caused by viral croup lessens with age. When the pediatrician is faced with a child whose stridor worsens or persists rather than improves, coexisting or alternate diagnoses should be considered, and appropriate diagnostic testing should be initiated. In addition, persistent symptoms may indicate a different laryngeal abnormality. For example, mild stridor caused by a subglottic hemangioma may initially be attributed to a more common problem such as laryngomalacia. Similar to laryngomalacia, obstruction from a hemangioma tends to worsen after initial presentation as the lesion enlarges. Unlike laryngomalacia, natural resolution of the hemangioma, and thus the stridor, may take several years rather than months. History of a hoarse voice or cry suggests glottic disease and might result from chronic irritation of the vocal cords. Other clues that suggest more ominous conditions include constant stridor, failure to thrive, difficulty swallowing, and severe and sudden onset of symptoms. Last, onset of stridor in an older child or

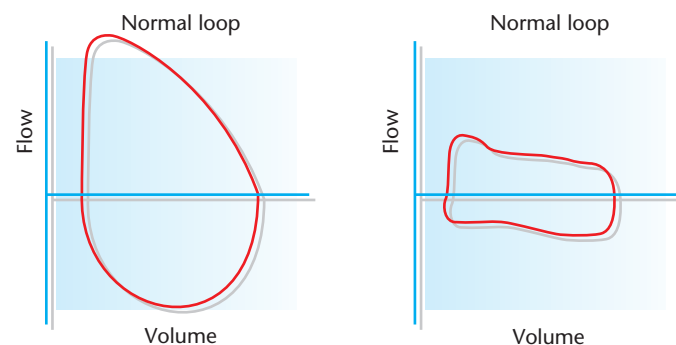
adolescent with no previous history should prompt a more thorough evaluation.

### Physical Examination

Laryngeal stridor represents airway obstruction at the level of the supraglottis, glottis, or subglottis. Although these anatomic regions can be difficult to examine without the use of specific diagnostic tests, several clues from thorough physical examination can help confirm suspicions elicited on history. General inspection of the patient should include an assessment of position—extension of the neck is often described in patients with a serious infection such as epiglottitis or retropharyngeal abscess—as well as any drooling, which might suggest mass effect or edema in the posterior pharynx causing dysphagia in addition to the stridor (of note, these patients often exhibit stertor rather than stridor). Because such entities can be difficult or even dangerous to visualize, attention should focus on keeping the patient calm and maintaining the airway. An oropharyngeal examination might reveal a retropharyngeal bulge, an enlarged epiglottis or a lateral displacement of the uvula, and swelling of a tonsillar pillar from an underlying infection in patients with acute onset of stridor. External examination of the neck might show suprasternal retractions when obstruction is severe and may also reveal displacement of the larynx, a mass obstructing the airway, or signs of trauma. Finally, the quality of the voice should be noted; given that hoarseness, aphonia, or a weak cry suggests vocal cord disease, one should examine the skin for any cutaneous lesions such as hemangiomas. Lastly, improvement of stridor with a jaw thrust could suggest pathology in the region of the epiglottis as opposed to the subglottis.

### Objective Testing

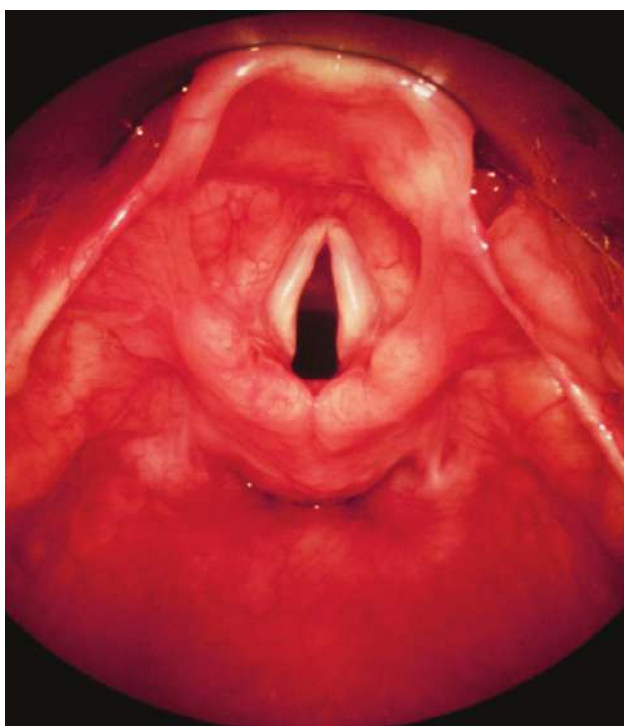
Although a detailed history and physical examination are often sufficient to make a diagnosis of laryngomalacia or viral croup, additional diagnostic tests are warranted for patients whose symptoms and clinical course seem unusual or overly severe. Laboratory testing has limited value in evaluating patients with stridor. Similarly, pulmonary function testing is not often necessary but can confirm suspicions of an extrathoracic obstruction (Figure 197-1). A simple radio-



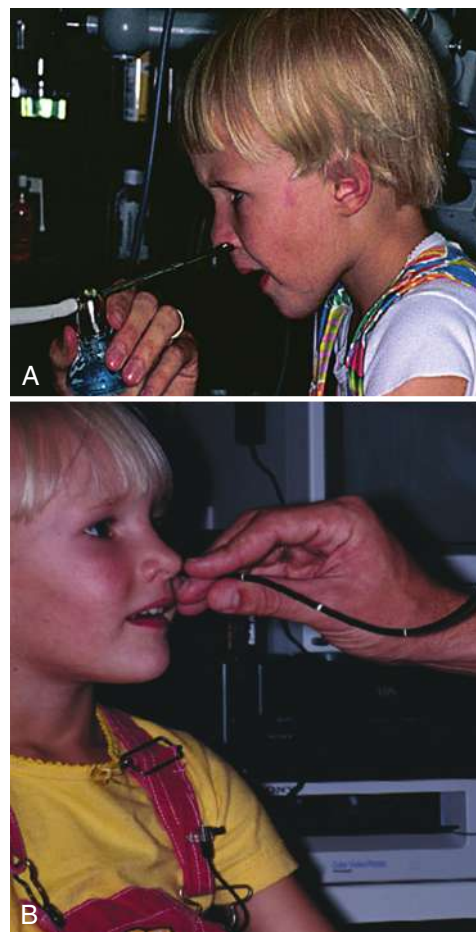
**Figure 197-1** Findings on spirometry. The normal flow-volume loop has a characteristic shape. In comparison, the flow-volume loop in a patient with severe subglottic stenosis is flat.



**Figure 197-2** The neck radiograph demonstrates a mass causing mild obstruction of the subglottic area (arrow) in a child with stridor.



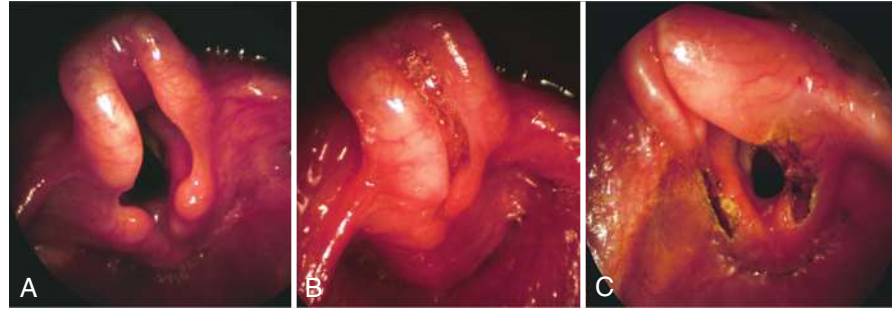
**Figure 197-3** Normal larynx. Flexible and direct laryngoscopy offers a direct view of the glottis and can identify an abnormality. Shown here is a normal view of the glottis.



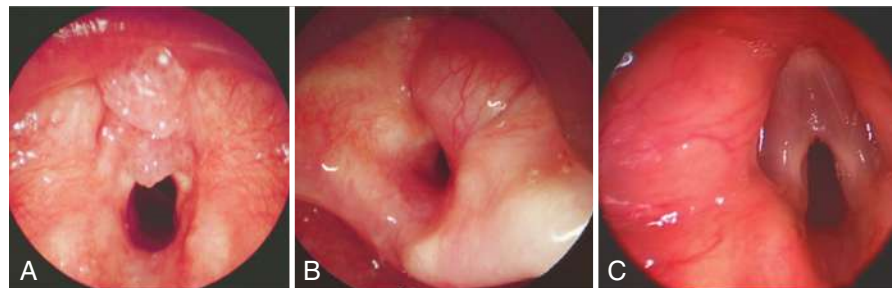
**Figure 197-4** Flexible laryngoscopy. A, Topical anesthetic is applied before performing flexible laryngoscopy. B, The procedure is usually well tolerated when performed by an experienced laryngoscopist.

graph of the neck can identify obstructive lesions in the retropharynx, glottis, and subglottic area (Figure 197-2). The classic *steep sign* on anteroposterior neck radiograph depicts subglottic narrowing but does not distinguish croup from subglottic stenosis. Direct visualization of the airway by flexible laryngoscopy often provides definitive information.

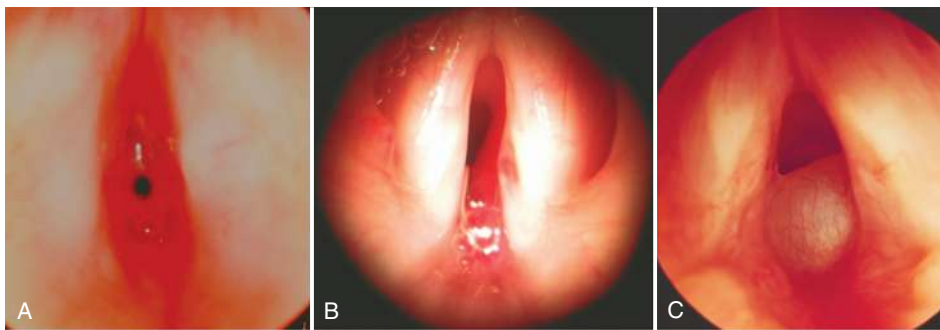
Flexible laryngoscopy is a routine procedure for the practicing otolaryngologist. Because the procedure offers direct visualization of the posterior pharynx and glottis (Figure 197-3), numerous other lesions causing laryngeal obstruction can be visualized, leading to a correct diagnosis. In fact, before routine use of office-based flexible laryngoscopy, laryngomalacia was known as *congenital laryngeal stridor*, reflecting physicians' incorrect assumption that all congenital laryngeal stridor might be attributed to a single cause. The procedure is usually well tolerated and can be performed most often with topical anesthesia alone (Figure 197-4). In many instances, laryngoscopy merely confirms the presence of laryngomalacia while excluding other causes of airway obstruction.



**Figure 197-5** Laryngomalacia as seen by flexible laryngoscopy. **A**, During expiration the glottis is patent, and no abnormal sound is heard. **B**, During inspiration the epiglottis and arytenoids collapse and compromise the glottic opening, causing inspiratory stridor. **C**, In cases of severe laryngomalacia, surgical resection of redundant tissue can improve the glottic patency even during inspiration.



**Figure 197-6** Obstructive lesions in the glottis. **A**, Laryngeal papilloma. **B**, Anterior saccular cyst. **C**, Glottic web.



**Figure 197-7** Obstructive lesions in the subglottic region. **A**, Severe subglottic stenosis. **B**, Right lateral subglottic hemangioma. **C**, Subglottic duct cyst.

(Figure 197-5, A and Figure 197-5, B). In cases of severe laryngomalacia, laryngoscopy can also identify specific structures of the larynx that are causing obstruction that might be amenable to surgical correction (Figure 197-5, C). Of course, direct visualization of the glottis can also identify other lesions that cause obstruction, as shown in Figure 197-6.

Successful flexible laryngoscopy is often dependent on patient cooperation, particularly with anxious, difficult-to-restrain, and younger school-aged children. Furthermore, although laryngoscopy often provides a clear view of the glottis and supraglottic structures, the subglottic area cannot be well visualized. Indeed, even with a cooperative patient, the presence of severe

laryngomalacia might obscure the view of the subglottic area such that a more distal lesion would not be visible. In such cases, direct visualization of the subglottic region and proximal trachea may be indicated to exclude a second lesion. Direct laryngoscopy and bronchoscopy under sedation or general anesthesia can help diagnose and quantify the severity of subglottic stenosis or identify other subglottic lesions that cause obstruction (Figure 197-7).

## MANAGEMENT

Because patients with laryngomalacia and viral croup are frequently encountered and will include most patients with stridor, the general pediatrician should



be comfortable with outpatient management. Most cases of laryngomalacia can be managed with observation alone, with particular attention given to adequate caloric intake and weight gain. For patients with severe episodes of stridor causing hypoxemia or cyanosis, or if symptoms progress over time, additional diagnostic testing is indicated, and referral to a subspecialist may be warranted. In certain instances, laryngomalacia requires surgical management to relieve the obstruction caused by redundant epiglottic folds or arytenoid tissue (see Figure 197-5). Tracheostomy is rarely required. As with laryngomalacia, most patients with viral croup can be managed with close observation alone. For children with more severe obstruction (nasal flaring, retractions), racemic epinephrine and dexamethasone may temporarily relieve symptoms of obstruction and alleviate inflammation, respectively. Hospitalization is indicated for children with hypoxemia, apnea, or poor feeding or dehydration.

As discussed previously, stridor that is continuous, progressive, or severe should prompt the pediatrician to initiate additional diagnostic tests. Referral to a pediatric otolaryngologist for further evaluation by laryngoscopy or bronchoscopy (or both) will facilitate diagnosis of other causes of glottic or subglottic obstruction, which might require surgical management. Laser therapy for a hemangioma or web can provide definitive cure, as can cricoid split and augmentation of the subglottic space for an acquired stenosis.

In summary, the pediatrician evaluating the child with stridor should be aware of the various clinical entities that can present with stridor, be able to recognize by history or physical examination patients who require further evaluation, initiate simple diagnostic tests, and refer to appropriate subspecialty physicians those children with unusual presentations or poor response to conventional therapies.

### WHEN TO REFER

- Progressive or continuous stridor
- Poor weight gain or growth associated with persistent stridor
- Repeated hospitalization
- Presence of cutaneous hemangiomas in association with persistent stridor

### WHEN TO ADMIT

- Respiratory distress or hypoxemia
- Inability to eat or drink
- Altered mental status or signs of fatigue
- Stridor associated with signs of increased intracranial pressure

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *What Is a Pediatric Otolaryngologist?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Otolaryngologist.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Otolaryngologist.aspx))

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## Chapter 198

# SUBSTANCE USE: INITIAL APPROACH IN PRIMARY CARE

Sharon Levy, MD, MPH; Sarah Bagley, MD

## INTRODUCTION

Pediatricians in primary care encounter many youth who have experience with alcohol, marijuana, and other drugs. They may identify a youth because parents or teachers have expressed a concern about use of substances, because the youth has physical signs or symptoms suggesting substance use, because there are nonspecific symptoms that may suggest substance use (eg, declining school performance or attendance, car crash, association with friends who are using substances), or because an asymptomatic youth has a positive substance-use screening test result. Whether the use identified is sporadic or regular, it can have negative health effects related to the direct consequences of the substances or associated risky behaviors. Identifying and addressing substance use to minimize harm is an important task for the primary care physician (PCP). Because substance use is closely associated with morbidity and mortality in this age group, the American Academy of Pediatrics (AAP) recommends that pediatricians achieve competence in identifying and intervening to reduce substance use by youth, as well as supporting the care of youth with substance use disorders (SUDs).

Perceived limitations of time for adequate psychosocial evaluation, discomfort addressing sensitive issues, or lack of familiarity with available therapeutic resources may prevent physicians from thoroughly and appropriately addressing substance use with adolescents. However, as with other disorders, assessment is required in order to determine the appropriate setting and level of care. More often than not, sensitivity to these issues, attention to adolescents' risk behaviors in general, and periodic follow-up in the primary care setting are adequate to help keep adolescents safe and healthy.



## ADOLESCENT BRAIN DEVELOPMENT

The human brain continues to develop until the middle of the third decade of life. The prefrontal cortex—which controls impulses, attention and organization—matures last, well after the parts of the brain that are involved in pleasure and reward. This developmental “imbalance” is correlated with stimulation seeking and risk-taking behavior that is typical of adolescence. Use of psychoactive substances is one way, albeit dangerous and unhealthy, in which youth may fulfill a natural inclination for stimulation and reward. It is not surprising, therefore, that rates of psychoactive substance use peak in adolescence and early adulthood. Seen in this perspective, substance use can be understood as an (unhealthy) mechanism for fulfilling a normal drive, rather than as purely deviant behavior. Adolescents also may use psychoactive substances for a variety of other reasons: to fit in social situations in which others are using substances; because of expectations that use will be pleasurable; as a form of risk taking or stimulation seeking; or to relax, relieve anxiety, improve mood, or relieve symptoms of a mental health disorder. Identifying the reasons that underlie substance use can help physicians to target counseling, advice, and strategies that are most salient to the adolescent.

Unfortunately substance use, even without symptoms that rise to the level of a “disorder,” is associated with significant health problems, including injuries, accidents, unintentional sexual activity, and sexually transmitted infections. Early initiation of substance use is also associated with increased risk of developing a severe SUD (otherwise known as addiction), which is a chronic medical condition that causes neurologic changes. The AAP recommends that physicians routinely screen every adolescent for substance use and deliver an appropriate intervention geared towards preventing or reducing substance use. When a child is referred for specialty care of a substance abuse problem, the AAP recommends that the physician remain involved with the child and family, supporting their positive view of treatment, monitoring progress, and providing complementary primary care services.

## PREVALENCE OF SUBSTANCE USE

Alcohol, marijuana, and tobacco are the most commonly used substances among youth. By the end of 12th grade, 52% of students report being drunk at least once, as do 12% of eighth-graders. Lifetime rates of use of any illicit drug increased in 2013, driven mainly by increasing rates of marijuana use. Perception of risk related to marijuana use continues to fall, likely foreshadowing continued increases in use over the next few years. Prescription drug misuse continues to be a concern, with 15% of 12th-graders reporting misuse of a prescription drug in the prior year. Rates of tobacco use by youth declined from 1996 to 2010, though over the past few years rates have plateaued. “E-cigarettes,” which are electronic devices that vaporize liquid nicotine, are marketed as a tobacco cessation device but are sold in flavors such as bubble gum and cotton candy that are attractive to children

who may initiate their “smoking careers” with these devices. Use of tobacco products often precedes use of other substances. Youth who smoke cigarettes are 5 times more likely than nonsmokers to use alcohol, 13 times more likely to use marijuana, and 7 times more likely to use cocaine or heroin.

## CLASSIFICATION OF SUBSTANCE USE DISORDERS

The *Diagnostic and Statistical Manual, 5th Edition (DSM-5)*, released in May 2013, included new criteria and replaced the terms “substance abuse” and “substance dependence” with SUD—mild, moderate, or severe. The new diagnostic classification is based on the number of criteria that are met: 2 to 3 constitute a mild disorder, 4 to 5 moderate, and 6 or more severe. Meeting criteria for a mild or moderate SUD indicates particularly hazardous use or that an individual has begun to have problems associated with use. Although there are no clear referral guidelines for adolescents with an SUD unless there is a co-occurring mental illness, those with a mild SUD can likely be managed in primary care. Patients with a moderate SUD may not require a referral to subspecialty care, and the referral decision can be left to the discretion of the PCP and his or her comfort with managing SUDs. Meeting criteria for severe SUD suggests that an individual would likely benefit from specialized treatment for SUDs. However, because many adolescents with a severe SUD will not accept a referral to treatment, PCPs should be prepared to manage these patients in primary care while trying to facilitate completion of the referral. While not an official diagnostic term, “addiction” refers to loss of control or obsessive use of a substance associated with neurologic changes in the brain’s reward center. Because there is no cure for addiction, long-term treatment is recommended. Effective, evidence-based treatments, including medication and psychosocial support, are available.

The following sections will describe the physician’s role in screening for substance use, assessment of severity, and management of adolescents who are using substances.

## CONFIDENTIALITY AND SUBSTANCE USE

Given that substance use is one of a number of sensitive topics that may come up in the course of adolescent care, PCPs should have a systematic way to establish “limits” of confidentiality with both youth and parents in the practice. This is particularly important before a pediatrician begins taking the medical history and screening for drug use. Discussions between the pediatrician and patient should remain confidential unless the pediatrician determines that the reported behaviors are putting either the patient or someone else at acute risk of harm. Determining whether a behavior requires breach of confidentiality is a matter of clinical judgment; in most cases reports of occasional tobacco, alcohol, or marijuana use can be kept confidential, though a physician may decide to involve parents if a child is very young or being

treated for a medical condition that could be dangerously affected by substance use. Even when there is no reason to breach confidentiality, it is often best to request permission from the youth to engage with parents for their support. In situations where a parent is already aware of use, the youth may be willing to share information, particularly if he or she has agreed to a quit attempt or to engage in further treatment.

## SCREENING TOOLS

At each health supervision visit with an adolescent or preadolescent patient, pediatricians should include a psychosocial interview to assess family and peer relationships, academic progress, recreational activities, sexual behavior, and drug use. HEADSSS is an acronym that can help physicians to inquire about key domains: home, education, activities, drugs, safety, sexuality, and suicide or depression. Pre-visit questionnaires are also available to capture this information.

This data gathering does not substitute for screening. Standardized, validated tools are recommended when screening for substance use in order to improve sensitivity of report and accuracy of triage based on screen results (Table 198-1). Using screening tools minimizes the likelihood that substance use problems or disorders are missed, as commonly occurs when screening on clinical impressions alone.

Screening allows pediatricians to stratify youth into risk categories. Each of the recommended tools does this in a slightly different way, though most include “no use,” “lower-risk use,” “moderate-risk use,” and “high-risk use,” with “lower-risk use” corresponding to use without a *DSM-5* SUD and “high-risk” corresponding to a mild, moderate, or severe SUD. In this chapter we describe interventions for each of these levels of risk. Some tools do not discriminate between moderate and high risk; in these cases the assessment is used to determine which youth have developed a

severe SUD that will benefit most from referral to subspecialty care. Interventions for each stage are described below, in the section on Counseling to Reduce Drug Use and High-Risk Behaviors.

## ADVICE AND COUNSELING FOR LOW-RISK YOUTH

PCPs should provide youth who are not using substances or are “lower risk” with positive encouragement about their smart and healthy choices. This is an opportunity to provide education about the risks of using substances in addition to anticipatory guidance about how to manage situations when alcohol or other drugs will be available. Importantly, it is recommended that the PCP include a discussion of the risks of impaired driving and help the adolescent plan for times when a driver may have used alcohol or drugs. Students Against Destructive Decisions (SADD) has a helpful framework for physicians to use with patients and parents for driving safety (see Tools for Practice: Engaging Patient and Family at the end of this chapter).

## PRIMARY CARE OF YOUTH WHO ARE USING SUBSTANCES

### Assessment

Assessment is performed with youth whose screen result puts them in the “moderate risk” or “high risk” category in order to determine the problems associated with use and the effect of substance use on their functioning at home, at school, and with peers. Assessment can include questions about age of initiation, frequency, and, for alcohol, quantity of use—information that assists the physician in identifying acute risk (such as very heavy alcohol consumption) as well as personalizing medical advice (such as discussing the effect of daily marijuana use on the adolescent brain). Asking about associated problems, troubles, regrets, and quit attempts may also identify areas of ambivalence that

**Table 198-1** Substance Abuse Screening and Assessment Tools for Use With Adolescents

### BRIEF SCREENS

S2BI

- 2-question frequency screen
- Screens for tobacco, alcohol, marijuana, and other illicit drug use
- Discriminates between no use, no SUD, moderate SUD, and severe SUD, based on *DSM-5* diagnoses
- Identifies problematic tobacco, alcohol, and marijuana use in pediatric settings
- 2-question screen
- Screens for friends’ use and own use

Brief Screener for Tobacco, Alcohol, and Other Drugs (BSTAD)  
NIAAA Youth Alcohol Screen

### BRIEF ASSESSMENTS

Car, Relax, Alone, Friends/Family, Forget, Trouble (CRAFTT)

- A good tool for quickly identifying problems associated with substance use
- Not a diagnostic tool
- Assesses for both SUDs and mental health disorders
- Assesses risky drinking
- Not a diagnostic tool

Global Appraisal of Individual Needs (GAIN)  
Alcohol Use Disorders Identification Test (AUDIT)

can be incorporated into a discussion of behavior change. These problems can be used as a fulcrum to turn the discussion toward a behavior change plan identified by the youth.

In general, open-ended questions such as “Tell me about your history of alcohol use” encourage more reporting than closed-ended questions. However, physicians may need to prompt adolescents for certain

information that is important for formulation. Suggested historical elements are listed in Table 198-2. With a focus on problems associated with substance use, a clinical history can be used as the first step in an intervention. Information about use of tobacco, inhalants, and other psychoactive and illicit substances and misuse of prescription or over-the-counter medications also helps to formulate clinical impressions and treatment recommendations. The National Institute of Alcohol Abuse and Alcoholism’s *Alcohol Screening and Brief Intervention for Youth: A Practitioner’s Guide* and the AAP Policy Statement on Screening, Brief Intervention, and Referral to Treatment both explain in detail the recommended approach to screening and brief intervention for adolescents.

A parent, teacher, or other caregiver may notice non-specific signs or symptoms that may indicate substance use. If these are reported, the youth should be assessed for a potential SUD through a careful history regardless of screen results. See Table 198-3 for other conditions that may mimic or co-occur with substance use. In addition, certain risk factors such as early initiation of use, family history of SUDs, and co-occurring mental health disorders increase a youth’s susceptibility to developing an SUD. When available, this information should be considered in the overall assessment of each patient.

As with screening, an accurate substance use history can be best obtained in an atmosphere of confidentiality, privacy, and trust; it is recommended that parents be excluded from the interview.

**Table 198-2** Key Details to Assess in High-Risk Patients

SUBSTANCE	KEY HISTORICAL ELEMENTS
Alcohol	<ul style="list-style-type: none"> <li>• Age of first drunkenness</li> <li>• Frequency of drinking episodes</li> <li>• Typical amount of alcohol consumed</li> <li>• Greatest amount of alcohol consumed</li> <li>• History of blackouts, overdose, emergency department visits</li> <li>• Problems associated with alcohol use</li> </ul>
Marijuana	<ul style="list-style-type: none"> <li>• Quit attempts</li> <li>• Age at initiation</li> <li>• Frequency of marijuana use</li> <li>• History of paranoia and/or hallucinations</li> <li>• Problems associated with marijuana use</li> <li>• Quit attempts</li> </ul>

**Table 198-3** Conditions That May Mimic or Co-occur With Substance Use

CONDITION	RATIONALE
Learning problems or disabilities	Unidentified learning difficulties can contribute to frustration and stress, school failure, and association with peers who use substances, all of which can increase the chances of developing a substance use disorder (SUD). See Chapter 172, Learning Difficulty, to explore this possibility.
Depression or bipolar disorder	Marked sleep disturbance, disturbed appetite, low mood, or tearfulness could indicate that a youth is depressed. Symptoms of depression rapidly alternating with cycles of agitation may suggest bipolar mood disorder. See Chapter 137, Depression.
Exposure to adverse childhood experiences (ACE)	Youth who have experienced or witnessed trauma, violence, a natural disaster, separation from a parent, parental divorce or separation, parental substance use, neglect, or physical, emotional, or sexual abuse are at high risk for developing emotional difficulties such as adjustment disorder or posttraumatic stress disorder (PTSD). Consider PTSD if the onset or acceleration of substance use was preceded by an extremely distressing experience. Physicians should speak separately and confidentially with the youth and parents to explore this possibility. Parents are often unaware of exposures that children may have had at school or in the community and may also underestimate the effect on children of major traumas in the family (eg, serious illness in a parent, maltreatment of the child, death or incarceration of a loved one). See also Chapter 129, Anxiety.
Other anxiety disorders	Anxiety disorders commonly co-occur with SUDs, and the relationship is bidirectional: anxious youth may be more likely to use substances, and conversely, substance use may cause or precipitate anxiety disorders.
Physical illness	Drug or alcohol withdrawal may present as a physical illness and is potentially a medical emergency. Psychiatric symptoms may be associated with medical illness (eg, encephalitis/cerebritis) and may be mistaken for drug intoxication.
Psychosis	Though rare, the onset of bipolar disorder or schizophrenia in late adolescence may be subtle and marked only by frightening hallucinations or delusions that the youth does not disclose. These symptoms may result from, precipitate, or accelerate the use of substances.
Attention-deficit/hyperactivity disorder (ADHD)	Adolescents with ADHD have higher rates of SUDs than peers. Some studies have suggested that stimulant treatment for adolescents with ADHD may lower the risk of developing an SUD, though findings have been inconclusive. There is no evidence that stimulant treatment increases risk of developing an SUD. See Chapter 168, Inattention and Impulsivity.

### Physical Examination

The medical complications of chronic substance use, although sometimes severe, usually do not appear until after adolescence. Nonetheless, a complete evaluation for an SUD includes a complete physical examination; signs and symptoms of acute intoxication or chronic use should be noted if present. Table 198-4 lists physical signs and symptoms of acute and chronic substance use.

### Laboratory Testing

Drug testing may be a useful part of a complete assessment for an SUD, particularly when a parent or other adult is concerned and the adolescent denies use. As with any laboratory test, this procedure yields limited information and should be used only as an adjunct to the history and physical examination. The use of drug testing in general populations (eg, school drug testing programs) has less utility and many associated ethical and legal concerns. Parents may request that the pediatrician perform a urine drug test; however, testing and sharing of the results should only be done with the permission of the adolescent. If an adolescent refuses a test that is indicated, parents can be coached to implement logical consequences as they would in other circumstances, such as refusal to do homework or chores. If there is concern for harm, then the pediatrician should consider breaching confidentiality. Drug testing

is a complex laboratory procedure with significant potential for false positive and false negative results; the AAP has produced a clinical report to help guide physicians on how to use this procedure most effectively.

### General Care

PCPs are positioned to provide effective care to youth who are using substances, including youth who also need specialty services.

### Reduce Stress

Consider the child's social environment (eg, family social history, parental depression screening, results of any family assessment tools administered, reports from child care or school). Questions to raise might include the following:

*Is an external problem (adverse experience such as abuse, bullying, or family socioeconomic stress) adding to the youth's stress?* Take steps to explore and reduce stressors, as feasible.

*Are the youth's peers using substances?* Explore options to increase healthy social and recreational activities and reduce contact with peers who are using substances. Youth with severe SUDs can be encouraged to change their phone numbers and eliminate old contacts to avoid being contacted by old friends with whom they previously used drugs. Unfortunately, it is impossible to isolate youth with SUDs from substances.

**Table 198-4** Physical Findings Potentially Indicating Substance Use and Abuse

	ACUTE INTOXICATION	CHRONIC IMPAIRMENT	DRUG(S) TO CONSIDER
<b>General Appearance</b>	Altered mood, strange/inappropriate behavior	Poor dress or hygiene	Any drug
<b>Vital Signs</b>		Weight loss	Heroin, cocaine
	Hypertension	Hypertension	Cocaine, amphetamine
	Hypotension, hypothermia		Heroin
	Hyperthermia		Cocaine, amphetamine, ecstasy
	Tachycardia		Marijuana, cocaine, amphetamine
<b>Ears, Nose, and Throat</b>	Conjunctival injection		Marijuana, inhalants
	Dilated pupils		Cocaine, amphetamines
	Constricted pupils		Opioids
	Sluggish pupillary response		Barbiturates
		Nasal irritation	Cocaine, inhalants, opioids (if sniffing)
<b>Cardiac</b>	Arrhythmias	Arrhythmias	Methadone, cocaine, amphetamine
<b>Chest</b>		Gynecomastia	Marijuana, anabolic steroids
<b>Genitourinary</b>		Testicular atrophy, clitoromegaly	Anabolic steroids
<b>Skin</b>		Acne, hirsutism	Anabolic steroids
	Abscesses, needle track marks		IV drug use
<b>Neurologic</b>	Altered sensorium		Any substance
	Ataxia		Alcohol, barbiturates
	Nystagmus		Barbiturates
	Hyporeflexia or hyperreflexia		Marijuana, cocaine, amphetamine



Part of treatment is teaching youths to identify high-risk situations, avoid them when possible, and use strategies to avoid use even when confronted with others who are using. In some communities, youth may be able to attend a recovery high school. Recovery high schools are accredited schools that provide a safe and sober environment for youth with a substance use history to continue their education. Every school has a different approach that includes provision of continued support for students' recovery.

The physician also can acknowledge and reinforce protective factors such as good relationships with at least 1 parent or important adult, prosocial peers, concerned or caring family, help-seeking, and connection to positive organizations.

### Encourage Healthy Habits

Encourage exercise, outdoor time, a healthy and consistent diet, sleep (critically important to mental health), limited screen time, one-on-one time with parents, and time with peers who are not using substances. Offer praise for positive behavior changes, acknowledgment of the youth's strengths, and acknowledgment of the challenges the youth may be facing with transitions including new schools, new friends, new social circles, and new academic demands. Acknowledge that while the patient's friends may be using substances heavily, most of their same-age peers do not binge drink or use drugs.

Encourage involvement in prosocial activities such as youth development, leadership, volunteer, and

after-school activities; sports teams, clubs, and mentoring; and faith-based programs. A strengths-based approach that capitalizes on interests, talents, and future goals is most effective.

### Offer Resources

Helpful resources are included in Tools for Practice: Engaging Patient and Family. Provide contact numbers in case of an emergency.

### Monitor Progress

School reports, as well as youth and parent feedback, can be helpful in monitoring progress.

### Counseling to Reduce Drug Use and High-Risk Behaviors

The strategies described below are common elements of evidence-based and evidence-informed psychosocial interventions for the use of substances. They are applicable to the primary care of youth in the early stages of substance use and to the initial management of youth in more advanced stages while readying them for, or awaiting access to, substance abuse specialty care.

*Tailor intervention to stage of use.* Depending on the screening tool used, levels of risk include abstinence, lower risk (ie, use but no SUD), moderate risk (ie, mild or moderate SUD), high risk (ie, youth with a severe SUD), and acute risk, which is determined as part of the assessment of moderate and high risk youth. Interventions for each stage of change are described in Table 198-5.

**Table 198-5** Substance Use Spectrum and Goals for Office Intervention

STAGE/TRIAGE CATEGORY	DESCRIPTION	OFFICE-BASED INTERVENTION GOALS
Abstinence	No use of drugs or alcohol	<b>Positive Reinforcement</b> Prevent or delay initiation of substance use through positive reinforcement. Include statement about use norms, especially for younger children.
No substance use disorder (SUD)	Use of alcohol or marijuana with peers in relatively low-risk situations; without related problems or interference with domains of functioning—such as school, sports, hobbies, or home life.	<b>Brief Advice</b> Encourage cessation through brief medically based advice, particularly as it relates to patient's future goals. Promote patient strengths.
Mild/moderate SUD	As defined by <i>DSM-5</i> . Adolescents with mild/moderate SUDs typically have associated problems or high-risk behaviors associated with use.	<b>Brief Motivational Intervention</b> Encourage cessation even for a brief trial period if patient is willing. Reduce potential harm by reducing use and focusing on highest-risk behaviors. Encourage parent involvement to help with follow-through. Follow up with primary physician or allied mental health professional to continue conversation and harm reduction.
Severe SUD (addiction)	As defined in <i>DSM-5</i> . Loss of control or compulsive drug use, as "dependence" is defined in <i>DSM-IV-TR</i> .	<b>Brief motivational intervention</b> targeting referral into ongoing treatment. Encourage reducing use and high-risk behaviors and engaging adolescent to accept a referral to treatment. Share diagnosis and referral information with parents, if possible. Follow-up by primary care physician to ensure compliance and encourage long-term treatment.
Acute risk	Use associated with acute risk of overdose or in a situation that is physically risky.	<b>Intervention for safety</b> may include breaching confidentiality to inform parents about use and referral to treatment in a timely fashion. Verbal contracts not to use while awaiting a formal evaluation and advice to parents on how to monitor and what to do in case of escalation may also be helpful.

From Levy SJ, Kokotailo PK. Substance use screening, brief intervention, and referral to treatment for pediatricians. *Pediatrics*. 2011;128(5):e1330–e1340.

**Table 198-6** Sample Framework for Brief Motivational Intervention

PROCESS	DESCRIPTION
Assessment and summary	Targeted assessment for areas of ambivalence to establish rapport and develop a discrepancy between current status and future goals. Sample questions <ul style="list-style-type: none"> <li>• <i>What problems (if any) have you had, related to your use of substances?</i></li> <li>• <i>What regrets (if any) do you have, related to your use of alcohol?</i></li> <li>• <i>What trouble (if any) have you had, related to your use of marijuana?</i></li> </ul>
Brief advice	Offer specific medical advice to quit or cut down substance use as a means for decreasing the types of problems reported during the assessment. Sample statement <ul style="list-style-type: none"> <li>• <i>Only you can decide whether or not to drink alcohol. In regard to your health, I recommend you quit.</i></li> <li>• <i>Having a blackout means that you have had enough alcohol to poison your brain cells, at least temporarily.</i></li> <li>• <i>Kids often make bad choices, like the decision to have sex without a condom, when they are drinking.</i></li> </ul>
Planning	Engage patient in setting personal goals and agenda for change and link to follow-up. Sample statement <ul style="list-style-type: none"> <li>• <i>It sounds like you really enjoy drinking and also don't want to have another blackout. What could you do to protect yourself?</i></li> </ul>

Use motivational interviewing techniques (Table 198-6). The physician can explore ambivalence about use and readiness to enter treatment and negotiate achievable next steps in an empathetic and supportive manner. For high-risk youth, change plans can focus on eliminating highest-risk behaviors (such as driving or riding with an impaired driver) and on engaging in ongoing treatment. The physician should help parents be supportive of behavior change and coach them to avoid inadvertently enabling ongoing use.

If the youth has a history of either driving or being driven by an individual who has been using alcohol, negotiate a safety plan. Students Against Destructive Decisions (SADD) has a Contract for Life that can be signed by both a parent and a youth to ensure that the youth has a plan for a safe ride home.

### Referral to Specialty Treatment

The challenge continually posed to pediatricians is to recognize when a patient's substance use becomes significant enough to warrant referral to a treatment program or facility rather than being treated solely in the primary care setting. The AAP statement regarding screening, brief intervention and referral to treatment (SBIRT) provides specific guidance for when to refer patients and to which level of care. Following is a list of indications for specialty referral:

- Child younger than 15 years with a positive screen for moderate- or high-risk substance use.
- Interventions by PCP have not reduced use.
- Drug use is endangering the youth or others.
- Drug use is threatening the achievement of developmentally important goals, such as school attendance and performance, or relationships.
- Co-occurring mental health disorders are present.
- Youth has a history of trauma.
- Youth is using drugs other than alcohol, marijuana, or tobacco.
- Parents are not involved, do not acknowledge concerns, or one or both parents have an active SUD.

If the child is referred to a specialist, the family will probably need assistance in navigating the requirements of their health insurance plan or the public mental health system and selecting an appropriate

physician. The PCP and specialist will need to reach agreement on respective roles in the youth's care and establish a mechanism for communicating progress. The PCP can support the youth by encouraging his or her positive view of treatment; monitoring progress in care and observing for co-occurring disorders; coordinating care provided by parents, school, medical home, and specialists; and encouraging parents to seek treatment for tobacco use and other dependencies. Resources available to help physicians in these roles are provided in Tools for Practice at the end of this chapter.

Adolescents (and in some cases their parents) may resist treatment of an SUD. In these cases the following steps may be helpful:

- If a referral is clearly indicated, partner with parents to increase the likelihood of follow-through. Clarify with the youth the relevant laws and protections for minors. In many states, parents can file an order with the police to help enforce house rules. Depending on the situation, it may be necessary to involve the designated child protection agency.
- Provide education and motivational counseling to youth (and family, as appropriate) to reduce harm and improve functioning at home. Even if the youth is unwilling to engage with specific substance use treatment, he or she may be willing to see a licensed clinical social worker or psychologist.

### SUMMARY

Primary care pediatricians commonly encounter adolescents whose parents or teachers have concerns about their use of substances, who have signs or symptoms of substance use, or who have a positive screening test for substance use. In adolescents who are known to be using substances or who have other concerning signs or history, PCPs can perform a full assessment, including a physical examination and detailed substance use history. Laboratory testing can be used as an adjunct to the history and physical examination.

PCPs are positioned to provide care to youth who are using substances. PCPs can reinforce strengths and healthy behaviors and, by applying evidence-based brief interventions, can often be effective in preventing these youth from escalating their use of

substances and in motivating them to decrease their use of substances. PCPs can also recognize those youth who need the care of substance abuse specialists, motivate youth and families to connect with needed services, and offer supportive primary care to youth who are involved in specialty care. If youth and their families resist referral for specialty care, PCPs can monitor the youth's progress and provide primary care interventions aimed at reducing substance use and risky behaviors while increasing their motivation to seek specialty care.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Adolescent Addiction* (Web site), Home Box Office ([www.hbo.com/addiction/adolescent\\_addiction](http://www.hbo.com/addiction/adolescent_addiction))
- *Become an EX* (Web site), American Legacy Foundation ([www.becomeanex.org](http://www.becomeanex.org))
- *Campaign for Tobacco-Free Kids* (Web site), ([www.tobaccofreekids.org](http://www.tobaccofreekids.org))
- *Contract for Life* (Web page), Students Against Destructive Decisions ([www.sadd.org/contract.htm](http://www.sadd.org/contract.htm))
- *Julius B. Richmond Center of Excellence* (Web site), American Academy of Pediatrics ([www.aap.org/richmondcenter](http://www.aap.org/richmondcenter))
- *National Institute on Drug Abuse* (Web site), ([www.drugabuse.gov](http://www.drugabuse.gov))
- *National Youth Anti-Drug Media Campaign* (Web Site), Office of National Drug Control Policy ([www.abovetheinfluence.com](http://www.abovetheinfluence.com))
- *NIDA for Teens* (Web site), National Institute on Drug Abuse ([teens.drugabuse.gov](http://teens.drugabuse.gov))
- *Talk. They Hear You* (campaign), Substance Abuse and Mental Health Services Administration ([teens.drugabuse.gov](http://teens.drugabuse.gov))
- *Smokefree.gov* (Web site), US Department of Health and Human Services ([www.smokefree.gov](http://www.smokefree.gov))
- *The Partnership at Drugfree.org* (Web site), ([www.drugfree.org](http://www.drugfree.org))

### Medical Decision Support

- *Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide* (book), National Institute of Alcohol Abuse and Alcoholism, American Academy of Pediatrics ([www.niaaa.nih.gov/Publications/EducationTrainingMaterials/Pages/YouthGuide.aspx](http://www.niaaa.nih.gov/Publications/EducationTrainingMaterials/Pages/YouthGuide.aspx))
- *CRAFT* (screen), ([www.ceasar-boston.org/clinicians/crafft.php](http://www.ceasar-boston.org/clinicians/crafft.php))
- *Drug Strategies Treatment Guide* (Web site), DrugStrategies.org ([www.drugstrategies.org/youths](http://www.drugstrategies.org/youths))
- *Mental Health Initiatives* (Web site), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/default.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/default.aspx))

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## Chapter 199

# SYMPTOMS OF EMOTIONAL DISTURBANCE IN YOUNG CHILDREN

Mary Margaret Gleason, MD

Although the child is the patient, the primary care physician (PCP) must remain vigilant that the child's behavior, particularly with respect to social-emotional problems, may reflect difficulty or dysfunction within the child's caregiving context. This chapter outlines the PCP's role in preventing, identifying, and addressing social-emotional problems in young children—a



role that is critical because of the numerous associated adverse outcomes, including child and family suffering, school failure, mental and physical illnesses, and fractured social networks throughout the lifespan. This chapter focuses on children in the first 5 years of life, using the term *social-emotional problems* to describe the full range of behavioral difficulties, emotional disturbances, and relationship difficulties that may occur in early childhood, especially in the context of adverse childhood experiences. This chapter will refer to the child's primary caregiver as the parents, who may be biologic parents, grandparents, foster parents, or other.

## BACKGROUND AND EPIDEMIOLOGY

During early childhood, social-emotional health develops through a complex interaction of a child's genetic makeup, temperament, and social and physical environment, particularly the primary caregiving relationships. Previously, biological risks were not thought to be easily modifiable. However, recent research demonstrates that a child's environment affects social-emotional development directly and can modify gene expression. This in turn influences the structure of the developing brain. Exposure to a wide range of developmental, behavioral, economic, social, educational, biologic, or family stresses (also known as adverse childhood experiences) can overwhelm the child's ability to cope, alter the brain's architecture, and lead to impaired social functioning and impulse control. Examples of events that may precipitate toxic stress responses include child neglect; physical, emotional, or sexual abuse; exposure to domestic violence; inconsistent parenting; separation from loved ones; impairment of parents or caregivers (eg, chronic parental depression or substance abuse); natural disasters; poverty; unsafe housing; and chronic illness or delays in the child's development. The effect of these stressors on children can vary greatly depending on their developmental stage, their social supports, and the type, intensity, frequency, and duration of the stressors. There is an additive effect of multiple stressors or risk factors, with increased numbers of adverse events related to increased risk of adverse outcomes, likely through the disruption of developmentally normative experiences or the repeated activation of the physiologic trauma responses. Therefore, it is important to identify and ameliorate sources of traumatic stress as early as possible. A study by Egger and Angold demonstrated rates of psychopathology in very young children similar to rates in older children. These disorders can persist and interfere with future development and school readiness.

A child's relationship with caring and nurturing adults is the most critical factor in developing resilience in the face of the normative stresses of childhood and buffering a child from the adverse effects of toxic stresses. Interventions that support the development of positive parent-child interactions can positively influence a young child's brain development, intelligence, and central nervous system hormonal patterns. Specifically, these interventions focus on ensuring that a child experiences sensitive caregiving, in which a caregiver anticipates and responds to a child's unique physical and emotional needs and responds to

a child's positive and negative behaviors consistently, persistently, and contingently. Beginning in infancy and continuing through childhood and into adolescence, parents and other caregivers can support their child's pro-social behaviors and emotional regulation by modeling and reinforcing these behaviors and helping a child organize emotions in response to challenging situations. The foremost role of the PCP is in primary prevention—supporting parents and fostering childhood resilience to buffer against the negative effects of toxic stress (topics addressed in the Institute of Medicine *From Neurons to Neighborhoods: The Science of Early Childhood Development*, *Bright Futures*, Substance Abuse & Mental Health Services Administration reports, and the American Academy of Pediatrics (AAP) Policy Statement on Toxic Stress, among others).

## Role of the Primary Care Physician

The PCP can collaborate with local community partners (eg, developmental-behavioral pediatricians, early childhood mental health professionals, early intervention professionals, early childhood educators in child care and schools, child advocates, and public health agencies) to identify and address stressors that put children in their community at high risk for social-emotional problems and to identify and strengthen protective factors. A summary of approaches for screening strategies and interventions can be found on the AAP Early Brain and Child Development Web site ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/EBCD/Pages/default.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/EBCD/Pages/default.aspx)). Each group of PCPs and other early childhood partners will address the issues unique to their community, but some examples may include advocating for the creation of safe outdoor spaces for children's exploration, for domestic violence shelters, for evidence-based nurse visitation programs, for increased access to Head Start or other enriched early childhood caregiving environments, or for appropriate access to prenatal care and postnatal nutrition. Universal prevention approaches also occur within the primary care practice. Physicians can create an environment in which parents feel comfortable raising questions about emotional or behavioral concerns by asking about social-emotional development with open-ended questions, including these topics as part of anticipatory guidance, and including literature promoting social-emotional well-being in the waiting room. For children with overt social-emotional problems, PCPs are often the first professionals who identify the problem as a clinical issue that warrants attention. Therefore, they are responsible for supportive communication about the concern, as well as collaborating with their community partners to enhance access to specialty treatment and monitoring treatment effects.

## Findings Suggesting Social-Emotional Problems or Risk Factors for Problems

The symptoms that suggest social-emotional problems for children younger than 5 years can be identified in the child, the caregiver, or the relationship between the child and caregiver. A summary of some



### BOX 199-1 Symptoms and Clinical Findings Suggesting Social-Emotional Problems in Children Younger Than 5 Years

#### CONCERNS ABOUT THE CHILD'S BEHAVIOR OR EMOTIONS

- Child has regulatory difficulties evidenced by difficulty calming, irregular sleep or feeding patterns, or excessive sensitivity to sensory experiences.
- Child demonstrates difficulty organizing behaviors and demonstrates extreme aggression or severe or persistent tantrums that involve injury or damage to objects.
- Child has experienced significant difficulty adjusting to child care or preschool or has been expelled from child care or preschool.
- Child's activity and impulsivity levels are excessive for developmental age.
- Child's mood is unhappy, irritable, or lacking in true joy more frequently than the average child.
- Child shows more anxiety than others his age, especially related to specific triggers or traumatic reminders, separation from caregiver, or experiencing new situations.
- Child will not talk in public even with reassurance.
- Child has excessively rigid behavioral patterns or "habits" that interfere with typical functioning.

#### CONCERNS ABOUT CAREGIVER

- Caregiver is unable to consider the child's strengths, becomes disorganized when talking about the child, or talks about the child using only a negative tone.
- Caregiver does not anticipate a child's need for comfort or does not offer appropriate comfort in new situations or times of distress.

- Caregiver is excessively protective of child and does not allow developmentally appropriate exploration.
- Caregiver is or has been abusive or neglectful (eg, involvement with child protection).

#### CONCERNS ABOUT RELATIONSHIP

- Child does not or cannot elicit comfort or reassurance effectively from caregiver in times of distress (eg, immunizations or separations).
- Child (older than 9 months [developmental age]) does not look to caregiver in novel situations or to share joy or excitement.
- Child does not manifest age-appropriate stranger anxiety.
- Child has not met appropriate social milestones related to social reciprocity, peer interactions, adult interactions, or focused attachment (comfort-seeking) behaviors with a primary caregiver.
- Child's relationship with caregiver has been disrupted (eg, foster care, military deployment of parent, death of parent).

#### RISK FACTORS FOR INCREASED SUSCEPTIBILITY

- History of maltreatment or significant caregiving disruption (such as is seen in children in foster care, those who have been adopted, or those with other caregiving disruptions)
- Family stressors (eg, poverty, divorce, single parenting, unemployment, limited access to health care, lack of safe and affordable housing or food, social isolation, community violence)
- History of adverse childhood experience in parents
- Parental substance abuse, mental illness, or domestic violence

the clinical findings that may indicate the need for further assessment can be found in Box 199-1.

#### Tools to Assist With Identification

Validated, standardized screening instruments may be used to identify children at high risk for having social-emotional problems, either because of parent-reported symptoms or the caregiving environment. Table 199-1 provides examples of general psychosocial screening instrument results that may suggest a child has social-emotional problems. Negative screens indicate that a child is within a lower-risk group, and can be an opportunity for positive feedback or may guide anticipatory guidance. A negative screen should not override clinical judgment if a PCP has concerns because of history or observations. With all parent report measures, but especially in early childhood mental health, it is particularly important to recognize that a parent report reflects that parent's perception of the child's behaviors. Positive screens may indicate that the child has a mental health problem, that the parent is experiencing extreme distress (because of the child or

another cause), or that there is a problem within the relationship between the parent and the child. All 3 possibilities have implications for the child's development and warrant clinical attention. Therefore, a positive screen should be followed by further assessment to determine more about the clinical concern.

#### ASSESSMENT

Assessment begins by differentiating the child's symptoms from normal behavior. Children vary in temperament and in their capacity to self-regulate and adapt. Virtually all young children exhibit challenging behaviors at times, especially during periods of adjustment to new environmental circumstances such as birth of a sibling, a move, a new child care arrangement, or a family crisis. Children with social-emotional problems may experience more severe and persistent emotional or behavioral reactions to these normative stresses or even in the absence of an acute stressor. There are also some conditions that may mimic or co-occur with social-emotional problems of young children. Table 199-2 provides a summary of these conditions.

**Table 199-1** General Psychosocial Screening Results Suggesting Social-Emotional Problems

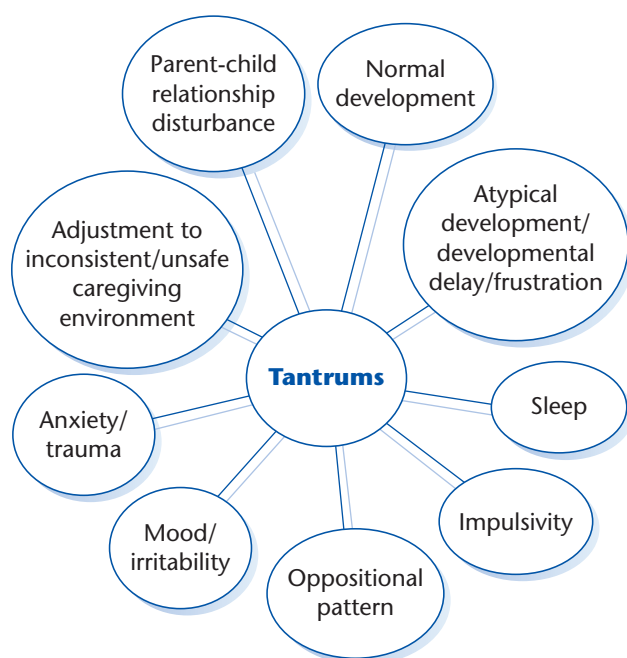
SCREENING AREA	SCREENING INSTRUMENT	SCORE
Child	Baby Pediatric Symptom Checklist (B-PSC) (irritability, inflexibility, difficulties in parenting)	A score of 3 or above is considered positive.
	Preschool PSC (internalizing, externalizing, attention, and parenting challenges)	A score of 9 or above is considered positive.
	Early Childhood Screening Assessment (assesses emotional and behavioral development in young children 18–60 months old and maternal distress)	A score of 18 or higher on items 1 through 36 indicates a higher than usual risk of disorder. A score above 1 on 37 or 38 may reflect parenting stress. A score of at least 1 on items 39 or 40 suggests risk of caregiver depression. Each measure includes specific instructions about cutoff score for that age.
Environment	Ages & Stages Questionnaire: Social-Emotional (ASQ:SE) (useful as early as 4 months to screen for problems in caregiver-infant bond and interaction)	Each measure includes specific instructions about cutoff score for that age.
	Edinburgh Postpartum Depression Scale	Score of 12 or above is considered positive.
	Parent Health Questionnaire-2	Any positive response is considered positive.
	Abuse Assessment Screen	Positive response to any question indicates high risk of interpersonal violence.
	Safe Environments for Every Kid (SEEK)	Positive responses suggest presence of family stressors.
	Caregiver Strain Questionnaire	Score of 7 or more suggests high level of caregiver strain.
	Bright Futures Surveillance Questions	Answers suggest social-emotional stressors.
	Parenting Stress Index	Results suggest high levels of stress associated with parenting, or within the parent-child relationship.

**Table 199-2** Differential Diagnosis of Extreme Emotional or Behavioral Dysregulation

DOMAIN	DIFFERENTIAL DIAGNOSIS	RATIONALE
Normal development Developmental delays/frustration	Cognitive and language disabilities	Extreme responses to normal limits, fatigue, hunger, or new situations are part of typical development in the third and fourth years of life.
	Hearing or vision problems	Children with language deficits may experience frustration expressing their needs and desires and therefore may exhibit symptoms of social-emotional problems. Children with intellectual disabilities may function at a level younger than their chronological age and size. This gap between their ability and adult expectations for their behaviors can lead to frustration for the child and caregiver.
	Autism spectrum disorders (ASDs)	All children who are manifesting atypical development or behavior should be screened for sensory deficits. A complete hearing assessment should be obtained for all young children with delay in language development. Children with ASDs have problems with social relatedness (eg, poor eye contact, preference for solitary activities, lack of joy in sharing with others, lack of empathy), language (delayed expressive language or unusual syntax or prosody), limitations in their range of interest (persistent and intense interest in a particular activity or subject), or atypical mannerisms that can interfere with their ability to function. They may have a need for routine and can become anxious or angry if a routine is disrupted. Accordingly, these children may manifest symptoms of social-emotional problems. In addition, children with ASDs are also at higher than usual risk of comorbid psychiatric disorders that may present in early childhood.
Regulatory problem	Sleep problems Feeding disorders	Sleep deprivation as a result of bedtime struggles, night waking, or obstructive sleep apnea can cause irritability and behavioral problems; conversely, social-emotional problems can cause sleep difficulties. Difficulties with feeding—either refusal, sensitivities, or overeating—can cause disruptive or distressed patterns in an infant or toddler, which can occur in a mutually escalating cycle with parental distress around the eating patterns.

**Table 199-2**      **Differential Diagnosis of Extreme Emotional or Behavioral Dysregulation—cont'd**

DOMAIN	DIFFERENTIAL DIAGNOSIS	RATIONALE
Child disruptive behavior problem	Attention-deficit/hyperactivity disorder (ADHD)	High levels of impulsivity, as well as inattentiveness and distractibility, may be seen in very young children with ADHD. It is especially important to assess whether the symptoms occur in multiple settings (as required in ADHD) or whether they are specific to a context or relationship, a pattern that would likely represent an adjustment to that situation. Because of the range of normal activity levels in very young children, ADHD must be distinguished from developmentally inappropriate expectations for young children and from parental symptoms that make normal child behaviors less tolerable, such as depression. In addition, symptoms suggestive of ADHD should be distinguished from lead toxicity and effects of medications such as steroids or sympathomimetics.
	Disruptive behavior disorders (oppositional defiant disorder, conduct disorder)	Disruptive behaviors in young children may present with extreme oppositional behaviors or conduct disorder symptoms, including aggression. These can occur when a child experiences an inconsistent or coercive caregiving environment.
Child mood symptoms	Depression	Very young children can present with all of the symptoms of major depressive disorder, and this diagnosis should be considered in children with extreme sadness or irritability. Associated symptoms include sleep and appetite changes, play or talk centered around death and dying, decreased joy in playing, and concentration difficulties. The validity of the diagnosis of bipolar disorder in preschool has not yet been established.
Child anxiety	Anxiety disorders	Preschoolers may present with general anxiety, extreme separation anxiety, school avoidance behaviors, and selective mutism, all often accompanied by extreme distress in the face of the trigger. Similarly, very young children with obsessive-compulsive behaviors may present with behavioral symptoms when asked to interrupt a compulsive behavior.
	Post-traumatic stress disorder and other trauma-related symptoms	In addition, children who have experienced traumatic events may exhibit a set of symptoms similar to the presentation of post-traumatic stress disorder seen in older children (re-experiencing the trauma in thoughts, speech, play, and dreams; emotional and physiologic hyperarousal to reminders of the trauma; avoidance of reminders of the trauma; and numbing symptoms). It is not uncommon for children who have experienced traumatic events to present with disruptive behaviors, perhaps related to their own inability to organize their reactions or because of less consistent parenting after the traumatic event.
Parent-child relationship disturbances	Parental mental health problems, substance abuse problems, or severe cognitive limitations	Young children who experience unpredictable or inconsistent parenting, especially if it includes neglectful or dangerous experiences, may present with inconsistent and sometimes dangerous behaviors. Treatment for parents and consideration of child protection involvement is critical in addressing these clinical scenarios. These patterns should be considered in children with a history of foster care or adoption. Depression or other mental illness, bereavement, substance abuse, cognitive disability, or disadvantaged socioeconomic circumstances may prevent a child's caregiver(s) from nurturing the child effectively and may contribute to social-emotional problems in the child.
	Disordered attachment or parent-child relationship difficulties	The bond between a child and his caregiver can be affected by characteristics of the child, caregiver, or temperamental "goodness of fit" between child and caregiver. Manifestations of a suboptimal parent-child relationship that increases the risk of attachment problems may include ineffective or inconsistent soothing, nurturing, or disciplinary behaviors of the caregiver, or lack of responsiveness of the child to his caregiver's soothing and nurturing efforts. A parent's own history of unsafe relationships (as a child or in romantic relationships) may shift how a parent thinks about herself in the intimate relationship of parenting and how the parent experiences the child's behaviors and needs. Relationship difficulties may present in the clinic with a parent who experiences the needs of her child as excessive or troublesome, with a child who develops a pattern of maladaptive ways of engaging the parent's attention, or with a child who does not seem to make any attempts to engage the parent even when he might be expected to need comforting.



**Figure 199-1** Differential diagnosis of emotional or behavioral dysregulation.

Extreme temper tantrums or emotional or behavioral responses to small events such as limit setting can reflect a range of clinical issues. Figure 199-1 provides categories of possible child, parent, or relationship difficulties that should be considered when a parent reports concerns about the child's emotional or behavioral development. Importantly, it should be considered that a maladaptive behavior often represents the only set of tools a child has to cope with an overwhelming emotion, such as anxiety, frustration (with self or other), or distress. Additionally, it is important to address parental concern about social, emotional, or behavioral patterns, even if the PCP does not identify atypical development. Providing parental support around parenting stresses, wondering about alternative attributions for behavior, strategizing around safe, consistent, nurturing responses to difficult behaviors, and close follow-up all may be helpful.

The special circumstance of a chronic or significant medical problem should be considered, as it may trigger social-emotional problems in a range of domains. Young children with chronic medical problems are more likely to experience developmental delays and traumatic experiences in the form of medical procedures and separations from parents, and may be seen as particularly vulnerable by their parents because of their medical condition. They may also take medications that may affect mood regulation (eg, steroids) or have primary central nervous system lesions that interfere with emotional, behavioral, or developmental regulation. Similarly, although all children with growth failure should be evaluated for underlying medical problems, psychosocial growth failure can occur in the context of an inadequate caregiving environment, and the role of the caregiving environment as a

protective or risk factor should be considered in all cases of growth failure. (See Figure 199-1.)

If a child or caregiver seems to be experiencing symptoms, the PCP can further assess for problems by collecting further information, refer to an appropriate specialist, or review diagnostic criteria for symptoms of disorders in the caregiver-child relationship.

The PCP can information from other caregivers, child care centers, and preschool about eating, sleeping, irritability, and aggression with peers, using behavior or food diaries or validated, structured measures, such as the Baby PSC, Preschool PSC, or Early Childhood Screening Assessment.

Referral may be to a developmental-behavioral pediatrician, mental health professional with expertise in assessment of young children and their families, or early intervention agency.

## PLAN OF CARE FOR CHILDREN WITH SOCIAL-EMOTIONAL PROBLEMS

The care of a child experiencing social-emotional problems can begin in the primary care setting. Universal screening or active surveillance for social-emotional problems can create an environment in which families feel comfortable discussing social-emotional issues. Following are the elements of providing care to a child with social-emotional problems identified in the primary care setting.

### Celebrate the Strengths and Engage Child and Family in Care

Physicians can engage families by recognizing and reinforcing the strengths of child and family and also by acknowledging the distress and emotional costs of the social-emotional concern. The PCP can acknowledge and reinforce protective factors (eg, good relationships with at least 1 parent or important adult, pro-social peers, concerned or caring family, help-seeking, or connection to positive organization[s]). In fostering engagement, it can be useful to use "common factors" techniques to build trust and optimism, including reaching agreement on incremental next steps and, ultimately, therapeutic goals, developing a plan of care (see the following clinical guidance), and determining the role of the PCP. The PCP's role may include providing intervention(s); providing initial intervention while awaiting family's readiness for or access to specialty care; collaborating with a specialist; coordinating with specialist(s), child care, school, or agencies; monitoring progress; and supporting the family's engagement in treatment. Without engagement, most families will not seek or continue in specialty mental health care. This process may require multiple primary care visits.

### Promote Safety

Families whose children experience social-emotional difficulties are at particularly high risk of exposure to unsafe situations. These may include family partner violence, child abuse, or community exposure to violence. In addition, some families may experience safety risks related to housing conditions or a child's access to potentially dangerous medications (diabetes



medications, sleeping medications, antihypertensive agents). Assessment for other risks, including weapons in the home, is an important role of the PCP.

### Address Basic Needs

Identifying families' basic needs is perhaps the most important universal intervention for all children with social-emotional problems. Family distress may be reduced by identifying and supporting families with basic needs issues, such as housing, child care, or access to food and a safe place to sleep. Without addressing these needs, it is unlikely that mental health referrals will be successful.

### Support Parental Mental Health

Whether a parent is experiencing a clinical-level problem or distress related to sleep deprivation, it is important for a parent to experience clinical interactions with the PCP as supportive. Even when there are concerns about specific parenting approaches, families will consider changing their behaviors only if they feel that the clinical approach is helpful and that their perspective is respected. Discussion of parental clinical mental health issues like depression or substance abuse, including those identified by screening, may be an important clinical step toward addressing the child's emotional needs.

### Reframe the Child's Behaviors

When a parent seems to perceive a child as overwhelmingly negative or interprets developmentally typical behaviors as intentionally disruptive to the parent, it can be helpful to reframe the behaviors in a way that may allow the parent to experience the same behaviors differently. For example, reframing "clingy and needy" behaviors in toddlers as demonstrating that they are using a parent for emotional support as they begin to venture out to explore their environment may be helpful. Using handouts such as those found on the AAP Early Brain and Child Development resource page or the Circle of Security handout ([circleofsecurity.org](http://circleofsecurity.org)) or video ([www.youtube.com/user/CircleOfSecurity](http://www.youtube.com/user/CircleOfSecurity)) may be helpful and efficient ways to inform parents. It is important to note that telling a parent the child's behavior is "normal" without putting it into a developmental or emotional context may be experienced as rejecting by parents who are worried about their child.

### Encourage Consistency in Child's Caregiving Environment

No matter what the clinical concern, children will benefit from predictable, consistent, and safe responses to both pro-social and negative behaviors. The PCP can encourage the primary caregivers to reflect on and enhance their own consistency. In addition, the PCP can assist the primary caregivers in developing strategies to increase the consistency the child experiences across caregivers, including mother, father, grandparents, babysitters, and child care providers.

### Explore Opportunities for Positive Parent-Child Interactions

Whether a clinical problem seems to be located primarily within the child, the parent, or their relationship,

it is likely that all family members are experiencing less joy and fulfillment from their interactions than they would like. Assisting a parent in identifying a child's strengths and positively reinforcing positive behaviors or efforts toward positive behaviors can be a useful first step toward healing. "Time in," as little as 5 minutes a day of interactive play time with the child, can be a way for parents to delight in their child, feel competent, and appreciated, and for the child to enjoy the parent. If a caregiver's own history of problematic relationships or mental health problems is affecting her relationship with the child, it can be useful to explore her readiness to address these problems as part of helping the child.

### Encourage Healthy Habits and Activities

The PCP can encourage healthy child and family habits that will provide a sound foundation for ongoing development. These healthy habits can include opportunities for active play, good nutrition, media-free family meals, regular bedtime routines, and adequate sleep. Discussions of media exposure and the dangers of frightening or violent media can be especially important for parents of children with anxiety, aggressive behaviors, or a history of trauma exposure. Additionally, the AAP media recommended limits to screen time can promote healthy brain development, increase interactive and exploration time, and reduce the potential for exposure to adult content or violence.

The PCP can direct the parent toward high-quality early childhood care and education such as Head Start and programs accredited by the National Association for the Education of Young Children (NAEYC). The PCP can also encourage communication between child care or preschool personnel and home and coach them to praise progress and effort, not just outcomes. The AAP Early Brain and Child Development Resources can be shared with parents to give to child care providers to promote consistency across a child's environments.

### Offer Initial Intervention(s)

Evidence-based psychosocial interventions for social-emotional problems include a number of "common elements" amenable to implementation in the primary care setting. Table 199-3 provides strategies that the physician can suggest to the family.

### Provide Resources

Helpful handouts, fact sheets, and Web sites are included in Tools for Practice at the end of this chapter.

### Monitor Progress

Symptoms can be tracked using screening measures described in Table 199-1 or disorder-specific measures. Nonproprietary general measures like the Baby and Preschool Pediatric Symptom Checklists and the Early Childhood Screening Assessment, or the proprietary Strengths and Difficulties Questionnaire, are useful in monitoring symptoms over time. Symptom-specific measures like the Eyberg Child Behavior Inventory (disruptive behaviors), and the Preschool Feelings Checklist (depression) are valuable and validated

**Table 199-3** Strategies for Building Child's Social-Emotional Skills and Resilience and in Addressing Behavior Problems

STRATEGY	ADVICE TO CAREGIVERS
Promote daily positive joint activities between parent(s) and child.	<ul style="list-style-type: none"> <li>• Enlist support of extended family, friends, faith group, or involved agency to relieve parent of some stresses and provide emotional support.</li> <li>• Educate about the importance of smiling with and talking and cooing to infants, attending to vocalizations or speech, and reading and playing at all ages.</li> <li>• Assist with recognizing a child's cues by labeling the child's behaviors and needs in the office and support the parent in responding sensitively.</li> <li>• Increase parent's one-on-one time with child (eg, interacting, feeding, reading, playing). Daily routines around mealtime and bedtime, for example, can ensure that these activities are well integrated into family life.</li> <li>• Promote resilience at every visit by using the anticipatory guidance of Bright Futures or the EBCD website and by emphasizing individual strengths.</li> </ul>
Apply positive parenting principles to toddlers and pre-schoolers (positive attention for positive behaviors; removing attention for low-level behaviors; and safe, consistent, calm consequences for unacceptable or unsafe behaviors).	<ul style="list-style-type: none"> <li>• Reinforce desired behaviors using parental attention (eg, "Catch them being good").</li> <li>• Help the child develop vocabulary to describe feelings.</li> <li>• Encourage praise and reinforcement ("rewards") for specific, desired (target) behaviors. The choice of target behaviors and the time intervals for reinforcements should be developmentally appropriate and sustainable.</li> <li>• Teach parents to reduce attention to ("ignore") minor, provocative behaviors. "Pick battles" and focus discipline on priority areas.</li> <li>• Reduce positive reinforcement of disruptive behavior.</li> <li>• Teach parents to recognize the child's anxiety, expose the child only to manageable anxiety-provoking situations, provide support around unavoidable anxiety-provoking situations, and praise the child's management of her feelings.</li> <li>• When possible, reorganize the child's day to avoid trouble by avoiding situations in which the child cannot control himself or herself. Examples include asking a neighbor to look after the child while the parent goes shopping, ensuring that activities are available for long car journeys, and arranging activities in separate rooms for siblings who are prone to fighting.</li> <li>• Talk to the child care center or preschool and suggest that similar principles be applied.</li> </ul>
Encourage parents to be calm and consistent.	<p>Suggest that parents do the following:</p> <ul style="list-style-type: none"> <li>• Set clear house rules agreed on by the primary caregivers</li> <li>• Give short, specific commands about the desired behavior, not prohibitions about undesired behavior (eg, "Please walk slowly," rather than "Don't run").</li> <li>• Provide consistent and calm consequences for misbehavior. Consequences should not be dangerous, drastic, or of extreme duration.</li> <li>• Use natural consequences, such as the child cleaning up a mess he or she has created.</li> <li>• When enforcing a rule, avoid getting into arguments or explanations, reduce additional attention for the misbehavior, and defer negotiations until periods of calm.</li> <li>• Consider parenting classes or community support.</li> </ul>

measures that provide more specific information about a child's course. Child care or preschool reports can be helpful in monitoring progress. Attention-deficit/hyperactivity disorder (ADHD) can be tracked using measures validated on older children, such as the Vanderbilt ADHD Rating Scales and the Conners-3. More extensive measures, such as the Child Behavior Checklist, are validated in children as young as 18 months of age, but are longer than a PCP can use regularly.

### Involve Specialist(s)

Involvement of a specialist may be considered appropriate under the following circumstances:

- A child younger than 5 years has symptoms of social-emotional problems causing functional impairment or distress; for example
  - The child has symptoms of anxiety, sadness, or irritability that limit participation in family

interactions, child care experiences, or other normative experiences.

- The child has behaviors that are disruptive in the home or in out-of-home settings, or that limit participation in developmentally appropriate experiences.
- The child does not use the caregiver effectively for emotional support or is indiscriminate in social interactions with strangers.
- The child exhibits sleep or eating problems are not responsive to primary care interventions.
- The parent is very negative toward child, compromised by physical or mental illness, disengaged, inconsistent in providing nurturing, or unresponsive to primary care guidance.
- The parent has difficulty allowing a child to have developmentally appropriate opportunities for exploration.

**Table 199-4** Psychosocial and Psychopharmacologic Treatments for Social-Emotional Problems in Young Children

### EVIDENCE-BASED PARENTING PROGRAMS

CLUSTER AREA	PARENTING PROGRAM
For disruptive behavioral problems	<ul style="list-style-type: none"> <li>• The Incredible Years (<a href="http://www.incredibleyears.com">www.incredibleyears.com</a>)</li> <li>• Triple P Positive Parenting Program (<a href="http://www.triplep.net">www.triplep.net</a>)</li> <li>• Parent-Child Interaction Therapy (<a href="http://pcit.php.ufl.edu">http://pcit.php.ufl.edu</a>)</li> <li>• “Helping the Noncompliant Child” parent training program (<a href="http://www.strengtheningfamilies.org/html/programs_1999/02_HNCC.html">www.strengtheningfamilies.org/html/programs_1999/02_HNCC.html</a>)</li> <li>• Nurse-Family Partnership (<a href="http://www.nursefamilypartnership.org">www.nursefamilypartnership.org</a>)</li> </ul>
For first-time, pregnant, low-income women prior to 28 weeks’ gestation	
For children in foster care	<ul style="list-style-type: none"> <li>• Attachment and Biobehavioral Catch-up (<a href="http://www.cachildwelfareclearinghouse.org/program/108/detailed">www.cachildwelfareclearinghouse.org/program/108/detailed</a>)</li> <li>• Multidimensional Treatment Foster Care Program for Preschoolers (<a href="http://www.uoregon.edu/~snaplab/SNAP/Projects.html">www.uoregon.edu/~snaplab/SNAP/Projects.html</a>)</li> <li>• Parent Child Interaction Therapy<sup>a</sup></li> </ul>
For parent-child relationship disturbances and high-risk parenting situations	<ul style="list-style-type: none"> <li>• Circle of Security (<a href="http://www.circleofsecurity.org">www.circleofsecurity.org</a>)</li> <li>• Promoting First Relationships (<a href="http://www.pfrprogram.org">www.pfrprogram.org</a>)</li> <li>• Parents as Teachers (<a href="http://www.parentsasteachers.org">www.parentsasteachers.org</a>)</li> <li>• Child Parent Psychotherapy</li> </ul>
For children exposed to trauma, including sexual abuse or domestic violence	<ul style="list-style-type: none"> <li>• Child Parent Psychotherapy (<a href="http://www.cachildwelfareclearinghouse.org/program/49/detailed">www.cachildwelfareclearinghouse.org/program/49/detailed</a>)</li> <li>• Cognitive behavioral therapy<sup>b,c,d</sup></li> </ul>

### PSYCHOPHARMACOLOGIC INTERVENTIONS<sup>E</sup>

There is limited evidence to support psychopharmacologic intervention in this age group. There is a single multisite, placebo-controlled, randomized trial of methylphenidate and another focused on atomoxetine as a treatment for attention-deficit/hyperactivity disorder in preschoolers. Both showed the medication was more effective than placebo, but less effective than in older children and was associated with a higher rate of adverse effects.<sup>f,g</sup>

Updates are available at [www.aap.org/mentalhealth](http://www.aap.org/mentalhealth).

<sup>a</sup>Chaffin M, Funderburk B, Bard D, Valle LA, Gurwitch R. A combined motivation and parent-child interaction therapy package reduces child welfare recidivism in a randomized dismantling field trial. *J Consult Clin Psychol*. 2011;79(1):84.

<sup>b</sup>Cohen JA, Mannarino AP. Factors that mediate treatment outcome of sexually abused preschool children: 6 and 12 month follow-up. *J Am Acad Child Adolesc Psychiatry*. 1998;37(1):44–51.

<sup>c</sup>Cohen JA, Mannarino AP. A treatment study for sexually abuse preschool children: outcome during one year follow-up. *J Am Acad Child Adolesc Psychiatry*. 1997;36(9):1228–1235.

<sup>d</sup>Scheeringa M, Weems CF, Cohen JA, Amaya-Jackson L, Guthrie D. Trauma-focused cognitive-behavioral therapy for posttraumatic stress disorder in three-through six year-old children: a randomized clinical trial *J Child Psychol Psychiatry* 2011;52(8):853–860.

<sup>e</sup>Lahey BB, Pelham WE, Loney J, et al. Three-year predictive validity of DSM-IV attention deficit hyperactivity disorder in children diagnosed at 4–6 years of age. *Am J Psychiatry*. 2004;161(11):2014–2020.

<sup>f</sup>Kratochvil CJ, Vaughan BS, Stoner JA, et al. A double-blind, placebo-controlled study of atomoxetine in young children with ADHD. *Pediatrics*. 2011;127(4):e862–e868.

<sup>g</sup>Greenhill LL, Kollins S, Abikoff H, et al. Efficacy and safety of immediate-release methylphenidate treatment for preschoolers with ADHD. *J Am Acad Child Adolesc Psychiatry*. 2006;45(11):1284–1293.

- The family is not able to maintain a calm, consistent, or safe environment. (In this instance, also consider reporting to child protective services.)

When specialty care is needed, a PCP should recommend evidence-informed treatment. A variety of evidence-based and evidence-informed psychosocial interventions are available for the treatment of social-emotional problems in children younger than 5 years of age. See Table 199-4.

No randomized controlled trials of medications have been carried out in young children with disruptive behavior, mood, or anxiety disorders, but ADHD has been studied using 2 different medications (methylphenidate and atomoxetine). Current evidence suggests that these two agents have higher rates of adverse effects in preschoolers than are reported in older children.

The PCP and specialist(s) should clarify roles in the child’s care. The PCP’s role may, for example, include engaging and encouraging the family’s positive view of interventions or referral and serving as the care coordination “hub” of the medical home. The specialist may monitor the child and family’s progress, observe for and addressing any comorbidities that may develop, and coordinate care provided by parents, child care center, preschool, medical home, early intervention agency, and specialists.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Connected Kids* (fact sheets), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

- *Everybody Gets Mad: Helping Your Child Cope With Conflict* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/healthy-living/emotional-wellness/Pages/Everybody-Gets-Mad-Helping-Your-Child-Cope-with-Conflict.aspx](http://www.healthychildren.org/English/healthy-living/emotional-wellness/Pages/Everybody-Gets-Mad-Helping-Your-Child-Cope-with-Conflict.aspx))
- *Parents' Roles in Teaching Respect* (handout), Bobbi Conner ([www.brightfutures.org/mentalhealth/pdf/families/mc/parent\\_role.pdf](http://www.brightfutures.org/mentalhealth/pdf/families/mc/parent_role.pdf))

### Medical Decision Support

- *The Abuse Assessment* (screen), National Institute of Justice ([www.crimesolutions.gov/ProgramDetails.aspx?ID=165](http://www.crimesolutions.gov/ProgramDetails.aspx?ID=165))
- *Ages & Stages Questionnaires: Social-Emotional (ASQ-SE)* (screen), Brookes Publishing ([www.brookespublishing.com/resource-center/screening-and-assessment/asq/asq-se](http://www.brookespublishing.com/resource-center/screening-and-assessment/asq/asq-se))
- *Edinburgh Postnatal Depression Scale (EPDS)* (screen), Cox JL, Holden JM, and Sagovsky R ([www2.aap.org/sections/scan/practicingsafety/toolkit\\_resources/module2/epds.pdf](http://www2.aap.org/sections/scan/practicingsafety/toolkit_resources/module2/epds.pdf))
- *M-CHAT* (screen), Diana L. Robbins, PhD ([mchatscreen.com](http://mchatscreen.com))
- *The Multidimensional Scale of Perceived Social Support* (article), *Journal of Personality Assessment*, Vol 52, Issue 1, 1988
- *Parent-Child Interaction Therapy* (Web page), University of Florida College of Public Health and Health Professions ([pcit.phhp.ufl.edu](http://pcit.phhp.ufl.edu))
- *Parenting Stress Index* (screen), PAR, Inc ([www4.parinc.com/products/Product.aspx?ProductID=PSI-4](http://www4.parinc.com/products/Product.aspx?ProductID=PSI-4))

### AAP POLICY

American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health, Committee on Early Childhood, Adoption, and Dependent Care, and Section on Developmental and Behavioral Pediatrics. Early childhood adversity, toxic stress, and the role of the pediatrician: translating developmental science into lifelong health. *Pediatrics*. 2012;129(1):e224–e231 ([pediatrics.aappublications.org/content/129/1/e224](http://pediatrics.aappublications.org/content/129/1/e224))

### SUGGESTED READINGS

- Committee on Integrating the Science of Early Childhood Development, Board on Children, Youth, and Families. *From Neurons to Neighborhoods: The Science of Early Childhood Development*. Shonkoff JP, Phillips DA, eds. Washington, DC: National Academy Press; 2000
- Egger HL, Angold A. Common emotional and behavioral disorders in preschool children: presentation, nosology, and epidemiology. *J Child Psychol Psychiatry*. 2006; 47:313–337
- Ginsburg S, Foster S. *Strategies to Support the Integration of Mental Health into Pediatric Primary Care*. Washington, DC: National Institute for Health Care Management. 2009. <http://nihcm.org/pdf/PediatricMH-FINAL.pdf>. Accessed November 18, 2014
- Knapp P, Mastergeorge AM. Clinical implications of current findings in neurodevelopment. *Psychiatr Clin North Am*. 2009;32:177–197
- Sameroff AJ, ed. *The Transactional Model of Development: How Children and Contexts Shape Each Other*. Washington, DC: American Psychological Association; 2009

## Chapter 200 SYNCOPE

Prema Ramaswamy, MD

### DEFINITION

Syncope, defined as a transient sudden loss of consciousness and postural tone, is a fairly common complaint in children, particularly adolescents. Pre-syncope is the presence of sensory and postural impairment without the actual loss of consciousness. The origin of the word *syncope* is a Greek term meaning *to cut short* or *interrupt*. Regardless of the underlying disorder, syncope is caused by interruption of essential energy substrates to the brain, usually from a transient reduction in cerebral blood flow. In children and adolescents, syncope is most often benign; however, in rare cases, it can be a first signal of potential sudden death, and hence identifying patients at risk is critical. Even when the cause is benign, syncope can result in injury, and it certainly provokes anxiety.

Although the exact incidence of syncope in children is not known, it affects 3.5% of the general adult population. Almost one-third of these adults will have recurrent syncope. The corresponding numbers for children are not known, but recurrence seems to be less common in childhood.

### CAUSES OF SYNCOPE

The most common cause of benign syncope is neurocardiogenic or vasovagal syncope, also termed the common faint, church faint, reflex syncope, or neurally mediated syncope (NMS). Another common cause of benign syncope is orthostatic hypotension. Together, these 2 causes are even more common in adolescents than in adults, and account for almost 80% of all cases. Both causes are more common during adolescence than at any other time in childhood. Syncope is also common in children from 6 months to 3 years of age, when breath-holding spells are prevalent. In particular, children with the pallid type of breath-holding spell have an increased risk for NMS as adults. Syncope that is not benign can stem from cardiac, neurologic, metabolic, and psychiatric causes. Box 200-1 lists the causes of syncope.

### Neurally Mediated Syncope

Naturally mediated syncope is classified into 3 types

1. *Central syncope* occurs in response to strong emotional stimulation such as pain, anticipated pain, or the sight of blood. In susceptible individuals, emotional stimulation can activate ill-defined areas within the central nervous system that, in turn, trigger sympathetic inhibition and parasympathetic activation.
2. *Postural syncope* is associated with the upright position, typically developing while the person is standing or walking. It is the most common type of NMS, much more frequent than central or situational syncope.



**BOX 200-1 Causes of Syncope****NEURALLY MEDIATED SYNCOPE**

- Emotional
- Postural
- Situational
  - Deglutition syncope
  - Micturition syncope
  - Weight-lifter's syncope
  - Defecation syncope
  - Carotid sinus hypersensitivity
  - Hair-grooming syncope

**ORTHOSTATIC HYPOTENSION**

- Primary
- Drugs
- Pregnancy
- Adrenal insufficiency
- Systemic mastocytosis
- Familial dysautonomia
- Postural orthostasis tachycardia syndrome

**BEHAVIORAL OR PSYCHIATRIC**

- Hyperventilation
- Hysteria, conversion reaction
- Breath-holding spells
- Cyanotic
- Pallid infantile syncope

**NEUROLOGIC**

- Seizure
- Migraine

- Trauma, concussion
- Narcolepsy

**CARDIAC**

- Structural abnormalities
  - Aortic stenosis
  - Hypertrophic cardiomyopathy
  - Tetralogy of Fallot
  - Pulmonic stenosis
  - Primary pulmonary hypertension
  - Coronary artery abnormalities
  - Marfan syndrome
- Arrhythmia
  - Bradycardia
  - Sick sinus syndrome
  - Atrioventricular block
  - Supraventricular tachycardia
  - Ventricular tachycardia, fibrillation
    - Myocarditis, pericarditis
    - Postoperative cardiac surgery
    - Prolonged QT syndrome

**METABOLIC**

- Hypoglycemia
- Anemia

3. *Situational syncope* occurs after the specific stimulation of sensory or visceral afferents, resulting in hypotension and then syncope. Examples include syncope evoked by the hypersensitivity of carotid baroreceptors, micturition syncope, defecation syncope, hair-grooming syncope, swallow syncope, cough syncope, and weight-lifter's syncope, all of which have been described in teenagers but are much less common than in adults.

**Pathophysiologic Features**

Although the pathophysiologic mechanism of NMS continues to be debated, investigators think it occurs in persons with a predisposition when they experience peripheral venous pooling and a fall in venous return. An increase in catecholamine release follows as a compensatory mechanism. The primary abnormality in patients who faint is unclear but may include  $\beta$ -adrenergic hypersensitivity, resulting in a relatively empty hypercontractile heart. Cardiac mechanoreceptors are stimulated, producing the Bezold-Jarisch reflex—a vagal response that includes sinus bradycardia, hypotension, and peripheral vasodilation. The syncope is termed *vasodepressor* if the more prominent element is hypotension, and *cardioinhibitory* if

bradycardia is more prominent. In most instances, the syncope is mixed, with both hypotension and bradycardia.

**Clinical Manifestations**

In NMS of childhood, loss of consciousness is typically preceded by light-headedness, nausea, yawning, a feeling of being hot, and sounds seeming distant to the ear. Typically brief (from a few seconds to 1 or 2 minutes), the loss of consciousness is most often brought about by pain or by prolonged standing, especially in warm environments such as in a crowded room or in a hot shower. Occasionally, the cause is not identifiable. Symptoms characteristically appear after the person has been upright for at least a few minutes, in contradistinction to the patient with orthostatic hypotension, whose symptoms occur within seconds of standing.

**Orthostatic Hypotension**

Orthostatic hypotension is the fall in blood pressure after assuming the upright position. The autonomic nervous system provides the principal responses to changes in position. When a person stands, cardiac output and cerebral perfusion are maintained by a

combination of pumping action of skeletal muscles, venous valves, and carotid baroreceptor-mediated arterial constriction and cerebral autoregulation. If these mechanisms are unable to maintain the blood pressure, then the decrease in the pressure in the carotid sinus leads to reduced afferent traffic in the carotid sinus and thus to an increase in the heart rate. The compensatory increase in heart rate is inadequate in patients with orthostatic hypotension, and symptoms of weakness and light-headedness develop, typically within seconds of standing. The sinus tachycardia of orthostatic hypotension sets this type of syncope apart from NMS, during which bradycardia is a prominent sign.

Volume depletion from any cause, but in children most often from vomiting and diarrhea, will exacerbate orthostatic hypotension. Drugs that cause vasodilation and diuretics can also stimulate orthostasis.

Pregnancy should always be considered when a woman of childbearing age faints; pregnancy-associated fainting results from increased estrogen and progesterone levels that cause decreased peripheral vascular resistance and hypotension.

In the past few years, an entity called the postural orthostasis tachycardia syndrome (POTS) has been described. The diagnosis of POTS requires orthostatic heart rate acceleration in excess of 120 beats per minute or an absolute increase of 30 beats per minute or greater in the absence of significant orthostatic hypotension. Two forms have been identified. In the more common peripheral variety, persistent tachycardia, associated with fatigue, exercise intolerance, and palpitations, is present while the patient is upright. The onset may occur after a viral illness, trauma, or surgery. The second type of POTS, the  $\beta$ -hypersensitivity (or central) form, is often associated with migraines, tremor, and excessive sweating. Both forms are more common in young women, and treatment can be frustrating.

Familial dysautonomia, an inherited autosomal recessive condition with abnormalities of the autonomic nervous system, is a rare but serious cause of orthostatic syncope, with affected patients at risk for sudden death.

### Behavioral or Psychiatric Causes of Syncope

#### Breath-holding Spells

Two types of breath-holding spells typically occur in children between 6 months and 3 years: cyanotic and pallid. In the former, an episode of cyanosis and apnea is precipitated after a child is upset and begins to cry. Stiffening of the body and a loss of consciousness may soon follow. Although the pathophysiologic basis is unclear, crying during expiration may cause increased intrathoracic pressure, which, in turn, leads to low cardiac output. Hypoxia combined with decreased cerebral blood flow leads to the loss of consciousness. The event is brief, and afterward, the child becomes fully conscious. Pallid breath-holding spells (pallid infantile syncope) are less common and usually begin with sudden pain. The mechanism differs in that the child suddenly becomes pale and limp and loses consciousness. The pathophysiologic basis is increased vagal tone, which

causes an apparent asystole. The event ordinarily lasts only seconds to minutes, and the child awakens to full consciousness (also see Chapter 201, Temper Tantrums and Breath-Holding Spells).

#### Hyperventilation

Another benign cause of syncope, hyperventilation is frequent among adolescents, especially in the presence of anxiety. The hyperventilation results in the washing out of carbon dioxide, and the resulting hypocapnia causes reduced cerebral blood flow, dizziness, and syncope. Classically, hypoventilation is also associated with numbness and paresthesia of the hands and feet.

#### Psychiatric Syncope

A child with hysterical syncope is likely to be unusually calm. No autonomic effects such as change in heart rate or blood pressure are noted during the episodes, which tend to be recurrent and frequent and to occur in front of an audience. Recovery of consciousness is often prolonged, and no injury is usually sustained.

#### Cardiac Syncope

Syncope can result from a low cardiac output secondary to either a structural problem or a dysrhythmia, and the abnormal rhythm underlying the syncope may be either too slow or too fast.

#### Bradyarrhythmias

Sick sinus syndrome is extremely rare in a child with a normal heart and is usually seen after extensive surgery in the atria with the Senning and Mustard operations, performed for transposition of the great arteries. Patients who have undergone the Fontan procedure for a single ventricle may also be at risk secondary to atriotomies and dilated atria.

#### Atrioventricular Block

Very slow heart rates from atrioventricular (AV) block can lead to syncopal episodes termed *Stokes-Adams attacks*. Congenital AV block in the presence of a structurally normal heart is most commonly associated with a history of systemic lupus erythematosus in the mother. The structural heart disease, which is most commonly associated with congenital AV block and has an ongoing risk for acquired AV block, is corrected transposition of the great arteries. AV block is also occasionally acquired after cardiac surgery or Lyme disease.

#### Pacemaker Malfunction

In any child with a pacemaker, syncope should prompt immediate interrogation of the pacemaker for either a malfunction or inappropriate programming.

#### Tachyarrhythmias

##### Supraventricular Tachycardia

Most children with supraventricular tachycardia have a structurally normal heart, and in those children, palpitations and dizziness are more common symptoms

of supraventricular tachycardia than syncope. However, with a structural abnormality resulting in reduced hemodynamic reserve, as with a single ventricle, syncope may be a presenting feature. In patients with congenital heart defects, Wolff-Parkinson-White syndrome is most often seen in children with disorders of the AV fibrous valve annuli such as Ebstein disease and corrected transposition of the great arteries.

### **Ventricular Tachycardia**

Although ventricular tachycardia (VT) is rare in children, it can cause sudden death; early identification of underlying conditions that predispose to VT can be lifesaving. Prolonged QT syndrome is one such condition in which patients are at risk for sudden death secondary to a polymorphic VT termed *torsades de pointes*. The prolongation of the QT interval may be part of a congenital syndrome such as Romano-Ward syndrome, which is autosomal dominant, or Jervell and Lange-Nielsen syndrome, which is autosomal recessive and associated with congenital neural deafness. Both syndromes are caused by mutations in genes encoding cardiac ion channels. Prolonged QT also may be caused by electrolyte imbalances, such as hypokalemia or hypocalcemia, and by a variety of drugs, such as tricyclic antidepressants, certain macrolide antibiotics, and antiarrhythmic medications. VT can also occur in children as a complication of myocarditis or in adolescents with tetralogy of Fallot who have undergone surgical repair in infancy.

### **Structural Heart Disease**

An acute reduction in cardiac output can result in reduced cerebral perfusion and syncope. With certain heart conditions discussed later, patients may be able to maintain an adequate cardiac output at rest but experience syncopal episodes with exercise.

### **Aortic Stenosis**

An impediment to the forward flow of blood from marked left ventricular hypertrophy, stimulation of the ventricular mechanoreceptors resulting in systemic vasodilation, and subendocardial ischemia causing a ventricular arrhythmia are all mechanisms that may contribute to syncope in children with severe aortic stenosis.

### **Hypertrophic Cardiomyopathy**

Syncope with exercise may be an important presenting sign of hypertrophic cardiomyopathy. Most affected patients have no left ventricular obstruction at rest; however, with exercise, they can develop a dynamic gradient with an acute reduction in cardiac output. In addition, these patients may develop VT from subendocardial ischemia. The electrocardiogram is frequently abnormal, and an echocardiogram is diagnostic.

### **Tetralogy of Fallot**

Children with unrepaired tetralogy of Fallot may have syncopal episodes in association with hypercyanotic *tet* spells, often precipitated by crying, straining with a bowel movement, or awakening from sleep.

### **Pulmonary Hypertension**

With exertion, children with pulmonary hypertension may experience syncope from the inability to maintain transpulmonary flow.

### **Coronary Artery Abnormalities**

A patient with syncope who is demonstrated to have a coronary artery aberrant either in its origin or course should be presumed at risk for sudden death. Typically, syncope occurs with exercise. Acquired abnormalities of the coronary arteries include coronary artery aneurysms and stenosis caused by Kawasaki disease in early childhood. Cocaine use can cause acute coronary vasoconstriction and ventricular arrhythmias, with consequent syncope.

### **Neurologic Causes of Syncope**

#### **Seizures**

Typically, generalized seizures are preceded by a prodrome and include tonic-clonic activity with loss of consciousness and a period of confusion and lethargy after recovery. However, atypical seizures can occasionally be difficult to differentiate from the benign forms of syncope. Loss of consciousness occurring in the recumbent position is more likely to be from a seizure than from syncope, especially if the heart is normal. Pallor is seen more often in benign syncope, and flushing is more common with seizures. Bowel incontinence points toward a seizure.

#### **Migraine**

The primary care physician should always ask about migraine in a child who has a syncopal episode that does not fit the pattern of typical neurally mediated syncope, particularly if dizziness occurs in the sitting position and no other provoking factors can be elicited. A history of flashing lights, severe headache preceding the episode of syncope, and a family history of migraines usually help clinch the diagnosis.

#### **Head Trauma**

Brief loss of consciousness with head trauma is not uncommon and signals concussion.

#### **Metabolic Causes**

Hypoglycemia can cause syncope, most commonly in a child with diabetes on medication. Presyncopal symptoms such as weakness, a feeling of hunger, and confusion may be present, and the syncope is typically not brief. Dehydration and severe anemia also predispose to syncopal episodes.

## **EVALUATION**

### **History**

The history is the most important tool in the diagnosis of syncope. It should include a detailed inquiry into the exact circumstances surrounding the event, including the time of the day, presence of an upper respiratory infection, time since last meal, posture during syncope and time spent in this posture before syncope, presence of prodromal symptoms, duration of loss of consciousness, bystander testimony, and any headache or prolonged disorientation after syncope.

Inquiry should also include the circumstances precipitating the event. For example, with vasovagal syncope, the child often is standing in a warm, stuffy room and is hungry, tired, or frightened. The prodrome of a seizure may consist of an aura, whereas a cardiac event often occurs without warning or is induced by exercise. There may also be a history of palpitations just before the episode. The primary care physician should determine whether the child was completely unconscious or whether some degree of responsiveness was present, suggesting hysteria or malingering. A truly unconscious person will not respond if the eyelashes are lightly brushed; a hysterical person will respond, albeit often with just a mild flickering of the lids. Seizure-like movements are important; however, generalized tonic-clonic movements may be seen in any form of syncope. The duration of the episode should be estimated. In general, the conscious state is regained quickly in the case of vasovagal syncope (a few seconds to 1 or 2 minutes), whereas a seizure may last longer, and the postictal state may be characterized by prolonged confusion and fatigue.

A history of congenital heart disease, seizure disorder, or endocrine abnormality such as diabetes would obviously be important. Recurrent syncopal episodes are unusual and may require more extensive testing.

The family history may be helpful. Seizure disorders and cardiac disease leading to syncope (eg, Marfan syndrome, hypertrophic cardiomyopathy, prolonged QT syndrome) may be inherited in an autosomal-dominant fashion. Breath-holding spells can also have a familial pattern.

### Physical Examination

Examination of a patient with a history of syncope should begin with an assessment of the level of consciousness; a child who is not alert and oriented has not had a benign syncopal episode and needs immediate evaluation for potentially life-threatening causes. In most children who are fully alert after a syncopal episode, the findings on physical examination tend to be normal. The presence of a cardiac murmur may point to an obstructive lesion, such as aortic or pulmonic stenosis. Listening to the heart in both the supine and upright positions is important because a mild obstructive gradient in hypertrophic cardiomyopathy may become audible only when the patient is upright. The heart rate and blood pressure should also be obtained in both the supine and upright positions to ascertain the presence of orthostatic intolerance.

### Evaluation

#### Electrocardiogram

The only test indicated in most patients with a history typical for benign syncope is an electrocardiogram, which may reveal the presence of AV block or a dysrhythmia. Abnormally large left ventricular forces, especially with left ventricular strain, may be the only evidence of hypertrophic cardiomyopathy in a patient with normal findings on physical examination. The

corrected QT interval should be measured in all children with syncope or seizures as an initial screen for prolonged QT syndrome.

#### Holter and Event Monitor

A 24-hour electrocardiographic monitoring test is indicated only if a cardiac dysrhythmia is strongly suspected based on either prominent palpitations that occurred before the episode or the presence of cardiac surgical history that may predispose a child to abnormal rhythms. An event recorder is more practical because patients are able to keep the monitor for a month and use it at the time of their symptoms.

#### Echocardiogram

When a suspicion exists based either on history (eg, syncope with exercise) or examination of a structural cardiac lesion, an echocardiogram is indicated and can usually adequately demonstrate the origin and course of the coronary arteries.

#### Electrophysiologic Testing and Cardiac Catheterization

Electrophysiologic testing and cardiac catheterization must be considered for any patient who has had syncope during active exercise in whom a physical examination, electrocardiogram, and echocardiogram has failed to demonstrate an abnormality.

#### Tilt-table Testing

By creating an orthostatic stress, tilt-table testing can provoke symptoms in patients with NMS and orthostatic hypotension. Patients are placed supine on a table that has a foot board. The table is then tilted up between 60 and 80 degrees for 30 to 60 minutes. Patients are monitored closely for a syncopal episode. Some centers use low-dose intravenous isoproterenol infusions to increase the sensitivity of the test, which ranges from 30% to 80%, depending on the laboratory. The specificity of a negative test without isoproterenol ranges from 80% to 100%.

Although the utility of head-upright tilt-table testing in children is still controversial, it has become a means of provoking vasodepressor syncope in susceptible individuals after other more serious causes have been ruled out. Some indications for the use of this test include the following:

1. Three or more syncopal episodes during a 12-month period with no evidence of heart disease
2. Syncope during exertion in which heart disease has been ruled out after an exhaustive workup
3. Recurrent syncopal episodes thought to be hysterical in nature

### MANAGEMENT

The management of cardiac, neurologic, and psychiatric syncope depends on the cause. The management of NMS includes some of the following approaches.

#### Reassurance

The most important interventions for most patients who have NMS or orthostatic hypotension are reassurance and education regarding the cause of the



syncope and how to avoid aggravating factors (avoiding extreme heat and standing still for long periods). Patients should be instructed to sit down or lie down at the onset of any prodromal symptoms to avoid injury. Drinking fluids regularly and eating salty foods may be helpful in preventing episodes.

### Isometric Exercises

In a small randomized trial of adults, intense gripping of hands and tensing of the arms for 2 minutes at the onset of the tilt-induced symptoms raised systolic blood pressure. Syncope occurred in 37% of these patients compared with 89% of those who did not perform the maneuver. The value of *tilt training* is still controversial, but it may be helpful to some patients; they are instructed to stand with their backs against a wall, initially for short periods, and slowly increasing the duration to approximately 30 minutes per day.

### Volume Expansion

A reduced frequency of syncope in adolescents with neurocardiogenic syncope was reported after consuming 2 liters of water in the morning.

Fludrocortisone is a synthetic mineralocorticoid that causes salt retention and the expansion of the central blood volume. One randomized trial in adolescents showed similar results to atenolol, but no placebo was studied.

### Beta-blockers

Although beta-blockers have been used for many years as therapy for neurocardiogenic syncope, studies of their effectiveness have at best been equivocal.

### Investigational Agents

Midodrine is a direct  $\alpha_1$ -receptor agonist that has been shown to reduce episodes in adults with severely symptomatic neurocardiogenic syncope. Because serotonin may have a role in regulating the sympathetic nervous system activity, selective serotonin reuptake inhibitors have also been considered for treatment of NMS. In a trial in adults, paroxetine was shown to be superior to placebo.

### Cardiac Pacing

Currently, cardiac pacing has a very limited role in the management of syncope. In pediatrics, cardiac pacing has been used for children in whom asystole is the prominent symptom in recurrent syncope caused by vagal hypertonia, including some patients with deglutition syncope.

### WHEN TO REFER

- Patient history of cardiac disease
- Family history of sudden death, cardiac disease, or deafness
- Recurrent episodes
- Recumbent episode
- Exertional syncope
- Prolonged loss of consciousness
- Associated chest pain or palpitations
- Medications that can alter cardiac conduction

### TOOLS FOR PRACTICE

#### Medical Decision Support

- *Isometric Arm Counter-Pressure Maneuvers to Abort Impending Vasovagal Syncope* (article), *Journal of the American College of Cardiology*, Vol 40, Issue 11, 2002

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## Chapter 201

# TEMPER TANTRUMS AND BREATH-HOLDING SPELLS

Gregory E. Prazar, MD

### TEMPER TANTRUMS

Children exhibit temper tantrums almost inevitably during the second through fourth years of life. Therefore a temper tantrum is generally a *problem behavior* rather than a *behavioral problem*. Helping parents cope with temper tantrums involves providing anticipatory guidance, sharing information on developmental psychology, and offering strategies to deal with tantrums.

Temper tantrums usually become part of the child's emotional repertoire during the second and third years of life. Early signs of the negativism that is part of tantrums can be appreciated as early as 12 months of age. Some children continue to display occasional tantrums until the age of 5 or 6 years. Tantrums typically reappear in a slightly less intense form during adolescence, when independence once more becomes an issue for the developing adolescent.

Several aspects of the toddler's development seem to make tantrums almost inevitable. First, because the 1-year-old can walk and climb, the child begins to achieve physical mastery over the environment. This increased physical independence and an insatiable curiosity frequently place the child in dangerous situations that require parental intervention. Imposition of adult safety limits thwarts and frustrates the child, often precipitating tantrums. Second, the child's increased exploration of the environment immediately creates a conflict because the child must adapt to rules of an adult world. The child enters an environment of adult social values, in which people are expected to use the bathroom appropriately, verbalize dissatisfactions rather than *act* them out physically, sit quietly

while eating, and sometimes subjugate their own wants to those of others. This process is too much for the egocentric toddler to bear, and frustration is inevitable. Third, between the ages of 1 and 4 years, the toddler begins to develop an increased awareness of how the child is separate and different from the mother. The child experiences a conflict between desires for autonomy and desires to remain close to the mother. Frustration in dealing with these intense feelings frequently results in tantrums.

Tensions are created in “establishing ego boundaries as separate from those of parents,” as Brazelton states, and in coping with physical limitations placed on exploring an adult world. Adults frequently deal with their own tensions and frustrations by verbalizing their feelings; the toddler, however, lacks a sophisticated ability to verbalize. A toddler’s frustration with the adult world may be displayed in doing the exact opposite of what the adult requests, by saying “no, no” yet following through with the adult request (what Fraiberg refers to as the “cheerful no”), by dawdling, or by displaying physical behavior outright (eg, kicking, screaming, lying on the floor, hitting, throwing, biting).

Most parents would probably agree that intellectual appreciation of the cause of tantrums does not necessarily aid in coping with a screaming and inconsolable child. Reasons for parental frustration are understandable. Well-meaning relatives and friends (who have likely forgotten their experience as young parents) may propagate myths about tantrums, which intensify parental anxiety and confusion. Myths of causation suggest that children who display tantrums are underdisciplined or parented inadequately. Myths of management suggest that tantrums can be quelled by spanking, dousing with cold water, or threats.

## ANTICIPATORY GUIDANCE FOR TANTRUMS

The primary care physician should provide anticipatory guidance about temper tantrums. Such guidance may forestall events that precipitate tantrums and prevent future parental confusion in dealing with negative behaviors. The physician has many opportunities during the child’s first 2 years to provide behavioral counseling.

Beginning in infancy, parents should be provided with anticipatory guidance regarding opportunities for positive interactions with the child within daily routines and activities such as feeding, pretend play, and reading aloud. Howard and others have recommended “‘special time’ provided every day as an approach to formalizing time-in.”

At the 6-month well-child visit, the importance of parental time away from the infant can be emphasized. Parents who occasionally leave their infants and toddlers with responsible babysitters provide their children with the security that adults can leave and will come back; they also provide themselves with important mental health holidays from the rigors of parenting.

At the 9- or 12-month infant visit, environmental engineering should be discussed. Providing home safety (eg, safety plugs in outlets, safety latches on

drawers), removing valuables or breakables from the child’s reach, and ensuring a safe place for the child to play (playpen or enclosed area) are examples of such engineering. Therefore this visit not only may reduce chances for childhood accidents but also may forestall potential adult-toddler power struggles over environmental dangers.

The 15- or 18-month visit provides the physician another opportunity to offer the parent alternatives to negative interactions with the toddler. Afternoon naps (to allow for renewal of toddler and parental energy), the importance of praising cooperative toddler efforts, and the concept of limited decision making for the toddler (“Do you want to wear the green or blue shirt today?” versus “Which shirt do you want to wear today?”) represent issues that may help parents minimize hostile encounters with their toddler.

The approach here should encourage parents to describe how they think tantrums should be handled, and should not simply display the physician’s personal biases about child rearing. Several excellent books describing turbulent toddlerhood can be suggested to parents, including Brazelton’s *Toddlers and Parents*, Ilg and Ames’ *Child Behavior*, and Schmitt’s *Your Child’s Health*. Furthermore, general guidelines concerning tantrums can be given. Tantrums are best ignored unless, as Fraiberg states, “they encroach on rights of others or potentially endanger.” If safety is the issue, then either environmental engineering should take place or the child should be restricted to the child’s bedroom for 2 to 3 minutes (a kitchen timer is helpful to remind both parent and toddler of the time). If the child hits, bites, or throws in anger, then room restriction for 2 to 3 minutes should once again be suggested. Some behavioral psychologists suggest 1 minute of time out for each year of age (so a 5-year-old child would have a 5-minute time-out). Other behaviorists recommend that the time-out not be fixed. Because the goal is to help the child develop self-regulation, the time-out should end when the tantrum subsides. The child should receive a brief hug or be praised and then be allowed to resume previous activity.

Parents may be reluctant to use bedroom restriction because they worry either that the child will associate the bedroom with unpleasant experiences or that the child will not feel adequately remorseful if placed in a room full of toys. Parents should be reassured that room restriction does not cause bedroom fears. Similarly, goals of discipline are to teach rules and to help the child understand which behaviors are acceptable. Discipline does not need to be severe to be effective. The physician should emphasize to parents that once the tantrum is over, the slate is wiped clean and there is no holdover of judgment or anger, even if the child has acted out badly.

Time-outs are an effective method of dealing with temper tantrums. Time-ins represent a method to reward acceptable behavior. Specifically, when a toddler is playing quietly, the parent should pat the child on the shoulder, give a brief hug, or otherwise offer some form of nonverbal affection. Such attention from the parent simply but effectively indicates approval of the current behavior. Some behavioral psychologists

consider time-ins to be a more powerful method of encouraging acceptable behavior than time-outs.

Temper tantrums occur much more frequently in the presence of parents; they are much less common in the presence of alternative child care providers. Most experienced child care providers feel comfortable dealing with temper tantrums. If the child care provider expresses concern to a parent about a child's temper tantrums, then several questions should be considered. Does the child care provider have adequate training to deal with such a common behavior? Is this child care setting the most appropriate for the child (in terms of adult-child ratio, philosophy of discipline used by the provider, and realistic developmental expectations for the child's behavior in the child care setting)? Are the child's temper tantrums much more severe or frequent than those of the child's peers? These questions should be addressed with the child care provider. Subsequently, parents and the child care provider should formulate a plan for dealing with the tantrums that is followed consistently at home and at the child care location. If the parent and the child care provider cannot agree on such a plan, then the child's primary care physician should be consulted.

More specific guidelines for managing tantrums may be necessary in other individual situations. Parents should be encouraged by the physician to vent their feelings (to the physician) about tantrums and be reassured that they are doing the best job they can for their toddler.

## MANAGEMENT OF PROBLEM TANTRUMS

Although tantrums represent a stage of the normal developing toddler's personality, several factors may suggest that further professional intervention is advisable. An important aspect of management is obtaining a detailed history, including the circumstances in which tantrums take place, a specific description of the tantrums, and what happens following the tantrums. This is referred to as antecedent, behavior, and consequence or "A,B,C." Toddlers who display persistent negativism or tantrums may suffer from too restrictive parenting, may receive too little positive reinforcement and affection, or may have parents who place unreasonable behavioral expectations on them. One study of 3-year-olds defined severe temper tantrums as "episodes of shouting, banging, kicking, or screaming occurring 3 or more times a day or lasting more than 15 minutes." Approximately 50% of these children had behavior problems. Furthermore, such severe tantrums were associated with specific psychosocial issues, including maternal depression, use of corporal punishment, marital stress, and low maternal education.

Children who display tantrums regularly beyond 5 or 6 years of age may be displaying signs of depression or poor self-esteem, or they may be children who live in a family in which emotional problems exist. When temper tantrums regularly occur at school, academic problems should be suspected because peer pressure usually inhibits displays of tantrums.

Children exhibiting persistent tantrums along with other associated behaviors (eg, inability to

concentrate, stereotypical behaviors, unrealistic fears, inability to display affection) may have more significant underlying problems, such as attention-deficit disorder, oppositional defiant disorder, or autism spectrum disorder. Similarly, parents who verbalize persistent frustration with tantrums or an inability to cope with age-appropriate tantrums may need more comprehensive counseling than the primary care physician can provide.

Many parenting groups are available to help parents cope with negative behaviors. Programs such as Systematic Training for Effective Parenting (STEP) and Parent Effectiveness Training (PET) provide valuable community referral sources for families. If such services are not available, or if more sophisticated professional counseling is obviously warranted, then the family should be referred to a psychiatrically trained counselor.

Referral should be discussed as soon as the physician anticipates its necessity and should stress the involvement of both parents. The physician should maintain contact with the family about the problem after the referral has been made. Such ongoing contact may solidify the family's commitment to obtain and adhere with the counseling.

## BREATH-HOLDING SPELLS

Breath-holding spells cause particular anxiety for parents. Spells occur between ages 4 months and 5 years, with most occurring between 12 and 36 months of age. According to Menkes, approximately 5% of all children display breath-holding spells. A positive family history of breath-holding spells occurs in approximately 25% of cases.

Such spells are precipitated by anger, frustration, fear, or minor injury (often a very minor head injury) and are categorized as cyanotic or pallid. Both types of spells are unlikely to occur more often than once a day and are not associated with an increased predisposition to epilepsy (although brief seizure-like activity can occur as a terminating event in either form of spell).

Cyanotic breath-holding spells are precipitated more often by anger or frustration than by fear or injury. The child emits a short, loud cry, takes a deep breath, and holds it. Cyanosis occurs after approximately 30 seconds. Either the episode terminates at this point or the child becomes rigid or limp and loses consciousness (loss of consciousness occurs in approximately 50% of all children who have breath-holding spells). In rare situations, mild clonic movements of the extremities follow.

Pallid breath-holding spells are similar to cyanotic spells in most respects but are more often precipitated by fear or minor injury. The initial cry is brief or silent. The spell then proceeds as with a cyanotic spell. Toddlers who suffer from pallid spells are often from families that have a history of syncope, and, in fact, these toddlers have an increased chance (approximately 15%) of syncopal attacks as adults.

Both cyanotic and pallid breath-holding spells are caused by autonomic nervous system dysregulation. Cerebral anoxia is responsible for spells that terminate with loss of consciousness. Furthermore, both

forms of spells are involuntary and reflexive, despite spells often being precipitated when the child is angry or frustrated.

Children who display pallid breath-holding spells may, as adults, suffer from neurocardiogenic syncope, a form of vasovagal response to postural changes. Adults who suffer from neurocardiogenic syncope are more likely to faint at the sight of blood or when injured than are adults who do not have this disorder.

Because both forms of breath-holding spells potentially can terminate with seizure-like movements, differentiation between spells and epilepsy is important. The occurrence of a precipitating factor (eg, minor injury, being frustrated) before the onset of the spell indicates that the episode is a breath-holding spell. Patients who have epilepsy display cyanosis during or after the seizures, not before seizure onset. Furthermore, electroencephalograms performed on patients who suffer from breath-holding spells are normal when not holding their breath; patients who have epilepsy often have abnormal electroencephalograms during seizure-free periods.

## MANAGEMENT OF BREATH-HOLDING SPELLS

No effective medical therapy exists for breath-holding spells, although some toddlers who experience seizure-like activity along with spells are prescribed anticonvulsant therapy. However, the decision to use medication remains controversial among pediatric neurologists.

Iron deficiency anemia has been associated with breath-holding spells. A study involving 67 children who had breath-holding spells revealed that iron therapy reduced spells in the treatment group by 88%. These results suggest that iron may be important in the regulation of the autonomic nervous system.

Coping with breath-holding spells can be extremely difficult for parents. Spells that terminate with loss of consciousness or with seizure-like movements are obviously frightening. Convincing parents that no harm will come to their child is important. Nevertheless, parents of a breath holder will frequently avoid enforcing limits for fear of precipitating the child's anger and a subsequent attack. Such parents need repeated reassurance and encouragement to continue age-appropriate limits on their child's behavior. To do otherwise will create an overindulged child who subsequently may fear loss of parental love because limits have been rescinded.

When to refer a breath-holding patient to a neurologist or a psychiatrically trained professional may not be an easy decision for the physician. If parents request further consultation, then their wish certainly should be respected, even if the physician is confident that further evaluation is unnecessary. If parents indicate agreement with the physician that spells are of no consequence yet continue to withhold appropriate limit setting, then referral to a mental health professional should take place. The physician who is unsure of the diagnosis of breath-holding (especially in situations in which loss of consciousness or seizure-like activity occurs) should always refer the family to a pediatric

neurologist. Referral must not end the physician-parent communication concerning the spells: an ongoing dialogue may ensure adherence with the referral.

## SUMMARY

Temper tantrums and breath-holding spells usually represent benign forms of childhood behavior evolving from the child's preverbal attempts to express feelings of frustration and anger. Unfortunately, parents frequently have difficulty appreciating the benign course of such behaviors when they daily must face a screaming, inconsolable toddler who may even lose consciousness and then display seizure-like movements. Parents can best deal with negative behaviors when they are adequately prepared by the physician before such behaviors occur and when they are offered empathic guidance and positive reinforcement during regular office visits.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Caring for Your Baby and Young Child: Birth to Age 5* (book), American Academy of Pediatrics (shop.aap.org)
- *Temper Tantrums: A Normal Part of Growing Up* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Top Tips for Surviving Tantrums* (Web page), American Academy of Pediatrics (www.healthychildren.org/English/family-life/family-dynamics/communication-discipline/Pages/Temper-Tantrums.aspx)

## SUGGESTED READINGS

- American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health. Guidance for effective discipline. *Pediatrics*. 1998;101:723-728
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## Chapter 202 TICS

Robert A. King, MD

*Tics*, which are recurring, nonrhythmic, sudden, rapid, stereotyped, involuntary movements or vocalizations, may be classified as motor or vocal and as simple or complex. The most common *simple motor tics* are eye blinking, neck twisting, shoulder shrugging, and grimacing; the most common *simple vocal tics* are coughing, throat clearing, sniffing, and grunting. *Complex motor tics* include more sustained, orchestrated, or



seemingly purposeful gestures, such as touching, stomping on, or sniffing objects; jumping; sustained dystonic movements; copropraxia (obscene gestures); or echokinesis (automatic imitation of another person's movements). *Complex vocal tics* include sudden changes in volume or prosody; syllables, words, or stock phrases spoken out of context; palilalia (repeating one's own words); echolalia (repeating the words of others); and coprolalia (uttering obscenities).

Tic disorders are model neuropsychiatric conditions demonstrating the complex interplay of genetic, neurobiological, environmental, and psychosocial factors. That is, they have a constitutional, probably genetic basis; are influenced by perinatal risk and environmental factors; demonstrate sexual dimorphism; show a changing course over development; and, although neurobiologically determined, can be affected by psychosocial factors, such as stress and cognitive behavioral interventions.

## CLINICAL MANIFESTATIONS

The most common age at onset for tics is 6 or 7 years. The usual initial motor tics are blinking or facial grimacing, with subsequent rostral-caudal involvement. The most common initial vocal tics are sniffing, coughing, and throat clearing. Not surprisingly, these symptoms are often initially mistaken for allergies or otolaryngologic or respiratory symptoms; but with tics, the other characteristics of such disorders are absent. Characteristically, tics wax and wane in intensity and frequency, with a tic disappearing only to have new ones take its place. Stress or excitement often exacerbates the tics.

Although children are generally unaware of their tics, premonitory urges are often reported in more severe cases or in older children. Tics are often transiently suppressible with effort, usually resulting in an increased urge to perform the tic. Many patients describe their tics as neither fully voluntary nor involuntary; some experience the effort to suppress tics in social situations to be as burdensome as are the tics themselves.

## INCIDENCE

It once was believed that *Tourette syndrome* (TS) was rare, persistent, severe, and disabling. It is now clear that tic disorders, including TS, exist on a clinical spectrum from transient, isolated, inconsequential tics to more persistent multiple motor and vocal tics that interfere with daily functioning. Isolated and transitory tics are common (occurring in as many as 24% of first- and second-graders) and of minimal consequence. Depending on ascertainment methods, childhood prevalence of TS is thought to be 2 to 185 per 10,000—much higher than previously believed, with many milder, uncomplicated cases not coming to clinical attention. Boys are affected more than girls, by a ratio as high as 9:1 to 14:1 in TS.

## ETIOLOGY

The cause of tics is unknown, but neurobiologic and behavioral research shows the boundaries between psychiatric and neurologic domains to be poorly

defined and increasingly obsolete. Most of this research has been on TS rather than on milder forms of tic disorder. Areas of interest have been basal ganglia and cortico-striatal-thalamo-cortical circuitry, genetics, and immunology. A multifactorial etiology for TS, with a convergence of genetic vulnerability, environmental and perinatal risk factors, and disturbances in the prefrontal cortex and basal ganglia, has been proposed. Several factors have been shown to be associated with tics and may give clues to their cause.

### Developmental Stage

Tics usually have their onset between 5 and 10 years of age, most commonly at 6 or 7 years. Although fluctuating in intensity from hour to hour and day to day, tics are usually at their most severe at around 10 to 13 years of age. Approximately 70% to 80% of the time, tics spontaneously diminish in severity during the course of adolescence and disappear or become minimal by young adulthood. Comorbid conditions, however, such as obsessive compulsive disorder (OCD), attention-deficit/hyperactivity disorder (ADHD), and anxiety disorder, may persist. The factors associated with spontaneous improvement or remission remain unclear and are important areas of research.

### Sex

Transient tics as well as chronic tic disorders are more common in boys than in girls. Androgens are implicated for multiple reasons—postnatal exposure to androgens may elicit TS; antiandrogen therapy may improve tics; and androgen-dependent alterations in prenatal brain development may be associated with TS.

### Prenatal, Perinatal, and Postnatal Factors

Factors that have been associated with tic severity also have been associated with other neuropsychiatric symptoms and disorders, such as hyperactivity; in particular, prenatal factors, such as maternal smoking, vomiting, psychosocial stress, drug use, fetal nutrition, and androgen exposure, and perinatal factors, such as low birth weight.

Experts have proposed that, in some cases, the acute onset of tics represents a form of pediatric autoimmune neuropsychiatric disorder associated with *Streptococcus* (PANDAS). This controversial hypothesis posits that group A  $\alpha$ -hemolytic streptococcal infection can cause an autoimmune reaction that attacks the basal ganglia, resulting in tics, OCD, or both. Despite much ongoing research, this hypothesized autoimmune condition remains unproven. In the absence of a biological marker, distinguishing which cases might represent true PANDAS as opposed to the non-specific coincidental occurrences of 2 common childhood conditions (streptococcal pharyngitis and tics or OCD) is difficult, at least at the onset. In one large study, children subsequently diagnosed with de novo tic disorder were found to have a greatly increased rate of streptococcal infections in the months before diagnosis.

Pending further research to clarify this matter, some primary care physicians have chosen to obtain

throat cultures from children with sudden onset or exacerbations of tics and from children with tics or OCD who have pharyngitis or who are exposed to *Streptococcus*. Children with positive throat cultures should receive appropriate antibiotic treatment. There is no established role for repeat posttreatment cultures to prevent streptococcal carrier states, nor does the use of prophylactic antibiotic treatment have any firm basis in evidence. Plasmapheresis or intravenous immunoglobulin therapy are only suitable in intractable cases as part of an approved investigational protocol.

### Psychological Factors

Anxiety, stress, and excitement can all exacerbate tics. Little is known about the psychological status of most children in the general population who have tics, because they are rarely seen in clinics. However, evidence exists for increased autonomic lability in individuals with TS, and children who have anxiety disorders are overrepresented in clinical samples.

### Psychiatric Disorders

Population and clinical studies of tics point to a strong relationship, most marked in TS, between tics and ADHD.

A relationship also exists between tics (especially in TS) and OCD, with symptoms (eg, premonitory urges, intrusive thoughts, compulsive actions), putative anatomic locus (cortical, striatal, or thalamic circuits), hypothesized pathophysiologic features (rogue reverberating microcircuits), and family pedigrees all showing elements in common.

Tics should never be assumed to indicate another psychiatric disorder or psychological problem unless they are associated with other signs or symptoms that affect other areas of function beyond the motor system. Although tics can be controlled to some degree in public situations (eg, school or a physician's office), an affected child should not be expected to control them most of the time. Such control requires considerable mental energy and effort and usually cannot be sustained for long. As soon as the child relaxes, is distracted, or lets up concentration, the tics will reappear.

### Genetic Factors

Many cases of tics, especially TS, appear to be genetic in origin. Mild and transient cases of tic disorder may coexist in the same pedigree as cases of TS, suggesting that protective and risk factors also exist. Even with monozygotic twins, the concordance rate is only 77%, which suggests that environmental factors (eg, low birth weight) also play a role. Although specific genes have been identified in a handful of pedigrees, the condition may well be heterogeneous (ie, different specific genes may be responsible in different pedigrees) and perhaps polygenic (ie, reflecting the interaction of multiple vulnerability loci). Penetrance increases if OCD is accepted as an alternative expression of the gene.

### Drugs

Amphetamine and other dopaminergic drugs induce stereotypies in rats and occasionally produce or

exacerbate tics in children. Cocaine, other stimulants, sympathomimetics, caffeine, serotonin uptake inhibitors and other antidepressants, and anabolic steroids may also produce or exacerbate tics.

## DIFFERENTIAL DIAGNOSIS

Tics are usually distinguishable from other neurologic disorders by their stereotyped nature, variability over time, transient suppressibility, accompanying premonitory urges, and lack of other neurologic symptoms. The differential diagnosis includes dystonia, myoclonus, chorea, seizures, athetosis, and stereotypies.

Tics are distinguishable from *chorea* (with which they are often confused) by their centripetal location, repetitive form, normal muscle tone, and lack of postural impersistence; and from most other neurologically based abnormal movements by their rapidity and normal muscle tone. Even so, tics rarely reflect or portend a neurologic disorder. Such tics are likely to be much more persistent and accompanied by signs of the disorder that causes them.

A more difficult diagnostic quandary in young children is distinguishing true tics from stereotypies or self-stimulating behaviors, such as rocking, head banging, flapping, or spinning. Tics are characterized by a later onset, lower complexity, fluctuating intensity and locus, and their intrusive, bothersome, disruptive, and involuntary nature. In contrast, stereotypies are most often bothersome to parents but not to the child, who may find them pleasurable and resist adult attempts to interrupt them. Self-stimulating movements mostly occur at times of boredom or excitement, but they rarely disrupt coordinated movements, and they persist without much change in form or anatomical location. Although stereotypies are often associated in many physicians' minds with intellectual disability or autism spectrum disorders, in fact they can also occur in children who are otherwise developmentally normal (see Chapter 192, Self-stimulating Behaviors).

The most recent edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* distinguishes 3 arbitrary subtypes of tic disorder: *provisional* (present for less than 1 year since first tic onset); *persistent (chronic)* (motor or vocal tics, but not both, that have persisted longer than 1 year since first tic onset); and *Tourette disorder*, also known as Tourette syndrome (multiple motor and at least one vocal tic, not necessarily concurrently, persisting at least 1 year from first tic onset). Whether these 3 classifications reflect varying severity of the same disorder is unknown. Most recent research has been restricted to TS but suggests that these subtypes are probably related.

## COMORBID DISORDERS

Persistent tics, even mild ones, seem to be associated with an increased risk of comorbid ADHD, which predates the tics or any accompanying OCD. This association is not simply the result of the bias toward comorbidity in clinical sample populations because it is also found in community sample populations. In

addition, many youngsters with TS whose concentration is basically good can become distracted and lose focus when their tics are in a period of exacerbation, presumably because of the tics themselves and the impingement of tic urges and efforts to suppress them.

Individuals with TS are also at risk for other anxiety disorders, depression, fine-motor difficulties, and uneven cognitive profile (performance IQ scores lower than verbal IQ scores). ADHD is common (present in 50% of patients with TS), and children with combined ADHD and tics have the greatest social and academic difficulties. ADHD severity is a better predictor of poor adjustment than tic severity. Although the presence of ADHD with tics increases the likelihood of disruptive behavior and learning problems, chronic tics are often associated with learning impairment independent of ADHD. Investigations of both community and clinical sample populations confirm that the presence of ADHD predicts greater disability than that associated with tic disorders alone.

OCD is found in up to 50% of patients with TS, with compulsions and obsessions most commonly involving symmetry, evening up, *just right* phenomena, sex, and aggression.

## TREATMENT

Most tics in children are mild and short lived and require no treatment. A careful clinical evaluation is needed to assess not only the current phenomenology, history, and effect of the tics, but also the presence of other symptoms (anxiety, impulsivity, inattention) or adaptive difficulties in the overall context of the child's social, family, and school life.

Once a tic has persisted for several months, treatment may be considered, but only if the tic is conspicuous, disabling, or distressing to the child. No treatment for tics can be said to be simple, entirely effective, or free from side effects. Treatments shown to have some limited efficacy are discussed in the following sections.

### Behavioral Methods

Although a variety of behavioral techniques (eg, relaxation, massed practice) have been tried for tic disorders, only comprehensive behavioral intervention for tics (CBIT) seems to have good empirical support. As the name conveys, CBIT is an effective evidenced-based behavioral approach to tics that combines habit reversal and contingency management techniques. Habit-reversal therapy is best carried out by a physician who is experienced in the technique and who is accustomed to working with children. Cognitive behavioral interventions may also be helpful for youngsters whose tic disorder is accompanied by disruptive behavior and explosive outbursts.

### Anxiety-Reducing and Supportive Procedures

Relaxation training and biofeedback are not of proven value in treating tics. Psychotherapy (specifically focused on stressful interpersonal difficulties), work with parents, and other means of addressing environmental stresses may be helpful, not because stress causes tics,

but rather because stress and high expressed emotion can exacerbate tics. These procedures should not be considered specific; rather, they are ancillary and holistic in meeting therapeutic objectives.

Many youngsters with tic disorders have difficulties at school, either from comorbid ADHD or an uneven neuropsychological profile, or difficulties with peer stigmatization. Close collaboration with school staff to ensure appropriate educational programming and accommodations is important.

### Acceptance

In most cases, the best management is explaining to parents, teachers, and peers that the tics are a physical disability, that the child cannot help them, and that acceptance of both child and tics is the kindest, safest, and simplest way to deal with them. Criticizing and belittling the child are likely to make tics worse and prolong their course. Peer problems can be a major difficulty for children with tics and TS, and collaboration with school staff to reduce peer teasing and stigmatization is a major therapeutic task. Helping to support and build upon the child's strengths is an important component in bolstering and protecting the child's self-esteem. In emphasizing that children cannot help their tics, the physician and parents should avoid the pitfall of concluding that the child cannot help other problematic behaviors related to impulsivity, for which consistent structure, expectations, and consequences are desirable and beneficial.

### Pharmacotherapy

Only physicians thoroughly familiar with the drugs indicated and experienced in their use in children with tics should undertake pharmacotherapy. The first consideration is deciding which symptom to target: the tics themselves or 1 of the common comorbid symptoms or conditions, such as OCD or ADHD, which are often a greater source of impairment.

### Pharmacotherapy for Tics

Various medications are effective in partially suppressing tics, but they are not curative in terms of affecting the underlying course or prognosis of tics. Furthermore, because of frequent side effects (especially sedation), medication should be administered only if the tics are significantly bothersome, disruptive, stigmatizing, or painful. The first mandate is to do no harm. In the case of tics, this approach means starting with low doses, titrating the dose upward only gradually, and avoiding sedation, cognitive blunting, or other distressing side effects (eg, acute dystonic reactions) that may be more burdensome than the tics themselves. Setting realistic goals in terms of reducing tics to tolerable levels is important; attempts to suppress tics completely often result in overmedication. Discontinuing anti-tic medications should be done gradually, because even when medications seem ineffective, abrupt discontinuation may produce bothersome acute rebound or withdrawal-related exacerbation of tics that may persist for several weeks.

Many physicians' first choice of anti-tic medication, especially in children with comorbid ADHD, is 1 of the



$\alpha$ -adrenergic agonists, clonidine or guanfacine. Although these agents are less potent and are effective in fewer patients with severe tics than the neuroleptics, they tend to have fewer and less severe side effects, with the principal dose-related side effects being sedation and hypotension. They are, however, potentially fatal in overdoses. Guanfacine, when available, is the preferred first choice because it is longer acting and less sedating than clonidine, and it seems to be more effective for attentional problems. Although sustained-release forms of both clonidine and guanfacine are available, it is usually preferable with younger children to begin on smaller doses of the short-acting form, titrating slowly with only small-dose increments to avoid sedation.

If the  $\alpha$ -adrenergic agents are not effective or if the tics are severe, then the next line of agents is the dopamine-blocking neuroleptics, now known as antipsychotic drugs. These agents seem to be effective because tics, whatever their cause, are executed through the basal ganglia, with an apparent relative overactivity in the dopaminergic nigrostriatal systems that inhibits cholinergic basal ganglia systems. However, the neurochemistry of tic disorder is complex and probably involves several neurotransmitter systems; therefore, inferring underlying deficits from the observed therapeutic effectiveness of various agents is difficult.

Of the traditional *typical* so-called *high-potency* (ie, nonatropinic) neuroleptics, haloperidol, pimozide, or fluphenazine have been shown to be effective, but have largely been replaced in clinical practice by the newer, so-called atypical antipsychotics. As with several of the other typical neuroleptics (eg, ziprasidone), caution must be exercised with pimozide in terms of cardiotoxicity and drug interactions, especially with drugs such as erythromycin that are metabolized through the cytochrome P450 3A4 isoenzyme system, because fatal drug interactions can result. Monitoring the QTc interval at baseline and with dose increases is prudent in patients receiving pimozide or ziprasidone. Even at relatively low doses, neuroleptics may produce acute dystonic reactions, sedation, cognitive blunting, medication-induced separation anxiety, parkinsonism, akathisia (restless legs), and, in the longer term, withdrawal or tardive dyskinesias, 1 rare type of which may be a worsening of tics caused by presumed dopamine-2 receptor hypersensitivity. If moderate doses are not effective, then higher doses are not likely to be either, and higher doses almost always increase the risk of side effects and make weaning the patient from the drug difficult without rebound exacerbation.

Although tardive dyskinesias are rare in children who receive modest doses of neuroleptics for tics, the traditional, or typical, antipsychotics are now being replaced by the newer so-called atypical antipsychotics, which seem to have a lower risk of tardive dyskinesia. However, atypical neuroleptics have the same other adverse effects as typical neuroleptics, including acute dystonic or extrapyramidal reactions, sedation, or dysphoria. In addition, risperidone and olanzapine may cause hyperphagia and weight gain, with potentially serious metabolic consequences. Clinical trials

have demonstrated the efficacy of risperidone, olanzapine, and ziprasidone for tics, but the lack of efficacy of the paradigmatic atypical neuroleptic clozapine indicates that not all atypical neuroleptics are equally effective.

When neither  $\alpha$ -adrenergic agents nor neuroleptics are effective, a variety of second-line drugs or augmentation strategies may be tried with caution. Although some neurologists use clonazepam to manage tic disorders, it should be used only in rare instances in children. Like the other benzodiazepines, clonazepam can cause cognitive blunting, sedation, irritability, and disinhibition, and its use can lead to dependence and withdrawal symptoms.

Tics should be treated pharmacotherapeutically only if significantly impairing, and only by a physician skilled in the use of the drugs concerned—ordinarily a child or adolescent psychiatrist or a pediatric neurologist. Such treatment should be carefully considered and discussed with parents, closely monitored, and undertaken only with knowledge and consideration of the risks and disadvantages involved.

### **Pharmacotherapy for Attention-Deficit/Hyperactivity Disorder, Obsessive-Compulsive Disorder, Anxiety, and Depression**

Pharmacotherapy for impairing comorbid ADHD, OCD, anxiety, or depression may be indicated in children with tic disorder, bearing in mind some considerations specific to tic disorder. Because ADHD is often more disabling than the child's tics, a cautious trial of a stimulant may be necessary, beginning with very low doses and increasing only gradually to avoid exacerbating tics. Alternatives to the stimulants are the  $\alpha$ -adrenergic agents (clonidine or guanfacine), atomoxetine, or 1 of the second-line drugs such as the older tricyclic antidepressants (with appropriate electrocardiogram monitoring). Most children with tics and ADHD are able to tolerate methylphenidate, and the combination of methylphenidate and clonidine seems more effective than either agent alone.

The SSRIs seem to be effective in children with OCD and tics, although evidence suggests that monotherapy with the SSRIs is less effective in the presence of tics. In such cases, augmentation with a low dose of a neuroleptic often boosts the treatment response. In rare cases, SSRIs can exacerbate or even precipitate tics, akathisia, or other movement abnormalities, or can increase suicidal thinking.

## **MANAGEMENT**

Most tics last only a few weeks, although they may flit from 1 muscle group to another or change their form at irregular intervals. Even the chronic tics of TS are likely to disappear in later adolescence, with tic severity peaking at age 10 to 12 or so. Although most tics improve by late adolescence, OCD or ADHD symptoms may persist. Because the prevalence of tics drops sharply after age 13, tics that persist into later adolescence are more likely to become chronic. Tic severity in adulthood is inversely proportional to caudate



volume in childhood and to childhood performance on a dominant hand fine-motor skill test.

Children with tics and especially TS can experience related problems of self-image when adult criticism and peer rejection result. Occasionally, severe complex motor tics result in injury or self-mutilation. Finally, OCD may develop during adolescence or late in TS and can be a persistent source of distress despite the improvement in tic severity with age.

Data from community surveys suggest that tic disorders, including TS, exist on a spectrum from transient to persistent multiple motor and vocal tics that in more severe forms interfere with daily living. The presence of isolated and transitory tics is common and seems to be of minimal consequence. On the other hand, persistent tics, even mild ones, seem to be associated with increased prevalence of ADHD, OCD, disruptive behavior, learning problems (although not necessarily a formal learning disability), and vulnerability to anxiety and depression.

Children should be referred to a specialist if the differential diagnosis is unclear, if a psychiatric disorder is present or is a possibility, if psychiatric drugs or treatments are needed, or if an expert opinion is required.

Referral is likely to be influenced as much by associated problems as by the tics themselves. The emphasis of treatment may thus focus less on tics per se than in mapping other areas of dysfunction.

Criteria for referring children to a specialist with expertise in the diagnosis and management of tics are the following: presence of tics associated with additional evidence of psychiatric disorder, such as ADHD, generalized anxiety, or OCD; presence of chronic or recurrent tics that seem to have a clear relationship to stress, particularly if a reason exists to think that psychosocial interventions may be helpful; presence of chronic, disabling, or discomforting tics for which differential diagnosis or treatment is needed; when the primary physician knows little about tics and wants an expert opinion; or when psychoactive drugs such as antipsychotics (neuroleptics) or  $\alpha$ -adrenergic agents may be indicated, because psychiatrists and developmental-behavioral pediatricians routinely use these medications and are well informed about risks, side effects, dose levels, and newer drugs.

Such referral may be only for consultation, not necessarily for continued management. In general, the preferred mental health specialist is a well-trained child or adolescent psychiatrist, or developmental-behavioral pediatrician—one who has a broad biopsychosocial perspective, including a good grasp of neuropsychiatry and pharmacotherapy but who will not overprescribe and who has a capacity to work closely with behavioral psychologists. This kind of specialist should also be alert to the possibilities of the rare neurologically induced tics and willing to order any appropriate neuroimaging studies and neurologic consultations. When the tic is disabling and no further diagnostic workup is required, or when pharmacotherapy is not an option or is already in place but further relief is necessary, referral

should be made to a child psychologist experienced in behavioral types of treatment. Consultation from a clinical psychologist is also useful if a child is having difficulties at school that are not simply caused by teasing or the distraction of tics or tic urges. Many children with tic disorders benefit from close collaboration with their school, which may include making the teacher aware of the tics and providing accommodations such as the ability to step out of class briefly when tics especially intrusive or bothersome.

### WHEN TO REFER

- Differential diagnosis is unclear
- A psychiatric disorder is present or a possibility
- Psychiatric drugs or treatments are needed
- For expert opinion

### WHEN TO ADMIT

- Never in the first instance (for tics alone)
- Occasionally, for complex assessments to initiate treatments or to taper a child from high doses of multiple medications

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *A Family's Guide to Tourette Syndrome* (book), Walkup JT ([store.tsa-usa.org/index.html](http://store.tsa-usa.org/index.html))
- *Tics, Tourette Syndrome, and OCD* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/emotional-problems/Pages/Tics-Tourette-Syndrome-and-OCD.aspx](http://www.healthychildren.org/English/health-issues/conditions/emotional-problems/Pages/Tics-Tourette-Syndrome-and-OCD.aspx))
- *Tourette Syndrome Association* (Web site), ([www.tsa-usa.org](http://www.tsa-usa.org))
- *What You Want to Know About TS* (Web page), New Jersey Center for Tourette Syndrome and Associated Disorders, Inc. ([www.njcts.org/what-you-want-to-know.php](http://www.njcts.org/what-you-want-to-know.php))

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## Chapter 203

# TORTICOLLIS

Philip O. Ozuah, MD, PhD; Catherine C. Skae, MD

The word *torticollis* originates from 2 Latin words: *tortus*, which means *twisted*, and *collum*, meaning *neck*. The classic clinical picture of torticollis is that of the head tilted to one side and rotated in such a way that the chin and face point to the contralateral side. Torticollis can be broadly classified as either *congenital* or *acquired torticollis*. Facial asymmetry is often observed in congenital torticollis but not in acquired torticollis. This finding can thus be useful in clinically distinguishing between the 2 forms.

## CLINICAL MANIFESTATIONS

### Congenital Torticollis

Muscular torticollis is by far the most common form of congenital torticollis, and it occurs clinically in the first 8 weeks of life. It is frequently not obvious at birth but begins to become apparent at approximately 2 weeks of age.

Several theories have been proposed to explain the cause of this disorder. One theory suggests that stretching of the neck during a difficult delivery results in rupture and hemorrhage within the sternocleidomastoid muscle (SCM). Subsequent muscle ischemia results from increased pressure from the blood trapped within the fascial compartment, producing progressive muscle fibrosis and contracture, with eventual clinical torticollis. Support for this theory comes from the fact that about 40% of patients with congenital torticollis have had a difficult birth, including forceps delivery and breech presentation. However, congenital torticollis has also been reported in children after uncomplicated births. In addition, specimens of SCM in patients with torticollis have sometimes shown no evidence of trauma or hemorrhage. Another theory, therefore, is that torticollis results from an intrauterine position that occludes venous drainage from the SCM, leading to vascular congestion, ischemia, muscle damage, and fibrosis. This theory is supported in that 75% of congenital muscular torticollis cases are right sided because of intrauterine, left occiput–anterior positioning, and about 20% of patients who have congenital torticollis also have other musculoskeletal anomalies, including congenital hip dysplasias, talipes equinovarus, and metatarsus adductus.

Congenital torticollis can produce some variation. Most commonly, a sternomastoid tumor or pseudotumor is palpable as a characteristically nontender, soft, and mobile mass in or next to the inferior aspect of the SCM. The mass enlarges in the first few weeks of life, reaching its maximal size at 1 month of age. Thereafter, it begins to shrink until it disappears by 4 to 6 months. The mass then regresses and is replaced by a fibrous band, leading to contracture, which prevents normal growth and normal range of motion of the neck, and facial asymmetry results from the uneven growth

forces. A second form of congenital torticollis involves thickening and tightness of the SCM itself. Finally, *congenital postural torticollis* occurs without the presence of a palpable mass or tightness of the SCM.

The twisted position of the neck can lead to positional plagiocephaly. Skull flattening on the contralateral side may result from sleeping supine. Thus, plagiocephaly can be the presenting sign of mild torticollis.

### Acquired Torticollis

As with congenital torticollis, most cases of torticollis encountered in older children are primarily muscular in origin. Cervical muscle or ligament injury arising from trauma can cause a head tilt and unilateral neck tenderness, a condition that can also occur on awakening, presumably as a result of awkward positioning of the neck during sleep.

*Benign paroxysmal torticollis* is a disease of infancy with an unknown cause, although a familial pattern has been described. Manifestations of the condition begin in the first year of life with recurrent episodes of head tilt that may be associated with emesis, pallor, agitation, ataxia, malaise, and behavioral changes. Attacks may last from several hours to several days. Spontaneous and complete remission usually occurs by 5 years of age. Some patients, however, go on to develop migraines or benign paroxysmal vertigo.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of torticollis is listed in Box 203-1.

### Congenital Torticollis

Several congenital cervical spine anomalies can occur in conjunction with torticollis. Most of these anomalies can be diagnosed by radiographic studies of the cervical spine. *Pterygium colli*, a congenital web of the skin of the neck extending from the acromial process to the mastoid, can be restrictive and result in torticollis. *Congenital remnant cysts* within the body of the SCM are a less common cause of torticollis. Unilateral absence of one SCM results in unopposed action of the other muscle and produces a contralateral torticollis.

### Acquired Torticollis

Conditions that need to be considered in the differential diagnosis of acquired torticollis include cervical spine subluxations, infections of the head and neck (Grisel syndrome), neurologic disorders, and neoplasia. Laxity of the transverse cervical ligaments results in atlantoaxial instability in up to 15% of patients with Down syndrome. Most of these children are asymptomatic, but subluxation of the cervical spine, most commonly a rotational atlantoaxial subluxation, may occur after trauma. Nontraumatic subluxations of the atlantoaxial spine may arise as a result of head and neck infections or juvenile idiopathic arthritis (JIA). Torticollis may be the presenting finding in either the systemic onset or polyarticular forms of JIA, but this is rare. The current theory is that inflammatory reactions around the spine produce hyperemia and edema, which, in turn, lead to laxity of the supporting

**BOX 203-1 Differential Diagnosis of Torticollis****CONGENITAL**

- Muscular torticollis
- Postural torticollis
- Cervical spine anomalies
- Hemivertebra
- Atlantooccipital fusion
- Klippel-Feil syndrome
- Sprengel deformity
- Pterygium colli (webbed neck)
- Sternocleidomastoid cysts
- Cystic hygroma
- Bronchial cleft cyst
- Unilateral absence of sternocleidomastoid
- Occipital condylar dysplasia

**ACQUIRED**

- Muscular
  - Cervical muscle injury
    - Traumatic
    - Awkward positioning during sleep
- Vertebral
  - Atlantoaxial subluxation
    - Laxity of the transverse cervical ligaments results in atlantoaxial instability in up to 15% of patients with Down syndrome.
  - C2–C3 subluxation
  - Rotary subluxation
  - Cervical fractures
  - Cervical vertebral osteomyelitis
  - Juvenile idiopathic arthritis (JIA)
    - Torticollis may rarely be the presenting finding in either systemic onset or polyarticular JIA.
    - Inflammatory reactions around the spine produce hyperemia and edema, which lead to laxity of the supporting ligaments and a predisposition to spontaneous subluxations and torticollis.
  - Acute cervical disk calcification caused by trauma or respiratory infection
- Infectious
  - Infection of the head and neck (Grisel syndrome)
  - Upper respiratory infection
  - Retropharyngeal abscess
  - Cervical lymphadenitis
  - Cervical vertebral osteomyelitis
  - Dental infection
- Neurologic
  - Ocular torticollis with
    - Strabismus
    - Nystagmus
  - Refractive errors
  - Paralysis of extraocular muscles
  - Spasmus nutans (nystagmus, head nodding, and torticollis)
    - No known cause.
    - Signs and symptoms usually develop within the first 2 years of life.
    - May persist for months to years, but the course is often benign and self-limited.
    - But if accompanied by ataxia, suspect a cerebellar tumor.
  - Dystonic torticollis
    - May follow the administration of phenothiazines, carbamazepine, or phenytoin.
    - Presence of other extrapyramidal signs can confirm a dystonic reaction.
  - Syringomyelia
  - Epidural hematoma
  - Labyrinthine torticollis
  - Brachial plexus palsy
  - Arnold-Chiari malformation
  - Accessory nerve palsy
  - Acute disseminated encephalomyelitis
  - Wilson disease
- Neoplastic
  - Cervical cord tumor
  - Posterior fossa tumor
  - Soft tissue tumor
  - Langerhans cell histiocytosis (histiocytosis X)
  - Infantile desmoid fibromatosis
- Other
  - Benign paroxysmal torticollis
  - Psychogenic torticollis
  - Sandifer syndrome
    - An abnormal posturing that includes torticollis and opisthotonos
    - Believed to be a protective mechanism adopted by some patients with gastroesophageal reflux, esophagitis, or hiatal hernia
  - Dermatogenic torticollis
    - A painful, stiff neck resulting from extensive local skin lesions
  - Spurious torticollis
    - Stiffness of the neck from dental malformations or caries

ligaments and a predisposition to spontaneous subluxations and torticollis.

Torticollis may also arise from acute cervical disk calcification caused by trauma or from an upper respiratory infection. *Ocular torticollis* may be caused by

paralysis of the extraocular muscles, strabismus, nystagmus, and refractive errors. *Spasmus nutans*, also known as *nodding spasms* or *salaam spasms*, includes a triad of acquired nystagmus, head nodding, and torticollis, without a known cause. Signs and symptoms

usually develop within the first 2 years of life and may persist for months to years. However, the clinical course often is benign and self-limited. A *dystonic torticollis* may follow the administration of several drugs, including phenothiazines, carbamazepine, and phenytoin. The presence of other extrapyramidal signs can often be used to distinguish patients who have dystonic reactions.

Neoplasms associated with torticollis include cervical cord tumors and cerebellar tumors. Posterior fossa masses may manifest similarly to spasmus nutans with nystagmus, head nodding, and torticollis. For patients with cerebellar tumors, however, ataxia is often a cardinal feature. *Sandifer syndrome* is an abnormal posturing that includes torticollis and opisthotonos. This syndrome is believed to be a protective mechanism adopted by some patients with one of several conditions, including gastroesophageal reflux, esophagitis, or hiatal hernia. *Dermatogenic torticollis* is a painful, stiff neck that results from extensive local skin lesions. Stiffness of the neck resulting from dental malformations and caries is called *spurious torticollis*.

## EVALUATION

### History

The first step in determining the cause of torticollis should be to obtain a thorough and detailed history. Particular attention should be given to duration of symptoms, variation in severity of symptoms at different times of day (morning stiffness), previous trauma, presence of fever, and other systemic manifestations, including other musculoskeletal system symptoms. In younger patients, the birth history is essential.

### Physical Examination

Physical examination should not be limited to the head and neck areas but should include all organ systems. Findings such as craniofacial asymmetry suggest a congenital torticollis of long duration. The presence of webs or cysts in the neck should raise the suspicion of pterygium colli or remnant cysts. Patients with acquired torticollis as a result of trauma often have a tender SCM. Point tenderness over the cervical spine may suggest an underlying fracture or subluxation. Cervical vertebral osteomyelitis should be suspected in patients who have point tenderness in association with an unexplained fever. A thorough examination of the musculoskeletal system is necessary to examine muscle tone, muscle strength, hip positions, and the alignment of the lower extremities and feet. All vertebrae must be examined, with attention paid to the presence of sacral dimples. Examination of peripheral joints should be done to assess for evidence of arthritis in the forms of joint swellings or limitations of movement in association with pain, warmth, or redness. A thorough neurologic exam must be completed, checking cranial nerves and including vision, sensation, reflexes, fine and gross motor skills, and cerebellar testing.

### Laboratory Evaluation

The presence of peripheral leukocytosis and increased sedimentation rate can be helpful adjuncts

in diagnosing torticollis caused by infection or inflammation.

### Imaging Studies

Imaging of the cervical spine should be obtained in all neonates with torticollis and in older children who have findings that suggest vertebral involvement or who have persistent torticollis. Ultrasound is the imaging modality of choice for initial evaluation. Patients with neurologic deficits should undergo prompt computed tomography scanning or magnetic resonance imaging of the head and neck.

## MANAGEMENT

Congenital muscular torticollis responds well to prompt conservative treatment during the first year of life. Medical management includes passive and active stretching of the neck. *Gentle (passive) stretching* can be performed daily by the parents of the child or by a physical therapist. *Active stretching* is achieved by manipulating the infant's environment in such a way that objects of interest are located on the opposite side of the room from the torticollis, inducing the infant to turn the neck in the desired direction.

Surgical correction is essential if the deformity persists beyond the first year of life, if range of motion is restricted more than 30%, or if residual craniofacial deformity exists. Craniofacial asymmetry is best reversed at an early age when the child's growth potential is at its maximum. The surgical procedure that has the best results involves a bipolar tenotomy of the affected SCM, followed by casting or bracing to maintain the corrected posture.

Acquired muscular or ligamentous torticollis is managed with local heat, massage, analgesics, muscle relaxants, and a soft cervical collar. Symptoms usually resolve in 7 to 10 days. Notably, however, patients with acquired muscular or ligamentous torticollis experience only mild discomfort. Any child with severe neck pain or tenderness over the vertebra requires immediate cervical immobilization until radiography can be performed to exclude the possibility of vertebral fracture or subluxation.

Drug-induced dystonic reactions are reversed by discontinuing the offending drug and administering intravenous diphenhydramine. The treatment of torticollis arising from other specific diseases should be directed at the cause.

### WHEN TO REFER

- Presence of craniofacial asymmetry
- Radiographic evidence of cervical spine abnormality
- More than 30% restriction in range of motion
- Persistence beyond the first year of life

### WHEN TO ADMIT

- Presence of neurologic deficits
- Severe neck pain
- Point tenderness over the vertebrae



## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Head Tilt* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/Cleft-Craniofacial/Pages/Head-Tilt.aspx](http://www.healthychildren.org/English/health-issues/conditions/Cleft-Craniofacial/Pages/Head-Tilt.aspx))
- *Positional Skull Deformities and Torticollis* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/head-neck-nervous-system/Pages/Positional-Skull-Deformities-and-Torticollis.aspx](http://www.healthychildren.org/English/health-issues/conditions/head-neck-nervous-system/Pages/Positional-Skull-Deformities-and-Torticollis.aspx))

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## Chapter 204

# VAGINAL BLEEDING

Maria Trent, MD, MPH; Alain Joffe, MD, MPH

The assessment of vaginal bleeding depends largely on the pubertal status of the patient. In prepubertal girls, vaginal bleeding usually reflects a localized problem in the vagina or uterus. In pubertal girls and young women, the differential diagnosis includes disorders affecting the hypothalamic-pituitary-ovarian (HPO) axis and complications of pregnancy in addition to local causes. In all cases, however, a complete history and thorough physical examination will provide important clues to the diagnosis.

## PREPUBERTAL GIRLS

In utero, maternal estrogen diffuses across the placenta into the fetal circulation. After birth, estrogen levels in the infant fall, resulting in a physiologic vaginal discharge that can be blood tinged or frankly bloody. No treatment except reassurance is necessary, and the discharge usually disappears within 10 days.

Several conditions can result in vaginal bleeding in the prepubertal child, including vulvovaginal infections, excoriations secondary to pruritus, foreign bodies, sexual abuse, trauma (eg, involving a straddle injury during bike riding), tumors, condylomata, hemangiomas, polyps, and coagulopathies. Any suggestion of sexual abuse, such as bruising, hymenal tears, or other signs of trauma, mandates obtaining a careful, nonthreatening history from the child and caretaker to determine the need for a referral to child protective services for full investigation including forensic interview and subspecialty medical evaluation.

Nighttime pruritus may indicate a pinworm infestation. The Scotch tape slide test, to look for pinworm eggs, can help establish *Enterobius vermicularis* infestation. If petechiae or numerous bruises are noted on

physical examination, a platelet count and clotting studies are indicated to screen for a coagulopathy. A foreign body in the vagina should always be considered, even if no history of such exists. Contrary to popular belief, most girls who have bleeding from a foreign body do not have an associated foul-smelling discharge. The physician should also make sure that the bleeding is vaginal in origin, given that a prolapsed urethra can mimic vaginal bleeding.

Excoriation, erythema, or a rash in the perineal area make vaginitis a distinct possibility. If a vaginal discharge is found and microscopic examination demonstrates large numbers of white blood cells, then vaginitis is highly likely. Concern about sexual abuse should prompt cultures for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Other bacterial cultures may be necessary. For example, a history of diarrhea in the weeks preceding onset of the bleeding suggests vaginitis caused by *Shigella* organisms. Group A beta-hemolytic streptococcus can also cause vaginitis.

Vaginal bleeding caused by a foreign body or vulvitis will respond to removal of the foreign body and proper perineal hygiene. Occasionally, systemic antibiotics may be necessary. Foreign bodies can often be washed out with a soft, flexible catheter; sharp objects should be removed carefully, under direct visualization. Care should be taken to avoid touching or manipulating the unestrogenized prepubertal hymen as to avoid pain to the child. Referral to a gynecologist may be required if the patient is uncooperative. After removal of a foreign body, bleeding should subside within 10 days. If it does not, then referral to a gynecologist is indicated. The entire foreign body may not have been removed, or a tumor, not readily visualized by the primary care physician, may be the actual cause of the bleeding. Similarly, when treatment of the presumed cause does not end the bleeding, referral for a more thorough examination is indicated.

## PUBERTAL GIRLS

### Evaluation

Abnormal vaginal bleeding in pubertal girls can indicate a variety of disorders. Evaluation of this symptom depends on the nature of the problem: Is she bleeding between normal periods, or have her previously regular menses become more frequent or heavier? A teenager whose prior menses have been regular might possibly begin to have infrequent but heavy menstrual bleeding. In general, normal periods in adult women (measured from the first day of 1 period to the first day of the next), range from 21 to 35 days with a flow of 3 to 7 days. Flow greater than 1 week is considered excessive. A similar cycle pattern is observed in adolescent girls, but cycle length is more variable, especially in the first few years after menarche. Although the normal blood loss during menses is 30 to 40 mL, with an upper limit of 80 mL, the quantity of blood loss is difficult to assess by history unless the patient reports very light flow. History should include an assessment of menstrual pattern and the quantity of pads or tampons used. Although research has demonstrated the value of pictorial assessment to determine menstrual blood loss, laboratory assessment of hemoglobin,

hematocrit, or both is useful for determining if significant blood loss resulting in anemia has occurred.

Normal menstrual function requires that the HPO axis function properly. Follicle-stimulating hormone (FSH) causes maturation of ovarian follicles, which produce estrogen. Rising levels of estrogen stimulate the endometrial lining of the uterus to proliferate and, at the same time, induce a midcycle surge of luteinizing hormone (LH) that causes the primary follicle to release an ovum, after which LH and FSH levels fall. The remnants of the follicle (*corpus luteum*) now produce progesterone, which converts the proliferative endometrium to a secretory phase. At the end of a normal cycle, the corpus luteum involutes, and both estrogen and progesterone levels fall. The endometrial lining is shed, and bleeding occurs.

In adolescents, especially young adolescents, the HPO axis is relatively immature and highly sensitive to disturbance by several endogenous and exogenous factors; this perturbation leads to irregular bleeding. Among young adolescents (but in some older adolescents as well), the axis has not yet matured, and most cycles are anovulatory. Thus the endometrium proliferates under estrogen stimulation from the maturing follicle, but the midcycle LH surge is absent, ovulation does not occur, and the progesterone-secreting corpus luteum never forms. Toward the end of the cycle, the follicle involutes, estrogen levels fall, and bleeding occurs. Influenced by estrogen only, endometrial shedding is incomplete and irregular, accounting for the excessive bleeding of anovulatory cycles. Alternatively, fluctuating estrogen levels during an anovulatory cycle result in estrogen withdrawal bleeding. The occasional ovulatory cycle helps stabilize endometrial growth, and because the corpus luteum produces progesterone, a more organized withdrawal bleed occurs. Hence, any condition that increases the frequency of anovulatory cycles is more likely to produce the kind of uterine bleeding that prompts the teenager to seek medical care.

Most teenagers who seek evaluation for genital bleeding in the first few years after menarche will have abnormal uterine bleeding (AUB) secondary to an immaturity of the HPO axis, with resultant anovulatory cycles. Because this is a diagnosis of exclusion, the primary care physician should search for other causes that affect the integrity of the HPO axis and can mimic AUB from this cause. Anovulatory cycles may also occur in patients with a mature HPO axis who have disorders such as polycystic ovary syndrome, thyroid disease, or conditions resulting in hypothalamic amenorrhea (emotional stress, eating disorders, chronic illness, or intense athleticism). Additional causes of abnormal bleeding in this age group include disorders of pregnancy, other endocrine abnormalities, cervicitis, vaginitis, pelvic inflammatory disease, other sexually transmitted infections, foreign bodies, tumors, coagulopathies, drugs, and systemic disorders (Box 204-1). Heavy bleeding at menarche, significant anemia, or the need to be hospitalized to control the bleeding all increase the likelihood that a coagulopathy or another pathologic condition is the cause of the bleeding. Family history, however, has been shown to be a better predictor of coagulopathy than menstrual

history. While the International Federation of Gynecology and Obstetrics [FIGO] and the American College of Obstetrics and Gynecology (ACOG) have disregarded many of the old terms used to describe menstrual abnormalities and developed a new nomenclature for use in adult women termed PALM-COEIN (PALM [structural causes: poly, adenomyosis, leiomyoma, malignancy and hyperplasia]; COEIN [nonstructural causes: coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified]), it is important to adequately explore the diagnostic entities common in pubertal girls such as anovulatory bleeding, pregnancy, sexually transmitted infections, and von Willebrand disease.

### History

Most causes of vaginal bleeding or abnormal uterine bleeding (see Box 204-1) can be ruled out by history and physical examination. Maternal support during the initial history taking can be useful. Many mothers track the menstrual periods of their adolescent daughters, especially in the first years after menarche, and are keenly aware of the amount of bleeding based on the quantity of feminine products purchased, stained laundry, evidence of fatigue, and general level of their activity and behavior. A mother can often provide detailed family medical histories for first-degree female relatives, as well as that of her daughter.

Certain key aspects of the history may be difficult to obtain. A young woman may hesitate to reveal that she has engaged in sexual intercourse or that she has been sexually abused. The patient should be interviewed alone regarding sexual activity, sexually transmitted infections (including associated symptoms such as cramping, vaginal discharge, and dyspareunia), abuse, stress, weight changes and eating habits, participation in sports and other activities, chronic illnesses, other bleeding problems, medication use (particularly contraceptives), and substance use patterns. If a discharge is foul smelling and bloody, then a foreign body or retained tampon is likely; however, necrotic tumors can result in similar bleeding patterns. Pruritus or dysuria suggests vaginitis or cervicitis as the cause of the bleeding. Bleeding between periods is common during the first 2 or 3 cycles of oral contraceptive use and generally does not require any additional therapy; however, cervicitis secondary to *N gonorrhoeae* or *C trachomatis* infection or vaginitis secondary to *Trichomonas vaginalis* may also result in intermenstrual spotting. Young women who receive depot medroxyprogesterone acetate (Depo-Provera) injections often have frequent and irregular periods of excess bleeding, particularly in the first months after beginning use of this contraceptive method. Teenagers who forget to take 1 or 2 oral contraceptive pills may also have some bleeding. Occasionally, women may have a small amount of bleeding or spotting after sexual intercourse, and some will have spotting around the time they ovulate. A complete family history is important to determine if other family members have any kind of bleeding problem. Complications of pregnancy (ectopic pregnancy or incomplete abortion) are more likely if a history of 1 or 2 missed periods exists, if the prior menstrual

**BOX 204-1 Possible Causes of Abnormal Uterine Bleeding****PREGNANCY COMPLICATIONS**

- Spontaneous abortion
- Ectopic pregnancy
- Retained gestational products
- Trophoblastic disease

**HEMOSTATIC DISORDERS**

- von Willebrand disease
- Idiopathic thrombocytopenia
- Coagulation factor deficiency
- Platelet dysfunction (eg, Glanzmann disease, Bernard-Soulier syndrome)

**THROMBOCYTOPENIA**

- Immune thrombocytopenia
- Bone marrow infiltration by malignancy (eg, leukemia)
- Bone marrow failure disease (eg, aplastic anemia)

**SYSTEMIC DISEASE**

- Systemic lupus erythematosus
- Renal failure
- Hepatic failure
- Malignancy

**CONDITIONS OF THE REPRODUCTIVE TRACT****Vagina**

- Vaginitis
- Trauma
- Foreign body
- Congenital anomaly (septum)
- Neoplasia

**Cervix**

- Cervicitis, erosion
- Cervical polyp
- Neoplasia

**Uterus**

- Endometritis
- Endometrial polyp
- Submucosal leiomyoma

- Arteriovenous malformation
- Congenital anomaly
- Neoplasia

**Pancreas**

- Diabetes mellitus

**Pelvis**

- Endometriosis

**ENDOCRINE DISORDERS****Hypothalamus, Pituitary**

- Immature HPO axis
- Hyperprolactinemia
- Anorexia nervosa, malnutrition
- Excessive exercise

**Ovary**

- Polycystic ovary syndrome
- Luteal phase abnormality
- Primary ovarian insufficiency
- Neoplasia (hormone secreting)

**Adrenal**

- Congenital adrenal hyperplasia
- Cushing disease
- Adrenal insufficiency
- Neoplasia

**Thyroid**

- Hypothyroidism
- Hyperthyroidism

**Iatrogenic**

- Hormonal contraceptives
- Anticoagulants
- Neuroleptics
- Intrauterine contraceptive device
- Androgens
- Spironolactone
- Antipsychotic medication
- Platelet inhibitors

period was lighter than normal, if other symptoms of pregnancy are present (breast tenderness or nausea), or if the bleeding is accompanied by crampy, lower abdominal pain. A history of passing tissue or tissue present in the vaginal canal is also suggestive of complications of pregnancy. Blood dyscrasias, such as thrombocytopenia or von Willebrand disease, can cause heavy vaginal bleeding without other cutaneous manifestations of bleeding. Symptoms of endocrine disorders, such as cold intolerance, polyuria, nipple discharge, headache, acne, and increased facial hair, can be easily assessed using a comprehensive review of systems.

**Physical Examination**

The physical examination should include measurement of height, weight, and blood pressure, as well as thorough palpation of the thyroid gland. Visual field and funduscopic examinations are necessary to help rule out a prolactinoma. Increased facial hair is consistent with polycystic ovaries or an adrenal tumor. Striae suggest Cushing disease. An enlarged clitoris is consistent with an androgen-secreting tumor or late-onset 21-hydroxylase deficiency. Normal findings on physical examination, including pelvic examination, help rule out the many causes of vaginal bleeding or abnormal uterine bleeding listed in Box 204-1. Vulvar

or vaginal bruising or lacerations suggest the probability of sexual abuse, although the most common finding after sexual abuse is a normal examination without any evidence of trauma. Lack of abdominal pain with adnexal or cervical motion tenderness excludes pelvic inflammatory disease. If the ovaries are of normal size, then ovarian tumors or cysts are unlikely sources of the bleeding. A minimally enlarged uterus, consistent with early pregnancy, may not be noted by an inexperienced examiner. Endometrial polyps or submucous leiomyomas are distinctly unusual in women younger than 20 years, and they cannot be palpated by the examiner on the usual pelvic examination. With a patient who has an intractably heavy flow, these entities should be considered.

### Laboratory Tests

For most cases of vaginal bleeding, relatively few laboratory tests are needed. A complete blood count with indices provides an objective measurement of the amount and duration of bleeding and guides the treatment approach for patients with an otherwise negative evaluation. A urinalysis and urine pregnancy test should also be obtained. Bleeding associated with crampy lower abdominal pain may indicate ectopic pregnancy, and a quantitative serum pregnancy test is indicated. Screening for *N gonorrhoeae*, *C trachomatis*, trichomonas, and bacterial vaginosis is indicated for sexually active patients or when there is any suspicion of sexual abuse. A pelvic sonogram is indicated if ectopic pregnancy is suspected, if a pelvic mass is found on bimanual examination, or if the pelvic examination is difficult.

Thyroid-stimulating hormone function tests, prolactin, LH and FSH levels, and coagulation tests should be ordered if hormonal therapy is contemplated. Any evidence of hyperandrogenism necessitates measurement of androgens, which may initially include free and total testosterone, and dehydroepiandrosterone sulfate. Coagulation tests such as a prothrombin time, partial thromboplastin time, von Willebrand panel, and platelet aggregation studies are indicated if the patient has profuse hemorrhage, menorrhagia at menarche, a family history of bleeding disorders, or unexplained heavy vaginal bleeding. Measures of iron stores (eg, ferritin, reticulocyte count, hemoglobin content) may also be useful in managing iron deficiency even in the absence of anemia.

### Management

Sexually transmitted infections are easily diagnosed and can usually be treated with antibiotics. The complications of pregnancy, such as threatened or spontaneous abortion, can be managed in the outpatient setting. However, a physician experienced in the management of early pregnancy should be consulted. For patients with bleeding disorders, consultation with a hematologist may be required.

Most cases of vaginal bleeding in adolescent girls are caused by anovulatory cycles. In other instances, the physician must manage the bleeding without knowing the cause. Treatment decisions can be guided using the patient's clinical symptoms and the results of basic laboratory testing. Although some physicians

may feel comfortable using hormonal therapy, others may prefer the guidance of a more experienced physician. Because many patients with DUB are early adolescents accompanied by their parents, the primary care physician should include the parents in the decision to begin hormonal treatment in a non-sexually active patient. Assuring the parents that combined oral contraceptives (COCs) are, in this instance, being used as treatment; COCs are the most convenient way to package and deliver hormonal treatment; short-term use of COCs for 3 to 6 months is anticipated; and close follow-up will be provided during the treatment period, will often alleviate concerns about hormonal treatment and prevent rejection of these methods by the family. All patients with abnormal vaginal bleeding should be instructed to maintain a menstrual calendar to facilitate follow-up management.

Mild cases of AUB that do not result in anemia and that do not greatly upset the patient and her parents can be managed expectantly with no immediate, specific therapy. Those who have mild anemia (hemoglobin value 11–12 g/dL) should receive iron supplementation. Some problems will resolve in 3 or 4 cycles. For a sexually active patient, oral contraceptive pills can be prescribed to treat the bleeding, as well as to provide contraception. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen or naproxen, can also be used for their demonstrated antiprostaglandin effects. It should be noted that patients with von Willebrand disease or other hemostatic abnormalities may have increased bleeding if NSAIDs are prescribed. Patients with mild bleeding should be reevaluated in 6 to 8 weeks.

In addition to iron supplementation, hormonal therapy is indicated in teenagers who have moderate AUB (enough to cause a decrease in hemoglobin to less than 11–12 g/dL). Girls who have menses every 1 to 3 weeks also need treatment. Treatment includes COCs or progestin alone. As previously mentioned, COCs are easier to use (1 pill is taken daily every day of the month). If the patient has a condition in which COCs are contraindicated or this method is rejected by the patient or her parents, then medroxyprogesterone 10 mg orally can be given daily for 10 to 14 days, beginning on the first day of each month (calendar method) or on the fourteenth day of the menstrual cycle (day 1 being the first day of bleeding). The patient with moderate bleeding should be reassessed in 4 to 6 weeks.

Patients with severe prolonged heavy AUB accompanied by a drop in hemoglobin to 10 g/dL or less need to be treated more aggressively. In this instance, adolescent medicine or gynecologic consult should be sought, clotting studies obtained, and hospitalization strongly considered. For patients with severe bleeding, COCs (1 tablet taken twice daily for 3 to 4 days) will generally stop the bleeding. However, prescribing a COC such as ethinyl estradiol-norgestrel-28 every 4 hours may be necessary initially until the bleeding stops, then every 6 hours for 24 hours, then every 8 hours for 4 days, and then twice daily to complete 3 weeks of hormonal therapy. Antiemetic medications may be required to counteract the side effects of the high levels of estrogen contained in this regimen. A



withdrawal bleed will occur 2 to 4 days after completion of this initial course of therapy. Patients with significant AUB should avoid the placebo pills contained in the COC pill packs and remain on continuous COCs until the hemoglobin and hematocrit begin to normalize. Iron and folic acid supplementation should be included as a part of the therapeutic plan.

The need for blood transfusion will depend on the hemodynamic stability of the patient. Although some physicians prefer to use conjugated estrogens (25 mg intravenously every 4 hours) to stop the bleeding, use of ethinyl estradiol-norgestrel-28 or a similar COC given 6 times a day and then gradually tapered to once a day over the next 7 to 10 days will usually stop the bleeding. Endometrial biopsy or dilation and curettage is rarely indicated. Even when these measures succeed in controlling the vaginal bleeding, affected adolescents require long-term, close follow-up because an appreciable number of them will continue to have menstrual abnormalities.

### WHEN TO REFER

- Patient is experiencing severe bleeding or initial attempts to control the bleeding by the primary care physician have failed.
- Vaginal bleeding seems to be secondary to a chronic illness that the primary care physician is unable to manage.
- Primary care physician feels uncomfortable performing a pelvic examination.
- Long-term hormonal therapy is required.
- Evidence of anatomical abnormality exists.
- Evidence of a complicated endocrine disorder exists.
- Evidence of a coagulopathy exists or additional guidance is required for further evaluation of a coagulation or hemostatic disorder.
- Evidence of a malignancy exists.
- Evidence of sexual abuse exists.

### WHEN TO ADMIT

- Patient shows evidence of hemodynamic instability.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *All About Menstruation* (Web page), Nemours Foundation ([kidshealth.org/teen/sexual\\_health/girls/menstruation.html](http://kidshealth.org/teen/sexual_health/girls/menstruation.html))
- *The Pelvic Exam* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Puberty—Ready or Not, Expect Some Changes* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

#### Medical Decision Support

- *American College of Obstetricians and Gynecologists* (ACOG), ([www.acog.org](http://www.acog.org))
- *STD Treatment Guidelines* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/std/treatment](http://www.cdc.gov/std/treatment))

- *Young Women's Health Center* (Web site), Boston Children's Hospital ([www.youngwomenshealth.org](http://www.youngwomenshealth.org))

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## Chapter 205

## VAGINAL DISCHARGE

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Vaginal discharge is a common complaint to pediatricians. However, the presence of discharge is not necessarily abnormal; this symptom may represent the vagina's response to changes in estrogen levels, and the pediatrician need only reassure the patient and her parents. In most circumstances, the age of the patient, her pubertal status, and whether she has ever had sexual intercourse are key elements in sorting out the cause of the discharge.

### NEWBORN PERIOD

In utero, the vaginal epithelium of the neonate is stimulated by maternal hormones that cross the placenta into the fetal circulation. After delivery, these hormone levels fall rapidly, and the parents may note a thick, grayish-white, mucoid discharge from the neonate's vagina. In many instances, the discharge is blood tinged or even grossly bloody. No treatment is needed, and the discharge usually resolves by 10 days of age.

## PREPUBERTAL GIRLS

The genital area of prepubertal girls is more susceptible to infection than that of older, pubertal girls. The labial folds are smaller and lack pubic hair, and the distance between the vagina and the rectum is relatively short compared with adolescents and adults. Low levels of circulating estrogen render the vaginal mucosa relatively thin and susceptible to irritation or infection. The alkaline pH (approximately 7.0) of the vaginal secretions affords a hospitable environment to bacteria, which together with poor perineal hygiene, allows fecal flora to establish themselves more easily in the genital area. Box 205-1 lists causes of vaginal discharge in prepubertal girls.

### Evaluation

When evaluating a premenarchal girl who has vaginal discharge, the physician should inquire about her hygiene. Wiping from the rectum toward the vagina brings intestinal flora to the vaginal introitus. Use of chemicals such as bubble baths, deodorants, or strong detergents to launder underwear can irritate the vulva and vagina. Occlusive nylon or rayon underwear provides a moist environment for potential pathogens, and the material itself can be an irritant. Although accounting for less than 5% of cases of vaginal

discharge, the possibility that the child or an abuser placed a foreign body, such as toilet paper, a coin, a small toy, or other objects, in her vagina should be considered. In such cases, the child has a discharge that can range from scant to abundant; can be white, brown, or bloody; and is frequently malodorous.

The parents should be asked about recent or concomitant illness. For example, vaginal discharge is associated with *Streptococcus pyogenes* infection (with or without scarlet fever) and with *Shigella* infection, occurring coincident with or after an episode of diarrhea. Systemic illnesses such as varicella also may be associated with vaginal discharge. Rectal infestations with *Enterobius vermicularis* (pinworms) can lead to vaginitis if the eggs are deposited around or in the vagina. A history of nocturnal itching accompanying vaginal discharge suggests this diagnosis. *Candida vulvovaginitis* is an uncommon cause of vaginal discharge or vulvovaginitis in prepubertal girls unless the child has recently taken antibiotics, has diabetes mellitus, is still in diapers, or is immunocompromised.

Sexually transmitted organisms, such as *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis*, are known to cause vaginal infections in prepubertal girls. Whereas *N gonorrhoeae* clearly causes vaginal discharge, evidence that *C trachomatis* alone does so is limited. The possibility of sexual abuse should always be considered in the evaluation of any child with vaginal discharge.

Although these other entities should be considered carefully as the physician evaluates the young patient, nonspecific vaginitis, in which no clear causative agent for the discharge can be established, accounts for 25% to 75% of cases of vulvovaginitis. Rare causes of discharge include polyps or tumors; ectopic ureters, which drain urine into the vagina, resulting in a wetness that is mistaken for discharge; a draining pelvic abscess; or a prolapsed urethra, often associated with a bloody discharge.

The physical examination should include the entire genital and rectal area. The condition of the vulva, urethral meatus, and vaginal introitus should be noted. Infections in prepubertal girls usually involve the vulva as opposed to only the vagina. The presence of bruises, lacerations, or scrapes in the genital area is suggestive of sexual abuse, although it must be remembered that in most cases of child sexual abuse, the examination reveals no evidence of trauma. Excoriations around the rectum or vagina suggest itching caused by pinworms. A rash that spares skin folds is consistent with an irritative cause; one that is predominantly within the skin folds suggests candidiasis.

Having the girl sit on her mother's lap with her legs spread so that they dangle outside her mother's legs will often afford the examiner a clear view of the vulva and vaginal introitus. Alternatively, she may lie on her back in the frog-leg position or face down on the examining table in the knee-chest position. Care should be taken to avoid touching or manipulating the sensitive unestrogenized hymen of a prepubertal child to minimize pain. If a foreign body is thought to be present (because of a thick discharge that is often bloody and sometimes foul smelling) but not visualized, then irrigating the vagina with a soft, flexible catheter and

### BOX 205-1 Causes of Vaginal Discharge in Prepubertal Girls

- Nonspecific vaginitis (the most common cause)
- Irritative (bubble baths, sand); the vulva is often involved as well. Nonabsorbent, occlusive clothing such as nylon undergarments, tights, bathing suits also irritate the vulva, leading to skin breakdown and infection. Although uncommon, *Candida* species infections can arise under these circumstances.
- Poor perineal hygiene
- Foreign body
- Associated systemic illness (group A streptococci, varicella)
- Other respiratory pathogens (eg, *Haemophilus influenzae*) may also cause discharge
- Enteric infections
- *Escherichia coli* with foreign body
- *Shigella* organisms
- *Yersinia* organisms
- *Enterobius vermicularis*
- Sexually transmitted infections (strong presumption of sexual abuse)
- *Neisseria gonorrhoeae*
- *Trichomonas vaginalis*
- *Chlamydia trachomatis* (Whether this organism alone can cause discharge is unclear. *C trachomatis* is often isolated in conjunction with *N gonorrhoeae*.)
- Primary vulvar skin disease
- Tumor, polyps (rare)

tepid saline solution will often flush out bits of toilet paper or small objects.

If sufficient vaginal discharge is present, then several drops of the secretion should be placed on 2 glass slides. If the discharge is scant, then a saline-moistened cotton swab can be introduced into the vagina to obtain samples for the glass slides. Several drops of normal saline solution should be added to 1 slide to create a wet preparation. Several drops of 10% potassium hydroxide should be added to the second slide, which should then be gently heated to dissolve epithelial cells, allowing visualization of hyphae. Slides should be examined, as indicated in Table 205-1. If indicated, cultures for *N gonorrhoeae* and *C trachomatis* should be performed; alternatively, evaluation with nucleic acid amplification tests may be easier to perform and provide more sensitive testing. A piece of cellophane tape with its sticky side applied to the perianal area and then onto a glass slide for microscopic examination may reveal the typical eggs of *E vermicularis*.

### Management

If the history or physical examination suggests an irritative origin, then parents should discontinue the offending agent and have the child wear cotton underpants. Sitz baths will provide temporary relief until natural healing takes place. Removal of a foreign body will result in rapid improvement and cessation of the discharge. Pinworm infestations should be treated in the usual manner. Infections caused by poor personal hygiene will respond to the general measures just listed, coupled with instructions about proper perineal hygiene. If the discharge is associated with another infection (such as *S pyogenes* or *Shigella* organisms), then it will disappear as the underlying infection is treated.

When the organism causing the vaginal discharge is found to be sexually transmitted, more comprehensive evaluation and treatment are required. Appropriate antibiotic treatment should be prescribed and a report to child protective services made.

Nonspecific vaginitis will usually respond to thorough perineal hygiene, sitz baths, and mild soaps. Patients should be advised to wear white cotton underpants and loose-fitting pants or skirts, to avoid nylon tights and tight pants, to avoid sitting for long periods in nylon bathing suits, and to wipe only from front to back. For persistent cases, the condition can be treated with amoxicillin, amoxicillin clavulanate, a cephalosporin, or clindamycin in standard childhood doses for 10 to 14 days. Alternatively, a 1- to 2-month daily low-dose antibiotic may be helpful. If these approaches are unsuccessful, then antibiotic creams (mupirocin, gentamicin, metronidazole, or clindamycin) or estrogen creams may be used. If symptoms persist, the patient should then be referred to a pediatric gynecologist.

### PUBERTAL AND POSTPUBERTAL ADOLESCENTS

With the onset of puberty, circulating estrogen and progesterone levels rise, stimulating vaginal mucus production and an increase in the turnover of vaginal

epithelial cells. Bartholin and sebaceous glands are also stimulated. Generally, the clear mucoid discharge that results will not cause problems. The amount of secretion, however, can increase with sexual excitement, as well as midway through a normal menstrual cycle. Discharge is particularly prominent at the onset of puberty (physiologic leukorrhea). Examination of a wet preparation will reveal vaginal epithelial cells only. The high protein content of this discharge, absorbed onto underwear, causes yellow staining. Traditionally, occlusive nylon or rayon underpants have been alleged to cause a nonspecific vaginal discharge; however, that association may be spurious.

A wide variety of organisms are normally found in the vagina. These organisms, especially the lactobacilli, help maintain the normal acidic pH of the vagina, which resists infection. Some of the organisms that cause vaginitis and vaginal discharge in this age group are sexually transmitted or associated with sexual activity. Because many teenagers fear admitting to sexual intercourse, a negative response to queries about sexual activity should not rule out consideration of a sexually transmitted organism as the cause of the discharge. Sexual abuse and the presence of a foreign body (eg, a retained tampon or condom) should also be considered. If a sexually transmitted organism has caused the discharge, then the patient's sexual partner should be notified and treated. Patients should refrain from sexual intercourse until they complete treatment. Otherwise, reinfection from the partner may occur. Use of spermicides or douching can cause vaginitis.

The organisms and conditions commonly responsible for vaginal infections or vaginal discharge in pubertal young women and their treatments are listed in Table 205-1. Although the characteristics of each type of infection are said to be typical, the discharge observed on examination does not always fit these classic presentations. The laboratory methods outlined in Table 205-1 therefore are of considerable diagnostic utility. However, they are not 100% sensitive. *T vaginalis* may not be noted during microscopic examination even if the vaginal fluid is examined immediately under the microscope to avoid drying of the organisms. The vaginal wet preparation is 64% to 80% sensitive at identifying trichomonads compared with culture, depending on the presence of symptoms and the experience of the microscopist. Nucleic acid amplification tests (NAAT) are the most sensitive commercial tests for detecting trichomonas infection but are not available as a point-of-care test. Other FDA-cleared tests are the OSOM Trichomonas Rapid Test (results in 10 minutes) and the Affirm VP III (results in 45 minutes). *T vaginalis* can be found on Pap tests but the Pap test is not considered a diagnostic test for trichomoniasis. Although the Centers for Disease Control and Prevention consider a Gram stain the gold standard for the diagnosis of bacterial vaginosis, it is not widely used in clinical practice. In the absence of a Gram stain, 3 of 4 clinical criteria should be met to make the diagnosis: (1) homogeneous, thin white discharge evenly coating the vaginal walls; (2) clue cells on microscopic examination; (3) vaginal fluid pH higher than 4.5; (4) positive "whiff test"—a fishy odor

**Table 205-1** Major Causes of Vaginal Discharge in Pubertal Girls

AGENT	DISCHARGE	ODOR; pH	DYSURIA; PRURITUS	OTHER CLUES	DIAGNOSIS	TREATMENT <sup>a</sup>
<i>Candida albicans</i>	Thick, white, curdlike, cheesy	None usually; pH 4.5 (obtained from midvagina with nitrazine paper)	Dysuria frequent; pruritus (4+)	Vulva affected; association with use of some oral contraceptives and, in some women, with antibiotic use	Hyphae on potassium hydroxide examination	A variety of effective treatments are available for vaginal candidiasis, including creams, suppositories, and intravaginal tablets. Three-, 5-, and 7-day therapies offer no advantage over single-day treatments. Fluconazole 150 mg orally as a single dose is as effective as other regimens; however, more systemic side effects may occur. Ultimately, the best treatment is a combination of patient preference, what treatments are covered by her insurance policy, and whether it is less expensive or more convenient for the patient to obtain a prescription medication or purchase an over-the-counter treatment.
<i>Trichomonas vaginalis</i>	Frothy; yellow-green or gray	Foul smelling; pH 5.2–5.5	Dysuria frequent; pruritus	Low abdominal pain; “strawberry” cervix; punctate vaginal hemorrhages	Motile trichomonads on wet preparation; avoid drying specimen; NAAT most sensitive; other antigen detection tests also available	Metronidazole 2 g orally in a single dose or tinidazole 2 g orally in a single dose. Alternative regimen is metronidazole 500 mg twice daily for 7 days. If failure occurs with either of the indicated regimens (and reinfection is excluded), the patient should be treated with metronidazole 500 mg twice daily for 7 days. Repeated failures should be treated with tinidazole or metronidazole at 2 g orally for 7 days. The patient should be advised to avoid alcohol until 24 hours after completion of therapy with metronidazole or 72 hours after treatment with tinidazole.
Bacterial vaginosis <sup>b</sup>	Homogeneous, thin, white discharge that smoothly coats the vaginal walls	A fishy odor of vaginal discharge before or after addition of 10% KOH (ie, the whiff test); pH >4.5	No dysuria; slight pruritus	Occurs in association with anaerobes and <i>G vaginalis</i>	Clue cells on wet preparation (bacteria-coated epithelial cells); affirm VP III & OSOM BV Blue tests are commercially available tests when microscopy is not available	Metronidazole 500 mg orally twice daily for 7 days, metronidazole gel 0.75% 1 full applicator (5 g) intravaginally once daily for 5 days or clindamycin cream 2%, 1 full applicator (5 g) intravaginally every night at bedtime for 7 days. Alternative regimens include tinidazole 2 g orally once daily for 2 days or tinidazole 1 g orally once daily for 5 days or clindamycin 300 mg orally twice daily for 7 days or clindamycin ovules 100 mg intravaginally 1 at bedtime for 3 days. The patient should be advised to avoid alcohol until 24 hours after completion of therapy with metronidazole or 72 hours after treatment with tinidazole.

<sup>a</sup>Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines. *MMWR Recomm Rep*. 2015;64(RR-3):1–137.<sup>b</sup>Must have 3 of these 4 criteria to make diagnosis.Data from Amsel R, et al. *Am J Med*. 1983;74:14; Brunham RC, et al. *N Engl J Med*. 1984;311:1; Rein MF, Chapel TA. *Clin Obstet Gynecol*. 1975;18:73; and Sobel J. *N Engl J Med*. 1997;337:1896.



to the vaginal discharge before or after the addition of 10% KOH. A DNA probe-based test, as well as a card test to detect increased pH and trimethylamine and proline-aminopeptidase, may also be useful in the diagnosis of bacterial vaginosis.

The role of *N gonorrhoeae* and *C trachomatis* in causing vaginal discharge has been reassessed recently. The presence of yellow vaginal discharge on speculum examination has been associated with infection by either organism; in contrast, neither profuse vaginal discharge nor a foul or fishy odor predicted infection with either. Nonetheless, because sexually transmitted infections often co-occur, appropriate screening tests for *N gonorrhoeae* and *C trachomatis* should be part of the evaluation of vaginitis if *T vaginalis* is found or if the patient reports a new sexual partner.

Bacterial vaginosis is a complex syndrome characterized by decreased *lactobacilli* and increased concentrations of several anaerobic microorganisms. The pathogenesis of this disorder continues to be poorly understood. Bacterial vaginosis is associated with having multiple sex partners, douching, smoking, and the presence of sexually transmitted infections. However, because it sometimes occurs in women who have never had sexual contact, bacterial vaginosis is not considered a sexually transmitted infection. Current evidence indicates that women who have bacterial vaginosis are at increased risk for developing pelvic inflammatory disease after instrumentation of the genital tract and, if pregnant, are more likely to deliver a premature infant or experience postpartum complications. Therefore, prompt treatment is essential. Treatment of sexual partners is not currently recommended because it does not affect the disease process.

Occasionally, herpesvirus infections of the vulvovaginal area or cervix (or both) are associated with vaginal discharge. Typically, pain or a burning sensation is felt in the genital area. The vulva is reddened, and groups of small vesicles are noted on the vulva, in the vagina, or on the cervix. If the vesicles have ruptured, then the examiner sees only small ulcerations. Inguinal adenopathy, fever, and malaise are usually present if this attack is the first one.

A teenager who has a persistent discharge that is unresponsive to therapy may not be complying with treatment or may have become reinfected by an untreated partner. If such is not the case, and if *N gonorrhoeae*, *C trachomatis*, and *T vaginalis* are excluded, and the discharge does not appear to fit any of the causes described earlier, then a trial of sitz baths, use of cotton as opposed to nylon underwear, and careful attention to perineal hygiene are warranted. If symptoms persist, then the patient should be referred to an adolescent medicine specialist or a gynecologist.

Candidal infections can be especially difficult to treat and may recur. Factors that predispose to candidiasis include oral contraceptive use, broad-spectrum antibiotic use, and diabetes mellitus. In cases of recurrent vulvovaginal candidiasis, either topical therapy for 7 to 14 days or oral fluconazole 150 mg repeated 72 hours after the first dose is recommended as initial

treatment. If more intensive treatment is warranted, a recent study of adult women with recurrent vulvovaginal candidiasis demonstrated significant reduction of symptoms among those treated with oral fluconazole 150 mg once weekly for 6 months after initial treatment of 1 dose every 3 days for 3 doses. A variety of monthlong antifungal treatments have been successful; however, intravaginal treatment over a long period is inconvenient for most patients. Although long-term ketoconazole has been used to suppress recurrent infection, hepatotoxicity is a concern. Male sexual partners should also be treated if they have any signs or symptoms of penile candidal involvement.

### WHEN TO REFER

- Physician is uncomfortable with evaluating genital complaints in prepubertal girls
- Physician lacks experience in performing pelvic examinations
- Evaluation yields evidence of sexual abuse
- Discharge persists despite seemingly appropriate therapy

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Center for Young Women's Health* (Web page), Boston Children's Hospital ([www.youngwomenshealth.org](http://www.youngwomenshealth.org))
- *Info for Teens* (Web page), Planned Parenthood ([www.plannedparenthood.org/info-for-teens](http://www.plannedparenthood.org/info-for-teens))
- *The Pelvic Exam* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

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## Chapter 206

# VOMITING

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Vomiting, a common symptom of acute and chronic illness in childhood, is an active process requiring coordination between autonomic and somatic nervous systems. It must be distinguished from regurgitation, which is passive reflux of gastric contents into the esophagus and mouth through a relaxed lower esophageal sphincter. Vomiting is usually preceded by nausea in association with increased salivation, pallor, and diaphoresis. Retching (coordinated contraction of abdominal and intercostal muscles, as well as the diaphragm, with simultaneous closure of the glottis) immediately precedes the actual vomiting. Reflux of duodenal contents into the stomach, resulting from nonperistaltic contractions of the small bowel, is associated with elevation and relaxation of the proximal stomach and inhibition of antral motility. Increased intragastric pressure from contraction of the abdominal wall musculature and lowering of the diaphragm then result in expulsion of stomach contents. Brainstem signals transmitted to a cerebral site, not yet identified, result in the conscious sensation of nausea. Psychogenic causes of nausea (eg, anticipatory nausea) presumably occur directly at a cerebral site.

Five classes of stimuli provoke nausea and vomiting: (1) toxic substances within the lumen of the gastrointestinal tract, which initiate release of mediators by enteroendocrine cells (including 5-hydroxytryptamine, substance P, and cholecystikinin [CCK]); (2) absorbed or parenterally administered toxins, which act directly on the area postrema (also referred to as the *chemoreceptor trigger zone*—a major lower brainstem center for coordination of drug-induced vomiting); (3) pathologic processes in viscera (eg, gastrointestinal dilation or inflammation, renal failure); (4) central nervous system (CNS) stimuli (eg, fear, anticipatory nausea, raised intracranial pressure); and (5) vestibular stimuli (eg, motion sickness) that result in nausea and vomiting by way of the autonomic nervous system. Motor outputs of retching and vomiting are coordinated by brainstem nuclei (known in the past as the “vomiting center”). Vomiting provoked by CNS stimuli may occur with little or no prodrome of retching or nausea.

Understanding the role of neurotransmitters as mediators in the initiation of vomiting has led to a range of new antiemetics. The area postrema, as well as autonomic pathways and other brainstem nuclei, is rich in enkephalins, 5-hydroxytryptamine type 3 (5-HT<sub>3</sub>) receptors, dopamine receptors, and neurokinin-1 (NK<sub>1</sub>) receptors. Enkephalins and 5-HT both stimulate release of dopamine. Dopamine receptor, 5-HT<sub>3</sub>, and NK<sub>1</sub> antagonists have been successful in the treatment of chemotherapy-induced nausea and vomiting. Antihistamines and anticholinergics prevent motion sickness by acting at histamine (H<sub>1</sub>) and muscarinic cholinergic receptors, respectively, in the nucleus

ambiguus in the lower brainstem and in the lateral vestibular nucleus in the midpons.

## CAUSES AND DIFFERENTIAL DIAGNOSIS

Box 206-1 lists the most frequent causes of vomiting in infants and children. In infancy, regurgitation, or spitting up, is very common and most often a developmental event that has no sequelae and gradually resolves. Pathologic gastroesophageal reflux (ie, gastroesophageal reflux disease) is defined by the association of regurgitation with complications, including esophagitis (sometimes with anemia or stricture), recurrent apnea, aspiration pneumonia, or failure to thrive. Bilious vomiting, especially when associated with the first vomitus, usually occurs only with ileus or intestinal tract obstruction below the ampulla of Vater (second portion of the duodenum). In newborns, bilious vomiting can be associated with necrotizing enterocolitis. In older children who vomit persistently, reflux of bile from the duodenum into the stomach may lead to bilious vomiting without gastrointestinal tract obstruction. Projectile vomiting commonly occurs with pyloric stenosis. When this condition persists, however, gastric atony may eliminate the projectile character. A succussion splash (the splashing sound present when a patient who has fluid in a hollow organ is gently shaken on physical examination) may be present, as in other causes of gastric outlet obstruction. Vomiting associated with increased intracranial pressure may be projectile and may take place in the absence of nausea or retching.

Persistent vomiting in a newborn or young infant who has no evidence of infection usually suggests a congenital gastrointestinal anomaly, inborn error of metabolism, or CNS abnormality such as hydrocephalus or subdural effusion. If the history and physical examination results do not suggest a cause, then evaluating all 3 possibilities simultaneously is best. When the sudden onset of bilious vomiting develops in a previously well newborn, especially within the first few days of life, the physician must consider a malrotation with secondary midgut volvulus. Midgut volvulus is a surgical emergency requiring early diagnosis and surgical intervention. In a sick newborn, the diagnosis of necrotizing enterocolitis must be considered in the event of bilious vomiting, especially with blood in the stool. Beyond the first week of life but within the first 2 months, pyloric stenosis is the most common cause of persistent vomiting in an otherwise well infant. In the older infant or child, the entire spectrum of causes of vomiting listed in Box 206-1 should be considered. Patients who have celiac disease may occasionally have minimal or no diarrhea but prominent vomiting. When an older child exhibits acute vomiting and somnolence, the physician should always consider drug overdose (especially acetaminophen, aspirin, or iron), meningoencephalitis, and inborn errors of metabolism (especially mitochondrial fatty acid oxidation) in the differential diagnosis. Persistent or recurrent vomiting without other symptoms may be the major manifestation of an emotional disorder in childhood. Therefore, a complete psychosocial history is an important part of the evaluation.

**BOX 206-1 Causes of Vomiting (Arranged by Usual Age of Earliest Occurrence)****INFANCY/EARLY CHILDHOOD****Gastrointestinal****Congenital**

- Regurgitation—gastroesophageal reflux (developmental or pathologic)
- Atresia—stenosis (tracheoesophageal fistula, antral web, intestinal atresia, annular pancreas)
- Gastrointestinal tract duplication
- Volvulus (secondary to an error in rotation and fixation or to Meckel diverticulum)
- Congenital bands
- Meconium ileus (cystic fibrosis), meconium plug
- Hirschsprung disease

**Acquired**

- Acute infectious gastroenteritis
- Food allergy, cow milk protein intolerance, eosinophilic gastroenteritis
- Eosinophilic esophagitis
- Pyloric stenosis
- Intussusception
- Celiac disease—risk is inherited, but clinical manifestations occur only after introduction of gluten in diet
- Incarcerated hernia—inguinal, internal secondary to old adhesions
- Postviral gastroparesis<sup>a</sup>
- Adynamic ileus—the mediator for many nongastrointestinal causes of vomiting
- Neonatal necrotizing enterocolitis
- Chronic granulomatous disease with gastric outlet obstruction

**Nongastrointestinal**

- Infectious—otitis, urinary tract infection, pneumonia, upper respiratory tract infection, sepsis, meningitis
- Metabolic—aminoaciduria and organic aciduria, galactosemia, fructosemia, adrenogenital syndrome, renal

tubular acidosis, hyperammonemia, disorders of fatty acid oxidation (eg, medium-chain acyl-coenzyme A dehydrogenase deficiency), mitochondrial disease

- Central nervous system—trauma, tumor, infection, increased intracranial pressure, ventriculoperitoneal shunt failure, diencephalic syndrome, rumination, autonomic responses (pain, shock), anticipatory nausea and vomiting

**CHILDHOOD/ADOLESCENCE****Gastrointestinal**

- Appendicitis
- Food poisoning (staphylococcal, clostridial)
- Peptic disease—ulcer, gastritis, duodenitis, *Helicobacter pylori* infection
- Trauma—duodenal hematoma, traumatic pancreatitis, perforated bowel
- Pancreatitis—viral, trauma, drug induced, cystic fibrosis, hyperparathyroidism, hyperlipidemia, organic acidemias, hereditary pancreatitis, cystic fibrosis gene mutation
- Gallbladder—cholelithiasis, choledochal cyst
- Crohn disease
- Adhesions—congenital or secondary to previous abdominal surgery
- Visceral neuropathy or myopathy
- Superior mesenteric artery syndrome<sup>b</sup>

**Nongastrointestinal**

- Medications—anticholinergics, alcohol, idiosyncratic reaction (eg, codeine), chemotherapy, radiation therapy, overdose (especially aspirin or acetaminophen)
- Central nervous system—cyclic vomiting, migraine, anorexia nervosa, bulimia nervosa
- Motion sickness
- Metabolic—diabetic ketoacidosis, acute intermittent porphyria
- Pregnancy

<sup>a</sup>Sigurdsson L, Flores A, Putnam PE, et al. Postviral gastroparesis: presentation, treatment, and outcome. *J Pediatr*. 1997;131(5):751–754.

<sup>b</sup>Blank V, Werlin S. Superior mesenteric artery syndrome in children: a 20-year experience. *J Pediatr Gastroenterol Nutr*. 2006;42:522.

Cyclic vomiting is characterized by repeated episodes of intense nausea and vomiting with at least 3 attacks over a 6-month period or 5 attacks in any interval. Episodes last 1 hour to 10 days and are separated by at least a week. In an individual, the attacks are very stereotypic. Uncontrollable vomiting and retching (at least 4 times in an hour for at least 1 hour) are typical of an attack; but between episodes, children act well. Approximately 10% of these children have an identifiable gastrointestinal or extraintestinal (eg, renal, metabolic, or neurologic) disorder as the probable cause.

Abdominal migraine is a common cause of cyclic vomiting and is characterized by the paroxysmal onset of repetitious attacks often relieved with sleep. A strong family history of migraine is common.

Headache typical of migraine may rarely occur with episodes; abdominal pain is not unusual. Cyproheptadine, amitriptyline, topiramate, and propranolol are highly effective as prophylactic treatment for abdominal migraine; treatment success helps confirm the diagnosis. Abdominal epilepsy is a much less common cause of cyclic vomiting. A complete history of the sequence of events and electroencephalographic evaluation are useful in the evaluation, and anticonvulsants can be tried when this condition is suspected.

**EVALUATION**

Patient history is often the most helpful in narrowing the wide range of potential causes of vomiting. Evaluation of the gastrointestinal tract usually includes an

upper gastrointestinal contrast roentgenographic study. However, in an infant with persistent vomiting between 2 and 12 weeks of age, the first study is often an ultrasound of the abdomen for pyloric stenosis. Food allergy is in the differential diagnosis for gastroesophageal reflux in infants; therefore, with intractable reflux symptoms, it is reasonable to undertake a 2-week feeding trial with hypoallergenic formula. In the older infant or child with intractable reflux symptoms, eosinophilic esophagitis should be a consideration and requires endoscopic evaluation of the esophagus. Endoscopy is feasible in all children, even newborns, if performed by an experienced examiner using an appropriately sized instrument. Esophageal pH monitoring and impedance monitoring, esophageal biopsies, and gastroesophageal scintiscan are all useful in establishing a diagnosis of gastroesophageal reflux. Endoscopically placed wireless esophageal pH capsule monitoring can be performed in children older than 2 to 3 years and is generally well tolerated.

If brain tumor is a consideration, magnetic resonance imaging is more sensitive than a computed tomography scan of the head. Further workup for metabolic or neurologic disease should be considered, as appropriate. With persistent vomiting, the physician should expect to see a metabolic alkalosis; metabolic acidosis raises concerns about an underlying metabolic disorder or drug intoxication. Metabolic workup often includes a urine test for organic acids and amino acids, urinalysis for ketones as well as serum glucose, blood urea nitrogen, electrolytes, lactate, ammonia, and total carnitine and acylcarnitine levels. In a postpubertal girl, pregnancy must always be considered in the differential diagnosis of vomiting.

When a midgut volvulus is suspected in a newborn or older child, a plain radiograph of the abdomen may show a paucity of gas distal to the upper small intestine; however, the radiograph may not be helpful. An upper gastrointestinal contrast radiographic study should be done at once, with the controlled introduction of barium through a nasogastric tube after gastric aspiration. A barium enema investigation of cecal position is a less reliable study when evaluating a patient for malrotation because of the lack of complete correlation of developmental rotation of the cecum with that of the duodenum.

## COMPLICATIONS

The most significant complications of vomiting include dehydration and electrolyte imbalance, especially when the vomiting is persistent, as well as aspiration pneumonia, hemorrhage from prolapse gastropathy (a hemorrhagic area on the posterior wall of the proximal stomach), or, less commonly, a tear at the gastroesophageal junction (Mallory-Weiss syndrome) and rupture of the esophagus (very uncommon in children). Feeding refusal may follow persistent vomiting, especially in infants.

## TREATMENT

Acute intercurrent vomiting without serious underlying disease or significant dehydration should be treated by administering clear liquids by mouth (eg, in

acute gastroenteritis or otitis media). The usually advisable course is to start with a period of 4 to 6 hours without oral intake and then begin with frequent small quantities of clear liquids (1 teaspoonful every few minutes for infants) and gradually increase the volume and extension of the period between oral fluids. If vomiting is associated with diarrhea and dehydration, then oral rehydration solution is indicated. Carbonated beverages may increase vomiting. Fluids of high osmolality, long-chain triglycerides, and anticholinergic drugs all tend to slow gastric emptying and should be avoided.

The drugs used most commonly, when necessary, for symptomatic improvement of acute or persistent vomiting are ondansetron and promethazine. If emesis interferes with administration, ondansetron is available as an oral disintegrating tablet and promethazine as a suppository. Ondansetron is generally preferred because of fewer side effects. When indicated, ondansetron has been used in children older than 6 months for vomiting associated with gastroenteritis, reducing the frequency of emesis and need for intravenous hydration.

For chemotherapy-induced vomiting, 5-HT<sub>3</sub> receptor antagonists (especially ondansetron and granisetron) have been effective. Dexamethasone and NK<sub>1</sub> receptor antagonists (aprepitant) can be added when necessary. Metoclopramide is added occasionally, but less frequently than in the past. Unfortunately, these treatments are not as effective in controlling nausea as vomiting.

H<sub>1</sub> receptor antagonists (including diphenhydramine, dimenhydrinate, meclizine, and promethazine) and muscarinic cholinergic receptor antagonists (eg, scopolamine) prevent motion sickness. Low-dose erythromycin or metoclopramide has been used to treat poor gastric emptying when there is not a mechanical obstruction (eg, postviral gastroparesis).

Patients should be monitored for signs of dehydration. For persistent vomiting with feeding, a nasoduodenal infusion may be useful. Significant vomiting that requires intravenous fluid therapy is usually associated with hypochloremic alkalosis with secondary hypokalemia. Intravenous fluids should repair the deficits.

Management of gastroesophageal reflux must be individualized. The extent of treatment necessary depends on the volume of emesis and the presence of complications of reflux. Medical management for infants includes thickening feedings with cereal (a standard concentration is 1 tablespoonful of cereal for each 1 to 2 ounces of formula) or the use of commercial antiregurgitant formula, which can reduce the amount of overt emesis but not reflux into the esophagus. Although prone positioning of young infants reduces reflux, this should only be done when the infant is observed and awake because the risk for sudden infant death syndrome is increased in this position. Prone positioning may be useful after 1 year of age. Left lateral decubitus positioning is discouraged for sleeping infants as well because these infants may become prone during sleep. Elevating the head of the bed remains standard therapy for older children and adults. Older children may benefit from avoiding snacks or liquids after dinner and agents that exacerbate esophagitis (alcohol, caffeine, and smoking).



Medications are commonly used to decrease exposure of the esophageal mucosa to acid (antacids, H<sub>1</sub> receptor blockers, or proton pump inhibitors). Attempts to improve lower esophageal function and gastric emptying (eg, metoclopramide) have been less successful because of unacceptable medication side effects. Baclofen has been suggested as an agent to reduce the frequency of inappropriate relaxations of the lower esophageal sphincter, but there is still limited experience in children. A slurry of sucralfate (a cytoprotective agent) is used occasionally for management of acid damage to the esophagus. When a child has severe gastroesophageal reflux, medical management may be unsatisfactory. In this case, antireflux surgery (fundoplication) should be considered. In this group of children, the results of surgery are generally good when performed by an experienced surgeon, and the benefits can be long lasting. In children who have psychomotor retardation and gastroesophageal reflux, antireflux surgery may not eliminate respiratory symptoms because other factors, such as swallowing dysfunction, may contribute to these findings. Among children undergoing a Nissen fundoplication, the risk for postoperative complication may be in the range of 10% to 30% and underscores the need for careful patient selection for this operation.

### WHEN TO REFER

- Persistent vomiting
- Recurrent episodes of vomiting
- Vomiting associated with a significant underlying process (eg, surgical abdomen, neurologic problem)

### WHEN TO ADMIT

- Intractable vomiting with dehydration
- Vomiting in association with symptoms or signs of an acute abdominal process (eg, acute appendicitis, pancreatitis, cholecystitis)
- Vomiting in association with symptoms or signs of raised intracranial pressure

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Caring for Your Baby and Young Child: Birth to Age 5* (book), American Academy of Pediatrics (shop.aap.org)
- *Treating Vomiting* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/abdominal/Pages/Treating-Vomiting.aspx](http://www.healthychildren.org/English/health-issues/conditions/abdominal/Pages/Treating-Vomiting.aspx))

#### Medical Decision Support

- *Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN)* (article), *Journal of Pediatric Gastroenterology and Nutrition*, Vol 49, Issue 4, 2009

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Lichtdale JR, Gremse DA; American Academy of Pediatrics Section on Gastroenterology, Hepatology, and Nutrition. Gastroesophageal reflux: management guidance for the pediatrician. *Pediatrics*. 2013;131(5): e1684–e1695 ([pediatrics.aappublications.org/content/131/5/e1684](http://pediatrics.aappublications.org/content/131/5/e1684))

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## Chapter 207 WEIGHT LOSS

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Weight loss in an infant, child, or adolescent is an uncommon but highly significant event. As the chief complaint or as an incidental finding, weight loss should be evaluated and followed up carefully by serial measurements and documentation on standardized growth charts. Revised growth charts from the Centers for Disease Control and Prevention released in January 2002 represent a broad cross-section of children in the United States. The charts are based on 5 large national samples that included breastfed and formula-fed infants, adolescents to the 20th birthday, and a racially and ethnically diverse population. With emphasis on growth parameters and body mass index, the charts include both 3rd and 97th percentile curves, which may be valuable in assessing weight loss. The definition of significant weight loss varies by the child's age and includes acute and chronic causes.

Subjective impressions of weight loss should be verified objectively before an evaluation is undertaken. True weight loss, however, may sometimes be difficult to differentiate from factitious weight loss, even when weights are documented in the medical record. Errors in weighing children occur at frequencies ranging from 5% to 20% of all children weighed, most commonly from faulty equipment or poor technique, such as weighing with the child's clothes on.

### NEWBORNS AND YOUNG INFANTS

The full-term healthy newborn may lose 5% to 10% of birth weight in the first few days but should regain

this weight by day 10 of life. A loss of more than 10% to 12% of birth weight is uncommon and should be investigated. The assessment should include overall health of the infant, adequacy of oral intake, and calculation of fluid losses from vomitus, urine, or stool. In general, an infant should gain 25 to 30 g each day in the first 3 months of life.

The most common reason for the breastfed infant to lose more weight than expected or to fail to regain the lost weight by 10 days of age is inadequate intake at the breast. The parental perception that the mother's milk supply is insufficient or less nutritious than formula should not be reinforced. Inadequate weight gain occurs because of infrequent or short feedings, failure of the let-down reflex, or improper positioning of the infant for an effective suck. The infant may appear well or may have signs of significant dehydration. Mothers may report that the infant has less than 6 urinations a day and few bowel movements. Lack of bowel movements in the breastfed newborn is a key indicator of inadequate caloric intake.

The breastfeeding mother should be observed nursing, if possible, and specific evidence of a let-down reflex should be sought, including uterine cramps, milk dripping or spraying from the opposite breast, and a pins-and-needles sensation in the breast at the beginning of each nursing. The infant should be observed latching onto the breast correctly, and loud swallowing or occasional choking may be noted at the beginning of the feeding. The mother's motivation to breastfeed and her positive or negative feelings about the experience should be discussed. Encouragement and support should be given for continuation of nursing, including specific suggestions for maternal rest, nutrition, and nursing frequency (every 2–3 hours in the day) to build up the milk supply. Formula or other fluids should not be recommended unless serious concerns exist about the infant's well-being. Recommending discontinuing breastfeeding prematurely is inappropriate for the physician. An appropriate weight gain in the following few days provides evidence that the infant is well and confirms the diagnosis of initial underfeeding. Infants who fail to thrive while breastfeeding require more intensive nutritional rehabilitation while still preserving breastfeeding.

The formula-fed newborn rarely loses more than 5% of birth weight in the first few days, inasmuch as complete nutrition is available beginning a few hours after birth. Weighing less than birth weight at the age of 10 days is unusual for a formula-fed infant, and such an infant should be evaluated thoroughly. An error in feeding caused by maternal inexperience is the usual explanation, with poor caloric intake most often from either inadequate feedings or faulty preparation of formula. If such is not the case, then a thorough search for an organic problem and an evaluation of family dynamics, support mechanisms, and adjustment to the newborn are indicated. In rare instances, a newborn will lose weight as a result of inadequate intake for other reasons, such as infection, congenital heart disease, inborn error of metabolism, somnolence from maternal medications or substance abuse,

or poor suck resulting from a craniofacial or central nervous system (CNS) abnormality. Weight loss can also result from excessive fluid loss, such as vomiting associated with congenital gastrointestinal malformations (duodenal atresia, annular pancreas, volvulus), or from diarrhea or polyuria (diabetes insipidus, renal disease) (Box 207-1).

## OLDER INFANTS, PRESCHOOLERS, AND SCHOOL-AGED CHILDREN

The most common reason for weight loss in older infants and toddlers is fluid loss as a result of fever, vomiting, and diarrhea. The loss of weight typically amounts to less than 10% of premorbid body weight and is usually reversed after a few hours of oral or intravenous fluid replacement.

Infants who lose more than 10% of their body weight from excessive vomiting require further investigation for pyloric stenosis and malrotation as well as for tumors of the CNS, which may cause vomiting, anorexia, and cachexia.

Weight loss may also accompany any severe febrile illness, such as pneumonia, pyelonephritis, septic arthritis, osteomyelitis, or meningitis, as well as less severe illnesses, such as stomatitis and pharyngitis. Resolution of the infection is often followed by a period of catch-up growth and weight gain.

Inefficient use of caloric intake can also result in weight loss. Cystic fibrosis, the most common disease in which malabsorption occurs in childhood, may appear in infancy as poor weight gain or actual weight loss. Intestinal disorders such as celiac disease, Hirschsprung disease, inflammatory bowel disease, and other causes of malabsorption will also lead to weight loss or poor weight gain.

Weight loss from chronic diarrhea may be caused by a variety of infectious diseases, including HIV infection. A diagnosis of tuberculosis should also be considered in every child who has lost weight.

Children with new-onset insulin-dependent diabetes mellitus commonly lose weight (often 10% or more of body weight) despite polyphagia and polydipsia. Hyperthyroidism is another endocrine disorder that may lead to weight loss in childhood.

Malignancies, including leukemia, lymphoma, and neuroblastoma, may have weight loss as part of their presenting picture or even as their initial symptom.

Poverty remains the greatest single risk factor for failure to thrive in the United States; however, other psychosocial factors (poor parent-child interaction, depression, rumination) often underlie an infant's or a child's poor growth and development. Actual weight loss is much less common in this setting than a slow-down or cessation of weight gain and linear growth. Psychosocial dysfunction that results in a child's weight loss requires a prompt and thorough evaluation. Eating disorders have been described in prepubertal children as young as 7 years. In addition, as reported by the Agency for Health Care Research and Quality, the largest increase in the rate of hospitalizations for eating disorders occurred in children younger than 12 years.

**BOX 207-1 Differential Diagnosis of Weight Loss by Age Group****NEWBORNS AND YOUNG INFANTS**

- Difficulties in establishing breastfeeding
- Inappropriate dilution or choice of formula
- Inadequate intake
- Infection
- Metabolic abnormality
- Craniofacial abnormalities
- CNS dysfunction
- Somnolence from maternal medications/substance abuse
- Congenital heart disease
- Maternal depression/inexperience/lack of knowledge
- Excessive losses secondary to vomiting or diarrhea
- Vomiting because of gastrointestinal malformations (duodenal atresia, others)
- Polyuria (diabetes insipidus, renal disease)
- Diarrhea

**OLDER INFANTS, PRESCHOOLERS, AND SCHOOL-AGED CHILDREN**

- Pyloric stenosis
- Gastroesophageal reflux
- CNS tumors
- Vomiting
- Diarrhea
- Fever and infection
- Diabetes mellitus
- Excessive activity
- Inadequate intake

- Fever and infection
- Tuberculosis
- Surgery
- Medication effect (loss of appetite)
- Malignancy
- Congenital heart disease
- Malabsorption syndromes
- Inflammatory bowel disease
- Immunodeficiency disorders, especially HIV infection
- Psychosocial dysfunction
- Poverty
- Neglect; nonorganic failure to thrive
- Parental depression
- Childhood depression
- Rumination
- Childhood eating disorder

**ADOLESCENTS**

- Dieting behavior
- Adolescent eating disorders
- Anorexia nervosa
- Bulimia nervosa
- Other eating disorders
- Psychiatric affective disorders, especially depression
- Malignancy
- Inflammatory bowel disease
- Diabetes mellitus
- Hyperthyroidism
- Tuberculosis

CNS, central nervous system; HIV, human immunodeficiency virus.

**ADOLESCENTS**

Monitoring the adolescent growth curve, including body mass index, is crucial to the recognition of weight loss and should be a part of every encounter. The prevalence of obesity in children and adolescents has increased in the past decade, leading to an unhealthy emphasis on dieting and weight loss among children and adolescents. Planned dieting must be distinguished from an eating disorder such as anorexia nervosa or bulimia nervosa. The 2010 American Academy of Pediatrics policy statement regarding the identification and management of eating disorders estimates that 0.5% of female adolescents have anorexia nervosa, that 1% to 2% meet criteria for bulimia nervosa, and that up to 5% to 10% of all cases of eating disorders occur in boys. The American Psychiatric Association acknowledges that a large number of patients do not meet the strict diagnostic criteria for anorexia nervosa and bulimia nervosa; in the 2013 revision of the *Diagnostic and Statistical Manual of Mental Disorders*, these individuals are labeled OSFED (Other Specified Feeding or Eating Disorder). The

prevalence of this diagnosis is estimated to be between 0.8% and 14%; these adolescents remain at risk for both physical and psychological complications from their altered eating habits.

Anorexia nervosa should be suspected when the adolescent is unwilling or unable to maintain body weight over a minimally normal weight for age and height and when attitudes and behaviors about eating or body image are distorted. The anorectic female adolescent may experience amenorrhea associated with emaciation and overactivity. The patient may demonstrate clinical signs of malnutrition such as hypothyroidism, bradycardia, hypothermia, and growth of lanugo-like hair on the body and extremities. Nutritional rehabilitation and psychiatric treatment are indicated. Adolescents who have bulimia indulge in binge eating, followed by self-induced vomiting, self-starvation, overactivity, or the use of cathartics or diuretics to reduce weight. These behaviors are practiced in secret, and the adolescent often denies them. An elevated serum bicarbonate level, hypokalemia, or high urine pH may provide evidence of chronic

vomiting. The patient is often depressed and self-deprecating and may seek medical aid when the eating-vomiting pattern becomes compulsive and out of the patient's control. Psychiatric evaluation and intervention are indicated.

Young adults who participate in sports may follow unhealthy weight-control practices to seek advantage in their athletic activities, including food restriction, vomiting, overexercise, diet pills, stimulants, insulin, nicotine, and voluntary dehydration. For adolescents who participate in sports in which weight loss is a goal (eg, wrestling, gymnastics, ice skating, running, swimming, diving, dancing), a thorough dietary and supplement history should be elicited.

Although significant weight loss during adolescence can often be ascribed to eating disorders, other diagnoses must be considered. These conditions include psychiatric disturbances (especially affective disorders), CNS tumors (particularly those of the hypothalamus, sella turcica, or other midline areas), malignancies (especially lymphoma), or gastrointestinal problems such as inflammatory bowel disease or other malabsorption syndromes. Systemic disorders such as diabetes mellitus, hyperthyroidism, autoimmune disease, and renal disease may cause significant weight loss in adolescents. Infectious diseases such as HIV infection and tuberculosis should be considered when an adolescent patient reports weight loss.

## INITIAL EVALUATION OF A COMPLAINT OF WEIGHT LOSS

The following should be included in the initial evaluation (Table 207-1):

1. A complete history and thorough physical examination, with special attention to dietary intake, family functioning, and the patient's emotional well-being. The growth chart should be reviewed and updated.
2. A complete blood cell count (CBC) and erythrocyte sedimentation rate (ESR). The CBC screens for oncologic factors and provides an overview of the nutritional state. The ESR may be elevated in autoimmune diseases, chronic infections, certain malignancies, and inflammatory bowel disease; it may be abnormally low in anorexia nervosa.
3. Serum electrolyte and kidney function tests should be obtained to evaluate for dehydration, to reveal evidence of pernicious or self-induced vomiting, and to rule out renal or adrenal disease.
4. Serum protein and albumin levels to assess liver function, to determine whether the weight loss represents malnutrition, and to rule out protein malabsorption. Reversal of the albumin-to-globulin ratio is often seen in autoimmune diseases and malignancies.
5. Tuberculosis skin test.
6. Stool for occult blood and tests of malabsorption to diagnose gastroenteritis, inflammatory bowel disease, and the various causes of malabsorption. The serum carotene level may be low in infancy and in malabsorptive conditions but is often elevated in anorexia nervosa.

**Table 207-1**

## Laboratory Studies Helpful in Weight Loss

SUGGESTED STUDIES	SUGGESTED DIAGNOSES
Complete blood cell count, smear	Anemia Infection Nutritional deficiencies Malabsorptive syndromes Malignancy
ESR	Autoimmune disease Infection Inflammatory bowel disease Malignancy Anorexia nervosa (very low ESR)
Serum electrolytes, kidney function tests	Dehydration Vomiting, self-induced or pernicious Renal dysfunction Adrenal disorders Metabolic disorder (with acidosis) Autoimmune disease
Serum protein and albumin levels	Liver dysfunction Malignancy Malnutrition Protein malabsorption Protein-losing enteropathy
Tuberculosis skin test	Tuberculosis
Stool for occult blood	Gastroenteritis Inflammatory bowel disease Enteropathies
Serum carotene; specific tests of malabsorption	Malabsorption syndromes Cystic fibrosis Anorexia nervosa (high carotene)
Urinalysis, including specific gravity; urine culture	Diabetes mellitus Diabetes insipidus Dehydration Urinary tract infection Renal disease Adolescent eating disorder (high pH)

ESR, erythrocyte sedimentation rate.

7. Urinalysis and urine culture to rule out diabetes mellitus, diabetes insipidus, dehydration, urinary tract infection, and renal disease. The urine pH may be high (>8) in adolescents who have eating disorders, particularly when vomiting occurs.

## WHEN TO REFER

Evidence or suspicion of

- Malignancy
- Endocrinopathy (thyroid, adrenal, pituitary)
- Gastrointestinal disorder (eg, gastroesophageal reflux; malabsorption, including cystic fibrosis; inflammatory bowel disease)
- Pancreatitis
- Heart disease
- Renal disease
- Pulmonary disease



- Rheumatologic condition
- CNS abnormality
- Metabolic disorder
- Surgical abdominal problem (eg, pyloric stenosis, Hirschsprung disease, volvulus)
- Immunodeficiency
- Unusual infection
- Psychiatric diagnosis in child or caretaker
- Anorexia nervosa or bulimia nervosa in the child or adolescent

### WHEN TO ADMIT

A newborn, when

- Weight loss cannot be managed as outpatient
- Weight loss of more than 12% to 15% of birth weight
- Excessive fluid loss (vomiting, diarrhea, polyuria)
- Evidence of infant hypernatremic dehydration
- Suspicion of infection, metabolic abnormality, congenital heart disease, other conditions requiring evaluation
- Extreme passivity of the infant, which may require tube feeding
- Need for intensive maternal education and support

At any age, when

- Weight loss is excessive (more than 5%–10% of previous weight)
- Excessive fluid loss from vomiting or diarrhea
- New-onset diabetes mellitus (usually)
- Evidence of severe febrile illness (pneumonia, pyelonephritis, osteomyelitis, meningitis, septic arthritis, others)
- Evidence of dehydration
- Physiologic instability
- Severe bradycardia
- Hypotension
- Hypothermia
- Orthostatic changes
- Electrolyte abnormalities (eg, hypernatremia, hypokalemia)
- Evidence of significant psychosocial dysfunction

An adolescent, when

- Eating disorder cannot be managed as outpatient
- Severe malnutrition, with weight
- Evidence of dehydration or electrolyte abnormalities
- Physiologic instability
- Acute food refusal
- Uncontrollable binge eating and purging
- Acute medical complication of malnutrition (syncope, seizures, cardiac failure, pancreatitis)
- Suicidal intent or ideation, or psychosis

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *About BMI for Children and Teens* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/nccdphp/dnpa/bmi/childrens\\_BMI/about\\_childrens\\_BMI.htm](http://www.cdc.gov/nccdphp/dnpa/bmi/childrens_BMI/about_childrens_BMI.htm))

- *Eating Disorders in Children* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/emotional-problems/Pages/Eating-Disorders.aspx](http://www.healthychildren.org/English/health-issues/conditions/emotional-problems/Pages/Eating-Disorders.aspx))
- *New Mother's Guide to Breastfeeding*, 2nd ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

#### Medical Decision Support

- *BMI Percentile Calculator for Child and Teen* (interactive tool), Centers for Disease Control and Prevention ([nccd.cdc.gov/dnpabmi/Calculator.aspx](http://nccd.cdc.gov/dnpabmi/Calculator.aspx))
- *Breastfeeding Handbook for Physicians*, 2nd ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Eating Behaviors of the Young Child: Prenatal and Postnatal Influences for Healthy Eating* (book), Dietz W, Birch L ([shop.aap.org](http://shop.aap.org))
- *Growth Charts—tutorials and information* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/growthcharts](http://www.cdc.gov/growthcharts))
- *Growth Charts* (chart), Centers for Disease Control and Prevention ([www.cdc.gov/growthcharts](http://www.cdc.gov/growthcharts)), also available at American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Pediatric Nutrition Handbook*, 7th ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

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## Chapter 208

# WHEEZING

Alfin G. Vicencio, MD; Joshua P. Needleman, MD

### DEFINITION

Wheezing, a continuous musical sound that represents turbulent intrathoracic airflow, is usually most prominent during expiration, but it may also be present in inspiration. A history of wheezing reported by family members, however, is insensitive and nonspecific because untrained observers without appropriate equipment often mistake many other respiratory sounds for wheezing.

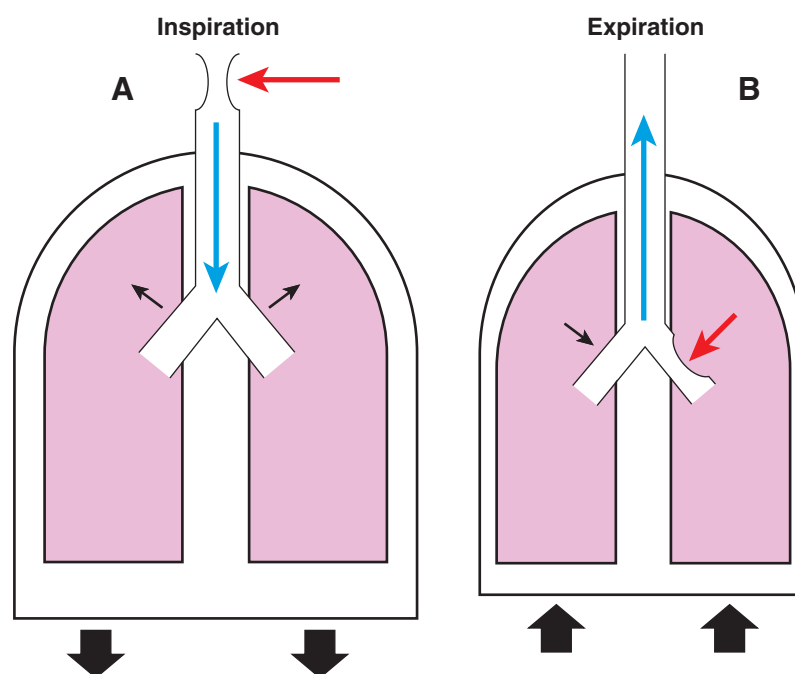
During the normal respiratory cycle, rhythmic expansion and contraction of the thorax lead to dynamic changes in thoracic pressures, allowing air to flow into and out of the lungs (Figure 208-1). On inspiration, the thoracic cavity expands, resulting in negative intrathoracic and airway pressures (relative to atmospheric pressure), allowing air to flow into the lungs. Extrathoracic airway obstruction, signaled by stridor (see Chapter 197, Stridor), is most likely to cause turbulent airflow during this phase of the respiratory cycle (see Figure 208-1, A). Expiration is accomplished by contracting the volume of the thoracic cavity, creating positive pressure in the thorax, which is

transmitted to the intrathoracic airways. Thus, during expiration, the intrathoracic airways are more prone to obstruction leading to turbulent airflow (see Figure 208-1, B). It should be noted that obstruction occurring at the thoracic inlet or severe fixed obstruction at any level of the airway may cause abnormal noises that are not limited to one phase of the respiratory cycle, including biphasic wheezing.

Although wheezing is most commonly associated with the distal airway obstruction seen in viral bronchiolitis or asthma, several other diseases can cause small airway obstruction and can be indistinguishable on physical examination. Similarly, abnormalities causing obstruction of the mid or distal trachea or main-stem bronchi, both of which reside within the thorax, can cause wheezing. Thus, although bronchiolitis and asthma will certainly account for most children who wheeze, the general pediatrician should be prepared to initiate a more extensive evaluation for the wheezing child, particularly for patients with unusual presentations or if conventional treatment yields less than optimal results.

### DIFFERENTIAL DIAGNOSIS

The differential diagnosis of wheezing is extensive and includes any process that can cause obstruction of intrathoracic airways. Because the intrathoracic airways include large centrally located airways and smaller peripheral bronchioles, determining the level of obstruction is often helpful before generating a list of differential diagnoses (see Evaluation).



**Figure 208-1** The respiratory cycle and related airway changes. **A**, During inspiration, negative intrathoracic pressures generated by thoracic expansion are likely to cause obstruction in the extrathoracic airway (red arrow) leading to stridor. **B**, During expiration, positive intrathoracic pressures generated by thoracic compression are likely to cause obstruction in the intrathoracic airways, including the mid and distal trachea, main-stem bronchi, and small bronchioles, leading to wheeze.

Viral bronchiolitis and asthma account for most wheezing localized to the small peripheral airways. A major challenge in evaluating the wheezing child is determining when the wheeze is not caused by asthma or bronchiolitis, but rather by a different process requiring different diagnostic approaches and alternate treatment strategies. For example, cystic fibrosis, a severe genetic disease causing progressive small airway obstruction, can be mistaken for poorly controlled asthma. Similarly, early congestive heart failure can produce intractable wheezing from peribronchial edema. Pulmonary hemosiderosis, a rare disorder, can cause anemia and recurrent wheezing because blood irritates the peripheral airways. In a similar manner, gastroesophageal reflux and recurrent aspiration can also result in persistent or recurrent wheezing and may also complicate large airway abnormalities.

Distinguishing large airway obstruction (ie, trachea or main-stem bronchi) from small airway obstruction (ie, asthma) is difficult because both can cause expiratory wheeze. In addition, a variety of abnormalities can cause large airway obstruction, further complicating evaluation and diagnosis. Dynamic lesions of the large airways such as tracheomalacia or bronchomalacia are fairly common causes of congenital wheezing and can also be associated with gastroesophageal reflux, tracheoesophageal fistula, or prolonged mechanical ventilation in premature infants. External compression of large airways can be seen with vascular abnormalities (rings and slings), mediastinal masses, or infectious agents, most notably lymphobronchial tuberculosis or histoplasmosis.

For any child with a sudden onset of wheezing or a history of choking, the possibility of a foreign body should be of particular concern. Importantly, many patients with foreign body aspiration will not have an obvious history of choking, and as such one should always maintain a suspicion for this possibility, even in a child whose wheezing has been present for days or weeks. Finally, intrinsic airway abnormalities, including complete tracheal rings and webs, and acquired obstructions, such as tracheal stenosis or granulation tissue, can cause intractable wheezing.

## EVALUATION

### History

A major challenge in evaluating the wheezing child is to determine when a wheeze is not caused by viral bronchiolitis or asthma. Wheezing caused by viral bronchiolitis is usually preceded by upper respiratory symptoms and fever, often worsens within the first few days of onset, and tends to improve slowly thereafter. Asthma exacerbations are often initiated by vigorous activity, changes in weather, upper respiratory infection, or exposure to a triggering allergen. Such exacerbations typically respond well to inhaled  $\beta$ -agonist therapy with or without systemic corticosteroids. Persistent or recurrent episodes of wheezing that do not fit these profiles and have a family history that supports the diagnosis of asthma should be evaluated more thoroughly.

A detailed and focused history can often provide clues to an accurate diagnosis. Wheezing that appears

at birth or soon afterward should prompt an evaluation for congenital airway abnormalities such as tracheomalacia, complete rings, or vascular abnormalities or compression. Wheezing after a recent surgical procedure or intubation suggests acquired obstruction, whereas abrupt onset of wheezing accompanied by a history of choking should prompt an evaluation for aspiration of a foreign body. Other clues that suggest underlying illnesses or abnormalities include constant wheezing, failure to thrive, hemoptysis, difficulty swallowing, frequent vomiting, positional wheezing, worsening with agitation or crying, and poor response to conventional therapy.

### Physical Examination

Location of airway obstruction can often be determined by thorough physical examination and can direct the ensuing workup. Unilateral wheezing, most often associated with aspiration of a foreign body, can also accompany unilateral bronchial compression or stenosis and should be evaluated thoroughly. In addition to determining whether the wheezing is bilateral or unilateral, detailed assessment of the auditory characteristics can help determine whether the obstruction is central or peripheral. For example, wheezing that varies in pitch and can be heard throughout the chest (musical, heterophonous) typically represents small airway obstruction. In contrast, central airway obstruction tends to sound more even in pitch (monophonic, homophonous) and can often be heard best in central locations such as the sternal notch, although this may be unreliable in a small infant. In addition, large airway obstruction is more likely than small to be heard throughout the entire expiratory phase.

In addition to the auditory composition of a wheeze, positional characteristics can help determine cause. For example, wheezing caused by a dynamic lesion such as tracheomalacia is often worse when a patient is supine. Mediastinal structures such as the heart and the great vessels, which lie immediately anterior to the trachea, tend to fall posteriorly in the supine position and can be obstructive. In contrast, these structures tend to fall anteriorly when the patient is prone, relieving pressure on the airway and improving the wheeze. Wheezing caused by small airway obstruction or fixed compression of a large airway does not typically change with position.

### Objective Testing

Although a detailed history and physical examination can help the physician narrow the list of potential diagnoses, additional testing is often helpful and may guide therapy. Information obtained through the history and physical examination should guide further evaluation. Table 208-1 highlights the features of some common abnormalities that cause wheezing.

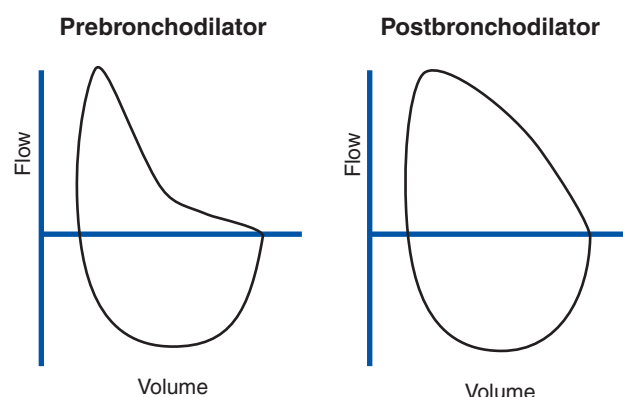
Laboratory testing may be indicated to diagnose specific clinical entities. For example, a sweat test is required if cystic fibrosis is suspected, and viral studies can identify respiratory syncytial virus or influenza as a cause of small airway wheezing in an infant with upper respiratory symptoms.

Pulmonary function testing can help characterize a wheeze objectively in patients older than 5 or 6 years.

**Table 208-1** Causes of Recurrent or Persistent Wheeze

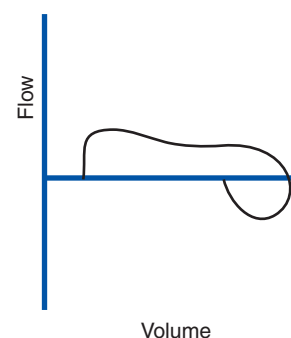
	FEATURES	OBJECTIVE FINDINGS
Asthma	Worse with exercise or respiratory infections Responds to bronchodilators Responds to steroids Family history of atopy	Reversible obstruction on PFTs Homophonous wheeze Positive bronchoprovocation
Tracheomalacia	Worse with activity or agitation Poor response to bronchodilators Poor response to steroids	Homophonous wheeze Airway collapse on fluoroscopy Collapsible trachea on bronchoscopy
Bronchomalacia	Worse with activity or agitation Poor response to bronchodilators Poor response to steroids	Heterophonous wheeze Airway collapse on fluoroscopy Collapsible bronchus on bronchoscopy
Foreign body	Sudden onset May have a history of choking	Asymmetrical breath sounds Asymmetrical hyperinflation or collapse on radiograph
Heart failure or pulmonary edema	Poor response to bronchodilators Poor growth	Hepatomegaly Radiograph with increased fluid Responds to diuresis
Bronchiolitis	Infant: URI symptoms	Positive viral studies
Vocal cord dysfunction	Poor response to all therapies Severe distress reported	PFTs: normal or with abnormal inspiratory loop Laryngoscopy: vocal cord adduction during inspiration
Cystic fibrosis	Poor growth, GI symptoms Recurrent pneumonia	Positive sweat test
Gastroesophageal reflux and aspiration	Variable response to bronchodilators Often worse after meals	Positive reflux evaluation (upper GI, nuclear scan, or pH probe)
Vascular compression	Central wheeze No bronchodilator response	Indentation on esophagram Anatomy demonstrated on thoracic MRI
Large airway abnormality (stenosis, complete rings, compression)	No response to therapy Worse with activity Stridor noted at times	Flattened or square flow-volume loop Obstruction visible on imaging or bronchoscopy

GI, gastrointestinal; MRI, magnetic resonance imaging; PFT, pulmonary function test; URI, upper respiratory infection.



**Figure 208-2** Pulmonary function test demonstrating small airway obstruction. Small airway obstruction, such as that seen in asthma, has a distinctive scooped appearance on spirometry. Normalization of the flow loop after bronchodilator treatment strongly suggests asthma as the underlying cause of recurrent wheezing.

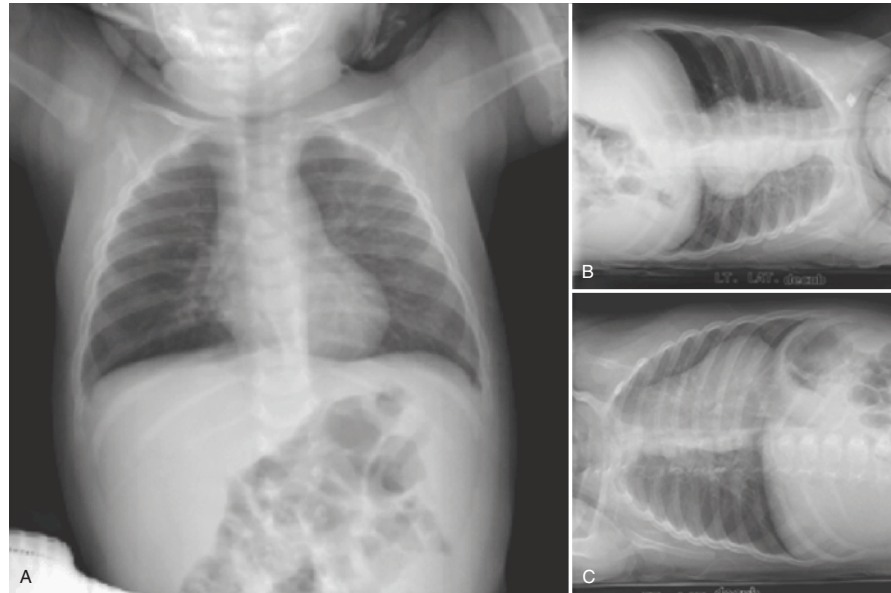
The expiratory loop shown in Figure 208-2 demonstrates small airway obstruction that improves after bronchodilator therapy, suggesting asthma as the underlying cause of recurrent wheezing. In contrast, small airway obstruction that does not demonstrate



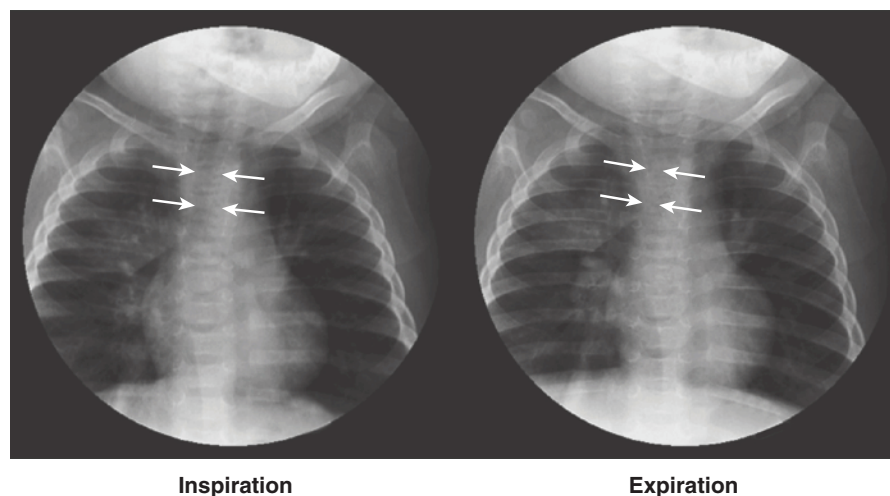
**Figure 208-3** Pulmonary function test demonstrating large airway fixed obstruction. Fixed obstruction of a large airway by compression or stenosis will result in a characteristic flat expiratory loop on spirometry. No change will occur after administering bronchodilator.

reversibility after bronchodilator therapy may require additional workup; several disease processes, including cystic fibrosis, congestive heart failure, and obliterative bronchiolitis, can cause fixed small airway obstruction. Similarly, expiratory loops suggesting fixed large airway obstruction (Figure 208-3) may require further evaluation for stenosis, rings, or compression.





**Figure 208-4** Foreign-body aspiration. **A**, Chest radiograph demonstrates mild hyperaeration of the right lung and mild flattening of the right hemidiaphragm on anteroposterior view. **B**, On left lateral decubitus view, the hyperaeration of the right lung is accentuated. **C**, On right lateral decubitus view, the heart does not shift with gravity, and the right lung remains well inflated. A peanut was found in the right main-stem bronchus during bronchoscopy.



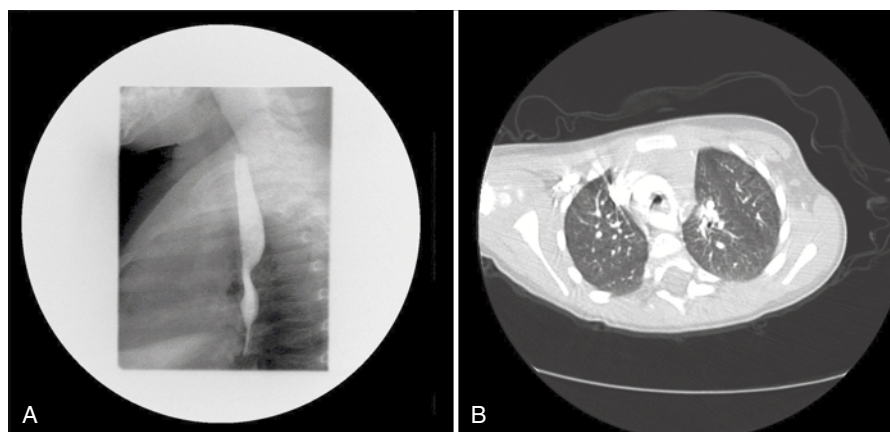
Inspiration

Expiration

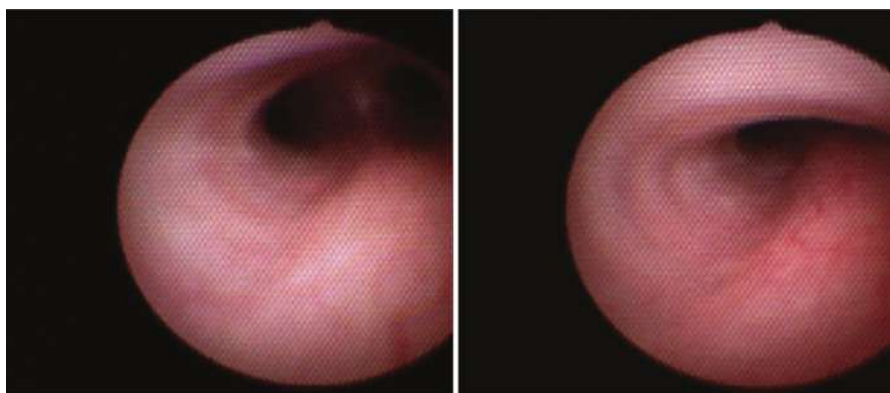
**Figure 208-5** Airway fluoroscopy. Airway fluoroscopy demonstrates a normal trachea during inspiration (arrows). On expiration, severe collapse of the trachea is demonstrated, indicating tracheomalacia.

Radiographic studies can be helpful when evaluating a patient with persistent or recurrent wheeze, particularly when asthma or viral bronchiolitis is not likely the cause. Chest radiography can detect thoracic masses that cause obstruction of airways. In addition, chest radiography with decubitus films or inspiratory and expiratory views can be helpful in diagnosing foreign-body aspiration (Figure 208-4). If history and physical examination suggest tracheobronchomalacia as an underlying diagnosis, then airway fluoroscopy (Figure 208-5)

can confirm the diagnosis and help quantify the severity. An esophagram or upper gastrointestinal series is useful if a vascular abnormality is suspected. However, although a vascular abnormality can be easily identified by an esophageal notch in an esophagram, a computed tomographic scan with contrast (Figure 208-6) or magnetic resonance image is ultimately required to determine the exact anatomic variant, which may include a double aortic arch, a right aortic arch with aberrant left subclavian, or a pulmonary artery sling.



**Figure 208-6** Esophagram and computed tomographic scan. **A**, Esophagram demonstrates a posterior indentation suggestive of a vascular ring. **B**, Computed tomographic scan of the chest confirms the presence of a double aortic arch



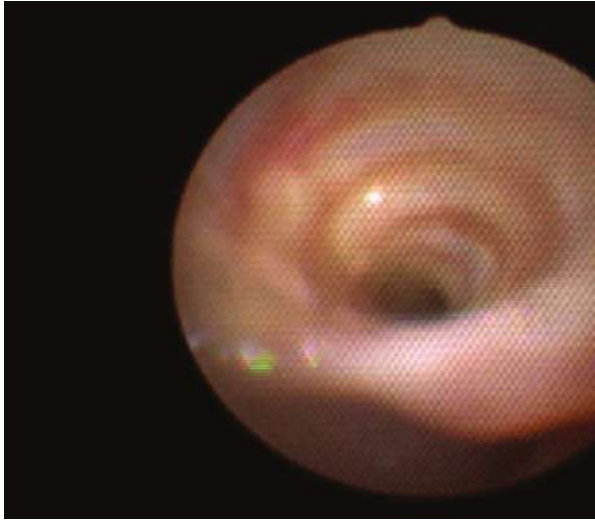
**Figure 208-7** Images from fiberoptic bronchoscopy. Fiberoptic bronchoscopy demonstrates normal tracheal caliber during inspiration. During expiration, the distal trachea collapses, consistent with tracheomalacia.

Direct visualization of the airway via flexible bronchoscopy is increasingly used to better characterize dynamic lesions such as tracheobronchomalacia (Figure 208-7). Intrinsic airway abnormalities, such as complete cartilaginous rings, often require bronchoscopy to make a diagnosis (Figure 208-8). Improved radiologic techniques, such as 3-dimensional airway reconstruction, may be useful, although the high radiation dose should limit their use (Figure 208-9). Furthermore, rigid bronchoscopy can be useful in both diagnosis and treatment of tracheal stenosis (Figure 208-10). Bronchoscopy can help assess the severity of airway compression by a thoracic mass and confirm patency after resection (Figure 208-11).

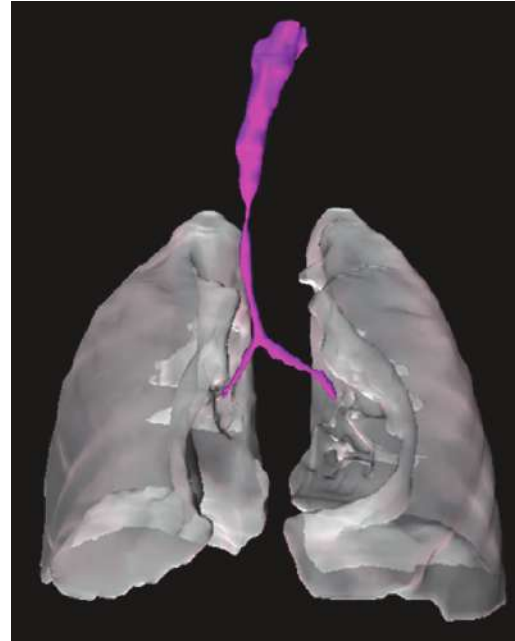
## MANAGEMENT

Most patients with wheezing have viral bronchiolitis and asthma and should be managed accordingly. Although some children with viral bronchiolitis or asthma require hospitalization for severe respiratory

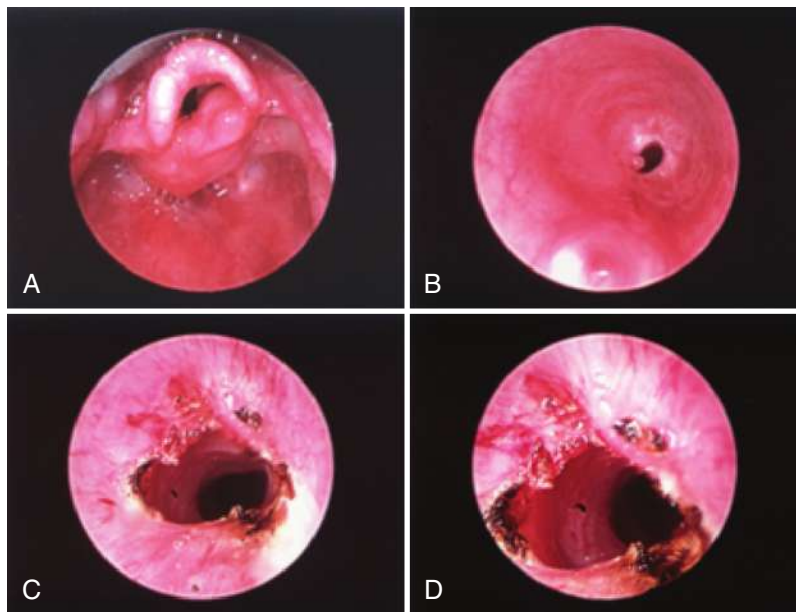
distress, hypoxemia, poor feeding, or dehydration, the general pediatrician can care for most children in an outpatient setting. An important point to note is that, currently, no evidence exists to support the regular use of  $\beta$ -agonist therapy in viral bronchiolitis. Hypertonic 3% saline has recently been used as adjunctive therapy for hospitalized patients with bronchiolitis. Hospital admission or referral to a subspecialty physician may be indicated for chronic wheezing associated with failure to thrive, which can be a sign of a significant underlying disease. Similarly, an unusual history or physical examination should prompt more detailed evaluation and may require alternate treatment regimens, depending on the cause. In general, the pediatrician evaluating the child with wheeze should be aware of the various clinical entities that can produce wheezing, be able to recognize by history or physical examination patients who require further workup, initiate simple diagnostic tests, and refer to appropriate subspecialty physicians children with unusual presentations or poor response to conventional therapies.



**Figure 208-8** Image from fiberoptic bronchoscopy. Fiberoptic bronchoscopy demonstrates complete cartilaginous rings causing severe obstruction of the trachea.



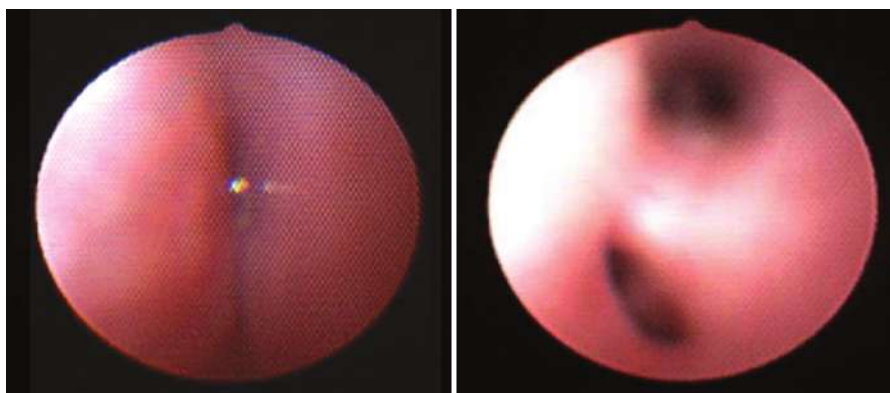
**Figure 208-9** Three-dimensional reconstruction of computed tomographic image. Severe circumferential narrowing of the trachea starting at the thoracic inlet and extending to the main-stem bronchi.



**Figure 208-10** Images from rigid bronchoscopy. **A**, Epiglottis. **B**, Severe stenosis secondary to a tracheal web. **C** and **D**, After laser resection of the stenosis. (Courtesy of Sanjay Parikh, MD.)

#### WHEN TO REFER

- Persistent or recurrent wheezing in an infant younger than 1 year
- Apparent paradoxical response to bronchodilators
- Poor weight gain or growth associated with chronic or recurrent wheezing
- Repeated hospitalization or multiple courses of oral corticosteroids
- Persistent asymmetric wheezing



**Figure 208-11** Images from fiberoptic bronchoscopy. Complete obstruction of the distal left main-stem bronchus secondary to a mediastinal mass. Immediately after resection of the mass, the segmental branch points of the left lung are easily identified.

### WHEN TO ADMIT

- Respiratory distress unresponsive to therapy
- Hypoxemia
- Tachypnea interfering with ability to eat or drink
- Altered mental status or signs of fatigue

### SUGGESTED READINGS

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## PART 7

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# Specific Clinical Problems

- 209 Acne
- 210 Adjustment Disorder in Children and Adolescents
- 211 Adrenal Dysfunction
- 212 Allergic Rhinitis
- 213 Altitude Sickness
- 214 Amblyopia and Strabismus
- 215 Animal and Human Bites
- 216 Anorexia Nervosa, Bulimia Nervosa, and Other Eating Disorders
- 217 Apparent Life-Threatening Events
- 218 Asthma
- 219 Atopic Dermatitis
- 220 Attention-deficit/Hyperactivity Disorder
- 221 Autism Spectrum Disorder
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- 223 Brain Tumors
- 224 Bronchiolitis
- 225 Cancers in Childhood
- 226 Cerebral Palsy
- 227 Chickenpox
- 228 Chronic Fatigue Syndrome
- 229 Cleft Lip and Cleft Palate
- 230 Coagulation Disorders
- 231 Colic
- 232 Colorectal Disorders
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- 234 Congenital and Acquired Heart Disease
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- 237 Conversion Reactions and Hysteria
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- 239 Cystic Fibrosis
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- 242 Diaper Rash
- 243 Disorders of Sex Development
- 244 Down Syndrome: Managing the Child and Family
- 245 Drug Eruptions, Erythema Multiforme, Stevens-Johnson Syndrome
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252 Fractures and Dislocations  
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254 Fungal Infections (Systemic)  
255 Gastroesophageal Reflux Disease  
256 Gastrointestinal Allergy  
257 Gastrointestinal Obstruction  
258 Giardiasis  
259 Gluten-Sensitive Enteropathy (Celiac Sprue)  
260 Guillain-Barré Syndrome  
261 Hemangiomas  
262 Hemoglobinopathies and Sickle Cell Disease  
263 Hemolytic-Uremic Syndrome  
264 Henoch-Schönlein Purpura  
265 Hepatitis  
266 Herpes Infections  
267 Human Herpesvirus-6 and Human Herpesvirus-7 Infections  
268 Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome  
269 Hydrocephalus  
270 Hyperthyroidism  
271 Hypocalcemia, Hypercalcemia, and Hypercalcuria  
272 Hypospadias, Epispadias, and Cryptorchidism  
273 Hypothyroidism  
274 Immune (Idiopathic) Thrombocytopenia Purpura  
275 Infectious Mononucleosis and Other Epstein-Barr Viral Infections  
276 Inflammatory Bowel Disease  
277 Insect Bites and Infestations  
278 Intellectual Disability  
279 Iron-Deficiency Anemia  
280 Kawasaki Disease  
281 Klinefelter Syndrome  
282 Labial Adhesions  
283 Lead Poisoning  
284 Learning Disorders  
285 Leukemias  
286 Lipid Abnormalities  
287 Lyme Disease  
288 Medical Errors, Adverse Events, and Patient Safety  
289 Meningitis  
290 Meningoencephalitis  
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292 Münchausen Syndrome by Proxy: Medical Child Abuse  
293 Muscular Dystrophy  
294 Nephritis  
295 Nephrotic Syndrome  
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297 Neurocutaneous Syndromes  
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299 Obstructive Uropathy and Vesicoureteral Reflux  
300 Ocular Trauma  
301 Oliguria and Anuria  
302 Oppositional Defiant Disorder  
303 Osteochondroses  
304 Osteomyelitis  
305 Otitis Media and Otitis Externa  
306 Pancreatitis  
307 Papulosquamous Diseases  
308 Parasitic Infections  
309 Pectus Excavatum and Pectus Carinatum  
310 Pertussis (Whooping Cough)

311 Pharyngitis and Tonsillitis  
312 Phimosis  
313 Pierre-Robin Sequence  
314 Pinworm Infestations  
315 Pneumonia  
316 Positional Deformational Plagiocephaly  
317 Post-traumatic Stress Disorder  
318 Prader-Willi Syndrome  
319 Preseptal and Orbital Cellulitis  
320 Psoriasis  
321 Pyloric Stenosis  
322 Renal Tubular Acidosis  
323 Rheumatic Fever  
324 Rheumatologic Diseases  
325 Rocky Mountain Spotted Fever  
326 Seborrheic Dermatitis  
327 Seizure Disorders  
328 Septic Arthritis  
329 Sexual Abuse of Children  
330 Sexually Transmitted Infections  
331 Sinusitis  
332 Spina Bifida  
333 Spinal Deformities  
334 Sports Musculoskeletal Injuries  
335 Stomatitis  
336 Substance Use Disorders  
337 Sudden Unexpected Infant Death  
338 Tobacco and Nicotine Use  
339 Tonsillectomy and Adenoidectomy  
340 Toxic Shock Syndrome  
341 Tuberculosis  
342 Turner Syndrome and Noonan Syndrome  
343 Umbilical Anomalies  
344 Urinary Tract Infections  
345 Verrucae (Warts)  
346 Vitamin D Inadequacy





## Chapter 209

### ACNE

Catherine Chen, MD; Judith V. Williams, MD

Acne is so prevalent in adolescents and young adults that some people consider it a physiologic event. This perspective does not take into account the effect of acne on the patient, and it may preclude therapeutic intervention. Acne is a treatable disease that deserves medical attention.

### ETIOLOGY

#### Hormones

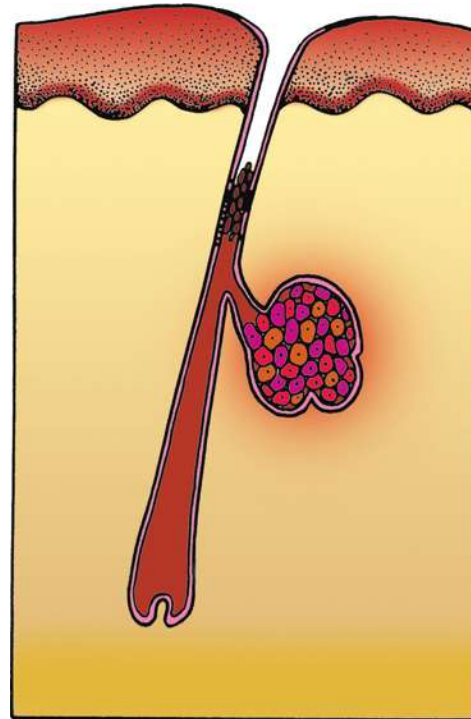
Acne is a disease of the pilosebaceous unit. Androgens stimulate the sebaceous glands, which enlarge and increase their production of sebum. Before puberty, the responsible androgens are of adrenal origin. After puberty, gonadal androgens further stimulate the sebaceous glands. Patients who have acne may have normal levels of circulating testosterone; therefore, tissue androgen metabolism may be an important factor in the pathogenesis of acne. One of the major organs for androgen metabolism is the skin, where the enzyme 5- $\alpha$ -reductase metabolizes testosterone to dihydrotestosterone, which has significantly increased potent activity at the tissue level. 5- $\alpha$ -reductase may be more active in the skin of patients with acne than those without, increasing androgenic stimulation of the sebaceous glands and ultimately causing acne. Increased sebaceous gland activity is necessary for acne to develop; alone, it is insufficient to cause disease.

#### Follicular Obstruction

If sebum is allowed to drain freely to the surface, the surface skin then becomes oily, but acne does not develop. Acne can develop only if the outlet of the follicular canal is obstructed, which occurs when adherent, keratinized cells within the canal accumulate and form an impaction that blocks the flow of sebum (Figure 209-1). Production of keratinized cells within the lining of the follicular canal is normal, but accumulation and subsequent impaction are not. This follicular obstruction, which may also be influenced by androgens, is a prerequisite for the development of acne.

#### Bacteria

Sebum and keratinous debris accumulate proximal to the follicular outlet obstruction. This accumulation provides an attractive environment for the growth of anaerobic bacteria, particularly *Propionibacterium acnes*, which play a role in the pathogenesis of inflammatory acne. Several factors may be involved in causing the inflammation. One theory suggests that the lipase enzymes elaborated by *P acnes* hydrolyze sebaceous lipids, releasing free fatty acids, which then cause irritation when the follicle ruptures. *P acnes* also



**Figure 209-1** Obstruction of the pilosebaceous unit in acne.

produce chemotactic factors that may attract inflammatory cells directly to a sebaceous follicle. Some evidence indicates that complement-mediated inflammation is directed against *P acnes* itself. Regardless of the mechanism of inflammation, little question remains as to the therapeutic benefit of antibiotics.

The events in the pathogenesis of acne include androgenic stimulation of sebaceous glands, which increases sebum production; keratinous impaction in the pilosebaceous canal, causing outlet obstruction; accumulation of sebaceous and keratinous debris behind the obstruction; and proliferation of *P acnes*, which alters this milieu in such a way as to contribute to the rupture of the dilated pilosebaceous unit, resulting in extravasation of its contents into the surrounding dermis and inflammatory acne lesions.

### CLINICAL FINDINGS

Not surprisingly, acne lesions have a predilection for skin that is rich in sebaceous glands. Accordingly, the face is the prevailing site, although acne is also often found on the chest and back. Occasionally a patient may have involvement of the conchal bowls of the ears. The lower portions of the trunk, buttocks, and thighs are involved much less frequently, and the distal extremities are always spared.

The disease process may begin at a surprisingly young age. In a study of premenarchal girls, 78% were found to have some acne. The same investigators found acne to be present in 100% of adolescent boys. Although the severity of the disease increases during

adolescence, acne is by no means confined to these years. For acne activity to continue into the third and fourth decades of life is not uncommon.

The pathogenic mechanisms previously described result in noninflamed open and closed comedones and inflammatory papules and pustules, as well as cystic acne in more severe cases. Cystic acne is made up of nodules greater than 5 mm in diameter and true cysts, which are compressible nodules under normal-seeming skin. These nodules and cysts can result in permanent acne scars.

The acne found in prepubertal children is predominantly noninflammatory and thus may easily be overlooked. The open comedo (blackhead) and closed comedo (whitehead) are lesions caused purely by obstruction of the pilosebaceous canal, with no accompanying inflammation. Inflammatory and comedonal acne is rare in young children between 1 and 7 years of age and suggests a possible hyperandrogenic condition, such as that associated with congenital adrenal hyperplasia or even a rare androgen-secreting tumor. Girls should be examined for virilization, and boys and girls should be checked for precocious puberty. Screening blood studies should include serum levels of testosterone, androstenedione, dehydroepiandrosterone sulfate (DHEA-S), and 17-hydroxyprogesterone. Bone age, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) may also be assessed if appropriate. Referral to a pediatric endocrinologist should be considered if there is reason to suspect a hyperandrogenic basis for the acne.

## DIFFERENTIAL DIAGNOSIS

Diagnosing acne is rarely difficult. Usually, the condition can be diagnosed from across the room, although comedonal lesions may require closer inspection (Figure 209-2). Occasionally acne may be confused with flat warts, milia, or adenoma sebaceum; acne variants may occur.

### Flat Warts

Small, flesh-colored warts may be confused clinically with closed comedones. The question can usually be resolved with close inspection. A flat wart has a sharp, right-angled edge and a finely roughened surface; a closed comedo has a dome shape and a smooth surface. Flat warts also vary in size; closed comedones are uniformly small (Figure 209-3).

### Milia

Milia are small epidermal inclusion cysts that are sometimes confused with comedones and occasionally with inflammatory pustules, especially in infants who have neonatal acne.

### Adenoma Sebaceum

A misnamed disorder (the lesions are actually angiofibromas), adenoma sebaceum is one of the skin manifestations in tuberous sclerosis and also can be seen in multiple endocrine neoplasia. Clinically, the lesions appear as pink papules, which are occasionally confused with the lesions of acne. Adenoma sebaceum



**Figure 209-2** Closed comedones (whiteheads) appear as dome-shaped, flesh-colored papules that often are overlooked.



**Figure 209-3** Flat warts.

should be anticipated if the papules are clustered primarily in the center of the face, persistent, and resistant to acne therapy.

### Acne Rosacea

Acne rosacea is an acneiform eruption that can be distinguished from acne by a background blush of



**Figure 209-4** Rosacea.

erythema and telangiectasia and by the absence of comedones (Figure 209-4). In addition, rosacea occurs most often in middle-aged adults.

### Steroid Acne

Both systemic and topical steroids can induce acne. Acne from systemic steroids usually appears as numerous small, uniform-sized papules and pustules that have a predilection for the upper trunk. The hallmark of steroid-induced acne is a lack of comedones. The condition involutes slowly and spontaneously after the steroids are discontinued.

### Gram-Negative Folliculitis

Gram-negative organisms can occasionally produce a pustular folliculitis in patients being treated for acne with systemic antibiotics. This condition should be thought to exist in any patient whose disease flares up during therapy, especially if the flare-up produces numerous pustules. A bacterial culture with antibiotic sensitivity studies should be performed so that the diagnosis can be confirmed and the antibiotic therapy changed.

### Acne Conglobata

Acne conglobata is an unusually severe acne variant that may develop as a result of a sudden deterioration of existing active acne, or it may be a recurrence of acne that has been quiet for many years. It occurs most commonly in 18- to 30-year-old men. Lesions consist of comedones, cysts with foul-smelling seropurulent material, and burrowing and interconnecting abscesses, leaving irregular and disfiguring scars. At times, acne conglobata has been associated with systemic diseases such as hidradenitis suppurativa, pyoderma gangrenosum, renal amyloidosis, and musculoskeletal syndrome. The mainstay of treatment is isotretinoin.

### Acne Fulminans

Acne fulminans is a rare and severe form of acne, usually occurring in men and characterized by sudden

onset of painful acne nodules and, rarely, ulcerative lesions, as well as systemic symptoms, including fever, leukocytosis, polyarthritis, splenomegaly, erythema nodosum, and lytic bone lesions in long bones, clavicle, and sternum. Treatment involves a combination of systemic corticosteroids initially followed by isotretinoin. The prognosis is good, although residual scarring and disfigurement may persist.

## PSYCHOSOCIAL CONSIDERATIONS

Acne can be a devastating disease. In an ironic quirk, it occurs at a time of life when personal appearance is of prime concern and when self-consciousness is at its peak. Although some young people seem to be more affected psychologically by acne than others, no one is comfortable with it. Patients who have severe cystic acne may be socially ostracized. Regardless of the acne's severity, the condition is important to the patient who is seeking help and deserves serious attention. Patients are not impressed with advice that trivializes their disease and reassures them that they eventually will *outgrow it*. Fortunately, a wide array of medical therapies are available that can produce effective, gratifying results.

## MANAGEMENT

Five methods of treatment have proved effective for acne: topical comedolytic agents, topical and systemic antibiotics, systemic retinoids, and systemic hormonal therapy. The most traditional and effective treatment regimen is a combination of comedolytics and antibiotics.

### Comedolytics

Topical retinoids are the mainstay of acne treatment because they help disimpact the comedone—the keratinous plug in the follicular canal. They include tretinoin (Atralin, Retin-A, Retin-A Micro, Tretin-X), adapalene (Differin), and tazarotene (Tazorac, Fabior). They now are available in combination with other acne medications, such as tretinoin combined with clindamycin (Veltin, Ziana) and adapalene with benzoyl peroxide (Epiduo, Epiduo Forte), which can help with compliance. Other comedolytic agents include benzoyl peroxide (Benzac AC, Benzac W, Brevoxyl, Desquam-E, Desquam-X, Triaz, ZoDerm), salicylic acid, and sodium sulfacetamide (Klaron, Plexion, Rosula, Sebizon). Although topical retinoids have been traditionally viewed as having a primarily comedolytic effect, and more so than other topical medications, they also reduce inflammatory lesions and enhance penetration of other medications. In fact, consensus has now formed that, in most cases, topical retinoids (alone or in combination) should be used as first-line therapy for mild to moderate inflammatory acne in addition to comedonal acne. They are also preferred for maintenance therapy.

When a topical retinoid is used in a regimen with another topical “leave-on” agent, the patient should be instructed to apply the retinoid at bedtime and the other agent each morning. However, if the other agent is a wash, both agents can be applied in either the morning or evening, which may facilitate compliance. Topical comedolytics are available in a variety of



**Table 209-1**     **Tretinoin Preparations**

	MILDEST	MILD	MODERATE	STRONGER	STRONGEST
Cream	0.025%	0.05%	0.1%		
Gel		0.01%	0.025%	0.05%	0.1%
Solution					0.05%

preparations. The strength of a given preparation reflects its irritancy and probably also its efficacy. For tretinoin, the strength of the preparation depends both on the concentration of the drug and the nature of the vehicle in which it is contained (Table 209-1). Adapalene is marketed as a cream in a concentration of 0.1%, and as a gel in concentrations of 0.1% and 0.3%. Tazarotene is also available as a cream or as a gel, and each is available in concentrations of 0.05% and 0.1%, and as a foam in a concentration of 0.1%. Benzoyl peroxide gels are marketed in concentrations of 2.5%, 5%, and 10%. Salicylic acid is marketed in a large variety of preparations and concentrations. Sodium sulfacetamide is available as a lotion in 10% concentration. Patients are initially prescribed the mildest preparations, and the potency is increased at subsequent visits if necessary.

Skin irritation is the major side effect of the comedolytics and can be associated with overuse. Patients should be counseled to use no more than a pea-sized amount of medication for the entire face. Adjunctive use of emollients can also mitigate this effect. In addition, approximately 1% of patients develop a true allergic contact dermatitis to benzoyl peroxide, in which case permanent discontinuation of this agent is required. Given that topical retinoids may make the skin more susceptible to the effects of sunlight, patients should be instructed to avoid excessive exposure to the sun and to use oil-free sunscreens if they need to be exposed to the sun for prolonged periods. Additionally, patients should be told that benzoyl peroxide can bleach clothing and linens.

### Antibiotics

Antibiotics are also indicated for patients who have inflammatory acne lesions. Topical agents such as clindamycin and erythromycin preparations (Cleocin, Clindagel, Evoclin, T-Stat) can be used, although their use as monotherapy for more than a few weeks is not recommended because of slow onset of action and predictable emergence of antibiotic-resistant bacterial organisms. Combinations of benzoyl peroxide and erythromycin or clindamycin, or tretinoin and clindamycin, are often prescribed before oral antibiotics. Benzamycin gel (5% benzoyl peroxide and 3% erythromycin), and Benzacilin or Duac gels (5% benzoyl peroxide and 1% clindamycin phosphate) can be applied twice daily. Acanya gel (2.5% benzoyl peroxide and 1.2% clindamycin) can be applied once daily. Veltin or Ziana gels (0.025% tretinoin and 1.2% clindamycin) can be applied nightly.

If acne lesions are inflammatory and either are extensive enough to make topical therapy impractical (ie, involving neck, shoulders, and upper trunk) or are

unresponsive to a topical regimen, then systemic antibiotics are warranted. The tetracycline class is preferred in patients older than 8 years of age. The second-generation tetracyclines doxycycline and minocycline are preferred because of their flexible dosing options (twice daily, or once daily if using extended-release formulations Doryx [doxycycline], Oracea [doxycycline], or Solodyn [minocycline]), increased lipophilicity and follicle penetration, and high efficacy against *P. acnes*. However, doxycycline is more likely to cause photosensitivity, and minocycline can be expensive. In addition, although rare, drug hypersensitivity syndrome, Stevens-Johnson syndrome, and a lupus-like syndrome may occur with administration of minocycline. Erythromycin may also be used as an alternative, but it has the highest rate of *P. acnes* resistance among oral antibiotics prescribed for acne, limiting its efficacy. Resistance to *P. acnes* may affect as many as 25% of patients receiving antibiotics; therefore, measures should be taken to counter this trend, such as limiting the use of oral antibiotics to shorter periods, combining topical comedolytics (especially topical retinoids) with topical antibiotics, and avoiding the use of oral antibiotics as maintenance therapy.

### Systemic Retinoids

Isotretinoin (Absorica, Amnesteem, Claravis, Myorisan, Sotret, Zenatane) was approved by the US Food and Drug Administration (FDA) in September 1982 for use in treating severe cystic acne. Its original formulation, Accutane, is no longer commercially available. Isotretinoin reduces follicular keratinization, sebum production, and intrafollicular bacterial counts. The result of these (and possibly other) effects is a dramatic improvement in acne. The therapeutic effect usually takes several months to appear and often persists long after the course of therapy is discontinued. Historically, 6-month courses have been used. However, in recent years, some physicians focus more on total dose given instead of duration, aiming for a 100- to 150-mg/kg total dose. Unfortunately, side effects are common. Almost all patients experience mucocutaneous reactions (cheilitis, conjunctivitis, and dry mucous membranes of the mouth and nose), and extracutaneous complications also occur. For example, systemic retinoids can elevate plasma lipid levels, cause asymptomatic vertebral hyperostoses, and, rarely, cause depression and pseudotumor cerebri.

An association between isotretinoin and inflammatory bowel disease (IBD; in particular, ulcerative colitis) may exist in a small subset of patients. However, any association may be confounded by many factors, such as the overlap between the highest age of IBD



occurrence and the age when severe acne occurs and isotretinoin is used, an extended history of antibiotic use in most patients receiving isotretinoin, and the possibility of a link between IBD and inflammatory acne itself.

Although evidence supporting an association between isotretinoin and mood disorders exists, it has been almost all anecdotal, plus 1 small open-label study whose data were confounded by a disparity in acne severity between the 2 treatment groups, with the more severe cases receiving isotretinoin, which could be related to the more severe depressive symptoms in the group. By contrast, larger well-designed epidemiologic studies have not supported a cause-and-effect relationship between isotretinoin and depression. Rather, acne severity is a proven predictor of mental health issues and suicidal ideation. Although patients taking isotretinoin should still be carefully observed for mood changes, the evidence is reassuring.

Most important is the medication's teratogenicity. Exposure to isotretinoin in pregnancy has been associated with a 25-fold increased risk for major fetal malformations. Thus, female patients must exercise strict birth control while taking this drug. To ensure compliance with these guidelines and to prevent pregnancies from occurring during treatment, the FDA requires that all patients being prescribed isotretinoin be enrolled in a national registry. Isotretinoin is recommended only for those who have severe cystic or scarring acne (or both) and for a minority of patients who have severe noncystic acne and have not responded to therapy with topical comedolytics and oral antibiotics.

### Hormonal Therapy

Hormonal therapy can be an excellent option for women with moderate to severe acne if oral contraception is desired, an alternative to repeated courses of isotretinoin is preferred, or certain endocrine disorders are present. If a patient has no endocrine disorders, it is best to wait until 1 year after the onset of menstruation to allow the development of as much bone mineral density as possible before initiating oral contraceptives. All combination contraceptives reduce free testosterone and have a positive effect on acne, with no single preparation being demonstrably superior. Contraceptives containing only progestins should be avoided if possible, given that some of them have intrinsic androgenic activity and may aggravate acne. Only the progestins norgestimate, desogestrel, and drospirenone have no or low risk for increasing testosterone receptor activity and can be used in combination formulations. The relationship between oral contraceptive use and thromboembolism is under review by the FDA. A history of tobacco use and a family history of thrombotic events should be obtained before oral contraceptives are prescribed.

Spironolactone is an aldosterone antagonist that reduces receptor binding by testosterone and dihydrotestosterone in sebaceous glands and, like oral contraceptives, reduces free testosterone. Its efficacy may be apparent clinically more quickly than when oral contraceptives are used, often in 2 to 3 months

instead of 3 to 4 months. Its dose range is from 25 to 200 mg daily. Blood pressure and serum potassium levels should be monitored because, at higher doses, it can lower blood pressure and raise potassium levels.

### Patient Compliance

Patient compliance is the single most important aspect of successful acne treatment. Without patient compliance, even the most effective medications are doomed to failure. To maximize compliance, the physician must take time at the initial visit to explain in detail the use of each medication, as well as the effects and side effects to be expected. To reinforce these instructions, giving the patient printed instructions is helpful, an example of which is shown in Box 209-1. Depending on the situation, medications can be taken once or twice daily. If this activity is linked to an established daily routine, such as brushing the teeth, then it too can become habitual. Given careful, specific instructions, most patients who have acne are exceptionally compliant and, given time, obtain good results for their efforts. The concept that the treatment will take time to be effective needs to be emphasized to all patients; otherwise, they may become prematurely, and inappropriately, discouraged. The acne instruction sheet can also be used to answer several other questions, often unasked, that patients or their parents frequently have. The most common of these issues pertain to diet, cleanliness, cosmetics, and picking at the lesions.

### Diet

Although diet has long been dismissed as a factor in the development of acne, recent studies are changing that view. Research suggests that diets with a high glycemic load may exacerbate acne. High glycemic loads can lead to diet-induced hyperinsulinemia, which increases production of androgens, insulin growth factor-1 (IGF-1), and IGF-binding protein-3 (IGFBP-3) and decreases retinoid receptor activity. All of these changes stimulate follicular plugging and sebum production, thereby aggravating acne. Although more studies need to be completed before carbohydrate restriction can be strongly recommended for patients with acne, it is reasonable to recommend a low-glucose-load diet as an adjunct to existing acne therapy.

Although the evidence supporting an association between dairy intake and acne has not been as strong as that involving glycemic loads, dairy products may also have an effect on acne through changes in endocrine pathways. Milk contains testosterone precursors and 5- $\alpha$ -reduced molecules that are all converted to dihydrotestosterone after ingestion, stimulating sebum production and follicular plugging. Interestingly, skim milk has been particularly suspect in this regard because these ingredients are more bioavailable in skim milk. In addition, skim milk is associated with higher IGF-1 levels and contains less estrogen, a hormone that reduces acne. An even greater culprit is the fermentation process in cheese production, which increases testosterone production from androgen precursors. Although more research is needed to prove this link more rigorously, it would be fitting to advise

**BOX 209-1 Acne Instruction Sheet****TOPICAL MEDICATIONS**

1. Action
  - a. Help open up clogged pores.
  - b. Benzoyl peroxide and sodium sulfacetamide also help kill bacteria in the pores.
2. Method of use (apply to *all* affected areas)
  - a. Apply retinoid at bedtime.
  - b. *Do not* use acne scrub cleaners.
  - c. Apply benzoyl peroxide, salicylic acid, or sodium sulfacetamide in the morning.
3. Possible problems
  - a. May make the condition look worse in first several weeks, before improvement is seen (known as *bringing acne to the surface*).
  - b. May cause irritation (eg, redness, dryness, tenderness). If too much irritation occurs, then use every other night until the skin becomes accustomed to it. If irritation is severe, then medication should be stopped and a return visit scheduled.

**TETRACYCLINE**

1. Action: Helps kill bacteria; particularly useful for deep and inflamed lesions.
2. Method of use: Needs to be taken on an *empty* stomach. Therefore, take it as soon as you get out of bed in the morning (wait ½ hour before eating breakfast) and at bedtime (at least 1 hour after eating any evening snack).
3. Potential side effects
  - a. Uncommon; most patients have no trouble.

- b. May upset stomach and cause nausea, diarrhea, or both.
- c. Occasionally causes a yeast vaginitis, particularly if you are taking birth control pills.
- d. Should not be taken if you are pregnant or trying to get pregnant.

**GENERAL**

1. Diet: For most patients, foods have no effect on acne. If you notice that a certain food aggravates the condition, then simply avoid that food. Otherwise, no restrictions are necessary.
2. Washing: Acne cannot be washed off. Wash your face with a mild cleanser 2 to 3 times per day, and bathe or shower daily.
3. When to expect results from medicines: *It takes time*, usually several months, to begin to see benefits. At a return visit in 2 to 3 months, some improvement should be present, but the acne will not likely be cleared. The medications and their doses will be altered at that time, depending on the response.
4. Conscientious and *regular* use of the medications is essential. They will not do any good if not used regularly.
5. Cosmetics: They may aggravate your acne. If you must use them, then do so sparingly, and use only those that are water based. You may also consider some of the newer foundations that contain salicylic acid.
6. No picking!

patients that dairy products may incrementally aggravate their acne. However, if patients decide to avoid dairy products or to significantly reduce their ingestion, they also need to be counseled regarding vitamin D and calcium supplementation. As supplementation guidelines change, both physician and patient will have to adjust accordingly (see Table 209-2).

Although early studies asserted that eating chocolate does not affect acne, a recent preliminary study evaluating adolescent boys eating 6 ounces of 100% cocoa found that it significantly increased the number of comedones as soon as 4 days later. The cause was not clear. A randomized trial is underway to confirm these findings. Whether or not other dietary components such as omega-3 fatty acids, antioxidants, zinc, and fiber play a significant role in acne pathogenesis remains to be seen.

**Cleanliness**

The question of cleanliness is pondered more by parents than it is by patients. To help maintain peace at home, the notion that acne is a function of poor hygiene should be dispelled. It is not. In general, cleaning agents for acne need not be recommended because most irritate the skin, unnecessarily compounding the

irritation caused by topical comedolytics. The use of a mild soap-free cleanser is often suggested.

**Cosmetics**

Because cosmetics have been implicated as possibly contributing to the acne process, it is preferable to avoid using them. If cosmetics are used, then they should be water-based and used sparingly. If the eruption is prominent and negatively affecting the patient's self-image, corrective camouflage is an option.

**Picking**

For many patients who have acne, much of the skin damage is self-inflicted. Although the temptation to squeeze a fresh pustule can be overwhelming, the practice must be discouraged. Picking, probing, and squeezing cause more tissue damage and sometimes produce scars. For some patients with acne, picking may become so obsessive that excoriations are the only lesions seen.

**COMPLICATIONS**

The major complications of acne are its psychosocial ramifications. In addition to the cosmetic liability of active lesions, permanent scars compound and

**Table 209-2** Dietary Reference Intakes for Calcium and Vitamin D

LIFE-STAGE GROUP (AGE AND GENDER)	CALCIUM		VITAMIN D	
	RDA (MG/DAY)	UPPER LIMIT (MG/DAY)	RDA (IU/DAY)	UPPER LIMIT (IU/DAY)
0–6 mo (M + F)	200	1,000	400	1,000
6–12 mo (M + F)	260	1,500	400	1,500
1–3 yr (M + F)	700	2,500	600	2,500
4–8 yr (M + F)	1,000	2,500	600	3,000
9–13 yr (M + F)	1,300	3,000	600	4,000
14–8 yr (M + F)	1,300	3,000	600	4,000

RDA = recommended dietary allowance; intake that covers needs of 97.5% of the healthy normal population.

Reflects Adequate Intake (AI) reference value rather than RDA. RDAs have not been established for infants because of insufficient data.

Calcium and vitamin D RDAs are the same for pregnant or lactating females in these age groups.

Reprinted with permission from 2011 *Dietary Reference Intakes for Calcium and Vitamin D*, by the National Academy of Sciences. Courtesy of the National Academies Press, Washington, DC.

perpetuate the problem in some patients, mainly those who have inflammatory lesions. Established scars are difficult to treat. Many patients have been disappointed with the results of dermabrasion. Patients who have been treated with isotretinoin should wait for at least 1 year before having dermabrasion. Bovine collagen injections have been used in some patients, producing short-term improvement, but repeated injections are often necessary, and the long-term results are not yet known. Laser resurfacing by experienced operators has produced some promising results. Acne scars are best treated when inflammatory lesions are quiescent. Given that scars are easier to prevent than to treat, the emphasis in acne is on early, aggressive medical therapy.

## PROGNOSIS

With proper treatment, the prognosis for acne is good, if not excellent. Patients should understand that most therapy controls the disease instead of curing it and that improvement does not occur overnight. However, improvement does occur, usually within 2 to 3 months of starting therapy, and this time is best for the first scheduled return visit. At this visit, the acne regimen can be adjusted as necessary. For example, the potency of the comedolytics can be increased (or reduced) and the dose of the antibiotic altered, depending on the initial response. Continued improvement is to be expected with continuation of therapy. For many patients, the dose of systemic antibiotics can be reduced gradually and eliminated after 6 to 12 months. However, most patients also require prolonged maintenance therapy (often over years) with topical agents and, in some cases, continued topical antibiotic therapy.

Historically, cystic acne has been the most difficult to treat, but isotretinoin has become a powerful tool for dealing with this disease. This drug has the potential to effect prolonged remissions, sometimes lasting for years after a single course of therapy. However, as

discussed previously, isotretinoin has serious side effects, and its use is usually reserved for patients who have severe cystic or scarring acne (or both) that does not respond to standard treatment.

## WHEN TO REFER

- Patient is unresponsive to oral antibiotics and topical comedolytics.
- Patient has cystic or scarring acne.
- Patient is a young girl with acne or a girl with acne and irregular menses.
- Patient has acne fulminans (abrupt onset of cystic acne, fever, arthralgia).

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Acne: How to Treat & Control It* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Teens and Acne Treatment* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/teen/Pages/Teens-and-Acne.aspx](http://www.healthychildren.org/English/ages-stages/teen/Pages/Teens-and-Acne.aspx))
- *What is a Pediatric Dermatologist?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Dermatologist.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Dermatologist.aspx))

### Medical Decision Support

- *Pediatric Dermatology: A Quick Reference Guide* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

## SUGGESTED READINGS

- Eichenfield LW, Krakowski AC, Piggott C, et al. Evidence-based recommendations of the diagnosis and treatment of pediatric acne. *Pediatrics*. 2013;131(Suppl 3):S163–S186

## Chapter 210

## ADJUSTMENT DISORDER IN CHILDREN AND ADOLESCENTS

George Alvarado, MD; Danielle Laraque, MD

## FOUNDATION

## Definition

An adjustment disorder (AD) is a maladaptive response to a stressor, resulting in clinically significant emotional or behavioral symptoms not meeting criteria for a more specific disorder. Clinical significance is determined by marked distress that is in excess of what would be expected from exposure to the stressor or impairment in social or occupational (academic) functioning. Several subtypes of AD are distinguished by the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*), based on the nature of the disturbance: with depressed mood; with anxiety; with mixed anxiety and depressed mood; with disturbance of conduct; with mixed disturbance of emotions and conduct; and unspecified. While there is no minimum duration of symptoms necessary to qualify for the diagnosis, symptoms must occur within 3 months of the onset of the stressor. Additionally, symptoms cannot persist for more than 6 months after the termination of the stressor, with the exception of cases of chronic adjustment, where the stressor is persistent.

## Epidemiology

While it is widely accepted that AD is common in childhood and adolescence, epidemiologic data, along with other types of research on the diagnosis, are fairly sparse. Looking at a sample of children in the general population in Puerto Rico, Bird and colleagues found a prevalence of 4.2% to 7.6%, depending on the cutoff score used on the Children's Global Assessment of Functioning Scale (GAF). Higher rates have been reported in clinical samples, including various pediatric settings. In a study conducted at an urban pediatric emergency setting, 14% of pediatric psychiatry consultations were diagnosed with AD. Another study of a suburban emergency department reported 34.4% of adolescents to have an AD diagnosis, the most common subtype being with depressed mood. The highest rates of AD have been found in those medically hospitalized, comprising up to 12% of referrals to psychiatry. While similar studies have not been done in children, it is reasonable to postulate that similarly high levels exist. With regard to medical diagnosis, high prevalence rates of adjustment have also been reported in children with chronic medical disorders, such as diabetes mellitus, with estimates between 36% and 60%.

## Etiology and Risk Factors

Given the requisite identification of a stressor, the causes of AD are necessarily broad, ranging from problems at home (eg, divorce) to conflicts at school, to interactions with peers, to acute and chronic medical illness. There may be a single or multiple stressors,

## BOX 210-1 Common Stressors

- Bullying
- Relationship breakup
- New school
- Parental divorce
- Economic stress
- Move, displacement, homelessness
- Medical illness/hospitalization
- Death of a loved one
- Sexual identity ("coming out," or being "outed")
- *Foster care placement*
- *Parental illness (including mental illness)*
- *Parental incarceration*
- *Parental substance abuse*
- *Witnessing domestic or other violence*

Italicized items indicate toxic stressors.

and they may be continuous or recur periodically. A stressor may accompany a specific life event, such as starting school, moving away from home, or becoming a parent. The single common pathway for all of these events is that they overwhelm the youth's ability for healthy coping, resulting in emotional, behavioral, or functional disturbance. Several common stressors are listed in Box 210-1.

Despite this wide range of stressors, it is important to note that none is uniformly overwhelming, so as to always result in an AD (with the important exception of toxic stress, indicated above and discussed later in this chapter.) Many children and adolescents may encounter highly stressful events without experiencing marked difficulties with adjustment. This fact points to the presence of important individual and environmental factors that can play a crucial role in moderating the role of stress on the individual. Such stressors have been designated as "tolerable," in the sense that, while challenging and nonnormative, they can be overcome, particularly with the help of a caring and involved adult relationship.

The concept of adaptation has been extensively studied in medically ill children, pointing to several factors that can affect the response to the stress of illness. These include individual factors of temperament, cognitive development, and problem-solving skills, as well as "social ecological" factors of family environment, social support, and availability of resources. Along these same lines, the concept of resilience serves to describe individuals who can achieve good adjustment despite high levels of stress or adverse events. In a study of the relationships of adverse life events to resilience, Tiet and colleagues found that "resilient youth received more guidance and supervision by their parents and lived in higher functioning families." Additionally, high IQ seemed to positively affect resilience for youth experiencing high levels of adverse life events.

In contrast to tolerable stress, toxic stressors, given their nature and timing in development, have been



shown to be almost uniformly deleterious to healthy development. Examples would include physical abuse or neglect, sexual abuse, parental depression, parental substance abuse, domestic violence, and other situations in which the primary caregiver is either directly causing the distress or otherwise failing to adequately mediate its effects. In practice, new-onset, seemingly tolerable stressors can often be superimposed on pre-existing toxic stressors, necessitating careful assessment in differentiating AD from a more pervasive problem resulting from trauma. Thus, a child with a history of several toxic stressors, presenting with a maladaptive response to new problem, will likely require a greater degree of intervention compared to a child with an otherwise stable caregiver relationship and unremarkable psychosocial history.

## DIAGNOSIS

With this wide range of causes and resulting manifestations of distress, appropriate identification of adjustment can be challenging. Given the absence of more concrete, objective criteria, diagnosis necessarily entails some subjective assessment on the part of the physician in regards to what constitutes a stressful event and a maladaptive response. The pediatrician is often in a unique position to make this determination. Whereas the mental health professional often first comes into contact with the child in the midst of a crisis, the pediatrician often has worked with the child and family over a long period of time and has a working sense of his or her developmental level, coping skills, and strengths. This can serve as an invaluable point of reference in assessing the effects of stress and the resulting departure from the child's psychological and functional baseline. It is in this context that the diagnostic construct of AD seems to provide the greatest clinical utility.

### Signs, Symptoms, and Differential Diagnosis

The signs and symptoms of AD include distress and impairment in functioning manifested by decreased performance in school, work, or relationships. Children and adolescents, as compared with adults, are more likely to present with behavioral disturbance than with depressed mood. However, the symptom presentation is also dependent on the subtype. For example, for young children with a depressed mood this may be manifested by sadness, tearfulness, change in appetite and sleeping pattern, or loss of interest in play. For older children and teens there may be irritability, loss of energy, fatigue, feeling slowed down or burned out, excessive feelings of guilt, inability to concentrate, indecisiveness, and hopelessness. Thoughts of suicide, substance use, and somatic complaints are also common. In those with the anxiety subtype of AD, symptoms of nervousness, worry, jitteriness, or fear of separation may predominate. Disturbances in conduct and emotions may also occur. In developing the differential diagnosis, careful review is needed to determine if the child or teen meets criteria for another disorder inclusive of but not limited to major depressive disorder, dysthymia, a generalized anxiety disorder, acute stress/post-traumatic stress, somatization disorder, oppositional defiant disorder,

conduct disorder, or substance abuse. Importantly, unlike the stressor in AD, in post-traumatic stress disorder the stressor is extreme and involves actual or threatened death or serious injury accompanied by a specific constellation of symptoms. Trauma always needs to be considered in the differential diagnosis. Conversely, a child may be suffering from the effects of early toxic stress (described earlier), and such a history should alert the physician to the possibility of complex developmental trauma and its attendant psychological and behavioral sequelae. Thus, a pattern of frequent, recurrent "adjustment reactions" can point to the presence of a more pervasive psychiatric disorder.

Box 210-2 is illustrative of a typical presentation in the primary care setting. The alerts for the physician are noted, as are the assessment strategy and shared-treatment planning and monitoring necessary with the child/adolescent and parent.

## MANAGEMENT

### Treatment Approach

In planning treatment for a patient with AD, the goals are to reduce emotional and behavioral distress and to improve functioning. Wissow and colleagues have described the *common factors* approach for the treatment of mental health problems in the primary care setting. Drawing from the active core elements of various evidence-based treatments, the model takes a transdiagnostic approach to the application of effective practice elements rather than applying a specific protocol for a certain diagnosis. This has been shown to help improve outcomes across a range of diagnoses and could be particularly useful in AD, given the subsyndromal, potentially evolving (transient, temporary) nature of this diagnosis. Common factors can provide well defined and manageable tools that physicians can use to further the discussion on mental health and engage patients in addressing these problems. This can be accomplished through interventions both at the level of the individual and the level of the larger environment, depending on the particular circumstances of the case.

At the individual level, fostering resilience—identifying and bolstering coping skills, as well as problem solving around issues related to the stressor—can be a good place to start. Parents can be important partners in this process, particularly for younger patients, by encouraging healthy means of coping. To this end, educating both the child and parents about the effects of stress and the role of coping can serve an important role in promoting recovery and wellness. Identifying other supports, such as teachers, counselors, or coaches, can provide additional sources of support in coping with stressors. Scheduling a follow-up psychosocial visit to check in with the patient is important to signal that the physician deems that the teen's distress merits attention and can determine whether the symptoms are improving or if further intervention is needed. Developing a safety plan in case symptoms worsen or dangerousness (suicidal or homicidal ideation) arises should also be discussed with the patient and his or her family.

Another potentially important avenue of intervention lies in the environment itself, given the pivotal

**BOX 210-2 Adjustment Disorder Case**

AJ is a 17-year-old who comes to the office for a chief complaint of throat pain. He is a senior in high school known to his physician since birth. He hasn't attended school in several days. His affect is depressed and he is anxiously moving about in the office.

The physician asks how he is. AJ says he doesn't feel well. His responses are short and uncharacteristic. After examining him and obtaining a throat culture, the physician sits down with AJ. In a relaxed manner she inquires a bit further and offers AJ the opportunity to talk a bit more. The physician learns that AJ is distraught because his girlfriend of 6 months broke up with him 1 week ago. He is not sleeping well, has lost his appetite, and has disengaged from a number of activities that he enjoys. He denies any drug or alcohol use. He is having trouble focusing in school. Review of system is otherwise normal. The physician is considering an adjustment disorder.

*What would be reasonable next steps in the evaluation?*

Reasonable next steps in the assessment include reviewing the symptoms' duration; determining if this is an AD; assessing the related risks to this patient, regardless of diagnosis; and determining the frequency and type of monitoring needed for AJ. The physician in this case has a longitudinal relationship with the teen and may have discussed issues of confidentiality, but a review of confidentiality and of the limits of confidentiality is appropriate at this session. AJ's reactions are in response to an identified stressor that is within the time period delineated by the definition of AD. In addition, while AJ has some symptoms of depression and anxiety, he does not meet criteria for major depression, depression not otherwise specified, or anxiety, as manifested by the relatively short duration of his symptoms.

A review of AJ's past psychiatric history as well as family psychiatric history is relevant since they will help target a youth at particular risk for bad outcomes. Assessment of functioning in his home, school, and personal life is relevant. Given this teen's depressed affect, a more formal assessment of depressive symptoms and also suicidal risk are relevant. It may also be important to identify additional stressors. Given his age, it is likely that applications for college are imminent and may be adding to this teen's distress at this point in time. Assessing school performance in general, family and school pressures are also relevant.

*Are there any screening tools that might be useful in this encounter?*

There are several tools that may be useful to the evaluation of youth in the primary care setting. Most of these tools are in the public domain, short, psychometrically sound, and helpful in the evaluation. The following tools are representative.

*Tools for Pediatricians* (see also the Tools for Practice section at the end of the chapter)

1. Pediatric Symptom Checklist (PSC-17): a general psychosocial screen for the identification of symptoms in the domains of attention, internalizing, and externalizing.

2. PHQ-9M: a modified screen for depression in teens; maps onto the DSM criteria for depression and has been modified to include questions on suicidality.
3. CRAFFT (car, relax, alone, forget, friends, trouble): queries teens regarding riding in a car with someone who is "high" with alcohol or drugs; whether the teen uses alcohol or drugs to relax; uses these alone; has forgotten events after using; whether family and friends are worried about his/her use; and whether he or she has gotten in trouble as a result of use. This validated tool is short, and scoring can be used to assess probability of abuse or dependence. The physician should also remember to inquire about tobacco use.
4. Risk assessment for suicide: The SAD PERSONS + Family History mnemonic is useful in this regard and includes **S**ex (females attempt more often but males are more likely to complete), **A**ge over 16, **D**epression (and comorbid conduct/impulsive aggression/anxiety), **P**revious attempts, **E**thanol abuse (or other substance), **R**ational thinking lost (eg, psychotic/intoxicated), **S**ocial supports lacking, **O**rganized plan present (highly lethal and unusual method with wish to die/concealment), **N**o significant other available (eg, a close friend); **S**ickness (stressors); and a first-degree relative who has completed a suicide.

*What are reasonable next steps before AJ leaves the physician's office?*

1. Review with AJ the results he reported on the PSC-17, CRAFFT, and PHQ-9M. These tools can facilitate a discussion. For example, ask for clarification regarding answers that are positive for a particular symptom. A sample question/comment may be "I see that you checked this off. Tell me more about that."
2. Establish the family/peer support available to the teen and discuss issues of confidentiality and the limits of confidentiality in the case of safety concerns about self-harm, harm to others, or harm from others.
3. Discuss suicidal risk using the SAD PERSONS mnemonic, with a clear plan for follow-up. For teens with increased risk, a discussion with the relevant family support person is indicated, including assessing for access to weapons or other lethal means. Psychiatric assessment may be needed along with possible hospitalization if there is imminent risk. Education regarding adjustment issues may help to alleviate some stress and may also help engage the child/teen in active treatment planning.
4. Assist the teen in identifying coping skills (eg, relaxation, deep breathing, talking to others, self-talk).
5. Actively engage the teen in discussion regarding returning to normal activities, including school attendance and participation in sports and other extracurricular activities. General sleep hygiene and encouragement of regular meals should be discussed.
6. Develop a treatment plan inclusive of the steps listed above.

role of stressors in adjustment problems. This can include parents, family, school, peers, or the larger community, all of whom can play a role in predisposing, precipitating, or perpetuating the presenting problem. For example, if bullying is leading to problems of maladjustment, contacting the school and discussing intervention strategies with the staff can be instrumental in improving the situation and alleviating individual symptoms. Many other forms of stressors (eg, a contentious parental divorce) do not lend themselves to similar types of swift intervention but require attention nonetheless, because they are likely to perpetuate or even exacerbate symptoms of adjustment over time. In this regard, lapses or failures in the relationship to the primary caregiver(s) can be particularly deleterious and difficult to correct. In this manner, treatment of AD calls for a broad, systemic view of the patient's problems. It also necessarily entails communication and collaboration with other systems of care outside of the traditional office setting.

### Specific Treatments, Indication for Admission, and When to Refer

Should problems with coping persist or worsen, referral to mental health services may be warranted. The treatment of choice is psychotherapy. While no empirically validated treatments exist specifically for the treatment of AD, there are many different forms of psychotherapeutic treatments for full-blown syndromes such as depression, generalized anxiety, disruptive behavior disorders, and trauma. These can, in theory, be applied to the prominent symptoms of the particular adjustment syndrome. Examples include cognitive behavioral therapy (CBT) and interpersonal therapy for depression, CBT for anxiety, and trauma-focused CBT. These treatments are delivered in a variety of individual and group formats; however, at present, little is known about the optimal structure, frequency, and intensity of these treatments in cases of AD. Looking again to the systemic aspects of adjustment, family therapy can be another important intervention to consider in cases of severe and persistent distress.

Similarly, medication does not have an established evidence base in the treatment of AD, and the US Food and Drug Administration has not approved any medication for the treatment of AD. Benzodiazepines have not shown efficacy in controlled trials in childhood anxiety, although they have been used clinically with SSRIs as adjunctive short-term treatment to address severe anxiety symptoms and facilitate exposure to CBT. Their role in AD has not been studied. They are contraindicated with substance use and have a side effect profile that includes sedation, disinhibition, cognitive impairment, and difficulty with discontinuation. In adults, in cases of prolonged stress, such as chronic illness and medical hospitalization, SSRIs have been used to help bolster resilience and recovery. There are no reports or similar studies in children with AD. Given the prominent psychosocial determinants of AD, the nonpharmacologic interventions outlined above are the treatments of choice.

Hospitalization of a child or teen with AD is unlikely to be necessary in the absence of severe impairment and active suicidal thoughts or plan. Ongoing follow-up with primary care or mental health specialty care is indicated for monitoring of symptom resolution and return to normal social functioning. Literature reviews indicate that more children and teens, as compared to adults, experience a poor outcome with continued disturbance and progression to specific disorders, although for most of them the prognosis is good. The area of prevention is not at all addressed in the literature and many important questions remain unanswered. Further research is needed to determine if AD is a subthreshold presentation of post-traumatic stress disorder; a variant of a less severe affective, anxiety or behavioral disorder; or an entirely different disorder independent of any of these conditions.

## TOOLS FOR PRACTICE

### Medical Decision Support

- *The CRAFFT Screening Tool* (questionnaire), Center for Adolescent Substance Abuse Research ([www.ceasar-boston.org/CRAFFT/index.php](http://www.ceasar-boston.org/CRAFFT/index.php))
- *Enhancing Pediatric Mental Health Care: Algorithms for Primary Care* (article), *Pediatrics*, Vol 125, Suppl 3, 2010 ([pediatrics.aappublications.org/content/125/Supplement\\_3/S109](http://pediatrics.aappublications.org/content/125/Supplement_3/S109))
- *Evidence-Based Child and Adolescent Psychosocial Interventions* (chart), PracticeWise, American Academy of Pediatrics ([www.aap.org/en-us/Documents/CRPsychosocialInterventions.pdf](http://www.aap.org/en-us/Documents/CRPsychosocialInterventions.pdf))
- *Feelings Need Check Ups Too* (booklet), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/children-and-disasters/Documents/Feelings-Need-Checkups-Toolkit\\_0823.pdf](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/children-and-disasters/Documents/Feelings-Need-Checkups-Toolkit_0823.pdf))
- *Mental Health Screening and Assessment Tools for Primary Care* (chart), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH\\_ScreeningChart.pdf](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH_ScreeningChart.pdf))
- *Pediatric Symptom Checklist* (screen), Massachusetts General Hospital ([www.massgeneral.org/psychiatry/services/psc\\_home.aspx](http://www.massgeneral.org/psychiatry/services/psc_home.aspx))
- *The Resilience Project: Clinical Assessment Tools* (Web page), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/resilience/Pages/Clinical-Assessment-Tools.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/resilience/Pages/Clinical-Assessment-Tools.aspx))
- *Screen for Child Anxiety Related Disorders (SCARED): Child Version* (questionnaire), University of Pittsburgh ([www.psychiatry.pitt.edu/sites/default/files/Documents/assessments/SCARED%20Child.pdf](http://www.psychiatry.pitt.edu/sites/default/files/Documents/assessments/SCARED%20Child.pdf))
- *Screen for Child Anxiety Related Disorders (SCARED): Parent Version* (questionnaire), University of Pittsburgh ([www.psychiatry.pitt.edu/sites/default/files/Documents/assessments/SCARED%20Parent.pdf](http://www.psychiatry.pitt.edu/sites/default/files/Documents/assessments/SCARED%20Parent.pdf))
- *Strengths & Difficulties Questionnaire* (screen), Youth in Mind ([www.sdqinfo.com](http://www.sdqinfo.com))

## AAP POLICY

American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health and Task Force on Mental Health. The future of pediatrics: mental health competencies for pediatric primary care. *Pediatrics*. 2009;124(1):410–421. Reaffirmed August 2013 (pediatrics.aappublications.org/content/124/1/410)

## SUGGESTED READINGS

- American Academy of Child and Adolescent Psychiatry Committee on Health Care Access and Economics Task Force on Mental Health. Improving mental health services in primary care: reducing administrative and financial barriers to access and collaboration. *Pediatrics*. 2009;123(4):1248–1251
- Newcorn JH, Strain J. Adjustment disorder in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 1992;31:318–326
- Shonkoff JP, Garner AS; Committee on Psychosocial Aspects of Child and Family Health; Committee on Early Childhood, Adoption, and Dependent Care; Section on Developmental and Behavioral Pediatrics. The lifelong effects of early childhood adversity and toxic stress. *Pediatrics*. 2012;129:e232–e246
- Tiet QQ, Bird HR, Davies M, et al. Adverse life events and resilience. *J Am Acad Child Adolesc Psychiatry*. 1998;37:1191–1200

## Chapter 211 ADRENAL DYSFUNCTION

Phyllis W. Speiser, MD

Adrenal cortical disease, especially adrenal insufficiency, is far more common than adrenal medullary disease and often goes unrecognized for extended periods. Physicians caring for children should consider the diagnosis of adrenal insufficiency in any patient with unexplained hypoglycemia, growth failure, weight loss, vomiting, or lethargy. These nonspecific signs and symptoms may be mistaken for, and should be differentiated from, infection, malnutrition, gastrointestinal disease, inborn errors of metabolism, anorexia, chronic fatigue syndrome, and depression.

## ANATOMY AND PHYSIOLOGY

The adrenal glands each weigh approximately 4 g in term neonates at birth, which is equivalent to the weight of adult glands; however, adrenal size decreases by approximately 50% to 60% within the first week of life. The adrenal glands are made up of an inner medulla and an outer cortex that are linked by vascular supply and hormonal influence. Within the mature adrenal cortex are 3 functionally distinct zones: the glomerulosa, comprising approximately 15% of the gland; fasciculata, the largest zone, comprising approximately 75% of the gland; and the reticularis, comprising approximately 10% of the gland.

The adrenal medulla is regulated by the sympathetic nervous system and secretes catecholamines, whereas the 3 zones of the cortex secrete steroid hormones

categorized, respectively, as mineralocorticoids, glucocorticoids, and sex steroids. Mineralocorticoid production, exemplified by aldosterone, is principally regulated by the renin-angiotensin axis and by ambient potassium levels. Mineralocorticoids affect sodium and potassium homeostasis, and deficiencies in their production or action cause hyponatremia, hyperkalemia, and dehydration. Glucocorticoid and adrenal sex steroid production are primarily regulated by pituitary corticotropin (adrenocorticotrophic hormone [ACTH]) and hypothalamic corticotropin-releasing hormone, secreted mainly in the early morning hours (4:00 to 8:00 am). Cortisol is the main glucocorticoid, and dehydroepiandrosterone (DHEA) is the main adrenal sex hormone. The latter is only a weak androgen, but it may be converted via androstenedione to either estrogens or androgens. The placenta uses fetal adrenal DHEA to produce estrogens. The main gestational hormone so derived, estriol, excreted in maternal urine, is a sign of fetal viability. Rising levels of DHEA and its sulfate later in childhood signal adrenarche, which usually precedes the development of body hair and apocrine odor at puberty.

Glucocorticoids are generally catabolic, promoting protein and lipid breakdown and inhibiting protein synthesis. The effects of cortisol counterregulate those of insulin, increasing the concentration of glucose by stimulating gluconeogenesis and by decreasing glucose utilization in muscle. Amino acids and glycerol produced by catabolic actions of cortisol on protein and fat are used as gluconeogenic substrates. The net effect is increased production and conservation of glucose for use by essential tissues, such as the brain and red blood cells, at the expense of less essential tissues during times of stress or starvation. Supraphysiologic doses of exogenous glucocorticoids suppress growth by antagonizing the production and action of growth hormones (GHs).

Cortisol contributes to the maintenance of normal blood pressure through several mechanisms. Under normal baseline conditions, cortisol increases urine flow by stimulating glomerular filtration rate and decreasing water resorption. At high concentrations, cortisol acts as a mineralocorticoid agonist, causing sodium and water retention. Other vascular actions of cortisol include stimulating angiotensinogen synthesis by the liver and increasing vascular sensitivity to pressors. In the adrenal medulla, cortisol is required for the enzymatic activity of phenylethanolamine *N*-methyltransferase, which converts norepinephrine to epinephrine. Epinephrine stimulates cardiac output, as well as hepatic glucose production. Cortisol decreases capillary permeability as well as the production and activity of nitrous oxide and the vasodilatory kinin and prostaglandin systems during stress, preventing life-threatening hypotension. Cortisol or aldosterone deficiency, or both, often results in shock if unrecognized and untreated.

## ADRENAL INSUFFICIENCY

### History and Physical Examination

The symptoms of cortisol deficiency include lethargy, fatigue, weakness, dizziness, and anorexia. Signs



detected at physical examination include hyperpigmentation, orthostatic hypotension, tachycardia, and weight loss. These findings are nonspecific and gradual in onset, and they may be mistaken for infection, malnutrition, gastrointestinal disease, inborn errors of metabolism, anorexia, chronic fatigue syndrome, and depression. In some patients, gastrointestinal symptoms such as abdominal cramps, nausea, vomiting, and diarrhea are prominent. In adolescents and adults, sexual or reproductive dysfunction, or both, with decreased libido, potency, or amenorrhea may accompany either primary or secondary adrenal insufficiency. Orthostatic hypotension is more marked in primary than secondary adrenal insufficiency because primary adrenal insufficiency is often associated with both aldosterone and catecholamine deficiency.

The most commonly recognized screening laboratory findings are hypoglycemia and low plasma cortisol. Children with these findings should be referred to a pediatric endocrinologist for further evaluation. Children with chronic primary adrenal insufficiency often have hyperpigmentation of the skin and mucosal surfaces, which is the result of the high plasma corticotropin and accompanying melanocyte-stimulating hormone secretion that result from absent cortisol feedback. This hyperpigmentation may be difficult to appreciate in dark-skinned individuals. Clues to its presence may be hyperpigmentation of the creases of the palms and of the oral mucosal surfaces. In contrast, patients with secondary adrenal insufficiency tend to be pale. Another symptom of primary adrenal insufficiency is a craving for salt, which is a result of aldosterone deficiency and resultant sodium wasting. Weight loss and failure to thrive may also be observed. Loss of axillary or pubic hair is common among hypoadrenal patients, which is attributable to low levels of adrenal androgens.

Children with secondary adrenal insufficiency might have delayed growth and puberty and manifestations of GH and gonadotropin deficiencies, in addition to ACTH deficiency. Headaches, visual disturbances, polyuria, and polydipsia, or any combination of these reactions indicative of diabetes insipidus may also be seen in pituitary disorders. Physicians caring for children with chronic unexplained signs or symptoms such as those described previously should consult with a pediatric endocrinologist to determine whether a referral is required. Children in hypotensive crisis or shock at the time they seek care should be treated urgently in the office or transferred immediately by ambulance to the nearest emergency center.

### Pathologic Forms

Primary adrenal disease may be associated with either hypoplasia or hyperplasia related to variable adrenal function. The most common forms of adrenal disease involve either deficient or excessive cortisol production. Box 211-1 lists various causes of adrenal disease. Only the most commonly encountered disorders will be reviewed in detail in this chapter. Online Mendelian Inheritance in Man (OMIM) should be consulted for a more detailed discussion of rarer diseases; OMIM catalog numbers for each adrenal disease are listed in Box 211-1.

### Primary Causes of Adrenal Failure

In primary adrenal insufficiency in children younger than 18 years, the most common cause is congenital adrenal hyperplasia (CAH; 72%). Thirteen percent have autoimmune adrenal insufficiency, and the remaining 15% include various rare syndromes such as adrenoleukodystrophy, Wolman disease, triple A syndrome (ACTH resistance, achalasia, alacrima), Zellweger syndrome, and unexplained adrenal insufficiency. In non-CAH primary adrenal insufficiency, causes include autoimmune adrenal insufficiency, X-linked adrenoleukodystrophy, adrenal hypoplasia congenita, and the IMAGe syndrome (intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia congenita, and genital anomalies) (see Box 211-1).

CAH is the most common inborn error in adrenal function. It is most often caused by deficiency of steroid 21-hydroxylase. In classic severe salt-wasting CAH, both cortisol and aldosterone production are impaired, and adrenal androgen production is excessive. As a result of the lack of the vital hormones cortisol and aldosterone, both boys and girls are susceptible to potentially lethal adrenal insufficiency if untreated; this susceptibility is also true of other forms of CAH that interrupt synthesis of these hormones (eg, 3- $\beta$  hydroxysteroid dehydrogenase deficiency, cholesterol desmolase deficiency). Excess androgen production, a side effect of 21-hydroxylase deficiency, causes genital ambiguity in newborn girls. In contrast, however, boys affected with severe 21-hydroxylase deficiency have no overt genital anomalies, and may not come to medical attention until they seek care while in extremis. To prevent mortality from adrenal crisis, among other reasons, the United States and many other countries perform newborn screening for this disease. Prompt treatment with glucocorticoids and mineralocorticoids is life saving. About one-fourth of patients with classic CAH produce enough aldosterone to avoid salt-wasting crises and are termed *simple virilizers*.

A milder, nonclassic form of CAH not associated with genital ambiguity or adrenal insufficiency may be missed by newborn screening programs. Although nonclassic CAH is not always detected by random blood hormone measurements, it is much more prevalent at all ages than the classic forms of the disease. Because nonclassic CAH is characterized by less marked adrenal androgen excess, symptoms and signs typically do not develop before middle childhood. These symptoms and signs often include early pubic hair and rapid advances in height in both sexes. In many cases, these disorders either go undetected or are diagnosed in adolescent girls or women with hirsutism, oligomenorrhea, or acne. The mild form of CAH may be mistaken in girls for polycystic ovarian syndrome.

Not all persons with increased 17-hydroxyprogesterone typical of nonclassic 21-hydroxylase deficiency are symptomatic. Boys, in particular, are much less likely to be troubled by this mild adrenal hormone imbalance. Even some girls and women remain asymptomatic. Thus, children who do not exhibit precocious pubarche and adolescents who are not troubled with symptoms of androgen excess may not

**BOX 211-1 Causes of Adrenal Cortical Insufficiency****PRIMARY**

- Disorders associated with adrenal gland hyperplasia
  - 21-Hydroxylase deficiency (gene *CYP21A2*, OMIM 210910)
  - 3-Beta hydroxysteroid dehydrogenase deficiency (gene *HSD3B2*, OMIM 201810)
  - Cholesterol desmolase deficiency (gene *CYP11A*, OMIM 201710, 118485)
  - Lipoid hyperplasia (gene *STAR*, OMIM 201710)
  - POR deficiency (gene *POR*, OMIM 201750)
  - Glucocorticoid resistance (gene *GCCR*, OMIM 138040)
  - Wolman disease (gene *LIPA*, OMIM 278000)
- Disorders associated with adrenal gland hypoplasia
  - Adrenal hypoplasia congenita (gene *NROB1* [*DAX-1*], OMIM 300200)
  - Adrenocortical insufficiency with or without ovarian defect (gene *NR5A1* [*SF-1*], OMIM 184757)
  - Familial glucocorticoid deficiency (ACTH resistance) (gene *MC2R/MRAP*, OMIM 202200)
  - Triple A (ACTH resistance, achalasia, alacrima) (gene *AAAS*, OMIM 231550)
  - IMAGe (intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia congenita and genital anomalies) syndrome (X-linked, OMIM 300290)
- Metabolic diseases
  - Adrenoleukodystrophy (X-linked) (gene *ABCD1*, OMIM 300100)
  - Smith-Lemli-Opitz syndrome (gene *DCHR7*, OMIM 270400)
  - Kearns-Sayre syndrome (gene *mitochondrial DNA deletions*, OMIM 530000)
  - Disorders associated with isolated aldosterone deficiency
    - Pseudohypoaldosteronism, type 1 (AR) (gene *ENaC*, OMIM 264350)
    - Pseudohypoaldosteronism, type 1 (AD) (gene *MR*, OMIM 177735)
    - Pseudohypoaldosteronism, type 2 (AR) (gene *WNK4;WNK1*, OMIM 145260)
    - Corticosterone methyl oxidase deficiency I (gene *CYP11B2*, OMIM 124080)
    - Corticosterone methyl oxidase deficiency II (gene *CYP11B2*, OMIM 610600)

**ACQUIRED**

- Autoimmune adrenalitis, isolated
- Autoimmune polyendocrine syndrome type 1 (gene *AIRE*, OMIM 240300)
- Autoimmune polyendocrine syndrome type 2 (gene *MICA5.1* and *HLA-DR3/DQ2*, OMIM 269200)

- Hemorrhage or infarction caused by:
  - Trauma
  - Waterhouse-Friderichsen syndrome
  - Anticoagulation
  - Drug effects (aminoglutethimide, mitotane, ketoconazole, metyrapone, medroxyprogesterone, megestrol, etomidate, rifampin, phenytoin, barbiturates)
  - Infection
  - Virus (HIV, cytomegalovirus)
  - Fungus (coccidiomycosis, histoplasmosis, blastomycosis, cryptococcosis)
  - Mycobacterium (tuberculosis)
  - Amebic
  - Infiltrative
    - Hemochromatosis, histiocytosis, sarcoidosis, amyloidosis
    - Neoplasm

**SECONDARY****Hypothalamus**

- Congenital
  - Septooptic dysplasia (gene *HESX1*, OMIM 182230)
  - Corticotropin-releasing hormone deficiency (gene *CRH*, OMIM 122560)
  - Maternal hypercortisolemia
- Acquired
  - Inflammatory disorders
  - Trauma
  - Radiotherapy
  - Surgery
  - Tumors
  - Infiltrative disease (sarcoidosis, histiocytosis X)
  - Steroid withdrawal after prolonged administration

**PITUITARY**

- Congenital
  - Pituitary hormone deficiency, combined (gene *POU1F1/PIT1*, OMIM 173110; gene *PROP-1*, OMIM 601538)
  - Pro-opiomelanocortin deficiency (gene *POMC*, OMIM 609734)
  - Proconvertase 1 (gene *PCSK1*, OMIM 600955)
  - Isolated ACTH deficiency (gene *TBX19/TPIT*, OMIM 604614)
- Acquired
  - Trauma
  - Tumor (craniopharyngioma)
  - Radiotherapy
  - Lymphocytic hypophysitis
  - Steroid withdrawal after prolonged administration

ACTH, adrenocorticotrophic hormone; OMIM, Online Mendelian Inheritance in Man.

require treatment, or they may discontinue treatment when symptoms have abated and growth is complete.

### Laboratory Evaluation

The diagnosis of CAH rests on both the clinical manifestations and the specific hormone measurements. Deficiency of steroid 21-hydroxylase can be identified by measuring high levels of hormones that serve as enzyme substrates. The gold standard test is a corticotropin-stimulated serum 17-hydroxyprogesterone, although analysis of serum or saliva levels of this hormone taken at 8:00 am may also be diagnostic. This circumstance is true because of the natural circadian pattern of endogenous ACTH secretion, which is highest between 4:00 am and 8:00 am. Measuring adrenal hormones in an endocrine specialty laboratory that employs strict quality-control standards is important to avoid false-positive high levels generated by nonspecific measurement of cross-reacting hormones.

Stimulated serum 17-hydroxyprogesterone levels are usually moderately increased, usually exceeding 1,500 ng/dL (approximately 45 nmol/L) in individuals affected with nonclassic 21-hydroxylase deficiency. In contrast, both basal and stimulated 17-hydroxyprogesterone levels are markedly increased, generally exceeding 10,000 ng/dL (approximately 300 nmol/L) in classic simple virilizing or salt-wasting CAH. Moreover, cortisol levels are invariably low and fail to respond robustly to stress or exogenous stimulation in classic forms of CAH. Early-morning basal serum 17-hydroxyprogesterone measurements below 200 ng/dL (approximately 6 nmol/L) usually rule out even mild forms of 21-hydroxylase deficiency. Newborn screening test results from filter paper samples are measured differently and are not comparable to serum hormone levels. Each state's laboratory has its own reference range for screening tests.

### Genetics

Phenotypic variability in CAH is attributable to allelic variation in the gene encoding active steroid 21-hydroxylase CYP21A2. The disease is inherited as an autosomal-recessive trait. More than 100 known disease-causing mutations have been found, but approximately 10 mutations comprise 80% to 90% of alleles in most populations. The spectrum of disease ranges from severe to mild, depending on which CYP21A2 mutations a patient carries. Genotyping can

be useful in verifying an equivocal hormonal diagnosis; it is particularly valuable in prenatal diagnosis and genetic counseling.

### Management and Long-Term Follow-up

CAH is treatable with oral corticosteroid medications. In its classic form, CAH requires lifelong medical management. Patients with salt wasting require both glucocorticoids and mineralocorticoids; however, with older age and increasing dietary salt consumption, mineralocorticoids may be tapered and in some cases discontinued. Infants who consume very little dietary sodium, patients in tropical climates, and those who engage in intense exercise with excessive sweat sodium losses may require supplemental sodium chloride. Poorly controlled patients with simple virilizing CAH also benefit from mineralocorticoid therapy because it spares the use of high-dose glucocorticoids in some cases. Symptomatic nonclassic patients require low-dose glucocorticoid therapy only. Some physicians prefer to treat CAH with a higher dose of cortisol or a longer-acting glucocorticoid at night in an attempt to suppress the early-morning ACTH-mediated adrenal androgen production, but there are scant data to support this practice.

When growth is nearly complete, if satisfactory control of adrenal androgens is not achieved with such a regimen, more potent and long-acting glucocorticoids, such as prednisone or dexamethasone, may be used. Table 211-1 lists approximate relative glucocorticoid potencies.

Dosing should be titrated to maintain the levels of adrenal androgen precursors in the normal to mildly increased range. The physician should assay 17-hydroxyprogesterone, androstenedione, and testosterone; plasma renin activity is added to this profile in patients requiring mineralocorticoid replacement. Attempts to suppress 17-hydroxyprogesterone to the normal range usually require excessively high glucocorticoid doses and have the undesirable consequence of growth suppression and iatrogenic Cushing syndrome. Measurement of ACTH is not helpful; this hormone seldom is completely suppressible in patients who have been treated for CAH. An important point to recognize is that testosterone is not as useful a hormonal marker of adequate therapy in adolescent boys and men, although it is helpful in managing prepubertal children of both sexes, as well as adolescent girls and women.

**Table 211-1** Glucocorticoid Potencies

DRUG	POTENCY RELATIVE TO CORTISOL	EQUIVALENT CORTISOL DOSE	MINERALOCORTICOID ACTIVITY
Cortisol (hydrocortisone)	1	100	Present
Cortisone	0.8	125	Present
Prednisone	5	20	Absent
Prednisolone	5	20	Absent
Methylprednisolone	6	17	Absent
Dexamethasone	50	2	Absent

Other aspects of CAH treatment include ensuring that adolescent girls with severe forms of CAH undergo gynecologic examination in anticipation of sexual activity; vaginoplasty may be necessary, depending on whether or which genital surgical procedures may have been performed in the past. Psychological counseling should be provided to these young women by a professional who is experienced in treating this type of disorder.

Adolescent boys should undergo careful testicular palpation and sonography to rule out testicular adrenal rests that can compromise fertility. Strict control of adrenal hormone levels can shrink such benign tumors in many cases.

### Other Causes of Adrenal Failure

Primary adrenal insufficiency is estimated to affect approximately 100 per 1 million people. The syndrome, originally described by English physician Thomas Addison, included wasting, hyperpigmentation, and adrenal gland atrophy. In adults, more than 80% of cases are caused by autoimmune adrenal destruction, which is most prevalent in women aged 25 to 45 years but which is observed in both sexes at any age. The female-to-male ratio is approximately 3:1. Autoimmune adrenalitis may be isolated or found in association with other autoimmune syndromes. Autoimmune polyendocrine syndrome type 1 is associated with mucocutaneous candidiasis, Addison disease, and autoimmune hypoparathyroidism. Other systemic problems may include autoimmune pernicious anemia, hepatitis, thyroiditis, and diabetes. The age at onset and severity of each of these problems are variable. Autoimmune polyendocrine syndrome type 2, also termed *Schmidt syndrome*, is associated with Addison disease, autoimmune thyroiditis, and diabetes. Box 211-1 lists the diseases associated with adrenal insufficiency.

Adrenal infiltration by tuberculosis is the second most common cause worldwide. HIV is another potential infectious cause of adrenalitis; both of these infections tend to cause insidious progression to hypoadrenalism. In contrast, catastrophic adrenal hemorrhage during overwhelming bacterial sepsis causes the abrupt onset of adrenal failure.

Perhaps because of its rarity in children or its non-specific symptoms, the diagnosis of adrenal insufficiency is often delayed or missed. If unrecognized, adrenal insufficiency may produce a life-threatening crisis, with acute cardiovascular collapse. The child's caregivers may have to seek the advice of more than one physician before a diagnosis will be made, which may result in a lengthy delay between the onset of the first symptoms and the diagnosis.

### History and Physical Examination

As noted previously, signs and symptoms of adrenal insufficiency may include abdominal pain, headache, anorexia, weight loss, lethargy, postural hypotension or shock, proneness to dehydration, salt craving, and hyperpigmentation. Patients with adrenal insufficiency with and without GH deficiency may have hypoglycemia, but this condition is seldom severe enough to cause seizures.

### Laboratory Evaluation

Primary adrenal insufficiency can be detected based on low early-morning (8:00 am) cortisol accompanied by increased ACTH. If zona glomerulosa function is affected, then hyponatremia and hyperkalemia will be accompanied by a high plasma renin activity and low serum aldosterone. In adrenal insufficiency resulting from pituitary or hypothalamic dysfunction, ACTH levels will be low. The diagnosis of primary adrenal insufficiency can be confirmed by absence of at least a twofold increment in serum cortisol 60 minutes after stimulation with a standard dose of intravenous cosyntropin (ACTH 1-24). A low dose of cosyntropin can be used to test ACTH reserve in cases of suspected secondary adrenal insufficiency.

### Imaging Studies

If adrenal hemorrhage is suspected, then it can be detected by ultrasonography or computed tomography (CT) scan.

### Management

When the diagnosis of adrenal insufficiency is established, frequent reminders to patients, families, and medical personnel regarding the need for higher doses of glucocorticoid replacement therapy during intercurrent illness and surgery are required. Failure to increase glucocorticoid supplementation during physical stress remains a significant cause of morbidity and mortality in these patients. Patients should be given letters explaining their condition and appropriate emergency management. Sample letters may be found on the Web sites of the National Adrenal Diseases Foundation for patients with Addison disease, and the CARES Foundation (Congenital Adrenal Hyperplasia Research Education and Support) for patients with CAH (see Tools for Practice).

### Secondary Adrenal Insufficiency

Secondary adrenal insufficiency is more common than primary adrenal insufficiency. The estimated prevalence is 150 to 280 per million people. Abrupt discontinuation of glucocorticoid therapy exacerbated by stress is the most common cause and results from the widespread use of exogenous glucocorticoids. Acute hypoglycemia has been reported after the use of inhaled glucocorticoids. An important point to recognize is that normal statural growth does not preclude adrenal suppression while being treated with inhaled glucocorticoids.

Administration of steroids orally, intramuscularly, intranasally, inhaled, transdermally, or intraorbitally may result in suppression of the hypothalamic-pituitary-adrenal axis. In adults, as little as 2 weeks of high-dose glucocorticoid treatment may result in suppression of endogenous cortisol production for up to 1 year. In children being treated for leukemia, a 4-week course of glucocorticoids may suppress the hypothalamic-pituitary axis for up to 8 weeks after discontinuation. Suppression of the axis cannot be reliably predicted by either the dose or the duration of therapy.

Documentation of an intact hypothalamic-pituitary-adrenal axis should be obtained before subjecting to



surgery a patient who has a known history of high-dose, long-term glucocorticoid treatment. This task may be accomplished by documenting plasma cortisol level taken at 8:00 am of more than 10 mcg/dL or by performing a cosyntropin (ACTH 1-24) challenge test and observing cortisol levels above 15 to 18 mcg/dL after 30 to 60 minutes. These levels have been derived mainly from adult studies and may not be relevant to infants and small children. Another robust test of ACTH reserve is insulin-induced hypoglycemia; however, many physicians are reluctant to use this test because of the danger of potential hypoglycemic seizures. If such documentation cannot be obtained in time, then treating patients with supplemental stress corticosteroid coverage in the perioperative period within 1 year of withdrawal of therapy is safest.

Most secondary adrenal insufficiency that is unrelated to withdrawal of glucocorticoid therapy occurs in association with other pituitary hormone deficiencies. *Panhypopituitarism*, or deficiency of 2 or more pituitary hormones, may be either congenital or acquired. Anatomic abnormalities in the pituitary or stalk may be evident on MRI. Alternatively, the physician may elicit a history of head trauma or cranial surgery with resulting pituitary injury.

Aside from these causes of secondary adrenal insufficiency, several other rare syndromes have been found. These syndromes include ACTH resistance associated with triple A syndrome (ACTH resistance, alacrima, and achalasia). This clinical picture is caused by mutations in the *AAAS* gene encoding a protein of uncertain function. In contrast, an isolated form of ACTH resistance is caused by a different genetic defect in the gene encoding the ACTH receptor *MC2R*. The latter syndrome is characterized by a familial form of glucocorticoid deficiency associated with hyperpigmentation and hypoglycemia without accompanying systemic abnormalities. Granulomatous diseases such as sarcoidosis or histiocytosis can also cause pituitary failure. The risk for adrenal crisis in adults with primary adrenal insufficiency is slightly higher (3.8 admissions per 100 patient-years) compared with secondary adrenal insufficiency (2.5 per 100 patient-years). Information concerning mortality in secondary adrenal insufficiency mostly comes from recent reports regarding follow-up of individuals treated with pituitary GH. An up to fourfold increase in mortality compared with the general population in children treated with pituitary GH has been reported. This increase is presumably because patients with a pituitary hormone deficiency are likely to develop other hormone deficiencies. Deaths were attributed to hypoglycemia or secondary adrenal insufficiency. These preventable deaths were observed in individuals of all ages and were associated with a variety of causes of hypopituitarism; 74% were said to occur in individuals with known multiple pituitary hormone deficiencies. The death rate resulting from secondary adrenal insufficiency remained fairly constant throughout middle childhood and with advancing age (1 per 113 to 173 person-years).

Management of secondary adrenal deficiency is similar to that of primary adrenal insufficiency. Measuring ACTH or cortisol levels in plasma to gauge the

efficacy of treatment with corticosteroids is usually not helpful. Rather, the patient's growth, weight gain, and vital signs, as well as the patient's own sense of well-being, should guide therapy.

## RELATIVE ADRENAL INSUFFICIENCY IN THE INTENSIVE CARE UNIT

Annane and colleagues found that critically ill adults with a normal baseline cortisol but inappropriately low response of serum cortisol to acute stimulation demonstrated improved survival when treated with stress doses of hydrocortisone, although these findings have not been replicated.

Among critically ill children, a low incremental cortisol response to ACTH does not predict mortality, although the effect of glucocorticoid treatment is not known.

Much controversy still exists regarding how best to look for adrenal insufficiency in hospitalized children and adults, as well as whether and when to treat. Thus, the decision to treat a critically ill patient with glucocorticoids must be made on a case-by-case basis until further definitive evidence is available.

## MANAGEMENT OF ACUTE ADRENAL INSUFFICIENCY

Hypotension and lethargy are common signs at presentation of acute adrenal insufficiency; patients and family members should be taught to recognize a change in energy level or demeanor as a potential warning sign. Acute adrenal insufficiency may occur during febrile illness, especially when accompanied by dehydration, vomiting, diarrhea, or any combination of these reactions. Individuals who are unable to tolerate oral maintenance or stress doses during an illness require parenteral glucocorticoid administration. Another option, especially if parenteral administration is not feasible, and provided that the patient does not have diarrhea, is to administer hydrocortisone suppositories.

After the patient is seen in the emergency department, a large-bore intravenous catheter should be inserted for repletion of intravascular volume with saline solutions containing 5% dextrose. More concentrated dextrose (eg, 25% dextrose in water) should be administered to treat refractory hypoglycemia. If the patient's adrenal status is unknown, then blood should be drawn for cortisol, electrolytes, glucose, ACTH, plasma renin activity, and aldosterone, preferably before exogenous steroids are administered. If acute and severe adrenal insufficiency is suspected, however, then treatment should not be delayed for diagnostic testing. Simultaneous with the administration of fluids, stress doses of glucocorticoids should be given. Hydrocortisone is the treatment of choice because of its quick onset of action and mineralocorticoid activity. Prednisone and dexamethasone are long-acting glucocorticoids with a slower onset of biologic action. Table 211-1 lists the relative potencies of various steroid medications. Prednisone is not an ideal choice for treating acute adrenal crisis because it must be converted to prednisolone to be effective. Dexamethasone does not cross-react in cortisol

assays; thus, a diagnostic ACTH stimulation test may be performed right after its administration.

Liberal quantities of intravenous sodium chloride accompanied by large doses of hydrocortisone will usually restore normotension and correct electrolyte abnormalities, obviating mineralocorticoid treatment or pressor agents in the acute situation. As vital signs stabilize, glucocorticoids and fluid infusions are tapered over several days. When the patient is able to eat and take oral medications, oral glucocorticoids may be substituted. Supplemental sodium chloride may be provided if dietary salt intake is inadequate.

### Chronic Replacement Therapy

Maintenance glucocorticoid replacement therapy is based on estimated normal cortisol secretion rates. Glucocorticoid dosing must be individually adjusted to avoid signs and symptoms of adrenal insufficiency while also avoiding the growth retardation and cushingoid features that can accompany overtreatment. When growth is complete, longer-acting glucocorticoids such as dexamethasone may be considered to enhance compliance. In general, lower doses of glucocorticoids are required to treat Addison disease compared with CAH. Measuring plasma cortisol or ACTH levels in titrating the glucocorticoid dose is not usually helpful. Patients with low serum sodium, high potassium, or increased plasma renin activity should receive daily oral fludrocortisone and sodium chloride supplements, adjusted to normalize these analytes. The patient's own sense of well-being, energy level, and blood pressure can help guide the adequacy of therapy in patients with Addison disease. Frequent headaches, lethargy, nausea, or abdominal pain may indicate inadequate treatment. Objective signs of inadequate replacement therapy are orthostatic pulse or blood pressure changes. If skin hyperpigmentation becomes more prominent in primary adrenal insufficiency, then plasma ACTH levels may be helpful.

DHEA has been considered an optional hormone supplement for older women with adrenal insufficiency and low energy or libido, but no data on its use in adolescents have been collected.

### Stress Dosing

Patients with adrenal insufficiency (primary or secondary, and patients with CAH) must be informed about the need to increase their glucocorticoid dose during stress to prevent a potentially lethal adrenal crisis. All such patients should wear a medical alert tag and carry an emergency medical information card to ensure that medical providers know about the underlying disorder.

Mild physical stresses such as immunizations, uncomplicated viral illnesses, and low-grade fever (temperature  $<101.3^{\circ}\text{F}$  [ $<38.5^{\circ}\text{C}$ ]) do not require stress doses of glucocorticoids. Athletic activity and emotional stress also do not usually require a boost in glucocorticoid dose. Adolescents with CAH who received an additional morning dose of hydrocortisone causing a 100% increase in serum cortisol level did not alter their athletic performance. No changes were observed in blood glucose, lactate, free fatty

acids, or epinephrine levels during short-term, high-intensity exercise compared with placebo.

More severe stresses such as illness accompanied by higher fever (temperature  $\geq 101.3^{\circ}\text{F}$  [ $\geq 38.5^{\circ}\text{C}$ ]), surgery, and major trauma should be accompanied by tripling of oral hydrocortisone maintenance doses to prevent hypoglycemia, hypotension, and even cardiovascular collapse. Supplemental parenteral hydrocortisone is suggested before general anesthesia and surgery. Doses are empiric and are not determined by evidence-based guidelines. Intravenous or oral stress doses may be gradually tapered as the patient recovers until the maintenance dose is attained.

## ADRENOCORTICAL HYPERFUNCTION

The spectrum of disorders causing adrenal hyperfunction (Box 211-2) is more limited compared with those causing hypofunction.

### Premature Adrenarche

Adrenal androgen excess is most commonly observed in children with early onset of pubic and body hair growth. The traditional age limit has been 8 years for the onset of pubic hair in girls and 9 years in boys. The lowest age limit for girls has been contested after a large cross-sectional study revealed the relatively common occurrence of either early pubic hair or breast enlargement in healthy black girls after age 6 years and in white girls after age 7.

### Definition

The early onset of adrenal androgen secretion accompanied by pubic hair (*pubarche*) is termed *premature adrenarche*.

### BOX 211-2 Causes of Adrenal Cortical Hyperfunction

- Iatrogenic
  - Glucocorticoid or mineralocorticoid treatment
  - ACTH treatment
- Pituitary
- Pituitary tumors
- Adrenal tumors
  - Carcinoma
  - Adenoma
- Adrenal nodular hyperplasia
  - Carney complex (AD) (gene *PRKAR1A*, OMIM 160980)
  - McCune-Albright syndrome (gene *GNAS1*, OMIM 174800)
- Ectopic ACTH-producing tumors
- Apparent mineralocorticoid excess (gene *HSD11B2*, OMIM 218030)
- Glucocorticoid remediable hyperaldosteronism (AD) (gene chimeric *CYP11B1/B2*, OMIM 103900)

ACTH, adrenocorticotrophic hormone; AD, autosomal dominant; OMIM, Online Mendelian Inheritance in Man.

### Laboratory Evaluation

Premature adrenarche is heralded by mildly increased levels of DHEA and DHEA-sulfate. These hormone levels tend to be consistent with the child's Tanner stage of pubic hair. DHEA, a weak androgen, is the most abundantly produced adrenal steroid. The sulfated form has a longer half-life in the circulation and thus is not subject to circadian variability, making it a more robust screening tool. Premature adrenarche is generally considered a benign condition that does not warrant treatment with glucocorticoid suppression. Presence of isolated pubic hair or axillary hair with or without apocrine body odor does not necessarily presage early breast development and menstruation. In most cases, children with premature adrenarche do not exhibit rapid statural growth or advanced bone age.

Because premature adrenarche is most often a benign condition, telephone consultation with a pediatric endocrinologist should be considered before referring such children. Endocrine evaluation should be reserved for children who exhibit unusually early pubarche, multiple signs of early puberty, rapidly progressive pubertal development or statural growth (or both), or nonisosexual puberty (eg, a girl with hirsutism or other signs of virilization, a prepubertal boy with gynecomastia).

Overweight children secrete more adrenal sex hormones than lean children and can metabolize these weak adrenal sex hormones in fat to more active sex hormones. Mean free testosterone is sixfold higher in obese girls than nonobese girls across pubertal stages 1 to 3. Consequently, they may develop secondary sexual characteristics at an earlier than average age. In contrast to nonobese children with premature adrenarche, obese children often show advanced bone ages, but they are not usually short.

Most overweight and obese children who are growing in height at a normal pace do not have a causal underlying endocrine disease. Thus, the pediatrician should institute dietary counseling and advise a rigorous exercise program to determine whether weight gain can be controlled. Telephone consultation with a pediatric endocrinologist is advised if in doubt. Reports have surfaced that a subset of girls with premature adrenarche go on to develop polycystic ovarian syndrome, insulin resistance, or metabolic syndrome. The precise cause of this tendency is uncertain but has been related to prenatal growth restriction, especially with rapid postnatal catch-up growth. In light of the role of obesity in androgen excess, intuitively, individuals with body mass indices in the overweight to obese range might be at highest risk. At present, no strong evidence has been found to warrant preventive drug treatment in anticipation of the possible occurrence of polycystic ovarian syndrome in young girls who have had premature adrenarche.

The differential diagnosis of premature adrenarche includes nonclassic forms of CAH and adrenal virilizing tumors. The most common nonclassic form of CAH can be detected by measuring early-morning or ACTH-stimulated levels of 17OHP. The much rarer occurrence of tumors can be detected by finding markedly increased levels of DHEA-sulfate and often

other hormones as well. Imaging studies are required to verify a clinical suspicion of an adrenal tumor.

### Cushing Syndrome

*Cushing syndrome* refers to any form of glucocorticoid excess, whereas *Cushing disease* refers to glucocorticoid excess caused by ACTH hypersecretion. Although Cushing disease is rare, it is the most commonly identified noniatrogenic etiology for glucocorticoid excess in adolescents, occurring in approximately 0.5 per million persons per year. Box 211-2 lists causes of glucocorticoid excess.

### History and Physical Examination

Prominent clinical features of adrenocortical hyperfunction in adolescents are excess central body weight gain with stunted statural growth. An important point to emphasize is that most obese adolescents do not have Cushing syndrome and do not require screening unless growth arrest or other suspicious signs are observed. An obese child with statural growth arrest should be referred to a pediatric endocrinologist for more complete evaluation. Examination of annual school photographs can often help reveal subtle changes in physiognomy and habitus over time. Other characteristic findings are easy bruisability, broad and purplish striae, hyperglycemia, and hypertension.

Therapeutic glucocorticoids are in widespread use for a variety of inflammatory and neoplastic diseases. Exogenous administration of relatively high doses of these drugs over long periods by any route is the most common cause of Cushing syndrome as well as secondary adrenal insufficiency. Although the relative safety of alternate-day oral and inhaled glucocorticoids has been demonstrated, individual differences in drug metabolism or sensitivity may cause an increase in bioavailable levels of these potent compounds, many of which have very long biologic half-lives. Therefore, obtaining a thorough medication history in children treated with these drugs is important. If possible, glucocorticoids should be tapered as soon as is practical while substituting other therapeutic agents. In some patients, attenuation of cushingoid features and improvement of statural growth may take months to years.

### Laboratory Evaluation

Clinical suspicion of Cushing syndrome in the absence of exogenous glucocorticoid administration should prompt appropriate screening diagnostic studies, including measurement of increased midnight salivary cortisol, high 24-hour urinary free cortisol, or both. The diagnosis may be confirmed by finding a non-suppressed morning cortisol after dexamethasone administration. The latter test has been refined by the postdexamethasone administration of corticotropin-releasing hormone. An inappropriately brisk rise in plasma ACTH after corticotropin-releasing hormone suggests an ACTH-producing pituitary tumor, and MRI with attention to this portion of the brain is indicated. If the tumor cannot be localized by imaging, then selective catheterization of the inferior petrosal sinuses with measurement of ACTH level on either side may be done at a specialized center. Ancillary



laboratory studies often reveal impaired glucose tolerance and low bone density on radiographs or dual x-ray absorptiometry.

Adrenal carcinomas (but not typically adenomas) will secrete cortisol as well as mineralocorticoids and androgens. Adrenal tumors are the most common cause of endogenous steroid excess in young children. The typical case appears in a round-faced, ruddy child with rapidly advancing premature pubarche, hypertension, and an abdominal mass. If adrenal carcinoma is suspected based on ACTH-independent (ie, nonsuppressible) cortisol excess, then the patient should undergo additional hormone measurements of aldosterone and plasma renin activity as well as DHEA-sulfate and androgens.

### Imaging Studies

Thin-slice CT or MRI of the abdomen including the adrenal glands should be performed. Carcinoma will often show a necrotic center, calcification and irregular borders, or both, whereas benign nonfunctioning adenomas are typically more similar in density to normal adrenal tissue and are homogeneous. Ectopic ACTH production by carcinomas is almost never seen in children.

### Management

Cushing disease has traditionally been treated primarily with transsphenoidal tumor resection. Surgical success largely depends on the skill of the surgeon and the nature of the lesion. The cure rate ranges from 60% to 80%. Data show that directed radiotherapy, such as gamma knife and linear accelerator techniques, can also induce gradual remission of ACTH hypersecretion. After ACTH levels have decreased, the patient needs chronic glucocorticoid replacement therapy.

Patients with an adrenal tumor or nodular hyperplasia as the source for cortisol excess will most often undergo adrenalectomy. Another alternative for Cushing syndrome or Cushing disease is medical therapy with drugs such as ketoconazole or mifepristone. This therapy can be used either in the short term (eg, while waiting for radiotherapy to take effect) or the long term to reduce cortisol secretion; however, this type of treatment will not induce a permanent cure.

## Adrenal Medullary Diseases

### Neuroblastoma

In young children, the most common tumor encountered is a neuroblastoma. The yearly incidence is approximately 1 in 100,000 children younger than 15 years. The average age at diagnosis in North America is 2 years; mass screening of infants is done in Japan to allow earlier diagnosis.

Common presenting signs include abdominal mass, fever of unknown origin, hematuria, spinal cord compression, pathologic fracture, and hypertension. Metastases to liver and bone occur in approximately 50% of cases by the time of tumor detection. Biochemical markers include plasma and urinary dopamine, vanillylmandelic acid, and homovanillic acid.

Bone scan is usually informative, revealing bone metastases, soft tissue calcifications, or both. Other imaging modalities are discussed later in this chapter

in conjunction with pheochromocytoma diagnostic tests. The medical and surgical management of such tumors depends on staging risk; a possibility exists of spontaneous regression in low-grade tumors.

### Pheochromocytoma

**HISTORY AND PHYSICAL EXAMINATION.** In the adolescent, medullary disease is most often caused by a pheochromocytoma, a rare tumor that may cause either episodic or chronic hypertension, usually accompanied by tachycardia, headaches, anxiety, sweating, flushing, or any combination. Weight loss may also be observed. The differential diagnosis in adolescents most saliently includes panic attacks, thyrotoxicosis, renovascular disease, and drug abuse (especially cocaine or amphetamines).

**LABORATORY EVALUATION.** Screening tests, besides documenting hypertension in the office, may include 24-hour ambulatory blood pressures. Chemistry profile may demonstrate hyperglycemia. Such findings should prompt referral to appropriate specialists. Extreme hypertension in a child should prompt immediate emergency referral and hospitalization.

The diagnosis of pheochromocytoma is made by measuring increased 24-hour urinary free metanephrines (collected in an acid container). Urinary free metanephrines are superior to urinary vanillylmandelic acid, urinary catecholamines, and plasma catecholamines. Alternatively, high-performance liquid chromatography is used for measurement of plasma free metanephrines. Blood should be obtained from an indwelling venous catheter in a patient who has fasted overnight and has been at rest for at least 20 to 30 minutes; the sample tube must be iced and processed immediately. If possible, psychoactive drugs, especially tricyclic antidepressants, should be discontinued at least 2 weeks before testing.

**IMAGING STUDIES.** Confirmatory imaging may be done by metaiodobenzylguanidine scan. Metaiodobenzylguanidine is a norepinephrine analog labeled with radioiodine that is taken up specifically by catechol-producing tumor tissue but not normal adrenal medulla. This imaging test is particularly helpful in cases in which thin-slice, contrast-enhanced CT or MRI fails to show a mass, yet biochemical tests and the clinical scenario are suggestive of pheochromocytoma. Other new imaging options include positron emission tomography and use of somatostatin analogs.

A thorough family history should be obtained for endocrine tumors, especially medullary thyroid carcinoma and hyperparathyroidism, because multiple endocrine neoplasia type 2 may be associated with pheochromocytoma. Genotyping for the *RET* oncogene should be performed in the patient, and, if positive, other family members should be tested. Transmission is autosomal dominant. Other syndromes prone to adrenal tumors or pheochromocytomas include von Hippel-Lindau disease, neurofibromatosis type 1, paraganglioma, and tuberous sclerosis. Approximately 30% of young patients with pheochromocytoma have one of these familial disorders and should therefore be genotyped for the appropriate genes. Familial cases are more often bilateral.



Children with a family history of familial tumor syndromes should be referred to the appropriate specialists for evaluation because early detection of affected genetic status may dictate intervention before tumors develop.

**MANAGEMENT.** Calcium channel-blocking drugs such as nifedipine are primarily used to control hypertension because calcium is needed for catechol secretion. In preparation for surgery, the patient should be treated for at least 1 week with a drug with both alpha-adrenergic blocking (eg, phenoxybenzamine) and beta-adrenergic blocking (eg, labetalol) properties. Unopposed alpha blockade would precipitate a hypotensive crisis at surgery, whereas unopposed beta blockade would exacerbate the hypertension from endogenous epinephrine, a potent vasoconstrictor. In addition, alpha-methyl-L-tyrosine (Demser) is used to inhibit the rate-limiting step of catechol synthesis. Approximately 10% of pheochromocytomas are bilateral, and thus, at the time of surgery, both adrenals should be explored. If both adrenals are removed, then substitution therapy will be required as primary adrenal insufficiency. Malignancy and recurrence may occur in approximately 10% to 15% of cases. Careful long-term follow-up of patients with regular checks of blood pressure and catechol measurements are crucial.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Emergency Instructions: Caring for your child with Congenital Adrenal Hyperplasia in Times of Stress* (brochure), CARES Foundation ([www.caresfoundation.org/wp-content/uploads/2014/09/EmergencyInstructions.pdf](http://www.caresfoundation.org/wp-content/uploads/2014/09/EmergencyInstructions.pdf))
- *Getting Ready for School* (Web page), CARES Foundation ([www.caresfoundation.org/weight/school](http://www.caresfoundation.org/weight/school))
- *Tools for Life - Emergency ID and Medical Information* (Web page), National Adrenal Diseases Foundation ([www.nadf.us/tools-for-life/emergency-id-medical-information](http://www.nadf.us/tools-for-life/emergency-id-medical-information))

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## Chapter 212

# ALLERGIC RHINITIS

Frank S. Virant, MD

Recent data from the National Health and Nutrition Examination Survey (NHANES III) suggest that 45% of children 6 to 9 years of age and 55% of children 10 to 19 years of age have sensitization to at least 1 of 10 common allergens. The most common clinical manifestation of sensitization is allergic rhinitis. Although some children have only rhinitis, many experience associated asthma or atopic dermatitis. Allergic rhinitis is relatively uncommon before the age of 3 years, but then increases in frequency throughout childhood, with a peak prevalence in adolescence. Seasonal allergic rhinitis caused by pollens often becomes apparent in early school-aged years and is quite obvious in the spring, summer, or early fall. Perennial allergic rhinitis caused by dust mites, cockroaches, animal dander, or indoor mold can occur at any age, but typically is more subtle and can be easily confused with other forms of rhinitis.

## ETIOLOGY

The likelihood of developing allergic rhinitis has a significant genetic component: if one parent has allergic rhinitis, the likelihood for a given child is 40%; if both parents are affected with allergic rhinitis, the likelihood jumps to 80%. When a child with genetic predisposition to allergic rhinitis is exposed to a relevant allergen, specific immunoglobulin E (IgE) is produced, which then binds to high-affinity receptors on mast

cells in the upper airway. Further exposure to the allergen activates a type I (immediate hypersensitivity) reaction as IgE binds to the allergen, triggering the release of preformed mediators, such as histamine, and the production of others, such as prostaglandins, leukotrienes, and cytokines. Histamine causes most of the immediate clear rhinorrhea, congestion, and sneezing seen with allergic rhinitis. Cytokines primarily guide inflammatory cells, such as eosinophils, to the site of reaction, leading to more edema (congestion) and nasal hyperresponsiveness. Severity of symptoms is influenced by several factors, including condition of the nose before exposure, level of specific IgE, and intensity of antigen exposure.

Common allergic rhinitis allergens include the following:

- *Dust mites*: These arthropods represent the major allergen in house dust and prosper in warm, moist indoor environments. They survive off shed human skin cells, and therefore tend to be particularly an issue on pillows, mattresses, and carpets. Dust mites are the major cause of perennial allergic rhinitis.
- *Cockroaches*: Much like dust mites, cockroaches thrive in warm, humid areas and are a common urban reason for perennial allergic rhinitis.
- *Animals*: Dander and saliva from cats and dogs can cause more subtle perennial as well as severe intermittent symptoms. Rodent allergens (also found in urine) can occur from pets such as hamsters, gerbils, or guinea pigs as well as from unwanted pests such as mice and rats.
- *Molds*: Indoor molds can be an issue if moisture accumulates at high levels, such as in poorly ventilated bathrooms or at the base of single-pane windows. Outdoor molds can cause seasonal symptoms during the spring, summer, and fall in colder areas or year-round in warmer climates.
- *Pollens*: Trees (late winter, spring), grasses (spring, summer), and weeds (summer, fall) represent the major reason for seasonal allergic rhinitis symptoms. Clinical presentation varies greatly by location and can be affected by several factors, including ambient temperature, precipitation, wind, local vegetation, and size of pollen grains. In a particular region, however, the reappearance of major allergens is highly predictable each year.

## CLINICAL FEATURES

Typical clinical features of allergic rhinitis include clear rhinorrhea, sneezing, congestion, and localized pruritus (nose, eyes, and occasionally palate, pharynx). Younger children generally have perennial allergic symptoms caused by dust mites, cockroaches, animal dander, or indoor molds. Seasonal pollen allergy often becomes evident by 4 to 5 years of age, but can also start much later in childhood because of individual variations in genetic predisposition to make IgE, as well as geographical differences in pollen distribution. The diagnosis of seasonal allergic rhinitis is often based on the patient's history and knowledge of local pollen seasons. Specific pollen counts can add further support for the diagnosis (local pollen counts from certified stations are logged on the American

Academy of Asthma, Allergy and Immunology Web site [www.aaaai.org]). Although children with perennial allergic rhinitis may have episodic rhinorrhea and sneezing, the primary clinical effect is from inflammation and associated congestion of the upper airway. This can lead to a multifaceted clinical picture, including frequent viral upper respiratory infections (URIs), chronic serous otitis media, recurrent suppurative otitis media, nasal speech, decreased hearing, mouth breathing, snoring, poor sleep pattern, and fatigue. Perennial allergic rhinitis also increases the risk for bronchial hyperresponsiveness during viral URIs. Rhinorrhea caused by allergic triggers is typically clear and watery, but this can be overshadowed by purulent secretions if the child also has infectious rhinitis or sinusitis. Histamine release often creates intense itching in the nose and oropharynx, leading patients to intensely rub their nose (the "allergic salute") or make strange clucking or throat-clearing noises to try to get relief.

The physical examination in moderate to severe uncomplicated allergic rhinitis shows pale, bluish, boggy turbinates with a clear serous discharge. Often, the turbinates are so enlarged that they touch the nasal septum and can completely occlude the upper airway. Because of chronic congestion and associated obstruction of venous drainage, many children have dark, swollen infraorbital areas, or "allergic shiners." Other common findings are Dennie-Morgan lines (extra folds under the lower eyelids caused by edema and rubbing) and an allergic crease (horizontal line across the lower bridge of the nose caused by rubbing). Children with more severe chronic allergic rhinitis are obligate mouth breathers; this can lead to elongated facial growth and various orthodontic changes (eg, overbite and high-arched palate). Tonsils and adenoids are often enlarged because of allergic immune stimulation (but this can also be a separate primary problem). Chronic middle ear effusion is also common in children with more severe allergic rhinitis. Although nasal polyps may occur with intense allergic disease, this is rare in childhood and more commonly caused by cystic fibrosis or eosinophilic nonallergic rhinosinusitis.

## COMPLICATIONS

In younger children, significant perennial allergic rhinitis causes increased swelling in the upper airway (nose, eustachian tubes, sinus ostia), creating an environment that may increase the incidence of respiratory infection, acute otitis media, chronic serous otitis media, eustachian tube dysfunction, hearing loss, and sinusitis. Chronic congestion from allergic rhinitis can also lead to elongated facies, high-arched palate, and malocclusion of the teeth caused by tongue thrusting. Upper airway allergic disease can increase bronchial hyperresponsiveness and thus lower the threshold for asthma as a result of other triggers, such as viral URIs, cold air, dry air, and exercise.

## LABORATORY FINDINGS

Nasal cytology can be a useful diagnostic adjunct when the clinical diagnosis of allergic rhinitis is in question. Secretions from the nose can be obtained by

having the child blow the nose onto plastic wrap or by swabbing the nose with a cytology brush. The secretions are then transferred to a glass slide, dried, and treated with either Hansel stain or Wright stain. If cellular microscopy reveals more than 10% eosinophils, then underlying eosinophilic rhinitis is suggested. In most children, this cellular response is caused by allergy, but eosinophilic nonallergic rhinitis cannot be excluded; this can be clarified by the presence or absence of specific IgE to allergens, as discussed later. Concurrent infection will create a significant neutrophilic response that can obscure underlying allergy, and the absence of eosinophils in a nasal smear does not preclude allergy because the sample of secretions may not be adequate (few cells) or may be influenced by recent corticosteroid therapy.

Peripheral eosinophilia is often observed in patients who have allergic rhinitis with more than 5% eosinophils or a total eosinophil count of more than 250/ $\mu$ L. Elevated total IgE does suggest atopy, but many patients with allergic rhinitis have levels in the normal range, and some patients with normal levels are atopic. Accordingly, peripheral eosinophil counts and total serum IgE are not recommended for allergic rhinitis screening because they are neither specific nor sensitive.

Determination of specific IgE with skin or serologic tests can be useful to help direct environmental control and determine appropriate components for immunotherapy. Overall, both types of tests tend to provide the same information, but skin tests are often preferred because they are less expensive and have somewhat better sensitivity. If a child has a poor clinical course despite aggressive environmental controls and appropriate frontline medications, referral to a board-certified allergist is recommended.

## DIFFERENTIAL DIAGNOSIS

The diagnosis of seasonal allergic rhinitis is generally straightforward based on clinical presentation, physical examination, and a knowledge of the local pollen pattern. In contrast, the diagnosis of perennial allergic rhinitis can be more challenging because symptoms are often more subtle or may be obscured by other conditions that cause rhinorrhea, congestion, and cough (eg, viral URI, recurrent acute or chronic rhinosinusitis, vasomotor rhinitis, adenoid hypertrophy, and turbinate hypertrophy).

Viral URI can typically be differentiated from allergic rhinitis on the basis of acute onset of fever, purulent rhinorrhea, red swollen nasal mucosa, and sore throat. Nasal cytology will show a predominance of neutrophils, but this does not preclude an allergic component as well.

Recurrent acute rhinosinusitis often presents as viral URI that does not resolve after 10 to 14 days. Symptoms may overlap with mild allergic rhinitis, but typically patients have significant nasal obstruction and nocturnal cough. Protracted acute sinusitis may lead to a chronic low-grade infectious component or induce eosinophilic nonallergic rhinosinusitis. Nonallergic rhinitis with eosinophilia syndrome (NARES) is relatively rare in young children, but increases in frequency in older children. When NARES occurs, it may

be associated with nasal polyps and asthma, much like more severe allergic rhinitis. By definition, NARES patients have negative skin tests.

Vasomotor rhinitis describes a condition of nasal hyperresponsiveness to nonspecific irritant stimuli (eg, volatile organic compounds, perfumes, smoke, and pollutants). Affected patients have chronic nasal congestion that is typically minimally improved by environmental controls or medications (unless they have associated allergic rhinitis or rhinosinusitis). Children with isolated vasomotor rhinitis have normal nasal cytology, negative skin test results, and normal total and specific IgE test results, and they lack signs of associated atopic disease (eg, asthma or atopic dermatitis).

Nasal turbinate hypertrophy and adenoid hypertrophy represent important anatomic variants that cause chronic nasal obstruction. Ironically, both conditions may worsen in a child with significant allergic rhinitis, so allergic triggers should first be defined and aggressively treated with environmental controls and anti-inflammatory medications (eg, montelukast, nasal corticosteroids). Typically, children with significant nasal turbinate or adenoid hypertrophy are always congested and exhibit snoring. This congestion can lead to chronic serous otitis media, decreased hearing, decreased appetite, poor sleep pattern (including sleep apnea), and orthodontic abnormalities (high-arched palate, overbite, malaligned teeth).

Other less common conditions that can mimic some symptoms of allergic rhinitis include nasal foreign body, choanal atresia, rhinitis medicamentosa, cystic fibrosis, ciliary dyskinesia, and nasopharyngeal tumors.

## TREATMENT

Treatment of allergic rhinitis is initially based on history and physical examination, which provides a framework of likely triggers and clinical severity. Management includes allergen avoidance measures, pharmacotherapy, and occasionally immunotherapy. Therapy should be thoughtfully individualized based on the patient's age, unique environmental factors, symptom severity, and presence of associated medical conditions (eg, otitis media, sinusitis, asthma, and atopic dermatitis). If a child with perennial symptoms fails to respond to appropriate medication or if seasonal allergies become refractory to frontline therapy, consultation with a board-certified allergist should be considered. An allergist can help confirm the primary diagnosis, including identification of relevant allergic triggers; exclude other subtle upper and lower airway nonallergic diseases; fine-tune environmental control and pharmacotherapy; and, for select patients, prescribe allergen-specific immunotherapy.

Allergy treatment should always start with aggressive environmental controls. Although any exposure is important, controls should target the child's bedroom and any other areas where a fair amount of time is spent. When dust mite allergy is suspected, important measures include encasing the pillow, mattress, and box spring with dust mite-impervious covers, washing the bedding at least weekly in hot water, and minimizing stuffed animals or other dust collectors in

the bedroom. Ideally, animals should be removed if they are an important cause of symptoms, but this can be challenging for a family. Compromise measures include keeping the pet out of the bedroom at all times and, if feasible, washing the pet several times a month to help remove allergens that would otherwise end up throughout the home. If indoor molds are a concern, this is best remedied by decreasing moisture levels (eg, more effective exhaust fans in the bedroom and kitchen), installing double-pane windows, or using a dehumidifier. For children with pollen allergy, it is helpful to keep windows closed and use an air conditioner. In homes with forced-air heating and cooling, it can be helpful to install a filter that can remove all indoor allergens (<5 microns) and a humidifier or dehumidifier to maintain relative humidity in the 40% to 50% range. Keeping the humidity in this middle range provides a good compromise by discouraging dust mites, cockroaches, and mold growth at higher levels, but also avoiding the irritant effect of dry air at lower levels.

Primary pharmacotherapy for allergic rhinitis includes antihistamines (oral and nasal), leukotriene antagonists, and nasal corticosteroids. Adjunctive medications include decongestants, nasal cromolyn, nasal ipratropium, and oral corticosteroids.

Oral antihistamines are the first-line treatment for allergic rhinitis. These medications work by blocking histamine-1 receptors on mast cells, thus preventing rhinorrhea, sneezing, and itching caused by histamine. Recently developed antihistamines (eg, fexofenadine, cetirizine, levocetirizine, loratadine, and desloratadine) are typically effective with relatively low risk for side effects such as sedation. Although first-generation antihistamines such as chlorpheniramine, diphenhydramine, hydroxyzine, and triprolidine are also effective, their utility is often limited because of their sedative side-effect profile. Nasal antihistamines (eg, azelastine and olopatadine) represent an alternative approach to oral antihistamines, but also carry some risk for sedation because the medication is absorbed from the nose.

The leukotriene receptor antagonist montelukast is also approved for treating both perennial and seasonal allergic rhinitis. Montelukast is generally well tolerated and can be used as monotherapy or combined

with antihistamines. It can be particularly useful in children who have concurrent asthma or will not comply with the use of nasal sprays.

Nasal corticosteroids are the most effective monotherapy for treating allergic rhinitis, and some formulations have been approved for use in children 2 years and older. Available formulations include beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone propionate, fluticasone furoate, mometasone furoate, and triamcinolone (Table 212-1). Growth suppression is a theoretical risk with nasal steroids, so the lowest effective dose should be used. Fortunately, several of the newer formulations have reduced bioavailability and are typically well tolerated.

Decongestants may be useful in the short term to help reverse the effects of acute congestion, but oral formulations carry a significant potential for causing irritability, hyperactivity, or sleep disturbances. The use of nasal decongestants should also be limited because prolonged therapy can actually induce rebound congestion (rhinitis medicamentosa). Nasal cromolyn sodium is well tolerated, but its use is limited because optimal efficacy requires use 4 to 6 times a day. Nasal ipratropium will help control rhinorrhea, but typically has little effect on other symptoms. Oral corticosteroids can be useful in the short term to help reduce acute severe allergic inflammation; in addition to providing symptom relief, these agents reduce nasal obstruction and nasal hyperresponsiveness and thus create a more favorable environment for the use of nasal therapy.

When allergic rhinitis does not respond adequately to environmental controls and appropriate pharmacotherapy, allergy consultation should be considered to clarify allergic triggers and exclude a nonallergic rhinitis component. If the diagnosis of moderate to severe allergic rhinitis is confirmed in this setting, allergen-specific immunotherapy becomes a consideration. Traditional allergy immunotherapy typically entails a 3- to 5-year series of subcutaneous injections in a controlled setting to help induce tolerance; such treatment is most effective for seasonal allergic rhinitis (pollen) and dust mite allergy, but may also have efficacy when animal dander and molds are an issue. Recently, sublingual allergy immunotherapy has become available to treat grass or ragweed allergy.

**Table 212-1** Nasal Corticosteroids

GENERIC NAME	TRADE NAME	CHILD DOSING	ADULT DOSING
Azelastine/fluticasone propionate	Dymista	1/nosril bid ( $\geq 12$ yr)	1/nosril bid
Beclomethasone	QNASL	NA	2/nosril qd
Budesonide	Rhinocort Aqua	1–2/nosril qd (6–12 yr)	1–4/nosril qd
Ciclesonide	Omnaris	1–2/nosril qd (6–12 yr)	2/nosril qd
Ciclesonide	Zetonna	NA	1/nosril qd
Flunisolide	(generic)	2/nosril bid (6–14 yr)	2/nosril bid–tid
Fluticasone propionate	Flonase (generic available)	1–2/nosril qd (4–12 yr)	1–2/nosril qd
Fluticasone furoate	Veramyst	1–2/nosril qd (2–11 yr)	1–2/nosril qd
Mometasone furoate	Nasonex	1/nosril qd (2–12 yr)	2/nosril qd
Triamcinolone	Nasacort AQ (generic available)	1/nosril qd (2–5 yr)	1–2/nosril qd ( $\geq 6$ yr)

*bid*, twice a day; *qd*, every day; *tid*, 3 times a day.



Sublingual treatment is started 12 weeks before the relevant pollen season and is continued on a daily basis through the season.

## PROGNOSIS

The prognosis for patients with allergic rhinitis is often related to environmental triggers, unique genetic factors, and willingness to comply with suggested treatment. Typically, children with perennial allergic triggers tend to have fewer problems as they get older. This is partially because environmental controls have an increased effect on indoor allergen exposure (dust mites, cockroach, animals, indoor molds), but also because these allergens tend not to induce much more IgE production over time. Accordingly, as the patient's airway gets bigger, the relative effect of these perennial factors tends to lessen—less congestion and less risk for otitis media, sinusitis, and asthma. In contrast, seasonal allergy caused by pollens tends to worsen over time because there is a predictable heavy exposure to each allergen every year that stimulates significant increases in specific IgE. These seasonal allergies can be positively modulated by changes in environment (moving), nasal corticosteroids, and allergen immunotherapy.

## WHEN TO REFER

Consider referral to a board-certified allergist in children with

- Persistent perennial rhinitis symptoms
- Poorly controlled seasonal rhinitis symptoms
- Recurrent otitis media, recurrent sinusitis, or worsening persistent or intermittent asthma
- Symptoms that warrant consideration of allergen-specific immunotherapy

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Allergies in Children* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Allergy Medication Guide* (interactive tool), American Academy of Allergy, Asthma & Immunology ([www.aaaai.org/patients/resources/medication\\_guide/default.stm](http://www.aaaai.org/patients/resources/medication_guide/default.stm))
- *What Is a Pediatric Allergist/Immunologist?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Allergist-Immunologist.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Allergist-Immunologist.aspx))

### Medical Decision Support

- *When Should Students With Asthma or Allergies Carry and Self-Administer Emergency Medications at School* (fact sheet), National Heart, Lung, and Blood Institute, AAP endorsed ([www.nhlbi.nih.gov/files/docs/resources/lung/emerg\\_med.pdf](http://www.nhlbi.nih.gov/files/docs/resources/lung/emerg_med.pdf))

## SUGGESTED READINGS

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## Chapter 213

# ALTITUDE SICKNESS

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## FOUNDATION

Because of a growing interest in adventure travel, increasing numbers of people are venturing to high altitude to partake in activities such as trekking, climbing, and sight-seeing. Because many of these trips occur in the setting of family vacations, it is likely that children will accompany their parents. As with adults, children who travel to high altitude are at risk for developing some form of acute altitude illness. This discussion considers the key environmental differences at high altitude and the basic physiologic responses to acute hypoxia and the acute altitude illnesses, including acute mountain sickness (AMS), high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE). The emphasis throughout the chapter will be on risks associated with acute exposure and not issues related to long-term residence at high altitude.

High altitude is generally defined as elevations greater than 2,400 meters (~8,000 feet), although it should be noted that some important physiologic responses to acute hypoxia begin at elevations of about 2,000 meters (~6,000 feet). The defining feature of the environment at these and higher elevations is the decrease in barometric pressure relative to sea level. As a result, the inspired partial pressure of oxygen falls, leading to lower alveolar and arterial oxygen tensions. The fraction of inspired oxygen at 8,000 feet is still about 21%, but the decreased partial pressure makes it comparable to breathing 15% oxygen at sea level. In addition to hypobaric hypoxia, there are other important environmental changes at high altitude that should not be overlooked, including significant increases in ultraviolet exposure as well as decreased humidity and air temperature relative to lower elevations.

There are characteristic cardiopulmonary responses to the lower barometric pressures experienced at high altitude. Much of our understanding of these responses is derived from studies in adults, although more recent studies have included children and reported similar findings. The pattern of response is consistent across individuals, although the magnitude

of the observed responses is highly variable. The decreased arterial partial pressure of oxygen leads to an increase in minute ventilation (referred to as the *hypoxic ventilatory response*) as well as increases in heart rate and cardiac output. Arterial hypoxemia will also trigger an increase in serum erythropoietin concentrations that, over a period of days to weeks, leads to a rise in hemoglobin concentration. Decreased alveolar oxygen tensions cause hypoxic pulmonary vasoconstriction and a subsequent rise in pulmonary vascular resistance, which, in conjunction with the increase in cardiac output, leads to a rise in pulmonary artery pressure. Unlike the other responses described previously, hypoxic pulmonary vasoconstriction is not necessarily a beneficial response and may lead to complications in some individuals.

### ACUTE ALTITUDE ILLNESS

Individuals traveling to altitudes at or above 2,400 meters are at risk for developing 1 of 3 forms of acute altitude illness: AMS, HACE, and HAPE. AMS and HACE represent a spectrum of cerebral disorders, whereas HAPE is a pulmonary disorder. AMS is the most common high-altitude illness in adults and children but is not life threatening, whereas HACE and HAPE are much less common but represent serious and potentially life-threatening conditions.

### EPIDEMIOLOGY AND RISK FACTORS FOR ACUTE ALTITUDE ILLNESS

Between 24% and 61% of adult travelers to high altitude are affected by AMS, and children seem to be at equal risk. The prevalence of HACE in children is unknown, but it rarely occurs. The prevalence of HAPE in children is also not well known. A study of lowland children who traveled to the Tibetan plateau reported a prevalence of HAPE of 0.7% to 1.5%, similar to the reported prevalence in adults (0.2%–6%). However, re-entry HAPE, a form that occurs among high-altitude residents who return to high altitude after travel to lower elevations, may be more common among children than adults.

The primary risk factor for the development of acute altitude illness is an overly rapid ascent to too high an elevation, with the altitude at which someone sleeps being a more important determinant of risk than the highest altitude they may reach during the day. Other risk factors include a history of high-altitude illness, obesity, and overexertion. Good physical condition is not thought to protect against altitude illness. Pre-existing respiratory infections have been associated with an increased risk for HAPE in children. However, it is unclear whether this association is spurious; it may be explained by the increased frequency of viral infections in children compared with adults. Preexisting pulmonary hypertension and Down syndrome may be risk factors for HAPE in children as well.

### CLINICAL SYNDROMES OF ACUTE ALTITUDE ILLNESS

The clinical features of the various forms of acute altitude illness are summarized in Table 213-1. AMS usually occurs within 4 to 10 hours after arrival at

elevations at or above 2,400 meters, although the elevation at which symptoms begin varies among individuals. It is defined by the presence of headache plus 1 or more of the following symptoms: anorexia, nausea, vomiting, insomnia, dizziness, lassitude, or fatigue, in a person who recently arrived at altitude. Diagnosis is based solely on reported symptoms, and there are no characteristic physical examination findings or laboratory abnormalities. When individuals develop evidence of neurologic dysfunction, they are thought to be developing HACE. From a pathophysiologic standpoint, HACE is likely the same disease as AMS but at opposite ends of the spectrum of severity. HACE typically occurs in people with preceding AMS and usually progresses over hours to days. Characteristic signs include ataxia or evidence of altered mental status, including confusion, hallucinations, or drowsiness and, in severe stages, coma. Focal neurologic symptoms may be present but are not as common as signs of global encephalopathy. Abrupt symptom onset, focal neurologic deficits, and meningeal signs are rarely seen in HACE, and their presence should prompt consideration of other diagnoses. When HACE is not recognized and treated promptly, patients can progress to somnolence, coma, and death because of brain herniation.

HAPE is a potentially fatal form of noncardiogenic pulmonary edema typically seen in unacclimatized lowlanders 2 to 4 days after ascent to 2,400 meters or higher. The underlying pathophysiology differs significantly from AMS and HACE, with the primary mechanism being an overly large rise in pulmonary artery pressure on acute exposure to hypoxia. Elevated pulmonary artery pressure leads to an increase in hydrostatic pressures and subsequent leakage of protein and fluid from the vasculature into the interstitial and alveolar spaces. Early symptoms include decreased exercise performance, increasing dyspnea on exertion, and dry cough. As the disease progresses, individuals develop dyspnea with simple activities, such as walking on flat ground, and profound fatigue. Very late findings indicative of severe disease include cyanosis, respiratory distress, and a cough that produces pink or bloody sputum.

### DIAGNOSIS OF HIGH-ALTITUDE ILLNESS

The diagnosis of AMS is based on presenting symptoms and signs and does not require laboratory testing. The Lake Louise Scoring System (LLSS) is a validated scoring system for diagnosing AMS in adults (Box 213-1).

The LLSS asks 5 questions related to headache, gastrointestinal symptoms, fatigue, dizziness, and sleep-related symptoms. It is probably reliable in older children; however, younger children may have difficulty understanding the questions. Among children aged 4 to 10 years, for example, the LLSS underestimated the frequency of AMS symptoms compared with a scoring system using age-appropriate communication. To address this problem, the Children's Lake Louise Score (CLLS) has been developed for children younger than 3 years. Adapted from the LLSS, the CLLS replaces the headache score with a fussiness

**Table 213-1** Clinical Characteristics of Acute Altitude Illness

ALTITUDE ILLNESS	RISK FACTORS	SIGNS AND SYMPTOMS	TREATMENT	PREVENTION
AMS	Individual susceptibility; rate of ascent, absolute elevation gained, final elevation	Headache or unexplained fussiness with nausea, vomiting, anorexia, dizziness, or sleep disturbances in a child who recently arrived at altitude	Mild to moderate illness: rest, analgesics or antiemetics; may consider acetazolamide Severe illness: descent, oxygen, acetazolamide or dexamethasone	Gradual ascent; avoid overexertion; spend a night at an intermediate altitude; consider acetazolamide if slow ascent not possible or in children with a history of AMS. If AMS is mild, waiting 1-2 days for spontaneous recovery before descending is reasonable
HACE	Individual susceptibility; rate of ascent, absolute elevation gained, final elevation	AMS symptoms that progress to confusion, hallucinations, ataxia, altered mental status, or rarely focal neurologic deficits	Immediate descent and oxygen; dexamethasone (should not be used in lieu of descent and oxygen). If descent not feasible and oxygen not available, portable hyperbaric chamber	Gradual ascent; avoid overexertion; acetazolamide may prevent HACE by preventing AMS
HAPE	Individual susceptibility; rate of ascent, absolute elevation gained, final elevation; preexisting pulmonary hypertension or certain congenital anomalies (eg, absent pulmonary artery); preceding respiratory illness	Early: decreased exercise tolerance, progressive dyspnea on exertion, dry cough; tachypnea; hypoxemia Late: dyspnea with simple activities, profound fatigue, productive cough with pink or frothy sputum; cyanosis, severe hypoxemia	Immediate descent and oxygen; nifedipine may be considered in settings without access to medical services and if symptoms are not improving with descent and oxygen. If descent not feasible and oxygen not available, portable hyperbaric chamber	Gradual ascent; avoid overexertion; nifedipine for those with a prior history of HAPE or known predisposing condition

AMS, acute mountain sickness; HACE, high-altitude cerebral edema; HAPE, high-altitude pulmonary edema.

score. A pediatric symptom score (see Box 213-2) is also calculated based on the child's eating, activity, and sleep. The fussiness and pediatric symptom scores are totaled, and AMS is diagnosed if the total CLLS score is 7 or greater. Although there is no gold standard for comparison, the CLLS has been shown to have excellent interobserver agreement between parents in terms of classifying whether or not a child has AMS. Caregivers and physicians must be aware, however, that diagnosing AMS in children is complicated. Children often report AMS symptoms at baseline or with changes in their routine (such as traveling) without gaining elevation. Therefore, rather than relying solely on symptom scores, caregivers and physicians should have a low threshold to diagnose AMS in a child who has recently arrived at altitude. When a child has symptoms such as a change in behavior, fussiness, headache, poor appetite, or sleep disturbances that cannot be explained by an alternative diagnosis, AMS should be considered.

Caregivers should also be aware that difficulty breathing, cough, cyanosis, altered mental status, and other neurologic abnormalities are not part of AMS. The presence of any of these symptoms should prompt consideration of HACE or HAPE. HACE is usually preceded by AMS. Like AMS, HACE is a clinical diagnosis, and formal diagnostic tests, such as a head computed tomography scan, are not necessary. HACE can be fatal if not recognized and treated promptly. If any neurologic signs are present, treatment should be initiated immediately.

The diagnosis of HAPE is also largely clinical and should be considered in the presence of declining exercise performance, increasing dyspnea on exertion and at rest, or profound fatigue and cyanosis. In the field, pulse oximetry may be the only diagnostic tool available; the key finding is decreased oxygen saturation relative to asymptomatic individuals at the same elevation. When interpreting pulse oximetry values, it is important to consider that normal oxygen saturations

**BOX 213-1 Lake Louise Scoring System (LLSS)****HEADACHE**

- 0: No headache
- 1: Mild headache
- 2: Moderate headache
- 3: Severe headache, incapacitating

**GASTROINTESTINAL SYMPTOMS**

- 0: No gastrointestinal symptoms
- 1: Poor appetite or nausea
- 2: Moderate nausea or vomiting
- 3: Severe nausea or vomiting, incapacitating

**FATIGUE AND/OR WEAKNESS**

- 0: Not tired or weak
- 1: Mild fatigue/weakness
- 2: Moderate fatigue/weakness
- 3: Severe fatigue/weakness, incapacitating

**DIZZINESS/LIGHTHEADEDNESS**

- 0: Not dizzy
- 1: Mild dizziness
- 2: Moderate dizziness
- 3: Severe dizziness, incapacitating

**DIFFICULTY SLEEPING**

- 0: Slept as well as usual
- 1: Did not sleep as well as usual
- 2: Woke many times, poor night's sleep
- 3: Unable to sleep

**BOX 213-2 Pediatric Symptom Score**

Rate how well your child has eaten today

- 0: Normal
- 1: Slightly less than normal
- 2: Much less than normal
- 3: Vomiting or not eating

Rate how playful your child is today

- 0: Normal
- 1: Playing slightly less than normal
- 2: Playing much less than normal
- 3: Not playing

Rate ability of your child to sleep today

- 0: Normal
- 1: Slightly less or more than normal
- 2: Much less or more than normal
- 3: Not able to sleep

From Yaron M, Waldman N, Niermeyer S, Nicholas R, Honigman B. Diagnosis of acute mountain sickness in preverbal children. *Arch Pediatr Adolesc Med.* 1998;152:683-687. Copyright © American Medical Association. Reprinted with permission.

will be decreased at altitude and that there is considerable individual variability in observed normal values. Most healthy children have oxygen saturations greater than 90% at 2,500 meters (8,200 feet) and greater than 85% at 3,200 meters (10,500 feet). For individuals who have access to health care facilities, such as a clinic in a ski resort community, pulse oximetry can be supplemented with chest radiography to confirm the presence of parenchymal opacities. The presence of a normal chest radiograph should prompt consideration of an alternate diagnosis.

**MANAGEMENT**

The mainstay of treatment for high-altitude illness is descent to lower elevation. Mild to moderate AMS can be treated conservatively while remaining at the same elevation, although if symptoms do not improve with appropriate measures over several hours to 1 day, descent is indicated. If symptoms are worsening, descent should be considered sooner. Mild AMS may be treated with rest and hydration. Hydration does not treat AMS per se but does eliminate any element of dehydration that can mimic AMS. Symptomatic pharmacologic treatment options include antiemetics or analgesics such as acetaminophen (avoid aspirin in children). Oxygen is also effective. Because the natural history of AMS in children is not well understood, children with moderate to severe AMS should be treated cautiously. Descent and oxygen remain the best options. In addition to symptomatic therapy, children may be started on acetazolamide. Treatment for 48 hours is usually sufficient to relieve symptoms. The most common adverse reactions in adults are paresthesia and taste alterations. Although not studied, these are likely to be the most common reactions in children as well. Acetazolamide is a diuretic; therefore, there is a theoretical risk that children who are continent may have daytime accidents or bedwetting. Acetazolamide contains a sulfonamide, and although the risk for cross-reactivity and anaphylaxis in someone with a sulfa allergy is low, its use in a child with a sulfa allergy is contraindicated. Acetazolamide is contraindicated in pregnancy (class C) but can be used by nursing mothers. Dexamethasone is a suitable alternative treatment for severe AMS in children with a sulfa allergy or in extreme situations in which oxygen is not available and descent is not possible. Table 213-2 lists recommended doses for medications used to treat acute altitude illness in children.

The most important treatment for HACE or HAPE is descent to a lower altitude. If descent is not feasible, the child should be treated with supplemental oxygen or placed in a portable hyperbaric chamber (Gamow bag). These measures should not be delayed. Pharmacologic treatment should only be used in emergent situations in which neither descent nor oxygen is feasible or if the child is not improving with oxygen or descent. Children with HACE can be treated with dexamethasone, although its use for this purpose has not been studied in this patient population. Children who develop HAPE may be started on nifedipine, although this also has not been studied in this age group. The decision to use this therapy should reflect the setting in which HAPE occurs. Its use is reasonable when HAPE develops in a remote area away from



**Table 213-2** Recommended Pediatric Dosages for Medications Used in the Prevention and Treatment of Acute Altitude Illness

MEDICATION	INDICATION	ROUTE	DOSAGE
Acetazolamide	AMS prevention	Oral	1.25 mg/kg/dose every 12 hr (max 125 mg/dose)
	AMS treatment	Oral	2.5 mg/kg/dose every 8 to 12 hr (max 250 mg/dose)
Dexamethasone	AMS, HACE prevention	Oral	Should not be used for prophylaxis
	AMS, HACE treatment	Oral, IV, IM	0.15 mg/kg dose every 6 hr
Nifedipine	HAPE prevention	Oral	0.5 mg/kg/dose every 4 to 8 hr <sup>a</sup>
	HAPE treatment <sup>b</sup>	Oral	0.5 mg/kg/dose every 4 to 8 hr

AMS, acute mountain sickness; HACE, high-altitude cerebral edema; HAPE, high-altitude pulmonary edema; IM, intramuscular; IV, intravenous.

<sup>a</sup>For children weighing less than 20 kg, liquid-filled capsules (10 mg/0.34 mL) can be punctured. For children weighing more than 60 kg, the adult dosing regimen can be used (30 mg of sustained release formulation orally every 12 hours).

<sup>b</sup>Although the use of tadalafil, a phosphodiesterase inhibitor, for treatment of HAPE has been documented in adults, it has never been systematically studied in this regard and should not be used in children for this purpose.

medical resources, but for children who can access health facilities, it may not be necessary if the child is responding appropriately to supplemental oxygen or descent. The treatment dose for nifedipine has been extrapolated from adult data (Table 213-2).

## PLANNING AND PREVENTION

With proper planning and prevention, most children will enjoy high altitude without problems. Proper planning involves considering the child's age, medical history, and availability of medical services while at altitude. Equally important are the rate of ascent, elevation of the destination, and duration of exposure at altitude. Healthy children older than 4 to 6 weeks probably do not need any specific medical evaluations before traveling. However, neonates and those with preexisting illnesses should be evaluated by their physician before traveling to high altitude. Neonates are in transition from fetal to adult circulation. During this transition, they are particularly susceptible to the hypoxia associated with high altitude. Hypoxic pulmonary vasoconstriction may cause right-to-left shunting through a still patent foramen ovale or ductus arteriosus, leading to severe hypoxia. Full transition to adult circulation may take up to 3 months, but infants born at sea level will likely have a stable transition by 4 to 6 weeks. Children with cardiopulmonary disease should be evaluated carefully. At high altitude, hypoxemia may worsen in children with cystic fibrosis or other chronic lung diseases. Hypoxemia and shunting may also worsen in children with congenital heart disease. Children with Down syndrome or congenital heart disease associated with pulmonary hypertension may be at higher risk for HAPE. Depending on the severity of these diseases, travel to high altitude may not be advised. The risks and benefits of traveling should be carefully considered for any child who uses supplemental oxygen at baseline or had recent need for this therapy. Children currently on oxygen therapy may need to increase flow rates while at altitude. These children should be evaluated before traveling and may benefit from a high-altitude simulation test to determine how much additional oxygen may be needed.

Caregivers should consider the availability of medical services and rescue support at their intended destination and should strongly consider purchasing travel insurance, particularly when traveling with children with underlying medical problems. The risks of travel to destinations with easy access to medical care are much different than of travel to remote locations. Decisions about which high-altitude locations are safe and appropriate for children should be made on a case-by-case basis. However, a higher degree of caution is necessary with planned travel to remote locations without easy access to medical services or rescue, and these locations may not be appropriate for all children.

A gradual ascent, allowing the body to acclimatize to high altitude, is the single most important factor in diminishing the risk for AMS, HACE, and HAPE. In many cases, travel plans can be moderated to help minimize the risk. For example, families traveling from sea level to a Colorado ski resort could choose to spend the first night in Denver (~1,600 meters) before ascending to higher elevations for the rest of the vacation. At higher elevations (>3,000 meters), it is recommended that individuals not increase their sleeping elevation by more than 500 meters per night. Also, every 3 to 4 days, or with any overly large increase in the sleeping elevation, individuals should sleep at the same elevation for a second night. Although this approach has never been rigorously tested in controlled studies, it is generally accepted.

If a rapid ascent is unavoidable (eg, flying into Cuzco, Peru [~3,400 meters] on a trip to Machu Picchu), or if a child has a history of altitude illness, pharmacologic prophylaxis should be considered. Acetazolamide is the standard prophylactic agent for AMS. It should be started 24 hours before ascent. Use can be discontinued on descent to a lower altitude or, for children who will remain at altitude, 48 hours after arrival to the target altitude. Prophylaxis for HAPE should only be considered in children with a history of HAPE or a condition known to predispose to this disorder (eg, Down syndrome with pulmonary hypertension). Although its use has not been studied in children, nifedipine is the recommended agent for prophylaxis of HAPE.

## ADDITIONAL RISKS OF HIGH ALTITUDE

Ultraviolet light exposure is increased at high altitude and increases the risk for sunburns and ultraviolet keratitis. This risk is present even in cloudy conditions and is particularly high when individuals are traveling on snow or water because both increase the amount of reflected light. Caregivers should apply sunscreen frequently and liberally (sun protection factor  $\geq 30$ ) and ensure children have adequate head, eye, and lip protection at all times. Long sleeves, hats, and sunglasses should also be used. Because of lower humidity and air temperature, the risks for dehydration, hypothermia, and frostbite are also increased at altitude. Children are at higher risk than adults for these complications because they have a higher ratio of body surface area to body mass, resulting in proportionally higher fluid and heat losses. Children should be encouraged to drink plenty of fluids. It may be helpful to bring some favorite foods and drinks to ensure adequate food and liquid intake because altitude may affect the child's appetite and travel can disrupt the usual feeding schedule. Furthermore, in some locations the local diet may not be familiar to the child. To prevent cold exposure, adequate clothing is needed. Children who are carried may need extra layers because they are not generating as much heat as their caregivers who are exerting themselves. Layered clothing is recommended to allow for changes in weather and comfort.

## ONGOING CARE

Because a prior history of high-altitude illness is a risk factor for recurrence, any child who experiences high-altitude illness should be evaluated by a physician. A history of mild AMS may be preventable in the future with counseling of the importance of a slow ascent. If this is not possible, prophylactic treatment may be indicated before the next trip. A history of life-threatening illnesses such as HAPE or HACE should prompt a discussion about the risks and benefits of returning to high altitude. Given the high prevalence of undiagnosed chronic pulmonary hypertension and other cardiopulmonary abnormalities in children diagnosed with HAPE, these children should be screened for possible pulmonary hypertension or occult congenital heart defects. Children with a history of HAPE should be advised to not return to altitude if they have a current or recent viral illness.

## SUMMARY

Access to high altitude has become easier than ever, and more children are traveling to high altitude. Most children can travel to altitude safely, and known risks can be minimized with appropriate pretravel planning. Caregivers should be counseled regarding the recognition, prevention, and treatment of acute altitude illness as well as other risks not related to hypobaric hypoxia, including sunburn, dehydration, and hypothermia. Emphasis should be placed on the role of gradual ascent in preventing these illnesses and the central role descent plays in the treatment of severe disease.

## SUGGESTED READINGS

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## Chapter 214

# AMBLYOPIA AND STRABISMUS

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## DEFINITIONS

*Amblyopia* is decreased visual acuity in the absence of an ocular structural disorder of the visual pathway.

*Strabismus*, an important cause of amblyopia, is a misalignment of the eyes that may be manifest at distance or near, constant or intermittent, and may be present in any field of gaze.

Many times, parents will note strabismus and bring it to the attention of the pediatrician. Amblyopia, however, is more commonly discovered via screening tests such as visual acuity testing or red reflex testing in the preliterate child. Both conditions warrant referral to an ophthalmologist for further care.

*Orthophoria* is normal eye alignment in which both eyes are simultaneously directed at an object of regard (Figure 214-1).

*Heterophoria* is an ocular misalignment that is latent and only occurs with stress, fatigue, and other conditions that may interrupt fusion of an image. Large heterophorias can cause bothersome symptoms such as intermittent diplopia and eye strain (asthenopia).

*Heterotropia* is a manifest misalignment of the eyes, present at all times. When the visual axis of the deviated eye is directed inward (toward the nose), *esotropia* is present (Figure 214-2). *Exotropia* is present when the visual axis of the deviated eye is divergent or directed outward (Figure 214-3). Likewise, *hypertropia* describes an eye deviated upward and *hypotropia* an eye deviated downward. The latent (not present at all times) counterparts of these deviations are described as *esophoria*, *exophoria*, *hyperphoria*, and *hypophoria*.

Strabismus is *comitant* when the deviation is the same in any direction of gaze and *incomitant* when it varies with direction of gaze. *Monocular* strabismus describes a preference to fixate consistently with the same eye, whereas *alternating* strabismus implies no ocular preference with fixation shifting from one eye to the other. Any strabismus present by age 6 months



**Figure 214-1** Orthophoria: Note the centered corneal light reflexes.



**Figure 214-2** Esotropia: Note the laterally misplaced corneal light reflexes.



**Figure 214-3** Exotropia: Note the medially displaced corneal light.

is defined as *infantile* and all other deviations are *acquired*. Finally, a deviation that is the same whether fixation is at distance or near is said to have a normal accommodative convergence (AC) to accommodation (A) ratio (AC/A). A *high* AC/A implies that convergence with accommodation is excessive so that an esotropia is greater at near fixation than distant fixation, whereas a *low* AC/A ratio implies that convergence with accommodation is deficient.

## EPIDEMIOLOGY

Amblyopia has a frequency ranging from 1.3% to 3% in preschool and school age children. The prevalence in the general population is between 2% and 2.5%.

Strabismus, a common cause of amblyopia, affects between 2% to 5% of preschool children. Esotropia is the most common type of ocular deviation in the



**Figure 214-4** Pseudoesotropia: Esotropic appearance because of epicanthal folds, which obscure the medial sclera of the right eye. Note the corneal light reflexes are centered, indicating orthophoria.

pediatric population, representing more than 50% of cases.

## ETIOLOGY

Amblyopia develops early in childhood when there is aberrant development of the visual system. In a series of landmark studies, Hubel and Wiesel revealed the role of visual stimulation in shaping the architecture of the cortical visual pathway. By depriving kittens of the use of one eye during the “critical period” of visual development, they showed that input to the visual cortex became dominated by signals from the functioning eye. Normal binocular vision develops only when clear and focused images project onto corresponding areas of both retinas. If the image from one eye is distorted or misaligned during the critical period of cortical pathway development, input from that eye is decreased and amblyopia is the consequence. Although amblyopia more commonly occurs in a unilateral fashion, it can be bilateral. The different causes of amblyopia will be discussed under Classification. Strabismus is one of the most common causes of amblyopia and may be congenital or accommodative, or occur as a feature of several syndromes.

## DIAGNOSIS

### Differential Diagnosis

In the condition known as *pseudostrabismus*, the visual axes are aligned accurately, but there is a false appearance of strabismus because of prominent epicanthal folds; a flat, broad nasal bridge, or a narrow interpupillary distance. This “optical illusion” occurs because one or both eyes seem to turn inward when a smaller amount of white sclera is observed nasally than would be expected. Pseudoesotropia (Figure 214-4) is a very common condition prompting referral to a pediatric ophthalmologist.

### Diagnostic Approach

#### Strabismus

Pseudostrabismus is differentiated from true strabismus by observation of the corneal light reflex, which is symmetrical in both eyes when the eyes are aligned properly. In addition, the cover/uncover test is used to determine whether a true strabismus is present: on cover/uncover testing, a refixation movement indicates a true strabismus.



### Amblyopia

Amblyopia can be detected by identifying a difference in visual acuity between the two eyes, generally greater than 2 lines on the eye chart. The “crowding phenomenon” is a characteristic of amblyopia wherein the visual acuity measurement is better if tested with single, isolated symbols instead of a group of symbols. This improved visual acuity with single-symbol testing can be useful in distinguishing amblyopia from loss of vision secondary to other causes because children with nonamblyopic vision loss have equally poor vision when tested with one versus a group of symbols.

Amblyopia can be detected in children unable to perform subjective visual acuity testing (generally <3 years of age) by evaluating their fixation behavior with occlusion. A child with an amblyopic eye will object to occlusion of the nonamblyopic eye. This technique is also useful in children with strabismus. A strabismic child who spontaneously alternates fixation is unlikely to have amblyopia in either eye, whereas a child who consistently turns one eye is likely to have amblyopia in the deviated eye. If occlusion of the “straight” eye results in wandering fixation or lack of visual interest, suspect amblyopia.

Recently, instrument-based visual screening was developed to screen children younger than 5 years of age for risk factors of amblyopia. Photoscreeners, autorefractors, and other instruments are used to detect the presence and magnitude of ocular conditions that can lead to amblyopia. Instrument-based visual screening is quick and requires minimal cooperation from the child. However, it must be administered and interpreted by appropriately trained individuals and does not replace vision acuity testing in the literate child.

### Classification

#### Amblyopia

Amblyopia is classified according to the underlying ophthalmic condition that is causing abnormal binocular interaction or interruption of a clear image projected onto the retina. Conditions that result in amblyopia include strabismus, significant refractive errors, anisometropia (difference in the refractive error between the two eyes), and visual deprivation from occlusion or obscuration of the visual axis.

*Strabismic amblyopia* results from improper alignment of the eyes, causing a disruption of the binocular fixation required for normal visual development. If the child strongly favors the aligned eye, amblyopia will likely develop in the deviated eye.

*Refractive amblyopia* can occur in eyes with very large or sometimes even small degrees of hyperopia (farsightedness), myopia (nearsightedness), or astigmatism (irregular corneal curvature). Children at greatest risk of developing refractive amblyopia have refractive errors greater than 4.5 diopters (measure of optical lens power) of hyperopia or 2.5 diopters of astigmatism. Conditions such as ptosis (lid drooping) and orbital tumors can mechanically change the shape of the cornea and thereby induce an astigmatism, leading to refractive amblyopia.

*Anisometropic amblyopia* is a subcategory of refractive amblyopia. Anisometropia is unequal refractive error between the two eyes. If the difference in refractive error is more than 1.5 diopters of hyperopia or astigmatism, or 3.0 diopters of myopia, amblyopia is likely to develop in the eye with the greater refractive error.

*Visual deprivation amblyopia* results from any abnormality in the visual axis preventing the formation of a clear, focused image on the retina during the period of visual development. Corneal opacities, congenital cataracts, and vitreous hemorrhage can blur the visual axis and induce amblyopia.

### Strabismus

*Infantile esotropia* (formerly called congenital esotropia) is by definition an esotropia present by 6 months of age. It is not unusual for variabilities in alignment to occur during the first few weeks of life, but they usually clear by 2 or 3 months of age. In children with infantile esotropia, the misalignment continues after 6 months of age, is often readily apparent, and measures greater than 30 prism diopters (measure of deviation). Affected children usually alternate fixation and have good vision in both eyes. However, a preference to fixate with one eye may indicate poor vision in the nonfixating eye, which must be treated to prevent amblyopia. These children often have a refractive error that is in the normal range for young children.

- *Cross fixation* is often present and indicates that the child is looking at the left visual field with the right eye and the right visual field with the left eye, giving the appearance of a bilateral abduction defect (such as occurs with cranial nerve VI) in which neither eye seems able to turn outward.
- *Inferior oblique overaction*, seen in 72% of children with infantile esotropia, is an upswing of the eye when it is in the adducted position.
- *Dissociated vertical deviation*, characterized by elevation and excyclotorsion (outward, rotational movement) of the nonfixating eye, is present in 46% to 90% of children with infantile esotropia.

*Accommodative esotropia* occurs when a child's large accommodative reserve (focusing power) is linked to an abnormally large convergence (inward eye movement), causing an esotropia when focusing. Children with large hyperopic refractive errors are at particular risk. Onset is, on average, at 2.5 years but can range from 6 months to 7 years. The deviation, which may begin intermittently, can eventually become constant, independent of fixation distance and spectacle correction. If the child develops a fixation preference, amblyopia may develop.

*Constant exotropia*, a constantly present out-turning of the eye, can be congenital or can result from decompensation of an intermittent exotropia. It can also occur after significant loss of vision in one eye (usually after 5 years of age), or can occur from overcorrection following muscle surgery for esotropia.

*Intermittent exotropia*, the most common type of divergent strabismus in children, is characterized by an outward drifting of one eye, usually at distance fixation. Visual acuity is usually good and binocular vision maintained because the eyes initially can be



kept straight most of the time. Intermittent exotropia tends to occur between infancy and 4 years. The consensus among pediatric ophthalmologists is that the frequency and magnitude of deviation with intermittent exotropia will not improve with time, and affected children are at risk for decompensating into constant exotropia. Children with this condition should be evaluated early by an ophthalmologist to monitor progression.

*Paralytic strabismus* occurs when paralysis or paresis of an extraocular muscle causes a motor imbalance, resulting in a deviation that varies with the direction of gaze and fixation with the involved or uninvolved eye (noncomitant deviation). The diagnosis is suggested by detecting deficient eye movement in the field of action of the paretic muscle. Newly acquired double vision and an increase in deviation with fixation of the paretic eye can also suggest paralytic strabismus.

- *Third cranial nerve palsy* is more commonly congenital than acquired. When congenital, the cause is generally either a developmental anomaly or birth trauma. Acquired third cranial nerve palsy requires immediate evaluation because it may result from a brain aneurysm or tumor. Blunt trauma, infection, and ophthalmic migraine can also cause an acquired third cranial nerve palsy. It is prudent to perform imaging of the basal structures, including the orbit on a child with a nontraumatic, acquired third nerve palsy. Examination findings consistent with the diagnosis are exotropia, hypotropia, and ptosis of the upper lid. Pupillary dilation can also be present if the parasympathetic fibers of the third nerve are affected. The child will have difficulty with adduction (inward eye movement), elevation, and depression of the affected eye. Aberrant regeneration of the nerve fibers can result in adduction of the eye on attempted upgaze or downgaze and retraction of the upper lid on downgaze (pseudo-Graefe sign).
- *Fourth cranial nerve palsy* is either congenital or, if acquired, secondary to head trauma. Palsy of the fourth nerve results in weakness of the superior oblique muscle, which causes the child to tilt his head to the opposite shoulder in an attempt to compensate for the vertical deviation of the eye. Correction of this abnormal head posture requires addressing the ocular misalignment.
- *Sixth cranial nerve palsy*, which results in weakness of the lateral rectus muscle, is rare in its congenital form but can occur transiently in newborns, with resolution by 6 weeks of age. It is important to evaluate affected children for congenital esotropia and for disorders resembling sixth nerve palsy such as Duane retraction syndrome and Moebius syndrome. Acquired forms of this palsy result most commonly from trauma, and also from meningitis, hydrocephalus, and a variety of brain tumors, in particular medulloblastomas, brainstem gliomas, and posterior fossa astrocytomas. Rarely, sixth nerve palsy can follow a nonspecific febrile illness or upper respiratory infection. The palsy generally starts 1 to 3 weeks after the illness and begins to improve within 3 to 4 weeks, with

complete resolution by 10 weeks. Gradenigo syndrome is a condition in which the sixth nerve is pinched against the petrosphenoid ligament (Gruber ligament) as the nerve passes between the ligament and the dura (Dorello canal). This can occur secondary to otitis media, mastoiditis associated with petrositis and edema of the dura, or venous sinus thrombosis. Antibiotic treatment is effective in limiting the duration of palsy to 3 to 6 weeks. Whatever the cause, abduction deficits and large esotropias in primary gaze are seen with sixth nerve palsy. Binocular vision can be maintained with lateral gaze away from the palsied eye, which results in a compensatory head turn toward the palsied eye. The greatest eso-deviation is observed in the field of action of the paretic lateral rectus muscle.

### Strabismus Syndromes

*Duane retraction syndrome* is characterized by the inability to abduct or adduct the affected eye(s) partially or completely. This results in restricted horizontal movement. In addition, when the eye attempts to adduct, the globe retracts and the palpebral fissure narrows. The oculomotor disturbance causing this syndrome seems to be the result of paradoxical innervation of the lateral rectus muscle. As a result, lateral gaze is poor from improper lateral rectus contraction, and adduction is also poor because of the dual contraction of the medial and lateral rectus muscles. The combined stimulation of the medial and lateral recti also acts to pull the globe into the orbit, causing globe retraction and narrowing of the palpebral fissure. This syndrome occurs twice as often in the left eye, and girls are more likely to be affected than boys by a 3:2 ratio. Affected children often have normally aligned eyes in the primary position throughout childhood, but some develop an increasing eso-deviation, which may lead to a compensatory head turn. If the esotropia is significant with a compensatory head turn, surgery is indicated.

*Brown syndrome* is typically a unilateral condition in which the ability to elevate the eye is limited in the up and in position. Elevation is usually normal when the eye is abducted. Often there is no abnormality in primary position, but sometimes the involved eye is lower. If this occurs, fusion can only occur in lateral gaze and, as a result, a compensatory face turn is assumed. The cause of Brown syndrome is a tight, relatively inelastic superior oblique muscle. This can be evaluated using a forced duction test: the child is examined under anesthesia and forceps are used to grasp the conjunctiva and underlying sclera. The eye is then mechanically moved to detect any movement restriction. In affected children, the test reveals restriction of elevation in the adducted eye. A superior oblique weakening procedure can be performed if a vertical deviation exists.

*Moebius syndrome* consists of lateral gaze paralysis, usually esotropia, and varying degrees of facial diplegia resulting from underdevelopment of the sixth and seventh cranial nerves. Although vertical rotations are often full, total ophthalmoplegia may be present. A wide variety of musculoskeletal anomalies

may occur, including pectoral muscle defects, brachial malformations, and clubfoot. Palsy of the tongue, a common associated defect, is often manifest during infancy by a poor suck reflex.

The eye findings in this condition are thought to arise from fibrotic and thickened extraocular muscles. Surgery is reserved for significant esotropia, but the range of horizontal eye movements does not tend to normalize.

*Double elevator palsy (monocular elevation deficit)* is a monocular deficit of elevation that occurs both in adduction and abduction, either from a paresis of the superior rectus and the inferior oblique muscles, both elevators of the eye, or possibly from fibrosis of the inferior rectus muscle. As a result, hypotropia is seen in the paretic eye and ipsilateral upper lid pseudoptosis may occur when the child fixates with the nonparetic eye. Once fixation is switched to the paretic eye, the nonparetic eye becomes hypertropic and the ptosis disappears. Surgery is helpful only if a vertical deviation in primary gaze exists; the surgery is performed with the intention of improving alignment.

*Cyclic strabismus* is a rare entity characterized by alternating 24-hour periods of misalignment and orthophoria, usually acquired in children 3 to 4 years of age and typically manifesting as an esotropia. Treatment is with surgery to correct the full deviation. Results are generally satisfactory and do not produce exotropia on the nonstrabismic day.

## MANAGEMENT

### Treatment Approach

In amblyopia, treatment is initiated to achieve equal and normal vision between both eyes. The likelihood of achieving this goal is greater if treatment begins at an early age.

Treatment is aimed at aligning eyes to help promote binocularity and prevent amblyopia. Surgery can also be performed to correct misaligned eyes that are socially unacceptable or cause an unwanted head posture.

### Specific Treatments

#### Amblyopia

In 40% of children with amblyopia, optical correction alone can adequately treat the amblyopia when there is a significant refractive error. However, the effect is not immediate; it requires prolonged and consistent wear of appropriate spectacle correction. If optical correction does not fully treat the amblyopia, penalization therapy may be needed in addition to glasses.

Penalization therapy is used in the treatment of amblyopia caused by nonrefractive conditions and in refractive conditions where glasses alone do not resolve the amblyopia. Penalization therapies usually involve occlusion or optical blurring of the nonamblyopic eye. Occlusion therapies include opaque adhesive patches that cover the eye completely (Figure 214-5). When used with spectacles, the adhesive patch should still be placed directly on the eye (Figure 214-6). Slip on, press on, or clip on occluders can also be used in children with glasses (Figure 214-6). Initial therapy involves



**Figure 214-5** Occlusive patch to treat amblyopia right eye.

several awake hours of occlusion daily. Follow-up appointments are made at routine intervals to monitor the success of treatment, help the parents work out patching difficulties, and assess for reverse amblyopia of the patched eye.

Children, especially those with very profound amblyopia, may not tolerate occlusion. If so, it is often helpful to institute patching progressively over the first week of treatment. Rarely, and only if necessary, mittens taped to hands, or devices that prohibit elbow flexion, may be used for short periods of time to prevent the child from removing the patch, allowing occlusion therapy the chance to be effective.

Optical blurring is another treatment modality for amblyopia. A cycloplegic eyedrop or ophthalmic ointment, usually atropine, is used to blur the sound eye at close range, causing fixation preference to switch to the amblyopic eye. Treatment schedules include daily use of atropine or, more recently, weekend use only, because the cycloplegic effects of atropine persist for several days after treatment. This technique is not effective when amblyopia is severe (visual acuity is poorer than 20/100 in the amblyopic eye) because atropine does not create enough reduction in visual acuity to switch the fixation preference.

Successful treatment depends on maintaining improved visual acuity until the age at which the child



**Figure 214-6** Occlusive patch and glasses to treat anisometropic amblyopia.

reaches visual maturity, generally considered to be 9 years of age. Recent studies demonstrated improvement in vision with amblyopia treatment in older children, indicating that the critical period until visual maturity may be prolonged in some individuals.

If visual acuity decreases after the cessation of penalization, ongoing therapy may be necessary to maintain improved visual acuity in the amblyopic eye. Maintenance therapy is instituted using part-time patching or a reduced cycloplegia schedule. Therapy is reduced gradually to the lowest level needed to maintain visual acuity. Routine scheduled follow-up is important in amblyopia treatment.

### Strabismus

Pseudostrabismus does not require treatment but should prompt a re-evaluation if there is any change in the alignment.

Treatment of infantile esotropia begins with correcting hyperopia with spectacles, if necessary, and penalization therapy if one eye has poor vision. The deviations are measured over serial examinations. If the misalignment persists despite treatment, and if the measurements are consistent, surgery is performed to correct the alignment.

Accommodative esotropia is managed by fully correcting the hyperopic refractive error, which reduces the need for accommodation and helps reduce the excessive convergence. If residual convergence occurs

at near fixation, bifocals can sometimes be used to reduce this residual accommodation. In the past, anticholinesterase miotics were used with or in place of glasses, because they constrict the pupil, induce ciliary spasm, and reduce the accommodative effort. These drugs can have significant side effects such as iris cysts, lens changes, and reduced plasma and red-cell cholinesterase, which limit their utility. They are used very rarely in the treatment of residual convergence. Muscle surgery is reserved for children who have significant residual deviation uncorrected by glasses. Although the prescription for glasses may change after surgery, glasses usually remain a necessary part of accommodative esotropia treatment.

Intermittent exotropia is managed with observation if the deviation is small and infrequent. Alternate patching or over-minus glasses that increase convergence by encouraging accommodation are also used. Large deviations or deviations that are increasing in frequency and threatening binocular function are treated with muscle surgery.

Constant exotropia is managed with amblyopia therapy if poor vision is present. Surgery is reserved for cases that cause psychosocial distress, with stable deviation measurements.

Third nerve palsy is treated with occlusion therapy if amblyopia is present. Poor vision may affect the contralateral eye if the patient prefers fixation with the palsied eye. After visual acuity is improved, surgery is considered to maximize range of motion and align the eyes in the primary position. Ptosis correction can be achieved surgically with a frontalis sling.

Fourth nerve palsy is managed with muscle surgery to improve alignment and eliminate abnormal head posture.

Sixth nerve palsy, when acquired, and in a child without a history of trauma or recent febrile illness, should be evaluated carefully for neurologic cause. If secondary to a febrile illness or trauma, the condition tends to resolve or at least improve considerably over time. Temporary improvement of alignment can be achieved with botulinum injections into the opposing medial rectus muscle. Surgery is indicated if a large deviation in primary position and a face turn are present after 6 months.

## ONGOING CARE

### Follow-up

Children being treated for amblyopia with penalization therapy need to be re-examined at routine intervals. The exact schedule is determined by the child's age and the manner of therapy. Younger children are reexamined more frequently than older children because of the increased plasticity of the younger cortical visual pathways. Even after the amblyopia is successfully treated, children need to be monitored for recurrence.

Children with strabismus also need to be followed for ongoing problems related to their strabismus. Visual acuity, binocular function, and refractive errors need to be addressed throughout childhood.



### Complications

Amblyopia complications are related to the loss of vision in one or both eyes. Complications of amblyopia therapy include reverse amblyopia. Penalizing the sound eye can result in amblyopia of that eye. Close follow-up by the ophthalmologist is required to detect this condition and treat it. Compliance to therapy can be problematic; parents need to be supported in their efforts to patch or atropinize their children. Contact dermatitis can develop from the adhesive material of an eye patch. Atropine is an anticholinergic drug and can cause high fevers and hyperactivity if absorbed systemically. These side effects can be mitigated by using pressure to occlude the punctum during installation in an effort to decrease absorption systemically through the nasolacrimal system. A recurrence of amblyopia can occur after the cessation of therapy. This usually occurs in the first 3 months after treatment concludes. Therefore, regularly scheduled follow-up appointments are important after penalization therapy ceases.

Complications of strabismus include amblyopia, decreased binocular function as manifest by decreased depth perception, or diplopia. Older children may develop psychosocial distress from their strabismic appearance. Complications of treatment include recurrent or residual strabismus and consecutive strabismus (misalignment in the opposite direction after strabismus surgery).

### Prognosis

The prognosis for amblyopia varies with the child's age and the type and depth of amblyopia. Younger children tend to respond more positively to treatment. Dense amblyopia is more difficult to treat successfully. The early treatment of amblyopia carries a more favorable prognosis.

The prognosis for strabismus depends on the type and duration of strabismus. In general, the earlier treatment is initiated, the better the prognosis.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Eye Health Information About Babies, Children, and Teenagers* (Web page), American Academy of Ophthalmology ([www.geteyesmart.org/eyesmart/living/babies-children-teenagers-eye-health/index.cfm](http://www.geteyesmart.org/eyesmart/living/babies-children-teenagers-eye-health/index.cfm))
- *Strabismus* (fact sheet), KidsHealth From Nemours ([kidshealth.org/parent/general/eyes/strabismus.html](http://kidshealth.org/parent/general/eyes/strabismus.html))
- *Strabismus (Crossed Eyes)* (fact sheet), American Optometric Association ([www.aoa.org/patients-and-public/eye-and-vision-problems/glossary-of-eye-and-vision-conditions/strabismus](http://www.aoa.org/patients-and-public/eye-and-vision-problems/glossary-of-eye-and-vision-conditions/strabismus))
- *Your Eyes* (fact sheet), KidsHealth From Nemours ([kidshealth.org/kid/htbw/eyes.html](http://kidshealth.org/kid/htbw/eyes.html))

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## Chapter 215

## ANIMAL AND HUMAN BITES

Neil E. Herendeen, MD; Peter Szilagyi, MD, MPH

Estimates indicate that each year more than 4.5 million people across the United States are bitten by animals. Dog bites account for more than 90% of these injuries, and cat bites account for most of the remainder, with human bites accounting for less than 2%. Although wild animal bites are rare, they are potentially more serious, given the risk of rabies and other infections. One-half of all animal bites are trivial and require no medical treatment; only 10% are severe enough to require suturing, and 2.5% result in hospitalization. Bite wounds account for an estimated 1% of pediatric emergency department visits. Children experience the greatest number of animal bites (the peak age group is 5–14 years), with 50% of all school-aged children reporting an animal bite at some point in their lives. One-half of toddlers attending child care centers will experience 1 or more bites from a peer, but only 2% of those bites break the skin. With dog bites, adults are bitten on an extremity; children, however, are bitten primarily on the head or neck 75% of the time. Boys are twice as likely to be bitten by a dog, whereas girls receive twice as many cat bites. Not surprisingly, most of the animals live in the victim's neighborhood (75%) or home (15%); in most instances, the bites are provoked by humans.

The major morbidity from animal bites results from direct trauma and infection. Although dog bites are more likely to cause lacerations or avulsions, these open wounds can be debrided and cleaned to prevent infection. However, puncture wounds, which usually



**Table 215-1** Risk Factors for Infection in Animal Bites

RISK FACTOR	INFECTION RATES
Location of bite	Hand (18%–36%) > arm or leg (12%–16%) > face (5%–11%)
Type of wound	Puncture with laceration (17%–26%) > laceration alone (9%–12%)
Interval between bite and medical care	If >24 hr, risk of infection increases
Type of animal	Cat bites (40%–50%) Dog bites (10%–30%) Human bites (13%–40%)

do not require suturing, can result in deep-tissue infections.

As shown in Table 215-1, the risk of infection varies according to several factors. Hand wounds are most likely to become infected, partly because of the type of wound (most frequently a puncture wound), the relatively poor vascular supply, and the vulnerability of the closed spaces of the hand. If more than 24 hours elapses before medical attention is sought, then the risk of infection is greatly increased. Cat and human bites pose a greater risk of infection than dog bites, partly because these bites more often cause puncture wounds, whereas dog bites frequently cause open lacerations.

Most bacteria associated with bite wounds are common organisms that reside in the animal's oral cavity. Bacteria on the victim's skin may also contribute to infection. Most infections involve several pathogens, often both aerobes and anaerobes. *Pasteurella multocida*, a Gram-negative, facultative anaerobe found in the mouths of most dogs and cats, is highly associated with cat bite infections (up to 80%) and to a lesser extent with dog bite infections (up to 50%). Although the exact prevalence of other pathogenic bacteria isolated from infected animal bites varies, staphylococci, streptococci, *Moraxella*, and *Neisseria* are common.

Another group of Gram-negative bacteria, capnocytophaga, has frequently been isolated from dog bite wounds. Interestingly, human bites are rarely infected by *P. multocida* but are often associated with Gram-positive organisms, Gram-negative anaerobes, or *Eikenella corrodens*, a genus almost unique to human bites that in rare cases is found in cat bites. Human bites have the potential to transmit human immunodeficiency virus and the hepatitis B virus and should be evaluated in persons who are bitten by those at high risk for infection.

## EVALUATION

### History

Important points to elicit while taking the history of the wound include the length of time since injury, the type of animal (including domestic or wild), whether the attack was provoked or unprovoked, the animal's

present location, the child's immunization status and health, and prior wound management.

### Physical Examination

The physical examination entails a thorough musculoskeletal and neurologic examination to determine whether underlying structures were damaged and a thorough inspection of the wound for signs of infection. Special attention must be given to bites on the hand because, particularly in deep puncture wounds, superficial signs of infection (redness, swelling, purulent drainage) may be absent. Finally, the physician should be aware that deep infections of tendons or bones and systemic infections can occur if animal bites go untreated.

### Laboratory Evaluation

Gram stain of a wound specimen is not useful, because findings do not correlate with culture results. Cultures of clinically infected animal bite wounds are reported to have no growth in as many as one-third of cases; conversely, cultures of clinically noninfected bite wounds grow a wide spectrum of oral flora bacteria in the same proportion of cases. Moreover, such cultures do not predict the likelihood of subsequent infection, nor do results correlate with culture findings when clinical infection becomes apparent. However, cultures of clinically infected wounds may help ensure that the causative bacteria are sensitive to the antibiotic used. Radiologic studies of deep puncture wounds may be necessary to determine whether the periosteum has been penetrated. These studies include those of the calvaria of small children who experience bites to the head.

## MANAGEMENT

### Wound Care

The initial step in treating animal bites is meticulous wound care. This process involves gently cleaning the wound with soap and water and vigorously irrigating with saline solution. Saline irrigation of the wound with a syringe and a 19-gauge needle generates increased pressure on the tissues that facilitates cleansing of the wound and reduces the risk of infection. Devitalized tissue should be debrided. Puncture wounds should be cleaned, but irrigation is ineffective and may result in further damage to underlying structures. Elevation and immobilization are important for significant extremity injuries. The child's immunization status should be assessed and tetanus prophylaxis provided if indicated.

Primary closure of lacerations caused by animal (or human) bites is controversial. Wounds that are clearly infected should not be closed. The consensus is that most noninfected lacerations can be sutured, after meticulous cleansing and irrigation, for cosmetic purposes or for hemostasis, without increasing the risk of infection. Hand wounds may be an exception because of the great likelihood of infection and the risk of serious complications from deep, closed-space infections; in these cases, suturing is suggested only for large wounds.

The use of prophylactic antibiotics in noninfected animal bite wounds is controversial. Prophylactic antibiotic therapy reduces the risk of infection after human bites or animal bites of the hand; however, no evidence has been found that it is effective for other types of cat or dog bites. If infected, bite wounds brought to medical attention after 24 hours should then be treated with antibiotics. The choice of antibiotics depends on culture results or, if cultures are not available, on the likely pathogens. Although penicillin is active against *P multocida* and many oral flora, the addition of a penicillinase-resistant antibiotic provides more effective coverage. Amoxicillin/clavulanic acid is an excellent choice for the empirical treatment of bites from all animals. Patients with infected hand bites, those with moderate to severe infections at other bite sites, and those who present with systemic symptoms such as high fever should be treated with intravenous antibiotics (ampicillin-sulbactam). Penicillin-allergic children may be treated with an extended-spectrum cephalosporin or trimethoprim-sulfamethoxazole plus clindamycin. Doxycycline with activity against *P multocida* and MRSA provides another alternative in persons 8 years and older.

Infections

The time of the infection’s onset may be a clue to the cause of infection. Cellulitis from *P multocida* generally develops rapidly, within hours of the animal bite, whereas systemic signs (fever, lymphangitis) are usually absent. A cellulitis that develops gradually, over days, is more likely the result of Gram-positive cocci or other pathogenic bacteria.

The physician should remember that cat-scratch disease is a relatively common complication of cat bites and, less commonly, of bites by other animals. This disease often begins with the development of a red, painless papule at the site of a recent scratch or bite. Within weeks, a tender, enlarged, regional lymph node appears, usually associated with fever, malaise, and other systemic symptoms. This self-limited illness, which is caused by *Bartonella henselae*, can be diagnosed clinically or confirmed by serologic testing. Antibiotics offer minimal clinical benefit, and because the disease is self-limited, their use seldom is indicated. Large, tender, fluctuant lymph nodes may require aspiration or incision and drainage.

Wild Animal Bites

Animal bites from nondomestic animals require special attention. Although most primary care physicians will never treat a child who has rabies, they will evaluate children who may have been exposed to it. With the increasing spread of rabies among nondomestic animals, the number of people exposed to rabies and requiring vaccination is increasing dramatically. A full postexposure vaccination series can cost \$2,000 or more and requires 4 visits to the physician in a single month. Knowing when and whom to treat requires an understanding of rabies transmission and its epidemiologic mechanism. Rabies is an RNA virus present in saliva and transmitted by bites or by licking of the mucosa or open wounds. In the United States, in all cases of rabies resulting from a dog or cat bite, the infected animal has been noted to become ill during the standard 10-day confinement and observation period. Thus, location, confinement, and observation of the animal are important.

In cases involving wild animal bites, consultation with the local health department is helpful in determining the risk of rabies in a specific animal for a particular geographic region. In general, bats, skunks, foxes, raccoons, and other carnivores are considered rabid until proved otherwise by laboratory tests; in the interim, or if the animal cannot be found, treatment with human rabies immunoglobulin (HRIG/RIG) and human diploid cell vaccine is suggested. Current recommendations call for most, if not all, of the HRIG/RIG dose (20 IU/kg of body weight) to be infiltrated in and around the site of the bite. Rabies prophylaxis is now also suggested after exposure to bats in a confined setting, such as finding a bat in the bedroom on awakening, even when no bites are visible. Because the location of a bat bite is rarely known, the total HRIG/RIG dose may be given in the thigh. If the bat can be captured and submitted for testing, then rabies prophylaxis can be avoided in 60% of the cases (Table 215-2). Rabies, which was previously considered a fatal disease, has been treated with the induction of a coma (Milwaukee protocol); however, severe neurologic sequelae remain.

A variety of rare diseases have been described after wild animal bites; consultation with the local health department may help in establishing the diagnosis and managing treatment. Rat-bite fever, a systemic illness

Table 215-2 Rabies Vaccination Guidelines	
ANIMAL	MANAGEMENT
Wild carnivores	Begin HRIG/RIG and HDCV. Submit animal’s head for testing.
Healthy domestic dogs and cats	Quarantine animal; treat only if animal develops symptoms.
Stray or sick dogs and cats	Submit animal’s head for testing. Delay treatment until test results are known unless clinical likelihood of rabies is high. If animal is unavailable, then complete full series of HRIG/RIG and HDCV.
Rodents, rabbits	Unlikely to be rabid (except woodchucks). Treat only if animal acted strangely and cannot be tested.

HDCV, Human diploid cell vaccine; HRIG/RIG, human rabies immunoglobulin. From Centers for Disease Control and Prevention. Human rabies prevention—United States, 1999. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep.* 1999;44(RR-1):1–21.

caused by *Streptobacillus moniliformis* or *Spirillum minus*, is one such example. The American Academy of Pediatrics *Red Book* contains comprehensive, up-to-date descriptions of unusual diseases transmitted by various domestic and wild animals.

## ANTICIPATORY GUIDANCE

Although pets provide hours of delight and companionship for children, education about the responsible care of a pet is important. Preschool-aged children should not be left alone with a pet, and they should be advised never to tease animals, approach strange animals, or play with pets that are eating. Families who have children should be advised not to buy wild animals or dogs bred for aggressiveness. Finally, vaccinations for pets and routine visits to a veterinarian should be encouraged (see Chapter 42, Safety and Injury Prevention, for a more detailed discussion of animal safety rules for children). Families traveling with children should be on the alert for stray animals in foreign countries, given that animal control is often poor. If families are planning to spend an extended period in a country where rabies is endemic, then prophylactic rabies vaccine should be strongly considered.

### WHEN TO REFER

- Complex wounds that require surgical repair
- Bites to the face or hand that require plastic surgery
- Infected wounds not responding to initial treatment
- Children with human bites from an adult

### WHEN TO ADMIT

- Infected wounds requiring intravenous antibiotics
- Extensive facial wounds requiring skilled nursing care

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *What You Should Know About Dog Bite Prevention* (handout), American Medical Veterinary Association ([www.aap.org/advocacy/releases/dogbiteprevention.pdf](http://www.aap.org/advocacy/releases/dogbiteprevention.pdf))

### Medical Decision Support

- *Rabies* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/rabies/exposure/index.html](http://www.cdc.gov/rabies/exposure/index.html))
- *Rabies: Information for Doctors* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/rabies/specific\\_groups/doctors/index.html](http://www.cdc.gov/rabies/specific_groups/doctors/index.html))

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## Chapter 216

# ANOREXIA NERVOSA, BULIMIA NERVOSA, AND OTHER EATING DISORDERS

Marcie Schneider, MD; Martin Fisher, MD

## INTRODUCTION

The eating disorders, a group of conditions that affect primarily adolescents and young adults, increased significantly in prevalence during the past several decades. From 1999 to 2006, there was an increase in hospitalizations for patients with eating disorders, especially those younger than 12 years. Marked by a combination of medical and psychological factors in their etiology and outcome, they include predominantly the well-known entities of anorexia and bulimia nervosa. Anorexia nervosa (AN) is viewed most simply as the purposeful loss of weight beyond a healthy state, whereas bulimia nervosa (BN) is marked by recurrent episodes of binge eating along with purging behaviors. The diagnosis and prevalence of these disorders are much debated, and many questions remain about their etiology and outcome. Nevertheless, the growing incidence and prevalence of eating disorders in adolescents and adults require that the primary care physician has some knowledge of the principles involved in the evaluation and treatment of both anorexia and bulimia nervosa.

## ETIOLOGY

Several factors most likely converge in the development of an eating disorder. The adolescent who is culturally primed, biologically at risk, and psychologically vulnerable may begin dieting or vomiting in response to a particular precipitant (often an insult by family or friends, exposure to another individual who has an eating disorder, or a stressful situation). The positive psychological feedback that initially accompanies a perceived improved appearance and the biochemical changes that occur in response to decreased nutrition may serve to perpetuate the behavior.

Genetic factors have been linked to anorexia nervosa and bulimia nervosa. There may be pubertal activation of these factors. Additionally, there is evidence of interplay between genetic and environmental factors. Leptin and endocrine abnormalities in the hypothalamic pituitary adrenal axis have been linked to eating disorders. Dieting itself is an important risk factor for developing an eating disorder. More recently the predilection of many in society to eat “healthy



diets” leads to dietary restrictions that cause weight loss and the onset of an eating disorder.

## DEFINITIONS

For more than 20 years, the diagnostic criteria for the eating disorders were based on the fourth edition (and fourth edition revised) of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV and DSM-IV-TR)*. The publication of the Fifth Edition (*DSM-5*) in May 2013 has resulted in significant changes in the definition of the major eating disorders, which have, in turn, resulted in improved diagnostic accuracy. Whereas more than 50% of pediatric and adolescent patients with eating disorders were receiving diagnoses of “eating disorders not otherwise specified” (EDNOS) using the *DSM-IV* criteria, almost all children and adolescents with eating disorders are now receiving specific diagnoses using the new *DSM-5* criteria.

The 4 major eating disorders in the *DSM-5* are anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED), and a newly described diagnosis referred to as avoidant/restrictive food intake disorder (ARFID).

Anorexia nervosa, per the *DSM-5*, is defined by the restriction of dietary intake, which results in a low body weight compared to what is expected in the context of the patient’s age, sex, pubertal stage, and physical health. Additionally, there is an intense fear of gaining weight and a distortion in body image. Patients are also categorized as having restricting or bingeing and purging subtypes of AN.

Bulimia nervosa, per the *DSM-5*, is defined by binge eating and participating in repeated behaviors to avoid weight gain (eg, vomiting; use of laxatives, diuretics, or diet pills; restricting food; and/or over-exercise) at least once a week over a three-month period of time. Patients with BN feel overly influenced by the appearance of their body.

Binge eating disorder, per the *DSM-5*, is defined by binge eating at least once a week for three months without any compensatory behaviors and marked distress about bingeing.

Avoidant/restrictive food intake disorder, per the *DSM-5*, is defined by a problem with eating that causes significant weight loss or lack of expected gain, a decline in social functioning, and possible dependence on nutritional supplements, all of which are not due to a medical cause or lack of available nutrition. Importantly, there is no body image distortion present, as is found in patients with AN.

Specific changes from *DSM-IV* to *DSM-5* in these diagnoses are as follows:

1. The requirements that an individual be at least 15% below ideal body weight (IBW) and have amenorrhea of at least 3 months have been eliminated from the diagnostic criteria for AN. In addition, a new category, called *atypical anorexia nervosa*, has been added, to account for those who have lost a lot of weight and have eating disorder thinking and behaviors, but who are not underweight. These changes have added significant flexibility to the diagnosis of AN, decreasing the need to categorize patients as having EDNOS, which was a frequent diagnosis using the *DSM-IV* criteria.

2. The diagnosis of BN is also more flexible, partly because the bingeing requirement was decreased from 2 times per week in *DSM-IV* to once per week in *DSM-5*, but more importantly because a new diagnosis of purging disorder has been added to *DSM-5*. This new diagnosis includes the many patients (especially adolescents) who purge but do not binge, who previously received a *DSM-IV* diagnosis of EDNOS.
3. Binge eating disorder has become an official diagnosis in *DSM-5*, after being a provisional diagnosis in *DSM-IV*. This diagnosis is made infrequently in children and adolescents, however, with most patients with BED being 18 years of age or older.
4. The new diagnosis of ARFID, on the other hand, very specifically applies to pediatric and adolescent patients. The patients who fit into the category of ARFID are those who have poor nutrition and/or weight loss or poor growth not resulting from a fear of weight gain. Subcategories of patients with the diagnosis of ARFID include those who have had a choking or vomiting episode that is making them afraid to eat, those with restricted diets since early childhood, and those who will not or cannot eat well because of gastrointestinal symptoms or anxiety.

## CLINICAL MANIFESTATIONS

### Incidence

#### Anorexia Nervosa

Conservatively, AN occurs in 0.5% to 1% of girls and young women and 0.2% of boys and young men. A bimodal peak of onset occurs during the adolescent years at 14.5 and 18 years of age. Increasingly, the onset of AN has been seen in both prepubertal children and adults. Mortality is higher than in any other psychiatric illness, up to 5% per decade after the onset of the eating disorder.

#### Bulimia Nervosa

Up to 15% of adolescents report binge eating, purging, or both. However, only 2% of female adolescents and 0.3% of male adolescents actually meet full diagnostic criteria for BN. The peak prevalence of lifetime BN is reported to be 2% to 4% among white Western girls and women aged 17 to 25 years, with a modal age of onset of 18 to 19 years. BN occurs in patients younger than age 14 years, but this situation is very rare.

### Risk Factors

#### Anorexia Nervosa

Serotonergic, dopaminergic, opioidergic, appetite regulatory, food intake regulatory, weight regulatory, and other genes have been explored as possibly causative in AN, but because samples are small and data are inconsistent, findings to date are inconclusive. Chromosomes 1, 2, 4, and 13 have possible links to AN. Low self-esteem, perfectionism, and obsessiveness are associated with AN. Additionally, a family history of eating disorders, family dieting, and a focus on weight in the family are all linked to the onset of AN. Interestingly, very preterm small-for-gestational-age infants have a higher risk for developing AN. Psychiatric illnesses can coexist with AN, including depression, anxiety, and obsessive-compulsive disorder.



### **Bulimia Nervosa**

Dieting has been documented as a risk factor for the development of BN. Chromosomes 10 and 14 have been linked to BN. As with AN, particular gene categories may be involved, but the studies are inconclusive. BN is associated with early menarche, early sexual experiences, and increasing age in girls and with very early or late puberty and early sexual experiences in boys. Personal and parental obesity are each risk factors for BN. Urbanization, not socioeconomic status, has been found to be a risk factor for BN, which occurs at a rate 5 times higher in large cities than in rural areas. Because it occurs in all ethnic and racial groups, being a member of an ethnic subculture does not apparently protect against the sociocultural factors that promote body dissatisfaction among teenage girls. Childhood sexual abuse has been reported to be a significant risk factor, especially when psychiatric comorbidity is present. Premorbid negative self-evaluation, parental alcoholism, low parental contact, and high parental expectations have each been associated with a higher risk for development of the disorder. In addition, BN is associated with impulsivity, stressful life events, high levels of family conflict, inadequate expression of emotions, lack of parental warmth and care, inappropriate parental control, and a family history of affective disorders or eating disorders. A family history of eating disorders increases the risk for having an eating disorder by 7- to 12-fold. A greater prevalence of eating disorders in monozygotic versus dizygotic twins is present, and 54% to 83% of the variance in BN can be accounted for by genetic factors. Twin studies have shown AN to be heritable in 33% to 84% of cases and BN heritable in 28% to 83%. Molecular genetic research on several genes, including the most recent study on estrogen-related receptor  $\alpha$  (ESRRA) and histone deacetylase 4 (HDAC4) mutations, provide a new and exciting area of study aimed at gaining an understanding of the genetics of these disorders.

### **DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of the eating disorders includes possible medical causes of weight loss or vomiting and other psychiatric causes of poor appetite. Included in the differential diagnosis are malignancies and central nervous system tumors; gastrointestinal problems, including malabsorption, celiac disease, and inflammatory bowel disease; endocrinologic problems such as diabetes mellitus, hyperthyroidism, and hypopituitarism; chronic illnesses and chronic infections; and the superior mesenteric artery syndrome. The history, physical examination, and baseline laboratory tests should help rule out most of these diagnoses; further testing may be necessary if the weight loss or vomiting cannot be explained adequately. Magnetic resonance imaging (MRI) of the brain, gastrointestinal series, or other tests may be considered in some cases for patients who claim to be eating well or not vomiting on purpose. In some instances, a patient may show obvious pleasure in the weight loss or vomiting brought on by another disorder; however, this circumstance must not be confused with a positive diagnosis

of AN or BN. Psychiatric causes of weight loss can include depression, obsessive-compulsive disorder, and psychosis (especially schizophrenia). The patient who refuses to eat because of a desire to lose weight must be differentiated from the patient who cannot eat because of depression or the patient who will not eat because of delusional fears (eg, that the food is poisoned). Although patients may have concomitant depression or psychosis with AN or BN, separate criteria must be used to establish each entity. A full psychosocial history must be obtained as part of the initial evaluation to establish both the diagnosis and the psychosocial severity of the disorder. The patient's functioning in the family, in school, and among peers must be evaluated, and possible psychiatric symptoms such as sleep disorders, hallucinations, delusions, or obsessions should be elicited. Almost all patients with eating disorders exhibit psychosocial changes with the onset of the illness. These changes generally include fighting with the family, withdrawing from friends, and performing less optimally in school, although some patients paradoxically report improved school performance as they withdraw from friends and family. If additional psychiatric symptoms are found, the possibility of an additional diagnosis should be pursued.

### **EVALUATION**

Evaluation of the specific diagnostic criteria for eating disorders listed in the *DSM-5* serves to both elucidate the diagnosis and determine the severity of the illness. Distortion of body image, a hallmark in the diagnosis of AN, may be evaluated by exploring the patient's views of initial, current, and desired weight. Establishing the patient's eating and exercise patterns and use of vomiting or medications designed to promote weight loss (including diet pills, laxatives, diuretics, or ipecac) provides hints to both the diagnosis and the possibility of medical complications. Care must be taken to avoid being misled by the patient who is not completely forthright; the results of the physical examination and laboratory tests often suggest the true extent of the patient's disorder.

### **Anorexia Nervosa**

#### **History**

Initial evaluation of the patient with weight loss includes a determination of the diagnosis and its severity, an evaluation of other possible causes of weight loss and the effects of malnutrition, an analysis of the psychological context of the illness, and a decision about treatment. Relevant history includes patients' recollection of height, maximum weight, minimum weight, current weight, and desired weight. Additionally, evaluation for a distortion in body image, a history of bingeing or purging, and overexercising is necessary. On the review of systems, symptoms of malnutrition, including alopecia, cold hands and feet, dry skin, constipation, fatigue, and amenorrhea, may be present (Box 216-1). For girls, a full menstrual history should be obtained, including age at menarche, last normal menstrual period, usual length of menses, heaviness of flow, presence of dysmenorrhea, and regularity of menses.

### BOX 216-1 Physical Findings and Medical Complications of Anorexia Nervosa and Bulimia Nervosa

#### ANOREXIA NERVOSA

- Acrocyanosis
- Alopecia
- Dry skin
- Lanugo
- Ecchymosis
- Fatigue
- Hypothermia
- Muscle wasting
- Bloating
- Postprandial fullness
- Decreased subcutaneous fat
- Decreased deep-tendon reflexes
- Constipation
- Delayed gastric emptying
- Delayed gastric motility
- Orthostatic hypotension
- Bradycardia
- Mitral valve prolapse
- Pericardial effusion
- Electrocardiographic abnormalities, including prolonged QT interval
- Decreased left-ventricular mass and contractility
- Psychomotor retardation
- Growth delay
- Pubertal delay
- Amenorrhea or menstrual irregularity
- Osteopenia, osteoporosis
- Cortical atrophy on magnetic resonance imaging

- Electrolyte abnormalities from water loading or purging
- Hypercholesterolemia without hyperlipidemia
- Euthyroid sick syndrome
- Low luteinizing hormone, follicle-stimulating hormone, prolactin
- Elevated cortisol level
- Low insulin-like growth factor 1
- Low leptin

#### BULIMIA NERVOSA

- Hypertension or hypotension
- Electrolyte abnormalities, including hypokalemia, hypochloremia, elevated serum bicarbonate
- Dehydration
- Erosion of dental enamel
- Calluses on the dorsum of the hand
- Parotid enlargement
- Acute pancreatitis
- Acute gastric dilation or rupture
- Mallory-Weiss tears
- Gastric and esophageal irritation
- Gastric and esophageal bleeding
- Gastric esophageal reflux disease
- Barrett esophagus
- Aspiration pneumonia
- Diarrhea, constipation, steatorrhea
- Emetine cardiomyopathy
- Menstrual irregularity
- Polycystic ovarian syndrome
- Osteopenia, osteoporosis

#### Physical Examination

The first steps in the physical examination of the patient who is thought to have AN include measuring height, weight, and vital signs; plotting the height, weight, and body mass index (BMI) on the patient's growth curve; and calculation of the percentage below ideal body weight (IBW). The percentage below IBW, which may be calculated by comparing the patient's current weight with the average weight expected for height, age, and sex (as determined by standard pediatric growth charts), serves both as one of the diagnostic criteria and as a gross estimate of the degree of malnutrition. In general, body weight more than 25% below IBW represents severe malnutrition, 20% below IBW represents moderate malnutrition, and weight not yet 20% below IBW represents mild malnutrition. For example, a 16-year-old girl who is 5 feet 4 inches tall would be expected to have a body weight of 120 pounds, plus or minus 10%; she would be 20% below IBW at 96 pounds and 25% below IBW at 90 pounds. Pediatric growth charts ([www.cdc.gov/growthcharts](http://www.cdc.gov/growthcharts)) are needed especially

for premenarchal girls and growing boys to determine previous heights and weights to establish appropriate weight goals for achievement of expected adult height. Plotting height, weight, and BMI on the patient's growth curve gives perspective to the current weight and the current height. Vital signs provide further evidence of the degree of malnutrition because chronic malnutrition is accompanied by declines in blood pressure, pulse, and electrocardiographic voltage. Other cardiovascular changes can include sinus bradycardia, prolonged QTc, orthostatic hypotension, increased vagal tone, poor myocardial contractility, mitral valve prolapse, pericardial effusion, and decreased left-ventricular mass. To document orthostatic changes accurately, the patient's blood pressure and pulse should be checked in the sitting position, followed by standing for 2 minutes. An increase of 20 beats per minute in pulse, a decrease of 20 mm Hg in systolic blood pressure, or a decrease of 10 mm Hg in diastolic blood pressure is considered significant. Other physical findings associated with malnutrition include scaphoid abdomen,

muscle wasting, acrocyanosis, decreased subcutaneous fat, lanugo hair similar to that seen in newborns, ecchymoses, diminished reflexes, and dry skin.

### Laboratory Evaluation

Laboratory tests further elucidate the severity of the illness. Most patients who have anorexia nervosa have normal laboratory results initially, although all organ systems are probably affected by the malnutrition. The laboratory abnormalities found on routine testing are related generally to the individual's particular nutritional pattern. Thus, the patient who is chronically malnourished may have leukopenia, occasionally thrombocytopenia, and, in rare cases, severe anemia (being protected for some time from iron-deficiency anemia by the concomitant amenorrhea). The patient who restricts fluid intake may show evidence of dehydration (including an elevated sodium or blood urea nitrogen), whereas the patient who drinks excessive fluids to satisfy hunger or the physician's scale may show signs of hyponatremia and dilute urine. Conversely, the patient who vomits or uses laxatives may show evidence of hypokalemia, which is often severe in persons who use both methods of weight control. Nutrient values, including levels of zinc, calcium, magnesium, copper, vitamin B<sub>12</sub>, and folate, may all be altered in the malnourished patient, but are usually normal. Hormonal testing may produce evidence of dysfunction in endocrine systems. Development of a relative hypothyroidism caused by a combination of euthyroid sick syndrome and decreased production on a hypothalamic basis is believed to be an adaptive response to inadequate nutrition. Hypothyroidism is generally evident by low-normal levels of triiodothyronine, thyroxine, thyroid-stimulating hormone, or any combination. Amenorrhea, or menstrual irregularity, may develop and is accompanied by low levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Hypercortisolemia with loss of diurnal variation, low levels of insulin-like growth factor 1 (IGF-1) and leptin, increased ghrelin, and increased peptide YY are seen in patients with AN, although these tests need not be performed in most patients.

In general, the initial laboratory workup of patients with AN includes a complete blood cell count, evaluation of serum electrolytes, liver and thyroid function tests, and levels of LH, FSH, estradiol, and prolactin in patients who have amenorrhea. Obtaining a urinalysis for specific gravity and ketonuria is often helpful. An electrocardiogram (ECG) is performed for persons with bradycardia. This battery of tests is generally sufficient to provide a barometer of current status, a baseline to monitor further changes, and screening for other possible causes of weight loss. Data have demonstrated that patients who have eating disorders, especially those whose amenorrhea is prolonged because of malnutrition, show evidence of osteopenia on bone density studies. Initial studies have shown that this effect may not be preventable, even with calcium supplementation or hormonal replacement, or completely reversible, even after patients regain their normal weight. A threefold increase in the long-term risk for fracture development has been seen in patients with a history of AN. Studies are underway to

determine the possible causes of osteopenia, including hypoestrogenemia, hypercortisolemia, and decreased IGF-1. Bone density values in patients with AN are correlated with BMI, age at onset, and duration of illness. Bone densitometry, using dual-energy x-ray absorptiometry, has become a common test in the evaluation of patients who have eating disorders and amenorrhea of at least 6 to 12 months' duration. Evidence of abnormalities may be found on computed tomography and MRI of the brain, but these tests are generally reserved for evaluating other possible causes when the diagnosis is in question. MRI changes in the brain, including gray matter deficits and increased ventricular volume seem to be reversible with weight recovery. Additionally, delayed gastric emptying and decreased gastrointestinal motility can be seen in AN. Gastric emptying studies can be done to evaluate these abnormalities, if necessary.

### Bulimia Nervosa

#### History

Initial evaluation of a patient with BN includes determining the diagnosis and its severity and evaluating other causes of the symptoms. Relevant history includes frequency of bingeing; frequency of purging behaviors, including laxative, diuretic, diet pill, or ippecac use; and frequency of vomiting or exercising. History of maximum, minimum, and usual weight is also obtained. Similar to patients with AN, symptoms of malnutrition, including cold hands and feet, hair loss, and irregular menses, may be present. Symptoms related to purging, which include heartburn, hematemesis, constipation, and diarrhea, should be explored.

#### Physical Examination

Patients with BN may be underweight, overweight, or normal weight. Specific abnormalities on the physical examination are rarely found; therefore, more subtle changes in vital signs, the complete physical examination, and laboratory tests should be sought (see Box 216-1). Vital signs will vary depending on the substances used to control weight. For example, persons using diet pills may have tachycardia, hypertension, or both, whereas those using substances that cause dehydration, such as stimulant laxatives or diuretics, may have tachycardia, hypotension, or both. Vomiting can cause hypovolemia and, in turn, tachycardia and hypotension. For persons who exercise excessively, resting heart rates may show significant bradycardia. Thus, the initial physical examination generally begins with measurements of weight, height, blood pressure, and pulse. If dehydration needs to be ruled out, then measuring blood pressure for orthostatic changes as previously described is needed. Hands should be examined for Russell sign (ie, irritation on the dorsum of the joints of the fingers used to induce vomiting); teeth should be examined for erosion of enamel as a result of vomiting; and parotid enlargement from vomiting may also be seen.

#### Laboratory Evaluation

Blood tests include a complete blood cell count with differential, electrolytes, lipid studies, liver function

tests, and serum chemistries. Amylase levels and urinary pH may be elevated in some patients who have BN. The urinalysis may reveal an elevated specific gravity in dehydration, ketones in starvation, increased pH in the presence of vomiting, or any combination. A hormonal workup is performed if menstrual periods are problematic; these tests include thyroid function tests, as well as assessments of LH, FSH, estradiol, and prolactin (if amenorrheic). If potassium levels are abnormal or if a history of ipecac use exists, then an ECG should be performed. If patients are oligomenorrheic or amenorrheic, then a bone density assessment looking for osteopenia should be pursued.

### Binge Eating Disorder

The prevalence of BED among adults 18 years and older is 1.6% in females and 0.8% in males, and BED is equally prevalent across racial and ethnic groups. Between 1% and 2% of adolescents have BED. Most patients with BED are overweight, so obese populations have a higher prevalence of BED compared with nonobese populations. The mean age of onset of BED is 17.2 years. Binge eating predates dieting (14.3 and 15.0 years of age, respectively). Half of those with BED had the onset before the age of 18 years. Of those with the younger age of onset, weight problems, followed by bingeing, and then dieting started at a mean age of 12.2 years, 12.8 years, and 14.4 years, respectively. Because of the frequency of onset in the adolescent years, BED is important to recognize. Because patients with BED are not purging, there are fewer medical risks aside from those significantly related to obesity, which are beyond the scope of this chapter.

### Avoidant/Restrictive Food Intake Disorder

In studies reviewing patients with eating disorders who were classified under the new *DSM-5* criteria, 5% to 22% qualified for the diagnosis of ARFID. The limited study on this group of patients to date suggests that they are younger, more reliant on nutritional supplements, and may have fears of vomiting, choking, or the texture of food. Anxiety is more prevalent in the group of patients with ARFID than in those with other eating disorders. As much as this is a definition separate from AN because there is no body image distortion, the medical findings on physical and laboratory examinations and the medical ramifications are the same as with AN.

## TREATMENT

The patient who has an eating disorder may seek medical care in a variety of ways. Some patients visit their pediatrician or family physician because of concern about weight loss, vomiting, or abnormal eating attitudes noticed by family, friends, or school authorities; others visit a gynecologist because of the menstrual irregularities that characteristically accompany the disorder. Many patients are seen first by a psychiatrist, psychologist, or social worker; others may be seen for the first time in an emergency department because of dehydration or other medical complications. Some patients may be seen within weeks of the disorder's onset; others

avoid medical care for months or even years. Being brought in for their initial evaluation against their will is common for many patients, although some may seek help willingly. Many patients who have mild to moderate eating disorders, both AN and BN, avoid medical care altogether by hiding or denying their illness.

### Team Approach

The combination of medical and psychological interventions required in the treatment of eating disorders makes the task of being proficient in all aspects of care difficult for any single professional. No single individual can be responsible totally for any patient's care beyond the initial evaluation or for the most straightforward of cases. Rather, a team approach is most often used. The team may consist of a primary care physician; a psychiatrist, psychologist, or social worker; and a nutritionist, with the exact combination determined by local expertise, availability, and preference. Generally, each team member manages specific aspects of care, and team meetings and discussions are held frequently to prevent miscommunication that can sabotage the treatment.

### Medical and Nutritional Rehabilitation

Determination of the treatment setting as inpatient, outpatient, or in a day program is made by the evaluating provider. The malnutrition that accompanies AN is directly responsible for most, if not all, of the physical abnormalities noted in the disorder, as well as for some of the mental deterioration. Accordingly, medical and nutritional rehabilitation is crucial in the treatment of the patient who has AN. Restoration of body weight, generally to within 10% of IBW, with restoration of menses if amenorrheic, should be among the main goals of treatment. For many patients whose malnutrition is mild to moderate (15% to 25% below IBW), this task may be accomplished on an outpatient basis; patients who have moderate to severe malnutrition (more than 25% below IBW) can rarely accomplish the required weight gain without hospitalization. Medical treatment includes management of electrolyte abnormalities, cardiovascular issues, endocrine disorders, and other organ system dysfunction. These aspects of care are managed simultaneously with and are abetted by nutritional rehabilitation, which is generally achieved through oral feedings. Whether in the inpatient or outpatient setting, a daily intake of 3 substantial meals and 3 to 4 snacks is usually sufficient to bring about required weight gain and improvement of medical parameters. On inpatient units, meals are generally provided as part of a strict regimen, and snacks generally consist of high-calorie supplements, available as liquids or puddings in various brands and flavors. Care is taken to avoid overfeeding patients whose malnutrition is severe because a too-rapid weight gain has been associated with severe metabolic abnormalities (that is, the refeeding syndrome) in some patients. Slow refeeding and phosphorus supplementation are required in patients with severe malnutrition to prevent this syndrome, which may result in cardiac failure, hemolysis, coma, and death. For BN, the medical rehabilitation is focused on treating the patient's physical symptoms or



laboratory abnormalities and stopping or at least decreasing the patient's participation in risky behaviors, including bingeing, vomiting, and laxative and diet pill abuse, while the nutritional rehabilitation is focused on normalizing eating patterns and ensuring balanced nutrition.

### **Dietary Plan**

In the outpatient setting, an appropriate meal pattern may be developed based on the patient's and the family's prior eating habits or on a specific dietary plan offered by the physician or a nutritionist, or by the parents if they are in family-based treatment. The dietary plan should be specific to prevent ambiguities that can lead to family fighting; it should provide approximately 2,000 to 3,000 calories a day. Some of these calories may be supplied in the form of high-calorie supplements. The plan should be well balanced and include foods from each of the major food groups. Outpatient gains should be 1 to 2 pounds per week, whereas inpatient gains may be 2 to 4 pounds per week. Compliance with the dietary regimen may be evaluated by having the patient keep a diet diary; however, many patients do not always keep these records accurately and honestly. A similar dietary plan, without the high-calorie supplements, may be offered to healthy-weight patients who have BN because these patients generally require nutritional adjustment rather than nutritional rehabilitation. Caloric requirements for persons with BN will depend on the need for weight gain, loss, or maintenance. Because caloric restriction may often spark binge eating episodes, the implementation of a nonrestrictive, well-balanced diet is warranted. If hospitalization is necessary for uncontrolled binge or purge cycles, abnormal electrolytes, or unstable vital signs, then supervision after meals, locked bathrooms, and restricted access to food are often necessary.

### **Menses Restoration in Those With Amenorrhea**

Menses restoration generally requires an estradiol level of 30 to 50 mg/dL. Resumption and presence of menses have been linked to improved cognitive function in patients with AN. Researchers are exploring other treatments, such as recombinant human IGFs, dehydroepiandrosterone, bisphosphonates, testosterone, and a combination of recombinant human insulin-like growth factor (rhIGF1) and oral estrogen, in an effort to find ways to protect the bones of patients with eating disorders. Oral estrogen-progesterone combination pills are not effective in increasing bone density. Physiologic estrogen replacement in the form of a transdermal patch along with cyclic progesterone has been found to possibly increase the rate of bone accrual in adolescents with AN in one recent study. Still, regaining weight is the only definitive treatment to bring about the return of menses.

### **Treatment Settings**

#### **Inpatient and Residential Settings**

Patients are admitted to inpatient hospitals for the reasons previously outlined, which are either medically or psychiatrically emergent. They are put on

protocols to ensure weight gain and to guard against refeeding syndrome. Many units begin with food, moving to oral supplements or nasogastric feeds if meals are not consistently consumed. In fact, there is some evidence that using nasogastric tubes at the time of admission can increase the rate of weight gain.

After patients are stabilized, they are often transferred to residential programs, which have less medical monitoring and more psychological support. Various behavioral approaches may be used, including several phases of treatment, with patients moving from one phase to another based on achievement of progressively higher weight goals or improved behaviors or attitudes. Each phase incorporates additional privileges into the patient's daily activities (eg, food choices, food preparation, passes for outings with family).

### **Day Programs and Intensive Outpatient Programs**

After patients are ready to leave the residential setting, they are stepped down to a day program, which generally runs 5 days a week, providing 2 to 3 meals and snacks daily. Following this, it is ideal to step down again to an intensive outpatient program (IOP), which generally runs 3 hours per day, 3 days a week, providing a meal and a group. In both settings, patients still live at home, and with the IOPs, patients can attend school. Often, IOP and day programs are used as a step up from a general outpatient setting, in an effort to avoid the next higher level of care.

### **Outpatient Settings**

This least intensive option often includes medical monitoring, nutritional support, psychiatric treatment, and therapy, which may include individual, family, and/or group therapy.

### **Therapy Options**

Individual therapy, cognitive behavioral therapy (CBT), dialectical behavioral therapy (DBT), and family-based treatment (FBT) are the most commonly used modalities for patients with eating disorders. Individual therapy is varied and difficult to study for this reason.

Cognitive behavioral therapy was formulated by Fairburn in 1981. Use of CBT for eating disorders is aimed at decreasing nutritional restriction, normalizing eating, developing skills for coping with situations that trigger binge eating or purging (or both), and changing perceptions and overconcern with body weight and shape. CBT is the treatment of choice in adults with BN and BED. Both CBT and FBT have also been studied in adolescents with BN and found to be effective.

Family-based treatment was developed at the Maudsley Hospital in England and is often referred to as the *Maudsley approach*. In this method, there is no blame placed on parents or the patient. Rather, there is an understanding that the parents need to manage the patient's eating because the patient has not been able to do that and that the patient's health is in jeopardy. Parents are, therefore, empowered to refeed their child. The entire family is involved in the treatment. There are 3 phases—refeeding by caregivers, transferring the eating responsibility back to the

patient, and working on relapse prevention. The therapist needs to be trained in this method. Using this method, 50% to 60% of patients are in remission by the end of the first year, 25% to 35% practically recover, and 15% are resistant. This is in comparison to those who receive more traditional treatment, of which less than half recover within 2 to 5 years, one-third have partial recovery, and 20% are resistant. Because of these statistics, FBT has become a first-line treatment in many settings when there is a trained therapist available.

### Psychopharmacologic Therapy

The use of medication to treat eating disorders has a long history of decidedly mixed results. Numerous medications have been tried, from thyroid hormone and insulin in the 1940s and 1950s to phenytoin and hydroxyzine in the 1960s and 1970s, as attempts were made to improve appetite, increase weight gain, and reverse physiologic abnormalities. More recently, pharmacologic treatment of the eating disorders has concentrated on psychoactive medications, especially the selective serotonin reuptake inhibitor (SSRI) antidepressants. Two specific lines of reasoning have guided the use of these medications. In patients who are diagnosed as having an eating disorder along with, or as part of, another psychiatric diagnosis, medication for the associated diagnosis is offered with the expectation that the eating disorder will improve as other psychiatric symptoms are relieved. Alternately, more recent evidence has demonstrated that use of these medications diminishes the urge to binge and purge in patients who have BN and helps treat obsessive-compulsive symptoms in patients with either AN or BN. Only physicians who are familiar with the use of psychopharmacologic agents should prescribe these medications as part of the treatment, given the recent concerns about the potential for SSRI medications to increase the risk for suicide in a minority of children and adolescents treated for depression. The SSRI medications have not been shown to be effective in promoting weight gain in AN or treating symptoms of depression or obsessive-compulsive disorder when body weight is low; some questions remain about whether they may be effective in preventing relapse in patients initially treated successfully for AN. Atypical antipsychotic agents at low doses can improve weight gain and treat symptoms of depression and obsessional thoughts in patients with severe eating disorders, including both AN and BN. Again, only physicians who are familiar with the use of psychopharmacologic agents should prescribe these medications as part of the treatment.

Various types of antidepressant medications have been studied for the treatment of BN, including tricyclics, monoamine oxidase inhibitors, and SSRIs. All of these agents seem to be roughly equivalent in decreasing bulimic behaviors at the end of short-term treatment; with any of these medications: approximately 30% of patients are abstinent, and 70% have decreased bulimic behaviors. Fluoxetine has been the most intensively studied medication: a dose of 60 mg per day has been found to yield the best treatment outcome for

decreasing bulimic symptoms, relieving symptoms of depression and anxiety, and decreasing concerns with shape, weight, and desire to restrict food intake. Topiramate has been effective in decreasing binge eating if the SSRIs are not of help. Other drugs, including anticonvulsants, serotonergic agents, and lithium, have also been studied, with modest (anticonvulsants) or no significant (serotonergic agents or lithium) changes in symptoms. Use of CBT, followed by the introduction of medication if necessary, has been suggested as a logical treatment approach in the treatment of BN.

### OUTCOME AND PROGNOSIS

Eating disorders must be viewed as a chronic illness, similar to other medical or psychiatric chronic illnesses. A wide range of outcomes can be expected. Adolescents who have severe AN have a protracted disease course, yet recovery estimates 10 to 15 years later vary from 24% to 76%. Although many different approaches are used to evaluate outcome, at least an estimated 50% of patients do well in the long term, 30% show varying degrees of improvement, and 20% do poorly despite adequate treatment. Patients who are younger, as well as those whose forms of the disease are milder, appear to have a better prognosis than these general numbers indicate. Follow-up of patients with BN has recently been reviewed and has improved in studies done after 2004 compared with those done before 2004. Approximately 70% recover, 20% experience relapse, and 10% continue to meet the full criteria for BN 5 years after diagnosis. Numerous personal, family, and treatment factors may predict the outcome of an eating disorder; none of these may be predictive for an individual patient. For instance, a poorer outcome in AN has been associated with factors such as older age, vomiting, and premorbid personality problems, yet any particular patient who has this constellation of findings may do well with treatment. Furthermore, no specific treatment has been shown by controlled studies to be more effective than others, in general or for any particular type of patient.

### PREVENTION

Although a focus on both primary and secondary prevention has increased of late, the best strategies for the prevention of eating disorders remain unclear. There is increasing evidence that eating disorders and obesity may be related, with dieting, weight-related teasing, and body dissatisfaction as risk factors; therefore, using an integrated approach to prevention is sensible. To date, several programs geared toward both teenage boys and girls, primarily in school settings, have been implemented. These programs generally provide factual information and are aimed at maintaining a healthy body image, healthy eating, and promoting self-esteem without relation to weight, and they appear to succeed in terms of increasing awareness of and knowledge about eating disorders. However, whether these programs prevent or actually promote eating-disordered behaviors is debatable. The concept of preventing eating disorders through more generic programs focused on building self-esteem is currently being explored. In keeping with this effort, the concept

of a comprehensive school-based approach has been advocated. This approach would include classroom interventions, staff training throughout the school, informal discussions between staff and students, integration of material about eating issues into the curriculum, more intensive work with persons at high risk, changes within the school with respect to cafeteria food and physical education, and referrals and outreach, both within the school and to the community. A recent meta-analysis of prevention studies found that interactive, multiple sessions targeted at those at risk and older than 15 years were the most likely to succeed. Early case detection remains the most effective preventive measure currently available. For most patients, the earlier an eating disorder is treated, the easier the treatment will be and the less entrenched the disease becomes. Therefore, families, friends, school personnel, and health professionals must be vigilant for the signs and symptoms of an eating disorder so that early treatment can be initiated.

### WHEN TO REFER

- If the patient is medically stable, refer to a therapist. Also refer to a dietitian to reinforce the primary care physician's nutritional recommendations or to set a nutritional plan with the patient if the primary care provider does not have the time or expertise.
- Refer to a psychotherapist if the patient is open to therapy.
- Refer to a psychotherapist if the patient is unable to attain goals set by the physician, even if the patient is resistant.
- Refer for psychopharmacologic evaluation if both the physician and the therapist believe that the patient might benefit from medication (if the patient is bingeing and open to medication or if obsessive-compulsive symptoms are interfering with treatment).
- Refer to an adolescent medicine specialist if the primary care physician is not comfortable with treating the patient or does not have the time to do so, or if the patient does not adhere to the physician's treatment plan.

### WHEN TO ADMIT

Anorexia nervosa:

- Less than 75% ideal body weight or ongoing weight loss despite intensive management
- Refusal to eat
- Body fat <10 %
- Heart rate <45 beats/min daytime; <40 beats/min nighttime
- Systolic pressure <90 mm Hg
- Orthostatic changes in pulse (>20 beats/min) or blood pressure (>10 mm Hg)
- Temperature <96°F
- Arrhythmia
- Failure to respond to outpatient treatment

Bulimia nervosa:

- Syncope
- Serum potassium concentration,  $\leq 3.2$  mmol/L
- Serum chloride concentration <88 mmol/L
- Esophageal tears
- Cardiac arrhythmias including prolonged QTc
- Hypothermia
- Suicide risk
- Intractable vomiting
- Hematemesis
- Failure to respond to outpatient treatment

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Eating Disorders: Anorexia and Bulimia* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *National Association of Anorexia Nervosa and Associated Disorders* (Web site), (www.anad.org)
- *National Eating Disorders Association* (Web site), (www.nationaleatingdisorders.org)

### Medical Decision Support

- *Enhancing Pediatric Mental Health Care: Algorithms for Primary Care* (article), *Pediatrics*, Vol 125, Suppl 3, 2010 (pediatrics.aappublications.org/content/125/Supplement\_3/S109)
- *Evidence-Based Child and Adolescent Psychosocial Interventions* (chart), PracticeWise, American Academy of Pediatrics (www.aap.org/en-us/Documents/CRPsychosocialInterventions.pdf)
- *Mental Health Screening and Assessment Tools for Primary Care* (chart), American Academy of Pediatrics (www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH\_ScreeningChart.pdf)

## AAP POLICY

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## Chapter 217

# APPARENT LIFE-THREATENING EVENTS

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Apparent life-threatening events (ALTEs) in infants younger than 12 months are common and often present challenging diagnostic dilemmas for first responders and pediatricians. Although most patient evaluations usually take place in a hospital, primary care physicians often are asked to contribute to various stages of the management of these children, from initial evaluation of the infant to decisions about long-term monitoring. The reported incidence of infants experiencing ALTEs ranges from 0.6% to 0.8%, although there is marked variation (0.05%–6%) depending on the affected infant's underlying risk factors. The management of a child with an ALTE requires an understanding of the constellation of symptoms exhibited by the infant, the broad range of potential underlying etiologies and contributing factors, and the appropriate management strategies.

In a 1986 National Institutes of Health Consensus Report on Infantile Apnea and Home Monitoring, an ALTE was defined as “an episode that is frightening to the observer and is characterized by some combination of apnea, color change, marked change in muscle tone, choking, or gagging” in which, “in some cases, the observer fears that the infant has died.” This definition was intended to replace the term *aborted crib death* or *near-miss sudden infant death syndrome (SIDS)*, which inappropriately implied an association between ALTEs and SIDS. An ALTE is not a diagnosis, but rather a reflection of a symptom constellation (“chief complaint”) that requires evaluation to determine an etiology that will guide both risk assessment and subsequent therapeutic response.

Infants with ALTEs are a heterogeneous group with varying ages and diverse pathophysiology as to the cause of the events. The clinical challenge is that most ALTEs are benign, yet it is important to identify any infant who presents with an ALTE that is a manifestation of a serious underlying illness, such as sepsis, seizures, or child maltreatment. A review of the infant's history and physical examination is important to identify the infant at risk for a future adverse event or serious underlying condition, the scope of diagnostic testing needed, and whether hospitalization is required.

Although not the primary focus of this chapter, it is important to define apnea. Apnea is typically classified into 3 categories based on the presence or absence of upper airway obstruction: central, obstructive, and mixed. Central apnea (CA) is characterized by a total cessation of inspiratory efforts with no evidence of obstruction. An infant with obstructive apnea tries to breathe against an obstructed upper airway, resulting in chest wall motion without airflow throughout the apneic episode. Mixed apnea consists of obstructed respiratory efforts, usually following central pauses. Upper airway obstruction occurs primarily in the pharynx, although it also may occur at the larynx or involve both the pharynx and the larynx.

To create a uniform framework and help pediatricians apply consistent definitions to concepts related to infant apnea, the NIH report provided a series of descriptors for the commonly used terms to describe infant apnea and respiratory patterns exhibited by infants. These definitions are listed in Table 217-1. Most notably, pathologic apnea was defined as “a respiratory pause that is prolonged, lasting 20 seconds or longer, or is associated with cyanosis, pallor, hypotonia or bradycardia.” In contrast, periodic breathing, which is commonly noted in young infants, is “a breathing pattern in which there are 3 or more respiratory pauses of greater than 3 seconds' duration with less than 20 seconds of respiration between pauses.”

**Table 217-1** Definitions of Breathing Patterns and Concepts Related to Apparent Life-Threatening Events (ALTEs)

CONCEPT	DEFINITION
Periodic breathing	A breathing pattern in which there are 3 or more respiratory pauses > than 3 seconds' duration with <20 seconds of respiration between pauses. Periodic breathing can be a normal event.
Apnea	Cessation of respiratory air flow. The respiratory pause may be central or diaphragmatic (ie, no respiratory effort), obstructive (usually because of upper airway obstruction), or mixed. Short (15 seconds), central apnea can be normal at all ages.
Pathologic apnea	Respiratory pause that is prolonged (20 seconds) or associated with cyanosis, pallor, hypotonia, or bradycardia
Apnea of infancy	Unexplained episode of pathologic apnea with onset at >37 weeks' gestational age in infants for whom no specific cause of ALTE can be identified
Apnea of prematurity	Periodic breathing with pathologic (symptomatic) apnea in a premature infant. Apnea of prematurity usually ceases by 37 to 38 weeks' postmenstrual gestation, but occasionally persists to 1 month past term (43–45 weeks' postmenstrual age)
Sudden infant death syndrome	Sudden death of any infant or young child that is unexplained by history and by postmortem examination (Note that death scene recreation where feasible is now an additional important factor to eliminate accidental suffocation as the cause)

From National Institutes of Health. Infantile apnea and home monitoring. *Natl Inst Health Consens Dev Conf Consens Statement*. 1986;6:1–10.



Pauses in breathing without any physiologic consequences also occur in premature infants and term newborns. Review of a detailed history and physical examination help the pediatrician separate pathologic from nonpathologic witnessed events.

More recently, in 2007, the American Academy of Sleep Medicine (AASM) defined CA in children as, “cessation of breathing during sleep without any breathing effort for a duration of 20 seconds or longer, or lasting at least 2 breaths’ duration with 3% oxygen desaturation or arousal.” The AASM further noted that, “In infants, the CA is at least 2 breaths in duration and is associated with a decrease in heart rate to less than 50 beats per minute for at least 5 seconds, or less than 60 beats per minute for 15 seconds. Periodic breathing is a form of CA that has been described as greater than 3 episodes of CA lasting 3 seconds separated by no more than 20 seconds of normal breathing.” Brief CAs following body movements and periodic breathing are common in healthy infants during the first months of life; the duration and frequency improves with age. These “physiologic” CAs lasting longer than 15 seconds reflect developmental immaturity and rarely persist after 3 months of age. Most apneas occur during rapid eye movement (REM) sleep or as the infant is transitioning between sleep states. See Chapter 337, Sudden Unexpected Infant Death for a more detailed discussion about SIDS; and Chapter 100, Respiratory Distress and Breathing Disorders in the Newborn and Chapter 112, Continuing Care of the Infant After Transfer From Neonatal Intensive Care for further information.

The understanding of the frequency, duration, and significance of episodes of apnea and periodic breathing in young infants has been enhanced by the seminal Collaborative Home Infant Monitoring Evaluation (CHIME) study that characterized the breathing patterns of 1,100 infants during sleep. The group of infants studied included healthy term infants, siblings of infants with a family history of SIDS, healthy preterm infants, and term and preterm infants with ALTE. Study findings demonstrated that in otherwise healthy young infants, apnea of 20 seconds’ duration not associated with bradycardia is common. Investigators also noted that extreme events, described as apneas longer than 30 seconds associated with bradycardia, occur more commonly in preterm infants and typically reduce in frequency approximately 1 month after reaching term gestation (after 43 weeks’ postmenstrual age). Developmental immaturity increases the risk for central and obstructive apneas and periodic breathing in preterm infants, particularly in infants born at less than 26 weeks’ gestation. Bronchopulmonary dysplasia is an additional medical comorbidity that contributes to a longer duration of apnea and bradycardia in extremely preterm infants.

## PREVALENCE

The exact frequency and prevalence of ALTEs are unknown because of difficulties in classifying the subjective and heterogeneous nature of presenting symptoms and discharge diagnosis. The reported incidence of ALTEs in infants varies widely, with estimates between 0.46 and 10 per 1,000 live births, accounting

for 0.8% to 1% of all emergency department (ED) visits of patients younger than 1 year and 2% of pediatric hospitalizations. Recurrence rates for ALTEs vary from 0% to 24%. A cause for the ALTE is identified in approximately half of the affected infants. The history may reveal that the infant has feeding difficulties, including feeding with cough, lack of coordination, or rapid feeding. Risk factors for ALTEs include second-hand smoke exposure, preterm birth, exposure to pertussis, respiratory syncytial virus, or recent general anesthesia. Premature infants are especially susceptible to ALTEs, with causes such as aspiration with feedings, anemia, hypoglycemia, posthemorrhagic hydrocephalus, cardiac arrhythmias, respiratory syncytial virus, bordetella pertussis, sepsis, gastroesophageal or laryngeal esophageal reflux disease with or without aspiration, and seizures. Infants with an ALTE are more commonly younger than 10 weeks, with a median age of presentation ranging between 7 and 8 weeks of age; sex distribution has been reported to reveal a male gender predominance. Approximately one-third of infants with an ALTE had a history of prematurity, and 19% had a history of a previous ALTE. The morbidity and mortality resulting from an ALTE vary by the underlying diagnosis; the mortality of infants with apnea of infancy ranges between 0% and 6%.

## APPARENT LIFE-THREATENING EVENT AND SUDDEN INFANT DEATH SYNDROME

Strong epidemiologic evidence suggests that ALTEs and SIDS are not related. The average age of patients with an ALTE is 1 to 3 months younger than that of infants who die of SIDS, and ALTE episodes are generally reported by parents and caregivers to occur during the day with the infant in supine position. Moreover, while SIDS mortality rates markedly decreased between 1986 and 1994, the incidence for ALTEs has not changed significantly. Despite the lack of an epidemiologic association between SIDS and ALTEs, it is important to note that a very small minority of ALTEs do go on to have SIDS and that a small minority of SIDS deaths had a preceding ALTE. Franco and colleagues identified in a group of infants who experienced an ALTE and impaired arousal response from sleep with fewer spontaneous arousals during non-REM sleep at 2 to 3 and 5 to 6 months of age. In addition, infants who experienced an ALTE had less total sleep time, less sleep efficiency, less REM sleep, more awake time, and more CAs between 2 and 3 months of age. Maternal smoking further impaired the infants’ arousal responses and sleep architecture, and increased obstructive episodes throughout the study period (2–9 months of age).

## SUDDEN UNEXPECTED POSTNATAL COLLAPSE

Sudden unexpected postnatal collapse (SUPC) is a rare but well-described event that includes both severe ALTE and sudden infant death occurring during the

first week of life in infants where the postnatal adaptation seems normal. The estimated incidence of SUPC in a presumably healthy infant after birth differs widely, ranging from 2.6 cases to 133 cases per 100,000. Reported instances of SUPC typically exclude infants with known risks for ALTE and SIDS, infants born at fewer than 35 weeks' gestation or with diagnosed congenital malformations, and babies who experience perinatal asphyxia. When a defined time for the SUPC event is described, approximately one-third of reported events occur during the first 2 hours, between 2 and 24 hours, and between 1 and 7 days after birth, respectively. Most reported events that occur within 2 hours of birth have been during skin-to-skin contact and the first breastfeeding attempt. The transition from fetal to extrauterine life could make the newborn more vulnerable during the first hours of life, because the initial surge of adenosine, prostaglandins, and catecholamines during and after birth is followed by a period of diminished responsiveness to external stimuli and increased vagal tone. Prone positioning of the infant placed in skin-to-skin care, unsupervised breastfeeding during the first 2 hours, primiparous mother, and parents left alone with the baby during first hours after birth as well as distractions, such as smartphone use, have been identified as contributing factors. Extensive use of smart phones, messaging, and social networking after delivery are of particular concern. Maternal fatigue and sedation following an exhausting labor has been speculated to be an additional contributing factor. Infants born late preterm and early term (37–38 weeks' gestation) comprise an important risk group. Mothers may fail to recognize their infant's deterioration because of inexperience and a lack of awareness of the signs that an infant is having difficulty. Signs such as a change in the infant's color or respiratory effort may also be more difficult to observe if maternal mobility is impaired because of pain, postoperative status, or spinal anesthesia.

Reported survival rates vary from 50% to 80%. Among survivors, half have neurologic sequelae. Among infants who die and undergo postmortem examination, underlying congenital anomalies and conditions have been described, including antenatal brain injury, infection, metabolic defects, congenital central hypoventilation syndrome, and congenital adrenal hypoplasia, as well as cardiac abnormalities such as structural anomalies, cardiomyopathy, infarction, and conduction abnormalities. In those infants dying unexpectedly in the first week of life, almost 60% of deaths are explained following postmortem examination. Improved information, active surveillance, and rapid hypothermia treatment in severe cases are recommended. All infants who suffer a sudden and unexpected cardiorespiratory collapse within the first week of life should undergo comprehensive investigation to determine the underlying cause. If the infant dies, a complete postmortem examination should be performed and should include metabolic, mitochondrial disorder, and genetic testing. This should be followed by a multidisciplinary investigation and case review that explores the family, obstetric, pregnancy, delivery, and postnatal history, including the health of the

infant until collapse, postnatal transition and feeding, circumstances surrounding collapse, and resuscitation details.

## DIFFERENTIAL DIAGNOSIS

Because an ALTE describes a subjective report of a clinical syndrome rather than a specific diagnosis, a variety of different disorders can lead to an episode. The most common types of problems associated with an ALTE are gastrointestinal, neurologic, respiratory, cardiovascular, metabolic, or endocrine in nature. The most common, specific diagnoses associated with ALTEs include gastroesophageal reflux (31%), seizures (11%), and lower respiratory tract infections (8%), although many different diagnoses have been recorded. Up to 50% of cases of ALTEs remain unexplained and are considered idiopathic.

Although gastroesophageal reflux (GER) is the diagnosis most often associated with an ALTE, its precise role in these cases is debated. A relationship between apnea and GER disease (GERD) has been posited, but a definite causal relationship has not been demonstrated. Hasenstab and Jadcherla studied a group of infants following ALTE episodes and assessed tidal ventilation, respiratory function, esophageal motility, and frequency of spontaneous respiratory events (SREs, defined as an apneic event lasting longer than 2 seconds with at least 2 missed breaths). SREs, common in otherwise healthy infants, occurred more often in ALTE infants, suggesting exaggerated respiratory inhibition during pharyngeal swallowing events. The significance of this presumed central respiratory discoordination and brainstem dysregulation of aerodigestion has not been fully delineated. Further research in this area is warranted, because treatment with H-2 blocker and proton pump inhibitor medications often prescribed to infants with histories of reflux and ALTE may not be efficacious.

Neurologic and respiratory disorders are the second and third most commonly associated diagnoses in patients with an ALTE. The most common specific diagnoses are seizures in the former category, and pertussis and respiratory syncytial virus infection in the latter. Other important but less common diagnoses in infants with an ALTE include urinary tract infections (UTIs), inborn errors of metabolism, cardiac arrhythmias, brain tumors, persistent ductus arteriosus, and opioid-related apnea.

Child abuse (nonaccidental trauma and suffocation) and factitious illness (caregiver-fabricated illness) may account for up to 11% of unexplained ALTEs. (Box 217-1). All pediatric providers should be aware of the potential relationship, be trained to recognize the historical features and physical examination findings, and have a systematic approach to screen all ALTE patients for abuse.

## EVALUATION

Most patients will be discharged from the ED or hospital without a specific diagnosis or with a self-limited condition not requiring treatment. However, a minority may have one of a vast array of occult disorders that can lead to significant morbidity or mortality if not identified. No single accepted standard exists for

**BOX 217-1 Signs of Intentional Suffocation**

When a death occurs in an infant with a prior history of apparent life-threatening event (ALTE), the following circumstances should indicate the possibility of intentional suffocation:

- Previous recurrent cyanosis, apnea, or ALTE while in the care of the same person
- Age at death older than 6 months
- Previous unexpected or unexplained deaths of 1 or more siblings
- Simultaneous or nearly simultaneous death of twins
- Previous death of infants under the care of the same unrelated person
- Discovery of blood on the infant's nose or mouth in association with ALTEs

Adapted from Hymel K; American Academy of Pediatrics Committee on Child Abuse and Neglect, and National Association of Medical Examiners. Distinguishing sudden infant death syndrome from child abuse fatalities. *Pediatrics*. 2006;118(1):421–427.

evaluating these events, but a stepwise approach beginning with a detailed history and physical examination is most prudent. A thorough clinical assessment is more likely than an array of diagnostic studies to lead to a diagnosis of the underlying problem. The selection of any diagnostic studies and the extent and duration of observation should be based on the findings of the clinical assessment and not on an undirected battery of tests.

**History**

Seeking a detailed history and description of the infant at the time of the ALTE is particularly important because most infants appear normal by the time of the evaluation.

The most important item of the history is to determine, if possible, whether an “event” actually occurred. If a reliable observer reports what seems to be a frightening event, the baby should be hospitalized to determine whether a cause for the event can be found. If the observer is unreliable, and the history is equivocal, the baby might be discharged from the ED. If the history is equivocal, the best choice may be to hospitalize and evaluate, especially in a community hospital where a pediatrician might not be available in the ED. Consistency of the described event should be evaluated because fabricated events may suggest child abuse. Important historical questions to address are listed in Box 217-2. The case in Box 217-3 provides an example of the type of young infant who might present to a pediatrician or an ED following a 911 call. Of note in this infant's history are risk factors related to the infant's preterm birth at 36 weeks' gestation, feeding difficulties, and history of recurrent emesis and exposure to secondhand smoke. In addition, the fact that the infant experienced a second episode during the transport to the hospital places the infant at greater risk and should prompt hospitalization and evaluation even if the infant seems well at the time of presentation to the ED.

A complete history should include a review of the patient's medical and family history, a description of the patient's living conditions, descriptions of events immediately before and during the ALTE, and prior history or family history of SIDS or ALTEs. All patients should be screened for risk factors for child abuse. The case in Box 217-4 illustrates the similarities in presentation between an ALTE and an occult brain injury following child abuse. This reinforces the importance of a thorough history and comprehensive evaluation when an infant experiences repeated or atypical events.

**Physical Examination**

Although most infants with an ALTE are found to be normal at the time of the initial evaluation, a detailed physical examination is essential to uncover any clues to the underlying cause. The pediatrician should pay particular attention to neurologic, respiratory, and cardiac abnormalities that may account for the infant's symptoms, noting any evidence for physiologic compromise (eg, mental status changes, cyanosis, apnea). Physical examination features for child abuse, such as unexplained bruising, bleeding, or petechiae of the face, should be noted. Documentation of physical findings of trauma should be well described in the chart and should include photographs labeled with the child's name and birthdate.

**Laboratory Evaluation**

No minimal standard set of diagnostic studies to evaluate infants with an ALTE has been developed. Although a detailed history of the event and the physical examination of the infant often yield a suspected cause for the ALTE, laboratory testing may be a useful adjunct to confirm the diagnosis. In infants younger than 12 months, the basis of the diagnosis can be found in 21% of patients by only history and physical examination. With no additional information gained from laboratory testing, the yield of diagnostic testing can be low (only 2.5%). Therefore, using the findings of the history and physical examination is important to direct appropriate diagnostic testing.

A greater challenge is presented by infants without suggestive findings at the initial history and physical examination. When selecting diagnostic studies for this group, it is important to remember that the yield of most studies is low, and even if a positive result is found, the question of a causal relationship still remains.

In evaluating an infant with an ALTE, the focus must be first on identifying emergent and life-threatening causes, and then on extending the evaluation to additional studies if no answers are found. Box 217-5 lists the evaluations that may be considered. These studies may not be available in all hospitals, and a pediatric specialist may need to be consulted to interpret the results of the tests.

When evaluating the infant with an ALTE, there is an associated diagnosis of GERD more than 50% of the time. However, this diagnosis likely includes common choking episodes following emesis or reflux of stomach contents. Such an event is most often a self-limited, mixed obstructive event. Although further

**BOX 217-2 Essential Elements in the History of Apparent Life-Threatening Events (ALTEs)****PERSONAL AND FAMILY HISTORY**

- Perinatal history
  - Full-term or preterm birth
  - Pregnancy or perinatal complications
- Medical and surgical history
  - Previous evaluations and treatments
  - Prior hospitalizations
  - Medications
- Feeding habits
  - Breastfeeding or bottle feeding
  - Usual amount and frequency of feedings
  - Timing of last feeding relative to the event
  - Feeding difficulties—choking, coughing, arching, grimacing, emesis/reflux episodes
  - Usual behavior and temperament
- Breathing and sleep history
  - Sleep patterns
  - Breathing irregularities, respiratory pauses or shallow breathing
  - Episodes of cyanosis, pallor
- Family history
  - Siblings with ALTE, sudden infant death syndrome, or early death
  - Family history of genetic, metabolic, cardiac, or neurologic problems
- Parental or caretaker history
  - Smoking or drinking habits
  - Recent medical problems and treatments

**DAILY LIFE CONDITIONS**

- Usual sleep conditions
  - Sleep position when placed down for sleep and when found
  - Sleep location
  - Sleeping attire
  - Bedding materials
- Other conditions
  - Clothing, accessories (necklace, bracelet)
  - Room temperature, overbundling
  - Use of pacifiers

**EVENTS IMMEDIATELY PRECEDING THE ALTE**

- Recent fever or illness
- Medications of the infant and others in the home

- Immunizations
- Sleep deprivation
- Change in daily life routine

**DESCRIPTION OF THE ALTE**

- Place and time
  - Exact place in which the ALTE occurred (eg, child's bed, parent's bed, parent's arms, bathroom, sofa, car)
  - Time of event
  - Time since last feeding
  - Estimated time to recover from the ALTE
  - Estimated duration of event
- Witnesses and interventions
  - Who discovered or witnessed the ALTE
  - Reason that led to the discovery of the ALTE (noise, unusual cry)
  - Any interventions performed (gentle stimulation, shaking, cardiopulmonary resuscitation)
  - Child's response to the intervention
- Description of infant during ALTE
  - State of infant when event began—asleep or awake
  - If asleep:
    - Child's body position
    - Type of bedding
    - Face covered or free
  - If awake:
    - Was the child being fed, being handled, crying, being bathed?
  - Child's appearance when found:
    - Consciousness
    - Muscle tone
    - Color
    - Respiratory effort
    - Choking
    - Gasping
    - Emesis
    - Sweating
    - Limb or eye movements
    - Pupil size
    - Skin or rectal temperature

Adapted with permission from Kahn A, European Society for the Study and Prevention of Infant Death. Recommended clinical evaluation of infants with an apparent life-threatening event. Consensus document of the European Society for the Study and Prevention of Infant Death, 2003. *Eur J Pediatr*. 2004;163(2):108–115.

workup or treatment may not be needed, infants with apparent symptomatic reflux may benefit from a trial of therapy with medication. Infants diagnosed with GERD are nearly 2 times more likely to have recurrent ALTE, and treatment with antireflux medications may lower this risk. Further evaluation may be indicated in less common events of “silent” reflux followed by CA

or aspiration requiring intervention. The upper gastrointestinal (UGI) series is not recommended to diagnose GERD, because GER is present in most infants. In rare circumstances, a UGI series may be used to identify intestinal obstruction (eg, volvulus, gastric outlet obstruction) or congenital esophageal abnormalities (eg, tracheoesophageal fistula, vascular rings)



**BOX 217-3 Case Report 1**

A 2.5-month-old infant was transferred to the local hospital ED after presenting to the primary care physician with a history of a frightening episode of cyanosis and hypotonia witnessed by the mother approximately 90 minutes after feeding. The infant responded to stimulation by the mother and at present is alert, well seeming, and active. Vital signs in the doctor's office were: HR 110, RR 30; T 99.1°F [37.3°C], SpO<sub>2</sub> 98%. During the ambulance ride to the hospital, the infant had a similar episode, becoming limp and pale with shallow, irregular respirations. Again, the infant responded to stimulation and on arrival at the hospital was alert and well seeming once again. Review of the infant's

medical history is notable for birth at 36 weeks' gestation with a newborn nursery stay of 6 days because of jaundice and feeding difficulties. The infant's birth weight was 2,850 g the maternal medical and pregnancy histories were unremarkable except for maternal gestational diabetes and maternal smoking before realizing she was pregnant. The mother disclosed that because of the stress of the baby needing special care in the hospital she had resumed smoking, although she was trying to limit her tobacco use and not smoke in the home. The infant is breast and formula feeding and is reported to have frequent episodes of emesis, although the baby has gained weight well and hasn't had any choking episodes.

**BOX 217-4 Case Report 2**

A distraught mother brings her 3-month-old son for evaluation. She describes an episode in which her son turned blue and became limp. A health care worker by training, she relates how she provided rescue breathing before coming to the hospital. A similar episode occurred twice before and required the infant to be hospitalized once. The infant is again hospitalized for further evaluation. Initial diagnostic studies, including

a complete blood count, urinalysis, chest radiograph, electrocardiogram, and upper gastrointestinal series, are all normal. A computed tomography scan of the head is obtained and reveals a left temporoparietal subdural hematoma. A subsequent skeletal survey reveals multiple healing rib fractures with callus formation. Child abuse is suspected, and child protective services are contacted for further investigation.

**BOX 217-5 Evaluating an Infant Who Experienced an Apparent Life-Threatening Event**

The initial basic set of tests that might be considered in infants with no identified cause after initial clinical assessment includes

- Complete blood count
- Basic metabolic panel and ammonia
- Urinalysis
- Electrocardiogram
- Chest radiograph
- Blood culture
- Urine culture

Additional studies that might be considered after an initial period of observation include

- Polysomnogram or pneumogram
- Esophogram and gastroesophageal reflux study
- Modified barium swallow study
- Neuroimaging
- Tests for respiratory pathogens as indicated
- Liver function tests to screen for occult abdominal injury

that contribute to GERD. If GERD is the suspected cause for an ALTE, then a 24-hour pH probe is preferable; however, while up to 89% of infants with an ALTE may have a positive study, only 41% of these infants have a correlating clinical diagnosis. This circumstance highlights the problem of exhaustively testing all infants if the clinical history or physical examination does not suggest a diagnosis. If enough tests are performed, especially when the index of suspicion is low, then the increasing likelihood of false-positive results will diminish the diagnostic use of these studies and unnecessarily increase the risk for iatrogenic complications.

Pediatric polysomnography (PSG) is a multichannel diagnostic study used most commonly to evaluate children for obstructive sleep apnea and to evaluate cardiorespiratory function in infants and children with chronic lung disease or neuromuscular disease when indicated. In comparison, a pediatric pneumocardiogram (also referred to as a *pneumogram* [PNG]) is a 12- to 24-hour recording of breathing effort, heart rate, oxygen level, and airflow to the lungs during sleep. The study is useful in identifying abnormal breathing patterns, with or without bradycardia, especially in premature infants. PNGs are less expensive and can be performed in the home or hospital setting, whereas PSG requires hospitalization, typically overnight, although there are reports that a 4-hour period of monitoring during sleep periods may be sufficient to identify central, obstructive, and mixed apneas. If a

pH probe is used, the relationship between the apneas and GER, if present, can be examined.

When the history and physical examination do not suggest a probable diagnosis for an ALTE, the following studies or interventions are often considered: white blood cell count and blood culture, urinalysis and culture, cerebrospinal fluid analysis and culture, viral antigen and pertussis testing, chest radiograph, neuroimaging, and PSG. Pediatric polysomnography may provide more detailed information about cardiopulmonary abnormalities during sleep and feeding, but is not widely available. An alternative is the PNG, which might detect CA events with oxygen desaturation or bradycardia and could confirm a relationship to acid reflux events if paired with a pH probe monitor. The risk compared to the benefit of routine testing in this population is unknown. However, a single-center study looking at hospitalized patients showed that for many tests the likelihood of a positive result was low and the likelihood of a contributory result was even lower. Routine testing may be warranted in higher-risk groups. For example, a single-center ED study of infants younger than 2 months and with a history of prematurity does suggest in 2.7% of cases occult infections such as UTI, bacteremia, and pertussis.”

Because many victims of child abuse can present with ALTE, a high index of suspicion should be maintained, especially when the history and physical examination do not indicate a likely cause. Although little evidence suggests routine testing in this population, the pediatrician should judiciously consider a dilated funduscopic examination, neuroimaging, toxicology screen, and skeletal survey.

Seizures may account for 5% of ALTEs, and a 5-year follow-up study showed that up to 3.6% of all patients with an ATLE will go on to develop epilepsy; however, routine neurology workup is not indicated in these patients unless traumatic brain injury is suspected. Without suggestive findings in the history or physical examination, the results of tests of chemistries, cerebrospinal fluid, nasopharyngeal aspirates, echocardiogram, and electrocardiogram will likely be unrevealing.

## MANAGEMENT

Simple observation is insufficient. Several studies have demonstrated that significant cardiorespiratory events can be missed by nursing observation accompanying simple, unrecorded cardiorespiratory monitoring and oximetry at the bedside. PSG can also detect obstructive and central respiratory events, although adequate normative data on obstructive sleep apnea in infants are not available. A home PNG by an equipment company is not as effective as a PNG in the hospital where nurses and parents can observe the patient and document movements, feeding, etc. Also, a hospital PNG can easily include esophageal reflux to document any relation between cardiorespiratory events and GER.

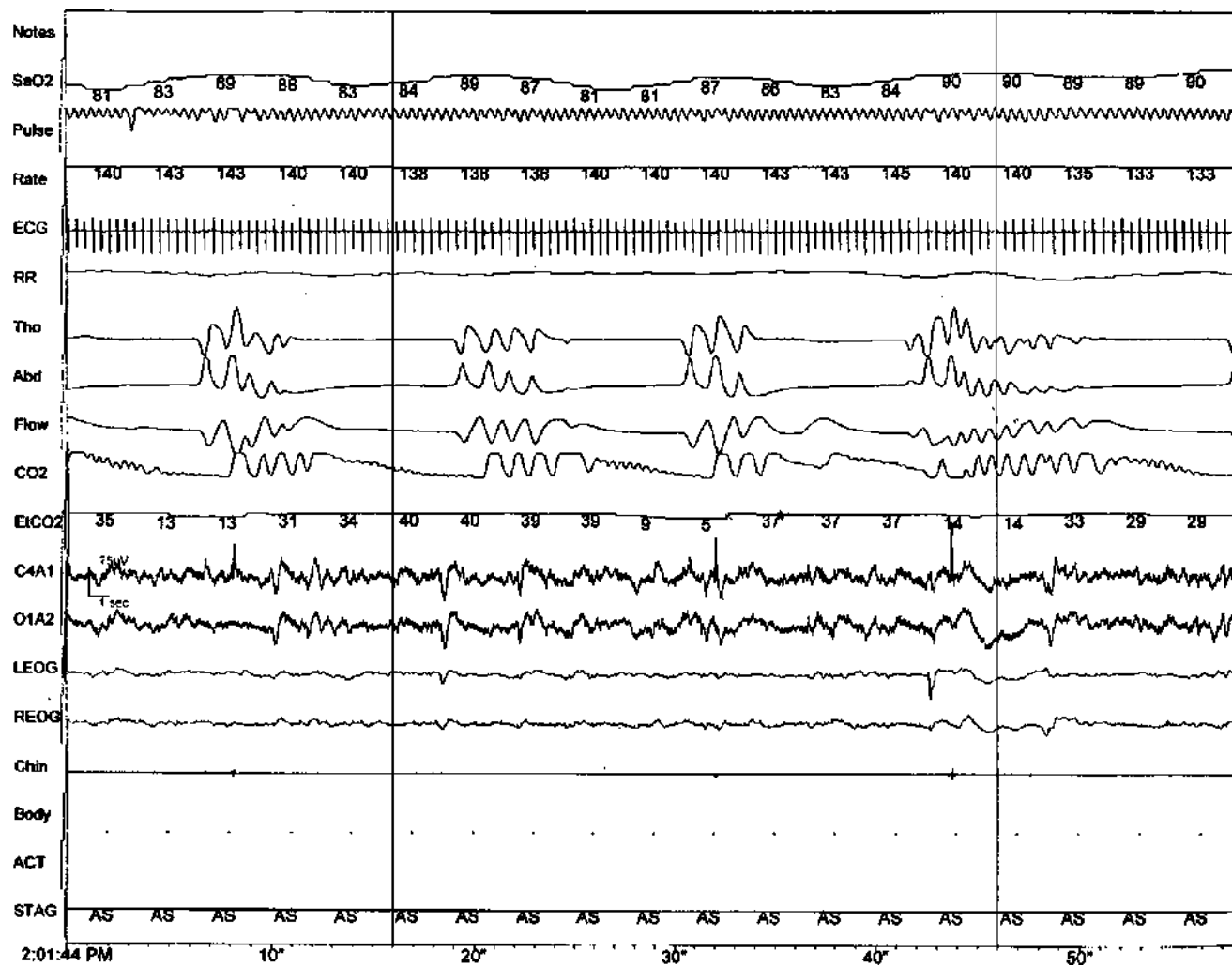
Assessments of suspected child abuse should be referred to child protective services and law enforcement. There is no evidence to support routine hospitalization of all patients with ALTEs. The decision to hospitalize infants should be guided by the findings of

the initial assessment along with some special consideration for higher-risk groups (including whether or not there is a responsible adult in the home who has CPR training). Infants whose postmenstrual age is less than 44 weeks are a higher-risk group, particularly if born premature. One study from a tertiary care pediatric hospital showed little benefit in routine hospital admission of infants older than 1 month where there was no clear etiology and the infant was well seeming after an ED evaluation. In another study from an ED, 2.7% of afebrile infants younger than 2 months with a history of prematurity had bacteremia, UTI, or pertussis. However, if the ALTE was not the first episode, the situation requires vigorous stimulation (eg more than light touching, but not shaking) from a reliable pediatrician, or when the initial physical examination reveals an abnormality, then hospitalization with continuous cardiorespiratory monitoring and further evaluation are more likely to be beneficial. The hospital environment may help document recurrent ALTEs, provide time for test results to return, and reveal social concerns indicative of child abuse. For example, continuous cardiorespiratory monitoring with pulse oximetry may detect apnea, bradycardia, and hypoxemia. It is important to note that typical apnea settings of 20 seconds on a cardiorespiratory monitor may miss bradycardia, clinically relevant respiratory pauses (<20 sec), or obstructive and mixed apnea events that lead to hypoxemia. Documentation of apnea, bradycardia, and hypoxemia events in the hospital setting should warrant further evaluation and consultation with a pulmonary specialist.

The benefit to hospitalization must also be weighed against unintended consequences, such as increasing parental anxiety, risk for nosocomial infections, and unnecessary testing or use of hospital resources. If the witnessed event or a review of the history suggests severe cardiorespiratory compromise, then the infant should be admitted to an intensive care unit. Treatment directed at the underlying diagnosis determined by the evaluation should be started—for example, antibiotics for suspected bacterial infection, anticonvulsants for an infant with seizures, and medications for GERD.

A routine PSG is unnecessary but may contribute to a diagnosis in cases where there is significant respiratory compromise, concern for CA, or anatomic abnormalities of the head and neck, or when there has been more than 1 ALTE. At institutions where PSG is not available, home equipment companies may arrange for the data acquisition of respiratory and cardiac events by using a PNG, which an outside consultant reviews. PNGs are unattended studies that collect data on respiratory effort (by using a thoracic impedance monitor), nasal flow, oxygenation, and cardiac rhythm, but not sleep staging, carbon dioxide signal, or abdominal effort. More technical artifacts exist from PNGs because no technician adjusts the leads and maintains adequate signal quality. Because the PSG is more informative, PNGs should be limited to medical centers where PSG is unavailable.

In preparation for discharge home, parents and other caregivers must be taught safe sleeping tips and counseled on CPR. If the child is going home on a



**Figure 217-1** Polysomnographic tracing of a 3-month-old infant with hypoxemia noted on monitoring in hospital for an ALTE. The infant has periodic breathing, with respiratory pauses of much less than 20 seconds (see thoracic and abdominal leads with no flow when respiration stops). Cardiorespiratory monitors routinely sound an alarm only when breathing has ceased for 20 seconds or more, and they would not detect periodic breathing unless the event led to bradycardia with the heart rate below the alarm's limit. This infant has brief pauses in series that lead to hypoxemia; thus, this event denotes pathologic periodic breathing. Polysomnography is able to detect a cause for the hypoxemia that the hospital monitor might not. Treatment would be caffeine to stimulate breathing.

monitor, all caregivers must be trained in how to respond to alarms. The American Academy of Pediatrics (AAP) policy on SIDS stresses the hazards of adults sleeping with an infant in the same bed because of the potential for accidental suffocation. Co-sleeping should be discouraged, because the safest place for an infant to sleep for the first 6 months of life is in a crib in the parents' room. In severe cases requiring CPR or where apneas were demonstrated during hospitalization, especially where there is not a clear etiology, home cardiorespiratory monitoring may help determine when the events have resolved and provide reassurance for the family. The AAP policy statement on apnea, SIDS, and home monitoring notes that an indication for home monitoring may include infants who have had an ALTE. An important point to remember is that episodes of periodic breathing and obstructive

apnea events will not be captured on home cardiorespiratory monitoring unless a secondary effect of these events on heart rate occurs (Figure 217-1). The cardiorespiratory monitor results should be reviewed by a pediatrician or specialist who is trained in their review, and the physician should establish a specific plan for periodic review. In most cases, results should be reviewed monthly if the guardian has no concerns about the baby or sooner if the guardian reports 1 or more significant events. The CHIME Study Group suggested that healthy term and premature infants may have apnea events and that these events become rare by 43 weeks' postmenstrual age. Monitoring may be discontinued once no further physiologically significant events have occurred and home monitoring shows no further objective evidence of pathologic events for at least 6 weeks. If obstructive apnea is

identified as a cause for an ALTE, then repeat PSG may be necessary to determine when and if intervention is needed.

Long-term outcomes for infants with an unexplained ALTE are unpredictable. Infants with a severe event who require resuscitation and experience a recurrent ALTE or a seizure disorder have a risk for death higher than 25%. However, other studies have reported normal cognitive and behavior outcomes up to 10 years after an ALTE.

## SUMMARY

An ALTE is a common, nonspecific disorder of the young infant that is usually self-limited, although it is potentially serious and life threatening. By understanding the definition, and by eliciting a complete history and performing a thorough physical examination, the physician can focus on determining the best laboratory and imaging studies to diagnose the underlying cause of the event. If a benign cause is not evident, a period of observation with cardiorespiratory monitoring in the hospital is necessary to gather additional information and direct appropriate diagnostic studies. Education and guidance should be provided to the guardian, with monitoring in the home setting after hospitalization to detect the infrequent recurrence of ALTEs.

### WHEN TO REFER

- When home CR monitoring is considered after a severe event requiring CPR
- Suspected seizure disorder
- Suspected hypoxemia or hypercarbia
- Suspected central, obstructive, or mixed apnea
- Suspected cardiac dysrhythmia
- Vascular ring identified
- Congenital craniofacial anomalies with suspected obstructive apnea
- Evidence of child abuse
- Atypical manifestation

### WHEN TO ADMIT

- History of prematurity
- Witnessed apnea (central or obstructive) with oxygen desaturation or bradycardia by medical staff
- Age younger than 2 months or 48 weeks post-menstrual age
- Family history of SIDS
- Suspected child abuse
- Multiple ALTEs
- Suspicion for central or obstructive apnea

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *First Candle* (Web site), ([www.firstcandle.org](http://www.firstcandle.org))

### Medical Decision Support

- *Guidelines for the Investigation of Newborn Infants Who Suffer a Sudden and Unexpected Postnatal Collapse in the First Week of Life: Recommendations*

*From a Professional Group on Sudden Unexpected Postnatal Collapse* (guideline), British Association of Perinatal Medicine ([www.bapm.org/publications/documents/guidelines/SUPC\\_Booklet.pdf](http://www.bapm.org/publications/documents/guidelines/SUPC_Booklet.pdf))

- *Recommended Clinical Evaluation of Infants With an Apparent Life-threatening Event* (article), *European Journal of Pediatrics*, Vol 163, Issue 2, 2004

## AAP POLICY

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## Chapter 218 ASTHMA

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## EPIDEMIOLOGIC FEATURES

Asthma is a chronic inflammatory condition of the airways characterized by episodic airway obstruction. Of the 25 million people in the United States with asthma, almost 7.1 million are children. The prevalence of childhood asthma, although steady since 1996, remains at historically high levels, with 13.1% of



children diagnosed as having asthma during their lifetime. Asthma is a serious public health problem resulting in an annual cost of nearly \$56 billion. It is the third-ranking cause of hospitalization among children younger than age 15 years, and among the most common causes of childhood emergency department (ED) visits (593,000 ED visits in 2006). Asthma can cause significant morbidity. Every day in the United States, 44,000 people have an asthma exacerbation, 36,000 children miss school because of asthma, and 27,000 adults miss work because of asthma. Most asthma care is delivered by primary care physicians, with only 1 in 5 children seeking specialty care. Visits to primary care settings (physician offices and hospital outpatient departments) represent most health care use for persons with asthma.

Risk factors and triggers associated with childhood asthma have been identified. Although the most common trigger of wheezing in young children is viral respiratory tract infection, the strongest single predictor for wheezing continuing into asthma is atopy. A significant association exists between serum immunoglobulin E (IgE) level and the development and severity of asthma. The risk for asthma is increased by certain allergens, such as cockroach allergen among children with asthma in the inner city, and irritant exposures such as tobacco smoke. Although more than 100 candidate genetic loci have been identified based on epidemiologic linkage studies, the more consistent associations have been with the pro-allergic loci (interleukin-4 gene cluster on chromosome 5), chromosome 5q31 (bronchial hyperresponsiveness), chromosome 11q13 (high-affinity IgE receptors), and chromosome 14q (T-cell antigen receptor). Other studied genes include ADAM-33 (member of the metalloproteinase family), the gene for the prostanoid DP receptor, and receptor polymorphisms causing biologic variations in response to  $\beta$ -agonist medications.

Racial, ethnic, and socioeconomic disparities have been identified as factors relating to the burden of the disease. Blacks have higher rates of asthma ED visits (330% higher), hospitalizations (220% higher), and deaths (180% higher) than whites. The rate of asthma among Puerto Ricans is 113% higher than among non-Hispanic whites and 50% higher than among non-Hispanic blacks.

Many pediatricians and primary care physicians do not realize that childhood asthma can have fatal outcomes (2.3 asthma-related deaths per 1 million children; a total of 167 deaths in 2005). Of great concern is that many of these fatal outcomes occur in children viewed as having mild disease. Risk factors associated with death from asthma include the following:

1. History of sudden severe exacerbations
2. Prior admissions to an intensive care unit
3. Prior intubation for asthma
4. Two or more hospitalizations or 3 or more ED visits in a 12-month period
5. Use of more than 1 canister per month of inhaled short-acting  $\beta$ -agonist
6. Chronic use of oral corticosteroids
7. Difficulty perceiving airflow obstruction or its severity

## PATHOPHYSIOLOGIC FEATURES

The exact cause of childhood asthma is not known and is best understood as having derived from a complex gene-environment interaction. The combination of environmental exposures and genetic-biologic susceptibilities causes pathogenic changes in the airways. After asthma develops, ongoing exposures increase the risk for exacerbations.

Asthma is, therefore, often described as a lung disease characterized by 3 features.

1. *Airway obstruction* that is at least partially reversible by bronchodilator treatment
2. *Airway hyperreactivity or hyperresponsiveness* to a variety of external stimuli. This is considered a hallmark feature that correlates well with severity.
3. *Chronic inflammation* characterized by mast cell activation, inflammatory cell infiltration by eosinophils, and helper T-cell type 2 ( $T_H2$ ) lymphocytes and neutrophils (the latter is seen in sudden-onset fatal asthma exacerbations). These features result in anomalous tissue repair and airway remodeling.

The symptoms of asthma are caused by airflow obstruction resulting from the cumulative effects of smooth muscle constriction around airways; airway wall edema caused by increased vascular permeability; mucus hypersecretion and intraluminal mucus accumulation caused by goblet cell hyperplasia; inflammatory cell infiltration of the submucosa, causing disruption of the bronchial epithelium; and smooth muscle hypertrophy and basement membrane thickening secondary to type IV collagen deposition from increased fibroblast proliferation. This deposition may cause airway remodeling, which clinically exhibits as nonreversible obstructive lung disease. Many of these pathologic changes are reflected in the sputum, such as Charcot-Leyden crystals (eosinophil remnants), Curschmann spirals (airway lumen casts of exudate), and Creola bodies (clumps of sloughed epithelial cells). Children with fatal asthma usually exhibit marked pathologic changes in the segmental and subsegmental bronchi with involvement of the small airways down to, but usually sparing, the respiratory bronchioles. Multiple cytokines, including leukotrienes, and IgE antibodies, have been implicated in disease severity and progression, and impaired glutathione homeostasis, a biomarker of oxidant stress, has been associated with airway injury in severe asthma.

The most common triggers in childhood (Box 218-1) include viral respiratory infections, exercise, irritants such as tobacco smoke, indoor and outdoor allergens, and a change in the weather, particularly cold air. Stress and emotional expression such as laughter and anger have been associated as triggers as well. In the presence of symptoms that seem to be worse at night or with reclining posture, the pediatrician may consider the possibility of sinusitis or gastroesophageal reflux as contributory comorbid clinical conditions. However, it should be noted that a recent multicentered trial demonstrated that adding prescription acid controllers to standard inhaled steroid treatment does not improve asthma symptoms or control in children with undetected or "silent" gastroesophageal reflux.

An allergic asthma exacerbation is biphasic, with an early phase or immediate response occurring within

**BOX 218-1 Factors That Exacerbate Asthma**

- Viral respiratory tract infections
- Environmental allergens in sensitized individuals
  - Outdoor allergens (eg, seasonal allergens such as tree pollen, grass pollen, weed pollen, molds)
  - Indoor allergens (eg, animal dander, dust mites, cockroach, indoor molds, mouse)
- Irritants
  - Environmental tobacco smoke
  - Air pollutants (eg, ozone, sulfur dioxide)
  - Particulate matter (eg, wood or coal burning smoke)
  - Mycotoxins
  - Endotoxin
  - Dust
  - Strong odors or fumes (eg, perfumes, hair sprays, cleaning agents, incense sticks, scented candles)
- Occupational exposure (eg, farm and barn exposure, formaldehyde, cedar, paint fumes, others)
- Cold, dry air
- Exercise
- Emotions: crying, laughter, hyperventilation
- Comorbid conditions (eg, rhinitis, sinusitis, gastroesophageal reflux, nasal polyps)

minutes of trigger exposure characterized by bronchospasm and bronchoconstriction. This episode is followed physiologically by an immediate drop in forced expiratory volume in 1 second (FEV<sub>1</sub>), which returns to normal within a few hours after exposure. A second, more severe drop (late-phase inflammatory) occurs later, approximately 6 to 24 hours after exposure to the trigger. The initial reaction tends to respond well to inhaled bronchodilator agents, whereas the late bronchoconstriction responds less well to inhaled  $\beta$ -agonists and requires the use of corticosteroids. Corticosteroids are, therefore, given early during a severe asthma exacerbation to avoid or mitigate the second-stage relapse.

Within minutes of an exposure to a trigger, IgE molecules on the surface of mast cells bind the inciting allergen, leading to mast cell degranulation and release of mediators, including histamine, prostaglandin D<sub>2</sub> (PGD<sub>2</sub>), and cysteinyl leukotrienes (LTC<sub>4</sub>, D<sub>4</sub>, and E<sub>4</sub>). These mediators cause airway smooth muscle contraction and stimulation of reflex neural pathways that are largely reversible by  $\beta$ -agonist administration. Within hours of the initial trigger, the late-phase response occurs triggered by the influx of inflammatory and immune cells, particularly the eosinophils, basophils, neutrophils, helper T cells, and dendritic cells. The mast cells and eosinophils are key players in the inflammatory cascade. In addition to producing bronchoconstricting mediators, mast cells also store and release tumor necrosis factor- $\alpha$ , which is important in the recruitment and activation of inflammatory cells and in modifying the function and growth of airway smooth muscle. Eosinophils release tissue-damaging

enzymes and proteins such as major basic protein, eosinophil cationic protein, eosinophil-derived neurotoxin, and eosinophil peroxidase.

The T-cell lymphocyte population in the asthmatic airway is characterized by the T<sub>H</sub>2 of lymphocytes that generates a specific panel of cytokines, including IL-3, IL-4, IL-5, IL-13, and granulocyte-macrophage colony-stimulating factor (GM-CSF) when stimulated with antigen. The T<sub>H</sub>2 lymphocytes also express the chemokine receptors (CCR4 and CCR8) and the chemoattractant receptor like molecule (CRTH2), a receptor for PGD<sub>2</sub>, suggesting potential signaling and interactions between the mast cell, eosinophils, and T<sub>H</sub>2 cells that promulgate airway inflammation. Basophils, in addition to producing histamine and leukotrienes, are potent producers of IL-4 and IL-13 cytokines, exceeding levels produced by T cells. The innate immune system (dendritic cells, neutrophils, toll-like receptors) also is postulated to play an important role in the development of allergic airway inflammation.

Another important pathway in the pathophysiologic features of allergic asthma is the arachidonic acid pathway, which is responsible for the production of prostaglandins by cyclooxygenase or leukotrienes through the 5-lipoxygenase pathway. Mast cells and eosinophils synthesize significant amounts of LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub>. Cysteinyl leukotrienes are responsible for significant bronchoconstriction 100 to 1,000 times greater than histamine and contribute to increased mucus secretion, decreased mucus clearance, eosinophil infiltration, and eosinophil activation.

**DIAGNOSING ASTHMA IN CHILDREN**

The most common symptoms that arouse a suspicion of asthma are intermittent and repetitive episodes of cough and noisy breathing or wheezing triggered by respiratory infections, allergen or irritant exposure, exercise, or play, with symptoms often awakening the child at night. Older children may report shortness of breath and chest tightness, particularly associated with physical activity. Nonspecific symptoms may include self-imposed limitation of physical activities, general fatigue, and difficulty keeping up with peers. Recurrent “croup” in an older child or frequent “clinical pneumonias” or “bronchitis” may also alert the pediatrician to consider evaluating for possible asthma. To make the diagnosis of asthma, the pediatrician must determine the following:

1. The child has recurrent episodic symptoms of airway obstruction, such as cough, wheezing, shortness of breath, or chest tightness.
2. Airway flow obstruction or airflow limitation is at least partially reversible by administration of a bronchodilator. In older children and adults, spirometry before and after bronchodilator use can serve as an ambulatory test to delineate bronchial hyperresponsiveness. In a younger child, a positive clinical response to an inhaled  $\beta$ -agonist may be useful to determine partial reversibility.
3. Alternative diagnoses are excluded.

Noninvasive, bedside demonstration of airway inflammation, as with exhaled nitric oxide testing recently approved by the US Food and Drug Administration

(FDA), may provide additional supplementary information regarding the diagnosis and severity of asthma.

A detailed medical history is the first step in establishing the diagnosis. The history should focus on the nature and frequency of symptoms, response to medications, precipitating factors, and concomitant atopic features, if any. The physical examination should focus on the upper respiratory tract, chest, and skin. Signs of allergic disease, such as eczematous skin, erythematous conjunctiva with cobblestoning, allergic shiners, Denny Morgan lines, allergic salute, allergic nasal crease, pale boggy turbinates, rhinorrhea, and polyps, should be noted. A transverse nasal crease and features of atopy are tell-tale signs of allergic diathesis. Nasal polyps in a younger child may raise the suspicion of cystic fibrosis. The chest examination may be unremarkable in children with asthma, although dyspnea with speech and with exertion, characterization of breath sounds, and measurement of the inspiration-to-expiration ratio may be of value.

Unfortunately, the diagnosis of asthma in a child is often delayed or the severity underestimated. Underdiagnosis is frequent in children because pediatricians commonly use labels such as reactive airway disease, recurrent bronchitis, or wheezy bronchitis for asthma. Use of this terminology is not advisable and may hinder appropriate diagnosis and therapy. Symptoms and signs that are not consistent with asthma, including failure to thrive, cyanosis, and clubbing, should alert the pediatrician to alternative diagnoses such as ciliary dyskinesia or cystic fibrosis. Chronic cough alone may also be a manifestation of asthma, especially in young children, leading to the term *cough-variant asthma*. The diagnosis of cough-variant asthma may be made by monitoring peak expiratory flow or methacholine inhalation challenge if applicable, to clarify whether there is bronchial hyperresponsiveness consistent with asthma. Use of bronchodilators on a trial basis may be helpful to demonstrate reversibility of the bronchospasm and improvement in symptoms. If there is clinical improvement, then treatment should follow the stepwise approach to long-term management of asthma. However, cough-variant asthma is as often overdiagnosed as it is underdiagnosed; therefore, an alternate diagnosis (eg, allergic rhinitis or chronic sinusitis with postnasal drainage, infectious causes such as pertussis, and psychogenic or habit cough) should be sought if symptoms do not respond to traditional asthma therapies.

### Laboratory Evaluation

Current national and international guidelines recommend evaluation for potential inhalant allergen triggers, particularly in those with persistent asthma. Assessment of sensitivity to environmental allergens using in vivo (skin testing) or in vitro (specific IgE) methods followed by clinical correlation may help identify allergic predisposition and triggers and suitability to receive targeted therapies. Sputum and nasal eosinophil evaluation is not commonly performed in children. A baseline chest radiograph may help exclude other conditions that mimic asthma, such as foreign body aspiration or vascular ring, but routine and repetitive chest radiographs during asthma exacerbations are not

recommended. White cell count and differential and quantitative immunoglobulins and sweat chloride when indicated may be of value to rule out immune dysregulation and cystic fibrosis, respectively.

### Pulmonary Function Testing

Assessment of spirometric measures of airflow and lung volumes during forced expiratory maneuvers is strongly recommended as standard of care for asthma diagnosis and monitoring. Prebronchodilator and postbronchodilator spirometry, particularly in children who are poor perceivers of airflow, is strongly recommended to confirm the diagnosis and classify disease severity and to provide insight into the pathophysiologic processes. Spirometry should be performed on any child 5 years of age or older who is capable of performing this test. Objective measures of lung function enable the pediatrician to do the following:

1. Diagnose airflow obstruction, as well as reversibility.
2. Monitor changes over time, including daily variations.
3. Manage exacerbations, including those resulting in severe airway obstruction.

Spirometry is generally preferred to peak flow monitoring for the diagnosis of asthma because peak flow measurements primarily assess large airway function, require establishment of individual baseline values to facilitate meaningful interpretation, and are effort-dependent maneuvers. Spirometry should be performed by trained personnel before a child inhales a short-acting bronchodilator and again 15 to 20 minutes afterward.

This test helps determine the presence and degree of airflow obstruction of large and small airways and whether the airflow obstruction is reversible. The key measurements assessed are the forced vital capacity (FVC), FEV<sub>1</sub>, forced midexpiratory flow rate (FEF<sub>25-75</sub>), and an examination of the flow volume loop. Reproducible spirometric measurements (FEV<sub>1</sub> values within 5% on 3 attempts) are an indicator of test validity. A baseline spirometry should also be performed once a year during follow-up evaluations. In an asthmatic child, airway obstruction results in reduced airflow with forced exhalation and smaller midexpiratory air flow rates. The FEV<sub>1</sub> should be adjusted for the hyperinflation typically seen in asthma and, in general, an FEV<sub>1</sub>/FVC ratio of less than 85% predicted is indicative of the presence of airflow obstruction. Low FEV<sub>1</sub>, as a percentage of predicted norms, is one of the criteria used to assign severity in asthma. Because other conditions can cause airflow obstruction, demonstration of the presence of an improvement in FEV<sub>1</sub> of more than 12% and more than 200 mL from baseline and 10% or greater of predicted FEV<sub>1</sub> after inhaled bronchodilator use is considered evidence of reversibility consistent with asthma. It should be noted that children with asthma have been reported to have much better baseline lung function compared to adults with asthma; therefore, the spirometry can occasionally be normal in a clinical scenario suggestive of asthma. Recent observations questioned the degree of improvement that signifies the presence of reversible airway hyperresponsiveness in children with asthma,



with studies suggesting poor sensitivity associated with the commonly used 12% cutoff in children with asthma compared with adults. Lesser amounts of reversibility may be indicative of airway hyperresponsiveness in children with asthma because there is so much variability of this test in children.

Provocative testing used to demonstrate bronchial hyperresponsiveness, such as exercise challenges, methacholine, cold air, and most recently, mannitol challenges, is performed only when the determination of asthma is difficult despite routine evaluation.

Assessment of exhaled nitric oxide, a measure of airway inflammation in allergic asthma, is gaining support as a tool in aiding the management of asthma.

Peak flow meters are inexpensive home-use devices that lack the sensitivity for diagnostic use, and reference values vary widely and according to the brand. Peak flow zones are established after the child has the opportunity to monitor daily (or twice daily) for 2 weeks or more to establish his personal best. Peak flow monitoring at home can, however, be useful because it can help determine whether airway narrowing is occurring before children become symptomatic; additionally, it can help the pediatrician to do the following:

1. Monitor the effect of medication addition or withdrawal.
2. Determine when to seek help.
3. Determine the effect of triggers.
4. Determine changes in lung function.

## DIFFERENTIAL DIAGNOSIS

A common medical school teaching is that “all that wheezes is not asthma.” Common asthma imposters such as gastroesophageal reflux and sinusitis can be challenging to diagnose in children. Masqueraders of asthma can be approached anatomically as upper respiratory conditions, including allergic or chronic rhinosinusitis and tonsillar or adenoidal hypertrophy; middle respiratory tract conditions, including foreign body aspiration, vocal cord dysfunction, airway lesions such as airway stenosis, tracheal webs or tracheobronchomalacia, vascular rings, mediastinal masses, and vocal cord dysfunction or paralysis; or lower respiratory tract conditions, such as viral bronchiolitis, bronchiectasis, immotile cilia syndrome, hypersensitivity pneumonitis, interstitial pneumonias, bronchopulmonary aspergillosis, pulmonary edema, pulmonary eosinophilic disorders, cystic fibrosis, pneumonia, tuberculosis, and adverse effects of medications such as angiotensin-converting enzyme inhibitors. It is important to note that many of these latter conditions may coexist with and exacerbate the severity of asthma.

## RISK FACTORS FOR ASTHMA

Hypotheses to explain the increased frequency of asthma include improved hygiene (“hygiene hypothesis”), increased indoor air pollution, greater frequency of early-onset respiratory viral infections, enhanced host susceptibility, and improved awareness and recognition of asthma. In most children with asthma, the onset of symptoms occurs before 5 years of age.

However, of all the preschoolers who wheeze (50%), only a minority (20%) continue to have persistence of asthma in late childhood. Risk factors predicting the persistence of asthma have been identified based on studies of birth cohorts. A popular index used frequently is the modified asthma predictive index, which includes major criteria, such as parental history of asthma, atopic dermatitis, and inhalant allergen sensitization, and minor criteria, such as allergic rhinitis, wheezing apart from colds, eosinophilia at or above 4%, and food allergen sensitization. Symptom-based phenotypes of asthma classify wheezing into 2 main types—episodic (viral) wheeze (wheezing during discrete time periods only, usually associated with common viral respiratory tract infections) and multitrigger wheeze (wheezing during discrete exacerbations and between episodes; triggers include viruses, allergens, exercise, and environmental irritants and pollutants).

## CLASSIFYING ASTHMA SEVERITY AND CONTROL IN CHILDREN

The National Asthma Education and Prevention Program Expert Panel Report 3 (EPR3) was published in the latter part of 2007. A key component of the new guidelines emphasizes asthma control in addition to asthma severity.

Severity is the intrinsic intensity of the disease and is emphasized for initiating therapy. The 2 general categories are “intermittent” and “persistent” asthma, with the latter further subdivided into mild, moderate, and severe. Asthma severity is best assessed during a child’s initial evaluation and when the child is not using a controller medication. When classifying asthma severity into 1 of the 4 classifications, the presence of a single feature is sufficient to categorize the child in the most severe applicable category. Asthma control represents the degree to which manifestations of asthma are minimized and the goals of therapy are met, and should be used as a guide to either maintain or adjust therapy. Responsiveness refers to the ease with which prescribed therapy achieves asthma control.

Attainment of optimal asthma control necessitates monitoring control in multiple domains and adjusting therapy. Asthma control is classified into 3 categories—well controlled, not well controlled, and very poorly controlled. The degree of control can change over time; thus, constant review of symptoms and treatment every 1 to 6 months is helpful. Apart from the assessment of severity and control, the predisposition to risk for exacerbations should also be kept in mind. For instance, a child with intermittent asthma may not need daily controller medication based on the initial assessment of severity, but the child may still have an unexpectedly severe exacerbation triggered by, for example, a viral infection. This would not necessitate the child requiring regular controller medication, but might necessitate rapid escalation of therapy or addition of a controller medication during the high-risk season. Therefore, children with intermittent asthma who are experiencing severe exacerbations requiring hospitalization or intensive care may require further evaluation and referral to an asthma specialist.



## ASTHMA MANAGEMENT STRATEGIES

### Goals of Asthma Therapy

The goals of asthma therapy may be categorized into 2 domains—reduction in impairment and reduction of risk.

Impairment refers to the intensity and frequency of asthma symptoms and the degree to which the child is limited by the symptoms. Specific goals for reducing impairment include the following:

- Freedom from frequent or troublesome symptoms of asthma, especially including those that disturb sleep
- Minimal need (<2 times a week) for inhaled short-acting  $\beta$ -agonists (SABAs) to relieve symptoms
- Optimization of lung function
- Maintenance of normal daily activities, including work, school, participation in athletics, and physical activity
- Satisfaction with the asthma care on the part of the patient and family

Risk pertains to adverse outcomes associated with asthma and its treatment. Specific goals for reducing risk include the following:

- Prevention of recurrent exacerbations and need for ED visit or hospital care
- Prevention of reduced lung growth and loss of lung function
- Optimization of pharmacotherapy with minimal or no adverse effects

Appropriate asthma management includes 4 components of care.

1. Regular assessment and monitoring
2. Patient education and partnership
3. Control of aggravating factors
4. Pharmacotherapy

### Component 1: Regular Assessment and Monitoring

Assessment of asthma control should not be based solely on individual single measurements and limited interactions, but rather on a combination of multiple parameters, including FEV<sub>1</sub>, peak expiratory flow, daily symptom scores,  $\beta_2$ -agonist use, nocturnal symptoms, and activity limitations. Several recommended standardized questionnaires to assess asthma control include the Asthma Therapy Assessment Questionnaire, the Asthma Control Questionnaire, the Asthma Control Test, and the asthma control score. Key elements captured are the child's recall of symptoms, physical activity, quality of life, need for rescue medications in the past 2 to 4 weeks, and pulmonary function. Objective measurements of lung function include spirometry and peak flow monitoring. The EPR3 guidelines have criteria for 3 age groups—0 to 4 years, 5 to 11 years, and 12 years and older—for the evaluation of both severity (Tables 218-1 and 218-2) and control (Tables 218-3 and 218-4).

The parameters related to assessing asthma control should be checked at every visit. Although, typically, most medical visits for asthma are for urgent care, effective asthma management requires a proactive, preventative approach because it is a chronic disease. Therefore, follow-up visits are recommended every 2 to 6 weeks until good asthma control is achieved and

then 2 to 4 times per year, depending on the attainment of control. Domains assessed at each visit should include the following: signs and symptoms, pulmonary function, quality of life, exacerbations, adherence to treatment, medication side effects, and patient satisfaction with care.

### Component 2: Patient Education and Partnership

Patient education should be geared to empowering children with self-management skills. The children and families should be taught basic facts about asthma, preferably using visual props such as models and colored pictures. Topics should include the following:

- Differences between normal and asthmatic airway
- The link between airway inflammation, hyperreactivity, and bronchoconstriction
- Identification and abatement of triggers
- Role and mechanism of action of long-term controller and quick reliever medications (preferably using patients' own inhalers, demonstration devices, or color pictures)
- Instructions on daily and step-up medication regimens in the form of written asthma action plans
- Practical instructions on being aware of the amount of doses left in the inhaler, correct technique of inhaler use along with spacer, and reinforcement on need to take the daily medication even when the child is asymptomatic

Individualized goals and priorities of asthma management should be set in partnership with the child and family (Box 218-2). Provide an asthma action plan with written instructions for daily management, as

### BOX 218-2 Checklist of Asthma Management Strategies

- Set individualized goals of asthma management.
- Provide effective education that includes
  - Basic facts about asthma
  - Differences between normal and asthmatic airway, preferably using models
  - Links between airways inflammation, hyperreactivity, and bronchoconstriction
  - Long-term controller and quick reliever medications (preferably using patient's inhalers or color pictures)
- Teach, demonstrate, and have patient show proper technique for
  - Inhaled medication use (spacer use with MDI)
  - Peak flow meter (optional)
- Tailor therapy to severity and patient preference.
- Proactively seek out and address concerns about potential adverse effects of medications.
- Explore and manage asthma triggers.
  - Environmental exposures
  - Comorbid conditions
- Provide asthma action plan.
  - Involve patient and family.
  - Also provide asthma plan for school.

Table 218-1 Classifying Asthma Severity and Initiating Therapy in Children

PERSISTENT												
INTERMITTENT					MODERATE					SEVERE		
COMPOONENTS OF SEVERITY					AGES		AGES		AGES		AGES	
					0-4		5-11		0-4		5-11	
Impairment	Symptoms	≤2 days/week		>2 days/week but not daily		Daily		Throughout the day				
	Nighttime awakenings	0	≤2x/month	1-2x/month	3-4x/month	3-4x/month	>1x/week but not nightly	>1x/week	Often 7x/week			
	Short-acting β <sub>2</sub> -agonist use for symptom control	≤2 days/week		>2 days/week but not daily		Daily		Several times per day				
	Interference with normal activity	None		Minor limitation		Some limitation		Extremely limited				
	Lung Function	N/A	Normal FEV <sub>1</sub> between exacerbations >80%		N/A	>80%	N/A	60-80%	N/A	<60%		
Risk	• FEV <sub>1</sub> (predicted) or peak flow (personal best)	>85%		>80%		75-80%		<75%				
	• FEV <sub>1</sub> /FVC											
	Exacerbations requiring oral systemic corticosteroids (consider severity and interval since last exacerbation)	0-1/year (see notes)		≥2 exacerbations in 6 months requiring oral systemic corticosteroids, or ≥4 wheezing episodes/1 year lasting >1 day AND risk factors for persistent asthma		≥2x/year (see notes) Relative annual risk may be related to FEV <sub>1</sub>						

**Table 218-1** Classifying Asthma Severity and Initiating Therapy in Children—cont'd

		PERSISTENT							
		INTERMITTENT		MILD		MODERATE		SEVERE	
		AGES 0-4	AGES 5-11	AGES 0-4	AGES 5-11	AGES 0-4	AGES 5-11	AGES 0-4	AGES 5-11
COMPONENTS OF SEVERITY		Step 1 (for both age groups)	Step 2 (for both age groups)	Step 2 (for both age groups)	Step 3: medium-dose ICS option and consider short course of oral systemic corticosteroids	Step 3 and consider short course of oral systemic corticosteroids	Step 3 and consider short course of oral systemic corticosteroids	Step 3 and consider short course of oral systemic corticosteroids	Step 3: medium-dose ICS option OR step 4 and consider short course of oral systemic corticosteroids
Recommended Step for Initiating Therapy (See Table 218-5 for treatment steps. <sup>a</sup> )		In 2–6 weeks, depending on severity, evaluate level of asthma control that is achieved. <ul style="list-style-type: none"> <li>Children 0–4 years old: If no clear benefit is observed in 4–6 weeks, stop treatment and consider alternative diagnoses or adjusting therapy.</li> <li>Children 5–11 years old: Adjust therapy accordingly.</li> </ul>							

FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids; ICU, intensive care unit; N/A, not applicable.

<sup>a</sup>The Stepwise Approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.

- Level of severity is determined by both impairment and risk. Assess impairment domain by caregiver's recall of previous 2–4 weeks. Assign severity to the most severe category in which any feature occurs.
- Frequency and severity of exacerbations may fluctuate over time for patients in any severity category. At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and severe exacerbations (eg, requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients with  $\geq 2$  exacerbations described above may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

Adapted from National Heart, Lung, and Blood Institute. *National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. US Department of Health and Human Services; 2007.

**Table 218-2** Classifying Asthma Severity and Initiating Treatment in Youths 12 Years of Age and Adults

Assessing severity and initiating treatment for patients who are not currently taking long-term control medications

**CLASSIFICATION OF ASTHMA SEVERITY  $\geq$  12 YEARS OF AGE****PERSISTENT**

<b>COMPONENTS OF SEVERITY</b>			<b>INTERMITTENT</b>	<b>MILD</b>	<b>MODERATE</b>	<b>SEVERE</b>
<b>Impairment</b> Normal FEV <sub>1</sub> /FVC: 8–19 yr 85% 20–39 yr 80% 40–59 yr 75% 60–80 yr 70%	Symptoms		$\leq 2$ days/week	$> 2$ days/week but not daily	Daily	Throughout the day
	Nighttime awakenings		$\leq 2$ x/month	3–4x/month	$> 1$ x/week but not nightly	Often 7x/week
	Short-acting $\beta_2$ -agonist use for symptom control (not prevention of EIB)		$\leq 2$ days/week	$> 2$ days/week but not daily, and not more than 1x on any day	Daily	Several times per day
	Interference with normal activity		None	Minor limitation	Some limitation	Extremely limited
<b>Risk</b>	Lung Function		<ul style="list-style-type: none"> <li>Normal FEV<sub>1</sub> between exacerbations</li> <li>FEV<sub>1</sub> <math>&gt; 80\%</math> predicted</li> <li>FEV<sub>1</sub>/FVC normal</li> </ul>	<ul style="list-style-type: none"> <li>FEV<sub>1</sub> <math>&gt; 80\%</math> predicted</li> <li>FEV<sub>1</sub>/FVC normal</li> </ul>	<ul style="list-style-type: none"> <li>FEV<sub>1</sub> <math>&gt; 60\%</math> but <math>&lt; 80\%</math> predicted</li> <li>FEV<sub>1</sub>/FVC reduced 5%</li> </ul>	<ul style="list-style-type: none"> <li>FEV<sub>1</sub> <math>&lt; 60\%</math> predicted</li> <li>FEV<sub>1</sub>/FVC reduced <math>&gt; 5\%</math></li> </ul>
	Exacerbations requiring oral systemic corticosteroids		0–1/year (see note)	$\geq 2$ /year (see note)		
<b>Recommended step for initiating treatment</b> (See Table 218-6 for treatment steps.)			Step 1	Step 2	Step 3	Step 4 or 5
			In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

EIB, exercise-induced bronchospasm; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit.

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
  - Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
  - At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (eg, requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had  $\geq 2$  exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.
- Adapted from National Heart, Lung, and Blood Institute. *National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. US Department of Health and Human Services; 2007.



Table 218-3

## Assessing Asthma Control and Adjusting Therapy in Children

		WELL CONTROLLED		NOT WELL CONTROLLED		VERY POORLY CONTROLLED	
COMPONENTS OF CONTROL		AGES 0–4	AGES 5–11	AGES 0–4	AGES 5–11	AGES 0–4	AGES 5–11
<b>Impairment</b>	Symptoms	≤2 days/week but not more than once on each day		>2 days/week or multiple times on ≤2 days/week		Throughout the day	
	Nighttime awakenings	≤1x/month		>1x/month		>1x/week	
	Interference with normal activity	None		Some limitation		Extremely limited	
	Short-acting $\beta_2$ -agonist use for symptom control (not prevention of EIB)	≤2 days/week		>2 days/week		Several times per day	
	Lung Function • FEV <sub>1</sub> (predicted) or peak flow personal best • FEV <sub>1</sub> /FVC	N/A		N/A		N/A	
<b>Risk</b>	Exacerbations requiring oral systemic corticosteroids	0–1x/year		2–3x/year		>3x/year	
	Reduction in lung growth	N/A		N/A		N/A	
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.					

Continued

Table 218-3 Assessing Asthma Control and Adjusting Therapy in Children—cont'd

	WELL CONTROLLED		NOT WELL CONTROLLED		VERY POORLY CONTROLLED	
	AGES 0–4	AGES 5–11	AGES 0–4	AGES 5–11	AGES 0–4	AGES 5–11
<b>Recommended action for treatment</b> (See Table 218-5 for treatment steps.) <b>The stepwise approach is meant to assist, not replace, clinical decisionmaking required to meet individual patient needs.</b>	<ul style="list-style-type: none"><li>• Maintain current step.</li><li>• Regular follow-up every 1–6 months.</li><li>• Consider step down if well controlled for at least 3 months.</li></ul>		Step up 1 step	Step up at least 1 step	<ul style="list-style-type: none"><li>• Consider short course of oral systemic corticosteroids</li><li>• Step up 1–2 steps</li></ul>	
	<ul style="list-style-type: none"><li>• <b>Before step up:</b> Review adherence to medication, Inhaler technique, and environmental control. If alternative treatment was used, discontinue it and use preferred treatment for that step.</li><li>• <b>Re-evaluate the level of asthma control in 2–6 weeks to achieve control; every 1–6 months to maintain control.</b> Children 0–4 years old: If no clear benefit is observed in 4–6 weeks, consider alternative diagnoses or adjusting therapy, Children 5–11 years old: Adjust therapy accordingly.</li><li>• <b>For side effects,</b> consider alternative treatment options.</li></ul>					

EIB, exercise-induced bronchospasm; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit; N/A, not applicable.

- The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient's or caregiver's recall of previous 2–4 weeks. Symptom assessment for longer periods should reflect a global assessment, such as whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (eg, requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control.

Adapted from National Heart, Lung, and Blood Institute. *National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. US Department of Health and Human Services; 2007.

**Table 218-4** Assessing Asthma Control and Adjusting Therapy in Youths  $\geq 12$  Years of Age and Adults

CLASSIFICATION OF ASTHMA CONTROL (≥12 YEARS OF AGE)				
COMPONENTS OF CONTROL		WELL CONTROLLED	NOT WELL CONTROLLED	VERY POORLY CONTROLLED
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤2x/month	1–3x/week	≥4x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting β <sub>2</sub> -agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	FEV <sub>1</sub> or peak flow	>80% predicted/ personal best	60%–80% predicted/ personal best	<60% predicted/ personal best
	Validated questionnaires ATAQ ACQ ACT	0 ≤0.75* ≥20	1–2 ≥1.5 16–49	3–4 N/A ≤15
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2/year (see note)	
		Consider severity and interval since last exacerbation		
	Progressive loss of lung function	Evaluation requires long-term follow-up care.		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of Intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended action for treatment (See Table 218-6 for treatment steps.)		<ul style="list-style-type: none"><li>• Maintain current step.</li><li>• Regular followup at every 1–6 months to maintain control.</li><li>• Consider step down If well controlled for at least 3 months.</li></ul>	<ul style="list-style-type: none"><li>• Step up 1 step.</li><li>• Re-evaluate in 2–6 weeks.</li><li>• For side effects, consider alternative treatment options.</li></ul>	<ul style="list-style-type: none"><li>• Consider short course of oral systemic corticosteroids.</li><li>• Step up 1–2 steps.</li><li>• Re-evaluate in 2 weeks.</li><li>• For side effects, consider alternative treatment options.</li></ul>

\*ACQ values of 0.76–1.4 are indeterminate regarding well-controlled asthma.  
EIB, exercise-induced bronchospasm; ICU, intensive care unit.

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient's recall of previous 2–4 weeks and by spirometry or peak flow measures. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (eg, requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had  $\geq 2$  exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.

ATAQ = Asthma Therapy Assessment Questionnaire

ACQ = Asthma Control Questionnaire

ACT = Asthma Control Test

Minimal Important Difference: 1.0 for the ATAQ; 0.5 for the ACQ; not determined for the ACT.

#### Before step up in therapy:

- Review adherence to medication, inhaler technique, environmental control, and comorbid conditions.
- If an alternative treatment option was used in a step, discontinue and use the preferred treatment for that step.

Adapted from National Heart, Lung, and Blood Institute. *National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. US Department of Health and Human Services; 2007.

well as a plan for asthma exacerbations. While formulating the plan, proactively seek out and address concerns about potential adverse effects of medications. The therapy should be kept as simple as possible by limiting the number of medications and doses. If children cannot adhere to a medication regimen, investigate the reasons for their nonadherence. The child and caretaker should be encouraged to demonstrate proper technique for inhaled medication use (eg, spacer use with metered dose inhaler [MDI]) and peak flow meter (optional).

The correct asthma medication regimen and administration technique should be reinforced and evaluated. The pediatrician should establish patient priorities on an individual basis and enlist family and peer support to ensure the asthma action plan is implemented. Physical activity should be encouraged by using the appropriate medications to prevent exercise-induced symptoms and by allowing students to carry and administer medication (such as SABAs) at school with parent and physician approval. Physicians should ensure that teachers and school personnel understand the plan for each child with asthma. Families, teachers, and pediatricians should be concerned if  $\beta$ -agonist use is greater than 1 MDI canister per month, if controller medication refills are occurring one-half as often as prescribed, or if the child complains that  $\beta$ -agonists do not seem to help as much as they used to.

It is important to remember that adherence to asthma medication regimens tends to be suboptimal, with reported rates of nonadherence ranging from 30% to 70%. Factors affecting adherence include medication-related factors, patient variables, and physician factors. Medication characteristics such as taste, dosing schedule, difficulties with devices, side effects, and expense are critical. Patient variables such as health beliefs, misperception of disease severity, misunderstanding instructions, fear of side effects, dissatisfaction with health care professionals, forgetfulness, and complacency can affect the management of disease. Physician factors such as poor communication, failure to monitor patients regularly, and incorrect medication and dosage need to be addressed. One critical step to improve adherence is to promote open communication and establish the goals of therapy in collaboration with the child. The pediatrician should be friendly and attentive. All attempts should be made to identify reasons for nonadherence, address concerns, and allay fears. The child should be encouraged and praised for successes. The regimen should be simplified, and children should be educated in an interactive manner at their level of understanding.

### Component 3: Control of Aggravating Factors

Modifiable factors that worsen asthma include both environmental exposures (infectious, allergic, and irritant) and comorbid conditions (Box 218-1). See the earlier section, Pathophysiologic Features, for the most common types of triggers in childhood. Because most children with asthma have an allergic component to their disease, measures to explore and mitigate environmental exposures, when possible, are recommended.

Reliable and patient-friendly educational handouts may be found at some of the sources listed in Tools for Practice at the end of this chapter. It should be noted that, in children with uncontrolled asthma and no overt symptoms of gastroesophageal reflux, treatment with proton pump inhibitors does not help.

### Component 4: Pharmacotherapy

A stepwise approach to asthma pharmacotherapy focuses on minimizing impairment and risk with the goals of relieving obstruction and treating underlying inflammation. The initial therapy is chosen based on degree of asthma severity, and subsequent adjustments are made based on assessment of control and responsiveness to therapy. The key objective of this approach is to distinguish those with persistent asthma requiring daily anti-inflammatory medication from those with intermittent asthma that can be managed with SABA rescue medication as needed. The type and amount of controller medications required are determined by the degree of severity and control. The National Heart, Lung, and Blood Institute (NHLBI) guidelines elegantly lay out the stepwise approach (steps 1–6) to asthma management based on initial assessment of asthma severity and age of the child (<4 years, 5–11 years, and >12 years). Tables 218-5 and 218-6 serve to outline their approach and serve as a ready reference.

Asthma medications are defined and categorized in 2 ways—*relief medication* for quick relief of acute symptoms and exacerbations, and *controller medication* for long-term control of the underlying pathophysiologic mechanism of asthma. Quick-relief medications include SABAs, systemic corticosteroids, and anticholinergic agents. Long-term controller medications include inhaled corticosteroids (ICS), combination ICS and long-acting  $\beta$ -agonists (ICS-LABA), leukotriene receptor antagonists (LTRA), and others that are less commonly used, such as theophylline, cromolyn, and other steroid-sparing medications.

The preferred therapy for children with persistent asthma is daily ICSs, either as monotherapy or in combination with adjunctive therapy. Alternative medications for mild persistent asthma (step 2 therapy) include LTRA (montelukast) and, rarely, cromolyn and theophylline (for older children). For children younger than 4 years with moderate to severe persistent asthma, medium-dose ICS therapy is recommended. Combination therapy of medium-dose ICS-LABA is recommended only for step 4 or higher levels of uncontrolled asthma. Combinations of medium-dose ICS with LTRA may also be considered for step 4 or higher treatment. Options for children with severe persistent asthma (steps 5 and 6) include ICS-LABA combinations, long-term oral steroids, and omalizumab if they are older than 12 years of age. Allergen immunotherapy may be considered for children older than 5 years of age requiring steps 2–4 care.

When control is achieved and sustained for 3 months or more, stepping down to minimum required dose to maintain control is recommended. If control is not attained, the therapy may be increased by 1 step if not well controlled, or by 2 steps if asthma is very poorly controlled, with close monitoring.



**Table 218-5** Stepwise Approach for Managing Asthma Long Term in Children, 0–4 Years of Age and 5–11 Years of Age**CHILDREN 0–4 YEARS OF AGE**

Step down if possible (and asthma is well controlled at least 3 months)		Assess control		Step up if needed (first check inhaler technique, adherence, environmental control, and comorbid conditions)			
Intermittent Asthma		Persistent Asthma: Daily Medication					
		Consult with asthma specialist if step 3 care or higher is required. Consider consultation at step 2.					
		STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6
Preferred		SABA PRN	Low-dose ICS	Medium-dose ICS	Medium-dose ICS + LABA or Montelukast	High-dose ICS + LABA or Montelukast	High-dose ICS + LABA or Montelukast + Oral corticosteroids ICS
Alternative			Cromolyn or Montelukast				
Quick-Relief Medication		<b>Each Step: Patient Education and Environmental Control</b> <ul style="list-style-type: none"><li>SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms.</li><li>With viral respiratory symptoms: SABA q 4–6 hours up 24 hours (longer with physician consult). Consider short course of oral systemic corticosteroids if exacerbation is severe or patient has history of previous severe exacerbation</li></ul> Caution: Frequent use of SABA may indicate the need to step up treatment.					

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- If an alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- If clear benefit is not observed within 4–6 weeks, and patient's/family's medication technique and adherence are satisfactory, consider adjusting therapy or an alternative diagnosis.
- Studies on children 0–4 years of age are limited. Step 2 preferred therapy is based on Evidence A. All other recommendations are based on expert opinion and extrapolation from studies in older children.
- Clinicians who administer immunotherapy should be prepared and equipped to identify and treat anaphylaxis that may occur.

**Alphabetical listing is used when more than one treatment option is listed within either preferred or alternative therapy.** ICS, inhaled corticosteroid; LABA, inhaled long-acting  $\beta_2$ -agonist; LTRA, leukotriene receptor antagonist; oral corticosteroids, oral systemic corticosteroids; SABA, inhaled short-acting  $\beta_2$ -agonist.

Continued

**Table 218-5** Stepwise Approach for Managing Asthma Long Term in Children, 0–4 Years of Age and 5–11 Years of Age—cont'd**CHILDREN 5–11 YEARS OF AGE**

Step down if possible (and asthma is well controlled at least 3 months)		Assess control		Step up if needed (first check inhaler technique, adherence, environmental control, and comorbid conditions)			
Intermittent Asthma		Persistent Asthma: Daily Medication					
		Consult with asthma specialist if step 3 care or higher is required. Consider consultation at step 2.					
	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6	
Preferred	SABA PRN	Low-dose ICS	Low-dose ICS + LABA, LTRA, or Theophylline	Medium-dose ICS + LABA or Montelukast	High-dose ICS + LABA	High-dose ICS + LABA + Oral corticosteroids	
Alternative		Cromolyn, LTRA, Nedocromil, or Theophylline	OR Medium-dose ICS	Medium-dose ICS + LTRA, or Theophylline	High-dose ICS + LTRA, or Theophylline	High-dose ICS + LTRA, or Theophylline + Oral corticosteroids	
Quick-Relief Medication	<b>Each Step: Patient Education, Environmental Control, and Management of Comorbidities</b> Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have persistent, allergic asthma. <ul style="list-style-type: none"><li>SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed</li></ul> Caution: Increasing use of SABA or use >2 days a week for symptoms relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.						

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- If an alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Theophylline is a less desirable alternative due to the need to monitor serum concentration levels.
- Steps 1 and 2 medications are based on Evidence A. Step 3 ICS and ICS plus adjunctive therapy are based on Evidence B for efficacy of each treatment and extrapolation from comparator trials in older children and adults—comparator trials are not available for this age group; steps 4–6 are based on expert opinion and extrapolation from studies in older children and adults.
- Immunotherapy for steps 2–4 is based on evidence B for house-dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than adults.
- Clinicians who administer immunotherapy should be prepared and equipped to identify and treat anaphylaxis that may occur.

**Alphabetical listing is used when more than one treatment option is listed within either preferred or alternative therapy.** ICS, inhaled corticosteroid; LABA, inhaled long-acting  $\beta_2$ -agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting  $\beta_2$ -agonist.

Adapted from National Heart, Lung, and Blood Institute. *National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. US Department of Health and Human Services; 2007.

**Table 218-6** Stepwise Approach for Managing Asthma In Youths  $\geq 12$  Years of Age and Adults

<b>Step down if possible</b> (and asthma is well controlled at least 3 months)		<i>Assess Control</i>		<b>Step up if needed</b> (first, check adherence, environmental control, and comorbid conditions)	
<b>Intermittent Asthma</b>		<b>Persistent Asthma: Daily Medication</b>			
Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.					
<b>STEP 1</b>	<b>STEP 2</b>	<b>STEP 3</b>	<b>STEP 4</b>	<b>STEP 5</b>	<b>STEP 6</b>
<i>Preferred:</i> SABA PRN	<i>Preferred:</i> Low-dose ICS <i>Alternative:</i> Cromolyn, LTRA, Nedocromil, or Theophylline	<i>Preferred:</i> Low-dose ICS + LABA OR Medium-dose ICS <i>Alternative:</i> Low-dose ICS + either LTRA, Theophylline, or Zileuton	<i>Preferred:</i> Medium-dose ICS + LABA <i>Alternative:</i> Medium-dose ICS + either LTRA, Theophylline, or Zileuton	<i>Preferred:</i> High-dose ICS + LABA AND Consider Omalizumab for patients who have allergies	<i>Preferred:</i> High-dose ICS + LABA + Oral corticosteroid AND Consider Omalizumab for patients who have allergies
<b>Each step: Patient education, environmental control, and management of comorbidities.</b> Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).					
<b>Quick-Relief Medication for All Patients</b> <ul style="list-style-type: none"><li>SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.</li><li>Use of SABA &gt;2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.</li></ul>					

Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy. ICS, inhaled corticosteroid; LABA, longacting inhaled  $\beta_2$ -agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting  $\beta_2$ -agonist.

- The stepwise approach is meant to assist, not replace, the decision making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Zileuton is a less desirable alternative due to limited studies as adjunctive therapy and the need to monitor liver function. Theophylline requires monitoring of serum concentration levels.
- In step 6, before oral corticosteroids are introduced, a trial of high-dose ICS + LABA + either LTRA, theophylline, or zileuton may be considered, although this approach has not been studied in clinical trials.
- Step 1, 2, and 3 preferred therapies are based on Evidence A; step 3 alternative therapy is based on Evidence A for LTRA, Evidence B for theophylline, and Evidence D for zileuton. Step 4 preferred therapy is based on Evidence B, and alternative therapy is based on Evidence B for LTRA and theophylline and Evidence D for zileuton. Step 5 preferred therapy is based on Evidence B. Step 6 preferred therapy is based on (EPR—2 1997) and Evidence B for omalizumab.
- Immunotherapy for steps 2–4 is based on Evidence B for house-dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults.
- Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.

Adapted from National Heart, Lung, and Blood Institute. *National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. US Department of Health and Human Services; 2007.

### Quick-Relief Medications

Short-acting inhaled  $\beta_2$ -agonists are the most widely used quick-relief medications because of their rapid onset of action (within minutes) and effectiveness in reversing bronchospasm. They promote smooth muscle relaxation, decrease vascular permeability, and enhance mucociliary clearance. Notably, the long-acting  $\beta$ -agonists, such as salmeterol and formoterol, are not currently recommended for use as quick-relief inhalers because the FDA expressed concerns about increasing the risk for severe asthma exacerbations.  $\beta_2$ -Agonists also can limit exercise-induced bronchospasm. Side effects include tachycardia, tremor, headaches, and palpitations. Levalbuterol, the racemic R isomer, has been observed by some investigators to have fewer systemic effects for the same degree of bronchodilation than albuterol, with others reporting negligible clinical effect. These symptoms can be

reduced by use of selective  $\beta$ -agonist medications such as those listed previously and spacer/holding chambers. Metabolic abnormalities, such as hypokalemia and hyperglycemia, have been reported with frequent or continuous use of  $\beta$ -agonists, although the clinical significance of these findings is unclear. Excessive reliance on quick relievers has been associated with increased risk for death or worsening asthma. Use of more than 1 canister per month is associated with poorly controlled asthma and risk for exacerbations, whereas use of more than 2 canisters of albuterol per month is associated with risk for fatal asthma exacerbations. It is important to remember that most canisters have 200 inhalations in each unit (100 doses of 2 puffs each); hence close monitoring of SABA use may help detect children unable to recognize inadequate asthma control. It is also important that children keep close track of the number of

inhalations used per canister, particularly for inhalers that do not have a counter built in.

Anticholinergic agents in combination with albuterol have been shown to have a positive effect on reducing the rate of hospitalizations during acute asthma exacerbations, although, singly, they are less potent than SABAs. The most common anticholinergic agent in use is ipratropium bromide because it is available in both MDI and nebulized forms and has limited central nervous system side effects. This agent decreases vagal tone (resulting in bronchodilation) and blocks reflex bronchoconstriction to irritants.

Oral short courses of corticosteroids are used to treat asthma exacerbations and may be considered quick-relief medications. These drugs have broad anti-inflammatory effects and are usually used as a short 3- to 5-day course to gain initial control of asthma and to speed resolution of moderate or severe persistent exacerbation. The available preparations—prednisone, prednisolone, and methylprednisolone—are rapidly and completely absorbed, with peak plasma concentrations occurring within 1 to 2 hours. They are typically administered in a dose of 1 to 2 mg/kg/day. Requirement of less than 2 corticosteroid courses per year is one of the criteria indicating well-controlled asthma. Recently the use of 1 to 2 doses of dexamethasone in the ED setting as equivalent therapy to prednisone/prednisolone for acute asthma exacerbations in pediatric patients was explored. Although there was no significant difference in relative risk for relapse, the palatability and the large quantity of the liquid dexamethasone preparation that needs to be ingested may be a limitation to its widespread use among children.

### Long-Term Controller Medications

As discussed earlier, children identified as having persistent asthma should be prescribed daily controller medications. The types of controller medications are ICS, LABAs, ICS-LABA combinations, leukotriene modifiers, sustained-release theophylline, mast cell stabilizers (cromolyn and nedocromil), omalizumab, and low-dose corticosteroid therapy.

Inhaled corticosteroids are recommended as the first-line treatment for most types of persistent asthma. These drugs bind to the glucocorticoid receptors in cytoplasm and translocate into the nucleus, where they regulate transcription of target genes, leading to inhibition of inflammatory cytokines and upregulation of  $\beta_2$ -receptor responsiveness. They block late-phase reaction to allergens, reduce airway hyperresponsiveness, and are the most potent and effective anti-inflammatory medications currently available. They lessen asthma symptoms, improve pulmonary function, reduce the need for quick-relief medications, and halve the amount of urgent care visits, systemic corticosteroid use, and hospitalizations for acute asthma exacerbations.

There are different formulations of ICS approved by the FDA for use in children, available in different preparations—as an MDI, dry powder inhaler, or nebulizer solution. Direct comparisons of efficacy and safety in children are limited and, notably, approval age varies with each preparation.

In general, ICS are well tolerated and safe at the recommended dosages. The dose-response curve for ICS treatment begins to flatten for many measures of efficacy at low to medium doses. Most benefit is achieved with relatively low doses, whereas the risk for adverse effects increases with higher doses. The major concern with long-term use of ICS is growth delay, with a recent study suggesting a decrease in height of up to half an inch. Other potential side effects of long-term ICS use include osteoporosis and, in the older population, ocular problems such as cataracts and glaucoma. The most common side effect is oral candidiasis. The choice of ICS preparation prescribed depends on the relative potential for adverse effects and the desired level of symptom control in individual children. Issues to consider include the drug delivery device, dose level, formulation of the preparation, bioavailability, potency of the inhaled corticosteroid, and deposition either in the pulmonary system or in the gastrointestinal system. Strategies to minimize side effects include using the lowest dose needed to control asthma, using less bioavailable formulations, using spacers or holding chambers with MDI, rinsing the mouth after inhalation, adding LABA to a low-medium dose of ICS rather than increasing ICS, monitoring growth, and ensuring age-appropriate dietary intake of calcium and exercise. It should be noted that children may relapse when inhaled corticosteroids are reduced or discontinued; hence, regular monitoring is recommended.

Leukotriene modifiers include inhibitors of leukotriene synthesis such as 5-lipoxygenase inhibitors (zileuton) and LTRAs, such as montelukast and zafirlukast, that block LTD<sub>4</sub> receptors. These medications are popular because they can be administered in oral form and have been shown to have bronchodilator and anti-inflammatory properties and mitigate exercise-, allergen-, and aspirin-induced bronchospasm. Only montelukast (>6 months of age) and zafirlukast (>5 years of age) are FDA approved for children. As single agents, they are considered “alternate” therapy in mild persistent asthma. They can also be used with inhaled corticosteroids. The medications may have some drawbacks, particularly because they can, in some cases, affect the pharmacokinetics of certain medications (eg, zafirlukast affects warfarin). Rare cases of Churg-Strauss syndrome have been reported in adults with corticosteroid-dependent asthma treated with LTRA, although it is not clear if they merely “unmasked” underlying disease or caused it. Recent post-marketing reports have raised awareness about potential for neuropsychiatric and behavioral effects of montelukast ranging from headaches and agitation to nightmares, oppositional behavior, anxiety and depression, and even suicidal thinking and behavior.

Long-acting  $\beta_2$ -agonists, such as salmeterol and formoterol, are not intended for treating acute exacerbations or as monotherapy for persistent asthma. These medications have long lipophilic side chains and anchor them to the cell membrane, allowing them to interact repetitively with  $\beta$ -receptors, thereby increasing the duration of action for up to 12 hours. These medications act by relaxing bronchial smooth muscle, improving symptoms, and reducing the need for quick-relief



medication. Formoterol has a quick onset of action, similar to SABA, whereas salmeterol has a longer onset of action. Fixed-dose combination therapy of ICS-LABA (fluticasone/salmeterol, budesonide/formoterol, mometasone/formoterol) is available and is recommended over using separate inhalers. Their major indication is as an add-on agent when asthma is uncontrolled by ICS therapy alone. In those children, the ICS-LABA combination therapy has been shown to be synergistic and superior to increasing ICS dose, both in terms of efficacy and minimizing steroid-induced side effects. Notably, the FDA requires all LABA-containing medications to carry a black box warning regarding potential for worsening asthma while on therapy. The FDA also specifies that LABAs should be discontinued when asthma control is achieved, and asthma should be maintained with controllers such as ICS.

Cromolyn sodium and nedocromil sodium are mast cell stabilizers that can attenuate the early- and late-phase response after allergen challenge. They are considered alternate anti-inflammatory agents for children with mild persistent asthma. Although they have good safety profiles, they need to be administered frequently (4 times a day) and are not as efficacious as ICS or leukotriene antagonists. Cromolyn is dispensed in a nebulizer solution or as an MDI. Nedocromil is also available as an MDI, although it has not been in favor in recent years because of its unpleasant taste. Both nedocromil and cromolyn may be used as an adjunct to pretreatment with SABA for exercise-induced bronchospasm. Although these medications are listed in the NHLBI guidelines document, it should be noted that they are not regularly used and may be difficult to find in pharmacies.

Theophylline (methylxanthine), a phosphodiesterase inhibitor, has anti-inflammatory effects in addition to bronchodilatory properties, although its role has diminished in the treatment of children with asthma. Although methylxanthines can reduce asthma symptoms and are considered alternate agents for older children with mild persistent asthma, they are a challenge to use because of their narrow therapeutic window and require frequent monitoring. In addition, their use is limited by numerous side effects, such as headaches and vomiting, including some that are life-threatening, such as cardiac arrhythmias, seizures, and death. Theophylline metabolism and serum levels are altered by fever, viral illnesses, certain drugs such as cimetidine and erythromycin, and liver disease. They are, therefore, generally not used for mild persistent asthma. Theophylline may rarely be considered for use in recalcitrant severe asthma by some asthma specialists, particularly for reduction of nocturnal symptoms. Suggested target peak levels are now 5 to 10 mcg/dL as opposed to the higher levels (10–20 mcg/dL) that were previously used; serious adverse effects are much less common with this dosing strategy.

Omalizumab is an anti-IgE humanized monoclonal antibody that binds circulating IgE, thereby binding the high-affinity receptor and preventing IgE-mediated allergic responses and inflammatory cascade. It does not activate complement or bind to IgE attached to mast cells. When bound, it forms small biologically inert anti-IgE complexes and decreases circulating

serum IgE levels. Studies have shown that serum IgE levels directly correlate with the odds ratio for the development of asthma. In addition, total serum IgE has been shown to be directly related to asthma and wheezing in the first 5 years of life. Omalizumab has been shown to improve lung function, to significantly reduce sputum eosinophil counts, and to improve quality of life. It is FDA approved for children 12 years of age and older with moderate to severe asthma, documented hypersensitivity to a perennial aeroallergen, and inadequate disease control with ICS or oral corticosteroids. Hypersensitivity reactions (including anaphylaxis) have been variably reported, and the FDA has mandated a black box warning of potentially serious anaphylactic reactions with its use. Although initial concerns about increased risk for malignancies is now mitigated, the FDA announced a new safety communication describing an increased risk for cardiac and brain adverse events, particularly in adults, and there is a question of cardiac effects in adults. Currently, it is used only by asthma specialists, is administered every 2 to 4 weeks subcutaneously, and dose depends on the child's weight and serum IgE level.

## APPROACH TO DIFFICULT-TO-MANAGE DISEASE

Five issues should be assessed when dealing with a child who does not respond to reasonable therapy.

1. Is it asthma? Anatomic lesions or other medical conditions should be ruled out.
2. Is the child adherent to the medication regimen, and is her technique for the medication delivery appropriate?
3. Did the child run out of medication and not realize it or say so?
4. Is a continual exposure present, environmental or otherwise, that is continuing to cause problems for the child?
5. A referral or a second opinion from a specialist should be considered if the desired effect is not being achieved.

## WHEN TO REFER

- A child older than 5 years of age requires step 4 care or higher, or a child younger than 5 years of age requires step 3 care or higher.
- A child has life-threatening asthma exacerbation or intensive care admission.
- Goals of therapy are not met after 3 to 6 months of treatment.
- Diagnosis or management is complicated by comorbid conditions (eg, sinusitis, nasal polyps, severe rhinitis, uncontrolled gastroesophageal reflux, and vocal cord dysfunction).
- Additional diagnostic tests are needed (eg, allergy skin testing, bronchoscopy).
- Allergen immunotherapy is a consideration.
- The asthma is difficult to control.
- Occupational triggers are suspected.
- Psychological or psychiatric issues are suspected.

### WHEN TO ADMIT

- Children who are moderately to severely ill on arrival and do not respond to  $\beta$ -agonist rescue therapy
- Continued symptoms despite treatment
- Significant wheezing and retracting (hunched posture, chest and neck pulling in), trouble speaking, gray or blue lips or fingernails
- Altered mental status, such as drowsiness or agitation
- Peak flows less than 50% of personal best
- Requiring  $\beta$ -agonists every 2 to 3 hours
- Continued need for supplemental oxygen despite initial therapy

Additional factors that may influence the decision about hospitalization include

- Use of  $\beta_2$ -agonists/glucocorticoids before ED visit
- History of poor adherence to the medical regimen
- Caretaker inability to provide careful medical care and supervision at home
- Inadequate access to medical care
- History of rapid progression of severity in past exacerbations

### TOOLS FOR PRACTICE

#### Community Coordination and Advocacy

- *Asthma-Friendly Schools Initiative* (toolkit), American Lung Association, AAP endorsed ([www.lung.org/lung-health-and-diseases/lung-disease-lookup/asthma/asthma-education-advocacy/asthma-friendly-schools-initiative/afsi-toolkit.html](http://www.lung.org/lung-health-and-diseases/lung-disease-lookup/asthma/asthma-education-advocacy/asthma-friendly-schools-initiative/afsi-toolkit.html))

#### Engaging Patient and Family

- *Allergies and Asthma: What Every Parent Needs to Know* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Asthma and Your Child* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *What is a Pediatric Allergist/Immunologist?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Allergist-Immunologist.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Allergist-Immunologist.aspx))

#### Medical Decision Support

- *Asthma* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/asthma](http://www.cdc.gov/asthma))
- *EQIPP: Asthma—Diagnosing and Managing in Pediatrics* (online course), American Academy of Pediatrics ([pedialink.aap.org](http://pedialink.aap.org))
- *Guidelines for the Diagnosis and Management of Asthma* (guideline), National Heart, Lung, and Blood Institute ([www.nhlbi.nih.gov/guidelines/asthma/index.htm](http://www.nhlbi.nih.gov/guidelines/asthma/index.htm))
- *My Asthma Action Plan* (form), American Academy of Allergy, Asthma, and Immunology ([www.aaaai.org/Aaaa/media/MediaLibrary/PDF%20Documents/Libraries/NEW-WEBSITE-LOGO-asthma-action-plan\\_HI.pdf](http://www.aaaai.org/Aaaa/media/MediaLibrary/PDF%20Documents/Libraries/NEW-WEBSITE-LOGO-asthma-action-plan_HI.pdf))
- *Pediatric Environmental Health*, 3rd ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

- *Sample Asthma Action Plan* (form), American Academy of Pediatrics Schooled in Asthma Project ([www2.aap.org/sections/schoolhealth/schooledinasthma/asthmaactionplan.pdf](http://www2.aap.org/sections/schoolhealth/schooledinasthma/asthmaactionplan.pdf))
- *Sample Asthma Intake Form* (form), American Academy of Pediatrics Schooled in Asthma Project ([www2.aap.org/sections/schoolhealth/schooledinasthma/asthmaform.pdf](http://www2.aap.org/sections/schoolhealth/schooledinasthma/asthmaform.pdf))
- *Sample Dear Doctor Form Letter*, American Academy of Pediatrics Schooled in Asthma Project ([www2.aap.org/sections/schoolhealth/schooledinasthma/deardoctoletter.pdf](http://www2.aap.org/sections/schoolhealth/schooledinasthma/deardoctoletter.pdf))
- *Sample Asthma Encounter Form* (form), American Academy of Pediatrics Schooled in Asthma Project ([www2.aap.org/sections/schoolhealth/schooledinasthma/asthmaencounterform.pdf](http://www2.aap.org/sections/schoolhealth/schooledinasthma/asthmaencounterform.pdf))
- *When Should Students with Asthma or Allergies Carry and Self Administer Emergency Medications at School?* (fact sheet), National Heart Lung and Blood Institute ([www.nhlbi.nih.gov/files/docs/resources/lung/emmer\\_med.pdf](http://www.nhlbi.nih.gov/files/docs/resources/lung/emmer_med.pdf))

### AAP POLICY

American Academy of Pediatrics Committee on Environmental Health. Ambient air pollution: health hazards to children. *Pediatrics*. 2004;114(6):1699–1707. Reaffirmed April 2009 ([pediatrics.aappublications.org/content/114/6/1699](http://pediatrics.aappublications.org/content/114/6/1699))

American Academy of Pediatrics Committee on Environmental Health. Environmental tobacco smoke: a hazard to children. *Pediatrics*. 1997;99(4):639–664. Reaffirmed May 2007 ([pediatrics.aappublications.org/content/99/4/639](http://pediatrics.aappublications.org/content/99/4/639))

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## Chapter 219 ATOPIC DERMATITIS

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### DEFINITION

Atopic dermatitis (AD) is a multifactorial dermatologic condition involving chronically relapsing inflammation of the skin. It is sometimes referred to as eczema, which is a general term used to describe skin that is

erythematous, scaling, vesicular, and crusting. AD is common in individuals with the genetic propensity to develop immunoglobulin E (IgE)-mediated diseases. The associated IgE-mediated diseases include allergic rhinitis, asthma, and food allergies. AD may be the initial condition signaling the progression to further allergic diseases, known as the atopic march.

## ETIOLOGY

The exact cause of AD is unknown, but genetic and environmental factors play a role in its development. Dysfunction of the immune system, specifically abnormal IgE-mediated type I and cell-mediated type IV reactions, and dysfunction of the epidermal barrier occur. Filaggrin is a structural protein in the stratum corneum, and mutations in the filaggrin gene (*FLG*) have been reported to have a key role in the pathogenesis of AD. Loss of function mutations in *FLG* lead to increased transepidermal water loss and increased entry of allergens and microbes. The T cells responsible for atopy are mainly  $T_H2$  subtype cells. An area of debate is the hygiene hypothesis, which theorizes that decreased exposure to microbes, immunizations, the use of antibiotics, and environmental exposures in early childhood stunts immunologic maturation of  $T_H1$  subtype cells, thereby increasing the risk for development of atopic disease later in life caused by an imbalance in  $T_H2$  and  $T_H1$ , with overexpression of  $T_H2$  responses compared with  $T_H1$  responses.

Other cells implicated in the development of AD include macrophages, IgE-bearing Langerhans cells, eosinophils, and mast cells, which release or produce several proinflammatory agents such as histamine, leukotrienes, and prostaglandins. The resulting inflammatory reactions lead to disruption of the epidermis.

Airborne allergens (dust mites, cat and dog dander, molds, pollen), foods (especially milk, eggs, and peanuts), infectious agents, and other contact allergens have been implicated as potential antigenic triggers. Psychological stress may exacerbate AD.

## EPIDEMIOLOGIC FEATURES

Atopic dermatitis is predominantly a disease of infancy and childhood. Onset occurs in the first year of life in most affected individuals. The prevalence of disease varies depending on age; more than 10% of infants and young children may be affected, whereas one-half this rate occurs in adolescents. DaVeiga reports a remission rate of 60% in a review about AD in children and adults. A survey in 2007 found that almost 18 million Americans had a self-reported diagnosis of AD, and more than one-third of them had diagnosis confirmed by a physician. Both sexes are affected equally. The yearly health care cost of AD in the United States has been projected to be as high as almost \$4 billion.

## DIAGNOSIS

The diagnosis of AD is determined solely by history and clinical examination. The criteria for diagnosis of AD were defined by Hanifin and Lobitz. These criteria

### BOX 219-1 Clinical Criteria of Atopic Dermatitis

- A. Essential features (must be present) of atopic dermatitis (AD)
  1. Pruritus
  2. Eczema (acute, subacute, chronic)
    - a. Typical morphology and age-specific patterns<sup>a</sup>
    - b. Chronic or relapsing history
- B. Important features (seen in most cases, adding support to the diagnosis)
  1. Early age at onset
  2. Atopy
    - a. Personal and/or family history
    - b. IgE reactivity
  3. Xerosis
- C. Associated features (these clinical associations help to suggest the diagnosis of AD but are too nonspecific to be used for defining or detecting AD for research or epidemiologic studies)
  1. Atypical vascular responses (eg, facial pallor, white dermographism, delayed blanch response)
  2. Keratosis pilaris/hyperlinear palms/ichthyosis
  3. Ocular/periorbital changes
  4. Other regional findings (eg, perioral changes/periauricular lesions)
  5. Perifollicular accentuation/lichenification/prurigo lesions

*Exclusionary conditions:* It should be noted that a diagnosis of AD depends on excluding conditions such as scabies, seborrheic dermatitis, allergic or irritant contact dermatitis, ichthyoses, cutaneous lymphoma, psoriasis, and immune deficiency diseases.

<sup>a</sup>Patterns include: (1) facial, neck, and extensor involvement in infants and children; (2) current or prior flexural lesions in any age group; (3) sparing of groin and axillary regions  
From Eichenfield LF, Hanifin JM, Luger TA, Stevens SR, Pride HB. Consensus conference on pediatric atopic dermatitis. *J Am Acad Dermatol.* 2003;49: 1088–1095, with permission from Elsevier.

are presented in Box 219-1 and are useful in identifying characteristics of patients who have AD. However, patients may have AD and not meet the criteria as originally defined.

## DIFFERENTIAL DIAGNOSIS

Differentiating AD from other skin conditions may be difficult in some instances, but certain characteristics will aid in the diagnosis (Box 219-2). Seborrhea is associated with scaling, commonly on the scalp, forehead, and around the eyebrows; it can also be accompanied by pruritus. The diagnosis of contact dermatitis often requires a positive exposure history to a potential offending agent and will be limited in distribution on the body to the area of contact. Contact dermatitis is more likely to have an acute onset and localized appearance. Absence of a family history also favors a diagnosis of seborrhea or contact dermatitis.



**BOX 219-2 Differential Diagnosis for Atopic Dermatitis**

- Seborrheic dermatitis
- Contact dermatitis (allergic and irritant)
- Psoriasis
- Scabies
- Dermatophyte infection
- Wiskott-Aldrich syndrome
- Leiner disease
- Histiocytosis X
- Ataxia
- Telangiectasia
- Ahistidinemia
- Severe combined immunodeficiency
- Eosinophilic esophagitis
- Acrodermatitis enteropathica (zinc deficiency)
- Niacin deficiency
- Phenylketonuria

**CLINICAL MANIFESTATIONS**

Atopic dermatitis may exhibit as an acute dermatitis associated with severe pruritus, redness, vesicles, and exudation, or it may have a subacute pattern of pruritus, redness, and scaling. Chronic lesions are marked by excoriations, lichenification (thickened skin and deeper or exaggerated skin lines), and postinflammatory hypopigmentation or hyperpigmentation.

AD has three distinct stages: infantile, childhood, and adult. In infants, AD is characterized by an eruption of erythematous papules on facial cheeks and extensor surfaces of arms and legs. The hair is dry, and the scalp is often scaly. The childhood stage begins at approximately age 3 and lasts through puberty. The areas most affected include the antecubital and popliteal folds, neck, and flexor surfaces of wrists and ankles. Clinically, patients in this stage display a more subacute and chronic dermatitis. The adult stage, beginning at puberty onward, is an extension of the childhood stage. Additional clinical signs include diffuse involvement of the body, with xerosis, lichenification, and central facial pallor.

Other associated clinical manifestations include keratosis pilaris, lichen spinulosus, pityriasis alba, Dennie-Morgan folds, urticaria, hyperlinear palms, juvenile plantar dermatosis, nummular eczema, and cataracts (anterior subcapsular, to distinguish from those secondary to corticosteroids). Keratosis pilaris is a disorder of hyperkeratosis. Its characteristic goose-flesh appearance is secondary to multiple, small, skin-colored or mildly erythematous keratotic papules located on the upper arms, thighs, and facial cheeks. Lichen spinulosus also involves hyperkeratosis; in this condition, tiny hairlike spines top the small papules that occur in crops on various locations on the body. Juvenile plantar dermatosis mainly affects the feet, rarely the hands, and produces shiny, fissured skin on the plantar surfaces.

**LABORATORY EVALUATIONS**

No routine laboratory studies are needed to diagnose AD. Specific tests to rule out the disorders in the differential list may be necessary on a case-by-case basis if the diagnosis is in question. For example, if recurrent infections occur in the patient, then an immunodeficiency workup should be considered. Bacterial cultures of encrusted or exudative skin lesions and nares to detect colonization with staphylococcal organisms are warranted in any patient in whom secondary infection is suspected and improvement is not noted with standard therapy. Patch testing may be considered to pinpoint potential antigenic triggers, which may add a component of contact dermatitis to the existing AD. Skin biopsy may be necessary when definitive diagnosis is in question.

**MANAGEMENT****Uncomplicated Case**

Treatment of AD is directed at relieving dryness, inflammation, and pruritus and eradicating secondary bacterial infections. Daily applications of emollients, especially after brief warm baths, in the form of creams or ointments are the most efficacious way of treating dryness. Ointments are better in more severe cases and are better than creams. However, if discomfort (ie, stinging sensation) occurs with ointment application, or if the ointment feels too occlusive, such as in humid warm weather, then creams can be substituted. Bathing should last no longer than 5 minutes, and mild soaps or nondetergent cleansers are recommended to wash the body. The patient should be patted dry with a towel, the emollient applied immediately to all skin, and the prescription topically applied to affected areas.

Inflammation is best treated with topical corticosteroids. Generally, ointments tend to work better than creams. However, creams are sometimes preferred for cosmetic appeal and can be used for acute weeping, erythematous lesions. Ointments remain the choice for chronic dermatitis in which dryness and lichenification predominate. A low-potency topical steroid such as 1% to 2.5% hydrocortisone or desonide can be used for mild disease even on the diaper area and face; twice-daily dosing should be limited to a 2-week course or less. Mid- to high-potency steroids, such as triamcinolone or fluocinonide, can be used in more severe cases of AD on the trunk and extremities. Strong, halogenated steroids should not be applied to the face, axillae, or groin, and an oral systemic steroid should rarely be prescribed. The adverse effects of topical steroids increase with increasing potency. The most worrisome side effects include dermal and epidermal atrophy and suppression of the pituitary-adrenal axis. Applying topical steroids to the occluded groin area of a diapered child increases the risk for systemic side effects.

Topical tacrolimus and pimecrolimus are relatively new anti-inflammatory agents approved for children aged two years and older. Most efficacious in mild to moderate disease, these nonsteroidal immunomodulators are calcineurin inhibitors and alternatives to topical steroids that can be applied to the face. The US



Food and Drug Administration has added a black-box warning to tacrolimus ointment and pimecrolimus cream based on a theoretical risk for malignancy derived from safety profiles of oral calcineurin inhibitors. In general, these topical medications are considered safe and effective. Other medications for AD, such as coal tar (can be useful for scalp, ie, in shampoos) and doxepin (a tricyclic antidepressant with antihistaminic properties), are not routinely prescribed by pediatricians. In recent years, more attention has been placed on the development of barrier-repair creams to help patients with AD. These medications represent a steroid-sparing option.

Although evidence is lacking that antihistamines help relieve the pruritus associated with AD, they are often prescribed, especially for patients with accompanying allergic rhinitis, urticaria, and sleep disturbance. Non-sedating antihistamines such as loratadine can be used daily. The sedating antihistamines, hydroxyzine and diphenhydramine, are most useful at bedtime. Behavior modification such as teaching the child to rub rather than scratch and wearing mittens or socks on the hands to bed at night will help lessen the itch-scratch cycle. Frequent trimming of the child's fingernails may decrease the amount of trauma applied to skin and reduce secondary infection.

The role of dietary management of patients with AD remains controversial. Dietary changes should be judicious. Peanuts, milk, and eggs are the most common food culprits. If food allergies are highly likely as determined by a pediatric allergist, then strict avoidance of foods that serve as antigenic triggers should be encouraged, remembering that more than 90% of IgE-mediated food allergies in children are caused by 8 foods: cow milk, hen eggs, soy, peanuts, tree nuts (and seeds), wheat, fish, and shellfish. Children with documented food allergies should avoid ingesting the involved foods and antigens, receive nutritional counseling and education about reading nutrition labels, and have growth closely monitored. The efficacy of alternative medicine treatments for food allergies, such as herbal or probiotic supplementation, remains unclear, and clinical trials have varying results.

### Complicated Case

If AD continues to flare despite adherence with medication and appropriate skin care, then secondary infection may be responsible. Many patients who have AD have significant colonization with *Staphylococcus aureus*. Along with susceptibility to recurrent bacterial infection, the patient with AD is also prone to herpes simplex virus, human papillomavirus (HPV), and molluscum contagiosum. Secondary bacterial infections usually respond well to topical or oral antibiotics. Cephalexin, dicloxacillin, amoxicillin-clavulanate, azithromycin, and clindamycin are reasonable choices for oral treatment, and mupirocin is the topical antibiotic of choice. Dilute bleach baths (along with intranasal mupirocin) have been reported to improve outcomes (decreased severity of AD) when patients had signs of secondary bacterial infections. If recalcitrant *S aureus* superinfection occurs, then hospitalization for aggressive care and intravenous antibiotics may be required. Cultures of the skin may help identify

appropriate antibiotic sensitivities. Application of nasal mupirocin may be necessary to eradicate bacterial carriage. A widespread herpes infection, known as eczema herpeticum or Kaposi varicelliform eruption, will require treatment with intravenous acyclovir. Various treatment modalities are available for HPV and molluscum contagiosum infection in the patient with AD, who is likely to have a more severe, persistent course of these usually self-limited conditions. HPV treatments include vesicants, immunomodulators, cryotherapy, or ablation with carbon dioxide laser. Molluscum contagiosum can be treated with manual expression, cryotherapy, or topical application of cantharidin or imiquimod.

More aggressive interventions such as systemic immunomodulators or ultraviolet light therapy for severe cases would be prescribed at the discretion of the skin experts.

## PREVENTION

Atopic dermatitis cannot be cured, but meticulous adherence to proper skin care can control symptoms and secondary infection. Moisturization of the skin with daily applications of emollients, especially after bathing, is crucial to keep the skin hydrated. Prevention or delay of onset of AD may be possible with the use of hydrolyzed formula in the first 4 to 6 months of life for infants who are not exclusively breastfed. Extensively hydrolyzed formulas likely have an advantage over partially hydrolyzed formulas. Although some reports suggest that breastfeeding increases the risk for AD, evidence exists supporting breastfeeding as means of reducing the risk for AD.

### WHEN TO REFER

- Recalcitrant cases to dermatologist or an allergist
- To dermatologist for aggressive treatment of secondary HPV or molluscum contagiosum infection

### WHEN TO ADMIT

- Severe cases requiring systemic immunomodulation
- Extensive secondary bacterial infection requiring intravenous antibiotics
- A widespread herpes infection (eczema herpeticum, Kaposi varicelliform eruption)

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Atopic Dermatitis: Tips for Managing* (fact sheet), American Academy of Dermatology ([www.aad.org/dermatology-at-to-z/diseases-and-treatments/a--d/atopic-dermatitis/tips](http://www.aad.org/dermatology-at-to-z/diseases-and-treatments/a--d/atopic-dermatitis/tips))
- *Eczema (Atopic Dermatitis)* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Eczema: How to Help Your Child Avoid the Itch* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/skin/Pages/Eczema.aspx](http://www.healthychildren.org/English/health-issues/conditions/skin/Pages/Eczema.aspx))

**Medical Decision Support**

- *Atopic Dermatitis* (guidelines), American Academy of Dermatology ([www.aad.org/education/clinical-guidelines](http://www.aad.org/education/clinical-guidelines))
- *Dermatology: Atopic Dermatitis* (on-line course), American Academy of Pediatrics ([pedialink.aap.org/visitor/cme/course-series/dermatology-course-series](http://pedialink.aap.org/visitor/cme/course-series/dermatology-course-series))
- *Pediatric Dermatology: A Quick Reference Guide* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

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**Chapter 220****ATTENTION-DEFICIT/  
HYPERACTIVITY DISORDER**

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**CASE REPORT**

Bethany, a 12-year-old girl, arrives for her first visit at your office with her aunt, Cassandra. Cassandra is Bethany's legal guardian and is concerned that Bethany is failing school. Cassandra, who has raised Bethany from birth, tells you that Bethany was born 2 months early to a mother who abused drugs and alcohol during pregnancy. Although Bethany was a colicky infant who was difficult to feed, she had no major problems after birth and has been healthy except for a few early ear infections. She has since developed into a very social child with endless energy and is currently active with cheerleading. Bethany's talkativeness appeared in preschool and has been noted by every teacher since then. At age 6, she was unable to read simple words but was reported to have made "adequate" progress on reading through elementary school. Although Bethany has never received evaluations or services through school, Cassandra has been helping significantly by structuring Bethany's approach to her schoolwork and by paying for private tutoring. Bethany is a slow reader, has been very unhappy about her academic performance, is having trouble falling asleep, and is difficult to arouse in the morning. Her appetite has been poor, although she insists that she is just not hungry. She denies any suicidal thoughts. Her grades had been average until last year, when she began middle school and started failing. On

physical examination, Bethany is at the 75<sup>th</sup> percentile for height, weight, and head circumference. Her vital signs, vision screening, and hearing screening are normal. She has no dysmorphic features and her physical examination is normal. Bethany is articulate and answers your questions willingly.

**DEFINITION OF TERMS**

Bethany illustrates a frequently occurring presentation to pediatric primary care offices—the child or adolescent with school problems of unclear cause. Attention-deficit/hyperactivity disorder (ADHD), one of the most common neurodevelopmental disorders in children and adolescents, is often diagnosed in children with academic achievement or behavioral problems in primary care settings.

According to the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5), the hallmarks of this disorder are hyperactivity, impulsivity, and inattention that are inconsistent with developmental level and directly affect social and academic/occupational activities. The criteria, as depicted in Box 220-1, require that a child meet a minimum of 6 of 9 inattention criteria or 6 of 9 hyperactivity or impulsivity criteria for at least 6 months duration (this requirement drops to 5 of 9 criteria for adolescents ages ≥17). Furthermore, the criteria stipulate that symptoms must be present before age 12 years; occur in 2 or more settings (eg, home and school); interfere with or reduce the quality of social, academic, or occupational functioning; not occur exclusively during the course of schizophrenia or another psychotic disorder; and not be better accounted for by another mental disorder. The current diagnostic criteria do not account for differences in presentation by age, gender, race, or ethnicity. Therefore, physicians will need to exercise judgment in their use of the criteria.

**PREVALENCE**

A review of community-based epidemiologic studies has estimated the prevalence of ADHD at 6.8% of school-aged children. Boys are diagnosed at a rate 3 times that of females (9.2% vs. 3.0%). The rates of diagnosed ADHD increase with age up to 9 years of age and level off or decline depending on whether children are taking medications. Differences exist in diagnosed prevalence by race or ethnicity; white children are diagnosed at a greater rate (8.6% vs. 7.7% and 3.7%) than black or Hispanic children.

**CLINICAL MANIFESTATIONS**

The core symptoms associated with ADHD interfere with attainment of many of the normal developmental milestones of childhood and adolescence, such as academic, fine motor, social, and adaptive skills. Children identified with ADHD and monitored into adolescence demonstrate an increased risk for poor academic attainment, impaired familial and peer functioning, lower self-esteem, substance abuse, delinquency, and driving-related accidents. Some evidence suggests that treatment may ameliorate some of this risk, particularly for substance abuse. Although many children with ADHD continue to experience symptoms

**BOX 220-1 DSM-5 Criteria for ADHD**

A. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):

1. Inattention: Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

NOTE: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least 5 symptoms are required.

- a. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (eg, overlooks or misses details, work is inaccurate).
- b. Often has difficulty sustaining attention in tasks or play activities (eg, has difficulty remaining focused during lectures, conversations, or lengthy reading).
- c. Often does not seem to listen when spoken to directly (eg, mind seems elsewhere, even in the absence of obvious distraction).
- d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (eg, starts tasks but quickly loses focus and is easily sidetracked).
- e. Often has difficulty organizing tasks and activities (eg, difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).
- f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (eg, schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).
- g. Often loses things necessary for tasks or activities (eg, school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
- h. Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).
- i. Is often forgetful in daily activities (eg, doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).

2. Hyperactivity and Impulsivity: Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

NOTE: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least 5 symptoms are required.

- a. Often fidgets with or taps hands or feet or squirms in seat.
  - b. Often leaves seat in situations when remaining seated is expected (eg, leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
  - c. Often runs about or climbs in situations where it is inappropriate. (Note: In adolescents or adults, may be limited to feeling restless.)
  - d. Often is unable to play or engage in leisure activities quietly.
  - e. Is often “on the go,” acting as if “driven by a motor” (eg, is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).
  - f. Often talks excessively.
  - g. Often blurts out an answer before a question has been completed (eg, completes other people’s sentences; cannot wait for turn in conversation).
  - h. Often has difficulty waiting his or her turn (eg, while waiting in line).
  - i. Often interrupts or intrudes on others (eg, butts into conversations, games, or activities; may start using other people’s things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).
- B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.
- C. Several inattentive or hyperactive-impulsive symptoms are present in 2 or more settings, (eg, at home, school or work; with friends or relatives; in other activities).
- D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.
- E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder, and are not better explained by another mental disorder (eg, mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

*Combined presentation:* If both Criterion A1 (inattention) and Criterion A2 (hyperactivity-impulsivity) are met for the past 6 months.

*Predominantly inattentive presentation:* If Criterion A1 (inattention) is met but Criterion A2 (hyperactivity-impulsivity) is not met for the past 6 months.

*Predominantly hyperactive-impulsive presentation:* If Criterion A2 (hyperactivity-impulsivity) is met and Criterion A1 (inattention) is not met for the past 6 months.

Because symptoms can change over time, the presentation may change over time as well.

From American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association; 2013; 59–60. Reprinted with permission.



into adulthood, an age-dependent decline seems to exist in apparent symptoms as children grow older. Hyperactivity and impulsivity tend to remit at a greater rate than inattention.

## DIAGNOSIS

Although the diagnosis of ADHD can be made reliably in children using a standardized approach, concerns regarding the validity of the diagnosis of ADHD often arise. At present, no biological marker or gold standard diagnostic test exists that can reliably identify those with and without ADHD. Furthermore, whether the symptoms of ADHD represent a unique disorder or merely one end of the continuum of age-appropriate behavior is unclear. Data that support the validity of ADHD as a unique disorder come from multiple sources. First, cohort studies have consistently shown similar long-term outcomes for children identified with ADHD (predictive validity). Second, twin studies have demonstrated higher concordance rates of ADHD among monozygotic twins than among dizygotic twins or related siblings, suggesting a genetic predisposition. Third, genetic studies have shown higher rates of gene alterations involving dopamine neurotransmission in subjects with ADHD. Finally, brain imaging and physiologic studies have shown a greater proportion of abnormalities among persons with ADHD than similar controls without ADHD, which suggests a neurodevelopmental process leading to ADHD.

Diagnosing ADHD is complicated by the fact that presentations of ADHD in clinical practice can vary substantially. The core symptoms of ADHD result in 3 distinct subtypes recognized in the *DSM-5* (see Box 220-1): a predominantly inattentive subtype (ADHD-IA), a hyperactive/impulsive subtype (ADHD-HI), and a subtype that includes a combination of both inattentive and hyperactive/impulsive features (ADHD-CT). Children with ADHD-IA often present with school underachievement and may go unrecognized by parents and teachers. In contrast, children with ADHD-HI or ADHD-CT commonly present with school underachievement, disruptive classroom behavior, and poor relationships with both peers and family members. In addition, many conditions, including autism, can co-exist with ADHD, further adding to variation in presentation.

Despite these complexities, the American Academy of Pediatrics (AAP) recognizes ADHD as a chronic condition and encourages increasing responsibility for the care of children with ADHD in primary care settings. The AAP published revised evidence-based diagnostic and treatment guidelines for use by primary care pediatricians. These guidelines expanded the age range for ADHD from 6 through 12 years to 4 through 18 years, expanded the scope of recommendations to children with hyperactive or impulsive problem behaviors that do not meet diagnostic criteria, and combined diagnostic and treatment recommendations into a single document.

The decision to support the diagnosis and treatment of ADHD in primary care reflects the high prevalence rates of ADHD in the community, families' perception of the approachability of primary care physicians, an

insufficient supply of child mental health professionals, and the fact that more than 50% of children with ADHD currently receive their care in primary care settings. To support physicians in caring for children with ADHD, the AAP developed an online, interactive training program and, with its Quality Improvement Innovation Network (QuIIN), partnered with the National Initiative for Children's Healthcare Quality (NICHQ) to develop a revised toolkit titled *Caring for Children with ADHD: A Resource Toolkit For Clinicians*, 2nd Edition ([www.aap.org/en-us/professional-resources/practice-support/quality-improvement/Quality-Improvement-Innovation-Networks/Pages/Guidelines-and-Tools-to-Improve-Care-for-Children-with-ADHD-Improvement-Project.aspx](http://www.aap.org/en-us/professional-resources/practice-support/quality-improvement/Quality-Improvement-Innovation-Networks/Pages/Guidelines-and-Tools-to-Improve-Care-for-Children-with-ADHD-Improvement-Project.aspx)). In addition, *Bright Futures in Practice: Mental Health* contains a variety of tools for the early identification of childhood behavioral problems ([www.brightfutures.org/mentalhealth](http://www.brightfutures.org/mentalhealth)). This 2-volume set considers the mental health of children in a developmental context, presenting information on early recognition and intervention for specific mental health problems and mental disorders, including ADHD, and provides a hands-on toolkit for health professionals and families for use in screening, care management, and health education of mental health problems in primary care. The AAP Task Force on Mental Health has also produced a number of resources on the management of mental health concerns in primary care that may be helpful ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/Key-Resources.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/Key-Resources.aspx)).

## DIFFERENTIAL DIAGNOSIS

Because no definitive biologic or imaging markers exist for ADHD, a diagnosis of ADHD requires determining whether a child meets the *DSM-5* diagnostic criteria for ADHD (see Box 220-1) and ascertaining whether any other disorders or factors exist that may better explain a child's symptoms and impairment. Many medical, psychosocial, psychiatric, or neurologic conditions may exhibit symptoms similar to those of ADHD (see Box 220-2). These conditions may be the primary cause of the child's behavioral and attention difficulties or may increase a child's level of impairment if co-morbid with ADHD. The primary care physician is responsible for determining if these conditions are present and, if so, whether they are the primary cause of the child's dysfunction or whether they co-exist with ADHD. Determining the cause of a child's difficulties and any conditions that may coexist requires time and effort, but the evaluation can be streamlined through a careful history and thorough physical examination as reviewed here.

Although other professionals may assist in identifying mental health or educational disorders, establishing whether any medical conditions are present is paramount for primary care physicians. For instance, poor visual acuity or hearing loss can contribute to academic difficulties. Obstructive sleep apnea caused by enlarged tonsils or adenoids or both can be associated with daytime somnolence, hyperactivity, and academic problems. Medication side effects may also explain unusual drowsiness and lack of attention in



**BOX 220-2 Conditions That May Mimic or Co-occur With ADHD****DEVELOPMENTAL DIFFERENCES/NORMAL VARIANTS**

*Normal variation; giftedness; sociocultural differences in expectations or parenting*

**MEDICAL CONDITIONS**

*Medication side effects; substances of abuse; hearing impairment; visual impairment; sleep disorders including obstructive sleep apnea and poor sleep hygiene; toxins (eg, chronic lead exposure or acute lead intoxication; chronic iron-deficiency anemia); thyroid disorders; chronic disease complications*

**NEUROLOGIC/DEVELOPMENTAL CONDITIONS**

*Learning disabilities; autism spectrum disorder; tic disorders (Tourette's); communication disorders; processing disorders; intellectual disability; neuro-developmental syndromes (eg, fetal alcohol syndrome, fragile X syndrome); cerebral palsy; seizure disorders (petit mal or developmental delays); sequelae of central nervous system trauma/infection; neurodegenerative disorders; motor coordination disorders*

**PSYCHOSOCIAL/ENVIRONMENTAL PROBLEMS**

*Stress in family situation (marriage, separation/divorce, birth of sibling, death); stress in environment (new home, new school); family dysfunction; parenting dysfunction; neglect or abuse; parental psychopathology; parental substance abuse; inappropriate educational program*

**EMOTIONAL/BEHAVIORAL CONDITIONS**

*Oppositional defiant disorder; conduct disorder; depressive disorders; anxiety disorders; bipolar disorder; obsessive-compulsive disorder; posttraumatic stress disorder; adjustment reaction; schizophrenia*

Conditions that in general occur more commonly are italicized. The prevalence of any of these conditions vary depending on the characteristics of the setting in which a child is being evaluated.

the classroom. Dermatologic findings, such as café au lait spots, may suggest neurofibromatosis or other neurologic disorders associated with learning and behavioral difficulties. A history of 20 to 50 episodes a day of repeated staring pauses lasting several seconds in both the home and the school settings may lead a physician to consider absence seizures.

**COEXISTING CONDITIONS**

Coexisting conditions commonly found in children with ADHD include oppositional defiant disorder, conduct disorder, mood disorders, anxiety disorders, and learning disabilities (see Chapter 302, Oppositional Defiant Disorder; Chapter 139, Disruptive Behavior and Aggression; Chapter 129, Anxiety; Chapter 137, Depression; Chapter 284, Learning Disorders). A recent review of these disorders found high rates of comorbidity with ADHD across multiple studies. Oppositional defiant disorder was the most common, with an average prevalence rate of 35.2%

(range: 27.2%–43.8%). Conduct disorder 25.7% (range: 12.8%–41.3%), anxiety disorders 25.8% (range: 17.6%–35.3%), and depressive disorders 18.2% (range: 11.1%–26.6%) were also common. Rates of coexisting learning disabilities are also high, ranging from 12% to 50%. For many of these disorders, a careful history will provide important clues for further evaluation. For example, a history of speech delay in early childhood, family history of learning disabilities, problems with decoding words in the early elementary school years, or disparate skill acquisition across math, reading, and spelling suggest a learning disability. Psychosocial and environmental factors also are common and essential to consider (see Box 220-2).

**EVALUATION**

The AAP recommends that children who present with inattention, hyperactivity, impulsivity, academic underachievement, or behavior problems should undergo an evaluation for ADHD. The evidence supporting this recommendation is strong and is derived from clinical studies showing a high prevalence of ADHD among school-age children exhibiting developmental and behavioral concerns. In the opening case report, Bethany's talkativeness and high energy level may represent hyperactivity, impulsivity, or both. This situation combined with her history of academic difficulties, particularly on entry to middle school when attention to detail and organizational skills are increasingly necessary, should prompt an evaluation for ADHD and related conditions.

**History**

A comprehensive history with particular attention to the presenting complaint, development, school history, family history, and social history is essential to the evaluation and can help identify other problem areas or provide clues to other diagnoses. Sample comprehensive intake forms are available as part of the revised ADHD toolkit. The physical examination, though usually normal, can help identify other problems that may contribute to or represent the cause of a child's behavior problems. In addition, the history and physical examination may allow the opportunity to determine whether there are any suggestions of medical problems that may explain a child's symptoms and to assess a child's mental status and interaction with caregivers.

**Laboratory and Imaging Studies**

Laboratory or imaging tests are not indicated in the routine assessment of ADHD, but may be appropriate if the review of symptoms or physical examination suggests an alternative diagnosis. For example, plumbism and thyroid dysfunction are often thought to be associated with behavioral problems. However, blood lead levels and thyroid hormone levels are infrequently abnormal in children with ADHD, and little evidence exists that these tests adequately discriminate between children with ADHD and without. Children with ADHD often have abnormalities noted on brain imaging or electroencephalography. However, the abnormalities are not consistent, do not usually

represent clinically significant findings, and do not adequately discriminate between children with and without ADHD. Continuous performance tests are often touted as scientific measures of vigilance and distractibility that can help confirm a diagnosis of ADHD, but systematic reviews of these tests find that their sensitivity and specificity (<70%) are inadequate to reliably distinguish between children with and without ADHD.

### Diagnostic Criteria and Diagnostic Tools

The current AAP guidelines recommend that a child must meet *DSM-5* criteria to receive a diagnosis of ADHD. The AAP supports the use of these criteria to ensure a valid diagnosis is made in primary care and to decrease variation in the diagnostic process among physicians. ADHD-specific behavior rating scales probe for the presence of ADHD diagnostic criteria and other behavioral problems and can be used to ensure uniformity in how diagnostic criteria are met (Table 220-1). In addition, ADHD rating scales provide cut-point scores that, when exceeded, indicate an increased likelihood that ADHD is present. Several excellent ADHD rating scales for parent and teacher respondents are commercially available to physicians (see Tools for Practice), including the Vanderbilt Rating Scales, the ADHD Rating Scale, the Conners' Rating Scales, and the SNAP rating scales. The Vanderbilt Rating Scales are also available in the public domain at no cost. Other more general behavior rating scales, such as the Child Behavior Checklist and the Behavior Assessment System for Children do not

include ADHD diagnostic criteria and lack adequate sensitivity and specificity (approximately 86%) for the diagnosis of ADHD and related disorders. However, they may be used to triage children for specific rating scales or diagnostic interviews or to give a more global impression of a child's functioning. None of these tools alone can determine whether a child has a particular disorder; only a trained clinician should make a diagnosis after a thorough evaluation. Any symptoms suggestive of possible harm to self or others warrant immediate evaluation by a skilled clinician.

In addition to determining whether children meet symptom criteria, clinicians should determine whether children demonstrate poor functioning as a result of symptoms. For example, the Vanderbilt Rating Scales have questions that address academic and social functioning and can be used to assess relative strengths and weaknesses. Clinicians should obtain this information from both parents and teachers. Given that children spend a substantial amount of time in the classroom, the AAP guidelines stipulate that clinicians should obtain data from schools on children's level of functioning and academic achievement. Data that may be helpful in formulating a diagnostic impression of a child include information on the *DSM-5* diagnostic criteria for ADHD and results of multidisciplinary evaluations, Individual Educational Plan (IEP), achievement tests, grades, and written or verbal teacher narratives. Many of the ADHD rating scales discussed previously use teacher versions that can facilitate endorsement of diagnostic criteria or to assess for other conditions by school or after-school personnel

**Table 220-1** Sensitivity and Specificity of Rating Scales for the Diagnosis of ADHD

RATING SCALE	AGE (YEARS)	GENDER	EFFECT SIZE	95% CI
Conners Parent Rating Scale (CPRS-R:L-ADHD Index)—1997 Revised Version: Long Form, ADHD Index Scale	6–17	MF	3.1	2.5, 3.7
Conners Teacher Rating Scale (CTRS-R:L-ADHD Index)—1997 Revised Version: Long Form, ADHD Index Scale	6–17	MF	3.3	2.8, 3.8
Conners Parent Rating Scale (CPRS-R:L-DSM-IV Symptoms)—1997 Revised Version: Long Form, DSM-IV Symptoms Scale	6–17	MF	3.4	2.8, 4.0
Conners Teacher Rating Scale (CTRS-R:L-DSM-IV Symptoms)—1997 Revised Version: Long Form, DSM-IV Symptoms Scale	6–17	MF	3.7	3.2, 4.2
ACTeRS—Parent Version ADD-H: Comprehensive Teacher Rating Scale, Hyperactivity Subscale	6–14	MF	1.5	1.3, 1.7
ACTeRS—Parent Version ADD-H: Comprehensive Teacher Rating Scale, Attention Subscale	6–14	MF	2.0	1.8, 2.2
SNAP-III (Hyperactivity Subscale)	7–12	MF	5.1	3.9, 6.3
SNAP-III (Inattention Subscale)	7–12	MF	4.2	3.2, 5.2
SNAP-III (Impulsivity Subscale)	7–12	MF	5.5	4.3, 6.7
School Situations Questionnaire (SSQ-O-I)—Original Version, Number of Problem Settings Scale	6–11	F	1.3	0.5, 2.2
School Situations Questionnaire (SSQ-O-II)—Original Version, Mean Severity Scale	6–11	F	2.0	2.2, 3.5
Vanderbilt AD/HD Diagnostic Parent Rating Scale (VADPRS)	6–12	MF	N/A	N/A
Vanderbilt AD/HD Diagnostic Teacher Rating Scale (VADTRS)	6–12	MF	N/A	N/A

CI, confidence interval; F, female; M, male.

From Green M, Wong M, Atkins D, Taylor J, Feinleib M. *Diagnosis of Attention-Deficit/Hyperactivity Disorder. Technical Review No. 3.* Rockville, MD: Agency for Health Care Policy and Research; 1999. AHCPR Publication No. 99-0050.

(see Table 220-1). For children who are home-schooled or who spend a fair amount of time in after-school programs, clinicians may want to obtain information from the adults overseeing aspects of these programs, such as coaches, religious educators, after-school caregivers, and tutors.

An algorithm that may be helpful in evaluating a child for ADHD is shown in Figure 220-1. Patients with behavior problems or academic difficulties are scheduled for a complete physical examination, including hearing and vision testing, and are given assessment materials. The assessment materials may contain a pediatric intake history form, a request for school records, behavior rating scales, or educational materials. Once the assessment materials have been completed, rating scales scored, and a current physical examination documented, patients may be scheduled for an evaluation. The number of visits needed to complete the evaluation depends on the complexity of complaints and the amount of time available at each visit. The time reported to complete the overall evaluation, review background records, provide patient and family education, and establish a treatment plan ranges from 90 to 240 minutes. Offices have found multiple solutions for obtaining assessment materials and completing evaluations, including the use of a written assessment or computerized packets, longer appointments scheduled at designated times (eg, evenings, Saturday mornings, 1 particular clinic session every other week), partnerships with local schools, or the use of affiliated health personnel, including social workers or mental health professionals. The revised ADHD toolkit includes the Vanderbilt Rating Scales, both parent and teacher initial assessment and follow-up forms, and a sample cover letter.

### Evaluating Children Who Fail to Meet Attention-deficit/Hyperactivity Disorder Criteria

Some children may not meet diagnostic criteria for ADHD because they have fewer than the required number of DSM-5 criteria or because of conflicting reports among parents and school staff. In these circumstances, physicians should carefully evaluate for other conditions that may mimic ADHD (Box 220-2). In addition, physicians may want to counsel families on behavioral interventions. The *Bright Futures in Practice: Mental Health Tool Kit* website ([www.bright-futures.org/mentalhealth](http://www.bright-futures.org/mentalhealth)) contains current procedural terminology (CPT) billing codes for mental health services in the primary care setting and information on limit-setting, charting positive behavior, parenting anxious children, sleep hygiene, homework tips, and anger management that can assist families in caring for children with attentional and hyperactivity problems.

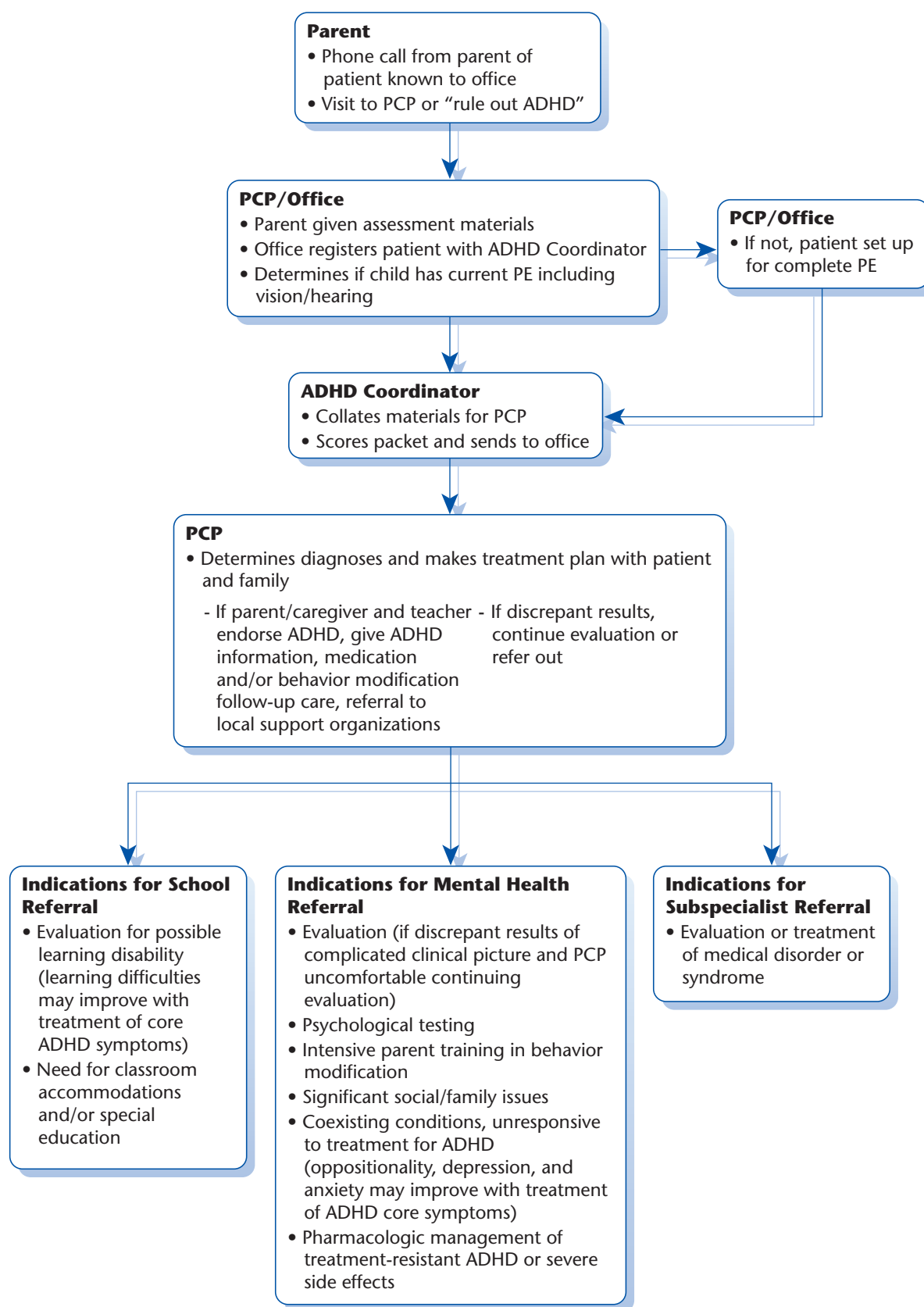
### Evaluating Co-occurring Conditions

Many children with ADHD have co-occurring behavioral or developmental conditions that may impair functioning, and the AAP guidelines recommend that all children undergoing an evaluation for ADHD be screened for these conditions. Several excellent tools are available that supplement a thorough history and

aid the primary care physician in screening for these conditions. Several of the ADHD ratings scales (eg, Vanderbilt Rating Scales, the Conners' Rating Scales-Revised, and the SNAP-IV Scales) include items that query for symptoms of depression/anxiety, oppositional-defiant disorder, and conduct disorders. Global behavioral rating scales such as the Pediatric Symptom Checklist, Child Behavior Checklist (CBCL), and the Behavior Assessment System for Children (BASC) can provide an overall perspective on a child's functioning, although they do not identify specific co-occurring conditions.

For the interested physician, rating scales also exist that specifically target the assessment of particular conditions, including depression, anxiety, and disruptive behaviors. Some examples include the Center for Epidemiological Studies Depression Scale for Children (CES-DC), the Multidimensional Anxiety Scale for Children, and the Eyberg Child Behavior Inventory. A detailed description of rating scales and screening tools specific to a variety of childhood mental health symptoms is available online ([www2.massgeneral.org/schoolpsychiatry/for\\_clinicians.asp](http://www2.massgeneral.org/schoolpsychiatry/for_clinicians.asp)). Questionnaires are also available that review DSM-5 criteria for most common childhood mental health disorders in a single instrument, such as the Child Symptom Inventory (CSI) and the DISC Predictive Scales.

The algorithm (Figure 220-1) directs the physician to refer to another professional (eg, developmental-behavioral pediatrician, mental health provider, or school-based psychologist) if a comorbid condition is suspected and if the physician is not equipped to evaluate sufficiently for these types of disorders in the office setting. Compiling a mental health resource list in the office can assist families in identifying local mental health providers on common insurance plans who can evaluate the child for possible comorbid mental health disorders. The Bright Futures toolkit provides a template for mental health referrals that can be used to structure referral information. For school referrals, parents should be directed to draft a letter requesting a multidisciplinary evaluation, including psychoeducational testing, if the history suggests a possible learning disability such as a reading disorder (dyslexia), mathematics disorder (dyscalculia), a disorder of written expression, or a communication disorder. An example of such a letter is included in the AAP ADHD toolkit. Handouts regarding school problems are available from Bright Futures, including one on common signs of learning disorders. Public schools are required to respond to family requests for evaluations within a specified period determined by local school district policies; even children attending private schools or who are home-schooled are eligible to receive an evaluation through their local school district. Families may also be referred to independent psychologists for psychoeducational evaluations through their insurance plans, but physicians should inquire whether their local school district accepts outside evaluations before making any referrals. In any event, the algorithm recommends that treatment for ADHD not be delayed while awaiting the results of referrals, given that symptoms of many of these conditions may improve with treatment of the ADHD core symptoms.



**Figure 220-1** Sample ADHD primary care office flowchart. *ADHD*, attention-deficit/hyperactivity disorder; *PCP*, primary care physician; *PE*, physical examination.



## MANAGEMENT

The AAP treatment guidelines recommend that families, school personnel, and physicians first recognize that ADHD is a chronic condition that will require ongoing, collaborative care. The Chronic Care Model, first developed by Wagner and colleagues and then modified for children by NICHQ, highlights the importance of patient and family education in the management of any chronic condition. Child and family education is particularly important in treating ADHD for several reasons. First, ADHD affects children across multiple domains of functioning. Second, parents are important partners in treatment, because they implement any treatment programs in the home setting. Third, children with ADHD are often cared for by a spectrum of health and school professionals; parents, especially with latency-age children, function as essential case managers in any ADHD management plan. Last, as children age, it becomes increasingly important that they take on the role of case manager with the ultimate outcome that they are ready to assume management of their ADHD upon adulthood. Handouts, book or website reference lists, or evening/weekend informational sessions in the office for children and families with ADHD are some educational mechanisms that have been used successfully by primary care physicians (see Tools for Practice at the end of the chapter). Additional strategies include educational and support groups such as Children and Adults with ADD (CHADD) or the Learning Disabilities Association (LDA), which provide important information to children and families regarding ADHD and its comorbid disorders, access to mental health and school-based services, and day-to-day lifestyle strategies to address the effect of ADHD on the child and family (see Table 220-2).

The AAP recommends that physicians, parents, and the child, in collaboration with school personnel, identify specific target outcomes in child functioning that they hope to effect through a treatment/management plan. Treatment strategies of choice delineated in the guidelines include evidence-based medication strategies or psychosocial interventions (or both) and are discussed in more detail below. The guidelines also state that child functioning should be systematically monitored over time to evaluate whether target outcomes are achieved or adverse side effects to treatment develop. If a child is not meeting targeted outcomes, then physicians, parents, and school personnel should collaboratively determine the validity of the diagnosis, adherence to all components of the treatment plan, and the possibility of any previously unidentified co-existing conditions. The ADHD toolkit includes sample management plans and follow-up parent and teacher forms to assist physicians in monitoring treatment.

Although the AAP guidelines specifically discuss medications and psychosocial interventions, 3 broad treatment modalities have been recommended in the literature, most often combined in what is commonly referred to as multimodal treatment. Multimodal treatment includes medications, psychosocial interventions directed at the child in the home and school

settings, and classroom assistance. These treatment types are reviewed in the subsections later in this chapter. Data are drawn from 4 sources: (1) the Agency for Healthcare Research and Quality's 1999 evidence report and technology assessment on the treatment of ADHD, (2) Jensen and Cooper's 2002 volume reviewing the state of the evidence regarding diagnosis and treatment of ADHD, (3) results from the recent Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (MTA), and (4) the American Academy of Child and Adolescent Psychiatry's 2007 practice parameters for the assessment and treatment of children and adolescents with ADHD. In general, solid evidence supports the use of medication, behavioral modification strategies, and their combination in the treatment of ADHD. Other treatments have been studied although not as extensively, and the evidence supporting their use is less robust.

## Medication

Psychostimulants (eg, methylphenidate, dextroamphetamine, and the mixed salts of amphetamine) with careful medication management are the most commonly prescribed medications for ADHD (see Table 220-3). Although the mechanism of attentional enhancement is unknown, the psychostimulants are thought to have effects on central catecholamine pathways. In short-term studies, psychostimulants have been found to address the core symptoms of ADHD and improve sustained attention, organization, and motor inhibitor control. They also decrease disruptive behaviors (eg, fidgetiness, impulsive interrupting, aggression, relational interactions, oppositionality) in the classroom, on the playground, in social settings, and at home. With respect to cognitive functioning, these medications increase the accuracy of performance and improve short-term memory, reaction time, and seatwork computation; however, the effect size is smaller than that seen for behavioral challenges. An initial trial showed that stimulants, with careful medication management, were effective for approximately 70% of children diagnosed with ADHD. This percentage increases to over 90% if an alternative stimulant is tried following failure of an initial stimulant.

The most rigorous long-term trial of stimulant medications is the National Institute of Mental Health-funded MTA Study. This study was designed to compare the effects of 4 14-month treatments for school age children with ADHD-CT: (1) stimulants and medication management alone, (2) behavioral interventions, (3) combination therapy (stimulants plus behavioral interventions), or (4) assessment and referral to community care. The stimulant medication and management arm included careful titration of methylphenidate to the maximum dose that improved functioning with the fewest side effects, a 3-times daily schedule, manualized algorithm for dosage adjustment and trial of alternative medications, and monthly pharmacotherapist-performed clinical assessments with parent(s) and teacher. Results demonstrated that carefully managed stimulant medication, either alone or in combination with behavioral interventions,

**Table 220-2** Select ADHD Internet Resources for Clinicians, Families, and Educators

RESOURCE	TARGET AUDIENCE	CONTENTS
American Academy of Pediatrics (AAP) Health Issues ( <a href="http://healthychildren.org/English/health-issues/conditions/adhd/Pages/default.aspx">healthychildren.org/English/health-issues/conditions/adhd/Pages/default.aspx</a> )	Parents	Fact sheets and articles for parents of children with ADHD
American Academy of Pediatrics (AAP) Caring for Children with ADHD: A Resource Toolkit for Clinicians ( <a href="http://shop.aap.org">shop.aap.org</a> )	Clinicians	For purchase; provides forms for the office, screening tools, and handouts for youth and families
American Academy of Pediatrics (AAP) ADHD: What Every Parent Needs to Know, 2nd ed ( <a href="http://shop.aap.org">shop.aap.org</a> )	Parents	Guidance from the AAP for parents of children with ADHD
Children and Adults with ADHD (CHADD) Website for public and members ( <a href="http://www.chadd.org">www.chadd.org</a> )	Parents, youth, clinicians	Provides support and information about ADHD
Children and Adults with ADHD (CHADD) National Resource Center on ADHD Website supported by a cooperative agreement between CHADD and the Centers for Diseases Control and Prevention ( <a href="http://www.help4adhd.org">www.help4adhd.org</a> )	Parents, youth	Provides information about ADHD, diagnosis and treatment, dealing with systems, educational issues, and living with ADHD
Massachusetts General Hospital School Psychiatry Program ( <a href="http://www2.massgeneral.org/schoolpsychiatry/screeningtools_table.asp">www2.massgeneral.org/schoolpsychiatry/screeningtools_table.asp</a> )	Clinicians	Provides a table of all screening tools and rating scales for symptoms of anxiety, social anxiety, obsessive-compulsive disorder, depression, bipolar disorder, suicide risk, ADHD, Asperger disorder, disruptive behaviors, and nonverbal learning disabilities
National Initiative for Children's Healthcare Quality ADHD Toolkit ( <a href="http://www.nichq.org/childrens-health/adhd/resources/adhd-toolkit">www.nichq.org/childrens-health/adhd/resources/adhd-toolkit</a> )	Clinicians	Provides forms for the office, screening tools, and handouts for youth and families; toolkit is available in English and Spanish
Center for Parent Information and Resources ( <a href="http://www.parentcenterhub.org/nichcy-resources">www.parentcenterhub.org/nichcy-resources</a> )	Parents, youth	Includes a limited amount of material on ADHD; good resource on IDEA and other comorbid disabilities
National Institute of Mental Health Health Information: ADHD ( <a href="http://www.nimh.nih.gov/health/topics/attention-deficit-hyperactivity-disorder-adhd/index.shtml">www.nimh.nih.gov/health/topics/attention-deficit-hyperactivity-disorder-adhd/index.shtml</a> )	Parents	Includes general information on ADHD
Sandra Rief ADHD ( <a href="http://www.sandrarief.com">www.sandrarief.com</a> )	Teachers, parents	Includes handouts and other resources specifically focused on classroom and home interventions to improve behavior and academic performance in children with ADHD
Section on Developmental Behavioral Pediatrics ( <a href="http://www2.aap.org/dbpeds">www2.aap.org/dbpeds</a> )	Clinicians	Includes general materials on behavioral-developmental problems including ADHD with a section that links to special article features, handouts for parents, and practice tools.
Bright Futures in Practice: Mental Health Volume II. Toolkit. ( <a href="http://www.brightfutures.org/mentalhealth/pdf/tools.html">www.brightfutures.org/mentalhealth/pdf/tools.html</a> )	Clinicians	Addresses mental health supervision in primary care, mental health across the developmental spectrum, identification of specific types of disorders (including ADHD), and diagnostic criteria, and provides forms for the office, screening tools, and handouts for youth and families
Office of Special Education and Rehabilitative Services, US Department of Education. ( <a href="http://www.ed.gov/teachers/needs/speced/adhd/adhd-resource-pt2.doc">www.ed.gov/teachers/needs/speced/adhd/adhd-resource-pt2.doc</a> )	Teachers, parents	Provides information on policies and research regarding educational interventions for children with ADHD.

Table 220-3

Stimulant Medications, Dosing, and Onset/Duration of Effects In Alphabetical Order<sup>a</sup>

ACTIVE INGREDIENT	DRUG NAME	DOSING	ONSET/DURATION OF EFFECTS
<b>AMPHETAMINE-BASED</b> Amphetamine, mixed salts (Dextroamphetamine/levoamphetamine)	Adderall Tablets ( <i>scored</i> ): 5, 7.5, 10, 12.5, 15, 20, 30 mg Generic available	Initial: 5 mg in AM Increase: 5 mg weekly Frequency: 1–3 doses/day Maximum recommended daily dose: 40 mg/day	Onset: 30 minutes Duration: 4–6 hours
	Adderall XR Extended release capsule ( <i>sprinkleable</i> ): 5, 10, 15, 20, 25, 30 mg Generic available	Initial: 5 mg in AM Increase: 5 mg weekly Frequency: 1 dose/day Maximum recommended daily dose: 30 mg/day	Onset: 30–45 minutes Duration: 8–12 hours
Amphetamine	Evekeo Tablet: 5, 10 mg ( <i>scored</i> )	Initial: 2.5–5 mg in AM Increase: 2.5–5 mg weekly Frequency: 1–3 doses/daily Maximum recommended daily dose: 40 mg/day	Onset: 30 minutes Duration: 4–6 hours
Dextroamphetamine	Dexedrine Tablet: 5 mg Dextrostat Tablet ( <i>scored</i> ): 5, 10 mg Generic Available	Initial: 2.5–5 mg in AM Increase: 2.5–5 mg weekly. Frequency: 2–3 doses/day Maximum recommended daily dose: 40 mg/day	Onset: 20–60 minutes Duration: 4–6 hours
	Dexedrine Spansules Sustained release capsule ( <i>can not be chewed</i> ): 5, 10, 15 mg	Initial: 5 mg in AM Increase: 5 mg weekly Frequency: 1–2 doses/day Maximum recommended daily dose: 40 mg/day	Onset: 60–90 minutes Duration: 6–10 hours
	Procentra Solution 5 mg/5 ml solution	Initial: 2.5–5 mg in AM Increase 2.5–5 mg weekly Frequency: 2–3 doses/day Maximum recommended daily dose: 40 mg/day	Onset: 20–60 minutes Duration: 4–6 hours
Lisdexamfetamine	Vyvanse Extended release capsule (can be dissolved in water): 20, 30, 40, 50, 60, 70 mg	Initial: 10–20 mg in AM Increase 10 mg weekly Frequency: 1 dose/day Maximum recommended daily dose: 70 mg	Onset: 50 min Duration: 10–14 hours
<b>METHYLPHENIDATE-BASED</b> Dexmethylphenidate	Focalin Tablets ( <i>scored</i> ): 2.5, 5, 10 mg Generic available	Initial: 2.5 mg in AM Increase: 2.5 mg weekly Frequency: 2–3 doses/day Maximum recommended daily dose: 30 mg	Onset: 20–30 minutes Duration: 4–5 hours
	Focalin XR Capsule ( <i>sprinkleable</i> ): 5, 10, 15, 20 mg, 25, 30, 35, 40 mg Generic available	Initial: 5 mg in AM Increase: 5 mg weekly Frequency: 1 dose/day Maximum recommended daily dose: 30 mg	Onset: 30 min Duration: 8–12 hours
Methylphenidate	Ritalin Methylin Tablets ( <i>scored</i> ): 5, 10, 20 mg Methylin Chewable tablets: 2.5, 5, 10 mg Methylin Oral solution: 5, 10 mg/5 mL Generic available	Initial: 5 mg in AM Increase: 2.5–5 mg weekly Frequency: 2–3 doses/day Maximum recommended daily dose: 50–60 mg depending on formulation	Onset: 15–20 minutes Duration: 3–5 hours

Continued

**Table 220-3****Stimulant Medications, Dosing, and Onset/Duration of Effects In Alphabetical Order<sup>a</sup>—cont'd**

Ritalin-LA Capsule ( <i>sprinkleable</i> ): 10, 20, 30, 40 mg Ritalin-SR Tablet: 20 mg SR Metadate ER Tablet: 10, 20 mg extended release Methylin ER Tablet: 10 mg extended release Metadate CD Capsule ( <i>sprinkleable</i> ): 10, 20, 30, 40, 50, 60 mg extended release Generic available	Initial: 10 mg in AM Increase: 10 mg weekly Frequency: 1 dose/day Maximum recommended daily dose: 60 mg	Onset: 30 minutes Duration: 6–10 hours
Concerta Capsule ( <i>noncrushable</i> ): 18, 27, 36, 54, 72 mg Generic available (make sure uses OROS-delivery system)	Initial: 18 mg in AM Increase: 18 mg weekly Frequency: 1 dose/day Maximum recommended dose: 72 mg	Onset: 30–45 minutes Duration: 8–12 hours
Daytrana Patch: 10, 15, 20, 30 mg patch	Initial: 10 mg worn daily for 9 hours beginning in AM Increase: 10 mg/9 hours weekly Frequency: Apply in AM as early as possible; worn daily for 9 hours Maximum recommended daily dose: 30 mg/9 hour Note: Skin sensitization (e.g., edema, papules, vesicles) that does not significantly improve within 48 hours or spreads beyond the patch site) may occur rarely and differs from an erythematous contact rash.	Onset: 60–120 minutes Duration: Variable, lasts 2–3 hours after patch removed
Quillivant XR Liquid: 25 mg/5 mL	Initial: 20 mg in AM Increase: 20 mg weekly Frequency: 1 dose/day Maximum recommended daily dose: 60 mg Start at 20 mg in am and increase by 10–20 mg increments until good control is achieved. Before administering dose, vigorously shake the bottle for at least 10 seconds to ensure the proper dose is administered. Maximum recommended dose: 60 mg	Onset: 45–60 minutes Duration: 10–12 hours

<sup>a</sup>Dose and frequency should be based on the child's schedule demands, metabolism, response, side effects, and parent/patient choice (eg, parents choosing to only provide medication during school times). Decision making may be documented in the medical record.

was effective in reducing the core symptoms of ADHD, reducing oppositional-aggressive and anxiety symptoms, and improving social skills.

The effects of stimulants are primarily compensatory and not curative. The effect lasts only as long as the child takes the medication. Unfortunately, very few long-term studies of the efficacy of the stimulant medications have been conducted; specific studies that are available are limited by their retrospective study design, lack of adherence measures, limited use of titration, and poor identification of comorbid conditions. A meta-analysis by Swanson and colleagues

concluded that the effect of stimulant medications over time on academic achievement was significantly less than the effect on behavior and cognition. In addition, many children with ADHD continue to show symptoms as they mature and enter adult life, including troublesome interpersonal relationships with family members and peers, career underachievement, and poor self-esteem. However, these earlier studies were not adjusted for the onset of treatment and the intensity of intervention offered. More recent retrospective studies demonstrate that treatment may protect against poor outcomes. For example, children treated



for ADHD with stimulant medication may be less likely to experiment with substances during adolescence compared with their untreated peers with ADHD.

The decision regarding the use of psychostimulants requires careful consideration of the associated benefits and risks. Common side effects of the psychostimulants include headaches, stomachaches, insomnia, and anorexia. The MTA study has documented a persistent growth delay, particularly when children were on higher and more consistent doses. Recent data suggest that the medications do not seem to consistently exacerbate tics. Less commonly reported adverse events include irritability, emotional lability or constriction, and compulsive picking of the nose or skin. Preschool children may experience more dysphoria and mood lability. These medications are also classified as schedule II medications with possible high abuse potential, although the research does not suggest a preferential use of stimulants in individuals with ADHD and substance use disorders.

Other safety concerns were the focus of a US Food and Drug Administration (FDA) review in 2006 and in 2011 and included cardiovascular and psychiatric complications related to the stimulant medications. Cardiovascular concerns included elevations in heart rate and blood pressure, and rare cardiovascular events such as stroke, myocardial infarction, and sudden death in children with preexisting cardiac disease. The panel concluded that children should be monitored for the emergence of hypertension. In addition, children starting on medication should have a complete history taken (including a family history of heart disease or arrhythmias, symptoms of shortness of breath, chest pain, dizziness, or palpitations on exertion) and a physical examination. In 2008, the AAP reiterated the role of an in-depth cardiac history and physical examination, with a follow-up electrocardiogram if indicated or a cardiology referral in cases with a family history or personal history of cardiac disease or symptoms prior to starting stimulant medications. Psychiatric concerns raised by the FDA review included new onset or acute exacerbation of aggressive symptoms and rare hallucinogenic symptoms, particularly visual hallucinations related to insects. Although all of these complications are rare, as with any medication, careful monitoring and vigilance are essential.

If parents, in concert with a child and physician, decide to try a psychostimulant, all must realize that medication choice, dose, and time interval must be carefully titrated to meet the needs of the individual child. In fact, several trials may be necessary before the most effective medication type and dose with the fewest side effects are identified. Carefully monitored titration that includes documentation of changes in ADHD symptoms and target outcomes and the development of any side effects is essential. Although the AAP guidelines do not stipulate the frequency of return visits, they do recognize ADHD as a chronic condition and recommend return visits to reassess academic performance, behavior, and side effects. More intensive visits may be necessary around predictable periods of change such as entry into middle or high school. Trials of medication are important to conduct but

should be scheduled so as to not overlap with the beginning of school terms, examinations, or family stressors. Families, children, and physicians should consider carefully the use of medication in the afternoons and evenings, on weekends, and during the summer, taking into account the severity of a child's dysfunction, the effect on family and peer relationships, cultural expectations, and the presence of any decrease in weight or height velocity. Sample follow-up forms are included in the ADHD toolkit. Management of possible side effects is delineated in Table 220-4.

Psychostimulants should be considered second-line therapy for preschool children aged 4 to 5 years, given results from the Preschool ADHD Treatment Study that suggest a strong response to behavioral interventions without medication. The guidelines support the use of stimulants if children still have moderate to severe impairment after implementing behavioral therapies. Dextroamphetamine has an FDA indication for preschool-aged children with ADHD, although there is more evidence for efficacy and safety in this age group than with methylphenidate. Preschool-aged children metabolize stimulants at a slower rate than older children and report more side effects, so lower doses should be prescribed to start and increased in smaller increments.

Regardless of the child's age, the AAP guidelines recommend certain nonstimulant medications as second-line treatment of ADHD after psychostimulants, including a selective norepinephrine reuptake inhibitor (atomoxetine), and the  $\alpha$ -agonists (clonidine and guanfacine) (see Table 220-5). These medications are currently considered second-line treatment because of fewer rigorous research trials, more adverse side effects, or less efficacy in comparison with the stimulants. In brief, the  $\alpha$ -agonists clonidine and guanfacine have moderate effects on hyperactivity and impulsivity, aggression, and tics. Given their effect on the cardiovascular system, care must be taken to not stop these medications abruptly, as this might result in rebound hypertension. In addition, sedation, particularly with clonidine, can be a significant problem. Bupropion, an atypical antidepressant not recommended in the AAP guidelines, has a few studies relating to its use in ADHD, and has been suggested as an option in children with comorbid depression. Atomoxetine was approved for the treatment of ADHD in 2003; common side effects include stomachache, nausea, appetite suppression, and weight loss. With increasing use of atomoxetine in the community over the last several years, warnings have surfaced regarding aggression, suicidality, reversible hepatotoxicity, and cardiac effects. The tricyclics have historically been used as second-line agents for ADHD, but their narrow toxic-to-therapeutic ratio has virtually eliminated their use in children with ADHD. Modafinil is currently approved for treatment of narcolepsy, and recent studies suggest its possible use in ADHD, although its application for approval for treatment with ADHD was denied by the FDA in 2006. No long-term studies on these medications in the management of ADHD have been completed. As with all medications, physicians should continue to monitor new scientific information about efficacy and adverse events.

**Table 220-4****Common Side Effects of Stimulant Medications and Recommended Clinical Management**

SIDE EFFECTS	RECOMMENDED CLINICAL MANAGEMENT
General	<ul style="list-style-type: none"> <li>• For mild side effects, allow 7–10 days for tolerance to develop.</li> <li>• Evaluate time-action and determine if timing of administration can be adjusted to minimize side effect.</li> <li>• Determine whether side effects are related to other disorders or current environmental stressors and adjust accordingly.</li> <li>• If these strategies fail, consider an alternative stimulant.</li> </ul>
Weight loss/anorexia	<ul style="list-style-type: none"> <li>• Administer medication at or after a meal.</li> <li>• Try calorie enhancement strategies, such as high-protein instant breakfasts, protein bars, etc.</li> <li>• Get eating started with any highly preferred food before giving regular foods.</li> <li>• Allow grazing in the evening when appetite suppression wanes.</li> <li>• Change stimulant medications.</li> <li>• Consider drug holidays.</li> </ul>
Dizziness	<ul style="list-style-type: none"> <li>• Monitor blood pressure and pulse.</li> <li>• Encourage adequate hydration.</li> <li>• If associated only with peak drug effect, try longer-acting preparation.</li> </ul>
Insomnia/nightmares	<ul style="list-style-type: none"> <li>• Establish bedtime routine.</li> <li>• Omit or reduce last dose or change to standard, short-acting version if using longer-acting preparation.</li> <li>• Administer medication earlier in the day.</li> <li>• Try a different stimulant.</li> <li>• Give “Parenting Tips for Better Sleep” handout (sample available at <a href="http://www2.aap.org/sections/dbpeds">www2.aap.org/sections/dbpeds</a>).</li> </ul>
Dysphoric mood, emotional constriction	<ul style="list-style-type: none"> <li>• Consider additional medication as a last resort.</li> <li>• If peak effect, reduce dose, or switch to longer-acting preparation.</li> <li>• Evaluate when occurs. See below for guidance on rebound.</li> <li>• Try a different stimulant.</li> <li>• Consider comorbid anxiety or depression disorders requiring alternative or adjunctive treatment.</li> </ul>
Rebound	<ul style="list-style-type: none"> <li>• Consider additional medication as a last resort.</li> <li>• Try to decrease precipitous drop in blood levels by using a “stepped down” dosage at the end of the day through increasing morning long-acting dose or adding a smaller dose of short-acting medication toward the end of the day.</li> <li>• Switch to longer-acting preparation.</li> <li>• Combine longer-acting and short-acting preparations.</li> <li>• Overlap stimulant dosing.</li> </ul>
Tics	<ul style="list-style-type: none"> <li>• Conduct drug trial at different doses, including no medication, to be sure tics are drug related.</li> <li>• For mild tics that abate after 7–10 days, reconsider risk vs benefit, and negotiate a new informed consent with the parent/guardian.</li> <li>• Conduct drug trial to see if tics abate with another stimulant.</li> <li>• Consider nonstimulant treatment, such as clonidine, alone or in combination with a stimulant, or refer to mental health specialist or neurologist skilled in the management of tics.</li> <li>• If tics appear suddenly after a sore throat or sinus infection, consider strep-associated tics or PANDAS (Pediatric Autoimmune Neurologic Disorders Associated with Strep) and treat with appropriate antibiotic.</li> </ul>
Psychosis	<ul style="list-style-type: none"> <li>• Check that correct dose is being administered.</li> <li>• Discontinue stimulant treatment.</li> <li>• Assess for presence of coexisting bipolar or thought disorder.</li> </ul>
Skin irritation	<ul style="list-style-type: none"> <li>• Consider alternative treatments, or referral to a mental health specialist.</li> <li>• Skin irritation may arise with use of the patch, either because of hypersensitivity to methylphenidate or other components in the product (eg, acrylic adhesive).</li> <li>• Rotation of the patch may help.</li> <li>• Use of the patch may lead to contact sensitization indicative of allergic contact dermatitis and should be suspected if erythema is accompanied by evidence of a local and intense reaction with edema, papules, or vesicles or if physical manifestations spread beyond the area of the patch.</li> <li>• Use should be discontinued, allergic diagnostic testing considered, and use of an oral methylphenidate under close medical supervision initiated.</li> </ul>

Adapted from Conners CK, Jett JL. *Attention Deficit Hyperactivity Disorder (In Adults and Children): The Latest Assessment and Treatment Strategies*. Kansas City, MO: Compact Clinicals; 1991; Block SL. Attention-deficit disorder: A paradigm for psychotropic medication intervention in pediatrics. *Pediatr Clin North Am*. 1998;45(5):1053–1083; Wilens TE. *Straight Talk About Psychiatric Medications for Kids*. New York, NY: Guilford Press; 1999.

**Table 220-5** Additional Medications for Treatment of ADHD (in alphabetical order by drug class)

DRUG	FORM	DOSING	COMMON SIDE EFFECTS	DURATION OF BEHAVIORAL EFFECTS	BENEFITS	PRECAUTIONS
ALPHA AGONISTS						
Catapres® or Generic Clonidine	Tablets: 0.1, 0.2, 0.3 mg	Initial: 0.05 mg at bedtime Increase: 0.05 mg every 3–7 days Frequency: 2-4 doses/day Maximum recommended dose: 0.4 mg/day	Sleepiness, irritability, hypotension, dizziness, dry mouth, constipation.	Tablet: 3–6 hours	Helpful for ADHD patients with significant comorbid tics; may be helpful for ADHD patients with aggression or insomnia.	Side effects include sedation, dizziness, nausea, orthostatic hypotension, depression, nightmares. Sedation decreases over time. To avoid daytime tiredness, give tablet initially at night. Sudden discontinuation could result in rebound hypertension. When discontinuing, the total dose should be tapered in decrements of no more than 0.1 mg every 3–7 days. See FDA for other precautions.
Catapres or Generic Clonidine	Patches TTS-1 TTS-2 TTS-3	Initial: TTS 1 patch Increase 0.1 mg every 2 weeks Frequency: change every 5–7 days; rotating sites on back	Sleepiness, irritability, hypotension, dizziness, dry mouth, constipation. Local-zed skin reactions with patch	Patch: 1–5 days		
Kapvay Clonidine Extended Release	Tablets: 0.1, 0.2 mg	Initial: 0.1 mg tablet at bedtime. Increase: 0.1 mg weekly Frequency: 2 doses/day; with either an equal or higher split dosage being given at bedtime. Maximum recommended daily dose: 0.4 mg/day	Sleepiness, irritability, hypotension, dizziness, dry mouth, constipation.	12–24 hours	May be helpful for ADHD patients either as monotherapy or as an adjuvant therapy.	
Tenex or Generic Guanfacine	Tablet: 1, 2 mg	Initial: 0.5 mg at night. Increase: 0.5 mg weekly. Frequency: Give as 1–2 dose/day Maximum recommended daily dose: 3 mg/day	Irritability, tiredness, confusion at higher doses, agitation.	About 24 hours in the body, but must be taken 2 (or 3) times/day.	May cause less sedation and irritability than clonidine.	Side effects include sedation, dizziness, nausea, orthostatic hypotension, insomnia, agitation, headaches, nightmares. Sedation decreases over time. To avoid daytime tiredness, starting dose given at bedtime and increased slowly. Sudden discontinuation could result in rebound hypertension; wean slowly. See FDA for other precautions.
Intuniv Guanfacine Extended Release	Tablet: 1, 2, 3, 4 mg	Start with 1 mg and increase by no more than 1 mg/week. Maintain dose in range of 1–4 mg/day.	Irritability, tiredness, confusion at higher doses, agitation.	24 hours	May be helpful for ADHD patients as monotherapy or as an adjuvant therapy. May cause less sedation and irritability than clonidine.	

Continued

Table 220-5 Additional Medications for Treatment of ADHD (in alphabetical order by drug class)—cont'd

DRUG	FORM	DOSING	COMMON SIDE EFFECTS	DURATION OF BEHAVIORAL EFFECTS	BENEFITS	PRECAUTIONS
SELECTIVE NOREPINEPHRINE REUPTAKE INHIBITORS						
Strattera	Capsules: 10, 18, 25, 40, 60, 80, 100 mg	Initial: 0.5 mg/kg in AM Increase: Frequency: Usually single dose per day but can split if GI issues or fatigue.	Nausea, vomiting, fatigue, decreased appetite decreased, dizziness, tiredness, aggression, constipation, dry mouth, insomnia,	18–24 hours	Helpful as second-line treatment for ADHD or for ADHD patients with comorbid anxiety	If sedation, consider moving initial dosing regimen to evening. Common side effects include fatigue, lightheadedness, GI upset, dry mouth, sweating, insomnia, weight loss, headache. Rare side effects include mood swings, sexual and menstrual changes, 2 cases of liver damage. See FDA for other precautions.
Atomoxetine		Recommended maximum daily dosage: 1.44 mg/kg/day or 100 mg/day	decreased libido, and mood swings			



### Psychosocial Interventions

Several studies show that psychosocial interventions, predominantly using behavioral management principles, decrease ADHD symptoms and impairment. Behavioral interventions usually consist of parent training programs for use at home, child-focused intensive summer camp programs, behavioral modification in the classroom, and peer interventions. In general, these interventions focus less on improving the core symptoms of ADHD (inattention, impulsivity, and hyperactivity) and instead seek to improve parenting practices, school functioning, and peer relationships. Common to many of these approaches is the use of behavioral techniques such as positive reinforcement, time-out, response costs, or token economies (see Table 220-6). Individual psychotherapy and play therapy have not been shown to reduce core ADHD symptoms in children; however, there is some evidence for cognitive therapy in adults. These nonbehavioral therapies may benefit some children with ADHD who have associated mental health conditions responsive to these therapies.

The MTA trial examined the efficacy of behavioral interventions compared to stimulant medication alone or in combination with behavioral therapy. Components of the behavioral interventions in the MTA Study included 27 group and 8 individual parent training sessions, child participation in an 8-week intensive therapeutic all-day summer camp program, and teacher consultation plus 12 weeks of a half-time behaviorally trained paraprofessional aide in the classroom. The results of this trial have been interpreted in

conflicting manners, with some suggesting that the MTA study demonstrates the superiority of medication either alone or in combination with behavioral therapy, and others highlighting the potential importance of psychosocial interventions. Medication in combination with behavioral approaches was found to be particularly effective for children with ADHD and with associated anxiety disorder, ADHD with both anxiety and oppositionality, or children in single-parent households or from low-income families. Combined treatment was also superior to medication alone for outcomes such as parent-child relations and consumer satisfaction.

Several advantages of behavioral interventions that deserve mention include: (1) use in combination with medication may allow for a reduced dose of medication; (2) the therapeutic benefits of stimulant medication usually occur during the day, whereas behavioral interventions may be used in the late afternoon or evening in place of an additional dose of medication; (3) disruptive disorders that commonly co-occur with ADHD have been shown to respond to behavioral modification; (4) psychosocial treatment may help to enhance parents' positive perception of their children and of their own parenting abilities; and (5) the results for medication last only as long as a child continues to take it, whereas behavioral interventions may extend over time. In addition, not all children and families accept the use of long-term medication treatment for ADHD or respond to stimulants. Finally, medications may be more expensive than behavioral interventions in the long run.

**Table 220-6**

### Evidence-Based Behavioral Treatments for Attention-deficit/Hyperactivity Disorder

INTERVENTION TYPE	DESCRIPTION	TYPICAL OUTCOME(S)	MEDIAN EFFECT SIZE <sup>a</sup>
Behavioral parent training (BPT)	Behavior-modification principles provided to parents for implementation in home settings	Improved compliance with parental commands; improved parental understanding of behavioral principles; high levels of parental satisfaction with treatment	0.55
Behavioral classroom management	Behavior-modification principles provided to teachers for implementation in classroom settings	Improved attention to instruction; improved compliance with classroom rules; decreased disruptive behavior; improved work productivity	0.61
Behavioral peer interventions (BPI) <sup>b</sup>	Interventions focused on peer interactions/relationships; these are often group-based interventions provided weekly and include clinic-based social-skills training used either alone or concurrently with behavioral parent training and/or medication	Office-based interventions have produced minimal effects; interventions have been of questionable social validity; some studies of BPI combined with clinic-based BPT found positive effects on parent ratings of ADHD symptoms; no differences on social functioning or parent ratings of social behavior have been revealed	

<sup>a</sup>Effect size = (treatment median – control median)/control SD.

<sup>b</sup>The effect size for behavioral peer interventions is not reported, because the effect sizes for these studies represent outcomes associated with combined interventions. A lower effect size means that they have less of an effect. The effect sizes found are considered moderate. From American Academy of Pediatrics Subcommittee on Attention-deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2011;128(5):1007–1022.

Disadvantages of behavioral interventions primarily reflect challenges related to accessing these services. The psychosocial interventions with demonstrated effectiveness in the literature are usually quite intensive, including the behavioral intervention in the MTA study, 9-week summer day camp for children with ADHD, and intensive social-skills training sessions for parents and children. These types of intensive interventions are often difficult to access for most children because of a lack of identified mental health providers trained in these programs, lack of insurance coverage, and limited services available through schools.

Physicians caring for children with ADHD can access these types of services through several mechanisms. First, mental health professionals are increasingly being trained in behavioral modification techniques; knowing which providers in the community offer these types of services is essential. Physicians may also choose to provide parenting programs in their office setting or through their health plan. Several practices that participated in a year-long quality improvement program on ADHD care sponsored by the NICHQ, AAP, and Carolina Center for Children's Healthcare Improvement chose to implement behavioral intervention programs for parents in their office settings using available protocols. Behavioral intervention programs for the school setting have also been published and are available online (see [www.ed.gov/teachers/needs/speced/adhd/adhd-resource-pt2.doc](http://www.ed.gov/teachers/needs/speced/adhd/adhd-resource-pt2.doc) for examples of such materials). These types of programs can be requested through the schools as described below.

### School-Based Services

School-based services are a critical part of a comprehensive management plan for several reasons. First, the behaviors observed in children with ADHD are contextually driven and often manifest themselves more in concentration-demanding situations such as school. Communication with school personnel is essential for making the diagnosis of ADHD and for optimal titration of medication, if prescribed. Second, a solid evidence base supports the effectiveness of highly structured behavioral management strategies implemented by school staff in addressing many of the behavioral and organizational challenges experienced by children with ADHD. These interventions can range from daily report cards to point or token systems with primary outcomes consisting of following classroom rules, complying with teacher requests, improving peer interactions, and increasing classroom productivity. The effects tend to be greater for more intensive programs in special class settings, though gains are also seen in regular classrooms. Third, comorbid learning disabilities are not uncommon, and physicians, families, and school personnel should closely monitor each child to ensure that the problems associated with ADHD are not masking coexisting learning disabilities that would require formal testing for learning problems, identification of areas of disability, and specific learning interventions under an IEP as stipulated under the Individuals with

Disabilities Education Act (IDEA) (Public Law 94-142, amended in 1997 under Public Law 105-17). Learning disabilities coexistent with ADHD usually fall into the category of language-based disorders of learning or impaired mathematics performance.

A child with ADHD who does not meet criteria for a specific learning disability may still commonly experience challenges with academic work. The child may demonstrate motor challenges, including dysgraphia, with resultant poor handwriting, and problems related to poor visual-motor abilities (eg, copying materials off of a board or textbook onto paper). Other challenges include inconsistent performance, delayed acquisition of core reading and math skills, low productivity, delay in rapid retrieval of facts, difficulty with higher-level problem solving involving multiple steps, impaired reading comprehension, and poor metacognitive abilities (eg, organization, time management, breaking tasks down into smaller components). These problems can often be inappropriately attributed to laziness or lack of motivation. Education of the child, parents, and school personnel regarding the inadvertent labeling of behaviors related to these difficulties as oppositionality rather than as cognitive challenges associated with ADHD is critical. Interventions such as direct remediation of learning problems, bypass strategies, and metacognitive skills training are all-important academic tools in planning curricula for children with ADHD. Intervention practices not specific to ADHD have been developed and are reviewed in Kavale and Forness' monograph titled *Efficacy of Special Education and Related Services*.

Children can access school-based services via their local public school system through several mechanisms. Individual teachers often modify the curriculum or classroom environment to address a child's needs. Many schools have an interdisciplinary council (eg, student study team, multidisciplinary assessment team) that informally reviews a child's academic performance and behavior and suggests possible remediation. Through Section 504 of the Rehabilitation Act, school systems are mandated to provide accommodations in the mainstream classroom. Under IDEA, school systems also provide a continuum of special education services, ranging from accommodations in the mainstream classroom to a special day class in a public or private placement. Children with ADHD often qualify for special education services because of a coexisting specific learning disability, language disorder, or severe emotional disturbance. In 1991, the US Department of Education also stated that individuals with ADHD might be considered disabled under the "Other Health Impaired" categorization under IDEA, potentially increasing access to school-based special education services for children with ADHD.

Because academic underachievement is so commonly seen in children with ADHD, physicians need some comfort level with the types of interventions available through the public school system. Accommodations requested through a 504 plan or IEP should address a child's individual areas of need. For example, children with ADHD often need preferential seating close to the teacher and daily or weekly

progress reports for both behavior and academic performance sent to the home to allow for close monitoring of school success. Children may also need reduction of the amount of written work, modified homework assignments, or extra time to complete assignments or tests. Organizational difficulties may require supervision of the writing of homework assignments in a planner, an extra set of books at home, and assistance breaking large projects into small steps. Problems with handwriting may indicate a need for access to a computer for written work, copies of teacher lectures, or electronically recorded textbooks. If behavior interferes with the individual child's academic performance or the ability of other children in the classroom to learn, then a behavioral intervention plan is necessary that delineates what behaviors a child displays, factors that escalate or dampen the behavior, and appropriate behavioral interventions. If a child does have a coexisting learning or language disorder, then specific interventions for these disorders should also be included in any plan. Consideration should be given to the appropriate educational placement of a child (eg, mainstream classroom with or without assistance from a resource specialist, special day class, private nonpublic placement). Sample letters requesting a 504 plan or IEP as well as additional information on these programs are available in the ADHD toolkit and on the Bright Futures website.

Concerns are often raised by physicians, parents, and teachers that these types of accommodations may lead to children who feel entitled to extra assistance and will not be able to function adequately in college or the workplace setting. For these reasons, accommodations must be provided within the context of teaching a child to understand his or her own strengths and weaknesses and develop compensatory strategies for addressing their areas of challenge.

### **Alternative Treatments for Attention-deficit/Hyperactivity Disorder**

Alternative approaches to treatment for ADHD abound and have included dietary recommendations, ocular training, and hypnotic and biofeedback regimens. Some treatments have been demonstrated to be efficacious (eg, oligoantigenic diet or restricted elimination diet in ADHD children with food sensitivities), disproven (eg, sugar in the diet), or are potentially unsafe (eg, megavitamin dosages, chelation). Most lack a substantial evidence base for or against their use at this time. Three new studies deserve mention. One recent randomized controlled trial of a restricted elimination and rechallenge diet (mainly rice, vegetables, meat, pears, and water) found a reduction of at least 90% of symptoms in 64% of children with ADHD. Issues with blinding and effort to make sure children adhered to the diet were noted by the authors. A published meta-analysis of 10 randomized clinical trials found a modest effect size for omega-3 fatty acid supplementation compared to placebo. Another trial found neurofeedback to be as effective as methylphenidate for the treatment of ADHD symptoms. If a decision is made to try these types of modalities, the AAP

guidelines recommend similar monitoring of symptoms and functioning using rating scales, histories, and physical examinations. A full discussion of these modalities is beyond the scope of this chapter but an excellent review is available (see Suggested Readings).

### **CASE REPORT: RESOLUTION**

Following a detailed history and physical examination, you are increasingly convinced that Bethany's talkativeness, endless energy, and poor school performance may represent ADHD. You are concerned that her mood and somatic complaints may represent depression, and her early reading difficulties may represent a learning disability. You decide to have her guardian and teacher(s) complete the Vanderbilt Rating Scales, given that they are available in the public domain, facilitate documentation of diagnostic criteria, and can be used to explore the possibility of a comorbid depressive disorder. You compose a brief letter to her teachers using the sample form in the ADHD toolkit as a guide to request their assistance in completing the scales, and you ask that they send any additional school information, such as grades, achievement test results, or narrative summaries, to you. You also instruct Bethany's guardian to draft a letter to her school to request a multidisciplinary assessment for learning disabilities. You elect not to pursue any laboratory or imaging tests, given that Bethany's history and physical examination do not suggest cardiac disease, vision or hearing difficulties, or another diagnosis that would be assessed by such tests.

On a follow-up visit, you review the results of the Vanderbilt Rating Scales and school information obtained from her teacher with Bethany and her guardian. You note that in both her parent and teacher scales she meets 6 of 9 criteria for the predominately hyperactive/impulsive subtype. You also note that she screens positive on 3 of 7 anxiety or depression symptoms. Narrative information from her homeroom teacher corroborates the rating scales and affirms her guardian's concerns that her grades have been slipping. The letter also informs you that the school has scheduled Bethany for psychoeducational testing in the near future. You inform Bethany and her guardian that she meets criteria for ADHD and discuss cause and possible treatment options. You provide educational materials on ADHD that you compiled from the AAP and other selected sites. You relate your concerns that Bethany might be displaying signs of depression. In collaboration with the family, you structure a treatment plan and goals for Bethany using the sample management plan in the ADHD toolkit. The treatment plan includes a prescription for a psychostimulant, a referral to a child psychologist to assess for depression, and a community referral to a local program that sponsors parent behavioral training courses. With Bethany's and her guardian's permission, you draft a letter to the school to inform them of Bethany's diagnosis and to encourage their ongoing collaboration with you in Bethany's care. You also distribute Vanderbilt Follow-up Scales to her guardian and teacher(s) to document any changes in

her symptoms that will assist you in titrating her medication dosage optimally.

At her next several visits, you review Bethany's progress in meeting her goals. You note substantial improvement in her total symptom scores and in her average performance scores on the Vanderbilt Rating Scales. Bethany relates that she initially had stomach pain and headaches with the medication, as you had anticipated with the family at the previous visit, but that these symptoms have resolved. You also check and find that her pulse and blood pressure are within normal limits. Bethany states that she is feeling better about her academic work. Her guardian states that Bethany has been less talkative at home and more organized and focused with her homework since she implemented a behavioral management plan. Next, you review the results of the psychology referral with the family, which confirms a diagnosis of ADHD but does not support a diagnosis of depression or anxiety. Bethany notes that her depressive symptoms have decreased as her ability to succeed at school and on homework have improved with medication and other interventions. However, Bethany continues to struggle with reading. Several weeks later, you receive the results of the psychoeducational testing from the school. You note that Bethany meets criteria for a reading disability and that an IEP was established to assist Bethany in improving her reading abilities and to provide classroom accommodations (eg, seating in front, reduction in distractions, and a daily homework report card). You are pleased with Bethany's progress to date, and you make plans with the family to continue to monitor her closely in the future.

Over time, your goal is to help Bethany and her aunt identify Bethany's strengths as well as areas of challenge related to her ADHD and reading disability. In concert with any mental health professionals and school personnel involved in her care, you will partner to help Bethany develop strategies to address her areas of challenge and to best manage her ADHD symptoms so that she can become a productive, healthy adult.

## CONCLUSION

Attention-deficit/Hyperactivity Disorder is a common, chronic disorder of childhood and adolescence affecting multiple domains of functioning and often continuing into adulthood. Diagnosis and treatment are complicated by the lack of a biological marker, high rates of comorbid conditions, and the need to coordinate care across multiple settings. However, children with ADHD can successfully function in the home and school settings. Families, school personnel, and physicians often observe that children whose symptoms are recognized, assessed, and managed at an early age will show improved self-esteem and success in the classroom, both of which are essential for normal psychosocial and educational development. Although as many as 70% of children and adolescents continue to be symptomatic in adulthood, outcomes are improved with familial stability and support, an ongoing therapeutic relationship with a physician, and a higher IQ. The primary care physician's role is to help children, in partnership with their families and teachers, achieve this goal.

General guidelines for referral are provided in the When to Refer section below. These guidelines should be modified depending on the constellation of symptoms and coexisting conditions a particular child exhibits and the skill-set and comfort level of the primary care physician in managing the treatment of ADHD and any coexisting conditions. If assistance is needed in evaluating a child, then referral to a mental health professional, school professional, or medical specialist might be indicated. Referral to a mental health professional is indicated for pharmacologic management of treatment-resistant ADHD, more intensive behavioral modification training for the home setting than can be provided in the primary care office, or psychosocial or pharmacological interventions for a coexisting mental health disorder. Mental health professionals may also play an important role if the family is experiencing significant familial stress related to a child's ADHD or if psychopathology exists in the family, including domestic violence, substance abuse, and other conditions. Schools are essential partners in the diagnosis and management of ADHD, whether a child has a coexisting learning disability. Children with severe emotional impairment secondary to any mental health disorder, including ADHD, are also eligible for development of an intensive behavioral management plan under the IEP mechanism through their local school district. Referral to a medical subspecialist is indicated if the history or physical examination suggests evaluation for an additional medical disorder.

## WHEN TO REFER

- Evaluation (if discrepant results or complicated clinical picture exists and the primary care physician is uncomfortable continuing evaluation)
- Psychological testing
- Intensive parent training in behavior modification
- Significant social and family issues
- Coexisting conditions that are unresponsive to treatment for ADHD (oppositionality, depression, and anxiety may improve with treatment of ADHD core symptoms)
- Pharmacologic management of treatment-resistant ADHD or severe side effects
- Major depressive disorder as an immediate referral before initiating treatment for ADHD
- Active substance abuse

## WHEN TO ADMIT

The core symptoms of ADHD should not necessitate admission to a medical or psychiatric hospital. Indications for admission would include:

- Symptoms related to any of the mental health conditions that may co-occur with ADHD
- Adverse event secondary to medication for the treatment of ADHD
- A medical condition resulting from the core symptoms of inattention, hyperactivity or impulsivity associated with ADHD (eg, accidental injury)



## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *Cover Letter to Teachers* (letter), American Academy of Pediatrics, in *Caring for Children With ADHD: A Resource Toolkit for Clinicians* (shop.aap.org)
- *Teaching Children With Attention Deficit Hyperactivity Disorder: Instructional Strategies and Practices* (booklet), US Department of Education ([www2.ed.gov/rschstat/research/pubs/adhd/adhd-teaching.html](http://www2.ed.gov/rschstat/research/pubs/adhd/adhd-teaching.html))

### Engaging Patient and Family

- *ADHD and Your Health Insurance Plan* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *ADHD and Your School-Aged Child* (fact sheet), American Academy of Pediatrics (pediatrics.aapublications.org/cgi/data/108/4/1033/DC1/1)
- *ADHD Management Plan—Sample 1* (form), American Academy of Pediatrics, in *Caring for Children With ADHD: A Resource Toolkit for Clinicians* (shop.aap.org)
- *ADHD Management Plan—Sample 2* (form), American Academy of Pediatrics, in *Caring for Children With ADHD: A Resource Toolkit for Clinicians* (shop.aap.org)
- *Clinician ADHD Economy Pack (English and Spanish Tools)* (toolkit), American Academy of Pediatrics (shop.aap.org)
- *How to Establish a School-Home Daily Report Card* (report), American Academy of Pediatrics, in *Caring for Children With ADHD: A Resource Toolkit for Clinicians* (shop.aap.org)

### Medical Decision Support

- *Center for Epidemiologic Studies Depression Scale for Children (CES-DC)* (scale), Bright Futures ([www.brightfutures.org/mentalhealth/pdf/professionals/bridges/ces\\_dc.pdf](http://www.brightfutures.org/mentalhealth/pdf/professionals/bridges/ces_dc.pdf))
- *Evidence-Based Child and Adolescent Psychosocial Interventions* (chart), PracticeWise, American Academy of Pediatrics ([www.aap.org/en-us/Documents/CRPsychosocialInterventions.pdf](http://www.aap.org/en-us/Documents/CRPsychosocialInterventions.pdf))
- *Mental Health Screening and Assessment Tools for Primary Care* (booklet), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH\\_ScreeningChart.pdf](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH_ScreeningChart.pdf))
- *Patient Health Questionnaire-9 Modified for Teens* (questionnaire), American Academy of Pediatrics, in *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* (shop.aap.org)
- *Scoring Instructions for NICHQ Vanderbilt Assessment Scales*, American Academy of Pediatrics ([www2.aap.org/sections/dbpeds/pdf/VanderbiltRatingScaleScoringInstructions.pdf](http://www2.aap.org/sections/dbpeds/pdf/VanderbiltRatingScaleScoringInstructions.pdf))

## AAP POLICY

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## SUGGESTED READINGS

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## Chapter 221

## AUTISM SPECTRUM DISORDER

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Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by significant developmental delays in language and communication skills; abnormalities in language when it does develop; significant impairments in reciprocal social behavior; a restricted and narrow repertoire of interests and behaviors; ritualized and repetitive behavior patterns; and stereotyped, destructive, and disruptive behavior problems. The diagnosis is made based on the child's behavior, in part historically and in part by concurrent observation or behavior reporting. Children with ASD often function within the intellectually disabled range of general intellectual ability and have limited adaptive behavior. ASD is most often a pervasive and lifelong disability that is difficult to treat.

Because ASD is a categorical disorder, based on observation and historical report rather than quantitative measurement, the description of diagnostic criteria and methods for making a diagnosis have shifted greatly over the years. As a result, there have been dramatic shifts in the estimated prevalence of the disorder since data were first collected in the late 1960s. Historically, autism was thought to occur at a rate of 2 to 5 in every 10,000 children. By the early 2000s, prevalence estimates rose to 10 to 20 in every 10,000

children. More recent data indicate that the incidence of autism may be far greater, with estimated rates ranging from 110 to about 147 per 10,000 children. This trend of steadily increasing rates of autism has caused controversy as to whether increases are related to a truly greater incidence or to other factors, such as greater awareness, changing diagnostic criteria, earlier age at diagnosis, changing diagnostic methods, methodological differences in data collection, and even increased parent demand for the diagnosis so the child can meet treatment and educational service eligibility criteria. It should be noted that despite widely varying prevalence rates, ASD has remained far more common in boys than in girls, with a ratio ranging between 4:1 and 5:1 over the last decade.

The most debilitating aspect of autism is comorbid intellectual disability (ID). Although previously thought to occur in about 70% of children with ASD, the prevalence of ID has most recently been reported to occur at a much lower estimated rate of approximately 31% of all cases of autism. Intellectual disability remains the most difficult aspect of autism to ameliorate, and the presence of ID with autism has the poorest prognosis. Children with both autism and ID fail to benefit from conventional social and educational experiences—the same experiences that allow other children opportunities for cognitive growth and learning. Other comorbid conditions include anxiety, attention problems, seizures, gastrointestinal (GI) problems, and sleep difficulties. Children with autism also often have associated behavioral problems, including pica, self-injury, and aggression.

No known, single cause of autism has been found, and most researchers have accepted that autism likely has multiple causes. Twin studies have indicated a heritability of 38% to 90%, indicating a strong genetic link in ASD, although several pre- and postnatal environmental factors have also been linked to an increased risk for ASD. These include increased maternal stress, maternal age, pre- and postnatal infections, and exposure to neurotoxins. Therefore, evidence is growing for a complex epigenetic relationship that affects neurologic development as early as the prenatal period, and the search for both autism susceptibility genes and environmental catalysts is ongoing. It should, however, be noted that there is no credible evidence supporting the theory that vaccines, such as the measles, mumps, and rubella vaccine, cause ASD. Outside of a specific biological cause, several medical and genetic conditions have been associated with autism, including fragile X syndrome, Cornelia de Lange syndrome, Rett's syndrome, Prader-Willi syndrome, Angelman syndrome, Smith-Lemli-Opitz syndrome, CHARGE syndrome, and tuberous sclerosis.

## DIFFERENTIAL DIAGNOSIS

Diagnostic criteria were significantly reorganized in the fifth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. In *DSM-IV*, the cluster of symptoms most often associated with ASD was split into 3 diagnostic categories: autistic disorder, Asperger disorder, and pervasive developmental disorder not otherwise

specified (PDD-NOS). Childhood disintegrative disorder and Rett's disorder were also included in the *DSM-IV* under the category of pervasive developmental disorders as separate diagnostic categories with a similar set of symptoms. Autistic disorder described a child who met full diagnostic criteria in terms of language deficits, deficits in social interaction, and repetitive, restricted behaviors. Asperger disorder was diagnosed when typical language development was present in the context of impaired social interactions and repetitive, restricted behaviors. The diagnosis of PDD-NOS was reserved for cases in which the central features of language delay, impaired reciprocal social interaction, or restricted, repetitive behaviors were present but not in the degree that would warrant a more specific diagnosis. Childhood disintegrative disorder was described in the *DSM-IV* as differing from ASD in that it was marked by a period of developmental regression after at least 2 years of normal development. In the *DSM-5*, these 4 disorders were collapsed under the single heading of Autism Spectrum Disorder, as previous research found differential diagnosis between the categories to be unreliable. Furthermore, communication and social deficits were collapsed into a single category of possible deficits and children must meet the criteria for all 3 social/communication deficits to meet criteria for ASD. They must also exhibit at least 2 symptoms under the category of restricted, repetitive behaviors.

Additionally, the *DSM-5* now considers Rett syndrome to be a separate diagnosis from ASD because of its specific genetic etiology. Rett syndrome is associated with mutations of the *MECP2* gene on the X chromosome. It may be distinguished from ASDs in most cases by the loss of purposeful hand movements, gait abnormalities, development of specific stereotyped hand movements (hand wringing or mouthing), and severe to profound language and cognitive delays. It is predominantly expressed in girls, but a few cases in boys have been identified.

Publication of the *DSM-5* stimulated concerns that some children who previously would have met criteria in *DSM-IV* might now be excluded and not qualify for services. Studies have since demonstrated that most children who meet criteria for autistic disorder would now be diagnosed with ASD using *DSM-5*, although results have been mixed as to whether all those who would have been diagnosed with PDD-NOS or Asperger disorder under *DSM-IV* criteria would still be diagnosed with ASD under the *DSM-5* criteria. The *DSM-5* states that individuals diagnosed under *DSM-IV* criteria do not need to be rediagnosed, so these changes should not affect the services available to children who have already been diagnosed. Further study is necessary to assess the effect of the new classification system on children who have been evaluated for a possible ASD diagnosis since the *DSM-5* was published.

Autism spectrum disorder should be distinguished from a developmental language disorder. Language disorders are characterized by significant delays in receptive or expressive language skills (or both), but social interaction skills are not qualitatively impaired. It should be noted, however, that children with developmental language disorders may exhibit social deficits

because of their inability to maintain social interactions involving language. Other children and adults may unconsciously withdraw from a child who is not verbally responding, limiting the child's opportunities to develop social skills. Children with language disorders do not, however, usually demonstrate repetitive, restricted behavior patterns.

## EVALUATION

Diagnosing autism is not a straightforward process. No single biological marker, laboratory test, or procedure exists to identify children with autism. Although the diagnosis of autism is primarily a behavioral one based on a comprehensive history, direct observation, and standardized assessment, several medical procedures should be followed to rule out specific known causes of expressed behaviors. Guidelines for medical screening and diagnosis have been widely recognized by scientific and professional societies. The American Academy of Pediatrics (AAP) clinician fact sheet, *Initial Medical Evaluation of a Child Diagnosed With an Autism Spectrum Disorder*, provides an excellent overview of the diagnostic process for physicians.

Because of significant advances within the past 20 years in early behavioral and educational interventions for ASD, children clearly benefit from diagnosis as early as possible and referral to appropriate, effective intervention services. In accordance with this, the AAP recommends that primary care physicians screen for developmental concerns at every well-child preventive care visit. If concerns are raised, physicians should complete a standardized developmental screening test to determine if further evaluation is necessary. In addition, standardized screening tests for developmental delays should also be administered at the 9-, 18-, and 24- or 30-month visits. Specific to screening for ASD, the AAP guidelines recommend that an autism-specific tool should be administered to all children at the 18-month and 24- or 30-month visits. While the AAP recommends several standardized autism-specific tools, the Modified Checklist for Autism in Toddlers (M-CHAT) is one of the most widely used. Because the M-CHAT is designed to be an initial screener to identify the largest possible number of at-risk children, it has a high false-positive rate. The creators of the instrument developed a structured follow-up interview that physicians should use to better identify those in need of further evaluation.

## History

A comprehensive medical, developmental, and psychosocial history is the most important aspect of an evaluation for autism. An evaluator should document birth and neonatal history, developmental milestones, and any developmental regression. History that indicates delays in language and social development, excessive irritability, self-injury, feeding or sleeping problems, or any combination would support a diagnosis of autism, as would extreme hyperactivity, pica, or seizures. Family history of autism, ID, learning difficulties, language delays, mental health problems, and social difficulties should also be explored.

## Physical Examination

General physical examinations for children with suspected autism should consider several suggestive factors. Among children with autism, early childhood head circumference is sometimes larger than in typically developing children. Motor stereotypies of a nonfunctional character (eg, hand flapping) are the most common motor impairments in autism, although hypotonia and limb apraxia have been reported. The latter impairments are more common among children with isolated ID and other developmental disabilities than among children with autism. It is important to rule out hearing problems, as young children with hearing problems also often present with language delays and even some repetitive behavior (eg, shaking their heads back and forth).

*Tuberous sclerosis*, a neurocutaneous disorder affecting the brain and other organs, can account for 0.4% to 3% of children diagnosed with autism. Although 2 gene loci have been identified, the most common initial signs are ash leaf-shaped depigmented macules observed with exposure to ultraviolet light. Any child being assessed for autism should be exposed to ultraviolet light to exclude tuberous sclerosis. If the assessment is positive, the child should be referred to a geneticist.

## Laboratory Evaluation

Given the high rates of heritability in ASD and an increasing body of research that links the occurrence of ASD with epigenetic factors, it is recommended that a genetic consultation be completed with all children diagnosed with ASD (see Schaefer and Mendelsohn [2013] for more detailed guidelines on genetic consultation for patients with ASD). A microarray that tests developmentally significant regions of the genome and for common genetic syndromes, and a DNA study for fragile X syndrome should be offered to all families. It should be explained to families that although genetic testing will not change the treatment for specific ASD symptoms, results may provide an etiology for current symptoms, help the family better understand the risk of recurrence in siblings, and help identify other potential medical concerns associated with specific genetic syndromes. Metabolic and further genetic testing should be considered when additional physiologic signs (eg, unusual and dysmorphic features, seizures, abnormal growth) are observed, to rule out other possible syndromes associated with symptoms of ASD. Specific testing should be considered for:

- *PTEN* gene mutation when head circumference is greater than 2.5 standard deviations above the mean
- *MECP2* gene mutation to rule out Rett syndrome and related phenotypes when a child presents with microcephaly, deceleration of head growth, developmental regression, or the stereotypical "hand-wringing" movement associated with this syndrome. Although *MECP2* mutations are rare in males, further genetic testing should be pursued if these characteristic features are present
- Angelman syndrome when seizure disorder is present along with symptoms of ASD in early childhood,



as well as ID, overly happy affect, and repetitive hand waving/clapping

Electrophysiologic testing is necessary only in cases of suspected comorbid seizure disorder, severe sleep problems, or developmental regression.

### Imaging Studies

No imaging evaluation procedures are needed in a routine evaluation for autism. When other neurologic findings, such as seizure, asymmetric motor functioning, cranial nerve dysfunction, or severe headache, co-occur with suspected autism, the principles of standard clinical assessment apply.

## MANAGEMENT

The primary care physician's role in managing ASD begins with the careful screening of development during early childhood, and referral when needed for a specialist evaluation of developmental delays and unusual behaviors. After an accurate diagnosis of ASD is made, the physician's role is to provide ongoing care for the child within a medical home model of primary pediatric care, in accordance with AAP guidelines. More specifically, the pediatrician should strive to provide accessible, comprehensive, family-centered care for children with ASD, while evaluating for and helping manage common medical comorbidities, identifying the need for and perhaps managing psychopharmacologic interventions, coordinating specialty services and referrals, and advocating for effective psychosocial and behavioral interventions. Using a medical home model of care helps ensure that children receive needed preventive care and access to specialty services in a timely manner, and also helps avoid duplicating services by improving care coordination and communication between health care providers.

### Screening and Referral

Table 221-1 provides a description of some of the most common comorbid disorders and difficulties associated with ASD, along with considerations for screening and diagnosis, management, and referrals to specialty care.

### Psychopharmacology

To date there are no medications approved to treat the core symptoms of ASD (eg, social/communication deficits, restricted/repetitive behaviors), although there is evidence that behavioral problems commonly associated with ASD can be partially managed with medication. Medical providers must carefully weigh the possible benefits with the adverse effects commonly associated with these medications.

Symptoms of attention deficit/hyperactivity disorder (ADHD) are often seen in children with ASD, and the *DSM-5* now allows for both diagnoses to be given together. Physicians should carefully evaluate symptoms of hyperactivity, impulsivity, and inattention using current accepted standards of care to evaluate whether symptoms are significantly affecting functioning across environments (eg, school, home), ruling out other possible causes for these symptoms (eg, sleep problems, constipation/GI problems, anxiety/depression). If the child does meet the criteria for

comorbid ADHD, the physician should help the family connect with additional services (eg, school and mental health professionals) to set up appropriate behavioral and academic interventions. After appropriate interventions are put into place, the severity of the ADHD symptoms and effects on everyday functioning should be re-evaluated to determine if a trial of medication is necessary. Physicians should then follow the recommended guidelines for choosing an appropriate medication to begin treatment of ASD symptoms. Although stimulant medications (eg, methylphenidate and amphetamine preparations) are still most often prescribed as the first-line choice for treating comorbid ADHD, initial research has indicated that the rate of therapeutic response may be lower and the rate of side effects (particularly significant irritability) may be higher in children with both ASD and ADHD than in children with only a diagnosis of ADHD. Limited evidence suggests that atomoxetine and  $\alpha$ -2 agonists (eg, guanfacine and clonidine) may be effective in reducing ADHD symptoms, although research on effectiveness and side effects, particularly in an ASD population, is limited.

To date, risperidone and aripipazole, both atypical antipsychotic medications, are the only medications approved by the US Food and Drug Administration for treating behavioral problems in autism. While both of these medications have been shown to be effective in reducing irritability, aggression, self-injury, stereotypy, and hyperactivity in some children with ASD, they are also associated with several significant side effects including increased weight gain, sedation, and risk of extrapyramidal symptoms. Selective serotonin reuptake inhibitors (eg, fluoxetine, sertraline) have not been found to improve repetitive behaviors, and have been frequently associated with adverse effects in children with ASD. As of yet, no longitudinal studies have been completed that examine the long-term effects of any of these medications on the neurophysiologic development of young children. Further research on the effectiveness and long-term side effects of these medications in children with ASD is greatly needed to improve patient care.

### Advocating for Treatment

After an ASD diagnosis is made, primary care physicians are placed in the role of advocating for families to access the services and supports recommended by the developmental specialist. Helping families connect with the most effective treatment services while helping them avoid committing time, energy, and money to treatments with no known effectiveness is a difficult yet invaluable role.

The first step in advocating for effective treatment services is helping families access the support provided by state and local government agencies. If the child is younger than 3 years, a referral should be made to early intervention services. If the child is older than 3 years, a referral should be made to developmental disability services. What services are available and how these services are structured vary greatly from state to state. If families need further financial help, they can be advised to apply for social security benefits for their child.



**Table 221-1** Common Comorbid Disorders and Difficulties Associated With ASD

DESCRIPTION	CONCERNS RELATED TO SCREENING AND DIFFERENTIAL DIAGNOSIS	MANAGEMENT AND REFERRALS TO CONSIDER
<p><b>SEIZURE DISORDER<sup>a</sup></b> Estimated to occur in 7%–35% of children with ASD Peak risk periods for onset are in early childhood and in adolescence All types of seizures are seen but complex partial seizures are most common in ASD Most often seen with comorbid ID, dysmorphic features, and motor impairment</p> <p><b>SLEEP DISORDERS<sup>a</sup></b> Estimated to occur in 40%–80% of children with ASD Most common problems are with:</p> <ul style="list-style-type: none"> <li>• Sleep onset</li> <li>• Sleep maintenance</li> <li>• Sleep duration</li> </ul> <p>Children with ASD often have disrupted sleep patterns in which they wake during the night for periods up to 2–3 hours, during which time they may laugh, talk, or get up to play. Sleep problems in general tend to be more serious in children with ASD than typically developing children Sleep disturbance can lead to behavioral problems such as hyperactivity, inattention, or irritability</p> <p><b>GASTROINTESTINAL DISORDERS<sup>a</sup></b> Estimated to occur in 9%–70% of children with ASD Most common GI problems in children with ASD include:</p> <ul style="list-style-type: none"> <li>• Chronic constipation</li> <li>• Abdominal pain</li> <li>• Chronic diarrhea</li> <li>• Symptoms of GERD</li> <li>• Gastritis; esophagitis</li> <li>• Inflammatory bowel disease; celiac disease; Crohn disease; colitis</li> </ul>	<p>It can be difficult to distinguish between motor mannerisms and seizure activity Staring spells, cessation of activity, eye fluttering, eye deviations to one side, and behavioral changes such as confusion or fatigue may indicate concern for seizures It may be helpful to have parents take a video or keep a record of possible seizure activity to aid in differential diagnosis</p> <p>It is recommended that all children with ASD be screened for sleeping problems Possible screening tools:</p> <ul style="list-style-type: none"> <li>• Children's Sleep Habits Questionnaire (CSHQ)<sup>c,d</sup></li> <li>• Pediatric Sleep Questionnaire (PSQ)<sup>e,f</sup></li> </ul> <p>Rule out or address other problems that may be causing sleep disturbance</p> <ul style="list-style-type: none"> <li>• Obstructive apnea</li> <li>• Respiratory compromise secondary to enlarged tonsils and adenoids</li> <li>• Parasomnias</li> <li>• Side effects of medication</li> <li>• Anxiety/depression</li> <li>• GI disorders (eg, GERD)</li> <li>• Constipation</li> </ul> <p>A thorough medical history and physical evaluation, including nutritional assessment, should be completed Accurate evaluation of abdominal pain may be difficult given communication deficits In lower-functioning and nonverbal individuals, irritability, aggression, and self-injury may be signs of pain and discomfort</p>	<p><b>Referrals to consider:</b></p> <ul style="list-style-type: none"> <li>• EEG to evaluate seizure activity</li> <li>• Neurologist for further evaluation and medication management</li> </ul> <p>For further information see physician fact sheet and family handout in AAP toolkit<sup>b</sup></p> <p><b>Management:</b></p> <ul style="list-style-type: none"> <li>• Review appropriate sleep hygiene with families (eg, consistent bedtime routine, limit electronics 2 hours before bed, limit bedroom to sleeping). Family handouts available through AAP and ATN toolkits<sup>b,g</sup></li> <li>• May consider trial of melatonin, although it should be noted that rigorous efficacy studies have not yet been completed</li> </ul> <p><b>Referrals to consider:</b></p> <ul style="list-style-type: none"> <li>• Sleep specialist</li> <li>• Neurologist</li> <li>• ENT specialist</li> </ul> <p><b>Management:</b></p> <ul style="list-style-type: none"> <li>• Milder problems, such as constipation and GERD, may be managed in an outpatient setting following current recommended guidelines<sup>h</sup></li> </ul> <p><b>Referrals to consider:</b></p> <ul style="list-style-type: none"> <li>• GI specialist to evaluate and treat more serious/persistent problems</li> </ul> <p>For further information see physician fact sheet and family handout in AAP toolkit<sup>b</sup></p>

Continued

Table 221-1

Common Comorbid Disorders and Difficulties Associated With ASD—cont'd

DESCRIPTION	CONCERNS RELATED TO SCREENING AND DIFFERENTIAL DIAGNOSIS	MANAGEMENT AND REFERRALS TO CONSIDER
<b>FEEDING DIFFICULTIES<sup>i,j,k</sup></b> Feeding difficulties are estimated to occur in up to 90% of children with ASD Most common concerns include: <ul style="list-style-type: none"> <li>• Food refusal</li> <li>• Food selectivity by texture or type</li> <li>• Low appetite/failure to thrive</li> <li>• Oral motor delay</li> <li>• Dysphagia</li> </ul> See Kerzner et al (2015) for a detailed algorithm on identifying and managing feeding difficulties in a primary care setting <sup>k</sup>	It is necessary to rule out other GI problems that may be contributing to low appetite or food selectivity Having family complete a food inventory or diary of meals for a few days may help in differential diagnosis Evaluation of oral motor skills may help determine if problem is related more to skill deficits or behavior problems A swallow study may be indicated to rule out aspiration and dysphagia Admission to the hospital or placement of a feeding tube may be necessary for severe malnutrition resulting from feeding problems	<b>Management:</b> <ul style="list-style-type: none"> <li>• Counsel families on appropriate nutrition and feeding guidelines to improve mealtimes<sup>k</sup></li> <li>• Prescribe a nutrient supplement as needed (eg, pediasure, multivitamin)</li> </ul> <b>Referrals to consider:</b> <ul style="list-style-type: none"> <li>• Psychologist/behavior specialist for feeding therapy if problem is more behavioral</li> <li>• Speech/occupational therapist for feeding therapy if problem is more related to oral motor deficits</li> <li>• If outpatient therapy is unsuccessful, a referral to an inpatient feeding clinic could be considered</li> </ul> For further information see physician fact sheet and family handout in AAP toolkit <sup>b</sup>
<b>PICA<sup>i</sup></b> Reported in up to 25% of individuals with ID Considered to be one of the most severe forms of self-injury, as deaths related to ingesting harmful inedible substances are higher than for any other form of self-injury	Complete lab work to rule out any vitamin or nutrient deficit that may be causing pica, particularly an iron deficiency	<b>Management:</b> <ul style="list-style-type: none"> <li>• Provide education to family on creating a safe environment (eg, safety locks on cupboards, removal of lead-based paint, close monitoring at all times)</li> <li>• Provide emergency contact information for poison control</li> <li>• Monitor lead levels</li> </ul> <b>Referrals to consider:</b> <ul style="list-style-type: none"> <li>• Behavior therapy to develop a plan with family to decrease pica</li> </ul>
<b>TOILET TRAINING DIFFICULTIES<sup>i</sup></b> Difficulties with toilet training are common in children with ASD, particularly in those with comorbid ID or GI problems	Extremely important to rule out constipation and other GI/urinary tract difficulties, which may be causing pain that is contributing to the child's aversion of toilet training	<b>Management:</b> <ul style="list-style-type: none"> <li>• Manage constipation to minimize pain in toileting</li> <li>• Educate families on appropriate expectations for toilet training</li> <li>• Recommend a guide, such as <i>Toilet Training in Less Than a Day</i> by Azrin &amp; Foxx, to give families further guidelines on successful toilet training<sup>m</sup></li> </ul> <b>Referrals to consider:</b> <ul style="list-style-type: none"> <li>• Psychologist or behavior specialist to create and help implement an intervention plan for families to address toileting difficulties</li> </ul> For further information see physician fact sheet and family handout in AAP toolkit <sup>b</sup>

Table 221-1 Common Comorbid Disorders and Difficulties Associated With ASD—cont'd

DESCRIPTION	CONCERNS RELATED TO SCREENING AND DIFFERENTIAL DIAGNOSIS	MANAGEMENT AND REFERRALS TO CONSIDER
<p><b>MOTOR DELAYS<sup>a,o</sup></b> Both fine and gross motor delays are often present in children with ASD</p> <p>Motor delays are often identified before ASD is diagnosed</p> <p>Motor delays can interfere with the acquisition of self-care skills (eg, dressing, toilet training, self-feeding)</p> <p><b>SAFETY CONCERNS<sup>p,q</sup></b> Children with ASD are at elevated risk for a number of safety concerns including:</p> <ul style="list-style-type: none"> <li>• Elopement</li> <li>• Drowning</li> <li>• Suffocation</li> <li>• Injury from burns, falls, etc.</li> <li>• Ingestion of harmful substances</li> <li>• Injury during car accident</li> </ul> <p>Drowning and suffocation are the leading causes of accidental death in people with ASD</p> <p>Risk for these safety concerns increases with severity of symptoms and comorbid ID</p>	<p>Screening for motor delays at the 9-, 18-, and 24- or 30-month visits is recommended by the AAP</p> <p>Additional screening for coordination and graphomotor problems at the 48-month visit is also recommend in preparation for children entering kindergarten</p> <p>Screen for possible safety concerns as part of preventive health care visits</p> <p>Parents may not bring up these concerns on their own because of embarrassment, belief that the pediatrician may not be able to help, or concerns that they will be blamed for the injury</p>	<p><b>Referrals to consider:</b></p> <ul style="list-style-type: none"> <li>• Occupational therapy evaluation to evaluate and treat fine motor deficits</li> <li>• Physical therapy evaluation to evaluate and treat gross motor deficits</li> </ul> <p><b>Management:</b> Provide education on possible safety concerns and environmental and behavioral modifications to maximize prevention with all families:</p> <ul style="list-style-type: none"> <li>• Safety locks, dead bolts, or chain locks placed high on doors to prevent elopement</li> <li>• Safety locks on storage areas to prevent access to harmful substances</li> <li>• Child gates to prevent access to possibly dangerous areas (eg, kitchen or bathroom)</li> <li>• Fences around pools or blocking other bodies of water</li> <li>• Modified car seats to prevent child from getting up while driving</li> </ul> <p><b>Referrals to consider:</b></p> <ul style="list-style-type: none"> <li>• Psychologist or behavior specialist to help family modify behavior related to safety concerns</li> </ul>

AAP, American Academy of Pediatrics; ASD, autism spectrum disorder; ATN, Autism Treatment Network; EEG, electroencephalogram; ENT, ear, nose, and throat; GERD, gastroesophageal reflux disease; GI, gastrointestinal; ID, intellectual disability.

<sup>a</sup>Bauman ML. Medical comorbidities in autism: challenges to diagnosis and treatment. *Neurotherapeutics*. 2010;7(3):320–327.

<sup>b</sup>American Academy of Pediatrics. Caring for children with autism spectrum disorders: a resource toolkit for clinicians. Available at: [www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Pages/Caring-for-Children-with-Autism-Spectrum-Disorders-A-Resource-Toolkit-for-Clinicians.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Pages/Caring-for-Children-with-Autism-Spectrum-Disorders-A-Resource-Toolkit-for-Clinicians.aspx). Accessed June 16, 2015.

<sup>c</sup>Goodlin-Jones BL, Sitnick SL, Tang K, Liu J, Anders TF. The Children's Sleep Habits Questionnaire in toddlers and preschool children. *J Dev Behav Pediatr*. 2008;29(2):82–88.

<sup>d</sup>Screening tool available at: [www.education.uci.edu/childcare/pdf/questionnaire\\_interview/Childrens%20Sleep%20Habits%20Questionnaire.pdf](http://www.education.uci.edu/childcare/pdf/questionnaire_interview/Childrens%20Sleep%20Habits%20Questionnaire.pdf). Accessed June 16, 2015.

<sup>e</sup>Chervin RD, Hedger K, Dillon JE, Pituch KJ. Pediatric sleep questionnaire (PSQ): validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems. *Sleep Med*. 2000;1(1):21–32. Screening tool available at: [secure.nouvant.com/umich/technology/3766/license/7](http://secure.nouvant.com/umich/technology/3766/license/7). Accessed June 16, 2015.

<sup>f</sup>ATN Sleep Kits. Available at: [www.autismspeaks.org/science/resources-programs/autism-treatment-network/tools-you-can-use/sleep-tool-kit](http://www.autismspeaks.org/science/resources-programs/autism-treatment-network/tools-you-can-use/sleep-tool-kit). Accessed June 16, 2015.

<sup>g</sup>Furuta GT, Williams K, Kooros K, et al. Management of constipation in children and adolescents with autism spectrum disorders. *Pediatrics*. 2012;130(Suppl 2):S98–S105.

<sup>h</sup>Field D, Garland M, Williams K, Kooros K, et al. Correlates of specific childhood feeding problems. *J Pediatr Child Health*. 2003;39(4):299–304.

<sup>i</sup>Kodak T, Piazza CC. Assessment and behavioral treatment of feeding and sleeping disorders in children with autism spectrum disorders. *Child Adolesc Psychiatr Clin N Am*. 2008;17(4):887–905.

<sup>k</sup>Kerzner B, Milano K, Maclean WC, et al. A practical approach to classifying and managing feeding difficulties. *Pediatrics*. 2015;135(2):344–353.

<sup>l</sup>Kroeger KA, Sorensen-Burnworth R. Toilet training individuals with autism and other developmental disabilities: A critical review. *Res Autism Spectr Disord*. 2009;3(3):607–618.

<sup>m</sup>Azrin N. *Toilet Training in Less Than a Day*. New York: Simon & Schuster; 1989.

<sup>n</sup>Zwaigenbaum L, Bryson S, Lord C, et al. Clinical assessment and management of toddlers with suspected autism spectrum disorder: insights from studies of high-risk infants. *Pediatrics*. 2009;123(5):1383–1391.

<sup>o</sup>Noritz GH, Murphy NA, Hagan JF, et al. Motor delays: Early identification and evaluation. *Pediatrics*. 2013;131(6):e2016–e2027.

<sup>p</sup>Anderson C, Law JK, Daniels A, et al. Occurrence and family effect of elopement in children with autism spectrum disorders. *Pediatrics*. 2012;130(5): 870–877.

<sup>q</sup>Shavelle RM, Strauss DJ, Pickett J. Causes of death in autism. *J Autism Dev Disord*. 2001;31(6):569–576.

Effective psychosocial interventions for children with ASD have been developed, and early, intensive intervention is critical. Primary care physicians are placed in the role of advocate for a child's timely placement within highly intensive, behaviorally oriented intervention programs that are based on several decades of research. Nearly one-half of children with autism who receive at least 2 years of one-on-one behavioral instruction for 40 hours a week have been reported to achieve age-level functioning, including normal intelligence, average adaptive behavior, and regular educational placement. These findings have been partially replicated by other research groups, suggesting that early and intensive behavioral intervention can lead to improved cognitive and adaptive functioning outcomes for children with autism. This form of psychosocial intervention is known by many names, including applied behavior analysis, discrete trial training, intensive behavioral intervention, or early intensive behavioral intervention (EIBI). Early intensive behavioral intervention is the most descriptive of these terms and so will be used for the remainder of this section. This intervention typically occurs early (between the ages of 2 and 7 years), is intensive (20–40 hours per week), and is based on the principles of applied behavior analysis.

In an EIBI program, teaching methods and curricula are individually designed. This type of program consists of multiple teachers, sometimes called aides or therapists, working in 2- or 3-hour sessions, one-on-one with a child for up to 40 hours a week. Programs often last for several years, to ensure that children continue to make developmental progress. Each session includes structured, teacher-directed activities and free play. Early intensive behavioral intervention sessions are initially implemented within the child's home, but as treatment progresses, sessions are conducted in community and school settings. The child is taught new skills in a systematic, step-by-step fashion, and instruction is quickly paced, which helps keep the child engaged and interested. Teaching methods involve reinforcing children with favorite foods, preferred activities, and praise for successfully completing developmental tasks. The teachers help the children perform tasks that are initially too difficult for them using a system of prompts that are gradually phased out to promote an independent response. The curriculum used in EIBI programs is individually designed, hierarchically sequenced, and paced at each child's learning rate. The curriculum includes learning the prerequisites to language (eg, imitation, matching), expanding language and communication, play skills, self-help skills, and social skills, as well as early school-related concepts. Parents are also trained in the behavioral teaching methods and work to generalize the child's learning from the EIBI teaching sessions into everyday situations at home. The most successful children in EIBI programs are those who eventually discover how to learn from natural environments and typical educational experiences. Early intensive behavioral intervention has been recognized as an effective treatment by the US Surgeon General since 1999.

Many areas now offer school- or center-based EIBI programs for children with ASD that apply this teaching

method in a more traditional classroom model. Some special education departments in public schools are also adapting EIBI models to teach children with ASD and other developmental disabilities, although this dissemination process has been slow. While EIBI is often misperceived as a treatment modality only for very young or "low-functioning" children, this teaching method has been effectively incorporated into treatment models to teach social skills and other adaptive skills to children of all ages and functioning levels.

For families unable to access EIBI services or who plan to use a combination of EIBI and public education services, advocating for appropriate special education services in a public school setting is paramount. Families should be encouraged to have their child evaluated by their school to create an Individualized Education Plan (IEP) under the educational classification of autism. Understanding what services and supports are available to a child under the Individuals with Disabilities Education Act is difficult for any family. Physicians are encouraged to access or develop a short list of appropriate local and state advocacy resources for parents who are having difficulty accessing appropriate education services for their child.

Speech and occupational therapies are also indicated for most children with ASD. While many children will have these services provided to them through their IEP, it is also recommended that families access these services privately to maximize intervention time and to develop intervention plans that can be implemented specifically in the home environment. Older children with better language skills may also benefit from evidence-based social skills training focused on improving pragmatic language skills needed for effective communication and interaction with peers and adults. As children continue to develop, primary care physicians should begin to talk with families about plans for transition services once children graduate high school, including plans for health care, further education or vocational services, housing, guardianship, and financial management. These conversations should be started early so that a firm plan is in place by the time the child reaches 18 years.

Several commonly implemented interventions for ASD have emerging support of effectiveness (eg, TEACCH, Floortime), while others have been shown to be ineffective and even dangerous (eg, facilitated or supported communication, rapid prompting, auditory integration training, specialty diets, chelation, etc.). Medical providers should advise families to review carefully the evidence of effectiveness for any treatment before committing valuable resources.

## PROGNOSIS

The future has brightened for children diagnosed with autism over the past 20 or 30 years. Since the early 1990s, home childrearing and the availability of community special educational services for all developmentally disabled children has decreased the behavioral morbidities associated with institutionalization and restricted access to learning experiences. Parents and professionals have learned how to advocate effectively for these children, and these efforts



### BOX 221-1 Organizations Supporting Autism Research and Awareness

- Autism Speaks, Inc. Available at: [www.autismspeaks.org](http://www.autismspeaks.org). This organization and its Web site are dedicated to increasing public awareness about autism, providing advocacy, and supporting autism research. The Web site provides text and video segments to educate about autism.
- Cambridge Center for Behavioral Studies. Autism and Applied Behavior Analysis, Introduction to the Autism Section. Available at: [www.behavior.org/interest.php?id=2](http://www.behavior.org/interest.php?id=2). This organization, along with its Web site, provides resources and articles describing science-based information on effective autism treatment.
- Organization for Autism Research. Available at: [www.researchautism.org](http://www.researchautism.org). This organization, along with its Web site, is dedicated to promoting science in autism treatment. Several parent- or teacher-oriented publications on autism and Asperger disorder are available that can be downloaded free of charge, including the "Life Journey Through Autism" series.

have resulted in much wider adoption of empirically validated interventions in schools and health service settings. Intense study of ASD has become a federal research priority, and several private research advocacy groups have formed to support research and information dissemination efforts (see Box 221-1). Advances in epigenetics will likely shed light on the various causes of ASD and thereby provide prevention options.

### WHEN TO REFER

Children between 12 and 24 months of age should be referred to a developmental specialist if any one of the following exists:

- Delays in expressive communication: lack of babbling by 12 months, single words by 18 months, or phrases (not just echoed language) by 24 months
- An inability to follow simple instructions or imitate others by 12 months
- Little interest in social games by 12 months
- Little eye contact or social smiling by 12 months
- A lack of pointing out objects of interest by 18 months
- An inability to direct the child's attention or lack of response to name by 18 months
- No simple pretend play (eg, feeding a doll) by 18 months
- Little interest in other children by 24 months
- Loss of language or social skills at any age
- Repetitive motor movements or atypical body posturing (eg, hand flapping, body or facial tensing)

Children with a diagnosis of ASD may need to be referred for further evaluation and treatment for common comorbid conditions including:

- Seizures
- Sleep disorders
- GI concerns (eg, severe constipation, food allergies, malnutrition)
- Feeding difficulties
- Fine or gross motor delays
- Significant behavior problems (eg, aggression, self-injury, noncompliance)
- Mental health concerns (eg, significant anxiety or depression)

### WHEN TO ADMIT

- Severe malnutrition related to feeding difficulties
- Severe seizures
- Long-term electroencephalogram monitoring
- Life-threatening self-injurious behavior or aggression
- Psychopharmacologic toxicity
- Psychiatric stabilization

### TOOLS FOR PRACTICE

#### Community Advocacy and Coordination

- *AIR-P Tool Kits* (Web page), Autism Intervention Research Network on Physical Health ([www.airpnetwork.org/site/c.7oJGLPPsFiJYG/b.9151551/k.8682/AIRP\\_Tool\\_Kits.htm](http://www.airpnetwork.org/site/c.7oJGLPPsFiJYG/b.9151551/k.8682/AIRP_Tool_Kits.htm))
- *Life Journey Through Autism: An Educator's Guide* (booklet), Organization for Autism Research ([www.researchautism.org/resources/OAR\\_Educators\\_Guide.pdf](http://www.researchautism.org/resources/OAR_Educators_Guide.pdf))
- *Life Journey Through Autism: An Educator's Guide to Asperger Syndrome* (booklet), Organization for Autism Research ([www.researchautism.org/resources/OAR\\_Guide\\_Aasperger.pdf](http://www.researchautism.org/resources/OAR_Guide_Aasperger.pdf))

#### Engaging Patient and Family

- *Facts About ASD* (fact sheets), Centers for Disease Control and Prevention ([www.cdc.gov/ncbddd/autism/facts.html](http://www.cdc.gov/ncbddd/autism/facts.html))
- *Is Your Toddler Communicating with You?* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Life Journey Through Autism: A Parent's Guide to Research* (booklet), Organization for Autism Research ([www.researchautism.org/resources/parents%20guide.pdf](http://www.researchautism.org/resources/parents%20guide.pdf))
- *Understanding Autism Spectrum Disorders (ASD)* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

#### Medical Decision Support

- *Ages & Stages Questionnaires (ASQ)* (Web site), Brookes Publishing Co. ([agesandstages.com](http://agesandstages.com))
- *Asperger Syndrome Diagnostic Scale* (scale), Myles BS, Bock SJ, Simpson RL ([proedinc.com/customer/productView.aspx?ID=1842](http://proedinc.com/customer/productView.aspx?ID=1842))
- *Autism Diagnostic Interview: Revised (ADI-R)* (interview), Rutter M, Le Couteur A, Lord C ([www.wpspublish.com/store/p/2645/autism-diagnostic-interview-revised-adi-r](http://www.wpspublish.com/store/p/2645/autism-diagnostic-interview-revised-adi-r))

- *Autism Diagnostic Observation Schedule – Second Edition (ADOS-2)* (package), Lord C, Rutter M, et al. ([www.wpspublish.com/store/p/2648/autism-diagnostic-observation-schedule-second-edition-ados-2](http://www.wpspublish.com/store/p/2648/autism-diagnostic-observation-schedule-second-edition-ados-2))
- *Caring for Children With Autism Spectrum Disorders: A Resource Toolkit for Clinicians* (toolkit), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Childhood Autism Rating Scale*, 2nd ed (CARS2) (scale), Schopler E, Van Bourgondien M, Wellman G, Love S ([www.pearsonclinical.com/psychology/products/100000164/childhood-autism-rating-scale-second-edition-cars2.html](http://www.pearsonclinical.com/psychology/products/100000164/childhood-autism-rating-scale-second-edition-cars2.html))
- *Developmental Surveillance and Screening Algorithm Within a Pediatric Preventive Care Visit* (algorithm), American Academy of Pediatrics ([pediatrics.aappublications.org/content/118/1/405/F1.expansion.html](http://pediatrics.aappublications.org/content/118/1/405/F1.expansion.html))
- *Modified Checklist for Autism in Toddlers (M-CHAT)* (checklist), Robins DL, Fein D, Barton ML, Green JA ([www.m-chat.org](http://www.m-chat.org))
- *PEDS Tools* (Web site), Parents' Evaluation of Developmental Status ([www.pedstest.com](http://www.pedstest.com))
- *Social Communication Questionnaire: SCQ* (questionnaire), Rutter M, Bailey A, Lord C. ([www.wpspublish.com/store/p/2954/social-communication-questionnaire-scq](http://www.wpspublish.com/store/p/2954/social-communication-questionnaire-scq))
- *Social Responsiveness Scale: SRS* (scale), Constantino JN ([www.wpspublish.com/store/p/2993/social-responsiveness-scale-srs-by-john-n-constantino-md](http://www.wpspublish.com/store/p/2993/social-responsiveness-scale-srs-by-john-n-constantino-md))

### AAP POLICY

- American Academy of Pediatrics Council on Children With Disabilities, Section on Developmental and Behavioral Pediatrics, Bright Futures Steering Committee, and Medical Home Initiatives for Children With Special Needs Project Advisory Committee. Identifying infants and young children with developmental disorders in the medical home: an algorithm for developmental surveillance and screening. *Pediatrics*. 2006;118(1):405–420. Reaffirmed August 2014 ([pediatrics.aappublications.org/content/118/1/405](http://pediatrics.aappublications.org/content/118/1/405))
- Johnson CP, Myers SM; American Academy of Pediatrics Council on Children With Disabilities. Identification and evaluation of children with autism spectrum disorders. *Pediatrics*. 2007;120(5):1183–1215. Reaffirmed August 2014 ([pediatrics.aappublications.org/content/120/5/1183](http://pediatrics.aappublications.org/content/120/5/1183))
- Myers SM, Johnson CP; American Academy of Pediatrics Council on Children With Disabilities. Management of children with autism spectrum disorders. *Pediatrics*. 2007;120(5):1162–1182. Reaffirmed August 2014 ([pediatrics.aappublications.org/content/120/5/1162](http://pediatrics.aappublications.org/content/120/5/1162))

### SUGGESTED READINGS

- Maurice C, Green G, Luce S. *Behavioral Intervention for Young Children With Autism*. Austin, TX: Pro-Ed; 1996
- Mulick JA, Foxx RM. *Controversial Therapies for Autism and Intellectual Disabilities*. 2nd ed. New York, NY: Routledge; 2015
- Pediatrics – Subspecialty Collections: Autism/ASD. Available at: [pediatrics.aappublications.org/collection/autismasd](http://pediatrics.aappublications.org/collection/autismasd). Accessed February 22, 2016
- Taubman MT, Leaf RB, McEachin, J. *Crafting Connections: Contemporary Applied Behavior Analysis for Enriching*

- the Social Lives of Persons With Autism Spectrum Disorder*. New York, NY: DRL Books; 2011
- Volkmar FR, Wiesner LA. *Healthcare for Children on the Autism Spectrum: A Guide to Medical, Nutritional, and Behavioral Issues*. Bethesda, MD: Woodbine House; 2004

## Chapter 222

## BACTERIAL SKIN INFECTIONS

Kalyani Marathe, MD, MPH; Judith V. Williams, MD

Bacterial infections of the skin are common. They are most often caused by gram-positive bacteria, specifically *Staphylococcus aureus* and group A streptococci. The clinical disease that results depends on the infection's location within the skin. For example, impetigo involves only the most superficial layer of the epidermis; cellulitis is an infection deep in the dermis, even involving subcutaneous fat.

### IMPETIGO

#### Etiology

*S aureus* is the major cause of impetigo in childhood. It is responsible for virtually 100% of bullous impetigo and causes approximately 75% of nonbullous impetigo; the remainder is caused by group A  $\beta$ -hemolytic *Streptococcus* (GABHS). In developing nations and warm climates, GABHS is still more common than staphylococcus as a cause of impetigo.

In nonbullous impetigo, the skin lesions may start with small vesicles or pustules, but these are often not evident by the time the physician sees the patient. Crusts, usually honey colored, are seen instead. Removing these crusts exposes a moist, glistening base, which is a superficial erosion of the epidermis; culture usually reveals *S aureus*.

#### History

The patient usually has no history of preceding trauma to the skin. Mild to moderate itching may be associated with the lesions. Other family members also may be affected.

#### Physical Findings

Impetigo is found most commonly on the face and may appear as single or multiple lesions. Lesions may be scattered elsewhere on the body as well. The usual findings are yellow or honey-colored crusts, which when removed reveal a pink, superficially eroded, glistening base. The culture sample should be obtained from this base. With bullous impetigo, intact bullae, if present, contain deceptively clear fluid. These blisters break easily, leaving behind a superficially denuded skin surface covered with a thin, brown, varnish-like crust that is surrounded by a thin rim of loose, ragged epidermis, which represents the remnants of the blister roof (Figure 222-1). Surrounding erythema is minimal, and regional lymphadenopathy is rare.



**Figure 222-1** Bullous impetigo. The roof of the bulla is thin and delicate; the contents consist of some leukocytes that have settled at the inferior pole and some slightly turbid supernatant fluid. The larger adjacent bulla already has ruptured and discharged its contents. The delicate roof has collapsed onto the base. Lesions of this type may be caused by exfoliatin-producing organisms.

In bullous impetigo, the roof of the bulla is thin and delicate; the contents consist of some leukocytes that have settled at the inferior pole and some slightly turbid supernatant fluid. The larger adjacent bulla already has ruptured and discharged its contents. The delicate roof has collapsed onto the base. Lesions of this type may be caused by exfoliatin-producing organisms.

### Laboratory Evaluation

A Gram stain of either the clear blister fluid or the serum underlying the crusts shows gram-positive cocci. Cultures grow *S aureus* or *Streptococcus pyogenes*.

### Differential Diagnosis

Herpes simplex virus (HSV) infection is the condition most often confused with impetigo. Clinical clues that suggest herpes rather than impetigo are as follows:

1. Intact vesicles are more likely to be appreciated by both the patient and the physician in HSV infection than in impetigo. In HSV infection, as the vesicles age, they become cloudy and ultimately result in crusts that also may be honey colored. This crusted phase most often causes the diagnostic confusion.
2. HSV infection tends to be a recurrent condition, with the recurrences often in the same location (usually oral and perioral lesions). Such recurrence is not the case with impetigo.
3. When an impetiginous pustule is unroofed, it is noticeably filled with pus; a herpetic lesion may appear to be pus filled, but when it is unroofed, only a scant amount of clear fluid is found. In impetigo, Gram staining shows numerous gram-positive cocci. In HSV infection, Wright staining of a scraping from the base of a crust (or preferably a vesicle) reveals multinucleated giant cells.

### Exclusion From School

Given the potentially infectious nature of both staphylococcal and streptococcal skin infections, school nurses are appropriately concerned about this disease, and a child may be asked to leave school until the infection is treated. The period of infectiousness of impetigo is unknown. Most child care centers and schools recommend exclusion as long as open lesions persist. In reality, staphylococcal impetigo represents a rather low risk for spread in these settings; therefore, as long as lesions are covered, the child can return to school without posing a significant risk to other children.

### Management

Both topical and systemic antibiotics have been advocated for treating impetigo. Methicillin-resistant *S aureus* (MRSA) has become an increasingly common cause of skin infections in children. Several studies have indicated that up to 75% of community-associated *S aureus* skin infections in children are caused by MRSA, and 60% of community-onset health care-associated *S aureus* skin infections in children are caused by MRSA. Mupirocin topical antibiotic ointment has been reported to equal or exceed the efficacy of oral erythromycin in the treatment of bacterial impetigo and is recommended for initial treatment. A cream form is also available. The infected area should be washed carefully and the crusts gently removed, if possible, once a day, and the antibiotic cream or ointment is applied 3 times daily to the site. Traditional topical preparations that contain bacitracin or neomycin, either alone or in combination, have been used. However, because they are poorly absorbed, these preparations are not particularly effective. Topical mupirocin should be considered whenever feasible because it can be effective in treating impetigo caused by MRSA. However, mupirocin resistance is increasing in the MRSA USA 300 clone, the predominant circulating strain in the United States, and similar cases have been reported in different clones in other countries. Remarkably, mupirocin may retain the ability (albeit reduced) to decolonize patients with resistant strains. However, mupirocin is not effective in treating active infection with resistant strains. To optimize its efficacy, mupirocin should be used judiciously. Some authors recommend sampling MRSA populations for mupirocin susceptibility before incorporating mupirocin into infection-control programs and avoiding extended mupirocin use where MRSA is endemic. New topical preparations are in development. One such product, retapamulin, has some activity against MRSA in vitro, but clinical data are currently lacking.

Systemic antibiotics should be used for more extensive lesions. A study looking at medications most commonly prescribed for impetigo found that most physicians prescribe systemic antibiotics, even for uncomplicated infections. The traditional choices in the pre-MRSA era were erythromycin, a penicillinase-resistant penicillin (eg, dicloxacillin), amoxicillin-clavulanic acid, or cephalexin. These agents would still be appropriate for treatment of disease caused by methicillin-sensitive *S aureus* (MSSA) or *S pyogenes*.



Clindamycin or trimethoprim-sulfamethoxazole might be an appropriate choice in the era of MRSA, although one study about the treatment of skin and soft tissue infections found neither to confer benefit over penicillins. The treatment course should be 7 to 10 days. Patients with more extensive disease who fail traditional empirical antibiotic therapy should have cultures and susceptibility studies performed.

### Complications and Prognosis

With appropriate antibiotic therapy, prompt healing is expected; most patients show marked improvement within several days. Bacteriologic cures occur within 7 to 10 days in nearly all cases. If the infection does not respond rapidly to therapy, then it may be caused by an antibiotic-resistant strain. In such cases, the initial culture and susceptibility results serve as a guide in selecting an alternate antibiotic.

Historically, differentiating between staphylococcal and streptococcal impetigo was deemed important, given that glomerulonephritis can be a sequela of the latter form. Evidence now shows that treatment of streptococcal skin infections does not alter the risk for developing glomerulonephritis, but will prevent the cardiac complications of rheumatic fever.

## PYODERMA

### Etiology

In contrast to the superficial nature of impetigo, which mainly involves the top layers of the epidermis, pyoderma frequently extends through the epidermal layer into the underlying dermis. The process may start with small erythematous papules and rapidly proceed through vesicular, pustular, and crusted stages, during which stage it might be clinically confused with impetigo. Streptococcal pyoderma is more common in warm, humid environments; higher humidity favors the survival of group A streptococci on normal skin. Presumably, trauma to the skin results in inoculation followed by infection.

### History

Streptococcal pyoderma may occur in epidemics among children of lower socioeconomic status who live in crowded conditions in warm, humid environments. In contrast to impetigo the streptococcal skin lesions occur most commonly on the lower extremities, where they are usually preceded by trauma such as a scratch or insect bite. Family members also may be affected.

### Physical Findings

The early lesion is a pustule (hence the term *pyoderma*) with surrounding erythema, but the more advanced lesion of ecthyma is seen more often. At first glance, this lesion seems thick, usually brown crust surrounded by erythema. When the crust is removed, an actual ulcer is revealed (Figure 222-2), in contrast to the superficial erosion underlying the crust of impetigo. Also in contrast to impetigo, regional adenopathy is often present with streptococcal pyoderma.

In streptococcal pyoderma (ecthyma), lesions progress to become necrotic in appearance with deep



**Figure 222-2** Streptococcal pyoderma (ecthyma). Lesions progress to become necrotic in appearance with deep punched-out ulcers. The surrounding erythema and the location on the lower leg are typical of this streptococcal lesion.

punched-out ulcers. The surrounding erythema and the location on the lower leg are typical of this streptococcal lesion.

### Laboratory Evaluation

A culture sample taken from the base of the denuded ulcer usually grows GABHS. *S aureus* is occasionally recovered concomitantly, in which case it is thought to be a secondary invader.

### Differential Diagnosis

Ecthyma gangrenosum is an uncommon but serious manifestation of sepsis in immunocompromised hosts. It has been most frequently associated with *Pseudomonas aeruginosa* infection but can be seen with other gram-negative organisms or even with fungi. Clinical features that help differentiate this lesion from ecthyma are (1) the location (ecthyma gangrenosum is often on the upper extremities or in the inguinal or axillary folds), (2) the lesion's appearance (a deeper ulcer covered with a tightly adherent, black [gangrenous] crust), and (3) the host (a seriously ill, usually immunocompromised patient who exhibits other signs of sepsis).

### Management

Pyoderma is treated with antibiotics, although the most appropriate route of administration is still a matter of debate. Some evidence indicates that applying topical antibiotics to scratches and insect bites reduces the incidence of subsequent pyoderma; thus topical antibiotics may be advocated prophylactically for traumatic skin lesions. Although topical mupirocin has proved effective for impetigo caused by group A



streptococci, systemic antibiotics still are recommended for streptococcal infections, particularly if the infection is extensive. Injectable benzathine penicillin G is effective, but a 7- to 10-day course of oral penicillin or erythromycin is preferred if the patient is likely to be adherent to the prescribed regimen. Penicillin treatment occasionally fails, presumably because of the persistence of coexisting penicillinase-producing *S aureus* organisms. Even in the age of MRSA, penicillin should be the first-line therapy. Trimethoprim-sulfamethoxazole monotherapy has been shown to have higher failure rates than penicillins or clindamycin.

### Complications

Complications are uncommon, although both local and systemic problems can result from streptococcal pyoderma. Cellulitis may develop if the infection extends into larger and deeper areas of skin and subcutaneous tissue. Some strains of group A streptococci produce the toxin responsible for scarlet fever.

As mentioned previously, acute glomerulonephritis may follow streptococcal infection of the skin. It is caused by only a few nephritogenic serotypes (49, 55, and 57) of pyoderma-inducing streptococci. The usual period from onset of infection to development of the glomerulonephritis is 18 to 21 days. Fortunately, skin infection with streptococci never leads to acute rheumatic fever. Systemic antibiotic therapy clears the skin infection and helps to reduce the spread of streptococcal infection to the patient's playmates and family.

### Prognosis

The aforementioned complications are uncommon, and in most patients the lesions heal uneventfully. Because they are deeper, streptococcal lesions often take longer than staphylococcal lesions to heal; however, bacteriologic cures are usually accomplished within a week. If a prompt response is not achieved, then a secondary infection from a penicillinase-producing staphylococcal strain should be considered, particularly if penicillin was used for treatment. Erythromycin-resistant strains of group A streptococci also may be encountered.

## FOLLICULITIS

### Etiology

Bacterial folliculitis is a moderately common disorder that primarily affects older children and young adults. It is an infection of the hair follicles, caused almost exclusively by *S aureus*. In rare cases, the infection is caused by gram-negative organisms, which occurs occasionally in patients whose acne is being treated with antibiotics. Also, *P aeruginosa* is the usual cause of hot tub folliculitis, which causes pruritic papules and pustules on the trunk and proximal extremities. The lesions usually clear without treatment, although antipruritics can be used. Typically, however, *S aureus* causes folliculitis, and this type of infection is the subject of discussion here.

### History

Staphylococcal folliculitis appears most commonly as a chronic eruption unaccompanied by symptoms,

although occasionally a patient has mild discomfort or pruritus.

### Physical Findings

The lesions in staphylococcal folliculitis are usually located on the buttocks and upper portion of the thighs, over which individual small papules and pustules are scattered. The key to the diagnosis is that, on close inspection, hairs can be seen growing out of the very center of many of the lesions.

### Laboratory Evaluation

In the typical case, culturing is not usually necessary. If, however, the presentation is atypical and laboratory confirmation is desired, then the contents of a fresh pustule should be cultured.

### Differential Diagnosis

Clinically, folliculitis caused by gram-negative organisms differs from staphylococcal folliculitis in its distribution, with lesions occurring primarily on the face (often concentrated in the perioral and perinasal areas) and shoulders. Hot tub folliculitis usually appears on the lower trunk and areas most exposed to the contaminated water in the tub.

Keratosis pilaris is another common follicular disorder that exhibits as tiny, rough, scaling papules on the back of the upper parts of the arms, the buttocks, and the thighs. Although the distribution may be similar to that of staphylococcal folliculitis, the appearance of the lesions is not. In keratosis pilaris, the lesions are smaller, more numerous, and scaling, but not pustular.

### Management

The usual mild case of staphylococcal folliculitis can be managed by having the patient use an antiseptic cleanser (eg, chlorhexidine) or antibacterial soap containing triclosan or triclocarban daily or every other day for at least several weeks. Topical clindamycin lotion or solution applied twice a day may be a useful therapy. For more extensive involvement, a 7- to 10-day course of systemic antibiotics (eg, cephalexin or dicloxacillin) is suggested in addition to the topical regimen.

### Complications and Prognosis

Most patients respond to treatment; if not, then a bacterial culture should be performed to rule out infection by gram-negative organisms or MRSA. Some patients are plagued with recurrences, for which a more prolonged course of antibiotic therapy is recommended. In rare cases, the follicular infection extends deeply, producing a furuncle.

## FURUNCLES AND ABSCESES

### Etiology

Unchecked folliculitis may result in furuncles (pus-filled nodules or boils) that are almost always caused by *S aureus*. Although most physicians use the terms *furuncle* and *abscess* interchangeably, abscesses are collections of pus within the dermis and deeper skin tissues that do not originate from a primary folliculitis. Bacteria may be inoculated into the skin and underlying soft

tissue by traumatic injury, including surgery. Most skin abscesses are caused by *S aureus*, but gram-negative and anaerobic organisms also can be causes.

### History

A history of trauma may be elicited but often is not, especially with furuncles. Immunodeficiency states and diabetes may predispose certain patients to bacterial skin infections, but the typical patient who has a furuncle or abscess has no underlying medical disease.

### Physical Findings

Furuncles and abscesses are fluctuant masses filled with pus. They often begin as hard, tender, red nodules and become more fluctuant and painful with time. Abscesses tend to be larger and deeper than furuncles, but the 2 lesions may sometimes be difficult to differentiate clinically.

### Laboratory Evaluation

A Gram stain of the pustular material may provide a clue to the bacterial cause. However, for precise identification, cultures are required. If anaerobic cultures are desired, then material is ideally collected by aspirating the pus, sealing the syringe, and promptly delivering it to the laboratory. If insufficient material is available to aspirate, then a swab culture can be used for anaerobic, as well as aerobic, cultures. Blood culture results rarely are positive in patients with furuncles or abscesses and are not indicated unless the patient shows signs of sepsis.

Differentiation between an abscess and cellulitis can sometimes prove challenging. To avoid unnecessary incision and drainage procedures and ensure appropriate treatment, the use of ultrasound has gained popularity. An abscess classically has an anechoic or hypoechoic complex fluid collection, whereas cellulitis usually shows diffuse thickening, increased echogenicity of the skin and subcutaneous tissues, and hypoechoic strands traversing between the fat and connective tissue.

### Management

Very small furuncles can be treated with moist heat, which promotes drainage. For larger furuncles, incision and drainage are the mainstay of therapy. Clinical evidence suggests that, for furuncles less than 5 cm in diameter, incision and drainage alone result in complete healing in most cases. For patients with abscesses larger than 5 cm, or for those with surrounding cellulitis or signs of systemic illness such as fever, systemic antibiotics should be used. If lesions are seen early in their development, then systemic antibiotics may result in involution, obviating the need for incision and drainage. In the recent past, dicloxacillin, cephalexin, and erythromycin were considered the antibiotics of choice; however, this consideration needs to be re-evaluated in light of the increased incidence of MRSA in furunculosis. Pantón-Valentine leukocidin (PVL) factor-positive strains may be especially virulent; studies have shown that most strains causing furuncles are positive for PVL factor. Most community-associated MRSA isolates are susceptible

to trimethoprim-sulfamethoxazole, and many are sensitive to clindamycin. Clindamycin has the advantage of excellent penetration into the infected tissues; however, some erythromycin-resistant strains of MRSA have inducible resistance to clindamycin. The physician is advised to know local susceptibility patterns. Culture results from abscesses may help in the ultimate selection of the appropriate antibiotic.

### Complications

Recurrent furunculosis sometimes prompts a search for an underlying immunodeficiency, a search that almost always goes unrewarded. However, many such patients harbor *S aureus* in a sequestered mucocutaneous site, the most common of which is the anterior nares. Application of mupirocin to the external nares twice daily for 5 days, repeating the process monthly or every 2 months, decreases recurrences by approximately one-half. Some experts recommend an every-other-day total-body scrub with an antiseptic cleansing agent, such as chlorhexidine, or antibacterial soap containing triclosan or triclocarban, although overuse of these antiseptic soaps may dry the skin, harming skin integrity. Some physicians are also advocating the addition of a small amount of bleach to the bath water to reduce staphylococcal skin colonization.

Fritz et al found that a regimen of dilute bleach baths, intranasal mupirocin, and education effectively eradicated *S aureus* over a 4-month period better than topical antibiotics alone or in combination with chlorhexidine.

Most oral antibiotics do not eradicate nasal carriage of *S aureus*, but clindamycin is an exception. In cases that are refractory to all the previously described methods, a single oral dose of clindamycin, given twice daily for 7 days, may be effective at eliminating recurrences.

In rare cases, a staphylococcal abscess may be the focus of toxin production, resulting in staphylococcal scalded skin syndrome (most commonly seen in infants and neonates), toxic shock syndrome, or staphylococcal scarlet fever.

### Prognosis

Untreated lesions often rupture and drain spontaneously. After either surgical or spontaneous drainage, uneventful healing is the rule. Larger lesions may leave scars.

## CELLULITIS

### Etiology

Cellulitis is a deep, locally diffuse infection of the skin that has systemic manifestations and life-threatening potential. It usually involves the face, an extremity, or the perianal area. On an extremity, the bacteria presumably have been externally inoculated into the deep dermal tissue, although the portal of entry is often undetectable clinically. A hematogenous or lymphangitic source is also possible and may explain the development of cellulitis in some cases in which the overlying skin is unbroken. Before the introduction of protein-conjugated *Haemophilus influenzae* type b (Hib) vaccines in 1988, Hib was a

frequent cause of facial cellulitis (*buccal cellulitis*), usually accompanied by bacteremia, in children. The incidence of invasive infections from this organism in the United States has declined by 95% and now occurs primarily in undervaccinated populations or in infants who have not completed the primary Hib vaccine series. Almost 90% of cases of facial cellulitis in the post-Hib vaccine era are related to trauma or to dental or sinus infection. Buccal cellulitis is a disappearing disease.

Other organisms figure more prominently in cellulitis at other sites. Preseptal (periorbital) cellulitis is likely to be caused by *Streptococcus pneumoniae* in younger children and by group A streptococci in older children. *S aureus* and group A streptococci more commonly are responsible for cellulitis of the extremities. *S aureus* and group A streptococci are the most common causes of perianal dermatitis, with two-thirds of the latter patients also having positive pharyngeal cultures. In rare cases, other aerobic and anaerobic bacterial organisms, as well as deep fungal agents such as *Cryptococcus neoformans*, can cause cellulitis. These infections usually occur in immunosuppressed individuals.

### History

Children who have cellulitis often feel and seem ill. Fever is frequently present and may precede the clinical skin signs. Patients may complain of pain in the affected area. Symptoms of an accompanying otitis media may be present in buccal cellulitis. Patients who have perianal cellulitis often have pain on defecation. However, patients who have this infection are not usually systemically ill; thus, the disease may persist for weeks or months before it is correctly diagnosed.

### Physical Findings

Fever at the time of presentation is common. The area of involved skin shows the classic signs of inflammation: redness, swelling, heat, and tenderness.

### Laboratory Evaluation

Leukocytosis is a common finding. The causative pathogen is usually assumed from the history and physical examination, given that identifying it by culture is fraught with difficulty. Blood cultures are positive in less than 5% of cases. In neonates or undervaccinated hosts who have facial cellulitis, lumbar puncture with culture of cerebrospinal fluid may disclose unsuspected meningitis.

### Differential Diagnosis

Erysipelas is a form of cellulitis caused most commonly by group A streptococci. Because infection is limited to the upper dermis, erysipelas has raised and sharply demarcated borders. Bedside differentiation of erysipelas from cellulitis, however, is sometimes difficult and clinically not particularly useful because therapeutic considerations are generally the same for both conditions.

A severe, local, confluent contact dermatitis may sometimes be confused with cellulitis in that both may show marked erythema of the skin. The important differences are that with contact dermatitis, the patient complains of itch rather than pain, the skin

usually is not tender, and the patient is not febrile. The presence of vesicles also favors contact dermatitis, although vesicles and bullae may sometimes occur in erysipelas or cellulitis as the condition evolves.

Perianal dermatitis, originally thought to be a cellulitis but now known to be a more superficial infection, may be misdiagnosed as candidiasis or diaper dermatitis. Bright-pink erythema and pain or tenderness of the involved skin suggest bacterial infection, and a swab culture usually shows *S aureus* or group A streptococci. Laboratory personnel must be aware that they are to look for these organisms; otherwise, they will look for enteric flora with a culture from this site. Necrotizing fasciitis is a fulminant skin infection most often caused by group A streptococci (*flesh-eating bacteria*). It is characterized by warm, violaceous, exquisitely tender, and markedly edematous (orange peel-like) skin with indeterminate edges. Systemic toxicity with fever, leukocytosis, thrombocytopenia, hypocalcemia, and hyponatremia is often seen. Systemic antibiotics are an adjunct to prompt surgical debridement, which is the mainstay of therapy. Erythema of the cheeks occurs characteristically in erythema infectiosum (fifth disease, caused by parvovirus B19), in which a slapped-cheek appearance is noted. Important diagnostic differences between erythema infectiosum and cellulitis are that in the former, the involvement is bilateral, the site is not usually very tender, and the patient does not seem toxic, although the patient may be mildly febrile.

### Management

Systemic antibiotics are the mainstay of cellulitis therapy. Mild cases of cellulitis on an extremity may be treated with an oral antibiotic, warm soaks, and outpatient follow-up in several days. Because cellulitis of the extremity most often is caused by Gram-positive organisms, erythromycin, dicloxacillin, and cephalexin are appropriate drugs to use. More seriously ill patients, including infants and young children, patients with predisposing medical conditions such as diabetes mellitus, patients with immunodeficiencies or on immunosuppressive therapies, and those in whom sepsis is suspected, should be hospitalized for parenteral antibiotic therapy.

### Complications and Comorbid Conditions

In some instances, findings that are clinically diagnosed as cellulitis may actually be a clue to an underlying, deeper-seated infection. Cellulitis of the periorbital tissues may be secondary to sinusitis; abdominal wall cellulitis may hide an underlying peritonitis; redness, warmth, and swelling of tissues overlying bones or joints may indicate septic arthritis or osteomyelitis; facial cellulitis may be caused by an undiagnosed dental abscess; redness of the neck is sometimes a clue to underlying deep neck space infections; inflammation of the skin of the sacrum might be from an infected pilonidal cyst; redness of the pinna or postauricular area may point to malignant otitis externa or mastoiditis. Uncomplicated cellulitis was once a serious, life-threatening disease, but antibiotics have now reduced the fatality rate to nearly 0% in otherwise healthy patients.

### Prognosis

With appropriate antibiotic therapy, fever usually resolves within 24 hours. If it does not, then a change in antibiotic therapy should be considered, optimally guided by early culture and bacterial sensitivity results. The skin reaction resolves more slowly than does the fever, sometimes taking a week or longer to subside completely.

## COMMUNITY-ASSOCIATED METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS INFECTIONS

The prevalence of community-associated MRSA is ever increasing. In fact, these strains cause most MRSA cases acquired in the community and are appearing in health care settings, traditionally the province of hospital-acquired strains. The most frequently reported presentation is furunculosis, followed by skin abscesses and cellulitis. Less frequently reported are bullous and nonbullous impetigo, nodules, pustules, and scalded skin syndrome. Community-associated MRSA strains are generally more susceptible to non- $\beta$ -lactam antibiotics (especially clindamycin and trimethoprim-sulfamethoxazole) than are nosocomial MRSA strains. However, some erythromycin-resistant strains develop resistance to clindamycin during treatment. The microbiology laboratory should provide results of a D-test for strains resistant to erythromycin; if the D-test is negative, then clindamycin can be used.

Community-associated MRSA is becoming a significant health concern, and studies are underway to find ways to reduce the spread of MRSA in families, schools, and communities.

### WHEN TO REFER

- Preseptal cellulitis
- Treatment failure
- Recurrent bacterial skin infections

### WHEN TO ADMIT

- Cellulitis with suspected sepsis or suspected underlying serious infection
- Invasive infections (necrotizing fasciitis)
- Staphylococcal scalded skin syndrome
- Toxic shock syndrome

## TOOLS FOR PRACTICE

### Medical Decision Support

- *Dermatology: Skin Infections* (online course), American Academy of Pediatrics ([pedialink.aap.org](http://pedialink.aap.org))
- *Pediatric Dermatology: A Quick Reference Guide*, 2nd ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Red Book: 2015 Report of the Committee on Infectious Diseases* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

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## Chapter 223

# BRAIN TUMORS

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The primary care physician (PCP) is often the first person to evaluate children with brain tumors; in one-half of children ultimately diagnosed with brain tumors, the diagnostic process was initiated by the PCP. Brain tumors, although rare, are the second most common cancer and the most common solid tumor in childhood. Therefore, PCPs should be mindful of the possibility of a brain tumor among the other potential explanations of a child's illness. A delay in making the diagnosis may ultimately affect the child's outcome. Some low-grade (previously referred to as benign) tumors can be cured with surgery. Many high-grade (previously referred to as malignant) brain tumors do not share the favorable prognosis of other common pediatric cancer diagnoses, and aside from a few exceptions, including medulloblastoma and nongerminomatous germ cell tumors, recent advances have only modestly improved outcomes. The prognosis depends on myriad factors, including tumor histology, molecular genetics, size, extent of dissemination, location, and age. Children who survive may experience substantial morbidity.

## DEFINITIONS

*Primary brain tumors* are tumors of the brain parenchyma, cranial nerves, meninges, and the pituitary gland and immediate surrounding structures. Brain tumors arise from a persistence of the embryologic precursors of neurons themselves (primitive neuroectodermal tumors [PNETs]), glial elements that provide structural and nutritional support to the neurons (astrocytomas and oligodendrogliomas), germ cell elements (germinoma and nongerminomatous germ cell tumors), the lining cells, such as the arachnoid (meningioma), the nerve sheath (schwannoma), the



pituitary gland (pituitary adenomas), or intracranial rests (craniopharyngiomas).

## INCIDENCE

In the United States, the incidence of primary brain and central nervous system (CNS) tumors is approximately 5.4 cases per 100,000 person-years, with an estimated 3,420 new cases to be diagnosed in the United States in 2015. The overall incidence is age-stratified, with the highest incidence occurring in the youngest children (0–4 years), with 5.8 cases per 100,000 person-years, and in the oldest children (15–19 years), with 5.91 cases per 100,000 person-years. Incidence is not affected by gender overall, but there is a slightly higher incidence of embryonal tumors and germ cell tumors in males. Reports suggest the incidence of childhood cancer, and particularly brain tumors, has been rising over the last 3 decades. The increase may be the result of improvements in diagnostic technology and reporting patterns, as well as possible environmental or other unexplained factors. For example, a substantial increase was observed after 1984 when magnetic resonance imaging (MRI) became widely available. While the incidence continued to rise, it stabilized from 2007 to 2011 with only a small decline in mortality associated with brain tumors. However, overall survival rates have improved over time, with 10-year survival rates of 56.3% (1982–1986), 65.4% (1992–1996), and 69.2% (2002–2006).

## RISK FACTORS

Only a few risk factors for brain tumors are universally accepted: previous therapeutic radiotherapy, predisposing genetic syndromes, and some aspects of maternal diet. Therapeutic low-intensity radiotherapy, such as that used in the 1950s for tinea capitis, is now linked to a long-term relative risk of meningiomas and malignant brain tumors as a result of total-dose of radiation exposure. Children who received therapy for acute lymphoblastic leukemia, including radiotherapy, are at increased risk for second malignant neoplasms, including CNS tumors.

Interestingly, children with primary CNS neoplasms without a documented genetic syndrome demonstrate an increased risk of a second CNS neoplasm. A 10-year cumulative incidence of 1.4%, regardless of previous therapy with radiotherapy or chemotherapy, has been reported. Inherited syndromes are also associated with a higher risk for childhood brain tumors, although they are only present in a minority of cases. These include neurofibromatosis types 1 and 2, tuberous sclerosis types 1 and 2, von Hippel-Landau syndrome, Li-Fraumeni syndrome, nevoid basal cell carcinoma syndrome, Turcot syndrome, ataxia-telangiectasia syndrome, Gardner syndrome, and Down syndrome. Certain aspects of maternal diet influence the risk of PNETs in young children, with strong protective dose-response relations observed for maternal consumption of fruit, vegetables, vitamin C, nitrate, and folate.

Other notable associations worth mentioning include pineoblastoma in children with retinoblastoma, pituitary tumors in children with various endocrine

adenomatosis syndromes, and the high incidence of pineal germinomas in Japan. Primary CNS lymphoma may be seen as a result of primary or secondary disorders of the immune system, as in acquired immunodeficiency syndrome, Wiskott-Aldrich syndrome, or ataxia-telangiectasia syndrome, and after solid organ transplantation.

## CLASSIFICATION

Brain tumors are classified according to their histology, but the location and extent of spread are important factors that affect treatment planning and prognosis. The most widely recognized classification system is the World Health Organization (WHO) classification of tumors, published in 2000, with more than 120 entries. This criteria system was established with the intention of encouraging and standardizing multicenter clinical trials. The system is designed to integrate histopathologic criteria with clinical, epidemiologic, radiologic, biologic, molecular genetic, and predictive factors and therefore continues to evolve, with new diagnoses continually being added.

The WHO classification recognizes 4 malignancy grades or estimates of malignant potential. However, the pathologic distinction between malignant and nonmalignant tumors may not always reflect the clinical course of the disease. Physicians now avoid using terms such as *benign* or *malignant* in favor of *low-grade* or *high-grade*, because the former terms can be misleading. Furthermore, the prognosis for some high-grade tumors is better than for some low-grade tumors. For example, an infiltrating low-grade glioma may have a less favorable long-term prognosis than a high-grade (malignant) PNET that is low-stage, completely resected, and treated with appropriate radiotherapy or chemotherapy. As another example, the craniopharyngioma has a benign histology, but if this tumor produces infiltration into the hypothalamic structures, then the course may be anything but benign. Finally, in some circumstances, such as infiltrating brainstem gliomas, the biopsy specimen may seem to be low-grade but the disease may still have an aggressive course.

## DELAY IN DIAGNOSIS

In contrast to many pediatric malignancies, especially leukemias, many weeks or months may pass for children with brain tumors between the onset of symptoms and diagnosis. Only one-third of children with brain tumors are diagnosed within the first month after the onset of signs or symptoms. The interval between the onset of symptoms and the time of diagnosis is approximately 9 weeks, including a parental delay of 5 weeks after noticing symptoms and a physician's delay of an additional 3 weeks. This time to diagnosis correlates with the child's age and the location and histologic type of the tumor. A shorter delay is common in infants, possibly because of closer supervision by their PCPs. Older children tend to have more subtle neurologic findings and are more likely to have a longer time from initial symptom onset to the definitive diagnosis.

## EVALUATION

### History

The manifestations of childhood brain tumors depend on the site of tumor origin, the child's age and developmental level, and whether accompanying hydrocephalus exists. No single clinical historical detail or physical finding is pathognomonic. Children will typically have a progression of symptoms and physical findings, which may not correlate with the grade of the underlying disease. Most children will have several suggestive features at the time of diagnosis; only 12% of children have just a single symptom. In infants, increased intracranial pressure (ICP) may exhibit insidiously with nonspecific signs such as drowsiness or lethargy, irritability, vomiting, abnormal tilting of the head, or developmental stagnation or regression. In older children, declining academic performance; fatigue; and emotional, appetite, or personality changes may occur before overt headaches and vomiting.

A well-studied symptom of brain tumor is headache. Headaches may be frontal, occipital, unilateral, or diffuse in location and may be exacerbated by Valsalva maneuvers, cough, or position. In most circumstances, headaches of more than 4 months duration, without neurologic features, are seldom caused by brain tumors. Other features that warrant further evaluation of a child with headache include the presence of a neurologic abnormality, ocular findings such as papilledema or decreased visual acuity, vomiting not otherwise explained by a viral illness, increase in frequency or severity of the headaches, recurrent morning headaches or pain that awakens the child from sleep, the presence of short stature or deceleration of linear growth, diabetes insipidus, age younger than three years, or a child with neurofibromatosis.

Vomiting is also an established symptom of childhood brain tumors and may be the result of increased ICP or, less commonly, direct irritation of the vagal nuclei on the floor of the fourth ventricle. Vomiting may be associated with morning or waking headaches and may also relieve the headaches.

In contrast to adults, seizures are not as frequently observed in children with brain tumors. However, aside from some well-characterized seizure syndromes, patients of any age who have seizures with a focal onset, either simple partial (focal) seizures or partial seizures with secondary generalization, should be evaluated for a tumor by MRI.

More specific symptoms may help localize the tumor. Infratentorial tumors commonly produce cerebellar symptoms such as clumsiness, worsening handwriting, scanning speech, or frank symptoms of ataxia and increased ICP. The infiltrating brainstem glioma may produce typical localizing signs of ataxia, cranial nerve symptoms (particularly diplopia because of sixth-nerve palsy), and long-tract signs (hemiparesis or tetraparesis), because this tumor invades the crossing cerebellar outflow tracks, brainstem nuclei, and the descending corticospinal tract. The nonlocalizing signs of this tumor can be headache and vomiting resulting from an obstruction of cerebrospinal fluid (CSF) flow and increased ICP.

Supratentorial tumors may result in symptoms specific to the location of the disease. Complaints of hemiparesis (muscle weakness) suggest the presence of disease in the cerebral hemispheres. Visual loss or visual field defects may be the result of disease localized anywhere along the optic tracts, and when associated with hormonal changes such as growth failure, diabetes insipidus, or precocious puberty, they imply the presence of tumors near the optic chiasm and hypothalamus. Tumors of the hypothalamus may also be associated with diencephalic syndrome in infants, which is characterized by failure to thrive, emaciation, and a euphoric mood.

### Physical Examination

In addition to a thorough history, a complete and thorough neurologic examination will reveal both localizing and nonlocalizing findings. These neurologic findings, with or without a complementary history, are required for further investigation and for referring the child to a specialist. Repeated neurologic examinations may be revealing because signs are often progressive in situations in which the diagnosis remains in question. Tumors may cause macrocephaly, generally seen when the tumor impairs the normal circulation of CSF, resulting in hydrocephalus. In an infant, this condition produces head circumference measurements that cross percentile lines on a standard chart. The findings of fontanel bulging, split cranial sutures, lack of upgaze, and alteration in tone are all indicative of hydrocephalus. Some infants will seem to be failing to thrive as a result of vomiting caused by the increased ICP. Papilledema is uncommon in infants because their skulls can expand, and the ICP does not increase enough to cause symptoms until much later in the course. In children with fused cranial sutures, hydrocephalus will result in increased ICP and cause papilledema. Focal or localizing signs can help identify the location of the tumor. Tumors of the cerebral hemisphere can result in personality changes, focal weakness, language dysfunction, visual field defects, or sensory changes. Tumors involving the visual pathway will obviously result in visual-field deficits. Pineal tumors and tumors involving the midbrain tectum cause *Parinaud syndrome*, a triad of paralysis of upward gaze with associated convergence-retraction nystagmus, lid retraction, and light-near dissociation of the pupils. If the tumor involves the midline structures of the cerebellum, then truncal ataxia will be the dominant sign. Tumors involving the brainstem can result in ataxia, corticospinal tract findings, and focal brainstem signs. Tumors involving the suprasellar and hypothalamic region may be associated with signs of an endocrine disturbance such as precocious or delayed puberty, growth failure, or constipation and dry skin indicative of hypothyroidism. The symptoms and signs of spinal cord tumors depend on the location of the tumor and its extent of infiltration into the surrounding tissue.

### Differential Diagnosis

Space-occupying lesions and causes of ICP are listed in Box 223-1.

**BOX 223-1 Differential Diagnosis**

- Arteriovenous malformations
- Subdural hematoma, effusion, or empyema
- Abscess
- Infarction
- Hemorrhage
- Demyelination
- Pseudotumor cerebri (Idiopathic intracranial hypertension)
- Hemiplegic migraine
- Todd paralysis
- Venous sinus thrombosis

**Laboratory Evaluation**

Patients with tumors of the pituitary gland and tumors that involve the pituitary stalk and hypothalamus should undergo evaluation of endocrine function before surgery. If the tumor involves the pituitary stalk or the posterior portion of the gland, then electrolytes and osmolality measurements can help diagnose diabetes insipidus. Children with midline supratentorial tumors should be evaluated for non-germinomatous germ cell tumors, such as choriocarcinoma, yolk-sac tumors, embryonal cell tumors, and the mixed variety. These tumors can excrete  $\alpha$ -fetoprotein,  $\beta$ -human chorionic gonadotrophin, and alkaline phosphatase. If present, these are most easily found in CSF, but they may also be detected in serum. Germinomas do not typically secrete these markers. Human immunodeficiency virus serologic testing may be useful if a diagnosis of primary CNS lymphoma is suspected, although this tumor rarely occurs in children.

**Imaging Studies**

Advances in neuroradiology have helped physicians make prompt and accurate diagnoses of childhood brain tumors. Computed tomography (CT) scanning is widely available, has short imaging times, and requires less sedation in young children, so it is often the first modality to be used. The initial CT scan can provide important immediate information about the presence of hydrocephalus, cerebral edema, midline shifts, and risk of uncal herniation. However, tumors of the brainstem, visual pathway, posterior fossa, and mesial temporal lobe structures may not be clearly visible.

Magnetic resonance imaging is the imaging modality of choice for the definitive diagnosis of CNS neoplasms. An MRI is more sensitive than a CT scan for most brain tumors and is the best imaging modality for tumors of the brainstem, posterior fossa, mesial temporal lobe, and spinal column. As with CT, a contrast agent will help detect many tumors because the gadolinium contrast agent accumulates in tissues that lack an intact blood-brain barrier. High-grade tumors infiltrate the surrounding tissues, inducing more surrounding edema and usually resulting in better contrast enhancement. In comparison, low-grade

gliomas, the most common childhood tumor, are well demarcated and generally have little surrounding edema.

**MANAGEMENT**

Treatment of most children with brain tumors requires a multidisciplinary team approach that includes pediatric subspecialists from the disciplines of neurosurgery, neurology, oncology, pathology, radiology, radiation oncology, endocrinology, and ophthalmology. In addition, these patients benefit from experienced pharmacologists; nurses; neuropsychologists; audiologists; nutritional experts; child life specialists; physical, occupational, and speech therapists; and social workers. The outcome of treatment for children with cancer has been shown to be better when care is provided at a specialized tertiary-care cancer center. In light of this circumstance, the American Academy of Pediatrics released a statement outlining guidelines for facilities, capabilities, and available personnel.

Children benefit from being treated with protocols developed by large cooperative cancer consortiums. Therefore, children should be considered for enrollment into a clinical trial whenever one is available. Clinical trials are carried out by single institutions in addition to collaborative groups such as the Children's Oncology Group and the Pediatric Brain Tumor Consortium.

The optimal therapy combination for most brain tumors is still being determined through clinical trials. However, the initial treatment of many brain tumors is often surgery. Presurgical corticosteroid therapy is essential for children with brain edema and increased ICP. Brain tumors contain tumor vessels that behave abnormally, favoring the formation of edema within and around the tumor as a result of the disruption of the blood-brain barrier. Methylprednisolone reduces capillary permeability in the tumor and adjacent brain tissue. Children treated with methylprednisolone often develop rapid and marked resolution of the edema with corresponding improvement of their symptoms and a more relaxed brain during the operative procedure. Other steroids with glucocorticosteroid effects, such as prednisone or dexamethasone, can be used as well.

Excision removes the tumor and resolves the surrounding edema. Neurosurgical techniques improved during the last 20 years, along with safer anesthesia and better intensive care management. The use of stereoscopic microscopes coupled with real-time surgical navigation systems is the most striking advance. A navigation system permits the operative burr hole to be placed with high precision; thus, allowing tumor resection through small openings. In addition, modern microscopes, coupled with surgical navigation, allow the surgeon to distinguish between healthy brain and tumor, resulting in a greater likelihood of total resection. Electrophysiologic monitoring during surgery also contributes to safer and bolder approaches. Intraoperative MRI has benefited select cases, but its widespread use is limited by its high cost and the often considerably longer operating times.

Although surgical resection is the goal for many tumors, some tumor types are best diagnosed by



neuroimaging or by histologic evaluation of biopsy material, when it can be obtained without substantial morbidity. Because of location, tumors situated in the deep gray matter, such as the thalamus and basal ganglia, are often biopsied by means of a stereotactic navigation system. Diffuse pontine gliomas and tectal plate gliomas are biopsied less frequently because of the risk of damaging essential structures and because they have a predictable histologic appearance and clinical course. The neuroimaging characteristics of visual pathway gliomas and intrinsic pontine gliomas are classic; therefore, pathologic corroboration of a diagnosis is seldom helpful. However, there is continuing debate over the need for more aggressive approaches for tumors in the deep, midline, or critical regions of the brain.

Most cerebellar and hemispheric low-grade gliomas are pilocytic astrocytomas. The strategy of choice for treating these children is gross total resection, which is often accomplished with the cerebellar forms of this tumor. For other tumors, debulking of the primary tumor allows for more effective chemotherapy and radiotherapy. Chemotherapy has improved the survival of many patients with CNS tumors, and radiotherapy is an important treatment modality for all but the youngest patients. In very young patients, new treatment protocols were developed involving intensive chemotherapy with stem cell rescue in an effort to replace radiotherapy and avoid its long-term consequences.

Current radiotherapies vary and include external-beam, 3-dimensional, and intensity-modulated radiotherapy, as well as stereotactic radiosurgery and gamma-knife surgery, which allow small-volume or local irradiation while sparing surrounding tissues and essential structures. Proton beam radiation is increasingly used to treat some pediatric CNS tumors. Long-term outcomes data are still needed to understand its role in pediatric radiation therapy. Radiation is the best therapy for many tumors, but it may result in growth failure, failure of intellectual and emotional development, and an increased risk for later development of malignancy caused by radiation exposure. For treatment decisions, especially in young children, one must consider the chance of cure and weigh it against the potential for profound morbidity and late effects.

The potential for further improvements in outcomes likely lies in collective clinical trials of new treatment strategies, including antiangiogenesis medications, monoclonal antibodies, immunotherapy, differentiation agents, anti-angiogenic agents, and gene therapy. Such trials are best conducted in collaboration with a network of experienced investigators working in specialized tertiary-care cancer centers.

### WHEN TO REFER

Children with a history that suggests brain tumor and children with focal findings at physical examination require further evaluation. Ordering a neuroimaging study is within the scope of practice for pediatricians and pediatric nurse practitioners and should be done emergently if the

symptoms and examination suggest a brain tumor or other intracranial pathology. Oncologists, neurologists, and neurosurgeons prefer early referrals, hoping that if the diagnosis of a neoplasm is made, then the tumor will be smaller and easier to resect, thereby causing less damage to adjacent brain tissue. New strategies to expedite and simplify referrals in other countries, including referral guidelines and cancer referral forms, have been used with good satisfaction rates, and adopting these strategies may be beneficial in local medical networks for streamlining the care of these children.

### WHEN TO ADMIT

Patients with signs of increasing ICP should be admitted urgently for evaluation and imaging. Computed tomography scanning can provide immediate information about ventricular size, the volume of the normal cisternal spaces, shifting of normal brain structures, and degree of ICP. Progressive life-threatening symptoms may include increasing blood pressure and decreasing heart rate, sixth-nerve palsy, or occipital headaches caused by irritation of posterior roots of the cervical cord. These symptoms may quickly progress to neck stiffness and eventually opisthotonus, a spasm of the body in which the head and heels are bent backward and the body is bowed forward. In addition, children with supratentorial mass lesions may exhibit pupillary dilatation, often unilateral initially, from uncal herniation. This manifestation may culminate in tonsillar herniation, which is also a potential sequela of an untreated posterior fossa mass lesion, obstructive hydrocephalus, or both. In all these clinical situations, a neurosurgeon should be consulted urgently.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *CureSearch* (Web site), ([www.curesearch.org](http://www.curesearch.org))
- *What Is a Pediatric Hematologist/Oncologist?* (fact sheet), American Academy of Pediatrics ([healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Hematologist-Oncologist.aspx](http://healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Hematologist-Oncologist.aspx))

#### Medical Decision Support

- *Central Brain Tumor Registry of the United States: Pediatric Incidence Report Statistics* (database), Central Brain Tumor Registry of the United States (CBTRUS) ([www.cbtrus.org/cbtrus-bin/interactive/public/2005/search\\_pedincidence](http://www.cbtrus.org/cbtrus-bin/interactive/public/2005/search_pedincidence))

### AAP POLICY

American Academy of Pediatrics Section on Hematology/Oncology. Guidelines for pediatric cancer centers. *Pediatrics*. 2004;113(6):1833–1835. Reaffirmed October 2008 ([pediatrics.aappublications.org/content/113/6/1833](http://pediatrics.aappublications.org/content/113/6/1833))



**SUGGESTED READINGS**

- Keating RF, Goodrich JT, Packer RJ, eds. *Tumors of the Pediatric Central Nervous System*, 2nd ed. Washington, DC: Thieme Medical Publishers; 2013
- National Institute for Health and Care Excellence (NICE). Suspected Cancer: Recognition and Referral, 2015. Available at: [www.nice.org.uk/guidance/ng12](http://www.nice.org.uk/guidance/ng12). Accessed September 23, 2015
- Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th ed. Philadelphia, PA: Wolters Kluwer; 2015

## Chapter 224

# BRONCHIOLITIS

Caroline Breese Hall, MD<sup>†</sup>

**DEFINITION**

Bronchiolitis is a common, acute viral lower respiratory tract illness of children occurring during the first 2 years of life. It is the number one cause of hospitalizations for infants in the United States. Furthermore, the number of bronchiolitis admissions has increased in recent years among infants in the United States and Canada. This has resulted in an appreciable and escalating economic burden to our health care system.

The clinical picture of bronchiolitis has been described since the beginning of the 20th century, but the disease was associated with a variety of sobriquets, including wheezy or asthmatic bronchitis, acute

<sup>†</sup>Deceased

catarrhal bronchitis, and spastic bronchopneumonia. The syndrome was not recognized as a separate entity until Engle and Newns gave it distinction by designating the infantile disease as bronchiolitis.

Although *bronchiolitis* means inflammation of the small airways, the bronchioles, it is usually defined by its clinical and epidemiologic manifestations. The American Academy of Pediatrics (AAP) characterizes bronchiolitis as “a constellation of clinical symptoms and signs including a viral upper respiratory prodrome followed by increased respiratory effort and wheezing in children less than 2 years of age.” Bronchiolitis may be further defined to include only children within the first year of life with an initial episode of wheezing. This definition emphasizes bronchiolitis as an acute lower respiratory tract disease with wheezing, which distinguishes it from the recurrent wheezing among older children that is frequently associated with upper respiratory tract infections, such as the rhinoviruses. The consensus definition of bronchiolitis from the United Kingdom, which also is based on the epidemiologic and acute clinical manifestations, is “a seasonal viral illness characterised by fever, nasal discharge, and dry wheezy cough. On examination there are fine inspiratory crackles and/or high pitched expiratory wheeze.”

**ETIOLOGY**

Although initially bacteria were thought to be the cause of bronchiolitis, respiratory viruses, primarily respiratory syncytial virus (RSV), the parainfluenza viruses, and human metapneumovirus (hMPV), are now recognized as the major agents of bronchiolitis (Table 224-1). RSV is the most frequently identified cause of bronchiolitis and the one most commonly identified as the sole agent. RSV has been estimated to

**Table 224-1** Causes of Bronchiolitis by Season

VIRUS	FREQUENCY OF DETECTION IN BRONCHIOLITIS	SEASONAL OCCURRENCE
Respiratory syncytial virus	++++	Major outbreaks annually Fall to spring
Human metapneumovirus	++	Annual, fall to spring
Parainfluenza virus type 1	+	Fall, every other year
Parainfluenza virus type 2	+	Sporadic, mostly fall, winter
Parainfluenza virus type 3	++	Yearly, spring into fall
Influenza A or B	+	Late fall to spring Onset, strains, prevalence vary yearly
Rhinoviruses	+ - ++	Endemic
Enteroviruses	+	Summer to fall Prevalence, type vary yearly
Human coronaviruses NL63, HKU1, 229E, OC43	+	All year; Geographic variation
Adenoviruses	+	Endemic

cause 50% to 85% of bronchiolitis cases. The relative roles of other viruses have been variably reported depending on the methods and population. The determination of the agent causing the acute manifestations also is confounded by the frequency of viral infections that occur in young children and by the occurrence of coinfections in as many as 30% of young children with respiratory symptoms. Many agents infecting infants have prolonged and asymptomatic shedding, such as bocaviruses, adenoviruses, and picornaviruses (enteroviruses and rhinoviruses). Rhinoviruses are frequently detected among young children with acute respiratory illness, especially of the upper respiratory tract. Although rhinoviruses are well associated with reactive airway disease, their role in bronchiolitis and lower respiratory tract disease in infants is less clear.

The frequency of hMPV as a cause of bronchiolitis has been variably reported, but it appears to contribute an appreciable proportion of bronchiolitis cases. The course and epidemiology associated with hMPV infection are similar to those of RSV, but hMPV is acquired at a slightly older average age and more slowly. All the parainfluenza viruses may cause bronchiolitis, but the major one is parainfluenza virus type 3, which causes primary infection and bronchiolitis in the first year of life. Influenza A and B are important causes of acute respiratory illness in young children and of hospitalizations among infants. However, the proportion of influenza infections in young children that manifest as bronchiolitis is relatively small. The role and importance of the non-severe acute respiratory syndrome (SARS) human coronaviruses, such as HCoV-NL63 and HCoV-HKU1, detected in young children with respiratory illnesses continues to be defined.

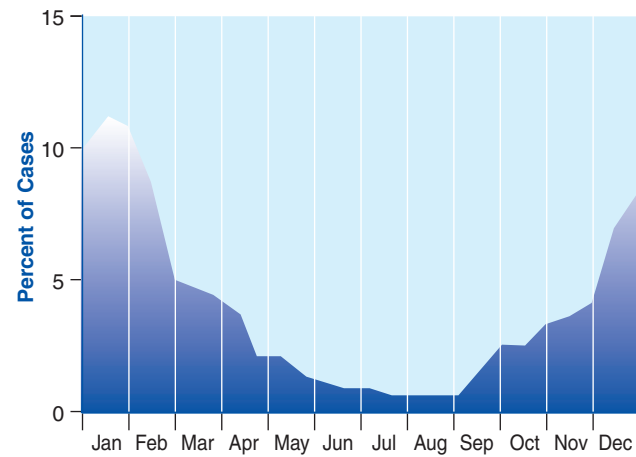
### EPIDEMIOLOGIC CHARACTERISTICS

The seasonal pattern of bronchiolitis is well determined in temperate climates and reflects the activities of its viral agents, particularly RSV (Figure 224-1).

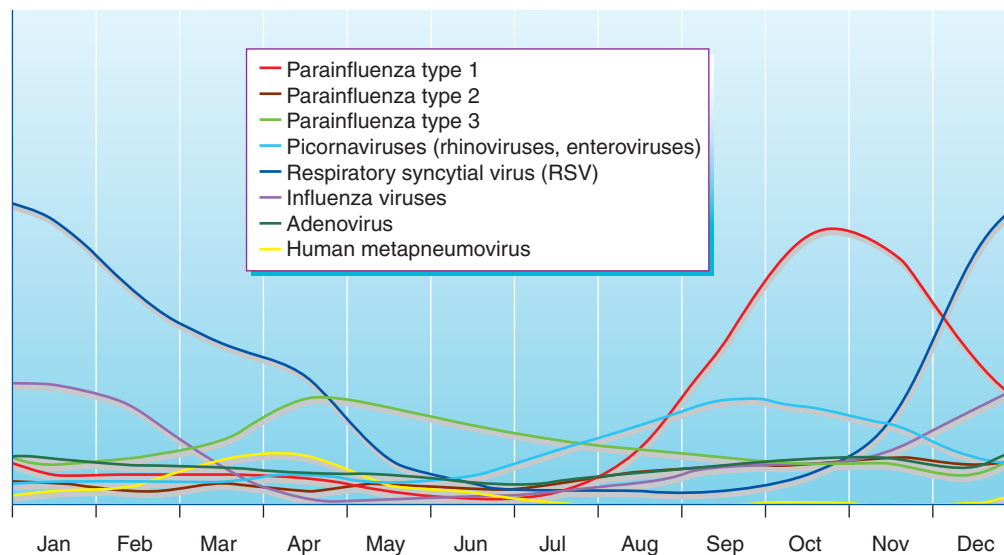
Yearly outbreaks of bronchiolitis occur during the winter to spring when RSV is epidemic in the community (Figure 224-2). Lesser peaks are observed during the fall, when the parainfluenza viruses are present in the community, and during the spring, concurrent with the major activity of parainfluenza virus type 3.

Bronchiolitis occurs primarily in children within the first 2 years of life, and more than 80% of bronchiolitis cases occur during the first year of life. The peak attack rate among hospitalized children is less than 6 months of age, whereas among children cared for in pediatric practices, the highest attack rate is observed in the second 6 months of life.

The rates of hospitalization for bronchiolitis estimated in 1996 from national databases were 31.2



**Figure 224-1** Seasonal occurrence of bronchiolitis cases obtained over a 26-year period from a community surveillance program in Monroe County, New York.



**Figure 224-2** Seasonal pattern of major respiratory viruses; respiratory syncytial viruses; parainfluenza viruses types 1, 2, and 3; influenza viruses; human metapneumoviruses; picornaviruses; and adenoviruses. Data from laboratory-confirmed surveillance in Monroe County, New York.

per 1000 children younger than 1 year of age and 2.3 per 1000 children 1 to 4 years of age. However, the rates of hospitalization for bronchiolitis among infants enrolled in a Tennessee Medicaid program were estimated as 71 per 1000 infants, and the rates estimated for the emergency department and outpatient visits were 77 and 238 per 1000 infants, respectively. In addition, 19% to 40% of bronchiolitis visits to emergency departments have been reported as resulting in hospital admission. Recent population-based studies in the United States have estimated RSV-associated hospitalization rates, 85% of which were bronchiolitis, to be 17 per 1000 children younger than 6 months of age and 5 per 1000 children 6 to 12 months of age each year. These rates are more than 3 times the rates associated with the parainfluenza viruses or with influenza among the same population. The rates of outpatient visits for bronchiolitis or RSV are less well studied but seem to be much greater, 10 to 20 times higher, than the rates for hospitalized patients.

Multiple anatomic, genetic, and environmental factors have been associated with an increased risk for more severe bronchiolitis (Figure 224-3). Boys are about 1.5 times more likely to develop bronchiolitis

than girls. Anatomic and physiologic differences between boys and girls, such as airway tone, may partly explain the male preponderance. Among the socioeconomic and environmental factors that have been correlated with a greater likelihood of developing bronchiolitis are lower socioeconomic status, exposure to tobacco smoke, lack of breastfeeding, contact with other young children (including having one or more siblings), and child care attendance. Most important, however, are young age, particularly within the first several months, and the presence of underlying conditions that affect cardiopulmonary function with and without chronic lung disease.

## DIFFERENTIAL DIAGNOSIS

Several conditions with wheezing and respiratory distress in young children may seem similar to bronchiolitis. Asthma is the major consideration in the differential diagnosis of bronchiolitis. Often in a single episode, differentiating these 2 entities is not possible. Wheezing associated with both bronchiolitis and asthma in young children is engendered by viral infections. Differentiation is further confounded by the possibility that a link exists between them, with RSV infection in infancy leading to subsequent wheezing episodes associated with asthma. Nevertheless, previous episodes of wheezing and a family history of atopy are more suggestive of asthma than of bronchiolitis.

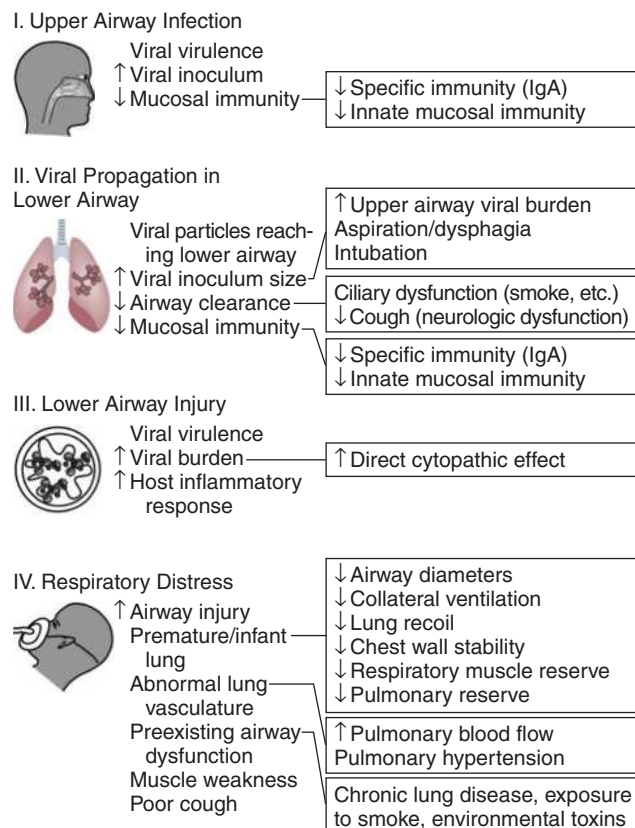
Another diagnostic consideration is gastroesophageal reflux, which in the infant may exhibit primarily episodes of wheezing and may produce a picture clinically identical to that of bronchiolitis. However, history of the timing in relation to feeding and frequency of the wheezing episodes, as well as the lack of upper respiratory tract signs typical of a viral infection, are helpful in differentiating gastroesophageal reflux from bronchiolitis.

Other entities that may result in wheezing and respiratory distress in the age group of children with bronchiolitis that should be considered include obstruction from an aspirated foreign body, a vascular ring, retropharyngeal abscess, and, rarely, significantly enlarged adenoids. Wheezing also may occur in congestive heart failure and in chronic lung disease, such as that associated with prematurity and cystic fibrosis.

## EVALUATION

### History

A carefully obtained history of wheezing in a child is integral in both determining the diagnosis and assessing the potential for developing severe or complicated illness. The diagnosis of bronchiolitis is usually based on the clinical history and physical findings. Features that strongly support the diagnosis include the illness occurring during a community outbreak of one of the major viral agents, mainly RSV; young age (especially <12 months); and no prior episode of wheezing. The risk factors, as noted in Epidemiologic Characteristics, for the development of more severe disease need to be assessed, especially the presence of prematurity,



**Figure 224-3** Factors that contribute to severity of viral bronchiolitis. (Reprinted with permission from Hall CB, McBride J. Bronchiolitis. In: Mandell J, Bennett J, Dolin R, eds. Principles and Practice of Infectious Diseases. 7th ed. New York, NY: Churchill Livingstone; 2009:885–890.)

cardiopulmonary disease, immunodeficiency, and other underlying diseases.

The infant with bronchiolitis typically has a recent history of signs compatible with a common cold: rhinorrhea, nasal congestion, a low-grade fever, and cough. As infection spreads to the lower respiratory tract, the cough becomes more prominent, followed by tachypnea. Fever is commonly present during the prodromal period but is usually not high. By the time bronchiolitis associated with RSV develops, only about 50% of children are febrile.

### **Clinical Manifestations and Pathogenesis of Physical Findings**

On physical examination, an increased respiratory rate is almost always evident. Whether a child is tachypneic must be judged based on age. The overall respiratory rate in full-term newborns is about 50 breaths per minute but decreases over the first year of life to a mean of about 40 per minute at 6 months and a mean of 30 per minute at 1 year of age. Tachycardia commonly accompanies the tachypnea. The infant may appear irritable, lethargic, or anxious. Flaring of the nasal alae and expiratory grunting signify an increased work of breathing. Retractions of the chest wall in the subcostal, intercostal, and suprasternal areas and use of the accessory muscles of respiration also may be evident.

Respiratory distress arises from the inflammation of the respiratory epithelium of the upper and lower respiratory tract and obstruction of the medium and small bronchi and bronchioles. The viral infection causes increased mucus production, edema, and necrosis of the bronchiolar epithelium, which is sloughed into the lumen of the small airways. Because resistance to the flow of air is related inversely to the radius of the lumen, the small diameter of the bronchioles makes the infant particularly vulnerable to obstruction caused by the edema and inflammatory exudate.

Peripheral to the sites of partial obstruction, air becomes trapped by a process similar to a ball-valve mechanism. During inspiration, the negative intrapleural pressure allows air to flow past the site of partial obstruction. On expiration, however, the positive intrathoracic pressure decreases the diameter of the bronchiolar lumen, causing an increase in the degree of obstruction, and hyperinflation of the lung ensues. If the inflammation progresses, complete obstruction can occur, and when the trapped air is absorbed, multiple areas of focal atelectasis result.

This characteristic hyperinflation is evidenced on the physical examination by an increased diameter rounding the chest and hyperresonance on percussion. The liver and spleen may become easily palpable from the downward placement of the overinflated lungs. The airway obstruction is further reflected by a prolonged expiration that may be difficult to detect in a young infant who has a rapid respiratory rate. The flow of air also is impeded on inspiration but to a lesser extent. Auscultation usually reveals wheezing with or without crackles, but these findings may vary from hour to hour. Indeed, fluctuating physical findings on examination is characteristic of bronchiolitis in infants. However, a decrease in the auscultatory findings

accompanied by increasing respiratory distress may indicate progressive obstruction to the flow of air in the small airways and impending respiratory failure.

Additional clinical findings may develop from acute complications during the infant's course. Apnea is an infrequent but potentially fatal acute complication of bronchiolitis and RSV infections among infants, and it may be the first manifestation of the respiratory illness. Most at risk for apnea are infants of premature gestation and those whose postconceptional age is less than 44 weeks. The subsequent prognosis for children with apnea associated with RSV infection is generally good and does not appear to be associated with an increased risk for subsequent apnea, even during subsequent viral infections. Otitis media is also present in 3% to 30% of infants and may be caused by the infecting virus, bacteria, or both. The risk for dehydration complicating the course of infants with bronchiolitis arises from paroxysms of coughing that trigger vomiting and by the decreased fluid intake resulting from congested nasal passages and from the respiratory distress. In addition, tachypnea and fever may increase fluid requirements. Aspiration has been noted to occur frequently among infants hospitalized with RSV bronchiolitis and has been correlated with an increased risk for subsequently developing hyperreactive airway disease. This risk, however, has been shown to be abrogated by the prophylactic administration of thickened feeds for the prevention of aspiration.

### **Clinical Course**

Most infants who have bronchiolitis improve appreciably within several days, and the cough and other respiratory signs resolve gradually thereafter over 1 to 2 weeks. Most hospitalized children are discharged within a few days, often 2 to 3 days. Radiographic resolution of atelectasis, however, may require several weeks. Among ambulatory children, the median duration of illness has been reported to be 12 days for those younger than 24 months. However, 18% remained symptomatic after 3 weeks and 9% after 4 weeks. The clinical course tends to be more prolonged in young infants, those with underlying conditions, and those who acquired the infection nosocomially. Whether simultaneous infection with more than 1 virus in children with bronchiolitis results in more severe clinical disease is unclear. Although 1 small study reported an increased risk for requiring assisted ventilation among children who were coinfecting with RSV and hMPV infection, other studies have not found a greater severity of infection when more than 1 virus is detected.

### **Laboratory Testing**

Laboratory diagnostic tests for healthy infants with their first episode of wheezing are not routinely recommended because the diagnosis of bronchiolitis is usually based on the history and clinical findings. Unless the child's course is atypical or abruptly changes, diagnostic tests such as the complete blood cell count, measurement of arterial oxygen saturation, serum chemistries, and cultures to detect bacterial infection are generally not helpful or necessary for the management of previously normal children who have not had



prior wheezing. Furthermore, limiting diagnostic testing has been associated with benefits in both cost and clinical outcomes.

Pulse oximetry, which is a common part of the evaluation of children with bronchiolitis, has been demonstrated not to improve the outcome for infants with bronchiolitis, and its use has been associated with a lower threshold for hospitalization, higher rates of admission to intensive care units, and mechanical ventilation.

Tests for viral identification also are not routinely recommended because most children respond to supportive care alone. Assays to identify the specific virus may be warranted for selected and more severely ill children in whom specific antiviral therapy for RSV or influenza is being considered. Specific viral testing may also be beneficial in determining feasible infection control procedures, such as cohorting.

The laboratory tests most commonly used to determine the viral causes of bronchiolitis are rapid antigen detection assays because of their ease, cost, and rapid results. Rapid antigen detection assays are available for most of the respiratory viruses commonly causing bronchiolitis, including RSV, the parainfluenza viruses, influenza viruses, and hMPV, and assays for many additional viruses have been developed and are becoming more widely available. The sensitivity and specificity of these rapid antigen assays vary, and the positive predictive value significantly diminishes when the prevalence of the viral agent is low in the community. Thus, these assays preferably should be used during periods of peak activity. Reverse-transcriptase polymerase chain reaction (RT-PCR) and other molecular diagnostic assays are highly sensitive and specific for the diagnosis of multiple viral agents. Because of their sensitivity, infecting agents may be detected over prolonged periods, leading to confusion about which agent is the cause of the acute illness. Quantitative PCR assays may help in some instances. Viral isolation techniques are rarely used because of their variability, the technical expertise required, their cost, and the fact that some agents of bronchiolitis cannot be readily isolated in cell culture. Recent increased use of RT-PCR has consistently demonstrated these assays to be significantly more sensitive than viral isolation.

Antibody determinations on acute and convalescent sera in the young infant are rarely helpful in clinical management because of the time required to obtain a convalescent serum, the presence of passive maternal antibody, and the diminished antibody response of young infants to some viral respiratory agents that cause bronchiolitis.

### Imaging

Imaging should not be used routinely in the previously healthy child in whom the diagnosis of bronchiolitis can be made based on clinical and historical findings. In a prospective study of children 2 to 23 months of age being evaluated in an emergency department, routine chest roentgenograms provided little benefit. Less than 1% identified findings consistent with bronchiolitis. Furthermore, chest roentgenograms led to greater use of unwarranted antibiotics. Radiographic evaluation, therefore, should be reserved for those patients in

whom the diagnosis of bronchiolitis is not clear and the course is not as expected. Chest roentgenograms also should not be used to monitor the course of an infant with bronchiolitis or to decide admission or discharge. Importantly, the findings on the chest roentgenograms commonly are relatively benign and do not correlate with the severity of illness. The characteristic findings associated with bronchiolitis are increased bronchovascular markings radiating out from the hila and scattered small areas of atelectasis. The observed areas of atelectasis may be mistakenly interpreted as areas of pneumonic infiltration and of bacterial infection. Prospective studies have shown that the outcome and duration of illness among children with suspected lower respiratory tract infections who were evaluated with chest roentgenograms were not improved.

### MANAGEMENT

Management of most infants who have bronchiolitis, whether they are outpatients or hospitalized, consists primarily of supportive care, including adequate rest, comfort, hydration, and antipyretics, if necessary. Congestion of the nasal passages and upper airway, which may contribute to an infant's work of breathing, may be alleviated by gentle nasal suctioning and positioning of the infant. Mist therapy has not been shown to be beneficial. Chest physiotherapy, including percussion and vibratory techniques, have been of no clinical value and are not recommended. For the more severely affected child who is hospitalized, the need for supplemental oxygen administration should be judged by repetitive readings indicating an inadequate oxygen saturation level. Consensus does not exist on the level of oxygen saturation that indicates the need for supplemental oxygen, but the recent AAP bronchiolitis guidelines recommend initiating supplemental oxygen when the oxyhemoglobin saturation is persistently less than 90% and considering discontinuation of the supplemental oxygen when the level is persistently at or above 90%.

Beyond these measures, little agreement exists within the United States or among other countries about the value and use of therapeutic modalities. Although evidence is lacking that shows benefit for most of the commonly used therapies, especially for those who are first-time wheezers, corticosteroids, antivirals, antibiotics, and especially bronchodilators are frequently administered.

Studies evaluating the use of bronchodilating agents in bronchiolitis have given variable and contrasting results. Most controlled trials and reviews of the use of  $\beta$ -adrenergic agents have not shown consistent clinical benefit in children hospitalized with their first episode of wheezing. Among outpatient children, some studies have suggested transient or short-term clinical benefit when evaluated by varying clinical score systems. The AAP recommends that bronchodilators should not be used routinely in the management of bronchiolitis but that a carefully monitored trial of inhaled  $\alpha$ - or  $\beta$ -adrenergic agents is an option. However, the bronchodilator should be continued only if a beneficial clinical response is clearly documented.

Corticosteroid medications are frequently administered to infants with bronchiolitis. In some facilities,

most infants with bronchiolitis are treated with systemic glucocorticosteroids. However, meta-analyses have not shown consistent or statistically significant benefit, and the AAP recommends that therapy with corticosteroid medications should not be used routinely for the care of infants with a first episode of bronchiolitis. A large multicenter double-blind randomized trial evaluating the administration of corticosteroids to children with bronchiolitis was conducted in 20 emergency departments in the United States and completed in 2006. Children 2 to 12 months of age with a first episode of wheezing from moderate to severe bronchiolitis received a single dose of oral dexamethasone (1 mg/kg) or placebo over 3 respiratory seasons. No significant difference between the 2 groups was observed in the requirement for hospitalization. The same lack of benefit of corticosteroid therapy was observed in the subgroups of children with asthma or with a family history of asthma. A multicenter study from the Pediatric Emergency Research Canada Network subsequently confirmed the lack of benefit from corticosteroid administration. The network of emergency departments evaluated 600 previously well infants presenting with their first episode of bronchiolitis treated with a 6-day course of dexamethasone and also found no significant clinical benefit compared with placebo, even among infants who received corticosteroids along with nebulized epinephrine.

Antivirals that are potentially useful for viral agents that cause bronchiolitis are few. Inhaled ribavirin, a synthetic nucleoside, which has in vitro antiviral effect against a wide spectrum of respiratory viruses, is the only agent currently approved for the treatment of RSV lower respiratory tract disease in infants. Ribavirin is not recommended routinely to treat children with bronchiolitis and generally should only be considered for use in infants with conditions that place them at high risk for developing severe disease. The drug is expensive and difficult to administer to ventilated patients, and the benefits in clinical outcome are controversial. Its use therefore should be decided on an individual basis after consideration of its relative clinical benefit to its cost in the child's management. Antivirals for influenza have not been approved as therapy for young infants or evaluated in the management of bronchiolitis. Antibiotics should not be used unless a bacterial infection is documented or evidence strongly indicates the concurrent presence of a bacterial infection, which is uncommon in bronchiolitis and RSV lower respiratory tract disease.

## PROGNOSIS

Despite the recent increasing number of hospitalizations for bronchiolitis, the mortality associated with bronchiolitis and RSV has declined. The mortality among children younger than 5 years associated with bronchiolitis between 1979 and 1997 was estimated by the Centers for Disease Control and Prevention to be an average 95 cases, with a range of 66 to 127 cases each year for all children younger than 5 years and highest in those younger than 1 year. Deaths in infants associated with RSV infection more recently have been estimated to be less than 400 per year.

The most frequent sequela of bronchiolitis, especially that caused by RSV, is recurrent wheezing, which is reported to occur in 30% to 50% of the children who had a history of hospitalization for bronchiolitis. Episodes of recurrent wheezing tend to occur most frequently during the first 2 years after the initial episode of bronchiolitis. Most of these children subsequently improve and become symptom free. However, lung function abnormalities may persist beyond 10 years, despite the clinical improvement. Significantly reduced mean expiratory flow rates and an increased risk for bronchial hyperreactivity during adolescence have been demonstrated.

Other follow-up studies, however, have shown that these children, when reaching school age, have no greater risk for hyperreactive airway disease than children with no history of bronchiolitis. One episode of bronchiolitis and less severe bronchiolitis not requiring hospitalization also have not been associated with later pulmonary abnormalities. The relationship between bronchiolitis in early infancy and the subsequent development of hyperreactive airway disease is unclear and confounded by the increasing recognition that asthma or hyperreactive airway disease is a heterogeneous group of disorders with variable pathogenesis.

### WHEN TO REFER

- When episodes of bronchiolitis or wheezing are recurrent or started at birth
- When wheezing continues despite clinical improvement

### WHEN TO ADMIT

- When oral intake is inadequate
- When the child appears toxic or has marked tachypnea or lethargy
- When respiratory distress is rapidly progressive
- When history suggests apneic episodes

## TOOLS FOR PRACTICE

### Community Coordination and Advocacy

- *Managing Infectious Diseases in Child Care and Schools* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

### Engaging Patient and Family

- *Bronchiolitis and Your Young Child* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Respiratory Syncytial Virus (RSV)* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Respiratory Syncytial Virus (RSV)* (fact sheet), American Academy of Pediatrics ([healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/Respiratory-Syncytial-Virus-RSV.aspx](http://healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/Respiratory-Syncytial-Virus-RSV.aspx))
- *Suctioning the Nose with a Bulb Syringe* (fact sheet), Cincinnati Children's Hospital Medical Center ([www.cincinnatichildrens.org/health/info/newborn/home/suction.htm](http://www.cincinnatichildrens.org/health/info/newborn/home/suction.htm))

**Medical Decision Support**

- *Bronchiolitis: recent evidence on diagnosis and management* (article), *Pediatrics*, Vol 125, Issue 2, 2010
- *The Diagnosis, Management, and Prevention of Bronchiolitis* (guideline), *Pediatrics*, Vol 134, Issue 5, 2014
- *Evidence-based clinical practice guideline for medical management of bronchiolitis in infants less than 1 year of age* (guideline), Cincinnati Children's Hospital Medical Center ([www.guideline.gov/content.aspx?id=34411](http://www.guideline.gov/content.aspx?id=34411))
- *National Respiratory and Enteric Virus Surveillance System (NREVSS)* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/surveillance/nrevss/rsv/index.html](http://www.cdc.gov/surveillance/nrevss/rsv/index.html))
- *Respiratory Syncytial Virus Infection (RSV)* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/rsv/index.html](http://www.cdc.gov/rsv/index.html)).

**SUGGESTED READINGS**

- Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection among healthy children. *N Engl J Med*. 2009;360(6):588–598
- Martinez FD, Wright AL, Taussig LM, et al. Asthma and wheezing in the first six years of life. *N Engl J Med*. 1995;332:133–138
- Vicencio AG. Susceptibility to bronchiolitis in infants. *Curr Opin Pediatr*. 2010;22(3):302–306

**Chapter 225****CANCERS IN CHILDHOOD**

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Advances in the treatment of solid tumors of childhood during the past 20 years have ensured the long-term survival of approximately three-fourths of children with these diagnoses. The pediatrician who discovers a solid tumor may not—and need not—know the best treatment available. However, early referral of such a child to the appropriate specialist, a pediatric oncologist, greatly affects the likelihood and the quality of survival. Whenever possible, children with solid tumors should be offered enrollment on clinical trials to treat their cancer, such as those offered through the Children's Oncology Group (COG) cooperative mechanism.

Initial evaluation by the primary care pediatrician appropriately involves evaluation of acute symptoms, careful physical examination, consideration of personal and family history predisposing to malignancy, preliminary imaging studies, and rapid referral to a pediatric oncologist. Many common tumors are unique in children. For all solid tumors in children, therapies must be designed to minimize effects on growth and development. Appropriate use of the therapeutic modalities (surgery, chemotherapy, and radiation) provides maximal efficacy and minimal toxicity

of therapy. Early integration of palliative care for most children diagnosed with cancer also aids in management regardless of the overall prognosis because therapy for cancer includes significant effect on quality of life.

The child and parents should be encouraged to plan for the future. Educational and developmental needs must be addressed by the pediatric team, with the generalist and specialist working together. Such a team is also able to address the needs of the child, the parents, and the siblings if treatment is not successful. Fortunately, most children are cured and will return to the pediatrician for many years of general pediatric care.

This chapter describes the following solid tumors seen in children: Wilms tumor, neuroblastoma, retinoblastoma, rhabdomyosarcoma, germ cell tumors and teratomas, Ewing sarcoma, osteosarcoma, non-Hodgkin lymphoma, and Hodgkin disease. The role of the pediatrician in the care of these children is also examined.

**WILMS TUMOR**

Wilms tumor, or nephroblastoma, is a malignant renal tumor of childhood that occurs at an annual rate of approximately 8 per 1 million children in the United States. It is the second most common abdominal tumor of childhood. Wilms tumor comprises 5% to 6% of pediatric cancers. This number translates to approximately 600 to 700 new cases diagnosed each year in the United States. Children are usually between 2 and 5 years of age. Only rarely does the tumor occur in teenagers and adults. Bilateral disease occurs more commonly in younger children and in girls. The presence of bilateral disease should prompt consideration of genetics evaluation for inherited syndromes or germline mutations. It is one of the few pediatric malignancies that occurs more often in black children than in white children.

The chemosensitivity and radiosensitivity of this tumor, in conjunction with the ability to resect most nonmetastatic tumors, have allowed a multidisciplinary approach to be highly successful. Wilms tumor has become the model for treatment of childhood cancer. Over the last 4 decades, the National Wilms Tumor Study (NWTs) and the COG have evaluated successive therapeutic regimens, with the goal of increasing the cure rate and decreasing the duration and toxicity of therapy. The cooperative group approach has made possible the gathering of more data than might have been obtained at single institutions. The findings, such as the superiority of multiagent chemotherapy and the importance of tumor histology, are relevant for many tumors.

**Etiology**

Most Wilms tumors occur sporadically. Wilms tumor also occurs at increased frequency in siblings, cousins, and parent-child pairs, particularly in association with specific congenital anomalies and bilateral disease. Genetic counseling for patients with these family history risk factors is appropriate. Of children who have Wilms tumor, 15% to 20% have a genetic predisposition to the disease; however, a much lower incidence

of Wilms tumor in children who have affected relatives has been reported (approximately 1% to 2%).

Congenital anomalies occur in 13% to 28% of children with Wilms tumor, although most children who have the disease do not have anomalies. Most of the reported anomalies involve the genitourinary tract. Hemihypertrophy is second in frequency, sometimes noted as a component of the Beckwith-Wiedemann syndrome (excessive growth of many body organs). Children with isolated hemihypertrophy also have an increased incidence of Wilms tumor. Of children who have the sporadic form of congenital aniridia, 33% will develop Wilms tumor. WAGR syndrome is the association of Wilms tumor, aniridia, genitourinary abnormalities, and intellectual disability. Denys-Drash syndrome represents the association of Wilms tumor with ambiguous genitalia and diffuse glomerular disease. Both WAGR syndrome and Denys-Drash syndrome are associated with germline mutations of the *WT1* gene, located at 11p13. *WT1* abnormalities have also been identified in a small subset of patients, 6% to 10%, who have apparently sporadic Wilms tumor, usually in association with genitourinary anomalies. Mutations in *WT1*, *WTX*, and *CTNIB1* underlie the genetic basis of about one-third of Wilms tumors. A Wilms tumor suppressor locus may be at 11p15, which is also the locus for the familial form of Beckwith-Wiedemann syndrome. Genetics consultation may assist in the evaluation of these genetic syndromes.

Loss of heterozygosity at 1p and 16q has also been identified in Wilms tumors, and NWTs/COG demonstrated a worse prognosis for children with tumor-specific loss of heterozygosity at these chromosome regions. *WT1* mutations and 11p15 loss of heterozygosity are associated with relapse in children with very low-risk Wilms tumor who do not receive chemotherapy. In fact, ongoing clinical trials use these mutations as

biomarkers to facilitate risk stratification for patients. Further investigation of chromosomal abnormalities and genetic markers in Wilms tumor and other malignancies will provide insight into tumorigenesis and potential new directions for therapy.

Screening for Wilms tumor by ultrasound and urinalysis in patients who have aniridia, WAGR syndrome, Denys-Drash syndrome, isolated hemihyperplasia, or Beckwith-Wiedemann syndrome is recommended every 3 months until age 7 years. Screening may also be appropriate for children who have unexplained nephropathy and who have other multiple congenital anomaly syndromes and for siblings of children with bilateral Wilms tumor.

### Clinical Manifestations

Wilms tumor in children is usually characterized as a painless mass discovered by a relative, often during bathing. The mass usually is firm, occasionally lobulated, and confined to 1 side of the abdomen. Rapid abdominal enlargement, anemia, and hypotension (perhaps because of a sudden subcapsular hemorrhage) are occasionally present when the child seeks care. Hypertension, malaise, abdominal pain, hematuria, and fever each occur in 20% to 30% of patients. Hypertension has been attributed to hyperreninemia. Wilms tumor tends to extend locally through the venous system as well as to spread hematogenously to lungs, liver, and, rarely, brain or bone.

Table 225-1 presents the differential diagnosis of abdominal and pelvic tumors of childhood that may mimic Wilms tumor.

### Evaluation

The evaluation of a child with possible Wilms tumor begins with a history and physical examination. Particular attention should be paid to the associated

**Table 225-1**

**Differential Diagnosis of Abdominal and Pelvic Tumors in Infants and Children**

TUMOR <sup>a</sup>	AGE	CLINICAL SIGNS	LABORATORY FINDINGS
Wilms	Preschool	Unilateral flank mass, aniridia, hemihypertrophy	Hematuria
Neuroblastoma	Preschool	GI or GU obstruction, raccoon eyes, myoclonus-opsoclonus, diarrhea, skin nodules (infants)	Increased VMA, increased HVA, increased ferritin, stippled calcification in mass
Non-Hodgkin lymphoma	>1 yr	Intussusception in >2 yr old	Increased urate
Rhabdomyosarcoma	All	GI or GU obstruction, sarcoma botryoides, vaginal bleeding, paratesticular mass	—
Germ cell or teratoma	Preschool, teens	Girls: abdominal pain, vaginal bleeding Boys: testicular mass, new-onset hydrocele	Increased hCG, increased AFP
Hepatoblastoma	Birth to 3 yr	Sacroccygeal mass or dimple	Increased AFP
Hepatoma	School age, teens	Large, firm liver Large, firm liver; hepatitis B, cirrhosis	Increased AFP

AFP, Alpha-fetoprotein; GI, gastrointestinal; GU, genitourinary; hCG, human chorionic gonadotropin; HVA, homovanillic acid; VMA, vanillylmandelic acid.

<sup>a</sup>Other causes: constipation, splenomegaly, hydronephrosis, kidney cyst, full bladder.



congenital anomalies and the family history. Laboratory studies should include a complete blood cell count, urinalysis, and renal and liver function tests. Bleeding within the tumor may cause anemia. An erythropoietin-secreting Wilms tumor may cause polycythemia. Hypercalcemia may occur in children who have congenital mesoblastic nephroma or a rhabdoid tumor of the kidney.

A plain-film radiograph of the abdomen may show coarse calcifications, unlike the fine, stippled pattern commonly seen in neuroblastoma. Mass effect may be noted on the film. Ultrasonography is often performed first; this modality is particularly helpful in evaluating the renal vein, vena cava, and the right side of the heart for tumor spread. An abdominal computed tomography (CT) scan or magnetic resonance imaging (MRI) with contrast may reveal an intrarenal mass displacing and distorting the collecting system of the involved kidney. The tumor may be very large, and minimal kidney parenchyma may be identified. Six percent of children will have bilateral disease, and in 12% multifocal involvement in a single kidney may be recognized. Liver metastases may be diagnosed by ultrasound, CT scan, or MRI. Magnetic resonance imaging may be used to define the extent of the abdominal tumor to minimize diagnostic radiation exposure over the long term. A chest radiograph may demonstrate pulmonary nodules. A CT scan of the chest to detect small pulmonary metastases should be performed before surgery because postoperative atelectasis can obscure the presence of metastatic nodules. Bone scans are indicated in children who are ultimately diagnosed with clear cell sarcoma of the kidney, which often spreads to bone. At the time of surgery, the tumor is staged, as outlined in Box 225-1.

Wilms tumors are pathologically designated as being of either favorable histology (FH) or unfavorable histology (UH). Favorable histology indicates the absence of unfavorable features. Unfavorable histology involves the presence of anaplasia, defined by

the presence of gigantic polypoid nuclei within the tumor sample. Anaplasia may be focal or diffuse. Anaplasia conveys a worse prognosis, diffuse more than focal, which seems to be caused by resistance to chemotherapy and radiotherapy and not to biologically more aggressive disease. Anaplasia is present in 5% of patients, is more frequent in older children than younger children, and is more common in black children than children in other ethnic groups. Two other renal tumors—clear cell sarcoma of the kidney and rhabdoid tumor of the kidney—were previously considered Wilms tumor variants, but they are now considered as separate entities. In the COG, they are treated specifically as high-risk renal tumors.

### Management

Currently, in the United States, the initial therapeutic approach is complete resection by nephrectomy. This approach requires meticulous and gentle surgical techniques to prevent the tumor from spilling. A large transabdominal incision facilitates full exploration and excision. The entire ureter is removed, and lymph nodes are sampled. Previously, the practice was to examine the contralateral kidney and abdominal cavity for evidence of disease. However, this approach may not be required with current radiologic techniques; tumors too small to be identified on CT can be expected to be treated adequately with chemotherapy. Tumors deemed unresectable by clinical and radiologic evaluation are biopsied initially, with second-look resection performed after adequate chemotherapy-induced shrinkage is achieved.

For bilateral disease, chemotherapy is initiated based on imaging findings alone; older approaches of performing bilateral biopsy or immediate resection of the most involved site as was done in previous years are now discouraged because of risk for intra-abdominal seeding. Second-look excision of residual disease may be accomplished by partial nephrectomies, when possible. Patients with underlying syndromes, such as WAGR syndrome, should be considered for partial nephrectomies similar to patients with bilateral disease because of the high risk for renal failure. Because the risk for renal failure is only 0.25% to 0.6% in children with sporadic disease, the higher surgical and recurrence risk does not currently justify routine use of partial nephrectomies in this population, although it may be considered in certain children.

Most patients receive postoperative chemotherapy, and patients with higher stages of disease undergo radiation therapy. Actinomycin D and vincristine were noted to be effective systemic agents in the mid-1960s. The initial study revealed that radiotherapy in combination with a single agent (actinomycin D or vincristine) provided approximately 55% relapse-free survival in children with localized disease. An 81% relapse-free survival rate was found when both agents were administered in conjunction with radiation. These 2 drugs are now the mainstay of chemotherapy for Wilms tumor. Subsequent studies have demonstrated that radiotherapy is not necessary for low-stage tumors. The addition of doxorubicin as well as low-dose (10 Gy) radiation to vincristine and actinomycin D improved the prognosis for children who had stage III or IV FH

#### BOX 225-1 Staging of Wilms Tumor

- Stage I: Tumor is limited to the kidney and is completely resected. Renal capsule is intact.
- Stage II: Tumor extends beyond the kidney, but is completely resected.
- Stage III: Residual non-hematogenously spread tumor confined to the abdomen, including abdominal-pelvic lymph node involvement, peritoneal contamination before or during surgery, peritoneal implants, or any residual tumor postoperatively. Unresectable tumors, those biopsied only, and those treated with preoperative chemotherapy are also stage III.
- Stage IV: Hematogenous metastases are present. Sites include lung (only site in 80% of patients who have metastases), liver, distant lymph node, and, less commonly, bone, brain, and other sites.
- Stage V: Indicates bilateral renal involvement is present, although for treatment purposes each kidney is staged independently (I through III as above).

tumors, as well as for those who had stages II to IV tumors with focal anaplasia. Cyclophosphamide, carboplatin, and etoposide are added to vincristine, actinomycin D, and doxorubicin for children who have stages II to IV tumors with diffuse anaplasia and other high-risk histology. Current COG protocols risk-stratify patients based on loss of heterozygosity (LOH) at 1p and 16q, with patients found to have LOH receiving additional chemotherapy. Some children with very low risk disease, young children with small, FH, stage I tumors, may be treated with surgical resection only. Local tumor rupture is treated with low-dose flank irradiation. Peritoneal seeding or major tumor rupture necessitates radiation of the entire abdomen. In the United States, radiation is used for pulmonary metastases visible on CT that do not resolve with initial chemotherapy and for other hematogenous metastases.

Future directions for therapy include further risk stratification strategies to allow titration of treatment to optimize cure and minimize late toxicity. The role of initial surgery versus preoperative chemotherapy as used in Europe, the role of pulmonary radiation based on imaging and response to chemotherapy, and the role of first-line doxorubicin therapy are also areas for continued study.

### Prognosis

The prognosis of children who have Wilms tumor is determined primarily by the histopathologic factors of the tumor; that is, more patients with UH tumors die compared with children with FH tumors. Unfavorable histology tumors, particularly diffuse anaplasia, continue to confer a worse prognosis. More intensive regimens continue to be studied for patients with UH features.

Prognosis also depends on the stage of disease at diagnosis and LOH. Most relapses occur within 2 years of diagnosis. Two-year relapse-free survival for stages I to III disease with FH findings is approximately 91%. The 2-year relapse-free survival rate is 84% for children who have stage IV disease and FH features. Children who have diffuse anaplasia have a poor prognosis, with only 59% with stage II, 45% with stage III, and 7% with stage IV disease surviving 4 years after diagnosis. Four-year event-free survival is 74.9% for children with focal anaplasia. Children who experience relapse have a better prognosis if their initial management did not include radiotherapy or doxorubicin. Autologous transplantation procedures are being investigated in children with high-risk, relapsed disease. Future therapy will focus on improving the outcome in children with UH tumors, incorporating prognostic tumor chromosomal analyses into treatment assignments, and limiting treatment for those with positive prognostic factors.

### Follow-up

Children are monitored for disease recurrence at the primary site, usually with abdominal ultrasound alternating with CT or MRI of the abdomen, and in the lungs, usually with chest radiography alternating with chest CT. Some children may be followed up with CT of the chest and abdomen. Such monitoring continues

at increasing intervals until approximately 5 years after diagnosis. Long-term survival is likely in children who have Wilms tumor. Virtually all patients have had a nephrectomy. Contact sports are often discouraged, although evidence for a significant risk for renal injury is lacking. Some experts suggest a kidney guard for particularly active children, if only to serve as a reminder of the need for caution. In addition, patients should have their renal function and blood pressure monitored.

Children should be monitored for specific late effects of chemotherapy depending on agent and cumulative dose received. Consensus guidelines for monitoring survivors of childhood cancer are available from COG. Children treated with doxorubicin need to have cardiac monitoring, although current cumulative doses of anthracycline for most children with Wilms tumors should not place them at significant risk for cardiomyopathy. Children treated with cyclophosphamide and etoposide need to be monitored for secondary malignancy.

Scoliosis was a major problem for early survivors treated with moderate-dose radiation (30 to 40 Gy), particularly if the entire vertebrae was not included in the field, because of impaired growth of the irradiated portion of the vertebrae. The use of lower-dose radiation (10 Gy) and irradiation of the entire width of the vertebrae adjacent to the renal bed have decreased the severity, but has not entirely prevented the development, of scoliosis. Alterations of vertebral growth and tethering caused by hypoplasia of soft tissues may still result in some degree of curvature. Close observation of children who received irradiation, particularly during the growth spurt during puberty, remains necessary. Hypoplasia with a decrease in adipose tissue occurs in the radiation field and is accentuated by obesity; therefore, prevention of obesity minimizes this asymmetry.

Fertility is preserved in most females who have Wilms tumor, although a risk for ovarian failure exists with whole-abdomen radiotherapy. The average size of infants born to female survivors of irradiation is smaller than that of nonirradiated women, and increased miscarriages and premature births in female survivors of Wilms tumor who received radiotherapy have been reported. In addition, some of these patients may have underlying uterine anomalies. Continued follow-up of these offspring is necessary to evaluate the genetic factors involved in the occurrence of Wilms tumor.

## NEUROBLASTOMA

Neuroblastoma is a cancer, primarily of early childhood, that arises from the fetal neural cells that normally develop into the sympathetic nervous system. It is a tumor that provides insight into the biologic processes of malignancy. There is a spectrum of clinical phenotypes ranging from tumors in infants, which often demonstrate spontaneous regression or maturation into benign ganglioneuromas, to children older than 1 year of age who have disseminated disease. These children with metastatic disease remain difficult to cure despite aggressive use of multimodal therapy.

Neuroblastoma is the most common extracranial solid tumor in children and is the most common malignancy of infants, accounting for more than one-half of cancers in infants. Neuroblastoma accounts for 7% of all diagnosed cases of cancer in children and for 15% of childhood cancer mortality. Approximately 9.7 white children and 7.4 black children per million in the United States are diagnosed with neuroblastoma each year—about 800 to 900 new cases. Ninety percent of children who have neuroblastoma are younger than 5 years of age, and 97% are diagnosed before the age of 10 years.

### Etiology

The high incidence of neuroblastoma in early infancy suggests that its development may be related to abnormal maturation of fetal neural crest cells. The finding of microscopic nodules of adrenal neuroblastoma in infants younger than 3 months of age who died of unrelated causes suggests that spontaneous maturation or regression occurs in many children.

Families have been reported in which neuroblastoma occurred in multiple siblings or occasionally in multiple generations. A family history of neuroblastoma is found in about 1% to 2% of newly diagnosed cases. The presentation of familial neuroblastoma differs from sporadic disease in that children are diagnosed at an early age and with multiple primary tumors. The *ALK* gene has been identified as a major familial neuroblastoma predisposition gene. Familial neuroblastoma is also rarely associated with Ondine's curse (congenital central hypoventilation syndrome) with germline mutation of the *PHOX2B* gene. Some researchers have proposed that 20% to 25% of neuroblastomas occur in children who have a prezygotic germline mutation. Neuroblastoma has been reported to occur with an increased incidence in children who have Hirschsprung disease. The genetic bases for these familial and Hirschsprung-related cases are being elucidated. Although reported in other syndromes, no clear increased frequency has been determined. Recent studies have demonstrated that diet, particularly folic acid intake, and breastfeeding may protect against the development of neuroblastoma.

### Clinical Manifestations

Neuroblastoma may arise anywhere along the sympathetic nervous system chain, including the adrenal gland (40%), the paraspinal regions of the abdomen (25%), the thorax (15%), the neck (5%), and the pelvis at the organ of Zuckerkandl (5%). The incidence of primary site varies by age, with thoracic and cervical tumors more common in infants. The presenting features largely depend on the location of the tumor. A large, firm, irregular abdominal mass that may cross the midline is often the first sign of disease. Disturbances of bowel or bladder function may be the result of compression by a pelvic mass. Thoracic masses may cause a persistent cough or respiratory distress and are detected by a chest radiograph. Cervical masses are often initially diagnosed as lymphadenitis, but they do not respond to antibiotic therapy. Either

Horner syndrome or heterochromia iridis suggest the possibility of neuroblastoma.

Neuroblastomas that arise in the paravertebral ganglia tend to grow into the intervertebral foramina, forming a dumbbell-shaped mass. Pain, weakness of an extremity, paralysis, or incontinence may result from spinal cord compression by the intraspinal component. Incontinence may be difficult to assess, however, because many patients will still be in diapers. Cord compression is an oncologic emergency that requires surgical decompression, radiation, or chemotherapy to prevent permanent paraplegia. Studies have shown that long-term functional outcome may be better in children treated with chemotherapy compared with laminectomy.

Approximately one-half of the children who have neuroblastoma have metastatic disease at the time of diagnosis. The symptoms may then be related to the metastatic tumor instead of the primary tumor. Infants may have metastatic hepatic involvement. Rapid liver enlargement can cause marked abdominal distention followed by respiratory compromise. Bluish skin nodules, which may release catecholamines if palpated, are sometimes noted in infants who have neuroblastoma. Palpation causes an erythematous cutaneous flush, lasting for 2 to 3 minutes, and is followed by blanching caused by vasoconstriction.

The 2 most common sites for metastases are bone marrow and bone; other common sites include lymph nodes, liver, and intracranial and orbital sites. Disease in the lung and central nervous system (CNS) is uncommon. Infiltration of the bone marrow may cause pancytopenia. Bone involvement may produce pain, with or without palpable bone masses. Lytic bone lesions are found most often in the skull, orbit, or proximal long bones. A raccoon-like appearance caused by proptosis and eyelid ecchymosis has been described in children who have orbital involvement. Intracranial disease usually results from meningeal metastases. In infants, this disease may show as separation of cranial sutures caused by increased intracranial pressure. Infants and children who have neuroblastoma may also have fever, malaise, and failure to thrive. Secretory products of the tumor may be the cause of intractable diarrhea, which may be a presenting sign of neuroblastoma. Vasoactive intestinal polypeptide has been found in 7% to 9% of children who have neural crest tumors, most frequently ganglioneuromas or ganglioneuroblastomas.

An unusual symptom of neuroblastoma is the syndrome of opsoclonus-myoclonus. These children have acute cerebellar ataxia and rapid, dancing-eye movements. Although these children often have localized disease and usually are cured, residual neurologic dysfunction, including residual ataxia and intellectual disability, is common. The etiology of this syndrome is unclear, although it may have an autoimmune factor, perhaps an antibody directed against neuroblastoma that cross-reacts with the cerebellar cell antigen. Immune therapies such as steroids, intravenous immunoglobulin, and rituximab are being employed in the treatment of opsoclonus-myoclonus.

Table 225-1, Table 225-2, and Table 225-3 list the differential diagnosis of abdominal, pelvic, head, neck, and mediastinal tumors that may mimic neuroblastoma.

**Table 225-2** Differential Diagnosis of Head and Neck Tumors in Infants and Children

TUMOR <sup>a</sup>	AGE	CLINICAL SIGNS	LABORATORY FINDINGS
Non-Hodgkin lymphoma	>1 yr	Lymphadenopathy NR to antibiotics, immunodeficiency, EBV (in Africa)	Increased urate
Hodgkin disease	>10 yr	Lymphadenopathy NR to antibiotics; weight loss, night sweats, fever, pruritus	Increased ESR
Rhabdomyosarcoma	All	Orbital mass, hoarseness, persistent otitis, sinusitis	—
Neuroblastoma	Preschool	Heterochromia iridis, Horner syndrome, myoclonus-opsoclonus, raccoon eyes, skin nodules (infants)	Increased HVA, VMA, or both in urine; calcification
Retinoblastoma	Preschool	Cat's-eye reflex, strabismus, family history	Calcification

EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; HVA, homovanillic acid; NR, nonresponsive; VMA, vanillylmandelic acid.

<sup>a</sup>Other causes: infectious lymphadenopathy, histiocytosis, Caffey disease, acquired immune deficiency syndrome.

**Table 225-3** Differential Diagnosis of Mediastinal Tumors in Infants and Children

TUMOR <sup>a</sup>	AGE	CLINICAL SIGNS	LABORATORY FINDINGS
Non-Hodgkin lymphoma	All	Cough, respiratory distress, anterior mediastinal mass, immunodeficiency syndrome	Increased urate, malignant effusion
Hodgkin disease	>10 yr	Middle mediastinum lymphadenopathy NR to antibiotics, weight loss, night sweats, fever, pruritus	Increased ESR, increased copper
Neuroblastoma	Preschool	Posterior mediastinum, heterochromia iridis, opsoclonus-myoclonus, raccoon eyes, skin nodules (infants)	Increased HVA, increased VMA, calcification
Thymoma	>10 yr	Anterior mediastinum, myasthenia gravis, red cell aplasia, hypogammaglobulinemia	—
Germ cell or teratoma	All	Anterior mediastinum (rarely, posterior mediastinum), cough, wheeze, dyspnea	Increased AFP, increased hCG

AFP, Alfa-fetoprotein; ESR, erythrocyte sedimentation rate; hCG, human chorionic gonadotropin; HVA, homovanillic acid; NR, nonresponsive; VMA, vanillylmandelic acid.

<sup>a</sup>Other causes: infection, bronchogenic cysts, aneurysms, lipid tumors, thoracic meningocele.

### Evaluation

After the initial physical examination, evaluation of a child who has neuroblastoma requires radiologic examination of the area of primary disease, as well as of areas to which neuroblastoma metastasizes. A CT scan of the abdomen, pelvis, and chest should be performed. For children with cervical masses, the CT scan should include this area. Because paravertebral lesions may extend into the intervertebral foramina, any child who has such a lesion should be evaluated by MRI. A skeletal survey and a bone scan should be performed to detect bony lesions. Radiographs are useful for detecting small lytic lesions at the end of bones; the bone scan helps find lesions of the skull and tubular bones. Because of the frequency of metastatic involvement, bone marrow biopsy specimens should be obtained in all patients; the only exception may be patients with low-risk, resected tumors. Bilateral specimens should be obtained to increase the probability of detecting metastases. The liver should be examined by contrast CT scan in all patients and by biopsy in those who have abdominal disease. Metaiodobenzylguanidine (MIBG) is taken up by neuroblastomas and has

become a standard methodology used for staging and response assessment. Positron emission tomography (PET) scanning may also be helpful in assessing neuroblastoma.

The previously used Evans and St Jude staging systems were synthesized into the International Neuroblastoma Staging System. Stage 1 includes tumors with complete gross resection and microscopically negative ipsilateral and contralateral lymph nodes. Stage 2 tumors are unilateral tumors with complete or incomplete gross resections, but, at the most, only ipsilateral microscopically positive lymph nodes. Stage 3 includes tumors that cross the midline or unilateral tumors that have contralateral lymph node involvement. Stage 4 designates metastatic disease. Stage 4S (for special) tumors occur in infants younger than 1 year of age who have stage 1 or 2 primary tumors with dissemination limited to liver, skin, or bone marrow. More recently, limitations of this methodology of risk group assessment led to the development of the International Neuroblastoma Risk Group (INRG) Staging System, a system that stratifies on the basis of clinical factors identifiable before surgery.



Neuroblastoma is diagnosed by histologic examination after biopsy. In children who have localized disease, the biopsy specimen must be obtained from the primary tumor. For those who have metastatic disease, neuroblastoma cells can be identified in the primary tumor or in areas of metastases, including the bone, bone marrow, or liver. Neuroblastoma produces small round cells with scant cytoplasm that must be differentiated from other small round blue cell tumors of childhood, including lymphoma, leukemia, Ewing sarcoma, and retinoblastoma. Secretion of catecholamines from tumor granules results in increased levels of vanillylmandelic acid (VMA) and homovanillic acid (HVA) in 24-hour urine samples or in increased VMA/creatinine or HVA/creatinine ratios in spot urine samples. These findings can be used to confirm the diagnosis of neuroblastoma in children who have a small, round, blue cell infiltrate in the bone marrow. In addition, increased urinary catecholamine levels can be used to monitor the response to therapy. Ferritin and lactic dehydrogenase levels may be obtained and have prognostic significance in that increased levels predict a poor prognosis.

Amplification of the *N-myc* oncogene is an intrinsic biologic property of some neuroblastomas and has been associated with poor prognosis regardless of clinical stage (although it is most commonly seen in children who have advanced disease). Conversely, tumors that are hyperdiploid (DNA index >1) are sensitive to chemotherapy, resulting in a good prognosis. Specimens should be analyzed for both of these biologic features, which are used to determine risk groups for treatment purposes. Additional findings, such as the association of the tyrosine kinase receptor TrkA with good risk and the association of deletion of chromosomes 1p and 11q with poor risk, even in children with low- or intermediate-risk features, suggest that continued study of the molecular biology of neuroblastoma may lead to additional prognostic factors and new therapeutic approaches. Gene microarray technology may also contribute to identification of tumors with different biologic behavior.

### Management

Neuroblastoma is sensitive to both chemotherapy and radiotherapy. Surgical therapy alone may suffice for localized disease. In patients with lower risk disease, minimal residual disease may regress spontaneously. Although complete removal of the tumor offers the best chance of cure in higher-risk patients, often only a diagnostic biopsy is feasible. Tumor recurrence in such children is often at the site of the primary tumor. Surgical reduction after initial cytoreductive therapy may enhance the likelihood of cure.

Chemotherapy is the major modality of therapy in neuroblastoma. Complete and partial responses have been found with several agents, including cyclophosphamide, doxorubicin, cisplatin, epipodophyllotoxin, and vincristine. Ifosfamide, carboplatin, and topotecan are also effective agents. Combination therapy is used most intensively in the more advanced stages of disease.

A risk-stratified treatment approach is employed with neuroblastoma. In intermediate-risk neuroblastoma,

a high survival rate has been achieved with reduction of doses and number of chemotherapeutic cycles compared with the regimens used in earlier protocols.

In high-risk neuroblastoma, an aggressive multimodality treatment approach is necessary. Survival with conventional therapy remains inadequate for children older than 1 year of age who have stage 3 disease with unfavorable biologic features (eg, *N-myc* amplification) or stage 4 disease. However, recent studies have demonstrated that children between the ages of 12 and 18 months with metastatic disease, but nonamplified *N-myc*, have a more favorable prognosis and may not require the same intensity of therapy as children with amplified *N-myc*. These intensive regimens are at the limits of bone marrow tolerance. Myeloablative therapy followed by purged autologous stem cell transplantation to restore hematopoiesis improves event-free survival; the differentiating agent, *cis*-retinoic acid, improves survival for high-risk children, regardless of whether stem cell transplantation was used. Other retinoids, such as fenretinide, are actively being studied. The retinoids are of particular interest because their mechanisms include both differentiation and induction of apoptosis.

Neuroblastoma is a radiation-sensitive tumor. Although rarely needed in early-stage disease, radiotherapy may facilitate surgical resection of residual disease or may reduce the risk for recurrence in surgically unresectable disease. Emergent situations, such as a large mediastinal mass resulting in respiratory compromise or a dumbbell lesion protruding into the intervertebral foramen that causes cord compression, may be treated with radiation. Total-body irradiation is generally not a component of the preparative regimen used before hematopoietic stem cell transplantation, although radiation may be used for sites of residual disease in conjunction with stem cell transplantation. In the terminal stage of neuroblastoma, bone pain or compression of organs such as the trachea, bowel, or urinary tract may require palliative radiotherapy.

Investigations continue into other treatments to improve the outcome and potentially reduce the toxicities of therapy for children who have high-risk neuroblastoma. Overall success rates have improved for high-risk neuroblastoma by incorporation of autologous stem cell transplantation as consolidative therapy followed by 13-*cis*-retinoic acid to induce tumor cell maturation. The addition of chimeric anti-GD2 antibody ch14.18, combined with granulocyte-macrophage colony-stimulating factor and interleukin-2 has further improved the event-free survival for high-risk neuroblastoma patients in remission after stem cell transplantation. There are also promising data on the use of radiolabeled MIBG in high-risk neuroblastoma patients. This therapeutic modality is being investigated in cooperative group trials. Other novel approaches include inhibition of TrkB activity with Lestaurinib and *ALK* inhibition.

### Prognosis

Age of the child and stage of disease seem to be the most important predictors of survival. Children who are younger than 1 year of age do much better than those who are older than 2 years of age. Children who have stage 1, 2, or 4S neuroblastoma with favorable

biologic features have survival rates higher than 90%. Biologic factors of the tumors, including *N-myc* amplification, also adversely affect outcome. Although some studies dispute the poor prognosis of *N-myc*-amplified tumors in infants, other studies report a significantly lower survival rate for these children. Long-term survival for children who have stage 3 neuroblastoma has improved, with children younger than 1 year of age and with those who have favorable biology having, respectively, survival rates of 100% and 90% at 4 years. Thus, intensive multiagent chemotherapy seems to result in improved cure rates for these children. In studies of children with stage 4 disease who are treated with stem cell transplantation, event-free survival is 23% to 47% at 3 to 6 years after treatment. Skeletal disease and persisting bone marrow involvement were predictive of a poorer outcome, and children who have a complete response to chemotherapy benefit most from transplantation.

### Follow-up

Although late recurrences have been reported, most tumors recur while children are receiving therapy or shortly afterward. Close follow-up with physical examination and radiologic studies should continue after completing therapy. Urinary catecholamine levels may be useful in the surveillance of children who had increased values at diagnosis. Children should be monitored for late toxicities of chemotherapy (eg, cyclophosphamide, doxorubicin, cisplatin) and radiotherapy. High-dose therapy associated with autologous hematopoietic stem cell procedures may result in significant late effects, including hearing loss, renal insufficiency, growth impairment, and gonadal failure.

## RETINOBLASTOMA

Retinoblastoma is the most common intraocular cancer in childhood. Retinoblastoma is diagnosed 95% of the time before age 5 years. In the United States, the mean age-adjusted incidence rate of retinoblastoma is 11.8 cases per million children younger than 4 years. The incidence of retinoblastoma does not vary by race or gender.

Two-thirds of these cases occur before age 2 years. Older age is usually associated with more advanced disease and a poorer prognosis. No difference by gender, race, or left versus right eye has been found. Bilateral disease represents a hereditary form of this tumor that occurs at an earlier age and is present in 30% to 40% of patients. Unilateral disease is a sporadic form of the tumor in 90% of children with this presentation; the other 10% have familial retinoblastoma.

This tumor is the model for understanding the role of genetics in the development of malignancy. The pediatrician plays an important role in initially detecting this disorder and in providing support to the family, who may carry a genetic predisposition to this malignancy.

### Etiology

Two independent mutations must occur in a single retinal cell for retinoblastoma to develop. The initial mutation may occur in a germinal cell (inheritable form) or in the somatic retinal cell itself (sporadic

form). Children who have an abnormality in the germinal cell have 1 mutation in each retinal cell. A second mutation is relatively likely to occur, causing retinoblastoma (often multiple, bilateral tumors). If the initial mutation arises in a retinal cell, then it must be followed by a second mutation in the same cell for the sporadic form of retinoblastoma to arise. The likelihood of 2 such events is low; hence, single unilateral tumors develop. Because the germinal cell is not involved, the mutation is not inherited.

A child who has a family history of retinoblastoma or bilateral retinoblastoma has a germinal mutation and, therefore, the hereditary form of the disease. Penetrance is approximately 90%; thus, these patients have a 45% chance of transmitting retinoblastoma to their children. The germinal mutation also may have arisen in an unaffected parent or in a parent who had an undiagnosed retinal lesion. Parents ought to undergo an ophthalmologic examination. If the first child of noncarrier parents has unilateral retinoblastoma, then their second child has a 1% risk for being affected; siblings should have ophthalmologic examinations also. All families should be referred for genetic counseling.

In some families, recombinant DNA techniques may aid in determining whether the disease is hereditary and which relatives are predisposed to retinoblastoma. Abnormalities of chromosome 13q14 have been detected in patients who have retinoblastoma. This retinoblastoma (*Rb*) gene has been cloned, and the *Rb* gene product is a regulator at the cell cycle checkpoint between G1 and entry into S phase. Deletion or dysfunction of the gene also has been found in nonretinal tumors such as osteosarcomas, soft-tissue sarcomas, and breast carcinomas. Testing patients and family members for mutations in the *Rb* gene requires sophisticated techniques and fails to detect the abnormality in approximately 20% of children with bilateral disease. Improving the ease, availability, and sensitivity of testing for families with retinoblastoma is a goal for the future. Other chromosomal abnormalities have also been identified in retinoblastoma, and as with other pediatric malignancies, they are being studied for their relationship to tumorigenesis and biologic behavior. Another area of research is the role of human papillomavirus in sporadic retinoblastoma.

### Clinical Manifestations

Infants who have a family history of retinoblastoma should be screened by examination under anesthesia at birth and every 2 to 4 weeks initially, then again at increasing intervals to detect disease before the occurrence of clinical symptoms. Screening should continue until age 5 years for these patients and for patients diagnosed with unilateral disease. Pediatricians and parents usually detect the abnormality in children who have the sporadic form of disease by routine evaluation because young children rarely complain of unilaterally decreased vision. The pediatrician plays an important role in detecting the signs and symptoms of retinoblastoma. Leukocoria, or cat's eye reflex, describes a whiteness detected in the pupillary area caused by a large retrolental mass. It is the most commonly encountered sign of retinoblastoma. If a

normal red reflex is not present in a young child, then it should be investigated. The second most common presenting feature is strabismus. Although common in childhood because of abnormalities of ocular muscle strength, strabismus rarely arises suddenly in a child who has had normal extraocular movements. In rare cases, pain in the eye may occur as a result of glaucoma. New-onset strabismus or an abnormal red reflex (leukocoria) requires prompt ophthalmologic evaluation.

The differential diagnosis of retinoblastoma includes Coats disease, retrolental fibroplasia, persistent hyperplastic primary vitreous, toxoplasmosis, *Toxocara canis* infection, and other causes of severe uveitis. Although children sometimes have non-neoplastic disorders at the time of enucleation, this occurrence is uncommon with newer diagnostic methods, including ultrasonography and MRI. If retinoblastoma is a possibility, then referral should be made to an ophthalmologist experienced in ophthalmologic oncology who has a working relationship with radiation and pediatric oncologists.

### Evaluation

Examination under anesthesia after dilating the pupils is necessary to fully evaluate the retina in a young child. Ultrasonography is useful to evaluate the mass, particularly if the fundal examination is obscured by hemorrhage or retinal detachment. Calcification in retinoblastoma may be apparent on radiograph, ultrasound examination, or CT scan. The CT scan helps demonstrate the extent of intraocular disease and may detect possible extraocular extension. Magnetic resonance imaging can help to evaluate the tumor involvement with the optic nerve, the subarachnoid, and the brain. Biopsy is not a feasible method of diagnosis for retinoblastoma. If a family history of bilateral disease exists, then a tissue diagnosis is unnecessary. In many cases of unilateral disease, enucleation may be necessary to establish the diagnosis and to treat the tumor. For high-risk children, bone marrow and cerebrospinal fluid specimens are obtained for evidence of dissemination. The extent of local disease (extension beyond the globe or optic nerve infiltration) is assessed at the time of enucleation. The Reese-Ellsworth classification has been used for decades as a method to describe tumors based on size, location, and multiplicity. Its original intent was to predict prognosis and vision in eyes treated with different radiation techniques, but its consistent use maintained its usefulness as therapy evolved. However, new classifications have been proposed to account for the emergence of new therapies, particularly chemotherapy. The International Classification for Intraocular Retinoblastoma, a new classification system for retinoblastoma, was incorporated into the most recent COG treatment studies. It has assisted with risk stratification and also guidance in determination of which patients can be spared enucleation or external-beam radiotherapy (EBR) and still attain cure.

### Management

Treatment of retinoblastoma is individualized based on the extent of disease and the possibility for vision preservation. Treatments available include enucleation,

EBR, plaque brachytherapy, cryotherapy, photocoagulation, and chemotherapy. Most children who have unilateral sporadic disease have large lesions and compromised vision. Enucleation is usually required, with removal of the longest segment of the optic nerve possible. Photocoagulation and cryotherapy are used for small lesions, most commonly in children who have hereditary bilateral disease. Until recently, radiotherapy was the standard of care for children who had massive bilateral disease; but now, chemotherapy is used to allow local therapy to preserve vision. Significant tumor shrinkage can be achieved, but local therapy is required for cure. Some evidence suggests that chemotherapy also prevents pineoblastoma, a usually fatal second cancer in children with hereditary retinoblastoma. The most commonly used agents are vincristine, carboplatin, and etoposide. Radiotherapy, enucleation, or a combination of both can be avoided with the use of chemotherapy in intermediate-stage disease; chemotherapy also plays an increasing role in the treatment of advanced-stage disease. Periocular administration of carboplatin chemotherapy has also been studied and used in specific clinical situations. Emerging therapy also includes the use of transpupillary thermotherapy with or without adjuvant chemotherapy.

Cyclosporine has been used with chemotherapy to overcome multidrug resistance and has been shown to improve the long-term response to chemotherapy, although definite benefit remains to be proved. Bone marrow transplantation or peripheral blood stem cell support after high-dose therapy for the treatment of recurrent disease has been reported.

### Prognosis

Survival of children who have retinoblastoma is excellent; more than 85% have no recurrence of their tumor, and survival from the primary tumor is more than 95%. Unfortunately, children who have hereditary retinoblastoma have a high incidence of a second malignancy. Approximately 50% of second malignancies occur within the radiation field; osteosarcoma or other sarcomas in particular are common. Children irradiated when they are younger than 1 year of age are at increased risk. Approximately one-third of such children have a second malignancy within 15 years. By 30 years, up to two-thirds have a second malignancy. Avoiding radiotherapy may reduce, but not eliminate, this risk.

### Follow-up

Children who were treated for retinoblastoma will need close follow-up for evidence of recurrence and for second malignancies. Most recurrences happen within 3 years of diagnosis. Examinations under anesthesia should be performed every 2 to 3 months during the first year, every 3 to 4 months during the second year, and every 6 months thereafter until age 6 years. Long-term risk depends on treatment. After enucleation, a prosthesis is necessary. Radiation impairs orbital growth and increases the risk for cataract development and retinal vascular injury. Growth and pubertal development are usually unaffected by orbital radiation, but monitoring hypothalamic-pituitary axis function is warranted. The risk for a second malignancy

is high in children who have bilateral or familial disease, particularly in the radiation field. Medical care should be sought promptly for unexplained masses, pain, or other symptoms.

## RHABDOMYOSARCOMA

Rhabdomyosarcoma is one of the small, round, blue cell tumors of childhood (along with neuroblastoma, Ewing sarcoma, and lymphoma). It arises from embryonal mesenchyme that can differentiate into skeletal muscle. Rhabdomyosarcoma occurs almost anywhere in the body, even in sites that do not normally contain skeletal muscle. It can be an aggressive tumor that disseminates early in the course of disease. Before the advent of chemotherapy, cure required extirpative surgery of localized disease and then radiotherapy. Marked improvement in prognosis, with survival rates increasing from less than 20% in the 1960s to more than 70% in the late 1990s, is the result of the multidisciplinary cooperative group approach of the Intergroup Rhabdomyosarcoma Study.

Rhabdomyosarcoma is the most common pediatric soft-tissue sarcoma, accounting for 2% to 4% of childhood malignancies and 5% to 15% of childhood solid tumors. Its annual incidence among children through 18 years of age in the United States is 4.5 per million; thus, about 400 new cases are diagnosed each year. The incidence in boys is greater than in girls, and it is more common in white children than in black children. Fifty percent of cases are seen in the first decade of life. The incidence of alveolar rhabdomyosarcoma does not vary based on age or gender. However, there is a bimodal distribution for embryonal rhabdomyosarcoma with a smaller second peak in adolescence for males only.

### Etiology

The cause of this tumor is unknown. It has occurred in association with neurofibromatosis, with Beckwith-Wiedemann syndrome, in families who have a history of multiple tumors, and in children who have congenital abnormalities of the CNS, the heart, the gastrointestinal tract, and the urinary tract. Germline mutations in the *p53* tumor suppressor gene, which cause Li-Fraumeni syndrome, are associated with childhood sarcomas, particularly rhabdomyosarcoma. Families of children with sarcomas at a young age should consider genetic testing for *p53* mutations and genetic counseling. Families diagnosed with Li-Fraumeni syndrome can proceed with routine cancer screenings to aid in earlier diagnosis of malignancy.

Two major histopathologic subtypes of rhabdomyosarcoma have been noted—embryonal and alveolar. Embryonal rhabdomyosarcoma, which accounts for more than one-half of cases, may have LOH at 11p15; the alveolar subtype is associated with characteristic chromosomal translocations involving the *PAX* gene, most commonly t(2;13). Alveolar rhabdomyosarcoma is more common in extremity and trunk sites and in older children. Younger children who have alveolar rhabdomyosarcoma may have t(1;13), which is associated with a somewhat better prognosis than t(2;13), particularly in children with metastatic disease. Molecular testing can be used in addition to histopathologic

analysis to ensure accurate diagnosis. As in other pediatric malignancies, further investigation of the cytogenetic alterations identified in the histopathologic subtypes will provide insight into tumorigenesis. There is ongoing analysis about the molecular classification and clinical characteristics of the histopathologic subtypes of rhabdomyosarcoma. Undifferentiated sarcomas do not express lineage markers, but have traditionally been treated by the same regimens used to treat rhabdomyosarcoma.

### Clinical Manifestations

Rhabdomyosarcoma typically produces a painless mass with poorly defined margins. A mass may not be palpable, but patients may experience disturbance of a normal body function resulting from the presence of tumor. Pain may also be a presenting symptom. About 40% of rhabdomyosarcomas arise in the head and neck region, 25% in the genitourinary region, 20% in the extremities, and the remainder in the trunk and other sites. One common site of involvement is the orbit, in which swelling, proptosis, discoloration, and limitation of extraocular motion occur. Children who have a tumor of the head and neck may have hoarseness, difficulty swallowing, nasopharyngeal polyps, nasopharyngeal obstruction, decreased hearing acuity, persistent otitis, sinusitis, bloody nasal discharge, parotitis, or cranial nerve palsies. In parameningeal sites, penetration to the brain may cause headache, vomiting, or diplopia. A retroperitoneal tumor may exhibit as a mass or partial or complete bowel obstruction. Vaginal bleeding, pelvic or perineal masses, hematuria, urinary frequency, and urinary retention suggest genitourinary tract involvement. A tumor may even be extruded from the bladder or female genital tract. A hydrocele, incarcerated hernia, testicular torsion, or testicular mass may be an indication of paratesticular rhabdomyosarcoma. Symptoms may be related to metastatic disease, such as pain or refusal to ambulate resulting from bone metastases. Patients may also have systemic symptoms, such as fever, fatigue, or weight loss.

### Evaluation

Initial evaluation should include a complete history and physical examination. Radiographs, CT scans, or MRI, and, in some instances (eg, genitourinary tract), ultrasound examination of the involved and adjacent areas should be performed. For genitourinary disease, a cystourethrogram, barium enema, and cystoscopic and pelvic examinations may also be needed. There is an emerging role for PET with fluorine-18-fluorodeoxyglucose (FDG) scans in the evaluation of rhabdomyosarcoma. Positron emission tomography scans can identify areas of possible metastatic disease not seen by other imaging modalities and may be predictive of outcome. Future studies will determine whether PET will become a standard imaging tool at diagnosis in rhabdomyosarcoma.

Bone surveys, bone scan, bilateral bone marrow aspirate and biopsy, and chest and abdomen CT scan are necessary to assess for metastatic disease. Basal skull erosion may be seen by CT scan, and spinal fluid may reveal meningeal disease in children who have parameningeal tumors. If spinal cord symptoms are



present, then a spinal MRI is necessary. Biopsy of the lesion establishes the diagnosis and should be performed before extensive resection. Rhabdomyosarcomas are assigned a stage determined by preoperative extent and site of disease and to a clinical group based on postoperative residual disease.

### Management

Rhabdomyosarcoma is a tumor that requires a multi-therapeutic approach, including chemotherapy, surgery, and radiation. Aggressive surgical approaches have become less essential as chemotherapy and radiotherapy have become more efficacious.

The initial surgical procedure should be a diagnostic biopsy. A wide resection of the primary tumor, including surrounding normal tissue, is preferable if excessive functional and cosmetic morbidity can be prevented. Complete resection is correlated with a better outcome, but is possible in only approximately 20% of patients. Extensive en bloc lymph node dissection is no longer indicated; however, biopsy should be performed on large regional nodes. Second-look surgery after chemotherapy may allow resection with reduction of surgical morbidity, provides assessment of therapeutic response, and potentially reduces the dose of radiotherapy.

All patients with rhabdomyosarcoma require multi-agent chemotherapy. Regimens are determined by risk group, which is based on stage, group, histology, and age. Vincristine, actinomycin D, and cyclophosphamide are the primary agents. Although other chemotherapy agents have been studied and have activity, none has proved better than this combination. The addition of topotecan in intermediate-risk rhabdomyosarcoma did not improve event-free survival. Other new agents continue to be developed and studied to improve the treatment of high-risk and relapsed patients. Vincristine with irinotecan is promising, with a response rate of 70% in children with recurrent or refractory disease.

Rhabdomyosarcoma is an infiltrative disease, and radiation portals should include the entire extent of tumor volume. Radiation is required for children with embryonal histology who have residual disease after surgery and for all children with alveolar histologic features. High doses of radiation (50 to 65 Gy) can control local residual disease very well, but substantial late morbidity results. Lower doses of radiation may be indicated with good tumor response or complete surgical resection.

### Prognosis

The likelihood of survival for patients who have rhabdomyosarcoma is determined by the site and the stage of disease. Overall, survival is 73% at 5 years from diagnosis. The prognosis is particularly good for patients who have orbital tumors, nonbladder and nonprostate genitourinary tract tumors, and localized tumors that can be resected fully (90% to 95% long-term survivors). Children with stage IV (metastatic) disease who are younger than 10 years of age and have embryonal histology have a better prognosis than older children who have stage IV disease. Extremity lesions are particularly difficult to treat, perhaps because many co-occur with metastatic disease.

Treatment of genitourinary primary tumors has improved markedly in recent years with the use of extensive chemotherapy. Pelvic exenteration and other morbid surgeries can now be avoided in most patients, and radiotherapy may be avoided in some. Cranial radiation and intrathecal chemotherapy were once used in all children who had parameningeal lesions. Intrathecal chemotherapy is rarely used, and early radiotherapy is reserved for children who have basal skull lesions, CNS involvement, or spinal cord compression.

Twenty percent of children have metastatic disease at diagnosis; these children continue to have a low likelihood of survival. Current studies indicate that 25% to 30% of these children will survive 5 years from diagnosis. Meta-analysis has not shown that hematopoietic stem cell transplantation improves outcome; however, new agents may offer hope to these patients. Eighty percent of recurrences occur within 2 years of treatment. Local relapse is most common, although distant spread to the lungs, CNS, lymph nodes, bone, liver, bone marrow, and soft tissues does occur. For children who experience relapse, survival depends on histologic features, initial grouping, and staging. Shorter time to recurrence was associated with higher risk for mortality from recurrent rhabdomyosarcoma. Twenty percent of children who experience relapse have favorable features with 50% 5-year survival; the other 80% have only 10% 5-year survival.

### Follow-up

Children who have rhabdomyosarcoma should receive close follow-up for evidence of recurrent disease for at least 3 to 5 years from the time of diagnosis. Computed tomography or MRI of the primary site, chest CT scans, and bone scans are frequently used for surveillance. Radiotherapy often results in unacceptable cosmetic effects in patients who have orbital tumors. For children who have orbital or other tumors located in a region of the head or face and received radiation to the sinuses, hypothalamus, and pituitary gland, sinusitis is a common complaint, and hormone levels (eg, growth hormone, gonadotropins) may need monitoring. Patients should also be monitored for any potential late effects of chemotherapeutic agents (Table 225-4).

## GERM CELL TUMORS AND TERATOMAS

Germ cell tumors are growths arising from primordial germ cells. They account for 3% of tumors in children, with an annual incidence of approximately 4 cases per million children younger than 15 years of age. Incidence is greatest in adolescents and very young children. The sacrococcygeal teratoma (named from the Greek *teras*, meaning *monster*) is the most common germ cell tumor of childhood and is benign in 80% of children. It occurs in 1 per 35,000 live births and is more common in girls than in boys (2:1 to 4:1). Sixty percent of childhood germ cell tumors originate in other sites, including the gonads, mediastinum, intracranial region, and retroperitoneum.

### Etiology

Germ cells appear in the yolk sac endoderm, migrate around the hind gut to the genital ridge on the posterior

**Table 225-4 Long-Term Side Effects of Chemotherapy<sup>a</sup>**

DRUG	POTENTIAL ORGAN DAMAGE	EVALUATION
Anthracyclines (eg, doxorubicin)	<i>Cardiac:</i> myocardial damage, congestive failure, arrhythmias	<i>History:</i> exercise intolerance, palpitations; ECG (QTc interval); echocardiogram scheduled based on age, dose, and radiation exposure; Holter monitor; exercise ECG; exercise nuclear angiography
Bleomycin	<i>Pulmonary:</i> fibrosis, impaired diffusion capacity, exacerbated by increased oxygen delivery (eg, during anesthesia or scuba diving)	<i>History:</i> shortness of breath, dyspnea on exertion, cough; chest radiograph and pulmonary function tests (with diffusion capacity) baseline and with symptoms
Cyclophosphamide, ifosfamide	<i>Gonadal:</i> infertility, sterility, early menopause	<i>History:</i> menses, question of fertility; luteinizing hormone, follicle-stimulating hormone, testosterone or estradiol during pubertal development, or if a problem with fertility or amenorrhea (or both) exists; semen analysis (as required to conceive)
	<i>Bladder:</i> hemorrhagic cystitis	Urinalysis annually
	<i>Marrow:</i> secondary acute myeloblastic leukemia	Complete blood cell count annually
Lomustine (CCNU) Carmustine (BCNU) Cisplatin	Pulmonary, gonadal	Pulmonary, gonadal evaluation
	<i>Kidney:</i> decreased glomerular filtration rate	Serum creatinine baseline and per guidelines
	<i>Ears:</i> hearing loss (high frequency)	Creatinine clearance baseline and per guidelines
		Audiogram baseline and per guidelines
Methotrexate	Liver dysfunction <i>CNS:</i> learning impairment (high intravenous dose)	Liver function tests baseline and per guidelines Neuropsychology testing baseline and per guidelines
6-Mercaptopurine, 6-thioguanine, actinomycin D	Liver dysfunction	Liver function tests baseline and per guidelines

CNS, Central nervous system; ECG, electrocardiogram.

<sup>a</sup>See [www.survivorguidelines.org](http://www.survivorguidelines.org) for more details.

abdominal wall of the embryo, and congregate, becoming part of the developing gonad. A slightly aberrant path of migration may account for the occurrence of extragonadal germ cell tumors along the dorsal wall of the embryo in midline sites (sacroccygeal, retroperitoneal, mediastinal, and pineal regions). Children who have sacroccygeal teratomas have an approximately 15% incidence of associated anomalies (eg, imperforate anus, rectal stenosis). An association with a family history of twinning resulted in early theories suggesting that teratomas were abortive attempts at the development of twins. Of interest, the common sites of teratomas—brain, mediastinum, abdomen, and sacroccygeal region—are all sites of twin attachment. A genetic tendency for abnormal germ cell development may exist in some families. These tumors have been reported to develop in siblings, twins, and subsequent generations. Gonadal dysgenesis has been associated with dysgerminoma or gonadoblastoma. The type of germ cell tumor that forms is determined by the subsequent development of the germ cell; those that maintain their total potentiality become embryonal sarcomas. The development of extraembryonic structures results in the formation of choriocarcinomas (placental tumors) or endodermal sinus tumors (yolk sac tumors). Mixed

tumors are not uncommon. Seminomas or dysgerminomas arise when the gonads differentiate. Teratomas form as a result of embryonal differentiation into ectoderm, mesoderm, and endoderm.

### Clinical Manifestations

The clinical manifestations of a germ cell tumor depend on the tumor's location. Sacroccygeal tumors occur as a mass between the anus and the coccyx. An abnormality of the overlying skin may be noted. An intrapelvic tumor may be associated with an external tumor or may be the only evidence of disease, noted by the onset of urinary or rectal obstruction. The incidence of intradural tumor extension is 3% to 5%. Maternal polyhydramnios may be associated with infantile sacroccygeal teratomas.

Ovarian tumors in infants occur as abdominal masses. Older girls have symptoms of abdominal pain, nausea, vomiting, constipation, or urinary tract obstruction, with palpable masses noted in 50%. Torsion or hemorrhage within the tumor may be responsible for acute abdominal pain; 5% of such children have bilateral tumors. Vaginal germ cell tumors in preschool-aged girls (<3 years) may cause bloody vaginal discharge.

Testicular tumors most often occur as symptom-free scrotal masses, sometimes with a coexisting hydrocele. Torsion of the tumor in an undescended testis may result in acute abdominal pain. An undescended testis is an established risk factor for testicular germ cell tumor. Because the ipsilateral or contralateral testis may be affected, an intrinsic testicular defect is likely.

Retroperitoneal teratomas that occur in children younger than 2 years are usually symptom-free abdominal masses. In older children, anorexia, vomiting, or abdominal pain may be noted. Intradural extensions may also occur, and gastric and hepatic tumors have been reported. The symptoms of children who have germ cell tumors of the anterior mediastinum include coughing, wheezing, dyspnea, and chest pain. Newborns may require immediate intubation for respiratory distress caused by mediastinal, cervical, or oropharyngeal germ cell tumors. Intrapericardial tumors can cause heart failure and cardiac tamponade. In the fetus with an oropharyngeal mass, the inability to swallow can cause maternal polyhydramnios. Cranial tumors (80% in the pineal region) cause hydrocephalus and increased intracranial pressure in infants. Teenagers have headaches, lethargy, vomiting, diabetes insipidus, seizures, and visual disturbance, especially loss of upward gaze.

The differential diagnosis of children who have germ cell tumors depends on the location of the primary tumor. For children who have sacrococcygeal masses, meningocele is the most frequent alternative diagnosis. Abdominal or pelvic masses may be the result of neuroblastoma, Wilms tumor, rhabdomyosarcoma, or lymphomas. Nonmalignant disorders such as hydronephrosis, benign ovarian cysts, constipation, and splenomegaly must be considered. Anterior mediastinal tumors include T-cell lymphoma, leukemia, or thymoma. The differential diagnosis for an intrascrotal mass includes testicular torsion, epididymitis, and testicular infarction. (See Table 225-1 and Table 225-3 for details of the differential diagnosis of germ cell tumors.)

### Evaluation

As in any ill child, evaluation includes a thorough physical examination. For children who have a sacrococcygeal mass or abdominal pain, particular attention should be paid to the abdominal and rectal examination. A pelvic examination (performed under anesthesia in young girls) will be necessary if an ovarian or a vaginal tumor is suspected.

Thorough evaluation by CT, ultrasound, or both is essential. A CT scan of benign germ cell tumors will often reveal calcifications. A teratoma frequently shows cystic and solid components, including fat, on radiologic examination. Malignant germ cell tumors often have areas of hemorrhage and necrosis. A chest CT scan and bone scan should be performed to detect pulmonary and bony metastases.

Malignant germ cell tumors that have evidence of extraembryonic differentiation often produce proteins elaborated by the corresponding normal embryonic structure. Serum levels of these markers, alpha-fetoprotein (AFP) and  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG), should be assayed before surgery. Alpha

fetoprotein is found in germ cell tumors that have endodermal sinus tumor histologic features. The evaluation of AFP levels must account for their increase during fetal development; they do not return to normal levels until the child is about 9 months of age.  $\beta$ -hCG, a glycoprotein normally produced by specialized placental cells, is present in increased quantity in children who have choriocarcinomas, children who have hydatidiform moles, and women during pregnancy. In adolescent girls who have an abdominal mass and increased  $\beta$ -hCG, pregnancy should not be assumed, especially if she denies sexual activity or symptoms are atypical. Detection of AFP or  $\beta$ -hCG improves the ability to monitor the disease status. The rate of disappearance after resection reflects the adequacy of the tumor removal. With response to chemotherapy, the levels of these proteins decrease. A significant increase in these levels suggests disease recurrence.

### Management

Germ cell tumors may have components of teratoma, endodermal sinus tumor, embryonal carcinoma, choriocarcinoma, seminoma, or dysgerminoma. Teratomas are classified as mature or immature or as teratoma with malignant components. Mature teratomas (well-differentiated tissues) and immature teratomas (embryonic-appearing neuroglial elements and mature elements) are most commonly found in infants, although more than one-half of germ cell tumors that have a major component of immature teratoma are mixed tumors, all of which will contain elements of yolk sac tumor. Malignant evolution may occur years after removal of an apparently benign tumor, particularly in the sacrococcygeal area. For this reason, complete excision of the coccyx is often suggested, and close follow-up is necessary.

In the past, malignant teratomas, embryonal carcinomas, endodermal sinus tumors, and choriocarcinomas were almost always fatal. Complete surgical resection was rarely attained and only infrequently curative. Only embryonal carcinoma of the infant testis might be cured by radical orchiectomy. In the 1960s, however, the efficacy of methotrexate chemotherapy for gestational choriocarcinomas and testicular germ cell tumors was demonstrated. Ovarian tumors responded to vincristine, actinomycin D, and cyclophosphamide. In the 1970s, additional agents such as vinblastine and cisplatin were found to have significant single-agent response in testicular germ cell tumors of young men. The combination of these 2 agents with bleomycin produced a 70% complete remission rate and a 55% long-term disease-free survival rate for patients who have advanced testicular carcinoma. The regimens initially studied in adults also proved effective in children. Chemotherapy is now the standard for significant subsets of children with germ cell tumors.

Current studies stratify patients as follows: low risk—stage I testicular and ovarian tumors; intermediate risk—stages II to IV testicular, stages II and III ovarian, stages I and II extragonadal malignant germ cell tumors; and high risk—stages III and IV extragonadal tumors. Therapies include surgery and observation for

low-risk children, and standard therapy with cisplatin, etoposide, and bleomycin (PEB) for intermediate-risk children. The advent of cisplatin-based chemotherapy has significantly improved the survival rates for pediatric extracranial germ cell tumors, with 5-year survival rates of more than 90%. The Children's Cancer Group and the Pediatric Oncology Group studied the use of PEB for germ cell tumors. Specifically, they conducted randomized trials to explore the use of high-dose cisplatin in children with extragonadal and high-risk germ cell tumors. The intensification of cisplatin provided an improvement in event-free survival, but not in overall survival. Additionally, the use of high-dose cisplatin had a higher incidence of ototoxicity and nephrotoxicity.

### Prognosis

The French Society of Pediatric Oncology identified 3 prognostic groups for children older than 1 year of age who had localized disease. Children with stage III disease (more than microscopic residual disease), sacrococcygeal or mediastinal primaries, and AFP more than 10,000 ng/mL had a 43% 3-year disease-free survival. Stage I disease (complete resection) or stage II disease (microscopic residual), testicular, ovarian, perineal, or retroperitoneal primary tumor, and AFP less than 10,000 ng/mL were associated with a 100% 3-year disease-free survival. The remaining children were in an intermediate-prognosis group and had an 81% disease-free survival rate. This study also detected improved prognosis for children treated with cisplatin versus carboplatin. The prognosis continues to improve, with event-free survival rates for most patient groups better than 80% and up to 100%, with overall survival rates of 90% to 100%.

The prognosis for a teratoma depends on its degree of maturity and age. Sacrococcygeal teratomas are usually benign in children younger than 2 months; thereafter, the likelihood of malignant evolution increases rapidly. This factor may be the reason that intrapelvic teratomas that are not detected early often are found to be malignant. Mediastinal teratomas behave benignly in children and young teenagers; in older patients, they are more aggressive. Cervical and intracranial teratomas in infants are usually benign; those in adolescents and adults are often malignant.

Immature teratomas can be treated with surgery alone, with event-free survival rates of 97.8%, 100%, and 80% for children who have ovarian, testicular, and extragonadal tumors, respectively. For children who experience relapse, cisplatin-based chemotherapy offers an excellent chance of cure.

### Follow-up

The response of malignant germ cell tumors to chemotherapy is encouraging, but relapse may occur as many as 10 years from the time of diagnosis. Late-brain metastases have also been described. For this reason, close follow-up care is essential, including frequent physical examinations, radiologic evaluations, and monitoring AFP and  $\beta$ -hCG levels, if they are found to be high at diagnosis. Salvage therapy may prolong survival or even provide a cure. Late effects of the chemotherapeutic agent administered

(eg, bleomycin, cisplatin) should be monitored (see Table 225-4).

## EWING FAMILY OF TUMORS

The Ewing family of tumors includes Ewing sarcoma of bone, extraosseous Ewing, and peripheral primitive neuroectodermal tumors (PNETs). These tumors are malignant tumors that usually arise in bone, but may also occur in soft tissues. A PNET of the chest wall is referred to as *Askin tumor*.

The Ewing family of tumors accounts for 3% of childhood cancers and is the most common bone tumor in children younger than 10 years. In the second decade of life, it is second in incidence to osteosarcoma. The peak incidence is between the ages of 11 and 17 years, when the annual incidence is approximately 7 per million. Ewing sarcoma is extremely rare in children younger than 5 years of age or older than 30 years of age, as well as in black and Asian children.

### Etiology

The Ewing tumor is a primitive small, round, blue cell tumor. These tumors are of neural origin, with variable degrees of differentiation. Most share a common chromosomal translocation, t(11;22). The resulting gene fusion rearrangements provide insight into tumorigenesis of these malignancies; specific fusion products may have prognostic significance. No evidence suggests hereditary transmission of Ewing sarcoma, nor has it been associated with known congenital syndromes or constitutional karyotypic abnormalities. No specific environmental risk factors have been identified.

### Clinical Manifestations

Children who have Ewing sarcoma most commonly consult the physician for pain. Swelling may also be present. Symptoms often begin insidiously, several months before diagnosis, and may initially be attributed to trauma. At the time of diagnosis, a mass is palpable in 60% of patients resulting from the propensity of this tumor to break through the bony cortex and involve the surrounding tissue. This disruption of the cortex may also result in a pathologic fracture. The primary tumor site is evenly distributed between central and extremity lesions. The primary lesion is most often found in the femur (22%), the fibula or tibia (21%), or the pelvis (22%). The ribs and vertebrae are other common sites of origin. Demonstrable metastatic lesions are present in 14% to 35% of children, occurring in the lungs, bones, lymph nodes, and bone marrow. Central nervous system involvement is uncommon.

The differential diagnosis includes osteosarcoma, osteomyelitis, benign bone tumors, and bone cysts. Other tumors that occasionally involve the bone and have a similar histologic pattern of small round cells include lymphoma, leukemia, neuroblastoma, and rhabdomyosarcoma (Table 225-5).

### Evaluation

A radiograph should be obtained in a patient who has a mass overlying bone or bone pain that is not characteristic of trauma (by lack of history or prolonged duration of symptoms). Radiographs of a bone that



**Table 225-5** Differential Diagnosis of Malignant Tumors Involving the Extremities

TUMOR <sup>a</sup>	AGE	CLINICAL SIGNS	IMAGING AND LABORATORY FINDINGS
Ewing sarcoma	≥5 yr	Pain, swelling; genitourinary or skeletal anomaly; weight loss, fever; malaise (metabolic)	Onion skin appearance on radiograph; elevated LDH
Osteogenic sarcoma	Teens	Pain, swelling; familial retinoblastoma; prior radiation to bone; Paget disease	Codman triangle (cortical elevation, new bone formation); sunburst ossification of soft tissue; soft tissue mass; increased alkaline phosphatase level
Lymphoma	All	Pain, swelling	Elevated LDH or uric acid associated with rapidly growing lymphomas
Fibrosarcoma	Infants, teens	Painless mass; prior radiation; plastic implant	—
Rhabdomyosarcoma	All	Mass	—
Synovial sarcoma	Teens	Mass	Calcification (40%)

LDH, lactate dehydrogenase.

<sup>a</sup>Other causes: trauma, bone cysts, osteomyelitis.

has Ewing sarcoma often show a destructive lesion in the diaphysis. An onion-skin appearance arises from periosteal elevation and subperiosteal new bone formation associated with tumor extension through the cortex. A mottled pattern may be seen as a result of bone destruction, sclerosis, and cystic formation. An associated soft-tissue mass occurs in more than 50% of children who have primary tumors of long bones. Computed tomography and MRI are necessary to determine the extent of the primary lesion.

Radionuclide bone scanning detects primary and metastatic lesions, but it is not particularly useful in determining the extent of the primary disease. A CT scan of the chest is necessary to determine whether pulmonary lesions are present. The possibility of bone marrow involvement should be evaluated by bilateral bone marrow aspirates and biopsies. Identification of micrometastases in the bone marrow by polymerase chain reaction may identify high-risk patients without other evidence of metastases. Cerebrospinal fluid should be examined in patients who have parameningeal tumors. Positron emission tomography scanning may also be used to follow the course of disease in these children and is starting to replace radionuclide bone scanning as the primary mechanism to detect metastatic lesions. There are emerging data about the role of PET scanning in staging and therapy planning for Ewing sarcoma.

A biopsy of the lesion is necessary to establish the diagnosis. If possible, diagnostic tissue should be obtained from soft tissue rather than from cortical bone to reduce the potential for pathologic fracture.

Large tumors, primary tumors on the trunk and pelvis, and increased lactic dehydrogenase levels have been associated with worse prognosis, but they may be less important with current aggressive treatment regimens. Older age is associated with worse prognosis. The most significant prognostic indicators are tumor stage and size. The presence of metastatic disease is particularly relevant for prognosis. Metastatic

disease at the time of diagnosis is present in 20% to 25% of children. Isolated pulmonary metastases may be associated with a better prognosis than metastases to other sites, but this association is not confirmed. Histologic response also affects prognosis in that children who have marked tissue necrosis after chemotherapy have a better prognosis.

### Management

Approximately 75% of children who have Ewing sarcoma do not have identified metastases, but may have micrometastatic tumor. Therefore, local therapy alone (surgery or radiotherapy) is unlikely to be curative. Chemotherapy has made it possible to cure most patients who have localized Ewing sarcoma and has improved the outcome in children with metastatic disease.

The choice of radiation or surgery for local control is made based on the likelihood of preserving function. Functionally expendable bones should be removed. Aggressive surgical procedures, including limb-sparing excisions, are frequently performed. Some evidence suggests that complete surgical resection may improve prognosis. However, radiotherapy is required for local control and will improve the prognosis when resection with appropriate margins is not achieved or when the tumor is unresectable. Preoperative radiotherapy may also provide benefit. The local failure rate for children treated with radiotherapy on more recent protocols is 22.5%, with higher failure rates in children with central versus noncentral tumor sites. Children receiving radiotherapy are a negatively selected group with unfavorable tumor sites or size. Radiotherapy may also be helpful for treatment of pulmonary or osseous metastases.

Ewing sarcoma is extremely chemosensitive. Standard chemotherapy now includes vincristine, doxorubicin, and cyclophosphamide alternating with etoposide and ifosfamide. Studies have demonstrated the effectiveness

of these regimens for extraosseous Ewing and peripheral PNETs.

Dose intensity of the more active agents (cyclophosphamide and doxorubicin) has played a major role in improving disease-free survival. However, the outcome remains extremely poor for patients with metastatic disease. Additional chemotherapeutic agents, alone and in combination, and dose intensification are being studied for activity against Ewing tumors. Hematopoietic stem cell transplantation has also been used to treat high-risk Ewing tumors. However, the heterogeneous patient population and regimens make assessment of benefit difficult. Benefit may occur by using high-dose busulfan and melphalan, and allogeneic transplants may provide the additional benefit of a graft-versus-tumor effect as a result of an immune response to proteins derived from the characteristic gene fusion present in these tumors.

### Prognosis

Before the advent of multiagent chemotherapy, 85% of children who had Ewing sarcoma died within 2 years of diagnosis. Five-year, disease-free survival is approximately 75% for nonmetastatic disease, with event-free survival of 12% to 24% for children with metastatic disease. The outcome for children who experience relapse is very poor, with the small number of survivors usually among patients who experience relapse more than 2 years from initial diagnosis or those who experience relapse with lung metastases only.

### Follow-up

Children who have Ewing sarcoma require close follow-up for evidence of recurrent disease for at least 5 years from the time of diagnosis. Recurrences may occur later. Particular attention should be paid to the irradiated field of long-term survivors because second malignancies may arise (Table 225-6). Bone films should be obtained periodically. Children who have lower-extremity lesions whose growth is incomplete should be monitored for evidence of leg-length discrepancies, which may require arresting the growth in the opposite limb. Monitoring for potential late effects of the specific chemotherapeutic agents administered (eg, cyclophosphamide, doxorubicin) is important (see Table 225-4). Therapy-related myelodysplasia and acute myeloid leukemia (t-MDS/AML) are well-documented complications of alkylator therapy used in the Ewing sarcoma therapeutic protocols.

## OSTEOSARCOMA

Osteosarcoma is the most common bone tumor encountered in the first 3 decades of life. The incidence is 8.7 per million; about 400 patients are diagnosed per year in the United States. Osteosarcoma comprises 60% of malignant bone tumors. A male-to-female ratio of approximately 1.5:1 has been noted. The peak incidence occurs at age 14.5 years for boys and 13.5 years for girls, corresponding to the age of their growth spurts, although osteosarcoma can occur before puberty and after the adolescent growth spurt. Previous evidence that taller children are at increased risk has not been confirmed.

### Etiology

The hallmark of osteosarcoma is the production of osteoid or mature bone by proliferating malignant spindle cell sarcoma. The high incidence of this tumor in adolescents who are undergoing rapid skeletal growth, as well as individuals who have Paget disease of the bone, suggests that increased bone growth may play a role in the induction of the malignancy. Although children often report a history of trauma before the diagnosis, injuries most likely allow the recognition of an already-proliferating tumor.

Children at increased risk for osteosarcoma include those who have received irradiation to the bone, usually for the treatment of malignancy. Although radiation itself can be causative, children who have 1 tumor may be at increased genetic risk for a second primary malignancy. Children who have hereditary retinoblastoma and thus a constitutive deletion at *Rb*, the *Rb* tumor suppressor gene, have an increased incidence of osteosarcoma. Although one-half of these tumors occur within the radiation field, the risk for sarcoma is far greater, regardless of radiation exposure, because the abnormality at the *Rb* gene itself confers predisposition to osteosarcoma. Osteosarcoma in otherwise normal hosts also frequently involves mutation or loss of the *Rb1* gene, with inactivation of the tumor suppression pathway. Inactivation of *p53*, another tumor suppressor gene, is commonly detected in osteosarcoma. Germline mutations of this gene result in the Li-Fraumeni syndrome (an autosomal-dominant predisposition to multiple malignancies). Germline mutation of *p53* is present in 3% to 4% of children who have osteosarcoma. Many other chromosomal abnormalities have also been detected in osteosarcoma. As in many other malignancies in children, advances in genetic and molecular characterization are being pursued to understand tumorigenesis, to predict the behavior of disease, and to develop therapies to improve prognosis. No environmental risk factors for osteosarcoma have been identified.

### Clinical Manifestations

The presenting symptom in virtually all patients is pain. Palpable masses, swelling, and limited motion are common signs. Weight loss and other systemic effects such as anorexia are rarely seen; if these effects are present, then overt metastatic disease is likely. A few patients have fractures. Cough, chest pain, or dyspnea may occur with extensive pulmonary metastases, although most patients who have pulmonary metastases are symptom free. Ninety percent of tumors occur in the extremities; the metaphyses of bones are common sites of osteosarcoma origin. The lower extremities are involved most frequently, with approximately 60% of tumors occurring around the knee, 40% in the distal femur, and 20% in the proximal tibia. The sacrum, jaw, and phalanges are less commonly involved. Children who have Paget disease of the bone or those who have undergone radiotherapy in the area of the orbit may have osteosarcoma of the cranial bones.

The presenting symptom, bone pain, is ubiquitous and is commonly associated with trauma. Prolonged symptoms, or a history inconsistent with trauma,

**Table 225-6** Long-term Side Effects of Radiation

IRRADIATED AREA	RISKS	MONITORING
Cranium and nasopharynx	Cataracts Growth: impaired  CNS: learning impairment  Dentition: abnormal formation Thyroid: overt or compensated hypothyroidism High dose (>2,500 Gy): Hypothalamic dysfunction (decreased growth hormone; decreased gonadotropin, hyperprolactinemia) Hearing (especially with cisplatin) Hypoplasia of bone or soft tissues	Physical examination Growth charts (bone age, growth hormone, organ system function as appropriate) Monitoring of school function; neuropsychological evaluation Dental evaluation Free T <sub>4</sub> , TSH levels  — Growth; pubertal, menstrual, and fertility history (growth hormone, LH, testosterone, estrogen, prolactin levels) Audiogram Examination of area Dental evaluation
Neck and mandible	Dentition: abnormal formation, abnormal salivary function Thyroid: hypothyroidism Hypoplasia (includes impaired chest wall growth)	Free T <sub>4</sub> , TSH Examination of area
Thorax	Thyroid: hypothyroidism Lungs: fibrosis, decreased capacity  Cardiac: pericardial and valvular thickening; possibility of early myocardial infarction Breasts: impaired growth, possibility of increased malignancy Hypoplasia (including scoliosis)	Free T <sub>4</sub> , TSH levels History, pulmonary function tests, chest film baseline and as appropriate History, ECG, echocardiogram scheduled based on age, dose, and radiation exposure Breast self-examination, early mammograms start 8 yr after therapy or at age 25 yr Examination of area, radiograph of spine during puberty Liver function tests Serum creatinine, urinalysis protein (24-hr collection for creatinine, protein) Pubertal, menstrual, and fertility history, LH, follicle-stimulating hormone, estradiol or testosterone levels during puberty and if fertility is doubtful, semen analysis
Abdomen/pelvis	Liver (if in field) Kidneys (if in field)  Gonads (if in field)	Nutritional history Examination of area
Extremities	Gastrointestinal tract Hypoplasia	

CNS, central nervous system; ECG, Electrocardiogram; LH, luteinizing hormone; T<sub>4</sub>, thyroxine; TSH, thyroid-stimulating hormone.

For all patients, consider radiographs of bones every 5 to 10 years after ≥35-Gy radiation (risk for secondary malignancy). Examine skin for abnormal pigmented nevi (risk for second malignancy).

suggest the need for further diagnostic consideration. Bone abnormalities that may be confused with osteosarcoma include benign cysts, Ewing sarcoma, lymphoma, or tumor metastases. Table 225-5 provides the differential diagnosis of osteosarcoma involving the extremities.

### Evaluation

Radiographs of the involved bone show bony destruction with periosteal new bone formation. A sunburst appearance is characteristic, a result of the eruption of tumor through the cortex with subsequent formation of new bone. Soft-tissue swelling is often noted. Adequate histologic examination and analysis of biopsy samples are necessary to establish the diagnosis of osteosarcoma. The biopsy site is of critical importance, and the biopsy should be performed by an orthopedic surgeon with experience in oncology.

Osteoid found within a sarcomatous tumor is the characteristic histologic pattern. Osteosarcoma in

the child or adolescent is usually a high-grade tumor characterized by osteoblasts that demonstrate pleomorphism and bizarre mitoses. Necrosis, fibrosis, and calcification may be noted. This classic form usually arises from the medullary cavity. A less-aggressive form of osteosarcoma arises in the parosteal area of the bone and tends to spread along the shaft of the bone without invading the cortex. Periosteal, intracortical, and extraskeletal osteosarcomas have also been described.

Baseline lactic dehydrogenase and alkaline phosphatase levels should be obtained. The extent of the primary lesion is defined further by CT or, more frequently and preferentially, MRI. Approximately 20% of children will have metastatic disease identified at diagnosis. Metastatic disease in the lung should be sought by CT. Eighty percent of children with metastases will have pulmonary involvement. Bone scans can be helpful both for outlining the primary tumor and for detecting multiple primary lesions and

metastasis. Positron emission tomography scanning has become increasingly important in the staging, monitoring or response, response assessment, and aid in choice of treatment modalities.

### Management

When therapy of osteosarcoma was amputation of the affected limb, the natural history of disease was notable for the rapid appearance of pulmonary metastases 6 to 12 months after diagnosis, consistent with the presence of micrometastases at diagnosis. Five years after diagnosis, only 10% to 20% of children treated with amputation alone were alive. High-dose radiotherapy was even less effective than amputation. In the early 1970s, favorable responses to high-dose methotrexate with leucovorin and to doxorubicin were noted, and survival rates improved. A report of almost 50% survival after surgery alone attributed the better outcome to improved surgical techniques rather than chemotherapy. Adjuvant chemotherapy, therefore, was not suggested by many physicians until the 1980s, when studies confirmed the benefit of adjuvant chemotherapy. High-dose methotrexate, doxorubicin, and cisplatin are now considered standard therapy for osteosarcoma. Dose intensification and the role of other chemotherapy agents, including ifosfamide, etoposide, and carboplatin, continues to be investigated, both as front-line therapy and for patients whose disease responds poorly to initial therapy. International studies may facilitate addressing these issues. Targeted therapies, such as the use of trastuzumab (Herceptin), a monoclonal antibody against the epidermal growth factor 2 receptor, are also being studied. Addition of muramyl tripeptide to chemotherapy is being studied, and there are promising data showing it may enhance event-free survival and overall survival in children newly diagnosed with osteosarcoma.

The availability of effective chemotherapy and improved surgical technique made limb-sparing or subamputative therapies possible for many patients who have osteosarcoma. Survival after limb salvage is comparable to survival after amputation. Although the complication rate is higher, function is better. The portion of bone involved with tumor is removed and replaced by a prosthesis, a bone graft, or a composite. This procedure can be performed only if the vascular and neurologic integrity of the limb is not compromised. Preoperative chemotherapy may reduce the size of the mass enough to make such surgery possible. For lower extremity tumors, limb-salvage procedures were previously limited to children who had achieved most of their growth, but, currently, even younger children may be candidates. For children who have lesions of the humerus, any preservation of hand function will greatly improve quality of life.

For children in whom pulmonary metastases develop, surgical resection of these nodules may result in long-term survival, even if multiple surgeries are required. A similar approach has been used in patients found to have metastatic pulmonary disease at the time of diagnosis.

### Prognosis

Randomized studies have confirmed the role of adjuvant chemotherapy in improving the long-term,

disease-free survival of children who have nonmetastatic osteosarcoma. Approximately 65% to 75% overall disease-free survival can be achieved. The histologic response of the tumor to neoadjuvant chemotherapy has prognostic significance, with greater than 90% necrosis at the time of tumor resection resulting in improved overall outcome. Whether subsequent tailoring of therapy following poor necrosis achieves a better result than aggressive, early chemotherapy for all patients is unclear. The outcome after preoperative chemotherapy is similar or better than with immediate surgical excision. Preoperative chemotherapy improves the possibility of limb-salvage procedures by decreasing tumor size, and it allows early treatment of potential or demonstrated metastases. Preoperative chemotherapy also allows the assessment of tumor response to chemotherapy. The degree of tumor necrosis can be evaluated at the time of tumor resection and may help guide additional chemotherapy recommendations. Alkaline phosphatase level has also been shown to have independent prognostic significance. Other factors that may influence prognosis are related to the size and site of the tumor (children who have distal tumors may have better outcomes than those who have proximal or central-axis tumors) and the child's age (outcome improves with older patients). The most significant prognostic variable is the presence of metastatic disease. The presence solely of pulmonary metastases is associated with a better prognosis than bone metastases. Among children who have pulmonary disease, unilateral disease or fewer than eight nodules may carry a better prognosis, with survival in these groups of approximately 65% to 75%, compared with 25% to 35% for other patients with pulmonary involvement at diagnosis. The prognosis for patients with bone metastases at diagnosis or relapse is grim.

### Follow-up

Adjuvant chemotherapy has resulted in an increased number of long-term survivors of osteosarcoma. Virtually all children will have undergone either amputation or limb-salvage procedures. The hope is that less-disabling therapies will someday be feasible. Most of these children maintain a relatively normal lifestyle, including participation in various low-impact sports, but certain activities will be restricted. Long-term follow-up care includes imaging of the primary tumor site, bone scans, and chest CT scans performed semi-annually for 5 years and then at least chest radiographs annually until 10 years from the time of diagnosis to monitor for recurrent disease. Orthopedic evaluations and monitoring for late effects of the chemotherapeutic agents used (eg, doxorubicin, cisplatin, methotrexate, ifosfamide, etoposide) are also necessary.

## NON-HODGKIN LYMPHOMAS

Non-Hodgkin lymphoma (NHL) of childhood comprises a heterogeneous group of malignancies arising from lymphocytes and lymphoid precursors. The migratory nature of these cells is reflected by the variable sites at which the tumors occur and to which they spread. Recognition of the systemic nature of the disease, even in children who have only locally detectable



disease, has resulted in a marked improvement in survival rates. Childhood NHL is markedly different from adult NHL both in the immunohistopathologic types that occur and in the better survival rates noted in children. Current classification defines the following 4 main subtypes of childhood NHL: (1) lymphoblastic lymphoma, which comprises 30% of cases; (2) anaplastic large cell lymphoma (ALCL), 10% of cases; (3) Burkitt lymphoma, 40% of cases; and (4) diffuse large B-cell lymphoma (DLBCL), 20% of cases. Primary mediastinal B-cell lymphoma is now considered a distinct entity from mature B-cell lymphomas occurring in other sites. Other rare NHLs can also occur in children, including follicular lymphoma, peripheral T-cell lymphoma, mucosal-associated lymphoid tissue lymphoma, and post-transplantation lymphoproliferative disease.

Improved diagnostic techniques have resulted in emphasis on immunophenotype in diagnosis, staging, and treatment, with development of more tumor-specific treatment regimens. Burkitt lymphoma and DLBCL are both mature B-cell immunophenotypes with surface immunoglobulin. Lymphoblastic lymphoma is divided into precursor B-cell and T-cell immunophenotypes, the latter being the most common. Lymphoblastic lymphomas almost invariably express the enzyme terminal deoxynucleotidyl transferase demonstrating their more immature origins. Anaplastic large-cell lymphomas arise from T-cell lineage and generally have T-cell receptor gene rearrangements and *ALK* translocations. Advances in molecular techniques and gene profiling continue to provide insights into tumorigenesis and definition. These insights will affect development of therapies.

Lymphomas account for approximately 10% of childhood cancer; 60% of lymphomas are NHLs. The incidence of NHL is low in children younger than 5 years of age and then increases steadily throughout life. Non-Hodgkin lymphoma occurs more commonly in boys than in girls (2:1 to 3:1), with the greatest sex difference in Burkitt lymphoma, in which the male-to-female ratio is approximately 4.5:1. Non-Hodgkin lymphomas of childhood have a rapid growth rate, with the percentage of actively dividing tumor approaching 100% in some cases, and short doubling times that can be as few as 12 hours. They have a high frequency of dissemination, particularly to the bone marrow and CNS. Although the distinction between lymphoma and lymphocytic leukemia is defined by less than 25% versus more than 25% bone marrow lymphoblasts, respectively, the distinguishing biologic parameters are not clear.

### Etiology

The cause of childhood NHL is largely unknown. Immunodeficiency states, either congenital or acquired, are associated with the development of NHL, usually of the mature B-cell variety. Human immunodeficiency virus infection is associated with both NHL and Hodgkin lymphoma development and can be treated successfully if chemotherapy is used in combination with antiretroviral therapy. Lymphomas occur with increased frequency in children receiving immunosuppressive therapy following renal, cardiac, or bone marrow allografts.

Post-transplantation lymphoproliferative disease can sometimes be managed with withdrawal of immunosuppressive therapy alone, allowing reconstitution of the native immune system.

Epstein-Barr virus (EBV) infection may play a role in development of pediatric NHL, particularly in Burkitt lymphoma. Burkitt lymphoma of equatorial Africa almost always harbors EBV, compared with the North American variety, which does so only occasionally. The presence of EBV in lymphoma specimens suggests that viral infection may play a role in the development of NHL. A defect of T-cell regulation that permits the expansion of EBV-affected clones of B cells has been hypothesized to result in lymphomas, particularly in immunologically abnormal hosts.

Specific chromosomal aberrations have been described in Burkitt lymphoma, which place the *C-myc* oncogene adjacent to immunoglobulin heavy or light chain constant region genes. Cases of Burkitt lymphoma in equatorial Africa may have different breakpoints than cases outside of this area. Several specific, nonrandom chromosomal abnormalities have been reported in lymphoblastic lymphoma and large cell lymphomas.

### Clinical Manifestations

Seemingly localized lymphadenopathy is a common presentation of NHL, but locally advanced or disseminated disease is frequently found on evaluation.

Lymphoblastic lymphoma commonly involves supradiaphragmatic sites such as cervical, axillary, and mediastinal areas, or Waldeyer's ring. Dissemination to the bone marrow, the CNS, or the gonads is common in lymphoblastic lymphoma. Patients may also have skin or soft tissue involvement, particularly those who have B-lineage lymphoblastic lymphoma. B-lineage lymphoblastic lymphoma is more likely to be localized, and T-lineage lymphoblastic lymphoma is more likely to involve the mediastinum, CNS, or bone marrow. Lymphoblastic lymphoma is distinguished from lymphoblastic leukemia by percentage of bone marrow involvement, with lymphoma defined as less than 25% involvement. This distinction may be arbitrary, and research into biologic differences between lymphoblastic leukemia and lymphoma is ongoing. Children who have mediastinal masses frequently have a history of cough and, occasionally, acute respiratory distress. Because this malignancy advances rapidly, careful attention must be paid to the state of the airway because obstruction can occur during evaluation, even in children who have few symptoms, particularly with the administration of sedation. The obstruction may involve the lower airway, beyond the reach of an endotracheal tube, resulting in an inability to effectively ventilate the lungs.

Burkitt lymphoma and DLBCL can present with localized adenopathy or with a large abdominal or chest mass. An abdominal mass that may involve the ileocecal region, mesentery, ovaries, or retroperitoneum is seen in 30% to 40% of patients. Endemic Burkitt lymphoma in equatorial Africa frequently involves the facial bones. Anaplastic large cell lymphoma may produce peripheral adenopathy, although potential primary sites include the mediastinum and extranodal sites, including the tonsils, lungs, bone, testicles, and soft tissue.

Children whose disease is localized often feel well without systemic symptoms; those who have disseminated disease experience weight loss, fever, and malaise, as well as symptoms referable to the primary site of the disease.

The differential diagnosis of cervical adenopathy includes a variety of infectious and inflammatory processes. Malignant processes that cause enlarged cervical nodes include Hodgkin disease, neuroblastoma, leukemia, nasopharyngeal carcinoma, rhabdomyosarcoma, and thyroid carcinoma. Anterior mediastinal masses may be caused by T-cell leukemia or thymoma. Abdominal masses may be caused by constipation, splenomegaly, Wilms tumor, rhabdomyosarcoma, or neuroblastoma. Lymphoma is a rare type of primary bone tumor. Table 225-1, Table 225-2, and Table 225-3 provide differential diagnostic aids in evaluating patients who have NHL.

### Evaluation

The diagnosis of NHL should be established by pathologic evaluation of suspicious tissue. If adenopathy is present, then removal of the most suspicious node is suggested. Complete resection of the diseased area is not necessary because most NHLs in children are highly sensitive to chemotherapy. Frozen section and needle biopsies are discouraged to ensure proper diagnosis. The primary diagnosis is based on histologic findings and immunophenotyping by flow cytometry and immunohistochemistry. Gene rearrangement studies may be helpful. If possible, cytogenetic studies should be performed. A sufficient number of malignant cells may be present in bone marrow or pleural effusion fluid to establish the diagnosis without biopsy of the primary lesion. Use of polymerase chain reaction or other new techniques to identify morphologically inapparent bone marrow involvement may also be beneficial for prognosis and treatment decisions. For patients with a large mediastinal mass, biopsy may be contraindicated because of the risk for airway obstruction. In extreme cases, empirical treatment with corticosteroids or localized radiation to the mediastinum may be necessary before the diagnostic specimen is obtained. Alternative sites for obtaining diagnostic specimens must then be considered.

A lumbar puncture should be performed with cytocentrifugation of cerebrospinal fluid to detect meningeal involvement. Imaging studies should include a chest radiograph and a CT scan of the chest, abdomen, and pelvis in all patients. Bone scans and gallium scans can be helpful in selected patients, although PET scanning is being used with increasing frequency and may replace these modalities. The role of PET scans may be limited in staging, but is more important in evaluating response and monitoring for recurrence.

A variety of staging systems are used for lymphomas. The most common, the Ann Arbor system used for Hodgkin disease, is not of prognostic significance in NHL in children because of noncontiguous patterns of spread. The Murphy staging system is the most widely applied for NHL in children. Stage I disease indicates a single tumor, nodal or extranodal. Stage II indicates the involvement of 2 or more nodal or extranodal sites, both on the same side of the diaphragm.

Gastrointestinal tumors with only mesenteric nodes involved are also stage II. Stage III tumors involve both sides of the diaphragm, extensive abdominal disease, paraspinal or epidural tumors, or any primary intrathoracic tumors. Stage IV designates CNS or bone marrow involvement.

### Management

Most children who have NHL have disseminated disease at the time of diagnosis. Even clinically localized disease is not curable with localized surgery or radiotherapy alone. The choice of chemotherapeutic regimens is based on the clinical stage and the immunohistologic tumor subtype.

Lymph node biopsy is usually required for diagnosis and characterization of NHL. Removal of the tumor may be indicated only for patients who have Burkitt lymphoma whose tumor can be removed en masse (90%) with minimal morbidity. In general, major surgical procedures should be avoided because the healing time may delay initiation of chemotherapy, the most essential component of treatment.

The high incidence of micrometastatic disease at the time of diagnosis necessitates that all children who have NHL receive chemotherapy. Many agents are active in lymphomas. Optimal treatment regimens and strategies differ for patients with different subtypes of NHL; the histologic class of lymphoma predicts the efficacy of the regimens. Effective agents include cyclophosphamide, vincristine, prednisone, methotrexate, doxorubicin, cytosine arabinoside, etoposide, and ifosfamide. Children who have localized nonlymphoblastic lymphoma can be treated with short-course, low-intensity chemotherapy. Children who have localized lymphoblastic lymphoma require longer maintenance therapy. High-stage children with lymphoblastic lymphoma are treated with acute lymphoblastic leukemia-like protocols. Leukemia-like therapy may also be beneficial for children with ALCL. As new targeted therapeutic agents become available, treatment protocols are becoming more specific for each subtype of NHL. Rituximab, an anti-CD20 monoclonal antibody, may improve prognosis and allow dose decrease in standard chemotherapy for children with CD20-positive Burkitt lymphoma and DLBCL. The monoclonal antibody may work through mechanisms of direct cytotoxicity and chemosensitization. Other monoclonal antibody therapies are also being actively developed and investigated. Specific *ALK* inhibitors are being investigated for ALCL.

Relapsed or refractory mature B-cell NHL is extremely difficult to treat. Autologous or allogeneic stem cell transplantation is frequently recommended. Enrollment on novel therapeutic trials should be considered. Recurrent ALCL can be treated with single-agent vinblastine. Molecularly targeted therapies are also important considerations in the relapse setting.

Local control measures are rarely essential in the treatment of childhood NHL. Although lymphomas are radiosensitive, the use of radiotherapy does not improve survival in chemotherapy-responsive patients, and unnecessary morbidity may result. Radiotherapy is helpful in treating emergent situations, such as airway compromise or spinal cord compression, and for

treating overt meningeal involvement. Radiotherapy also plays a role in treating children who do not achieve a complete remission after standard chemotherapy or those who require bone marrow transplantation or palliative therapy.

### Prognosis

The prognosis is excellent for most children who have NHL, with more than 95% survival for those with localized disease and 80% to 90% survival for those with advanced disease, although subsets of children with worse prognosis can be found, including those with Burkitt lymphoma who have bone marrow and CNS involvement, those with mediastinal diffuse large B-cell lymphoma, and some patients with widespread anaplastic large cell lymphoma. Histologic findings are of prognostic significance for outcome, and they provide the basis for the choice of therapeutic regimen. Clinical staging is relevant because it is determined by a combination of the primary site, tumor burden, disease extent, and primary location. Age and sex may affect prognosis, even within histologic subtypes. Other prognostic factors include significantly elevated lactic dehydrogenase before therapy and, as with other malignancies, response to therapy. Investigations may permit evolution of treatment strategies to lower intensity of therapy for some patients, whereas new intensive chemotherapy or bone marrow transplantation regimens should improve the likelihood of survival in patients whose prognosis is poor or who experience relapse.

### Follow-up

Children who have NHL and are disease free 2 years from the time of diagnosis are usually cured. During this initial period, these children should be monitored for clinical symptoms and with complete blood cell counts, chest radiograph or CT scan, and evaluation of the primary site of disease. The follow-up of long-term survivors of childhood lymphomas should reflect the types of therapy (eg, cyclophosphamide, doxorubicin, methotrexate) administered (see Table 225-4).

## HODGKIN DISEASE

Hodgkin disease, or Hodgkin lymphoma, is a malignancy of the lymphoreticular system characterized by multinucleated giant cells, known as *Reed-Sternberg cells*, interspersed in an infiltration of normal-appearing cellular elements (lymphocytes, macrophages, histiocytes, plasma cells, and eosinophils). The Reed-Sternberg cells are the malignant cells of Hodgkin disease. Recent evidence supports a B-lymphocyte origin of the Reed-Sternberg cell with a cytokine-induced cellular infiltrate. Rare cases of clonal T-cell receptor gene rearrangements have been reported. The transformative steps that lead to the development of the malignant cell continue to be actively studied.

Hodgkin disease comprises approximately 6% of malignancies in children; about 600 cases are diagnosed in children in the United States each year. In developed nations, the incidence of Hodgkin disease exhibits 2 age peaks, one in young adults (15 to 30 years of age) and another in late adulthood. In

developing nations, the early peak occurs in preadolescence. Ten percent to 15% of the total incidence of Hodgkin disease occurs in children younger than 16 years. Hodgkin disease is extremely rare before the age of 5 years. A male predominance is present throughout the preadolescent age range; thereafter, the incidence is approximately equal in both sexes. Hodgkin disease in older teenagers and young adults is most common among whites.

### Etiology

The role of environment or genetics in the acquisition of Hodgkin disease is suggested by national and racial differences in the epidemiologic features of the disease. First-degree relatives of children who have Hodgkin disease have an increased risk for acquiring the disease, possibly because of genetic susceptibility or similar exposures (viral, environmental). Genetic risk is supported by a study demonstrating that monozygotic twins have a much higher concordance for disease development than dizygotic twins. Environmental factors that influence or delay exposure to common infection may play a role in the etiology of Hodgkin disease.

Epstein-Barr virus found in tumor DNA may reflect a causative role for the virus. Alternatively, patients may have an inappropriate immune response to this virus. Evidence of EBV infection is greater in certain subtypes of Hodgkin disease, that is, mixed cellularity, and may influence response to chemotherapy. The incidence of Hodgkin disease is known to be increased in patients who have certain underlying immunodeficiency diseases (eg, ataxia-telangiectasia, acquired immune deficiency syndrome).

### Clinical Manifestations

The most common presenting feature of Hodgkin disease is painless enlargement of the lower cervical lymph nodes. Approximately 50% of children who have this manifestation also have mediastinal disease. The classic pattern of spread is from the cervical lymph nodes to the mediastinum and then into the spleen and abdominal lymph nodes. Spread through the thoracic duct may result in disease of the right side of the neck and of the abdomen, without mediastinal involvement. Axillary or inguinal adenopathy or extranodal primary sites (eg, bone) are occasionally seen. Mediastinal disease is present in 76% of adolescents and 33% of 1- to 10-year-old children who have Hodgkin lymphoma. Pleural involvement occurs in approximately 10% of patients. Renal, skin, or nervous system involvement is less common. Constitutional symptoms related to Hodgkin disease occur in approximately one-third of patients at the time of diagnosis. The symptoms that predict a poor prognosis (*B* disease) are fever (oral temperature  $>38^{\circ}\text{C}$  [ $101^{\circ}\text{F}$ ]), weight loss ( $>10\%$  of body weight within 6 months), and drenching night sweats. Absence of these symptoms provides a better prognosis (*A* disease). Hematologic abnormalities may be present in Hodgkin disease (usually in advanced stages), even in the absence of bone marrow involvement. Hemolytic disease or the anemia of chronic disease associated with impaired mobilization of iron storage may occur. Neutrophilia in the absence of



infection occurs in approximately 50% of patients. Thrombocytopenia caused by immunologically mediated platelet destruction is also seen.

Lymphadenopathy occurs in children for various reasons, including infection (with bacteria, viruses, tuberculosis, atypical mycobacteria, and toxoplasmosis), malignancies (NHL, nasopharyngeal carcinoma, soft-tissue sarcoma, neuroblastoma), histiocytosis, and other inflammatory processes. A chest radiograph, a complete blood cell count, and a sedimentation rate should be obtained in any patient who has lymphadenopathy that is atypical for infection. Persistent lymphadenopathy, even after a transient response to antibiotic therapy, requires biopsy. Table 225-2 and Table 225-3 provide differential diagnostic aids in evaluating patients who have Hodgkin disease.

### Evaluation

Evaluation of the child who has a possible diagnosis of Hodgkin disease should begin with a complete history and thorough physical examination. Particular attention should be paid to B disease symptoms. Lymphatic areas to be evaluated include Waldeyer's ring and the cervical, supraclavicular, axillary, and inguinal lymph nodes. The sizes of the nodes found should be recorded carefully, and whether they are tender should be noted. In addition, a thorough abdominal examination should be performed, particularly to evaluate liver and spleen size. Retroperitoneal lymph nodes are not palpable. The blood cell counts may show anemia (caused by hemolysis or chronic disease), abnormal neutrophil count, or thrombocytopenia. Increase in the sedimentation rate, serum copper level, and ferritin level are probably related to cytokines induced by the tumor; they may be useful for monitoring response to therapy. Serum hepatic alkaline phosphatase isoenzyme levels may also be increased.

Radiographic evaluation of a patient who has a possible diagnosis of Hodgkin disease includes a chest radiograph and CT scans of the chest and abdomen. FDG-PET scanning is particularly useful for detecting disease in obscure sites and for monitoring response. Although bone involvement is rare, a bone scan should be considered in children who have advanced disease, particularly those who have bone pain or an increased serum alkaline phosphatase level. Bone marrow biopsies should be performed in all but those with stage IA or IIA disease.

The importance of defining subdiaphragmatic involvement is most clear when radiotherapy is the primary therapeutic modality. A staging laparotomy with splenectomy was used in earlier years to define the extent of necessary radiation. Improved imaging techniques and the use of chemotherapy in virtually all children and adolescents with Hodgkin disease obviate the need for staging laparotomy, thus preventing the risk for overwhelming bacteremia with polysaccharide-encapsulated organisms. Survivors of earlier eras who had splenectomy during childhood should have vaccines for pneumococcus, *Haemophilus influenzae* type b, and *Neisseria meningitidis* as recommended. Prophylactic antibiotics and empirical treatment for fevers are also necessary to limit risk.

The extent of disease spread is usually classified by the Ann Arbor staging system by means of either the clinical stage or the pathologic stage. The pathologic stage implies that the most extensive degree of involvement has been confirmed pathologically:

Stage I: involvement of 1 lymphatic region only

Stage II: involvement of 2 or more lymphatic regions on the same side of the diaphragm

Stage III: involvement on both sides of the diaphragm, including nodal regions, the spleen, or both

Stage IV: involvement of extranodal organs such as lungs, liver, bone marrow, kidneys, bone, or skin, in addition to lymph nodes

The Cotswold modification further divides stage III based on specific subdiaphragmatic nodal sites involved. In addition to symptom designation by A or B, it also adds a subscript X for bulky mediastinal disease and a subscript E for involvement of a single nodal site that is contiguous with a known nodal site of disease.

Four subtypes of Hodgkin disease are described by review of pathologic specimens. The nodular sclerosing subtype is distinctive because of collagenous bands that divide the lymphoid tissues into nodules and the presence of a *lacunar variant* of the Reed-Sternberg cell. It is the most common subtype in children, occurring in approximately 75% of adolescents and 40% of children younger than 10 years. The lymphocyte-predominant Hodgkin disease subtype is characterized by destruction of the lymph node architecture, with the cellular proliferation of benign-appearing lymphocytes. Reed-Sternberg cells are rarely found in the absence of fibrosis. This subtype is more common in young children; 33% of cases are in children younger than 15 years. Disease is usually localized. In the mixed-cellularity Hodgkin disease subtype, lymph node architecture is not preserved. Approximately 10 Reed-Sternberg cells are seen per high-power field, often with interstitial fibrosis; necrosis is not pronounced. It is more common in children younger than 10 years of age than in adolescents and is associated with high-risk disease. The lymphocyte-depleted Hodgkin disease subtype is characterized by the presence of fibrosis, necrosis, and abnormal cells (but only a rare lymphocyte). It is rare in children.

### Management

Hodgkin disease responds to radiation or chemotherapy. Protocols that use radiotherapy alone, chemotherapy alone, or both forms of therapy have all been successful, at least in some groups of patients. Choosing an appropriate therapeutic plan necessitates assessing the risk for disease recurrence and the potential risk for long-term ill effects in a particular patient.

Contiguous spread of Hodgkin disease by lymphoid organs allowed for success with radiotherapy alone. Full-dose radiotherapy (35 to 45 Gy) was standard therapy for adults with low-stage (I, II, and III) disease; chemotherapy is increasingly being used in this setting. When high-dose radiation was used, the involved fields, as well as 1 field beyond the area of proven disease, were treated. Skeletal and soft-tissue growth, particularly in the neck and clavicular areas,



are severely compromised when these doses of radiation are used in children. Cardiac and pulmonary complications, such as coronary artery disease, valvular disease, pneumonitis, or pulmonary fibrosis, occur as well. Low-dose radiotherapy (20 to 25 Gy) to involved fields only, and not extended fields, in conjunction with chemotherapy results in fewer and less severe late effects from the radiation.

Hodgkin disease is a chemotherapy-sensitive disease. The original chemotherapy agent combination that proved successful in the treatment of Hodgkin disease was mechlorethamine, Oncovin (vincristine), procarbazine, and prednisone (MOPP). In 1974, 10 years after the initial application of MOPP, the regimen of Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine (ABVD) was devised for the treatment of children who experienced relapse. The efficacy of this combination resulted in hybrid ABVD-MOPP regimens. MOPP is now rarely used because of significant long-term toxicity. Current protocols use a backbone of therapy with ABVE, prednisone, and cyclophosphamide (ABVE-PC) for treatment investigations, including the appropriate number of chemotherapy cycles for rapid and slow responders, appropriate additional chemotherapy regimens for children who do not have a good initial response, and the role of radiotherapy for patients who respond completely and rapidly to chemotherapy. Because cures with chemotherapy alone, even in higher stage disease, have been described, defining appropriate children who can avoid even the limited side effects of lower dose-involved field radiation will be important.

In the 1980s, combined modality therapy became the standard recommendation for younger patients who had not completed their growth and for those with advanced-stage disease, and it can play a role in patients with lower stage disease, even in mature patients. The advantages of combined therapies (chemotherapy and radiation together) include improved cure rates in patients with poor prognosis and reduction in the dose of radiotherapy administered to children so that skeletal development will proceed more normally. Chemotherapy also has side effects, including infertility after MOPP chemotherapy, cardiotoxic effects of the doxorubicin of ABVD, and pulmonary toxicity caused by bleomycin. Secondary leukemias have been described, particularly after the combination of MOPP and radiation. In choosing an appropriate regimen for a given child, the following must be considered: (1) the age and skeletal maturity of the child (likely effects on the developing child), (2) the extent of disease present (how much therapy is necessary), and (3) symptoms that might predict a poor prognosis. The response to initial therapy is also a significant factor in treatment decisions. Because so many regimens currently seem equivalent in terms of outcome, an investigational protocol should be used (if available) to help delineate the best treatment for patients in the future while ensuring appropriate treatment for those under study.

### Prognosis

Radiotherapy alone may cure up to 70% of children who have stage I or IIA Hodgkin disease and 50%

who have stage IIB or IIIA disease. The subsequent use of chemotherapy enables one-half of children who experience relapse after radiotherapy to be cured of the disease. However, single-modality treatment with radiation is not appropriate in children. Combined-modality therapy results in 5-year disease-free survival of approximately 90% to 100% for children who have localized disease and 80% to 90% for those who have high-risk disease. High-risk features include advanced-stage disease, a large mediastinal mass, more than 4 sites of involvement, and B symptoms. In children whose disease progresses or relapses, cure may be accomplished with intensive chemotherapy and radiation or with stem cell transplantation. Salvage rates of more than 60% are reported, with children whose diseases progress while they are receiving therapy having a poorer prognosis than those who experience relapse after treatment.

### Follow-up

Children who have Hodgkin disease should be monitored for evidence of recurrent disease for as long as 10 to 15 years after the original diagnosis. In addition to a thorough physical examination, useful tests for prolonged follow-up include a complete blood cell count, a sedimentation rate, and a chest radiograph.

After high-dose radiotherapy to the neck and mediastinum, soft-tissue and bone growth abnormalities include shortening of clavicles and underdevelopment of the soft tissues of the neck. Sitting height decreases after radiation to the axial skeleton in proportion to the growth potential remaining at the time of radiation. In prepubertal girls, breast development may be impaired. The incidence of breast cancer may be increased after chemotherapy and irradiation, particularly for girls who received radiotherapy in early adolescence during breast tissue proliferation. Patients should undergo annual mammographic examinations beginning 8 years after therapy or at age 25 years.

Overt hypothyroidism (low thyroxine and increased thyroid-stimulating hormone [TSH]) occurs in approximately 5% to 10% of patients who undergo irradiation, whereas compensated hypothyroidism (increased TSH and normal thyroxine [ $T_4$ ]) occurs in 50% to 90% of such patients. Thyroid function should be assessed for at least 15 years. Thyroid replacement therapy is suggested when the TSH level is increased.

Children who receive mediastinal irradiation may have pulmonary fibrosis with variable abnormalities detected by pulmonary function testing. Late cardiac abnormalities include pericardial thickening and, occasionally, valvular dysfunction. Early myocardial infarctions have been reported. These toxicities may be exacerbated by the use of bleomycin and anthracyclines.

Fertility in women is affected by the use of radiation and chemotherapy. Pelvic irradiation of a woman causes infertility unless oophoropexy (moving ovaries to the midline) is performed. After oophoropexy, all teenaged girls treated with radiation alone and 88% of those treated with combined-modality therapy maintained normal menses. Women older than 30 years of age experience ovarian failure after treatment with MOPP more frequently than do younger women. All

women should be advised of the possibility of early menopause. A menstrual history should be elicited at each visit.

Testes are more severely affected by cytotoxic therapies than are ovaries. Fortunately, the radiation fields used in Hodgkin disease spare the gonads in male patients. Six courses of MOPP chemotherapy, however, always result in male sterility. Approximately 50% of patients treated with 3 courses of MOPP are sterile. ABVD causes less impairment of spermatogenesis, and current regimens also carry less risk. Men interested in fathering a child may consider sperm banking, post-therapy monitoring of gonadotropin levels, and semen analysis. Recovery has been documented in previously sterile men.

Acute myelogenous leukemia occurs in patients who survive Hodgkin lymphoma at the rate of approximately 1% per year for the first 10 years after treatment with MOPP and radiotherapy. Thereafter, the risk seems to decrease. The incidence is lower with single modality therapy or after ABVD and radiation, and the risk is expected to be lower with current therapy. Other solid tumors in addition to breast cancer may occur after treatment for Hodgkin lymphoma, including thyroid cancer, bone tumors, and NHL.

Children who had a splenectomy are at risk for overwhelming infection, particularly by encapsulated organisms. Empirical treatment with intravenous antibiotics is recommended for fever ( $>101^{\circ}\text{F}$  [ $38^{\circ}\text{C}$ ]) in these children.

## GENERAL ONCOLOGIC CARE

### Referral to a Pediatric Oncologist

Fortunately, children who have malignancies represent a very small proportion of patients in a general pediatric practice. The treatment of such children is highly specialized. Often, the evaluation and management of these patients needs to happen very rapidly. Proper care begins with referral to a pediatric oncologist, even if the initial procedure indicated is surgical. The pediatric oncologist will coordinate care with appropriate surgical and diagnostic radiology.

Recognition of potential malignancy in the differential diagnosis of a child's presentation is essential to ensure that inappropriate therapy will not be administered—for example, corticosteroids should not be provided to a patient whose symptoms mimic EBV infection or reactive airway disease. For many tumors, appropriate baseline studies must be obtained before surgical procedures are instituted. For example, AFP and hCG levels decrease rapidly after removal of a germ cell tumor, as do catecholamine levels after removal of a neuroblastoma. Delayed assays for such markers may result in an inability to recognize an important indicator of recurrent disease in a given patient. The chest CT scan should be performed before surgical procedures are performed because perioperative atelectasis may interfere with the detection of metastatic disease in the pulmonary parenchyma.

The tumors of childhood often behave differently from those of adults, even when histologically

identical. In addition, children tolerate radiation and chemotherapy differently than adults. Therefore, all children should benefit from the care of a pediatric oncologist. Services available for children and their families at pediatric referral hospitals often ease the burden of being diagnosed with a life-threatening disease. Pediatric social workers, child life workers, and nurses experienced in dealing with children and adolescents who have cancer are available. For children living at a distance from a center, initiating therapy at a referral medical center and administering a portion of the subsequent treatments and evaluations closer to the child's home are often possible. At times, a local oncologist can assist in administering chemotherapy to children living at a distance from a center; however, such oncologists should not choose a therapeutic regimen or evaluate major problems that may arise without corroboration with the pediatric oncologists at the referral medical center. Several excellent resources are available for children, families, and care physicians, including CureSearch ([www.curesearch.org](http://www.curesearch.org)), a component of the COG. The American Cancer Society and National Cancer Institute also have Web sites with beneficial information oriented to the care of children. Adolescents and young adults are a special group within the practice of pediatric oncology, in which most patients are young children. The official COG Web resource for this population is available at [www.teenslivingwithcancer.org](http://www.teenslivingwithcancer.org), a component of Melissa's Living Legacy.

Several oncologic emergencies exist that general primary care physicians must recognize. Cord compression may result from neuroblastoma, Ewing sarcoma, lymphoma, or any other tumor that invades the spinal canal. Such children experience incontinence, loss of reflexes in the lower extremities, or decreased ability to use the lower extremities. Rectal sphincter tone may be decreased. Rapid institution of therapy may reverse such findings, markedly changing the long-term functioning of the patient. Thus, recognition of such findings should prompt immediate referral to a pediatric oncologist, who, in conjunction with a neurosurgeon or radiation therapist, will be able to deliver emergent therapy.

Children whose bone marrow is infiltrated by leukemia, Ewing sarcoma, neuroblastoma, or lymphoma may have pancytopenia and thus be at risk for infection as a result of neutropenia, bleeding caused by thrombocytopenia, and congestive heart failure as a result of anemia. Rapid lysis of cells (tumor lysis syndrome) because of the high cell turnover rate of the tumor itself (as is seen in Burkitt lymphoma) or to cytotoxic therapy is characterized by increased uric acid (risk for urate nephropathy), hyperkalemia, hypocalcemia, and hyperphosphatemia. Medical management includes allopurinol or urate oxidase, urinary alkalization, and binders of potassium and phosphate. Dialysis may be necessary. If delayed arrival to the medical center is anticipated, allopurinol should be started by the referring physician when a tumor that has a large cell burden (eg, leukemia, Burkitt lymphoma, and bone marrow involvement with either neuroblastoma, Ewing sarcoma, or rhabdomyosarcoma) is suspected.

Primary care physicians should recognize the signs and symptoms of superior vena cava syndrome, which may include swelling, plethora, and cyanosis of the face, neck, and upper extremities; engorged vessels; cough and wheezing; chest pain; headache; diaphoresis; and visual changes. Lymphomas and other malignancies are the leading causes of superior vena cava syndrome, which may progress rapidly enough to be life threatening. Therefore, prompt recognition of the potential for mediastinal mass as the cause of the symptoms and appropriate referral is essential.

### **Role of the Primary Care Physician During Therapy**

The most prominent toxicity that results from chemotherapy is myelosuppression. Infections in children with neutropenia can rapidly result in septic shock, particularly if gram-negative organisms are involved. Primary care physicians who monitor these children can help by recognizing the risk of fever and immediately referring the patient to the pediatric oncologist when he or she becomes febrile. If the center is at a distance, then the primary care physician becomes the front-line caretaker, obtaining proper culture specimens and initiating antibiotic therapy (usually an aminoglycoside and semisynthetic penicillin or a fourth-generation cephalosporin). In such circumstances, the primary care physician should discuss aspects of care with the pediatric oncologist to ensure that all appropriate measures are taken. Many children receiving intensive chemotherapy have indwelling central venous catheters that increase the risk for septicemia with gram-positive organisms. These children, even in the absence of neutropenia, should have blood drawn for culture, and therapy with antibiotics should be considered if fever develops. Any person who is febrile and had a splenectomy should be given antibiotics empirically to treat potential infections with polysaccharide-encapsulated organisms. In the absence of splenectomy and a central line, treatment of children whose blood cell counts are normal is usually similar to that of a healthy child. The primary care physician can see such children for common pediatric complaints, including skin rashes, earaches, and respiratory and gastrointestinal infections because these children seem to handle such infections without undue difficulty. Varicella, however, is a major threat to all immunocompromised children because dissemination of disease is likely even in the absence of neutropenia. Before the availability of acyclovir and the varicella vaccine, significant morbidity and mortality occurred in such children. Immunocompromised children who are exposed to varicella by a sibling or a close playmate should receive varicella-zoster immunoglobulin (VZIG) within 4 days of the exposure. If Varicella-zoster immunoglobulin is not available, patients can be treated with prophylactic antiviral therapy such as acyclovir or sometimes with general immunoglobulin. If active varicella disease occurs, then the patient should be treated with acyclovir or related new-generation antiviral drugs, often as an inpatient. Chemotherapy is usually withheld during the treatment of varicella.

Children who are receiving treatment for a malignancy should continue to see their primary pediatrician for well-child visits. This effort is in anticipation of their ultimate successful treatment and cure. Immunizations are delayed until 1 year after therapy is terminated because live vaccines may cause disease, and inactivated vaccines rarely result in a normal immune response. An exception is made for the inactivated influenza vaccine and not the live virus influenza vaccine. This treatment may be performed by the oncologist, but may also be requested of the pediatrician. In addition, the child's family should be immunized. The pediatrician should remain involved in continuing developmental issues that are, at times, exacerbated by the treatment of a malignancy. With the current success rates in treating children who have cancer, pediatricians should anticipate the return of these children to their practice for most of their care. When children with cancer do not survive, the pediatrician also has an important role in continued care of the family, particularly the siblings. Therefore, maintaining a relationship with the patient and family is essential.

### **Integration of Palliative Care**

Children with cancer often experience distressing symptoms and side effects throughout the course of their disease. Early involvement of palliative care principles and providers can assist with symptom management related to cancer presentation, therapy toxicities, and progressive disease. Pediatric palliative care can also support psychosocial, spiritual, and emotional adjustment and coping as well as provide support through illness from diagnosis to death or survival. When necessary, palliative care will include grief counseling and bereavement issues. Although important for all families living with childhood cancer, palliative care may be particularly important for those with an overall poor prognosis. Palliative care providers will work closely in collaboration with pediatric oncologists and the multidisciplinary psychosocial support team.

### **Care of Long-term Survivors**

Children treated for malignancy have, for the most part, received several extremely toxic agents, the long-term implications of which are not known in their entirety. Studies of a new treatment regimen's late toxicities are often in their early stages, and, as therapy evolves, so do the potential late side effects. Children should continue to return at least annually to the treating institution or to a similar institution elsewhere to be monitored for potential side effects and to be informed of problems occurring in patients treated similarly. Many factors, including patient preference, aging out of pediatric facilities, and distance, will result in the primary care physician becoming the central figure in ensuring that children undergo appropriate follow-up. Knowledge of late effects and appropriate screening is essential, as is understanding the heterogeneity of treatment, the differences in regimens from different eras, and the variability in toxicities experienced by patients treated with similar



regimens. Toxicities of currently used chemotherapeutic agents and of radiation to particular areas are listed in Table 225-4 and Table 225-6, respectively, and follow-up studies are described. The COG has developed long-term follow up guidelines (available at [www.survivorshipguidelines.org](http://www.survivorshipguidelines.org)).

Multidisciplinary clinics, which evaluate all survivors for potential late effects, are being formed in some hospitals. Subclinical evidence of cardiac damage after anthracycline administration and of pulmonary toxicity (decreased diffusing capacity) after bleomycin administration is found in some survivors. The course of the toxicity is not clear, but evidence has been found for progression of cardiac abnormalities. The long-term effects on renal function and hearing are not yet known. Fertility has been impaired in some adolescent patients who received alkylating therapies, but the incidence of this dysfunction is lower than in adults treated similarly. Radiation to the gonads also causes infertility. Affected women need hormone replacement for feminization and to prevent the osteoporosis associated with estrogen depletion. Testosterone levels in treated male subjects usually remain in the normal range, but they should be monitored. Endocrine dysfunction after radiation may involve the thyroid, hypothalamus, and pituitary. Studies of the mechanism of impairment may help in treating other affected patients more effectively. Thyroid radiation often causes compensated (increased TSH, normal  $T_4$ ) or overt (increased TSH, decreased  $T_4$ ) hypothyroidism and should be treated with thyroid hormone therapy.

Secondary malignancies are reported in long-term survivors. Mutagenic agents such as mechlorethamine, cyclophosphamide, etoposide, and radiotherapy play a role. A genetic predisposition to malignancy exists for patients who have certain disorders (eg, bilateral retinoblastoma).

Neurocognitive function and school performance will be affected in many children who are going through or who underwent treatment for childhood cancer. Education specialists, pediatric oncology nurse practitioners, or persons from both fields can be extremely helpful to the child and the child's teachers by explaining the child's diagnosis and treatment to school administrators and teachers, and, when appropriate, to classmates; defining the problems and limitations the child will have in keeping up with schoolwork during periods of intensive treatment; and providing or arranging (through the school system) for lessons and special tutoring during prolonged hospitalizations and recovery periods at home.

The psychosocial effects of childhood cancer also differ from child to child. Some children were so young when they received treatment that they do not remember the ordeal; others were unable to participate in normal childhood experiences because of their illness. Some children have no physical deficits; others have permanent deformities (eg, amputations, scoliosis, hair loss, scars). Despite these issues, most survivors rate their health as good. Most children are emotionally intact people who are able to live and work normally within mainstream society, although mental health impairment is reported by survivors across the

diagnostic spectrum. Unfortunately, certain workplaces and insurance companies continue to discriminate based on a history of cancer. Businesses and agencies must be taught to accept people who are cured and are likely to have a normal future. Legal protection is available to survivors through the Americans With Disabilities Act, and advocacy resources exist at both the community and national level.

Pediatricians must be advocates for these successfully treated people. Past medical conditions that will not interfere with future health should not be a barrier to success. Furthermore, pediatricians must remain aware of potential late effects of therapy. Screening for toxicities will allow for interventions that can maintain health.

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## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Cancer in Children* (Web page), American Cancer Society ([www.cancer.org/docroot/CRI/CRI\\_2\\_6x\\_Children\\_and\\_Cancer.asp](http://www.cancer.org/docroot/CRI/CRI_2_6x_Children_and_Cancer.asp))

### Medical Decision Support

- *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* (guideline), Cure Search ([survivorshipguidelines.org](http://survivorshipguidelines.org))

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## AAP POLICY

- American Academy of Pediatrics Section on Hematology/Oncology. Guidelines for pediatric cancer centers. *Pediatrics*. 2004;113(6):1833–1835. Reaffirmed May 2008 ([pediatrics.aappublications.org/content/113/6/1833](http://pediatrics.aappublications.org/content/113/6/1833))
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## Chapter 226

# CEREBRAL PALSY

Nancy Murphy, MD

Cerebral palsy (CP) is a clinical descriptive term for a continuum of disorders of the development of movement, posture, and coordination caused by nonprogressive disturbances affecting the brain in its early development (fetal, infantile, and early childhood). The motor disorder is often accompanied by a combination of disturbances of sensation, cognition, communication, perception, or behavior or by a seizure disorder, contributing further to activity limitation and restricted participation. Most children with CP develop some impairment of form or function in the musculoskeletal system. The most common impairments are contractures (eg, equinus deformity), torsional changes in long bones (eg, femoral and tibial torsion), and joint instability (eg, hip displacement).

### EPIDEMIOLOGIC FEATURES

With a prevalence of 3.6 per 1,000, more than 100,000 children in the United States have CP. Although some variation has been described, the incidence has generally remained stable over the past 20 years. CP is more common with lower birth weight and with younger gestational age at birth. For instance, among 1,812 infants born before 33 weeks' gestation, CP was diagnosed at 5 years of age in 159 children (prevalence 9%).

Cerebral palsy affects body structures and function, as well as activities and participation. Among children with CP, 8% have an autism spectrum disorder and 35% have epilepsy; 56% are able to walk independently, while 33% have limited or no walking ability. Children with CP have longer average hospital stays (6.3 vs 4.1 days), have more diagnoses (5.6 vs 3.0), and undergo more procedures (1.7 vs 1.1) than children without the disorder. The risk for CP is higher in infants of very low birth weight and those from multiple pregnancies. CP in preterm infants is associated most commonly with periventricular leukomalacia, with or without severe periventricular bleeding or infarction. An increasing proportion of infants from both of these groups survive into childhood. The biggest challenge to the prevention of CP remains the prevention of prematurity. A recent study found that the prevalence of CP in very low-birth-weight infants and those born at less than 32 weeks' gestation decreased from 6% of live births in 1980 to 4% in 1996. This improvement occurred despite an increase in live births at very low birth weight, a decrease in neonatal deaths, and an increase in multiple births.

### ETIOLOGY

A definite cause cannot be identified for many cases of CP, but when a cause can be identified, it is usually of prenatal origin. Intrapartum events play a limited role. Neither sophisticated fetal monitoring nor a higher

rate of cesarean deliveries has reduced the occurrence of CP. Isolated risk factors, such as fetal bradycardia, neonatal acidosis, intraventricular hemorrhage in the absence of periventricular leukomalacia, and low Apgar scores taken in isolation, are poor predictors of CP, especially in full-term infants. However, low birth weight (2,000 g or less), periventricular leukomalacia (necrosis of white matter near the lateral ventricles), hydrocephalus, congenital malformations, and newborn encephalopathy (recurrent seizures, hypotonia, coma) are all associated with CP. Prenatal maternal chorioamnionitis has been shown to increase significantly the risk for CP in both term and preterm infants. In approximately 10% of children who have CP, the cause of the condition is thought to be post-neonatal (after 28 days). Causes include infections (eg, meningitis, encephalitis), asphyxia, and accidental injury. In some instances, CP may be prevented by reducing the occurrence of injuries during childhood and by minimizing periventricular leukomalacia in premature infants through improving circulation and countering the effects of excitatory neurotransmitters (eg, head cooling in the newborn who has had a hypoxic or ischemic event). The timing of the insult to the brain may affect the manifestations of CP. For example, disturbances occurring between 24 and 28 weeks' gestation are more likely to produce spastic diplegia or tetraplegia (quadriplegia), whereas those occurring at term are more likely to produce dyskinesia.

More recently, there is increasing evidence to suggest that multiple genetic factors contribute to the etiology of CP. For example, noncerebral congenital anomalies are more prevalent in children with CP than in typical children; there is a higher concordance rate for CP in monozygotic twins than in dizygotic twins; and higher than expected recurrence rates of CP syndromes in families support a genetic etiology.

### CLASSIFICATION AND DIAGNOSIS

CP may be classified according to the type, distribution, and severity of motor abnormality (Box 226-1). This classification system can be simplified into the following 3 categories: spastic (involving the pyramidal tracts), dyskinetic (involving the extrapyramidal tracts), and mixed (involving both). Spasticity is defined as velocity-dependent passive resistance of muscle to stretch. It is associated with neurologic signs that include hyperreflexia, clonus, extensor

#### BOX 226-1 Classification of Cerebral Palsy

- Spastic
  - Diplegic
  - Quadriplegic
  - Hemiplegic
- Dyskinetic
  - Choreoathetotic
  - Dystonic
  - Ataxic
- Mixed

plantar response, co-contraction of muscles, persistent primitive reflexes, and abnormal postural control. These abnormalities impair normal movements, such as gait and the manipulation of objects, in complex ways. Movement is often described as stiff, and patterns of movement, such as fisting of the hands, retraction of the shoulders, scissoring of the legs, and toe-walking, are often abnormal. Although most attention has been focused on the extremities, evaluating the trunk is important as well. Hypotonia of the trunk and neck is common, as are impairments that affect function in a child who has spastic quadriplegia.

In diplegia, the legs are affected, with relative sparing of the arms. In quadriplegia, all 4 limbs are involved. In hemiplegia, only 1 side is involved, with the arm usually more impaired than the leg. In extrapyramidal CP, the impairment is diffuse, with marked discoordination and the presence of involuntary activity. Dyskinesia includes the involuntary movements of athetosis and chorea, which are most pronounced when the child initiates a movement, as well as dystonia. Dystonia is characterized by sustained muscle contractures that lead to abnormal posture and twisting of the limbs. Dysarthria commonly occurs with dyskinesia. Ataxia involves incoordination of movement and impaired balance and may be associated with an intention tremor. Because the fibers in the corticospinal tract that control the legs are closest to the ventricles, any periventricular injury is likely to lead to spastic diplegia. This condition most commonly occurs with hypoxic-ischemic injury in a preterm infant between 28 and 36 weeks' gestation, in which the periventricular area is most susceptible to injury because of immature cerebral vascularization. This injury is often characterized by subsequent enlargement of the ventricles or development of periventricular leukomalacia. Children of any gestational age with hydrocephalus are also more likely to develop spastic diplegia. Generally, children who have spastic quadriplegia have more generalized and extensive lesions, and they are more likely to have intellectual disabilities (64% have an IQ below 50) and seizures (56%) than children who have other kinds of CP. Children who have spastic quadriplegia are also more likely to have feeding difficulties, severe joint contractures, and scoliosis. Children with extrapyramidal CP frequently have problems with feeding and communication because of oral-motor discoordination. The most common system for classifying the severity of CP is the Gross Motor Function Classification System (GMFCS), a 5-level system to classify severity of motor involvement in children with CP based on their functional abilities and their need for assistive technology and wheeled mobility.

Each form of CP can be caused by a multitude of conditions, and a single etiologic factor (eg, meningitis) can lead to different forms of CP. Therefore, a direct link between the type of CP and its cause (when a cause can be found) cannot be established without using diagnostic evaluations such as cranial ultrasonography or magnetic resonance imaging (MRI). Additionally, chromosomal disorders and inborn errors of metabolism can be misdiagnosed as atypical CP, and genetic evaluations may be diagnostic when the CP remains unexplained.

## EARLY AND DIFFERENTIAL DIAGNOSIS

Although the brain lesion or anomaly that was recognized in early childhood is no longer progressive, the clinical manifestations of CP change over time, especially in the first several years of life. Abnormal patterns emerge as the damaged nervous system matures. For example, the child who is destined to have spastic quadriplegia will often be hypotonic in early infancy. At 6 months of age, as tone increases, the child may develop adduction of the thumb (palmar thumb) followed in 1 to 2 months by scissoring of the legs when held upright. By 9 months of age, the child may have diffuse spasticity and hyperactive deep-tendon reflexes. Dyskinetic patterns may not be obvious until approximately 18 months of age. Ataxia may not be apparent until even later. In a study of 1,726 children from 5 urban school districts, the mean age at which CP was diagnosed was 10 months. Therefore, in addition to the formal developmental screening recommended for all children, those at risk for developing CP should have regular careful physical examinations, with special attention paid to their neurologic status.

Early diagnosis of CP is aided by a history of an abnormal pregnancy, labor, delivery, or neonatal period or by the occurrence of a serious acute illness and trauma. The diagnosis is further aided by evaluating the child's primitive reflexes (eg, the asymmetrical tonic neck response), postural responses (righting the head when tilted to the side), muscle tone, motor milestones, and neurobehavioral responsiveness. Persistent or exaggerated primitive reflexes, a delay in the emergence of postural reactions, hyperreflexia, asymmetry, and abnormal muscle tone all suggest the possibility of CP. Other early signs that suggest CP include difficulty feeding because of abnormal oral-motor patterns (tongue thrusting, tonic bite, oral hypersensitivity), irritability, and delayed milestones such as head control. Children with CP may benefit from timely referral to formal early-intervention programs, which are mandated under the Individuals with Disabilities Education Act (IDEA).

A diagnosis of CP implies that the neurologic process is not progressive and that the disorder is in the brain. The differential diagnosis includes neurodegenerative disorders, inborn errors of metabolism, developmental or traumatic lesions of the spinal cord, severe neuromuscular disease, movement disorders, spinocerebellar degeneration, neoplasms, hydrocephalus, and subdural hematoma. Repeated examinations are necessary to rule out a progressive degenerative condition. Recurring subclinical seizures or adverse reactions to anticonvulsants may worsen the clinical condition of children who have CP. Hypotonia in association with weak muscles and depressed tendon reflexes suggests a neuromuscular disease, although many children with both spastic and extrapyramidal CP are hypotonic in early infancy. Extrapyramidal signs in early infancy or marked worsening during periods of illness also make the diagnosis of CP a possibility. If a child diagnosed as having dyskinetic CP has symptoms that worsen significantly as the day progresses, dopa-responsive dystonia should be considered. This rare but treatable form of dystonia may begin with toe-walking and difficulties with gait; it

responds dramatically to administration of levodopa. In most instances, no history can be found of a pre-existing condition that would be consistent with CP. Other rare inborn errors of metabolism, such as arginase deficiency and glutaric aciduria, may mimic CP. However, these conditions cause progressive deterioration, whereas CP does not. If a child has a parent who has CP and has late-onset spastic diplegia with no preceding history of prenatal or neonatal problems, then hereditary spastic diplegia may be the cause.

### ASSOCIATED DISORDERS

Table 226-1 lists disabilities and impairments associated with CP. All types of language impairments may be encountered, from aphasia to disorders of

articulation. Speech impairments may be related to hearing, intelligence, experience, language development, the integration of motor mechanisms of the oropharynx, and coordination of breathing patterns. Nearly 75% of individuals who have CP are cognitively impaired. Approximately 40% have learning disabilities, 35% have epilepsy, 20% have visual impairments, and 9% have infantile hydrocephalus. In persons who function in the normal range of intelligence, specific learning disabilities, such as visual-spatial impairment, are common. Impaired mobility is also common and may result from spasticity with or without joint contractures and scoliosis. Self-care and hygiene may be impaired by gross-motor and fine-motor abnormalities and associated conditions, such as drooling. Impairments in gastrointestinal functioning include

**Table 226-1**

### Disabilities and Impairments Associated With Cerebral Palsy in Children and Possible Interventions

DISABILITY OR IMPAIRMENT	POSSIBLE INTERVENTION	POSSIBLE CONSULTATION
Impaired communication	Augmentative communication aids	Speech therapist, audiologist
Impaired cognition	Early intervention, special education program, formal educational testing	Education specialist, psychologist, school advocate
Weakness or impaired mobility	Orthoses (braces), walker, wheeled mobility and strength training, hippotherapy Constraint therapy for hemiplegia	Orthopedist, orthotist, physiatrist Physical therapist specialty program, gait laboratory Hippotherapist Occupational therapist
Spasticity	Medications, selective dorsal rhizotomy, intrathecal baclofen, botulinum toxin injections	Orthopedist, neurodevelopmental specialist, physiatrist, neurologist, neurosurgeon
Joint contractures	Range of motion, orthoses, surgery	Physical therapist, orthopedist, orthotist
Scoliosis	Orthoses, surgery	Orthopedist, orthotist
Impaired self-care and hygiene	Assistive technologic devices, home modifications, training	Occupational therapist, rehabilitation engineer
Drooling	Scopolamine patch, glycopyrrolate, surgery, botulinum toxin injections, acupuncture	Otolaryngologist, acupuncturist
Sexual functioning	Education, adaptive devices	Gynecologist, urologist, psychologist
Impaired nutrition or feeding	Education, monitoring, medical evaluation, medication, enteral routes of feeding	Dietitian, gastroenterologist, speech therapist, occupational therapist, surgeon
Dental caries, malocclusion	Repair of dental caries, orthodonture	Dentist, pedodontist, orthodontist
Seizures	Medication, surgery	Neurologist, neurosurgeon
Impaired vision or hearing	Assistive devices, surgery	Ophthalmologist, otolaryngologist
Impaired access to care	Financial counseling, care coordination, transportation	Financial counselor, care coordinator, specialty program
Adverse effects on family	Parent support group, counseling, support, respite	Social worker, psychologist, specialty program, care coordinator
Impaired transition to adulthood	Counseling, adult-oriented health care, care coordination, transportation, recreation, vocational services, financial planning, guardianship	Internist, family physician, care coordinator, vocational specialist, independent living specialist, attorney, psychologist, financial planner

drooling (31%), dysphagia (19%), and constipation (25%). In general, physical growth is inhibited, and osteoporosis is common in patients with severe quadriplegia and immobility. Many of these children fail to thrive, especially those who have dyskinesia or spastic quadriplegia. Feeding difficulties caused by oropharyngeal incoordination, gastroesophageal reflux, and recurrent vomiting occur and may be associated with aspiration. Dental disease (malocclusion and dental caries) is common. Seizures are common, as are impaired vision and hearing. Behavioral problems are 5 to 8 times more likely to occur in children who have CP than in their uninvolved peers, especially in those who have hemiplegia. Sociocultural risk factors have a profound effect on development and interact with biologic risk factors. Perinatal and other biologic risk factors can lead to intellectual impairment.

## EVALUATION

Neuroimaging techniques such as ultrasonography, computed tomography, and MRI have increased physicians' understanding of the structural abnormalities associated with CP and may help clarify the timing of a lesion. Neuroimaging may demonstrate periventricular leukomalacia, postischemic necrosis, cerebral dysgenesis, hydrocephalus, porencephaly, tumor, prenatal ischemic injury, or leukodystrophy. The information gained with brain imaging can confirm the diagnosis of CP and can be useful to the physician in explaining (or demonstrating) the specific cause of a child's CP to the parents. The electroencephalogram is an important part of the diagnosis and management of associated seizures, but is not helpful in the diagnosis of CP; continuous electroencephalogram monitoring with videography may help differentiate seizures from other movement disorders. The presence of dysmorphic features may trigger a search for a chromosomal abnormality or a genetic syndrome. Evaluation of complications such as altered gait and feeding disorders may require special diagnostic studies, such as gait analysis and videofluoroscopic swallowing studies. Routine screening for metabolic and genetic disorders is not recommended unless the child has atypical features, such as unusual facial features, or a progressive condition.

## INTERVENTION

Pathophysiologic abnormalities of the brain (eg, leukomalacia) lead to impairments such as spasticity. Spasticity then leads to alterations in functioning (eg, shortened stride length), which leads to disabilities (eg, difficulty ambulating independently). The functional impairments associated with CP may affect independence, emotional and social well-being, community participation, and life satisfaction. Adults with CP have identified communication skills, self-care activities, and mobility as the 3 most important issues they face. Consequently, interventions (eg, medications, surgery, braces or adaptive equipment) should focus on promoting developmental and functional outcomes that address these issues rather than on simply reducing spasticity, improving range of motion, or correcting deformity in isolation. No intervention, including therapy and surgery, will be worthwhile in

the long term if it does not improve the child's ability to function. Interventions should also stress the prevention of complications.

Table 226-1 lists referrals and interventions that might improve outcomes for children with CP. No single professional can address the multifaceted medical, social, psychological, educational, and therapeutic needs of a child with CP. Comprehensive management requires an interdisciplinary team of physicians who guide interventions designed to maximize the development and function of each child. IDEA mandates access to early intervention services for infants at risk for disabling conditions. These services include special education; physical, occupational, and speech therapies; adaptive equipment; training for mobility and living skills; and communication. The therapies may not change the basic disorder significantly; however, the interventions guide parents in how to position and handle their infant, provide options for play and learning activities, and facilitate feeding and the parent-child relationship. In addition to therapies, early intervention providers can offer anticipatory guidance and family support as they adjust to the responsibilities of raising a child with CP.

The care provided should be integrated. For example, children whose legs are spastic often have dorsiflexion at the ankle, flexion at the knee, and flexion and adduction at the hip. Multiple interventions are possible, including muscle strengthening, orthotics (eg, ankle-foot orthoses), oral medications, botulinum toxin injections (with or without serial casting), intrathecal baclofen therapy, selective dorsal rhizotomy, and orthopedic surgeries. Deciding on the best approach requires the input of the child and family in collaboration with a team of physicians, including therapists, orthotists, nurses, physicians, and social workers. Even with a single intervention (eg, orthopedic surgery), multiple options are available. For instance, orthopedic repair of only 1 or 2 of these problems may leave the child unimproved or worse, and therefore all 3 problems should be addressed. Gait analysis using videography, electromyogram, and sensors has improved the orthopedic care given to these children. After orthopedic surgery, therapy should be started to maximize range of motion, strength, and function.

Oral medications (eg, diazepam, baclofen, tizanidine, dantrolene) can be used to reduce spasticity, but these drugs may have adverse effects, and evidence for their functional benefits is limited. Selective dorsal rhizotomy and intrathecal baclofen are neurosurgical interventions that reduce spasticity and increase range of motion. Intramuscular botulinum toxin, toxin type A, is effective in children who have functional spasticity in transiently reducing spasticity in individual limbs. Although these treatments can reduce spasticity, they cannot improve selective motor control, difficulties with balance, and weakness. Strength training has shown promise in improving function. Various casting and splinting techniques that may maintain muscle length and inhibit increased tone may be helpful. In many cases, orthopedic procedures such as tenotomies, tendon releases, and transfers are necessary to address soft tissue and bone problems. Information regarding the



effect of surgery on function is limited. Constraint therapy (ie, immobilizing the dominant upper extremity) while providing therapy to enhance the function of the affected limb has been shown in several studies to improve function in children who have spastic hemiplegia. Evidence suggests that constraint therapy produces anatomic changes in the brain on functional MRI.

Drooling is often a significant social problem for children with CP and may be managed with scopolamine, which is available as a transdermal patch and as a tablet; glycopyrrolate; botulinum toxin injections into salivary glands; or surgical removal of the salivary glands. Because children who have CP are at increased risk for nutrition and feeding problems, careful monitoring of their physical growth is critical. Both linear growth and weight may be affected; therefore, monitoring weight for length rather than weight alone is important. Reliable measures of height or length in children who have CP are often impossible to obtain because of the scoliosis, fixed joint contractures, involuntary muscle spasms, and poor cooperation stemming from cognitive deficits. Tibial length has been used as a proxy for height. Evaluating the child whose growth is impaired includes evaluation of dietary intake for calories and content and evaluation for gastroesophageal reflux (using impedance probe, endoscopy with biopsy, or radionuclide gastric emptying study). A clinical feeding evaluation includes assessing the child's seating and posture during meals, as well as assessing the swallowing mechanism, which can be aided by a videofluoroscopic swallowing study using foods of different consistencies. The videofluoroscopic swallowing study can also assess the risk for aspiration. The assistance of feeding specialists is invaluable in this evaluation. Treatment options may include providing special seating devices to maintain the child in an upright, neutral position; thickening feedings; or inserting a gastrostomy tube with or without fundoplication. Enteral nutrition generally promotes weight gain and overall health, but may not restore longitudinal growth. As children who rely on caregivers for total assistance grow, their increasing body size can pose barriers for family and community participation. In these instances, parents may consider growth attenuation; however, physicians are encouraged to consult with endocrinologists and ethicists because there has been significant public debate surrounding this approach to care.

Pediatricians and primary care physicians should advocate for each child with CP in their care. In addition to the individual needs of children and their families, physicians are encouraged to advocate for educational and other community services that promote participation of persons of all abilities. Primary care physicians cannot be expected to understand all the nuances of the interventions used in the treatment of their patients with CP (Which braces are best? Should the child be treated with botulinum or baclofen?), but they can be active participants in the overall care of the child by monitoring the child's function (nutrition, mobility, activities of daily living, communication, and ensuring participation at the maximal level).

Because many conventional therapies do not adequately address the secondary conditions of CP,

families often turn to complementary therapies. The pediatrician should inquire about the use of these treatments and be aware of their nature, possible interactions with medications, and potential for harm. Complementary, integrative, and alternative treatments, such as equine-assisted therapy (hippotherapy) and acupuncture, have been shown to offer functional benefits to some children with CP. There is no evidence to support the use of hyperbaric oxygen to promote the motor function of children with CP, which also is associated with risks for increased seizures and barotrauma to tympanic membranes. Similarly, patterning and various forms of electrical stimulation have undergone trial, but evidence for their effectiveness is lacking.

## PROGNOSIS

Survival in children who have CP depends on the severity of the condition. For example, a 2-year-old with severe CP would be expected to have a 40% chance of living to age 20 years, whereas a child with mild CP would have a 99% chance. Respiratory diseases (eg, pneumonia), epilepsy, and congenital malformation are the most commonly recorded causes of death in childhood. Life expectancies among adolescents and adults with CP are lower for those with more severe limitations in motor function and feeding skills, although over the past 3 decades, significant improvements in survival are noted overall.

Children who have intellectual disability, no independent mobility (ie, rolling), or limited spontaneous movement and can be fed only by gastrostomy tube are at the greatest risk for early death. Prognostication before the child's second birthday may be difficult, except at the extremes of involvement. In general, the prognosis for functioning is related to the clinical type of CP, pace of motor development, evolution of infantile reflexes, intellectual abilities, sensory impairment, and emotional-social adjustment. Patients who sit unsupported by 24 months of age and crawl by 30 months of age are more likely to eventually walk independently. Most children who first sit between 3 and 4 years of age walk only with aids or braces or have restricted functional ambulation. Retention of obligatory primitive reflexes at 18 months of age makes independent ambulation unlikely. Virtually all children who have hemiplegia learn to walk, as do many who have dyskinesia or ataxia. Children who walk before 2 years of age are more likely to have a normal or borderline IQ. Individual achievement is related to many factors, such as intelligence, physical functioning, ability to communicate, and personality attributes. The availability of accessible primary and specialty health care, strong educational and vocational programs, supportive family involvement, and opportunities for community participation contributes to adult functional outcomes.

Long-term planning and preparation are required to help children with CP make the transition from adolescence to adulthood, particularly when a child has multiple needs. A variety of assistive technologies, such as switches that improve the individual's ability to control the environment, computers, and small electric motors that may replace some motor activities,

are available. Speech synthesizers, symbol charts, or spelling boards can enhance an individual's ability to communicate effectively. Simple environmental enhancements, such as ramps or accessible showers, and assistive devices, such as a pencil holder or mouth-activated switch, can improve the quality of life dramatically for individuals with CP. IDEA requires that school-aged children who have disabilities be assessed for the utility of assistive devices and be given the support needed to use them effectively. Gaining access to these services requires coordination of care, knowledge of the resources available in the community, referral to experts, and financial assets. The physicians who care for children with CP are encouraged to ensure that these services are available both to the patient and to the family.

The overall goal for children with CP should be to maximize functional independence and participation in family and community activities with their typically developing peers. Opportunities for participation may be limited, but physicians should be diligent in identifying these opportunities and encouraging children to participate in any and all activities that are available.

### WHEN TO REFER

- In the United States, all infants who have CP who are younger than 3 years should be referred to an early intervention program.
- All children who have moderate or severe CP should be referred to an interdisciplinary clinic, if one exists. If not, then they should be referred to an orthopedist, physical therapist, and a professional (developmental pediatrician, neurologist, pediatric rehabilitation specialist) who understands the needs of children with CP and can manage spasticity and other abnormalities of tone, and optimize functioning.
- Children who have CP and seizures should be referred to a neurologist. The primary care physician in the medical home should coordinate these referrals and ensure that the child is receiving coordinated, comprehensive care.
- Gastroenterologist or aerodigestive clinics should be consulted for children with CP who have feeding or nutritional impairments that might need the support of enteral feeding.
- When the etiology of CP is not established, or when the child is following an atypical course and showing congenital anomalies, consultation with geneticists is encouraged.

### WHEN TO ADMIT

- Some children who have CP aspirate food or saliva into their lungs; others have inadequate nutrition. Therefore, they demonstrate increased susceptibility to acute illnesses, such as pneumonia, and are likely to become more ill with these illnesses. They should be hospitalized if they are severely ill or cannot be managed at home. They should be hospitalized for most major surgeries as well, such as complex orthopedic procedures.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *Building the Legacy: IDEA 2004* (Web page), US Department of Education ([idea.ed.gov](http://idea.ed.gov))
- *Let's Put the Person First, Not the Disability!* (fact sheet), Disability Is Natural ([www.disabilityisnatural.com/explore/people-first-language](http://www.disabilityisnatural.com/explore/people-first-language))

### Engaging Patient and Family

- *All About the IEP* (fact sheet), Center for Parent Information and Resources ([www.parentcenterhub.org/repository/iep](http://www.parentcenterhub.org/repository/iep))
- *Building Your Care Notebook* (Web page), American Academy of Pediatrics ([medicalhomeinfo.aap.org/tools-resources/Pages/For-Families.aspx](http://medicalhomeinfo.aap.org/tools-resources/Pages/For-Families.aspx))
- *Cerebral Palsy* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/developmental-disabilities/Pages/Cerebral-Palsy.aspx](http://www.healthychildren.org/English/health-issues/conditions/developmental-disabilities/Pages/Cerebral-Palsy.aspx))
- *Cerebral Palsy* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/ncbddd/dd/ddcp.htm](http://www.cdc.gov/ncbddd/dd/ddcp.htm))
- *Emergency Information Form for Children With Special Needs* (form), American Academy of Pediatrics ([www.aap.org/advocacy/blankform.pdf](http://www.aap.org/advocacy/blankform.pdf))
- *Medical Plus Health Topics—Cerebral Palsy* ([www.nlm.nih.gov/medlineplus/cerebralpalsy.html](http://www.nlm.nih.gov/medlineplus/cerebralpalsy.html))
- *Pediatric Care Plan* (form), American Academy of Pediatrics ([medicalhomes.aap.org/Documents/PediatricCarePlan.pdf](http://medicalhomes.aap.org/Documents/PediatricCarePlan.pdf))
- *Pediatric Specialists* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/default.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/default.aspx))
- *Transitioning Youth to an Adult Care Provider* (booklet), Got Transitions ([www.gottransition.org/resourceGet.cfm?id=208](http://www.gottransition.org/resourceGet.cfm?id=208))

### Medical Decision Support

- *Gross Motor Function Classification System—Expanded & Revised* (fact sheet), CanChild ([canchild.ca/en/resources/42-gross-motor-function-classification-system-expanded-revised-gmfc-e-r](http://canchild.ca/en/resources/42-gross-motor-function-classification-system-expanded-revised-gmfc-e-r))
- *National Center for Medical Home Implementation* (Web site), ([medicalhomeinfo.aap.org/Pages/default.aspx](http://medicalhomeinfo.aap.org/Pages/default.aspx))

## AAP POLICY

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## Chapter 227 CHICKENPOX

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Chickenpox (varicella) is a childhood viral disease characterized by a pruritic vesicular rash that appears in crops. It is highly contagious and has been regarded as a relatively benign disease, in as much as complications are rare in healthy children. However, in the pre-vaccine era, more than 100 persons died every year from varicella, and the increasing number of children who are at risk for severe disease because they are immunosuppressed ensures that varicella remains a pathogen capable of causing significant mortality and morbidity. Additionally, the economic and social costs of days lost from school and from the work force by parents have driven interest in this disease and in its prevention through immunization.

The *chicken* in *chickenpox* is thought to derive from its likeness to the chickpea *Cicer arietinum*, or from the French for chickpea, *pois chiche*. Other researchers postulate that the name may come from the Old English word for itch, *gican*. The word *varicella* is derived from a disease that is similar in appearance but is much more severe, namely variola (smallpox).

### ETIOLOGY

Chickenpox is caused by the varicella-zoster virus (VZV), a DNA virus and member of the herpesvirus family. The same virus causes both chickenpox and herpes zoster, the latter being a reactivation (after a usually prolonged latent phase) of the initial varicella infection. Varicella-zoster virus can be detected in the vesicles of both chickenpox and herpes zoster, as well as in blood, tissue, and respiratory secretions during active disease. The virus is highly labile, losing its infectivity quickly in the external environment. Inactivation can also be accomplished by heat and trypsin. Only 1 serotype of VZV has been isolated, but different virus strains, including vaccine strains, can be identified by means of polymerase chain reaction (PCR).

### TRANSMISSION

Chickenpox is one of the most contagious viral infections to cause disease in humans, with an attack rate of 87% in susceptible individuals, making it only slightly less contagious than measles and smallpox. Infection is thought to be spread by respiratory secretions because airborne particles from patients can transmit infection before onset of the rash. Virus only rarely has been cultured from these secretions, although its presence can be detected by PCR. Contact with the vesicular fluid of chickenpox or herpes zoster also may result in the transmission of chickenpox infection.

Indirect contact (fomite transmission) is probably rare because of the lability of VZV, although viral DNA has been found on environmental surfaces during outbreaks. Chickenpox in a seronegative



pregnant woman can also lead to transmission of infection to her fetus or newborn. Transplacentally acquired antibody to VZV is partially protective to the newborn, but chickenpox can occur in young infants born to immune mothers. This may be more likely in mothers who did not have chickenpox disease but rather were immunized against varicella. Zoster is much less contagious than chickenpox (approximately 15% attack rate), and transmission of chickenpox from zoster is thought to occur primarily from direct exposure to the rash, although cases have been reported of virus being transmitted despite appropriate contact precautions being taken. Virus has been cultured from saliva in patients with zoster, and DNA has been found to persist in the saliva for up to 12 years. Furthermore, virus was cultured in asymptomatic, stressed astronauts, raising the question of the role of asymptomatic or persistent shedding of virus in chickenpox transmission.

### EPIDEMIOLOGIC FACTORS

Humans are the only known reservoir, or natural host, of VZV. The communicability period lasts from 1 or 2 days before the onset of the rash until 5 days after the onset or until all vesicles have crusted. Most vesicles no longer have detectable virus particles after 5 days. The incubation period is between 10 and 21 days, with an average of 14 to 16 days, although this period can be shortened in immunocompromised patients and prolonged in persons who receive immunoglobulin therapy as postexposure prophylaxis. Secondary household cases are often more severe because of increased exposure inoculum.

In temperate climates, chickenpox is mainly a disease of childhood, with 80% to 90% of children historically having been infected by 9 to 10 years of age. Historically, the highest incidence of varicella in the United States was among children aged 1 to 9 years. In the pre-vaccine era (eg, before 1995), approximately 4 million chickenpox cases occurred yearly in the United States, with 90% of cases occurring in children. The disease occurred throughout the year, but most cases occurred during the winter and spring months. Children in tropical climates have a lower rate of infection, and up to 40% to 90% enter adulthood without having had chickenpox, creating a much larger pool of susceptible persons among older age groups in the tropics than in temperate climates.

Subclinical infections with serologic conversion rarely occur. However, because varicella infects most people in temperate climates as children, most adults who report a negative or equivocal history of chickenpox are immune. Infection generally confers lifelong immunity in normal hosts, but second clinical infections can occur. Many such *second cases* may represent situations in which a prior nonvaricella exanthematous illness was erroneously labeled as chickenpox.

Case fatality rates from chickenpox fluctuated in the pre-vaccine era, but during the period of 1990 to 1994, they were estimated to be 4.7 per 100,000 infant cases, 0.8 per 100,000 cases for 1- to 4-year-olds, 1 per 100,000 cases for 5- to 9-year-olds, 1.6 per 100,000 cases for 10- to 14-year-olds, 5.9 per 100,000 cases for 15- to 19-year-olds, and 21.3 per 100,000 cases for affected individuals

older than 20 years. The case fatality rates are higher for neonates, older adults, and immunocompromised patients. In the pre-vaccine era, varicella caused more than 10,000 hospitalizations annually, predominantly in children. Annual deaths from varicella ranged from approximately 40 to 150, with a shift from most (80%) deaths occurring in children in the early 1970s to most (54%) occurring in adults in the early 1990s. More than 90% of the childhood deaths occurred in children who had no risk factors for severe varicella.

The incidence of varicella in the United States has changed markedly since the recommendation for varicella immunization of all US children older than 1 year was made in 1995. By 2000, the incidence of chickenpox decreased overall by 71% to 84% in populations with varicella immunization coverage rates for 1- to 3-year-olds of 74% to 84%. The incidence decreased in every age group, with the greatest decrease (83% to 90%) seen in the 1- to 4-year-old age group. More recent data show that peak incidence has shifted from children younger than 10 years to the 10- to 14-year age group, although overall varicella incidence remains markedly lower than in the pre-vaccine era. By 2001, the varicella-related hospitalization (VRH) rate in the United States had declined by 75% overall, with fewer than 3,800 such hospitalizations by 2001. This reduction in VRH was seen in all age groups but was greatest for young children, such that adults accounted for nearly one-half of VRHs by 2001, compared with only one-third of VRHs in the pre-vaccine period. In a similar fashion, deaths in the United States caused by varicella in the vaccine era have dropped by 88% overall, with a 97% decline in mortality of children and adolescents younger than 20 years. It is interesting to note that in 2008, the only 2 deaths caused by varicella reported to the Centers for Disease Control and Prevention (CDC) occurred in unimmunized adults born outside the United States.

### PATHOGENESIS

Varicella virus gains entry into the susceptible individual through the respiratory tract or conjunctiva through droplet or airborne transmission. It migrates to the regional lymph nodes, where primary replication occurs. Approximately 4 to 6 days later, a primary viremia spreads the virus to internal organs, where secondary replication occurs. This event is followed by a secondary viremia, which spreads the organism to the skin and is followed by clinical chickenpox. Viremia has been documented in blood-borne monocytes 9 to 12 days after exposure but 1 to 5 days before onset of the rash. The appearance of the rash in crops may be the result of an intermittent secondary viremia.

The rash is, at first, macular and then progresses to a papular lesion that contains a minute vacuole. Fluid accumulates in the vacuole, causing a vesicle to appear on a reddened base to produce the classic *dew-drop on a rose petal* lesion. Multinucleated giant cells and intranuclear inclusions can be identified microscopically in the base and on the edges of the vesicle. As the rash resolves, the vesicle becomes cloudy and fills with fibrinous fluid and leukocytes. A crust develops that may remain attached for 1 to 2 weeks. As the rash progresses, all stages (papule, vesicle, crust) are



present simultaneously, distinguishing it from smallpox, in which all lesions are in the same stage of progression. When a vesicle occurs on mucous membranes, its roof sloughs to leave a shallow ulcer. Evidence suggests that interferon, produced by the polymorphonuclear cells in the lesion, may contribute to resolution of the disease.

## CLINICAL MANIFESTATIONS

### Healthy Children

Chickenpox begins with a mild febrile prodrome in 36% of unvaccinated and 25% of vaccinated children. Prodromal symptoms usually are more noticeable in adults but can occasionally be severe in children as well. A complaint of malaise, vomiting, upper respiratory infection, or other prodromal symptoms can be present in up to 45% of unvaccinated children. This phase is followed in a few hours to days by a macular rash, usually beginning on the scalp, neck, or upper portion of the trunk. The macules progress to a papular, vesicular, pruritic rash, usually within 12 to 24 hours. Vesicles appear in crops, with a new crop occurring every 1 to 2 days over the next 2 to 5 days, resulting in multiple crops during the illness. Typical childhood cases produce a total of 250 to 500 lesions. The vesicles turn to pustules and then crust over. The illness usually runs its course in 5 to 10 days. At the height of the disease, lesions in all phases from early vesicles to crusts can be seen. Fever varies from none to 102°F (38.9°C) at the onset of the disease and may continue until vesicles cease to appear. The rash spreads centrifugally and involves all areas of the skin in severe cases. Vesicles are pruritic, and exco-riations frequently are seen. Lesions occur more frequently in areas of irritation or dermatitis or in skin folds. Occasionally, the rash appears as a macular rash in the diaper area or on the trunk and remains for 1 or 2 days before becoming vesicular, making early diagnosis more difficult. Vesicles may occur on the mucous membranes of the mouth, conjunctiva, esophagus, trachea, rectum, or vagina. Generally, little scarring occurs, unless the lesions become superinfected or are continually traumatized. Areas where chickenpox lesions have occurred, however, may remain hypopigmented or hyperpigmented months after the rash has resolved. Occasionally, lesions are bullous as a variant of the disease itself, but these are more often caused by staphylococcal superinfection. White blood cell counts and other laboratory test results are usually normal in uncomplicated varicella.

### Older Children and Adults

Chickenpox in older children and adults usually is more severe than it is in younger age groups, with a prodrome that may include irritability, listlessness, headaches, chills, anorexia, and myalgia. Fever is usually present and is higher and more prolonged than it is in the young child. The rash also tends to be more severe, and the risk for complications is greater.

### Breakthrough Chickenpox in Previously Immunized Children

Breakthrough disease is defined as wild-type chickenpox that occurs 42 days or later after vaccination. Risk

factors for breakthrough disease include immunization before 15 months of age, low 6-week postvaccination varicella zoster antibody titers, longer elapsed time since immunization, oral steroid use, and receipt of measles-mumps-rubella vaccine (MMR) within 28 days before varicella vaccine. In most children, breakthrough disease typically produces milder systemic symptoms and fewer lesions (usually <50) that are less pruritic and crust over faster. In some cases, the lesions may appear only as papules that never vesiculate, making diagnosis difficult. In addition, children with typical, mild breakthrough varicella are also approximately one-half as likely to transmit the disease to household contacts.

### Immunocompromised Children

Immunocompromised children usually have the most severe symptoms; they, along with neonates, are at greatest risk for death from chickenpox infection. *Progressive varicella* can be seen in children who have an immunocompromising condition or who are being treated with immunosuppressive therapy for leukemia or another malignancy. After a more severe prodrome, up to 30% of such immunocompromised children develop progressive varicella, with spread of VZV to the lungs, liver, pancreas, or central nervous system. Vesicles may be larger and hemorrhagic. All complications of chickenpox are increased in this population, with varicella pneumonia the most common cause of death. Even if progressive varicella does not develop, these patients still have higher fevers and more prolonged vesicular eruption than do nonimmunocompromised children.

Although severe varicella can occur in children who are infected with human immunodeficiency virus (HIV), especially those who have very low CD4 percentages, most children infected with HIV, including those who have low CD4 percentages, do not develop severe acute varicella. Many experts use oral valacyclovir or high-dose oral acyclovir to manage selected children infected with HIV who have relatively normal CD4 values, whereas others still manage *all* children infected with HIV with parenteral acyclovir (see Treatment).

Children who receive systemic steroid therapy for diseases other than cancer also are at risk for more severe involvement and complications. Children who receive 2 mg/kg or 20 mg prednisone (or equivalent) or more for 2 weeks or longer should be considered at increased risk for severe varicella. Inhaled corticosteroids do not seem to increase risk for severe varicella, but definitive data are lacking; some experts would still consider antiviral therapy in this group.

### Congenital and Neonatal Varicella

In cases of primary maternal varicella during pregnancy, VZV can cross the placenta, leading to congenital varicella syndrome in 2% of cases when maternal infection occurs during the first 20 weeks of gestation. Although congenital varicella syndrome does not usually occur late in pregnancy, there have been a few cases reported occurring after 20 weeks' gestation, the latest at 28 weeks' gestation. Cicatricial skin lesions or skin loss in a dermatomal distribution

(76%), neurologic defects (60%), eye diseases (51%), and skeletal anomalies (49%) occur in affected infants. Such infants have a mortality risk of 30%.

Maternal infection during the late third trimester of pregnancy may result in transplacentally acquired varicella in the newborn. When mothers have clinical chickenpox in the 2 weeks before delivery, 24% of their infants will develop neonatal varicella. If the onset of maternal rash occurs more than 5 days before delivery, or if rash initially erupts in infants younger than 4 days, then risk for death seems to be small. This reprieve is probably attributable, at least in part, to maternally transferred immunity. If, on the other hand, the *maternal* rash emerges between 5 days before and 2 days after delivery, or if the *newborn* rash begins at 5 to 10 days of age, then an associated 20% to 30% neonatal mortality occurs. The risk is uncertain for infants who are nursing when the mother contracts chickenpox.

Herpes zoster in pregnant women, on the other hand, seems to confer minimal risk for infection to the fetus. In a series of 366 women who had herpes zoster in pregnancy, none of the infants had evidence of intrauterine infection.

### Zoster

Zoster, or shingles, is the reactivation of VZV that has remained dormant after clinical chickenpox. The virus resides in the dorsal nerve ganglia and is reactivated by periods of decreased host immunity or other unknown stimuli. During reactivation, the rash covers the dermatome that corresponds to the infected nerve root. Disseminated zoster, however, also can occur, involving multiple dermatomes. Zoster has been described in all age groups, including in infancy after prenatal exposure to varicella virus resulting from maternal chickenpox.

Children who have varicella infections at younger ages, especially when the infection occurs before the child is 1 year of age, have an increased incidence of zoster later in life. Children with leukemia who experience varicella develop zoster at an increased incidence of 25 cases per 1,000 person-years, a significantly lower rate than that for children infected with HIV. Twenty-seven percent of children infected with HIV (before anti-HIV drugs were available) who had primary varicella after 1 year of age developed zoster 2 years (on average) after primary varicella; among children whose CD4 percentage was less than 15% at the time of varicella infection, 70% developed zoster in the same time period. The varicella vaccine seems to be quite effective in preventing zoster in children with HIV.

## COMPLICATIONS

### Secondary Bacterial Infection

Secondary bacterial infection is the most common complication of chickenpox. Children younger than 5 years seem to be at increased risk. Symptoms of secondary bacterial infection begin, on average, 4 days after the appearance of the varicella rash, often with a secondary fever. Infections are usually caused by group A streptococci or *Staphylococcus aureus*, but

serious invasive infections such as necrotizing fasciitis can be polymicrobial and often include gram-negative and anaerobic organisms. Bacterial complications include impetigo, cellulitis, abscess, necrotizing fasciitis, myositis, gangrene, arthritis, osteomyelitis, pneumonia, empyema, conjunctivitis, toxic shock syndrome (usually streptococcal), sepsis, and erysipelas. Bullous lesions caused by *S aureus* may begin on the second or third day of the rash and present as bullous impetigo.

### Neurologic Complications

Nervous system complications are the second most common complication of varicella and include acute cerebellar ataxia, encephalitis, seizures, aseptic meningitis, myelitis, and peripheral neuropathy. Many of the seizures occurring with chickenpox may just be febrile seizures; in one series, 12 of 23 patients who had varicella and seizures had concomitant fever. In older series, the mortality from neurologic complications reached approximately 10% overall, but most of the deaths occurred among cases of encephalitis, some of which may have represented unrecognized Reye syndrome.

Acute cerebellar ataxia (ACA) is the most common neurologic complication of varicella, occurring in 1 in 4,000 cases of chickenpox. The average age of patients with ACA is 4 years, with most cases occurring among children younger than 5 years. The onset of symptoms usually occurs 1 to 2 weeks after onset of varicella but ranges from 2 to 21 days after the appearance of the rash and, uncommonly, may even precede the rash. The usual clinical features of varicella-related ACA are acute onset of vomiting and ataxic gait disturbance without major disturbance in mental status. Dysmetria (68%) and trunk ataxia (74%) also occur frequently; fever and nystagmus are much less common (5% to 10%). Laboratory studies usually reveal a normal peripheral white blood cell count, normal to mildly elevated cerebrospinal fluid protein, and, in 50% of patients, cerebrospinal fluid pleocytosis. Between 95% and 100% of normal children who have varicella-related ACA recover completely with only supportive care. Most cases are mild enough that hospitalization is not necessary. Recovery usually takes place within the first 3 months, although it may take longer for some children.

### Varicella Pneumonia

Varicella pneumonia occurs most often among adults, adolescents, and immunocompromised children. It is one of the more common causes of death resulting from varicella. In children, varicella pneumonia occurs in fewer than 1 per 10,000 cases of chickenpox. In adults, the rate is higher, at 3.1 per 10,000 cases of chickenpox. Manifestations range from abnormal chest radiograph findings alone to cough, rales, tachypnea, hemoptysis, chest pain, cyanosis, and respiratory failure. Onset of pneumonia typically occurs 5 to 6 days after onset of rash in immunodeficient children and adults but occurs within the first 3 days of rash onset in immunocompetent hosts (adults). Chest radiographs typically show diffuse, reticulonodular densities of various sizes, which are best viewed in the lung periphery. As the disease progresses, nodules may enlarge and coalesce into extensive infiltrates.

Treatment of varicella pneumonia with intravenous acyclovir is recommended; however, mortality is still 10% to 20%, reaching higher rates among severely immunodeficient patients.

### Hematologic Complications

Thrombocytopenia is the most common hematologic abnormality seen with varicella. Thrombocytopenia may occur with an invasive secondary bacterial infection or sepsis, in which case it is associated with more severe illness and worse outcome. In the absence of secondary bacterial infections, however, varicella may produce thrombocytopenia (or even pancytopenia) that is attributed to infection-related suppression or antibody-mediated destruction (immune thrombocytopenic purpura) of platelets. Onset occurs 3 days to 3 weeks after the chickenpox rash appears. Febrile purpura, malignant chickenpox with purpura, postinfectious purpura, purpura fulminans, and Henoch-Schönlein purpura have all been described in association with varicella infection.

### Hepatitis

Hepatitis has been reported during chickenpox infections and is marked by the onset of abdominal pain, vomiting, and continued fever on the second to fourth day after the rash appears. Liver function tests become abnormal but return to normal with resolution of the abdominal symptoms. No progression to classic Reye syndrome occurs, and the blood ammonia level is normal. However, some experts think that some of these cases may represent low-grade Reye syndrome. One study of 39 children who had uncomplicated chickenpox found 47% to have a mildly increased level of aspartate transaminase (serum glutamic-oxaloacetic transaminase) and 29% to have significantly increased aspartate transaminase levels.

### Reye Syndrome

Reye syndrome is an acute illness occurring almost exclusively in children and characterized by encephalopathy and fatty degeneration of the liver. Reye syndrome carries a high case fatality rate of 30% overall, reaching rates of 43% for children younger than 5 years. In 1980, the association between Reye syndrome and use of aspirin during varicella or influenza illnesses was first reported. This report led to an advisory from the CDC in 1980, a Surgeon General advisory in 1982, and mandatory warning labels on all aspirin-containing medications in 1986 cautioning physicians and parents to avoid using salicylates in children who have varicella or influenza-like illnesses. The annual number of reported cases of Reye syndrome in the United States fell from a high of 555 cases in 1980 to no more than 36 cases per year from 1987 to 1993 and no more than 2 cases per year from 1994 to 1997. Given its rare occurrence, any child suspected of Reye syndrome should be evaluated thoroughly for the presence of another metabolic disorder.

Salicylates should be avoided in any child who has chickenpox. Reye syndrome has not been described in relation to varicella vaccination, but it is recommended that salicylates be avoided for 6 weeks after varicella vaccination.

### Other Complications

Appendicitis, myocarditis, arthritis (viral), nephritis, orchitis, splenic hemorrhage and rupture, pancreatitis, pericarditis, and parotitis have been reported, although rarely. The most common ophthalmologic complication is papillary conjunctivitis, but keratitis, uveitis, optic neuritis, chorioretinitis, acute retinal necrosis, and progressive outer retinal necrosis also can occur.

### DIAGNOSIS

Chickenpox is usually diagnosed clinically. A history of exposure in the previous 10 to 21 days may be present. White blood cell counts are usually normal. Historically, a Tzanck test (scraping of the base of a vesicle and staining with Giemsa or Wright stain) is positive for multinucleated giant cells in VZV infections. However, herpes simplex types 1 and 2 also produce a positive Tzanck test. Varicella zoster virus-specific direct fluorescent antibody (DFA) testing of vesicle scrapings can provide specific diagnostic confirmation within hours. Scrapings of the vesicle base can also be cultured for VZV, but growth may take weeks, and overall yields are low. PCR tests have been demonstrated to be superior to viral culture in identification of varicella virus from vesicles and can be used to distinguish eruptions caused by wild-type and vaccine virus, as well as to distinguish chickenpox from monkeypox or smallpox. Viral titers during acute and convalescent stages can document a recent infection if acute titers are obtained early in the illness (preferably day 1 or 2), and higher titers are noted during convalescence 2 to 6 weeks later. Commercially available antibody tests should be interpreted with caution because they may not be sensitive enough to reliably detect vaccine-induced immunity and frequently are negative even when wild-type chickenpox was clearly present earlier in life. The only methods to reliably detect vaccine-induced antibody in serum are gpELISA and FAMA, neither of which are generally commercially available.

### DIFFERENTIAL DIAGNOSIS

Smallpox (variola) was historically the most important disease to be differentiated from chickenpox and has once again become a concern because of its use as a bioterrorism agent. The clinical prodrome of smallpox is typically more severe than that of chickenpox. Unlike varicella, in which lesions in all stages of evolution are present at once, smallpox produces an eruption in which most of the lesions are present in a uniform stage of development, progressing together from macules to papules to deep-seated vesicles and finally crusting. Involvement of palms and soles is much more typical of smallpox. Testing with VZV PCR is available through local health departments on a rapid, emergent basis when smallpox is a concern. Direct fluorescent antibody testing may also be useful to confirm varicella in cases in which smallpox is a concern.

Monkeypox is a zoonotic illness that has a prodrome and rash similar to smallpox, although usually less severe. Lymphadenopathy is prominent, unlike smallpox. Cases in the United States are rare and have been associated with animals imported from Africa.



As with smallpox, rapid testing such as VZV PCR and DFA may be useful in differentiating monkeypox from chickenpox.

Vaccinia (cowpox) produces a vesicular rash resulting from exposure to infected livestock or, when smallpox vaccine use was commonplace, from direct contact with a smallpox vaccination.

Disseminated herpes simplex can resemble the chickenpox rash, but the history and progression of the disease usually differentiate these entities. Confusion ordinarily arises only in newborns because disseminated herpes is rare; a Tzanck test will be positive in both diseases, but DFA, culture, and PCR are specific.

Rickettsialpox can resemble chickenpox, but its vesicles are deeper and are at a uniform stage of development, and prodrome is more severe.

Other viruses, especially coxsackievirus and echovirus, can produce vesicular exanthemas that usually do not crust and that follow a distinctly different course. The Tzanck test is negative in these infections. Lesions of Stevens-Johnson syndrome can resemble chickenpox, but the 2 diseases follow different clinical courses, and the rashes develop differently. A Tzanck test will be negative. Contact dermatitis may produce a rash similar to that of chickenpox, including pruritus, but has a different distribution and evolution.

Insect bites and scabies occasionally cause confusion if they are vesicular. Bullous impetigo (especially staphylococcal skin infection) may produce bullae that resemble chickenpox.

## TREATMENT

Treatment with acetaminophen for control of fever and relief of prodromal symptoms, along with measures to control pruritus, usually is sufficient. Concern has surfaced that use of nonsteroidal anti-inflammatory drugs during varicella infection may increase the risk for necrotizing fasciitis and other secondary bacterial (streptococcal) infections, but an association has not been firmly established, and its causal relationship may be confounded by the use of ibuprofen for the signs (eg, secondary fever) of incipient bacterial complications. Pruritus can be controlled with an oral antihistamine (eg, diphenhydramine), calamine lotion, Cetaphil lotion, or 0.25% menthol lotion. Uncommon but reported encephalopathic side effects of diphenhydramine may mimic neurologic complications of varicella.

Patients should be encouraged to take daily baths to help prevent bacterial superinfection. Adding baking soda or oatmeal preparations (Aveeno) to a warm bath helps relieve the pruritus. Children's nails should be kept clean and trimmed to help discourage scratching. Occasionally, gloves or socks on the hands are required to prevent opening of lesions by scratching. If superinfection is present, then it usually is a result of group A streptococci or *S aureus*. Mild superinfection of a few lesions can be treated topically with mupirocin ointment; superinfection of many lesions or of lesions in difficult areas (eg, around nares or the mouth) can be treated systemically with an antibiotic that has activity against group A streptococci and *S aureus*. Choice of empirical therapy should be based

on the local antibiotic resistance profile and severity of superinfection.

Aspirin should be avoided in the management of chickenpox because of its association with Reye syndrome. Physicians caring for patients who are taking aspirin chronically for juvenile idiopathic arthritis or other diseases need to consider the risks versus the benefits of this therapy on an individual basis if such a patient contracts chickenpox.

Hospitalization should be avoided whenever possible because hospital epidemics can occur even when the strictest isolation procedures are followed. Generally, spread is by infection of staff members who were thought to be immune or by airborne spread of the virus through ventilation systems. When unavoidable, hospitalization requires strict isolation. Hospitalization on an adult ward that has no immunosuppressed patients may lessen the chances of spread in hospitals where effective strict isolation is not available. All health care workers should have immunity to varicella verified at the time of hire.

## Antiviral Therapy

Acyclovir has been shown to be effective in treating varicella infections in healthy children and adolescents. When instituted within 24 hours of the onset of rash, treatment has resulted in modest reductions in duration of illness, number of cutaneous lesions, fever, and systemic symptoms. In one study, treatment of the index case with acyclovir did not change the transmission rate to other susceptible household contacts. Use of acyclovir for varicella infection in adolescents should be considered because they are at greater risk for more severe disease; however, use of acyclovir in healthy preadolescent children is not routinely recommended. Acyclovir can also be considered for other nonimmunocompromised children who are at increased risk for more severe varicella, including children with chronic lung disease, those with chronic skin disorders, those on salicylate therapy, those taking aerosolized or low-dose systemic corticosteroids, and those who are secondary household cases. Valacyclovir, a prodrug of acyclovir, has greater oral bioavailability than oral acyclovir. Its use is approved by the US Food and Drug Administration for children 2 years of age and older with varicella. Nonimmunocompromised patients 2 years and older in whom therapy is desired on an outpatient basis may be given valacyclovir at 60 mg/kg per day in 3 divided doses (maximum, 3,000 mg/day) for 5 days. Its effectiveness has not been studied extensively in children. A recipe for compounding valacyclovir for use in younger children is available in the package insert. Alternatively, oral acyclovir at 80 mg/kg per day in 4 divided doses (maximum, 3,200 mg/day) for 5 days may be used in all age groups. Famciclovir has been licensed for treatment of zoster in adults, but it has not been adequately studied in children for the treatment of chickenpox. Healthy children who develop complications suggestive of severe or disseminated disease, such as pneumonitis, encephalitis, or other visceral involvement, should be hospitalized and treated with intravenous acyclovir.



Acyclovir, generally by the intravenous route, has been recommended for the treatment of immunocompromised children who develop varicella infection because it can prevent severe disseminated disease in this group of patients. Because dissemination usually occurs within the first few days, benefit is most likely achieved if started within the first 24 hours after the appearance of rash. However, viral replication may be prolonged beyond the typical 72 hours that is seen in immunocompetent patients, and starting acyclovir beyond that time may still ameliorate disease. Intravenous acyclovir is given at 30 mg/kg per day in 3 divided doses if younger than 1 year, and 1,500 mg/m<sup>2</sup> per day in 3 divided doses if 1 year or older (some experts would recommend 30 mg/kg per day in 3 divided doses in all age groups). Length of therapy is usually at least 7 to 10 days, but therapy should be continued until no new lesions have occurred for 48 hours. Occasionally, lesions can recur after cessation of acute therapy in immunocompromised patients. In this situation, new lesions after a short course of therapy are not likely a result of antiviral resistance. Some experts would recommend another course of acyclovir in this setting. Increasingly, children infected with HIV, particularly those who have higher CD4 percentages, have been treated successfully for primary varicella with oral valacyclovir or oral acyclovir.

Localized zoster uncommonly occurs in immunocompetent children. The risk for dissemination and severe disease is unlikely in this population and typically does not require antiviral therapy. The exception to this is zoster ophthalmicus, in which systemic and topical acyclovir therapy may be indicated to treat ocular disease and prevent severe sequelae. Valacyclovir may also have benefit in this setting, but its use for this indication has not been evaluated in children. Patients with zoster ophthalmicus should have serial ophthalmologic evaluations. In immunocompromised patients, the risk for dissemination from zoster is higher, and intravenous acyclovir therapy should be instituted, preferably within the first 72 hours of rash onset.

Acyclovir resistance is rare in varicella and most often occurs in immunocompromised patients on prolonged antiviral therapy. Foscarnet is the drug of choice for treatment of acyclovir-resistant varicella disease.

Varicella zoster immune globulin (VariZIG) and immune globulin intravenous (IGIV), although useful in postexposure prophylaxis, are not effective once disease is established and are not recommended as treatment in this situation.

## Prevention

Every attempt should be made to prevent disease in susceptible individuals. This is done by providing age-appropriate immunization before exposure, and during an outbreak by limiting exposure to persons with chickenpox. If a patient is exposed to VZV, options for post-exposure passive immunization, active immunization, and antiviral prophylaxis are outlined in Figure 227-1.

Isolation or exclusion of the child who has chickenpox to prevent exposure of individuals who are

susceptible is the easiest prevention strategy in institutional settings such as hospitals, schools, or child care facilities. This measure is not always effective, given that the disease is contagious 1 to 2 days before the appearance of the rash. Generally, isolation is not feasible for preventing household exposures.

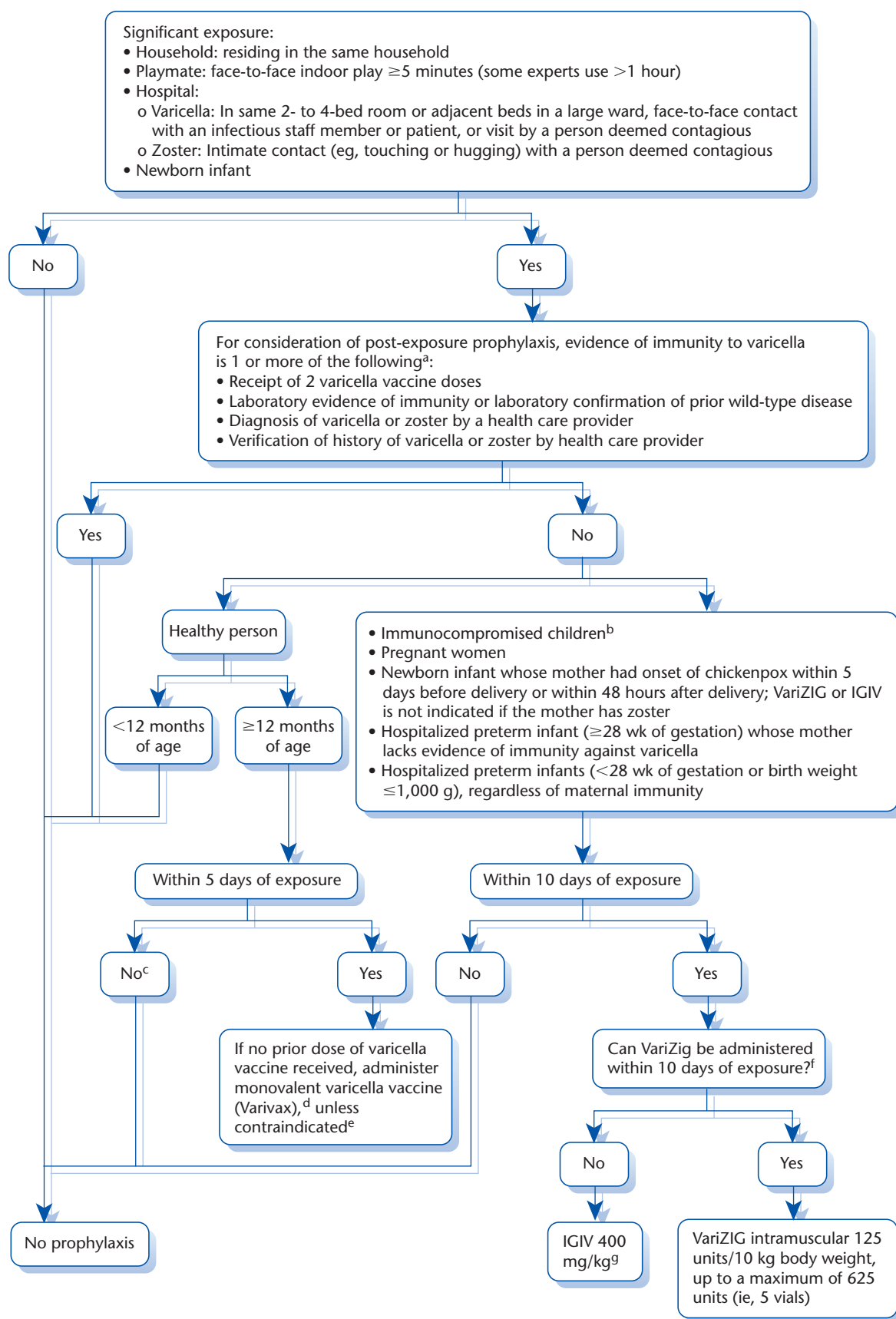
## Varicella Vaccine

A live-attenuated vaccine using the Oka strain of varicella was licensed by the US Food and Drug Administration in 1995 for the prevention of moderate to severe chickenpox in healthy persons 12 months and older. In 2005, varicella vaccine with the MMR vaccine as a combination product (MMRV) was licensed for use in healthy children aged 12 months to 12 years based on its safety and immunogenicity in children. A second varicella vaccine dose was recommended in 2006 to also protect against mild chickenpox.

Varicella vaccine has been shown to be effective in preventing varicella infection in most recipients, often attenuates infection in the case of breakthrough disease, and may decrease rates of zoster. Ten-year efficacy of a 2-dose vaccination regimen is 96% for prevention of all disease, and 100% for prevention of severe disease. This degree of protection is equivalent to immunity conferred by wild-type disease. Limited data demonstrate persistence of humoral and cell-mediated immunity following vaccination for up to 20 years in Japan, but the contribution of boosting by continued circulation of wild-type varicella to maintaining immunity is unknown.

All healthy children who lack evidence of immunity (Box 227-1) should receive 2 doses of varicella vaccine. The first vaccine dose is recommended at 1 year of age, and the second at 4 to 6 years of age. For catch-up immunization in children 12 years and younger, 2 doses should be given at least 3 months apart (if the second dose is given  $\geq 28$  days after the first dose, it does not need to be repeated). For catch-up immunization in children 13 years and older, 2 doses of varicella vaccine should be given at least 28 days apart. MMRV is not licensed for use in children 13 years or older. Data are not available regarding safety, immunogenicity, or efficacy of MMRV vaccine in HIV-infected children. MMRV vaccine should not be administered as a substitute for the single-antigen varicella vaccine when vaccinating these children. The titer of Oka VZV is higher in combination MMRV vaccine than in single-antigen varicella vaccine, a minimum of 3.99 log<sub>10</sub> PFUs compared with 1,350 PFUs (approximately 3.13 log<sub>10</sub>) in each 0.5-mL dose. The other constituents are similar to those in the single-antigen varicella vaccine.

Because the varicella vaccine is an attenuated live virus vaccine, it generally is not recommended for use in pregnant women or in immunocompromised patients. This includes children who have T-lymphocyte immunodeficiency (congenital or acquired), including patients with leukemia, lymphoma, and other malignant neoplasms affecting the bone marrow or lymphatic systems, as well as children receiving long-term immunosuppressive therapy. Children receiving high-dose systemic steroids (2 mg/kg per day or more of prednisone or its equivalent, or 20 mg/kg per day of



**Figure 227-1** Prevention for children exposed to varicella-zoster virus.

<sup>a</sup>Persons who receive bone marrow transplants should be considered nonimmune regardless of previous history of varicella disease or varicella vaccination in themselves or in their donors.

<sup>b</sup>Immunocompromised children include those with congenital or acquired T-lymphocyte immunodeficiency, including leukemia, lymphoma, and other malignant neoplasms affecting the bone marrow or lymphatic system; children receiving immunosuppressive therapy, including  $\geq 2$  mg/kg/day of systemic prednisone (or its equivalent) for  $\geq 14$  days; all children with HIV infection regardless of CD4 %; and all bone marrow transplant patients regardless of pretransplant immunity status.

<sup>c</sup>No postexposure prophylaxis, but age-appropriate vaccination still recommended for protection against subsequent exposures. If the exposure occurred during an outbreak, 2-dose vaccination is recommended for preschool-aged children under 4 years of age for outbreak control.

<sup>d</sup>If 1 prior dose of varicella vaccine has been received, a second dose should be administered at  $\geq 4$  years of age. If the exposure occurred during an outbreak, a second dose is recommended for preschool-aged children under 4 years of age for outbreak control.

<sup>e</sup>Contraindications include patients who are allergic to a vaccine component, or who are immunocompromised (see above footnote), or pregnant. Caution should be used in patients on salicylates. Vaccine may not be as effective if patient has recently received IGIV, whole blood, or plasma transfusions, and for this reason it is recommended that varicella vaccine be withheld for 3–11 months, depending on the dose, after administration of these products.

<sup>f</sup>VariZIG was approved by the United States Food and Drug Administration in December 2012. The product is manufactured by Cangene Corporation (Winnipeg, Canada) and distributed in the U.S. by FFF Enterprises (Temecula, California; 800-843-7477; [www.fffenterprises.com](http://www.fffenterprises.com)).

<sup>g</sup>If VariZIG and IGIV are not available, some experts recommend prophylaxis with oral acyclovir (20 mg/kg per dose administered four times per day, with a maximum daily dose of 3,200 mg) or oral valacyclovir (if  $>3$  months of age; 20 mg/kg per dose administered 3 times per day, with a maximum daily dose of 3,000 mg) beginning 7 to 10 days after exposure and continuing for 7 days.

### BOX 227-1 Evidence of Immunity to Varicella for Determining Need for Immunization

#### DOCUMENTATION OF AGE-APPROPRIATE IMMUNIZATION

- Preschool-aged children  $\geq 12$  months of age: 1 dose
- School-aged children, adolescents, adults: 2 doses at least 28 days apart

Postimmunization serologic testing is neither necessary nor recommended after immunization, including in health care personnel.

#### LABORATORY EVIDENCE OF IMMUNITY OR LABORATORY CONFIRMATION OF DISEASE

##### VARICELLA DIAGNOSED BY A PHYSICIAN OR VERIFICATION OF HISTORY OF DISEASE

- For people reporting or presenting with typical disease, verification can be performed by any health

care professional (eg, school or occupational clinic nurse, nurse practitioner, physician assistant, physician).

- For people reporting or presenting with atypical or mild cases, assessment by a physician or physician's designee is recommended, and 1 of the following should be sought: (a) an epidemiologic link to a typical varicella case or to a laboratory-confirmed case; or (b) evidence of laboratory confirmation, if it was performed at the time of acute disease. When such documentation is lacking, people should not be considered as having a valid history of disease because other diseases may mimic mild atypical varicella.

##### HISTORY OF HERPES ZOSTER DIAGNOSED BY A PHYSICIAN

Adapted from American Academy of Pediatrics. Varicella-zoster virus infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:857.

prednisone or its equivalent) for 14 days or more should not receive varicella vaccine. Vaccine may be administered if systemic steroids have been stopped for at least 1 month. There is no contraindication to administering varicella vaccine to patients receiving inhaled, nasal, or topical steroids. Patients with nephrotic syndrome receiving chronic, alternate-day prednisone may benefit from varicella vaccine. HIV-infected children aged 1 to 8 years should receive 2 doses of single-antigen varicella vaccine at least 3 months apart starting at 12 to 15 months of age if their CD4 percentage is at least 15%. Patients whose CD4 percentage was previously less than 15% may be immunized after stable immune reconstitution occurs as evidenced by a CD4 percentage of at least 15% for

at least 3 months while on highly active antiretroviral therapy. Older children with HIV may be immunized with 2 doses of single-antigen vaccine at least 3 months apart if they have CD4 counts greater than or equal to 200 cells/mm<sup>3</sup>, although vaccination in this age group is less well studied, and risk versus benefit of vaccination should be considered.

Vaccine may also be administered to patients with impaired humoral immunity. A patient in whom some degree of immunodeficiency is present, but in whom vaccine is not contraindicated, should receive single-antigen varicella vaccine (but not MMRV). Vaccination of a patient with leukemia in remission is controversial and should only be undertaken with expert guidance after weighing risks and benefits. Generally, live virus

vaccines should be withheld for at least 3 months after cessation of immunosuppressive chemotherapy, but other factors affecting immune reconstitution, including radiation therapy, underlying disease, and immunosuppressive therapy, must be considered. A patient whose first-degree family member has a history of congenital or hereditary immunodeficiency should not receive the vaccine unless the immune competence of the potential vaccine recipient is verified.

Vaccination is also contraindicated if a patient has had an anaphylactic reaction to any component of the vaccine. Caution should be used in patients with severe acute illness or thrombocytopenia. Because of the theoretical risk for Reye syndrome, the vaccine manufacturer recommends avoiding the use of salicylates for 6 weeks after receiving the varicella vaccine.

The adverse event attributed most commonly to varicella vaccine is pain and swelling at the injection site. A mild (2 to 5 lesions on average) maculopapular or varicelliform rash at the injection site may occur in 1% to 3% of vaccine recipients, and an additional 3% to 5% of vaccine recipients may develop a more generalized varicella rash in the month following varicella vaccination. When tested by PCR, however, most rashes occurring within 2 weeks of varicella immunization are determined to be a result of infection with wild-type virus rather than vaccine strain virus. Other, more serious but much less common adverse events—encephalitis, ataxia, erythema multiforme, pneumonia, thrombocytopenia, seizures, herpes zoster—occur at lower frequencies than would be expected following natural infection.

Febrile seizures may occur after varicella vaccine, and postmarketing studies showed a seizure risk of 3 to 4 additional febrile seizures per 10,000 first-dose vaccine recipients. First-dose MMRV has a slightly higher risk of 7 to 9 febrile seizures per 10,000 vaccine recipients between 12 and 47 months of age. It is important to note that febrile seizures do not predispose to epilepsy, neurodevelopmental delays, or other long-term health impairment. Because of the slightly increased risk for febrile seizures with first-dose MMRV use, a personal or family history of seizures is a precaution for first-dose MMRV vaccination between 12 and 47 months of age. These patients should be immunized separately with MMRV and single-antigen varicella vaccines. The increased risk for seizures is not seen with second-dose MMRV vaccination, and a personal or family history of seizures is not a precaution in this situation.

Transmission of vaccine virus to susceptible contacts has been extremely rare and has occurred only in the presence of a vaccine-associated rash; therefore, vaccinees who develop a rash should avoid direct contact with susceptible, immunocompromised individuals until the rash has resolved. Presence of an immunocompromised or pregnant contact does not preclude vaccination of an otherwise eligible child. Because the rash that occurs in relation to varicella vaccine is rare and transmission is extremely unlikely, postexposure prophylaxis with VariZIG is not recommended in immunocompromised individuals exposed to a vaccine-related rash.

Because immune globulin or other blood products (except washed red blood cells) may interfere with the

immune response to varicella vaccination, vaccine should be deferred for 3 to 11 months after receipt of blood products, depending on the dose and type of blood product use. VariZIG recipients should wait 5 months before vaccination if vaccine is not contraindicated (Table 227-1). If possible, immune globulin preparations should be avoided for 2 weeks after administration of varicella vaccine. If such products must be given, the patient should at the appropriate interval either be revaccinated or tested for evidence of immunity and revaccinated if seronegative. Measles-mumps-rubella vaccine and varicella vaccine should not be given fewer than 28 days apart, but they may be given simultaneously, including as the combination product MMRV, without reducing efficacy. Antiviral medications with activity against herpes viruses can affect vaccine efficacy. It is recommended when possible that such antivirals be discontinued at least 24 hours before immunization until at least 21 days after immunization with varicella vaccine.

MMRV can temporarily suppress tuberculin skin test (TST) reactivity. Although the effect of varicella vaccine on TST reactivity is unknown, it is recommended that TST be delayed if possible by 4 weeks after vaccine administration. The same approach is suggested with respect to the interferon- $\gamma$  release assays (IGRA) as well. However, a TST may be placed, or an IGRA may be obtained simultaneously with varicella vaccine or MMRV administration.

### Postexposure Prophylaxis

The decision to use postexposure prophylaxis is based on several factors. The type of exposure, possible immunity of the exposed individual, risk for disease severity, and possible risk and benefit of the intervention must all be considered. Face-to-face contact carries a high risk for disease transmission, especially among household contacts. Experts disagree about what length of time of exposure constitutes a significant risk for disease transmission. As little as a 5 minutes could be significant, although some would argue that more than 1 hour is necessary. Sharing a hospital room with an infectious person is also deemed to be high risk. Transient interaction with infected staff at hospitals carries less risk, although infection is not impossible. Localized zoster is much less infectious, and risk for transmission is low unless the patient has close contact (touching or hugging) with someone with localized zoster.

In healthy, nonpregnant individuals 12 months of age or older who lack evidence of varicella immunity, vaccination is recommended as postexposure prophylaxis because it may prevent or attenuate disease when given within 3 to 5 days after varicella exposure (Figure 227-1). Few data exist with regard to postexposure prophylaxis benefit of administering a second dose of vaccine to single-dose vaccine recipients exposed to varicella. Administration of an age-appropriate second dose (provided at least 3 months have elapsed since last vaccine dose) could be considered in this situation to bring the patient's immunizations up to date and to possibly provide improved postexposure prophylaxis. In an outbreak setting, a second vaccine dose is recommended for both school-aged and preschool-aged children who have only



**Table 227-1** Suggested Intervals Between Immune Globulin or Blood Product Administration and Varicella Vaccine Administration

PRODUCT	ROUTE	DOSE		
		U OR mL	mg IGG/kg	INTERVAL, MO <sup>a</sup>
Tetanus prophylaxis (TIG)	IM	250 U	10	3
Hepatitis A prophylaxis (IG)	IM	0.02 or 0.06 mL/kg	3.3 or 10	3
Hepatitis B prophylaxis (HBIG)	IM	0.06 mL/kg	10	3
Rabies prophylaxis (RIG)	IM	20 IU/kg	22	4
Varicella prophylaxis (VariZIG)	IM	125 U/10 kg	20–40	5
Measles prophylaxis (IG)				
• Standard	IM	0.25 mL/kg	40	5
• Immunocompromised host	IM	0.50 mL/kg	80	6
RSV prophylaxis (palivizumab <sup>b</sup> )	IM	—	15 mg/kg	None
CMV immune globulin	IV	3 mL/kg	150	6
Blood transfusion				
• Washed RBCs	IV	10 mL/kg	Negligible	0
• RBCs, adenine-saline added	IV	10 mL/kg	10	3
• Packed RBCs	IV	10 mL/kg	20–60	5
• Whole blood	IV	10 mL/kg	80–100	6
• Plasma or platelet products	IV	10 mL/kg	160	7
Replacement (or therapy) of immune deficiencies (IGIV)	IV	—	300–400	8
Therapy for ITP (IGIV)	IV	—	400	8
Therapy for ITP	IV	—	1,000	10
Therapy for ITP or Kawasaki disease (IGIV)	IV	—	1,600–2,000	11

CMV, cytomegalovirus; HBIG, hepatitis B immune globulin; IG, immune globulin; IgG, immunoglobulin G; IGIV, immune globulin intravenous; IM, intramuscular; ITP, immune (formerly idiopathic) thrombocytopenia purpura; IV, intravenous; RBCs, red blood cells; RIG, rabies immune globulin; RSV, respiratory syncytial virus; TIG, tetanus immune globulin; VariZIG, varicella-zoster immune globulin.

<sup>a</sup>These intervals should provide sufficient time for decreases in passive antibodies in all children to allow for an adequate response to varicella vaccine. Physicians should not assume that children are protected fully against varicella during these intervals. Additional doses of IG or varicella vaccine may be indicated after exposure to vaccine (see text).

<sup>b</sup>Monoclonal antibodies, such as palivizumab, do not interfere with the immune response to vaccines.

received a prior single vaccine dose, provided at least 3 months have elapsed since last vaccine dose. If more than 5 days have passed since exposure in healthy, susceptible individuals, and the patient does not develop varicella, the vaccine should be offered to prevent future varicella disease. If vaccination is contraindicated in a healthy individual, no other prophylaxis is recommended, although acyclovir or valacyclovir may be considered as postexposure prophylaxis in healthy adults that cannot receive the vaccine.

In certain high-risk individuals with whom vaccination is not possible, VariZIG, a lyophilized purified human immune globulin preparation with high anti-varicella antibody titer, should be administered after exposure to individuals with chickenpox. VariZIG has been FDA approved for use in postexposure prophylaxis. VariZIG prophylaxis is recommended ideally within 96 hours but up to 10 days after exposure in individuals without evidence of immunity and who are at risk for severe disease (Figure 227-1). Of note, stem cell transplant recipients should be considered nonimmune for postexposure prophylaxis purposes regardless of pretransplantation immunity of donor or recipient.

VariZIG is produced by Cangene Corporation (Winnipeg, Canada) and distributed by FFF Enterprises (Temecula, CA). Physicians may contact FFF

Enterprises by calling 800-843-7477, 24 hours a day to obtain VariZIG. The product can usually be delivered to the institution within 24 hours. It is available in 125-U vials, and recommended dosing is 125 U/10 kg given intramuscularly, with a minimum dose of 125 U and maximum dose of 625 U. The duration of VariZIG protection is unknown, but it should last 3 weeks (1 half-life of immunoglobulin G). Individuals re-exposed to varicella 3 weeks or longer after administration of VariZIG should receive a repeat dose.

If VariZIG cannot be obtained, IGIV at a dose of 400 mg/kg may be used. IGIV contains anti-varicella antibodies, but the titer varies from lot to lot and is not tested routinely. Individuals receiving regular high-dose IGIV infusions ( $\geq 400$  mg/kg) are likely to be protected if the most recent dose of IGIV was within 3 weeks of exposure.

If VariZIG cannot be obtained, and IGIV is unavailable, a 7-day course of oral acyclovir at a dose of 20 mg/kg per dose administered 4 times a day, with a maximum daily dose of 3,200 mg, or oral valacyclovir (if  $>3$  months of age) at a dose of 20 mg/kg per dose administered 3 times per day with a maximum dose of 3,000 mg beginning 7 to 10 days after exposure can be used in high-risk outpatients beyond the newborn period to prevent or attenuate chickenpox; however, this use of acyclovir or valacyclovir is not approved by

the FDA; it is based on small studies, and its potential effect on the immune response has not been fully evaluated.

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### WHEN TO REFER

- Chickenpox in an immunodeficient child
- Chickenpox in a pregnant woman
- Disseminated varicella
- Ocular involvement

### WHEN TO ADMIT

- Varicella pneumonia, or other visceral organ involvement
- Moderately to severely immunosuppressed host
- Moderate to severe bacterial complications
- Chickenpox in a neonate
- Encephalopathy
- Hemorrhagic varicella
- Ocular involvement

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Chickenpox Vaccine Information Statements* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/vaccines/hcp/vis/vis-statements/varicella.html](http://www.cdc.gov/vaccines/hcp/vis/vis-statements/varicella.html))
- *Varicella (Chickenpox)* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/vaccine-preventable-diseases/Pages/Varicella-ChickenPox.aspx](http://www.healthychildren.org/English/health-issues/vaccine-preventable-diseases/Pages/Varicella-ChickenPox.aspx))
- *Varicella (Chickenpox) Vaccination* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/vaccines/vpd-vac/varicella/default.htm](http://www.cdc.gov/vaccines/vpd-vac/varicella/default.htm))

#### Medical Decision Support

- *Chickenpox (Varicella)* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/chickenpox/hcp/index.html](http://www.cdc.gov/chickenpox/hcp/index.html))
- *Collecting Specimens for Varicella Zoster Virus (VZV) Testing* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/chickenpox/lab-testing/collecting-specimens.html](http://www.cdc.gov/chickenpox/lab-testing/collecting-specimens.html))

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### Chapter 228

## CHRONIC FATIGUE SYNDROME

Leonard R. Krilov, MD

Chronic fatigue syndrome (CFS) describes an illness characterized by prolonged periods of debilitating fatigue for which no definitive cause is known. The Centers for Disease Control and Prevention (CDC) have created a working definition of CFS that includes severe fatigue of longer than 6 months' duration limiting activity to less than 50% of premorbid function in association with multiple other symptoms, including new or more intense headaches, decreased ability to focus, recurrent sore throats, sensation of tender cervical lymph nodes, low-grade temperature elevations, myalgias, arthralgias, postexertional fatigue lasting more than 24 hours, and sleep disturbances (hypersensitivity or insomnia) (see Box 228-1); however, CFS is not a well-defined clinical entity. No specific

### BOX 228-1 Centers for Disease Control and Prevention Definition of Chronic Fatigue Syndrome

The following symptoms should have persisted or recurred during 6 or more consecutive months of illness and cannot have first appeared before the fatigue:

1. The individual has had severe chronic fatigue for 6 or more consecutive months that is not caused by ongoing exertion or other medical conditions associated with fatigue (these other conditions need to be ruled out by a doctor after diagnostic tests have been conducted).
2. The fatigue significantly interferes with daily activities and work.
3. The individual concurrently has 4 or more of the following 8 symptoms:
  - A. Postexertion malaise lasting more than 24 hours
  - B. Unrefreshing sleep
  - C. Significant impairment of short-term memory or concentration
  - D. Muscle pain
  - E. Pain in the joints without swelling or redness
  - F. Headaches of a new type, pattern, or severity
  - G. Tender lymph nodes in the neck or armpit
  - H. Sore throat that is frequent or recurring

causative agent or agents and no characteristic pathophysiologic models have been identified for CFS. Debate centers on the contributions of infectious and other medical conditions and immunologic and psychological factors to the clinical manifestations of CFS. All these factors likely interact to produce CFS, albeit to differing degrees in each individual.

A recent Institute of Medicine task force developed a set of criteria and suggested a new name—systemic exertion intolerance disease—to replace CFS in an attempt to better characterize this symptom complex.

Historically, a variety of syndromes that seem similar to CFS have been described. These conditions include chronic infectious mononucleosis, total allergy syndrome, chronic candidiasis, hypoglycemia, neurasthenia, myalgic encephalomyelitis, postviral syndrome, and fibromyalgia. In 2009, a newly discovered retrovirus, xenotropic murine leukemia virus-related retrovirus (XMLV), was proposed as a possible cause of CFS, but subsequent studies failed to confirm these observations, including 2 reports using samples from the patients reported in the original studies. It is thought that the polymerase chain reaction primers in the original studies were contaminated, and XMLV has been discarded as a possible cause of CFS.

Despite the lack of association of ongoing Epstein-Barr virus infection with CFS, Katz and colleagues observed that infectious mononucleosis may be an antecedent risk factor for development of CFS in adolescents.

Cases of CFS have been reported to occur both sporadically and epidemically. Overall, the CDC estimates a prevalence rate of approximately 200 cases of CFS-like illness per 100,000 adults older than 18 years in the United States. Dobbins and colleagues extracted data regarding adolescents from 3 CDC studies of fatiguing illness and reported a prevalence of CFS-like illness of approximately 20 per 100,000.

Most reported cases of CFS have occurred in white women with a median age of 35 to 40 years and from upper socioeconomic groups, although adolescents who have the diagnosis also have been described. Minorities, the indigent, and people living in developing countries are strikingly underrepresented in reports of CFS. Whether this shortage reflects a bias in patient selection or predisposing factors for development of CFS remains to be determined.

## CLINICAL MANIFESTATIONS

The primary manifestation of CFS is severe fatigue longer than 6 months in duration in association with substantial reduction in occupational, school, social, or recreational activities. Associated symptoms frequently include sore throat, low-grade fever (oral temperatures of 37.5° to 38.6° C), painful lymph nodes, unexplained generalized weakness, myalgias or arthralgias (or both), prolonged fatigue after exercise, headaches, difficulty concentrating or memory loss, and sleep disturbances (hypersomnia or insomnia). Most patients describe a sudden onset of the syndrome with an initial mononucleosis or influenza-like illness, although, in some cases, a more gradual onset is related. Many patients also describe a history of atopy or multiple allergies, or both.

The initial history should include questions about the nature and duration of symptoms, as well as possible exposures to or contacts with ill persons or risk factors, that might suggest an alternative diagnosis. Personal and social history to assess family dynamics, prior level of functioning, response to illness, family history of psychiatric illness, and psychological or family marital problems may be helpful.

The physical examination may reveal abnormalities, including mild inflammation of the pharynx, cervical or axillary lymphadenopathy, or low-grade temperature elevation in up to 50% of cases. However, the primary goal of the physical examination is to eliminate other causes for the patient's symptoms. Significantly elevated temperatures, enlarged lymph nodes (>2 cm), weight loss of more than 10% of body mass index without dieting, or focal neurologic abnormalities should suggest an alternative diagnosis. The differential diagnoses of illnesses associated with extensive fatigue are listed in Box 228-2.

## PSYCHOLOGICAL FACTORS

Physicians and investigators have noted a relationship of CFS to depressive symptoms, frank depression, and a family history of depression. Conceptually, depression may be both part of the cause of CFS and a reaction to having CFS. Family dynamics and perception (vs confirmation) of severity of illness may contribute to the development of CFS in adolescents. School-avoidance behaviors related to expectations for high academic performance compared with the teenager's abilities have been noted frequently. In many families, overprotection and overindulgence of the child have been observed, often associated with difficulty in

### BOX 228-2 Differential Diagnosis of a Patient Who Is Chronically Fatigued

- Malignancy
- Autoimmune disease
- Localized infection (eg, occult abscess)
- Chronic or subacute infection (eg, endocarditis, tuberculosis)
- Human immunodeficiency virus infection
- Fungal disease (eg, histoplasmosis, coccidioidomycosis, blastomycosis)
- Parasitic disease (eg, toxoplasmosis)
- Chronic inflammatory disease (eg, sarcoidosis, Wegener granulomatosis)
- Endocrine disease (eg, hypothyroidism, Addison disease, diabetes)
- Neuromuscular disease (eg, myasthenia gravis, multiple sclerosis)
- Drug dependency
- Side effects of chronic medications or other toxic agents (eg, chemical solvent, heavy metal, pesticide)
- Psychiatric disorder (eg, depression)
- Sleep disorders or sleep deprivation

mother-teen separation. A recent analysis of adolescents who have CFS compared with age-matched adolescent survivors of childhood cancer and a healthy control group showed that the CFS group had higher scores on measures of somatic complaints, depression, internalizing symptoms, and feeling different from others.

The manifestations of CFS can be considered in this framework as a conversion reaction in which an infection or other stressor serves as a model for persistent symptoms that offer the individual a mechanism by which to maintain an overprotective environment or to avoid going to school (see Chapter 237, Conversion Reactions and Hysteria).

### LABORATORY DIAGNOSIS

No specific laboratory tests exist by which to diagnose CFS. As with the physical examination, the primary aim of laboratory evaluations is to eliminate other conditions that may be responsible for the patient's symptoms. A suggested battery of screening tests might include a complete blood count and differential; measurement of the erythrocyte sedimentation rate, serum electrolytes, creatinine, blood urea nitrogen, and glucose; liver enzymes and function tests; thyroid function tests; tuberculin skin test with controls; measurement of alkaline phosphatase and human immunodeficiency virus (HIV) antibody; and possibly chest radiograph. Additional tests may be indicated based on history and physical examination findings. Although potential immunologic abnormalities, including altered lymphocyte subsets, qualitative defects in natural killer cell activity, hypogammaglobulinemia or hypergammaglobulinemia, elevated titers to herpes viruses (eg, Epstein-Barr virus, human herpesvirus type 6), abnormal lymphokine levels, and decreased lymphocyte proliferation responses, have been described in patients who have CFS, they have not been observed consistently in different groups of patients. Additionally, the magnitude of immunologic abnormalities detected in patients who have CFS has been small compared with those who have classic immunodeficiencies; the degree of immune aberrations does not correlate with the severity of symptoms, and opportunistic infections do not occur in CFS.

An association between low blood pressure (postural orthostatic tachycardia syndrome [POTS]) and CFS has been suggested. The role of POTS in CFS is intriguing. Assessment of upright heart rate in CFS patients with chronic orthostatic intolerance to define POTS may be helpful in a subset of CFS patients in whom dizziness is a significant complaint. Sustained excess tachycardia without hypotension and in the presence of concurrent symptoms during testing define POTS. Whether all patients with CFS should be evaluated for POTS is currently unknown.

Although of uncertain significance, increased white matter on T2-weighted magnetic resonance imaging scans suggestive of possible infiltration of the perivascular spaces, focal demyelination, or disease of the small blood vessels of the cerebral white matter has been reported in a number of patients with CFS. Presently, routine magnetic resonance imaging is not indicated in the evaluation of a patient being evaluated for CFS.

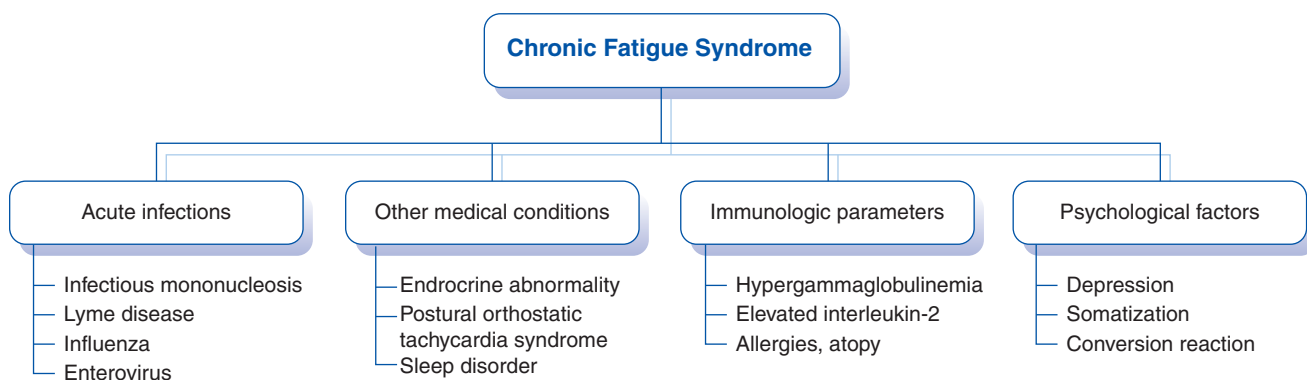
Other investigators have proposed hormonal factors, such as depressed cortisol response, as contributing to the signs and symptoms of CFS.

### PROPOSED MODEL OF PATHOGENESIS

The exact definition of a case of CFS is difficult in that few objective findings are found in these individuals, and their most severe symptoms are difficult to quantify. To date, no specific infectious cause for CFS has been defined, and a single infectious agent is not likely responsible. A reasonable suggestion would be that it is the interaction of multiple factors that results in the development of CFS (Figure 228-1). The relative importance of each of the factors probably varies from individual to individual.

### THERAPY

No specific therapy for CFS has been proved to be effective. However, management aimed at alleviating the patient's symptoms may help. If POTS is documented, then dietary (eg, increased fluid and salt intake) or pharmacologic management, or both, with drugs such as fludrocortisone, propranolol, or midodrine may be beneficial. However, treatment of POTS has been only of partial benefit in relieving CFS symptoms. Similarly, sleep studies and therapies may offer some symptomatic relief for some people with CFS.



**Figure 228-1** Pathogenesis of chronic fatigue syndrome.



An approach to the management of CFS is outlined in Box 228-3. The primary goals of this treatment are to provide counseling and symptomatic relief for depression, sleep disorders, and musculoskeletal pains; to offer emotional support with involvement of a social worker, psychologist, or psychiatrist, as needed; to identify and eliminate *secondary gain* from continuing to contribute to the illness; and to devise programs with the patient to increase school (or work) attendance and exercise capability gradually. Periodic physical examinations for possible other conditions are also important. Family therapy often helps the parents manage these issues and addresses the role of family dynamics in the evolution of a patient's symptoms. A team approach with coordination of services to avoid *doctor shopping* and fad therapy is critical to the successful management of the patient who has CFS.

Some of the unproved fad therapies described are megavitamin treatment, immune modifiers (eg, Amplegen, thymic extract, interleukin-2), magnesium sulfate, liver extract injections, anti-*Candida* diets, colonic irrigation, and removal of dental fillings. Immunoglobulin injections have been reported to be beneficial in a study of patients with CFS, although 2 subsequent studies failed to confirm this observation.

## PROGNOSIS AND FUTURE PROSPECTS

Despite the vagaries associated with the diagnosis of CFS and differences in each case, long-term follow-up suggests that most individuals report improvement or resolution of symptoms over a 2- to 3-year period. Few patients report progressive symptoms, although symptoms may wax and wane in severity. With better definition of the nature of the neurologic, cardiovascular, endocrinologic, and immunologic alterations in

CFS, additional therapeutic approaches may become available.

### WHEN TO REFER

- To resolve issues relating to possibility of ongoing infection or inflammation that may be causing the patient's symptoms.
- Given the often extensive and varied complaints of patients with CFS, multiple specialists may become involved and multiple laboratory tests may be ordered. A coordinated team approach to avoid redundant or unnecessary testing can be beneficial.
- To provide an increased level of supportive care or counseling than can be provided in the office setting, especially if the individual is not able to attend school or participate in normal activities.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Chronic Fatigue Syndrome* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/cfs](http://www.cdc.gov/cfs))
- *Patient Resources* (Web page), Solve ME/CFS Initiative ([solvecfs.org/mecfs-resources/patient-resources](http://solvecfs.org/mecfs-resources/patient-resources))

### Medical Decision Support

- *Chronic Fatigue Syndrome* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/cfs/hcp.html](http://www.cdc.gov/cfs/hcp.html))

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### BOX 228-3 Management of Pediatric Patients Who Are Chronically Fatigued

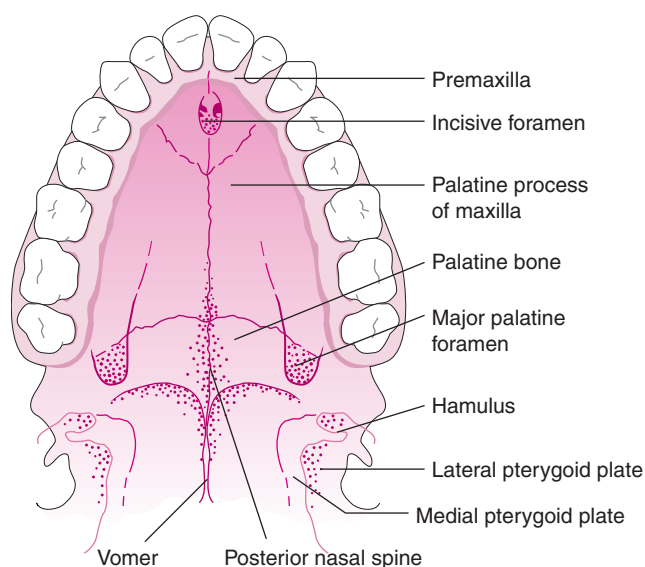
- Confirm the diagnosis of chronic fatigue syndrome and acknowledge the symptoms as real.
- Explain and explore the potential relationship to psychological symptoms.
- Stress a coordinated approach; minimize *doctor shopping*, unnecessary testing, and unconventional therapies.
- Consider tilt-table testing or cardiologic evaluation, or both, if dizziness is a prominent complaint.
- Use stress-coping skills: modify lifestyles, decrease stress, develop a realistic schedule including working with school (gradual return to classes, home tutoring, neuropsychometric testing), and develop a graduated exercise program.
- Use cognitive-behavioral approaches: pay attention to sleep patterns and nutrition; increase activity gradually.
- Provide psychological support: provide individual therapy and family therapy; decrease secondary gain.
- Maintain follow-up: monitor physical symptoms and psychological issues; provide ongoing guidance and continued reassurance.

## Chapter 229

## CLEFT LIP AND CLEFT PALATE

Arlene A. Rozzelle, MD; Jugpal S. Arneja, MD, MBA

Clefts of the lip and palate are complicated, multifaceted problems that provide an immense challenge for treating specialists. Clefting may occur in isolation or may have several associated anomalies that represent a syndrome. As such, these problems are best addressed in a multidisciplinary team-oriented setting to maximize the child's final functional and aesthetic



**Figure 229-1** Normal palatal anatomy. (From Millard DR Jr. *Cleft Craft: The Evolution of Its Surgery*. Boston, MA: Little, Brown & Company; 1980:19.)

outcome. Aside from surgical specialists (plastic surgeons, otolaryngologists, oral and maxillofacial surgeons), cleft team members include medical specialists (pediatricians, geneticists, child psychiatrists), dental specialists (orthodontists, prosthodontists, pediatric dentists), speech and hearing specialists (speech pathologists, audiologists), and nursing specialists (pediatric or cleft-trained nurses). Results are often based on the severity of the problem, the timing of nonsurgical and surgical intervention, the experience and training of the involved specialists, and patient adherence, given that treatment is initiated at birth and is often not completed until well into late adolescence. Despite the multitude of advancements in cleft care, questions remain regarding optimizing outcomes of facial growth, dental reconstruction, speech, facial form, and psychological well-being. This chapter outlines the theoretical basics and practical approach to managing these challenging, although ultimately rewarding, patients.

## DEFINITIONS

The primary palate consists of all structures anterior to the incisive foramen (lip and alveolus), whereas the secondary palate includes all structures posterior to the incisive foramen (hard palate and soft palate). Figure 229-1 illustrates the pertinent cleft-related anatomy of the primary and secondary palate. The development of a comprehensive and completely accepted classification method for cleft anomalies has been elusive. Most classification systems are too basic, too complex, or not comprehensive enough to include all possible clinical presentations.

An early classification system divided clefts into 4 groups: (1) soft palate clefts alone, (2) clefts of both the hard and soft palate, (3) complete unilateral clefts of

the lip and palate, and (4) complete bilateral clefts of the lip and palate. In 1962, the American Association for Cleft Palate Rehabilitation proposed a complicated classification system that has not found universal acceptance. In 1971, a simple yet comprehensive diagrammatic representation of cleft classification, termed the *striped Y*, was introduced; this classification was later modified to include nasal and pharyngeal deformities. This classification system has found acceptance at numerous cleft palate centers. In 1989, a palindromic method of classifying clefts was described; the letters LAHSHAL represent the lip (L), alveolus (A), hard palate (H), and soft palate (S). In addition, a numerical recording system was proposed for the classification of clefts, termed the *RPL system*. Invariably, the method that is often used to classify and describe clefts among physicians is simply a description of the anatomic severity of the cleft of the primary or secondary palate and whether the cleft is incomplete or complete (Figure 229-2). On occasion, a complete cleft of the primary palate has a degree of skin bridging the superior aspect of the lip, termed a *Simonart band*.

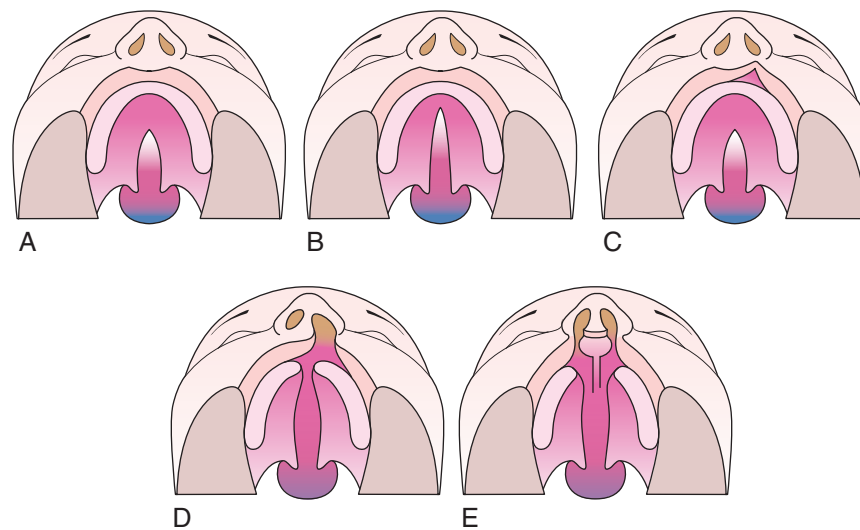
## EMBRYOLOGY

Normal facial embryonic development occurs between weeks 3 and 12 of gestation with the fusion of 5 facial prominences (Figure 229-3). Specifically, palate development initiates at the end of week 5 and is completed by the end of week 12. The primary palate is derived from the fusion of the medial nasal prominences with the maxillary prominence, whereas the secondary palate is derived from the fusion of the lateral palatine processes and the nasal septum, with closure extending from the incisive foramen posteriorly. Fusion is completed by the end of week 12 with formation of the lip, alveolus, hard palate, soft palate, and uvula.

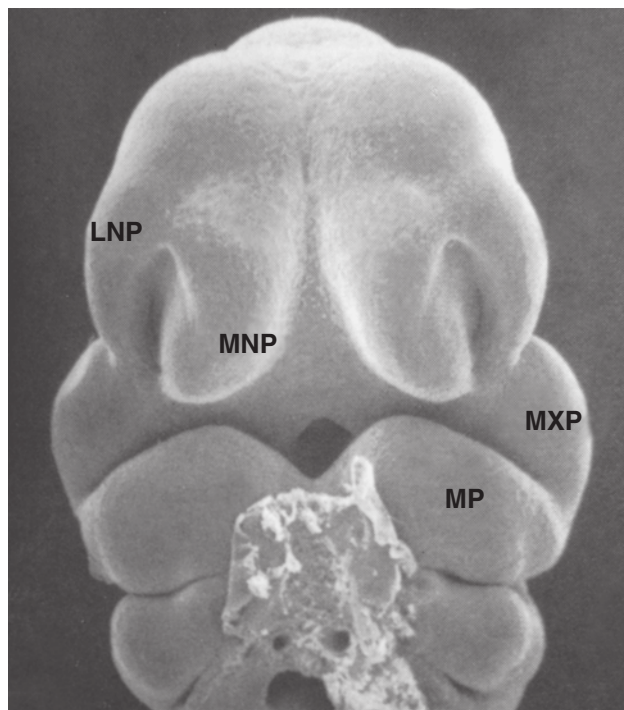
Failure of penetration or fusion of the mesenchymal masses of the 5 facial prominences forms the embryologic basis of cleft formation. Isolated failure of fusion of the medial nasal prominence with the maxillary prominence on 1 side results in a unilateral cleft lip, whereas a bilateral cleft lip results from failure of both medial nasal prominences to fuse with the maxillary prominence. Palatal clefts result from incomplete fusion of the lateral palatine processes with the nasal septum at any stage of development. As the secondary palate fuses in an anterior-to-posterior direction, soft palate clefts that occur are much more common because the fusion of the soft palate follows hard palate closure. The most accepted theory as to why secondary palatal clefts occur is delayed elevation of the palatal shelves in a vertical-to-horizontal direction.

## INCIDENCE

Clefting is the second most common congenital anomaly, after clubfoot, with an overall historical incidence of cleft lip with or without cleft palate of approximately 1 in 700 new births and an overall incidence of isolated cleft palate of approximately 1 in 1,000 new births. A 2006 study found a more accurate incidence of clefting to be 10.54 per 10,000 births, or 1 per 948. Racial differences are seen in incidence,



**Figure 229-2** Anatomic classification of cleft lip and palate. A, Incomplete cleft secondary palate. B, Complete cleft secondary palate. C, Left incomplete cleft primary palate and incomplete cleft secondary palate. D, Left complete cleft primary palate and complete cleft secondary palate. E, Bilateral complete cleft primary palate and complete cleft secondary palate.



**Figure 229-3** Embryologic development of the primary palate. LNP, lateral nasal process; MNP, medial nasal process; MXP, maxillary process; MP, mandibular process. (From Bronsky PT. Effects of hypoxia on facial prominence development in CL/fr mice. M.S. Thesis, University of North Carolina, 1985.)

with children of Asian descent having a higher incidence (2.1 in 1,000) and those of African descent having a lower incidence (0.41 in 1,000) compared with white children (1.3 in 1,000). Cleft lip and palate are more common in boys than girls (2:1); isolated cleft

palate occurs twice as often in girls as in boys, likely the result of later palatal closure in girls. Clefts are more common on the left side and theorized to be related to earlier closure of the right side, making the left side more susceptible to insult in utero. Unilateral cleft lips occur much more commonly than bilateral cleft lips (4:1). The relative frequency of orofacial clefting between cleft lip to cleft palate and cleft lip and palate is 1:1.2:2.5.

### Genetics and Risk Factors

Clefting may be in isolation or associated with other conditions that meet the criteria of a syndrome. More than 300 syndromes are associated with clefting; the more common syndromes include van der Woude syndrome, velocardiofacial syndrome, Pierre Robin sequence, Goldenhar syndrome, Treacher Collins syndrome, Down syndrome, and Stickler syndrome. Cleft lip with or without cleft palate has been suggested to be etiologically different than isolated cleft palate. Syndromes are associated with approximately 29% of orofacial clefts, with an isolated cleft of the secondary palate the most common syndromic presentation.

Most clefts are nonsyndromic and generally postulated to be multifactorial in nature or as a result of changes at a major single-gene locus. Over the past 10 years, increased study has found associations between craniofacial clefting and genetic disruptions in Sonic Hedgehog (ectodermal development), TGF- $\alpha$  (extracellular matrix protein development), TGF- $\beta_3$  (midline epithelial degradation), IRF6 (transcription), and others related to allelic association and linkage MSX1, retinoic acid receptor- $\alpha$ , homeobox genes, and B-cell leukemia or lymphoma.

Risk factors for the development of clefting include family history and environmental agent exposure. Several teratogens have been found to increase the rate of clefting during the first trimester of pregnancy. Clefting has been produced in animal models with



**Table 229-1****Familial Risks for Nonsyndromic Cleft Lip and Palate**

<b>FAMILY HISTORY</b>	<b>CLEFT LIP WITH OR WITHOUT CLEFT PALATE</b>	<b>CLEFT PALATE</b>
No family history of cleft lip or cleft palate	0.1%	0.04%
Unaffected parents with 1 previously affected child	4%	2%
Unaffected parents with 2 previously affected children	9%	1%
One affected parent	4%	6%
One affected parent and 1 previously affected child	17%	15%

From Kirschner RE, LaRossa D. Cleft lip and palate. *Otolaryngol Clin North Am*. 2000;33(6):1191–1215, v–vi. Copyright © 2000, Elsevier, with permission.

exposure to several agents, including corticosteroids, ethanol, ionizing radiation, phenytoin, isotretinoin, diazepam, and methotrexate. Many of these agents have been shown to increase the risk for clefting in vivo as well; in addition, exposures to caffeine and tobacco are theorized to also increase the risk for clefting. Finally, infections, including rubella and toxoplasmosis, in the first trimester of pregnancy have also been implicated in the development of clefting. Many of these agents and exposures may act in unison in children who are biologically and genetically susceptible. A family history of clefting is a risk factor for future cleft occurrences. Table 229-1 characterizes the risk for clefting to future offspring for nonsyndromic cleft lip and palate, based on the number of parents with clefts and the number of siblings with clefts. Interestingly, although folic acid supplementation has been shown to reduce neural tube defects, there was no clear advantage to folic acid supplementation for the prevention of facial clefting until recently. Based on a recent Norwegian study, it is now suggested that folic acid supplementation of 400 mcg before conception reduces the risk for isolated cleft lip and/or cleft palate by about one-third.

### Prenatal Evaluation

Increasingly, a diagnosis of cleft lip or cleft palate can be reliably established by prenatal ultrasound, with cleft lip often easier to diagnose than cleft palate; transvaginal ultrasound can reliably detect a cleft lip by 13 to 16 weeks of gestation. Clefts of the secondary palate can be diagnosed at 19 weeks of gestation using real-time magnetic resonance imaging. Although

these techniques offer numerous advantages to the parents, in certain societies, they may result in pregnancy termination, raising important ethical concerns. Screening for other birth defects that are associated with or in isolation from clefting is now performed on a routine basis.

### MANAGEMENT

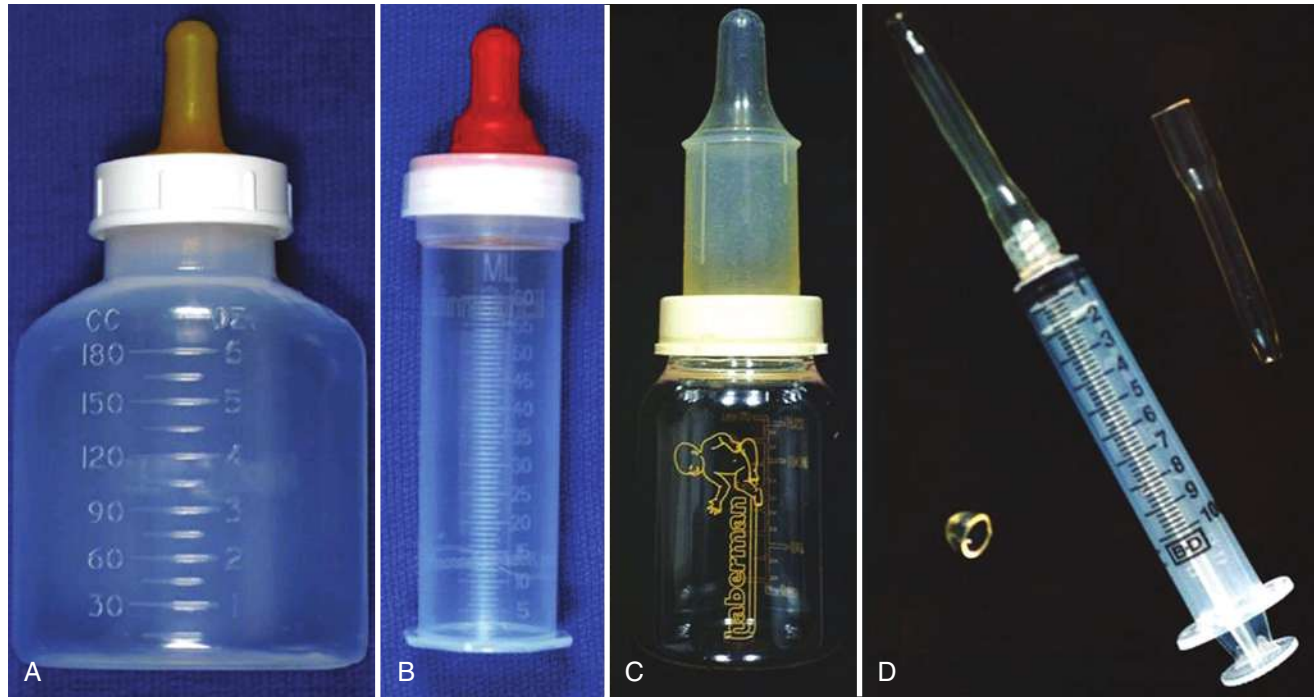
Of primary concern in the newborn with a cleft are airway stability and feeding optimization. Additionally, at this newborn time period, a general medical evaluation to rule out any associated conditions (ie, cardiac, hypocalcemia, other midline associations such as hypospadias) or syndromes is performed. Syndromic association is more likely found with an isolated cleft palate. Specifically, syndromes that are most commonly associated with facial clefting include velocardiofacial syndrome, Pierre Robin sequence, Stickler syndrome, and van der Woude syndrome. For suspicion of a syndromic association, consultation by a geneticist is recommended.

After these important issues are addressed, the remainder of the initial management plan in the first 3 to 4 months of age includes audiologic evaluation, ear-nose-throat evaluation for middle ear abnormalities, and possible orthodontic evaluation for the use of presurgical orthopedics. Surgical management follows with lip repair at 3 to 4 months and palate repair at about 1 year. Speech evaluation and therapy with or without possible surgical management of velopharyngeal insufficiency are performed in children between 2 and 4 years of age. In late childhood and during the teen years, alveolar bone grafting, lip and nose revisions, orthodontics, and orthognathic surgery follow on an as-needed basis. Care is usually coordinated through a multidisciplinary cleft team (plastic surgeon, speech therapist, audiologist, otolaryngologist, oral surgeon, dentist, orthodontist, nurse, and social worker or psychologist) following the guidelines of the American Cleft Palate-Craniofacial Association. Children with clefts are evaluated annually and, in many instances, until their management plan is completed in their late teens or early 20s. The goal of management is to achieve normal function, characterized by normal occlusion, speech, and hearing with as normal growth as possible, as well as optimal form, characterized by normal lip, nose, and facial aesthetics.

### Fetal Surgery

Much consideration has been given to repair of diagnosed cleft lips in utero, given the potential for a scarless repair and the potential for the prevention of many of the dentoalveolar and facial growth abnormalities that follow normal cleft surgery. In scarless fetal wounds, collagen is deposited in an organized, fine reticular pattern, whereas in postnatal scarring, wounds have thick and disorganized collagen matrices. However, as exciting as this procedure may sound, it is a topic of much debate, and enthusiasm should be tempered, given the intrinsic risks for premature labor and death to the mother and fetus. In addition, although an invisible scar is possible to obtain, numerous anatomic elements would remain out of position,





**Figure 229-4** Cleft feeding bottles (from left to right: Mead-Johnson nurser, Pigeon feeder, Haberman feeder, Breck feeder [syringe]).

rendering the residual lip with a potentially unnatural appearance. Currently, fetal cleft surgery is a novel concept, with no current safety and ethical standards available for clinical utility. More important than consideration of fetal surgery, if a diagnosis of cleft lip or palate is made prenatally, is appropriate consultation with specialists, including those in plastic surgery, otolaryngology, genetics, and nursing, to provide council for what is to be expected postnatally.

### Early Management Feeding

The cleft-team nurse is usually the feeding expert and will carefully monitor the nutritional status of the infant to ensure adequate caloric intake. Other feeding specialists may include occupational therapists, lactation consultants, or speech therapists. Neonates with a cleft of the primary palate (lip and alveolar ridge) can usually feed using a regular bottle or breastfeed without significant difficulty. However, infants with a cleft of the secondary palate (hard and soft palate) usually require special bottles that do not require the child to create a suction seal. These special bottles include the Haberman feeder (Medela), the Pigeon nurser (Respi-ronics), and the Mead Johnson nurser. In some cases, the infant may have to be fed with a syringe (Breck feeder) or nasogastric tube. Figure 229-4 illustrates the common cleft palate bottles used.

In addition, an infant with a cleft of the secondary palate is unlikely to be able to breastfeed because of the inability to create adequate suction. If the mother wishes to attempt breastfeeding, then a lactation expert with experience in cleft feeding should be consulted. The infant should be monitored closely by the

pediatrician, cleft-team nurse, and surgeon, with frequent weight checks. Receiving human milk is desirable for the infant, even if by bottle. To this end, supporting the mother is important, which involves a lactation consultant if necessary and providing a hospital-grade breast pump.

Many centers fit their infants with a cleft of the secondary palate with a feeding plate that is custom fabricated by the dentist or orthodontist (Figure 229-5). The feeding plate obturates the hard palate cleft, allowing infants to use their tongues to milk the nipple on the roof of the mouth and to decrease nasal regurgitation and irritation.



**Figure 229-5** Feeding plate.

### Auditory Dysfunction

Children with a cleft of the secondary palate (but not a cleft of the lip and alveolus alone) have a high incidence of middle ear disease, which is thought to be caused by eustachian tube dysfunction. This condition is caused by abnormal muscular orientation, resulting in limited drainage of the middle ear through the eustachian tube and potentially causing conductive hearing loss. These children are monitored closely for middle ear effusion and hearing impairment and are almost universally treated with myringotomy tubes to prevent chronic hearing loss and cholesteatoma, which occurred with great frequency in the past. Even a mild hearing loss of 20 decibels can result in difficulty understanding the spoken word, resulting in speech impairment. Depending on the preference of the otolaryngologist, myringotomy tubes are placed either at the time of the lip repair (about 4 months of age) or at the time of the cleft palate repair (about 9 to 12 months of age).

### Presurgical Orthopedics

Presurgical orthopedics may be passive (nasalveolar molding appliance, Figure 229-6) or active (Latham appliance, Figure 229-7). The goal of each device is to



**Figure 229-6** Nasalveolar molding appliance.



**Figure 229-7** Latham appliance.

align the alveolar segments to facilitate lip repair and improve nasal symmetry. Passive nasalveolar molding has become many centers' standard of practice whereupon the cleft of the lip is narrowed, the cleft nostril is elevated into a more normal configuration, and the alveolar ridges become aligned. Presurgical orthopedics are performed by a pediatric dentist or orthodontist, who monitors the child weekly, progressively modifying the appliance from birth to the time of lip repair as the child grows. Figure 229-8 illustrates the significant nonsurgical correction of the cleft deformity possible before the formal lip and nose repair performed at about 3 to 4 months of age.

### Cleft Lip and Palate Repair

Primary lip repair is usually performed between 3 and 4 months of age, depending on the optimization of feeding and on the results of presurgical orthopedics. The traditional metric regarding the timing of lip repair was the 10-10-10 rule: 10 weeks of age, 10 g of hemoglobin, and weight of 10 pounds. Surgical techniques for lip repair include the rotation advancement repair (Millard), the subunit repair (Fischer), and the less common triangular flap repair (Tennison-Randall). Most cleft surgeons now also perform a primary cleft rhinoplasty at the time of the lip repair, which results in enhanced nasal aesthetic outcomes. In some cases, the alveolus may also be repaired at the time of the lip repair (gingivoperiosteoplasty), providing the framework and potential for ossification of the cleft alveolar arch. Some surgeons perform a lip adhesion in the first few weeks of life, before the formal lip repair, which also molds the alveolar ridges, especially when used with a feeding plate, in preparation for the definitive lip repair several weeks later. Figure 229-9 and Figure 229-10 illustrate respective images of unilateral and bilateral cleft lip and nose repairs.

Cleft palate repair (palatoplasty) is usually performed in children between 9 and 12 months of age, although protocols vary widely at cleft centers. Repairing the palate at about 9 to 12 months of age is desirable to maximize normal speech development; however, repairing too early might result in poor maxillary growth. The 2 most common procedures to repair the soft palate are the Furlow double-opposing Z-plasty and the intraalveolar veloplasty technique of levator muscle reorientation. Various operations used to repair the hard palate include the von Langenbeck and Bardach 2-flap techniques.

### Further Management

#### Cleft Palate Speech

Even after palatoplasty, some children will exhibit velopharyngeal insufficiency or incompetence, also known as cleft palate speech, because of either muscular incoordination (as is frequently the case in velocardiofacial syndrome) or a short palate. Speech is formally assessed by a trained speech therapist in children between 18 and 24 months of age to establish a diagnosis of velopharyngeal insufficiency. A diagnosis of velopharyngeal insufficiency is often treated with speech therapy in conjunction with or without surgical management. Techniques most commonly





**Figure 229-8** A, Cleft lip and nose, pre-nasoalveolar molding. B, Cleft lip and nose, post-nasoalveolar molding.



**Figure 229-9** A, Unilateral cleft lip and nasal deformity, preoperatively. B, Unilateral cleft lip and nasal deformity, postoperatively.



**Figure 229-10** A, Bilateral cleft lip and nasal deformity, preoperatively. B, Bilateral cleft lip and nasal deformity, postoperatively.

performed include a pharyngeal flap or sphincter pharyngoplasty in children between 3 and 6 years of age. These surgical procedures partly obturate the oronasopharynx, resulting in decreased air escape through the nose, necessitating careful monitoring of the airway.

#### **Lip and Nose Revisions**

Intermediate lip and nose revisions are performed as necessary before the child starts school (4 to 5 years of age). A final septorhinoplasty or lip revision, or both, is performed when children have completed growth, generally in the late teen years, at which time the deviated nasal septum and asymmetrical nasal bones or lip (or both) are reconstructed.

#### **Orthodontics/Cleft Alveolus Management**

Orthodontics may be started as early as 3 to 4 years of age and continue through the teen years. The teeth adjacent to the cleft site may be missing, misshapen, or misaligned. In some cases, teeth may need to be passively molded or even extracted. Patients for whom no gingivoperiosteoplasty was performed or for whom gingivoperiosteoplasty failed, orthodontics are applied before secondary alveolar bone grafting. This procedure involves cancellous bone harvested from the iliac crest and grafted into the alveolar cleft site to allow complete ossification of the alveolar arch and to allow preservation of the canine tooth. Some surgeons advocate primary bone grafting in infancy (in which case a small piece of rib is used), although most surgeons perform the alveolar bone graft as needed in children between 7 and 9 years of age during the mixed dentition period.

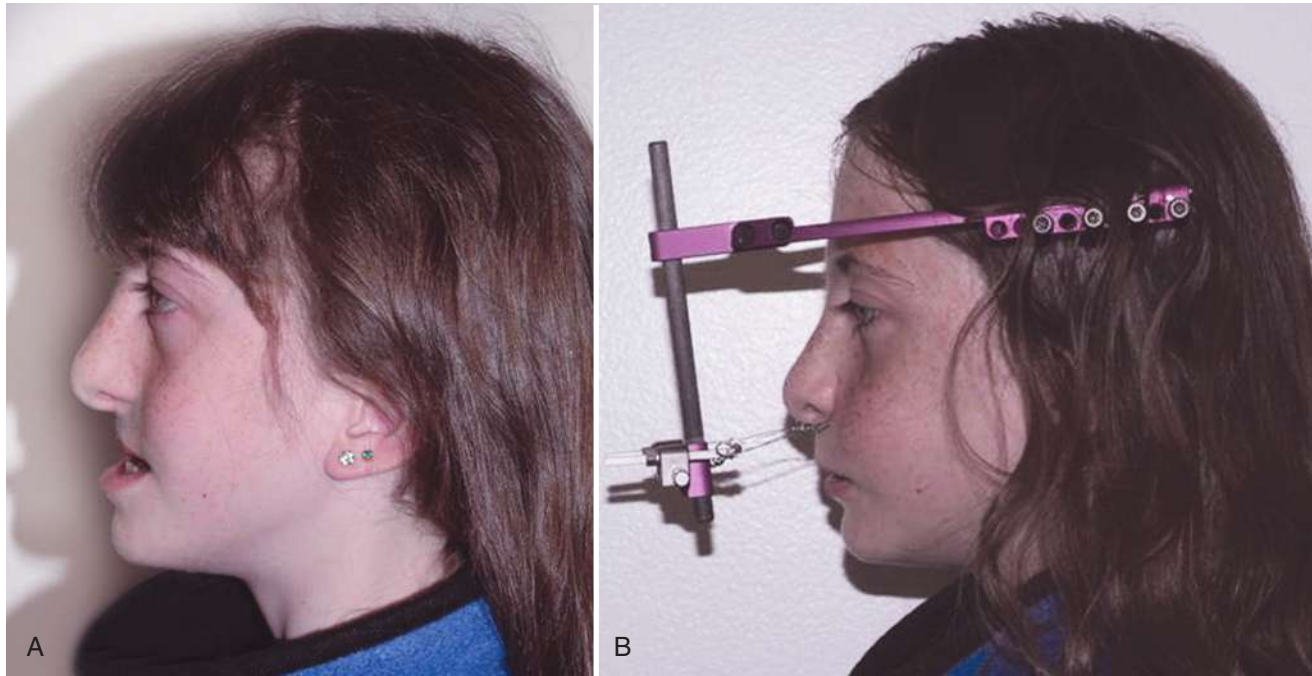
#### **Orthognathic Surgery**

Orthognathic surgery (surgery of the jaws [maxilla, mandible, or both]) is sometimes needed to align the jaws in a normal occlusal relationship. Children with clefts often have maxillary retrusion caused by intrinsic maxillary deficiency or from scarring resulting from surgical repair. A maxillary advancement (LeFort I osteotomy, Figure 229-11) may be performed by distraction osteogenesis in school-aged children or through the more traditional advancement osteotomy with rigid titanium plate fixation in the teenage years. In some cases, the mandible is set back to meet the maxilla. Factors considered in timing orthognathic surgery include upper airway obstruction, sleep apnea, malocclusion, articulation errors, masticatory problems caused by malocclusion, and the psychosocial effects of facial disharmony. Final prosthodontic care, including dental implants or bridges, may be needed for missing or malformed teeth around the cleft site in the late teenage years.

#### **Pierre Robin Sequence**

Pierre Robin sequence consists of micrognathia, glossoptosis, and upper airway obstruction, with or without cleft palate. An infant with a small mandible and upper airway obstruction should be placed in the prone position to allow the tongue to fall forward out of the pharynx and should be kept on a pulse oximeter to assess his or her oxygen saturation. If this conservative measure is not adequate to alleviate the obstruction and maintain oxygen saturations above 94%, then a nasal trumpet may be placed (12 or 14 French). If necessary, the baby may be bag-ventilated with a jaw thrust, nasal trumpet, or oral airway in





**Figure 229-11** A, LeFort I distraction osteogenesis, preoperatively. B, LeFort I distraction osteogenesis, postoperatively.

place and endotracheal or nasotracheal intubation carried out in a controlled environment by the medical staff. If necessary, the tongue may be pulled forward with a piece of gauze between the fingers or, rarely, a towel clamp.

Further workup for these infants includes a 3-dimensional craniofacial computed tomographic scan to evaluate the size of the mandible and the position of the tongue in the pharynx and to rule out choanal atresia and other anomalies, nasoendoscopy to evaluate the position of the tongue in the pharynx with spontaneous respirations, and direct laryngobronchoscopy to rule out other airway anomalies (laryngomalacia or tracheomalacia). Infants with Pierre Robin sequence may also have gastroesophageal reflux disease and should be evaluated and treated as necessary. A polysomnogram may be performed if the child is stable enough. Newborns with Pierre Robin sequence may be unable to feed adequately with a bottle because of their airway obstruction and may have to be fed through a nasogastric tube or syringe until more definitive treatment is carried out.

Indications for surgical intervention include continued upper airway obstruction and oxygen desaturation such that the baby cannot be taken out of the prone position, need for nasal trumpet or intubation, an abnormal apnea-hypopnea index on sleep study, inability to be fed with a bottle, and failure to thrive. The 2 most common surgical interventions include mandibular distraction osteogenesis and tongue-lip adhesion; other operations include subperiosteal release of the floor of the mouth and tracheostomy for the most severe cases.

Mandibular distraction osteogenesis involves lengthening the mandible using either internal or external devices. The mandible is distracted 1.0 to 1.5 mm/day until the mandible is in a normal or over-corrected position and the airway obstruction and feeding difficulties are alleviated. The regenerated bone consolidates within 6 to 8 weeks, and the distractors are removed. Complications include device failure, possible tooth bud damage or inferior alveolar nerve paresis, and poor scar formation. Future growth of the mandible is unknown at this time because distraction osteogenesis does not have sufficient long-term follow-up.

Tongue-lip adhesion involves suturing a flap of muscle and mucosa from the undersurface of the tongue to a similar flap on the inner surface of the lower lip to prevent tongue base prolapse, which results in airway obstruction. Complications include a dehiscence, inability to feed with a bottle, and failure to alleviate the upper airway obstruction. The tongue-lip adhesion is reversed (usually at about 9 to 12 months of age) to allow normal oral-motor coordination for speech and swallowing, after the mandible has grown sufficiently such that the tongue base no longer obstructs the airway. The cleft palate is repaired during the tongue-lip adhesion reversal operation as well.

## CONCLUSION

The child with a cleft should be followed closely from before birth through adulthood by a multidisciplinary team. Successful treatments result in a well-adjusted child with normal facial harmony, dental occlusion, speech, and hearing.

**WHEN TO REFER****Prenatally**

- Refer to plastic surgery, otolaryngology, genetics, and nursing specialists to provide appropriate counsel for what is to be expected postnatally.

**From birth until 3 to 4 months of age**

- Audiologic evaluation
- Ear-nose-throat evaluation for middle ear disease
- Possible orthodontic evaluation for the use of presurgical orthopedics
- Surgical management with cleft lip and nose repair

**9 to 12 months of age**

- Palate repair
- 2 to 8 years of age
- Speech evaluation and therapy with or without surgical management of velopharyngeal insufficiency

**Late childhood and teen years**

- Alveolar bone grafting as needed
- Lip and nose revisions as needed
- Orthodontics and orthognathic surgery as needed

**TOOLS FOR PRACTICE****Medical Decision Support**

- *American Cleft Palate-Craniofacial Association* (Web site), ([www.acpa-cpf.org](http://www.acpa-cpf.org))
- *Cleft Lip and Palate* (Web page), US National Library of Medicine and National Institutes of Health ([www.nlm.nih.gov/medlineplus/cleftlipandpalate.html](http://www.nlm.nih.gov/medlineplus/cleftlipandpalate.html))

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**Chapter 230****COAGULATION DISORDERS**

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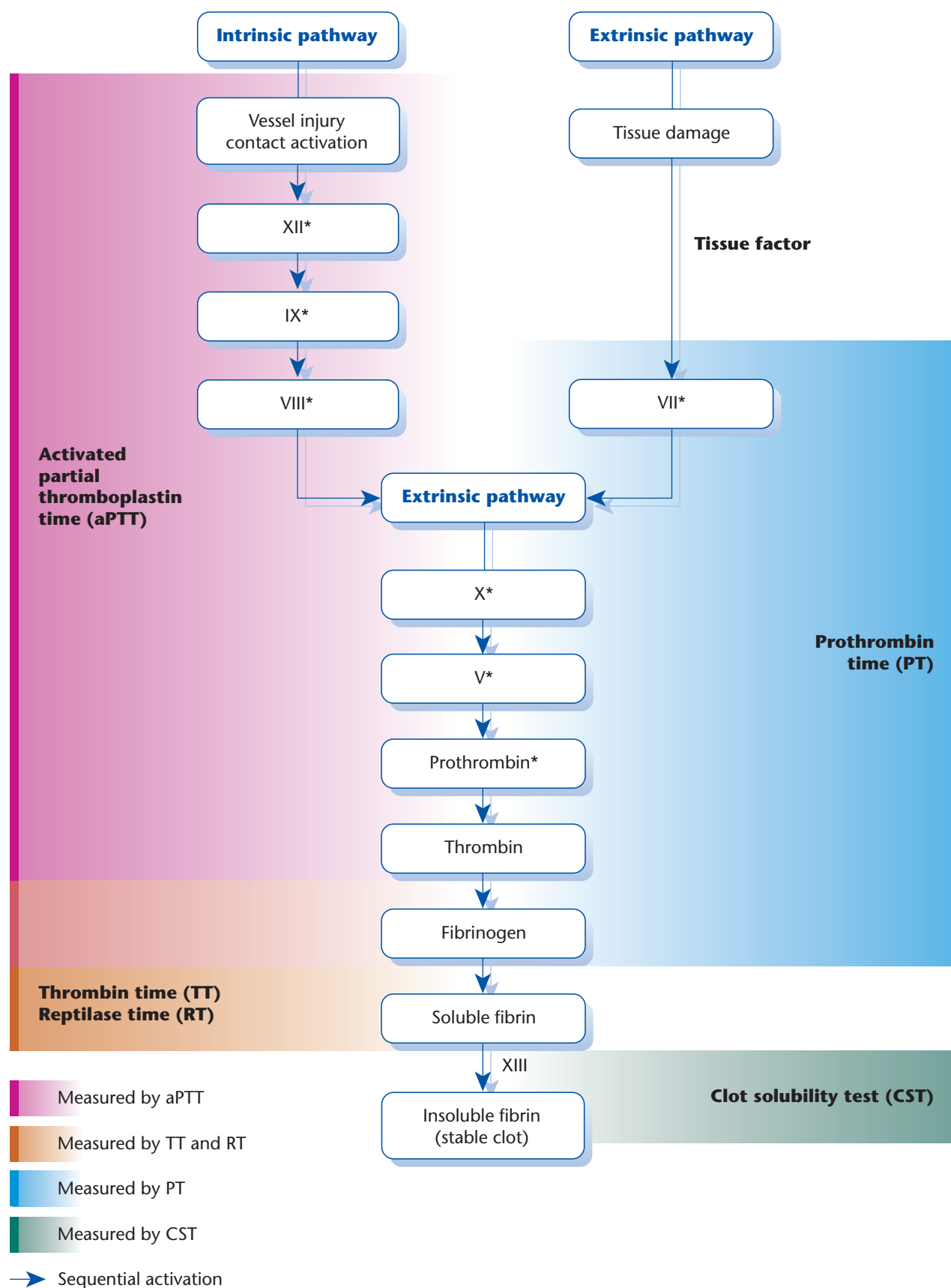
Hemostasis is vital for maintaining the integrity of the high-pressure vascular system. The functions of the coagulation system go far beyond just blood

clotting. The hemostatic system plays an important role in tissue healing, growth, and inflammatory responses. Blood coagulation requires adhesion of platelets to an injured vascular endothelium and aggregation of additional platelets with the formation of a platelet plug. This leads to activation of coagulation factors, resulting in the formation of a fibrin clot that interacts with the platelet aggregate to form a stable hemostatic seal. Coagulation and fibrinolysis are complex physiologic processes that involve interactions between plasma proteins, platelets, leukocytes, phospholipids, and endothelial cells. In mammalian blood, coagulation is intimately linked to and followed by fibrinolysis (the process of fibrin degradation), which is essential for maintenance of patent vascular and circulatory systems. The coagulation factors and the fibrinolytic factors exist in the blood mostly as zymogen precursors that become activated to become enzymes or cofactors and, in turn, activate other clotting factors (Figure 230-1).

**EVALUATION TO DETECT ABNORMALITIES OF HEMOSTASIS**

A pediatrician is often faced with the decision to evaluate patients who have unusual, spontaneous, prolonged, or delayed bleeding. As in any other field of medicine, when a physician is confronted with a child with a possible bleeding disorder, a detailed assessment of the patient's bleeding history and a physical examination guide appropriate laboratory studies. Normal "childhood-pattern bruising" needs to be differentiated from pathologic bruising. The pattern of childhood bruising is often related to the degree of mobility. Bruising in babies who are not able to walk is very uncommon (<1%) and, if present, should be evaluated for coagulation disorders or non-accidental trauma. Bleeding disorders are clinically indistinguishable from abusive bruising in immobile, young children. All immobile, young children with bruising and no reasonable history should be evaluated for the presence of a bleeding disorder and nonaccidental trauma simultaneously. On the other hand, most school-aged children have bruises that are generally small, sustained over bony prominences, and found on the front of the body. A detailed history should also specify the site of bleeding, the age at which bleeding was first noticed, the severity, and the triggers for bleeding. A detailed history of medications and previous hemostatic challenges in the form of bleeding after surgeries and dental procedures should also be sought. The extent to which one investigates bleeding should always be guided by the clinical history. It is also important to take a complete family history as part of the bleeding evaluation, not just a personal history of the patient. Recently, bleeding assessment questionnaires and tools have been developed and are being validated in children.

Additionally, a detailed family history of bleeding should be obtained. Hemophilia A and hemophilia B are X-linked recessive disorders, and a history of a similar bleeding pattern in other male members may suggest their presence. However, the absence of a family history should not deter a physician from



**Figure 230-1** Sequential activation of zymogen cofactors results in conversion of fibrinogen to an insoluble clot. aPTT measures activity of intrinsic and common pathways; PT measures extrinsic and common pathway; TT and RT measure clottable fibrinogen; CST detects very low factor XIII activities. \*Factors become activated and, in turn, propagate the cascade.

further investigations because spontaneous mutations causing hemophilia are seen in 30% to 40% of patients with hemophilia. On the other hand, most other clotting factor deficiencies are inherited in an autosomal-recessive pattern, and a history of consanguinity may be helpful. Von Willebrand disease (vWD) is also inherited, and family members may be affected. The most common type, type 1 vWD, has an autosomal-dominant pattern of inheritance, but may have variable expression in affected members.

A properly drawn blood sample is crucial for proper interpretation of results of coagulation tests. Blood for coagulation assays should be obtained by clean venipuncture without air bubbles and without contamination with tissue fluids. In general, drawing of the sample from indwelling catheter often results in sample contamination with heparin or intravenous fluids and thus spuriously abnormal values. Improper sample collection is one of the most common reasons for falsely elevated clotting times.

The usual screening tests are a complete blood count with review of the morphology of the peripheral blood. An activated partial thromboplastin time (aPTT) and prothrombin time (PT) can also be obtained. Falsely prolonged clotting times may result from an insufficient amount of blood in the specimen tube or difficulty accessing the vein with release of tissue factor and consumption of coagulation factors. The tests are sensitive to clotting factor levels less than 30% to 40% of normal. If the PT or aPTT is prolonged, either repeating the tests or referral to a specialist may be indicated based on the presence and severity of the bleeding symptoms.

### Prothrombin Time

The PT is performed by adding a thromboplastin reagent containing calcium chloride to the citrated plasma sample. The time required for clot formation is recorded using an automated instrument that signals the endpoint, as defined by optical or electromechanical change. The normal (reference) range varies depending on the laboratory (its instrumentation and the lot of thromboplastin), but is generally 10 to 11 seconds. The PT measures the activities of factors I (fibrinogen), II (prothrombin), V, VII, and X. Prolongation of the PT beyond the reference range is generally not seen until the functional level for one of these factors is less than 30% or until fibrinogen is less than 100 mg/dL. An isolated prolongation of the PT may reflect factor VII deficiency. Although rare, the PT can also be prolonged by a circulating inhibitor or by the presence of abnormal fibrinogen molecules or D-dimer fragments in the circulation.

The PT is also quite useful for monitoring the effect of coumarin-type anticoagulants. When the PT is used to monitor a patient on warfarin, the differences in the sensitivities of the thromboplastin need to be taken into account. This has led to the development of a standardized method of expressing the prolongation as an international normalized ratio (PT-INR). The INR is calculated as  $INR = (\text{patient's PT}/\text{control PT})^{\text{International Sensitivity Index (ISI)}}$ . The ISI should be determined for each thromboplastin reagent and instrument.

### Activated Partial Thromboplastin Time

The aPTT is performed by adding a “partial thromboplastin” reagent, which is a source of phospholipids without tissue factor, to the patient’s citrated plasma sample, plus introducing controlled activation of the contact factors (factors XI and XII, prekallikrein, and high-molecular-weight kininogen) by preincubation with a surface-activating reagent (eg, celite, kaolin, silica, or ellagic acid). This mixture is incubated for 2 to 5 minutes before calcium chloride is added, and the time required for clot formation is recorded. As for the PT, automated instruments are generally used. The aPTT measures factors I (fibrinogen), II (prothrombin), V, VIII, IX, X, XI, and XII; prekallikrein; and high-molecular-weight kininogen. Deficiency of any of the latter 3 factors can result in a markedly prolonged aPTT in the absence of clinically significant bleeding. Isolated prolongation of the aPTT in a patient with clinical bleeding is likely to result from a deficiency of factor VIII, IX, or XI. It should be noted that the sensitivity and reproducibility of the aPTT are highly dependent on the specific reagents used (particularly the activator in the partial thromboplastin reagent). The laboratory should establish a reference range for each new lot of reagent and each new method of clot detection. The reference range will generally be approximately 26 to 35 seconds for children and adults, but longer (30 to 54 seconds) in term infants, and often even longer in premature infants.

The aPTT is somewhat less sensitive than the PT to the deficiency of vitamin K-dependent factors, but is more sensitive to the presence of circulating anticoagulants and heparin. The aPTT can detect circulating anticoagulants (such as lupus anticoagulants) and is routinely used to monitor standard heparin therapy. Among hospitalized infants or children, unintentional contamination of patient samples with heparin is a common cause for an unexpected prolongation of the aPTT that does not correct on mixing.

### Thrombin Time

The thrombin time (TT) measures the thrombin-induced conversion of fibrinogen to fibrin and is performed by adding bovine thrombin to the patient’s citrated plasma and recording the clotting time. The TT measures the amount and the clotting function of fibrinogen and is also prolonged in the presence of heparin or circulating fibrin degradation products. An extremely prolonged TT usually indicates a heparin effect. The snake venom protease, reptilase, clots fibrinogen in the presence of heparin and can be used to identify heparin as the cause of the prolonged TT. Thus, in the presence of heparin, the TT is prolonged while the reptilase time is normal. Alternatively, one can test for heparin activity by its anti-factor Xa activity or with the use of commercial heparinase. The sensitivity of the TT can be increased by dilution of the thrombin to give a control thrombin clotting time (TCT) of 16 to 18 seconds.

Normal values differ from 1 laboratory to another and between instruments and reagents. Thus, obtained values should be compared with the normal range for that laboratory. Additionally, in children, the normal values for coagulation and anticoagulant



proteins differ with age. Thus, the values obtained should be compared with normal values for the age of the patient.

The bleeding time, once considered to be a useful screening test for vWD, is difficult to standardize with poor sensitivity and specificity and high interobserver and intraobserver variations. It has been replaced in many centers by the platelet function analyzer (PFA-100), a screening test using a commercially available instrument. The test is quantitative, simple, rapid, and reproducible and measures, under high shear stress, the time taken for a platelet plug to occlude a microscopic aperture in a membrane coated with platelet agonists. However, it lacks the sensitivity for mild vWD and platelet disorders. Thus, if the history is suggestive, performing vWD level analysis or formal platelet aggregation tests may be appropriate.

## HEMOPHILIA A AND B

Hemophilia A (deficiency of factor VIII, or antihemophilic factor) and hemophilia B (deficiency of factor IX, or Christmas factor) are X-linked recessive disorders with similar clinical manifestations with an estimated incidence of 1:10,000 and 1:30,000 males, respectively. A positive family history is seen in approximately two-thirds of the patients, and in one-third of the patients there are new mutations. Hemophilia A and hemophilia B occur worldwide with no racial predilection.

## DIAGNOSIS

The diagnosis can often be suspected based on family and personal history of bleeding. Laboratory studies often show a prolonged aPTT with a normal PT and normal tests for platelet function. Specific factor assays for factors VIII and IX identify the deficiency. Severe hemophilia accounts for 80% of cases of hemophilia A and 60% of cases of hemophilia B and is defined by a factor VIII or IX level lower than 1%. Levels between 5% and 40% are associated with mild disease, and levels between 1% and 5% are associated with moderate disease. It is important to diagnose the severity of the disease accurately because spontaneous bleeding is common in severe hemophilia, whereas patients with moderate to mild hemophilia have trauma-induced bleeding. In most families, diagnosing hemophilia prenatally is now possible by chorionic villus biopsy or amniocentesis. The factor VIII and factor IX genes have both been cloned, and many different mutations have been identified in both conditions.

## Bleeding Manifestations

### Hemarthrosis

Recurrent bleeding into joints is the hallmark of patients with severe hemophilia. The knees, ankles, and elbows are commonly involved, but bleeding can occur in any joint. Hemarthrosis must be treated as soon as pain, tingling, or limping begins, even if evidence of swelling is not visible. Watchful waiting is not appropriate for the child who has moderate or severe hemophilia. Prompt replacement of either factor VIII or factor IX should be continued until signs of joint swelling resolve. Primary prophylaxis before the first bleed is an effective therapy for reducing joint bleed-related morbidity; and after a joint bleed occurs in a patient

with hemophilia, factor prophylaxis given twice or thrice a week should be strongly encouraged. The difficulties of intravenous access often interfere with starting prophylaxis early, and central venous access devices may be considered to circumvent this issue.

Many patients with hemophilia have a particular target joint in which recurrent episodes occur and in which chronic changes are most likely to result. Synovial thickening and vascular friability may develop, resulting in increased susceptibility to bleeding. Synovitis accompanied by chronic effusion often develops and may progress to joint destruction (hemophilic arthropathy) and severe disability. With prompt, adequate treatment or prevention of bleeding, the incidence of these complications is significantly decreased. Synovectomy may be effective if medical management fails and may be accomplished by open, arthroscopic or radionuclide approaches. Intensive physical therapy is required in conjunction with the procedures. Radiosynovectomy is a simpler procedure, requiring less factor replacement and physical therapy. Although this procedure has been performed in young children with good joint outcomes, some concern exists about the possibility of inducing malignancy.

### Soft Tissue Bleeding

Superficial hematomas, unless very large, do not often require treatment. However, bleeding into muscles or closed soft tissue compartments may result in nerve or vascular compression, muscle fibrosis, and contractures; such bleeding may be difficult to diagnose because swelling is often minimal. Bleeding into the iliopsoas muscle may cause femoral nerve damage, and it must be considered whenever pain occurs in the lower abdomen, hip, or groin. Limping and flexion of the hip are often the only positive findings. Sonography or computed tomography (CT) may help in making the diagnosis. Because the iliopsoas represents a large potential space, patients can lose enough blood to compromise perfusion and induce shock before obvious symptoms develop, so the index of suspicion for iliopsoas bleeding must be high and the threshold for therapy and imaging low in the setting of vague abdominal pain. Calf bleeding may result in peroneal nerve damage. Bleeding into the thigh may cause accumulation of a large amount of blood without much external change and may result in significant anemia.

### Life-Threatening Bleeding

Intracranial bleeding can occur after trauma or spontaneously. All but the most minor head injuries must be considered to be significant and treated promptly. Appropriate imaging should be considered based on the age of the child. In the newborn period, an ultrasound may be obtained; in older children, a CT scan of the head may be more appropriate. It is important to treat with factor replacement before obtaining imaging studies because delay in therapy may have an adverse outcome.

Airway compromise must be considered a potential threat with any hematoma of the neck or the submental or sublingual areas, as well as the retropharyngeal

or parapharyngeal regions; a severe sore throat or dysphagia also suggests bleeding and should be evaluated and treated immediately. Retroperitoneal bleeding may be massive before it can be detected and must be considered when abdominal or groin pain is present. In these situations, CT or magnetic resonance imaging may be helpful in evaluating the patient.

### **Mouth Bleeding**

The lip, tongue, and frenulum are areas of frequent trauma in mobile young children. Additionally, although epistaxis is not common in hemophiliac patients, the amount of blood loss can be significant and can often result in iron deficiency. Factor replacement should be accompanied by the use of  $\epsilon$ -aminocaproic acid or tranexamic acid to prevent fibrinolysis of the clot, although these drugs must be used cautiously in patients receiving prothrombin complex or any activated coagulation factors because the combination can lead to thrombosis or disseminated intravascular coagulation (DIC).

### **Hematuria**

Hematuria must be evaluated with noninvasive procedures, as in the normal individual, to rule out intrinsic renal disease. It usually resolves spontaneously with or without factor replacement, although bed rest and hydration are often suggested. Fibrinolytic agents and factor replacement should be avoided, unless the bleeding is known to originate in the lower urinary tract, because they can result in obstruction of the renal pelvis by clot formation. The role of steroids in the treatment of hemophilia hematuria is controversial, but is likely not beneficial.

## **GENERAL PRINCIPLES OF TREATMENT**

Ideal management of patients who have hemophilia is in a comprehensive hemophilia treatment center where all the needs of the patient can be met, including medical, orthopedic, physical rehabilitation, dental, and psychosocial therapies. All elective surgical procedures must be performed in a center that has experienced personnel, immediate availability of blood clotting factor assays, and a ready supply of clotting concentrates, and they should be preceded by evaluation for factor inhibitors. Nerve blocks, intramuscular injections, and arterial blood draws should be avoided. In general, antiplatelet medications, such as aspirin and other nonsteroidal anti-inflammatory drugs, should be avoided. Factor replacement should always be given as promptly as possible when bleeding is suspected, before radiographic examination or other diagnostic studies are performed. A patient who has a severe injury or life-threatening bleeding should be given an immediate dose of the appropriate clotting factor to raise its level to 100% and then be transferred to a hemophilia center.

Any significant injury must be treated promptly, even without apparent evidence of active bleeding, given that bleeding is often delayed. A small, superficial laceration, if not bleeding or in need of cleaning or sutures, may be managed with a simple pressure dressing; however, if bleeding occurs or if suturing is

required, then the appropriate clotting factor must be administered immediately. Casts should not be applied unless factor has been administered beforehand and is continued for several days afterward; the involved area should be watched closely for evidence of nerve or vascular compression. Factor replacement must be provided before all surgical procedures, arterial punctures, and lumbar punctures.

Pain should be managed on acetaminophen whenever possible; however, codeine and other oral narcotics can be provided if necessary. Although aspirin must be avoided, nonacetylated salicylates (eg, choline magnesium trisalicylate) can be used, and nonsteroidal anti-inflammatory agents such as ibuprofen can be given cautiously if the patient is not also receiving zidovudine. Although cyclooxygenase-2 inhibitors showed early promise as analgesic agents for patients with hemophilia, cardiovascular toxicity that led to the withdrawal of rofecoxib from the market suggests that these drugs should not be used routinely until more is known about them. Ketorolac may be more effective for the treatment of musculoskeletal and joint pain. Treating bleeding episodes as early as possible helps to limit severe pain so that the need for narcotics can be minimized.

### **Factor Replacement**

Products available for the treatment of coagulation disorders are described in Table 230-1. Whole plasma can raise factor VIII levels to only 40% and factor IX levels to 20% because of the large volume and protein load that accompany its use. Early in the acquired immunodeficiency syndrome (AIDS) epidemic, experts suggested that plasma or cryoprecipitate be provided when possible, rather than concentrates made from large donor pools. However, the safety of current concentrates makes them the preferred mode of treatment in most situations. Recombinant factors VIII and IX are available and effective and seem to be free of viral contamination. Some studies have indicated an increased incidence of inhibitor development with these products, although other studies have not agreed with this finding. Factor IX is available in the form of prothrombin complex, as well as in purified and recombinant forms. Although mild bleeding requiring a single treatment can be managed with the complex, this approach has a danger of thrombosis or DIC from activated factors in the complex, particularly in patients with liver disease. The cost of these products increases with the degree of purification. The Medical and Scientific Advisory Committee of the National Hemophilia Foundation recommends the use of recombinant factor products when available because of the decreased risk for viral infections. Generally, a patient should be treated when possible with only 1 brand of factor product, and switching products should be minimized because it may be associated with inhibitor development.

The desired levels of factor VIII or IX for managing different clinical problems are listed in Table 230-2. Preassayed concentrates are available in vials containing varied doses. Whole vials containing the calculated, desired dose or a higher level should be given because these products are too expensive to waste.

**Table 230-1** Products Available for Treatment of Coagulation Disorders

PRODUCT	CONTENT	DOSE, CONCENTRATION, SIZE OF UNITS	INDICATIONS, COMMENTS
Fresh frozen plasma	Whole plasma	5–15 mL/kg; 1 U of each of the coagulation factors/mL; 220 or 600 mL/bag	Multiple factor deficiency; DIC; reversal of Coumadin effect; HUS or TTP; unknown coagulation defect; when no specific concentrate exists; not virus inactivated
Cryoprecipitate	Factor VIII, factor XIII, fibrinogen, fibronectin	1 U/kg raises factor VIII 2%; 75–100 U factor VIII and WF/bag; volume approximately 20 mL; not assayed	Factor XIII deficiency, hypofibrinogenemia; derived from single-donor units; not virus inactivated
Factor VIII	Factor VIII	1 U/kg raises factor VIII 2%; preassayed; up to 100 U/mL	Hemophilia A; made by various methods, with different levels of purification; recombinant product available; virus inactivated <sup>a</sup>
Humate P	Factor VIII, vWF	Preassayed; factor VIII 20–40 U/mL; 50–100 U/mL	Severe vWD; mild to moderate vWD if DDAVP ineffective or inadequate; virus inactivated <sup>a</sup>
Factor IX	Factor IX	1 U/kg (1.2–1.4 U/kg of recombinant) raises factor IX 1%; preassayed; up to 100 U/mL	Hemophilia B; recombinant product available; virus inactivated <sup>a</sup>
Prothrombin complex	Factor II, VII, IX, X	Preassayed for factor IX; content of other factors varies among products	Hemophilia B when purified factor IX cannot be used; mild bleeding in hemophilia A with inhibitor; congenital deficiency of factor II or X; danger of thrombosis (including MI and DIC) in presence of liver disease, prolonged use; virus inactivated <sup>a</sup>
Activated prothrombin complex	Factor II, VII, IX, X; factor VIII <i>bypassing</i> activity	Preassayed for ability to shorten aPTT of plasma with high-titer factor VIII inhibitor	Hemophilia A or B with inhibitor; cannot evaluate response by measuring factor VIII activity; risk for DIC and thrombosis
NovoSeven	Recombinant factor VIIa	Preassayed	Hemophilia A or B with inhibitor; factor VII deficiency; risk for thrombosis

aPTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; HUS, hemolytic uremic syndrome; MI, myocardial infarction; TTP, thrombotic thrombocytopenic purpura; vWD, von Willebrand disease; vWF, von Willebrand factor.

<sup>a</sup>Virus attenuation processes may not inactivate parvovirus, hepatitis A, and possibly other viruses.

Continuous infusion can be used for patients who are undergoing surgery or who are bleeding extensively.

### Health Care Maintenance

Routine immunizations, which must include hepatitis B and hepatitis A vaccines, should be given subcutaneously, if possible, with a 25-gauge needle; pressure should be maintained for 5 to 10 minutes. Although the effectiveness of hepatitis A vaccine administered subcutaneously is clearly good, this is less clear for other vaccines. Intramuscular injections are controversial, but are probably safe when a small needle

(23 gauge or less) is used and pressure is held for 1 to 2 minutes. Intramuscular injections can also be scheduled after routine factor replacement in patients on prophylaxis. Routine dental evaluation, prophylaxis, and hygiene should begin by 3 years of age. The most difficult part of managing the child who has hemophilia is to use appropriate caution, but, at the same time, allow for the development of independence. Family education about the disease is essential, and support groups are beneficial. These patients and their families should be closely monitored for psychosocial issues. Not only do they have to live with a serious

**Table 230-2 Treatment of Bleeding Episodes in Hemophilia**

TYPE OF BLEEDING	DESIRED LEVEL OF FACTOR VIII OR IX	DURATION OF TREATMENT	ANCILLARY TREATMENT
Hematoma, simple	20%–40%	Usually once	—
Hemarthrosis, mild muscle hematoma	30%–40%	Once, as soon as symptoms begin; if severe, repeat daily until better clinically.	Non-weight bearing and rest; gradual initiation of passive physical therapy; pain control
Severe muscle hematoma	50%–100%	3–7 days	Check hemoglobin because large hematomas may cause anemia; non-weight bearing and rest; gradual initiation of passive physical therapy; pain control
Mouth bleeding, epistaxis, dental extractions	80%–100%	Once	Start EACA 75–100 mg/kg every 6 hr or tranexamic acid 25 mg/kg every 6–8 hr by mouth for 3–7 days (until clot is gone)
Gastrointestinal bleeding	100%	3–7 days	EACA or tranexamic acid
Hematuria	Factor may not be needed	3–7 days	Bed rest; hydration; do not use EACA
Life-threatening, central nervous system, airway obstruction, retroperitoneal	100%; do not allow drop <50%	7–14 days	Monitor factor and inhibitor levels
Surgery	100%; do not allow drop <50%	7–14 days	Preoperative inhibitor testing; monitor levels
Prophylaxis	20–40 U/kg	3 times per week for factor VIII; 2 times per week for factor IX	Demonstrated to improve joint outcomes

EACA, *ε*-aminocaproic acid.

A total of 1 U/kg of factor VIII increases plasma level by 2%; biologic half-life = 10–12 hours. A total of 1 U/kg of factor IX increases level by 1%; 1 U/kg of recombinant factor IX increases level by 0.8%; biologic half-life = 20–24 hours. Slightly lower levels of factor IX than of factor VIII are effective.

Initial dose = 50 U/kg of factor VIII and 80–100 U/kg of factor IX; repeat one-half the factor VIII dose in 8–12 hours and one-half the factor IX dose in 12–24 hours, or provide a continuous infusion of 3–4 U/kg/hr of either factor VIII or factor IX after initial bolus dose.

chronic illness associated with frequent pain and limitation of normal activities, but also the effect of AIDS on the adult population has been devastating and, in many cases, has eroded trust in medical caretakers. Additionally, the cost of hemophilia therapy often presents unique difficulties for patients obtaining and maintaining insurance. Counseling around this topic is essential.

There is an important implication for future pregnancies to the families of children diagnosed with hemophilia, vWD, or other congenital factor deficiencies. Because these are inherited conditions (although in hemophilia, there can be spontaneous mutations), screening other family members may be appropriate. Referral to a geneticist specializing in bleeding disorders may be appropriate, especially to identify carriers and to counsel them regarding future pregnancies.

### Home Management

If a child has reasonably easy venous access and family dynamics permit it, then parents can be taught to administer treatment to children as young as 3 years of age, and 9- or 10-year-olds can be taught to self-administer factor concentrates. This approach allows for much earlier treatment of bleeding episodes, provides the satisfaction of self-sufficiency, and

prevents some of the frustrations of having to get to a treatment center or emergency department. Indwelling venous access devices are being used with increasing frequency and have simplified home, as well as in-hospital, management, although infections and thrombosis have been problems with these devices. Home intravenous therapy is also a convenient way to administer prophylaxis or immune tolerance induction. Before initiation of home therapy, caregivers should receive adequate education and training and perform infusions under the supervision of medical staff until proficient and comfortable with the technique.

### Mild Hemophilia

The patient who has mild hemophilia is more likely than the patient with severe disease to receive inadequate treatment of bleeding episodes because neither the family nor the physician may be aware of the need for treatment. Significant injuries in patients with mild hemophilia require management similar to those with severe disease, although smaller doses of factor concentrates may be sufficient to attain the desired factor levels. Desmopressin (DDAVP) is a vasopressin analog that results in release of factor VIII from the endothelial cells where it is produced,



resulting in almost a threefold increase of the level. It may, therefore, be effective if the baseline factor VIII level is more than 5%, depending on the level desired. Overhydration must be prevented because water retention and hyponatremia may occur with DDAVP therapy, particularly in young children and with repeated doses. A concentrated intranasal preparation is available and has been used in children 6 years of age and older. A stimulation test with response assessment should be performed in each patient with either intravenous or nasal preparations before they are used therapeutically for the first time. The response to DDAVP often correlates with the underlying genetic mutation causing hemophilia and the age of the patient. Although DDAVP response has been tested in infants as young as 11 months of age, there is no consensus on the optimal age for testing the DDAVP response. Because of concerns of hyponatremia and of the possibility of a lack of response at a younger age, most centers wait until the patient is older than 3 years for the DDAVP challenge. DDAVP is ineffective in factor IX deficiency.

### Prophylaxis

Prophylactic factor concentrate treatment administered several times a week is considered to be the optimal care for children who have severe hemophilia to prevent hemarthrosis and joint damage and to normalize their lives. Although this form of treatment is more expensive than episodic treatment for bleeding, the additional cost saving by preventing future orthopedic complications is considerable. The psychological benefits also must be considered. Children who have moderate hemophilia and behave like mild cases are treated similarly to children with mild hemophilia. Those who have spontaneous bleeding (often with levels of 1%–3%) are most often treated as severe cases.

### Inhibitors

Approximately 30% of patients who have severe hemophilia A and 3% who have hemophilia B develop antibodies that inhibit factor VIII or factor IX activity, usually early in their treatment, although many of these antibodies are present in low titer and may subsequently disappear. Such patients should be managed only by experienced physicians. Inhibitor antibodies are more common in patients with severe hemophilia, those with large gene deletions, and those with a family history of inhibitors. Most inhibitor antibodies develop before the 20th infusion of factor products, but they can develop at any time. Management may include the use of large doses of factor VIII or factors that bypass factor VIII in the coagulation cascade (prothrombin complex, activated prothrombin complex, recombinant factor VIIa) or the use of porcine factor VIII. Induction of immune tolerance by continuous exposure to high doses of factor over many weeks to months, with or without concomitant immunosuppression, has been found to be effective in controlling the inhibitor in most cases. An inhibitor should be suspected if the response to appropriate therapy is inadequate, and it should be sought regularly in all patients and before all elective surgery. A Bethesda inhibitor assay will determine the presence

and strength of an inhibitor. Patients who have hemophilia B with inhibitors may develop anaphylaxis or nephrotic syndrome when given factor IX. Management is much more difficult than for hemophilia A, but recombinant factor VIIa has been effective. Because of the incidence of life-threatening anaphylactic reactions in hemophilia B, the first 20 to 30 factor infusions should be administered in a medical facility capable of treating anaphylaxis.

### Acquired Immunodeficiency Syndrome and Other Viral Infections

Most patients who had severe hemophilia in the United States in the late 1970s and early 1980s became infected with HIV. The treatment of hemophilia with clotting factor concentrates from large donor pools in the era before the virus was identified resulted in massive exposure to HIV. Chronic liver disease has also been a major problem, most often caused by hepatitis C and sometimes by hepatitis B virus infection. Currently, both donor testing and several methods to inactivate viruses in the production process make the concentrates safe with regard to HIV. Hepatitis B and C have also been largely eliminated. (See Chapter 59, Blood Products and Their Uses.) The increasing availability and use of recombinant factors may eliminate the problem of viral infections.

### Gene Therapy

Although gene transfer of both factor VIII and factor IX genes has been accomplished in several animal models, as well as in a small number of clinical trials, the results have been disappointing. In addition, concerns about the possibility of inducing malignancy or liver disease remain. However, investigations into this modality of therapy continue to be pursued.

### VON WILLEBRAND DISEASE

Von Willebrand disease is the most common hereditary coagulation disorder, with estimates of an incidence as high as 1% of the population, although most of these individuals are asymptomatic and the incidence of symptomatic is probably closer to 1 in 10,000 individuals. Von Willebrand factor (vWF) is the carrier protein for factor VIII and exists in a series of different-sized multimers of smaller subunits. Additionally, vWF acts as a bridge between the platelet and the damaged endothelium and is important for platelet adhesion. Decreased vWF is associated with a corresponding decrease of factor VIII activity and decreased platelet function in most cases. The inheritance is usually autosomal dominant with variable penetrance, but autosomal-recessive variants occur. The gene is on chromosome 12 and has been cloned, and many genetic mutations have been identified. In addition to bleeding after surgery and trauma, the major manifestation of vWD is mucosal bleeding, which most frequently exhibits as epistaxis. Menorrhagia and, less commonly, gastrointestinal bleeding also may occur. Hemarthrosis and deep hematomas may be seen in severe (type 3) vWD. Several components of the vWF-factor VIII complex and function can be determined: factor VIII activity, vWF activity (ristocetin cofactor, vWF:RCO), vWF antigen (vWF:Ag), and the pattern of

multimers. In hemophilia, the vWF is normal. Many variants of vWD exist. The most common is type 1, in which all components are similarly reduced and the multimer pattern is normal. Type 2 results from qualitative defects in vWF and can include decrease or absence of the larger multimers; type 2B exhibits increased binding to platelets. Type 2N results from impaired binding of factor VIII and resulting low factor VIII levels and can be misdiagnosed as mild to moderate hemophilia A. Type 2N should be considered in the differential diagnosis of mild or moderate hemophilia A, particularly in the absence of family history, and is often diagnosed after poor response to factor VIII replacement or when an affected female family member is found to have low factor VIII activity. Type 3 represents severe homozygous deficiency with very low or absent levels of all components.

vWD may be difficult to diagnose. The bleeding time and PFA-100 test are fairly sensitive, but nonspecific, and are prolonged in most patients; most cases are associated with mildly decreased levels of factor VIII. However, the aPTT may be normal if factor VIII is greater than 30% to 40%. All of the studies may be variable, both from patient to patient and in the same patient from time to time. Even if the laboratory test results are normal, they should be repeated if the index of suspicion is high. vWF varies with blood type and with several environmental factors. Levels of 35% to 50% may exist in both patients with vWD and normal individuals with blood type O, making the definitive diagnosis even more difficult. A major differential diagnosis, although much rarer, is one of the disorders of platelet function (see Chapter 181, Petechiae and Purpura).

Most patients who have type 1 vWD will respond to DDAVP as in mild hemophilia A, and this approach can be used for most bleeding episodes. Most patients who have type 2A and all who have type 3 vWD do not respond to DDAVP, and its use is contraindicated in type 2B disease because it may cause platelet aggregation and DIC. A trial dose of DDAVP should be used to assess the response to DDAVP with levels tested before administration and up to 4 hours after dosing because some patients respond poorly and to detect variants with rapid clearance of endogenous vWF. Patients who have severe bleeding or those who do not respond to DDAVP should be treated with a concentrate that contains both factor VIII and vWF. Although fresh frozen plasma or cryoprecipitate can be used, neither is suggested because of the possibility of viral contamination. Mild epistaxis can often be controlled with  $\epsilon$ -aminocaproic acid or tranexamic acid; these agents should also be used as adjunctive therapy for mucosal bleeding other than hematuria.

## OTHER COAGULATION DEFECTS

The other coagulant deficiencies are inherited as autosomal recessive genes with prevalences in the general population varying between 1 in 500,000 and 1 in 2 million for the homozygous forms (see Table 230-3). Factor XI deficiency, afibrinogenemia, and dysfibrinogenemia can be associated with bleeding in both their

heterozygous and homozygous forms. Factor XIII deficiency cannot be detected with the usual screening tests; a normal screening workup in a patient who has a significant bleeding history should be followed with a clot solubility test. The contact factors prekallikrein, high-molecular-weight kininogen, and factor XII are necessary to initiate clotting in vitro; their absence results in a markedly prolonged aPTT, but is not associated with clinical bleeding.

Although all of these deficiencies can be treated with fresh-frozen plasma, concentrates are preferable for treating factor VII deficiency because of its short half-life, as well as other deficiencies when available because they are virus depleted. Recombinant factor VIIa is commercially available. Prothrombin complex products also contain factor VII, as well as factors II and X, but the content of each factor varies in different lots. These products contain activated coagulation factors that may induce thrombosis or DIC, and they must be used cautiously, particularly in patients with liver disease. Fibrinogen and factor XIII are concentrated in cryoprecipitate, and a factor XIII concentrate may be available for compassionate use. Fresh frozen plasma can be used for patients with factor V or XI deficiency or in an emergency for patients who are bleeding but whose deficiency has not yet been identified. Factor XI concentrates are available in some European countries, but not yet in the United States.

### WHEN TO REFER

- All children with hemophilia should be seen at least once a year at a comprehensive hemophilia center if possible
- All elective surgery should be performed at a hemophilia center
- All patients with significant trauma or potentially life-threatening bleeding should be given an initial loading dose of factor (to 100%) and transferred to a hemophilia center
- All patients with inhibitors should be managed at a hemophilia center
- Children with vWD should have an initial evaluation by a specialized coagulation laboratory
- All newly diagnosed patients with a bleeding disorder should be referred to a geneticist for consultation regarding implications and screening (if necessary) in other family members

### WHEN TO ADMIT

- Significant trauma is present
- Bleeding is present in a potentially life-threatening area
- Severe abdominal pain exists
- Any surgical procedure must be performed

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *What Is Hemophilia?* (fact sheet), National Heart, Lung, and Blood Institute ([www.nhlbi.nih.gov/health/dci/Diseases/hemophilia/hemophilia\\_what.html](http://www.nhlbi.nih.gov/health/dci/Diseases/hemophilia/hemophilia_what.html))

**Table 230-3** Rare Inherited Coagulation Defects

COAGULATION DEFECT	INCIDENCE	INHERITANCE	SEVERITY	TREATMENT
Factor XI	Rare, 5% in Ashkenazi Jews	Autosomal recessive (4q32q3)	Mild to severe	Fresh frozen plasma Half-life 52 hr Factor XI concentrate available in Europe
Prothrombin (factor II)	1:2,000,000	Autosomal recessive (11p11–q12)	Mild to moderate	Prothrombin complex Half-life 60 hr
Factor V	1:1,000,000	Autosomal recessive (1q21–q25)	Mild to moderate	FFP Half-life 15 hr
Factor VII	1:500,000; 1:1,500 mild	Autosomal recessive (13q34)	Mild to severe	Recombinant Half-life 5 hr
Factor X	1:500,000	Autosomal recessive (13q34)	Mild to severe	FFP Half-life 40 hr
Factor XII	Rare	Autosomal recessive 5q33	No bleeding	No treatment
Prekallikrein	Rare	Autosomal recessive 4q35	No bleeding	No treatment
High molecular weight kininogen	Rare	Autosomal recessive 3q27	No bleeding	No treatment
Factor XIII	1:1,000,000	A subunit: 6p24–p25B subunit: 1q31–q32	Moderate to severe	Factor XIII concentrate Cryoprecipitate Half-life 150 hr
Afibrinogenemia	Rare	Autosomal dominant (various mutations at 4q31)	Variable	Cryoprecipitate RiaSTAP
Dysfibrinogenemia	Rare	Autosomal dominant (various mutations at 4q31)	Variable	Cryoprecipitate Anticoagulation if thrombosis
Hypofibrinogenemia	Rare	Autosomal dominant (various mutations at 4q31)	Variable	Cryoprecipitate RiaSTAP (fibrinogen concentrate)
Combined F5 and F8	Rare	Autosomal recessive (18q21, 2p21)	Moderate to severe	Recombinant factor VIII Assess response to Desmopressin (DDAVP)
Combined deficiency of vitamin K–dependent clotting factors	Rare	Autosomal recessive (16q12–q21, 2p12)	Variable	FFP FFP

**Medical Decision Support**

- *Hemophilia* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/ncbddd/hbd/hemophilia.htm](http://www.cdc.gov/ncbddd/hbd/hemophilia.htm))
- *Hemophilia Treatment Centers* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/ncbddd/hemophilia/HTC.html](http://www.cdc.gov/ncbddd/hemophilia/HTC.html))

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## Chapter 231

# COLIC

Rebecca Baum, MD

Few events are more overwhelming than bringing a newborn baby home from the hospital. Parents are often filled with excitement, exhaustion, and uncertainty. Imagine the parents' reaction when, once home, their infant begins to experience bouts of inconsolable crying and seemingly cannot be soothed despite their best efforts. This scenario forms the basis for the following review on colic.

### DEFINITIONS

All babies cry, but what is *normal*? In 1962, Brazelton surveyed mothers being cared for in a pediatric practice and showed that healthy newborns experienced a similar pattern of crying. Crying began to increase during the second week of age, peaked at 6 weeks, and decreased in frequency and duration thereafter. At their peak, these healthy babies cried for nearly 3 hours per day, and the episodes of crying often clustered in the evening. Decades later, studies have replicated this pattern of crying in babies in the United States as well as in European and non-European cultures where parenting practices differ. Infants with colic show a similar pattern, but their symptoms are more intense.

The most widely used definition of colic was proposed in 1954 by Wessel et al, who noted that *seriously fussy* babies cried for more than 3 hours a day, more than 3 days a week, and for longer than 3 weeks. This has since become known as the *rule of threes*. Wessel et al characterized the infants' symptoms as "unexplained paroxysms of irritability, fussing, or crying which may develop into agonized screaming. The infant may draw up his knees against his tense abdomen as if there were abdominal pain." Today, modified Wessel criteria are often used, eliminating the stipulation that symptoms be more than 3 weeks in duration. The chronicity of symptoms in babies with colic follows the typical crying curve, starting in the second week, peaking at 6 weeks, and often resolving by 4 months of age. The similarity in the crying patterns between babies with and without colic suggests that colic may represent the upper end of the continuum of *normal* crying.

Especially frustrating for parents is the fact that babies with colic may seem inconsolable during these periods of crying. The infant may continue to cry despite various interventions such as feeding, diaper changes, and soothing techniques. Continued crying can lead to feelings of inadequacy, anxiety, and frustration for parents and caregivers. Parents often perceive their infant to be in pain and may attribute excessive gas as a potential cause of the infant's distress. Rather, gas is likely a result of swallowed air caused by excessive crying and not the primary cause of the infant's symptoms.

The exact cause of colic remains elusive, and if colic is thought to represent the upper limits of

normal crying, it is possible that true pathology may not necessarily be present. A number of theories exist, including food allergy, gastrointestinal tract immaturity, parental stress, and infant temperament. Maternal smoking has also been implicated, and recent research suggests a possible association with migraine. Colic is a common concern in primary care practice, but exact estimates have been difficult to define. Prospective studies suggest a prevalence of between 3% and 28% of babies. These variable estimates likely reflect differences in study design and the population sampled.

### DIFFERENTIAL DIAGNOSIS

One of the most salient features of the infant with colic is that the child is an otherwise healthy baby. Because crying in the newborn can be a hallmark of a myriad of other disease processes, these must be excluded before a diagnosis of colic is made.

Some common disorders can be associated with excessive crying. The diagnosis of gastroesophageal reflux disease (GERD) may be suggested by episodes of fussiness. Fussy periods for the baby with GERD are often accompanied by emesis and typically occur soon after feeding. Milk protein intolerance can produce excessive crying but is often accompanied by diarrhea or hematochezia. Infants born to mothers who have used alcohol or other drugs during the pregnancy can be excessively fussy.

Other acute processes must be excluded. Such entities include corneal abrasion or hair tourniquet. Acute abdominal processes such as volvulus, intussusception, or an incarcerated hernia may produce irritability and constitute a medical emergency. Symptoms such as anorexia or vomiting may be present. Infectious processes such as otitis media, urinary tract infection, and meningitis are often accompanied by fever. Inflicted injuries such as fractures and intracranial bleeding must also be considered. These disorders typically exhibit persistent, rather than paroxysmal, symptoms.

### EVALUATION

#### History

A complete history is one of the physician's most important diagnostic tools in the evaluation of colic. The colicky baby is fussy, and parents may complain of excessive gas or crying and may be concerned that the infant is in pain. The physician must learn when these symptoms began, how often they occur, during what part of the day they occur, and how long they last. The chronicity and pattern of the symptoms is important. Parents can be asked what methods they have tried to reduce the symptoms and what, if anything, seems to help. The physician can use this opportunity to understand how the parent responds to the infant when the baby is in distress.

The physician should inquire about any concerns during the pregnancy, such as maternal drug use or infections. Family history includes a focus on metabolic or allergic disorders. Social factors are important. Parental anxiety regarding real or perceived health



concerns can affect their tolerance for normal infant crying. Understanding who in the family is responsible for caregiving and the types of supports available to the family is crucial.

The review of systems should be tailored to exclude signs and symptoms of organic illness such as fever, lethargy, vomiting, diarrhea, or hematochezia. A review of feeding techniques is important. For the formula-fed infant, care must be taken to ensure that the formula is mixed properly and that the baby is not being underfed or overfed. For breastfed infants, the physician should assess the mother's supply of milk and review how often and for how long the baby is fed.

### Physical Examination

The physical examination generally serves to exclude pathologic abnormalities and will in most cases be normal. The physician should perform a complete physical examination that focuses on the exclusion of organic causes of irritability. The infant will seem well, and parents may be frustrated that their overly fussy baby is quietly participating in the physical examination. This may serve as a teachable moment for physicians to highlight normal findings and the infant's overall health. Watching a physician conduct a thoughtful, thorough physical examination can help reassure parents that their concerns are taken seriously and that other diagnoses are not prematurely excluded. Abdominal processes, hair tourniquet around fingers or toes, and otitis media will be excluded by a thorough physical examination. Attention must be paid to adequate growth in weight, length, and head circumference, and these parameters should be plotted on the growth chart. Poor growth suggests inadequate nutrition or other organic causes. Increasing head circumference may raise concerns for hydrocephalus, including causes resulting from child abuse.

### Laboratory Evaluation

Laboratory testing is seldom indicated in the evaluation of colic. In most cases, the diagnosis can be made by a complete history and thorough physical examination. Laboratory testing is most often reserved for cases in which an organic cause is suspected. Unnecessary laboratory testing should be avoided unless clinically indicated because it may convey to parents the message that the baby is ill.

## MANAGEMENT

The management of colic primarily involves parental education and support. Foremost, the physician must help the parents understand that their baby is not sick and that the baby's excessive crying is not harmful. The baby's normal growth and physical examination can be used to help illustrate this point. Parents should be reassured about their abilities as caregivers and that they are not to blame for their baby's symptoms. Physicians should acknowledge the parents' frustration and let them know that the office will provide the family with support. Rather than informing the parents that colic may take months to resolve, physicians should remain positive and let parents know that some simple interventions will likely help alleviate the problem.

Parents can be encouraged to respond to their baby's fussiness with a predictable set of actions; having a plan to use during these fussy periods can be particularly reassuring. After first making sure that the baby is not hungry, soiled, or tired, parents can try to soothe the baby by encouraging non-nutritive sucking, swaddling, or gentle motions such as rocking or swinging. When crying continues despite these interventions, parents should be given permission to allow the infant to cry for a short period. This approach can allow parents to regroup and also provides the baby with some time to blow off steam. When conceptualized in these terms, parents may feel less anxious about the infant's continued crying. The pediatric office can provide families with support by offering a telephone contact in a few days to follow up on the infant's symptoms. Especially anxious parents can be offered an office visit within 1 week. Last, parents should be encouraged to take care of themselves, get adequate rest, and enlist family members or friends to take over from time to time to reduce caregiver stress.

Few medical interventions have proved helpful for colic. If indicated by history, a brief dietary change to a hypoallergenic formula or an elimination diet for breastfeeding mothers can be considered. Treatment for GERD can be instituted for infants with symptoms that suggest reflux. Pharmacologic therapies specific for colic have largely been found to be unhelpful and possibly harmful. Simethicone, a drug with few side effects, is not effective in symptom reduction. Dicyclomine, an anticholinergic drug, is effective; however, the manufacturer has advised against its use in children younger than 6 months because of case reports of adverse effects in infants. An herbal tea mixture of chamomile, vervain, licorice, fennel, and balm-mint has been shown to be effective, but the large volume of fluid (120 mL taken 3 times a day) might cause potential harm, such as hyponatremia or decreased milk intake. Recent studies using specific probiotic strains of *Lactobacillus reuteri* have shown promising results, although more studies are needed before probiotics can be universally recommended.

The prognosis for babies with colic is reassuring. For most babies, the symptoms of colic decrease dramatically by 4 months of age. Parents may be encouraged to know that the presence of colic in an infant does not necessarily predict a more difficult temperament as an older baby. Despite this favorable prognosis, care must be taken to support parents until they feel more comfortable managing their child's symptoms. Excessive parental anxiety and frustration may lead to later parent-child interaction problems, such as prolonged night waking, overfeeding, or the vulnerable child syndrome.

Education on infant crying and support for parents is important for caregivers of all newborns: in the hospital setting, at newborn visits, and at well child care appointments. Many parents are surprised to learn how much *healthy* babies cry, and excessive crying has been implicated as a stimulus for shaken baby syndrome. Prevention programs have been developed to promote positive coping techniques for infant

crying and to educate parents on the dangers of infant shaking. These programs include the Period of PURPLE Crying program, which uses the mnemonic PURPLE to remind parents of the characteristics of infant crying: P for the peak pattern, U for the unexpected timing of episodes, R for resistance to soothing, P for pain-like look, L for long bouts, and E for the evening cluster of symptoms. A similar program developed by Dias et al showed reduced rates of abusive head trauma when implemented in the community setting. Other support options for families include home visiting programs, such as the Nurse Family Partnership, which has shown decreased rates of child maltreatment when implemented in high-risk settings.

### WHEN TO REFER

Babies with colic seldom require a referral to a specialist. In rare cases, referral to specialists in developmental or behavioral pediatrics or mental health may be useful when parents are extremely anxious or in need of additional reassurance. Physicians should be alert for the parent who is overwhelmed by the infant's crying and in danger of harming the infant. In such a case, referral to children's services is necessary for the protection of the infant and support of the parent.

### WHEN TO ADMIT

In most cases, colic can be successfully managed in the outpatient setting. In rare situations when the history is confusing or suggests more serious symptoms, admission might be useful for observation to exclude other causes of irritability.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Crying and Your Baby: How to Calm a Fussy or Colicky Baby* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *The Period of PURPLE Crying* (Web site), National Center on Shaken Baby Syndrome ([www.purplecrying.info](http://www.purplecrying.info))

### Community Advocacy and Coordination

- *Interventions to Prevent Child Maltreatment and Associated Impairment* (article) *Lancet*, Vol 373, Issue 9659, 2008

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## Chapter 232

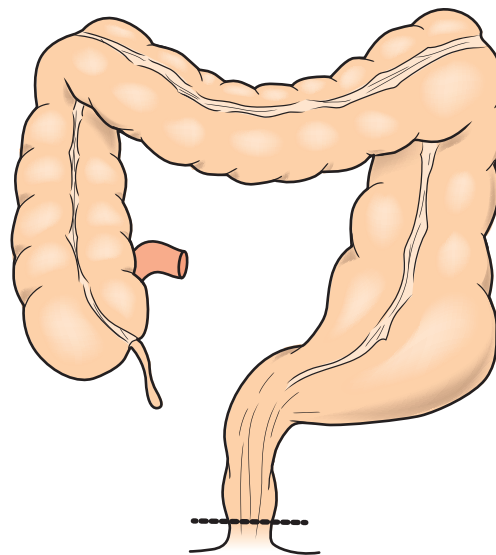
# COLORECTAL DISORDERS

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## HIRSCHSPRUNG DISEASE

### Introduction

Hirschsprung disease is characterized by partial or complete colonic obstruction associated with the absence of intramural ganglion cells. The aganglionic portion of the colon is always located distally, but the length of the segment varies. The most frequent variation (two-thirds of patients) is the one in which the aganglionic segment includes the rectum and much of the sigmoid colon (Figure 232-1). The long segment variety (10% of cases) has an aganglionic portion extending to any level between the hepatic flexure and the descending colon. Total colonic aganglionosis (10%) is a very serious condition in which the entire



**Figure 232-1** Hirschsprung disease affecting the rectum and much of the sigmoid colon.

colon is aganglionic, frequently including a variable length of terminal ileum.

The aganglionic portion of the colon appears narrow when compared with the distended, proximal part and demonstrates the absence of intramural, submucosal, and intermuscular ganglion cells with increased size and prominence of nerve fibers (hypertrophy >40 microns) and an increase in the enzyme acetylcholinesterase. Between these 2 areas is the *transition zone*.

Hirschsprung disease is believed to be caused by a failure in the development of tissue derived from the neural crest, with an arrest in the craniocaudal migration of the neuroenteric ganglion cells from the neural crest into the upper gastrointestinal tract, down through the vagal fibers, and along the distal intestine. As a consequence, ganglion cells are missing from the Auerbach myenteric plexus (located between the circular and longitudinal layers of the bowel wall), Henle plexus (located in the deep submucosa), and Meissner plexus (in the superficial submucosa). Ganglia are the final common pathway for both sympathetic and parasympathetic influences; their absence may produce the uncoordinated contractions of the affected bowel, leading to partial or total colonic obstruction.

### Epidemiology

Hirschsprung disease occurs in about 1 in 5,000 births and is more common in whites. Males are more frequently affected, but the long segment manifestation is seen at least as often in females. Inheritance patterns seem to be multifactorial. Down syndrome is found in 5% of these infants. A deletion in the long arm of chromosome 10 has been found, which seems to overlap the region of the *RET* proto-oncogene. Patients with multiple endocrine neoplasia type IIA also have a deletion of this proto-oncogene.

### Clinical Manifestations

Infants suffering from Hirschsprung disease usually become symptomatic during the first 24 to 48 hours of life. Occasionally, a child may have minimal or absent clinical manifestations during the first days or weeks and exhibit moderate, intermittent bouts of symptoms at a later age.

Abdominal distention, delayed passage of meconium, and vomiting represent the most frequent symptoms and may be followed by a spontaneous or induced explosive passage of liquid bowel movement and gas, which dramatically improves the baby's condition. This is followed by a period of hours or days of relative absence of symptoms followed by recurrence of the same manifestations. Stools are frequently liquid and foul. When the abdomen is distended, the infant can be very ill from sepsis, hypovolemia, and endotoxic shock. Volume loss is the result of diarrhea or intraluminal accumulation of fluid.

### Differential Diagnosis

The differential diagnosis includes any condition that causes distal intestinal obstruction in the newborn. Meconium plug syndrome, meconium ileus, small left colon syndrome, and other nonsurgical conditions such as hypothyroidism, adrenal insufficiency, opiate

intoxication, and cerebral injury can present with abdominal distention.

For late presenters, the diagnosis may be confused with chronic constipation. In the latter condition, children usually become symptomatic after the sixth month of life; they do not vomit or become seriously ill. A very important characteristic in this group of patients is overflow incontinence or encopresis—a constant, chronic soiling. Rectal examination reveals a severe fecal impaction just above the anal canal. Patients with Hirschsprung disease may have an empty rectum, or examination may disclose only a small amount of feces, and they often have chronic distention, failure to thrive, and episodes of enterocolitis.

### Diagnosis

#### Radiologic Studies

It is very difficult to differentiate distended colon from small bowel on a plain abdominal film of a neonate with intestinal obstruction. Therefore, one can only suspect the diagnosis of Hirschsprung disease from this study. The presence of air-fluid levels is evidence of obstruction, but it is nonspecific.

A water-soluble contrast enema examination (barium should be avoided) is the most valuable radiologic study for establishing the diagnosis. This study may reveal the presence of a distended proximal colon, the transition zone, and a “contracted” distal rectosigmoid (Figure 232-2). The older the patient, the more



**Figure 232-2** Water-soluble contrast enema examination showing distended proximal colon, transition zone, and “contracted” rectosigmoid.

obvious the size difference between the normal ganglionic intestine and the abnormal aganglionic bowel. The typical changes are not very obvious during the neonatal period, but usually the transition zone is recognizable. In instances of total colonic aganglionosis, contrast enema may reveal a short colon, with retraction of the hepatic and splenic flexures and straightening of the sigmoid.

### **Rectal Biopsy**

Confirmation of Hirschsprung disease requires finding the absence of ganglion cells and the presence of hypertrophic nerves in an adequate rectal biopsy. The specimen must be taken at least 1 cm above the pectinate line because closer to the dentate is always aganglionic. Suction biopsy is easily performed, is associated with virtually no risk for perforation, and does not require an anesthetic. The specimen usually measures 1 × 3 mm and should include mucosa and submucosa. A full-thickness biopsy done under anesthesia is required when the suction biopsy is nondiagnostic and in older children.

### **Medical Treatment**

Bowel irrigation with saline solution is an extremely valuable procedure for the emergency management of distention and vomiting. Decompressing the bowel in this way may dramatically improve a very ill infant.

It is extremely important to clarify the difference between an irrigation and an enema. To confuse these terms may be dangerous for babies with Hirschsprung disease. An enema is a procedure in which a determined amount of fluid is instilled into the rectum and colon with the expectation that this volume will be spontaneously expelled. A rectal irrigation, on the other hand, is a procedure in which a large tube is introduced through the rectum and small amounts of saline solution are instilled through the lumen of the tube to cleanse the bowel. The rectal and colonic content is expected to drain through the lumen of the tube. The tube is then rotated in different directions and moved back and forth. The operator continues to instill small amounts of saline solution, allowing the evacuation of gas and liquid stool through the tube.

Patients with Hirschsprung disease suffer from a very serious dysmotility disorder. An enema may aggravate the condition of the patient rather than help because the patient does not have the capacity to expel the infused volume of fluid. With an irrigation, the patient benefits from the evacuation of the recto-sigmoid contents through the lumen of the large tube, which overcomes the functional obstruction of the aperistaltic bowel, interfering with stasis and thus the ensuing bacterial overgrowth. This technique is vital to treat distention and enterocolitis before definitive surgery as well as after surgery if an episode of enterocolitis occurs.

### **Surgical Treatment**

#### **General Principles**

The ideal management of patients with Hirschsprung disease is to perform a primary procedure during the

neonatal period without a protective colostomy. The circumstances for performing the surgery are different from country to country, and there is often much variability in the experience of surgeons. In addition, the availability of experienced clinical pathologists may be limited. When performing a primary neonatal pull-through procedure, the surgeon must rely on frozen section analysis. For this, the surgeon must interact with an experienced pathologist who is familiar with the histologic diagnosis of Hirschsprung disease. A very ill newborn with enterocolitis or one who suffers from concomitant serious medical conditions may benefit from an initial fecal diversion. Similarly, a patient suffering from enterocolitis and unresponsive to irrigation may need a temporary diversion. With good neonatal care, effective irrigations, and experienced pathologists, this is rarely needed.

### **Definitive Operations**

In all surgical approaches, the goal is to resect the aganglionic segment and transition zone, pull through normal bowel, and preserve the continence mechanism.

#### **Swenson Procedure**

The Swenson procedure was initially done transabdominally, but it now can be done transanally. Laparoscopy has emerged as an excellent technique added to each type of Hirschsprung pull-through. Resection of the full-thickness aganglionic portion of the colon is performed, including that of the most dilated portion of the bowel (Figure 232-3). In most cases, the sigmoid readily reaches the perineum. Sometimes, mobilization of the splenic flexure is needed, which is easily done with laparoscopy. The long segment type may necessitate mobilization of the right colon to obtain sufficient length.

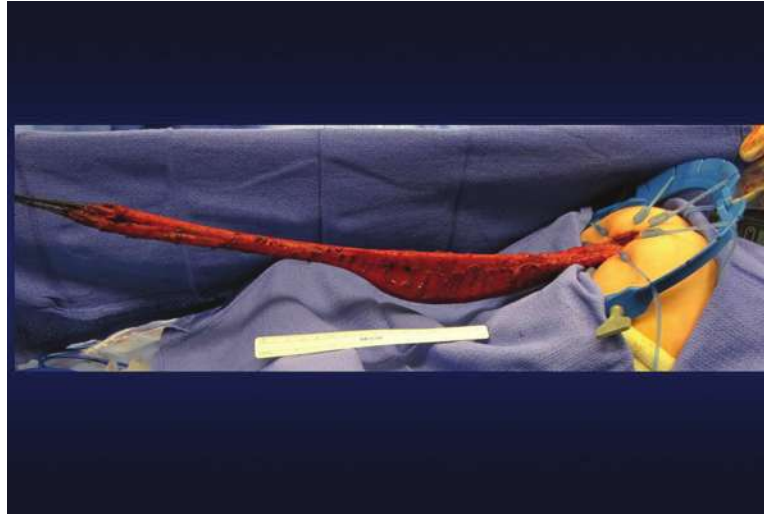
#### **Duhamel Procedure**

The Duhamel procedure was devised to avoid the pelvic dissection required of the Swenson operation. This is accomplished by preserving the aganglionic rectum and dividing the bowel at the peritoneal reflection as distally as possible. The rectal stump is then closed. Normal (ie, ganglionic) intestine, usually above the most dilated portion, is pulled through a presacral space that has been created by blunt dissection. The posterior rectal wall is incised above the dentate line, entering the previously dissected retrorectal space. The new, normally innervated colon is pulled through the rectal incision, and a stapler is used to effect anastomosis to the aganglionic rectum. The anastomosis between the colon and the aganglionic rectum must be created as wide as possible, and the rectal stump must be as small as possible to avoid fecal accumulation.

#### **Soave Procedure**

The Soave procedure removes the aganglionic recto-sigmoid by an endorectal dissection, which is begun 1 or 2 cm above the peritoneal reflection, theoretically minimizing the risk for pelvic injury associated with the Swenson procedure. The normally innervated colon is passed through a perirectal muscular cuff.





**Figure 232-3** Transanal approach to the management of Hirschsprung disease.

### Transanal Approach

In 1998, de la Torre and Langer both reported a transanal approach to the management of Hirschsprung disease. The basic concept consisted of approaching the resection of the aganglionic portion through the anus. A special retractor is ideal for this dissection (Figure 232-3). The circumferential traction exposes and protects the anal canal, the pectinate line, and the rectal mucosa. Multiple fine sutures are placed in the rectal mucosa in a circumferential manner to exert uniform traction and to facilitate the dissection of this part of the bowel. A circumferential incision distal to the multiple silk sutures is performed, and the dissection of the rectum commences and continues to the peritoneal reflection. As the dissection progresses, full-thickness biopsies are taken that are sent to pathology looking for the presence of ganglion cells as well as the thickness of the nerve trunks. The transition zone sometimes shows an area of hypoganglionosis and thickened nerves. The dissection continues until one goes above the transition zone to be sure that normoganglionic bowel is pulled down. The normoganglionic bowel is transanally anastomosed to the anal canal 1 cm above the pectinate line.

Considering that most patients with Hirschsprung disease have a transition zone in the sigmoid colon, it is possible to repair the entire defect using only the transanal approach without a laparotomy or laparoscopy. However, when the transition zone is located higher, laparoscopy or laparotomy is needed to mobilize the colon. An alternative is to commence the procedure laparoscopically, performing a colonic biopsy to identify the transition zone, mobilizing the sigmoid colon laparoscopically, and then dissecting transanally.

It is important to keep in mind that the resection must include not only the aganglionic part but also the dilated part of the bowel (Figure 232-3). Pulling down a very dilated segment of colon will result in severe constipation later in life because dilated bowel tends to lose its peristaltic ability.

### Post-Pull-Through Problems

After a technically sound pull-through, some patients may have difficulties with stooling for a few weeks after the operation. Post-pull-through enterocolitis is reported in 5% to 42% of patients; the wide variation is because of difference of opinion on what constitutes mild enterocolitis. The pathophysiologic mechanisms underlying the occurrence of enterocolitis after surgery are not completely known, but most patients do well when managed with rectal irrigation and metronidazole. Similarly, senna-based laxatives are beneficial in patients who are constipated. It is important to prevent a cycle of constipation provoking megacolon, which in turn produces more severe constipation.

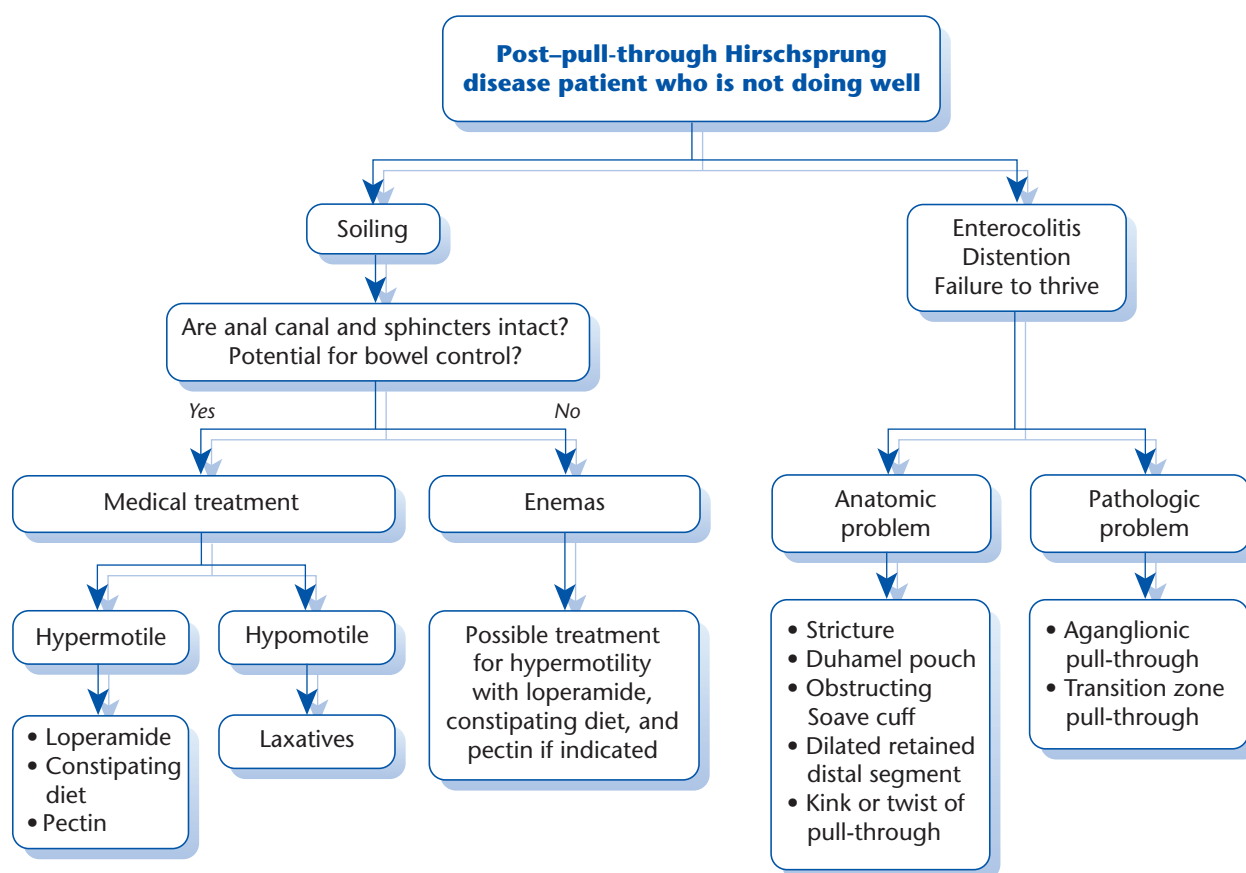
However, in a child with recurrent enterocolitis, persistent constipation or impaction, failure to thrive, and fecal incontinence, further evaluation is warranted. Patients with recurrent enterocolitis or constipation may have mechanical problems such as strictures, megarectal pouches, obstructing cuffs, or dilated segments. These could also be caused by retained aganglionic segments or a transition zone pull-through. Patients with fecal incontinence may have a lost or injured anal canal or sphincter mechanism. An algorithm (Figure 232-4) to evaluate and treat the patient is beneficial.

### WHEN TO REFER

- Features of enterocolitis
- Chronic abdominal distention
- As soon as the diagnosis is made
- Recurrent enterocolitis or failure to thrive after the pull-through
- Soiling after the pull-through

### WHEN TO ADMIT

- Enterocolitis unresponsive to irrigation and metronidazole



**Figure 232-4** Algorithm for the management of the patient with Hirschsprung disease who is not doing well after a pull-through.

## ANORECTAL MALFORMATIONS

### Incidence

About 1 of every 5,000 newborns will have an anorectal malformation (ARM). Males seem to suffer from this condition more frequently than females. The most common type of malformation seen in boys is rectourethral fistula, and the most common type of anomaly in girls is a rectovestibular fistula. There is an increased incidence of imperforate anus in children with Down syndrome, frequently consisting of a low-lying rectal pouch without a genitourinary or perineal fistula.

### Classification

Anorectal malformations include a spectrum of anomalies. Thus, in attempting to separate these groups of defects into categories, one risks being arbitrary and artificial. The anatomic classification shown in Box 232-1 is very useful for therapeutic purposes.

### Anatomy

The posterior sagittal approach used for the repair of ARM permitted the conceptualization of the anatomic details of a male (Figure 232-5) and a female (Figure 232-6) with ARM. The sphincter complex is

### BOX 232-1 Classification of Anorectal Malformations

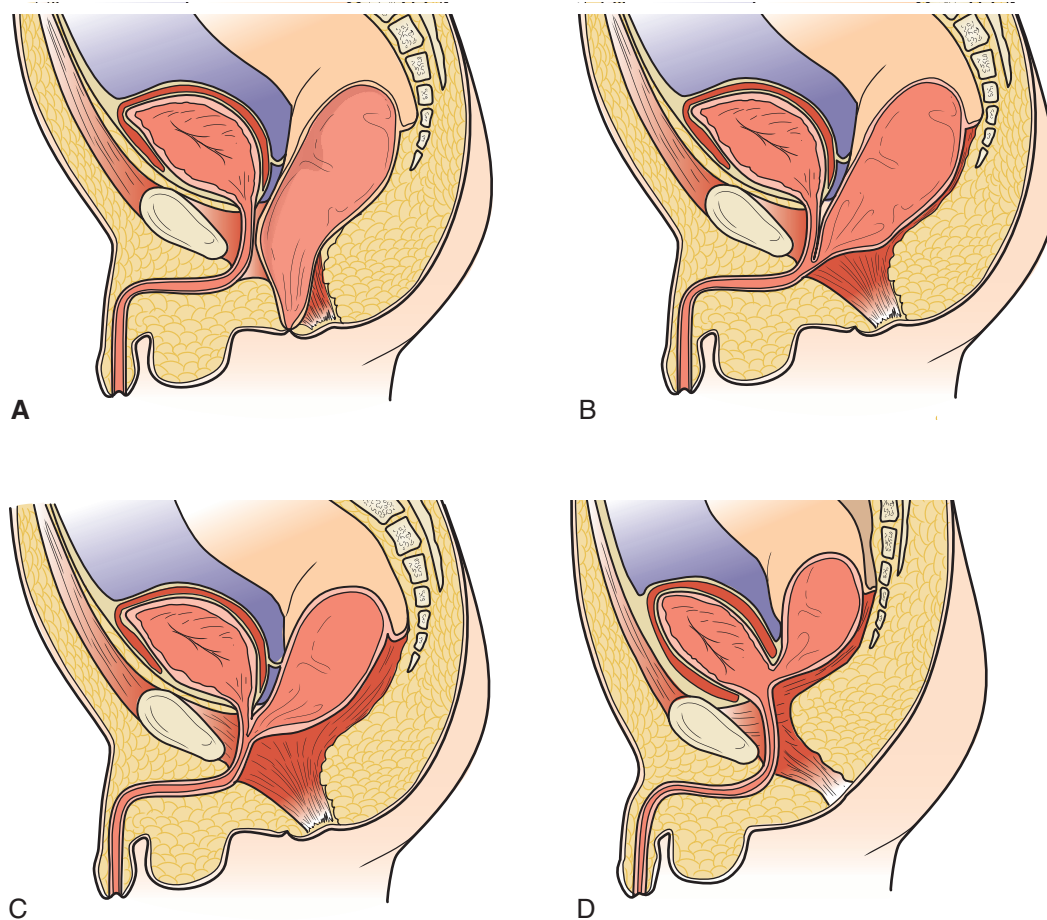
#### MALE

- Rectoperineal fistula
- Rectourethral bulbar fistula
- Rectourethral prostatic fistula
- Rectobladder neck fistula
- Imperforate anus without fistula
- Rectal atresia/rectal stenosis

#### FEMALE

- Rectoperineal fistula
- Rectovestibular fistula
- Rectovaginal fistula (extremely rare)
- Cloaca
- Imperforate anus without fistula
- Rectal atresia/rectal stenosis

#### COMPLEX MALFORMATIONS



**Figure 232-5** Spectrum of male defects. (A) Perineal fistula. (B) Bulbar urethral fistula. (C) Prostatic urethral fistula. (D) Bladder neck fistula.

represented by a group of muscles that form a funnel-shaped continuum. The surgeon must find the distal rectum, mobilize it, and place it within the sphincter mechanism.

### Anorectal Malformations in Males

#### Perineal Fistula

Perineal fistula is the lowest malformation (Figure 232-5). In this malformation, the rectum has passed normally through much of the sphincter mechanism, but the distal part of the rectum is anteriorly deviated and ends as a perineal fistula anterior to the center of the sphincter mechanism. Frequently, the fistula tract lies immediately below a very thin layer of skin, with the external opening somewhere in the midline from the anus to the ventral portion of the penis. One often perceives beneath the midline skin a black or white ribbon-like structure due to meconium or mucus. The infant with this defect can undergo an anoplasty without a colostomy. Prognosis is excellent because the patient has all the necessary anatomic elements for maintaining bowel control.

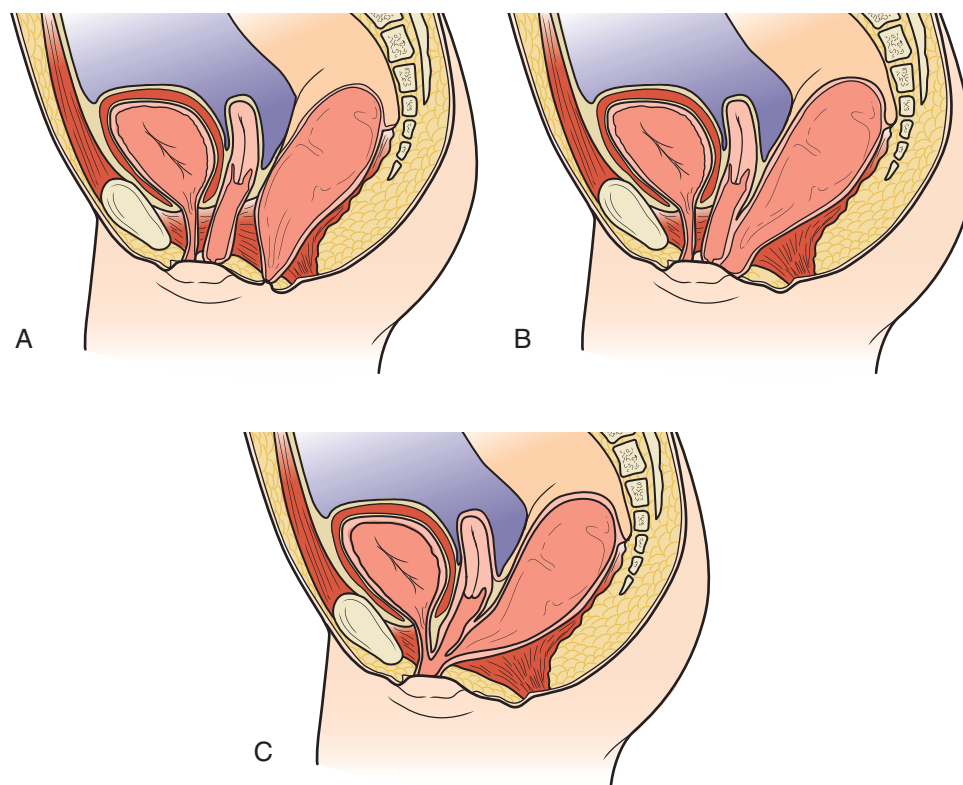
#### Anal Stenosis and Rectal Atresia

Anal stenosis and rectal atresia are defects that consist of a ring of fibrous tissue located at the anal verge. The

anal canal is normal. The fibrous ring causes a stricture, but the muscle structure and the anal canal are completely normal. A Hegar dilator or thermometer is introduced to detect the malformation. The typical symptom is difficulty moving the bowels; the parent describes a ribbon-like appearance to the feces. This defect is particularly associated with a presacral mass, usually a teratoma.

#### Rectourethral Fistula

Rectourethral fistula is the most frequent malformation seen in males. The rectum descends through a considerable portion of the funnel-shaped muscle structure, but at some point, it deviates anteriorly and connects with the urethra. The most frequent site of the fistula is the bulbar urethra (Figure 232-5). A significant number of urethral fistulas open at the prostatic urethra (Figure 232-6). The quality of muscle in an infant with a rectourethral fistula is usually good. Higher malformations are more frequently associated with a poor sacrum and consequently poor innervation and deficient sphincter muscle. These newborns require a colostomy at birth followed by a posterior sagittal anorectoplasty (PSARP) performed in the first few months of life.



**Figure 232-6** Spectrum of female defects. (A) Perineal fistula. (B) Vestibular fistula. (C) Cloaca.

### **Rectal-Bladder Neck Fistula**

In the case of a rectal–bladder neck fistula, the rectum opens at the level of the bladder neck (Figure 232-5). The sphincter complex is frequently underdeveloped. The frequency of association with an abnormal sacrum, “flat bottom,” and urologic problems is very high. These infants must be treated with a colostomy at birth followed by a PSARP with a laparotomy or laparoscopy. This group represents about 10% of males. Ninety percent of infants with this anomaly have other defects. The ultimate functional result is poor.

### **Imperforate Anus Without Fistula**

Imperforate anus without fistula is a rare anomaly, occurring in 5% of all children with ARM, half of whom suffer from Down syndrome. More than 90% of the patients with Down syndrome who have an ARM have this specific defect. Despite the fact that these children have the trisomy 21 anomaly, 80% will have voluntary bowel control later in life.

The rectum usually ends blindly about 2 cm above the perineal skin. Even without a fistula, only a very thin membrane separates the rectum from the urethra. These infants usually have good muscle quality and a well-developed sacrum. Treatment consists of a colostomy in the newborn period followed by a PSARP at several months of life.

## **Anorectal Malformations in Females**

### **Perineal Fistula**

Perineal fistula is the most benign defect on the female spectrum. As with the male abnormality, the rectum

traverses most of the sphincter mechanism, deviating in its most distal portion to communicate with the skin through a fistula located a few millimeters anterior to the center of the sphincter mechanism (Figure 232-6). These infants have all the necessary elements for bowel control. An anoplasty (ie, minimal PSARP) is sufficient to treat this type of malformation without the need for a colostomy.

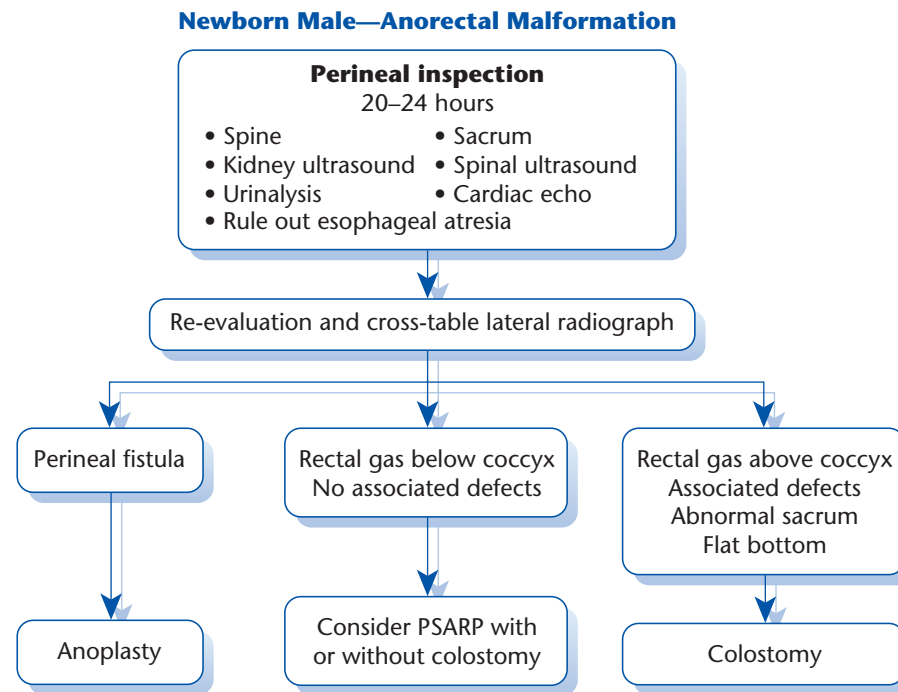
### **Vestibular Fistula**

Vestibular fistula is the malformation most frequently seen in females. The bowel is anteriorly deviated at a higher level, opening immediately behind the hymen into the vestibule (Figure 232-6). The rectum and the vagina have only a very thin, common wall separating them. The quality of sphincter muscle is usually excellent. Most patients have the potential for normal continence, a normal-appearing sacrum, adequate innervation, and a normal-looking perineum. There are exceptions in which one can find a vestibular fistula associated with rather inadequate muscle and a poor sacrum.

This malformation is frequently misdiagnosed as a *rectovaginal fistula*. A true vaginal fistula is extremely rare. Meticulous examination of the genitalia of a newborn is required to precisely localize the fistula site and make an accurate anatomic diagnosis.

An infant born with this defect, with no associated anomalies, who is otherwise well, can be operated on within the first 48 hours without a colostomy. However, one must be mindful that a protective colostomy is still a very valuable adjunct under several circumstances.





**Figure 232-7** Algorithm for the management of a newborn male with an anorectal malformation. PSARP, posterior sagittal anorectoplasty.

The most common one is the lack of experience in the performance of the definitive repair. Also, a baby with an associated defect or in very poor clinical condition may be optimally managed with a colostomy.

This particular malformation is the one that is unfortunately most frequently managed incorrectly. Even when these children have a high likelihood of bowel control, a failed procedure will often jeopardize that potential. A simple cut-back procedure, which does not include separating the vagina from the rectum, will almost always require a secondary repair as a consequence of incontinence and inadequacy of the perineal body.

#### **Imperforate Anus Without Fistula**

Imperforate anus without fistula is an uncommon malformation in females. The rectum is usually located about 2 cm above the skin. There is a good sphincter muscle, a good-looking perineum, and a well-developed sacrum. Half of these female babies, like the males, have Down syndrome. The surgeon can approach the patient posterosagittally and without a colostomy during the newborn period. The creation of a colostomy is still a reasonable alternative when the clinical circumstances are not ideal.

#### **Anal Stenosis and Rectal Atresia**

Anal stenosis and rectal atresia are treated in the same manner in females and males. Again, the surgeon must look for a presacral mass.

#### **Persistent Cloaca**

Persistent cloaca represents the extreme in the spectrum of complexity of female malformations. With this

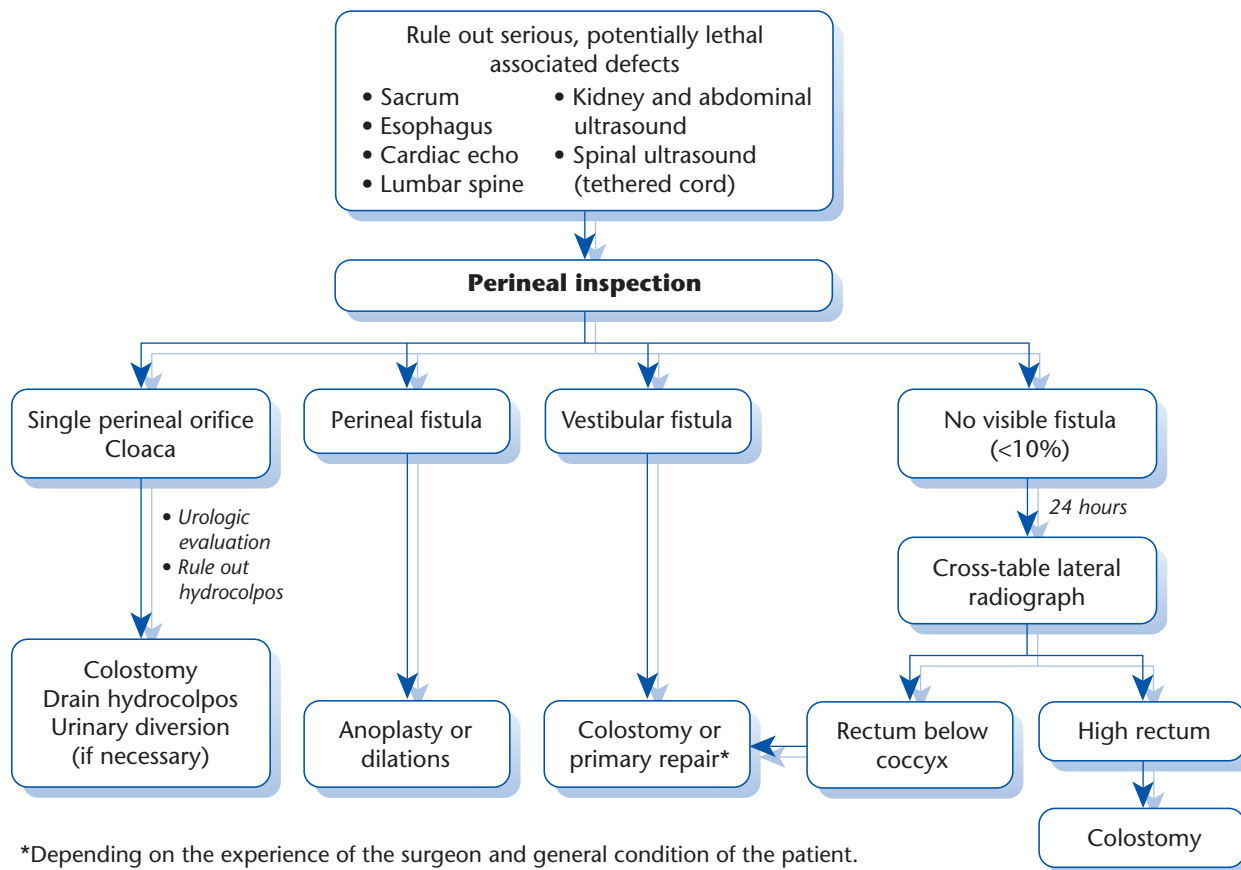
anomaly, the rectum, vagina, and urinary tract meet and fuse together into a single channel (Figure 232-6). Meticulous examination discloses a single orifice at the urethral site with no evidence of vagina or rectum.

Persistent cloaca is represented by a spectrum of defects. Many infants have a double or septated vagina, with different degrees of septation or division of the uterus. Frequently, the vaginal opening into the cloaca does not drain and thus collects urine, with a resultant hydrocolpos. The length of the common channel varies from 1 to 7 cm, which affects how challenging the repair will be. Lower, short cloacae, with good sphincter muscles and sacrum, are easier to repair; longer cloacae are frequently associated with poor muscles and inadequate sacrum, have poor potential for continence, and are a significant technical challenge to repair, often requiring complex maneuvers including vaginal replacement.

In managing this malformation, one is committed to achieving bowel control, urinary continence, menstruation, sexual function, and childbearing potential for the patient. These malformations are frequently associated with urologic concerns. In the newborn period, patients must have a colostomy, sometimes need a vaginostomy for decompression of a hydrocolpos, and occasionally require urinary diversion. At an appropriate interval, these procedures are followed by a definitive reconstruction, a posterior sagittal anorectovaginourethroplasty.

#### **Management in Males**

Figure 232-7 and Figure 232-8 illustrate an algorithmic approach to decision making in the management of newborn infants (male and female) with ARM.

**Newborn Female: Anorectal Malformation**

\*Depending on the experience of the surgeon and general condition of the patient.

**Figure 232-8** Algorithm for the management of a newborn female with an anorectal malformation.

Simple perineal inspection and a urinalysis in about 90% of cases will allow one to determine whether the patient needs a colostomy. It takes a significant amount of intraluminal bowel pressure to overcome the muscle tone of the sphincter mechanism to allow the meconium or the gas to reach the most distal part of the bowel and be forced through a tiny fistula orifice. This explains why diagnostic studies aimed at determining the height of the malformation and the location of the fistula, when performed before 16 to 24 hours of life, lead to an erroneous diagnosis of a “high” ARM. During the initial hours of life, potentially lethal conditions, mainly cardiac, esophageal, and urologic, must be ruled out. The baby should receive intravenous fluids and antibiotics and receive no oral food or fluids, with a nasogastric tube to avoid vomiting and aspiration. Abdominal ultrasound, spinal ultrasound, radiography of the lumbar and sacral spine, and an echocardiogram are performed. After 24 hours of observation, with a good index of suspicion and a perineal inspection, the surgeon will have enough information to determine whether the baby needs a colostomy or a primary repair. For a minority of patients (10%), a cross-table lateral film with the baby in prone position is needed; this will show the presence of gas in the most distal rectum and can help the

surgeon to determine whether to approach the baby with or without a colostomy.

### Management in Females

Determination of the need for a colostomy is an easier decision in female infants because in 95% of cases the bowel opening in the perineum is evident. Decisions concerning colostomy or primary repair should not be made before 24 hours of life. The first hours of life should be used to evaluate for hydrocolpos, hydronephrosis, a cardiac malformation, esophageal atresia, tethered cord, or other spinal defects. The presence of a cutaneous fistula (Figure 232-6) is evidence of a very low malformation, which can be treated with a minimal PSARP without a colostomy.

The presence of a vestibular fistula (Figure 232-6) can be an indication for a colostomy or primary approach, depending on the specific surrounding circumstances. If the surgeon has experience with the primary approach and the baby is full term and has no significant associated malformations, the operation can be done primarily within the first few days of life. If the baby is sick for other reasons or has significant associated defects, or if the surgeon does not have the necessary experience, it is better to open a colostomy and to postpone the main repair until a later date. Dilatation of the fistula with delayed reconstruction is also an option.

If the baby has a single perineal orifice, the diagnosis of a cloaca is established (Figure 232-6). The infant requires a full urologic evaluation and evaluation for a hydrocolpos. A colostomy is indicated, and it is mandatory to drain the hydrocolpos, if present, during the same operation. Occasionally, babies with a cloaca have a near atresia of the urethra and therefore need a vesicostomy.

If the baby does not have a visible fistula, which happens in about 5% of cases, a cross-table lateral radiograph with the baby in prone position can show rectal gas below the coccyx, and depending on the surgeon's experience, the patient can be approached primarily or posterosagittally; if the gas is located much higher than the coccyx, it is advisable to open a colostomy.

### Prognosis

Individuals born with an absent or poorly developed sacrum have poor potential for fecal and urinary continence. Infants with a normal sacrum and good sphincter muscle structures usually attain fecal and urinary control. PSARP permits reconstruction of these defects by placing the rectum in the optimal position to achieve the best functional results. However, many patients continue to have bowel management problems, primarily because of anal canal sensory impairment, sphincter deficiency, and motility disturbance. These can contribute to varying degrees of soiling and constipation.

In one series, voluntary bowel movements were noted in 75% of patients. When separated by diagnosis, the percentages varied: 100% in patients with rectal atresia and perineal fistulas, 95% in those with vestibular fistula, 80% in those with rectourethral bulbar fistula, 70% in those with cloacae, 65% in those with rectourethral-prostatic fistula, and 15% in patients with bladder neck fistula. Despite the fact that patients may have voluntary bowel movements, about 50% of them occasionally soil their underwear, particularly if the stools are loose. Constipation was a problem in 40% of all children and was more frequently noted in those with lower defects. Urinary incontinence was present in about 5% of males and females (excluding cloacal reconstructions). In those with cloacae, urinary incontinence was found in 20% of females who had a common channel shorter than 3 cm and in 80% of those who had longer common channels, but this can be managed with intermittent catheterization. Definitive conclusions about sexual function, menses, and obstetric potential require longer follow-up. Patients with fecal incontinence can be kept clean artificially with a bowel management program, which consists of a tailored daily enema.

### WHEN TO REFER

- As soon as diagnosis is made (prenatal or at birth)
- In a child with repaired ARM, with soiling at the age of potty training

### WHEN TO ADMIT

- A single perineal opening in a female
- Male newborn with a rectourinary fistula
- Major associated anomalies
- When there is abdominal distention, regardless of the presence of fistula

## RECTAL PROLAPSE

### Introduction

Rectal prolapse is a relatively common problem in children. It is usually seen before the age of 4 years, with a peak incidence in the first year of life, probably related to the relatively vertical configuration of the sacrum, a sigmoid colon that is very mobile, and rectal mucosa that is loosely attached to the underlying muscularis. Rectal prolapse ranges in severity from involvement of only a small ring of mucosa to involvement of all rectal layers. The mildest form, mucosal prolapse, is the most common form seen in children. The mucosa prolapses intermittently during defecation or crying and reduces spontaneously. It is particularly problematic when the child has severe constipation. The prolapse may progress to full thickness, which can only be reduced manually. The most severe form occurs when the prolapse cannot be reduced manually, which leads to venous congestion, vascular compromise, and ulceration.

### Causes

Rectal prolapse is usually idiopathic, but there may be an underlying cause that must be sought. Malnutrition, a common predisposing factor in the developing world, produces a depletion of the perirectal cushion and its supportive role for the pelvic diaphragm. Improvement of the nutritional status usually leads to resolution of prolapse.

Parental anxiety with premature attempts at toilet training and constipation is implicated in many cases of idiopathic rectal prolapse. Straining during defecation, spending long sessions on the toilet, protracted diarrhea, and chronic constipation allow stretching of the pelvic diaphragm and result in prolapse. Increased intra-abdominal pressure caused by straining during coughing spells, especially with lung diseases and straining during urination, are also known to produce prolapse in children.

Cystic fibrosis is present in up to 25% of cases of rectal prolapse in children. This prolapse is often recurrent and related to poor nutrition, poor muscle tone, increased intra-abdominal pressure due to the pulmonary component of the disease, and passage of large volumes of stool. Patients with neurologic disorders affecting the innervations of the pelvic floor, such as myelomeningoceles, often have paralysis of the levators and, with raised intra-abdominal pressure, are predisposed to having full-thickness rectal prolapse.

Rectal prolapse occurs in 3% of children who have had surgery for ARM. The severity of the prolapse after PSARP is related to the type of malformation. A higher malformation is indicative of more severe caudal regression and therefore weaker pelvic sphincter

muscles and nerves and a higher likelihood of rectal prolapse.

### Clinical Features

The parents usually make the diagnosis in most mild cases of rectal prolapse. They report a dark red, fleshy mass protruding from the anus following complaints of discomfort at the anus by the child while defecating. This may be seen along with mucus or blood but is usually painless. The prolapse may reduce spontaneously or after manual efforts by the child or parents. In most cases, the prolapse is absent between defecation and is not present when the child is examined. The history is geared toward identifying a predisposing factor.

A useful maneuver is to ask the child, if old enough to cooperate, to squat and see whether the prolapse can be identified. Digital rectal examination findings are usually normal. Differentiation between a mucosal and a full-thickness prolapse can be done by feeling the mass between the thumb and middle finger of the examining hand. The prolapse, if present, should be reduced gently and the rectum examined for the presence of an occasional polyp, which may be the predisposing factor. A patulous anus with a gaping anal canal may signify an underlying problem with pelvic innervation.

With a full-thickness prolapse that has been difficult to reduce manually, the child may present with pain and copious mucous discharge associated with the mass. Bluish discoloration is suggestive of venous congestion, and if the mass has been present for a long time, there may be areas of hyperemia and ulceration. It may be difficult to reduce in the clinic given the amount of edema, which can be helped by sprinkling sugar on the edematous area.

### Differential Diagnosis

It is important to differentiate rectal prolapse from a prolapsing intussusception of the sigmoid colon. The examining finger, in intussusception, feels a deep sulcus around the circumference of the mass such that the apex cannot be reached by the finger from below. This is unlike rectal prolapse, in which the finger runs in a continuous fashion over the mass and onto the rectal mucosa. It is sometimes impossible to clinically differentiate these 2 and an abdominal ultrasound or contrast enema is necessary.

Another differential diagnosis is a prolapsing rectal polyp occurring in the absence of a rectal prolapse. The polyp may appear during defecation or episodes of straining, and it reduces spontaneously.

### Management

Most cases of idiopathic rectal prolapse can be managed conservatively, which involves reduction of the prolapse, identification and treatment of predisposing factors, and prevention of constipation and straining. The prolapse, if present in the examining room, should be reduced. This can be done by grasping the mass between the fingers and pushing it gently back into the anus. In the presence of edema, reduction can be achieved by maintaining a gentle but firm and

steady pressure on the mass. Sprinkling sugar on the protruded mucosa helps eliminate some of the edema. In some instances, the mass may prolapse after reduction. Reduction should be repeated, and the buttocks may then be strapped together with adhesive tapes for a few hours to prevent repeat prolapsing. If the prolapse is recurrent, the parents can be taught how to effect a gentle reduction at home while the patient is being investigated for an underlying cause. Constipation usually can be managed appropriately once the primary condition is resolved. Laxatives may be beneficial in patients with chronic constipation.

Some changes to the toilet training technique may be beneficial. Having the child use a child-specific “potty” rather than an adult commode and prevention of prolonged sitting on the toilet are helpful to reduce the recurrence of the prolapse.

If there is recurrence despite conservative measures, a sigmoidoscopy to evaluate for the presence of rectal polyps should be performed.

Numerous options have been employed for surgical treatment after failure of a conservative approach. Injection sclerotherapy has a success rate of 75% to 90% and may need to be repeated or combined with other modalities to achieve better results. Complications include perirectal inflammation, ischiorectal abscess, urinary retention, and necrosis of the rectal mucosa. Perianal cerclage with Silastic bands or nonabsorbable sutures (Thiersch procedure) tightens the anal canal and prevents prolapse while allowing for the integrity of the perianal musculature to be restored. The success rate has been reported at more than 90%; complications include breakage of the cerclage and anal erosion. Open posterior rectopexy involves fixation of the rectum to the sacrum. Laparoscopic rectopexy involves suturing of the rectum to the periosteum of the sacral promontory. Other surgical techniques include cauterization therapy, mesh rectopexy, anterior sling rectopexy, rectosigmoid resection, mucosal stripping, and a transanal approach to resect the prolapse and perform an anoplasty similar to a Hirschsprung type of operation. The surgery is done under direct visualization, with protection of the dentate line and avoidance of fecal incontinence.

### Prognosis

Most patients (90%) with rectal prolapse between the ages of 9 months and 3 years are successfully managed conservatively. The prognosis, in terms of resolution of the prolapse, is poorer in children who develop prolapse after the age of 4 years. These children are likely to have neurologic or pelvic floor disorders.

#### WHEN TO REFER

- Irreducible prolapse
- Failure of conservative measures and having excluded a predisposing cause

#### WHEN TO ADMIT

- Irreducible prolapse



## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Pull-thru Network* (Web site), ([www.pullthrunetwork.org](http://www.pullthrunetwork.org))

### Medical Decision Support

- *Colorectal Center* (Web site), Cincinnati Children's Hospital ([www.cincinnatichildrens.org/service/c/colorectal/default](http://www.cincinnatichildrens.org/service/c/colorectal/default))

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## Chapter 233 COMMON COLD

Howard Fischer, MD

Colds are viral infections of the upper respiratory tract, and the mucosal surfaces that are lined with respiratory epithelium are involved. Thus, nasal passages, sinuses, eustachian tubes, middle ear spaces, conjunctivae, and the nasopharynx are potentially affected. The distribution of this illness is worldwide, and adults and children of all ethnic groups are susceptible. Colds are most common in preschool children, who average 6 to 8 colds per year, a number that is about 4 times the number expected in adults. Children who attend child care centers or who are exposed to other school-aged children tend to have more colds

than children who spend most of their time at home. Frequent infection in the preschool years might lower the frequency of colds in the school years.

## EPIDEMIOLOGIC FEATURES

Colds have always tended to occur more frequently during the cooler months in temperate climates, probably leading to the popular myth that exposure to cold weather leads to a cold. Fortunately, the common cold has been researched extensively in the past few decades, allowing primary care physicians to have a more scientific understanding of this illness. In fact, in the northern hemisphere, the incidence of colds peaks in early fall, remains high during the winter, and decreases in the spring. Studies have shown that exposure to a cold environment neither causes a cold nor decreases immunity that may potentially allow a viral infection to begin. Clearly, however, colds are more frequent in crowded situations, and evidence suggests that the infection begins most commonly after self-inoculation of a virus onto the individual's own nasal or conjunctival mucosa.

Because the viruses of infected individuals are shed in large numbers in nasal secretions, they can be spread easily by way of fingers and hands to objects such as clothing and environmental surfaces, where fingers of other children can acquire them and then self-inoculate their respiratory tracts by picking their noses or rubbing their eyes. Inhalation of virus-containing aerosols is also an effective means of virus acquisition. Studies in adult populations have shown that colds are more likely to develop after inoculation by rhinovirus in persons who are under chronic stress; whether this likelihood is the case in children is not known.

## ETIOLOGY

More than 100 different infectious agents can cause cold symptoms, with rhinoviruses and small RNA viruses of the picornavirus family implicated most frequently. In addition to many rhinovirus serotypes, other viruses and a few nonviral organisms are associated with the common cold (Table 233-1). Although respiratory syncytial virus and parainfluenza viruses most commonly cause a croupy cough and bronchiolitis in infants, they may cause a cold in older children and adults. Adenoviruses and enteroviruses tend to cause other

**Table 233-1** Causative Agents of Colds

AGENT	RELATIVE IMPORTANCE	PEAK SEASON
Rhinovirus	Most frequent cause	Autumn
Coronavirus	Frequent cause	Winter
Influenza virus	Less frequent cause	Winter
Respiratory syncytial virus	Less frequent cause	Winter
Parainfluenza virus	Less frequent cause	Autumn and spring
Enterovirus	Occasional cause	All seasons
<i>Mycoplasma pneumoniae</i>	Occasional cause	All seasons
Metapneumovirus	Unknown	Autumn and winter

Modified from Heikkinen T, Järvinen A. The common cold. *Lancet* 2003;361:51–59; Welliver RC. The common cold. In: Long SS, Pickering LK, Prober CG, eds. *Principles and Practice of Pediatric Infectious Diseases*. New York, NY: Churchill Livingstone; 1997; Esper F, Boucher D, Weibel C, et al. Human metapneumovirus infection in the United States: clinical manifestations associated with a newly emerging respiratory infection in children. *Pediatrics*. 2003;111:1407–1410.

symptoms in addition to those of a common cold, including pharyngitis and gastrointestinal problems.

### **PATHOPHYSIOLOGIC FEATURES**

When a cold-causing virus is introduced into the host's respiratory tract, assuming no immunity exists to the particular serotype, a local infection usually begins after an incubation period, the length of which depends on the specific virus. However, not all people who have a viral respiratory tract infection (defined as evidence of viral shedding and an increase in antibody titers) develop symptoms of a cold. In one study, only 75% of experimentally infected adults who shed rhinovirus type 2 and developed a greater than 4-fold rise in antibody titers actually developed symptoms. The symptoms of a cold are related primarily to the host's production of interleukin-8 and other vasoactive peptides in response to the viral infection, resulting in increased vascular permeability and mucus hypersecretion.

### **CLINICAL PRESENTATION**

Infants may begin their illnesses with fever; an older child, however, is usually afebrile, with a stuffy nose and watery nasal discharge, followed in a few days by sneezing. Generalized symptoms such as headache, malaise, and myalgia are uncommon with a rhinovirus infection, although they are seen in adenoviral and other viral infections. Infants tend to be irritable, have changes in feeding and sleep patterns, and sometimes develop mild diarrhea. By the third or fourth day of the illness, a dry cough may be present, and the nasal discharge usually becomes more purulent. Although such purulence has been interpreted in the past as indicating a secondary bacterial infection (eg, sinusitis), little evidence is available to support this impression. Of adults who had colds and sinus abnormalities on computed tomography scan, only 2% developed bacterial sinusitis. Furthermore, examination of purulent secretions has not shown increased aerobic bacterial growth or sloughing of nasal epithelial cells, and biopsies in volunteers demonstrate only loss of cilia and ciliated cells. Although viral sinusitis is a common finding during a cold, progression to bacterial sinusitis is probably quite rare in children.

Generally, the symptoms of a cold last about 1 week; however, a child may occasionally have mild rhinorrhea and a dry cough for 2 to 3 weeks. The cilia necessary for proper function of the respiratory epithelium may take as long as 3 weeks to return to their normal state, thus delaying the return to a symptom-free condition.

### **DIFFERENTIAL DIAGNOSIS**

Persistent nasal symptoms can also be caused by allergy. For allergies to be diagnosed initially as colds and later recognized as seasonal or associated with nasal eosinophilia is not uncommon. Cold symptoms associated with significant pharyngitis, rashes, or other systemic symptoms are usually caused by viruses other than those causing the common cold. Streptococcal pharyngitis is not usually associated with rhinorrhea or cough.

Occasionally, a persistent purulent nasal discharge in children younger than 2 years results from a  $\beta$ -hemolytic

streptococcal infection, although this condition is usually associated with mild excoriations around the nares. Unilateral nasal discharge must also be evaluated carefully to rule out a nasal foreign body. Finally, irritation and swelling of the nasal passages from inhalation of drugs such as cocaine or the chronic use of medicated nasal sprays should be considered in the older child who has persistent cold symptoms. The possibility of infection with *Bordetella pertussis* should be considered in a child with persistent cough. Children who have been partially immunized may not have a characteristic whoop associated with *B pertussis* infection.

## **MANAGEMENT**

### **Laboratory Procedures**

No routine tests exist to diagnose the common cold. Viral cultures are expensive and generally unnecessary; thus, the diagnosis should be made on clinical grounds. The most common concern is that an underlying bacterial infection (eg, sinusitis, acute otitis media) is missed or treated improperly. If a cold follows its expected course of causing usual symptoms for 5 to 7 days, then a concurrent bacterial infection is unlikely. When the symptoms of a cold are prolonged, a secondary infection may be present, especially if fever persists or is prominent or if ear pain or a productive cough develops. Thus, ear and lung examinations are essential for a child whose cold has persisted longer than expected. The routine use of radiographs or computed tomography scans to diagnose sinusitis is not necessary because when studied (albeit in older individuals), the radiologic finding of opacification of the sinuses has not correlated with the clinical indications of sinusitis.

### **Treatment**

The various remedies available for the common cold provide—at best—symptomatic rather than curative treatment. In children, most of the remedies give only marginal symptomatic relief, if any; in many cases, they are potentially quite harmful. Over-the-counter cough and cold medications should not be used in children younger than 2 years because serious and potentially life-threatening side effects can occur from their use. Furthermore, studies have shown that these medications are generally ineffective in children younger than 6 years. Most pediatricians, at most, suggest saline nose drops with the use of a bulb syringe to aspirate secretions and a cool-mist vaporizer to humidify room air. The malaise and fever sometimes associated with a cold can be treated with acetaminophen or ibuprofen; aspirin should be avoided in children because of its association with Reye syndrome. Some studies suggest that ibuprofen may be more beneficial during a cold than acetaminophen because it leads to a shorter period of viral shedding and a better neutralizing antibody response.

Studies conducted on preschoolers have not demonstrated a beneficial effect of decongestants or antihistamines, singly or in combination. In older children and adolescents, an oral decongestant such as pseudoephedrine hydrochloride, either alone or

with an antihistamine (probably owing to antihistamine's anticholinergic effect), provides symptomatic relief with a low possibility of side effects. The use of nasal spray or drops containing vasoconstrictors such as oxymetazoline hydrochloride should be discouraged because of the high incidence of rebound nasal congestion after only a few days of use. Although studies in adults indicate some decrease in symptoms when steroid or atropine-like nasal sprays are used, their use in children has not been evaluated. The use of mast cell stabilizers, such as nedocromil and sodium cromoglycate given intranasally or by inhalation, has shown some promise in adult studies. Their place in pediatric care is not clear.

The use of zinc lozenges to reduce the duration of cold symptoms has been studied extensively in adults in recent years with conflicting results. Despite at least 8 placebo-controlled trials and several reviews of these studies, the efficacy of zinc lozenges remains controversial. Studies of potential antirhinoviral drugs are still too preliminary to judge their therapeutic potential. Many parents will ask about the advisability of giving vitamin C during a cold, and many will request that the physician prescribe antibiotics. Vitamin C use has not been proved efficacious. Discouraging antibiotic use is particularly important when bacterial infection is unlikely, given current evidence of the increasing drug resistance among some bacterial pathogens.

Because of the lack of effective treatment for the common cold, parents may turn to alternative treatments. A commonly used cold treatment is an extract of the plant *Echinacea*. A recent randomized clinical trial showed no benefit to the use of extract of *Echinacea purpurea* in treating children 2 to 11 years of age at the onset of their colds. Similarly, a randomized clinical trial in adults using *E angustifolia* extract showed no benefit in treating experimental rhinovirus infection.

## COMPLICATIONS

Most colds are self-limited and resolve without the help of the physician or of any medication. When a fever arises 3 to 4 days after cold symptoms begin or symptoms continue longer than expected, a complication such as otitis media or pneumonia should be suspected. A cold can apparently contribute to eustachian tube dysfunction, especially in younger children, resulting in acute otitis media. A fever, headache, and unilateral purulent nasal discharge may herald a secondary bacterial sinusitis, although this condition is probably diagnosed more frequently than it occurs. On rare occasions, a lower respiratory tract infection develops and may progress to pneumonia, characterized by cough, tachypnea, and usually fever. The pneumonia may have a viral origin or may be caused by a secondary bacterial infection. Chest radiograph can confirm the diagnosis.

The role of rhinovirus infection as a trigger of exacerbation of reactive airway disease has now been well documented; thus, the development of wheezing or a prolonged cough after a cold should alert the physician to this possibility.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *About Antibiotic Use and Resistance* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/getsmart/community/about/index.html](http://www.cdc.gov/getsmart/community/about/index.html))
- *Children and Colds* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/ear-nose-throat/pages/Children-and-Colds.aspx](http://www.healthychildren.org/English/health-issues/conditions/ear-nose-throat/pages/Children-and-Colds.aspx))
- *Respiratory Syncytial Virus (RSV)* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Sinusitis and Your Child* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

### Medical Decision Support

- *Red Book: 2015 Report of the Committee on Infectious Diseases*, 30th ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

## AAP POLICY

American Academy of Pediatrics Committee on Drugs. Use of codeine- and dextromethorphan-containing cough remedies in children. *Pediatrics*. 1997;99(6):918–920. Reaffirmed October 2006 ([pediatrics.aappublications.org/content/99/6/918](http://pediatrics.aappublications.org/content/99/6/918))

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## Chapter 234

# CONGENITAL AND ACQUIRED HEART DISEASE

Michael A. McCulloch, MD; Robert J. Gajarski, MD, MHSA

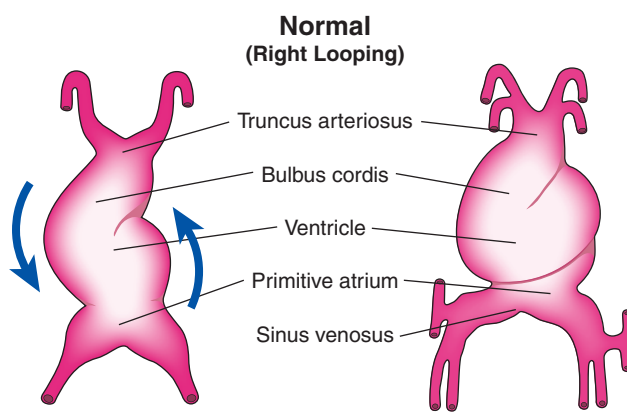
The initial evaluation, continued care, and timing for referral of children with congenital and acquired heart disease are aided by a basic understanding of cardiac embryology, genetics, anatomy, and physiology.

## EMBRYOLOGY

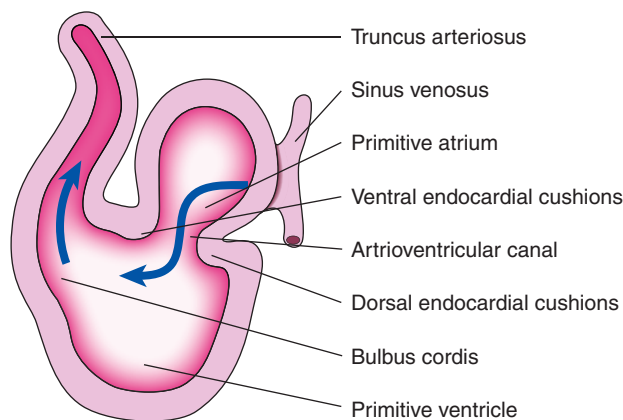
Understanding fetal cardiac embryology allows insight into possible sources of error and how these imperfections can lead to clinically significant congenital heart diseases (CHDs).

The primitive heart starts as a linear tube that begins pulsating in a coordinated fashion to produce forward flow at approximately 17 days postconception and becomes the first functioning organ in the developing embryo. Small invaginations separate the primitive heart into 5 distinct regions. From caudal to cranial, they are the sinus venosus, primitive atrium, primitive ventricle, bulbus cordis (conus), and truncus arteriosus. These segments ultimately form the cardiac chambers and some of the extracardiac blood vessels.

At approximately 20 to 23 days postconception, the primitive heart segments demonstrate differential rates of growth, resulting in curving or looping of the heart on itself (Figure 234-1). As a result, the sinus venosus and primitive atrium are positioned dorsal and cranial to the primitive ventricle, whereas the bulbus cordis and truncus arteriosus are slightly ventral and cranial. At this stage of development, the individual cardiac segments have experienced very little differentiation. The primitive atrium is a single chamber receiving all blood from the sinus venosus. This blood is then propelled forward into the primitive ventricle, bulbus cordis, truncus arteriosus, and the rest of the developing embryo (Figure 234-2).



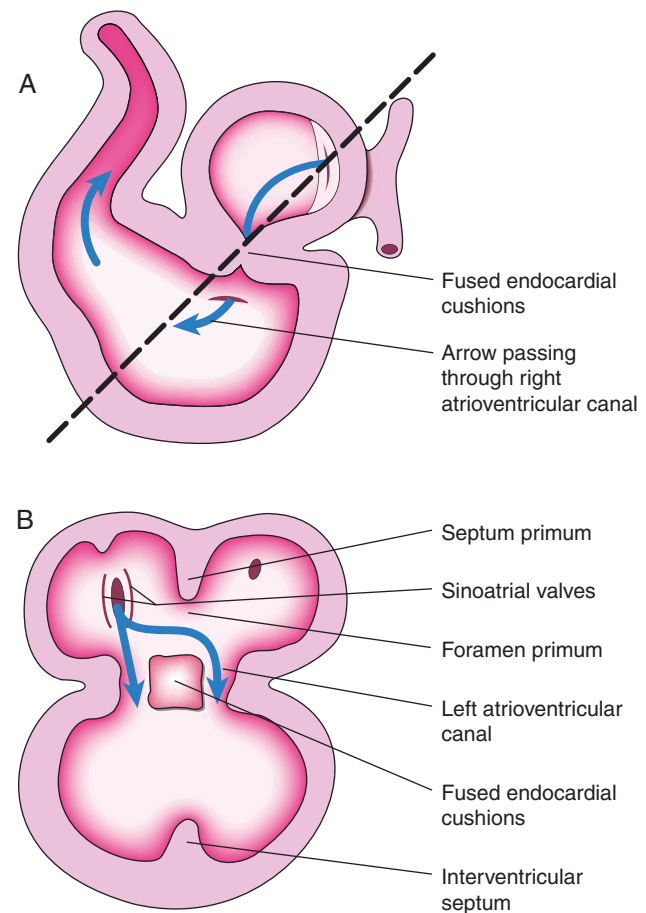
**Figure 234-1** Depiction of the embryologic heart tube undergoing normal, rightward looping. The primitive atrium and sinus venosus ultimately change their location from posterior and caudal to dorsal and cephalad. (From Moore KL, Persaud TVN. *The cardiovascular system*. In: Moore KL, Persaud TVN, eds. *The Developing Human: Clinically Oriented Embryology*. 5th ed. Philadelphia, PA: WB Saunders; 1993, with permission. Copyright © 1993, Elsevier.)



**Figure 234-2** Rightward looped embryologic heart sectioned along its sagittal plane. The arrows depict the normal course of blood flow at 20 to 23 days postconception. (From Moore KL, Persaud TVN. *The cardiovascular system*. In: Moore KL, Persaud TVN, eds. *The Developing Human: Clinically Oriented Embryology*. 5th ed. Philadelphia, PA: WB Saunders; 1993, with permission. Copyright © 1993, Elsevier.)

In the beginning of the fourth week, the atrioventricular valves begin to form. Two collections of cells, called endocardial cushions, proliferate from the ventral and dorsal surfaces of the primitive heart at the junction of the primitive atrium and primitive ventricle. These endocardial cushions grow toward each other and ultimately fuse. Concurrent with this formation is the development of walls, or septa, which ultimately separate the primitive atrium into right and left atria, the primitive ventricle into the left ventricle, and the bulbus cordis into the right ventricle (Figure 234-3). The crux of the heart is formed when the atrial and ventricular septa attach to the fused endocardial cushions, transforming the linear heart tube into 4 distinct chambers.

While the atrioventricular valves and cardiac septa are being formed, the truncus arteriosus is simultaneously dividing into the primitive aorta and pulmonary



**Figure 234-3** Rightward looped embryologic heart sectioned along its coronal plane. Illustration demonstrates fusion of the endocardial cushions and the resulting sites of the future mitral and tricuspid atrioventricular valves. At this stage of development, postconception days 22 to 25, the developing embryologic heart has double-inlet left-ventricle and double-outlet right-ventricle morphology. (From Moore KL, Persaud TVN. *The cardiovascular system*. In: Moore KL, Persaud TVN, eds. *The Developing Human: Clinically Oriented Embryology*. 5th ed. Philadelphia, PA: WB Saunders; 1993, with permission. Copyright © 1993, Elsevier.)



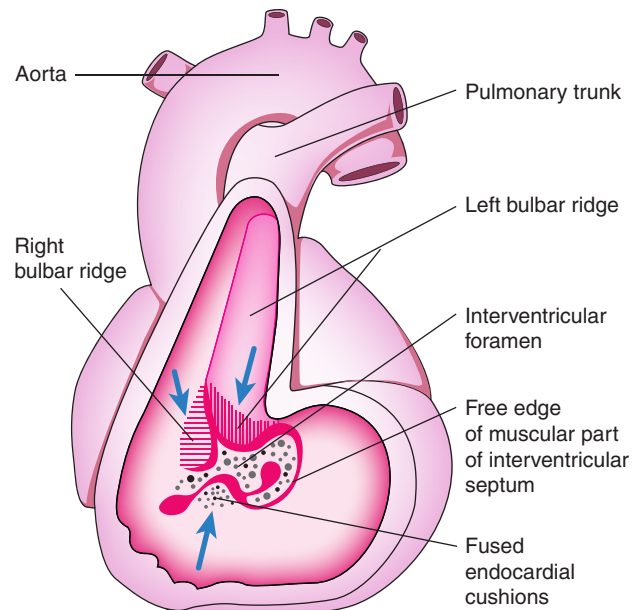
artery (Figure 234-4). The aortopulmonary septum is formed when 2 ingrowths of tissue develop and proliferate toward one another. When they meet in the midline, the truncus arteriosus is divided approximately in half. The caudal end of this septum will ultimately fuse with the region of endocardial cushion and atrioventricular septal connection (Figure 234-5).

Before fusion of the endocardial cushions and aortopulmonary and atrioventricular septa, all the blood flow from the left and right atria returns directly to the primitive ventricle (future left ventricle), through the bulbo-ventricular foramen to the bulbous cordis (future right ventricle), and ultimately to the truncus arteriosus. The truncus arteriosus then provides blood to the developing pulmonary arteries and aorta. Therefore, at this stage in development, the heart is functionally a double-inlet left ventricle and a double-outlet right ventricle.

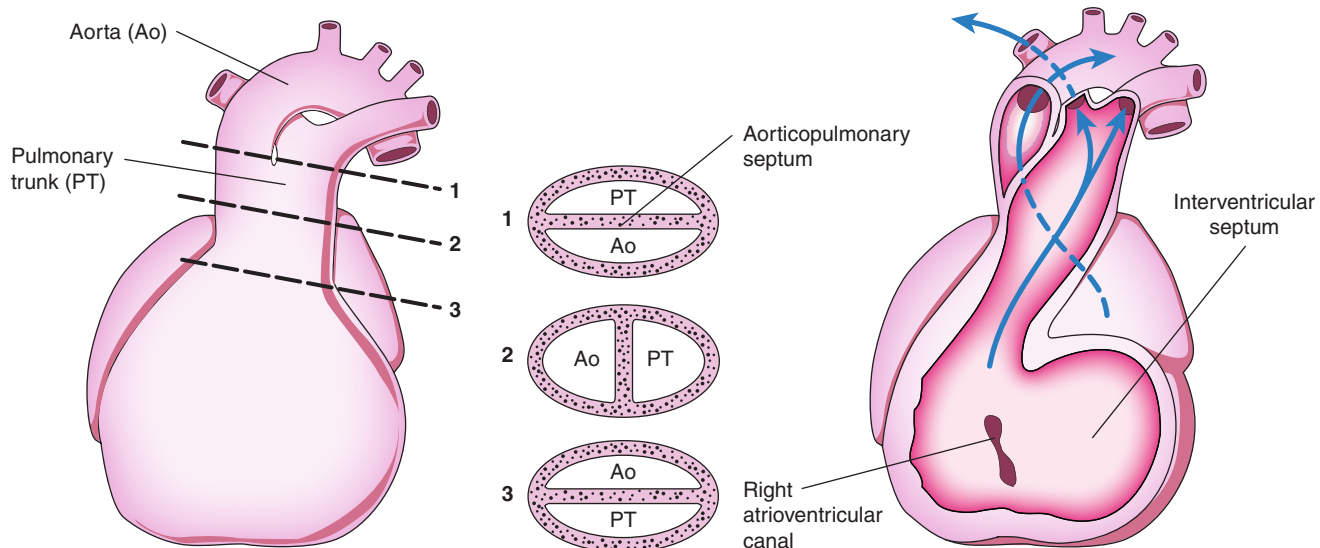
The progression from a double-inlet left ventricle and double-outlet right ventricle heart to a 4-chambered heart with separate great arteries to the body and lungs is understandably complex. This process involves migration of the developing atrioventricular valves, with their respective atria, and the truncus arteriosus, with its developing great arteries, toward one another. This relocation of the major heart structures results in the atria and great arteries being positioned directly over their respective ventricles. Final cardiac anatomic form is achieved by approximately 8 weeks postconceptional age and only increases in size until birth.

## GENETICS OF CONGENITAL HEART DISEASE

CHD is the most common birth defect in the United States, with an incidence of 8.1 to as high as 50 per 1,000 live births, depending on inclusion criteria. As a



**Figure 234-5** Final stages of cardiac development demonstrated in the coronal plane, removing the ventral portion of the developing right ventricle and pulmonary artery. Both the atrioventricular canal and great arteries have been formed. The superior portion of the IVS and the inferior portion of the aortopulmonary septum will meet at the region of the fused endocardial cushions. Once this step is completed, the embryologic heart will be separated into 4 distinct chambers and function as a mature heart. (From Moore KL, Persaud TVN. *The cardiovascular system*. In: Moore KL, Persaud TVN, eds. *The Developing Human: Clinically Oriented Embryology*. 5th ed. Philadelphia, PA: WB Saunders; 1993, with permission. Copyright © 1993, Elsevier.)



**Figure 234-4** Division of the truncus arteriosus into the pulmonary artery and aorta. The aortopulmonary septum is formed by 2 opposing ingrowths of tissue and results in a spiraling of the forming great arteries around one another. (From Moore KL, Persaud TVN. *The cardiovascular system*. In: Moore KL, Persaud TVN, eds. *The Developing Human: Clinically Oriented Embryology*. 5th ed. Philadelphia, PA: WB Saunders; 1993, with permission. Copyright © 1993, Elsevier.)

growing number of these patients survive to have children of their own, understanding the genetic basis of their heart defect becomes increasingly important. However, this endeavor is significantly complicated by CHD's genetic heterogeneity, because different gene mutations cause similar heart defects and single gene mutations can produce a variety of different heart defects. The fetal environment further influences gene expression. Therefore, although autosomal-dominant inheritance can exist with multiple syndromes (eg, DiGeorge, Williams, Alagille, Noonan, Holt-Oram), even these recognizable phenotypes are commonly caused by sporadic mutations. A large cross-sectional study of 1.7 million Danish citizens demonstrated only 2.2% of CHD patients had affected first-degree relatives, supporting a larger role for spontaneous or recessive genetic mutations whose expression may be accentuated by in utero exposures.

Conversely, many well-recognized genetic syndromes are associated with specific CHDs. Approximately 50% of trisomy 21 patients have CHD, with atrioventricular canal defects present in 45%. Children with Turner syndrome commonly have abnormalities of the aortic valve and aortic arch with some form of CHD occurring in 21%. Aneuploidy of chromosomes 18 and 13 are almost universally associated with hemodynamically significant ventricular or atrial septal defects and valvular disease. Noonan syndrome (pulmonary stenosis, hypertrophic cardiomyopathy), 22q11 deletion/DiGeorge syndrome (left ventricular outflow tract obstruction, aortic arch anomalies), Alagille syndrome (peripheral pulmonary stenosis) and many other common syndromes have a relatively predictable CHD profile.

Although chromosomal abnormalities were historically documented in only 8% to 13% of all neonates with CHD, the advent of fluorescence in situ hybridization (FISH) and other testing modalities has significantly increased the incidence of documented gene malformations in these patients. Such information could prove invaluable by identifying other possible organ system involvement, long-term prognostic information, commensurate reproductive risks for children and their family, and determining whether other family members should also undergo genetic testing. For these reasons, some institutions obtain genetics consultations for all patients newly diagnosed with CHD.

## CONGENITAL DEFECTS

### Intracardiac Shunting Lesions

Shunting lesions are heart defects in which a proportion of the blood volume from one side of the heart is added to the blood volume on the other side. Shunting can be from the left side of the heart to the right, the right side of the heart to the left, or bidirectional. The right heart is composed of the systemic veins (inferior vena cava [IVC] and superior vena cava [SVC]), an atrium, a ventricle, and a great artery; generally, these structures are the right atrium, right ventricle, and pulmonary artery, respectively. Conversely, the left heart is composed of the pulmonary veins, an atrium, a ventricle, and a great artery; generally, these

structures are the left atrium, left ventricle, and aorta, respectively.

### Physiology

The process of *adding* or shunting blood from one side of the heart to the other is regulated by a few basic principles of physics. First, blood flows from the higher resistance circuit into a lower resistance circuit. In a normal heart, left-sided resistance are considerably higher than those on the right, and, if given the opportunity, blood will preferentially shunt from left to right. The volume of shunted blood also depends on the size of the defect through which it flows. A very large defect will allow considerably more flow to shunt from the left heart to the right than a small defect. However, even if the defect is large, if the resistance difference is minimal (as with pulmonary hypertension), the volume of shunted blood will be small.

Different components of the cardiovascular system will respond uniquely to volume or pressure loading. Atria and ventricles will gradually dilate to accommodate excess blood volume (preload) being added to their respective chambers. If faced with excess pressure (or afterload), then the ventricular myofibers will hypertrophy not only to generate the required driving pressure, but also to minimize myocardial wall stress for maximal pump efficiency. The pulmonary arterioles can also hypertrophy when subjected to prolonged periods of high pressure. However, although cardiac dilatation and hypertrophy are generally reversible, the pulmonary arteriolar hypertrophy associated with longstanding pulmonary hypertension often is not and can result in increased pulmonary vascular resistance (PVR) and fixed, deadly pulmonary hypertension.

### Clinical Manifestations

A cardiac murmur is audible blood flow through the heart or vascular system. A murmur can be auscultated in a normal heart resulting from hyperdynamic function or a thin chest wall. Generally, a diastolic murmur is not normal. A systolic murmur may be normal (functional) or it may be pathologic. Regardless of the timing, location, or cause of the murmur, its frequency and pitch depend on the size of the opening through which the blood flows and on the pressure gradient across it.

### Left-to-Right Shunting Lesions

#### Ventricular Septal Defect

One of the most common types of CHD is the ventricular septal defect (VSD). Nearly 20% of patients in heart disease registries have a solitary VSD. This defect, or hole, in the septum separating the 2 ventricles allows blood to traverse from one side of the heart to the other. Left-sided heart pressure generally exceeds that on the right side. Therefore, blood will preferentially shunt from left to right. Given that most VSDs are positioned in the membranous septum near the aortic and pulmonary valves, the volume of shunted blood is not *seen* by the right ventricle and is instead added directly to the pulmonary

circulation. In the case of large VSDs, this addition of blood results in left-ventricle volume overload. Over time, the left heart will dilate to accommodate this increased volume. This dilatation is likely mediated by fiber realignment in response to the volume load, which causes increased wall stress. Increased muscle mass, or myocyte hypertrophy, occurs to normalize this wall stress. However, the abnormal mechanical stresses that are inherent in the chronically volume-loaded, dilated ventricle can ultimately result in myocyte dysfunction and heart failure. In contrast, although a small VSD will still result in left-to-right shunting, the smaller defect will allow a proportionately smaller volume of shunted blood that may never be hemodynamically significant.

### **Atrial Septal Defect**

Another differential lesion with left-to-right shunting is the atrial septal defect (ASD). Similar to the VSD, the volume of shunted blood depends on the size of the defect. In contrast to the VSD, however, shunting across an ASD is dependent on a difference in atrial compliances, not a difference in resistances. A difference in chamber compliance is the dominant force directing blood from left to right. The highly compliant right atrium becomes a sink for blood draining into the smaller, less compliant left atrium by the pulmonary veins. This additional blood volume is then routed into the right ventricle, resulting in right-heart dilatation over time.

### **Clinical Manifestations of Atrial Septal Defect and Ventricular Septal Defect**

Despite increasing sensitivity of fetal echocardiography, smaller ASDs and VSDs may not be detected prenatally. Instead, they are usually detected by the presence of a murmur, with or without the signs of heart failure. The timing of their presentation depends on the size of the defect and whether the infant has fully transitioned from fetal circulation.

Right- and left-sided resistances are nearly equivalent shortly after birth and do not produce a substantial pressure gradient for the shunting of blood. During the transition to postnatal circulation, as the PVR falls, the left-right gradient increases along with the volume of oxygen-rich blood shunted to the right heart. A small VSD with a high pressure gradient between the 2 ventricles will produce a high-pitched, holosystolic murmur that continues from the onset of ventricular systole through the closure of the atrioventricular valves (obscuring the first heart sound) to the closure of the semilunar valves. A large VSD may not produce a murmur because the interventricular pressure gradient will be minimal. The VSD murmur will be loudest at the left lower sternal border and may be best described as a mid-frequency blowing murmur. Auscultation of an ASD will differ significantly from that of a VSD. The lack of a marked pressure gradient between the 2 atria does not produce a murmur at the site of shunting. Rather, the murmur of an ASD is caused by excess volume traversing the pulmonary valve, commonly described as a “relative” pulmonary stenosis. It is described as a mid-frequency systolic ejection murmur best auscultated at the left sternal

border and will commonly radiate to the lung fields bilaterally.

By definition, left-to-right shunting results in pulmonary overcirculation. However, the symptoms of pulmonary edema typically do not develop until the pulmonary artery blood flow has doubled in volume. A neonate with a large VSD may demonstrate poor weight gain and lethargy as PVR decreases, increasing the gradient for shunting from the left ventricle to the right; if untreated, then heart failure (marked pulmonary overcirculation) may ensue. Conversely, the relatively smaller volume of blood shunting across a comparably sized ASD will remain asymptomatic for many years. Regardless of the mechanism, the PVR will reflexively increase in proportion to the degree of shunt volume (in ASD and VSD) and pressure (in VSD) to reduce stress on the arteriolar walls. Over time, these pulmonary arterioles can become quite hypertrophied and unable to vasodilate. This irreversible state of pulmonary arteriolar vasoconstriction results in pulmonary hypertension.

### **Evaluation of Atrial Septal Defect and Ventricular Septal Defect**

**ELECTROCARDIOGRAM.** The electrocardiogram (ECG) can be normal for age in patients with both ASDs and VSDs. As chamber dilatation or hypertrophy occurs, however, signs of ventricular or atrial enlargement may develop (Figure 234-6). The classically described ECG finding for patients with ASDs is an RSR' in lead V1 from volume overload of the right ventricle. The ECG may also be helpful for identifying the onset of pulmonary hypertension by the gradual development of right-ventricular hypertrophy (Figure 234-7).

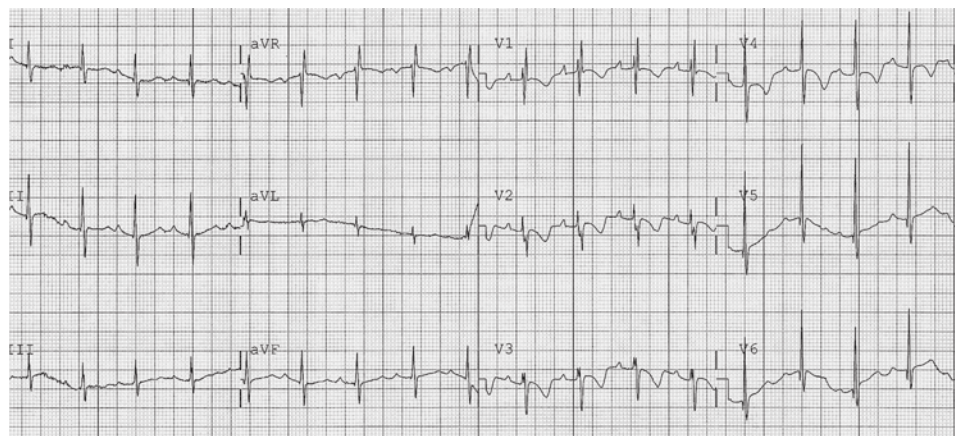
**CHEST RADIOGRAPH.** Chest radiography is generally noncontributory in diagnosing left-to-right shunt lesions before the onset of pulmonary overcirculation and the resulting pulmonary edema. Once pulmonary overcirculation has developed, however, the cardiac silhouette will gradually increase in area, and pulmonary vascular markings will become substantially more prominent. Chest radiography can also be used to help assess effectiveness of medical management such as diuretic therapy.

**ECHOCARDIOGRAM.** Any child with a known congenital heart defect should be primarily managed by a pediatric cardiologist along with his or her primary care pediatrician. When present, a 2-dimensional echocardiogram will show a defect in the interatrial or inter-ventricular septum and allow for determination of cardiac function (Figure 234-8). Doppler flow velocities across the defect can estimate pressure differences between the respective chambers. Together, this information can help guide timing and type of surgical correction, if indicated.

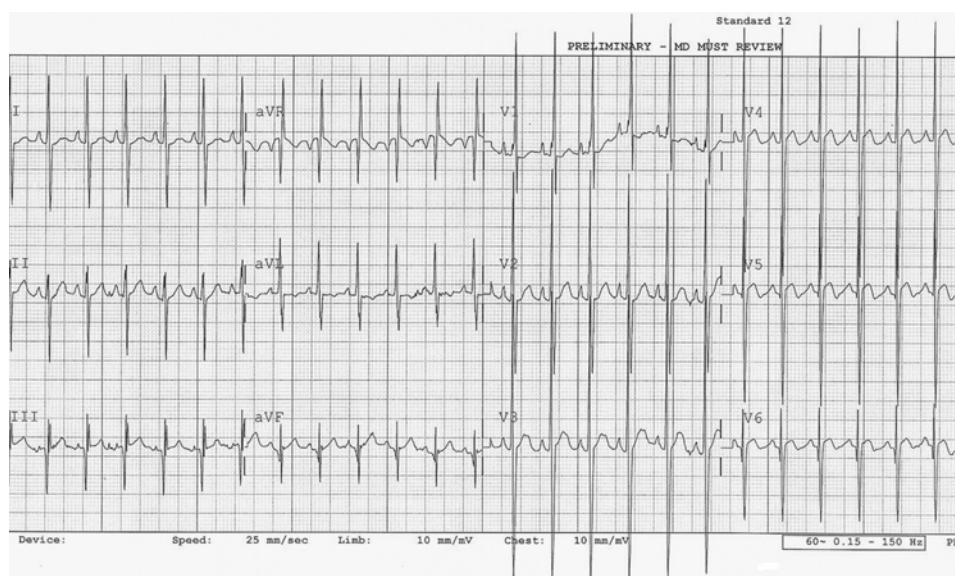
### **Management of Atrial Septal Defect and Ventricular Septal Defect**

Children with known septal defects should be monitored closely for weight gain, development, and clinical status. Any signs of respiratory distress or failure to thrive will generally occur during the first 6 months of





**Figure 234-6** ECG of a 3-year-old boy with a large ASD. Note the RSR' in lead V1 and mildly peaked P waves in leads V1 and II. These findings are consistent with right-ventricular and right-atrial dilatation, respectively.



**Figure 234-7** ECG of a 2-year-old child with a large VSD. Note the large voltages of both R and S waves in all of the precordial leads as well as right-axis deviation of the QRS axis. These findings are consistent with biventricular hypertrophy and elevated PVR caused by longstanding exposure of the pulmonary vasculature to left-sided blood pressures.

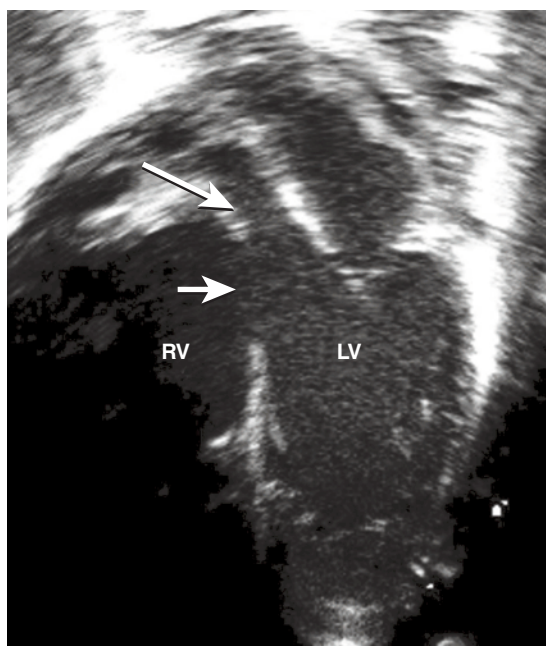
life and should prompt re-evaluation by the pediatric cardiologist. Although medical management (ie, diuretics, potentially afterload reduction) can temporarily improve these complications, definitive closure of either an ASD or VSD is indicated when signs of pulmonary overcirculation develop.

#### **Prognosis of Atrial Septal Defect and Ventricular Septal Defect**

Small ASDs and VSDs can close spontaneously. Small defects in the muscular portion of the interventricular septum (IVS) are often closed by the trabeculated muscle growth of the right ventricle; VSDs in other regions of the IVS may also close, but this is relatively less common. Researchers have suggested that the natural history of secundum-type ASDs is largely

dependent on the initial defect size, with nearly 85% of those less than 5 mm in diameter closing spontaneously versus less than 2% when the defect is more than 8 mm in diameter. Children with moderate or large VSDs that do not close spontaneously or are not associated with pulmonary overcirculation are at risk for developing the serious complication of pulmonary vascular obstructive disease (PVOD). The normal, physiologic decline of PVR after birth is altered when the lungs are subjected to excess volume from left-to-right shunting. In some children, the PVR never decreases after birth or decreases at a slower rate and then increases. These children will have few or no symptoms of pulmonary overcirculation. As a result, they may not be brought to a physician's attention. Persistently elevated PVR, especially if associated with





**Figure 234-8** Apical 4-chamber echocardiographic view of a 4-month-old infant with a large VSD (*short arrow*). Note the dilated left ventricle and the relationship of the defect to the aortic valve (*long arrow*).

hypoxemia, is a potent stimulus for intimal and medial thickening of the pulmonary arterioles. Elevated PVR produces elevated pulmonary artery pressures and eventually pulmonary hypertension (mean pulmonary pressures exceed 25 mm Hg at rest). If unrepaired, children with this physiologic situation will have persistently elevated PVR that can eventually become irreversible. This state can occur as early as 6 months of age, particularly in children with trisomy 21 (Down syndrome) and as early as 1 year in children without Down syndrome. When pulmonary artery pressures exceed those of the left ventricle, the direction of shunted blood will become right to left, producing central cyanosis (Eisenmenger syndrome). Therefore surgical correction of these defects must be accomplished in a timely fashion.

Surgical mortality rates are reported as less than 1% for both ASDs and VSDs. Alternatively, device closure of ASDs in the cardiac catheterization laboratory is becoming more common. A recent study comparing device closure of ASD with surgical correction demonstrated a failure rate requiring surgical repair in 4% of device patients but a complication rate of only 7.2% compared with 24% in the surgical group. Device closure of VSDs is currently being performed in limited situations. Success rates have been reported to be 99% but have been associated with a nearly 50% serious complication rate. Ongoing cardiology care is recommended throughout childhood and adolescence to monitor for intermediate-term or late sequelae, including development of subpulmonic stenosis or aortic insufficiency (after VSD closure) or atrial tachyarrhythmias (particularly after late ASD closure).

## Other Common Left-to-Right Shunting Lesions

### Patent Ductus Arteriosus

When the ductus arteriosus does not involute shortly after birth, it is a potential source of shunting from the aorta to the pulmonary arteries once PVR decreases. A patent ductus arteriosus (PDA) is most commonly encountered in premature infants and can be associated with worsening chronic lung disease, poor renal perfusion, hemodynamic instability, intraventricular hemorrhage, and necrotizing enterocolitis. If the usual treatment with indomethacin is contraindicated or unsuccessful, then the PDA can often be surgically ligated. If persistent into childhood and a source of symptomatic left-to-right shunt, then surgical ligation or catheter-based coil embolization (in appropriately selected candidates) can be performed.

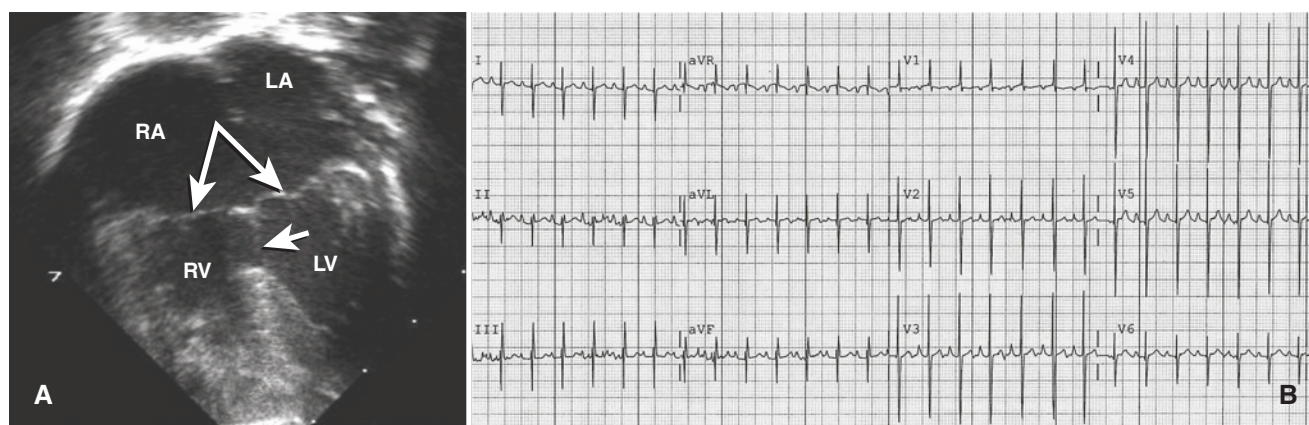
### Atrioventricular Septal Defects

Nearly 50% of all children with trisomy 21 have CHD; nearly 50% of these are atrioventricular septal defects (AVSDs; also known as atrioventricular canal defects or endocardial cushion defects). Approximately 70% of all children with AVSD have trisomy 21. This defect describes a continuum of malformations from a partial type (primum type ASD with a cleft mitral valve) to a complete type (single atrioventricular valve spanning the entire width of the heart; Figure 234-9, A) with variability in the attachment of the atrioventricular valve leaflets to the IVS. These defects can result in a significant left-to-right shunt volume. Timing of the surgical repair for complete AVSD follows the same principles for the simple VSD described previously and is generally performed between 3 and 6 months of age to minimize the potential for irreversible pulmonary hypertension. A partial AVSD follows ASD physiologic characteristics and can generally be repaired up to a few years of age with a low risk of developing irreversible pulmonary hypertension. The ECG of children with the complete defect generally demonstrates a northwest, superior QRS axis and some element of ventricular hypertrophy (Figure 234-9, B).

Surgical repair of a complete AVSD includes patch closure of the ASD and VSD and the creation of 2 functioning atrioventricular valves from the single, frequently regurgitant common atrioventricular valve. Postoperative outcomes depend on the severity of any residual atrioventricular valve regurgitation and the presence of pulmonary vascular disease. With detection of a change in the systolic regurgitant murmur or presence of a new harsh systolic ejection murmur during routine general care, the primary care physician can assist the cardiologist in monitoring for progression of any residual postoperative mitral regurgitation or development of new subaortic outflow tract obstruction, respectively, which are possible sequelae following AVSD repair.

### Arteriovenous Malformation

Arteriovenous malformation (AVM) is a direct connection between the arterial and venous vascular systems resulting in shunting of blood to the right heart



**Figure 234-9** A, Apical 4-chamber echocardiographic view of a 3-month-old infant with Down syndrome and a complete AVSD. Note the large ASDs and VSDs (top and bottom arrows, respectively) and the dilatation of both atria and ventricles. The double arrow points to the common atrioventricular valve spanning both ventricular chambers. B, ECG of the same patient demonstrating a northwest QRS axis (QRS forces are predominantly negative in leads I and aVF) with a small Q wave in lead aVL; this finding is typical in patients with AVSDs. In addition, note the large voltages in the precordial leads and peaked P waves in leads II and aVF consistent with biventricular dilatation and right atrial enlargement, respectively.

and possible high-output, right/left-sided heart failure. Common AVM locations in children are cerebral and abdominal. If amenable to interventional occlusion, coil embolization may reduce or reverse heart failure in many cases.

### Right-to-Left Shunting Lesions

Systemic, central cyanosis is the key difference between left-to-right and right-to-left shunting lesions. By definition, a right-to-left shunting lesion is one in which oxygen-poor blood is being shunted or added to the oxygen-rich, systemic blood. As with left-to-right shunting lesions, the volume of shunted blood depends on the size of the defect and the pressure gradient across it.

### Tetralogy of Fallot

Tetralogy of Fallot is one of the most commonly encountered cyanotic heart defects, occurring in 0.33 per 1,000 live births and comprising approximately 7% of heart defects. Although its embryologic origin remains controversial, one of the prevailing theories asserts that this defect occurs as a result of disproportionate segregation of the truncus arteriosus into the pulmonary artery and aorta. This uneven distribution results in malalignment of the aortopulmonary septum with the developing IVS creating a VSD, which then underlies both the aortic and pulmonic valves. This anatomic arrangement, coupled with the stenotic pulmonary valve and concomitantly narrowed right-ventricular outflow tract (RVOT), results in right-to-left shunting of right-ventricular blood through the VSD into the aorta, producing systemic, central cyanosis. Not surprisingly, the volume of shunted blood can vary with alteration of the pressure gradient through the RVOT. The proverbial *Tet spell*, or hypercyanotic event, occurs when systemic vascular resistance (SVR) decreases, resulting in an increased right-to-left shunt. Some researchers have suggested that muscle contractions or spasms in the RVOT

increase the obstruction to pulmonary flow and thereby worsen cyanosis. Regardless of the cause, treatment for a hypercyanotic spell is the same. Supplemental oxygen, fluid boluses, anxiolytics, sedatives, and increased SVR (ie, knee-to-chest positioning, phenylephrine) work to decrease the amount of right-to-left shunting. If not reversed, hypercyanotic spells can be fatal.

### Eisenmenger Syndrome

Although less common in the current era, another potential cause for right-to-left shunting occurs in the setting of unrepaired VSDs or large ASDs with secondary pulmonary hypertension and is known as Eisenmenger syndrome. Significant shunting and progressive cyanosis with this physiologic phenomenon will only occur once the pulmonary vascular resistance is higher than the systemic vascular resistance. In addition to the complications of systemic cyanosis and the compensatory rise in hematocrit, patients with pulmonary hypertension are at a significantly elevated risk for right-ventricular failure and sudden death.

### Pulmonary Hypertension

Pulmonary arterial hypertension (PHTN) is a progressive disease of the pulmonary vascular bed resulting in increased afterload and strain on the normally low-pressure right ventricle. Untreated, the median survival is less than 4 years, with death typically occurring from right-ventricular failure or ischemia-induced dysrhythmias. The last 2 decades of research, however, have significantly improved our understanding of PHTN's molecular pathology, and the associated advancement of currently available medical therapies has increased 10-year survival to nearly 80%.

Lung biopsies of patients with severe PHTN demonstrate a continuum of pathologic changes to the pulmonary arteriole. Dysfunction of the endothelial cells within the intima is commonly indicted as the sentinel event of this disease process with progressive loss of

the vasodilatory component of autoregulation. Such changes result in hypertrophy and hyperplasia of the medial smooth muscle layer, a concomitant decrease in luminal cross-sectional area, and increased pulmonary vascular tone. This level of disease typically remains amenable to medical therapy. Without intervention, however, the intimal layer will progressively occlude and the medial layer becomes fibrotic, resulting in fixed obstruction to affected regions. Medical therapies are designed to replete the vasodilatory pathways (nitric oxide, prostaglandin  $I_2$ ), inhibit the maladaptive vasoconstrictive agents (endothelin-1), and prevent platelet aggregation and thrombosis.

The diagnosis of a child with PHTN is often delayed by several years from the onset of symptoms, and is often not considered in the differential diagnosis until the nonspecific complaints of fatigue, decreased activity levels, episodic exercise-induced chest pain, or shortness of breath become associated with syncope, cyanosis, or aborted sudden death. These symptoms are secondary to progressive right-ventricular dysfunction with inadequate systemic cardiac output. Physical examination may be grossly normal, but more advanced disease can present with hepatomegaly, jugular venous distention, peripheral edema, a loud second heart sound, and the murmur of tricuspid regurgitation. An ECG will demonstrate right axis deviation with right-ventricular hypertrophy. The echocardiogram is used to initially rule out CHDs (see Eisenmenger syndrome). In a structurally normal heart with severe PHTN, the echocardiogram will demonstrate a dilated right heart with right-ventricular hypertrophy and pressure estimates (using tricuspid regurgitation jet, pulmonary insufficiency jet, or interventricular septal position) that are commonly classified as sub systemic, systemic, or suprasystemic. There is often a patent foramen ovale or atrial septal defect that allows blood to shunt from the right atrium to the left when right-ventricular pressures are acutely elevated. This atrial level ‘pop-off’ can result in systemic cyanosis, but in the setting of a pulmonary hypertensive crisis (acute, severe elevation of PVR reducing flow through the pulmonary vascular bed), it can allow for important filling of the left ventricle that it would not otherwise receive. Cardiac catheterization is used to confirm the diagnosis and provide hemodynamic data to help guide medical therapy. Extensive laboratory and imaging studies are also necessary to help differentiate primary (idiopathic) from secondary PHTN, which can develop from autoimmune, pro-coagulant, infectious, toxin-mediated, or pulmonary parenchymal processes.

Calcium channel blockers were historically the only available vasodilator for PHTN. However, their extensive side effect profile and poor long-term efficacy (less than 25% of pediatric patients will continue to respond after 12 months) have significantly limited their role in present-day medical regimens. Instead, oral sildenafil and bosentan have become first-line agents along with prostaglandin  $I_2$  analogues. Sildenafil is a phosphodiesterase-5 inhibitor which promotes vasodilation by accentuating the nitric oxide-mediated vasodilatory response in vascular smooth muscle,

**Table 234-1**

**Description of the  
6 Grades of Systolic or  
Diastolic Murmur Severity**

MURMUR SEVERITY	DESCRIPTION
Grade I	Barely audible and may require several cardiac cycles to detect
Grade II	Soft, but easily audible
Grade III	Moderately loud murmur without a thrill
Grade IV	Loud murmur with a thrill
Grade V	Loud murmur heard with the stethoscope barely off the chest
Grade VI	Loud murmur heard without the stethoscope touching the chest

while bosentan is a nonselective endothelin-1 receptor antagonist that inhibits vasoconstriction. Epoprostenol is a prostaglandin  $I_2$  analogue commonly viewed as the most potent extrinsic pulmonary vasodilator available to the physician and likely has survival advantages over the commonly used oral therapies, but is typically administered as a continuous intravenous infusion in children and carries a significant side effect profile.

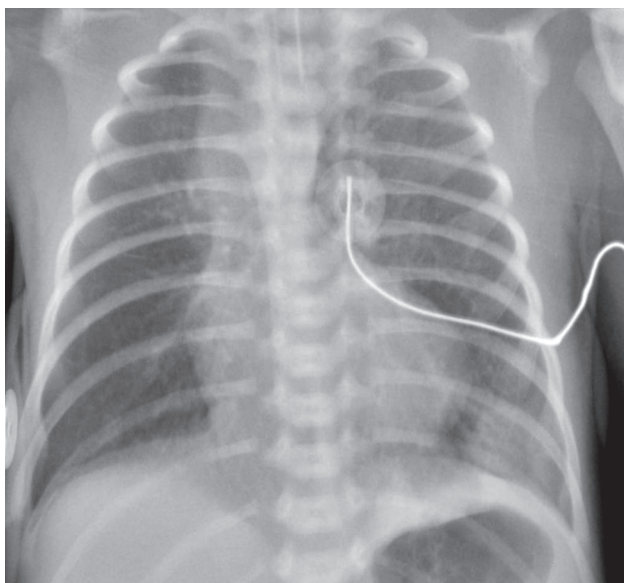
### **Clinical Manifestations of Right-to-Left Shunting Lesions**

Tetralogy of Fallot is a defect commonly detected by prenatal ultrasound between 18 and 22 weeks' gestation. The clinical presentation can be extremely varied depending on the degree of pulmonary stenosis or the presence of pulmonary atresia (no prograde flow across the pulmonary valve).

In addition to cyanosis, newborns with tetralogy of Fallot will commonly demonstrate an audible murmur. A systolic murmur may be appreciated at the left upper sternal border and is produced by the narrowing of the RVOT. Its grade (I-VI/VI) and quality (harsh or soft) depends on the degree of obstruction (Table 234-1). In the newborn with tetralogy of Fallot and pulmonary atresia, the RVOT murmur is replaced by a continuous flow murmur through the ductus arteriosus, the only source of pulmonary blood flow.

With the exception of cyanosis and softer murmurs, the physical examination of a child with pulmonary hypertension caused by an untreated septal defect (Eisenmenger syndrome) may be virtually indistinguishable from that of a simple ASD or VSD. One other subtle difference may be a loud pulmonary valve (P2) component of the second heart sound. Idiopathic pulmonary hypertension (see previous section) or pulmonary hypertension secondary to bronchopulmonary dysplasia may demonstrate cyanosis (from intrapulmonary or right-left atrial level cardiac shunting), and a loud P2 may not have an associated cardiac murmur (in the absence of pulmonary or tricuspid insufficiency). Equal ventricular pressures in





**Figure 234-10** Chest radiograph of a newborn with tetralogy of Fallot demonstrating a *boot-shaped* heart. The *toe* of the boot is formed by the cardiac apex being lifted off the diaphragm from right-ventricular hypertrophy. Note the absent pulmonary artery knob expected to exist at the left sternal border between the fourth and sixth ribs.

a patient with Eisenmenger syndrome secondary to a VSD will not produce an audible murmur.

#### Evaluation of Right-to-Left Shunting Lesions

**ELECTROCARDIOGRAM.** Tetralogy of Fallot and pulmonary hypertension often produce evidence of right-ventricular hypertrophy. Right-axis deviation and tall R waves in the early or right-sided precordial leads can be seen on ECG.

**CHEST RADIOGRAPH.** Right-to-left shunting, by definition, is associated with decreased pulmonary blood flow. As a result, pulmonary vascular markings may be significantly decreased in children with either tetralogy of Fallot or secondary pulmonary hypertension. The classic radiographic finding of tetralogy of Fallot is the boot-shaped cardiac silhouette. This result is caused by the superiorly displaced cardiac apex produced by right-ventricular hypertrophy and absence or reduction of the pulmonary knob (Figure 234-10). The relative right-ventricular hypertrophy in the normal newborn often results in the erroneous reading of a boot-shaped cardiac silhouette on initial chest radiographic examination.

**ECHOCARDIOGRAM.** Two-dimensional and Doppler echocardiogram evaluations define cardiac anatomy, function, and direction of blood flow across any cardiac defects. Doppler flow velocity across the RVOT allows estimation of outflow gradient, degree of obstruction, and any evidence of branch pulmonary artery stenosis.

#### Management of Right-to-Left Shunting Lesions

**TETRALOGY OF FALLOT.** Surgical management of tetralogy of Fallot has changed significantly over the last two decades. The advent of microsurgical and novel bypass techniques has allowed for repair during infancy or the newborn period. For this reason, true

hypercyanotic episodes in toddlers are rarely observed in present day.

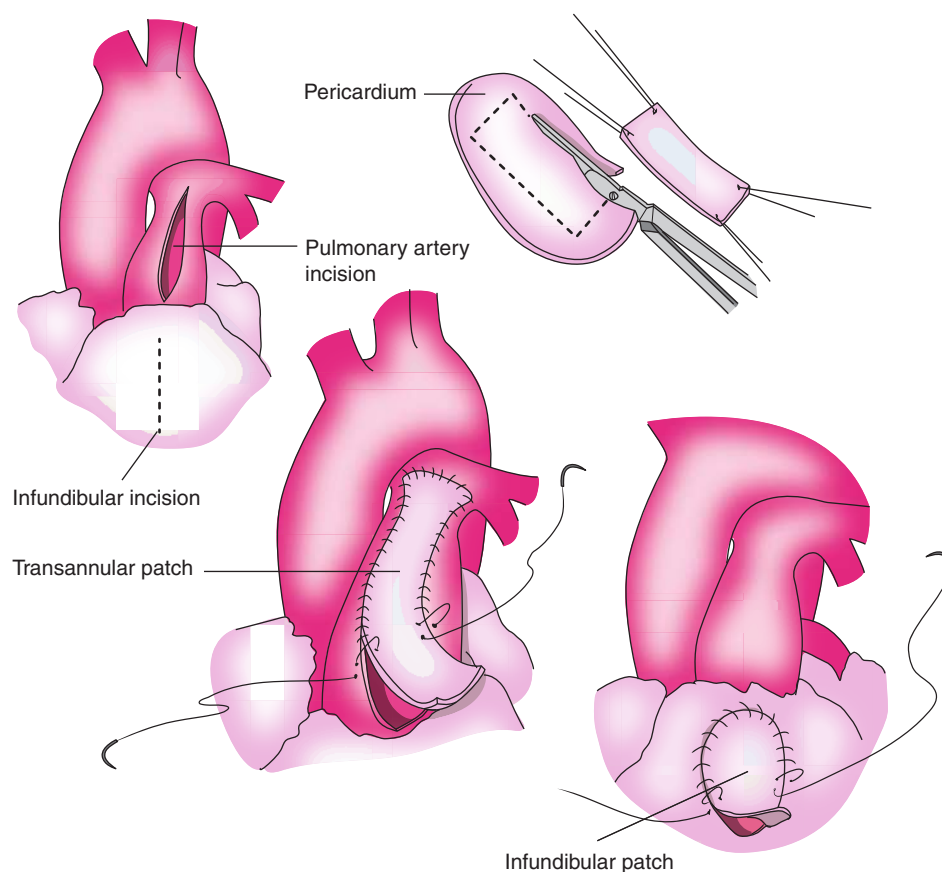
**TETRALOGY OF FALLOT WITHOUT PULMONARY ATRESIA.** Once diagnosed, children with tetralogy of Fallot without pulmonary atresia are generally monitored in the intensive care unit until their ductus arteriosus (if present) closes. If these children are able to produce enough pulmonary blood flow to maintain arterial oxygenation saturations ( $\text{SaO}_2$ ) greater than 80%, they may be discharged from the hospital and allowed to grow. The occurrence of a hypercyanotic spell (Tet spell) is generally considered a semi-urgent indication for repair. Otherwise, in the absence of earlier unacceptable cyanosis ( $\text{SaO}_2 < 75\%$ ), elective repair is performed when the child is 4 to 6 months old.

Operative correction consists of patch closing the VSD and removing obstruction to pulmonary blood flow through the narrowed RVOT. This can be accomplished through trans-atrial resection or division (or both) of RVOT muscle bundles, and, depending on the pulmonary valve and proximal artery anatomy, performing a pulmonary valvotomy or placing a trans-annular patch after valvectomy to relieve distal outflow obstruction (Figure 234-11). In many cases, since pulmonary valvectomy will be required as part of the repair, patients will be left with significant pulmonary insufficiency (PI). This will necessitate long-term, regular follow-up given that the progressive RV dilatation and eventual dysfunction associated with PI are long-term morbidities that will often require surgical or catheter-based pulmonary valve placement.

**TETRALOGY OF FALLOT WITH PULMONARY ATRESIA.** If tetralogy of Fallot is associated with pulmonary atresia, then a prostaglandin E1 infusion will maintain ductal patency until surgical repair. If pulmonary artery size is favorable (ie,  $> 3$  mm in diameter), then complete repair can be performed in the neonate; otherwise, an aortopulmonary shunt is placed to allow pulmonary artery growth until a complete repair is performed later. In the patient without confluent pulmonary arteries who relies instead on multiple aortopulmonary collaterals, the surgical options are more difficult. The collateral arteries can be unifocalized through a single or staged procedure to a patch-augmented native outflow tract or conduit arising from the right ventricle. The early and long-term results of this procedure have been promising with 10- and 20-year actuarial survival rates of 86% and 75%, respectively, and freedom from surgical reintervention rates of 55% and 29% at 10 and 20 years.

**EISENMENGER SYNDROME.** Management of patients with an unrepaired septal defect who have developed Eisenmenger syndrome poses a unique problem. Right-to-left shunting in this situation occurs to maintain adequate cardiac output at the expense of systemic oxygenation. Surgical closure of the septal defect will worsen the outcome if the pulmonary hypertension cannot be ameliorated first. Therefore, multiple approaches are used to decrease pulmonary artery pressure and ultimately the amount of right-to-left shunting. Calcium channel blockers, nitric





**Figure 234-11** Depiction of surgical repair for tetralogy of Fallot. In the setting of a hypoplastic pulmonary valve annulus, a patch of fixed bovine pericardium is sized to fit the vertical incision site, which starts in the main pulmonary artery and traverses the pulmonary valve into the right ventricle's infundibulum. The *transannular* patch placement is depicted in the middle drawing. The bottom right drawing depicts the surgical approach to repairing a patient with tetralogy of Fallot without a hypoplastic pulmonary valve. The main pulmonary artery incision is made to allow patch augmentation of the main pulmonary artery, and the incision in the right-ventricular infundibulum is made to permit patch augmentation of the RVOT. Not shown is repair of the VSD or muscle bundle resection, which is usually performed through the tricuspid valve.

oxide donors, endothelin receptor antagonists, inhaled oxygen therapy, and, in severe cases, continuous infusions of prostacyclin have all been found to improve symptoms in patients with pulmonary hypertension (see previous section on pulmonary hypertension). If the pulmonary vasculature proves to be reactive with these measures, surgical intervention may then be considered. When the pulmonary vasculature does not respond to these medications, lung transplantation (in acceptable candidates) or supportive, symptomatic care may be the only therapeutic options available.

### Other Right-to-Left Shunting Lesions

**PULMONARY ATRESIA WITH INTACT VENTRICULAR SEPTUM.** Researchers have proposed that membranous pulmonary atresia and intact ventricular septum with 2 adequately sized ventricles occurs late in embryologic development. This otherwise structurally normal heart develops complete fusion of the pulmonary valve preventing any forward flow into the pulmonary artery from the right ventricle. Blood entering the right ventricle is instead regurgitated through the tricuspid valve back into the right atrium

where it mixes with SVC and IVC blood. The increase in blood volume increases right atrial pressure, resulting in shunting of blood across the patent foramen ovale to the left atrium. This circuit does not change with transition from fetal circulation, and pulmonary blood flow becomes dependent on a persistent PDA. Once diagnosed, the pulmonary valve may be opened in the cardiac catheterization laboratory using balloon dilatation or radiofrequency ablation to perforate through the valve cusps. This latter approach is controversial, and, in many institutions, surgical valvotomy remains the preferred approach for valve atresia.

Another subset of patients develops pulmonary atresia much earlier in cardiac development. The subsequent lack of right-heart blood flow in utero results in hypoplasia of the right ventricle and tricuspid valve and, in some cases, can be associated with sinusoidal connections between the hypoplastic right ventricle and coronary arteries. When present, decompression of the right ventricle through a pulmonary valvotomy can result in myocardial ischemia, infarction, and death. If the right heart structures are significantly

affected, the patient must instead follow the single-ventricle treatment route (see later discussion of single-ventricle physiology). The surgical specifics of that single-ventricle palliation will be determined by the presence or absence of the sinusoids described previously.

**ISOLATED PULMONARY VALVE STENOSIS.** Isolated stenosis of the pulmonary valve is a relatively common CHD, affecting 3.8 of 10,000 live births. While similar from an embryologic and anatomic perspective, isolated pulmonary valve stenosis and pulmonary atresia with an intact ventricular septum are different in many ways. By definition, stenosis differs from atresia by the presence of prograde flow across the pulmonary valve. Although probably inaccurate, it is convenient to compare the 2 lesions by considering isolated pulmonary valve stenosis as an incomplete version of its more severely affected counterpart. Most importantly, however, is the lack of coronary sinusoidal formation or the right-ventricular dependent coronary artery flow often accompanying the more severe forms of pulmonary atresia with intact ventricular septum.

During the normal transition from fetal to postnatal circulation, PVR decreases significantly with the baby's first breaths. As this progresses, the ductus arteriosus gradually closes, removing this as an additional source of pulmonary blood flow. During this time pulmonary valve stenosis may become evident. The clinical manifestations of this lesion occur along a continuum based on the degree of valvar obstruction. Mild narrowing of the pulmonary valve is associated most often with a crescendo systolic ejection murmur, acyanosis, and few related symptoms. A more harsh and later peaking murmur is common with more advanced stenosis and can be associated with cyanosis from right-to-left shunting through a PFO/small ASD or from inadequate pulmonary blood flow in the absence of a PDA. Importantly, until closed, left-to-right shunting through the PDA can delay presentation of significant valvar stenosis by providing an additional source of pulmonary blood flow thereby delaying the appearance of central cyanosis.

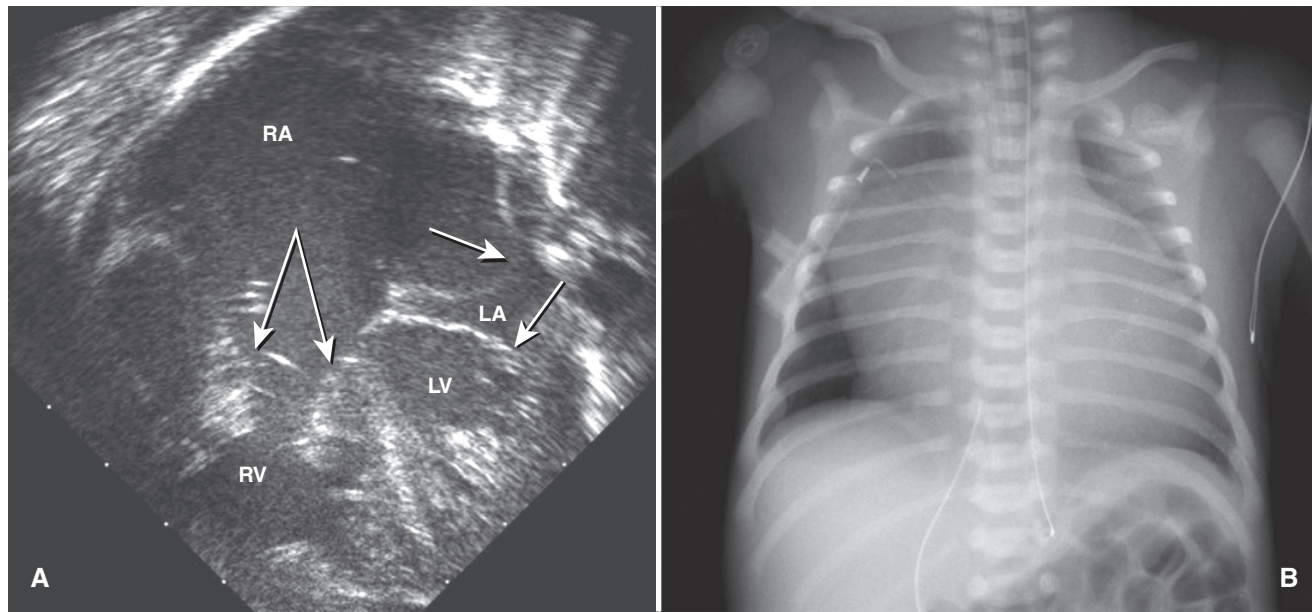
The progression of pulmonary valve stenosis is typically not as malignant as with aortic valve stenosis caused by the lower resistance of the vascular bed beyond the affected valve. Less than 30% of newborns diagnosed with mild pulmonary valve stenosis will develop moderate or severe gradients; this occurs in only 15% of those presenting after 1 month of age. Intervention is typically reserved for those children with inadequate cardiac output or a transpulmonary valve gradient of greater than 50 mm Hg. In most centers, the standard of care for pulmonary valve stenosis is balloon valvuloplasty in the cardiac catheterization lab. This procedure is typically very well tolerated with rare complications, and gradient reductions to less than 15 to 20 mm Hg can be achieved in more than 90% of patients. The risk of restenosis is low following balloon valvuloplasty for isolated pulmonary valve stenosis, while progressive pulmonary valve insufficiency is the greater concern. One series documented moderate to severe pulmonary valve insufficiency in 57% of

patients following an average of 12 years post-intervention. However, even severe insufficiency of the pulmonary valve is relatively well tolerated because of the lower pressures associated with the pulmonary circulation. Nonetheless, periodic follow-up with a cardiologist will be required to assess for recurrence of valvar or subvalvar obstruction as well as the development of clinically important pulmonary insufficiency.

**EBSTEIN ANOMALY.** Ebstein anomaly is characterized by apical displacement of the tricuspid valve's septal leaflet, resulting in both tricuspid valve insufficiency and atrialization of a section of the right ventricle (Figure 234-12, A). Ebstein anomaly has a wide spectrum of severity, ranging from diagnosis at postmortem examination in adulthood to presentation in infancy requiring single-ventricle palliative surgery. When significant, this anomaly is commonly a right-to-left shunting lesion in the newborn period when PVR remains elevated. The course of blood flow is much the same as in pulmonary atresia with intact ventricular septum. With worsening tricuspid valve incompetence, the effectively smaller right ventricle is less able to propel blood across the pulmonary valve, which is usually narrowed or stenotic, or both. This blood instead returns to the right atrium and crosses the patent foramen ovale. Effective pulmonary blood flow is then dependent on the PDA. Chest radiograph usually demonstrates marked cardiomegaly from right-atrial dilatation (Figure 234-12, B). These children are closely monitored until their PDAs close and PVR has decreased at which time the degree of forward pulmonary blood flow can be reassessed and a more definitive care plan can be made.

The short- and intermediate-term outcomes of children with this diagnosis are determined, in part, by the severity of disease (ie, degree of cyanosis) at presentation. When clinical symptoms are present shortly after birth and unacceptable cyanosis is unremitting ( $\text{SaO}_2$  less than 70%–75%), the single-ventricle treatment algorithm is generally required, with outcomes similar to those of children with hypoplastic left heart syndrome. Conversely, fetal diagnosis with early severe tricuspid regurgitation can be associated with pulmonary hypoplasia secondary to severe right-atrial enlargement. Severely hypoplastic lungs will preclude cardiac palliation, and most of these infants succumb shortly after birth. Newborns with acceptable saturations and adequate cardiac output can be discharged from the hospital and followed expectantly with intervention that may be necessary only during older childhood or adolescence when exercise intolerance or pronounced exercise-associated cyanosis develops.

**TOTAL OR PARTIAL ANOMALOUS PULMONARY VENOUS RETURN.** Embryologically, total anomalous pulmonary venous return (TAPVR) occurs when the pulmonary veins do not connect with the posterior wall of the left atrium. They instead form a confluence that then drains via a vertical vein indirectly to the right atrium. This vertical vein returns to either a supracardiac or infracardiac structure, generally the innominate or hepatic veins, respectively. Blood then returns to the right atrium and is shunted right to left through an obligate ASD into the left atrium providing



**Figure 234-12** A, Apical 4-chamber echocardiographic view of a newborn with Ebstein anomaly of the tricuspid valve. The double arrow points to the apically displaced septal and posterior tricuspid valve leaflets, which result in ineffective coaptation of the tricuspid valve. The short arrow depicts right-to-left bowing of the atrial septum caused by the high right-atrial pressure from the regurgitant tricuspid valve volume. The perforated arrow demonstrates the relative size of the normal mitral valve. B, Chest radiograph of the same patient depicting cardiomegaly caused by severe right atrial enlargement.

the only source of systemic cardiac output. Conversely, partial anomalous pulmonary venous return (PAPVR) is the anomalous return of 1 or more pulmonary veins to the right heart. Unless more than 1 of the pulmonary veins returns anomalously, this anomaly rarely becomes hemodynamically significant and may not require surgical correction unless symptoms develop (ie, exercise intolerance).

The diagnosis of TAPVR or PAPVR can be difficult to confirm by echocardiogram and, particularly in cases of complex anatomy, may require cardiac catheterization or magnetic resonance imaging if clinically suspected. Infradiaphragmatic drainage often becomes obstructed at some point along the extended, tortuous course of the vertical vein into the liver and, when present, constitutes a surgical emergency. Surgical correction for uncomplicated TAPVR consists of reanastomosis of the pulmonary venous confluence to the posterior wall of the left atrium. The most common postoperative complications are obstruction at the site of the anastomosis, pulmonary vein stenosis, and left-atrial dysrhythmias. Periodic long-term cardiology follow-up is necessary since, if unrecognized, prolonged obstruction of the anastomosis or pulmonary veins can result in irreversible pulmonary venous obstructive disease, pulmonary vascular disease, and eventual right-heart failure.

### Dextrorotation or Rightward Transposition of the Great Arteries

Dextrorotation or rightward transposition of the great arteries is an embryologic defect of the conotruncus in which the aortic valve is positioned rightward and anterior to the pulmonary valve instead of rightward

and posterior as in the normal heart. This anatomic arrangement results in a right-ventricular connection with the aorta and a left-ventricular connection with the pulmonary artery. Thus, the pulmonary and systemic circulations are in parallel rather than in series and result in prohibitive cyanosis unless adequate mixing of the 2 circulations is established.

To provide adequate mixing, bidirectional flow through a PFO or ASD is necessary. If inadequate (ie, low  $\text{SaO}_2$  or partial pressure of oxygen), the physician must consider whether a balloon septostomy (Rashkind procedure) of the atrial septum is necessary to increase blood exchange and systemic oxygen delivery. Patency of the ductus arteriosus can supplement the volume of blood exchange by increasing the blood return to the left atrium, which permits better mixing at the atrial level but is usually insufficient to achieve acceptable saturations in the absence of a large interatrial communication.

In general, oxygen-poor blood is shunted from the aorta to the pulmonary artery via the PDA, which results in equal, 4-extremity cyanosis. Conversely, if persistent fetal circulation exists, with PVR greater than SVR, then oxygenated blood will shunt from the pulmonary artery to the aorta producing paradoxical cyanosis with higher  $\text{SaO}_2$  in the legs (downstream from the ductus) compared with the arms and brain. Therefore, adequacy of upper extremity (and brain)  $\text{SaO}_2$  must be assessed; this is typically done by monitoring pre- and post-ductal saturations.

### Clinical Signs and Symptoms

Dextrorotation or rightward transposition of the great arteries can be diagnosed prenatally and is the most



common type of cyanotic heart disease. These patients generally are cyanotic at birth without associated respiratory distress. Physical examination will therefore be remarkable for cyanosis and possibly a ductal murmur, but should otherwise be normal for a newborn.  $\text{SaO}_2$  will not increase significantly with supplemental oxygen (failed hyperoxia challenge test). Care should be taken to assess lower extremity pulses as coarctation of the aorta can be associated with dextro-looped transposition of the great arteries (d-TGA). Prostaglandin E1 infusion should be initiated once this defect is suspected.

### Evaluation

**ELECTROCARDIOGRAM.** The ECG will generally be unremarkable for a newborn and will not offer added information unless other cardiac defects exist.

**CHEST RADIOGRAPH.** The classic radiographic finding for d-TGA is the *egg on a string*. The great arteries are often oriented anterior-posterior (the string) instead of perpendicular, removing the aortic and pulmonary knobs. This great artery orientation can also create a mesocardic orientation of the heart, producing an egg-shaped cardiac silhouette.

**ECHOCARDIOGRAM.** Two-dimensional echocardiogram will confirm the diagnosis and can evaluate the extent of intra- and extracardiac shunting. ASD size, direction of ductus arteriosus shunting, and presence of a VSD are important components of intercirculatory mixing. Furthermore, coronary artery anomalies are common with this CHD and can complicate the surgical repair. Therefore, coronary anatomy and abnormalities of the aortic arch should be fully delineated prior to surgical repair.

### Management

Transposition of the great arteries can be one of the more complex CHDs to manage in the newborn period. The single most important component of preoperative management is maintaining adequate atrial-level shunting. Although the presence of a VSD is important when considering surgical options, ventricular-level shunting does not usually contribute a significant amount of intracardiac mixing in the newborn period.

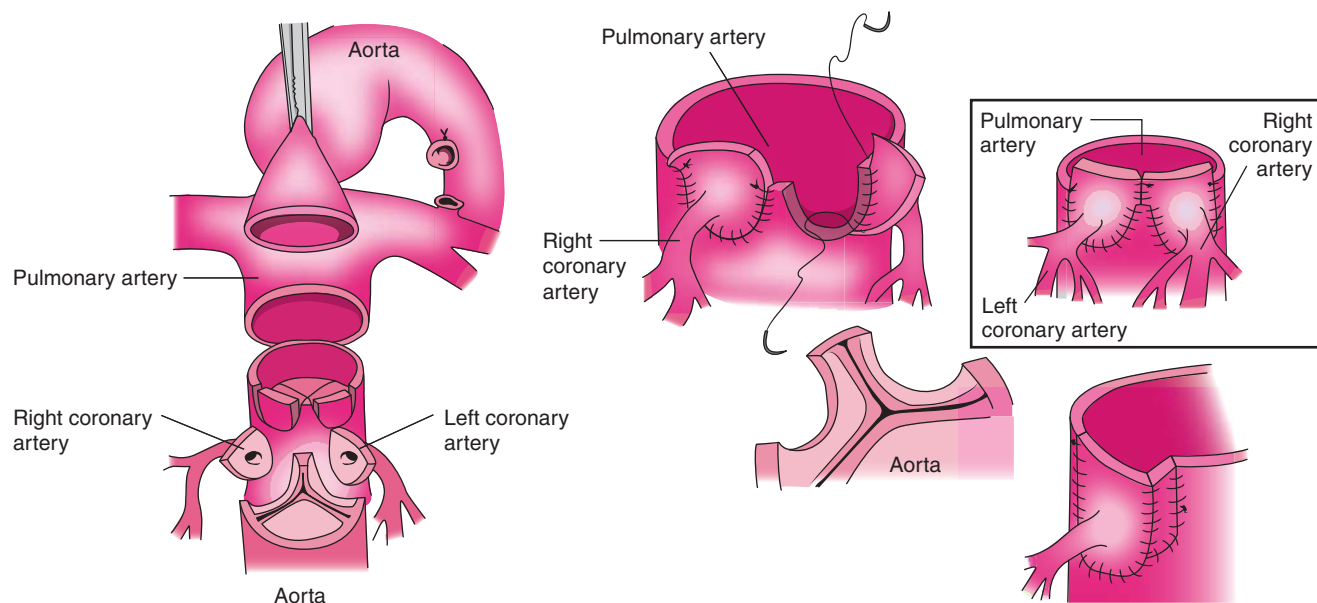
Many patients with d-TGA have already begun receiving prostaglandin E1 infusions at the time of diagnosis after failing the hyperoxia challenge. Continued assessment for paradoxical cyanosis (as seen with persistent fetal circulation),  $\text{SaO}_2$ , and arterial oxygen content are necessary. In general, an arterial oxygen content greater than 30 mm Hg (typical fetal partial pressure of oxygen in arterial blood [ $\text{PaO}_2$ ]) with a corresponding  $\text{SaO}_2$  of more than 75% to 80%, in the absence of metabolic acidosis, are predictive of adequate atrial-level mixing and systemic oxygen delivery. If these conditions are not met and the newborn demonstrates any signs of respiratory distress with marked cyanosis, then the ASD is likely restrictive and needs to be enlarged. This task can be accomplished by balloon septostomy, blade septostomy, or radiofrequency ablation of the atrial septum in the catheterization laboratory. Although these procedures are necessary life-saving interventions, they can be associated with significant risks of morbidity and mortality.

### Surgical Correction

With the advent of microsurgical techniques came the ability to reimplant coronary arteries (Figure 234-13). This procedure allowed for the successful arterial switch (Jatene) operation, which has been the surgical option of choice for most patients with d-TGA since the 1980s. As a result, the atrial switch operation (Mustard and Senning procedures) has largely become obsolete. The process of switching the great arteries is conceptually intuitive but technically very complex. Once the patient is placed on cardiopulmonary bypass, the aortic and pulmonary arteries are transected above their native valves. Next, the surgeon removes the coronary arteries from the aortic root (arising from the right ventricle) by cutting small buttons of tissue surrounding the ostium of each coronary artery. Similarly sized buttons of tissue are removed from the pulmonary artery (arising from the left ventricle), and the coronary arteries are sutured into the native pulmonary artery root (arising from the left ventricle). The aorta is freely mobile within the thorax and readily sutured to the exposed pulmonary artery root. The main and branch pulmonary arteries remain attached to the lungs and are subsequently more restricted in their range of motion. To minimize surgical stretch and subsequent obstruction, the Lecompte maneuver is performed, which drapes the main and branch pulmonary arteries over, instead of underneath, the ascending aorta.

Abnormal coronary artery anatomic configuration is relatively common, occurring in approximately 30% of all patients with d-TGA. This abnormality can produce one of the major complications of the arterial switch operation. A single coronary artery origin of both the right and left coronary arteries necessitates *flipping* of the button before reimplantation and is often associated with kinking and compromise of coronary artery flow. Although no coronary pattern precludes a *switch*, transmural (coursing through the arterial wall) coronary artery anatomy and others may increase the risk of the procedure, necessitating alternative surgical approaches. Discordant annulus size of the great arteries can also produce difficulty but is often not an absolute contraindication to an arterial switch. Compared with long-term atrial switch results, the outcomes data for patients with d-TGA after an arterial switch operation are substantially better, but significant morbidity persists. An overall mortality rate of 7% was reported in a study of 223 patients with d-TGA after the arterial switch operation; coronary artery pattern was not associated with an increased risk of death. However, 2 studies with a total of 1,263 patients demonstrated a rate of coronary artery events between 7% and 8% over 15 years of follow-up. Abnormal coronary artery vasomotor function has also been demonstrated in asymptomatic children after the arterial switch operation. Furthermore, a retrospective study of 119 postoperative patients with d-TGA followed for a median of 65 months found progressive aortic root dilatation without an increased prevalence of aortic insufficiency. The clinical significance of these findings requires further study. Though the arterial switch operation remains the best surgical option available, this patient population requires continued long-term follow-up by





**Figure 234-13** Stages of the arterial switch operation used in patients with d-TGA. The first picture demonstrates transection of the aorta and pulmonary artery just distal to their respective valves. In the middle picture, the coronary artery buttons are rotated from the original aortic root to the *neoaortic* root and sutured into place.

a cardiologist who can periodically evaluate for postoperative morbidities including those mentioned above as well as supravale and branch pulmonary stenosis related to the LeCompte maneuver.

### Left-Sided Obstructive Lesions

Left-sided obstructive lesions are characterized by impedance to blood flow from the systemic ventricle (generally the left) to the body. As with nearly all heart lesions, the severity of the obstruction determines the age of presentation and clinical manifestations.

#### Aortic Stenosis

Valvar aortic stenosis can occur in isolation or be associated with either subvalvar or supravalar obstruction. With the exception of an audible click heard in valvar stenosis, the presentation and alteration of cardiovascular physiologic characteristics are very similar among the 3 defects. When the stenosis is mild or moderate, a cardiac murmur may be the only sign of an abnormality in the newborn period. However, depending on ductal dependency, a severe or critical degree of aortic stenosis, is associated with inadequate cardiac output and will present in the newborn period as heart failure or clinical extremus.

A large portion of fetal cardiac output is provided by ductal flow from the pulmonary artery to the descending aorta. The transition to postnatal circulation occurs with closure of the ductus arteriosus. In the newborn with severe or critical aortic stenosis, this process is associated with a significant decrease in systemic blood flow. Although the output will be fully

oxygenated, the volume will be inadequate, and evidence of congestive heart failure and low cardiac output will ensue. Diaphoresis with feeding, irritability, lethargy, and fatigue will bring these children to a physician's attention. The infant will be acyanotic but ashen, and will have a systolic ejection murmur of variable intensity and harshness (depending on cardiac output) and diminished or absent peripheral pulses. Increasing severity of stenosis is therefore associated with increased dependence on ductal flow for systemic cardiac output, which is then associated with an earlier presentation.

Several studies have demonstrated that valvar aortic stenosis severity can change dramatically during the first 6 months of life and that final valvar gradients are poorly predicted by initial gradients. Most pediatric cardiologists will monitor infants with aortic stenosis on a frequent basis to plan timely intervention for rapidly progressive stenosis before congestive heart failure and systemic shock occur. Children not requiring intervention before 6 months of life are less likely to develop heart failure or become critically ill during the follow-up period.

Milder degrees of aortic stenosis may not present until childhood. These patients will typically be asymptomatic, and examination will reveal an ejection click followed by a harsh systolic ejection murmur best auscultated at the right upper sternal border. ECG evaluation of these patients may or may not demonstrate signs of left-ventricular hypertrophy and is unlikely to show any signs of myocardial ischemia. Particularly in the pediatric population, mild to

moderate aortic stenosis will not produce exercise intolerance, chest pain, syncope, or shock. As a result, these children are often referred to a pediatric cardiologist after the characteristic murmur is heard during a routine physical examination.

### Evaluation

**ELECTROCARDIOGRAM.** ECG findings associated with aortic stenosis depend on disease severity. In the newborn with critical stenosis, ST segment elevation or depression, T wave inversion, and sinus tachycardia may be present; right-ventricular hypertrophy is usually noted, and voltage criteria for left-ventricular hypertrophy may already be present or develop quickly. As mentioned previously, mild-to-moderate disease will likely demonstrate voltage criteria for left-ventricular hypertrophy, but ST or T wave changes are less likely.

**CHEST RADIOGRAPH.** A chest radiograph is helpful only if pulmonary edema has developed because of left heart failure. The anteroposterior (AP) projection of the cardiac silhouette is usually not particularly helpful.

**ECHOCARDIOGRAM.** Two-dimensional echocardiogram is adequate to make the diagnosis of aortic stenosis. Hyperdynamic systolic function of a hypertrophied left-sided ventricle may be found. A bicuspid aortic valve will be present in nearly 60% of cases. Doppler flow can approximate the systolic flow gradient across the obstructed region. In the setting of subvalvar aortic stenosis, flow acceleration begins below the valve and can be associated with aortic valve regurgitation. Supravalvar aortic stenosis is commonly seen with Williams syndrome and should prompt a search for the associated lesions of coronary ostial stenosis and pulmonary branch stenosis. In the neonate with aortic stenosis, patency of the ductus arteriosus and its direction of flow are important to help plan an appropriate management strategy.

### Management

Balloon valvuloplasty became the standard of care for valvar aortic stenosis in the 1990s, when several investigators demonstrated that this approach was equally effective with less morbidity and mortality when compared with surgical valvotomy. However, timing of intervention is perhaps the most difficult element in the management of this disease. As discussed earlier, the progression rate of aortic stenosis during the first 6 months of life is unpredictable. If diagnosed prenatally or shortly after birth in an otherwise healthy, stable newborn, careful monitoring alone is justified. Mild-moderate stenosis with a peak gradient by echocardiogram of less than 50 mm Hg with good LV function and either a closed or left-to-right shunting ductus arteriosus does not generally require urgent intervention, and the newborn can be discharged from the hospital with close follow-up. Right-to-left shunting through the ductus arteriosus suggests ductal-dependent systemic cardiac output (in the absence of persistent fetal circulation), and the child should remain monitored in the hospital until a final decision regarding the need for intervention is reached.

Once the infant is home, most pediatric cardiologists will arrange biweekly or monthly visits for the first 6 months of life. During this rapid phase of somatic growth, changes in clinical status or aortic stenosis gradient can occur quickly. When neonatal intervention is required, frequent return visits may occur for at least the first 6 months of life because the frequency of restenosis is between 15% and 30%.

In most cases, aortic valvotomy, whether performed in the catheterization laboratory or in the operating room, results in some degree of aortic insufficiency. Separation of fused commissures allows for less encumbered prograde flow but also disrupts intrinsic leaflet coaptation. Fortunately, the degree of insufficiency is usually mild and is well tolerated for many years.

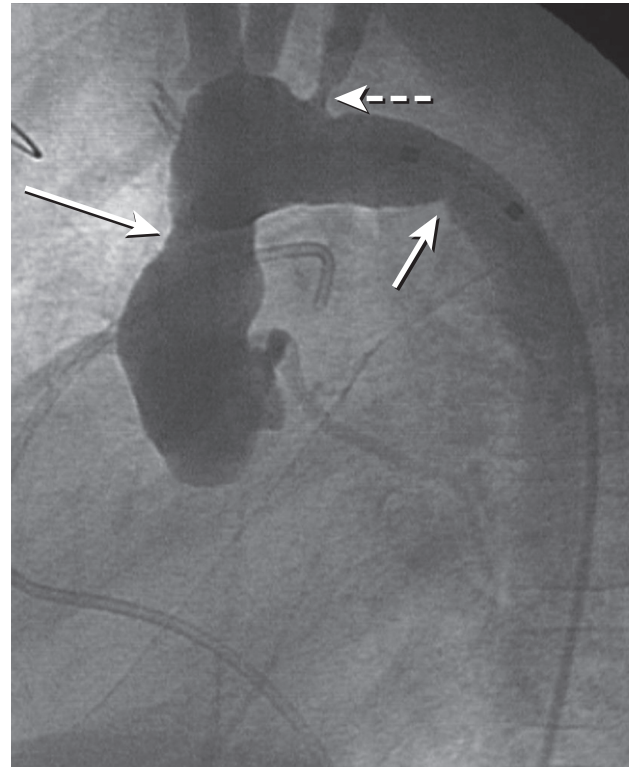
Valvar aortic stenosis tends to increase at a slower, more predictable rate after the first year of life. Non-emergent intervention is indicated in the setting of progressively severe left-ventricular hypertrophy with a transvalvar gradient (found at catheterization) above 50 mm Hg. Most cardiologists would also intervene in the presence of syncope, exercise intolerance, chest pain, or an abnormal exercise stress test. For isolated valvar stenosis, balloon valvuloplasty is the preferred interventional procedure. However, if stenosis is also accompanied by significant valvar insufficiency, or if severe insufficiency develops after a balloon procedure with associated LV dilatation and dysfunction, then surgical intervention will be the only effective therapy. Surgical options include valve replacement with a prosthetic mechanical valve, cadaveric homograft, porcine xenograft, or a pulmonary valve autograft (Ross procedure). When deciding which option is best, the important considerations are the child's age, size, lifestyle, and future adherence to an anticoagulation regimen.

With the exception of an absent valve click, subaortic stenosis is clinically indistinguishable from valvar stenosis. However, the pathophysiologic circumstance is different in several important ways. In subvalvar aortic stenosis, the left-ventricular outflow tract (LVOT) is obstructed by a superfluous tissue membrane, hypertrophy of the IVS immediately below the aortic valve, or both. The blood flow velocity becomes accelerated before reaching the aortic valve and gradually damages the leaflets over time, which can result in progressive valvar regurgitation. Surgical resection of this subaortic region is indicated to relieve obstruction and prevent progressive aortic valve damage and resultant insufficiency. A recurrence rate of 20% to 30% for subaortic obstruction after resection coupled with an inability to predict significant valve damage accurately makes the decision to intervene extremely difficult. In general, surgical resection is performed with the onset of any degree of aortic insufficiency or outflow gradients between 20 to 40 mm Hg. Furthermore, the rate of progression of subaortic stenosis is insidious and is not associated with acute cardiovascular decompensation. Progressive valvar damage can ultimately require valve repair or replacement with a homograft valve, artificial valve, or autograft valve via the Ross procedure.

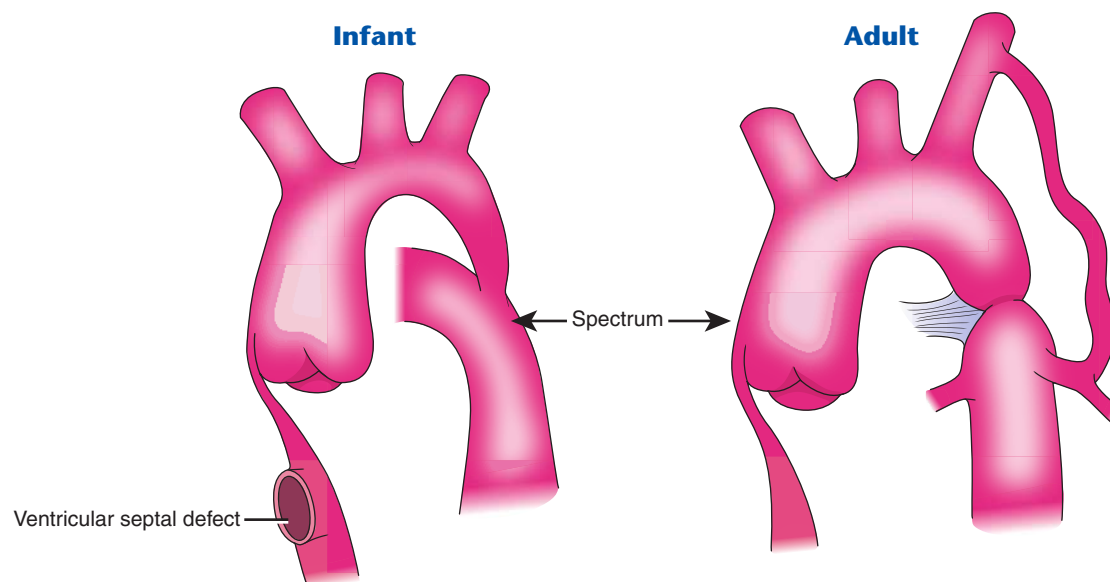
Supravalvar aortic stenosis is the least commonly encountered form of aortic stenosis. Its frequent association with Williams syndrome also places these patients at increased risk for supravalvar branch pulmonary stenosis and obstruction at the origin of other major vessels (ie, coronary arteries, subclavian arteries, carotid arteries, splenic arteries; Figure 234-14). As with subvalvar aortic stenosis, this anatomic variant has an insidious disease progression marked by significantly elevated coronary artery perfusion pressures. Furthermore, given that the pressure gradient is located superior to the aortic root, the proximal portions of the coronary arteries are dilated in response to the persistently elevated pressures they experience. When surgery is indicated, patch aortoplasty of the narrowed region is corrective but also reduces the coronary artery perfusion pressure and can produce coronary artery ischemia if not proactively managed in the postoperative cardiac intensive care unit.

### Coarctation of the Aorta

Coarctation can occur as a discrete narrowing or in association with diffuse hypoplasia of the transverse and aortic arch isthmus often in the presence of a bicuspid aortic valve. Although a discrete coarctation can occur in virtually any portion of the aorta, it is typically found near the insertion of the ductus arteriosus (juxtaductal). Patient presentation tends to have a bimodal distribution; those with diffuse arch hypoplasia are typically diagnosed shortly after birth, and those with an isolated discrete narrowing may not be diagnosed until later in infancy or childhood (Figure 234-15).



**Figure 234-14** Aortogram of a 2-year-old child with non-Williams congenital supravalvar aortic stenosis (*long arrow*) with coarctation of the aorta (*short arrow*). The perforated arrow demonstrates the narrowed origin of the left subclavian artery.



**Figure 234-15** Infantile and adult types of coarctation of the aorta. The left picture demonstrates a diffusely hypoplastic aortic arch extending into the proximal descending aorta at the insertion of the ductus arteriosus. The right picture shows a more discrete area of narrowing with a large collateral vessel spanning the coarctation site.

In children with severe coarctation, a tissue ledge protrudes from the posterior wall into the lumen of the isthmus of the aorta. During the transition from fetal circulation, the ductus arteriosus tissue begins to contract in response to rising oxygen concentrations. Constricting ductal tissue in combination with the adjacent posterior ledge forms an obstructive shelf. If this shelf of tissue is significantly obstructive to limit lower body flow, then systemic underperfusion and shock can ensue. Once diagnosed, infusion of prostaglandin E1 can reopen the ductus and provide ductal flow to the lower body, minimize the juxtaductal obstruction to flow, or both.

Aortic coarctation diagnosed during adolescence has a distinctly different presentation. The fact that these children survive through infancy without either detection or intervention suggests a different pathophysiology. The most likely difference is that a discrete, relatively undersized segment of the aorta, which was adequate for early postnatal life, did not continue to grow at a rate commensurate with the remainder of the aorta. Given that the segment never becomes acutely obstructive, the body has time to produce multiple collateral arteries connecting the aorta proximal and distal to the obstruction thus bypassing the coarctation. If undetected for many years, the intercostal arteries supplying the collateral artery system can become extensive and produce indentations or notching of the ribs. Unlike the neonatal presentation, these patients exhibit only a systolic murmur, upper extremity hypertension, or both. Upper extremity or pre-coarctation hypertension is the result of increased pressure proximal to the obstruction and increased renin-angiotensin activity intended to maintain normal perfusion pressure to the renal arteries. Any evaluation of pediatric hypertension should include an evaluation for coarctation of the aorta.

### Evaluation

**ELECTROCARDIOGRAM.** As with aortic stenosis, the ECG is unlikely to contribute to the diagnosis of coarctation of the aorta unless left-ventricular hypertrophy or strain is present.

**CHEST RADIOGRAPH.** In the adolescent with longstanding, unrepaired coarctation of the aorta, rib notching may be seen from engorgement of the intercostal blood vessels, which will provide collateral circulation around the coarctation segment.

**ECHOCARDIOGRAM.** Two-dimensional echocardiogram can be used to diagnose the presence of a hypoplastic aortic arch or discrete narrowing of the aorta. Although Doppler flow can estimate the blood pressure gradient, upper and lower extremity blood pressures are perhaps a more accurate modality for determining the clinical coarctation gradient. As with aortic stenosis, the echocardiogram should be used to evaluate for any other left-sided obstructive lesions to help guide management.

### Management

The newborn with coarctation of the aorta may present in several different ways. Because this lesion may not be detected by prenatal ultrasound, palpation of

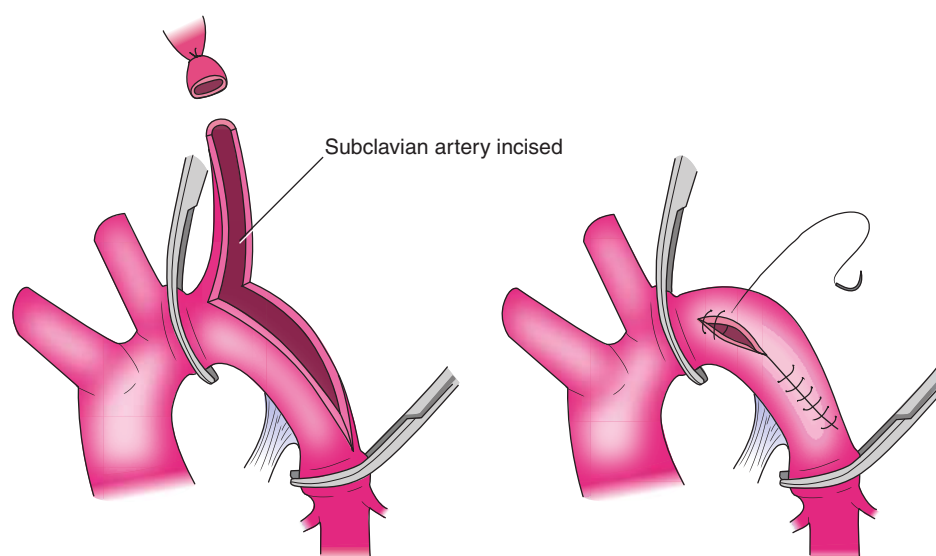
the femoral pulses becomes a crucial part of the newborn examination. When not palpable in an otherwise healthy-seeming infant, both upper and one lower extremity blood pressure should be obtained with the infant supine and calm. Blood pressure should be checked in both arms because the left subclavian artery may arise either proximal or distal to the coarctation site. Although rare, if it arises distal to the coarctation and only the left arm was monitored, then no blood pressure gradient would be demonstrated because both the leg and left arm would have postobstruction blood pressures. However, checking only a right arm blood pressure can be misleading as well. In the case of an aberrant right subclavian artery arising distal to an aortic coarctation, both the leg and right arm would again have postobstruction blood pressures and would not demonstrate a blood pressure gradient. Other than isolated, unilateral femoral artery stenosis, no circumstances are found in which a blood pressure gradient exists between the lower extremities; therefore a single leg blood pressure should be adequate.

If a gradient is demonstrated by blood pressure cuff, then a pediatric cardiology consultation should be obtained. Although extremity blood pressures are far more accurate in determining the actual gradient across the coarctation, an echocardiogram is needed to determine if the coarctation is ductal dependent and to evaluate for other left-sided obstructive lesions. Determining the presence of a PDA is of critical importance. Additionally, because of the presence of ductal tissue in the aorta, a coarctation cannot be excluded with certainty until the ductus has closed. If the ductus is closed and a blood pressure gradient by cuff or narrowing by echocardiogram is not found, then a hemodynamically significant coarctation does not exist. Therefore, if concerns for the existence of a coarctation are present, then the patient should not be discharged until the ductus arteriosus has completely closed or close follow-up has been arranged.

Hemodynamically significant (ductal-dependent) coarctation of the aorta in the newborn period requires intensive management. The initial treatment should be initiation of a prostaglandin E1 infusion to maintain ductal patency or regain it should the ductus be closed or small. The patient should receive no enteral feeds because of possible intestinal underperfusion, and renal function should be monitored closely. For the discharged newborn whose ductus closed at home insidiously, resulting in a coarctation, shock is likely to be present from poor lower body perfusion. These patients should be treated similarly but will also require frequent blood gas monitoring for assessment and correction of acidosis, possible mechanical ventilation, upper and lower extremity blood pressures to track the success of the prostaglandin infusion in regaining ductal patency, as well as possible inotropic support. If the physician is unable to reestablish adequate lower body perfusion, then emergent intervention may be required.

**SURGICAL MANAGEMENT.** Though balloon aortoplasty has been used in treating infant native coarctation of the aorta, most pediatric cardiologists consider surgical correction the standard of care. The surgical





**Figure 234-16** Subclavian flap repair of a discrete coarctation of the aorta.

technique used depends on the extent of the coarctation and surgeon preference. Historically, for discrete coarctations, the 2 most common surgical approaches were subclavian flap repair and patch aortoplasty. In the former, the subclavian artery closest to the coarctation (generally the left) is ligated distally and filleted open (Figure 234-16). The coarctation region is also filleted open, and the flap of subclavian artery tissue is then rotated and sutured in place. The alternative to ligation of the subclavian artery is use of a patch to open the coarctation. Of the 2 approaches, use of the subclavian flap procedure is less likely to result in aneurysmal dilatation of the segment of aorta but, until adequate arterial collateralization occurs, can be associated with a mild growth retardation and loss of strength in the respective arm.

Currently, for both standard discrete coarctations and those in which the coarctation is associated with some element of isthmic hypoplasia, particularly in infants, the preferred surgical approach is coarctation segment resection with *extended end-to-end* reanastomosis. By beveling the 2 ends before anastomosis, the circumferential sutures are distributed over a larger area and are less likely to fibrose and form a recoarctation. The rate of recoarctation varies but is reported between 5% and 25%.

Coarctation associated with a diffuse segment of transverse arch hypoplasia is generally not amenable to an extended end-to-end reanastomosis unless the descending aorta can be fully mobilized and advanced proximally to the distal ascending aorta without disrupting cervical vessels. In these instances, arch repair will be quite extensive and usually requires arch augmentation with homograft material that is sewn around the lesser curvature of the arch, from the transverse arch beyond the resected coarctation segment to the proximal descending aorta to reduce the risk of subsequent restenosis.

The actual surgical incision site may change based on the extent of the coarctation. A discrete region of

affected aorta without associated intracardiac malformations will generally be repaired through a lateral thoracotomy. An intercostal incision is made in the mid-axillary line and visualization is achieved by separation of the left upper and lower lung lobes. When diffuse aortic hypoplasia or intracardiac malformations exist, a midline sternotomy approach is preferred to maximize exposure and ability to repair the defect adequately.

**PROGNOSIS AFTER SURGERY.** Given a potentially significant restenosis rate after initial repair, balloon dilatation in the cardiac catheterization laboratory is an invaluable tool for these patients. A gradient of more than 20 mm Hg is generally considered the clinical indication for intervention. Balloon dilatation results in splitting or tearing of intimal or proximal medial tissue planes and will often be repeated 2 to 3 times to ensure adequate luminal diameter. Several studies have demonstrated postballoon dilatation restenosis rates of less than 20%, but associated transverse arch hypoplasia was associated with a higher rate of reintervention. Stent placement during balloon dilatation has been shown to reduce the rate of restenosis and provide significant relief from obstruction in intermediate follow-up studies (3–6 years). However, these studies predominantly evaluated adults. Stent placement in the proximal descending aorta of young children is not commonly employed, however, because these stents cannot typically be adequately dilated to compensate for growth.

Postoperative or postprocedural treatment of coarctation of the aorta is often complicated by paradoxical hypertension or systemic blood pressure higher than preoperative measures. Animal studies have shown that stimulation of sympathetic nerve fibers located between the media and the adventitia of the aorta increases norepinephrine release, which increases systemic blood pressure. The spinal reflex is a positive feedback loop, which responds to this hypertension by increasing renin secretion from the juxtaglomerular cells of the kidney. These findings have been supported by human data

in patients immediately after coarctation repair. A persistent hyperdynamic state of the left ventricle likely plays a causative role as well. On this basis,  $\beta$ -blocker medications are often employed to treat hypertension in the immediate postoperative period. When hypertension persists beyond the first few postoperative days, most physicians will use angiotensin-converting enzyme inhibitors to offset the renin-mediated phase of hypertension. Finally, some research suggests that dysfunctional vasodilatory mechanisms may play a large role when systemic hypertension persists after postoperative recovery. Although less likely in infants and young children, patients who undergo coarctation repair during or after adolescence have demonstrated a higher rate of persistent hypertension, which may be caused by an inability to adapt to the spinal reflex described previously. Routine cardiology follow-up will be necessary even after a “perfect” coarctation repair to assess for possible associated longer-term morbidities including persistent systemic hypertension (less likely if repaired as an infant), recoarctation or arch aneurysm (depending on type of surgical repair performed), progressive aortic valve disease (bicuspid valve can become stenotic or regurgitant), occurrence of symptomatic cerebral aneurysms, and coronary artery disease.

### Complete Mixing Lesions or the Single-Ventricle Heart

By definition, a complete mixing lesion is one in which the  $\text{SaO}_2$  of blood is the same in both the aorta and the pulmonary arteries. Systemic and pulmonary venous blood volumes drain into a single ventricle, and this combination of oxygen-rich and oxygen-poor blood produces a partially desaturated blood volume perfusing both the body and the lungs. Hypoplastic left heart syndrome will be used as the prototype for this classification of heart lesions, but the physiologic mechanism and management is applicable to most variations of the single-ventricle heart.

#### Hypoplastic Left Heart Syndrome

Hypoplastic left heart syndrome (HLHS) is a group of cardiac anomalies characterized by underdevelopment

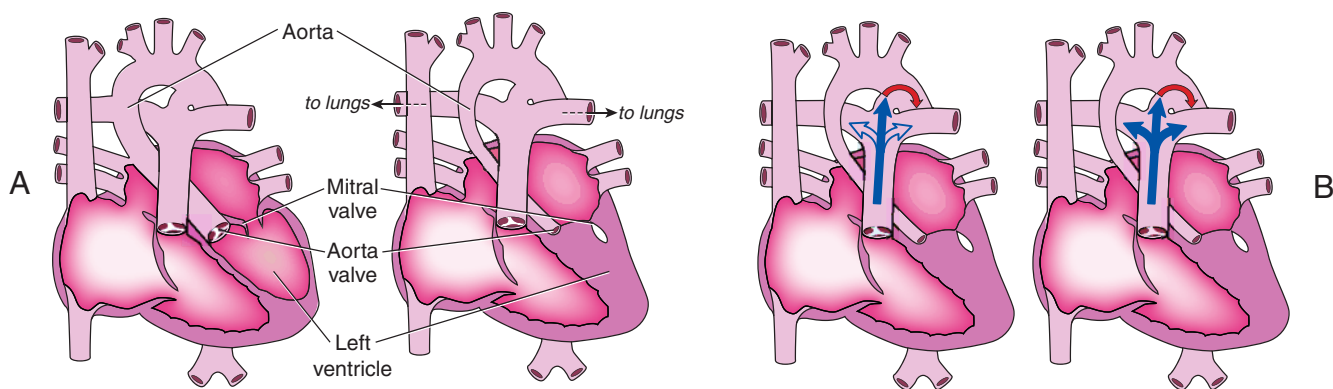
of the aortic arch, aortic valve, mitral valve, and left ventricle. Embryologically, this series of anomalies is likely propagated by inadequate blood flow through a stenotic or atretic aortic valve. Inadequate prograde flow through the left ventricle results ultimately in diminished growth. Fortunately, in utero, the fetal circulation can be adequately supplied by the right ventricle, and normal somatic growth continues. Therefore, most newborns with HLHS are able to achieve normal birth weight and gestational age.

Unless diagnosed prenatally, the newborn with HLHS may not be immediately recognized, and, unless systemic saturations are monitored or cyanosis is noted, these infants may not be diagnosed during their newborn hospitalization. The timing of presentation is dependent on closure of the PDA in conjunction with the delicate balance between pulmonary and systemic blood flow. All egress of blood from the single, right ventricle occurs through the pulmonary artery. Blood within the main pulmonary artery will flow to either the lungs or through the PDA into the descending aorta and retrograde into the ascending aorta (Figure 234-17). Since all systemic output is ductal dependent, as the PVR decreases and pulmonary blood flow increases, systemic blood flow is decreased. Untreated, the oxygen-sensitive ductal tissue begins to constrict, further decreasing systemic blood flow. This condition will result in pulmonary overcirculation and systemic shock and is typically the state in which previously undiagnosed patients with HLHS present. When the condition results in end-organ damage or a delay in surgical intervention, morbidity and mortality increase significantly.

#### Evaluation

**CHEST RADIOGRAPH.** Unless pulmonary overcirculation occurs, radiography is unlikely to contribute much to the diagnosis of HLHS except, possibly, to differentiate a cardiac from a pulmonary source of cyanosis.

**ELECTROCARDIOGRAM.** The healthy newborn's ECG will demonstrate right-ventricular hypertrophy with a right-axis deviation as a result of its hypertrophy relative to the left ventricle. This pattern will



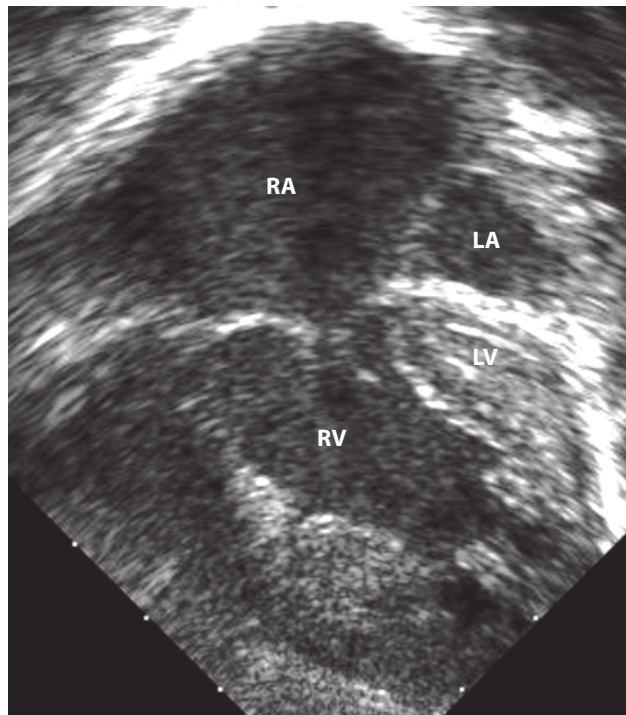
**Figure 234-17** A, Comparison of the anatomy and relative structure sizes between a normal, 4-chambered heart and a hypoplastic left heart with atresia of both the mitral and aortic valves. B, These 2 figures depict the relative blood flow between the pulmonary and systemic circulations in a patient with HLHS. The left-sided drawing shows the relative blood flows in a patient with mildly elevated PVR and systemic  $\text{SaO}_2$  levels of 70% to 80%. When PVR is decreased, however, systemic  $\text{SaO}_2$  levels increase to 90% with a concomitant increase in pulmonary blood flow and a decrease in systemic blood flow.

continue with the newborn with HLHS, but it may be more pronounced. A distinguishing feature may be a relative paucity of left-ventricular forces in the lateral precordial leads.

**ECHOCARDIOGRAM.** Echocardiogram is the confirmatory study. The sonographer should document the presence or absence of the PDA and flow through both the aortic and mitral valves, estimate the left-ventricular volume, determine the size of the ascending aorta and ASD (to verify no significant restriction), and characterize the aortic arch and coarctation. Furthermore, size and competency of the pulmonary and tricuspid valves, and right-ventricular function are critical information to obtain to stratify surgical morbidity and mortality risks (Figure 234-18).

### Management

The first step in management of HLHS is defect recognition. Early clinical manifestations can be subtle. The newborn with HLHS may not demonstrate profound systemic cyanosis until the  $\text{SaO}_2$  falls below approximately 85% (or lower in dark-skinned children). A cardiac murmur is commonly not present or appreciated. Therefore, palpation of femoral pulses becomes a critical step in every newborn's routine evaluation (see chapters in Part 4: Care of Healthy and High-Risk Infants). As with isolated coarctation of the aorta or critical aortic stenosis, the newborn with HLHS will commonly have decreased femoral pulses. These pulses will become progressively weaker as the ductus arteriosus closes. If aortic atresia exists, then all 4 extremity pulses will diminish with ductal closure.



**Figure 234-18** Apical 4-chamber echocardiographic view of a newborn with HLHS. Notice the severely underdeveloped left atrium and left ventricle.

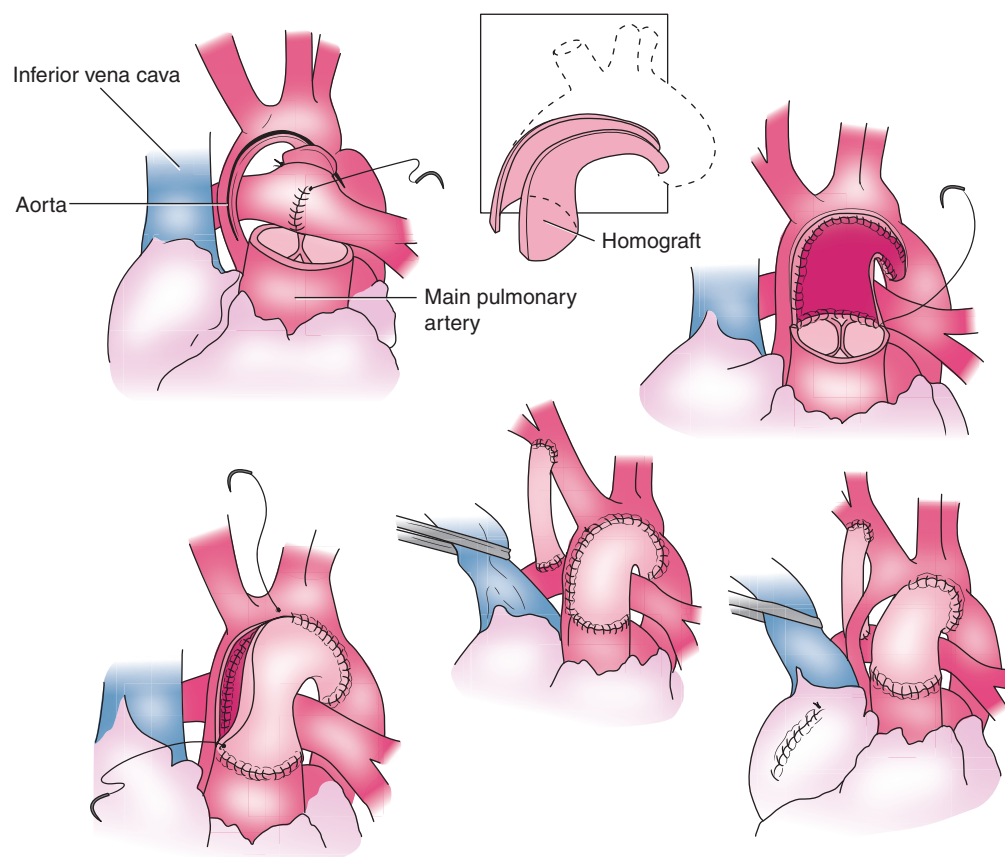
Once a clinical suggestion for the diagnosis of HLHS exists, a prostaglandin E1 infusion should be started immediately. Starting doses can vary widely based on clinical status, but all can result in apnea. If a cardiac lesion is strongly suspected, beginning a prostaglandin E1 infusion should not be delayed awaiting pediatric cardiology consultation.

When the diagnosis of HLHS is confirmed, arterial and venous catheters should be inserted, if possible. The specific preoperative medical management of these newborns varies between institutions. However, the parameters directing management are the same and include renal function (assessed by urine output and serum creatine), blood pressure,  $\text{SaO}_2$ , and arterial blood gases. When followed serially, these measurements provide a surrogate for the balance between pulmonary and systemic blood flow. If renal function and blood pressure are decreased with a concomitant rise in serum lactate, then systemic oxygen delivery is inadequate. This circumstance generally occurs in the presence of increased  $\text{SaO}_2$  or a relative pulmonary overcirculation. Multiple strategies exist to remedy this situation, including hypoxia (ie, producing subambient oxygen by increased nitrogen infusion into the inhaled gas mixture), hypercarbia (ie, increasing carbon dioxide content of inhaled gas mixture), permissive hypercapnea (ie, when intubated, decreasing minute ventilation with resultant pulmonary vasoconstriction), or decreasing SVR via vasodilatory medications (ie, milrinone, nitroprusside and phenoxybenzamine). Regardless of which method is used or whether the patient is intubated, the primary endpoints of the preoperative therapy are to provide balanced pulmonary and systemic blood flow.

The surgical intervention strategy for all single-ventricle hearts is based on 2 simple premises: (1) A single ventricle is not able to perform the function of 2 ventricles indefinitely, and (2) the PVR is elevated initially after birth and, in most cases, does not decrease completely for weeks to a couple months. The physiologic characteristic does not change regardless of which ventricle is hypoplastic. However, the surgical options available to each patient depend on how blood flow is provided to the lungs and body.

Again, using the HLHS as the prototype for the single-ventricle heart, Figure 234-19 demonstrates the first-stage palliative surgery called the Norwood procedure. This procedure, introduced by Dr William Norwood in 1980, produces a neo-aorta from the main pulmonary artery and the hypoplastic ascending aorta. The main pulmonary artery is ligated at its branch bifurcation point and then attached to the ascending aortic arch, usually in a side-to-side fashion. After resection of a coarctation segment, the remainder of the hypoplastic aortic arch is augmented with homograft. As a result, the pulmonary valve becomes the systemic semilunar valve, and the coronary arteries, which arise normally from the aortic root, are perfused retrograde through the ascending aorta. The surgery is completed by providing pulmonary blood flow through either an aortopulmonary shunt (ie, Blalock-Taussig shunt from the innominate artery to right pulmonary artery) or a right ventricle-to-pulmonary artery conduit (ie, Sano conduit). The right





**Figure 234-19** Depiction of the steps involved in the Norwood procedure. The main pulmonary artery is ligated at its insertion into the confluence of the branch pulmonary arteries. The main pulmonary artery is then connected in a side-side fashion to the hypoplastic ascending aorta. After an appropriately sized homograft patch is made by the surgeon, the new patch material is sewn to the underside of the transverse and proximal descending aortic arch augmenting the previously hypoplastic aortic arch in its entirety to a point beyond the site of native coarctation, which should eliminate any arch obstruction. This process completes the neo-aortic arch reconstruction. Pulmonary blood flow is then provided through a modified Blalock-Taussig shunt, which is a Gore-Tex tube graft connecting the pulmonary arteries to the right subclavian artery.

ventricle is thus transformed into a systemic ventricle responsible for pumping blood to the body and lungs.

This initial palliation is necessary but suboptimal for the single-ventricle heart. The PVR does not fully decline for several months and requires systemic blood pressures to overcome elevated pulmonary artery pressures. The right ventricle is then obligated to perform as both a right and a left ventricle and is also volume overloaded from shunt-mediated pulmonary overcirculation. Once PVR decreases, the second stage of the palliative surgeries decreases the work of the single ventricle by removing the need for active pumping of the pulmonary blood supply. Either the Glenn or hemi-Fontan procedure connects the SVC to the pulmonary artery, and the previously placed shunt or conduit is ligated. By doing so, pulmonary blood flow is provided passively from the SVC into the low-resistance and low-pressure pulmonary arteries (Figure 234-20).

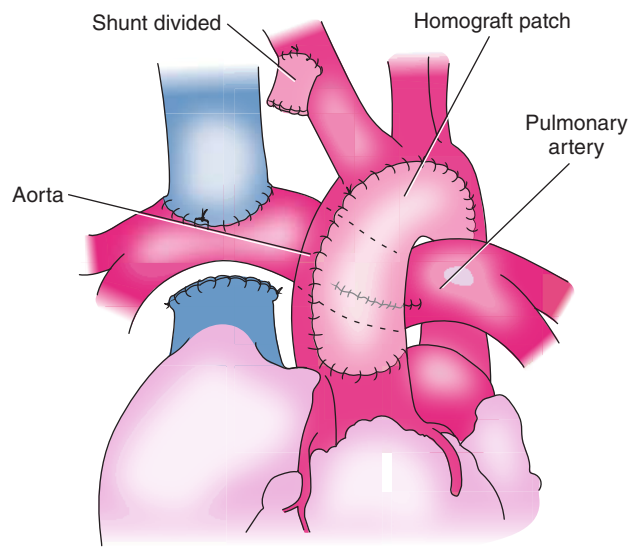
The systemic  $\text{SaO}_2$  in patients after these first 2 palliative procedures will generally remain 75% to 85%. These children will typically have a higher hemoglobin concentration than acyanotic children in

response. The third and final stage of these palliative surgeries is the Fontan procedure, which baffles the IVC to the pulmonary artery, routing all systemic venous return directly into the lungs. Therefore, oxygen-rich is separated from oxygen-poor blood, and the systemic  $\text{SaO}_2$  is typically near normal (>90%).

### Prognosis

A multi-institution study randomizing newborns undergoing the Norwood procedure to receive either a BT shunt or an RV-PA conduit demonstrated 1-year mortality rates of approximately 35% and 25%, respectively. This study underscored the complexity of this patient population, which carries into adulthood. Cardiac dysrhythmias, cerebrovascular accidents with seizures, myocardial ischemia, pleural effusions, and the need for multiple cardiac catheterizations have all been described in this patient population. Improved survival after the Fontan procedure has been shown to be strongly correlated with shorter cardiopulmonary bypass and aortic cross-clamp times. A spectrum of neurodevelopmental outcomes has also been





**Figure 234-20** Depiction of the extracardiac anatomy after the bidirectional Glenn procedure. The Blalock-Taussig shunt is ligated, and the cardiac end of the SVC is divided and anastomosed to the pulmonary arteries becoming the sole source of pulmonary blood flow. The neo-aorta created during the Norwood procedure remains unaltered.

reported for this patient group. Recent studies have shown that most postoperative 8- to 9-year-olds had cognitive scores comparable to the general population, but approximately 18% demonstrated IQ scores under 70. Some of these children have also had varying degrees of developmental motor delay and behavioral problems, including obsessive-compulsive disorder and attention-deficit/hyperactivity disorder. This palliative approach for single-ventricle physiologic arrangement may ultimately serve as an extended bridge to cardiac transplantation, given that some studies have shown that 20% to 30% of patients after undergoing the Fontan procedure develop heart failure, resulting either in successful orthotopic heart transplantation or death.

### Other Complete Mixing Lesions

#### Tricuspid Atresia

Though tricuspid atresia is also considered a single-ventricle anatomy with complete mixing lesion physiology, its clinical manifestations depend on the anatomic variant in each patient. In utero, the atretic tricuspid valve does not allow forward flow into the right ventricle or pulmonary artery, causing them to also become hypoplastic or atretic. As a result, the single ventricle is a left ventricle that is generally connected to the aorta. Distinct types of tricuspid atresia are classified based on the relationship of the great arteries, presence of a VSD, and degree of associated pulmonary stenosis. The most common type consists of tricuspid atresia with normally related great arteries with or without significant pulmonary stenosis. Unless the pulmonary stenosis protects the pulmonary vascular bed by limiting pulmonary artery pressure and flow, an

initial procedure to limit pulmonary blood flow is necessary either via pulmonary artery banding or ligation of the main pulmonary artery and placement of an aorto-pulmonary shunt. In patients who have tricuspid atresia and d-TGA, the aorta arises from the hypoplastic RV and is itself potentially hypoplastic with an associated coarctation. With closure of the PDA, these patients can present in a manner similar to HLHS patients. Like the HLHS patients, this form of tricuspid atresia requires creation of a neo-aorta and placement of an aorto-pulmonary shunt via the Norwood procedure. Since this lesion ultimately follows the surgical single-ventricle reconstruction pathway described for HLHS patients, timing and technique of the Glenn and Fontan surgeries remain unchanged.

## ACQUIRED HEART DISEASE—INFECTIOUS ETIOLOGIES

For a discussion on rheumatic heart disease, see Chapter 323, Rheumatic Fever. For a discussion on Kawasaki disease, see Chapter 280.

### Endocarditis

Endocarditis is a bacterial infection of the endocardium or endothelium of the heart. Generally, endocarditis is associated with a procedural or surgical intervention. Spontaneous endocarditis does occur but is exceedingly rare without predisposing risk factors. Infective endocarditis (IE) is of clinical interest because of the significant morbidity and mortality it produces. With the increased sophistication of interventional catheterization procedures and the dramatic improvement in survival profiles for children with CHD, IE prevalence has risen substantially over the last 2 decades.

Before the 1970s, fewer than 50% of all children with IE had an associated CHD; these children now account for approximately 90% of all cases. The remaining cases are generally associated with indwelling venous catheters without associated structural heart disease.

The pathogenesis for IE is relatively well understood. Intact endocardium will not predispose the area to bacterial attachment or activation of the coagulation pathway. However, cardiac endothelium can be directly damaged by venous catheters or indirectly by the turbulent flow produced with many congenital heart defects. In either situation, thrombogenesis can occur with deposition of sterile clumps of fibrin, platelets, and red blood cells.

Staphylococci, streptococci, and enterococci remain the most common pathogens because of their ability to interact with platelets and resist the host's immune response. The known risks of developing IE in the preoperative state of CHDs are as follows: tetralogy of Fallot, more than 30%; VSD, 12% to 14%; PDA, 8%; aortic stenosis, 2%; and pulmonary stenosis, 1%.

### Diagnosis

The clinical course of IE is typically indolent but, in rare cases, can cause cardiogenic shock. Affected patients may have recurrent low-grade fevers (90%), arthralgias (25%), gastrointestinal discomfort (15%),

fatigue, rigors, or other nonspecific findings. Physical examination may be significant for a new cardiac murmur (rare), splenomegaly (55%), and neurologic changes (20%). The classically described findings of Osler nodes (tender subcutaneous nodules on pads of fingers), Janeway lesions (nontender hemorrhagic macules on palms or soles), Roth spots (pale-centered oval hemorrhages on retina), and splinter hemorrhages in the nail beds are rare in children.

In 1994 the Duke criteria for diagnosis of IE were introduced. Using these lists of major and minor criteria has improved diagnostic accuracy. The Duke criteria for IE are met if a patient demonstrates both major criteria, 5 of the 6 minor criteria, or 1 major and 3 minor criteria. Because direct visualization of infected thrombi is difficult, most physicians require 2 distinct blood cultures with identical bacterial pathogens before considering the diagnosis of IE. Although transthoracic echocardiography (TTE) has excellent specificity, the poor sensitivity limits its role in the diagnosis of IE; transesophageal echocardiography (TEE) is the preferred visual diagnostic modality, with a sensitivity of 80% to 90%, and should be strongly considered in highly suggestive cases even if TTE is negative. Overall, the minor criteria are often used when diagnosing pediatric IE.

### Treatment

The therapy for IE entails a prolonged course of intravenous antibiotics to eradicate the high concentration of organisms deeply embedded within the fibrin-platelet matrix. For a complete review of the suggested regimen of antibiotic therapy, see the American Heart Association recommendations for IE therapy in adults. In brief, duration of intravenous therapy will vary between 2 and 6 weeks depending on bacterial speciation and antimicrobial sensitivity. Blood cultures should be repeated during and after antibiotic therapy to ensure eradication of the offending organism.

### Prognosis

Before the era of antibiotics, IE was universally fatal. Today, however, survival has increased by 70% to 80%. Long-term prognosis is primarily determined by the presence of complications. If treatment is initiated early, then valvar damage, heart failure, embolic events, and heart block can be prevented. However, complete eradication becomes significantly more difficult if the endocarditis involves a prosthetic valve or is caused by a *Staphylococcus* species. In these scenarios, the prognosis is more guarded.

### Prevention

The complications associated with IE along with its difficult management make prevention an integral step in caring for persons at risk. Good oral hygiene and appropriate antibiotic prophylaxis constitute the primary means for achieving this goal. Inappropriate prophylaxis can pose more risk than benefit when considering hypersensitivity reactions to antibiotics. Likely, the best prevention strategy is to maintain good oral hygiene and avoid any unnecessary interventions. The guidelines for IE prophylaxis have

recently been updated, and many conditions previously necessitating prophylaxis have been eliminated. The following are cardiac conditions associated with the highest risk for adverse outcome from IE for which prophylaxis is reasonable: prosthetic cardiac valve or prosthetic material used for cardiac valve repair; history of previous IE, unrepaired CHD including palliative shunts and conduits; completely repaired CHD defects using prosthetic material or a device placed surgically or by catheter-based delivery system (during first 6 months following procedure); repaired CHD with residual defects at the site or adjacent to the site of prosthetic patch or device (which inhibits endothelialization); and cardiac transplant recipients who develop valvulopathy.

### Myocarditis

Myocarditis is a generalized inflammation of the cardiac muscular walls. In a 10-year study of 14,000 cardiac patients cared for at Texas Children's Hospital between 1954 and 1977, 0.5% of patients were diagnosed with myocarditis at presentation and another 2% to 5% at autopsy. Nearly 20% of pediatric sudden deaths may be related to myocarditis. Though its incidence is low in the pediatric population, an accurate and timely diagnosis is critical for improving the related morbidity and mortality. Mortality rates vary inversely with age of onset; nearly 75% of all newborns and infants who develop myocarditis will succumb to the disease. In older children with less fulminant disease, the mortality rate is approximately 25%, with 50% exhibiting a complete recovery and another 25% becoming asymptomatic but having persistent abnormal cardiac function.

### Pathophysiologic Features

Histologically, myocarditis is characterized by viral infiltration of myocytes and the associated immune-mediated cell lysis. Although the enteroviruses, particularly the coxsackievirus B3 and B4 serotypes, are typically reported to be common causative agents, studies using polymerase chain reaction (PCR) amplification have also found adenovirus, and more recently parvovirus, to be regularly associated with myocarditis. The mechanism by which these viruses produce their cellular toxicity is unclear, but an autoimmune response has been suggested by some investigators. Recent evidence shows that these viruses may cause direct damage to the myocardial cells by disrupting sarcomeric linkage proteins, particularly dystrophin, which will interfere with force transduction and result in myocyte dysfunction and heart failure.

### Clinical Manifestations

The clinical presentation in patients with myocarditis can range from mild ECG abnormalities in an otherwise asymptomatic child to fulminant congestive heart failure. Older children will typically have less fulminant presentations, occurring 7 to 10 days after a viral upper respiratory infection or gastroenteritis. Signs and symptoms may include fever, malaise, chest pain, dyspnea, pallor, and poor perfusion. Physical examination may demonstrate muffled heart sounds and a

gallop rhythm, suggesting congestive heart failure. With severe, fulminant onset, cardiogenic shock may be present.

### Evaluation

Laboratory values in a child with myocarditis will be nonspecific and generally consistent with a diffuse inflammatory process. Erythrocyte sedimentation rates, C-reactive protein, and white blood cell and platelet counts may all be elevated. Measures of cardiac cell damage, including troponin-I and creatinine kinase-MB fraction, can be used to establish that myocyte injury has occurred and then to follow these levels to monitor the progress of the condition. Serum viral cultures, serologic titer assays, or PCR amplification of viral genome (or all) may help verify a cause, but an endomyocardial biopsy is required for the definitive diagnosis of myocarditis.

The pathognomonic electrocardiographic finding in myocarditis is decreased precordial voltages consistent with a loss of functioning myocardium (Figure 234-21, A). This finding can generally be differentiated from pericarditis by the absence of diffuse ST segment elevation commonly present in pericarditis. First-, second-, and third-degree atrioventricular block may develop, as well as wide-complex ventricular tachycardias. A chest radiograph often demonstrates global cardiac enlargement and increased pulmonary vascularity with varying degrees of edema (Figure 234-21, B). Two-dimensional echocardiography commonly demonstrates global cardiac chamber enlargement with atrioventricular valve regurgitation and poorly contracting ventricles.

### Treatment

The treatment for myocarditis remains largely supportive. Though antiviral medications, steroids, and intravenous gamma globulin are often administered, limited and somewhat controversial data exist supporting their use. For milder cases, bed rest and hospitalization are sufficient until the child's cardiac status returns to baseline. More severely affected children, however, commonly require

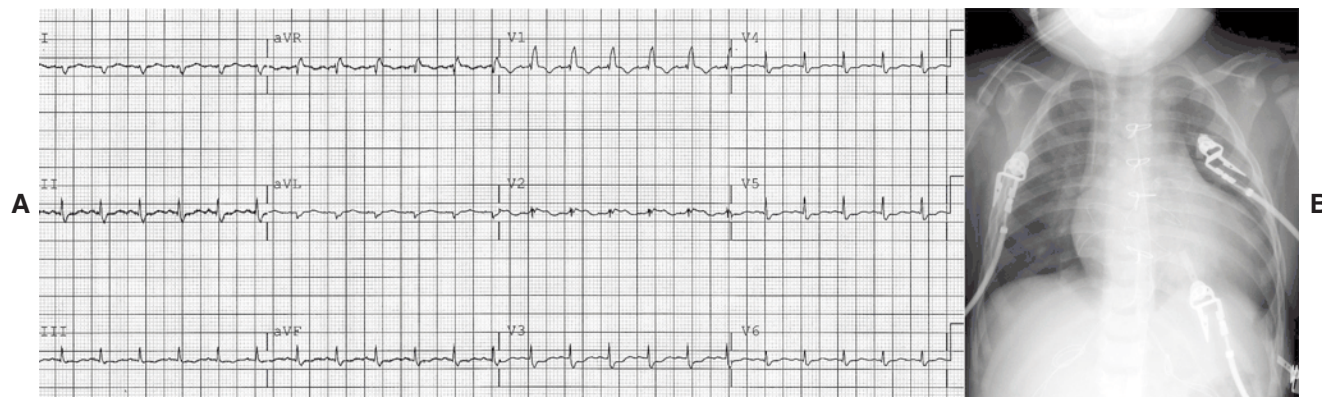
aggressive diuresis, inotropy, chronotropy, afterload-reducing medications, antiarrhythmic agents, ventilator support, and even mechanical circulatory support (ie, extracorporeal membrane oxygenation, ventricular assist devices).

### Management

For children who survive the initial phase but do not fully recover ventricular function or develop chronic heart failure, long-term medical therapy is typically required. Diuresis, afterload reduction, and, in some instances, long-term antiarrhythmic medications (or automatic implantable cardioverter defibrillators [AICDs]) are used. Adult studies examining the use of beta blockers (carvedilol, metoprolol, and bisoprolol) in the setting of heart failure have shown that these agents can reverse abnormal cardiac remodeling, minimize clinical symptoms, and decrease hospitalizations and cardiac-associated deaths. Results from a similar, multicenter, randomized, controlled trial of beta-blocker use in a heterogeneous pediatric population showed no significant outcome benefit with therapy (carvedilol), but there was a trend toward improved ventricular function in the patient subgroup with a morphologic left ventricle. When patients fail to respond adequately to medical or mechanical support, cardiac transplant is the only alternative for long-term survival in appropriately selected patients.

### Pericarditis

Pericarditis is an inflammation of the pericardium and is often associated with effusion (fluid accumulation) within the pericardial sac. However, in conditions such as myxedema (hypothyroidism), patients may have pericardial effusion in the absence of pericarditis. Pericarditis can have both infectious and noninfectious causes. Among infectious agents, the enteroviruses (especially coxsackievirus B), influenza, cytomegalovirus, and Epstein-Barr virus are the most common viral causes, whereas *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae* are the most common bacterial pathogens.



**Figure 234-21** A, ECG of a 6-year-old with myocarditis. Note the low QRS voltages throughout limb and precordial leads. Although not seen in every patient with myocarditis, this ECG finding is pathognomonic for this diagnosis. B, Chest radiograph of the same patient who developed myocarditis-induced DCM.



Tuberculous and fungal pericarditis are unusual. Rheumatic fever, autoimmune diseases, postcardiac surgery, uremia, and malignancies such as leukemia are some of the noninfectious causes of pericarditis.

### **Pathophysiologic Features**

Both the parietal and the visceral layers of the pericardium are inflamed, and the pericardial fluid can be serous, serofibrinous, hemorrhagic, or purulent in nature. Myocarditis is often associated with infectious pericarditis, more so with viral than with bacterial agents. However, depending on the virulence of the offending organism, pericarditis can be the more pathologic component of the 2 processes.

The clinical features of pericarditis and the associated effusion are caused by diastolic dysfunction related to abnormal, restricted filling of the heart. Therefore, the symptoms and signs depend on the fluid volume within the pericardial space, the rapidity with which the fluid collects, and myocardial function. A rapid collection of fluid, as occurs in bacterial infections, may cause severe circulatory compromise (cardiac tamponade). A gradually developing pericardial effusion allows the pericardium to stretch, and therefore the increase in the pericardial pressure is slower, which is usually much more readily tolerated. However, if the myocardial function is depressed, then even this gradual increase in pericardial fluid and pressure may cause significant circulatory compromise.

With the onset of cardiac tamponade, the following compensatory mechanisms are activated:

- Tachycardia to improve the cardiac output
- Increase in SVR to raise the falling blood pressure
- Constriction of systemic and pulmonary veins to improve diastolic filling

### **Clinical Manifestations**

A history of viral upper respiratory infection 10 to 14 days before the development of pericarditis is common. Children typically exhibit pain in the left side of the chest, which is worse in the supine position or with deep breathing and relieved on sitting or leaning forward. The pain may radiate to the left shoulder or to the neck.

The child may be febrile, especially with bacterial pericarditis, and may be pale, gray, hypotensive, tachypneic, and tachycardic (signs of low cardiac output). A pericardial friction rub (a biphasic sound) is the cardinal sign of early pericarditis. With further accumulation of pericardial fluid, the friction rub may disappear and the heart sounds may become muffled. In pericardial tamponade, because of the pressure caused by the large amount of pericardial fluid around the heart, the venous return during inspiration is compromised, resulting in a paradoxical rise in the jugular venous pressure (known as the Kussmaul sign) and a decrease in cardiac output and systolic blood pressure (known as pulsus paradoxus). These children will also have other signs of low cardiac output such as pale, clammy skin, gray (sometimes mottled) appearance, dyspnea, and tachycardia.

### **Evaluation**

Chest radiograph may be normal when the pericardial effusion is small. However, with a large effusion, the cardiac silhouette appears enlarged and has a globular appearance. The pulmonary vascular marking may be prominent in patients with tamponade. An ECG may show low-voltage QRS complexes with substantial pericardial effusion; it may also show changes caused by associated myocarditis such as diffuse ST elevation in initial stages. Gradually, the ST segment begins to normalize, with decrease in the T wave amplitude eventually leading to T wave inversion. These ECG changes may resolve completely with the exception of T wave abnormalities, which may persist for long periods.

Echocardiography is most often used to assess the size of a pericardial effusion, which can occur with pericarditis; it is also very useful in detecting evidence for cardiac tamponade and associated conditions (ie, myocarditis).

Computed tomography and magnetic resonance imaging are indicated when the echocardiogram is inconclusive and when pericardial effusion is suspected to be loculated or hemorrhagic. When the pericardial fluid collection is large or rapidly increasing, as in the case of bacterial pericarditis or when tuberculous pericarditis is suspected, performing a diagnostic and therapeutic pericardiocentesis may be necessary. This procedure will drain the fluid to minimize the potential for clinical decompensation from tamponade and allow possible etiologic diagnosis after evaluation of cell count (total and differential), glucose, protein concentration, Gram and acid-fast stain, and appropriate cultures (with viral PCR as indicated) and cytologic assays.

### **Management**

The management of pericarditis depends on the size and etiology of the effusion, as well as its effect on cardiac function. Urgent decompression by percutaneous pericardiocentesis or surgical drainage is life saving in patients with cardiac tamponade. Similarly, urgent drainage is necessary for suspected purulent pericardial effusion. This task can be accomplished with a large-bore pericardial drain or a surgically created pericardial window to permit continuous drainage of purulent material and to prevent development of tamponade. Intrapericardial infusion of a fibrinolytic agent such as streptokinase has been used in patients, including children with purulent pericarditis, and has been shown to decrease the recurrence of pericardial effusion. Appropriate antibiotics should be given intravenously for 4 to 6 weeks. In many cases, after treatment of purulent effusions, a partial or total pericardiectomy will be necessary to prevent the development of constrictive pericarditis related to fibrotic scarring and adhesions within the pericardial space.

The viral form of pericarditis does not require any specific treatment other than a short course of anti-inflammatory medication such as ibuprofen. In children with pericarditis associated with other conditions, such as autoimmune disease and uremia, treatment of the underlying condition leads to the resolution of the



pericardial effusion. Steroids can be considered as a treatment option for persistent or refractory viral or secondary pericarditis.

## CARDIOMYOPATHIES

A cardiomyopathy refers to any structural or functional abnormality of the ventricular myocardium that is not associated with CHD or diseases of the coronary arteries, cardiac valves, or pulmonary vasculature. Four general types of cardiomyopathy exist, and in order of decreasing frequency are dilated, hypertrophic, restrictive, and miscellaneous cardiomyopathies.

### Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) accounts for 60% to 70% of pediatric cardiomyopathies, with an annual incidence of between 5 and 20 cases per million children. A viral cause is identified in 2% to 15% of cases with biopsy-proven myocarditis; the remaining cases are classified as idiopathic but are likely genetic. Autosomal-dominant, autosomal-recessive, X-linked, and mitochondrial inheritance patterns have been described. Adult studies have shown approximately 20% of patients with DCM have a familial form. Regardless of the cause, the progressive cardiac dysfunction associated with DCM is likely related to the remodeling response of the heart after an inciting injury.

### Pathophysiologic Features

The remodeling cascade consists of the neurohumoral response to inadequate cardiac output. Increased levels of plasma catecholamines, renin, angiotensin II, atrial- and brain-type natriuretic peptides, and overexpression of various cytokine transcripts have been identified in this cascade. Unregulated compensation by these pathways can result in excessive vasoconstriction, intravascular volume expansion, hypertrophy of functioning myocytes, and dilatation of the cardiac chambers. If unchecked, this change in

myocardial structure and function can become irreversible.

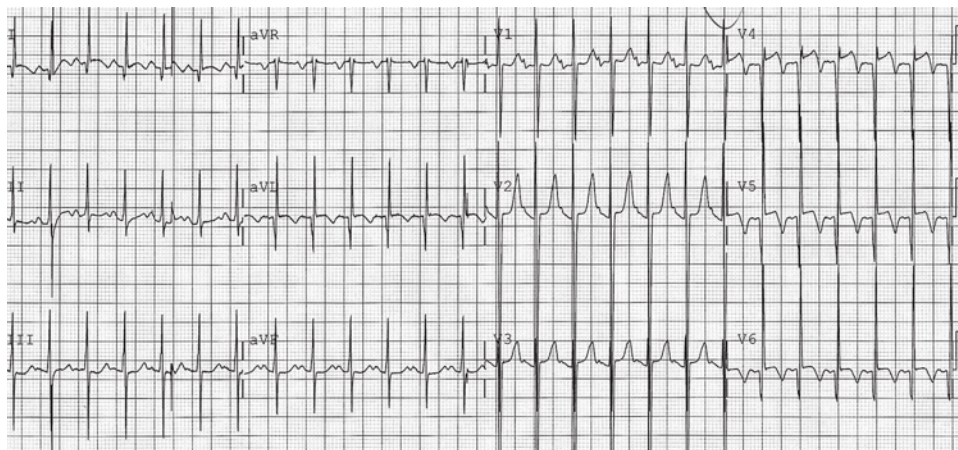
### Clinical Manifestations

The clinical presentation of DCM can vary from progressive exercise intolerance with pulmonary congestion to systemic decompensation with cardiovascular collapse. Regardless of severity, diagnosis typically does not occur until the cardiac reserve is exhausted or is nearly exhausted. For this reason, patients with DCM are often diagnosed after an acute viral illness that elevates their resting state metabolism enough to exceed the failing heart's compensatory mechanisms.

In symptomatic patients, the physical examination will be consistent with congestive heart failure. Tachycardia, cachexia, sallow color, and a gallop may be appreciated. Pulmonary congestion will cause tachypnea and, in older children, orthopnea. Progressive ventricular dilatation or infarction of a left-ventricular papillary muscle can cause the early systolic, regurgitant murmur of mitral regurgitation. Hepatomegaly and weakened peripheral pulses may be found with severe cardiac dysfunction. A chest radiograph will generally show cardiomegaly with or without increased pulmonary vascular markings (see Figure 234-21, B). An ECG may show biventricular hypertrophy by voltage criteria with ST segment and T wave abnormalities (Figure 234-22). The echocardiogram will ultimately confirm the diagnosis. Dilated cardiac chambers, atrioventricular valve regurgitation, and depressed systolic function are nearly universal findings for these patients.

### Treatment

Multiple treatment modalities have been implemented to improve left-ventricular systolic function in children with DCM. The primary intervention is pharmacologic and is directed toward treating the symptoms of congestive heart failure and blunting the neurohumoral



**Figure 234-22** ECG of a 2-month-old infant with DCM secondary to the left coronary artery arising anomalously from the pulmonary artery. Note the large QRS voltages in the precordial leads consistent with biventricular hypertrophy and dilatation. The deep Q waves in leads I and aVL are consistent with a lateral myocardial infarction. Inverted T waves in left lateral precordial leads represent a repolarization abnormality and are consistent with left-ventricular strain.

cascade responsible for the pathologic ventricular reverse remodeling. Aggressive diuresis helps reduce pulmonary edema and hepatic congestion when present and helps reduce any excessive intravascular volume expansion. Spironolactone improves outcomes in adults with congestive heart failure by inhibiting part of the neurohumoral axis. Afterload reduction, typically using angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, also decreases morbidity and mortality in this population; its use is discouraged in the acute, decompensated period. The use of beta-blocker therapy, however, is among the few medical interventions for congestive heart failure that has evidence supporting its use in both adults and children. A study by Shaddy et al demonstrated significant improvement in systolic ventricular function after 23 months of beta-blocker therapy in 15 children with DCM and associated congestive heart failure. This class of medication is thought to reverse the maladaptive remodeling effects produced by the excessive catecholamine levels exhibited in these patients. However, results from a multicenter, randomized, controlled trial of beta-blocker (carvedilol) use in a heterogeneous pediatric population showed no significant outcome benefit with therapy, but there was a trend toward improved ventricular function in the patient subgroup with a systemic LV dysfunction. Because this study was somewhat underpowered by a limited enrollment sample, and other smaller series have shown efficacy, many cardiologists continue to use beta blockers as mainstay therapy. Anticoagulation therapy (ie, aspirin, warfarin) is also commonly used to reduce the risk of thrombus formation, which is inherently elevated in the relatively low flow state associated with poor ventricular function and DCM.

Cardiac resynchronization therapy (CRT) is a novel pacing modality used in patients with DCM and heart failure that is refractory to conventional medical management. By decreasing intraventricular conduction delay and the associated uncoordinated muscle contraction, CRT can synchronize ventricular wall motion, improve both diastolic filling and systolic ejection fraction, and, ultimately, reduce patient symptoms. Its use in children is limited by the lack of controlled study data, and more research is needed before CRT can be widely prescribed in this group. In severe cases, ventricular assist devices, extracorporeal membrane oxygenation, or even cardiac transplantation may be indicated in appropriately selected patients if other treatment regimens are unsuccessful.

### **Hypertrophic Cardiomyopathy**

Hypertrophic cardiomyopathy (HCM) is the second most common form of cardiomyopathy (20% to 30%) in children, with an annual incidence ranging between 4 and 6 per 1,000,000. Autosomal-dominant, autosomal-recessive, and mitochondrial inheritance patterns have been described, with approximately 100 mutations mapped to at least 13 different cytoskeletal or sarcomeric genes. Multiple familial forms of HCM exist, with nearly 40% to 50% demonstrating a point mutation on chromosome 14q1 (β-myosin heavy chain). HCM has also been shown to occur in

association with both Noonan syndrome and Friedrich ataxia.

### **Pathophysiologic Features**

HCM is characterized by wall hypertrophy of all 4 heart chambers but most notably of the IVS and left-ventricular posterior wall. Hypertrophy may be concentric (50%) or asymmetric. If the IVS is disproportionately thickened, then left-ventricular outflow tract obstruction (LVOTO) can ensue in 30% of cases. Furthermore, when hypertrophy is severe, flow through the intramural coronary arteries may be decreased or even occluded, resulting in myocardial ischemia. The primary abnormality associated with HCM is diastolic dysfunction of the left ventricle, which often produces progressive exercise intolerance. In the absence of LVOTO, worsening diastolic dysfunction is sufficient to produce this symptom. When severe IVS thickening does occur, the increased left-ventricular outflow gradient experienced during exercise results in performance and duration limitations.

### **Clinical Manifestations**

The clinical presentation of patients with HCM varies, from infants with congestive heart failure to asymptomatic children with or without a heart murmur. Although the classic presentation is that of a syncopal patient with a loud cardiac murmur, this is rarely the case. More often, a routine examination will demonstrate a harsh systolic ejection murmur at the left sternal border with radiation to the neck. If present, this murmur of LVOTO is then accentuated when a squatting patient is asked to stand, decreasing the SVR and increasing the gradient across the LVOT. The remainder of the physical examination is typically normal. Obtaining a family history is critical because nearly one-half of all patients with HCM will have a first-degree relative with the diagnosis or with a history of syncope or sudden death.

### **Evaluation**

The ECG is abnormal in 90% to 95% of children with HCM, with large voltages in the precordial leads, suggesting biventricular hypertrophy, either ST segment elevation or depression, T wave inversion, and abnormally deep Q waves. The delta wave of Wolff-Parkinson-White syndrome is occasionally noted in association with HCM. Although LVOTO is often considered the source of morbidity and mortality for these children, ischemia-induced arrhythmias are much more likely. This finding is suggested by both the relatively low prevalence of LVOTO in patients with HCM (20% to 30%) and the tendency for frequent episodes of ventricular tachycardia and ST segment elevation on ECG during exercise. Importantly, sudden death (usually from ventricular fibrillation) is the most common cause of death in undiagnosed adolescents and young adults.

Echocardiography is the method of choice for diagnosis of HCM. Attention should be focused on the type of hypertrophy (concentric vs asymmetric), ratio of IVS to left-ventricular posterior wall thickness ( $>1.5$  is diagnostic), presence of LVOT or RVOT obstruction, and systolic anterior motion (SAM) of the anterior

mitral valve leaflet. Historically, SAM is thought to be caused by the Venturi effect of fluid movement in which turbulent blood flow through the ventricular outflow tract produces a pressure gradient, pulling the anterior mitral leaflet into the ventricular outflow tract, resulting in mitral regurgitation. Recent data have suggested that mid-cavitary obstruction common in HCM causes *drag* forces that may also contribute to SAM.

### Treatment

Once diagnosed, the primary focus of treatment for the child with HCM is providing symptomatic relief and minimizing the risk of lethal arrhythmias. Pharmacologic intervention is indicated for children who have symptoms or LVOTO at rest. First-line therapy for these patients is usually beta blockers. Though its mechanism of action is unclear, beta blockade reduces heart rate and myocardial oxygen demand, allows for increased diastolic filling time, and may have some inherent antiarrhythmic properties. Furthermore, by decreasing heart rate and increasing the diastolic filling period, a larger stroke volume will be produced per heartbeat and may minimize the severity of LVOTO. If beta blockers are poorly tolerated, then calcium channel blockers have been shown to produce similar effects. In addition, patients will generally be asked to participate in exercise stress tests and have 24-hour Holter monitoring to help stratify their risk for ventricular tachycardia and sudden death. The presence of asymptomatic, nonsustained ventricular tachycardia on Holter monitor has been shown to increase the risk of sudden death 8 to 10 times compared with HCM patients without this anomaly; the overall risk of sudden death in patients with HCM is 1% to 2% per year (may be as high as 4%–5% in adolescents). When tachycardia is present, most experts recommend the antiarrhythmic medication amiodarone as the drug of choice or an AICD implantation (or both) for the treatment of malignant ventricular ectopy in this patient population. Prophylactic implantation of AICDs is being studied and has been strongly recommended under the following conditions: left ventricle wall thickness greater than 3.0 cm, family history of death related to HCM, unexplained syncope, and nonsustained ventricular tachycardia on Holter monitor. AICD placement as secondary prevention (in patients with aborted sudden death or documented ventricular tachycardia or fibrillation) is now considered standard of care.

In patients with HCM whose symptoms are related to their degree of LVOTO, reduction of flow gradient is recommended. The Brock or Morrow procedure is a surgical myomectomy reserved for symptomatic, medically refractory patients with a ventricular outflow tract gradient of more than 50 to 60 mm Hg. Although the 10-year survival rate after this procedure is approximately 86%, the intraoperative mortality rate can approach 5%. Medical septal reduction is an alternative method of improving LVOTO by infusing desiccated alcohol into the septal perforating coronary vessels within the IVS using TEE guidance in the cardiac catheterization laboratory. As with surgical myomectomy, this procedure has been advocated

for patients with HCM who are failing medical management and has been used with a resting ventricular outflow tract gradient as low as 40 mm Hg. It reduces the morbidity and mortality related to surgery, but even in experienced centers, an increased risk exists of coronary artery dissection, uncontrolled myocardial infarction, and a 5% to 10% risk of complete heart block requiring pacemaker placement.

### Restrictive Cardiomyopathy

Restrictive cardiomyopathy (RCM) is the rarest form of cardiomyopathy in children. It is characterized by a loss of ventricular compliance with a subsequent increase in end-diastolic filling pressures. Systolic ventricular function is preserved, but diastolic relaxation is compromised. The cause of RCM is unknown but is thought to be associated with both genetic (ie, mutations in the desmin, troponin I, transthyretin I $\beta$  genes) and nongenetic causes (sarcoid or amyloidosis, which are common causes in adult patients but reportable in pediatric cases). Care must be taken to distinguish RCM from constrictive pericarditis using echocardiogram, catheterization, magnetic resonance imaging studies, or any combination of these measures. Diagnosis is made via echocardiography, which shows normal ventricular size and function associated with dilated atria caused by the ventricular diastolic dysfunction. Elevated left-ventricle end-diastolic pressures can ultimately result in pulmonary hypertension and pulmonary vascular disease, which is one of the most common and severe complications of RCM. This form of cardiomyopathy is typically nonresponsive to conventional pharmacologic therapy, but anticoagulation is indicated since the risk of intracavitary thrombosis and stroke is increased in these patients. Transplant is the only known definitive therapy. Unfortunately, owing to its usual late diagnosis, pulmonary hypertension that is unresponsive to pulmonary vasodilators is the most commonly cited problem preventing heart transplantation in these patients. Without transplant prognosis is poor, with death occurring within 1 to 4 years of diagnosis (in symptomatic patients, usually from pulmonary hypertensive crises or sudden death). Therefore, such patients should be referred for heart transplantation once the diagnosis is made.

### Miscellaneous Cardiomyopathies

Arrhythmogenic right-ventricular dysplasia (ARVD) and mitochondrial and noncompaction cardiomyopathies comprise only 2% to 3% of pediatric cardiomyopathies. Dysplasia of the right ventricle in patients with ARVD develops from fatty deposits within the ventricular walls. As a result, these patients are at risk for life-threatening ventricular tachycardias, particularly in affected individuals younger than 30 years of age. Diagnosis of ARVD is typically made from dysrhythmias, echocardiogram, or magnetic resonance imaging. Treatment is directed at preventing life-threatening arrhythmias through the use of both medications and AICDs. Patients with mitochondrial cardiomyopathies often exhibit the condition early in life with a hypertrophied or, less commonly, dilated, poorly functioning



heart. In general, this maternally inherited disorder can be variably associated with other muscle, liver, neurologic, and developmental abnormalities.

Last, left-ventricular noncompaction cardiomyopathy (LVNC) is characterized by deep crevices or trabeculations within the normally smooth-walled left ventricle, which reduces cardiac function. The cardiac dysfunction associated with LVNC has been demonstrated to have a varying age of onset, from the newborn period to adulthood. This cardiomyopathy may also be associated with other mitochondrial, metabolic, and systemic (Barth syndrome) disorders.

## CARDIAC TRANSPLANTATION

Orthotopic heart transplantation (HTx) has become a standard therapy for treating both end-stage congenital and acquired heart disease. Although the indications for HTx are similar across the pediatric population, the frequency of each indication changes with age. More than 75% of all recipients younger than 1 year of age undergo HTx because of surgically irreparable CHD; this comprises only approximately 25% of the 11- to 17-year-old HTx recipients. Conversely, cardiomyopathy-related heart failure and dysrhythmias that are unresponsive to medical therapy result in HTx in 17% and 62% of the infant and adolescent population, respectively.

Once HTx is indicated, an extensive evaluation is necessary to determine its feasibility. Cardiac catheterization is required to determine both hemodynamics and PVR. Significantly elevated PVR or elevated PVR that is unresponsive to vasodilatory therapy (ie, oxygen and nitric oxide) can preclude HTx candidacy, whereas active malignancy and hepatic cirrhosis are absolute contraindications. The presence of bacterial or viral infection is a relative contraindication, and the decision to proceed with HTx should be made based on the individual patient's clinical status. A complete antiviral antibody titer panel (for herpes simplex virus, cytomegalovirus, HIV, Epstein-Barr virus, and hepatitis A, B, and C) should be obtained to rule out infection and to help guide the use of antiviral medications in the immediate postoperative period. Panel reactive antibody testing is necessary to assess the amount of circulating preformed human leukocyte antigen antibodies in the recipient's serum, which may limit acceptable donor organs or cause hyperacute rejection in the recipient if the donor has antigens to which the recipient has already made antibodies. Finally, both social and financial screening evaluates a potential recipient's emotional coping skills and verifies that the financial burden of the transplant is minimized.

Transplant status classification is the next critical step and strongly influences the expected waiting time. Potential recipients listed as UNOS (United Network for Organ Sharing) status 1a will generally wait several days to months before receiving a heart transplant, assuming survival is possible for this period. This classification, however, requires a patient to be inotrope dependent and hospitalized. Depending on weight and blood type, infants older than 6 months listed as status 2 can expect to wait up to several months; and adolescent children may require as long

as 2 years before a suitable heart is located. Transplant status can change at any time if the clinical condition improves or worsens.

A thorough discussion of the surgical procedure involved in HTx is beyond the scope of this text. Briefly, the donor heart is harvested in its entirety, with the exception of a cuff of posterior left atrial wall, which contains the pulmonary veins. Once the recipient is placed on cardiopulmonary bypass, the heart is removed in a reciprocal fashion. Anastomosis of the donor heart to the recipient is performed by either a biatrial or, more commonly, a bicaval (SVC-IVC) connection. The postoperative period for HTx recipients poses the unique challenge of managing a patient with a denervated heart that has been ischemic for as long as 4 hours. Without the sympathetic and parasympathetic nerve fibers innervating the sinoatrial and atrioventricular nodes, the resulting heart rate is entirely dependent on the intrinsic sinoatrial nodal rate. Neither Valsalva nor carotid massages will influence heart rate; atropine, the cholinergic receptor antagonist, is also ineffective. Although the resting heart rate of a transplanted heart is typically higher than normal controls, it is often abnormally slow in the immediate postoperative period because of sinoatrial node ischemia related to harvest and transplantation. Therefore, chronotropy can be provided by the selective  $\beta_1$  agonist isoproterenol and titrated to produce the desired heart rate. As the transplanted heart begins to recuperate from the surgical insult, heart rate and cardiac output will increase to meet the patient's needs.

Immunosuppressive medications are typically started soon after the transplantation is complete. Most HTx recipients receive a regimen that includes a calcineurin inhibitor (ie, tacrolimus or cyclosporine), an antimetabolite (ie, mycophenolate mofetil or azathioprine), and corticosteroids. Corticosteroids are generally weaned within the first few post-HTx months, so long as no treatable rejection is detected. These medications all carry a significant side effect profile that often directs dosing and choice of medication. Both cyclosporine and tacrolimus are associated with hypertension, nephrotoxicity, and derangement of the lipid profile. These adverse effects are more common with cyclosporine than with tacrolimus. Tacrolimus and cyclosporine drug levels are monitored, with the therapeutic target levels gradually decreasing with time post-transplant. Azathioprine also necessitates frequent blood monitoring because of its adverse effects of neutropenia and hepatotoxicity. Mycophenolate is known to produce lymphopenia and gastrointestinal distress and may require dose adjustments accordingly. Side effects of corticosteroids have been well described.

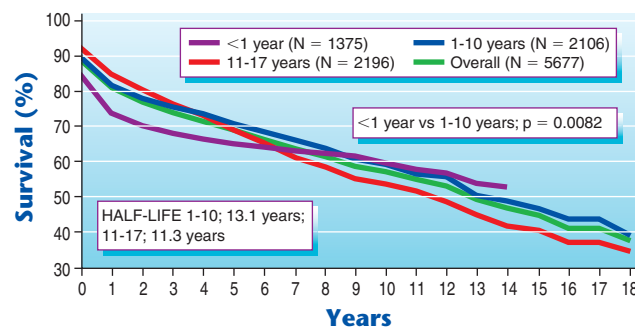
The immunosuppressed state in which these patients live increases the risk of several potential complications. During the early phase of immunosuppression and the subsequent 6 months, patients are at the highest risk for bacterial and opportunistic infections, occurring in 52% and 15% of HTx recipients, respectively. After 6 months, the predominant infectious organisms shift from bacterial to viral (83% of infections), and the specific microbes parallel those afflicting the general, nonimmunosuppressed pediatric



population (ie, cytomegalovirus, Epstein-Barr virus, adenovirus, enterovirus, influenza) as the immunosuppression medications are decreased to maintenance dosing. For patients still requiring routine immunizations, live viral vaccines (ie, oral poliovirus, measles-mumps-rubella, varicella, live attenuated influenza [FluMist], rotavirus) should not be given because of the risk of active infection. Furthermore, the immunosuppressed patient's response to vaccinations will be blunted, particularly during the early post-HTx period, and any systemic antigenic response may precipitate a rejection episode. Therefore, all nonlive vaccinations should be given approximately 3 months post-transplant to minimize rejection.

Although excess immunosuppression predisposes these patients to serious infectious complications, deficiency in these medications places them at significant risk for rejection. This potentially life-threatening situation occurs when immunosuppression is unable to prevent the recipient's body from recognizing and attacking the donor heart's nonself antigens. Cellular rejection is the most common subtype and is a T cell-mediated injury that can begin within the first 5 to 7 days post-transplant, with the highest incidence during the first 3 post-transplant months. Patients may exhibit complaints of malaise, anorexia, gastrointestinal distress, low-grade fever, or nonspecific changes in sleeping patterns. If significant rejection is present, then physical examination will reveal hepatomegaly, a mild elevation in heart rate from baseline, and, possibly, a new murmur or gallop. These patients require prompt evaluation and assessment, which will likely include an echocardiogram to assess cardiac function and, if indicated, an endomyocardial biopsy. If disease proves the presence of rejection, then pulse steroids are administered, and the maintenance immunosuppressive regimen will usually be augmented. Repeat biopsy is necessary to verify effective treatment for the rejection episode, and any interventions (ie, scheduled vaccinations) that might upregulate the immune response should be delayed for approximately 3 months after resolution of the episode.

As pediatric heart transplantation has become increasingly successful, the medical community is learning more about the associated long-term complications. Post-transplant lymphoproliferative disease is an abnormal growth of lymphoreticular cells in immunosuppressed patients and has been linked to primary post-transplant Epstein-Barr virus infection. It occurs in approximately 5% to 10% of pediatric HTx recipients. Some patients will respond to a decrease in immunosuppression, while others will require chemotherapy and possibly even surgical resection. The other significant long-term complication is post-transplant coronary vasculopathy (TCAV). This condition is described as a progressive intimal and medial thickening of the transplanted heart's coronary arteries, with loss of coronary flow reserve and eventual luminal obliteration. The risk of TCAV increases with each episode of rejection (particularly after the first year), certain infections (ie, cytomegalovirus), original harvest time, and associated donor ischemic time; it is also increased in the presence of abnormal lipid profiles.



**Figure 234-23** Kaplan Meier survival curve for 5,677 pediatric patients after orthotopic heart transplant. (From Boucek MM, Edwards LB, Keck BM, et al. *Registry of the International Society for Heart and Lung Transplantation: 8th official pediatric report-2005*. J Heart Lung Transplant. 2005;24(8):968-982, with permission. Copyright © 2005, Elsevier.)

Because of their ability to lower the cholesterol-low-density lipoprotein fraction and their antioxidant/antiproliferative properties, many physicians are recommending statins (ie, pravastatin, atorvastatin) in their transplant recipients. Freedom from TCAV decreases with time from transplant and with each decade of life after which the transplant occurs. Although newer immunosuppressant agents (ie, sirolimus) have shown initial promise as potential treatments for TCAV, retransplantation is currently the only definitive therapy.

Actuarial survival curves currently demonstrate an overall 50% survival at 13 years post-transplant (Figure 234-23). Younger age at transplant is associated with longer survival and decreased need for retransplant. Although transplantation is a formidable treatment strategy for most children and their parents, approximately 90% of HTx recipients surveyed at 1, 3, and 5 years post-transplant report excellent quality of life with no activity limitations. Transplantation seems to be an acceptable end point for patients with irreparable congenital or acquired heart disease but continues to be limited by the number of available donor hearts; approximately 20% to 30% of all patients die while awaiting a suitable donor. Additional research investigating novel immunosuppression or alternative biologic cardiac replacement strategies may help change the fate of these end-stage patients.

## WHEN TO CONSULT A PEDIATRIC CARDIOLOGIST

The question of when to refer a newborn to a pediatric cardiologist can be difficult. This issue is further complicated when practicing in rural areas where a *consult* may mean transport to another hospital or discharge home with the uncertainty of a family keeping their appointment with the pediatric cardiologist. Although some clinical findings can be pathognomonic for a cardiac anomaly, many lesions have only subtle clinical findings. The astute physician is one who can identify *abnormal* from the myriad of patients they encounter in a day. The pediatric cardiologist is

continuously indebted to the general pediatrician's ability to perform this function. Likely, one of the most stressful parts of a pediatrician's practice is determining when a newborn's cardiac murmur is pathologic (see Chapter 101, The Newborn With a Heart Murmur or Cyanosis). Diminished or absent femoral pulses are never normal and should always be evaluated by a pediatric cardiologist. The transition from normal fetal circulation to normal postnatal circulation can produce a variety of cardiac murmurs; distinguishing physiologic from pathologic requires patience and experience.

A PDA is classically described as producing a *machinery* murmur because of its continuous, undulating character. The murmur is appreciated during both systole and diastole because both systolic and diastolic pressures are higher in the aorta than in the pulmonary arteries. Therefore, blood is continuously shunting from the aorta to the pulmonary artery (left to right). As the ductus arteriosus begins to close, the pressure gradient across this vascular conduit increases, making the murmur higher in pitch, but may result in loss of the diastolic component. The ductus arteriosus arises from the proximal portion of the left pulmonary artery and generally inserts into the aorta distal to the left subclavian artery. This anatomic feature results in the murmur being best auscultated in the left, upper sternal border of the chest and may radiate to both lung fields. A pediatric cardiology consult is warranted if this murmur exists in the presence of decreased renal perfusion or pulmonary overcirculation because medical or surgical closure may be indicated. Otherwise, in a healthy infant, outpatient follow-up is recommended. Generally, PDAs close within days to months postnatally. PDAs persisting beyond the young infant period can usually be closed by coil occlusion in the catheterization laboratory.

Similar to a PDA, the systolic murmur produced by coarctation of the aorta will also be loudest at the left upper sternal border. Unlike a PDA, however, a coarctation murmur will generally radiate to the back, medial to the left scapula. In this scenario, palpable femoral artery pulses must be verified, and upper and lower extremity blood pressures must be obtained to assess for a blood pressure gradient. If pulses are absent or thready, or if lower extremity blood pressures are more than 15 mm Hg less than upper extremities, then a pediatric cardiology consult should be obtained immediately (see previous section on coarctation of aorta).

Peripheral pulmonary branch stenosis, which is accompanied by a physiologic murmur, does not require urgent consultation. A short, relatively high-pitched II/VI systolic ejection murmur that is auscultated equally on both sides of the sternum with diffuse radiation to both lung fields is characteristic of this natural transition period from fetal to postnatal circulation. The fact that this natural state has been declared a *diagnosis* is unfortunate because it results in undue angst for both physicians and families. Most physicians are concerned they may be missing the murmur produced by pulmonary stenosis. This murmur is distinct from that of peripheral pulmonary stenosis in both its severity and focality. A murmur produced by

significant valvar pulmonary stenosis will be harsh in character, at least grade III on a severity scale of I to VI (see Table 234-1) and is often preceded by a valve click. It will be best auscultated at the left sternal border but will radiate to both lung fields. Conversely, peripheral pulmonary branch stenosis will be a softer, less intense murmur that is equally audible throughout the chest.

Another common scenario the pediatrician faces is the newborn with Down syndrome. Estimates suggest that nearly 40% to 60% of these children are born with some form of CHD and comprise approximately 9% of the pediatric cardiologist's practice. The AVSD is the most common defect in these patients, occurring in approximately 60%, with nearly 70% of all patients with AVSD having trisomy 21. As discussed in the section on left-to-right shunting lesions, these lesions may not produce an audible murmur until PVR decreases significantly. However, because neither lesion is typically fatal in the first several weeks of life, discharging them from the hospital before seeing a pediatric cardiologist is reasonable if the patient is otherwise stable and acyanotic. Of note, the AVSD is one of the defects that can be suspected with ECG. The normal newborn ECG will meet voltage criteria for right-ventricular hypertrophy and have a concomitant right axis. The AVSD, however, will demonstrate a left axis deviation and a small Q wave in lead aVL (see Figure 234-9, B). Regardless of their immediate postnatal course, all patients with Down syndrome should be evaluated by a pediatric cardiologist within the first month of life.

Last is the issue of managing the cyanotic newborn. In most of these situations, a cardiac lesion is not the cause. This notion is supported by the fact that only 5 to 8 of 1,000 live births are affected by a congenital heart lesion, and a significantly smaller number of those are cyanotic heart lesions. Pulmonary disease is more commonly the culprit. Nevertheless, the general physician can take several steps to help elucidate an etiology.

First, the physician must verify that cyanosis is truly present. Acrocyanosis is a common occurrence in newborns, particularly in the setting of volume depletion or cool extremities. The  $\text{SaO}_2$  should be obtained on a warm, well-perfused, calm infant on both upper and at least 1 lower extremity. If this setting is difficult to attain, then ear lobe  $\text{SaO}_2$  offers an alternative. Once obtained, if saturations remain lower than approximately 92%, then a difference in saturation between upper and lower extremities should be evaluated. Although rare, *paradoxical cyanosis*, or lower  $\text{SaO}_2$  in the upper extremities than lower extremities, occurs in d-TGA with persistent fetal circulation. Lower-extremity cyanosis alone can occur with pulmonary hypertension, severe coarctation of the aorta, and critical aortic stenosis. Right-to-left shunting of oxygen-poor blood through a ductus arteriosus into the descending aorta is the etiology of the asymmetric cyanosis in these settings. Full-body cyanosis can occur in a number of scenarios, including respiratory distress syndrome, any of the cardiac lesions categorized as *right-to-left shunting lesions*, d-TGA

(without persistent fetal circulation), or complete mixing lesions.

Paradoxically, these same lesions can produce  $\text{SaO}_2$  levels of more than 92% in the newborn period. This discrepancy can be produced by the high oxygen affinity of fetal hemoglobin. Therefore, if a cyanotic heart lesion is suspected, then obtaining arterial  $\text{PaO}_2$  values is mandatory. A hypoxemic  $\text{PaO}_2$  of 60 mm Hg produces an  $\text{SaO}_2$  of more than 90%, which alone might falsely reassure the physician. Persistent hypoxemia (<70–80 mm Hg) despite adequate oxygen therapy should increase the level of suspicion for a CHD. Failure of the *hyperoxia* challenge is often sufficient evidence for evaluation by a pediatric cardiologist and arguably for commencement of a prostaglandin E1 infusion.

This medical intervention constitutes a critical step in the management of a patient with suspected cyanotic heart disease. With the exception of the significant side effects associated with prostaglandin E1 infusion and its use in the setting of obstructed TAPVR, generally no physiologic scenario is worsened by this medication. Apnea, irritability, hyperthermia, jitteriness, and, possibly, decreased white blood cell function are the recognized complications. The major concession the physician must make is accepting the high probability of intubation, which is often already required for patient stability. Prophylaxis with caffeine or aminophylline may decrease the risk of prostaglandin E1-associated apnea. Prostaglandin E1 dosing ranges from 0.01 to 0.2 mcg/kg/min. As with most medications, higher doses inherently increase the side effect profile. Notably, the PDA diameter cannot generally be titrated by changing infusion doses. Once open, only doses of 0.01 to 0.02 mcg/kg/min are usually required to maintain patency.

Before or concurrent with the previously mentioned interventions, a chest radiograph and ECG should be performed. The former can help evaluate pulmonary vasculature and size of the cardiac silhouette. Cyanosis can occur in the presence of diffusely increased pulmonary vascular markings (ie, pulmonary etiology, cardiac disease with pulmonary edema) or near absence of pulmonary vascular markings (ie, cardiac lesion with inadequate pulmonary blood flow). The cardiac silhouette is generally only helpful when extreme cardiomegaly exists, as with severe Ebstein anomaly. The classic descriptions of a *boot-shaped heart* (ie, tetralogy of Fallot) or *egg on a string* (ie, d-TGA) are often overdiagnosed on chest radiographs because of the relative right-ventricular hypertrophy and mesocardia seen in many normal newborns. The newborn's ECG can help suggest the diagnosis of AVSDs (northwest QRS axis), hypoplastic left or right ventricles (decreased voltage in left or right precordial leads, respectively, and abnormal QRS axes), and Ebstein anomaly (right atrial enlargement) (Figure 234-24).

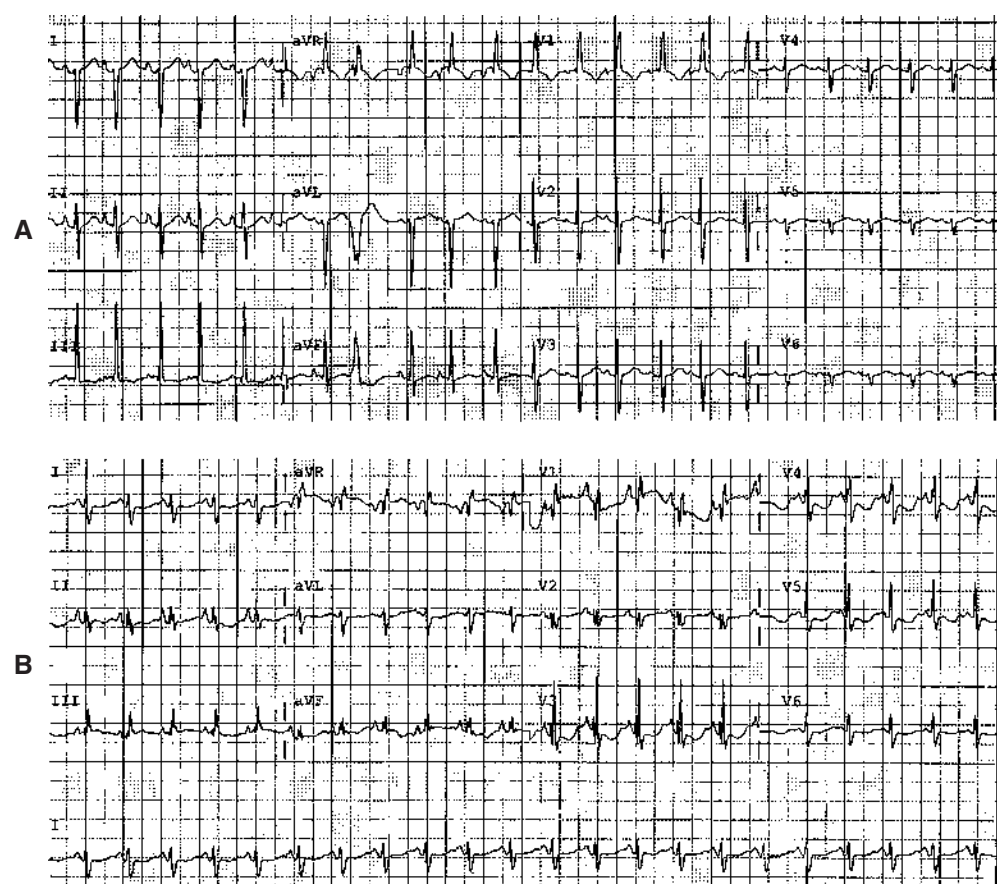
The pediatric cardiologist's echocardiogram can confirm a suggested diagnosis in most situations. Cardiac catheterization is required in a limited number of lesions to verify anatomy or for atrial septostomy if the existing ASD is inadequate (ie, d-TGA,

single-ventricle hearts with atrioventricular valve stenosis or atresia).

The remaining management decisions entail determining whether surgical intervention is required and maintaining cardiovascular stability until that time. As described in the previous section on Complete Mixing Lesions, the major concerns during the preoperative period are end-organ perfusion and oxygen delivery. Proper preoperative management maximizes survival and minimizes morbidity and mortality. This goal is best achieved through an integrated approach involving nurses, allied health team members, family members, and physicians. Available information regarding diagnosis, prognosis, and possible morbidities should be freely exchanged to enable an informed and realistic outlook for all persons involved.

In contrast to patients needing surgical intervention, children with several of the acquired heart diseases can be primarily managed by their general pediatrician. Kawasaki disease can generally be diagnosed and treated before a pediatric cardiologist is ever consulted. An echocardiogram is needed to evaluate for coronary artery aneurysms and, in some cases, to confirm the diagnosis of atypical Kawasaki disease. However, in the absence of cardiac involvement at either presentation or a 2- to 4-week follow-up appointment, further evaluation by a pediatric cardiologist is probably unnecessary. IE is another example of heart disease that the pediatrician can both diagnose and manage with limited involvement of a pediatric cardiologist. Multiple positive blood cultures demonstrating the same organism constitute the most accurate method for diagnosing IE. The low sensitivity of TTE for septic, valvar vegetations decreases its effectiveness in the diagnosis of IE. If IE is strongly suspected, then the more sensitive TEE can be performed if repeated TTEs have been negative. However, all types of CHD (ie, bicuspid aortic valve, VSD) must be ruled out and an adequate history of central venous catheters must be obtained to determine an etiology. Once the patient has received adequate therapy and demonstrated several negative blood cultures, the infection can generally be considered *cleared*. If no evidence exists of CHD or significant valvar derangement, then continued evaluation by a pediatric cardiologist may not be indicated. Last, patients diagnosed with rheumatic carditis should continue to be treated aggressively for all episodes of streptococcal pharyngitis and receive appropriate procedural antibiotic prophylaxis.

The patient with cardiomyopathy typically requires long-term involvement of a pediatric cardiologist. During the first 3 or 4 years of life, however, these patients will see their general pediatrician more frequently, making this relationship crucial for the recognition of progressive disease. Weight loss or a plateau in weight gain, missed developmental milestones, fatigue, activity intolerance, or personality changes can all be subtle indicators of declining cardiac function. In the presence of a murmur, new gallop, or abnormal ECG or chest radiograph, evaluation by a pediatric cardiologist is indicated.



**Figure 234-24** A, ECG of a newborn with HLHS. Note the left-axis deviation of the QRS vector and the paucity of left-ventricular QRS forces in the precordial leads. B, ECG of a newborn with Ebstein anomaly of the tricuspid valve. Note the peaked P waves in leads II and V1 consistent with severe right atrial enlargement.

Heart transplant recipients present another complicated situation for the general pediatrician. Their immunosuppressed status is typically the source of much concern and confusion. A febrile, immunosuppressed heart transplant recipient warrants a thorough evaluation, and, if an obvious, treatable etiology cannot be identified (ie, otitis media, viral upper respiratory infection), then their transplant cardiologist should be involved in the evaluation to minimize the chance that graft rejection will be misinterpreted as a common, benign infectious illness. New-onset fatigue, shortness of breath, exercise intolerance, low-grade fever, vomiting, or diarrhea may all be signs of rejection and require the expertise of the transplant cardiologist. Unexplained abdominal distention, pain, or vomiting should prompt evaluation for an ileus or intussusception because post-transplant lymphoproliferative disease can produce these symptoms; abdominal pain may also be a sign of intestinal angina caused by decreased cardiac output. Because the transplanted heart is denervated, C-fibers, which relay anginal-type chest pain to the brain, have been cut, and the absence of chest pain should not be comforting to the physician. Furthermore, the denervated, transplanted heart will not become significantly tachycardic in response to fever or pain. Therefore, baseline heart rates in

these patients become critical information for the physician, given that an increase of only 10 beats per minute may indicate imminent cardiovascular collapse. The previously mentioned scenarios are intentionally broad and nonspecific; they are intended to demonstrate the subtle clinical changes that may be harbingers of serious illness and to provide guidelines for the pediatrician to consider consultation with a pediatric transplant cardiologist.

Finally, for the previously mentioned cardiac diseases, an important point to note is that the recommendations regarding physical activity and sports participation in patients with CHD vary significantly. The subject of exercise intensity, duration, or participation in any type of athletic event should be discussed with the health care team (including cardiologist and pediatrician), with the patient, and with the patient's family to ensure that no unnecessary or unknown risks are taken.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Heart* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/heart/Pages/default.aspx](http://www.healthychildren.org/English/health-issues/conditions/heart/Pages/default.aspx))



**Medical Decision Support**

- *CardioVillage* (Web site), University of Virginia (cardiovillage.com)
- *Comprehensive Care Planning* (booklet), Medical Home Learning Collaborative (www.medicalhomeinfo.org/downloads/pdfs/ComprehensiveCarePlanning.pdf)
- *S.T.A.B.L.E. Cardiac Student Handbook and Cardiac Slide Program* (booklet and CD-ROM), Karlson KA, (shop.aap.org)
- *Strategies for Implementing Screening for Critical Congenital Heart Disease* (article), *Pediatrics*, Vol 128, Issue 5, 2011 (pediatrics.aappublications.org/content/128/5/e1259)

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## Chapter 235

# CONTACT DERMATITIS

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As the name implies, contact dermatitis is inflammation of the skin secondary to contact with an offending agent. Two broad types of contact dermatitis include *irritant contact dermatitis* and *allergic contact dermatitis*. The clinical presentation and treatment of these 2 entities are similar.

**ETIOLOGY****Irritant Contact Dermatitis**

Irritant contact dermatitis is the result of skin exposure to substances that cause an inflammatory reaction that is not immune mediated. An array of irritant agents may be present in the home, child care center, or school, and may include harsh detergents and cleaning materials. Parents or pediatricians may be aware immediately of the offending agent or may use a diary to chart symptoms and associated activities

and exposures. If the irritant dermatitis is acute, then identifying the culprit is often easy, given that it may be only a single agent. In chronic cases, multiple offenders are often present. If a child has repeated episodes of irritant contact dermatitis that compromise the protective skin barrier, then a fertile environment for subsequent allergic contact dermatitis may result.

Diaper dermatitis is a common irritant dermatitis in children. Urine, feces, and persistent moisture macerate the occluded skin of the perineum. Of note, typical irritant diaper dermatitis does not involve the creases of the infant's skin. If the femoral creases or anal area are involved, then the infection is likely to be candidal. Candidiasis produces red, often macerated plaques accompanied by satellite papules or pustules. Diaper rash that persists longer than 3 days is likely secondarily infected with yeast. (See Chapter 242, Diaper Rash.)

Irritant contact dermatitis caused by airborne agents (dust or volatile chemicals) is often missed and must be considered in all cases. Solvent sniffers, typically preteens and young adolescents who inhale aerosols to alter mental status, are susceptible to irritant contact dermatitis secondary to the airborne agent. These patients may have irritant dermatitis of the arms and chest, along with the eczematous changes found mostly around the nose and mouth.

**Allergic Contact Dermatitis**

Allergic contact dermatitis is immune mediated and is a type IV delayed hypersensitivity reaction. Such reactions require prior exposure to the allergen to produce the event of dermatitis. Delayed hypersensitivity reactions are caused by primed T cells, producing a cascade of cytokines and chemotactic factors leading to dermatitis.

As with irritant dermatitis, an initial episode of allergic contact dermatitis may be easily identified because the rash usually is localized to a specific area, and the history of the offending agent can be ascertained. Poison ivy and nickel are very common causes of allergic reactions.

Commonly, poison ivy is given as an example when allergic contact dermatitis is described; it represents *Toxicodendron* (Rhus) dermatitis. This plant, along with poison oak, poison sumac, Japanese lacquer tree, the cashew nut tree (allergen in the nutshell), mango (allergen in rind, leaves, or sap), Rengas tree, and Indian marking nut tree, are members of the Anacardiaceae family of plants. The dermatitis that these plants trigger appears within 48 hours of exposure in a previously sensitized individual, often producing linear arrays of vesicles where the offending plant has come in contact with the skin. Another common site in young boys includes the genitals because, in many cases, they transfer the allergen to this area when voiding.

An allergic reaction to nickel is common and remains the most frequently positive patch test allergen in North America. With the increased incidence of body piercing in the pediatric population, allergic reaction must be considered when an area at a piercing site is red, scaling, and irritated (Figure 235-1). Nickel is also located on areas of clothing such as the snaps and zippers on trousers or blouses (Figure 235-2), and it has even been detected in electronics.



**Figure 235-1** Nickel contact dermatitis at the site of an earring.

Other allergens becoming more important include topical antibiotic preparations, such as those containing neomycin, which have shown a notable increase in positive patch test reactions since the 1970s; hair dye products that contain paraphenylenediamine; and latex in children who have repeated exposure to it in clinical settings. Most recently, methylisothiazolinone (MI) has shown up as an evolving allergen in the pediatric population. This allergen is found in skin and hair products and functions as a preservative. It is important to note that MI is commonly found in products marketed as “sensitive,” “gentle,” “organic,” or “hypoallergenic,” and it is often a component of cleansing wipes. Thus, in recalcitrant dermatitis of the mouth, hands or genital/anal regions, use of products containing MI should be investigated.

### EPIDEMIOLOGIC CONSIDERATIONS

Contact dermatitis affects both genders, all ages, and all races. Differences among individuals pertain mostly to habits of exposure. In addition, regional differences can exist, depending on the allergens or irritants in the environment. Contact dermatitis represents 6% to 10% of visits to dermatologists' offices, and about 10% of dermatology consultations for hospitalized pediatric patients.

Irritant contact dermatitis is seen more commonly than allergic contact dermatitis in very young children because they lack the repeated exposure needed for allergic contact dermatitis to develop. However, some experts suggest that allergic contact dermatitis may account for at least 20% of all childhood dermatitis.

### DIFFERENTIAL DIAGNOSIS

The differential diagnoses for contact dermatitides include atopic dermatitis, seborrheic dermatitis, tinea, and psoriasis. Rare conditions, such as acrodermatitis enteropathica from zinc deficiency or Letterer-Siwe disease, a serious disorder of histiocytes, can mimic diaper dermatitis and must be considered.



**Figure 235-2** Contact dermatitis caused by nickel in a clothing snap or belt buckle affecting the lower abdomen.

### CLINICAL MANIFESTATIONS

The clinical presentation of both types of contact dermatitis can be similar. Allergens and irritants can produce a range of responses from eczematous changes of the skin noted by pink, scaling, irritated plaques to severe vesiculobullous eruptions characterized by blistering changes of the skin and severe pruritus.

Irritant contact dermatitis can lead to lichenification, which is characterized by accentuation of skin lines, often with hyperpigmentation, and an almost hardening of the skin. Acute irritant dermatitis can occur within minutes to hours after exposure. The intensity of the reaction is related to the nature of the chemical, the concentration, and the duration of contact. Conditions that foster a more severe reaction include wet skin and skin under friction, occlusion, or pressure. In addition, patients with a history of atopic dermatitis are likely to experience contact dermatitis.

Allergic contact dermatitis can also produce bullous, purpuric, lichenoid, papular, urticarial, pigmented, and hypopigmented reactions.

### MANAGEMENT

#### Uncomplicated Case

Treatment is similar for both irritant and allergic contact dermatitis. Topical steroids and emollients for milder disease and systemic medications including oral corticosteroids and antihistamines for more dramatic presentations are the basic treatments. Although the effectiveness of topical steroids has been well documented in allergic contact dermatitis, it is less well defined for irritant dermatitis. Elimination of the offending agent and liberal application of emollients are usually curative for mild irritant contact dermatitis, given that this form of treatment will speed resolution and decrease the chance of impetiginization resulting from scratching. Identifying the causative factors so they may be avoided is accomplished by good history taking by the physician. In chronic cases, a parent or older patient may need to keep a diary. More involved cases warrant a trial of topical steroids, given that the risks are minimal when they are used for a short time. In rare, severe cases of irritant dermatitis, just as with allergic contact dermatitis, systemic steroids are appropriate and can be given

for 2 weeks at a dose of 0.5 to 1.0 mg/kg with a rapid wean. A dermatologist may need to be consulted if the diagnosis is in question.

The treatment of diaper dermatitis requires gentle application of protective barrier ointments such as zinc oxide and petrolatum. Lowest-potency corticosteroids can be used in severe cases 2 to 3 times daily for a limited time (initially 3 days, and no longer than 2 weeks), and long-term exposure should be avoided in the occluded diaper area. Care of the diaper area includes bathing the child in water with minimal use of nondetergent soaps, followed by liberal use of emollients. Barrier ointments should be used with each diaper change with care not to produce excess friction. The involved areas should be kept dry and free of urine and stool, and caregivers should be encouraged to change the diaper frequently, as often as every 2 hours or more. Commercial cleansing wipes, if used, should be fragrance free and alcohol free. Topical antifungal agents work well for secondary candidal infection of the diaper area and should be considered in irritant rashes that are present for more than 3 days. Combination steroid-antifungal topical products should not be used in the diaper area.

With regard to the treatment of allergic contact dermatitis, Rhus dermatitis specifically, management includes washing the skin and other items that may have come in contact with the plant. Once the patient develops skin lesions, systemic antihistamines are usually needed. Topically, mild to moderate-strength (class 7 to 4) topical steroids are appropriate. In addition, topical pramoxine, an antihistamine, is safe and can be used over large areas of the body 2 to 3 times per day. If the lesions are limited but very pruritic, then a more potent topical steroid cream (class 1 or 2) can be applied for no more than 2 weeks. If the lesions are more extensive, then systemic steroids for 2 weeks at a beginning dose of 0.5 to 1.0 mg/kg followed by a rapid taper over the subsequent 2 weeks is justifiable. Dermatologists do not favor quick bursts of systemic steroids because they are often associated with rebound of the rash.

### Complicated Case

A suspected contact dermatitis that has not responded to treatment in a month, has involvement of a large body surface, or displays severe reactions (such as bullae) is a complicated case and may require skin biopsy. Patients who require patch testing (gold standard for identification of allergens causing allergic contact dermatitis) will require a referral to a dermatologist or pediatric allergist.

Patch testing involves the application of suspected allergens to intact, uninflamed skin. The substances of interest are usually applied to the back and are left on for 48 hours. After 48 hours, the patches are removed and the coded sites evaluated for the presence of a reaction, which can be erythema or bullae formation. Some positive reactions may not show for up to 7 days; thus, having the patient evaluated again at 5 and 7 days is useful. A commercially available patch testing system composed of 35 common allergens can be performed easily in the dermatologist's office. For more extensive patch testing, use of individually

prepared aluminum chambers with multiple allergens can be placed and then applied with hypoallergenic tape to the back. Of note, the technique of photopatch testing that detects contact photoallergy is also available. In this test, the patch is applied, and then after 24 hours the area is exposed to ultraviolet A light; the patch is read 48 hours later. Although data are limited, treatment of severe cases of contact dermatitis may involve topical or oral immunomodulators at the discretion of the dermatologist.

### PREVENTION

Irritant contact dermatitis can best be prevented by maintaining the skin barrier and by avoiding irritants. Parents and older children must be educated about common irritants including soaps and detergents, especially those with fragrance and dye additives. Formaldehyde, formaldehyde releasers, and other clothing treatments can aggravate the skin of children; clothing should be washed before wearing. Barrier function of the skin is preserved by maintaining a healthy stratum corneum. Skin should be well hydrated (but not overly hydrated) and well moisturized.

Allergic contact dermatitis is best prevented by identifying trigger factors and then educating the parent and older child about avoidance of triggers. Patients and their families should be taught to identify a poison ivy plant so that it can be avoided and removed, if possible. Commercial nickel spot tests are available from several sources. These user-friendly tests allow patients to detect the presence of nickel in metal items with which the patient may come in contact.

Finally, it is often simple and best for the patient if the entire family eliminates allergens. For example, the family of a patient sensitive to fragrances should all be practicing fragrance-free routines.

### WHEN TO REFER

- A child with presumed irritant contact dermatitis (including diaper dermatitis) that has persisted for a month or longer despite aggressive topical treatment should be referred to a dermatologist.
- A child with involvement of a large body surface area or displaying severe reactions (eg, bullae) or an atypical presentation may require referral to a dermatologist for a skin biopsy.
- Patients in need of patch testing should be referred to a dermatologist or qualified pediatric allergist.

### WHEN TO ADMIT

Generalized or systemic contact dermatitis as may occur from exposure to smoke of a burning antigen (ie, Rhus/Anacardiaceae family plant).

- Patient experiencing fever, chills, nausea, vomiting, or hypotension.
- Secondary bacterial infection requiring intravenous antibiotics.
- Secondary infection with a herpesvirus requiring intravenous antivirals.



## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *What is a Pediatric Dermatologist?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Dermatologist.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Dermatologist.aspx))

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## Chapter 236

# CONTAGIOUS EXANTHEMATOUS DISEASES

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*Exanthem*, meaning to bloom or to break out, refers to a skin eruption or rash that may be associated with fever. In children, the etiology is most often infectious, and may be caused by viruses, bacteria, parasites, or fungi; however, pediatric exanthems may also indicate noninfectious conditions, including rheumatologic, immunologic, and allergic diseases, as well as medication-related effects. These eruptions are extremely common in children and can present physicians with a major challenge in forming the differential diagnosis given the similarities in rash morphology and distribution among various illnesses. Careful exploration of the history and clinical manifestations other than rash is necessary to distinguish one disease from another. These factors include the incubation period, prodromal symptoms and signs, age of the patient, immunization history, contact or exposure history, distribution and progression of the rash, evidence of other organ involvement, and presence of pathognomonic signs (eg, Pastia lines or Koplik spots). Laboratory findings, including cultures and molecular testing, may be helpful in select cases and may assist in differentiating between infectious and noninfectious etiologies.

Some exanthems herald diseases for which treatment is necessary; others signal the need for specific isolation measures, reporting to public health departments, or perhaps further medical or epidemiologic evaluation. For example, certain infectious exposures pose risks to specific populations, such as a nonimmune pregnant woman exposed to rubella, or household contacts exposed to a patient with confirmed meningococcemia. Acute communicable diseases causing rash that respond to specific therapy

require special consideration. Recognition of the exanthem associated with *Neisseria meningitidis* infection (meningococcemia), for example, is essential for early and potentially lifesaving antibiotic treatment. Given the very different management strategies, careful differentiation between infectious exanthems and Kawasaki disease is important for appropriate treatment and monitoring (see Chapter 280, Kawasaki Disease). Additionally, it is important to differentiate between the exanthems of toxin-mediated streptococcal and staphylococcal disease, particularly in the era of increasing methicillin-resistant *Staphylococcus aureus* (MRSA).

Some of the differentiating characteristics of these and other eruptions are found in Chapter 186, Rash. This chapter focuses on exanthems associated with contagious viral and bacterial infections and does not discuss rashes associated with infections not transmitted person to person, such as Lyme disease (see Chapter 287).

## VIRAL EXANTHEMS

### Measles

Measles is one of the most serious of the childhood exanthems because of the morbidity and mortality associated with both the acute infection and the long-term permanent sequelae that can occur. The measles virus is highly contagious and is transmitted via respiratory droplets or by airborne transmission. The incubation period is typically 10 to 11 days. The prodromal illness is characterized by increasing fever, cough, conjunctivitis, and coryza. Fever commonly is high (104°F [40°C]) and, by day 4 of illness, the rash erupts. A deep erythematous macular rash begins on the face and neck and spreads down the trunk and extremities, similar to what occurs from a rubella infection. However, the rash on the face and upper portion of the trunk soon becomes confluent to produce the characteristic morbilliform rash, whereas the rash seen with rubella tends to remain discrete. The fever subsides and the rash begins to fade by day 6 of illness, leaving a faint brown pigmentation of the skin; a fine desquamation then ensues. With widespread use of measles vaccine, the differential diagnoses for a measles-like rash include Kawasaki disease along with a number of more common infections from enteroviruses, adenoviruses, and Epstein-Barr virus to bacteria such as *Mycoplasma pneumoniae* and streptococcal species.

The enanthem of measles is pathognomonic. Koplik spots, tiny bluish-white spots on an erythematous base that cluster adjacent to the upper molars on the buccal mucosa, begin approximately 2 days before the rash erupts and increase in number until day 1 or 2 of the exanthem. The combination of Koplik spots, fever, cough, conjunctivitis, and a morbilliform rash is sufficient to make a presumptive clinical diagnosis of measles. Although children are usually very ill, they recover rapidly by day 8 or 9 of illness and are often fully recovered by day 10 or 12; hence, the common term “10-day measles.”

Acute complications of measles are usually related to the inflammation that the virus induces throughout the respiratory tract, which can result in otitis media, bronchiolitis or laryngotracheobronchitis, and pneumonia. Otitis media is the most common complication, followed by pneumonia, which can be difficult to



distinguish clinically as to whether these symptoms are caused by measles virus or secondary bacterial infections. All children who have measles should have careful monitoring, and the examiner should have a high degree of suspicion for secondary bacterial infections of the upper and lower respiratory tracts. Rarely, other organ systems may be involved, including the central nervous system (CNS) with acute encephalitis (1 in 1,000 cases of measles). Vitamin A supplementation should be considered for immunodeficient patients and patients 6 months to 2 years of age who are hospitalized as a result of measles and its complications; limited data exist for Vitamin A use in the United States.

A rare but major complication of measles virus infection is subacute sclerosing panencephalitis (SSPE), also known as Dawson encephalitis. Disease occurs because of persistent measles virus infection in the CNS, with slowly progressive symptoms. Epidemiologic estimates of SSPE in the United States range from 4 to 11 cases of SSPE per 100,000 cases of measles, with increased risk if measles infection occurred prior to 2 years of age. Initially, SSPE produces headache, vomiting, drowsiness, and personality/behavioral changes, followed by progressive symptoms such as seizures and coma. In most cases, the cerebrospinal fluid (CSF) reveals pleocytosis and elevated protein levels with high CSF measles antibody titers. The prognosis is poor, with permanent neurologic sequelae and death commonly occurring within 1 to 3 years of diagnosis. Rare exceptions have been reported, with individuals showing remission or reversal of symptoms. Although numerous therapies have been attempted, none have proven to be efficacious or curative.

Endogenous measles transmission in the United States has been eliminated with the adoption of a routine 2-dose immunization schedule. Prevention of measles is discussed in Chapter 20, Immunizations.

### Atypical Measles

Atypical measles syndrome occurred in some children who were exposed to the wild-type measles virus and who had been previously immunized with inactivated measles vaccine used many decades ago (between the years 1963 and 1968). The constitutional symptoms and the distribution of the rash were similar to that of Rocky Mountain spotted fever. Elicitation of a history of having received killed measles vaccine assists in making the diagnosis. The inactivated measles vaccine is no longer available in the United States.

### Mumps

An exanthem will develop in fewer than 10% of persons infected with the mumps virus. When present, the lesions are maculopapular or morbilliform, pale pink, discrete, and concentrated on the trunk. The virus more typically involves the salivary glands, the testicles (after puberty), the pancreas, the kidney, and the meninges. After an incubation period of 16 to 18 days, clinical signs and symptoms develop in approximately 60% to 70% of infected persons. The remaining one-third of persons have inapparent or subclinical infections, without salivary gland swelling. Transmission is through direct contact with secretions from the respiratory tract.

The typical illness begins with 1 or 2 days of anorexia, headache, and mild to moderate fever. This period is followed by complaints of pain around the ear and discomfort when chewing. A diffuse but noticeable enlargement and tenderness of the parotid gland is present, often unilateral initially, then becoming bilateral in about 70% of cases. Occasionally, other salivary glands may be involved as well. Parotitis can be distinguished from lymph node enlargement in that it extends anterior to the ear and below the ramus of the mandible posteriorly to the mastoid bone, usually obliterating the angle of the jaw. Lymph nodes are more discrete and generally submandibular in location. Accompanying the parotitis, erythema is commonly seen around the opening of the Stensen duct. Differential diagnosis for parotitis includes other viruses (including human immunodeficiency virus, parainfluenza types 1 and 3, enteroviruses, and influenza), bacteria, and noninfectious causes such as parotid duct stones, tumor, and Sjögren syndrome.

CNS disease, manifested as meningitis or encephalitis, is estimated to occur in up to 10% of mumps cases and is characterized by headache, nausea, vomiting, and mild nuchal rigidity. It may occur before, during, or after the parotitis phase of the disease. CNS involvement follows a course similar to that of aseptic meningitis caused by other viruses, and it usually has no sequelae. In fewer than 2% of cases with CNS involvement, long-term neurologic sequelae or death occur. Cerebrospinal fluid pleocytosis has been noted in as many as 50% of mumps cases with parotitis, despite more than 90% of individuals with mumps showing no clinical evidence of meningeal irritation.

Orchitis is uncommon in children, but unilateral involvement of the testes and epididymis is observed in approximately 25% of male patients who are infected with mumps virus after puberty. Patients who have orchitis are usually quite ill; however, sterility rarely occurs. The pancreas and other exocrine glands are rarely involved. The kidney can be affected and result in a nephritis.

Prevention is achieved through immunization, with a current 2-dose recommended schedule. Unvaccinated or undervaccinated persons represent many cases of mumps occurring in the United States and worldwide, although more recent investigations have noted waning immunity to be a major contributor during outbreaks.

### Rubella

Rubella, also known as “German measles” or “3-day measles,” is caused by infection with rubella virus. These names served to distinguish the disease from rubeola (“hard measles” or “10-day measles”). Rubella was initially described as a clinical syndrome in the early 1800s by German physicians; however, it was not until 1962 that the virus was first isolated in tissue culture. The clinical spectrum of disease was documented more thoroughly during a United States epidemic in the mid-1960s that included more than 20,000 documented cases of congenital rubella syndrome. Transmission is through direct or droplet contact from respiratory secretions. The incubation period is 2 to 3 weeks, with a peak at 16 to 18 days. The period of

maximal communicability is 1 to 2 days before and up to a week after onset of the rash.

The typical clinical illness is mild and brief. In most children, the rash itself is the first sign of infection. It is typically a pink, maculopapular eruption beginning on the face and spreading downward to involve the trunk and extremities. The lesions remain discrete and pink, which contrasts with the raised, confluent, and deeply erythematous macular papules seen with rubeola. The facial rash clears as the extremity rash begins, and complete resolution of the entire exanthem occurs by day 3 to 5 of illness.

Fever is very mild (99°–101°F [37.2°–38.3°C]). Lymphadenopathy (usually posterior auricular and suboccipital lymph nodes) is frequently impressive. The affected nodes are usually tender at the onset of the rash, but the tenderness resolves rapidly over 2 to 3 days. Although lymphadenopathy is an important sign of rubella infection, it is not specific. An erythematous enanthem of pinpoint lesions or petechiae (known as Forchheimer spots) may occur on the soft palate; these lesions are often indistinguishable from those seen with scarlet fever or rubeola. The rubella virus is present in the pharynx within 5 days of the onset of the rash, but is difficult to culture. Serologic diagnosis is made by demonstrating an antibody titer rise between acute and convalescent sera taken 2 to 3 weeks apart.

Complications of rubella are rare in younger children. Arthralgias and arthritis can develop in approximately 15% of adolescents and young adults and can last up to a month, but the arthritis rarely becomes chronic. The most serious complications of rubella virus are usually related to congenital infections. If a susceptible pregnant woman is infected during the first trimester of pregnancy, there is a high probability that the fetus will become infected, causing multi-organ dysfunction or fetal demise. Since the introduction of the rubella vaccine in 1969, successful childhood vaccination efforts have decreased rubella infections from a high of 12.5 million in 1964 to fewer than 10 reported cases a year in the last decade, and have nearly eliminated congenital rubella syndrome cases in the United States. See Chapter 80, Perinatal Preventive Care: Fetal Assessment, for details on congenital rubella syndrome.

### Exanthem Subitum (Roseola)

Human herpesvirus-6 (HHV-6) is the infectious agent of roseola, also known as exanthem subitum (“sudden rash”) or roseola infantum (“rose rash of infants”). Transmission occurs via secretions containing the virus, most likely from an asymptomatic contact. Roseola is characterized by 3 or 4 days of high fever (104°–105°F [40°–40.6°C]), followed by abrupt resolution of the fever and development of a pink maculopapular rash that begins on the neck, sparing the face, and then spreads to the trunk and extremities. The lesions are discrete and last only for 1 or 2 days. While a seizure may occur in a small number of infants and children during the febrile phase, the child usually has no other manifestation of illness and does not seem as ill as the severity of the fever might imply.

Roseola occurs year-round and is generally limited to children between the ages of 6 months and

3 years. However, HHV-6 infections can cause a wide disease spectrum in persons of all ages, from asymptomatic shedding to encephalitis and seizures. See Chapter 267, Human Herpesvirus-6 and Human Herpesvirus-7 Infections, for a more complete discussion of these viruses.

### Erythema Infectiosum

Erythema infectiosum, or “fifth disease,” is caused by infection with parvovirus B19. Susceptible persons are infected by contact with respiratory droplets. The incubation period ranges from 4 to 14 days.

The typical clinical presentation is one of rash without fever or other systemic signs, though fever can occur in 15% to 30% of patients. The rash first presents as bright erythema of the cheeks and forehead with circumoral pallor, 7 to 10 days after nonspecific symptoms of malaise, myalgias, and headache. This “slapped-cheek” appearance is the result of many large macules and papules coalescing to form a confluent bright erythematous rash. These confluent areas are palpable and hot to the touch, but nontender. After a single day of facial rash, a maculopapular exanthem next appears on the proximal extremities, and can vary from faint to an intense erythematous exanthem. The rash spreads gradually to the trunk and distal extremities, leaving a reticular or “lace-like” appearance as it clears. This second stage lasts 2 to 4 days. In a third stage, the same rash may reappear transiently when the skin is exposed to pressure, sunlight, or temperature extremes of hot and cold. The rash usually resolves without any desquamation or pigmentation of the involved area. Arthritis and arthralgia, which often occur with infection in adults, are uncommon findings in children. The exanthem and arthritis are likely caused by immune complex deposition in the skin and joints.

Parvovirus B19 is an erythrovirus that, as the name suggests, has a predilection for infecting erythrocytes. Mild myelosuppression can occur, but typically goes unnoticed in healthy individuals, whereas a life-threatening red cell aplasia may occur in patients with shortened erythrocyte survival, such as those with hemoglobinopathies (eg, sickle cell disease or hereditary spherocytosis). This dramatic manifestation is primarily caused by the virus infecting erythroid precursor cells in the bone marrow, which results in premature red cell lysis.

Clinical suspicion may be confirmed, when necessary, by testing for anti-parvovirus B19 immunoglobulin M (IgM) in the immunocompetent patient or, in the case of the immunodeficient patient, by polymerase chain reaction (PCR) on blood/plasma. Those with aplastic crises may require transfusion. In immunodeficient patients with chronic infection, intravenous immunoglobulin (IVIG) therapy should be considered.

### Enteroviral Exanthems

With the widespread administration of effective rubeola (measles) and rubella vaccines, enteroviral infections have now become one of the most common causes of viral exanthems in children in the United States. Given the multitude of enteroviral serotypes, clinical manifestations may take a wide variety of

forms. Associated rashes may be macular, papular, pustular, morbilliform, petechial, urticarial, ulcerative, or vesicular, thus making diagnosis challenging. Many echovirus and coxsackievirus serotypes are, for example, associated with generalized maculopapular rashes that have discrete lesions similar to those of rubella. Other enteroviral exanthems may mimic a typical roseola infection, with an initial 2 to 3 days of fever followed by the rash. However, the enteroviral fever prodrome is usually much lower than that seen with roseola. Although maculopapular rashes predominate with enteroviral infections, vesicular lesions have been observed with certain enteroviruses, including coxsackievirus A5, A6, and A16, as well as echovirus 6. The clinical syndrome known as “hand-foot-mouth disease” is commonly caused by coxsackievirus A16 infection and is exhibited by small erythematous macules that evolve into small vesicles on the palms and soles and are often associated with discrete ulcers in the mouth (primarily involving the gums, tongue, and inner cheek areas).

Enteroviral exanthems typically occur in the late summer and early fall in temperate climates, and transmission occurs via the fecal-oral route. A number of enteroviruses are associated with epidemics of aseptic meningitis. A more detailed discussion of enteroviral infections and aseptic meningitis can be found in Chapter 248, Enterovirus and Evolving Infections, and Chapter 289, Meningitis.

### Infectious Mononucleosis

The exanthem associated with Epstein-Barr viral infections occurs in approximately 15% of children. The lesions are discrete, pink to red macules, or are maculopapular and have no specific distinguishing characteristic; therefore, the disease is most often diagnosed based on other signs of infectious mononucleosis and confirmed by the peripheral blood smear and serologic tests. The administration of ampicillin to persons who have infectious mononucleosis results in approximately 50% of them developing a much more intense rash, which may also occur with other penicillins. The ampicillin-associated rash is deeply erythematous and confluent, giving it a morbilliform appearance. This iatrogenic exanthem resolves spontaneously within a week after discontinuing the antibiotic. Appearance of such a rash in a patient treated for presumptive group A streptococcal pharyngitis is cause to reconsider the diagnosis. The physician should reassure parents that this rash does not represent penicillin hypersensitivity. The full spectrum of Epstein-Barr viral infection is discussed in Chapter 275, Infectious Mononucleosis and Other Epstein-Barr Viral Infections.

### Varicella Zoster Virus

#### Primary Infection (Chickenpox)

Varicella zoster virus (VZV) causes primary and reactivation vesicular exanthems. Recent advancement with widespread immunization in the United States has led to a large decline in wild-type varicella infections, commonly known as “chickenpox.” In this post-varicella vaccine era, the lesions of VZV infection in partially immune children may seem quite different than those of classic chickenpox seen routinely prior

to vaccine introduction. These more mild symptoms may include very few lesions that do not follow the typical pattern (as described in the following text). Physicians must have high suspicion to consider VZV resulting from this more atypical presentation. The exanthem of varicella infection (in either early classic or mild atypical form) can be readily confused with noninfectious conditions such as insect bites, allergic dermatitis, and drug reactions, as well as infections with enteroviruses or *S aureus*.

Nonimmune individuals with primary VZV infection typically develop classic chickenpox. The incubation period of the virus is lengthy, ranging from 10 to 21 days, with symptoms starting around day 14. Many children have a 24- to 48-hour prodrome of mild, nonspecific symptoms prior to rash eruption. The virus is initially spread via respiratory droplets, then additionally via secretions from the vesicular lesions once they erupt.

The chickenpox rash begins as erythematous macules that develop into vesicles containing clear fluid, classically described as the “dew drop on a rose petal.” The rash is often intensely pruritic. Within 2 days, the fluid begins to cloud and the lesions scab or crust. The initial lesions form on the scalp, the face, and occasionally the trunk. As these lesions begin to resolve, new vesicles erupt in stages over the trunk and extremities. This pattern continues for 1 to 7 days in otherwise healthy children. The number of lesions usually does not exceed 300, but children can develop more than 2,000 lesions in more severe cases. The lesions self-resolve slowly over 1 to 2 weeks. Fluid from the open vesicles contains live virus, thus transmissibility is decreased as the lesions dry and form scabs. Acyclovir may be used in certain groups to shorten the disease course and limit eruption of new vesicles.

Complications of varicella infection in immunocompetent persons can include most common secondary bacterial infections, as well as less common virus-related complications such as encephalitis, hepatitis, thrombocytopenia with hemorrhage, and, rarely, nephritis or arthritis. Given the pruritic nature of the rash, scratching can cause extensive excoriations, further increasing the risk of secondary bacterial skin infections. Usual bacteria include *S pyogenes* and *S aureus*, both of which can lead to a spectrum of concomitant disease from impetigo and cellulitis to invasive soft tissue infections to toxin-mediated disease and life-threatening sepsis. Immunocompromised hosts, including neonates and young infants, may exhibit more extensive and progressive disease with VZV infection.

Of note, 1% to 4% of healthy children who receive varicella vaccine may develop a mild, brief, atypical chickenpox rash (usually only a few lesions) within 1 to 2 weeks after vaccination. In these cases, the child is considered contagious, particularly if in contact with immunocompromised persons, until the lesions are crusted or resolved. See Chapter 227, Chickenpox, for full discussion of VZV infections and management.

#### Reactivation (Herpes Zoster)

Reactivation of VZV, known as “herpes zoster,” can occur in both healthy and immunocompromised persons. Herpes zoster manifests as a localized vesicular



exanthem in a dermatome pattern, related to the sensory nerve distribution containing the latent virus. The initial lesions resemble those of primary VZV infection, but progress into larger, coalesced areas and are usually associated with neuralgia and hyperesthesia in addition to pruritis. New lesions can continue to appear for up to 1 week, followed by crusting of lesions and slow resolution over an additional 2 weeks. The most common complication is post-herpetic neuralgia, which occurs more often in adolescents and adults. Secondary bacterial infections can also occur, as with primary VZV infection. Antivirals may be indicated for certain patient populations.

See Chapter 227, Chickenpox, for full discussion of herpes zoster presentations and management.

### Herpes Simplex Virus

Herpes simplex virus (HSV) causes both vesicular exanthems and enanthems, with wide clinical variation based on age, affected body site, primary infection versus reactivation, mode of acquisition, and host immune status. Many HSV infections or reactivations (with either HSV-1 or HSV-2) are asymptomatic. If lesions are apparent, they can be either mucosal or cutaneous, and may affect a number of different body sites.

Mucosal manifestations can include lesions of the mouth, pharynx, lips (vermillion or mucocutaneous border), eye (conjunctiva), female genital tract (vagina and adjacent structures, cervix), and male genital tract (urethra). These lesions can be vesicular or ulcerative, are usually painful, and may be associated with nonspecific constitutional symptoms. In young children, primary herpes gingivostomatitis is usually caused by HSV-1 and presents as extensive, painful vesicles of the oral mucosa and palate, with extension to the lip, tongue, and face. In older children and adults, pharyngitis may represent primary HSV infection and can be difficult to distinguish from other, more common causes of pharyngeal edema and erythema, such as Group A streptococci or Epstein-Barr virus. Orolabial HSV lesions (reactivation HSV) are quite common in the general population, and are usually seen as single or grouped, tender, vesicular lesions on an erythematous base at the vermillion border, often preceded by paresthesias. Ocular herpes infections, or keratoconjunctivitis, can be severe and cause permanent corneal scarring with potential vision loss, although milder forms can occur.

Cutaneous manifestations of HSV infections can take a wide variety of forms. Vesicular lesions are observed most often over skin near affected mucosal surfaces, such as the perioral and genital areas. However, lesions can develop on any area of skin, and cutaneous eruptions have been associated with transmission of HSV during certain contact sports, such as wrestling and rugby (known as *herpes gladiatorum* or *mat pox* and *herpes rugbiorum* or *scrum pox*, respectively). HSV can also cause infection within an already disrupted skin barrier, as in *eczema herpeticum*. Additionally, cutaneous HSV infections can present as infection of the pulp or nail bed of a finger or toe, known commonly as “herpetic whitlow.” Infection can initially resemble a bacterial cellulitis, but usually follows vesicular or pustular lesions on the affected digit. The symptoms are not responsive to antibiotics and

usually progress to a purple to gray discoloration of the digit. Finally, a less common cutaneous presentation associated with HSV is the nonvesicular exanthem of erythema multiforme (EM), especially in recurrent EM cases.

In immunocompromised persons, including neonates, HSV disease can be life threatening. For these patients, HSV exanthems or enanthems seem similar; however, disease may be more severe, more difficult to control (increased frequency of reactivation), or more likely to disseminate. Mucocutaneous lesions are part of the spectrum of neonatal HSV disease known as “skin, eye, and mucus membrane disease.” These lesions may occur with or without more serious, life-threatening invasion (dissemination or CNS involvement). The lesions are vesicular, and virus can be isolated from specimens of the conjunctiva, oral mucosa, rectum, and skin lesions.

Nonexanthematous manifestations of HSV infection can occur, including encephalitis, hepatitis, esophagitis, pneumonitis, and other disseminated forms. For a full discussion on infections caused by HSV and corresponding management, see Chapter 266, Herpes Infections.

### Molluscum Contagiosum

This benign, usually asymptomatic skin infection is common in infants and children and is caused by a poxvirus. Adolescents and adults can also acquire the infection through sexual activity and certain types of sports (eg, wrestling). Humans are the only known source of the virus. Typical lesions are discrete papules, 1 mm to 6 mm in diameter, that can be skin-colored, erythematous, or translucent (and mimic a vesicle) and are sometimes umbilicated. The rash can occur in any cutaneous location but is more common on the face, eyelids, neck, chest, axillae, folds of the extremities, and genital region. Lesions may be linear because of autoinoculation, and there may be an associated dermatitis in the area of the papules in 10% of patients. The diagnosis is typically made clinically; however, scraping a characteristic papule and staining the materials with Giemsa or methylene blue reveals a molluscum (Henderson-Patterson) body with direct microscopy.

Molluscum contagiosum lesions may resolve spontaneously over an extended period of time (months), and watchful waiting is an acceptable management plan. However, many parents will request treatment, and therapy may be warranted to alleviate discomfort, reduce autoinoculation, and limit transmission to close contacts. Options for therapy include either curettage or cryotherapy with liquid nitrogen of the individual lesions. Both of these therapies are effective but may be traumatic for young children; curettage may also cause spread of lesions and scarring. Application of cantharidin (blister beetle extract) or imiquimod cream are both off-label options. Imiquimod cream is applied 3 times per day, and contact dermatitis can be a problem with this therapy. Facial lesions, in particular, can be treated with topical retinoids (eg, tretinoin), but because this therapy’s mechanism of action is induction of irritant dermatitis, this type of treatment may also have limiting side effects.



Severe disease in immunocompromised individuals can be treated with intravenous cidofovir, however, this agent is associated with known toxicities, including renal failure.

When the diagnosis is uncertain, if extensive disease is present, or if the condition is associated with poorly controlled atopic dermatitis, referral to dermatology or infectious disease specialists should be considered.

## BACTERIAL CONTAGIOSUM

### Meningococcemia

One of the most serious, contagious exanthematous diseases in adults and children is caused by *Neisseria meningitidis*. Roughly two-thirds of patients with meningococcemia will develop cutaneous manifestations. Transmission of the organism occurs via respiratory droplets or direct/indirect oral contact, with an incubation period of 1 to 10 days.

Symptoms of meningococcemia, at the onset, may mimic those associated with a viral illness (fever, myalgia, headache, nonspecific constitutional symptoms). Initially, erythematous, urticarial, or morbilliform macules and papules may appear, and petechiae, pustules, and vesicles may also develop. The hallmark manifestations of the disease, and the most disturbing features, are purpuric lesions with jagged edges. These lesions may progress to necrosis, ulcers, and eschars. Profound hypotension and shock occur with overwhelming meningococcemia. Purpura fulminans, purpuric and necrotic plaques combined with disseminated intravascular coagulation, is associated with significant mortality (invasive meningococcemia mortality is 8%–10%) and morbidity (loss of limbs, digits, or other body parts).

Physicians need to be knowledgeable about the presenting signs and symptoms as well as the treatment of meningococcemia. Cultures of the blood and cerebrospinal fluid (CSF) are confirmatory. Supportive management including fluids and vasoactive agents, usually within a critical care setting, is often required. Treatment with an empiric antibiotic, such as ceftriaxone, is required to provide adequate coverage of the CNS as well as a variety of bacteria capable of causing sepsis. Once the cause of the patient's illness is confirmed to be *N meningitidis*, definitive treatment is recommended. (See Chapter 289, Meningitis.) Five to 7 days of intravenous antibiotics should be given. Close contacts within 7 days prior to patients presenting with invasive meningococcal disease are at high risk and should receive antibiotic prophylaxis, ideally within 24 hours after the index patient has been identified.

Effective vaccines exist for 4 of the 5 serogroups of *N meningitidis* that are responsible for most cases of meningococcemia (A,C,Y,W-135), including meningococcal conjugate vaccines for use in persons 9 months through 55 years of age. Routine recommendation for use of meningococcal vaccine exists for all adolescents 11 to 12 years of age with a second dose at 16 to 18 years of age; additional recommendations for immunocompromised and high-risk populations have recently been forthcoming. As of 2015, 2 serogroup B meningococcal (MenB) vaccines have been approved by the US Food and Drug Administration for use in

persons 10 to 25 years of age. The US Centers for Disease Control and Prevention (CDC) recommends routine vaccination against serogroup B meningococcal disease for people aged 10 years and older who are at increased risk of disease, including those with persistent complement component deficiencies, with anatomic or functional asplenia, or at increased risk because of a disease outbreak. Further, the CDC Advisory Committee on Immunization Practices recently added the recommendation that a MenB vaccine series may be administered to adolescents and young adults aged 16 to 23 years to provide short-term protection against most strains of serogroup B meningococcal disease (preferred age is 16–18 years).

All confirmed, presumptive, and probable cases of invasive meningococcal disease should be reported to the appropriate health department.

### *Mycoplasma pneumoniae*

Cutaneous signs are a minor manifestation of *Mycoplasma pneumoniae* (*M pneumoniae*) infections. A maculopapular eruption may appear on the trunk and extremities of 10% to 15% of persons infected with *M pneumoniae*. Even more commonly associated with *M pneumoniae* infection are the rashes that result from an immune-mediated or allergic response. The spectrum of these rashes is broad, and includes urticaria, erythema multiforme, and vesicles or bullae. Such patients often have had a prodromal illness of fever, headache, malaise, and cough. Pneumonia may be subclinical, with chest radiographic findings out of proportion to what is found on clinical presentation or examination. Macrolide antibiotics, doxycycline for those 8 years or older, and levofloxacin for older adolescents and adults may be used to treat *M pneumoniae* infections. (See Chapter 315, Pneumonia.)

### Scarlet Fever (*Streptococcus pyogenes*)

Scarlet fever is a clinical syndrome of fever, pharyngitis, and rash often with associated nausea, abdominal pain, and headache. The rash of scarlet fever is caused by an erythrogenic exotoxin produced by some strains of Group A  $\beta$ -hemolytic streptococci (GABHS or *S pyogenes*). This rash is characterized by a fine papular eruption on a brightly erythematous macular base. The papular rash is typically concentrated on the trunk and proximal extremities and has been likened to "fine sandpaper." Transverse erythematous streaks of coalesced petechiae (Pastia lines) are sometimes present, usually in the antecubital spaces. In addition, the rash is commonly associated with prominent erythema of the lips, soles, and palms along with circumoral pallor. The examination of the tongue may reveal prominent papillae on a very erythematous base, giving a "strawberry tongue" appearance. During the recovery phase, desquamation typically occurs and can resemble the peeling associated with mild sunburns; desquamation may be more prominent at the fingertips and along the palms and soles.

It is important to distinguish streptococcal infections causing rash from staphylococcal infections causing similar dermatologic manifestations. *S aureus* produces a wide range of toxins, including an

exfoliative toxin that may cause a scarlet fever–like rash with erythroderma and desquamation. Attempting to distinguish these 2 clinical entities is important to choose appropriate antibiotic therapy, particularly in light of the increasing prevalence of community-associated methicillin-resistant *S aureus* (CA-MRSA).

Streptococcal infections are treated with penicillin or erythromycin, whereas methicillin-susceptible *S aureus* (MSSA) infections can be treated with first-generation cephalosporins (cephalexin), penicillinase resistant penicillins (dicloxacillin, oxacillin, nafcillin), or clindamycin (if susceptible). Because of the high incidence of skin and soft tissue infections caused by CA-MRSA in the United States, either trimethoprim-sulfamethoxazole (TMP-SMX) or clindamycin is often selected to empirically treat these focal infections when CA-MRSA is suspected. However, caution is advised when choosing TMP-SMX if the causative pathogen could be GABHS, since this antibiotic will not eradicate that organism. When possible, cultures from the focal infection site should be obtained to guide antibiotic therapy options.

Kawasaki disease must be carefully differentiated from scarlet fever, because coronary artery disease may be a complication that requires distinct therapy in a significant percentage of children with Kawasaki disease. The cutaneous manifestations overlap remarkably with those of scarlet fever, but it can usually be distinguished by the additional signs of discrete bulbar conjunctivitis without exudate, cracking of the lips, tender lymphadenopathy (usually solitary, unilateral, and more than 1.5 cm in diameter), meatitis, diarrhea, and changes in the extremities including induration/edema with erythema of palms and soles. These children are profoundly irritable, and their fever persists beyond 5 days in most cases (diagnostic criterion). Just as in scarlet fever, however, patients usually have erythema of the palms and soles, erythematous lips, and a strawberry tongue, with striking desquamation during the second and third weeks of the illness; the desquamation with Kawasaki disease typically involves the periungual areas and groin. Kawasaki disease is presented in more detail in Chapter 280.

### **Staphylococcus aureus**

Beginning in the early 1990s, infections caused by *S aureus* increased dramatically, and the most common manifestation involved the skin and soft tissues. Specifically, this increase in *S aureus* infections has been attributed to CA-MRSA. The differential diagnoses associated with *S aureus* skin infections, and specifically, CA-MRSA skin infections, include *S pyogenes* infections. Transmission is presumed to be by close contact with infected or colonized skin or contaminated fomites (eg, towels, razors). Common skin manifestations of CA-MRSA infections include impetigo, ecthyma, and folliculitis; these infections are limited to the epidermal layer of the skin or in the case of folliculitis, the hair follicles within this layer. Although erysipelas is usually caused by *S pyogenes*, in the era of CA-MRSA infections, staphylococci must also be considered as a causative pathogen. With erysipelas, the skin appears erythematous and warm with

some edema; usually, there are also associated systemic symptoms including fever and chills. The superficial dermis and lymphatic channels are often involved. Cellulitis, now most commonly caused by *S aureus* and not *S pyogenes*, usually presents as erythema with some degree of purulence and involves the epidermis, dermis, and subcutaneous fat layers of the skin. Superficial skin abscesses are by far the most common CA-MRSA-related skin infection. These abscesses usually involve suppurative collection of fluid or pus in the cutaneous and epidermal layers of the skin and often coexist with cellulitis. Furuncles (commonly referred to as “boils”) and carbuncles (coalescence of multiple furuncles) are suppurative in nature and often extend beyond the epidermal layer to involve the dermis or subcutaneous tissue.

For suspected CA-MRSA skin infections, use of clindamycin, TMP-SMX, or doxycycline is typically recommended. Over the last decade, increasing rates of clindamycin resistance among CA-MRSA isolates have been demonstrated, so empiric antibiotic treatment should be based on local or regional antibiograms for MRSA isolates. Additionally, the D-test is recommended for detection of inducible clindamycin resistance in erythromycin-resistant, clindamycin-susceptible isolates. For purulent cellulitis, where there is purulent drainage or exudate in the absence of a drainable abscess, empiric therapy is also recommended pending culture results. In some cases of small abscesses (<5 cm) without evidence of systemic symptoms, incision and drainage alone without antibiotics may be sufficient for treatment; this is usually not recommended if infection involves an infant or young child or if the infection is spreading quickly or involves multiple lesions.

For a complete discussion of *S aureus* infections and toxin-mediated syndromes, see Chapter 340, Toxic Shock Syndrome.

## **TOOLS FOR PRACTICE**

### **Engaging Patient and Family**

- *Chickenpox Vaccine: What You Need to Know* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/safety-prevention/immunizations/Pages/Chickenpox-Vaccine-What-You-Need-to-Know.aspx](http://www.healthychildren.org/English/safety-prevention/immunizations/Pages/Chickenpox-Vaccine-What-You-Need-to-Know.aspx))
- *Molluscum Contagiosum* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/skin/Pages/Molluscum-Contagiosum.aspx](http://www.healthychildren.org/English/health-issues/conditions/skin/Pages/Molluscum-Contagiosum.aspx))

## **SUGGESTED READINGS**

- Cherry JD, Demmler-Harrison GJ, Kaplan SL, et al, eds. *Textbook of Pediatric Infectious Diseases*. 7th ed. Philadelphia, PA: WB Saunders; 2013
- Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Redbook: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015
- Krowchuk DP, Mancini AJ, eds. *Pediatric Dermatology: A Quick Reference Guide*. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012
- Long SS, Pickering LK, Prober C, eds. *Principles and Practice of Pediatric Infectious Diseases*. 4th ed. Edinburgh: Elsevier Saunders; 2012

## Chapter 237

CONVERSION REACTIONS  
AND HYSTERIA

Gregory E. Prazar, MD

DEFINITION, INCIDENCE,  
AND ETIOLOGY

The amalgamation of emotions and physical symptoms in patients challenges the primary care physician to formulate priorities in history taking, diagnosis, and management. Some somatic complaints, such as headaches, nausea, and vomiting, can result directly from emotional upsets. Indeed, anxiety is often associated with palpitations, sweating, and tremulousness; depression is often exhibited by symptoms of fatigue and weakness. Other somatic complaints reflect organic disorders, such as neuromuscular headaches, which may be associated with emotional turmoil. Still other physical problems are attributed to conversion symptoms. The terms *conversion symptom*, *conversion reaction*, and *conversion disorder* are often used interchangeably. Somatic or functional complaints differ from conversion symptoms in that patients with somatic or functional complaints are aware of emotional distress associated with the symptom. Patients with conversion symptoms are not cognizant of any associated emotional distress.

Conversion reactions are a way of communicating the uncomfortable, or as Engel writes,

... a psychic mechanism whereby an idea, fantasy, or wish is expressed in bodily rather than in verbal terms and is experienced by the patient as a physical symptom rather than as a mental symptom.

The idea or wish is psychologically threatening to individuals or is unacceptable for them to express directly. A conversion symptom serves as a form of decompression whereby unpleasant feelings associated with acknowledgment of the wish are dissipated through the use of a somatic symptom. Because the wish is completely unconscious, patients in no way relate any psychologic stigmata to the somatic complaint. As Hollender succinctly states, "The conversion symptom is a code that conceals the message from the sender as well as from the receiver."

To understand why a wish or thought is represented by a bodily symptom, exploring patterns of everyday behavior and infant development is necessary. Body activity (ie, gesturing) is used to express ideas during verbal interaction. Common conversational phrases often allude, metaphorically, to the intermixing of emotion and body functioning. "I'm fed up" and "He is a pain in the neck" are 2 such examples. Developmentally, infants express feelings and communicate through visible behavior long before spoken language becomes their dominant mode of communication. Furthermore, infants explore and learn about their environment, including the people in it, by using their bodies as investigative tools (eg, placing new objects in the mouth) and as a means of

making contact. Any bodily process that can be perceived by the individual can serve as the focus for conversion symptoms. Similarly, somatic symptoms of relatives or close friends also can serve as the source of a patient's complaints. The patient's interpretation of the other person's symptom provides a model for the somatic complaint. When the symptom is adapted from one observed in the other person, that person often evokes strong feelings in the patient. Because the patient expresses guilt about feelings or impulses toward that person, the patient may take the other person's symptoms as a form of self-punishment while at the same time psychologically expressing the forbidden idea or wish.

All body systems may be invoked in a conversion reaction. The sensory system frequently is involved (eg, paresthesia, anesthesia, or diffuse pain), although typically these symptoms are not distributed in the correct pattern of innervation of the implicated cutaneous nerves. Motor system involvement can be represented by paralysis, tremors, or weakness of an extremity. Hyperventilation and dizziness are other common conversion symptoms, as are nausea and vomiting and visual problems.

A common conversion symptom seen in children and young adolescents is abdominal pain. After an extensive investigation of 100 children who had abdominal pain, Apley found an organic cause in only 8 cases. Another study by Oster revealed abdominal pain in 14% of the children studied. The incidence was highest in individuals 9 years of age and lowest in those 16 to 17 years of age. Recurrent abdominal pain and its causes remain controversial (see Chapter 125, Abdominal Pain). However, an important point to remember is that many patients who have recurrent abdominal pain may have emotional concerns of which they are unaware. Many of these patients may be experiencing conversion symptoms.

Although the incidence of certain individual somatic complaints has been studied, the specific overall incidence of conversion symptoms in children and adolescents is not known. Available data suggest an incidence of 5% to 13%. Lack of more definitive data reflects the difficulty in ascertaining whether a somatic complaint indeed represents a conversion symptom. Conversion symptoms may seem to be more common among adolescents than among younger children because the former more often have alarming somatic complaints, such as chest pains and fainting spells, whereas younger children frequently suffer from more indolent complaints, such as sporadic abdominal pains. Conversion symptoms are 2 to 3 times more common in girls than in boys and may appear as early as 7 or 8 years of age. No correlation seems to exist between the occurrence of conversion symptoms and socioeconomic status; however, patients with less sophisticated understanding of medical issues tend to have rare or very unusual and physiologically unexplained symptoms. Therefore, the more classic conversion symptoms (eg, paralysis or blindness) are less likely to be seen by physicians in Western societies. These physicians are more likely to diagnose conversion symptoms in patients presenting with chronic abdominal pain or chronic headaches.



Conversion symptoms can appear as a group phenomenon. Such a situation is often referred to as *epidemic hysteria*. Adolescent girls swooning and fainting at rock concerts is an easily appreciated example. In this situation, the unacceptable wish relates to sexualized thoughts involving rock stars. Other examples of epidemic hysteria are explained less easily. Episodes of epidemic hysteria seem to have several characteristics in common—audiovisual cues (eg, seeing ambulances arrive to care for accident victims) seem to be important as precipitators; girls are involved more often than boys; the reaction is more likely if it is initiated by a group member identified either as a leader (of a large subgroup) or as an outsider; and episodes are likely to involve larger numbers of adolescents if the youngsters are allowed to confer among themselves without adults present. Entire school populations may be involved in mass conversion reactions.

Although conversion symptoms have no organic basis by themselves, their perpetuation may result in biochemical or physiologic body changes, known as conversion complications. These events can include changes such as muscle atrophy caused by long-standing paralysis and respiratory alkalosis secondary to acute hyperventilation.

## INTERVIEW TECHNIQUES

Because symptoms caused by conversion and somatic processes can be easily confused, the physician evaluating any youth who has a somatic complaint should always consider the possibility of a conversion symptom. Attention to personal history (family functioning, school performance, and peer relationships) and to physical functioning demonstrates to the youth and family that the physician appreciates without prejudice the importance of all elements that may be contributing to ill health. Showing respect for the importance of emotional-physical interaction is thereby suggested so that this concept will not be foreign if it is later presented to the family in a diagnostic framework. Such an approach also contributes to the physician's understanding, as Engel states, "of those personal, family, and social circumstances that are most relevant to the understanding of the illness and the care of the patient, whether or not the ultimate diagnosis is conversion."

Nondirective interviewing proves more rewarding than direct questioning. For example, asking the patient to describe the pain ("Tell me how it feels.") almost always provides insight into the emotions that the patient associates with the symptom. Suggesting how the symptom feels to the patient ("Is it dull or sharp pain?") limits possible responses. If the patient spontaneously offers information about recent events, then the interviewer should obtain further data related to such changes in the youth's life. However, care should be taken to avoid suggesting a cause-and-effect relationship between the youth's feelings and the symptoms. Because people who have conversion symptoms have no conscious knowledge of such an association, the suggestion of such a relationship may alienate them and prevent the establishment of a trusting relationship.

## DIAGNOSTIC CRITERIA FOR CONVERSION SYMPTOMS

The conversion symptom has a specific, but unconscious, symbolic meaning to the patient. In other words, the conversion symptom is often related to an unconscious wish, and the physical impairment serves to prevent acting out the wish. For example, the adolescent boy who has hand paralysis may have anxieties about masturbating. The physician treating children and adolescents may not always be aware of the symbolic meaning of the symptom. Indeed, the concept that conversion symptoms have a symbolic meaning to the patient was formulated only after a series of these patients had undergone extensive psychotherapy. Although being cognizant of the presence of the symbolic meaning may be intellectually rewarding for the physician, ignorance of the specific symbolism does not prevent adequate treatment (Box 237-1).

Adolescents who have conversion symptoms often display characteristic patterns of behavior, sometimes designated as traits of the *hysterical personality*. Such characteristics include egocentricity; labile emotional states (quick shifts from sadness to elation and from anger to passivity); dramatic, attention-seeking behavior; and sexual provocativeness (displayed in gestures and in dress). Adolescents who have such characteristics are also usually demanding, display an air of pseudomaturity, and are dependent in personal interactions. Their personal relationships, however, are rarely intimate or satisfying. Although many aspects of the hysterical personality are seen in adolescent patients who have conversion symptoms, such characteristics are also demonstrable in adolescents who do not have such symptoms. Therefore, hysterical behavior traits in adolescents are not synonymous with conversion symptoms and, in isolation, are not indicative of a psychopathologic condition.

The manner in which patients who have a conversion symptom describe their problem is often distinctive. The account frequently is dramatic. A pain may be described as "thousands of burning needles thrust into my leg" or as "a giant spike being driven into my chest." Because these patients are suggestible, any symptom description alluded to by the physician may be adopted readily and thereafter reported, which again emphasizes the importance of a nondirective approach in the interview.

### BOX 237-1 Case Report

Jane, a 12-year-old, suddenly developed an inability to walk. Physical examination, including a neurologic evaluation, revealed no abnormalities. Interviews by a psychiatrist and a pediatrician working as a team revealed no apparent symbolic causative factor. The pediatrician formulated a system to reward Jane's progress in walking and implemented this approach; the psychiatrist was similarly supportive with the patient. Over a period of 3 weeks, the patient regained her ability to walk.



Conversion symptoms are adopted unconsciously in an attempt to reduce unpleasant feelings, especially anxiety, depression, and guilt. Therefore, although patients may describe incapacitating pain, they often affect an air of unconcern. Psychiatrists refer to this as *la belle indifference*. The extent to which the conversion symptom diminishes the unpleasant feeling and symbolically communicates the forbidden wish for the patient is referred to as the *primary gain*. Patients who have conversion reactions are often stubborn in their belief that the symptom is caused by organic problems, which reflects denial of the underlying emotional problem. Conversely, insistence (especially by an adolescent) that a symptom is psychologic in origin may indicate denial of a physical problem. Therefore, differentiating between conversion symptoms and physical disease in adolescent patients cannot depend solely on the youth's emotional response.

Conversion symptoms not only result in a primary gain for patients, but they also help them cope with the environment. In this respect, the conversion symptom achieves a secondary gain for patients. For example, patients who have a conversion symptom defending against homosexual thoughts may be excused from attending school, where anxiety may have been intensified (eg, in the locker room). Limitations imposed by the symptom may contradict patients' verbalized wishes to participate in activities but, nevertheless, remove them from potentially threatening social interactions. Interference with daily activities also provides a secondary gain in that attention and more frequent expressions of love are elicited from concerned parents and friends. This situation may be resistant to change, not only because the symptom is reinforced continually, but also because the symptom meets the parents' psychological needs. In effect, the symptom may provide the parents with a reason for inappropriately attending to or infantilizing their children. Consequently, patients and their entire families may fall into a vicious circle of dependence on the symptom.

Demonstration of a secondary gain does not ensure a diagnosis of conversion. To an extent, all illness is involved with some secondary gain. Bedridden patients must accept increased attention to cope with their physical confinement. Therefore, a degree of secondary gain is necessary for adequate adaptation to a physical disability. However, in the case of a conversion symptom, secondary gain not only intensifies symptoms but also may be associated with further occurrence of somatic complaints. Because perpetuation of secondary gain depends on concern from others, a conversion symptom is exhibited more readily in the presence of individuals meaningful to the patient.

Children and adolescents who develop conversion symptoms are often overprotected and become extremely dependent on their parents. Daily familial communication may have been invested heavily in somatic complaints, with children recognizing how often activities may have been canceled because of a father's headaches or a mother's cramps. Therefore, a child's symptoms may conform to the unspoken interactional rules of the family. Family members indirectly

reinforce patient problems, although the family may assume an air of indifference with respect to the symptoms (Box 237-2).

Precipitation of a conversion symptom may be related to specific stressful events. A change of school, final examinations, new social experiences, and parental conflict are examples of events that may induce a conversion symptom. Unresolved grief reactions may represent a source of stress that can precipitate a conversion symptom. Examples of grief reactions include death of a parent, divorce, or moving. Furthermore, adolescent and adult patients experience pseudoseizures more often in families in which an *unspeakable dilemma* is present. Specifically, the dilemma is often associated with a fear of physical or sexual assault. Even though other family members are aware of the specific dilemma, they often underestimate how severely the family member who experiences the pseudoseizures is affected by the dilemma. Because the patient's association between conflict and the conversion reaction is unconscious, a history is helpful only if the interviewer elicits details about daily activities. The stressful event precipitating a conversion symptom often becomes apparent only after many visits (Box 237-3).

#### BOX 237-2 Case Report

James was a 13-year-old who had severe abdominal pain and was referred to a pediatrician by his family physician. Physical examination revealed little objective evidence of abdominal pain in the physician's office. However, his return home quickly resulted in intensified pain. Abdominal pain seemed to be well controlled during a subsequent 4-day hospitalization (all organic tests were unremarkable). His return home again produced an immediate exacerbation of the abdominal discomfort. Furthermore, John, James' identical twin, began exhibiting signs of abdominal pain. The boys' mother admitted feeling trapped by the demands of her children and volunteered that, in the past, she had been treated for chronic abdominal pain. The appearance of abdominal pain in both twins reassured her that the pain was "probably a virus." She chose not to pursue further counseling for the boys.

#### BOX 237-3 Case Report

Chip, a 13-year-old, was brought by his mother to his pediatrician because of chronic abdominal pain, which seemed to be precipitated by his competing in horse-riding events. His history revealed the death of a grandparent 4 months previously, but his mother related that her son's pain preceded the onset of the fatal illness. Other family stresses were denied. The teenager did not appear for follow-up care but returned 6 months later, primarily because his mother wanted to discuss her son's reaction to her upcoming divorce. At this visit, the mother volunteered that marital stress had been ongoing for several years.

Symptom selection is based on the unconscious remembrance of the patient's own body function or understanding of symptoms in others. The patient's conversion symptom may seem quite dissimilar to that displayed by the other (often a parent or a close relative) because the patient's perception of disease governs the display of symptoms. Parents and relatives often misinform children and adolescents about diseases, fearing that the truth would be too frightening. However, such misinformation may actually potentiate the adolescent's fantasies and result in the development of a symptom quite different from that actually experienced by the individual serving as the model (Box 237-4).

The choice of a symptom may also be based on a physical illness the patient had experienced previously. Thus, patients who have a history of seizures may, after many years of adequate anticonvulsant control, have atypical and physiologically unexplainable seizures. Unfortunately, these patients often receive only a physiologic workup for seizures. Despite the atypical history, the physician assumes that the diagnosis rests *where the money is, or was*, in the past (Box 237-5).

Because the complaint expressed by the patient is based on a model symptom, a physical disease often

is mimicked. Close scrutiny of the symptom's history and description often reveals anatomic and physiologic discrepancies. The child or adolescent who has a stocking anesthesia—an anesthesia confined to a specific area of an extremity without any relationship to cutaneous nerve innervation—demonstrates an example of such symptom inaccuracy. It is based on the concept of the patient's own body rather than on anatomic principles.

A thorough history may not only elicit symptom inconsistencies in the present illness, but may also reveal a record of inexplicable or recurrent bouts of illness associated with life events. A history of chronic abdominal pain that occurs only on school days, a history of somatic complaints associated with stressful social events, or documentation of abdominal surgery with equivocal findings should raise suspicion that the current problem represents conversion. A list of the diagnostic criteria for conversion symptoms appears in Box 237-6. No single criterion can be confirmatory, and each patient who has a conversion symptom may not display every criterion listed. However, a conversion symptom cannot be diagnosed solely based on negative physical and laboratory findings; it is not a diagnosis of exclusion.

## DIFFERENTIAL DIAGNOSIS

Other psychosomatic disorders at times may be confused with conversion symptoms. Patients exhibiting hypochondriasis, a common entity, especially in adolescents, view their symptoms with extreme concern. None of the apparent indifference seen in patients who have conversion symptoms exists. Patients who have conversion symptoms often seem relieved when an organic cause is considered; patients who have hypochondriasis become more concerned if an organic diagnosis is suggested because they suspect and fear a serious or fatal disease. However, neither type of patient is reassured more than transiently by being informed that he or she has no disease.

Malingering is an uncommon problem in adolescents, except in institutionalized adolescents or those who

### BOX 237-4 Case Report

During a routine physical examination, Jeff, a 14-year-old, mentioned that he experienced "migraine headaches," which seemed to be focused "behind my left eye" and occurred approximately once a month. Jeff's mother attached more importance to the symptoms than did Jeff. Initially, exploration of the family history proved unremarkable. Persistent questioning about stress led the mother to mention almost parenthetically that she had recently been diagnosed as having multiple sclerosis. She felt that the case was mild and, therefore, had not told Jeff and her other children directly about the diagnosis, although she sensed that the children knew. Her initial symptom that precipitated the diagnosis of multiple sclerosis was temporary loss of vision in her left eye.

### BOX 237-5 Case Report

Terry, a 15-year-old girl, recently had been treated for otitis media, which was characterized by pain and some dizziness. After the ear seemed adequately healed, her dizziness persisted. By Terry's physician encouraging her to discuss her daily schedule, the fact that she was under significant academic pressure became apparent, having recently transferred to an extremely competitive private school. In addition, extracurricular pressures were heavy, including her fervent commitment to gymnastics and her hope to achieve professional status. On further questioning, Terry related that she had had dizzy spells in past years just before competitions.

### BOX 237-6 Criteria for Diagnosis of Conversion Symptoms

- The symptom has symbolic meaning to the patient.
- The patient frequently exhibits characteristic interpersonal behaviors.
- Symptoms are often reported in a characteristically dramatic style.
- The symptom helps patients cope with their environment (*secondary gain*). Health issues and symptoms frequently are used in family communication.
- Symptoms occur at times of stress.
- The symptom has a model.
- History and physical findings often are inconsistent with anatomic and physiologic concepts.

From Prazar G. Conversion reactions in adolescents. *Pediatr Rev.* 1987;8: 279–286.

are in restrictive situations (eg, military service). Malingering may even be regarded as an appropriate means of avoiding threatening or unpleasant circumstances. Attempts to feign illness often are naive, especially in younger patients. As Engel states, malingerers exhibit “an intense need to be nurtured or suffer.” Many of these individuals appear to be accident prone and may submit to painful procedures readily and without objection. Malingering adolescents are aloof and hostile to the physician; thus, discovery of their deception often is delayed. In contrast, patients who have conversion symptoms are often appropriately fearful of procedures and may appear charming and garrulous with the physician. Malingerers and patients who have conversion symptoms are similar in that their parents may have an unconscious psychological need to have their children be ill and, therefore, may reinforce their children’s symptoms.

Somatic delusions are symptoms of psychosis and usually are not confused with conversion symptoms. Other signs of severe mental illness are usually present, such as an inability to relate to peers, visual or auditory hallucinations, and stereotypical behaviors. Furthermore, the symptoms described sometimes are intermittent and often extremely bizarre. For example, patients who have somatic delusions may express the conviction that their heart is shriveling or that something is wrong with the blood that is running from the head to the leg.

Psychophysiologic symptoms may occur when conversion symptoms have failed to dissipate anxiety. Thus, continuing anxiety activates biologic systems (especially the autonomic nervous system), resulting in physiologic changes such as tachycardia, hyperperistalsis, and vasoconstriction. A patient’s cognizance of these changes is exhibited by palpitations, diarrhea, and sweating. In this situation, the symptom itself has no organic symbolic meaning and results from a reaction to actual body changes. Therefore, psychophysiologic symptoms can occur when conversion symptoms have failed. Similarly, conversion symptoms can replace psychophysiologic symptoms.

## CARE OF THE CHILD OR ADOLESCENT WHO HAS CONVERSION SYMPTOMS

Children and adolescents who have conversion symptoms are seen most often initially, and eventually are treated, by pediatricians or other primary care physicians. Families see this course of action as appropriate because the obvious aspect of the problem is physical. They typically will accept a diagnosis of conversion only from a medical professional they consider an expert in physical disease. Nevertheless, when physicians undertake a case of suspected conversion, their interviewing acumen and sensitivity to the patient’s feelings are paramount. The initial interaction between the physician and the patient is crucial to the degree of success achieved in dealing with a conversion symptom. In essence, treatment begins before a definitive diagnosis is made. Some considerations involved in the initial evaluation of patients suspected of having conversion symptoms appear in Box 237-7.

The physician should advise the patient and family that the cause of any disorder involves both physical and emotional factors. As Schmitt states, the family should be told that “everyone’s body has a certain physical way of responding to emotional stress.” Similarly, every individual has an emotional response to physical stress. Simple examples should be given (eg, most people have learned that headaches often are intensified when they are upset). If the physician communicates an appreciation of the role of emotions in physical disease, then the family may volunteer information more readily about psychosocial functioning. Furthermore, an eventual diagnosis involving emotional aspects may be more acceptable because the family has been prepared for the possibility. Focusing only on a strictly physical diagnosis intimates to the parents that psychological involvement is unlikely, unimportant, and improbable. Turning to psychological issues after all physical tests prove unremarkable implies to parents that this approach was chosen as a last resort because the physician was unable to ascertain an organic cause. A concurrent physical–psychological diagnostic approach not only prepares the physician to consider the problem with some psychotherapeutic intent, but may also save the family time and money because multiple laboratory tests can often be avoided.

After the evaluation has been completed, the physician must develop a treatment plan. Before embarking on this venture, the physician must be satisfied with the completeness of the medical evaluation. Common sense should dictate when the physician thinks that further organic tests will be futile. The patient and family can often sense a physician’s uncertainty, especially if the family is averse to accepting a psychologic diagnosis. Therefore, a prudent step would be to ask the family what additional tests they might expect to have performed and what other diagnoses they may have considered. Involvement of the patient and family in this diagnostic process

### BOX 237-7 Important Considerations in the Initial Evaluation of Patients Suspected of Having Conversion Symptoms

From the outset, the parents and patient should be told that “everyone’s body has a certain physical way of responding to emotional stress”. The parents and patient should be encouraged to suggest diagnostic tests that they may want performed and to suggest possible diagnoses for consideration by the physician.

The parents and patient should understand that the symptom may persist, but that the goal is to help maintain normal daily functioning in school and with peers. The parents and patient should understand that referral to a psychiatrically trained professional may be necessary if progress is not made in coping with the symptom.

Modified from Prazar G. Conversion reactions in adolescents. *Pediatr Rev.* 1987;8:279–286.

frequently dissipates anxiety and allows eventual psychological counseling.

Although patients who have conversion symptoms are suggestible, reassurance that the symptom will go away rarely is effective and also does not contribute to a psychological investigation of the symptom. On the contrary, suggesting that the symptom will persist allows time to work out a therapeutic relationship with the patient and sometimes has a paradoxical effect. Because the symptom is unlikely to disappear after 2 or 3 visits, the patient will retrospectively view the physician's suggestion as sound. Trust in the physician will be reinforced, and the patient may be more comfortable communicating information about feelings. Anxiolytic medications may reduce attendant anxiety transiently in some cases of conversion symptoms; however, using medication as the sole therapy rarely results in lasting improvement. Because medication does not relieve the underlying conflict responsible for the symptom, another symptom eventually may appear. Furthermore, a risk that the medication's side effects may become the model for new conversion symptoms—or that new symptoms may be confused with side effects—does exist.

At the conclusion of the evaluation, the number of anticipated follow-up sessions should be discussed with the family. The number of sessions should be flexible so that it can be renegotiated if needed. Follow-up sessions with the teenager can usually be limited to 15 to 20 minutes every 2 to 4 weeks. More frequent visits may be necessary if symptoms interfere with school attendance, peer relationships, or family functioning. During follow-up sessions, the youth should be encouraged to talk about daily life (eg, school, friends, family, and dating). If the youth volunteers information about recurrence of the symptom, then the physician should inquire about events that were transpiring concurrently when the symptom occurred and how the youth felt about these events. In this way, the physician can help the patient become reacquainted with how daily events and feelings are related. Keeping a symptom diary may be helpful: The patient records when the symptom occurred and what was happening at the time the symptom began. Such a record may illustrate to the patient the association of the symptom with feelings or emotionally charged life events.

When physicians feel comfortable acting as both therapist and provider of acute medical care, occasions may arise when the youth has a new physical symptom or complaint that requires attention. If the physician suspects a physical illness that is unrelated to the conversion symptom, whatever evaluation that is indicated must be performed, including a full or partial physical examination. However, an overzealous search for disease should be avoided. Treatment goals need to be realistic. Conversion symptoms seldom disappear completely. However, patients often acquire increased coping skills so that their daily functioning is unimpaired, and dependence on secondary gain is minimized.

For physicians with sufficient expertise, follow-up visits with parents should take place every 4 to 6 weeks. Such meetings should serve to elicit persistent or new

concerns that parents may have about their child or teenager's progress and should be used to assess the parents' reaction to continuing complaints. The physician should emphasize the validity of the youth's concerns so that misconceptions about the symptom being faked are dispelled. Furthermore, positive reinforcement needs to be offered so that parents think they are doing what is best for their child. Selected follow-up sessions with the parents should include the child. Not only do such family meetings demonstrate to the patient that confidentiality of individual sessions is not being violated, but they also offer the physician an opportunity to observe parent-child interaction. These observations may provide an important index to the effectiveness of ongoing therapy.

## REFERRAL

Referral to mental health professionals is indicated if symptoms continue to interfere with the patient's daily activities or functioning or when the physician or school personnel think that the symptoms have not diminished. School officials can provide valuable information about the effect of the conversion symptom on school functioning and peer interaction. Referral is indicated if the family thinks that inadequate progress has been made after an agreed-on duration of therapy.

Referral also is indicated if the patient's symptom creates uncomfortable feelings in the pediatrician. Situations involving sexually suggestive adolescent behavior in association with a conversion symptom may create feelings in the pediatrician that can prevent effective intervention. Assuming that a pediatrician can treat all psychological and medical problems adequately is unrealistic. Cognizance of one's own limitations is an important professional attribute. Another situation requiring referral involves the patient or family member who is a social acquaintance or a relative of the pediatrician. Dealing with the emotional problems of friends' or relatives' children is inappropriate. Obtaining personal details of family or sexual functioning is often indicated in the evaluation and may jeopardize the social relationship. Conversely, failure or hesitancy to obtain appropriate data may jeopardize subsequent resolution of the problem.

In all cases when referral is suggested, parental and patient compliance with the referral is improved if the possibility has been mentioned as a contingency early in the evaluation. The pediatrician should always help families understand that seeing a psychiatrically trained professional does not connote *craziness*. Rather, the pediatrician may suggest that a mental health professional might help because a physician or professional trained in mental health can help patients understand feelings about prolonged or unusual symptoms better than most pediatricians. The physician should recommend a specific counselor rather than offering a list of suggested counselors. Before the name of the counselor is given to the family, the physician should verify that the counselor feels comfortable with the referral and has time available to see the patient.

After the referral is made, continued pediatrician contact with the family concerning the conversion



### BOX 237-8 Indications for Referral of Patients Who Have Conversion Symptoms

- The symptom continues to interfere with daily functioning (school attendance, participation in extracurricular activities, involvement with peers).
- Parents and patient think that no progress is being made in dealing with the symptom.
- The physician feels uncomfortable with the patient's symptom or behavior (eg, patients exhibiting sexually suggestive behavior).
- The patient's family includes a social friend or relative of the physician.

From Prazar G. Conversion reactions in adolescents. *Pediatr Rev.* 1987;8: 279–286.

symptom promotes adherence with the therapy. Indications for referring patients who have conversion symptoms are listed in Box 237-8.

The prognosis for patients who have conversion reactions is unknown. In a report of 74 children who had psychogenic pain, many patients were judged to be improved after several years regardless of whether professional intervention took place. In a 7-year follow-up of patients hospitalized with conversion, 23 of 41 patients no longer experienced their presenting physical symptom, were free of underlying stress, and had experienced no symptom substitution or new associated complaint. Patients who have conversion symptoms, indeed, may have an encouraging future. On the other hand, in some patients, adolescent conversion symptoms mark the beginning of a lifelong course of conversion illness.

### SUMMARY

Conversion reactions represent an emotionally charged issue not only literally for the adolescent but also figuratively for the physician, because patients displaying such symptoms often elicit a wide range of emotions from their physician. The physician's emotional response results from the frustration in dealing with such difficult patients. Patients have feelings about their symptoms. An evaluation of any complaint should involve inquiry into aspects of the patient's family, school attendance and performance, and peer relationships. A better understanding of the patient's baseline emotional functioning can be achieved in this way. The physician must advise both parents and patient that having feelings about symptoms is acceptable. Both family and patient may be much more accepting of primary emotional involvement if permission for expressing feelings is given early in the physician–patient relationship. The diagnosis of a conversion reaction should never be one of exclusion and should follow specific diagnostic criteria.

Care of the patient who has a conversion reaction involves establishing a renegotiable number of regular visits, encouraging the patient to discuss daily activities and interrelated feelings, meeting with parents regularly to provide them with emotional support

and counseling, and knowing that palliation rather than a cure may be the end goal. When the physician feels uncomfortable treating a patient who has a conversion reaction, or when ongoing follow-up care seems to have made no progress in reducing the symptoms, the patient should be referred to a mental health professional. However, referral should not end the physician's contact with the patient because ongoing physician interest may improve patient adherence with the referral source and may increase the physician's ability to resume responsibility later for the patient's care. The patient who has a conversion symptom usually will not outgrow it in the short term. Such patients severely tax the primary care physician's diagnostic and therapeutic acumen. However, the physician who respects the involvement of emotions with symptoms can help patients who have conversion symptoms cope with their disorders.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Building Resilience in Children and Teens*, 3rd ed (book), Ginsburg KR ([shop.aap.org](http://shop.aap.org))
- *Helping Your Child Cope With Life* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Stressed? Read This*. (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

### AAP POLICY

American Academy of Pediatrics. Insurance coverage of mental health and substance abuse services for children and adolescents: a consensus statement. *Pediatrics*. 2000;106(4):860–862 ([pediatrics.aappublications.org/content/106/4/860](http://pediatrics.aappublications.org/content/106/4/860))

### SUGGESTED READINGS

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### Chapter 238

## CYSTIC AND SOLID MASSES OF THE FACE AND NECK

Neil E. Herendeen, MD; Peter Szilagyi, MD, MPH

The causes of neck masses range from common inflamed lymph nodes and cysts to rare neoplasms. An orderly approach to the workup and management of a neck mass is, therefore, needed. The most practical approach involves differentiating the anatomic location of the mass into lateral neck masses versus midline neck masses and determining the exact anatomic position of the mass. Localizing a lateral neck mass further

into either the anterior cervical triangle (anterior to the sternocleidomastoid muscle) or the posterior cervical triangle is helpful.

## DEFINITIONS

Masses in the neck can be classified into 2 broad categories—cystic lesions and solid masses. Cystic lesions are either congenital cysts or vascular malformations; however, traumatic hematomas and abscesses may seem to be cystic. Solid neck masses usually consist of inflammatory lymph nodes or, rarely, neoplastic lesions. In general, a complete history and thorough physical examination will lead to the correct diagnosis. Carefully chosen laboratory tests or imaging studies then confirm the diagnosis.

## DIFFERENTIAL DIAGNOSIS

When evaluating neck masses, the primary care physician (PCP) should be familiar with key anatomic structures of the neck. Because most neck masses encountered by pediatricians are lymph nodes and not cysts, understanding the location of the different groups of lymph nodes within the anterior and posterior anatomic triangles of the neck is crucial. Figure 238-1 shows the location of the major groups of lymph nodes, the sternocleidomastoid muscle, and the typical locations of the congenital cysts encountered most commonly.

## EVALUATION

### History

The physician should determine whether the neck mass was observed at birth, whether it has increased or decreased in size, whether it has changed color, and whether the lesion has drained or opened. Knowing the age at onset may help, because lymph nodes greater than 1 cm in diameter rarely appear at birth,

whereas many congenital cysts are noted in the newborn period. Some congenital cysts, however, may not be noted until childhood or beyond and are detected only when they become infected.

The history of pain or tenderness is important. Congenital cysts are nontender unless they become infected. Inflamed lymph nodes are tender and painful. Pain during eating suggests parotid gland involvement. History of fever, other systemic symptoms such as loss of weight, and fatigue may need to be elicited while considering the possibilities of infectious processes and malignancies.

### Physical Examination

The first step in the physical examination is to determine whether abnormalities exist in other parts of the body, such as other cysts, lymphadenopathy, hepatosplenomegaly, skin lesions, or signs of infection. The exact anatomic location of the neck mass must be determined, and the physician should note whether the mass is in the typical location of a lymph node (see Figure 238-1). The consistency, color, and firmness of the mass should be noted, as well as the presence of tenderness. The size of the mass should be measured.

Midline masses are usually associated with a thyroid abnormality. Masses that move with swallowing or with tongue protrusion suggest a thyroglossal duct cyst; these lesions may be tethered to the foramen cecum by the thyroglossal duct remnant. A mass along the anterior edge of the sternocleidomastoid muscle that moves with swallowing or that has a sinus opening to the surface of the overlying skin is likely to be a branchial cleft cyst. Both cysts and benign lymph nodes are freely mobile; malignant lesions are more likely to be fixed to underlying structures.

Rapidly growing, painless neck masses are worrisome because they might be neoplastic. Additional signs associated with a neoplastic process include fixation of the mass to subcutaneous tissue, firm consistency, size greater than 3 cm, and presence of constitutional symptoms. Supraclavicular nodes are the most likely neck mass to be malignant and should always be investigated.

### Laboratory Evaluation

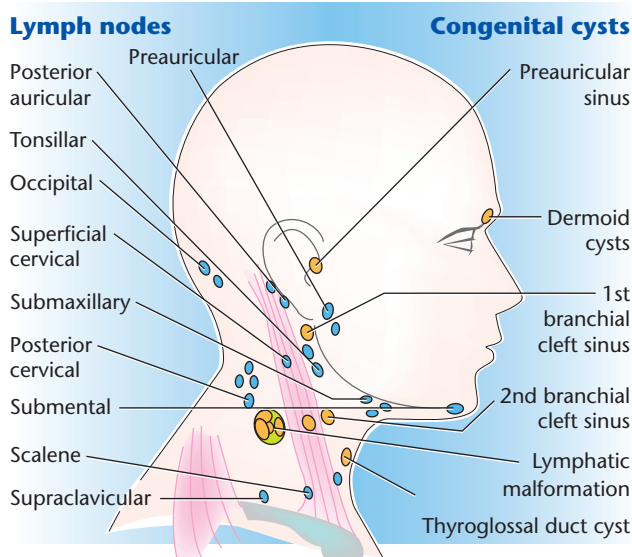
A complete blood count and blood culture can sometimes be helpful in assessing a tender, erythematous mass. Thyroid hormone levels should be measured if the thyroid gland is enlarged.

### Imaging Studies

Ultrasound or magnetic resonance imaging (MRI) scan can determine whether the mass is cystic or solid or whether it extends to deeper structures within the neck. Technetium scans can confirm the presence of thyroid tissue before a surgical procedure.

## CONGENITAL CYSTS

The following lesions account for most congenital masses of the head and neck. The major challenges in the differential diagnosis involve differentiating congenital masses from lymph nodes and determining the type of congenital lesion.



**Figure 238-1** Common locations for cystic (orange circles) and lymph nodes (blue circles) of the face and neck.

### Thyroglossal Duct Cysts

Thyroglossal duct cysts account for more than 70% of congenital cysts of the neck, branchial cleft cysts for more than 20%, and vascular malformations and other lesions for 4% to 5%.

Thyroglossal duct cysts result from failure of the embryologic thyroglossal duct to degenerate during the fifth week of gestation, leaving a fistula, sinus tract, or cyst at the midline of the neck just below the hyoid bone. Thyroglossal duct cysts are not often detected at birth and are usually noted first after the age of 2 years. They may initially show as inflamed, tender masses. When not infected, they are smooth, firm, mobile, and nontender and move upward with tongue protrusion or with swallowing. The differential diagnosis includes sebaceous cysts, epidermal cysts, submandibular lymph nodes, and lipomas. Unless normal thyroid tissue is palpable, the physician needs to confirm the presence of the thyroid gland by ultrasonography or technetium scan, because what may seem to be a thyroglossal duct cyst may actually be an ectopic thyroid gland, and its removal would leave the child dependent on thyroid hormone supplementation for life. Because the likelihood of infection is high, thyroglossal duct cysts should be removed surgically.

### Branchial Cleft Cysts

Branchial cleft cysts are congenital remnants of the lateral 4 branchial pouches and clefts. Most branchial cleft cysts arise from the second cleft or pharyngeal pouch. They appear as a small dimple or opening anterior to the middle portion of the sternocleidomastoid muscle. The cyst is nontender, firm, and mobile, and is located just under the skin. A small sinus, which occasionally drains fluid to the surface of the overlying skin, may be present, and a long fistulous tract may extend from it to the tonsil bed. Branchial cleft cysts without sinuses are often unnoticed until later childhood when they become infected. Infected cysts can easily be confused with lymphadenitis. Other lesions included in the differential diagnosis are sternocleidomastoid muscle masses associated with torticollis, small lymphatic malformations, epidermoid cysts, neurofibromas, lipomas, and an ectopic thyroid gland. Treatment involves surgical removal of the cyst and fistula.

### Lymphatic Malformations

Lymphatic malformations are congenital, avascular masses derived from congenital obstruction of lymphatic vessels. They are generally multilocular, fluid-filled, soft, compressible, painless masses located in the posterior triangle just behind the sternocleidomastoid muscle and in the supraclavicular fossa. Lymphatic malformations can usually be transilluminated. These masses may grow rapidly because of accumulation of lymph and can reach an enormous size, compressing important structures and obstructing the airway. Although the diagnosis is usually obvious during the physical examination, smaller lymphatic malformations may resemble hemangiomas or other cysts. Ultrasound will reveal fluid and multiple cystic components, confirming the diagnosis. Macrocystic lesions can usually be dramatically reduced with injection sclerotherapy. Surgical removal

is usually employed only if there are microcysts that can't be sclerosed. Lymphatic malformations occur infrequently in the axilla, on the trunk, or on the extremities; in older children, when they occur within the subcutaneous tissues, they may be mistaken for a lipoma or a hemangioma.

### Epidermoid Cysts

Epidermoid cysts are relatively common masses that may arise from an embryologic or fusional defect. They are usually located at midline on the face, most often at the level of the eyebrows. These small cysts feel doughy and smooth and contain sebaceous material and sometimes even hair, cartilage, or bone. One-third of these cysts are present at birth; the remaining two-thirds appear by school age. Because these cysts may become infected and may form deep tracts, surgical excision is indicated.

### Preauricular Cysts and Sinuses

Preauricular cysts and sinuses are the most common anomalies arising from an embryologic fusion failure of precursor tissues that develop into the external ear. The sinuses are pinhole-size pits that are usually located anterior to the helix (see Figure 238-1), and they may contain a short sinus tract. Preauricular cysts often are bilateral. These sinuses and cysts are inherited in an autosomal-dominant manner, with incomplete penetrance, and are found more commonly in blacks than in whites. They are a far more common cause of preauricular lesions than are first branchial cleft cysts and sinuses, which are located in the same area. Because preauricular cysts and sinuses may become infected, elective surgical removal is preferred. Hearing deficits may be associated with these lesions, but their prevalence is unknown.

### DEEP HEMANGIOMAS

Deep hemangiomas are vascular lesions within the subcutaneous tissues that may appear in any part of the body and may be difficult to differentiate from congenital cysts.

They are often noted in the newborn period and enlarge, sometimes rapidly, during the first year of life. Deep hemangiomas are less firm, more diffuse, and more easily compressible than cystic masses (except for lymphatic malformations). Unlike lymphatic malformations, deep hemangiomas do not transilluminate, and the skin overlying these vascular lesions is often bluish. Deep hemangiomas often begin to increase in size during the first few months of life, but usually regress spontaneously by school age. For masses that compress vital structures or have the potential to cause severe disfigurement, oral propranolol can be used to hasten involution.

### SOLID NECK MASSES

Cervical lymph nodes are often palpable in healthy children and can be distinguished by their location (see Figure 238-1), size, shape, consistency, and mobility. Enlarged cervical lymph nodes (>1 cm) should be defined further by their association with surrounding nodes or generalized adenopathy, the presence of an infection of the head or pharynx, and localized signs



of inflammation and erythema. Cervical adenitis typically develops as a swollen, tender, erythematous mass in a child who has a fever. *Staphylococcus aureus* and *Streptococcus pyogenes* account for 80% of acute unilateral cervical adenitis and usually respond to oral antibiotics such as a penicillin or cephalosporin. Lymph node aspiration is usually reserved for patients whose disease does not respond to initial therapy. Incision and drainage is an option for masses that become fluctuant. Some of the various causes of cervical lymphadenopathy include viral infections of the upper respiratory tract, bacterial infections, human immunodeficiency virus (HIV) infection, Kawasaki disease, and systemic disorders such as systemic lupus erythematosus, juvenile idiopathic arthritis, sarcoidosis, and histoplasmosis. Chronic inflammation of the lymph nodes can be seen with infections such as cat-scratch disease (see Chapter 215, Animal and Human Bites), atypical mycobacterium, and toxoplasmosis.

Malignant tumors are often found as a single supraclavicular mass or as multiple or matted masses crossing into both the anterior and the posterior triangles. More than 25% of children who have malignancies have a tumor of the head or neck. The most common neck malignancies include Hodgkin and non-Hodgkin lymphoma, neuroblastoma, lymphosarcoma, rhabdomyosarcoma, fibrosarcoma, and thyroid tumors.

## MANAGEMENT

All congenital cysts and masses should be monitored closely by the PCP. Acute bacterial infections of cysts should be treated with systemic antibiotics. Patients who have thyroglossal duct cysts, branchial cleft cysts, or epidermal cysts should be referred to a surgeon who is experienced at excising these congenital lesions. Lymphatic malformations can often be sclerosed if necessary, thus avoiding surgical removal.

Elective surgery before an infection develops is preferable because excision of an entire sinus tract, fistula, or embryologic connection is more difficult after an infection. Many PCPs and surgeons prefer to delay surgery until the child is beyond infancy and can better tolerate the procedure. For patients who have thyroglossal duct cysts, a PCP or surgeon should confirm the presence of normal thyroid tissue by ultrasound or by a technetium scan. Hemangiomas can be observed without referral unless they begin to impinge on vital structures. Hemangiomas that interfere with physiologic functions (blocking the vision, interfering with eating, among other functions) may be treated with propranolol or glucocorticoid steroids, or referred to a surgeon for management.

For children who have enlarged cervical lymph nodes and evidence of infection, the antibiotic therapy should improve the condition within 7 days; the condition should resolve completely over the next few weeks. If the adenopathy is persistent, if inflammation is not present, and if any characteristics are worrisome (eg, size >3 cm, immobile, associated with systemic symptoms, in an abnormal location), then the child should be evaluated further and treated for the underlying cause of an enlarged lymph node if one can be identified, or otherwise monitored closely until the lymphadenopathy resolves.

## WHEN TO REFER

- Cysts or tracts that are congenital (all congenital cysts or tracts should be removed)
- Mass that does not resolve with antibiotic therapy ( $\geq 2$  weeks)
- Mass in the thyroid gland
- Mass in the parotid gland
- Rapidly enlarging mass ( $> 3$  cm)
- Mass that is fixed or lymph nodes that are matted
- Mass in a concerning area (eg, supraclavicular)
- Abnormal chest radiograph
- When systemic signs and symptoms (eg, fever, weight loss, easy fatigability, hepatosplenomegaly) are present

## WHEN TO ADMIT

- Infected mass that is unresponsive to oral antibiotics
- Worrisome mass requiring immediate intervention and imaging
- Mass compromises the airway

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Infantile Hemangiomas* (fact sheet), Children's Hospital of Wisconsin ([www.chw.org/medical-care/birthmarks-and-vascular-anomalies-center/conditions/infantile-hemangiomas](http://www.chw.org/medical-care/birthmarks-and-vascular-anomalies-center/conditions/infantile-hemangiomas))
- *Neck Lumps and Bumps* (fact sheet), Patient.co.uk ([www.patient.co.uk/doctor/Neck-Lumps-and-Bumps](http://www.patient.co.uk/doctor/Neck-Lumps-and-Bumps))

### Medical Decision Support

- *Initiation and Use of Propranolol for Infantile Hemangioma: Report of a Consensus Conference* (article), *Pediatrics*, Vol 131, Issue 1, 2013

## SUGGESTED READINGS

- Chesney PJ. Cervical lymphadenitis and neck infections. In: Long SS, Pickering LK, Prober CG, eds. *Principles and Practice of Pediatric Infectious Diseases*. New York, NY: Churchill Livingstone; 2003
- Geddes G et al: Pediatric neck masses. *Pediatr Rev* 34:115, 2013
- Nield LS, Kamat, D. Lymphadenopathy in children: when and how to evaluate. *Clin Pediatr*. 2004;43:25–33

## Chapter 239 CYSTIC FIBROSIS

Donna Beth Willey-Courand, MD; Bruce C. Marshall, MD, MMM

Cystic fibrosis (CF) is an autosomal-recessive disease involving multiple organs, especially the pancreas and lungs. When the disease was first described in 1938, the median survival for children with CF was less



than 1 year. Today, the predicted median survival for people with CF in the United States is approaching 40 years of age, demonstrating how dramatically the face of this disease has changed over a relatively short period.

## INCIDENCE

Cystic fibrosis occurs with a frequency of approximately 1 in 3,600 live births in the white population, in whom it is the most common inherited lethal disease. The incidence is 1 in 15,000 in blacks and 1 in 6,500 in Hispanics. Because the carrier state is asymptomatic, the birth of a child with CF is often the first knowledge parents have that they carry a mutation.

## PATHOPHYSIOLOGIC FEATURES

The CF gene consists of 250 kilobase-pairs located on the long arm of chromosome 7. It codes for a 1,480-amino acid glycoprotein product known as the cystic fibrosis transmembrane-conductance regulator (CFTR). Currently, more than 1,000 mutations of the CFTR gene have been found that alter CFTR structure and function and result in the development of CF. The most common mutation in North America and Europe, accounting for approximately 70% of alleles in the United States, is a deletion of 3 base pairs, resulting in the deletion of phenylalanine (F) at position 508 (F508del). Although the CFTR genotype is highly predictive of pancreatic function, it is less predictive of the pulmonary disease. Recent evidence suggests that gene modifiers, as well as environmental factors, contribute to the pulmonary phenotype.

The CFTR glycoprotein is located in numerous organs throughout the body, including the lungs, upper respiratory tract, sweat glands, pancreas, intestines, liver, and reproductive tract. CFTR is a cyclic adenosine monophosphate-regulated membrane-channel protein that secretes chloride and other ions across the cell membrane and regulates several other proteins, including an epithelial sodium channel. Reduction or absence of CFTR activity results in impaired movement of chloride across the cell membrane and increased reabsorption of sodium. Because passive reabsorption of water molecules follows that of sodium, hydration of secretions is reduced in the affected organs. In CF airways, this results in a decreased periciliary fluid layer volume and height; and because sufficient fluid is critical for proper ciliary function, patients with CF experience impaired mucociliary clearance. CFTR also facilitates  $\text{HCO}_3^-$  transport across the epithelial membrane, and loss of CFTR function results in a decrease in airway surface liquid pH and reduced antimicrobial activity. Other cellular effects of CFTR loss, such as changes to pH and fatty acid ratios, have pleiotropic results at the tissue level, including altered pH of glandular secretions and an exaggerated inflammatory response.

## CLINICAL MANIFESTATIONS

### Infection

Ineffective mucociliary clearance and other changes predispose CF airways to infection. *Staphylococcus aureus* and *Haemophilus influenzae* are important

bacterial pathogens, but *Pseudomonas aeruginosa* has become the primary pathogen in this disease. Initially, nonmucoid environmental strains of *P. aeruginosa* are detected in patients. However, the CF airway environment leads to a transition to mucoidy and to a biofilm mode of growth, which results in an accelerated rate of decline in lung function.

### Lower Respiratory Tract

Despite the chronic nature of the airway infection, ongoing neutrophilic inflammation is typical. DNA released from dying neutrophils increases the viscosity of the airway secretions. Impaired ciliary function and tenacious secretions lead to stasis, and the distal airways become plugged. Bronchoscopic studies of infants with CF reveal that even if the children appear clinically well, neutrophil and proinflammatory (interleukin-8) mediator levels are increased. Chest computed tomographic (CT) scans also show that structural changes in the lung can often be detected despite normal pulmonary function. The battle in the lungs of patients with CF begins very early in life and may progress unnoticed.

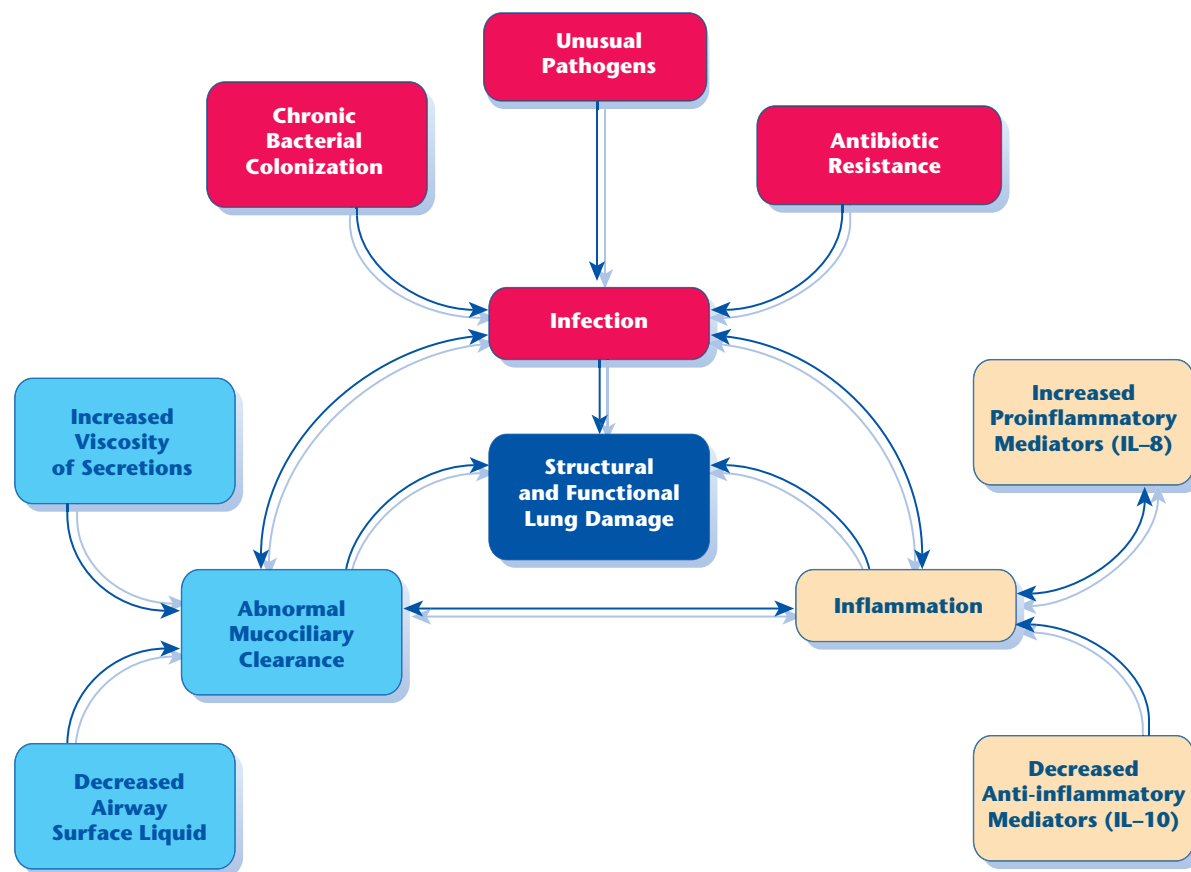
A cycle of infection and inflammation (Figure 239-1) develops in the lungs of patients with CF, typically punctuated by acute exacerbations. This process eventually damages and destroys the airways, leading to bronchiectasis. Complications such as hemoptysis and pneumothorax may appear as the lung disease progresses. Death most commonly results from respiratory failure and cor pulmonale caused by recurrent or chronic pulmonary infections.

### Upper Respiratory Tract

The same pathophysiologic mechanism also affects the upper respiratory tract. Even a moderate loss of CFTR activity can adversely affect the sinuses, and children with CF are predisposed to recurrent and chronic sinusitis despite normal nasal mucociliary clearance. Hypoplasia of the sinuses is a common finding. Nasal polyps are also common, especially among individuals who are homozygous for F508del CFTR. The etiology of polyposis is unknown, although it does not appear to be associated with allergies. Polyps may obstruct the nasal passages and contribute to the development of sinusitis.

### Gastrointestinal Tract

CFTR is also located throughout the gastrointestinal tract in the pancreas, intestines, and liver. In the pancreas, abnormal electrolyte secretion from the epithelial cells lining the pancreatic ducts results in dehydration of the ductal secretions and blockage of the pancreatic ducts. Destruction of the pancreatic acini occurs, and pancreatic enzyme secretion is significantly decreased. Bicarbonate secretion from the pancreatic ducts is also reduced, which further decreases the effectiveness of the pancreatic enzymes. This condition, known as pancreatic insufficiency (PI), occurs in 85% to 90% of patients with CF. In general, good correlation exists between pancreatic status and genotype. Patients with 2 severe mutations, such as F508del/F508del, have PI, and patients with 1 or 2 mild mutations are much more likely to have pancreatic



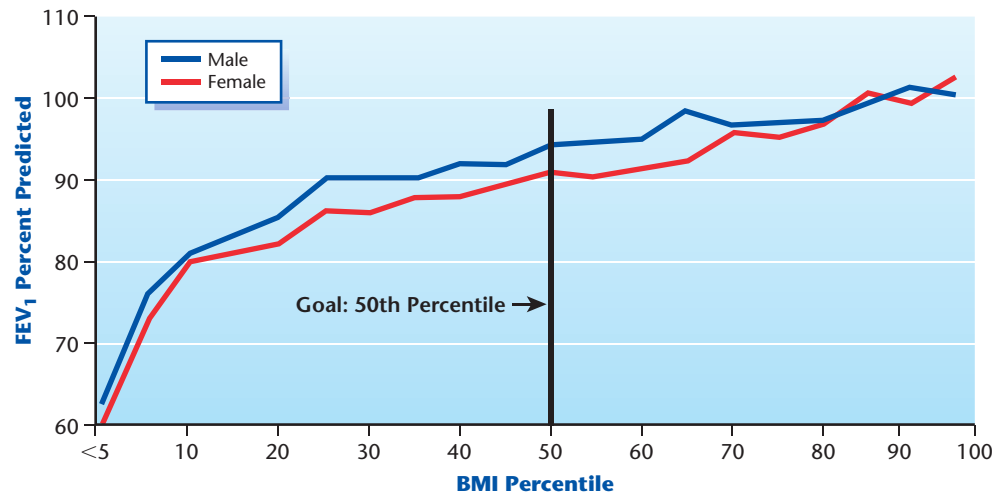
**Figure 239-1** The evolution of cystic fibrosis-related lung disease, the end result of a multifactorial process involving abnormal mucociliary clearance, inflammation, and infection. IL, interleukin.

sufficiency, although they are at increased risk for pancreatitis. Individuals who have pancreatic sufficiency generally have better clinical outcomes than patients with PI. PI results in the malabsorption of fats, proteins, carbohydrates, and the fat-soluble vitamins A, D, E, and K. Children with PI have difficulty growing and gaining weight. Optimization of nutritional status is essential to maintaining pulmonary function (Figure 239-2).

Patients with PI are at risk for intestinal dysfunction. Intestinal manifestations of CF may be present even before birth. Fetal ultrasound may reveal hyperechoic bowel, suggesting retention of mucous material in the intestine. Approximately 10% of infants with CF present with meconium ileus, an obstruction of the distal ileum with thick, inspissated, poorly hydrated material. Clinically, newborns exhibit delayed passage of meconium, abdominal distention, and a bubbly or granular-appearing material in the region of the terminal ileum on radiograph. Volvulus, intestinal atresia, and meconium peritonitis may occur as complications of meconium ileus. In older children and adults, poor hydration of intestinal contents, decreased secretion of pancreatic enzymes, inspissated intestinal secretions, and fecal stasis may produce a partial or complete obstruction of the small or large intestine. This distal intestinal obstruction syndrome (DIOS) may develop as an acute event or may occur chronically. Symptoms

include vomiting, abdominal distention, crampy abdominal pain, and, possibly, a mass in the abdomen, most often in the right lower quadrant. Patients may continue to pass stool around a partial obstruction. As in meconium ileus, bubbly, granular material can be detected by radiograph in the region of the obstruction, and regions of stool retention may serve as lead points for intussusception. Some patients experience rectal prolapse secondary to difficulty passing stool and from increased intra-abdominal pressure from coughing.

Symptomatic liver disease is an uncommon manifestation of CF but leads to death in a small minority of the patient population. The characteristic pathologic findings are focal biliary cirrhosis with edema, chronic inflammatory cell infiltration, and bile duct proliferation with patchy accumulation of eosinophilic material in the intrahepatic ducts. The localization of CFTR to the apical membrane of the intrahepatic bile duct cells suggests that a reduction in CFTR activity in CF may result in dehydration and increased viscosity of the bile, which may be a key factor in the pathophysiologic features of the hepatic disease. Prolonged jaundice can occur in neonates, and some patients may develop fatty infiltration of the liver; but the characteristic liver lesion in CF is focal or multilobular cirrhosis. Hepatomegaly is variably detected on examination, and the secondary development of splenomegaly suggests the possibility of portal hypertension. Other



**Figure 239-2** Cross-sectional analysis of the CF Foundation Patient Registry Annual Data Report showing the association between body mass index (BMI) percentile and pulmonary function. Note the decreased lung function associated with BMI below the 50th percentile. (Reprinted with permission from Cystic Fibrosis Foundation Patient Registry, 2011 Annual Data Report. Bethesda, MD: Cystic Fibrosis Foundation; 2012.)

features of portal hypertension such as variceal bleeding have been reported in CF but are relatively rare.

### Body Fluids

The identification of increased electrolytes in the sweat of people with CF, described decades before the identification of the CF gene, provided important insights into the pathophysiologic mechanism of the disease and led to the development of the diagnostic sweat test. The loss of body electrolytes caused by sweating in patients with CF can cause metabolic alkalosis either acutely or chronically. Acute illness, vomiting, and thermal stress may be contributing factors. Children may initially present with failure to thrive, irritability, and vomiting. Salt crystals are sometimes seen caked on the skin. Laboratory tests reveal increased serum pH and bicarbonate levels, as well as decreased serum levels of sodium, chloride, and potassium. The increased consumption of salty foods in older children and the addition of salt to the formula for infants are usually adequate to prevent salt loss syndrome.

### Pancreas

Patients with CF are also prone to the development of diabetes, particularly in their late teens and adulthood. This important complication has been associated with increased morbidity and mortality in patients with CF. Cystic fibrosis-related diabetes (CFRD) results primarily from a relative insulin deficiency caused by gradual destruction of the islet cells in the pancreas, but an element of insulin resistance has also been reported. Patients with CFRD rarely develop diabetic ketoacidosis, but they are at risk for other complications of diabetes such as retinopathy, renal dysfunction, and neuropathy. Patients may have the classic symptoms of diabetes such as polyuria and polydipsia and weight loss, but many have minimal symptoms. CFRD should be considered as a possible cause for poor growth, delayed puberty, increased frequency

of pulmonary exacerbations, or unexplained decline in pulmonary function. Patients who do not have CFRD should have annual screening with a 2-hour glucose tolerance test beginning at 10 years of age. Hospitalized patients, particularly those receiving supplemental feedings via gastrostomy tube, should have frequent blood sugar measurements because altered glucose metabolism may be present only during times of acute illness or stress. Patients with CFRD should *not* be placed on a diabetic diet because a significant reduction in caloric intake might result, which can compromise the patient's overall nutritional status. Instead, patients are taught how to distribute carbohydrates more equally throughout the day and to replace sweetened beverages with diet drinks. Insulin is the therapy of choice. Patients with CFRD should have hemoglobin A1C levels measured quarterly to assess adequacy of glucose control.

### Skeletal Complications

Osteopenia and osteoporosis are relatively common in adolescents and adults with CF for several reasons, including failure to thrive, delayed pubertal development, liver disease, physical inactivity, and malabsorption of calcium, magnesium, and vitamins D and K. Steroid use may further exacerbate the problems. Patients with decreased bone mineral density are predisposed to atraumatic fractures, especially of the spine and ribs. Patients may also experience transient arthritis that may be monoarticular, pauciarticular, or polyarticular. The knees, ankles, wrists, and proximal interphalangeal joints of the hands are the most often affected.

### Puberty

Pubertal development is often delayed in both boys and girls with CF. Poor nutritional status and a decrease in glucose tolerance, accompanied by a delay in the rise in sex hormone levels, result in delayed or

blunted pubertal development. Female infants with CF demonstrate excessive cytoplasmic and extracellular mucus, which can continue into childhood; the thickened cervical secretions may reduce fertility. Girls with CF may have abnormal menstrual cycles, as well as primary and secondary amenorrhea. Nevertheless, increasing numbers of successful pregnancies are occurring as the CF population ages. Boys with CF may have reduced testicular and epididymal size and reduced testosterone levels. In the majority of boys, bilateral absence of the vas deferens occurs secondary to obstruction and subsequent resorption of the structure, resulting in infertility. However, a variety of assisted reproductive technologies have recently been developed and used to successfully treat infertility in men with CF.

## DIFFERENTIAL DIAGNOSIS

The institution of newborn screening for CF has significantly altered the clinical picture of the newly diagnosed child. In 2013, 62% of all new diagnoses arose from a positive newborn screen. These infants are generally asymptomatic from the pulmonary standpoint. They may exhibit signs of malabsorption and weight gain issues depending on their pancreatic status. There are still patients, both pediatric and adult, however, who are diagnosed each year based on their clinical picture. For these patients, they most commonly exhibit respiratory symptoms such as recurrent pulmonary infections (18% of patients at presentation), failure to thrive or malnutrition (5%), steatorrhea or abnormal stools (6%), meconium ileus or intestinal obstruction (10%), or a family history of CF (9%). Vitamin deficiency (specifically deficiencies in the fat-soluble vitamins A, D, E, and K) may be seen. Other manifestations of CF that may trigger initial patient encounters include salt loss syndrome, nasal polyps, hepatobiliary disease, and impaired fertility.

For patients not diagnosed in the newborn period, the common pulmonary symptoms at presentation include a recurrent cough that is productive of purulent sputum, difficult-to-control wheezing, nasal polyps, recurrent otitis media, sinusitis, and pneumonia. The differential diagnosis includes asthma, environmental allergies, immunodeficiency syndromes, ciliary agenesis or dyskinesia,  $\alpha$ -1-antitrypsin deficiency, and foreign body aspiration.

From the gastrointestinal standpoint, infants with CF may present with steatorrhea, abdominal bloating with feedings, and difficulty gaining weight. Older children most commonly present with failure to thrive (see Chapter 149, Failure to Thrive: Pediatric Undernutrition) or steatorrhea (see Chapter 138, Diarrhea and Steatorrhea).

## EVALUATION

### Relevant History

In the majority of cases, no known family history of CF is found.

Infants diagnosed based on newborn screening are generally asymptomatic with the possible exception of steatorrhea, or frequent foul-smelling stools. For older children diagnosed based on symptoms, cough is the

most common presentation. The cough is often dry at first but becomes progressively productive of purulent sputum. Over-the-counter therapies are generally ineffective, and antibiotic treatment can produce only transient, partial improvement in the cough, which recurs with the cessation of therapy. The cough is present both day and night and may be exacerbated by physical activity and, in infants, by crying. Recurrent wheezing may also be present. Some children with CF also have asthma. Parents often report that their child has had recurrent pneumonia, sinusitis, bronchitis, and otitis media, necessitating repeated courses of antibiotics. Pneumonia and atelectasis may have occurred repeatedly in the same area of the lung. A history of nasal polyps without a concomitant history of nasal allergies is highly suggestive of CF. Finally, parents may have noted changes to the child's nail beds consistent with clubbing.

From the gastrointestinal standpoint, infants with CF are often described as voracious feeders despite having poor weight gain. The infants' stools are frequent, bulky, loose, foul smelling, and voluminous enough that parents will often complain that they overflow the diaper. Grease may be seen in the stool, absorbed in the diaper, or, in the case of older children, in the toilet bowl. Abdominal cramping and bloating after eating are common complaints. Foul-smelling flatulence may be described. Any neonate born with meconium ileus or with delayed passage of meconium and any infant or child with rectal prolapse should be tested for CF.

## Physical Examination

### Vital Signs

Respiratory rates and heart rates should be monitored relative to age-appropriate normal values. Fever and exacerbation or progression of the underlying lung disease may elevate both values. Oxygen saturation should be assessed at each visit. The use of overnight pulse oximetry or polysomnography should be considered to evaluate for nocturnal hypoxemia and hypercarbia in patients with more advanced disease.

### Growth Parameters

At all ages, particular attention should be paid to growth parameters, including weight, height, head circumference, and weight for length in children younger than 2 years and weight, height, and body mass index (BMI) in children older than 2 years. The child's height percentile should be compared with that predicted from the parental height. Concern should arise whenever a child fails to gain weight, loses weight, or crosses percentiles for height or weight.

### Head and Neck

Otoscopic examination should be performed at all visits to assess for otitis media. If a child has recurrent otitis media or is exposed to frequent doses of aminoglycosides, then audiometry should periodically be performed. The nasal mucosa should be inspected for discharge, swelling of the tissue, or polypoid tissue. Palpation of the sinuses should be performed.



Examination of the oropharynx should include assessment of the tonsils and the posterior pharynx because children with CF have similar risk for the development of adenotonsillar hypertrophy as children without CF. The posterior pharynx should be checked for exudates emanating from the nasopharynx.

### **Chest and Lungs**

Coughing frequency and the productivity of the cough should be assessed. The child's ability to communicate without coughing and becoming dyspneic, and without accessory muscle use is indicative of the status of the lung disease. Auscultation of the lungs may reveal clear breath sounds. With exacerbation of the underlying lung disease, wheezing, rhonchi, or crackles may be heard. As the patient's pulmonary status worsens, these findings may not change with antibiotic therapy; any clearing that does occur may be short lived. As the lung disease progresses, breath sounds may become globally decreased, and tubular breath sounds may be heard in areas of severe tissue destruction or bronchiectasis and fibrosis. Unilaterally decreased breath sounds, particularly in association with an acute onset of dyspnea, should raise concern about the development of a pneumothorax. With progression of the obstructive component of CF lung disease, there is increasing hyperinflation of the lungs, and the chest may take on a barrel shape with an increased anterior-posterior diameter. Progression of the fibrotic component of the lung disease results in the development of tachypnea and decreased vital capacity.

### **Heart**

With the progression of the lung disease and development of cor pulmonale, fixed splitting of the first and second heart sounds with increased loudness of the second heart sound may be heard.

### **Abdomen**

Infants may present with protuberant abdomen. Distention of the abdomen with pain on palpation may be noted in children with acute intestinal obstructions. The frequency and distribution of bowel sounds should be assessed by auscultation. Palpation should be performed to assess for retention of stool (most commonly in the right lower quadrant), tenderness, hepatomegaly, and splenomegaly.

### **Genitourinary Tract**

Tanner staging should be performed either by direct inspection or by having the child indicate developmental status from a series of pictures. Girls should be questioned about the onset of menstruation, the regularity of their cycles, and associated symptoms. All sexually active girls should undergo annual pelvic examinations.

### **Extremities**

Joints should be examined for swelling that may be caused by CF-related arthropathy. The digits and nail beds should be examined for clubbing and cyanosis. Edema may arise from hypoproteinemia, especially in newly diagnosed malnourished infants and in patients with end-stage lung disease and cor pulmonale.

## **Laboratory Testing**

### **Diagnostic Testing: Sweat Testing and Genotype Analysis**

The diagnosis of CF requires either 2 positive sweat tests or genotype analysis revealing 2 *CFTR* mutations known to cause CF plus 1 of the following:

- Chronic sinopulmonary disease
- Gastrointestinal or nutritional abnormalities
- Obstructive azoospermia in boys
- Salt loss syndrome
- CF in a first-degree relative

The pilocarpine iontophoresis technique of Gibson and Cooke is the gold standard for the diagnosis of CF. Pilocarpine stimulates the secretion of sweat. The volume of sweat and concentration of chloride secreted are then measured. Sweat testing should be performed in accordance with the Clinical and Laboratory Standards Institute (formerly National Committee for Clinical Laboratory Standards) guidelines. Normative sweat chloride values are age dependent. Normal sweat chloride values in infants up to 6 months of age are less than or equal to 29 mEq/L. Levels between 30 and 59 mEq/L are borderline, and repeat sweat testing/genetic testing should be performed. Values greater than or equal to 60 mEq/L are indicative of CF. Normal chloride values in individuals older than 6 months of age are less than 40 mEq/L. Values between 40 and 60 mEq/L are considered borderline, and repeat sweat testing or genetic testing is required to make a definitive diagnosis. For some borderline cases, referral to specialized centers for an assessment of *CFTR* function by measuring nasal potential difference may be needed to confirm or rule out the diagnosis of CF. For example, in the case of a borderline sweat test result with identification of only 1 *CFTR* mutation, abnormal results on 2 nasal potential difference tests are indicative of a CF diagnosis. Chloride values greater than 60 mEq/L are considered diagnostic of CF, but many possible causes of false-positive sweat tests exist, including laboratory error, untreated adrenal insufficiency, autonomic dysfunction, ectodermal dysplasia, glucose-6-phosphate deficiency, hypothyroidism, malnutrition, mucopolysaccharidosis, glycogen storage disease (type 1), fucosidosis, hereditary nephrogenic diabetes insipidus, Mauriac syndrome, pseudohypoaldosteronism, or familial cholestasis. A repeat confirmatory sweat test should be performed together with genetic mutation analysis. In asymptomatic newborns, sweat testing triggered by a positive CF newborn screening report should be performed when the infant is at least 2 weeks of age and weighs more than 2 kg. In symptomatic newborns, sweat testing may be performed as early as 48 hours of age, but the probability of inconclusive results is greater at this age. False-negative values can result from edema, malnutrition, and laboratory error. Several *CFTR* mutations that cause CF can also result in a false-negative sweat test.

In cases in which genetic testing is done as part of a newborn screen algorithm or when genetic testing alone is performed, the presence of 2 mutations known to cause CF is diagnostic; however, sweat testing is still recommended to confirm *CFTR* protein dysfunction. In cases in which genetic testing is done to resolve a

borderline sweat test or following an abnormal sweat test, the presence of 2 mutations known to cause CF is confirmatory of the diagnosis. DNA from blood or buccal swabs can be used for genetic testing. With the advent of mutation-specific therapies to treat patients with CF, it is recommended that all patients undergo genetic testing to identify both CF-causing mutations.

### Newborn Screening

Newborn screening for CF has been universally adopted in the United States. An expert panel convened by the Centers for Disease Control and Prevention (CDC) and the Cystic Fibrosis Foundation in November 2003 reviewed the data on the risks and benefits of newborn screening with the recommendation that “on the basis of evidence of moderate benefits and low risk for harm, CDC believes that newborn screening for CF is justified.” Evidence exists to support the efficacy of newborn screening in the areas of improved nutritional status, cognitive development, economic benefit, and improved survival. The impact of newborn screening on pulmonary status is variable. The benefit of improved height and weight on pulmonary status is well known and believed to outweigh the variability in data concerning pulmonary outcomes for newborn screening.

Newborn screening for CF is typically a 2-tier test. The first tier involves measuring serum immunoreactive trypsinogen (IRT) levels. IRT values are elevated in newborns with CF, but false-negative results may occur, particularly in infants with meconium ileus. All infants with meconium ileus should undergo sweat testing or genetic analysis. The second tier of testing varies between states and may use either repeat IRT measurement or limited genetic mutation analysis. Sweat testing is performed to confirm results of newborn screening. In cases in which the child has signs and symptoms consistent with CF, sweat testing or genetic analysis should be performed regardless of newborn screening results.

### Recommended Monitoring of Patients With an Established Diagnosis of Cystic Fibrosis

The Cystic Fibrosis Foundation has developed guidelines for the management of infants with CF that are applicable for those infants diagnosed by newborn screening as well as those whose diagnosis was initially suggested through symptoms or clinical presentation such as meconium ileus. Infants should be seen monthly for at least the first year of life and then every 2 to 3 months for the second year. After 2 years, it is recommended that all patients with CF should be evaluated in an accredited CF center at least quarterly. The Cystic Fibrosis Foundation recommends that infants with CF should have a complete blood count with differential, fat-soluble vitamin levels (retinol,  $\alpha$ -tocopherol, 25-hydroxyvitamin D), albumin and pre-albumin, prothrombin time, and measurement of liver enzymes performed initially between 1 and 3 months of age. After that, patients should have these studies repeated annually. Pancreatic functional status should be assessed in all infants diagnosed by newborn screening using fecal elastase measurement within the first month of life. Patients 10 years and older should be screened for CF-related diabetes mellitus on an annual basis (Figure 239-3). Patients who are on chronic inhaled aminoglycoside therapy or who receive frequent courses of intravenous aminoglycosides should have at least annual measurement of renal function. All patients should receive a complete physical examination, including hearing and vision screening annually, which is particularly relevant for patients receiving multiple courses of aminoglycosides because of their potential ototoxicity.

### Microbiologic Assessment

Cultures to assess lower respiratory tract flora should be obtained initially 1 week after diagnosis or at 1 month of age and then at 3, 6, and 12 months of age. After 1 year of age, clinically stable patients should undergo culture of the respiratory tract at least quarterly and

#### Healthy Outpatients

- OGTT of choice
- Diagnosis based on
  1. FPG  $\geq 126$  mg/dL
  2. 2-hr OGTT glucose  $\geq 200$  mg/dL
  3. A1C  $\geq 6.5\%$
  4. Random glucose  $> 200$  mg/dL plus polyuria, polydipsia
- All but #4 should be repeated

#### Acute Illness, Systemic Steroids

- Diagnosis based on hyperglycemia that persists for  $> 48$  hr
- Hyperglycemia is defined as
  1. FPG  $\geq 126$  mg/dL
  2. 2-hr postprandial glucose  $\geq 200$  mg/dL
- If measured by SMBG, should be confirmed by laboratory measurement

#### Continuous Drip Feedings

Diagnosis based on mid- or immediate postfeeding glucose  $\geq 200$  mg/dL  
Should be confirmed on 2 separate nights  
If measured by SMBG, should be confirmed by laboratory measurement

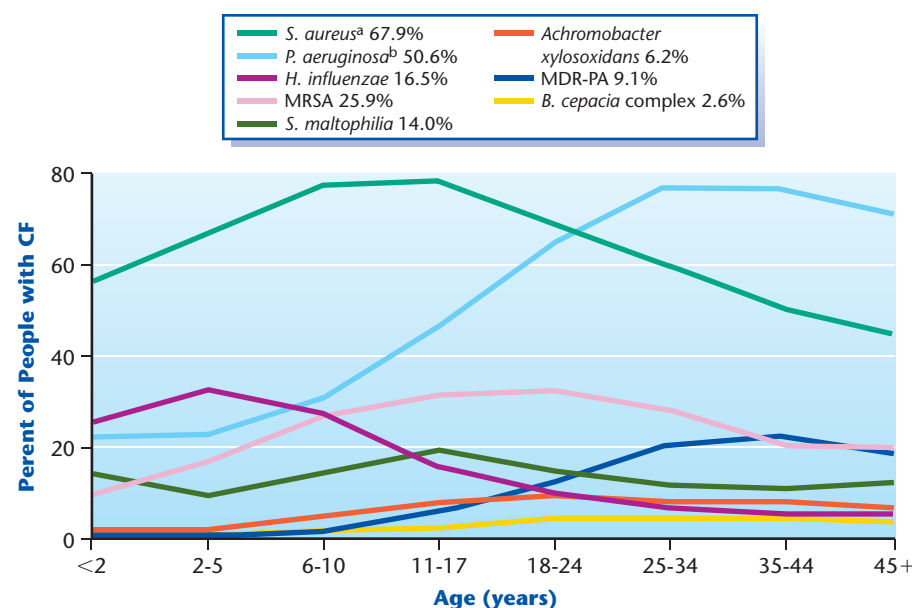
**Figure 239-3** Screening algorithm for diabetes. All children 10 years or older should undergo an oral glucose tolerance test (OGTT) annually. FPG, fasting plasma glucose; SMBG, self-monitoring blood glucose. (Modified with permission from Moran A, Brunzell C, Cohen RC et al. *Clinical Care Guidelines for Cystic Fibrosis-Related Diabetes: A position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society*. Diabetes Care. 2010;33:2697–2708.)

whenever there is any change in clinical status. Due to the relatively high prevalence of NTM infections in patients with CF, annual screening with mycobacterial cultures is recommended for those patients who can expectorate sputum. An expectorated sputum sample is the usual way to obtain this culture. In infants and young children who are unable to expectorate, a throat swab or cough swab is often obtained, but it is not necessarily predictive of lower airway pathogens. In young children, *S aureus* and *H influenzae* are the most common organisms. With advancing age, *P aeruginosa* becomes the predominant pathogen. Other pathogens such as *Burkholderia cepacia* complex and *Stenotrophomonas maltophilia* can also infect the CF lungs (Figure 239-4). The prevalence of methicillin-resistant *S aureus* has been increasing over the past decade. Specialized media are recommended to ensure isolation of common CF pathogens. *P aeruginosa* is best detected using MacConkey agar, *S aureus* on mannitol salt agar or Columbia or colistin-nalidixic acid, *H influenzae* on horse blood or chocolate agar, and *B cepacia* complex using *B cepacia* selective agar, oxidation-fermentation polymyxin bacitracin lactose agar, or *Pseudomonas cepacia* agar. After a pathogen has been isolated, antimicrobial susceptibility testing should be determined using an agar-based diffusion assay such as E-tests (antibiotic-impregnated strips) or antibiotic discs rather than automated commercial systems, which have been shown to be inaccurate in these circumstances. Organisms in the *B cepacia* complex and other unidentified gram-negative rods should be sent to a reference laboratory, such as the Cystic Fibrosis Foundation-sponsored *B cepacia* laboratory at the University of Michigan, for further evaluation.

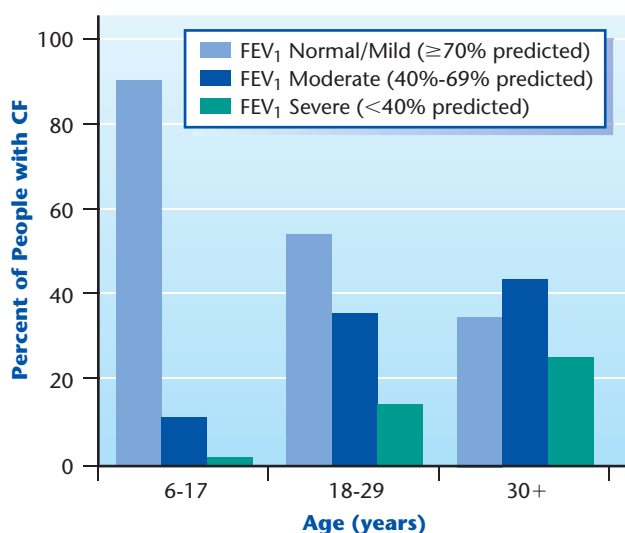
### Spirometry

Spirometry should be performed every 3 to 6 months and as needed based on the patient's pulmonary status. Although most children younger than 6 years are unable to perform the test reliably, new approaches are being developed that may allow the extension of this test to younger patients, and infant pulmonary function testing is available at many CF centers. Spirometry is best performed with the supervision of a certified respiratory therapist who is trained to work with children because it may be difficult to get a reliable, reproducible effort, especially when the child is first learning to perform the test.

The changes seen in pulmonary function are obstructive in nature secondary to plugging of the small airways with thick secretions. The severity of pulmonary disease as defined in the *CF Foundation Patient Registry Annual Data Report* is categorized based on the percentage predicted forced expiratory volume in 1 second (FEV<sub>1</sub>). Normal lung function is defined as an FEV<sub>1</sub> more than 90%, mild lung disease 70% to 89%, moderate 40% to 69%, and severe less than 40%. Less than 20% of children reported in the *CF Foundation Patient Registry Annual Data Report* have moderate to severe lung disease (Figure 239-5). One measure of the health of the small airways is FEF<sub>25%-75%</sub> (forced expiratory flow between 25% and 75% of vital capacity), the average amount of air expelled over the middle half of all the air expelled during spirometry. Researchers have suggested that changes may be seen in a forced expiratory flow of 25% to 75% before FEV<sub>1</sub>, and therefore clinicians should consider this value, particularly in younger children.



**Figure 239-4** Prevalence of pulmonary pathogens based on the age of the patient. MDR-PA, multidrug-resistant *Pseudomonas aeruginosa*; MRSA, methicillin-resistant *Staphylococcus aureus*. <sup>a</sup>*S aureus* includes people with MRSA. <sup>b</sup>*P aeruginosa* includes people with MDR-PA. (Reprinted with permission from Cystic Fibrosis Foundation Patient Registry, 2011 Annual Data Report. Bethesda, MD: Cystic Fibrosis Foundation; 2012.)



**Figure 239-5** Variability in severity of pulmonary function in adults and children classified by predicted percentage FEV<sub>1</sub>. Children: derived from Wang X, Dockery DW, Wypij D, et al. Pulmonary function between 6 and 18 years of age. *Pediatr Pulmonol.* 1993;15(2):75–88. Adolescents (boys >17 years and girls >15 years) and adults: derived from Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. *Am J Crit Care Med.* 1999;159(1):179–187. (Reprinted with permission from Cystic Fibrosis Foundation Patient Registry, 2011 Annual Data Report. Bethesda, MD: Cystic Fibrosis Foundation; 2012.)

### Imaging

A chest radiograph should be performed on infants initially between 2 and 6 months of age, at 1 and 2 years of age, and then every 2 to 4 years in patients who are clinically stable, annually in patients with declining pulmonary function, and as clinically indicated at times of pulmonary exacerbation in all patients. Bronchial wall thickening, together with hyperinflation caused by small airway obstruction, is the first change noted. Bronchiectasis develops with time. Acute or chronic infiltrates may be noted depending on the clinical status of the patient. The progression of radiographic changes varies between patients and may be more sensitive than changes in pulmonary function tests. Pulmonary function may be relatively well maintained at the same time that radiographic changes may be fairly advanced.

Chest CT scans also show that structural changes in the lung can often be detected before symptoms are present. Although some enthusiasm has existed for periodic chest CT scans, concerns about the radiation exposure have limited adoption of this approach. No current formal recommendations have been made for routine performance of CT scanning in patients with CF.

Patients 8 years or older with CF who are malnourished, have severe pulmonary disease, are on chronic glucocorticoid therapy, have delayed puberty, or have low levels of 25-hydroxyvitamin D are at increased risk for bone disease. Lateral chest radiographs of these patients should be examined for fractures at

least annually. Children with these risk factors who are at least 8 years of age should undergo a dual radiograph absorptiometric scan to measure bone density. All children with CF should have bone densitometry performed by their 18th birthday. An abdominal ultrasound should be performed if a change is noted in liver function tests or if hepatomegaly or splenomegaly is detected.

### MANAGEMENT

All children diagnosed with CF and those who have clinical stigmata of CF but equivocal diagnostic test results should be referred to a local CF care center for evaluation. At the center, children are evaluated by a pediatrician (most often a pediatric pulmonologist), nurse, respiratory therapist, dietitian, and social worker who are highly experienced in the management of CF. These individuals are able to provide counseling and support to families of newly diagnosed children, as well as education about the disease. Pulmonary and gastrointestinal therapies can be initiated. Infants should be seen monthly for the first year of life and then every 2 to 3 months during the second year to facilitate ongoing education of the family about CF, to assure adequate growth and nutrition for the child, and to adjust or initiate therapies as needed. Children should be seen at least quarterly in the CF care center where the adequacy of their therapies, as well as their growth, nutrition, and pulmonary function, can be assessed and therapies adjusted accordingly. The CF social worker is an invaluable resource for families and can help them deal with the psychological and financial aspects of raising a child with CF. The team will work with the child over the years to help them develop into an adult capable of managing the disease independently. CF centers are also able to make available to patients clinical trials of the newest cutting-edge therapies. The CF center should not be considered, however, as a replacement for the primary care pediatrician. The child absolutely must continue to receive routine well-child care. CF centers generally have physicians available at all times to consult on medical management issues relating to CF. A list of accredited CF care centers in the United States can be accessed via the Cystic Fibrosis Foundation Web site ([www.cff.org](http://www.cff.org)).

### Pulmonary Therapy

The Cystic Fibrosis Foundation has developed a series of guidelines related to airway clearance, chronic medications, management of pulmonary exacerbations, and management of pulmonary complications such as hemoptysis and pneumothorax. From the moment a child is diagnosed with CF, the family should be counseled to minimize environmental tobacco smoke exposure. Children, especially adolescents, should be educated about the detrimental effects of tobacco smoke and illegal inhalants on their lungs. Infants and children with CF should receive all routine childhood vaccinations including annual vaccination for influenza. Nasal spray vaccination for influenza should not be used. Currently, the American Academy of Pediatrics does not recommend palivizumab prophylaxis for all infants with cystic fibrosis. It should be



considered for infants with evidence of chronic lung disease and/or nutritional compromise. The decision to pursue authorization for palivizumab prophylaxis should be based on risk/benefit and cost discussions between the provider and the family. Annual influenza vaccination is recommended for children with CF older than 6 months and their families.

The cornerstone of pulmonary therapy for children and adults with CF is chest physiotherapy (CPT). Patients are prescribed a daily regimen of CPT to help them mobilize and expectorate the thick, tenacious secretions in their airways. The frequency of therapy is generally increased during times of acute exacerbations. Numerous airway clearance modalities are available for CPT, including manual percussion with postural drainage, autogenic drainage, or a vest that inflates and vibrates the chest at different frequencies. Several different handheld devices are designed to shear the mucus off the airways and provide back-pressure to stent the airways open such that secretions may be expelled. Each modality has specific advantages, but no single modality is superior. Because CPT is a time-consuming process, the choice of therapy should be based on the method that is the most effective for that patient and that fits best into the family's lifestyle to optimize adherence. Physical activity and regular exercise should be recommended as an integral part of the regimen.

Bronchodilators are often given before CPT to maximally dilate the airways and thus help facilitate clearance of the secretions. Patients with CF have a variable response to  $\beta$ -agonists, and some patients exhibit a transient decline in pulmonary function most likely secondary to collapse of bronchiectatic airways. Patients with CF should be assessed for bronchodilator response by pulmonary function testing and therapy adjusted accordingly. Long-acting  $\beta$ -agonists, however, may be beneficial in some patients with CF and asthma.

The chronic inflammatory process in CF lung disease has led to considerable interest in anti-inflammatory therapies. Alternate-day prednisone therapy has been shown to improve lung function in patients chronically infected with *P aeruginosa*, but an increased incidence of growth restriction, glucose abnormalities, and cataracts has dampened enthusiasm for this therapeutic approach. Inhaled steroids and leukotriene modifiers are attractive alternatives and are widely prescribed. However, because of a lack of evidence of efficacy for CF treatment, their use should be limited to patients with concomitant asthma. In patients with CF who have mild lung disease, high-dose ibuprofen has been shown to decrease the rate of decline in lung function and the need for hospitalization. However, the requirements for a pharmacokinetic study to determine the optimal dose of ibuprofen and concerns about safety have limited penetration of this therapy into clinical practice.

Dornase alpha, a recombinant human deoxyribonuclease, was developed for nebulization into the airways, where it cleaves the viscous DNA released by dying neutrophils as part of the exaggerated inflammatory response characteristic of CF lung disease. Deoxyribonuclease treatment improves the rheologic

properties of the sputum and enables the patient to expectorate the sputum more easily. It is generally administered once a day. A multicenter study of dornase alpha revealed an improvement in lung function and a decrease in the frequency of pulmonary exacerbations with chronic use. This therapy is recommended for children 6 years of age or older unless they have documented intolerance for the drug. Inhaled hypertonic saline is one of the newest therapies in the CF armamentarium. The hypothesis is that inhaling a highly concentrated saline solution (7% saline) increases the osmotic load and stimulates water movement into the airways. The improved hydration of the secretions results in better mucociliary clearance, and patients are better able to clear their secretions. A 48-month trial of 7% saline inhaled twice daily revealed improved pulmonary function, and treated patients had fewer pulmonary exacerbations compared with controls who inhaled 0.9% saline twice daily. Some patients may experience wheezing with the medication, which can be attenuated by pretreatment with a bronchodilator. This therapy is recommended for children 6 years of age or older.

Chronic daily antibiotic therapy to prevent the initial infection or to treat chronic bacterial infection is not well supported by evidence in medical literature. Antibiotic therapy is generally recommended for treating acute exacerbations when the bacterial burden increases and patients develop associated symptoms such as increased cough frequency and sputum production or declining pulmonary function with or without radiographic changes. One of the exceptions to this rule is the chronic use of macrolide antibiotics. Research has shown that 3-times-a-week administration of the macrolide antibiotic azithromycin for older children and adults with CF who are chronically colonized with *P aeruginosa* has a positive impact on lung function, weight, and the frequency of pulmonary exacerbations. As such, this therapy is recommended for children 6 years of age and older with *P aeruginosa* persistently present in their airway cultures. A study of the use of 3-times-a-week administration of azithromycin in older children and adults who were culture negative for *P aeruginosa* for at least 1 year showed a positive impact on weight, frequency of pulmonary exacerbations, and cough frequency. A high-dose preparation of nebulized tobramycin given twice a day on alternating months to patients chronically infected with *P aeruginosa* reduced the need for hospitalization and improved pulmonary function. This therapy is recommended for children 6 years of age and older with *P aeruginosa* persistently cultured from the airways independent of the severity or acuteness of the lung disease. A nebulized form of aztreonam lysine was shown to improve patient-reported respiratory symptoms, FEV<sub>1</sub>, sputum density of *P aeruginosa*, and weight. This therapy has been approved for use in children 6 years of age and older with *P aeruginosa* cultured from the airways.

When patients experience an exacerbation of bronchopneumonia or an apparent viral respiratory illness, antibiotic therapy directed against their most recently cultured pathogen is recommended. If the patient does not have respiratory distress or hypoxemia, then

oral outpatient therapy may be initiated. When patients exhibit an acute worsening of their respiratory status, hypoxemia, or respiratory distress, hospitalization with the administration of intravenous antibiotics and aggressive chest physiotherapy is recommended. *P. aeruginosa* is routinely treated with 2 antipseudomonal antibiotics. The duration of antibiotic therapy depends on the severity of the exacerbation but is generally 10 days or longer based on the response to treatment. Airway clearance therapies should be increased in frequency. Chronic maintenance therapies should be continued during treatment for an acute exacerbation.

Hemoptysis and pneumothorax are both common complications of CF lung disease. Patients with CF may have blood-streaked sputum; however, if the volume of blood expectorated is large ( $>240$  mL), then treatment with bed rest, intravenous antibiotics, and cessation of any medications with anticoagulant properties should be initiated. If the bleeding does not resolve or becomes life threatening, then bronchial artery embolization may be required. Resection of the bleeding segment is the therapeutic option of last resort. Pneumothorax occurs annually in approximately 1% of patients with CF. Patients with respiratory distress or with a large pneumothorax ( $>3$  cm between the apex and cupola) should be treated with a chest tube. Pleurodesis is recommended for patients with recurrent large pneumothoraces.

As the lung disease progresses, intervals of stability between exacerbations may become shorter. Patients may require supplemental oxygen therapy because of progressive hypoxemia. Noninvasive ventilation may be instituted when evidence exists of carbon dioxide retention or sleep-disordered breathing.

Lung transplantation is a final therapeutic option for the treatment of progressive, severe lung disease. It is an inherently risky procedure, with a 5-year post-transplantation survival of approximately 50% to 60%. Referral for lung transplantation should be made when other therapeutic options are exhausted. Survival models have been developed that facilitate the calculation of a patient's predicted survival without a transplant to help in the selection of patients most likely to gain a survival advantage from the procedure. Patients are informed of the advantages, risks, and potential complications of undergoing the procedure. They are made aware that the complicated medical regimen that they follow to treat their CF-related lung disease is replaced by a transplant medical regimen that is often equally as complicated. Active tuberculosis, human immunodeficiency virus infection, and hepatitis B are contraindications to lung transplantation. Additionally, patients with significant psychosocial dysfunction that would preclude adherence to the post-transplantation medical regimen are not good surgical candidates for transplantation. Ivacaftor is a drug that acts to optimize the function of the CFTR channel in patients with G551D and other gating mutations by helping to increase the time that the CFTR channel remains open at the cell surface. Clinical trials have shown that patients with the G551D mutation who take the drug demonstrate significant improvement in lung function, risk for pulmonary

exacerbations, patient-reported respiratory symptoms, and sweat chloride concentration. The drug has been approved for the treatment of G551D and other gating mutations. Research is ongoing for the development of other drugs that potentiate CFTR function and correct the abasic genetic defect with the goal that CF patients with all the different genetic mutations will ultimately be able to be treated. Clinical trials have shown that patients with the G551D mutation who took the drug demonstrated significant improvement in lung function, risk for pulmonary exacerbation, patient-reported respiratory symptoms, weight, and sweat chloride concentration. This drug has recently received US Food and Drug Administration approval for treatment of patients with the G551D mutation. Research is ongoing for the development of other drugs that potentiate CFTR function and correct the basic genetic defect with the goal that CF patients with all the different genetic mutations will ultimately be able to be treated.

### Gastrointestinal Therapy

Nutritional therapy is a cornerstone of good CF therapy. Infants and children with CF who have PI should receive at least 120% to 130% of the recommended daily allowance of age-appropriate calories. Fat intake should make up 35% to 40% of the daily required calories compared with less than 30% in people without CF. For infants with CF, nutritional status, adequacy of weight gain, and caloric intake should be assessed at each visit. Human milk is the preferred initial type of feeding, but if this is not possible, standard infant formulas should be used. Increased calorie concentrations may be needed if there is inadequate weight gain. Infants less than 2 years of age should receive  $\frac{1}{8}$  teaspoon of table salt per day starting at diagnosis, and this should be increased to  $\frac{1}{4}$  teaspoon beginning at 6 months of age. Children older than 2 years should be evaluated at least annually by a dietitian who is knowledgeable about CF. Caloric requirements are higher when acute illness or exacerbation of the pulmonary disease is present and when catch-up growth is needed. Lack of appetite caused by intercurrent illness and an inability to consume the increased number of calories needed to sustain normal growth, to make up for lost weight, or to achieve catch-up growth is a frequent nutritional problem faced by both adults and children with CF. Modifications are initially made to increase the caloric density of the child's regular diet. High-calorie, high-fat supplements in the form of shakes and formulas are also recommended. If the child cannot orally consume the needed daily requirement of calories, then supplementation via nasogastric or gastrostomy tube is recommended.

Pancreatic enzyme supplements are given with each fat-containing meal or snack. The recommended dose for infants is 2,000 to 5,000 units of lipase per 120 mL of formula or per breastfeeding. The dose may be adjusted to no greater than 2,500 lipase units per kilogram per feeding, with a maximum daily dose of 10,000 lipase units per kilogram. Low-dose, enteric-coated enzyme preparations can be administered to infants with a small amount of apple sauce or other nonalkaline food. Brand-name enteric-coated enzymes

**Table 239-1** Dosages for Vitamin Supplementation

	VITAMIN A (IU)	VITAMIN E (IU)	VITAMIN D (IU)	VITAMIN K (MG)
0–12 months	1,500	40–50	400–500	≥0.3 mg
1–3 years	5,000	80–150	800–1,000	≥0.3 mg
4–8 years	5,000–10,000	100–200	800–1,000	≥0.3 mg
>8 years	10,000	200–400	800–1,000 (upper limit increases to 2,000 at >10 years)	≥0.3 mg

Derived from Tangpricha V, Kelly A, Stephenson A, et al. An update on the screening, diagnosis, management, and treatment of vitamin D deficiency in individuals with cystic fibrosis: evidence-based recommendations from the Cystic Fibrosis Foundation. *J Clin Endocrinol Metab.* 2012; 97(4):1082–1093; modified from Cystic Fibrosis Foundation. Pediatric nutrition for patients with cystic fibrosis. In: *Consensus Conferences: Concepts in CF Care, 2001*. March 28–29, 2001. Reprinted by permission of the Cystic Fibrosis Foundation.

should be used exclusively. Infants are at risk for developing ulceration of the oral mucosa if the enzymes are not completely cleared from the oral cavity. Enteric coating protects the enzymes from being destroyed by stomach acids. Generic preparations should be avoided because of a lack of standardization of the enzyme dose. Enzyme dosing is initially determined based on the patient's weight and subsequently adjusted based on clinical symptoms of continued malabsorption (frequency and consistency of stools, perceived greasiness of stools, and abdominal cramping). Enzyme therapy for children younger than 4 years should be initiated at a dose of 1,000 units of lipase per kilogram per meal; therapy for children 4 years or older should be initiated at a dose of 500 units of lipase per kilogram per meal. Doses should generally be kept to less than 2,500 units of lipase per kilogram per meal or less than 10,000 units of lipase per gram-fat per day to reduce the risk for developing fibrosing colonopathy.

Children with CF should receive a standard, age-appropriate dose of non-fat-soluble multivitamins. Children with pancreatic insufficiency should also receive supplements of vitamins A, D, E, and K (Table 239-1). Vitamin K is supplemented at higher levels in patients with liver disease and abnormalities in clotting or who are on prolonged antibiotic therapy. Special high-dose preparations of these vitamins are available for patients with CF.

Acid blockers should be used as needed to treat gastroesophageal reflux, which is common in patients with CF. In addition, acid suppression may be beneficial for optimization of pancreatic enzyme function.

Distal intestinal obstruction syndrome is a common complication of CF, and patients with vomiting, crampy abdominal pain, and decreased stool output should be evaluated for intestinal obstruction by imaging. If DIOS is diagnosed, then oral intake should be withheld, and intravenous fluids or total parenteral nutrition should be initiated. The obstruction may be relieved with the performance of a gastrografin enema or oral or nasogastric administration of osmotic laxatives (polyethylene glycol). If this therapy does not result in relief of the blockage, then surgical intervention may be needed. Other diagnostic considerations for these symptoms include appendicitis, pancreatitis, cholecystitis, intussusception, and *Clostridium difficile* colitis.

Elevated liver enzymes and abnormal liver function test results or the detection of hepatomegaly or splenomegaly (or both) during examination should raise concern about the possible development of cirrhosis. An abdominal ultrasound should be ordered. Ursodeoxycholic acid has been shown to benefit patients with cholestatic diseases such as primary biliary cirrhosis and is often administered in patients with CF who have hepatobiliary disease in an effort to improve bile flow and to limit further liver damage. Liver transplantation is a therapeutic option when end-stage liver disease develops.

### CFTR Monitors

Recent advances have been made in the development of a new drug, ivacaftor, that acts to optimize the functioning of the CFTR channel in patients with the G551D mutation by helping to increase the time that the CFTR channel remains open at the cell surface. Clinical trials have shown that patients with the G551D mutation who took the drug demonstrated significant improvement in lung function, risk for pulmonary exacerbation, patient-reported respiratory symptoms, weight, and sweat chloride concentration. This drug has recently received US Food and Drug Administration approval for treatment of patients with the G551D mutation. Research is ongoing for the development of other drugs that potentiate CFTR function and correct the basic genetic defect with the goal that CF patients with all the different genetic mutations will ultimately be able to be treated.

### SUMMARY

The improved survival for patients with CF over the recent decades is likely to continue as more is learned about the pathobiologic characteristics of the disease. The therapeutic options for patients with CF have significantly increased over the past decade. The challenge to the CF practitioner is in choosing the best, most appropriate combination of therapies for the individual patient aimed at maintaining optimal health status. Consultation with the regional CF care center and physicians who are experienced with the nuances of CF care is strongly recommended. More specific therapies aimed at the basic defect in CF are now being developed, with the ultimate goal of delivering a therapy to infants with CF that will provide them with long and healthy lives.

We gratefully acknowledge Dr Terry B. White for her assistance in the final editing and referencing of the chapter.

### WHEN TO REFER

- All children with CF should be referred to a local CF center for ongoing care.

### WHEN TO ADMIT

- The patient who has pulmonary exacerbations characterized by increased cough, sputum production, and a decline in pulmonary function should be admitted. Associated symptoms may include fever, wheezing, dyspnea, malaise, and weight loss. Acute changes in the chest radiograph may or may not be seen. If the patient has normal oxygen saturation on room air, then efforts are made to treat the patient initially with increased pulmonary toilet and oral antibiotics based on the microbiologic characteristics of the most recent sputum culture.
- The patient should be admitted for intravenous antibiotic therapy if response to oral antibiotic therapy is inadequate.
- If the patient is hypoxemic or has major hemoptysis, then the patient should be admitted to the hospital for further management. Hemoptysis of more than 240 mL in 24 hours or more than 100 mL per day over 3 to 7 days is defined as major hemoptysis and should lead to admission. Patients with respiratory distress or with a large pneumothorax ( $>3$  cm between apex and cupola) should be admitted. A patient with a small pneumothorax, who is otherwise clinically stable, may be closely observed as an outpatient depending on the reliability of the patient and family and their ease of access to health care.

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## Chapter 240 DENTAL PROBLEMS

Martha Ann Keels, DDS, PhD; Melinda B. Clark, MD

### BACKGROUND

Oral health is a vital component of overall health, and understanding of the oral-systemic disease connection is increasing. This chapter provides pediatricians and other health care professionals the tools to evaluate, triage, and educate families on common conditions of the oral cavity. Pediatricians are responsible for addressing children's health care needs, including oral health, and arranging care with other qualified professionals as needed. This translates into the ability to diagnose, manage, and triage common oral pathology, appropriately reassure or refer, and provide anticipatory guidance to families regarding dental development, teething, oral hygiene, dietary practices, and caries prevention.

### CONGENITAL ORAL FINDINGS

#### Neonatal Oral Findings

Inclusion cysts are small, white or translucent papules or cysts that develop in utero. These congenital findings are seen in 75% of newborns and resolve spontaneously by 3 months of age. Because inclusion cysts are asymptomatic, there is no need for further evaluation or management other than reassurance. Three types of inclusion cysts can be found in newborns.

1. Epstein's pearls are the most common congenital inclusion cysts, occurring in 75% to 80% of all neonates. They are found along the midline raphe of the hard palate and represent epithelial remnants of



palatal fusion. These cysts resolve spontaneously with no intervention.

2. Bohn's nodules are heterotopic salivary gland remnants located on the buccal or lingual mucosal surface of the alveolar ridge (not the crest) or on the hard palate, away from the raphe.
3. Dental lamina cysts are heterotopic salivary gland remnants located on the crest of the alveolar ridge.

### Ankyloglossia

Tongue-tie (ankyloglossia) is a physical defect that results in limited tongue movement and occurs in 4% to 10% of children. Ankyloglossia ranges from a bulky, short membrane of connective tissue to an essentially immobile tongue caused by excessive fiber anchoring the tongue to the floor of the mouth. This restricted tongue movement can lead to a variety of problems in infants and children, such as inability to latch with breastfeeding, improper speech development, and compromised oral health. A constricted lingual frenum has been correlated with increased incidence of dental caries resulting from inability to remove food from the teeth. Intervention for ankyloglossia varies from observation to surgical release of the frenum. If feeding, speech development, or oral health are compromised, then referral to a dentist, plastic surgeon, or otolaryngologist is indicated to evaluate the need for surgical release of the frenum. The surgical procedure, termed a frenectomy or a frenotomy, can be completed with either blunt scissors, cautery, or laser.

## CONDITIONS RELATED TO TOOTH EMERGENCE

### Natal or Neonatal Teeth

Tooth eruption can occur before birth (natal teeth) or within the first month of life (neonatal teeth). Central mandibular incisors are the most likely to erupt early, and these are most often the primary dentition, not extra teeth. Incidence of natal teeth is approximately 1:2,000 to 1:3,000 live births. It is most commonly an isolated finding, but can be associated with genetic syndromes such as chondroectodermal dysplasia. Extraction may be considered if the teeth are mobile and present an aspiration risk, interfere with breastfeeding, or lead to Riga-Fede disease (ulceration). Otherwise, only observation is indicated.

### Eruption Cyst/Hematoma

An eruption cyst is a dome-shaped soft-tissue lesion overlying the erupting tooth that presents 1 to 3 weeks prior to tooth eruption. As the tooth breaks through, the fluid mixes with blood to become blue or purplish and is referred to as an eruption hematoma. No treatment is recommended, because the cyst will resolve spontaneously when the tooth erupts completely. Reassurance should be provided.

### Teething

A number of studies have looked at teething and associated symptoms and have determined that increased drooling, biting, chewing, sucking, rubbing of the gums and ears, facial rash, crying, decreased appetite, mild

temperature elevation, and poor sleep are all statistically associated with teething. No single symptom occurred in more than 35% of infants, and no symptom occurred more than 20% more often in teething than in non-teething infants. Potentially serious symptoms such as fever ( $>100.4^{\circ}\text{F}$ ) and diarrhea should not be attributed to teething and may require further evaluation to rule out a bacterial source of infection.

The recommended intervention for teething is the use of cold items as an anesthetic for the gums. Items that can be refrigerated include pacifiers, spoons, wet washcloths, and teething rings. Topical teething gels sold over the counter (OTC) are often used for teething, but carry serious risks such as local reactions, seizures with overdose, and methemoglobinemia. They should not be used in children younger than 2 years of age. If necessary, parents should be instructed on proper dosing of OTC analgesic medications such as acetaminophen or ibuprofen.

### Atypical Emergence or Exfoliation

Tooth eruption or emergence tends to occur in a predictable pattern, although the timing can vary considerably. Mandibular central incisors typically emerge first, between 5 and 10 months of age. Delayed emergence of more than 12 months can be caused by oral space issues, pacifier or digit pressure, infection, hypertrophied gingival tissue, endocrine or genetic disorders, or radiation therapy. Space limitation, including impacted teeth or another tooth blocking eruption, is the most common reason for isolated tooth eruption delay. Endocrine disorders, including hypothyroidism, hypoparathyroidism, and hypopituitarism can result in eruption delays. Among genetic disorders, ectodermal dysplasias, Down syndrome, and cleidocranial dysostosis include a component of abnormal tooth emergence. Failure to erupt teeth by 18 months of age warrants referral to a dentist for evaluation and radiographs. Even if the timing is normal, an atypical pattern of eruption can be the first presenting sign of a systemic condition. For example, Langerhans cell histiocytosis can present with premature eruption of the molars before the incisors.

Permanent dentition begins to emerge around age 6 years, resulting in exfoliation or loss of the primary teeth. Timing of this process is affected by gender, ethnicity, and family history. Girls tend to erupt permanent teeth earlier than boys. Familial delays in tooth eruption have been linked to *PTHR1* gene mutations, and black children tend to erupt permanent teeth earlier than their white or Asian counterparts. Of note, 15% to 20% of people fail to develop all 4 third molars (wisdom teeth). In an American study, agenesis of the third molars was more common in white than in black adolescents (16% vs 6%) and slightly more common in females than in males (19% vs 14%). Localized premature tooth loss is most often caused by tooth trauma and root necrosis or severe dental caries. Premature tooth loss affecting many or all teeth can be associated with Langerhan cell histiocytosis, endocrine disorders (hypophosphatasia or diabetes mellitus), immune disorders (disorders of neutrophil function, cyclic neutropenia), and connective tissue disorders (eg, Ehlers-Danlos syndrome). Emergence of the permanent teeth is the stimulus for

exfoliation of the primary teeth (natural tooth loss). Therefore, endocrine disorders (hypothyroidism, hypopituitarism, rickets) and genetic conditions (ectodermal dysplasia, trisomy 21, and cleidocranial dysostosis) that are associated with delayed emergence of permanent teeth will be characterized by delayed exfoliation of the primary teeth.

## COMMON ORAL CONDITIONS IN CHILDHOOD

### Dental Caries

Dental caries, one of the most common chronic childhood diseases of childhood, is reviewed separately in Chapter 40, Oral Health.

### Oral Ulcers

Oral ulcers are fairly common in children. There are 3 basic types of ulcers.

1. Traumatic ulcers typically result from mechanical or thermal injury and are the most common oral ulcers in children. They are usually seen on the buccal mucosa, tongue, lips, or palate. Eating or drinking very hot foods can burn the mucosa; traumatic ulcers result from objects in the mouth, lip biting or tongue biting, abuse, and self-injurious behavior. Traumatic ulcers typically heal quickly, within days of the inciting event.
2. Infectious ulcers are also very common in childhood. The most common infections causing oral ulcers are herpes simplex virus (HSV primary or recurrent) and coxsackievirus infections (herpangina and hand-foot-mouth disease). These conditions are discussed in more detail in Chapter 266, Herpes Infections, and Chapter 248, Enterovirus and Evolving Infections.
3. Aphthous ulcers are best known as “canker sores” and appear as round or oval, yellowish-grey ulcers with surrounding erythematous “halo.” They can be located on any mucous membrane, but are most commonly noted on the buccal mucosa. Etiology of aphthous ulcers is unknown, but they may be infectious, autoimmune, allergic, nutritional, or traumatic in nature. Aphthous ulcers are more common in individuals with inflammatory bowel disease, celiac disease, immunosuppression, cyclic neutropenia, rheumatologic disorders (eg, juvenile rheumatoid arthritis, systemic lupus erythematosus), or nutritional deficiencies ( $B_{12}$ , folate, iron, zinc). Aphthous ulcers present in 3 ways—as minor aphthous ulcers, major aphthous ulcers, and herpetiform ulcers. Minor aphthous ulcers are the most common form, accounting for 80% of cases, and are characterized by small (2–5 mm) lesions that last 5 to 12 days and heal without scarring. Major aphthous ulcers are larger in diameter (up to 1 cm), can take several weeks to heal, and may scar. Herpetiform ulcers are the least common type of aphthous ulcers, accounting for less than 10% of cases. These are very painful, multiple 1- to 2-mm papules, vesicles, or ulcers that are grouped together and can coalesce to form a larger lesion. Treatment for all types of aphthous ulcers is supportive, with bland diet. Topical anesthetic creams, topical steroid creams, or mouth

rinses can be tried, but the benefits are not well established. Recurrence is likely.

### Mucocoele/Ranula

A mucocoele is a translucent or blue pseudocyst resulting from accumulation of mucous behind a traumatized minor salivary gland. Mucocoeles are usually painless, located on the lower lip or buccal mucosa, and range from very small to several centimeters in size. They are usually 1 cm or less in diameter, but can fluctuate in size. Mucocoeles are among the more common pediatric oral lesions, accounting for 11.6% to 24.5% of all pediatric oral biopsies. Mucocoeles generally require no treatment; many resolve spontaneously. If the lesion is large or uncomfortable, excision may be warranted.

Ranulas are a type of mucocoele that result from blockage of a larger salivary duct located on the floor of the mouth, resulting in a unilateral collection of mucous under the tongue. Unlike other mucocoeles, ranulas require marsupialization surgical excision because they are likely to become large and may interfere with swallowing, mastication, speech, or breathing. Mucocoeles commonly recur.

### Angular Cheilitis

Angular cheilitis, also known as angular stomatitis and perleche, is inflammation at the corners of the mouth that manifests as erythema, fissures, erosions, and discomfort. Common triggers include lip licking and sensitivity to a topical compound applied to the lips. Less commonly, persistent angular cheilitis is caused by a nutritional deficiency (riboflavin or iron). Primary or secondary infection with *Staphylococcus* or *Candida* is quite common, so treatment includes topical yeast treatment (Nystatin) and topical antibiotic agents (Mupirocin), with or without low-dose topical steroids. Pediatricians should encourage use of thick emollient application, good oral hygiene, and trigger avoidance.

### Benign Migratory Glossitis

Benign migratory glossitis, more commonly known as “geographic tongue,” results from loss of the filiform papillae on discrete areas of the tongue, making it look smooth, red, and shiny. Areas of depression are most commonly noted on the dorsum and lateral aspects of the tongue, and the location and pattern vary over time, so it seems to “migrate.” There is no effect on ability to taste, but some children report tongue irritation with spicy or acidic foods. Benign migratory glossitis affects about 1% of children; its cause is unknown. The condition is self-limiting, with waxing and waning. No treatment is necessary, as benign migratory glossitis does not cause harm, nor is it associated with any medical issues. Reassurance should be provided. In contrast, complete atrophic glossitis involving the entire tongue can be associated with underlying systemic conditions, especially autoimmune disorders (eg, celiac disease) or deficiencies in nutrients such as iron, folate, or  $B_{12}$ .

### Gingival Hyperplasia

Gingival hyperplasia in children can be hereditary or result from medications, inflammation, or infiltration.

- Hereditary or idiopathic hyperplasia. This is a rare, progressive enlargement of all the gingiva that begins in early childhood.
- Inflammatory. Chronic gingivitis can trigger gingival overgrowth in a general or localized pattern. Inflammatory hyperplasia often resolves when the plaque and gingivitis are adequately controlled.
- Infiltrative. Leukemic cells can infiltrate the gingival tissues and cause gingival hypertrophy. This condition is most often seen in acute monocytic leukemia and is characterized by inflamed, friable gingiva that bleeds easily.
- Drug-induced. Medications can also cause hyperplasia. Common offenders include phenytoin, calcium channel blockers (eg, nifedipine), and cyclosporine. The gingival enlargement is fibrous, and, therefore, neither painful nor very prone to bleeding.

Gingival hyperplasia can interfere with oral hygiene, tooth eruption, and chewing, and can cause gingivitis. Treatment of gingival hyperplasia includes meticulous oral hygiene to minimize inflammation and discontinuing any offending medication. Gingivectomy should be considered if the hyperplasia is severe, especially with hereditary gingival hyperplasia.

### Enamel Defects

Enamel is a protective layer on the visible part of the crown of the tooth. It is the hardest and most highly mineralized substance of the body. The formation of enamel is very sensitive, and disturbances during the tooth development can result in enamel defects of the primary or permanent teeth. Enamel defects can appear as pitted, rough surfaces or as white, yellow, or brownish discoloration of a single tooth or multiple teeth. A tooth with an enamel defect can be considered “weak,” with reduced thickness and poor enamel quality. Teeth with enamel defects are more prone to increased sensitivity, wear, fracture, and increased risk of dental caries. Many risk factors for enamel defects in primary and permanent teeth have been identified in children. Common risk factors include adverse maternal health events during pregnancy (illnesses, nutritional deficiencies, medications), birth difficulties (prematurity, hypoxia), early childhood illnesses (high fever, pneumonia, middle ear infection, viral infections), poor childhood nutrition (diet deficient in calcium, phosphate, or vitamins A, C, or D), and trauma to the mouth or primary teeth before the age of 4 years. Rarely, enamel defects can be inherited and affect all the teeth in both dentitions. This condition is called amelogenesis imperfecta.

Children with enamel defects should be evaluated by a dentist. The aim of treatment is to reduce tooth sensitivity, strengthen teeth, and improve tooth appearance. The type of treatment required will depend on the severity and symptoms of the enamel defect and may include fluoride varnish for sensitivity and strengthening, dental restoration with a tooth-colored resin or crown, or even extraction for severely affected teeth.

### Dental Acid Erosion

In the past decade, dental erosion has become more of a concern in the pediatric population globally. The

prevalence of acid erosion of the dentition among a sample of 11- to 13-year-old children was 41% in the United States and 37% in the United Kingdom. The World Health Organization has adopted Pindborg’s definition of dental erosion as “the progressive irreversible loss of dental hard tissue that is chemically etched away from the tooth surface by extrinsic and/or intrinsic acids by a process that does not involve bacteria; which differentiates it from dental caries process.” Extrinsic causes of tooth erosion include acidic drinks, foods, and candies. Gastric acid is the most common intrinsic cause of dental erosion as a manifestation of gastroesophageal reflux disease or bulimia. The exposure of the tooth structure to an acid source with a pH below 4 will result in erosion. The titratable acidity is the amount of available acid or the erosion potential of the dietary source, reflecting the amount of alkali needed to neutralize an acid. For example, orange juice has a pH of 3.8 and a titratable acidity index of 4.5 reflecting high erosion potential compared to the low erosion potential of sparkling water with a pH of 5.3 and titratable acidity of 0.1. Various teeth and tooth surfaces will be affected by the acidic dietary trigger and by eating behavior. The anterior teeth (incisors) are predominantly affected by frequent consumption of acidic drinks, swishing or mouth holding of acidic drinks, or exposure to the emesis associated with bulimia. The posterior teeth (molars) are affected mainly by mastication of acidic foods as well as by gastric acid exposure from gastroesophageal reflux disease (GERD) and severe cases of bulimia. Treatment of dental acid erosion involves identifying and removing or reducing the acid source. If the enamel loss is causing sensitivity, dental restorative care is indicated.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *A Guide to Children’s Dental Health* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *What Is a Pediatric Dentist?* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)

### Medical Decision Support

- *Pediatric Guide to Oral Health Flip Chart and Reference Guide* (chart), American Academy of Pediatrics ([www2.aap.org/compeds/doch/oralhealth/PediatricGuides.html](http://www2.aap.org/compeds/doch/oralhealth/PediatricGuides.html))
- *Protecting All Children’s Teeth (PACT): A Pediatric Oral Health Training Program* (online course), American Academy of Pediatrics ([www2.aap.org/ORALHEALTH/pact/index-cme.cfm](http://www2.aap.org/ORALHEALTH/pact/index-cme.cfm))

## AAP POLICY

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## Chapter 241 DIABETES MELLITUS

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Peter Tebben, MD

Diabetes mellitus consists of a heterogeneous group of conditions with diverse underlying pathophysiologic factors that result in defects in insulin secretion or action, leading to elevated blood glucose levels. Although altered glucose metabolism is the most prominent abnormality, fatty acid and protein metabolism are also regulated by insulin. Diabetes mellitus is currently classified into 4 types, the 2 most common of which are type 1 and type 2 diabetes (T1D and T2D). T1D is further divided into type 1A, which is immune mediated, and type 1B, which is typically idiopathic. The remaining forms are gestational diabetes and “other” causes of diabetes, such as genetic defects in  $\beta$ -cell function or insulin action, diseases of exocrine pancreas (eg, cystic fibrosis), and drug- or chemical-induced diabetes. Type 1 diabetes refers to conditions that result in an elevated blood glucose level caused by an absolute insulin deficiency, whereas T2D results from progressive insulin secretory defect in the setting of insulin resistance.

### INCIDENCE

The incidence of T1D in the United States has been estimated at approximately 12 per 100,000 person-years for individuals younger than 20 years. Certain ethnic groups such as individuals from Northern European countries have a much higher risk than individuals from most Asian countries. Several authors have documented that the worldwide incidence, including the United States, of T1D has been increasing. The cause of this global increase in T1D is not known.

Historically, T2D contributed to only a fraction of the total number of children diagnosed with the disease, but with obesity as a strong correlate, the incidence of T2D has risen significantly in recent years, especially among certain ethnic groups, such as African Americans, Hispanics, and Native Americans.

### ETIOLOGY

#### Type 1 Diabetes

Type 1 diabetes results from T-cell-mediated destruction of insulin-producing  $\beta$  cells in the pancreatic islets of Langerhans. Although its precise cause is unknown, T1D occurs in genetically susceptible subjects, and the process is likely triggered by one or more environmental agents. Concordance rates for monozygotic twins have ranged from 17% to 50%, significantly higher than concordance rates reported in dizygotic twins or nontwin siblings of individuals with T1D. These rates likely underestimate the lifetime risk for developing diabetes because the patients were only followed for a finite period. Studies using life-table analysis have predicted significantly higher concordance among monozygotic twins.

#### Genetic Factors

Many genes have been implicated in conferring genetic susceptibility to T1D, but the strongest associations have been found with the genes encoding human leukocyte antigen (HLA) molecules on chromosome 6p. Individuals with T1D express the HLA DR3-DQ2/DR4-DQ8 genotype at a significantly higher rate than the general population. Furthermore, a monozygotic twin without diabetes expressing DR3-DQ2/DR4-DQ8 whose twin has diabetes is at significantly higher risk for developing the disease than twin pairs without this genotype. Other HLA molecules seem to offer protection against the development of diabetes. The notion that offspring of fathers with T1D are more likely to develop diabetes than offspring of mothers with T1D has also been suggested. Several other genes and chromosomal regions have been implicated in the development of T1D. These data clearly show that the development of T1D has a genetic component, although genetic susceptibility is not solely responsible.

#### Environmental Factors

Environmental exposures have been implicated in the development of T1D in genetically susceptible individuals. Viral infections have long been considered to play a role, but many of the data are conflicting. However, congenital rubella syndrome has consistently been shown to confer added risk for the development of T1D. A link between childhood immunizations and



several autoimmune disorders, including T1D, has been postulated. This association was explored in a large study from Denmark that included almost 740,000 children and 4.7 million person-years of follow-up and found no association between T1D and immunization status.

### Dietary Factors

Dietary factors such as duration and timing of breast-feeding, introduction of cow's milk, timing of introduction of cereals to the diet, gluten, and nitrate exposure have also been implicated, but definitive data are lacking. Although conclusive evidence does not exist, an association between vitamin D repletion and protection from development of T1D has been suggested. Too little information is available regarding dietary antigen exposure to make definitive recommendations regarding introduction of certain foods to infants and children in an attempt to prevent T1D.

### Antibodies

The autoimmune nature of T1D is supported by the high rate of detectable antibodies against pancreatic islet cells in patients recently diagnosed with T1D. These antibodies are usually present long before the clinical onset of disease. Antibodies against islet cell antigens, glutamic acid decarboxylase, and insulin have all been used to predict progression to diabetes in high-risk individuals with HLA susceptibility or a family history of diabetes. Whether these antibodies are causal or simply a marker of disease is unclear. Although routine clinical use of antibody measurement for the prediction of development of T1D is controversial, it may be of use in initial diagnosis of T1D. T1D is also associated with other autoimmune conditions such as celiac disease, thyroid disease, adrenal insufficiency, and polyglandular autoimmune failure.

### Type 2 Diabetes

In contrast to T1D, T2D is caused by a relative insulin deficiency, peripheral resistance to its action, or both. The increase in childhood T2D has paralleled the marked rise in childhood obesity, which has prompted many communities, public health organizations, and medical societies to initiate programs to treat and prevent childhood obesity. The American Academy of Pediatrics (AAP) has published a policy statement regarding the prevention of pediatric obesity. The AAP offers practical guidelines for early identification and intervention in high-risk children. Several studies have demonstrated that most children or adolescents with T2D are obese, have clinical evidence of insulin resistance (acanthosis nigricans), or have a significant family history of T2D. These characteristics should prompt the primary care physician to screen a child for diabetes. The American Diabetes Association (ADA) has published a consensus statement regarding T2D in children and adolescents, including recommendations for screening individuals from high-risk populations, which is also endorsed by the AAP (Box 241-1). The ADA recommendations focus on overweight and obese children because most cases occur in this patient population. Additionally, identification of at-risk

#### BOX 241-1 Criteria for Screening High-Risk Children for Diabetes

Overweight (body mass index >85th percentile for age and sex), **AND** any 2 risk factors:

- Family history of type 2 diabetes in a first- or second-degree relative
- High-risk race or ethnicity (Native American, African American, Latino, Asian American, and Pacific Islander)
- Signs of insulin resistance or associated conditions:
  - Acanthosis nigricans
  - Hypertension
  - Dyslipidemia
  - Polycystic ovarian syndrome
  - Small for gestational age
- Maternal history of diabetes or gestational diabetes

Age to initiate screening:

- 10 years, **OR**
- Onset of puberty if younger than 10 years

Frequency: every 3 years

Preferred screening test: plasma glucose after an 8-hour fast

Adapted from American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37(Suppl 1):S14–80. Copyright © 2014 American Diabetes Association. Reprinted with permission.

#### BOX 241-2 Criteria for the Diagnosis of Diabetes

- Symptoms of diabetes (polyuria, polydipsia, and unexplained weight loss) and a casual<sup>a</sup> plasma glucose of 200 mg/dL or greater, **OR**
- Fasting plasma glucose of 126 mg/dL or greater (fasting for at least 8 hours), **OR**
- Plasma glucose of 200 mg/dL or greater 2 hours after an oral glucose challenge. Glucose load should contain 75 g of glucose for adults or 1.75 g/kg in children<sup>b</sup> (maximal dose of 75 g), **OR**
- HbA1c of 6.5% or more

<sup>a</sup>Casual: any time of day without regard to time of last meal.

<sup>b</sup>A dose of 1.75 g/kg of glucose has been suggested when performing an oral glucose tolerance test in children, but this dose is less well established than the 75-g dose used in adults.

Adapted from American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37(Suppl 1):S14–80. Copyright © 2014 American Diabetes Association. Reprinted with permission.

children requires only the calculation of the body mass index, which can be performed quickly and inexpensively. However, these recommendations are based on few data, and clinical judgment may need to supersede strict adherence to these guidelines. Measurement of a fasting plasma glucose level is the suggested screening tool in children at high risk for developing diabetes because it is simple to perform and inexpensive, but other methods may be appropriate in establishing the diagnosis (Box 241-2).

**BOX 241-3 Classification of Disorders of Glycemia**

- |  |  |
|--|--|
| <ul style="list-style-type: none"> <li>A. Type 1 diabetes               <ul style="list-style-type: none"> <li>1. <math>\beta</math>-Cell destruction, leading to absolute insulin deficiency</li> <li>2. Type 1A</li> <li>3. Type 1B</li> </ul> </li> <li>B. Type 2 diabetes               <ul style="list-style-type: none"> <li>1. Relative insulin deficiency with or without insulin deficiency</li> </ul> </li> <li>C. Other types of diabetes/hyperglycemia               <ul style="list-style-type: none"> <li>1. Genetic defects of <math>\beta</math>-cell function</li> <li>2. Maturity-onset diabetes of the young (MODY)                   <ul style="list-style-type: none"> <li>a. Chromosome 12, HNF-1 <math>\alpha</math> (MODY3)</li> <li>b. Chromosome 7, glucokinase (MODY2)</li> <li>c. Chromosome 20, HNF-4 <math>\alpha</math> (MODY1)</li> <li>d. Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)</li> <li>e. Chromosome 17, HNF-1 <math>\beta</math> (MODY5)</li> <li>f. Chromosome 2, neuro D1 (MODY6)</li> <li>g. Mitochondrial DNA</li> <li>h. Others</li> </ul> </li> <li>3. Genetic defects in insulin action                   <ul style="list-style-type: none"> <li>a. Type A insulin resistance</li> <li>b. Leprechaunism</li> <li>c. Rabson-Mendenhall syndrome</li> <li>d. Others</li> </ul> </li> <li>4. Diseases of the exocrine pancreas                   <ul style="list-style-type: none"> <li>a. Pancreatitis</li> <li>b. Trauma/pancreatectomy</li> <li>c. Neoplasia</li> <li>d. Cystic fibrosis</li> </ul> </li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>e. Hemochromatosis</li> <li>f. Others</li> <li>5. Endocrinopathies               <ul style="list-style-type: none"> <li>a. Acromegaly</li> <li>b. Cushing syndrome</li> <li>c. Glucagonoma</li> <li>d. Pheochromocytoma</li> <li>e. Hyperthyroidism</li> <li>f. Somatostatinoma</li> <li>g. Aldosteronoma</li> <li>h. Others</li> </ul> </li> <li>6. Drug or chemical induced               <ul style="list-style-type: none"> <li>a. Vacor</li> <li>b. Pentamidine</li> <li>c. Nicotinic acid</li> <li>d. Glucocorticoids</li> <li>e. Thyroid hormone</li> <li>f. Diazoxide</li> <li>g. Thiazides</li> <li>h. Others</li> </ul> </li> <li>7. Infections               <ul style="list-style-type: none"> <li>a. Congenital rubella</li> <li>b. Cytomegalovirus</li> <li>c. Others</li> </ul> </li> <li>8. Uncommon forms of immune-mediated diabetes               <ul style="list-style-type: none"> <li>a. Stiff-man syndrome</li> <li>b. Anti-insulin receptor antibodies</li> <li>c. Others</li> </ul> </li> <li>D. Gestational diabetes mellitus</li> </ul> |
|--|--|

Adapted from American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2012;35(Suppl 1):S64–S71. Copyright © 2012 American Diabetes Association. Reprinted with permission.

**Maturity-Onset Diabetes of the Young**

Monogenic forms of diabetes include a group of rare disorders known as maturity-onset diabetes of the young (MODY) (Box 241-3). These disorders likely represent between 2% and 5% of all cases of diabetes. The clinical course can range from mild to progressive disease with the development of microvascular complications. MODY is often misclassified as T1D or T2D and should be suspected if there is a family history suggestive of autosomal-dominant inheritance, especially if diabetes develops at a young age in a thin individual and there is a lack of autoimmunity based on antibody testing. Because the clinical course and treatment vary considerably among the different forms of MODY, the specific type of MODY should be characterized if the diagnosis is made or suspected. An in-depth discussion of these infrequent forms of diabetes is beyond the scope of this chapter; however, recent reviews can provide additional information.

**DIAGNOSIS**

The ADA has outlined several ways to diagnose diabetes based on a patient's symptoms and plasma glucose concentration (see Box 241-2). The diagnosis can be established in a child who has symptoms consistent with diabetes (polyuria, polydipsia, unexplained weight loss) and a casual plasma glucose level of 200 mg/dL or greater. The ADA has defined *casual* as any time of day without regard to time since the last meal. T1D is usually diagnosed by these criteria and has a relatively acute-subacute onset of symptoms (days to weeks). T2D is more insidious than T1D in onset, and patients are typically overweight and may have signs of insulin resistance, including acanthosis nigricans and elevated lipid levels. Whereas most patients with T1D are symptomatic at the time of diagnosis, individuals with T2D can be asymptomatic, and the diagnosis may often be the result of screening. This fact highlights the need for identification of high-risk individuals in an effort to prevent or postpone diabetes or intervene early in the disease.

A plasma glucose level of 126 mg/dL or greater after an 8-hour fast will establish the diagnosis and is a simple test to perform in the outpatient setting. Diabetes can also be diagnosed using an oral glucose tolerance test, with a cutoff of 200 mg/dL 2 hours after the glucose load being diagnostic of diabetes. This method is more costly and labor intensive but may identify some individuals with diabetes who have a fasting plasma glucose level less than 126 mg/dL.

## DIFFERENTIAL DIAGNOSIS

Hyperglycemia has many causes other than diabetes that should be considered when an elevated plasma glucose concentration is found (see Box 241-3). A thorough history, physical examination, and review of the patient's medications are often sufficient to determine the cause of hyperglycemia. The precise origin of hyperglycemia should be sought for each child to tailor therapy specific to the underlying pathophysiologic condition.

It can be difficult to differentiate between T1D and T2D in some cases. Although insulin therapy may not always be necessary for children with T2D, it is a safe and effective choice if it is not initially clear whether the patient has T1D or T2D. If excess glucocorticoids or other medications cause diabetes, dose reduction or elimination of the drug (if possible) may be all that is required.

## EVALUATION

### Pertinent History

Hyperglycemia from any cause can lead to symptoms related to an osmotic diuresis. Polyuria and polydipsia occur as a result of the loss of glucose in the urine as the plasma concentration exceeds the renal threshold for glucose reabsorption ( $\approx 180$  mg/dL), although glucose may be seen in the urine of some normoglycemic individuals. Glycosuria alone cannot be used for the diagnosis of diabetes because several other conditions, including renal injury, lead to glycosuria. Because of this glycosuria, the child with T1D or T2D loses calories, which manifests as weight loss in the face of an increased appetite. Depending on the timeliness of diagnosis of diabetes, particularly T1D, symptoms of nausea and abdominal pain may develop from metabolic acidosis caused by ketone body buildup from use of adipose tissue as fuel.

Although an infrequent occurrence in T2D, diabetic ketoacidosis (DKA) has been reported, and the presence of ketosis cannot always reliably distinguish between T1D and T2D. If severe hyperglycemia and metabolic acidosis are left uncorrected, neurologic sequelae, including seizures and coma, may occur. Recognizing the early symptoms of diabetes may help prevent severe DKA and potentially fatal outcomes. T1D can occur at any age, including in the neonatal period. With the rise in childhood obesity, T2D is occurring in younger children, although children who develop T2D most commonly do so during puberty, a period of relative insulin resistance.

### Physical Examination

No pathognomonic physical findings are associated with T1D or T2D. Particularly in the case of T1D, because it has an acute-subacute onset, physical examination findings such as signs of dehydration, weight loss, or tachycardia may be present commensurate with the duration and severity of hyperglycemia and metabolic acidosis. If moderate or severe ketoacidosis is present, tachypnea and a characteristic *fruity* odor to the breath caused by the ketosis may be noted. Altered mental status or seizures may occur in severe DKA.

The typical patient with T2D will often have polyuria and polydipsia. Weight loss may also be apparent, but patients are invariably obese at the time of diagnosis. Many children with T2D have acanthosis nigricans that is a result of their insulin resistance and may be hypertensive.

### Laboratory Studies

In the appropriate clinical setting, a few basic laboratory studies are usually sufficient to differentiate between T1D and T2D. Irrespective of the type, diabetes can be diagnosed using the criteria adopted by the ADA (see Box 241-2). Hyperglycemia and glycosuria are the predominant features in both conditions. Significantly elevated blood and urine ketone levels are traditionally associated with T1D but are occasionally present in patients with T2D. Additional laboratory abnormalities associated with DKA are discussed in Chapter 354, Diabetic Ketoacidosis. Insulin and C-peptide concentrations are generally low in patients with established T1D compared with the elevated concentrations in patients with T2D. Severe DKA is seen less frequently in T2D.

Although certain HLA haplotypes are associated with an elevated risk for T1D, they play no role in the diagnosis. Most children with T1D have antibodies directed against insulin or pancreatic islet cell antigens at the time of diagnosis. Although these antibodies can be elevated in children who may not develop disease for many years or never develop diabetes, they can be useful in making or confirming the diagnosis of T1D.

As pancreatic  $\beta$ -cell function declines and endogenous insulin secretion diminishes, C-peptide concentrations fall. Plasma C-peptide concentrations that are very low or undetectable in the face of hyperglycemia are consistent with the diagnosis of T1D. However, C-peptide concentrations are often not helpful at the time of diagnosis because endogenous insulin (and thus C-peptide) production has not completely failed. Low C-peptide concentrations can be seen in MODY or T2D with glucose toxicity, which may make it less helpful at time of diagnosis.

## MANAGEMENT

### Type 1 Diabetes

The clinical management of T1D requires an integrated multidisciplinary team consisting of physicians, nurses, diabetes educators, dietitians, social workers,

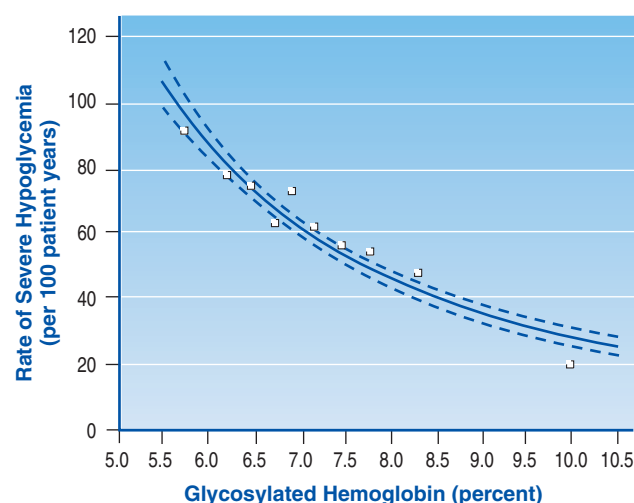
and psychologists. Patients and families must be adequately educated and supported to safely achieve as near euglycemia as possible because of the unequivocal evidence that tight glucose control prevents complications of diabetes. Because a sizable portion of a child's day is spent in school, close communication with school or child care personnel is essential for optimal diabetes management. Without adequate education, safe and successful diabetes management is difficult to attain. The education should be tailored to provide developmentally appropriate participation by the child. Teenagers should be able to assume more responsibility for their care than toddlers. Although improved glycemic control improves outcomes with regard to microvascular and macrovascular complications, these benefits do not come without risk. The main risk posed in achieving near euglycemia is increased frequency and severity of hypoglycemia. In the Diabetes Control and Complications Trial (DCCT), the rate of severe hypoglycemia in the intensive insulin group was 62 events per 100 patient-years compared with 19 events per 100 patient-years in the conventional group. Most long-term trials showing improvement in chronic complication rates have been performed in adults. However, a part of the Epidemiology of Diabetes Interventions and Complications (EDIC) trial evaluated the adolescent patients who were initially enrolled in the DCCT (13 to 17 years of age at enrollment). At the end of the DCCT, the intensive treatment group had significantly lower HbA1c values, but this effect was lost during the 4-year EDIC follow-up of this cohort. Despite the patients having similar control of their diabetes by the end of the study, those previously treated intensively had a marked reduction in the progression of diabetic retinopathy, which suggests that tight glycemic control is important even in this adolescent population.

Several models of successful diabetes education programs exist, but all are centered on the goal of achieving as close to euglycemia as possible while minimizing adverse events, primarily hypoglycemia. The ADA has proposed age-adjusted guidelines regarding target blood glucose values and targets for HbA1c (Table 241-1). Less tight control is recommended for younger children in whom the risks for hypoglycemia may be greater and the advantages of very tight control have not been proved. Postprandial

glucose targets are widely used in the management of diabetes during pregnancy. However, these targets are not commonly used outside pregnancy because their value has not been studied rigorously in children. These goals are suggested, and individualized goals may be necessary. Lower HbA1c values may be safely obtained in select patients in whom the risk for severe hypoglycemia is deemed low. However, the lower the HbA1c level, the higher the risk for severe hypoglycemia (Figure 241-1).

### Type 2 Diabetes

The treatment options available for patients with T2D are more diverse. Although many effective medications with a variety of mechanisms of action are available, few are indicated for the treatment of T2D in children. The type of therapy must be tailored to fit the clinical situation of the patient. If diabetes is discovered in an asymptomatic patient with a normal or near-normal HbA1c level, lifestyle modification,



**Figure 241-1** Increased risk for severe hypoglycemia with lower HbA1c. (From Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329(14):977-986. Copyright © 1993 Massachusetts Medical Society. All rights reserved.)

**Table 241-1**

**American Diabetes Association Guidelines for Glycemic Control in Children and Adolescents**

AGE (YR)	PLASMA GLUCOSE (MG/DL)		HBA1c (%)
	PREMEAL	BEDTIME OR OVERNIGHT	
0-6	100-180	110-200	8.5
6-12	90-180	100-180	8.0
13-19	90-130	90-150	7.5
Adults	90-130	—	7

Adapted from American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care.* 2014;(Suppl 1):S14-80. Copyright © 2014 American Diabetes Association. Reprinted with permission.



including medical nutrition therapy, may be the most appropriate treatment. Weight loss and exercise can significantly improve insulin sensitivity in the setting of T2D. These approaches may be adequate for maintenance of glycemic goals in individuals willing to participate regularly in physical activity and modify their eating behaviors. The Diabetes Prevention Program found that lifestyle modification intervention reduced the development of T2D in adults by 58% over the 2.8 years of follow-up. In the recently completed Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) trial to maintain glycemic control in youths with T2D, metformin therapy alone achieved durable glycemic control in only about half of the adolescents enrolled.

In addition to lifestyle changes, metformin should be considered first-line pharmacologic therapy for children with T2D. However, when a patient is experiencing symptomatic hyperglycemia and has a significantly elevated HbA1c (>8% to 9%), insulin therapy is usually required. In many instances, children with T2D are able to improve their glycemic control with less intensive programs than are needed for patients with T1D; once- or twice-daily, intermediate- or long-acting insulin may be sufficient. Lifestyle intervention and medical nutrition therapy remain the cornerstone of treatment.

The United Kingdom Prospective Diabetes Study (UKPDS) showed that improvements in HbA1c levels in adults with T2D improved outcomes with respect to microvascular complications, highlighting that good glycemic management is equally important for T2D as for T1D. The only oral agent approved for use in children is metformin. Metformin is approved for children 10 years of age and older with T2D. It has the advantage of not inducing hypoglycemia when used as monotherapy and is also associated with weight stabilization or mild weight loss. The major side effect of metformin is gastrointestinal disturbance, which can be largely prevented by slowly titrating the dose. It should not be used in patients with significant liver disease or renal impairment.

## INSULIN

### Insulin Programs

With the availability of multiple forms of insulin (Table 241-2), many options exist for designing an insulin regimen for each patient. All patients will need to have an individualized plan with respect to the type and dose of insulin, timing of injections, and appropriate frequency of home glucose monitoring, depending on their daily routine. No single program will be acceptable for every patient. As patient needs and technology change, programs should be updated to maintain glycemic goals. Typical doses of insulin in children range from 0.5 to 1 unit of insulin per kilogram per day. However, during puberty, because of insulin resistance, children usually require higher insulin doses to achieve the same control.

The 3 most commonly used insulin programs are split-mixed, multiple daily injection (MDI), and continuous subcutaneous insulin injection (CSII). Each program should be designed to mimic human physiology such that even in the fasting state, insulin is normally produced and secreted by the pancreas to maintain euglycemia (basal insulin). During a meal, additional insulin is secreted from the pancreas as the blood glucose level begins to rise when carbohydrate is absorbed from the intestinal mucosa (bolus insulin). Therefore, for patients with T1D, a basal bolus regimen of insulin should be followed whereby intermediate- or long-acting insulin is used as the basal insulin, and a short-acting insulin bolus is used to control the postmeal glucose rise (Figure 241-2).

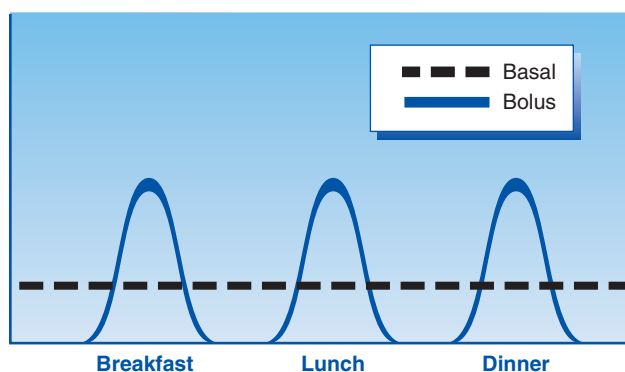
### Split-Mixed Program

A split-mixed program can be used in younger patients in whom fewer injections may be desirable. A short-acting and an intermediate-acting insulin are mixed and given as a single injection before breakfast and again before the evening meal. Considerably higher doses are generally required in the morning compared with the evening. A typical ratio would be two-thirds to three-fourths of the total daily dose

**Table 241-2** Onset, Peak, and Duration of Action of Currently Available Insulin

	ONSET	PEAK	DURATION
<b>SHORT ACTING</b>			
Regular	30 min	2–4 hr	4–6 hr
Lispro	<15 min	1 hr	3–4 hr
Aspart	<15 min	1 hr	3–4 hr
Glulisine	<15 min	1 hr	3–4 hr
<b>INTERMEDIATE ACTING</b>			
NPH	2–4 hr	4–6 hr	10–16 hr
Lente	3–4 hr	6–10 hr	10–20 hr
<b>LONG ACTING</b>			
Glargine	2–3 hr	None	≥24 hr
Detemir	1–2 hr	3–9 hr <sup>a</sup>	6–23 hr <sup>a</sup>

<sup>a</sup>Higher doses result in delayed peak and longer duration of action.



**Figure 241-2** Bolus insulin is used to maintain blood glucose in the goal range after a meal. Basal insulin is used to maintain blood glucose in the goal range between meals and overnight.

given in the morning and the remainder in the evening. Approximately two-thirds of the morning dose is intermediate-acting insulin, and the rest is short acting. Equal amounts of intermediate- and short-acting insulin are given with the evening meal. A snack at bedtime can prevent nighttime hypoglycemia because the intermediate-acting insulin can peak in the early morning hours. Although many patients like this program because only 2 shots are required daily, achieving adequate glycemic goals is sometimes not possible. The regimen is acceptable for young patients in whom the frequency of injections is ideally kept to a minimum and glycemic targets are also not as stringent as in adolescents and adults. A split-mixed program also requires patients to be on a fixed diet with respect to timing and nutrient content at each meal in an attempt to match consistently the insulin dose with the time and amount of food eaten. Because of these limitations, patients are often changed to or started on a more intensive insulin program (MDI or CSII).

### Multiple Daily Injection Program

The MDI program consists of intermediate- or long-acting insulin as the basal insulin and short-acting insulin as a bolus with each meal. In contrast to a split-mixed program, MDI requires 3 or 4 (or more) injections each day. This program offers more flexibility with regard to timing and content of meals than split-mixed programs. Basal insulin constitutes approximately one-half of the total daily dose and is usually given in the evening. The amount of short-acting insulin given with each meal will depend on the amount of carbohydrate consumed at that meal. If the patient has been prescribed an exchange diet with a fixed amount of carbohydrate for each meal, then the dose of insulin will be the same from day to day. However, many patients will choose to vary the amount of carbohydrate at each meal within an overall meal plan and will adjust their insulin according to the amount of carbohydrate consumed. This regimen also employs a correction dose of short-acting insulin if the premeal glucose is outside the target range.

### Continuous Subcutaneous Insulin Injection Program

Insulin pumps have improved significantly since they were first introduced. The initial pumps were large and heavy, with few safety features. Today's pumps are considerably smaller and can be concealed under a person's clothing. A cartridge filled with short-acting insulin serves as both the basal and bolus insulin. Multiple basal rates can be programmed for patients whose basal insulin requirements are not constant throughout the day. This feature is not available with a split-mixed or MDI program. The insulin is delivered through tubing that is connected to a flexible plastic cannula inserted subcutaneously. The tubing and cannula are changed every 2 to 3 days, significantly reducing the number of injections required. Many, but not all, studies suggest there may be a slight improvement in HbA1c in patients treated with CSII compared with MDI. Doyle and colleagues performed a randomized, prospective trial in children comparing CSII (aspart) to MDI (glargine and aspart). These authors found a significant reduction in HbA1c at the end of 16 weeks in the CSII group compared with the MDI group (7.2% vs 8.1%, respectively). In the recently completed longest follow-up study of children treated with insulin pumps, with mean duration of follow-up of 3.5 years, insulin pump therapy was associated with a sustained improvement in glycemic control and with reductions of severe hypoglycemia and hospitalization for DKA compared with a matched cohort using injections.

Current insulin pumps contain numerous safety features that minimize the previous concerns of malfunction seen with earlier-generation pumps. In addition, newer pump technology has begun to combine CSII with continuous glucose monitoring. No long-term data are available to suggest that microvascular or macrovascular complications are reduced with CSII compared with MDI. The goals of therapy should be the same despite the insulin program used (see Table 241-1).

### Monitoring and Adjusting

Appropriate insulin dosing cannot be accomplished without adequate blood glucose monitoring because there is a strong correlation between frequency of monitoring and glycemic control. The glucose values must be recorded in a log and reviewed on a regular basis to determine whether insulin doses need to be adjusted. The data from many home glucose meters and insulin pumps can be transferred to a computer to assist in tracking glycemic control. For patients with T1D and some patients with T2D treated with insulin, blood glucose concentrations should be monitored before meals, at bedtime, and occasionally at night. For individuals with T2D treated with lifestyle modification or oral agents, less frequent monitoring is required. Additional glucose determinations may be needed during illness or exercise, or with symptoms of hyperglycemia or hypoglycemia. Many good home glucose monitors are available. All of these monitors should be checked periodically for accuracy, and patients should receive training on proper technique.

Adjusting insulin doses is necessary to maintain good glycemic control. The glucose log serves as a guide to making appropriate changes. Because many variables exist that cannot be accounted for, patients should be informed that their blood glucose concentration will not always fall in the normal range. For some people, this circumstance can be discouraging and lead to improper insulin adjustments. For others, lack of education or fear of hypoglycemia leads to improper dose adjusting.

When discussing insulin doses in the context of hypoglycemia or hyperglycemia, physicians must be clear about the difference between insulin adjustments and corrections. Insulin doses are adjusted based on patterns of blood glucose concentrations recorded in the log. The purpose of an adjustment is to prevent future abnormal glucose levels. Physicians should commonly ask patients to look for a trend of hyperglycemia over at least several days before making an adjustment. For example, if a patient consistently has glucose values before their evening meal that are higher than the goal range, an increase in the short-acting insulin before the noon meal would need to be made.

Because patients will often have a glucose concentration fall outside their goal range, corrections are used to rectify this situation. A correction is used to address a glucose concentration that is currently abnormal. For example, if a patient has a blood glucose level that is below the goal range before breakfast, then insulin would be subtracted from their morning bolus dose of short-acting insulin. If the glucose is above the goal range, then correction insulin may be added to the bolus dose of short-acting insulin at that meal to correct the hyperglycemia. The correction is used to remediate the abnormal glucose, whereas the bolus dose of short-acting insulin is used to account for the food that will be eaten at a meal.

### Meal Plan

One of the major determinants of blood glucose concentration is carbohydrate ingestion. Matching the amount of food intake with the appropriate amount of insulin requires knowledge of the onset, peak, and duration of action of the various types of insulin available (see Table 241-2).

Many meal plans have been used in the care of patients with diabetes to optimize glycemic control. Although a particular diabetes program may advocate one meal plan over another, comparative trials showing that one is superior to another are lacking. As children grow and vary their activity levels, caloric requirements can change significantly. Advice from a dietitian experienced in the management of children with diabetes is necessary for the implementation of any successful diabetes program. Commonly used meal plans include a consistent carbohydrate or exchange diet and carbohydrate counting. These plans require specific education to ensure that patients are able to assess the nutrient content of the foods they eat and how this factor affects the management of their disease.

A consistent carbohydrate or exchange diet requires a patient to eat a consistent amount of nutrients

at each meal from day to day. For example, a patient may be prescribed 45 g of carbohydrate for breakfast, 60 g for lunch, and 60 g for dinner. The patient would be expected to eat according to this pattern each day. The amount of fat and protein may also be prescribed for each meal. Foods are categorized according to nutrient content, and this list is used to create a meal. Foods with equivalent nutrient content can be *exchanged* for each other to introduce variety in the diet. Snacks are usually incorporated into this diet depending on the individual patient's needs and preferences. The advantage of this diet is that nutrient intake is consistent, allowing insulin dosing to also be consistent. This diet can be used for patients on split-mixed, MDI, or CSII programs.

Carbohydrate counting is a more complex but increasingly popular option. This diet would not be appropriate for patients on a split-mixed insulin program because nutrient intake may vary substantially from meal to meal and day to day. Insulin doses in a split-mixed program cannot easily be adjusted to account for the dietary variability of carbohydrate counting. However, this diet can be used for patients on an MDI or CSII insulin regimen. For this meal plan, patients must also be familiar with the carbohydrate content of each food they eat. For each unit of carbohydrate taken, a certain amount of insulin must be given to maintain euglycemia. A typical ratio may be 1 unit of short-acting insulin for each 15 g of carbohydrate eaten. This ratio is adjusted for each patient and may even vary based on time of day for a given individual. Carbohydrate counting has the advantage of being able to vary the amount of food at a meal according to how much the patient desires to eat. Because patients are able to take more insulin to maintain glycemic control while overeating, carbohydrate counting must be a part of an overall meal plan so that overeating does not lead to obesity or contribute to hyperlipidemia. As long as healthy, well-balanced eating is maintained, carbohydrate counting offers an alternative to the exchange diet, with more flexibility in the timing and content of each meal. Carbohydrate counting requires specific education and a motivated patient and family to be implemented correctly.

### Exercise

Exercise can be performed safely, and children should not be discouraged from participating in sports simply because they have diabetes. Attention to the effects of activity on glucose levels can assist in preventing hypoglycemia during or after exercise. Because exercise may alter the absorption of subcutaneous insulin and can enhance insulin sensitivity, hypoglycemia may occur if changes are not made in the amount of food eaten or insulin taken. Two methods have been developed for preventing hypoglycemia during planned physical activity. The dose of short-acting insulin given at the previous meal might be reduced, or a snack can be given just before or during the activity. If the activity is not planned, then a snack will be the only option. The blood glucose level should be checked before and again after exercise to determine the effect of the activity on glucose concentrations. If the activity

is prolonged (>45 to 60 minutes), the blood glucose level should also be checked periodically during the activity. Only by documenting the effect of exercise on an individual's glucose level can appropriate decisions be made to prevent hypoglycemia. Checking a nighttime blood glucose level is advised when prolonged activity has taken place, especially in the evening. The effect of exercise may be sustained and lead to delayed hypoglycemia.

### Illness

Parents and patients need to be aware that illness can have a notable effect on blood glucose values. Hypoglycemia or hyperglycemia may result, depending on the severity of the illness and the amount of food eaten. A common error made is the omission of insulin injections because the child is not eating. Regardless of food intake, insulin is necessary in health or illness. Although the dose may change, some insulin should be given even if the child is not able to eat. Some practical guidelines can assist in appropriate care during illness:

1. Never completely omit insulin. Insulin requirements may increase.
2. Monitor and record blood glucose concentrations every 2 to 4 hours.
3. Monitor urine ketone concentrations frequently, even if the blood glucose level is not significantly elevated (>250 mg/dL). Some patients with T1D can develop ketosis in the absence of hyperglycemia when ill.
4. Encourage adequate hydration.

By following these simple guidelines, most children with minor illnesses can avoid hospitalization and emergency department visits. They will need to be seen if they have persistent moderate or large urine ketone levels, are unable to treat hypoglycemia effectively, or become significantly dehydrated.

## COMPLICATIONS

Before the discovery of insulin, T1D was a fatal disease. Progressive metabolic abnormalities, including ketoacidosis, would eventually lead to death. With the availability of insulin for clinical use beginning in the early 1920s, patients were able to survive the more immediate threat of severe acidosis. Initial goals of therapy were to prevent symptoms of hyperglycemia and ketoacidosis. With the initiation of insulin therapy, hypoglycemia and the chronic complications of diabetes became apparent.

### Microvascular Complications

The DCCT was a pivotal study in understanding the importance of maintaining euglycemia, revealing that patients with T1D who received intensive insulin therapy had significantly fewer microvascular complications. Development or progression of retinopathy was reduced by 63%, and the need for laser therapy was reduced by 51%. The development of albuminuria (>300 mg/day) was reduced by 54% and clinical neuropathy by 60%. The population enrolled was relatively young at the beginning of the study (mean age 27 years) and did not show a statistically significant decline in macrovascular events. The EDIC trial was

an extension of the original DCCT cohort. After 17 years of follow-up from initial randomization, more than 90% of the patients were assessed for macrovascular disease. The EDIC trial found at 17-year follow-up that patients who had previously been treated with intensive insulin therapy had a significantly lower number of macrovascular events, including acute myocardial infarction and stroke. This instance was the first time a benefit in the reduction of macrovascular disease had been reported in patients with T1D as a result of intensive insulin therapy.

The reduction in microvascular complications has also been demonstrated for patients with T2D. Undoubtedly, diabetes (type 1 or type 2) greatly increases the risk for blindness, chronic kidney disease, neuropathy, cardiovascular disease, and stroke. The evidence is clear that these risks can be attenuated in adolescents and adults treated with intensive diabetes management. Merely treating to avoid symptoms of hyperglycemia is not acceptable. Data regarding the prevention of chronic complications of diabetes in younger children and infants with intensive glucose management are not available.

### Hypoglycemia

Hypoglycemia is a common complication of intensive diabetes management. In addition to the frequency of hypoglycemia, the severity of hypoglycemia should be assessed. Mild hypoglycemia is the result of the adrenergic response to low blood glucose levels. Severe hypoglycemia is defined as an episode requiring treatment. With severe hypoglycemia, the patient has neurologic symptoms, which can include confusion or loss of consciousness. The DCCT clearly showed that the incidence of severe hypoglycemia markedly increased with lowering of the HbA<sub>1c</sub> level (see Figure 241-1).

When a child experiences symptoms of hypoglycemia, the blood glucose level should be checked to document that the symptoms are caused by a low blood glucose level. Some symptoms of hypoglycemia are nonspecific, and unnecessary treatment should be avoided. If hypoglycemia is mild or moderate, generally 10 to 15 g of carbohydrate will correct the situation. The glucose level should be rechecked in 15 to 20 minutes to be certain the hypoglycemia has resolved. Glucose tablets and gels are available and easy to carry. Some form of carbohydrate should always be available to the patient for the treatment of hypoglycemia.

In an unconscious child, severe hypoglycemia may be treated with glucagon or intravenous glucose. Training on the proper use of glucagon should be provided to individuals caring for the child, such as parents, school nurses, older siblings, and others. Glucagon is reserved for patients with severe hypoglycemia who are not able to ingest carbohydrate. Glucagon effectively raises blood glucose by stimulating glucose release from the liver. However, this response is relatively short lived, and as soon as practical, the child should eat (although the nausea that frequently accompanies glucagon administration makes this requirement more complicated). After an episode of hypoglycemia is successfully treated, a cause of the hypoglycemia should be considered. If no cause is readily apparent, then an adjustment in the



insulin dose should be made the next day to avoid additional hypoglycemia. This advice is in contrast to monitoring glucose trends before making adjustments to prevent hyperglycemia. One episode of unexplained hypoglycemia should prompt an insulin adjustment.

Less tight glycemic control should be considered for patients with frequent severe hypoglycemia because of the possibility of long-term neurologic consequences. Children younger than 5 or 6 years of age at the time of diagnosis appear to be at particularly high risk for experiencing frequent hypoglycemia and cognitive impairment.

### Other Considerations

The successful management of diabetes is complex and requires a committed team of health care providers and significant social support for the child. Although the focus of treatment is centered on safely achieving glycemic goals in an attempt to avoid complications, these complications cannot be prevented in all patients. Screening for chronic complications must be performed to intervene early to reverse or slow disease progression. Screening for diabetic retinopathy is recommended for all individuals with diabetes. Developing retinopathy within the first 3 years of diagnosis is unusual for a child, especially if the child is younger than 10 years. Ophthalmologic evaluation for children with T1D should start at age 10 years in those who have had T1D between 3 and 5 years, with annual follow-up thereafter.

Diabetic nephropathy is a leading cause of chronic kidney disease and need for dialysis. Similar to retinopathy, diabetic nephropathy is uncommon in the young or newly diagnosed patient with T1D, and screening should start at age 10 years in children who have had T1D for at least 5 years. The ADA recommends screening with a random urine sample to determine the microalbumin-to-creatinine ratio. A ratio of 30 mg/g (albumin to creatinine) or greater is considered abnormal, and further testing may be indicated. Because other factors may contribute to albuminuria, including exercise, 2 to 3 abnormal determinations may need to be obtained to confirm the diagnosis. Treatment with an Angiotensin converting enzyme (ACE) inhibitor, titrated to normalization of albumin excretion, should be considered when elevated albumin-to-creatinine ratio is subsequently confirmed on two additional specimens from different days over at least 2 months. Girls should be counseled on the teratogenicity of ACE inhibitors. Screening for hypertension should be performed at each routine visit. Children found to have high-normal blood pressure or hypertension should have their blood pressure confirmed on a separate day, and if the blood pressure is consistently elevated to more than 90th percentile for age, height, and gender, ACE inhibitor therapy is the first-choice treatment.

Screening for dyslipidemia should be performed on children older than 2 years soon after diagnosis (after glucose control has been established) if there is a family history of hypercholesterolemia or a cardiovascular event before age 55 years, or if family history is unknown. If family history is not of concern, first lipid screening can be obtained at puberty ( $\geq 10$  years of age). For children diagnosed with diabetes at or after puberty, consider obtaining a fasting lipid profile soon

after the diagnosis (after glucose control has been established). If lipids are abnormal, annual monitoring is reasonable, with institution of lifestyle changes. If low-density lipoprotein cholesterol values are within the accepted risk levels ( $<100$  mg/dL), a lipid profile repeated every 5 years is acceptable.

Patients with T1D are at increased risk for developing other autoimmune disorders, including thyroid disease and celiac disease. Screening for thyroid disease should begin at or shortly after diagnosis by measurement of sensitive thyroid-stimulating hormone and performed annually thereafter. The ADA also recommends biochemical screening of children for celiac disease because patients with T1D are at higher risk for this disease, which can significantly affect the nutritional requirements of the child. Screening for celiac disease can be performed by measuring tissue transglutaminase antibodies. Normal total immunoglobulin A concentrations should also be documented. If unexplained hypoglycemia is occurring (especially with decreasing insulin requirements), evaluation for adrenal insufficiency should be undertaken.

### CONCLUSION

Although significant advances have been made in the types of insulin available and the tools used to monitor blood glucose concentrations, the ability to replicate the function of an intact pancreas is crude at best. Therefore, the child with diabetes requires a significant amount of effort on a daily basis. Providing adequate, individualized education and support for children with diabetes is imperative for successful treatment.

#### WHEN TO REFER

- All newly diagnosed children with T1D or T2D
- When a multidisciplinary diabetes program is needed and not available

#### WHEN TO ADMIT

- Considered for all patients with newly diagnosed T1D
- Diabetic ketoacidosis
- Considered for severe hypoglycemia or dehydration

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *A Parent's Guide to Childhood Obesity: A Road Map to Health* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Diabetes: Basics* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/diabetes/basics/index.html](http://www.cdc.gov/diabetes/basics/index.html))
- *Diabetes* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/chronic/Pages/Diabetes.aspx](http://www.healthychildren.org/English/health-issues/conditions/chronic/Pages/Diabetes.aspx))
- *Diabetes Mellitus (Type 1 Diabetes)* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/chronic/Pages/Diabetes-Mellitus-Type-1-Diabetes.aspx](http://www.healthychildren.org/English/health-issues/conditions/chronic/Pages/Diabetes-Mellitus-Type-1-Diabetes.aspx))

- *For Parents and Kids* (Web page), American Diabetes Association ([www.diabetes.org/living-with-diabetes/parents-and-kids](http://www.diabetes.org/living-with-diabetes/parents-and-kids))
- *Tips for Teens With Diabetes: Make Healthy Food Choices* (fact sheet), National Diabetes Education Program ([www.ndep.nih.gov/teens/MakeHealthyFoodChoices.aspx](http://www.ndep.nih.gov/teens/MakeHealthyFoodChoices.aspx))
- *Tip Sheets for Kids with T2 Diabetes—Be Active!* (fact sheet), National Diabetes Education Program ([ndep.nih.gov/publications/PublicationDetail.aspx?PubId=169](http://ndep.nih.gov/publications/PublicationDetail.aspx?PubId=169))
- *Tip sheets for kids with T2 Diabetes—What is Diabetes?* (fact sheet), National Diabetes Education Program ([ndep.nih.gov/publications/PublicationDetail.aspx?PubId=171](http://ndep.nih.gov/publications/PublicationDetail.aspx?PubId=171))
- *What Is a Pediatric Endocrinologist?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/pages/What-is-a-Pediatric-Endocrinologist.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/pages/What-is-a-Pediatric-Endocrinologist.aspx))

### Medical Decision Support

- *Obesity Prevention in Pediatrics* (online course), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Pediatric Obesity: Prevention, Intervention, and Treatment Strategies for Primary Care* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Research and Practice* (Web page), American Diabetes Association ([www.diabetes.org/research-and-practice](http://www.diabetes.org/research-and-practice))
- *Type 2 Diabetes in Children and Adolescents* (consensus statement), *Diabetes Care*, Vol 23, Issue 3, 2000

### Community Advocacy and Coordination

- *Childhood Obesity Facts* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/healthyschools/obesity/facts.htm](http://www.cdc.gov/healthyschools/obesity/facts.htm))
- *Continuous Glucose Monitoring* (fact sheet), National Diabetes Information Clearinghouse ([diabetes.niddk.nih.gov/DM/PUBS/glucosemonitor/index.aspx](http://diabetes.niddk.nih.gov/DM/PUBS/glucosemonitor/index.aspx))
- *Diabetes Care in the School and Day Care Setting* (article), *Diabetes Care*, Vol 33, Suppl 1, 2010
- *Helping the Student With Diabetes Succeed: A Guide for School Personnel* (book), National Institutes of Health and Centers for Disease Control and Prevention ([ndep.nih.gov/publications/PublicationDetail.aspx?PubId=97](http://ndep.nih.gov/publications/PublicationDetail.aspx?PubId=97))

### Practice Management

- *Obesity and other Co-Morbidities Coding Fact Sheet for Primary Care Pediatricians* (fact sheet) American Academy of Pediatrics ([www2.aap.org/pubserv/codingforped/obesitycodingfactsheet0208.pdf](http://www2.aap.org/pubserv/codingforped/obesitycodingfactsheet0208.pdf))

### AAP POLICY

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- Barlow SE. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary

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- American Diabetes Association. Type 2 diabetes in children and adolescents. *Pediatrics*. 2000;105(3 Pt 1):671–680
- Silverstein J, Klingensmith G, Copeland K, et al. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. *Diabetes Care*. 2005;28(1):186–212

## Chapter 242 DIAPER RASH

Daniel Krowchuk, MD

Diaper rash is the most common skin disorder of infancy. As many as 25% of infants and toddlers are affected; the peak incidence is between 9 and 12 months of age. Diaper rashes may be separated into 2 groups—those that primarily affect the diaper area and are related to wearing a diaper, and those that are associated with systemic disorders that may involve the perineum. The 2 most common forms of primary diaper dermatitis, irritant contact dermatitis (ICD) and candidiasis, will be discussed in detail here. The key features of other forms of primary diaper dermatitis and systemic disorders that may affect the diaper area will be summarized in Table 242-1 and Table 242-2.

### ETIOLOGY

Irritant contact dermatitis is responsible for most rashes in the diaper area. Several factors contribute, including excessive skin moisture, friction, and fecal enzymes. Excessive hydration makes the skin more susceptible to the effects of frictional forces, predisposing to the development of erosions; enhances skin permeability, permitting more rapid penetration of irritating substances; and promotes the growth of microorganisms. Feces contain proteases and lipases, both of which may act as skin irritants. These enzymes are activated at higher pH

levels, a condition that occurs when urea in urine is converted to ammonia. Not surprisingly, reduced frequency of diaper changing (fewer than 8 times per day) and diarrhea are associated with the development of ICD. Once the skin has been damaged by ICD or another process, infection with *Candida albicans* may occur. Candidiasis should be suspected when an apparent ICD does not respond to standard therapy or when a diaper rash appears during or shortly after antibiotic therapy. Ten days of oral amoxicillin therapy has been associated with a twofold increase in the recovery of *C. albicans* from the rectum and skin.

## HISTORY

Elements of the history that may be useful in evaluating diaper rash include the following:

- Duration of the eruption (ICD present for more than 72 hours often is secondarily infected with *C. albicans*)
- Associated symptoms (eg, diarrhea)
- Type of diaper used (disposable or cloth)
- Laundering method (if cloth diapers used)
- Frequency of diaper changing
- Medication use (eg, antibiotic therapy that predisposes to *C. albicans* infection or potent topical corticosteroid use that may contribute to granuloma gluteale infantum)
- Presence of rash elsewhere or systemic symptoms (which might indicate a systemic cause of the diaper rash)
- Family history (which might be helpful when considering psoriasis)

## PHYSICAL EXAMINATION

ICD appears on the convexities of the lower abdomen, perineum, buttocks, and proximal thighs with relative sparing of the creases (eg, inguinal folds). In mild cases,



**Figure 242-1** Irritant diaper dermatitis. Erythematous patches sparing the skin folds.

there is erythema, possibly with scaling, while more severely affected individuals exhibit superficial erosions (Figure 242-1). Infection with *C. albicans* typically produces “beefy”-red patches that involve the convexities and creases. Scaling, particularly at the periphery of patches, or satellite papules or pustules may be present (Figure 242-2). The physical findings associated with other causes of diaper rash are summarized in Table 242-1 and Table 242-2 and shown in the figures.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of common and less common forms of diaper rash occurring in infants and toddlers is presented in Table 242-1 and Table 242-2. A number of infections (herpes simplex virus infection, molluscum contagiosum, hand-foot-and-mouth disease) or infestations (scabies) may involve the diaper area, but lesions would also be expected elsewhere or systemic symptoms would normally be evident. Kawasaki disease may produce perineal erythema and desquamation during the first week of symptoms; in some patients, this may be the only rash. The eruption involves the convexities and creases with an appearance similar to that of toxin-mediated erythemas like scarlet fever. Bullae or erosions affecting the diaper area may result from bullous impetigo (Table 242-1), burns (including those from nonaccidental trauma), senna-containing laxatives (Table 242-2), or epidermolysis bullosa.

## LABORATORY FINDINGS

Laboratory studies are not needed in the evaluation of most diaper rashes. Tests that may be helpful include the following:

- Potassium hydroxide preparation to demonstrate the pseudohyphae and spores of candidiasis or the hyphae of tinea corporis (a fungal culture might be performed instead)
- Mineral oil preparation to confirm scabies infestation (mites, eggs, or fecal material might be observed)



**Figure 242-2** Erythematous patches that involve the creases and convexities are characteristic of candidal diaper dermatitis. Satellite lesions and scaling are present.



**Table 242-1** Other Common Forms of Diaper Rash

CONDITION	CAUSE	CLINICAL FEATURES	TREATMENT
Seborrheic dermatitis (Figure 242-3)	<ul style="list-style-type: none"> <li>• Cause unknown</li> <li>• Associated with sebaceous gland function</li> <li>• May represent an inflammatory response to yeasts of the genus <i>Malassezia</i></li> </ul>	<ul style="list-style-type: none"> <li>• Begins at 3–4 weeks of age and resolves by the end of the first year of life</li> <li>• Salmon-pink patches with greasy scale that involve the convexities and inguinal creases</li> <li>• Involvement of the scalp, face, retroauricular creases, umbilicus, or chest may be present</li> </ul>	<ul style="list-style-type: none"> <li>• Skin: Topical low-potency corticosteroid or antifungal preparation (eg, nystatin, clotrimazole)</li> <li>• Scalp: Oil massage and brushing or antiseborrheic shampoo (containing, eg, pyrithione zinc or selenium sulfide)</li> </ul>
Bullous impetigo (Figure 242-4)	<ul style="list-style-type: none"> <li>• Infection with <i>Staphylococcus aureus</i> that elaborates epidermolytic toxin</li> </ul>	<ul style="list-style-type: none"> <li>• Flaccid blisters filled with clear or purulent fluid</li> <li>• Blisters rupture rapidly, leaving round or oval crusted erosions with a rim of scale</li> </ul>	<ul style="list-style-type: none"> <li>• Oral antistaphylococcal antibiotic (the agent selected depends on local antibiotic resistance patterns)</li> </ul>
Folliculitis (Figure 242-5)	<ul style="list-style-type: none"> <li>• Infection of hair follicles with <i>S aureus</i></li> </ul>	<ul style="list-style-type: none"> <li>• Pustules with surrounding erythema that are centered around hair follicles</li> </ul>	<ul style="list-style-type: none"> <li>• Many lesions: Oral antistaphylococcal antibiotic (the agent selected depends on local antibiotic resistance patterns)</li> <li>• Few lesions: Topical antibiotic (eg, mupirocin, clindamycin, retapamulin)</li> <li>• Bleach baths may be useful for patients with persistent/recurrent infections</li> </ul>
Intertrigo (Figure 242-6)	<ul style="list-style-type: none"> <li>• Rubbing of apposed skin surfaces complicated by heat and moisture</li> </ul>	<ul style="list-style-type: none"> <li>• Erythema and superficial erosions located in the inguinal creases</li> <li>• May become secondarily infected with <i>Candida</i> species or <i>Streptococcus pyogenes</i></li> </ul>	<ul style="list-style-type: none"> <li>• Absorbent powder (to reduce moisture and friction)</li> <li>• Antifungal preparation (if candidal infection) or antibiotic (if streptococcal infection)</li> </ul>
Jacquet's erosive diaper dermatitis (Figure 242-7)	<ul style="list-style-type: none"> <li>• Multiple factors, including moisture, friction, enzymes in stool</li> <li>• Considered a variant of irritant dermatitis</li> </ul>	<ul style="list-style-type: none"> <li>• Well-defined shallow ulcers or ulcerated nodules</li> </ul>	<ul style="list-style-type: none"> <li>• Topical low-potency corticosteroid twice daily and barrier preparation at all diaper changes</li> </ul>

Adapted from Mancini AJ, Krowchuk DP, eds. *Pediatric Dermatology: A Quick Reference Guide*. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2016.

- Bacterial culture for *S aureus*
- Serum zinc concentration if suspicion exists for acrodermatitis enteropathica (other testing will be required to identify nutritional disorders that produce similar physical findings, such as essential fatty acid deficiency or kwashiorkor)
- Skin biopsy if concern exists for Langerhans cell histiocytosis
- Osseous survey if nonaccidental trauma is suspected in a child younger than 2 years of age

## MANAGEMENT

A key to managing ICD is to reduce moisture through frequent diaper changes (every 3 to 4 hours and after soiling). Although it would be helpful to allow diaper-free periods, this may not be feasible. When the perineum is soiled, bathing or cleansing with a disposable wipe or a washcloth and water is indicated. Wipes are convenient to use. Current varieties contain water,

an emollient, and surfactants; they have been found to be safe for use on normal infant skin and skin that has been damaged. Choosing a product that is fragrance free may help avoid sensitization. Preservatives occasionally may induce allergic contact dermatitis, but can be more difficult to avoid. After cleansing, the skin should be allowed to dry before diapering. Applying a barrier preparation at each diaper change will protect the skin from moisture. Zinc oxide paste and petrolatum are commonly used and effective. Zinc oxide adheres well to the skin and, as a result, provides greater protection. It may also adhere to the diaper; if this becomes a problem, the zinc oxide may be covered with a thin layer of petrolatum. Both zinc oxide and petrolatum are available individually and are the active ingredients in many combination products, along with beeswax, lanolin, mineral oil, olive oil, and other agents.

If ICD is moderate or severe, a low-potency topical corticosteroid (eg, hydrocortisone 1% or 2.5%) may be applied twice daily. The use of more potent preparations





**Figure 242-3** Salmon-pink patches with greasy scale involve the creases and convexities in seborrheic dermatitis.



**Figure 242-6** Intertrigo, shown here involving the neck, produces superficial erosions in areas where moist skin surfaces are in apposition.



**Figure 242-4** Flaccid bullae that rupture easily leaving round, crusted erosions occur in bullous impetigo.



**Figure 242-7** Jacquet's erosive diaper dermatitis. Well-defined shallow ulcers and ulcerated nodules.



**Figure 242-5** Folliculitis produces pustules and erythematous papules that are centered around hair follicles.

should be avoided. Recall that the perineum is occluded by the diaper and that the epidermis is thin—factors that enhance the absorption of topical steroids and increase the likelihood of adverse effects locally (eg, atrophy, striae) and systemically (eg, Cushing syndrome).

If the physical examination suggests candidiasis (or if ICD has been present for more than 72 hours and is not improving with standard treatment), nystatin or an imidazole (eg, clotrimazole, miconazole, ketoconazole, etc) should be used. Imidazoles may be a more convenient choice in view of twice-daily dosing. If both a topical corticosteroid and an imidazole are to be used, an alternating application schedule may be selected. A barrier preparation should be applied at all diaper changes where the topical corticosteroid or antifungal is not being used. In infants with skin of

**Table 242-2** Some Less Common Forms of Diaper Rash

CONDITION	CAUSE	CLINICAL FEATURES	TREATMENT
Psoriasis (Figure 242-8)	Unknown	<ul style="list-style-type: none"> <li>Erythematous scaling papules or plaques (scaling of the scalp and umbilicus may be present)</li> <li>Lesions in the diaper area often lack scale characteristic of lesions located elsewhere</li> <li>May be difficult to distinguish from seborrheic dermatitis</li> </ul>	Topical emollient and topical low-potency corticosteroid.
Allergic contact dermatitis (ACD)	<ul style="list-style-type: none"> <li>Allergy to a diaper component (eg, dye or adhesive)<sup>a,b</sup></li> <li>Senna-containing laxative (may be allergic or irritant)<sup>c</sup></li> <li>Wipes (preservative)<sup>d</sup></li> </ul>	<ul style="list-style-type: none"> <li>Diaper: Erythematous patch, possibly with scaling or lichenification. Rash located at site of contact with offending agent; often the hips (adhesive) or diaper margin (dye)</li> <li>Senna: Bullae and erosions that may mimic findings in child abuse</li> <li>Wipes (preservative): Persistent or recurrent eruption in the perineum or on the buttocks</li> </ul>	<ul style="list-style-type: none"> <li>Diaper: Change diaper variety/consider testing for ACD; apply topical low-potency corticosteroid.</li> <li>Senna: Manage as wound with topical antibiotic; avoid senna-containing laxatives.</li> <li>Wipes: Change wipe variety/consider testing for ACD; apply topical low-potency corticosteroid.</li> </ul>
Acrodermatitis enteropathica (Figure 242-9)	<ul style="list-style-type: none"> <li>Autosomal-recessive disorder</li> <li>Defective transport protein causes impaired zinc absorption</li> </ul>	<ul style="list-style-type: none"> <li>Often begins when infants are weaned from human to cow milk formula</li> <li>Scaling erythematous eruption located around the mouth and in the diaper area</li> <li>Infants may have sparse hair, diarrhea, or failure to gain weight</li> </ul>	<ul style="list-style-type: none"> <li>Oral zinc supplementation.</li> <li>Topical low-potency corticosteroid.</li> </ul>
Langerhans cell histiocytosis (Figure 242-10)	Rare disorder; Langerhans cells (antigen-processing cells in the skin) accumulate in skin or other organs	<ul style="list-style-type: none"> <li>Lesion types: vesicles or pustules (often with a hemorrhagic crust); erythematous, orange, or yellow-brown papules or nodules; petechiae; erosions (in the diaper area)</li> <li>Areas affected: scalp, palms and soles, skin folds, diaper area</li> <li>Other features: affected infants may have hepatosplenomegaly, lymphadenopathy</li> </ul>	Refer to pediatric dermatologist or pediatric oncologist for evaluation.
Congenital syphilis (Figure 242-11)	Intrauterine infection with <i>Treponema pallidum</i>	<ul style="list-style-type: none"> <li>Symptoms: rash, bloody diarrhea, rhinorrhea, irritability, pain with movement</li> <li>Skin lesions: condyloma lata (ie, flat-topped papules and plaques located in the diaper area or at the angles of the mouth), scaling copper-colored papules and plaques on the trunk and extremities, or vesicles and bullae</li> </ul>	Consult with a pediatric infectious diseases specialist regarding evaluation and therapy

Adapted from Mancini AJ, Krowchuk DP, eds. *Pediatric Dermatology: A Quick Reference Guide*. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2016.

<sup>a</sup>Smith WJ, Jacob SE. The role of allergic contact dermatitis in diaper dermatitis. *Pediatr Dermatol*. 2009;26(3):369–370.

<sup>b</sup>Alberta L, Sweeney SM, Wiss K. Diaper dye dermatitis. *Pediatrics*. 2005;116(3):e450–e452.

<sup>c</sup>Smith WA et al. Senna-containing laxative inducing blistering dermatitis in toddlers. *Arch Dermatol*. 2012;148(3):402–404.

<sup>d</sup>Chang MW, Nakrani R. Six children with allergic contact dermatitis to methylisothiazolinone in wet wipes (baby wipes). *Pediatrics*. 2014;133(2):e434–e438.

color, the inflammation caused by ICD or other forms of diaper dermatitis may cause hypopigmentation. Parents should be advised that this is temporary but may require several months to resolve.

## PREVENTION

Gregory Liptak, MD, the previous author of this chapter, wrote in the first edition, “If no diapers existed, no diaper rashes would occur.” Because going diaper

free is unacceptable, parents must choose between disposable and cloth diapers. Some issues that influence this decision include effectiveness, prevention of diaper dermatitis, cost, and ecologic effect. Studies conducted during the 1980s demonstrated that the use of disposable diapers containing absorbent gelling material (AGM, the substance that stores liquid in the core of the diaper keeping it away from the skin) was associated with reductions in the frequency and severity of diaper dermatitis when compared with the use of either



**Figure 242-8** Psoriasis in the diaper area produces erythematous patches or plaques. Unlike lesions elsewhere, scale may be absent.



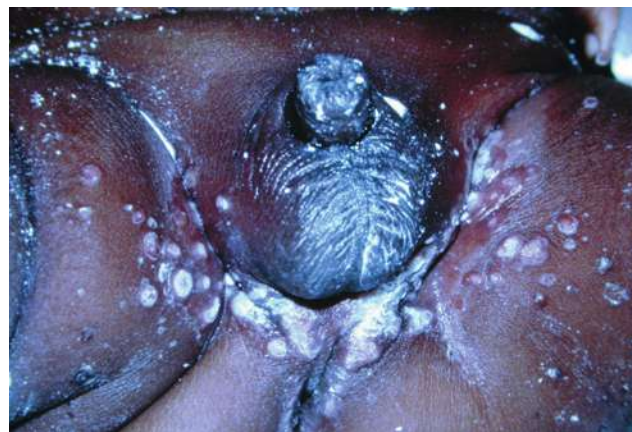
**Figure 242-9** Acrodermatitis enteropathica causes erythematous patches in the diaper area and around the mouth.

cloth or cellulose-only diapers (ie, disposable diapers without AGM). However, there are no published data comparing disposable diapers and the current generation of cloth diapers. The increasing popularity of cloth diapers likely reflects, in part, satisfaction with their performance. Depending on the brand, these diapers use a cloth insert (to enhance absorbency) and a breathable waterproof cover to contain moisture. Some varieties also use a flushable inner liner to contain fecal material, eliminating the need to rinse the diaper before placing it in the diaper pail.

Disposable diapers are convenient, but comparatively more expensive than cloth varieties. A *Consumer Reports* Diaper Buying Guide (updated November 2012) estimates that a family might spend \$2,500 or



**Figure 242-10** Erythematous papules of Langerhans cell histiocytosis.



**Figure 242-11** Condylomata lata, flat-topped papules and plaques, occur in the diaper area in congenital syphilis.

more on disposable diapers by the time a child is toilet trained. If a biodegradable variety is used, the cost may be \$3,500. Cloth diapers are less expensive, especially if the family does the laundering (ie, does not use a diaper service). In addition, cloth diapers could be used for more than a single baby.

The environmental effect of disposable diapers is an issue of concern. Past estimates suggested that non-biodegradable disposable diapers made up 1% to 2% of landfills. However, washing cloth diapers requires water and energy, along with detergent and human effort. These factors must be considered in weighing the overall environmental effect of these products. In an analysis by the Environmental Agency of the United Kingdom, a child using 2006-type disposable diapers for 2½ years contributed a global warming effect of approximately 550 kg of carbon dioxide equivalents.



Reusable diaper use resulted in 570 kg of carbon dioxide equivalents (assuming average washer and dryer use). The latter amount could be reduced by 40% by washing diapers in fuller loads, line drying them all the time, and using the diapers for a second child.

Beyond appropriate diapering, measures that prevent diaper dermatitis include frequent diaper changes, appropriate cleansing promptly after soiling, and the application of a barrier preparation after cleansing the diaper area (particularly for infants who experience recurrent episodes of diaper dermatitis).

### WHEN TO REFER

- If an infant fails to respond to appropriate therapy (to consider alternate diagnoses and possibly perform skin biopsy) or if nonaccidental trauma is suspected.
- If Langerhans cell histiocytosis is considered, refer to a pediatric dermatologist or pediatric oncologist.
- Consultation with a pediatric infectious diseases specialist is warranted if an infant is suspected of having congenital syphilis.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Diaper Rash* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/baby/diapers-clothing/Pages/Diaper-Rash.aspx](http://www.healthychildren.org/English/ages-stages/baby/diapers-clothing/Pages/Diaper-Rash.aspx))
- *Diaper Rash Solution* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/baby/diapers-clothing/Pages/Diaper-Rash-Solution.aspx](http://www.healthychildren.org/English/ages-stages/baby/diapers-clothing/Pages/Diaper-Rash-Solution.aspx))
- *When Diaper Rash Strikes* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/baby/diapers-clothing/Pages/When-Diaper-Rash-Strikes.aspx](http://www.healthychildren.org/English/ages-stages/baby/diapers-clothing/Pages/When-Diaper-Rash-Strikes.aspx))

### SUGGESTED READINGS

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## Chapter 243

# DISORDERS OF SEX DEVELOPMENT

Lindsey Loomba-Albrecht, MD; Dennis M. Styne, MD

### EPIDEMIOLOGY

Patients with ambiguous genitalia have *disorders of sex development* (DSD), previously termed *intersex conditions*. These are congenital conditions in which

development of chromosomal, gonadal, or anatomic sex is atypical. Physical findings in patients with DSD may range from an apparently normal phenotype to complete ambiguity. Disorders of sex development is considered an endocrine emergency because many common forms of DSD (ie, congenital adrenal hyperplasia [CAH]) are associated with life-threatening electrolyte abnormalities, hypotension, and shock. In addition to the potential medical emergency, the psychological stress to the family cannot be overstated. Gender assignment in patients with genital ambiguity should be made only after careful investigation by a multidisciplinary team; increasingly, surgical decisions are delayed until the child is able to participate in the decision-making process.

### NORMAL HUMAN SEXUAL DIFFERENTIATION

Phenotypic sex results from the culmination of many specific genetic and hormonal processes. Humans possess 23 pairs of chromosomes (22 pairs of autosomes and 1 pair of sex chromosomes), with females possessing 2 X chromosomes and males possessing 1 X and 1 Y chromosome. Early in gestation, the fetus has a bipotential gonad that can develop into either ovaries or testes. Genes on the sex chromosomes, as well as on the autosomes, influence formation of this bipotential gonad into either ovaries or testes. Additionally, both the Wolffian and Müllerian ducts are present early in gestation; these have the potential to develop into either male or female nongonadal reproductive structures, respectively.

#### Male Sexual Differentiation

The presence of a specific gene on the Y chromosome, the sex-determining region Y (*SRY*) gene, is the initial trigger for testicular development and, eventually, the male phenotype. When the *SRY* gene is present, the bipotential gonad begins to differentiate into a testis at day 43 to 50 of gestation. Soon after, the testes begin to produce testosterone from the Leydig cells and anti-Müllerian hormone (AMH) or Müllerian-inhibiting substance from the Sertoli cells. The anti-Müllerian hormone acts locally to repress ipsilateral development of the Müllerian ducts through apoptosis. Because AMH is produced through early childhood, it can be used as a marker for Sertoli cell presence and function until 8 to 10 years of age. The Wolffian ducts differentiate in the male and, with high local concentrations of testosterone from the ipsilateral testes, ultimately form the vas deferens, epididymis, seminal vesicles, and ejaculatory ducts.

Testosterone secretion early in gestation (during the critical period of sex determination) is stimulated by placental human chorionic gonadotropin (hCG); later the stimulus for testosterone secretion is luteinizing hormone (LH) released from the fetal pituitary. Testosterone is locally metabolized by the enzyme 5 $\alpha$ -reductase into dihydrotestosterone (DHT), which is responsible for masculinization of the external genitalia in the male. Thus, the development of a male phenotype begins with specific genetic signals that lead to gonadal (testis) formation; the gonads then produce androgenic hormones that allow for masculinization



of the genitalia. A critical window exists in which testosterone secretion must occur to lead to the normal male phenotype. If fusion of the labioscrotal folds does not occur by week 14 of gestation, then fusion will not occur even if high levels of androgen are present later. After this time, the phallus enlarges and the testes descend into the scrotum, but most male differentiation already occurred. A female with excessive androgen exposure from early gestation (eg, virilizing CAH) will have some degree of fusion of the labia; virilizing CAH is incompatible with a normal female unfused vaginal opening.

### Female Sexual Differentiation

Without the *SRY* gene, the bipotential gonad will develop into an ovary beginning between days 77 and 84 of gestation. Thus, the default pathway in gonadal development is said to be female, although more recently, other genes such as *Wnt4* have been identified that play a role in development of the ovary. Without the production of AMH, the Müllerian ducts develop into the fallopian tubes, uterus, and upper one-third of the vagina. The developing ovaries do not secrete hormones necessary for female sexual differentiation. Essentially, the absence of androgenic hormones allows the typical female external genitalia to develop.

In addition to the *SRY* gene, multiple other genes play a role in human sexual differentiation. Most of these genes act downstream of the *SRY* gene to further influence testicular or ovarian differentiation. Mutations in these genes, such as *WT1*, *SF1*, and *SOX9*, are often associated with additional physical findings in the infant or later in childhood or adolescence.

### DEFINITIONS

Recently, the nomenclature used to describe atypical sexual differentiation changed, largely the result of concern that the terminology was pejorative to children and confusing to medical practitioners. Historically, the term *male pseudohermaphrodite* was used to describe the child with incompletely masculinized external genitalia possessing XY chromosomes and a typical number of autosomes (46,XY karyotype). Incomplete masculinization of a fetus with testes may result from decreased synthesis or secretion of testosterone or DHT, peripheral tissue resistance to

androgen action, or defective production or action of AMH. These conditions, as well conditions in which the testes fail to normally develop, are now denoted as 46,XY DSD. The term *female pseudohermaphrodite* was commonly used to describe a child with a 46,XX karyotype and with masculinized external genitalia. This circumstance may result from abnormally high levels of androgen from either a fetal or exogenous source. Currently, these disorders, as well as disorders of ovarian development, are denoted as 46,XX DSD.

*Sex chromosome DSD* now describes sex chromosome abnormalities that affect gonadal development. These conditions may or may not involve genital ambiguity. In very rare cases, a child may have both ovarian and testicular tissue. These children called *true hermaphrodites* in the past, but may now be considered to have *ovotesticular DSD*.

## DISORDERS OF SEXUAL DEVELOPMENT

### 46,XX Disorders of Sexual Development

Virilization of a female fetus results from excess androgen exposure from either a fetal or maternal source. Timing is important; if the female is exposed to elevated androgen levels after week 8 of gestation, but before week 14, then the vaginal opening may fuse posteriorly and seem slit-like. Females with CAH, for example, will have posterior fusion of the labia and some degree of clitoromegaly given their high circulating androgen levels between weeks 8 and 14 of gestation. Exposure to androgen following weeks 12 to 14 of gestation (eg, exogenous administration to the mother) will result in clitoromegaly without fusion of the labioscrotal folds.

### Fetal Sources of Androgen Excess

**CONGENITAL ADRENAL HYPERPLASIA.** Overproduction of adrenal androgens by the female fetus may occur in virilizing CAH, a group of disorders in which a biochemical defect in cortisol synthesis leads to hyperplasia of the adrenal gland resulting from compensatory elevation in adrenocorticotrophic hormone (ACTH). These disorders are inherited in an autosomal recessive manner. The degree and timing of virilization, as well as the presence or absence of salt wasting, depend on the specific genetic lesion (Table 243-1).

**Table 243-1** Differential Diagnosis of Adrenal Enzyme Defects

DEFICIENCY	NEWBORN PHENOTYPE	POSTNATAL VIRILIZATION	OTHER
StAR (also called <i>lipoid congenital adrenal hyperplasia</i> )	Infantile female	—	Salt loss
3 $\beta$ -Hydroxylase	Ambiguous in XY and XX	+	Salt loss
17 $\alpha$ -Hydroxylase (P450c17)	Infantile female	—	Delayed puberty
11 $\beta$ -Hydroxylase (P450c11 $\beta$ )	Male in XY, ambiguous in XX	+	Hypertension
21-Hydroxylase (P450c21)	Male in XY, ambiguous in XX	+	Salt loss
18-Hydroxylase (P450c11B2)	Normal	—	Salt loss

StAR, steroidogenic acute regulatory protein.

From Styne D. *Pediatric Endocrinology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2004. Reprinted by permission.

Roughly 90% of classic CAH cases are caused by 21-hydroxylase deficiency, which occurs in 1 in 15,000 live births. P450c21 hydroxylase converts 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol; a deficiency in this enzyme leads to extreme elevation in 17-OHP levels, making serum levels of 17-OHP a useful diagnostic test. Defects in 21-hydroxylase will lead to low aldosterone and cause renal salt wasting and potassium retention in approximately 50% of children. In its most serious form, cortisol and aldosterone deficiency are severe enough to result in hyponatremia, hyperkalemia, dehydration, hypotension, shock, or death. Male infants die more frequently than female infants because of the lack of suspicion of the condition as a result of their visibly normal phenotype at birth, whereas female infants with virilization are usually evaluated quickly. Newborn screening should eliminate this gender discrepancy in timing of diagnosis.

Late-onset, or nonclassic, 21-hydroxylase deficiency usually occurs in childhood or the teenage years with excessive or premature acne and sexual hair. It is a milder, non-life-threatening form of CAH that does not cause genital ambiguity. It may be associated with increased growth, bone age advancement, and irregular menses, and is frequently evaluated in the workup of precocious puberty.

Defects in 11 $\beta$ -hydroxylation are rarer than defects in 21-hydroxylation, occurring in roughly 1 in 100,000 white births and more frequently in those of Middle Eastern descent. P450c11 hydroxylase deficiency typically results in hypertension in either gender as a result of elevated levels of 11-deoxycorticosterone and virilization of the female fetus as a result of increased adrenal androgen production. Diagnosis is usually made after the discovery of elevated levels of 11-deoxycortisol (compound S).

3 $\beta$ -Hydroxysteroid-dehydrogenase deficiency causes mineralocorticoid, glucocorticoid, and sex-steroid deficiency. Genetic females may be phenotypically normal or have varying levels of clitoromegaly or labial fusion. Virilization occurs in genetic females because of increased levels of dehydroepiandrosterone (DHEA) (and its sulfate DHEA-S). Additionally, peripheral conversion of DHEA to testosterone may cause virilization in females. 3 $\beta$ -Hydroxysteroid-dehydrogenase deficiency may be a cause of late-onset CAH. Salt loss, as a result of aldosterone deficiency, occurs to varying degrees. Genetic male fetuses may have genital ambiguity as well.

**AROMATASE DEFICIENCY.** In rare cases, deficiency in the enzyme aromatase caused by mutations in the *CYP19* gene may lead to virilization of the female fetus and often of the mother during pregnancy. Aromatase catalyzes the conversion of androgen to estradiol; a deficiency in this enzyme leads to elevated levels of androstenedione and testosterone and low levels of estrogens in these patients. At puberty, females often undergo progressive virilization and do not develop female secondary sexual characteristics. In addition, they have osteopenia and delayed bone age (given the estrogen deficiency) and may have ovarian cysts. A male with aromatase deficiency will be tall and have delayed bone age and osteoporosis caused by estrogen deficiency.

### Maternal or Exogenous Sources of Elevated Androgen Levels

Maternal use of androgenic steroids such as danazol or certain progesterone compounds during pregnancy may lead to virilization of the female fetus. Again, the time frame is important in the outcome, given that exposure to these compounds during weeks 8 to 14 of gestation may lead to significant ambiguity, whereas later exposure may result only in enlarged clitoral size. In rare instances, maternal CAH or a virilizing maternal tumor of ovarian or adrenal origin may lead to masculinization of the fetus. Luteomas of pregnancy are also reported to cause genital ambiguity in the newborn, although they more commonly result only in maternal virilization.

### 46,XY Disorders of Sexual Development Luteinizing Hormone-Receptor Defects

Testosterone secretion is controlled by hCG early in gestation and LH from the fetal pituitary later in gestation. Failure of hCG or LH to stimulate testosterone production at the critical times because of mutations in the LH/hCG receptor will result in incomplete masculinization of a male fetus. This failure may result in Leydig cell agenesis or hypoplasia. Stimulation testing with hCG will result in little or no rise in androgen levels. Basal and stimulated LH levels are typically elevated.

### Androgen Biosynthesis Defects

Enzyme defects in the pathways of testosterone biosynthesis may result in incomplete virilization of the male fetus; some of the defects additionally affect synthesis of corticosteroids and are thus forms of CAH.

The initial conversion of cholesterol to pregnenolone requires the enzyme P450scc (side chain cleavage), as well as the steroidogenic acute regulatory protein, which transports cholesterol to the inner mitochondrial membrane where P450scc is located. Patients with steroidogenic acute regulatory protein or P450scc enzyme deficiencies have lipid-laden adrenal glands, adrenal insufficiency, and sexual infantilism in males as a result of low testosterone levels.

3 $\beta$ -Hydroxysteroid dehydrogenase deficiency may result in mineralocorticoid, glucocorticoid, and sex-steroid deficiencies. Affected males may be incompletely masculinized at birth and often experience salt loss or adrenal crisis in infancy. They may experience gynecomastia around the time of puberty. The enzyme substrates, such as DHEA and pregnenolone, are elevated.

17-Hydroxylase deficiency caused by a defect in the *CPY17* gene results in deficiencies in cortisol and testosterone and thus can result in an incompletely masculinized 46,XY fetus. An excess of the mineralocorticoid deoxycorticosterone leads to hypertension in both sexes (caused by increased salt and water reabsorption), as well as hypokalemia and suppression of aldosterone production. Females with 17-hydroxylase deficiency are phenotypically normal at birth, but will not progress through pubertal changes. In some female patients, primary amenorrhea is the presenting feature.

Enzyme defects affecting testosterone biosynthesis without affecting corticosteroid production also occur. In a male fetus, 17,20 lyase (also called 17,20 desmolase) deficiency and 17 $\beta$ -hydroxysteroid dehydrogenase-3 deficiency will lead to an incompletely masculinized phenotype without any abnormalities related to mineralocorticoid or glucocorticoid effects. Virilization may occur at puberty in either condition. Gynecomastia may occur at puberty in those affected with 17,20 lyase deficiency.

### Defects in Androgen Action

The syndrome of complete androgen resistance (complete androgen insensitivity syndrome) results from a defect in the androgen receptor. Affected individuals are phenotypic females with a 46,XY karyotype and bilateral testes that secrete elevated levels of testosterone. The external genitalia are phenotypically female given the inability of the tissue to respond to dihydrotestosterone. Müllerian structures such as the cervix and uterus are absent or hypoplastic because production of AMH by the fetal Sertoli cells is normal, and thus the vagina ends in a blind pouch. At puberty, LH increases and leads to elevations in testosterone, some of which is converted peripherally to estrogens. This circumstance leads to the development of female secondary sexual characteristics. Pubic and axillary hair is sparse, if present at all, and menarche cannot occur. Diagnosis often follows a workup for primary amenorrhea and is suggested by ultrasound findings (showing absence of the corpus and cervix and the presence of testes) and elevated levels of testosterone. Removal of the testicular tissue is indicated, given the increased risk for neoplasm after puberty; however, the timing of removal is controversial. After the testes are removed, estrogen replacement is provided.

Incomplete forms of androgen resistance, also caused by mutations in the androgen receptor, have great phenotypic variability. External genitalia may range in appearance from completely ambiguous to mildly hypoplastic male genitalia with a small, but normally formed, phallus. Hypoplastic Wolffian duct structures are typically present, and Müllerian derivatives are absent because of production of AMH. At puberty, virilization is usually incomplete, and gynecomastia often becomes apparent. Axillary and pubic hair is normal in amount and distribution.

### 5 $\alpha$ -Reductase-2 Deficiency

Mutations in the *SRD5A2* gene coding for 5 $\alpha$ -reductase-2, an enzyme that converts testosterone to dihydrotestosterone, leads to DHT deficiency. At birth, affected males may have ambiguous genitalia or be phenotypically female as a result of decreased conversion of testosterone to DHT in the sexual skin during the critical times of male genital development. These patients have well-developed Wolffian ducts (because these structures are testosterone and not DHT responsive) and absent Müllerian structures (given that AMH is produced from the normal testes). During puberty, virilization occurs with growth of the phallus and testes, likely secondary to expression of a different form of the 5 $\alpha$ -reductase enzyme (type 1) in the liver and other tissues at that time with subsequent increases in

circulating DHT levels. Secondary sexual characteristics, such as increased muscle mass and voice deepening, occur. Laboratory testing reveals abnormally high testosterone/DHT ratios with normal to elevated testosterone and low to undetectable DHT. Confirmatory testing with mutation analysis of the 5 $\alpha$ -reductase-2 gene can be performed, but is not yet available commercially. Given the phenotypic appearance at birth, many affected male children with 5 $\alpha$ -reductase deficiency are raised as female. Following the physical changes that occur around the time of puberty, some children may adopt a male gender role in adolescence or early adulthood.

### Disorders of Gonadal Differentiation (Sex Chromosome Disorders of Sexual Development)

#### Klinefelter Syndrome

The most common form of primary hypogonadism in males is Klinefelter syndrome (47,XXY karyotype), with an incidence of 1 in 1,000 males. Before puberty, children may have decreased upper segment to lower segment ratios, small testes, an increased incidence of developmental delay (mainly in the areas of speech and language), and behavioral problems. Males are taller than expected from 5 to 6 years of age onward.

Onset of puberty is not usually delayed because Leydig cell function is characteristically less affected than seminiferous tubule function, and testosterone is often adequate to stimulate pubertal development. Serum gonadotropin levels rise after the onset of puberty as the testes become firm and rarely grow larger than 3.5 cm in diameter. After the onset of puberty, histologic changes of seminiferous tubule hyalinization and fibrosis, adenomatous changes of the Leydig cells, and impaired spermatogenesis occur. Gynecomastia is common (and later the risk for breast cancer is increased), and variable degrees of male secondary sexual development are found.

#### Turner Syndrome (Syndrome of Gonadal Dysgenesis)

Turner syndrome (45,X karyotype) is associated with a lack of secondary sexual development at the time of puberty, short stature, and a characteristic female phenotype that often includes webbing of the neck. It occurs in 1 in 2,500 live-born female infants and a far greater percentage of conceived pregnancies, given that roughly 15% of first-trimester spontaneous abortions have a 45,X karyotype. Cardiovascular anomalies are present in approximately 75% of women with Turner syndrome and include coarctation of the aorta in 12% and aortic valve abnormalities in 20%. The risk for aortic dissection is also greatly increased. However, in some cases, short stature may be the sole phenotypic manifestation of the syndrome. Classic manifestations of Turner syndrome are linked to the absence of the short stature homeobox (*SHOX*) gene on the X chromosome.

Children have streak gonads consisting of fibrous tissue without germ cells. Pubic hair may appear late and is usually sparse in distribution; adrenarche progresses in Turner syndrome even in the absence of



gonadarche. Serum gonadotropin concentrations in Turner syndrome are extremely high between birth and 4 years of age. They decrease toward the normal range in prepubertal children and then rise again dramatically after 10 years of age. Because of decreased ovarian secretion of estrogens, puberty does not usually begin spontaneously. Children have no pubertal growth spurt and reach a mean final height of 143 cm. Growth hormone function is usually normal in Turner syndrome, although growth hormone treatment increases growth rate and adult stature. Estrogen treatment is also offered in adolescence in these children to allow feminization. Health supervision guidelines should be followed to ensure comprehensive care for patients with Turner syndrome.

Various mosaic forms of Turner syndrome have been identified, with karyotypes such as 45,X/46,XX or 45,X/46,XY. These children may have any phenotype varying from normal female to normal male to manifestations of many of the features of Turner syndrome. Some have apparently normal gonadal function; others have an abnormality of 1 X chromosome, such as a ring X, which may be associated with severe intellectual disability and a variety of congenital malformations.

#### Other Disorders of Gonadal Development

Additional disorders of testicular development may be caused by complete XY gonadal dysgenesis (Swyer syndrome), partial gonadal dysgenesis, or gonadal regression. In these cases, *gonadal dysgenesis* is descriptive and bears no etiologic relationship to the *syndrome of gonadal dysgenesis* or Turner syndrome. In complete gonadal dysgenesis, 46,XY individuals fail to develop normal testes and instead have gonadal streaks, Müllerian duct development and Wolffian duct regression, and female external genitalia. Fifteen percent to 20% of these cases are caused by mutations in the *SRY* gene. Partial gonadal dysgenesis in 46,XY individuals leads to a variable amount of testosterone and AMH production; thus, it is usually associated with ambiguous genitalia and partial development of both the Wolffian and Müllerian ducts. In gonadal regression or vanishing testes syndrome, the testes are lost after the external genitalia and internal structures form. Thus, these 46,XY individuals will be phenotypically male except for absence of both testes. Given this circumstance, anorchia must be considered in all phenotypic male children with bilaterally nonpalpable testes.

Gonadal dysgenesis may occur in children with a 46,XX karyotype who may have streak gonads and failure to develop secondary sexual characteristics at the time of puberty, but none of the other characteristics of Turner syndrome. In addition to gonadal dysgenesis, genetic abnormalities such as translocation of the *SRY* gene can result in a 46,XX genotypic child developing testicular instead of ovarian tissue; these children may phenotypically resemble Klinefelter syndrome.

#### Ovotesticular Disorders of Sexual Development

Children with ovotesticular DSD have both ovarian and testicular tissue present. Most children have a 46,XX phenotype, and the remainder have a 46,XY

karyotype or 46,XX/46,XY chimerism. Great phenotypic variability exists in both the internal and external genitalia in these children. Although ovotesticular DSD should be considered in all children with DSD, a 46,XX/46,XY karyotype or a bilobate gonad in the inguinal region or labioscrotal folds should raise suspicion for the diagnosis.

### EVALUATION AND DIAGNOSIS

Infants with indeterminate gender, as well as some infants with relatively subtle genital findings, should be evaluated for a disorder of sexual differentiation. (Figure 243-1 and Figure 243-2 contain diagnostic algorithms.) In males, even very mild hypospadias can be considered to represent incomplete masculinization, although most uncomplicated cases do not need diagnostic evaluation. More severe degrees of hypospadias, especially when a testis is not palpable, should awaken concern for an identifiable abnormality. Thus, in an apparently phenotypic female, mild clitoromegaly may represent severe undervirilization in a genetic male who has undescended testes or, conversely, masculinization of a female fetus.

Specific recommendations exist for which genital findings should elicit concern for a sexual development disorder. In an apparent male born at term, bilateral nonpalpable testes, micropenis, perineal hypospadias, or a single undescended testis with hypospadias of any degree should be further evaluated. Because the testes do not normally descend until roughly 34 weeks of gestation, significantly preterm males with nonpalpable testes alone do not necessarily require evaluation. In an apparent female, clitoral hypertrophy of any degree, posterior labial fusion (but not just labial adhesions), or an inguinal or labial mass should alert the physician to a possibility of a sexual differentiation disorder. Of course, all infants with truly ambiguous genitalia and thus indeterminate gender also require evaluation. In addition, if a family history of DSD is present, or if discordance exists between the apparent gender of the infant and a previously obtained prenatal karyotype, then an evaluation should ensue.

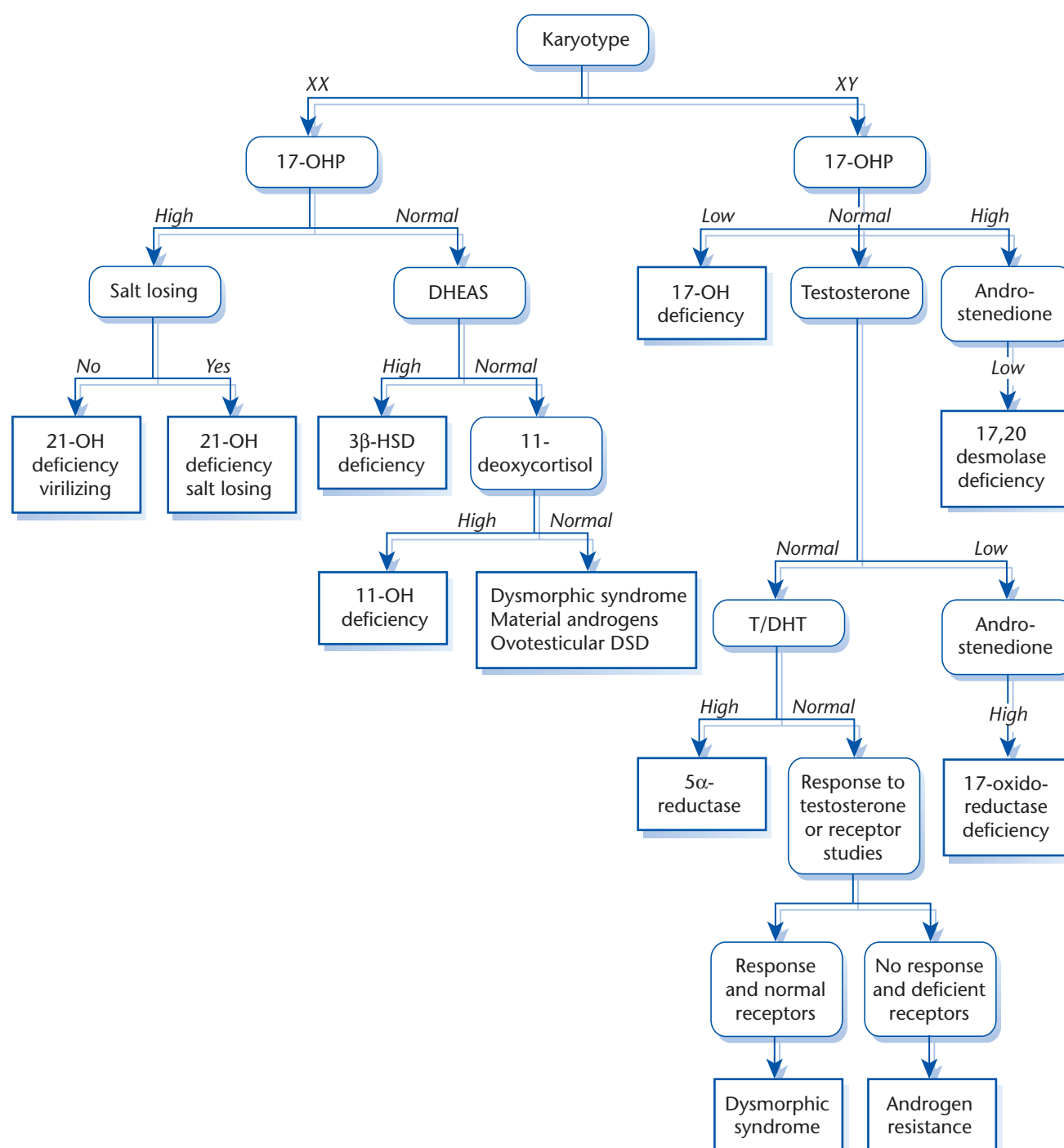
#### History

The evaluation of an infant with a DSD must include a detailed obstetric and family history. The child's mother should be asked about medication use and symptoms of virilization during pregnancy, which may occur in the case of aromatase deficiency or with androgen-secreting maternal ovarian or adrenal tumors. The family history should elicit a history of genital abnormalities, consanguinity, unexplained neonatal deaths especially in apparently normal phenotypic males (because males with CAH will not have the clue of genital ambiguity to raise suspicion for the possibility of adrenal crisis), infertility, and disorders of puberty. Many of the conditions associated with ambiguous genitalia are sporadic or inherited in an autosomal recessive manner.

#### Physical Examination

The initial physical examination should begin with an assessment of the general health of the child and an evaluation for malformations or dysmorphic features.

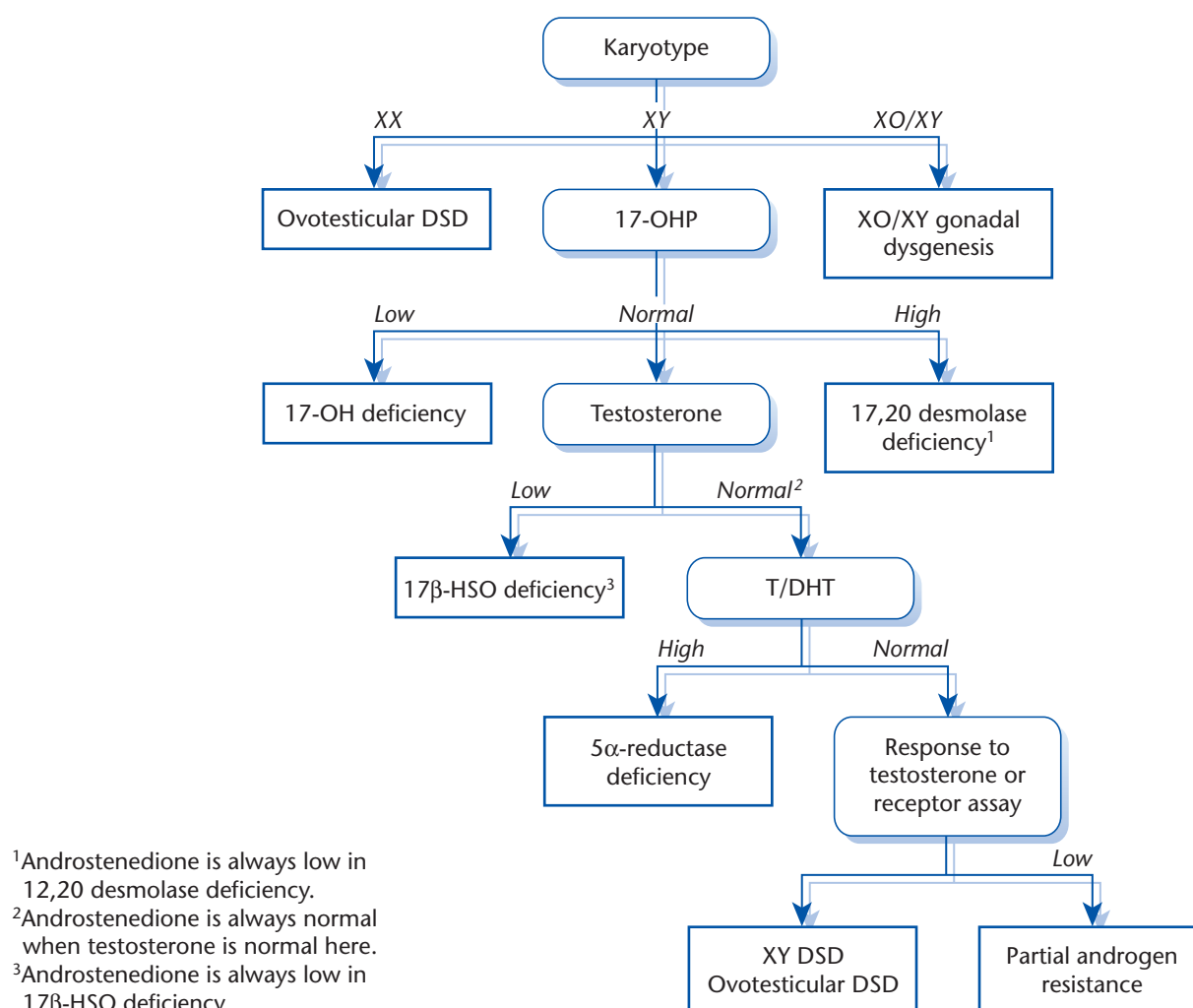




**Figure 243-1** Diagnostic algorithm for a child with ambiguous genitalia without palpable gonads is presented for information only. This complex clinical situation requires the assistance of a pediatric endocrinologist for ultimate diagnosis. *DHEAS*, dehydroepiandrosterone sulfate; *DSD*, disorders of sex development; *T/DHT*, testosterone/dihydrotestosterone. (From Styne D. *Pediatric Endocrinology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2004. Reprinted by permission.)

Unstable vital signs or hypoglycemia with no apparent cause should raise concern for cortisol deficiency associated with CAH. Typically, the onset of shock in children with CAH does not develop until day 4 to 5 of life, and normal electrolyte values in the few days after birth do not exclude salt loss. Children with ambiguous

genitalia may actually benefit from earlier diagnosis of salt loss and signs of cortisol deficiency than phenotypically normal children. Increased skin pigmentation caused by elevated levels of ACTH occurs well after the newborn period and thus is not helpful in making an early diagnosis.



**Figure 243-2** Diagnostic algorithm for a child with ambiguous genitalia with palpable gonads is presented for information only. This complex clinical situation requires the assistance of a pediatric endocrinologist for ultimate diagnosis. DSD, disorders of sex development; T/DHT, testosterone/dihydrotestosterone. (From Styne D. Pediatric Endocrinology. Philadelphia, PA: Lippincott Williams & Wilkins; 2004. Reprinted by permission.)

Stretched penile length in a term male infant should measure more than 2 cm; average length is approximately 3.5 cm. A normally formed phallus and scrotum indicates that testosterone production in the critical window of male differentiation was appropriate (around weeks 8 to 12 of gestation). Because further growth of the normally formed phallus is under the control of testosterone stimulated by fetal LH after midgestation (rather than hCG, which falls during this time), micropenis (penile length <2 cm) often indicates gonadotropin deficiency and may be a sign of hypopituitarism. Proper examination technique is critical because an infant with chordee or a generous suprapubic fat pad may be thought mistakenly to have micropenis. The position of the urethral meatus should additionally be noted, which sometimes requires observation of urination, because a urogenital sinus can sometimes be mistaken for the urethra and the indentation at the end of the glans penis can be mistaken for the opening of the penile urethra. The labioscrotal

folds should be examined for degree of fusion, as well as for symmetry, rugosity, and color. The presence or absence of a vaginal opening should of course be established. Gonads, when palpable bilaterally, are most often testes. A unilaterally palpable gonad may be a testis, an ovotestis, or an ovary. Sweeping the fingers down the path of the inguinal canal may allow palpation of gonads that could not otherwise be located. Physical examination may rule out certain diagnoses; for example, if gonads are palpable, the infant is not a virilized female with CAH because these children have gonads (ovaries) that are situated in the pelvis and are not palpable.

Nongenital anomalies on physical examination should also be noted and documented. Genital anomalies may occur in conjunction with an overall pattern of malformation or may be seen in certain syndromic diagnoses; dysmorphic features or specific nongenital anomalies may raise suspicion for one of these conditions. Again, discordance between the phenotypic sex

and genetic sex (known ahead of time as a result of prenatal testing) should raise suspicion for the possibility of DSD.

### Laboratory Evaluation

Basic serum chemistries should be obtained immediately to evaluate for salt wasting or hyperkalemia associated with CAH, but abnormalities may take days to become apparent. A karyotype will establish whether the child is genotypically XX or XY (or other) and should always be performed; although, it alone will not establish a diagnosis. Results from an urgently ordered karyotype can be available within approximately 3 days in some cytogenetics laboratories. Endocrine testing generally consists of measuring 17-OHP, testosterone, DHT, androstenedione, follicle-stimulating hormone, LH, and AMH performed in a national specialty laboratory with pediatric standards and sample sizes, rather than a local laboratory, which is most unlikely to have pediatric standards or appropriately sensitive techniques. Based on these results, additional tests may be performed. In the first weeks after birth, testosterone measurement may reveal the amplitude of the episodic spike of testosterone. After this period, hCG administration will help determine whether functional Leydig cells are present (given that functional cells will secrete testosterone in response to the hCG). Of course, serum testing of the steroid hormones involved in the pathways for cortisol and testosterone is indicated in many cases because rare forms of CAH will not uniformly cause elevations in 17-OHP levels. In some cases, stimulatory testing with ACTH is necessary to identify the defect.

Newborn screening for 21-hydroxylase deficiency (but not other forms of CAH) now occurs in all 50 states within the United States, as well as Washington, DC and Guam. Results can be returned several days after the specimens are drawn and are thus available within the first week of life, but not always before clinical symptoms develop. This screening test is most helpful in diagnosing the normal-seeming, but affected, male.

A trial of testosterone injections (eg, 25 mg of testosterone enanthate intramuscularly every month for 3 months) is given in some equivocal cases to assess whether phallus size responds to androgen, which may eliminate androgen resistance as a diagnostic possibility. However, the effect of this cannot be assessed for several months.

### Imaging

Imaging is useful to determine internal anatomy. Ultrasound examination, if performed by an experienced technician, determines the presence and appearance of Müllerian structures. Absent Müllerian structures imply that AMH was produced from testicular tissue and that the underlying problem is an abnormality of testosterone or DHT synthesis or action. Additionally, ultrasound is valuable in evaluating associated renal problems (seen in some syndromes such as Frasier syndrome) and for visualization of the adrenal glands. The gonads may be identifiable by ultrasound examination, although magnetic resonance imaging may be required, particularly if the gonads are intraabdominal.

## MANAGEMENT

A team approach is necessary to address the multiple issues surrounding management of patients with DSD. The team may consist of an endocrinologist, pediatric surgeon, pediatric urologist, neonatologist, and geneticist, as well as specialists in ethics, psychology, and social work. Gender assignment should be avoided while the evaluation is occurring, which may take days to weeks. Because CAH is the most common condition leading to ambiguous genitalia, a tendency may exist to tell parents that their child most likely has CAH. Guessing should be avoided because it potentially introduces confusion and may increase distress. The infant should be referred to using gender-neutral terms such as *your baby* or *the baby* rather than *he* or *she*. Completion of the birth certificate should be delayed, and the family should be supported by an experienced and well-trained social worker or psychologist. The ultimate gender assignment is based on many factors, including the underlying diagnosis, the genital appearance, surgical options, potential for fertility and sexual function, and the personal and cultural beliefs of the family.

When a gender assignment is reached, the gender role should be supported, although parents should understand that not all children with a given diagnosis will identify themselves in the same way over time. Because of this potential for discordance between assigned gender and later gender identity, surgical reconstruction of the genitalia is increasingly deferred until the child is able to participate in the decision-making process. Gender identity, the personal conception of oneself as male or female, is the result of a complex interplay between both biologic and environmental factors. It is distinct from sexual orientation and gender role. Hormonal effects (specifically androgen effect on the prenatal brain), brain structural differences, assigned sex of rearing, and sex-steroid effects at the time of puberty have all been shown to influence gender identity. Given this complexity, definitive predeterminations of gender identity are unlikely to ever be fully accurate, and a significant number of children who are assigned a particular gender are later dissatisfied. Unfortunately, outcome data for gender identity in DSD are relatively sparse. The largest study to date showed that genetic males with active prenatal androgen effects should be raised as males, given their high rates of male gender identity. Additionally, female infants virilized as a result of CAH should be raised female because more than 90% of these patients report satisfaction with an assigned female gender. However, gender identity outcomes are much more difficult to predict in other disorders, with high rates of gender change and gender dysphoria occurring with some diagnoses. This variability in gender identity again speaks to the reasoning behind deferring genital surgery in infancy.

In some instances, early surgery is indicated for medical reasons (as in the case of the long, common urogenital channel). The potential for malignant degeneration of a gonad (particularly in cases of 46,XY gonadal dysgenesis) must also be considered. Prophylactic gonadectomy was previously performed early in all cases of 46,XYDSD; now, tumor risk is predicted

based on molecular diagnosis. Guidelines for timing a gonadectomy have been proposed, but consensus is needed.

Long-term psychological support is required for most children with DSD. Help should be provided to the child by a mental health professional, preferably someone with experience in dealing with DSD. National and local support groups may provide information and support and may further assist with issues of gender identity and sexuality. Historically, there has been stigma associated with DSD, and care should be taken by the physician to reassure the family that there should be nothing stigmatizing or shameful about the DSD diagnosis. The genitalia may seem atypical but are the normal consequence of the underlying biologic pathways. The underlying condition and management (including surgical decisions) should be discussed with the child over time in an age-appropriate manner, just as one would when treating other chronic medical conditions.

## CONCLUSION

The differential diagnosis of the baby born with developmental anomalies of the external genitalia is extensive, given the complicated process of human sexual differentiation. The birth of such children naturally creates a stressful situation for the family which can be attenuated by the appropriate evaluation and management by an experienced multidisciplinary team. Because fatal results may occur with improper vigilance, hospitalization and close monitoring of the baby are indicated in all cases. Given that a child's gender identity cannot be predicted based solely on the underlying disorder or genital appearance, gender assignment requires careful consideration. In some cases, the assigned gender may not be concordant with the child's gender identity as the child ages. Throughout this process, the general pediatrician plays an important role in helping coordinate the care of these children.

## WHEN TO REFER

Given the possibility of significant electrolyte disturbances, cortisol insufficiency, and possible shock and death, all children with ambiguity of the external genitalia should be evaluated immediately by an experienced multidisciplinary team that includes a pediatric endocrinologist. In many cases, this process necessitates transferring the child to a medical center with a neonatal intensive care unit and the appropriate pediatric subspecialists. The child should never be sent home and referred to subspecialty care as an outpatient.

Indications for referral include the following:

All patients with genital ambiguity

Male-seeming infant with

- Bilateral nonpalpable testes
- Micropenis
- Perineal hypospadias
- Single undescended testis with hypospadias of any degree

Female-seeming infant with

- Clitoral hypertrophy of any degree
- Posterior labial fusion (not adhesion)
- Inguinal or labial mass

Patient with family history of DSD

Patient with discordance between genital appearance and prenatal karyotype

## AAP POLICY

Lee PA, Houk CP, Ahmed SF, et al, in collaboration with the participants in the International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. Consensus statement on management of intersex disorders. *Pediatrics*. 2006;118(2):488–500. AAP endorsed (pediatrics. aappublications.org/content/118/2/e488)

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## Chapter 244

# DOWN SYNDROME: MANAGING THE CHILD AND FAMILY

Marilyn J. Bull, MD

## INTRODUCTION

Primary care physicians (PCPs) are key professionals in the medical care of children with Down syndrome (DS), because they are best able to provide a medical home for the child and family. Caring for children with DS and their families requires long-term commitment and interest on the part of the PCP to ensure that such children realize their full potential and that families receive the support and education they need. This chapter provides current information about the special health care needs of children with DS and guidelines for meeting these needs. The guidelines also include coordination of care with medical subspecialists and early childhood educators.



## ETIOLOGY

DS is caused by a chromosomal abnormality called *trisomy 21*. Most individuals (95%) with trisomy 21 have 3 copies of chromosome 21; in approximately 5% of patients, 1 copy of chromosome 21 is translocated to another chromosome, most often chromosome 14 or 21. In 2% to 4% of cases with trisomy 21, mosaicism is recognizable with both a trisomic and a normal cell line present. Determining the genotype of a child with DS is important, because the recurrence risk for a subsequent pregnancy varies depending on the type of chromosome abnormality present.

### Origin of Trisomy 21

Trisomy 21 most commonly occurs because of an abnormality in chromosome replication. The abnormality, known as *nondisjunction*, occurs during meiosis. Normally during meiosis the process of disjunction reduces the number of chromosomes in the germ cell (sperm and ovum) from 46 to 23. At fertilization, the egg and sperm unite, giving the developing fetus the full complement of 46 chromosomes in 23 pairs. Nondisjunction is the abnormal division of the 46 chromosomes in the egg or the sperm, resulting in 1 carrying 24 chromosomes. At fertilization, the germ cell with 24 chromosomes unites with the germ cell with 23 chromosomes, resulting in a total of 47 chromosomes. DNA testing has shown that nondisjunction of chromosomes in the 21 group, responsible for 95% of cases of DS, occurs in the egg 95% of the time. The recurrence of DS in subsequent pregnancies for nondisjunction trisomy 21 is approximately 1 in 100 for women younger than 35 years, and is age related for older women.

A small group of patients with DS with trisomy 21 (2%–3%) have a mixture of cell types (mosaicism), some cells with 46 chromosomes and some with 47. The proportion of trisomic cells to cells with normal chromosomes can vary greatly from person to person and from tissue to tissue in the same person. The mosaicism is usually detected in the lymphocytes from a peripheral blood sample; thus, tests on other tissues are unnecessary. In some instances, cultures of fibroblasts found on skin biopsy are analyzed when low-level mosaicism is suspected. Experts do not know if any tissues are spared of trisomy cells. This mosaicism often results from an error in maternal meiosis and only in a few cases occurs after fertilization because of an error in mitosis. The mosaic type of DS may have less distinct physical features and, in most cases, show higher intellectual function, depending on the percentage of cells with trisomy 21. Very low levels of trisomy 21 cells are reported in patients with DS with higher intellectual function.

### Origin of Translocation Trisomy 21

*Translocation* refers to a chromosome rearrangement in which part of the extra chromosome attaches to another chromosome. In the case of DS, the long arm of one chromosome 21 attaches to another chromosome 21, 22, or 14. The karyotype shows the number of chromosomes as 46 and shows the abnormally attached additional chromosomal material. In one-third of cases of 14:21 translocation-type DS, one of

the parents is a carrier of a balanced translocation. The mother is the carrier in 90% of these cases. The remaining two-thirds of cases of 14:21 translocation type DS are *de novo*, with the translocation occurring in the noncarrier mother's egg cell during meiosis. In children with a 21:21 translocation, 93% of cases are *de novo* translocations. In *de novo* cases, the 21:21 translocation occurs because of a meiotic error in the egg cell. In about 7% of cases, the 21:21 translocation is the result of a balanced translocation in a carrier parent. In cases in which the 21:21 translocation is passed from carrier parent to child, the carrier is equally likely to be the mother as the father. All of these types of DS produce a similar range of clinical features, but the recurrence risk is higher for the translocation types of DS. Genetic counseling is therefore extremely important.

### Molecular Pathologic Features of Trisomy 21

The DNA sequence of chromosome 21 is now known, and between 200 and 300 genes have been identified. A DS-critical region on the long arm (q arm) has been identified; however, other genes outside this region of chromosome 21 also contribute to the clinical features of DS. This finding strongly suggests that DS is a contiguous gene syndrome with triplicate gene dose effects. This makes it unlikely that a single DS chromosomal region is responsible for most of the DS phenotypic features.

In fact, the variability in clinical features of DS among affected individuals is likely related to polymorphisms in nonchromosome 21 genes as well as to epigenetic factors. A few genes associated with particular characteristics of DS have been identified. For example, polymorphisms in the *DSCAM* gene on chromosome 21, which encodes a neural cell adhesion molecule, have been implicated as conferring an increased risk of Hirschsprung disease in individuals with DS and those without DS. The  $\beta$ -amyloid precursor protein (APP) has been implicated in the increased risk of early-onset Alzheimer disease in the DS population. Genome-wide association studies have revealed genetic loci on chromosome 21 and other chromosomes associated with an increased risk of atrioventricular cardiac septal defects. Moreover, there is emerging evidence of the role of epigenetic factors in the etiology of DS, as meta-analyses suggest that a lack of folic acid supplementation during the periconception period may result in aberrant methylation and increase the risk of meiosis II errors causing DS. Furthermore, methylation patterns in blood samples from individuals with DS demonstrate several regions of differential methylation across the genome, including chromosome 21, and involving genes important in the development and regulation of chromatin structure in particular. These are all areas of active research.

## INCIDENCE AND PRENATAL DIAGNOSIS

By current national prevalence estimates, DS occurs in approximately 1 in every 700 to 800 births. The incidence of DS is closely related to the age of the mother, and the likelihood of bearing a fetus with DS increases when the mother is older than 35 years. Recent advances in technology have improved screening and

diagnostic testing for identifying fetuses with DS. Recently, diagnostic prenatal testing of cell-free DNA from the plasma of the pregnant mother has become available as an option for screening for aneuploidy in women at increased risk. Regardless of maternal age, the American College of Obstetrics and Gynecology recommends a discussion of the risks, benefits, and alternatives of various methods of prenatal screening and diagnostic testing, including the option of no testing, with all patients. Additional prenatal diagnostic testing for the fetus diagnosed with DS, including fetal echocardiogram, can greatly improve the outcome for the mother and the infant.

## DIAGNOSIS

The birth of a child who has DS presents many issues of importance in the clinical care of the infant and for the family. The first critical task is making an accurate and prompt diagnosis, and the most sensitive test in the first 24 hours of life is the physical examination. Multiple features enable the experienced physician to suspect the diagnosis of DS. Some of the most common physical features include hypotonia, a relatively small brachycephalic head, epicanthal folds, flat nasal bridge, upward-slanting palpebral fissures, Brushfield spots, small mouth, small and often square shaped ears, increased skin at the nape of the neck, a single transverse palmar crease, and short fifth finger with clinodactyly. The degree of intellectual disability can only be determined with time, and although most individuals with DS have milder forms of intellectual disability, some may be more significantly affected. According to the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*, health professionals must consider the person's ability or impairment across 3 skill areas: conceptual, social, and practical life skills. Most individuals with DS have mild forms of intellectual disability, although the degree of disability varies greatly among individuals with the condition.

The prenatal diagnosis of DS is increasingly common. If chromosome analysis was performed, the results should be reviewed with the family and the report added to the infant's medical record. If the results of prenatal chromosome testing are not available, a blood sample should be obtained for postnatal cytogenetic analysis to confirm the diagnosis and rule out a chromosome translocation. If there was no prenatal diagnosis and the infant is clinically suspected of having DS, a blood specimen should be obtained for a chromosome analysis and rapid results requested. Results of fluorescence in situ hybridization (FISH) analysis should be available within 24 to 48 hours; if analysis confirms that an extra chromosome 21 is present, a complete chromosome analysis must be obtained to determine if a translocation is present. A detailed family history should also be obtained. The confirmation of DS diagnosis by chromosome analysis helps the parents accept the clinical diagnosis and forms the basis of genetic counseling for the parents regarding the risk of recurrence.

The first important aspect of helping families with an infant with suspected DS is to congratulate them on the birth of their infant. Ideally both parents, or the mother and a significant other, are present and the

delivery of the news for the child with the suspected diagnosis is coordinated by the obstetrician and pediatrician. The diagnosis should be given as soon as possible after the mother has recovered from the immediate delivery, in a private setting by the physicians familiar with the patient.

As soon as the diagnostic FISH and karyotype results are available, the results should be shared with the parents and the clinical manifestations of DS should be reviewed. The parents should be referred for genetic counseling if they were not seen by a genetic counselor prenatally.

A referral for parent-to-parent contact and local and national parent support organizations is helpful for prospective and new parents of a child with DS. It is also important for physicians to know that in several states they are legally mandated to connect parents to official information sources about DS. (See Tools for Practice: Engaging Patient and Family.)

Present the expectations for a child with DS to the family and enable them to learn the realities and possibilities for a healthy and productive life for the child. Share with families how, when, and what to tell siblings, family, and friends about the diagnosis. Assure them that resources and guidance to assist in the care of a child with long-term disabilities are available. Encourage them to enjoy their newborn. Discuss the efficacy and availability of early intervention resources in the community, and facilitate referrals as appropriate.

Arrange for a follow-up meeting with the family to give them time to begin adjusting to the new information and to formulate questions. Offer to meet extended family members to answer questions. Because newborn hospital care is often provided by a physician who is not part of the infant's medical home, it is important to ensure appropriate communication to provide a smooth transition for the family.

## Adoption

Most families are able to meet the needs of their child born with DS. Some families have greater initial difficulty and require more extended counseling. In rare cases, a family will not be able to accept a child who has DS. In this event, adoption should be discussed. In many instances, families are waiting to adopt children who have DS, and families with one child with DS may wish to adopt another. The National Down Syndrome Adoption Network can be contacted for information ([www.ndsan.org](http://www.ndsan.org)).

## HEALTH SUPERVISION

Early detection and correction of medical problems seen in children who have DS is important to minimize complications and optimize the child's potential growth and development. Children with DS require the usual preventive interventions and anticipatory guidance given to other children and families, but the special problems of children who have DS require additional evaluation and close monitoring.

## Birth to 1 Month of Age

When the clinical diagnosis of DS is considered, rapid chromosome testing is ordered, and the family is

counseled regarding the suspected diagnosis. Careful assessment of the infant is indicated.

### **Congenital Heart Defects**

Approximately 50% of infants with DS have congenital heart defects. An echocardiogram should be obtained for all infants and interpreted by a pediatric cardiologist. This is important even if a fetal echocardiogram had been done. All infants with an abnormal postnatal echocardiogram should be referred to pediatric cardiologist.

### **Gastrointestinal Problems**

Gastrointestinal problems, present in 15% of children with DS, may be evident very early in the newborn period or manifest later in infancy. Duodenal atresia, tracheoesophageal fistula, anorectal stenosis or atresia or Hirschsprung disease, and malrotation occur with increased frequency in children with DS. Appropriate evaluation and treatment should be instituted promptly if symptoms are present.

Constipation is common and often associated with a limited fluid intake, restricted diet, and hypotonia. Many infants require treatment with a stool softener. Hypothyroidism, gastroesophageal malformations including stenosis, and Hirschsprung disease (2%) should be considered if constipation is refractory to usual treatment.

### **Feeding Problems**

Most infants with DS can breastfeed successfully. Some will need supplementation with a bottle or tube until a successful nursing pattern is established. Infants who sleep for prolonged periods need to be awakened for feeds to ensure adequate caloric intake. Feeding may be facilitated by ensuring that nasal passages are clear and providing chin support for infants with low tone. Infants with feeding problems need to have weight gain monitored closely; if difficulty with nursing occurs, referral to a lactation consultant may be helpful.

Infants with hypotonia and slow feeding, choking with feeds, recurrent pneumonitis or other recurrent or persistent respiratory problems, or unexplained failure to thrive should be referred for a radiographic swallowing assessment. Alternative feeding methods should be used for infants at risk for aspiration until they mature and the difficulty has resolved.

### **Ophthalmologic Problems**

Assess infants with DS for the presence of a red reflex. Cataracts and congenital glaucoma occur with increased frequency and require treatment by an ophthalmologist with experience in managing children with DS.

### **Hematologic Abnormalities**

Leukemoid reactions and transient myeloproliferative disorder (TMD) are relatively common, occurring in about 10% and seen almost exclusively in newborns with DS. Polycythemia is also relatively common. Obtain a complete blood count and follow subspecialty recommendations for management. TMD usually resolves spontaneously but carries a 10% to 30% risk of later onset of leukemia.

Parents are often concerned about the increased risk of leukemia in children with DS, which occurs in only about 1% of these children. Parents should be counseled regarding the signs of easy bruising, petechiae, lethargy, or changes in feeding patterns, which could be early signs of leukemia.

### **Respiratory Complications**

Problems with breathing, including stridor, noisy breathing, upper airway obstruction with retractions, or wheezing, should be referred to a pediatric pulmonary specialist. Intubation may also be more difficult, because tracheal anomalies including tracheal rings and small tracheal size occur at an increased frequency.

Hearing should be evaluated at birth following universal newborn hearing screening guidelines, and any needed follow-up assessment should be completed by 3 months.

### **Congenital Hypothyroidism**

Obtain thyroid stimulating hormone (TSH) concentration if state newborn screening only measures free thyroxine (T4) to avoid missing congenital hypothyroidism, which occurs in approximately 1% of infants with DS. The management of children with abnormal thyrotropin or T4 levels should be discussed with a pediatric endocrinologist.

### **Atlantoaxial Instability**

Explain to parents the importance of cervical spine positioning precautions to avoid excessive extension or flexion. Atlantoaxial instability refers to backward movement of the odontoid process of the axis, which may compress the spinal cord and result in the signs and symptoms of cord compression including neck pain, head tilt, progressive weakness, and loss of bladder or bowel control. Neurologic examination reveals long-tract signs such as increased deep-tendon reflexes in the lower extremities, a positive Babinski sign, and ankle clonus.

Atlantoaxial subluxation is a neurosurgical emergency requiring immediate referral and treatment. Although atlantoaxial subluxation occurs in only 1.5% of children who have DS, it can be life threatening and may cause irreversible disability if not treated promptly. Any child with complaints of neck or radicular pain, weakness, spasticity or change in tone, gait difficulties, hyperreflexia, or change in bowel or bladder function must undergo plain cervical spine radiography in the neutral position. Refer caregivers to a pediatric neurosurgeon or pediatric orthopedic surgeon experienced in managing DS in children if plain cervical spine radiography in the neutral position is abnormal.

Routine radiographs of the cervical spine are no longer recommended as they do not predict well which children are at an increased risk of developing spine problems.

Furthermore, adequate vertebral mineralization and epiphyseal development for accurate radiographic evaluation of the cervical spine does not occur until 3 years of age.

The protection of the cervical spine during any anesthetic, surgical, or radiographic procedure is



important, but parents also need to be reassured that normal care, including therapy to develop head control, is not dangerous and is important for normal development.

### **Complementary and Alternative or Integrative Therapies**

Discuss with parents treatments that are considered integrative, and facilitate their understanding of which therapies are recognized to be safe and which are potentially dangerous.

Many families have questions about cognitive and developmental improvement with supplemental vitamins or with vitamins and minerals in high dosages. However, no studies have validated that improvement occurs, and there are known side effects of high doses of some vitamins. Care should be taken to ensure that parents understand the risks and that excessive doses are avoided.

### **1 Month to 1 Year of Age**

In many cases, families who have a child with DS need to see the PCP frequently for medical care and education. The parents' anxiety and questions decrease with time, but for the initial few months they need to be able to depend on the availability of their medical home for their needs. Ensuring that there are adequate time and resources in a busy office can be challenging, and using a system of care for the child with special health care needs (CSHCN) is important. Consultation with a dietician, nurse practitioner, or social worker can supplement the specialized care helpful to a family with an infant with DS. It is important to schedule a follow-up visit soon after hospital discharge for an assessment of the infant's progress and to provide the family an opportunity to discuss questions and concerns. Follow-up visits should include an assessment of the emotional status of the parents, adjustment of the siblings, and the effect of the baby on interfamilial relationships. Connection to early intervention services and their relationship to the needs of the infant and family should be reviewed.

During the first year, the family's understanding of the risk of recurrence of DS and the availability of prenatal diagnosis should be reviewed and a referral made for genetic counseling if not already provided.

Families should be encouraged to discuss questions they may have regarding therapies that are considered integrative at each well-child visit.

### **Growth and Nutrition**

Discuss feeding and nutritional intake carefully in the first visits, and routinely in each health care visit. Monitor weight and weight-for-height trends closely. Plot growth parameters using the standard growth charts of the National Center for Health Statistics or the World Health Organization. Previously used DS growth charts no longer reflect the current population of children. New DS growth charts have been developed, and patterns of growth can also be followed on the DS-specific growth charts.

### **Hearing**

Serous otitis media and associated fluctuating hearing loss are extremely common in young children with DS

(50%–70%). Infants who passed the newborn hearing screen should be reevaluated at age 6 months and every 6 months subsequently until they are able to participate reliably in ear-specific testing with headphones, usually after age 4 years. Any child who fails a hearing screen should be evaluated by an otolaryngologist comfortable with examining infants with stenotic ear canals to determine if middle ear problems are present.

### **Vision**

Within the first 6 months of life, infants with DS should be examined by a pediatric ophthalmologist or an ophthalmologist with expertise in caring for infants with disabilities to assess for cataracts, nystagmus, and strabismus. Lacrimal duct obstruction is also common because of the craniofacial configuration in DS; infants should be referred for surgical repair if any obstruction is not resolved by 9 to 12 months of age.

### **Thyroid Disease**

Repeat TSH testing at age 6 months, age 12 months, and annually thereafter because symptoms of hypothyroidism may be confused with unrelated findings seen commonly in children with DS.

### **Obstructive Sleep Apnea**

Children with DS are at an increased risk of obstructive sleep apnea, so the symptoms should be discussed. Any child with heavy breathing, snoring, restless sleep, uncommon sleep positions, frequent night awakening, daytime sleepiness, apneic pauses, and behavior problems that could be associated with poor sleep should be referred to a pediatric sleep laboratory for a sleep study or polysomnogram. Because the correlation between parent report of sleep obstruction symptoms and polysomnogram results is poor, it has been recommended that every child with DS be referred if possible for a sleep study by age 4 years. In addition, families should be counseled on obesity as a risk factor for obstructive sleep apnea.

### **Mortality**

Medical care for infants in this age group who have DS involves particular diagnostic and consultative procedures, given that more than 50% have serious medical disorders as a component of their condition. The first year of life holds the highest probability of death for children with DS who have an additional anomaly. Approximately 78% of infants with an additional anomaly survive, and 96% without an additional anomaly survive. Survival of children with cardiac malformations has improved, with only 8% to 9% mortality now being reported in children with DS and heart defects. Leukemia is a cause of death in less than 10% of cases.

### **Questions**

During office visits for periodic health assessments, the PCP should ask about the infant's feeding and discuss enrollment in an early education program. Extra time should be arranged at office visits to allow families to talk about how they are adjusting. The physician should review with them information about DS



provided earlier. The family should also be informed about Supplemental Security Income (SSI) and other programs that offer financial aid to help families with the extra costs of raising a child who has special needs. Parents of infants who have DS often ask questions about tongue protrusion. Contributing factors include hypotonia, a relatively small oral cavity, and upper airway obstruction with mouth breathing. Behavior-management techniques can be used to help manage tongue protrusion; for some children, oromotor exercises may be helpful.

Many families seek hope for an improvement of appearance and function for their child with DS through surgical and medical interventions. Tongue resection to improve speech, silicone implants to correct micrognathia, and surgical interventions for eye appearance have been implemented. The PCP should discuss these interventions when they are considered by the family and be prepared to communicate the risks and benefits of any surgical procedure. For example, no improvement in speech after tongue resection has been observed.

### 1 to 5 Years of Age

Children with DS need annual health assessments. At these office visits, the PCP should inquire about the caregiver's concerns and review the health supervision issues specific to children with DS.

### History and Anticipatory Guidance

A full history and physical examination should include attention to nutrition and growth. Height, weight, and weight for height or BMI should be plotted on the World Health Organization or US Centers for Disease Control and Prevention (CDC) growth charts. The new DS-specific charts can also be used to follow patterns of growth. Changes in diet may be recommended to ensure that the child receives adequate calcium, vitamin D, and iron, and that the fat content of the milk is appropriate for the child's weight for height or BMI. For children who are picky eaters, are unable to chew meat, or do not have an adequate intake of iron-containing foods, a complete chewable multivitamin that contains iron may be crushed and added to food.

Children with cardiac lesions should maintain follow-up with a pediatric cardiologist even after cardiac repair to monitor for residual lesions or the development of pulmonary hypertension.

Monitoring for strabismus and ensuring every child is seen at least annually until age 5 years for ophthalmologic assessment is important. The development of refractive errors and strabismus during preschool years is common, and children with these issues benefit from early detection and treatment.

Fluctuating hearing loss associated with serous otitis media is common in DS. Tympanometry and a behavioral audiogram should be arranged every 6 months until the child is capable of ear-specific audiologic testing, which is usually around age 6 years.

Continue to ask about heavy breathing, snoring, restless sleep, daytime sleepiness, apneic pauses, uncommon sleeping positions, and behavior problems that could be associated with poor sleep, and refer as

appropriate. The strong correlation between obstructive sleep apnea, cognition, and behavioral problems makes detection important. A sleep study is recommended for all children with DS by age 4 years.

A dental examination is recommended twice a year beginning at the first birthday. It is helpful to remind parents that delayed and irregular dental eruption and hypodontia are common in children with DS.

Discuss with caregivers and model the use of accurate terms for genitalia and private body parts. Teach the child and family that the only reason for viewing or touching private body parts is for doctor visits or bathing and showering.

It is also important to discuss with caregivers the increased risk of sexual exploitation and educate them that most commonly the perpetrators are people the child knows and trusts.

As discussed in previous visits, future pregnancy planning, recurrence risk, and resources for prenatal diagnosis should be provided during at least one visit when the child is between 1 and 5 years.

It is important to review the signs and symptoms of spinal cord compression associated with atlantoaxial instability and remind caregivers to contact a physician experienced with the condition immediately if they have concerns about possible symptoms.

Other topics to review include questions regarding integrative (complementary and alternative) therapies and eligibility for SSI, Medicaid, and any other needed social service benefits.

### Laboratory Tests and Vaccines

TSH screening should be performed annually, or sooner if symptoms of thyroid dysfunction occur.

A hemoglobin screening should be performed annually for all children, as well as ferritin and C-reactive protein screening for any child at risk of iron deficiency on the basis of decreased iron intake.

All routine immunizations should be provided and an influenza vaccine should be given annually to the child and encouraged for all household contacts. Ensure that children with respiratory and cardiac problems receive all recommended vaccines.

Children with symptoms potentially related to celiac disease and who are on a gluten-containing diet should have screening with a tissue transglutaminase immunoglobulin A (IgA) level and simultaneous serum IgA. Symptoms are varied and include diarrhea, protracted constipation, slow growth, unexplained failure to thrive, anemia, abdominal pain or bloating, and refractory developmental or behavioral problems. Patients with abnormal values should be referred for specialty assessment. There are no data and no consensus that patients with normal data on an initial evaluation warrant further laboratory tests.

### Early Intervention and Education

Review involvement in early intervention programs and therapy as indicated. Assess the involvement of caregivers in the child's developmental program and also the needs of the child and family related to the child's strengths and weaknesses. For children younger than age 3 years, review early intervention including physical, occupational, and speech therapy. It is helpful

to review the importance of caregiver involvement in the process. Discuss the transition from early intervention to preschool at the 30-month visit, because the family needs to understand the change from the Individualized Family Service Plan (IFSP) to the Individualized Education Plan (IEP) in public education.

The PCP needs to review the current IEP for children older than 3 years to ensure that the developmental program is appropriate and that the parents have had an opportunity to provide input in the IEP process. School problems may come to the physician's attention more often when children who have DS are placed in mainstreamed or regular classes. Typically developing children are excellent role models for children with DS, but additional supports in the school environment are often required. School learning problems require further evaluation. The history should be reviewed thoroughly to ensure that the parents' and teachers' expectations are appropriate for the child's developmental age and that appropriate educational interventions are selected for the child's specific learning style. Resources for teachers and caregivers that are specific to children with DS are available and referenced in the Tools for Practice section. Medical problems that can affect learning and behavior should be identified. For example, hearing and vision need regular evaluation as outlined previously, and methods of communication that are developmentally appropriate for the child should be integrated into the program.

### **Autism in Down Syndrome**

Children with DS are recognized with increasing frequency to have symptoms attributable to autism and may be diagnosed with autism spectrum disorder. This diagnosis can be challenging, because the findings are often attributed to DS alone and the assessment is most effective when done by a physician experienced in both DS and autism. The diagnosis should be considered whenever social and communication skills lag significantly behind those expected for the child's general developmental level.

### **Behavior Problems**

The PCP also should ask about behavior problems. The personalities of many children who have DS may not fit the stereotype of being placid or compliant, and parents may not volunteer information about obstinacy or noncompliance. When parents express concerns about behavior, a thorough history should be obtained, and the parents should be asked about changes in the environment or their expectations. A complete physical examination should be performed and laboratory tests performed, if warranted, to identify medical problems that may lead to behavior disorders. A trial of behavior management should be initiated for mild problems, and the diagnoses of autism or physical abuse should be considered. For severe behavior problems or persistent mild to moderate problems that have no apparent medical cause, the child should be referred to a behavior specialist familiar with behaviors seen in children with DS. In addition, an assessment for celiac disease should be considered for children with difficult-to-manage behavior problems.

## **5 to 13 Years of Age**

The child with DS should be seen for an annual health care visit that incorporates all aspects of well-child health supervision. The PCP may also receive many questions regarding behavior, nutrition, activity, and educational interventions for the child with DS. Social opportunities for children with DS often become more challenging as they grow older, and the family will benefit greatly from the advice of the trusted physician.

### **History and Anticipatory Guidance**

The comprehensive well-child visit for a child with DS should include a complete history, review of systems, and physical examination. Nutritional assessment should include plotting weight, height, and BMI on the CDC National Center for Health Statistics growth charts. New DS-specific charts have been developed that can also be used to follow patterns of growth. Monitoring weight and activity is extremely important at these ages because lifetime eating patterns are best established in childhood.

Hearing assessments should be made every 6 months until the child is able to accomplish ear-specific testing (usually around age 6 years). Hearing testing annually thereafter is important for development of optimal speech and communication.

An ophthalmologist experienced in caring for children with disabilities should perform a visual assessment every 2 years or more often, if problems are identified.

Evaluate the child for dermatologic problems, and remind the family that both cardiology follow-up as indicated and an annual dental evaluation are important.

The physical examination should be performed with particular attention to myelopathic signs. Review with parents the universal precautions for the protection of the cervical spine during anesthetic, surgical, or radiographic procedures. The PCP should be contacted immediately in the case of new onset of symptoms of myelopathy.

As children become involved with organized sports, parents should be advised that some contact sports may place children at increased risk of spinal cord injury. Football, soccer, and gymnastics for older children should be considered with caution; trampolines should be avoided unless under direct professional supervision. The Special Olympics has specific screening requirements for participation by all athletes. Review with caregivers any concerns about sleep including snoring, restless sleep, unusual sleep positions, and other concerns about sleep apnea. Discuss obesity as a risk factor for obstructive sleep apnea.

## **13 to 21 Years of Age**

Adolescence is a special challenge for any family. The physical, emotional, and educational needs in adolescents who have DS, however, require a special approach. During the annual health assessment visit, the PCP should discuss with the family their child's health, educational program, behavior challenges, and long-term plans for guardianship and care.

### **History and Anticipatory Guidance**

The comprehensive assessment needs to include an evaluation of nutritional status. Height, weight, and

BMI plotted on a standard CDC growth chart are an essential component of this evaluation, and the new DS-specific charts can also be used to follow patterns of growth. Nutritional counseling and evaluation of activity are extremely important, and it is helpful to include signs and symptoms of sleep disorder and the added risk of obesity for sleep apnea in the discussion.

The pediatrician should annually review with the patient and family the potential symptoms related to atlantoaxial instability and perform a careful examination for myelopathic signs. Prompt referral for assessment by a physician experienced in the disorder can minimize long-term disability. Continued emphasis on healthy lifestyle is important, and the Special Olympics can provide excellent opportunities for activity. The Special Olympics has special health screening requirements for all athletes.

At this age, it is critical to discuss current educational planning and its appropriateness for the individual. A discussion of training for adult life and planning for transition to adulthood is an essential component of the planning process. Explain the process of arranging for guardianship by age 18 years as appropriate, and discuss financial planning including enrollment in Medicaid and SSI. Families also benefit from recommended continuing speech and communication therapy for optimal functional skill development.

The PCP and family should also discuss a plan for the adolescent's living arrangements. Most communities have a spectrum of community living facilities that range from small, heavily supervised group homes to apartments that have minimal supervision. Families need to make living arrangements 3 to 6 years before they anticipate the need because there is often a waiting list for placement in a community facility.

A review of behavior and social development is important, and a child with any acute deterioration in function should be referred for assessment. Any history of possible seizures is an important consideration. Discuss normal and typical sexual development and behavior and provide understandable information on sexuality. It is essential for the family to receive information about contraception and prevention of sexually transmitted infections in both boys and girls at this age. The risk of having a child with DS should be discussed with girls. Although male patients with DS are usually infertile, instances of reproductive capability in men have been reported. Girls should receive routine gynecologic care, and any premenstrual behavioral concerns and menstrual hygiene issues should be reviewed.

Every young person and his or her family should be encouraged to continue to increase their development of independent hygiene and activities of daily living. Families appreciate counseling about teaching their child to avoid tobacco and drug abuse.

Additional medical considerations include a review of the cardiac history and an evaluation of older patients for acquired mitral valve and aortic valve disease, symptoms potentially related to celiac disease, and an annual TSH and hemoglobin screening. Ferritin and CRP screening should be performed for anyone at risk for iron deficiency. An annual review of immunization status and an influenza vaccine should continue.

A consultation for eye examination should occur every 3 years unless indicated sooner on the basis of ophthalmologist recommendations. Special attention should be given to ophthalmologic problems that typically occur after puberty, including cataracts, refractive errors, and keratoconus.

The family should be reminded to obtain an ear-specific audiogram and dental examination annually or sooner, if recommended by the specialist.

The transition to adult care is an important conversation to have with families. For many patients, identifying providers of adult subspecialty care can be challenging. Pediatric PCPs often continue to monitor adolescents into early adulthood to provide continuity of care. This can be helpful while the subspecialty care is established. Families are often attached to the pediatric PCP, and the discussion of adult care must center on aspects of preventive medical care for the young adult.

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## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *The Arc* (Web site), ([www.thearc.org](http://www.thearc.org))
- *Building the Legacy: IDEA 2004* (Web page), US Department of Education ([idea.ed.gov](http://idea.ed.gov))
- *Let's Put the Person First, Not the Disability!* (fact sheet), Disability Is Natural ([www.disabilityisnatural.com/explore/people-first-language](http://www.disabilityisnatural.com/explore/people-first-language))

### Engaging Patient and Family

- *Count Us In: Growing Up With Down Syndrome* (book), Kingsley J, Levitz M; Harvest Books, 1994
- *Got Transition* (Web site) ([www.gottransition.org](http://www.gottransition.org))
- *Understanding a Down Syndrome Diagnosis* (booklet), Joseph P. Kennedy Jr. Foundation ([www.lettercase.org](http://www.lettercase.org))
- *Welcome to Holland* (essay), Emily Perl Kingsley ([www.our-kids.org/archives/Holland.html](http://www.our-kids.org/archives/Holland.html))
- *Woodbine House* (publisher) ([www.woodbinehouse.com](http://www.woodbinehouse.com))
  - *Babies with Down Syndrome: A New Parents' Guide* (book), Stray-Gundersen K; 1995
  - *Bebés Con Síndrome De Down: Nueva Guía Para Padres* (book), Skallerup, SJ; 2008
  - *The Boys' Guide to Growing Up, Choices & Changes during Puberty* (book), Couwenhoven T; 2012
  - *Early Communication Skills for Children with Down Syndrome: A Guide for Parents and Professionals*, 3rd ed (book), Kumin L; 2012
  - *The Girls' Guide to Growing Up, Choices & Changes in the Tween Years* (book), Couwenhoven T; 2011
  - *Gross Motor Skills for Children with Down Syndrome, A Guide for Parents and Professionals*, 2nd ed (book), Winders P; 2014
  - *Teaching Reading to Children with Down Syndrome: A Guide for Parents & Teachers* (book), Oelwein P; 1995
  - *When Down Syndrome and Autism Intersect: A Guide for Parents and Professionals* (book), Froehle M, Zaborek R; 2012



### Medical Decision Support

- *A Toolkit to Improve Care for Pediatric Patients With Genetic Conditions in Primary Care* (e-book), Genetics in Primary Care Institute ([geneticsinprimarycare.aap.org/YourPractice/Documents/GPCI\\_Toolkit.pdf](http://geneticsinprimarycare.aap.org/YourPractice/Documents/GPCI_Toolkit.pdf))
- *Facts About Down Syndrome* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/ncbddd/birthdefects/DownSyndrome.html](http://www.cdc.gov/ncbddd/birthdefects/DownSyndrome.html))
- *Online Mendelian Inheritance in Man* (Web site), Johns Hopkins University ([www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM](http://www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM))

### AAP POLICY

Bull MJ; American Academy of Pediatrics Committee on Genetics. Health supervision for children with Down syndrome. *Pediatrics*. 2011;128(2):393–406 ([pediatrics.aappublications.org/content/128/2/393](http://pediatrics.aappublications.org/content/128/2/393))

### SUGGESTED READINGS

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Society for Maternal Fetal Medicine Committee on Genetics. Cell-free DNA screening for fetal aneuploidy. *Obstet Gynecol*. 2015;126:e31–e37

## Chapter 245

# DRUG ERUPTIONS, ERYTHEMA MULTIFORME, STEVENS-JOHNSON SYNDROME

Lauren Henderson, MD; Judith V. Williams, MD

Adverse drug reactions are seen in 1.5% of children in the outpatient setting and 11% of hospitalized children; they account for 2% of pediatric hospitalizations. The clinical expression of drug eruptions is extremely varied and includes rashes of varying morphology, symptoms, and associated conditions (Box 245-1).

This chapter discusses the types of drug eruptions seen most commonly in children: exanthematous, urticarial, serum sickness-like reactions, drug reaction with eosinophilia and systemic symptoms (DRESS; also known as drug-induced hypersensitivity syndrome [DIHS]), acute generalized exanthematous pustulosis (AGEP), erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN).

## EXANTHEMATOUS ERUPTIONS

### Etiology

Exanthematous eruptions represent the most common cutaneous expression of a drug reaction. Historically, these were known as morbilliform (measles-like), because they were clinically indistinguishable from viral causes. Although a variety of drugs can cause this reaction, the drugs that cause exanthematous or urticarial eruptions most often are listed in Box 245-2.

### History

A drug-induced exanthematous eruption often begins within 1 to 2 weeks after starting the drug, but delayed reactions can occur as late as 1 to 2 weeks after the drug is discontinued. Because no single laboratory test can identify the responsible drug, heavy reliance is placed on the history. Children simultaneously receiving more than 1 drug present a problem. In trying to select a single drug from a list, the 2 variables to consider are the temporal relationship between the administration of the drug and the onset of the rash, and the

### BOX 245-1 Cutaneous Adverse Reactions

- Exanthematous
- Urticarial and angioedema
- Serum sickness-like reactions
- DRESS/DIHS
- AGEP
- EM
- SJS
- TEN
- Drug-induced Sweet Syndrome
- Drug-induced lupus erythematosus
- Erythema nodosum
- Vasculitis
- Photosensitivity reactions
- Acneiform
- Alopecia
- Fixed drug eruptions
- Drug-induced pigmentary changes (minocycline)
- Lichenoid reactions
- Pruritus
- Blistering

AGEP, acute generalized exanthematous pustulosis; DIHS, drug induced hypersensitivity syndrome; DRESS, drug rash with eosinophilia and systemic symptoms; EM, erythema multiforme; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrosis.

Derived from Bigby M. Rates of cutaneous reactions to drugs. *Arch Dermatol*. 2001;137(6):765–770; Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med*. 1994;331(19):1272–1285.

### BOX 245-2 Allergic Skin Reactions to Drugs<sup>a</sup>

- |                             |                |
|-----------------------------|----------------|
| • Aminopenicillins          | • Erythromycin |
| • Sulfonamides              | • Penicillin G |
| • Ampicillin                | • Allopurinol  |
| • Semisynthetic penicillins | • NSAIDs       |
| • Blood                     | • Barbiturates |
| • Cephalosporins            | • Diazepam     |

NSAIDs, nonsteroidal anti-inflammatory drugs.

<sup>a</sup>Ranked from highest to lowest rate of reaction

Derived from Bigby M. Rates of cutaneous reactions to drugs. *Arch Dermatol*. 2001;137(6):765–770.



likelihood that a given medication can cause a drug eruption. For the latter variable, the specific drug incidence rates provide vital information regarding the most common causative drug. Aminopenicillins have the highest rate of reaction per recipients (4.4–8.0/100), followed by sulfonamides (2.5–3.7/100), while diazepam has the lowest rate (0.04/100). A concurrent viral infection can increase the chance of an exanthematous drug eruption, as in the commonly reported rash seen in children with Epstein-Barr virus following ingestion of amoxicillin. Most of these are morbilliform in nature. Their pathogenesis remains to be elucidated, but some studies suggest that an enhanced reaction to drug metabolites during an active viral infection results in cytotoxicity against infected cutaneous cells.

### Physical Findings

This type of eruption is generalized and consists of brightly erythematous macules and papules that tend to be confluent over large areas. It usually starts centrally on the trunk and spreads distally, with the legs being the last to become involved and also the last to clear. Palms and soles can be affected, but mucous membranes are usually spared. Pruritus is a common symptom, but not diagnostic. Drug fever has been well described, but most common exanthematous drug eruptions are not accompanied by an elevation in body temperature.

### Differential Diagnosis

For a generalized exanthematous eruption, the major differential diagnosis is a viral exanthem, drug reaction, or toxic erythema. A drug eruption may be more erythematous and confluent than a viral exanthem, but not always. Other clinical information can help establish the diagnosis, including a drug history and the presence or absence of other signs and symptoms of a viral infection. Acute and convalescent serologic tests can be obtained for some viral infections to provide a retrospective diagnosis.

In most cases, a presumptive diagnosis is made based on clinical data. Examples of toxic erythema are scarlet fever, staphylococcal-induced scarlatiniform eruptions, and possibly Kawasaki disease. Features that help distinguish these toxic erythemas from drug eruptions include a sandpaper-like roughened texture of the rash, mucous membrane involvement (scarlet fever and Kawasaki disease), fever, a focus of infection, and lymphadenopathy. Postinflammatory desquamation from the skin of the hands and feet often follows the rash of toxic erythema, but this sign is nonspecific. Drug eruptions as well as viral exanthems can involve the hands and feet, particularly the palms and soles. If the inflammation has been sufficiently intense, fine desquamation may follow.

### Laboratory Studies

Peripheral blood eosinophilia can occur during a drug eruption, but it is not diagnostic because eosinophilia can be seen in patients with allergic disease in general. The presence of eosinophils in a skin biopsy of the rash suggests a drug eruption. Unfortunately, no laboratory test at this time can incriminate a specific drug. In vitro tests to evaluate the cause of drug hypersensitivity reactions are an active area of

research; however, they are not developed sufficiently to be useful in clinical decision making.

For some drugs that can produce significant reactions in children with certain human leukocyte antigen (HLA) types, genetic pre-therapy testing can predict which children may be more susceptible to developing a drug reaction (clin pharmacol). The US Food and Drug Administration (FDA) recommends testing for HLA-B\*1502, particularly in individuals of Asian ethnicity, before starting carbamazepine to avoid developing SJS. Testing for HLA-B\*5701 can be done prior to starting abacavir.

### Treatment

When an offending agent is identified, its use should be discontinued. If a child is taking several drugs and the physician is uncertain of the offending agent, it is recommended to discontinue all nonessential medications. Whenever possible, any remaining possible offenders should be changed to alternative agents.

Therapy is directed toward the symptoms, with antihistamines used most commonly to alleviate pruritus. Topical agents are usually confined to moisturizers, which are most helpful during the desquamative phase of the reaction. Although topical steroids may be of some value in controlling pruritus, systemic steroids are rarely required.

### Complications

Most common exanthematous drug eruptions are without significant complications. However, continuing the use of the offending agent can result in 2 types of consequences—cutaneous and renal. When large areas of skin are inflamed, peripheral vasodilation can result in increased transepidermal water loss. This may become problematic in a critically ill child; however, it is usually well tolerated by most children. Most exanthematous drug eruptions heal without scarring. In children with dark-pigmented skin, postinflammatory hyperpigmentation or hypopigmentation may develop, but will fade over time. The renal risk is that of allergic interstitial nephritis, an uncommon development that is usually associated with penicillins and cephalosporins and only rarely with other drugs.

### Course

Drug eruptions gradually clear after the offending agent is discontinued, usually over 1 to 2 weeks. The rash may seem to worsen for several days after the offending agent has been stopped. The lesions then may darken to a tan or brown color and eventually fade. Although in some cases a drug eruption will clear even when use of the offending agent is continued, this should be avoided if an alternative agent is available. With exanthematous eruptions, if a responsible drug is identified, the reaction should be documented in the medical record. If there is doubt that a reaction reflects a true drug allergy, consultation with an allergist for further evaluation and possible oral challenge testing should be considered. Although an oral challenge is helpful in predicting immunoglobulin E (IgE)-mediated reactions, it is not helpful in predicting exanthematous ones. Very rarely, severe allergic reactions requiring hospitalization have occurred with

repeat drug challenges. Therefore, it is wise for drug challenges to take place in a controlled setting under the direction of an allergist.

## URTICARIA (HIVES)

### Etiology

Drug-induced hives can be mediated by either an immediate immunologic allergy (IgE- or immune-complex-dependent) or delayed nonimmunologic mechanisms. Immediate reactions are more common than delayed reactions. Drugs that induce urticaria by the nonimmunologic mechanism do not need previous sensitization, as they act as direct mediators for mast cell degranulation. Such medications include codeine, opiates, amphetamines, and radiocontrast media.

Conversely, drugs that are immunologically mediated require a period of sensitization. Once sensitization occurs, a type I hypersensitivity-mediated urticaria can develop within minutes following exposure. The most common offending agents are  $\beta$ -lactam antibiotics. Good management of urticaria depends on an understanding of the triggers and aggravating factors in addition to appropriate treatment options.

### History

The physician should obtain a history regarding timing of rash onset to drug, previous exposure to the drug, timing of discontinuation or decrease in symptoms upon removal of the drug, and specific symptoms and characterization of the rash (itching, migration of hives, associated bruising, associated angioedema). Over-the-counter medications and supplements should also be included in the history. It is important that physicians obtain a good history pertaining to the urticarial reaction as soon as possible, because often parents will not recall the details of the reaction once their child is referred to a specialist.

Many children and their parents tend to consider over-the-counter medications unimportant. Nonsteroidal anti-inflammatory drugs (NSAIDs) cause hives in some children and can aggravate them in those who have urticaria, regardless of its cause. Aspirin can cause hives, but is not widely used in children because of the possible risk of Reye syndrome.

A history of associated symptoms also may be important. Itching is almost a universal finding. Urticaria may be seen in combination with angioedema in 40% of cases. While urticaria rarely progresses to anaphylaxis, a combination of acute urticaria, angioedema, and extracutaneous symptoms (wheezing and cough) suggests anaphylaxis and necessitates immediate medical attention.

### Physical Findings

Hives usually appear as pink, edematous papules and plaques that are most often scattered, but can be generalized and even confluent. By definition, an individual hive is transient, lasting less than 48 hours, although new hives may develop continuously. Hives often assume geographic shapes, such as arcuate or annular. They can have pale or dusky centers and dark pink borders. Large or “giant” hives that are polycyclic with ecchymotic centers from vasoconstriction can be confused with EM and are termed “urticaria

multiforme” (UM) (Figure 245-1). This type of urticaria is more common in infants and preschoolers. It usually occurs acutely, often precipitated by a viral infection, immunizations, or recent antibiotic use. Urticaria in serum sickness reactions is commonly seen in conjunction with arthralgias, localized edema, fever, and lymphadenopathy.

### Differential Diagnosis

The differential diagnosis of urticaria may be approached in 2 ways—from the intrinsic causes of hives, and from consideration of the cause of lesions sometimes mistaken as hives. In children, the most common causes of acute urticaria are infection, drugs, and food allergies. Less often, physical modalities (eg, cold, pressure, or sunlight) and emotions can cause hives. Often, the precise cause remains elusive.

Urticaria multiforme should be considered on the differential diagnosis of acute urticaria. This benign hypersensitivity reaction is pathogenically similar to urticaria, but morphologically distinct. Usually following a viral infection, UM presents as polycyclic to annular urticarial plaques with a dusky center. They are commonly mistaken clinically for EM and serum sickness-like reactions. Unlike EM, the lesions of UM may have a dusky center, but are not targetoid (ie, they do not have a central necrotic or bullous component). Individual lesions in UM are transient, lasting 24 to 48 hours, while the lesions of EM are fixed



**Figure 245-1** Urticaria multiforme.

and can last for days to weeks. Children with UM may have edema of the face or extremities, but this is not usually seen with EM. Serum sickness–like reactions can mimic UM with polycyclic hives and localized edema, but those children also can have arthralgias, myalgias, and lymphadenopathy. Fever is usually higher than that seen in UM. A serpiginous band of erythema may be seen along the sides of the digits and along hands and feet. Drugs, especially antibiotics, are often the cause of serum sickness–like reactions. The cephalosporins have been documented to cause a serum sickness–like reaction in children.

Table 245-1 outlines clinical features of UM, EM, and serum sickness–like reactions.

Additionally, the individual lesions in juvenile rheumatoid arthritis behave similarly to hives in that they are transient, but differ in size (only 2–3 mm), color (typically salmon), and timing (usually appearing with fever spikes).

### Laboratory Studies

As with other drug eruptions, drug-induced hives may be accompanied by eosinophilia. To evaluate for hepatitis, the physician should check liver enzymes in children who have hives and fever. However, in afebrile children, laboratory tests are rarely helpful in eliciting a cause, and they are of no help in implicating a specific drug.

### Treatment

Use of any suspected medication should be discontinued. Symptomatic therapy is usually achieved with second generation H1 antihistamines, as they are well tolerated by children and have a decreased side-effect profile. It is recommended to schedule these medications, rather than dosing as needed. The safe maximum dose should be reached for 1 medication before adding additional oral antihistamines. If symptoms remain uncontrolled, the physician can decide, in a step-wise fashion, to add additional medications, including a second-generation H1 antihistamine, H2 antihistamine, leukotriene receptor antagonist, or first-generation antihistamine.

As with common urticaria, the lesions and pruritus of UM respond well to antihistamines and tend to resolve within a 1 to 2 weeks. Short courses of oral steroids may be used if antihistamines alone are unsuccessful.

### Complications

In rare cases, acute urticaria can be accompanied by anaphylactic reactions that require more immediate therapy; however, hives are usually more of a nuisance than a morbid threat. (See Chapter 350, Anaphylaxis.)

### Course

Acute drug-induced urticaria that is IgE mediated usually clears within 24 to 48 hours after the offending agent is discontinued. Once the agent is identified, the drug and members within that drug class should be avoided until further evaluation by an allergist. Skin-prick testing is available for penicillin and, if applicable, should be performed prior to any oral challenge with the drug so as to avoid a possible anaphylactic reaction.

## DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS/DRUG-INDUCED HYPERSENSITIVITY SYNDROME

Drug rash with eosinophilia and systemic symptoms is characterized by the clinical triad of fever, rash, and internal organ involvement (most commonly hepatitis, nephritis, pneumonitis, or myocarditis) that occurs within 2 to 6 weeks of initiation of the medication. Drug rash with eosinophilia and systemic symptoms is associated with the use of aromatic anticonvulsants (phenytoin, carbamazepine, phenobarbital), lamotrigine, NSAIDs, sulfonamides, minocycline, azathioprine, metronidazole and allopurinol. Cross-reactivity with structurally related drugs is common. The incidence of DRESS with anticonvulsants is estimated at 1 in 10,000 exposures. There is some evidence to suggest that reactivation of certain viruses, such as human herpesviruses 6 and 7, cytomegalovirus, and Epstein-Barr virus, may be involved in the spectrum of multisystem

**Table 245-1**

**Distinguishing Features of Giant Urticaria, Erythema Multiforme, and Serum Sickness–like Reactions**

	GIANT URTICARIA	ERYTHEMA MULTIFORME	SERUM SICKNESS–LIKE REACTIONS
Duration of lesions	<24 hours	Days to weeks	Days to weeks
Location	Trunk, extremities, face	Palms, soles	Trunk, extremities, feet
Fixed lesions	No	Yes	Yes
Mucous membrane involvement	Oral edema common, no erosions or blisters	Erosions and blisters may be present	Oral edema common, no erosions or blisters
Facial or acral edema	Yes	No	Yes
Associated symptoms	Pruritus	Pruritus, burning	Lymphadenopathy, arthralgia, myalgia
Common triggers	Antibiotics, immunizations, viral illnesses	Herpes simplex virus, mycoplasma	Antibiotics

Adapted from Shah KN, Honig PJ, Yan AC. "Urticaria multiforme": a case series and review of acute annular urticarial hypersensitivity syndromes in children. *Pediatrics*. 2007;119(5):e1177–e1783.



reactions in DRESS. Reactions typically occur 1 to 8 weeks into drug therapy. The long latency period for development of symptoms may represent the dynamic interplay of several factors to result in clinical disease. It is postulated that the inability to clear reactive drug products, combined with impaired defenses, such as viral or nutritional, results in susceptible individuals developing DRESS.

Clinical manifestations include fever early in the course; diffuse macules, papules, or pustules that can progress to an exfoliative dermatitis mimicking SJS or TEN; eosinophilia; atypical lymphocytosis; and abnormal liver function test results. The severity of the skin involvement does not correlate with the extent of internal organ involvement.

Treatment consists of immediate withdrawal of all suspected medications, followed by supportive care of symptoms. Recent studies demonstrated good cutaneous response to topical corticosteroids in the absence of life-threatening organ involvement. Systemic corticosteroids are generally used in the more severe cases involving significant exfoliative dermatitis, pneumonitis, or hepatitis. Systemic steroids have been used concomitantly with intravenous immunoglobulin (IVIG), but IVIG as a monotherapy may result in increased morbidity and mortality. Case reports have demonstrated use of IVIG as an adjuvant agent in severe steroid-dependent DRESS. There are no large controlled studies showing statistical benefit of a particular treatment. Children with a history of DRESS should be followed for possible late manifestations, including recurrence of symptoms as well as development of hypothyroidism and type 1 diabetes mellitus.

### ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

Acute generalized exanthematous pustulosis is characterized by the sudden onset of fever and multiple nonfollicular, subcorneal pustules over widespread erythema. The pustules are sterile and may clinically resemble pustular psoriasis. They affect the trunk and intertriginous areas, but also can involve the face. About one-half of affected children may have facial edema or purpura involving the legs. This is one of the neutrophilic dermatoses; neutrophil-activating cytokines may be responsible for the increase in neutrophils in the blood and skin seen in this disorder. Acute generalized exanthematous pustulosis is relatively uncommon in the pediatric population. Drugs are often the trigger in adults, while, in children, a viral infection (Coxsackie B4 virus, Epstein-Barr virus) or recent vaccination is more likely than antibiotics to be the cause of AGEP. Resolution usually occurs 1 to 2 weeks following discontinuation of a suspected drug. Spontaneous resolution occurs when no medication is implicated. In both situations, fine desquamation is noted as the lesions clear.

### ERYTHEMA MULTIFORME

Erythema multiforme is an acute, self-limited eruption of symmetrical, erythematous macules and papules that can evolve into target lesions (Figure 245-2). It was first described by Ferdinand von Hebra in 1860



**Figure 245-2** Erythema multiforme.

and was later divided into minor and major forms (the major form being synonymous with SJS). However, according to current thinking, EM is best viewed as a separate entity from SJS and TEN despite some clinical and histologic similarities.

#### Etiology

In children and adults, EM most often occurs in association with recurrent herpes simplex virus (HSV) types I and II. Circulating immune complexes have been detected in patients who have EM, a finding consistent with the concept that this distinctive cutaneous disorder is an immunologic reaction. Other infectious agents that are rarely implicated in EM include histoplasma capsulatum and viruses, possibly Epstein-Barr virus. Many reported cases of presumed EM, ascribed to innumerable causes, were more likely UM.

#### History

Several factors are implicated in the development of EM, which include infections, medications, autoimmune disease, malignancy, and immunizations. Infections represent approximately 90% of all cases, and the most common infectious agent is HSV. Characteristic EM lesions are noted a few days to 2 weeks following HSV orolabial or genital infections, usually preceded by a prodrome of malaise, fever, and myalgias.

#### Physical Findings

As the name suggests, EM is characterized by a variety of lesions, including erythematous plaques,



blisters, and targetoid lesions. Hives are sometimes confused with target lesions. The difference is that a hive has only 2 color zones—a central pale area surrounded by an erythematous halo. The criteria for a target lesion require 3 zones—a central dark area or blister, surrounded by a pale zone, surrounded by a peripheral rim of erythema. True target lesions are diagnostic for EM. They are seen more often on the palms and soles, but may occur anywhere. Typically, EM is a strikingly symmetrical eruption that most often favors the dorsal hands and forearms. Other areas that are also often involved include the neck, face, and trunk. Lesions can be quite numerous, often exceeding 100 in number, and may appear grouped on the elbows or knees. The Koebner phenomenon can be observed—after cutaneous trauma has occurred, target lesions may appear in the affected areas. Mild, discrete, oral erosions occur in more than one-half of children, but are usually few in number and can be relatively asymptomatic.

### Differential Diagnosis

The skin reactions most commonly considered in the differential diagnosis are UM, serum sickness-like reaction, subacute cutaneous lupus erythematosus, viral exanthems, vasculitis, staphylococcal scalded skin syndrome (SSSS), and other blistering eruptions. Individual hives last fewer than 48 hours, while the lesions in EM persist much longer. Viral exanthems are usually monomorphous and tend to be less red, more confluent, and more centrally distributed than the lesions of EM. Purpura is the distinguishing feature of vasculitic lesions. Because it can be triggered by significant sun exposure, recurrent EM caused by HSV also can be mistaken for the photosensitive disorders polymorphous light eruption and juvenile spring eruption.

### Laboratory Studies

For herpes simplex disease, if the responsible vesicular lesion is still present, then its base can be scraped for HSV direct fluorescent antibody, or its fluid can be cultured for herpesvirus or examined for multinucleated giant cells (Tzanck preparation). Otherwise, laboratory evaluation usually is not helpful, although a leukocytosis can be seen.

When the diagnosis is in doubt, a skin biopsy can be helpful in excluding conditions that mimic EM, such as lupus erythematosus or vasculitis.

### Treatment

No convincing evidence has been found that medical therapy favorably alters the course of EM. Treating a precipitating infection seems appropriate, even though no proof exists that it alters the course of the skin reaction. Acyclovir begun after the onset of EM has not proven to be effective. Symptomatic treatment can be helpful—antihistamines may reduce the sensation of stinging and burning, and antacid suspensions applied topically may alleviate oral ulcers.

### Course

Erythema multiforme is a self-limited condition with resolution of symptoms usually within 4 weeks. Erythema multiforme recurs in 10% to 20% of children,

and recurrence is particularly common in patients with milder disease that is precipitated by recurrent HSV infection. Children with frequently recurring EM caused by HSV may be good candidates for prophylactic acyclovir for 6 to 12 months.

## STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

Although previously thought to be more severe variants of EM, SJS and TEN are best viewed as separate entities. Stevens-Johnson syndrome and toxic epidermal necrolysis represent a continuous spectrum of a more severe process involving cell-mediated cytotoxic reactions aimed at epidermal cells. The process begins acutely with widespread skin lesions and mucocutaneous necrosis involving 2 or more mucosal sites, including conjunctiva, oral mucosa, the upper and lower gastrointestinal tract, and genital or anal mucosa. Stevens-Johnson syndrome produces more focal skin necrosis, with extensive areas of epidermal necrosis and resulting denudation occurring in TEN. The diagnosis of SJS is given when the child has less than 10% body surface area (BSA) involved. With 10% to 30% involvement, SJS/TEN overlap is used, and TEN is the diagnosis when more than 30% of BSA affected.

The current models of the pathophysiology of SJS/TEN involve widespread keratinocyte cell death in response to inappropriate immune activation caused by certain drugs, their metabolites, or infectious agents. Many soluble mediators of epidermal apoptosis and necrosis have been implicated, including Fas ligand, perforin, granzyme B, granulysin, interferon- $\alpha$ , and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Intracellular damage by reactive oxygen species formed in keratinocytes may precede the pro-apoptotic pathways. A domino-like effect with dying cells inducing further cytokine responses may amplify the process, resulting in widespread blister formation and denudation.

### Etiology

Medications are the most common cause of SJS and TEN. Antibiotics (mainly sulfonamides and less often penicillins, clindamycin, and quinolones), anticonvulsants (eg, phenobarbital, phenytoin, carbamazepine, and lamotrigine), oxicam-type NSAIDs, and allopurinol are implicated in about half of children. The TNF- $\alpha$  inhibitors were recently implicated as well as non-nucleoside reverse transcriptase inhibitors. A strong association exists with the genotype HLA-B\*1502 in Asians, especially people of Han Chinese ethnicity, and the development of SJS/TEN after exposure to carbamazepine. First-degree relatives of index cases have up to a 25% increased risk of developing SJS/TEN if exposed to a drug in that class. The FDA now recommends genetic screening for the HLA-B\*1502 allele in all individuals requiring carbamazepine if their ancestry puts them at risk. Testing for the HLA-B\*5701 genotype prior to therapy with the non-nucleotide reverse transcriptase inhibitor abacavir can determine if children would be at risk for SJS/TEN. In the future, perhaps more pretreatment genetic testing will be available for other classes of drugs to predict patient responses and thereby avoid a severe drug hypersensitivity reaction.

Infections, particularly from *Mycoplasma pneumoniae*, are the cause in about 30% of children. Many other infectious agents are reported to cause SJS/TEN, including viruses (Coxsackie, enteroviruses, influenza, mumps, hepatitis), bacteria (Group A *Streptococcus*, rickettsia, diphtheria, brucella, tularemia, typhoid, and Lymphogranuloma venereum), fungi (coccidia, histoplasma), and protozoa (malaria and trichomonas).

*Mycoplasma pneumoniae*-associated mucocutaneous disease is emerging as an entity distinct from EM, SJS, and TEN. Formerly known as “incomplete Stevens-Johnson syndrome,” this disease most commonly affects young males and presents with prominent mucositis and sparse cutaneous involvement. Cases have been treated successfully with oral antibiotic therapy and, occasionally, with IVIG. A few case reports show that IVIG is an effective second-line therapy in cases recalcitrant to oral antibiotics.

### History

Stevens-Johnson syndrome and TEN are usually preceded by a prodrome of up to 2 weeks of influenza-like symptoms followed by the abrupt onset of skin eruption. When drug related, the eruption typically begins 7 to 28 days after the causative drug is initiated. Drugs with longer half-lives are more likely to portend a worse prognosis than those with short half-lives, regardless of the structural similarity.

### Physical Findings

The eruption of SJS (Figure 245-3) and TEN (Figure 245-4) is initially macular or morbilliform, tender, dusky, and erythematous, with a widespread distribution. The skin sloughing occurs easily with minor friction (positive Nikolsky sign). Lesions gradually coalesce, and flaccid bullae develop that can extend



**Figure 245-3** Stevens-Johnson syndrome.



**Figure 245-4** Toxic epidermal necrosis.



laterally with central pressure (Asboe-Hansen sign). The bullae easily rupture and detach, leaving necrotic sheets of epidermis with a moist, bright red base. Mucosal erosions are seen in 90% of children and usually involve more than 2 mucosal sites. Thick, hemorrhagic crusts may appear on the lips. This process can progress for up to a week and is followed by re-epithelialization, which can take several weeks.

Constitutional symptoms also occur, especially in TEN. Systemic symptoms include fever, lymphadenopathy, hepatitis, and cytopenias. The epithelium of the respiratory tract is involved in 25% of cases, so management in an intensive-care setting is optimal. Additionally, gastrointestinal lesions may also occur, resulting in esophagitis and, less commonly, hemorrhagic diarrhea.

### Differential Diagnosis

The skin in SSSS is diffusely red and tender and also exhibits a Nikolsky sign. A skin biopsy helps distinguish SSSS from SJS. Histologically, the level of the blister is intraepidermal in SSSS, whereas the blister is subepidermal in SJS and TEN.

### Laboratory Findings

A chest radiograph is appropriate to screen for pulmonary involvement, including that caused by *M pneumoniae* infection, which can be confirmed further by cold agglutinins and acute and convalescent titers of immunoglobulin M antibodies to *Mycoplasma*. A complete blood cell count may show leukocytosis, and urinalysis may show hematuria or proteinuria.

Recent studies identified genetic variants associated with phenytoin-related cutaneous adverse reactions.

### Treatment

Any drug suspected of causing the reaction should be discontinued immediately, as early removal of an offending drug has improved survival. Early transfer of the patient to an intensive care unit that can manage children with severe skin burns also improves the ultimate outcome. Children with TEN can experience significant transepidermal fluid loss with associated electrolyte imbalance as well as respiratory, nutrition, and pain issues. Any underlying infection should be treated, and secondary infection should be prevented if possible. Patients who have severe oral involvement may be unable to eat and drink. Fluid replacement poses a unique challenge for children with SJS and TEN—unlike burn patients, the surface area involved in SJS and TEN may change, thus altering their fluid requirements. Fluid intake may need frequent adjustments to maintain constant urine output while avoiding fluid overload, which can lead to pulmonary edema, acute respiratory distress syndrome, and death. In fact, some experts recommend inserting a nasogastric tube on admission to maximize oral intake and decrease the need for intravenous fluids or parenteral nutrition, thus decreasing risk of fluid overload should the child's course become more complicated. In addition, parenteral nutrition requires a central venous line, with the attendant risks of sepsis and other line-associated complications. Local therapy with antiseptics and dressings may help prevent secondary

infection, and children who have severe involvement may require treatments similar to those for burn patients. In particular, silver nitrate-impregnated or newer biosynthetic or biologic dressings have been particularly helpful without causing further epidermal detachment on removal. Systemic analgesics are used for pain. Topical anesthetics may be used intraorally to provide temporary relief for children who have painful mouth lesions. Magic swizzle, containing 1 part each of diphenhydramine hydrochloride elixir, aluminum and magnesium hydroxide, and lidocaine viscous 2%, is one such agent. The physician should be mindful of the potential systemic effects of lidocaine when ordering this agent for young children.

The use of systemic steroids is controversial, because historically they were related to longer hospitalizations for sepsis and poor wound healing. However, more recent large retrospective studies found no increase in mortality with systemic steroid treatments in SJS and TEN in the past 15 years. Steroids alone were reported to be effective in SJS. Current studies are looking at the use of high-dose steroids very early in the course before significant denudation occurs, but well-controlled prospective studies are needed.

Intravenous immunoglobulin may hasten recovery from this disorder by blocking the mediators of the apoptosis cascade that leads to epidermal destruction. Intravenous immunoglobulin has been effective for SJS/TEN in children. Doses of 2 to 3 g/kg given early in the course lead to more rapid cessation of epidermal detachment and lower mortality. There are reports that systemic steroids given with IVIG may result in better outcomes in TEN and SJS/TEN overlap syndrome. Steroids and IVIG have been shown to improve the outcome in SJS and TEN, although well-controlled prospective studies are needed to determine optimal management.

### Course and Complications

The course of the disease can last as long as 4 to 6 weeks in children with severe involvement. Oral mucous membrane involvement can produce painful erosions, restricting intake and resulting in dehydration. Similar lesions in the genital mucous membranes can cause dysuria and urinary retention. Early ophthalmic evaluation is helpful since conjunctival involvement is common and can be severe. Internal organs are affected less often. Toxic epidermal necrosis in particular can affect the respiratory and gastrointestinal tracts. Respiratory involvement can lead to patchy pulmonary disease, bronchiolitis obliterans, and respiratory failure. Esophageal involvement can lead to dysphagia, malnutrition, and strictures. Involvement of the small intestine can lead to abdominal pain and diarrhea.

Long-term complications can be seen in up to 50% of children, with the skin and eyes most commonly affected. Postinflammatory hyper- or hypopigmentation is common. Even scarring can occur, depending on the depth of skin detachment. Nail changes are seen frequently and include Beau's lines, onychomadesis (nail shedding) and, occasionally, nail matrix scarring with permanent nail dystrophy. Xerostomia can result from SJS or TEN and, rarely, a Sjögren syndrome-like

**Table 245-2** Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN)

SCORTEN PARAMETER	INDIVIDUAL SCORE	SCORTEN (SUM OF INDIVIDUAL SCORES)	PREDICTED MORTALITY (%)
Age >40 years	Yes = 1, No = 0	0–1	3.2
Malignancy	Yes = 1, No = 0	2	12.1
Tachycardia (>120/min)	Yes = 1, No = 0	3	35.8
Initial surface of epidermal detachment >10%	Yes = 1, No = 0	4	58.3
Serum urea >10 mmol/L (28 mg/dL)	Yes = 1, No = 0	>5	90
Serum glucose >14 mmol/L (252 mg/dL)	Yes = 1, No = 0	—	—
Serum bicarbonate <20 mmol/L	Yes = 1, No = 0	—	—

Derived from Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol.* 2000;115(2):149–153.

exocrine insufficiency can occur, especially with pancreatic dysfunction. Conjunctivitis can produce residual ophthalmic complications, including keratitis sicca, corneal ulceration or scarring, permanent visual impairment, and occasionally neovascularization and blindness. Newer techniques to minimize eye sequelae include amniotic membrane grafting early in the course of the disease before severe corneal damage occurs.

The risk of death is less in SJS than in TEN; death occurs secondary to extensive loss of skin integrity or complications from involvement of other organ systems. Mortality rates as high as 30% in TEN have been reported, but the mortality rate is around 7.5% in children. A severity-of-illness score for TEN (SCORTEN) was developed in which 7 factors are used to predict mortality (Table 245-2).

Early diagnosis and management of SJS and TEN with referral to a tertiary care center may lessen morbidity and mortality and improve the outcome of the unfortunate child who develops this disease process.

#### WHEN TO REFER

- Recurrent erythema multiforme
- Serum sickness-like reaction
- Drug hypersensitivity reactions with multiorgan involvement
- Unclear diagnosis

#### WHEN TO ADMIT

- Drug rash with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome
- Acute generalized exanthematous pustulosis
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- *M. pneumoniae*-associated mucositis

### TOOLS FOR PRACTICE

#### Medical Decision Support

- *Dermatology: Skin Infections* (online course), American Academy of Pediatrics (pedialink.aap.org)
- *Visual DX* (online database) (www.visualdx.com)

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### Chapter 246

## DRUG INTERACTIONS AND ADVERSE EFFECTS

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Adverse medication effects and drug interactions, condensed into the term *adverse drug reaction* (or ADR), may occur despite the best of intentions. Before administering a medication to a patient, it is essential to verify the “5 rights”—right patient, right medication, right time, right dose, and right route. However, even when all the 5 rights have been observed, a potentially life-threatening ADR may still occur. An ADR is implicitly caused by the interaction between the drug or drugs and patient-specific characteristics, some of which may be unknown prior to the medication administration.

### DEFINITIONS

The definition of an ADR is “an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which



predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.” In an ADR, there is a causal link between the medication and the adverse event, and an imperative to determine the link by investigating the time relationship, pathophysiology of the drug, competing causes, and response of the patient to removal or reduction in the dose. Examples of such ADR scenarios include the occurrence of hypokalemia with the use of furosemide, gastrointestinal bleeding with the use of ibuprofen, or pancreatitis with the use of prednisone.

## EPIDEMIOLOGY

Adverse drug reactions are not uncommon occurrences during patient therapy, depending upon factors such as patient pharmacogenomics, the disease being treated, and medications being used, with 5% ADR occurrence for inpatients, and as high as 20% for outpatients, and an increasing risk for patients taking more than 4 drugs. In general, children are at approximately the same risk of ADRs as adults, and, in some cases, may be at higher risk. One systematic review of pediatric ADRs causing hospital admissions for children identified a rate of 0.4% to 10.3% (pooled estimate of 2.9%). In one pediatric study, a drug-drug interaction as a cause for hospital admission occurred rarely. In an international review of prospective, pediatric ADR studies, the skin and gastrointestinal system were most commonly involved, with an incidence of 1.5% to 19.9% among hospitalized children.

Adverse drug reactions generally occur by either a predictable, but excessive, pharmacologic effect caused by an increase in drug concentration or effect (type A), or by an unpredictable toxic or immunologic (eg, allergy, anaphylaxis) response (type B). A classification system of ADRs, evolving from the 2 categories of types A and B was initially proposed by Rawlins and Thompson, evolving from the 2 categories of types A and B, to 9 categories based on the known pharmacology and dose dependence of effects, further modified to include dose relatedness, timing, and patient susceptibility. For example, additional categories include type C (dose and time dependent [chronic] reactions), type D (delayed reactions), type E (withdrawal reactions), and type F (failure of therapy). Risks for ADR include previous adverse reaction to another drug, polypharmacy, prematurity, reduction in renal or hepatic function, larger medication dose, gender, and certain genetic polymorphisms. In the largest prospective, observational study of ADRs of all pediatric medical and surgical admissions, ADR risk factors included increasing age, oncologic disease, and number of medications taken. A gender predilection was not identified. The main classes of implicated drugs included opioid analgesics and anesthetic agents.

Pharmacogenomics, the study of the variability of the expression of individual genes relevant to the drug response at a cellular, individual, or population level, affects both the pharmacokinetics (absorption, distribution, metabolism, excretion) and pharmacodynamics of a drug. Genetic variations may provide some explanation

for significant differences in drug metabolism that can lead to toxicity and harm. There is significant potential through genetic testing to understand and predict not only medication efficacy, but also toxicity, with important differences attributable to gene expression changes during human development. For example, the death of a breastfed opioid-intoxicated neonate because of his mother's intake of prescription codeine-acetaminophen for episiotomy pain was later identified with the CYP2D6 ultra-rapid metabolizer genotype. The frequency of this genotype ranges from 1% in Finland and Denmark to 10% in Greece and Portugal and 29% in Ethiopia, and this genotype is associated with narcotic poisoning through otherwise routine dosing and even with secondary administration in the case of a breast-feeding infant. The pediatric fields of oncology, anticoagulation, psychiatry, and asthma in particular are advancing in the study of pharmacogenomics. To date there are more adult clinical applications, but the potential continues to be high. One comprehensive reference for pharmacogenetic data for individual drugs is located at [www.pharmgkb.org](http://www.pharmgkb.org).

## DRUG INTERACTION

Drug interaction is a generic term used when the efficacy or toxicity of a medication is changed by another medication or food. Several different mechanisms cause such interactions, and understanding them is critical for prevention, monitoring, and treatment. Drug-drug interactions can be further subdivided into pharmacodynamic, pharmacokinetic, and physical compatibility categories. Pharmacodynamic drug-drug interactions involve the basic pharmacologic effects of each medication opposing each other or having additive therapeutic or side effects. Examples include narcotic and benzodiazepine-potentiated sedative, as well as respiratory depressive, side effects. Pharmacokinetic drug-drug interactions encompass changes in the expected absorption, distribution, metabolism, or elimination caused by another medication (eg, liver enzyme induction or inhibition). The combination of amiodarone and digoxin or warfarin and trimethoprim-sulfamethoxazole are examples of pharmacokinetic interactions in which the combination results in toxicity of one or both agents, although each agent individually may not be an issue. Physical incompatibility is the third category of drug-drug interactions and involves medications that are combined in the same intravenous bag, syringe, or tubing, but for which there may be physical or chemical incompatibilities. Calcium and phosphate solubility is a common example.

Drug metabolism occurs in 2 phases. Phase I is characterized by modification reactions such that the parent drug is modified into a more hydrophilic compound. Phase II is characterized by conjugation such that the parent drug may be conjugated to a more polar, more readily excreted compound. Many drugs go through both phases, but some may only go through phase I or phase II. In some cases, the metabolite is metabolically active, or may be the source of toxicity, as with acetaminophen and its reactive metabolite N-acetyl-p-benzoquinone imine, associated with acute liver injury after an overdose. The most

**Table 246-1****Frequently Prescribed Drugs or Substances Used by Children Known to Inhibit or Induce Drug Metabolism**

<b>INHIBITOR</b>	<b>ENZYME INHIBITED</b>
Clarithromycin, erythromycin	CYP3A4
Itraconazole, ketoconazole, voriconazole	CYP3A4
Esomeprazole, pantoprazole, omeprazole	CYP2C19
Grapefruit juice	CYP3A4
<b>INDUCER</b>	<b>ENZYME INDUCED</b>
Phenobarbital	multiple CYPs
Rifampin	multiple CYPs
Dexamethasone	CYP2D6
Carbamazepine	multiple CYPs
Phenytoin	multiple CYPs
Ethanol	CYP2E1
St John's wort	CYP3A4s

CYP, cytochrome. P450.

From de Wildt S, Tibboel D, Leeder J. Drug metabolism for the paediatrician. *Arch Dis Child*. 2014;99:1137–1142. Reprinted with permission.

well-studied and common phase I system is the cytochrome P450 (CYP), which includes more than 50 genes that encode for functional enzymes. There are several well-recognized drug–drug interactions because of the interaction between specific drugs and drug metabolizing enzymes (see Table 246-1).

Evaluating the potential for drug–drug interactions can be challenging. There are published resources in both print and electronic formats, but the poor agreement among them and difficulties with the practical integration of alerting functions into clinical information systems has generally yielded a plethora of insensitive, low-value drug–drug interaction alerts. These alerts from medication orders require a significant amount of vigilance to ensure that the most appropriate interactions are flagged. One particularly useful tool for tailoring interaction alerting is provided by the Office of the National Coordinator drug–drug interaction list; another is the list from the Leapfrog Computerized Physician Order Entry testing standard. However, interaction data is predominantly adult-based. Despite assumptions that pediatric data would be similar, analysis of the 24 drug pairs studied in both adults and pediatrics indicates that pediatric patients can experience a higher, similar, or lower level of drug–drug interaction compared to adults.

Drug–food interactions can also be subdivided into separate categories, such as absorption, allergies, antagonism, and nutritional deficiencies. Food, in general, may inhibit or improve a medication's absorption, although concern for this type of interaction should be reserved for narrow therapeutic medications, such as methotrexate, or for when clear clinical consequences have been identified, such as calcium-rich foods binding quinolones or dietary iron interfering with tetracycline absorption. A drug's effect may also be antagonized by the specific content of food, such as high vitamin K content and warfarin, or calcium and calcium antagonists. These antagonism interactions

are generally not contraindications, but should be considerations for patient counseling about moderation. Nutritional deficiencies are a type of drug–food interaction that deserves monitoring, usually in chronic care settings rather than for short courses. Examples include valproic acid and its antifolate effect, and oral steroids severely affecting vitamin D levels.

## APPROACH TO ADVERSE DRUG REACTIONS

Developing a systematic approach to a patient with a suspected ADR can clarify and identify the source. In the case of a skin reaction, categorize the primary lesion as exanthematous, urticarial, blistering, or pustular. By including the presence or absence of systemic signs, an initial clinical impression can be formed and a differential diagnosis generated. Recommended next steps are as follows: (1) Obtain a complete history of the drugs taken, including types, doses, and duration. This history should include over-the-counter medications and herbal and naturopathic compounds. (2) Obtain a detailed description of the symptoms and signs, including onset, localization, and evolution. (3) Perform an examination of skin and mucosal membranes. (4) Assess vital signs and laboratory parameters that suggest warning signs (eg, hypotension, fever, skin blisters or bullae, complete blood count for lymphopenia or thrombocytopenia, eosinophilia, liver transaminases, renal function panel). In the absence of a definitive diagnosis, defining the reaction as highly probable, probable, possible, unlikely or almost excluded can be helpful. To fulfill the criteria for a highly probable reaction, the following principles of causality should be met: temporal relationship, a recognized response to the suspected drug, improvement after drug withdrawal, and reaction on rechallenge. A probable reaction includes principles 1 to 3; a possible reaction requires only a temporal relationship.

## DOCUMENTATION AND COMMUNICATION

Recognition is a key first step when an ADR occurs, allowing measures to be taken to minimize the recurrence if possible. Data are often captured in nurse charting, but may be inappropriately minimized or trivialized as side effects of a drug and thought to be unavoidable. One example is pruritus with morphine, which may not be seen as serious and may, therefore, be labeled as a side effect; but following this assessment could lead to compounding reactions, risking delirium if diphenhydramine is added to the patient's medication profile. With recognition of the initial ADR, alternative narcotics could be chosen and such risks minimized.

Documenting ADRs in the medical record is also helpful in preventing subsequent harm to patients given the high likelihood for recurrence and the causal association between the medication and symptom occurrence. Life-threatening ADRs merit documentation (eg, trimethoprim/sulfamethoxazole-induced toxic epidermal necrolysis or Stevens-Johnson syndrome). A valuable strategy when documenting ADRs is to note the severity of the reaction, the causal association between the medication use and the event, and the dosing variables. Often inpatient records with details do not translate well into the outpatient arena. A commonly overlooked step is clear communication with the family about the ADR and its causality and implications, including sharing these findings with other practitioners involved with the patient.

## REPORTING TO THE US FOOD AND DRUG ADMINISTRATION

It is essential that ADRs associated with new drugs be reported, because drugs entering the market are tested on relatively few patients before being released, and serious ADRs that occur at a frequency of 1 case per 1,000 population or less are unlikely to be detected prior to drug approval. This is especially true in pediatrics, which makes reporting even more crucial. The US Food and Drug Administration (FDA) is interested in "any [unexpected] adverse drug experience that is not listed in the current labeling for the product." Reporting is done through the online FDA Adverse Event Reporting program, and drug and drug class safety warnings issued by the FDA are available at [www.fda.gov/Safety/MedWatch](http://www.fda.gov/Safety/MedWatch).

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Choosing Over-the-Counter Medications for Your Child* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *A Guide to Your Child's Medications* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Medicine and the Media: How to Make Sense of the Messages* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

- *Prescription Medicines and Your Child* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

#### Medical Decision Support

- *Development of the Leapfrog Methodology for Evaluating Hospital Implemented Inpatient Computerized Physician Order Entry Systems* (article), *Quality and Safety in Health Care*, Vol 15, Issue 2, 2006
- *Reporting Serious Problems to FDA* (Web page), US Food and Drug Administration ([www.fda.gov/Safety/MedWatch/HowtoReport](http://www.fda.gov/Safety/MedWatch/HowtoReport))

### AAP POLICY

American Academy of Pediatrics Committee on Drugs. Metric units and the preferred dosing of orally administered liquid medications. *Pediatrics*. 2015; 135(4):784–787 ([pediatrics.aappublications.org/content/135/4/784](http://pediatrics.aappublications.org/content/135/4/784))

### SUGGESTED READINGS

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## Chapter 247 ENCOPRESIS

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### DEFINITION

Encopresis (soiling) is the intentional or involuntary passage of feces into the clothing by children with a developmental age greater than 4 years. Any child with a developmental age greater than 3 years who is not toilet trained, however, should be evaluated. Without professional advice for this age range, many parents mistreat encopresis with coercion or punishment, and the condition worsens. Sometimes constipation has been overlooked.

Most children who have encopresis leak fecal material involuntarily from constipation or an impaction (retentive encopresis). Some children simply pass normal stools into their underwear rather than use the toilet (nonretentive encopresis). Retentive and nonretentive encopresis should be separated because the treatment for each type is radically different. The minor fecal staining that occurs when children do not wipe themselves adequately after using the toilet should not be mistaken for encopresis.

## PATHOPHYSIOLOGY

Retentive encopresis is associated with constipation (see Chapter 134, Constipation). The type of constipation that is associated with encopresis is usually a result of stool holding. Young children may postpone bowel movements because of pain or because they want to cooperate with toilet training. Understanding of retentive encopresis also depends on an understanding of the pathophysiologic features of fecal impaction, which occurs when constipation has gone unrelieved for approximately 1 week. By then, the rectum is so distended with stool that the sacrospinal defecation reflex is no longer energized, and the mass is so wide that voluntary effort alone cannot force it through the anal canal. Hence, an impaction is almost irreversible by natural events. The pressure of the impaction dilates the internal anal sphincter and makes it incompetent. Small amounts of the lower impaction are extruded intermittently through the external sphincter as a result of gravity, exercise, and relaxation.

Nonretentive encopresis in children who are developmentally normal is usually a result of behavioral problems around toilet training. Children with irritable bowel syndrome of childhood or other causes of chronic diarrhea (see Chapter 138, Diarrhea and Steatorrhea) can also have delays in toilet training. Children with cerebral palsy, spina bifida, or other neuromuscular problems can have difficulty toilet training despite normal cognitive development.

## INCIDENCE

Encopresis affects approximately 5% of 4-year-olds who have normal development. It affects 2% of kindergarten and first-grade students. If their child is not bowel trained, most parents seek help by age 3 or 4 years. Some children who have encopresis are not brought in for examination until 5 years of age, when their symptom interferes with school entry. Affected boys outnumber affected girls by a ratio of 3:1.

## DIFFERENTIAL DIAGNOSES

Most constipation of childhood is caused by stool holding either as an attempt to avoid the pain associated with passage or because the child is enmeshed in a control struggle with a parent. Retentive encopresis has an organic basis in fewer than 5% of encopretic children. Organic causes of constipation and retentive soiling often are noted on physical examination (Table 247-1).

Approximately 10% to 20% of children who are encopretic are not constipated. Frequently, preschoolers who are of this type are resisting bowel training deliberately. Most school-aged children who have this type are postponing bowel movements (BMs) (*waiting too long*) because they do not want to leave some enjoyable activity (eg, video games) or they do not want to use public toilets (eg, school bathrooms). Many of them have a difficult or strong-willed temperament that makes them prone to engage in control battles.

Many encopretic children (of either type) eventually develop secondary emotional problems unless treated appropriately. Encopresis can take a great toll in shame. The unpredictable nature of the symptom

**Table 247-1**

### Organic Causes of Constipation and Retentive Soiling

ENTITY	DIAGNOSTIC CLUE
Constipating medication	History positive
Constipating diet	History positive
Chronic anal fissure	Examination positive
Perianal cellulitis	Examination positive
Hypothyroidism	Linear growth delayed
Anal or rectal stenosis	Finger cannot enter rectum
Pelvic mass	Mass found on rectal examination (usually posteriorly)
Hirschsprung disease	Rectal ampulla repeatedly empty; rectum is tight

in retentive children causes constant fear of exposure. Many of these children are *scapegoated* at home, teased by peers, and ostracized at school. Having a child with encopresis is very embarrassing and stressful for most parents. It may cause them to overreact and become negative in their childrearing, further compounding the problem.

## EVALUATION

### History

A thorough history usually distinguishes between retentive and nonretentive encopresis (Table 247-2). The pediatrician asks about size and consistency of stools and soiling intervals. In the retentive form, leakage occurs many times a day or even continuously. Commonly, the pediatrician elicits a history of periodic pain or crying with BMs, blood on the toilet tissue, passage of a huge BM that clogs the toilet, or posturing that suggests deliberate holding back. By contrast, the child who has nonretentive soiling passes a BM of normal size and consistency into the underwear once or twice a day; no symptoms of constipation are exhibited.

The pediatrician should clarify early on whether the child is toilet trained. By definition, most are not. Previous toilet training methods, rewards, and punishment are important. Information about sitting on the toilet is essential (eg, how many times per day and if sitting is spontaneous or prompted by parents or teachers). Refusal to sit on the toilet means that treatment will be difficult. If the stool pattern is unknown, then sending the parent home with an encopresis diary to complete for the child can be most illuminating. Feedback from the school or child care provider may be needed. Enuresis is also present in many of the children with retentive encopresis. Other helpful parts of the history pertain to diet: The intake of milk products (especially cheese), fruits and vegetables, and fiber should be recorded.

### Physical Examination

The physical examination provides definitive information. In retentive soiling, an abdominal mass is usually palpable. Although the mass sometimes extends throughout the entire colon, it more commonly



**Table 247-2**      **Differentiation of Retentive Soiling From Nonretentive Soiling**

	RETENTIVE SOILING	NONRETENTIVE SOILING
<b>HISTORY</b>		
Symptoms of constipation	Yes	No
Soiling interval	Many times per day	Once per day
Soiling amount	Small	Normal
Soiling consistency	Loose	Normal
Previous need for laxatives, suppositories, or enemas	Yes	No
<b>EXAMINATION</b>		
Abdominal mass	Yes	No
Abdominal distention	Often	No
Anal canal	Sometimes full	Empty
Rectum	Packed	Normal

involves only the rectosigmoid area. The mass is midline, suprapubic, irregular, and movable. The mass can be missed if the rectus abdominis muscles are not relaxed. The backup of gas and stool can cause a protuberant abdomen. Inspection of the anus should be part of the routine evaluation of encopresis. The lumbosacral area should be examined for midline defects.

A digital rectal examination is needed when it is not clear whether or not the child is retentive (constipated). It is also needed in children with retentive encopresis who do not respond to standard management. It can be done with minimal pain and distress in most children. Overlooking this part of the evaluation can lead to an erroneous diagnosis. Inspection of the anal opening often reveals protruding fecal material in children who are deliberate stool holders. This is uncommon in children who want to release the stool. By definition, the rectum in impacted children is dilated and packed with wall-to-wall stool (often 6 to 10 cm across). The consistency of the impaction more commonly is similar to wet clay, rather than hard. By contrast, the child who has nonretentive soiling has normal abdominal examination findings, and the rectal vault contains either a stool of normal caliber or nothing if the child has evacuated recently. Hirschsprung disease also causes an empty rectum despite a history of stool retention, but stool may be expelled immediately on removal of the finger.

### Laboratory Studies

Children who are encopretic generally need no routine laboratory confirmation of this diagnosis. Because an impaction can cause partial bladder emptying and urine retention, a urinalysis for nitrite and pyuria may be helpful to screen for urinary tract infection, especially if any associated enuresis exists. Any abnormal perianal erythema should be cultured for group A *Streptococcus*. Occasionally, thyroid function tests are warranted, especially in children with short stature or other signs of hypothyroidism.

### Radiographic Findings

If the examiner cannot determine whether the patient is impacted (eg, severe obesity, abdominal fullness

but empty rectum), a postvoiding, supine abdominal radiograph can be helpful. Other indications include sexually abused children who might be emotionally traumatized by a rectal examination and those who refuse a rectal examination. A child who is impacted will demonstrate on radiograph a rectum and sigmoid colon grossly dilated with granular stool and increased stool in the transverse and descending colon, which normally is empty. A healthy child will have stool only in the ascending colon and the rectosigmoid area. Also, the stool will be of normal diameter. A barium enema is rarely indicated in children with encopresis or constipation. One exception is if Hirschsprung disease is suspected based on an empty rectum on repeated examinations. Also, children who have retentive soiling and experience repeated treatment failures may warrant a barium enema to ensure that a rare diagnosis (such as an extrinsic mass pressing on the lower sigmoid or rectum) has not been overlooked.

## MANAGEMENT OF RETENTIVE ENCOPRESIS

In recent years, the treatment of constipation has become more uniform. The need for chronic medications to allow the lower bowel adequate time to return to normal diameter and function has gained acceptance. Most children older than 5 years want to stay clean. However, they may not understand how to do so. Physicians should tell these children that they need to pass a stool every day. They need to keep their rectum empty. Physicians should help them understand that holding back BMs is the main cause of leaking or messing their pants. (Box 247-1 outlines the treatment of encopresis.)

### Initial Disimpaction

Unless the impaction is removed, the child will be unable to regain bowel control. The traditional rapid way to remove an impaction is to give a daily sodium phosphate enema for 2 or 3 days. Warn the parents that phosphate enemas given in excessive doses can cause serious side effects. Although rare, these include tetany, dehydration, arrhythmias, and even death.

**BOX 247-1 Treatment of Retentive Encopresis**

- *Bowel clean out:* hyperphosphate enemas (1 daily for 2 or 3 days) to remove impaction (*other option:* oral clean out using high-dose stool softeners)
- *Maintenance medication:* polyethylene glycol or mineral oil for 3 to 6 months to keep the stools soft and painless; senna laxatives added to regimen if stool softeners are not completely effective
- *Toilet habits:* sitting on the toilet for 10 minutes after meals
- *Diet:* nonconstipating high-fiber diet
- *Rewards:* give incentives for release of stools; base amount on size of stool
- *Stool output diary:* parents need to track daily stool output, both complete stools and small "accidents"; this information aids the pediatrician in adjusting medication dosage or prescribing another clean out
- *Referral:* refer treatment failures to mental health professional or gastrointestinal subspecialist
- *Pediatrician role after referral:* stay involved to prevent reimpaction

For children who are resistant to enemas or parents who are unable to give them, administering high-dose polyethylene glycol or mineral oil orally can also dislodge the impaction if the treatment is continued for approximately 3 or 4 days. During this time, the child must stay at home because the timing of the large release cannot be predicted. A combination of these 2 approaches, starting with polyethylene glycol or mineral oil orally and followed by enemas on day 3, may be useful. Occasionally, enemas have to be administered in the office or clinic.

Rarely, for severe impactions involving the entire colon, a child needs to be hospitalized for the clean out. The usual procedure is to give polyethylene glycol-electrolyte solution by nasogastric tube for 8 to 24 hours.

**Stool Softeners**

As soon as the impaction is eliminated, the long-term treatment of constipation should be administered orally. Mineral oil or polyethylene glycol is prescribed (Table 247-3). Lactulose is less effective. The goal is the passage of 1 or 2 normal-sized BMs per day. Stool softeners must be continued for 3 months because bowel diameter and tone require this amount of time to return to normal. If the child refuses to take straight mineral oil, then parents can consider a better-tasting (although more expensive) emulsified derivative of mineral oil.

**Laxatives**

Stool softeners are the first line of therapy for constipation. If stool softeners are not effective, then laxatives (bowel stimulants) to help the child keep the rectum empty should be added. Laxatives are usually needed for children who deliberately hold back BMs

or for those who have acquired megarectum and megacolon (for dose levels, see Table 247-3).

Undermedicating is the main cause of treatment failure and recurrences. If the child is not having a normal-sized BM daily, then the dose should be increased. Some children temporarily require doses that exceed the standard dose recommended by textbooks and the package insert. Many parents worry unnecessarily about laxative dependency. They should be reassured that children can be tapered off laxatives successfully, even after 6 months of taking them. All affected children need stool softeners or laxatives for at least 3 months, and many for 6 months or longer. Many parents are in a hurry to stop the medications; they should be told on the first visit that to achieve a cure, medications need to be continued until the child has gone at least 1 month without any soiling. The medications then can be tapered gradually over 2 months.

**Toilet Habits**

The child should sit on the toilet for 5 to 10 minutes once a day with a timer. The gastrocolic reflex, which takes effect 20 to 30 minutes after a meal (especially breakfast), can be used to advantage. Any treatment that neglects this opportune timing will likely fail.

Children who have been impacted for many months may have no urge to defecate. The defecation urge may not return until the rectum is kept empty for 1 to 2 weeks. Many parents do not understand this and need to be educated that the return of bowel control will be gradual. Other important tips to impart to children are to flex the hips to open the rectum, to use a footstool for leverage, and to apply some pressure to the abdomen while pushing down. If they have no BM for 24 hours, then these children need to sit on the toilet more often and longer each time. Soiling (leakage) also requires sitting on the toilet, followed by a cleanup.

Some preschoolers and toddlers adamantly refuse to sit on the toilet, holding back their stools when they are forced to do so. The overriding goal is to produce a BM daily or at least every other day. Passing it into the diaper is better than holding it in. In cases such as these, pediatricians and parents need to lower their expectations. The child can be told that the "poop wants to come out every day, and it needs your help." Going in the diaper is fine. Rather than putting the child back in diapers or Pull-Ups full time, the child should be given access to them when the need to release a stool exists. This approach prevents the child from regressing with bladder control.

**Nonconstipating High-Fiber Diet**

All constipated children need more fiber in their diet, as is found in foods such as popcorn, grains, fruits, and vegetables. However, diet therapy alone will cure only children who have mild constipation. The only foods that have been shown to be constipating are milk products. Identifying the 10% or so of children who have impaction and who are drinking great amounts of milk (>32 oz per day) is important. Milk intake can be limited to 16 oz per day in children older than 1 year. Fluid

**Table 247-3 Medications for Constipation**

MEDICATION	DOSAGE	COMMENTS
<b>STOOL SOFTENERS</b>		
Mineral oil	1–2 mL/kg/dose twice daily Adolescents: 60 mL/dose (max: 8 oz/day)	Do not use in children who have gastro-esophageal reflux or vomiting or who are not yet walking. Emulsified types (Petrogalar, Agoral plain, Kondremul) taste better. This is a prescription item.
Lactulose	0.5–1.0 mL/kg/dose twice daily Adolescents: 15 mL twice daily (max: 3 oz/day)	
Polyethylene glycol (MiraLAX)	0.5 g/kg/day Adolescents: 17 g/day	MiraLax is nonprescription item. Identical prescription version is call GlycoLax.
Milk of Magnesia	1–2 mL/kg/dose Adolescents: 30–60 mL	1 Milk of Magnesia tablet = 2.5 mL liquid
<b>STIMULANT LAXATIVE</b>		
Senokot (senna)	<5 yr: 1–2 tsp syrup/day >5 yr: 2–3 tsp syrup Adolescents: 1 tbsp/day (max: 2.5 tbsp or 8 tablets)	1 tablet = 3 mL granules = 5 mL syrup
Fletcher's Castoria	<5 yr: 1–2 tsp/day >5 yr: 2–3 tsp Adolescents: 2 tbsp max	—
Ex-Lax (senna)	>5 yr: 1 square/day Adolescents: 2 squares	Chewable squares
Dulcolax, 5-mg tablet	>5 yr: 5 mg/day >12 yr: 10 mg (2 tablets) Adolescents: 4 tablets max	Liquid form not available.
<b>RECTAL SUPPOSITORIES</b>		
Glycerin suppository	1 or 2 suppositories	
Dulcolax suppository 10 mg	>2 yr: 1 suppository	
<b>ENEMA FOR DISIMPACTION</b>		
Mineral oil enema	1–2 oz/20 lb of weight/day Adolescents: 4 oz	Squeeze-bottle size: 4.5 oz
Sodium phosphate enema (Fleet)	1 oz/20 lb of weight/day Adolescents: 4 oz (max: 8 oz)	Squeeze-bottle size: 2.25 oz children, 4.5 oz adult Caution: avoid enemas if <2 years old
<b>ORAL DISIMPACTION</b>		
Mineral oil	1 oz/yr of age/day Max: 8 oz/day	—
Polyethylene glycol (MiraLax)	0.5 gm/kg/dose 3 times daily Max: 25 g or 1½ capfuls 3 times daily	—

requirements for constipated children can be met with fruit juices, especially those that have a high sorbitol content, such as pear, peach, or prune juice. Sorbitol can increase the frequency of stools.

### Follow-Up Visits

All children who have impaction need follow-up approximately 1 week into treatment; more than 30% still will be impacted. The abdominal examination and underwear check should be repeated even if patients tell you that they are having normal BMs and no soiling. Children who have an impaction actually can keep themselves clean temporarily by making a strenuous effort at control and sitting on the toilet several times a day. If the history and abdominal examination leave

uncertainty, then a rectal examination should be performed.

If a child still is impacted at the follow-up examination, then a more detailed explanation of the disimpaction process is necessary. Some children need enemas in the office at this point.

### Backup Plan for Recurrence of Constipation or Encopresis

Backup plans are critical for preventing all-too-frequent relapses. If the child goes for longer than 48 hours without a normal-sized BM, then the parents should be instructed to increase the dose of stool softener or laxative. This approach is critical to prevent impaction from recurring.

If soiling occurs more than twice over a few days, then the child is at risk for recurring impaction. At this point, the parents should intervene vigorously by giving a double dose of laxative, a suppository, or an enema. Merely mentioning an enema sometimes results in the child sitting on the toilet and producing a BM. For older children who are cooperative about sitting on the toilet, sitting there for 10 minutes out of every hour will usually relieve an early impaction. Again, the family should be helped to realize that soiling always means that the rectum is full and the impaction is returning.

Failure of these primary care interventions is usually a result of rectal hyposensitivity and inability to relax the external anal sphincter. The former is caused by prolonged stretching of the rectum. The latter results from constant voluntary attempts to prevent stool leakage or pain. Both of these pathophysiologic states usually recede after stool impaction is permanently resolved with more aggressive interventions.

## MANAGEMENT OF NONRETENTIVE ENCOPRESIS

For children who simply postpone BMs, a simple admonition to “find a toilet whenever you feel rectal pressure” or “don’t make your body wait” usually removes the symptom. Most children with nonretentive encopresis, however, are resistant to toilet training, and they need more intensive intervention (Box 247-2).

### Medications

Stool softeners, laxatives, and enemas are not needed for cases of nonretentive encopresis.

### Reminders and Lectures

The parents should be reassured that nothing more can be taught to their child. The parents should be told to stop all reminders about using the toilet and let the child decide when he needs to go to the bathroom. By transferring the control to the child, power struggles will end. Children should neither be reminded to go to the bathroom nor be asked if they need to go. Reminders, inquiries, and lectures are a form of pressure, and pressure does not work. The parents should not threaten punishment. Many young children try to hold back all BMs to avoid punishment, such as being spanked or grounded for soiling. They are under the mistaken impression that not passing any BMs is the best way to avoid punishment. The parents should be told about the importance of not punishing their child for soiling. The child should be reassured that soiling will no longer incur punishment. Parents also need to try to deal with soiling and cleanups in a calm way.

### Incentives

Incentives for passing BMs into the toilet should be given and the parents should be reassured that this approach is how they can turn the tide. If the child passes a BM into the toilet, then the parents should give immediate positive feedback, such as praise, a

## BOX 247-2 Treatment of Nonretentive Encopresis

- Tell the child, “You are in charge of your body and your poop.”
- Stop all reminders, lectures, or punishments (ie, dismantle the power struggle).
- Give incentives for passing stools into the toilet.
- For soiling, insist on immediate cleanup.
- Medications are not needed.
- Refer treatment failures to a mental health professional.
- The role of the pediatrician after referral is to stay involved for ongoing health care.

hug, and a sticker. To achieve a breakthrough with some children who have never had a BM into a potty chair or toilet, the parent can offer major incentives, such as going out to their favorite restaurant, watching their favorite video, or getting treats. A star chart also helps many children stay focused on the goal of releasing stool into the potty chair or toilet. Incentives are also helpful in younger children who hold back BMs and resist sitting on the potty.

### Changing Soiled Underwear

Soiling should not be ignored. The parents’ only remaining assignment is to help the child change clothes when they become soiled. As soon as the parents notice that the child has messy pants, they should clean the child immediately. Changing should be made a neutral, timely interaction.

## PROGNOSIS

Pediatricians should be independently able to manage most children with constipation. The management of constipation with encopresis may be more difficult. If the retentive encopresis is caused by pain avoidance, primary care management can cure 95% of these children’s constipation. If the retentive encopresis is caused by a toilet-training battle or other control issues, the challenge is combining medical and behavioral management. The pediatrician may be able to cure 70% of these children independently. For the others, she will need to collaborate with a mental health professional. Levine studied 127 encopretic children of the retentive type managed by a developmental pediatrician. After 1 year, 51% were cured, and 27% had marked improvement.

Nonretentive encopresis is much easier to treat than retentive encopresis. These children have good results if the problem is recent and poor results if the problem is longstanding (>5 years). In mildly resistive children, primary care management can achieve a 90% to 95% cure rate if the right incentives are identified and implemented. Children who have severe resistance need early referral. Box 247-3 lists the reasons for referral of encopretic children to a mental health professional.



**BOX 247-3 When to Refer Encopresis to a Mental Health Professional**

- Refuses to sit on the toilet and is older than 4 years
- Refuses to take medications
- Refuses to give up stool holding
- Has nonretentive encopresis and is unresponsive to pediatric management
- Has nonretentive encopresis and is older than 8 years
- Deliberately passes stools on family possessions or at school (overt anger)
- Has stool smearing that is a recurrent problem
- Has major developmental disability and cannot be toilet trained
- Has oppositional-defiant disorder, depression, or other serious mental illness
- Has severely strained or angry parent-child relationship

Referrals to a pediatric gastrointestinal specialist are needed less often than referrals to a behavioral pediatrician or mental health professional. Appropriate referrals are children with repeated impaction, unresponsive constipation, or constipation of unknown etiology.

**SUMMARY**

The pediatrician plays a critical role in evaluating children with encopresis. Initial sorting of retentive (constipated) from nonretentive encopresis is critical because they require different management strategies. Placing nonretentive children on stool softeners is unnecessary and will increase stool leakage. Not recognizing retentive children and not placing them on appropriate medications means their problem will only become worse.

The pediatrician can treat many of these children successfully. Because encopresis causes psychological stress for both the child and the family, severe cases that do not respond to pediatric management require prompt referral. If a child with retentive encopresis is referred to a mental health professional, the pediatrician must also see the patient at regular intervals to titrate medications and prevent impaction.

**TOOLS FOR PRACTICE****Engaging Patient and Family**

- *Constipation and Your Child* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Guide to Toilet Training* (book), American Academy of Pediatrics (shop.aap.org)

**AAP POLICY**

Jenny C, Crawford-Jakubiak JE; American Academy of Pediatrics Committee on Child Abuse and Neglect. The evaluation of children in the primary care setting when sexual abuse is suspected. *Pediatrics*. 2013;132(2):e558–e567 (pediatrics.aappublications.org/content/132/2/e558)

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**Chapter 248****ENTEROVIRUS AND EVOLVING INFECTIONS**

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**ENTEROVIRUS INFECTIONS**

Enteroviruses are members of the Picornaviridae family along with parechoviruses, and share a genus with rhinoviruses, coxsackieviruses, and polioviruses. All members of the genus *Enterovirus* have single-stranded RNA. Enteroviruses infect mammals. There are more than 110 subtypes of enteroviruses that can infect humans. A newer, more practical classification divides *Enterovirus* into 4 subtypes:

- Enterovirus A (25 viruses)
- Enterovirus B (61 viruses)
- Enterovirus C (23 viruses)
- Enterovirus D (5 viruses)

Enterovirus serotypes causing more severe disease include polioviruses (EV C), enterovirus 71 (EV A), and enterovirus 68 (EV D).

**Epidemiology**

In the United States, enteroviruses typically cause outbreaks in the late summer and early fall, but disease may occur at lower levels year round. In the tropics, *Enterovirus* infections occur year round. Children younger than 10 years have the highest incidence of *Enterovirus* infections. Humans shed enteroviruses in the feces for weeks after infection, and fecal-oral transmission is the predominant mode of transmission. Infection through the respiratory tract is possible and may be the predominant transmission mechanism for some individual viruses, such as enterovirus D68.

Certain enteroviruses have particularly significant epidemiologic importance. Polioviruses caused widespread outbreaks of disease, with a small percentage of infected patients developing acute flaccid paralysis. Currently enterovirus 68 infection is associated with an increased rate of respiratory illnesses requiring hospitalization. Enterovirus 71 is a major cause of disease in Asia. Coxsackievirus A24 and enterovirus 70 infections often lead to widespread hemorrhagic conjunctivitis outbreaks. Certain subtypes have a strong association with viral meningoencephalitis (echoviruses 13, 18, and 30). A recent study implicates enteroviruses as a trigger for type 1 diabetes mellitus.

A patient with a primary immunodeficiency has a higher risk for severe enterovirus infections. Patients with deficits in humoral immunity, particularly X-linked agammaglobulinemia, have the most severe illness and often develop chronic infections with high morbidity and mortality. Other immunodeficiencies associated with severe enterovirus infections include severe combined immunodeficiency, common variable immunodeficiency, and hyper-immunoglobulin M (IgM) syndrome.

### Symptoms

Enterovirus infection symptoms range from none to meningoencephalitis or a sepsis like presentation. Because most children with infections do not require medical care, the true incidence of enterovirus infections is unknown. Improved viral diagnostic testing for enteroviruses by polymerase chain reaction (PCR) means the diagnosis of infection is much easier. In one study, investigators identified *Enterovirus* species in 12.8% of all infants seen in a primary care setting during peak enterovirus season. Most infants, 80%, had asymptomatic disease. Those with symptoms presented with fever and lethargy. Approximately 50% of infants admitted with a fever of unknown origin have an enteroviral infection. Although most infants present with a nonspecific fever or meningoencephalitis, mortality is extremely low. These infants often present with fever, decreased oral intake, and fussiness. There is no evidence that enteroviral meningoencephalitis has long-term effects on central nervous system development later in life. Infants may present with a petechial rash. Rarely, infants with an enterovirus infection present with a sepsis like picture characterized by hepatic involvement and coagulopathy. Onset is very rapid, and the mortality rate reaches 24%. Circulatory collapse (shock) or hemorrhage causes most deaths. Infants may present with skin lesions such as petechiae and purpura, which may resemble purpura fulminans. An uncommon presentation in infants is myocarditis, which has a mortality rate greater than 70%.

Outside of the neonatal period, children often present with a fever and nonspecific symptoms. Children often present with gingivostomatitis, a febrile illness with vesicles and ulcers in the oropharynx or buccal mucosa. Symptoms may last for a week. Hand, foot, and mouth disease is a combination of oral lesions and vesicular lesions on the hands and feet, specifically the pulp of the fingers and toes. Coxsackievirus A16 is the most common cause of hand-foot-and-mouth disease in the United States. Widespread community

outbreaks of hemorrhagic conjunctivitis are associated with enterovirus 70 and coxsackievirus A24. Enteroviral meningoencephalitis presentations range from fever with a mild headache to changes in mental status.

In August 2014, 2 children's hospitals noted increased numbers of patients presenting with respiratory disease. The Centers for Disease Control and Prevention (CDC) identified enterovirus D68 in most of the children. At the time of publication, more than 43 states had confirmed cases of enterovirus D68 infections. Symptoms of enterovirus D68 infection range from a mild upper respiratory tract infection with cough, sneezing, and fever to a severe respiratory illness that may trigger severe wheezing and hypoxia. Treatment is supportive. Patients with respiratory enteroviral disease who have known reactive airway disease or asthma need to take controller medications as prescribed.

Infection with the polioviruses (3 separate enteroviruses) causes a nonspecific illness. These viruses have tropism for neurons, particularly those in the anterior horns of the spinal cord, and acute flaccid paralysis is the most serious complication. Vaccination programs eradicated polio from the Western hemisphere. Enterovirus 71 infections cause outbreaks of hand-foot-and-mouth disease in China each year. Enterovirus 71 is linked to neurologic disease in China, with symptoms ranging from meningoencephalitis to acute flaccid paralysis to fatal brainstem encephalitis. The cause of death in patients who have enterovirus brainstem encephalitis is autonomic nervous system dysfunction and acute respiratory distress syndrome. Pulmonary hemorrhage may be part of the spectrum.

In September 2014 the CDC issued a Health Advisory after 9 children in Colorado presented with acute focal limb weakness. Magnetic resonance imaging of the brain and spine demonstrated gray matter changes to the spinal cord. Many of these patients tested positive for enterovirus D68. National news agencies have reported similar presentations in other parts of the country. A recent article discussed the temporal association of enterovirus D68 infection and acute flaccid paralysis.

### Differential Diagnosis

The differential diagnosis of hemorrhagic conjunctivitis infection should include adenovirus. Gingivostomatitis caused by *Enterovirus* species tends to cause lesions on the tongue and pharynx, whereas herpes simplex virus (HSV) types 1 and 2 lesions usually involve the lips and anterior gingiva. *Echovirus* and *Parechovirus* can cause nonspecific febrile illnesses similar to the symptoms of enterovirus. Meningoencephalitis symptoms in infants and young children can present similarly to HSV infection. Unlike herpesvirus, enterovirus does not typically cause seizures. Because HSV disease has high morbidity and mortality, it is important to consider this virus in the differential diagnosis because HSV requires prompt treatment with acyclovir. In young infants, enterovirus infection may present with fever as the only symptom. In the neonate, occult bacteremia, meningitis, and pyelonephritis may also present with fever as the only symptom.

## Diagnosis

Before PCR techniques were available, the detection of *Enterovirus* species required viral culture. Enteroviruses grow slowly in cell culture, and results often required a 2- to 3-week wait. Viremia occurs in the acute phase of illness, and culture obtained after that time has a reduced sensitivity. PCR provides rapid results. Appropriate specimens for PCR testing include blood, cerebrospinal fluid, nasopharyngeal swabs, and rectal swabs.

A lumbar puncture is necessary to diagnose enteroviral meningoencephalitis. Cerebrospinal fluid testing should include cell count, protein, glucose, and bacterial culture as well as PCR. If a contraindication precludes a lumbar puncture, enteroviral PCR of the serum may help diagnose meningoencephalitis in patients with appropriate clinical symptoms. PCR testing of stool samples will detect enteroviruses. Because infants and young children may shed enterovirus in the stool for weeks, a positive test from a stool sample is not adequate to diagnose an enterovirus as the cause of an infection.

## Treatment

There is no specific treatment for *Enterovirus* species infections. Infection resolves after the body mounts an effective antibody response. Provide supportive care based on symptoms. Infants who are dehydrated might require intravenous fluids. Patients with severe respiratory distress may require intubation and mechanical ventilation. There are no commercially available antiviral agents with activity against enteroviruses. The medical literature is mixed on whether pleconaril, an antiviral agent effective against some picornaviruses, had significant activity against enteroviruses other than coxsackieviruses. Pleconaril is no longer available for clinical or research use. Two promising antiviral agents under study include a capsid binder (vapendavir) and a novel protease inhibitor (SG85). Wang and colleagues reported that intravenous immunoglobulin (IVIG) therapy could improve survival in patients with enterovirus brainstem encephalitis. At this time there are no conclusive studies to support the use of IVIG to treat enterovirus infections; however, IVIG therapy is often used to treat immunodeficient patients with enterovirus infections.

## Vaccination

Although oral and inactivated polio vaccines eradicated disease from all areas with high vaccination rates, there is no current vaccine effective against other enteroviruses. In Asia, multiple outbreaks of enterovirus 71 have caused permanent central nervous system disease or death. Inactivated viral particle vaccine studies are underway. The major challenge to the development of an enterovirus vaccine is that some subtypes, such as enterovirus 71, have multiple serotypes. Viruses of varying serotypes can recombine their RNA to create new proteins, which may confer resistance to a vaccine. In animal models, small segments of RNA may protect against disease.

When children present for care, the diagnosis of enterovirus infection is not confirmed. Treatment is supportive, and antipyretics and intravenous fluids

may be appropriate for some sick children. Criteria for referral to a children's hospital include the following:

- Seizures
- Encephalitis
- Acute flaccid paralysis
- Severe respiratory distress

Although the treatment is supportive, pediatric subspecialists in critical care medicine, neurology, radiology, and infectious diseases may be helpful in caring for these patients.

## Prognosis

Herpangina and mild febrile illnesses resolve with time. A sepsis like presentation with hepatitis and coagulopathy in neonates is an uncommon presentation, but the mortality rate is quite high. Encephalitis typically resolves without sequelae. Acute flaccid paralysis may be permanent.

## Prevention

Basic infection control practices prevent most cases of *Enterovirus* species infection. The CDC recommends hand hygiene with soap and water or a waterless alcohol rub. Health care workers should institute contact precautions (gown and gloves). The respiratory transmission of some enteroviruses means that cough etiquette and avoiding nasal secretions may be beneficial. For enterovirus in general, standard and contact precautions should be applied. For respiratory enterovirus infection (such as D68), droplet precaution should be added to standard and contact precautions regardless of the patient's age. When caring for children with respiratory enterovirus infection, consider adding a surgical mask (droplet precautions) as well.

## EBOLA VIRUS DISEASE

### Background

Ebola virus disease (EVD), previously known as *Ebola hemorrhagic fever*, is a severe and often fatal disease of humans and nonhuman primates. The first known EVD outbreak occurred simultaneously in Nzara, Sudan, and Yambuku, Zaire (now the Democratic Republic of Congo) in 1976. The disease received its name from the Ebola River, which passes near the Yambuku village in the Democratic Republic of Congo.

*Ebolavirus* is a genus in the family Filoviridae. Five species of *Ebolavirus* have been identified: Zaire Ebola virus, Sudan Ebola virus, Taï Forest Ebola virus, Bundibugyo Ebola virus, and Reston Ebola virus. Reston Ebola virus is not known to cause disease in humans. Given its extremely contagious nature both in the community and health care settings, a single case is considered an outbreak. In 2013 to 2014, the largest outbreak in recorded history started in Guinea and spread to Liberia, Sierra Leone, Nigeria, Mali, and Senegal in Africa. The suspected index case of this outbreak is thought to be a 2-year-old child who died in Guinea. This outbreak from Zaire Ebola virus has resulted in more than 27,000 confirmed cases and more than 10,500 deaths, based on the World Health Organization Ebola situation report on July 15, 2015. The total case-fatality proportion from prior outbreaks



in 1976 to 2008 is 79%, with the Zaire Ebola virus species carrying the highest risk for mortality. In the most recent outbreak in West Africa, individuals aged 15 to 44 years were approximately 3 to 4 times more likely to be affected by EVD than children 14 years and younger. The low number of pediatric EVD cases may result from cultural practices in which children are kept away from sick family members, resulting in reduced risk for Ebola virus exposure.

### Pathogenesis and Disease Transmission

Fruit bats are hypothesized to be the natural reservoirs of Ebola virus; however, this has not been confirmed. The hypothesis is that bats pass the virus on to other animals, such as apes, gorillas, and monkeys, and the virus is then transmitted to humans through the preparation of raw meat or butchering. Human-to-human transmission occurs by direct contact with blood, organs, secretions, and other body fluids (eg, urine, feces, semen, sweat, human milk, mucus, and vomit) of an infected person (alive or dead), as well as with surfaces and materials contaminated with these fluids. Infected medical supplies (eg, syringes and needles) and equipment are additional ways in which the virus can be transmitted from human to human. Virus persistence in the environment depends on many factors, including exposure to sunlight, temperature, and the material surface. It is not known to spread through air or water or by mosquito. The incubation period for EVD is 2 to 21 days. Children younger than 1 year exhibit a shorter incubation period than older children 10 to 15 years of age (6.9 days vs 9.8 days).

### Clinical Presentation

EVD symptoms can resemble other common febrile diseases, such as malaria, enteric fever, or dengue fever. In the early phase of the disease (days 1 to 7), symptoms include a sudden onset of high fever, loss of appetite, headache, nausea, emesis, abdominal pain, diarrhea, myalgia, arthralgia, intense fatigue, and conjunctivitis. A challenge facing physicians caring for children is being able to distinguish the signs and symptoms of early EVD from the features of much more common infectious diseases. In the late phase (day 8 and beyond), symptoms may include severe diarrhea and vomiting with significant hypovolemia, maculopapular rash, and hiccups. In severe cases, the patient may develop cerebral edema, respiratory distress syndrome, shock, multiorgan failure, and coagulopathy associated with hemorrhagic complications, such as mucosal hemorrhage, epistaxis, hemoptysis, hematemesis, rectal bleeding, hemorrhagic stroke, and uncontrolled bleeding from venipuncture sites. Routine laboratory evaluations generally yield leukopenia, thrombocytopenia, hyponatremia, hypokalemia, hypocalcemia, hypoalbuminemia, and elevated liver enzymes.

The case-fatality proportions in the recent outbreak are 73% for children younger than 15 years, 66% for those aged 15 to 44 years, and 80% for those older than 44 years. Children younger than 5 years had more rapid disease progression and a higher fatality rate compared with older children. Pregnant women

are more likely to have a spontaneous abortion and hemorrhagic complications. Neonates born to mothers with acute Ebola infection have not survived thus far.

Patients are considered infectious as long as they are symptomatic and as long as their blood and secretions contain the virus. It is currently unknown how long the virus can persist in sequestered areas of the body, such as the testicles, where the virus has been shown to be present in semen for more than 3 months, and the eye, where the virus has been demonstrated in the aqueous humor 14 weeks after the onset of EVD. Disability may persist after recovery because of complications of hemorrhage, such as hemiplegia from stroke. Moreover, survivors have reported extreme fatigue, arthralgia, myalgia, abdominal pain, anorexia, tinnitus, and hearing loss. Arthralgia has been described to be asymmetric and sometimes migratory involving large joints. Arthralgia and myalgia could persist up to 21 months after EVD onset. Late ophthalmologic manifestations have been reported among EVD survivors. These include ocular pain, photophobia, hyperlacrimation, and loss of visual acuity as a result of uveitis.

A high index of suspicion and active case surveillance are the key to diagnosis. Persons with the previously mentioned clinical symptoms who have traveled to or had contact with an ill traveler from an area where Ebola transmission is active should be evaluated and closely monitored for EVD. Laboratory diagnosis for EVD includes the detection of virus in blood specimens using real-time reverse-transcriptase PCR, and viral antigen detection by enzyme-linked immunosorbent assay (ELISA). Specific antibodies to Ebola virus may be detected by immunoglobulin (Ig) G and IgM ELISA or IgM capture ELISA starting a few days after symptom onset. However, patients with fatal disease may not develop detectable antibody responses. In the absence of these diagnostic tests in a resource-limited setting, a case definition based on clinical criteria can be used if the epidemiologic conditions support the diagnosis of EVD (ie, region with prior outbreak or travel from outbreak area).

### Treatment

Standard treatment consists of aggressive oral and intravenous fluid replacement, maintenance of electrolyte balance, and transfusion of blood products as necessary. Such treatments seem to be critical for a positive outcome in patients with EVD. Severely ill patients may require intensive care, which can include the need for dialysis, mechanical ventilation, or both. EVD survivors should be monitored and treated for long-term complications. Psychosocial support is often required to support the reentry of survivors into their communities. Currently, no approved specific therapy is available that has demonstrated efficacy in the treatment of EVD. Experimental treatments, including a plant-based monoclonal antibody therapy called ZMapp and the transfusion of blood products donated by EVD-recovered patients, were used to treat a small number of patients during the most recent outbreak. Several treatments are being evaluated in clinical trials at the time of this



writing; these include ZMapp, favipiravir, and convalescent blood products from patients who recovered from EVD.

### Prevention

No vaccines are approved for humans or animals, although several vaccine candidates are currently being tested. At the time of this writing, 2 Ebola vaccines using a chimpanzee adenovirus vector and vesicular stomatitis virus vector are being evaluated in phase II/III trials in Africa.

In the absence of effective treatment and vaccines, public awareness, proper patient isolation, and contact tracing are the keys to reduce human infection and death. For symptomatic patients with potential Ebola virus exposure, patient isolation and public health authority notification should be immediately implemented to arrange for safe transport to an appropriate health care facility. For asymptomatic persons with potential Ebola virus exposure, public health officials may implement either active monitoring or direct active monitoring, depending on the individual's exposure risk. Active monitoring consists of daily reporting of measured temperatures and symptoms by the individual to the public health authority, whereas direct active monitoring designates that a public health authority directly observes the individual at least once daily to review symptom status and monitor temperature, with a second follow-up per day being conducted by phone. Exclusion of the person from public places and travel restriction could be enforced by public health authorities. In general, all travelers from the outbreak region are monitored for 21 days after their last date of possible exposure to the virus. Infection among health workers may be prevented by strict adherence to infection prevention and control practices (such as proper hand-washing technique, appropriate use of personal protective equipment [PPE], and proper waste disposal of contaminated material). In pediatric settings, the presence of a family member might be needed in caring for children with EVD. A child with mild symptoms (eg, no bleeding, vomiting, or diarrhea) could be isolated with a family member so that the child can continue to be nurtured and supported while ill. This needs to be balanced with appropriate infection control procedures, including the use of PPE. To prevent sexual transmission of infection during the convalescent period, the World Health Organization recommends abstinence from all sexual activities for 6 months after the symptom onset or practicing safe sex through correct and consistent condom use until their semen has twice tested negative by reverse-transcriptase PCR. This interval may be adjusted as new information on sexual transmission of Ebola virus becomes available. The bodies of deceased individuals remain infectious and must receive safe burials as defined by the use of PPE before touching, washing, or manipulating the body and the use of a leak-proof body bag or coffin. Abstention from traditional practices, such as dressing or washing a body before the funeral, is necessary to avoid the infection of health workers who transfer a body and the infection of family,

community members, or funeral workers who participate in funerals.

### TOOLS FOR PRACTICE

#### Community Advocacy and Coordination

- *Managing Infectious Diseases in Child Care and Schools* (book), American Academy of Pediatrics (shop.aap.org)

#### Engaging Patient and Family

- *An Ounce of Prevention Keeps the Germs Away* (brochure), Centers for Disease Control and Prevention ([www.cdc.gov/ounceofprevention/docs/oonp\\_brochure\\_12-20-05.pdf](http://www.cdc.gov/ounceofprevention/docs/oonp_brochure_12-20-05.pdf))
- *Non-Polio Enterovirus Infections* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/non-polio-enterovirus/index.html](http://www.cdc.gov/non-polio-enterovirus/index.html))

#### Medical Decision Support

- *Enterovirus Surveillance—United States, 1970–2005* (report), Centers for Disease Control and Prevention ([www.cdc.gov/mmwr/preview/mmwrhtml/ss5508a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5508a1.htm))
- *Red Book: 2015 Report of the Committee on Infectious Diseases*, 30th ed (book), American Academy of Pediatrics (shop.aap.org)

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## Chapter 249 ENURESIS

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The acquisition of urinary continence is part of the transition from infant to child lower urinary tract function. Although incontinence in a child can be an

inconvenience, it is generally tolerated until a child falls behind her peers. Since parental concerns about voiding are common, it is important for primary care physicians to have an understanding of both the normal acquisition of continence and departures from those normal patterns. This chapter will provide the basis for the primary care physician to understand the definition, epidemiology, etiology, risk factors, differential diagnosis, evaluation, and management of enuresis in children.

## DEFINITION OF TERMS

### Definitions

Enuresis refers to intermittent urinary wetting while asleep and is defined as voiding on beds and clothes that occurs at least twice per week for at least 3 consecutive months in a child who is at least 5 years of age. Five years is considered the age of anticipated bladder control at night. Children who are mentally disabled should, therefore, reach a mental age of 5 years before they are considered enuretic. “Nocturnal” is often added to enuresis for more clarity. The child who wets during the daytime and at night has daytime incontinence and enuresis (or nocturnal enuresis). The term diurnal enuresis has been dropped. Enuresis is described as *primary* when it occurs in children who have never had a period of sustained dryness and *secondary* when it occurs in children who have been dry in the past for a period of at least 6 months. Nocturnal enuresis can be *monosymptomatic* when there are no other lower urinary tract symptoms, such as increased/decreased voiding frequency, daytime incontinence, urgency, hesitancy, straining, a weak stream, intermittency, holding maneuvers, a feeling of incomplete emptying, postmicturition dribble, and genital or lower urinary tract pain. When other lower urinary tract symptoms are present, enuresis becomes *nonmonosymptomatic* (polysymptomatic).

### Epidemiologic Mechanism

The available data on the prevalence of nocturnal enuresis need to be treated with caution given the inconsistency in methodology across epidemiologic surveys. Nocturnal enuresis occurs in approximately 20% of children at 5 years of age. At age 7, the prevalence of nocturnal enuresis is between 6% and 10%. In the United States, a recent National Health and Nutrition Examination Surveys (NHANES) study of children aged between 8 and 11 years found the prevalence of enuresis to be 4.45%. The annual spontaneous resolution rate is approximately 15%, with nocturnal enuresis persisting in 1% to 3% in the late teens. The incidence of primary enuresis is twice that of secondary enuresis. Nocturnal enuresis is 2 to 3 times more common in boys than girls and is monosymptomatic in more than two-thirds of cases. Daytime wetting is more likely in females. Ten percent of 5-year-olds experience daytime wetting at least once every 2 weeks.

### Etiology

A strong hereditary component to nocturnal enuresis has been noted. Twin studies demonstrate a concordance rate of 19% to 36% for dizygotic twins and 46% to 68% for monozygotic twins. Children with a

family history of nocturnal enuresis are more likely to experience nighttime wetting than their peers. Forty-four percent of children with 1 parent with a history of nocturnal enuresis will also have nocturnal enuresis; the percentage of affected children increases to 77% if the history of nocturnal enuresis is present in both parents. The inheritance pattern with nocturnal enuresis is most often autosomal dominant with high penetrance. In addition to genetics, developmental factors, such as delayed speech, delayed walking, and early toilet training, have been speculated to be associated with nocturnal enuresis; however, studies evaluating these associations have yielded conflicting results.

Several factors are involved with the pathophysiology of monosymptomatic nocturnal enuresis (MNE). Most children with MNE have relative nocturnal polyuria that exceeds the child's bladder capacity, leading to nighttime wetting. Normally, the secretion of antidiuretic hormone increases during sleep; however, in some children with MNE the secretion of antidiuretic hormone is decreased at night, resulting in increased urine production. Voided volumes have been demonstrated to vary in the daytime and nighttime. In children with enuresis, voided volumes have been found to be smaller at night compared to normal controls, suggesting some form of overactive bladder. Normally, if a child had a full bladder, whether caused by nocturnal polyuria or overactive bladder, he would awaken and void in an appropriate place. However children with MNE are more difficult to arouse from sleep than normal controls, or children with polysymptomatic nocturnal enuresis. Enuresis has been reported to be associated with some sleep disorders, particularly obstructive sleep apnea. Nocturnal enuresis is present in 33% of children with obstructive sleep apnea and resolves in 61% and decreases in 23% of children within 9 months following tonsillectomy and adenoidectomy. The presence of nocturnal hypercalciuria and aquaporin-2 dysfunction have also been postulated to play a role in the pathogenesis of enuresis.

Anatomic abnormalities may also contribute to nonmonosymptomatic enuresis. Urethral obstruction, as a result of posterior urethral valves or urethral stricture, is known to cause daytime incontinence or nocturnal enuresis. Ectopic ureters in females may lead to continuous leaking of urine because, unlike in males, the ectopic ureter does not insert proximal to the external sphincter. Lesions involving the spinal cord often result in a neurogenic bladder, which can lead to enuresis. However, the prevalence of spina bifida occulta has not been shown to be statistically different between children with functional bowel or urinary problems and age- and gender-matched controls. Vesicovaginal reflux occurring in females may lead to urine leakage and contribute to incontinence in these patients.

Daytime incontinence occurs when urine is held until the last minute, a behavior common in preschoolers and older children who avoid the restroom at school. Other forms of daytime urinary incontinence include increased daytime voiding frequency resulting

from an overactive bladder, wetting during coughing or sneezing as is seen in stress incontinence, and wetting during laughter in giggle incontinence. Attention-deficit/hyperactivity disorder (ADHD) has also been shown to be strongly associated with enuresis. Urinary tract infection (UTI) contributes to enuresis when cystitis causes spontaneous detrusor contractions; also, UTIs are more common in children who have abnormal genitourinary anatomy. Other risk factors that have been demonstrated to be associated with nocturnal enuresis include encopresis and emotional stress.

## DIFFERENTIAL DIAGNOSIS

Although enuresis is most often encountered as a primary disorder, it also may present secondary to other conditions. Underlying disorders that should be considered in the evaluation of enuresis are listed in Box 249-1.

## EVALUATION

### History

The history is a critical component in the evaluation of enuresis. A thorough history will help the pediatrician categorize the type of enuresis present and identify underlying conditions that might be contributing to the patient's symptoms. The International Children's Continence Society recommends the use of structured questionnaires for parents to complete prior to the evaluation. The questionnaire is available on request from the authors directly.

The time of onset, frequency, time of day of occurrence, and any relationship with environmental changes should be determined. It is important to obtain a history on the length of time of dryness prior to the onset of enuresis. The history of dryness is important because it makes the presence of a structural urinary problem unlikely, helps predict the chance of eventual dryness, and decreases the need for extensive

investigation. It is helpful to know the child's fluid intake and drinking habits, because some children drink large volumes of fluid in the evening, which may precipitate or exacerbate enuresis. Symptoms of polydipsia, polyuria, and recent weight loss may suggest diabetes mellitus. A history of symptoms such as urinary frequency, urgency, and dysuria should be obtained to help determine the presence of a UTI. It is important to determine the child's feelings about the symptom and any motivation for doing something about it, as this would eventually influence the decision to initiate therapy. It is also important to elicit what the child and parents have done about the symptom prior to this evaluation. A history of the child's sleeping patterns needs to be obtained because of the association of enuresis and sleep apnea. Symptoms of snoring and mouth breathing while asleep, restless sleep, and tiredness on waking up in the morning should be elicited in the history. In females, a history of being always wet might suggest ectopic ureter. A summary of questions to consider while taking a history of a child with enuresis are listed in Box 249-2.

Past medical history, including a thorough perinatal history, should be sought to determine if there are any neurologic explanations for enuresis. Specifically, a history of spina bifida or meningocele would be important in the pathogenesis of enuresis. Any history of delayed developmental motor milestones or spinal trauma should be obtained. Constipation in the child must be ruled out because of the strong association of constipation with enuresis. Any family history of enuresis or idiopathic hypercalciuria should be elicited because this would help in evaluating the cause of enuresis. Psychologic problems and psychosocial stressors are known to be associated with enuresis. These include poor self-esteem, chronic anxiety, child abuse, and delayed development.

### Physical Examination

Physical examination findings of the child with enuresis are often normal, but the examination should be thorough and focus on signs that may indicate any of the causes of enuresis. Abnormal vital signs or growth parameters may be an indication of chronic disease. A thorough oropharyngeal examination may reveal the presence of tonsillar enlargement, especially in a child with suspected obstructive sleep apnea. A complete neurologic examination, including an assessment of gait, muscle tone and strength, deep tendon reflexes, sensory abnormalities, and rectal sphincter tone, is necessary to exclude central nervous system disease, which may result in enuresis. An examination of the spine may reveal subtle signs of spinal dysraphism, such as dimples, hair tuft, and skin discoloration. Let the child grasp a pencil with his toes: if he is able to do so, it means that S1, S2 and S3, are intact. Ask him to do it bilaterally. An abdominal examination should pay particular attention to the presence of a distended bladder or constipation. A distended bladder may suggest the presence of an obstructing urethral lesion such as posterior urethral valves or stricture. The presence of constipation increases the risk of urinary

### BOX 249-1 Medical Conditions Associated With Enuresis

1. Urinary tract infections
2. Neurologic disorders, including neurogenic bladder or detrusor instability, and spinal cord pathology
3. Structural genitourinary tract abnormalities, including ectopic ureter, posterior urethral valves, urethral stricture, and vesicovaginal reflux
4. Constipation
5. Endocrine disorders, including diabetes mellitus and diabetes insipidus
6. Hypercalciuria
7. Sickle cell disease
8. Drugs, including caffeine and methylxanthines
9. Obstructive sleep apnea
10. Psychosocial stressors, including child abuse, parental divorce or separation, and death in the family

**BOX 249-2 Questions to Consider When Taking a History of a Patient With Enuresis**

1. Definition of the enuresis:
  - Determine between nocturnal and diurnal enuresis
    - *Does the wetting occur during the day, the night, or both?*
    - *How often does the wetting occur and at what times?*
    - *How often does the child void during the day and during the night?*
2. Type of enuresis:
  - Determine between primary and secondary enuresis
    - *At what age did the wetting start?*
    - *Has the child ever been dry? If so, for how long?*
    - *Has the child had any dry spells?*
    - *How long did dry spells last?*
3. Identify what the social situation is regarding the enuresis
  - How does the family handle wet nights?
  - Does the child wear training pants or is a plastic sheet used?
  - If sheets and clothing require laundering, who is responsible?
  - Do siblings tease the child?
  - Is the child punished for wetting?
  - Have there been any recent traumatic events or changes in the child's social situation at home or in school?
4. Identify fluid intake during the day and prior to bedtime
  - How much and how often does the child drink in the daytime?
  - How much and when does the child drink after supper?
5. Define sleep habits
  - Is the child difficult to awaken from sleep?
  - Are signs of obstructive sleep apnea (mouth breathing, snoring, and restless sleep) present?
6. Evaluate for daytime symptoms
  - Is urinary frequency (the normal frequency of voiding is 4–7 times/day), urgency, or dysuria present?
  - Is dribbling present between voids?
  - Does the child strain with voids?
  - Is the child always wet?
  - Is constipation present?
7. Evaluate past medical history and family medical history
  - Has the child had normal development?
  - Does the child have any psychologic conditions (ADHD, depression, or behavior disorders)?
  - Is there a family history of enuresis?
  - Has the child had any surgery?
  - Is there any history of polydipsia and polyuria?
  - Is there any history of recent weight loss?

tract infections. Flank examination should exclude the presence of renal masses that may indicate renal diseases. Lower abdominal tenderness may indicate a UTI. A careful genitourinary examination should be performed to evaluate for the presence of a rash, adhesions, trauma, foreign body, and, in girls, vulvitis and vaginitis. A rectal examination can reveal the presence of fecal impaction or decreased rectal tone. In some instances, observing a child void may reveal important clues to the presence of urethral obstruction, such as a weak urine stream and straining during micturition.

### Laboratory Investigations

The diagnosis of enuresis is largely dependent on a thorough history and physical examination. With MNE, a simple urinalysis can provide valuable information about the cause of enuresis. The presence of proteinuria, hematuria, and red blood cell casts may signal renal pathology, while glucosuria may be an indication of diabetes mellitus. A low specific gravity on urinalysis may be associated with diabetes insipidus or psychogenic polydipsia. The presence of white blood cells and bacteria may suggest a UTI, which may then be confirmed on a urine culture. If daytime symptoms are present or if the initial laboratory evaluation and physical examination reveal abnormalities, additional evaluations are indicated. Imaging studies should start with pre- and post-void renal and bladder ultrasound.

If the renal ultrasound is abnormal, a voiding cystourethrogram and urodynamic studies should be considered. If a spinal dysraphism is suspected, magnetic resonance imaging of the spine should be ordered.

### MANAGEMENT

Treatment of MNE should be considered in a child who is 6 years of age or older and must begin with careful and detailed explanation of the condition to both parents and child in language that is easily understood. The treatment of MNE is often a frustrating experience for both parents and child, as relapses often occur. The combination of a motivated child and a cooperative family is the best predictor of a positive outcome. Treatment programs should be individualized and realistic goals set for both the patient and the family. Primary and secondary nocturnal enuresis are treated similarly.

The options available for the treatment of enuresis depend on the presence or absence of any organic causes as previously discussed. Any underlying pathology must be addressed. Common organic causes of enuresis such as constipation or UTI, if present, should be treated first. Constipation has been shown to be a commonly unrecognized and undertreated cause of enuresis. If both daytime and nighttime symptoms are present, the daytime symptoms should be the initial focus. Good voiding hygiene and habits should be reinforced.



### Nonpharmacologic Therapy

Conservative measures that help minimize nocturnal polyuria include decreasing the amount of fluid intake several hours before bedtime. Voiding prior to going to bed minimizes the nocturnal bladder volume. The child may also be awakened and taken to the bathroom to urinate before parents go to bed. Other measures that have been shown to reduce the number of wet nights include the use of charts, mainly for positive reinforcement. Children are asked to fill out a chart depicting wet and dry nights symbolically (such as “stars” or “sun” for dry nights and “cloud” for wet nights). During the daytime, the child should be encouraged to void often and take the time to empty the bladder completely. In most cases of daytime incontinence, this helps alleviate symptoms. It is prudent to ask the child to void in the morning, at least twice during the school day, after school, at dinner time, and just before turning out the lights and going to sleep.

### Specific Therapy

The first-line therapy for MNE is either the enuresis alarm or desmopressin (DDAVP). For the well-motivated child and well-informed family, the enuresis alarm might be the initial choice. Families who are not as well motivated, who have had no success with the alarm (accurately used), or who are considered unlikely to fully comply with alarm treatment might do better with DDAVP.

#### Alarm

The bedwetting alarm has been shown to be very effective in the treatment of MNE. It is worn by the child every night. The alarm is triggered when a sensor in the sheets or night clothes becomes wet, setting off an auditory signal that then awakens the child. It must be emphasized to the family that response to the alarm is not immediate and patience is needed for successful therapy. The alarm should be used for 2 to 3 months or until the child is dry for 14 consecutive nights, whichever comes first. Although the response rate is not as rapid, alarm therapy is more effective than pharmacologic therapy in the treatment of enuresis. The response rate to the alarm is high in families who continue treatment for a sufficient period, with relatively low relapse rates. Relapses do not preclude future success. The percentage of children who remain dry long-term after alarm therapy is stopped is 47%, suggesting that the alarm is not only a management modality but also a cure. In some families, alarms may increase parental annoyance and place the child at risk for physical or emotional abuse. Physicians managing these children should follow up closely with families to identify areas of difficulty early and address concerns. Many children will not initially awaken with the alarm and need a parent to assist in awakening, so it is helpful for a parent to sleep in the room with the child. If the child seems not be able to wake up from the alarm after a short time (eg, 1–2 weeks), the treatment should be discontinued and eventually repeated at a later stage.

### Pharmacologic Therapy

The pharmacologic management of enuresis is dependent on the cause of the condition. Historically, 3 drugs have been used in the treatment of enuresis: DDAVP, imipramine, and oxybutynin.

#### Desmopressin

DDAVP is an analogue of vasopressin (also called antidiuretic hormone). Vasopressin is a polypeptide of 9 amino acids and is produced in the hypothalamus and released from the pituitary gland. The stimulus for the release of vasopressin is hyperosmolarity or intravascular volume depletion. Vasopressin acts on the collecting ducts and distal tubules in the kidney to enhance water reabsorption and also has vasopressor effects. DDAVP, on the other hand, has significantly increased antidiuretic activity, but absent vasopressor effects. DDAVP is used for the treatment of MNE. It has a dose-dependent effect, and the usual dose is 0.2 mg up to 0.6 mg orally at bedtime. Response to treatment might take up to 2 to 3 months. If treatment with DDAVP is successful, a 1-week interruption every 3 months is recommended to see if enuresis has resolved. In children in whom there is no response to DDAVP, alarm therapy should be considered if the child and the family are motivated. In the short term, DDAVP is reported to produce a more rapid improvement than alarm therapy, but in the long term, the alarms are more effective and have the highest overall cure rate in treating enuresis. Relapse is common with DDAVP use, with many children wetting again when treatment is stopped. Patients and parents should be educated on the side effects of DDAVP, some of which include nausea, vomiting, abdominal pain, headache, facial flushing, elevated blood pressure, chest pain, tachycardia, and hyponatremia from water intoxication. It is therefore important to screen the child with a good voiding diary and to exclude evening or nighttime polydipsia. Hyponatremia is particularly concerning. Recent data have suggested that there is decreased risk of hyponatremia with oral DDAVP compared to the intranasal formulation. Consequently, the US Food and Drug Administration has advised physicians not to use DDAVP in its intranasal form for the treatment of MNE. In children who do not respond to monotherapy with DDAVP or alarm therapy, combination therapies using both DDAVP and alarm may be considered as second-line therapy and have been shown to be effective in achieving dryness.

#### Oxybutynin

Oxybutynin is an anticholinergic as well as a smooth-muscle relaxant and has been useful in the treatment of daytime enuresis caused by detrusor overactivity. This drug may therefore be of benefit to those children with enuresis who have restricted bladder capacity because of bladder overactivity. The dose is 5 mg of oxybutynin at bedtime, but this dose may need to be doubled. Side effects of oxybutynin include nausea, vomiting, abdominal pain, diarrhea or constipation, urinary retention, dry mucous membranes, and blurred vision. Given alone, oxybutynin has been

shown to be no more effective than placebo in the treatment of primary enuresis. However, oxybutynin and the extended-release anticholinergic tolterodine may be helpful if given in combination with DDAVP in those who do not respond to DDAVP monotherapy. This combination has been shown to produce rapid results in the treatment of MNE. In addition to enuresis, anticholinergic medications are used to treat urge syndrome, Hinman syndrome, and the neurogenic bladder.

### Tricyclic Antidepressants

Tricyclic antidepressants, such as imipramine, are a last-line treatment option for MNE in patients who do not show any response to other treatment strategies. It is unclear how these medications produce their effects. It was previously thought that their effects were through their anticholinergic properties, but recent data have shown that patients who do not respond to anticholinergics can benefit from the use of imipramine. The efficacy of imipramine in the treatment of MNE is low, and relapse rates are high. Because of the potential for lethal effects in the setting of an accidental or intentional overdose, physicians should be cautious with the use of tricyclic antidepressants such as imipramine. In addition, imipramine may cause nausea, vomiting, constipation, blurry vision, urinary retention, cardiac arrhythmias, and hypotension. The anti-enuretic dose is 25 to 50 mg at bedtime, with the larger dose given in children older than 9 years of age. If tricyclic antidepressants are used, families must be aware not only of the dangerous potential of overdose, but also of safe storage practices and the need for supervision during administration.

### Other Therapies

Behavioral modifications, such as changes in toileting habits, waking after several hours of sleep to void, and the use of alarms, have formed an important aspect of management in patients with enuresis. A recent prospective, randomized study comparing the use of DDAVP and intensive behavior modification showed significant reductions in primary MNE in both arms of the study, with no significant difference between the 2 groups.

## SUMMARY

Several factors may contribute to nocturnal enuresis, including a genetic predisposition, decreased voided volumes caused by an overactive bladder, increased nocturnal urine production, and a diminished capacity for arousal from sleep. Because nocturnal enuresis may present secondary to organic causes or in association with other symptoms, a detailed history and physical examination are critical components of the evaluation. Once organic causes have been ruled out and daytime symptoms have been treated, intervention may be of benefit. Alarm treatment has the best long-term results, but does not provide immediate resolution of symptoms. Treatment, which often includes a combination of behavior and pharmacotherapy, may be individualized based on the needs of a

wide variety of patients. Because involvement of families is an important component in the management of enuresis, parents can be directed to relevant resources such as the publication *Waking Up Dry: A Guide to Help Children Overcome Bedwetting* by Howard J. Bennett, MD, or the National Kidney Foundation Parent Resource Web site at [www.kidney.org/patients/bw/BWparents.cfm](http://www.kidney.org/patients/bw/BWparents.cfm).

## WHEN TO REFER

- Abnormal urinalysis findings suggestive of a metabolic disorder
- Concerns about a neurologic bladder dysfunction
- Failure to respond to appropriate therapy
- Presence of any structural urinary tract abnormalities on imaging studies
- History of recurrent urinary tract infections
- History of significant constipation and encopresis
- History and findings suggestive of obstructive sleep apnea
- Significant behavioral or emotional problems
- Significant parent-child conflict or parental difficulties with coping with child's enuresis
- Attention deficit or learning problems

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Bedwetting* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Information for Parents* (Web page), National Kidney Foundation ([www.kidney.org/patients/bw/BWparents.cfm](http://www.kidney.org/patients/bw/BWparents.cfm))
- *Information for Kids and Teens* (Web page), National Kidney Foundation ([www.kidney.org/patients/bw/BWKidsTeens](http://www.kidney.org/patients/bw/BWKidsTeens))
- *Voiding History and Voiding Diary* (forms), National Kidney Foundation ([www.kidney.org/patients/bw/BWvoidingHist](http://www.kidney.org/patients/bw/BWvoidingHist))
- *Waking Up Dry: A Guide to Help Children Overcome Bedwetting* (book), Bennett HJ ([shop.aap.org](http://shop.aap.org))

### Medical Decision Support

- *Voiding Questionnaire* (tool), National Kidney Foundation ([www.kidney.org/sites/default/files/docs/voidhist.pdf](http://www.kidney.org/sites/default/files/docs/voidhist.pdf))

## SUGGESTED READINGS

- Bennett HJ. *Waking Up Dry: A Guide to Help Children Overcome Bedwetting*. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2014
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## Chapter 250

## FETAL ALCOHOL SPECTRUM DISORDERS

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## DEFINITION

Fetal alcohol spectrum disorders (FASD) refer to a continuum of physical, growth, and neurobehavioral abnormalities that occur as a result of prenatal exposure to alcohol. Since 1968, when researchers published a report highlighting the adverse effects of alcohol in offspring of mothers with heavy prenatal alcohol use, thousands of human and animal studies or reports have emerged that demonstrate the range of damaging effects of fetal alcohol exposure. Despite increasing awareness of the adverse effects of maternal alcohol consumption, prenatal alcohol exposure remains among the leading causes of developmental disability worldwide, and is considered to be the most common preventable cause of intellectual disability in the United States.

Several disorders fall under the umbrella term of FASD (Box 250-1), which by itself is not a specific diagnosis but refers to a group of disorders with overlapping physical, behavioral, and cognitive features. Fetal alcohol syndrome (FAS) describes individuals

who fit a well-defined set of clinical diagnostic criteria, including characteristic dysmorphic facial features, evidence of growth restriction, and neurocognitive deficits, in the presence of definite or unknown prenatal alcohol exposure. Fetal alcohol syndrome represents the most severe end of the FASD spectrum; however, the milder forms of FASD are much more common and at the same time often very challenging to diagnose accurately, since distinctive facial features or growth patterns may not be present. Further complicating the diagnosis of FASD, particularly in individuals who do not meet the criteria for full FAS, is the fact that while there are several published guidelines for the diagnosis of FASD, they are not all consistent with each other. However, correct diagnosis is important because individuals with the so-called milder types of FASD may nonetheless have significant, life-long deficits in behavior or cognition, as prenatal alcohol exposure is particularly harmful to the developing brain. Other disorders in the FASD spectrum include partial fetal alcohol syndrome, alcohol-related birth defects (ARBD), and alcohol-related neurodevelopmental disorder (ARND), as defined by the revised Institute of Medicine FASD diagnostic criteria. Partial fetal alcohol syndrome can be diagnosed with or without confirmed maternal alcohol exposure, and encompasses children with characteristic facial features of FAS and *either* growth deficiency or central nervous system (CNS) abnormalities. The term ARBD is used

## BOX 250-1 Fetal Alcohol Syndrome and Related Disorders

1. Fetal alcohol syndrome (FAS)
  - a. Requires all 3 of the following findings:
    - i. Documentation of all 3 facial abnormalities (smooth philtrum, thin vermillion border, and small palpebral fissures)
    - ii. Documentation of growth deficits
    - iii. Documentation of CNS abnormality
  - b. Facial dysmorphism (all 3 must be present)
    - i. Smooth philtrum (University of Washington Lip-Philtrum Guide rank 4 or 5)
    - ii. Thin vermillion border of the upper lip (University of Washington Lip-Philtrum Guide rank 4 or 5)
    - iii. Small palpebral fissures (length at or below 10th percentile)
  - c. Growth deficiency: Prenatal or postnatal height or weight (or both)  $\leq$  10th percentile, documented at any point in time and adjusted for age, sex, gestational age, and race/ethnicity
  - d. CNS abnormalities: 1 of the following, or a combination thereof
    - i. Structural abnormalities
      - (a). circumference at or below the 10th percentile adjusted for age and sex
      - (b). significant brain abnormalities observable through imaging
    - ii. Neurologic abnormalities: Neurologic problems not caused by a postnatal insult or fever or other soft neurologic signs
    - iii. Functional abnormalities: Performance substantially below that expected for an individual's age, schooling, or circumstances, as evidenced by either:
      - (a). Global cognitive or intellectual deficits representing multiple domains of deficit (or significant developmental delay in younger children) with performance below the 3rd percentile ( $-2$  SD for standardized testing)
      - (b). Functional deficits below the 16th percentile ( $-1$  SD for standardized testing) in at least 3 of the following domains:
        - Cognitive or developmental deficits or discrepancies
        - Executive functioning deficits
        - Motor functioning delays
        - Problems with attention or hyperactivity
        - Social skills
        - Other, such as sensory problems, pragmatic language problems, memory deficits, etc
  - e. Maternal alcohol exposure may be confirmed or unknown.

Continued

**BOX 250-1 Fetal Alcohol Syndrome and Related Disorders—cont'd**

2. Partial FAS (PFAS) with confirmed maternal alcohol exposure: requires all 3 of the following findings:
  - a. Confirmed maternal alcohol exposure
  - b. At least 2 of the following facial characteristics:
    - i. Small palpebral fissures (length at or below the 10th percentile)
    - ii. Thin vermilion border of the upper lip (University of Washington Lip-Philtrum Guide rank 4 or 5)
    - iii. Smooth philtrum (University of Washington Lip-Philtrum Guide rank 4 or 5)
  - c. One of the following other characteristics:
    - i. Height or weight at or less than the 10th percentile for age, sex, ethnicity
    - ii. Evidence of structural CNS abnormalities, including at least 1 of the following:
      - (a). Head circumference at or less than the 10th percentile
      - (b). Structural brain abnormalities
    - iii. Evidence of a complex pattern of behavioral or cognitive abnormalities inconsistent with developmental level that cannot be explained by genetic predisposition, family background, or environment alone, including:
      - (a). Marked impairment in performance of complex tasks
      - (b). Higher-level receptive and expressive language deficits
      - (c). Disordered behavior
3. Alcohol-Related Birth Defects (ARBD) - Requires all 3 of the following findings (a, b, c)
  - a. Confirmed maternal alcohol exposure
  - b. At least 2 of the following:
    - i. Small palpebral fissures (length at or below the 10th percentile)
    - ii. Thin vermilion border of the upper lip (University of Washington Lip-Philtrum Guide rank 4 or 5)
    - iii. Smooth philtrum (University of Washington Lip-Philtrum Guide rank 4 or 5)
  - c. Congenital structural defects in 1 or more of the following categories, including malformations and dysplasias (if the patient displays minor anomalies only, 2 or more must be present):
    - i. Cardiac: atrial septal defects, aberrant great vessels, ventricular septal defects, conotruncal heart defects
    - ii. Skeletal: radioulnar synostosis, vertebral segmentation defects, large joint contractures, scoliosis
    - iii. Renal: aplastic/hypoplastic/dysplastic kidneys, horseshoe kidneys, ureteral duplications
    - iv. Ocular: strabismus, ptosis, retinal vascular anomalies, optic nerve hypoplasia
    - v. Ears: conductive hearing loss, sensorineural hearing loss
    - vi. Minor anomalies: hypoplastic nails, short fifth digits, fifth finger clinodactyly, pectus carinatum or excavatum, camptodactyly, "hockey stick" palmar creases, refractive errors, "railroad track" ears
4. Alcohol-related neurodevelopmental disorder (ARND): Requires both a and b
  - a. Confirmed maternal alcohol exposure
  - b. At least 1 of the following:
    - i. Evidence of deficient brain growth or abnormal morphogenesis, including 1 or more of the following:
      - (a). Structural brain abnormalities
      - (b). Head circumference at or below the 10th percentile for age and sex
    - ii. Evidence of a complex pattern of behavioral or cognitive abnormalities inconsistent with developmental level that cannot be explained by genetic predisposition, family background, or environment alone, including:
      - (a). Marked impairment in performance of complex tasks
      - (b). Higher-level receptive and expressive language deficits
      - (c). Disordered behavior

CNS, central nervous system; SD, standard deviation.

From Bertrand J, Floyd RL, Weber MK, et al. Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis. Atlanta, GA: Centers for Disease Control and Prevention, 2004; Hoyme HE, May PA, Kalberg WO, et al. A practical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 Institute of Medicine criteria. *Pediatrics*. 2005;115(1):39–47; and Senturias Y, Asamoah A. Fetal alcohol spectrum disorders: guidance for recognition, diagnosis, differential diagnosis, and referral. *Curr Probl Pediatr Adolesc Health Care*. 2014;44(4):88–95.

for children with confirmed alcohol exposure, characteristic facial features, and 1 or more specific, congenital structural anomaly, in the absence of growth restriction or neurocognitive deficits. Alcohol-related neurodevelopmental disorder is diagnosed in individuals without evidence of impaired growth or characteristic facial anomalies who have confirmed maternal alcohol exposure and either structural or functional CNS deficits typical of FASD. Alcohol-related neurodevelopmental disorder is estimated to be the most common of all the disorders resulting from prenatal alcohol exposure.

The term *neurodevelopmental disorder associated with prenatal alcohol exposure* (ND-PAE) has been introduced in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* and is roughly equivalent to ARND. The diagnostic criteria for ND-PAE include evidence of "more than minimal" alcohol exposure during pregnancy and impairments in cognition, self-regulation, and adaptive functioning.

In the past, the term *fetal alcohol effects* initially coined as a population-based term rather than a specific clinical diagnosis, was used liberally to refer to children who had anomalies or cognitive deficits



thought to be related to prenatal alcohol exposure, but who did not meet the diagnostic criteria for FAS. However, this term has largely fallen out of favor, as it has no established diagnostic criteria and is therefore considered vague and without clinical utility. Fetal alcohol effects should no longer be used as a diagnostic term.

## EPIDEMIOLOGY

Fetal alcohol spectrum disorders occur worldwide, though specific subpopulations are known to have particularly high prevalence rates. Yearly, about 40,000 infants in the United States are born with adverse effects from prenatal alcohol exposure. According to the Centers for Disease Control and Prevention (CDC), FAS occurs at a rate of approximately 0.2 to 1.5 per 1,000 births in the United States; the Institute of Medicine (IOM) estimates the rate to be 0.5 to 3.0 per 1,000 children in North American communities. The prevalence of FASD is generally estimated to be around 1% in the US general population. Certain populations are known to have significantly higher rates of FASD, including children in the foster care system (rates of FAS may approach 15 per 1,000), youth in the justice system (estimated that >20% have FASD), and the Native American population. Worldwide, higher prevalence of FASD has been reported in certain regions or countries with heavy per capita consumption of alcohol. A well-studied example of this is Russia, particularly in orphanages, where the prevalence of FAS alone is estimated to be about 15 per 1,000 children.

There are many challenges to accurately estimating the incidence and prevalence of FASD, including the difficulty for many physicians to recognize children with subtle physical or cognitive characteristics of FASD, unavailability of prenatal alcohol exposure history (either because of foster care placement, adoption, or social stigma, which may prevent accurate maternal reporting of alcohol use), and frequent reliance on record review methods. For these reasons, many researchers feel that currently available prevalence data may underestimate the true rate of occurrence of FASD in the general population.

## ETIOLOGY, PATHOPHYSIOLOGY, AND RISK FACTORS

Fetal alcohol spectrum disorders occur only in individuals who were prenatally exposed to alcohol. However, the clinical diagnosis of FAS does not always require definitive proof of maternal alcohol use, since the full FAS facial phenotype is so specific that its presence confirms prenatal alcohol exposure when such history is not available. Alcohol from the maternal bloodstream freely crosses the placenta, and the fetus is exposed to the same blood alcohol level present in the mother's blood. The fetus is, however, exposed to the toxic effects of alcohol for longer periods than the mother because of the immaturity of the fetal liver; in addition, the amniotic fluid can act as a reservoir for alcohol. While the total amount of alcohol consumed during a pregnancy is the most important factor determining a fetus's risk for FASD, other important factors include the timing and pattern of

consumption, as well as maternal and fetal genetic factors (including maternal alcohol metabolism). Studies in various animal models, in cell and embryo cultures, and in humans, have demonstrated that ethanol and its metabolite acetaldehyde exert teratogenic effects in a number of ways. These include directly inducing cell damage via apoptosis and release of free radicals. This direct cytotoxicity results in the structural birth defects and dysmorphic features associated with FASD. In addition, ethanol interferes with cell signaling pathways, disrupts cellular differentiation and growth, interferes with DNA and protein synthesis, and inhibits cell migration. The transplacental transfer of nutrients (such as amino acids, folic acid, zinc, and others) is also reduced, indirectly affecting fetal growth because of intrauterine nutrient deprivation.

In 2005, the US Surgeon General issued a statement warning that there is no known safe amount of alcohol that can be consumed during pregnancy. Studies have shown that pregnancies exposed to as little as 1 drink per day have increased rates of miscarriage, preterm delivery, stillbirth, and intrauterine growth restriction. However, the highest risks for FASD seem to be associated with binge drinking (4 or more drinks consumed on 1 occasion). The timing of exposure is also important. There seems to be no period during pregnancy during which use of alcohol can be considered safe for the developing embryo/fetus. Exposure during the third to eighth weeks of gestation is associated with the highest risks for organ-specific birth defects as well as facial dysmorphism. While structural defects of the CNS, particularly the corpus callosum, can occur as a result of alcohol exposure prior to 8 weeks, the brain continues to develop throughout pregnancy, and the CNS remains vulnerable to the effects of alcohol through the end of the third trimester. First-trimester alcohol exposure is associated with the highest risks for microcephaly, but growth restriction can be seen in fetuses exposed at any time during pregnancy, including the third trimester. Exposure in the second trimester is particularly associated with increased rates of fetal loss.

Both animal and human studies have shown that pharmacogenetic factors may influence a fetus's susceptibility to alcohol-related effects. Genetic differences in either the mother or the fetus may affect the metabolism of alcohol, and lead to increased or decreased sensitivity to prenatal alcohol exposure. Other maternal risk factors that have been associated with higher rates of FASD include history of a previous child with FASD, higher maternal age, increasing number of pregnancies, poor maternal nutrition, and lower socioeconomic status.

## DIAGNOSIS

### Signs and Symptoms

The diagnosis of FAS and other FASD lies primarily in the history and physical examination, with other specific evaluations or tests, such as a neuropsychological evaluation and sometimes neuroimaging or other neurologic testing (eg, electroencephalography) playing a supportive role. It is important to note that there is no single consensus guideline for the diagnosis of FASD;

multiple published guidelines exist, not all of which are completely consistent with each other. Specific diagnostic criteria have been established by the National Center on Birth Defects and Developmental Disabilities at the CDC in collaboration with the National Task Forces on Fetal Alcohol Syndrome and Fetal Alcohol Effect. Similar diagnostic criteria were published by Astley in 1997, revised in 2004, and validated in 2013 (using data from the Washington State Fetal Alcohol Syndrome Diagnostic and Prevention Network) and by the IOM (published in 1996, with proposed revisions by Hoyme and colleagues in 2005).

Although a wide range of minor facial and other physical anomalies have been associated with FAS, clinical research has determined that 3 midline characteristics are discriminant for FAS: short palpebral fissure length, smooth philtrum, and a thin upper lip (Figure 250-1). Palpebral fissure length, which is measured from the inner corner to the outer corner of the eye while the child's eyes are open, is plotted on a nomogram to determine the standard deviation from the mean based upon the child's age. The University of

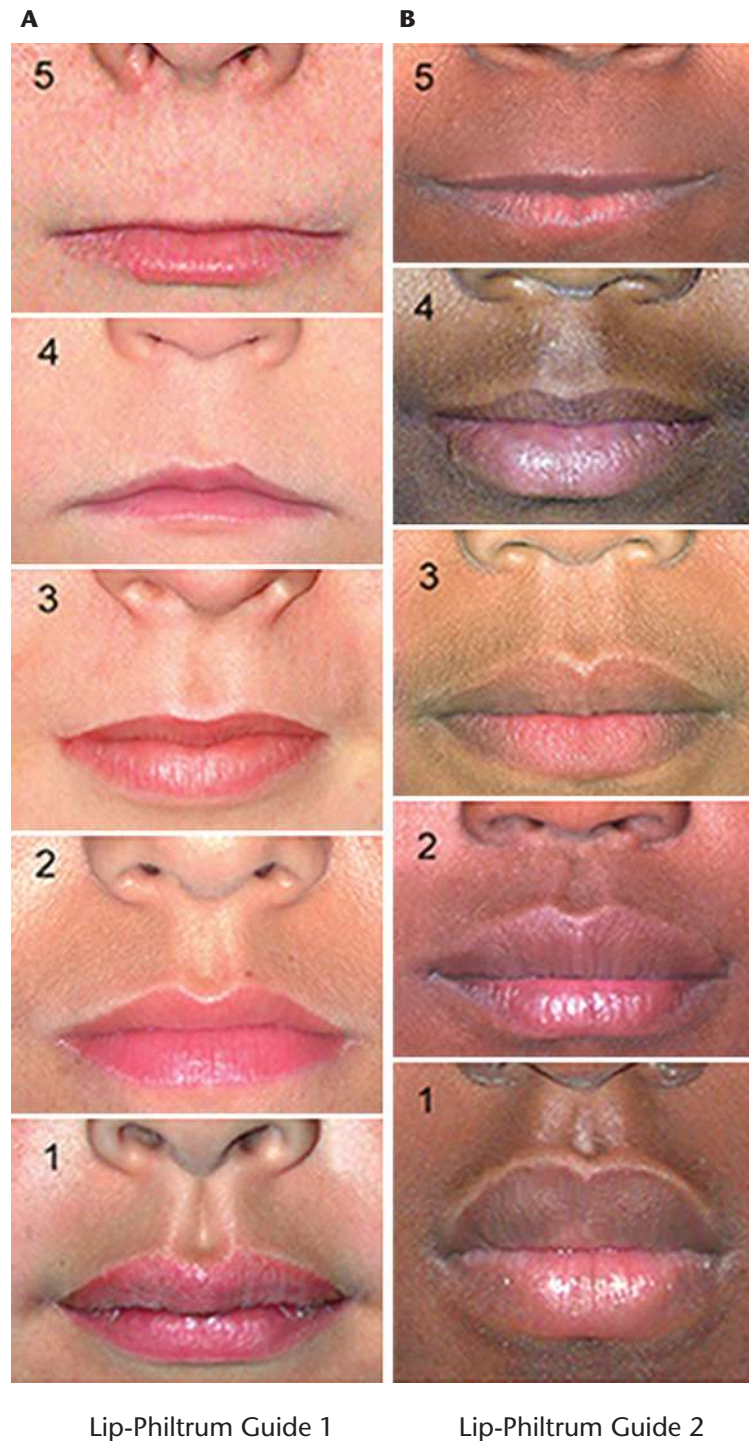
Washington Lip-Philtrum guides (Figure 250-2) allow scoring of philtrum smoothness and upper lip thinness on a 5-point Likert scale; one guide is utilized for whites and a second guide is used for blacks and all other ethnicities with lips similar to blacks. A diagnosis of FAS requires a score of 4 or 5 for both the philtrum and upper lip, as well as palpebral fissure measurement that is less than the 10th percentile for age. Other physical features or anomalies commonly seen in FASD, but not at a frequency or specificity high enough to warrant inclusion as diagnostic criteria, include epicanthal folds, ptosis, an upturned nose, flat nasal bridge, midface hypoplasia, underdeveloped ears (with a "railroad track" appearance, where there is a prominent superior crus of the helix and parallel inferior crus of the antihelix), nail hypoplasia, small and large joint contractures, clinodactyly of the fifth fingers, "hockey stick" palmar creases (upper transverse crease widens and ends between the second and third digits), hirsutism, and congenital cardiac defects.

Growth is measured using standard height/weight measurements and growth curves. Growth deficiency



**Figure 250-1** Examples of the FAS facial phenotype (small eyes, smooth philtrum, and thin upper lip) across 4 races: (A) white, (B) Native American, (C) black, (D) Hispanic. (Copyright 2016, Susan Astley PhD, University of Washington.)





Lip-Philtrum Guide 1

Lip-Philtrum Guide 2

**Figure 250-2** University of Washington Lip-Philtrum Guides 1 (A) and 2 (B) are used to rank upper lip thinness and philtrum smoothness. The philtrum is the vertical groove between the nose and upper lip. The guides reflect the full range of lip thickness and philtrum depth with Rank 3 representing the population mean. Ranks 4 and 5 reflect the thin lip and smooth philtrum that characterize the FAS facial phenotype. Guide 1 is used for whites and all other races with lips like whites. Guide 2 is used for blacks and all other races with lips as full as blacks. (Copyright 2016, Susan Astley PhD, University of Washington.) FAS, fetal alcohol syndrome.

is defined as height or weight that is at or less than the 10th percentile for age/gender as documented at any time (from birth onwards), as long as the poor growth is not thought to be secondary to postnatal influences such as chronic illness or malnutrition.

Structural, neurologic, or functional abnormalities in the CNS may fulfill the third criteria for FAS. Structural anomalies can include microcephaly (defined as head circumference  $\leq$  10th percentile for age/gender) or clinically-significant brain abnormalities of presumed prenatal onset identified on imaging studies. Structural CNS anomalies often observed in children with FASD include abnormalities of the corpus callosum (such as agenesis, partial agenesis, hypoplasia/thinning), cerebellum (particularly of the cerebellar vermis), and basal ganglia, and overall reduction in brain volume. Neurologic criteria can be fulfilled by the presence of seizures (as long as they are not attributable to postnatal events) or abnormal findings on neurologic examination. Functional deficit criteria are met when the child has a global cognitive deficit (eg, low IQ or global developmental delay) or possesses difficulties (scores  $>1$  standard deviation below the mean on standardized testing) in 3 or more of the following areas: cognition/development (such as specific learning disabilities, poor processing, discrepancy between verbal and nonverbal skills), executive functioning, motor functioning, inattention or hyperactivity, social skills, and “other” (which can include sensory problems, memory deficits, and others). Determination of functional CNS abnormalities typically requires formal neuropsychological or other developmental testing. The CNS features of FASD often persist into adulthood. Depending upon the specific neurobehavioral profile of the individual with FASD, there can be considerable risks for secondary disabilities, such as mental health disorders, disrupted school experiences (suspensions, expulsions, drop outs), substance abuse, and involvement with the legal justice system (arrests, incarceration).

Confirmed maternal use of alcohol during pregnancy is not required for a diagnosis of FAS in the presence of all 3 of the above criteria (facial features, growth, and CNS abnormalities). In cases of children who are adopted or are in foster care placement, information about the prenatal history may not be available. In the absence of self-reported maternal history, documentation of exposure could include direct observations by others, birth records that may note admission of maternal alcohol use or maternal blood alcohol records, or history of alcohol-related events (such as driving under the influence or alcohol abuse treatment) during the pregnancy. The diagnosis of ARBD, ARND, or the newly-defined ND-PAE does require confirmed maternal alcohol use at any time during the pregnancy.

### Diagnostic Approach

Pediatricians can diagnose FAS when patients meet the facial, growth, CNS, and alcohol exposure criteria established by the CDC. The American Academy of Pediatrics (AAP) developed a schema in collaboration with the CDC for early and streamlined identification of FASD in the medical home. The AAP recommends

that all children be screened for developmental and growth concerns in the context of the well child evaluation. In addition, a history of prenatal alcohol exposure and other risk factors should be sought as part of the comprehensive patient history. The recommended diagnostic algorithm (Figure 250-3), available as part of the AAP FASD Toolkit, suggests that any child with FASD signs or symptoms, risk factors for FASD (particularly known/suspected maternal alcohol or other substance use; sibling with FAS/FASD; child was adopted or ever in the foster care system), or any parental concern for FASD should prompt additional evaluation by the pediatrician for CNS abnormalities, growth deficits, or characteristic facial features. Fetal alcohol syndrome can be diagnosed by the pediatrician if growth, facial, and CNS features characteristic of FAS are present in addition to known prenatal alcohol exposure.

Recognition of CNS features of FAS by the physician requires familiarity with how the neurobehavioral features of the FASDs can manifest at different ages. Infants and toddlers may have difficulty with self-soothing and be prone to over-stimulation. Poor feeding is commonly seen in young infants with FAS. Sleep problems, difficulties with language comprehension, and poor problem solving abilities may emerge in young childhood. Older, school-age children are more likely to present with specific learning disabilities, poor social skills (social immaturity, lack of social boundaries), and poor adaptive skills.

Facial characteristics of FASD often change over time, and may become less apparent as the child approaches adulthood. For this reason, review of photographs from early childhood may aid the physician in the diagnostic process.

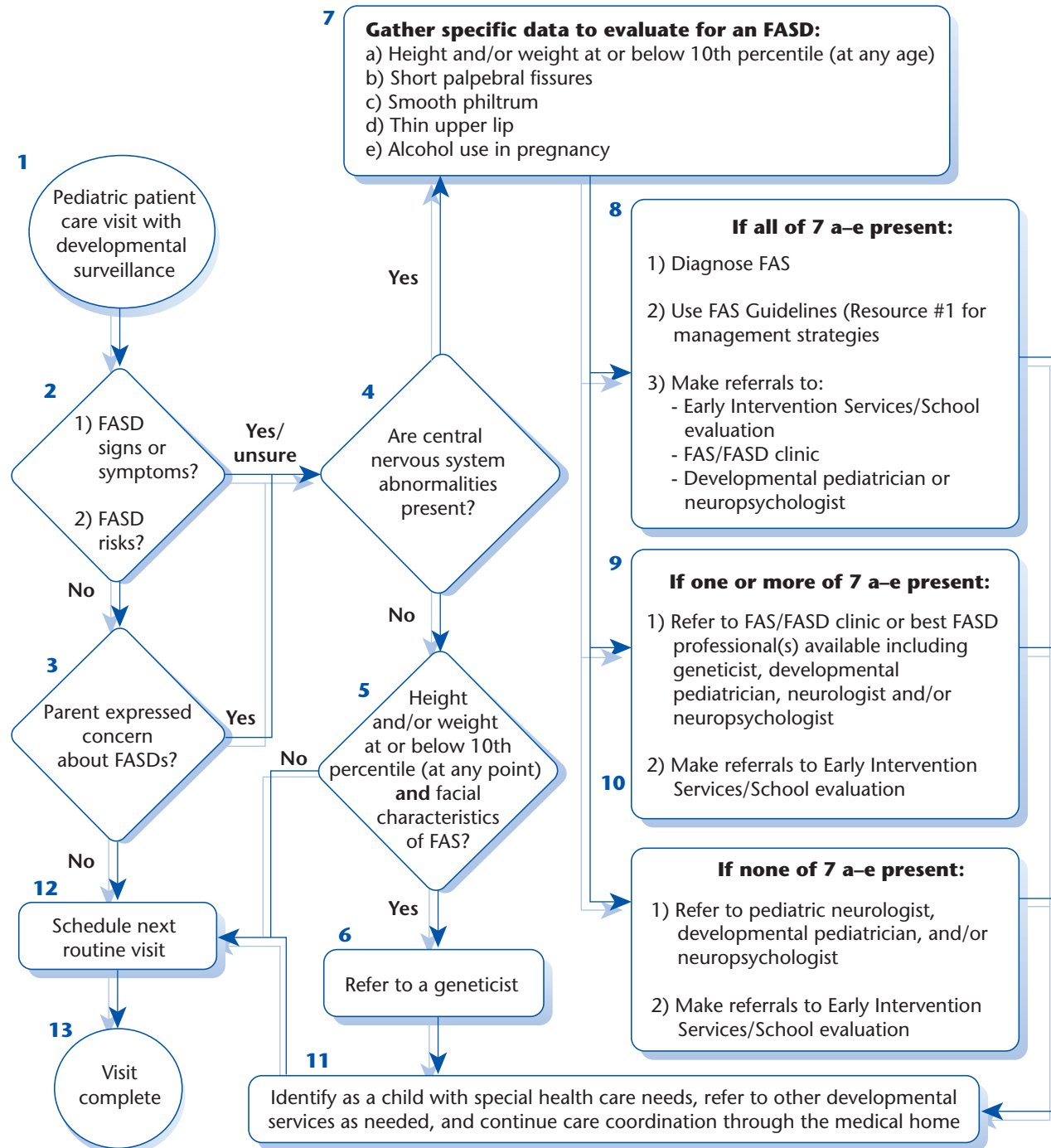
Referrals to specialists for further diagnostic investigations are indicated in certain circumstances:

1. If the child has growth restriction or any dysmorphic facial features, but no documented CNS abnormalities, referral to a geneticist is indicated for evaluation for possible alternate diagnoses.
2. If the child has CNS abnormalities but does not fulfill all the other facial, growth, and alcohol exposure criteria for FAS, referral to a FAS/FASD clinic or other appropriate specialist(s) (which may include a neurologist, geneticist, developmental pediatrician, or neuropsychologist) is indicated.
3. Referral to Early Intervention or school-based developmental services is warranted in any child with evidence of CNS abnormalities.

### Imaging and Diagnostic Studies

Imaging and other diagnostic or laboratory studies are not routinely indicated in individuals with FASD. However, intracranial imaging (ultrasound, computed tomography, or magnetic resonance imaging) may be performed in children because of the presence of microcephaly, seizures, or severe intellectual deficits. Results from neuroimaging studies can help support the diagnosis of FASD if clinically significant structural brain abnormalities are identified. Electroencephalograms may be performed when there is clinical suspicion of seizures. If there is a question of an alternate genetic diagnosis (see Differential Diagnosis),





**Figure 250-3** Algorithm for evaluation of fetal alcohol syndrome and fetal alcohol spectrum disorders within the medical home. FAS, fetal alcohol syndrome; FASD, fetal alcohol spectrum disorders. (From American Academy of Pediatrics. *Fetal Alcohol Spectrum Disorders Program* [www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/fetal-alcohol-spectrum-disorders-toolkit/Pages/Algorithm-for-Evaluation.aspx].)

diagnostic laboratory studies such as molecular genetic testing may be indicated to exclude other diagnoses with overlapping features. Neuropsychological testing is often needed not only to establish the presence of functional CNS deficits, but also to direct management (see Treatment Approach).

### Differential Diagnosis

The individual facial and other physical features that are characteristic of FASD are not unique and may overlap with those seen in a number of other teratogenic and genetic syndromes (Table 250-1 and Table 250-2). However, the combination of 3 facial features

**Table 250-1** Selected Differential Diagnosis for Individual Features Associated With FASD

FEATURE	ASSOCIATED SYNDROMES (OTHER THAN FASD)
Smooth philtrum	Touline embryopathy Maternal phenylketonuria effects Floating-Harbor syndrome X-linked Opitz G/BBB syndrome Geleophysic dysplasia Williams syndrome
Thin upper lip	Maternal phenylketonuria effects Touline embryopathy Cornelia de Lange syndrome Miller-Dieker syndrome Fetal valproate effects
Short palpebral fissures	Maternal phenylketonuria effects Touline embryopathy Dubowitz syndrome FG syndrome X-linked Opitz G/BBB syndrome Williams syndrome Feingold syndrome
Neurobehavioral features	22q11.2 deletion syndrome (DiGeorge syndrome, Velocardiofacial syndrome) Fragile X syndrome Turner syndrome 16p11.2 deletion syndrome 10p deletion syndrome
Pre- and postnatal growth delay	Associated with many chromosomal and single gene syndromes (too numerous to list)

FASD, fetal alcohol spectrum disorders.

Adapted from Bertrand J, Floyd RL, Weber MK, et al. *Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis*. Atlanta, GA: Centers for Disease Control and Prevention, 2004; and Senturias Y, Asamoah A. Fetal alcohol spectrum disorders: guidance for recognition, diagnosis, differential diagnosis, and referral. *Curr Probl Pediatr Adolesc Health Care*. 2014;44(4):88–95.

(smooth philtrum, thin vermilion border, and small palpebral fissures) is more than 95% specific to FAS and prenatal alcohol exposure. Teratogenic syndromes that most closely overlap with the features seen in FASD include fetal valproate syndrome, maternal phenylketonuria effects, and toluene embryopathy. Some of the facial features commonly seen in FASD can also occur in a wide range of specific single-gene syndromes or chromosome abnormalities. Growth restriction and CNS abnormalities are common in many teratogenic and genetic syndromes. The presence or absence of other associated dysmorphisms can often help the physician formulate an appropriate differential diagnosis. In some cases, specific chromosomal or single-gene testing may be indicated to evaluate for alternate diagnoses. Prenatal alcohol exposure and genetic or other teratogenic syndromes may co-occur in some children, and may further complicate diagnosis. Referral to a geneticist is helpful in cases where all of the facial, growth and CNS features are not present,

or where the child has additional dysmorphisms that are atypical for FASD.

## TREATMENT APPROACH

An early and accurate diagnosis of FASD, where possible, is the first step in treatment. Studies of individuals with FASD and the effect their disorder has on their lives suggest that making an early diagnosis of FASD (ie, before age 6) is associated with a more favorable outcome and lower prevalence of secondary disabilities. Once a diagnosis of FASD is established, by either the pediatrician, an FASD diagnostic clinic, or the pediatrician in collaboration with other specialists (in those children who have features of FAS but do not fulfill the strict criteria for a FAS diagnosis), involvement of other specialists is often needed to manage the multiple medical, developmental, and psychological needs of the child. The AAP FASD Toolkit includes lists of resources for parents, educators, and physicians, including informational handouts, example care plans, and referrals to outside agencies. Additional resources for parents and physicians can also be found through the National Organization for Fetal Alcohol Syndrome ([www.nofas.org](http://www.nofas.org)). Patients who have a diagnostic evaluation in a multidisciplinary FASD diagnostic clinic will typically be seen by multiple specialists, which could include developmental pediatricians, neurologists, geneticists, social workers, physical and occupational therapists, speech-language pathologists, and psychologists/neuropsychologists. Pediatricians may choose to refer their patients to any of these specialists individually, based upon the child's specific needs.

A full assessment of a child's medical needs should be made and updated frequently by the pediatrician. Poor growth is common, and this may warrant careful monitoring of growth parameters or evaluation by a nutritionist. Children should be screened periodically for potential vision, hearing, and sleep difficulties, which occur with increased frequency in individuals prenatally exposed to alcohol. In infants or children for whom clinical history or physical examination suggests the possibility of cardiac, renal, or spinal (such as tethered cord) anomalies, specific imaging studies may be indicated for diagnosis.

Nearly all children with FASD can benefit from developmental assessment, through either early intervention services (before age 3), the school system (after age 3), or a neuropsychologist, psychologist, or developmental pediatrician. Proper neuropsychological assessment allows the child's specific educational and behavioral needs to be more precisely defined, which can be invaluable for educators. Assessment through the school district for children aged 3 and older should routinely be requested by the pediatrician or family in order to ascertain that the child is receiving educational supports. All children with a diagnosis of FAS qualify for services under the Individuals with Disability Education Act. It is important to note that while many children with FASD have IQ or other developmental quotients that fall in the normal range, specific deficits in memory, executive functioning, behavior regulation, or other functional CNS

**Table 250-2** Differential Diagnosis of FASD and Distinguishing Features

CONDITION	OVERLAPPING FEATURES WITH FASD	DISTINGUISHING FEATURES FROM FASD
22q11.2 deletion syndrome (DiGeorge/Velocardiofacial syndrome)	Ptosis, cardiac defects (much more common in the 22q11 deletion), learning difficulties, speech delay, short stature, short palpebral fissures (occasionally)	Palatal defects, immune dysfunction, hypocalcemia; smooth philtrum and thin upper lip not typically seen
Dubowitz syndrome	Growth delay (prenatal onset), microcephaly, short palpebral fissures, ptosis	Eczema; high-pitched, hoarse cry; genital anomalies in males; syndactyly and other limb anomalies
Maternal phenylketonuria effects	Microcephaly, short palpebral fissures, long and smooth philtrum, thin upper lip	History of phenylketonuria in mother; intellectual disability is typically severe; rounded facies; short, upturned nose
Cornelia de Lange syndrome	Pre- and postnatal growth delay, thin upper lip	Synophrys, long eyelashes, high arched palate, limb anomalies
Toulene embryopathy	Short palpebral fissures, smooth philtrum, thin upper lip	Large anterior fontanelle, micrognathia, bifrontal narrowing, downturned corners of the mouth
Floating-Harbor syndrome	Short stature, smooth philtrum, thin lips, ADHD, learning disabilities	Long nose with narrow bridge, full tip, and an overhanging columella; triangular facies; deeply-set eyes; philtrum is usually short
Feingold syndrome	Short stature, microcephaly, short palpebral fissures, cardiac defects, learning disabilities	Gastrointestinal atresia, finger/toe anomalies (syndactyly, brachymesophalangy)
Fetal valproate effects	Epicanthal folds, thin upper lip, long and smooth philtrum, variable learning disabilities	Tall forehead, trigonocephaly, bifrontal narrowing, infraorbital creases, neural tube defects
Geleophysic dysplasia	Thin upper lip, long and smooth philtrum, short stature	Round and full face, coarsening of facial features over time, thick skin, joint contractures
Miller-Dieker syndrome	Thin upper lip	Vertical ridging and furrowing in the central forehead, bitemporal narrowing, severe neurologic features (seizures, intellectual disability)
FG syndrome	Short palpebral fissures, short stature	Macrocephaly, tall forehead, downward-slanting palpebral fissures, small ears, constipation
X-linked Opitz G/BBB syndrome	Learning disabilities, microcephaly, smooth philtrum, short palpebral fissures	Prominent forehead, widow's peak, cleft lip/palate, laryngotracheoesophageal defects, genital anomalies
Fragile X syndrome	ADHD, learning disabilities	Frequent autism, more severe intellectual disability (in males), long face, prominent ears, joint laxity, macro-orchidism
Turner syndrome	ADHD, learning disabilities, short stature	Females only; does not share craniofacial features with FASD; ovarian dysgenesis, cardiac defects (aorta coarctation, bicuspid aortic valve), short neck, low posterior hairline, broad chest

ADHD, attention-deficit/hyperactivity disorder; FASD, fetal alcohol spectrum disorders.

Adapted from Bertrand J, Floyd RL, Weber MK, et al. *Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis*. Atlanta, GA: Centers for Disease Control and Prevention, 2004; and Senturias Y, Asamoah A. Fetal alcohol spectrum disorders: guidance for recognition, diagnosis, differential diagnosis, and referral. *Curr Probl Pediatr Adolesc Health Care*. 2014;44(4):88–95.

domains may impair their ability to succeed in school. The AAP FASD Toolkit lists evidence-based educational and behavioral interventions that are specific to parents and educators working with children with FASD (Table 250-3). These may include such strategies as highly structured and systematic teaching, use of visual reminders, and breaking down tasks into small, manageable units. Some children with FASD may need special education services that are similar to those provided to children with non-FASD-related intellectual or learning disabilities. Educational strategies should be tailored to the individual child's strengths and needs.

While no pharmaceutical interventions have yet been shown to directly alter the CNS abnormalities in children with FASD, use of specific medications, in addition to behavioral therapies, may be indicated for treatment of coexisting psychiatric or neurologic diagnoses. For example, use of stimulant medications may be warranted in children who also meet criteria for a diagnosis of ADHD, and children with seizures are often treated with antiepileptic medications.

Parental counseling regarding the diagnosis of FASD is an important component of its management. The diagnosis should be discussed with the foster, adoptive, or biological family in a nonjudgmental

**Table 250-3 Evidence-based Educational and Behavioral Interventions Specific for FASD**

PROGRAM	OVERVIEW	OUTCOMES
Math Interactive Learning Experience (MILE), Emory University, GA	6-week mathematics learning program providing an active learning approach for children; workshops for caregivers providing information on FASD and learning strategies	Improved math skills and decreased problem behaviors
Good Buddies, UCLA, Los Angeles, CA	12 weekly separate sessions for parents and children, providing social skills training and education about FASD	Improved parent knowledge about FASD; for children, there was greater social skills knowledge, improvement in social skills, and decrease in problem behaviors following the intervention
Parents and Children Together (PACT), Children's Research Triangle, Chicago, IL	12-week program of weekly neurocognitive habilitation group therapy sessions; concurrent parent education group	Improved executive functioning and self-regulation skills amongst children
Families Moving Forward (FMF), University of Washington, Seattle, WA	In-home training program (16 sessions over 9–11 months) providing education and support to families	Improved caregiver comfort and knowledge about FASDs; improved problem behaviors
Parent-Child Interaction Therapy, University of Oklahoma	14-week program in which caregivers are provided with live, coached practice of parenting skills	Improved problem behaviors in children and decreased parent stress

FASD, fetal alcohol spectrum disorders.

American Academy of Pediatrics (AAP) FASD Expert Panel. AAP FASD Toolkit; available at [aap.org/fasd](http://aap.org/fasd). Accessed October 8, 2015; Senturias Y, Burns B. Managing children and adolescents with fetal alcohol spectrum disorders in the medical home. *Curr Prob Pediatr Adolesc Health Care*. 2014;44(4):96–101; and Bertrand J, Floyd RL, Weber MK, et al. *Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis*. Atlanta, GA: Centers for Disease Control and Prevention, 2004.

manner, explaining the basis for the diagnosis, the spectrum of signs and symptoms, and the need for FASD-specific interventions. Emphasis should be placed on using the diagnosis as a tool to better understand the child's medical, developmental, and behavioral needs, and to direct medical and educational management. Without focusing on assigning blame, parents should be educated about the underlying cause for FASD; if appropriate, the biological mother may be offered referral to counseling or alcohol abuse treatment services. In addition, there should be an assessment of the parents' ability to provide safe and appropriate care for the child, which may require referral for a formal evaluation by a social worker or psychologist. In cases where the family unit is severely dysfunctional, alternative placement of the child may be considered. Family counseling may be indicated.

Because no single treatment plan is applicable to all children with FASD, the pediatrician's main role is frequently that of care coordinator, which is invaluable amongst children with complex and changing medical and neurocognitive needs. The pediatrician often facilitates clear communication between the child, his or her family, and other specialists or educators who are participating in the child's care. As the child ages, the primary care physician must also facilitate transition of care for the child, not only to an adult primary care physician, but also potentially to other subspecialists as he or she moves out of the pediatric realm.

## CONCLUSION

Fetal alcohol spectrum disorders represent a common, complex continuum of disorders resulting from prenatal exposure to alcohol. Pediatricians should be

attentive to the signs, symptoms, and risk factors that suggest a possible diagnosis of FASD. Well-defined criteria allow the diagnosis of FAS in children who manifest the characteristic facial, growth, and CNS features and have known or suspected prenatal alcohol exposure. However, diagnosis of individuals who were prenatally exposed to alcohol but do not have all of the cardinal features of FAS may be more problematic, and involvement of other specialists or referral to FASD diagnostic centers may be needed. The early and accurate diagnosis of FASD allows targeted medical and especially educational interventions that can improve the long-term outcome of children with FASD. The AAP FASD Toolkit includes a diagnostic algorithm, and can assist pediatricians in both the diagnostic and referral process. Physicians should also be aware of the potential differential diagnoses for FASD and make referrals to other diagnosticians (geneticists, neurologists, psychologists, etc.) as appropriate.

## WHEN TO REFER

- Diagnostic evaluation (if the child does not meet strict criteria for FAS or if an alternate genetic diagnosis is suspected)
- Neurologic evaluation (if focal neurologic signs or seizure disorder are present or suspected)
- Neuropsychological or other developmental testing
- Significant social and family issues
- Nutrition evaluation if significant growth disturbance
- Pharmacologic management of co-existing psychological disorders



**WHEN TO ADMIT**

The typical management of a child with FASD does not require admission to a medical or psychiatric hospital. However, indications for admission could include symptoms related to any of the mental health or behavioral conditions that could co exist with FASD, refractory seizures or initial seizure work-up and management, or evaluation of severe growth failure.

**TOOLS FOR PRACTICE****Community Advocacy and Coordination**

- *Building the Legacy: IDEA 2004* (Web page), US Department of Education ([idea.ed.gov](http://idea.ed.gov))
- *Individualized Education Programs* (fact sheet), National Dissemination Center for Children With Disabilities ([www.parentcenterhub.org/repository/iep](http://www.parentcenterhub.org/repository/iep))

**Engaging Patient and Family**

- *Frequently Asked Questions About Section 504 and the Education of Children With Disabilities* (fact sheet), US Department of Education ([www.ed.gov/about/offices/list/ocr/504faq.html](http://www.ed.gov/about/offices/list/ocr/504faq.html))
- *Medication Guides* (Web page), US Food and Drug Administration ([www.fda.gov/Drugs/DrugSafety/ucm085729.htm](http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm))

**Medical Decision Support**

- *Evidence-Based Child and Adolescent Psychosocial Interventions* (chart), American Academy of Pediatrics ([www.aap.org/en-us/Documents/CRPsychosocialInterventions.pdf](http://www.aap.org/en-us/Documents/CRPsychosocialInterventions.pdf))
- *Fetal Alcohol Spectrum Disorders Toolkit* (Web page), American Academy of Pediatrics ([aap.org/fasd](http://aap.org/fasd))
- *Mental Health Screening and Assessment Tools for Primary Care* (chart), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH\\_ScreeningChart.pdf](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH_ScreeningChart.pdf))

**AAP POLICY**

American Academy of Pediatrics Council on Children With Disabilities, Section on Developmental and Behavioral Pediatrics, Bright Futures Steering Committee, Medical Home Initiatives for Children With Special Needs Project Advisory Committee. Identifying infants and young children with developmental disorders in the medical home: an algorithm for developmental surveillance and screening. *Pediatrics*. 2006;118(1):405–420. Reaffirmed August 2014 ([pediatrics.aappublications.org/content/118/1/405](http://pediatrics.aappublications.org/content/118/1/405))

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**Chapter 251****FOREIGN BODIES OF THE EAR, NOSE, AIRWAY, AND ESOPHAGUS**

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Foreign bodies of the ear, nose, and respiratory and digestive tracts are a common problem among children, particularly those younger than 5 years. Children are at risk as soon as the pincer grasp is achieved, around 9 months of age; the risk may be present sooner if they have older siblings. The scope of the problem was first underscored by National Safety Council data in 1969, which showed that more children died at home from accidental foreign-body ingestion or aspiration than from any other cause. By 1998, foreign-body aspiration and asphyxiation was the fourth-leading cause of accidental death in the home among children younger than 5 years. National Safety Council data from 2005 to 2006 reveal that 133 deaths per 100,000 population in children from birth to 4 years were caused by choking defined as suffocation by inhalation or ingestion of food or other objects. There has been no improvement, as this category continues to be the fourth leading cause of death in children younger than 5 years. The mortality rate stayed the same, according to the National Safety Council's Injury Facts, 2014 edition. From 2005 to 2010, international cases were collected from 70 centers in 32 countries and registered in the Susy Safe Project Database, into which 17,205 foreign body injuries in children aged 0 to 14 years were entered. Seven percent of children required admission to the hospital, and complications were seen in 8.9%.

The severity of the problems caused by the presence of a foreign body depends on the site, composition, and duration of time in the body. Removal of a foreign body is not usually an emergency, unless the airway is compromised or the object is a battery that might cause liquefaction necrosis. The use of button batteries is increasing in small electronics, remote control devices, watches, toys, and hearing aids. In 2009, the American Association of Poison Control Centers listed disk batteries as the most common cause of fatal ingestions in children younger than 5 years. There was a 6.7-fold increase in major or fatal outcomes between 1985 and 2009. In addition, there has been an increase in magnet ingestions in children. In one series of magnet ingestions in children presenting to emergency departments, the incidence of emergency department

(ED) visits increased 8.5-fold from 2002 to 2011. Removal of any foreign body should be attempted only if the physician has appropriate sedation or anesthesia, proper instrumentation and illumination and, most important, ability. Attempts to remove the foreign body without these elements may aggravate the problem and jeopardize the child's well-being.

## FOREIGN BODIES OF THE EAR

Foreign bodies of the external auditory canal are most common among children between 2 and 4 years of age. They can include food, insects, toys, buttons, pieces of crayons, pencil erasers, button-shaped batteries, and jewelry. Accidental entry of a foreign object through placement in the external auditory canal, either by the child or a companion, can occur during play. Insects also can fly or crawl into the ear canal. Some experts suggest that children who have chronic external otitis or itching are more likely than healthy children to place objects in their ear canal. Earrings can become embedded in the auricle when a chronic infection of the pierced site is followed by overgrowth of granulation tissue. The use of a spring-loaded gun to pierce ears has resulted in numerous cases of embedded earrings as well.

Inert substances, such as plastic, that are not obstructing the canal and are not abutting the tympanic membrane may not cause symptoms. Insects tend to incite local irritation, causing discomfort, erythema, and occasionally drainage. Food matter also may cause local inflammation that often leads to local pain and itching. Objects that touch the tympanic membrane cause pain, particularly with movement of the drum, as when swallowing. If the entire canal is obstructed, then hearing will likely be decreased.

### History and Physical Examination

Usually, eliciting a history of placing an object in the ear canal is difficult because most children are reluctant to admit to this activity. If insertion is not witnessed, then some foreign bodies may go undetected for extended periods. Findings depend on the depth of the foreign object within the external auditory canal, the nature and composition of the object, and its duration in the canal. Children may complain of ear pain, discomfort, bleeding, discharge, an odor, aural fullness, hearing loss, nausea, vomiting, coughing, tearing, or dizziness.

Several reports have been issued on button-size alkaline batteries in the ear canal that may leak battery alkali, causing a severe local tissue reaction or destruction, with pain, swelling, and discharge. This foreign body should be handled expeditiously to prevent serious injury to the canal, tympanic membrane, or middle ear.

When the history indicates a small foreign body but it cannot be visualized on examination, it may be lodged anteriorly in the tympanic sulcus. Instillation of water to fill the medial half of the external canal may act as a concave lens, allowing visualization of the tympanic sulcus. In a patient who has a small, narrow, or swollen external ear canal, microscopic evaluation will aid in visualization. Physicians should check the other ear for foreign bodies as well.

## Management

### Nonurgent Situations

Aural foreign bodies may be removed by irrigation, suction, or instrumentation. Nonreactive foreign bodies that do not occlude the external canal completely or impinge on the tympanic membrane do not present an emergency. These foreign bodies can be removed with various instruments; the most useful will depend on the shape and composition of the object. In many cases, Frazier tip suction, alligator forceps, or a right-angle hook may be used to retrieve the object. The hook is used by passing it beyond the object, hooking it from behind, and gently pulling it out. Gentle irrigation also may be used on nonabsorbable substances, provided the tympanic membrane can be visualized and is intact and no evidence of inflammation of the external canal exists. Food matter tends to swell when water is applied, making removal difficult. Irrigation is accomplished using an 18-gauge catheter attached to a 10- to 20-mL syringe. The flow of fluid should be directed around the retained object, allowing back-pressure to force the object out of the canal. Fluids should be warmed to avoid irritation of the labyrinths. A nonperforated tympanic membrane must be visualized before irrigation. Using a syringe in this way is an effective and easy way to remove foreign bodies. The pressure generated by a 14- or 16-gauge cannula and a 20-mL syringe is well below the pressure required to burst a tympanic membrane.

Management of embedded earrings includes local anesthesia, with an incision made for removal of the earring. Oral and intravenous antibiotics are also used for presence of infection or cellulitis.

### Urgent Situations

In older children who are cooperative, a local anesthetic injected with a small-gauge needle into the skin lining the external canal may allow complete removal of the foreign body and subsequent examination. For younger children, or for those who are uncooperative, general anesthesia may be necessary and is certainly preferable to traumatic removal if a child is unable to cooperate or cannot be restrained adequately.

When the tympanic membrane cannot be visualized, or if evidence exists of inflammation or injury to the external canal, then the foreign body should be removed immediately. Expeditious removal is particularly important with an alkaline battery, because tympanic membrane perforations have been reported within only 8 hours of entry. Magnets may be helpful in removing metallic objects such as batteries or metal beads.

### Insects

Insects should be killed before removal by instilling water, mineral oil, or topical lidocaine into the external canal. Extraction with suction or alligator forceps may then be undertaken.

### Postextraction Care

After any foreign body is removed, the external canal and tympanic membrane should be thoroughly inspected. If the external auditory canal seems infected or irritated, then topical antibiotic otic drops with

steroids may be instilled. The affected ear should be protected from water until it has healed completely.

Consultation with an otolaryngologist should be requested if the object cannot be removed or if perforation of the tympanic membrane is suspected. Schulze studied 698 consecutive cases of pediatric external auditory canal foreign bodies. Attempts under direct visualization by ED physicians had lower success rates with removing spherical objects, objects touching the tympanic membrane, and objects in the canal for more than 24 hours. The physicians concluded that these cases should be referred directly to otolaryngologists for otomicroscopic removal.

### Complications

Complications can be caused by the foreign body or by traumatic removal. Laceration or inflammation of the external canal is not usually serious and resolves with instillation of liquid analgesics and antibiotics. Perforations of the tympanic membrane require careful inspection to ensure that a flap of the membrane has not folded into the middle ear leading to a permanent perforation or a cholesteatoma. Similarly, when the tympanic membrane is not intact, the middle ear space can become contaminated, and otitis media can develop. Balbani et al reviewed 93 cases of foreign bodies in the ear and found that all 12 complications (11 canal lacerations and 1 tympanic membrane perforation) occurred in patients who had undergone previous attempts at removal. Engelsma reported a case of impacted foreign body following 2 attempts at removal that required surgical widening of the canal before extraction.

If safely removing a foreign object from the ear canal is not possible, if the tympanic membrane may have been injured by either the foreign body or its removal, or if hearing loss, nystagmus, vertigo, cranial nerve deficits, or deep-seated infection occurs, then the patient must be referred to an otolaryngologist.

## FOREIGN BODIES OF THE NOSE

Foreign bodies in the nose are typically soft, such as tissue paper, eraser material, or clay; however, they can also be hard, as with a bead, pebble, or piece of candy. The Nationwide Electronic Injury Surveillance System (NEISS) was evaluated for ED visits and found jewelry beads to be the most numerous. Occasionally a foreign object enters the nose accidentally while the child is attempting to sniff or smell it. The frequency has been noted to increase during the summer and Christmas, when toy sales increase. In addition, with increasing use of magnetic body jewelry, there is the problem of magnets being accidentally stuck to each other on both sides of the nasal septum and causing tissue damage.

Children will usually not admit to placing foreign bodies in the nose. The most common symptom of a foreign body in the nose is unilateral nasal discharge that is usually foul smelling. In fact, a unilateral nasal discharge in a young child should be considered evidence of a foreign body until proved otherwise. Occasionally, epistaxis is the presenting symptom. When an alkaline disk battery is lodged in the nose, the

symptoms may be acute. Tissue damage can occur through 3 mechanisms: electrical burn, liquefaction necrosis (from sodium hydroxide), and pressure necrosis.

The differential diagnosis of foreign bodies in the nose includes suppurative rhinitis, adenoiditis, sinusitis, and nasal or nasopharyngeal tumors. Nasal polyps also may cause unilateral nasal discharge, and in a young child, the diagnosis of cystic fibrosis must be ruled out.

### History and Physical Examination

If possible, the anterior nasal cavities should be examined with a nasal speculum and suction. The key to any evaluation is powerful illumination.

### Management

Nasal foreign bodies should be removed as quickly as possible, particularly in the case of an alkaline battery, which can cause severe local inflammation, with tissue damage occurring within 1 hour of placement. When an alkaline disk battery is in the nasal cavity, saline irrigation should be avoided because it can cause further tissue damage. Young children are averse to nasal instrumentation, and removing a nasal foreign body requires some degree of cooperation or restraint. Thus, sedation or general anesthesia may be advised. Topical application of a vasoconstrictor agent (eg, oxymetazoline, phenylephrine) in conjunction with removal of secretions by a small suction tip helps visualize the foreign object, particularly an object lodged in the middle or posterior nasal cavity. Use of an endoscope may enhance the ability to visualize this region. Most items are retrievable using grasping instruments such as straight forceps and mosquito clamps. Other methods include suction, irrigation, and adhesives. A foreign body that has remained in the nose for a long time may become calcified and form a rhinolith. Removing a rhinolith is often difficult and bloody.

Radiographs may be helpful if the object is radiopaque or has become calcified. An incidental finding of a nasal foreign body on a routine dental radiograph examination has been reported. US toy manufacturers are required by law to make toy parts radiopaque, a regulation that proves quite valuable when a physician is looking for foreign objects in the nasal cavity or in any part of the upper aerodigestive tract. However, toys and toy parts manufactured outside the United States do not have to conform to this regulation. In their review of children who had nasal foreign bodies, Tong et al reported that 28 of 71 (39%) radiographs demonstrated a foreign body.

Foreign-body removal using pepper to induce a sneeze while the uninvolved nostril is occluded or blowing in the child's mouth while the contralateral nostril is held shut is not suggested (although Cook, et al found an overall success rate of 59.9% for the "mother's kiss"). In a more controlled fashion, nebulized epinephrine together with nose blowing has been reported to expel nasal foreign bodies successfully. Ambu-bag insufflation of the mouth with the patient in Trendelenburg position has also been described. Another method of removal involves using a



Fogarty or a small Foley catheter. The catheter is placed beyond the foreign body into the posterior portion of the nasal cavity or nasopharynx and then inflated with 2 to 3 mL of saline solution. The catheter is then drawn gently forward and out of the nose, expelling the object. The danger with this technique is that the foreign object may be dislodged by pushing it posteriorly into the nasopharynx, which may lead to aspiration of the object.

Soft, friable objects can usually be removed with a Frazier tip suction device. If the foreign body is firm and flat or has an edge, then it may be removed by using a nasal bayonet or Hartmann or alligator forceps. A wire loop may be placed beyond the foreign body that is spherical and removed by pulling it forward. After removal, local inflammation exhibited by bloody or purulent oozing may be controlled with saline nose drops and an antibacterial ointment such as bacitracin or mupirocin. Sterile water should be used in place of saline if the foreign object removed was an alkaline battery.

For the situation in which magnets are stuck to each other on both sides of the nasal septum, Yeh and Robertson report using 2 cardiac pacemaker magnets and 2 forceps to remove them.

In addition, physicians should consider a second foreign body in the nose or elsewhere.

### Complications

Complications of nasal foreign bodies include epistaxis, local infection, inflammation, and nasal septal perforation. Occasionally a scar band, or synechia, may form between the turbinate and septum. Scar bands can be prevented by placing a splint made of Gelfilm or Silastic over the raw, exposed area. Nasal septal perforation has been reported. Obstruction of a sinus ostium by a foreign object may lead to the development of sinusitis, which typically causes pain and tenderness over the affected sinus or clouding and an air-fluid level on radiograph. Treatment includes oral antibiotics and nasal decongestant drops. Aspiration of a nasal foreign body can be prevented in most cases by prompt and skilled removal.

## FOREIGN BODIES OF THE AIRWAY

As of 2011, foreign body inhalation or ingestion account for 6% of all unintentional deaths in children ages 1 to 4 years. In 1 study, 184 patients younger than 16 years with a tentative diagnoses of foreign body aspiration were analyzed. The most frequently aspirated items were shelled nuts and seeds, such as sunflower seeds, pistachios, and hazelnuts. In a retrospective review of 2,165 autopsy cases from Great Ormond Street Hospital for Children, grapes were the foreign bodies involved in 4 out of 10 cases. The incidence of death declines rapidly among those older than age 5. Increased parental awareness of the risks of leaving small objects within the reach of young children and consumer education have been important in diminishing this hazard. In addition, lifesaving techniques, such as the Heimlich maneuver, that can be performed by people who are not health care workers accounts for a higher survival rate.

Complete airway obstruction is generally caused by globular foods such as hot dogs, nuts, candies, and grapes, or by toys or latex balloons. With regard to foreign-body impaction, the airway can be divided into 3 segments: larynx, trachea, and bronchial tree. Lima reviewed all airway foreign body admissions to a pediatric hospital from 1980 through 1987. Of the 91 cases, 11 involved a foreign body lodged in the larynx. Of these 11 patients, 5 died, and 3 suffered anoxic encephalopathy.

### Etiology

Curiosity or boredom may lead young children to put objects in their mouth. Infants in particular will place almost anything they can handle into their mouths. A startle may cause inadvertent ingestion or aspiration. Lack of complete dentition, as well as lack of attention to chewing, allows large food particles to enter the posterior pharynx. Incomplete development of mouth and tongue coordination and the neuromuscular mechanism for swallowing in young children also may account for a greater incidence of foreign-body ingestion or aspiration. A positive association between the occurrence of upper respiratory tract infections and foreign body aspiration has been noted possibly stemming from the need for continuous mouth breathing. An upper respiratory tract infection interrupts a smooth breathing-swallowing pattern, leading to an increase in aspiration. Although this situation typically occurs in the younger child, some estimates indicate that 23% occur in children older than 5 years. In addition, there are increasing reports of blowgun dart aspirations in adolescent males. During the deep inhalation required to blow a dart, the vocal folds maximally abduct, creating an increased risk of aspiration.

### History and Physical Examination

When an object is aspirated into the respiratory tract, it initially produces a choking, gagging, coughing, or wheezing episode. This may be followed by an asymptomatic interval during which little evidence remains to suggest the presence of a foreign body.

Depending on the site of the foreign body in the airway, a patient may exhibit a spectrum of findings, ranging from an almost complete lack of symptoms to signs of complete airway obstruction. A high index of suspicion and knowledge of the many possible presentation scenarios are the best insurance against the hazards of missed or delayed diagnoses.

Laryngeal foreign bodies are likely to produce the most acute and dramatic presentation. Large objects that completely obstruct the airway may result in stridor, high-pitched wheezing, cough, dysphonia, or worse—aphonia and cyanosis. Children who have small, partly obstructing objects that allow adequate air exchange have cough, stridor, hoarseness, and pain or discomfort.

Tracheal foreign bodies are usually associated with cough and some degree of stridor or wheezing, and may produce an audible *slap* as the object moves from the carina to the glottis with respiration. Bronchial foreign bodies usually cause wheezing or coughing if they are partly obstructing, which is often misdiagnosed as asthma. With complete obstruction of a



bronchus, an initial asymptomatic period is followed by a postobstructive pneumonitis or bronchiectasis. Sharp objects such as pins or tacks may cause pain or hemoptysis.

### Imaging

If aspiration of a foreign body into the upper airway is suspected, then plain-film radiographs may be useful. For objects suspected of being lodged in the laryngeal inlet, radiographs of the upper trachea or esophageal inlet should be obtained if the child's condition permits. Bronchial foreign bodies may be suggested by some form of dynamic radiographic study, such as inspiratory-expiratory films, lateral decubitus films, or videofluoroscopy. These studies can demonstrate air-trapping in the affected lung.

### Management

Foreign bodies that completely obstruct the laryngeal inlet create a life-threatening emergency and should be expelled immediately by using the Heimlich maneuver (abdominal thrusts). For infants younger than 1 year, the American Academy of Pediatrics recommends 5 back blows in the head-down position followed by 5 chest thrusts in the supine position, in place of the Heimlich maneuver. Blind finger sweeps are dangerous and should be avoided. If the foreign body cannot be expelled, then a large-bore needle or angiocatheter (14 gauge) should be inserted into the cricothyroid space to allow some degree of ventilation until the patient can be taken to the operating room for removal of the object. Alternatively, if skilled personnel are present, then an emergency tracheotomy may be necessary. Partly obstructing laryngeal foreign bodies should be treated in a manner that prevents total obstruction of the airway; therefore, back blows and abdominal thrusts should not be used in these cases.

Tracheal and bronchial foreign bodies should be removed by a physician specifically trained for the task. This usually requires controlled endoscopic removal (a rigid scope is the standard for airway foreign bodies) in the operating room. This situation is not usually an emergency; therefore, adequate preparations can be made.

### Complications

Abdominal and chest thrusts may damage intraabdominal contents (eg, liver, spleen) and ribs, respectively. Therefore, these techniques should be used only in cases of complete airway obstruction that would otherwise cause certain death. Conversion of a partial airway obstruction to a complete obstruction can best be prevented by having skilled personnel retrieve the foreign body. Pneumonia was the most common complication in 127 cases of foreign body aspiration.

A bronchial foreign body that remains in place for an extended period may cause air trapping and irreversible bronchiectatic changes distal to the obstruction.

Prolonged or difficult instrumentation of the airway during removal of a foreign body can lead to laryngeal edema or injury, with obstructive symptoms. This situation may require a period of intubation after surgery. As an alternative, postoperative edema can sometimes be prevented by using steroids during and after surgery.

## FOREIGN BODIES INVOLVING THE ESOPHAGUS

Young children are inquisitive and tend to explore objects orally. The objects are then intentionally swallowed or accidentally ingested as the result of a startle. Coins, food, marbles, buttons, pins, tacks, jewelry, magnets, and batteries are a few of the numerous foreign bodies children have ingested. Coins are the most frequent esophageal foreign body in children younger than 10 years, and fish bones are the most common in children older than 10 years. Developmentally delayed children are at high risk, as are children who have undergone esophageal surgery and those who have a damaged esophagus from prior caustic ingestions. Modern button batteries are twice as large (20mm vs 10mm) and twice as powerful (3 V vs 1.5 V) as old batteries. These larger batteries are more likely to get stuck at areas of physiologic narrowing. There is a rising incidence of these injuries. There is increasing popularity of these batteries in remote controls, car key fobs, and toys.

The esophagus has 4 physiologic areas of narrowing: the cricopharyngeal sphincter, the aortic arch, the region of the left main bronchus, and the gastroesophageal sphincter. These areas correspond to the 4 most common sites of foreign body obstruction. The cricopharyngeus is the most common; the arch of the aortic region is the most dangerous. If the foreign body is lodged at the lower border of the cricopharyngeus muscle, then it will be visualized at the level of the clavicles on chest radiograph.

Physicians need to be aware that the incidence of magnet ingestions is increasing. In addition, there are more high-powered (neodymium) magnets available that are being marketed as desktop toys. The site of attraction between ingested magnets can cause serious mucosal injury and mortality.

### History and Physical Examination

The history of foreign-body ingestion is often not obtained, and most foreign bodies pass through the normal esophagus undetected. A swallowed or aspirated object can cause a respiratory emergency, no symptoms at all, or anything in between. Objects that do not pass freely initially stimulate the larynx and cause gagging and coughing. Subsequent symptoms depend on the size, composition, and nature of the foreign body. With young children, poor feeding or refusal to eat or drink, as well as increased drooling, are typical. When the esophagus is completely or almost completely obstructed, choking and vomiting occur. The duration of obstruction can affect the clinical presentation; that is, the longer a foreign object is present, the greater the tissue reaction and local inflammation will be. Thus, in the later stages, patients can have pain on swallowing, airway compromise, fever, and leukocytosis.

### Imaging

When a foreign body is suspected, posteroanterior and lateral chest radiographs, in addition to neck radiographs, are diagnostic if the object is radiopaque, such as a coin. If the foreign body is a coin, then it will

most often be oriented in a transverse position because the opening of the esophagus is widest in a transverse position. However, it could also be oriented in the sagittal orientation, a finding that supports a coin in the trachea. Lateral radiographs are also important to determine the location of the object as well as presence of air trapping. Contrast studies can be used when an esophageal foreign body that does not show on routine radiographs is strongly suspected. Button batteries have a 'double ring' or 'halo' appearance on plain radiograph.

Metal detectors have also been diagnostically useful to detect foreign bodies. They are relatively inexpensive, easy to use, and have no risk of radiation exposure.

### Management

An esophageal foreign body that is an alkaline button battery or magnet requires emergency management. Other foreign bodies do not usually require emergency measures, but should be removed as soon as possible after proper evaluation and preparation. In many instances, children will have eaten recently, and generally, experts recommend that an appropriate period pass before they are given general anesthesia. If the foreign body is corrosive, such as an alkaline button battery, then it should be removed emergently to prevent severe inflammation and potential perforation of the esophageal wall. Multiple magnets lodged in the hypopharynx or esophagus can rapidly cause pressure necrosis and deserve prompt management as well. If there is no history of esophageal disease and no respiratory compromise, 12 to 24 hours of expectant management for spontaneous passage could be considered.

Endoscopic removal under anesthesia by a trained expert is most commonly used. With rigid esophagoscopy, optical forceps are passed through the central channel for retrieval of the foreign body. This technique allows for direct visualization of the esophagus, its mucosa, and the foreign body. Removal with flexible endoscopy is also possible. Once the scope is passed, a variety of flexible graspers, forceps, baskets, and magnets can be passed through the instrument channel to retrieve the object. Generally, flexible endoscopic removal of esophageal foreign bodies is recommended, rather than rigid esophagoscopy. Other nonendoscopic techniques for removing an esophageal foreign body (eg, with a Foley or Fogarty catheter) are used and are safe and effective when used by experienced medical professionals in appropriate settings on appropriate patients.

All button battery ingestions should be reported by physicians: call the National Battery Ingestion Hotline (NBH) administered by the National Capital Poison Control Center 202-625-3333 or go to [www.poisn.org](http://www.poisn.org). United States Consumer Product Safety Commission.

### Complications

Perforation of the esophagus can result from the endoscopic procedure or may be caused by the foreign body itself, especially if it is sharp or caustic. Several

recent reports highlight the serious complications related to button batteries: mediastinitis, tracheoesophageal fistula, aortic rupture, spondylodiscitis, and death. Endoscopic removal is particularly dangerous with objects lodged at the level of the aortic arch. If an esophageal tear is suspected, then a radiographic gastrograffin swallow study will usually confirm or negate the suspicion.

Retropharyngeal abscess has been reported as the most common complication of a sharp esophageal foreign body, such as a fish bone. Foreign bodies that have been in the esophagus for long periods can also cause a stricture to develop. In these cases, a contrast study, computed tomography scan, or esophagoscopy also should be performed to aid in the diagnosis.

During anticipatory guidance, parents and caregivers should be instructed not to leave small objects or inappropriate food where a young child can reach them or give them to a young infant.

### WHEN TO REFER

- Airway compromise exists
- When a battery is involved
- When magnets are involved in the airway or esophagus
- If the child cannot be restrained adequately
- If an object cannot be removed
- Ear:
  - Tympanic membrane cannot be visualized or perforation is suspected
  - Object is touching the tympanic membrane
  - Object is spherical or in the canal for more than 24 hours
  - Hearing loss, nystagmus, vertigo, central nervous system deficits, or deep-seated infection exists
- Nose: if a rhinolith has formed
- Airway: for tracheal and bronchial foreign bodies
- Esophagus: for endoscopic removal if object is stuck or if perforation is suspected

### WHEN TO ADMIT

- Airway:
  - Prolonged or difficult instrumentation of the airway occurred during removal of the foreign body
  - Postoperative edema develops
- Esophagus: if the object is sharp, corrosive, or magnetic and irretrievable by endoscope

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Children and Foreign Bodies in the Ear and Nose* (fact sheet), American Academy of Otolaryngology—Head and Neck Surgery ([www.entnet.org/KidsENT/Foreign\\_Bodies\\_Ear\\_Nose.cfm](http://www.entnet.org/KidsENT/Foreign_Bodies_Ear_Nose.cfm))
- *Choking Prevention* (fact sheet), American Academy of Pediatrics ([healthychildren.org/English/health-issues/injuries-emergencies/Pages/Choking-Prevention.aspx](http://healthychildren.org/English/health-issues/injuries-emergencies/Pages/Choking-Prevention.aspx))
- *Foreign Body Ingestion* (Web page), GI for Kids ([giforkids.com/diseases/foreign-body-ingestion](http://giforkids.com/diseases/foreign-body-ingestion))

- *Responding to a Choking Emergency* (Web page), American Academy of Pediatrics (healthychildren.org/English/health-issues/injuries-emergencies/Pages/Responding-to-a-Choking-Emergency.aspx)
- *TIPP Safety Sheets* (handouts), American Academy of Pediatrics (shop.aap.org)

#### Community Advocacy and Coordination

- *Prepare for Emergencies With American Red Cross First Aid, CPR and Automated External Defibrillator (AED) Courses* (Web page), American Red Cross (www.redcross.org/services/hss/courses)

#### Medical Decision Support

- *Airway Foreign Bodies in Children* (Web page), Radiopaedia (radiopaedia.org/articles/airway-foreign-bodies-in-children)
- *First Aid Choking/CPR Chart* (chart), American Academy of Pediatrics (shop.aap.org)

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## Chapter 252 FRACTURES AND DISLOCATIONS

R. Scott Strahlman, MD

Physicians who care for children see scores of fractures and dislocations each year. A familiarity with the proper triage and management of injuries is essential so that the physician can feel comfortable managing an injury conservatively or referring to an orthopedic specialist. This chapter covers the pathophysiologic features, clinical assessment, and classification of fractures and dislocations and discusses some of the more common fractures and dislocations encountered in primary care.

### DEFINITIONS

A *fracture* is defined as a break or crack in a bone. The fracture may occur directly at the site of injury or indirectly when the break occurs at a site different from the applied force. Stress fractures result from recurrent trauma to a bone and often occur in athletes (eg, long-bone fractures in

distance runners). Pathologic fractures can occur without trauma or with minor trauma when a bone is weakened, as with osteogenesis imperfecta or a tumor.

A *dislocation* is defined as a malposition of bone ends that normally oppose each other within a joint. Dislocations are far less common in children than are fractures because a child's ligaments are quite strong compared with an adult's; with an injury, a bone will more likely break or a growth plate will more likely separate than a ligament will tear.

Broad generalizations can be made about the pathophysiologic features of childhood fractures. First, fractures in children heal more quickly than in adults. For example, a fractured clavicle in a 4-year-old may heal in as little as 3 weeks. Second, the remodeling that occurs in the healing of pediatric fractures often corrects residual bony deformities. Third, children's bones are resilient; they may bend instead of break, or they may break on 1 side only (a greenstick fracture). Fourth, a phenomenon called *overgrowth* occurs in pediatric long-bone fractures. Overgrowth is an accelerated growth rate of bony fragments during healing. Long-bone fractures are therefore often corrected with overriding of the broken ends to prevent length discrepancies with the uninjured side. Finally, the growth plate must be protected when treating children's fractures because a growth plate injury can result in the loss of growth potential.

### EVALUATION

Whenever a fracture or dislocation is suspected, an accurate history is essential. Historical details may provide clues about the mechanism of injury. The physician should find out how, where, and when the injury occurred and where any pain is located. A fall off of a skateboard or scooter increases suspicion for a forearm fracture. Does the parent or child report any loss of function in the affected limb? Does the history show acute or recurrent trauma?

A complete physical examination, including vital signs and a neurovascular assessment, is key to reveal signs of serious trauma and secondary sites of injury. Pulses should be normal. Sensation should be intact, and movement, even if limited by discomfort, should be present. Absence of pulses, sensation, or movement signifies a serious injury requiring immediate medical attention. The examiner should look carefully for any unnatural or deformed position of joints or limbs, pain on palpation or attempted movement, or swelling and discoloration. Crepitus can sometimes be elicited at a fracture site. Any of these findings should alert the physician to order imaging studies.

Radiography is a mainstay in the diagnosis of fractures and dislocations. Radiographs from 2 angles are indicated to delineate subtle fractures. To rule out a dislocation, including the joint above and below the injury is sometimes helpful; in many cases, obtaining a film of the unaffected side for a comparison view may be helpful. Stress fractures are often missed on radiography. If a stress fracture is suspected, then a magnetic resonance image or a radionuclide bone scan may be indicated. Occasionally, when injury to the growth plate is a concern, other imaging techniques such as computed tomography can be useful.



## CLASSIFICATION

Fractures may be classified according to their clinical appearance. A closed fracture has no break in the skin. With an open, or compound, fracture, a bone fragment is exposed to the air, increasing the risk for infection and injury to adjacent nerves and blood vessels. A hidden fracture causes slight pain and swelling but no obvious bone deformity. Radiographs are necessary to confirm the diagnosis. An obvious fracture or dislocation is easily seen, even with a cursory examination. Immediate medical attention is necessary.

Fractures also are classified by their anatomic location and according to their radiographic appearance. Breaks in the bone may be described by their appearance as transverse, oblique, or spiral. A torus or buckle or incomplete fracture most commonly occurs after injury to the forearm and radiographically shows a wrinkled-appearing break of the distal radius on just 1 side of the bone. A fracture is comminuted when the bone has 3 or more fragments. With an impacted fracture, the bone ends are compressed into each other.

Probably the most important classification system for fractures is the Salter-Harris system of describing injury to the growth plate (Figure 252-1). Growth or epiphyseal plate injuries occur only in childhood. They must be treated with care to protect a bone's growth potential. Approximately 15% of all childhood fractures involve the growth plate. In a Salter-Harris I fracture, the epiphysis is separated from the metaphysis without a true break in the bone. Radiographs are often normal, and the diagnosis is made based on the clinical picture: tenderness over the area of the growth plate. Growth is usually not disturbed. The treatment is immobilization by cast for approximately 3 weeks. The most common growth plate fracture is the type II fracture, in which a fragment of metaphyseal bone separates from the epiphysis. Closed reduction of the fracture is usually possible; with proper casting, growth is not disturbed. A Salter-Harris III fracture involves a growth plate injury through the epiphysis and involves the articular surface. Open repair of the

fracture in the operating room is indicated to align articular surfaces and preserve joint function. A Salter-Harris IV fracture extends across the growth plate, injuring both the epiphysis and the metaphysis. The fracture must be perfectly realigned to protect growth potential. In a Salter-Harris V fracture, the growth plate is compressed. The prognosis for preserving growth is poor in this case because of a crush injury to the growth plate.

Chip fractures that do not cause any direct injury to the growth plate are not usually included in the Salter-Harris classification system.

## MANAGEMENT

Fractures and dislocations should be splinted and immobilized immediately. For most fractures and dislocations, consultation with an orthopedic specialist is necessary. Most pediatric fractures respond to closed reduction by the orthopedist. Even some compound fractures can be managed nonoperatively. If the growth plate is affected, however, then open reduction in the operating room is performed. Close pediatric and orthopedic follow-up are always important. A child in a cast should be comfortable; if pain is persistent, or if color changes or sensory changes to the casted extremity occur, then the child needs re-evaluation and possibly requires recasting.

## COMMONLY ENCOUNTERED FRACTURES AND DISLOCATIONS

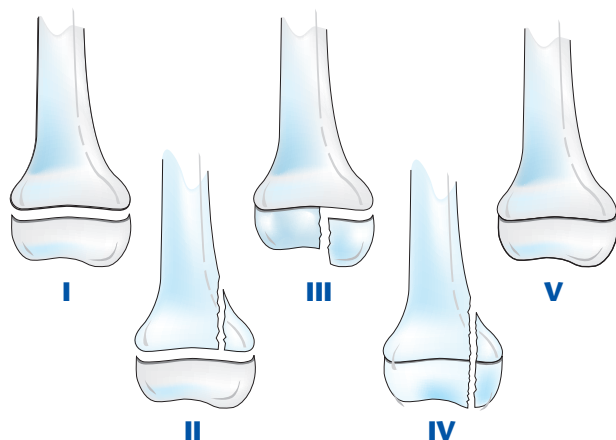
### Fractured Clavicle

A broken clavicle, or collarbone, is the most common pediatric fracture. It can occur at any time during childhood as a result of trauma. This fracture often occurs at birth when vaginal delivery is difficult. The incidence can be as high as 3.5% in babies delivered vaginally. Physical findings include decreased arm motion on the affected side, crepitus, and swelling at the fracture site. A radiographic or ultrasound study may be needed, if the diagnosis is in doubt, to confirm the diagnosis. If the condition is asymptomatic, then no treatment is needed; indeed, the diagnosis is often made after the fact, when a callus at the fracture site is noted at a well-baby visit. If the fracture causes pain or reduced arm movement, then immobilization of the arm on the affected side for 2 to 3 weeks is indicated. In older children, treatment requires splinting for 3 to 4 weeks in a simple sling. Figure-of-8 bandages have been found to be cumbersome and are no better than a sling. Most of the fracture's healing and realignment are spontaneous.

### Developmental Dysplasia of the Hip

The femoral head has a tendency to dislocate in as many as 5 of every 1,000 infants. This condition, formerly known as congenital hip dislocation, is termed *developmental dysplasia of the hip* (DDH). Because hip dysplasia is not always detected in the newborn period, children younger than 1 year should be examined for hip dislocation at every routine visit.

Although the exact cause is unknown, many factors contribute to DDH. The disorder may be related, in part, to abnormal intrauterine positioning and therefore is



**Figure 252-1** Salter-Harris classification of growth plate injuries. (See text for explanation.)



more common in breech deliveries and in infants delivered by cesarean section. DDH occurs in up to 23% of breech infants. The condition is 6 to 8 times more common in girls than in boys. Theories suggest that female fetuses are more sensitive to maternal hormones that can induce ligamentous laxity of the hip. DDH is 3 times more common on the left side than the right, and in approximately 20% of cases is bilateral. The tendency to occur more often on the left is believed to be the result of intrauterine positioning. Most fetuses are positioned left occiput anterior during the later stages of pregnancy. This position puts the left hip against the mother's spine, thereby putting additional pressure on the left hip to dislocate. A genetic predisposition also exists: the risk for DDH is increased when a positive family history of hip dislocation exists.

Radiographs are of limited value during the neonatal period in the diagnosis of developmental dysplasia of the hip. Therefore the physical examination is of utmost importance. The Ortolani test is used to detect a dislocated hip. With the baby laying supine, the hips and knees are flexed and the knees brought together. The examiner then places a hand on each of the baby's knees, with each middle finger over the greater trochanter and each thumb over the medial thigh. With gentle abduction of the knees, the dislocated femoral head will slip back into the acetabulum, and an audible or palpable *clunk* results. Notably, a hip *click* (without a *clunk* and without any movement of the femoral head) does not indicate a hip dislocation. The Barlow test is essentially the reverse of the Ortolani test: the femoral head can be felt slipping out of the acetabulum when the knees are brought back together. Both tests are important to perform because the Ortolani test pushes a dislocated hip *back into* the hip socket, and the Barlow test pushes a dislocatable hip *out of* the hip socket. An examiner may feel unusual laxity of the hip by pushing up and down on the thigh when the hips are flexed and adducted (sometimes called the *telescoping sign*). Older infants should be examined for limited hip abduction, asymmetry of the thigh skin folds, a limp when cruising or walking, and leg-length discrepancy. One way to determine leg-length discrepancy is the Galeazzi sign: With the infant lying supine, the examiner flexes the infant's thighs and brings the knees together. If one knee is higher than the other, then the Galeazzi sign is *positive*, and the possibility of a dislocated hip exists. If the diagnosis is in doubt, then an ultrasound study, and in infants older than 4 to 6 months a radiograph, will confirm or rule out a dysplastic hip. Treatment requires referral to an orthopedist for a harness or casting. Some newborns with mild DDH can be monitored with serial ultrasounds and do not require active intervention. Infants diagnosed before 6 months of age can be treated with a Pavlik harness, which is worn for up to 5 months. Infants diagnosed after 6 months of age, and infants in whom the harness was not successful, require casting and sometimes surgery. Treatment is more straightforward the earlier the diagnosis is made, which makes it imperative for the physician to assess for DDH at every routine pediatric visit. Because of the increased incidence of DDH in breech infants, it may be of benefit to do an initial screening

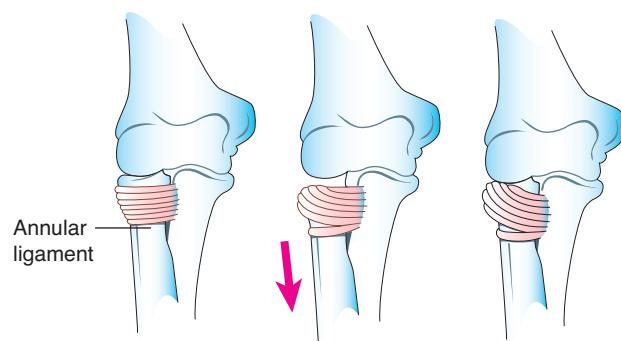
ultrasound of the hips in breech infants at birth, with a follow-up ultrasound at 6 weeks of age and a radiograph at 6 months of age to screen for DDH. There is growing evidence that tight swaddling may contribute to hip dysplasia in at-risk infants. It is therefore recommended that if babies are swaddled, their legs be left free to move so that the hips can remain flexed and abducted.

### Nursemaid's Elbow

*Nursemaid's elbow* is a common dislocation in pediatrics. The name derives from the fact that this dislocation occurred frequently during the 19th century in children under the care of nursemaids. It is a transient subluxation of the proximal radial head (Figure 252-2) caused by pulling or *yanking*, usually inadvertently, of a child's arm, often by a parent or caregiver. The annular ligament of the radial head becomes entrapped in the radiohumeral joint (see Figure 252-2). The condition usually occurs in children between 1 and 4 years of age. The child refuses to move the arm and keeps it flexed and pronated. Radiographs are rarely necessary; the history and characteristic posture of the child's arm confirm the diagnosis. The treatment, easily performed by the pediatrician, requires rapid, forceful supination of the forearm while pressure is placed over the proximal radial head, followed by extension then flexion of the elbow. Symptoms usually resolve within 30 minutes. The condition is sometimes recurrent, in which case great care must be taken when holding hands with the affected child, lest the child suddenly try to pull away.

### Child Abuse

Unfortunately, fractures and dislocations are all too commonly suggestive of child abuse (see Chapter 367, Physical Abuse and Neglect). Child abuse may be suspected when an unexplained injury occurs or when an inconsistency exists between the history and the physical findings in a childhood injury. The delay between the time of injury and the time that medical attention is sought may be unusually long. Multiple bruises may be noted on physical examination. If abuse is suspected, then a radiographic bone survey should be performed in younger children. Silent fractures, or multiple fractures in varying stages of healing, may be seen.



**Figure 252-2** Nursemaid's elbow.

When child abuse is suspected, child protective services and social services should be involved. If child protective services cannot respond in a reasonable time to make plans for the child's safety, the child may need to be hospitalized. The child may also need to be hospitalized for appropriate evaluation and orthopedic care. All practitioners of pediatric care have a moral and legal responsibility for detecting child abuse and reporting all suspected cases.

### Toddler's Fracture

Radiologists refer to a spiral fracture of the tibia as a *toddler's fracture* when the fracture occurs in a child younger than 6 years of age. Torsion of the foot creates a spiral break in the tibia. The trauma to the leg often is minor or unwitnessed; therefore, in many instances, no history of trauma can be found. Symptoms can be minimal; the child may be brought for medical attention only because of reluctance to bear weight on the affected leg. The physical examination is significant for tenderness over the affected area of the tibia. A diagnosis can be made with anteroposterior and lateral radiographs of the tibia-fibula, but the fracture is sometimes not evident on a radiograph for a few days. The physician therefore should not hesitate to repeat films on a child who has an unexplained limp that is not resolving spontaneously. Treatment requires immobilization in a cast for 3 to 4 weeks.

Because the signs and symptoms of a toddler's fracture can be subtle, the examiner should have a high index of suspicion in a child who has a limp or fails to bear weight. Because the cause of the fracture is often unexplained, child abuse is sometimes a consideration.

### Forearm Fractures

A forearm fracture is one of the most common fractures seen in a pediatric practice. The fracture occurs when a child falls, because of an innocent stumble or a sports-related fall, and stops the fall with an outstretched palm of the hand. Usually the fracture is located in the distal metaphysis of the radius. A fracture should be strongly suspected whenever there is a fall and there is localized tenderness in the distal radius (palmar side). It is important to order a radiograph in this situation. The typical radiographic appearance is an incomplete fracture, called a *torus* or *buckle fracture*. Although casting by an orthopedist is usually necessary for 3 to 4 weeks, mild fractures can sometimes be treated with splinting. When a fracture of the radius is more severe and causes angulation of the distal radius, it is referred to as a Colles fracture (named after the Irish doctor who first described this fracture in 1814). A Colles fracture requires realignment by the orthopedic surgeon followed by casting.

### Shoulder Dislocations

Shoulder dislocations are uncommon in children but increase in frequency during adolescence and are often sports-injury related (see Chapter 334, Sports Musculoskeletal Injuries). With a shoulder dislocation, there is usually anterior dislocation as a result of direct trauma to the shoulder. The anterior capsule of the shoulder is often damaged and may

predispose a child to recurrent dislocation. Radiographs may be necessary to rule out a fracture. Treatment consists of reducing the dislocation with gentle traction of the arm, downward and medially. Because shoulder dislocations are very painful, treatment may require sedation in an emergency department setting. After the dislocation is reduced, the shoulder is immobilized for 3 to 6 weeks, and then activities are slowly resumed, sometimes with the help of physical therapy. Referral to an orthopedic specialist is appropriate.

### WHEN TO REFER

- All dislocations and fractures not easily managed in a primary care setting, including displaced fractures needing reduction, intrarticular fractures, Salter-Harris III, IV, and V fractures require referral.
- Complicating factors such as compartment syndrome, vascular injury, open fracture, multiple trauma, and nerve injury require immediate referral.

### WHEN TO ADMIT

- Whenever child abuse is suspected or if the patient is not medically stable (ie, multiple injuries).

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Children and Broken Bones* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/injuries-emergencies/Pages/Children-And-Broken-Bones.aspx](http://www.healthychildren.org/English/health-issues/injuries-emergencies/Pages/Children-And-Broken-Bones.aspx))
- *Hip Dysplasia (Developmental Dysplasia of the Hip)* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Stress Fractures* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/injuries-emergencies/sports-injuries/Pages/Stress-Fractures.aspx](http://www.healthychildren.org/English/health-issues/injuries-emergencies/sports-injuries/Pages/Stress-Fractures.aspx))

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## Chapter 253

# FRAGILE X SYNDROME

Robert A. Saul, MD

## FOUNDATION

### Definition

Fragile X syndrome is an X-linked genetic condition characterized by trinucleotide repeats in the fragile X mental retardation 1 gene (*FMR1*) altering fragile X mental retardation protein (FMRP) expression. It is the most commonly inherited form of intellectual disability. Fragile X syndrome is one of the *FMR1*-related disorders—the other 2 being fragile X-associated tremor/ataxia syndrome (FXTAS) and primary ovarian insufficiency (POI). Males with fragile X syndrome can manifest significant developmental delay without obvious physical features early in childhood. Females can also be affected with usually milder developmental delay. The phenotype (physical and behavioral) can change over time.

FMRP plays an important role in protein synthesis regulation at the level of dendritic development at neural synapses. Abnormal dendrite development will lead to cognitive impairment, presumably because of abnormal synaptic function and plasticity. A unique feature of the fragile X syndrome is the nonclassical gene-disrupting alterations in protein expression caused by the trinucleotide repeat gene changes. Too many repeats in this region will lead to excess methylation in the promoter region of the gene, and FMRP protein production will decrease substantially. Rarely, a classic mutation of the gene can occur. Individuals with a normal number of repeats in their fragile X allele will have 5 to 44 CGG trinucleotide repeats in exon 1 of the gene. Individuals with an intermediate number of trinucleotide repeats (45 to 54) are typically unaffected, and individuals with 55 to 200 repeats are considered premutation carriers. This latter group is not usually at risk for intellectual disability, but women are at risk (as high as 20%) for POI (onset of menopause prior to age 40) and at risk for having affected children. Men who are premutation carriers are at risk for adult-onset FXTAS and will pass the premutation allele on to their female offspring. Males with greater than 200 repeats are at significant risk for intellectual disability and behavior problems, and females with more than 200 repeats also have some risk for intellectual disability and learning problems, but decreased risk compared to males with more than 200 repeats.

Mutations with greater than 200 repeats are termed *full mutations*.

### Epidemiology

The estimated prevalence of individuals with full mutations is 1 in 3,700 white males and 1 in 2,500 black males. However, a recent newborn incidence study for full mutation (>200 repeats) in males found the incidence to be 1 in 5,164 (ethnicity unknown). The prevalence of fragile X-affected heterozygous females is estimated to be 1 in 7,000. Prevalence for unaffected female premutation carriers is as high as 1 in 259.

### Etiology

As described earlier, fragile X syndrome is a disorder of trinucleotide repeat expansion. The gene for fragile X is located at the end of the long arm of the X chromosome (band Xq27.3). This X-linked condition is caused by an abnormal expansion of trinucleotide repeats (>200, which leads to excess methylation of the gene and subsequent gene silencing) and rarely by a direct mutation in the gene sequence. Either of these loss-of-function mutations in the *FMR1* gene leads to inadequate production of FMRP for those with a full mutation. FMRP is an RNA-binding protein. Its action through inhibition of dendritic protein synthesis modulates dendritic maturation and accompanying synaptic plasticity. The metabolic pathway affected (metabotropic glutamate receptor [mGluR]-mediated translation) is being targeted for potential therapeutic intervention with experimental trials underway.

Premutation carriers who are less affected in terms of cognitive delays are presumed to be influenced by a less than full reduction in the amount of FMRP than is seen in individuals with a full mutation. Affected individuals with premutations are also affected by an additional pathogenetic mechanism. Premutation individuals make an excess of messenger RNA (mRNA) transcript of the *FMR1* gene, although this mRNA increase does not lead to an increase in FMRP. An excess of mRNA transcript is not seen in full mutations because the gene is effectively silenced. The increased levels of mRNA seem to have a toxic effect on cell signaling. POI and FXTAS are associated with increased levels of *FMR1* gene mRNA transcript. The ovarian dysfunction in POI and the adult-onset neurologic abnormalities in FXTAS are tentatively causally linked to mRNA cellular toxicity.

### Risk Factors

Fragile X syndrome has no known ethnic or socioeconomic predilection. There are no known risk factors. Any individual, male or female, with an unknown cause for developmental delay should be strongly considered for evaluation.

## DIAGNOSIS

### Signs and Symptoms

Early recognition of the fragile X syndrome in childhood is very difficult; therefore, pediatricians and other physicians should have a high index of suspicion. Delayed diagnosis is a significant problem in early childhood. Delayed attainment of motor milestones,



hypotonia, developmental delay (especially speech), and unusual behaviors are the predominant features seen in early childhood. Feeding problems and gastroesophageal reflux are common. The characteristic physical signs in adults (large head, long face, prominent forehead, chin, and ears; joint laxity; macro-orchidism) usually do not develop until the postpubertal period. (See Figure 253-1, Figure 253-2, Figure 253-3, Figure 253-4, Figure 253-5, Figure 253-6, and Figure 253-7.)

Behavior issues in early childhood include features consistent with attention-deficit/hyperactivity disorder, obsessive or perseverative activity, emotional lability, or hypersensitivity to stimuli. Autism spectrum disorders and psychiatric comorbidities occur frequently.

Other potential abnormalities are seen in these additional areas—ophthalmologic (strabismus), orthopedic (joint laxity), cardiac (mitral valve prolapse), skin (excessive softness and smoothness), and neurologic (seizures). Neuroradiologic abnormalities have been reported.

Affected males typically have moderate intellectual disability, and affected females have mild intellectual disability.



**Figure 253-1** Patient 1 with Fragile X syndrome at 2 years of age, manifesting some of the physical signs (blue eyes, long face, prominent forehead) seen in Fragile X. The other features like large ears and prominent jaw are more obvious at ages 7 and 25, as is characteristic of Fragile X syndrome. See Figures 252-2 and 252-3.

### Differential Diagnosis

Other conditions to be considered in the differential diagnosis are Sotos syndrome (similar craniofacial features, overgrowth, and learning disability), Prader-Willi syndrome (a subset of fragile X patients can manifest hyperphagia, as seen in Prader-Willi syndrome, in addition to early hypotonia and developmental delay), autism spectrum disorders, and attention-deficit/hyperactivity disorder.

### Diagnostic Approach

Any child with delayed motor milestones, developmental delay (especially speech), intellectual disability, and autistic-like and other behaviors should be



**Figure 253-2** Patient 1 at 7 years of age.



**Figure 253-3** Patient 1 at 25 years of age.



considered for molecular testing, regardless of a negative family history. (See Figure 253-8.) A positive family history for intellectual disability (especially but not exclusively in males) is another strong indicator for testing. Concurrent microarray comparative genomic hybridization (CGH) is recommended to examine for non-fragile X conditions.

Adults in the family with signs or symptoms of primary ovarian insufficiency (onset of menopause prior to age 40 years) or tremor and/or ataxia (as seen in FXTAS) should be referred for testing.

### Laboratory Findings

Molecular fragile X testing typically analyzes the number of trinucleotide repeats in conjunction with Southern blot analysis and polymerase chain reaction. Newer techniques are being developed that overcome some current limitations in testing.

The laboratory testing was discussed earlier in the definition of fragile X syndrome. In brief, 5 to

44 repeats is a normal value; 45 to 54 repeats is an intermediate result usually without significance; 55 to 200 repeats is seen in premutation carriers; greater than 200 repeats is found in affected individuals. Females will have 2 alleles to be measured and males only 1 allele.



**Figure 253-4** Patient 2 with Fragile X syndrome at 1 year of age, with blue eyes and frontal bossing. Figures 253-5 through 253-7 demonstrate the progression of craniofacial features (long face, prominent forehead, and prominent jaw). Oftentimes the craniofacial features do not become obvious until after the onset of puberty.



**Figure 253-5** Patient 2 at 3 years of age.



**Figure 253-6** Patient 2 at 13 years of age.



**Figure 253-7** Patient 2 at 16 years of age.

### Imaging

Although neuroradiologic abnormalities (decreased cerebellar volume, increased ventricular volume, and increased white matter hyperdensity) have been reported in fragile X syndrome, routine neuroradiologic studies are not recommended. They should be performed as clinically indicated.

### Diagnostic Procedures

No additional diagnostic procedures other than those discussed earlier are necessary. Developmental and behavioral assessments will assist in the supportive and therapeutic management of affected individuals.

### Classification

Fragile X syndrome is the most common type of heritable intellectual disability. It is an X-linked semi-dominant condition with variable manifestation in males and females and has varied potential adult manifestations. It is one of the *FMR1*-related disorders that include fragile X syndrome, FXTAS, and *FMR1*-related POI.

## MANAGEMENT

### Treatment Approach

Currently, no specific treatment is available. Exciting advances are expected to make significant contributions to treatment based on the neurobiology of fragile X syndrome. Educational and behavioral interventions (occupational therapy, physical therapy, speech therapy, anticipatory management, and special education) are indicated for affected individuals. Pharmacologic therapy should be individualized, used to treat psychiatric presentations, and considered an adjunct for treatment of variable behavioral challenges not responding to environmental and behavioral interventions. An integrated behavioral and pharmacologic

program under the guidance of an experienced developmental team may prove helpful. Standard medical care is recommended for any health-related problem.

Because the fragile X syndrome is a genetic condition, close attention should be paid to a thorough examination of the family history and to the possibility of recurrence within the family. Genetic counseling to review recurrence risks and potential testing would be helpful. Premutation carrier females are at risk for having affected males and females because of the expansion of the trinucleotide repeats in female meiosis. The recurrence risk counseling is sufficiently complicated that referral to a medical geneticist or genetic counselor is indicated.

### Specific Treatments

Targeted treatments are under development.

## ONGOING CARE

### Follow-up

Appropriate behavioral, pharmacologic, and special education interventions should occur as indicated by the individual circumstances. Ongoing discussions about recurrence risk for subsequent offspring can be helpful to the family. Adults in the family should be aware of associated risks.

### Complications

Medical issues should be treated by standard interventions. Intellectual disability and behavioral problems are the predominant complications that need appropriate supportive and pharmacologic treatments. Family members should be counseled about possible primary ovarian insufficiency (onset of menopause prior to age 40 years) or FXTAS (tremors or ataxia after age 50 years).

### Prognosis

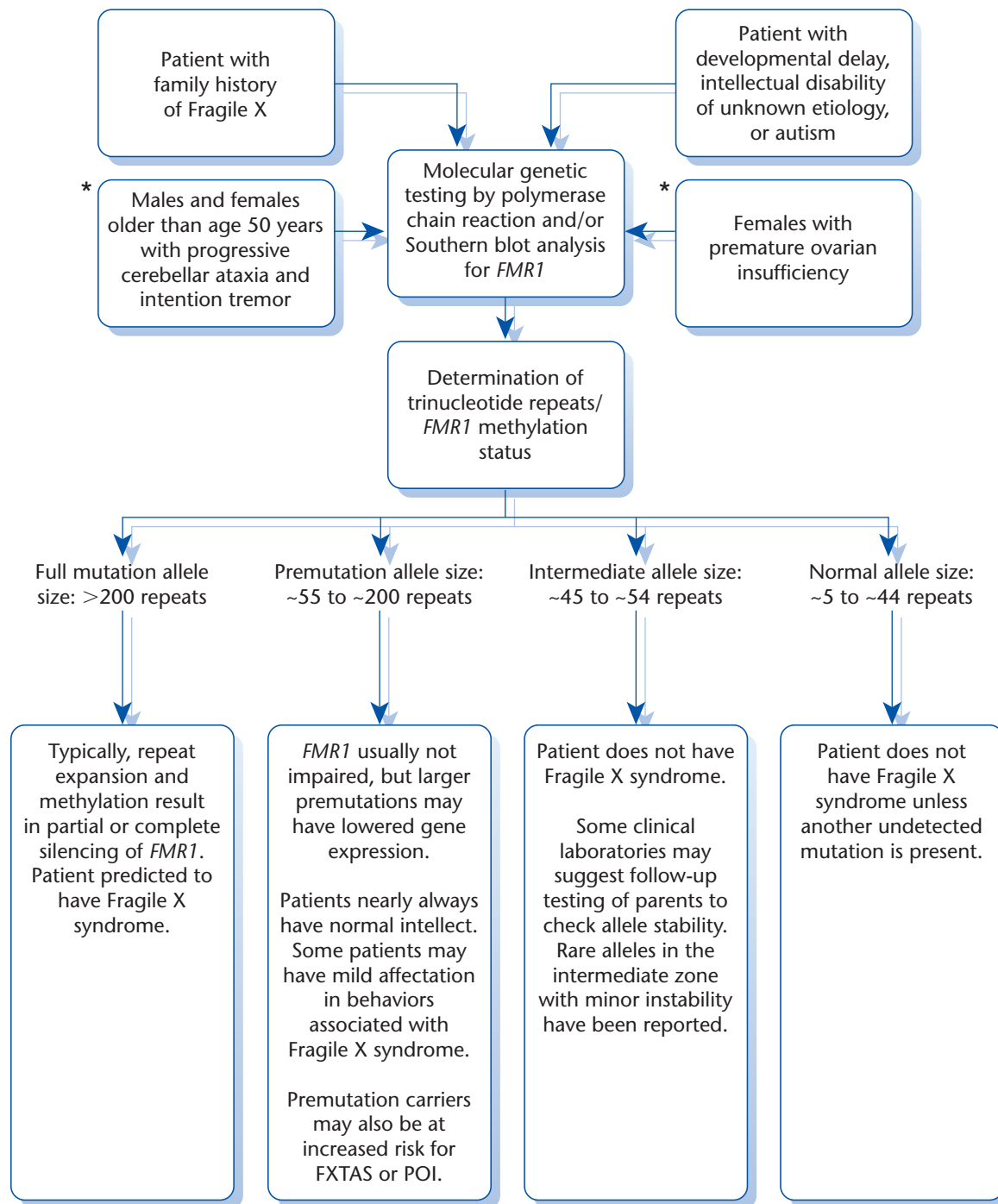
Children with fragile X syndrome will need significant educational and behavioral assistance. They will typically require custodial care as they make the transition to adulthood. Fragile X syndrome is one of the *FMR1*-related disorders, and assessment of additional family members should be considered because the additional risks will affect the longitudinal care of the patient and family.

### Prevention

Prenatal diagnosis is available for families that desire such testing. Population-wide neonatal screening is being investigated but is not currently available.

## WHEN TO REFER

- Delayed motor milestones
- Developmental delay, especially speech
- Abnormal behavior (nonisolated attention deficit/hyperactivity disorder or autistic features)
- Typical physical features (craniofacial abnormalities [long face; prominent forehead, chin, and ears] and macro-orchidism)



**Figure 253-8** Testing algorithm for *FMR1*-related disorders. The boxes identified with asterisks (\*) identify individuals to be considered for *FMR1* molecular testing. (From Saul RA, Tarleton JC. *FMR1*-related disorders. In: GeneReviews. Pagon RA, Adam MP, Ardinger HH, et al, eds. Copyright © 1993-2015, University of Washington, Seattle. All rights reserved. Available at: [www.ncbi.nlm.nih.gov/books/NBK1384](http://www.ncbi.nlm.nih.gov/books/NBK1384). Updated April 26, 2012.)

FXTAS, Fragile X-associated tremor/ataxia syndrome; POI, primary ovarian insufficiency



- Positive family history for intellectual disability, females with primary ovarian insufficiency (menopause prior to age 40 years), or males with adult-onset tremor or ataxia

### WHEN TO ADMIT

There are no unique situations pertinent to fragile X syndrome.

### TOOLS FOR PRACTICE

#### Community Advocacy and Coordination

- *Building the Legacy: IDEA 2004* (Web page), US Department of Education ([idea.ed.gov](http://idea.ed.gov))
- *Let's Put the Person First, Not the Disability!* (fact sheet), Disability Is Natural ([www.disabilityisnatural.com/explore/people-first-language](http://www.disabilityisnatural.com/explore/people-first-language))

#### Engaging Patient and Family

- *All About the IEP* (fact sheet), Center for Parent Information and Resources ([www.parentcenterhub.org/repository/iep](http://www.parentcenterhub.org/repository/iep))
- *Building Your Care Notebook* (Web page), American Academy of Pediatrics ([medicalhomeinfo.aap.org/tools-resources/Pages/For-Families.aspx](http://medicalhomeinfo.aap.org/tools-resources/Pages/For-Families.aspx))
- *Emergency Information Form for Children with Special Needs* (form), American Academy of Pediatrics ([www.aap.org/advocacy/blankform.pdf](http://www.aap.org/advocacy/blankform.pdf))
- *National Fragile X Foundation* (Web site), ([www.fragilex.org](http://www.fragilex.org))
- *Pediatric Care Plan* (form), American Academy of Pediatrics ([medicalhomes.aap.org/Documents/PediatricCarePlan.pdf](http://medicalhomes.aap.org/Documents/PediatricCarePlan.pdf))
- *Pediatric Specialists* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/default.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/default.aspx))
- *Transitioning Youth to Adult Care Providers* (booklet), Got Transition ([www.gottransition.org/resourceGet.cfm?id=208](http://www.gottransition.org/resourceGet.cfm?id=208))

#### Practice Management and Care Coordination

- *A Toolkit to Improve Care for Pediatric Patients with Genetic Conditions in Primary Care* (e-book), American Academy of Pediatrics Genetics in Primary Care Institute ([geneticsinprimarycare.aap.org/YourPractice/Documents/GPCI\\_Toolkit.pdf](http://geneticsinprimarycare.aap.org/YourPractice/Documents/GPCI_Toolkit.pdf))

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### Chapter 254

## FUNGAL INFECTIONS (SYSTEMIC)

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A systemic fungal infection in pediatrics is not a common occurrence. Nevertheless, in recent decades, the incidence of invasive fungal infections and the need to recognize and appropriately manage them in pediatrics have increased. More than 100,000 species of fungi have been identified, of which only a few are known to be pathogenic. This chapter includes the common systemic fungal infections seen in pediatrics. Though experts differ in their opinions regarding taxonomy and classification of fungi, in general, systemic mycoses are divided into 2 categories based on their pathogenicity:

- Primary systemic mycoses, such as histoplasmosis, coccidioidomycosis, and blastomycosis, which can infect immune-competent individuals.
- Opportunistic mycoses, such as invasive candidiasis, aspergillosis, cryptococcosis, and mucormycosis, which mainly infect immunocompromised individuals.

### ASPERGILLUS

#### Etiology

*Aspergillus* exists as a hyaline mold with septated hyphae that typically branch at acute angles. *Aspergillus* most commonly reproduces asexually, forming conidia, the infectious form of the mold (Figure 254-1 and Figure 254-2). There are more than 180 known species of *Aspergillus*, and an increasing number of *Aspergillus* species are being described as human pathogens. The species most commonly isolated in human disease is *A fumigatus*, which, on culture, appears as gray-green colonies. Other common human pathogens include the toxin-producing species, *A flavus* (colonies are yellow-brown on the surface and gold colored or red-brown underneath), an amphotericin B-resistant species, *A terreus* (colonies are beige to cinnamon-colored on the surface and white-brown underneath), *A niger* (colonies are black on the surface and white-yellow underneath), and *A nidulans* (colonies are green-yellow on the surface and purple-red or red-brown underneath).

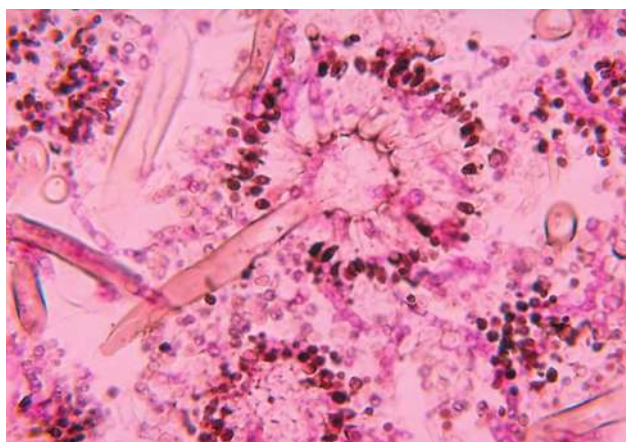
#### Epidemiology

*Aspergillus* species are ubiquitous in nature, and are present in soil, decaying vegetation, and air and water supplies. Humans acquire *Aspergillus* through the





**Figure 254-1** Conidia and phialoconidia of *Aspergillus fumigatus*. (Courtesy Red Book Online. [redbook.solutions.aap.org](http://redbook.solutions.aap.org))



**Figure 254-2** This micrograph depicts the histologic features of aspergillosis, including the presence of conidial heads. (Courtesy Red Book Online. [redbook.solutions.aap.org](http://redbook.solutions.aap.org))

constant inhalation of aerosolized conidia. As the conidia enter the lung, macrophages clear them, usually with little local inflammatory response. Occasionally, the conidia will germinate into the tissue-invasive hyphae form. These hyphae can invade the tissue and trigger a series of host-immune responses. In all cases of invasive aspergillosis, angioinvasion by *Aspergillus* hyphae, with resultant tissue hypoxia and necrosis, is an important factor in disease pathogenesis.

Fortunately, invasive aspergillosis is rare, yet it remains a common cause of morbidity and mortality in immunocompromised patients. The incidence of invasive disease depends on many factors, and varies between 0.1% and 11% among the various at-risk populations studied. Generally speaking, the incidence of invasive aspergillosis is highest among allogeneic hematopoietic stem cell transplant (HSCT) recipients (human leukocyte antigen [HLA]-mismatched individuals are at a higher risk than HLA-matched individuals),

followed by lung transplant recipients. Autologous HSCT and liver and kidney transplant recipients generally have lower incidence of invasive aspergillosis.

Just as the incidence of invasive aspergillosis varies among at-risk groups, so too does *Aspergillus*-related mortality. A systematic review by Lin and colleagues in 2001 showed that the crude fatality rate (CFR) of invasive aspergillosis was 58%. When stratified by underlying comorbidities, the CFR of HSCT was 86.7%, the highest of any group. Patients with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) had the next highest CFR, 85.7%; those with liver transplants had a CFR of 67.6%; and those with kidney transplants had a rate of 62.5%. Patients with leukemia and lymphoma along with lung and/or heart transplantation had the lowest CFR (49.3% and 31%, respectively). The lower incidence of mortality secondary to invasive aspergillosis among patients with lung transplants is likely because of the widespread post-transplantation use of prophylactic aerosolized antifungal agents. Allogeneic HSCT recipients with invasive aspergillosis generally face higher mortality rates than do autologous transplant recipients. Furthermore, mortality among patients with invasive aspergillosis and relapsed leukemia approaches 100%. Cerebral aspergillosis, which carries a mortality rate of more than 90%, is especially problematic. The incidence of cerebral aspergillosis is not well established; studies suggest that cerebral aspergillosis may be present in 30% to 39% of patients diagnosed with invasive aspergillosis at other sites.

In immunocompetent patients, invasive forms of aspergillosis occur rarely, typically after exposure to *Aspergillus* conidia. Infections in such patients include pulmonary aspergillosis, *Aspergillus* tracheobronchitis, sinusitis, and very rarely, disseminated disease. In patients predisposed to sinusitis and chronic lung disease, aspergillomas may form in the sinuses and in devitalized areas of the lungs.

A few diseases are attributable to noninvasive *Aspergillus* infections, most resulting from an exuberant immune response to the colonizing *Aspergillus*.

### Risk Factors

As with most fungal infections, host risk factors are related to underlying disease; few immunocompetent hosts develop invasive aspergillosis. Risk factors can be divided by level of associated risk. High-risk patients are those undergoing long-term immunosuppressive therapy (corticosteroids or immunomodulating agents), such as HSCT recipients with graft-vs-host disease, and solid organ transplant recipients with acute or chronic graft rejection. Also at high risk are patients with hematologic malignancies (particularly acute myelogenous leukemia, especially relapsed), and patients with prolonged and severe neutropenia. Intermediate-risk patients are those who have received autologous HSCTs and solid organ transplant recipients. Low-risk patients include those with severe malnourishment, multiple myeloma, long-term corticosteroid treatment, HIV/AIDS, diabetes, and obstructive pulmonary disease. Recently, select patients in intensive care units (ICUs; without malignancy) have been described as having an increased risk of invasive

aspergillosis. Patients with chronic granulomatous disease (CGD) have an elevated risk for invasive pulmonary aspergillosis, which typically presents insidiously within the first 20 years of life.

## Diagnosis

### Signs and Symptoms

The symptoms of invasive aspergillosis depend on the site of the disease.

**PULMONARY ASPERGILLOSIS.** Patients with invasive pulmonary aspergillosis typically present with fever, cough, dyspnea, and pleuritic chest pain. A pleural effusion and pneumothorax may be present, and if angioinvasion has occurred, hemoptysis may ensue. It should be noted that the presentation of pulmonary aspergillosis in children with CGD can be insidious, marked by vague complaints, fever, and an elevated erythrocyte sedimentation rate.

**ASPERGILLUS TRACHEOBRONCHITIS.** Patients with *Aspergillus* tracheobronchitis typically present with dyspnea, cough, chest pain, and fever. Hemoptysis and wheezing are sometimes present, and most patients have a demonstrable decrease in their measured pulmonary function. *Aspergillus* tracheobronchitis can present in 3 ways: obstructive tracheobronchitis (common in patients with AIDS and heart transplants), characterized by noninflammatory mucus obstruction; pseudomembranous tracheobronchitis (common in lung transplant recipients), characterized by extensive inflammation and a membranous cover of the respiratory mucosa; and ulcerative tracheobronchitis (seen primarily among lung transplant recipients), in which the infection occurs at the tracheal suture line between the graft and the host.

**ASPERGILLUS SINUSITIS.** Sinus disease typically presents with headache, fever, epistaxis, and ear or nasal discharge. Also commonly noted is localized pallor of nasal septum or mucosa. With disease advancement, proptosis and cranial nerve palsies can occur. Although *Aspergillus* sinusitis can lead to invasion of bone and deep soft tissues, these are late findings that are associated with high morbidity and mortality. It is important to note the similarity of *Aspergillus* sinus disease with mucormycosis sinus disease because antifungal therapies for these 2 entities differ.

**CEREBRAL ASPERGILLOSIS.** The cerebral form of invasive aspergillosis can be seen in up to 30% of patients with invasive aspergillosis and typically presents with focal neurologic symptoms, altered mental status, hemiparesis, and cranial nerve palsies. Headache, nausea, and vomiting are present less frequently. *Aspergillus* is the most common cause of cerebral abscesses in patients with HSCT, usually resulting from dissemination of pulmonary infection.

**DISSEMINATED ASPERGILLOSIS.** Disseminated aspergillosis is typically an extension (or progression) of pulmonary disease, and occurs in patients who have experienced a long period of immunosuppression. Patients with disseminated aspergillosis present with a combination of symptoms based on the location of the primary focus and disseminated sites.

**OTHER.** Osteomyelitis, septic arthritis, and cardiac as well as ocular infections are rare forms of invasive aspergillosis. Cardiac involvement may present as

endocarditis, pericarditis, or myocarditis. The presentation is clinically indistinguishable from cardiac disease because of other infectious causes. *Aspergillus* osteomyelitis presents similarly to bacterial osteomyelitis, with nonspecific symptoms, including fever and pain. The vertebral bodies and intervertebral disks are usually affected. Septic arthritis presents similarly to bacterial joint infections, with fever, joint pain, warmth, and erythema. Endophthalmitis may develop after *Aspergillus* keratitis infection or from hematogenous dissemination. Rarely, direct inoculation and surgical contamination have been implicated. This is a medical emergency because irreparable vision loss with destruction of the eye may occur. However, it is clinically indistinguishable from other infectious causes.

**NONINVASIVE.** *Aspergillus* species can cause several noninvasive forms of disease. Allergic bronchopulmonary aspergillosis, a form of steroid-dependent asthma, is characterized by elevated *Aspergillus* immunoglobulin (Ig) E, and occurs most commonly in patients with cystic fibrosis and asthma. Another form of noninvasive aspergillosis is allergic rhinitis/sinusitis. This is a localized infection, typically recurrent, in which patients present with hypertrophic sinus disease and nasal polyps. Lastly, aspergillomas (mycelial balls), a form of noninvasive disease, can also occur. In aspergillomas, *Aspergillus* grows in devitalized parts of the lung. Patients are typically symptom free, or may present with often life-threatening hemoptysis.

### Differential Diagnosis

The diagnosis of *Aspergillus* infections is challenging. Clinical symptoms early in the course of the disease are typically indistinguishable from infections caused by other pathogens. Advanced infections caused by *Aspergillus* are often easier to diagnose, but carry substantially higher rates of mortality and morbidity. Immunocompromised children must receive thorough evaluations, and special thought should be given to invasive *Aspergillus* infections. A high index of suspicion in the right setting (immunocompromised host at high risk) is required.

### Laboratory Findings

Early diagnosis of invasive aspergillosis is paramount because survival is related to early treatment. However, diagnosis remains difficult, as with many fungal diseases. *Aspergillus* is infrequently found on culture of bronchoalveolar lavage (BAL) specimens, and even very rarely on blood culture. Cultures of biopsy site specimens are also rarely diagnostic, and biopsy is often too risky, because patients with invasive aspergillosis tend to have other comorbidities (eg, thrombocytopenia). Accurate diagnosis of *Aspergillus* infection is also made challenging by the ubiquity of *Aspergillus* in the environment and the resultant frequent colonization of mucosal surfaces. This is strikingly important in the diagnosis of invasive sinus disease. Given the frequent colonization of mucosal surfaces, physicians must attempt to distinguish intercurrent *Aspergillus* colonization from invasive disease. For definitive diagnosis of *Aspergillus* sinusitis, pathologic evidence of tissue invasion is needed.

With the poor sensitivity of culture, several nonculture methods for the diagnosis of invasive aspergillosis have been established. A serum galactomannan (a polysaccharide component of the *Aspergillus* cell wall) assay has been developed for clinical use. The sensitivity and specificity of this assay have been studied and vary according to patient characteristics, definition of disease (proven, probable, or possible), and assay cutoff values. The reported sensitivity of the serum galactomannan assay for the diagnosis of invasive aspergillosis ranges from 16.4% to 100%; specificity is approximately 80%. The sensitivity of galactomannan in BAL fluid tends to be higher. Galactomannan levels can also be measured in cerebrospinal fluid (CSF) for the diagnosis of *Aspergillus* infection in the central nervous system (CNS), but their sensitivity and specificity are unknown. Only serum and BAL testing is currently approved by the US Food and Drug Administration (FDA). It is important to note that galactomannan assay results can be false-positive in samples from patients exposed to certain antimicrobials (eg, amoxicillin/clavulanate), from neonates colonized with *Bifidobacterium*, and rarely, from patients with other mycoses (eg, *Fusarium*, *Penicillium*, *Cryptococcus*, *Histoplasma*, *Blastomyces*). Despite some earlier reports, false-positive values are similar in children and adults.

Another nonculture diagnostic tool is a serum assay to detect (1,3)- $\beta$ -D-glucan (BDG; a fungal cell wall component). Again, sensitivity and specificity of the assay will vary according to patient characteristics, definition of disease (proven, probable, or possible), and assay cutoff values. This assay has a combined sensitivity of 55% to 100% and specificity of 87% to 93% for diagnosing invasive fungal disease in serum specimens; however, fungal expression of BDG is not limited to *Aspergillus*. Other fungi, including *Candida*, *Fusarium*, *Histoplasma capsulatum*, *Trichosporon*, *Saccharomyces cerevisiae*, *Sporothrix schenckii*, and *Acremonium* express BDG. In addition, BDG is a cell wall component of *Pneumocystis jiroveci*. As a consequence, BDG positivity in a sample is not specific for *Aspergillus*. Furthermore, as with the galactomannan assay, false-positive results can occur in patients receiving certain antibiotics (eg, cephalosporins, carbapenems, ampicillin/sulbactam) and in patients receiving intravenous immunoglobulins. False-positive BDG assay results can also occur with exposure to tubes and/or gauze containing cellulose membranes. Cerebrospinal fluid and BAL fluids may be tested as well, though sensitivities and specificities are unknown, and these are not FDA approved.

Polymerase chain reaction (PCR) assays have been developed to detect *Aspergillus*. A number of these assays are commercially available, but the lack of standardization makes them difficult to interpret. An evaluation of various commercially available methods found good overall results, with a sensitivity and specificity of 86.1% and 93.6%, respectively. Further research is needed before these methods become standard diagnostic tools that are universally recommended.

Other nonculture molecular methods for the diagnosis of invasive aspergillosis disease include in situ hybridization for detection of *Aspergillus* in histopathologic

specimens and a lateral flow device, a new device. The lateral flow device serves as point-of-care testing to detect *Aspergillus* antigen by a monoclonal antibody in BAL fluid and serum samples, with results analyzed in a short time. Preliminary studies are promising, but further research is needed.

When culture is available, it is important to verify the minimum inhibitory concentration of the drug, because of the emergence of triazole-resistant *A fumigatus* in certain parts of the world (particularly Europe). The predominant mechanism of resistance for these isolates is a mutation in TR<sub>34</sub>/L98H, which confers cross-resistance to the drug class. To date, very few azole-resistant isolates have been seen in the United States. A study that evaluated clinical *A fumigatus* isolates collected between 2011 and 2013 from different parts of the United States revealed a 5% incidence of *A fumigatus* isolates with a minimum inhibitory concentration greater than 1  $\mu$ g/mL to itraconazole, but none harbored the TR<sub>34</sub>/L98H mutation.

### Imaging

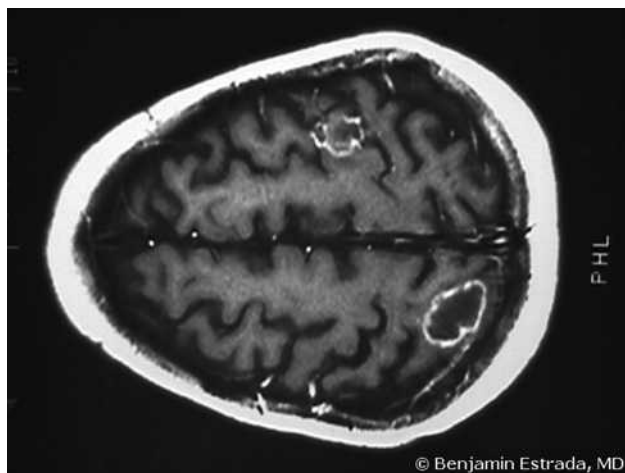
For sinus disease caused by *Aspergillus*, computed tomography (CT) frequently shows air-fluid levels, mucosal thickening, and with invasive disease, erosion of bony structures. In pulmonary infection in immunocompromised hosts, high-resolution CT will typically show ground glass attenuation surrounding a pulmonary nodule ("halo" sign). Following initial lesions, air crescents and cavitations may develop, usually as neutropenia resolves. Other characteristics of pulmonary aspergillosis seen on CT include enlarged lymph nodes, lobar infiltrates, and ground glass appearance of pulmonary parenchyma. Importantly, abnormal lung radiographic findings may not be as prevalent in younger children with pulmonary aspergillosis compared with the prevalence of abnormal findings in older children and adults. It should also be noted that, after the initiation of appropriate antifungal therapy, *Aspergillus* lesions will appear to worsen on imaging. This radiographic worsening is not itself indicative of treatment failure.

Patients with CGD who develop pulmonary aspergillosis often lack the lesions that are characteristically seen on radiologic imaging in other patients. Also, in some patients with CGD, aspergillosis evolves to a chronic, local progressive infection, most often involving the vertebrae, pleura, and chest wall.

In cerebral aspergillosis, CT scans may show 1 or multiple hypodense, well-demarcated lesions. These are sometimes noted as ring-enhancing lesions with surrounding edema, with or without associated hemorrhage, similar to other types of cerebral infections (Figure 254-3). Magnetic resonance imaging (MRI) may show an increased number of lesions with irregular ring enhancement, typically earlier in the disease process compared with CT scan.

Bone invasion by *Aspergillus* can be detected on plain film radiography, CT scan, and MRI. Bone involvement is seen most frequently in immunocompromised patients with advanced *Aspergillus* sinus disease, and in the chest wall and vertebra in patients with CGD. Radiographic findings of bone erosion caused by *Aspergillus* infection are similar to the





**Figure 254-3** Aspergillomas in a 10-year-old with Hodgkin lymphoma. (Courtesy Red Book Online. [redbook.solutions.aap.org](http://redbook.solutions.aap.org))

radiographic findings of bone erosion caused by other fungi or bacteria.

## Management

### Treatment Approach

Effective treatment of *Aspergillus* infections requires early diagnosis and aggressive treatment. Delayed therapy is associated with increased mortality. Thus, any symptomatic child with high or intermediate risk of invasive aspergillosis merits prompt evaluation and serious consideration for empirical therapy. Whenever possible, immunosuppression should be reduced.

The following recommendations are extracted from the *Clinical Practice Guidelines for the Treatment of Aspergillosis*, published by the Infectious Disease Society of America (IDSA).

### Specific Therapy

First-line therapy for any invasive *Aspergillus* infection is voriconazole. Voriconazole is a cytochrome P450 inhibitor; therefore, significant drug-drug interactions may occur. Voriconazole is typically well tolerated, and the most common side effects include visual disturbances and hallucinations. Caution must be taken when the intravenous formulation is used because it uses a cyclodextrin carrier (renally cleared), which may accumulate in patients with renal insufficiency. Also, voriconazole exhibits a high degree of interpatient pharmacokinetic variability, so drug levels should be monitored to ensure adequate drug exposure while preventing toxicity. Drug concentration after 1 week of exposure should be 1 to 5.5 mg/L (ideally >2 mg/L). Liposomal formulations of amphotericin B are an alternative to voriconazole as primary therapy. It must be emphasized that reduction of immunosuppression is paramount in the treatment of invasive aspergillosis.

Amphotericin B, itraconazole, posaconazole, and the echinocandins (capsfungin and micafungin) are reserved for disease that does not respond to voriconazole, and for those unable to tolerate voriconazole therapy. If itraconazole is used, drug levels should be

obtained to ensure a therapeutic range is obtained (because of the drug's erratic bioavailability). Posaconazole oral suspension exhibits erratic absorption, but the delayed-release tablet and intravenous formulation deliver reliable serum drug levels. When the oral suspension is used, therapeutic drug monitoring may be necessary, although clear values have not yet been defined. Currently, data on a recommendation of combination therapy as the first-line approach are insufficient. For salvage therapy, a combination of antifungals with differing mechanisms of action may prove useful. Another option is to switch the antifungal for one with a different mechanism of action.

Special caution must be taken when choosing an antifungal agent for sinus disease, because voriconazole does not offer coverage for disease caused by *Zygomycetes* glomeromycetes (eg, mucormycosis), another common fungal sinus infection in immunocompromised patients. When there is a high suspicion for *Zygomycetes* mucormycosis, or if it cannot be ruled out, amphotericin B is the drug of choice.

Optimal duration of therapy for invasive aspergillosis has not been determined. Most experts advocate treatment for months, and often until the patient is capable of mounting a sufficient immune response. In fact, when a child recovers from invasive aspergillosis, should she/he become immunosuppressed again, antifungal treatment is recommended for prevention of recurrent infection.

Surgical resection of affected tissues is often required as adjunct therapy, especially in select cases of hemoptysis, pericardial disease, empyema, endocarditis, osteomyelitis, sinusitis, and cerebral lesions.

Despite the limited data supporting their use, granulocyte colony-stimulating factors may be given to children with aspergillosis and neutropenia.

### When to Admit

Children with suspected *Aspergillus* infection should be admitted until an accurate diagnosis is made and response to therapy has been demonstrated.

### When to Refer

The care of children with invasive *Aspergillus* infections requires consultation with an infectious disease specialist. For children with suspected sinus disease caused by *Aspergillus*, consultation with an otolaryngologist is also recommended. When the eye is involved, an ophthalmologist should be promptly consulted. In cases in which a biopsy or resection is sought, a surgeon specialist should be consulted.

### Ongoing Care

#### Follow-Up

For patients demonstrating adequate response, voriconazole is available as an oral formulation with excellent bioavailability. Drug levels should be monitored to ensure therapeutic levels are maintained. Patients with poor response will require prolonged hospitalization and investigation.

### Complications

In patients whose immune systems cannot be reconstituted or whose immune suppression cannot be decreased, invasive *Aspergillus* infections are frequently



fatal. Side effects of azole antifungal agents are uncommon. Voriconazole side effects include transient visual disturbances, hepatotoxicity, rash, and visual hallucinations. It should be noted that voriconazole and posaconazole are cytochrome p450 inhibitors. As such, the pharmacokinetics of many medications, including those commonly used after organ and stem cell transplantation, are altered with voriconazole and posaconazole therapy.

### Prognosis

In recipients of HSCT and lung transplantations, the use of prophylactic antifungal agents has dramatically reduced the incidence of invasive aspergillosis. Unfortunately, once invasive aspergillosis occurs, prognosis remains poor. The mortality of invasive aspergillosis in patients with HSCT remains high (55%–80%).

### Prevention

Prophylaxis against invasive aspergillosis is recommended in 3 specific situations: HSCT patients with graft-vs-host disease who are receiving immunosuppressive agents, neutropenic patients with acute myelogenous leukemia, and neutropenic patients with myelodysplastic syndromes. Also, close monitoring of high-risk patients is paramount, because a high index of suspicion is needed for the early detection and treatment of invasive aspergillosis.

## CANDIDA

### Etiology

*Candida* are unicellular yeasts with thin, small cell walls. *Candida* species reproduce by budding. There are more than 150 *Candida* species, of which only a few are pathogenic in humans. *Candida albicans* is the most commonly recovered species causing human disease, followed by *C parapsilosis*, *C tropicalis*, *C glabrata*, and *C krusei*. *C dubliniensis* is similar to *C albicans*, and its importance in human disease was recognized only recently. *C guilliermondii*, *C pseudotropicalis*, *C lusitanae*, *C pelliculosa*, *C rugosa*, *C norvegensis*, and *C inconspicua* are rare causes of human disease.

### Epidemiology

*Candida* was first described as a pathogen in the 1840s when it was recognized as a cause of oral thrush. In recent decades, invasive *Candida* infections involving 1 or more organ systems have become increasingly common. *Candida* infections of the skin and mucus membranes (oropharynx, esophagus, vagina, skin) are regarded as noninvasive forms of disease.

*Candida* species account for the majority of invasive fungal infections in the developed world. In the United States, *Candida* species are the fourth most common cause of nosocomial bloodstream infections in adults, and are the third most common cause of nosocomial bloodstream infections in children. Beginning with the development of antimicrobials decades ago and the subsequent development of life-saving procedures, the increased incidence of invasive *Candida* infections parallels advancements in medical care. Stem cell and solid organ transplantation, the use of chemotherapy for treatment of malignancies, and the implantation of prosthetic devices are all associated with increased

risk of invasive *Candida* infection. Likewise, the increased use of both broad-spectrum antimicrobials and long-term indwelling catheters has contributed to the estimated 207% increase in invasive fungal infections between 1979 and 2000. Unfortunately, the treatment of fungal infections has lagged behind other medical advances, and the mortality of invasive candidiasis remains high.

*Candida* species are commonly found on the skin, gastrointestinal tract, sputum, and female genital tract. The presence of colonizing *Candida* makes it difficult to interpret cultures obtained from these sites. Isolation of *Candida* from a normally sterile site is indicative of a true infection and requires prompt initiation of therapy and further investigation. In particular, it should be noted that blood cultures are rarely contaminated with *Candida*; a blood culture growing *Candida* should be considered diagnostic of invasive *Candida* infection.

### Risk Factors

The most commonly cited factors associated with invasive *Candida* infections include admission to an ICU, use of broad-spectrum antimicrobials, presence of central venous catheters (CVC), use of parenteral nutrition, presence of prosthetic devices, solid organ and stem cell transplantation, surgery (particularly abdominal), severe burns, hemodialysis, use of immunosuppressive drugs (steroids, chemotherapy, immunomodulators), and colonization with *Candida*.

In infants, prematurity, intubation, and gastrointestinal disease have been identified as risk factors for invasive *Candida* infections. Notably, premature neonates with birth weights less than 1,000 g are at increased risk for invasive candidiasis. Interestingly, a study in 2010 that assessed risk factors and predictors of candidemia in a pediatric ICU found a 10.7% risk of developing invasive candidemia in children with an underlying malignancy who had a CVC and had received vancomycin therapy for more than 3 days. This risk increased to 46% when parenteral nutrition and antimicrobial therapy for more than 3 days with anaerobic coverage were also present.

Although *C albicans* remains the most common species causing human disease, non-*albicans* species are becoming increasingly common, often accounting for more than 50% of all isolated *Candida* (cumulatively). Non-*albicans* species are sometimes associated with specific patient factors. For example, *C krusei* infections are more common in patients with stem cell transplants, previous treatment with fluconazole, hematologic malignancy, and neutropenia. *C tropicalis* is more often isolated from neutropenic patients and those with leukemia. *C parapsilosis* is most often seen in neonates and those with CVCs. *C glabrata* is more often isolated from older adults, those previously treated with antifungals, and solid organ transplant recipients.

### Diagnosis

#### Signs and Symptoms

Invasive candidiasis affects various organs and therefore, can cause a wide array of symptoms.

**CANDIDEMIA.** The isolation of *Candida* on blood culture is associated with various symptoms ranging from asymptomatic CVC infection to fever and severe sepsis. Approximately 50% to 70% of candidemic patients will have at least 1 positive blood culture. After the onset of candidemia, multisystem organ failure may ensue quickly. Thus, a positive blood culture requires prompt evaluation and treatment. Candidemia in immunocompromised patients may present as persistent fever despite broad-spectrum antibacterial therapy. In the neonate, symptoms of candidemia are nonspecific and may include temperature instability, lethargy, abdominal distention, hyperglycemia, feeding intolerance, apnea, and persistent thrombocytopenia.

**ENDOCARDITIS.** Fungal endocarditis is rare (<5% of all cases of infective endocarditis), and *Candida* species account for just over half of these cases. *Candida* endocarditis usually presents insidiously: with fever, with or without a murmur, and with positive blood cultures. Echocardiographic lesions are generally larger in *Candida* endocarditis than in bacterial endocarditis.

**OCULAR INFECTIONS.** *Candida* can cause either endophthalmitis or chorioretinitis. Ocular disease is historically regarded as a rare consequence of untreated or inadequately treated candidemia, in which patients rarely develop disease if treated appropriately. As such, a careful retinal examination by an ophthalmologist is an important part of the evaluation of a child with candidemia, and is recommended by the IDSA. In 2011, a prospective study of the incidence and results of ocular lesions in blood culture-proven candidemia showed a 16% incidence of ocular involvement, with just 1.6% of patients exhibiting endophthalmitis.

**CENTRAL NERVOUS SYSTEM.** Invasive candidiasis of the CNS most commonly affects parenchymal tissues and the meninges, with occasional formation of microabscesses. CNS candidiasis is more common in extreme age groups (neonates and elderly) and is often a complication of a neurosurgical procedure. In neonates, the term *hematogenous Candida meningoencephalitis* (HCME) is used. HCME is present in approximately 15% of cases of neonatal candidemia. Long-term follow-up is essential after neonatal HCME, because neurocognitive deficits are common in this condition. The majority of CNS infections are caused by *C. albicans*.

**DISSEMINATED.** Acute disseminated candidiasis occurs most commonly in patients with neutropenia caused by a hematologic malignancy. These patients will have acutely ill presentations, with positive blood cultures and multiorgan involvement. Many will exhibit discrete skin lesions characteristic of small vessel vasculitis.

Chronic disseminated candidiasis is also known as *hepatosplenic candidiasis*. It occurs most often in the severely immunocompromised host with a hematologic malignancy (eg, leukemia). Hepatosplenic candidiasis often presents when neutrophil counts begin to rise after a period of chemotherapy-induced neutropenia. It is characterized by multiorgan lesions (primarily liver and spleen) and typically presents with fever, abdominal pain, hepatosplenomegaly, and an elevated serum alkaline phosphatase.

**OTHER.** Septic arthritis, tenosynovitis, osteomyelitis, urinary tract infections, and pneumonia are other manifestations of invasive candidiasis. Septic arthritis and tenosynovitis caused by *Candida* present similarly to bacterial joint infections: with fever, joint pain, warmth, and erythema. *Candida* osteomyelitis also presents similarly to bacterial osteomyelitis, with nonspecific symptoms including fever and pain. In adults with *Candida* osteomyelitis, disease occurs most commonly in the axial skeleton (vertebrae, rib, and sternum); in children, however, the long bones (femur and humerus) are most commonly affected.

Genitourinary candidiasis occurs most commonly as a consequence of urinary catheter use and resolves with removal of the catheter. However, in neonates and in neutropenic patients, candiduria should be assumed to be a manifestation of renal candidiasis, which typically occurs as a complication of candidemia (and as such, consideration should be given for an extensive workup including a liver/spleen/kidney ultrasound, cardiac echocardiogram, eye examination, and in young infants and symptomatic patients, a lumbar puncture with examination of CSF specimens). Patients with renal candidiasis may present with pyelonephritis, hypertension, rising serum creatinine levels, or ureteral obstruction. Mycetomas (or fungus balls) may be detected with imaging of the genitourinary tract. This complication is uncommon, yet occurs with a higher frequency among neonates with candiduria and/or candidemia.

*Candida* pneumonia is rare, and most often occurs in the setting of neutropenia. This form of invasive disease typically presents with fever and radiologic evidence of disease. Similar to its isolation from a urinary catheter, *Candida* species isolated from an endotracheal tube or tracheostomy site usually reflects colonization rather than infection.

### Differential Diagnosis

Infections caused by *Candida* are clinically indistinguishable from same-site infections caused by other pathogens. Laboratory studies must be undertaken to determine the causative organism.

### Laboratory Findings

For direct visualization, a wet mount is quickly diagnostic and will show hyphae, pseudohyphae, and budding yeast cells. Addition of potassium hydroxide (which clears epithelial cells) aids in the visualization of hyphae and pseudohyphae. Calcofluor white-stained smears are another way to visualize the fungi.

In invasive candidiasis, blood cultures are diagnostic in 50% to 80% of cases, with growth usually detected within 18 to 74 hours. In genitourinary tract candidiasis, urine specimens may show yeast sediment with growth of *Candida*, though interpretation requires caution because true infection must be distinguished from colonization. The presence of *Candida* in urine casts suggests renal tissue invasion.

In the diagnosis of *Candida* meningitis, the CSF may be normal or may demonstrate pleocytosis with a lymphocytic predominance. A wet mount or Gram stain is positive in approximately 40% of cases, and hypoglycorrhachia with an elevated protein count may be seen.

Direct tissue biopsy is often needed for the diagnosis of chronic disseminated candidiasis, because blood cultures are rarely positive. Similarly, *Candida* must be isolated from the synovial fluid for the diagnosis of septic arthritis and tenosynovitis. For osteomyelitis, biopsy of the affected area of the bone is often required because blood cultures are typically negative. Because *Candida* can colonize the respiratory tract, particularly in patients receiving broad-spectrum antibiotics, the accurate diagnosis of *Candida* pneumonia requires a lung biopsy. The biopsy must demonstrate direct invasion of the fungus into the lung parenchyma.

Several nonculture techniques have been developed for the diagnosis of fungal infections. An assay to detect and measure the titer of BDG, a component of the fungal cell wall, has been approved by the FDA. For detection of invasive candidiasis, this assay has a reported sensitivity greater than 65% and a specificity greater than 80%, depending on the study and the associated cutoff value. Expression of BDG is not limited to *Candida*; BDG is also present in *Aspergillus*, *Fusarium*, and *Trichosporon*. The BDG assay will also sometimes detect *Histoplasma*, *Sporothrix*, *Blastomyces*, and *Pneumocystis jiroveci*. False-positive results have been reported in patients receiving hemodialysis with cellulose membranes, in patients receiving intravenous immunoglobulins, and in patients receiving amoxicillin-clavulanic acid and other  $\beta$ -lactam antibiotics. A few bacteria, including *Alcaligenes faecalis*, *Streptococcus pneumoniae*, and *Pseudomonas aeruginosa* also produce BDG and may cause false-positive test results. Notably, this assay has not been validated in children, though a number of studies and reports show promise.

A second nonculture technique developed for the diagnosis of invasive candidiasis is the mannan and antimannan antibody assay. This assay has demonstrated a sensitivity of 80% and a specificity of 85% in the diagnosis of invasive candidiasis, and its sensitivity can be increased by serial testing. Although not yet standardized and not widely available, PCR assays are also used sometimes. In-house methods have shown more than 85% sensitivity and specificity, but no external validation studies have been conducted. Oligonucleotide probes that detect target nucleic acid sequences are also being developed, with the advantage of batch testing, but these are not widely available.

Newer studies are showing that a combination of nonculture diagnostics (BDG, mannan/antimannan antibodies/PCR) may offer increased sensitivity and specificity, leading to a quicker diagnosis of invasive candidiasis and earlier treatment of disease.

Once *Candida* has been identified as the cause of an infection, species determination is important as a predictor of antifungal susceptibility. *C. albicans* and *C. dubliniensis* strains are most often susceptible to the triazoles, polyene, and echinocandin antifungals, *C. glabrata* has an increased incidence of fluconazole resistance, and *C. krusei* is intrinsically resistant to fluconazole. *C. parapsilosis* strains tend to have higher echinocandin minimum inhibitory concentrations (MICs) compared with other species (though clinical significance of this observation remains unclear). *C. lusitanae* strains are resistant to amphotericin B.

For rapid identification of *C. albicans* and *C. dubliniensis*, the germ-tube test is used. An inoculum is placed into serum and it is monitored for germ-tube (hyphae) formation (occurs in <90 minutes). Another way to distinguish *C. albicans* from other *Candida* species is by peptide nucleic acid fluorescent in situ hybridization; this method is quicker but more expensive. Also, special media (eg, chromogenic media, in which species grow with differing pigments) can be used to isolate and identify *Candida*. Older methods of species identification, such as the API20C and API32C, which use biochemical assays to generate fungal profiles unique to different species, continue to be commonly used in today's laboratories.

### Imaging

Children with persistent candidemia and those suspected to have disseminated disease should undergo ultrasound imaging of the liver, spleen, and kidneys to further assess for disease. Echocardiography should also be performed to assess for *Candida*-related valvar and intracardiac vegetations, for annular and intramural abscesses, and for potentially infected intra- and extracardiac thrombi. Lumbar puncture and CNS imaging should be considered for all infants, and for older children with symptoms referable to the CNS. For patients with suspected pulmonary candidiasis, a CT scan is recommended. Lastly, all patients with candidemia should have an ophthalmology evaluation to rule out ocular disease.

### Management

#### Treatment Approach

The isolation of *Candida* from any normally sterile site is diagnostic of infection. As such, antifungal therapy should be initiated immediately. Selection of an appropriate antifungal agent is based on several considerations: How old is the child? Was the child recently treated with a triazole antifungal? What are the child's comorbidities? How ill is the child? Is there suspicion for disseminated or CNS infection? Does the child have intravascular catheters or other implanted foreign bodies? What strains of *Candida* are isolated most commonly in the care environment? What are the susceptibilities of *Candida* species in the care environment?

The following recommendations are extracted from the *Clinical Practice Guidelines for the Management of Candidiasis: 2009*, published by the IDSA.

#### Specific Therapy

Candidemia in the non-neutropenic host may be treated with fluconazole provided there is no recent history of triazole use and no concern for CNS disease and *C. glabrata* or *C. krusei*. An echinocandin is preferred if the patient is moderately to severely ill or was recently treated with a triazole antifungal drug, or if a likely fluconazole-resistant isolate is found (*C. glabrata* and *C. krusei*). As an alternative, moderately to severely ill children may be treated with amphotericin B (lipid formulation [preferred because of its decreased toxicity] or deoxycholate). Voriconazole can be used as step-down therapy for children with *C. krusei* or those with voriconazole-susceptible *C. glabrata*. Because



voriconazole has high intra- and interpatient variability, therapeutic drug monitoring should be performed for all patients being treated with this drug. Patients should be treated for at least 14 days after the first negative culture. Early removal of any indwelling intravascular catheters is essential.

For candidemia in neutropenic children, first-line therapy options include an echinocandin or lipid formulation amphotericin B. Fluconazole may be used if the child has had no recent triazole exposure, is only mildly ill, and is unlikely to be infected with *C glabrata* or *C krusei*. Voriconazole may be used when infection with molds is also suspected. For treatment of *C glabrata*, an echinocandin should be used. When *C parapsilosis* is isolated, fluconazole or liposomal amphotericin B is the drug of choice. In cases of *C krusei*, an echinocandin, liposomal amphotericin B, or voriconazole should be used. Again, patients should be treated for at least 14 days after the first negative culture or for 14 days after resolution of neutropenia (whichever is longer). Early removal of any indwelling intravascular catheters is strongly recommended.

When treating a neonate with candidiasis, disseminated infection is assumed, and treatment with either amphotericin B deoxycholate (lipid formulation amphotericin can be used if genitourinary involvement is excluded) or fluconazole is recommended. Treatment duration is typically 3 weeks; CSF and ophthalmologic evaluation is strongly recommended. Removal of CVCs is strongly advised.

Treatment of *Candida* endocarditis entails a 2-step approach. During the 6- to 8-week period of induction therapy, lipid formulation amphotericin B with or without flucytosine is used. Alternatively, an echinocandin or amphotericin B deoxycholate may be given. Surgical removal of any sized vegetation as well as removal of potentially infected prosthetic material is strongly recommended. Following the course of induction therapy, a protracted course of triazole treatment is recommended. In patients who cannot undergo removal of an infected valve, lifelong suppression therapy with fluconazole is recommended. In neonates, medical treatment alone may suffice, with amphotericin B deoxycholate being the most commonly used drug.

Treatment of *Candida* endophthalmitis requires active consultation with an ophthalmologist. Mild disease may be treated with fluconazole; severe disease should be treated with amphotericin B deoxycholate and flucytosine. For patients intolerant of amphotericin B deoxycholate, lipid formulation amphotericin B, voriconazole, or an echinocandin may be used. Treatment should continue for at least 4 to 6 weeks until there is clinical evidence of disease resolution. Surgical intervention is recommended in severe disease.

For *Candida* infections of the CNS, first-line therapy includes lipid formulation amphotericin B, with or without flucytosine, for several weeks, followed by fluconazole once the patient is clinically stable and a response to therapy is seen. Alternatively, fluconazole monotherapy may be used in patients who do not tolerate lipid formulation amphotericin B. Treatment should continue until signs and symptoms of disease abate and CSF abnormalities have resolved. Although voriconazole achieves high CSF concentrations, no

reports of its use in CNS candidiasis have been published. As such, the use of voriconazole for treatment of CNS *Candida* infections cannot be recommended at this time. Posaconazole crosses the blood-brain barrier poorly, so it is not recommended for treatment of CNS infections.

*Candida* infections of the genitourinary tract require investigation before initiation of treatment. Asymptomatic urinary catheter-associated candiduria is treated with catheter removal; no additional therapy is needed in the normal host. *Candida* urinary tract infections in neutropenic patients, low-birth-weight infants, and symptomatic immunocompetent patients should be viewed as manifestations of systemic infections and are, therefore, treated according to the recommendations for treatment of systemic candidiasis (neutropenic, neonate, and immunocompetent). Cystitis and pyelonephritis should be treated with oral fluconazole for 2 weeks. When a fluconazole-resistant strain is isolated, conventional amphotericin B should be used with or without the addition of flucytosine (for select cases of cystitis, flucytosine may be used alone). For “fungal balls” in the renal pelvis or collecting system, amphotericin B deoxycholate with or without flucytosine should be used until symptoms resolve and cultures are negative. Fluconazole may be an effective option. In neonates with fungal balls, medical therapy alone is usually effective; in older individuals, surgery is strongly recommended. Alternatively, fluconazole may be used when *C glabrata* is not suspected. When treating urinary tract infections, it must be noted that fluconazole is the only triazole antifungal that is excreted predominantly in the urine.

*Candida* osteomyelitis should be treated with lipid formulation amphotericin B for 2 weeks, followed by a 6- to 12-month course of fluconazole. Alternatively, fluconazole may be used for the entire treatment period. Alternative regimens for treatment of *Candida* osteomyelitis also include the use of an echinocandin for 2 weeks, followed by fluconazole for 6 to 12 months. Surgical debridement may be beneficial in some cases. Septic arthritis should be treated with fluconazole for at least 6 weeks or with a combination of lipid formulation amphotericin B (or an echinocandin) for 2 weeks, followed by fluconazole to complete 6 weeks of therapy.

### When to Admit

Children with an invasive *Candida* infection should be admitted until clearance of candidiasis is demonstrated and clinical improvement noted.

### When to Refer

All invasive *Candida* infections require consultation with an infectious disease specialist.

### Ongoing Care

#### Follow-Up

Because neurocognitive deficits are common in neonates with disseminated *Candida* infection, neonates with invasive *Candida* infection will need long-term care, including enrollment into an early intervention program. Children with endocarditis, and those with prosthetic devices that cannot be removed, will need long-term, and possibly lifelong, suppressive antifungal



therapy. Those receiving long-term therapy will need monitoring for adherence and toxicity.

### Complications

As noted before, neonates with disseminated disease are at high risk for developmental delay, and are at increased risk for periventricular leukomalacia, chronic lung disease, and retinopathy of prematurity. Other complications may arise from invasive procedures performed to aid in diagnosis (eg, biopsy) or treatment (eg, vegetation removal, prosthetic device removal, fungal ball resection, medication side effects) of *Candida* disease. Some patients may experience recurrence of infection.

### Prognosis

With reports of mortality as high as 47% and surveys demonstrating 14.5% mortality in adults and 10% in children, prognosis of invasive *Candida* infection continues to be poor. Improved survival has been demonstrated with early treatment initiation (within 12 hours of illness onset). Therefore, a high index of suspicion is needed for invasive *Candida* infection, and should be followed by prompt initiation of antifungal therapy, especially in patients with multiple risk factors.

### Prevention

In neonatal ICUs, the rates of *Candida* infections among very low-birth-weight infants vary widely; anti-*Candida* prophylaxis with fluconazole should be considered for very low-birth-weight infants in units with high incidence of *Candida* infections. Similarly, fluconazole prophylaxis is recommended for high-risk adults in ICUs, particularly in those with high rates of candidiasis. High-risk solid organ transplant recipients (pancreas, small bowel, and high-risk liver transplants [defined as patients with at least 2 of the following risk factors: retransplantation, creatinine >2 mg/dL, choledochojejunostomy, intraoperative transfusion of >40 units of blood products, surgery duration >1 hour, or known *Candida* colonization]) should receive fluconazole or lipid formulation amphotericin for 7 to 14 days after transplantation. In special circumstances, patients with an expected prolonged period of chemotherapy-induced neutropenia may start treatment with fluconazole, posaconazole, or capsosungin during induction therapy and continue for the duration of the neutropenia. Lastly, stem cell transplant recipients with neutropenia should receive fluconazole, posaconazole, or micafungin for the duration of the neutropenic phase.

The physician must be reminded that an important risk factor for invasive *Candida* infection is the use of broad-spectrum antimicrobials. Judicious use of antimicrobial therapy is warranted not only to prevent the emergence of multidrug-resistant bacteria, but also to decrease the incidence of invasive candidiasis.

## CRYPTOCOCCUS

### Etiology

*Cryptococcus* is an encapsulated yeast that is able to reproduce either sexually (*Filobasidiella*) or asexually. More than 30 species have been described, but only 2 are well documented as pathogenic in humans. The most commonly reported species causing human disease is *C. neoformans* (~88.6%). *C. gattii* is the other

common species causing human disease (~11.4%). Mycology advancements led to the division of pathogenic *Cryptococcus* species into 5 serotypes (based on capsular polysaccharides) and 8 molecular types. *C. neoformans* is composed of 3 serotypes and 4 molecular types (*C. neoformans* variant *grubii* [serotype A, molecular type VNI and VNII], *C. neoformans* variant *neoformans* [serotype D, molecular type VNIV], and hybrid *C. neoformans* [serotype AD, molecular type VNIII]). *C. gattii* species is divided into 2 different serotypes and 4 molecular types (serotype B and C, molecular types VGI, VGII, VGIII, VGIV). On a molecular level, with limited data, *C. neoformans* variant *grubii* (serotype A, VNI) is the most commonly isolated species. *C. gattii* VGII deserves special mention because it was recognized as the most commonly isolated species during a 2004–2010 outbreak in North America.

### Epidemiology

*Cryptococcus* species is ubiquitous in nature; ecologic niches are species dependent. *C. neoformans* variant *grubii* (serotype A) and *C. neoformans* variant *neoformans* (serotype D) can be found in the droppings and nests of pigeons, and less frequently in droppings of turkeys, chickens, canaries, and parrots. Historically, *C. neoformans* variant *grubii* (serotype A) has been identified worldwide and *C. neoformans* variant *neoformans* (serotype D) has primarily been isolated in Europe. In contrast, *C. gattii* (serotypes B and C) was not isolated from pigeon droppings, but was most commonly associated with the *Eucalyptus* tree. Historically, it was present in tropical and subtropical areas. However, the emergence of *C. gattii* in Vancouver, British Columbia, Canada, and the Pacific northwest United States since 2001 has changed this association. *C. gattii* is now isolated in a different (temperate) climate, and from different types of trees (fir, maple, and oak trees), as well as freshwater, seawater, and soil.

The emergence of *C. gattii* in British Columbia and the Pacific northwest United States highlights an important change of the environmental niche of the organism, as well as a change in the type of host infected. *Cryptococcus* was recognized primarily as an opportunistic pathogen, that is, one that causes illness in a predisposed host. Historically, most illnesses caused by *Cryptococcus* were found among patients with HIV/AIDS and other severely compromised immune systems. Of the 218 cases reported between 1999 and 2007 in British Columbia, 62% had no immunocompromising condition, whereas only 3 cases occurred in children (2 used inhaled corticosteroids, 1 for a chronic respiratory disease and 1 for a genetic disorder). In contrast, of 60 cases of *C. gattii* infection reported in the United States between 2004 and 2010, 81% had an underlying immunocompromising condition (3 had HIV).

*Cryptococcus* has been widely studied, and a number of virulence factors have been identified. Factors that are recognized as most important include its capsule, its ability to produce melanin, and its thermotolerance. Foremost is the polysaccharide capsule, whose virulence is multifactorial. Its necessity was demonstrated in a study with loss of virulence by an acapsular strain, with its return as the capsule was

restored. The ability of *Cryptococcus* to form melanin is also believed to be an important virulence factor, but the exact mechanism is not well understood. An early animal study demonstrated lower virulence in strains lacking melanin compared with melanin-producing strains. The third important virulence factor is the ability of *Cryptococcus* at both environmental and higher temperatures (ie, 37°C). Growth at higher temperatures is essential for pathogenic microorganisms. Distinction among species is important: it has been noted that *C gattii* infections tend to produce cryptococcomas more often than *C neoformans*, and their presence will affect management.

Invasive infection is largely dependent on the status of the host's immune system and the virulence of the infecting strain. Infection begins with the inhalation of aerosolized organisms (believed to be in the form of either dehydrated yeast or basidiospores) into the alveoli, where alveolar macrophages kill the organism and recruit cytotoxic cells and chemokines. In the majority of hosts, the yeast is fully eliminated. Alternatively, proliferation of the yeast can occur, with or without dissemination of the organism to other sites. In some cases, a small dormant lung-node complex is formed, and the organisms may be reactivated after immunosuppression. Rarely, direct inoculation of the yeast leads to a localized skin infection.

Before the AIDS epidemic, cryptococcal disease was scantily described. With the emergence of AIDS, *Cryptococcus* became a frequently diagnosed opportunistic infection. In developed countries, the incidence of cryptococcal disease in patients with AIDS has decreased with the use of highly active antiretroviral therapy (HAART), but it continues to be a major burden in low-to-middle-income regions, particularly sub-Saharan Africa. In the United States, incidence of disease in patients without HIV infection is estimated at 0.2 to 0.9 in 100,000. A higher incidence is noted in patients with AIDS (2–7 in 1,000) but it is significantly decreased from the pre-HAART era (17–66 in 1,000). In comparison, incidence among patients with AIDS in sub-Saharan Africa is 14 in 1,000, even in the post-HAART era. Worldwide, in patients with HIV/AIDS, approximately 950,000 cases of cryptococcal meningitis are seen each year. Interestingly, cryptococcal disease has remained rare in children, even in children with HIV/AIDS, with an occurrence rate of less than 0.1 per 100 child years. The reason for low incidence of disease in children is not well understood, because it has been shown that children are exposed to *Cryptococcus* at an early age as evidenced by antibody detection.

### Risk Factors

As with most invasive fungal infections, immunocompromised patients have the highest risk of acquiring an invasive cryptococcal infection. Typically, few patients with disease do not have HIV/AIDS or an identifiable risk factor (10%–40%), yet the recent emergence of *C gattii* infection in immunocompetent hosts in British Columbia highlights the importance of heightened vigilance and the need for a high index of suspicion in all patients.

The most important risk factors for invasive cryptococcal disease are HIV/AIDS, long-term use of steroids, solid organ transplant, hematologic malignancy,

and the use of immunomodulators. Also, patients with diabetes, sarcoidosis, CD4 lymphopenia, lymphoproliferative disease, hyper-IgM and hyper-IgE syndromes, renal failure (on peritoneal dialysis), liver disease (cirrhosis), and systemic lupus erythematosus are at increased risk for invasive disease.

Patients with HIV in particular have an increased risk for dissemination and CNS disease. These patients are more likely to have positive blood cultures, less CNS inflammation, a higher fungal burden, and increased antigen titers.

### Diagnosis

#### Signs and Symptoms

Signs and symptoms will depend on the organ infected as well as the host's immune status.

**LUNG.** Patients with cryptococcal lung infection can present with a range of symptoms, from asymptomatic (up to one-third of nonimmunocompromised patients), in which suspicion is raised based on an abnormal chest radiograph, to acute respiratory distress, which is more common in immunocompromised hosts. When presenting with nonspecific symptoms, fever, cough, chest pain, weight loss, and increased sputum production are commonly reported. Onset of disease can be insidious or acute. Immunocompromised patients tend to present with a more rapid progression, and patients with AIDS usually exhibit neurologic symptoms caused by dissemination at the time of diagnosis. Patients infected with *C gattii* will often present with cryptococcomas in the brain. When pulmonary disease is detected, further workup must be undertaken to evaluate for the presence of disseminated disease, and a lumbar puncture must be considered for the evaluation of CNS disease (especially in immunocompromised patients).

**CENTRAL NERVOUS SYSTEM.** Presentation can be acute or subacute. Symptoms of meningitis and meningoencephalitis are common, with headache, fever, cranial nerve palsies, lethargy, coma, and memory loss commonly seen. Alternatively, severe intermittent headaches may be the only symptom, and a few cases can present solely with altered mental status. CNS disease carries a high risk of concomitant elevated intracranial pressure (ICP), most commonly among patients with AIDS. In contrast, non-HIV-infected patients carry a higher risk of an inflammatory meningeal reaction and an increased likelihood of cryptococcomas. Cryptococcomas are also more common in patients infected with *C gattii*.

**PROSTATE.** Prostatic infection typically presents with symptoms of prostatitis, such as frequency, urgency, and dysuria. The prostate is viewed as a site for fungal sequestration. In some instances, relapse is thought to occur when viable organisms are dispersed from the prostate after successful antifungal therapy. Dissemination has also been reported after urologic procedures whereby instrumentation leads to seeding of the yeast.

**EYE.** Before the HIV/AIDS epidemic, CNS disease was associated with eye involvement approximately 45% of the time. Currently, eye disease occurs less frequently. Ocular nerve palsies, papilledema, and retinal disease have been described. Blindness may ensue either by direct fungal invasion of the optic nerve or by damage caused by elevated ICP.

**BONE.** Bone invasion is estimated to occur in approximately 5% to 10% of cryptococcal infection, predominantly because of dissemination of the yeast. Patients can present with pain and swelling, but invasion is commonly detected on unrelated radiographic images.

**BLOOD.** Cryptococcemia is typically seen in the setting of a severely immunocompromised state, for example, in patients with AIDS with a high yeast burden.

**SKIN.** Skin lesions are primarily a noninvasive form of cryptococcal infection, yet in the immunocompromised host, skin involvement usually results from disseminated infection. Noninvasive disease typically presents with a solitary lesion in an immunocompetent patient with environmental exposure to the yeast. When occurring as a result of dissemination, skin lesions may be papular or maculopapular, typically with a soft ulcerated center, often resembling molluscum contagiosum.

**IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME.** Two forms of immune reconstitution inflammatory syndrome (IRIS) exist: unmasking and paradoxical. Unmasking refers to the onset of cryptococcal disease symptoms after successful improvement of the immunocompromised state (eg, initiating HAART, decreasing immunosuppression in solid organ transplant recipients) in patients not known to be infected with the yeast. Paradoxical IRIS refers to the reappearance of old symptoms or the emergence of new symptoms while taking appropriate antifungal therapy after successful improvement of the immunocompromised state (eg, initiating HAART, decreasing immunosuppression in solid organ transplant recipients). Classic manifestations of IRIS in *Cryptococcus* infection appear as exaggerated inflammation (eg, fever, peripheral and mediastinal lymphadenopathy, and CNS signs/symptoms). With paradoxical IRIS, cultures for *Cryptococcus* will remain negative; this is not treatment failure or relapse, but a consequence of an overwhelming host response after an improvement in the status of the immune system. *Cryptococcus*-associated IRIS has been well described in 3 distinct populations: patients with HIV/AIDS, patients with organ transplants, and postpartum women.

### Differential Diagnosis

Pulmonary disease must be differentiated from malignancy (often the disease is diagnosed after a biopsy performed for suspicion of malignancy). Also, other infectious etiologies must be ruled out, such as *P. carinii*, mycobacteria (tuberculous and nontuberculous), and *Nocardia*. Coinfection with other organisms can occur. Skin infection must be differentiated from *Histoplasmosis*, *Coccidiomycosis*, and *Penicillium* with a biopsy.

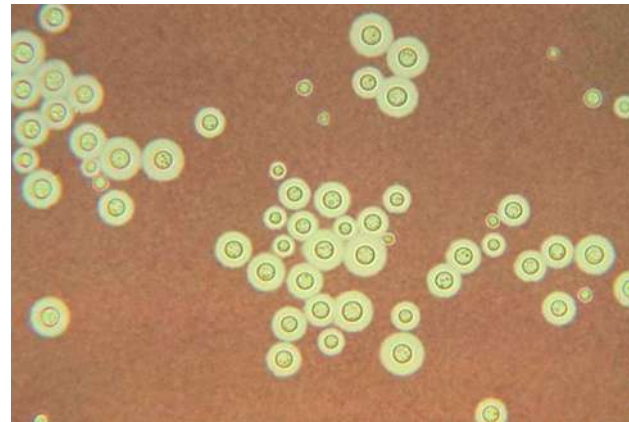
### Laboratory Findings

Diagnosis of *Cryptococcus* infection can be made with direct examination, culture, antigen testing, or PCR. Visualization of the capsule with India ink in the CSF (Figure 254-4) is diagnostic in approximately 30% to 50% of patients without AIDS and 80% of those with AIDS. *Cryptococcus* will appear as a poorly stained gram-positive organism. Other special stains that can be used on histopathology specimens include Calcofluor white, hematoxylin and eosin (H&E), mucicarmine,

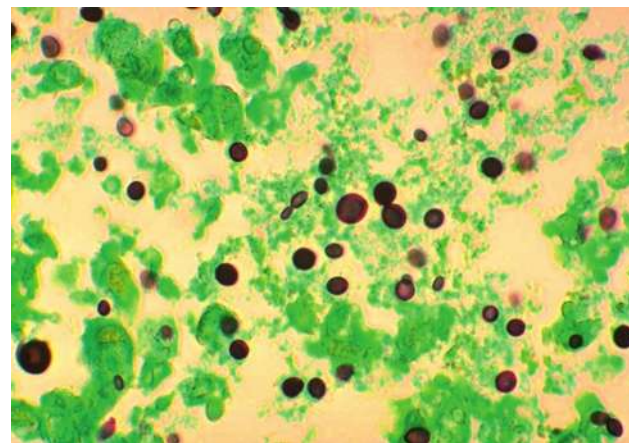
Alcian blue, Fontana-Masson, and Gomori methenamine silver (Figure 254-5).

Current blood culture methods are adequate for detection of *Cryptococcus*, with growth typically seen in 3 to 7 days, though sometimes a longer incubation time is required. *Cryptococcus* can also be identified with biochemical tests and antibody positivity (although the latter exhibits poor sensitivity and specificity). PCR technology is being developed to aid in the diagnosis of infectious diseases. To date, no FDA-approved PCR test for the detection of *Cryptococcus* exists, but there are some homegrown and commercial tests available demonstrating excellent sensitivity and specificity.

One of the most commonly used methods for the diagnosis of invasive disease is antigen detection. Three different assays exist: latex agglutination, an enzyme immunoassay (EIA), and lateral flow assay (approved in July 2011). These assays can be used on CSF and serum samples. The sensitivities of the antigen detection methods depend on the host's immune status, the type of disease, and the kit used. Also,



**Figure 254-4** *C. neoformans* using a light India ink staining preparation. (Courtesy Red Book Online. [redbook.solutions.aap.org](http://redbook.solutions.aap.org))



**Figure 254-5** Cryptococcosis of lung in patient with AIDS (methenamine silver stain). (Courtesy Red Book Online. [redbook.solutions.aap.org](http://redbook.solutions.aap.org))



when appropriate, caution must be taken, because the prozone effect has been well described in these assays (manage by dilution of the specimen). For the latex agglutination assays, sensitivity reaches 100% in patients with AIDS regardless of location of disease, whereas in HIV-negative patients with pulmonary disease, sensitivity can be as low as 56%. Overall specificity of the test is 93% to 98%. The EIA has a reported sensitivity of 93% to 100% and a specificity of 96% to 98% across serum and CSF samples in patients with HIV. These assays, when handled properly, have a low false-positive rate (can occur in the presence of rheumatoid factor or may cross-react with *Trichosporon*). False-negative results may be seen early in infection or in chronic indolent disease. The lateral flow assay has demonstrated CSF sensitivity and specificity greater than 99%, and serum sensitivity of 92% in HIV-infected patients with cryptococcal meningitis. More studies are needed with this detection assay. Thus far, this assay appears promising, especially in resource-limited countries, because it is cheaper and less labor intensive and provides results within minutes. Antigen detection assays can provide titer quantification, whereby a higher titer is associated with a higher burden of yeast, yet no correlations with outcomes have been made.

Several methods are available to differentiate among serotypes. Antibodies to capsules can be assessed, but this method is not very sensitive or specific and not commercially available. Biochemical tests can be used and serotypes B and C can be differentiated because they assimilate glycine, whereas serotypes A and D do not. Canavanine glycine bromothymol blue agar can be used to distinguish *C neoformans* variant *neoformans* from *C gattii*. Growth and a color change to medium blue will occur with *C gattii*, whereas little to no growth with yellow or green color is indicative of *C neoformans* variant *neoformans*. Lastly, molecular tests have been developed, but they lack standardization. These tests are also expensive and not readily available; work is in progress to standardize and facilitate them.

### Imaging

Chest imaging with lung disease is not specific and most commonly demonstrates a noncalcified node or multiple nodules. Other presentations include infiltrates, hilar adenopathy, cavitations, and pleural effusions. Immunocompromised hosts tend to have alveolar and interstitial findings more often.

In the setting of CNS disease, cryptococcomas may be seen on CT as small ring-enhancing lesions. Non-enhancing pseudocysts can also be seen on CT, most commonly in immunocompromised hosts. Hydrocephalus can be seen as a complication of meningitis.

Bone lesions typically present as lytic lesions with or without cold abscesses.

## Management

### Treatment Approach

The goal of therapy in CNS and disseminated disease is rapid sterilization; in pulmonary disease, the goal of treatment is control of signs and symptoms and

prevention of dissemination. Initiation of antifungal therapy must accompany assessment of underlying host risk factors with appropriate corrections. Treatment is targeted toward the type of infection, with duration of therapy also dictated by disease and host factors.

The following recommendations are extracted from the *Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010*, published by the IDSA. It is important to note that recommendations for treatment in children are extrapolated from adult data.

### Specific Therapy

**PATIENTS WITH HIV INFECTION.** Treatment of all forms of invasive *Cryptococcus* disease in HIV-infected individuals involves a 3-step approach: induction, consolidation, and maintenance. Induction includes amphotericin B deoxycholate (liposomal formulations can be used in patients who do not tolerate the conventional formulation) plus flucytosine for at least 2 weeks; this combination was demonstrated to be the quickest fungicidal regimen. Consolidation then follows with at least 8 weeks of high-dose fluconazole. Amphotericin B monotherapy can be used as induction therapy (when flucytosine is not available or not tolerated) for 4 to 6 weeks. Alternatively, amphotericin B plus high-dose fluconazole for 2 weeks can be used as induction therapy. High-dose fluconazole plus flucytosine is another alternative, but must be used for 6 weeks before starting consolidation therapy. When fluconazole monotherapy is used, high-dose therapy for 10 to 12 weeks is recommended for induction and consolidation. For the maintenance phase, fluconazole is recommended. Itraconazole is a less desirable alternative, and weekly amphotericin B infusions can be used in those who are unable to tolerate azoles.

For patients not receiving prior antiretroviral therapy, institution of HAART should be delayed for 2 to 10 weeks after the start of antifungal therapy to decrease the risk of IRIS. In adults, after 12 months of antifungal therapy, maintenance therapy can be stopped in patients receiving HAART who have a CD4 count greater than 100 cells/mm<sup>3</sup> and an undetectable viral load for at least 3 months. A similar recommendation for asymptomatic children older than 6 years of age has been made.

**ORGAN TRANSPLANT RECIPIENTS.** Similar to HIV-infected patients, treatment of CNS, moderately severe-to-severe non-CNS, disseminated, and severe pulmonary *Cryptococcus* disease in organ transplant recipients involves a 3-step approach. Induction therapy consisting of liposomal amphotericin B plus flucytosine for 2 weeks is followed by a consolidation phase of at least 8 weeks of high-dose fluconazole. Alternatively, when amphotericin B is used as monotherapy, the induction phase is prolonged to 4 to 6 weeks. Suppressive therapy consists of fluconazole for 6 to 12 months.

Treatment of mild-to-moderate non-CNS disease (including isolated pulmonary disease) consists of higher-dose fluconazole for 6 to 12 months (for all 3 phases of treatment). Liposomal amphotericin is preferred because the majority of transplant recipients will also be receiving a calcineurin inhibitor and the



use of conventional amphotericin with this agent is associated with increased risk of nephrotoxicity. Immunosuppressive therapies should be reduced in a cautious fashion to lower the risk of IRIS.

**PATIENTS WITHOUT HIV INFECTION AND TRANSPLANTS.** Treatment of CNS, severe pulmonary cryptococcal disease, and cryptococemia in this population also follows a 3-step approach. Patients exhibiting neurologic complications should receive induction therapy with amphotericin B plus flucytosine for 6 weeks followed by consolidation with high-dose fluconazole for at least 8 weeks. Maintenance therapy with fluconazole is then used and should last for at least 6 to 12 months. Patients without neurologic complications and with sterile CSF specimens after 2 weeks of treatment can receive a shortened 4-week induction treatment with combination therapy, followed by an 8-week consolidation phase with high-dose fluconazole, then the 6- to 12-month maintenance treatment with fluconazole. Patients who do not tolerate conventional amphotericin B can be treated with a liposomal formulation instead. Alternatively, patients with excellent response after 2 weeks who are at low risk can be treated with an induction time of 2 weeks (combination therapy) followed by fluconazole (high dose for the 8-week consolidation phase and standard dose for the 6–12 months of maintenance therapy). In cases in which flucytosine is not given, not tolerated, or interrupted, amphotericin induction monotherapy should be extended by at least 2 weeks.

Mild-to-moderate pulmonary disease and single site disease (not CNS or blood) in the absence of severe immunosuppression can be treated with fluconazole monotherapy for 6 to 12 months.

When infection is caused by *C. gattii*, length of treatment is dictated by imaging results. Presence of cryptococcomas will require prolonged therapy (corticosteroids are sometimes added to therapy) in both CNS and pulmonary infections. Large cryptococcomas may need surgical excision.

**COMPLICATIONS.** In cases of persistent disease, immune status must be re-evaluated and corrected when possible. Typically, relapse is caused by inadequate primary therapy and/or poor medical therapy compliance. Drug susceptibility testing should be considered at this point, because resistance has been described, although rarely. Fluconazole MICs greater than 16 mcg/mL and flucytosine MICs greater than 32 mcg/mL reflect fungal resistance. Salvage therapy with voriconazole and posaconazole has been used with some success. Interferon- $\gamma$  has been used in conjunction with antifungal therapy as well as salvage therapy with some success.

With CNS disease, elevated ICP can occur. CSF pressure should be measured on initial lumbar puncture and should be repeated in the face of focal neurologic symptoms or impaired mentation. For persistently elevated pressures, serial (daily) lumbar punctures can be performed or placement of a lumbar drain or ventriculostomy can be considered. Permanent ventriculoperitoneal shunts are sometimes required in the setting of continued elevated pressures and can be placed during an active infection if clinically necessary.

### When to Admit

Children with an invasive *Cryptococcus* infection should be admitted until clearance of the fungus is demonstrated and clinical improvement noted.

### When to Refer

Invasive *Cryptococcus* infections require complex care; consultation with an infectious disease specialist is recommended. Also, for CNS disease with increased ICP or cryptococcomas, consultation with neurosurgery is often needed.

### Ongoing Care

#### Follow-Up

Children whose cryptococcal disease is effectively treated but continue with immunosuppression should have continued prophylaxis depending on the level and extent of immunosuppression.

### Complications

Complications related to antifungal therapy may develop. Flucytosine can cause cytopenia, and drug levels should be monitored. If itraconazole is used, because of its erratic absorption, drug levels should be monitored to ensure a therapeutic range. Also, with newer agents (voriconazole and posaconazole), drug levels may need to be monitored as well (data lacking for cryptococcal disease). At times, persistence of fungal disease is encountered. When this occurs, ensure that immunodeficient states have been addressed (eg, initiation of HAART, decrease of immunosuppressants) and extend the induction phase. Also, doses of antifungal agents may need to be increased and a change in agent may be necessary. Determining the susceptibility profile is sometimes needed, although generally *Cryptococcus* is susceptible to amphotericin B, flucytosine, and fluconazole. Also, with CNS disease, eye involvement leading to blindness may occur. Another complication of CNS disease is an elevated ICP, which may require specific therapy. Another complication often seen is IRIS. No change in therapy is required, but with severe CNS symptoms (CNS inflammation with increased ICP), corticosteroids could be considered. CNS disease can involve the development of cryptococcomas; in such cases, treatment is prolonged as previously described. Corticosteroids are sometimes needed in the setting of mass effect and surrounding edema. Pulmonary disease can result in acute respiratory distress syndrome; supportive care is needed and corticosteroid therapy is sometimes warranted.

### Prognosis

*Cryptococcus* mortality assessments vary within geographic/economic regions. In high-income regions a 9% mortality rate is described; in low-to-middle-income regions, a 55% mortality rate is described; and in sub-Saharan Africa, a 70% mortality rate is described. In Zambia, a 2001 study showed a 100% 6-month mortality rate using fluconazole monotherapy. During the 1999–2007 *C. gattii* outbreak reported in Vancouver, British Columbia, an 8% case-fatality rate was reported. Globally, in patients with HIV/AIDS, cryptococcal meningitis is responsible for an average of 600,000 deaths within 3 months of infection.

### Prevention

In adults with HIV who live in *Cryptococcus*-endemic areas or have a high occupational risk, fluconazole prophylaxis is recommended when the CD4 count is less than 150 cells/mm<sup>3</sup>. In contrast, no such recommendation exists for children with HIV, because of the low incidence of disease. Further studies are needed to determine antigen and antibody reactions to formulate a vaccine that will provide a balanced level of protection for individuals with differing immune statuses.

## GLOMEROMYCETES

### Etiology

Glomeromycota is a phylum belonging to the fungi kingdom. With advances in molecular mycology, taxonomy of the Glomeromycota has been updated. Previously, phylum Zygomycota contained 8 orders, including the orders Mucorales and Entomophthorales. Taxonomic revisions have led to the abolition of phylum Zygomycota, and the creation of 4 subphyla within the Glomeromycota. Relevant to human disease are subphyla Mucormycotina (orders Mucorales and Mortierellales) and Entomophthoramycotina (order Entomophthorales). Of the Glomeromycota, members of the order Mucorales cause most human disease; this disease is commonly referred to as *mucormycosis*.

Glomeromycosis produces aseptate or pauciseptate hyphae and reproduces both sexually and asexually with the formation of zygospores (Figure 254-6). These spores are small and easily aerosolized; inhalation of the spores is the primary mechanism of infection. The hyphae form is responsible for angioinvasion and dissemination, which are characteristic of mucormycosis tissue infections.

### Epidemiology

Mucormycetes are found throughout the environment, commonly in spoiled matter such as bread, fruits, vegetables, and soil. They can also be found in animal excreta and can colonize environmental surfaces such as bandages, needles, and tongue depressors; nosocomial cases have been linked to contact with these contaminated objects. Also, there may be an association with

extremes of weather: following hurricanes Katrina and Rita, a cluster of infections with a rare *Mucor* species, *Syncephalastrum*, was reported. Similarly, following a tsunami in Southeast Asia, wound infection with *Apophysomyces elegans* was described. In 2011, following a tornado in Joplin, Missouri, multiple cases of cutaneous mucormycosis caused by *Apophysomyces* were reported.

Mucormycosis follows *Candida* and *Aspergillus* as the third most common cause of invasive fungal infection, yet the true incidence of invasive mucormycosis is not known. In the United States, the annual incidence of mucormycosis was estimated by Rees and colleagues to be 1.7 cases per million people, equaling approximately 500 cases a year. In France, an incidence of 1.2 per million people was reported in 2002. Notably, an increase in mucormycosis was reported in high-risk patients treated or receiving prophylaxis for *Aspergillus* infection with voriconazole (an azole antifungal with no activity against mucormycetes). Organisms belonging to the subphylum *Mucorales* are the most commonly reported Glomeromycetes causing human disease. *Rhizopus*, followed by *Mucor*, were the most prevalent in a review of 929 clinical cases. Organisms from the family *Cunninghamella* followed. Members from the subphylum Entomophthorales accounted for approximately 7% of isolated Glomeromycetes in the same review.

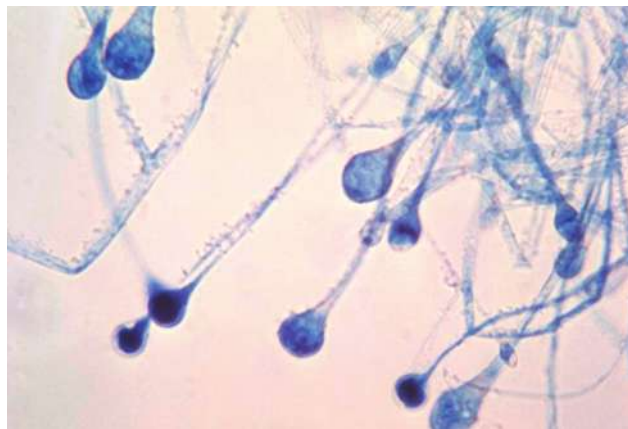
Entomophthoramycotina typically cause skin and subcutaneous tissue disease. Organisms include *Conidiobolus* and *Basidiobolus*. These fungi are commonly found in soil worldwide, yet most cases of infection are located in tropical Africa, South America, Central America, and Asia. *Basidiobolus* was recently described as causing gastrointestinal disease in patients in the United States.

As with most invasive fungal infections, despite multiple medical advances, treatment of infection has not progressed much and the mortality of invasive mucormycosis remains high (~50%). In children, mortality approaches 90% without treatment, but decreases to 36% with appropriate therapy. Site of disease and age prove to be important determinants of mortality. In a study in children, cerebral and gastrointestinal disease were associated with a 100% mortality rate, disseminated disease was associated with an 88% mortality rate, and cutaneous disease showed a 0% mortality rate. Another review showed a mortality rate of 64% in neonates and 56% in children, compared with 53% in adults.

Five common forms of invasive mucormycosis are described—rhinocerebral, pulmonary, gastrointestinal, disseminated, and cutaneous—as well as a few uncommon presentations.

### Risk Factors

Persons who are malnourished, those with poorly controlled diabetes mellitus, metabolic acidosis, trauma, and persistent neutropenia, as well as iron-overloaded patients (especially those receiving deferoxamine therapy) have an increased risk of invasive mucormycosis. High-risk transplant recipients (bone marrow and solid organ), especially those receiving steroid therapy, also have an increased risk of invasive mucormycosis.



**Figure 254-6** This photomicrograph reveals a number of young sporangia of a *Mucor* spp fungus. (Courtesy Red Book Online. [redbook.solutions.aap.org](http://redbook.solutions.aap.org))

Phagocytosis is an integral part of the host defense against mucormycetes. Neutropenic patients lack sufficient cells to effectively kill the fungus. Steroids impair the migration and phagolysosome function of macrophages. Similarly, patients with diabetic ketoacidosis demonstrate impaired neutrophil chemotaxis. Deferoxamine is of special mention: its use supports invasive mucormycosis because this agent acts as a siderophore for Mucorales.

Infection most often occurs after inhalation of the small-aerosolized spores, thus most infections occur in the sinuses and/or lungs. In immunocompetent hosts, direct inoculation is a more common portal of entry. Rarely, ingestion of spores can be the source of infection. The site of disease also differs by host status; rhinocerebral disease is the most common type of infection in diabetic patients. Transplant recipients and patients with malignancy are more likely to present with pulmonary disease. Patients receiving injected drugs tend to present with cerebral disease, whereas healthy hosts typically present with cutaneous lesions. Those receiving deferoxamine therapy commonly present with pulmonary, rhinocerebral, or generalized disease.

## Diagnosis

### Signs and Symptoms

Presentations of invasive disease depend on the site of infection and upon host factors.

**RHINOCEREBRAL INFECTIONS, INCLUDING RHINOSINUSITIS, PANSINUSITIS, RHINO-ORBITAL DISEASE, AND RHINOCEREBRAL INFECTION.** Symptoms of the various rhinocerebral infections often overlap; commonly reported ones include facial pressure, nasal obstruction and/or congestion, epistaxis, headache, mouth pain, otologic symptoms, hyposmia/anosmia, and fever. The presence of cough suggests that lung involvement has occurred. The angioinvasive nature of the fungus may lead to rapid development of necrosis (an eschar) in the area involved. Rapid progression with extension to the orbits (eyelid edema, chemosis, ptosis, proptosis with ophthalmoplegia) and the brain (epidural and subdural abscesses as well as cavernous and sagittal sinus thrombosis) can occur.

**PULMONARY.** Patients typically present with persistent fever despite broad-spectrum antimicrobial therapy, as well as with nonproductive cough, pleuritic chest pain, and dyspnea. In some cases, chest wall cellulitis can occur. With angioinvasion of large blood vessels, hemoptysis can occur.

**GASTROINTESTINAL.** Gastrointestinal invasive mucormycosis is uncommon and is rarely diagnosed antemortem. In gastrointestinal mucormycosis, ingestion of the spores in extremely malnourished patients and in those with severe systemic illness and systemic immunosuppression leads to disease. In neonates, the presentation will resemble necrotizing enterocolitis, whereas neutropenic patients typically develop a masslike lesion near the appendix or ileum. Neutropenic fever, typhilitis (neutropenic enterocolitis), and hematochezia can also be presenting symptoms.

**DISSEMINATED.** Antemortem diagnosis of disseminated mucormycosis is also rare. Symptoms are nonspecific and rapidly progressive. Pneumonia is common, as is brain involvement.

**SKIN AND SOFT TISSUE.** This spectrum of infection is primarily noninvasive, especially in the healthy host. However, in neutropenic patients who continue to be immunosuppressed, disseminated disease may ensue. Typically, an area of cutaneous erythema and induration develops, which may progress to involve the subcutaneous tissue and bone. Necrotizing fasciitis occurs rarely.

**OTHER.** Less commonly invasive presentations of mucormycosis include peritonitis, tracheitis, mediastinitis, endocarditis, and brain abscesses. Peritonitis has been described in patients who receive continuous ambulatory peritoneal dialysis with history of a prior or concurrent central line infection.

### Differential Diagnosis

Rhinocerebral disease presents similarly to other causes of sinusitis with the exception of the characteristic angioinvasive progression and extension to nearby structures. The absence of necrosis early in the disease course of a high-risk host does not eliminate mucormycosis as a diagnostic possibility.

Pulmonary disease caused by mucormycetes is virtually indistinguishable from invasive pulmonary aspergillosis, especially in patients with hematologic malignancies. The presence of concomitant pansinusitis, history of prophylactic drug use against *Aspergillus* (and not mucormycetes), and the lack of a positive *Aspergillus* galactomannan antigen test result point toward mucormycosis as the cause of the fungal pulmonary disease. Gastrointestinal disease will present in the same manner as other acute intra-abdominal infectious processes, such as enteritis, appendicitis, necrotizing enterocolitis, and typhilitis. Diagnosis of skin infection caused by mucormycetes requires a biopsy.

### Laboratory Findings

Diagnosis of infections caused by mucormycetes is almost always based on histopathologic evidence of fungal tissue invasion. On histopathology stains, mucormycetes can be distinguished from other molds by their broad, thin-walled, wide-branching, and ribbon-like, mostly aseptate, hyphae. Sporangia are rarely seen in tissue. Commonly used stains include Gomori methenamine silver, periodic acid-Schiff, and Calcofluor white stains. Entomophthoromycotina can sometimes be distinguished from mucormycotina on histopathology stains, because of the presence of eosinophils surrounding the hyphae.

Culture is required to differentiate among species once a diagnosis of mucormycosis is made, because most species are morphologically similar. However, cultures are only positive about 50% of the time. To enhance growth and recovery of the mold, mincing (instead of homogenizing) tissue and incubation at less than 37°C with relative anaerobic conditions are advised. Empirical antifungal therapy should be instituted regardless of culture results, because histopathology is sufficient for diagnosis, and culture results, although desirable, are delayed and often unnecessary.

Currently, no mucor-specific serology tests are available. Molecular testing using PCR assays for mucor nucleic acid is available at few research institutions; however, further studies are needed before



PCR-based fungal diagnostic tests can be validated and made available commercially.

### Imaging

In rhinocerebral disease, CT and MRI of the brain and sinuses usually reveal patterns suggestive of sinus disease: mucosal thickening, air-fluid levels, and bony erosion. Orbital mucosal thickening may be visualized, and is usually detected earlier on MRI than on CT. Thickening of the extraocular muscles can also signify orbital infection. Serial imaging is necessary to monitor disease progression and treatment response.

In pulmonary disease, chest radiographs may show lobar consolidation, nonspecific infiltrates, masses, nodules, and even cavities; frequently, the upper lobes are affected. Following angioinvasion, wedge-shaped areas of infarction can be seen. CT can show disease before a radiograph, usually presenting as multiple nodules and pleural effusions. Also, similarly to invasive aspergillosis, halo and air crescent lesions can be seen on CT.

### Management

#### Treatment Approach

Treatment of mucormycosis should begin as soon as disease is suspected and before a definitive diagnosis is made. Combined surgical and antifungal therapy is most often used. Surgery is paramount; because of the angioinvasive nature of the mucormycetes, antifungal agents often fail to penetrate infected tissue effectively.

Current treatment guidelines are based on case reports and data reviews of adult disease. Induction therapy with high-dose amphotericin B (a liposomal preparation is preferred) for 3 weeks followed by a prolonged course with posaconazole (if tolerated) is the current suggested regimen. Further, addition of an echinocandin (anidulafungin, caspofungin, micafungin) for combination therapy during induction is recommended by some experts. Glomeromycetes are intrinsically resistant to echinocandins, yet animal studies have demonstrated fungal killing synergy when echinocandins are used in combination with a polyene antifungal; this combination therapeutic approach has been supported by clinical reports.

During induction antifungal therapy, workup should be continued to evaluate the extent of fungal disease. Also, whenever possible, surgical excision of the affected tissues should be performed. In children, appropriate antifungal therapy reduces the risk of death by 92%, and surgery reduces the risk by 84%. Immunosuppression and hyperglycemia should be evaluated and corrected whenever possible.

Following induction therapy, posaconazole can be used for the remainder of the treatment course provided the patient's condition has improved and the drug is tolerated. Posaconazole oral suspension exhibits erratic absorption, but the delayed-release tablet and intravenous formulation deliver reliable serum drug levels. When the oral suspension is used, therapeutic drug monitoring may be necessary though clear values have not yet been defined (concentration greater than 1 mcg/mL is generally sought). It may be prudent to provide an overlap in treatment with amphotericin (with or without an echinocandin) and posaconazole until therapeutic posaconazole levels are attained.

When there is insufficient response to therapy, the dose of amphotericin B can be increased. Consideration may also be given to administration of granulocyte-macrophage colony stimulating factors and/or interferon- $\gamma$ . Hyperbaric oxygen is yet another supplemental therapy that can be used, mostly in cutaneous disease. Deferasirox, an iron chelator shown not to act as a siderophore (unlike deferoxamine), had shown promise, yet a recent phase II trial showed a higher mortality rate at 90 days with deferasirox treatment. Further studies are warranted given the limited sample size and imbalances of underlying disease at randomization in this study. Nonetheless, treatment with deferasirox is not currently recommended as first-line therapy for the treatment of mucormycosis.

### Specific Therapy

Antifungal therapy should be initiated at the first serious suspicion of mucormycosis, before confirmation of disease, because early presumptive therapy is associated with improved clinical outcomes. A significant increase in mortality with the delay of effective therapy has been described.

Standardized antifungal susceptibility testing has shown that Glomeromycetes are generally susceptible to amphotericin B and posaconazole, and are resistant to most other antifungal agents currently available. Current antifungal treatment of mucormycosis is amphotericin B alone or in combination with other agents previously described. Duration of therapy is not defined; most therapeutic courses are tailored individually, and use radiographic resolution and immune reconstitution as therapeutic endpoints.

### When to Admit

All children with suspected or proven mucormycosis should be admitted for aggressive evaluation and empirical therapy until demonstration of clearance and clinical improvement.

### When to Refer

All children with suspected or proven mucormycosis should be approached with a multidisciplinary team, including infectious disease specialists, ophthalmologists, otorhinolaryngologists, neurosurgeons, and clinical pharmacists.

### Ongoing Care

#### Follow-Up

Patients who recover from invasive mucormycosis infection and continue to require immunosuppression may benefit from antifungal prophylaxis with an anti-mucormycosis agent such as posaconazole. As noted before, patients receiving oral suspension posaconazole therapy should undergo regular therapeutic drug monitoring. Also, many patients who survive rhinocerebral diseases will have undergone disfiguring debridement surgeries. Such patients will require intensive psychological support. Reconstructive surgery, when possible, should be considered.

### Complications

Complications of mucormycosis are related to both disease and treatment. Severely immunocompromised patients and those with erosive disease will experience tissue damage, as a consequence of infection as



well as surgical management. Sometimes wide resections are necessary to control progressive disease. In the case of cutaneous disease, the innate integument barrier may further break down. The prolonged and high doses of antifungal agents also pose risks of complications, most notably renal and hepatic toxicity, and Q-T interval prolongation.

### Prognosis

Early treatment of suspected mucormycosis is essential; delayed therapy is associated with a twofold increase in the 12-week mortality rate. Mucormycosis survival is multifactorial because disease site, underlying host factors, and age can affect outcomes. In children, overall mucormycosis mortality, despite appropriate therapy, is 36% to 56%. One review demonstrated 62% survival in adults treated with antifungal therapy and 57% survival in patients treated with surgery, whereas patients treated with a combination of surgery and antifungal therapy had a 70% survival rate.

### Prevention

Prevention of mucormycosis is primarily directed at reducing risk factors, including controlling diabetes, using chelating agents other than deferoxamine to treat iron overload, and, when possible, reducing or correcting immune suppression. It should be noted that an increase in mucormycosis has been reported in high-risk patients. This increased rate of mucormycosis correlates with the introduction of voriconazole as prophylaxis against *Aspergillus* infections. Fortunately, mucormycosis remains a rare disease. As a consequence of the rarity of mucormycosis, routine antifungal prophylaxis directed against the mucormycetes is not generally indicated, even among high-risk patients.

## HISTOPLASMOSIS

### Etiology

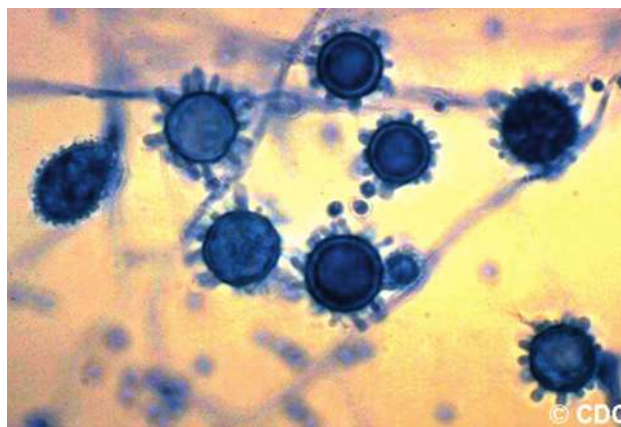
The dimorphic fungus *Histoplasma capsulatum* causes histoplasmosis. *H. capsulatum* grows in the environment in the mycelial (mold) form and converts to the yeast form in tissues at body temperature.

### Epidemiology

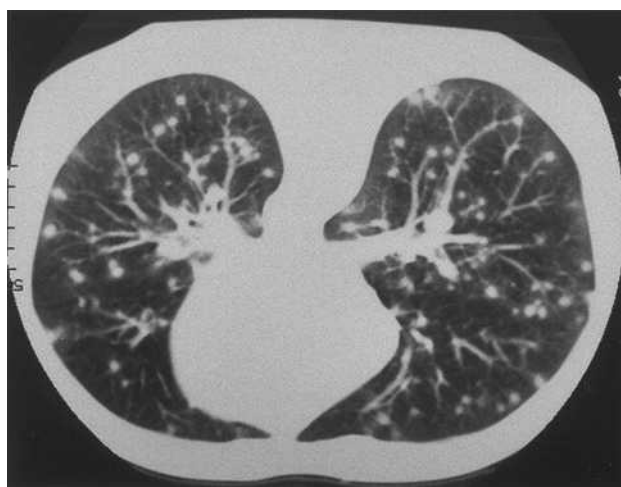
In the United States, *H. capsulatum* is endemic mostly in the central and southeastern states, along the Mississippi, Ohio, and Missouri river valleys. Internationally, *H. capsulatum* is found predominantly in eastern and southern Europe, parts of Africa, eastern Asia, and Australia. In epidemiologic studies, skin test reactivity against *H. capsulatum* commonly develops in people residing in hyperendemic areas. The mycelial form is found in moist soil, with growth facilitated by droppings of bat, bird, and chicken.

### Risk Factors

Infections occur sporadically or in outbreaks, and are associated with aerosolization of spores (Figure 254-7), typically under dry and windy weather conditions. Endemic area activities that have been linked to development of infection include gardening activities; playing in barns, hollow trees, caves, or bird roosts; excavation; and demolition, cleaning, or renovation of



**Figure 254-7** Asexual spores (conidia) of *Histoplasma capsulatum*. (Courtesy Red Book Online. [redbook.solutions.aap.org](http://redbook.solutions.aap.org))



**Figure 254-8** Computed tomography scan of lungs showing classic snowstorm appearance of acute histoplasmosis. (Courtesy Red Book Online. [redbook.solutions.aap.org](http://redbook.solutions.aap.org))

contaminated buildings. Person-to-person transmission of histoplasmosis does not occur. The severity of illness depends on the extent of exposure, size of inoculum, strain-specific virulence, and host immune status.

### Diagnosis

#### Signs and Symptoms

Infection with *H. capsulatum* has a wide spectrum of clinical manifestations. Symptomatic infection occurs in fewer than 5% of infected individuals. Based on the site, duration, and pattern of infection, histoplasmosis is classified into 3 types: acute pulmonary infection (Figure 254-8), chronic pulmonary histoplasmosis, and progressive disseminated histoplasmosis.

As noted before, more than 90% of patients with acute pulmonary infection are asymptomatic. For patients who become symptomatic, the incubation period for histoplasmosis is usually 1 to 3 weeks after exposure. Symptomatic disease occurs more commonly in

young children or in older adults. The prodrome of histoplasmosis is a flulike illness with fever, cough, headache, malaise, myalgia, abdominal pain, and chills. Intense exposures can cause diffuse pulmonary involvement, causing severe dyspnea. Asymptomatic pleural effusions can be present in up to 10% of infected individuals. Pericarditis and enlarged hilar and mediastinal lymph nodes are present in 5% to 10% of patients. Joint pain and skin lesions such as erythema nodosum occur most frequently in women and adolescents.

Chronic pulmonary histoplasmosis, an opportunistic infection encountered in the adult population, is rare in children. Pathologically, chronic histoplasmosis is characterized by centrilobular emphysema.

Progressive disseminated histoplasmosis can develop in healthy infants and children younger than 2 years of age. Fever can be present for weeks before the diagnosis is made. Other signs of progressive disseminated histoplasmosis in infants include failure to thrive and massive hepatosplenomegaly. If untreated, progressive disseminated histoplasmosis is followed by diffuse adenopathy, pneumonia, mucosal ulceration, pancytopenia, disseminated intravascular coagulopathy, and gastrointestinal tract bleeding. Meningitis occurs in about 60% of infected infants. Immunocompromised patients with cellular immune dysfunction can develop progressive disseminated histoplasmosis followed by acute pulmonary infection. Progressive disseminated histoplasmosis is an AIDS-defining illness in an HIV-infected individual.

### Differential Diagnosis

The differential diagnosis of symptomatic pulmonary histoplasmosis includes blastomycosis, coccidioidomycosis, and tuberculosis. Noninfectious etiologic considerations with mediastinal/hilar lymphadenopathy are lymphoma and sarcoidosis. Progressive disseminated histoplasmosis with pancytopenia, hepatosplenomegaly, and gastrointestinal hemorrhage can mimic reticuloendothelial or primary gastrointestinal tract neoplasm. Because severe disseminated histoplasmosis can be an opportunistic infection, screening for immunodeficiency disorder is warranted in an otherwise healthy individual infected with disseminated disease with no known risk factors.

### Laboratory Findings

Culture, serologic tests, tissue and body fluid examination, and EIA for *Histoplasma* antigen in the urine, serum, CSF, and bronchoalveolar lavage fluid are the principal laboratory specimens used for diagnosis.

Despite a long turnaround time, isolation of *Histoplasma* in culture is the definitive method of diagnosis. Culture specimens can be obtained from blood, bone marrow, sputum, and tissue. The sensitivity of the culture differs with type of infection, with the lowest sensitivity seen with acute pulmonary infection and highest sensitivity with progressive disseminated histoplasmosis. In the face of clinical suspicion, demonstration of typical intracellular yeast forms in the specimen using Gomori methenamine silver or other stains strongly supports the diagnosis of histoplasmosis.

Complement fixation and immunodiffusion assays are used for serologic diagnosis of histoplasmosis. These tests are positive in about 90% of cases in nonimmunocompromised patients. The titer of the complement fixation test is directly proportional to the degree of exposure and severity of illness. The complement fixation test is more sensitive but less specific than the immunodiffusion test because of assay cross-reactivity with other fungal antigens. In the immunodiffusion precipitin test, H bands are more suggestive of active infection than M bands.

Detection of *H capsulatum* galactomannan antigen in body fluids using a quantitative EIA is the most rapid and widely available diagnostic test for histoplasmosis. The *H capsulatum* galactomannan assay is sensitive in early primary pulmonary infection in patients with progressive dissemination, and is especially useful for diagnosis of histoplasmosis in immunocompromised patients with negative antibody titers. Because the test is not 100% sensitive, a negative test result does not exclude infection. Once positive, the antigen *H capsulatum* galactomannan assay is also useful in monitoring treatment response and relapse. Assay cross-reactivity is high with blastomycosis, coccidioidomycosis, and paracoccidioidomycosis infection.

### Imaging

Most children with acute pulmonary histoplasmosis have normal chest radiographs. Symptomatic patients typically have a patchy bronchopneumonia with variable hilar lymphadenopathy. There can be incidental findings of single or multiple calcified nodules in the lungs and hilar lymph nodes of asymptomatic residents of endemic regions. Chest CT is more sensitive than plain radiography. Depending on the level of exposure, a diffuse reticulonodular infiltrate can be observed.

### Management

#### Treatment Approach

Most *Histoplasma* infections in immunocompetent individuals are self-limiting and do not require treatment. Progressive disseminated histoplasmosis is the only disease manifestation requiring therapy in an otherwise immunocompetent child. Other indications for treatment include prolonged symptomatic infection (>4 weeks), seriously ill patients, obstructive granulomatous adenitis, and acute infection in immunocompromised individuals. Isolated pericarditis, presumed ocular disease, and rheumatologic syndromes do not require antifungal therapy. Fibrosis of mediastinal structures is not responsive to antifungal therapy.

#### Specific Treatments

Amphotericin B is recommended by the IDSA for disseminated disease and other serious infections in children. Azole antifungals can be used either after induction with amphotericin B or as monotherapy in mild or moderate disease. Itraconazole is preferred over fluconazole because of its effectiveness, better toxicity profile, and lower potential for induction of resistance.

For treatment of severe acute pulmonary histoplasmosis, amphotericin B followed by itraconazole for 12 weeks is recommended by the IDSA and the

American Academy of Pediatrics (AAP). Mild to moderate pulmonary infection persisting for longer than 4 weeks may require oral itraconazole for 6 to 12 weeks. Obstructive mediastinal adenitis requires concomitant use of a short course of corticosteroids with 6 to 12 weeks of itraconazole. For disseminated infection, amphotericin B may be given initially for 4 to 6 weeks followed by oral itraconazole maintenance therapy for 6 to 18 months (the duration of itraconazole therapy is determined by clearance of *Histoplasma* galactomannan). Patients with HIV with disseminated histoplasmosis require lifelong suppressive therapy with itraconazole.

### When to Admit

All immunocompromised children infected with *Histoplasma*; all children with severe acute pulmonary infections requiring intravenous therapy and supplemental oxygen; and all children with acute progressive disseminated histoplasmosis, regardless of immune status, should be admitted.

### When to Refer

All suspected or proven cases of histoplasmosis should be referred to infectious disease specialists. Disseminated histoplasmosis in an otherwise healthy child warrants referral to an immunologist.

### Ongoing Care

#### Follow-Up

All patients with histoplasmosis should be monitored periodically. Acute progressive disseminated histoplasmosis is associated with a high relapse rate especially among patients with AIDS. Histoplasmosis antigen is useful to monitor for relapse. A systemic evaluation should be conducted in cases of relapse.

### Complications

Acute progressive disseminated histoplasmosis is associated with overwhelming sepsis syndrome with disseminated intravascular coagulation, gastrointestinal bleeding, nephrocalcinosis, and hypercalcemia. Adrenal insufficiency develops in 5% to 10% of patients with subacute pulmonary disseminated histoplasmosis, regardless of treatment. Presumed ocular histoplasmosis, mediastinal fibrosis, chronic histoplasmosis, and endocarditis are manifestations that occur almost exclusively in adults.

### Prognosis

Acute pulmonary histoplasmosis usually has a good outcome. Acute progressive disseminated histoplasmosis is fatal without treatment and is associated with a relapse rate of 50% among treated individuals. In patients with *Histoplasma* meningitis, cure rates are only 50%, with a high rate of disease relapse. Chronic progressive disseminated histoplasmosis has a waxing and waning course. Intervening asymptomatic periods can last for years. If untreated, subacute progressive disseminated histoplasmosis results in death within 2 to 24 months.

### Prevention

Individuals traveling to or residing in endemic areas should be educated about minimizing exposure and

high-risk activities. For unavoidable activities, protective respiratory masks should be used. Decontaminating infected soil with a 3% formalin solution can prevent aerosolization of conidia.

## BLASTOMYCOSIS

### Etiology

Blastomycosis is caused by *Blastomyces dermatitidis*, a thermal dimorphic fungus that exists in the yeast form at 37°C in infected tissues, and as a white mold in the environment. The conidia, produced by mold form, convert to yeast and are infectious to humans.

### Epidemiology

The incidence of blastomycosis in children is low, constituting 2% to 10% of reported cases. The disease is endemic to the midwestern, north central, and south-eastern parts of the United States, with most cases seen in areas surrounding the Mississippi and Ohio rivers and the Great Lakes. Internationally, blastomycosis has been reported in Canada, India, Africa, and Central and South America.

### Risk Factors

Hunters or forestry workers in wooded endemic areas are at highest risk for infection.

### Diagnosis

#### Signs and Symptoms

The spectrum of disease ranges from asymptomatic infection to acute, chronic, or fulminant disease. The major clinical manifestations of blastomycosis are pulmonary diseases, cutaneous diseases, and disseminated infection. Acute pulmonary infection is the most common clinical manifestation of blastomycosis in children. Severity of respiratory symptoms varies from person to person. Symptoms of chronic pneumonia include weight loss, night sweats, cough, and fever (mimicking tuberculosis) and can persist for months. Extrapulmonary or disseminated disease usually follows pulmonary infection. The most common sites of dissemination of *Blastomyces* infection are skin, bone, CNS, and the genitourinary system. The cutaneous lesions caused by *Blastomyces* vary in morphology from nodular and verrucous to ulcerative (Figure 254-9). Bone infection has been reported in 25% to 50% of people with *B dermatitidis* infections.

### Differential Diagnosis

Acute pulmonary pneumonia caused by blastomycosis can be confused with bacterial pneumonia, especially with pulmonary tuberculosis. The typical verrucous or ulcerative cutaneous lesions may mimic skin cancers, such as basal cell carcinoma and squamous cell carcinoma.

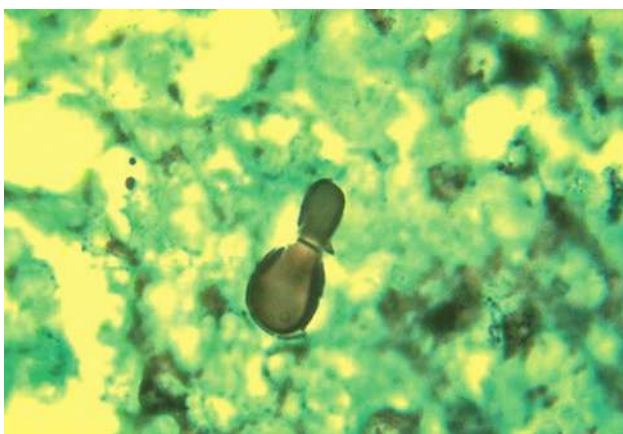
### Laboratory Findings

Definitive diagnosis of blastomycosis requires demonstration of thick-walled, figure-of-8-shaped, broad-based, single-budding yeast in body fluids or tissue specimens by staining (10% potassium hydroxide or a silver stain) (Figure 254-10) or culture. Serodiagnosis of blastomycosis infection using complement fixation





**Figure 254-9** Nodular skin lesions of blastomycosis, one of which is a bullous lesion on top of a nodule. (Courtesy Red Book Online. [redbook.solutions.aap.org](http://redbook.solutions.aap.org))



**Figure 254-10** Histopathology of blastomycosis. (Courtesy Red Book Online. [redbook.solutions.aap.org](http://redbook.solutions.aap.org))

antibodies and immunodiffusion precipitin bands has poor sensitivity and specificity and significant cross-reactivity with other fungi. *Blastomyces* antigen can be detected in urine, but cross-reactivity occurs with other endemic mycoses. Therefore, negative test results do not exclude the diagnosis of blastomycosis, and every attempt should be made to obtain a tissue or body fluid specimen for staining and culture. Skin testing is unreliable because of unpredictable waning of reactivity over time. An immunoassay to measure *B dermatitidis* antigenuria is reported to have good sensitivity (93%) and specificity (79%), but the test is not available widely.

### Imaging

In patients with blastomycosis, the chest radiograph is abnormal in most cases. Radiographic findings of blastomycosis include mass lesions, nodules, cavities, pleural effusion, fibrosis, and interstitial disease. For patients with extrapulmonary blastomycosis, CT or

MRI can be helpful for detecting skeletal lesions, which are typically multiple and lytic in nature and can involve long or flat bones. Lytic lesions of vertebrae, ribs, pelvis, or skull should raise suspicion of blastomycosis.

### Management

#### Treatment Approach

Asymptomatic acute pulmonary infections are often self-limited and resolve spontaneously. For symptomatic patients with acute pulmonary infection, recommendations have shifted toward treating with antifungals for at least 3 months. Mildly ill patients who are already improving without antifungal therapy can be observed for a short time before instituting treatment. Nonetheless, a careful evaluation for extrapulmonary infection should be performed and close follow-up is needed. Systemic antifungal treatment is recommended by the IDSA for chronic pulmonary infections and for all extrapulmonary forms of blastomycosis.

#### Specific Treatments

Amphotericin B is the drug of choice for initial treatment of severely ill patients followed by completion therapy with itraconazole. For patients with CNS involvement, amphotericin B is preferred for the entire course of therapy, because azoles have a limited role in treating CNS blastomycosis. For mild to moderately severe infections, oral itraconazole or fluconazole can be used alone or after a short course of amphotericin B. Duration of therapy recommended by the IDSA and AAP is at least 6 months for pulmonary and extrapulmonary disease and 1 year for osteomyelitis.

#### When to Admit

Admit all children with severe acute pulmonary infections requiring intravenous therapy and supplemental oxygen, and all children with CNS blastomycosis.

#### When to Refer

All suspected or proven cases of blastomycosis should be referred to infectious disease specialists. For children with high clinical suspicion for blastomycosis, surgeons, pulmonologists, and interventional radiologists should be involved to obtain tissue specimens for diagnosis.

#### Ongoing Care

##### Follow-Up

Long-term follow-up is required to identify late dissemination or relapse.

#### Complications

The major complications of blastomycosis are acute respiratory distress syndrome and extrapulmonary dissemination to the skin, bones, and genitourinary system. Contractures and scarring can develop with extensive cutaneous lesions. Involvement of the CNS has been reported in 40% of adults with blastomycosis and AIDS.

#### Prognosis

Historically, mortality rates for untreated blastomycosis without antifungals exceeded 60%. Now, in



appropriately treated cases, blastomycosis mortality is less than 10%. However, for immunocompromised patients, the prognosis for acute blastomycosis remains poor despite antifungal therapy, with mortality rates as high as 30% to 40%. Most deaths from blastomycosis tend to occur during the first few weeks of therapy.

### Prevention

Immunocompromised patients residing in endemic areas should be counseled about reducing the risk of acquiring blastomycosis by avoiding high-risk occupational and recreational activities. Currently there is no vaccine available for prevention, though there has been some progress.

## COCCIDIOIDOMYCOSIS

### Etiology

Coccidioidomycosis is an infection caused by the dimorphic fungi *Coccidioides immitis* and *C posadasii*. The 2 species do not have significant morphologic, antigenic, virulence, or phenotypic differences. In the soil, both *C immitis* and *C posadasii* exist as spore-forming mycelia with branching septate hyphae. After inhalation, infectious spores (arthroconidia) produced by hyphae enlarge to form endosporeulating spherules in the tissue.

### Epidemiology

In the United States, *Coccidioides* species are endemic to the southwestern states, including California, Arizona, New Mexico, Texas, southern Nevada, and Utah. Internationally, *Coccidioides* is found in northern Mexico and in some parts of Central and South America. *C immitis* is more prevalent in California, whereas *C posadasii* is found in Mexico and areas of Central and South America.

### Risk Factors

The risk of dissemination is increased in Filipinos, blacks, pregnant women, neonates, the elderly, diabetics, and immunocompromised individuals. Seismic activity, dust storms, and archeological and recreational activities in endemic areas are major preceding events. Extensive exposure is not needed to develop infection.

### Diagnosis

#### Signs and Symptoms

The incubation period for primary pulmonary *Coccidioides* infection ranges from 1 to 4 weeks. *Coccidioides* infection is asymptomatic in approximately 60% of patients. Those with primary pulmonary infection are symptomatic with cough, fever, fatigue, myalgias, chest pain, and dyspnea. Skin manifestations may be the only symptoms in some children, and include maculopapular rash, erythema multiforme, and erythema nodosum. Erythema nodosum and arthritic symptoms are mediated by cellular immunity, and their occurrence portends a low risk of dissemination. Chronic pulmonary infections, which occur only rarely



**Figure 254-11** Pulmonary coccidioidomycosis in an adolescent girl with pulmonary cavitation. (Courtesy Red Book Online. [redbook.solutions.aap.org](http://redbook.solutions.aap.org))

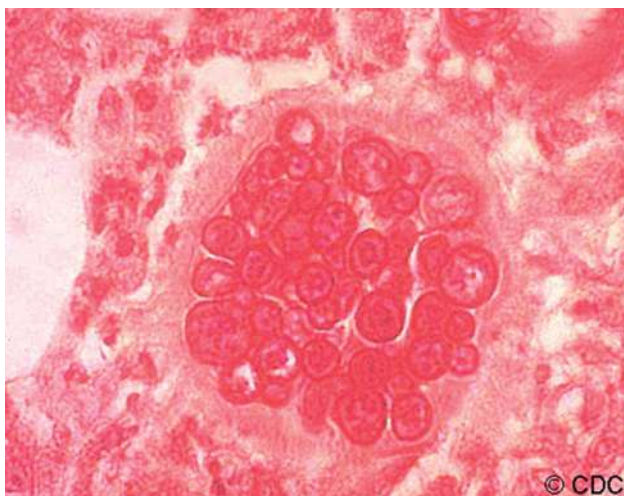
in children, manifest as progressive pneumonia, pulmonary nodules, and lung cavitations (Figure 254-11). Disseminated infection is uncommon in otherwise healthy children, occurring in less than 1% of infected patients. The common sites for dissemination are skin, soft tissue, joints, and lungs. Infections of the CNS most frequently involve the meninges.

### Differential Diagnosis

Because the symptoms for coccidioidomycosis are not specific, the differential diagnosis of *Coccidioides* infection is broad. Infectious causes include respiratory viral infections, bacterial pneumonias, atypical mycobacterium, tuberculosis, and other fungal infections. Noninfectious etiologic considerations include sarcoidosis, leukemias, histiocytosis, and lymphoproliferative disorders.

### Laboratory Findings

A definitive diagnosis of *Coccidioides* infection can be made by isolating the organism from normally sterile tissue sites. Specimens can be obtained from sputum, bronchoalveolar lavage fluid, blood, urine, bone marrow, lymph nodes, skin, bone, and CSF. The visualization of mature spherules containing endospores gives a presumptive diagnosis of *Coccidioides* infection (Figure 254-12). Direct examination of infected body fluids requires special staining and preparations including H&E, potassium hydroxide, or Calcofluor white. Stains of infected CSF are usually negative. If organisms are not seen with direct examination, the



**Figure 254-12** Spherule with endospores of *Coccidioides immitis* (periodic acid-Schiff stain). (Courtesy Red Book Online. [redbook.solutions.aap.org](http://redbook.solutions.aap.org))

diagnosis can be confirmed by culture. Cultures of *Coccidioides* require the use of special precautions by laboratory personnel because the mycelial form is very infectious.

Serologic tests help to confirm diagnosis and provide prognostic information, though false-negative results are possible in early infection and immunocompromised people. Most patients have IgM-specific coccidioidal antibody detectable within 10 to 21 days of being symptomatic. IgM is detected using immunodiffusion, latex agglutination test, or EIA. Though highly sensitive, the 2 latter methods lack specificity; hence positive results should be confirmed using more specific tests. The IgG response can be detected with immunodiffusion, EIA, or complement fixation (CF) test. IgG usually becomes detectable 1 to 3 months after infection. Higher CF titers ( $\geq 1:16$ ) are correlated with severity of the disease and are present in disseminated infections. Titers decrease with effective therapy and increase with disease progression. With meningeal involvement, CF is detected in CSF specimens of most patients.

The *Histoplasma* antigen EIA has been used to aid in diagnosis of coccidioidomycosis in endemic areas secondary to high cross-reactivity. However, a specific recently developed *Coccidioides* antigen EIA has higher sensitivity and specificity.

Skin testing has been used historically but is no longer available in the United States.

### Imaging

The chest radiograph of a patient with primary coccidioidomycosis can be normal or may have parenchymal infiltrates or effusions resembling viral or bacterial pneumonia. Unlike most acute pneumonias, hilar adenopathy is frequently seen with *Coccidioides* infection. Chronic pulmonary changes include thin-walled cavities, nodules varying in number and size,

and fibrosis. For detection of bony lesions, bone scanning and MRI are useful.

### Management

#### Treatment Approach

For patients without risk factors, treatment of minimally symptomatic or asymptomatic uncomplicated primary *Coccidioides* infections can be deferred provided there is close follow-up. Patients should be assessed periodically for 1 to 2 years to confirm resolution of symptoms and radiographic findings. The IDSA recommends therapy for patients with severe progressive pulmonary disease, for patients at risk for dissemination, and for patients who are experiencing significant morbidity (fever  $>3$  weeks, weight loss  $>10\%$ , persistent large infiltrates, severe malaise, CF titers  $\geq 1:16$ ). Treatment is recommended for all patients with extrapulmonary manifestations of coccidioidomycosis. Surgery may be required for persistent, refractory, localized pulmonary lesions or in cases with bone and joint involvement.

#### Specific Treatments

For patients with mild to moderate acute primary pulmonary infection, oral azoles are the treatment of choice. Duration of treatment needs to be individualized, but may vary from 3 to 6 months. For severe or progressive pulmonary disease, amphotericin B is recommended by the IDSA for initial management until respiratory symptoms resolve. Amphotericin B is also recommended for use in pregnant women, because azoles are potentially teratogenic. Azole antifungals are preferred for initial treatment of patients with CNS and meningeal involvement. For CNS infections refractory to fluconazole, repetitive intrathecal instillation of amphotericin B may be required. Duration of treatment for CNS infection and for HIV-infected patients is lifelong, because of the high risk of disease relapse in these patients.

### When to Admit

All children with severe acute pulmonary infections requiring intravenous therapy and supplemental oxygen, and all children with disseminated infections, especially those involving the CNS or meninges, should be admitted.

### When to Refer

All suspected or proven cases of coccidioidomycosis should be referred to infectious disease specialists. For children with persistent, refractory, localized pulmonary lesions or with bone and joint involvement, surgeons and interventional radiologists should be involved.

### Ongoing Care

#### Follow-Up

Periodic monitoring of symptoms and periodic radiological assessment of patients with primary pulmonary coccidioidomycosis is needed for 1 to 2 years or until disease resolution. For patients with disseminated coccidioidomycosis, CF titers should be monitored every month until titers have dropped to less than 1:8. Relapses of coccidioidomycosis can be

predicted by symptom recurrence, physical findings, and CF titer increases.

### Prognosis

In 90% to 95% of patients with primary coccidioidomycosis, the infection resolves without significant sequelae; the remaining 5% to 10% of patients develop chronic pulmonary or extrapulmonary disease. As discussed before, disseminated coccidioidomycosis is uncommon, typically involves infection of the skin, bone or joints, lymph nodes, or CNS, and is associated with increased morbidity and mortality. Mortality with disseminated infection among immunocompromised individuals can be as high as 70% despite appropriate therapy. Untreated meningitis is fatal in 100% of patients.

### Prevention

Currently no vaccine has been approved for the prevention of *Coccidioides* infection. Vaccine developments for high-risk individuals have been reviewed and appear promising. Primary prophylaxis with an azole is not recommended for HIV-infected individuals. Special measures should be taken in endemic areas to control dust at construction sites. People residing in or traveling to endemic regions should avoid high-risk activities and wear respiratory masks if exposure is unavoidable.

## SPOROTRICHOSIS

### Etiology

Sporotrichosis is a rare fungal infection caused by *Sporothrix schenckii*. *Sporothrix schenckii* is a thermally dimorphic fungus found in a mold or mycelial form at room temperature and as yeast at 37°C in host tissues.

### Epidemiology

Although *S. schenckii* has a global distribution, most cases of sporotrichosis are reported in tropical regions of the Americas. Most cases in North America have been reported in the Midwest. Sporotrichosis can occur in all age groups and has no racial or gender predilection. An increased frequency among men is attributable to occupational exposures. *S. schenckii* may be isolated from plants such as rosebush, barberry, straw, hay, sphagnum moss, and decaying vegetation. Animal-to-human transmission, most notably from cats and armadillos, has occurred.

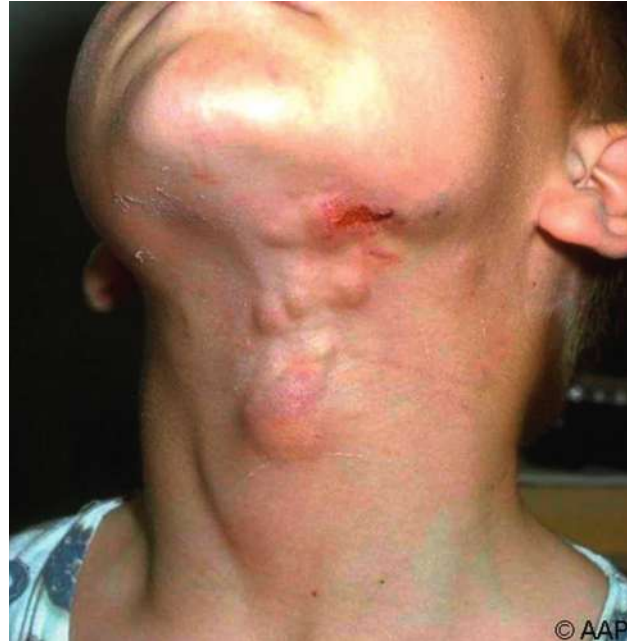
### Risk Factors

Individuals at increased risk of *S. schenckii* infections include farmers, gardeners, veterinarians, and laboratory workers. Other predisposing conditions for sporotrichosis include diabetes mellitus, alcoholism, and injection drug use. The risk of disseminated sporotrichosis is high among immunocompromised patients, including individuals with HIV infection.

### Dagnosis

#### Signs and Symptoms

Sporotrichosis can manifest as localized or fixed cutaneous, lymphocutaneous, or extracutaneous infection.



**Figure 254-13** *Sporothrix schenckii* was cultured from the biopsy specimen from an abscessed cervical lymph node of this 10-year-old boy. (Courtesy Red Book Online. [redbook.solutions.aap.org](http://redbook.solutions.aap.org))

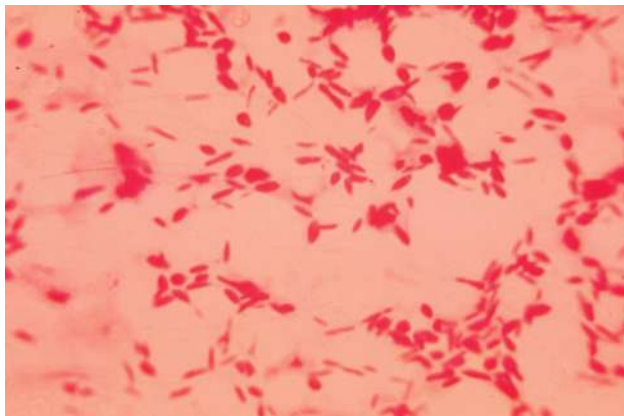
Lymphocutaneous sporotrichosis is the most commonly recognized form and accounts for more than 75% of pediatric cases. Lymphocutaneous sporotrichosis presents initially as a painless papule at the site of inoculation. Such lesions are more common on the face and hands and occur more frequently in children. The papule, over a varied period, evolves into a nodular, ulcerated lesion. In approximately 25% of children, *S. schenckii* infection remains as a solitary lesion without lymphatic spread. When lymphatic spread does occur, the infection spreads proximally along the lymphatic distribution of the affected extremity, producing nodular swellings that are often associated with palpable regional lymphadenopathy (Figure 254-13). Multiple disseminated cutaneous lesions are uncommon, but can occur with multiple inoculation sites, usually in immunocompromised individuals.

Pulmonary sporotrichosis follows inhalation of aerosolized spores and manifests as a subacute or chronic pneumonia that mimics tuberculosis. Disseminated sporotrichosis follows hematogenous or lymphatic spread from initial cutaneous or pulmonary infection. The usual organs of dissemination are the skin, joints, eyes, and CNS. Pulmonary and disseminated forms of sporotrichosis are rarely encountered in children.

### Differential Diagnosis

According to the epidemiologic settings and exposures, etiologic considerations include tuberculosis, lupus vulgaris, blastomycosis, chromoblastomycosis, paracoccidioidomycosis, and leishmaniasis. Some cutaneous infections are difficult to distinguish from actinomycosis, nocardiosis, and nontuberculous mycobacterial disease.





**Figure 254-14** *Sporothrix schenckii*, yeast phase; round, oval, and fusiform (cigar-shaped) cells. (Courtesy Red Book Online. [redbook.solutions.aap.org](http://redbook.solutions.aap.org))

### Laboratory Findings

Definitive diagnosis of *S. schenckii* infection requires isolation of the fungus in culture, or by detection of *S. schenckii* in tissue specimens using periodic acid–Schiff, methenamine silver, or immunohistochemical stains (Figure 254-14). The diagnostic yield of histopathologic specimens is low because of a paucity of organisms in infected tissue. Granulomatous inflammation with occasional asteroid bodies can be seen in histopathologic specimens. Serologic testing and PCR assay have high sensitivity and specificity, but are not available widely.

### Management

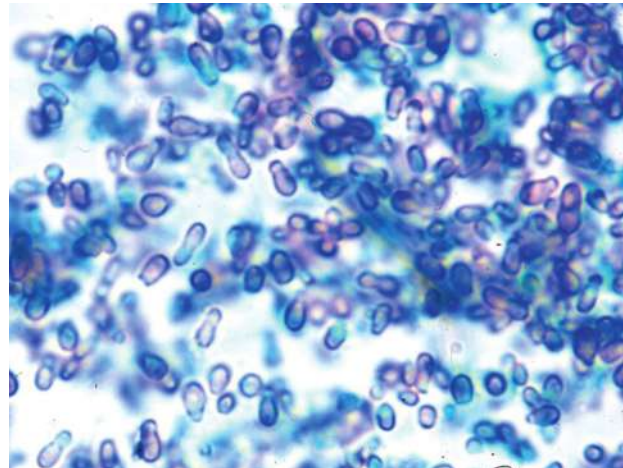
Lymphocutaneous sporotrichosis rarely resolves without treatment. The duration of therapy is usually 3 to 6 months. Itraconazole is the drug of choice for cutaneous and lymphocutaneous sporotrichosis and is more effective than fluconazole. For cutaneous and lymphocutaneous infections, a saturated solution of potassium iodide has been used and still is recommended as an alternative treatment option. Amphotericin B, followed by a prolonged course of itraconazole, is used for disseminated sporotrichosis and for severe pulmonary infection. Children with invasive sporotrichosis and HIV coinfection are treated initially with amphotericin B followed by lifelong itraconazole maintenance therapy.

### Ongoing Care

The prognosis of cutaneous and lymphocutaneous sporotrichosis after therapy is excellent. Osteoarticular sporotrichosis may be complicated by chronic osteomyelitis and arthritis with consequent deformity and loss of joint function. Disseminated sporotrichosis carries significant morbidity and mortality in immunocompromised hosts.

## MALASSEZIA

*Malassezia furfur* is a lipophilic, saprophytic, budding, dimorphic, oval-to-round yeast. *M. furfur* is part of the normal skin flora, and causes clinical disease only when there is substantial transformation of yeast to hyphal forms. *Malassezia* species are responsible for superficial skin infections in all age groups. The most common



**Figure 254-15** *Malassezia furfur*. Pneumonitis. (Courtesy Red Book Online. [redbook.solutions.aap.org](http://redbook.solutions.aap.org))

manifestation of cutaneous *Malassezia* infection is pityriasis versicolor. Pityriasis versicolor occurs globally, but is predominantly present in tropical and subtropical regions. Recently, *Malassezia* species have been increasingly recognized as a cause of invasive disease in premature infants and in other immunocompromised hosts who are receiving lipid-supplemented parenteral nutrition.

### Risk Factors

Among both infants and adults, exposure to intravenous lipid infusions through a CVC is the most important risk factor for systemic *Malassezia* infection. Neonates with low birth weight, low gestational age, and prolonged hospitalization are at high risk. Antibacterial therapy has been identified as an additional risk factor for disease.

### Diagnosis

#### Signs and Symptoms

*Malassezia* species can cause various superficial skin infections in humans, including pityriasis versicolor, folliculitis, seborrheic dermatitis, and even atopic dermatitis. Symptoms of catheter-associated fungemia secondary to infection with *Malassezia* species are indistinguishable from those related to other causes, but should be suspected in high-risk neonates with sterile blood cultures. Clinical manifestations of invasive *Malassezia* infection include fever, respiratory distress, apnea, bradycardia, and thrombocytopenia. The heart and lungs are the most commonly affected organs resulting in mycotic thrombi around the tips of catheters; mycotic vegetations on the endocardium and heart valves; vasculitis; and inflammation of alveoli, bronchi, and bronchioles. Usually, no signs of infection and no skin rash are evident at catheter insertion sites.

### Laboratory Findings

Direct microscopic examination of scrapings from skin lesions can reveal clusters of round to oval budding yeast cells and short hyphae (the so-called “spaghetti and meatball” appearance) (Figure 254-15).



**Table 254-1** Overview of Fungal Pathogens and Usual Pattern of Susceptibility to Antifungals

FUNGAL SPECIES	AMPHOTERICIN B FORMULATIONS					ITRACONAZOLE	VORICONAZOLE	POSACONAZOLE	ECHINOCANDINS
	FLUCONAZOLE	FLUCONAZOLE	FLUCONAZOLE	FLUCONAZOLE	FLUCONAZOLE				
<i>Aspergillus fumigatus</i>	+	—	+	+	+	+/—	++	+	+
<i>Aspergillus terreus</i>	—	—	+	+	+	+	++	+	+
<i>Blastomyces dermatitidis</i>	++	+	+	+	+	++	+	+	—
<i>Candida albicans</i>	+	++	+	+	+	+	+	+	++
<i>Candida glabrata</i>	+	—	+	+	+	+/—	+/—	+/—	+/—
<i>Candida krusei</i>	+	—	+	+	+	—	+	+	+
<i>Candida lusitanae</i>	—	++	+	+	+	+	+	+	+
<i>Candida parapsilosis</i>	++	++	+	+	+	+	+	+	+/—
<i>Candida tropicalis</i>	+	++	+	+	+	+	+	+	++
<i>Coccidioides immitis</i>	++	+	+	+	+	++	+	++	—
<i>Cryptococcus</i> spp	++	+	+	+	+	+	+	+	—
<i>Fusarium</i> spp	+/—	—	+	+	+	—	++	+	—
<i>Histoplasma capsulatum</i>	++	+	+	+	+	++	+	+	—
<i>Mucor</i> spp	++	—	+	+	+	+/—	—	+	—
<i>Paracoccidioides</i> spp	+	+	+	+	+	++	+	+	—
<i>Rhizopus</i> spp	++	—	+	+	+	—	—	+	—
<i>Sporothrix</i> spp	+	+	+	+	+	++	+	+	—

NOTE: ++ = preferred therapy(ies); + = usually active; +/- = variably active; — = usually not active.  
 Adapted from Bradley JS, Barnett ED, Cantey JB, et al, eds. 2016 Nelson's Pediatric Antimicrobial Therapy. 22nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2016: 130–131.

**Table 254-2 Summary of Systemic Fungal Infections in Pediatric Patients**

FUNGAL ORGANISMS	KEY FEATURES	PRESENTATION	DIAGNOSIS	TREATMENT <sup>a</sup>
<i>Aspergillus</i> spp	<ul style="list-style-type: none"> <li>Mold</li> <li>Ubiquitous in nature</li> </ul>	Pulmonary, tracheo-bronchial, sinus, CNS, and disseminated	<ul style="list-style-type: none"> <li>Direct examination (dichotomously branched, septated hyphae)</li> <li>Culture</li> <li>Galactomannan</li> <li>1,3-β-D glucan</li> </ul>	<ul style="list-style-type: none"> <li>Voriconazole</li> <li>Posaconazole</li> <li>Amphotericin B</li> <li>Echinocandins</li> </ul>
<i>Blastomycetes</i>	<ul style="list-style-type: none"> <li>Dimorphic</li> <li>Midwestern, north central, and southeastern regions of the US</li> </ul>	Pulmonary, cutaneous, and disseminated (skin, bone, CNS, and GU systems)	<ul style="list-style-type: none"> <li>Direct examination (thick-walled, figure-of-8-shaped, broad-based, single-budding yeast)</li> <li>Culture</li> <li>Serologic tests</li> </ul>	<ul style="list-style-type: none"> <li>Amphotericin B</li> <li>Itraconazole</li> <li>Fluconazole</li> </ul>
<i>Candida</i> spp	<ul style="list-style-type: none"> <li>Yeast</li> <li>Pseudohyphae</li> <li>Colonizes skin, mouth, GI, and female genital tract</li> </ul>	Mucous membranes, cutaneous, hematogenous, endocarditis, endophthalmitis, CNS, and disseminated (liver, spleen, kidney)	<ul style="list-style-type: none"> <li>Direct examination (pseudohyphae and budding yeast)</li> <li>Culture</li> <li>1,3-β-D glucan</li> <li>Platelia <i>Aspergillus</i> ELISA</li> <li>PCR</li> <li>Germ tube test</li> <li>PNA-FISH</li> </ul>	<ul style="list-style-type: none"> <li>Fluconazole</li> <li>Amphotericin B</li> <li>Echinocandins</li> <li>Flucytosine (only in combination)</li> </ul>
<i>Cryptococcus neoformans</i>	<ul style="list-style-type: none"> <li>Encapsulated fungus</li> <li>Pigeon droppings (var <i>neoformans</i>)</li> <li>Trees, in British Columbia, Canada, and Pacific Northwest in United States (var <i>gattii</i>)</li> </ul>	Pulmonary, CNS, cutaneous, eye, bone, and hematogenous	<ul style="list-style-type: none"> <li>Direct examination (encapsulated yeast using India ink or other stains)</li> <li>Culture</li> <li>Ag detection (using latex agglutination or EIA)</li> </ul>	<ul style="list-style-type: none"> <li>Amphotericin B</li> <li>Flucytosine (only in combination)</li> <li>Fluconazole</li> </ul>
<i>Coccidioides</i> spp	<ul style="list-style-type: none"> <li>Dimorphic</li> <li>Southwestern states (California, Arizona, New Mexico, Texas, southern Nevada, and Utah)</li> </ul>	Pulmonary, disseminated (skin, soft tissue, joints, lungs, and meninges)	<ul style="list-style-type: none"> <li>Direct examination (mature spherules containing endospores)</li> <li>Culture</li> <li>Serologic tests</li> <li>EIA for <i>Coccidioides</i> Ag</li> </ul>	<ul style="list-style-type: none"> <li>Amphotericin B</li> <li>Fluconazole</li> </ul>
<i>Histoplasma capsulatum</i>	<ul style="list-style-type: none"> <li>Dimorphic</li> <li>Central and southeastern states, along Mississippi, Ohio, &amp; Missouri river valleys</li> </ul>	Acute and chronic pulmonary, disseminated (HSM, GI hemorrhage, DIC, meningitis)	<ul style="list-style-type: none"> <li>Culture</li> <li>Serologic tests</li> <li>EIA for <i>Histoplasma</i> Ag</li> </ul>	<ul style="list-style-type: none"> <li>Amphotericin B</li> <li>Itraconazole</li> </ul>
<i>Glomeromycoses (Zygomycetes)</i>	<ul style="list-style-type: none"> <li>Aseptate or pauciseptate hyphae</li> <li>Spoiled matter such as bread, fruits, vegetables, and soil</li> </ul>	Rhinocerebral, pulmonary, disseminated, skin, and GI	<ul style="list-style-type: none"> <li>Direct examination (broad, thin-walled, mostly aseptate hyphae, tissue invasion, sporangium)</li> <li>Culture</li> </ul>	<ul style="list-style-type: none"> <li>Amphotericin B</li> <li>Posaconazole</li> </ul>
<i>Sporothrix schenckii</i>	<ul style="list-style-type: none"> <li>Dimorphic</li> <li>Central, South, and North America (Midwest)</li> </ul>	Cutaneous, lymphocutaneous, pulmonary, disseminated (skin, joints, eyes, and CNS)	<ul style="list-style-type: none"> <li>Direct examination (cigar-shaped yeast)</li> <li>Culture</li> <li>Serologic tests</li> <li>PCR</li> </ul>	<ul style="list-style-type: none"> <li>Amphotericin B</li> <li>Itraconazole</li> </ul>
<i>Malassezia furfur</i>	<ul style="list-style-type: none"> <li>Dimorphic</li> <li>Saprophytic</li> <li>Lipophilic</li> <li>Globally present</li> </ul>	Superficial skin infections, catheter-associated bloodstream infection	<ul style="list-style-type: none"> <li>Direct examination (round to oval budding yeast cells and short hyphae; "spaghetti and meatball" appearance)</li> </ul>	<ul style="list-style-type: none"> <li>Removal of colonized catheter and discontinuing the lipid infusion</li> <li>Amphotericin B</li> <li>Fluconazole</li> </ul>

Ag, antigen; CNS, central nervous system; DIC, disseminated intravascular coagulation; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; GI, gastrointestinal; GU, genitourinary; HSM, hepatosplenomegaly; PCR, polymerase chain reaction; PNA-FISH, peptide nucleic acid fluorescent in situ hybridization.

<sup>a</sup>See text for indications and duration of treatment.

With the exception of *M pachydermatis*, *Malassezia* do not grow readily on standard mycologic media, and require addition of olive oil to Sabouraud dextrose agar to provide the long-chain fatty acids needed for growth of *Malassezia* species.

### Management

Systemic *Malassezia* infection can be treated successfully with prompt removal of the colonized catheter and discontinuation of the contaminated lipid infusion. In cases of invasive fungemia, amphotericin B or fluconazole may be used. The use of fat emulsions containing medium-chain triglycerides inhibits the growth of *Malassezia* and may prevent infection.

### SUMMARY

Table 254-1 and Table 254-2 provide an overview of systemic fungal infections and antifungal agents.

### TOOLS FOR PRACTICE

#### Medical Decision Support

- National Center for Zoonotic, Vector Borne, and Enteric Diseases (help line), Centers for Disease Control and Prevention (800-232-4636)
- National Center for Emerging and Zoonotic Infectious Diseases Strategic Plan, 2012–2017 (report), Centers for Disease Control and Prevention ([www.cdc.gov/ncezid/pdf/strategicplan\\_ncezid.pdf](http://www.cdc.gov/ncezid/pdf/strategicplan_ncezid.pdf))

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### Chapter 255

## GASTROESOPHAGEAL REFLUX DISEASE

Jenifer R. Lightdale, MD, MPH

### DEFINITIONS

Gastroesophageal reflux (GER) is a normal physiologic process that entails relaxation of the lower esophageal sphincter independent of swallowing and allows gastric contents to pass into the esophagus. GER occurs transiently several times a day in healthy infants, children, and adults and is generally unaccompanied by symptoms. In contrast, gastroesophageal reflux disease (GERD) is globally defined as troublesome symptoms or complications associated with GER. The symptoms of GERD can be either esophageal or extraesophageal and can be further characterized by findings of mucosal injury on upper endoscopy.

Both GER and GERD can be associated with vomiting, which is defined as a forceful expulsion of gastric contents through a coordinated autonomic and voluntary motor response. Regurgitation occurs when gastric contents enter into the oropharynx. Vomiting and regurgitation can be further differentiated from rumination, in which recently ingested food is effortlessly regurgitated into the mouth, masticated, and reswallowed.

### EPIDEMIOLOGY

GER, as characterized by regurgitation, occurs in more than two-thirds of otherwise healthy infants and has been found to be a voiced topic of parental concern in 20% to 25% of 6-month well-child visits. The terms “spitting-up,” “possetting,” and “spilling” are considered equivalent to regurgitation, which is the most visible symptom of GER in infants. One study reported at least 1 episode of regurgitation per day in 0- to 3-month-olds, with peak-reported regurgitation in two-thirds of infants at 4 months and general resolution by 1 year of age. International reports suggest that infant regurgitation is a global phenomenon that is mainly prevalent in the first 5 months of life and almost always resolves by 12 to 14 months. (see Figure 255-1).

GERD is far less common than GER in pediatric populations, and determining its prevalence, particularly in infants who have variable clinical presentations, may be impossible. One rigorous study in the United Kingdom suggests the incidence per 1,000 person years is 0.84 in children 1 to 18 years of age. Recent studies suggest there is likely a genetic basis for GERD and its complications, including erosive esophagitis, Barrett esophagus, and esophageal carcinoma. Reports have been published of familial clustering of Barrett esophagus, and monozygotic twins have a higher concordance for GERD than dizygotic twins. However, data supporting a specific genetic link are lacking. It is not known whether pediatric symptoms of GERD are a risk factor for complications of GERD later in life. A few pediatric populations have been identified to be at high risk for GERD and its

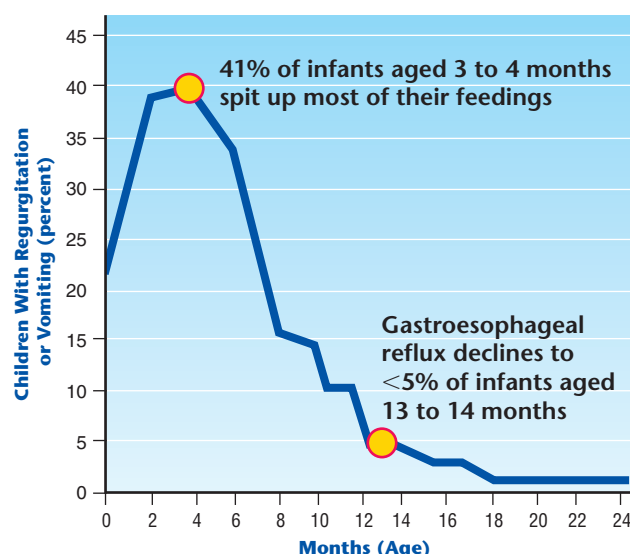
complications, including children with neurologic impairment, prematurity, and esophageal atresia.

## CLINICAL MANIFESTATIONS

Symptoms, many of which are troublesome, and signs of GERD generally depend on the age of the patient (see Box 255-1). Clinical manifestations may be different as children grow older and with the development of language (see Box 255-2). Common presenting symptoms in infants include refusing to eat or failing to thrive. Infant crying has also been presumed to be a symptom of discomfort from acid reflux, despite the fact that no studies have shown correlation of crying with GER. GERD in infants can also be associated with extraesophageal symptoms of coughing, choking, wheezing, or upper respiratory symptoms. Older children may complain of abdominal pain but may not localize the pain to the epigastrium or retrosternal areas. Adolescents are more likely to report heartburn or chest pain symptoms in a similar manner to adults. Extraesophageal symptoms and signs, such as wheezing, stridor, and dystonic neck posturing, may occur at any age.

## PATHOPHYSIOLOGY

The causes of GER and GERD are multifactorial and depend on anatomy, motility, and pathophysiologic factors. In an infant, the normally obtuse angle of His does not occlude the hiatus when the stomach is distended postprandially and may result in regurgitation. In line with the overall smaller body size, the infant esophagus is relatively short compared with an adult esophagus, and the infant's gastric capacity is less. In turn, gastric contents may more easily move into the esophagus and oropharynx (see Figure 255-2).



**Figure 255-1** Prevalence of gastroesophageal reflux in healthy infants in the first 2 years of life. (From Martin AJ, Pratt NJ, Kennedy D, et al. Natural history and familial relationships of infant spilling to 9 years of age. *Pediatrics*. 2002;109:1061–1067)

In both children and adults, the most common cause of GERD is inappropriate lower esophageal sphincter (LES) relaxation with inhibition of esophageal peristalsis. Transient LES relaxations typically occur up to 5 times in the immediate postprandial hour with episodic movement of gastric contents into the distal esophagus. These relaxations are vagally mediated, are brief in duration, and probably play a normal role in eliminating gas from the stomach. When the refluxate enters the esophagus, it is buffered by saliva and cleared by normal esophageal peristalsis. In patients with GERD, these relaxations last longer, from 5 to 35 seconds. During this period, a combination of LES hypotonia and inhibited esophageal peristalsis prolongs the contact time of the gastric contents with the esophageal mucosa and contributes to tissue injury. Inappropriate LES relaxation and delayed gastric emptying have been shown to occur in 28% to 50% of children with GERD.

Increasing intra-abdominal pressure (crying in infants, coughing, obesity) or gastric acid secretion, as well as consuming large meals, fatty foods, caffeinated

### BOX 255-1 Symptoms and Signs That May Be Associated With Gastroesophageal Reflux

#### SYMPTOMS

- Recurrent regurgitation with/without vomiting
- Weight loss or poor weight gain
- Irritability in infants
- Ruminative behavior
- Heartburn or chest pain
- Hematemesis
- Dysphagia, odynophagia
- Wheezing
- Stridor
- Cough
- Hoarseness

#### SIGNS

- Esophagitis
- Esophageal stricture
- Barrett esophagus
- Laryngeal or pharyngeal inflammation
- Recurrent pneumonia
- Anemia
- Dental erosion
- Feeding refusal
- Dystonic neck posturing (Sandifer syndrome)
- Apnea spells
- Apparent life-threatening events

From Vandenas Y, Rudolph CD, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr*. 2009;49:498–547. Reproduced with permission from Wolters Kluwer Health, Inc.



beverages, candy, and certain medications (theophylline, morphine, calcium-channel blockers) that lower the LES tone, have also been found to contribute to the presence and severity of GERD. Other risk factors include pathologic conditions such as malrotation, annular pancreas, or antral web. Impaired esophageal motility associated with repair of esophageal atresia or tracheoesophageal fistula or delayed gastric emptying may result in prolonged acid exposure in the

esophagus and eventual complications of GERD. Impaired buffering of acid in the esophagus by saliva may lead to esophagitis in children with cystic fibrosis or adults with autoimmune disease.

### Esophageal Complications

Gastrointestinal (GI) bleeding associated with hematemesis, melena, guaiac-positive stools, or anemia can occur as a complication of GERD resulting from erosive esophagitis. Peptic strictures are a long known complication of severe GERD, especially in patients with neurologic impairment or esophageal motility disorders. Children with peptic stricture may complain of dysphagia or refuse to eat solids. Impaction of food may be the initial presentation. Peptic strictures are readily seen by barium swallow and are usually located in the distal third of the esophagus. Barrett epithelium, which is defined as the replacement of normal stratified esophageal epithelium with columnar epithelium and goblet cells, is highly associated with peptic strictures in adults but is relatively rare in children. Barrett epithelium may be premalignant. Case reports have been issued of children with Barrett epithelium–associated adenocarcinoma, but the prevalence of esophageal cancer in children is extremely rare. Children with Barrett esophagus should be managed in accordance with adult guidelines and undergo appropriate surveillance for dysplasia.

### Extraesophageal Complications

#### *Chronic Cough, Stridor, Hoarseness*

Data linking GERD in children with chronic cough, stridor, and hoarseness are limited to case reports and case series, and controlled studies of the use of acid

### BOX 255-2 Common Presenting Symptoms of Gastroesophageal Reflux Disease in Children

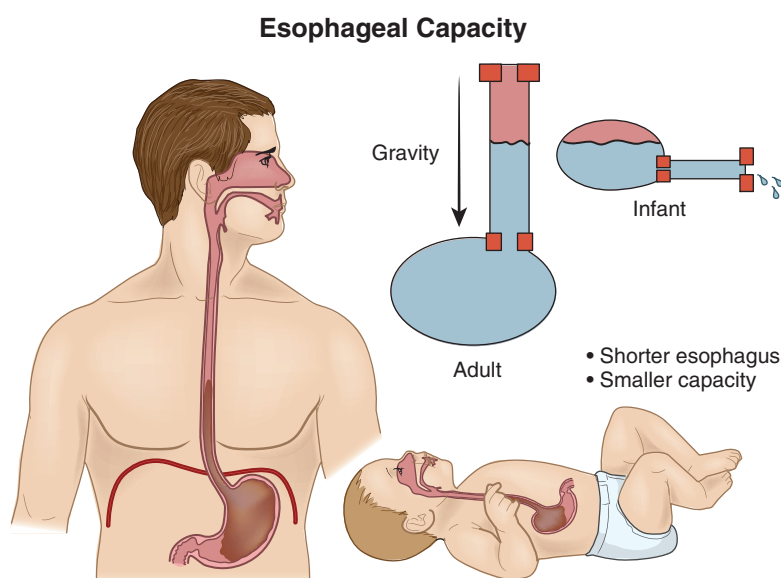
#### INFANTS

- Feeding refusal
- Recurrent vomiting
- Poor weight gain
- Irritability
- Sleep disturbance
- Respiratory symptoms

#### OLDER CHILDREN AND ADOLESCENTS

- Abdominal pain, heartburn
- Recurrent vomiting
- Dysphagia
- Asthma
- Recurrent pneumonia
- Upper airway symptoms (chronic cough, hoarse voice)

From Lightdale JR, Gremse DA; Section on Gastroenterology, Hepatology, and Nutrition. Gastroesophageal reflux: management guidance for the pediatrician. *Pediatrics*. 2013;131:e1684–e1695.



**Figure 255-2** A number of factors contribute to the frequency of regurgitation in infants. A shorter esophagus, the small capacity of the esophagus, and recumbent posture (lack of gravity) make it more likely that refluxed material in the infant will fill the esophagus and pass into the pharynx. The infant is thus more likely to regurgitate than the adult when gastric contents empty into the esophagus. The esophagus is approximately 11 cm at birth, with a diameter of 5 mm. By adulthood, the esophagus is 24 to 30 cm long, with lateral and anteroposterior diameters of 30 and 19 mm, respectively.

suppression to treat these presumed GERD-related symptoms have not shown clinical improvement. Recent guidelines from the North American Society of Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN) state that patients with these symptoms should not be assumed to have GERD without a comprehensive evaluation for other potential etiologies.

### **Recurrent Pneumonia**

GERD may cause recurrent pneumonia and interstitial lung disease and may occur without esophagitis. Although reflux causing recurrent pneumonia has been reported in otherwise healthy children, those with neurodevelopmental disorders present a special diagnostic problem because oropharyngeal incoordination may result in aspiration without reflux. Aspiration during swallowing in many patients, especially patients with neurodevelopmental disorders, may be more common than aspiration of refluxed material. In turn, diagnosing GERD as a factor in lung disease may be challenging. Although lipid-laden alveolar macrophages have been considered an indicator of aspiration, multiple studies have shown that this finding has poor sensitivity and specificity as an indicator of reflux-related lung disease.

### **Asthma**

Although symptoms of reflux are common in children with asthma, and a high percentage of children with persistent asthma have abnormal pH monitoring results, the relationship between asthma and GERD remains a challenge for the physician. Esophageal acid exposure per se has a minimal effect on pulmonary function but has been shown to contribute to increased airway responsiveness in asthmatic patients. A pathophysiologic explanation for this may lie in the fact that vagal afferents innervate both the esophagus and the bronchi and allow acid stimulation of receptors in the esophagus to induce reflex bronchoconstriction. Alternatively or additionally, micro-aspiration of gastric contents into the trachea may result in bronchoconstriction and laryngospasm.

The prevalence rates of GERD-associated asthma are reported to range from 25% to 75%. Interestingly, approximately 50% of patients with persistent asthma who test positive for GERD by pH monitoring have no or minimal symptoms of GERD. In one arm of a clinical trial of asthmatic children ages 5 to 10 years, children with normal pH monitoring results were randomized to receive a proton pump inhibitor (PPI) or no acid-suppression treatment. Approximately 25% of asthmatic children with normal pH probe studies were able to decrease their asthma medication, whereas children who were not treated with acid-suppression medication continued on the same dose of asthma medication. Studies have shown an improvement of asthma symptoms after a variety of medical therapies for GERD that have included positional therapy, thickening of formula without medication, promotility agents, and treatment with histamine-2 receptor antagonists (H2RAs). Currently, evidence in children is insufficient to establish optimal medical therapy for GER in patients with asthma, and the best diagnostic test to determine whether an association between asthma and GERD

exists remains an empirical trial of a PPI for acid suppression.

### **Apnea or Apparent Life-Threatening Event**

An apparent life-threatening event (ALTE) is an episode occurring in an infant that requires intervention and that is characterized by a combination of apnea, cyanosis, pallor, rubor, plethora, limpness, stiffness, choking, or gagging. (See Chapter 217, Apparent Life-Threatening Events.) To date, evidence to support a clear causal relationship between GERD and ALTE is lacking. Instead, it is recognized that in highly selected cases, reflux may be associated with pathologic, central, and obstructive apnea. Medical therapy of GERD in infants with ALTE should be considered a reasonable therapeutic option to pursue but cannot be considered a reliable means of preventing a subsequent ALTE. The use of surgical therapy for GERD to prevent ALTE remains unproved and should be considered only in infants with ALTE that is unresponsive to acid-suppression therapy and is known to be associated with GERD.

### **Sandifer Syndrome**

Sandifer syndrome is a rare complication of GERD usually seen in otherwise neurologically normal children and characterized by stereotypical, repetitive stretching and arching movements thought to be related to esophageal pain. These behaviors may be mistaken for atypical seizures or dystonia.

### **Dental Erosions**

An emerging association between GERD and dental erosions seems to correlate in severity to exposure of the proximal esophageal or oral cavity to acidic gastric contents. Young children and those with neurologic conditions may be at greatest risk. Beyond GERD, other contributing factors to dental erosions that can be considered either causal or additive include juice drinking, bulimia, and genetic factors that affect the characteristics of the enamel and saliva.

## **EVALUATION**

There is no single gold standard test or testing approach that allows a definitive diagnosis of GER or GERD. Instead, the diagnosis of reflux disorders is generally made on the basis of a description of symptoms in the absence of alternative diagnoses. To this end, there are a myriad of diagnostic modalities that can be used in a thoughtful and serial manner to provide specific information about the cause and severity of acid reflux and to investigate for associated or alternative conditions.

### **History and Physical Examination**

In most infants with vomiting, and in older children with regurgitation and heartburn, a history and physical examination are sufficient to reliably diagnose uncomplicated GER and GERD, recognize complications, and initiate treatment strategies (see Box 255-3 and Box 255-4). Obtaining a dedicated clinical history and performing a physical examination are also critical to excluding more worrisome diagnoses that can

### BOX 255-3 History in the Child With Suspected Gastroesophageal Reflux Disease

#### FEEDING HISTORY

- Amount/frequency (overfeeding)
- Primary source of dietary proteins
- Preparation of formula
- Recent changes in feeding type or technique
- Position during feeding
- Burping
- Behavior during feedings (choking, gagging, coughing, arching, discomfort, refusal)

#### PATTERN OF VOMITING

- Amount/frequency
- Pain
- Forceful
- Blood or bile
- Associated symptoms (constipation, fever, lethargy, diarrhea)
- Associated pattern of stooling

#### MEDICAL HISTORY

- Stool frequency and consistency
- Prematurity
- Growth and development
- Past surgery, hospitalizations
- Newborn screen results
- Recurrent illness (croup, pneumonia, reactive airways)
- Apnea
- Previous weight and height gain
- Warning signals (see Box 255-4)
- Other chronic conditions

#### MEDICATIONS

- Current, recent, prescription, nonprescription

#### FAMILY PSYCHOSOCIAL HISTORY

- Sources of stress
- Parental drug use
- Postpartum depression

#### FAMILY MEDICAL HISTORY

- Significant illness
- Family history of gastrointestinal disorders
- Family history of atopy

#### GROWTH CHART

- Length, weight, head circumference
- Weight-for-length, body mass index

Adapted from Vandenplas Y, Rudolph DC, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr.* 2009;49:498–547. Reproduced with permission from Wolters Kluwer Health, Inc.

### BOX 255-4 Warning Signs in the Vomiting Infant

- Bilious vomiting
- Gastrointestinal bleeding: hematemesis, hematochezia
- Consistent forceful vomiting
- Onset of vomiting after 6 months of life
- Failure to thrive
- Diarrhea
- Constipation
- Fever
- Lethargy
- Hepatosplenomegaly
- Bulging fontanelle
- Macrocephaly, microcephaly
- Seizures
- Abdominal tenderness, distention
- Documented or suspected genetic/metabolic disorders (eg, trisomy 21)

From Vandenplas Y, Rudolph DC, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr.* 2009;49:498–547. Reproduced with permission from Wolters Kluwer Health, Inc.

present with reflux, vomiting, and other symptoms associated with reflux disorders (see Box 255-5).

### Differential Diagnosis

A variety of conditions have clinical features that resemble GER, including eosinophilic esophagitis, food allergy, achalasia, cyclic vomiting syndrome, pill esophagitis, infectious esophagitis, and rumination syndrome. These conditions may be suspected based on characteristic features in combination with diagnostic testing. A failure of symptoms to respond to standard medical therapy for acid reflux may also be an indication to investigate for alternative diagnoses.

### Eosinophilic Esophagitis

Eosinophilic esophagitis occurs in young children, teenagers, and adults. Younger children may have symptoms suggestive of GERD such as abdominal pain or food refusal. Dysphagia or esophageal food impaction is more commonly noted in older children. A personal or family history of allergic disease can be found in 75% of cases. The diagnosis is suspected when white exudate, circular rings, or linear furrowing is seen during upper endoscopy. Establishing the diagnosis depends on finding more than 15 eosinophils per high-power field on an esophageal mucosal biopsy.

### Food Allergy

Infants with intolerance to cow's milk protein have been shown to experience regurgitation and vomiting indistinguishable from that associated with physiologic GER. Generally speaking, cow's milk protein is

**BOX 255-5 Differential Diagnosis of Vomiting in Infants and Children****GASTROINTESTINAL OBSTRUCTION**

- Esophageal ring or web
- Antral, duodenal web
- Pyloric stenosis
- Malrotation with intermittent volvulus
- Intermittent intussusception
- Intestinal duplication
- Hirschsprung disease
- Foreign body
- Incarcerated hernia

**OTHER GASTROINTESTINAL DISORDERS**

- Achalasia
- Gastroparesis
- Gastroenteritis
- Peptic ulcer disease
- Gastroesophageal reflux
- Eosinophilic esophagitis
- Eosinophilic gastroenteropathy
- Food allergy or intolerance
- Inflammatory bowel disease
- Pancreatitis
- Appendicitis

**NEUROLOGIC DISORDERS**

- Hydrocephalus
- Subdural hematoma
- Intracranial hemorrhage
- Intracranial mass
- Abdominal migraine, cyclic vomiting syndrome
- Chiari malformation

**INFECTION**

- Sepsis
- Meningitis

- Urinary tract infection
- Pneumonia
- Otitis media
- Hepatitis

**METABOLIC AND ENDOCRINE DISORDERS**

- Galactosemia
- Hereditary fructose intolerance
- Urea cycle defects
- Amino and organic acidemias
- Congenital adrenal hyperplasia

**RENAL DISORDERS**

- Obstructive uropathy, ureteropelvic junction obstruction
- Renal insufficiency

**TOXIC**

- Lead
- Iron
- Vitamin A or D
- Medications (eg, ipecac, digoxin, theophylline)

**CARDIAC DISORDERS**

- Congestive heart failure
- Vascular ring

**OTHERS**

- Cannabinoid hyperemesis syndrome
- Pediatric falsification disorder (Munchausen syndrome by proxy)
- Child neglect or abuse
- Self-induced vomiting
- Autonomic dysfunction

From Vandenplas Y, Rudolph DC, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr.* 2009;49:498–547. Reproduced with permission from Wolters Kluwer Health, Inc.

among the first and most common proteins in an infant's diet and accordingly is one of the most common causes of food allergy. The prevalence of infant sensitivity to intact milk and other protein in the diet has been reported to be as high as 17% in developed countries. Such sensitivities vary in severity of reactions, are most often related to non-immunoglobulin E mediated allergy, and may be temporally dissociated from ingestion and feeding times. Similarly, although there are no studies specifically evaluating soy protein allergy, intact soy protein may also be associated with formula intolerance and vomiting. In turn, several well-controlled rigorous trials lend strong support for the use of hypoallergenic (extensively hydrolyzed or amino acid-based) formulas in formula-fed infants as well as withdrawal of cow's milk and eggs from the maternal diet in breast-fed infants. Recent evidence has implicated vitamin D deficiency as a potential modifiable risk factor for food allergy, but guidelines

around prevention and treatment in this respect have not been developed.

**Achalasia**

Achalasia is a neurodegenerative motor disorder characterized by a lack of peristalsis in the distal two-thirds of the esophagus, an elevated resting pressure in the distal esophagus, and failure of the LES to relax. The result is a functional obstruction in the lower esophagus and accumulation of food in the esophagus. This condition is extremely rare in childhood, with an incidence of 0.11 per 10,000 children annually. Children may exhibit weight loss, regurgitation of undigested food, halitosis, cough (especially when supine), or pneumonia. The most common feature on chest radiograph is an absence of air in the stomach and an air-fluid level in the esophagus. A barium esophagram often reveals a symmetrical narrowing in the distal esophagus with the appearance of a bird



beak. However, in young children with achalasia, sphincter relaxation and occasional peristalsis may be present. Esophageal manometry is often diagnostic.

### **Cyclic Vomiting Syndrome**

Cyclic vomiting syndrome is a functional, debilitating GI disorder of childhood characterized by bouts of intractable nausea and vomiting lasting for hours, accompanied by lethargy and pallor and interspersed with complete symptom relief. Reported incidence rates range from 1.7% to 2.7% of school-aged children, and the disorder has been reported in a number of countries around the world. The exact pathogenesis of cyclic vomiting syndrome remains unknown, but it has been well linked to migraine and is considered centrally mediated. During episodes, children may require hospitalization and supportive care. Although these episodes are intense in severity, in contrast to GERD, the child is completely asymptomatic between episodes. Bouts of vomiting may be triggered spontaneously, by stress, or by menstruation, and there is often a strong family history of migraine. No diagnostic test or identifiable neurologic, metabolic, or other GI disease exists to explain the condition, but recent guidelines on cyclic vomiting syndrome have been issued from both NASPGHAN and its European counterpart society to clarify the diagnostic process. Both guidelines emphasize the importance of excluding other possible conditions, including identifiable metabolic diseases, obstructive uropathy, and intracranial processes, before diagnosing cyclic vomiting syndrome.

### **Pill Esophagitis**

Pill esophagitis occurs when a pill becomes lodged in the esophagus; it is characterized by an acute onset of severe midchest or substernal pain and dysphagia. Both antibiotic treatments for acne (eg, doxycycline, minocycline) and nonsteroidal anti-inflammatory medications (eg, ibuprofen), especially in adolescents who may swallow medications without adequate liquids, have been well described as culprits in this scenario. The condition should be suspected based on history, and endoscopy may not be necessary if symptoms improve with acid-suppression therapy or sucralfate.

### **Infectious Esophagitis**

Most infectious causes of esophagitis present with odynophagia and not dysphagia. Herpes simplex virus, cytomegalovirus, and fungal infections such as candidiasis may occur in both immunocompetent and immunocompromised hosts. Upper endoscopy may be beneficial in making the diagnosis both by histopathology and by culture.

### **Rumination Syndrome**

Rumination syndrome is characterized by the regurgitation of food into the mouth with subsequent reswallowing of the material. Repeated masticatory movements, swallowing air, and tensing abdominal musculature help distinguish rumination from effortless GERD. Rumination syndrome was previously thought to occur in neurologically compromised children but is now recognized as occurring in otherwise healthy

children and adolescents. It may also be a sign of underlying psychological distress or psychiatric disorders, and its treatment generally involves professional counseling and occasionally psychiatric medications.

### **Diagnostic Procedures**

Testing to definitively diagnose reflux disorders does not exist. Instead, thoughtful and serial diagnostic procedures should document the presence of reflux or gastric contents in the esophagus, detect complications, establish a causal relationship between reflux and symptoms, evaluate the efficacy of therapies, and exclude other conditions.

### **Esophageal pH and Impedance Monitoring**

Esophageal pH with impedance monitoring represents tools that can be used independently or in combination to quantify both acid and nonacid refluxate in the esophagus. Esophageal pH is evaluated using a transnasally placed probe that records the number and duration of acid reflux episodes. Multiple intraluminal electrical impedance measures changes in electrical resistance and conductance in the mucosa when a fluid bolus moves down the esophagus, and this resistance and conductance detects nonacid and acid reflux.

Generally speaking, both esophageal pH and impedance monitoring should be performed for a clinically meaningful period of time (ie, 12 to 24 hours) with recording, allowing the physician afterward to determine the frequency and duration of reflux as well as its pH. The percentage of total time during which the esophageal pH is less than 4, referred to as *reflux index*, is considered the most valid measure of reflux. A reflux index of 12% or greater in infants younger than 1 year and 6% or greater in children older than 1 year is considered abnormal. It has been reported that up to 95% of children with mucosal evidence of esophagitis have an abnormal reflux index. On the other hand, only 50% of children with a positive pH study have esophagitis, and the severity of esophagitis has not been found to correlate with the reflux index.

Mounting evidence over the past decade has suggested that independent esophageal pH monitoring is of limited value in evaluating pediatric reflux disorders and that combined pH and multiple intraluminal impedance testing should be considered the standard. Nevertheless, combined pH and multiple intraluminal impedance testing is best recognized as a means of detecting temporal relationships between specific clinical symptoms and acid reflux, rather than an independent means of diagnosing GERD.

### **Endoscopy and Esophageal Biopsy**

The performance of upper endoscopy allows for the direct visualization of the esophageal mucosa to determine the presence and severity of injury from the reflux of gastric contents into the esophagus. Esophageal biopsies should be obtained to allow for the evaluation of the microscopic anatomy. Upper endoscopy with esophageal biopsy is useful to evaluate inflammation in the esophageal mucosa from GERD and to exclude other associated conditions with symptoms that can mimic GERD such as eosinophilic esophagitis.

However, the diagnostic benefits of upper endoscopy and esophageal biopsy must be weighed against the minimal, but not negligible, procedural and sedation risks that have been well associated with its performance.

Endoscopy with esophageal biopsies may be indicated in children with suspected GERD who fail to respond to pharmacologic therapy, or as part of the initial management if symptoms of poor weight gain, unexplained anemia or fecal occult blood, recurrent pneumonia, or hematemesis exist. It may also be helpful in the assessment of other causes of abdominal pain and vomiting in children, such as esophageal or antral webs, Crohn esophagitis, peptic ulcer, *Helicobacter pylori* infection, and infectious esophagitis.

Erosive esophagitis is reported less often in infants and children with GERD than in adults with GERD. However, a normal endoscopic appearance of the esophageal mucosa in pediatric patients does not exclude histologic evidence of reflux esophagitis. In turn, the true value of esophageal biopsy is to evaluate for conditions that may mimic the symptoms of GERD, such as eosinophilic esophagitis, infectious esophagitis, Crohn disease, or Barrett esophagus. The NASPGHAN guidelines strongly recommend endoscopy and esophageal biopsy when indicated for the evaluation of GERD in children.

### Scintigraphy

Scintigraphy involves the oral intake of radiolabeled technetium-containing liquid (formula or juice) or solid (often scrambled eggs) followed by scanning the esophagus, stomach, and lungs to detect radiolabeled colloid that has been refluxed or aspirated. In addition, the gastric emptying time may be calculated; it provides additional information for potential therapeutic intervention. Because the techniques of performing scintigraphy are not standardized and age-specific normative data are not available, its role in evaluating GERD in children remains unclear. The NASPGHAN guidelines do not recommend its routine use in the evaluation of children with reflux disorders.

### Upper Gastrointestinal Radiography

Upper GI contrast radiography generally involves obtaining a series of fluoroscopic images of swallowed barium until the ligament of Treitz is visualized, and it should be used for the purpose of delineating anatomy. Upper GI radiographic images should not be obtained to evaluate GI function or to diagnose GER or GERD because they are too brief in duration to adequately rule out the occurrence of pathologic reflux, whereas the high frequency of nonpathologic reflux during the examination can encourage false-positive diagnoses. The observation of the reflux of a barium column into the esophagus during GI contrast studies does not correlate with the severity of GERD or the degree of esophageal mucosal inflammation in patients with reflux esophagitis.

An upper GI series can be useful in the evaluation of vomiting to screen for possible anatomic abnormalities of the upper GI tract but should be recognized as involving radiation exposure. Radiation-sparing imaging may therefore be preferable. For example, in infants with bilious vomiting, an upper GI may be

useful for evaluating for possible malrotation or duodenal web. However, if persistent nonbilious vomiting in an infant has led to a suspicion of pyloric stenosis, pyloric ultrasound should be performed first and upper GI reserved for those situations in which the results of the pyloric ultrasound are equivocal.

## MANAGEMENT

Best practices regarding the management of reflux disorders in infants and children begin with an emphasis on lifestyle changes. For children who require medication, options include buffering agents, acid secretion suppressants, and promoters of gastric emptying and motility. Surgical approaches should be reserved for children who are at risk for life-threatening complications of GERD.

### Lifestyle Changes in Infants

Lifestyle changes to treat GERD in infants may involve a combination of feeding changes and positioning therapy. Modifying maternal diet, changing formulas, and reducing the feeding volume while increasing the frequency of feeds may be effective strategies to address GERD in many children. In particular, the NASPGHAN guidelines emphasize that milk protein allergy can cause a clinical presentation that mimics GERD in infants. Therefore a 2- to 4-week trial of extensively hydrolyzed protein or amino acid-based formula is recommended in formula-fed infants with GERD symptoms, and a maternal elimination diet is recommended in breastfed infants. Several studies have found that breastfed infants may benefit from a maternal diet that restricts cow's milk and eggs.

In one study of formula-fed infants, GERD symptoms resolved in 24% of infants after a 2-week trial of changing to a protein hydrolysate formula thickened with 1 tablespoon of rice cereal per ounce, limiting the volume of feeding to 120 kcal/kg per day, avoiding seated and supine positions, and avoiding environmental tobacco smoke.

Another feeding management strategy involves the use of thickened feeds—either by adding up to 1 tablespoon of dry rice cereal per 1 oz of formula or changing to commercially thickened (added rice) formulas for infants who are not cow milk protein intolerant—that is, recognized in the NASPGHAN guidelines as a reasonable management strategy for infants with both GER and GERD.

Lifestyle changes that may benefit infants with GERD include keeping them in a completely upright position or even placing them prone. A number of recent studies that use impedance and pH monitoring have confirmed older studies that used pH monitoring to demonstrate significantly less gastroesophageal reflux in infants in the flat prone position compared with the flat supine position. However, the guidelines are unequivocal that the risk for sudden infant death syndrome (see Chapter 337, Sudden Unexpected Infant Death) in sleeping infants outweighs the benefits of the prone positioning in the management of GERD and therefore prone positioning should only be considered acceptable if the infant is observed and awake. Prone positioning is suggested to be beneficial in children older than 1 year with either GER or GERD because the risk for SIDS is greatly decreased in older

age groups. Semi-supine positioning, particularly in an infant carrier or car seat, may exacerbate GER and should be avoided when possible, especially after feeding.

### **Lifestyle Changes in Children and Adolescents**

Lifestyle changes that may benefit GERD in older children and adolescents are more akin to recommendations made for adult patients, including the importance of weight loss in overweight patients, cessation of smoking, and avoiding alcohol use. Recommendations for conservatively managing GERD in older children and adolescents again may involve dietary modification and positioning changes, such as elevating the head of the bed, although the effectiveness of the latter as a treatment for GERD in older children has not been as well studied as in infants. In terms of dietary changes, older children and adolescents are advised to avoid caffeine, chocolate, alcohol, and spicy foods as potential symptom triggers. The NASPGHAN guidelines also point out that three independent studies have demonstrated decreased reflux episodes with postprandial chewing of sugarless gum.

### **Pharmacotherapeutic Agents for Pediatric Gastroesophageal Reflux Disease**

Several different medications may be used to treat GERD in infants and children. The 2 major classes of pharmacologic agents for treating GERD are acid suppressants and prokinetic agents. In addition to growing evidence that demonstrates the former to be more effective than the latter, withdrawal of cisapride from commercial availability in most countries, including the United States, has led to a disproportionate use of acid suppressants to manage children with GERD.

#### **Acid Suppressants**

The main classes of acid suppressants are antacids, H2RAs, and PPIs. The principles of using these medications in the treatment of pediatric GERD are similar to those in adults, other than the need to prescribe weight-adjusted doses and the need to consider the form of the drug prescribed (ie, for ease of ingestion in infants and children). Dosage ranges for drugs commonly prescribed for pediatric GERD are listed in Table 255-1.

#### **Antacids**

Antacids are a class of medications that can be used to directly buffer gastric acid in the esophagus or stomach to reduce heartburn and ideally allow mucosal healing of esophagitis. There is limited historical evidence that the on-demand use of antacids can lead to symptom relief in infants and children. Although antacids are generally seen as a relatively benign approach to treating pediatric GERD, it is important to recognize that they are not entirely without risk. Indeed, several studies link aluminum-containing preparations with aluminum toxicity and its complications in children. Similarly, milk-alkali syndrome, a triad of hypercalcemia, alkalosis, and renal failure, has been described in children receiving calcium-containing preparations and adds to the need for caution. According to the NASPGHAN guidelines, chronic

antacid therapy is generally not recommended for the treatment of GERD in children. In addition, the safety and efficacy of surface protective agents, such as alginates or sucralfate, an aluminum-containing preparation, have not been adequately studied in children. As such, no surface agent is currently recommended as independent treatment for severe symptoms of GERD or erosive esophagitis in children.

#### **Histamine-2 Receptor Antagonists**

H2RAs represent a major class of medications that has completely revolutionized the treatment of GERD in children. H2RAs decrease the secretion of acid by inhibiting the histamine-2 receptor on the gastric parietal cell. Expert opinion suggests little clinical difference between the various formulations of H2RAs. Randomized placebo-controlled clinical trials in children have shown that cimetidine and nizatidine are superior to placebo for the treatment of erosive esophagitis in children. Pharmacokinetic studies in school-aged children suggest that gastric pH begins to increase within 30 minutes of the administration of an H2RA and reaches peak plasma concentrations 2.5 hours after dosing. The acid-inhibiting effects of H2RAs last for approximately 6 hours, so H2RAs are quite effective if administered 2 or 3 times a day.

H2RAs have some inherent limitations, however. In particular, a fairly rapid tachyphylaxis can develop within 6 weeks of the initiation of treatment, limiting its potential for long-term use. In addition, H2RAs have been shown to be less effective than PPIs in symptom relief and healing rates of erosive esophagitis. Although most of these downsides have been demonstrated most clearly in adults, they are also thought to affect children. It is also important to recognize that cimetidine has specifically been linked to an increased risk for liver disease and gynecomastia and that these associations may be generalizable to other H2RAs.

#### **Proton Pump Inhibitors**

Most recently, PPIs have emerged as the most potent class of acid suppressants by repeatedly demonstrating superior efficacy compared with H2RAs. PPIs decrease acid secretion by inhibiting H<sup>+</sup>/K<sup>+</sup>-ATPase in the gastric parietal cell canaliculus. PPIs are uniquely able to inhibit meal-induced acid secretion and have a capacity to maintain gastric pH >4 for a longer period of time than H2RAs. These properties contribute to higher and faster healing rates for erosive esophagitis with PPI therapy compared with H2RA therapy. Finally, unlike H2RAs, the acid suppression ability of PPIs has not been observed to diminish with chronic use.

The timing of dosing most PPIs is important for maximum efficacy. Both pediatricians and subspecialists must be diligent at educating their patients to administer PPIs ideally about 30 minutes before meals. All physicians should also recognize that the metabolism of PPIs is known to differ in children compared with adults, with a trend toward a shorter half-life, necessitating a higher dose per kilogram to achieve a similar peak serum concentration and area under the curve. A fairly wide range of effective doses is evident in children. For example, an open-label study of omeprazole in children revealed that an effective

**Table 255-1** Pediatric Doses of Common Medications Prescribed for Gastroesophageal Reflux Disease

MEDICATIONS	DOSES	FORMULATIONS	FDA INDICATED AGES
Cimetidine	30–40 mg/kg/day, divided in 4 doses	Syrup	≥16 yr
Ranitidine	5–10 mg/kg/day, divided in 2 to 3 doses	Peppermint-flavored syrup Effervescent tablet	1 mo–16 yr
Famotidine	1 mg/kg/day, divided in 2 doses	Cherry-banana-mint flavored oral suspension	1–16 yr
Nizatidine	10 mg/kg/day, divided in 2 doses	Bubblegum-flavored solution	≥12 yr
Omeprazole	1–3 mg/kg/day (can be single dose or divided in 2 doses). Should be administered 30 min before eating or on an empty stomach	Sprinkle contents of capsule onto soft foods	2–16 yr
Lansoprazole	1–3 mg/kg/day (can be single dose or divided in 2 doses). Should be administered 30 min before eating or on an empty stomach	Sprinkle contents of capsule onto soft foods or select juices Administer capsule contents in juice through nasogastric tube Strawberry-flavored disintegrating tablet Orally disintegrating tablet via oral syringe or nasogastric tube (≥8 French)	1–17 yr
Esomeprazole	Variable by age from 1 mo to >12 yr	Sprinkle contents of capsule onto soft foods Administer capsule contents in juice through nasogastric tube	1–17 yr
Rabeprazole	20 mg daily	Oral tablet	12–17 yr
Dexlansoprazole	30–60 mg daily	Oral tablet	No pediatric indication
Pantoprazole	40 mg daily (adult dose)	Oral tablet	No pediatric indication

dosage range was 0.7 to 3.3 mg/kg daily, based on improvement in clinical symptoms and the results of esophageal pH monitoring. Lansoprazole 0.7 to 3 mg/kg daily improved GERD symptoms and healed all cases of erosive esophagitis in the treatment of 1- to 12-year-old children with GERD. Other trials of PPI therapy support the efficacy of treatment for severe esophagitis and esophagitis refractory to H<sub>2</sub>RAs in children.

As in adults, PPIs are considered safe and generally well tolerated with relatively few side effects. In terms of their long-term use, published studies have reported PPI use for up to 11 years in small numbers of children. The US Food and Drug Administration has approved a number of PPIs for use in children in recent years, including omeprazole, lansoprazole, and esomeprazole for children 1 year and older and rabeprazole for children 12 years and older. Nonetheless, the new guidelines strike a note of caution when they also discuss reports describing a dramatic rise in past years in the number of PPI prescriptions written for children, particularly infants who may be at increased risk for lower respiratory tract infections.

The overuse or misuse of PPIs in infants with reflux is a matter for great concern. Placebo-controlled trials in infants have not demonstrated superiority of PPIs over placebo for reduction in irritability. Headaches, diarrhea, constipation, and nausea have been described

as occurring in up to 14% of older children and adults prescribed PPIs. Although considered a benign histologic change, enterochromaffin cell hyperplasia has recently been demonstrated in up to 50% of children receiving PPIs for more than 2½ years. Finally, a growing body of evidence suggests that acid suppression in general with either H<sub>2</sub>RAs or PPIs may be a risk factor for pediatric community-acquired pneumonia, gastroenteritis, candidemia, and necrotizing enterocolitis in preterm infants.

### Prokinetic Agents

The desired pharmacologic effects of prokinetic agents include improving the contractility of the body of the esophagus, increasing lower esophageal sphincter pressure, and increasing the rate of gastric emptying. To date, efforts to design a prokinetic agent with benefits that outweigh deleterious side effects have proved difficult. Even metoclopramide, the most common prokinetic agent still available, recently received a Black Box warning regarding adverse side effects, which have been reported in 11% to 34% of patients, including drowsiness, restlessness, and extrapyramidal reactions. Although a meta-analysis of 7 randomized controlled trials of metoclopramide in patients younger than 2 years with GERD confirmed a decrease in GERD symptoms, it was clearly at the cost of such significant side effects. Other drugs in this category



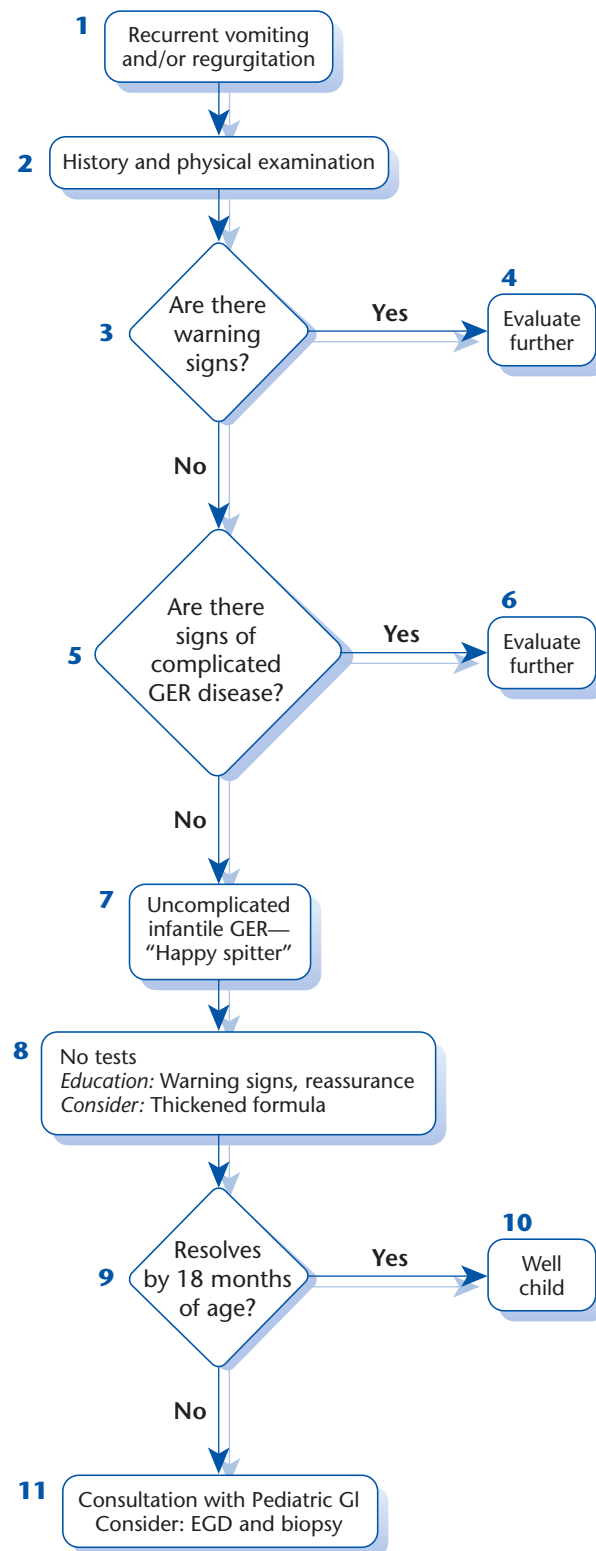
include bethanechol, cisapride, baclofen, and erythromycin. Each works as a prokinetic by using a different mechanism. Nevertheless, after careful review, the NASPGHAN guidelines unequivocally state that there is insufficient evidence to support the routine use of any prokinetic agent for the treatment of GERD in infants or older children.

### Surgery as a Management Strategy in Gastroesophageal Reflux Disease

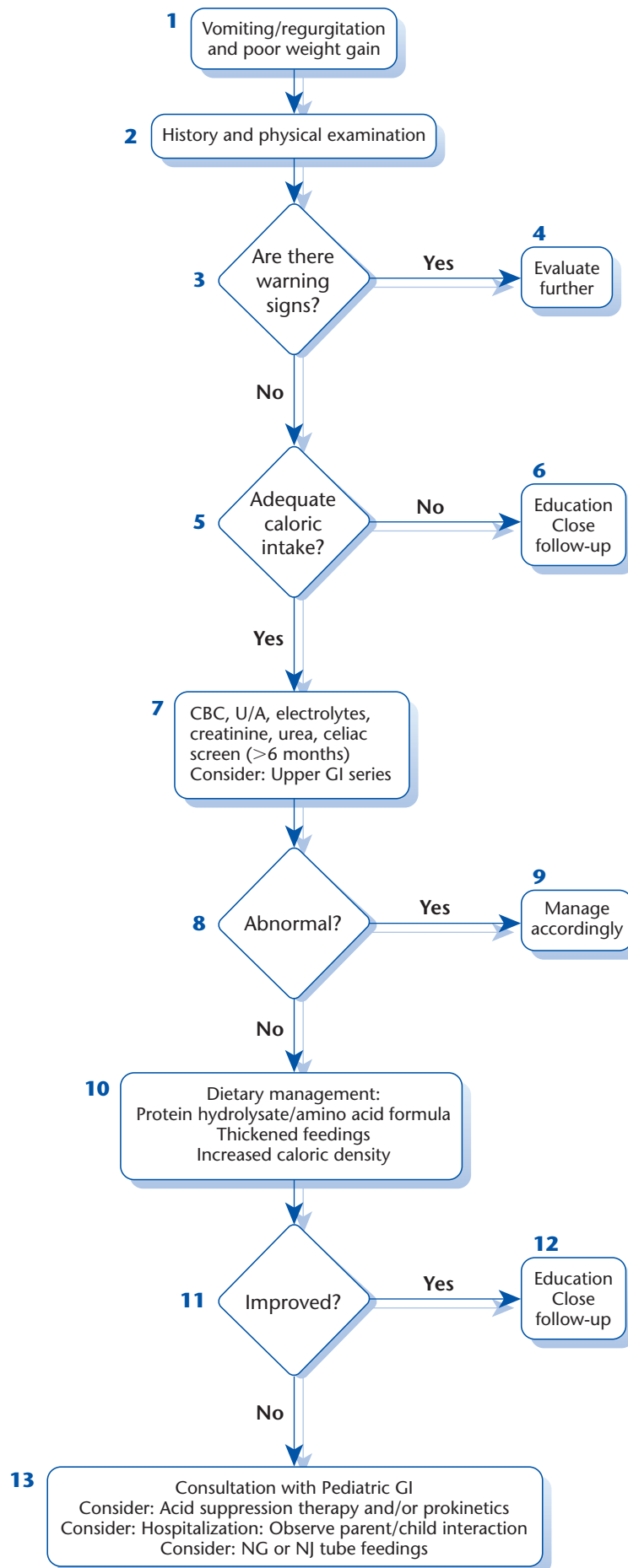
Several surgical procedures can be used to decrease gastroesophageal reflux disorders in children. Fundoplication, whereby the gastric fundus is wrapped around the distal esophagus, is most common and can prevent reflux by increasing the baseline pressure of the lower esophageal sphincter, decreasing the number of transient lower esophageal sphincter relaxations, and increasing the length of the esophagus that is intra-abdominal to accentuate the angle of His and reduce a hiatal hernia, if indicated. Total esophagogastric dissociation is another operative procedure that is rarely used after failed fundoplication. Both procedures carry significant morbidity and do not reduce the risk for the direct aspiration of oral contents. Careful patient selection is one of the keys to successful outcome. Children who have failed pharmacologic treatment may be candidates for surgical therapy, as are children at direct life-threatening risk for aspiration of their gastric contents. In most patients, if acid suppression with PPIs is ineffective, the accuracy of the diagnosis of GERD should be reassessed because fundoplication may not produce optimal clinical results. Clinical conditions such as cyclic vomiting, rumination, gastroparesis, and eosinophilic esophagitis should be carefully ruled out before surgery because they are likely to still cause symptoms after surgery. If anti-reflux surgery is pursued, the NASPGHAN guidelines also stress the importance of providing families with adequate counseling and education before the procedure so that they have a “realistic understanding of the potential complications . . . including symptom recurrence.”

### SUMMARY

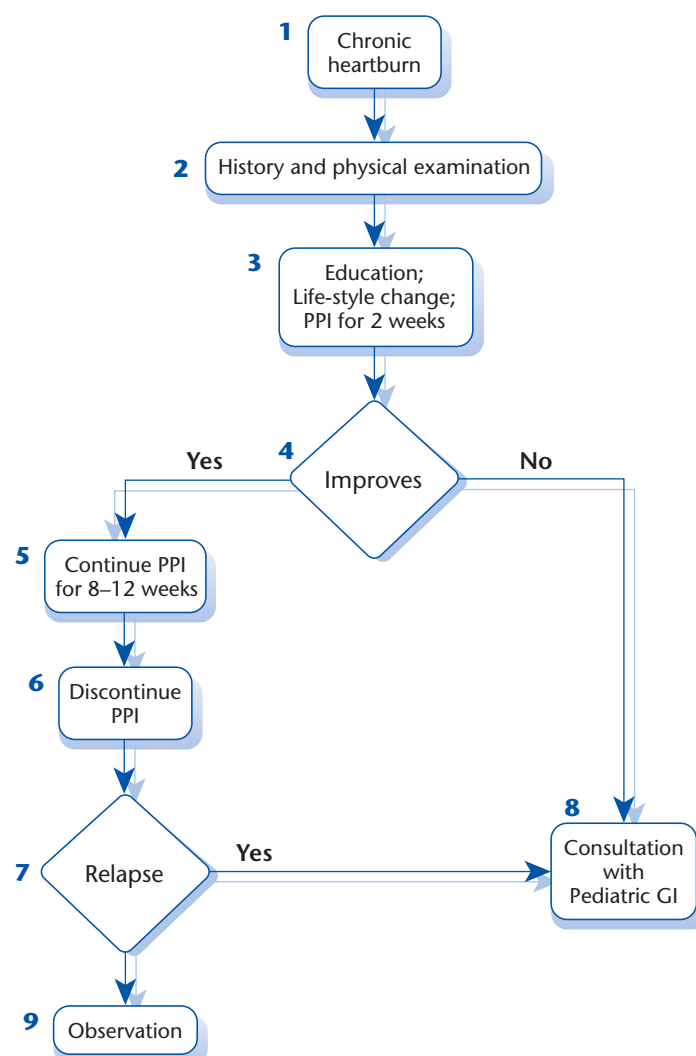
Reflux disorders affect all pediatric age groups. Using an evidenced-based, best practice approach to both testing and managing reflux in infants and children depends on distinguishing GERD from numerous other disorders. In the infant with uncomplicated recurrent regurgitation, it may be important to recognize physiologic GER that is effortless, painless, and not affecting growth (see Figure 255-3). In this situation, physicians should focus on minimal testing and conservative management that emphasizes lifestyle changes and avoids overuse of medications. Physicians must also be able to recognize infants with recurrent regurgitation and troublesome symptoms of GERD (see Figure 255-4). Weight loss or poor growth in infants may be a crucial warning sign that should alter clinical management. Older children with heartburn may benefit from empirical treatment with PPI (see Figure 255-5).



**Figure 255-3** Approach to the infant with recurrent regurgitation and vomiting. (From Vandeplass Y, Rudolph DC, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr.* 2009;49:498–547. Reproduced with permission from Wolters Kluwer Health, Inc.)



**Figure 255-4** Approach to the infant with vomiting, regurgitation, and weight loss. (From Vandenplas Y, Rudolph DC, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr.* 2009;49:498-547. Reproduced with permission from Wolters Kluwer Health, Inc.)



**Figure 255-5** Approach to the adolescent with complaint of chronic heartburn. (From Vandenplas Y, Rudolph DC, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr.* 2009;49:498–547. Reproduced with permission from Wolters Kluwer Health, Inc.)

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Infants Reflux Checklist* (handout), North American Society for Pediatric Gastroenterology and Nutrition (NASPGHAN) and NASPGHAN Foundation ([www.gikids.org/files/documents/resources/GERD-Infant%20checklist\\_.pdf](http://www.gikids.org/files/documents/resources/GERD-Infant%20checklist_.pdf))
- *Infant Reflux and GERD: Distinctions Management* (video), North American Society for Pediatric Gastroenterology and Nutrition (NASPGHAN) and NASPGHAN Foundation ([www.gikids.org/files/multimedia/pedgerd\\_v3\\_final.swf](http://www.gikids.org/files/multimedia/pedgerd_v3_final.swf))
- *Parent's Take Home Guide to GERD* (fact sheet), North American Society for Pediatric Gastroenterology and Nutrition (NASPGHAN) and NASPGHAN Foundation ([www.gikids.org/files/documents/resources/GERD%20Parent%20Take%20Home%20Guide\\_11-13-13.pdf](http://www.gikids.org/files/documents/resources/GERD%20Parent%20Take%20Home%20Guide_11-13-13.pdf))

- *Pediatric GERD* (video), Information Television ([www.itvisus.com/programs/hbhm/episode\\_1004\\_Pediatric\\_GERD.asp](http://www.itvisus.com/programs/hbhm/episode_1004_Pediatric_GERD.asp))

### Medical Decision Support

- *Reflux & GERD* (fact sheet), North American Society for Pediatric Gastroenterology and Nutrition (NASPGHAN) and NASPGHAN Foundation ([www.gikids.org/content/8/en/Reflux-GERD](http://www.gikids.org/content/8/en/Reflux-GERD))

## SUGGESTED READINGS

- Lightdale JR, Gremse DA. Gastroesophageal reflux: management guidance for the pediatrician. *Pediatrics.* 2013;131(5):e1684–e1695
- Vandenplas Y, Rudolph CD, Di Lorenzo C, et al; North American Society for Pediatric Gastroenterology, Hepatology and Nutrition; and European Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr.* 2009;49(4):498–547

## Chapter 256

# GASTROINTESTINAL ALLERGY

Minou Le-Carlson, MD; John A. Kerner Jr, MD

## INTRODUCTION

Food allergy is a common but often unsubstantiated diagnosis in pediatric practice. An adverse reaction to a food is any untoward reaction regardless of its cause. Such reactions can be classified under 2 general categories: food allergy or hypersensitivity, an immunologic response; and food intolerance, a nonimmunologic response.

## DEFINITIONS

### Food Allergy

The gastrointestinal (GI) tract contains lymphoid tissue capable of mounting an immunologic response to prevent the penetration of antigens across the epithelium. Lymphocytes and plasma cells, including those containing immunoglobulin A (IgA), are present in Peyer patches and the lamina propria of the small and large intestine. The aberrations in immunologic mechanisms that trigger GI allergic reactions are incompletely understood.

The subsequent immunologic response to antigen can be in the form of an immunoglobulin E (IgE)-mediated (immediate GI hypersensitivity and oral allergy syndrome), non-IgE/T-cell-mediated syndrome, or *mixed* GI reaction allergy syndromes. Non-IgE-mediated or T-cell-mediated allergic GI disorders include dietary protein enteropathy, protein-induced enterocolitis, and proctitis. Mixed GI allergy syndromes include eosinophilic esophagitis and eosinophilic gastroenteritis. All of these conditions share a common denominator: the response of the immune system to a specific protein, leading to pathologic inflammatory changes in the GI tract.

GI food allergy can be further divided into 2 types: that involving a specific allergy (a self-limited, mainly T-cell-mediated condition in younger patients that resolves in most by the toddler age), and that characterized by eosinophilic or allergic GI disease with multiple food sensitivities (a more permanent condition caused by a combination of immediate hypersensitivity and non-IgE mechanisms).

Foods that account for 90% of allergic reactions in children are cow's milk protein, eggs, peanuts, soy, tree nuts, wheat, and fish, including shellfish. Food allergies are much more common in infants than in older children because infants may be predisposed to protein allergy caused by enzymatic immaturity, increased gut permeability, and relatively low secretory IgA. Cow's milk protein allergy (CMPA) and soy protein allergy are the most clearly defined allergies in infants.

### Food Intolerance

Meanwhile, food intolerances, unlike food allergies, are non-immune mediated processes. Food intolerance

can occur because of an underlying congenital or acquired enzyme deficiency (eg, disaccharidase deficiency, galactosemia, hereditary fructose intolerance) in which a specific dietary nutrient cannot be metabolized properly; ingestion of a toxin in the food (*Staphylococcus*, shellfish, mushrooms); or ingestion of a pharmacologic agent (metabisulfite in wine or salad may cause bronchospasm, wine and monosodium glutamate may cause headache, and caffeine may cause arrhythmia).

## FOOD ALLERGY

### Clinical Manifestations

#### Cow's Milk Protein Allergy

$\beta$ -Lactoglobulin, the main whey protein, seems to be the most antigenic component of cow's milk, but some infants can be sensitive to casein or whey protein. Early studies showed that the incidence of CMPA was between 0.5% and 7% of all infants under the age of 6 months. Later studies suggested that 2.5% of newborns will have hypersensitivity to cow's milk in the first year of life. Rarely do infants develop CMPA after the first year of age. Previously, physicians counseled families that infants with CMPA would outgrow it by 2 years of age. Later studies revealed that allergy may persist in 72% at age 2, 44% at age 4, and 32% at age 6. Other studies are less pessimistic, finding 44% with persistent symptoms at 1 year, 33% at 2 years, and 23% at 3 years. Patients who have longer persistence of symptoms have a higher frequency of allergic disease and multiple food allergies, and develop symptoms later after initial introduction of milk.

The symptoms and signs of CMPA are listed in Box 256-1. GI symptoms predominate in many patients.

### BOX 256-1 Clinical Manifestations of Cow's Milk Protein Allergy

#### SYSTEMIC MANIFESTATIONS

- Anaphylaxis
- Iron-deficiency anemia (caused by gastrointestinal blood loss)
- Atopic dermatitis, urticaria
- Peripheral eosinophilia
- Poor sleep

#### RESPIRATORY MANIFESTATIONS

- Rhinitis
- Wheezing
- Pulmonary hemosiderosis
- Nasopharyngeal obstruction leading to cor pulmonale

#### GASTROINTESTINAL (GI) MANIFESTATIONS

- Vomiting or gastroesophageal reflux
- Diarrhea, malabsorption, protein-losing enteropathy
- Enterocolitis
- Constipation
- GI bleeding
- Failure to thrive



In other patients, anaphylaxis or pulmonary symptoms occur. Infants with severe atopic dermatitis should also be evaluated for possible CMPA and other food allergy.

The GI manifestations of CMPA depend on the site of predominant inflammation in the GI tract. Esophagitis causes recurrent vomiting and reflux; gastritis causes vomiting, irritability, pain, and occult GI bleeding; enteritis causes diarrhea, malabsorption, or protein-losing enteropathy; and colitis causes rectal bleeding with blood or mucus in the stool.

Although CMPA is more typically associated with colitis symptoms, other symptoms, including gastroesophageal reflux and cow's milk allergic esophagitis, are now well described. Food allergy or formula sensitivity should always be considered in patients with refractory reflux because these 2 conditions may coexist. Antral gastritis is a common finding in these patients, with increased eosinophils and inflammatory cells in the antrum. Duodenal biopsy specimens reveal patchy changes, ranging from normal mucosa to *flat gut* lesions. Differentiation from celiac disease is made by the absence of antiendomysial or anti-tissue transglutaminase antibodies (see Chapter 259, Gluten-Sensitive Enteropathy [Celiac Sprue]).

Again, the most common findings in CMPA are colitis findings, such as blood and mucus in the stool. Allergy is the most common cause of rectal bleeding among infants younger than 6 months. Rectal bleeding or guaiac-positive stools are among the most common symptoms in infants with formula sensitivity. A significant number of these infants experience straining or discomfort with stools.

In rare instances, some infants can exhibit severe enterocolitis. Profuse vomiting and/or diarrhea can lead to shock, anemia, and methemoglobinemia. Patients with milk protein-induced enterocolitis may be predisposed to a severe, rare form of enterocolitis to solid food antigens later in life. These children can develop severe reactions to food proteins considered to be of low allergenicity.

### Soy Protein Allergy

Among infants with enterocolitis caused by cow's milk allergy, 30% or more had similar reactions to soy-based formula. The clinical features of soy protein allergy are similar to those of CMPA discussed previously, including esophagitis, gastritis, enteritis, and colitis. In general, soy allergies are much less common than cow's milk allergies. Only 12% of all patients with CMPA will have concomitant allergy to soy protein.

### Human Milk Allergy

Infants who are breastfed may develop the same manifestations as patients who are formula fed, exhibiting either allergic colitis or evidence of esophagitis, gastritis, or enteritis; the most common seems to be colitis. These patients are often asymptomatic or may show significant irritability as a manifestation of their disease, with either occult blood or obvious rectal bleeding.

### Laboratory Abnormalities in Gastrointestinal Food Allergies

The results of IgE determinations and RAST (Radioallergosorbent test) to detect these IgE antibodies specific

for milk and soy proteins usually are negative, suggesting that the immunologic mechanism occurs by means of a non-IgE (T-cell-mediated) mechanism. A significant number of these patients also have a concomitant transient hypogammaglobulinemia or hypoalbuminemia caused by protein-losing enteropathy; treatment of the milk or soy allergy or other food allergy results in normalization of serum proteins. In addition, infants with formula allergy may not necessarily have elevated eosinophils in the blood, but typically will demonstrate an eosinophilic infiltration in GI biopsies. Reports indicate that more than 20 eosinophils per high-power field on rectal biopsy specimens is suggestive of an allergic cause for colitis. However, eosinophilic infiltration is a nonspecific finding that can occur in any inflammatory lesion of the GI tract, including infection.

### Management

Treatment of food allergy includes primary prevention to prevent sensitization to proteins. The previous recommendations of the American Academy of Pediatrics were revised in 2008 and are listed in Box 256-2. The most recent report from the GINI (German Infant Nutritional Intervention) study shows that the exclusive use of a partial or extensive hydrolysate formula significantly decreases rates of atopic dermatitis. Additional evidence for the benefit of partially hydrolyzed formulas for primary prevention has been recently supported by a meta-analysis and an accompanying editorial. Secondary prevention involves preventing recurrence of symptoms once they occur by removing specific food

#### BOX 256-2 American Academy of Pediatrics Recommendations for Prevention of Allergy

- Nutritional interventions are largely limited to infants at high risk of developing allergy (ie, infants with at least 1 first-degree relative with allergic disease).
- There is evidence that compared to intact cow's milk protein formula, exclusive breastfeeding for at least 4 months prevents or delays the occurrence of atopic dermatitis, cow's milk allergy, and wheezing.
- There is modest evidence that atopic disease may be delayed or prevented by the use of extensively or partially hydrolyzed formulas compared with intact cow's milk formula, particularly for atopic dermatitis.
- There is little or no current convincing evidence that the timing (delaying) of introduction of complementary foods beyond 4 to 6 months of age prevents the occurrence of atopic disease.
- There is no convincing evidence for the use of soy formula for allergy prevention.
- Current evidence does not support maternal dietary restrictions during pregnancy or lactation.

From Greer FR, Sicherer SH, Burks AW; American Academy of Pediatrics Committee on Nutrition and Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics*. 2008;121(1):183-191.

allergens from the diet to ameliorate symptoms. Secondary prevention is accomplished with either extensively hydrolyzed formulas or elemental formulas. Categories of formulas are listed in Table 256-1, and a comparison of partial versus extensive hydrolysates appears in Table 256-2.

### Cow's Milk or Soy Protein Allergy

Many choices are available for formula, and the primary care physician should be familiar with the different protein bases.

Once the formula-fed infant either is suspected of having, or has been diagnosed as having, a specific protein allergy, the infant initially should be fed a hypoallergenic formula. The choice of formula will depend on the formula the patient is taking at the time of diagnosis. If the patient is taking a milk-based or soy-based formula, then starting with an extensively hydrolyzed casein hydrolysate formula, such as Alimentum, Nutramigen, or Pregestimil, is appropriate. A partially hydrolyzed whey formula may be helpful in reducing the risk of CMPA, but should not be used as treatment of existing allergy symptoms. Among partially hydrolyzed formulas, Good Start has been studied extensively but Gentlease has not.

The allergy may last as little as 3 to 12 months; therefore, this period is one of trial and error as the patient is gradually retried on the previously proved allergen.

Approximately 10% to 15% of infants placed on casein hydrolysate formula still have a persistent sensitivity as evidenced by continual guaiac-positive stools or overt GI bleeding. Many of these patients respond to the L-amino acid formulas, such as Neocate and Elecare. These formulas are expensive and should be used only when persistent sensitivity to all other formulas is well documented.

Milk or milk products from animals other than cows have also been used anecdotally. An example is sheep's or goat's milk. A risk of using such a product is the possible cross-reactivity between cow's milk and sheep's or goat's milk proteins, as well as nutrient deficiencies (ie, folate deficiency in goat's milk).

Of note, studies have examined the long-term growth affects of using various types of formulas (including partial and extensive hydrolysates) on children during the first 16 weeks of life. In a prospective study following German children, there does seem to be a slowing of body mass index (BMI) in the first year of life for infants on extensively hydrolyzed formulas when compared to other types of formulas and breast milk. However, no appreciable growth differences among these children were noted when followed up to 10 years of age.

Treatment in breastfed infants who are sensitive to mother's milk and present with rectal bleeding involves persuading the mothers to avoid cow's milk and soy products, but not all infants will respond to this

**Table 256-1** Nonstandard Infant Formulas

PROTEIN SOURCE	ALLERGENICITY	EXAMPLES
Soy protein with L-methionine	—	Bright Beginnings Soy, Good Start Supreme Soy, Isomil Advance, Enfamil Prosobee
Partially hydrolyzed whey	—	Good Start Supreme
Partially hydrolyzed casein, partially hydrolyzed whey	—	Gentlease
Casein hydrolysate	Hypoallergenic	Alimentum, Nutramigen, Pregestimil
Amino acid base	Nonallergenic	Neocate, Elecare

**Table 256-2** Soy vs Partial vs Extensive Hydrolysates vs L-Amino Acid Formulas

CATEGORY	SOY	PARTIALLY HYDROLYZED <sup>a</sup>	EXTENSIVELY HYDROLYZED <sup>b</sup>	L-AMINO ACID
Decreases protein sensitization	No	Yes	Yes	Yes
Treatment for established CMPA	No	No	Yes	Yes
Type of formula	Routine	Routine	Specialty	Specialty
Cost	Comparable with standard cow's milk	Comparable with standard cow's milk formula	3 to 4 times more costly than standard	Even more expensive than extensively hydrolyzed formula
Palatability	Comparable with standard	Comparable with standard	Less than standard	Less than standard formula

CMPA, Cow's milk protein allergy.

<sup>a</sup>Partially hydrolyzed whey.

<sup>b</sup>Extensively hydrolyzed casein.

measure. Strict maternal diet avoidance of cow's milk, soy, and other potentially allergenic foods can be very challenging and lead to maternal nutritional deficiencies and weight loss. Mothers should be told that, by far, most infants who show sensitivity to foods the mother is eating do not have severe disease. Therefore, breastfeeding can be continued unless the symptoms are significant. Mothers who exclude multiple foods from their diets should consider vitamin and calcium supplementation. Sometimes using a hypoallergenic formula may be worth a trial to determine if the infant's symptoms disappear.

## EOSINOPHILIC GASTROINTESTINAL DISORDERS

Eosinophilic (or allergic) GI disorders (EGIDs) are a family of diseases characterized by the abnormal infiltration of the GI tract with eosinophils. EGIDs are subdivided into the specific anatomic area of inflammation within the GI tract, such as eosinophilic esophagitis (EoE), eosinophilic gastroenteritis, and eosinophilic colitis. With the exception of EoE, EGIDs are further classified by the depth of GI involvement into the categories of mucosal disease, muscular disease, and serosal disease.

For primary or allergic EGIDs, patients cannot have other causes of eosinophilic infiltration such as hypereosinophilic syndrome or parasitic infection, or reactive-type causes of inflammation such as inflammatory bowel disease, celiac disease, nutritional deficiencies, or neoplasms.

### Incidence

Although allergic gastroenteropathies were previously thought to be rare, EoE has become well recognized. Incidence is 4 in 10,000, but this may be underestimated because all incidence studies are based on referrals. The increased incidence seems to be the result of a combination of a higher index of suspicion and a true increase in pediatric allergy. Interestingly, the prevalence of EoE in children has been found to vary among certain populations: it was found to be 4% among patients with celiac disease in one cohort study. Meanwhile, the incidence of the rarer forms of EGIDs is not well characterized.

### Etiology

Causes for EGIDs have included sensitization to aeroallergens, autoimmune processes, ingested food allergies, and predisposition as a result of severe reflux or cutaneous atopy.

### Pathologic Considerations

IgE-dependent and IgE-independent mechanisms are thought to be involved in the pathogenesis of these conditions. The presence of peripheral eosinophilia, systemic allergies, elevated IgE levels, and therapeutic response to steroids indicates an allergic basis for this disease in some patients. Indeed, more than 50% of patients with EGID have a personal history of allergy, such as eczema, asthma, allergic rhinitis, or multiple food sensitivities.

## Clinical Manifestations

Patients with EoE have variable manifestations. Symptoms may include a feeding disorder, abdominal pain, or vomiting. Young children may have symptoms mimicking those of gastroesophageal reflux, but they usually have normal pH probe studies and fail to respond to antireflux medications. Older children may have dysphagia for solids or food impaction. A landmark study in 1995 involved a group of children previously diagnosed as having severe reflux that was unresponsive to medical and often surgical treatment. Esophageal biopsy specimens showed up to 100 eosinophils per high-power field. Allergies to multiple foods were found using a combination of prick skin tests and food challenges. The patients' symptoms resolved on an elemental diet. Follow-up biopsy specimens showed marked reduction in symptoms and esophageal eosinophils. Follow-up studies have corroborated these findings.

The other EGIDs have symptoms that vary with the anatomic site of eosinophilia and the depth of eosinophilic infiltration. Features are listed in Box 256-3. For example, mucosal disease causes dysphagia and heartburn if limited to the esophagus; nausea, bloating, and vomiting if involving the stomach; protein-losing enteropathy, malabsorption, and diarrhea if involving the small bowel; and bloody stools if involving the colon. In children, mucosal disease can often lead to anemia and growth failure. In submucosal or muscular disease, prominent inflammation in the stomach antrum can lead to pyloric obstruction. In serosal disease, which causes eosinophilic ascites, symptoms resemble peritonitis. The latter 2 types are less common in children. Because EGIDs have no classic symptoms, they can go undetected for several years. Furthermore, whether these entities are variants of similar disease processes or distinctly different conditions remains to be determined.

## Differential Diagnosis

The diagnosis of EGID is based on clinical features as well as laboratory and radiographic findings. Endoscopy is essential to confirm a diagnosis; therefore,

### BOX 256-3 Features of Eosinophilic (Allergic) Gastroenteritis<sup>a</sup>

#### MUCOSAL FORM

- Nausea, vomiting, colicky abdominal pain, diarrhea
- Occult blood loss, iron deficiency anemia
- Protein-losing enteropathy leading to hypoalbuminemia
- Failure to thrive/growth failure

#### MUSCLAR (TRANSMURAL) FORM

- Obstructive symptoms, mimicking pyloric stenosis or thickening of the gastric outlet

#### SEROSAL FORM

- Eosinophilic ascites

<sup>a</sup>Approximately 75% of affected patients have peripheral eosinophilia (with all 3 types).

collaboration with a pediatric gastroenterologist is necessary. A pediatric allergist can help direct specific testing for allergy.

For EoE, diagnosis is based on a typical patient or family history of allergy, an evaluation to rule out reflux, typical eosinophilic infiltration of the esophagus on the biopsy specimen, and allergy testing. Because the mechanism of allergic GI diseases is likely on a spectrum between immediate hypersensitivity and cell-mediated immunity, the value of any single test is variable. However, confirmation of food allergy is recommended, because 50% to 90% of suspected food allergies are not substantiated. Methods that collectively may play a role in the identification of food allergens include skin puncture test, directed IgE testing, food elimination, and oral food challenges. Peripheral eosinophilia occurs, and an elevated IgE level is a variable finding. Their absence does not rule out EoE. Radiographic studies, including an esophagram, may show thickened folds or a narrowing of the esophagus. On endoscopy, the mucosa may seem grossly normal, but suggestive findings are often apparent, especially the classic ringed or furrowed esophagus and white exudates (seen exclusively in EoE). Although scattered eosinophils are normal throughout the rest of the GI tract, they are pathologic when seen in the esophagus. In the past, eosinophils in the esophagus were attributed to reflux. Current research shows the esophageal eosinophilia in reflux is mild (<15 eosinophils per high-power field) and usually limited to the distal esophagus. In EoE, the eosinophilia is severe (>15 eosinophils per high-power field) and can involve most of the length of the esophagus.

The evaluation of other forms of EGID is similar, with identification of concurrent forms of allergy. Allergy testing, as mentioned, can be positive for multiple food allergies. Laboratory studies may also include elevated peripheral eosinophils and IgE levels, as well as hypoalbuminemia and low immunoglobulin levels caused by malabsorption and protein-losing enteropathy. If long-term blood loss exists, then laboratory studies may show iron-deficiency anemia. Radiographic studies, including an upper GI tract study, may show thickened folds caused by edema in the stomach or possibly gastric outlet obstruction. A small bowel follow-through may show an edematous or nodular small bowel. Although no strict criteria have been clearly established for nonesophageal forms of EGIDs, in general, less than 50 eosinophils per high-power field is considered consistent with EGID. Gastric abnormalities, found more commonly in the antrum, have been described as being consistent in the mucosal form of the disease. Typical findings include gastritis, with destruction and regeneration of gastric glands and surface epithelium, as well as marked eosinophilic infiltration. If the allergic gastroenteropathy involves the small bowel, then the lesions are in a patchy distribution, ranging from areas of normal mucosa to a flat villus lesion. Eosinophilic infiltration may be mild or marked.

### Management

Because allergic gastroenteropathies have variable manifestations and lapsing and remitting courses,

management must be individualized with the assistance of a pediatric gastroenterologist and allergist. Unless concomitant gastroesophageal reflux exists, patients do not usually respond to histamine-2 blockers or proton-pump inhibitors. Food diaries can be confusing; for example, if the patient experiences a delayed hypersensitivity reaction, then symptoms are not apparent when foods are ingested, but instead occur days later. However, if foods are identified as positive using a combination of tests for immediate or delayed hypersensitivity and food challenges, then these foods should be eliminated from the diet. The most common foods implicated are, in order, milk, egg, soy, corn, and wheat, although several foods may be found to cause symptoms. Dietary elimination of these allergens may alleviate most of the symptoms. In EoE, identification of individualized allergens has been demonstrated through a 6-food elimination diet in which several common allergens are collectively avoided (cow's milk, soy, wheat, egg, peanut, and seafood). Subsequently, each food is serially reintroduced followed by a repeat endoscopy in an attempt to identify causative antigens of inflammation. Some patients require complete dietary elimination via an L-amino acid-based formula. The advantage of dietary management is good rates of cure. However, severely restrictive diets may be difficult for children and may create social and behavioral issues. Exclusive reliance on specialized formulas can be extremely expensive. In instances of severe disease where elemental formulas are necessary, but refused orally, tube feeding (nasogastric or gastrostomy) may be considered.

For patients who are unable to follow a restrictive diet, corticosteroid therapy may be required intermittently. Systemic steroids have the advantages of quick improvement of symptoms and normalization of tissue on biopsy specimens. However, they cannot be used on a long-term basis, and eosinophilic infiltration and symptoms can recur after discontinuing therapy. Topical steroids, such as swallowed fluticasone propionate, improve symptoms and histologic findings in EoE. Oral budesonide, when mixed into a viscous, slurry form, is also effective, especially in younger patients who have trouble swallowing fluticasone. Again, symptoms and baseline histologic findings may return upon discontinuation. Topical treatment may be associated with esophageal candidiasis. Oral cromolyn sodium (Gastrochrome) has not been proved helpful in EoE but may have a beneficial role in eosinophilic gastroenteritis. Leukotriene receptor antagonists may be beneficial in eosinophilic gastroenteropathy in improving symptoms, but they do not change histologic findings. Symptomatic strictures resulting in food impactions or severe dysphagia may require endoscopic dilatations, and pyloric obstructive disease may require surgery. If patients have other symptoms of allergy or atopy, then these should be addressed as well.

### Prognosis

The natural history of EoE remains unclear. Among adults with misdiagnoses of reflux who were eventually found to have EoE, some develop strictures requiring dilation. The esophagus can be friable, tearing



with the mere passage of an endoscope. The possible evolution to Barrett esophagus remains to be studied.

Although extensive follow-up studies are lacking, evidence indicates that the EGIDs are lifelong conditions with remissions and exacerbations, often requiring careful dietary manipulation and intermittent steroid therapy. Preliminary data also suggest that younger adolescents go through a phase in which they are much better able to tolerate foods to which they were previously sensitive. If the EGID produces significant malabsorption, then osteoporosis may occur.

## CONCLUSION

GI food allergy is an immunologic response to an antigen often leading to nonspecific GI symptoms, depending on the anatomic location of involvement. Such GI allergy can involve a specific allergen, as is the case in cow's milk or soy protein allergy found in younger children, or multiple food sensitivities, as found in allergic or eosinophilic GI disease. The underlying immune mechanisms for cow's milk or soy protein allergy are thought secondary to non-IgE mechanisms, whereas EGIDs involve a combination of immediate hypersensitivity and non-IgE mechanisms. The diagnosis of cow's milk or soy protein allergy is largely clinical. For the diagnosis of EGIDs, allergy, laboratory, and radiographic testing may be supportive with confirmation of disease made through GI biopsies via endoscopy or colonoscopy. The mainstay of therapy is identification and avoidance of allergens. For EGIDs, medications and steroids often play a role in management. For specific allergens, such as cow's milk or soy protein, the condition is often self-limited. In the case of EGIDs, the condition is often a lifelong disease with a remitting and relapsing course.

### WHEN TO REFER

- Poor weight gain
- Immediate GI response after particular food or foods
- Incomplete response to exclusion or elemental diet
- Multiple food allergies
- Multiple allergic symptoms
- Malabsorption or protein-losing enteropathy
- Gastroesophageal reflux disease recalcitrant to appropriate therapy
- Suspicion of eosinophilic esophagitis

### WHEN TO ADMIT

- Anaphylaxis
- Severe malnutrition

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Kids With Food Allergies* (Web site), ([www.kidswithfoodallergies.org](http://www.kidswithfoodallergies.org))

## AAP POLICY

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## Chapter 257 GASTROINTESTINAL OBSTRUCTION

Jeffrey S. Mino, MD; Rosebel Monteiro, MD; Anthony Stallion, MD

Gastrointestinal obstruction (GIO) during infancy, childhood, and adolescence is relatively uncommon, but often presents a diagnostic challenge (Table 257-1). Obstructions that occur distal to the pylorus are potential surgical emergencies, and the younger the patient, the more ominous the probable cause and the more urgent the required therapy. Therefore, the pediatrician must be continually alert for a GIO to facilitate early diagnosis and thus prevent significant morbidity.

## EVALUATION

### History

The symptoms and signs of a GIO (Table 257-2, Figure 257-1) vary considerably but involve the following, either singly or in combination: vomiting (often bilious), abdominal pain, abdominal distention (see

**Table 257-1** Summary of Pediatric Gastrointestinal Obstruction and Surgical Intervention

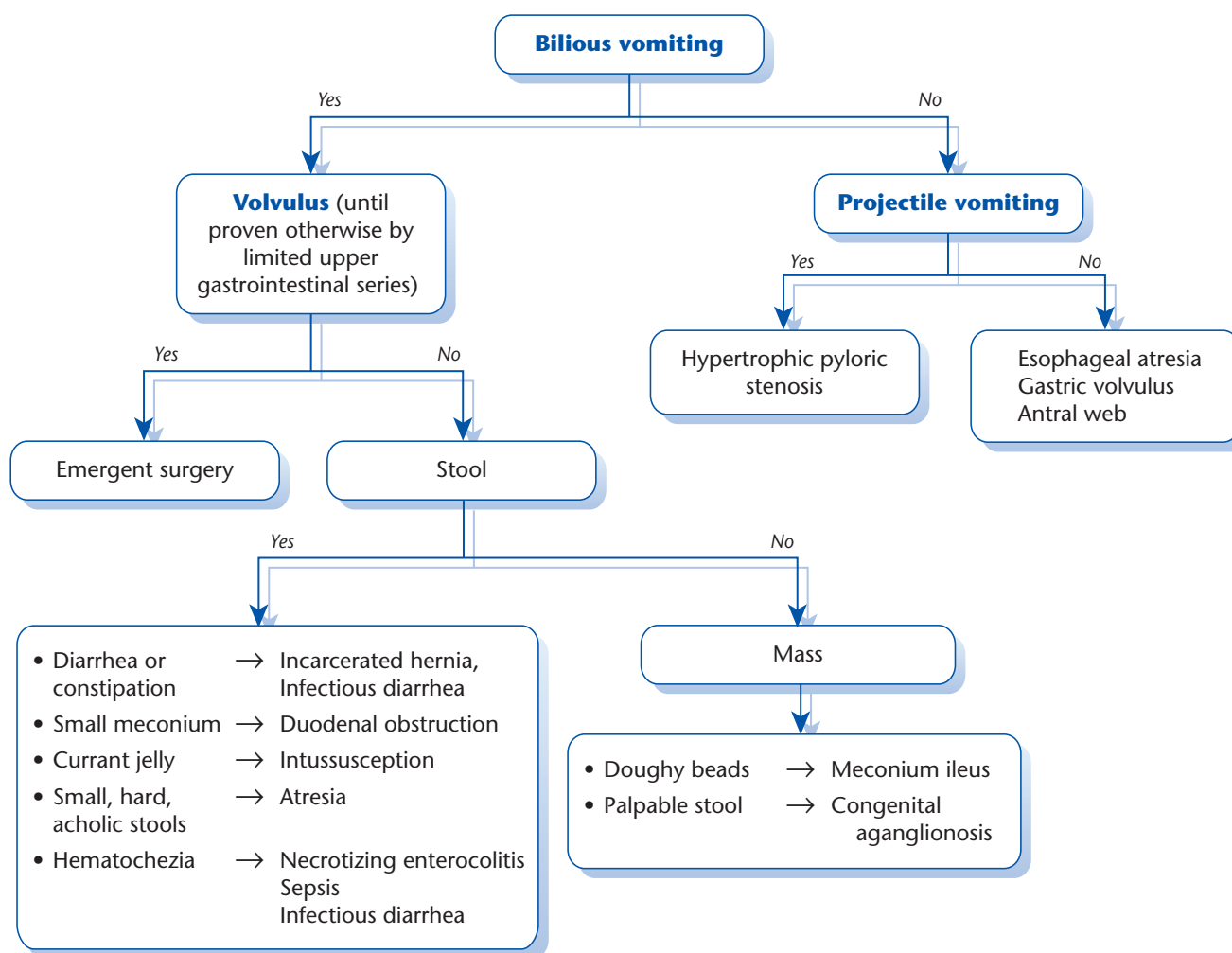
DISEASE	FREQUENCY	AGE	SURGICAL TREATMENT	COMPLICATIONS	PROGNOSIS
Esophageal atresia	1/3,000–1/5,000	Neonates	Division of fistula, anastomosis of esophageal ends ± gastrostomy	Aspiration, leak, GERD, strictures	Associated with cardiovascular abnormalities, imperforate anus, duodenal obstruction, malrotation If no cardiac anomaly, >95% survival
Gastric volvulus	Rare	Any	Gastropexy and gastrostomy tube ± resection	Sepsis, leak	If no necrosis—good; with necrosis—high mortality
Antral web	Rare	Infants	Divide web modified pyloroplasty, gastrostomy	Leak	Good
Hypertrophic pyloric stenosis	1/250	Neonates, infants	Pyloromyotomy	Incomplete, mucosal leak	Good
Volvulus	1/500	Infants, but 20% >1 yr of age	Detorsion of mesentery, divide Ladd bands, intestinal resection	Leak, sepsis, short-gut syndrome	If no necrosis—good; with necrosis—guarded
Intestinal atresia	1/2,700	Neonates	Resection and anastomosis	Strictures, leak, poor gut motility	50% associated with other anomalies
Meconium ileus	1/2,800	Neonates	Enema, intestinal cleansing through enterotomy, possible resection	Sepsis, malnutrition	Associated with cystic fibrosis immediately after surgery—good; long-term—poor
Hirschsprung disease	1/4,000	Neonates	Colostomy, delayed pull-through procedure	Sepsis, incontinence	Good
Imperforate anus	1/4,000	Neonates	Colostomy, delayed pull-through procedure	Sepsis, incontinence	High defects—guarded; low defects—good
Incarcerated hernia	1/1,000	Any	Reduction, possible intestinal resection	Sepsis	Good to guarded
Intussusception	1/1,000	3 mo–3 yr	Air-enema reduction ± resection	Ischemic bowel, leak, recurrence	May have pathologic cause in older children; good if no necrosis; with necrosis, potential short-gut syndrome
Duplication cyst	Rare	Any	Complete excision and anastomosis	Bile duct injury	Possible late malignant transformation
Meconium plug	1/500–1/1,000	Neonates	Rectal stimulation, enema	Leak, acute dehydration, shock	Associated with CF, small left colon, rectal aganglionosis
Functional obstipation of prematurity	Rare	Neonates	Colostomy for severe cases	Sepsis	Good

CF, Cystic fibrosis; GERD, gastroesophageal reflux disease.

Table 257-2

## Clinical Findings for Pediatric Gastrointestinal Obstruction

FINDINGS						
CAUSE	VOMITING	PAIN	STOOL PATTERN	DISTENTION	BOWEL SOUNDS	TENDERNESS
						ABDOMINAL MASSES
Esophageal atresia	Nonbilious (saliva)	No	Normal meconium	No	Absent to normal	No
Gastric obstruction	Nonbilious (curdled formula)	Severe with gastric volvulus; none with antral web	Normal meconium	Epigastric	Absent to normal	No
Hypertrophic pyloric stenosis	Nonbilious, projectile	No	Constipation (dehydration)	Epigastric	Hyperactive (epigastric)	Yes (olive-sized mass)
Duodenal obstruction	Bilious	Minimal	Small meconium stool	Epigastric	Absent to normal	No
Volvulus	Bilious	Severe	Hematochezia	Epigastric to generalized	Hyperactive	No
Jejunioileal atresia	Bilious	No	Small, hard, light-colored meconium stool	Generalized	Variable	No
Intussusception	Bilious	Yes (crampy)	Currant jelly stool	Generalized	Hyperactive	Yes (sausage shaped)
Meconium ileus	Bilious	No	Obstipation	Generalized	Variable	Yes (doughy beads)
Meconium plug	Bilious	No	Obstipation	Generalized	Variable	No
Congenital aganglionosis	Bilious	No	Obstipation, constipation, and intermittent diarrhea	Generalized	Hyperactive	Palpable stool
Obstipation of prematurity	Bilious	No	Obstipation	Generalized	Hyperactive	No
Incarcerated inguinal hernia	Bilious	Yes	Diarrhea or constipation	Generalized	Hyperactive	Inguinal or scrotal
Imperforate anus	Bilious	No	Obstipation	Generalized	Hyperactive	No



**Figure 257-1** Clinical findings in pediatric gastrointestinal obstruction.

Chapter 124, Abdominal Distention), change in bowel habits, fever, abdominal tenderness, or a palpable abdominal mass. The presence or absence of each of the key symptoms and signs, along with the child's age, are important clues to etiology.

### Vomiting

Vomiting is a ubiquitous symptom, the cause of which is most often not GIO. However, vomiting can be a sign of obstruction, particularly when marked by certain characteristics.

A small amount of nonbilious, nonprojectile vomitus by an infant is unlikely to indicate a GIO; it commonly denotes a benign, self-limited form of regurgitation or gastroesophageal reflux (chalasia). Gastroesophageal reflux can be ruled out in most cases by commonly accepted diagnostic tests such as a 24-hour pH probe study or a nuclear medicine milk reflux scan. However, nonbilious, nonprojectile vomitus in the newborn can also be associated with an esophageal obstruction (atresia). The neonate may have copious, frothy bubbles of mucus that cause rattling respirations,

coughing, choking, and cyanosis. Respiratory distress caused by tracheal aspiration of saliva retained in the upper esophagus or aspiration through the commonly associated tracheoesophageal fistula proximal or distal to the atresia can be associated with this anomaly. An esophageal block encountered during attempts to pass a size 8- or 10-French transoral soft catheter approximately 17 cm into the stomach denotes esophageal atresia.

Esophageal atresia and the rare entity of pediatric gastric volvulus are the 2 most likely neonatal conditions in which a congenital or early acquired esophageal obstruction is likely to be encountered. Acute gastric volvulus, unlike esophageal atresia, is often accompanied by severe pain and can be associated with signs of shock, chest pain, dysphagia, dyspepsia, and acute respiratory distress. Nonbilious vomiting can also be produced by the rare anomaly of a complete or incomplete gastric antral web. Frequently, this diagnosis is a delayed one that occurs in late infancy and is associated with failure to thrive.



The more dramatic projectile, nonbilious vomiting of early infancy is associated with the semi-urgent medical conditions of dehydration and electrolyte disturbances as a result of congenital hypertrophic pyloric stenosis. The electrolyte abnormalities are typically a hyponatremic, hypochloremic, hypokalemic contraction metabolic alkalosis with a possible late paradoxical aciduria (see Chapter 321, Pyloric Stenosis.)

Bilious vomiting, usually nonprojectile, is a more ominous problem and denotes GIO below the level of the ampulla of Vater. Concern arises because of the possibility of intestinal malrotation with a complicating midgut volvulus, which can produce GIO with ischemia and subsequent bowel necrosis within a few hours. Although a premature infant who has an immature pyloric sphincter can have bilious regurgitation without obstruction, especially when it is associated with an ileus related to an underlying septic process, the threat of intestinal vascular compromise caused by an underlying volvulus requires immediate radiologic examination for diagnosis. Clinical signs of peritonitis preclude radiologic study for diagnosis, and an immediate exploratory laparotomy is necessary. Usually an upper gastrointestinal (GI) radiographic series is the diagnostic study of choice in less ill neonates, although the diagnosis may also be made by ultrasound. Other causes of bilious vomiting in the neonate and infant include duodenal, jejunal, and ileal atresias; duodenal stenosis caused by an annular pancreas or Ladd bands (colonic peritoneal bands crossing the duodenum) associated with malrotation; meconium ileus; colonic atresia; congenital aganglionosis of the colon (Hirschsprung disease); and imperforate anus.

An infant or older toddler who has bilious vomiting may have a GIO produced by a foreign body ingestion, an incarcerated hernia, intussusception, or previously unrecognized malrotation with associated volvulus. The causes of bilious vomiting in an adolescent can include incarcerated hernias, postoperative adhesions, meconium ileus equivalent associated with cystic fibrosis, acute inflammation (appendicitis and pelvic inflammatory disease), chronic inflammation (regional ileitis or ulcerative colitis), and in rare instances, intermittent inflammation (celiac sprue). At this age, malrotation is less likely. In less developed countries, masses of worms, especially *Ascaris lumbricoides*, and tuberculosis also can be a cause of obstruction. A significant number of all patients who have persistent bilious emesis will have an underlying pathologic abnormality requiring early diagnosis and definitive surgical treatment.

Vomit containing small amounts of blood may be observed in infants who have congenital hypertrophic pyloric stenosis caused by gastric irritation as a result of repeated emesis. In rare cases, hematemesis with larger amounts of blood is associated with GIO. This may be found in the uncommon occurrence of an acute peptic ulcer, resulting in obstruction in a newborn or in an older, chronically stressed infant or child. Infection with *Helicobacter pylori* is also a potential cause of peptic ulcer disease in children, again more so in developing countries.

### Abdominal Pain

Abdominal pain, which may cause inconsolable crying or irritability in an infant, usually accompanies GIO. The pain is likely to be crampy or intermittent, and it results in crying and flexion of the legs to the abdomen interspersed with periods of decreased levels or absence of distress. This sign is exemplified best by the toddler who has an intussusception. However, approximately 10% of children who have intussusception will have lethargy as their only symptom. A complete or partial obstruction of the intestine produces acute intermittent abdominal pain because of an increase in the force and frequency of peristaltic waves in the bowel proximal to the obstruction. Within a matter of hours, the pain becomes constant and is caused by intestinal distention, peritoneal inflammation, or both. Bowel wall edema ensues, increasing the degree of obstruction and causing a progression of changes that place the intestine at further risk for ischemic damage.

### Stool

Obstipation in a newborn is an important finding. Full-term, healthy newborns spontaneously pass meconium within the first 24 hours of life. With premature newborns, those who are small for gestational age, and babies of mothers with diabetes, a delay of up to 72 hours may occur before the initial stool is passed. The initial bowel movement may also be delayed if pregnancy is complicated by maternal drug abuse (narcotics such as morphine), drug therapy (eg, magnesium sulfate for toxemia), or neonatal stress (hypoxemia or sepsis).

Atresias of the proximal portion of the intestinal tract do not usually cause obstipation except for those involving the most distal terminal ileum; however, the meconium passed by these infants is usually sparse and lighter in color, and it may be hard and dry. The differential diagnosis of newborn obstipation includes congenital aganglionosis of the colon (Hirschsprung disease), meconium ileus (with underlying cystic fibrosis), meconium plug syndrome (30% of these are associated with congenital aganglionosis of the colon or cystic fibrosis), small left colon syndrome, colonic atresia, imperforate anus, and, in rare cases, rectal atresia.

Strictures that occur as a result of episodes of neonatal necrotizing enterocolitis or intestinal surgery, as well as extrinsic compression of the GI tract caused by congenital cysts, intestinal duplication, inflammatory masses, or malignancies, produce obstipation or constipation in an older infant or child.

Particularly in neonates and infants, diarrhea or alternating diarrhea and constipation can occur as a sign of functional GIO or as a partial or intermittent GIO. Congenital colonic aganglionosis, intussusception, or intermittent volvulus may also be causes. The latter 2 conditions frequently occur along with hematochezia or melena.

Hematochezia, or grossly bloody stools, in association with GIO symptoms, indicates intestinal vascular compromise. It occurs most commonly in infants who have an intussusception or volvulus. The so-called *currant jelly stools* of intussusception result from the

admixture of blood and mucus and are a sign of superficial mucosal sloughing, but they can also accompany a full-thickness necrosis of the bowel wall. Occasionally, darker (mahogany to black), melena-type stools resulting from a more proximal intestinal bleeding site are noted, with the same potentially dire causes. In infants without grossly bloody stools, occult blood is present in up to 75% of intussusception cases. Thus, a hemoccult test should be performed in all infants with altered mental status.

### Physical Examination

With a history of vomiting, an infant first needs to be evaluated for signs of dehydration. Inspection of the anterior fontanel, rate and intensity of distal pulses, level of consciousness, perfusion of the extremities, and condition of the mucous membranes can aid in determining hydration status. When GIO is suspected, the physical examination of the abdomen includes evaluation for distention, which is likely to be prominent if the obstruction is distal to the duodenum (see Table 257-2 and Figure 257-1). Gastric obstruction caused by a congenital antral web, hypertrophic pyloric stenosis, or duodenal atresia produces only mild to moderate epigastric distention; distal intestinal atresias or other forms of lower GIO produce generalized distention. The presence or absence of abdominal distention does not aid in the diagnosis of a potential underlying midgut volvulus because the obstruction may be at the level of the duodenum, with few air- and fluid-distended bowel loops present.

Abdominal auscultation should be performed before any other aspect of abdominal examination. An effort should be made to listen to all the abdominal quadrants. Hyperactive, high-pitched, *tinkling* bowel sounds heard in rushes are diagnostic of a complete GIO. However, bowel sounds are often normal early, only becoming diminished or absent late in obstruction.

If the abdomen is moderately to grossly distended, then a mild amount of tenderness or discomfort with palpation is to be expected because pressure applied to gas- or fluid-filled loops of bowel causes pain. However, marked, diffuse tenderness clearly indicates an accompanying peritoneal inflammation. This inflammation (or peritonitis) in the setting of GIO indicates ischemia of the bowel wall with possible necrosis and demands immediate surgical evaluation and treatment. In this situation, diagnostic radiologic studies that use contrast material are contraindicated.

The presence of multiple *doughy*, compressible, mobile, nontender abdominal masses in a newborn who has GIO is associated with meconium ileus and indicates the presence of fecal impaction throughout the colon. On the other hand, a tender, palpable, immobile mass is most likely an area of cellulitis or abscess related to visceral perforation and is the result of necrotizing enterocolitis in infants or appendicitis or inflammatory bowel disease in children and adolescents. A non-tender, mobile mass that produces GIO symptoms is found with congenital intestinal duplication cysts or mesenteric cysts. A sausage-like mass in the right upper quadrant with absence of bowel in the right lower quadrant is pathognomonic of intussusception and is called the *Dance sign*. Malignancies in

the intestinal tract are rare and do not usually produce intestinal obstruction in infants and toddlers, but lymphomas may do so in older children. When they cause GIO, intestinal or mesenteric lymphomas in children older than 4 years of age commonly present as an intussusception. Additionally, an immunocompromised host who has a malignancy or acquired immunodeficiency syndrome may develop primary or secondary inflammatory lesions that lead to obstruction.

An incarcerated inguinal hernia is an important cause of GIO in children and adolescents. Detecting an inguinal hernia in an uncooperative, chubby infant is difficult and requires considerable patience and effort. Sedation with a tranquilizer, with or without an added narcotic analgesic, while keeping the child supine in the mild Trendelenburg position and applying an ice pack to the inguinal region may be helpful in the reduction of an incarcerated hernia. Medications must be used cautiously to prevent excessive sedation because vomiting and aspiration can occur. If possible, the hernia should be reduced gently and repaired later, when the effects of the GIO and local edema subside. If the hernia is reduced but left unrepaired, then recurrent incarcerations are likely, with the potential consequences of strangulation and necrosis of the bowel.

A rectal examination can often clarify the cause of GIO. In an infant who is suspected of having an incarcerated inguinal hernia, the pediatrician can often palpate the peritoneal side of the internal inguinal ring transanally and identify an exiting intraperitoneal structure. The rectal examination can be equally important in the diagnosis of any suspected colonic or distal GIO. Previously unsuspected perirectal or presacral pelvic masses (eg, hydrometrocolpos, appendiceal inflammatory mass, presacral teratoma) can be identified in this manner. Abnormal stool (as in the infant who has meconium plug syndrome) or blood (associated with intussusception or inflammatory bowel disease) can be detected during a rectal examination. In rare cases, an intraluminal rectal mass can be palpated, such as with a low-lying intussusception.

### Imaging Studies

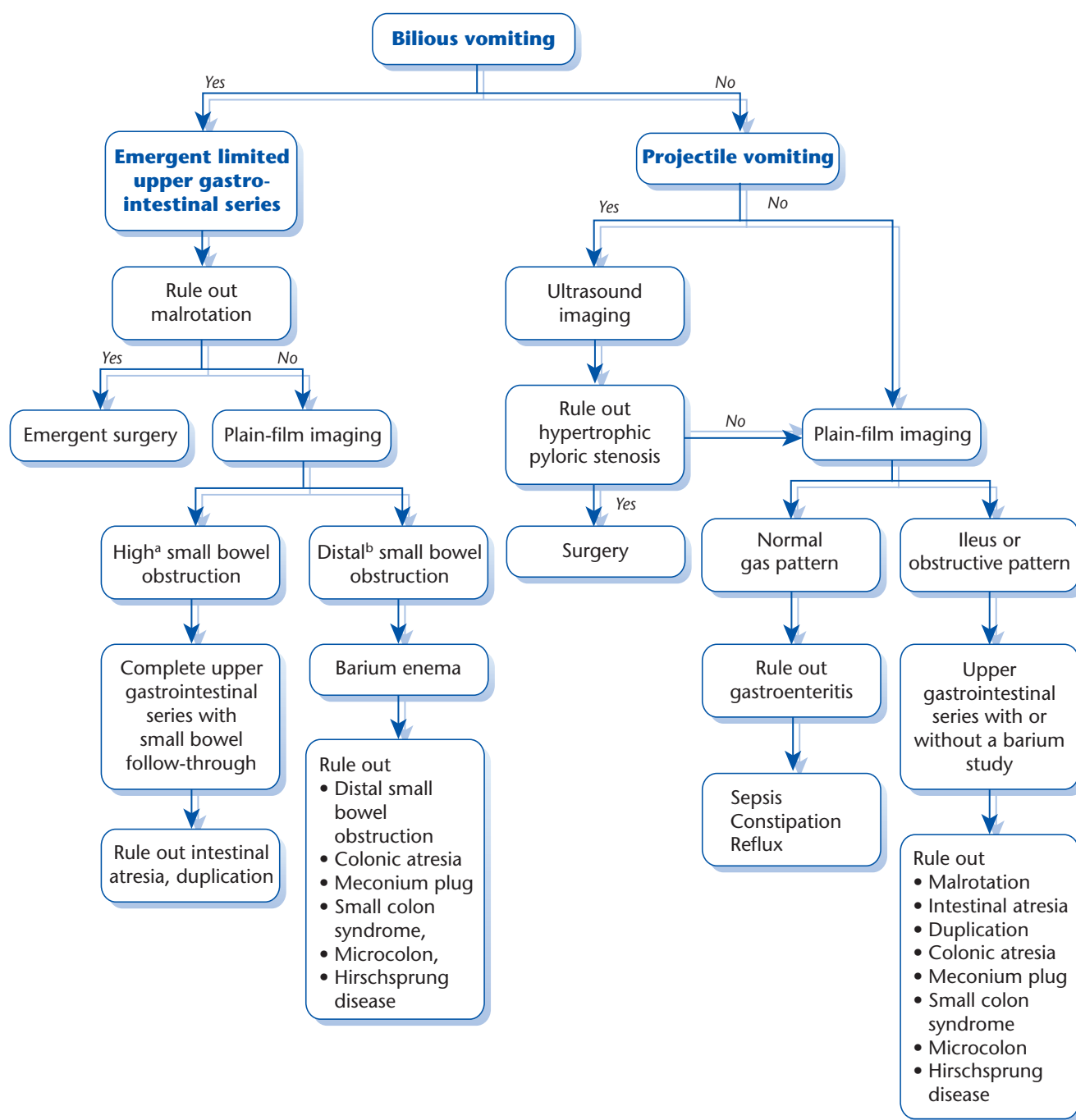
When deciding which radiologic tests to order, the physician must recall that estimated radiation exposure during the first 10 years of life poses a lifetime risk 3 to 4 times greater than exposure between the ages of 30 and 40 years. With the widespread use of prenatal ultrasound, GIO may be diagnosed before the birth of the child. In up to 40% of cases, findings such as polyhydramnios, an inability to identify the stomach, cystic abdominal lesions, and dilated loops of bowel strongly suggest the presence of an obstructive intestinal lesion. The prenatal diagnosis of GIO (ie, atresia, volvulus) alleviates the need for an emergent postnatal workup.

Table 257-3 and Figure 257-2 list radiographic diagnostic studies required for a child who has GIO and their expected findings; these studies are dictated by the results of the history and physical examination. A plain-film radiograph of the abdomen should be obtained for all children suspected of having GIO. Chest

**Table 257-3** Radiographic Findings for Common Causes of Pediatric Gastrointestinal Obstruction

CAUSE	FINDING					FURTHER STUDIES THAT MAY BE INDICATED
	DILATED AREA	AIR OR FLUID LEVELS	CALCIUM DEPOSITS	NON-CALCIUM OPACITIES		
Esophageal atresia	Esophagus (and stomach depending on type of fistula present)	Variable (usually gastric)	No	No	Esophageal air instillation	
Gastric obstruction	Stomach	Yes	No	No	Gastric barium instillation <sup>a</sup> Ultrasonography	
Hypertrophic pyloric stenosis	Stomach	Yes	No	No		
Duodenal obstruction	Stomach, duodenum (double bubble)	Yes	No	No	None	
Volvulus	Variable	Variable	No	No	Upper gastrointestinal series or barium enema	
Jejunioileal atresia	Stomach and small intestine	Yes	Yes (with prenatal perforation)	No	Barium enema to rule out nonrotation	
Intussusception	Stomach and small intestine	Variable	No	Yes (soft-tissue densities)	Ultrasonography, barium/air enema <sup>b</sup> , or both	
Meconium ileus	Stomach and small intestine	No	Yes (meconium peritonitis)	Yes (ground-glass appearance)	Water-soluble contrast enema <sup>c</sup>	
Meconium plug	Stomach to colon	Yes	No	No	Water-soluble contrast enema	
Congenital aganglionosis	Stomach to colon	Yes	No	No	Barium enema	
Obstipation of prematurity (short left colon syndrome)	Stomach to colon	Yes	No	No	Barium enema	
Incarcerated inguinal hernia	Stomach and small intestine	Yes	No	No	None	
Imperforate anus	Stomach to colon	Yes	No	No	Complete evaluation of genitourinary tract	

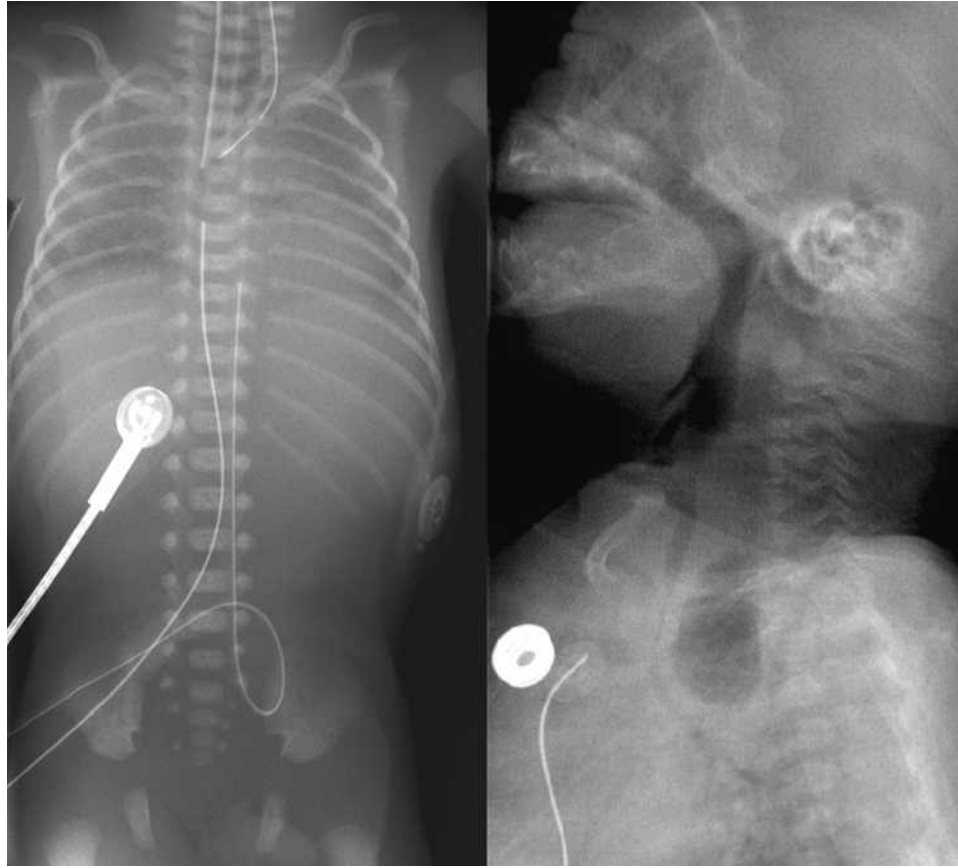
<sup>a</sup>Should be performed cautiously to avoid aspiration.<sup>b</sup>Should be performed cautiously to avoid bowel perforation.<sup>c</sup>May be therapeutic and diagnostic.

<sup>a</sup>Few distended loops of bowel<sup>b</sup>Multiple distended loops of bowel**Figure 257-2** Diagnostic workup for pediatric gastrointestinal obstruction.

radiography can demonstrate the curling of a nasogastric tube or dilated pouch in esophageal atresia (Figure 257-3). In a newborn, air localized to the stomach and duodenum (double-bubble sign) is diagnostic of a duodenal obstruction (Figure 257-4). If no distal intestinal intraluminal air is seen, then the GIO is usually caused by an atresia; however, if even a small amount of air is found distally, then the diagnosis of a

malrotation with possible volvulus must be suspected. Use of an upper GI series to determine the relationship among the duodenum, the jejunum, and the ligament of Treitz, or a barium enema to ascertain cecal position, is necessary to rule out a malrotation or nonrotation of the intestine. The presence of even a large number of air-filled loops on the plain-film radiographic study of the abdomen does not eliminate the





**Figure 257-3** Plain-film radiograph demonstrating curling of nasogastric tube in esophageal atresia without tracheoesophageal fistula (*left*). Lateral radiograph with dilated air-filled esophageal pouch compressing the trachea (*right*).

need for a contrast study because a volvulus still is possible. In a child with volvulus, contrast study may show a corkscrew appearance projecting forward, away from the posterior abdominal wall; color Doppler ultrasound may show a distorted relationship of the superior mesenteric vessels in a spiral pattern. Visualization by barium enema of an *unused*, small-caliber distal colon (microcolon) in a normal position makes the diagnosis of intestinal atresia or meconium ileus more likely than acute volvulus.

Calcifications visualized by an abdominal radiograph in a neonate with suspected GIO are evidence of an intrauterine intestinal perforation (meconium peritonitis), which is often associated with intestinal atresia. The calcifications may be small, single, or multiple and scattered throughout the entire peritoneal cavity, or they may outline the peritoneal cavity (Figure 257-5). Cystic fibrosis may be the underlying disease producing such a manifestation.

Infants suspected of having hypertrophic pyloric stenosis usually do not require an upper GI series to confirm the diagnosis. The classic symptoms of upper abdominal peristaltic waves and a palpable, olive-sized mass in the mid to right upper quadrant is diagnostic. An experienced pediatrician or surgeon will be successful in palpating the olive-sized mass in approximately 80% to 90% of affected infants. An

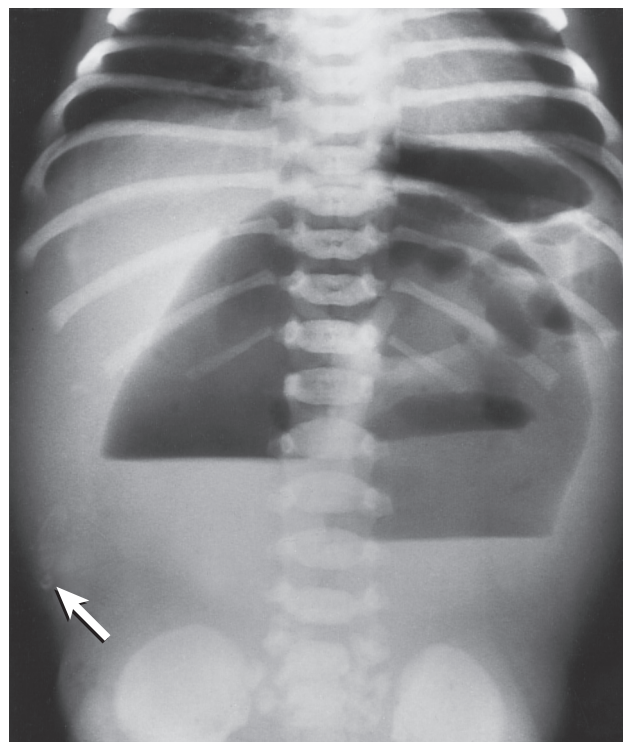
abdominal ultrasound scan can aid diagnosis in cases in which the pyloric stenosis is suspected, but no palpable mass exists. Radiographic confirmation is needless, costly, and potentially hazardous because residual barium may remain in the dilated, obstructed stomach at the time of induction of anesthesia (see Chapter 321, Pyloric Stenosis).

An unusual presentation is possible, with nonbilious vomiting and no clinically palpable olive-sized mass, a normal abdominal ultrasound examination, and a normal upper GI contrast study. This sequence of events may lead to a long delay in diagnosing an underlying partial gastric antral web. Barium study of the upper GI tract may show a normal duodenal bulb with a proximal antral chamber between the web and the pylorus, known as the double duodenal bulb appearance. This situation can be clarified by esophagogastroduodenoscopy to identify and potentially divide the web. If the web cannot be treated safely during endoscopy, then open gastric antroplasty is effective.

Duplication cysts can occur anywhere in the GI tract, but most frequently in the ileum, followed by the stomach. Ultrasound is the most useful radiologic modality to diagnose enteric duplication cysts. The *rim* sign is composed of an echogenic inner rim of mucosa and hypoechoic outer rim of the muscle layer. Peristalsis



**Figure 257-4** Duodenal atresia. An upright radiograph of a 4-day-old girl with persistent vomiting since birth. The double-bubble sign is classic, showing the large gastric fluid-filled air bubble on the right and the similar duodenal bubble on the left. (From *Micro X-ray Recorder, Inc., Chicago, IL.*)



**Figure 257-5** Ileal atresia with meconium peritonitis. An upright radiograph of a 36-hour-old girl with persistent vomiting since birth. The numerous dilated loops of small bowel with fluid levels indicate atresia of the ileum; the calcification (arrow) is diagnostic of meconium peritonitis caused by prenatal rupture of the small bowel. (From *Micro X-ray Recorder, Inc., Chicago, IL.*)

of the cyst wall and septations also aid in the diagnosis of duplication cysts.

An abdominal radiograph of GIO in association with suspected cystic fibrosis (meconium ileus) often has a peculiar hazy pattern described as a *ground-glass* or *soap bubble* appearance (Figure 257-6). Gas may be absent in the right iliac fossa because of a meconium cyst. This pattern is caused by the abnormal meconium mixed with air that is inspissated in the bowel lumen. Occasionally, this hard, dense stool, palpable as multiple abdominal masses, appears on the radiograph as a chain of radiolucencies, known as the *string of beads* sign. Meconium ileus, as with ileal atresia, is associated with a complete GIO; however, air-fluid levels are rare in meconium ileus. Meconium ileus and meconium plug syndrome are 2 neonatal GIO conditions that can be diagnosed and frequently can be treated with a water-soluble contrast enema.

A neonate who is suspected of having meconium ileus, who has no evidence of perforation, and who is well hydrated can be given a water-soluble contrast enema cautiously by an experienced radiologist. This procedure identifies the inspissated meconium, localized to the distal ileum, and may free it from the bowel wall for spontaneous expulsion. This technique is limited in application and duration, with subsequent surgical therapy required in as many as 50% of infants treated in this way. Uncomplicated meconium plug

syndrome—a lower GIO lesion infrequently associated with cystic fibrosis, but occasionally associated with congenital aganglionosis—is also diagnosed and treated successfully with a barium enema. Unlike meconium ileus, the abnormal meconium in meconium plug syndrome is localized to the distal colon. Contrast enemas in either syndrome are contraindicated when evidence exists of intestinal vascular compromise or perforation such as peritonitis, free intraperitoneal air, or intraperitoneal calcification. With meconium peritonitis, sonography may show ascites with echogenic debris, abnormal cystic masses, and thickening and dilation of the bowel wall.

Older infants and toddlers suspected of having GIO produced by intussusception can be diagnosed using ultrasound, revealing a thickened segment of bowel telescoped in on itself. Doppler flow may be absent in this segment if bowel wall edema has increased pressure beyond that of arterial inflow, indicating that ischemia is occurring and urgent intervention is necessary. Enema administration in intussusception is both diagnostic and therapeutic. In the past, this was traditionally performed with the use of barium. The study was performed with a limited-pressure (3 feet) barium column, and the intussusception was slowly reduced by the hydrostatic pressure generated. Because of the potential hazard of a barium perforation, a surgical team had to



**Figure 257-6** Meconium ileus. An upright radiograph of a 2-day-old boy with abdominal distention since birth. The loops of distended bowel of varying size without fluid levels are filled with meconium shadows (radiolucent soap bubbles). (From *Micro X-ray Recorder, Inc., Chicago, IL.*)



**Figure 257-7** Aganglionic megacolon (Hirschsprung disease). An upright radiograph of a 2-day-old boy with distended abdomen who failed to pass anything rectally shows extreme distention of the colon with several fluid levels. (From *Micro X-ray Recorder, Inc., Chicago, IL.*)

be standing by. The procedure, which could be used in approximately 75% of patients, successfully reduced the intussusception in 85% to 90% of these cases.

Air enema reduction of the intussusception has become available and is now the treatment of choice in intussusception reduction. This technique consists of air insufflation of the rectum and colon using an inline pressure-limiting valve while maintaining fluoroscopic or sonographic observation to ensure that the reduction is under control. The advantages of this technique are, first, elimination of barium, with the threat of severe chemical peritonitis if a perforation inadvertently occurs; and second, possibly an improved mechanical advantage by using air reduction. Investigators have stated that repeated attempts at pneumatic reduction improve the success rate without adverse outcome. In addition, it should be noted that edema of the bowel wall may prevent reflux of contents even if successful reduction has occurred; therefore, the enema may be repeated in 6 to 8 hours to determine whether passage of contents is occurring, indicating the reduction was successful and the edema has decreased, allowing patency of the lumen. The patient always should be observed for 12 to 24 hours in the hospital after successful intussusception reduction.

Surgical reduction is required in cases that are unable to be reduced radiologically. Some experts have advocated the use of laparoscopy to aid in this

reduction. The diagnosis can also be made effectively by computed tomography (CT) if necessary, but ultrasound or enema are usually sufficient and harbor no or minimal risks associated with radiation. Thus, CT should be reserved for cases in which ultrasound is nondiagnostic, physical examination is unremarkable, and history is equivocal.

Congenital aganglionosis of the colon (Figure 257-7), or Hirschsprung disease, in infancy can be lethal if complicated by enterocolitis. Hirschsprung disease seldom produces total GIO, which, when present, must be treated as an emergency. The initial diagnosis is made based on clinical suspicion because it cannot be verified by noninvasive diagnostic procedures. A barium enema or anorectal manometry reflecting an absent rectosphincteric reflex is often helpful in diagnosing Hirschsprung disease in older children, but either a rectal mucosal or full-thickness rectal wall biopsy specimen is required to confirm the diagnosis in infants.

Colonic dysfunction of prematurity, or *small left colon syndrome*, produces a functional mechanical obstruction that mimics Hirschsprung disease. Small left colon syndrome can be related to extreme prematurity, maternal diabetes, prenatal maternal medications for eclampsia (magnesium sulfate), hypothyroidism, or maternal narcotic use. Small left colon syndrome is a diagnosis of exclusion because its barium contrast appearance resembles Hirschsprung



disease. Surgically, a temporary colostomy is indicated only for failure to respond to careful, small-volume, saline enema therapy or in the presence of signs of peritonitis or intestinal perforation. The prognosis for uncomplicated cases is excellent.

In the infant or toddler, accidental and inflicted blunt injury to the abdomen can result in early obstruction both from bowel wall edema and from a hematoma. A full-thickness bowel wall injury will often produce late sequelae such as an intestinal leak, which initially produces a normal or equivocal examination resulting in a delay in diagnosis. The diagnosis of acute bowel wall trauma requires a high index of suspicion and often thorough and repeated radiologic evaluations.

Infants and toddlers also are at risk for accidental ingestion of objects. These are often radiopaque and will be readily apparent on a plain film. If the object is able to pass through the pylorus, it is unlikely to cause a significant bowel obstruction. However, 2 important exceptions exist. Water-absorbing silicone or polyethylene balls will expand over time, resulting in a complete obstruction and potentially even perforation depending on size. A careful history must be taken and surgical consultation obtained if these objects were ingested. The second exception involves the ingestion of multiple magnets. These magnets may attract one another through 2 different loops of bowel. This can lead to pressure necrosis resulting in fistulization or frank perforation of multiple segments of bowel. In certain studies, the rate of peritonitis approached 50% in this situation; thus, again, surgical consultation is warranted if the child's history reveals such ingestions.

## MANAGEMENT

### Medical Management

A child who has GIO requires gastric decompression to prevent continued bowel distention, vomiting, and possibly aspiration. Intravenous fluid therapy is required immediately to replace third-space (ie, intraluminal and intraperitoneal) fluid loss. When replacing the fluid deficit, the pediatrician must remember that luminal GIO losses are high in electrolyte content, requiring administration of higher than maintenance concentrations of sodium, chloride, and potassium. Therefore, solutions such as lactated Ringer's solution are needed to provide appropriate replacement. A urinalysis, with catheterization if necessary, and a complete blood count and blood chemistry studies should be performed. Because almost all children who have GIO require emergency or semiurgent surgery, they must be well prepared for anesthesia and the surgical procedure. This approach requires correcting fluid and electrolyte, hematologic, and metabolic imbalances before surgery. Such corrective measures should begin before extensive diagnostic radiologic studies are undertaken. Medical causes of failure to pass meconium that require nonsurgical therapy include hypothyroidism, hypercalcemia, hypokalemia, sepsis, and congestive heart failure.

### Surgical Management

The type of surgical procedure performed and the child's postoperative course and prognosis (see Table 257-1) depend on the type of lesion causing the GIO.

### Esophageal Obstructions

Esophageal atresia with associated tracheoesophageal fistula constitutes a relative emergency requiring either primary repair or a staged procedure with an initial gastrostomy for gastric decompression and prevention of aspiration. Subsequent definitive repair, including a division of the fistula and anastomosis of the esophageal ends, is carried out after treatment of any existing underlying pneumonic process. Occasionally, the gastrostomy and definitive repair are performed simultaneously, and, in selected children, the esophageal repair is performed without gastrostomy. Complications of the definitive procedure include esophageal leaks, infection, and strictures. Anomalies, particularly of the cardiovascular system, as well as imperforate anus, duodenal atresia, and intestinal malrotation, are associated problems in as many as 50% of cases. Children who have uncomplicated atresia and tracheoesophageal fistula have low morbidity and negligible mortality. However, associated cardiovascular anomalies and very low birth weight lead to a mortality rate as high as 70%. Late complications of atresia and tracheoesophageal fistula include congenital hypertrophic pyloric stenosis and chronic gastroesophageal reflux with reactive airway symptoms.

### Gastric Obstructions

Gastric volvulus is usually an acute problem that requires an immediate surgical gastropexy to prevent ischemia and necrosis and a temporary gastrostomy tube for fixation and decompression. If no gastric necrosis is found, then recovery is usually uneventful. Gastric necrosis with resulting peritonitis results in high morbidity and mortality. A gastric antral web is difficult to diagnose and often requires repeated diagnostic studies, but it is not a critical problem. Surgical therapy consists of simple incision of the web and performance of a modified pyloroplasty, resulting in few postoperative complications.

Hypertrophic pyloric stenosis requires surgical therapy after adequate correction of the associated, potentially life-threatening dehydration, hypochloremic alkalosis, and hypokalemia. The procedure is a muscle-splitting pyloromyotomy, leaving the mucosa intact. The procedure can be performed laparoscopically or through a right upper quadrant or supraumbilical incision with similar operative times, complications, and costs. Acute complications are unusual, with the child resuming postoperative feedings without sequelae within 8 to 24 hours, sometimes as early as in the immediate postoperative period in the recovery room. Chronic complications such as stricture related to intraoperative mucosal perforations and adhesions are rare.

### Duodenal Obstructions

Duodenal atresia, stenosis, and annular pancreas constitute semi-urgent problems unless accompanied by



an associated volvulus, which demands immediate abdominal exploration. Surgical therapy consists of bypassing the obstructed area by means of a duodeno-duodenostomy, a duodenojejunostomy, or a gastrojejunostomy. Moderate feeding problems necessitating a longer hospitalization may be encountered, particularly when a gastrojejunostomy is performed. The prognosis is good; however, with associated congenital cardiac problems, mortality can be as high as 50%. Duodenal atresia is associated with Down syndrome (trisomy 21) in as many as 10% of cases. Growth and development are normal in children who have uncomplicated and isolated duodenal obstructions. Duodenal and other intestinal duplication cysts are treated if possible with complete excision. At the least, excision of the mucosal lining should be performed, given that cysts are associated with a late malignant transformation.

### **Jejunal and Ileal Obstructions**

Jejunal and ileal atresia are also semi-urgent conditions unless they are associated with a volvulus. Surgical treatment involves excision of the atretic bowel and primary anastomosis of the dilated proximal and the narrowed distal segments. When multiple atretic segments of bowel, or small bowel atresias associated with the absence of the superior mesenteric artery, are present, the overall intestinal length and, therefore, the absorptive surface may be greatly reduced. Total parenteral nutrition is commonly required after surgery. Overall survival and prognosis are good unless the atresia is complicated by cystic fibrosis or the remaining small intestine is too short for adequate absorption.

Malrotation with a complicating volvulus is the most critical diagnosis in any child suspected of having GIO. The twisted bowel mesentery may lead to ischemia and bowel necrosis within 4 to 6 hours after the onset of symptoms. Untreated volvulus has a high acute mortality rate because of associated metabolic imbalance and sepsis. Even after successful surgical resection of the involved necrotic bowel, high long-term morbidity can be expected. The entire embryonically derived midgut may have to be resected, leading to reduced intestinal absorption of nutrients and the so-called *short-gut syndrome*. Thus, early diagnosis, rapid correction of fluid and electrolyte imbalances, and surgical reduction of the mesenteric torsion with or without resection of potentially necrotic bowel are imperative. Proximal and distal segments of involved intestine that seem ischemic, but may be viable, should be retained by creating abdominal enterostomas in lieu of extensive initial intestinal resection followed by a second-look operation performed in 24 hours. Postoperative complications include marked fluid and electrolyte disturbances, local and systemic infections, and malnutrition. Long-term parenteral nutrition, dietary adjustments, and repeated surgical procedures should be expected. Survival with a reasonable quality of life can be expected if the remaining viable small bowel is 30 cm or longer. Morbidity is lessened when the ileocecal valve remains intact. Long-term hospitalization and prolonged nutritional support through total parenteral nutrition are usually required.

As noted previously, meconium ileus may respond to water-soluble contrast enemas; however, evidence of an accompanying intestinal perforation or failure of a carefully managed water-soluble contrast enema necessitates surgical therapy. Cystic fibrosis, which is almost always present as an underlying disease, complicates the child's postoperative respiratory and nutritional status. Administration of cleansing solutions such as *N*-acetylcysteine by means of an enterotomy usually frees the intestinal lumen of the inspissated material. Associated atretic or necrotic intestinal segments are excised, and primary anastomoses are performed. Enterostomas are created for postoperative lavage of massively impacted meconium or in instances in which the viability of the remaining bowel segments is in question. A stoma may also be needed to protect an anastomosis. A transabdominal T tube may be left intraluminally to allow decompression and irrigation, and the appendix may be used as a conduit. The surgical survival is good; however, the morbidity is high, and the ultimate prognosis is related to the severity of the other manifestations of cystic fibrosis.

### **Colonic and Rectal Obstructions**

An intussusception uncomplicated by a lead point (ie, a Meckel diverticulum, a polyp, or a malignancy) can be successfully reduced hydrostatically or by air in up to 90% of appropriately selected children. Recurrences after air-hydrostatic reduction range from 5% to 7%. Surgical intervention is required if evidence of compromised bowel is found, such as a free perforation or peritoneal irritation, and in failures of air-hydrostatic reduction. Successful reduction requires retrograde reflux of contrast media or air into the terminal ileum. Most children who have intussusceptions that are reduced intraoperatively do well postoperatively, with a low 2% to 5% recurrence rate. Bowel resection is required when an intraoperatively recognized pathologic lead point is present or when an ischemic complication is found. Early diagnosis and treatment of intussusception reduce morbidity and mortality.

Rectal atresia and imperforate anus require diagnosis, initial therapy, and colostomy within 24 hours. Very low perineal lesions (anterior displaced anus and fourchet fistula) can be treated with initial dilations only. Definitive therapy, which includes a pull-through procedure and anoplasty, is performed when the infant is 2 to 3 months of age. If the lesion is not associated with any other congenital anomalies, then survival is good. The physician should look for other anomalies, particularly those of the genitourinary tract (rectovaginal and rectovesicular fistulas, lower urinary tract obstructions with megacystis, hydroureter, and hydronephrosis). Future stool continence is related directly to the severity of the deformity, which is influenced by the degree of normal embryologic descent of the colon through the levator muscle. Definitive surgery for high lesions, in which colon descent is limited to a position above the levator muscle, results in daytime stool continence in approximately 60% of patients. The overall continence rate for high lesions is 10% to 20%. Repair of low lesions, in which

the colon has descended below the levator muscle, results in an overall stool continence rate of at least 80% to 90%.

Surgical therapy for congenital aganglionosis of the colon (Hirschsprung disease) can include creating a colostomy by using a segment of proximal ganglionic colon, followed in 6 months to 1 year by excision of the affected aganglionic segment and anastomosis of the normally innervated (ganglionic) bowel to the anus (the pull-through procedure). Many children respond preoperatively to regular rectal stimulation and irrigations to evacuate the colon. This measure allows performance of a primary pull-through procedure during the immediate newborn period and up to several months of age and the avoidance of a colostomy. Infant morbidity and mortality rates are high when the disease is complicated by enterocolitis; however, patients who have no such complications usually do well, with good anal continence, growth, and development.

### Minimally Invasive Surgery

The availability of minimally invasive techniques and instruments for infants and toddlers has allowed many procedures such as pyloromyotomy, fundoplication, and endorectal pull-throughs to be performed laparoscopically. Obstructions from adhesions, inflammation (inflammatory bowel disease, appendicitis, and Meckel diverticulitis), and intussusception can be successfully treated with minimally invasive techniques by the skilled laparoscopist. However, procedures such as pyloromyotomy may be performed with a modified open technique, which is less expensive and has equally acceptable cosmetic results. In addition, the use of the minimally invasive technique for the Ladd procedure may be less effective than the original open Ladd procedure, which causes desired adhesion formation that will result in natural fixation of the intestine to prevent future volvulus. As smaller-sized instrumentation has improved and surgeons gain more experience, the list of procedures that can be performed laparoscopically continues to grow.

### Fetal Surgery

Fetal surgery is an alternative in the treatment of some congenital anomalies. Given the risk to the mother from invasive prenatal procedures, the death of the fetus or newborn without in utero treatment has to be almost certain for fetal surgery to be considered. This assumption also applies to endoscopic fetal procedures. Currently, open or endoscopic fetal surgery is performed for congenital cystic adenomatoid malformation, fetal sacrococcygeal teratoma, congenital diaphragmatic hernia, and obstructive uropathy that meet the previously mentioned criteria. None of the prenatal GIO diagnoses or their causes pose an immediate threat to the fetus or the mother, with overall combined mortality rates of less than 5%. The benefits to the baby do not outweigh the risk to the mother; therefore, these lesions are not appropriate for prenatal interventional therapy.

*The authors thank Dr Sunny Pitt for assistance with radiologic images.*

### WHEN TO REFER

- All patients with suspected and confirmed intestinal obstruction should be referred to pediatric surgery.

### WHEN TO ADMIT

- All patients with intestinal obstruction should be admitted.

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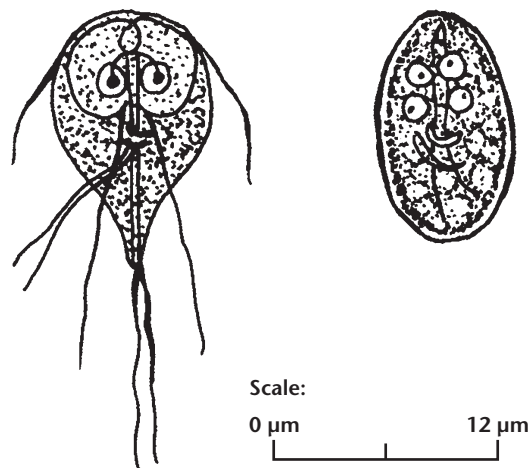
## Chapter 258 GIARDIASIS

Craig M. Wilson, MD

### ETIOLOGY

A *Giardia*-like organism associated with gastrointestinal symptoms was described by Dutch microscopist Anton van Leeuwenhoek in 1681, but only in the past few decades has the true pathogenicity of this flagellate protozoan been recognized. *Giardia intestinalis* (also known as *Giardia lamblia* and *Giardia duodenalis*) is one of the most common intestinal parasites in the United States.

A large sucking disk, which the parasite uses to attach to the intestinal mucosa, occupies most of the flat ventral surface. Attachment is regulated by contractile proteins, including actin and myosin, which alter the structure of the disk. The mechanism by which the organism evades degradation in the intestinal lumen is not clear. The motile trophozoites divide by longitudinal binary fission in the upper small bowel and then encyst as they pass into the colon. Trophozoites are usually seen only in the stool when diarrhea is present. Cysts, the more common form seen in stool specimens, are 9 to 12  $\mu\text{m}$  long. Recently formed cysts have 2 nuclei; mature cysts have 4, but cysts are generally infectious on emergence in stool (Figure 258-1). The oocysts are stable for weeks to months in the environment.



**Figure 258-1** *Giardia* organisms. The trophozoite (left) is 12 to 15  $\mu\text{m}$  long and has 4 pairs of flagella and 2 prominent nuclei. This form is not commonly seen in stools. Cysts (right) are 9 to 12  $\mu\text{m}$  long and may have 2 to 4 nuclei.

## EPIDEMIOLOGIC MECHANISM

*G. intestinalis* is one of the most commonly identified pathogens in waterborne diarrheal disease in the United States, where the organism is holoendemic. Infections are seasonal, with higher rates in late summer and early fall. In the United States, rates are highest among children younger than 5 years. Many large common-source outbreaks have been traced to contaminated drinking water. Epidemiologic studies have attributed these epidemics to cross-contamination of municipal drinking water supplies that have sewage, defective or deficient filtration facilities, and reliance on chlorination as the principal method of water disinfection. In mountainous regions, where the prevalence of disease appears to be higher, consumption of surface water is the principal problem. Although zoonotic infections have been documented, molecular epidemiologic studies suggest they may actually be quite rare. As suggested by the occurrence of epidemic giardiasis despite chlorination of municipal water supplies, routine chlorination may not be adequate for killing *G. intestinalis*. The level of chlorine necessary to kill cysts depends on many other factors, including pH, contact time, turbidity, and temperature. Thus, an adequate water purification system for clearing *G. intestinalis* should include filtration, sedimentation, and flocculation systems. Halogen-based, small-quantity disinfection methods are also affected by water clarity and temperature.

Because cysts may be shed in abundance in the stool, not surprisingly, *G. intestinalis* may be transmitted by the fecal–oral route. This route is undoubtedly the main route of spread in families, in institutions, and in child care centers. With intensive exposure to stool, as in child care centers caring for infants in diapers, giardiasis may quickly become hyperendemic. Foodborne giardiasis has been reported, but the implicated food probably was contaminated during preparation.

## PATHOGENESIS

Studies in human volunteers have demonstrated the high infectivity of *G. intestinalis* cysts. Although 1 cyst rarely was infectious, infection occurred in virtually all volunteers receiving 100 to 1 million cysts orally and in 36% of those exposed to 10 to 25 cysts. Molecular-based techniques suggest that *G. intestinalis* assemblages A and B are the predominant species infecting humans and that multiple other genotypes and species infect other hosts.

Many mechanisms have been postulated for the diarrhea and malabsorption caused by *G. intestinalis*. In all likelihood, the process is multifactorial, with the severity of symptoms dependent on the degree of focal small bowel injury. Infection is associated with injury to the mucosal brush border, with disruption of disaccharidase activity and transport mechanisms. A basal membrane and intraepithelial layer inflammatory cell infiltrate have been found, and evidence exists of an increased enterocyte turnover in the murine model. In either case, less efficient villus function would be expected. In the extreme, the microvilli atrophy results in the severe malabsorptive diarrhea, which is a major complication of giardiasis. Recent studies suggest that parasite products play a role in the pathophysiologic mechanism of this infection. Evidence also has been found that some *Giardia* strains produce more severe symptoms in humans than they do in other species, and differences in phenotype and genotype have been correlated with virulence in experimental models of infection.

Host defense mechanisms appear to be relatively inefficient, given the small number of organisms required to initiate infection and the frequency of relapse and reinfection. However, intraluminal secretory antibody response, nonspecific inflammatory responses at the level of the mucosa, and antibody-dependent cell-mediated cytotoxicity appear to be important in limiting the severity of disease. The role of antibody and antibody-dependent cell-mediated cytotoxicity in containing giardiasis is supported by the increased incidence and severity of disease in patients who have immunoglobulin deficiencies. Underlying immunoglobulin A deficiency and both X-linked and common variable hypogammaglobulinemia have been associated with severe or prolonged infection.

*G. intestinalis* should be considered in the evaluation of diarrhea or malabsorption in patients who have human immunodeficiency virus (HIV) infection. The role and extent of *G. intestinalis* infections in children who have HIV infection have not been established. Of course, diarrhea in patients who have acquired immunodeficiency syndrome is often multifactorial, and treatment of documented giardiasis may not result in clinical improvement if other pathogens still are present (see Chapter 268, Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome).

## CLINICAL MANIFESTATIONS

Based on experimental studies and point-source outbreak observational data, the incubation period of giardiasis is 7 to 14 days. Most patients infected by *G. intestinalis* probably remain asymptomatic, although they do shed cysts in their feces and are infectious.



Children are more likely than adults to have symptomatic disease.

The principal symptoms of giardiasis are gastrointestinal. Diarrhea, abdominal cramps, and nausea are reported most often. Vomiting, malodorous stools, flatulence, bloating, anorexia, and even constipation are noted less frequently. Because the colon and rectum are not involved, tenesmus should suggest another diagnosis. Blood almost never is found in the stool, and the presence of mucus is unusual. Gastrointestinal symptoms generally last 7 to 10 days, although a more protracted course is common. Because of the disaccharidase deficiency that accompanies severe infections, some patients complain of milk intolerance, which may last for weeks.

Constitutional symptoms are not prominent in giardiasis, but up to 25% of patients experience fatigue, headache, or a low-grade fever. Extraintestinal syndromes, such as urticaria, erythema multiforme, and arthralgia, have occurred, but very rarely, in association with giardiasis.

Some patients, particularly children, develop chronic diarrhea, frank malabsorption, weight loss, malnutrition, and growth restriction. Thus, giardiasis must be considered in the differential diagnosis of failure to thrive. Occasionally, giardiasis may be misdiagnosed as sprue, food allergy, or psychogenic abdominal pain, and its protean clinical manifestations may mimic a wide variety of gastrointestinal disturbances. Malabsorption leading to an iron deficiency anemia also has been reported with *G intestinalis*.

The physical examination is generally unremarkable unless secondary malnutrition has developed.

## LABORATORY EVALUATION

The clinical laboratory diagnosis of *G duodenalis* has predominantly changed from a microscopic examination of stool to either heat-stable antigen detection in stool or detection of parasites by fluorescence. These tests are quite often combined for simultaneous detection of *Cryptosporidium* species. Overall, these tests compare well with standard microscopic procedures and are in most cases more sensitive, although multiple samples may still be needed for optimal detection.

A few patients require additional measures to have the pathogen detected. Examining the duodenal contents provides the optimal yield, and this examination can be performed either by direct duodenal aspiration or by using the Entero Test. In rare patients with chronic symptoms in whom the diagnosis must be excluded, biopsy of the small bowel should be done. Several sections of the biopsy specimen stained with Giemsa stain may have to be examined to find the parasite; *Giardia* organisms are detected more easily in Giemsa-stained mucosal impression smears.

Serologic tests are valuable in epidemiologic studies but are of little use diagnostically. Upper gastrointestinal radiographs may reveal mild dilation of the small bowel, edema of the mucosa, segmentation of barium, and either increased or decreased transit times; however, these changes are nonspecific. The sedimentation rate is normal, and no eosinophilia is found because the parasite is noninvasive. Biochemical evidence of malabsorption may be found, including

disaccharidase deficiency, abnormal absorption of D-xylose and fat, and a deficiency of folic acid.

## THERAPY

Most authorities agree that giardiasis should be treated when recognized, even if the patient is asymptomatic, because carriers of the parasite are potential transmitters of disease and may have subclinical malabsorption. However, physicians may elect not to treat asymptomatic patients, particularly if re-exposure to *G intestinalis* seems unavoidable in some hyperendemic settings.

Metronidazole has been used widely to treat giardiasis in adults and children because it is well tolerated (except for the mild metallic aftertaste), has a very low incidence of serious side effects, and has an acceptable cure rate. Alcohol ingestion, including in concurrent medications, should be avoided with metronidazole because of disulfiram-like reactions. Of note, giardiasis is not an approved indication for metronidazole in the United States. Tinidazole, a nitroimidazole similar to metronidazole, which has been used extensively in a single-dose regimen outside of the United States, is approved for the treatment of giardiasis in children 3 years and older. Both metronidazole and tinidazole can readily be formulated as suspensions.

Furazolidone has the distinct advantages of having a pleasant taste and being available in a pediatric suspension. Side effects, which have been minimal in children, include mild gastrointestinal distress, hypersensitivity reactions, hemolysis in individuals who have glucose-6-phosphate dehydrogenase deficiency, brown discoloration of the urine, and disulfiram-like reactions. Furazolidone is contraindicated with monoamine oxidase inhibitors. The efficacy in children has been as high as 92%, which is comparable if not superior to cure rates seen with alternative agents.

Nitazoxanide is an approved antiparasitic agent with specific indications for the treatment of cryptosporidiosis and giardiasis in children. Cure rates in small, randomized trials were comparable to those of standard agents for giardiasis, and side-effect rates appear comparable to placebo. On rare occasions, yellow sclera is noted, which clears with discontinuation of the drug. Nitazoxanide is the most costly of the agents discussed here.

Albendazole has been reported to be as effective as metronidazole in a limited number of studies in children. Albendazole has the advantage of being active against a broad range of intestinal parasites, including helminths, if this is a consideration. Paromomycin, a nonabsorbable aminoglycoside, has been used to treat giardiasis in pregnancy, but data regarding its efficacy are limited. Quinacrine, a once commonly used therapy, is not commercially available in the United States but can be obtained if needed through compounding pharmacies, such as Panorama Compounding Pharmacy (6744 Balboa Blvd, Van Nuys, CA 91406 [800-247-9767]) or Medical Center Pharmacy (New Haven, CT [203-688-6816]). Other compounding pharmacies may be found through the National Association of Compounding Pharmacies (800-687-7850) or the Professional Compounding Centers of America (800-331-2498, [www.pccarx.com](http://www.pccarx.com)). Relapse is possible after using any of



these regimens. If this occurs, re-treatment with the same agent or an alternative drug is often successful. No well-documented evidence exists for actual drug resistance in *Giardia* on an individual clinical case level. In vitro sensitivity has shown variations but is assay and inoculum dependent. For cases of severe or recalcitrant infections, prolonged or combination therapy may be necessary.

## PREVENTION

Because giardiasis is so prevalent, total prevention of transmission is virtually impossible. When the disease is known to be present in a household, institution, or child care center, good hand washing is essential to limit spread by the fecal–oral route. Personal hygiene is especially important when infants in diapers are affected. When an outbreak is thought to occur in child care centers that have infants in diapers, the local health department should be contacted, and an epidemiologic investigation should be undertaken to identify and treat all symptomatic children, child care workers, and family members infected with *Giardia*.

As already noted, prevention of waterborne giardiasis is contingent on adequate water purification, including filtration, sedimentation, and flocculation in addition to chlorination. Tourists in endemic areas should avoid drinking tap water. Campers should not rely on chlorination tablets, which are ineffective against *Giardia* cysts. Boiling for at least 2 minutes, even at high altitudes, or filtration (pore size under 1 µm or with a filter rated for cyst removal) are satisfactory means for preparing drinking water free of *G. intestinalis*. General guidance for water filter specifications and recommendations are available at [www.cdc.gov/travel/foodwater.htm](http://www.cdc.gov/travel/foodwater.htm).

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Common Childhood Infections* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Diarrhea and Dehydration* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Giardiasis* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/parasites/giardia/index.html](http://www.cdc.gov/parasites/giardia/index.html))
- *Healthy Swimming/Recreational Water: Giardia* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/healthywater/swimming/rwi/illnesses/giardia.html](http://www.cdc.gov/healthywater/swimming/rwi/illnesses/giardia.html))

### Medical Decision Support

- *Giardiasis* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/dpdx/giardiasis/index.html](http://www.cdc.gov/dpdx/giardiasis/index.html))
- *Practice Guidelines for Management of Infectious Diarrhea* (article), *Clinical Infectious Diseases*, Vol 32, Issue 3, 2001

## SUGGESTED READINGS

Nitazoxanide (Alinia)—a new anti-protozoal agent. *Med Lett Drugs Ther.* 2003;45(1154):29–31

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Yoder JS, Harral C, Beach MJ; Centers for Disease Control and Prevention. Giardiasis surveillance - United States, 2006–2008. *MMWR Surveill Summ.* 2010;59:15–25

## Chapter 259

# GLUTEN-SENSITIVE ENTEROPATHY (CELIAC SPRUE)

Anca M. Safta, MD; John A. Kerner Jr, MD

Celiac disease (CD), also known as celiac sprue or gluten-sensitive enteropathy (GSE), is a condition characterized by clinical features of malabsorption and pathologic changes in the jejunal mucosa, both of which improve when gluten is removed from the diet and recur when it is reintroduced. CD is the second most common cause of malabsorption in children, the most common being cystic fibrosis. Even though CD is characterized by malabsorption, the disease is extremely protean in its manifestations and many children with CD may not have features of overt malabsorption.

The classic clinical description of CD was first provided in 1888. In 1950, the association between the ingestion of gluten and CD was noted. During World War II, when grain products were in short supply, the incidence of CD was markedly reduced, and children who had the disease improved. After the war, when cereal grain again became plentiful, the incidence of CD quickly returned to prewar levels. In 1954, the first accurate description of intestinal lesions in patients with CD was provided by studying surgical biopsy material. Not until 1968 was the discovery made that adult nontropical sprue and CD in childhood were the same disease.

## INCIDENCE

The precise incidence of CD is unknown because many patients have asymptomatic disease. Screening with serologic markers has increased the estimates of prevalence of CD in different areas. CD has been identified in Hispanic, Indian, Chinese, Sudanese, African Caribbean, and Middle Eastern people. Although the disorder was once thought to be more common in Europe than in the United States, such is no longer the case; in England the prevalence is 1 in 87, in Finland 1 in 99, in Spain 1 in 389, in Iran 1 in 166, in the Sahara 1 in 18, and in the United States 1 in 133. The worldwide average prevalence for CD is estimated to be 1 in 266.

In children, the average age at the time of diagnosis is under 24 months. Diagnosis occurs sooner in infants who are fed products containing gluten at an early age and have not been breastfed. The clinical incidence declines markedly after age 2 years, and diagnosing CD in a teenager is even less common. In



**Figure 259-1** Normal jejunal mucosa. Villi are tall, crypts are relatively short, and the crypt-villus ratio is approximately 1:4. Epithelial cells are columnar, with basally oriented nuclei. Some lymphocytes and plasma cells are found in the lamina propria.

adults, CD often clinically develops after a precipitating illness, such as infectious diarrhea, or after a surgical procedure, such as gastrectomy, with a peak between the third and fifth decades of life. As with other autoimmune diseases, CD is more prevalent in females with a female-to-male ratio of approximately 2–3:1; however, individuals diagnosed over the age of 60 years are more likely to be male.

Clinical diagnosis of CD has become much more common, which has led to increased incidence. This increase results from the advent of routine upper endoscopy in evaluating patients with abdominal pain and finding a flat villus lesion during routine small-bowel biopsy, and from the use of serologic markers in the routine screening of family members and screening for associated diseases.

The concept of the “celiac iceberg” is used to illustrate the fact that despite the high prevalence of CD, there remains a large number of undiagnosed patients. The tip of the iceberg represents only 3% to 5% of those diagnosed with CD and is comprised of symptomatic individuals with mucosal injury. The silent CD is the next level of the iceberg, and includes patients with mucosal injury who are asymptomatic. These are new patients picked up through family history and other associated disease screening. The largest portion of the iceberg is the bottom, the so-called latent CD. These are patients with the appropriate genetic makeup and autoimmune markers, but with no mucosal damage. Given the right environmental triggers, these patients can develop into full-blown symptomatic CD.

### **PATHOLOGIC FEATURES**

CD primarily affects the mucosa of the small intestine. The submucosa, muscularis, and serosa are not involved. The mucosal lesion of the small intestine in

CD varies in severity and extent; lesions in the jejunum are generally more severe than those in the ileum. This variability may explain the differences in the degree of malabsorption observed in some patients; those in whom more intestinal area is involved presumably have a greater degree of malabsorption. This difference in the distribution of the lesion suggests that the proximal intestine has greater exposure to undigested gluten than the distal intestine, because no greater sensitivity to gluten is found in the proximal mucosa than in the distal mucosa.

Among patients with active CD, surface epithelial-cell damage occurs, and more cells migrate from the crypt to the villus region. Compensatory crypt hypertrophy occurs, with a marked increase in mitotic activity, and gradual villus flattening develops (Figure 259-1 and Figure 259-2). The surface epithelial cells demonstrate a loss of the basal nuclei polarity and become more cuboidal. Many intraepithelial lymphocytes are noted, and the lamina propria shows a marked increase in plasma cells and lymphocytes. This flat villus lesion is not pathognomonic of CD; it may be seen in many other diseases. With the introduction of the flexible endoscope, which permits focused biopsy rather than blind suction biopsy, investigators have found nonspecific antral gastritis in 10% of patients who have GSE, which implies the presence of some gastric sensitivity. In addition, occult CD should be suspected in patients with chronic diarrhea and evidence of biopsy-proven lymphocytic or collagenous colitis.

### **PATHOGENESIS**

CD is a genetic disease, although the complete mode of inheritance remains to be fully elucidated. Several genes seem to be involved, with the most consistent





**Figure 259-2** Jejunal mucosa in gluten-sensitive enteropathy (celiac sprue). Mucosa is flat, villi are absent, and crypts are deep. Epithelial cells are cuboidal, and nuclei are not basally oriented. Increased numbers of mitoses in the crypts is found. Inflammatory cells, especially plasma cells and lymphocytes, are markedly increased ( $\times 160$ ).

genetic component being the presence of *HLA-DQ2* or *HLA-DQ8* genes. These genes are necessary to develop disease although not sufficient by themselves; therefore, patients who lack this genetic background cannot have GSE. The *HLA-DQ2* allele combination is found in 90% to 95% of patients with GSE (however, 20% to 30% of the normal population also has this combination); the remaining 5% to 10% of patients are *HLA-DQ8* positive. The disorder requires both the genetic background and exposure to gluten, which is present in wheat, barley, and rye.

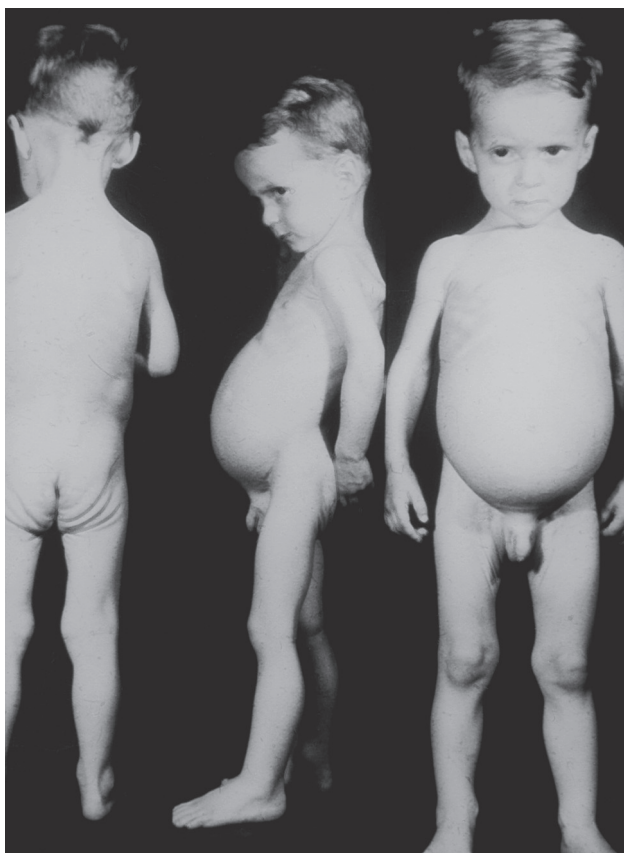
Two mechanisms of disease have been proposed. First, CD may result from the lack of a specific enzyme, a dipeptidase, which results in accumulation of toxic gluten peptides, such as the newly identified protein-rich peptide 33-mer, found in gluten. This peptide may be the primary initiator of the inflammatory response in susceptible individuals. 33-mer is the antigen that reacts with tissue transglutaminase and induces the gut-derived human T-cell lines. Second, gluten toxicity may be mediated through immunologic aberrations associated with genetically determined cell-surface markers.

Various immunologic abnormalities have been described in CD. First, increased levels of serum immunoglobulin A (IgA) and lowered levels of serum IgM are abnormalities that are reversed by a gluten-free diet (GFD). Second, intestinal mucosal immunoglobulin synthesis, notably IgA and IgM, is markedly increased in patients who have active CD. This synthesis returns to normal with remission. Fifty percent of the increased IgA is associated with specific anti-gluten antibody. Third, patients with active CD respond to corticosteroid treatment. Fourth, duodenal mucosa and peripheral lymphocyte transformation in response to gluten has been described in patients with CD.

## CLINICAL MANIFESTATIONS

Many patients with CD present with protean manifestations. However, a patient with an advanced case of CD is typically an irritable, anorectic child with chronic diarrhea, failure to thrive, a potbelly, and muscle wasting, especially of the buttocks and proximal limbs. These children are usually easy to diagnose (Figure 259-3). Nonetheless, many patients exhibit the disorder atypically. Box 259-1 lists atypical features of patients with CD. Such features are usually related to selective malabsorption of various nutrients. Therefore, patients with CD may have rickets, osteoporosis with bone pain, or pathologic fractures. Also seen are bleeding disorders that result from vitamin K deficiency, iron-deficiency anemia, and megaloblastic anemia, which is usually the result of folate deficiency. Vitamin B<sub>12</sub> deficiency is rare and usually indicates severe disease that extends to the terminal ileum. Constipation, rectal prolapse, clubbing of the fingernails, edema, and vomiting have also been reported. CD should always be considered in patients with specific nutritional defects who do not respond to nutrient replacement therapy.

Celiac crisis is a rare, life-threatening condition characterized by massive diarrhea, severe electrolyte imbalance, dehydration, or shock that needs to be recognized promptly. It can be triggered by severe malnutrition, an infectious process, poor compliance with the GFD, bacterial overgrowth caused by dysmotility, or hypoproteinemia. The patient needs to be admitted into the intensive care unit for further stabilization of electrolytes and fluids. Once the fluid shifts have stabilized, the goal is to start parenteral nutrition with total gut rest.



**Figure 259-3** Classic profile of patient with gluten-sensitive enteropathy (celiac sprue): potbelly, thin buttocks, and proximal muscle wasting.

#### **BOX 259-1 Atypical Manifestations of Gluten-Sensitive Enteropathy**

- Growth failure (without gastrointestinal symptoms)
- Anemia
- Iron deficiency
- Folate deficiency
- Vitamin B<sub>12</sub> deficiency (rare)
- Rickets, osteoporosis, pathologic features
- Bleeding disorders
- Edema
- Constipation
- Vomiting
- Recurrent abdominal pain

Slowly, introduction of a GFD with oral supplementation of iron, folic acid, vitamin D, and calcium should be attempted. These patients might require prolonged total parenteral nutrition.

Acutely, patients may require intravenous steroids to be stabilized.

#### **BOX 259-2 Common Causes of Flat Villus Lesion**

- Food sensitivity
- Gluten-sensitive enteropathy
- Cow's milk protein allergy
- Soy protein allergy
- Eosinophilic gastroenteritis
- Infection
- Viruses (rotavirus)
- Bacteria (*Escherichia coli*)
- Parasite (*Giardia lamblia*)
- Fungi (*Candida albicans*)
- Malnutrition (kwashiorkor, not marasmus)
- Tropical sprue
- Immunodeficiency disorders (most notably AIDS)
- Familial enteropathy
- Lymphoma
- Crohn disease
- Whipple disease

### **DIFFERENTIAL DIAGNOSIS**

In children younger than 18 months of age, flat villus lesions can have many causes besides GSE. Many gastrointestinal insults can damage surface epithelial cells, resulting in increased epithelial cell turnover, crypt hypertrophy, abnormal surface epithelial cells, and eventual villus flattening. Other causes of flat villus lesions are listed in Box 259-2.

For a definitive diagnosis of CD, the following criteria must be met: demonstration of clinical malabsorption and abnormal intestinal lesions; clinical and histologic response to gluten withdrawal; and subsequent gluten challenge that may exacerbate clinical symptoms, but that always produces abnormal intestinal histologic findings. The diagnosis must be made with certainty because CD means lifelong gluten restriction, and untreated patients are at a higher risk for developing gastrointestinal cancer in late adulthood.

#### **Serologic Markers**

Serologic markers emerged as a diagnostic tool and screening test for CD during the early 1980s. These serologic markers include anti-gliadin (AGA), anti-deaminated gliadin peptide antibody (anti-dGp), anti-reticulon antibody, anti-endomysial (anti-EMA) antibody, and anti-serum tissue transglutaminase (tTG) antibody. These serologic tests are used for symptomatic patients who need a biopsy; for screening of asymptomatic patients at risk, such as first- and second-degree relatives and those with other disorders associated with a high prevalence of CD; as supportive evidence for the disease; and to follow dietary compliance.

The first marker used for celiac serology screening was AGA antibodies. AGA antibodies are formed as a response to gliadin found in wheat, rye, and barley.



**Table 259-1** Celiac Serology

TEST	SENSITIVITY (REPORTED RANGE)(%)	SPECIFICITY (REPORTED RANGE)(%)	POSITIVE PREDICTIVE VALUE (%), PRETEST PROBABILITY OF 5%	NEGATIVE PREDICTIVE VALUE (%), PRETEST PROBABILITY OF 5%
IgA AGA	85 (57–100)	90 (47–94)	18	99
IgG AGA	85 (42–100)	80 (50–94)	31	99
EMA	95 (86–100)	99 (97–100)	83	99
IgA anti-tTG	98 (78–100)	98 (90–100)	72	99
IgG anti-tTG	70 (45–95)	95 (94–100)	42	99
IgA anti-DGP	88 (74–100)	95 (90–99)	44	99
IgG anti-DGP	80 (63–95)	98 (90–99)	68	99
IgA/IgG anti-DGP	97 (75–99)	95 (87–100)	51	99

AGA, anti-gliadin antibody; DGP, deamidated gliadin peptide; EMA, endomysial antibody; tTG, tissue transglutaminase.

From Leffler DA, Schuppan D. Update on serologic testing in celiac disease. *Am J Gastroenterol*. 2010;105:2520–2524. Reprinted with permission from Nature Publishing Group.

AGA IgA is more specific when compared to the AGA IgG (82%–95% vs 73%–90%) but lacks in sensitivity compared to its IgG counterpart (70%–90% vs 85%–98%). However, in children under 2 years, the tTG sensitivity is only 88% compared to 95% sensitivity in the older patient, making it helpful to use a panel of both AGA and tTG antibodies in such patients.

EMAs are developed in reaction to the ongoing damage to the intestinal lining by exposure to gluten in the predisposed individual. This test is more subjective because it is operator dependent, yet it has the best specificity (100%). Its sensitivity is also superior to the AGA antibodies (85%–98%). There are a few instances in which one can use it in the celiac panel to support the need for biopsies. In diabetic patients or patients with other autoimmune disorders, this test can be used together with a test for tTG antibodies. The tTG antibodies can be elevated primarily because of the nature of the other autoimmune disorder and not necessarily as an overlap with CD. A positive EMA IgA test increases the specificity of the serologic test and the need to biopsy.

tTG is the actual antigen that the anti-EMA antibody is detecting in the Immunofluorescence antibody assay (IFA) testing. In 1997, the EMA IFA was slowly replaced with tTG antibodies because this test is easier to perform by an enzyme-linked immunosorbent assay (ELISA) that is not operator dependent. The tTG antibodies have been evaluated as being perhaps even more sensitive than EMA antibodies (90%–98% vs 85%–98%); therefore, they are suggested as a first step in the screening process. EMA (IgA) antibodies should be used as a confirmatory test when the findings of tTG antibody testing are equivocal. These IgA-dependent tests could produce a false-negative result in patients with CD who are IgA deficient. In the IgA-deficient individual, the tTG IgG should be considered.

False-positive EMA and tTG antibody tests are unusual. A small-bowel biopsy should be performed to confirm the diagnosis of CD when serologic markers are positive. tTG has high specificity, but, rarely, other immune disorders, such as type 1 diabetes mellitus (T1D), Crohn disease, ulcerative colitis, autoimmune

hepatitis, severe heart failure, arthritis, and collagen vascular disorders, will also have positive tTG antibodies. If the EMA antibody testing is positive then, most likely, CD should be considered. A false-positive EMA result in a patient with normal tissue biopsies could be caused by poor tissue sampling, because this is a patchy disease; by distal small bowel disease that can be detected if using enteroscopes or wireless video capsule endoscopy to reach further into the jejunum/ileum; or by latent disease that has not manifested itself yet.

### New Tests and Their Value

Anti-DGP antibodies are the new generation of more sensitive and specific AGA antibodies both in IgA and IgG form. Measurement of DGP antibodies can be of use to the current serologic panel in situations of equivocal EMA or TGA results. Also, in IgA-deficient states, the DGP IgG assay may be more sensitive and used together with the tTG IgG antibodies to increase the positive predictive value of the test. Because the formation of DGP antibodies depends on the existence of tTG antibodies, they are not superior and cannot replace the use of tTG antibodies. In patients with only neurologic presentation, screening should still be performed by using AGA antibodies, because they have better sensitivity. Leffler and Schuppan have summarized the reliability of all the antibody screening in one table. (See Table 259-1).

### Genetic Markers

CD has a genetic predisposition, and recently the genes involved have been described. The major histocompatibility complex (HLA) class II genes *DQ2* and *DQ8* are involved in CD, above 90% and 8%, respectively. The use of these genetic markers in the screening process is not well clarified. These tests, if negative, exclude the possibility of CD; however, positive test results in patients who are asymptomatic and have normal biopsy results present a diagnostic and management dilemma. These genes are necessary, but not sufficient, for the development of CD. Thirty percent of the population has a positive *HLA-DQ2* and might never develop CD. Genetic testing is

recommended in the following instances: (1) patients who are on a GFD for more than 3 months prior to any testing and are refusing a gluten challenge; (2) patients who have equivocal changes on the intestinal biopsy; (3) patients who belong to high-risk groups with other autoimmune disorders and who want to avoid long-term serologic screening (one exception are those with T1D, because they can share the same genetic background); (4) in the screening process of family members who do not want periodic serologic screening.

### Family Screening

Because GSE is often asymptomatic, screening of family members of patients with confirmed GSE should be undertaken. Approximately 20% of family members may have GSE without being aware of it. The incidence in first-degree relatives is 1 in 18 to 22; for second-degree relatives, the incidence is 1 in 24 to 39. Parents and siblings should have serum tTG antibody screening and, if necessary, serum endomysial antibodies as a confirmatory screening test. In the IgA-deficient groups, tTG-IgG and endomysial antibody-IgG serologic markers should be assessed. If these tests are positive, then small-bowel biopsies should be performed.

### Associated Diseases

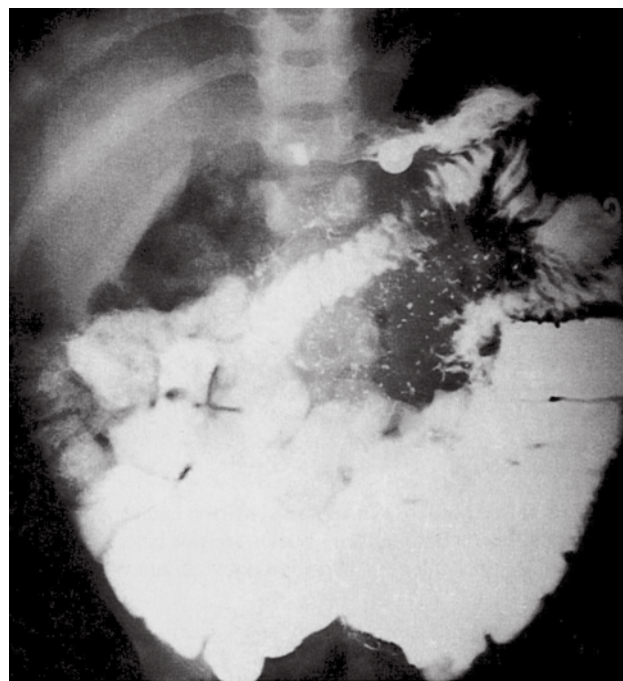
Diseases associated with an increased incidence of GSE include T1D; IgA deficiency; Down, Turner, and Williams syndromes; and autoimmune thyroiditis. These patients may be assessed for GSE with serum tTG antibody testing or *HLA-DQ2* and *HLA-DQ8* genetic screening, or both.

## EVALUATION

In children who present with symptoms of malabsorption, before evaluation for CD is pursued, a sweat test should be performed to exclude cystic fibrosis, the most common cause of malabsorption in childhood. Sometimes these 2 disorders coexist. Diagnostic tests are discussed in detail in Chapter 138, Diarrhea and Steatorrhea. Screening for GFD compliance should be conducted initially every 6 months until the patient has 2 consecutive negative tests, and annual screening should be conducted thereafter. Compliance screening should be done with the initial identified positive antibody.

### Laboratory Evaluation

Anemia is common in CD and usually occurs as a result of iron, folate, or vitamin B<sub>12</sub> malabsorption. Hypoprothrombinemia may occur as a result of vitamin K malabsorption. Because protein-losing enteropathy may occur in patients with CD, serum albumin and globulin levels should be measured. Electrolyte disturbances, especially hypokalemia, are common; calcium, phosphorus, and alkaline phosphatase levels may be abnormal in patients with rickets. The radiographic findings in CD, which are nonspecific (Figure 259-4), include distended small intestine and segmented barium as a result of hypersecretion of intestinal fluid.

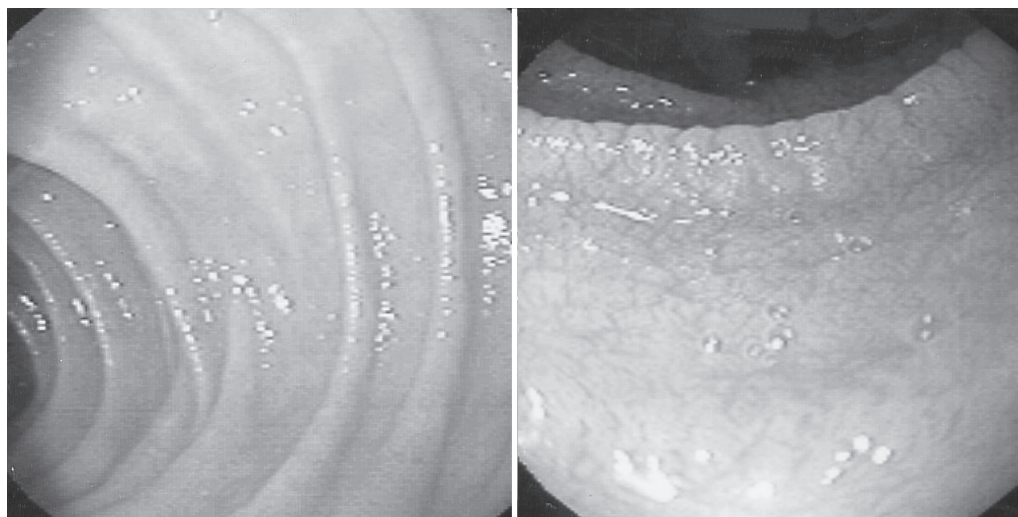


**Figure 259-4** Small-bowel follow-through of child with growth failure showing mild dilation of loops of small bowel, some dilation of barium distally, and mild flocculation. Duodenal biopsy revealed typical gluten-sensitive enteropathy (celiac sprue). Patient responded to a gluten-free diet.

### Intestinal Biopsy

Biopsy of the small intestine is the best way to diagnose CD. Previously, blind biopsies were performed with either the Crosby capsule or the Quinton-Rubin pediatric suction tube. Currently, biopsy specimens are routinely obtained by fiberoptic endoscopy to establish this diagnosis, and adequate tissue can be obtained by this technique. Endoscopy also permits visualization of the duodenum. Scalloping of the small intestinal valvulae of Kerckring has been described as pathognomonic for CD on endoscopy (Figure 259-5). In young infants, this appearance may be harder to visualize, but, in this patient population, edema of the duodenal mucosa is more common. Biopsies from the second portion of the duodenum showed the highest yield; however, a recent recommendation to increase the sensitivity of the test is to have duodenal bulb biopsies as well, since CD has a patchy and “proximal to distal” distribution.

In the past, authorities recommended that, after 1 or 2 years of a GFD, intestinal biopsies should be repeated to demonstrate complete recovery of the intestinal mucosa. A rechallenge with gluten was then initiated to initiate mucosal damage, which would be reassessed by intestinal biopsy. However, the recommendations for children older than 2 years of age have changed. Currently, repeat biopsy and rechallenge are not necessary if the child has become asymptomatic on a GFD. Instead, monitoring serum tTG or EMA



**Figure 259-5** Results of endoscopy showing scalloping of the small intestinal valvulae of Kerckring, a pathognomonic finding for gluten-sensitive enteropathy (celiac sprue).

antibodies (or both) is the preferred method. In contrast, children with indeterminate diagnosis should undergo another biopsy to demonstrate healing and then undergo rechallenge and another biopsy.

In patients who have normal histology and positive serology, consideration should be given to the video capsule endoscopy (VCE) to attempt to visualize the whole small bowel, because CD is a patchy disease and rarely it can present with distal distribution, making the classic diagnostic approach difficult. The VCE also should be considered in patients who are on a GFD but are symptomatic, especially those who present with alarm symptoms, such as fever, weight loss, and pain. Four endoscopic markers have been described in the pathogenesis of CD that help in making the diagnosis: scalloping, micronodularity, loss of folds, and mosaic pattern. The sensitivity of these markers has been reported from 47% to 100%, depending on the severity of the disease.

## MANAGEMENT

The treatment of CD is complete withdrawal of gluten from the diet, particularly exclusion of wheat, rye, and barley. Nutrition counseling by a qualified dietitian is an important component in the treatment of such patients. GFDs and recipes should be given to all patients or their parents. Although oats may be eaten by children with CD because oats do not contain gluten, they may be cross-contaminated with gluten during the manufacturing process.

Weeks may be required for symptoms to disappear completely after gluten is withdrawn from the diet; however, subjective improvement occurs within the first few days. In children, apathy is usually the first symptom to be alleviated, followed by progressive improvement in muscle tone, a decrease in abdominal

distention, and improvement of diarrhea. Disaccharidase activity is markedly depressed in CD; thus, a lactose-free diet is advocated during the initial 4 to 6 weeks of therapy to alleviate the diarrhea. Lactose may then be gradually reintroduced, provided that no concurrent infection, severe electrolyte imbalance, dehydration, or shock (celiac crisis) occurs.

Despite good compliance with a GFD, an estimated prevalence of refractory CD is between 7% and 30%, especially among adults. These patients are resistant to a GFD and require therapy with immune modulators. In an adult study, supplementation with pancreatic enzyme therapy has been proposed as beneficial in patients with chronic diarrhea and low fecal elastase, suggesting an exocrine pancreatic insufficiency.

Replacement iron, folic acid, vitamin K, vitamin D, and calcium should be initiated when appropriate. Compliance with a GFD can now be tracked by assessing the patient's serologic markers. An increase in tTG antibody will be observed if the patient does not comply with the diet.

The future is promising because much research is being conducted in the development of agents that can break down the gliadin and decrease the mucosal permeability, in addition to genetic engineering of safer grains and possible immunization to better tolerate or consume such grains.

## WHEN TO REFER

Referral to a gastroenterologist needs to be made based on clinical suspicion, the presence of positive serologic markers, first-degree relatives with GSE, syndromic presentations, and existence of other autoimmune disorders.



## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Celiac Disease* (fact sheet), National Institute of Diabetes and Digestive and Kidney Diseases ([digestive.niddk.nih.gov/ddiseases/pubs/celiac/](http://digestive.niddk.nih.gov/ddiseases/pubs/celiac/))

### Medical Decision Support

- *Celiac Disease* (Web page), North American Society for Pediatric Gastroenterology, Hepatology and Nutrition ([www.naspghan.org/content/51/en/Celiac-Disease](http://www.naspghan.org/content/51/en/Celiac-Disease))
- *Gluten Intolerance Group* (Web site), ([www.gluten.net](http://www.gluten.net))
- *Treatment Programs: Center for Celiac Research & Treatment* (Web page), MassGeneral Hospital for Children ([www.massgeneral.org/children/services/treatmentprograms.aspx?id=1723](http://www.massgeneral.org/children/services/treatmentprograms.aspx?id=1723))

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## Chapter 260 GUILLAIN-BARRÉ SYNDROME

Lalitha Sivaswamy, MD

The term Guillain-Barré syndrome (GBS) applies to a group of acquired, immune-mediated conditions affecting the peripheral nerves and nerve roots with occasional involvement of the cranial nerves. The term *acute inflammatory demyelinating polyradiculoneuropathy* (AIDP) was formerly synonymous with GBS because this was considered the primary pathology, but AIDP is now considered a subtype of GBS (see list of subtypes in Box 260-1). Other subtypes exhibit *axonal* pathology, thereby challenging the formerly held concept that GBS is an exclusively demyelinating disease.

The condition was initially described by Landry in 1859 as a cause of “ascending paralysis” and further elucidated by Guillain, Barré, and Strohl in 1916 as a polyneuritis with albuminocytologic dissociation on spinal fluid analysis. Hence, the condition could strictly

### BOX 260-1 Types of Guillain-Barré Syndrome

1. Acute inflammatory demyelinating radiculopolyneuropathy (AIDP); accounts for most cases in North America
2. Acute motor axonal neuropathy (AMAN)
3. Acute motor sensory axonal neuropathy (AMSAN)
4. Miller Fisher syndrome; can be considered a forme fruste of Guillain-Barré syndrome, and certain cases do ultimately involve the limbs and respiratory muscles
5. Polyneuritis cranialis; involves acute onset of multiple cranial nerve palsies
6. Acute sensory neuropathy
7. Acute pandysautonomia

be referred to as Landry-Barré syndrome but remains best known as GBS.

## EPIDEMIOLOGY

Guillain-Barré syndrome occurs with a frequency of about 0.5 to 1.5 in 100,000 in individuals younger than 18 years.

When children are affected, they are usually older than 3 years, with the most common age group being 4 to 8 years. The youngest patient described in the literature is a newborn, who presented at birth with generalized hypotonia.

Cases of children presenting in infancy have been described in the literature, hence physicians should entertain it as a differential diagnosis when encountering a floppy child in this age group. In the post-polio era, GBS has emerged as the most common cause of acute flaccid paralysis in childhood. Recent studies in the United States point to a slightly higher rate in the winter and spring compared with summer, reflecting the fact that GBS may follow antecedent viral respiratory infections such as influenza or influenza-like illnesses, which commonly exhibit seasonal predilection. In certain parts of Northern China and Mexico, it is more prevalent in the summer months because of its relationship with enteric pathogens. One-third of all GBS cases in such countries tend to be of the acute motor axonal neuropathy (AMAN) variety. A slight male predominance has been noted in most studies.

## ETIOLOGY AND RISK FACTORS

Guillain-Barré syndrome is an autoimmune condition and, in about two-thirds of cases, manifests as a postinfectious illness. Antecedent illnesses include chickenpox, hepatitis, cytomegalovirus, mycoplasma pneumonia, gastrointestinal illnesses, infections caused by Epstein-Barr virus, influenza-like illnesses, and urinary tract infections. The most well-documented association has been between the AMAN variant and



preceding *Campylobacter jejuni* infections. In the United States, such cases are relatively uncommon, but in certain areas of China they may account for more than 60%.

Epidemiologic studies have noted a 77 to 100 times higher risk for patients developing GBS in the 2 months following symptomatic *C. jejuni* infection compared with the general population, even in the Western world. A recent review of the world literature suggests that up to 30% of worldwide cases of GBS may be attributable to infection with *Campylobacter*.

Virologic studies using complement fixation testing noted serologic evidence of influenza infection in 3.5% of GBS patients admitted to a hospital setting in a large French cohort that primarily encompassed adults. Most patients had influenza A, and the subtypes were reflective of the prevalent epidemiologic strain. In addition, GBS has been reported following the 2009 H1N1 pandemic with D222E (H1N1) subtype of influenza.

Surgical procedures and some malignancies (particularly Hodgkin disease and some lymphomas) are temporally associated with GBS. The average time-frame between the preceding illnesses and neurologic symptoms is 1 to 3 weeks.

The administration of the A/New Jersey strain of the swine influenza vaccine in 1976 caused a sharp increase in GBS cases that year. The swine flu vaccination program was discontinued in 1977 because of this unacceptably high risk for GBS.

However, in the time period from 2006 to 2012, the administration of the seasonal influenza vaccine was followed by average attributable risk of 1 to 2 cases per 1 million doses. The risk was comparable to the 2009 H1N1 monovalent inactivated vaccine as well. Therefore, the influenza vaccine does seem to confer a very small, but possibly significant, risk for developing GBS. For physicians to assess the risk for GBS after influenza infection versus vaccination, it is worth considering that analysis of information from the United Kingdom General Practice Research Database has indicated that the relative incidence of GBS within 90 days of an influenza-like illness was 7.35, whereas after immunization it was 0.7. In summary, immunization against influenza seems to offer greater protection than risk both to society and to individuals. The Institute of Medicine has observed that “evidence is inadequate to accept or reject a causal relationship between influenza vaccine and GBS.”

Populations given the quadrivalent conjugated meningococcal vaccine demonstrated an increase of 1 additional case of GBS per 1 million individuals vaccinated.

The Centers for Disease Control and Prevention have issued guidelines with respect to these particular vaccines (see “Prevention”). Most evidence linking GBS to vaccines is temporal in nature, and causality has not been clearly established.

About half of all diagnosed cases of GBS, especially in the West, have no identifiable cause.

## **PATHOPHYSIOLOGY**

Guillain-Barré syndrome is believed to result from cross-reacting antibodies generated during a prior

infectious illness. The most common variant, AIDP, is characterized by macrophage-mediated destruction of myelin sheaths. The activated macrophages are believed to be targeted to epitopes on the myelin sheath. Pathologically, a mononuclear infiltrate is present around endoneurial blood vessels as part of the immune response to the inciting antigen. Animal models of AIDP, known as experimental allergic neuritis, are characterized by the presence of CD4<sup>+</sup> and CD8<sup>+</sup> T cells as well as macrophages around proximal nerves and nerve roots. These inflammatory cells produce a variety of proinflammatory mediators, including tumor necrosis factor- $\alpha$  and interferon- $\gamma$ , at the site. The exact antigenic target has not been clearly elucidated. This process is extensive and may involve the lower extremities, arms, trunk, nerves supplying the respiratory muscles, and select cranial nerves. The demyelination tends to occur both proximally, at the level of the nerve roots, and distally, producing the characteristic clinical features. Resting Schwann cells repair the injured segments by proliferation and laying down fresh myelin.

On the other hand, in acute motor sensory axonal neuropathy (AMSAN) and AMAN, the chief targets of immune attack are the axolemmal membranes. The outcome is variable and depends on whether this process occurs proximally or distally. The more proximally the nerve is injured, the more irreversible is the damage. AMAN is highly associated with antiganglioside antibodies to GM1a, GM1b, and GD1a, which are epitopes on gangliosides. Animal models of AMAN have noted the presence of immunoglobulin G against GM1 and GD1a, along with complement deposition at axolemmal membranes and nodes of Ranvier with limited demyelination and lymphocytic infiltrate.

Gangliosides are cell surface components of nerve tissue. They are glycosphingolipids and consist of a lipid bilayer with an oligosaccharide core. The terminal tetrasaccharide of GM1 gangliosides [Gal(beta 1-3) GalNAc(beta 1-4) NeuAc(alpha 2-3) Gal(beta)] is similar to the lipooligosaccharide of *C. jejuni*, lending credence to the theory of molecular mimicry.

Neuropathic strains of *C. jejuni* more frequently express cst-II, a genetic polymorphism, compared with enteric strains. In particular, patients with cst-II (Thr51) are more likely to be positive for anti-GM1 and anti-GD1a, whereas those with cst-II (Asn51) demonstrate anti-GQ1b antibodies.

The Miller Fisher variant of GBS can be considered a localized subtype, wherein antibodies are produced against GQ1b. GQ1b has been noted to be densely packed in the paranodal regions of the oculomotor nerves (ie, cranial nerves III, IV, and VI). This specific distribution factor would explain the relative frequency of extraocular muscle weakness in this variant.

## **DIAGNOSIS**

### **Symptoms and Signs**

Clinical features common to the various subgroups are discussed initially, and features regarding the individual subtypes are discussed in the latter half of this section.

Clinical events, in the form of an acute infectious illness before the onset of neurologic symptoms, occur in about half of affected children, and these most commonly include an upper respiratory illness.

The disease causes an acute- to subacute-onset quadriparesis or paraparesis. Children usually present with weakness in the lower extremities and can be brought in for refusal to walk, ataxia, or difficulty in climbing stairs. The weakness may then progress to the arms. In a significant minority (15% to 20%) of cases, weakness may remain proximal. Ataxia is caused by a combination of weakness and sensory loss, as opposed to cerebellar pathology. By definition, the nadir of weakness must be reached within 4 weeks, although in most affected children this occurs within 2 weeks.

Cranial nerve involvement (45%) is more frequently noted in children than in adults with GBS. Cranial nerves VII (facial), IX, X (glossopharyngeal and vagus), and VI/III (nerves that subserve extraocular muscles) are involved in that order of frequency. Facial nerve weakness is commonly bilateral. Pupillary involvement is rare, and an alternate diagnoses, such as tick paralysis, should be considered in these cases.

Pain is a common symptom and can be the primary manifestation in 50% of patients. Lower extremities are the most common location for pain, although other regions, including arms, lumbar and cervical regions, and abdomen, can be affected. Pain can be a “red herring” because it may lead to irritability, vomiting, and meningismus, causing diagnostic confusion. Sensory paresthesia can also be fairly prominent and contribute to the pain, although objective findings of sensory loss are rarely present. Distal paresthesia is typically present in both upper and lower extremities simultaneously, which distinguishes it from other polyneuropathies.

Sphincter disturbances, including urinary incontinence, urinary retention, constipation, and fecal incontinence, occur in 10% to 15% of affected children.

Symptoms and signs of dysautonomia may be present in about 25% of cases in the form of hypertension, tachycardia, cardiac arrhythmia, and hypotension. One case has been described of a patient requiring pacemaker placement for atrioventricular block. Mechanical ventilation is required in 15% of cases. Respiratory muscle weakness usually occurs subacutely and correlates with the degree of limb weakness. However, it is possible to have a severe degree of respiratory muscle involvement in the setting of mild limb weakness.

On examination, although the symmetrical nature of the weakness and areflexia is clearly apparent in most cases, patchy involvement may occur on initial presentation. The presence of sensory level is a red flag and should prompt the physician to initiate a search for spinal cord disease.

The natural course of the disease tends to follow 3 stages—progression, plateau, and recovery. The stage of progression is the period when there is immune-mediated damage to the myelin and axons in the nerve fibers. The plateau period represents slowing of the autoimmune-mediated nerve damage. Repair and regeneration of the myelin and axons occurs

in the recovery period. This phase may last for months.

The Miller Fisher variant is characterized by ataxia, areflexia, and ophthalmoplegia. However, this classic constellation of symptoms may not be present. Patients may present with bilateral facial palsy, eye muscle weakness, or central nervous system involvement suggestive of brainstem encephalitis. True motor weakness of the limbs is uncommon. Bickerstaff brainstem encephalitis is a condition that lays along the continuum of the Miller Fisher variant and has been associated with antibodies against GQ1b as well. The clinical features of brainstem encephalitis are mental status changes, ataxia, ophthalmoplegia, and weakness of the bulbar muscles.

Children with AMSAN and AMAN tend to have a more prolonged course with less than complete recovery. Children in this subgroup also have a higher incidence of requiring assisted ventilation.

The AMAN form has the strongest association with preceding *C jejuni* infection. The clinical presentation alone cannot distinguish it from the AIDP and AMSAN varieties.

Polyneuritis cranialis manifests with acute onset of bilateral lower motor neuron VII nerve palsies with frequent involvement of bulbar or extraocular muscles. This condition is distinct from the Miller Fisher variant mentioned previously.

Acute sensory neuropathy commonly presents with acute onset of ataxia with a positive Romberg test. Pandysautonomia causes prominent gastrointestinal and cardiovascular symptoms, reflective of pathology in the sympathetic and parasympathetic nervous system, particularly in the postganglionic efferent fibers.

The use of a clinical grading scale will ensure better communication between physicians (see Table 260-1).

### Differential Diagnosis

The differential diagnosis includes the conditions in Box 260-2. Children with spinal cord pathology, such as myelitis, can have pain and weakness with absent tendon reflexes. The presence of sphincter disturbances can further obscure the picture. Hence, early imaging may be of benefit when trying to differentiate between GBS and myelopathy. When peripheral neuropathy is being considered, usually these conditions

**Table 260-1**

### Guillain-Barré Clinical Grading Scale

0	Normal
1	Minor signs or symptoms
2	Able to walk 5 m without support
3	Able to walk 5 m with a walker or support
4	Bed or wheelchair bound
5	Requires assisted ventilation
6	Dead

Modified with permission from Hughes RAC, Newsom-Davis JM, Perkin GD, Pierce JM. Controlled trial of prednisolone in acute polyneuropathy. *Lancet*. 1978;312(8093):750–753.

can be distinguished by a detailed history and neurologic examination.

### Diagnostic Approach

Initial criteria for the diagnosis of GBS were formulated in 1978 under the auspices of the National Institute of Neurological Diseases and Stroke (NINDS), and subsequent modifications were suggested by Asbury and Cornblath in 1990. In brief, features required for diagnosis include progressive motor weakness of more than 1 limb with areflexia. Features that strongly support diagnosis include progression over 4 weeks, symmetry, cranial nerve involvement, recovery that

begins 2 to 4 weeks after progression stops, and autonomic dysfunction. Cerebrospinal fluid findings and electrophysiologic criteria that lend support include albuminocytologic dissociation and findings suggestive of demyelination, respectively.

More recently, the Dutch Neuromuscular Research Support Centre has proposed the following diagnostic and classification criteria for AIDP:

1. Subacutely developing flaccid paralysis
2. Weakness that tends to be symmetrical
3. Decrease or disappearance of tendon reflexes
4. Other causes for rapidly developing paralysis excluded by history and physical examination and, if necessary, additional testing

### Ancillary Testing

As implied by the previous discussion, a diagnosis of GBS is primarily based on clinical symptoms and neurologic examination. Although diagnostic procedures may lend support, they are not necessary to validate the diagnosis and do not supplant physical signs. In atypical cases, the physician may consider the following ancillary tests to confirm the diagnosis.

#### Laboratory Testing: Spinal Fluid Analysis

As a rule, there should be fewer than 50 cells/mm<sup>3</sup>, but usually there are fewer than 10 cells/mm<sup>3</sup>. A high cell count should raise suspicion for Lyme borreliosis, carcinomatous meningitis, or peripheral neuropathy associated with human immunodeficiency virus (HIV). Half of cases in the first week and 80% in the second week have elevated cerebrospinal fluid protein. In patients with the Miller Fisher variant, albuminocytologic dissociation is present in more than 75% of cases by the second week of illness.

#### Imaging

Enhancement of nerve roots with gadolinium on magnetic resonance imaging of the lumbosacral spine is commonly noted. A 1996 prospective study noted it in 18 of 19 patients with GBS. The disability scale was higher in those with greater enhancement and duration to recovery was longer in this subset. Interestingly, this finding was not related to the timing of imaging with respect to the course of the illness. In the Miller Fisher and polyneuritis cranialis variants, enhancement of the cranial nerves may be present.

### Diagnostic Procedures

**ELECTROPHYSIOLOGY** Care must be taken in deciding when to order nerve conduction studies because they remain normal early in the course of the illness. The earliest change is delayed or absent F waves. Abnormalities in the motor nerve conduction studies are present in 50% by 2 weeks and 85% by 3 weeks. Ten percent of cases may never fulfill the criteria for acquired demyelination. Electrophysiologic criteria, although beyond the scope of this chapter, broadly include the presence of at least 3 of the following:

1. Prolonged distal latency (time from application of the electrical stimulus to the recorded action potential in the muscle).

### BOX 260-2 Differential Diagnosis

#### DISEASES OF THE CENTRAL NERVOUS SYSTEM

Postinfectious cerebellar ataxia  
Structural cerebellar lesions  
Myelopathy

#### DISEASES OF THE PERIPHERAL NERVOUS SYSTEM

Anterior horn cell enteroviral infections, West Nile virus  
Peripheral neuropathy:

1. Noninfectious
  - a. Heavy metal and solvent poisoning: lead, arsenic, mercury, thallium, n-hexane, and organophosphates
  - b. Drug toxicity: isoniazid, nitrofurantoin, vincristine, cisplatin, phenytoin, and vitamin B<sub>6</sub>
  - c. Paraneoplastic polyneuropathy
  - d. Porphyric polyneuropathy
  - e. Critical illness polyneuropathy
  - f. Deficiency states, eg, vitamin B<sub>12</sub> deficiency
2. Infectious: Lyme disease (*Borrelia burgdorferi* infection), HIV, diphtheria. Spinal fluid in these cases usually reveals pleocytosis.
3. Food- and insect-borne polyneuropathy: neurotoxin fish poisoning, tick paralysis

#### NERVE ROOT DISEASE (POLYRADICULOPATHY)

Carcinomatous  
Sarcoidosis  
Lumbosacral plexopathy

#### DISEASES OF THE NEUROMUSCULAR JUNCTION

Myasthenia gravis: When ophthalmoplegia is prominent, this should be considered. Some patients do have proximal muscle weakness, although absence of myotactic reflexes should raise suspicion.  
Botulism, characterized by early loss of pupillary light reflex

#### MUSCLE DISORDERS

Electrolyte imbalances: Hypokalemia, hyperkalemia, hypermagnesemia, and hypophosphatemia can present with muscle weakness. These conditions do not show disease progression over time as is typical of GBS.  
Critical care myopathy  
Mitochondrial myopathy



2. Decreased conduction velocity (measure of the speed of the fastest conduction axons within the nerve).
3. Prolonged F response latency. (The F response is derived from “antidromic” travel of an electrical stimulus up a nerve to the anterior horn cell and orthodromic travel back to the muscle where it is recorded. Delay in recording F waves can be one of the earliest objective signs of GBS.)
4. Conduction block (when propagation of the impulse is completely or partially halted).

Myelin is essential to ensure rapid conduction along nerves. Accordingly, in conditions with predominant demyelination, there is slowing of the conduction velocity and prolongation of distal latencies. The proximal demyelination is reflected in the alterations in the F waves. Although GBS is in most instances predominantly demyelinating, secondary axonal loss may occur, which can be reflected in the needle electromyogram.

Electrophysiology also has a place in predicting the outcome. The compound muscle action potential (CMAP) is the best indicator of poor prognosis because a low CMAP is indicative of a prolonged course.

In essence, weakness is the result of conduction block or axonal damage, whereas paresthesia and pain are the clinical equivalent of sensory nerve damage.

**SEROLOGY** There is a strong correlation in patients with the Miller Fisher syndrome and its related subtypes, such as Bickerstaff encephalitis, and pharyngeal-cervical-brachial weakness with antibodies that react with gangliosides GQ1b, earning them the epithet “anti-GQ1b syndromes.” Anti-GQ1b antibodies are present in the Miller Fisher variant in more than 80% of cases, especially in the first week of the illness. Pure motor types, such as AMAN, demonstrate antibodies to GD1a and GM1a. Immunoglobulin G antibodies against GQ1b and GT1a are associated with rare anatomically limited forms, such as ophthalmoplegia and oropharyngeal palsy. Antibodies against GD1b are associated with sensory ataxia. Serologic evidence of recent *C jejuni* infections is also more common in patients with the Miller Fisher and AMAN variants. Appropriate serologic workup may help with classification and accurate classification of subtypes.

## MANAGEMENT

### Treatment Approach

The most important aspect of management is the early recognition and treatment of impending respiratory failure. Access to a facility that has a critical care unit well equipped to deal with affected children and an intensive care physician who can assist with this treatment is vital.

Pain management should take a close second place because pain can be prominent and the cause of significant morbidity. This is especially crucial in children who may not be able to clearly articulate their symptoms. The physician should be on the lookout for autonomic imbalance and consider intensive care unit admission if there is significant lability of hemodynamic parameters.

General aspects of care in the intensive care setting include hydration, nutrition, and early instatement of physical and occupational therapy. Treatment with immunomodulatory agents is generally employed when the manifestations are more severe, with prominent ataxia or bulbar or respiratory involvement. Treatment within 2 to 4 weeks of symptom onset may decrease recovery time.

### Specific Treatments

Corticosteroids are ineffective in the treatment of GBS.

#### Intravenous Immunoglobulin

No prospective placebo-controlled randomized trial has been conducted to study the role of intravenous immunoglobulin (IVIG) in children with GBS. Nonetheless, the consensus of opinion, on the basis of case series and retrospective analysis, indicates that IVIG can reduce duration of hospitalization and reduce the time to onset of ambulation. The total dose of IVIG is usually 2 g/kg over 3 to 5 days. Once again, there is no trial to indicate efficacy of this dose over other regimes. Common side effects include fever, rigors, chills, headache, rash, and myalgia. Aseptic meningitis, congestive heart failure, and renal failure are serious, but rarely encountered. Anaphylactic reactions in patients with immunoglobulin A deficiency are rare in clinical practice. The report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology recommends use of IVIG in children based on its effectiveness in adults.

#### Plasmapheresis

Plasmapheresis is a more invasive modality of treatment. A universally accepted protocol is not available. Most institutions use an alternate-day protocol ranging from 4 to 8 pheresis treatments. Potential complications can include hypotension, catheter-related infections, bleeding, and hypocalcemia.

A trial comparing plasma exchange to immunoglobulin noted that using a combined regimen with both modalities of treatment was no more effective than using either form of therapy alone. The American Academy of Neurology recommends use of plasmapheresis in adults with severe GBS that interferes with gait or respiratory function. No similar recommendations in children are available as of the last practice parameter in 2011.

## ONGOING CARE

Monitoring weakness by clinical examination and coordinating care with occupational and physical therapists are the main roles of the physician in cases of GBS. If progression of muscle weakness is present over 4 weeks or a relapsing or protracted course over 1 year is noted, alternate diagnoses must be entertained. Chronic inflammatory demyelinating polyneuropathy then becomes a diagnostic consideration.

### Follow-up

After discharge from a hospital setting, patients should continue occupational and physical therapy



services. Return to school may present certain challenges, and the pediatrician may need to advocate for certain allowances, such as use of elevators. Electro-physiology is rarely repeated after the acute period.

### Complications

The most common complications in the acute care setting are weakness of the respiratory muscles and autonomic instability. Other complications may include pneumonia, constipation, gastric paresis, deep vein thrombosis, and pressure sores. Treatment with IVIG carries the risk for certain side effects, as does plasmapheresis, and these have been discussed in the Specific Treatments section.

### Prognosis

More than 90% of children with GBS recover. Those who do not recover completely ambulate independently with minimal residual deficit. The average time-frame for the period of disease progression and the plateau phase is 4 weeks, respectively. A small subset (<5%) of children may progress to a chronic form referred to as chronic inflammatory demyelinating polyneuropathy (CIDP) or have relapses of GBS. Patients with CIDP, by definition, have progressive weakness for more than 2 months since the onset of weakness, with motor and sensory dysfunction in more than 1 limb and hyporeflexia or areflexia on examination. Unlike GBS, CIDP is characterized by relapses and remissions or a slowly progressive course. Electrodiagnostic criteria for the diagnosis of CIDP have been outlined by various academic bodies, including the American Academy of Neurology.

The mortality rate is currently estimated at less than 5%. Deaths are caused by respiratory failure, cardiac arrhythmia, and dysautonomia. As can be seen, it is an acute monophasic illness and in this manner distinguishes itself from other autoimmune peripheral neuropathies. In the Miller Fisher variant, ophthalmoplegia resolves in 1 to 2 months, and ataxia in 3 to 4 months.

### Prevention

Immunization against *Campylobacter* infection in countries where it is endemic may represent a method of disease prevention. However, as of now, no preventative treatments can be offered because vaccines for enterotoxigenic *Escherichia coli* and *Campylobacter* are currently in the preclinical stage. Families of children who have had GBS should discuss potential risks and benefits of receiving the influenza vaccine, although the preponderance of evidence seems to suggest that the benefits of vaccination outweigh the risks. The Centers for Disease Control and Prevention has cautioned physicians regarding administration of the influenza vaccine and the diphtheria, tetanus, and pertussis (DTaP) vaccine to those known to have experienced GBS within 6 weeks after a previous influenza or DTaP vaccination. Reports to the US Vaccine Adverse Events Reporting system shortly after the quadrivalent conjugated meningococcal vaccine raised concerns about a potential association between the vaccine and GBS. However, the Advisory Committee on Immunization Practices

(ACIP) does not consider a history of GBS to be a contraindication to administration of the meningococcal conjugate vaccine, although it remains listed as a precaution on the package insert.

The preponderance of evidence suggests that hepatitis B; measles, mumps and rubella; *Haemophilus influenzae* type B; rabies; and diphtheria and tetanus toxoid vaccines need not be withheld after an attack of GBS.

### WHEN TO REFER

- A neurologic consultation may be appropriate when a child with suspected GBS is admitted. This may be particularly crucial when the diagnosis is in doubt because of unusual clinical features or the recovery phase is atypical. A neurologist versed in electromyography can help with prognostication.
- Occupational and physical therapy referrals, when done early in the disease process, can be helpful both in the inpatient and outpatient settings to ensure prevention of joint contractures and optimize potential for functional recovery.
- A hospitalist well acquainted with the disease manifestations may prove invaluable in deciding on transfer to a facility that has a pediatric intensive care unit.

### WHEN TO ADMIT

- Any child suspected of having GBS should be admitted to the hospital for observation and close monitoring of respiratory status until it is clear that there is no further disease progression.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Children with GBS* (Web page), Guillain-Barré Syndrome/CIDP Foundation International ([www.gbs-cidp.org/gbs/children-gbs](http://www.gbs-cidp.org/gbs/children-gbs))

#### Medical Decision Support

- *Advisory Committee on Immunization Practices* (Web site), ([www.immunize.org/acip](http://www.immunize.org/acip))
- *Practice Parameter: Immunotherapy for Guillain-Barré Syndrome* (guideline), *Neurology*, Vol 61, Issue 6, 2003

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## Chapter 261

# HEMANGIOMAS

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## FOUNDATION

### Nomenclature and Classification

Confusing and nonspecific names for hemangiomas, including strawberry nevus and cavernous hemangioma, have been used throughout history. In their seminal work in 1982, Mulliken and Glowacki separated vascular anomalies into hemangiomas and vascular malformations based on their biologic properties. Infantile hemangioma, a type of vascular tumor, grows shortly after birth and slowly involutes through childhood, whereas a vascular malformation is present at birth, continues to grow, and does not resolve spontaneously. In contrast to vascular malformations, hemangiomas have different phenotypic presentations, the most common being the infantile hemangioma. Box 261-1 illustrates the most recent classification for vascular anomalies adopted by the International Society for the Study of Vascular Anomalies.

### BOX 261-1 International Society for the Study of Vascular Anomalies Classification of Vascular Anomalies

#### VASCULAR TUMORS

- Benign
- Locally aggressive or borderline
- Malignant

#### VASCULAR MALFORMATIONS

- Simple
  - Capillary malformations
  - Lymphatic malformations
  - Venous malformations
  - Arteriovenous malformations<sup>a</sup>
  - Arteriovenous fistula<sup>a</sup>
- Combined<sup>b</sup> CVM, CLM
  - LVM, CLVM
  - CAVM<sup>a</sup>
  - CLAVM<sup>a</sup>
  - Others
- Of major named vessels
- Associated with other anomalies

<sup>a</sup>High-flow lesions

<sup>b</sup>Defined as 2 or more vascular malformations found in 1 lesion

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### Epidemiology, Etiology, and Risk Factors

Infantile hemangioma is the most common tumor of infancy. Classically, these lesions present shortly after birth, with or without an initial precursor lesion or “herald patch,” and subsequently undergo several phases of unpredictable duration characterized by a proliferative phase, a plateau phase and finally, some degree of an involution phase; current thought is that the plateau phase is a balance between proliferation and involution.

In white term infants of normal birth weight, infantile hemangioma incidence is approximately 5% to 10%; for infants with a lower birth weight, the incidence is much greater. About 1 in 5 children will have multiple lesions, and the incidence is 3 times greater for girls. The exact pattern of genetic inheritance is unclear; it is thought that infantile hemangioma inheritance is sporadic. Previous case series and retrospective studies have suggested that female gender, prematurity, fair skin, and history of chorionic villous sampling may all be risk factors for the development of infantile hemangioma.

The exact cause for hemangioma has not been established; however, demographic, prenatal, and perinatal factors in patients with these lesions may provide clues to pathogenesis. There is general consensus that infantile hemangioma is of endothelial cell origin, but the source of the endothelial cells is debatable. There has been much conjecture as to whether these endothelial cells are of mutational or placental origin, if they fit into a developmental field defect, or if they are simply a derangement of angiogenesis. The expression of cellular markers of angiogenesis supports the theory that infantile hemangioma represents vasculature of placental origin or immature vascular growth expressing a placental phenotype.

### Natural History

Classically, the common postnatally acquired infantile hemangioma begins developing after birth and in some cases a precursor herald patch is seen. The herald patch appears in a variety of forms, including a bruise-like patch, a limited area of pallor with fine telangiectasia, or a macular erythematous lesion, or it may even be erroneously attributed to trauma. These lesions develop into a rapidly growing vascular tumor within the first 1 to 2 months of life, characterizing the proliferative phase, and while most growth is completed by 3 to 6 months, growth can continue to 9 months of life. In the plateau/early involution phase, several clinical changes may be seen, including color fading, softening, and reduction in volume. Involution continues with a decreased volume of tumor; however, this process may take several years and is often incomplete. In fact, many infantile hemangiomas leave behind residual cutaneous telangiectasia, scarring, fibrofatty residuum, or excess skin.

When a lesion is present at birth, a vascular malformation should be considered. These lesions are congenital structural anomalies that represent abnormal vasculature or lymphatics. Deeper malformations may only present with clinical symptoms or signs during the adolescent growth period.

## DIAGNOSIS

### Signs and Symptoms

A detailed history and clinical examination are still the most valuable diagnostic tools for infantile hemangioma. The most critical information is the presence of a growth shortly after birth followed by expansion of the lesion and then a period of plateau, culminating with involution. The clinical appearance of an infantile hemangioma depends on which level of the skin is affected; common presentations include superficial cutaneous, deep, or segmental plaque-like. Superficial cutaneous hemangiomas, previously named “strawberries,” are the raised, red tumors that are commonly seen. Their surface comprises a thin epidermal layer and is fragile and prone to injury. During the rapidly proliferative phase, ulceration is a possibility because of the thin epidermal layer which can easily become traumatized; an ulcerated hemangioma should prompt an early referral to a specialist. Deep lesions are located in the deeper dermis and subcuticular space; because of their depth, the perceived color is generally darker, and the lesion could be confused for a vascular malformation (usually venous malformation) or another solid lesion. Visible telangiectasia, dilated small vessels, or vascular papules can be associated with these deeper lesions, especially with draining veins at the periphery. Occasionally, hemangioma presents as a flat, plaque-like segmental lesion that grows radially, but does not develop into the more classical “fleshy” appearance. In certain anatomic locations, these lesions should warrant further evaluation. Hemangiomas can also be further classified as being of high risk (functional or aesthetic complications) or low risk (no functional or aesthetic concern). High-risk lesions are discussed in detail later in this chapter.

### Differential Diagnosis

Although infantile hemangioma is the most common presentation of a vascular birthmark, the differential diagnosis includes other types of vascular tumors (congenital hemangioma, pyogenic granuloma, tufted angioma, and kaposiform hemangioepithelioma [KHE]) as well as vascular malformations (capillary malformation, venous malformation, lymphatic malformation, arteriovenous malformation, and mixed malformations); if presenting with a subcutaneous mass, lesions to consider, include lipoma, neurofibroma, and rhabdomyosarcoma, among others.

Different subtypes of hemangioma, rapidly involuting congenital hemangioma (RICH) and non-involuting congenital hemangioma (NICH), present fully grown at birth and may be detected by ultrasound prenatally. These lesions are usually found on the head and neck or lower limbs and have similar imaging findings, but different temporal courses. RICH commonly presents as a single raised tumor that has a dark color with central telangiectasia, has a radial distribution of ectatic veins, and is surrounded by a pale halo region. These lesions do not grow, and they involute by 12 to 18 months. NICH is a solitary tumor, resembles a RICH clinically, grows with the patient or expands slightly over time, but does not regress.

Another vascular tumor that might resemble an infantile hemangioma is a pyogenic granuloma. Although presenting at any age, historically these were often known as “pregnancy tumors” and may be related to trauma. More commonly found in children, these grow rapidly to vascular and friable papules or tumors. They are most commonly found on the head and neck, but other sites have been described. These lesions often ulcerate and bleed, and are prone to recurrence with subtotal treatment.

KHE is a rare entity that may be found either in skin or as a retroperitoneal tumor. This lesion presents as a congenital tumor or develops shortly after birth. Histologic examination demonstrates dense and infiltrating spindle cell nodules with infrequent mitoses. Tufted angioma is another uncommon vascular tumor that usually presents in infancy or childhood, but has been found congenitally. This is a diffuse group of lesions including solitary tumors, large plaques or “port wine stain-like” lesions with a cobblestone presentation. The association with Kasabach-Merritt phenomenon (systemic coagulopathy resulting from thrombocytopenia) is established for KHE and tufted angiomas.

Vascular malformations, in contrast to infantile hemangioma, are present at birth, grow in proportion to the child, and may proliferate during periods of hormonal fluctuation (ie, puberty, pregnancy). Interestingly and of diagnostic concern, in the neonatal period the differential diagnosis of a cutaneous red patch might represent the early stages of a proliferating hemangioma, a congenital hemangioma, a capillary malformation, or a stage I arteriovenous malformation. A detailed discussion of vascular malformations can be found in Chapter 95, Neonatal Skin.

### High-Risk Lesions: Complications and Associations

#### Segmental Hemangioma

Specifically pertaining to infantile hemangioma, these lesions can be further subclassified depending on their pattern, type, and association with other lesions (see Box 261-2).

Segmental plaque-like hemangiomas in certain anatomic locations often warrant additional evaluation because of associated conditions that can be present. Large segmental hemangiomas in the facial region warrant consideration for PHACES syndrome, characterized by posterior fossa malformations; facial hemangiomas; arterial, cardiac, and eye abnormalities; and sternal clefting. Lumbar or pelvic segmental hemangioma may be associated with LUMBAR syndrome, manifested by arterial anomalies, spinal cord tethering, perineal-lumbosacral hemangioma, and genitourinary differences.

#### Visceral Hemangioma

About 15% of children will have more than 1 cutaneous hemangioma. The presence of more than 5 lesions can be associated with visceral involvement, and investigation by ultrasound or magnetic resonance imaging (MRI) for intra-abdominal hemangioma is recommended. Ultrasonography is the indicated screening test; MRI should only be done if ultrasound



**BOX 261-2 Classification of Infantile Hemangioma****PATTERN**

- Focal
- Multifocal
- Segmental
- Indeterminate

**DIFFERENT TYPES**

- Superficial
- Deep
- Mixed (superficial + deep)
- Reticular/abortive/minimal growth
- Others

**ASSOCIATION WITH OTHER LESIONS**

- PHACES syndrome
  - Posterior fossa malformations
  - Hemangioma
  - Arterial anomalies
  - Cardiovascular anomalies
  - Eye anomalies
  - Sternal clefting or supraumbilical raphe
- LUMBAR (SACRAL, PELVIS) syndrome
  - Lower body hemangioma
  - Urogenital anomalies
  - Ulceration
  - Myelopathy
  - Bony deformities
  - Anorectal malformations
  - Arterial anomalies
  - Renal anomalies

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shows lesions that are concerning for another diagnosis.

Intra-abdominal hemangioma most often manifests as a liver hemangioma, which is the most common pediatric hepatic lesion; the presenting feature clinically could be high-output cardiac failure. A single, large lesion detected by antenatal imaging or on physical examination or imaging at birth is usually a rapidly involuting congenital hemangioma. This type of lesion may be asymptomatic and require no therapy. It also may be associated with high-flow shunts causing high-output cardiac failure. These symptoms/signs may improve with rapid spontaneous involution, or may require embolization of high-flow shunts.

Multifocal lesions may be asymptomatic or may demonstrate high-flow causing high-output cardiac status. This should be treated with propranolol and followed closely. Many multifocal or closely packed, diffuse hemangiomas may cause consumptive hypothyroidism, which should always be investigated and treated aggressively if found.

**Airway Hemangioma**

Upper airway hemangioma (sometimes called subglottic hemangioma) carries a significant risk of airway compromise during the proliferative phase and usually presents clinically with stridor. About half of these infants will have a cutaneous lesion, but those with perioral lesions seem to be at the highest risk (60% of those with a “beard distribution” lesion will develop symptomatic upper airway difficulty). Respiratory failure can occur precipitously, and the combination of cutaneous infantile hemangioma and respiratory distress should warrant prompt referral to an otolaryngologist experienced in pediatric airway management.

**Periocular Hemangioma**

Up to 50% of periocular hemangiomas are amblyogenic, most commonly from refractive error (astigmatism, anisometropia) resulting from pressure imparted by an adnexal tumor on the cornea. Furthermore, amblyopia can be caused by deprivation from visual axis obstruction, optic nerve atrophy secondary to nerve compression or stretch, strabismus caused by tumor infiltration of extraocular muscles, or keratopathy caused by proptosis and corneal exposure. Infrequently, an infant presents with a lesion covering the visual field; patching of the normal eye may be indicated. These lesions must be urgently evaluated by an ophthalmologist to prevent irreversible amblyopia, and aggressive intervention could be warranted.

**Ulceration and Infection**

Ulceration is a common finding in patients with infantile hemangioma. Risk factors for hemangioma ulceration include large size; segmental distribution; regions prone to friction, trauma or maceration (perineum, lip); lesions in the proliferative phase; female gender; and premature birth. Ulceration can be caused by trauma or maceration. These lesions are notoriously challenging to manage, because they may take several weeks to heal regardless of which modality of treatment is employed. Furthermore, an ulcerated infantile hemangioma is very painful, and careful dressing care is important so as to avoid further trauma to an already complex wound.

A small subset of hemangiomas may become infected, and infection is associated with an ulcerated lesion because the open area can become colonized with bacteria, especially in the perineal-lumbosacral area. Once an infantile hemangioma becomes ulcerated, care should be taken to dress the ulcerated wound with a topical non-stick antimicrobial agent, which may help enhance wound healing rates, because colonized wounds take longer to heal.

Many of the common complications of infantile hemangioma include wound care issues. For perineal-lumbosacral lesions, frequent soiling and maceration can lead to ulceration, bleeding, and pain. Parent education regarding meticulous wound care in the form of topical antimicrobials and non-stick wound dressings is paramount.

**Other**

Hypothyroidism has been described in infants with massive hemangioma because of high levels of type 3



iodothyronine deiodinase within the lesion. In patients with large or multiple lesions, investigation of thyroid function may be required. Finally, lesions obstructing the auditory canal or perineal-lumbosacral region warrant specialist evaluation by an otolaryngologist or urologist/general surgeon, respectively.

### Imaging

The diagnosis of hemangioma is primarily clinical in nature, based on history. Plain radiography rarely aids in diagnosis; however Doppler ultrasonography and MRI may help guide diagnostics or management planning. In rare cases, a biopsy may be performed to rule out any other pathology. Doppler ultrasonography may demonstrate a well-circumscribed mass within which are anechoic channels and numerous fast-flow vessels. The flow should be correlated with the clinical stage of the lesion, because the arterial flow will be reduced during the involutional phase. Throughout the proliferative phase, there are numerous vessels with a high Doppler shift ( $>2$  kHz), low resistance, and nonspecific echogenicity.

MRI is useful for lesions causing a diagnostic dilemma as well as for presurgical planning to determine anatomic relationships between the tumor and the surrounding tissues. Well circumscribed, uniformly enhancing and densely lobulated structures with multiple flow voids as well as dilated arterial feeding and venous draining vessels, either at the periphery or within the center of the lesion, are characteristic findings that can be seen on MRI.

### Histopathology

Histopathologic findings of infantile hemangioma change according to the phase of its natural history. Early proliferative phase findings include plump endothelia with surrounding pericytes in unencapsulated and well-defined clumps and lobular arrangement of the lesion with large feeding and draining vessels. Many mitoses can be seen, but they are of a normal morphology. During this period of growth, the vascular endothelia undergo several changes with sinusoidal channels that are closely packed. Throughout the involutional phase, the number of mitoses and vessels decreases and fatty infiltration of the mass occurs. Increased mast cell proliferation is evident at the onset of involution and resolves during the involutional phase. A multilaminated basement membrane is seen with electron microscopy, but this is seldom practical or required for diagnosis. The immunohistochemical marker, GLUT-1, is found in all phases of the lesion's natural history and is helpful in differentiating infantile hemangioma from other vascular anomalies. Interestingly, congenital hemangiomas (RICH/NICH) are GLUT-1 negative.

## MANAGEMENT

### Treatment Approach

The benefits of any treatment must be weighed and balanced appropriately against the presenting problem. For an infantile hemangioma, the decision to employ observational management, medical management, or operative management is subject to debate.

In the 1940s through the 1960s, patients were given radiation therapy that effectively treated the lesion but also produced secondary undesirable sequelae. As a result, through the 1970s and 1980s, a hesitancy from the perspective of primary care physicians and dermatologists toward aggressive treatment was espoused. Since the 1990s, though, more aggressive and earlier treatment approaches have been the trend because infantile hemangiomas often do not involute completely, leaving behind excess skin, fibrofatty tissue, scarring, and telangiectasia.

Although there are numerous possible treatment options for hemangioma, this produces a treatment dilemma, because no definitive advice exists to guide the physician. In general, small, uncomplicated, low-risk lesions in unimportant cosmetic or functional areas may be managed without intervention, because spontaneous resolution is likely to yield an acceptable aesthetic and functional result. High-risk lesions producing functional or aesthetic distortion should prompt timely referral to a vascular anomalies team for additional evaluation and treatment considerations.

### Specific Treatments

#### Observational Management

For patients with low-risk lesions, regular visits to the primary care physician during the proliferative period are required, for both patient monitoring and reassurance. Photographic aids describing hemangioma natural history should be shared to limit parental anxiety. A multidisciplinary approach may also be helpful involving dermatologists, plastic surgeons, general surgeons, ophthalmologists, otolaryngologists, among others.

#### Medical Management

**CORTICOSTEROIDS.** Over the past 40 years, the mainstay of medical treatment for infantile hemangioma has been corticosteroids administered either systemically or intralesionally. Treatment is most effective in the rapidly proliferative phase, and on occasion rebound growth is found on cessation of therapy. The documented side effects of systemic corticosteroids (including irritability, cushingoid facies, hypertension, and gastroesophageal reflux) should be explained prior to initiation, and screened for while the patient is on the medication; these potential complications are temporary and resolve with discontinuation of treatment. Delivery of corticosteroid by injection can also be effective, although the sequelae of cutaneous atrophy, telangiectasia, and pigmentary changes can occur. Despite the complication profile, dramatic results have been found with corticosteroid administration, purportedly as a result of angiogenesis inhibition.

**BETA-BLOCKERS.** A recently discovered treatment modality for infantile hemangioma has been found through the use of the nonselective beta-blocker, propranolol. This drug has been the source of much interest, and numerous case series have found promising results in not only the proliferative phase, but also the plateau and involutional phases. The exact mechanism of action of beta-blockers for the treatment of hemangioma remains uncertain, although



**Figure 261-1** Clinical photographs of a 3-month-old infant with an extensive right facial hemangioma. (Top Row) Note the visual axis obstruction and impending obstruction of right nostril. (Center Row) There was a significant decrease in subcutaneous tumor bulk 1 month after treatment. (Bottom Row) Clinical photographs of the patient after treatment with oral propranolol for 6 months. Note the significant improvement of proptosis, facial contour, and right nostril position. (From Arneja JS, Pappas PN, Shwayder TA, et al. Management of complicated facial hemangiomas with beta-blocker [Propranolol] therapy. *Plast Reconstr Surg.* 2010;126:889–895, with permission.)

some hypotheses have suggested a vasoconstrictive, antiangiogenic, or cellular apoptosis effect. Propranolol has been administered orally at 2 (range 1–3) mg/kg/day in twice-daily or 3-times daily dosing. Complications to be screened for include bronchospasm, hypoglycemia, hypotension, and bradycardia; other potential complications can include limb cyanosis, hyperkalemia, and seizures. Although the long-term effects and efficacy of this therapy have not been established, early evidence suggests the complication profile is found less often than with corticosteroid, and outcomes to date are very encouraging. Figure 261-1 illustrates successful management of a large facial amblyogenic hemangioma with propranolol in the setting of failed and complicated corticosteroid treatment. Recently, the topical delivery

of beta-blocker has also met with clinical success and without the potential complication profile of medication taken orally.

**OTHERS.** Interferon- $\alpha$ , an angiogenesis inhibitor, has been used for hemangioma management, and both the isoforms 2 $\alpha$  and 2 $\beta$  have been used with equal success. Significant neurotoxicity in about 20% of cases (spastic diplegia) has limited the utility of this therapy. Vinca alkaloids have also been used with success, but are used much less often today.

#### Laser Therapy

Several different types of lasers have been developed to treat intact and ulcerated infantile hemangioma. The pulsed dye laser has been shown to be effective in



**Figure 261-2** Photographs of a 6-month-old girl with left lateral upper eyelid hemangioma causing blepharoptosis and astigmatism (3.0 diopters) preoperatively (left) and 15 months postoperatively (right), with astigmatism improvement (0.5 diopters). (From Arneja JS, Mulliken JB. Resection of amblyogenic periocular hemangiomas: indications and outcomes. *Plast Reconstr Surg.* 2010;125:274-281, with permission.)

the management of capillary malformations (port-wine stains), and has been widely used for the treatment of hemangiomas. Because its depth of penetration is only approximately 1 to 2 mm, the pulsed dye laser is used primarily to treat the cutaneous manifestations of the lesion. It may be most useful for treating the residual telangiectasia after involution, or for treating ulcerated infantile hemangioma. Multiple treatments might be necessary for optimization of aesthetics. Continuous-wave lasers such as the argon, neodymium:yttrium-aluminum-garnet (Nd:YAG) and potassium titanyl phosphate (KTP) have also been used, albeit less commonly than the pulsed dye laser.

### **Surgical Management**

The indications for patients with hemangioma to undergo surgery are varied, but can be divided according to phase or degree of complication. Complicated infantile hemangioma failing medical therapy should be considered for a surgical opinion, because left untreated it can produce permanent or undesirable sequelae. Furthermore, a facial hemangioma producing aesthetic distortion can also be considered for resection, because these tumors impart a significant degree of caregiver and patient anxiety and distress. Consideration should also be given to the development of the patient's facial image and self-concept, because this begins between 3 and 6 years of age, and peer ridicule can be problematic through the primary school years. For lesions producing aesthetic distortion, careful dialogue between patient, caregivers, and physician/

surgeon is necessary to determine appropriateness and timing of surgical intervention.

Surgical techniques go beyond the scope of this chapter; however, the figures herein illustrate what outcomes are possible with surgical intervention of an amblyogenic periocular hemangioma (Figure 261-2), a nasal tip hemangioma producing aesthetic distortion (Figure 261-3), and a symptomatic upper lip hemangioma (Figure 261-4).

## **ONGOING CARE**

### **Follow-Up**

For low-risk lesions, regular follow-up should occur during the proliferative phase and should be of a supervisory nature through the involutional phase. Primary care physicians should consider referral for optimization of final aesthetic outcome. Of note, early in the infantile hemangioma natural history, it is important to follow patients at regular weekly/biweekly intervals, because during the proliferative phase of rapid growth a relatively innocuously appearing lesion might become a high-risk lesion over the course of only a few weeks. High-risk lesions should be followed and managed according to specialist recommendations. Patients treated with medical therapy should be followed carefully to monitor progress and manage complications.

### **Prognosis**

Although infantile hemangioma is a benign tumor, the best way to characterize the lesion is by its





**Figure 261-3** Combined medical and surgical management resulted in an optimum aesthetic result in this patient. A bulbous, pigmented hemangioma is evident at 6 months of age (top). Following completion of treatment with intralesional steroids and pulsed dye lasertherapy, at age 3 years (center), the lesion has decreased in size, and cutaneous manifestations have resolved. Surgical correction was subsequently performed at 5 years of age, and served to “sculpt” the final appearance of the nose. A satisfactory result 1 year postoperatively (bottom). (From Arneja JS, et al. The “Cyrano Nose”: refinements in surgical technique and treatment approach to hemangiomas of the nasal tip. *Plast Reconstr Surg.* 2010;126:1291–1299, with permission.)

unpredictability. It is impossible to predict how long a tumor’s period of growth will be, how large it will become, what complications it will produce, how long the distinct phases will be, and to what degree it will involute. The potential exists for the development of

functional complications, associated conditions, and aesthetic distortion. It was classically described that 50% of hemangiomas involute by age 5, 70% by age 7, and 90% by age 9; however, these metrics are no longer considered reliable, because recent evidence





**Figure 261-4** A 12-month-old girl with a proliferative hemangioma of the upper lip (clockwise from bottom left) preoperatively, intraoperatively, and 1 year postoperatively. The hemangioma interfered with feeding, and this resolved after resection. (From Hynes S, et al. *Complicated infantile hemangioma of the lip: outcomes of early versus late resection*. *Plast Reconstr Surg*. 2013;131:373e–379e, with permission.)

illustrates that “approximately 20% to 40% of patients will have residual and disfiguring skin changes,” suggesting that a great number of lesions do not involute completely. Accordingly, to prevent long-term complications (functional and aesthetic), high-risk lesions should be treated aggressively, because complete involution is often unlikely and early treatment may prevent adverse sequelae.

#### WHEN TO REFER

- Ulceration
- Periocular lesion
- Airway symptoms (stridor, respiratory distress) or beard distribution
- Perineal-lumbosacral lesion
- Segmental lesion (facial, perineal-lower limb)
- Aesthetic distortion (cosmesis/deforming)
- Multiple lesions
- Uncertain diagnosis

#### WHEN TO ADMIT

- High-output cardiac failure
- Airway compromise

#### TOOLS FOR PRACTICE

##### Engaging Patient and Family

- *Birthmarks & Hemangiomas* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/skin/Pages/Birthmarks-Hemangiomas.aspx](http://www.healthychildren.org/English/health-issues/conditions/skin/Pages/Birthmarks-Hemangiomas.aspx))

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#### Chapter 262

### HEMOGLOBINOPATHIES AND SICKLE CELL DISEASE

Meera Chitlur, MD; Sharada A. Sarnaik, MD

The inherited hemoglobin disorders comprise the most common single-gene defects in humans. Worldwide, the frequency of the carrier state is estimated to be 270 million, with approximately 400,000 annual births per year of infants with serious hemoglobinopathies. The prevalence of hemoglobinopathies is on

the rise worldwide. This prevalence is of special importance in developing countries, where it increases the burden of the health care delivery system. In the United States and other developed countries, hemoglobinopathies remain a concern, particularly among certain ethnic populations.

### NORMAL HEMOGLOBIN STRUCTURE

Hemoglobin is a tetrameric protein with 4 peptide chains, 2  $\alpha$  or  $\alpha$ -like chains and 2 non- $\alpha$  (or  $\beta$ -like) chains. The molecule is held together by interactions between peptide chains. The amino acids in the globin polypeptide chain are assembled in a long, convoluted knot; lying within the knot is the heme moiety, which carries within it a molecule of oxygen. Its iron is in the  $\text{Fe}^{2+}$  form, and it does not change its valence with release of oxygen. Abnormalities that result in a change to the ferric form (methemoglobin, or hemoglobin [Hb] M) result in a hemoglobin molecule that is unable to carry oxygen. The  $\alpha_1\text{-}\beta_2$  interface is an important region for the unique oxygen-carrying function of hemoglobin, and abnormalities in this area will alter its oxygen affinity. The areas of the molecule where the globin chains are in contact with each other or with the heme molecules are functionally important and are evolutionarily highly conserved.

### GENETICS OF HEMOGLOBIN SYNTHESIS

The normal hemoglobins are adult hemoglobin (Hb A; 96% of the total content), fetal hemoglobin (Hb F; 1%), and hemoglobin A<sub>2</sub> (3%). Hemoglobin synthesis is directed by controlling genes that are switched on and off at certain stages of human life, resulting in different globin-chain synthesis at different times.

The first globin chains to be produced are the  $\epsilon$  chains, which have similar structural sequences to  $\beta$  chains, followed by the production of  $\alpha$ ,  $\zeta$ , and  $\gamma$  chains. This production results in the formation of the early fetal hemoglobins such as Hb Gower 2 ( $\alpha_2\epsilon_2$ ), Hb Portland ( $\zeta_2\gamma_2$ ), and Hb F ( $\alpha_2\gamma_2$ ). At birth, 55% to 65% of total hemoglobin synthesized is Hb F. A switch from  $\gamma$ -chain to  $\beta$ -chain production starts at approximately the ninth gestational week, when Hb A ( $\alpha_2\beta_2$ ), the predominant hemoglobin in adult red blood cells (RBCs), becomes detectable. Fetal hemoglobin synthesis declines but persists until 9 months of postnatal age, at which time the switch is complete. (This process also explains why  $\beta$ -chain abnormalities do not manifest clinically at birth.) A small amount of fetal hemoglobin ( $\leq 1\%$ ) persists in adults in a small clone of cells called F cells. The switching from Hb F to Hb A is delayed in infants of mothers with diabetes, in infants with metabolic diseases characterized by an inability to metabolize propionic acid, and in infants with chronic bronchopulmonary dysplasia.

The third (minor) normal hemoglobin seen in adults is Hb A<sub>2</sub> ( $\alpha_2\delta_2$ ). Normal A<sub>2</sub> levels are 1% to 3%. The importance of Hb A<sub>2</sub> is that it is increased in the  $\beta$ -thalassemias, and this helps in the diagnosis of  $\beta$ -thalassemia trait.

The genes controlling  $\alpha$ -like globin chains are located on chromosome 16, whereas genes for  $\beta$ -like chains are located on chromosome 11. Globin gene

expression is under intense research scrutiny because of the therapeutic possibilities of preferentially stimulating Hb F synthesis (by gene manipulation) to ameliorate  $\beta$ -chain disorders.

### SCREENING AND GENETIC DIAGNOSIS

The primary reason to screen patients for hemoglobinopathies is to identify their risk for producing offspring with a clinically important disease such as  $\beta$ -thalassemia major, sickle cell disease, or  $\alpha$ -thalassemia major (hydrops fetalis).

Screening can involve a simple test, such as a complete blood count, while paying attention to the RBC indices. Thalassemias are usually associated with a low mean cell volume (microcytosis), normal or near-normal mean cell hemoglobin concentration, increased or normal RBC count, and a normal or decreased hemoglobin concentration. Iron deficiency can present with similar indices, with the exception of the RBC count that is low (not increased or normal). It is prudent, however, to exclude iron deficiency before evaluating thalassemia trait. If iron studies are normal, then a hemoglobin evaluation or electrophoresis should be obtained to evaluate for increased Hb A<sub>2</sub> and Hb F, which suggests a diagnosis of  $\beta$ -thalassemia trait. Hemoglobin electrophoresis will also demonstrate structurally abnormal hemoglobins, such as Hb C, Hb S, or Hb E.

A prenatal diagnosis of a clinically important hemoglobinopathy can be made by DNA analysis by sampling fetal blood or the chorionic villus.

### CLASSIFICATION OF ABNORMAL HEMOGLOBIN SYNTHESIS

Abnormal hemoglobin synthesis is the result of the production of structurally normal, but decreased, amounts of globin chains (the thalassemias), production of structurally abnormal globin chains (Hb S, C, E), or failure to switch globin chain synthesis (hereditary persistence of fetal hemoglobin).

Inheritance of all these disorders is autosomal codominant. *Codominant* is the most accurate term because heterozygosity carries discernible, but minor, clinical findings.

### THALASSEMIAS

In 1925, a severe form of anemia and splenomegaly with characteristic bone changes was described in children of Italian origin. A milder form of the same condition was later described by several Italian investigators. Because all of the cases were reported in children of Mediterranean origin, the disease was called *thalassemia*, from the Greek word *thalassa*, meaning *sea*. Later, research showed that cases of the homozygous or compound heterozygous states were not confined to the Mediterranean area, but occurred throughout the tropical countries. The 2 important forms of this disorder,  $\alpha$ - and  $\beta$ -thalassemia, are now recognized as the most common monogenic diseases in humans.

The thalassemias, which are all caused by mutations in the globin gene cluster, result in a genetic decrease in globin chain synthesis. Theoretically, as many types of thalassemias exist as types of globin chains. Practically, the most clinically relevant thalassemias are  $\alpha$ - and  $\beta$ -thalassemia. The defects are

numerous—more than 200 different mutations have been described—and include deletional and nondeletional mutations. Mutations usually have a geographic and ethnic distribution.

### **α-Thalassemias**

#### **Definitions and Clinical Manifestations**

α-Thalassemias are characterized by decreased α-globin synthesis. The most common defect is deletional, although nondeletional defects have also been described. The α gene is duplicated, and 2 α-globin genes per haploid genome are present; thus, the abnormality can result from 1 to 4 gene deletions. α-Globin gene expression occurs throughout intrauterine life. Hence, serious gene mutations can have deleterious effects on fetal development, and death in utero may result. In contrast, deleterious gene mutations in the β-globin chain are manifest only several months after birth, when the switch from γ- to β-globin production is complete.

Recently accepted classification of the α-thalassemias is similar to the β-thalassemias: α<sup>0</sup> in which no normal α-globin is produced by the gene and α<sup>+</sup> in which globin product is reduced. When a single gene deletion and 3 intact genes exist, no abnormality is discernible; this state is known as the silent carrier state. The 2-gene deletion results in a minor clinical condition, with mild hypochromic, microcytic anemia, similar to iron deficiency. α-Thalassemia major results from deletion of 3 or more α-globin genes. Deletion of 3 genes, or Hb H (β-tetramer) disease, results in moderate anemia that is hypochromic and microcytic; hepatosplenomegaly caused by extramedullary hematopoiesis results. Deletion of all 4 genes is incompatible with life and results in hydrops fetalis or intrauterine death (Table 262-1). Recent development of successful intrauterine diagnosis of 4 gene deletions has allowed intrauterine blood transfusions of the fetus, and viable births have been possible.

#### **Differential Diagnosis**

Complete blood count shows hypochromia (mean cell Hb <27 pg); microcytosis (low mean corpuscular volume), and mild anemia. Confirmation of decreased

α chains is done by globin-chain analysis measured in reticulocytes, although this is expensive and difficult. Restriction fragment length polymorphism is reserved for prenatal diagnosis. Decreased α chains result in an excess of non-α chains, which are insoluble and form tetramers. These abnormal hemoglobin tetramers are shown by the presence of RBC inclusions on cresyl blue stain and by hemoglobin electrophoresis. They are rapid moving (faster than Hb A) and require special attention if older techniques of paper or gel electrophoresis are used. High-performance liquid chromatography has become the test of choice for the diagnosis of thalassemias and hemoglobinopathies because it reliably separates hemoglobin types. Hemoglobin Bart (γ-globin tetramers) is found in the first few weeks of life, and Hb H (β-globin tetramers) can be found in older patients.

Because the genes for α- and β-thalassemia are on separate chromosomes, they can be coinherited. Coinheritance of α-thalassemia can have beneficial effects on clinical severity in the phenotype of β-thalassemia, as well as the structural hemoglobinopathies, such as sickle cell disease.

**HEMOGLOBIN H DISEASE.** Patients with Hb H disease have only 1 functional α-globin gene, often the result of deletion of the 3 other α-globin genes. Twenty percent of patients have deletion of 2 genes along with a nondeletional mutation of the third gene. The most common nondeletional mutation of the α-globin gene results in a slow-moving hemoglobin called hemoglobin constant spring (Hb CS). Clinically, Hb H disease is characterized by hemolytic anemia of variable severity and splenomegaly. A serious drop in hemoglobin can occur with infections or with ingestion of substances that induce oxidant stress. Additionally, Hb H hydrops fetalis syndrome is a devastating complication associated with the nondeletional forms of Hb H disease. It is associated with similar fetal and maternal complications as Hb Bart hydrops fetalis, including death in utero.

**HEMOGLOBIN BART DISEASE.** If both parents carry the α<sup>0</sup>-thalassemia mutation in cis (−/+), then a 25% chance with each pregnancy exists that the offspring will inherit both sets of mutations and therefore

**Table 262-1** Classification of the α-Thalassemias

PHENOTYPE	NUMBER OF α GENES	α/β SYNTHETIC RATIO	HAPLOTYPE	GENOTYPE	CLINICAL FEATURES
Normal	4	1.0	α, α	αα/αα	None
Silent carrier	3	0.8	α <sup>+</sup> , α	−α/αα	No anemia, normal rbc count
2-Gene deletion (α-thalassemia 1)	2	0.6	α <sup>0</sup> , α or α <sup>+</sup> , α <sup>+</sup>	−−/αα or −α/−α	Mild anemia, hypochromia, and microcytosis
Hb H disease	1	0.3	α <sup>0</sup> , α <sup>+</sup>	−−/−α	Moderate anemia, fragmented cells with hypochromia and microcytosis
Hydrops fetalis	0	0	α <sup>0</sup> , α <sup>0</sup>	−−/−−	Death in utero caused by severe anemia

α, normal alpha globin; α<sup>0</sup>, No normal α-globin; α<sup>+</sup>, globin is reduced; Hb, hemoglobin; RBC, red blood cell.



lack all 4 genes for production of  $\alpha$ -globin chains. Many of these fetuses survive into the second or third trimester of pregnancy because of persistence of the embryonic  $\zeta$ -globin chains. The fetus, however, will experience serious consequences, such as anemia and hypoxia with resultant organ and cognitive dysfunction. They invariably die in utero or shortly after birth, unless treated with intrauterine blood transfusions. The  $\alpha^0$ -thalassemia mutation is also associated with life-threatening complications to the mother such as placentomegaly, hypertension and preeclampsia, disseminated intravascular coagulation, and hemorrhage. This syndrome accounts for 90% of all non-immune hydrops fetalis cases in Southeast Asia.

$\alpha$ -Thalassemia is also seen in nontropical populations in association with intellectual disability and is known as  $\alpha$ -thalassemia mental retardation (ATR). The association demonstrates 2 unusual features—first, it occurs in racial groups in which  $\alpha$ -thalassemia is otherwise rare, and second, the pattern of inheritance is different from that seen in  $\alpha$ -thalassemia. This pattern occurs in association with a deletion on chromosome 16 (ATR-16) and in association with the ATR-X syndrome, which results from mutations of the *XH2* gene, located on the long arm of the X chromosome (Xq13.3). This gene regulates  $\alpha$ -globin gene expression. The ATR-X syndrome is characterized by the presence of severe intellectual disability, minor facial anomalies, genital anomalies, and a mild form of Hb H disease.

## **$\beta$ -Thalassemia**

### **Definitions and Clinical Manifestations**

$\beta$ -Thalassemia is caused by a decrease in production of  $\beta$ -globin chains as a result of mutations in the  $\beta$ -globin gene. Approximately 200 point mutations (or, rarely, deletions) are known to cause this disease. The clinical presentation is variable because the mutations cause a variable impairment of  $\beta$ -globin synthesis. The  $\beta$ -thalassemias are prevalent throughout the Mediterranean region, Africa, the Middle East, the Indian subcontinent, Burma, Southeast Asia (including the Malay Peninsula), southern China, and Indonesia. The high frequency of occurrence in the tropics reflects a survival advantage of heterozygotes against *Plasmodium falciparum* malaria. (This is also true with  $\alpha$ -thalassemia.)

### **Clinical Forms**

Inheritance of 1 gene for  $\beta$ -thalassemia results in  $\beta$ -thalassemia trait (also called thalassemia minor). This condition can be diagnosed by simple screening for microcytosis and a high RBC count. The more severe forms of  $\beta$ -thalassemia result from homozygosity or compound heterozygosity for the mutant  $\beta$ -globin allele and result in thalassemia major or in thalassemia intermedia.  $\beta$ -Thalassemia major is characterized by early onset of anemia, characteristic blood changes, and high Hb F and Hb A<sub>2</sub>. Patients with thalassemia major show clinical symptoms in the first year of life and require regular transfusions for survival; those with thalassemia intermedia will exhibit symptoms later in life and will also need intermittent transfusions. The anemia in thalassemia intermedia is well

compensated and may be exacerbated by infection, folate deficiency, or increasing hypersplenism.

Population screening has been effectively carried out with the naked-eye single-tube RBC osmotic fragility test (NESTROFT). Although NESTROFT is not highly specific, it is highly sensitive, with few false-negative findings. It is relatively inexpensive and simple, and thus suited to large-scale population screening for thalassemia trait. Genetic counseling for couples at risk for offspring with homozygous  $\beta$ -thalassemia may be aided by NESTROFT.

### **Pathophysiologic Features and Clinical Manifestations of Thalassemia Major**

Severe  $\beta$ -thalassemia produces clinical features in the first year of life as a result of a decline in Hb F synthesis without concomitant increase in Hb A. The decreased  $\beta$ -globin synthesis in this condition results in an excess of  $\alpha$  globins, some of which are used for synthesis of other hemoglobins that do not have  $\beta$  chains, such as Hb F ( $\alpha_2\gamma_2$ ) or Hb A<sub>2</sub> ( $\alpha_2\delta_2$ ), which are then increased. Free  $\alpha$  chains left over form tetramers, which are insoluble; they accumulate and precipitate within the RBC, leading to increased fragility and cell death. The RBC life span is thus shortened, and RBCs may be destroyed within the marrow, leading to ineffective erythropoiesis, which is the hallmark of  $\beta$ -thalassemia. The lack of  $\beta$  chains leads to decreased hemoglobin content per cell, hypochromia, and microcytosis. Attempts to increase the RBC mass result in expanded marrow cavities and extramedullary erythropoiesis in the liver and spleen.

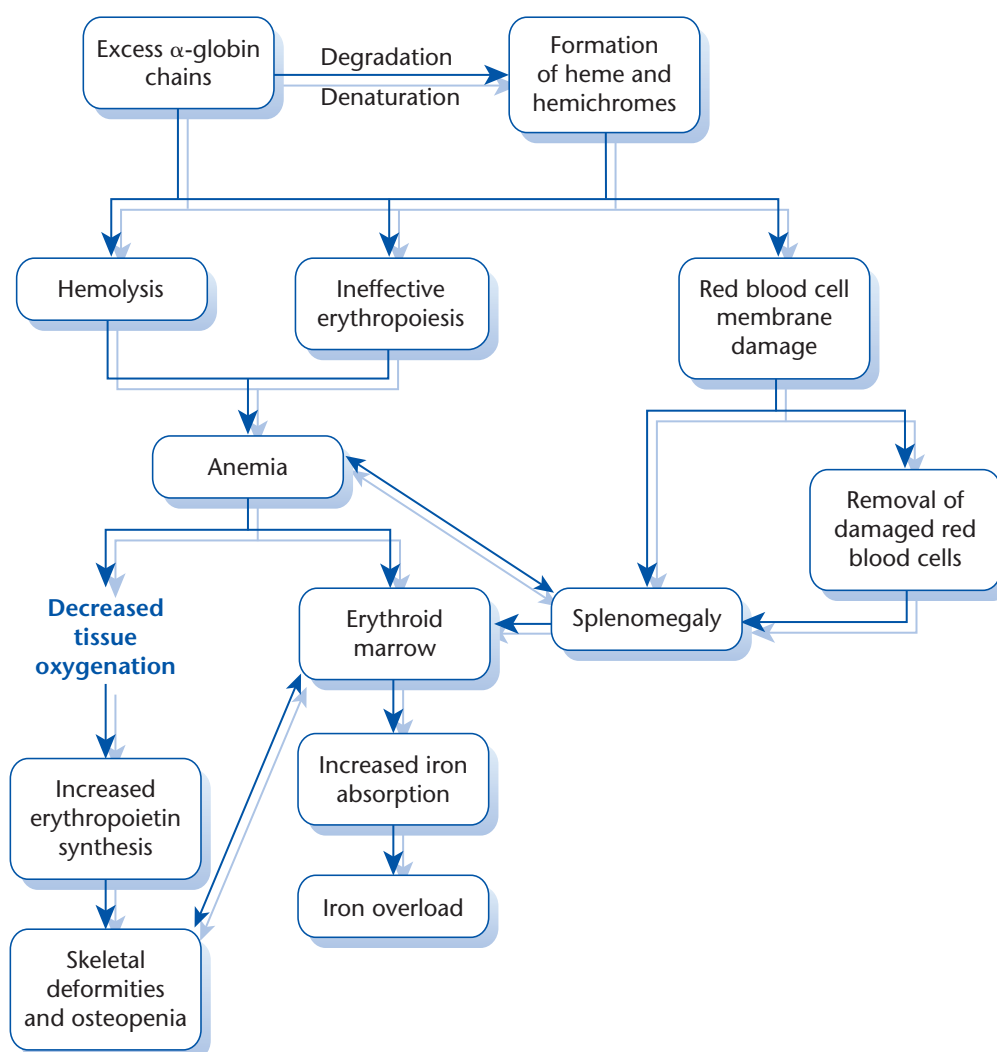
Children with thalassemia major exhibit symptoms at approximately 6 months of age with anemia that can be severe and symptomatic. Growth failure, cardiac dysfunction, pallor, jaundice, and hepatosplenomegaly are commonly seen. The bodies of these patients become loaded with iron, even when transfusions are sparingly given, because of increased iron absorption from the diet. Iron toxicity affects the liver (leading to cirrhosis), pituitary (leading to hypogonadism and growth failure), heart (leading to arrhythmia and cardiomyopathy), and bone (leading to pathologic fractures) (Figure 262-1).

### **Management**

Blood transfusions are provided to correct anemia, suppress erythropoiesis, prevent growth failure, and inhibit increased gastrointestinal absorption of iron. Splenectomy is usually performed when hypersplenism occurs and transfusion requirements increase.

Folic acid supplementation may be needed to meet the needs of increased RBC production. Iron chelation therapy is indicated when iron accumulation is seen following repeated RBC transfusions. Deferoxamine given as a daily 8-hour subcutaneous infusion through small portable pumps has been used since 1977 and is well tolerated and extremely effective. The oral iron chelator, deferasirox, was approved by the US Food and Drug Administration in November 2006. Deferasirox is much less cumbersome for patients and has had similar efficacy as deferoxamine in preclinical trials. The dose is 20 to 30 mg/kg/day, depending on the degree of iron overload, renal function, and





**Figure 262-1** Effect of excess free  $\alpha$ -globin chain production.

response to medication. Toxicities include proteinuria and elevation of creatinine, chemical hepatitis, or transaminase elevation. These toxicities usually respond to dose decreases of 10 mg/kg/day. Children with sickle cell disease have low creatinine, and rises in serum creatinine with toxicity may not reach levels above the normal for age; thus, increases of 30% over baseline should prompt dose decreases for such patients. Annual audiologic and ophthalmologic examinations, as well as echocardiographic examinations, are indicated for all chelation regimens to monitor for drug and iron toxicity. Chelation should be interrupted for serum ferritin levels of 500 ng/mL or less because of increased drug toxicity at low ferritin levels. Another oral chelator, deferiprone, may be used for chelation, although dose-related side effects such as neutropenia, arthropathy, agranulocytosis, and possibly hepatic fibrosis have been reported. This drug has been recently licensed in the United States for thalassemia only.

Clinically, treatment effectiveness is measured by monitoring the serum ferritin level, even though this

method is not the most accurate measure of total body iron stores. Ferritin levels lower than 2,500 mg/dL are associated with improved cardiac disease-free survival. Measurement of hepatic iron stores provides a quantitative, specific, and sensitive method for evaluating the body's iron burden, but this requires an invasive liver biopsy. Magnetic susceptometry provides a noninvasive method for measuring hepatic iron stores and has become increasingly available in many centers in the developed world, but still may not be easily available in low-income countries.

Hematopoietic stem cell transplantation may be performed in cases in which chronic transfusions and chelation are not possible. Transplantation, if successful, reverses the need for transfusions or chelation therapy, but it carries the risk for serious adverse effects such as graft failure, rejection, graft-versus-host disease, and death. In addition, preexisting and established growth failure, endocrinopathies, and gonadal dysfunction are not reversed. The availability of supportive care after transplantation must also be taken into consideration.

In the right setting, the use of either related or unrelated human leukocyte antigen (HLA)-matched donors results in excellent outcomes for low-risk patients who do not have preexisting severe organ damage.

## STRUCTURAL HEMOGLOBINOPATHIES

Structural hemoglobinopathies usually result from a point mutation in the  $\alpha$ - or  $\beta$ -globin gene, which produces an erroneous amino acid insertion in the polypeptide chain of the hemoglobin molecule. This results in a functional abnormality, the effects of which depend on where the missense mutation occurs. The mutation might result in the following effects: no physiologic abnormality and no clinical problem, an increased tendency to aggregate (Hb S, Hb C), an instability of the hemoglobin molecule resulting in a hemolytic anemia (Hb Zurich), increased oxygen affinity (Hb Bethesda), decreased oxygen affinity (Hb Kansas), and decreased oxygen-carrying capacity (Hb M).

More than 400 different abnormal hemoglobins have been described to date, but most are rare and cause no clinical disease. Sick cell disease is a frequent and clinically relevant structural hemoglobinopathy.

## Sickling Disorders

Sickling disorders depend on gene interactions. SS, known as sickle cell anemia, indicates homozygosity for the mutant Hb S, which results in no normal  $\beta$  alleles and, therefore, no Hb A. Hemoglobin SC disease indicates double heterozygosity for 2  $\beta$ -chain mutants, Hb S and Hb C, which results in no normal  $\beta$  alleles and, therefore, no Hb A. Sick  $\beta$ -thalassemia results from double heterozygosity for Hb S and  $\beta$ -thalassemia. In this disorder, 1  $\beta$  gene directs the synthesis of Hb S, and the other is either completely suppressed, and the patient has no Hb A (S  $\beta^0$ -thalassemia), or incompletely suppressed, and the patient produces a small amount of Hb A (S  $\beta^+$ -thalassemia). Hb A<sub>2</sub> is increased in the sickle  $\beta$ -thalassemia conditions and can be mildly elevated in Hb SS.

Finally, SO Arab and SD indicate double heterozygosity for Hb S and Hb O or D, respectively. Both of these conditions can have clinical phenotypes similar to Hb SS disease. Coinheritance of hemoglobins S and E, on the other hand, does not result in an abnormal phenotype, and individuals have a mild hypochromia, but are otherwise healthy.

In hereditary persistence of fetal Hb with Hb S, a failure to switch from  $\gamma$ - to  $\beta$ -chain synthesis is coinherited with Hb S. Patients have high levels of Hb F. Their clinical symptoms are mild because of the protective effects of Hb F.

## Pathophysiology of the Sickling Phenomenon

In its deoxygenated state, Hb S is extremely insoluble. Polymer formation within the RBC causes a shape change to the sickled form that gives the disease its name. Sickling is accompanied by increased rigidity, loss of deformability, increased adhesiveness to endothelial cells, and RBC membrane damage, all of which adversely affect the flow properties of the RBCs through the microvasculature. This produces vaso-occlusion, which sets up a vicious

cycle of stasis, low oxygen pressure in tissues, tissue acidosis, increased viscosity, further polymer formation, and more vaso-occlusion to complete and perpetuate the cycle. Membrane damage causes the RBC life span to be short (15 days instead of 120 days), resulting in a hemolytic anemia. Endothelial damage from vaso-occlusion also results in a hypercoagulable state that promotes sluggish circulation in the microvasculature.

## Clinical Manifestations

All of the sickling disorders mentioned previously are associated with similar clinical features; the heterozygous state resulting in Hb S trait (AS pattern) is generally asymptomatic except for painless hematuria in adults and complications during strenuous exercise with dehydration or at high altitudes. However, Hb S  $\beta^0$ -thalassemia is a double heterozygous condition may result in a disease as severe as Hb SS disease.

Hemolytic anemia results in pallor, jaundice, increased fatigue, gallstones, and poor growth. Aplastic crises occur after viral infections (parvovirus B19 most often implicated), in which even with transient viral marrow suppression, life-threatening drops in hemoglobin levels occur.

Vascular obstruction from intravascular sickling results in episodic, variable, and unpredictable musculoskeletal pain. This pain can be disabling if frequent and severe, although these so-called pain crises are usually uncomplicated and not life-threatening. Acute bone pain or infarction is common at all ages. Dactylitis, a swelling of the hands and feet, is a classic early childhood symptom. Osteonecrosis of the spine and femoral heads is often seen in adults; this commonly causes chronic pain. Splenic sequestration crisis may occur. This sudden pooling of blood in the spleen with hypovolemic shock is life-threatening and may recur during early childhood. Stroke, although uncommon, is recurrent if not treated appropriately with long-term blood transfusions after it occurs. In addition, a variety of cerebrovascular catastrophes, such as hemorrhage, can occur. Acute chest syndrome—pulmonary infarction or pneumonia (or both)—is common. Beginning in early childhood, the risk for severe bacterial infections with encapsulated organisms is lifelong, and such infections are a common cause of death. This is caused by the loss of splenic function (autosplenectomy) from recurrent vaso-occlusion and fibrosis. Renal manifestations include the loss of urine concentration capacity caused by sickling in vessels around the loop of Henle; large volumes of dilute urine are produced even in young children, underscoring the need for copious fluid intake to avoid dehydration. Further renal problems include hematuria and glomerular nephropathy. Other manifestations of vaso-occlusion include priapism, trophic leg ulcers, and blindness from retinopathy.

The disease is extremely variable in its severity. Factors that affect disease severity have not been clearly defined and remain the subject of research. Data suggest that factors influencing severity include genetic markers such as the  $\beta$ -globin gene haplotype, coinheritance of  $\alpha$ -thalassemia (beneficial), and the

amount and distribution of Hb F (higher levels are beneficial).

Sickle Cell Trait

Sickle cell trait is a benign carrier state, and most people have no clinical symptoms. The incidence of the trait in blacks varies from 6.7% to 10.1%. Sickle cell trait can cause hematuria and a loss of urine concentration capacity. Symptoms from intravascular sickling have been reported with strenuous exercise at high altitudes or without proper hydration and with flying at high altitudes in unpressurized aircraft.

Diagnosis

In most of the developed countries, including the United States, the diagnosis of sickle cell disease is established through the newborn screening program. Hemoglobin is separated from dried blood spots collected from infants in the newborn nursery and allows for the early identification of affected infants before the onset of clinical manifestations. In older patients in whom the diagnosis of sickle cell disease is suspected and who may have been born before the initiation of the newborn screening program or who were born outside the United States, their clinical history and physical examination are the first steps to diagnosing a sickling disorder.

The presence of Hb S is evaluated by the solubility test, which is inexpensive and sensitive to the carrier state, but does not distinguish trait from the disease. Hemoglobin electrophoresis confirms the exact genotype. Finally, the presence of hemolytic anemia (low hemoglobin, high reticulocyte counts, increased bilirubin, and lactic dehydrogenase) and morphologic sickling can be assessed by blood smears.

Management

Management consists of symptomatic and supportive care of complications such as treating pain episodes with analgesics (often opioids), placing local heat packs, ensuring adequate hydration, adjusting the acid-base balance, preventing hypoxia, avoiding exposure to cold, and treating febrile episodes early and aggressively with antibiotics.

Judicious use of blood transfusions will help prevent strokes in children. Elevated time-averaged mean velocity in the middle cerebral and distal internal carotid arteries on screening transcranial Doppler (TCD) has been shown to be associated with a high risk for overt stroke in patients with Hb SS. Thus, TCD screening and chronic blood transfusions for abnormal TCD results is now recommended. In 1995, the Stroke Prevention Trial in Sickle Cell Anemia (STOP) trial was conducted as a multicenter randomized trial to determine the efficacy of transfusion therapy for preventing strokes in patients with abnormal TCD. This intervention was extremely effective, and is now the standard of care for screening children younger than 16 years and for beginning chronic transfusions for elevated TCD.

Blood transfusions also help correct severe anemia (Hb <5 g/dL) from aplastic crises or splenic

sequestration and may also be of benefit in complicated pregnancies. Preoperative blood transfusion for invasive surgery with prolonged anesthesia is useful to avoid intraoperative and postoperative complications.

Management is optimized by early diagnosis with screening of newborns. Routine daily prophylactic penicillin and pneumococcal vaccine are used to prevent the high childhood mortality from infections.

Psychosocial support and self-help groups are important for improved disease adjustment, especially for adults. Pain attacks are often capricious, severe, and frequent. They can be a barrier to self-determination and independent living.

Recent advances have brought research strategies to the bedside. Agents that stimulate fetal hemoglobin production, such as hydroxyurea, have proved useful in preventing much of the morbidity of the disease. Peripheral or cord blood stem cell transplantation from an HLA-identical sibling, although a high-risk procedure, is curative. Stem cell transplantation is used for certain individuals with markers for adverse outcome, such as stroke in a young child, or severe and recurrent acute chest syndrome that has been associated with later pulmonary hypertension and early mortality. Finally, antisickling agents, such as membrane-active drugs, anticoagulants, and gene therapy, are being investigated as approaches of the future.

Rare Structural Hemoglobinopathies

Table 262-2 lists the rare structural hemoglobinopathies and their prototypes.

Unstable Hemoglobins

Unstable hemoglobins usually result from amino acid substitutions near the heme pocket. The instability causes a tendency of the heme to separate from the globin chain with the slightest oxidative stress. The denatured hemoglobin precipitates in the RBC and forms Heinz bodies, which cause the cells to sequester in the spleen, and a hemolytic anemia results.

Diagnosis is by demonstration of a hemolytic anemia, detection of Heinz bodies by staining, and the heat precipitation test. Hemoglobin electrophoresis is not always useful because of the tendency of the hemoglobin to rapidly denature.

Table 262-2 Rare Structural Hemoglobinopathies and Their Prototypes	
HEMOGLOBINOPATHY	PROTOTYPE
Unstable hemoglobins	Hb Zurich
Hemoglobins with high oxygen affinity	Hb Bethesda
Hemoglobins with low oxygen affinity	Hb Kansas
Hemoglobin M prototype	Hb M Boston

Hb, hemoglobin.

Management includes avoiding oxidant drugs, providing transfusions as clinically indicated, and removing the spleen if anemia is severe.

### **Hemoglobins With High Oxygen Affinity**

In hemoglobins with high oxygen affinity, the amino acid substitution is near the  $\alpha_1$ - $\beta_2$  interface, resulting in a tight binding of oxygen. Release of oxygen to tissues is slow, resulting in inefficient tissue oxygenation. The end result is increased hemoglobin production caused by high erythropoietin levels.

Diagnosis is made by the presence of familial erythrocytosis (polycythemia), exclusion of other causes of polycythemia (eg, polycythemia vera, cyanotic heart disease), high RBC mass, high arterial oxygen saturation, and a markedly left-shifted oxygen dissociation curve.

Management consists of maintaining hematocrit levels at 70% by phlebotomy to prevent high viscosity.

### **Hemoglobins With Low Oxygen Affinity**

In hemoglobins with low oxygen affinity, the amino acid substitution is also near the  $\alpha_1$ - $\beta_2$  interface. The hemoglobin picks up oxygen poorly from the lungs, and high deoxyhemoglobin levels result, causing cyanosis.

Diagnosis is made by the oxygen-dissociation curve, which is right shifted. The hemoglobin level and RBC mass are normal.

No specific management is necessary or effective. The cyanosis is relatively well tolerated if strenuous activities are avoided.

### **Hemoglobin M**

In Hb M, the amino acid substitution is near the heme pocket, close to the site of the iron (Fe) molecule. The mutant hemoglobin loses its ability to keep the Fe in its ferrous state, and the hemoglobin is constantly in the methemoglobin state,  $\text{Fe}^{3+}$ , and is unable to carry oxygen. Chronic cyanosis results.

Diagnosis is made by history of cyanosis since birth, with a normal oxygen saturation; by brown discoloration of freshly drawn blood, which does not change with aeration; and by spectrophotometry to confirm presence of methemoglobin. Electrophoresis also demonstrates the abnormal hemoglobin.

No management is needed because the amount of Hb M is insufficient to cause physiologic derangements.

### **Hemoglobin C, D, and E**

Structural variant hemoglobins are synthesized at a lower rate than normal  $\beta$  chains and comprise less than one-half the total hemoglobin in heterozygotes. Heterozygous Hb C (AC) results in mild target cells, but no anemia. Homozygous C (CC) produces a mild hemolytic anemia, marked RBC morphologic changes (target cells, hemoglobin crystals, and microspherocytes), and mild splenomegaly. Heterozygous E (AE) causes a mild thalassemic phenotype with mild microcytosis and hypochromia. Homozygous E (EE) results in a moderate thalassemic phenotype with hypochromia, microcytosis, and mild anemia. A combined E- and  $\beta$ -thalassemia inheritance results in a transfusion-dependent thalassemic phenotype. Hb E is common in Southeast Asia and in certain areas of the Indian subcontinent.

## **TECHNOLOGICAL ADVANCES**

### **Reproductive Options for Carriers of Hemoglobinopathy**

Prenatal screening and genetic counseling are now readily available and are good ways to provide reproductive options for couples at risk for having children with hemoglobinopathies. Nondirective genetic counseling should be provided and targeted to populations with a high prevalence of the hemoglobinopathy traits.

Prenatal diagnosis can be performed by chorionic villus sampling. Challenges include technical difficulties of the various methods used, as well as their expense. Furthermore, for safety and effectiveness, women with at-risk pregnancies must be assessed for prenatal diagnosis, ideally in the first trimester (8 to 14 weeks' gestation). This process requires awareness in communities with a high prevalence of the genetic defect. The choice of therapeutic abortion for involved pregnancies can be difficult depending on cultural and religious beliefs. Research studies report a higher acceptance of prenatal diagnosis if another child is affected.

Preconception diagnosis and implantation of normal embryos after in vitro fertilization is an alternative that is currently available in the West. It is extremely expensive and cannot be performed routinely.

In utero therapy that uses stem cell transplantation is an interesting and potentially exciting technology that would help at-risk couples that do not opt for termination. It allows for the relatively non-immunocompetent fetus to accept the stem cell transplant more easily without experiencing graft rejection and graft-versus-host disease. This therapy is currently in early research trials.

### **Improvements in Transfusion Safety**

The mainstay of care for children with hemoglobinopathies continues to be blood transfusion support. Transfusion safety is thus an important consideration, particularly the prevention of transfusion-transmitted infections. Donors should be screened for hepatitis B and C, human immunodeficiency virus, syphilis, and malaria. Donor screening may sometimes be ineffective because of insensitive tests, expired kits and reagents, and improper procedures, particularly in low-income countries. Transfusion-transmitted infections remain a risk.

### **Stem Cell Transplantation**

Improved techniques of stem cell transplantation that use HLA-matched sibling donors may cure hemoglobinopathies. Nonmyeloablative or reduced-intensity myeloablative stem cell transplantation, which has reduced morbidity, but leads to a chimerism in the recipient, is being explored as an investigational procedure. Gene therapy is now in early trials.

Simple awareness of genetic diseases and education and counseling of families at risk are crucial to avoiding the burden of these diseases, both to individuals and to society.



**WHEN TO REFER**

- All patients with thalassemia intermedia and thalassemia major should be followed by a hematologist.
- All children with sickle hemoglobinopathies, regardless of whether the child has experienced serious complications of sickle cell disease, should be regularly followed by a hematologist.
- Referral should occur immediately after a positive newborn screening result is returned.
- Serious complications can include stroke, splenic sequestration, and recurrent acute chest syndrome.
- Pregnant patients should be referred for care during pregnancy.

**WHEN TO ADMIT**

- Anemic crisis (Hb <5 g/dL or hemodynamic compromise)
- Sudden splenic enlargement
- Pain not responding to home opioids
- Difficulty breathing, chest pain
- Fever spikes (>38°C [100.4°F] core, repeated in 30 minutes)
- Any central nervous system symptoms

**TOOLS FOR PRACTICE****Engaging Patient and Family**

- *Sickle Cell Disease* (fact sheet), American Academy of Pediatrics ([www.aap.org/en-us/about-the-aap/Committees-Councils-Sections/section-hematology-oncology/Documents/SCD\\_factsheet.pdf](http://www.aap.org/en-us/about-the-aap/Committees-Councils-Sections/section-hematology-oncology/Documents/SCD_factsheet.pdf))
- *Sickle Cell Disease* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/ncbddd/sicklecell](http://www.cdc.gov/ncbddd/sicklecell))
- *Thalassemia* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/ncbddd/thalassemia/index.html](http://www.cdc.gov/ncbddd/thalassemia/index.html))

**Medical Decision Support**

- *The Child with Sickle Cell Disease: A Teaching Manual* (booklet), Children's Medical Center of Dallas ([www.aap.org/en-us/about-the-aap/Committees-Councils-Sections/section-hematology-oncology/Documents/SCDTeachingManual.pdf](http://www.aap.org/en-us/about-the-aap/Committees-Councils-Sections/section-hematology-oncology/Documents/SCDTeachingManual.pdf))
- *Emergency Information Form for Children With Special Needs* (form), American College of Emergency Physicians, American Academy of Pediatrics ([www.aap.org/en-us/about-the-aap/Committees-Councils-Sections/section-hematology-oncology/Documents/emergency\\_info\\_form.pdf](http://www.aap.org/en-us/about-the-aap/Committees-Councils-Sections/section-hematology-oncology/Documents/emergency_info_form.pdf))
- *Sickle Cell Disease and Trait: What Every Primary Care Physician Needs to Know* (slide show), American Academy of Pediatrics ([www.aap.org/en-us/about-the-aap/Committees-Councils-Sections/section-hematology-oncology/Pages/Sickle-Cell-Disease-Resource-Kit.aspx](http://www.aap.org/en-us/about-the-aap/Committees-Councils-Sections/section-hematology-oncology/Pages/Sickle-Cell-Disease-Resource-Kit.aspx))
- *Template Notification Letters: Sickle Cell Trait and Sickle Cell Disease* (form letters), American Academy of Pediatrics ([www.aap.org/en-us/about-the-aap/Committees-Councils-Sections/section-hematology-oncology/Pages/Sickle-Cell-Disease-Resource-Kit.aspx](http://www.aap.org/en-us/about-the-aap/Committees-Councils-Sections/section-hematology-oncology/Pages/Sickle-Cell-Disease-Resource-Kit.aspx))

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**Chapter 263****HEMOLYTIC-UREMIC SYNDROME**

Horacio Esteban Adroque, MD; Joseph Angelo, MD

**INTRODUCTION**

Hemolytic-uremic syndrome (HUS) is a systemic thrombotic microangiopathy clinically defined by the classic triad of nonimmune microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and acute kidney injury. The underlying pathologic process in HUS results in vascular endothelial injury leading to arteriolar-capillary occlusive lesions formed by platelet-fibrin thrombi. While the kidney is the most common and clinically significant site of injury, multiple organ systems including the central nervous system, gastrointestinal tract, heart, lungs, and pancreas can be affected. Broadly, HUS is categorized into 2 types. HUS that follows diarrheal illness or is related to specific infectious agents is designated as typical or D+ HUS, while atypical HUS (aHUS) is most commonly caused by genetic mutations in the complement cascade. Overall, typical HUS is much more common than aHUS, and most of these cases are related to infection by Shiga toxin-producing enterohemorrhagic *Escherichia coli* (EHEC). In addition, typical HUS tends to be self-limited and less severe than genetic forms of HUS. Genetic forms have a longer, potentially recurrent course and more frequently lead to chronic kidney disease. Of note, increased understanding of the pathophysiology of HUS and the availability of tests for genetic causes has led to classification schemes based on the specific etiology of HUS.

## ETIOLOGY AND PATHOGENESIS

### HUS Related to Shiga toxin

HUS is the most serious complication resulting from EHEC infection. The Shiga toxin (ST) produced by EHECs is structurally similar to toxins produced by other gram-negative organisms, including *Shigella dysenteriae*, and is also called verotoxin because of its ability to kill vero cells in culture. ST is released into the gastrointestinal tract, translocates across the intestinal epithelium, and enters the systemic circulation. The translocation of ST across the GI epithelium is promoted by intimin, a protein that helps with bacterial adherence to the epithelial cells, and the receptor Tir, which promotes ST entrance in the cell. Once ST enters the systemic circulation, it binds its target globotriaosylceramide (GB3) on the surface of host cells, including the glomerular endothelium. The classic view of STs is that once they are internalized by endothelial cells they lead to cellular apoptosis through the inactivation of ribosomes and, therefore, the inhibition of protein synthesis. While this is one mechanism of endothelial damage produced by STs, there is also evidence that the ability of STs to alter endothelial cell gene expression leads to a change in endothelial phenotype, which transforms the endothelium from its normal state into a proadhesive, prothrombotic, and inflammatory surface. These changes underlie the microangiopathic process that is a hallmark of HUS.

### HUS Related to Gene Mutations

HUS related to genetic mutations falls under the broader category of aHUS, which can also include forms of thrombotic microangiopathy (TMA) related to systemic illnesses such as pregnancy-associated HUS, hemolysis/elevated liver enzymes/low platelet count (HELLP) syndrome, and drug-related HUS. While similar pathologically and clinically to typical HUS, the underlying etiology of genetic forms of HUS are related to the dysregulation of the complement system. Thrombotic thrombocytopenic purpura (TTP) is another form of TMA related to HUS and is secondary to the loss of activity of ADAMTS-13, a protein which cleaves large multimers of von Willebrand factor. The loss of ADAMTS-13 activity can trigger a systemic TMA.

Several complement pathway mutations have been associated with HUS. Complement factor H (CFH) is a plasma protein that acts as a cofactor to complement factor I (CFI) in regulating the alternative complement pathway by promoting the dissociation of C3 convertase and also competes with complement factor B for C3b recognition. In addition to genetic mutations in CFH, inactivation of CFH by antibodies has been described in children with aHUS. CFI works together with CFH to cleave C3b and C4b. CFI mutations can affect 4% to 10% of patients with aHUS.

Mutations in another CFI cofactor, membrane cofactor protein (MCP), have been described in 10% to 15% of children with aHUS. MCP works with CFI to cleave C3b and C4b on cell surfaces, providing a protective effect on the glomerular endothelium.

Gain-of-function mutations in complement proteins have also been associated with aHUS. These include complement factor B (CFB) and C3. CFB mutations result in chronic alternative pathway activation in which C3 convertase hyperactivity results in enhanced C3b formation. Similarly, mutations in C3 reduce C3b binding to CFH and MCP, impairing the degradation of C3b.

More recently, there have been reports of noncomplement-related gene mutations, such as diacylglycerol kinase  $\epsilon$ , related to aHUS.

## EPIDEMIOLOGY

HUS is a common cause of renal failure in children, with most cases occurring in children younger than 5 years. Up to 90% of cases are of the typical HUS type, and 10% are aHUS. In the United States and Europe, *E coli* 0157:H7 is the most commonly implicated ST-producing organism causing typical HUS. However, other strains of *E coli* and *Streptococcus pneumoniae* have also been associated with outbreaks of HUS.

## CLINICAL PICTURE

An infection with one of the common causative agents of HUS typically starts with the development of watery diarrhea following an incubation period of 3 to 8 days. Watery diarrhea is then followed by bloody diarrhea, abdominal cramping, and nausea and vomiting in 50% of children. Fever is present in approximately 30% of children. These symptoms precede the development of more systemic symptoms such as malaise and pallor. Renal manifestations appear around the same time and are marked by the development of acute kidney injury, which is oligo-anuric. Hypertension develops in approximately 50% of children with HUS and is the result of fluid retention and edema in the acute phase. The hypertension may persist as chronic hypertension in the long term. While the kidney and GI tract are the most common systems affected, as many as 30% of children can have central nervous system involvement manifesting as lethargy, seizures, and sometimes cerebral edema and coma. Other organ systems involved include the pancreas and myocardium.

Laboratory studies reflect the underlying pathology of HUS and show anemia, thrombocytopenia, high levels of lactate dehydrogenase, low haptoglobin, and the presence of fragmented erythrocytes (schistocytes) on peripheral blood smear. The onset of renal involvement is evidenced by hematuria, red blood cell casts on urine microscopy, proteinuria, and elevated serum creatinine. Other laboratory abnormalities reflect damage to extrarenal organs such as elevated pancreatic enzymes and troponin levels.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis is wide and includes acute poststreptococcal glomerulonephritis, TTP, systemic lupus erythematosus, Henoch-Schönlein purpura, disseminated intravascular coagulation, sepsis, intussusception, and renal vein thrombosis. A major distinguishing feature of HUS is the presence of schistocytes on the peripheral blood smear. Renal vein thrombosis can be discerned by renal ultrasound, typically with

unilateral renal enlargement compared to HUS in which both kidneys are enlarged.

## MANAGEMENT

The management of HUS is similar to the therapy provided for children with acute kidney injury from other causes, with additional attention to those issues specific to HUS. The management of the electrolyte, acid-base, and volume overload associated with HUS continues to be based on medical management. Because of the potential need for initial fluid resuscitation and the deleterious effects of fluid overload, particularly in critically ill patients, strict attention to volume management is required. Patients without anuria can be treated early with loop diuretics. For those patients with anuria, the use of acute dialysis with hemodialysis, peritoneal dialysis, or continuous renal replacement therapy has contributed significantly to reducing the mortality rate from as high as 50% to between 3% and 5%. Two-thirds of children with HUS require acute dialysis, while the other one-third develop some degree of renal insufficiency.

In addition to aggressively managing the renal sequelae of HUS, specific attention must also be paid to the other affected organ systems. The use of antibiotics to treat typical HUS is controversial. While some studies have shown benefit from the use of antibiotics in HUS, several others have demonstrated not only a lack of benefit but also a potential for harm. No clear benefit has been demonstrated for the use of antibiotics in children in the acute phase of HUS, and their use is not currently recommended.

The use of antimotility agents is contraindicated in children with HUS. Although helpful with the symptomatic treatment of diarrhea, their use increases the risk of developing toxic megacolon in the setting of typical HUS.

As with antibiotics, the evidence for the use of plasma exchange in the treatment of typical HUS has not been definitive. However, some data support the use of plasma infusion or plasma exchange in this setting. Therefore, children who have a significant worsening of disease, such as severe renal failure, heart failure, or neurologic symptoms, should be considered for plasma therapy. Plasma therapy is contraindicated in children with HUS associated with *S pneumoniae*, because plasma contains preformed antibodies to the Thomsen-Friedenreich antigen and thus, can worsen the disease process.

While the response to plasma therapy in children with aHUS may vary depending on the underlying mutation causing the disease, the overall use of plasma exchange in children with aHUS has been shown to decrease mortality. A suggested regimen is the initiation of plasma exchange within 24 hours of disease onset using the exchange of 1 to 2 volumes/day or infusion of approximately 20 to 30 mL/kg body weight. Decisions regarding the initiation and continuation of plasma therapy should be made following consultation with a pediatric subspecialist experienced in the treatment of aHUS.

Thrombotic microangiopathies fall along a spectrum, and there can be overlap between HUS and TTP. TTP is defined by the 3 criteria of HUS (MAHA,

thrombocytopenia, and acute kidney injury) plus neurologic signs and fever. While there is renal impairment in patients with TTP, it usually is not the prominent feature and the patients rarely require dialysis. However, as both entities can present similarly, the differentiation is not always clear. Therefore, for those presenting with severe multisystem failure, plasma exchange should be initiated early.

More recently, the use of an anti-C5 monoclonal antibody, eculizumab, has shown benefit in the treatment of aHUS. While the reports demonstrated the termination of the microangiopathic process in HUS, some variability exists in these reports with respect to the prevention of the long-term consequences of HUS, including improvement in renal function. However, a recently published report of phase 2 trials of eculizumab in a more chronic setting did show improvement in the estimated glomerular filtration rate over the course of the trial, with earlier use showing the most significant result. Owing to an increased risk of meningococcal infection, children receiving eculizumab should receive meningococcal vaccination before or as soon as possible after starting treatment and should receive antibiotic prophylaxis against meningococcal infection.

The management of the hematologic effects of HUS should be performed cautiously and with close attention to the development of volume overload and pulmonary edema. Packed red blood cell infusions should be limited to cases when the hemoglobin is rapidly downtrending or the patient is having clinical changes related to anemia. The treatment of thrombocytopenia should also be limited because this may worsen the development of microthrombi in HUS. The indications for platelet transfusion are active bleeding or need for surgical procedures. To prevent further volume overload, the use of diuretic therapy in conjunction with blood product infusions is an important consideration.

## PROGNOSIS AND LONG-TERM SEQUELAE

With improvements in critical care and dialysis therapies, mortality rates in children with typical HUS now range between 3% and 5%, with mortality typically resulting from more severe and widespread effects on multiple organ systems. With better survival rates during the acute phase of HUS, long-term sequelae have become more clear. From a renal standpoint, one study showed that following acute HUS, 39% of 61 children had a risk of developing long-term complications including hypertension, proteinuria, and chronic or end-stage renal disease. Similarly, a meta-analysis showed that death or end-stage renal disease occurred in 12% of children with typical HUS, and that 25% of survivors had some long-term renal complications. In addition, histologic studies have shown an increased risk of developing chronic changes such as glomerulosclerosis and interstitial fibrosis following an episode of HUS. A notable finding is that the duration of oligo-anuria is a predictor of the occurrence of late complications following HUS. The high likelihood of long-term renal dysfunction in children



following HUS demonstrates the need for regular follow-up with a nephrologist to monitor parameters such as hypertension, proteinuria, growth, and progression of chronic kidney disease. The treatment of hypertension and proteinuria with angiotensin converting enzyme inhibitors is prudent in helping to reduce the further worsening of renal damage in the chronic setting.

## KIDNEY TRANSPLANTATION AFTER HUS

Children who progress to end stage renal disease following typical HUS are not at an increased risk of graft failure when compared to those patients without HUS. In contrast, children with HUS related to genetic mutations have a high rate of HUS recurrence in the kidney graft, up to 60% in one study, and an adult HUS study demonstrated that this recurrence is an independent risk factor for graft loss. The risk of HUS recurrence and graft loss can vary depending on the underlying genetic defect. For example, patients with defects in membrane-bound proteins, such as MCP, tend to have a lower risk of HUS recurrence in the transplanted kidney compared to those with circulating factor defects such as CFH and CFI. Some caution must be used in assessing these circumstances because a subset of patients with defective MCP can have combined errors in both MCP and also circulating factors. Given this variability in the risk of recurrence and the availability of existing and emerging treatment strategies, kidney transplantation in those patients with genetic forms of HUS should be a case-by-case consideration rather than an absolute contraindication in all cases. Along these lines, both plasma therapy and more recently eculizumab have shown some success in reducing the risk of post-transplant recurrence in those patients with genetic forms of HUS.

## CONCLUSION

Since the original description of HUS by Gasser et al in 1955, much has been learned about the etiology, pathophysiology, and treatment of children with HUS. Improvements have been made in the acute care of these patients, which has lowered their mortality rates. More recently, longer-term therapies have been used to treat those children with genetic defects underlying their HUS. Continued work on methods of prevention and treatment should produce further improvements in both acute and chronic outcomes related to HUS.

### WHEN TO REFER

- All patients with HUS should be referred to a pediatric nephrologist or pediatric hematologist as indicated.

### WHEN TO ADMIT

- All patients with HUS must be admitted.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *What Is a Pediatric Nephrologist?* (fact sheet), American Academy of Pediatrics (healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Nephrologist.aspx)

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## Chapter 264

# HENOCHE-SCHÖNLEIN PURPURA

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Henoch-Schönlein purpura (HSP) is the most common form of vasculitis in children. This small-vessel vasculitis is mediated by immunoglobulin A (IgA)-containing immune complexes and is characterized by nonthrombocytopenic purpura, abdominal pain, arthralgias, and renal disease. The diagnostic criteria published in 1990 by the American College of Rheumatology include palpable purpura, initial presentation at 20 years or younger, bowel angina, and typical biopsy findings. If 2 or more diagnostic criteria are present, then the sensitivity and specificity for the diagnosis of HSP are greater than 87%.

## EPIDEMIOLOGIC FACTORS

HSP is more common in Europe and Asia than it is in the United States, with an estimated annual incidence in the United Kingdom of 20:100,000 children. White children have the highest incidence, and black children the lowest.

HSP mainly affects young children, with a peak incidence at 4 to 6 years of age. Unlike most vasculitides, HSP affects males more often than females, with a 1.5:1 male-to-female ratio. HSP seems to be more prevalent during the winter and spring, and in at least 30% of cases, an upper respiratory infection precedes the onset of symptoms. The seasonal distribution supports the hypothesis that infectious agents trigger the development of HSP. Other infections, drug allergies, insect bites, and vaccines can also precipitate HSP.



Cases have also been reported in children with C2 and C4 complement deficiencies.

Hereditary fever syndromes such as familial Mediterranean fever can also precipitate HSP.

### CLINICAL PRESENTATION

The classic presentation of HSP includes lower extremity purpura, arthritis, abdominal pain, and renal disease. Cutaneous manifestations are the most common clinical features of children with HSP. In 50% of children, a macular-petechial rash is present. This rash is symmetric, sometimes purpuric, localized predominantly in the extensor surface of the lower extremities, forearms, and buttocks, and tends to spare the trunk. These lesions tend to fade with time, but new lesions can recur up to 3 months after the initial presentation. Nonpitting edema of the scalp, hands, and feet may be present in 30% to 70% of young children.

Joint manifestations occur in 60% to 80% of children; the knees, ankles, wrists, and fingers are most commonly affected. The joints involved are usually tender and swollen, but these symptoms resolve without any residual deformity.

Gastrointestinal manifestations develop in 50% to 70% of children with HSP, with a higher incidence in children with renal involvement. Gastrointestinal manifestations may precede the purpura by up to 2 weeks in as many as 20% of children. Intermittent colicky abdominal pain, vomiting, or gastrointestinal bleeding are most common, and up to 5% of children develop complications such as intestinal infarction, perforation, or intussusception.

Although most children may have some histologic evidence of renal inflammation, only 20% to 60% will exhibit urinary abnormalities. Renal disease rarely precedes the onset of rash, and evidence of HSP nephritis usually coincides with or follows the cutaneous manifestations. It is usually present within 4 weeks of the onset of the joint or gastrointestinal manifestations. The spectrum of renal involvement in HSP is broad and may include microscopic hematuria (transient or persistent), macroscopic hematuria (initial or recurrent), proteinuria, nephritic syndrome, and nephritic-nephrotic syndrome. When mild, HSP nephritis tends to resolve without any particular intervention. However, 2% to 5% of children with renal involvement progress to end-stage renal disease. Abnormal creatinine clearance at 3 years after onset, and ultrastructural abnormalities in the renal biopsy are the most consistent predictors of poor renal prognosis.

While most children with long-term renal involvement present early, there is evidence that a small subset of children may develop progressive renal disease even after having a benign urinalysis at presentation.

Testicular swelling and tenderness may be present in up to 35% of male children with HSP. If this manifestation is present, a thorough evaluation is necessary to rule out testicular torsion. Other serious complications such as pulmonary hemorrhage and central nervous system involvement have also been described.

The mean duration of symptoms is 3 to 4 weeks and up to one-third of children have at least 1 recurrence.

### EVALUATION

The diagnosis of HSP is based on clinical findings. There are no laboratory tests specific for HSP and the measurement of serum IgA levels is not helpful in confirming the diagnosis or providing prognostic information.

Urinalysis is an excellent screening test for assessing renal involvement and should be performed at diagnosis and at least monthly for 6 months even if the prior urinalysis was negative. The measurement of blood pressure should also be done at diagnosis and at subsequent visits for at least 6 months even if previously normal, as elevated blood pressures are associated with renal involvement.

In children with abnormal urinary sediment or elevated blood pressure, kidney function should be measured. A renal biopsy is not indicated in all children with a diagnosis of HSP; however, it should be considered in children with significant proteinuria for more than 1 month, renal insufficiency, hypertension, or nephrotic syndrome.

In atypical presentations of HSP, physicians should consider sending complete blood count, coagulation studies, and complement levels to evaluate for other causes of the clinical findings.

### DIFFERENTIAL DIAGNOSIS

A pediatrician faced with a child with acute purpuric and petechial eruptions must first ensure that the differential diagnosis is kept broad. Differential diagnoses include, but are not limited to, acute bacterial infections (invasive meningococcal disease), Rocky Mountain spotted fever, toxic shock, enteroviral infections, endocarditis, idiopathic thrombocytopenic purpura, parvovirus B19, Kawasaki disease, and acute hepatitis A.

In a child who presents with palpable purpura, abdominal pain, arthritis/arthralgia, or renal involvement, HSP nephritis is the most likely diagnosis. However some children may present atypically. The diagnosis is especially difficult in the child who presents without the characteristic purpuric rash; other causes of arthritis/arthralgia, abdominal pain, and renal disease should be investigated in this scenario.

### TREATMENT AND PROGNOSIS

Once other diseases are ruled out and a diagnosis of HSP is established, supportive care is the most important first step. Children should be monitored by their pediatrician and referred to a specialist if they develop signs of renal involvement, GI involvement, significant joint involvement, or demonstrate an atypical presentation.

Careful attention to nutrition, volume status, vital signs (especially blood pressure), and urinalysis is the cornerstone of treatment for most children. Although specific therapy for HSP remains controversial, carefully selecting children who are to receive more than standard supportive care is critical.

Mild cases of HSP do not require treatment provided that urine monitoring is conducted to detect modifications in the clinical follow-up, primarily during the first 6 months of the rash.

Mild abdominal pain can be monitored; however, children with significant abdominal pain may require steroids, which are initially given in high doses followed by a slow taper.

Children who do not display any urinary abnormalities within 6 months of diagnosis rarely develop chronic kidney disease (CKD). Steroids and other immunosuppressants are not indicated for the prevention of urinary abnormalities. Children who display only isolated hematuria or proteinuria have a very low risk of developing CKD (1.6%); they should therefore receive supportive care only, and not more aggressive treatment. Children who have nephritic or nephrotic syndrome have a much higher risk of CKD (10%–19.5%) and thus merit serious consideration for aggressive therapy. Girls are at higher risk for CKD (2.5 times higher than their male counterparts) and will likely benefit more from therapy.

Long-term follow-up of 219 patients (83 children younger than 16 years and 136 adults) with biopsy-proven HSP nephritis found that 60% of the children and 72% of the adults were treated with steroids, and 14% of children and 22% of adults received immunosuppressants. When kidney function outcomes (doubling of serum creatinine and eventual need for dialysis) were examined, the use of steroids or immunosuppressants failed to show any protective advantage over supportive care. Seven percent of these children ended up on dialysis after a mean follow-up of 6.7 years. Girls are at higher risk of eventual dialysis. The use of steroids in children with HSP should be decided on an individual basis, and cases that are considered for steroid treatment should be referred to a nephrologist. Another study of 27 children with HSP nephritis treated with long-term immunosuppression over a 10-year period showed that despite long immunosuppression, children with high-grade HSP nephritis had persistent renal abnormalities on long-term follow-up.

Evidence suggests that steroids for children with extrarenal manifestations may be helpful. Ronkainen and colleagues conducted a randomized, double-blind, placebo-controlled trial of early steroid treatment and monitored patients for 6 months. Of the 171 patients, 84 were treated with prednisone and 87 received a placebo. The endpoints were renal involvement at 1, 3, and 6 months and healing of extrarenal symptoms. These researchers found that the use of prednisone (1 mg/kg/day for 2 weeks, with weaning over the subsequent 2 weeks) was effective in reducing the intensity of abdominal pain (pain score, 2.5 vs 4.8;  $P = .029$ ) and joint pain (4.6 vs 7.3;  $P = .030$ ). Prednisone did not prevent the development of renal symptoms but was effective in treating them; renal symptoms resolved in 61% of the prednisone patients after treatment, compared with 34% of the placebo patients (difference = 27%; 95% confidence interval = 3% to 47%;  $P = .024$ ). The authors concluded that the general use of prednisone in HSP is not supported, but patients with disturbing symptoms may benefit from early treatment because prednisone reduces extrarenal symptoms and is effective in altering, but not preventing, the course of renal involvement.

A long-term follow-up study published by the same authors found that patients with nephritis at the onset

of disease had an increased risk for hypertension or urinary abnormalities (OR 3.6,  $P = 0.02$ ) 8 years later. There were no differences between the placebo and prednisone groups, leading to the conclusion that early prednisone therapy does not affect long-term outcome and should not be routinely used.

In a small but well-designed study, children with HSP who displayed hypertension, hematuria, and proteinuria were given 1,000 mg fish oil twice daily and Enalapril 2.5 to 10 mg per day. Enalapril was subsequently stopped in all patients within 1 year. A 6-month follow-up was recorded under continued treatment with fish oil. Renal function remained the same (creatinine at a mean of 0.6 mg/dL) before and after treatment. Hypertension (135/82 vs 100/54;  $P < .05$ ) remained better controlled and proteinuria (1,041 mg/day vs 104 mg/day;  $P < .05$ ) remained minimal at 6-month follow-up for those off angiotensin-converting enzyme (ACE) inhibition but on fish oil. Although this case series is very small, fish oil is a benign treatment that may provide other added benefits such as the reduction of hypertriglyceridemia. Fish oils (omega-3-acid ethyl esters) have been shown to be promising in IgA nephropathy, which many researchers think is part of the spectrum of disease related to HSP. The anti-inflammatory and immune-modulating effects of fish oil have been demonstrated in other studies. ACE inhibitors are also indicated for the control of hypertension, especially for children with proteinuria.

Other options for the treatment of HSP have been studied. Cyclosporine and prednisone, plasmapheresis, tonsillectomy, dapsone, and cyclophosphamide have all been tried, with varying degrees of success. These approaches have the possibility of toxicity, and many lack verification from blinded, controlled, and randomized studies.

In summary, most children with HSP should be managed with supportive care and with close monitoring of their renal function. Children with HSP who have persistent hematuria or proteinuria or those with abnormal renal function or elevated blood pressure should be referred to nephrologists for management. There is no evidence to support the use of steroids to prevent urinary abnormalities. However, in children with significant renal involvement because of HSP nephritis, steroids and other immunosuppressants, including cyclophosphamide, may have a role in treating the disease.

### WHEN TO REFER

Children should be referred to a pediatric nephrologist if they have

- Proteinuria or hematuria
- Hypertension
- Significant and persistent signs of kidney inflammation (nephritic or nephrotic syndrome)
- Acute kidney injury (elevation in blood urea nitrogen or creatinine levels)

### WHEN TO ADMIT

- Toxic appearance (febrile, lethargic, hypotensive, or hypertensive, with altered mental status or not acting themselves)

- Abdominal pain may indicate acute appendicitis, intussusception, small-bowel obstruction or infarction or pain caused by HSP. Obtaining a surgical consult is advisable if abdominal pain is particularly severe or out of proportion to the physical examination.
- A significant reduction in urine output for age and weight or inability to keep fluids down.
- Significant gastrointestinal bleeding
- Relative indication: A significant (>25% change) alteration from normal in the child's kidney function (serum creatinine)

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *What Is a Pediatric Nephrologist?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Nephrologist.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Nephrologist.aspx))
- *What Is a Pediatric Rheumatologist?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Rheumatologist.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Rheumatologist.aspx))

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## Chapter 265 HEPATITIS

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The term *hepatitis* simply describes inflammation of the liver and does not imply a cause. The causes of hepatitis vary with age, geographic location, and the presence or absence of underlying illness. Broadly speaking, hepatitis in children may be caused by infectious, autoimmune, and metabolic conditions or drug toxicity (Table 265-1). Systemic conditions such as ischemia and trauma (including abdominal battering from child abuse) may also result in elevated serum aminotransferases. Some conditions may cause elevated liver enzymes that are not because of hepatitis. These conditions include the myopathies (elevated serum aminotransferases) and bone disorders (elevated alkaline phosphatase) where the primary site of enzyme release is muscle or bone rather than the liver.

## EPIDEMIOLOGY AND CLINICAL COURSE

### Viral Hepatitis

The overall prevalence of viral hepatitis in children in the United States is declining, particularly with the implementation of routine vaccination programs for hepatitis A and B. Not included in these figures are numerous unrecognized anicteric cases, especially in children, in whom the anicteric to icteric case ratio is thought to approach 10:1. The clinical features (Table 265-2) vary from asymptomatic to fulminant hepatic failure, depending on the virus and host factors. Acute viral hepatitis may also progress to chronic liver disease, particularly with hepatitis B and C, resulting in chronic morbidity and mortality.

### Hepatitis A Virus

Hepatitis A virus (HAV) is a 27 nm ribonucleic acid (RNA) virus, a member of the picornavirus group. Transmission of HAV is predominantly by the fecal-oral route, although saliva may rarely be a vehicle. Contaminated shellfish, polluted water, and travel to endemic areas also have been identified in the acquisition of type A infection. Hepatitis A virus RNA can be detected in serum and stool as early as 2 to 3 weeks before acute illness and as much as 1 week after the onset of illness; recovery of virus in the stool decreases as jaundice becomes evident. Before symptoms develop, parenteral transmission is possible but uncommon.

Initial symptoms of HAV infection may be nonspecific and include fever, malaise, anorexia, nausea, vomiting, and upper abdominal discomfort. Darkening of the urine and enlargement and tenderness of the liver follow. Jaundice is uncommon in young children. The bilirubin level increases in both direct and indirect fractions, but, generally, does not exceed a total of 15 mg/dL. Aminotransferase elevation generally does not last more than 3 to 4 weeks. The disease rarely is fulminant; however, a small percentage of children with hepatitis A may have a relapsing or protracted course. Children with acute HAV infection may be completely asymptomatic, but are still infectious and, therefore, serve as a silent reservoir of disease.

### Hepatitis B Virus

Hepatitis B virus (HBV) is a highly infectious virus of the Hepadnaviridae family. Its double-stranded overlapping DNA codes for a surface antigen (HBsAg), a core antigen (HBcAg), e antigen (HBeAg), and DNA polymerase. Hepatitis B surface antigen is found in all body secretions and excretions from infected persons. However, transmission only occurs through contact with blood, vaginal and menstrual fluids, and semen. The virus is stable on environmental surfaces for at least 7 days. In hyperendemic areas (Asia, Africa, Southern Europe, Latin America), HBV infection is most often acquired perinatally or in early childhood by horizontal transmission from infected family members.

Improperly sterilized syringes, infected blood products, and nosocomial transmission are also means of acquisition in some parts of Africa and Asia.

Aggressive immunization programs in certain areas, such as Taiwan, have substantially lowered

**Table 265-1** Differential Diagnosis of Hepatitis

CATEGORY	CAUSES
Infectious	Hepatitis A, B, C, D, E, G, adenovirus, Epstein-Barr virus, cytomegalovirus, varicella zoster, human herpesvirus type 6, parvovirus B19, echovirus, coxsackievirus, rubeola virus
Autoimmune	Autoimmune type 1 and 2 and seronegative autoimmune hepatitis, Sclerosing cholangitis (neonatal and child forms)
Metabolic	Alpha <sub>1</sub> antitrypsin deficiency, galactosemia, hereditary tyrosinemia, hereditary fructose intolerance, progressive familial intrahepatic cholestasis types 1, 2, and 3, paroxysmal diseases, mitochondrial hepatopathies, neonatal hemochromatosis, glycogen storage disease, Niemann-Pick disease type C, inborn errors of bile acid metabolism, Wilson disease, nonalcoholic steatohepatitis
Drug induced	Sodium valproate, halothane, phenytoin, herbal medications, recreational drugs (ecstasy), toxins (eg, <i>Amanita phalloides</i> [wild mushrooms])
Other	Alagille syndrome, cystic fibrosis, ischemia, trauma (including child abuse)
Elevated liver enzymes without hepatitis	Myopathies, bone disorder, transient hyperphosphatasia, celiac disease

**Table 265-2** Clinical Features of Acute Viral Hepatitis

	HAV	HBV	HCV
<b>CHARACTERISTICS</b>			
Age distribution	Children and young adults	All age groups	All age groups
Route of infection	Predominantly fecal-oral	Parenteral	Parenteral
Incubation period (days)	15–40	50–180	20–90
Onset	Acute	Insidious	Insidious
Duration of clinical illness	Weeks	Weeks to months	Weeks to months
<b>VIRUS PRESENCE</b>			
Feces	Late incubation, acute	May be present	Absent
Blood	Late incubation, acute	Late incubation, acute, may persist for months	Present chronically
<b>SIGNS AND SYMPTOMS</b>			
Fever	High, common early	Moderate, less common	Moderate, less common
Nausea and vomiting	Common	Less common	Less common
Anorexia	Severe	Mild to moderate	Mild to moderate
Arthralgia or arthritis	Rare	Common	Absent
Rash or urticaria	Rare	Common	Absent
<b>LABORATORY FINDINGS</b>			
Aminotransferase elevation	1–3 weeks	Months	Fluctuates for months
Bilirubin elevation	Weeks	May be months	Unusual
HBsAg	Absent	Present	Absent
Severity	Usually mild	Often severe	Usually mild
Progression to chronic hepatitis	Rare	More common	High rate
Immunity	Homologous, lifelong	Homologous, lifelong	Unusual
Prevention	Immune serum globulin, vaccine	Hyperimmune globulin, vaccine	Screen donor blood

HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus.

Modified from Krugman S, Katz SL. *Infectious diseases of children*, 8th ed. St Louis, MO: Mosby; 1985; and deBelle RC, Lester R. Current concepts of acute and chronic viral hepatitis. *Pediatr Clin North Am*. 1975;22(4):943–961. Copyright © Elsevier, with permission.

both vertical and horizontal transmission rates as well as the average annual incidence of hepatocellular carcinoma.

In the United States, implementation of universal newborn hepatitis B immunization in 1991, followed in 1995 by routine vaccination of all adolescents 11 to 12 years, and, in 1999, to include children younger than

18 years of age who were not previously vaccinated resulted in a significant reduction of HBV in children. The rate of acute hepatitis B in children and adolescents decreased 89% between 1990 and 2002, and racial disparities in hepatitis B incidence narrowed. Despite these hepatitis B vaccination recommendations, a recent study showed that most homeless inner-city



children aged 13 to 18 years were not vaccinated against hepatitis B.

Age of acquisition of the virus is an important prognostic determinant. Perinatal transmission from mother to newborn leads to chronic hepatitis in 90% of affected children compared to less than 10% when the infection is acquired as an adult. Transmission and chronic infection in the newborn are more likely (up to 90%) if the mother is HBeAg positive and less likely (<5%) if the mother is HBeAg negative. Fulminant hepatitis in the newborn has been reported in the latter group and, although the mechanism is not clear, it is not thought to result from the selection of more potent mutant viruses. The principal route of infection at the time of birth is by microtransfusions or by swallowing blood and genital secretions at the time of delivery.

The clinical course of hepatitis B infection depends on several viral and host factors. Hepatitis B acquired either perinatally or horizontally at a very young age is generally asymptomatic.

In low-prevalence countries, hepatitis B occurs sporadically, and more often in adolescents. The onset is usually insidious. Extrahepatic manifestations such as skin rash and arthralgia are common and may be prodromal. In fact, hepatitis B should be kept in mind in the differential diagnosis of a serum sickness-like illness. Younger children may be asymptomatic. The duration of illness is usually 4 to 6 weeks. Aminotransferase elevation usually peaks approximately 1 month after the onset of illness.

The long-term effects of acquiring HBV in infancy include cirrhosis and hepatocellular carcinoma. Although most cases of HBV-related hepatocellular carcinoma occur in adults, many cases of HBV-related liver cancer have been described in children. Recent studies suggest that perinatal transmission is important in hepatocarcinogenesis, perhaps related to the high dose of HBV-DNA with subsequent tolerance and persistent necroinflammatory activity. In addition, the genotype of the virus may correlate with natural history, response to therapy, and risk of developing hepatocellular carcinoma.

### **Hepatitis C Virus**

Hepatitis C virus (HCV), recognized in 1989, is a single stranded RNA virus of the Flaviviridae family and was responsible for most post-transfusion non-A, non-B hepatitis prior to screening blood and blood products from 1990. The seroprevalence of HCV in the general US population is estimated at 1.8%. In children, the seroprevalence for those without known risk factors is 0.2% for those younger than 12 years of age and 0.4% for those 12 to 19 years of age. Prior to screening donor blood in 1990, most children were infected by parenteral exposure to contaminated blood and blood products. Since screening, the risk of HCV infection was substantially reduced to 0.004% to 0.0004% per unit transfused. The major cause of pediatric HCV infection is now perinatal with an overall risk of transmission of 6% from HCV antibody-positive mothers. The risk is minimal when the mother is HCV RNA negative, and higher when mothers are coinfectd with human immunodeficiency virus (HIV). A recent

European multicenter study showed no increase in transmission of HCV from HCV/HIV coinfectd mothers to their newborns. One of the explanations proposed was that effective highly active antiretroviral therapy treatment of coinfectd women leads to reduced immunosuppression and hence a reduced maternal viral load. This study also found that the risk of HCV infection doubles in female offspring, an observation that is novel and yet to be explained. Adolescents may acquire HCV through high-risk behaviors such as injection drug use, intranasal drug use, and body piercing. Horizontal transmission from parent to child, from sibling to sibling, and via sexual transmission is extremely low.

Acute HCV infection is asymptomatic in most children; however, both acute liver failure and cirrhosis have been reported in infancy. Two characteristic clinical features of HCV infection are fluctuation in the serum concentration of the aminotransferases and progression to chronicity in 50% to 90% of cases. Most infected children remain asymptomatic without stigmata of chronic liver disease. Liver histology shows mild to moderate hepatitis and fibrosis increases with duration of infection, but in an unpredictable manner. Children with chronic HCV infection who become infected with HAV are at substantial risk of fulminant hepatic failure. Chronic HCV infection predisposes to cirrhosis and hepatocellular carcinoma over 20 years in individuals with adult-acquired infection. The natural history of perinatally acquired HCV infection is still under evaluation in cohort studies.

### **Hepatitis D Virus**

Hepatitis D virus (HDV), discovered in 1977, is a defective virus that requires replication of hepatitis B virus for its own replication. The epidemiology is parallel to that for HBV infection, and prevalence has decreased significantly with better control of HBV infection. Replication occurs in the liver, and the pathologic effects of the virus are limited to this organ. The hepatitis D antigen (HDAg), can be found in both the liver and the serum of individuals who have the disease. Hepatitis D virus may occur as a coinfection with chronic HBV or as an acute superinfection of HBV; in both cases it causes a more severe illness with significant morbidity and mortality. Hepatitis D virus may also be transmitted perinatally with HBV. Acute HDV infection in a child who is a chronic HBV carrier may produce a severe episode of hepatitis with fulminant hepatic failure or chronic hepatitis.

### **Hepatitis E Virus**

Hepatitis E virus (HEV), a 27- to 34-nm single-stranded RNA virus, is the cause of epidemic, enteric transmitted hepatitis that has occurred in India, Pakistan, Nepal, Russia, China, Algeria, central Africa, Peru, and Mexico. A few imported cases have been identified in the United States and so have a few cases among persons with no history of travel to HEV-hyperendemic countries. The illness usually occurs in areas where the water supply is contaminated by feces. Hepatitis E is similar clinically to hepatitis A. Cholestasis may be more common than with hepatitis A, and elevation of serum aminotransferases is modest. The most unusual

clinical feature of the illness is its high mortality rate in pregnant women (approximately 10%).

### Hepatitis G Virus

The hepatitis G virus (HGV), identified in 1995, is an RNA virus of the Flaviviridae family and a distant relative of HCV. Hepatitis G virus is mainly transmitted parenterally through blood and blood products and through intravenous drug use. Its prevalence in children in the United States was estimated to be 13.8% based on a small study of blood bank samples. The infection may be self-limited, resulting in the production of neutralizing antibody to the E2 envelope protein, or it may result in a carrier state. The virus does not replicate in the liver and does not seem to alter the course and severity of those coinfecting with HCV, but it may be protective in HIV infection.

### TT Virus (2)

TT virus (TTV) is a DNA virus discovered in 1997 in the sera of 3 of 5 patients with biopsy-proven hepatitis and elevated serum alanine aminotransferase levels. In North America, the prevalence of TTV has been found to be 10% in volunteer blood donors, 13% of commercial blood donors, and 17% of intravenous drug users. The role of TTV in the pathogenesis of acute and chronic liver disease is yet to be determined.

### Autoimmune Hepatitis

Autoimmune hepatitis (AIH) is a chronic necroinflammatory hepatitis characterized by mononuclear cell infiltration of the portal tracts with piecemeal necrosis, hypergammaglobulinemia, and non-liver-specific auto antibodies. There are 2 types of AIH, classified according to the presence or absence of certain auto antibodies—AIH type 1 is characterized by the presence of an antinuclear antibody (ANA) and an anti-smooth-muscle antibody (ASMA), whereas AIH type 2 is characterized by anti-liver-kidney microsomal antibodies (anti-LKM). Approximately two-thirds of affected children are girls.

The mode of presentation of autoimmune hepatitis is highly variable; therefore, AIH should be excluded with serologic testing in all children presenting with signs of acute or chronic liver disease or liver failure. Hepatomegaly, splenomegaly, and jaundice are common findings. Autoimmune hepatitis is sometimes associated with inflammatory bowel disease and may precede or follow colitis. Associated extrahepatic manifestations reported include nephrotic syndrome, autoimmune thyroiditis, Behçet disease, insulin-dependent diabetes, urticaria pigmentosa, vitiligo, hypoparathyroidism, and Addison disease. Although AIH type 2 patients are more likely to present in acute liver failure, the overall prognosis of type 2 disease is not different from that of type 1 disease.

### Drug-Induced Hepatitis

Drug-induced liver disease may occur as an unexpected idiosyncratic reaction to a drug or be an expected consequence to a toxic dose and may cause signs of acute hepatitis and chronic hepatitis. Some forms of drug-induced liver disease result from the presence of polymorphisms of enzymes that metabolize

drugs, resulting in slower metabolism or the production of toxic intermediates by alternative pathways (eg, azathioprine and valproic acid-induced liver injury). The pattern and severity of injury may vary from asymptomatic abnormalities of liver function tests to acute liver failure. More than 900 drugs have been implicated as causes of liver injury.

### Metabolic Liver Disease

A large number of metabolic disorders can present as hepatitis in childhood, but a detailed discussion is beyond the scope of this chapter.

Alpha<sub>1</sub> antitrypsin ( $\alpha_1$ AT) deficiency is the most common genetic cause of liver disease in children, with an incidence of 1 in 1,600 to 2,000 live births. It results from the retention of the mutant  $\alpha_1$ AT inside the endoplasmic reticulum of liver cells, which may predispose certain individuals with homozygous ZZ phenotype to significant liver injury.

Wilson disease is an autosomal-recessive disorder affecting 1 in 30,000 people, resulting from a mutation in the *ATP7B* gene, which encodes a copper-binding membrane protein regulating the transport of copper across cell membranes. More than 200 mutations that may produce disease in humans have been identified. Accumulation of copper in the hepatocytes and other organs results in a constellation of clinical symptoms, including hepatitis, neuropsychiatric disease, and Kayser-Fleischer (KF) rings in the Descemet membrane of the cornea.

Tyrosinemia (hereditary tyrosinemia type 1) is an autosomal-recessive disease resulting from a deficiency in fumarylacetoacetate hydrolase, the last enzyme in the tyrosine degradation pathway. This deficiency leads to an accumulation of intermediary toxic metabolites such as maleyl- and fumaryl-acetoacetate, which are thought to cause hepatorenal damage and eventually hepatocellular carcinoma. The usual presentation in infants is acute liver failure with pronounced coagulopathy.

Galactosemia is an autosomal-recessive disorder caused by a deficiency of galactose 1 phosphate uridyl transferase. It presents in the neonatal period with cholestatic jaundice, hypoglycemia, encephalopathy, vomiting, failure to thrive, and hepatitis. Hereditary fructose intolerance (HFI) is a rare condition with an estimated prevalence of 1 in 20,000 individuals. The absence of the enzyme aldolase B results in the buildup of fructose-1-phosphate, which inhibits gluconeogenesis and glycolysis. The infant with ongoing fructose ingestion presents with metabolic acidosis, hypoglycemia, and liver failure.

Progressive familial intrahepatic cholestasis (PFIC) type 1, or Byler disease, results from a mutation in the *FIC1* gene, which codes for a P-type adenosine triphosphatase involved in aminophospholipid transport. The mechanism by which cholestatic injury occurs in this condition is still to be determined. Progressive familial intrahepatic cholestasis type 2 is caused by a mutation in the gene encoding for the main adenosine triphosphate-dependent bile acid pump on the canalicular membrane (BSEP). Progressive familial intrahepatic cholestasis type 3 results from a mutation in the gene encoding the multiple

drug resistance protein, which is a phospholipid flippase also located on the canalicular membrane. Progressive familial intrahepatic cholestasis types 1 and 2 present with cholestatic liver disease in infancy. The presentation of PFIC type 3 is variable in childhood. In infants it may present with clinical features of biliary obstruction, but a normal biliary tree on imaging, while older children may present with gallstones. Inborn errors of bile acid metabolism are also rare, but present with severe cholestatic liver disease necessitating early recognition and treatment as outlined in the following text.

Alagille syndrome, or paucity of the intrahepatic bile ducts, is caused by a mutation in the human *jagged 1* gene. Approximately 50% of patients inherit the disease in an autosomal-dominant fashion, while the other 50% of cases result from spontaneous mutations in the index case (proband). Although multiple mutations have been identified, genotype-phenotype correlations are a little more difficult, and the pathophysiology of the gene mutation is yet to be elucidated. More recently, mutations in the gene encoding the notch receptor were also found in patients with the clinical features of Alagille syndrome. Diagnosis in the proband still relies largely on clinical criteria and is based on the association of bile duct paucity together with at least 3 of the following: typical facies, posterior embryotoxon (ophthalmological examination), butterfly vertebrae (seen on chest radiograph), consistent cardiac disease (eg, pulmonary stenosis), and renal disease. Other features include a markedly elevated gamma-glutamyl transferase (GGT), hypercholesterolemia, growth retardation, and intracranial bleeding. Genetic testing available in selected centers may be useful in family studies, as the penetrance is variable.

### Evaluation

A careful clinical history and examination are important in making a timely diagnosis and avoiding the need for unnecessary investigations. Referral to a pediatric gastroenterologist is recommended, as many of the conditions are uncommon and require close monitoring. The evaluation of a child with hepatitis depends primarily on the child's age and the nature of the presentation. Common presentations include jaundice in infancy or childhood, the incidental finding of elevated liver enzymes during routine workup, or fulminant hepatic failure. Assessment of children in each of these categories is described in the following text.

**NEONATAL JAUNDICE.** The infant with jaundice and elevated liver enzymes may be otherwise well or have failure to thrive or even display signs of liver decompensation. It is important to determine if there is a family history of jaundice, liver or metabolic disease, or maternal exposure to drugs or toxins, as well as maternal serological status for hepatitis A, B, and C. Maternal illnesses during pregnancy should also be noted, particularly in an infant who is malnourished, suggesting the presence of an in utero infection. A careful dietary history to determine fructose ingestion in the infant either through feed or medication is required if HFI is suspected. The association of renal Fanconi syndrome and clotting abnormalities unresponsive to vitamin K therapy should suggest

tyrosinemia. Gestational alloimmune liver disease (formerly called "neonatal hemochromatosis") may also present with hepatitis but often presents with acute liver failure in newborns. Examination of the infant may reveal hepatosplenomegaly, icterus, and little else. Dysmorphic features and cardiac murmurs would be suggestive of Alagille syndrome.

Basic liver function tests will suggest whether the underlying condition is predominantly hepatocellular injury (elevated transaminases) or predominantly obstructive (elevated GGT and alkaline phosphatase), although in infants the pattern is often mixed. Investigations in the infant in whom an etiology is not obvious should include serology for viruses as well as general investigations such as a blood ammonia level, serum glucose, blood gases with pH, blood lactate level, urine metabolic screen and reducing substances, red blood cell galactose-1-phosphate uridyl transferase, thyroid function tests, and serum and urine bile acids. Other conditions that should be considered in an infant with jaundice include  $\alpha_1$  AT deficiency, cystic fibrosis, defects in amino acid synthesis, organic acid synthesis and fatty acid oxidation, glycogen storage disease, and Niemann Pick type C. More sophisticated tests are required for many metabolic and inherited disorders (see Table 265-3).

**THE CHILD WITH JAUNDICE.** Viral hepatitis, particularly HAV, HBV, HCV, and Epstein-Barr virus should be actively sought in this age group. Hepatitis A is diagnosed by the presence of immunoglobulin M class anti-hepatitis A, which is present 5 to 10 days after exposure. Hepatitis A virus immunoglobulin (IgG) is present at least 10 years after infection and probably confers lifelong immunity to the virus.

The presence of HBsAg in the serum implies hepatitis B infection (see Table 265-4). This is the first marker to appear and is detected 2 weeks to 6 months postexposure. Children with HBV infection are initially HBsAg and HBeAg positive. Hepatitis B virus e antigen reflects active viral replication and infectivity. During this immunotolerant stage, which may persist for years, viral replication and serum HBV-DNA levels are very high. The child is very infectious and may occasionally serve as a source of horizontal transmission in the community. Serum aminotransferase levels fluctuate and may be in the upper limit of normal range. During childhood, conversion from HBeAg to anti-hepatitis B e antigen (HBe) may occur spontaneously with a rate of 3% per year, although rates vary with the mode of acquisition. Seroconversion to anti-HBe is often preceded by a transient elevation in serum aminotransferases. After anti-HBe seroconversion, HBV-DNA levels remain low or undetectable. In this state, children may once again develop fluctuations of alanine aminotransferase and a rise in DNA levels, indicating increased replication of a precore mutant virus that does not produce e antigen.

Most children remain HBsAg positive, and this chronic carrier state is generally unassociated with overt disease during childhood. The annual HBsAg clearance rate is low (1%–2%) and may be associated with persistence of HBV-DNA. Liver cirrhosis is encountered in 3% to 5% of children with chronic HBV. These children are at risk for developing hepatocellular

**Table 265-3** Diagnostic Investigations for Liver Diseases

DISEASE	INVESTIGATION	INTERPRETATION
$\alpha_1$ AT deficiency	Serologic Pi type	MM (normal) ZZ ( $\alpha_1$ AT deficiency)
	Serum $\alpha_1$ AT	<50 mg/dL
	Liver biopsy	PAS-positive diastase-resistant granules in the hepatocyte endoplasmic reticulum
Tyrosinemia	Urinary succinyl acetone	Elevated
	$\alpha$ -fetoprotein	Raised (indicative of immature hepatocytes) May be raised in many types of neonatal hepatitis, but significantly raised in tyrosinemia
PFIC 1, 2, 3	Serum bile acids	Raised
PFIC 1, 2	GGT	Low
PFIC 3	GGT	High
Bile acid metabolic disorder	Fast atom bombardment mass spectroscopy of urine	Typical profiles
	Serum bile acids	Low
	GGT	Low
HFI	Urine-reducing substances	Positive when ingesting fructose
	Gene testing	22 mutations for HFI; 70% of patients have 2 mutations in exon 5 ( <i>A149P</i> , <i>A174D</i> )
Cystic fibrosis	Sweat chloride test	Sweat chloride >60 mEq/L
Autoimmune hepatitis		ANA; anti-SMA or anti-LKM
Neonatal hemochromatosis	Serum transferrin	Low (reflects low-functioning liver cell mass)
	Serum ferritin	Markedly raised (nonspecific)
	MRI	Siderosis of pancreas, myocardium
	Buccal biopsy	Siderosis of salivary glands
Niemann-Pick type C	Liver biopsy (electron microscopy)	Whirled inclusions of sphingomyelin in lysosomes
	Skin fibroblast culture	Measurement of sphingomyelinase activity

$\alpha_1$  AT,  $\alpha_1$ -antitrypsin; ANA, antinuclear antibody; *anti-LKM*, anti-liver-kidney microsomal antibodies; *anti-SMA*, anti-smooth-muscle antibody; GGT,  $\alpha$ -glutamyltransferase; HFI, hereditary fructose intolerance; MRI, magnetic resonance imaging; PAS, periodic acid-Schiff; PFIC, progressive familial intrahepatic cholestasis; SMA, smooth-muscle antibody.

**Table 265-4** Diagnostic Tests for Hepatitis B Virus (HBV) Antigens and Antibodies

FACTOR TO BE TESTED	HBV ANTIGEN OR ANTIBODY	USE
HBsAg	Hepatitis B surface antigen	Detection of acutely or chronically infected people; antigen used in hepatitis B vaccine; can be detected for up to a month after a dose of hepatitis B vaccine
Anti-HBs	Antibody to HBsAg	Identification of people who have resolved infections with HBV; determination of immunity after immunization
HBeAg	Hepatitis B e antigen	Identification of infected people at increased risk of transmitting HBV
Anti-HBe	Antibody to HBeAg	Identification of infected people with lower risk of transmitting HBV
Anti-HBc (total)	Antibody to HBcAg <sup>a</sup>	Identification of people with acute, resolved, or chronic HBV infection (not present after immunization); passively transferred maternal anti-HBc is detectable for as long as 24 months among infants born to HBsAg-positive women
IgM anti-HBc	IgM antibody to HBcAg	Identification of people with acute or recent HBV infections (including HBsAg-negative people during the "window" phase of infection; unreliable for detecting perinatal HBV infection)

HBcAg, hepatitis B core antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; IgM, immunoglobulin M.

<sup>a</sup>No test is available commercially to measure HBcAg.

From American Academy of Pediatrics. Hepatitis B. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee of Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:400–423.

carcinoma before adulthood. Although the best methods and frequency of surveillance have not been determined, careful follow-up, including serial serum  $\alpha$ -fetoprotein measurements and liver ultrasound examinations, should be performed on these children.

Hepatitis B virus DNA is detectable in serum very early in the infection. Hepatitis B virus DNA levels are now reported as international units per milliliter (IU/mL). The levels of HBV-DNA may vary considerably, and several assays with different dynamic ranges



are used. The most sensitive real-time polymerase chain reaction (PCR) assays can detect as little as 20 IU/mL; the branched chain DNA assays are less sensitive. The measurement of HBV-DNA levels is important in light of recent data suggesting that long-term outcome from HBV infection, particularly the development of hepatocellular carcinoma, is directly related to the degree of viral suppression resulting from therapy. Anti-hepatitis B surface antibody indicates immune response to immunization or past infection. The presence of anti-hepatitis B core antibody (HBc), which appears 3 to 5 weeks after HBsAg, implies exposure to the native virus. Anti-HBc does not appear after vaccination.

The presence of antibodies to HCV implies exposure to HCV virus, but does not confer protective immunity. Most laboratories currently use third-generation enzyme-linked immunosorbent assay which has over 99% sensitivity and specificity. However, these tests become positive weeks after exposure to the virus. In contrast, the highly sensitive PCR assay becomes positive within days after exposure to the virus. Assays for viral detection may be quantitative or qualitative. The latter are more sensitive; however, as quantitation is an important component of guiding therapy, quantitative assays are used more often. As with HBV infection, the international unit has been adopted as a means of overcoming the variability between laboratories and different commercially available assays. Vertically acquired infection is confirmed by the persistence of anti-HCV antibody beyond 18 months of age or the presence of HCV-RNA in serum after the first 3 months of life. Polymerase chain reaction (PCR) testing prior to this period is unreliable.

A test for anti-HDV is commercially available. Serologic identification of anti Hepatitis E Virus IgM (anti HEV IgM) is diagnostic, and real-time PCR was recently developed. Hepatitis G virus and TTV infections are diagnosed by detection of HGV-RNA and TTV-DNA by PCR methods.

Diagnosis of autoimmune hepatitis relies on a combination of hypergammaglobulinemia and raised anti-nuclear, smooth-muscle, or liver-kidney microsomal antibodies. Histologically, portal tracts are infiltrated by lymphocytes and plasma cells. Inflammatory cells often infiltrate the parenchyma, accompanied by necrosis of cells at the periphery of the hepatic lobule (piecemeal necrosis). Fibrosis may be seen to a variable degree, or true cirrhosis may be present. In 1999, the International Autoimmune Hepatitis group modified a scoring system to diagnose AIH in adults. This was evaluated by Schreiber and colleagues in 2004 and was found to be useful in children, particularly when the ratio of GGT:AST (aspartate aminotransferase) was used instead of the ratio of alkaline phosphatase:AST. The GGT to AST ratio is better at detecting autoimmune disease with a biliary component, such as overlap syndrome.

Metabolic diseases that present later in childhood include Wilson disease,  $\alpha_1$  AT deficiency, and fatty liver. Wilson disease should always be considered in the differential diagnosis of pediatric liver disease, as it has a variable presentation and effective therapy is available. There is no single test available to

diagnose Wilson disease. The combination of 2 or more of the following is highly suggestive: decreased serum ceruloplasmin ( $<20$  mg/dL), elevated urinary copper excretion ( $>100$  mcg/24 hours), elevated liver copper concentration ( $>250$  mcg/g of dry weight) and KF rings. Genetic confirmation is available in some centers.

Nonalcoholic steatohepatitis (NASH) is fat in the liver associated with inflammation. It has a slight male predominance and generally presents in the prepubertal age group. Nonalcoholic steatohepatitis is seen in children with a number of risk factors including obesity (body mass index  $>30$ ), diabetes, insulin resistance, and hypertriglyceridemia. Acanthosis nigricans is a marker of insulin resistance and should be looked for. While many children are obese, only a minority have NASH; hence, other mechanisms are clearly involved. A fatty liver can be identified on sonography by the presence of uniform or patchy increased echogenicity. Liver biopsy, although not necessary, shows steatosis, mixed lobular inflammation, and hepatocyte ballooning. Hereditary fructose intolerance can also present in the older child with an aversion to fructose-containing products who develops vomiting and elevation of serum aminotransferases after inadvertent ingestion.

To evaluate for drug- or toxin-induced hepatitis, a thorough medical history should be obtained for prescribed medications, herbal teas, poisons, and ingestion of wild mushrooms. Acetaminophen toxicity is the most common cause for acute liver failure in children in North America, so a serum acetaminophen level should be drawn on presentation and appropriate therapy instituted immediately as outlined in the following text. A urine toxicology screen should also be performed when the index of suspicion is high.

Liver biopsy is required when chronic liver disease is suspected and cannot be diagnosed with the investigations described earlier, and to determine the degree of inflammation and fibrosis, both of which may influence treatment. A needle biopsy is usually adequate, and the risks are low when clotting function is normal, ultrasound guidance is used, and the biopsy is performed by an experienced physician. The biopsy should be sent for histology with additional stains (eg, copper, iron), if necessary. If a metabolic liver disease is suspected, a small sample should be preserved in glutaraldehyde for electron microscopy. If Wilson disease is suspected, hepatic copper should be quantified; it is usually necessary to obtain a second biopsy core for this purpose.

**INCIDENTAL FINDINGS OF ABNORMAL LIVER ENZYMES.** Many liver diseases can present in a “silent” fashion in children, with abnormal liver enzymes being detected incidentally. These include viral hepatitis, metabolic disorders such as Wilson disease,  $\alpha_1$  AT deficiency, NASH, autoimmune hepatitis, and hemochromatosis. Conversely, systemic disorders may produce aminotransferases as outlined in Table 265-2. Raised aminotransferases have been found in 32% of children with celiac disease, and a celiac screen should be performed in all children with unexplained elevation of serum aminotransferases once hepatological causes are excluded. Similarly, evidence of muscle disorders (serum creatine kinase) and red cell

**Table 265-5** Recommended Doses and Schedules for Inactivated Hepatitis A Vaccines<sup>a</sup>

AGE (YR)	VACCINE	HEPATITIS A ANTIGEN DOSE	VOLUME PER DOSE (ML)	NUMBER OF DOSES	SCHEDULE
12 mo–18 y	Havrix	720 ELU	0.5	2	Initial and 6–12 mo later
12 mo–18 y	Vaqtat	25 U <sup>b</sup>	0.5	2	Initial and 6–18 mo later
19 y or older	Havrix	1440 ELU	1.0	2	Initial and 6–12 mo later
19 y or older	Vaqtat	50 U <sup>b</sup>	1.0	2	Initial and 6–18 mo later
18 y or older	Twinrix <sup>c</sup>	720 ELU	1.0	3 or 4	Initial, 1 mo, and 6 mo later OR Initial, 7 days, and 21–30 days, followed by a dose at 12 mo

ELU, Enzyme-linked immunosorbent assay units.

<sup>a</sup>Havrix and Twinrix are manufactured by Glaxo Smith Kline Biologicals (Research Triangle Park, NC); Vaqtat is manufactured and distributed by Merck & Co, Inc. (Whitehouse Station, NJ).

<sup>b</sup>Antigen units (each unit is equivalent to approximately 1 mcg of viral protein).

<sup>c</sup>A combination of hepatitis B (Engerix-B, 20 µg) and hepatitis A (Havrix, 720 ELU) vaccine (Twinrix) is licensed for use in people 18 years and older in 3- and 4-dose schedules.

From American Academy of Pediatrics. Hepatitis A. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:391–399.

disorders (complete blood count and peripheral smear, reticulocyte count, and haptoglobin levels) should be performed if there is no clinical evidence of liver disease.

**FULMINANT HEPATIC FAILURE.** The broad definition of fulminant hepatic failure (ie, hepatic encephalopathy within 8 weeks of onset of illness) is problematic in children because of the difficulty in detecting encephalopathy in infants and young children and the fact that encephalopathy may present late or not at all. The important components of the definition are the lack of a pre-existing liver disease and severe impairment of hepatic function as evidenced by a prolonged prothrombin time (>4 seconds over control) and an international normalized ratio (INR) greater than 1.5, unresponsive to large doses of vitamin K.

The cause of fulminant hepatic failure is age-dependent, but acetaminophen toxicity is the most common identified cause in the United States from the recent acute liver failure study group data. In infancy, metabolic disorders such as galactosemia, hereditary fructose intolerance, tyrosinemia, and gestational allo-immune liver disease may present with fulminant failure; therefore, appropriate investigations should be sent for these disorders (Table 265-3). In the older child, Wilson disease, autoimmune hepatitis (particularly type 2), and medications and toxins should be sought.

## THERAPY AND PREVENTION

### Viral Hepatitis

There are 2 inactivated vaccines against HAV currently approved in the United States for children 1 to 18 years old and for adults. The vaccine is given in a 2- or 3-dose schedule depending on the formulation. Table 265-5 shows the recommended doses for HAV vaccination. In the past, only children with underlying liver disease were recommended to receive HAV vaccination. However, the vaccine is now recommended for all children 1 to 18 years of age (Box 265-1). A combination of Hepatitis A and Hepatitis B vaccine is also available for individuals over 18 years old.

### BOX 265-1 Indications for Hepatitis A Virus Vaccination

- All children in the United States 12–23 months of age
- Catch-up immunization of unimmunized children 2–18 years of age, especially in the context of rising incidences or ongoing outbreaks among children and adolescents
- Travelers to endemic areas
- Close contacts of newly arrived international adoptees
- Patients with chronic liver disease
- Patients with clotting factor disorders
- Men who have sex with men
- Users of injection and illicit drugs
- Patients at high risk of exposure secondary to their occupation

Derived from American Academy of Pediatrics. Hepatitis A. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:391–399.

Recommendations for pre-exposure immunoprophylaxis of HAV for subjects of all ages are shown in Table 265-6. Either pediatric formulation induces seroconversion rates greater than 90% after the initial dose and 100% after the second dose.

Hospitalization generally is unnecessary for the child who has acute viral hepatitis; however, the infant and young child should be hospitalized if there is coagulopathy or other evidence of liver decompensation. No particular diet or restriction of activity seems to affect the course or outcome of acute viral hepatitis, because recovery of HAV in the child's stool decreases rapidly after the onset of jaundice. Return to school at this point, provided the child feels well, does not seem to present an undue risk of infection to others. Although household contacts of the child with hepatitis

**Table 265-6** Recommendations for Preexposure Immunoprophylaxis of Hepatitis A Virus for Travelers<sup>a</sup>

AGE	RECOMMENDED PROPHYLAXIS	NOTES
<12 mo	IGIM	0.02 mL/kg <sup>b</sup> protects for up to 3 mo. For trips $\geq 3$ mo, 0.06 mL/kg <sup>b</sup> should be given at departure and every 5 mo if exposure to HAV continues.
12 mo–40 y $\geq 41$ y	HepA vaccine <sup>c</sup> HepA vaccine, with or without IGIM <sup>c</sup>	If departure is in <2 wk, older adults, immunocompromised people, and people with chronic liver disease or other chronic medical conditions can receive IGIM with the initial dose of HepA vaccine to ensure optimal protection.

IGIM, immune globulin intramuscular; HepA, hepatitis A vaccine.

<sup>a</sup>All people 12 months or older at high risk of HAV disease should be immunized routinely.

<sup>b</sup>IGIM should be administered deep into a large muscle mass. Ordinarily, no more than 5 mL should be administered in one site in an adult or large child; lesser amounts (maximum 3 mL in one site) should be given to small children and infants.

<sup>c</sup>People who have a contraindication to HepA vaccine should receive IGIM.

From American Academy of Pediatrics. Hepatitis A. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:391–399.

**Table 265-7** Recommendations for Postexposure Immunoprophylaxis of Hepatitis A

TIME SINCE EXPOSURE	AGE OF PATIENT (YR)	RECOMMENDED PROPHYLAXIS
$\leq 2$ wk	<12 mo	IGIM, 0.02 mL/kg <sup>a</sup>
	12 mo–40 y	HepA vaccine <sup>b</sup>
	$\geq 41$ yr	IGIM, 0.02 mL/kg, <sup>a</sup> but HepA vaccine <sup>b</sup> can be used if IGIM is unavailable <sup>a</sup>
>2 wk	People of any age who are immunocompromised, have chronic liver disease, or contraindication to vaccination	IGIM, 0.02 mL/kg <sup>a</sup>
	<12 mo	No prophylaxis
	$\geq 12$ mo	No prophylaxis, but HepA vaccine may be indicated for ongoing exposure <sup>b</sup>

IGIM, Immune globulin intramuscular; HepA, hepatitis A vaccine.

<sup>a</sup>IGIM should be administered deep into a large muscle mass. Ordinarily, no more than 5 mL should be administered in one site in an adult or large child; lesser amounts (maximum 3 mL in one site) should be given to small children and infants.

<sup>b</sup>Dose and schedule of hepatitis A vaccine as recommended according to age in Table 265-5.

From American Academy of Pediatrics. Hepatitis A. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:391–399.

A are already likely to be infected by the time of diagnosis, infection control measures should be instituted, including scrupulous handwashing and the use of disposable eating utensils in the child's home until jaundice clears. Pooled serum Ig, when given within 2 weeks postexposure, is effective in preventing symptomatic infection, as is immunization within an 8-day window period. Immunoprophylaxis should be given to household, sexual, child care center, and hospital contacts, and may be recommended in some situations for schoolroom contacts and persons exposed in common source outbreaks (Table 265-7). Newborns of infected mothers do not need special care if the mother is not jaundiced. Children traveling to endemic areas should also be immunized prophylactically. Vaccination is preferable; however, if travel is imminent (ie, <1 month), IgG may be substituted per Centers for Disease Control and Prevention guidelines.

A significant reduction in the prevalence of Hepatitis B has been accomplished to some extent with infant and catch-up vaccination programs over the last 2

decades. Detailed recommendations regarding doses and pre-exposure and postexposure prophylaxis are provided in Box 265-2, Table 265-8, Table 265-9, and Table 265-10. A baby born to an HBsAg-positive mother, or a mother who had hepatitis B during pregnancy, should be given 0.5 mL of hepatitis B immune globulin (HBIG) intramuscularly within the first 12 hours of life and 0.5 mL of hepatitis B vaccine intramuscularly at a different site before hospital discharge, but definitely within the first week of life and again at 1 and 6 months of age. Data linking breastfeeding to the acquisition of viremia are equivocal, but HBsAg-positive mothers whose infants received immunoprophylaxis may breast feed without risk of transmitting HBV to the infant. Hepatitis B immunization also protects against HDV infection.

The decision to treat a child with HBV is complex and should be made in conjunction with a pediatric hepatologist. The 2 major classes of medication available are the interferons and nucleoside/tide analogs. Treatment does not usually eradicate the virus, but can

**BOX 265-2 Persons Who Should Receive Hepatitis B Immunization**

- All infants (infants of HBsAg-positive mothers require postexposure immunoprophylaxis with HBIG and vaccine)
- All children and adolescents not vaccinated as infants
- Inmates of juvenile detention correctional facilities
- **People at Risk of Infection by Sexual Exposure**
  - Sex partners of HBsAg-positive people
  - Sexually active people who are not in a long-term mutually monogamous relationship (eg, people with >1 sex partner during the previous 6 months)
  - People seeking evaluation or treatment for a sexually transmitted infection
  - Men who have sex with men
- **People at Risk of Infection by Percutaneous or Mucosal Exposure to Blood**
  - Current or recent injection drug users
  - Household contacts of HBsAg-positive people
- Residents and staff of facilities for people with developmental disabilities
- Health care and public safety workers with reasonably anticipated risk of exposure to blood or blood-contaminated body fluids
- People with end-stage renal disease, including predialysis, hemodialysis, peritoneal dialysis, and home dialysis
- People with diabetes mellitus who are >19 years of age
- **Others**
  - International travelers to regions with high or intermediate levels (HBsAg prevalence of  $\geq 2\%$ ) of endemic HBV infection
  - People with chronic liver disease
  - People with HIV infection
  - All other people seeking protection from HBV infection

HBIG, hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus. Modified from Centers for Disease Control and Prevention. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). Part II: immunization of adults. *MMWR Recomm Rep*. 2006;55(RR-16):1–33

**Table 265-8**      **Guide to Postexposure Immunoprophylaxis of Unimmunized People to Prevent Hepatitis B Virus (HBV) Infection**

TYPES OF EXPOSURE	IMMUNOPROPHYLAXIS <sup>a</sup>
Household contact of HBsAg-positive person	Administer hepatitis B vaccine series
Discrete exposure to an HBsAg-positive source <sup>b</sup> :	
• Percutaneous (eg, bite, needlestick, nonintact skin) or mucosal exposure to HBsAg-positive blood or body fluids	Administer hepatitis B vaccine + HBIG; complete vaccine series
• Sexual contact or needle sharing with an HBsAg-positive person	Administer hepatitis B vaccine + HBIG; complete vaccine series
• Victim of sexual assault/abuse by a perpetrator who is HBsAg positive	Administer hepatitis B vaccine + HBIG; complete vaccine series
Discrete exposure to a source with unknown HBsAg status:	
• Percutaneous (eg, bite, needlestick) or mucosal exposure to blood or body fluids with unknown HBsAg status	Administer hepatitis B vaccine series
• Victim of sexual assault/abuse by a perpetrator with unknown HBsAg status	Administer hepatitis B vaccine series
Susceptible child biting someone with chronic HBV infection	Initiate or complete the hepatitis B vaccine series Do not give HBIG (assumes no oral mucosal disease when the amount of blood transferred from a child with chronic HBV infection is small)

HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen.

<sup>a</sup>Immunoprophylaxis should be administered as soon as possible, preferably within 24 hours after exposure. Studies are limited on the maximum interval after exposure during which postexposure prophylaxis is effective, but the interval is unlikely to exceed 7 days for percutaneous exposures and 14 days for sexual exposures.

<sup>b</sup>If person previously was immunized with hepatitis B vaccine series, administer hepatitis B vaccine booster dose.

From American Academy of Pediatrics. Hepatitis B. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:400–423.

result in seroconversion, suppression of the viral load, and a reduction in inflammation. Treatment is generally offered to children who have prolonged significantly abnormal liver function tests and who fail to seroconvert spontaneously or those with evidence of hepatocellular injury on biopsy. Regardless of

treatment, all children with HBV should be monitored for signs of evolving chronic liver disease, including clinical examination, liver function tests, alpha fetoprotein, and viral markers as outlined earlier. Recommendations for both monitoring and treating HBV in children were recently published.



Table 265-9 Recommended Dosages of Hepatitis B Vaccines

PATIENTS	VACCINE <sup>a</sup>		COMBINATION VACCINES		
	RECOMBIVAX HB <sup>b</sup> DOSE, $\mu$ G (mL)	ENGRIX-B <sup>c</sup> DOSE, $\mu$ G (mL)	COMVAX <sup>d</sup> DOSE, $\mu$ G (mL)	PEDIARIX <sup>e</sup> DOSE, $\mu$ G (mL)	TWINRIX <sup>f</sup> DOSE, $\mu$ G (mL)
Infants of HBsAg-negative mothers and children and adolescents <20 y	5 (0.5)	10 (0.5)	5 $\mu$ g HBsAg (0.5)	10 $\mu$ g HBsAg (0.5)	Not applicable
Infants of HBsAg-positive mothers (HBIG [0.5 mL] also is recommended)	5 (0.5)	10 (0.5)	5 $\mu$ g HBsAg (0.5)	10 $\mu$ g HBsAg (0.5)	Not applicable
Adolescents 11–15 y of age <sup>b</sup>	10 (1)	Not applicable	Not applicable	Not applicable	Not applicable
Adults $\geq$ 20 y	10 (1)	20 (1)	Not applicable	Not applicable	20 (1)
Adults undergoing dialysis and other immunosuppressed adults	40 (1) <sup>g</sup>	40 (2) <sup>h</sup>	Not applicable	Not applicable	Not applicable

HBsAg, hepatitis B surface antigen; HBIG, hepatitis B immune globulin.

<sup>a</sup>Both vaccines are administered in a 3-dose schedule at 0, 1, and 6 months; 4 doses may be administered if a birth dose is given and a combination vaccine is used (at 2, 4, and 6 months) to complete the series. Only single-antigen hepatitis B vaccine can be used for the birth dose. Single-antigen or combination vaccine containing hepatitis B vaccine may be used to complete the series.

<sup>b</sup>Available from Merck & Co Inc. (Whitehouse Station, NJ). A 2-dose schedule, administered at 0 months and then 4 to 6 months later, is licensed for adolescents 11 through 15 years of age using the adult formulation of Recombivax HB (10  $\mu$ g [Merck & Co Inc.]).

<sup>c</sup>Available from GlaxoSmithKline Biologicals (Research Triangle Park, NC). The US Food and Drug Administration also has licensed this vaccine for use in an optional 4-dose schedule at 0, 1, 2, and 12 months for all age groups. A 0-, 12-, and 24-months schedule is licensed for children 5 through 16 years of age for whom an extended administration schedule is appropriate based on risk of exposure.

<sup>d</sup>Available from Merck & Co Inc. A combination of hepatitis B (Recombivax, 5  $\mu$ g) and *Haemophilus influenzae* type b (PRP-OMP) vaccine is approved for use at 2, 4, and 12 through 15 months of age (Comvax). This vaccine should not be administered at birth, before 6 weeks of age, or after 71 months of age.

<sup>e</sup>A combination of diphtheria and tetanus toxoids and acellular pertussis (DTaP), inactivated poliovirus (IPV), and hepatitis B (Engerix-B 10  $\mu$ g) is approved for use at 2, 4, and 6 months of age (Pediarix [GlaxoSmithKline]). This vaccine should not be administered at birth, before 6 weeks of age, or at 7 years of age or older.

<sup>f</sup>A combination of hepatitis B (Engerix-B, 20  $\mu$ g) and hepatitis A (Havrix, 720 enzyme-linked immunosorbent assay units [ELU]) vaccine; Twinrix is licensed for use in people 18 years of age and older in a 3-dose schedule at 0, 1, and 6 months. Alternately, a 4-dose schedule at days 0, 7, and 21 to 30 followed by a booster dose at 12 months may be used.

<sup>g</sup>Special formulation for adult dialysis patients given at 0, 1, and 6 months.

<sup>h</sup>Two 1-mL doses given in 1 or 2 injections in a 4-dose schedule at 0, 1, 2, and 6 months of age.

From American Academy of Pediatrics. Hepatitis B. In: *Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:400–423.

**Table 265-10** Recommendations for Hepatitis B Virus (HBV) Prophylaxis After Occupational Percutaneous or Mucosal Exposure to Blood or Body Fluids<sup>a</sup>

EXPOSED PERSON	TREATMENT WHEN SOURCE IS		
	HBsAg POSITIVE	HBsAg NEGATIVE	UNKNOWN OR NOT TESTED
Unimmunized	Administer HBIG <sup>b</sup> (1 dose) and initiate HBV series	Initiate HBV series	Initiate HBV vaccine series
Previously immunized			
Known responder	No treatment	No treatment	No treatment
Known nonresponder		No treatment	If known high-risk source, treat as if source were HBsAg positive
After 3 doses:	HBIG: 1 dose and initiate reimmunization <sup>c</sup>		
After 6 doses:	HBIG: 2 doses separated by 1 month		
Response unknown	Test exposed person for anti-HBs <sup>d</sup>	No treatment	Test exposed person for anti-HBs <sup>d</sup>
	If adequate, no treatment		• If adequate, no treatment
	If inadequate, HBIG × 1 and vaccine booster		• If inadequate, vaccine booster dose <sup>e</sup>

HBsAg, hepatitis B surface antigen; HBIG, hepatitis B immune globulin; anti-HBs, antibody to HBsAg.

<sup>a</sup>Centers for Disease Control and Prevention. Immunization of health-care personnel: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2011;60(RR-7):1–45

<sup>b</sup>Dose of HBIG, 0.06 mL/kg, intramuscularly.

<sup>c</sup>The option of giving 1 dose of HBIG (0.06 mL/kg) and reinitiating the vaccine series is preferred for nonresponders who have not completed a second 3-dose vaccine series. For people who previously completed a second vaccine series but failed to respond, 2 doses of HBIG (0.06 mL/kg) are preferred, 1 dose as soon as possible after exposure and the second 1 month later.

<sup>d</sup>Adequate anti-HBs is  $\geq 10$  mIU/mL.

<sup>e</sup>The person should be evaluated for antibody response after the vaccine booster dose. For people who receive HBIG, anti-HBs testing should be performed when passively acquired antibody from HBIG no longer is detectable (eg, 4–6 months); for people who did not receive HBIG, anti-HBs testing should be performed 1 to 2 months after the vaccine booster dose. If anti-HBs is inadequate (less than 10 mIU/mL) after the vaccine booster dose, 2 additional doses should be administered to complete a 3-dose reimmunization series, followed by postimmunization testing for anti-HBs and HBsAg.

From American Academy of Pediatrics. Hepatitis B. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:400–423.

Currently, no vaccine is available for the prevention of HCV infection. Natural infection does not protect from reinfection with the same or different genotypes either in patients or experimentally infected chimpanzees. The most important strategies for controlling hepatitis C include screening donor blood for anti-HCV, identifying and educating those at risk, and risk minimization programs for intravenous drug users. Recommendations for screening include injection drug users, hemodialysis patients, recipients of 1 or more units of blood or blood products before 1992, children with clinical non-A hepatitis, non-B hepatitis, infants born to mothers infected with HCV after 12 months of age, and international adoptees born to high-risk mothers.

Perinatal transmission of HCV is now the most common route of infection in children, with rates on the order of 4% to 6% of births to HCV-infected mothers. Maternal-fetal transmission has also been linked to in utero monitoring and prolonged rupture of membranes; it does not seem to be prevented by cesarean section.

Although HCV RNA has been detected in breast milk, current evidence suggests that breastfeeding is not contraindicated. However, mothers should consider abstaining from breastfeeding if their nipples are cracked and bleeding. Patients with HCV infection should be counseled to avoid hepatotoxic medications and alcohol and should receive vaccination against

HAV and HBV infections to prevent additional liver damage.

Treatment regimens for HCV have advanced considerably over the last 5 to 10 years with the development of individualized treatment algorithms based on genotype of the virus and response rates at various times during therapy. More recently, the development of a genetic marker for interferon sensitivity (IL28B), as well a marker for the risk of hemolysis with ribavirin, allowed further refining of individualized treatment pathways. Treatment of HCV (unlike HBV) can eradicate the virus and hence is a much more attractive proposition. More recent studies identified powerful viral suppressing polymerase and protease inhibitors which, when used in interferon-free regimens, produce viral clearance in those with difficult-to-treat genotypes and those who have failed therapy previously. The direct-acting antiviral agents (DAA's) have not yet been approved for children but pediatric trials are underway. The decision to treat is based on a number of factors; treatment requires close monitoring and hence should only be undertaken by those experienced in treating children. Treating those with favorable viral genotype and IL28B is expected to lead to viral eradication in greater than 80% of patients. Recommendations of the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition for the Management of Children with Hepatitis C were recently published.

Treatment of hepatitis E is supportive. Prevention rests on improving hygiene; however, a recombinant peptide vaccine was developed and seems to be safe and highly effective in a high-risk population. Further testing in low-risk populations and long-term efficacy is awaited.

### Autoimmune Hepatitis

Prednisone is a potent anti-inflammatory agent usually used as first-line therapy in autoimmune hepatitis. Because of its side effects, particularly on growth, a second immunosuppressive, azathioprine is often added. This allows a reduction or complete weaning of the prednisone. Some children who are refractory to azathioprine and steroids have responded to cyclosporine or tacrolimus.

Prednisone is begun in a dosage of 2 mg/kg/day (maximum 60 mg daily). When evidence of improvement is seen, the prednisone dosage may be tapered at weekly intervals to a dosage that achieves and maintains clinical and biochemical remission. Azathioprine (1–2 mg/kg/day) may be added after evidence of improvement. Toxicity of azathioprine (eg, hematopoietic toxicity) must be monitored for, particularly in children with thiopurine S-methyl-transferase deficiency. The latter can be diagnosed by PCR for the major mutations or by assays of enzyme activity. In addition, adequacy of thiopurine exposure and avoidance of toxicity may be determined by measuring thiopurine metabolites where available. Remission is defined as absence of clinical symptoms, an aminotransferase level no more than 2 times normal, decreasing serum gamma globulin levels, and resolution of the aggressive histologic appearance on a liver biopsy specimen. Duration of therapy, once remission is achieved, is controversial. Generally, once remission is achieved, steroids may be tapered gradually. Long-term treatment with a low-dose steroid or azathioprine is often required.

Clinical remission generally occurs within 3 to 6 months, biochemical remission within 6 to 12 months, and histologic remission within 12 to 24 months. During the steroid taper, the child must be watched at 2- to 4-week intervals for approximately 3 months for evidence of early recurrence of disease. If a recurrence does not manifest within that time, the frequency of observation can be decreased. At least 80% of children seem to achieve initial remission, and although relapses are common, long-term control is usually achieved with continuous immunosuppressive therapy. The child with autoimmune hepatitis and fulminant hepatic failure poses a difficult therapeutic problem. Prednisone and azathioprine have been used in this situation with success; however, liver transplantation may be necessary for survival. The long-term outcome of chronic active hepatitis has been evaluated in several pediatric studies. Most children are likely to have a prolonged survival on minimal long-term immunosuppression.

### Drug-Induced Hepatitis

The profound effects of acetaminophen toxicity can be treated with intravenous *N*-acetylcysteine. In all other cases of suspected drug-induced hepatitis, supportive care is recommended along with discontinuation of the suspected drug.

### Metabolic Liver Disease

The aim of therapy in Wilson disease is copper chelation in a controlled manner. The first-line therapy is penicillamine in most cases; however, penicillamine has significant side effects, including allergies and renal disease, and therapy needs to be closely monitored. Triethylene tetramine hydrochloride (trientine) has been effective in the same dose as penicillamine and is associated with milder side effects. Tetrathiomolybdate in a more stable form recently became available and may be the preferred treatment for neurologic Wilson disease with better control of free serum copper. Zinc may be used as initial therapy in children without clinical disease who are diagnosed incidentally on family screening.

There is no specific therapy for  $\alpha_1$ AT deficiency, and liver transplantation should be considered for end stage liver disease. Carbamazepine was recently shown to decrease the hepatic load of mutant  $\alpha_1$ AT protein and improve fibrosis in a mouse model. This therapy is currently undergoing evaluation in humans. Dietary restriction of galactose is the treatment of choice for galactosemia. Tyrosinemia may be treated with a phenylalanine and tyrosine-restricted diet together with nitisinone ([2-nitro 4-trifluoromethyl benzoyl]-1, 3-cyclohexanedione). Nitisinone is an inhibitor of an early enzyme in the tyrosine degradation pathway and is thought to prevent the accumulation of toxic products, resulting in a clinical improvement in most patients. Although costly, it has been proposed as an alternative to liver transplantation. Whether it will decrease the risk of developing hepatocellular carcinoma remains to be determined. Bile acid replacement therapy is the treatment of choice for inborn errors of bile acid synthesis. Progressive familial intrahepatic cholestasis 1, 2, and 3 have no specific therapy apart from supportive treatment. Liver transplantation may be required for end-stage liver disease. Ursodeoxycholic acid may be used in the treatment of liver disease secondary to cystic fibrosis and may halt disease progression.

### Fulminant Hepatic Failure

Fulminant hepatic failure in children needs to be managed in a setting with liver transplantation expertise. The requirements of liver support must be balanced with the management of fluids, nutrition, and encephalopathy, which is a late and ominous finding in children. It is preferable to transfer a child with severe hepatitis early before intensive care management is required.

### Liver Transplantation

Liver transplantation has improved the outlook for children who have any of a wide variety of severe liver diseases both in terms of mortality and morbidity. Apart from liver failure, indications may include growth failure and intractable itch from cholestasis. The management of the child before transplantation involves aggressive nutritional therapy and prevention of complications such as bacterial peritonitis and variceal hemorrhage, which may adversely affect outcome. Transplantation for chronic liver failure secondary to hepatitis B is complicated by almost 100% recurrence of infection; however, the use of HBIG followed by lamivudine improves the outcome. Recurrence of hepatitis C following transplantation is

around 90%, but transplantation is recommended because recurrent disease is mild in most adults. Recently, recurrence of HCV after transplantation in children has been reported as severe in a small series. Liver transplantation for all causes results in long-term survival rates of over 80% in children. Focus is now directed toward improving morbidity related to immunosuppressive medications and quality of life issues for children and their families.

### WHEN TO REFER

- Children with fulminant liver failure of any cause should be promptly referred to a specialist affiliated with a pediatric liver transplant center.
- Children with uncomplicated hepatitis A can usually be managed by a general pediatrician. However, children with chronic hepatitis B, C, or D should be referred to a pediatric gastroenterologist or infectious disease specialist for consideration for treatment.
- Children with metabolic liver disease, drug-induced hepatitis, or AIH should be referred to a pediatric specialist in metabolic disease or gastroenterology as appropriate.
- Fulminant hepatic failure, defined as a lack of a pre-existing liver disease and severe impairment of hepatic function as evidenced by the following laboratory abnormality: prolonged prothrombin time ( $>4$  seconds over control) that is unresponsive to large doses of vitamin K.
- HbsAg-positive serologic test in children 1 year of age or older.
- Anti-HCV positive serologic test in children 3 years of age or older.
- Any diagnosis of drug-induced hepatitis (unexplained elevation of serum aminotransferases or bilirubin in a child who is taking or recently took any medication).
- Any diagnosis of metabolic liver disease (unexplained elevation of serum aminotransferases or bilirubin in a child) and a positive screening test, such as low ceruloplasmin, low galactose-1-phosphate uridyl transferase, and positive urine-reducing substances.

### WHEN TO ADMIT

- Prolonged prothrombin time ( $>4$  seconds over control) or INR greater than 1.5 in a child with severe hepatitis of any cause
- Acute encephalopathy in a child with severe hepatitis of any cause
- Dehydration requiring intravenous fluid resuscitation in a child with severe hepatitis
- Gastrointestinal bleeding in a child with acute or chronic hepatitis

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Travel Information Center* (Web page), Centers for Disease Control and Prevention ([wwwnc.cdc.gov/travel/page/traveler-information-center](http://wwwnc.cdc.gov/travel/page/traveler-information-center))

### Medical Decision Support

- *Viral Hepatitis* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/ncidod/diseases/hepatitis/index.htm](http://www.cdc.gov/ncidod/diseases/hepatitis/index.htm))
- *Viral Hepatitis Serology Training* (online course), Centers for Disease Control and Prevention ([www.cdc.gov/hepatitis/Resources/Professionals/Training/SerologyStart.htm](http://www.cdc.gov/hepatitis/Resources/Professionals/Training/SerologyStart.htm))

### AAP POLICY

Advisory Committee on Immunization Practices and Centers for Disease Control and Prevention. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States. *Pediatrics*. 2006;118(1):404. AAP endorsed ([pediatrics.aappublications.org/content/118/1/404](http://pediatrics.aappublications.org/content/118/1/404))

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## Chapter 266

## HERPES INFECTIONS

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### DEFINITIONS

Herpesvirus hominis, or herpes simplex virus (HSV), is among the most common agents infecting humans; although 85% to 95% of primary infections may be asymptomatic, in certain circumstances infections can be fatal. HSV is a DNA virus with a protein coat. After an incubation period of 2 to 12 days, the primary infection, if apparent, is usually heralded by constitutional symptoms such as malaise, fever, anorexia, and irritability, and by the classic herpetic enanthem or exanthem. Lesions are painful vesicles, usually several millimeters in diameter, on an erythematous base. After healing and recovering from the initial infection, the infection is not eradicated. Rather, the organism is presumed to remain in a latent phase in the ganglion cells or nerves innervating the region of localized infection. Various stimuli, including sunlight, fever, physical or emotional trauma, or menses, may induce a recurrent infection. Recurrent episodes demonstrate a similar vesicular eruption in the same general anatomic



area as the primary eruption but without concomitant constitutional symptoms.

Pathologically, HSV infection is characterized by the presence of multinucleated giant cells and eosinophilic intranuclear inclusions seen in tissue scrapings taken from the base of a vesicle and stained with Giemsa (Tzanck preparation), Papanicolaou, or hematoxylin-eosin techniques. Herpes infections can be divided definitively into 2 immunologic types that correlate with clinical manifestations—herpes simplex virus type 1 (HSV-1), which tends to be associated with disease above the waist, and herpes simplex virus type 2 (HSV-2), associated with disease below the waist, with sexually related transmission, or with disease acquired neonatally.

## EPIDEMIOLOGIC FACTORS

Studies have shown a sharp rise in the prevalence of antibodies to HSV-1 between 1 and 4 years of age and a slower rise of antibody acquisition between 5 and 14 years of age. Current data suggest that more than 25% of children in the United States have positive serology for HSV-1 by age 7 years.

According to research, HSV-1 seroprevalence has been decreasing in the last few years where HSV-2 (see epidemiologic data in the following text) has been on the rise. It is hypothesized that the decrease in HSV-1 is related to improved hygiene, which has led to delayed (or possibly reduced) exposure to the virus, while the rise of HSV-2 is a result of changes in sexual behavior.

HSV-2 antibody is now detectable in at least 1 of 5 persons 12 years or older nationwide. In 2002, a study demonstrated that 80% to 100% of adults in lower socioeconomic groups, in locations where crowding probably plays an important epidemiologic role, demonstrate antibodies to HSV-1; 30% to 40% or more may be positive for HSV-2. Of persons of higher socioeconomic circumstances, 21% demonstrate antibodies to HSV-2.

## HERPES SIMPLEX VIRUS TYPE 1

### Epidemiologic Factors

Transmission of HSV-1 is presumed to occur via person-to-person respiratory spread and probably involves close contact, such as kissing an infected person. Transmission can occur whether or not the source is symptomatic with an apparent vesicular lesion at the time. The clinical manifestation varies with site of entry, and the clinical diagnosis rarely requires laboratory confirmation.

### Clinical Manifestations

#### Gingivostomatitis

Acute gingivostomatitis is the most common form of HSV-1 seen in children, although about 10% of cases are caused by HSV-2. The peak incidence in the pediatric population is between 6 months and 5 years of age, with a second peak occurring in the early 20s. The disease is characterized by an abrupt onset of fever, irritability, poor feeding, and, 1 to 2 days later, very tender, red, friable mucous membranes surrounding 2- to 3-mm white ulcerations, and severe halitosis. The

vesicular stage is rarely seen, but large, tender anterior cervical and submandibular lymphadenopathy is common. The duration of the illness varies from 5 to 14 days, and the severity ranges from mild to so severe that oral intake becomes negligible, and hospitalization for intravenous hydration may be required. Although this condition is usually benign, bacteremia caused by *Kingella kingae*, part of the normal flora of the mouth, has been observed in a few cases and has been speculated to progress to focal skeletal infection such as osteomyelitis.

### Herpes Labialis

Herpes labialis (or cold sores) represents the most common manifestation of HSV reactivation in the trigeminal ganglia. The most common location of the lesions is on the vermilion border and adjacent skin of the lips, although lesions can occur on the chin, cheeks, and skin around the nose. The lesions usually crust and heal without scarring in 7 to 10 days, but recurrence at the same site is extremely common.

### Herpetic Whitlow

Herpetic whitlow (or herpetic paronychia) is a less common presentation of HSV that may occur as a result of auto-inoculation in children with orofacial herpes and is common in thumb-suckers. It is a result of inoculation at the site of local trauma. This condition is extremely painful and involves herpetic infection of a digit. Although the sore may resemble a bacterial paronychia, it should not be incised. While bacterial paronychia is a confined local infection, herpetic whitlow is sometimes associated with systemic symptoms such as fever and malaise, especially in infants. The disease usually subsides completely within 3 weeks. Unlike bacterial paronychia, which is identified by the presence of suppurative fluid, the lesion of herpetic whitlow typically contains clear fluid in the initial stage that may become cloudy after a week due to accumulation of white blood cells in the lesion.

### Ocular Herpes

Ocular herpes is among the most common causes of corneal blindness in the United States and is estimated to be the cause of 40,000 new cases of severe monocular visual impairment or blindness annually in the world. An estimated 500,000 people in the United States have ocular HSV. HSV-1 has much greater association with ocular pathology than HSV-2 and can manifest as conjunctivitis, iridocyclitis, acute retinal necrosis, and keratitis. However, the primary infection usually involves acute keratoconjunctivitis with intense swelling of the lids but without exudates. Typical herpetic vesicles are often found on the skin surrounding the involved eye. Recurrent disease can be even more severe and may involve superficial or deep epithelial ulceration, stromal damage, or uveitis. Fortunately, treatment is available (see the discussion on treatment in this chapter), but these children should always be referred to an ophthalmologist for care. Indeed, the pediatrician should be aware that devastating results can occur with the use of topical steroid preparations in a probable case of ocular herpes. This

circumstance underlines the necessity of an ophthalmologic consultation before prescribing topical corticosteroids for any use in the eye.

### **Herpes and Sports/Herpes Gladiatorum**

Certain sport activities, such as wrestling and rugby, that result in close skin contact, may increase the risk of HSV skin infection. Wrestlers may acquire herpes gladiatorum (HG) as a result of viral shedding from an infected opponent. In National Collegiate Athletic Association (NCAA) Division I Wrestling, researchers estimate an incidence as high as 20% to 40%. Transmission usually takes place via skin-to-skin contact through areas of skin breakdown.

While these conditions are fairly benign and self-limited, complications such as ocular involvement (blepharitis, follicular conjunctivitis, keratitis, scleritis, and urethritis) can arise and have been described in up to 8% of players in wrestling camps. This is a specific concern because research has shown that the face is the most common site of infection among wrestlers. Perhaps the most serious complication is dendritic keratitis with subsequent corneal scarring, which may lead to permanent blindness.

### **Differential Diagnosis**

The most common ulcerative enanthem to be considered in the differential diagnosis is Coxsackievirus A herpangina. This infection results in lesions very similar in appearance to HSV infection, but is located in the posterior oral cavity, as contrasted with the anterior clustering of herpetic lesions. In addition, Coxsackievirus infections tend to occur during the warm summer months and are less common in the winter season. Other infections to include in the differential diagnosis of HG are localized bacterial, viral, or fungal infections such as impetigo, molluscum and tinea. A critical difference that could help in differentiating among these possibilities is the extensive regional adenopathy observed in HG and the propensity of these lesions to cross the hairline onto the scalp. Infections with varicella, cytomegalovirus, and syphilis should be considered as well, in addition to autoimmune diseases such as Behcet syndrome, Reiter syndrome, and inflammatory bowel disease. Systemic lupus erythematosus and cyclic neutropenia might also be considered in a broader differential. However, with these conditions, the remainder of the clinical presentation would direct the diagnostician to culture for herpes, confirming the final diagnosis if necessary.

### **Complications**

Although HSV-1 infections are usually self-limited, certain human hosts are at more serious risk for contracting or developing severe disease with HSV-1 than are others. Individuals who have deficiencies in cell-mediated immunity, those undergoing immunosuppressive therapy for cancer or transplantation, and those who are extremely malnourished may be more likely to show serious disseminated disease.

Eczema herpeticum is a severe form of a superimposed HSV skin infection in a patient with existing

lesions of atopic dermatitis or other chronic skin diseases. This condition can vary in severity from mild to fatal, and the patient usually experiences constitutional symptoms such as fever and malaise. The lesions, which mostly appear on the head, neck, and trunk, are vesicular and seem to be at the same stage. Wide areas of skin can become denuded, with large fluid, protein, and electrolyte losses, which potentially may be life threatening. Secondary bacterial infection may complicate the condition. Recurrences tend to be milder than the initial infection.

HSV-1 is considered the most common cause of sporadic, fatal encephalitis, with 2 peaks of illness—first between 6 months and 20 years of age and second in patients older than 50 years. Overall, there are 250 to 500 cases per year. The disease is characterized by fever and personality change, and often involves seizures. A rapidly progressive encephalopathy culminates in death in 1 to 2 weeks in more than 70% of untreated cases, and of those patients who do survive, few avoid significant neurologic morbidity. Many will develop developmental delay, behavioral impairment, language disturbance, focal motor deficits, and epilepsy that is often difficult to control. The infection is most often localized to the frontotemporal area, which correlates with symptoms and signs of aphasia, personality changes, and focal seizures. Currently, HSV DNA by polymerase chain reaction (PCR) in cerebrospinal fluid is the most sensitive test to confirm the diagnosis. Treatment has improved the prognosis of this disastrous condition among children, but is most effective when initiated early in the course of the disease.

## **HERPES SIMPLEX VIRUS TYPE 2**

### **Epidemiologic Factors**

As a result of the increase in sexual activity among young adolescents in recent years, pediatricians have been faced with the challenge of diagnosing and treating all types of sexually transmitted infections. The frequency of infection is high and underestimated by clinical history in the adolescent population. The latest HSV-2 data by the Centers for Disease Control and Prevention from March 2010, indicate that the overall national HSV-2 prevalence in persons 14 to 49 years old is as high as 16.2%, but even higher in black women, where it is as high as 39.2%. Genital HSV-2 is of increasing concern to pediatricians not only because of its incidence in adolescent patients, but also because of the potential harm to the offspring of infected mothers.

### **Clinical Manifestations**

Clinically, HSV-2 usually manifests as typical herpetic vesicles on the penile shaft, prepuce, or glans penis in the male patient, and on the labia minora or labia majora, mons, or nearby skin or within the vagina in the female patient. Primary infection is accompanied by significant local pain, burning, or paresthesia and constitutional symptoms of fever and malaise, dysuria, and inguinal lymphadenopathy; recurrent bouts are less severe than initial occurrences. The 5% to 10% of cases of genital herpes associated with HSV-1 are thought to result from orogenital sex.

### Evaluation

Viral culture is, in general, the most sensitive method of diagnosis, but requires several days, depending on the size of the inoculum, for a definitive result. Vesicles, stool, urine, and mucosal surfaces may be used as sites to obtain the culture sample. When lesions are available for scraping, direct detection methods, including fluorescent antibody and immunoperoxidase assays, give a rapid answer, but with lower sensitivity; therefore, a viral culture is still required for confirmation of a negative finding. Tzanck test and Papanicolaou stains are neither specific nor sensitive enough to serve as a screen for HSV. PCR of cerebrospinal fluid is highly specific and sensitive and can discriminate between the HSV-1 and HSV-2 in cerebrospinal fluid; it is the diagnostic method of choice in HSV encephalitis.

## NEONATAL HERPES

### Epidemiologic Factors

Although most neonatal herpes infections are caused by HSV-2, antibodies to HSV-1 are associated with 25% of cases. The prevalence of HSV-2 in healthy American women ranges from 10% to 60%. As many as 50% to 60% of women from lower socioeconomic groups in the United States have antibodies to HSV-2. This proportion translates to an estimated 1,500 to 2,200 infants per year in the United States infected with HSV. Postnatal transmission from a caregiver accounts for approximately 10% of cases.

Infection occurs most commonly during the second stage of labor while the neonate moves through an infected birth canal. Transplacental transmission of HSV, though uncommon, can occur and may induce spontaneous abortion or, in rare cases, congenital anomalies in newborns. In a very small percentage of cases, infection takes place as a result of postnatal exposures to parents or health care workers.

Because HSV is not a reportable disease, the estimated incidence of neonatal herpes in the United States varies with sampling technique and between different populations, ranging between 8 and 60 per 100,000 live births.

The greatest risk of neonatal HSV infection occurs when the mother has contracted primary herpes 2 to 4 weeks before delivery, although the disease may be transmitted to the infant in recurrent cases with or without a clinically detectable herpetic lesion. Transmission of HSV infection to the fetus is most often related to shedding of the virus at the time of delivery. The risk of neonatal herpes for a child born vaginally to a mother with primary genital infection occurring close to delivery is estimated to be 25% to 60%. This is in contrast to a neonate whose mother is shedding HSV because of reactivation of infection acquired during (or before) 20 weeks of gestation, where the likelihood of transmission is significantly reduced and is estimated to be 2% or less. Distinguishing primary versus recurrent infection may be impossible because both may be asymptomatic. Indeed, approximately 75% of infants with HSV infection are born to women without a history of physical or symptomatic evidence of infection. Risk factors for neonatal disease include

a history of a first HSV infection during the third trimester, invasive monitoring of the fetus, delivery at less than 38 weeks of gestation, and maternal age younger than 21 years. Neonatal HSV disease must always be included in the differential diagnosis when a newborn or infant exhibits a skin rash ranging from vesiculopapular to vesiculoulcerative.

### Clinical Manifestations

The presentation of neonatal herpes, similar to other infections in the neonatal period, is nonspecific, at least initially. Presentation is usually acute, with signs and symptoms occurring in the first week or so of life, but can uncommonly occur as late as 3 or 4 weeks of age. Symptoms may include poor feeding, vomiting, fussiness or lethargy, fever or hypothermia, jaundice, and hepatosplenomegaly. Seizures, cyanosis, and apnea may also occur. Most infants, though notably not all, who have neonatal herpes eventually demonstrate a vesicular rash as either individual lesions or clumps of vesicles.

Classically, neonatal HSV infection is classified into three categories based on clinical manifestations.

1. Infants who have disseminated disease involving visceral organs with or without central nervous system (CNS) involvement: These cases comprise up to 25% of neonatal HSV infections and are considered the most lethal, with greater than 80% mortality without treatment and 31% mortality even with prompt administration of high-dose acyclovir. In those patients, AST elevation of more than 10 times the upper limit of normal has been shown to be a poor prognostic sign. Infants who have HSV-1 disseminated infection have poorer outcomes than those who have HSV-2 infection. In disseminated infection, the liver and lungs tend to be most involved, and hepatoadrenal necrosis is virtually always found. Many survivors develop microcephaly, hydrocephalus, intellectual disability, or seizures.
2. Infants with CNS abnormalities without involvement of viscera: These cases represent 30% of neonatal infections. This group of neonates with HSV-2 infections have poorer long-term outcomes, including developmental delay, epilepsy, blindness, or cognitive disabilities. Mortality exceeds 50%, and morbidity exceeds 90% without antiviral therapy. With appropriate antiviral therapy, mortality has fallen to 6%, but morbidity remains high.
3. Infants whose skin, eyes, or mouth (SEM) are involved, but not the CNS or viscera: These cases present with isolated vesicular lesions only and represent 45% of the total. Infants who had SEM involvement before antiviral drugs became available were not expected to die, and only 20% to 30% were left neurologically impaired; many who seemed to have SEM involvement, however, went on to develop disseminated or CNS involvement and to suffer disastrous consequences.

### Prevention

The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists have developed joint guidelines for managing labor in women who have a history of genital herpes. These



guidelines suggest expeditious cesarean delivery if active genital lesions are present at the time of delivery or symptoms that might indicate imminent outbreak, such as vulvar pain or burning, are present. Scalp electrodes should be avoided when the mother is suspected of having active genital HSV infection. In addition, isolation criteria are delineated to protect healthy infants from their HSV-infected mothers, other infected infants, or infected staff. The guidelines also recommend that women with active recurrent genital herpes at or beyond 36 weeks of gestation should be offered suppressive viral therapy, although there are limited scientific efforts to support this plan.

Currently, it is unclear if the risks associated with preterm birth outweigh the risks of HSV infection in women with premature rupture of membranes. Cesarean delivery is not recommended in women with a history of HSV infection without active genital disease during labor.

Neither routine antepartum genital HSV cultures in asymptomatic patients with recurrent disease nor routine HSV screening of pregnant women is recommended.

## TREATMENT

Although no universal cure exists for herpes infections, the prognosis for its many syndromes has improved greatly with currently available therapies. Since the 1980s, acyclovir has become the first-line treatment of choice, with more recent work demonstrating some decreased mortality with prolonged high-dose (60 mg/kg/day divided every 8 hours) intravenous acyclovir.

Treatment should always begin early when there is suspicion of disease. In a multicenter, retrospective cohort study done between January 2003 and 2009, treatment with early acyclovir therapy (within 1 day after hospital admission) was associated with a statistically significant lower mortality rate in comparison to cases in which treatment was initiated after 1 day (6.6% vs 9.5%). Empiric treatment is, therefore, recommended, especially given the low risk for serious side effects of acyclovir.

Current therapy not only emphasizes early treatment, but evidence now suggests that prolonged therapy with oral acyclovir may result in improved long-term outcomes. In a recent study, suppressive therapy with oral acyclovir for 6 months was associated with improved neurodevelopmental outcomes when compared to placebo for neonatal HSV survivors with CNS involvement.

Oral antiviral therapy for first episodes of genital herpes shortens the duration of symptoms and viral shedding and is indicated for at least a 10-day course (Box 266-1). If begun within 1 day of the onset of the first lesion, then episodic therapy may limit the duration and severity of recurrences as well. The same medications have been shown to decrease recurrences by 70% to 80% when used as chronic suppressive therapy in patients with particularly severe or frequent recurrences, though the cost of such therapy may be a limiting factor in its usefulness. Therapy for immunosuppressed individuals with genital HSV may warrant hospitalization and the use of intravenous acyclovir.

### BOX 266-1 Recommended Treatment Regimens for Genital Herpes Infections

#### FIRST CLINICAL EPISODE OF GENITAL HERPES

- Acyclovir 400 mg orally 3 times a day for 7–10 days (max dose in children at 80 mg/kg/24 hr divided q6h to q8h), OR
- Famciclovir 250 mg orally 3 times a day for 7–10 days, OR
- Valacyclovir 1 g orally twice a day for 10 days

Note: Treatment may be extended if healing is incomplete after 10 days of therapy.

#### EPISODIC THERAPY FOR RECURRENT GENITAL HERPES

- Acyclovir 200 mg orally 5 times a day for 5 days, OR
- Acyclovir 400 mg orally 3 times a day for 5 days, OR
- Acyclovir 800 mg orally twice a day for 5 days, OR
- Famciclovir 125 mg orally twice a day for 3–5 days, OR
- Valacyclovir 500 mg orally twice a day for 3 days

#### SUPPRESSIVE THERAPY FOR RECURRENT GENITAL HERPES

- Acyclovir 800–1,000 mg a day, divided in 2–5 times a day for up to 1 year (max dose in children at 80 mg/kg/24 hr divided q6h to q8h), OR
- Famciclovir 250 mg orally twice a day for 1 year, then reassess, OR
- Valacyclovir 500–1,000 mg orally once a day for a year then reassess for recurrences. Patients with <9 recurrences per year may be dosed at 500 mg/dose PO once a day for a year, OR

Derived from Engorn B, Flerlage J. *The Harriet Lane Handbook*. 20th ed. Philadelphia, PA: Elsevier Saunders; 2015: 670–671, 781, 968–969.

Treatment for other herpetic syndromes has also been evaluated. Oral acyclovir can shorten the duration of herpetic gingivostomatitis in children by 6 days if begun within the first 72 hours of illness, with the potential for significant cost savings because of the frequent need for intravenous hydration among children with this syndrome. Only modest efficacy has been shown with treatment of episodic oral herpes; topical antiviral therapy for recurrences has been demonstrated to decrease the duration of symptoms by 1 day or less. Topical antivirals are used to treat superficial keratitis effectively; oral acyclovir may be beneficial in situations of recurrent ocular lesions. Oral antivirals have been shown to prevent herpes gladiatorum at wrestling camps.

Intravenous acyclovir remains the mainstay of treatment for herpes encephalitis. For infants younger than 3 months, the treatment regimen should be continued for at least 21 days; for children older than 3 months, treatment should last 14 to 21 days. Acyclovir has significantly decreased mortality from this condition but has only modestly affected morbidity. Therapy



must be initiated promptly to ensure the most favorable outcome.

Acyclovir resistance has been shown to differ significantly with type of infection and immunologic status of the patient (more common in immunocompromized patients), but this resistance has been repeatedly shown to be fairly low and stable in immunocompetent patients and without adverse clinical outcome. Despite multiple efforts to develop an effective vaccine against HSV, no vaccine exists at this time.

### WHEN TO REFER

- All infants who are thought to have neonatal herpes should be considered potentially critically ill and would benefit from subspecialty involvement to include critical care or neonatology and infectious disease, among others, as indicated.
- Regardless of age, patients who have known or suggested immunosuppression who contract herpes may benefit from subspecialty consultation.
- Children in whom ocular steroid therapy is considered may benefit from ophthalmologic consultation to rule out any possibility of ocular herpes infection.

### WHEN TO ADMIT

- Infants who have suspected or confirmed neonatal herpes must be carefully monitored and treated with intravenous acyclovir.
- All individuals thought to have herpes encephalitis must be hospitalized and treated expectantly with intravenous acyclovir.
- Immunosuppressed individuals with herpes infections may require intravenous antiviral therapy and will require hospitalization.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Caring for Cold Sores* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/skin/Pages/Caring-For-Cold-Sores.aspx](http://www.healthychildren.org/English/health-issues/conditions/skin/Pages/Caring-For-Cold-Sores.aspx))
- *Genital Herpes* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/std/herpes/stdfact-herpes.htm](http://www.cdc.gov/std/herpes/stdfact-herpes.htm))
- *Herpes Simplex Virus (Cold Sores)* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/skin/Pages/Herpes-Simplex-Virus-Cold-Sores.aspx](http://www.healthychildren.org/English/health-issues/conditions/skin/Pages/Herpes-Simplex-Virus-Cold-Sores.aspx))
- *Types of Sexually Transmitted Infections* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/sexually-transmitted/Pages/Types-of-Sexually-Transmitted-Infections.aspx](http://www.healthychildren.org/English/health-issues/conditions/sexually-transmitted/Pages/Types-of-Sexually-Transmitted-Infections.aspx))

### AAP POLICY

American Academy of Pediatrics Committee on Sports Medicine and Fitness. Medical conditions affecting sports participation. *Pediatrics*, 2008;121(4):841–848. Reaffirmed June 2014 ([pediatrics.aappublications.org/content/121/4/841](http://pediatrics.aappublications.org/content/121/4/841))

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### Chapter 267

## HUMAN HERPESVIRUS-6 AND HUMAN HERPESVIRUS-7 INFECTIONS

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### INTRODUCTION

Human herpesviruses type 6 (HHV-6) and type 7 (HHV-7) are ubiquitous, lymphotropic,  $\beta$ -herpesviruses. They are 2 of the known causative agents of roseola infantum, also known as exanthem subitum. It is now understood that in otherwise healthy children, the spectrum of diseases associated with HHV-6 and HHV-7 is far broader than the benign illness of roseola. Furthermore, these viruses commonly reactivate in the immunocompromised host and can potentially be associated with severe disease in these patients.

### CLASSIFICATION

Both HHV-6 and HHV-7 are enveloped, double-stranded DNA viruses that belong to the *Roseolovirus* genus. They were the sixth (HHV-6) and seventh (HHV-7) herpesviruses identified. They can be distinguished from other herpesviruses by DNA hybridization or by reactions with virus-specific monoclonal antibodies.

Two subgroups of HHV-6 are distinguishable by their genetic and epidemiologic characteristics: variant A and variant B. Although the nucleotide sequences are 90% identical, HHV-6B is the variant typically associated with postnatal childhood illnesses, such as roseola. HHV-6A has rarely been associated with disease. The frequency and scope of HHV-7 infections are unclear.

## EPIDEMIOLOGY

Both HHV-6 and HHV-7 are ubiquitous human infections worldwide, with primary infection occurring in childhood. Humans are the only natural hosts. Most children are seropositive for HHV-6 by 2 years of age, with a peak period of acquisition occurring between 6 and 9 months of age (median of 8 months). In a prospective study of 277 children followed from birth through 24 months of age, primary HHV-6 infection was symptomatic in more than 90% of cases and occurred in 40% of children by 12 months of age, increasing to more than two-thirds by 24 months of age. HHV-7 acquisition also occurs in early childhood, although later than HHV-6 and at a slower rate. Nearly all adults are seropositive for both HHV-6 and HHV-7, and maternally derived antibodies are uniformly detected in infants during the first week of life. Congenital infection with HHV-6 but not HHV-7 occurs in approximately 1% of newborn infants.

Like all human herpesviruses, HHV-6 and HHV-7 establish lifelong latency after initial exposure. During the acute phase of the primary infection, they can be isolated from peripheral blood mononuclear cells (PBMCs) and from saliva. Viral DNA can subsequently be found in multiple body sites, including PBMCs, saliva, lung, skin, brain (only HHV-6), and human milk (only HHV-7). Virus is shed in the saliva of asymptomatic individuals and is likely transmitted to susceptible children by this route.

The incubation period is approximately 9 to 10 days for HHV-6 but is not known for HHV-7. Most HHV-6 and HHV-7 infections are sporadic, although family and institutional outbreaks of roseola have been occasionally reported. There is no seasonality to infection. Having at least one older sibling is a risk factor for earlier acquisition of HHV-6.

## CLINICAL MANIFESTATIONS

Clinical manifestations have been well defined for HHV-6. The spectrum of disease remains unclear for HHV-7. Nevertheless, the rate of infection with minor or no signs or symptoms is likely underestimated. Following primary infection, both viruses remain latent and may reactivate. In immunocompetent people, the

manifestations of reactivation are unclear. However, viral reactivation in the immunocompromised host can be associated with severe disease.

### Nonspecific Viral Illness

Frequently, HHV-6 infections manifest as undifferentiated febrile illness and account for about 20% of all emergency department visits for fever in infants 6 to 12 months of age. Body temperature of 39°C to 40°C or higher, typically lasting 5 to 7 days, and irritability are common. In fact, children with HHV-6 infection have significantly higher temperatures, appear sicker, and are more irritable than age-matched children with acute febrile illnesses attributed to other causes. The abrupt onset of high fever is characteristic. Additional symptoms may include fussiness, nonspecific upper respiratory symptoms such as cough or rhinorrhea, inflamed tympanic membranes, rash, vomiting, and diarrhea (see Table 267-1).

In contrast to HHV-6, primary infections with HHV-7 are less frequently recognized. Most primary HHV-7 infections are likely asymptomatic or mild and nondistinctive. In a prospective study, 53% of children were seropositive for HHV-7 by 24 months. However, acute HHV-7 infection, defined by the presence of viremia, was infrequent and detected in only 1% of children presenting with an acute illness. Of those with viremia, 77% had primary and 23% had reactivated HHV-7 infections. High fever followed by seizures, nonspecific febrile illness, upper respiratory tract infections, and gastroenteritis were the most common presenting diagnoses. Whether HHV-7 is the only causative agent for these illnesses or the clinical manifestations result from the ability of HHV-7 to reactivate HHV-6 is a matter of debate.

### Roseola

Roseola infantum—also known as exanthem subitum, 3-day fever, sixth disease, and pseudorubella—is a self-limited, acute illness characterized by fever for 3 days followed by a rash. It was first described in the early 1900s, but HHV-6 and HHV-7 were discovered in 1986 and 1990, respectively. Approximately one-fourth of primary HHV-6B infections in young children in the United States manifest as roseola. HHV-7 causes a

**Table 267-1** Relative Frequency of Presenting Symptoms in Children With Primary HHV-6 and HHV-7 Infections

	HHV-6	HHV-7
Median age (months)	8	26
Fever	++++	++++
Irritability	+++	++++
Upper respiratory symptoms	++/+++	+
Rash	++	+
Vomiting/diarrhea	++	++
Seizures	+	+++

Key: + = ~0%–25%; ++ = ~26%–50%; +++ = ~51%–75%; ++++ = ~76%–100%.

Data derived from Hall CB et al. Human herpesvirus-6 infection in children. A prospective study of complications and reactivation. *N Engl J Med.* 1994;331:432–438; Caserta MT et al. Primary human herpesvirus 7 infection: a comparison of human herpesvirus 7 and human herpesvirus 6 infections in children. *J Pediatr.* 1998;133:386–389; Zerr DM et al. A population-based study of primary human herpesvirus 6 infection. *N Engl J Med.* 2005;352:768–776; Hall CB et al. Characteristics and acquisition of human herpesvirus (HHV) 7 infections in relation to infection with HHV-6. *J Infect Dis.* 2006;193:1063–1069.

similar illness, which may explain the occasional second episode of roseola in a young child. Recognition of the illness is based almost entirely on the observation of a classic clinical course.

Typically, the disease begins with a sudden onset of high fever that usually lasts 3 to 4 days and is often accompanied by irritability. The fever resolves dramatically while an erythematous maculopapular rash simultaneously appears initially on the face, neck, or trunk and then spreads to the extremities. It is usually not painful and does not itch. The macules/papules do not blanch or blister and may be surrounded by a light halo. The rash fades within hours to 2 days. With defervescence, the child seems to have recovered, despite the rash.

The disease may be accompanied by painless posterior auricular, suboccipital, or cervical lymphadenopathy, slight eyelid edema, and Nagayama spots, which are erythematous macules appearing on the soft palate and base of the uvula. Less common features include cough, rhinorrhea, or bulging fontanel. Bulging fontanel is present in one-fourth of patients.

### Central Nervous System Manifestations

#### Seizures

Both HHV-6 and HHV-7 have been associated with febrile seizures and status epilepticus in children. Moreover, some evidence suggests that HHV-6B may play a role in certain types of epilepsy. Overall, primary HHV-6 infection has been found in 10% to 40% of children with febrile seizures within the first 2 years of life and in one-third of patients with febrile status epilepticus. In addition, HHV-6 infection appears to be associated with more severe, atypical, prolonged, and recurrent seizures. Compared with HHV-6, febrile seizures appear to be more common in children with HHV-7 infections. Nevertheless, it is unclear how HHV-6 and HHV-7 contribute to the pathogenesis of febrile seizures. Infections with these viruses may simply serve as common febrile illnesses during the age of highest susceptibility. One small study of children with a first or second febrile seizure showed that the incidence of primary HHV-6 infection was comparable to that in febrile age-matched children without seizures. Additionally, a large prospective study of children presenting with acute febrile illnesses showed similar rates of seizures in those with and without HHV-6.

#### Other Neurologic Manifestations

Occasional cases of meningitis and severe encephalitis attributable to HHV-6 and HHV-7 infections have been reported in children, often associated with long-term sequelae. HHV-6 has also been implicated in cases of progressive multifocal leukoencephalopathy, multiple sclerosis, and other neurologic diseases. In some patients, HHV-6 has been found in brain tissue by immunohistochemical staining. Nevertheless, causation has not been established, and further research is needed.

Cerebrospinal fluid (CSF) abnormalities associated with HHV-6 central nervous system (CNS) disease are infrequent and similar to those found in other infectious causes of meningitis or encephalitis. Brain magnetic resonance imaging (MRI) may be negative or show involvement of the white matter or multifocal

involvement of the hippocampus, amygdala, or temporal lobe. The diagnosis of HHV-6 or HHV-7 as causative agents of CNS disease is often made by the identification of viral DNA in the CSF. However, because these viruses may establish latency, HHV-6 or HHV-7 DNA has been detected in the CSF of infected children with and without seizures.

### Other Manifestations in Immunocompetent Hosts

Different case reports implicate HHV-6 as a cause of chronic and acute hepatitis, ranging from mild to fulminant disease. Although some case reports have relied on seroconversion to define the causative role of HHV-6, others have identified HHV-6 DNA in liver biopsy specimens.

The differential diagnosis for mononucleosis-like illnesses in adults should include HHV-6, which accounts for about 9% of cases. It generally causes mild but prolonged symptoms, lasting up to 3 months.

Both HHV-6 and HHV-7 have been isolated from patients with many other conditions. Among these are pityriasis rosea, lichen planus, Gianotti-Crosti syndrome, and several other dermatologic diseases as well as drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome, immune thrombocytopenic purpura, aplastic anemia, myocarditis, and hemophagocytic syndrome. Because reactivation may occur during acute illnesses, causality of the viruses is difficult to ascertain. The role of HHV-7 in other diseases is even less clear than its association with roseola.

### Congenital Infection

Congenital infection appears to be uncommon. In a large prospective study, congenital HHV-6 infection, defined as viral DNA in cord blood, occurred in 1% of children. Interestingly, although most postnatally acquired HHV-6 infections are caused by the variant B virus, in one-third of the congenital cases the virus detected was HHV-6A. No cases of congenital HHV-7 infection have been reported.

Intrauterine transmission of HHV-6 may occur by either transplacental infection or chromosomal integration in germ cells. HHV-6 has the ability to integrate its genome into human chromosomes and can thus be inherited from one or both parents. Congenital infection exhibits no distinct features or clinical abnormalities in the neonate. It is not known whether clinical manifestations or long-term sequelae may subsequently develop. However, a recent study involving 57 infants with congenital HHV-6 infection demonstrated possible detrimental effects on neurodevelopment at 12 months of age compared with controls without infection.

### Infection in Immunocompromised Patients

Reactivation of HHV-6 may occur during periods of immunosuppression, particularly in patients with depressed T-cell function. Reactivation of HHV-6 has been associated with fever, rash, encephalitis, pneumonia, hepatitis, delayed engraftment, leukopenia, and thrombocytopenia early after transplantation when immunosuppression is highest, especially in hematopoietic stem cell transplant (HSCT) recipients.



Thus, it is challenging to ascertain whether symptoms in immunocompromised patients are directly attributable to HHV-6. Of those illnesses, limbic encephalitis (insomnia, short-term memory loss, hallucinations, and MRI abnormalities in the amygdala and hippocampus) is one of the best-documented manifestations. In addition, HHV-6 viremia has been implicated in graft-versus-host disease. Following solid-organ transplantation (SOT), overt clinical disease directly associated with HHV-6 occurs in less than 1% of patients, but the immunomodulatory effects of HHV-6 infection likely play a role in other associated diseases. As such, HHV-6 is associated with higher rates of rejection and invasive fungal infections, and HHV-6 and cytomegalovirus (CMV) codetection may indicate increased risk for severe CMV disease.

Disease caused by HHV-7 reactivation is not well characterized. Following HSCT, HHV-7 has been reported in cases of encephalitis and myelitis. Like HHV-6, the immunomodulatory effects of HHV-7 infection may predispose transplant recipients to opportunistic infections or severe CMV disease. However, clinical findings have been less frequently reported with HHV-7 than with HHV-6 reactivation. The role of HHV-6 or HHV-7 in human immunodeficiency virus (HIV) infection is inconclusive, with conflicting data regarding whether HHV-6 potentiates or inhibits HIV replication. HHV-6 infection does not seem to affect the progression of HIV to acquired immunodeficiency syndrome (AIDS).

## DIAGNOSIS

Except for roseola, which is the only manifestation that is easily recognized clinically, the diagnosis of HHV-6 and HHV-7 infections is confounded by the intrinsic characteristics of herpesviruses, making it difficult to differentiate acute from past from reactivated infection. During acute HHV-6 infection, white blood cell counts, as well as absolute lymphocyte and neutrophil counts, are decreased compared with other febrile illnesses. In some cases, relative thrombocytopenia is also observed. Results of other routine laboratory tests are typically normal.

Multiple assays for detecting HHV-6 and HHV-7 infection have been developed, including serologic tests, isolation of virus by tissue culture, and detection of viral DNA or RNA by polymerase chain reaction. However, relying on a diagnosis based only on seroconversion, rise in antibody titers, or viral isolation can be misleading. For instance, seroconversion is not always evident in infants because of interference with maternal antibodies. In addition, increases in immunoglobulin G and immunoglobulin M titers have been identified during viral reactivation and therefore do not necessarily indicate new infection. Further, blood viral DNA may be detected with both primary and latent infections, and detection of DNA in other body fluids and tissues does not differentiate between new infection and persistence of virus from past infection. Therefore, a combination of serology (acute and convalescent) and direct viral identification is recommended for the diagnosis when clinically indicated:

- Serologic tests used include immunofluorescent antibody, neutralization, and enzyme immunoassays. These tests do not differentiate between HHV-6A and

HHV-6B and may cross-react with HHV-7. Detection of low-avidity (within 6 weeks of the infection) and high-avidity (>6 weeks) HHV-6 and HHV-7 antibodies may help to confirm recent primary infection. Seroconversion from negative to positive in paired sera provides evidence for recent primary infection.

- HHV-6 and HHV-7 DNA can be detected in blood and CSF in reference laboratories. However, viral DNA detection does not necessarily differentiate between acute infection and viral DNA persistence from past infection. In addition, these assays are not specific enough to differentiate chromosomally integrated HHV-6 infection. The diagnosis of chromosomally integrated HHV-6 is suspected based on the presence of consistently high viral HHV-6 loads in blood and is confirmed by detection of HHV-6 DNA in hair follicles.
- In cases of invasive disease, histopathology and immunohistochemical stains from biopsy specimens may be helpful.

Newly developed diagnostic methods to differentiate latent virus from actively replicating virus may eventually shed light on both the diagnosis and the pathogenesis of diseases associated with HHV-6 and HHV-7.

## DIFFERENTIAL DIAGNOSIS

Roseola is often confused with other exanthematous diseases (see Chapter 236, Contagious Exanthematous Diseases). In rubella, the rash and fever are concurrent, and enlarged lymph nodes are often tender. Coryza, respiratory symptoms, and Koplik spots distinguish rubeola (measles). Enteroviruses and parechovirus may cause a nonspecific exanthem in both older and younger children and are more common in the late summer and fall. Parvovirus B19 causes erythema infectiosum, or fifth disease, which affects school-aged children and involves the face initially with the classic slapped-cheek appearance. Scarlet fever has a more confluent, sandpaper-like rash and is associated with marked pharyngitis. Drug eruptions, especially those resulting from sulfa-containing preparations, are not regularly preceded by fever and tend to be diffuse. Kawasaki disease is accompanied by more prolonged fever along with bilateral conjunctival injection, and the rash is concurrent with the fever.

## MANAGEMENT

In most cases, the management of HHV-6 and HHV-7 infections is supportive and is based entirely on symptoms. Acetaminophen is effective in controlling the fever. Reassuring caregivers that the rash is a sign of recovery often comforts them and may prevent unnecessary office visits.

In the immunocompromised host, the cornerstone of therapy is reduction of immunosuppression to the degree possible. In vitro, HHV-6 is susceptible to ganciclovir, foscarnet, and cidofovir, but the role of antiviral medications has not been extensively studied. Clinically, antivirals have been used most often in immunocompromised subjects to treat HHV-6 encephalitis, with varying success. There are no recommendations for preemptive or prophylactic antivirals for HHV-6 or HHV-7 following HSCT or SOT.

While hospitalized, standard precautions are recommended.



**WHEN TO REFER**

- Primary HHV-6 or HHV-7 infections almost never are clinically recognized until the disease is over.
- Referral is rarely needed except to rule out an alternative diagnosis such as a seizure disorder or treatable encephalopathy or encephalitis.
- Severe clinical symptoms in immunocompromised patients should always be managed in consultation with an infectious diseases specialist.

**WHEN TO ADMIT**

- Hospitalization is indicated in infants with a toxic appearance or if there is CNS involvement such as meningitis, encephalitis, bulging fontanel, or seizures.
- Immunocompromised patients may develop severe HHV-6 or HHV-7 disease, but they are typically hospitalized for their severe clinical presentation—ie, pneumonitis, encephalitis, or suspected graft-versus-host disease—rather than for suspicion of HHV-6 or HHV-7 infection.

**TOOLS FOR PRACTICE****Engaging Patient and Family**

- *Roseola* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/skin/Pages/Roseola-Infantum.aspx](http://www.healthychildren.org/English/health-issues/conditions/skin/Pages/Roseola-Infantum.aspx))

**SUGGESTED READINGS**

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**Chapter 268****HUMAN IMMUNODEFICIENCY VIRUS INFECTION AND ACQUIRED IMMUNODEFICIENCY SYNDROME**

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Children who have acquired immunodeficiency syndrome (AIDS) were first identified in 1983, 2 years after the description of AIDS in adults. Subsequently it

became clear that AIDS was a manifestation of advanced human immunodeficiency virus (HIV) infection. By the end of 2007, an estimated 4,000 children younger than 21 years were living with HIV infection in the United States. AIDS was the case definition used to describe the collection of opportunistic infections or cancers that were noted in HIV-infected individuals before it was known that HIV was the etiologic agent responsible for the predisposition to these opportunistic conditions. This case definition remains valuable but does not fully describe the effect of HIV infection. AIDS continues to represent advanced stages of HIV infection and results from progressive immune dysfunction.

There are 2 separate HIV viruses: HIV-1, which is the predominant virus responsible for disease in the United States and the rest of the world, and HIV-2, which is primarily detected in patients in West Africa. HIV-2 infection has been detected in the United States in individuals from West Africa or in those who have had sexual contact with individuals from West Africa. Clinical manifestations of HIV infection range from asymptomatic infection to debilitating disease and death. Administration of antiretroviral therapy can considerably modify disease progression. Prepubertal children most commonly acquire HIV infection through maternal–infant transmission, but they also rarely can be infected through receipt of infected blood or blood products and through sexual abuse. At the present time, a substantial number of adolescents are contracting HIV infection through adult behaviors such as unprotected sexual activities and intravenous drug use. Before the widespread use of antiretroviral prophylaxis to prevent maternal–child transmission, as many as 1,800 HIV-infected children were born in the United States annually. Now, fewer than 50 infants are perinatally infected with HIV each year in the United States. The greatest burden of pediatric HIV infection worldwide is in the resource-poor countries of Africa and Asia. However, recent efforts to bring antiretroviral therapy to these areas is already showing evidence of reduced perinatal transmission of HIV and prolonged survival of those who are HIV infected.

Advances in the diagnosis, treatment, and prevention of pediatric HIV infection bring hope to many HIV-infected children, their families, and those who care for them, but a cure remains elusive. The care of HIV-infected children is complex and requires a multidisciplinary team to address the multiple medical, psychological, social, and economic issues that confront HIV-infected children and their families. As HIV infection has been managed more effectively with antiretroviral medication combinations, the psychosocial issues and adverse effects of medical therapy present the greatest challenges to successfully caring for the HIV-infected child.

**TRANSMISSION OF HIV TO CHILDREN**

Perinatal transmission is the most common mode of acquisition of HIV infection among nonadolescent children in the United States. Not all infants born to HIV-infected women acquire HIV infection; estimated perinatal transmission rates in untreated women to

their infants range from 13% to 30%. Appropriate antiretroviral therapy can reduce the rate to less than 2%. Perinatal HIV transmission can occur by 3 mechanisms: transplacental infection in utero, intrapartum infection during labor and delivery, and postpartum infection through mother's milk. Premastication of food for young infants by HIV-infected mothers has recently been noted as a rare cause of HIV infection in young infants. Poor oral hygiene and oral bleeding seem to increase the likelihood of this form of transmission. Before antiretroviral chemotherapy was available to prevent perinatal HIV transmission, intrapartum transmission was the most common mode of transmission in children. High maternal plasma HIV levels (viral load) correlate with increased risk for transmission. Thus, women who have advanced HIV disease or recently acquired infection are more likely to transmit HIV to their newborns. Antiretroviral therapy administered to women during pregnancy and delivery, and to infants during the first 6 weeks of life, greatly reduces the rate of perinatal HIV transmission. Although the total number of perinatal infections has declined, the proportion resulting from intrauterine transmission has increased. This supports the role of antiretroviral therapy and mode of delivery in affecting intrapartum transmission. Perinatal HIV transmission in the United States primarily occurs in women who have poor prenatal care and in women whose viral load is not adequately suppressed because of poor medication compliance or viral resistance.

Routine testing of blood donors for HIV antibody began in March 1985. Children who received blood or blood products before this time were at risk for HIV infection. Children who had hemophilia were at particularly high risk because they received pooled factors from hundreds to thousands of donors. The risk for HIV infection from blood or blood products is now extremely low, estimated to be 1 in 675,000 from a single unit of blood.

HIV transmission through sexual contact occurs in children who are sexually abused or in sexually active adolescents. Behaviors that place adolescents at high risk for HIV infection are initiation of sexual activity at a young age, multiple sexual partners, and unprotected sexual intercourse (vaginal and anal). Given that perinatal transmission has been reduced substantially, adolescents who acquire HIV through adult behaviors represent the most common newly infected pediatric patients.

### **PATHOPHYSIOLOGIC FEATURES OF HIV INFECTION IN CHILDREN**

Perinatal HIV infection occurs during the development and maturation of the immune system. This distinguishes pediatric HIV infection from adult infection and has profound effects on the clinical course, nature, and timing of opportunistic infections and immune responses to immunizations.

HIV infects several different cell types, but the primary target for HIV replication is the CD4<sup>+</sup> T lymphocyte. In addition to the CD4 cell surface molecule, HIV requires a chemokine coreceptor to enter cells. Polymorphisms in chemokine receptors are associated with differing resistance to HIV infection and different

rates of disease progression. Reverse transcription, in which viral DNA is synthesized from viral RNA, is carried out by the enzyme reverse transcriptase. Viral DNA is then transported to the nucleus and integrated into cellular DNA with the help of the viral enzyme integrase, persisting for the life span of the cell. Subsequently, a messenger RNA is produced using human enzymes. This messenger RNA is transported outside the nucleus and is used as a blueprint for synthesizing a large viral polypeptide (HIV proteins and enzymes) that requires cleavage by a viral protease. These newly made HIV proteins and enzymes gather along with HIV RNA to form new viral particles, which are then released from the cell. Currently available antiretroviral therapy works by interfering with the functions of these enzymes: nucleoside and nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, entry chemokine receptors or fusion inhibitors, and integrase inhibitors.

The number of copies of HIV RNA in plasma can be quantified. Because HIV, like other viruses, is an obligate intracellular parasite, viruses in the plasma represent replicating viruses looking for new host cells. Plasma HIV RNA levels are useful in predicting the rate of disease progression, for modifying antiretroviral therapy, and in understanding viral dynamics. In children who have perinatally acquired HIV infection, HIV RNA levels peak in the first few months of life and decline slowly over several years. Steady-state HIV RNA levels in untreated children are not achieved until 2 to 6 years of age. In contrast, HIV RNA levels in adults decline rapidly to steady-state levels within several months after primary infection. Despite the decline in HIV RNA levels, intense viral replication continues to occur. Combination therapy with reverse transcriptase and protease inhibitors or NNRTIs (highly active antiretroviral therapy [HAART]) block HIV replication and can result in a dramatic decline in virus production and undetectable plasma HIV RNA levels. HIV persists within cellular compartments, however, and a cure is not achievable with current therapies.

Infection with HIV leads to a progressive decrease in CD4<sup>+</sup> T lymphocytes. CD4<sup>+</sup> T lymphocytes are helper T cells that provide stimulatory signals to cells responsible for cellular and humoral immunity and phagocytosis. Qualitative changes in the function of CD4<sup>+</sup> T lymphocytes occur before the decline in number. Because CD4<sup>+</sup> T lymphocytes are crucial to B-lymphocyte function, humoral immunity (antibody production) can be significantly impaired in HIV-infected children, resulting in poor antibody responses to encapsulated bacteria and immunizations, despite increased levels of total immunoglobulins (hypergammaglobulinemia).

### **DIAGNOSIS OF HIV INFECTION IN CHILDREN**

The most important factor in identifying HIV-infected women and children is that the diagnosis be considered. Several risk factors are associated with HIV infection in women of childbearing age, including history of multiple sexual partners, illicit drug use, and sexual contact with

persons at high risk. However, the absence of identifiable risk factors does not exclude HIV infection.

Because maternal HIV antibody will cross the placenta and reach the fetus, detection of HIV DNA or RNA by polymerase chain reaction (PCR) is the preferred method for diagnosing HIV infection in infants (age <18 months). PCR amplifies HIV DNA or RNA sequences and is extremely sensitive in detecting small amounts of virus. Almost all HIV-infected infants have a positive HIV PCR result by 1 month of age, and 40% of HIV-infected infants can be identified in the first 2 days of life. False-positive results have occurred on rare occasions because of laboratory contamination. Positive results should be confirmed by PCR testing of a second blood specimen. Because early detection of HIV infection allows for the initiation of combination antiretroviral therapy in infancy, HIV-exposed infants should be tested by 48 hours of age. A positive PCR result at 48 hours of age signifies intrauterine infection. If negative, repeat PCR testing should be performed at 14 days of age because more than 90% of infected infants will have a positive PCR result by 2 weeks of age. Infants negative for HIV by PCR at 48 hours and at 14 days should be tested at 4 weeks of age and, if negative, again at 4 to 6 months of age. HIV infection is diagnosed by 2 positive HIV PCR tests performed on separate blood samples. Two negative PCR results in a nonbreastfed infant, the first performed at 1 to 2 months and the second at 4 to 6 months of age, make the diagnosis of HIV infection extremely unlikely. Negative HIV PCR results at 2 and 4 weeks of age or 1 negative HIV PCR at 8 weeks of age can be used to provide evidence for presumptive non-HIV infection. This is relevant because it influences the requirement for initiating *Pneumocystis jirovecii* (PCP) prophylaxis. It is not necessary to begin PCP prophylaxis for infants who are presumptively negative. Presumptive negative results need to be confirmed by testing at 4 to 6 months of age. Testing for HIV antibody at 18 months of age is optional.

The HIV enzyme immunosorbent assay (ELISA) detects antibody to HIV and is the appropriate screening test for children older than 18 months. The HIV ELISA has high sensitivity. False-positive results occur but are rare with current tests. Positive ELISA reactions for HIV are confirmed by Western blot analysis. The Western blot detects antibodies to several HIV proteins and is highly specific. False-negative results may occur shortly after primary infection because antibodies to HIV do not achieve detectable levels until 1 to 3 months after infection. Serologic methods should not be used to confirm HIV infection in children younger than 18 months because transplacentally derived maternal antibodies result in a positive HIV ELISA result in infants born to HIV-seropositive women even if the child is not infected. These maternal antibodies can persist for 18 months.

## CLINICAL MANIFESTATIONS OF HIV INFECTION IN CHILDREN

The time from infection to onset of clinical symptoms may be shorter for children who have perinatally acquired HIV infection than for children infected through

blood or blood products, and it is usually shorter than for HIV-infected adults. HIV-infected infants are without symptoms in the neonatal period. Before the widespread use of prophylaxis for PCP and early antiretroviral therapy, a subset of HIV-infected children had rapidly progressive disease and died within the first year of life, often from PCP. Other children remain asymptomatic or have few symptoms for many years, some into adolescence. However, most children who have perinatal HIV infection and are untreated develop symptoms by 2 years of age. High plasma HIV levels and low CD4<sup>+</sup> T-lymphocyte cell counts predict a poor prognosis.

Most of the clinical manifestations attributed to HIV infection can be prevented by appropriate use of antiretroviral medications and careful monitoring of immune status, viral load, and medication toxicity. However, some children may experience complications of HIV infections despite medication compliance and good viral control. Untreated or inadequately treated children, or those who have developed antiretroviral resistance, may exhibit failure to thrive, developmental delay, persistent oral candidiasis, lymphadenopathy, hepatosplenomegaly, chronic diarrhea, recurrent bacterial infections, and recurrent herpesvirus infections. PCP was a common illness found in affected infants before routine prophylaxis of HIV-exposed infants. Laboratory abnormalities often include anemia, thrombocytopenia, and increased immunoglobulin levels.

HIV infection and secondary opportunistic infections can involve all organ systems. Pulmonary disease is common in HIV-infected children. PCP is a fulminant pulmonary infection characterized by tachypnea, cough, hypoxemia, and, most commonly, diffuse alveolar infiltrates on chest radiograph. However, early in the course of PCP in older children, the chest radiograph may be normal or show minimal changes despite significant cough and even hypoxia. Lymphoid interstitial pneumonitis (LIP) is a chronic lung disease of HIV-infected children resulting from lymphoid hyperplasia in the lungs. Children who have LIP may be asymptomatic or may have chronic cough and wheezing. Bilateral, reticulonodular densities are seen on chest radiographs resembling miliary tuberculosis. Children who have LIP are typically older than those who have PCP and often have generalized lymphadenopathy and parotid enlargement.

Central nervous system disease is also more common in HIV-infected children. Microcephaly, developmental delay, spasticity, abnormal reflexes, and gait abnormalities may be present. Characteristic findings on computed tomographic scan include cerebral atrophy and basal ganglia calcifications. Hematologic abnormalities associated with HIV infection include leukopenia, anemia, and thrombocytopenia. Thrombocytopenia may be the presenting illness. In addition, drug-induced bone marrow suppression can follow therapy with zidovudine, co-trimoxazole, and ganciclovir. Hepatomegaly and increases in hepatic transaminases are commonly seen, often in the absence of clinically apparent liver disease. HIV cardiomyopathy may lead to congestive heart failure. HIV nephropathy is a common cause of proteinuria and can progress to nephrotic syndrome. HIV nephropathy is more common in black children.

Chronic diarrhea, resulting from several opportunistic gastrointestinal pathogens, can be debilitating.

Dermatologic conditions include recurrent herpes simplex and varicella-zoster virus infections, severe molluscum contagiosum, chronic fungal infections, atopic dermatitis, and drug-induced eruptions, particularly with co-trimoxazole. HIV-infected children in whom virus replication is not controlled by antiretroviral therapy are often stunted in their growth, and severe wasting may be seen in advanced disease. Malignancies are not as common in HIV-infected children, but lymphomas and leiomyosarcomas can occur.

In 1984, the Centers for Disease Control and Prevention (CDC) developed a classification system based on clinical diseases to categorize HIV infection and AIDS in children. The CDC classification was revised in 1994 to incorporate advances in the understanding of the natural history of HIV infection in children and age-specific CD4<sup>+</sup> T-lymphocyte cell counts (Table 268-1). HIV-infected children are classified into 1 of 4 clinical categories (N, A, B, or C) on the basis of clinical signs and symptoms and into 1 of 3 immunologic categories (1, 2, or 3) on the basis of age-specific CD4<sup>+</sup> T-lymphocyte

cell counts or the percentage of the CD4<sup>+</sup> T-lymphocyte count. However, variability in clinical status exists even within a category (Table 268-2).

### COMMON CLINICAL PROBLEMS IN HIV-INFECTED CHILDREN

Most HIV-infected children who have fever and a normal clinical examination have self-limited febrile illnesses similar to those of HIV-uninfected children. However, as with other immunocompromised children, in HIV-infected children with moderate or severe immunosuppression, fever may indicate a serious infection. A detailed clinical history and careful physical examination, with close attention to general appearance and potential areas of focal inflammation such as skin, ears, sinuses, lungs, and gastrointestinal tract, are essential in the initial assessment of the febrile HIV-infected child. Bacteremia with *Streptococcus pneumoniae* and *Salmonella* can occur in the absence of physical findings. Additional diagnostic studies should be performed on the basis of the child's age, clinical appearance, degree of immunosuppression, and signs and symptoms at the time the patient seeks

**Table 268-1**

**Immunologic Categories Based on Age-Specific CD4<sup>+</sup> T-Lymphocyte Count and Percentage of Total Lymphocytes**

SUPPRESSION	AGE					
	<1 YEAR		1–5 YEARS		6–12 YEARS	
	MCL	%	MCL	%	MCL	%
No evidence of suppression	≥1500	≥25	≥1000	≥25	≥500	≥25
Evidence of moderate suppression	750–1,499	15–24	500–999	15–24	200–499	15–24
Severe suppression	<750	<15	<500	<15	<200	<15

From Centers for Disease Control and Prevention. 1994 Revised classification system for Human Immunodeficiency Virus infection in children younger than 13 years of age. *MMWR*. 1994;43(RR-12):1–10.

**Table 268-2**

**Categories of Human Immunodeficiency Virus Classification in Children**

IMMUNOLOGIC CATEGORY	CLINICAL CATEGORY			
	N	A	B	C
	NO SIGNS OR SYMPTOMS	MILD SIGNS OR SYMPTOMS	MODERATE SIGNS OR SYMPTOMS	SEVERE SIGNS OR SYMPTOMS
1. No evidence of suppression	N1	A1	B1	C1
2. Evidence of moderate suppression	N2	A2	B2	C2
3. Severe suppression	N3	A3	B3	C3

From Centers for Disease Control and Prevention. 1994 Revised classification system for Human Immunodeficiency Virus infection in children younger than 13 years of age. *MMWR*. 1994;43(RR-12):1–10.



care. Laboratory tests to be considered include a complete blood count with differential, large-volume blood culture, chest radiograph, urinalysis and urine culture, and lumbar puncture. Administration of empirical antibiotic therapy is not always necessary and depends on the results of the clinical assessment and laboratory tests, as well as the likelihood of adequate monitoring and follow-up. A third-generation cephalosporin such as ceftriaxone or cefotaxime can be used as empirical antibiotic therapy to provide therapy against both gram-positive and gram-negative bacteria. Ill-seeming children should be hospitalized. Persistent fever in the HIV-infected child can be a diagnostic challenge, but identifiable and treatable causes include mycobacterial infection and drug-induced fever.

*Streptococcus pneumoniae* is the most common bacterial cause of pneumonia in HIV-infected children, who may develop severe disease as a result of infection with common respiratory pathogens such as respiratory syncytial virus, parainfluenza virus, influenza virus, and adenovirus if they have significant immunocompromise. HIV-infected children who have advanced immunosuppression are susceptible to many opportunistic pulmonary pathogens. PCP is the most common opportunistic infection in HIV-infected infants and typically appears at 3 to 6 months of age with cough, tachypnea, and hypoxemia. Early diagnosis and treatment, usually with co-trimoxazole and corticosteroids, is critical. Physicians caring for HIV-infected children must carefully consider the diagnosis of PCP in HIV-infected children who have respiratory tract symptoms. In infants younger than 12 months, neither the CD4<sup>+</sup> cell count nor the CD4 percent is a good predictor of the risk for PCP. However, in children older than 12 months, PCP is unusual in those whose CD4<sup>+</sup> cell count or CD4 percent is normal or who exhibit only moderate immunosuppression, or if the child is receiving appropriate PCP prophylaxis and is adherent with this medication. HIV-infected children who have pulmonary disease and who fail to respond to empirical antibiotic therapy, those who are severely ill, and those who are suspected of having PCP should undergo an invasive diagnostic procedure such as bronchoscopy with bronchoalveolar lavage or lung biopsy.

Persistent diarrhea can significantly compromise the quality of life and nutritional status of HIV-infected children. Infectious causes of diarrhea in HIV-infected children include all of the pathogens of healthy children in addition to numerous opportunistic pathogens. Common parasitic pathogens causing persistent diarrhea include *Giardia lamblia*, *Entamoeba histolytica*, *Cryptosporidium* species, and *Isospora belli*. Cytomegalovirus may cause colitis in children who have advanced immunosuppression. Diagnostic studies should include stool cultures for bacterial and viral pathogens, as well as antigen detection for *Giardia* and *Cryptosporidium* species and possibly ova and parasites. Endoscopy should be considered in refractory cases.

Bacterial and viral pathogens causing meningitis and encephalitis in HIV-infected children are similar to those in nonimmunocompromised children. Opportunistic pathogens causing meningitis and encephalitis

in HIV-infected children who have advanced immunosuppression include *Cryptococcus neoformans*, *Toxoplasma gondii*, and cytomegalovirus. Initial diagnostic studies include analysis of cerebrospinal fluid and brain imaging. Rarely, central nervous system lymphomas can occur.

HIV-infected children with immunocompromise are at increased risk for disseminated varicella and recurrent herpes zoster. HIV-infected children who are susceptible to varicella (no prior natural infection or age-appropriate varicella immunization) should receive a varicella-zoster immunoglobulin preparation (or intravenous immunoglobulin if varicella-zoster immunoglobulin is not available) within 96 hours of exposure to varicella. Disseminated infection can occur with herpes zoster, and oral or parenteral therapy with acyclovir is warranted.

Growth failure is common in untreated HIV infection in children early in the course of disease. The diagnosis of HIV infection should be considered in children who fail to thrive. Frequent measurements of weight and height are important in detecting growth disturbances early and monitoring response to interventions. Effective antiretroviral therapy with suppression of viral replication, as well as nutritional supplementation, is important to the maintenance of growth. However, supplementation with high-calorie foods or formulas often results in increased body fat rather than lean body weight.

Delayed acquisition of developmental milestones or loss of previously acquired milestones is also a common manifestation of untreated HIV infection in children. Effective antiretroviral therapy can minimize or reverse the neurocognitive effects of HIV infection.

## PREVENTING MATERNAL-INFANT HIV VIRUS TRANSMISSION

Identifying HIV-infected women before or during pregnancy is critical in preventing perinatal HIV transmission. Prenatal HIV counseling and testing should be provided to all pregnant women. Initial HIV antibody testing should be performed early in pregnancy and repeated in the third trimester for women at risk for HIV infection, such as those with a history of multiple sexual partners, illicit drug use, or a sexual partner at risk for HIV infection. Administering zidovudine to women during pregnancy and labor and to infants for the first 6 weeks of life has been shown to reduce perinatal HIV transmission by two-thirds (26% to 8%). This regimen was previously the standard of care for HIV-infected pregnant women and their newborns. Other regimens should be used based on the clinical, immunologic, and viral status of the mother. In general, HIV-infected pregnant women should receive the optimal medical and antiretroviral therapy required for their own health. For those women for whom deferral of antiretroviral therapy is acceptable because of normal immune status, antiretroviral therapy is still indicated during pregnancy as a means to optimally suppress the HIV viral load in order to prevent maternal-infant HIV transmission. Early identification of HIV-infected pregnant women also allows for appropriate care of the mother,

avoidance of ongoing HIV exposure of the infant through human milk, and early institution of PCP prophylaxis for the infant at 4 to 6 weeks of age. Cesarean delivery can also reduce the risk for perinatal HIV transmission. All HIV-infected pregnant women should be counseled concerning the benefit and risks of cesarean delivery. For women with viral loads consistently greater than 1,000 copies/mL, it should be strongly encouraged. For women with viral loads less than 1,000 copies/mL, the benefits of cesarean delivery may not outweigh the risks.

### CARE OF THE HIV-INFECTED CHILD

Proper care of HIV-infected children requires a multidisciplinary team including pediatricians, experts in antiretroviral therapy, nutritionists, physical therapists, pharmacists, psychologists, social workers, and outreach workers. The pediatrician should rely on HIV care providers for the management of antiretroviral drugs.

#### Immunization of the HIV-Infected Child

Immunizations are generally safe for HIV-infected children, although the immune suppression caused by HIV results in less assurance of protection after immunization than in non-HIV-infected children. However, the small risk for serious complications from live viral vaccines has led to special recommendations for HIV-infected children. Live oral rotavirus vaccine should not be administered to severely immunocompromised children. However, HIV-exposed infants with testing that does not support HIV infection may receive their initial dose of live oral rotavirus vaccine before documentation that the infant is not infected (negative PCR after 4 months of age).

Toxoids, subunit vaccines, inactivated vaccines, and recombinant vaccines are not associated with increased risk for complications in HIV-infected children. Vaccines in these categories include diphtheria and tetanus toxoids, acellular pertussis vaccines, inactivated polio virus vaccine, *Haemophilus influenzae* type b, meningococcal and pneumococcal conjugate vaccines, inactivated influenza vaccine, and hepatitis A and B vaccines. The human papillomavirus vaccine should be given to HIV-infected females and males at 11 to 12 years of age with catch-up to age 26 years. These vaccines should be administered to HIV-infected children according to the routine immunization schedule. Because of an increased risk for invasive infection with *Streptococcus pneumoniae*, immunization of HIV-infected children with pneumococcal conjugate vaccine is particularly important. HIV-infected children may develop lower antibody titers than healthy children after immunization and are more likely to lose protective antibody earlier. The Infectious Diseases Society of America is developing guidelines that should assist physicians determining optimal primary series and booster dosing of vaccines for HIV-infected children.

Live virus vaccines, such as varicella, and measles, mumps, and rubella vaccines, may result in infections and diseases from vaccine virus in severely immunocompromised HIV-infected children, although the risk is quite small. After the report of a death caused by

measles vaccine virus after immunization, advisory groups in the United States recommended withholding measles vaccine from HIV-infected children with severe immunosuppression, defined as CD4<sup>+</sup> T lymphocytes less than 15%. Measles-mumps-rubella (MMR) vaccine should be administered to HIV-infected children at 12 months of age and a second dose at 1 month (minimum of 28 days) later unless the children are severely immunocompromised (CD4<sup>+</sup> <15%). As with other vaccines, the immune response to measles vaccine in HIV-infected children may be poor, and vaccinated children may remain susceptible to measles virus infection despite prior immunization. The combination vaccine MMRV should not be given to HIV-infected children. Serious complications after mumps or rubella immunization have not been reported.

Live varicella virus vaccine also is recommended for HIV-infected children on the basis of their degree of immunosuppression and symptoms. The American Academy of Pediatrics Committee on Infectious Diseases recommends varicella vaccine at 12 months of age and a second dose 3 months later for asymptomatic and mildly symptomatic HIV-infected children who have CD4<sup>+</sup> T-lymphocyte percentages of 15% or more. Serious adverse events after administration of varicella vaccine to HIV-infected children are rare.

#### Antimicrobial Prophylaxis

Because of the high mortality rate associated with PCP in early infancy, PCP prophylaxis should be administered to HIV-exposed infants beginning at 6 weeks of age, if HIV infection status is not established. Criteria for discontinuing PCP prophylaxis are age related and include evidence of immune reconstitution for at least 3 months on effective antiretroviral therapy. Lifelong PCP prophylaxis is recommended for children who have a history of PCP, despite immune reconstitution. Prophylaxis is continued until 12 months of age or until the diagnosis of HIV infection has been excluded. For children 1 to 5 years of age, PCP prophylaxis is administered if the CD4<sup>+</sup> T-lymphocyte cell count is less than 500 cells/mm<sup>3</sup> and for children 6 to 12 years of age if it is less than 200 cells/mm<sup>3</sup>. The recommended regimen is co-trimoxazole taken orally 3 days a week. Alternative regimens include dapsone or pentamidine.

HIV-infected children who have recurrent oral candidiasis may benefit from antifungal prophylaxis with oral nystatin, clotrimazole, or fluconazole. Oral azithromycin weekly or clarithromycin daily for prophylaxis against *Mycobacterium avium-intracellulare* infection is indicated in children based on age-related CD4<sup>+</sup> cell counts (children >6 years with CD4<sup>+</sup> cell counts <50 cells/mm<sup>3</sup>; children 2 to 5 years with CD4<sup>+</sup> cell counts <75 cells/mm<sup>3</sup>; children 1 to 2 years with CD4<sup>+</sup> cell counts <500 cells/mm<sup>3</sup>; and infants <1 year with CD4<sup>+</sup> cell counts <750 cells/mm<sup>3</sup>). Immunoglobulin should be provided to susceptible (no age-appropriate measles immunization) HIV-infected children within 6 days of exposure to a person who has measles. Measles immunization should be delayed 6 months after receipt of immunoglobulin.

### Antiretroviral Therapy

The treatment of HIV infection with antiretroviral drugs is complex. Management of antiretroviral therapy should be directed by a specialist who has knowledge of the mechanisms of action of antiretroviral agents, potential toxicities, drug interactions, and cross-resistance patterns. Because most children acquire HIV infection during or near the time of birth, antiretroviral therapy should be initiated in infancy. Although early therapy restores immunologic function, the risks for drug toxicity and acquisition of drug-resistant virus are increased. Decisions to initiate early therapy require balancing the benefits and risks. Combination antiretroviral therapy is indicated for all infants diagnosed with HIV infection in the first year of life, regardless of clinical, immunologic, or virologic status. For children diagnosed after 12 months of age, the decision to start treatment should be based on clinical symptoms, plasma HIV RNA levels, and CD4<sup>+</sup> T-lymphocyte counts.

The choice of antiretroviral regimen for children is based on several factors, including the availability of pediatric formulations, potential drug interactions, the frequency of drug dosing, and potential interactions with other medications. Before therapy begins, the child's clinical, virologic, immunologic, and nutritional status should be documented. Neuropsychometric testing should be performed in children with suspected neurodevelopmental deficits. Baseline laboratory studies should include a complete blood count with differential, liver function tests, a CD4<sup>+</sup> T-lymphocyte cell count, and plasma HIV RNA level.

Combination antiretroviral therapy consists of a protease inhibitor or NNRTI in combination with 2 or more nucleoside reverse transcriptase inhibitors (NRTIs). Protease inhibitors that may be used in children include lopinavir/ritonavir (preferred), nelfinavir, ritonavir (alone), amprenavir, and indinavir. Lopinavir/ritonavir, nelfinavir, ritonavir, and fosamprenavir are available in liquid formulations. Atazanavir, darunavir, tipranavir, and saquinavir are available protease inhibitors with insufficient data in children to recommend for initial therapy at this time. They may be used in adolescents. Preferred 2-NRTI backbones include abacavir plus lamivudine or emtricitabine, didanosine plus lamivudine or emtricitabine, tenofovir plus lamivudine or emtricitabine, and zidovudine plus lamivudine or emtricitabine. Alternate 2-NRTI backbones include zidovudine plus abacavir and zidovudine plus didanosine. In special circumstances, stavudine plus lamivudine or emtricitabine could be used as the 2-NRTI backbone. Stavudine plus didanosine should not be used or should be used only with substantial caution because of their potential synergistic toxicities. Several combinations are not recommended either because of antagonism (stavudine-zidovudine) or because of overlapping toxicities. The NNRTIs nevirapine, delavirdine, and efavirenz can be used in combination with the NRTIs. Nevirapine is preferred in children younger than 3 years, and efavirenz is preferred in children 3 years or older. Efavirenz is only available in capsule form.

Regimens containing etravirine, maraviroc, raltegravir, and enfuvirtide (T-20) should not be used in initial treatment regimens for children. However, in children who have failed other regimens because of antiretroviral resistance, these medications may provide the only options available. They should be used with caution in children because safety and dosing are not well established for children.

The following are antiretroviral regimens or components that should *never* be offered as treatment of HIV infection in children: monotherapy; 2 NRTIs alone; tenofovir plus abacavir plus lamivudine or emtricitabine; tenofovir plus didanosine plus lamivudine or emtricitabine; dual NNRTI combinations; combinations of lamivudine plus emtricitabine; combinations of stavudine plus zidovudine; and unboosted saquinavir, darunavir, or tipranavir (these protease inhibitors requiring boosting with ritonavir because of poor bioavailability). Efavirenz should never be given in the first trimester of pregnancy or to sexually active adolescent girls of childbearing potential when reliable contraception cannot be ensured. Nevirapine should not be initiated in adolescent girls with CD4<sup>+</sup> cell counts of >250 cells/mm<sup>3</sup> or adolescent boys with CD4<sup>+</sup> cell counts of >400 cells/mm<sup>3</sup>.

Common side effects of NRTIs are anemia and neutropenia with zidovudine, pancreatitis with didanosine, peripheral neuropathy with didanosine and stavudine, and an influenza-like hypersensitivity reaction with abacavir. Rechallenge with abacavir after a hypersensitivity reaction can be fatal. Common side effects of the NNRTIs nevirapine, delavirdine, and efavirenz are rashes and hepatitis. Efavirenz can cause nightmares, hallucinations, confusion, and impaired concentration. Gastrointestinal symptoms are the major side effects of protease inhibitors. Long-term complications of combination antiretroviral therapy include lipoatrophy, lipodystrophy, hypercholesterolemia, metabolic syndrome, and bone demineralization.

Adherence to complex drug regimens can be hindered by the large number or volume of medications, poor palatability, varied dosing schedules, and different effects of food on drug bioavailability. Mixing the drugs with foods, such as peanut butter or ice cream, may improve adherence in children. Behavioral therapy, begun before combination therapy is initiated, can be helpful in designing a routine medication schedule, teaching parents and caregivers methods to improve adherence, and teaching the child techniques for swallowing unsavory medications. Gastric tubes may be necessary and helpful to ensure medication adherence in children because of medication taste or volume problems.

Strict adherence to the treatment regimen is essential for the prevention of drug resistance. Because of cross-resistance, resistance to one drug can limit the effectiveness of other drugs of the same class. Viral sequences obtained from plasma samples can be tested for drug resistance mutations and for susceptibility profiles to guide treatment decisions. Plasma HIV RNA levels should be measured 4 weeks after the child has started therapy to assess response. The frequency of follow-up visits depends on many factors, including



the child's clinical status and expected compliance with therapy, but should include measurements of HIV RNA levels and CD4<sup>+</sup> T-lymphocyte counts.

### **Drug Interactions With Antiretroviral Therapy**

HIV protease inhibitors, as well as the NNRTIs, are metabolized in the liver by a cytochrome P-450 enzyme. Protease inhibitors have the potential to inhibit this enzyme and interfere with the metabolism of many other drugs. Protease inhibitors also can act as potent inhibitors of 2 other P-450 enzymes active in the metabolism of analgesics, beta blockers, and phenytoin. Ritonavir can stimulate glucuronidation, thus decreasing the concentration of drugs metabolized by this pathway, including sedatives such as lorazepam and the narcotics morphine and codeine.

Many drugs that have altered metabolism because of protease inhibitors are used in pediatric emergencies, including narcotic analgesics, anticonvulsants, antiarrhythmics, calcium channel blockers, and corticosteroids. These drugs should be used with caution in children receiving protease inhibitors. Drugs that have narrow therapeutic margins require particularly careful monitoring for adverse effects and measurement of drug concentrations. Drugs contraindicated for use with protease inhibitors include meperidine, midazolam, astemizole, terfenadine, cisapride, and rifampin. Additional medications may be added to this list based on new experience and reports.

A number of other medications often prescribed for HIV-infected children are inhibitors of cytochrome P-450 enzymes, including ketoconazole, itraconazole, clarithromycin, and erythromycin. Inhibition of cytochrome P-450 enzymes by these medications may lead to an increase in the plasma concentration of protease inhibitors. Dose reduction of the protease inhibitor may be required. Conversely, inducers of the cytochrome P-450 enzyme system are also commonly prescribed for HIV-infected children. Antimycobacterial drugs (rifampin, rifabutin), anticonvulsants (phenobarbital, phenytoin, carbamazepine), and glucocorticoids (dexamethasone) are inducers of cytochrome P-450 enzymes. Increased metabolism of protease inhibitors may result in subtherapeutic levels, with the potential emergence of drug resistance.

### **POSTEXPOSURE PROPHYLAXIS AFTER COMMUNITY NEEDLESTICK INJURIES**

Parents, caretakers, and physicians often are most concerned about transmission of HIV after accidental injury from a discarded needle. However, no consensus or recommendation is available to guide management in such circumstances. The risk for HIV transmission after occupational exposure to HIV-infected blood is 0.3%. Most experts agree that the risk after community needlestick injury is lower than the risk after occupational exposure. Factors to be considered in the use of antiretroviral agents for postexposure prophylaxis after community needlestick injuries include the potential risk for HIV transmission, drug toxicities, and the ability and willingness of the family to adhere to therapy. Regimens

for occupational postexposure prophylaxis may be followed.

### **CHILD CARE AND SCHOOL FOR THE HIV-INFECTED CHILD**

Because the risk for HIV transmission seems to be negligible, HIV-infected children should not be restricted from attending child care or school. Special consideration may be warranted for children who have unusual risk factors for transmission, such as frequent biting or scratching, severe dermatitis, or bleeding disorders. In such circumstances, the pediatrician should assess the need to protect other children.

### **HIV-INFECTED ADOLESCENT**

An increasing number of adolescents are infected with HIV through unprotected sex. Because the onset of AIDS occurs years after sexual transmission, AIDS in young adults reflects acquisition of HIV during adolescence. Pediatricians caring for adolescents must ensure that their patients have knowledge of the risks for acquiring HIV and other sexually transmitted infections through unprotected sex and be counseled on safe-sex practices.

Primary HIV infection in adolescents and adults is often accompanied by a mononucleosis-like illness characterized by fever, sore throat, lethargy, and lymphadenopathy (seroconversion syndrome). Because HIV antibodies take several months to achieve detectable levels, nucleic acid-based assays (PCR) should be used to diagnose symptomatic primary HIV infection.

### **ROLE OF THE PEDIATRICIAN IN THE CARE OF HIV-INFECTED CHILDREN**

The pediatrician plays a critical role in the care of HIV-infected children and their families. Responsibilities include diagnosing HIV infection; providing well-child care, including monitoring growth and development and administering immunizations; coordinating care among the multiple specialties and services, including experts in antiretroviral therapy, developmental and psychological assessment, nutritional support, and dental care; managing common medical problems; and directing the family to social and financial support services.

Many parents or guardians are not willing to tell the child that he or she is infected with HIV. However, most children are made aware of their illness through frequent medical visits and medications. The pediatrician is often in the best position to promote and assist with disclosure. Appropriate disclosure tailored to the child's cognitive level is helpful in alleviating guilt and allows for discussion between the child, caregivers, and health care professionals. Uninfected siblings of HIV-infected children also are emotionally affected by the diagnosis and should be included in support groups and counseling.

The pediatrician also plays a critical role in providing advice and support as the child nears death, helping the family interpret the complexities of critical care and decisions on the appropriateness of heroic



interventions. In some circumstances, the pediatrician may even be able to assist the family in caring for the dying child at home if critical care is deemed futile. After the death of the child, the pediatrician should continue to support the family through the grief process. Because many pediatricians invest much time and emotional energy in caring for an HIV-infected child, many take the opportunity to express their sympathy by attending the child's funeral. This can be an important gesture for both the family and the pediatrician.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *Condoms and STDs: Fact Sheet for Public Health Personnel* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/condomeffectiveness/latex.htm](http://www.cdc.gov/condomeffectiveness/latex.htm))

### Engaging Patient and Family

- *Deciding to Wait* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Helping Teens Resist Sexual Pressure* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/teen/dating-sex/Pages/Helping-Teens-Resist-Sexual-Pressure.aspx](http://www.healthychildren.org/English/ages-stages/teen/dating-sex/Pages/Helping-Teens-Resist-Sexual-Pressure.aspx))
- *Know the Facts About HIV and AIDS* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Making Healthy Decisions About Sex* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *No Condom, No Sex* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/teen/dating-sex/Pages/No-Condom-No-Sex.aspx](http://www.healthychildren.org/English/ages-stages/teen/dating-sex/Pages/No-Condom-No-Sex.aspx))
- *Talking With Your Teen About Sex* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

### Medical Decision Support

- *HIV/AIDS & STDs* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/std/hiv/default.htm](http://www.cdc.gov/std/hiv/default.htm))
- *Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings* (guideline), Centers for Disease Control and Prevention ([www.cdc.gov/mmwr/preview/mmwrhtml/rr5514a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5514a1.htm))

## AAP POLICY

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- American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health and Committee on Adolescence. Sexuality education for children and adolescents. *Pediatrics*. 2001;108(2):498–502. Reaffirmed October 2004 ([pediatrics.aappublications.org/content/108/2/498](http://pediatrics.aappublications.org/content/108/2/498))
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## Chapter 269

# HYDROCEPHALUS

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### INTRODUCTION

Hydrocephalus is a condition of excessive intracranial cerebrospinal fluid (CSF) volume resulting in increased intracranial pressure, ventriculomegaly, or macrocephaly in children, and may be congenital or acquired. Treatment is surgical diversion of CSF, either by alleviating the obstruction, rerouting the flow, or artificial shunting to extracranial cavities capable of absorbing excess fluid. In chronic cases, patients may have a good quality of life punctuated by unexpected failures of therapy, repeated medical evaluations, and surgical procedures. Adverse effects on brain function can range from mechanical distortion or impaired cerebral blood flow to changes in metabolism and neurotransmission.

### FOUNDATION

#### Definition

Hydrocephalus refers to an excessive CSF volume that disrupts normal brain function. Its manifestations are specific to developmental stages (eg, association with abnormal brain development in the fetus, ventriculomegaly or macrocephaly in the neonate, and intracranial hypertension in older children with closed cranial sutures). It is not synonymous with ventriculomegaly. Hydrocephalus can occur with ventricles of normal size that lack the compliance required for expansion in response to higher pressure, whereas ventriculomegaly refers to large ventricular size. Ventriculomegaly might be a more appropriate term than hydrocephalus in cases for which intracranial pressure is not measurable. Hydrocephalus *ex vacuo* specifically refers to an enlargement of the ventricles resulting from brain atrophy without increased intracranial pressure.

#### Epidemiology

The reported incidence of congenital hydrocephalus is 7 per 10,000 births (live and stillborn), with approximately 10% involving additional, multiple congenital abnormalities. In the United States, hydrocephalus results in approximately 40,000 pediatric hospital admissions per year, with estimated total hospital charges of around \$2 billion.

#### Etiology

The traditional view and classification of hydrocephalus relies on a paradigm of CSF flow obstruction between the site of production within the ventricles and sites of drainage into the dural venous sinuses. This is an appropriate model when there is an identifiable blockage on imaging studies (eg, a posterior fossa tumor or congenital aqueductal stenosis). On the other hand, cases of hydrocephalus may occur

following infection or hemorrhage in the absence of an obvious flow obstruction. These may be disorders of fluid absorption, but a growing body of literature suggests that they result from abnormal CSF pulsations and brain compliance. In some cases, the lack of an appropriate gradient between intracranial and central venous pressure can result in poor CSF absorption, as with small babies or patients undergoing large craniectomies for stroke or trauma, where intracranial pressure cannot exceed atmospheric pressure and thus CSF fails to be reclaimed into the venous system.

L1 syndrome is the most common genetic form of congenital hydrocephalus, arising from 1 of more than 200 possible *L1CAM* gene mutations on Xq28 that disrupt the normal production of cell adhesion molecules. Children with L1 syndrome have the associated findings of intellectual disability, adducted thumbs, aqueductal stenosis, spastic paraplegia from pyramidal tract hypoplasia, and agenesis of the corpus callosum.

#### Classification

Hydrocephalus has most often been classified as noncommunicating or communicating depending on whether there is an identifiable point of obstruction to CSF circulation (Table 269-1). This classification scheme has proved to be inadequate in patients shunted for hydrocephalus in infancy who later develop severe intracranial hypertension without ventriculomegaly on occasions of shunt failure. Thus, some authors have advocated a more specific classification system based on the site of obstruction, though in some cases aberrant CSF pulsations and subarachnoid compliance may cause hydrocephalus.

#### Risk Factors

Posthemorrhagic ventricular dilatation occurs in one-third of premature infants with intraventricular hemorrhage, caused either by hydrocephalus *ex vacuo* from encephalomalacia or by intracranial hypertension. Approximately 15% of these require permanent CSF diversion.

Infection is cited often as a predisposing factor for hydrocephalus, although the actual risk following infection is not well documented. Hydrocephalus occurs with an estimated incidence of 31% among survivors of neonatal meningitis. Radiographic findings of ventriculomegaly have been attributed to cytomegalovirus (CMV), toxoplasmosis, syphilis, and varicella, along with rare case reports of lymphocytic choriomeningitis and mumps viruses, the latter of which have been associated with acquired aqueductal stenosis. In regions endemic for tuberculosis, hydrocephalus is among the most common complications of tubercular meningitis, occurring in more than 70% of cases. Infection is also a risk factor for multiloculated (complex) hydrocephalus, which occurs in rare cases when the ventricular system becomes trabeculated and encysted.

Mass lesions arising at any stage of childhood are risk factors for acute hydrocephalus through obstruction of the ventricular system. Congenital malformations of the posterior fossa, including the genetically

**Table 269-1** Classification of Hydrocephalus

NONCOMMUNICATING HYDROCEPHALUS	COMMUNICATING HYDROCEPHALUS
<b>CONGENITAL CAUSES</b> Atresia of the foramen of Monro Chiari malformations Dandy-Walker syndrome Intracranial cysts Aqueductal stenosis Rare genetic syndrome (L1 syndrome)	<b>CONGENITAL CAUSES</b> Dandy-Walker syndrome Chiari malformations Encephalocele Intracranial cysts Subarachnoid villi noncompliance
<b>ACQUIRED CAUSES</b> Intraventricular hemorrhage Infectious (bacterial/fungal) Chemical Neoplastic/mass	<b>ACQUIRED CAUSES</b> Infectious (bacterial/fungal) Chemical Leptomeningeal neoplasms Subarachnoid hemorrhage/siderosis

heterogeneous Dandy-Walker syndrome and other similar cerebellar hypoplasias, are associated with up to 4% of all hydrocephalus cases. These may include cysts or stenotic foramina that cause discontinuities in the ventricular system, although these potential mechanical obstructions are not universally accepted as the etiology. Similarly, for reasons that are still not entirely clear, hydrocephalus occurs in 80% to 90% of patients with myelomeningoceles.

## DIAGNOSIS

### Signs and Symptoms

Acute hydrocephalus may present with rapidly worsening symptoms, in which case the neurologic examination should be focused on whether the patient has a level of consciousness sufficient for airway protection and whether immediate neurosurgical consultation for CSF diversion is warranted prior to any further evaluation. In more chronic conditions, symptoms are dependent upon the child's stage of development (Table 269-2).

Routine pediatric physical examinations may reveal a slow compensatory cranial expansion accompanied by delayed suture closure, frontal bossing of the forehead, and prominent scalp veins, but no neurologic deficits. In older children, gradual cognitive and motor decline becomes apparent with missed developmental milestones. Loss of visual acuity or fields, cranial nerve palsies, and acute papilledema can occur before ventricular dilatation, although a normal examination does not rule out intracranial hypertension. Longstanding hydrocephalus may result in optic atrophy and amblyopia, which may confound the evaluation for acute decompensation in affected patients.

### Differential Diagnosis

In the absence of signs or symptoms of intracranial hypertension, a head circumference 2 standard deviations above the mean or above the 98th percentile for age is usually caused by benign isolated macrocephaly or familial macrocephaly. This presents in an autosomal dominant pattern within a family and is associated with normal intellectual development. In some cases, these children may have mild suture diastasis

that is not associated with intracranial hypertension. Imaging studies in the first months of life may demonstrate prominent bifrontal subarachnoid spaces with widened interhemispheric fissures, prompting the designation *benign external hydrocephalus* for this normal variant by some authors.

A child's head may seem large despite normal circumference because of frontal bossing (eg, in cases of cranial hyperostosis, rickets, and liposomal storage disorders). Bilateral frontal and parietal prominence resulting in a "box-shaped" skull may herald chronic subdural hematomas (eg, with nonaccidental trauma, coagulopathy, or glutaric aciduria type I). Relative macrocephaly (less than 2 standard deviations above the mean, but disproportionately large relative to height and weight) may be caused by short stature, which could be related to intrauterine growth restriction, achondroplasia, or other skeletal dysplasias.

Macrocephaly is a common reason for a medical genetics referral. Consultations must include evaluation for neurocutaneous and systemic stigmata of relevant syndrome associations, such as neurofibromatosis and lysosomal storage diseases. Syndromes of systemic overgrowth (such as Sotos, Simpson-Golabi-Behmel, Bannayan-Ruvalcaba-Riley, Weaver, Fragile X, and macrocephaly-cutis marmorata telangiectatica congenita), or of macrocephaly without somatic overgrowth (such as Opitz-Kaveggia, Greig cephalosyndactyly, acrocallosal syndrome, and Gorlin syndrome), must be considered.

### Diagnostic Approach

The appropriate diagnostic approach includes a careful medical and family history, with attention to developmental milestones, intellectual and academic ability, visual disturbances, headaches, neurologic symptoms, and stigmata of syndromic associations. The examination should include objective measurements of head circumference, height, and weight, along with fundoscopy, visual acuity and fields, assessment of fontanelles and sutures, and a complete neurologic and physical examination. Imaging studies should be appropriate for developmental stage and should be used to verify or rule out clinical suspicions. In some cases, a multidisciplinary approach with

**Table 269-2** Clinical Signs and Symptoms in Pediatric Hydrocephalus

AGE GROUP	SYMPTOMS	SIGNS
Premature infants	Attacks of apnea or bradycardia	Tense and non-pulsatile anterior fontanel Distended scalp veins Abnormal head contour with prominent forehead Rapid (>1 cm/wk) skull circumference increase
Full-term infants	Irritability Vomiting Drowsiness	Full or tense anterior fontanel Distended scalp veins Frontal bossing Widening of cranial sutures Cracked pot sign on percussion (Macewen sign) Macrocephaly Poor head control Sixth cranial nerve palsy Setting sun sign (appearance of sclera above iris) Impairment of upward gaze
Older children	Steady or progressive headache Vomiting Blurred vision, diplopia Lethargy Personality and behavior changes	Papilledema Spasticity, more in lower limbs Sixth cranial nerve palsy Neuroendocrinopathies

neurologic, ophthalmologic, neurosurgical, and medical genetics referrals is warranted.

### Laboratory Findings

Laboratory studies are most useful in cases of suspected infection, which may alter therapy decisions. Cultures and cytology derived from CSF may be helpful in diagnosing active central nervous system (CNS) infection, in which case placement of a permanent shunt is usually deferred for a temporizing measure such as medical management, serial ventricular or lumbar taps, or ventriculostomy for continuous external CSF drainage.

### Imaging

Skull radiography may demonstrate open sutures and erosion of the dorsum sellae, but is more of historical interest and not generally used for definitive diagnosis. The diagnosis can be made with ultrasonography in the neonatal period, as the open fontanelles provide a corridor for insonation. In older children, computed tomography (CT) was previously the first-line modality used to demonstrate the typical findings of ventriculomegaly, interstitial periventricular edema, and sulcal effacement. Calvarial thinning or delayed suture closure may be present in chronic cases. It should be noted that many centers are replacing CT with magnetic resonance imaging (MRI) as a first-line modality in order to avoid excessive radiation exposure with repeated scans.

On initial evaluation, MRI is recommended to evaluate for aqueductal stenosis and arachnoid adhesions that would not be obvious on CT. This modality is also appropriate for assessing causes of macrocephaly associated with leukoencephalopathy (eg, Alexander and Canavan disease, childhood ataxia with central hypomyelination/vanishing white matter disease, glutaric aciduria type I, L-2-hydroxyglutaric aciduria, and

megalencephalic leukoencephalopathy with subcortical cysts). Prenatal MRI scans are also increasingly available when prenatal ultrasounds are worrisome.

### Diagnostic Procedures

In the absence of space-occupying mass lesions, lumbar puncture may be helpful for identifying increased intracranial pressure. In patients with known shunted hydrocephalus, access to the shunt reservoir via a subcutaneous puncture can allow interrogation of the shunt system and collection of CSF for laboratory evaluation, but this should be used only in rare and specific cases. In some cases, accessing the intrathecal space for cisternography using dye studies allows for accurate identification of a site of flow obstruction.

### MANAGEMENT

Management decisions for hydrocephalus are made in light of its natural history, in which the upfront untreated mortality is about 50% and the chance of reaching adulthood is about 20%, with most deaths occurring before 18 months of age. Mortality has decreased to 15% since the advent of shunting in the second half of the 20th century.

Some untreated patients probably survive because of slow evolution or arrest of their hydrocephalus and have variable disability, ranging from mild visual disturbance and gait abnormalities to blindness, bed confinement, and a requirement for total nursing assistance. Without treatment, about 40% of those few survivors have normal intellect. Despite the vast improvement in survival with treatment, only about 50% of those patients have normal intellect and a similar percentage are free of severe behavioral disorders. In patients with cognitive deficits, there is no proven relationship between intellectual ability and head circumference or cortical thickness.



### Treatment Approach

Emergency management of the patient *in extremis* from acute hydrocephalus requires airway protection and immediate CSF diversion prior to further evaluation. This is a treatment algorithm distinct from that required for patients with the subacute or chronic presentation. Medical management of childhood hydrocephalus with agents such as acetazolamide, furosemide, or steroids is mostly ineffective and usually only used as a temporizing measure in mild cases.

The first step in surgical evaluation is to determine whether an obstruction to flow exists, such as a posterior fossa tumor, arachnoid cyst, or aqueductal stenosis, whose removal or bypass would allow for reestablishment of normal CSF circulation. Tumors are resected and cysts may be fenestrated to accomplish this goal. In the case of aqueductal stenosis, perforation of cisternal barriers (eg, third ventriculostomy), may be performed to restore continuity of flow from the ventricles to the subarachnoid space. Shunting of multiple compartments may be performed in more complex cases, such as multiloculated hydrocephalus, or Dandy-Walker syndrome.

In cases for which there is no obvious obstruction, disorders of CSF circulation may occur from impaired absorption. Persistent hydrocephalus occurs after resection of obstructive posterior fossa tumors in approximately one-third of cases, requiring placement of a shunt even after normal CSF corridors seem to be reestablished. In cases of ventricular dilatation after intraventricular hemorrhage of prematurity, small infants may be unable to tolerate placement of a ventriculoperitoneal shunt, so CSF diversion is often accomplished in these cases with serial lumbar or ventricular taps, external ventricular drains, ventriculostomy, or subcutaneous ventricular access devices, depending on the institutional experience. Ventricular size may stabilize after several weeks of these temporizing measures, so ventriculoperitoneal shunt placement is deferred until hydrocephalus is shown to persist after the infant weighs at least 2,000 g because of an improved risk-benefit ratio with surgery.

Hydrocephalus in the setting of active bacterial CNS infection is managed with medical treatment and temporary CSF diversion with serial ventricular or lumbar taps, or ventriculostomy for continuous external CSF drainage. Permanent CSF diversion is used for persistent hydrocephalus after an infection is cleared. Multiloculated (complex) hydrocephalus is often related to previous infection, and poses a difficult surgical problem for which multiple catheter placements and endoscopic procedures may be required.

Experts from areas endemic for tuberculosis state that hydrocephalus of tubercular origin is among the most dreaded and difficult types to manage. The disease process involves thick gelatinous exudates within the basal cisterns and tenacious arachnoid scarring that complicate surgical and, in particular, endoscopic treatments. In some centers, medical management of this form of hydrocephalus may be beneficial for clearance of exudate from the basal cisterns in very select cases under strict treatment protocols. A similarly difficult infection that is increasingly seen among

immigrants to the United States is neurocysticercosis, which results in hydrocephalus in 15% to 30% of patients with neurologic symptoms.

### Specific Treatments

#### Cerebrospinal Fluid Shunting

Permanent diversion of CSF from the ventricle to an extracranial absorptive cavity is through a silastic catheter attached to a 1-way valve and pump/reservoir, which may be accessed with a subcutaneous needle for diagnostic procedures. Valves are selected based on the anticipated intracranial pressure of patients, or have magnetically programmable versions than can be adjusted for changing needs. Common shunt types drain into the peritoneum, pleura, or atrium. Flow-control devices may be included in these systems to reduce siphoning effects that occur when the patient is in the upright position.

#### Endoscopic Third Ventriculostomy

Perforation of the floor of the third ventricle and arachnoid membranes of the basal cistern may be accomplished with an endoscope introduced through a frontal burr hole into the ventricular system. This procedure is ideal for aqueductal stenosis, cases in which shunting is problematic because of repeated infections or failures, and hydrocephalus related to pineal region tumors that can be endoscopically biopsied in conjunction with the procedure. The procedure has a higher likelihood of success in older patients with aqueductal stenosis, compared with infants with post-hemorrhagic hydrocephalus.

### ONGOING CARE

#### Follow-up

Children are usually examined 2 to 4 weeks after surgery, then every 3 months for the first year, every 6 months in the second year, and then annually or, at some institutions, biannually. Clinical assessments include developmental milestones, head circumference, and symptoms and signs of increased intracranial pressure or CNS infection.

Adult survivors of childhood hydrocephalus require life-long follow-up, and many patients require shunt surgery during adulthood. Less than 4% of patients can be weaned from their shunt. Therefore, a transition from pediatric to adult care should be coordinated for these patients when they reach the appropriate age.

#### Complications

Common complications of shunting are shown in Box 269-1. In patients followed into adulthood, the overall incidence of shunt failure is reportedly more than 80%. Thus, hospital admissions for shunt complications are more common than for initial placements. Complications are more common in children with shunts from prematurity, which have increased risk of slit-ventricle syndrome, loculated hydrocephalus, and infection.

The most common cause of shunt failure is obstruction of the proximal catheter, usually caused by infiltration by choroid plexus. The overall incidence of

**BOX 269-1 Shunt Complications**

- Infection
- Mechanical failure: breaks, kinks, or migration of catheter into ventricle or brain tissue
- Overdrainage—slit ventricles
- Overdrainage—subdural hygroma or chronic subdural hematoma
- Blockage: proximal or distal, total or partial intermittent
- Complications specific to ventriculocardiac shunts:
  - Thrombosis around the distal tube
  - Cor pulmonale
  - Shunt nephritis
  - Septicemia and pyemic abscesses
- Complications specific to ventriculopleural shunts:
  - Hydrothorax: characterized by respiratory distress
  - Pyothorax
- Abdominal complications of ventriculoperitoneal shunts:
  - Bowel perforation: rare with current catheter materials
  - Pseudocyst: sterile or infected and presenting as obstruction or abdominal swelling
  - Ascites: malabsorption of CSF; sterile or infected
  - Hernia: at shunt insertion incisions

CSF, cerebrospinal fluid.

shunt obstruction is about 40% during the first year, and is higher (45%) with posthemorrhagic hydrocephalus.

**Shunt Obstruction**

Prior to surgical exploration, it may be difficult to determine whether the site of obstruction is at the proximal or distal catheter or at the valve, although a depressed reservoir unable to be pumped or tapped may indicate a proximal obstruction. On the other hand, small ventricles may collapse around a functioning catheter, making the reservoir unable to be pumped without having a true obstruction. The ability to pump a reservoir does not rule out an obstruction, since a functional blockage could potentially be overcome by manual pumping. Tapping the shunt is only indicated in rare and specific cases, and most obstructions can be diagnosed correctly by other means. For programmable shunts, a first step should be to interrogate the setting to ensure that it has not been inadvertently changed.

**Overdrainage**

Overdrainage is a common complication that results in headaches from intracranial hypotension, and can lead to subdural hematomas or hygromas, especially with cases of severe cortical thinning. Anti-siphon valves and programmable shunts have been designed to help alleviate this problem, but it remains quite common. With programmable shunts, the first step to alleviate symptoms is to increase resistance in the valve.

**Infection**

Infection is a frequent complication of shunting, and usually involves skin flora, such as *Staphylococcus epidermidis*, *Propionibacterium*, and *Staphylococcus aureus*. Younger age is a risk factor for infection, the overall rate of which is approximately 7% in infants. Treatment requires explantation of the shunt system with temporary external drainage and intravenous antibiotics. Shunts are reinserted following clearance of infection, as documented by negative cultures.

**PROGNOSIS**

In chronic cases, hydrocephalus patients may have a good quality of life punctuated with unexpected failures of therapy, repeated medical evaluations, and surgical procedures. Shunt malfunction is a permanent risk, with most patients requiring reoperations into adulthood. Endoscopic third ventriculostomy is available as an alternative to shunting for some patients, but also carries a risk of delayed rapid deterioration that may be fatal.

The etiology of hydrocephalus and the timing of surgical treatment are among the most important prognostic factors for outcome. As this condition is the result of a heterogeneous collection of sequelae from congenital anatomic aberrations, intraventricular insults, and infectious or neoplastic processes across the entire span of childhood, it is almost impossible to determine its independent long-term effects. Both congenital and acquired causes of hydrocephalus may have deleterious effects apart from hydrocephalus, such as dysgenesis of the corpus callosum, whereas the direct effects of hydrocephalus from any cause may include ependymal destruction, compression and collapse of cerebral vasculature, white matter displacement, and cortical neuronal injury.

Early studies failed to find a relationship between brain cortical thickness and intellectual ability, but the effect of these anatomic features cannot be isolated from the contributions of associated medical comorbidities and exposures to repeated surgical procedures and their complications.

In a single-institution retrospective study of 156 cases in Japan, fetal hydrocephalus associated with arachnoid cyst, atresia of the foramen of Monro, corpus callosum agenesis, or fetal intracranial hemorrhage resulted in relatively good outcomes, whereas cases associated with holoprosencephaly, encephalocele, genetic syndromes, or viral infections led to poor outcomes.

**PREVENTION**

Reduction of modifiable risk factors through prenatal care and campaigns to decrease endemic infections are likely to have some effect on the incidence of congenital hydrocephalus. Efforts are underway by multi-center networks to establish standard procedure protocols to reduce shunt complications.

**WHEN TO REFER**

- Pediatric neurology referral for macrocephaly with loss of developmental milestones, headaches, or progressive cognitive deficits
- Ophthalmology consultation for papilledema or suspected deficit in visual acuity or fields

- Urgent neurosurgical consultation with radiographic evidence of hydrocephalus
- Rapid increase in head circumference, crossing growth chart lines, should prompt age-appropriate brain imaging

### WHEN TO ADMIT

- Symptoms of acute or chronic hydrocephalus (see Table 269-2)
- Suspected shunt malfunction/infection in patients with treated hydrocephalus

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Hydrocephalus Fact Sheet* (fact sheet), National Institute of Neurological Disorders and Stroke (NINDS) ([www.ninds.nih.gov/disorders/hydrocephalus/detail\\_hydrocephalus.htm](http://www.ninds.nih.gov/disorders/hydrocephalus/detail_hydrocephalus.htm))
- *What Is a Pediatric Neurosurgeon?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Neurosurgeon.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Neurosurgeon.aspx))

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hypothyroidism (Hashimoto thyroiditis) before thyroid function is diminished, a hyperfunctioning thyroid nodule, pituitary resistance to thyroxine ( $T_4$ ) that results in excess secretion of thyrotropin, and factitious hyperthyroidism caused by administration of exogenous thyroid hormone. Graves disease occurs most frequently in early adolescence, is rare in infancy, and occurs infrequently in childhood. Affected patients often have a family history of thyroid disorders. The prevalence of Graves disease is 6 to 8 times greater in girls than it is in boys.

Graves disease, similar to Hashimoto thyroiditis, is an autoimmune disorder that occurs in patients who have a genetic predisposition, which is itself linked to certain human leukocyte antigen haplotypes. The disease results from the interaction between environmental influences and genes, some of which are thyroid-specific genetic loci while others are susceptibility or immunoregulatory genes. The hyperfunction of the thyroid gland in those with Graves disease is caused by autoantibodies directed against the receptor for thyrotropin. These antibodies, called thyrotropin receptor antibodies (TRAbs), are characterized by an overall predominant stimulatory effect on thyroid cells leading to excessive production and release of  $T_4$ . Included among the TRAbs are (1) thyroid-stimulating immunoglobulins (TSIs) that mimic thyrotropin in their stimulatory action on the production of  $T_4$ , (2) thyrotropin-binding inhibitory immunoglobulins (TBIs) that prevent thyrotropin from binding at its receptor and do not stimulate thyroid cells, and (3) thyrotropin-blocking antibodies. Other antibodies detected in patients who have Graves disease include thyroid growth-stimulating antibodies, which contribute to goiter formation, and antithyroglobulin and antithyroperoxidase antibodies that also are found in patients with Hashimoto thyroiditis. Graves disease can occur in conjunction with other endocrine autoimmune diseases, such as type 1 diabetes mellitus, hypoparathyroidism, and Addison disease, or with other autoimmune diseases, such as myasthenia gravis, periodic paralysis, and vitiligo.

### DIFFERENTIAL DIAGNOSIS

Rarely, children who have Hashimoto thyroiditis are thyrotoxic and have a high titer of TSI autoantibodies in addition to antithyroid antibodies. This condition has been called hashitoxicosis and may be differentiated from routine Graves disease in that the hyperthyroidism is usually a transient phase before the progression to permanent hypothyroidism. Other causes of hyperthyroxinemia are rare, including generalized resistance to thyroid hormone that is found in association with attention-deficit/hyperactivity disorder, factitious hyperthyroidism from excessive administration of thyroid hormone, thyrotropin-secreting pituitary adenomas, and binding-protein changes characterized by normal free  $T_4$  and thyrotropin levels. Finally, hyperthyroidism caused by autonomous thyroid adenomas is rare and can be seen in association with the McCune-Albright syndrome (precocious puberty, café-au-lait pigmentation, and polyostotic fibrous dysplasia).

## Chapter 270 HYPERTHYROIDISM

Nicholas Jospe, MD

### DEFINITIONS

Hyperthyroidism is the result of excessive activity of the thyroid gland. The clinical manifestation of excessive circulating thyroid hormone is called thyrotoxicosis.

### ETIOLOGY

With a few exceptions, thyrotoxicosis in children is the result of Graves disease. Other causes of thyrotoxicosis include the early phase of autoimmune

**Table 270-1** Clinical Signs and Symptoms of Children Who Have Graves Disease

SIGNS AND SYMPTOMS	PREVALENCE (%)		
	SAXENA ET AL <sup>a</sup>	MAENPAA ET AL <sup>b</sup>	BARNES ET AL <sup>c</sup>
Goiter	100	100	97
Prominence of eyes	100	69	79
Exophthalmos	77	—	—
Tachycardia	91	41	88
Nervousness	80	74	92
Increased appetite	71	—	67
Weight loss	67	59	50
Emotional lability	41	—	40
Heat intolerance	40	—	25
Frequent stools	16	35	13

<sup>a</sup>Saxena KM, Crawford JD, Talbot NB. Childhood thyrotoxicosis: a long-term perspective. *BMJ*. 1964;2:1153–1158.

<sup>b</sup>Maenpaa J, Hiekala H, Lamberg BA. Childhood hyperthyroidism. *Acta Endocrinol*. 1966;51:321–336.

<sup>c</sup>Barnes VH, Blizzard RM. Antithyroid drug therapy for toxic diffuse goiter (Graves' disease): thirty years experience in children and adolescents. *J Pediatr*. 1977; 91(2):313–320.

### Relevant History and Physical Examination

Table 270-1 lists the clinical signs and symptoms of children who have Graves disease. Early nonspecific findings include changes in behavior such as nervousness, sleeplessness, emotional lability, decreased school performance, or deteriorating handwriting; these findings largely reflect hyperactivity of the sympathetic nervous system. Graves disease often remains undiagnosed for a long time because children can continue their normal activities without complaints that are overtly suggestive of hyperthyroidism. More prominent cardiovascular signs include tachycardia, a widened pulse pressure, and an overactive precordium. Neuromuscular signs and symptoms include tremor, a shortened deep-tendon reflex relaxation phase, fatigability, and proximal muscle weakness. Despite an increased appetite, the child loses weight more often than he or she gains weight and has frequent, loose bowel movements. Increased perspiration, warmth, heat intolerance, and smoothness of skin appear later. With long-standing disease, tall stature may accompany advanced skeletal maturation in childhood; curtailment of final height as a result of early closure of the epiphyses does not occur.

The size of the goiter when first examined is variable, and its presence often goes unnoticed. However, the thyroid gland, usually seen as diffusely enlarged, is soft and has a clearly delineated border. Thyroid gland enlargement may be difficult to discern in overweight or obese youngsters. The examination should include palpating for the presence of a thrill and auscultating for the presence of a bruit. Measuring the size of the lobes and the isthmus is essential in monitoring disease course. Eye findings also are variable, although severe ophthalmopathy is far less common in children than in adults and, if present, is more likely to resolve completely. Findings include prominence of the eyes (proptosis or exophthalmos), a conspicuous stare (caused by lid retraction and a widened palpebral fissure [Figure 270-1]), and lag of the upper lid on downward gaze. These eye findings are caused by a combination

of hyperactivity of the sympathetic system and of mucopolysaccharide accumulation and infiltration of the orbital fat and ocular muscle cells. The TRAbs are thought to be the cause of ophthalmopathy, because orbital fibroblasts express thyrotropin receptors. Most affected children can be treated with topical ophthalmic lubrication, but orbital fat decompression may be required in patients who have advanced conditions. The management of severe ophthalmopathy can be either medical or surgical (orbital decompression, eye muscle surgery or lid surgery). Medical management includes high-dose glucocorticoids or orbital radiotherapy, either alone or in combination. In children, mucopolysaccharide accumulation in skin and subcutaneous tissue, as with pretibial myxedema, is uncommon.

### Laboratory Evaluation

The initial assessment should include measuring serum free  $T_4$  because, in patients with binding protein increases, total  $T_4$  may be high, yet free  $T_4$  and thyrotropin are normal, thereby ruling out hyperthyroidism. This circumstance is particularly relevant to women taking oral contraceptives, in whom the estrogen raises the binding protein levels, thus increasing the levels of total  $T_4$ , and of total triiodothyronine ( $T_3$ ), but does not affect free  $T_4$  or thyrotropin concentrations. The diagnosis of Graves disease rests on demonstrating elevated levels of  $T_4$  and depression of thyrotropin levels to below the lower limit of detectability in a third-generation thyrotropin assay. A comparison of the patient's levels and age-appropriate normal values of  $T_4$  must be performed before a diagnosis of hyperthyroidism can be made. Measurement of  $T_3$  may help confirm the diagnosis of  $T_3$  toxicosis, although this assessment is rarely necessary. In thyrotoxicosis, the response of thyrotropin to thyroid-releasing hormone is blunted severely or absent. The thyroid-releasing hormone stimulation test is necessary only when Graves disease is thought to exist but the diagnosis is unclear. In equivocal situations, measuring TRAbs, which are present in 95% of patients





**Figure 270-1** The patient on the right exhibits a widened palpebral fissure and goiter; her twin, on the left, was unaffected at the time of this photograph, although later she also developed Graves disease.

who have Graves disease, may help to confirm the diagnosis. In pregnant patients, high TSI levels are predictive of neonatal Graves disease.

Measuring thyroid gland uptake of radioiodine ( $^{123}\text{I}$ ) or technetium ( $^{99\text{m}}\text{Tc}$ ) is useful only to distinguish painless thyroiditis from Graves disease. Patients who have thyroiditis (hashitoxicosis) have a low uptake; patients who have Graves disease have a high uptake. Generally, this study is not necessary at the time of diagnosis. However, measuring the thyroid gland uptake is required if radioablative therapy is performed.

## MANAGEMENT

### Antithyroid Medications

#### Thioamides

The aim of treatment is to reduce thyroid hormone production and block its effect on tissue peripherally. To this end, methimazole (Tapazole) is usually prescribed first. Propylthiouracil (PTU) should no longer be given first. Historically, both PTU and methimazole have been used to reduce thyroid hormone synthesis by inhibiting the oxidation and organification of iodide into  $\text{T}_3$  and  $\text{T}_4$ . PTU also blocks the peripheral conversion of  $\text{T}_4$  into the more active form  $\text{T}_3$ . In 2008, a task force investigated reports of increased rates of PTU-induced liver failure in children. This task force and subsequent studies found that the risk of PTU-induced liver failure leading to transplantation was 5-fold higher (1:2,000) in children than in adults. Furthermore, the risk of reversible PTU-induced liver injury was as much as 1 in 200. Because PTU-induced liver injury can be sudden in onset, rapidly progressive, and potentially irreversible, screening transaminases is not helpful in managing risk. Accordingly, PTU use is strongly discouraged in the pediatric population, and the current recommendations limit its use as a bridge to definitive therapy in the setting of an allergy to methimazole or in early pregnancy. PTU and methimazole are equally effective in inhibiting thyroid hormone production. The half-life is

3 to 4 hours for PTU and 6 to 13 hours for methimazole. Both drugs cross the placenta, although PTU does so less than methimazole and therefore is the preferred drug during early pregnancy. Both drugs are present in small quantities in human milk, and breastfeeding may be continued. Therapy induces euthyroidism somewhat faster with methimazole than with PTU—within weeks to a few months—depending on the size of the thyroid gland. Starting doses of PTU range from 5 to 10 mg/kg body weight, with a maximum of 300 mg/day, given in 3 to 4 divided doses; the dose of methimazole is approximately 0.3 to 0.5 mg/kg, with a maximum of 15 mg/day, given in 2 to 3 divided doses. Once thyroid hormone secretion is depressed, maintenance doses may be given in 2 to 3 daily doses for PTU and 1 to 2 for methimazole. Some older adolescents may require more than 15 mg/day, especially at the start of therapy.

#### Graves Disease

Optimal long-term therapy for Graves disease continues to be the subject of research and some controversy. At present, the recommendation is to titrate the dose of antithyroid medication to maintain the patient in a euthyroid state. In a setting of rapidly relapsing and remitting Graves disease, some physicians administer antithyroid medication until the patient becomes hypothyroid and thereafter, supplement with thyroid hormone. These varying approaches have no effect on rates of relapse.

Therapy with antithyroid medication is usually maintained for a minimum of 18 to 24 months, during which time monitoring the size of the thyroid gland and the TRAb levels can be useful, because shrinkage of the thyroid gland and decreasing TRAb titers predict a greater likelihood of remission after discontinuation of therapy. Thereafter, treatment with antithyroid medication can be stopped, and 20% to 40% of patients remain in remission. The risk of relapse after treatment for a median period of 2 years is higher in patients with severe hyperthyroidism at diagnosis,

younger children, and nonwhite children. Continued patient monitoring with thyroid function tests every 6 months is indicated to detect any subclinical relapse of Graves disease. With variable consensus, because the rate of sustained remission is lower than the initial rate of remission and because the relative utility of the markers has not been reached, the following features do predict a lower rate of remission: a gland greater than 2.5 times normal for age, age younger than 12 years, nonwhite ethnicity, elevated baseline TRAb titer and free  $T_4$  greater than 4 ng/dL.

### Side Effects

Potential side effects of the thioamides include minor reactions that subside spontaneously. These reactions include a purpuric and papular rash, urticaria, joint pain, stiffness, hair loss, nausea or headaches, and a serious reaction—agranulocytosis. Agranulocytosis is an idiosyncratic reaction that occurs in 1 in 500 to 1 in 1,000 cases, usually within the first 3 months of therapy after either form of antithyroid medication. Agranulocytosis is commonly dose-dependent with methimazole, and occurs rarely at lower doses. White blood cell count monitoring is not useful in anticipating agranulocytosis because its onset is sudden. Patients thus need to be told about the significance of a sore throat, mouth sores, and fever as potentially heralding agranulocytosis. In addition to supportive treatment, such as antibiotic therapy, discontinuation of thioamide therapy is necessary. Agranulocytosis spontaneously reverses, and the resumption of therapy with a different thioamide does not usually cause agranulocytosis to recur. Finally, reactions such as drug fever, nephritis, hepatitis, or lupus-like reactions are rare.

### Adjuvant $\beta$ -Adrenergic Blockade

In addition to antithyroid medication, adjuvant  $\beta$ -adrenergic blockade may be accomplished with propranolol or atenolol to control the sympathetic hyperactivity of severe Graves disease. This form of therapy is necessary but only until the hyperthyroidism resolves. There may be relative or absolute contraindication in patients who have cardiac failure or asthma. Patients at relative risk may better tolerate  $\beta_1$ -selective drugs such as atenolol.

### Iodide

Iodide has a minor short-term role as adjuvant therapy in patients who develop toxicity to either PTU or methimazole or as adjunctive therapy immediately before thyroidectomy and for treatment of severe thyrotoxicosis. In practice, it is seldom used. The recommendation by the American Thyroid Association is for routine use of supersaturated potassium iodide for attainment of the euthyroid state, with some gland shrinkage and reduced vascularity before thyroidectomy. Iodide works by transient inhibitory effect on iodine organification, leading to a fall in  $T_4$  and  $T_3$ .

### Definitive Therapy

If a relapse of Graves disease occurs when antithyroid medication is discontinued, then the therapeutic choices include either resumption of antithyroid medication or definitive therapy consisting of radioactive iodine (RAI)

or surgery. The choice depends on factors that affect the chances of success of each form of therapy, such as adherence, patient preference, and surgical expertise. The choice between radioactive iodine and surgical thyroidectomy is a matter of personal preference for many, but not all, patients. Patients with very large glands ( $>80$  g) are poor candidates for RAI. Likewise, patients with poorly controlled Graves disease ( $T_4 >20$  ug/dl or free  $T_4 >5$  ng/dl) should undergo RAI with caution because of the risk of thyroid storm. Furthermore, some data suggest that Graves ophthalmopathy can be exacerbated by RAI, so it should be used cautiously in affected patients. Patients who are pregnant, breastfeeding, or at high risk for pregnancy should not undergo RAI. Finally, although the use of RAI has been expanded in recent years to treat younger and younger patients and has not been demonstrably associated with the development secondary thyroid neoplasms, the role of RAI in children younger than 5 years (who are at the highest risk of thyroid cancer after external radiation) is still under investigation.

Although surgery resolves the symptoms faster, RAI is easy to administer, safer, and equally efficacious except in patients (as noted above) for whom it cannot be safely recommended. The potential for surgical complications from injury to adjacent structures (recurrent laryngeal nerve damage and hypoparathyroidism) dictates that referral be made to an experienced surgeon. This recommendation is predicated on a lower rate of complications in the hands of experienced thyroid surgeons compared to general pediatric surgeons. Permanent hypothyroidism after surgery is the desired outcome. RAI therapy is being used more extensively in children because fears regarding thyroid carcinoma, leukemia, and radiation and genetic damage after treatment with a radioactive substance have been alleviated. RAI concentrates in the thyroid gland and induces cell death over time. On average, three-quarters of patients are cured of hyperthyroidism after 1 dose of radioiodine, and a small fraction may require a second dose months after the first dose. However, there remains debate regarding risks and benefit of total thyroidectomy versus RAI therapy because data on long-term cancer risks are missing or equivocal. Pregnancy is a contraindication for RAI therapy because the iodine crosses the placenta and destroys the fetal thyroid. Following RAI, short-term follow-up care including thyroid function tests is required to determine when to institute thyroid hormone replacement, and long-term follow-up care is required as with anyone else on this therapy.

On rare occasions in children, because most nodules are asymptomatic, thyroid nodules grow or cause symptoms and require treatment. For these, minimally invasive approaches appear effective and safe, such as ultrasound-guided laser or radiofrequency thermal ablation, or percutaneous ethanol injection. Finally, hyperfunctioning nodules remain best treated with RAI.

## COMPLICATIONS

### Thyrotoxic Crisis

Unfortunately, no consistently reliable factors predict the natural course of Graves disease in a given patient, aside possibly from goiter size and the severity of

disease at onset. The clinical course of Graves disease ranges from progression to overt hypothyroidism on one hand to progression to thyrotoxic crisis on the other. Thyrotoxic crisis is an exceptional but severe complication. This diagnosis rests on finding uncontrolled hyperthyroidism and is characterized by a constellation of findings, including cardiac failure, tachycardia, hyperthermia, and central nervous system abnormalities such as confusion, apathy, or coma. Infection (even relatively minor) and trauma can be precipitating factors. Therapy must be expeditious and aggressive and should include antithyroid medication, iodide (Lugol iodine or potassium iodide),  $\beta$ -blockade, antipyresis, glucocorticoids, and medications to prevent cardiac failure. The initial setting for care should be an intensive care unit, to ensure aggressive control of hyperthermia with ice packs and cooling blankets, and thyroidectomy may be performed after 1 week of iodine, which also reduces the vascularity of the gland and the risk for thyroid storm.

### Neonatal Thyrotoxicosis

Graves disease is rare in neonates, affecting approximately 2% of the offspring of affected mothers, and is caused by the transplacental passage of thyroid-directed immunoglobulins from the mother. Transplacental passage of maternal antibodies may occur, even if the mother no longer has active thyroid disease. In addition, stimulatory and blocking maternal thyroid antibodies may disappear at different rates, making the course of neonatal Graves disease difficult to predict. Thus its onset may be immediate or delayed for weeks, and its duration may be brief or prolonged, lasting up to 6 months. Notably, transient neonatal hypothyroidism may result from the transfer of maternal TBII. Neonatal hypothyroidism may also be caused by suppression of the hypothalamic-pituitary-thyroid axis by placentally transferred maternal  $T_4$  from mothers with hyperthyroidism.

The clinical signs and symptoms of neonatal Graves disease include microcephaly, frontal bossing, tachycardia, hypertension, irritability, failure to thrive, flushing, exophthalmos, and goiter. Vomiting, diarrhea, hepatosplenomegaly, jaundice, and thrombocytopenia can also occur. Cardiac failure and arrhythmias account for a mortality that approaches 25% when the disease is severe and treated inadequately. Long-term complications are severe and include hypothyroidism, premature craniosynostosis, and intellectual deficits. Until the disease resolves spontaneously, usually within 1 to 3 months as the maternal antibodies are degraded, adjunctive therapy may be necessary, including potassium iodide (KI, Lugol iodine). In severely hyperactive neonates, propranolol, 2 mg/kg/day, and digitalis for cardiac failure may be required. Glucocorticoid therapy may also be beneficial.

### WHEN TO REFER

New diagnosis of hyperthyroidism.

### WHEN TO ADMIT

Routine diagnosis and therapy of hyperthyroidism do not require hospitalization. Some severe complications of the disorder or its therapy (ocular, cardiovascular, and infectious) may be managed by appropriate subspecialists and with hospitalization.

### SUGGESTED READING

Srinivasan S, Misra M. Hyperthyroidism in children. *Pediatr Rev.* 2015;36:239–248

### Chapter 271

## HYPOCALCEMIA, HYPERCALCEMIA, AND HYPERCALCIURIA

Edna Mancilla, MD; Michael A. Levine, MD

Calcium is a fundamental component of the skeleton and is critical in many physiologic processes, including membrane excitability, neuronal activation, muscular contraction, hormonal secretion, and coagulation. Ninety-nine percent of the body's calcium is found in the skeleton in the form of hydroxyapatite crystals, which provide an exchangeable pool of calcium that participates in maintaining the concentration of extracellular calcium within a narrow physiologic range. Overall control of calcium homeostasis requires a complex interplay between the skeleton, intestine, and kidneys and the integrated action of 2 hormones, parathyroid hormone (PTH) and vitamin D. PTH is the principal calciotropic hormone and is secreted from parathyroid glands in inverse proportion to the concentration of serum calcium. The presence of specific calcium-sensing receptors (CaSR) on the surface of parathyroid glands allows the parathyroid cell to monitor the extracellular calcium concentration and facilitates rapid changes in the secretion of PTH. Ultraviolet (UV) light converts 7-dehydrocholesterol in the skin to cholecalciferol (vitamin  $D_3$ ). Alternatively, vitamin D as ergocalciferol (vitamin  $D_2$ ) or cholecalciferol is ingested. Vitamin D is transported by proteins to the liver, where it is converted to 25-hydroxyvitamin D. PTH increases serum calcium levels directly via activation of osteoclastic bone resorption, and indirectly by stimulating renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (calcitriol), which activates intestinal absorption of calcium and osteoclastic bone resorption. When PTH is suppressed because of hypercalcemia, levels of 1,25-dihydroxyvitamin D decline, and thus intestinal calcium absorption declines.

Both calcitriol and PTH stimulate calcium reabsorption in the distal renal tubule. Calcitonin is a minor contributor to regulation of serum calcium levels and can decrease serum calcium by its effects on bone and kidney. Thus, the intestines, kidneys, and bones are the target organs for the calcium-regulating hormones,

**Table 271-1** Representative Normal Values for Age for Serum Total Calcium Concentration

		SERUM TOTAL CALCIUM (MG/DL)	
	AGE	MALE	FEMALE
INFANT	0–7 days	7.6–11.3	7.8–11.2
	8–30 days	8.8–11.6	8.6–11.8
	31–90 days	8.7–11.2	8.2–11
	91–180 days	8.5–11.3	8.0–11.4
	181–365 days	8.0–10.9	8.1–11.0
CHILDREN	1–3 years	8.9–9.9	8.9–9.9
	4–11 years	9.0–10.1	9.0–10.1
	12–13 years	9.0–10.6	9.0–10.6
	14–15 years	9.3–10.7	9.3–10.7
	16–19 years	9.0–10.7	9.0–10.7

Modified from Ghoshal AK, Soldin SJ. Evaluation of the Dade Behring Dimension RxL: integrated chemistry system-pediatric reference ranges. *Clin Chim Acta*. 2003;331(1–2):135–146.

and an abnormality in either the target organs or the hormones involved in mineral homeostasis can lead to hypocalcemia, hypercalcemia, or hypercalciuria.

The normal values for serum calcium are age dependent. The normal range is broader in infants than for older children, and the upper limit decreases with age. Representative normal values for different ages are shown in Table 271-1, but these concentrations will vary slightly depending on specific laboratory technique or assay.

Most laboratories report the total serum calcium level; about half the plasma calcium is ionized and freely diffusible, whereas 10% is bound to citrate and phosphate but able to diffuse into cells. This is the biologically active form of plasma calcium. The remaining 40% is plasma protein bound and not diffusible into cells. Accordingly, when levels of serum albumin are not normal, the total serum calcium will not correspond to the actual level of active (free) calcium. To determine the level of active calcium, one should measure the serum concentration of ionized calcium ( $iCa^{2+}$ ) or measure both serum total calcium and albumin. A useful formula for estimation of “corrected” total calcium, based on the level of serum calcium, is: adjusted total Ca = measured total Ca +  $[0.8 \times (4.0 - \text{measured albumin})]$ . Simple correction algorithms can also be found on many Web sites (see Tools for Practice at the end of the chapter).

## HYPOCALCEMIA

### Definition

Hypocalcemia is defined as a serum calcium level below the normal age-specific reference range (Table 271-1).

### Epidemiology and Etiology

There are unique causes of hypocalcemia that occur during the first days of life (Box 271-1); the etiology of hypocalcemia in the neonatal period is discussed in Chapter 100, Respiratory Distress and Breathing Disorders in the Newborn. Box 271-1 and Table 271-2

### BOX 271-1 Early Neonatal Hypocalcemia (Within 96 Hours After Birth)

#### CAUSE

- Prematurity
- Low birth weight
- Asphyxia
- Respiratory distress
- Hypomagnesemia
- Hypermagnesemia
- Transfusions
- Respiratory or metabolic alkalosis
- Maternal diabetes mellitus
- Maternal hyperparathyroidism/hypercalcemia
- Toxemia of pregnancy

show the more frequent causes of early neonatal (up to 96 hours), late neonatal (days 4–10 of life), and childhood hypocalcemia. Early-onset hypocalcemia is typically associated with a difficult labor or delivery or low birth weight caused by intrauterine growth restriction or prematurity. Late neonatal hypocalcemia is more frequently observed in formula-fed babies and is caused by high phosphate intake; maternal vitamin D deficiency can also cause late-onset hypocalcemia. The prevalence of vitamin D insufficiency is increasing throughout the world, and it is important to note that severe vitamin D deficiency can cause hypocalcemia. The typical causes of vitamin D insufficiency include decreased sun exposure, use of sun blockers, and low dietary intake of vitamin D. Newborns of vitamin D-deficient mothers may have congenital rickets and hypocalcemia. Moreover, infants who are exclusively breastfed and who do not receive vitamin D supplements are at particular risk for vitamin D deficiency after 6 months of age. Another cause of hypocalcemia



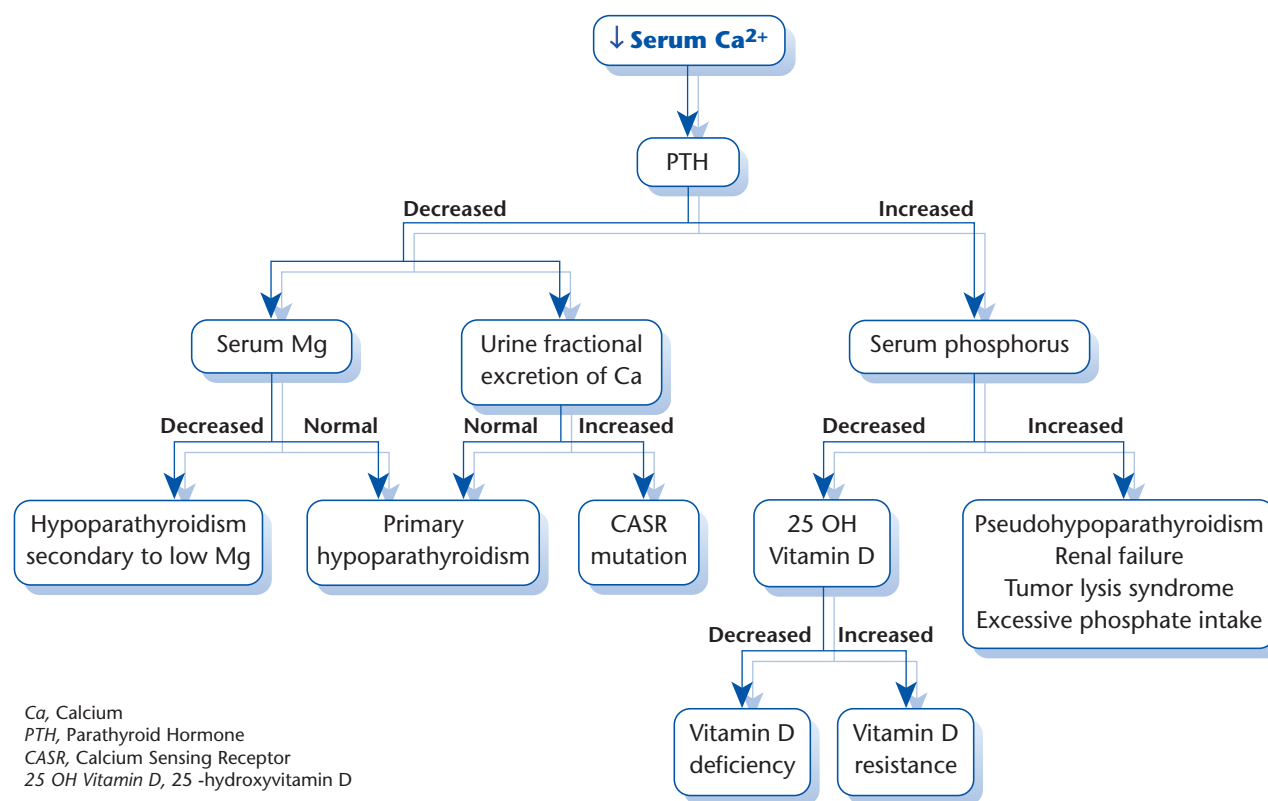
**Table 271-2** Late Neonatal and Childhood Hypocalcemia

CAUSE	GENE	OMIM
<b>HYPOPARATHYROIDISM</b>		
Di George Syndrome	<i>TBX1</i>	188400
Familial: autosomal dominant (AD) autosomal recessive (AR) X-linked	<i>GCM2</i> , <i>PTH</i>	146200
Sporadic		307700
<i>CASR</i> mutation	Activating mutation <i>CASR</i>	601198
Kenny-Caffey syndrome	Tubulin-specific chaperone ( <i>TBCE</i> )	244460
Barakat syndrome (HDR)	<i>GATA3</i>	146255
Kearns-Sayre syndrome	Mitochondrial DNA deletion	530000
Autoimmune polyglandular syndrome type 1	<i>AIRE</i> (autoimmune regulator)	240300
<b>PSEUDOHYPOPARATHYROIDISM</b>		
Type 1a	Loss-of-function mutation in <i>GNAS</i>	103580
Type 1b	Methylation and imprinting defects in <i>GNAS</i>	603233
<b>ACQUIRED HYPOPARATHYROIDISM (CHILDHOOD)</b>		
Autoimmune		
Activating antibodies to <i>CASR</i>		
Postsurgical		
Infiltrative disease (hemochromatosis, Wilson disease, thalassemia, granulomatous disease)		
Radiation		
Hypomagnesemia		
Hypermagnesemia		
<b>VITAMIN D DEFICIENCY</b>		
Nutritional		
Malabsorption		
Vitamin D–dependent rickets type 1 <i>VDDR1</i>	25 -OH D <sub>3</sub> -1- $\alpha$ -hydroxylase ( <i>CYP27B1</i> gene)	264700
Vitamin D–dependent rickets type 2 <i>VDDR2</i>	Vitamin D receptor	277440
<b>HYPERPHOSPHATEMIA</b>		
Excessive ingestion of phosphate (evaporated milk)		
Renal failure		
Tumor lysis		
<b>DRUGS</b>		
Diuretics		
Chemotherapy		
<b>SEPSIS, BURNS</b>		

in young infants is congenital hypoparathyroidism. Hypoparathyroidism may be the result of genetic defects in genes involved in parathyroid gland formation, such as loss of *TBX1* as occurs in DiGeorge sequence or *GCM2* as occurs in isolated hypoparathyroidism. By contrast, mutations in the *PTH* gene or the *CASR* gene impair synthesis or secretion of PTH, respectively. In the older child, hypoparathyroidism is the most common endocrine presentation of autoimmune polyglandular syndrome type 1 (APS1) caused by homozygous mutations in the *AIRE* gene. Pseudohypoparathyroidism (PHP) is an unusual cause of biochemical hypoparathyroidism, but circulating levels of PTH are markedly elevated as a result of renal resistance to PTH. Patients with PHP 1a have mutations on the maternal *GNAS* allele that reduce expression or function of Gs $\alpha$ , the protein that couples

many heptahelical receptors to activation of adenylyl cyclase. *GNAS* is a complex imprinted gene, and patients with PHP 1b have other mutations that cause epigenetic *GNAS* defects that impair expression of the maternal *GNAS* allele. Patients with PHP 1a also have resistance to other hormones and manifest hypothyroidism, growth hormone deficiency, and hypogonadism caused by resistance to thyrotropin, growth hormone-releasing hormone, and gonadotropins, respectively. In addition, patients with PHP 1a also manifest a constellation of skeletal defects that are collectively termed Albright hereditary osteodystrophy and that include short stature, brachydactyly, and ectopic ossification.

Hyperphosphatemia can induce hypocalcemia and may occur in children of any age. Hyperphosphatemia can result from excessive intake of phosphate in the form of laxatives or enemas, or secondary to renal



**Figure 271-1** Diagnostic algorithm for hypocalcemia.

failure or tumor lysis syndrome. Lastly, disorders of magnesium homeostasis are common causes of hypocalcemia; hypomagnesemia impairs renal responsiveness to PTH, whereas hypermagnesemia reduces parathyroid secretion of PTH.

### Diagnosis

#### Signs and Symptoms

Hypocalcemia leads to increased neuromuscular excitability causing hyperreflexia, jitteriness, apnea, paresthesias, laryngospasm, and tetany. The older child with hypocalcemia will have a positive Chvostek or Trousseau sign. Central nervous symptoms include irritability, localized or generalized seizures, fatigue, depression, and coma. Cardiac conduction defects may also be observed.

#### Laboratory Findings

Laboratory evaluation should include measurement of serum total and ionized calcium, phosphorus, magnesium, PTH, 25-hydroxyvitamin D; a spot urine calcium and creatinine can be helpful because the calcium-to-creatinine (Ca/Cr) ratio should be very low in patients with hypocalcemia. The vitamin D metabolite that best reflects the body's vitamin D status is 25-hydroxyvitamin D, and thus this metabolite, and not 1,25-dihydroxyvitamin D, should be measured in the initial evaluation. Electrocardiography may show a prolonged QTc interval. Patients with hypoparathyroidism will have low (or inappropriate) normal serum PTH levels, whereas patients with PHP will have

elevated serum levels of PTH. In both conditions, serum phosphorus levels are elevated. By contrast, patients with vitamin D deficiency will have elevated serum PTH levels and hypophosphatemia because proximal renal tubular reabsorption of phosphorus is reduced in response to PTH action.

#### Imaging

Cerebral calcifications may be observed in chronic hypocalcemia when the calcium-phosphate product has been elevated because of hyperphosphatemia. It is recommended to maintain the calcium-phosphate product less than  $55 \text{ mg}^2/\text{dL}^2$  for several years. This occurs most commonly in patients with hypoparathyroidism, PHP, and chronic renal insufficiency.

Long bone radiographs may show demineralization and rachitic changes, such as cupping and fraying of the metaphysis, when hypocalcemia is associated with hypophosphatemia. This occurs most commonly in patients with vitamin D deficiency or resistance, in whom secondary (adaptive) hyperparathyroidism leads to reduced tubular resorption of phosphorus.

#### Diagnostic Approach

A reasonable diagnostic approach is summarized in the algorithm in Figure 271-1.

### Management

#### Neonatal Hypocalcemia

Early-onset hypocalcemia may require treatment with oral calcium supplementation (40–80 mg/kg per day in

divided doses) for several days; in cases of symptomatic hypocalcemia, intravenous infusion of calcium may be required. Neonates with late-onset hypocalcemia will require supplementation of infant formula with elemental calcium to achieve a 4:1 ratio of calcium to phosphorus; vitamin D or calcitriol may also be necessary.

### Outpatient Management

Optimal treatment of hypocalcemia requires both vitamin D and oral calcium supplementation. A typical regimen is 20 to 50 mg per kg of elemental calcium daily in divided doses; calcium should best be taken with meals when the serum phosphorus level is elevated. Various calcium salts are available and differ in the amount of elemental calcium per gram of salt: calcium carbonate (40% calcium), calcium citrate (21% calcium), or calcium gluconate (9% calcium). In cases of concomitant antacid medication, calcium citrate is preferred. Magnesium supplements should be used when serum magnesium is low. Vitamin D deficiency is treated with vitamin D in the form of cholecalciferol (vitamin D<sub>3</sub>) or ergocalciferol (vitamin D<sub>2</sub>), 1,000 to 4,000 units per day, with careful monitoring to ensure adequate replacement and to avoid toxicity.

Patients with chronic hypocalcemia, as in hypoparathyroidism, PHP, or vitamin D-dependent rickets, should be treated with calcium supplements plus calcitriol (50–90 ng/kg/day in 2 divided doses). Calcitriol has a much shorter half-life than other forms of vitamin D and does not require PTH action for full biologic effect.

### Admission to Hospital

Patients with acute and symptomatic hypocalcemia require hospital admission and treatment with intravenous calcium. Injections of calcium salts are recommended only in acute cardiac emergencies. In all other cases of symptomatic hypocalcemia, a continuous infusion of calcium, at a rate of 1 to 3 mg/kg per hour of elemental calcium (such as 10% calcium gluconate) will safely normalize serum calcium levels and maintain constant concentrations better than repeated bolus infusions. Once the serum calcium level has been normalized, the patient can be transitioned to oral therapy with calcium and vitamin D.

### Ongoing Care

Regular follow-up by an endocrinologist is indicated in chronic hypocalcemia. Calcium supplements and vitamin D treatment should be adjusted to maintain calcium levels in the low-normal range to avoid hypercalciuria.

### Complications

Nephrocalcinosis and nephrolithiasis are rare complications of hypercalcemia and hypercalciuria. Thus, both serum and urine calcium concentrations should be regularly monitored. Spot urine collections may be used to determine urinary calcium and creatinine concentrations for screening Ca/Cr ratios (normal values detailed below in the section on hypercalciuria).

### Prevention

Calcium and vitamin D deficiency should be prevented by an adequate diet and sun exposure. The current recommended daily intake for vitamin D is 400 IU for infants, children, and adolescents, but some children may require higher doses to maintain normal serum levels of 25-hydroxyvitamin D (>30 ng/mL). All breast-fed infants will need to be supplemented with 400 IU of vitamin D per day. The recommended calcium intake by age in the United States increases from 210 mg/day at 0 to 6 months of age to 1,300 mg/day at 9 to 18 years.

## HYPERCALCEMIA

### Definition

Hypercalcemia is defined as a serum calcium level above the normal age specific range (Table 271-1).

### Epidemiology and Etiology

In children and adolescents, the most common causes of hypercalcemia are increased PTH secretion, increased vitamin D ingestion or activation, decreased serum phosphate levels, or increased bone resorption from immobilization, cancer, or hyperthyroidism. Osteoclastic bone resorption is increased in nearly all cases of hypercalcemia. The causes of hypercalcemia may be categorized by age. In particular, hypercalcemia in the neonatal period may be related to maternal disorders of mineral metabolism, which are described in Chapter 100, Respiratory Distress and Breathing Disorders in the Newborn. When hypercalcemia occurs within the first few weeks of life, the cause is usually hyperparathyroidism owing to prior gestational hypocalcemia or familial hypocalciuric hypercalcemia (FHH), subcutaneous fat necrosis, or Williams syndrome. Some newborns may present with life-threatening hypercalcemia and marked skeletal demineralization, a variant of FHH that has been termed *severe neonatal hyperparathyroidism* (NSHPT). In older children, hypercalcemia is most commonly caused by primary hyperparathyroidism, immobilization, malignancy, and granulomatous disease (Table 271-2). A comprehensive listing of the causes of hypercalcemia in these 2 age groups is presented in Table 271-3 and Table 271-4.

### Diagnosis

#### Signs and Symptoms

The signs and symptoms of hypercalcemia will reflect the acuity and degree of hypercalcemia as well as the patient's age. Moderate to severe hypercalcemia affects the nervous system, leading to weakness, hypotonia, lethargy, and seizures. Significant polyuria leading to dehydration is produced by stimulation of the CaSR in the renal collecting ducts. When hypercalciuria is severe, nephrocalcinosis, nephrolithiasis, and hematuria may be initial manifestations of hypercalcemia. Gastrointestinal complaints such as anorexia, nausea, vomiting, and abdominal pain may be observed and are often accompanied by failure to thrive. Cardiovascular signs include hypertension and abnormalities in cardiac conduction. In neonates and infants, symptoms are nonspecific and hypercalcemia may be detected in the workup for failure to thrive.

**Table 271-3** Early-Onset Hypercalcemia (up to 2 years of age)

CAUSE	GENE	OMIM
<b>Maternal</b>		
Hypoparathyroidism or hypocalcemia		
Pseudohypoparathyroidism		
Vitamin D deficiency		
<b>Calcium or vitamin D excess</b>		
<b>Hypophosphatemia</b>		
<b>Hyperparathyroidism</b>		
Neonatal severe due to <i>CASR</i> mutation	Homozygous inactivating <i>CASR</i> mutations	239200
Familial hypocalciuric hypercalcemia	Heterozygous inactivating <i>CASR</i> mutations	145980
<b>Williams syndrome</b>	<i>DEL7q11</i>	194050
<b>Subcutaneous fat necrosis</b>		
<b>Infantile hypophosphatasia</b>	<i>ALPL</i>	241500
<b>Jansen metaphyseal chondrodysplasia</b>	Activating mutations <i>PTH1</i>	156400
<b>Lactase (disaccharidase) deficiency</b>		
<b>Bartter syndrome</b>	Na-K-2Cl cotransporter <i>NKCC2</i> ( <i>SLC12A1</i> )	601678
	Adenosine triphosphate-sensitive potassium channel <i>ROMK</i> ( <i>KCNJ1</i> )	241200

**Table 271-4** Late Hypercalcemia (over 2 years of age)

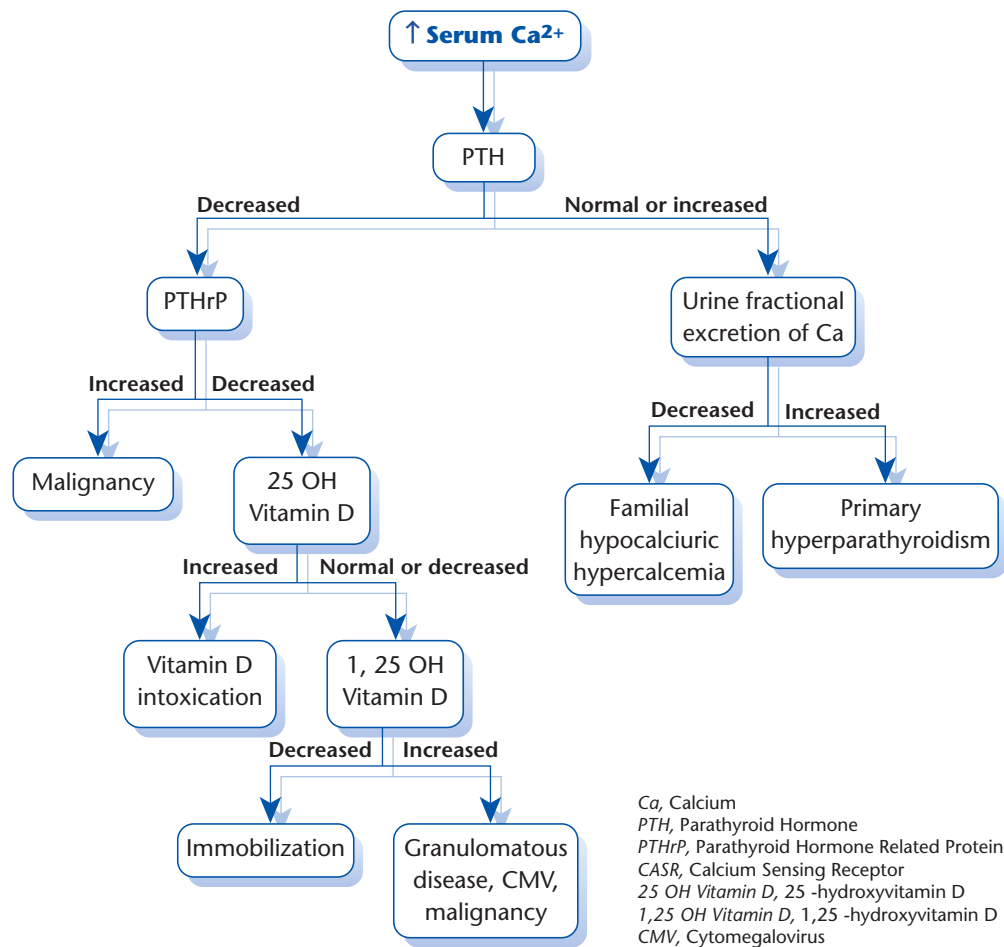
CAUSE	GENE	OMIM
<b>Excessive calcium intake</b>		
<b>Hypophosphatemia</b>		
<b>Hyperparathyroidism</b>		
Sporadic		
Familial		
MEN 1	<i>MEN1</i>	131100
MEN 2A	<i>Ret</i>	171400
Hyperparathyroidism—jaw tumor	<i>CDC73</i>	145001
CASR inactivating mutation	<i>CASR</i>	145980
<b>Jansen metaphyseal chondrodysplasia</b>	<i>PTH1</i>	156400
<b>Vitamin D excess</b>		
Nutritional		
Inflammatory/granulomatous disease		
<b>Immobilization</b>		
<b>Associated with malignancy</b>		
PTH-related peptide-mediated humoral hypercalcemia of malignancy		
Osseous metastasis		
Primary bone tumors		
<b>Renal tubular acidosis, proximal</b>		179830
<b>Renal tubular acidosis, distal</b>	<i>SLC4A1</i>	179800
<b>Endocrine disorders</b>		
Hyperthyroidism		
Hypoadrenalism		
Pheochromocytoma		
Vasoactive intestinal peptide-secreting tumors		
<b>Drugs</b>		
Thiazide diuretics, lithium, theophylline, retinoid derivatives		

### Laboratory Findings

Laboratory evaluation should include measurement of serum total and ionized calcium, phosphorus, magnesium, PTH, 25-hydroxyvitamin D, and calcitriol, as well as urinary calcium and creatinine. Hypercalcemia with hypophosphatemia is observed in hyperparathyroidism,

and an inappropriately elevated PTH level for the calcium level will confirm this diagnosis. Children with FHH or NSPHT will have very low urinary calcium levels with fractional calcium excretion (FeCa) that is less than 1%. Hypercalcemia with a low PTH level may be caused by increased vitamin D intake (elevated





**Figure 271-2** Diagnostic algorithm for hypercalcemia.

serum 25-hydroxyvitamin D) or activation (elevated serum calcitriol) or malignancy (often with increased PTHrP levels). Immobilization and calcium gluttomy are associated with low serum levels of PTH and vitamin D metabolites but markedly increased urinary calcium excretion.

### Imaging

Imaging studies should be reserved for confirmation of a biochemical diagnosis. Technetium-99m sestamibi scanning and neck ultrasound can identify a solitary parathyroid adenoma in 60% to 90% of patients with primary hyperparathyroidism. End-organ damage is assessed by renal ultrasound and radiographs. Renal ultrasound may reveal the presence of nephrocalcinosis or nephrolithiasis. Skeletal radiographs may disclose demineralization or subperiosteal resorption in some cases of primary hyperparathyroidism, but dual-energy x-ray absorptiometry (DXA) is a far more sensitive procedure that can demonstrate reduced bone density in most patients with longstanding hypercalcemia.

### Diagnostic Approach

A suggested diagnostic approach is found in the algorithm in Figure 271-2.

### Management

#### Outpatient Referral

Children with mild asymptomatic hypercalcemia should be referred for outpatient evaluation. The need for treatment depends on the degree of hypercalcemia and the presence or absence of clinical symptoms. If calcium levels are lower than 12 mg/dL and the patient has no symptoms, it is usually unnecessary to treat the hypercalcemia. Children with mild hypercalcemia, Williams syndrome, or vitamin D excess may require nothing more than a low-calcium, low-vitamin D diet. Patients with asymptomatic hypercalcemia caused by FHH require no intervention.

#### Admission to Hospital

Patients with moderate calcium elevations (12–14 mg/dL) and symptoms consistent with hypercalcemia should be admitted to the hospital. Patients without symptoms may require only adequate hydration. Patients with calcium levels higher than 14 mg/dL should be treated aggressively, regardless of symptoms. The main goals of treatment are to increase urinary calcium excretion and decrease bone resorption. Aggressive hydration with normal saline is the initial treatment with the aim of inducing a natriuresis

that will enhance urinary calcium excretion. Volume expansion using intravenous saline infusion will result in a marked increase in sodium, calcium, and water delivery to the loop of Henle, with consequent marked increase in urinary excretion of calcium as well as sodium, potassium, chloride, magnesium, and water. It is important to replace water, sodium, potassium, and chloride continuously and, if this regimen exceeds 10 hours, to replace magnesium. In older adolescents, the urinary flow should exceed 250 mL/hr during this time, and the serum calcium level will start decreasing within 2 to 4 hours and approach the normal range in 12 to 24 hours. In most patients, the intravenous infusion of saline will effect a satisfactory diuresis; potent loop diuretics are rarely necessary and should be avoided or used with extreme caution because these agents may paradoxically worsen hypercalcemia by inducing dehydration and decreasing the glomerular filtration rate. Parenteral calcitonin and intravenous bisphosphonates decrease osteoclastic activity and are generally effective in hypercalcemic patients with increased bone resorption regardless of the etiology. Calcitonin can be given subcutaneously or intramuscularly every 12 hours (4 IU/kg). Its action is rapid (4–6 hours), and the calcium level is usually lowered by 1 to 2 mg/dL. However, calcitonin is effective in only 60% to 70% of patients, and most of them develop tachyphylaxis in 48 to 72 hours. Intravenous bisphosphonates can lower the serum calcium level with a maximal effect in 2 to 4 days. The duration of effect is 1 to 4 weeks and varies according to the underlying cause of hypercalcemia and the specific bisphosphonate. Pamidronate and zoledronate are the most effective bisphosphonates for treatment of hypercalcemia. Zoledronate is the most potent bisphosphonate and has the longest lasting effect; it is given in a 30-minute IV infusion (up to 4 mg). Pamidronate is given by IV infusion over 4 to 24 hours. The initial dose varies, and in children with normal renal function, a typical dose consists of 1 to 2 mg/kg, up to 30 mg if the calcium level is lower than 12 mg/dL, 60 mg if the calcium level is 12 to 13.5 mg/dL, and 90 mg if the calcium level is above that level. A subsequent dose of an intravenous bisphosphonate can be given after 7 days. Because it may take several days for bisphosphonates to reduce the serum calcium level, these agents should be used in combination with rapid-acting therapies such as IV saline infusion and calcitonin injections. Initial treatment is followed by etiology-specific treatment (eg, cinacalcet or surgery in primary hyperparathyroidism; corticosteroids or ketoconazole, chloroquine, and hydroxychloroquine to inhibit calcitriol production in cases of lymphoma or granulomatous disease).

### Ongoing Care

Follow-up will depend on the etiology. Hyperparathyroidism caused by adenomas in children is most often from a single adenoma and is cured by surgery. Other causes may require chronic follow-up to prevent complications.

### Complications

Bone disease secondary to increased resorption in hyperparathyroidism should be prevented by timely

**Table 271-5** Spot Urine Ca/Cr Ratio

AGE	CA/CR RATIO
<7 months	0.07–0.86
7–18 months	0.07–0.6
18 months–6 years	0.03–0.42
Adult	0.05–0.22

Derived from Sargent JD, Stukel TA, Kresel J, Klein RZ. Normal values for random urinary calcium to creatinine ratios in infancy. *J Pediatr.* 1993; 123(3):393–397.

resection. Renal disease secondary to hypercalcemia should be prevented or ameliorated by adequate management of the hypercalcemia.

### Prevention

Acute hypercalcemia and end-organ damage are prevented by etiology-specific and prompt symptomatic treatment.

## HYPERCALCIURIA

### Definition

Hypercalciuria is defined as excessive renal excretion of calcium, measured as a urinary calcium excretion of more than 4 mg/kg/day and/or an elevated Ca/Cr ratio for age, in either a spot or timed urine collection (Table 271-5).

### Epidemiology and Etiology

Hypercalciuria occurs in 3% to 6% of children and is most often idiopathic. Causes of hypercalciuria are listed in Table 271-6, including primary and secondary renal tubular disorders, drugs such as the carbonic anhydrase inhibitors, chronic acidosis caused by dietary factors such as a ketogenic diet, increased gastrointestinal absorption of calcium, and increased osteoclastic bone resorption. Hypercalciuria is a risk factor for nephrolithiasis, nephrocalcinosis, and low bone density. The relative risk for stone production seems to be a continuous function of urinary calcium excretion rather than a threshold effect, such that a single arbitrary level cannot distinguish healthy people from those who form stones. Although the total 24-hour urinary calcium excretion remains a useful measure, it is likely that the urinary calcium concentration is a more reliable predictor of stone formation risk.

The most common types of clinically significant hypercalciuria are absorptive, renal leak, resorptive, and renal phosphate leak. Although the genes involved in many forms of hypercalciuria are now known, the genetic basis for hypercalciuria in most patients remains unknown. The most common cause of hypercalciuria is absorptive hypercalciuria, which is characterized by an increase in the gastrointestinal absorption of calcium. This produces a mild increase in serum calcium levels that depresses PTH secretion. Typically, serum PTH is in the low-normal range. Serum levels of 1,25-dihydroxyvitamin D are elevated in about half of affected patients. Absorptive hypercalciuria can be classified into 3 types. Type I is relatively uncommon

**Table 271-6** Causes of Hypercalciuria

CAUSE	GENE	OMIM
<b>Familial idiopathic hypercalciuria</b>		
<b>Dent disease</b>	<i>CLCN5</i>	300009
<b>Bartter syndrome</b>	<i>NaK-2Cl (SLC12A1)</i> <i>ROMK (KCNJ1)</i>	601678 241200
<b>Distal renal tubular acidosis</b>		
Autosomal dominant	Erythrocyte anion exchanger	179800
Autosomal recessive	H <sup>+</sup> ATPase	
<b>Familial hypomagnesemia with hypercalciuria</b>		248250
<b>Familial hypomagnesemia with hypercalciuria and ocular involvement</b>	<i>Claudin 19 (CLDN19)</i>	248190
<b>Activating CaSR mutation</b>	<i>CASR</i>	601198
<b>Hereditary hypophosphatemic rickets with hypercalciuria</b>	<i>NPT2c (SLC34A3)</i>	241530
<b>Lowe syndrome</b>	<i>OCRL1</i>	309000
<b>Ketogenic diet</b>		
<b>Associated with hypercalcemia</b>		
<b>Drugs</b>		
Topiramate, Zonisamide		

and is the most severe type of absorptive hypercalciuria. Urinary calcium excretion is relatively unresponsive to dietary modifications, including severe dietary calcium restriction, but can normalize during periods of fasting. Type II absorptive hypercalciuria is the most common form and is responsive to moderate dietary calcium restriction. Type III absorptive hypercalciuria is related to a renal phosphate leak and is also relatively uncommon. Renal hyperphosphaturia is related to a defect in expression or function of sodium-phosphate cotransporters and causes mild hypophosphatemia. The low serum phosphate suppresses serum levels of FGF23, a phosphatonin that decreases expression of sodium-phosphate cotransporters and activity of the CYP27B enzyme that catalyzes 1 $\alpha$ -hydroxylation of 25-hydroxyvitamin D. Thus, suppression of FGF23 increases the synthesis of 1,25-dihydroxyvitamin D and thereby increases intestinal absorption of both phosphate and calcium. The unnecessary calcium absorbed is ultimately excreted in the urine, causing the hypercalciuria.

Renal leak hypercalciuria is far less common than absorptive hypercalciuria and is caused by defects in the kidneys that impair renal calcium resorption. The primary renal loss of calcium leads to mild hypocalcemia and secondary hyperparathyroidism, which is useful in diagnosing this condition.

Resorptive hypercalciuria is the result of increased osteoclastic bone resorption. Calcium and phosphorus are released from the skeleton in response to unknown factors, which suppresses serum levels of PTH and 1,25-dihydroxyvitamin D. The low serum levels of PTH and 1,25-dihydroxyvitamin D inhibit renal calcium reabsorption, and in the face of an increased filtered load of calcium, significant hypercalciuria ensues.

## Diagnosis

### Signs and Symptoms

Hypercalciuria may present with symptoms such as dysuria or abdominal or flank pain; there may

be nephrolithiasis, recurrent urinary tract infections, or osteoporosis. Physical examination may reveal growth restriction as a manifestation of renal tubular acidosis. Symptoms of hypercalcemia may be predominant when hypercalciuria is secondary to one of the hypercalcemic disorders listed in the previous section.

### Laboratory Evaluation

Evaluation of urinary calcium excretion preferably includes a 24-hour urine collection for calcium, creatinine, sodium, potassium, citrate, and oxalate. Serum calcium should be measured, and if elevated, a comprehensive evaluation of hypercalcemia should follow, as detailed in the section above.

### Imaging

Renal ultrasound may show nephrolithiasis or nephrocalcinosis. Computed tomography scan or intravenous pyelogram may be necessary to clarify a questionable obstruction or stones.

## Management

### Outpatient Referral

Patients with an active renal stone or a past history of renal stone should be referred for evaluation by a specialist. Management will depend on the pathophysiology as described previously. Symptomatic hypercalciuria should be treated with dietary measures and pharmacotherapy. Dietary management consists of increasing fluid intake and reducing the daily intake of sodium. Sodium intake should not exceed the recommended daily allowance of 1.2 g/day for 4- to 8-year-olds and 1.5 g/day for 9- to 18-year-olds. Calcium intake should be maintained at recommended values for age to avoid bone demineralization. Primary pharmacologic therapy focuses on reducing urinary excretion of calcium and includes thiazides, orthophosphates, and potassium citrate. Other therapies are more directed at reducing intestinal absorption

of calcium through the use of sodium cellulose phosphate and increased fiber. Dipyridamole has been used with limited success to increase the renal tubular reabsorption of phosphorus and reduce synthesis of 1,25-dihydroxyvitamin D, and is a particularly attractive option in patients with a renal phosphorus leak. Patients with increased osteoclastic bone resorption, so-called resorptive hypercalciuria, may benefit from use of bisphosphonates, such as oral alendronate or intravenous pamidronate or zoledronic acid, which increase bone deposition of calcium, thus removing it from the circulation before it can be excreted. This improves bone density and helps reduce urinary calcium levels. The main benefit may be in protecting the bones from calcium depletion and demineralization in hypercalciuric patients.

Potassium citrate prevents nephrolithiasis and is especially useful in patients with renal tubular acidosis. It has also been suggested to prevent lithiasis in patients with a ketogenic diet. In many instances, several drugs will be required to effectively reduce excessive urinary calcium excretion. Ultimately, the success of these therapeutic interventions will be limited by several factors that together reduce adherence over time. First, patients are often disappointed by the development of medication side effects, which range from hypokalemia and hypomagnesemia from thiazides to diarrhea and gastrointestinal distress from phosphate salts. Second, patients often become discouraged by the necessity for lifelong treatment. And lastly, in the absence of clinically active stone disease, patients are usually asymptomatic despite significant hypercalciuria and thus do not perceive any benefit from long-term treatment.

### Admission to Hospital

Hypercalciuria per se will not require hospitalization unless there is obstructive stone disease or infection.

### Ongoing Care

Follow-up is scheduled at regular intervals to monitor therapy and complications.

### Complications

Complications include renal infection or insufficiency secondary to untreated lithiasis.

### Prevention

Nutritional and medical treatment should be maintained in symptomatic patients to prevent recurrent lithiasis.

## SUMMARY

In summary, a few basic laboratory tests, including serum calcium, phosphorus, alkaline phosphatase, 25-hydroxyvitamin D and PTH, and urine studies, will direct the physician toward an effective diagnosis of patients with hypercalcemia, hypocalcemia, or hypercalciuria. Further testing and imaging studies may be needed depending on the initial findings and are usually deferred to the specialist. We have increasing knowledge of the molecular etiology of many genetic disorders of mineral metabolism, and these gene tests may be of value in confirming the diagnosis and providing the basis for genetic counseling.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Hypercalcuria in Children* (fact sheet), University of Wisconsin-Madison School of Medicine and Public Health ([www.uwhealth.org/healthfacts/parenting/5701.pdf](http://www.uwhealth.org/healthfacts/parenting/5701.pdf))

### Medical Decision Support

- *Calcium Correction for Hypoalbuminemia* (clinical calculator), MDCalc ([www.mdcalc.com/calcium-correction-for-hypoalbuminemia](http://www.mdcalc.com/calcium-correction-for-hypoalbuminemia))
- *Corrected Calcium Calculator* (clinical calculator), Global RPh ([www.globalrph.com/calcium.htm](http://www.globalrph.com/calcium.htm))

## AAP POLICY

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## Chapter 272

# HYPOSPADIAS, EPISPADIAS, AND CRYPTORCHIDISM

Brian Inouye, MD; Ali Tourchi, MD; John P. Gearhart, MD

Abnormal neonatal genitalia worry parents. While male hypospadias, epispadias, and cryptorchidism are readily accessible for observation, and thus cause more parental preoccupation, female hypospadias and epispadias are also problematic. While cosmesis and sexual function are the initial concerns, genitourinary complications may arise and warrant pediatric urologic consultation.

## GENITAL ABNORMALITY

An external genital deformity in the infant boy is usually obvious. Penile size is one cause of parental distress that is not often noted at birth but perhaps



several weeks later as the baby gains weight. A retracted penis may seem to disappear despite being 4 cm long in a suprapubic pad of fat. The parents should be assured kindly that the condition will correct itself in time. Only rarely does a real problem exist, namely a micropenis, in which the penis has a stretched length of less than 2 standard deviations below the mean or is less than 2.5 cm in length, which suggests a dysmorphic abnormality. Circumcision should be delayed in infants who have micropenis and should not be performed until a thorough evaluation has been performed by a pediatric endocrinologist and a pediatric urologist.

### Hypospadias

Hypospadias is one of the most frequent genital problems, occurring approximately in 1 out of 200 male births, with recent studies suggesting an increasing incidence. This anomaly consists of maldevelopment of the ventral aspect of the penis, urethra, corpora spongiosum and cavernosa, and ventral prepuce. It also commonly presents with chordee and penile hypoplasia.

The exact mechanism remains unknown; however, it is most likely multifactorial. Endocrine disruptors, such as maternal use of progestins and in vitro fertilization, seem to increase the risk of hypospadias. Furthermore, over the past 3 decades, the incidence of hypospadias has increased with the use of environmental chemicals such as polychlorinated biphenyls and polyhalogenated hydrocarbons and phthalates.

This anomaly is a continuum, with approximately 70% of cases having an aberrant meatus at the glans penis, subcoronal margin, or on the corona. The remaining hypospadias cases are characterized by a more proximal meatus located at the mid-shaft, scrotal or perineal region (Figure 272-1). Classification used to be determined by the location of the urethral meatus before repair. However, recent classification schema additionally consider the location of the meatus after chordee correction, the glans (cleft, incomplete cleft or flat), the quality and width of the urethra, the prepuce (incomplete or complete), and the degree of the penile curvature and presence of scrotal transposition. This system classifies hypospadias as either anterior, middle, or posterior. Anterior hypospadias, which occurs in 65% of cases, has been further categorized as glanular or subcoronal. Middle hypospadias, which is seen in 15% of cases, is further delineated into distal penile, midshaft, or proximal penile classifications. Posterior hypospadias, occurring in 20% of cases, can be further described as penoscrotal, scrotal, or perineal. Description of the glans can be separated into 3 categories: cleft glans with deep groove and proper clefting, incomplete cleft glans with split glans and shallow groove, or flat glans with no groove and short-ending urethral plate at the glans. Although different categorizations have been proposed to describe hypospadias, it is thought that the severity of hypospadias is still best judged at the time of surgery.

All patients should undergo a complete history and physical examination. Pediatricians should attempt to classify the hypospadias during the examination, making note of chordee, meatal stenosis, penoscrotal

transposition, and penile torsion. Feeling a bulge or dribbling of urine may indicate a diverticulum.

In approximately 10% of cases, an associated unilateral or bilateral cryptorchidism is present. About 25% of these patients have an intersex anomaly requiring consultation from a pediatric endocrinologist and geneticist to evaluate genetic gender and endocrinological abnormalities. Severity of hypospadias is also significantly correlated with intersex disorders requiring the same referral and workup.

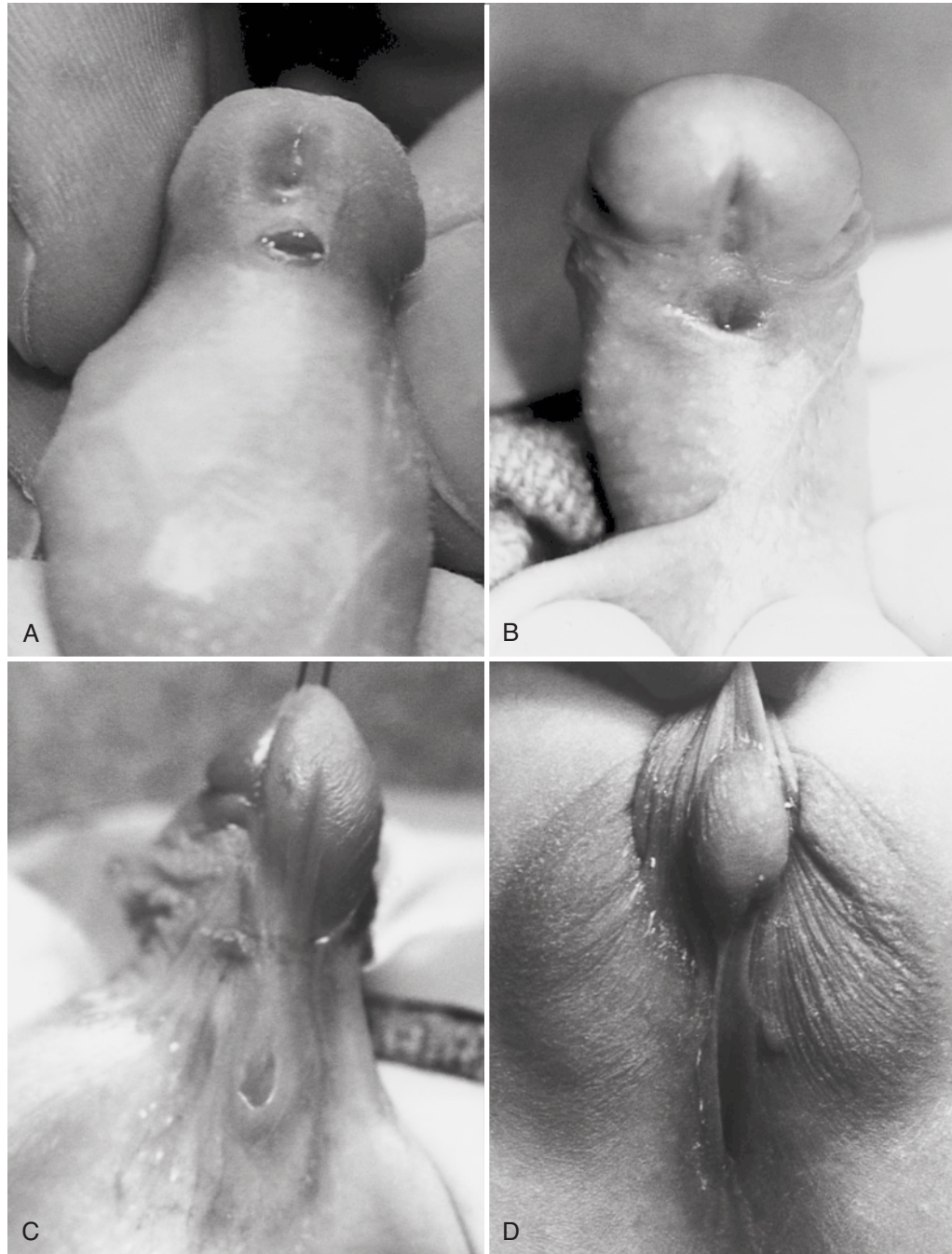
Voiding cystourethrography or retrograde urethrography are rarely performed in patients with anterior hypospadias. However, a voiding cystourethrogram should be carried out in the patient with an enlarged prostatic utricle to understand the utricle anatomy and assess possible future problems in regard to urinary stasis, infection, stone formation, and difficulty with catheterization.

Hypospadias requires surgical correction to create a straight penis, approximate the urethral meatus, normalize voiding and erections, and reconstruct a uniform urethra and glans. Many techniques have similar outcomes after repairing the urethra, skin, and ventral chordee. Because sufficient penile tissue is required for hypospadias repair, circumcision should not be performed prior to hypospadias repair.

The 5 steps in hypospadias repair—orthoplasty, urethroplasty, meatoplasty, scrotoplasty, and skin coverage—can be done in a single stage or multiple stages. While microsurgery favored single-stage repairs in the past, recent techniques for mobilizing and transecting the urethral plate while lengthening the corpora have popularized the 2-staged approach. Still, the 2-staged approach is usually reserved for cases that need a corporoeplasty or if there is a paucity of healthy tissue. Because of similar outcomes, the best technique depends on surgeon experience, meatal position, the meatus and glans configuration, presence or absence of chordee, quality of ventral skin coverage, the quality of urethral plate, the availability of foreskin, and the circumcision status.

Timing of hypospadias repair depends on the environment in which the patient will be managed, risk of anesthesia, penile size, and the psychosexual milestones in infancy and early childhood. Previous guidelines recommended hypospadias surgery after 4 years of age to prevent separation anxiety between the patient and parent. Improved surgical and anesthetic techniques have led to surgery being a 1-day, outpatient procedure that minimizes separation anxiety, allowing it to be done earlier in life to minimize potential psychological disruptions caused by genital surgery. As the risk of anesthesia after the age of 6 months does not differ from that in older patients, the American Academy of Pediatrics suggests that the optimal time for hypospadias repair is between 6 and 12 months of age.

Perioperative hormonal therapy is controversial. Five percent testosterone cream or intramuscular injections of testosterone propionate can enhance penile size before the surgery by inducing better penile vascularization and increasing size of the urethral plate. Furthermore, several studies have advised androgen stimulation in patients with a small genital tubercle



**Figure 272-1** Varieties of hypospadias. **A**, Coronal. **B**, Distal shaft. **C**, Penoscrotal. **D**, Perineal.

(<25 mm long) or small gland (diameter <15 mm) during the first year of life.

### Epispadias

Epispadias is a rare entity that occurs in 1 in every 117,000 male births, and only 1 of every 484,000 female births, and is usually described as a part of the exstrophy epispadias complex (EEC). This anomaly represents a spectrum of abdominal and pelvic midline malformations ranging in severity from

epispadias to classic bladder exstrophy and cloacal exstrophy. Complete epispadias (CE) is the least severe form of EEC and presents with a dorsally open urethral meatus with mild pubic diastasis and a closed anterior abdominal wall and bladder. CE can be categorized into glandular, coronal, shaft, or penopubic epispadias. A more proximal deformity may be associated with complete urinary incontinence because of involvement of the bladder neck area along with distortion of the normal architecture of the pubic bones.

In most cases of epispadias, the prepuce is usually absent at the dorsum of the penis and is redundant tissue hanging from the ventral side, leaving the glans uncovered. The gland is broad and spade-like, with a dorsally directed preputial opening and an upward urinary stream. A dorsal chordee or abnormalities of penile raphe can suggest epispadias in difficult diagnostic cases, such as if the prepuce is covering the urethral defect.

Early consultation with the pediatric urologist is necessary and circumcision should be avoided in these patients to avoid reducing tissue. Epispadias repair corrects the dorsal chordee, reconstructs the glans and urethra, and closes the penile skin. Since these patients may also have a pubic diastasis, they may require a pelvic osteotomy for complete repair.

## CRYPTORCHIDISM

The testes are normally descended in a full-term newborn (depending on the birth weight), and may differ in size. Given that the testes descend from within the abdomen to the scrotum by approximately week 36 of fetal life, the incidence of cryptorchidism (undescended testes) is much higher in the premature infant, ranging from 20% to 40% instead of 2.2% to 3.8% in term neonates weighing 2,500 g or more at birth. Besides prematurity and low birth weight, other risk factors for cryptorchidism include breech presentation and maternal diabetes. There is a 10-fold risk of cryptorchidism in twins, and a 3.5-fold increase in brothers.

Seventy-five to 80% of undescended testicles are palpable and right-sided. The testes are nonpalpable in 10% of cryptorchidism cases. Of these nonpalpable cases, 50% of the testes are located in the inguinal canal or abdomen while 50% of the time the testis is absent secondary to fetal torsion and infarct. Even though premature infants have higher rates of cryptorchidism than term infants, they have a higher rate of spontaneous descent (80%–90% vs 50%–70%) that also occurs earlier (by age 1–3 months).

Diagnosis relies on examination. It is recommended to examine testicular position in an infant in the supine, cross-legged, and standing positions to ensure proper classification and overcome an overactive cremasteric reflex. To palpate the testis, the examiner must feel from above downward, *milking* the testis from the inguinal canal into the scrotum. The older patient can help this process by coughing or straining. Cold hands and abrupt palpation can invoke the cremasteric reflex. If one or the other of the testes is not palpable, then the examiner should search beyond the scrotum and the inguinal canal to the femoral triangle and the inner thigh. Many undescended testes are associated with an inguinal hernia and possibly a hydrocele; these masses can make palpation of the testes even more difficult. If the testis is impalpable and a hernia is present, then the testis usually lies just inside the internal inguinal ring. Ultrasound and magnetic resonance imaging may be helpful for inguinal testis location, but have low sensitivities for intraabdominal testes, so surgical exploration is still the diagnostic

standard for diagnosis of nonpalpable testes. Further testing, such as karyotype and hormone analysis, may be warranted if there are additional anomalies, as these may be indications of syndromic cryptorchidism.

If the nonpalpable testis is absent secondary to torsion, there is a high likelihood of perinatal asynchronous torsion of the contralateral testis, which has led some to recommend emergent exploration and orchiopexy. Otherwise, observation is indicated for the first 6 months of life, because spontaneous descent is unlikely after a year, testicular growth is more likely after early orchiopexy, and orchiopexy may be aided by the early hormonal surge at this time. Continued observation is required in cases of successful descent to monitor for recurrent cryptorchidism. Even if the testis is normal at birth, acquired cryptorchidism, where it spontaneously ascends, may occur. This accounts for 2% to 20% of all orchiopexies.

Cryptorchidism has been associated with infertility and malignancy. While sperm and sex hormone levels are decreased in men with a unilateral undescended testis, paternity data is similar to that of normal men. However, bilateral cryptorchid men have significantly lower fertility potential compared to a normal man. Early orchiopexy may aid fertility, as there are more Sertoli and germ cells in testes that undergo orchiopexy at 9 months versus 3 years. There is a 2.5- to 8-fold increase in overall risk for malignant transformation of all undescended testes. Undergoing a prepubertal orchiopexy confers a 2- to 3-fold increase in risk of malignancy in the testis, while an orchiopexy at age 10 to 13 years of age increases the risk another 2- to 6-fold. Controversy exists over whether the noncryptorchid contralateral testis is at increased risk of malignancy.

Surgery is indicated if the testis is not down by 12 months of age. Surgery is currently done on an ambulatory basis with either open orchiopexy for palpable testes or laparoscopic exploration and subsequent orchiopexy for nonpalpable testes. There is no difference in outcomes between open and laparoscopic techniques for nonpalpable testes. If there is a ipsilateral hernia, with or without hydrocele, then herniorrhaphy should be done to decrease the risk of incarceration postoperatively. Seventy-five percent of cryptorchid patients have a correct postoperative testicular position. Still, periodic examinations are important for any abnormalities. An orchiectomy with a prosthesis placement may be done if the testis is abnormal.

If the parents refuse or are reluctant to allow surgery, human chorionic gonadotropin (hCG) at 1,500 IU/m<sup>2</sup> body surface area has been given intramuscularly twice a week for 4 weeks. hCG has been seen to lead to testicular descent, but these rates are only 10% greater than placebo. Complications are mild with this dosage, but include possible re-ascent, so monitoring is required. Still, controversy exists over whether hCG is truly useful as adjunct therapy for true cryptorchidism, in determining retractile versus true cryptorchidism, and in stimulating germ cells. If the testis remains undescended or retracts, surgery must be done.



**WHEN TO REFER**

- All cases of hypospadias to pediatric urology.
- All cases of epispadias to pediatric urology.
- Undescended testis in a 1-year-old to pediatric urology.
- Cryptorchidism whose parents want to avoid surgery to pediatric endocrinology for hormonal treatment.
- Genital abnormalities that present with hypospadias and cryptorchidism to pediatric endocrinology.

**WHEN TO ADMIT**

- All procedures can be done at an ambulatory, same-day surgery center.

**TOOLS FOR PRACTICE****Engaging Patient and Family**

- *Epispadias* (fact sheet), Urology Care Foundation ([www.urologyhealth.org/urologic-conditions/epispadias](http://www.urologyhealth.org/urologic-conditions/epispadias))
- *Hypospadias* (fact sheet), Urology Care Foundation ([www.urologyhealth.org/urologic-conditions/hypospadias](http://www.urologyhealth.org/urologic-conditions/hypospadias))
- *Undescended Testes* (fact sheet), Urology Care Foundation ([www.urologyhealth.org/urologic-conditions/cryptorchidism](http://www.urologyhealth.org/urologic-conditions/cryptorchidism))
- *What Is a Pediatric Urologist* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Urologist.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Urologist.aspx))

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**Chapter 273****HYPOTHYROIDISM**

Craig C. Orlowski, MD

**INTRODUCTION**

Few diseases affect multiple systems so severely yet are associated with so many subtle symptoms and signs as hypothyroidism. The clinical manifestations of congenital hypothyroidism differ markedly from those of acquired disease in children and adolescents; for this reason, the primary care physician must distinguish between congenital and juvenile-acquired hypothyroidism. Congenital and acquired hypothyroidism may be either familial or sporadic, may occur with or without enlargement of the thyroid gland (goiter, thyromegaly), and may be transient, or progress to a more permanent disorder.

**DEFINITION**

Hypothyroidism is the underproduction of thyroid hormones. This deficiency may result in a range of signs and symptoms from mild to severe. Primary hypothyroidism is insufficient thyroid hormone production caused by a failure of the thyroid gland. Secondary and tertiary hypothyroidism result from the insufficient production of *thyrotropin* from either pituitary or hypothalamic abnormalities, respectively.

**ETIOLOGY**

The causes of congenital and juvenile hypothyroidism usually differ (see Box 273-1). In most cases of permanent congenital hypothyroidism, the underlying mechanism of the condition is unknown. Approximately 85% of patients with congenital hypothyroidism have no thyroid tissue (athyreosis), an ectopic thyroid gland, or a hypoplastic thyroid gland found in the normal anterior cervical location. Mutations in genes currently known to be involved in thyroid genesis explain only a small portion of cases of congenital hypothyroidism. Several inborn errors of thyroid hormone synthesis are inherited as autosomal-recessive traits and usually cause thyromegaly noted on physical examination. Several types of transient hypothyroidism can occur. In 2% of cases, antibodies that block the thyrotropin receptor are produced by a mother who has autoimmune thyroid disease, and these antibodies cross the placenta, blocking the function of the fetal thyroid gland. This form of transient hypothyroidism can persist for several weeks or months; the affected newborn or infant requires thyroxine therapy until the antibodies disappear. Another type of transient congenital hypothyroidism may occur when drugs prescribed for the mother, such as propylthiouracil, methimazole, or iodides, cross the placenta and block the fetal thyroid gland. Iodine-containing medications should be applied to the skin or mucous membranes of neonates sparingly, because the iodine is absorbed easily and excessive iodine



**BOX 273-1 Causes of Hypothyroidism****CONGENITAL HYPOTHYROIDISM**

- A. Thyroid dysgenesis
  - 1. Thyroid aplasia
  - 2. Thyroid hypoplasia
  - 3. Ectopic thyroid gland
- B. Familial abnormalities of thyroid hormone synthesis and metabolism (familial dysmorphonogenesis)
- C. Maternal disease
  - 1. Therapeutic doses of iodine-131 after the 11th week of gestation
  - 2. Transplacental autoimmune thyroiditis
  - 3. Ingestion of goitrogens
- D. Endemic goiter and cretinism
- E. Hypothalamic-pituitary hypothyroidism
  - 1. Pituitary agenesis or aplasia
  - 2. Thyrotropin deficiency: isolated
  - 3. Hypothalamic hormone deficiency
    - a. Isolated thyrotropin deficiency
    - b. Multiple tropic hormone deficiencies
    - c. Septo-optic dysplasia
    - d. Anencephaly
  - 4. Hypothalamic-pituitary lesions

**JUVENILE HYPOTHYROIDISM**

- A. Thyroiditis, autoimmune (Hashimoto thyroiditis)
- B. Congenital thyroid dysgenesis
  - 1. Ectopic thyroid
  - 2. Hypoplastic
- C. Congenital defects in thyroid hormone synthesis or metabolism
- D. Iatrogenic thyroid ablation
  - 1. Surgical
  - 2. Radioactive iodine-131
- E. Ingestion of goitrogens
- F. Endemic goiter
- G. Hypothalamic-pituitary disease

blocks the newborn's thyroid gland. On the other hand, transient iodine deficiency in the newborn can cause temporary hypothyroidism. Rarely, congenital secondary (pituitary) hypothyroidism is caused by mutations in the genes that code for pituitary transcription factors. Milder forms of congenital hypothyroidism may be missed by newborn screening programs, with symptoms not appearing until childhood. Children with these milder symptoms usually have either familial goitrous hypothyroidism (dysmorphonogenesis) or thyroid dysgenesis with an ectopic thyroid gland located somewhere between the foramen cecum of the tongue and the anterior mediastinum. Thyroid hormone levels in the premature newborn are lower than in the term newborn, with the smallest and most premature having the lowest levels. These levels normally increase postnatally, and unless there is evidence for primary hypothyroidism as

indicated by an elevated thyrotropin level, treatment with levothyroxine does not benefit the newborn.

The most common cause of hypothyroidism in children beyond the neonatal period is autoimmune thyroiditis. Similar to other autoimmune conditions, autoimmune thyroiditis is thought to be the result of the interplay between unknown environmental factors and a genetic predisposition, which is itself associated with certain human leukocyte antigen types. Occasionally, patients who have hypothalamic or pituitary disease may be seen initially with hypothyroidism. These children usually have other clinical features to suggest an abnormality of the hypothalamus or pituitary. Up to 23% of obese children may have mild elevations of thyrotropin without decreases in circulating T3 or T4 levels. In these cases, the thyroid abnormalities seem to be the result of obesity, not the converse.

**INCIDENCE**

Congenital hypothyroidism is present at birth and has an estimated incidence in iodine-sufficient regions of the world of approximately 1 newborn for every 4,000 live births, with a female-to-male ratio of 2 to 1. The incidence is greater in iodine-deficient regions. Juvenile-acquired hypothyroidism generally occurs outside the newborn period and is most often caused by autoimmune thyroiditis, also known as Hashimoto or chronic lymphocytic thyroiditis. The incidence of juvenile hypothyroidism in the US population, as defined by elevated serum thyrotropin concentrations, is approximately 2% of children 12 to 19 years of age.

**DIFFERENTIAL DIAGNOSIS**

The range of nonspecific symptoms and physical findings associated with hypothyroidism (Box 273-2) may result in other diagnoses being considered initially. For example, in the newborn, prolonged jaundice may raise concerns about liver abnormalities; however, as discussed later in this chapter, most newborns with congenital hypothyroidism will be diagnosed not based on clinical suspicion, but via newborn screening programs. In older children, other conditions often cause problems that may be suggestive of hypothyroidism. These problems include chronic fatigue in children with depression, delayed growth in children with simple delayed puberty, and weight gain in children with exogenous obesity.

**EVALUATION**

Hypothyroidism can affect many different organ systems to varying degrees. Therefore, a diagnosis of hypothyroidism should be considered when a patient exhibits any of the signs or symptoms listed in Box 273-2. Many of the symptoms and signs of hypothyroidism are different during infancy, compared with childhood, and will be considered separately.

**History**

During the first month of life, affected newborns may have no clinical symptoms or signs of hypothyroidism. In newborns who have no functioning thyroid tissue, clinical symptoms and signs are usually not present at birth, but are almost always present by 6 weeks of age. The clinical symptoms and signs in older children who

### BOX 273-2 Symptoms and Signs of Hypothyroidism

#### HISTORY

##### *Congenital Hypothyroidism*

- Decreased stooling (<1 stool per day)
- Prolonged hyperbilirubinemia (bilirubin >10 mg/dL after 3 days of age)
- Respiratory distress in a term newborn
- Birth weight >4,000 g
- Feeding problems
- Sleepiness
- Hoarse cry

##### *Acquired Juvenile Hypothyroidism*

- Growth retardation (<4 cm/yr)
- Delayed dental development and tooth eruption
- Onset of puberty—usually delayed; rarely precocious
- Menstrual disorders
- Galactorrhea
- Constipation
- Cold intolerance
- Weight gain
- Fatigue

#### PHYSICAL FEATURES

##### *Congenital Hypothyroidism*

- Facial edema
- Large posterior fontanelle (>0.5 cm)
- Rectal temperature <95°F (35°C)
- Umbilical hernia
- Macroglossia
- Bradycardia (pulse <100 beats/min)
- Lethargy
- Cutaneous mottling, vasomotor instability
- Hirsute forehead

##### *Acquired Juvenile Hypothyroidism*

- Delayed bone maturation
- Short stature
- Myopathy and muscular pseudohypertrophy
- Increased skin pigmentation
- Physical and mental torpor
- Pale, gray, cool, mottled, thickened, coarse skin
- Coarse, dry, brittle hair
- Bradycardia
- Delayed deep-tendon reflexes

have acquired hypothyroidism may be subtle and insidious in their development. If the disease has been present for more than 6 months, then growth deceleration should be evident, because normal thyroid hormone secretion is essential for normal linear growth. Hence, many patients who have juvenile hypothyroidism have either thyromegaly or a deceleration of growth and are usually short in stature. Deceleration of linear growth should be identified by

the primary care physician routinely measuring the height of the patient; an early diagnosis will prevent the development of long-standing hypothyroidism, cessation of linear growth, and the risk of a decrease in final adult height. Frank obesity is uncommon in children who have hypothyroidism.

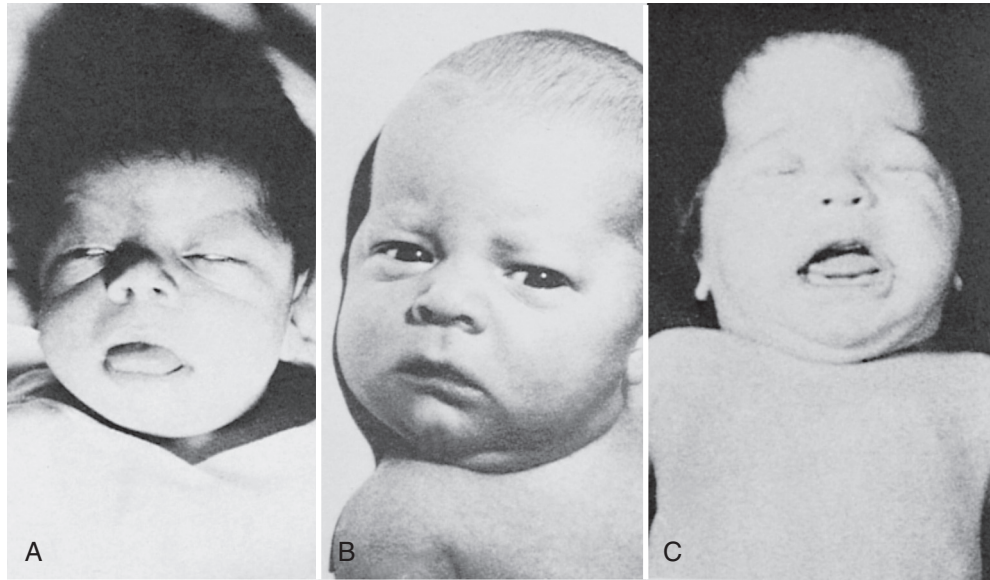
#### Physical Examination

Diagnosing congenital hypothyroidism on clinical grounds is difficult because of the varying manifestations of the disease (Figure 273-1). Some nonhypothyroid newborns may have clinical features suggestive of hypothyroidism and yet have normal thyroid studies. Conversely, some hypothyroid newborns may have minimal clinical features, such as mild periorbital edema, an enlarged posterior fontanelle, decreased stooling, and abdominal distention. Children who have advanced hypothyroidism and myxedema are usually chubby and have periorbital edema. Inspection and palpation of the anterior cervical area enables the examiner to identify an enlarged thyroid gland, even in the neonate. The easiest method for examining the thyroid gland of a newborn is to place the newborn in the supine position with the neck hyperextended over the edge of the examining table and feel for the isthmus of the thyroid, just below the hyoid bone. After identifying the isthmus, the primary care physician should palpate laterally to delineate the lobes, which are difficult to define in a healthy newborn. The thyroid examination of an older child is easier; because the thyroid rises during swallowing, having the patient swallow water will facilitate the identification and delineation of both lobes of the thyroid gland as distinct from other adjacent tissue.

#### Laboratory Evaluation

##### *Thyroid Function Tests*

The most useful thyroid function tests are usually measurement of serum thyrotropin and free thyroxine ( $T_4$ ), the latter of which has widely supplanted the determination of total  $T_4$ . Total  $T_4$  values are significantly influenced by circulating protein concentrations and are therefore less clinically useful. An elevation of the serum thyrotropin value is the most sensitive test result for identifying primary hypothyroidism. The combination of a low serum  $T_4$  value and an elevated thyrotropin value is diagnostic of primary hypothyroidism. A normal free  $T_4$  level and an elevated thyrotropin level are indicative of mild hypothyroidism. In patients with low free  $T_4$  and thyrotropin levels, hypothalamic or pituitary hypothyroidism is strongly suspected and deserves further evaluation. Male patients with normal free  $T_4$  and thyrotropin levels, but low total  $T_4$  levels, are likely to have thyroid binding-protein deficiency, a benign condition. The free  $T_4$  determination by direct dialysis is the most accurate method and the least likely to give false-positive or false-negative results from interfering drugs or other substances in serum. Occasionally, a child or infant who has a coexisting and severe illness may have the nonthyroidal illness syndrome (euthyroid sick) in which the free  $T_4$  level may be low, the serum triiodothyronine ( $T_3$ ) value is low, the thyrotropin value is



**Figure 273-1** A, Normal infant referred at 8 months of age who had clinical signs, but no clinical symptoms of congenital hypothyroidism. B, Infant with documented primary hypothyroidism at 4 weeks of age. Her clinical features at this age were minimal and included only mild periorbital edema, an enlarged posterior fontanelle, decreased stooling, and abdominal distention. C, Infant at age 6 months who has athyreosis and severe congenital hypothyroidism. (From Foley TP Jr. *Sporadic congenital hypothyroidism*. In: Dussault JH, Walker P, eds. *Congenital hypothyroidism*. New York, NY: Marcel Dekker; 1983.)

normal, and the reverse  $T_3$  levels are borderline or frankly elevated.

Tests other than the serum  $T_4$  and thyrotropin determinations are not usually required for children in whom a diagnosis of hypothyroidism is suspected; however, the finding of elevated serum thyroid peroxidase or thyroglobulin antibodies confirms the presumptive diagnosis of autoimmune thyroiditis. Transient congenital hypothyroidism may be caused by thyrotropin receptor–blocking antibodies acquired from the mother who has autoimmune thyroid disease and primary hypothyroidism.

The diagnosis of congenital hypothyroidism is rarely made on clinical grounds; rather, the newborn is identified via a newborn hypothyroidism detection program using a dried blood spot collected in the first 24 to 48 hours of life, which is then analyzed at a central laboratory. In most programs, thyrotropin levels are determined either for all newborns or for newborns whose total  $T_4$  level falls below a threshold value. Newborns identified in these programs must have confirmatory laboratory measurements of free  $T_4$  and thyrotropin performed as soon as possible.

#### Radioisotopic Studies

Although some experts recommend the use of radioisotopic studies for all newborns with suspected congenital hypothyroidism, others do not, and the thyroid scan is listed as an *optional diagnostic study* in the most recent American Academy of Pediatrics (AAP) guidelines. If a thyroid scan is performed, then iodine-123 or technetium-99m should be used rather than iodine-131, which exposes the neonatal thyroid to higher radiation doses. The thyroid scan will

distinguish sporadic disease, such as thyroid dysgenesis, from familial goitrous thyroid dysmorphogenesis, a distinction important for genetic counseling. With dysgenesis, the scan will be consistent with agenesis and atopic thyroid tissue. In familial dysmorphogenesis, a normally sized or enlarged thyroid gland will be found in the normal anterior cervical location of the neck.

Radioisotopic studies are rarely needed in older patients who have juvenile hypothyroidism. Thyroid uptake studies are indicated when the patient has diffuse thyromegaly and biochemical evidence of hypothyroidism not caused by autoimmune thyroiditis or goitrogen ingestion. However, it may be necessary to perform an ultrasound or, rarely,  $^{123}\text{I}$  scintigraphy, in case a nodule is felt. In these cases, biopsy or excision biopsy may be necessary to rule out any neoplasm. Although not essential, the assessment of skeletal maturation can provide additional data regarding the duration of hypothyroidism. A bone age determination consistent with that of a healthy newborn would suggest recently acquired, mild, congenital hypothyroidism, whereas notation of the absence of ossification centers at the knee, in addition to the presence of only the 2 ossification centers in the foot, indicates that the fetus was affected by hypothyroidism during the third trimester of pregnancy. In children, a significantly delayed bone age indicates long-standing and severe hypothyroidism and may aid in guiding long-term therapy.

#### MANAGEMENT

The treatment of choice for hypothyroidism in infancy and childhood is the daily administration of oral L-thyroxine (Table 273-1).

**Table 273-1** Doses of L-Thyroxine Used to Treat Hypothyroidism in Infancy and Childhood

AGE	T <sub>4</sub> DOSE/DAY (MCG)	T <sub>4</sub> DOSE/KG/DAY (MCG)
Full term	50	10–15
<6 mo	25–50	8–10
6–12 mo	50–75	6–8
1–5 yr	75–100	5–6
6–12 yr	100–125	4–5
>12 yr	100–200	2–3

T<sub>4</sub>, Thyroxine.

### Congenital Hypothyroidism

The initial L-thyroxine dose in a term newborn is 50 mcg daily for the first 1 to 2 weeks and should be started promptly at the initial visit when screening test results are abnormal and serum samples have been sent for confirmatory tests or, whenever the scan is abnormal. Newborns who have hypothalamic or pituitary hypothyroidism generally have milder hypothyroidism and should be given 25 mcg/day. At the end of the second and fourth week, serum T<sub>4</sub> and thyrotropin values should be measured to verify that the amount of L-thyroxine is adequate, but not excessive. Clinical studies have indicated that the more rapid normalization of serum free T<sub>4</sub> and thyroid-stimulating hormone levels with initial dosing of 50 mcg L-thyroxine daily is associated with better long-term development outcomes than is using 37.5 mcg daily initially. After 1 or 2 weeks, the 50-mcg/day dose may need to be reduced to 37.5 g/day and infrequently to 25 mcg/day if clinical symptoms of hyperthyroidism develop or if the serum T<sub>4</sub> value exceeds 16 mcg/dL. In athyrotic newborns who have low T<sub>4</sub> values, usually 50 mcg/day is adequate. The AAP guidelines for monitoring free T<sub>4</sub> and thyrotropin values are outlined in Table 273-2. However, it should be noted that recent data suggest that more frequent testing between the ages of 6 months and 3 years may be needed.

Therapy should be adjusted to maintain the serum T<sub>4</sub> levels during infancy in the upper half of the age-adjusted normal range to optimize developmental outcome. Concomitant administration of soy formula, iron, calcium, simethicone drops, and high-fiber foods may interfere with absorption of the L-thyroxine and should be avoided when possible. Compounding of liquid suspensions from levothyroxine tablets by local pharmacists should be discouraged, as the dose delivered to the newborn or infant may be inconsistent. Occasionally the thyrotropin value will not return to normal even if the T<sub>4</sub> dose is excessive and causes clinical thyrotoxicosis. These babies may have an abnormality in the feedback set point of thyrotropin secretion. The goal of therapy in this situation should be to maintain normal serum T<sub>4</sub> values and clinical euthyroidism. Discontinuing L-thyroxine therapy some time after 3 years of age is a way of testing for

**Table 273-2** American Academy of Pediatrics Guidelines for Monitoring Congenital Hypothyroidism\*

AGE	INTERVAL
<6 mo	Every 1–2 mo
6 mo–3 yr	Every 3–4 mo
3 yr–completion of growth	Every 6–12 mo

\*Recheck thyroxine and thyroid-stimulating hormone 2 to 3 weeks after starting therapy.  
From Rose SR; American Academy of Pediatrics Section on Endocrinology and Committee on Genetics, American Thyroid Association, Brown RS; Public Health Committee, Lawson Wilkins Pediatric Endocrine Society. Update of newborn screening and therapy for congenital hypothyroidism. *Pediatrics*. 2006;117(6):2290–2303.

transient congenital hypothyroidism. Serum T<sub>4</sub> and thyrotropin levels are then determined 2 to 4 weeks later. This trial period off therapy is not necessary for patients documented to have thyroid aplasia, ectopic thyroid dysgenesis, or elevated thyrotropin values after the initial period of therapy. Mild sensorineural hearing impairment may be fairly common in congenital hypothyroidism and should be screened for to allow early intervention.

### Acquired Hypothyroidism

Older children who have hypothyroidism do not share the same degree of urgency in achieving the euthyroid state. Although patients who have had a recent onset of mild hypothyroidism may be given a full replacement dose of L-thyroxine, children 3 years and older who have chronic hypothyroidism and clinical symptoms should be given a low dose that is gradually increased every 2 to 4 weeks to the full replacement dose. The rapid correction of the hypothyroid state can often be associated with undesirable behavioral side effects. These children act as though they are thyrotoxic despite biochemical euthyroidism; they are often restless, have a short attention span, and are emotionally labile. In such cases, a gradual increase in dose seems to minimize these problems in adjustment from the hypothyroid to the euthyroid state. Adequacy of L-thyroxine therapy is monitored by free T<sub>4</sub> and thyrotropin determinations every 6 to 12 months once the patient is receiving a full replacement dose with normal values. An elevated thyrotropin level with or without a low T<sub>4</sub> value indicates either inadequate therapy or poor compliance; the latter is often characterized by variable serum T<sub>4</sub> and thyrotropin values. For example, the levels may be normal on one occasion, but discordant (normal or elevated T<sub>4</sub> value with elevated thyrotropin value) on subsequent determinations, despite no change in therapy.

### PROGNOSIS

Most infants who were treated adequately for congenital hypothyroidism since the first month of age have an excellent prognosis for normal intellectual function and linear growth. However, delays in diagnosis and institution of adequate therapy are usually associated with an



increased risk of intellectual disability. Also, infants who have severe fetal hypothyroidism indicated by delayed skeleton maturation and very low  $T_4$  values have an increased risk for impaired intellectual function. In contrast, no permanent intellectual impairment is found among patients who have juvenile hypothyroidism. Adolescents who have chronic hypothyroidism and severe growth retardation may never achieve their full growth potential. In many cases, their linear growth response to therapy is not accelerated, and the height percentile achieved as an adult is lower than that predicted by their growth before the development of hypothyroidism.

### WHEN TO REFER

- Severe congenital hypothyroidism.
- The cause of hypothyroidism is not established on the initial evaluation.
- Initial therapy does not normalize thyroid function test results within the normal range for age, which is often not necessarily the normal range provided by the laboratory. The physician must know the normal range of thyroid function test results for age for patient management during the first 2 decades of life.
- Acquired hypothyroidism is atypical or complex. The disease occurs in infancy or early childhood or is associated with other endocrine or nonendocrine autoimmune diseases.
- When the diagnosis is hypothalamic or pituitary hypothyroidism based on a low free  $T_4$  level (by a method validated in infants and children) and normal or low thyrotropin level. Rarely is this form of hypothyroidism an isolated disease. It is expected to be associated with other hypothalamic-pituitary abnormalities; if it is isolated, then genetic evaluation is needed to define the cause and potential for recurrence in a family.

### WHEN TO ADMIT

- Myxedema coma
- Parental nonadherence with treatment of the newborn, infant, and young child who is at increased risk for permanent impairment of central nervous system function if thyroid function test results are not maintained in the normal range.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- American Thyroid Association Patient Education Web Brochures (handouts), American Thyroid Association ([www.thyroid.org/patients/brochures.html](http://www.thyroid.org/patients/brochures.html))

### AAP POLICY

Rose SR; American Academy of Pediatrics Section on Endocrinology and Committee on Genetics, American Thyroid Association, Brown RS, Public Health Committee, Lawson Wilkins Pediatric Endocrine Society. Update of newborn screening and therapy for congenital hypothyroidism. *Pediatrics*. 2006;117(6):2290–2303. Reaffirmed December 2011 ([pediatrics.aappublications.org/content/117/6/2290](http://pediatrics.aappublications.org/content/117/6/2290))

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### Chapter 274

## IMMUNE (IDIOPATHIC) THROMBOCYTOPENIA PURPURA

Jawhar Rawwas, MD

Immune thrombocytopenic purpura (ITP) of childhood is an acquired immune-mediated, and usually self-limited, condition of low platelet counts. ITP is caused by antibodies (mostly immunoglobulin G [IgG]) directed against antigens normally present on platelet membranes such as glycoproteins IIb/IIIa and Ib/IX. The antibody-coated platelets are then recognized and destroyed by reticuloendothelial cells found mostly in the spleen. There is increasing evidence that cellular immune mechanisms play an important role in ITP. The production of antiplatelet antibodies by B cells requires antigen-specific, CD4<sup>+</sup> helper T cells, and cytotoxic T cells may play a role in the destruction of platelets and influence platelet production.

### INCIDENCE

The incidence of ITP is estimated to be between 4 and 8 cases per 100,000 children annually, but the rate is likely higher because of subclinical cases. ITP is most common in children ages 2 to 10 years, with a peak incidence at 2 to 4 years of age. A history of a preceding infection, subsequently resolved, is elicited in most patients. In some cases, ITP is seen after measles, mumps, and rubella (MMR) immunization. The best estimate of absolute risk for ITP with MMR vaccination is 1 in 24,000 doses and usually occurs within 6 weeks of vaccination. This number is considerably less than ITP that occurs after natural infections with measles, mumps, or rubella. More than 70% of cases of ITP occur after virus infections. Persistent or chronic ITP has been associated with HIV, hepatitis C virus, and *Helicobacter pylori* infections in adults and possibly in children from high-prevalence populations. In children, both sexes are equally affected, but female predominance over boys (2.3:1) is seen during adolescence and adulthood.

## CLINICAL PRESENTATION

A child with ITP typically has sudden onset of petechia, purpura, and ecchymosis in the absence of other signs of illness. A history of a recent viral illness usually exists. Mucosal (nose, mouth, and gingival surfaces) bleeding may be present. The Intercontinental Childhood ITP Study Group (ICIS) conducted a prospective registry defining severe hemorrhage at diagnosis and during the following 28 days in children with ITP. Of 863 eligible and evaluable patients for bleeding severity assessment at diagnosis and during the subsequent 4 weeks, 2.9% had severe bleeding at diagnosis and 0.6% had new severe hemorrhagic events during the ensuing 28 days, suggesting that severe bleeding is rare in ITP over the first month of diagnosis. Intracranial hemorrhage (ICH), the most serious complication of ITP, is rare, occurring in 0.1% to 1% of acute ITP cases. Other than these manifestations of thrombocytopenia, patients with ITP usually have no significant abnormalities on history and physical examination. Other systemic symptoms, such as fever, weight loss, and bone or joint pain, are absent. On physical examination, no significant enlargement of lymph nodes, liver, or spleen is present. If any of these symptoms or physical findings is present, then the case is not typical of ITP, and other diagnoses should be considered.

## EVALUATION

For a patient with mucocutaneous signs of bleeding who is otherwise healthy, a reasonable workup includes obtaining a complete blood count, peripheral blood smear, reticulocyte count, blood typing, and direct antiglobulin test (Coombs test). In children with ITP, thrombocytopenia is usually the only laboratory abnormality, and the platelet count is usually lower than 20,000/mcL. A peripheral blood smear will reveal morphologically normal white blood cells and red blood cells (RBCs). Because acute leukemia can present much like ITP with thrombocytopenia and related symptoms of bruising or bleeding, examination of the peripheral smear by a hematopathologist in the setting of suspected ITP is essential to exclude the presence of leukemic blasts in circulation. Large, freshly produced platelets are usually seen. These young reticulated platelets contain messenger RNA and are metabolically active, which may explain why patients with ITP do not bleed as severely as patients with bone marrow failure who have similarly low platelet counts. If other abnormalities are seen on the peripheral smear, then obtaining additional tests such as viral antibodies (HIV, cytomegalovirus, Epstein-Barr virus, varicella, rubeola, mumps, or parvovirus, depending on the clinical picture) or tests for rheumatologic and other hematologic conditions (eg, leukemia, bone marrow failure) may be indicated.

The reticulocyte count is a helpful test when the diagnosis of ITP is not straightforward, such as in cases in which associated mild anemia exists, which is not a rare occurrence. The purpose of blood typing is not transfusion but determination of Rh status, which determines whether a patient is treatable with anti-D antibodies. Both reticulocyte count and blood typing

are not strictly needed for evaluation, but blood should be drawn and kept aside for reticulocyte count and blood typing if needed instead of performing multiple traumatic blood draws on a thrombocytopenic child. Direct antiglobulin test (Coombs test) is recommended to rule out the possibility of associated anti-RBC antibodies as seen in Evans syndrome. In the absence of associated anti-RBC antibodies and in the absence of hemolysis, the mean corpuscular volume (MCV) of RBCs should be normal. If the MCV is increased in the setting of thrombocytopenia, additional evaluation should be done to exclude a clonal abnormality such as that seen in Fanconi anemia.

Although ITP is caused by platelet antibodies, platelet antibody tests are sensitive but not specific, and therefore they are not indicated for the diagnosis of acute ITP in children. In ITP, bleeding time is prolonged, but assessment of bleeding time is an unnecessary test and is traumatic and inaccurate in children. Prothrombin time and activated partial thromboplastin time are normal and are also unnecessary tests. In the past, many pediatric hematologists performed a bone marrow aspiration on patients with ITP to exclude acute lymphocytic leukemia, especially before starting a patient on steroids, for fear of partially treating and thus masking a leukemic process. Now, pediatric hematologists prefer to perform bone marrow aspiration and biopsy only on patients who have clinical or laboratory features that are atypical of ITP at presentation, for example a significantly increased MCV, suggesting an alternate diagnosis such as acute leukemia or a bone marrow failure syndrome.

Marrow examination is also indicated for patients who are initially diagnosed as having ITP but who do not respond to treatment. Response to intravenous immunoglobulin (IVIG) or anti-D antibodies is usually seen within 1 to 2 days and to steroids within 1 week. The choice as to when to perform a bone marrow evaluation is an individualized decision. The most likely time for the bone marrow examination to be performed is between 7 and 14 days after treatment is begun and when response to treatment is poor. Bone marrow examination should also be considered in patients who have an atypical clinical course, in patients in whom splenectomy is contemplated, for additional confirmation of the diagnosis of ITP, and to rule out any possibility of a malignant process. The bone marrow in ITP is cellular, with normal erythroid and myeloid precursors, and usually shows increased numbers of megakaryocytes.

## DIFFERENTIAL DIAGNOSIS

Immune thrombocytopenic purpura is a diagnosis of exclusion after considering the likelihood of other causes of isolated thrombocytopenia. These causes include the following:

1. Infections such as Epstein-Barr virus, hepatitis C virus, and HIV type 1. These can be ruled out by history and physical examination, and, if needed, by obtaining liver function tests and viral studies.
2. Drugs such as heparin and sulfonamides. These can be ruled out by history.
3. Other autoimmune diseases, such as systemic lupus erythematosus, which may be difficult to diagnose.

These autoimmune diseases are more likely to affect teenagers and adults than younger children. Common variable immunodeficiency (CVID) and autoimmune lymphoproliferative syndrome (ALPS) should be considered in cases of multiple autoimmune cytopenias.

4. Acute leukemia or bone marrow failure. Children with leukemia usually have other symptoms along with abnormal physical findings, especially hepatosplenomegaly and lymphadenopathy, which are absent in ITP. Leukocytosis (white blood cell count  $>10,000/\text{mcL}$ ) and significant anemia (hemoglobin count  $<10/\text{dL}$ ) are usually seen in leukemia, but not in ITP. In acquired aplastic anemia, a low platelet count is usually associated with other significant changes in the peripheral blood, such as macrocytic anemia, leukopenia, or neutropenia.
5. Destructive thrombocytopenias, such as thrombotic thrombocytopenic purpura (TTP) and disseminated intravascular coagulation (DIC), although patients with these conditions present with other clinical and laboratory abnormalities and are usually sicker at presentation than ITP patients.
6. Inherited thrombocytopenia. Although thrombocytopenia in most children is either autoimmune or drug related, keeping this category in mind is important. Eliciting a family history of thrombocytopenia, especially parent-child or maternal uncle-nephew, may be important. Diagnostic features on a peripheral smear such as abnormal size of platelets (either small or giant); absence of platelet alpha granules (gray platelets); Döhle-like bodies, or microcytosis may point to an inherited thrombocytopenia. Clinically, bleeding out of proportion to the platelet count, onset of thrombocytopenia early in life, and associated features such as absent radii, intellectual disability, renal failure, high-frequency hearing loss, cataracts, and history of a stable level of thrombocytopenia for years suggest inherited thrombocytopenia.
7. Type 2B von Willebrand disease is a condition that results in increased spontaneous binding of the high-molecular-weight von Willebrand factor (vWF) multimers to platelets, which can lead to increased clearance of platelets from circulation, resulting in variable thrombocytopenia. This condition is usually of autosomal dominant inheritance, so obtaining family history regarding mucocutaneous bleeding is important. If suspected, vWF studies including multimer analysis should be done in consultation with a hematologist.

## MANAGEMENT

Pediatric hematologists differ in their approach to the management of children with ITP. Approximately 80% of children with ITP will recover within a few months, with or without treatment. Early treatment has not been shown to alter the risk for occurrence of intracranial hemorrhage. Patients whose platelet counts do not return to normal ( $>150,000/\text{mcL}$ ) within 6 months were historically defined as having chronic ITP. In an effort to standardize definitions and criteria of response in ITP, an international work group suggested coining a new category, called *persistent ITP*, to define the period lasting between 3 and 12 months

from diagnosis. This category includes patients not achieving spontaneous remission or not maintaining their response after stopping treatment between 3 and 12 months from diagnosis. The chances of spontaneous remissions are still significant during this period, making deferral of more aggressive therapeutic approaches reasonable. The term *chronic ITP* will be reserved for patients with ITP lasting for more than 12 months. Early treatment does not alter the natural course of ITP and does not affect the development of chronic ITP.

## GENERAL ADVICE

General useful advice to families with an affected child includes avoiding activities that are associated with increased likelihood of trauma such as contact sports, making sure that children use helmets when riding bicycles, and avoiding medications that interfere with platelet function such as aspirin and nonsteroidal anti-inflammatory drugs.

## INTRACRANIAL HEMORRHAGE

Even though ICH is rare, it is the most likely cause of death in ITP. Recognizing which patients are more likely to develop ICH is difficult. A literature review of 62 reported pediatric and adolescent cases of ICH in the setting of ITP showed that the median time from the diagnosis of ITP to ICH was 32 days (range, 0 days to 8 years), and 72% of cases occurred within 6 months of diagnosis. The platelet count was less than  $10,000/\text{mcL}$  in 71.4% of the cases. Treatment before the ICH was primarily steroids but also included IVIG, splenectomy, and others. A significant number of patients developed ICH despite having already initiated steroid treatment of ITP. Many patients with ICH have other risk factors, including preceding head injury, other preceding mucocutaneous bleeding, prior aspirin treatment, and arteriovenous malformations.

Management of ICH in the setting of ITP is an emergency that requires immediate imaging (computed tomographic scan) to determine the location and extent of the bleeding and immediate consultation with a pediatric intensivist, hematologist, neurosurgeon, and general surgeon. Treatment includes the administration of IVIG, steroids, continuous platelet transfusions to rapidly increase the platelet count, and surgical intervention, if needed, including craniotomy (especially with posterior fossa hemorrhages that are more likely to cause herniation or brainstem compression) and possibly splenectomy.

## MANAGING BLEEDING

Any intervention in a patient with ITP is directed at early control of symptoms, such as stopping bleeding and preventing recurrent bleeding. Most ITP cases in children can be managed on an outpatient basis. Although the consensus is that treatment is indicated for the patient with overt bleeding, the nature of the treatment and the question of management recommendations for patients with ITP who have different clinical manifestations remain a subject of debate. Therefore current therapy recommendations are not evidence based but based on expert consensus opinions.



The American Society of Hematology guidelines suggest that children with ITP who have platelet counts greater than 30,000/mcL require no treatment if they have few or no symptoms, as is usually the case. Patients with platelet counts between 10,000 and 30,000/mcL have treatment recommendations based on the presence and severity of associated bleeding symptoms or the risk for bleeding. Because the severity of symptoms depends on the degree of thrombocytopenia, the lower the platelet count, the more likely the patient is to receive treatment, even in the presence of relatively mild symptoms. Patients with extensive purpura of the mucosal membranes may have a higher bleeding risk and should be treated more often than not. Children with platelet counts below 10,000/mcL and only minor purpura are usually treated. Children with any concomitant or preexisting bleeding disorder should also be treated.

Other important factors that play a role in the decision regarding treatment include the age of the child and his or her degree of activity. Social variables such as the reliability of the caregivers and ease of access to emergency medical care always play a role in the decision to treat or not to treat.

When therapy is indicated, the primary treatment options for the newly diagnosed patient with ITP are corticosteroids, IVIG, or intravenous anti-D immunoglobulin. All of these agents are effective in shortening the duration of thrombocytopenia. Platelet transfusions are only temporarily effective because the transfused platelets are destroyed, but they are to be used in cases of emergency.

### TREATING WITH CORTICOSTEROIDS

Corticosteroids have been used for many years for the management of ITP in all age groups. Steroids reduce the risk for symptoms in patients with ITP by different mechanisms but most likely by reducing reticuloendothelial system phagocytosis of antibody-coated platelets. Most pediatric hematologists use prednisone for 2 to 3 weeks. Shorter courses at higher doses are also effective. Intravenous or oral methylprednisolone for up to 3 to 7 days and dexamethasone for 4 days every 4 weeks have been given. About 75% of patients with ITP respond to steroids, and the response is faster when higher doses are given; thus response can be seen as early as 72 hours after starting treatment. However, platelets usually decrease after the steroids are discontinued if the titer of platelet antibodies remains elevated. A second course of treatment may be necessary if bleeding develops or if the platelet count drops to fewer than 10,000/mcL. Side effects of brief courses of corticosteroids include behavioral changes, sleep disturbance, increased appetite, hyperglycemia, and weight gain. These side effects are more pronounced at higher dose levels. Caution should be taken when using steroids in the setting of active infection, especially with varicella infection.

### TREATING WITH INTRAVENOUS IMMUNOGLOBULIN

Rapid improvement in platelet numbers in patients with ITP who are receiving IVIG, usually within 24 hours, is seen compared with patients receiving

steroids. Response to IVIG is seen in more than 80% of treated patients. IVIG likely interferes with Fc receptor activity, resulting in prolonged survival of antibody-coated platelets. Other mechanisms of action for IVIG include regulatory properties of antibodies in IVIG as well as the IVIG effects on cytokine synthesis and on receptors for cytokines and complement. One intriguing proposal for the mechanism of action is that concentration-dependent elimination of IgG can be found from the plasma and that IVIG administration causes acceleration of the rate of IgG catabolism. Such a process would eliminate individual IgG molecules in direct proportion to their relative concentration in plasma. Thus elimination of antiplatelet antibodies is accelerated.

Side effects of IVIG include chills, fever, headache, and nausea and vomiting. Side effects tend to be more pronounced in older patients. Neutropenia (absolute neutrophil count, <1,500/mcL) develops in approximately 30% of patients. In addition, IVIG is far more expensive than steroid therapy.

### Treating With Anti-Rho(D)

Anti-Rho(D) immunoglobulin binds to the D antigen in Rh-positive individuals, and the antibody-coated RBCs block the Fc receptor of reticuloendothelial cells, resulting in a rapid increase in platelet count, usually in 1 to 2 days. The dose regimen commonly used is a single dose of 50 to 75 mcg/kg. This achieves an increase in platelet count that is comparable to what is seen with IVIG therapy. Response rate is about 50% to 77%, depending on the dose used. An average drop in the hemoglobin level of approximately 1.3 g is seen as a result of the mild hemolysis of the patient's Rho(D)-positive red cells. Anti-Rho(D) should be used with caution in children with preexisting anemia, and it should probably be given only to children with a hemoglobin level greater than 10 g/dL and after consultation with a pediatric hematologist experienced with its use. With increased use of anti-Rho(D), there have been a few cases of patients developing increased hemolysis leading to severe anemia, acute renal insufficiency, DIC, and multisystem organ failure; therefore it should always be used with caution. It is recommended that patients treated with anti-Rho(D) receive intravenous fluids and be observed for the development of hematuria and hemoglobinuria for at least 8 hours. Signs and symptoms of intravascular hemolysis include back pain, shaking chills, fever, and discolored urine or hematuria. Absence of the signs and symptoms of intravascular hemolysis within 8 hours does not indicate that intravascular hemolysis cannot occur subsequently. Laboratory evaluation for intravascular hemolysis includes plasma hemoglobin, haptoglobin, lactate dehydrogenase, and plasma bilirubin (direct and indirect).

### FOLLOW-UP

Patients should have blood counts done once or twice weekly for follow-up. In most cases, with early recovery, complete resolution of the thrombocytopenia occurs in 2 to 3 months. When the platelet count is stable, greater than 30,000/mcL, or increasing with time, blood counts should be done less frequently.



## OUTCOMES

Treatment does not alter the course of ITP (ie, the incidence of patients who go on to develop chronic ITP); however, it does shorten the duration of thrombocytopenia in some patients. For typical cases of childhood ITP, 80% of patients will have the platelet counts return to normal within 2 months of presentation, with or without therapy. Another 10% will recover normal platelet levels in the next few months, and about 10% will go on to have chronic thrombocytopenia (>6 months' duration). Approximately 25% of children with ITP will have a relapse after initial treatment. The 25% of patients who will have a relapse after initial treatment consists of 10% who will have chronic ITP, 10% who will have recurrence but resolution within 6 months, and 5% who will have episodes of ITP recurrences and remissions throughout their lives.

## COMPLICATIONS

Approximately 15% to 20% of all pediatric patients with ITP develop moderate or major hemorrhagic problems. Life-threatening bleeding, including ICH, is rare, with an incidence of 0.1% to 1%. When ICH or any other life-threatening hemorrhage occurs, immediate interventions, including IVIG and high-dose steroids, platelet transfusions, and emergency splenectomy, should be considered. For patients with ITP who are unstable or have progressive ICH, emergency craniotomy may be necessary.

### Immune Thrombocytopenia in the Neonate

Most neonatal thrombocytopenia is not immune in nature but is caused by sepsis, congenital infections, drugs, asphyxia, and necrotizing enterocolitis. Two conditions occur when immune thrombocytopenia is seen in neonates. Neonatal alloimmune thrombocytopenia (NAIT) is a condition whereby the mother develops antiplatelet antibodies directed against specific antigens found on fetal platelets but lacking on hers. An associated 20% risk for ICH occurs, and treatment usually involves administration of maternal washed platelets and IVIG. The importance of detection and accurate diagnosis of NAIT is in the ability to prevent complications in future pregnancies by treating the mother with IVIG and steroids as well as performing in utero blood sampling and intervening in case of thrombocytopenia. Parental platelet typing may help define the risk for development of NAIT in future pregnancies. A hematologist and a high-risk fetal-maternal specialist should be involved in the management of patients with NAIT. Another less serious condition is that resulting from passive transfer of maternal platelet autoantibodies in a mother with ITP. Only 4% of babies born to mothers with ITP have platelet counts less than 20,000/mcL. The risk for ICH is low (<1%), and no proof exists that cesarean delivery alters that risk. Neonatal ITP usually resolves within a few weeks as the antibodies are used up, but physicians may choose to treat the babies with IVIG in case the platelet count drops to less than 30,000/mcL. Maternal ITP is not a contraindication to breastfeeding.

### Chronic Immune Thrombocytopenic Purpura

Chronic ITP is defined as persistence of thrombocytopenia lasting for more than 12 months from the time

of diagnosis. Approximately 10% of patients with typical ITP develop chronic thrombocytopenia. In a prospective Dutch study, variables that predicted the development of chronic disease included a platelet count greater than 10,000/mcL at the onset, the absence of infection shortly before the onset of the disease, and the 232I/T Fc receptor IIB genotype. In another meta-analysis, female gender and older age (>11 years) at presentation, among other variables, correlated with increased likelihood of developing chronic ITP. Management of children with chronic ITP should focus on minimizing the individual's risk for bleeding and maintaining a safe platelet count, knowing that many patients will require no treatment. Given sufficient time (even years), a significant proportion of such patients will improve or remit. If treatment is needed, periodic short courses of steroids may be given. In case of chronic need for steroids, alternate-day dosing may be effective in preventing bleeding while reducing side effects. IVIG and anti-Rho(D) have also been used in patients with chronic ITP, but these measures are only temporary. Some patients with chronic ITP may be good candidates for splenectomy. All children with refractory ITP should be referred to a pediatric hematologist.

The same principles of treatment of acute ITP apply to a certain extent to management of chronic ITP. Other options of therapy include splenectomy, immunosuppressive therapy, rituximab, and thrombopoietin (TPO) receptor agonists.

### Splenectomy

Splenectomy is effective in improving the platelet count and reducing the associated risk for bleeding in 60% to 90% of children with chronic ITP. However, the anticipated improvement in hemostasis and platelet count must be balanced with the consideration of the small but real risk for overwhelming postsplenectomy sepsis, which may be life-threatening. In practice, splenectomy in children with chronic ITP is now rarely performed. If contemplated, splenectomy is usually delayed until the child is older than 5 years because the risk for overwhelming sepsis decreases with age. Presplenectomy immunizations and subsequent penicillin prophylaxis are necessary for all age groups. No universally accepted standards for the timing of splenectomy in chronic ITP exist, but the American Society of Hematology guidelines recommend waiting until at least 12 months after diagnosis, if possible. Platelet counts in splenectomized patients are generally monitored for an indefinite period; any drop in platelet counts or increase in symptoms should prompt an assessment for the presence of an accessory spleen. If not previously done, then recommendations are to perform a bone marrow biopsy on patients who are being considered for splenectomy.

### Immunosuppressive Therapy

For the treatment of refractory chronic ITP with clinically severe course, several agents are available. Examples of immunosuppressive drugs used include cyclosporine and cyclophosphamide. Immunosuppressive therapy should be directed by a pediatric hematologist or oncologist.

### Rituximab

Rituximab, a chimeric murine-human anti-CD20 monoclonal antibody, has also been successfully used. Rituximab acts by destroying B lymphocytes by activating complement-dependent and antibody-dependent cellular toxicity. Therefore the mechanism of action is a slow but effective decrease in the production of antibodies. In a study of 24 patients (2 to 19 years of age) who received 375 mg/m<sup>2</sup> of rituximab in 4 weekly doses, 63% achieved complete remission for 4 to 30 months (platelet count >150,000/mcL). Rituximab use may be associated with infusion-related reactions and with the development of transient hypogammaglobulinemia. Although long-term remissions have been documented, the use of rituximab in the treatment of ITP is relatively recent, and long-term follow-up may be needed for accurate prognostication.

### Thrombopoietin Receptor Agonists

A number of studies with TPO receptor agonists have shown encouraging results in adults. Some children have been successfully treated, and new information about safety and response is emerging. Assuming that the long-term safety of these agents is confirmed, they could be useful in the management of children. There is some evidence that TPO levels are suboptimal in ITP. There is also evidence that there is decreased production of platelets in ITP and that the problem is not limited to increased platelet destruction. Treatment with TPO receptor agonists, however, does not treat the cause of the ITP, and thrombocytopenia recurs when these medications are discontinued.

#### WHEN TO REFER

- History of fevers or bone pain
- Hepatomegaly, splenomegaly, significant lymphadenopathy
- Family history of thrombocytopenia
- Platelet count less than 20,000/mcL
- Abnormal white blood cell count or peripheral smear or associated anemia
- Absence of response to initial therapy

#### WHEN TO ADMIT

- Significant bleeding symptoms
- Severe anemia
- Significant concern for possible traumatic injury
- Any neurologic change in the setting of thrombocytopenia

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### Chapter 275

## INFECTIOUS MONONUCLEOSIS AND OTHER EPSTEIN-BARR VIRAL INFECTIONS

Leonard R. Krilov, MD

### EPIDEMIOLOGY

Infection with Epstein-Barr virus (EBV), a member of the herpesvirus group, is extremely common but often not apparent clinically. In Africa a strong association exists between infection with EBV and development of Burkitt lymphoma and nasopharyngeal carcinoma; this association, however, has been demonstrated less clearly in Western countries where infection with EBV often occurs at a later age. In the United States, interest in EBV infection focusses on the typical clinical syndrome—*infectious mononucleosis*—and on its emerging relationship with an increasing number of tumors, noted for the most part in immunocompromised patients.

In childhood, EBV infection is usually inapparent clinically or characterized by a nonspecific, uncomplicated episode of upper respiratory tract infection or pharyngitis. Although EBV antibodies are developed in 70% to 90% of children from low socioeconomic groups by age 5 years, these antibodies occur in only 40% to 50% of those from high socioeconomic groups. Primary infections that do not occur until adolescence and young adulthood are much more likely, for reasons that are unclear, to produce infectious mononucleosis. Thus the annual incidence of infectious mononucleosis is highest among white high school and college students, approximately 1 in 2,500 students. Usually, infection follows entry of EBV into the oropharynx, and its collection from this site can be documented up to 16 months after illness. Apparently, EBV establishes latency in the epithelial cells of the oropharynx, and the virus is periodically shed from this site throughout an individual's lifetime. Transmission from one individual to another seems to occur most often from contact with saliva (thus its description as the *kissing disease*). In the absence of such contact, transfer of infection is less likely. In a study of families that have a childhood index case of infectious mononucleosis, seroconversion occurred in 34.6% of the susceptible siblings over a period of several months. Even though the rate of transmission of the EBV infection was relatively low and slow, the development of infectious mononucleosis was quite high (55.6%) in sibling contacts who showed seroconversion. Secondary infection in typical college settings is lower.

### CLINICAL PRESENTATION

After an incubation period of 2 to 6 weeks (usually 20 to 30 days), signs of classic infectious mononucleosis are seen: fever, severe sore throat, and lymphadenopathy. This constellation of symptoms and signs may be preceded by vague symptoms of fatigue, malaise, and anorexia.

Because infectious mononucleosis is the result of a systemic viral infection, every organ system may be involved. Clinical manifestations compatible with infectious mononucleosis are listed in Figure 275-1.

The fever is usually not higher than 103°F (39.5°C), but the sore throat, frequently accompanied by tonsillar exudate (or in adolescents, more likely a grayish-white necrosis of the tonsillar surfaces) and a palatal enanthem, can be excruciating. Lymphadenopathy, perhaps the most striking feature of the illness, can be limited to the cervical nodes but can also be so extensive as to involve virtually all lymph node groups. Posterocervical adenopathy is frequently noted. The lymph nodes are not usually intensely tender and rarely demonstrate other signs of inflammation. However, palpation of the neck can elicit moderate to severe pain as reflection of the intense inflammation of the pharynx and surrounding tissue.

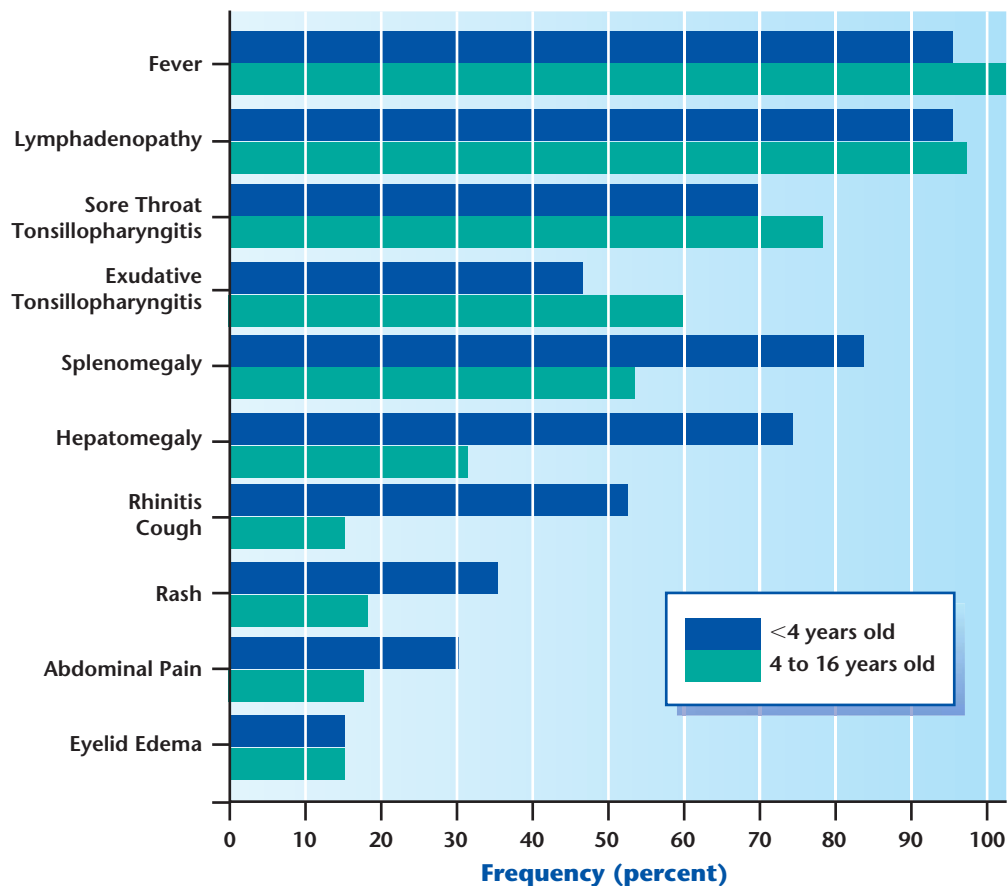
Enlargement of the spleen and possibly the liver, together with posterocervical adenopathy, is the physical sign that should alert the physician to the possible diagnosis of infectious mononucleosis. Some patients with this illness, however, lack palpable splenic enlargement; massive enlargement of the spleen suggests an alternative diagnosis. Liver enzyme levels are elevated in virtually all patients, but jaundice is infrequent.

A rash, which can be erythematous, petechial, erythema multiforme-like, urticarial, or scarlatiniform, develops in approximately 20% of children who have this illness. A rash develops in 70% to 90% of young adult patients and in a proportion of younger children treated with ampicillin or amoxicillin during acute EBV infection. In some cases the ampicillin-related rash will appear after the medication has been discontinued.

The severity of illness is extremely variable, and some individuals may have relatively few manifestations of infection, whereas others will demonstrate virtually all the symptoms listed in Figure 275-1. In general, the acute clinical manifestations of the illness last approximately 2 to 3 weeks, with peak involvement during the second week. Upper eyelid edema (Hoagland sign) occurs in about 25% of patients.

### DIAGNOSIS AND SEROLOGIC FINDINGS

Infectious mononucleosis is diagnosed by the presence of a triad of typical clinical, hematologic, and serologic findings. In addition to the clinical profile described in the preceding section, minimal hematologic features should include a lymphocytosis of 50% or more of all leukocytes and an atypical lymphocyte count of 10% or more of all leukocytes. Other general



**Figure 275-1** Frequency of clinical findings in 2 age groups of children with documented Epstein-Barr virus infectious mononucleosis: younger than 4 years and 4 to 16 years of age. (From Sumaya CV, Ench Y. Epstein-Barr virus infectious mononucleosis in children. I. Clinical and general laboratory findings. *Pediatrics*. 1985;75:1003-1010.)

laboratory findings usually include a decline in the number of granulocytes and platelets.

Paul-Bunnell antibodies are not EBV specific but are heterophilic immunoglobulin M (IgM) produced by EBV-infected B cells and react with horse, sheep, and cow erythrocytes, but not with guinea pig kidney cells. These are the basis for most rapid “mono” tests but will be present in 50% or fewer of children younger than 4 years. Among school-aged children and young adults, Paul-Bunnell antibody is detectable 80% to 90% of the time during the second week of clinical illness. Occasionally the heterophil response will be brief and minimal, particularly in young children, or will occur late in the illness. Therefore results are often negative early in the course of the illness. Commercial diagnostic kits, which rely on differential red blood cell adsorption to detect the heterophile antibody, are readily available and easy to use in a physician’s office; they are 96% to 99% sensitive when the antibody is present and give a result in 2 minutes. False-positive results can occur in cases of rubella, hepatitis, serum sickness, drug reactions, and systemic lupus erythematosus and through improper use of the kit or inaccurate interpretation of the agglutination reaction. The magnitude of the heterophile antibody titer does not correlate with clinical severity, and repeat testing, once a positive test result is obtained, provides no additional information regarding waxing or waning of the illness beyond that gained from clinical assessment of the patient. Heterophile tests can remain positive for years and are not useful in testing after the initial episode of mononucleosis if similar symptoms reappear.

If heterophile test results are negative and EBV infection is strongly suspected, then confirmation of EBV infection should be sought by other serologic tests. A variety of antibodies directed against various EBV components can be detected by hospital, state health, or commercial laboratories. Patients with EBV mononucleosis but with negative heterophile results will have antibodies against specific EBV components.

Four different antibodies define the EBV serologic profile: IgM antibody to viral capsid antigen (VCA-IgM), IgG antibody to viral capsid antigen (VCA-IgG), IgG antibody to early antigen (anti-EA), and IgG antibody to Epstein-Barr nuclear antigens (anti-EBNA). Not all laboratories test for anti-EA, which may be

detected in 2 patterns: diffuse and restricted. The clinical implication of diffuse or restricted is not clear for mononucleosis but is used to follow some EBV-induced lymphoma patients.

These EBV-specific antibodies appear in patients who have or have had primary EBV infection. The pattern of antibody responses can help the physician in determining the relative onset of an individual’s EBV infection. In most cases an individual develops a VCA-IgM antibody response in the acute period (first 2–3 weeks) after EBV acquisition. The same is true for the VCA-IgG antibody. Although IgG antibodies to VCA persist for life, VCA-IgM tends to disappear in 2 to 3 months. Although the height of the VCA-IgG response decreases as the acute infection resolves, serial measurements of antibody titers are not clinically beneficial as a rule. The EA response peaks at 3 to 4 weeks into the illness and was initially thought to persist only for several months; therefore, in the past, it was considered a good marker for an acute or recent infection. However, recent evidence suggests that the anti-EA response may persist for years in some children and may not develop at all in others. Finally, the anti-EBNA antibody response usually appears several weeks to months after a primary infection and is therefore a marker for past or convalescent infection. Thus, anti-EBNA has to be interpreted in light of the clinical situation. Although a few children develop this response in the late stages of the acute phase of their infection, 10% to 20% may never develop detectable EBNA. In summary, children who acquire EBV infections typically develop antibodies in the same sequential pattern (Table 275-1); however, not all patients will necessarily follow the same pattern, and clinical judgment remains important in the interpretation of such findings. Additionally, interlaboratory variability in results of EBV antibody testing has been observed, making the reliability of these tests suspect in some cases. If both the heterophile test and EBV-specific serologic results are negative, then non-EBV causes for an infectious mononucleosis-like illness should be suspected.

## COMPLICATIONS AND DEATHS

Most patients who have infectious mononucleosis recover uneventfully. Serious complications, however, have resulted from this illness; death occurs in approximately

**Table 275-1** Interpretation of Epstein-Barr Virus Serology

	HETEROPHILE ANTIBODY	EPSTEIN-BARR VIRUS SPECIFIC ANTIBODIES			
		VCA-IgM	VCA-IgG	EA	EBNA
No or first week of infection	—	—	—	—	—
Acute infection	+ / —	+	+ (>1:320)	+ / —	—
Past infection	—	—	+ (1:80–1:160)	+ / —	+

Note: Other patterns may occur in an individual patient; the above profile is for a typical individual.

EA, early antigen; EBNA, Epstein-Barr nuclear antigen; VAC-IgG, IgG antibody to viral capsid antigen; VCA-IgM, IgM antibody to viral capsid antigen.

Derived from Sumaya CV, Ench Y. Epstein-Barr virus infectious mononucleosis in children. I. Clinical and general laboratory findings. *Pediatrics*. 1985;75:1003–1010.



1 in 3,000 cases. The true complication and death rates during this illness are uncertain because many reports do not include strict diagnostic criteria for infectious mononucleosis. The relative frequencies of more common complications associated with this illness, as documented in 1 large study, are listed in Table 275-2. Many other complications, representing virtually every body organ, have also been reported with this disease.

Of 20 deaths clearly associated with infectious mononucleosis in 1 series, 9 cases were of neurologic origin, 3 were caused by secondary infection, 3 by splenic rupture, 2 by hepatic failure, 1 by probable myocarditis, and 2 from an undetermined cause. Because abdominal pain is an infrequent symptom of this illness, its appearance, particularly if severe and in the left upper quadrant, should alert the physician to the possibility of impending or actual splenic rupture. Fatal cases of Reye syndrome associated with serologic evidence of EBV infection also have been reported.

**Table 275-2**      **Complications Present in 113 Children With Epstein-Barr Virus Infectious Mononucleosis**

COMPLICATION	NUMBER OF CHILDREN %
<b>RESPIRATORY TRACT</b>	
Pneumonia	6 (5.3)
Severe airway obstruction*	4 (3.5)
<b>NEUROLOGIC</b>	
Seizures	4 (3.5)
Meningitis, encephalitis	2 (1.8)
Peripheral facial nerve paralysis	1 (0.9)
Guillain-Barré syndrome	1 (0.9)
<b>HEMATOLOGIC</b>	
Thrombocytopenia with hemorrhages	4 (3.5)
Hemolytic anemia	1 (0.9)
<b>INFECTIOUS</b>	
Bacteremia	1 (0.9)
Recurrent tonsillopharyngitis	3 (2.7)
<b>LIVER</b>	
Jaundice	2 (1.8)
<b>RENAL</b>	
Glomerulonephritis	1 (0.9)
<b>GENITAL</b>	
Orchitis	1 (0.9)
<b>TOTAL</b>	31†

\*Criteria consisted of nasal alar flaring, suprasternal retractions, or stridor.

†Because 4 children had more than 1 of these complications, this total is composed of 24 different children, or 21.2% of the study group.

From Sumaya CV, Ench Y. Epstein-Barr virus infectious mononucleosis in children. I. Clinical and general laboratory findings. *Pediatrics*. 1985;75:1003-1010.

## MANAGEMENT

Because most patients who have infectious mononucleosis recover uneventfully, physicians need do little except establish the diagnosis, explain the nature of the illness, and reassure the patient and parents. No specific therapy is indicated. Patients should rest to the extent that they believe necessary. As long as the patient can consume adequate amounts of fluids and calories, hospitalization is unnecessary. To minimize the danger of splenic rupture, ambulatory patients should avoid strenuous physical exercise and contact sports for at least 1 month or until the spleen is no longer palpable. Recent guidelines from a panel of sport medicine specialists provide clarity on re-engaging in sports after mononucleosis. Patients who have late onset of the heterophil antibody response may have a prolonged convalescence.

Corticosteroids are of unproved value in treating this illness. They should not be used routinely merely to attempt to shorten patient symptoms. Most physicians believe that their use is justified in treating severe hemolytic anemia, significant airway obstruction secondary to tonsillar hypertrophy, and thrombocytopenia. However, controlled studies documenting their efficacy for these indications are lacking. Some authorities suggest using corticosteroids if neurologic involvement is significant; but again, proof of efficacy is not available. High-dose, short-term courses of steroids (dexamethasone 0.25 mg/kg every 6 hours, methylprednisolone 1 mg/kg every 6 hours, oral prednisone 40 mg/day) have been used with dramatic improvement in airway obstruction and, at times, in neurologic signs typically noted over 24 to 72 hours. The antiviral agent acyclovir has reasonable activity in high concentrations against EBV in vitro, but it has not been shown to be beneficial in a number of clinical trials that involve patients who had infectious mononucleosis. At this time, routine acyclovir use is not recommended. Several antivirals (acyclovir, ganciclovir, vidarabine) and immunomodulating agents (interferon- $\gamma$ , interferon- $\alpha$ , interleukin-2) have been used in severe EBV infections, with varying degrees of success. For lymphoproliferative diseases, a new reasonably successful approach has been the use of anti-B-cell monoclonal antibodies (eg, anti-CD22). Other novel therapeutic approaches under investigation for the treatment of EBV-associated lymphoproliferative disease include bone marrow transplantation, treatment with ex vivo expanded EBV-specific cytolytic T cells, and infusions of donor peripheral leukocytes.

In as much as the pharyngitis of infectious mononucleosis can be indistinguishable from that of group A streptococcal pharyngitis, culture or rapid antigen testing of specimens of the pharynx may be obtained. Patients who have positive results may be treated accordingly, although some may be carriers. The physician should avoid ampicillin or amoxicillin if EBV is suspected, given that these drugs induce rash in many EBV-infected school-aged children and most young adults. The ampicillin effect has not been as well demonstrated in young children with infectious mononucleosis.

Because secondary infection in typical college settings is low, and 10% of asymptomatic young adults

appear to secrete EBV in saliva, isolation of the recently diagnosed EBV patient is unnecessary. Instead, separation of drinking and eating utensils (eg, avoiding drinking from the same glass) and avoidance of activities that cause saliva exchange are all that is required.

Accounts are increasing (although still rare) of infectious mononucleosis episodes that are quite severe, are fatal, or result in significant long-lasting problems. Most of these patients had some form of immunologic abnormality, such as X-linked lymphoproliferative syndrome, renal or bone marrow transplantation, or Chédiak-Higashi syndrome, among others. The definitive management of these patients remains unclear.

### EPSTEIN-BARR VIRUS INFECTION AND CHRONIC FATIGUE SYNDROME

In the 1980s, several reports described individuals who reportedly developed a chronic EBV or mononucleosis-like syndrome following a bout of acute mononucleosis. These patients never seemed to recover completely from their acute illnesses and complained of persistent fatigue, pharyngitis, lymphadenitis, and low-grade fevers. Subsequent studies, however, demonstrated normal immune responses to EBV and clearance of the virus in these patients. These individuals today fall under the rubric of chronic fatigue syndrome, a chronic, debilitating illness characterized by extreme fatigue, neuropsychological abnormalities, and a myriad of other problems. Although many patients who have chronic fatigue syndrome date the onset of their illness to an episode of infectious mononucleosis, virologic and clinical studies have confirmed that active EBV infection is not responsible for the illness. At present, no single infectious or other cause has been identified for chronic fatigue syndrome (see Chapter 228, Chronic Fatigue Syndrome).

### EPSTEIN-BARR VIRUS-NEGATIVE INFECTIOUS MONONUCLEOSIS

Rubella, hepatitis A, toxoplasmosis, cytomegalovirus (CMV), human herpesvirus-6 and adenovirus infections, systemic lupus erythematosus, and drug reactions can produce symptoms similar to those of EBV infection. Negative EBV titers and heterophile antibody responses strongly suggest one of these other agents or conditions as the cause of the illness under consideration. In hepatitis A, in which the heterophil test can give a false-positive result, liver enzyme levels generally are much more elevated than those seen with EBV-infectious mononucleosis. Results of serologic tests for hepatitis A will be positive, as will rubella titers (virus-specific IgM and IgG) in rubella infection. CMV generally does not produce pharyngitis with CMV-induced mononucleosis. Serology can be difficult to interpret with CMV because CMV IgM can be detected in reactivation of CMV. Illnesses that mimic infectious mononucleosis but lack serologic confirmation of EBV infection should be classified as heterophile-negative infectious mononucleosis rather

than atypical mononucleosis. The cause of most of these cases remains unknown.

### EPSTEIN-BARR VIRUS INFECTION AND MALIGNANCY

B lymphocytes that contain certain forms of EBV genome can divide indefinitely and thus can potentially cause EBV-related cancers. The virus remains latent in human hosts for the remainder of the host's life. EBV will reactivate, often multiple times per year. A robust T-cell immune system is responsible for restricting growth of the EBV-infected cells and preventing evolution of cancers when reactivations occur. These observations, together with the known association of EBV and African Burkitt lymphoma and nasopharyngeal carcinoma, have shown that EBV infection is also oncogenic in the United States. Some cases of leukemia occurring shortly after the onset of infectious mononucleosis have been reported, but no other evidence exists to support it as a cause of acute leukemia. Although in the United States the association between EBV and classic Burkitt lymphoma is not as strong as in Africa, a significant number of lymphomas and lymphoproliferative lesions that contain EBV markers (including markers of viral replication) have been found in patients in the United States. The EBV genome can be detected in about 50% of Reed-Sternberg cells found in patients with the mixed cellularity form of Hodgkin lymphoma. EBV is also a known cause of nasopharyngeal cancers. EBV has thus been associated with and is thought to be an essential factor in several forms of lymphoproliferative disease. EBV has also been associated with several lymphoreticular malignancies in patients who have AIDS. These malignancies include malignant B-cell lymphoma and colonic lymphoid hyperplasia. Additionally, EBV has been associated with oral hairy leukoplakia and lymphoid interstitial pneumonitis in individuals with AIDS. EBV is also associated with lymphoproliferative disease seen in patients immunosuppressed after solid organ transplantation. This has led to development of novel approaches in which T cells are harvested and EBV-specific activity is induced in vitro. These EBV-specific T cells are then reinfused to attack the tumors. In addition, the anti-B-cell monoclonal antibodies targeting EBV-infected B-cell cancer cells have shown gratifying results.

#### WHEN TO REFER

- Hospitalization may be necessary in the presence of airway compromise, splenic rupture, neurologic complications, or severe hemolytic anemia or thrombocytopenia.
- Consultation with appropriate subspecialists for the above complications would also be warranted.

### TOOLS FOR PRACTICE

#### Medical Decision Support

- *Epstein-Barr Virus and Infectious Mononucleosis* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/epstein-barr/index.html](http://www.cdc.gov/epstein-barr/index.html))

- *Infectious Mononucleosis* (book), Medline Plus ([www.nlm.nih.gov/medlineplus/infectiousmononucleosis.html](http://www.nlm.nih.gov/medlineplus/infectiousmononucleosis.html))
- *Red Book: 2015 Report of the Committee on Infectious Diseases* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

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## Chapter 276

# INFLAMMATORY BOWEL DISEASE

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### DEFINITION

Inflammatory bowel diseases (IBDs) are a group of chronic, relapsing inflammatory conditions affecting the digestive system. Inflammatory bowel disease is characterized by inflammation generally limited to the colonic mucosa in children with ulcerative colitis (UC) and discontinuous transmural intestinal inflammation in children with Crohn disease (CD). Approximately 25% of incident cases of IBD occur during childhood; the rest occur throughout adulthood, peaking in the second and third decades of life.

### EPIDEMIOLOGY

Inflammatory bowel disease affects more than 1,000,000 individuals in North America; more than 60,000 are children. Both incidence and prevalence of IBD are increasing over time, in the West and in previously low-incidence areas such as Southeast Asia and the Middle East.

### ETIOLOGY

The exact cause of IBD remains unknown, but it is speculated that it results from an aberrant immune response to gut microbiota in genetically susceptible individuals. Rapid advances in genetic testing and analyzing technologies such as genome-wide association studies have identified multiple single nucleotide polymorphisms, with the latest studies showing approximately 163 IBD-associated gene loci, of which 110 are associated with both diseases, 30 are CD

specific, and 23 UC specific. A number of environmental triggers have also been implicated, including smoking and drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs). Inflammatory bowel disease fits the model of a polygenic complex disorder with multiple potentiating triggers.

### DIAGNOSIS

#### Signs and Symptoms

Pediatric IBD may present with a variety of symptoms, including diarrhea, hematochezia, abdominal pain, fever, weight loss, and growth delay. Although diarrhea is the most common symptom and is present in 70% to 85% of children with IBD, a child's predominant complaint may be less obvious at first glance and may change depending on the child's age or the location of the disease. For example, diarrhea and abdominal pain are common to both disorders, but up to 35% of children with CD have altered growth and development, whereas children with UC may experience growth problems only 10% of the time. Bloody diarrhea occurs in most children with UC (90%), while children with CD experience this between 15% and 60% of the time. Many patients complain of pain or cramping, and sometimes the location of pain (particularly right lower-quadrant) may be confused with pain typical of appendicitis. Stooling history should be elicited for patients with concern for IBD, particularly with CD, and could be described as tenesmus, urgency, anal pain, labial pain, or other symptoms surrounding defecation. Patients may present with intestinal complications that differ by diagnosis. Children with ulcerative colitis may develop toxic megacolon, in which the colon becomes large and dilated; this is associated with hemodynamic instability, extreme pain, and decreased bowel sounds, and may lead to bowel perforation. Children with CD may develop vomiting, fever, abdominal fullness, pain related to obstruction, intra-abdominal abscess, or fistulae.

Extraintestinal symptoms are present in more than half of children with IBD, and often are present at diagnosis. These symptoms may include arthralgias or arthritis, liver disease (autoimmune hepatitis or primary sclerosing cholangitis), skin manifestations (erythema nodosum or pyoderma gangrenosum), or ocular findings such as uveitis or iritis. Aphthous ulcers in the mouth are common in CD, but other oral lesions may occur in the mouth or on the tongue and may point to deficiencies in micronutrients such as zinc or iron. Although children with CD may be more affected by growth and pubertal delay than children with UC, either condition may put them at risk for slow weight gain, growth failure, or altered bone health related to nutrition, chronic inflammation, and steroid exposure.

#### Differential Diagnosis

Diarrhea is among the most common presenting complaints among children with IBD, but, because it is a common pediatric complaint, this symptom is unreliable on its own to diagnose IBD. Initial differential diagnosis should include infectious causes of diarrhea (eg, bacteria, including *Clostridium difficile*, viruses, and parasites such as *Giardia* or *Cryptosporidium*)



because they are common in the general population. In the setting of weight loss or other concerning symptoms, causes to consider could include malabsorptive conditions such as celiac disease or pancreatic insufficiency, immune deficiency (which is often associated with diarrhea in childhood), bacterial overgrowth (particularly in the setting of previous bowel surgery where intestinal motility may be altered), or hormonal causes (rare endocrine tumors such as VIPomas, hyperthyroidism). In the absence of weight loss or other red flags, irritable bowel syndrome may also be a potential etiology for nonbloody diarrhea. Bloody diarrhea should be investigated with infectious testing, but other causes such as vascular abnormalities, cancer or polyps (rare in childhood), other inflammatory conditions such as Behçet syndrome, or toxin-mediated conditions such as NSAID exposure should also be kept in mind as possible causes.

### Diagnostic Approach

Of key importance in the diagnosis of IBD is determining which children may be evaluated as outpatients and which need to be admitted to undergo diagnostic testing. Symptoms may have been present for months prior to diagnosis, so vital signs should be obtained for all children to evaluate for volume depletion related to fluid or blood loss. History should be obtained to determine timing of diarrhea (>2 weeks may more likely be associated with IBD), whether blood is present, and whether a child is waking at night to defecate—a feature that may differentiate more benign forms of diarrhea such as irritable bowel syndrome. Patients should be examined for signs of chronic disease such as pallor, wasting, or growth problems. Abdominal examination should be performed to evaluate for the location and nature of pain and also to assess for possible complications suggestive of obstruction (distention, decreased bowel sounds), perforation (abdominal rigidity, pain, decreased bowel sounds), or areas of fullness or mass suggestive of abscess. Rectal examination (inspection and digital examination) is a critical part of the physical examination that may provide clues to underlying IBD. Patients with CD will often have anal tags, fissures, or fistulae, and unless these are actively sought out, they may be missed on simple symptom elucidation. Signs of extraintestinal manifestations such as oral lesions, erythema nodosum, or liver involvement may also be found. Testing for occult blood is also an important aspect of the physical examination. Children thought to be at risk for IBD should be referred to a gastroenterologist for appropriate diagnostic procedures, such as endoscopy, to make a formal diagnosis.

### Laboratory Findings

Initial laboratory findings in IBD may be helpful and point toward the diagnosis of this chronic inflammatory condition, but there is no single laboratory marker indicative or diagnostic for IBD. Commonly evaluated tests include inflammatory markers (erythrocyte sedimentation rate [ESR] and C-reactive protein) and elevated acute phase reactants such as elevated white blood cell count and platelet count. For children

with chronic symptoms or bloody diarrhea, hemoglobin is often useful, as these children are likely to be anemic. Albumin may also be helpful and is a marker of malabsorption or protein losses. Unfortunately, almost 30% of patients with mild IBD may have normal ESR, hemoglobin, platelet count, and albumin, so stool biomarkers of inflammation such as fecal calprotectin may identify at-risk individuals. Fecal calprotectin is a neutrophil protein elevated in many types of intestinal inflammation, including infection, and has been shown to have up to 92% sensitivity and 76% specificity as a screening tool for IBD. Fecal calprotectin has been shown to correlate with mucosal inflammation, may predict relapse, and may be used to monitor response to medical therapies.

Biomarkers and genetic predictors for IBD may help predict disease activity over time. More than 100 genes have been identified as potential contributors to IBD, with *NOD2* among the most extensively studied as a risk factor for the development of more aggressive disease course in CD. Biomarkers typically are antibodies to microbes in the gastrointestinal tract, such as anti-neutrophil cytoplasmic antibodies, anti-*Saccharomyces cerevisiae* antibodies, and antibody to *Escherichia coli* outer membrane porin. Patterns of biomarker positivity may differ by diagnosis (UC vs CD), but may be better suited to predict risk of disease complications among children with CD. Presence or absence of biomarkers is not typically useful for diagnosis of IBD (particularly as a single test) since they may be present in the general population and are often absent in children with IBD.

### Imaging

Imaging is a necessary part of the early diagnostic workup of children with IBD and often is needed in some form after diagnosis. The type of imaging required depends on the situation and urgency. Potential reasons for imaging include categorizing disease extent, evaluating for complications, or monitoring response to treatment. Techniques employed may vary based on experience of the center and availability of technology. Basic radiographic techniques for evaluation of disease include the following:

- Plain abdominal radiograph: typically helpful for acute changes or emergencies (vomiting, acute pain, distention, concern for perforation or bowel obstruction)
- Upper gastrointestinal (GI) series with small-bowel follow-through (plain radiographs with ingested contrast being followed throughout the GI tract): widely used and well-tolerated examination used for evaluation of small bowel disease extent, particularly if there is no concern for an intra-abdominal process (abscess, stricture, fistula) or perianal disease.
- Magnetic resonance imaging (MRI) and computed tomography (CT): traditional MRI and CT are used for evaluating disease extent and providing additional benefit of intra-abdominal abscesses and fistulae identification. Enterography techniques are available employing a different oral contrast designed to distend the bowel wall as well as glucagon to change GI motility. These provide additional information about areas of narrowing or stricture



and intra-abdominal complications, and may identify other extraintestinal complications. Depending on availability, these examinations (particularly CT enterography) are thought to be the gold standard for evaluation of small bowel disease extent. Magnetic resonance imaging of the pelvis is the typical modality for evaluation of perianal disease that cannot be properly evaluated by an IBD surgeon or if complex perianal disease is suspected. Standard abdominal CT is helpful for more urgent evaluation of complications.

- **Ultrasound:** a radiation-free technique is being developed as a tool to evaluate for disease extent and intra-abdominal complications, but may be limited by operator experience and body habitus. Endoscopic ultrasound and pelvic ultrasound are available, but are more invasive and require special expertise for interpretation.

### Diagnostic Procedures

Endoscopic procedures are the main type of diagnostic procedures for IBD and are necessary to determine disease type and extent. Conventional ileocolonoscopy and microscopic examination of biopsies remain the gold standard for diagnosis of IBD. The entire colon and ileum should be examined, because visualization of the distal colon only with proctosigmoidoscopy may not give enough information to make an appropriate diagnosis. Endoscopic examination of the upper digestive tract may also help differentiate types of disease in children, but is not absolutely necessary. Biopsies during endoscopy are crucial to help classify type of disease. Subsequent endoscopies after diagnosis may be needed if a change in therapy is being considered or to examine for dysplastic changes after diagnosis. If the small intestine cannot be examined visually during upper or lower endoscopy, capsule endoscopy (use of a wireless ingested camera to visually examine the mucosa) may provide visual assessment of disease extent as an alternative to radiographic procedures, but cannot provide biopsies.

### Classification

At diagnosis, a physician must differentiate between CD and UC (or indeterminate colitis if a diagnosis is not yet available) to guide therapeutic or surgical options and possibly offer some idea about prognosis. Distinction is made by a combination of endoscopic and histologic criteria. At time of diagnosis, differentiation can sometimes be made between conditions by examining the distribution and location of disease—UC typically has continuous involvement of part of or the entire colon, while CD may be patchy and can affect any part of the luminal GI tract. However, these features may not be straightforward since UC may be associated with mild gastritis and “backwash ileitis” from adjacent inflammation of the colon, and CD may affect the colon only. Microscopic criteria such as patchy disease, granulomas, or transmural disease are associated with CD rather than UC. Crohn disease tends to be more segmental and sometimes has deep linear ulcers at diagnosis, segmental colitis, or findings of perianal disease. The presence of complications

such as stricturing disease or internal abscesses is associated with CD and not UC.

### TREATMENT APPROACH

Treating IBD depends on degree of severity, disease location, and potential complicating features such as fistulae or abscesses. In general, the goals of therapy are to provide symptom relief, minimize side effects of medications, ensure adequate growth, and maintain good quality of life. For mild disease presentations, first-line therapy would usually include aminosalicylates such as mesalamine. For disease affecting the rectosigmoid area, topical therapy such as mesalamine suppositories or enemas may be beneficial. For more moderate disease activity, corticosteroids are normally used to induce remission, but alternate therapy will be needed for maintaining remission once achieved. These maintenance medications include immunomodulators or enteral therapy. The potential side effects of immunomodulators need to be discussed and screened for at periodic intervals and include bone marrow toxicity, hepatotoxicity, and risk of malignancies. Enteral therapy is effective in inducing and maintaining remission in up to 85% of children with CD who are treated. For severe disease, step-up therapy with biologics (biologic response modifiers) is usually employed with pediatric response rates over 80%.

Drugs from different therapeutic classes may, at times, be used additively. Occasionally, for some children with complicated disease (eg, fistulizing disease, growth delay, or severe ulcerative colitis), a step-down approach with early introduction of stronger agents, such as the anti-tumor necrosis factor (TNF) agents, has been advocated to prevent progression of complications and improve outcomes.

### ONGOING CARE

#### Prevention Strategies

Children with IBD should receive all recommended childhood vaccinations, but with some potential adjustments based on medications. Patients on corticosteroid therapy may not respond to vaccinations, so they should be given before starting therapy or 3 months after they stop therapy. Children on immunosuppressive medications should not receive live-virus vaccinations, so if these medications are being considered, live-virus vaccines should be administered prior to the need for immunosuppressives. Varicella and hepatitis B may be 2 particular conditions that should be intentionally investigated prior to initiating therapy because of risk of severe disease associated with some types of treatments, particularly anti-TNF. If varicella exposure is unknown or if vaccination is uncertain, titers should be checked and vaccine administered prior to starting therapy (if appropriate for the clinical condition). Latent hepatitis B may be reactivated in the setting of anti-TNF therapy, and patients with IBD may have a lower rate of immunity to hepatitis B vaccine, so hepatitis B surface antibody and antigen should be considered before initiating these agents.

Children living with any chronic disease may struggle with coping and psychological issues surrounding

their disease. Children with IBD struggle with a variety of issues, including anxiety, depression, body image and social isolation. Children should be screened for these issues and offered access to psychologists early in the disease course, if possible. Children and families may benefit from support groups and services and should be encouraged to seek out resources even if they feel they are coping well. These resources may provide additional benefits in terms of education, development of self-management skills, and answers to common questions or concerns.

### Prognosis and Natural History

Inflammatory bowel disease does not affect overall life expectancy, but patients may have significant morbidities related to disease progression. Many children with IBD, particularly those with childhood-onset disease, may have more severe disease resulting in hospitalization or surgery. Up to 30% of children with CD and UC require surgery within the first 5 years after diagnosis. Gastrointestinal infections, particularly *Clostridium difficile* infection, are a common reason for hospitalization among children with IBD and have a high recurrence rate. Children requiring medications affecting the immune system (steroids, TNF- $\alpha$  inhibitors, or immunomodulators) have a higher rate of serious infections.

Other risks for children with IBD include nutritional and potential oncologic complications. Children with IBD have suboptimal bone health related to a variety of factors such as frequent steroids, suboptimal nutritional status, and inflammation, which place them at increased risk for osteopenia or osteoporosis, resulting in increased fractures. Vitamin deficiencies may occur in children who had bowel resections and should be monitored closely. Children with IBD, particularly with colitis, are at a 1.5- to 2-times higher risk of colorectal cancer than individuals without IBD, and patients with younger onset of disease may have an even higher risk of developing disease.

Cancer surveillance is recommended to begin at about 8 years from diagnosis and then every 1 to 3 years. Medications used for IBD may impose a slightly higher rate of skin-related cancers, so a skin examination should be performed at routine visits. Some medications used for treating IBD (particularly immune modulators) may be associated with an increased risk of lymphomas, but these risks remain small in proportion to the risk of untreated disease.

### Comanagement

In general, the approach to outpatient pediatric care for children with IBD should be similar to that for children without chronic disease, but with special attention to growth and developmental complications, and infection and malignancy risk. Children with IBD may see the GI specialist only once or twice a year, so both the GI specialist and primary care physician should comanage certain parts of every visit such as growth and development (height and weight at every visit), assessing psychological coping, and a complete physical examination. Communication between the primary care physician and GI specialist is critical, with some expectations set upfront for general pediatric care, need for GI specialist input,

monitoring for potential medication side effects (eg, bone marrow and hepatotoxicity with immunomodulators), and growth parameters. A routine physical examination should be done at every visit to assess for intestinal complications, drug toxicity, or malignancy (particularly of the skin and lymphatic systems). Routine vaccinations should be maintained by the general pediatrician if possible, although vaccination for influenza or vaccine boosters for nonresponders (such as hepatitis B) can be given whenever the child is medically able to receive them in an effort to avoid return visits. Every effort should be made to return the child to the primary care physician for coordination of services, particularly if the child sees multiple providers for other conditions. The GI specialist should remain available for GI-related issues (weight loss, vomiting or diarrhea, change in abdominal pain, ongoing fever, or concern for flare). A document (either clinic notes or a medical passport) may help detail the ongoing issues and facilitate communication.

### WHEN TO REFER

“Red flags” that would warrant a referral to a GI specialist include historical factors such as

- Poor growth or weight loss
- Persistent rectal bleeding with no obvious source on examination
- Recurrent perirectal abscess

Laboratory values obtained during evaluation that may warrant a referral to GI specialist include

- Microcytic anemia
- Elevated acute phase reactants
- Hypoalbuminemia
- Elevated fecal markers of inflammation (fecal calprotectin, lactoferrin)

### WHEN TO ADMIT

- Recurrent fevers or concerns for abscess
- Persistent vomiting or bloody diarrhea suggesting obstruction, dehydration, or need for blood transfusion
- Severe abdominal pain and distention suggesting “toxic megacolon” (severely dilated colon)
- Significant malnutrition for nutritional rehabilitation with oral supplementation or intravenous hyperalimentation

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *CIRCLE* (newsletter), ImproveCareNow ([improvecarenow.org/subscribe](http://improvecarenow.org/subscribe))
- *GI Buddy* (mobile app), Crohn’s & Colitis Foundation of America ([gibuddy.ibdetermined.org](http://gibuddy.ibdetermined.org))
- *ImproveCareNow* (Web site), ([improvecarenow.org](http://improvecarenow.org))
- *Inflammatory Bowel Disease* (Web page), North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition ([www.gikids.org/content/7/en/ibd](http://www.gikids.org/content/7/en/ibd))
- *Just Like Me! Teens with IBD* (Web site), ([www.justlikemeibd.org](http://www.justlikemeibd.org))

- *Participate in Research* (Web page), Crohn's & Colitis Foundation of America ([www.ccfa.org/research/participate-in-research](http://www.ccfa.org/research/participate-in-research))

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## Chapter 277

## INSECT BITES AND INFESTATIONS

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### INSECT BITES

Insect bites and stings are an expected, frequent consequence of childhood activities but can cause serious illness and threaten life in susceptible individuals. Insects and arachnids (mites, ticks, and spiders) can produce anaphylaxis or act as vectors of serious or fatal disease, including viral encephalitis and malaria. Worldwide, malaria and other insect-carried diseases are among the most common causes of serious childhood morbidity and death. In the United States, ticks are the most common insect vectors of disease, spreading Lyme disease and other infections, which are discussed elsewhere. The prevalence of harmful insect species varies over time; for example, there is a current widespread increase in bedbug infestations, which have now affected numerous public buildings, including both acute care and chronic care health facilities in many US cities. (Figure 277-1). The Centers for Disease Control and Prevention (CDC) offer abundant current information on vector-borne diseases ([www.cdc.gov/nceid/dvbd](http://www.cdc.gov/nceid/dvbd)).

### Patient Evaluation

A history of being bitten or stung, or simply of localized itch, burning, or pain, may be present. On examination of the skin, insect or arachnid bites appear as discrete, erythematous, or flesh-colored papules, nodules, wheals, vesicles, or bullae, which sometimes display pigment alteration and are usually pruritic (Figure 277-2). Bites are most commonly found on surfaces left uncovered by clothing and may be clustered, or in a linear, arc-like or other pattern,



**Figure 277-1** Bed bug. Note the flattened, oval body of this bug, which was brought in to the clinic by the patient's mother. (Krowchuk DP, Mancini AJ, eds. *Pediatric Dermatology: A Quick Reference Guide*. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012.)



**Figure 277-2** Mite bites. Multiple, clustered, edematous red papules and plaques. (Krowchuk DP, Mancini AJ, eds. *Pediatric Dermatology: A Quick Reference Guide*. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012.)

especially when a crawling insect bites (Figure 277-3). Some bites have central puncture marks or vesicles; others are capped by pustules or by hemorrhagic or serous crusts. On occasion a whole or partial insect body may remain attached to the skin, especially in the





**Figure 277-3** Flea bites. Note the *breakfast, lunch, and dinner* sign. (Paller AS, Mancini AJ. Hurwitz Clinical Pediatric Dermatology: A Textbook of Skin Disorders of Childhood and Adolescence. 4th ed. Philadelphia, PA; Elsevier Saunders; 2011, with permission from Elsevier.)

case of a tick bite. Careful examination with magnification may be indicated to preclude insect parts remaining in the skin, especially from tick bites. Excoriations or changes consistent with dermatitis (reddish, ill-defined areas with an altered surface texture and often scaling or scale-crust) are common. Larger nodules or blisters may appear as more robust reactions to insect- or arachnid-associated toxins, particularly in those with prior exposure (sensitization) to insect antigens. Immediate (anaphylactic) reaction in those with or without known prior exposure can be life-threatening. Multicentimeter plaques, sometimes referred to as *large local reactions*, may be severe, reaching more than 10 cm in 1 or 2 days after a bite or sting. Such reactions may increase the risk for more severe outcomes upon additional antigen exposure from bites.

Additional complications of bites include localized infection or more widespread dermatitis (eczematous dermatitis); other localized or widespread hypersensitivity reactions, including papular urticaria; and other systemic immune reactions. More acute or widespread complications can also result from the application of topical remedies, such as topical antibiotics, especially neomycin, or other easily available and advertised products, thus causing irritant or allergic contact dermatitis and greatly increasing itch or leading to ever more acute clinical findings.

Systemic infections, such as viral encephalitis or tickborne disease, should be considered as potential

complications necessitating more thorough follow-up. Bacterial infection of bites can lead to cellulitis or a multitude of toxin-induced or immune-mediated complications such as nephritis. Papular urticaria is a common hypersensitivity reaction to insect bites and consists of recurrent crops of urticarial (hive-like) papules, nodules, or wheals that may be either new areas or reactivated old bites. Papular urticaria occurs in sensitized individuals and can last days, weeks, or months, plaguing the patient with profound itch and areas of disrupted skin barrier function, which are susceptible to bacterial infection, especially if the papules are repeatedly scratched or otherwise traumatized. Scratching can also leave scarring or postinflammatory pigment change, most often as hyperpigmentation. The differential diagnosis of insect or arthropod bites includes papules from various eczematous conditions (eczematous dermatitis) or follicular inflammation (folliculitis) as well as inflamed viral molluscum, other viral infections, and reactions to foreign material deposited in the skin.

### Treatment of Insect Bites

Bites from insects should ideally be prevented primarily by protecting as much of the body as possible with clothing or bed nets (especially for infants) and by judicious, careful use of repellents. Highly efficacious repellents include Picaridin and DEET (DEET is known, worldwide, by more than 1 chemical name, including N,N-diethyl-m-toluamide). Picaridin may be the safer of the 2 widely available repellents (see [www.epa.gov/opp00001/chem\\_search/reg\\_actions/registration/fs\\_PC-070705\\_01-May-05.pdf](http://www.epa.gov/opp00001/chem_search/reg_actions/registration/fs_PC-070705_01-May-05.pdf)). The use of oils of lemon eucalyptus is widely recommended and likely efficacious, but numerous preparations offered through many suppliers may lack standardization or comparable potency among products. Any of these repellents can be applied to exposed clothing or to skin in small amounts with care, avoiding children's hands, eyes, and mouth areas. Repellents are best washed off when no longer needed to reduce skin irritation and potential for toxicity. DEET is usually safe to use intermittently and in moderation at concentrations of 30% or less in children older than 2 months, but toxicity has been reported, and current recommendations of the American Academy of Pediatrics, CDC, or Environmental Protection Agency should be consulted. Susceptibility to mosquito bites may be decreased by avoiding other potential attractants, such as bright clothing. When available, the use of bed nets impregnated with repellents may be protective during rest periods.

Those at risk for anaphylaxis after being bitten or stung should be treated immediately with epinephrine and should always have epinephrine autoinjectors immediately available. Ice or cold packs should be applied to bites as quickly as feasible to reduce itch and inflammation because of hypersensitivity, inflammatory reaction, or potential diffusion of insect toxins. Topical antipruritic products such as plain calamine may be soothing. Low- to mid-potency topical corticosteroid creams, such as 2.5% hydrocortisone or 0.025% to 0.1% triamcinolone, reduce inflammation and itch and are the primary treatment, along with



cold packs and oral  $H_1$  blocking agents. Topical antihistamines and topical antibiotics should always be avoided; they are ineffective and may cause allergic contact dermatitis. Hydrocortisone at 1% concentration has little efficacy, owing to the depth of insect bite reactions in skin. In rare cases, for extensive bites with ensuing hypersensitivity manifesting as widespread papules, a limited 1- to 2-week or shorter course of oral systemic steroid at approximately 0.5 mg/kg of prednisone or equivalent might be considered. Topical corticosteroid therapy should be started at the same time to reduce chances of a rebound phenomenon upon cessation of oral corticosteroid use.

## PEDICULOSIS

Human lice are obligate ectoparasites that create pruritic dermatoses after their bites puncture the skin and inject saliva, which incites inflammation and sometimes hypersensitivity. Lice can transmit human diseases, including typhus, and are spread primarily by close human contact but also by fomites; for example, the body louse is primarily spread in clothing. Outbreaks of head lice occur among groups of all types and ages that spend long periods in close contact but especially among school-aged children. Lice infestation of the scalp is called *pediculosis capitis* (Figure 277-4); infestation of the eyelashes is known as *pediculosis palpebrum*; and pubic area involvement is called *pediculosis pubis*. In each situation, lice live just above the skin, often on hair shafts, but feed from the underlying skin surface. *Pediculosis corporis* describes an infestation of the limbs and trunk with lice living in clothing or on bedding, rather than on terminal (mature and pigmented) hair, as lice do in the other types of infestation noted.

On careful examination with the eye or low magnification (3× to 10×), the grayish, crawling, 6-legged louse is seen near the skin in areas of thick terminal hair growth or on fomites. Louse egg or larval sheaths, called *nits*, appear as minute, white-gray, firmly fixed attachments to hair shafts. In the absence of visible lice, nits may not be diagnostic of active infestation. Importantly, several types of debris or small masses of dead skin from scalp inflammation or infection, such as fungal infection, may be easily mistaken for nits. Specialized combs are often helpful in finding lice or nits when they are challenging to find. Pruritus, sometimes accompanied by erythematous papules, 1 to 3 mm in diameter, caused by bites of the head louse, may be noted around the nape of the neck and the hairline or on other areas of skin. Cervical adenopathy and occasionally urticarial-like changes or similar involvement of other body areas may be present. Family members should also be examined, especially if combs, towels, and other personal items are shared. *Pediculosis pubis* is often sexually transmitted, and affected individuals may have other sexually transmitted infections.

*Pediculosis corporis* should be suspected when widespread pruritus is present along with erythematous papules and signs of scratching, especially on covered or hairy body areas. Excoriations, impetiginization, eczematous changes, overt bacterial or other infection, and pigment changes are common. Body



**Figure 277-4** Head lice. Note numerous nits attached to hair shafts. (Krowchuk DP, Mancini AJ, eds. *Pediatric Dermatology: A Quick Reference Guide*. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012.)

lice and nits may be seen in the seams of clothing or on bedding or other fomites.

## Treatment of Pediculosis

For head lice or pubic lice, repeated physical removal of lice and nits is essential. Only when needed, and as an adjunct to careful physical removal, should permethrin, dimeticone, or pyrethrins be tried. The use of chemicals is to be avoided in infants and during pregnancy or while nursing. Resistance of lice to chemical agents is greatly increasing, and some medications may be completely ineffective. Mechanical means of removal, especially using surface agents such as silicone, is increasingly useful, as are other “physically active” compounds. Retreatment is usually necessary about 1 week after the first application to kill lice that have hatched from viable nits that were not killed initially. Malathion used as a 0.5% solution must be left on for 8 to 12 hours and is flammable. Dimethicone 4% may also be effective, even as a single application. Insecticides, especially lindane ( $\gamma$ -benzene hexachloride [GBH]), are highly toxic and less effective compared with other measures and should be avoided. Two doses of oral ivermectin given at least 7 days apart have been shown to be effective in the treatment of several kinds of lice infestation, although this application is an off-label use. Chemical treatments for pediculosis, especially those containing lindane, should not be used for infants and for pregnant or nursing women.

Clothing, bedding, combs, towels, and other items used by lice-infested persons should be washed in hot water of at least 149°F (65°C). The most effective treatment for body lice is the total-body application of 5% permethrin cream (Elimite) for 8 to 14 hours. Permethrin 1% should never be used because of resistance. Simultaneously, all potentially infested clothing must be treated with wet or dry heat (or both) at a minimum of 149°F (65°C) preferably for at least 30 minutes. The use of multiple modes of treatment with differing treatment methods may be needed. A vinegar rinse may help remove stubborn nits. All clothing, stuffed

animals, comforters, and other items that cannot be washed or dry-cleaned should be stored in a plastic bag and sealed for 2 weeks or more. No-nit policies aimed at excluding children from school are ineffective. Overlooking nits is easy, and such policies penalize children excessively by causing missed school days. The American Academy of Pediatrics recommends avoiding such policies.

Pruritus may continue for 2 weeks or more after treatment, perhaps because of continued presence of dead lice or related antigens. In addition, topical agents may cause irritant dermatitis. Patients should be advised that they might continue to itch so that they do not over-treat themselves through excessive repeated applications. Oral antipruritic agents, such as mild antihistamines ( $H_1$  blockers), soothing bland lotions, and topical steroids, can help control pruritus. Additional current information for patients and providers is available at [www.cdc.gov/parasites/lice/index.html](http://www.cdc.gov/parasites/lice/index.html).

Pediculosis palpebrum can be treated by applying plain petrolatum to the eyelashes 4 to 5 times daily. Treatment is required for approximately 8 to 10 days, and a fine comb should be used daily to remove lice and nits from the eyelashes. Other infested body areas should be treated simultaneously. If this method fails, then physostigmine 0.25% may be similarly applied to eyelashes and is usually curative in 3 or 4 days but may interfere with vision.

Pediculosis pubis is also treated with measures to physically remove lice and with permethrin or pyrethrins, at 5% concentration. Nonprescription pyrethrin preparations are probably less effective, and optimal lengths of application are shortest with 5% permethrins; but here, too, resistance to chemical agents continues to increase, and physical removal of nits and lice should also be undertaken.

## SCABIES

Infestation with the mite *Sarcoptes scabiei hominis* causes scabies, a common and extremely pruritic dermatosis that usually affects several regions of the skin in a characteristic distribution. Confirmation of scabies infestation is sometimes possible, as described later, but is *often unobtainable* because of an absence of any adequately specific or sensitive diagnostic test. It is likely that children are affected more often than adults owing to frequent close contact with other children, especially in schools, child care, or other institutional settings.

Scabies is usually spread by close personal contact, most often by skin-to-skin contact, such as through individuals sleeping in the same bed or holding an affected child close to one's body, as well as during close play among children. It has been estimated by various researchers that 20 to 30 minutes of close contact is optimum for transmission, but shorter contact may often be sufficient. After *initial* infestation, clinical signs develop after about 2 to 6 weeks; overt clinical findings follow the initial burrowing of scabies mites into the epidermis, with subsequent development of delayed (cell-mediated) host immunity. New infection of a previously immune host can result in itching and rash in as little as 1 to 3 days. Acquisition of scabies from fomites is thought to be much less common

because mites generally survive no more than 3 days off of a host, even in ideal conditions of high humidity. Nonhuman varieties of scabies mites, such as those that infest dogs or larger mammals, lead only to self-limited skin changes on human skin; this is because scabies mites are highly specific to a host species and mites fail to effectively reproduce on species other than their primary host species.

In many instances, history will reveal that several people in a dwelling have a rash and widespread persistent itching. Clinical diagnosis of scabies should be based primarily on the distribution of erythematous papules, nodules, or other inflammatory changes and, where present, more specific findings, such as burrows. Examination of close contacts with suggestive skin findings is often helpful for confirmation. Burrows, seen as fine (1- to 2-mm wide) flesh-colored to slightly pink, minimally raised, linear or serpiginous plaques are created by female mites and may help to establish the diagnosis; however, burrows are generally not obvious and are present in fewer than one-half of all patients. Burrows are most often found in the finger webs or on the wrist area but are frequently disguised by excoriations, eczematous reactions, or superimposed infection. Most commonly, papules, nodules, eczematous changes (eczematous dermatitis), or excoriations are found on the digital web spaces, the extensor surface of the elbows and knees, and the flexor aspect of the wrists, as well as the axillary, upper trunk, waist, and groin area. Only in infants is involvement of the palms and soles, especially with vesicles, common, as are findings on the face and head. In patients who are immune suppressed for any reason or who cannot effectively scratch, extensive and widespread urticarial, eczematous, or crusted changes can mimic many other inflammatory skin diseases, especially arthropod bites or other forms of eczematous dermatitis. Widespread eczematous infestation with numerous mites is sometimes called *crusted scabies* or *Norwegian scabies*.

Confirmatory ova, mites, or feces are often difficult to visualize because most involved areas of skin do not contain mites or ova. Light microscopy of scrapings of the bottom of burrows or papules from distal body sites after a drop of mineral oil is placed on the skin and examined under less than 40 $\times$  magnification can be confirmatory, especially if mites, with their characteristic anatomy, are seen. The clinical differential diagnosis for scabies includes insect bites and papular urticaria, as discussed earlier, and various forms of eczematous dermatitis and folliculitis. Papules, pustules, vesicles, eczematous dermatitis, and even urticarial plaques can occur in sarcoptic infestation and justify the reputation of scabies as a great masquerader. In the setting of worsening or persistent widespread pruritus with inflammatory skin changes, a diagnosis of scabies must be considered, especially if close contacts are also itching. The distribution of skin changes over the body, rather than the detailed appearance of each area, is usually the best clue to the diagnosis.

## Treatment of Scabies

Family members, sexual partners, and other close contacts of index cases, especially those having

skin-to-skin contact, should always be simultaneously treated because they are often asymptomatic carriers. Carriage and spread of scabies mites can result from delays of up to several weeks before clinical changes appear (see earlier discussion), if such changes do eventually appear at all. Not all individuals develop hypersensitivity findings that are clinically evident, and failure to examine or treat close contacts is likely to result in transmission to others and even repeated infestation of the originally treated individuals. Animals, such as pets, do not need to be treated in conjunction with scabies in humans, for the reasons noted previously. The treatment of choice for scabies is the very thorough application of 5% permethrin to the entire body, and the simultaneous treatment of all close contacts, such as those living in the same household, who are likely to have had skin-to-skin or other very close contact with the patient. Repeat application about 7 to 10 days later is sometimes justified, especially if there are concerns over compliance with treatment or potentially untreated contacts. Because the most common rash of scabies—excluding “crusted” scabies—are largely attributable to cell-mediated immunity, full resolution of the rash can take weeks. Additional treatment for itch, with mid-potency topical steroid (0.025% to 0.1% triamcinolone) and oral antihistamines such as hydroxyzine or cetirizine, should be offered.

Oral ivermectin offers the best alternative to topical permethrin, including much better patient adherence than topical treatment, but with oral ivermectin, 2 separate doses spaced 7 to 14 days apart are needed because of failures of this widely used alternative to eradicate unhatched ova in skin. Published clinical treatment data in young children are very limited, but the response to treatment and severity of infestation should determine the need for repeated treatment. Diagnosis and various treatments have recently been more extensively compared (see Suggested Readings).

Lindane and other insecticides should be avoided because they are considerably less effective and have a meaningful risk for adverse reactions, especially with repeated treatment. Any topical treatment can cause an irritant dermatitis, but lindane is most likely to do so. Current literature lacks population-based studies adequately demonstrating the efficacy of malathion, another toxic organophosphate insecticide. Crotamiton 10% (Eurax) is probably less efficacious, must be applied at least twice, and is used less frequently in the United States. Benzyl benzoate is used widely as an inexpensive emulsion and is sometimes recommended by the World Health Organization, although it is not generally available in the United States.

Epidemiologic studies have demonstrated a high rate of spread within families and between multiple individuals sleeping in the same bed. Therefore, bed linens, clothing, and towels should always be washed in hot water immediately after the simultaneous treatment of all individuals in the same household or facility. Fomites or nonwashable clothes, worn during the days before treatment, may be secured in plastic bags, dry-cleaned, or wrapped for 3 days to remove any risk for contagion.

Although pruritus and rash may persist for at least 2 to 8 weeks or longer after successful eradication of an infestation because of continued hypersensitivity

and traces of antigen in skin, repeat treatment to kill mites should be undertaken only when continued infestation with live mites is highly suspected. Some individuals develop red to purple discrete nodules up to 2 cm in diameter on surfaces usually covered by clothing, particularly on the genitals or around the axilla, and these nodules may persist for many months. These *nodular scabies* or *post-scabetic nodules* are thought to represent a robust hypersensitivity reaction. These nodules heal slowly but usually respond to topical or intralesional injections of corticosteroids for itch. Additional precautions regarding chemical treatments outlined previously for pediculosis also apply for scabies.

Complications of scabies, pediculosis, or other infestations, such as superficial or deeper bacterial infection (cellulitis), sometimes with toxin-producing bacterial strains, may necessitate systemic treatment, especially in young or immune-suppressed children. Attention must be given to the potential for long-term sequela of bacterial infection, such as nephritis.

### WHEN TO REFER

- The patient may be referred to allergists if the patient develops severe allergic reaction to insect bites, especially repeatedly, or if hymenoptera allergy is suspected.
- Dermatology referral is appropriate for suspected scabies, especially if there is risk for contagion within an institutional setting like a school or hospital or if suspected infestation is unresponsive to treatment and for other persistent itchy eruptions.

### WHEN TO ADMIT

- If the patient has severe systemic allergic reactions, such as anaphylaxis, to insect bites
- If the patient needs intravenous antibiotics to treat secondary bacterial infection, cellulitis, or systemic infection
- If the patient develops acute noninfectious complications such as acute postinfectious glomerulonephritis and hypertension
- If the patient is suspected of having contracted viral meningitis or other severe or systemic illness through insect bites

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *A Parent's Guide to Insect Repellents* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Choosing an Insect Repellent for Your Child* (Web page), American Academy of Pediatrics (www.healthychildren.org/English/safety-prevention/at-play/Pages/Insect-Repellents.aspx)
- *Head Lice* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Head Lice - Frequently Asked Questions* (fact sheet), Centers for Disease Control and Prevention (www.cdc.gov/parasites/lice/head/gen\_info/faqs.html)



- *Insect Repellent Use and Safety* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/westnile/faq/repellent.html](http://www.cdc.gov/westnile/faq/repellent.html))
- *Treating Head Lice Infestation* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/parasites/lice/head/treatment.html](http://www.cdc.gov/parasites/lice/head/treatment.html))

### Medical Decision Support

- *Lice Infestation* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/parasites/lice/index.html](http://www.cdc.gov/parasites/lice/index.html))
- *Pediatric Dermatology: A Quick Reference Guide* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Pediculosis* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/dpdx/pediculosis/index.html](http://www.cdc.gov/dpdx/pediculosis/index.html))
- *Scabies* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/dpdx/scabies/index.html](http://www.cdc.gov/dpdx/scabies/index.html))

### AAP POLICY

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## Chapter 278

## INTELLECTUAL DISABILITY

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### DEFINITIONS

More than 50 years ago, the term *mental retardation* replaced terms such as idiot, imbecile, and moron as the descriptor of choice to describe intellectual disability. Because the term mental retardation has now acquired a pejorative connotation, in 2006, the membership of the American Association on Mental Retardation voted to change its name to the American Association on Intellectual and Developmental Disabilities (AAIDD). In

2010, the US Congress followed suit and passed Rosa's Law, making "intellectual disability" the new legal definition for the diagnosis formerly known as "mental retardation." In 2013, the American Psychiatric Association published the *Diagnostic and Statistical Manual, Fifth Edition (DSM-5)*, also changing the diagnosis to ID (Intellectual Developmental Disorder). Therefore, primary care physicians, and others, should now use the term *intellectual disability* (ID) to assist their patients in obtaining appropriate supports.

In 2002, the AAIDD published 5 important elements to serve as guidelines for the accurate use of the term *intellectual disability*.

1. The level of functioning of individuals should be considered within their particular social and cultural context.
2. Any assessment of cognitive and adaptive ability should take into account communication, as well as sensory, motor, and behavioral functioning.
3. An individual's strengths must be emphasized in assessments and included in support plans.
4. The purpose of assessing limitations is to guide the development of appropriate supports for the individual in question.
5. The provision of individualized supports is expected to improve functioning significantly.

Implicit in these guidelines is the understanding that, although many cognitive and adaptive impairments are not reversible, ID can be ameliorated by environmental modifications and supports.

Much confusion exists about a variety of terms used to describe children who are not developing as expected. One commonly used term is *developmental delay*, which reflects functioning significantly behind expectations for chronologic age in a particular developmental domain (eg, gross motor, fine motor, cognition, communication). Some children experience this developmental delay in a single domain, whereas others have delays in multiple or all domains. This term is often perceived by parents and laypeople to suggest that the child will, at some time, make up the delay, as would a delayed train that finally arrives at a destination. Such catch-up frequently does occur in the case of delays in isolated domains (eg, in expressive language). On the other hand, clearly, the child who is delayed in all domains, although frequently described as having *global developmental delay*, is less likely to catch up. This situation is particularly true the greater the magnitude of the delay. In general, professionals are hesitant to describe these children as having ID until they are approximately at the age of school entry. At a practical level, this hesitation allows parents to focus on interventions that maximize the child's potential while minimizing the focus on what the child cannot accomplish. Furthermore, this term is less difficult to use by physicians and less difficult to hear by families. On the other hand, professionals and laypeople alike often continue to use the term *developmental delay* far beyond the time when there is any uncertainty in diagnosis, well into the school years, and defer the use of "intellectual disability" excessively.

The AAIDD defines ID as significant impairments in cognitive functioning and in adaptive behavior, which

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develop before age 18 years (Box 278-1). Many professionals think that any child with cognitive impairment has ID. Given that the definition of ID includes both cognitive and adaptive impairment as essential criteria, clarifying the differences here is important. *Cognitive impairment* is defined as performance in the abnormally low range on standard assessments of intelligence. The *intelligence quotient* (IQ) is defined by a mean of 100, with standard deviation of 15. Cognitive impairment is also defined as an IQ 2 or more standard deviations below the mean. Furthermore, cognitive impairment implies significantly low scores in all domains of intelligence testing. Widely discrepant scores in various domains (eg, a verbal IQ in the normal range and a nonverbal score in the range of impairment) would be best defined as a learning disability, not as ID. Adaptive impairment is defined by functioning in the abnormally low range (more than 2 standard deviations below the mean) on formal measures of adaptive functioning, such as the Vineland Adaptive Behavior Scales. Adaptive skills include domains such as communication, self-care, home living, social or interpersonal skills, ability to use community resources, self-direction, functional academic skills, work, leisure, health, and safety.

### BOX 278-1 Criteria for Diagnosis of Intellectual Disability

1. Cognitive impairment is defined as an IQ 2 or more standard deviations of 15 below a mean of 100 ( $\text{IQ} \leq 70$ ).
2. Adaptive impairment (adaptive skills include domains such as communication, self-care, home living, social or interpersonal skills, use of community resources, self-direction, functional academic skills, work, leisure, health, and safety) is identified by functioning more than 2 standard deviations below the mean in these areas (as measured by formal testing of adaptive functioning, such as the Vineland Adaptive Behavior Scales).
3. Children with intellectual disability experience the onset of cognitive and adaptive impairment during the developmental period (usually <18 years of age). Onset of cognitive and adaptive impairment after the developmental period would be referred to by etiology, for example, as traumatic brain injury.

## CLASSIFICATION OF INTELLECTUAL DISABILITY

ID is traditionally subdivided by level of functioning into mild, moderate, severe, and profound. The purpose of such subdivisions should be to identify the level of support that will help that individual function best in society. Table 278-1 summarizes these levels with respect to estimated IQ, expected academic achievement by age 18 years, and anticipated level of recommended support. Adults with mild ID generally function well independently and are able to work in competitive employment and manage domestic affairs adequately. However, individuals with mild ID may have difficulty with stressful situations (eg, following a physician's recommendations). For this reason, individuals with mild ID usually benefit from the intermittent support of a care coordinator. Most adults with moderate ID are able to work in the community, but often require ongoing job coaching, particularly to cope with any changes in routine. In addition, adults with moderate ID are typically able to manage many aspects of their domestic life, such as hygiene and taking public transportation, but require some assistance with daily living. Adults with severe or profound ID are typically unable to work in the community and often require significant daily assistance with many aspects of their domestic life.

## COMMUNICATING WITH FAMILIES

Communicating with families and patients about a diagnosis of ID is challenging. Thoughtful communication is essential in helping families acknowledge a diagnosis that is difficult to accept and readying the family to access important services. Thoughtful communication requires careful and specific use of diagnostic labels and the consistent use of person-first language. To state the impairment first, as in *the intellectually disabled child*, implies that the disability is the most salient characteristic of the child. Using the term *child with an intellectual disability* is preferable. Sensitive use of language demonstrates respect to patients with intellectual disabilities and compassion for their families. The cases presented in this chapter demonstrate that the careful attention to these subtle language differences can promote emotional healing and acceptance despite the inability to cure.

**Table 278-1** Levels of Intellectual Disability

LEVEL	CORRESPONDING IQ	EXPECTED ACADEMIC ACHIEVEMENT BY AGE 18 YEARS	SUPPORT LEVEL
Mild	55–70	Fifth-grade academics	Intermittent
Moderate	40–55	Second-grade academics	Limited
Severe	25–40	Preschool academics	Extensive
Profound	<25		Pervasive

## DIFFERENTIAL DIAGNOSIS AND MANAGEMENT

Given the long-standing history of conflating mental illness and ID, it is important to clarify that the diagnosis of ID does not necessarily imply any specific behavioral disorders. In other words, most children with ID do not have significant or atypical behavior problems. However, behavioral problems and psychiatric disorders may occur at a higher rate among individuals with ID compared with the general population. Several behavioral symptoms that have often been associated with ID, such as irritability, aggression, and self-injury, are worthy of mention. These symptoms are also often seen in autism, which is a common comorbidity of ID. Autism does occur at a higher rate in individuals with ID, and a diagnosis of autism would prompt differences in management from ID alone. For this reason, specialists strongly recommend that the diagnosis of autism be considered, particularly in the face of characteristic symptoms. Also important to note is that such symptoms as irritability and aggression have long been seen as intrinsic features of ID, to the disservice of individuals with this diagnosis. In other words, the presence of ID has often precluded and continues to preclude more meticulous investigation into the cause of such behavioral symptoms. Frequently, irritability and aggression may be symptoms of psychiatric illness, such as depression or anxiety. Self-injury may be a sign of physical illness; for example, hitting the chest may be an indication of undiagnosed gastroesophageal reflux. Apparent hypersexuality, such as dropping the pants in public, may be a manifestation of an uncomfortable erection in the context of inadequate sexuality education. As illustrated in some of the cases presented here, avoiding diagnostic overshadowing or attributing all symptoms to ID is important.

Four cases are presented to illustrate the diagnosis and management of ID, learning disability, and global developmental delay.

### Case 1

*Jenny Miller, a 6-year-old girl, is accompanied by her parents to your office for a discussion about recent recommendations made by personnel at Jenny's school. Jenny has a history of global developmental delay. She has been attending a developmental preschool and has been receiving private speech therapy to supplement her Individualized Education Program (IEP) since she was 3 years old. Mr and Mrs Miller are very upset about the prekindergarten assessment report that they just received. The report states that Jenny has "mild mental retardation" and recommends learning support placement in kindergarten. Mr Miller explains that the school psychologist told them that he was giving Jenny this label so that she could access special education services. Mr Miller takes this statement as evidence that the psychologist is stretching the criteria for this purpose and questions whether the services are worth a label that will follow Jenny for life.*

*You review the evaluation report. On the Wechsler Intelligence Scale for Children (WISC-IV, an IQ test), Jenny received a verbal IQ of 67 and a performance IQ*

*of 64. The full-scale IQ is reported as 63. On the Bracken Basic Concept Scale, a measure of early childhood academic achievement, she received a standardized score of 68. On the Adaptive Behavior Composite of the Vineland Adaptive Behavior Scales, Jenny received a standard score of 55.*

*On physical examination, Jenny is at the 50th percentile for height and weight. During the examination, Jenny is able to recite some of the alphabet by rote, but she has poor articulation and does not recognize her letters. She can count to 5, but incorrectly names the number of fingers you hold up. When you ask her to place the stethoscope on her heart, she places it on her belly. She is unable to dress herself after the examination and turns to her parents for help.*

*After the examination, Mr and Mrs Miller tell you that, instead of allowing Jenny to be placed in special education, they are thinking about keeping Jenny in preschool 1 more year. This way, they hope she can catch up and enter mainstream kindergarten the following year. They ask for your advice about this plan.*

### Case 1 Discussion

Jenny fulfills all 3 of the diagnostic criteria for ID (see Box 278-1). First, intelligence testing estimates her cognitive abilities to be more than 2 standard deviations below the mean. Second, Jenny also has had formal assessment of adaptive skills, with a reported score on the adaptive scale of more than 2 standard deviations below the mean. In corroboration of the formal measures, the physician also has the opportunity to observe in the office pronounced delays in academic skills and communication, a notably small fund of knowledge, and significant difficulties with self-care, such as dressing. Third, of course, Jenny qualifies for the final criterion, being 6 years of age. The school psychologist's use of the term *mental retardation* is inappropriate here, given that this term has now been replaced by *intellectual disability* as the currently accepted legal term. Unfortunately, as of this writing, more than 4 years after the passage of Rosa's Law, the term *mental retardation* is still being used by professionals and is still encountered in various paperwork, such as IEPs, in violation of Rosa's Law.

The questions Mr and Mrs Miller pose raise several important issues. When Jenny's parents express their concern about giving her a label, they are likely expressing their sadness about a diagnosis, which they fear and do not want. In coming to the physician for a second opinion, they are searching for a more palatable diagnosis. This delicate situation calls for a gentle, compassionate, and honest approach. Jenny will benefit from the services that can be provided by the diagnosis of ID. Holding this 6-year-old child back in preschool 1 more year would not address Jenny's learning needs, and the parents would face the same difficult situation the following year. Therefore, the best way to support Jenny's development and learning is to respectfully counsel that, as a professional opinion, Jenny will not likely make sufficient progress without adequate learning support services.

Equally important is the way in which this advice is given. Mr and Mrs Miller may seem to be naive or to be in denial. Actually, they are afraid to accept special

education and its implications and are hoping to defer the inevitable for another year. Therefore, in giving this advice, acknowledging that Mr and Mrs Miller are mourning for the loss of their idealized child is important. Nevertheless, acknowledging Jenny's educational needs now rather than deferring the inevitable for another year would be best. Although the school psychologist attempted to soften the blow by stating that the label was being used to procure services, this approach resulted in confusion for the family. In fact, the psychologist was accurately reflecting Jenny's abilities and leading the family to an appropriate educational placement.

A somewhat different approach from the psychologist would include an effort to (1) avoid use of the term *mental retardation*, (2) dispel myths about the meaning of ID, (3) be straightforward that the diagnosis of ID is justified and that it is the currently accepted legal and educational term, and (4) actively empathize with the family's distress. To dispel myths, a helpful approach would be to start by asking, "What does ID mean to you?" For many families, hearing "mental retardation" conjures up images of common syndromes associated with mental retardation, such as Down syndrome. The use of the term *ID* does help to resolve such confusion. However, even when specific syndromes do not come to mind, many parents may believe that a child with ID would be unable to learn. This belief understandably contributes to confusion for parents such as the Millers, whose daughter has mild impairments. In such cases, the professional needs to explain that individuals with mild ID often do develop functional literacy and some arithmetic proficiency. It is comforting to parents to hear that "developmental disabilities" or "brokerage supports" exist in most communities, which can help young adults with intellectual disabilities obtain supported employment and living situations. Also, it should be noted here that children with even more severe forms of ID have some capacity to learn.

## Case 2

*Your office is the medical home for Max Smith, a 14-year-old boy with a history of diabetes and ID. Max is accompanied by his mother today for a school physical examination before starting high school. On the subject of school, Mrs Smith mentions that "Max had a difficult school year, with his grandpa passing away and his parents finalizing their divorce last fall." Max has an IEP. He has been receiving learning support for all of his core academic courses and has been in mainstream classes for his electives.*

*Max's most recent psychoeducational assessment was performed 2 years ago. The evaluation report states that Max has a verbal IQ of 67, a performance IQ of 62, and a full-scale IQ of 66 on the WISC-IV. On the Weschler Individual Achievement Test-III, an academic skills assessment test, Max's standard scores ranged from the high 50s to the low 70s. On the Adaptive Behavior Composite of the Vineland Adaptive Behavior Scales, Max received a standard score of 68. The evaluation report notes that Max is consistently described by his teachers as "good-natured" and that he "tries to follow directions and is friendly."*

*School reports from the last year note that Max has become increasingly withdrawn, disorganized, and irritable. Mrs Smith reports that when she asked the school counselor about Max's declining school performance, the counselor noted that, "most kids with ID have the same problem when they enter high school—they start to struggle even with the learning support curriculum and often become withdrawn as they realize that they 'don't fit in.'"*

*During the appointment, Max is quiet and withdrawn. His answers to your questions are appropriate, though somewhat concrete. Mrs Smith tells you that, citing Max's current difficulties, the school counselor recommended placing Max in a self-contained life skills classroom. She asks for your opinion about this recommendation.*

## Case 2 Discussion

Max has a history of mild ID, with a relatively acute onset of academic decline. His most recent psychoeducational data—with cognitive, academic, and adaptive testing 2 or more standard deviations below the mean—support the diagnosis of ID. Adolescents with intellectual disabilities often find academic work increasingly challenging in higher grades as the demands intensify and the curriculum becomes more abstract. Nonetheless, attributing all of Max's current difficulties to his ID, as the school psychologist has done, may be misguided. Unfortunately, this tendency to assume that all functional impairments in a person with a given disability may be attributed to the disability is an error that physicians and sometimes school personnel commonly make. To avoid this type of assumption, or diagnostic overshadowing, a patient's functioning should be evaluated in different domains, and the physician should avoid equating a patient's functioning in any domain with a diagnosis.

Max's declining grades, in the context of significant social stressors such as his parents' divorce and his grandfather's death, may be indicative of depression, a common comorbidity of ID. At this visit, assessing or evaluating for depression with a standardized measure and considering referral for mental health evaluation and treatment would be prudent. Although not a factor in this particular case, another common comorbidity in adolescents with cognitive impairment is anxiety, which may be interpreted as attention-deficit/hyperactivity disorder (ADHD) or as a behavior problem. Anxiety or depression may not be obvious during an office visit, particularly in the context of cognitive impairment. Depression and anxiety disorders are at least as prevalent in individuals with ID as in the general population, and some studies have shown an increased prevalence. Therefore, standardized assessment is recommended to increase detection of these common comorbid conditions.

In all adolescents, particularly those with disabilities or chronic health conditions, some thought should be given to planning for the transition to adulthood. Max will likely need considerable support in managing his diabetes care. Even if Max had no chronic health conditions, careful planning for adulthood is warranted. Between the ages of 14 and 16 years, all



students with IEPs should be invited to the IEP meetings and begin to make substantive contributions to vocational and educational planning. Max and his family should start thinking about where and with whom Max is going to live when he becomes an adult. What supports will he continue to need? What interventions are necessary now to prepare Max adequately to succeed with minimal supports?

As Max's pediatrician, some thought should be given to the transfer of Max's care to an internist. How can the primary care physician support Max in finding a physician for this young man with complex needs? Adolescents with disabilities should make regularly scheduled visits throughout adolescence to organize their transition process. The primary care physician can play a helpful role in pooling input from various pediatric subspecialists before transferring care to an internist and adult subspecialists. A primary care physician who has a long-standing relationship with an adolescent can also assist the adolescent and family by providing counseling related to sexuality issues or by referring to an appropriate resource for sexuality education for adolescents with intellectual disabilities. A subspecialist with training in developmental and behavioral pediatrics or in neurodevelopmental disabilities can facilitate and organize transition planning. The International Classification of Functioning is a useful organizing framework (Table 278-2).

### Case 3

*Hannah Ruiz is an 8-year-old new patient to your practice with a diagnosis of Coffin-Siris syndrome, a very rare congenital malformation syndrome, including prenatal-onset growth deficiency, mild to moderate ID, moderate to severe hypotonia, seizures, coarse facies, hirsutism, and hypoplastic to absent fifth distal phalanges. She is accompanied by her mother and maternal grandmother. During the interview, Mrs Ruiz tells you proudly that Hannah's IQ is 88, which the geneticist said is one of the highest IQs ever reported for anyone with Coffin-Siris syndrome. She then mentions that this*

*situation is a source of confusion for her, given that Hannah is not doing well in school despite the fact that she has normal intelligence.*

*During the interview, Hannah requires constant redirection by her mother and grandmother. She bolts out into the hallway on several occasions. When seated, she fidgets continuously. During the examination, Hannah grabs at the stethoscope and the otoscope. Her speech is difficult to understand because of severe articulation problems. Her allergies are clearly in full force, with her nose continually running. Her mother wipes her nose frequently during the visit, to which Hannah objects strenuously. Her mother asks whether you have any thoughts about her academic difficulties.*

### Case 3 Discussion

Hannah clearly does not have a cognitive disability, with an IQ in the normal range at 88. Although most people with Coffin-Siris syndrome have moderate to severe ID, she is an exception. This situation illustrates the important point that functional assessments are much more useful than diagnostic labels or genetic diagnoses in estimating abilities and in developing care plans. Although Hannah's general intelligence is technically in the normal range, it is clearly in the low-normal range, and she would be expected to be a slow learner. She may have significant discrepancies among various subscales that may be affecting her school performance, for which she would qualify for a diagnosis of learning disability. Furthermore, her adaptive skills are clearly impaired. Hannah's academic performance is being affected by inattention, hyperactivity, and impulsivity. In summary, Hannah has significant impairment of adaptive functioning but not of intellectual functioning; therefore, she does not qualify for a diagnosis of ID.

The discrepancy between Hannah's IQ and her academic achievement may be the result, in part, of inattention and hyperactivity, but the explanation is likely to be more complex given the many components of IQ. Comprehensive cognitive and academic testing

**Table 278-2**

### International Classification of Functioning, Disability, and Health to Organize Evaluation and Care Plan

DOMAINS	ELEMENTS TO INCLUDE IN EVALUATION
Learning and applying knowledge General tasks and demands Communication	Learning, thinking, problem solving, and decision making Carrying out tasks, organizing routines, handling stress Use of language, signs, and symbols; receiving and producing messages; carrying on conversation; use of communication devices and techniques
Mobility	Moving body position or location; transferring from one place to another; carrying, moving, and manipulating objects; walking running, and climbing; using transportation
Self-care Domestic life	Washing, dressing, grooming, eating, drinking, hygiene, health practices Acquiring food, clothing, and place to live; household chores; assisting others
Interpersonal interactions and relationships	Basic and complex interactions with people, including strangers, friends, relatives, immediate family members, and intimate relations in a socially appropriate manner
Major life areas Community, social, and civic life	Carrying out tasks related to education, work, and economic transactions Recreation and leisure, religion or spirituality, political life or citizenship



would help in identifying specific learning disabilities and in guiding the design of appropriate learning supports. Hannah's parents can request of her principal that school personnel perform a multidisciplinary evaluation for the identification of learning disabilities; the physician can support the family by explaining this process (see When to Refer).

Although IQs are generally considered to be stable over time for any given individual, seeing some change in IQs in children with learning disabilities is not uncommon. For example, at an early age, Hannah may have achieved an IQ in the normal range, largely owing to strong memory skills. Over time, as IQ tasks favor reasoning over rote memorization, and calculations require multiple steps, Hannah's score would then drop significantly. Notably, this situation would not represent a true regression, but would be a phenomenon of standardized testing. In addition, depending on which test instrument was used, and when it was used, an erroneously elevated IQ score may have been given; as these tests are revised and upgraded, different versions of the same test do not yield comparable results.

Considering Hannah's adaptive impairments, she would likely benefit from care coordination for services through state or local programs for ID. Having psychological assessments repeated as she progresses through school would likely be to Hannah's advantage, both to guide her IEP and to identify if she might qualify for a diagnosis of ID with its accompanying service qualifications. An important point to bear in mind, however, is that Mrs Ruiz is proud of Hannah's relatively high IQ and that such a diagnostic reclassification would need to be handled sensitively despite the advantages it would bring to Hannah.

Hannah has significant symptoms of inattention, hyperactivity, and impulsivity, which may represent ADHD. Such symptoms are common comorbidities of learning disabilities and ID. Effective interventions are available for inattention, hyperactivity, and impulsivity, including school accommodations and medications.

#### Case 4

*Gavin Park, a 2½-year-old boy, is accompanied by his parents in your office. This session is the first follow-up appointment since Gavin established care with you 3 months ago. At the initial visit, you noted significant delays in speech and motor development, and you referred the family to Early Intervention (EI) (partially federally funded, locally provided developmental services for children birth to 3 years of age). In the evaluation for EI, Gavin's developmental level was found to be at approximately 18 months in all domains. Mr and Mrs Park are very pleased with the EI services they have received. They note that Gavin is making good progress in his new preschool. Today, they want your opinion about Gavin's prognosis.*

#### Case 4 Discussion

Gavin is a toddler with moderate global developmental delays. At the chronologic age of 30 months, Gavin is functioning at a mental and motor developmental age of 18 months based on Bayley Scales of Infant

Development (III) standardized testing. This results in a developmental quotient (DQ) of approximately 60 for both mental and motor development. (The DQ equals the developmental age on standardized tests of, for example, intelligence, language, or motor, divided by the chronologic age with this fraction then multiplied by 100.) Cognitive and adaptive skills are included together in the DQ-mental. With a DQ between 2 and 3 standard deviations below the mean, Gavin is at high risk for having ID. For Gavin to catch up, not only would he have to make developmental progress at a rate commensurate with his peers, but he would also have to actually accelerate in his development such that he would outpace his peers. Gavin is making some nice progress in EI, but considering the global nature of his delays, he will not likely accelerate in his development. However, it should be noted here that in circumstances in which the cause of the delays can be identified and reversed, such as elimination of neglect or abuse, or diagnosis and treatment of a metabolic disorder, children may demonstrate such acceleration in development that they can "graduate" from severe to milder delays or from mild delays to typical development.

Nevertheless, making a diagnosis of ID is unnecessary at this point. A diagnosis of ID would likely be difficult for the family to hear and would not be necessary for Gavin's ability to obtain appropriate services. Therefore, the most appropriate diagnosis at this point would be global developmental delay. Although the diagnosis of ID may be deferred, the opportunities for appropriate and early interventions and diagnostic workup should not be delayed. Gavin is already receiving EI services. All children with global or isolated developmental delays should be referred to EI and considered for specialized medical evaluations (because EI is *not* a medical program). Early Intervention physicians should be working with the family to develop an appropriate transition plan for special education services through the school district to start after the child turns 3 years of age. Even when the physician is uncertain that a significant delay exists, if the parents are concerned about their child's development, then their concerns should be validated by encouraging this evaluation. Children with global developmental delay should also be evaluated for possible causes of their developmental differences. Physical examination findings that may suggest the cause of the delays are available in Table 278-3, Table 278-4, and Table 278-5. Table 278-6 provides recommendations regarding the diagnostic workup for children with global developmental delay.

#### EVALUATION

A diagnosis of ID requires documentation of impairment of cognition and of adaptive functioning acquired during development. A useful framework for organizing the collection of these data, and for organizing the care plan, is provided by the *International Classification of Functioning, Disability and Health* (ICF) (see Table 278-2). The ICF was developed by the World Health Organization in 2002 in response to criticism that the 10th edition of the *International Statistical Classification of Diseases and*

**Table 278-3****Minor Anomalies Seen in Specific Syndromes Associated With Intellectual Disability**

SYNDROME	SIGNIFICANT FEATURES ON PHYSICAL EXAMINATION
Down syndrome	Brachycephaly, microcephaly, epicanthal folds, Brushfield spots, up-slanting palpebral fissures, small ears, small nose with low nasal bridge, brachydactyly and clinodactyly, single transverse palmar crease, wide gap and plantar crease between first and second toes, hypotonia, short stature
Fragile X syndrome	High forehead, long jaw or face, large protuberant ears, velvety palmar skin with dorsal redundancy, hyperextensible joints, peripubertal macroorchidism, early-onset overgrowth, initial shyness, repetitive behaviors and stereotypes (note that many of these characteristic dysmorphic features may not be apparent in the younger child)
Fetal alcohol syndrome	Microcephaly, short palpebral fissures, maxillary hypoplasia, flat philtrum, thin upper lip, small distal phalanges and small fifth fingernail, joint anomalies of position and function, short stature
Williams syndrome	Stellate iris, short palpebral fissures, medial eyebrow flare, periorbital fullness, flat nasal bridge, anteverted nares, long philtrum, prominent lips, hoarse voice, heart murmur, hyperactive deep-tendon reflexes, friendly personality, hyperactivity, short stature
Velocardiofacial syndrome (VCFS)	Narrow palpebral fissures, cleft palate, velopharyngeal insufficiency, prominent nose with narrow base, abundant scalp hair, long face, retruded mandible, heart murmur, slender, hypotonic limbs with hyperextensible hands and fingers (note that VCFS is a contiguous gene syndrome and, as such, exists in a spectrum with DiGeorge syndrome)
Rett syndrome	Acquired delay in head growth, acquired diminished eye contact and loss of speech, repetitive purposeless midline hand movements such as wringing or washing, apraxia, hypotonia (principally in girls)

**Table 278-4****Nonspecific Dysmorphic Features Associated With Anomalous Brain Development**

FEATURE	ABNORMALITY	PATHOGENESIS OR POSSIBLE SIGNIFICANCE
Cranium	Microcephaly Asymmetry	Reduced brain growth Premature suture fusion vs deforming external forces vs abnormal underlying brain growth
Hair	Absent or multiple (>2) parietal whorls Cowlick, or anterior upsweep of scalp hair	Abnormal brain development between 10 and 16 weeks' gestation Posterior displacement of junction of parietal and frontal hair streams, resulting from reduced frontal brain development
Eyes	Short palpebral fissures Up-slanted palpebral fissures	Deficient frontal brain growth Relatively deficient frontal brain growth compared with midface
Ears	Low-set (top of helix below outer canthi) Posterior rotation (axis tilted backward >15 degrees)	Reflects delayed morphogenesis because ears are low-set in the early fetus Reflects delayed morphogenesis because ears are posteriorly rotated in the early fetus
Mouth	High arched	Persistent lateral palatal ridges, indicative of oral hypotonia or other oral-motor dysfunction

*Related Health Problems* emphasized diagnostic labels over function and consequently maintained the equation of disability with poor health. With an emphasis on function over diagnostic labels and consideration of environmental factors, the ICF provides a framework for assessment that is congruent with the guidelines put forth by the AAIDD, which were enumerated earlier. Practically speaking, for the primary care physician, the ICF can serve as a *review of functional status*, which complements the review of systems of the traditional medical model. The primary care physician may use Table 278-2 to

assist with the thorough review and documentation of functioning of a comprehensive set of domains during the medical interview and during formation of the care plan.

## PHYSICAL EXAMINATION AND LABORATORY TESTS

The physical examination does more than point to a possible diagnosis. In addition to determining potential causes of ID, the physical examination plays an important role in establishing a connection with the

**Table 278-5** Neurocutaneous Findings Associated With Intellectual Disability

SYNDROME	FINDINGS ON PHYSICAL EXAMINATION	DESCRIPTION
Tuberous sclerosis complex	Hypomelanotic macules	Oval or ash-leaf shaped, few mm to cm, mostly on trunk or extremities; may occur in infancy
	Shagreen patches	Firm yellow to red clusters of nodules, few mm to cm, on dorsum of body, particularly lumbosacral area; typically occurring at puberty (less commonly before)
	Facial angiofibroma	Pink or red shiny nodules on face, especially on nasolabial folds; usually appearing between 2 and 5 years of age
	Forehead fibrous plaque	Yellow-brown or flesh-colored, raised soft or hard plaque, few mm to cm, on forehead or scalp; can occur at any age
	Periungual fibroma	Reddish or flesh colored, arising from nail bed or cuticle, found on toes more often than fingers; usually occurring at puberty or later
Neurofibromatosis	Café au lait macules	Usually hyperpigmented but also includes hypopigmented macules 5 mm or greater
	Axillary freckling	Small brown macules in axillae and perineum
	Cutaneous neurofibroma	Small, raised, soft, pigmented nodules
Sturge-Weber syndrome	Cranial port-wine stain	Light pink to deep purple birthmark, typically involving at least 1 upper eyelid and the forehead

**Table 278-6** Diagnostic Workup for Global Developmental Delay or Intellectual Disability<sup>a</sup>

TEST	INDICATIONS
Ophthalmologic assessment	Recommended in all children with moderate to severe global developmental delay or ID.
Audiologic assessment	Recommended in all children with moderate to severe global developmental delay or ID.
Karyotype	Recommended in all children with moderate to severe global developmental delay or ID.
Metabolic workup	Not generally recommended if newborn screen is documented; recommended with specific family history, consanguinity, regression, or episodic decompensation
Fragile X syndrome (DNA methylation testing)	Recommended in boys with moderate to severe global developmental delay or intellectual disability (ID); particularly recommended when characteristic features present (see Table 278-4).
Rett syndrome ( <i>MECP2</i> gene testing)	Recommended in girls with moderate to severe global developmental delay or ID; particularly recommended when characteristic features present (see Table 278-4).
Subtelomeric fluorescence in situ hybridization (FISH) <sup>b</sup>	Before the development of complete genomic hybridization technology, this was the best test for the detection of small subtelomeric rearrangements. This test has been replaced by microarray comparative genomic hybridization.
Microarray comparative genomic hybridization <sup>c</sup>	Consider in mild to severe global developmental delay or ID. This test has higher yield when 1 or more of the following features are present: family history of unexplained moderate to severe ID, prenatal onset growth restriction, or postnatal growth abnormalities, including microcephaly or macrocephaly or short or tall stature, more than 2 dysmorphic facial features or nonfacial congenital anomalies.
Thyroid function testing	Recommended if no newborn screen documented or with characteristic symptoms, such as late tooth eruption or fontanel closure, weight for age above height for age, constipation, delayed relaxation phase of deep-tendon reflexes.
Lead testing	Has been found to be elevated at higher rate in children with risk factors and global developmental delay or ID compared with children with risk factors without, given that pica is a behavioral characteristic associated with ID.
Electroencephalogram	Recommended only if a clinical indication of seizures is present.
Brain magnetic resonance imaging	Recommended for global developmental delay, although clinical picture should be taken into account. Lower yield in mild global developmental delay, which tends to be familial. Higher yield with focal or abnormal neurologic examination, in the presence of cranial anomalies (see Table 278-4) or neurocutaneous features (see Table 278-5).

<sup>a</sup>Many of these tests are generally ordered by subspecialists. This information is provided to give the generalist an idea of the workup for ID.<sup>b</sup>DNA complete genomic hybridization microarray technology has replaced subtelomeric FISH.<sup>c</sup>Consensus Statement: Chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disability or congenital anomalies. *Am J Hum Genet.* 2010;86(5):749–764.

child and in assessing interpersonal interactions. Table 278-3 summarizes key features of some common syndromes associated with ID. Table 278-4 summarizes findings that, although not pathognomonic of particular syndromes, may indicate anomalous brain development. Table 278-5 summarizes and describes the features of selected neurocutaneous syndromes.

In most cases of mild ID, the cause is multifactorial; no single cause is identified or, indeed, identifiable. In contrast, in cases of moderate to severe ID, a single cause is more commonly implicated and may be identified by systematic investigation, including through physical examination. An aspect of the examination that deserves special mention is the formal assessment of hearing and vision; referrals for thorough evaluation of these senses should be made in the workup of global developmental delay or ID. In the absence of clues from the physical examination, guidelines from the American Academy of Neurology may be used for the diagnostic workup of ID and global developmental delay. These guidelines are summarized in Table 278-6.

### WHEN TO REFER

- Infants and toddlers failing to meet developmental milestones using standard screening and surveillance instruments, such as Ages & Stages Questionnaires, the Child Development Inventory, or Bright Futures Guidelines, should be referred to Early Intervention (EI) for evaluation. In addition, if a parent expresses concern, a pediatrician may refer for evaluation through the EI program even if in-office screens do not detect developmental delays. Referrals can be based on objective criteria or clinical judgment. If the primary care physician even suspects developmental delay, erring on the side of caution would be advisable.
- Parents who express concerns about their child's development should have their concerns validated by a referral to EI services.
- Children who have had a new diagnosis of global developmental delay or of ID should have a complete medical evaluation to determine the causes of the delays. The primary care physician may wish to refer to subspecialists in genetics, neurology, developmental and behavioral pediatrics, or neurodevelopmental disabilities to assist with this evaluation.
- Children who are suspected of having ID and who have not had a formal psychological assessment should be referred for evaluation of cognitive abilities, academic achievement, and adaptive skills. Families may obtain such psychological testing free of charge through their local school district by making a formal request for a multidisciplinary evaluation. Primary care physicians can support families in this endeavor by providing references to the process of requesting an evaluation through the school district. Families may also obtain an independent psychological evaluation from a private pediatric psychologist or pediatric neuropsychologist.

### ACKNOWLEDGMENT

*I dedicate this revision to my original coauthor and mentor, Bill Cohen. Also, I would like to thank Dr Anne Tsai for helpful comments on this revision.*

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Overview of Early Intervention* (Web page), Center for Parent Information and Resources ([www.parentcenterhub.org/repository/ei-overview](http://www.parentcenterhub.org/repository/ei-overview))
- *What Is a Multidisciplinary Evaluation?* (fact sheet), The Child Advocate ([www.childadvocate.net/MDE.htm](http://www.childadvocate.net/MDE.htm))

#### Community Advocacy and Coordination

- *All About the IEP* (fact sheet), Center for Parent Information and Resources ([www.parentcenterhub.org/repository/iep](http://www.parentcenterhub.org/repository/iep))
- *Disabilities* (Web page), Center for Parent Information and Resources ([www.parentcenterhub.org/repository/disability-landing](http://www.parentcenterhub.org/repository/disability-landing))
- *People First Language* (fact sheet), Disability Is Natural ([www.disabilityisnatural.com/explore/people-first-language](http://www.disabilityisnatural.com/explore/people-first-language))

### AAP POLICY

American Academy of Pediatrics Committee on Children with Disabilities. The pediatrician's role in development and implementation of an Individual Education Plan (IEP) and/or an Individual Family Service Plan (IFSP). *Pediatrics*. 1999;104(1):124–127 ([pediatrics.aappublications.org/content/104/1/124](http://pediatrics.aappublications.org/content/104/1/124))

American Academy of Pediatrics Council on Children With Disabilities, Section on Developmental and Behavioral Pediatrics, Bright Futures Steering Committee, Medical Home Initiatives for Children With Special Needs Project Advisory Committee. Identifying infants and young children with developmental disorders in the medical home: an algorithm for developmental surveillance and screening. *Pediatrics*. 2006;118(1):405–420. Reaffirmed August 2014 ([pediatrics.aappublications.org/content/118/1/405](http://pediatrics.aappublications.org/content/118/1/405))

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Murphy NA, Elias EA; American Academy of Pediatrics Council on Children With Disabilities. Sexuality of children and adolescents with developmental disabilities. *Pediatrics*. 2006;118(1):398–403. Reaffirmed July 2013 ([pediatrics.aappublications.org/content/118/1/398](http://pediatrics.aappublications.org/content/118/1/398))

### SUGGESTED READINGS

American Academy of Pediatrics National Center of Medical Home Implementation. *What Is a Medical Home?* Available at: [medicalhomeinfo.aap.org/overview/Pages/Whatisthemedicalhome.aspx](http://medicalhomeinfo.aap.org/overview/Pages/Whatisthemedicalhome.aspx)

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## Chapter 279

# IRON-DEFICIENCY ANEMIA

Lakshmanan Krishnamurti, MD

Iron-deficiency anemia (IDA) is the most common nutritional deficiency worldwide. In the United States, it is most common among women and young children. It affects 2.4 million US children. Iron is an important ingredient of hemoglobin and is involved in numerous cellular processes. Children with iron deficiency in infancy continue to have poorer cognition and school achievement and more behavior problems into middle childhood. Iron deficiency is also associated with deficits in work productivity, and severe anemia is associated with maternal and child mortality. Prevention of iron deficiency in early childhood is, therefore, an important public health issue.

## IRON-CONTAINING COMPOUNDS IN THE BODY

Iron is the most abundant heavy metal in the body. The multiple iron-containing compounds serving metabolic functions include heme- and nonheme-containing compounds. Heme is composed of a protoporphyrin ring with noncovalently bound iron in the ferrous form ( $\text{Fe}^{2+}$ ). The most abundant heme-containing protein in the body is hemoglobin, which transports oxygen from the lungs to the tissues and accounts for more than 60% of total body iron. Myoglobin, which accounts for 10% of total body iron, is a heme protein that provides oxygen for use during muscle contraction. The other major heme proteins, the cytochromes, are found in the mitochondria and are necessary for the oxidative production of cellular energy. There also are several nonheme iron proteins, such as the iron-sulfur complexes and flavoproteins. Many of these proteins are found in the mitochondria and also are involved in oxidative metabolism.

## REGULATION OF IRON ABSORPTION, HOMEOSTASIS, AND STORAGE

Basic studies in humans and in a variety of animal models have helped define the pathways and transporters involved in iron absorption and the signal transduction mechanisms involved in iron homeostasis. Divalent metal transporter-1 (DMT-1) mediates absorption of iron in duodenal and jejunal enterocytes and in the delivery of iron to erythroid precursors. Body iron stores, ineffective erythropoiesis, and

hypoxia, as well as dietary factors such as phytate, polyphenols, calcium, and ascorbic acid, regulate iron absorption. Ferroportin is a transmembrane protein found in all cells involved in iron transport that mediates iron export from enterocytes and from macrophages recycling senescent red blood cells (RBCs) to plasma. Hepcidin is a negative regulator of iron export that inhibits export of iron to plasma by binding to ferroportin and removing it from the cell surface. Anemia, defective erythropoiesis, iron stores, hypoxia, and inflammation regulate hepcidin. Hemojuvelin (HJV) is a membrane-bound and soluble protein that regulates hepcidin expression. Membrane-bound HJV is a critical part of the signaling mechanism for hepcidin transcription. The soluble form of HJV functions as a competitive inhibitor of the membrane-bound HJV. High levels of transferrin-bound iron in the plasma inhibit the production of soluble HJV, leading to hepcidin-mediated inhibition of iron transport into the plasma by ferroportin. Ceruloplasmin and hephaestin are enzymes that oxidize ferrous iron exported by ferroportin to ferric form to facilitate plasma transport of iron by transferrin. Transferrin is a  $\beta_1$ -globulin capable of binding atoms of iron in the ferric form. It transports iron from the intestinal epithelium to the bone marrow, where it binds to transferrin receptors on the surface of differentiating RBCs. The transferrin receptor complex is then internalized and thus supplies iron for the synthesis of hemoglobin. Transferrin also mediates transport of iron exported out of macrophages recycling senescent RBCs. Ferritin, an iron storage compound found in all cells of the body, is composed of a hollow protein shell encapsulating iron molecules. Hemosiderin, which also serves to store intracellular iron, is thought to be a partially degraded form of ferritin.

## PREVALENCE OF IRON DEFICIENCY AND IRON-DEFICIENCY ANEMIA

Iron deficiency is common, despite the generally good standard of nutrition and the widespread use of iron-fortified foods. The prevalence of iron deficiency is greatest among toddlers aged 1 to 2 years and adolescent girls and adult women aged 12 to 49 years. The prevalence of iron deficiency is 2 times higher among non-Hispanic black and Mexican American women (19% to 22%) than among non-Hispanic white women (10%). The National Health and Nutritional Examination Survey (NHANES) revealed that prevalence of iron deficiency between 1988–1994 and 1999–2002 remained unchanged at 9% in children 1 to 2 years of age. The prevalence of iron deficiency increased from 4% in 1988–1994 to 6% in 2003–2006 in children 3 to 4 years of age. Thus, the prevalence of IDA remains higher than the goal of the national health objectives for 2010, and no significant progress was made toward the goal to reduce iron deficiency in vulnerable populations by 3 to 4 percentage points.

## ETIOLOGY AND PATHOPHYSIOLOGY

The 4 most important factors in the development of iron deficiency in children are the iron endowment at birth, the iron needs during rapid body growth,

**Table 279-1** Causes of Iron Deficiency

**INCREASED IRON REQUIREMENTS**

- Blood loss
  - Menstruation
  - Gastrointestinal tract
    - Milk enteropathy
    - Food sensitivity
    - Inflammatory bowel disease
    - Meckel diverticulum
    - Peptic ulcer disease
    - Reflux esophagitis
    - Hookworms
    - Malignancy
- Genitourinary tract
- Respiratory tract
  - Idiopathic pulmonary hemosiderosis
  - Cystic fibrosis
  - Pulmonary tuberculosis
- Cardiac
  - Hemosiderinuria caused by cardiac hemolysis
- Blood donation
- Pregnancy
- Growth
  - Prematurity
  - Infancy
  - Adolescence

**INADEQUATE IRON ABSORPTION**

- Diet low in bioavailable iron
  - Formula not fortified with iron
  - Cow milk before the age of 6 months
  - Strict vegetarian diet
  - Poor dietary habits in adolescents
- Impaired absorption
  - Intestinal malabsorption
  - Gastric surgery
  - Hypochlorhydria

Modified from Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency in the United States. *MMWR Recomm Rep.* 1998;47(RR-3):1–29.

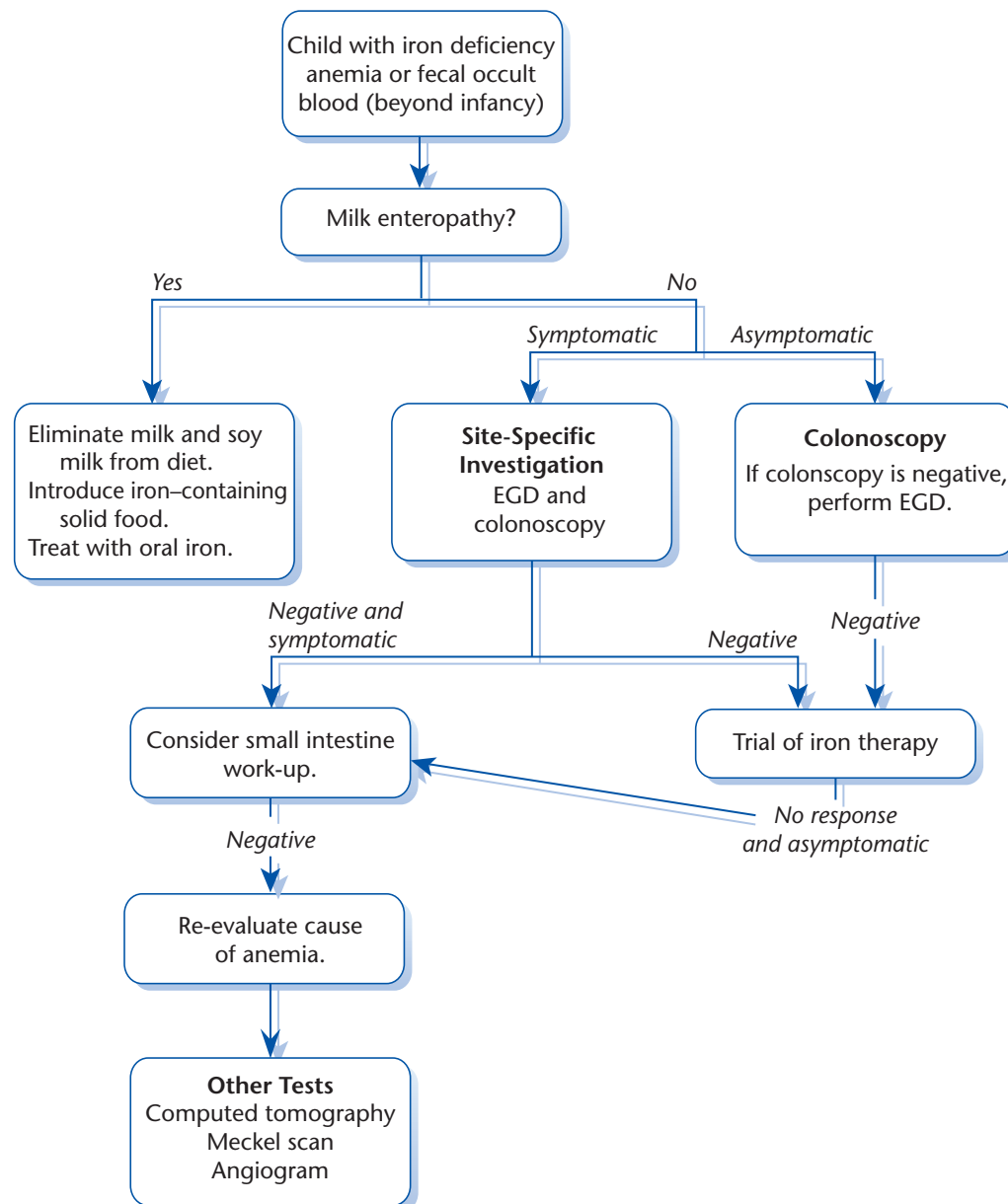
exogenous iron absorption, and blood loss. The causes of iron deficiency are summarized in Table 279-1.

During gestation, the level of iron stores in newborns is related to maternal iron status, and the maternal-fetal unit is dependent on exogenous iron. The ratio of iron content to weight in the human fetus remains constant throughout gestation. The healthy full-term infant has sufficient iron stores to last for 6 months, if sufficient small amounts of iron are ingested from the diet. The infant's iron endowment can be compromised by blood loss during the pregnancy or the perinatal period. Common causes of blood loss include third-trimester bleeding, such as abruptio placentae, placenta previa, fetomaternal hemorrhage, and twin-to-twin transfusions.

Gestational conditions that result in lower newborn iron stores include severe maternal iron deficiency, maternal hypertension with intrauterine growth restriction, and maternal diabetes mellitus. Stable, very low-birth-weight (VLBW) premature infants are also at risk for early postnatal iron deficiency because they accrete less iron during gestation, grow more rapidly after birth, are typically undertreated with enteral iron, and receive fewer RBC transfusions than sick VLBW infants. Iron is needed not only for many metabolic functions and tissue replacement, but also for growth. Growth rates vary with age and are maximal during infancy and adolescence, the same

periods associated with the highest frequency of iron deficiency.

Iron balance is maintained by regulation of iron absorption. The amount of iron absorbed depends on the amount and the bioavailability of dietary iron, as well as on regulation of iron absorption by the intestinal mucosa. Most dietary iron occurs in the nonheme form and is much less bioavailable than that in heme proteins. The iron in hemoglobin and myoglobin is particularly bioavailable; up to 30% is directly absorbed by the gastrointestinal tract. Human milk and cow milk contain small amounts of iron (0.2 to 0.3 mg/1,000 mL). However, 50% of the iron in breast milk is absorbed, compared with only 10% in cow milk. Full-term infants who are exclusively breastfed for the first 6 to 9 months do not become iron deficient. In a double-blind randomized study, Friel and colleagues demonstrated that iron supplementation starting at 4 months of age resulted in higher hemoglobin and mean corpuscular volume at 6 months of age and significantly higher visual acuity and psychomotor developmental index at 13 months. Exclusive breastfeeding beyond 6 months of age is associated with an increased risk for iron deficiency by 9 months. Iron deficiency at 6 months is related to growth velocity. Bran in cereals, polyphenols in many vegetables, and tannins in tea inhibit nonheme iron absorption. Complementary foods, including iron-fortified cereals,



**Figure 279-1** Algorithm for approach to iron deficiency with occult intestinal blood loss. EGD, esophagogastroduodenoscopy. (Modified from Feldman M. Sleisenger & Fordtran's Gastrointestinal and Liver Disease. 7th ed. Copyright © 2002 Elsevier, with permission.)

vegetables with high iron content, and red meats, should be introduced early.

Blood loss causes iron deficiency in children less frequently than in adults. In infancy and childhood, iron deficiency caused by blood loss is most commonly associated with the ingestion of unprocessed cow milk and with parasitic infections. Hypersensitivity to whole cow milk causes an exudative enteropathy and frequently leads to gastrointestinal blood loss (Figure 279-1). Other less common causes of blood loss in children include Meckel diverticulum, intestinal duplication, peptic ulcer disease, hemorrhagic telangi-

ectasia, and the chronic use of medications that prolong the bleeding time (eg, nonsteroidal anti-inflammatory drugs).

### STAGES OF IRON DEFICIENCY

Iron deficiency occurs when total body iron content is diminished. When absorption exceeds losses, the iron surplus is stored in the reticuloendothelial system, principally the liver, spleen, and bone marrow. Iron is removed from the reticuloendothelial storage pool to compensate for negative iron balance. The development of iron deficiency proceeds through a series of

overlapping stages. The major public health importance of iron deficiency is that it is associated with significant neurodevelopmental and long-lasting behavioral problems. Therefore, it is important to identify, prevent, and manage iron deficiency before the development of hematologic complications with IDA.

Iron deficiency is considered to develop in 3 stages. The first stage of iron deficiency is storage iron depletion. During this stage, there is no deficit of iron supplied to the erythroid marrow for RBC production. The decrease in body iron stores is typically measured by serum ferritin. If the negative iron balance continues, the second stage, iron-deficient erythropoiesis (IDE), will occur. During this stage, erythroid iron supply is diminished, but the hemoglobin concentration remains in the normal range. Serum transferrin saturation is increased in the first or second stage of iron deficiency. In this stage, soluble transferrin receptors (sTfRs) are increased, zinc protoporphyrin (ZnPP), is increased, and reticulocyte hemoglobin concentration (CHr) is decreased. If the negative iron balance persists, IDA finally develops. This third stage is characterized by a decrease in the hemoglobin concentration and a reduction in RBC size and hemoglobin content. Hematologic abnormalities in iron deficiency progress as there is progressive impairment of hematopoiesis. Anisocytosis and an increased percentage of microcytic cells are the first hematologic abnormalities; at the second stage the mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) decline; and the final stage of iron deficiency is associated with a low MCHC and low hemoglobin concentration.

Functional iron deficiency is a condition that occurs primarily as a result of treatment with recombinant human erythropoietin. During the supraphysiologic burst of RBC production after a pharmacologic dose of recombinant human erythropoietin, the small circulating iron pool (0.1% of total body iron) may be insufficient to supply the stimulated erythron. Thus, even with normal iron stores, IDE may occur, with further iron repletion often required for normal erythropoiesis to resume. Inflammation may also be a contributory factor.

Specific laboratory findings are associated with each of the 3 stages of iron deficiency. The laboratory test findings characteristic of each stage are summarized in Table 279-2.

## DIFFERENTIAL DIAGNOSIS

Diagnosis of iron deficiency is made by the combination of RBC indices and serum transferrin saturation or ferritin. Transferrin saturation and ferritin may be altered by infection, inflammation, malignancy, and starvation. Serum transferrin receptor levels help discriminate iron deficiency from the anemia of inflammation or chronic disease.

Although the absence of iron stores in the bone marrow remains the gold standard for making the diagnosis of iron deficiency, this test is rarely performed for this purpose because of the obvious discomfort involved and the difficulty of standardizing bone marrow iron stain.

After the diagnosis of IDA is made, efforts should be undertaken to establish the cause of the deficiency

**Table 279-2**

### Laboratory Abnormalities in the 3 Stages of Iron Deficiency

STAGE	DESCRIPTION
I: Iron depletion	Serum ferritin ↓ Bone marrow iron ↓
II: Iron-deficient erythropoiesis	Serum ferritin ↓ Bone marrow iron ↓ Serum iron ↓ TIBC ↑
III: Iron-deficiency anemia	Serum iron ↓ Serum ferritin ↓ Bone marrow iron ↓ TIBC ↑ Hemoglobin ↓ Hematocrit ↓ MCV ↓ RDW ↑

↑ Indicates increased; ↓, decreased.

MCV, mean corpuscular volume; RDW, red blood cell distribution width;

TIBC, total iron-binding capacity.

From Roper D, Stein S, Payne M, Coleman M. Anemias caused by impaired production of erythrocytes. In Rodak BF, ed. *Diagnostic Hematology*. Philadelphia, PA: WB Saunders; 1995. Reprinted by permission.

(Table 279-1). In infancy (a period when iron demands resulting from rapid growth may outstrip the supply of iron), in adolescence, and during pregnancy, iron deficiency and IDA are the result of a physiologic increase in iron requirement that is not being met by the oral supply of iron. Beyond infancy, blood loss is the most common cause of iron deficiency and IDA.

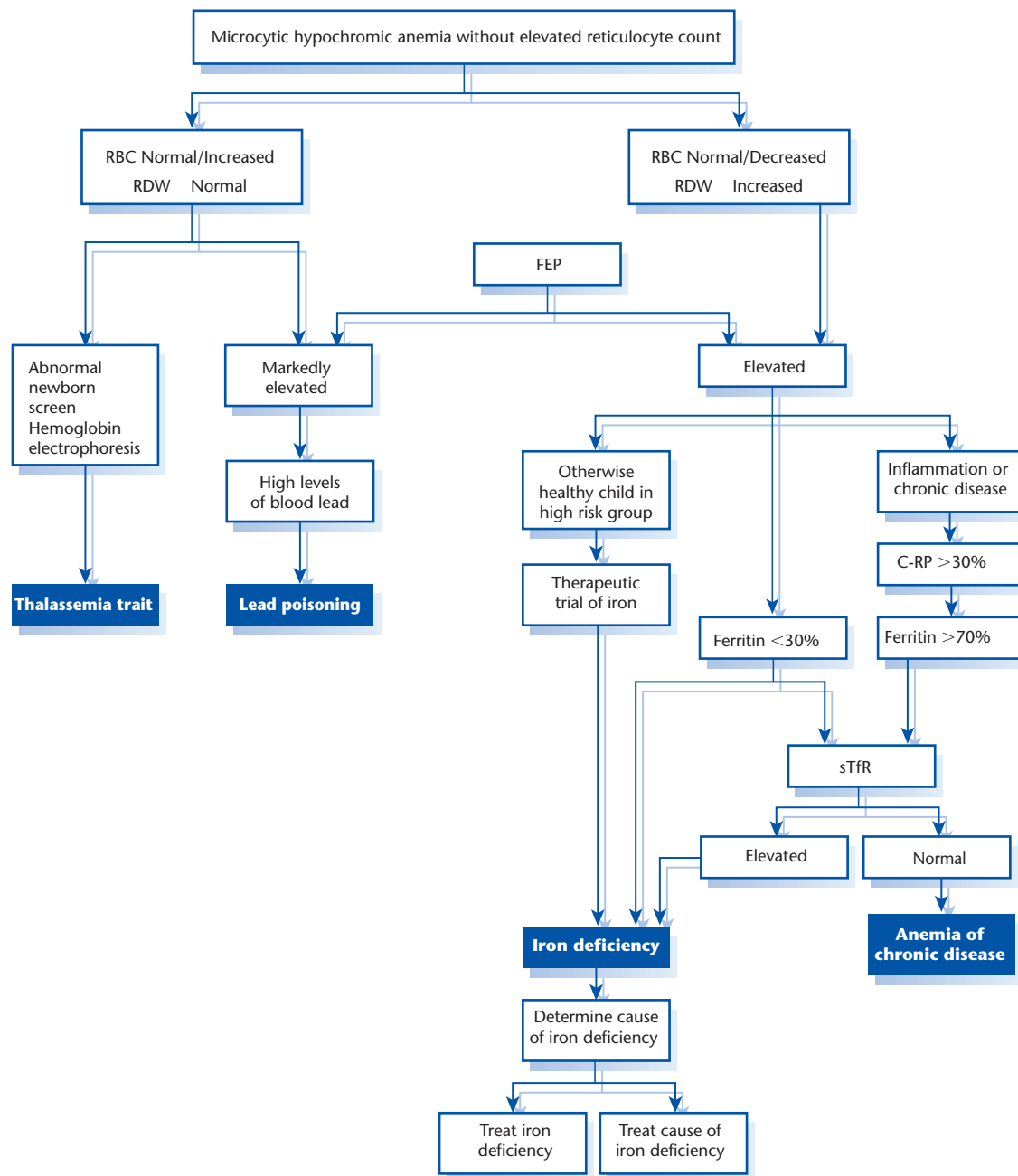
Iron-deficiency anemia must be distinguished from other causes of hypochromic microcytic anemia (Figure 279-2). Red blood cell indices in infancy and childhood are described in Table 279-3.

## Thalassemia Trait

Iron-deficiency anemia and thalassemia trait are the most common causes of mild microcytic anemia with hemoglobin 9 g/dL or more. Red blood cell count often is increased above normal despite the presence of a mild anemia and microcytosis in thalassemia trait, whereas RBC count is reduced in IDA. The RBC distribution width (RDW) is increased in iron deficiency. The Mentzer index, defined as the MCV divided by the RBC count in millions, can help distinguish the anemia of iron deficiency from that of  $\beta$  thalassemia trait. In IDA, the Mentzer index often is greater than 13.5; in  $\beta$ -thalassemia trait, it is less than 11.5 with 82% specificity. An RDW index (RDWI), which is calculated by the formula  $RDWI = (MCV/RBC \times RDW)$ , of at least 220 is indicative of IDA, whereas an index of less than 220 is indicative of thalassemia trait with a specificity of 92%. RBC count and RDWI are the most reliable discrimination indices in differentiation between  $\beta$ -thalassemia trait and IDA.

If  $\alpha$ - and  $\beta$ -thalassemia trait or hemoglobin E disease is suspected, the diagnosis can be established





**Figure 279-2** Algorithm for an approach to microcytic anemia. *C-RP*, C-reactive protein; *FEP*, free erythrocyte protoporphyrin; *RBC*, red blood cell; *RDW*, red blood cell distribution width; *sTfR*, soluble transferrin receptor.

by reviewing the newborn screen or by obtaining a hemoglobin electrophoresis. Electrophoretic methods can be diagnostic in the case of  $\beta$ -thalassemia or hemoglobin E, but may not be informative in  $\alpha$ -thalassemia beyond the newborn period. Because  $\beta$ -thalassemia or hemoglobin E trait or homozygous hemoglobin E is frequently not associated with hemoglobin of less than 9 g/dL, it is not included in the differential diagnosis in severe anemia. However, patients who are double heterozygotes for  $\beta$ -thalassemia and hemoglobin E may have moderate to severe

anemia. Diagnosis of  $\alpha$ -thalassemia trait can be assumed when a child with a familial hypochromic microcytic anemia has normal results of iron studies (including ferritin), normal levels of hemoglobin A<sub>2</sub> and hemoglobin F, and a normal hemoglobin electrophoresis. It is a diagnosis of exclusion, except in the newborn period, when infants with  $\alpha$ -thalassemia trait have 3% to 10% hemoglobin Barts ( $\gamma_4$ ), which may be detected in the newborn screen if there is a mutation involving the deletion or loss of function of 1 or more of the  $\alpha$ -globin genes.

**Table 279-3** Red Blood Cell Indices During Infancy and Childhood

AGE	HEMOGLOBIN (G/DL)		HEMATOCRIT (%)		RETICULOCYTES (%)	MCV (FL)
	MEAN	RANGE	MEAN	RANGE	MEAN	LOWEST
<b>CHILD</b>						
Cord blood	16.8	13.7–20.1	55	45–65	5.0	110
2 wk	16.5	13.0–20.0	50	42–66	1.0	107
3 mo	12.0	9.5–14.5	36	31–41	1.0	80
6 mo–6 yr	12.0	10.5–14.0	37	33–42	1.0	70–74
7–12 yr	13.0	11.0–16.0	38	34–40	1.0	76–80
<b>ADULT</b>						
Female	14	12.0–16.0	42	37–47	1.6	80
Male	16	14.0–18.0	47	42–52	1.6	80

MCV, mean corpuscular volume; WBC, white blood cells.

Modified from Behrman RE. *Nelson Textbook of Pediatrics*. 17th ed. Philadelphia: WB Saunders; 2004. Copyright © 2004, Elsevier, with permission.

### Hemoglobin H Disease

Hemoglobin H disease, another form of  $\alpha$ -thalassemia, results from deletion of 3 of the 4  $\alpha$ -globin genes. It also is characterized by hypochromia and microcytosis, but, in addition, there is a mild hemolytic component from instability of the  $\beta$ -chain tetramers (Hb H) resulting from a deficiency of  $\alpha$ -globin chains. Beyond infancy, Hb H is readily identified by hemoglobin electrophoresis. During the newborn period, the moderately severe  $\alpha$ -globin deficiency allows for the accumulation of more  $\gamma$  chains, and the concentration of hemoglobin Barts is more than 20%.

### Anemia of Chronic Disease and Inflammation

Inflammation impairs the supply of iron to the plasma and ultimately results in a form of anemia called *anemia of chronic disease* or *anemia of inflammation*. It is usually normocytic, although, occasionally, it may be slightly microcytic. Because inflammation alters screening tests for iron status in the same manner as true iron deficiency, the distinction between anemia of chronic disease and IDA requires tissue-related iron measurements. However, the usefulness of the serum ferritin in the diagnosis of IDA is compromised by the effect of inflammation on the value. Consequently, a serum ferritin concentration below 30 mcg/L suggests IDA in the presence of inflammation. However, because specificity for iron deficiency falls sharply with increasing ferritin levels, there is considerable overlap between iron-deficient and iron-replete children, and ferritin levels between 20 and 100 mcg/L are often inconclusive, whereas serum ferritin levels higher than 100 mcg/L usually exclude iron deficiency.

C-reactive protein is generally considered to be the best laboratory marker of inflammation. If it is less than 30 mg/L, it is generally considered unlikely that the inflammation is sufficient to raise the serum ferritin. The sTfR measurement for identifying IDA is one in which the concentration is not affected by inflammation. Use of the sTfR/log ferritin ratio of more than 1.70 further improves the specificity of the diagnosis

of IDA and may eliminate the need for bone marrow examination for assessment of iron stores.

### Lead Poisoning and Anemia

Lead poisoning and IDA both are associated with high levels of erythrocyte ZnPP. Iron deficiency and lead poisoning frequently coexist. Although the nature of their relationship is not completely elucidated, characterization of a common iron-lead transporter and epidemiologic studies among children strongly suggest that iron deficiency may increase susceptibility to lead poisoning. In cases of lead poisoning associated with iron deficiency, the RBCs are morphologically similar, but coarse basophilic stippling of the RBCs is frequently prominent. Increases in blood lead, zinc protoporphyrin ratio (ZnPP/H), and urinary coproporphyrin levels are seen.

## EVALUATION

### History

The onset and progression of iron deficiency is usually gradual, and most children will not have major symptoms. Iron deficiency in infants and children is associated with generalized weakness, irritability, easy fatigability, headaches, poor feeding, anorexia, pica, and poor weight gain.

### Physical Examination

The physical examination is usually unremarkable except for marked pallor of the mucous membranes and skin. Other physical findings associated with IDA, but rarely observed, include mild hepatosplenomegaly, lymphadenopathy, glossitis, stomatitis, blue sclerae, and koilonychia (spoon-shaped nails). The physical examination is usually unremarkable except for marked pallor of the mucous membranes and skin. Most mild cases of IDA do not include pallor.

### Laboratory Evaluation

Laboratory tests for identifying iron deficiency include screening and definitive tests. Screening tests

**Table 279-4****Laboratory Findings Associated With the Differential Diagnosis of Microcytic Anemias**

FINDING	IRON DEFICIENCY	LEAD POISONING	β-THALASSEMIA TRAIT	CHRONIC DISEASE
Ferritin	↓	Normal	Normal	↑
Serum iron	↓	Normal	Normal	↑
Total iron-binding capacity	↑	Normal	Normal	↓
Erythrocyte zinc protoporphyrin	↑	↑↑	Normal	↑
Red blood cell distribution width	↑	Normal	Normal	Normal
Serum transferrin receptor	↑	Normal	↑	Normal

↑, Increased; ↑↑, very increased; ↓, decreased. Iron deficiency and lead poisoning frequently co-exist.

identify IDE by demonstrating either a reduced supply of plasma iron or poor hemoglobinization of circulating RBCs. Definitive tests identify IDA by measuring iron-related proteins derived from either the iron storage compartment in macrophages or the iron utilization compartment in RBC precursors.

### Screening Measurements

#### Hemoglobin Concentration

Although hemoglobin concentration is the most commonly used screening test for IDA, it is relatively insensitive for the diagnosis of iron deficiency because an individual with normal body iron stores must lose a large portion of body iron before the hemoglobin falls below the laboratory definitions of anemia. Further, low hemoglobin does not distinguish among the causes of anemia other than iron deficiency, and additional testing is required.

#### Serum Iron and Transferrin Saturation

Serum iron levels normally fluctuate daily, with maximal levels occurring in the morning and minimal levels in the evening. The total iron-binding capacity (TIBC) varies less than serum iron, but is harder to measure accurately. The normal TIBC is 250 to 400 mg/dL, but, as serum iron levels decrease, the TIBC increases to 450 mg/dL or more. Iron and TIBC measurements are useful in distinguishing IDA from anemia of chronic disease. Serum iron levels decrease with both, but the TIBC levels also decrease in chronic disease states (Table 279-4). The degree of iron saturation of plasma transferrin is calculated as follows: transferrin saturation = (serum iron concentration/total iron-binding capacity) × 100.

Serum iron and TIBC levels help confirm the diagnosis of iron deficiency, with a low serum iron level and a high transferrin level resulting in a transferrin saturation of less than 10% to 15%. Transferrin levels are increased in iron-deficiency states because of increased hepatic synthesis of the protein and greater liberation of apotransferrin (the transport protein without iron) from hemoglobin-synthesizing

sites. This relatively inexpensive measurement is widely available. However, marked diurnal variation in plasma iron values and the numerous clinical disorders that affect the transferrin saturation limit its use in the clinical setting. A normal or high transferrin saturation is as useful for excluding IDA as a low value is for identifying it. Among other conditions, pregnancy and oral contraceptives may be associated with elevated transferrin level and transferrin saturation, thus complicating the diagnosis of IDA. In these situations, combining laboratory studies, such as serum ferritin and sTfR, may be useful in the diagnosis of iron deficiency.

#### Red Blood Cell Indices

The development of electronic counters has made the use of RBC indices widely available for the initial screening of infants and children for iron deficiency. These tests are highly reproducible and less subject to sampling error compared with hemoglobin determinations because tissue fluid dilution does not affect RBC size. The RBCs become smaller than normal with decreased MCV, and their hemoglobin content decreases with decreased MCHC. The RDW approximates the standard deviation of the RBC population. Normal RDWs occur in the range of 12% to 17%. In IDA, there is a marked dispersion in cell volumes (sizes) so that the RDW increases. RBC indices in infancy and childhood are described in Table 279-3.

#### Zinc Protoporphyrin

A simple and reliable measurement of IDE is the erythrocyte zinc protoporphyrin level, a product of abnormal heme synthesis. Normally, a trace of zinc rather than iron is incorporated into protoporphyrin during the final step of heme biosynthesis. In states of IDE, ZnPP formation is enhanced. Increase in the ZnPP/H of greater than 80 mmol/mol is demonstrated to be a sensitive, specific, and cost-effective test for identifying preanemic iron deficiency. A major advantage of this well-established assay is the ability to

measure the ZnPP/H directly on a drop of blood on a dedicated portable instrument called a hematofluorometer. Initially, ZnPP was erroneously characterized as metal-free protoporphyrin, free erythrocyte protoporphyrin (FEP), or erythrocyte protoporphyrin. In fact, most presumed metal-free protoporphyrin in erythrocytes is now known to be largely an artifact of the analytical procedures used at the time and still used in some laboratories, which required an acid extraction that removed zinc to form metal-free or free protoporphyrin. Because about 95% of the non-heme protoporphyrin in erythrocytes is ZnPP, this procedure does not create a diagnostic problem because, in most cases, ZnPP/H is an indicator of iron available to the developing erythrocytes in the bone marrow regardless of the etiology, such as iron deficiency, inflammation, or functional iron deficiency as in chronic renal failure. Another significant limitation of the ZnPP is that with lead toxicity and even the normal range with environmental lead exposure, infections, inflammatory diseases, and protoporphyria. However, ZnPP/H is not increased in thalassemia trait. This makes ZnPP/H determinations helpful in distinguishing iron deficiency from  $\alpha$  or  $\beta$  thalassemia trait in addition to its role in screening for iron deficiency (see Table 279-4).

### Reticulocyte Hemoglobin

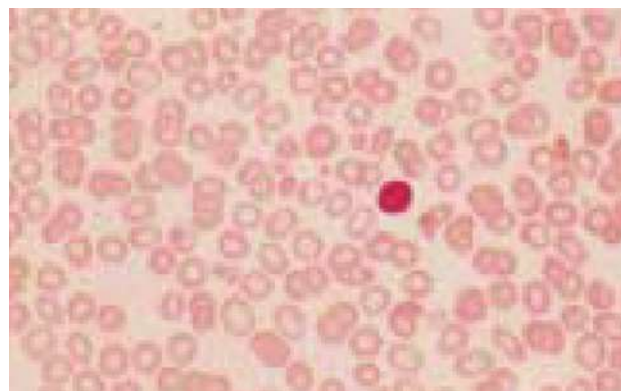
The mean CHR is analogous to the RBC MCHC, but with the advantage of monitoring the hemoglobinization of the most recently produced RBCs. A CHR of less than 26 pg is an early indicator of iron-restricted hematopoiesis and IDA in children. Median reticulocyte hemoglobin was 2.0 fmol in the non-iron-deficient patient group and 1.5 fmol in the iron-deficient patient group ( $P < .01$ ), with overlap between 1.2 and 2.2 fmol, which includes 90% of the data. The sTfR median was 6.4 mg/L in the iron-deficient group and 3.3 mg/L in the non-iron-deficient group ( $P < .01$ ), with 27% of the data falling into the overlapping interval of 4.6 to 14.5 mg/L. The diagnostic power of CHR is limited in patients with high MCV or with RBC disorders such as thalassemia.

### Peripheral Blood Smear

Examination of the blood smear in IDA reveals hypochromic microcytes, poikilocytes, elliptocytes, and target cells (Figure 279-3). The presence of basophilic stippling suggests associated lead poisoning. However, the RBC changes seen on the blood smear are not specific for iron deficiency. The white blood cell count and morphology in IDA are usually normal. Both thrombocytosis and thrombocytopenia occur with iron deficiency.

### Definitive Tests

The absence of stainable iron in the bone marrow is a definitive test for IDA, but is not routinely applicable for obvious reasons, and the bone marrow iron stain must be performed in standard conditions to be reliable. The 2 key definitive measurements for diagnosing iron deficiency are the serum ferritin, which measures the size of iron stores, and the serum transferrin receptor, which measures the extent of tissue iron deficiency.



**Figure 279-3** Iron-deficiency anemia. Many red blood cells are microcytic (smaller than the nucleus of the normal lymphocyte near the center of the field) and hypochromic (with central areas of pallor that exceed one-half of the diameter of the cells). (From Goldman L. Cecil Textbook of Medicine. 22nd ed. Copyright © 2004 Elsevier, with permission.)

### Serum Ferritin

Definitive serum ferritin levels vary with age during infancy and childhood. In healthy individuals, serum ferritin levels reflect body iron stores. Ferritin is an acute-phase reactant. Serum ferritin levels are increased during infections and inflammatory processes as well as with liver disease. Although low serum ferritin is diagnostic of iron deficiency, a high ferritin level associated with inflammation or liver disease does not rule out concomitant iron deficiency. In children younger than 5 years, serum ferritin levels below 12 mcg/L and less than 30 mcg/L in the presence of infection indicate iron deficiency. In children older than 5 years, serum ferritin levels higher than 15 mcg/L indicates iron deficiency.

### Serum Transferrin Receptor

The proteolytic cleavage of transferrin receptors can be measured in the serum as sTfR, which directly correlates with the total mass of erythroid precursor. The sTfR is high in iron deficiency and in conditions resulting in increased production of RBCs, including thalassemia and sickle cell disease. It is not affected by inflammation, and hence it is useful in distinguishing iron deficiency from chronic inflammatory states that do not have high sTfR (Table 279-4). Infants have higher baseline sTfR levels than do children and adults, indicating the need to establish age-specific reference values. Using NHANES data, Mei and colleagues derived the cutoff values (97.5th percentile in a defined healthy reference population) for defining elevated sTfR in the US as 6.00 mg/l for children 1 to 5 years of age and 5.33 mg/l for non-pregnant women 15 to 49 years of age. The ratio of sTfR to serum ferritin (R/F ratio) has been shown to have excellent performance in estimating body iron stores, but is limited by the lack of standardization for sTfR assays. Use of the sTfR/log ferritin ratio of more than 1.70 improves the specificity of the diagnosis of IDA.



**Table 279-5** Responses to Iron Therapy in Iron-Deficiency Anemia

TIME AFTER IRON ADMINISTRATION	RESPONSE
12–24 hr	Replacement of intracellular iron enzymes; subjective improvement; decreased irritability; increased appetite
36–48 hr	Initial bone marrow response; erythroid hyperplasia
48–72 hr	Reticulocytosis, peaking at 5–7 days
4–30 day	Increase in hemoglobin level
1–3 mo	Repletion of stores

Modified from Behrman RE. *Nelson Textbook of Pediatrics*. 17th ed. Philadelphia: WB Saunders; 2004. Copyright © 2004, Elsevier, with permission.

### Bone Marrow Iron

The staining of a normal bone marrow aspirate sample with Prussian blue dye reveals the presence of iron in RBC precursors (normoblasts) and serves as a reliable index of body iron stores. In iron deficiency, the number of iron granules in normoblasts is decreased, and stainable iron in the marrow aspirate is almost completely absent. Bone marrow aspiration is almost never needed to establish a diagnosis of iron deficiency.

### Diagnosis of Iron Deficiency, Iron Deficiency Anemia, and the Underlying Cause

Hemoglobin, the most commonly used screening test for IDA, is limited by the fact that anemia does not occur until there is marked depletion of storage iron and progression of iron-restricted erythropoiesis. Serum ferritin is limited as a measure of iron stores by the fact that it is an acute phase reactant. Although sTfR is a marker of tissue iron deficiency, it is not decreased until there is substantial iron-restricted erythropoiesis. Thus, in the absence of inflammation, in healthy populations in high-resource countries with low incidence of IDA, serum ferritin remains the most useful screening test for iron deficiency without anemia. Microcytic anemia can result from a number of causes, and every effort must be made to establish or exclude the diagnosis of IDA as well as to determine the underlying cause. Because no single clinical finding or laboratory test is diagnostic of iron deficiency, a combination of all available clinical findings and laboratory data must be taken into consideration to establish the diagnosis. The sTfR can distinguish between IDA and functional iron deficiency caused by inflammation. The CHr can distinguish between IDA and anemia related to hemoglobinopathy trait.

## MANAGEMENT

### Therapeutic Trial of Iron

Therapeutic trial of iron has been proposed as a convenient method to diagnose iron deficiency in patients with anemia. Although this is a reasonable approach in otherwise healthy individuals, in those at high risk for deficiency, such as infants, teenage girls, and pregnant women, it is better to make a definitive laboratory diagnosis at the outset. Further, this approach requires good follow-up and good adherence with

medication intake, which may not be the case in many situations in which IDA is suspected.

### Treatment of Iron Deficiency

The treatment of choice for iron deficiency is the oral administration of iron. Although various iron salts are available, ferrous sulfate is inexpensive and well tolerated, although there may be adverse effects such as nausea, dyspepsia, constipation, and diarrhea. Adverse effects can be managed by administering the iron with or immediately after meals. If symptoms persist, reducing the amount of iron in each dose or reducing the frequency to a single daily dose may help control the side effects. If there is persistent intolerance, switching to ferrous gluconate may be helpful. Iron polysaccharide complex also has the advantage of being available as tablets or elixir and is well tolerated. About twice as much iron is absorbed on an empty stomach as at mealtime. Milk consumption should be limited to allow increased intake of iron-rich foods, and to reduce blood loss from intolerance to cow milk proteins.

Because soy-based formulas can also lead to blood loss, children with milk enteropathy should be switched to a primary diet of iron-containing solids or an extensively hydrolyzed formula or an amino acid–based formula. In the absence of ongoing blood losses, response to iron therapy is rapid and predictable (Figure 279-1). A response with decreased irritability and increased appetite to oral iron therapy has been noted within 12 to 24 hours (Table 279-5). The reticulocyte response peaks at 5 to 7 days after iron therapy. In an otherwise healthy individual, the recovery from anemia is about two-thirds complete within 1 month. The hemoglobin should be measured again at 1 month to check the therapeutic progress and to emphasize compliance.

If after 4 weeks the anemia does not respond to iron treatment despite compliance with the iron supplementation regimen and the absence of acute illness, the anemia can be further evaluated by using other laboratory tests, including MCV, RDW, and serum ferritin concentration. After the diagnosis of iron deficiency is confirmed, either by a response to a therapeutic trial or by further laboratory tests, oral therapy with elemental iron at 3 to 6 mg/kg per day should be continued for 2 to 3 months after normal hemoglobin levels are restored. This allows the repletion of body iron stores. Anemia, microcytosis, and increased FEP levels are corrected completely with 3 to 5 months of treatment.

### **BOX 279-1 Recommendations for the Diagnosis and Prevention of Iron Deficiency in Infants, Young Children, and Adolescents**

#### **BREASTFEEDING AND IRON-FORTIFIED FORMULA**

- Full-term, healthy infants are at increased risk for iron deficiency after 4 months. Exclusively breastfed or partially breastfed infants should be started on an oral iron preparation at 1 mg/kg/day at age 4 months to be continued until the introduction of iron-containing complementary foods, red meats, or vegetables with high iron content.
- The iron needs of formula-fed infants can be met by standard formula and complementary foods, including iron-fortified cereal introduced after age 4 to 6 months.
- Whole milk should not be introduced before age 12 months.
- Infants 6 to 12 months of age should receive 11 mg iron/day.
- Complementary foods, red meats, and iron-rich vegetables should be introduced early. If their intake is not meeting iron requirements, an oral iron preparation at 1 mg/kg/day should be given.
- Toddlers 1 to 3 years of age should receive a daily iron intake of 7 mg through iron-fortified cereals, red meats, and iron-rich vegetables. If iron requirements are not being met, they should receive an oral iron preparation at 1 mg/kg/day.
- Beyond 3 years of age, children may receive chewable multivitamins.
- Preterm infants require 2 mg/kg/day of iron starting at age 1 month through when they are weaned to an iron-fortified formula or complementary food that can provide the daily iron requirement of 2 mg/kg/day.

#### **SOLID FOODS**

- At age 4 to 6 months or when the extrusion reflex disappears, recommend that infants be introduced to plain, iron-fortified infant cereal. Two or more servings per day of iron-fortified infant cereal can meet the requirement for iron at this age.
- By approximately age 6 months, encourage 1 feeding per day of foods rich in vitamin C (eg, fruits, vegetables, juice) to improve iron absorption, preferably with meals.
- Suggest introducing plain, pureed meats after age 6 months or when the infant is developmentally ready to consume such food.

#### **ADOLESCENT GIRLS AND NONPREGNANT WOMEN**

- Encourage adolescent girls and women to eat iron-rich foods and foods that enhance iron absorption and to optimize their dietary iron intake.

From Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency in the United States. *MMWR Recomm Rep*. 1998; 47(RR-3):1–29; Baker RD, Greer FR, American Academy of Pediatrics Committee on Nutrition. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0–3 years of age). *Pediatrics*. 2010;126(5):1040–1050.

Systematic reviews and meta-analyses of the literature have not revealed intravenous iron infusions to be associated with severe adverse events or increased risk for infections as was previously suspected. With the exception of high-molecular-weight dextran preparations, iron infusions have been found to be safe and only associated with infusional reactions, which may in fact be related to premedication administered. The availability of new intravenous iron formulations with an improved safety profile and ease of administration has expanded the option of this route of iron administration in select populations. Iron sucrose and ferric gluconate can be used to administer a total dose of iron in 1-hour infusions. New iron preparations such as ferumoxytol bind iron more avidly, thus reducing the risk of release of labile iron during infusions. Large single doses can be administered safely in as little as 15 minutes. Intravenous iron preparations have hitherto been reserved for conditions such as chronic kidney disease and failure of iron absorption caused by inflammatory bowel disease or bariatric or other gastrointestinal surgery. Improved ease of administration and lack of side effects are expanding the consideration of this treatment to other conditions.

A blood transfusion is indicated only when severe anemia leads to congestive heart failure and cardiovascular compromise. If a blood transfusion is clinically

warranted, then packed RBCs should be given slowly or a partial exchange transfusion performed. Vital signs should be monitored carefully.

#### **Failure to Respond to Therapy**

When a patient fails to respond to oral iron treatment, the following factors should be considered: (1) non-compliance with oral therapy; (2) inadequate iron dose; (3) persistent or unrecognized blood loss; (4) malabsorption of iron (eg, primary gastrointestinal disease); (5) other diagnoses (eg,  $\alpha$ - or  $\beta$ -thalassemia trait and hemoglobin E disease); and (6) poor iron utilization (eg, chronic inflammatory disease, sideroblastic anemia, lead poisoning, and congenital atransferrinemia).

#### **PREVENTION**

Increased iron intake among infants has reduced childhood IDA in the United States. Consequently, the use of screening tests for anemia has become a less efficient means of detecting iron deficiency in some populations, whereas for women of childbearing age, iron deficiency has remained prevalent. Recommendations are provided for primary prevention of iron deficiency through appropriate dietary intake (Box 279-1), and secondary prevention through detecting and treating IDA (Box 279-2).

**BOX 279-2 Recommendations for Screening for Iron Deficiency in Infants, Children, and Adolescents**

- Universal screening for iron deficiency should occur at age 12 months and 6 months later and should include evaluation of hemoglobin and risk factors for iron deficiency, such as
  - Preterm or low-birth-weight infants
  - Infants fed a diet of non-iron-fortified infant formula for >2 months
  - Infants introduced to milk before age 12 months
  - Breastfed infants who do not consume a diet adequate in iron after age 6 months (ie, who receive insufficient iron from supplementary foods)
  - Children who consume >24 oz daily of cow milk
  - Children who have special health care needs (eg, children who use medications that interfere with iron absorption and children who have chronic infection, inflammatory disorders, restricted diets, or extensive blood loss from a wound, an accident, or surgery)
- If, at 12 months of age, hemoglobin is <11 g/dL, additional evaluation for iron-deficiency anemia (IDA) should be undertaken. Potentially useful tests include ferritin, transferrin saturation, soluble transferrin receptor with C-reactive protein, or reticulocyte hemoglobin concentration.
- In cases of mild anemia (hemoglobin 10–11 g/dL), an alternative diagnostic approach would be to document an increase of hemoglobin by at least 1 g/dL following 1 month of appropriate therapeutic doses of an oral iron preparation.
- Annual assessment of children ages 2 to 5 years for risk factors for IDA (eg, a low-iron diet, limited access to food because of poverty or neglect, special health care needs).
- In populations of infants and preschool-aged children at high risk for IDA (eg, children from low-income families, children eligible for the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), migrant children, or recently arrived refugee children), screen for anemia between ages 9 and 12 months, 6 months later, and annually from ages 2 to 5 years.
- Starting in adolescence, screen all nonpregnant women for anemia every 5 to 10 years throughout their childbearing years during routine health examinations.
- Annually screen for anemia women having risk factors for iron deficiency (eg, extensive menstrual or other blood loss, low iron intake, a previous diagnosis of IDA).

From Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency in the United States. *MMWR Recomm Rep*. 1998;47:1–29; Baker RD, Greer FR; American Academy of Pediatrics Committee on Nutrition. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0–3 years of age). *Pediatrics*. 2010;126(5):1040–1050.

**WHEN TO REFER**

- Cause of anemia is unknown.
- Gastrointestinal blood loss is suspected.
- Anemia is not explained by nutritional imbalance.
- Anemia is refractory to treatment.
- Child requires intravenous iron.
- Diagnosis of iron deficiency is questionable.

**WHEN TO ADMIT**

- Child exhibits signs of cardiac failure.
- Child requires intravenous iron.
- Child has moderate to severe blood loss.

**TOOLS FOR PRACTICE****Engaging Patient and Family**

- *Anemia and Your Young Child* (handout), American Academy of Pediatrics (patiented.solutions.aap.org).

**AAP POLICY**

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## Chapter 280

# KAWASAKI DISEASE

Mary Anne Jackson, MD

Kawasaki disease is an acute, multisystem vasculitis of infancy and early childhood characterized by high fever, rash (Figure 280-1), conjunctivitis (Figure 280-2), inflammation of the mucous membranes (Figure 280-3), erythematous induration of the hands and feet, and unilateral cervical adenopathy. Formerly known as *mucocutaneous lymph node syndrome*, Kawasaki disease is the main cause of acquired heart disease in children in the developed world. It was first described in 1967 by a Japanese pediatrician, Tomisaku Kawasaki; in 1974 the first cases of Kawasaki disease were reported in the United States. In retrospect, illnesses that are similar to Kawasaki disease were described as early as 1871. Landing and Larson compared the features of Kawasaki disease with infantile periarteritis nodosa and found that the 2 conditions shared many clinical signs and had indistinguishable pathologic findings.

### EPIDEMIOLOGIC FEATURES

The peak age incidence of Kawasaki disease occurs during the second year of life. More than 80% of all cases occur in children younger than 5 years; the disease is uncommon beyond 9 years of age, but cases in older children clearly occur. Boys are more commonly affected than girls, with a male-to-female ratio of nearly 1.5:1. Now, Kawasaki disease is recognized as having a worldwide distribution, although it is most prevalent in Japan and in children of Japanese ancestry. The Centers for Disease Control and Prevention estimate that the incidence for children 8 years or younger in the continental United States is 32.5 cases per 100,000 in those of Asian or part Asian descent, 16.9 per 100,000 in blacks,

11.1 per 100,000 in Hispanics, and 9.1 per 100,000 in whites. Kawasaki disease occurs more commonly in winter and spring, and numerous temporal clusters have been reported in the United States and Japan.

Recurrent cases of Kawasaki disease have been reported in the United States and Japan, with rates ranging from 0.3% to 5% in Japan and 1% to 2% in the United States.

### ETIOLOGY

No established cause for Kawasaki disease has been found, although clinical and epidemiologic features suggest an infectious process.

### PATHOGENESIS

Kawasaki disease is associated with increased production of cytokines by T cells and monocytes, and this feature is thought to play an important role in the pathogenesis of vascular endothelial cell injury during acute Kawasaki disease because these cytokines elicit proinflammatory and prothrombic responses in endothelial cells. Cytokines and chemokines have been



**Figure 280-2** Child with Kawasaki disease with conjunctivitis. Note the absence of conjunctival discharge. (Courtesy Red Book Online. [redbook.solutions.aap.org](http://redbook.solutions.aap.org).)



**Figure 280-1** Characteristic distribution of erythroderma of Kawasaki disease. The rash is accentuated in the perineal area in approximately two-thirds of children. (Courtesy Red Book Online. [redbook.solutions.aap.org](http://redbook.solutions.aap.org).)



**Figure 280-3** Child with Kawasaki disease with striking facial rash and erythema of the oral mucous membrane. (Courtesy Red Book Online. [redbook.solutions.aap.org](http://redbook.solutions.aap.org).)



detected in tissue obtained from patients in the acute stage of Kawasaki disease. More recent data suggest 3 components to the arteriopathy that characterizes Kawasaki disease. Within the early clinical phase, a necrotizing neutrophilic vasculitis predominates and may lead to coronary damage manifest as dilation or aneurysm formation. This is followed in the subacute phase by lymphocytic, plasma cell and eosinophilic vascular infiltration. In the late phase, myofibroblastic proliferation can lead to vascular stenosis.

## DIFFERENTIAL DIAGNOSIS

The clinical picture of Kawasaki disease, after all major features have exhibited, is generally not difficult to differentiate from other mucocutaneous syndromes, although diagnostic challenges may occur in cases in which the patient is very young or has an unusual or incomplete presentation. In the first days of the illness, a whole spectrum of acute febrile diseases might be considered. Three to 5 days after the onset, certain clinical features may be singled out as compatible with other diagnoses, for example, strawberry tongue, which is suggestive of streptococcal infection. The 2 conditions that most commonly mimic Kawasaki disease are streptococcal and staphylococcal exfoliative toxin syndrome. However, if all the signs and symptoms are considered carefully, then the diagnosis is more readily apparent. The clinical features of Kawasaki disease and other mucocutaneous disorders are shown in Table 280-1. Other conditions that share some aspects of Kawasaki disease are rubella, rubeola, infectious mononucleosis, other viral exanthems, juvenile rheumatoid arthritis, and febrile drug reactions or Stevens Johnson syndrome (eg, anticonvulsants or trimethoprim with sulfamethoxazole). The similarities between fatal Kawasaki disease and fatal infantile polyarteritis nodosa are striking; pathologically, the 2 diseases cannot be distinguished. However, the exact relationship between them is undetermined.

## CLINICAL MANIFESTATIONS

To make the diagnosis of typical Kawasaki disease, 5 of the 6 major clinical characteristics associated with the condition must be present (Box 280-1). Illnesses having similar features should be considered. The detection of common respiratory viral pathogens (eg, rhinovirus, human metapneumovirus, parainfluenza virus, influenza virus) does not exclude Kawasaki disease. Symptoms vary in severity, but more than 90% of patients fulfill the first 5 clinical criteria. All of the symptoms are not apparent simultaneously, but the timing of their appearance is remarkably constant.

The course of the disease can best be described as triphasic. The acute phase consists of fever, conjunctival hyperemia, oropharyngeal erythema, lip cracking and fissuring, swelling of the hands and feet, a polymorphous erythematous rash, and unilateral cervical lymphadenopathy. Fever, rash, and lymphadenopathy fade after 10 to 12 days of the illness, marking the beginning of the subacute phase when arthralgias or arthritis (or both) and desquamation of skin overlying the tips of the fingers and toes, thrombocytosis, and cardiac disease may occur. The convalescent stage usually begins approximately 25 days after onset and

is characterized by the absence of clinical signs of disease but with the persistence of residual inflammation, marked by an elevated erythrocyte sedimentation rate (ESR).

Fever is the most prominent symptom of the acute phase of the disease. Temperatures show a high-spiking remittent pattern in the range of 38.4°C (101.1°F) to higher than 40°C (104°F). Fever persists despite the use of empirical antibiotics and standard doses of antipyretics. Fever is present on average for approximately 12 days, although prolonged courses of up to 5 weeks have been reported; defervescence occurs over 1 to 3 days. Discrete engorgement of the bulbar conjunctivae blood vessels (without associated discharge, exudate, keratitis, chemosis, or pseudomembrane formation) and an anterior uveitis develop shortly after the onset of fever but are usually resolved after 7 days. The cornea, lens, and retina are not involved. Early oropharyngeal signs include dryness and reddening of the lips and of the buccal and pharyngeal mucosa. The absence of aphthous ulceration or hemorrhagic bullae is noticeable. A strawberry tongue is frequently present. Later, as the intensity of the erythema subsides, the lips usually become cracked and fissured.

The most characteristic and unique feature of Kawasaki disease relates to changes that occur in the hands and feet. Early on, they become diffusely indurated and swollen, and the overlying skin develops a woody firmness suggestive of acute scleroderma. The palms and soles usually become erythematous or take on a purplish hue. Fusiform swelling of the fingers also occurs, which limits the child's ability to grasp objects. The feet are painful to the touch, and many children will refuse to stand or walk. Two to 3 weeks after the onset of illness and after the early signs involving the extremities have disappeared, an unusual desquamation of the skin beginning at the subungual and periungual regions of the fingers and toes occurs in nearly all cases (Figure 280-4). Progression to complete peeling of the palms and soles may occur, but exfoliation generally does not extend to the remainder of the body surface. During the convalescent phase, deep transverse grooves (Beau lines) may appear across the fingernails and toenails, presumably as a result of arrested growth during the illness.

A polymorphous, erythematous rash appears 1 to 5 days after the onset of fever; it usually begins on the extremities and spreads centripetally. The 3 most common patterns of rash are maculopapular (morbilliform), erythema multiforme-like with iris lesions, and scarlatiniform.

The rash may be coalescent, producing large, irregular, raised plaques, and it may be pruritic. Vesicles, pustules, and bullae are not seen. The rash is not petechial or purpuric and typically does not involve the face. It usually fades within 1 week but occasionally persists longer or recurs.

Lymphadenopathy typically involves a single cervical node measuring more than 1.5 cm in diameter. The node is usually not tender or warm and does not become fluctuant. Generalized lymphadenopathy does not occur. The lymph node diminishes in size with defervescence of the disease. Lymphadenopathy is the least often seen of the major criteria; it occurs in only

**Table 280-1** Clinical Features of Kawasaki Disease and Other Mucocutaneous Diseases

	<b>KAWASAKI DISEASE</b>	<b>STEVENS-JOHNSON SYNDROME</b>	<b>STREPTOCOCCAL SCARLET FEVER</b>	<b>STAPHYLOCOCCAL TOXIN SYNDROME</b>	<b>STAPHYLOCOCCAL TOXIC SHOCK SYNDROME</b>	<b>LEPTOSPIROSIS</b>
Age (yr)	Usually <5	Usually 3–30	Usually 5–10	Usually 2–8	Usually adolescent	Usually >2
Fever	Prolonged	Prolonged	Variable	Variable	Usually variable	—
Eyes	Hyperemia of ocular conjunctivae with limbic sparing; uveitis	Catarrhal conjunctivitis; chemosis; iritis; uveitis; panophthalmitis	No change	Hyperemia of ocular conjunctivae	Hyperemia of ocular conjunctivae	Suffusion of ocular conjunctivae; uveitis
Lips	Red, dry, fissured	Erosions; crusted, fissured, bleeding	No change	No change	Red	No change
Oral cavity	Diffuse erythema; strawberry tongue	Erythema; bullae, ulcers; pseudomembrane formation	Pharyngitis; palatal petechiae; strawberry tongue	Pharyngitis	Erythema; pharyngitis	Pharyngitis
Peripheral extremities	Erythema of palms and soles; indurative edema; periungual, palmar, and plantar desquamation after 2–3 wk	No change	—	No change	Swelling of hands and feet; dry gangrene, peripheral desquamation after 1–2 wk	Gangrene of hands and feet (rare)
Exanthem	Erythematous, polymorphous after 2–3 wk	Erythematous, polymorphous; iris lesions, vesicles, bullae, crusts	Finely papular erythroiderma; Pastia lines; circumoral pallor, generalized rash may desquamate	Finely papular erythroiderma; Pastia lines	Erythroderma	Erythematous, maculopapular, petechial, or purpuric
Cervical lymph nodes	Nonpurulent swelling, unilateral	Nonpurulent swelling (occasional)	Nonpurulent or purulent swelling (frequent)	Nonpurulent or purulent swelling (occasional)	No change	Nonpurulent swelling (infrequent)
Other	Meatitis; diarrhea; arthralgia and arthritis; aseptic meningitis	Malaise; cough, rhinorrhea, pneumonitis; vomiting; arthralgia; recurrent episodes	Malaise; vomiting; headache	—	Headache; confusion; hypotension; icteric hepatitis; diarrhea; coagulopathy; renal injury	Headache myalgia; abdominal pain; icteric hepatitis; meningitis

### BOX 280-1 Diagnostic Criteria for Kawasaki Disease

#### PRINCIPAL SYMPTOMS

Fever of unknown cause lasting  $\geq 5$  days and at least 4 of the following 5 symptoms:

- Bilateral congestion of ocular bulbar nonexudative conjunctivae with limbic sparing
- Changes of lips (fissuring, redness) and oral cavity (erythema of mucosa, strawberry tongue)
- Polymorphous rash without vesicles or crust
- Unilateral nonsuppurative lymphadenopathy measuring  $>1.5$  cm
- Changes of the peripheral extremities (indurative edema, reddened palms and soles; late periungual desquamation)

#### OTHER SIGNIFICANT SYMPTOMS OR FINDINGS

- Carditis, especially myocarditis or pericarditis
- Diarrhea
- Arthralgia or arthritis
- Proteinuria and increase of leukocytes in urine sediment

#### CHANGES IN BLOOD TESTS

- Leukocytosis with shift to the left
- Slight decrease in erythrocyte and hemoglobin levels
- Increased sedimentation rate
- Elevated C-reactive protein
- Thrombocytosis in convalescent phase

#### CHANGES OCCASIONALLY OBSERVED

- Aseptic meningitis
- Mild jaundice or slight increase of serum transaminase
- Hydrops of gallbladder

approximately 60% of patients in most US series. Occasionally, lymphadenopathy is the heralding of Kawasaki disease and has been noted usually in boys older than 5 years. In some cases, retropharyngeal phlegmon is present. In cases in which lymph node only is noted at onset, other features of Kawasaki disease may follow.

In addition to the 6 major clinical signs, other features of Kawasaki disease are frequently noted. Irritability, mild meningismus, and lethargy are seen in nearly all of these children. Diarrhea is seen in approximately 50% of the children. Passing 5 to 15 stools per day for 2 to 7 days during the acute or subacute phase is common. Stools do not contain polymorphonuclear cells and do not test positive for occult blood.

Either arthralgias, arthritis, or both occur in 30% to 40% of children. Large joints, particularly the knees and ankles, are involved most often. Usually, no more than 2 or 3 joints will be affected. Joint symptoms occur 8 to 12 days after the onset of disease. Joint fluid, if analyzed, will reveal findings similar to those of rheumatoid arthritis.

Pneumonia, tympanitis, and photophobia are observed somewhat less commonly. Acute hydrops of



**Figure 280-4** Desquamation of the skin involving the subungual and periungual regions of the fingertips. (Courtesy Red Book Online. [redbook.solutions.aap.org](http://redbook.solutions.aap.org).)

the gallbladder, jaundice, convulsions, encephalopathy, Bell palsy, hearing loss, pancreatitis, orchitis, and pleural effusions are rarely seen but are clearly associated features of Kawasaki disease. In addition, a small subset of patients can present with hypotensive shock.

The most critical complications of Kawasaki disease are those in the cardiovascular system. If untreated, up to 25% of patients will develop coronary artery involvement, with some developing coronary aneurysms. The mortality of the disease is the result of coronary artery aneurysm rupture or occlusion. During the acute phase, tachycardia and gallop rhythms may appear; however, the most serious manifestations of cardiac involvement occur during the subacute phase. These manifestations include serious arrhythmias, congestive heart failure, pericardial effusion, mitral insufficiency, and myocardial ischemia or infarction.

### LABORATORY FINDINGS

Although Kawasaki disease has no pathognomonic laboratory findings, certain laboratory abnormalities are frequently seen and therefore help establish the diagnosis. Either erythrocyte sedimentation rate  $>40$  mm or C-reactive protein  $>3$  mL/dl are present in virtually all cases. In the acute phase of the disease, most patients exhibit an elevated white blood cell (WBC) count with an associated left shift; WBC counts of 15,000 to 20,000/mm<sup>3</sup> are common and may remain elevated for 1 to 3 weeks; normocytic, normocytic anemia for age may occur. Sterile pyuria occurs in 70%; 10 to 100 WBCs per high-power field may be observed on a clean-catch voided urine specimen. No WBCs will be seen on a bladder aspiration specimen because the sterile pyuria is caused by urethral inflammation or ulceration. Occasionally, a child will demonstrate trace proteinuria or hematuria. Mild transaminitis may occur in 50% of cases. If cerebrospinal fluid (CSF) is analyzed, it typically shows 25 to 100 WBCs/mm<sup>3</sup> with normal amounts of glucose and protein. In addition, elevated serum bilirubin, hypoalbuminemia,

thrombocytopenia early on, and hyponatremia can be seen. Low albumin, anemia, and thrombocytopenia are poor prognostic factors.

In the second to third week of the illness, patients characteristically develop significant thrombocytosis, with platelet counts averaging in excess of 700,000/mm<sup>3</sup>. Importantly, the results of several laboratory studies are negative. Routine cultures of blood, CSF, urine, throat, and lymph node aspirates reveal no growth or normal flora. Serologic studies for bacterial and viral agents are negative, including the antistreptolysin titer. Antinuclear antibodies, rheumatoid factor, and other autoantibodies are absent. The detection of a common respiratory virus-like parainfluenza, influenza, rhinovirus, or human metapneumovirus does not exclude the diagnosis in a child who otherwise meets criteria for Kawasaki disease. A diagnostic challenge may be posed in the child with fever and exudative pharyngitis related to adenovirus infection. In such cases, if adenovirus is confirmed by detection of adenovirus in a nasopharyngeal swab, the diagnosis of Kawasaki disease is considered unlikely. Consultation with a pediatrician who has expertise in the diagnosis of Kawasaki disease should be sought in such cases.

Sinus tachycardia, nonspecific ST segment and T wave changes, and evidence of mild left ventricular hypertrophy may be seen on an electrocardiogram in the acute phase.

A baseline echocardiogram should be performed as soon as the diagnosis of Kawasaki disease is suspected to evaluate cardiac function and the anatomy of the coronary arteries and to assess for the presence or absence of pericardial effusion. However, in most cases, the baseline echocardiogram is normal and does not exclude the diagnosis. Coronary artery abnormalities may develop as early as 5 to 7 days after onset of illness but are generally apparent by the third or fourth week of the illness. The findings in incomplete Kawasaki disease are listed in Box 280-2. Coronary artery disease rarely, if ever, develops after 6 to 8 weeks.

Severe or even fatal coronary abnormalities can develop after illnesses that resemble but do not fulfill the classic diagnostic features of Kawasaki disease. Important aspects of incomplete Kawasaki disease are listed in Box 280-3. Children who have incomplete Kawasaki disease may display prolonged high fever, nonspecific rash, arthralgia or arthritis, fissuring of the lips, nonexudative conjunctivitis, and extreme irritability. An algorithm for evaluating suspected incomplete Kawasaki disease is shown in Figure 280-5. In infants younger than 6 months, Kawasaki disease may present solely with prolonged fever or is likely to produce subtle manifestations (Box 280-4); this group is at highest risk ( $\geq 50\%$ ) for coronary artery lesions if untreated.

## MANAGEMENT

Intravenous immunoglobulin (IVIG) with aspirin is the best available therapy for preventing coronary artery abnormalities in Kawasaki disease and should be administered to all patients diagnosed within the first 10 days of the illness. Physicians should institute treatment as soon as the diagnosis is established and as

### BOX 280-2 Echocardiogram

- Should be performed at baseline in all cases of suspected Kawasaki disease. A normal study does not exclude the diagnosis.
- Should be performed in follow-up of all children treated for Kawasaki disease and in those who present with classic periungual desquamation in cases in which the diagnosis was missed.
- Useful in evaluating children with prolonged fever and some features of Kawasaki disease.
- Although aneurysms rarely form before day 10 of the illness, ectasia of the coronary arteries can be seen in the acute stage of disease.
- Other findings
  - Decreased left ventricular contractility
  - Mild valvular regurgitation (mitral regurgitation)
  - Pericardial effusion

From Newberger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Pediatrics*. 2004;114(6):1708–1733.

### BOX 280-3 Unusual Clinical Manifestations of Kawasaki Disease

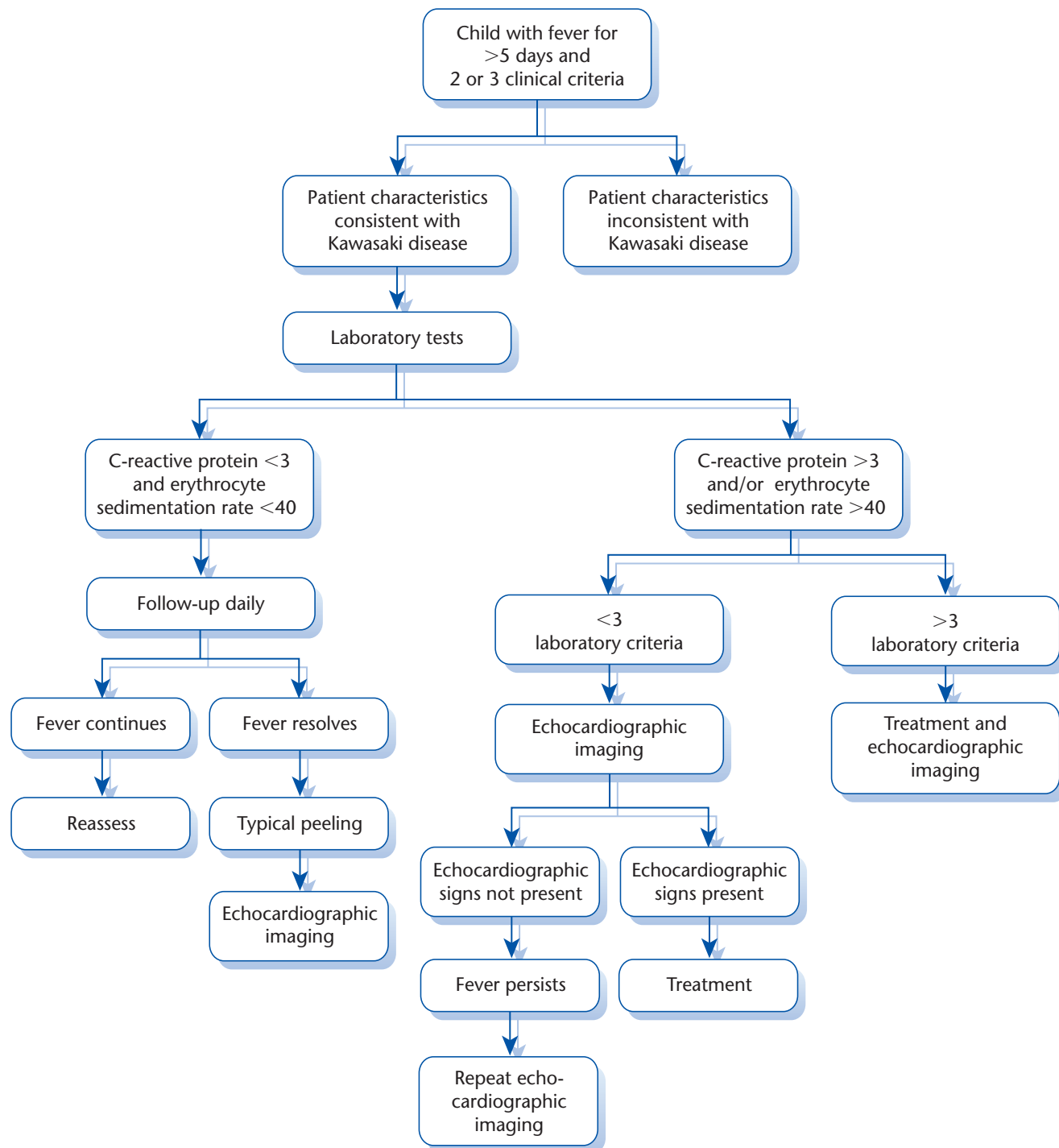
- Consider Kawasaki disease in infants and children with unexplained fever for  $> 5$  days and 2 or 3 of the principal diagnostic criteria.
- Young infants may have fever only.
- Laboratory results are similar to those of classic cases.
- A shock presentation may be seen and mimic bacterial sepsis.
- A lymph node first presentation may occur, often in boys, and may mimic bacterial lymphadenitis. Usually more typical features of Kawasaki disease follow the initial presentation, and laboratory features are consistent with Kawasaki disease.

From Newberger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Pediatrics*. 2004;114(6):1708–1733.

early as possible in the course of the illness. Aspirin, given in high doses (80 mg/kg/day) every 6 hours, reduces the length and severity of Kawasaki disease during the acute phase. Aspirin use early in the course of the disease may also reduce coronary artery involvement. Dosages should be reduced to 3 to 5 mg/kg/day after the child has been afebrile for 48 to 72 hours. If coronary aneurysms are recognized, then salicylates (3 to 5 mg/kg/day) should be continued long term with careful cardiology follow-up and discontinuation with aneurysm resolution.

High-dose IVIG is effective to prevent coronary artery lesions in Kawasaki disease. A single dose of 2 g/kg is infused over 10 to 12 hours. No apparent





**Figure 280-5** Evaluation of suspected incomplete Kawasaki Disease. (From Newberger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Pediatrics*. 2004;114[6]:1708–1733.)

difference exists in efficacy among particular IVIG products currently commercially available. Children should be monitored carefully during IVIG infusions for signs of anaphylaxis and immune hemolysis. Eighty percent to 90% of children treated with IVIG respond favorably with decreased fever and reduced

mucocutaneous findings. The remainder has persistent or recurrent fever, with or without mucocutaneous signs. If ongoing fever cannot be attributed to another cause, then the assumption should be made that Kawasaki disease is persisting or has relapsed. Because fever may be viewed as a sign of continued

**BOX 280-4 Kawasaki Disease in Infants Younger Than 6 Months**

- These infants usually lack full diagnostic criteria.
- Manifestations are often subtle: fever, rash, and cerebrospinal fluid pleocytosis may be misdiagnosed as viral meningitis. Inflammatory markers are routinely elevated.
- These infants have high risk for coronary abnormalities.
- Echocardiography should be performed.

From Newberger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Pediatrics*. 2004;114(6):1708–1733.

vasculitis, retreatment with IVIG is advocated. Most patients treated again after a single dose of IVIG therapy has failed will respond to retreatment. Patients who remain symptomatic beyond the tenth day may still benefit from IVIG. However, the decision to administer IVIG later than the tenth day of the illness must be individualized. The timing of retreatment is important: retreatment with IVIG is recommended if fever recurs or persists 36 hours after the end of the first IVIG infusion.

If therapy fails (particularly after 2 treatments), pulse doses of methyl prednisolone at 30 mg/kg per dose for 1 to 3 days or infliximab 5 mg/kg as a single infusion should be administered. This therapy should be reserved for children who are clearly refractory to other, more established treatments (ie, failure of 2 doses of IVIG). Antibiotics are not indicated. It is important to counsel parents and pediatricians that live vaccines must be delayed for 11 months after IVIG and on the signs and symptoms of Reye syndrome while on aspirin therapy.

## COMPLICATIONS

The major complication of Kawasaki disease is the development of coronary artery aneurysms. If IVIG is not administered, then aneurysms occur in 15% to 25% of cases and are usually apparent by echocardiogram during the subacute phase of the illness. Coronary artery abnormalities can also be seen in 2% to 4% of cases, despite appropriate early therapy. Most patients who have aneurysms are asymptomatic; however, in some cases, formation of an aneurysm, particularly a giant aneurysm ( $>8$  mm in diameter), is followed by thrombosis or rupture, resulting in a fatal myocardial infarction. The care of a child with coronary involvement should always include consultation with a pediatric cardiologist experienced in management of Kawasaki disease. Treatment of moderately large aneurysms may require anticoagulation with clopidogrel (1 mg/kg/day) in combination with low-dose aspirin. For those with giant (or in young infants with an increase in coronary artery size  $>6$  mm), anticoagulant therapy with warfarin or low-molecular-weight heparin is required. The indication for and timing of angiography is controversial. Percutaneous

transluminal coronary angioplasty has been attempted by several groups with mixed results.

For long-term management of patients with Kawasaki disease, a risk stratification scheme may be of benefit (Table 280-2). For children at level I risk, the primary care physician may fully assume care after the first year anniversary of Kawasaki disease onset. Physical activities should not be restricted. For children with level II risk, a pediatric cardiologist should be consulted every 1 to 2 years; at least 1 stress test evaluating myocardial functioning should be performed at approximately 10 years of age. For children in risk level III, daily low-dose aspirin therapy and annual cardiac follow-up with echocardiography and electrocardiography may be appropriate. Periodic stress tests are recommended. For children in risk level IV, low-dose aspirin therapy should be maintained, and low-dose warfarin should be considered. Coronary angiography may be considered 6 to 12 months after the acute disease resolves to delineate coronary artery anatomy. Physical activities should be modified to minimize the risk for hemorrhage. Strenuous or competitive sports should be avoided. Children at risk level V should receive daily low-dose aspirin, and warfarin should be considered. Patients should be evaluated for indications of bypass graft surgery.

The coronary artery aneurysms seen in Kawasaki disease develop more frequently in boys than they do in girls, in children younger than 1 year, and in those who have a triphasic fever pattern or fever for longer than 2 weeks when a gallop rhythm or other arrhythmia is noted or when the ESR exceeds 50 mm/hr (Box 280-5). Cases of incomplete Kawasaki Disease followed by typical coronary artery involvement have led to the suggestion that an echocardiography examination be undertaken in children who have prolonged unexplained febrile illnesses associated with subsequent peripheral desquamation.

## PROGNOSIS

Kawasaki disease has a 0.2% mortality rate. Death occurs almost exclusively in children who have giant aneurysms, mainly as a result of coronary artery thrombosis, massive myocardial infarction, and cardiogenic shock. Eighty percent of children whose aneurysms are small to moderate in size have complete resolution without apparent sequelae within 5 years. The remaining children may experience persisting aneurysms, coronary artery stenosis or obstruction, or aortic regurgitation. Emerging evidence suggests that a portion of this last group of children may be at risk for the subsequent development of significant cardiovascular disease such as coronary arteriosclerosis or persistent aneurysms, placing some of them at risk for sudden death from aneurysm rupture or thrombosis, cardiac arrhythmias, angina, or hypertension.

## PSYCHOSOCIAL ASPECTS

Kawasaki disease is almost always a self-limited illness without complications, which should be emphasized to the parents. Recurrent disease occurs months to years later in 2% of cases.

Even if coronary artery aneurysms do develop, they resolve spontaneously in more than 50% of cases

**Table 280-2****Levels of Risk for Determination of Methods for Management of Kawasaki Disease–Induced Coronary Artery Disease**

RISK LEVEL	DESCRIPTION
I	No coronary artery abnormalities at any stage of the illness
II	Transient coronary artery ectasia followed by regression
III	Small to medium solitary coronary artery aneurysm
IV	One or more giant aneurysms or multiple aneurysms without obstruction
V	Coronary artery obstruction (thrombosis or stenosis)

From Newberger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Pediatrics*. 2004;114(6):1708–1733.

**BOX 280-5 Risk Factors for Coronary Artery Aneurysms in Kawasaki Disease**

- Missed or delayed diagnosis including fever lasts >14 days
- Boys
- Extremes of age (<6 months, >9 years)
- Asian or Pacific Islander, Hispanic children
- Recurrent Kawasaki disease

within 2 years and 80% within 5 years. Long-term risks still remain undefined, and only as physicians gain prospective experience with the disease over several more decades will the true incidence of cardiovascular sequelae become evident.

**TOOLS FOR PRACTICE****Engaging Patient and Family**

- *Kawasaki Disease* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/heart/Pages/Kawasaki-Disease.aspx](http://www.healthychildren.org/English/health-issues/conditions/heart/Pages/Kawasaki-Disease.aspx))
- *Kawasaki Disease* (fact sheet), American Heart Association ([www.heart.org/HEARTORG/Conditions/More/CardiovascularConditionsofChildhood/Kawasaki-Disease\\_UCM\\_308777\\_Article.jsp](http://www.heart.org/HEARTORG/Conditions/More/CardiovascularConditionsofChildhood/Kawasaki-Disease_UCM_308777_Article.jsp))
- *Kawasaki Foundation* (Web site), ([www.kdfoundation.org](http://www.kdfoundation.org))
- *Kawasaki Syndrome* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/kawasaki/index.html](http://www.cdc.gov/kawasaki/index.html))

**Community Coordination and Advocacy**

- *Kawasaki Case Report Form* (form), Centers for Disease Control and Prevention ([www.cdc.gov/kawasaki/docs/ks\\_case\\_report-fillable.pdf](http://www.cdc.gov/kawasaki/docs/ks_case_report-fillable.pdf))

**AAP POLICY**

Newberger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease

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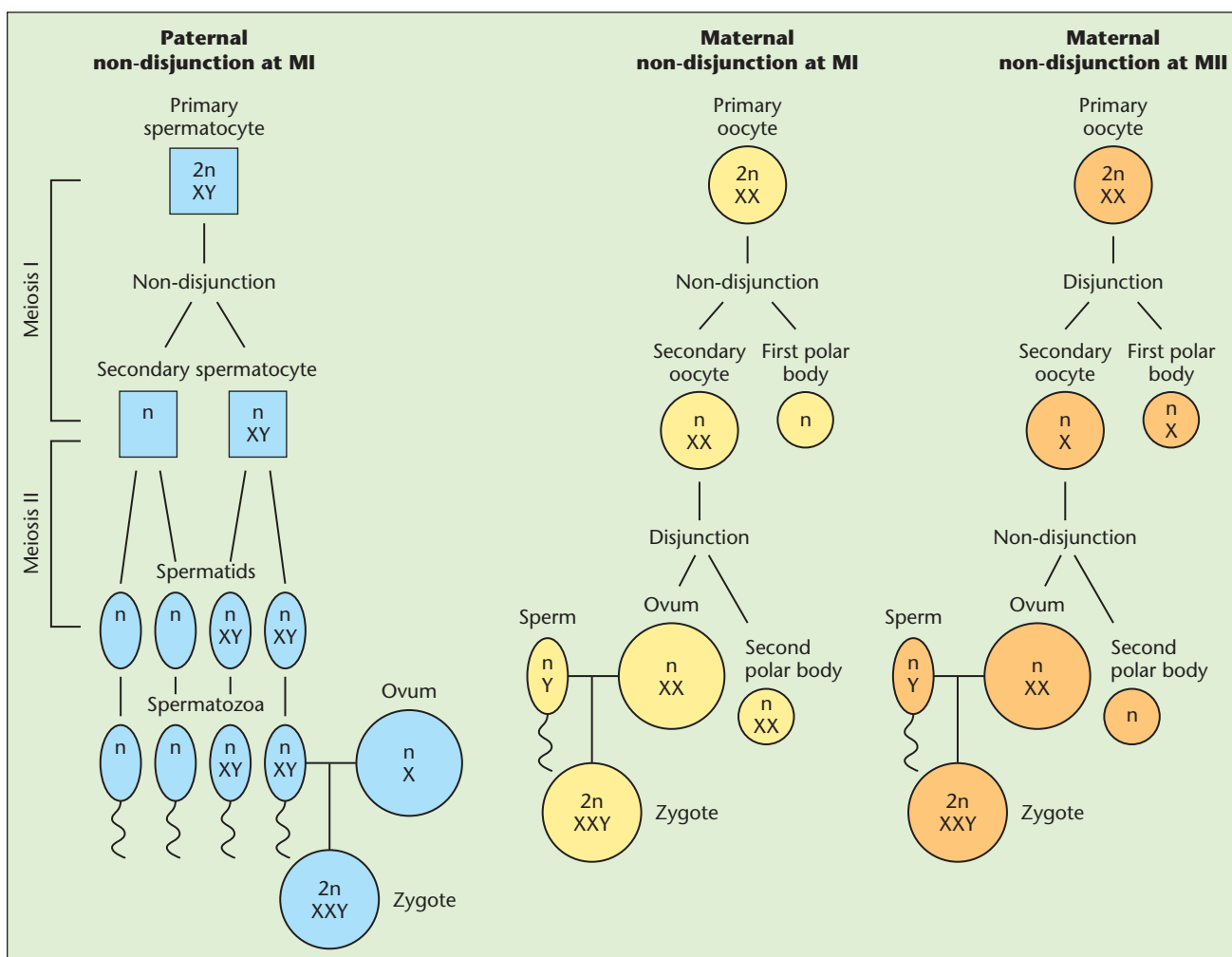
**Chapter 281****KLINEFELTER SYNDROME**

Parul Jayakar, MD; Michail Spiliopoulos, MD

**DEFINITION**

Klinefelter syndrome describes a group of disorders characterized by the presence of at least 1 extra X chromosome in a male. Approximately 80% of cases are caused by 1 extra X chromosome with karyotype 47,XXY (see Figure 281-1). The original series of 9 patients was described by Klinefelter in 1942, but the karyotypic abnormality was not discovered until 1959 by Jacobs and Strong. As more patients with the syndrome were tested, other chromosomal aneuploidies were noted in 20% of them, such as 48,XXXY; 48,XXYY and 49,XXXXY. Mosaics like 46,XY/47,XXY and patients with structurally abnormal X chromosomes were also found.

The typical patient with Klinefelter syndrome has been described as tall with long limbs, narrow shoulders, sparse hair, small penis and testes with azoospermia and gynecomastia. Infertility is very common, as are difficulties in expressive language and reading. Despite this “typical” phenotype, many patients with very subtle clinical features remain undiagnosed for several years. The findings of a national registry study



**Figure 281-1** Klinefelter syndrome karyotype. (From Lanfranco F, Kamischke A, Zitzmann M, Nieschlag E. Klinefelter syndrome. *Lancet*. 2004;364:273–283, with permission from Elsevier.)

from Denmark showed a high degree of underdiagnosis of Klinefelter syndrome, with less than 10% of the patients diagnosed before puberty.

## EPIDEMIOLOGY

Aneuploidy for XXY is considered to be the most common sex chromosomal abnormality and has a prevalence of approximately 1 in 500 males. Approximately 250,000 men in the United States have Klinefelter syndrome, although most of them are never diagnosed. The presence of other sex chromosomal abnormalities resulting in Klinefelter syndrome is much less frequent. More specifically, 48,XXYY and 48,XXXY are present in approximately 1 in 17,000 to 1 in 50,000 births. Even more rare is 49,XXXXY, which has an incidence of 1 in 85,000 to 1 in 100,000 male births. The actual prevalence of Klinefelter syndrome could be underestimated because of bias present in most studies from a high degree of underdiagnosis.

## ETIOLOGY AND PATHOGENESIS

The aberrations in the number of sex chromosomes occurring in Klinefelter syndrome are caused by

nondisjunction, most commonly during paternal meiosis I. This mechanism accounts for approximately 50% of the cases, with the rest of them attributed to errors in maternal meiosis I, or maternal meiosis II. Paternal errors can only occur during meiosis I, because this is the only mechanism that can produce a gamete with both the X and the Y chromosome present. An error occurring in paternal meiosis II, when X and Y are already separated, can only produce gametes with XX or YY chromosomes that, in combination with a normal oocyte, would result in a XXX or XYY karyotype. The evidence behind errors in paternal meiosis is not as clear, with some studies suggesting that older fathers have a higher tendency to produce XY sperm, while others have shown no affect of age on XY recombination. Because the female oocyte carries only X chromosomes, errors occurring either in meiosis I or II can produce gametes with 2 X chromosomes and hence a zygote with XXY karyotype. Most maternal errors occur in meiosis I. An association of aneuploidy with advanced maternal age has been reported, although it has only been seen with errors occurring during meiosis I; meiosis II errors do not



seem to be more common with increasing maternal age. A postzygotic mitotic error can also contribute to the Klinefelter phenotype in a small number of cases. Some patients have been found to have a mosaic karyotype, including cells with XY and XXY. The degree of mosaicism varies between patients and even between different tissue samples of the same patient. Individuals with XXY/XY mosaicism tend to have a better prognosis for testicular function.

Klinefelter syndrome has phenotypic variability because of the X chromosome inactivation that normally takes place in all human cells that contain more than 1 X chromosome. All but 1 X chromosome undergo inactivation per Lyon hypothesis (with the formation of an equal number of Barr bodies) and this is the mechanism by which overexpression of genes located on the X chromosome is prevented. In the case of Klinefelter syndrome, as in several other genetic conditions, the process of inactivation does not occur randomly, but a specific X chromosome, either paternal or maternal, tends to be inactivated more frequently. This is a process known as preferential or skewed X chromosome inactivation and has important clinical implications. The androgen receptor gene AR, by which testosterone exerts its action, is located on the X chromosome and contains a trinucleotide (CAG) repeat sequence. Every X chromosome contains a different number of CAG repeats in the AR gene, and shorter numbers of repeats have been associated with better response to androgen therapy and higher level of education compared to longer repeats. Most patients with Klinefelter syndrome have been shown to have the X chromosome with the shorter CAG repeat number preferentially inactivated; thus, the allele with the longer CAG repeats is active in most cells and is thought to be the cause of hypogonadism in most patients with Klinefelter syndrome.

Klinefelter syndrome results in a form of primary testicular failure, decreased testosterone production, and thus elevated levels of gonadotrophin luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Testicular function can be markedly decreased from fetal life, although in most patients it remains at normal levels until puberty when a significant increase in gonadotrophin levels is noted with a concomitant decrease of testosterone production in the lower levels of normal.

## DIAGNOSIS

The diagnosis of Klinefelter syndrome at birth is difficult to make, because most patients do not have specific phenotypic characteristics or distinct facial dysmorphic features. Some 47,XXY male newborns and infants will present for evaluation of cryptorchidism or small phallus. Up to 26% of newborns and infants were found to have minor dysmorphic features, such as clinodactyly, in a recent study, while 18% had major malformations. As toddlers, patients will usually present with developmental delay involving expressive language. At school age, most affected individuals will require assistance with reading and spelling. In addition to learning difficulties, some children might have behavioral and social problems. At an older age or during puberty, patients might seek evaluation for incomplete pubertal development, gynecomastia, and small testes.

In adulthood, infertility and breast cancer are common reasons for referral of patients with Klinefelter syndrome.

Klinefelter syndrome can be diagnosed prenatally based on the chromosome analysis of amniocytes obtained through amniocentesis (14–16 weeks) or chorionic villi from a chorionic villus sampling (11–12 weeks) in pregnancy. Diagnosis is also possible with noninvasive prenatal testing using cell-free DNA in the maternal blood (screening test). If the diagnosis is not made in the prenatal period, chromosome analysis from peripheral blood lymphocytes can be performed based on findings of the clinical examination. Barr-body analysis is a quick alternative for diagnosis, with sensitivity as high as 82%, although it is not widely used today. Additionally, androgen receptor gene quantitative real-time PCR (AR-qPCR) technique is a screening technique that detects the number of AR genes present and thus the number of X chromosomes.

## SIGNS AND SYMPTOMS

### Physical Examination

Individuals with Klinefelter syndrome tend to have longer arms and legs, with a low upper-to-lower segment ratio. Biacromial diameter is also low, probably secondary to low testosterone levels. Height ranges from the 25th to the 99th percentile for age, while mean height is at the 75th percentile. Most of the gain in height takes place between the ages of 5 and 8 years. Head circumference and weight are usually at the 50th percentile.

During childhood, testicular volume and penile length are slightly lower than normal. Later in development during adolescence, testicular size remains small, with a length usually less than 2.5 cm and average volume of less than 4 mL. Many individuals will enter puberty normally, but testosterone levels tend to decrease in late adolescence to adulthood. With an insufficient amount of androgens present, usually less than half the level seen in unaffected individuals, secondary sexual characteristics do not completely develop and virilization is inadequate. Sparse body and facial hair is present, along with gynecomastia in more than half of adolescent patients. Most patients are infertile, with hyalinization and fibrosis of the seminiferous tubules by mid-puberty. Although only a minority of individuals with Klinefelter syndrome have viable sperm in the ejaculate, and thus are able to provide sperm for cryopreservation, recent advances in reproductive technology including testicular sperm extraction (TESE) and intracytoplasmic sperm injection (ICSI) have significantly increased their reproductive potential.

Fifth finger clinodactyly is the most common minor anomaly and is present in almost one-third of patients. Cleft palate, cryptorchidism, and inguinal hernia are other major anomalies. Other abnormalities reported are mitral valve prolapse, scoliosis, increased frequency of chronic bronchitis and diabetes mellitus, severe acne, and hypospadias.

### Psychological Performance

The intelligence quotient (IQ) scores for Klinefelter syndrome patients vary widely, from well below to well above average. The mean IQ score is reported to be

between 85 and 90. The number of extra X chromosomes adversely affects the final intellectual performance, and it is thought that each extra chromosome decreases the IQ score by 15 to 16 points. The verbal IQ score is usually lower than the performance IQ score, most likely secondary to auditory processing and expressive language difficulties. Auditory memory is also affected, causing reading and spelling problems. Expressive language is more severely affected than receptive skills and comprehension. Individuals with 47,XXY karyotype tend to present with a variety of behavioral issues—more commonly shyness, immaturity and social insecurity. Problems in the formation of peer relationships also occur, while 1 study reported increased anxiety and substance abuse among adolescents with Klinefelter syndrome. Significant psychiatric problems are not commonly encountered.

## DIFFERENTIAL DIAGNOSIS

Since the clinical presentation of Klinefelter syndrome can vary, a high index of clinical suspicion is necessary to reach a diagnosis in most patients. More specifically, the diagnosis should be suspected and karyotype testing should be considered in the presence of the following:

- Small testicular size
- Long upper and lower extremities
- Infertility
- Developmental delay
- Behavioral problems
- Hypogonadism (weakness, fatigue, gynecomastia, decreased libido, erectile dysfunction)

Other causes of hypogonadism, such as Kallmann syndrome, should be considered. The physician should also consider and exclude other causes of infertility in males. The tall stature and lean physical features of the syndrome should prompt for evaluation of potential signs of Marfan syndrome. In addition, speech delay and low IQ scores in a male patient can be seen with Fragile X syndrome, for which simple genetic testing is available. Finally, males with SRY gene translocations to the X chromosome have a 46,XX karyotype and can present with several of the characteristic findings of Klinefelter syndrome, such as hypogonadism, azoospermia, gynecomastia, and hyalinization of the seminiferous tubules.

## LABORATORY FINDINGS

Karyotype analysis as a gold standard will reveal 2 or more X chromosomes in addition to a Y chromosome in a phenotypical male. Chromosomal microarray analysis would also detect Klinefelter syndrome, because it represents duplication of X-chromosomal material. FSH, LH, and estradiol levels are elevated. Testosterone levels when not on testosterone therapy are in a low to low-normal range. Inhibin B decreases to undetectable levels after puberty. A complete hormonal evaluation includes FSH, LH, testosterone, estradiol, insulin-like growth factor (IGF)-1, and prolactin levels. Cortisol levels should be measured because of the increased frequency of adrenal steroidogenic deficiency in patients with Klinefelter syndrome.

The decreased bone formation and increased bone resorption resulting in osteopenia are manifested by

decreased serum osteocalcin levels and increased hydroxylproline-to-creatinine ratio. Routine bone density screening is recommended to test for osteopenia or osteoporosis.

Although individuals with Klinefelter syndrome are at increased risk of deep venous thrombosis and pulmonary embolism, it is not clear whether routine testing for thrombophilia in all patients with the syndrome is indicated.

## HISTOLOGY

Histologic findings from testicular biopsies of prepubertal patients reveal reduced numbers of germ cells with normal numbers of Sertoli and Leydig cells. Later in adulthood, hyalinization of seminiferous tubules with fibrosis and rare, if any, foci of spermatogenesis are seen. Gynecomastic breasts reveal hyperplasia of interductal tissue.

## IMAGING

Mitral valve prolapse can be diagnosed with the use of echocardiography. Diagnostic radiography is performed to evaluate for radioulnar synostosis and taurodontism (vertical enlargement of the body of the tooth affecting molar teeth) that are occasionally seen in this disorder.

## MANAGEMENT

The treatment of patients with Klinefelter syndrome should be based on a multidisciplinary approach by different specialists, including pediatricians, geneticists, endocrinologists, infertility specialists, and speech therapists. Support from a clinical psychologist or psychiatrist is often necessary.

Management strategies depend on the age at diagnosis, and speech delay should be carefully addressed by a speech therapist in early childhood because it is among the most common presenting symptoms and can affect future performance at school. Other learning disabilities are also common, and monitoring of school performance with appropriate specialist referrals as needed is necessary.

Males with 47,XXY presenting with motor skills delay can be hypotonic, with balance and coordination impairment. Also, fine motor skills are affected and dyspraxia can be prominent. These patients can benefit from expert assessment by physical and occupational therapists.

Treatment with testosterone should be started as early as possible, and certainly by the onset of puberty when gonadotrophin levels begin to increase. Although testosterone supplementation will not treat infertility, gynecomastia, and small testicular size, it is considered necessary for an increase in muscle bulk and bone mineral density. Other benefits of testosterone treatment are proper development of secondary sexual characteristics along with increases in energy and concentration ability. It has also been shown that, when on testosterone treatment, patients tend to have fewer problems with social interactions. Treatment should be continued for life to reduce the occurrence of osteoporosis, autoimmune disease, diabetes mellitus, and obesity.

It is suggested that treatment begin at around the age of 12 years, at the beginning of puberty, even if the levels of testosterone are in the low-normal range.

Careful adjustment of the dose can lead to normalization of serum concentrations of testosterone, estradiol, FSH, and LH. All patients with increased gonadotrophin levels should be treated, as well as those with symptoms of hypogonadism, such as decreased libido and fatigue. The aim is to achieve a testosterone level in the middle of the normal range. Testosterone treatment can cause weight gain secondary to increased lean body mass and fluid accumulation. Acne, low HDL cholesterol levels, and erythrocytosis are other potential complications.

Patients diagnosed with micropenis can be treated with topical testosterone in the form of a cream or testosterone injections with encouraging results. Gynecomastia can be treated with mastectomy.

### Fertility-Reproductive Options

Testosterone replacement therapy does not have any positive effect on fertility, and it is suggested that it might negatively affect future fertility treatments with techniques such as ICSI and TESE. Testosterone can block spermatogenesis at the stage of spermatogonial differentiation.

Individuals with Klinefelter syndrome have significantly decreased fertility rates, and spontaneous paternity has only been reported in anecdotal cases. Recent techniques of recovery of spermatozoa from the testes of patients with the use of TESE and ICSI have dramatically changed the fertility outcomes. Livebirth rate was reported to be as high as 20% in 1 study. Because patients with 47,XXY have a progressive-germ cell depletion even before infertility occurs, the option of cryopreservation of sperm for the future should be offered. Most of the offspring born to patients with Klinefelter syndrome have a normal karyotype, which is anticipated because most spermatozoa obtained with TESE and implanted through ICSI are normal. Nevertheless, the frequency of hyperploid spermatozoa produced by Klinefelter patients is increased compared to unaffected individuals, and a higher risk of offspring with Klinefelter syndrome should be explained during counselling.

## GENETIC COUNSELING

Karyotypic analysis is not routinely performed in parents of patients with Klinefelter syndrome. The recurrence risk is thought to be less than 1%. There is an increased risk of aneuploidy and a higher frequency of trisomy 21 in the offspring. Preimplantation genetic diagnosis and prenatal diagnosis should be offered.

## COMPLICATIONS

### Breast Carcinoma and Other Tumors

The risk for breast carcinoma in patients with 47,XXY is several times higher than that of karyotypically normal males of the same age. Although a Danish study with cancer registry data did not show an increased incidence of breast cancer in those patients, the risk in other studies has been reported to be 20 to 50 times higher. This has been attributed to the increased concentration of estradiol in men with Klinefelter syndrome, secondary to peripheral conversion of testosterone to estradiol. Nevertheless, the risk seems to

be less than that of normal females. Increased surveillance for breast cancer during routine annual physical examination seems reasonable given the above data, even though more studies are necessary to assess the cost-benefit ratio of such an approach. The Danish registry that could not confirm the increased risk of breast cancer did show an association with mediastinal germ-cell tumors. Also, mortality from lung cancer and incidence of non-Hodgkin lymphoma seem to be elevated.

### Autoimmune Diseases

The risk of autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, and Sjögren syndrome, is increased and considered to be similar to that seen in females.

### Endocrine Complications

Patients with Klinefelter syndrome are at increased risk of developing diabetes mellitus, as shown by recent epidemiologic data. They tend to have increased levels of LDL cholesterol and decreased levels of HDL cholesterol compared to controls, while most of them fulfill criteria for the diagnosis of metabolic syndrome. In concordance with these findings, fasting plasma insulin levels and insulin resistance are higher in Klinefelter patients compared to controls.

Hypothyroidism and hypoparathyroidism are also known to occur more frequently.

### Varicosities

Venous stasis can result in the development of varicose veins and venous ulcers. The prevalence of venous leg ulcers is 20 to 50 times higher than the general population.

### Osteoporosis

Hypogonadism is known to be a cause of secondary osteoporosis, and multiple studies have shown decreased bone mineral density in patients with Klinefelter syndrome compared to controls. Between 25% and 40% of the patients will have decreased bone density of various severity, which can progress to osteoporosis. It seems that there is an increased morbidity and mortality from this complication since epidemiologic studies have shown increased rates of admission to the hospital for hip, forearm, and spine fractures, and an increased risk of death from hip fractures.

### Cardiovascular Disease

Two studies have demonstrated increased mortality from cardiovascular disease in patients with Klinefelter syndrome. This is not attributed to the mortality risk from ischemic heart disease, which is actually lower in those patients, but to the higher incidence of mitral valve prolapse and hypostatic leg ulcers. Mitral valve prolapse is related to increased risk of sudden death, and leg ulcers have been associated with increased risk of deep venous thrombosis and pulmonary embolism.

## PROGNOSIS

The overall prognosis of Klinefelter syndrome is considered to be good, although the final prognosis depends on the occurrence of complications. Males



with 47,XXY karyotype may have difficulties through adolescence and they may encounter academic difficulties as well as behavioral issues. Most of them will become independent from their families in later life and achieve normal functional levels. Life span is also considered to be normal.

### TOOLS FOR PRACTICE

#### Community Advocacy and Coordination

- *Building the Legacy: IDEA 2004* (Web page), US Department of Education ([idea.ed.gov](http://idea.ed.gov))
- *Let's Put the Person First, Not the Disability!* (fact sheet), Disability Is Natural ([www.disabilityisnatural.com/explore/people-first-language](http://www.disabilityisnatural.com/explore/people-first-language))

#### Engaging Patient and Family

- *All About the IEP* (fact sheet), Center for Parent Information and Resources ([www.parentcenterhub.org/repository/iep](http://www.parentcenterhub.org/repository/iep))
- *Building Your Care Notebook* (Web page), American Academy of Pediatrics ([medicalhomeinfo.aap.org/tools-resources/Pages/For-Families.aspx](http://medicalhomeinfo.aap.org/tools-resources/Pages/For-Families.aspx))
- *Emergency Information Form for Children with Special Needs* (form), American Academy of Pediatrics ([www.aap.org/advocacy/blankform.pdf](http://www.aap.org/advocacy/blankform.pdf))
- *Klinefelter Syndrome* (Web page), Genetics Home Reference ([ghr.nlm.nih.gov/condition/klinefelter-syndrome](http://ghr.nlm.nih.gov/condition/klinefelter-syndrome))
- *Klinefelter Syndrome* (Web page), National Organization for Rare Disorders ([rarediseases.org/rare-diseases/klinefelter-syndrome](http://rarediseases.org/rare-diseases/klinefelter-syndrome))
- *Pediatric Care Plan* (form), American Academy of Pediatrics ([medicalhomes.aap.org/Documents/PediatricCarePlan.pdf](http://medicalhomes.aap.org/Documents/PediatricCarePlan.pdf))
- *Pediatric Specialists* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/default.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/default.aspx))
- *Transitioning Youth to Adult Care Providers* (booklet), Got Transition ([www.gottransition.org/resourceGet.cfm?id=208](http://www.gottransition.org/resourceGet.cfm?id=208))

#### Practice Management and Care Coordination

- *A Toolkit to Improve Care for Pediatric Patients With Genetic Conditions in Primary Care* (e-book), Genetics in Primary Care Institute ([geneticsinprimarycare.aap.org/YourPractice/Documents/GPCI\\_Toolkit.pdf](http://geneticsinprimarycare.aap.org/YourPractice/Documents/GPCI_Toolkit.pdf))

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## Chapter 282

# LABIAL ADHESIONS

Linda S. Nield, MD

Labial adhesions, also known as labial agglutination or synechia vulvae, are membranous structures that develop as a result of fusion of the adjacent mucosal surfaces of the labia minora. The membranous structure can vary from thin and transparent to thick and fibrous. Any degree of labial involvement can occur, including covering of the urethral meatus. The condition is self-limited, and spontaneous resolution in affected individuals has been reported to occur in 50% of cases within 6 months, 90% of cases within 12 months, and 100% of cases within 18 months.

## ETIOLOGY

The exact cause of labial adhesions is uncertain, but the condition is likely caused by chronic irritation and inflammation of the hypoestrogenic vulva. Physical or chemical trauma, infection (*Candida albicans*, *Enterobius vermicularis*, and various bacteria), and poor hygiene are the triggers for the chronic inflammation. Sexual abuse may also be a source of chronic irritation, but labial adhesions are generally considered a nonspecific finding. During healing of the irritated area, the medial edges of the labia minora adhere to each other, forming an adhesion.

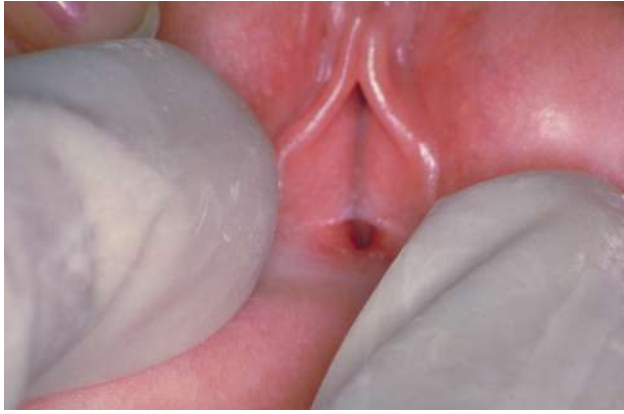
## EPIDEMIOLOGIC MECHANISM

Prepubertal girls in the first 5 years of life are most prone to this condition. A rise in endogenous estrogen levels during the prepubertal period may be the reason for a decrease in the occurrence of labial adhesions in older preadolescent girls. Improved hygiene may also be a factor. Reported incidences of labial adhesions in preadolescent girls in the general pediatric setting range from approximately 2% of girls who are identified by inspection alone to 39% of girls identified with inspection plus magnified photographic images of the vulva. Labial adhesions were found in 15.6% of girls who were referred to a gynecology clinic for various hymenal findings that were documented during well-child evaluations. Labial adhesions in a neonate are a rare occurrence, presumably because of the protective influence of maternal estrogen. Healthy, postpubescent young women do not develop labial adhesions, but they have been described after episiotomy, herpes infection, trauma, treatment with chemotherapy, and graft-versus-host disease.

## DIFFERENTIAL DIAGNOSIS

Ambiguous genitalia, vaginal agenesis, imperforate hymen, or septated hymen may be confused with labial adhesions, but physical examination easily differentiates these entities from one another. A line of demarcation between the clitoral hood and labia minora is seen with labial adhesions (Figure 282-1), but not with ambiguous genitalia secondary to androgen





**Figure 282-1** A commonly found presentation of labial adhesion in a 3-year-old.

excess. In vaginal agenesis and hymenal variants, the labia are normal and unfused, and the characteristic findings of these entities are located within the vaginal introitus.

### CLINICAL MANIFESTATIONS

Labial adhesions are often asymptomatic and are typically discovered at routine well-child visits or brought to the attention of the pediatrician by the child's caregiver. However, the adhesions can partially dehisce, leading to spotting of a minute amount of blood as well as irritation. Uncommonly, affected girls may complain of vaginal pain or of pain with ambulation or urination, or may suffer from a urinary tract infection, urinary retention, or an altered urinary stream.

The condition is diagnosed by visual inspection of the vulva, which includes a hymenal examination in the supine frog-leg or prone knee-chest position. The labia majora should be gently stretched apart, and a membrane of variable length and thickness is seen in the midline. A small opening near the clitoris allows the outflow of urine. A line of adhesion between the 2 nonrugated labia minora or raphae can also be seen.

### MANAGEMENT

#### Uncomplicated Case

If the child has no accompanying symptoms, then labial adhesions should not be treated. The parents should be informed of the diagnosis, and an opportunity to visualize the adhesion should be provided so that the parents are not surprised and concerned about the unusual appearance of the vulva. Reassurance of the benign, self-limited nature of this condition and education about potential symptoms should be provided.

#### Complicated Case

If the child has accompanying symptoms such as pain on urination or ambulation, altered urinary stream, urinary retention, or a history of urinary tract infections, then a urinalysis and urine culture should be obtained. Any documented urinary tract or vulvar infection should be treated accordingly. The first-line treatment of the complicated labial adhesion is the

application of topical estrogen. Retrospective reviews of girls treated with topical betamethasone have revealed its similar efficacy to topical estrogen. A cream containing 0.625 mg/gm of conjugated estrogen (Premarin Vaginal Cream, Wyeth Ayerst) can be applied to the adhesion and labial edges with a finger tip or cotton swab. Gentle traction can be placed on the opposing labia during the application of the estrogen cream. Although the optimal dosing and length of treatment are unknown, a course of twice-daily application for 2 weeks is a reasonable starting point. The goal is to use the least amount of medication that will achieve separation of the adhesion. Topical estrogen should be applied for 10 to 14 days with a cotton-tipped applicator with light pressure over the adhesion; this treatment is highly effective for most thin, transparent adhesions, but less so in others that are dense and fibrous or longstanding. Even the dense adhesions should be treated initially with topical estrogen because this treatment produces thinning of the line of fusion that facilitates manual labial separation in the office. The possible adverse effects of the topical estrogen include local irritation, breast budding, breast tenderness, and vulvar hyperpigmentation, all of which are reversible with discontinuation of the medication. After the estrogen therapy has separated the labia, a topical lubricant (eg, white petroleum jelly) should be applied to the affected area for several months on a daily basis to ensure complete healing and persistent separation of the opposing labial edges.

Treatment with estrogen cream is considered unsuccessful if labial separation has not occurred within 8 weeks or if the child suffers untoward effects from the estrogen and cannot continue using it. If topical estrogen is unsuccessful and the girl's accompanying symptoms persist, then manual separation of adhesions can be performed. Before manual separation is performed, topical anesthetic must be applied to the affected area. After the anesthetic has taken effect, firm traction on the opposing edges of the labial minora is applied to separate the fused edges. The edges should be smoothly peeled away from each other. After separation, a lubricant should be applied to the affected area on a daily basis for several months to prevent readherence. Warm soaks or sitz baths in the days following separation may provide relief if the vulva is irritated from the procedure.

Rarely, in cases of thick labial adhesions that cannot be separated by the previously described treatments and those that are associated with complications, surgical lysis by a pediatric urologist or gynecologist while under general anesthesia may be required (Figure 282-2). Postoperative care includes sitz baths in the immediate postoperative period and several months of application of topical lubricant. The decision to treat labial adhesions with surgery is made by weighing the significance and severity of symptoms after less aggressive treatments have failed versus the risks of general anesthesia.

### PREVENTION: ADVICE TO PARENTS

The physician should explain the value of proper hygiene of the vulva and educate the parents about practices to help their child avoid recurrent labial which



**Figure 282-2** Extensive labial adhesion in a 4-year-old. Hydronephrosis is a potential rare complication of an extensive labial adhesion.

include: (1) wiping front to back after urination or defecation, (2) wearing cotton underwear, (3) avoiding the application of detergents in the genital area, and (4) avoiding wet, tight clothing against the vulva for prolonged periods.

#### WHEN TO REFER

A symptomatic child with persistent or recurrent labial adhesions who has a history of urinary tract infections or complaints of urinary retention, altered urinary stream, dysuria, or pain with ambulation and has failed topical estrogen therapy should be referred to a pediatric urologist or gynecologist for surgical lysis.

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## Chapter 283 LEAD POISONING

Michael Weitzman, MD

The near eradication of acute lead encephalopathy represents one of the great pediatric public health success stories in the United States. Virtually no children in the United States die from this disease any longer,

and most pediatricians today have never seen a child who has overt symptoms resulting from this condition. Despite this success, however, a large number of children continue to be identified with levels of lead exposure that affect their health, and severe toxicity and even deaths still occur, as evidenced by reports of accidental ingestion of lead-containing necklaces and metallic charms. More commonly, children often are exposed at low levels previously thought to be harmless but that are now recognized to impair cognition and behavior. Thus, continued efforts in the areas of primary prevention, screening, public education, and removal of sources of lead are needed.

### EPIDEMIOLOGIC FEATURES OF CHILDHOOD LEAD POISONING

Blood lead levels of children in the United States have declined dramatically, as measured by the National Health and Nutrition Examination Surveys. The geometric mean blood lead level of children 1 to 5 years of age has declined from 15 mcg/dL in the 1976 to 1980 survey, to 2.7 mcg/dL in 1991 to 1994, and most recently to 1.34 mcg/dL in 2007–2010. These changes have been accompanied by corresponding declines in the prevalence of 1- to 5-year-old children with elevated blood levels ( $\geq 10$  mcg/dL), from 77.8% (1976–1980), to 4.4% (1991–1994), to 1.6% (1999–2004) to 0.8% (2007–2010). Racial differences in mean blood lead levels and rates of elevated blood lead levels have also diminished, as has the difference between the rates of elevated blood lead levels in those covered by Medicaid and those not covered by Medicaid, although black children and children covered by Medicaid continue to have higher rates than white children and those not covered by Medicaid. At the same time that these declines occurred, a consistent and widely accepted research literature has emerged demonstrating adverse neurodevelopmental and behavioral consequences of lead exposure in children at levels previously believed to be safe. In fact, the Centers for Disease Control and Prevention (CDC) has recently stated that it is now clear that there is no known threshold below which adverse effects of lead are absent.

### SOURCES OF LEAD

For most children, lead-contaminated interior and exterior household paint that has chipped, peeled, or chalked in their primary residence or in the homes of relatives, babysitters, or child care providers remains the most common and the most concentrated source of exposure. Most often, lead-contaminated dust, rather than actual paint chips, is the source of the exposure. As detailed in a survey report by the US Department of Housing and Urban Development, the older the house, the more likely it is to contain lead-based paint; the less affluent the family, the more likely this paint is to be in disrepair. Housing built before 1950 poses the greatest danger of exposure, although lead-based paint was not completely banned until the late 1970s. Nationwide, the number of pre-1950 housing units decreased from 29.2 million in 2001 to 28.2 in 2009, indicating a decline in such

housing because of aging of our housing stock and consequent demolition.

Numerous other sources of lead exposure exist. Children may be exposed to lead in water, food, soil, toys, or ceramics. Parents whose clothing becomes contaminated with lead at work may inadvertently bring lead into the home. Occupations at high risk for take-home exposures include those involving battery production or recycling, the making of pottery, smelting, printing, paint contracting, and working on a firing range, in a brass foundry, or on the demolition or renovation of outdoor structures. In addition, a significant number of hobbies can place children at risk, such as making lead fishing sinkers or bullets, collecting lead figurines, spending time at indoor firing ranges, and making ceramic pottery.

In certain cultures, such as many Latin American and Southeast Asian cultures, some home remedies, such as azarcon and greta, can serve as sources of lead poisoning. Certain cosmetics, such as kohl, an eye makeup from the Middle East and South Asia, can contain more than 80% lead. Lead-glazed ceramic dishes and containers also can cause lead poisoning, especially if acidic foods such as salad dressings or citric acid juices are served on or stored in them. These sources should be considered when children who are recent immigrants are poisoned. Lead plumbing also remains an important source, especially in areas with older water supplies. This contamination was evidenced in 2003 to 2004 by the elevated lead concentrations found in Washington, DC, after changes in water disinfection procedures caused leaching of lead out of water service pipes. In addition, maternal lead stores can be transferred to infants prenatally and in breast milk, thereby contributing to an infant's lead exposure. Although not advocating universal screening of pregnant and lactating women, the CDC has offered guidance to state and local health departments in identifying populations at increased risk for lead exposure and identifying community-specific risk factors to guide physicians in determining the need for population-based blood lead testing of these women.

### ADVERSE HEALTH EFFECTS

Exposure to lead has numerous adverse health consequences. Most pediatricians' concerns, however, focus on the adverse neurocognitive effects of lead toxicity. Adverse neurocognitive effects caused by blood lead levels above 10 mcg/dL have been recognized for some time. Over the past decade, it has become increasingly recognized that lead levels well below 10 mcg/dL cause similar negative outcomes. A pooled analysis of findings from 7 prospective studies involving 1,333 children has shown lowered IQ scores that are independently associated with the lowest measurable levels of blood lead: as blood lead levels increase from 2.4 to 10 mcg/dL, there is a 3.9 IQ point decrease; between 10 and 20 mcg/dL, there is an additional 1.9 IQ point decrease; and between 20 and 30 mcg/dL, there is an additional 1.1 IQ point decrease. At this time, it is not possible to ascertain whether a child's peak blood lead level, the average over the child's early years, or a blood lead level taken

in proximity, time-wise, to a child's standardized IQ test is most predictive of the magnitude of IQ decrease. An impressive array of studies now show IQ losses and increased rates of adverse outcomes for a substantial number of other aspects of children's functioning, including attention, vigilance, language development, the transfer of information from short-term to long-term memory, aggression, and antisocial or delinquent behaviors associated with blood lead levels as low as 5 mcg/dL. These findings clearly indicate that blood lead levels well below 10 mcg/dL are associated with subtle but potentially serious alterations of children's neurocognitive functioning. No apparent threshold exists for the toxic effects of lead; that is, negative cognitive effects occur at the lowest measurable levels of blood lead. As a consequence, The CDC now defines a blood lead level that is at the 97.5th percentile, which currently is 5 mcg/dL, as being elevated. Prenatal lead exposure has also been studied and has been negatively associated with intellectual development of school-aged children.

### SCREENING FOR ELEVATED BLOOD LEAD LEVELS

Primary prevention has certainly proved the most effective means of eliminating lead poisoning in the United States, and even more intensive large-scale primary preventive measures, such as more aggressive housing rehabilitation, have been advocated. However, to identify children who need individual interventions to reduce their blood lead levels, screening of blood samples remains an essential tool in the prevention of childhood lead poisoning. Guidance from the CDC has been pivotal in defining national standards for screening programs. The CDC recommends the use of venous or capillary blood lead level as the laboratory examination of choice.

Although capillary blood samples collected by finger stick are acceptable, the potential for contamination by lead deposits on the skin dictates that capillary specimens with values at or above 5 mcg/dL be confirmed with a venous sample. An important point to recognize is that the allowable error established by the Clinical Laboratory Improvement Amendments for lead testing is  $\pm 4$  mcg/dL or 10% of value, whichever is greater. At low levels of blood lead, allowable laboratory error can result in misclassification that might affect management recommendations for an individual child.

CDC guidelines advise state health officials to develop universal or targeted screening programs (or both) based on the risk characteristics of their local communities. Within the state or the locale for which recommendations are made, the CDC advises that child health care professionals use blood lead tests to screen 1- and 2-year-olds (and 3- to 6-year-olds who have not been screened previously) who meet one or more of the criteria in Box 283-1.

Screening by questionnaire to evaluate risk has been suggested by the CDC, but substantial variability in the sensitivity and specificity of screening questionnaires limits the usefulness of this screening strategy. Screening questions are still used by some states and localities as one component of an overall lead-screening strategy,



### BOX 283-1 Recommendations for Lead Screening in Children at Risk

Universal screening of all children on Medicaid between 9 and 12 months and at 2 years of age has been required, but with decreases in the rates of elevated blood lead levels between those covered by Medicaid and those not covered by Medicaid, the CDC has recommended that state and local officials have the flexibility to develop blood lead screening strategies that reflect local risks for elevated blood lead levels. In addition, or until local health officials provide data-based guidelines for screening, the following guidelines are useful for deciding whether a child should be screened:

1. A child whose parents are concerned that the child may have been exposed
2. A child who lives in or regularly visits a house with peeling or chipping paint built before 1980
3. A child who lives in or regularly visits a house with recent or ongoing renovation or remodeling
4. A child who has a sibling or a playmate with an elevated blood lead level
5. A child who lives with an adult whose job or hobby involves exposure to lead
6. A child who lives near an active lead smelter, battery recycling plant, or other industry likely to release lead
7. A child who is a recent immigrant, refugee, or foreign adoptee
8. A child who has a household member who uses traditional, folk, or ethnic remedies or cosmetics or who routinely eats food imported informally (eg, by a family member) from abroad
9. A child who has recently immigrated to the United States or who has been internationally adopted

From Centers for Disease Control and Prevention. Recommendations for blood lead screening of Medicaid-eligible children aged 1-5 years: an updated approach to targeting a group at high risk. *MMWR Morb Mortal Wkly Rep.* 2009;58(RR09):1-11.

often with modifications in the specific questions used based on the locale. State- and locale-specific screening strategies are available on the CDC Web site at [www.cdc.gov/HealthyHomes/programs.html](http://www.cdc.gov/HealthyHomes/programs.html). The Web site [www.aoc.org/pehsu.htm](http://www.aoc.org/pehsu.htm) lists regional pediatric environmental health specialty programs that may be extremely useful to physicians caring for children.

In addition to following state- or local-level guidelines, health care professionals are encouraged to go beyond these recommendations by remaining vigilant in identifying children who should be screened because of exposure to less common sources of lead, such as those resulting from various parental occupations or hobbies. Similarly, if parents or health care professionals suspect lead exposure, prompt performance of a blood lead test should be undertaken, regardless of patient age, general health department recommendations, or responses to screening questionnaires.

Of course, to be optimally effective, a screening policy is not enough; physicians must participate in and comply with the recommended program. Also,

effective treatment of children with elevated blood lead levels requires that primary care physicians collaborate with local health, public housing, and social services to help identify sources of a child's exposure and ways to eliminate them or to provide the children with alternative housing when necessary.

*Healthy People 2010* called for the elimination by the year 2010 of all lead levels over 10 mcg/dL in children. Although most physicians agree that lead exposure remains a major problem, concern is growing about the cost benefit of using blood lead level as a screening tool in an era of declining prevalence. This concern is addressed in a 2005 policy statement from the American Academy of Pediatrics, which reviews a cost-benefit analysis of lead screening. Although the cost of lead screening is not trivial, the projected loss of income among individuals who suffered IQ decrements caused by lead exposure in childhood is in the hundreds of billions of dollars.

### Follow-Up of Positive Screening Tests

The CDC has recommended a schedule of follow-up testing based on the initial screening result (Table 283-1).

#### Children with blood lead values above 5 mcg/dL

All children with blood lead levels at or above 5 mcg/dL are encouraged to have ongoing monitoring for continuing lead exposure. If the elevated blood lead level was obtained by a finger-stick blood test, it should be confirmed with a venous blood lead test. All children with venous blood lead levels of 5 mcg/dL or higher are recommended by the CDC to receive both medical and environmental evaluations and medical and environmental counseling.

The evaluation consists of (1) a detailed medical, nutritional, developmental, and environmental history, and a complete physical examination; (2) a laboratory evaluation of iron status, including hematocrit and mean corpuscular volume; those with a low hematocrit or low mean corpuscular volume should be tested either with a ferritin level or iron and iron-binding capacity levels to identify iron deficiency; and (3) an environmental history to identify potential sources of the child's exposure, such as living in or visiting a home built before 1950, or one built between 1950 and 1978, when lead-based paint was still being used in some homes. The physical examination is unlikely to reveal overt signs of neurological damage, but this in no way precludes the possibility that the child has sustained neuropsychological injury that may manifest as attention-deficit/hyperactivity disorder or specific learning disabilities.

Such children should receive a nutritional assessment to identify eating patterns that may result in increased absorption of lead from the gastrointestinal tract, such as iron deficiency, low calcium intake, or infrequent meals. Many children with blood lead levels of 5 mcg/dL or higher are eligible for support from the Special Supplemental Nutrition Program for Women, Infants and Children and should be referred for evaluation of eligibility. Iron deficiency, even in the absence of anemia, should be treated with iron supplements, because iron deficiency increases the amount of



**Table 283-1** Recommended Schedule for Obtaining a Confirmatory Venous Sample

SCREENING TEST RESULT (mcg/dL)	RECOMMENDATION FOR CONFIRMATION TESTING
5–<10	Confirm with a venous lead level, within 1–3 months if possible; this should be ongoing until the level is <5 mcg/dL
10–44	Confirm the blood lead level with a venous sample within 1–3 months for those children with a blood lead level of 10–24 mcg/dL and within 2 weeks–1 month for those children with a blood lead level of 25–44 mcg/dL. Repeat confirmations at the same intervals until blood lead levels decline (ie, for children with repeat blood lead levels of 25–44 mcg/dL, repeat the blood lead test at 2 weeks–1 month intervals until it is in the range of 5–24 mcg/dL, at which time blood lead testing should be repeated at 1–3 month intervals until it is below 5 mcg/dL.

The higher the blood lead level on the screening test, the more urgent will be the need for confirmatory testing. Adapted from Centers for Disease Control and Prevention. *Screening Young Children for Lead Poisoning: Guidance for State and Local Public Health Officials*. Atlanta, GA: US Department of Health and Human Services; 1997.

ingested lead that is absorbed from the gastrointestinal tract and has also been found to be independently associated with increased rates of neurobehavioral problems. Although the protective effect has not been proved, increased calcium intake is generally recommended, especially when calcium intake is low. Increasing meal frequency may decrease lead absorption, but this action should be prescribed in the context of a diet that is not excessive in calorie content. All such children should receive general nutritional counseling consistent with American Academy of Pediatrics guidelines.

As elevated lead levels increase the risk for decreased IQ and subtle or overt neurocognitive and behavioral problems, monitoring these aspects of child function is particularly important, and referral for formal developmental, neuropsychological, or educational psychology evaluations are indicated if there is any concern about the child’s development, educational performance, or behavior, such as inattention or hyperactivity. The potential need for early intervention or special educational services for children evidencing possible difficulties in these areas should be an important consideration in the management of children with blood lead levels at or above 5 mcg/dL.

Families need education about potential sources of lead exposure, means to reduce exposure (Box 283-2), and housing and public health regulations concerning lead that may assist them in reducing their children’s lead exposure. A detailed history to help identify potential sources of lead exposure is indicated. In many communities children with elevated blood lead levels of varying degrees (eg, 15, 10 or even 5 mcg/dL) will become involved with local health departments that may do home inspections to identify lead paint hazards, household dust that has elevated amounts of lead, or other potential sources of exposure, and facilitate recommended or mandated abatement of lead-based household paint. Although often a lengthy process, abatement of lead-based hazards and subsequent dust control are cornerstones of treatment for children with exposure to lead resulting in elevated blood lead levels.

Thus it is obvious that children with elevated blood lead levels often benefit from case management

involving professionals from multiple fields, and a medical home is essential to their care, with pediatricians involved in all aspects of their lead-related care.

Families should be counseled to (1) have lead-based paint abatement performed by a properly licensed contractor and, if possible, with supervision of the local health department; (2) relocate children and pregnant women to another site while abatement is being performed; and (3) have a thorough cleanup of dust before allowing children to reinhabit the home.

The use of chelating agents for children whose blood lead levels are less than 45 mcg/dL is not indicated. A prospective study randomized 2-year-old children with lead levels between 25 and 44 mcg/dL to receive succimer (dimercaptosuccinic acid) or placebo, with up to 3 treatment courses of 26 days each, over 6 months. The authors found no appreciable difference in lead levels and no significant differences in measures of cognition or behavior between the succimer-treated and placebo groups at follow-up at age 7 years. The effects of succimer when used in more prolonged or more repeated treatment courses would require further study.

The CDC recommends that any blood lead value that is at or above the reference value of 5 mcg/dL and less than 10 mcg/dL should be confirmed within 1 to 3 months, and this should be ongoing until the level comes down to below 5 mcg/dL. Blood lead values of 10 to mcg/dL and higher should be confirmed as follows:

- 10 to 24 mcg/dL: confirm within 1 to 3 months
- 25 to 44 mcg/dL: confirm within 2 weeks to 1 month
- 45 to 69 mcg/dL: confirm within 48 hours

Patients with blood lead values of 70 mcg/dL or higher: should be treated emergently and have their blood lead levels retested immediately.

**Children with blood lead values of 45 mcg/dL or higher**

The clearest management strategies exist for children in this category because they are at the greatest risk for overt lead encephalopathy. Broad consensus exists that such children must be removed from sources of lead in their environments and receive chelation therapy, as described in Chapter 369, Poisoning. Any

### BOX 283-2 Avoiding Lead Hazards in the Home

Cover leaded paint that is chipping or peeling.  
 Move cribs, playpens, furniture, and play areas away from chipping or peeling paint.  
 Wet-mop floors and wet-clean windowsills and window wells with a high-phosphate detergent.  
 Avoid dry dusting or sweeping.  
 Wash children's hands, toys, and pacifiers regularly.  
 Use cold water for cooking; run tap water for 2 to 3 minutes every morning before using.  
 Repair deteriorated windowpanes inside the house and on porches.  
 Replace old windows.  
 Remove paint in old homes (only by trained contractors). Families must be out of their homes during paint removal.  
 Postabatement cleanup, preferably by professional house cleaners, is essential, and the measurement of lead in household dust (dust clearance testing) after such work is advisable.  
 Relocate the family to lead-safe housing.

child with a blood lead level of 45 mcg/dL or higher should be referred, if possible, to a pediatrician who is familiar with the pharmacologic management of childhood lead poisoning. This is especially salient as children's blood lead levels have come down so that few physicians have experience using the various available chelating agents, managing their potential side effects, or managing lead encephalopathy. If such a referral is not immediately available, the treating physician may consider consulting with an individual with such experience, such as a pediatrician not in the area, a toxicologist, or a poison control center.

### TOOLS FOR PRACTICE

#### Community Coordination and Advocacy

- *Screening Young Children for Lead Poisoning: Guidance for State and Local Public Health Officials* (report), Centers for Disease Control and Prevention ([www.cdc.gov/nceh/lead/publications/screening.htm](http://www.cdc.gov/nceh/lead/publications/screening.htm))

#### Engaging Patient and Family

- *Lead* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/lead/](http://www.cdc.gov/lead/))
- *Lead Is a Poison: What You Need to Know* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

#### Medical Decision Support

- *Eliminating Childhood Lead Poisoning: A Federal Strategy Targeting Lead Paint Hazards* (report), President's Task Force on Environmental Health Risks and Safety Risks to Children ([www2.epa.gov/lead/eliminating-childhood-lead-poisoning-federal-strategy-targeting-lead-paint-hazards-february](http://www2.epa.gov/lead/eliminating-childhood-lead-poisoning-federal-strategy-targeting-lead-paint-hazards-february))
- *Low Level Lead Exposure Harms Children: A Renewed Call for Primary Prevention* (report), Centers

for Disease Control and Prevention ([www.cdc.gov/nceh/lead/ACCLPP/Final\\_Document\\_010412.pdf](http://www.cdc.gov/nceh/lead/ACCLPP/Final_Document_010412.pdf))

- *Managing Elevated Blood Lead Levels Among Young Children: Recommendations from the Advisory Committee on Childhood Lead Poisoning Prevention* (report), Centers for Disease Control and Prevention ([www.cdc.gov/nceh/lead/CaseManagement/caseManage\\_main.htm](http://www.cdc.gov/nceh/lead/CaseManagement/caseManage_main.htm))
- *Pediatric Environmental Health*, 3rd ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Preventing Lead Poisoning in Young Children* (report), Centers for Disease Control and Prevention ([www.cdc.gov/nceh/lead/publications/PrevLeadPoisoning.pdf](http://www.cdc.gov/nceh/lead/publications/PrevLeadPoisoning.pdf))
- *Recommendations for Blood Lead Screening of Medicaid-Eligible Children Aged 1-5 Years: An Updated Approach to Targeting a Group at High Risk* (report), Centers for Disease Control and Prevention ([www.cdc.gov/mmwr/preview/mmwrhtml/rr5809a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5809a1.htm))

### SUGGESTED READINGS

- Centers for Disease Control and Prevention. *Guidelines for the Identification and Management of Lead Exposure in Pregnant and Lactating Women*. Atlanta, GA: US Department of Health and Human Services; 2010
- Dietrich KN, Ware JH, Salganik M, et al, for the Treatment of Lead-Exposed Children Clinical Trial Group. Effect of chelation therapy on the neuropsychological and behavioral development of lead-exposed children after school entry. *Pediatrics* 2004;114:19-26
- Weitzman M, Schwartz J, Bellinger D, et al. A review of the evidence of adverse health effects associated with blood lead levels <10 µg/dl in children. In: Centers for Disease Control and Prevention. *Preventing Lead Poisoning in Young Children*. Atlanta, GA: Centers for Disease Control and Prevention; 2005

## Chapter 284

## LEARNING DISORDERS

Laura L. Bailet, PhD

### FOUNDATION

#### Definition

The term *learning disability* (LD) represents a broad array of specific learning challenges that significantly impede one's ability to perform at the expected level in an important area of academic performance. LD generally occurs in the context of normal sensory functioning and otherwise normal cognitive capabilities and is not the result of a primary emotional disorder or lack of opportunity.

A formal definition of LD was first delineated in federal law in 1975 as part of the Education for All Handicapped Children Act. That law is now called the Individuals With Disabilities Education Improvement Act (IDEA) of 2004, which specifies regulations pertaining to public education services for persons

with disabilities, and incorporates the following LD definition:

[A] disorder in one or more basic psychological processes involved in understanding or in using language, spoken or written, that may manifest itself in an imperfect ability to listen, think, speak, read, write, spell, or to do mathematical calculations, including conditions such as perceptual disabilities, brain injury, minimal brain dysfunction, dyslexia and developmental aphasia . . . . The term does not include learning problems that are primarily the result of visual, hearing, or motor disabilities, of mental retardation, of emotional disturbance, or of environmental, cultural, or economic disadvantage. 20 U.S.C. § 1401(30).

The *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (*DSM-5*) definition of Specific Learning Disorder describes “Difficulties learning and using academic skills . . .” (p66). Subtypes include impairment in reading, written expression, and mathematics, which are further specified by severity level. The *DSM-5* also specifies that, although the learning difficulties begin during the school-age years, they may only become fully evident as academic demands increase and thereby exceed the individual’s capabilities. *Dyslexia* and *dyscalculia* are listed as alternative terms for impairment in reading and mathematics, respectively. The term *dyslexia*, first coined by physicians in the late 1800s, is commonly used by clinical professionals to refer to specific reading disability, whereas educators prefer “learning disability.” School personnel often are reluctant to talk about dyslexia, leading to confusion for parents, and often, delays in identification and treatment for affected children. Dyslexia is specifically named as 1 type of LD in the 2004 IDEA, although many educators do not know this and may misinform parents. It can be helpful for pediatricians to talk with teachers and parents about this for clarity. For all practical purposes, the terms can be used interchangeably, as is the case in this chapter. Similar to the federal definition, the *DSM-5* states that, “The learning difficulties are not better accounted for by intellectual disabilities, uncorrected visual or auditory acuity, other mental or neurological disorders, psychosocial adversity, lack of proficiency in the language of academic instruction, or inadequate educational instruction” (p67). Unlike the federal definition, the *DSM-5* definition does not include receptive or expressive oral language disorders, which are categorized separately.

### Epidemiology

Learning disabilities are quite common, although precise prevalence estimates are difficult to pinpoint. The most commonly cited prevalence estimates range from about 9% to 20% of school-aged children for reading disability, and about 6% for math disability. Estimates vary significantly depending on the severity cutoff used and whether the estimate is based only on the number of public school students identified by IDEA as having an LD for which exceptional student education (ESE) services are provided.

Epidemiologic studies indicate that both boys and girls are affected by LD in significant numbers, with boys having a slightly greater prevalence. Boys are

much more likely to be referred for assessment and treatment, however, because they display a higher rate of concomitant disruptive behavior problems. LD tends to last into adulthood, but early identification and intervention (remedial, accommodative, or both) will optimize outcomes. This is particularly true for reading disability or dyslexia (these terms are used synonymously in this chapter), for which early warning signs and effective treatments as early as pre-kindergarten and the early elementary school years have been thoroughly researched and validated.

LD occurs on a continuum of severity, with most affected individuals experiencing mild to moderate impairment. Learning disabilities are notoriously heterogeneous, and it is not uncommon for an individual to have more than 1 LD, which complicates diagnosis, treatment, and prognosis. In addition, the presenting symptoms will vary according to the child’s age and the developmental demands that are placed on him or her, such that diagnosis can be challenging unless the pediatrician has training and experience with LD across the life span.

### Etiology

Learning disability is considered part of the broad spectrum of developmental disorders. A number of genetic syndromes (eg, Turner syndrome) and childhood medical conditions are associated with an increased frequency of LD, particularly those directly involving the brain (eg, epilepsy, neurofibromatosis type I). In cases in which a child has progressed normally and then begins displaying LD after an acute medical event (eg, stroke, encephalitis), the LD is considered acquired rather than developmental. These cases are rare compared with developmental LD but occur with substantial frequency among children with various medical conditions and events. Diagnostic classification may differ in such cases, but treatment should follow the same approach.

Research indicates that both genetic and environmental factors contribute to developmental LD. Most such research has been conducted on dyslexia and has shown that if an adult has dyslexia, each of his or her offspring has about a 30% to 50% chance of also having the condition. Genetic variants associated with several chromosomes have been identified for dyslexia. Research using various types of postmortem and neuroimaging studies has confirmed neurobiologic differences in brain structure and function for individuals with dyslexia compared with normal readers. The left hemisphere of the brain, and in particular the left posterior quadrant, consistently emerges as the key locus for neuroanatomic anomalies and resultant dysfunctional neural circuits associated with reading impairment, likely reflecting neurodevelopmental aberrations that occur prenatally.

Other risk factors for dyslexia include a history of speech and language disorder or attentional deficits in childhood. Reading is primarily a language-based process, so it is not surprising that reading disability is strongly associated with other types of language impairment. There is substantial literature addressing central auditory and visual processing

disturbances in some children with dyslexia, although the precise nature and significance of these deficits continue to be debated. Achieving reading proficiency is a complex neurodevelopmental process that typically takes several years of focused instruction, effort, and practice. Therefore, children with concomitant attentional deficits, anxiety, or depression may struggle with learning to read simply as a result of an inability to focus as required. Attention-deficit/hyperactivity disorder (ADHD) and dyslexia often co-occur as primary conditions, in which case simultaneous treatment for both disorders is essential to maximize outcomes.

Math disability shows similar degrees of familiarity and heritability, particularly when co-occurring with dyslexia. Neuroimaging research on math disability is sparse compared with dyslexia but shows a more bilaterally distributed pattern that includes both posterior and frontal cortical foci. Math disability often co-occurs with ADHD, reading disability, and written expression disability.

For all types of LD, the presence of any of these risk factors may also be exacerbated by inadequate exposure in early childhood to high-quality language and learning experiences at home and in child care, or low-quality academic instruction. On the other hand, the presence of these risk factors does not forebode a poor response to intervention. On the contrary, neuroscience research shows that emphasizing, from birth, key language and literacy milestones and home and child care activities to support their development has a significant positive effect on early brain development and later reading success for all children. Pediatric programs such as Reach Out and Read (ROR) are based on and contribute to this research. Particularly in the context of programs such as ROR and high-quality early literacy activities in child care or preschool settings, most children at risk for LD will make good progress if identified and treated early, regardless of etiology.

## DIAGNOSIS

### Signs and Symptoms

The major presenting complaint that should raise concern about a possible LD is in a child who shows normal capabilities in most developmental areas and significant discrepancies in a set of specific skills. It is important to pursue diagnosis and intervention for LD as early as possible. Research on reading development and dyslexia indicates that children must acquire reading proficiency by the end of third grade to have a high probability of future academic success. The prime window of opportunity for effective targeted intervention is from preschool through third grade. Beyond that time, remedial intervention is much more costly in terms of time and money and has diminishing returns. Although it is never too late for a person to learn to read, the earlier appropriate instruction begins, the better. The same is likely true for all types of LD, although there is less research from which to draw solid conclusions. Core symptoms of reading, mathematics, and written expression disorders are shown in Table 284-1, Table 284-2, and Table 284-3. A more comprehensive list of symptoms by cognitive/developmental category is available from the National Center for Learning Disabilities.

### Differential Diagnosis

The primary differential diagnoses for LD include ADHD and generalized intellectual impairment. Further complicating the differential diagnosis and treatment planning is the frequent comorbidity of these various conditions (especially LD and ADHD), for which a comprehensive evaluation by an appropriately trained examiner is critical. For the growing number of American children whose first language is not English, their academic difficulties may or may not have an LD component. Again, a thorough evaluation that includes an examiner with expertise in bilingual learning issues is essential in developing an appropriate education plan.

**Table 284-1** Signs and Symptoms of Reading Disability (Dyslexia)

GRADE	DIFFICULTY WITH
<i>Pre-Kindergarten–Grade 1</i>	Letters versus pictures or numbers Letter names and letter sounds Simple, high-frequency words (eg, <i>cat, boy, who</i> ) Rhyming Separating and blending sounds within words
<i>Grades 2–5</i>	Phonics Automatic word recognition Reading aloud Spelling Sounding out longer words Longer reading and writing assignments Reading speed
<i>Grades 6 and Above</i>	Reading comprehension Skills listed for grades 2–5 Written expression skills Learning a foreign language



### Diagnostic Approach and Procedures

A formal LD diagnosis typically does not occur until a child is 6 years of age or older because a major defining characteristic is persistent impairment in an academic skill. Diagnosis at an earlier age should be considered tentative, with frequent reevaluation to clarify whether the cognitive pattern of concern is persisting. A diagnosis of LD is made on the basis of clinical and academic history and the results of a

comprehensive evaluation using a battery of standardized cognitive, language, academic, behavioral, and emotional measures. The goals of the evaluation are to rule out other plausible causes for the learning problem, document specific patterns and severity of learning deficits, and identify significant comorbid conditions. An equally important outcome is the identification of learning strengths, from an intervention planning standpoint and for the affected individual's

**Table 284-2** Signs and Symptoms of Mathematics Disability

GRADE	DIFFICULTY WITH
<i>Pre-Kindergarten–Grade 1</i>	Names of written numerals 1-to-1 correspondence Rapid recognition of set size (eg, set of 3, set of 5) Concepts of <i>more</i> , <i>less</i> , and <i>equal to</i> Concepts of addition and subtraction Meanings of math symbols
<i>Grades 2–5</i>	Memorizing simple addition and subtraction facts, 0–9 Memorizing addition and subtraction facts, 0–20 Concept of place value Addition and subtraction with regrouping Relationships among numbers and strategic counting (eg, 2's, 5's, 10's) Word problems Concepts of time, money, and measurement Concepts of fractions and decimals Concepts of multiplication and division
<i>Grades 6 and Above</i>	Memorizing multiplication and division tables Skills listed for grades 2–5 Interpreting and creating charts and graphs Complex word problems Abstract geometric and algebraic concepts Math applications for personal finance (eg, calculating sales tax, interest rates)

**Table 284-3** Signs and Symptoms of Written Expression Disability

GRADE	DIFFICULTY WITH
<i>Pre-Kindergarten–Grade 1</i>	Writing own name Writing all alphabet letters Copying Spatial aspects of writing (eg, writing on the line, spacing between letters and words) Spelling of simple sight vocabulary and words that follow basic phonics or orthographic patterns
<i>Grades 2–5</i>	Handwriting and copying Written grammar Spelling Basic aspects of written composition (eg, introductory or concluding sentences; logical sequence of sentences)
<i>Grades 6 and Above</i>	Basic rules of written composition (eg, punctuation, capitalization) Skills listed for grades 2–5 Taking notes from lecture Paragraph and essay structure Different styles and purposes of writing Complex grammar structures Use of cohesive ties between sentences and paragraphs (eg, pronouns, connector terms such as <i>however</i> , <i>therefore</i> , <i>in contrast</i> ) Editing and proofreading

emotional well-being. Pediatricians are crucial in identifying children who may have LD, but a formal psychological evaluation is required to establish a firm diagnosis.

Through IDEA, public school systems are required to provide, at no charge, evaluations of both public and private school students for whom there are concerns of possible LD. Parents sometimes prefer to access private resources for such evaluations, which may provide a more complete picture of the child's learning profile and more comprehensive treatment planning support. Such evaluations can be expensive and typically are not covered by health insurance, but they are often invaluable in elucidating the child's learning problem. IDEA regulations for LD are complex. Parents should educate themselves on these laws through online resources ([www.wrightslaw.com](http://www.wrightslaw.com)). They should also ask their physicians how closely they work with local schools, and whether they will help the family find appropriate therapists or tutors after completion of the evaluation. Pediatricians may also fulfill this function with families by getting to know local psychologists and remedial learning specialists who specialize in assessment and treatment for LD.

The reauthorization of IDEA in 2004 included sections on an additional approach to addressing educational needs of struggling learners, called *response to intervention* (RTI). RTI is an educational framework with multiple tiers of progressively more intensive instructional support, based on student need, that is implemented in the regular classroom context. Specific practices vary by state, but in general students who are not making satisfactory progress in a critical learning skill (eg, reading, math, behavior) should receive targeted, small group extra instruction for some length of time, with frequent, brief assessments to gauge progress. With adequate progress, the targeted instruction ends; with poor progress, more intensive instruction should ensue. Although RTI was never intended to impede the timely provision of an individual comprehensive evaluation to determine eligibility for ESE services, it is widely recognized that this often occurs. Further complicating the picture is that teachers often are left to determine for themselves what type of intervention to provide, how often, and for how long. Time slips by, and parents see their children falling further behind. Pediatricians should let parents know that, by law specified through IDEA, RTI cannot be used to delay or deny the comprehensive evaluation of a child with a suspected disability, and that the parent has the right to request the evaluation at any time. The school can deny the request but must provide written notice of the decision, at which point the parent can challenge it by requesting a due process hearing.

### Laboratory Findings

Laboratory or other medical studies are generally not needed to diagnose LD. Such studies may be needed to rule out underlying medical conditions that may cause or contribute to the learning problem. For example, it is essential that any child who is struggling in school have comprehensive vision and hearing evaluations to rule out sensory impairment.

Additional medical studies should be performed only if the child presents with symptoms other than possible LD that would warrant such studies. Genetic and neuroimaging studies generally are not necessary for diagnosing LD or guiding treatment planning.

### Classification

The psychologist who completes the evaluation should provide a specific diagnosis and classification. This can vary depending on whether the psychologist is working within a public school system, which uses IDEA classifications, or in a community setting, where DSM-5 classifications are likely to be used. Under IDEA, public schools must determine whether a child meets criteria for "specific learning disability," compared with other covered conditions (eg, intellectual or sensory impairment) or with no covered condition. Many children have LDs that do not meet the threshold of criteria for IDEA classification and associated educational services. A particularly challenging aspect of LD identification or diagnosis is the aptitude and achievement discrepancy issue. Although virtually all practitioners agree conceptually that LD is characterized by such discrepancies, establishing specific psychometric criteria remains controversial from a theoretical, statistical, and ethical perspective. One result of this ongoing controversy is that individual states differ in how they operationalize IDEA regulations, such that a child may meet criteria for LD services in 1 state, but not another. It is this very issue that often brings families to their pediatrician for advice. Having knowledge of available community resources, books, and Web sites on LD is a valuable service that pediatricians can provide in such cases.

### MANAGEMENT

Learning disability is not a disease, and thus there generally is no cure. Rather, LD is a cognitive condition to be managed proactively to the extent possible, to limit its adverse effects and maximize the child's opportunities to achieve at the level of his or her potential. The keys to successful outcomes are early identification and appropriate intervention, accommodations when needed, a balance of focus on the child's learning weaknesses and strengths or interests, and strong parental advocacy when the child is young and self-advocacy as the child becomes older. LD symptoms tend to remain present throughout the life span. Expanding accommodation options and a growing awareness of the strengths that individuals with LD often possess, however, mean that higher education and employment options are many.

### Treatment Approach

Robust scientific evidence now supports interventions for reading disability. Much of this evidence was synthesized in the report to Congress of the National Reading Panel in 2000. Five critical skills were identified that support reading proficiency by the end of third grade for all children: phonemic awareness, phonics, vocabulary, fluency, and comprehension. For those with dyslexia, 80% or more have a core deficit in phonemic awareness, which refers to the ability to

identify and work with individual speech sounds that make up words. Through extensive research, several critical instructional features have been established for dyslexia treatment. Reading instruction should be explicit, sequential, systematic, and intensive in order for struggling readers to make adequate gains. A critical component for long-term success is explicit instruction in “cracking the code,” that is, understanding how speech sounds map onto written symbols (letters). Two of the 5 critical skills identified by the National Reading Panel, phonemic awareness and phonics, are the essential starting point for teaching children with dyslexia to read and spell. In addition, instruction must focus explicitly on developing automatic word recognition. Many research-based remedial reading programs are widely available and effective in increasing word decoding and word recognition skills for students with dyslexia, when used as designed and with sufficient frequency and intensity. Intervention incorporating such instructional methods has been shown through functional neuroimaging to actually change brain function toward a more normal state. The best outcomes from these studies were associated with individual or small group instruction. The effect on text-level reading fluency and comprehension is variable but tends to be better when intervention is begun early.

Research on intervention for other types of LD is less well developed, but several important instructional principles have emerged (see Box 284-1). Individual or small-group instruction that incorporates these strategies will likely be more effective than large-group instruction. More instructional time also is central to catch-up growth for students with LD, which in most cases should be the academic goal.

Another important component of LD treatment involves accommodations (see Box 284-2). Technology plays a major role in accommodations, and new options are rapidly becoming available. Decisions about instructional supports and accommodations should be made in the context of the effect and severity of the LD at a given time in the child’s life, rate of progress with remedial intervention, and the child’s perspective. Older children and adolescents with LD may be uncomfortable with visible supports or modified academic requirements. Choosing less visible accommodations may make the most sense in such situations. Striking the proper balance is important and will likely need adjusting during different developmental stages. Finally, efforts to develop the attributes of persistence and resilience in children with LD will help them manage their challenges, cultivate goals and hope for their future, and support a favorable prognosis. Pediatricians’ words of encouragement and ability to take the longer-term view can be highly encouraging for families in this regard.

### When to Refer

If there are concerns about LD, the child should either undergo an evaluation through the public school system or be referred to a psychologist with current LD expertise working in the community. Even if the child has had a public school evaluation, a second opinion

### BOX 284-1 Common Instructional Supports for Learning Disabilities

- Explicit instruction describing the task and method for completing it
- Explicit explanation and demonstration of appropriate problem-solving strategies
- Properly sequenced instruction and step size from simpler to more complex tasks or concepts
- Emphasis on concepts that are confusing (eg, for ending consonant blends *nd* as in *land*, and *mp* as in *lamp*: color-coding the letters of interest; over-articulating and directing attention to the mouth when pronouncing words with *nd* versus *d*, or *mp* versus *p*; explicitly comparing and contrasting written word pairs: *lap* – *lamp*, *lad* – *land*, *lip* – *limp*, *led* – *lend*)
- Shortened assignments
- Task structuring to reduce complexity (eg, spelling test with words that follow only 1 spelling pattern, such as short *a*; fewer math problems on a page)
- Multisensory teaching strategies (visual, auditory, tactile and kinesthetic)
- Concrete examples of abstract concepts (eg, manipulative materials to represent numeric concepts such as addition with regrouping)
- Immediate corrective feedback
- Frequent repetition and review
- Multiple-choice rather than recall testing format
- Cue cards to reduce memory load (alphabet strip on child’s desk as he is learning to write letters; index card with steps for subtraction with regrouping)
- Separation of longer assignments into several smaller steps
- Graphic organizers (eg, tree diagrams to represent hierarchic concepts; visual mnemonic images)
- Demonstration of problem-solving strategies (eg, identifying known from unknown key issues; developing sequential steps toward a solution)

by another psychologist may be helpful. School-based evaluations often focus primarily on determining whether the child qualifies for services under the IDEA, and parents may have questions or concerns that have not been addressed.

## ONGOING CARE

### Follow-Up

After a diagnosis has been made and intervention is underway, it is important to follow up on the child’s progress. With most LDs, one should expect an educational program of sufficient intensity to achieve catch-up growth. Simply holding steady in one’s skills is neither sufficient nor justified in most cases. Quick, targeted assessment of key skills being taught should occur at least every few months so that timely adjustments in teaching methods and intensity can be made. Periodic comprehensive reevaluation every few years is advisable as well to obtain an objective

### **BOX 284-2 Common Accommodations for Learning Disabilities**

- Extra time to complete assignments and tests
- Ability to take tests in a quiet, private room
- Waiver or modification of foreign language requirement
- Computer or electronic keyboard in lieu of handwritten assignments and tests
- Calculator
- Computer technology to listen to scanned reading materials (eg, Kurzweil Education Systems, [www.kurzweiled.com](http://www.kurzweiled.com), or WYNN Literacy Software Solution, [www.freedomscientific.com/LSG/products/wynn.asp](http://www.freedomscientific.com/LSG/products/wynn.asp))
- Recorded versions of reading assignments (all types of books, including textbooks, are available through Learning Ally, [www.learningally.org](http://www.learningally.org))
- Speech recognition software to convert speech into print (eg, Dragon Naturally Speaking, [www.nuance.com/dragon/index.htm](http://www.nuance.com/dragon/index.htm))
- Preferential seating
- Copies of teacher notes from lectures
- Copies of notes from a good student notetaker
- Ability to mark answers directly on the test rather than on a separate answer form
- A reader for tests
- Option to answer test questions orally rather than in writing
- Tutors
- Study halls
- Learning strategies classes

assessment of progress, adjust the treatment plan according to current needs, and ensure that intervention gains are maintained over time. When parents have evidence that their child's educational needs are not being met by his or her school program, they need to advocate assertively for appropriate changes. Resources that are helpful are listed at the end of this chapter.

Parents should be cautioned about unproven therapies and given information about reputable Web sites and book references. For example, various types of optometric treatments are routinely promoted for LD. The AAP has had a position statement on this topic for many years, which states explicitly that scientific evidence does not support eye exercises, vision therapy, or colored lenses as a treatment for LD.

### **Complications**

The major complication of LD tends to be lack of progress or worsening of the adverse effects. In such situations, further evaluation, or reevaluation is often helpful. Undiagnosed comorbid conditions should be considered, particularly ADHD, along with a review of the nature, intensity, and duration of interventions undertaken. In many situations, remedial therapy or tutoring may be needed over and above services that are provided at school. Students who chronically

struggle and fail academically are at high risk for dropping out of school. The longer a child struggles without proper assistance, the more difficult the academic situation becomes, and the greater the emotional toll on the child and family. Appropriately aggressive intervention and follow-up of progress are therefore paramount.

### **Prognosis**

All but the most severely affected individuals with LD should be expected to complete high school and function independently as adults, with many participating in postsecondary education programs. Individuals with LD can achieve at high levels in all types of employment and professions. Although they may need accommodations throughout their life span, they often display outstanding intelligence, problem-solving skills, persistence, and creativity that are advantageous in the workforce and in adult life. Explicitly acknowledging and nurturing each child's strengths and interests, both within school and through nonschool activities, while also addressing the LD, is essential for preventing debilitating emotional and behavioral difficulties that often arise in response to undiagnosed or poorly treated LD.

### **Prevention**

The keys to LD prevention are early identification, preferably during the preschool years, of children at risk for learning problems; rapid deployment of research-based intervention for children identified as at risk; ongoing progress monitoring and continued intensive intervention as needed; and proactive adjustment of supports as the child becomes older. Pediatricians are ideally suited to lead this effort, owing to their knowledge and surveillance of child development, familiarity with individual patient families, ability to identify science-based versus unproven treatments, and status among parents as a trusted professional.

During the preschool years, guidance on basic child development best practices, such as cautioning against too much screen time and emphasizing the importance of having print materials in the home and reading daily with children, can go a long way toward prevention of problems with kindergarten readiness, which currently affects about 40% of children. LD prevention research has been conducted primarily in relation to dyslexia and reading failure, and results are encouraging. Participation in the ROR pediatric program, previously mentioned, significantly increases oral language skills in low-income preschoolers and the home literacy activities of their parents. ROR begins at 6 months of age, is easy to implement in a pediatric practice, and is highly cost-effective. Preschool children can also be screened on early literacy skills with a tool such as Get Ready to Read (GRTR), which was developed in conjunction with the National Center on Learning Disabilities and is available online, for free, in both English and Spanish ([www.getreadytoread.org](http://www.getreadytoread.org)). Psychometric characteristics are excellent for a screening instrument, and free home literacy activities are on the GRTR Web site, along with other parent-friendly information.



Research using GRTR as a premeasure and a post-measure has shown that intensive early literacy instruction results in significant and sustained early literacy gains. This intervention program is being used with at-risk young learners in hundreds of public and private preschool and kindergarten classrooms in multiple states. Children screened in pediatricians' offices and identified as at risk thus have growing opportunities to receive effective early intervention in their communities. Targeted parent intervention also shows promise for preventing reading problems in kindergarten and beyond.

### TOOLS FOR PRACTICE

#### Community Advocacy and Coordination

- *Building the Legacy: IDEA 2004* (Web page), US Department of Education. ([idea.ed.gov](http://idea.ed.gov))
- *Wrightslaw* (Web site) ([www.wrightslaw.com](http://www.wrightslaw.com))

#### Engaging Patient and Family

- *All About the IEP* (fact sheet), Center for Parent Information and Resources ([www.parentcenterhub.org/repository/iep](http://www.parentcenterhub.org/repository/iep))
- *Frequently Asked Questions About Section 504 and the Education of Children With Disabilities* (fact sheet), US Department of Education ([www.ed.gov/about/offices/list/ocr/504faq.html](http://www.ed.gov/about/offices/list/ocr/504faq.html))
- *Get Ready to Read!* (Web site) ([www.getreadytoread.org](http://www.getreadytoread.org))
- *International Dyslexia Association* (Web site) ([www.interdys.org](http://www.interdys.org))
- *LD Online* (Web site) ([www.ldonline.org](http://www.ldonline.org))
- *Learning Ally* (Web site) ([www.learningally.org](http://www.learningally.org))
- *Learning Disabilities* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/learning-disabilities/Pages/default.aspx](http://www.healthychildren.org/English/health-issues/conditions/learning-disabilities/Pages/default.aspx))
- *National Center for Learning Disabilities* (Web site) ([www.nclld.org](http://www.nclld.org))
- *Smart Kids With Learning Disabilities* (Web site), Smart Kids with Learning Disabilities ([www.smartkidswithld.org](http://www.smartkidswithld.org))

### AAP POLICY

American Academy of Pediatrics Section on Ophthalmology, Council on Children with Disabilities, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus, American Association of Certified Orthoptists. Learning disabilities, dyslexia, and vision. *Pediatrics*. 2009;124(2):837–844. Reaffirmed July 2014 ([pediatrics.aappublications.org/content/124/2/837](http://pediatrics.aappublications.org/content/124/2/837))

### SUGGESTED READINGS

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- Pennington BF. *Diagnosing Learning Disorders*. New York, NY: Guilford Press; 2009
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## Chapter 285 LEUKEMIAS

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The incremental increase in survival among children with acute lymphoblastic leukemia (ALL) over the last 50 years is often cited as the great success story in clinical oncology. In the spectrum of childhood ailments, leukemias remain quite rare; but, among childhood malignancies, the leukemias are the most common. Accurate diagnosis and risk stratification are still the first steps and, in many cases, the most important steps toward cure. The role of the pediatrician in leukemia treatment does not usually end with the initial referral to an oncologist. A significant portion of treatment for ALL is done on an outpatient basis, and children should still be seen periodically by their pediatrician throughout treatment for routine care. As the number of long-term survivors among children with leukemias continues to increase, so too will the role of the general pediatrician in their care. An understanding of the biology, treatment, prognosis, and short- and long-term side effects of childhood leukemias will be necessary for primary care physicians of children and adults in the future. This chapter reviews the epidemiologic features, pathogenesis, classification, treatment, prognosis, and outcomes in childhood leukemia.

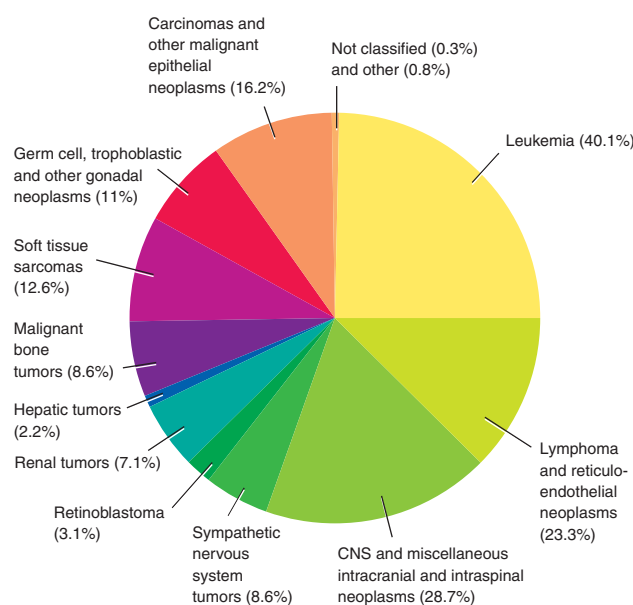
### EPIDEMIOLOGY

Leukemia remains the most common malignancy of childhood (Figure 285-1) with an annual incidence of 45 cases per 1,000,000 children in the United States. Leukemias account for a quarter of all childhood malignancies. In the United States, more than 3,000 children younger than 20 years of age will be diagnosed with leukemia each year, 80% of which are types of ALL.

The peak incidence of childhood leukemia is approximately 4 years of age, although this peak is due almost entirely to patients diagnosed with ALL. Acute myelogenous leukemia (AML) is equally distributed among patients 0 to 10 years of age, with a slight increase in incidence in adolescence. Acute lymphoblastic leukemia is more common among whites than it is among blacks in the United States, but AML is equally distributed among all ethnic groups. Early reports of worse outcomes for blacks with leukemia have been largely refuted in recent publications. The incidence of leukemia is also slightly higher among boys than it is among girls. The ratio of boys with leukemia to girls with leukemia is greatest during adolescence, particularly in the subset of patients with T-cell ALL.

### LEUKEMOGENESIS

The exact cause of most leukemias is not known, although several predisposing factors and exposures have been identified (Box 285-1). In all likelihood, the causes of most leukemias are multifactorial and



**Figure 285-1** Incidence of cancer types from 1996 to 2002 in children aged 0 to 19 years. Malignancies are classified according to International Classification of Childhood Cancer. Incidence is expressed as rates per 1,000,000 and are age-adjusted to the 2000 United States standard population. CNS, central nervous system. (From *US Cancer Statistics Working Group. United States Cancer Statistics: 1999-2002 Incidence and Mortality Web-based Report Version*. Atlanta, GA: Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute; 2005.)

include genetic, immune, infectious, and environmental factors.

### Genetic Factors

The association of leukemia with various constitutional chromosomal abnormalities, the reports of familial leukemias, and several reported karyotypic abnormalities in leukemia cells all suggest that a predisposition to childhood leukemia may be inherited.

Patients with Down syndrome (trisomy 21) have a 15-fold increased risk of developing leukemia when compared to healthy children. Infants with Down syndrome have a high incidence of a transient myeloproliferative phenomenon in infancy and the rare M7, megakaryocytic form of AML. Most of the cases of transient myeloproliferation resolve within a couple months with little or no therapy, although 25% to 33% of children will develop a true leukemia within 2 years of diagnosis. Acute myelogenous leukemia in young children with Down syndrome can usually be treated with less-intense therapy and carries a more favorable prognosis than AML in children without trisomy 21. Older children with Down syndrome carry a risk of relapse similar to that of the general population. Numeric and structural changes in chromosome 21 in leukemia cells are also commonly associated with ALL and AML in otherwise healthy children and adults. Trisomy 21, whether it is present in the germ

### BOX 285-1 Factors Associated With a Higher Risk of Developing Leukemia

#### GENETIC PREDISPOSITION

##### ALL

- Siblings of patient with a childhood leukemia, with a higher risk for a twin
- Down syndrome
- Bloom syndrome
- Ataxia telangiectasia
- Congenital hypogammaglobulinemia
- Neurofibromatosis
- Klinefelter syndrome

##### AML

- Down syndrome
- Fanconi anemia
- Bloom syndrome
- Paroxysmal nocturnal hemoglobinuria
- Wiskott-Aldrich syndrome
- Neurofibromatosis
- Klinefelter syndrome
- Shwachman-Diamond syndrome

#### ENVIRONMENTAL EXPOSURES

##### AML

- Ionizing radiation (therapeutic or environmental exposure)
- Epipodophyllotoxin or alkylator-based chemotherapy

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia.

line or a random event occurring in a hematopoietic progenitor cell, may be the first of 2 mutations leading to an acute leukemia, the second being a random somatic event.

A well-documented high incidence of leukemia exists among children with the autosomal-recessive chromosomal fragility disorders of Bloom syndrome, ataxia telangiectasia, and Fanconi anemia. In these syndromes, the propensity of dividing cells to develop random genetic mutations is likely the cause of the increased incidence of leukemias, as well as other malignancies. Although ALL is reported, both Bloom syndrome and Fanconi anemia are associated more frequently with the development of AML. Additional syndromes associated with an increased risk of AML include Shwachman-Diamond syndrome (abnormal ribosome processing), Kostmann syndrome (severe congenital neutropenia), and dyskeratosis congenita (abnormal telomere maintenance).

The concordance of ALL in monozygotic twins is estimated as high as 50% in the first year of life, with more recent studies suggesting the concordance rate among monozygotic twins to be 15% to 20% after the first year of life. The risk is highest in infancy and diminishes with age. The concordance rate for monozygotic, monochorionic twins with ALL with mixed lineage

leukemia (MLL) fusion gene is greater than 95%. By age 7 years, the risk of leukemia in the unaffected twin is close to that of the general population. Possibly, the concordance is because of a genetic predisposition or a common environmental exposure in infancy. In fact, a 1.3- to 4-fold greater risk of developing leukemia is found among singleton siblings of children with leukemia. However, an alternative exists for the exceptionally high concordance rate among twins. By sequencing the leukemia fusion gene in 3 twin pairs, Ford and colleagues demonstrated that the rearrangement in the leukemia fusion gene in each twin pair was identical. These data suggest that transplacental transfer of leukemia cells in monozygotic twins may also contribute to the concordance.

Recent genome-wide association studies in children with ALL identified germ line polymorphisms in 2 genes, *IKZF1* and *ARID5B*, that were associated with an elevated risk of developing childhood ALL. Polymorphisms in *ARID5B* are associated with hyperdiploid ALL, a subtype with excellent prognosis. Genetic alterations in *IKZF1* have been associated with high-risk ALL and generally portend a poor prognosis. Children with immunodeficiencies are also at an increased risk for lymphoid malignancies.

### Environmental Factors

The risk of leukemia, mainly AML, after exposure to ionizing radiation is well established. The first report of the association between ionizing radiation and leukemia came in 1944 in a publication citing a 9-fold increase in the incidence of leukemia among radiologists when compared with other physicians. Subsequently, a 10- to 20-fold increased risk of leukemia was reported among the survivors of the atomic bomb detonations in Hiroshima and Nagasaki in 1944. Finally, an increased incidence in leukemia was reported in patients exposed to radiation either in utero or for treatment of tinea capitis, ankylosing spondylitis, or thymic hyperplasia.

Studies suggest a role of maternal infections in the pathogenesis of leukemia in children (reviewed in 28 studies); however, currently definitive evidence supporting this hypothesis is lacking.

Several studies have examined the DNA derived from neonatal Guthrie cards in singleton children diagnosed with ALL. In the first report, Gale and colleagues identified the t(4;11) translocation (typically associated with infant ALL) in the diagnostic specimens and Guthrie cards in children 2, 5, and 6 years old at diagnosis of their leukemia. Several subsequent reports analyzing dried blood spots using polymerase chain reaction-based approaches probing for specific mutations, clonal immunoglobulin rearrangements, or T-cell receptor rearrangements confirmed these results and are thoroughly reviewed by Taub and Ge. Whether the abnormal cells detected on the Guthrie cards reflect a leukemic clone or a preleukemic cell is unknown. In many of the cases examined, evidence of an abnormal clone was found in the Guthrie cards of children 5 to 13 years old. This long latency period argues for the role of postnatal events in the pathogenesis of childhood leukemias. Greaves and colleagues speculate that

the mutation detected in the Guthrie cards is the first of 2 genetic hits required for a leukemic transformation. In support of this theory is the fact that a high concordance rate of leukemias exists among twins with *MLL* chromosome band 11q23 fusion genes, but only a 5% concordance rate among twins with the *ETV6/RUNX1* (*TEL/AML1*) mutation. These data suggest that, in certain subtypes of ALL (*ETV6/RUNX1* and hyperdiploid ALL) and AML (associated with t[8;21]), the first preleukemic event occurs in utero, but postnatal events are necessary for the transformation to a leukemic phenotype. A recent study using whole-genome sequencing in monozygotic twins with ALL identified the *ETV6/RUNX1* fusion as the only shared mutation between leukemia cells in an infant pair; supporting the role of the *ETV6/RUNX1* fusion as the initiating defect. In addition, this hypothesis is possibly supported by one study's description of late relapse *ETV6/RUNX1* ALL in which the recurrence is actually a second *de novo* ALL derived from an identical premalignant stem cell.

To identify the possible prenatal and postnatal insults necessary for the leukemic transformation, investigators have examined the role of toxins, electromagnetic fields, pesticides, nitrites, population mixing, seasonal and climatic variations, birth weights, socioeconomic status, breastfeeding, and maternal history of fetal loss in leukemogenesis. However, little, if any, conclusive evidence exists. Equally unclear is the role of in utero and childhood infections in the pathogenesis of childhood leukemia. In recent case-controlled studies, infections in childhood were associated with both a protective effect against leukemia and an increased risk for leukemia. Most studies evaluating childhood vaccination and leukemia demonstrated a protective effect, whereas one study suggested an increased risk for childhood leukemia after measles-mumps-rubella vaccination. Numerous other trials reviewed by McNally and Eden demonstrate only nonsignificant effects after childhood immunizations. Using child care attendance as a surrogate for infectious exposures in children, no studies to date demonstrate an increased risk of leukemia among children in child care. On the contrary, 5 recent case-controlled studies demonstrate a protective effect of child care attendance. No study to date identifies evidence of viral genomic inclusion in leukemia cells. The data suggest that exposure to certain infections may provide a protective effect against leukemias, presumably through early development of a mature and experienced immune repertoire. The data may also suggest that exposure to infections in children with a relatively naïve immune system later in childhood may increase the risk for leukemia.

The possible environmental contributors to leukemia risk in childhood are reviewed only briefly earlier in this chapter. With improvements in genomic technology, the molecular pathways involved in the development of childhood leukemia are being increasingly defined; however, the interplay between genetic predisposition and environmental influences in leukemogenesis is likely to be complex and multifactorial. Ultimately, whether the cause is from low-level radiation, infection, toxin exposure, or an unknown carcinogen, DNA

damage and inadequate DNA repair is the initial insult. Subsequently, 1 or more events, which may be influenced by environmental exposures, initiate the transformation to a malignant phenotype. The future of preventive medicine in childhood leukemia relies on further characterization of molecular events in leukemogenesis and the influence of environmental forces on these events.

## CLINICAL MANIFESTATION

### Presenting Signs and Symptoms

The presenting clinical features of childhood leukemias (Table 285-1) reflect the uncontrolled proliferation of malignant cells leading to replacement and suppression of normal hematopoietic progenitor cells and infiltration into extramedullary spaces. Symptoms often accumulate in days to weeks, culminating in some event that brings the child to medical attention. A common question of parents and practitioners alike is whether the leukemia might have been caught sooner. Many researchers would argue that the biological characteristics of the leukemia are determined

at the moment the first leukemia cell transforms. Signs of aggressive disease, such as a high white blood cell (WBC) count, extramedullary disease, or significant cytopenias may reflect the underlying biological features of the disease rather than timing of diagnosis.

The common clinical signs and symptoms of childhood leukemias are similar to common complaints among children with benign illnesses. Fever is present at diagnosis in most children with leukemia. Only subtle findings may exist on examination or in the history distinguishing fever in a child with leukemia from fever in normal children. Complaints of bone pain (manifesting as a limp in younger children), significant and diffuse lymphadenopathy, hepatosplenomegaly, pallor and petechiae, unexplained ecchymoses, and bleeding are all signs that often trigger further studies. More subtle and less specific complaints of fatigue and anorexia typically warrant close follow-up. Laboratory studies are typically necessary to corroborate clinical evidence.

### Laboratory Findings

The WBC count may be normal, increased, or decreased in a patient newly diagnosed with leukemia, and blasts may or may not be present on the peripheral blood smear. Anemia and thrombocytopenia are common, but not always present. In other words, although a complete blood count is certainly the first laboratory study necessary in the diagnosis of leukemia, a normal complete blood count result does not rule out leukemia. Continued close follow-up or referral to a hematologist should be guided by clinical evidence and laboratory findings.

Other abnormal laboratory findings include measures of tumor burden and cell turnover—increased potassium, increased phosphorus, decreased calcium, increased uric acid, and increased lactate dehydrogenase. These findings are hallmarks of the tumor lysis syndrome. Usually most severe after administration of chemotherapy, signs of tumor lysis may be present at diagnosis because of rapid proliferation and destruction of leukemic cells. Children at risk for significant electrolyte abnormalities and even renal failure are those with evidence of high tumor burden—high WBC count, massive organomegaly, and mature B-cell leukemia (Burkitt type), especially if an extramedullary tumor mass is present. Preemptive management decreases clinical manifestations and secondary consequences of tumor lysis syndrome in childhood leukemias.

Mediastinal masses are present in 5% to 10% of children with leukemia, especially older boys, who are more likely to have a T-cell leukemia. A chest radiograph is necessary in all children suspected of an acute leukemia and should be performed before administering anesthesia for any procedures. Though not required in the diagnostic evaluation of childhood leukemia, radiographs of long bones will often demonstrate evidence of leukemic infiltration of the periosteum and bone. Patients with particularly high leukemic cell burdens may seem osteopenic; others may demonstrate signs of subperiosteal new bone formation, radiolucent bands in the metaphysis (leukemic lines), discrete osteolytic lesions, and growth arrest lines.

**Table 285-1** Common Clinical and Laboratory Findings Present at Diagnosis in Children With Leukemia

	ALL (%) <sup>a</sup>	AML (%) <sup>b</sup>
<b>CLINICAL FEATURES</b>		
Fever	61	34
Pallor	55	25
Petechiae, purpura, bleeding	48	33
Anorexia or weight loss	33	22
Fatigue, malaise	30	19
Bone, joint pain	38	18
Lymphadenopathy	50	14
Hepatosplenomegaly	68	55
Swollen gingivae	—	8
Cough, dysphagia	—	41
Recurrent infection	—	3
Neurologic symptoms	3	10
<b>LABORATORY FEATURES</b>		
<b>White Blood Cell Count (per mL)</b>		
<10,000	53	39
10,000–49,000	30	29
>50,000	17	32
<b>Hemoglobin (g/dL)</b>		
<7	43	41
7–11	45	48
>11	12	11
<b>Platelet Count (per mL)</b>		
<20,000	28	15
20,000–99,000	47	67
>100,000	25	18
Coagulopathy	—	17

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia.

<sup>a</sup>Miller DR. Acute lymphoblastic leukemia. *Pediatr Clin North Am.* 1980;27(2):269–291.

<sup>b</sup>Choi SR, Simone JV. Acute nonlymphocytic leukemia in 171 children. *Med Pediatr Oncol.* 1976;2(2):119–146.



### Extramedullary Leukemia

Approximately 5% of patients will have evidence of disease in the central nervous system (CNS) at diagnosis. However, few children will have symptoms of disease at diagnosis, including vomiting, headache, and lethargy. Papilledema and cranial nerve palsies, which are significant signs of extensive CNS involvement, are not common. Cranial nerve palsies are typically reflective of meningeal infiltration of leukemic cells rather than increased intracranial pressure. Children at greatest risk for CNS disease are those with mature B-cell leukemia, T-cell ALL, those younger than 2 years of age, and those with monoblastic forms of AML. Painless enlargement of 1 or both testicles has been reported in fewer than 2% of boys diagnosed with leukemia and is more common in ALL (particularly T-cell ALL) than AML.

### Chloromas

Chloromas, or granulocytic sarcomas, are solid collections (tumors) of malignant cells in patients with AML. Chloromas can occur anywhere, including the skin, CNS, and bones. Rarely, chloromas can occur independently of or before evidence of bone marrow disease.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of individual or concurrent cytopenias includes several common infectious and noninfectious diseases of childhood (Box 285-2). The spectrum of signs and symptoms of childhood

leukemias mirrors the spectrum of many more common illnesses. Differentiating childhood leukemia from these other illnesses often requires either periodic reassessment of clinical and laboratory parameters of disease or, in cases in which the index of probability is sufficient, a more definitive bone marrow aspiration and biopsy. If the leukemic cell burden is sufficient to elicit clinical symptoms, then findings on a bone marrow evaluation will not be subtle. Identifying children with signs and symptoms severe enough to warrant a bone marrow evaluation (often requiring anesthesia in younger children) can be challenging. In children with atypical findings of common diseases, the general pediatrician's best tools are a high index of suspicion and frequent follow-up. An acute leukemia cannot hide for long before declaring itself.

Many illnesses more common than leukemia produce fever, rash, lymphadenopathy, hepatosplenomegaly, mild cytopenias, or lymphocytosis. The appearance of atypical and variant lymphocytes on the peripheral blood smears of children with infections such as Epstein-Barr virus, pertussis, and paraptosis often bring leukemia into the differential diagnosis. Diseases such as systemic lupus erythematosus and juvenile idiopathic arthritis may be associated with bone or joint pain and cytopenias that are indistinguishable from an acute leukemia. For many diseases, eliminating leukemia from the differential diagnosis becomes of paramount importance in specific diseases that require use of corticosteroids (systemic lupus erythematosus, juvenile idiopathic arthritis, immune thrombocytopenia purpura, hemolytic anemia, and even infectious processes precipitating an acute asthma exacerbation). In these instances, if leukemia is possible or probable, then referral to an oncologist may be necessary. Inadvertent administration of corticosteroids may impair or delay the diagnosis of leukemia and may necessitate more intensive high-risk chemotherapy for children with otherwise standard-risk disease.

### BOX 285-2 Differential Diagnosis of Childhood Leukemia

#### NONMALIGNANT DISEASES

- Juvenile idiopathic arthritis
- Systemic lupus erythematosus
- Infectious mononucleosis
- Immune thrombocytopenia purpura
- Aplastic anemia
- Pertussis, paraptosis
- Benign lymphocytosis
- Leukemoid reaction
- Sepsis
- Osteomyelitis
- Hemophagocytic histiocytosis
- Kawasaki disease
- Hemolytic uremic syndrome
- Thrombotic thrombocytopenic purpura
- Multifocal recurrent osteomyelitis

#### MALIGNANCIES

- Neuroblastoma
- Ewing sarcoma
- Rhabdomyosarcoma
- Lymphoblastic lymphoma

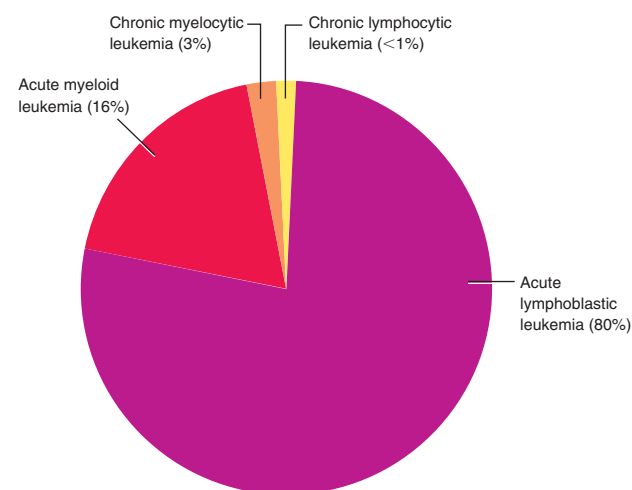
## CLASSIFICATION

Leukemias are a heterogeneous group of disorders classified by immunophenotype and subclassified based primarily on prognostic features. Leukemias can be classified as acute or chronic and lymphoblastic or myelogenous. In a normal marrow, blasts, which are hematopoietic progenitor cells, make up less than 5% of the total nucleated-cell population. Rarely are these cells found in the peripheral blood, except in instances of significant infection, bleeding, or a malignant process occupying the marrow space, including metastatic disease from solid tumors. According to the 2008 World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia, the acute leukemias are defined as a clonal expansion of hematopoietic progenitor cells (blasts) such that the number of these cells exceeds 25% of the total nucleated-cell population in the marrow for ALL or 20% for AML. If known, recurring cytogenetic abnormalities are found in the blast population, a diagnosis of ALL can be made with less than 25% blasts in the bone marrow, and of AML with less than 20%. Acute

myelogenous leukemia can also present with extramedullary disease and minimal or no bone marrow involvement. The expansion of leukemia cells in the confined marrow space and their impingement on normal marrow progenitors is often reflected in the relatively rapid onset of symptoms in patients with acute leukemia. In contrast, in chronic leukemia, a hyperproliferation of mature hematopoietic elements can be found, often in the absence of life-threatening cytopenias. Chronic leukemias have a more insidious onset than the acute leukemias. Although the initial management may not be as problematic, long-term eradication of the disease is more difficult in chronic leukemias.

Acute leukemia cells likely arise from a single, mutated progenitor cell that proliferates, but does not differentiate into a functional mature cell. In the diagnostic bone marrow specimen, the abnormal cells predominate and determine the leukemia type. Classification into myeloid or lymphoid lineages, and good or poor prognosis, is based on morphology, immunophenotype, cytogenetics, and behavior. Acute lymphoblastic leukemia is the most common form of leukemia (Figure 285-2). Subclassification into B precursor, mature B cell, and T cell lymphoblastic leukemias is essential to treatment and prognostic stratification of patients (Table 285-2). The myeloid leukemias (Table 285-3) can be categorized based on cytogenetic and morphologic features. The traditional French-American-British (FAB) system,

which used morphology for classification, has been largely replaced by the WHO system. The WHO system stratifies based on cancer cytogenetics, weighs molecular features of the disease more heavily than morphologic features, and has greater prognostic utility.



**Figure 285-2** Classification and frequency of leukemias in children. (Derived from Pui C-H. *Childhood leukemias*. N Engl J Med. 1995;332(24):1618-1630.)

**Table 285-2** Immunophenotypic and World Health Organization Classification of Acute Lymphoblastic Leukemias

COMMON NAME	COMMON FEATURES OF IMMUNOPHENOTYPE	PATIENTS	COMMENTS
Early pre-B cell, CD10–	CD10–, CD19+, CD20+, TdT+	5.2%	Common in infants <1 year, associated with t(4;11)
Early pre-B cell, CD10+	CD10+, CD19+, CD20+, TdT+	63.1%	Peak incidence in early childhood
Pre-B cell	CD10+/-, CD19+, CD20+, TdT+, cytoplasmic immunoglobulin+	15.5%	Clinically similar to early pre-B cell ALL
Mature B Cell	CD19+, CD20+, TdT+, surface immunoglobulin+	3.9%	Burkitt-type leukemia, treated differently than pre-B cell ALL
Pre-T Cell	CD2+, CD3+, CD7+, TdT+	12.3%	More common in adolescents and in boys Associated with high WBC count and bulky extramedullary disease, particularly a mediastinal mass
<b>WORLD HEALTH ORGANIZATION CLASSIFICATION OF ACUTE LYMPHOBLASTIC LEUKEMIA</b>			
<b>B lymphoblastic leukemia/lymphoma</b>			
B lymphoblastic leukemia/lymphoma, NOS			
B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities			
B lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2); BCR-ABL1			
B lymphoblastic leukemia/lymphoma with t(v;11q23); MLL rearranged			
B lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22); ETV6/RUNX1			
B lymphoblastic leukemia/lymphoma with hyperdiploidy			
B lymphoblastic leukemia/lymphoma with hypodiploidy			
B lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32); IL3-IGH			
B lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); TCF3-PBX1			
<b>T lymphoblastic leukemia</b>			

ALL, acute lymphoblastic leukemia; NOS, not otherwise specified; WBC, white blood cell.

Immunophenotype

Classification of leukemia by immunohistochemical or immunoflow cytometric detection of lineage-specific antigens allows for a precise and biologically relevant description of the leukemia cells. From the first bone marrow aspiration and biopsy, a crucial distinction between AML and ALL is made. Acute lymphoblastic leukemia is often treated with a 3- or 4-drug induction regimen of limited toxicity, whereas AML is treated with much more aggressive induction regimens. Surface and cytoplasmic antigens differentially expressed on cells of myeloid or lymphoid origin can be used to reliably distinguish AML from ALL and to subclassify within each lineage.

Acute Lymphoblastic Leukemias

Many lymphoid malignancies (B and T lineage) will express terminal deoxynucleotidyl transferase. No

antigen is truly lineage-specific in leukemia samples, and some cases are mixed lineage or undifferentiated, but most B-cell leukemias will express CD10, CD19, CD22, or any combination, whereas T-lineage leukemias will express CD3, CD7, or both. Among 3,073 children enrolled in the ALL-BFM (Acute Lymphoblastic Leukemia, Berlin-Frankfurt-Munster) 86 and ALL-BFM 90 trials, 403 (13%) had T-cell ALL, and 2,690 (87%) had B-cell ALL. The distinction between T- and B-lineage lymphoblastic leukemia is important to prognosis and treatment.

Early-cell ALL arises from a precursor B cell that is too immature to produce cytoplasmic immunoglobulin and that accounts for approximately 60% of all childhood ALL. Most of these immature leukemias express CD10 (common acute lymphoblastic leukemia antigen), CD19, and CD22, but do not express cytoplasmic immunoglobulin. CD10-negative, CD19-positive, CD22-positive early pre-B-cell ALL are derived from an earlier precursor lymphoblast. When found in infants, the CD10-negative early pre-B-cell phenotype is typically associated with rearrangements involving the MLL locus (11q23) and with a poor outcome.

Derived from a slightly more mature clone, the pre-B-cell ALLs express cytoplasmic (but not surface) immunoglobulin, 90% express CD10, and most express CD19, CD22, or both. Pre-B-cell ALL accounts for approximately 15% of all cases of ALL. The t(1;19) (q23;p13) translocation is found in approximately 25% of cases of pre-B-cell ALL, but only 5% of all cases of ALL. This translocation results in a fusion of the *E2A* and *PBX* genes. Despite the adverse prognostic effect of this translocation in older studies, recent intensification of therapy resulted in an improved survival for these children.

Mature B cell accounts for 3% to 4% of all ALL in childhood. Characteristic immunotypic features include the presence of surface immunoglobulin (usually IgM), CD20 (a mature B-cell marker), CD19, and human leukocyte antigen-DR. Cells are invariably CD10 negative. Mature B-cell leukemias are indistinguishable from Burkitt lymphoma with bone marrow involvement. Nearly all of these malignancies are associated with translocations involving the *MYC* oncogene on chromosome 8.

T-cell ALL affects boys predominantly and is more common in adolescence. Although T-cell malignancies account for only 13% of all lymphoid leukemias in childhood, they are diagnosed in nearly 40% of all children 10 to 18 years of age with ALL. When compared with B-cell ALL, patients with T-cell ALL are more likely to have extramedullary disease. Mediastinal mass, testicular involvement, and CNS leukemia are all more common in patients with T-cell ALL. Historically, T-cell ALL is associated with a less favorable prognosis. However, the historical difference in prognosis between T-cell ALL and B-cell ALL has largely been erased because of intensification of therapy for patients with T-cell ALL.

Acute Myelogenous Leukemia

Acute myelogenous leukemia occurs in approximately 1 in 130,000 individuals younger than 20 years of age, accounting for only 16% of all childhood leukemias.

Table 285-3	Classification of Acute Myeloid Leukemia
FAB CLASSIFICATION	PATIENTS
M1 AML without maturation	24%
M2 AML with maturation	23%
M3 Promyelocytic leukemia	5%
M4 Myelomonocytic	27%
M5 Monocytic	10%
M6 Erythroleukemia	2%
M7 Megakaryocytic	7%
WORLD HEALTH ORGANIZATION CLASSIFICATION OF ACUTE MYELOID LEUKEMIA	
AML with recurrent genetic abnormalities	
• AML with t(8;21)(q22;q22), ( <i>AML/ETO</i> )	
• AML with inv(16)(p13q22), or t(16;16)(p13;q22), <i>CBFβ/MYH11</i>	
• APML with t(15;17)(q22;q12), ( <i>PML/RARα</i> )	
• AML with t(9;11)(p23;q34) <i>MLLT3-MLL</i>	
• AML with t(6;9) (p23;q34) <i>DEK-NPU213</i>	
• AML (megakaryoblastic) with t(1;22)(q13;q13) <i>RBM15 MKL1</i>	
• Provisional entity: AML with mutated <i>NPM1</i>	
• Provisional entity: AML with mutated <i>CEBPA</i>	
AML with multilineage dysplasia	
Therapy-related AML and MDS	
AML, NOS	
Myeloid sarcoma	
Myeloid proliferations related to Down syndrome	
Blastic plasmacytoid dendritic cell neoplasm	
WORLD HEALTH ORGANIZATION CLASSIFICATION OF ACUTE LEUKEMIAS OF AMBIGUOUS LINEAGE	
Acute undifferentiated leukemia	
Mixed phenotype acute leukemia with t(9;22)(q34;q11.2) <i>CR-AL1</i>	
Mixed phenotype acute leukemia with t(v;11q23); <i>MLL</i> rearranged	
Mixed phenotype acute leukemia, B-myeloid, NOS	
Mixed phenotype acute leukemia, T-myeloid, NOS	
Provisional entity: natural killer cell lymphoblastic leukemia/lymphoma	

AML, acute myelogenous leukemia; APML, acute promyelocytic leukemia; FAB, French-American-British; NOS, not otherwise specified; MDS, myelodysplastic syndromes; MPD, myeloproliferative disorders.

Significant differences can be found in the surface antigen expression among the FAB subtypes of AML (see Table 285-3). The common myeloid antigens used to differentiate ALL from AML are CD13, CD33, CD117, CD14, CD64, glycophorin A, and CD41. CD14 and CD64 are monocytic markers, glycophorin A is an erythroid marker, and CD41 is a megakaryocytic marker.

### Biphenotypic or Mixed Phenotype Acute Leukemia

In 1995, the European Group for the Immunological Classification of Leukemias developed a scoring system of lineage specificity for different markers and later revised the system in 1998. In this system, AML is distinguished from ALL based on a scoring system (Table 285-4). Biphenotypic or mixed-lineage leukemia is defined as a score of 2 or more in 2 separate lineages. Applying the European Group's criteria to 676 patients newly diagnosed with leukemia, Owaidah and colleagues identified biphenotypic phenotypes in 3.4% of children. Among these children, the Philadelphia (Ph) chromosome (17%) and MLL (26%) abnormalities

were common. The more recent 2008 WHO classification includes cytogenetic abnormalities in addition to immunophenotype in its subclassification of acute leukemias of ambiguous lineage.

### Cytogenetic and Molecular Markers

Researchers have hypothesized that for an acute leukemia to develop, at least 2 relatively broad mutations must occur—class I and class II. Class I mutations offer a proliferative or survival advantage (eg, *RAS* or *FLT3* mutations), whereas class II mutations inhibit differentiation. Identification of these mutations not only offers insight into the pathogenesis of an acute leukemia, but these genetic events also significantly influence prognosis. Table 285-5 reviews the common genetic events that are hallmarks of childhood ALL and AML.

### Acute Lymphoblastic Leukemia

**PLOIDY.** An increase in the modal number of chromosomes (>46) can be detected in nearly one-third of newly diagnosed cases of ALL. Hyperdiploidy is associated with increased sensitivity to chemotherapeutic agents in leukemia cells cultured in vitro. Event-free survival in children with hyperdiploid leukemia cells exceeds 75% to 90%, making it a reliable marker of a good prognosis. Specifically, children with simultaneous trisomies of chromosomes 4 and 10 have a 7-year event-free survival in excess of 90%. Unfortunately, children with fewer than 45 chromosomes (hypodiploidy) have a worse prognosis. The event-free survival for children with 33 to 44 chromosomes is 40%, and for children with fewer than 28 chromosomes, the event-free survival is 25%.

In addition to changes in chromosome number, nearly one-third of childhood leukemias will harbor chromosomal translocations independent of ploidy. Included here is a discussion of a few translocations and mutations, each associated with a distinct biological subset.

**MIXED-LINEAGE LEUKEMIA.** Translocations involving the *MLL* gene at 11q23 and more than 30 potential partner chromosomes can be found in 6% of childhood ALL cases. The t(4;11)(q21;q23) mutation resulting in the *MLL-AF4* fusion product is commonly seen in

**Table 285-4** Scoring System From the European Group for the Immunologic Characterization of Leukemias

POINTS	B-CELL ALL	T-CELL ALL	AML
2	cyCD79 cyCD22	cyCD3 or memCD3	MPO
1	cylgM CD19 CD20 CD10	Anti-TCR CD2 CD5 CD8 CD10	CD117 CD13 CD33 CD65
0.5	TdT CD24	TdT CD7	CD14 CD15

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; cy, cytoplasmic; mem, membrane; MPO, myeloperoxidase; TCR, T-cell receptor; TdT, terminal deoxynucleotidyl transferase.

**Table 285-5** Common Cytogenetic Abnormalities of Childhood Leukemias

	KARYOTYPE	FUSION GENE	FREQUENCY IN CHILDHOOD LEUKEMIA
ALL	t(12;21)(p13;q22) 11q23 abnormalities	<i>ETV6/RUNX1</i> Multiple <i>MLL</i> fusion genes are reported	25%–30% of ALL 6% of ALL
	t(1;19)(q23;q13) t(9;22)(q34;q11) Hyperdiploidy	<i>E2A/PBX</i> <i>BCR/ABL</i> —	5% of ALL 3%–5% of ALL 30% of ALL
AML	t(8;21)(q22;q22) inv16(p13;q22) t(15;17)(q22;q21)	<i>AML1/ETO</i> <i>CBFB-MYH11</i> <i>APML/RARα</i>	10%–15% of AML 6%–12% of AML 8%–10% of AML

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia.  
*HOX11* overexpression is a common abnormality in T-cell ALL and is identified in 5%–10% of patients.



infant ALL and is associated with an event-free survival of only 20% to 25%. In children older than 1 year of age, the negative effect of *MLL* gene rearrangements on survival is less; however, most protocols will still include these children in a high-risk group despite other features. In T-cell ALL, the t(11;19)(q23;q13.3) translocation fusing *MLL* with the *eleven nineteen leukemia (ENL)* locus on chromosome 19 is associated with a favorable prognosis.

**E2A/PBX.** Pre-B-cell ALL is often characterized by t(1;19)(q23;q13), resulting in a fusion of the *E2A* and *PBX* genes. Pre-B-cell ALL was once thought to be associated with a poor prognosis, but recent studies with more intensive therapies have shown improved survival.

**BCR-ABL.** The Ph chromosome results from a balanced translocation between the long arms of chromosomes 9 and 22 (t(9;22)[q34;q11]), resulting in the fusion of the *BCR* and *ABL* genes. In 3% to 5% of childhood ALL and 20% of ALL cases in adults, the *BCR-ABL* fusion encodes a 185-kDa dysregulated tyrosine kinase responsible for the malignant transformation. A 210-kDa variant is the hallmark of more than 90% of chronic myelogenous leukemias. Ph+ childhood ALL used to be among the most difficult subsets to cure, with a long-term, event-free survival of less than 50%. The incorporation of imatinib, a tyrosine kinase inhibitor, in a recent Children's Oncology Group study led to a 3-year event-free survival of 80%, which is significantly higher than historical controls. Whereas matched-sibling bone marrow transplant for children with Ph+ ALL in first remission used to be the standard of care, current recommendations are to assess children's response to chemotherapy with a tyrosine kinase inhibitor. Newer-generation tyrosine kinase inhibitors (dasatinib, nilotinib) are currently being investigated for children with imatinib-resistant Ph+ leukemia. The hope is that the identification of other biologically targetable molecular markers will also lead to improvements in survival for other children with high-risk disease.

**ETV6/RUNX1 (TEL/AML1).** The t(12;21)(p13;q22) translocation is the most common in pediatric ALL and is identified in up to 25% of B-precursor ALL. Fusion of the *TEL* locus at 12p13 with the *AML1* gene at 21q22 results in a fusion transcript that serves as a co-repressor of *AML1* target genes. Children with the ETV6/RUNX1 translocation do very well with conventional therapy and may be preferentially sensitive to protocols containing augmented therapy with asparaginase. Children with ETV6/RUNX1-positive leukemias tend to relapse late, and salvage after relapse remains excellent.

**IKZF1.** Mutations in the gene *IKZF1* occur in 15% of patients with B cell ALL and are associated with poor overall survival. *IKZF1* encodes IKAROS, a transcription factor that is essential for normal lymphocyte hematopoiesis. Deletions in *IKZF1*, as well as sequence mutations, lead to abnormal expression of IKAROS and abnormal lymphocyte development. Alterations in *IKZF1* are associated with a higher risk of relapse and treatment failure. Mutations in *IKZF1* are often found in Ph+ ALL and Chronic myelogenous leukemia

(CML) in blast crisis. However, mutations are also found in a subgroup of patients with high-risk Ph- ALL whose leukemia cells have gene expression patterns similar to blast cells from children with Ph+ ALL. This may have implications for the use of targeted tyrosine kinase inhibitors in children with ALL and alterations in *IKZF1*. Additional studies are needed to further understand the implications of the effect of mutations in the *IKZF1* gene.

### Acute Myelogenous Leukemia

**PML/RAR $\alpha$ .** One characteristic chromosomal abnormality in childhood AML is the t(15;17) translocation. The resulting chimeric protein, *PML/RAR $\alpha$* , is formed by the fusion of the retinoic acid receptor- $\alpha$  (*RAR $\alpha$* ) gene from chromosome 17 and the promyelocytic leukemia (*PML*) gene from chromosome 15. The *PML-RAR $\alpha$*  fusion protein suppresses gene transcription and blocks differentiation of myeloid progenitor cells. Retinoic acid may still bind to the abnormal *RAR $\alpha$*  portion of the protein, promoting differentiation.

**CORE-BINDING FACTOR.** Both inv16 and t(8;21) involve subunits of the transcription factor complex core-binding factor (CBF), disrupting the normal functions of this gene. The CBF is a family of heterodimeric transcription factors containing 1 of 3 CBF $\alpha$  subunits (CBF $\alpha$ 1, *AML1* [also known as *RUNX1* or CBF $\alpha$ 2], or CBF $\alpha$ 3) and a common  $\beta$  subunit (CBF $\beta$ ). The CBF $\alpha$  subunits are involved in both DNA binding and interaction with CBF $\beta$ . CBF $\beta$  functions to enhance binding of CBF $\alpha$  and increases the affinities of the CBF $\alpha$  subunits for DNA. Together, the CBF complex is a critical transcriptional activator of genes involved in hematopoiesis and bone development. The inv16(p13;q22) abnormality results in a fusion of the CBF $\beta$  gene and the myosin heavy chain (*MYH11*). The 8;21 translocation involves the CBF $\alpha$  (*AML1*) gene on chromosome 21 juxtaposed with the *ETO* gene on chromosome 8. Disruption of both the CBF $\beta$  gene by CBF $\beta$ -*MYH11* and the CBF $\alpha$  subunit by the *AML1/ETO* fusion leads to deficient transcription of *CBFA-CBFB*-controlled genes and myeloid maturation arrest. As with the *ETV6/RUNX1* mutation, these CBF-related mutations have been found in the Guthrie cards of patients who develop leukemia well into their second decade. The long latency implies that class II CBF-related mutations may be only the first hit in leukemogenesis. Class II mutations altering expression and function of *FLT3*, *c-KIT*, and *RAS* may provide the second hit and a requisite proliferative advantage to preleukemic cells with already-abnormal differentiation signaling. Patients with t(8;21) or inv(16) have a favorable prognosis when treated with intensive chemotherapy. Additional, but unfavorable, abnormalities identified in AML samples include: -5/del(5q), -7/del(7q), inv(3)/t, +8, and complex karyotypes.

**NPM1.** Mutations in the nucleophosmin gene *NPM1* occur in 8% to 10% of children with AML and are associated with a favorable prognosis. *NPM1* encodes a protein involved in ribosome biosynthesis, centrosome processing, and regulation of p53, and mutations in

*NPM1* are often seen in adult patients with AML and other hematologic malignancies. In children, *NPM1* is associated with *FLT3*-ITD; however, favorable prognostic outcomes are only seen in children with mutations in *NPM1* who lack *FLT3*-ITD.

**CEBPA.** Mutations in the CCAAT/enhancer binding protein- $\alpha$  (*CEBPA*) gene occur in 4% to 5% of children with AML and are associated with a favorable prognosis. *CEBPA* encodes a transcription factor that plays an essential role in terminal granulocytic differentiation. Ho and colleagues reported that in 847 children with AML, the presence of a *CEBPA* mutation was associated with significantly improved 5-year event-free survival (70% vs 38%,  $p = 0.015$ ).

**FLT3-ITD.** Point mutations and internal tandem duplications (ITDs) in the FMS-like tyrosine kinase 3 (*FLT3*) gene occur in approximately 15% of children with AML, and *FLT3*-ITD is associated with a poor prognosis. *FLT3* is a tyrosine kinase whose downstream signaling regulates proliferation, differentiation, and apoptosis. Mutations in *FLT3* often lead to constitutive activation of the receptor, and a *FLT3*-ITD ratio/wild-type allelic ratio greater than 0.4 is associated with progression-free survival of less than 20%. Studies are currently investigating the efficacy of tyrosine kinase inhibitors in children with *FLT3*-ITD.

## TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA

### Risk-Stratified Therapy

Before the 1950s, no classification system existed for childhood leukemias. However, regardless of the myeloid or lymphoid origin of the disease, childhood leukemias were uniformly fatal within months of diagnosis. Djerassi and colleagues were the first group to attempt chemotherapy as a means to treat childhood leukemia. Initial trials with folic acid only made the disease worse; thus, an antagonist of folate metabolism, aminopterin (a methotrexate analog) was used instead to induce the first temporary responses. Subsequently, 6-mercaptopurine (6-MP) and prednisone were tried, both as single agents. Responses, but not cures, were observed. Nonetheless, from this point on, pediatric leukemia trials evolved, each sequential trial expanding from the success and failures of previous trials. Today, risk-adapted therapies, based on clinical features (age, WBC count, and response to induction therapies) and biological features (ploidy and mutations of known prognostic significance), are used to maximize response and cure rates while minimizing long-term side effects (Table 285-6).

Table 285-6

Common Prognostic Features of the Acute Leukemias<sup>a</sup>

	CLINICAL FEATURES	CYTOGENETICS AND MUTATION STATUS
B-cell-precursor ALL	<b>Favorable</b> Age between 1 and 9.99 years	<b>Favorable</b> t(11;22)(p13;q22), ETV6/RUNX1 fusion Hyperdiploidy (>50 chromosomes) Trisomies 4, 10, and 17
	<b>Unfavorable</b> Age >10 years Initial WBC count >50,000/mcL Poor response to induction therapy End induction minimal residual disease Extramedullary disease	<b>Unfavorable</b> MLL rearrangements in infants
T-cell precursor ALL	<b>Favorable</b> Good response to steroids <sup>b</sup>	<b>Favorable</b> HOX11 overexpression t(11;19) MLL-ENL fusion
	<b>Unfavorable</b> Poor early response to treatment Low-intensity chemotherapy regimens	<b>Unfavorable</b> —
AML	<b>Favorable</b> Acute promyelocytic leukemia AML in Down syndrome	<b>Favorable</b> t(8;21) AML1-ETO fusion inv(16) or t(16;16)(p13;q22) t(15;17)(q22;q21), APML/RAR $\alpha$ fusion CEBPA mutation NPM1 mutation
	<b>Unfavorable</b> WBC count >100,000/mcL Secondary AML or AML after MDS	<b>Unfavorable</b> Monosomy 7 (7q-) FLT3-ITD

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; WBC, white blood cell.

<sup>a</sup>Adapted from Pui CH, Schrappe M, Ribeiro RC, Niemeyer CM. Childhood and adolescent lymphoid and myeloid leukemia. *Hematology Am Soc Hematol Educ Program*. 2004;118–145.

<sup>b</sup>Adapted from Schrappe M. Evolution of BFM trials for childhood ALL. *Ann Hematol*. 2004;83(Suppl 1):S121–S123.

Patients between 1 and 9.99 years of age with an initial WBC count less than or equal to 50,000/mcL are classified as standard risk according to National Cancer Institute and Rome criteria. Children younger than 1 year of age and older than 10 years of age or children with an initial WBC count of more than 50,000/mcL are classified as high risk. In many multi-institutional, international cooperative group studies, age and initial WBC count have proven to be reliable and independent predictors of prognosis. Other clinical features used to stratify therapy include gender, leukemia phenotype, and response to initial therapy. Multiple trials have shown the prognostic value of assessing the bone marrow for minimal residual disease (MRD) both during and at the end of induction therapy. Children with MRD at the end of induction (presence of as few as 1 leukemia cell per 10,000 mononucleated cells) have a poorer prognosis, and their therapy is intensified in an attempt to improve survival (definition of induction and the timing of measurement of MRD is often protocol-dependent and may differ among protocols). Children with ALL who fail to go into remission after induction chemotherapy have a very poor prognosis, with overall survival less than 35%, even with intensified therapy. Recently, the Children's Oncology Group included an additional risk stratification for children with certain high-risk presenting features, as well as those with poor response to initial induction chemotherapy. The goal is to alter and intensify therapy for these children classified as very high risk in hopes of improving outcomes. Girls seem to have a more favorable prognosis than boys; however, recent studies showed less of a disparity in overall survival between genders. The reason for these gender differences is not known.

Leukemia cells that express aberrant myeloid markers, but do not meet strict criteria for biphenotypic leukemia, have historically yielded inferior outcomes; however, this effect is abrogated in recent trials. T-cell phenotype is associated with an inferior outcome, although the clinical features of older age, male gender, and extramedullary disease often associated with T-cell ALL may partly account for the greater risk for relapse. However, with T-cell directed therapy, which includes intensive asparaginase and dexamethasone, recent studies have shown survival greater than 85% for this population. The identification of leukemia cells in the CNS disease at diagnosis continues to be an adverse prognostic feature of childhood ALL despite attempts to intensify CNS-directed therapy.

Response to induction therapy is predictive of outcome and is used to stratify children for more intensified therapy when necessary. At the end of the initial cycle of chemotherapy known as induction, the presence of MRD is associated with significantly poorer outcomes compared with children who have less than 0.01% leukemia cells in the bone marrow. Children with more than 1.0%, 0.1% to 1.0%, and less than 0.01% leukemia blast 29 days after starting chemotherapy had a 5-year event-free survival of 30%, 49%, and 59%, respectively, compared with 88% for children who did not have MRD. Among children with a

slow early response to induction therapy, those who receive intensified therapy will have an improved outcome when compared with those who remain on standard therapy.

### Principles of Treatment

Leukemia cell infiltration in marrow space and other organ systems in children newly diagnosed with ALL may result in pancytopenia, as well as many systemic symptoms. Resolution of symptomatic disease and recovery of normal bone marrow function can only be achieved with the administration of potentially myelosuppressive and immunosuppressive chemotherapy. Therapy is often divided into phases of remission induction, consolidation with extramedullary disease treatment or prophylaxis, and maintenance. The timing, number, and chemotherapy components of each phase may differ between protocols, but the principles of therapy are similar. Remission induction is achieved in most cases with 3 drugs (vincristine, asparaginase, and a corticosteroid) or 4 drugs (addition of doxorubicin). The goal is to induce a complete remission, defined as the reduction of the leukemia cell burden below 5% in the bone marrow after recovery of normal blood counts. With current chemotherapeutic regimens, remission induction is possible in more than 95% of children with ALL. Many protocols follow the induction phase with a consolidation phase heavy in antimetabolites to secure or consolidate the remission.

Delayed intensification is a second phase of intensified chemotherapy used by some cooperative groups and is similar to the induction and consolidation phases. The addition of a delayed-intensification phase by the BFM group led to significant improvement in survival in all patients with childhood ALL. Subsequent trials in the United States and Europe confirmed the importance of post-induction intensification in the long-term survival of patients with ALL. Survival among patients with high-risk leukemia may be further improved by augmenting the post-induction intensification regimen.

Although the first successful treatment of CNS leukemia included 2,400 to 3,600 cGy cranial radiation, in the last 2 decades, several trials have demonstrated that CNS radiation may be reduced (to 1,200–1,800 cGy) or eliminated in children with low-risk B-cell ALL with a rapid early response to induction therapy. The Total Therapy Study XV suggested that prophylactic cranial irradiation could be eliminated for all children with ALL. Children at high risk for bone marrow and CNS relapse received intensified treatment, including additional doses of intrathecal chemotherapy. Reduction in cranial radiation is designed to reduce long-term endocrine and cognitive effects, as well as the risk of secondary malignancies. However, the use of intensified intrathecal therapy and high-dose methotrexate (MTX) are also associated with late cognitive side effects even when administered without radiation therapy. Radiation therapy was eliminated from management in all CNS negative children with precursor B-cell ALL in the United States. The optimal CNS prophylaxis for T-cell ALL is not yet clearly defined.

Unlike treatment paradigms for most malignancies, successful therapy for childhood ALL includes a protracted maintenance period. Although the components of maintenance therapy vary between cooperative group studies, attempts to reduce therapy to less than 24 months have never been successful. Most maintenance therapy consists of oral mercaptopurine, oral MTX, intravenous vincristine, oral corticosteroid pulses, and intrathecal therapy once every several months. The therapy is adjusted to maximize the dose within a range that maximizes the antileukemic effect and minimizes toxicity, including myelosuppression and immunosuppression. Many children on maintenance chemotherapy may return to school and normal daily activities.

### Infant Acute Lymphoblastic Leukemia

In the 1970s, the survival among children older than 1 year of age with ALL approached 50%, and fewer than 20% of children younger than 1 year survived. Currently, infants still have a higher incidence of relapse, death from toxicity, and long-term side effects when compared with older children. Studies with intensified therapy in infants younger than 6 months of age demonstrated an event-free survival of less than 10%, and infants older than 6 months had an event-free survival of 40%. Incremental improvement in survival was achieved by simultaneously intensifying chemotherapy and modifying such intensity to reduce treatment-related mortality. Bone marrow transplantation for infants in first remission has been a subject of study for several years. However, to date, bone marrow transplant has not significantly improved outcomes for these patients. Transplantation poses several problems, including the fact that total body radiation is associated with significant long-term side effects in young infants. Alternatively, intensified multiagent chemotherapy, combined with novel targeted therapy, is currently being evaluated, with the use of bone marrow transplantation reserved for the setting of a relapse or for very high-risk infants. Ongoing studies in this unique and challenging subset of children will help further define the role of transplantation and intensified chemotherapy.

## TREATMENT OF ACUTE MYELOGENOUS LEUKEMIA

### Principles of Therapy

Unlike treatment strategies in ALL, the event-free survival rate in childhood AML has reached a plateau at 60% despite aggressive intensification of therapy. Individualized treatment regimens have worked to improve survival rates significantly in children with acute promyelocytic leukemia, but have done little for other subsets of AML.

About 85% to 90% of children will obtain a complete remission with cytarabine and daunorubicin in combination with either etoposide or thioguanine. Attempts to improve remission induction rates and long-term survival by substituting idarubicin or mitoxantrone for daunorubicin or by increasing the dose of cytarabine have largely yielded comparable efficacy and occasionally greater toxicity. Alternative approaches currently under investigation include the introduction of a

monoclonal antibody directed against CD33 (a surface antigen expressed on most myeloid neoplasms), the use of proteasome inhibitors (bortezomib), as well as the use of the multi-kinase inhibitor sorafenib for children with FLT3-ITD-positive AML.

Intensive postremission therapies were developed using multiagent regimens cycled every 4 to 6 weeks. No randomized head-to-head comparisons have been made of the different regimens, but none have succeeded in improving long-term, event-free survival beyond 60%. Allogeneic stem cell transplantation (STC) has been extensively evaluated in childhood AML. Some studies nonrandomly assign transplantation to patients with high-risk features, such as monosomy 5 or 7, or who remain MRD positive after induction. Relapse-free survival is generally better in the children who undergo transplantation, but overall survival is comparable because of transplant-related mortality. Among children with t(8;21), t(9;11), t(15;17), and *inv16*, NPM1, and CEBPA, all favorable molecular features, STC is currently not recommended in first remission (reviewed in 52 studies).

### Acute Promyelocytic Leukemia

When treated with standard AML therapy, children with acute promyelocytic leukemia (APL) fared poorly. Recent regimens intensifying the anthracycline dose and incorporating all-trans retinoic acid (ATRA) early in induction, with mercaptopurine, MTX, and ATRA maintenance therapy led to 5-year survival rates exceeding 80% among children with APL. Early death secondary to coagulopathy, including both hemorrhage and thrombosis, remains a major concern. Because of the success of a recent clinical trial that treated adult patients with APL with retinoic acid and arsenic trioxide alone, the Children's Oncology Group is evaluating the efficacy of using these 2 agents without additional chemotherapy in children. Given the late toxicity of chemotherapy described in the following text, the possibility of avoiding chemotherapy while still maintaining high cure rates is most desirable; however, the late side effects of the combination of ATRA and arsenic are not yet known.

## CHRONIC MYELOGENOUS LEUKEMIA

Chronic myelogenous leukemia (CML) accounts for approximately 3% of childhood leukemias. In children and adults, CML is characterized by the presence of the Ph chromosome. In CML, *BCR-ABL* encodes a 210-kDa dysregulated tyrosine kinase, which is found in more than 90% of childhood and adult CML cases.

Chronic myelogenous leukemia in childhood typically produces leukocytosis, which is marked by the presence of myeloid progenitor cells at all levels of differentiation, and thrombocytosis. Hepatosplenomegaly is present in most children. Symptoms of fatigue, weight loss, bone pain, and low-grade fevers may be present for weeks to months. Most children are diagnosed in the chronic phase with cytogenetic evidence of disease with fewer than 5% blasts in the marrow. Blast crisis is reflective of more advanced disease and is indistinguishable from AML, with the exception of the presence of the Ph chromosome as well as significant splenomegaly.



Until recently, standard therapy for CML in children and adults included hydroxyurea, interferon, and low-dose cytarabine. Although clinical improvements in hematologic parameters were possible with these therapies, cytogenetic remission was uncommon. More recently, imatinib mesylate was developed as a specific inhibitor of the *BCR-ABL* tyrosine kinase. Results from recent clinical trials have rapidly established imatinib as the standard of care for CML. Approximately 60% of patients who are refractory to interferon achieved a major cytogenetic response with imatinib, with infrequent hematologic toxicities. Imatinib is reportedly most effective in patients with chronic-phase CML (76% major cytogenetic response rate reported) compared with the accelerated phase, or blast crisis. A recent phase III prospective trial of more than 1,000 patients conclusively demonstrated that imatinib is superior to interferon- $\alpha$  plus low-dose cytarabine in inducing cytogenetic disease remission and prolonging progression-free survival in adult patients with chronic-phase CML. The effectiveness of imatinib in children with CML in chronic phase was recently reported, with 98% of children achieving a complete hematologic response, 61% achieving a complete cytogenetic response, and 31% achieving a major molecular response at 1 year after initiation of therapy. For children with CML resistant to imatinib, tyrosine kinase inhibitors dasatinib or nilotinib are often effective. Studies are ongoing to assess the use of newer-generation tyrosine kinase inhibitors in children with imatinib-resistant CML.

Imatinib mesylate and the newer-generation tyrosine kinase inhibitors dramatically changed therapy for CML, but do not constitute a cure. The only proven curative strategy for children with CML is allogeneic SCT. Survival after SCT for CML was previously reported to be 70% to 80% with a matched-sibling donor and 40% to 60% when unrelated donors are used. It is likely, with improved supportive care leading to decreased treatment-related mortality, that survival outcomes are now even greater after SCT. Whereas previously SCT was first-line therapy for children with CML, current expert opinion recommends SCT only for children who become refractory to imatinib. In the current era of imatinib mesylate therapy, once-unattainable cytogenetic and molecular remissions are not only possible, but also expected. If newer generation tyrosine kinase inhibitors yield durable remissions for children with imatinib-resistant CML, recommendations for SCT may be delayed further. However, it is important to note the potential need for lifelong treatment and that response to tyrosine kinase inhibitors and control of disease is significantly affected by adherence to therapy.

## JUVENILE MYELOMONOCYTIC LEUKEMIA

Juvenile myelomonocytic leukemia (JMML) is a clonal disorder of early childhood, occurring at a median age of 1.8 years. Hallmarks of the disease at diagnosis include marked hepatosplenomegaly, peripheral blood monocyte count of more than  $1 \times 10^9/L$ , and myeloid precursors in the peripheral blood. Chronic infections, lymphadenopathy, rash (eczema, xanthomas,

café-au-lait spots), and failure to thrive are also common. Association of JMML with several genetic syndromes has been established, including NF1 and Noonan syndrome. Bone marrow aspiration will reveal hypercellularity with a predominance of all stages of granulocyte maturation and a blast count of less than 20%, which is similar to the findings in CML with 1 key exception—patients with JMML do not harbor the Ph chromosome. With the exception of proving that no Ph chromosome is present, bone marrow aspiration is not diagnostic in JMML, as it is in the acute leukemias. The diagnosis of JMML can be made from clinical history and peripheral blood findings, with corroboration from bone marrow findings.

Monosomy 7 can be identified in 25% of children with JMML; 65% will have a normal karyotype. Thirty-five percent of patients will have somatic mutations of *PTPN11*, the gene encoding SHP-2, a tyrosine kinase involved in hematopoietic cell development. *RAS* and *NF-1* mutations have each been identified in 25% of children, and mutations in *CBL* (E3 Ubiquitin ligase) have been identified in 17% of children. Mutations in *PTPN11*, *RAS*, *NF-1*, and *CBL* seem to be mutually exclusive in JMML. Each may independently activate signaling through the *RAS*/MAP kinase-signaling pathway, increasing sensitivity of cells to granulocyte monocyte colony stimulating factor (GM-CSF).

The natural history of JMML, if untreated, is death within a median of approximately 1 year. At an age older than 2 years, thrombocytopenia and high hemoglobin F at diagnosis are all predictors of more aggressive disease. The European Working Group of Myelodysplastic Syndrome in Childhood reported a 5-year event-free survival in approximately 50% of children with JMML transplanted from matched-related and matched-unrelated donors. Treatment failures were primarily a result of disease recurrence within the first year after transplant. The role of conventional chemotherapy in the pretransplant setting or in children without an appropriate donor is not clearly defined. Most European trials typically use mercaptopurine or no therapy, whereas the current Children's Oncology Group trials in the United States administer cytarabine, fludarabine, and retinoic acid. GM-CSF agonists and farnesyltransferase inhibitors are currently being studied, but their role is yet to be defined. Children with JMML and Noonan syndrome may undergo spontaneous resolution, and watchful waiting and close observation are the standard of care.

## MYELODYSPLASIA

Myelodysplastic syndromes (MDS) are clonal disorders of ineffective or abnormal hematopoiesis that often precede AML or aplastic anemia. The most common chromosomal abnormality associated with MDS in children is monosomy 7 (7q-), although monosomy 5 and trisomy 8 are reported as well. Myelodysplastic syndromes may occur spontaneously or after exposure to radiation, epipodophyllotoxin, or alkylators. Diagnosis of the disease is based on identification of dysplastic features in the bone marrow, as well as characteristic cytogenetic abnormalities. Further classification is based on the number of blasts present in the marrow and is used primarily to predict progression

to AML. Acute myelogenous leukemia after contracting MDS is typically more difficult to treat than de novo AML. Currently, the only available therapy for MDS includes supportive care and (SCT). Lenalidomide, a derivative of thalidomide, induces cytogenetic remissions in adults with MDS, and studies are needed to assess the efficacy of lenalidomide in children with MDS.

## MYELOPROLIFERATIVE DISEASES

Current WHO classification of childhood leukemias includes JMML (discussed previously) among the myeloproliferative diseases of childhood. In addition, essential thrombocytosis and polycythemia vera are also reported in children. Newborns with Down syndrome may develop a myeloproliferation syndrome called transient abnormal myelopoiesis, also known as transient myeloproliferative disease, with clinical features that are indistinguishable from AML, including leukocytosis, organomegaly, fevers, and cytopenias with circulating blasts. The blasts typically express megakaryocyte markers and have mutations in GATA1, a transcription factor that is essential for normal hematopoiesis. Although life-threatening complications may occur in a minority of children, most experience spontaneous remission within a few months. Approximately 25% will develop leukemia within 1 to 3 years, and whether transient abnormal myelopoiesis is a malignant disease or a true myeloproliferative syndrome is unclear.

## RELAPSED LEUKEMIAS AND STEM CELL TRANSPLANTATION

### Acute Lymphoblastic Leukemia

Despite development of successful therapies in childhood leukemias, 20% to 25% of children with ALL and 50% of children with AML will relapse after chemotherapy treatment. In fact, more children are diagnosed with relapsed leukemia than Hodgkin disease and pediatric sarcomas. In most children with relapsed leukemia, long-term, event-free survival is less than 50%, even with SCT.

Two reliable predictors of survival after relapse are the duration of the first remission (improved survival after a longer first remission) and phenotype (relapsed B-lineage leukemias are more curable than T-lineage leukemias). According to the BFM group, a very early relapse occurs after a first remission of less than 18 months; an early relapse occurs after a first remission greater than 18 months but less than 6 months after completion of therapy; and a late bone marrow relapse occurs after a first remission of more than 18 months and more than 6 months after completion of therapy. Many centers are recommending systemic chemotherapy without SCT for children with a late relapse.

The Children's Cancer Study Group (CCG) 1900 series of clinical trials were completed between 1997 and 2002, and 4,464 children were treated on ALL trials. Bone marrow relapse occurred in 539 children (12%), CNS relapse in 194 (4%), and testicular relapse in 56 (1.5%). The overall 3-year survival after marrow relapse was 28% and 60% for CNS and testicular

relapse, respectively. Remission reinduction after relapse is relatively good, but overall survival remains poor owing to a deficiency in effective therapies. Most studies comparing SCT to chemotherapy approaches demonstrate an advantage to SCT. However, these studies typically include a significant selection bias (based on donor availability and response to remission reinduction). In 2005, Gaynon published a telling summary of data from the CCG 1941 study. Of a total of 214 children with marrow relapse within 12 months of the completion of primary therapy, approximately 75% achieved second remission. Children who achieved a second remission and who had matched-sibling donors were nonrandomly assigned to receive SCT. The remaining children were randomized to either an alternative donor (unrelated donor or mismatched related donor) transplant or continued chemotherapy. The disease-free survival at 3 years for the children receiving a matched sibling transplant and an unrelated donor transplant are approximately 50%. The 3-year event-free survival for children with a first remission less than 18 months is 4%, 18 to 30 months is 10%, and longer than 30 months is 41%. Most events occur within 6 months of relapse, and less than one-half of the children assigned to unrelated-donor transplants actually made it to transplant in second remission. These results are striking and speak strongly to the need for additional therapies for children with relapsed ALL.

Novel, targeted immunotherapy is currently being evaluated in children with relapsed and refractory ALL. Chimeric antigen receptor-modified T cells are T cells that are engineered to bind tumor cells via specific cell surface antigens, activate T cells upon binding, and induce cell death in the tumor cell. A recent case series in the *New England Journal of Medicine* reported that the CTL019 chimeric antigen receptor-modified T cells, which bind with specificity to common B ALL surface antigen CD19, induced a complete remission in 2 children with very high-risk, relapsed, or refractory ALL. The study showed significant expansion of the effector CTL019 cells in both children, and the engineered T cells were detected in the cerebrospinal fluid, a site where leukemia cells often escape the cytotoxic effects of systemic chemotherapy because of the blood-brain barrier. There is great promise for using chimeric antigen receptor-modified T cells to treat children with ALL not just in the relapsed or refractory setting, but also in children with newly diagnosed leukemia. However, large-scale studies are needed to further assess the safety and efficacy of this treatment modality.

### Acute Myelogenous Leukemia

As is the case with ALL, hematologic relapse remains the most common adverse event in children with AML. Approximately 30% to 40% of children who achieve a remission will relapse, and 25% will have residual disease after intensive induction therapy. Children with AML with high-risk features, such as monosomy 5 or 7 or persistent MRD, often undergo SCT in first remission; nevertheless, as many as 40% to 50% still relapse, and their relapse therapy may be severely limited or complicated by post-transplant toxicities. Remission reinduction rates for all children

with AML in first relapse ranges from 50% to 80% using multiagent chemotherapy. Overall survival after relapses is a dismal 30% to 40%. Although in ALL, a subset of children who relapsed late may still be salvaged with conventional chemotherapy, the only curative alternative for patients with relapsed AML remains SCT.

## PHARMACOGENETICS

Pharmacogenetics is the study of genetic differences in sensitivity of individuals to certain drugs. Genetic polymorphisms in specific genes that are responsible for regulating drug metabolism, transport, and target expression can have a profound effect on both therapeutic and toxic responses to leukemia therapies. Understanding the incidence and implications of polymorphisms affecting drug metabolism and distribution will ultimately help control individual variability in leukemia treatment protocols, with the goal of further reducing toxicity while maximizing efficacy.

### Thiopurine Metabolism

Thiopurine methyltransferase (TPMT) is a key enzyme in the metabolism of azathioprine, 6-mercaptopurine, and thioguanine. One in 300 individuals will have 2 alleles with TPMT polymorphisms, resulting in very low TPMT enzyme activity. Ten percent of individuals will have intermediate enzyme activity, resulting from 1 abnormal allele. Nearly 90% of the population is wild-type and defined as having normal enzyme activity. All patients with low activity, 35% with intermediate activity, and 7% with wild-type activity require 6-MP dose reductions. In terms of survival, not only are higher doses of 6-MP associated with improved outcomes, but defective TPMT metabolism is also associated with a higher incidence of topoisomerase II inhibitor-induced secondary AML and a higher risk of brain tumors in patients who receive concomitant radiation therapy. Commercially available genotype and phenotype analysis of the TPMT enzyme helps guide current thiopurine therapy, but it is still an evolving science and the results need to be interpreted with caution.

### Antifolate Metabolism

Ever since Sidney Farber gave aminopterin to a patient with childhood leukemia, antifolates (MTX eventually replaced aminopterin) have remained essential in the treatment of ALL. Polymorphisms in MTX transport, metabolism, and target expression may all affect leukemia cell sensitivity to MTX and illustrate how multiple polymorphisms may alter efficacy and toxicity of a single drug. The reduced folate carrier (RFC) is an active transport system for MTX. A decrease in RFC expression will lead to a decrease in the amount of MTX that accumulates intracellularly. Though not yet correlated to RFC function, specific RFC polymorphisms are associated with worse outcomes with standard therapy for ALL. MTX is a tight-binding inhibitor of dihydrofolate reductase, and the concentration of MTX required to achieve inhibition of enzyme activity increases in direct proportion to the amount of the enzyme in the target cells. Amplification of the

dihydrofolate reductase gene is seen in 30% of children with relapsed ALL, but only 10% of children with newly diagnosed ALL. Also implicated in survival in pediatric ALL are polymorphisms in other enzymes involved in MTX metabolism, including methylenetetrahydrofolate reductase (an enzyme responsible for the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate) and thymidylate synthase (a target of MTX).

In addition to the enzymes specifically involved in metabolism of MTX and thiopurines, several detoxifying enzyme systems have profound effects on a broader range of chemotherapeutic agents. The cytochrome P450 enzymes are involved in the activation or inactivation of a variety of anticancer agents. Polymorphisms in the cytochrome system have been implicated both in treatment efficacy and in toxicities, including vincristine neuropathies and treatment-related leukemias. Deletions in NR3C1 and BTG1 are associated with leukemia cell resistance to corticosteroids, and are found in a higher percentage of bone marrow samples obtained at the time of relapse compared to initial diagnosis. In addition, the pharmacokinetic interactions between chemotherapeutic agents are actively being uncovered. For example, higher exposure to asparaginase is associated with decreased clearance of dexamethasone, and thus increased leukemia cell exposure to corticosteroids. The combination of higher serum concentrations of both asparaginase and dexamethasone is associated with improved survival.

## LATE EFFECTS OF THERAPY

The successful treatment of childhood leukemias has come with a significant price. Nonetheless, the leukemias represent one of the most curable and common malignancies in childhood, and the number of survivors of childhood leukemia is ever increasing. The long-term side effects of treatment need to be monitored, anticipated, and treated effectively.

### Cognitive Function

Changes in cognitive function after cranial radiation are among the most well-studied side effects of leukemia therapy. Radiation-induced white-matter changes may result in deficits in speed of information processing, potentially progressive decrements in IQ testing, and poor school performance. Age at the time of treatment and total dose of radiation administered are the most reliable predictors of late cognitive effects. Patients receiving cranial radiation who are younger than 5 years of age, and especially younger than 3 years of age, are more susceptible to resultant cognitive deficiencies. Other significant observations include a dose-dependent effect between cognitive deficiencies after 1,800, 2,400, and 3,600 cGy cranial radiation. Accordingly, many recent treatment regimens attempt to eliminate cranial radiation for patients at lowest risk for CNS recurrence and to reduce the dose of radiation to 1,200 or 1,800 cGy for patients at highest risk for CNS recurrence. Pui and colleagues recently reported that cranial irradiation can potentially be eliminated for all patients with ALL while maintaining high cure rates. Intensifying intrathecal



therapy has proven to be effective prophylaxis against CNS recurrence while maintaining baseline long-term cognitive function; however, the late side effects of intensified intrathecal chemotherapy are not yet understood.

### Cardiac Effects

Anthracyclines will likely remain a crucial component of effective therapy for ALL and AML. The incidence and severity of cardiac toxicity relates to the cumulative dose of anthracycline; concomitant use of mediastinal radiation, cyclophosphamide, or ifosfamide; and younger age at diagnosis. Most current treatment regimens in childhood cancer are capped at a total cumulative anthracycline dose of 350 to 400 mg/m<sup>2</sup> to reduce late cardiac toxicities. Most ALL treatment regimens do not approach this level; however, increased risk of cardiotoxicity is seen at doses as low as 100 to 150 mg/m<sup>2</sup>. Polymorphisms in the CBR3 are associated with increased risk of cardiotoxicity with low doses of anthracyclines. In addition to cumulative doses, female gender and young age at diagnosis are also associated with a higher risk of late cardiac toxicities. Cardiac toxicities usually affect function, and may be asymptomatic until years after completion of therapy, usually exhibiting at times requiring rapid increases in cardiac output (eg, puberty, pregnancy, weight training). After a median of 450 mg/m<sup>2</sup> of anthracycline, a reported 23% of children have echocardiographic abnormalities 7 years after treatment. Children receiving high cumulative doses of anthracycline should maintain diligent follow-up, especially if echocardiographic abnormalities are detected before completion of therapy. The Children's Oncology Group recommends the frequency of cardiac monitoring with echocardiogram and electrocardiogram be based on the dose of anthracyclines administered and the child age at the time of treatment.

### Endocrine Effects

Craniospinal radiation may reduce adult standing height, resulting from both deficient growth of the vertebral bodies after spinal radiation and growth hormone deficiency after cranial radiation. Reduction in the dose of cranial radiation has reduced the incidence of growth hormone deficiency in survivors of childhood leukemia. For some children, growth hormone supplementation may be necessary and effective. Referral for an endocrine evaluation should be considered for all survivors of childhood leukemia with short stature or early puberty. Poor bone health, including osteoporosis and osteonecrosis, after corticosteroid administration is another significant problem that may affect growth and cause physical impairment.

Infertility is a rare side effect of ALL therapy and can occur secondary to chemotherapy (especially with alkylator-based regimens) and radiation (especially in boys who required testicular radiation). Abnormal gonadal development and function may result from direct damage to the gonads after radiation or to the hypothalamic-pituitary axis after cranial radiation. In a study of 60 survivors of ALL, Sklar and colleagues identified significant germ cell dysfunction (increased

follicle-stimulating hormone and reduced testicular volume) in 55% of children treated with testicular radiation and 17% of children treated with craniospinal radiation. Leydig cell function was relatively preserved. Total alkylator dose and age at diagnosis are other predictors of fertility after treatment.

### Second Malignant Neoplasms

The risk and development of a second malignancy is a devastating side effect of both chemotherapy and radiation therapy for childhood ALL, although the risk is significantly less than that reported for other childhood malignancies. The cumulative incidence of any second neoplasm in survivors of childhood leukemia is reportedly 1.18% at 10 years (95% confidence interval is 0.8%–1.5%), which is a 7.2-fold increased risk above the general population, and the 25-year cumulative incidence is 5.2%. Cranial radiation, relapse, and female gender have all been associated with an increased risk for developing a second malignancy. Secondary leukemias and myelodysplasia, soft-tissue sarcomas, brain tumors, and solid tumors are all reported, although secondary CNS malignancies are the most common in children who received cranial spinal radiation. Deficiencies in TPMT may predispose children to secondary brain tumors. In a protocol incorporating high doses of antimetabolites, the 8-year cumulative incidence of secondary brain tumors among TPMT-deficient children was 43%. Children with normal TPMP activity had an 8-year cumulative incidence of secondary brain tumors of 8.3%. This exceptionally high incidence of secondary brain tumors in both groups likely reflects the concomitant use of cranial radiation and high-dose antimetabolites.

Identification of the possible late side effects of leukemia therapy has been key in the development of risk-stratified therapy. Reducing cumulative doses of agents with significant short- and long-term side effects while maintaining excellent cure rates in children with ALL is one of the great triumphs of oncology clinical trials. As more is learned, future therapies may take into account not only the biological features of the leukemia that are predictive of chemoresponsiveness, but also the host factors that determine risk for acute and long-term toxicities.

### CONCLUSIONS

Treatment of childhood leukemias is widely touted as a great success in oncology clinical trials, largely because of the continued incremental increases in long-term survival in children with ALL. Significant challenges still lay ahead as we define new strategies for treating AML and relapsed leukemias, as well as the myeloproliferative and myelodysplastic disorders. Application of risk-adapted therapy to patients with ALL and AML has allowed for continued improvement in long-term event-free survival and a reduction in long-term side effects. What has been learned about leukemia biology, host pharmacogenetics, and environmental influences on leukemia development has led to the development of effective treatment for childhood leukemias. The next frontier in cancer therapy in general, and leukemia therapy specifically, is targeted treatment plans based on leukemia cell and host



genetics. Imatinib mesylate and FLT3–targeted therapies are early examples of such approaches, but there is still a significant amount of work to be done to apply genomics to all leukemias in all children.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Childhood Cancer* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/cancer/Pages/Childhood-Cancer.aspx](http://www.healthychildren.org/English/health-issues/conditions/cancer/Pages/Childhood-Cancer.aspx))
- *Leukemia in Children* (Web page), American Cancer Society ([www.cancer.org/cancer/leukemiainchildren/index](http://www.cancer.org/cancer/leukemiainchildren/index))

### AAP POLICY

- American Academy of Pediatrics Section on Hematology/Oncology. Guidelines for pediatric cancer centers. *Pediatrics*. 2004;113(6):1833–1835. Reaffirmed May 2008 ([pediatrics.aappublications.org/content/113/6/1833](http://pediatrics.aappublications.org/content/113/6/1833))
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## Chapter 286 LIPID ABNORMALITIES

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A pediatrician must consider multiple factors when assessing a child's global risk for premature cardiovascular disease. Other chapters in this text cover

general aspects of screening, the physical examination, and specific diagnoses, such as hypertension (see Chapter 163, High Blood Pressure), heart failure (see Chapter 361, Heart Failure), and congenital and acquired heart disease (see Chapter 234, Congenital and Acquired Heart Disease). This chapter describes 3 major topics that should be routinely addressed when assessing children and adolescents for the risks of cardiovascular disease, especially those with lipid abnormalities: (1) atherosclerosis, (2) obesity, and (3) smoking with a focus on atherosclerosis. The behavioral recommendations to patients and families, screening tests, and practice guidelines needed to provide care are summarized to serve as a quick reference for any preventive care consultation.

### ATHEROSCLEROSIS

Atherosclerosis continues to be a leading cause of death and disability in the United States. Although myocardial infarction, stroke, and other manifestations of atherosclerosis usually occur in adults, evidence is mounting that pathogenesis begins much earlier. Furthermore, overwhelming epidemiologic evidence has established that atherosclerosis is not an inevitable consequence of aging but rather, in many cases, an acquired disease with well-described risk factors that begins in childhood. Many risk factors for heart disease are beyond the control of the individual; some, such as hyperlipidemia and level of physical activity, can be modified; and at least one factor—smoking—is completely avoidable. A goal of pediatric primary care is to prevent the development of cardiovascular risk factors and the associated cardiovascular diseases to reduce their morbidity and mortality. Several risk factors for coronary heart disease are now easily identified during childhood, and evidence-based recommendations to begin prevention in childhood have been developed. Because the process of atherosclerosis and the habits that influence the risk for heart disease begin early in life, preventive measures should be initiated during childhood (see Table 286-1).

The known risk factors for atherosclerosis include hypertension, smoking, elevated low-density lipoprotein cholesterol (LDL-C), decreased high-density lipoprotein cholesterol (HDL-C), diabetes mellitus, advancing age, male sex, a family history of premature heart disease, hypertriglyceridemia, sedentary lifestyle, and obesity. Primary prevention in childhood should seek to eliminate or minimize these risk factors. A relatively new concept, “primordial prevention,” also challenges health care providers to address the social and environmental conditions that create and maintain the risk factors themselves. Changing these systemic conditions is particularly important in controlling obesity, smoking, and sedentary lifestyles.

A classic study by Enos, Beyer, and Holmes of military personnel killed in the Korean War illustrates the importance of early influence of environmental factors. The study revealed that young American soldiers had a 77% incidence of coronary arterial lesions, whereas such lesions were virtually nonexistent among young Korean soldiers. This study not only described the early beginnings of the atherosclerotic

## Table 286-1

		AGE				
RISK FACTOR	BIRTH TO 12 MO	1-4 Y	5-9 Y	9-11 Y	12-17 Y	18-21 Y
		At 3 y, evaluate family history for early CVD: parents, grandparents, aunts/uncles, men $\leq 55$ y old, women $\leq 65$ y old; review with parents and refer as needed; positive family history identifies children for intensive CVD RF attention	Update at each nonurgent health encounter	Reevaluate family history for early CVD in parents, grandparents, aunts/uncles, men $\leq 55$ y old, women $\leq 65$ y old	Update at each nonurgent health encounter	Repeat family-history evaluation with patient
Tobacco exposure	Advise smoke-free home; offer smoking-cessation assistance or referral to parents	Continue active antismoking advice with parents; offer smoking-cessation assistance and referral as needed	Obtain smoke exposure history from child Begin active antismoking advice with child	Assess smoking status of child; active antismoking counseling or referral as needed	Continue active antismoking counseling with patient; offer smoking-cessation assistance or referral as needed	Reinforce strong antismoking message; offer smoking-cessation assistance or referral as needed
Nutrition/diet	Support breastfeeding as optimal to 12 mo of age if possible; add formula if breastfeeding decreases or stops before 12 mo of age	At age 12-24 mo, may change to cow's milk with 2% percentage of fat decided by family and pediatric care provider; after 2 y of age, fat-free milk for all; juice $\leq 4$ oz/d; transition to CHILD-1 diet by the age of 2 y	Reinforce CHILD-1 diet messages	Reinforce CHILD-1 diet messages as needed	Obtain diet information from child and use to reinforce healthy diet and limitations and provide counseling as needed	Review healthy diet with patient
Growth, overweight/obesity	Review family history for obesity; discuss weight-for-height tracking, growth chart, and healthy diet	Chart height/weight/BMI; classify weight-by BMI from age 2 y; review with parent	Chart height/weight/BMI and review with parent; BMI $\geq 85$ th percentile, crossing percentiles: Intensify diet/activity focus for 6 mo; if no change: RD referral, manage per obesity algorithms <sup>a</sup>	Chart height/weight/BMI and review with parent and child; BMI $\geq 85$ th percentile, crossing percentiles: Intensify diet/activity focus for 6 mo; if no change: RD referral, manage per obesity algorithms <sup>a</sup>	Chart height/weight/BMI and review with child and parent; BMI $\geq 85$ th percentile, crossing percentiles: intensify diet/activity focus for 6 mo; if no change: RD referral, manage per obesity algorithms <sup>a</sup>	Review height/weight/BMI and norms for health with patient; BMI $\geq 85$ th percentile, crossing percentiles: intensify diet/activity focus for 6 mo; if no change: RD referral, manage per obesity algorithms <sup>a</sup>

Table 286-1 Integrated Cardiovascular Health Schedule—cont'd

		AGE				
RISK FACTOR	BIRTH TO 12 MO					
		1-4 Y	5-9 Y	9-11 Y	12-17 Y	18-21 Y
Lipids	No routine lipid screening	Obtain FLP only if family history for CVD is positive, parent has dyslipidemia, child has any other RFs or high-risk condition	Obtain FLP only if family history for CVD is positive, parent has dyslipidemia, child has any other RFs or high-risk condition	Obtain universal lipid screen with nonfasting non-HDL = TC – HDL, or FLP: manage per lipid algorithms <sup>a</sup> as needed	Obtain FLP if family history newly positive, parent has dyslipidemia, child has any other RFs or high-risk condition; manage per lipid algorithms <sup>a</sup> as needed	Measure 1 nonfasting non-HDL or FLP in all: review with patient; manage with lipid algorithms <sup>a</sup> per ATP as needed
BP	Measure BP in infants with renal/urologic/cardiac diagnosis or history of neonatal ICU	Measure BP annually from the age of 3 y; chart for age/gender/height percentile and review with parent	Check BP annually and chart for age/gender/height: review with parent; workup and/or management per BP algorithm <sup>a</sup> as needed	Check BP annually and chart for age/gender/height: review with parent; workup and/or management per BP algorithm <sup>a</sup> as needed	Check BP annually and chart for age/gender/height: review with adolescent and parent; workup and/or management per BP algorithm <sup>a</sup> as needed	Measure BP: review with patient; evaluate and treat per JNC guidelines <sup>a</sup>
Physical activity	Encourage parents to model routine activity; no screen time before the age of 2 y	Encourage active play; limit sedentary/screen time to ≤2 h/d; no TV in bedroom	Recommend MVPA of ≥1 h/d; limit screen/sedentary time to ≤2 h/d	Obtain activity history from child: recommend MVPA of ≥1 h/d and screen/sedentary time of ≤2 h/d	Use activity history with adolescent to reinforce MVPA of ≥1 h/d and leisure screen time of ≤2 h/d	Discuss lifelong activity, sedentary time limits with patient
Diabetes	—	—	—	Measure fasting glucose level per ADA guidelines <sup>a</sup> refer to endocrinologist as needed	Measure fasting glucose level per ADA guidelines <sup>a</sup> refer to endocrinologist as needed	Obtain fasting glucose level if indicated; refer to endocrinologist as needed

ADA, American Diabetes Association; ATP, Adult Treatment Panel III ("Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults"); JNC, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; MVPA, moderate-to-vigorous physical activity; RD, registered dietitian; RF, risk factor

<sup>a</sup>All algorithms and guidelines mentioned in this schedule are included in the summary report. The full and summary reports of the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents can also be found on the National Heart, Lung, and Blood Institute Web site ([www.nhlbi.nih.gov](http://www.nhlbi.nih.gov)). From Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: summary report. *Pediatrics*. 2011;128(suppl 5):S213–S256. Available at: [pediatrics.aappublications.org/content/128/Supplement\\_5/S213](http://pediatrics.aappublications.org/content/128/Supplement_5/S213).

process but also suggested the importance of dietary and lifestyle modifiers in its development. Similarly, the Bogalusa Heart Study and the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study group showed that risk factors, such as cholesterol levels and smoking, contribute to the formation of atherosclerosis in a graded manner and that these factors are present in children and young adults long before the onset of clinical heart disease. In addition, several large studies, including the Bogalusa, Louisiana study and others in Australia and Finland, using carotid intima media thickness as a noninvasive measure of atherosclerosis, have established that dyslipidemia in childhood correlates with dyslipidemia in adulthood.

Hypercholesterolemia is a primary target for preventing atherosclerosis. Total cholesterol measures the cholesterol contained in several lipid particles, including LDL-C, HDL-C, and very-low-density lipoprotein cholesterol (VLDL-C). Whereas LDL-C is one of the atherogenic lipoproteins and receives the focus for screening algorithms, HDL-C protects against the development of coronary heart disease.

Both genetic and environmental factors are important in the development of hypercholesterolemia. Plasma cholesterol levels are influenced by the quantity and quality of dietary fat intake and by the individual's ability to synthesize and degrade cholesterol. Severe or familial hypercholesterolemia secondary to a defect in the LDL receptor occurs in approximately 1 in 500 individuals. Children with this inherited defect commonly have LDL-C values between 200 and 300 mg/dL, which is 2 to 3 times higher than the acceptable limits of normal (see Table 286-2). These children have a strong predilection for atherosclerotic heart disease as young adults. More than 600 different mutations of the LDL receptor have been described. Approximately 50% of men who have one of these mutations will have a myocardial infarction by age 50 years, and between 75% and 85% will have a myocardial infarction by age 60 years. Approximately 50% of women will develop ischemic heart disease by age 60 years. Fortunately, even in these high-risk patients, treatment can decrease the incidence of heart disease.

In 1991, the National Cholesterol Education Program (NCEP) issued guidelines for preventing heart disease in children. In 1998, the American Academy of Pediatrics (AAP) published a revised statement that

included additional scientific justifications for emphasizing cholesterol screening and treatment. In 2002, the American Heart Association (AHA) issued a scientific statement supporting the NCEP's guidelines for both screening and treatment strategies that included a comprehensive and easy-to-follow review of other key areas in preventive cardiology. In 2008, the AAP revised its policy statement, which emphasizes screening overweight children and that proposes a lower age for pharmacologic treatment. The National Heart, Lung, and Blood Institute (NHLBI) created an Expert Panel to perform a systematic review of the evidence and issue new comprehensive guidelines for cardiovascular health, which were published in 2011 and endorsed by the AAP. The most recent adult guidelines, which transitioned ownership from the NHLBI's NCEP to the AHA and American College of Cardiology, limit their conclusion to those aged 21 years or older. Readers interested in an in-depth evaluation of the pertinent topics in preventive cardiology are referred to the NHLBI Expert Panel summary report.

### Recommendations for Cholesterol Screening

The 2007 report by the United States Preventive Services Task Force, despite good evidence for dyslipidemia tracking from childhood into adulthood, concluded that this evidence was insufficient to recommend for or against screening of lipid disorders in children and adolescents. The NHLBI Expert Panel suggests 2 separate approaches to hypercholesterolemia screening in children: a broad, population-based approach, and an individualized patient approach. The NHLBI Expert Panel was concerned that 30% to 60% of dyslipidemic children are missed, and has issued a significant change to screening, as discussed in the next section.

### Population Screening and Prevention

The NHLBI Expert Panel recommends universal screening at one time between the ages of 9 and 11 years and again between ages 17 and 21 years with either a random non-HDL cholesterol level (total cholesterol minus HDL-C) or a fasting LDL-C. For the remainder of children, the panel suggests that all children older than 2 years of age follow the CHILD-1 Diet, which is relatively low in fat: no more than 30% of total calories should come from fat, less than 10% of total calories should come from saturated

**Table 286-2**

**Classification of Total and Low-Density Lipoprotein Cholesterol Levels in Children and Adolescents From Families With Hypercholesterolemia or Premature Cardiovascular Disease**

CATEGORY	TOTAL CHOLESTEROL (MG/DL)	LOW-DENSITY LIPOPROTEIN CHOLESTEROL (MG/DL)
Acceptable	<170	<110
Borderline	170–199	110–129
High	≥200	≥130

From American Academy of Pediatrics. National Cholesterol Education Program. Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics*. 1992;89(3 Pt 2):525–584.



fat, and total cholesterol consumption should be less than 300 mg per day. This diet should contain a variety of foods and should be adequate to support growth and maintain an ideal body weight for height and age. In 2009, a consensus statement issued by the AHA and endorsed by the AAP contained more detailed dietary recommendations for all children (see Box 286-1, Box 286-2). Overall, the population approach attempts to “shift the distribution” and reduce exposure throughout the population, the hallmark activity of public health, with pediatricians being a vital part of this reduction (see Table 286-3).

### Individualized Screening

In addition to population-wide screening and dietary recommendations, the guidelines suggest risk assessment and cholesterol testing in children older than 2 years of age with a family history of atherosclerotic disease, that is, whose parent or grandparent has or had premature coronary heart disease, defined as onset of disease before age 56 years. Conditions suggesting heart disease in families include documented myocardial infarction, angina pectoris, peripheral vascular disease, cerebrovascular disease, or sudden cardiac death, as well as coronary atherosclerosis as determined by angiography or by a history of balloon angioplasty or coronary artery bypass graft surgery. In addition, children who have a parent with hypercholesterolemia (total cholesterol  $\geq 240$  mg/dL) also should be screened. Children whose parental history is unknown or unobtainable, especially if they have other risk factors, may also be screened to identify those in

need of nutritional advice. Parents with unknown cholesterol levels should be encouraged to obtain a full lipoprotein analysis (a lipid profile). Cholesterol levels may also need to be determined for children at higher risk for coronary heart disease independent of family history (eg, children who smoke, are obese, have diets rich in saturated fats and cholesterol, or have diabetes mellitus). For children with a family history of premature heart disease and with personal risk factors listed above, the guidelines suggest obtaining a fasting lipid profile that includes total cholesterol, LDL-C, HDL-C, and triglycerides once between 2 and 8 years of age and again between 12 and 16 years of age if the initial screening is normal and the child is not already under treatment, or if any risk factors are newly discovered or present at time of subsequent clinical encounter.

The NHLBI Expert Panel endorsed a risk stratification and treatment algorithm for children at increased risk for premature coronary heart disease. Children needing special consideration for cardiovascular risk factors are those with homozygous or heterozygous familial hypercholesterolemia, diabetes mellitus (type 1 or 2), chronic kidney disease or end-stage renal disease, Kawasaki disease, congenital heart disease, and chronic inflammatory disease, and survivors of transplant surgery or cancer treatment. Children with these

#### BOX 286-1 American Heart Association Recommended Pediatric Dietary Strategies for Parents and Families With Children Older Than 2 Years

- Balance caloric intake with physical activity to maintain normal growth.
- Engage in 60 minutes of moderate to vigorous play or physical activity daily.
- Eat vegetables and fruits daily and limit juice intake.
- Use vegetable oils and soft margarines low in saturated fat and trans fatty acids instead of butter or most other animal fats in the diet.
- Eat whole-grain breads and cereals rather than refined grain products.
- Reduce the intake of sugar-sweetened beverages and foods.
- Use nonfat (skim) or low-fat milk and dairy products daily.
- Eat more fish, especially oily fish, broiled or baked.
- Reduce salt intake, including salt from processed foods.

From Gidding SS, Lichtenstein AH, Faith MS, et al. Implementing American Heart Association Pediatric and Adult Nutrition Guidelines. *Circulation*. 2009;119:1161–1175. © American Heart Association, Inc. Reprinted with permission.

#### BOX 286-2 Tips for Parents to Implement the American Heart Association Pediatric Dietary Guidelines

- Reduce added sugars, including sugar-sweetened drinks and juices.
- Use canola, soybean, corn, safflower, or other unsaturated oils in place of solid fats when preparing food.
- Use the recommended portion sizes given on food labels when preparing and serving food.
- Use fresh, frozen, and canned vegetables and fruits and serve at every meal; be careful with added sauces and sugar.
- Introduce and regularly serve fish as an entrée.
- Remove the skin from poultry before eating.
- Use only lean cuts of meat and reduced-fat meat products.
- Limit high-calorie sauces such as Alfredo, cream sauces, cheese sauces, and Hollandaise.
- Eat whole-grain breads and cereals rather than refined produces; read the labels to ensure that *whole grain* is the first ingredient on the food label of these products.
- Eat more legumes (beans) and tofu in place of meat for some entrées.
- Breads, breakfast cereals, and prepared food, including soups, may be undesirably high in salt or sugar or both; read food labels for content, and choose high-fiber, low-salt, low-sugar alternatives.

From Gidding SS, Lichtenstein AH, Faith MS, et al. Implementing American Heart Association Pediatric and Adult Nutrition Guidelines. *Circulation*. 2009;119:1161–1175. © American Heart Association, Inc. Reprinted with permission.

**Table 286-3** Cardiovascular Health Integrated Lifestyle Diet (CHILD) Macronutrient Recommendations for Age 12 Months or Older

NUTRIENT	CHILD-1	CHILD-2
Calories	Adequate for normal growth	
Total fat	≤30% of calories	Same
Saturated fat	<10% of calories	≤7%
Polyunsaturated fat	Up to 10% of calories	Same
Monounsaturated fat	Remainder of fat calories	Same
Carbohydrates	Approximately 55% of calories	Same
Protein	Approximately 15%–20% of calories	Same
Cholesterol (mg/day)	<300	<200

Data from Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: summary report. *Pediatrics*. 2011;128(suppl 5):S213–S256.

**Table 286-4** Classification of Children at High Risk for Cardiovascular Disease: Condition-Specific Treatment Recommendations

RISK	RATIONALE	DISEASE PROCESS OR CONDITION
Tier I: high risk	Manifest coronary artery disease before age 30 years; clinical evidence	<ul style="list-style-type: none"> <li>• Homozygous familial hypercholesterolemia</li> <li>• Diabetes mellitus, type 1</li> <li>• Chronic kidney disease or end-stage renal disease</li> <li>• Postorthotopic heart transplantation</li> <li>• Kawasaki disease with current coronary aneurysms</li> </ul>
Tier II: moderate risk	Accelerated atherosclerosis: pathophysiologic evidence	<ul style="list-style-type: none"> <li>• Heterozygous familial hypercholesterolemia</li> <li>• Kawasaki disease with regressed coronary aneurysms</li> <li>• Diabetes mellitus, type 2</li> <li>• Chronic inflammatory disease</li> </ul>
Tier III: at risk	High-risk setting for accelerated atherosclerosis: epidemiologic evidence	<ul style="list-style-type: none"> <li>• Cancer treatment survivor</li> <li>• Congenital heart disease</li> <li>• Kawasaki disease without detected coronary involvement</li> </ul>

From Kavey R-EW, Allada V, Daniels SR, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: Endorsed by the American Academy of Pediatrics. *Circulation*. 2006;114(24):2710–2738. © American Heart Association, Inc. Reprinted with permission.

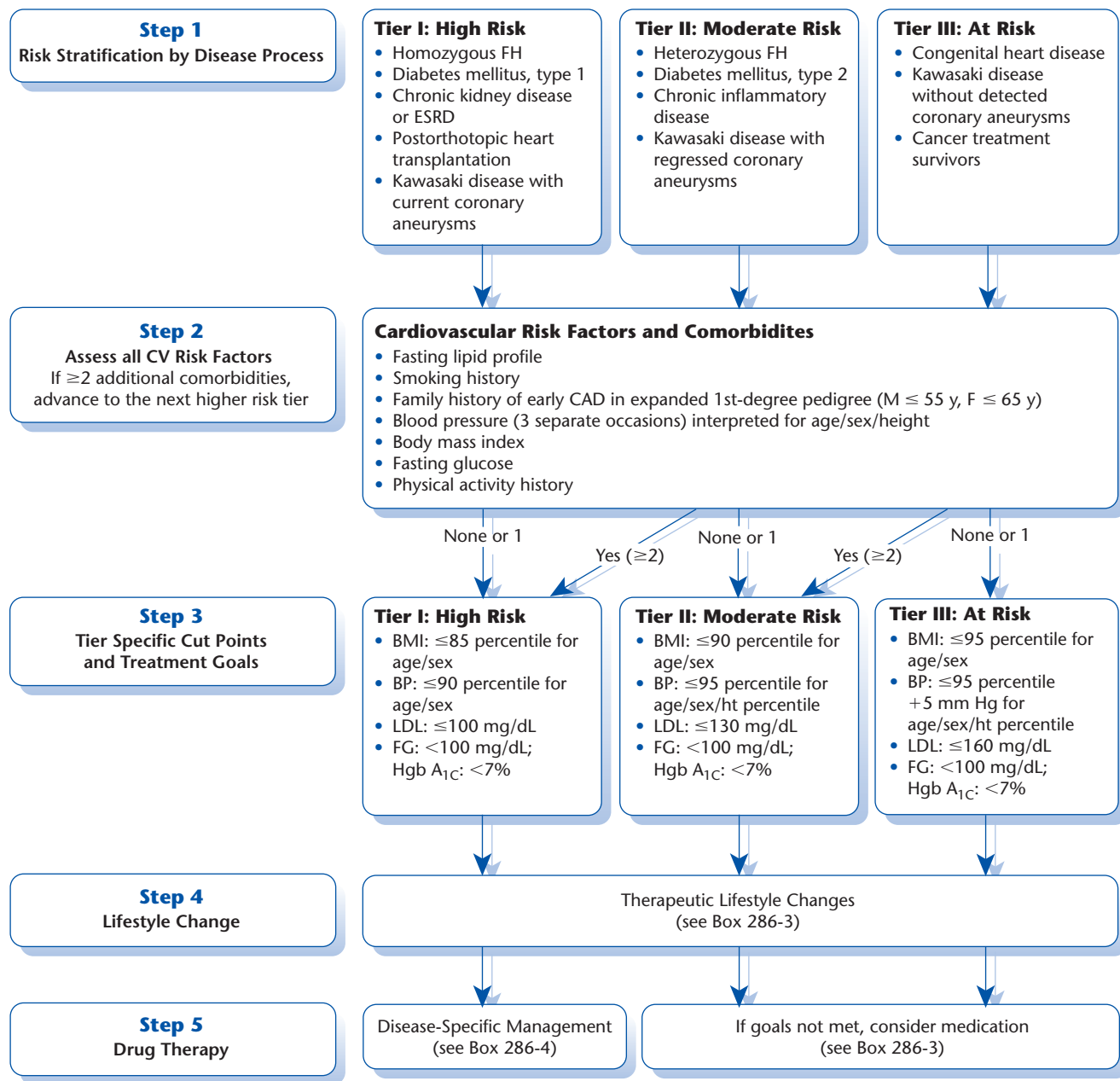
conditions are categorized into 3 tiers (see Table 286-4). An algorithm for screening with tier-specific cutoff values is provided (see Figure 286-1). Also included (see Box 286-3) are therapeutic goals for all tiers, as well as condition-specific recommendations for children in the highest tier, tier I (see Box 286-4).

### Recommendations for Treatment

Most of the information regarding the risk for heart disease in adults is based on fasting LDL-C values; therefore, recommendations for children are also based on fasting LDL-C values. Because cholesterol standards vary by age, treatment values are based on percentile ranks of children in the United States that exceed the upper norms. A total cholesterol level

greater than 200 mg/dL and an LDL-C level greater than 130 mg/dL represent values above the 95th percentile for children and are designated as high. A total cholesterol level less than 170 mg/dL and an LDL-C level less than 110 mg/dL represent values below the 75th percentile and are acceptable. Values between these limits are considered borderline (see Table 286-2).

All of these cutoff values were approved by consensus of the NCEP Expert Panel on Blood Cholesterol Levels in Children and Adolescents and are based on data published in 1980 from the Lipid Research Clinics Prevalence Study from children ranging from 1 to 19 years of age for total cholesterol and from 5 to 19 years of age for LDL-C. The NHLBI Expert Panel



**Figure 286-1** High-risk pediatric populations: risk stratification and treatment algorithm. Directions: Step 1: Risk stratification by disease process (see Table 286-4). Step 2: Assess all cardiovascular risk factors. If two or more comorbidities exist, then assign patient to the next higher risk tier for subsequent management. Step 3: Tier-specific intervention cut points or treatment goals defined. Step 4: Initial therapy: for tier I, initial management is therapeutic lifestyle change (see Box 286-3) plus disease-specific management (see Box 286-4). For tiers II and III, initial management is therapeutic lifestyle change (see Box 286-3). Step 5: for tiers II and III, if goals are not met after initial management, consider medication as outlined in Box 286-3.

BP, Blood pressure; CAD, coronary artery disease; CV, cardiovascular; ESRD, end-stage renal disease; FG, fasting glucose; FH, familial hypercholesterolemia; Hgb A<sub>1C</sub>, hemoglobin A<sub>1C</sub>; ht, height; LDL, low-density lipoprotein.

(Modified from Kavey R-EW, Allada V, Daniels SR, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation*. 2006;114(24):2710-2738. © American Heart Association, Inc. Reprinted with permission.)

### BOX 286-3 Treatment Recommendations for Children at High Risk for Cardiovascular Disease, by Indication

#### GROWTH AND DIET

- Nutritionist evaluation, diet education for all (see Step 1 Diet recommendations in Table 286-3)
- Calculate body mass index (BMI) percentile for sex and height. Normal BMI values for age and sex are available at [www.cdc.gov/growthcharts](http://www.cdc.gov/growthcharts)
- If initial body mass index is >95th percentile:
  - Age-appropriate, reduced-calorie training for child and family
  - Specific diet and weight follow-up every 2 to 4 weeks for 6 months; repeat body mass index calculation at 6 months
  - Activity counseling (see ACTIVITY)
- If follow-up body mass index is >85th percentile for tier I, >90th percentile for tier II, or >95th percentile for tier III:
- Referral to weight-loss and exercise training programs appropriate for cardiac status

#### BLOOD PRESSURE (TIERS I, II, AND III)

- Blood pressure measurement or interpretation for age, sex, and height
  - If SBP or DBP is between the 90th and 95th percentiles or BP is >120/80 mm Hg (on 3 separate occasions within 1 month):
    - Recommend decreased calorie intake and increased activity for 6 months.
  - If initial SBP or DBP is >95th percentile (confirmed within 1 week) or 6-month follow-up or SBP or DBP is >95th percentile:
    - Initiate pharmacologic therapy per Fourth Task Force recommendations.

#### LIPIDS

- Low-density lipoprotein cholesterol, LDL-C (tiers II and III)
- See Box 286-4 for recommendations for LDL-C in tier I.
- If initial LDL-C is  $\geq 130$  mg/dL (tier II) or >160 mg/dL (tier III):
  - Nutritionist training for Step 2 Diet (see Table 286-3) along with avoiding trans fats for 6 months
- If repeat LDL-C is  $\geq 130$  mg/dL in tier II or >160 mg/dL in tier III and the child is older than 10 years:
  - Initiate statin therapy with LDL-C goal of 130 mg/dL.

#### TRIGLYCERIDES

- If initial triglyceride levels are between 150 and 400 mg/dL:
  - Nutritionist training for low-simple-carbohydrate, low-fat diet
  - If elevated triglycerides are associated with excess weight, nutritionist referral for weight loss

management: energy balance training plus activity recommendations (see ACTIVITY)

- If triglycerides are between 700 and 1,000 mg/dL, initial or follow-up:
  - Consider fibrate or niacin if >10 years of age. (Triglyceride levels  $\geq 1,000$  mg/dL are associated with substantial risk for acute pancreatitis. A fasting triglyceride of 700 mg/dL is likely to rise to >1,000 mg/dL postprandially. Treatment recommendations are congruent with those for managing dyslipidemia in diabetic children.
  - Weight loss is recommended when elevated triglycerides occur with overweight or obesity.

#### GLUCOSE (TIERS I, II, AND III, EXCEPT FOR PATIENTS WITH DIABETES MELLITUS)

- If fasting glucose is between 100 and 126 mg/dL:
  - Recommend reduced-calorie diet, increased activity aimed at 5% to 10% decrease in weight over 6 months.
- If repeat fasting glucose is between 100 and 126 mg/dL:
  - Recommend insulin-sensitizing medication as per endocrinologist.
- A casual glucose >200 mg/dL or a fasting glucose >126 mg/dL indicates diabetes mellitus. Refer to endocrinology for evaluation and management.
- Maintain hemoglobin HbA1c <7%.

#### SMOKING (TIERS I, II, AND III)

- Obtain parental smoking history at every visit; child smoking history beginning at age 10. Provide active antismoking counseling for all; smoke-free home strongly recommended at each encounter.
- Provide smoking cessation referral for any history of cigarette smoking.

#### ACTIVITY (TIERS I, II, AND III)

- For children in all tiers, participation in activity is at the discretion of the physician(s) directing care. For specific cardiac diagnoses, such as Kawasaki disease and congenital heart disease, activity guidelines are referenced in Box 286-4.
  - Obtain specific activity history for the child, focusing on time spent in active play and screen time (television + computer + video game times). Goal is  $\geq 1$  hour of active play per day; screen time limited to  $\leq 2$  hours/day.
- Encourage activity at every encounter.
  - After 6 months, if goals are not met, consider referral for exercise testing and recommendations from exercise specialist.

Specific treatment goals for each risk factor and each tier are given in the algorithm (see Figure 286-1).

BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

From Kavey R-EW, Allada V, Daniels SR, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation*. 2006;114(24):2710-2738. © American Heart Association, Inc. Reprinted with permission.



### BOX 286-4 High-Risk Stratification for Cardiovascular Disease: Treatment Recommendations for Tier-I Conditions

- Rigorous, age-appropriate education in diet, activity, and smoking cessation for all patients.
- Specific therapy as needed to achieve BP, LDL-C, glucose, and HbA1c goals as indicated for each tier outlined in the algorithm (Figure 286-1); timing should be individualized for each patient and diagnosis. Step 1 and step 2 therapy for all outlined in Box 286-3.

#### HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

- LDL management: scheduled apheresis every 1 to 2 weeks beginning at diagnosis to maximally lower LDL-C, plus statin and cholesterol absorption inhibitor.
- Prescription per cardiologist or lipid specialist. (Specific therapeutic goals for LDL-C are not meaningful with this diagnosis.)
- Assess body mass index, blood pressure, and fasting glucose: step 1 management for 6 months.
- If tier I goals are not achieved, proceed to step 2.

#### DIABETES MELLITUS, TYPE 1

- Intensive glucose management by endocrinologist, with frequent glucose monitoring or insulin titration to maintain plasma glucose levels <200 mg/dL and HbA1c <7%.
- Assess body mass index, BP, fasting lipids: step 1 management of weight, lipids for 6 months.
- If goals not achieved, proceed to step 2; statin prescription if >10 years of age to achieve tier I treatment goals.
- If initial BP is >90th percentile: step 1 management plus no added salt, increased activity for 6 months.

- BP consistently >95th percentile for age, sex, and height: initiate angiotensin-converting enzyme inhibitor therapy with BP goal <90th percentile or <130/80 mm Hg, whichever is lower.

#### CHRONIC KIDNEY DISEASE OR END-STAGE RENAL DISEASE

- Optimize renal failure management with dialysis or transplantation as per nephrologist.
- Assess body mass index, BP, lipids, fasting glucose: step 1 management for 6 months.
- If goals not achieved, proceed to step 2; statin prescription if >10 years of age to achieve tier I treatment goals.

#### AFTER HEART TRANSPLANTATION

- Optimize antirejection therapy, treatment for cytomegalovirus, routine evaluation by angiography or perfusion imaging per transplant physician.
- Assess body mass index, BP, lipids, fasting glucose; initiate step 2 therapy, including statins, immediately in all patients older than 1 year of age to achieve tier I treatment goals.

#### KAWASAKI DISEASE WITH CORONARY ANEURYSMS

- Antithrombotic therapy, activity restriction, ongoing myocardial perfusion evaluation as per cardiologist.
- Assess body mass index, BP, lipids, fasting glucose: step 1 management for 6 months.
- If goals not achieved, proceed to step 2; prescribe statins if older than 10 years of age to achieve tier I treatment goals.

BP, blood pressure; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol.

From Kavey R-EW, Allada V, Daniels SR, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation*. 2006;114(24):2710–2738. © American Heart Association, Inc. Reprinted with permission.

included recommended values for non-HDL-C which are associated with persistent dyslipidemia, atherosclerosis, and future cardiac events. In practical terms, it can be measured in a non-fasting state. Normative values for other lipid particles, including HDL, apoprotein A-1 and apoprotein B, have been provided, but the Panel only made recommendations for treatment values on LDL-C, TG, and non-HDL-C (Table 286-2).

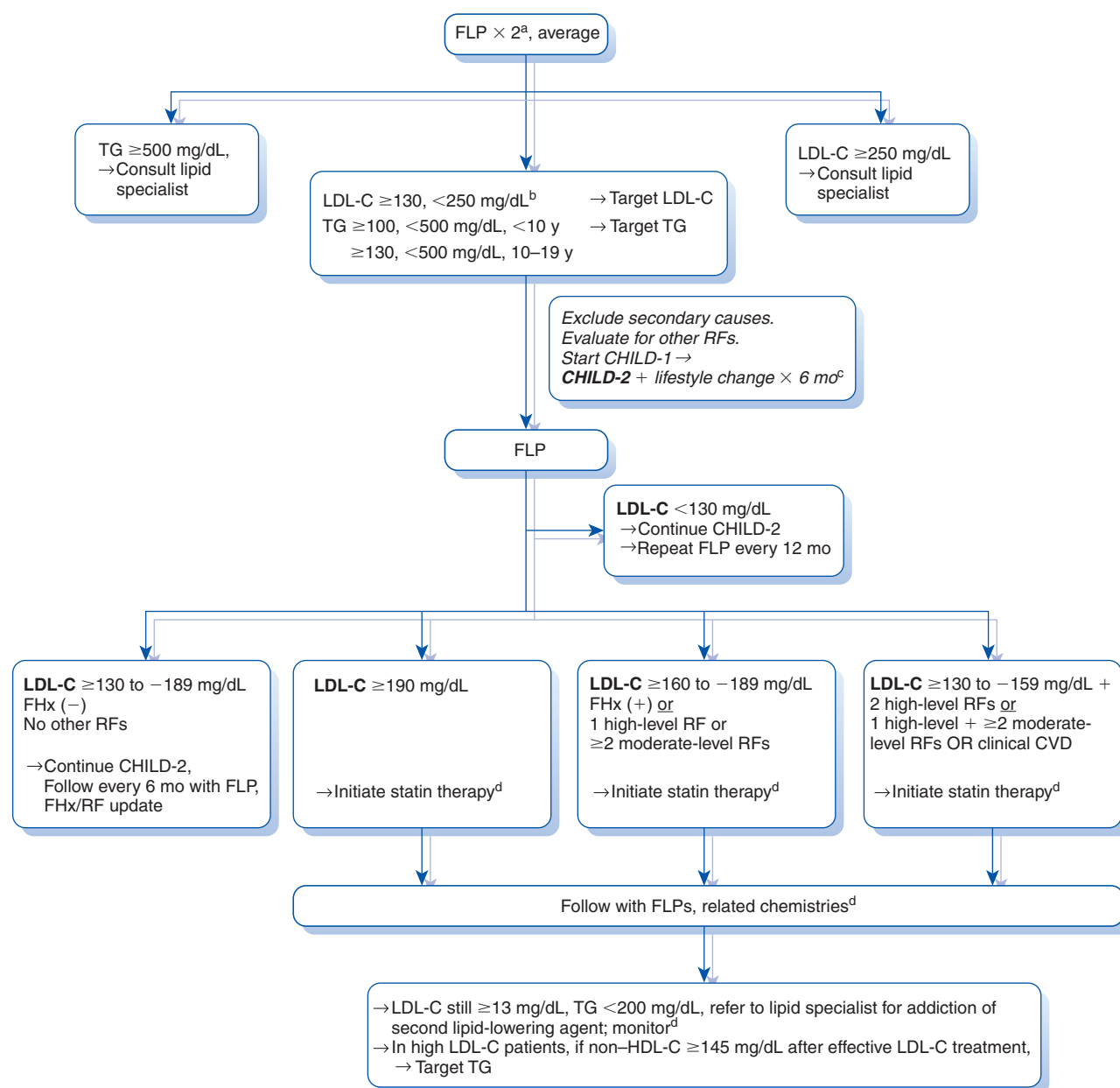
The determination for treatment should be based on the average of at least 2 LDL-C measurements, from fasting lipid panels taken at least 2 weeks, but no more than 3 months, apart, and treatment should follow the general strategy described below and in Figure 286-2:

- For acceptable levels (LDL-C <110 mg/dL) and for borderline levels (LDL-C 110 to 129 mg/dL): Advise the family to follow the CHILD-1 Diet, provide advice regarding other risk factors, and re-evaluate

the child at the next appropriate age cohort (17 to 21 years) or as per adult guidelines.

- For high levels (LDL-C  $\geq$ 130 mg/dL): Obtain a history detailing the use of drugs, such as isotretinoin (Accutane), steroids, and alcohol, to identify any secondary cause of hypercholesterolemia. In addition, screen for other secondary causes of elevated cholesterol, such as liver, thyroid, and renal disease (see Box 286-5).
- Hypertriglyceridemia is also a target for treatment. Referral to a lipid specialist should be considered when greater than 500 mg/dL (see Figure 286-3).

The initial dietary treatment is to follow a CHILD-2 Diet (see Table 286-3). This diet is safe and efficacious for managing children with borderline to high LDL-C levels. However, the child must consume adequate calories while decreasing fat intake. Current dietary guidelines suggest that all children should consume enough calories to reach or maintain desirable weight.



**Figure 286-2** Dyslipidemia algorithm: target LDL cholesterol. Values given are in mg/dL. To convert to SI units, divide results for TC, LDL cholesterol, HDL cholesterol, and non-HDL cholesterol by 38.6; for triglycerides, divide by 88.6. C, cholesterol; FHx, family history; FLP, fasting lipid profile; RF, risk factor; TG, triglycerides. <sup>a</sup>Obtain FLPs at least 2 weeks but no more than 3 months apart. <sup>b</sup>Use of drug therapy is limited to children aged 10 years and older with defined risk profiles. <sup>c</sup>In a child with an LDL cholesterol level of >190 mg/dL and other risk factors, a trial of the CHILD-2-LDL may be abbreviated. <sup>d</sup>For more details on statin initiation and monitoring, please see Table 9-11 and 9-12 in the source. (From Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: summary report. Pediatrics. 2011;128(suppl 5):S213–S256.)

With the increase in the prevalence of overweight and obesity in children, weight reduction in these children often helps correct cholesterol profiles. However, in contrast to adults, some children with hypercholesterolemia are not overweight, and in children who are not overweight, caloric restriction is not the primary treatment for hypercholesterolemia, as it is often for adults.

The CHILD-2 Diet (see Figure 286-4), with no more than approximately 30% of calories from total fat (similar to the CHILD-1 Diet) and less than 7% of calories (compared with 10% in CHILD-1 Diet) from saturated fat, is advised (see Table 286-3). Adherence to the CHILD-2 Diet is often improved by having the family meet with a registered dietitian trained in managing hyperlipidemia in children. Nonpharmacologic

### BOX 286-5 Causes of Secondary Hypercholesterolemia in Children

#### EXOGENOUS

- Drugs: corticosteroids, isotretinoin (Accutane), thiazides, anticonvulsants, beta blockers, anabolic steroids, certain oral contraceptives
- Alcohol
- Obesity

#### ENDOCRINE AND METABOLIC

- Hypothyroidism
- Diabetes mellitus
- Lipodystrophy
- Pregnancy
- Idiopathic hypercalcemia

#### STORAGE DISEASES

- Glycogen storage diseases
- Sphingolipidoses

#### OBSTRUCTIVE LIVER DISEASES

- Biliary atresia
- Biliary cirrhosis
- Alagille syndrome

#### CHRONIC RENAL DISEASES

- Nephrotic syndrome

#### OTHERS

- Anorexia nervosa
- Progeria
- Collagen disease
- Klinefelter syndrome

Modified from American Academy of Pediatrics. National Cholesterol Education Program: Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics*. 1992;89(3 Pt 2):525–584.

treatment can include increasing supplemental fiber intake calculated as the child's age plus 5 g/day, up to a dose of 20 g/day at 15 years of age. Consider drug treatment with binding resins, such as cholestyramine or colestipol, for children older than 10 years whose LDL-C level remains above 190 mg/dL after 6 to 12 months of dietary therapy. Medications should also be considered for those who maintain a level of LDL-C above 160 mg/dL and who have a family history of premature cardiovascular disease (see Figure 286-4).

Commercially available dietary products, such as special margarines with plant sterols and stanols to reduce LDL-C absorption, are available in supermarkets; however, the 2005 AHA/AAP Dietary Recommendations caution against using these spreads, given the possible decrease in absorption of fat-soluble vitamins and beta-carotene. Other medications, such as 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (HMG CoA-reductase inhibitors, or statins) are not routinely recommended for children except in consultation with a lipid specialist. The 2008 AAP Recommendations suggest lowering the statin treatment

age from 10 to 8 years old, based on experience in treating children with familial hypercholesterolemia. The NIH Panel adds that treatment should be considered when the LDL-C does not improve after diet intensification and the child has high-risk features. A 2014 Cochrane review of the same studies echoed the short-term safety but called into question the unknown implications of long-term exposure.

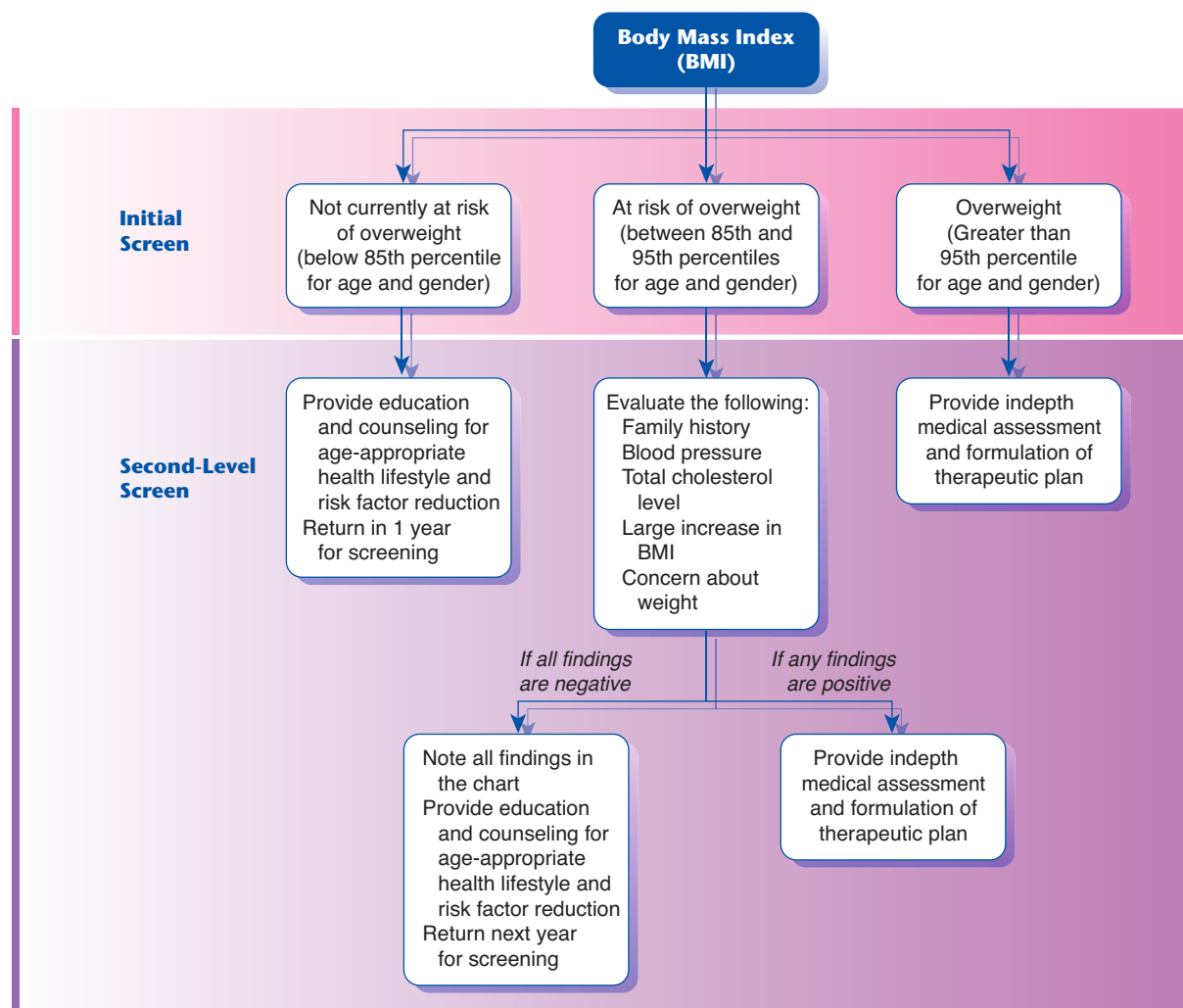
Cholesterol screening and dietary treatment guidelines can be initiated safely by a pediatrician (see Figure 286-1 and Figure 286-2) interested in nutrition and the prevention of heart disease. Initiation includes a review of family history, evaluation for secondary causes of hyperlipidemia (see Box 286-5), and dietary counseling. In addition, identifying children who have risk factors for coronary heart disease should lead to screening other family members, including parents, because many risk factors tend to cluster in families. If the primary care pediatrician is not comfortable managing children who have severe hypercholesterolemia that is unresponsive to dietary treatment or children who are from families with early-onset heart disease, then evaluation by a lipid specialist with continued general support from the pediatrician is recommended.

### OBESITY AND PHYSICAL ACTIVITY

Obesity increases the risk for heart disease through its association with abnormalities such as dyslipidemia, hypertension, insulin resistance, glucose intolerance, and possibly through other, as yet undefined, mechanisms that some refer to as "metabolic syndrome." The magnitude of the effect of childhood obesity on cardiac risk is an area of intense investigation with substantial implications for health, as summarized by the AHA. For example, the PDAY study found that body mass index and the thickness of the panniculus adiposus (ie, subcutaneous fat as measured by a skin-fold test) were correlated with the degree of coronary atherosclerosis in young adults. Several studies have suggested a relationship between the degree of obesity and abnormal lipid profiles.

The standard definition of obesity in children is based on age and sex percentiles of BMI, which is easy to calculate ( $BMI = \text{weight [kg]} / \text{height}^2[\text{m}]$ ). Children who have a BMI at the 95th percentile or higher are considered obese, and those with a BMI between the 85th and 95th percentiles are considered overweight. The terms *overweight* and *obesity* are often used interchangeably, a fact that should be kept in mind when reading the scientific literature.

Charting BMI by age and sex should be a part of every primary care physician's practice. Free templates can be obtained online from the Centers for Disease Control and Prevention. On the basis of the strong association between adiposity in childhood and adiposity in adulthood, and using BMI as a measure of obesity, the US Preventive Services Task Force in 2010 changed its recommendation for screening children for obesity, that physicians screen children aged 6 years and older and offer or refer them to comprehensive, intensive behavioral interventions to promote improvement in weight status (Grade B Recommendation). Current recommendations



**Figure 286-3** Evaluation of overweight in children.

from the AHA and AAP suggest that pediatricians should chart BMI, beginning at 2 years of age, and counsel parents to address the eating and activity patterns of at-risk children (see Chapter 35, Healthy Weight).

Body mass index can be easily calculated and plotted for all children (see Table 286-1). Obese children should be further screened for hypertension, orthopedic problems, hypoventilation, and abnormalities of lipids and glucose metabolism (see Figure 286-3). Additional specialty evaluations should be considered in individual situations, with the magnitude of the abnormalities being an important consideration. No single treatment program for overweight children has been uniformly successful. The first-line approach is diet and exercise therapy with behavioral modification and family counseling.

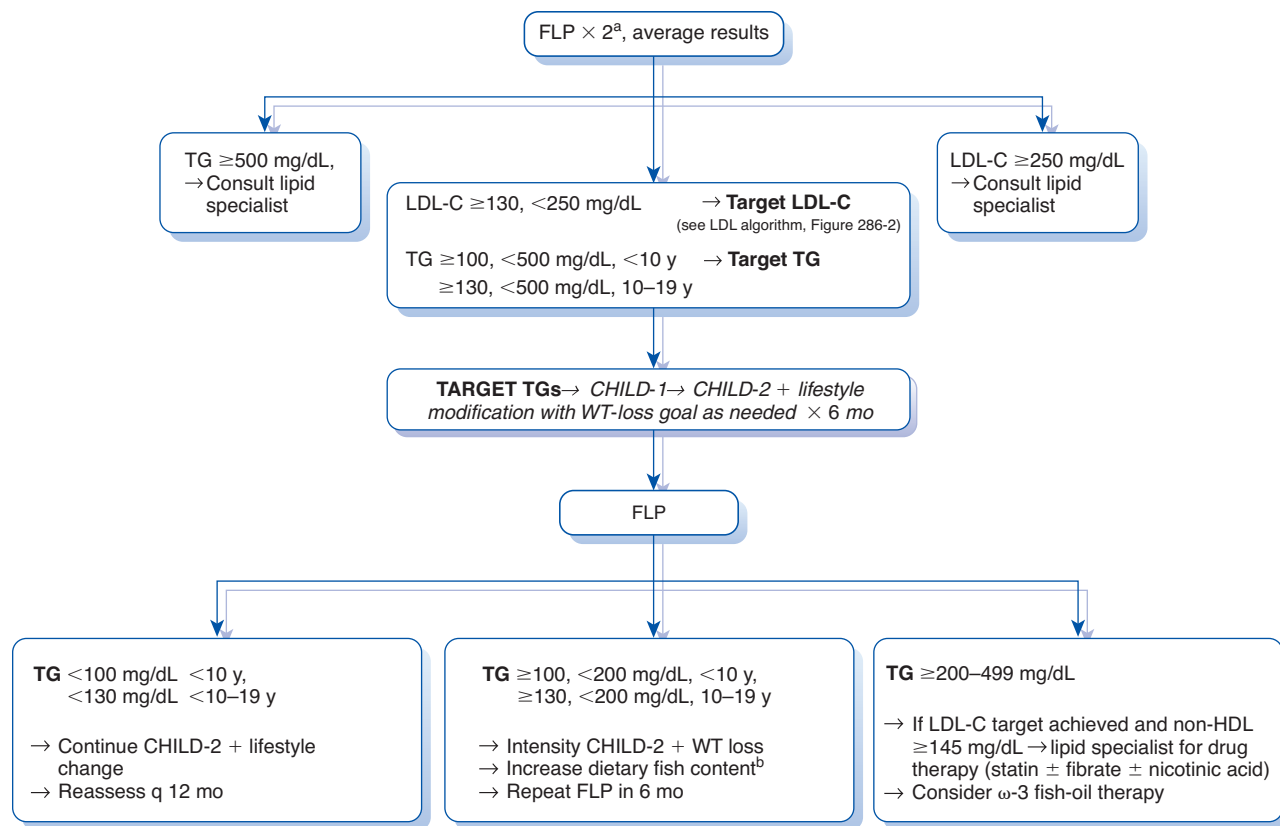
The AHA Scientific Statement on Metabolic Syndrome does not recommend a specific treatment, instead opting for the general approach of reducing obesity, increasing physical activity, and achieving blood pressure and lipid goals. However, the component

signs and symptoms of metabolic syndrome cluster in overweight children.

The importance of physical activity in preventing or ameliorating other cardiac risk factors, such as obesity, hyperlipidemia, and hypertension, has been recognized increasingly over the past several years. Furthermore, in adults, higher levels of physical activity have been associated with decreased rates of heart disease, above and beyond those associated with changes in known cardiac risk factors.

Health care professionals should encourage children of all ages to make physical activity a part of their daily routine (see Box 286-6). Children and their families should be encouraged to be physically active, and children are more likely to be physically active if their parents are active (see Table 286-1). Recent recommendations by the AHA and endorsed by the AAP stress the importance of age-appropriate physical activity. For example, school children should participate in regular physical activity most days of the week for at least 1 hour per day and should limit “screen time” (television, video game, and computer time) to less





**Figure 286-4** Dyslipidemia algorithm: target triglycerides. Values given are in mg/dL. To convert to SI units, divide results for TC, LDL cholesterol, HDL cholesterol, and non-HDL cholesterol by 38.6; for triglycerides, divide by 88.6. C indicates cholesterol; a Obtain FLPs at least 2 weeks but no more than 3 months apart. b The FDA and the Environmental Protection Agency advise women of childbearing age who may become pregnant, pregnant women, nursing mothers, and young children to avoid some types of fish and shellfish and to eat fish and shellfish that are lower in mercury. For more information, call the FDA's food information line toll-free at 1-888-SAFEFOOD or visit [www.cfsan.fda.gov/~dms/admeHg3.html](http://www.cfsan.fda.gov/~dms/admeHg3.html). (From Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: summary report. Pediatrics. 2011;128(suppl 5):S213–S256.)

than 2 hours per day. Children involved in competitive athletics should be counseled on issues related to weight control and strength training.

## SMOKING

The evidence that cigarette smoking is a risk factor for cardiovascular disease is overwhelming. Studies as early as 1940 documented a relationship between tobacco use and coronary artery disease. In 1964, the Surgeon General first reported the link between smoking and heart disease. In 1979, the Surgeon General addressed the growing problem of children who smoked or were exposed to smoke and, in 1994, addressed the need for smoking prevention in young people. A 1996 AHA task force presented more evidence that tobacco use increases the risk for cardiovascular disease.

Tobacco use adversely affects lipid levels and is associated with decreased exercise capacity, increased platelet aggregation, an increased incidence of respiratory illness, an increased incidence of low-birth-weight deliveries, and increased infant mortality. In addition, exposure to passive smoking is linked with

increases in risk factors for vascular and coronary artery disease in children. Passive smoking is associated with reduced HDL-C in nonsmoking children, as well as in those with high-risk lipid profiles. In 2006, the Surgeon General updated recommendations to eliminate secondhand or passive smoke exposure for children. The most recent AAP recommendation in 2009 continues its firm stance against smoking initiation and exposure to secondhand smoke.

Adolescents are more likely to smoke or use tobacco than any other age group. In 2009, the National Youth Tobacco Survey estimated that 8% of middle school and 24% of high school students were current users of tobacco products. However, the National Youth Risk Behavior Survey, 1991 to 2009, showed a decline in self-reported current tobacco use and in the frequency of use among high school students. The risk for smoking initiation increases from ages 12 to 16 years, with most adolescents initiating and becoming addicted during this critical period of development. Although most youth do not become nicotine dependent until after 2 to 3 years of smoking, addiction can occur after smoking as few as 100 cigarettes.

**BOX 286-6 Guidelines for Healthy Physical Activity Among Children**

Physicians and health care professionals should promote active healthy living within each family by

- Serving as role models for leading an active lifestyle.
- Inquiring about nutritional intake, calculating and plotting body mass index, identifying obesity-related comorbidities, and promoting healthy behaviors.
- Documenting the number of hours per day spent on sedentary activities and limiting screen time (television, video game, and computer) according to the AAP guidelines.
- Determining physical activity levels of the child and family members at regular health care visits.
- Tabulating the amount of daily physical activity each child or adolescent does at home, at school, or at child care as part of transportation, work, recreation, and unorganized sports. Tabulations should include the actual minutes each week of formal physical education and recess-related physical activity. In addition, the number of times per week spent in outdoor play for at least 30 minutes or the number of daily steps taken (as determined with a pedometer) should be documented. Specific involvement in organized sports and dance also should be noted.
- Encouraging children to be active for a total of at least 60 minutes a day, either continuously or cumulatively. Activities should be varied and of moderate intensity and may include sports, recreation, walking, chores, work, planned exercise, and school-based physical education classes. Activities should be fun to achieve best results.
- Identifying barriers to increasing physical activity, such as lack of time, competing interests, perceived lack of motor skills, fear of injury, and parental concerns about financial and safety issues.
- Educating the family about the importance of lifelong physical activity and helping them to identify strategies to overcome barriers.
- Recommending that parents become good role models by increasing their own level of physical activity, especially with activities that involve the entire family. Encourage children to play outside as much as possible, and to use appropriate safety measures, such as bicycle helmets, elbow and kneepads, life jackets, etc).
- Supporting children in participating in developmentally and age-appropriate sports and recreational activities, especially those favored by the child. These activities might occur during extracurricular activities in which parents or grandparents can take part as leaders and coaches.
- Suggesting that overweight children partake in activities that take advantage of their height and strength, such as water-based sports and strength training, rather than those that require weight bearing (eg, jumping, jogging).
- Recommending that parents of overweight children and youth play a supporting, accepting, and encouraging role in returning them to healthier lifestyles to increase self-esteem.
- Encouraging youth to promote physical activities among their peers and become role models and leaders for younger students.

Modified from American Academy of Pediatrics Council on Sports Medicine and Fitness and Council on School Health. Active healthy living: prevention of childhood obesity through increased physical activity. *Pediatrics*. 2006;117:1834–1842.

Children whose parents or siblings smoke are at an increased risk for beginning to smoke. Other factors that may predict smoking include peer influence, lower socioeconomic status, psychiatric and substance abuse disorders, Alaskan native and Native American ethnicity, and military service. Identifying these factors and addressing them openly is helpful in counseling. Primary care physicians should advise parents who smoke about the risks and refer them to a smoking cessation program. Pediatricians should actively participate in and support school and community antismoking campaigns. Although the current decline in the prevalence of smoking among children is a positive change, the potential for addiction brings smoking prevention into the realm of pediatric practice. The risks of smoking should be a part of routine preventive care discussions (see Table 286-1).

## CONCLUSION

Given the prevailing evidence from adults with atherosclerotic cardiovascular disease, the presence of risk factors in children, and the emerging data from long-term studies on cardiovascular disease outcomes in adults with childhood risk factors, pediatric primary care physicians should identify and treat these risk factors in children. Even more important, these physicians

can educate children and families about strategies to prevent the development of these risk factors and their continued presence into adulthood.

## TOOLS FOR PRACTICE

### Medical Decision Support

- *American Heart Association Guidelines for Primary Prevention of Atherosclerotic Cardiovascular Disease Beginning in Childhood* (guidelines), American Heart Association ([circ.ahajournals.org/cgi/content/full/107/11/1562](http://circ.ahajournals.org/cgi/content/full/107/11/1562))
- *Cardiovascular Health in Childhood: A Statement for Health for Health Professionals From the Committee on Atherosclerosis, Hypertension, and Obesity in the Young (AHOY) of the Council on Cardiovascular Disease in the Young*, American Heart Association (policy statement), American Heart Association ([circ.ahajournals.org/cgi/content/full/106/1/143](http://circ.ahajournals.org/cgi/content/full/106/1/143))
- *Growth Charts—Tutorials and Information* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/growthcharts](http://www.cdc.gov/growthcharts))
- *Growth Charts* (chart), Centers for Disease Control and Prevention ([www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical\\_charts.htm#Clin%201](http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical_charts.htm#Clin%201))
- *Pediatric Obesity: Prevention, Intervention, and Treatment Strategies for Primary Care* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

- *Understanding Obesity in Youth: A Statement for Healthcare Professionals From the Committee on Atherosclerosis and Hypertension in the Young of the Council on Cardiovascular Disease in the Young and the Nutrition Committee, American Heart Association* (policy statement), American Heart Association ([www.circ.ahajournals.org/cgi/content/full/94/12/3383](http://www.circ.ahajournals.org/cgi/content/full/94/12/3383))

### AAP POLICY

- American Academy of Pediatrics Committee on Nutrition. Lipid screening and cardiovascular health in childhood. *Pediatrics*. 2008;122(1):198–208. Reaffirmed May 2011 ([pediatrics.aappublications.org/content/122/1/198](http://pediatrics.aappublications.org/content/122/1/198))
- American Academy of Pediatrics Committee on Nutrition. Cholesterol in childhood. *Pediatrics*. 1998;101(1):141–147. ([pediatrics.aappublications.org/content/101/1/141](http://pediatrics.aappublications.org/content/101/1/141))
- American Heart Association. Dietary recommendations for children and adolescents: a guide for practitioners: consensus statement from the American Heart Association. *Circulation*. 2005;112(13):2061–2075 (AAP endorsed)
- Kavey R-EW, Allada V, Daniels SR, et al. Cardiovascular risk reduction in high-risk pediatric populations. *Circulation*. 2006;114(24):2710–2738 (AAP endorsed)

### SUGGESTED READINGS

- Gidding SS, Lichtenstein AH, Faith MS, et al. Implementing American Heart Association pediatric and adult nutrition guidelines: a scientific statement from the American Heart Association Nutrition Committee of the Council on Nutrition, Physical Activity and Metabolism, Council on Cardiovascular Disease in the Young, Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Cardiovascular Nursing, Council on Epidemiology and Prevention, and Council for High Blood Pressure Research. *Circulation*. 2009;119:1161–1175
- Juonala M, Magnussen CG, Venn A, et al. Influence of age on associations between childhood risk factors and carotid intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study, the Childhood Determinants of Adult Health Study, the Bogalusa Heart Study, and the Muscatine Study for the International Childhood Cardiovascular Cohort (i3C) Consortium. *Circulation*. 2010;122:2514–2520
- Vuorio A, Kuoppala J, Kovanen PT, et al. Statins for children with familial hypercholesterolemia. *Cochrane Database Syst Rev*. 2010(7):CD006401

## Chapter 287 LYME DISEASE

H. Cody Meissner, MD

### EPIDEMIOLOGY, ETIOLOGY, AND PATHOGENESIS

Lyme disease was first recognized in 1975 after an investigation of a cluster of arthritis cases among children in Lyme, Connecticut, and soon thereafter the

black legged deer tick *Ixodes scapularis* was implicated as the vector of this disease. In 1982 a previously unrecognized spirochete, *Borrelia burgdorferi*, was detected in the midgut of the tick and identified as the etiologic agent. In 2013, more than 25,000 cases of Lyme disease were reported to the Centers for Disease Control and Prevention (CDC), making this condition the most common tickborne infectious disease in the United States. Because of under-reporting, it is likely that more than 10 times this number actually occurred. Although Lyme disease has been reported in almost every state, 95% of all cases are concentrated in 11 states from 3 geographic regions: the Northeast from Maine to Maryland, the Midwest in Wisconsin and Minnesota, and the West in Northern California and Oregon. The occurrence of disease corresponds with the distribution of the tick vectors *I. scapularis* in the East and Midwest and *I. pacificus* in the West. *B. burgdorferi* live in mice, squirrels, and other small animals and are transmitted among these animals and to humans by the bite of the tick. The tick lives for 2 years and has 3 stages: larvae, nymph, and adult. A blood meal is required at each stage of development. When the tick feeds on an infected animal, the spirochete is acquired, and when the tick feeds again the spirochete can be transmitted to a new host. Most cases of human Lyme disease are acquired in June, July, or August, when the nymphal stage is most active and human outdoor activity is greatest. Although deer are important for maintaining the tick population, deer do not become infected by the spirochete. *B. burgdorferi* have been divided into 3 pathogenic groups: North American strains belong to the group *B. burgdorferi sensu stricto* while most isolates from Europe and Asia are classified as *B. garinii* or *B. afzelii*.

### CLINICAL MANIFESTATIONS

Because the clinical manifestations of Lyme disease vary with the time that elapses after inoculation by the tick, the infection has been divided into early localized (stage 1), early disseminated (stage 2), and late phases (stage 3).

#### Early Localized Phase

Erythema migrans (EM) is the most common manifestation of early Lyme disease. Approximately 70% to 80% of patients exhibit or have a history of a skin lesion at the site of the tick bite. The macule gradually expands over several days to a large erythematous lesion that may increase in size to 5 cm or greater, sometimes with central clearing. Early lesions may not have central clearing or the characteristic target-like appearance. The rash may be warm but is not painful. Influenza-like symptoms that include malaise, fatigue, headache, arthralgia, myalgia, fever, or regional lymphadenopathy may accompany the skin lesion. Cough, rhinorrhea, vomiting, or diarrhea are not typical. The rash typically appears within 7 to 14 days (range 3 to 32 days) of the tick bite and, if untreated, resolves within 3 to 4 weeks.

#### Early Disseminated Phase

In the absence of antimicrobial therapy, hematogenous spread of the spirochete may occur, producing

the disseminated phase of early Lyme disease. Within days or weeks, in an untreated person, early disseminated disease may produce influenza-like symptoms including arthralgia, myalgia, headache, and fatigue. Other symptoms that may occur in this stage include multiple secondary EM lesions, Bell palsy, lymphocytic meningitis, or conjunctivitis. Serum antibody to *B burgdorferi* is usually not present during this stage of early disease, requiring 3 to 4 weeks to appear. However, the spirochete is cultured from the skin more easily during early infection than at any other time in the illness.

Months after onset of illness, approximately 60% of untreated patients will develop monoarticular or oligoarticular arthritis, which generally involves 1 or more large joints, especially the knees. Approximately 5% to 10% of untreated patients will develop neurologic manifestations within weeks of the early disseminated phase. Nervous system involvement may include cranial neuropathy (especially unilateral or bilateral facial palsy) and radiculopathy. Central nervous system involvement may include lymphocytic meningitis. Encephalopathy associated with late-stage Lyme disease, consisting of mild abnormalities of memory and cognitive function, is poorly understood and rare. Less than 5% of untreated patients will develop cardiac disease. Cardiac involvement is characterized most commonly by varying degrees of atrioventricular block but may include myopericarditis. Hospitalization is appropriate for patients with syncope, dyspnea, or chest pain. Complete heart block is usually brief, and only temporary cardiac pacing is needed. In untreated persons, symptoms involving the joints, central nervous system, or heart, reflecting spread of the spirochete to other parts of the body, may occur months after the tick bite.

### Late-Stage Disease

Among untreated patients, late-stage disease may produce recurrent oligoarticular arthritis that involves the knees. A small number of patients may develop neurocognitive symptoms, fatigue, difficulty with concentration, or sleep disturbances. These symptoms are not specific to Lyme disease. They may be triggered by a number of conditions and should not be referred to as chronic Lyme disease. Many of these patients have no evidence of previous or current infection by *B burgdorferi* and do not benefit from antimicrobial therapy.

### Congenital Infection

Although other spirochetal infections during pregnancy (eg, syphilis) can cause congenital infection, no causal relationship between maternal Lyme disease and congenital disease has been documented. No evidence exists to support transmission of *B burgdorferi* via human milk. Doxycycline should not be used to treat Lyme disease in pregnant or lactating patients.

### Coinfections

The same tick that transmits *B burgdorferi* also may transmit the agents of ehrlichiosis or anaplasmosis as well as the intraerythrocytic protozoa *Babesia microti* (the agent of babesiosis), either as a mixed infection or

as a single infection. Ehrlichiosis or anaplasmosis should be suspected in the appropriate epidemiologic setting in a patient with fever, chills, and headache in association with thrombocytopenia, leukopenia, or increased liver enzyme levels. Babesiosis in symptomatic patients may produce fever, malaise, chills, and sweats.

### Post-Lyme Syndromes

Considerable confusion surrounds the topic of post-Lyme disease syndromes. This is partly because of the lack of a widely accepted definition for this entity. A recent report from the Infectious Disease Society of America reviewed this issue and confirmed the following conclusions: (1) “there is no convincing biologic evidence for the existence of symptomatic chronic *B burgdorferi* infection among patients after receipt of a recommended treatment regimen for Lyme disease and (2) antibiotic therapy has not proven to be useful and is not recommended for patients with chronic (>6 months) of subjective symptoms after a recommended treatment regimen for Lyme disease.”

### DIFFERENTIAL DIAGNOSIS

In children who have what seems to be Lyme arthritis, the differential diagnosis may include oligoarticular juvenile arthritis, septic arthritis, and acute rheumatic fever. Other considerations in the differential diagnosis may include aseptic meningitis caused by enterovirus infection, Bell palsy caused by herpes simplex virus, varicella zoster virus, Epstein Barr virus or mycoplasma, a peripheral neuropathy not caused by *B burgdorferi*, or multiple sclerosis. Although such diagnoses are less likely after a history of a recent tick bite and EM, some patients with Lyme disease may offer no history of these events. Especially during summer months in an endemic area, Lyme disease should be considered in a patient who has lymphocytic meningitis or arthritis involving the knee.

### SEROLOGIC TESTING

Erythema migrans can be diagnosed in a person who lives in or has traveled to an endemic area and generally is a sufficient basis for a clinical diagnosis without laboratory confirmation. Serologic testing in a person with typical EM generally is discouraged because of the lack of sensitivity at this early stage of disease. As many as 60% of cases will have a false-negative antibody test result at this stage. However, not all patients with Lyme disease will develop EM, and many may not recall a tick bite. Isolation of *B burgdorferi* from a symptomatic patient is diagnostic of Lyme disease. However, culture media are not widely available and sensitivity is low.

Serologic testing may be useful in the few patients in whom a diagnosis is uncertain, particularly when symptoms have been present for more than several weeks. A 2-tier approach to serologic testing for Lyme disease should be used with both acute- and convalescent-phase serum specimens. Initial testing is most often conducted using an enzyme immunoassay (EIA). If positive or equivocal results are obtained, then a standardized Western immunoblot for both Lyme-specific immunoglobulin M (IgM) and IgG should



be performed, using the same serum specimen for tier 1 and tier 2 testing. A second step is necessary because false positive results are common with EIA resulting from cross-reactive antibodies. Based on CDC guidelines, an IgM immunoblot is considered positive if 2 of 3 bands are present. An IgG immunoblot is defined as positive if at least 5 of 10 bands are detected. In endemic areas, a positive immunoblot result is not always a result of an active *B burgdorferi* infection and may reflect previous infection. Two-tier testing should be used because of the high sensitivity but low specificity of the commercial enzyme immunoassays used in the first step. Testing by immunoblot should not be performed without first performing an enzyme immunoassay. The C6 peptide enzyme linked immunosorbent assay for measuring IgG antibody to a spirochete peptide is an acceptable alternative to 2-tier testing. Laboratory testing should not be performed for people who do not have symptoms of Lyme disease because of an increased likelihood of a false-positive test result. Testing of individual ticks is not useful for deciding whether antibiotic therapy should be initiated after a tick bite. Early antibiotic therapy may prevent seroconversion. Other laboratory tests such as urine antigen assays, immunofluorescence staining for cell wall deficient forms of *B burgdorferi*, and lymphocyte transformation assays have not been validated and should not be used.

## MANAGEMENT

### Pharmacotherapy

Patients with early localized or disseminated disease who do not have neurologic or cardiac involvement should be treated for 14 to 21 days with doxycycline (for children 8 years and older) except for pregnant or lactating women. An advantage of doxycycline is efficacy against the agent of human granulocytic ehrlichiosis, which may be a coinfecting microbe. Amoxicillin should be used for children younger than 8 years and in pregnant women. In patients who are unable to take doxycycline or amoxicillin, cefuroxime axetil is a third drug of choice. Clinical trials show resolution of symptoms in more than 90% of patients with EM treated with doxycycline, amoxicillin, or cefuroxime axetil. Macrolide antibiotics are less effective than other antimicrobial agents and should be reserved for patients who are unable to take preferred agents. Intravenous ceftriaxone is not superior to oral agents except in patients with neurologic or cardiac involvement.

Oral antimicrobial agents are effective for treating multiple EM and uncomplicated Lyme arthritis. Oral agents can be used to treat most people with facial nerve palsy, but central nervous system involvement such as meningitis with pleocytosis or neurologic abnormality should be treated with parenteral antibiotic therapy. Although first-degree atrioventricular block usually responds to oral therapy, higher-grade blocks are usually treated with parenteral therapy with ceftriaxone or penicillin for at least part of the course. Persistent or recurrent arthritis should be treated with either parenteral ceftriaxone or penicillin. Specific dosages and durations are given in Table 287-1.

### Vaccine

In December 1998 the US Food and Drug Administration approved a vaccine against Lyme disease (LYMERix) for individuals 15 to 70 years of age, but the vaccine was withdrawn voluntarily by the manufacturer in 2002 and is no longer available.

### Prophylaxis After a Tick Bite

Clinical practice guidelines developed by the Infectious Diseases Society of America for prevention of Lyme disease after a tick bite suggest that the following conditions be satisfied: (1) The biting tick is identified as *I scapularis*, with an estimated attachment time of more than 36 hours based on the size of the engorged tick, (2) prophylaxis can be started within 72 hours of tick removal, (3) local rates of tick infection by *B burgdorferi* exceed 20%, and (4) the use of doxycycline is not contraindicated. Doxycycline is the only antibiotic shown to be effective for postexposure prophylaxis. If doxycycline is administered for prophylaxis, a single 200 mg dose (4.4 mg/kg for body weight <45 kg) for people 8 years of age or older is recommended by some experts. No data are available to support amoxicillin use in this setting.

## PREVENTION OF TICK BITES

Ticks are most likely to be located in wooded and bushy areas with high grass. When walking in a tick-infested area, people should walk in the center of the path to avoid contact with grass and brush. Insect repellent containing DEET should be applied to skin and clothing. DEET-containing compounds can be used for children older than 2 months, should not be applied to the face or hands, and should be removed from skin with soap and water once the risk of exposure is over. Permethrin kills ticks on contact and can be applied to clothing but should not be applied directly to skin because it is inactivated by skin lipids. Long pants and sleeves will help keep ticks off skin, and light-colored clothing makes the task of spotting ticks easier. Daily tick checks should be performed. If a tick is attached for less than 24 hours, then the risk of acquiring Lyme disease is extremely small. Attached ticks should be removed as soon as possible using fine-tip forceps at the point of attachment. The overall risk of acquiring Lyme disease following a tick bite in a highly endemic area is 1% to 3%.

### WHEN TO REFER

- Cardiac involvement (heart block, pericarditis, myocarditis)
- Neurologic involvement (except isolated facial palsy in patients with definite Lyme disease diagnosis)
- Nonspecific clinical history but positive or equivocal laboratory testing
- Persistent arthritis

### WHEN TO ADMIT

- Cardiac involvement
- Meningitis or encephalopathy

**Table 287-1** Treatment Regimens for Lyme Disease

DISEASE CATEGORY	DRUG(S) AND DOSE <sup>a</sup>
<b>EARLY LOCALIZED DISEASE<sup>a</sup></b>	
8 years or older	Doxycycline, 4 mg/kg per day, orally, divided into 2 doses (maximum 200 mg/day) for 14 days <sup>b</sup>
Younger than 8 years or unable to tolerate doxycycline <sup>b</sup>	Amoxicillin, 50 mg/kg per day, orally, divided into 3 doses (maximum 1.5 g/day) for 14 days <b>OR</b> Cefuroxime, 30 mg/kg per day in 2 divided doses (maximum 1000 mg/day or 1 g/day) for 14 days
<b>EARLY DISSEMINATED AND LATE DISEASE</b>	
Multiple erythema migrans	Same oral regimen as for early localized disease, for 14 days
Isolated facial palsy	Same oral regimen as for early localized disease, for 14 days (range 14–21 days) <sup>c,d</sup>
Arthritis	Same oral regimen as for early localized disease, for 28 days
Recurrent arthritis	Same oral regimen as for first-episode arthritis, for 28 days <b>OR</b> Preferred parenteral regimen: Ceftriaxone sodium, 50–75 mg/kg, IV, once a day (maximum 2 g/day) for 14 days (range 14–28 days) Alternative parenteral regimen: Penicillin, 200 000–400 000 U/kg per day, IV, given in divided doses every 4 hr (maximum 18–24 million U/day) for 14 days (range 14–28 days) <b>OR</b> Cefotaxime 150–200 mg/kg per day, IV, divided into 3 or 4 doses (maximum 6 g/day) for 14 days (range 14–28 days) Symptomatic therapy
Antibiotic-refractory/persistent arthritis <sup>e</sup>	
Atrioventricular heart block or carditis	Oral regimen as for early disease if asymptomatic <sup>f</sup> or not hospitalized, for 14 days (range 14–21 days) <b>OR</b> Parenteral regimen initially for hospitalized patients, dosing as for recurrent arthritis, for 14 days (range 14–21 days); oral therapy can be substituted to complete the 14–21 day course
Meningitis	Ceftriaxone <sup>g</sup> or alternatives of cefotaxime or penicillin <sup>g</sup> : dosing as for recurrent arthritis, for 14 days (range 10–21 days) <b>OR</b> Doxycycline, 4–8 mg/kg per day, orally, divided into 2 doses (maximum 100–200 mg for 14 days (range 14–21 days) <sup>b</sup>
Encephalitis or other late neurologic disease <sup>h</sup>	Ceftriaxone <sup>g</sup> or alternatives of cefotaxime or penicillin <sup>g</sup> : dosing as for recurrent arthritis, for 14 days (range 14–28 days)

IV, intravenously.

<sup>a</sup>For patients who are allergic to penicillin, alternatives are cefuroxime, azithromycin, and erythromycin.

<sup>b</sup>Tetracycline-based antimicrobial agents, including doxycycline, may cause permanent tooth discoloration for children younger than 8 years if used for repeated treatment courses. However, doxycycline binds less readily to calcium compared with older tetracyclines, and in some studies, doxycycline was not associated with visible teeth staining in younger children.

<sup>c</sup>Corticosteroids should not be given.

<sup>d</sup>Treatment has no effect on the resolution of facial nerve palsy; its purpose is to prevent late disease.

<sup>e</sup>Arthritis is not considered persistent unless objective evidence of synovitis exists at least 2 months after completion of a course of parenteral therapy or of two 28-day courses of oral therapy. Some experts administer a second course of an oral agent before using an IV-administered antimicrobial agent.

<sup>f</sup>Symptoms for heart block or carditis include syncope, dyspnea, or chest pain.

<sup>g</sup>For treatment of meningitis or encephalitis with ceftriaxone, cefotaxime or penicillin, drug should be administered IV.

<sup>h</sup>Other late neurologic manifestations include peripheral neuropathy or encephalopathy.

From American Academy of Pediatrics. Lyme disease. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015: 516–525.

## TOOLS FOR PRACTICE

### Engaging Patients and Family

- Lyme Disease (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/ncidod/dvbid/lyme/index.htm](http://www.cdc.gov/ncidod/dvbid/lyme/index.htm))
- *A Parent's Guide to Insect Repellents* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org/](http://patiented.solutions.aap.org/))

### Medical Decision Support

- *Red Book: 2015 Report of the Committee on Infectious Diseases* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

## SUGGESTED READING

Plotkin SA, Wormser GP. The need for a new Lyme disease vaccine. *Clin Infect Dis*. 2011;53:S247–S275

## Chapter 288

## MEDICAL ERRORS, ADVERSE EVENTS, AND PATIENT SAFETY

Daniel R. Neuspiel, MD, MPH

Patient safety is the freedom from accidental or preventable injuries produced by medical care. (This should be distinguished from home and community injury prevention, another important role of pediatricians in ensuring child safety.) In 1999, the Institute of Medicine published the landmark report, *To Err Is Human: Building a Safer Health System*, which noted that errors caused by the health care system are a leading cause of death and injury. Medical errors in pediatrics cause significant harm, are costly, and are largely preventable.

Several terms are commonly used in patient safety and require definition (see Table 288-1). A *medical error* occurs when an act of commission or omission occurs that either causes an undesirable outcome or invokes risk for such an outcome. An *adverse event* (AE) occurs when injury or harm is caused by medical care. Adverse events may be *preventable*, when patient harm is related to a medical error, or *nonpreventable*, when patient harm occurs in the absence of a medical error. *Adverse drug events* are AEs caused by medication. A *near miss* is an error that does not result in an AE; also known as a “close call.” A *slip* is an error resulting from an unconscious lapse in otherwise automatic task performance caused by distraction, and may be considered a failure of execution. A *mistake* is an error resulting from an incorrect choice and is related to faulty knowledge, training, or information; it may be considered a failure of planning. Other terms are defined later in this chapter.

## EPIDEMIOLOGY

The epidemiology of medical errors in pediatrics may be categorized by type (eg, errors related to diagnosis, medication, surgery, technology, communication) as well as location (eg, inpatient, outpatient, emergency department, home, school). The relative incidence of various types of pediatric medical errors is not yet well established. Although most publications to date have focused on medication errors, it is not clear whether these are the most frequent types of errors in pediatrics.

## Diagnostic Errors

In a survey of 726 pediatricians and pediatric residents, 54% of physicians reported making a diagnostic error at least once or twice per month. The error rate among trainees was 77%. Errors harmful to patients occurred at least once or twice annually among 45% of respondents. The most frequently reported process lapse was failure to gather adequate clinical information. The most commonly reported system error was inadequate coordination of care and teamwork. Among specific errors, the most frequent were viral infections diagnosed as bacterial, followed by misdiagnosis of adverse reactions to medications, psychiatric disorders, and appendicitis.

In a systematic review of diagnostic errors in the neonatal intensive care unit (NICU) and the pediatric intensive care unit (PICU) settings, major diagnostic errors were found in 20% of autopsied PICU and NICU deaths. Although missed infections were most common in both settings, missed vascular events were more common in the PICU and missed congenital conditions in the NICU.

Reviews of closed pediatric malpractice claims indicate that the most frequent basis of these events was diagnostic error. Failure to correctly diagnose was listed as the primary issue in 36% of claims reported between 2003 and 2012. Among pediatric claims paid in 2012, 48% reported diagnostic error as the primary allegation. Among claims involving errors in diagnosis, meningitis was the most prevalent condition that was incorrectly diagnosed by pediatricians, followed by appendicitis, pneumonia and fever. Errors in diagnosing meningitis resulted in the highest percentage of paid claims (49%), and errors in diagnosing fever contributed the highest average payment (\$529,548).

## Medication Errors

Medication errors commonly affect children in the inpatient, outpatient, home, and school settings. Such errors occur at the stages of medication ordering, transcribing, dispensing, and administration. Children may be of particular risk for medication errors because of varied sizes, stages of development, communication barriers, and treatment by health care staff unfamiliar with this age group.

In the outpatient setting, as many as 15% of pediatric prescriptions have been reported to have dosing errors. Preventable adverse drug events have been reported to occur in 3% of children receiving prescriptions. Both errors and preventable adverse events occur more frequently among younger children and those receiving multiple prescriptions. Errors have been reported in 15% of pediatric emergency department prescriptions, higher among less experienced providers and on nights and weekends.

Children with special needs who take multiple medications seem to be at higher risk for home medication errors. These include children receiving outpatient oral chemotherapy for acute lymphoblastic leukemia, with an error rate of 19% over a 2-month period, related to incorrect dosing or failing to administer an indicated medication. Home medication use in children with cancer has been reported with an error rate of 70%; errors with injury 4%, and potential injury 36%. Among children with sickle cell disease and seizure disorders, 22% of reviewed home medications revealed medication errors, often consisting of failure to fill prescriptions or to change to new recommended dosing. Patients' physicians were unaware of 80% of the detected home medication errors. Errors have also been reported in medication prescriptions for children with depression and attention deficit/hyperactivity disorder.

Communication barriers between health care providers and the caregivers of children are important sources of error. The accuracy of liquid medication administration by parents varies from 15% to 50%. Calibrated syringes show the highest accuracy for home medication dosing. Over-the-counter liquid

**Table 288-1** Definitions in Patient Safety

TERM	DEFINITION	EXAMPLE
Adverse drug event	Adverse event caused by medication	Diarrhea caused by amoxicillin
Adverse event	An occurrence of injury or harm caused by medical care	Laceration caused by wall ophthalmoscope falling on infant
Cause-and-effect (fishbone or Ishikawa) diagram	A method to sort all possible causes of an error into useful categories	After serious adverse event, a team is assembled to conduct root cause analysis using a cause-and-effect diagram to assist their discussion
Clinical decision support	A system to improve clinical decision-making by providing direct access to evidence-based information	Electronic medical record includes feature that allows the physician to click on "diagnosis" to open a screen that shows recommendations from the latest AAP clinical practice guideline
Failure modes and effects analysis	A quality improvement process used to prospectively identify the risk of error within a process	To reduce inpatient pediatric prescribing errors, teams analyzed drug delivery process to identify potential failures and plan practice changes
Forcing function	A limit built into a process that prevents an action with high risk of error	Gastrostomy tubing cannot fit into intravenous port
Human factors science	A discipline that attempts to identify and address safety problems arising from the interaction between people, technology, and work environments	A human factors approach was used to analyze adverse events during pediatric cardiac surgery and found that communication breakdowns were a major cause
Medical error	An act of commission or omission that causes or entails risk of undesirable patient outcome	Vaccine given to wrong patient
Mistake	Error resulting from incorrect choice, related to faulty knowledge, training, or information; a failure of planning	Physician prescribes wrong antibiotic for infection
Near miss	Error that does not result in AE (ie, "close call")	Physician orders wrong vaccine, but the error is detected by a nurse before it is administered
Nonpreventable AE	Patient harm in the absence of medical error	Child on stimulant for attention deficit/hyperactivity disorder loses weight because of drug-induced appetite suppression
Preventable AE	Patient harm related to a medical error	Caused by lack of follow-up of newborn screening results, an infant with congenital hypothyroidism remains untreated for months and develops intellectual disability
Redundancy	Duplication of key part of process to reduce chance of error	Two nurses sign off on all chemotherapy orders before administration
Root cause analysis	A process of comprehensive investigation of all underlying causes of an error, emphasizing systems rather than individual performance	After serious medication error, a team of relevant staff is assembled to investigate possible causes and to recommend solutions to reduce or prevent recurrence of the error
Sentinel event	An unexpected occurrence involving actual or potential death or serious physical or psychological injury	Suicide of patient receiving around-the-clock care; infant abduction or discharge to wrong family; hemolytic transfusion reaction involving administration of blood or blood products with major blood group incompatibilities; surgery on wrong patient or body part; medication error resulting in major permanent loss of function or death
Serious reportable (never) event	An event that is unambiguous, serious, and usually preventable	Wrong-side surgery; invasive procedure on the wrong patient; death or serious injury caused by contaminated drugs or equipment; death caused by electric shock in health care setting



**Table 288-1** Definitions in Patient Safety—cont'd

TERM	DEFINITION	EXAMPLE
Six sigma	A quality improvement process that aims to reduce errors to approach <3.4 per million events	A children's hospital used six sigma approach to improve the accuracy of weight determination for pediatric burn patients to reduce medication and fluid administration errors
Slip	Error resulting from unconscious lapse in automatic task performance caused by distraction; a failure of execution	A physician intends to consult subspecialist about complex patient, but fails to do so because of distraction
Trigger tool	A measurable signal for detecting likely AEs	Using a Global Trigger Tool, investigators at a children's hospital detected incidence of harm 2 to 3 times higher than previously published pediatric rates

AAP, American Academy of Pediatrics; AE, adverse event.

From Lago P, Bizzarri G, Scalzotto F, et al. Use of FMEA analysis to reduce risk of errors in prescribing and administering drugs in paediatric wards: a quality improvement report. *BMJ Open*. 2012;2(6):pii:e001249; Galvan C, Bacha EA, Mohr J, Barach P. A human factors approach to understanding patient safety during pediatric cardiac surgery. *Prog Pediatr Cardiol*. 2005;20(1):13–20; Lighter DE. The application of lean six sigma to provide high-quality, reliable pediatric care. *Int J Pediatr Adol Med*. 2014;1(1):8–10; and Kirkendall ES, Kloppenborg E, Papp J, et al. Measuring adverse events and levels of harm in pediatric inpatients with the Global Trigger Tool. *Pediatrics*. 2012;130(5):e1206–1214.

medications for children are often provided with highly variable and inconsistent dosing directions and measuring devices, which may contribute to errors. Information materials provided by pharmacies, if provided at all, are often at health literacy levels above those of parents. Caregivers with limited English proficiency have additional barriers in understanding medication instructions; even when pharmacies provide translated instructions, these often contain errors generated by interpretation software. Adolescents with less parental supervision may also have increased risk for home medication error.

In the pediatric inpatient environment, medication error rates have ranged from 5% to 27%. A systematic review reported that dosing errors were the most frequent type of inpatient pediatric medication errors, and the medications most often involved were antibiotics and sedatives. Increased risk for inpatient medication errors have been reported during evening and weekend shifts, possibly attributable to less availability of hospital pharmacists. Dosing errors have been reported to be higher in overweight and obese pediatric inpatients. There is often confusion of pounds and kilograms in calculating doses. Tenfold medication errors, involving the omission or addition of zeroes, are a frequent source of inpatient dosing error. These occur often because of incorrect programming of infusion pumps, overriding alarm limits, or paper-based ordering or in urgent situations. Tenfold errors are most frequently reported with opioid medications. Medication errors in the PICU are better detected by direct observation than voluntary reporting.

### Surgical, Anesthesia, and Intensive Care Errors

Little has been reported on errors related to pediatric surgery. A single study of 64 pediatric surgical patients during a 1-month period detected 108 errors, with 28% resulting in adverse outcomes. Among all

adverse events, 47% were attributed to medical errors. Among all patients, 67% experienced at least 1 error, and 33% had an adverse outcome. Most frequent errors were in communication, postoperative monitoring and care, and diagnosis.

In a children's hospital in the United Kingdom, 668 incidents related to pediatric anesthesia were reported, a rate of 2.4% of all anesthetics recorded. Most incidents were related to airway and respiratory system (52%). Most frequent human factors involved were errors in judgment (43%), failure to check (18%), technical failures of skill, such as errors in central venous access or airway management (9%), inexperience (8%), inattention or distraction (6%), and communication errors (6%).

Among 606 pediatric anesthesia incidents from a national reporting system in the United Kingdom, 6 resulted in deaths and 48 in severe harm. Medication errors were involved in 36% of incidents, especially duplication of dosing in the operating room and floor. Other errors involved airway/ventilation (19%), cardiovascular events (6%), failure or unavailability of equipment (16%), and communication or organizational problems (9%).

Using a voluntary reporting system, among 464 incidents from 23 PICUs, medication errors were the most frequent type. Line, tube, and airway incidents accounted for one-third, but with higher degree of harm than other incidents. A systematic review of incidents and error in the NICU also found medication errors to be most frequently reported. The error rate was much higher in studies using voluntary versus mandatory reporting.

### Serious Reportable and Sentinel Events

*Serious reportable events* (formerly known as *never events*) are AEs that are easily identified and measured, serious, and usually preventable. The National Quality Forum initially defined these events in 2002,

currently consisting of 29 events grouped into 6 categories: surgical, product or device, patient protection, care management, environmental, radiologic, and criminal. A current list of serious reportable events may be found at [www.qualityforum.org/Topics/SREs/Serious\\_Reportable\\_Events.aspx](http://www.qualityforum.org/Topics/SREs/Serious_Reportable_Events.aspx).

Since 1995, The Joint Commission has recommended hospital reporting of *sentinel events*, defined as unexpected events involving death or serious injury, or risk for such occurrences. Sentinel events include all serious reportable events. After a sentinel event occurs, The Joint Commission requires a *root cause analysis* (RCA) (see Management).

In 2007, the Centers for Medicare and Medicaid Services announced that Medicare would cease payment for additional costs that resulted from many preventable errors, including serious reportable events. Similar policies have been adopted by many states and private insurers. Many states also mandate public reporting of serious reportable events and other serious AEs.

### Errors Specific to Outpatient Pediatrics

In a study of 14 pediatric practices, 147 medical errors were reported. The largest group of errors was related to medical treatment (37%), but errors were also associated with patient identification (22%), preventive care, including immunizations (15%), diagnostic testing (13%), patient communication (8%), and other causes.

In an outpatient pediatric department with approximately 36,000 visits per year, 80 errors were reported over a 12-month period (2.2 errors reported/1,000 visits/year). Errors were classified as involving office administration (34%), medications and other treatment (24%), laboratory and diagnostic testing (19%), and communication (18%). The most frequent office administration errors included wrong demographic information or date of visit (9%), misfiled papers in medical records (9%), and delays in processing patients because of misplaced registration forms (9%). The most frequent errors attributed to medication and other treatment included miswritten vaccine and medication order near miss (6%), wrong vaccine administered (5%), wrong outside prescription dispensed (4%), incomplete prescription returned by pharmacy (4%), and patient revaccinated too early (4%). Among errors attributed to laboratory and diagnostic testing, the most common were missed specimen pickup (10%) and mislabeled specimens (4%). The most frequent communication errors were patients leaving the practice before ordered vaccines were administered (8%).

In a pediatric clinic with approximately 26,000 visits per year, there were 216 medical errors reported over 30 months (3.3 errors/1,000 visits/year). The most frequently reported errors were misfiled or erroneously entered patient information (31%), laboratory test delayed or not performed (13%), error in medication prescribing or dispensing (11%), vaccine error (10%), patient not given requested appointment or referral (7%), and delay in office care (7%).

### Errors in Emergency Department Setting

In the pediatric emergency department (ED), errors may occur related to a busy environment with frequent

interruptions, faulty communication during patient handoffs, provider fatigue, decision-making by multiple providers, many verbal orders, language barriers with patients, lack of familiarity of adult staff with children, and treatment outside of the patient's medical home with lack of access to medical records. Medications are often grabbed out of a medication dispensing cabinet before profiling by a pharmacist.

Medication errors in the pediatric ED setting have been described in 10% to 15% of opportunities, with higher risk when ordered by inexperienced trainees, outside of regular daytime hours, or for very ill children. Inaccurate dosing of acetaminophen by pediatric ED staff has been reported 22% of the time.

### Errors Related to Information Technology

Health information technology has been implicated in a new breed of medical errors. Commonly reported errors among these include computer or network malfunction, truncated input data, inability to order items, incorrect default dosages for medications, data entered under wrong patient name, incorrect merging of more than 1 patient's data, lack of follow-up of critical abnormal test result alerts, discontinuation of medication without notifying staff, and billing requirements leading to inaccurate documentation. Electronic health records may exacerbate the risk for error by physicians overlooking data that are difficult to locate. Precompleted templates may contain inaccurate information that is not deleted or outdated information that is copied forward from prior notes. Electronic notes may import test results that were not reviewed.

## DIAGNOSIS

### Error Reporting

Awareness of medical errors is dependent on a reliable reporting system. Error reports may be filed electronically by call-in or on paper. They may be *anonymous*, *confidential*, or *open*. Traditional hospital incident reporting systems are open, with all involved individuals identified. These are often perceived as punitive, are poorly used, and miss many clinically significant events. The Institute of Medicine recommends a blame-free nonpunitive error reporting system that includes both adverse events and near misses, and a systems-based approach to analyzing errors. Such an approach shifts the blame away from individuals and to faulty or inadequate systems that contribute to medical errors. The American Academy of Pediatrics emphasizes the importance of creating a patient safety culture in which providers and staff understand the importance of patient safety and in which constant attention is paid to avoiding errors.

Anonymous reporting has been advocated to promote more complete error reporting. Although easier in theory, anonymous reporting has some limitations. True anonymity may be compromised when data in the report provide enough information for others to identify the specific situation and individuals involved. Also, anonymous reports may omit important data about a particular adverse incident, and the reporter cannot be contacted for more details.

**BOX 288-1 Examples of Pediatric Trigger Tools**

- Episode of cardiopulmonary arrest
- Hospital readmission within 30 days
- Emergency department readmission within 48 hours
- Return to surgery
- Naloxone administration
- Apgar score of <7 at 5 minutes

Confidential reporting enables the ability to conduct follow-up interviews and obtain more information from those involved in a specific event by potentially eliminating the fear of reporting. The promise of confidentiality is based on the premise that data will be accessible only to those who need it. This requires staff and leadership commitment to a safety culture in which unintentional errors are not punished. However, staff may not entirely trust such a system, fearing the disclosure of confidential information that could lead to punishment or litigation. Also, when confidential data are collected and shared with a third party, there may be concerns about possible discovery during a lawsuit. In a “just” safety culture, the parties involved have reasonable protection from legal and other harms.

**Trigger Tools**

Trigger tools use recognized measurable indicators to monitor and detect medical errors and adverse events. Typically, a trigger tool analysis involves retrospective review of a random sample of patient records using “triggers” (or clues) to identify possible adverse events (see Box 288-1). Detailed trigger tools for use in the PICU setting are available (see Tools for Practice). To date, outpatient trigger tools have not been established in pediatrics.

**MANAGEMENT**

Reports of medical errors may be managed with several processes, including RCA, morbidity and mortality conferences, patient safety organizations (PSOs), disclosure, and apology, as described later.

**Root Cause Analysis**

An RCA is a comprehensive method to identify as many causes for the error as possible, going beyond simple explanations to digging deeply into all contributing factors. To be successful, this method requires skilled leadership and an interdisciplinary team that includes expertise and interests of all parties relevant to the event. The goal of RCA is to focus on systemic factors leading to the error in order to develop preventive strategies to avoid recurrences of similar events. When present, human error should also be addressed. A cause-and-effect (fishbone or Ishikawa) diagram is often used to assist in showing root causes into specific categories, such as measurement, materials, methods, environment, staffing, and equipment.

Figure 288-1 is an example of a partial cause-and-effect diagram for a RCA of a report of wrong vaccine administration.

**Morbidity and Mortality Conferences**

Traditional hospital morbidity and mortality conferences may be helpful ways to present medical errors in an educational forum. When performed under the hospital’s quality assurance process, morbidity and mortality conferences are protected from legal exposure.

**Patient Safety Organizations**

Authorized by the Patient Safety and Quality Improvement Act of 2005 to improve quality and safety of health care delivery in the United States (see [www.pso.ahrq.gov/statute/pl109-41.pdf](http://www.pso.ahrq.gov/statute/pl109-41.pdf)), PSOs allow individual physicians and health care organizations to voluntarily report and share medical errors in a framework that is protected from legal discovery. Eligible organizations may apply to become PSOs to create a secure environment to collect, aggregate, and analyze patient safety data in order to identify and reduce risks and hazards resulting from medical care. A current list of federally approved PSOs is available at [www.pso.ahrq.gov/listing/alphabet.htm](http://www.pso.ahrq.gov/listing/alphabet.htm).

**Error Disclosure and Apologies**

Following a significant medical error, patients and their families often express their desire to know what happened, why it happened, and what will be done so that it does not happen again. Establishing trust with families by initiating early and full disclosure may reduce tensions and save time, resources, and strain on families and physicians. Lack of communication about errors may make patients feel worse and lead to physician feelings of anxiety, unworthiness, and guilt. Pediatricians and institutions should develop policies and procedures for disclosing adverse events to families, as well as to children when age appropriate.

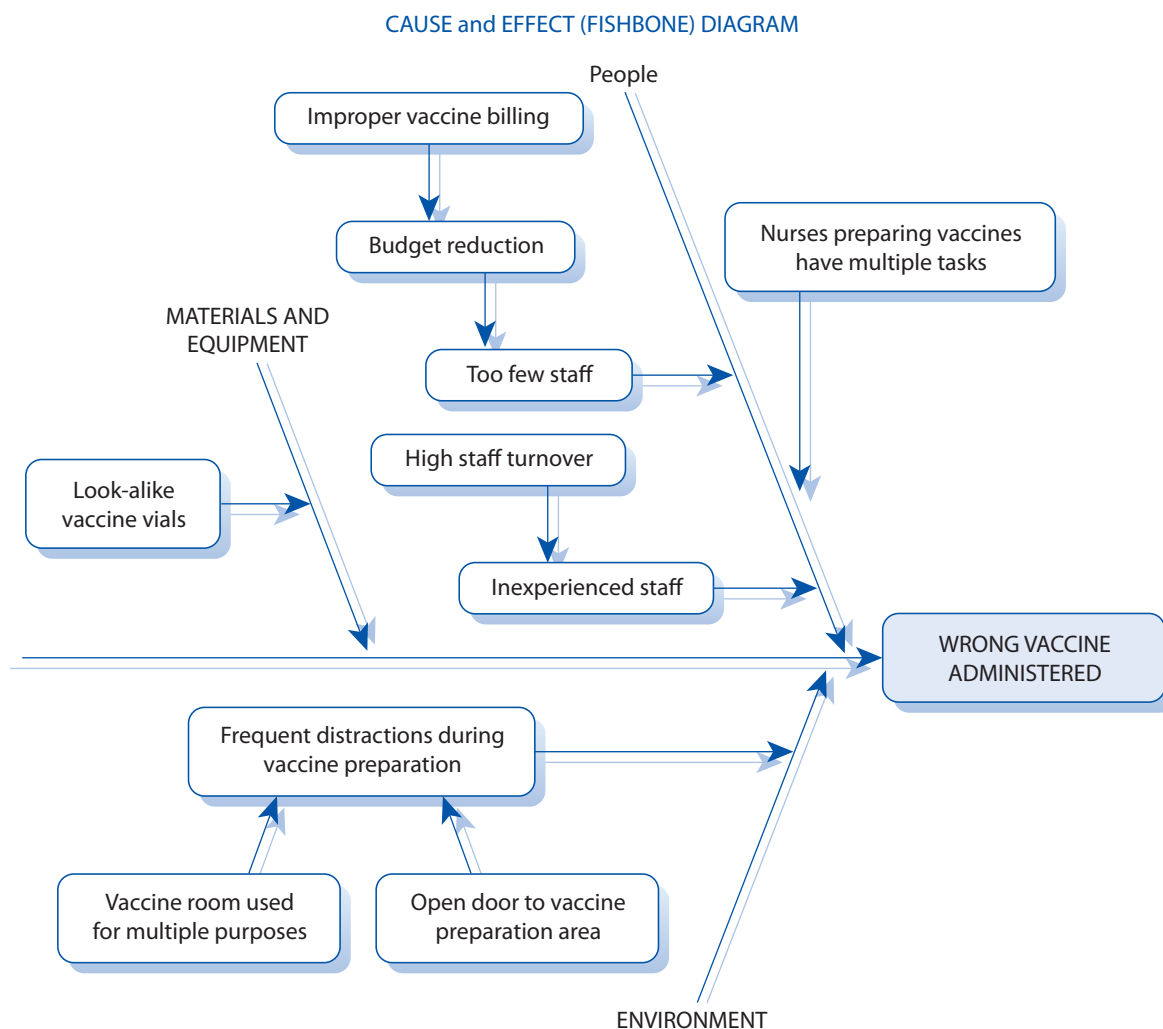
Physicians may hesitate to apologize about an error if doing so can be used as an admission of wrongdoing in a legal action. Acknowledging this phenomenon, many states enacted statutes protecting apologies from admission as evidence in malpractice litigation. Most states now have “apology laws” to protect a physician statement such as “I’m sorry,” but may not protect admissions of fault ([sorryworkssite.bondwaresite.com/apology-laws-cms-143](http://sorryworkssite.bondwaresite.com/apology-laws-cms-143)). Pediatricians and other child health care providers should discuss specific institutional policies and state disclosure statutes in effect with their malpractice carriers or risk managers.

**PREVENTION**

There are many ways that pediatricians and other physicians caring for children can improve patient safety and reduce the risk for adverse events. Efforts to prevent medical errors in pediatrics are multifaceted and are summarized in Table 288-2.

**Human Factors**

Human factors science is the study of designing systems and equipment to fit the human body and its cognitive abilities. It looks at the intersection of



**Figure 288-1** Cause-and-effect (fishbone) diagram.

people, technology, and work processes to design efficient, high-reliability systems with reduced chance of error.

### Design Modifications

Design and storage modifications to promote pediatric safety include changes to avoid confusion between look-alike, sound-alike medications for hospital and office staff, as well as smart infusion pumps in the inpatient setting. In the home setting, improving caregiver dosing tools may reduce medication errors. Including pictographic dosing diagrams with written medication instructions among parents with low health literacy reduced medication administration errors compared with text-only recipients. A sliding-card-based dosing tool was effective in improving accuracy of home administration of acetaminophen. Dosing errors by parents were more frequent with measuring cups compared with droppers, spoons, or syringes.

### Medication Reconciliation

*Medication reconciliation* may reduce medication errors, particularly during transitions of care. Since 2005, medication reconciliation has been a national

patient safety goal of the Joint Commission ([www.jointcommission.org/sentinel\\_event\\_alert\\_issue\\_35\\_using\\_medication\\_reconciliation\\_to\\_prevent\\_errors](http://www.jointcommission.org/sentinel_event_alert_issue_35_using_medication_reconciliation_to_prevent_errors)). This process compares a patient's medication orders to all the medications that the child has been taking. It is done to avoid medication errors, such as omissions, duplications, dosing errors, or drug interactions, and should be done at every transition of care when new medications are ordered or existing orders are rewritten. Transitions in care include changes in setting, service, physician, or level of care (see Box 288-2).

Medication reconciliation in pediatrics has primarily focused on the inpatient setting, but its use is also valuable in ambulatory care.

Errors may occur in the medication reconciliation process because of inaccurate medication histories. Parents may not be aware of the specific medications taken by their children. Some electronic health records may not automatically remove short-term medications from the child's medication list.

### Clinical Pharmacists

The presence of clinical pharmacists has been effective in reducing medication errors in the pediatric inpatient



**Table 288-2** Strategies to Improve Patient Safety

STRATEGY	INPATIENT EXAMPLE	OUTPATIENT EXAMPLE
Attention to human factors	Standardize devices in hospital to make training easier and increase reliability	Alcohol-based gel dispensers are placed at entry to all examination rooms
Design modifications of medications and dosing tools	Avoid colocating look-alike or sound-alike medications	Use standardized dosing syringes for all oral liquid medications
Regular medication reconciliation, especially after transitions of care	Conduct medication reconciliation at hospital admission and discharge for all patients	Conduct medication reconciliation at all outpatient visits
Clinical pharmacists at the point of practice	Pharmacist joins inpatient team for daily rounds	Pharmacist is based in outpatient practice
Bar code systems	Nurse must swipe bar code on medication, patient's wristband, and nurse's identification badge before medication administration	A bar code system is used to match a patient's wristband with labels used for outpatient laboratory tests
Standardization and checklists	A preprocedure checklist is used to reduce catheter-related bloodstream infections	Nursing staff uses a checklist to maintain standardized examination room stocking of needed equipment and supplies
Standard communication and handoff procedures	The I-PASS (I: illness severity; P: patient summary; A: action items; S: situation awareness and contingency planning; S: synthesis by receiver) handoff bundle is used to promote safer inpatient care ( <a href="http://www.ipasshandoffstudy.com/about">www.ipasshandoffstudy.com/about</a> )	SBAR (situation, background, assessment, recommendations) is used to structure standard communication when sending a patient from the outpatient practice to the emergency department
Forcing functions	Intravenous pumps and gastrostomy tubing have different connectors to avoid errors	Prescription dosing on an electronic medical record is limited by the patient's weight to avoid underdosing and overdosing
Redundancy	Pharmacist and 2 nurses check medication dose before administration	Physician and nurse check vaccine order with immunization registry record before administration
Health information technology	An electronic order set is used to standardize management of inpatients with asthma exacerbations	Electronic prescriptions assist in reducing errors in medication orders filled by community pharmacies
Quality improvement methodology	A hospital-wide quality improvement collaborative was effective in reducing adverse drug reactions	An outpatient pediatric practice aims to improve informing parents about newborn screen results to a level of 90% within the next 6 months and uses plan-do-study-act cycles to achieve this aim
Education of staff and trainees	All inpatient pediatric staff are trained in the TeamSTEPPS process to improve communication and teamwork skills ( <a href="http://teamstepps.ahrq.gov">teamstepps.ahrq.gov</a> )	All pediatric practice staff are given training in medication reconciliation to reduce medication errors

Derived from McClead RE, Catt C, Davis JT, et al. An internal quality improvement collaborative significantly reduces hospital-wide medication error related adverse drug events. *J Pediatr*. 2014;165(6):1222–1229.

### BOX 288-2 Steps of Medication Reconciliation

1. Develop a list of current medications.
2. Develop a list of medications to be prescribed.
3. Compare the medications on the 2 lists.
4. Make clinical decisions based on the comparison.
5. Communicate the new list to appropriate caregivers and to the patient.

setting. Pharmacists trained in pediatric pharmacotherapy may promote safe and effective drug therapy for children and prevent harm from medication errors, particularly when these professionals are integrated into the medication prescription process from the beginning.

### Bar Code Systems

The implementation of a bar code medication administration system reduced preventable adverse drug events in an NICU by 47%. Bar code systems are also implemented to prevent errors in patient identification.

However, new errors may occur when workarounds are used, such as wearing patient bar-coded labels on nursing scrubs or affixing them to computer carts to avoid scanning the patient's identification wristband each time medication is administered.

### Standardization and Checklists

Preprinted order sets have led to reduced pediatric sedation errors. Other printed and computerized order sets may be of value in preventing medication errors. A checklist was effective in reducing the rate of technical prescription writing errors in a pediatric inpatient setting. The 19-item WHO Surgical Safety Checklist was developed to decrease errors and adverse events and increase teamwork and communication in surgery. It has been effective in reducing surgical morbidity and mortality and has been implemented internationally ([www.who.int/patientsafety/safesurgery/checklist/en](http://www.who.int/patientsafety/safesurgery/checklist/en)).

### Standard Communication and Handoff Procedures

Patient handoff communication errors are a major source of adverse events. A resident handoff bundle, including standardized communication and handoff training, a verbal mnemonic, and a new team hand-off structure, was effective in reducing handoff errors among hospitalized children.

### Forcing Functions

A forcing function is a limit built into a process that impels the user to take the correct action. It prevents a target action or allows it to occur only if another specific action happens first. An example of a forcing function is the removal of concentrated potassium from general inpatient units.

### Redundancy

Redundancy is duplication of the key part of a process to reduce the likelihood of error. An example is 2 nurses checking medication orders and preparation. These double-checking or backup systems may not ensure safety because they often rely on human behavior.

### Health Information Technology

Electronic prescribing has the potential to reduce outpatient medication errors, particularly if the program is incorporated into an electronic health record, with access to patient medication histories, allergies, and clinical decision support. In the pediatric inpatient setting, computerized physician order entry has reduced medication prescription errors but has variable effect on patient outcomes.

Computerized clinical decision support, either stand-alone or in combination with computerized physician order entry, has been associated with decreased adverse drug events and error rates, but its effect on patient outcomes is uncertain. Specific alerts for duplicate medications, drug interactions, and drug allergies have not shown consistent benefit. Dosing calculators and dose range alerts may lower dosage errors, but alerts are frequently overridden by providers. Evidence-based reminders may help promote better adherence to evidence-based clinical practice guidelines.

### BOX 288-3 Steps in Failure Modes and Effects Analysis

- Define steps in the process under study.
- Delineate potential failure modes (ie, What could go wrong?).
- Analyze causes of potential failure in the process.
- Describe consequences of each failure.

### Quality Improvement Methodology and Multidisciplinary Safety Teams

Quality improvement efforts involving multidisciplinary teams to detect errors and implement system changes may help us understand the factors contributing to pediatric medical errors and generate more effective strategies to prevent them. A continuous quality improvement approach with voluntary, nonpunitive error reporting systems, coupled with multidisciplinary teams to analyze reports and recommend rapid system changes, has been effective in addressing medical errors in the ambulatory setting. Reports of effective use of quality improvement methodology to reduce medical errors in the pediatric inpatient setting have been reported among general pediatric and neonatal patients, as well as in pediatric subspecialty units caring for children with cardiac, oncologic, and neurologic conditions.

One type of quality improvement methodology that is useful in addressing adverse events before they occur is *failure modes and effects analysis* (FMEA). This is used to proactively evaluate processes for possible failures and to prevent them rather than reacting to medical errors that have already occurred. FMEA is a systematic preventive quality improvement method to identify potential sources of failure of a process and to assess the relative effect of different failures, with the goal of identifying the steps in the process where changes would be effective in reducing the risk for errors (see Box 288-3). FMEA may be particularly useful in evaluating a new process before implementation and in assessing the effect of a proposed change to an existing process. FMEA has been used effectively to prevent medication errors in the pediatric inpatient setting.

### Educational Interventions

A physician prescribing tutorial may reduce prescription errors in the pediatric inpatient setting by 46%. Proper medication administration by NICU nurses may improve with a multifaceted educational program. Pediatric trainees may improve their prescription competency by ongoing training and monitoring and after participating in an e-learning program.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *The Chance of a Lifetime: Team Up With Your Doctor and Your Pharmacist to Ensure Your Future Health* (handout), Families Launching Action Against Medication Errors (FLAAME) ([www2.aap.org/saferhealthcare/FlaamePamphlet.pdf](http://www2.aap.org/saferhealthcare/FlaamePamphlet.pdf))

- *Five Steps to Safer Health Care* (fact sheet), Agency for Healthcare Research and Quality ([www.ahrq.gov/patients-consumers/care-planning/errors/5steps/index.html](http://www.ahrq.gov/patients-consumers/care-planning/errors/5steps/index.html))
- *Safer Health Care for Kids* (Web site), American Academy of Pediatrics ([www.aap.org/saferhealthcare](http://www.aap.org/saferhealthcare))
- *Twenty Tips to Help Prevent Medical Errors in Children* (fact sheet), Agency for Healthcare Research and Quality ([www2.aap.org/saferhealthcare/files/5907\\_20tipkid.pdf](http://www2.aap.org/saferhealthcare/files/5907_20tipkid.pdf))

### Medical Decision Support

- *Safer Health Care for Kids: Resources* (Web page), American Academy of Pediatrics ([www2.aap.org/saferhealthcare/resources.html](http://www2.aap.org/saferhealthcare/resources.html))

### Practice Management and Care Coordination

- *Institute for Healthcare Improvement* (Web site), ([www.ihl.org](http://www.ihl.org))
- *Patient Safety Network* (Web site), Agency for Healthcare Research and Quality ([www.psnet.ahrq.gov](http://www.psnet.ahrq.gov))
- *PICU Trigger Instruction Manual: Measuring Adverse Events in the PICU Using a PICU Trigger Tool* (booklet), Child Health Corporation of America ([www.chca.com/triggers/docs/PICU\\_triggertoolkit\\_for%20CHCAwebsite.pdf](http://www.chca.com/triggers/docs/PICU_triggertoolkit_for%20CHCAwebsite.pdf))

### AAP POLICY

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## Chapter 289 MENINGITIS

Geoffrey A. Weinberg, MD; Ann M. Buchanan, MD, MPH

The meninges of the central nervous system (CNS) include 3 membranes that support, protect, and nourish the brain and spinal cord. The outermost layer, the

dura mater, is a tough, inelastic, connective tissue layer that sheaths the brain and spinal cord and terminates caudally at the first coccygeal vertebra. The middle and innermost layers, the arachnoid and the pia mater, respectively, are similar in structure and are often referred to singly as the leptomeninges. The arachnoid and pia are partly separated, leaving a subarachnoid space containing cerebrospinal fluid (CSF). The CSF is formed in the choroid plexuses within the ventricles of the brain, which communicate with the subarachnoid space through the foramina of the fourth ventricle (via the median aperture of Magendie and the lateral apertures of Luschka). The CSF slowly circulates in both directions around the brain and spinal cord; it is reabsorbed predominantly by the arachnoid villi of the superior sagittal sinus.

Meningitis, or inflammation of the meninges, is most often caused by an infectious agent and less commonly by a chemical (medication) or malignancy. Bacterial meningitis, also known as *pyogenic meningitis*, is often quickly fatal, making early diagnosis and treatment essential.

Aseptic meningitis refers to inflammation of the meninges, as demonstrated by CSF pleocytosis, without the presence of visible micro-organisms on routine Gram staining and a negative culture for bacteria. Nonpolio enteroviruses cause 85% of cases of aseptic meningitis in the United States. However, fungi, parasites, reactions to medications, and atypical bacteria not well seen on Gram staining may also cause aseptic meningitis. Thus, the term is not synonymous with viral meningitis, although the 2 terms are often used interchangeably. The CSF findings characteristic of both pyogenic and aseptic meningitis are listed in Table 289-1 and Table 289-2. When encephalitis accompanies aseptic meningitis, the cause may be distinct, and the clinical course may be much more severe (see Chapter 290, Meningoencephalitis).

In partially treated meningitis, antibiotics have been provided before lumbar puncture is performed, rendering Gram staining and bacterial culture less useful (because of the possibility of temporary bacterial sterilization). Distinguishing partially treated bacterial meningitis with false-negative CSF cultures from aseptic meningitis can be difficult, although the accompanying CSF laboratory studies (white blood cell [WBC] count and differential, CSF protein, and glucose concentrations) may often be of assistance.

A number of reviews summarize in detail the epidemiology, pathophysiology, diagnosis, and treatment of meningitis in children and adults; this chapter highlights pertinent aspects of pediatric and neonatal meningitis.

### EPIDEMIOLOGIC FEATURES

The incidence of bacterial meningitis is related closely to age, and has been tremendously reduced overall in the past 20 years because of the implementation of routine bacterial polysaccharide-protein conjugate vaccinations. As an example, in the pre-conjugate vaccination era in the United States, as recently as the late 1980s, during the first month of life, the age-specific incidence was as high as 300 to 400 cases per 100,000 live births; cases of bacterial meningitis decreased to

141 per 100,000 during the second month of life and to less than 50 per 100,000 in the second year of life. A second peak occurred at 6 to 8 months, with an incidence of nearly 180 per 100,000 infants. This second peak, which was caused by *Haemophilus influenzae* type b (Hib) meningitis, has declined dramatically since 1988, when Hib conjugate vaccines were approved for use. Between 1987 and 1997, the incidence of Hib meningitis fell from 40 cases per 100,000 children younger than 5 years to 1 case per 100,000, and current annual estimates are as low as 0.1 cases per 100,000 (Figure 289-1). This remarkable decline in Hib meningitis converted bacterial meningitis to a disease predominantly of adults rather than of infants and young children, with the median age at diagnosis

25 years in 1995 as opposed to 15 months in 1985 (Figure 289-2).

With the implementation of routine immunization in the United States with pneumococcal conjugate vaccine in infancy in 2000, a 70% to 90% decline was documented in cases of invasive pneumococcal disease, including meningitis (Table 289-3). In 2009, a 13-valent pneumococcal conjugate vaccine replaced the 7-valent vaccine in the US immunization schedule, and the annual incidence rates of invasive pneumococcal disease in children ages 5 years or younger have fallen to approximately 20 per 100,000 children per year, as opposed to 100 per 100,000 children per year before routine conjugate vaccination began. Bivalent and tetravalent meningococcal conjugate

**Table 289-1** Characteristic Cerebrospinal Fluid (CSF) Findings in Children With and Without Meningitis<sup>a</sup>

CSF FINDINGS	NORMAL	BACTERIAL	VIRAL	FUNGAL OR TUBERCULOUS
<b>LEUKOCYTES/<math>\mu</math>L</b>				
Usual	<5	>500	<500	50–750
Range	0–10	10–20,000	0–1000	10–1500
<b>POLYMORPHONUCLEAR NEUTROPHILS (% OF LEUKOCYTES)</b>				
Usual	2	>80	<50	<50
Range	0–20	20–100	0–100	0–80
<b>GLUCOSE, MG/DL</b>				
Usual	60	<40	>40	<40
Range	45–65	0–65	30–65	5–50
Usual CSF/blood (%)	$\geq 60$	<30	30–60	<40
<b>PROTEIN, MG/DL</b>				
Usual	$\leq 30$	>100	<100	50–200
Range	0–40	40–500	20–200	40–1500
<b>OTHER POSITIVE TESTS</b>	None	Gram stain, antigen detection	Polymerase chain reaction	Cryptococcal antigen, acid-fast stain

<sup>a</sup>See Table 289-2 for CSF findings of neonates.

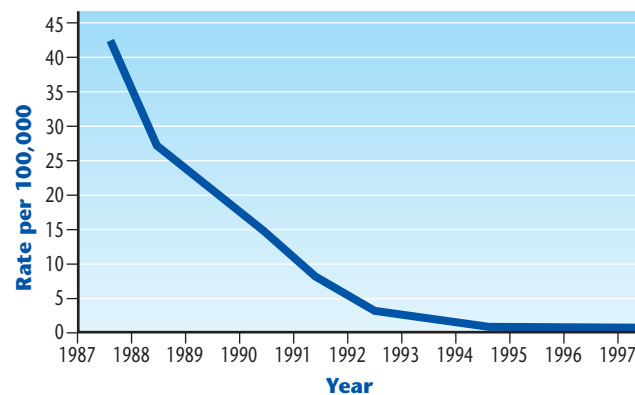
**Table 289-2** Representative Cerebrospinal Fluid (CSF) Findings in Neonates Without Meningitis<sup>a</sup>

CSF FINDING	FULL-TERM NEONATES MEAN (RANGE)		PRETERM NEONATES MEAN (RANGE)	
	0–7 DAYS	8–28 DAYS	0–7 DAYS	8–28 DAYS
Leukocytes/ $\mu$ L	8 (1–30)	6 (0–18)	4 (1–10)	7 (0–44)
Polymorphonuclear neutrophils (% of leukocytes)	5	3	7	9
Protein (mg/dL)	81	64	150 (85–222)	148 (54–370)
Glucose (mg/dL)	46	51	72 (4–96)	64 (33–217)
CSF/blood glucose (%)	0.73	0.62	Not reported	Not reported

<sup>a</sup>Data from Ahmed A, Hickey SM, Ehrett S, et al. Cerebrospinal fluid values in the term neonate. *Pediatr Infect Dis J*. 1996;15(4):298–303; Rodriguez AF, Kaplan SL, Mason EO Jr. Cerebrospinal fluid values in the very low birth weight infant. *J Pediatr*. 1990;116(6):971–974; Byington CL, Kendrick J, Sheng X. Normative cerebrospinal fluid profiles in febrile infants. *J Pediatr* 2011;158(1):130–134; and Kestenbaum LA, Ebberson J, Zorc JJ, Hodinka RL, Shah SS. Defining cerebrospinal fluid white blood cell count reference values in neonates and young infants. *Pediatrics* 2010;125(2):257–264.



vaccines have been licensed for use in selected infants and children, and for general use in adolescents; similar monovalent and bivalent conjugate vaccines provided to infants and younger children have reduced meningococcal meningitis rates in Europe (see Table 289-3). In the United States, however, because the fraction of meningococcal disease in young children caused by the nonconjugate vaccine serogroup B is greater than that in Europe, use of the current tetravalent conjugate vaccine (serogroups ACYW135) will not eliminate meningococcal infection in infants.



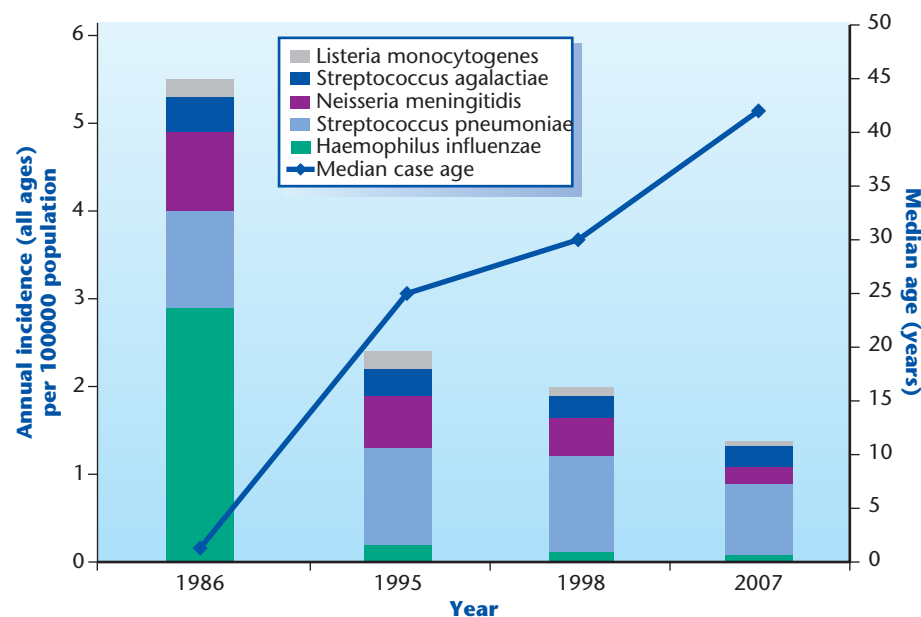
**Figure 289-1** Incidence of *Haemophilus influenzae* type b meningitis per 100,000 children younger than 5 years of age in the United States, 1987-1997. (From Centers for Disease Control and Prevention. Progress toward eliminating *Haemophilus influenzae* type b disease among infants and children—United States, 1987-1997. MMWR Morb Mortal Wkly Rep. 1998;47(46):993.)

In addition to the age-related changes in incidence, the spectrum of etiologic agents of bacterial meningitis changed remarkably with age—at least before the routine implementation of antibiotic prophylaxis for group B  $\beta$ -hemolytic streptococci and the licensure of conjugate vaccines (Figure 289-3). Until recently, during the first month of life, more than two-thirds of the cases of neonatal bacterial meningitis were caused by group B  $\beta$ -hemolytic streptococci (*Streptococcus agalactiae*) or gram-negative enteric organisms, primarily *Escherichia coli*, *Klebsiella*, and *Enterobacter* species. With antibiotic prophylaxis, the contribution of group B  $\beta$ -hemolytic streptococci to early-onset meningitis is decreasing (although late-onset disease has not decreased). In some regions, another fairly common cause of neonatal meningitis is *Listeria monocytogenes*. After the first month of life, *Listeria* organisms are found as the cause of meningitis mostly in immunocompromised or elderly persons.

The incidence of aseptic meningitis (predominantly caused by enteroviruses) ranges, in different years, from 1.5 to 4 cases per 100,000 population. The incidence in children is actually much higher because aseptic meningitis is still a disease of the young, with few reported cases occurring in persons older than 30 years; however, age-adjusted incidence rates are not available.

## BACTERIAL MENINGITIS AFTER THE NEONATAL PERIOD

Most cases of bacterial meningitis in children older than 1 month are caused by *Neisseria meningitidis* or, increasingly less often, *Streptococcus pneumoniae* or Hib in regions where pneumococcal and Hib conjugate vaccines are widely used (Figure 289-3 and



**Figure 289-2** Incidence and median age of cases of bacterial meningitis in the USA during selected years 1986-2007, caused by *Listeria monocytogenes*, *Streptococcus agalactiae*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. (From McIntyre PB, Brien KL, Greenwood B, van de Beek D. Effect of vaccines on bacterial meningitis worldwide. Lancet. 2012;380[9854]:1703-1711. Used by permission.)

**Table 289-3** Changes in Incidence of Invasive Bacterial Disease (Including Meningitis) With Universal Implementation of Immunization With Conjugate Vaccines

INFECTION	STUDY POPULATION	AGE GROUP, Y	INCIDENCE PER 100,000 POPULATION PER YEAR		
			PRECONJUGATE VACCINE USE	POSTCONJUGATE VACCINE USE	PERCENTAGE CHANGE
<i>Haemophilus influenzae</i> b	US children <sup>b</sup>	<5	23	0.3	–99
<i>Streptococcus pneumoniae</i> (all serotypes) <sup>a</sup>	US children <sup>c</sup>	<2	188	59	–69
	US children <sup>d</sup>	<2	112	10	–91
<i>Neisseria meningitidis</i> serogroup C	UK children and adolescents <sup>e</sup>	<17	74	1.4	–81

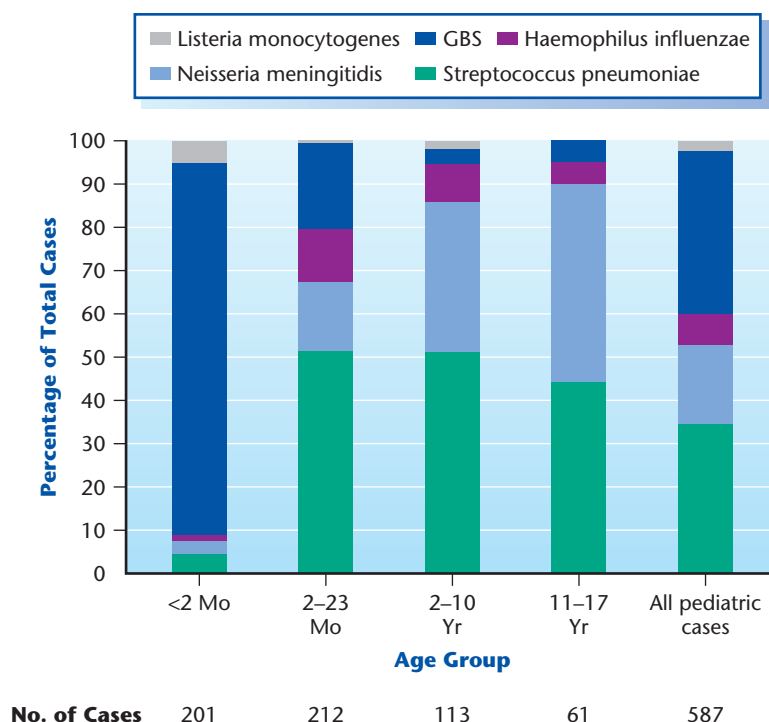
<sup>a</sup>Both studies demonstrated herd effects of lowered rates of pneumococcal invasive disease in adults after initiation of conjugate immunization in children. Decreases in outpatient pneumonia and otitis reported to be 10- to 100-fold greater than that of the invasive disease in other studies of US children.

<sup>b</sup>Centers for Disease Control and Prevention. Progress toward eliminating *Haemophilus influenzae* type b disease among infants and children—United States, 1988–2000. *MMWR*. 2002;51:234–237.

<sup>c</sup>Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med*. 2003;348:1737–1746.

<sup>d</sup>Black S, Shinefield H, Baxter R, et al. Postlicensure surveillance for pneumococcal invasive disease after use of heptavalent pneumococcal conjugate vaccine in Northern California Kaiser Permanente. *Pediatr Infect Dis J*. 2004;23:485–489.

<sup>e</sup>Miller E, Salisbury D, Ramsay M. Planning, registration, and implementation of an immunization campaign against meningococcal serogroup C disease in the UK: a success story. *Vaccine*. 2002;20(suppl 1):S58–S67.



**Figure 289-3** Proportions of 587 cases of pediatric bacterial meningitis in the USA in 2003–2007 caused by each pathogen, according to age group. GBS, group B *Streptococcus* (*Streptococcus agalactiae*). (From Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States, 1998–2007. *New Engl J Med* 2011;364(21):2016–2025. Used by permission.)

Table 289-3). Current mortality rates vary according to the pathogen and have been reported to be up to 10% for *S pneumoniae*, 4% for *N meningitidis*, and less than 1% for Hib.

All 3 of these pathogens can be isolated from the throat or nasopharynx of healthy individuals. Most studies of microorganism carrier states suggest that

children at highest risk for disease are also the most likely to be colonized. In the pre-Hib conjugate vaccine era, approximately 70% of toddlers and 48% of the preschool-aged children in some child care centers were colonized with Hib, but no invasive Hib disease was observed. Thus, colonization with Hib, *S pneumoniae*, or *N meningitidis*, does not always cause

meningitis. Indeed, nasopharyngeal colonization may be a partially immunizing event that contributes to future host defense; however, when microbial virulence factors overcome host defense, bacterial meningitis ensues.

The successful meningeal pathogen must follow several sequential steps. Nasopharyngeal mucosal colonization is facilitated by various microbial-binding adhesins and secreted enzymes such as immunoglobulin A (IgA) protease, which cleaves host secretory IgA. Next, invasion across the epithelium, followed by survival of bacteria in the bloodstream (by evading the action of the alternative complement pathway) are required. Finally, the bacteria must invade the CSF by crossing the blood-brain barrier.

Meningitis may occasionally occur after head trauma, particularly with fractures of the paranasal sinuses or middle ear. The pathogens most often associated with meningitis after trauma are *S pneumoniae* (often less pathogenic capsular serotypes) and *H influenzae* (often nontypable or encapsulated but non-type b strains). Post-traumatic meningitis can recur if CSF leakage persists.

Meningitis can also occur by direct spread from a congenital dermal sinus that communicates with the CNS. Any time meningitis is caused by bacteria that normally reside on the skin or in the gastrointestinal tract, a diligent search of the craniospinal axis should be made. Meningitis can develop after neurosurgery and is not uncommon after procedures performed to shunt ventricular fluid. Coagulase-negative staphylococci are the organisms most often associated with shunt infections. Cochlear implantation has been recognized as an additional risk factor for bacterial meningitis.

Once bacteria establish growth in the CSF, cell wall products, such as lipopolysaccharide (endotoxin), teichoic acid, and peptidoglycans, are liberated, which induce the local production and secretion of inflammatory cytokines (especially interleukin-1 and -6 and tumor necrosis factor). The action of these cytokines results in activation of leukocytes and vascular metabolism, which leads to leukocyte migration (diapedesis), endothelial injury, and blood-brain barrier breakdown. The injury to the cerebral microvasculature, along with increasing inflammation, culminate in brain edema, reduction of cerebral blood flow, thrombosis, and impairment of oxygen and glucose delivery.

### Differential Diagnosis

Signs and symptoms suggesting meningeal inflammation or increased intracranial pressure can arise from infections of the CNS other than pyogenic meningitis. The most common cause of meningeal inflammation is enteroviral aseptic meningitis, which is discussed later in this chapter. Aseptic meningitis can also be caused by Lyme disease spirochetes (*Borrelia burgdorferi*), *Mycobacterium tuberculosis*, fungi, parasites, or inflammatory conditions. Meningitis or meningoencephalitis may also be present in children who have Rocky Mountain spotted fever (see Chapter 325), Kawasaki disease (see Chapter 280), cat-scratch disease, or toxic shock syndrome (see Chapter 340), and is often associated with or occurs after mumps, rubeola, rubella, varicella, infectious mononucleosis, roseola, and erythema

infectiosum (Table 289-4). A brain abscess, epidural abscess, primary amebic meningoencephalitis, embolic diseases (eg, endocarditis, thrombophlebitis), venous sinus thrombosis, space-occupying lesions, reactions to medications (eg, intravenous immunoglobulin, intravenous monoclonal antilymphocyte antibody, oral trimethoprim-sulfamethoxazole, some oral nonsteroidal anti-inflammatory drugs), ingestion of toxins (eg, lead), spider bites, pemphigus, and Behçet syndrome can mimic bacterial meningitis. However, interpretation of the CSF findings in the context of the clinical manifestations usually differentiates bacterial meningitis from other diseases. Eosinophilic meningitis is rarely seen; the differential diagnosis includes reactions to ventriculoperitoneal shunts, unusual presentations of bacterial or *Toxoplasma* infection, or parasitic roundworms. Conditions that can simulate a clinical picture of meningitis, but that usually have normal CSF findings, include pharyngitis (see Chapter 311, Pharyngitis and Tonsillitis), retropharyngeal abscess (see Chapter 348, Airway Obstruction), cervical adenitis (see Chapter 175, Lymphadenopathy), cervical spine arthritis or osteomyelitis (see Chapter 304), pyelonephritis (see Chapter 294, Nephritis), pneumonia (see Chapter 315), torticollis (see Chapter 203), tetanus, and oculogyric crisis.

### Clinical Manifestations

Children who have bacterial meningitis usually have a fever; however, the absence of fever in a child who has signs of meningeal irritation does not preclude the diagnosis. Inflammation of the meninges can be characterized by irritability, anorexia, headache, nausea, vomiting, confusion, back pain, nuchal rigidity, and photophobia. Kernig and Brudzinski signs can be assessed during the physical examination to demonstrate meningeal inflammation (Figure 289-4). Kernig sign is elicited in the supine child by extending the leg at the knee while the hip is flexed at 90 degrees. When positive, this maneuver causes extensor spasm of the knee and pain in the hamstrings of a person who has meningitis when the lower leg is extended to approximately 135 degrees. Brudzinski sign is elicited by flexing the neck of a child in the supine position; in a positive test, the child will involuntarily flex the hips and knees. Stiffness of the neck is a sensitive (80%–98%) indicator of true bacterial meningitis in children, adolescents, and adults.

In a young infant, however, signs of meningeal inflammation can be minimal or absent. Thus, in children younger than 12 months, the absence of nuchal rigidity must not be used to exclude meningitis. Distinguishing nuchal rigidity from voluntary movement and guarding can also be difficult in a sick infant with irritability. In this case, the additional signs of lethargy, poor feeding, and restlessness may be helpful. Additionally, laying the infant near the edge of the examining table with the head supported by the examiner's hand, but gently extended off the edge of the table, may be useful. The natural tendency for the infant in this position will be to try to lift the head, at which time the examiner can feel whether nuchal rigidity, rather than voluntary guarding or noncooperation, is preventing flexion of the neck.

**Table 289-4** Selected Causes of Aseptic Meningitis<sup>a</sup>

CAUSE	COMMON	UNCOMMON	RARE
Viruses	Enteroviruses Arboviruses Herpes simplex type 2  Human herpesvirus 6	HIV-1 Epstein-Barr virus Lymphocytic choriomeningitis virus Mumps	Adenovirus Varicella zoster virus Cytomegalovirus  Measles Rubella Parvovirus B19 Influenza A and B <i>Chlamydia psittaci</i> <i>Chlamydia pneumoniae</i> <i>Rickettsia prowazekii</i> <i>Coxiella burnetii</i> <i>Brucella abortus</i> <i>Streptobacillus moniliformis</i> Various molds
Bacteria	Pyogenic (partially treated) <i>Mycobacterium tuberculosis</i> <i>Borrelia burgdorferi</i> <i>Mycoplasma pneumoniae</i> <i>Leptospira</i> species	<i>Treponema pallidum</i> <i>Borrelia</i> species <i>Bartonella henselae</i> <i>Rickettsia rickettsii</i> <i>Ehrlichia canis</i>	
Fungi	<i>Candida</i> species <i>Cryptococcus neoformans</i> <i>Histoplasma capsulatum</i> <i>Coccidioides immitis</i>	<i>Blastomyces dermatitidis</i>	
Parasites	—	<i>Toxoplasma gondii</i> Neurocysticercosis	<i>Angiostrongylus cantonensis</i> <i>Baylisascaris procyonis</i> <i>Strongyloides stercoralis</i> Free-living amoebae Sarcoidosis
Miscellaneous	Parameningeal infections  Kawasaki disease Foreign bodies (CSF shunts) CNS leukemia, tumors ADEM	Medications (TMP-SMX, IgIV, ibuprofen) Systemic lupus erythematosus	Behçet syndrome Heavy metal poisoning — —

ADEM, acute disseminated encephalomyelitis; CNS, central nervous system; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; IgIV, intravenous immunoglobulin; TMP-SMX, trimethoprim-sulfamethoxazole.

<sup>a</sup>Common, uncommon, and rare refer to relative frequencies within each broad category of etiologic agents (eg, viruses, bacteria). Overall, enteroviruses cause at least 85% of the aseptic meningitis diagnosed in children in the United States, and arboviruses cause approximately 5%; all other causes combined account for the remaining 10% or less of cases.

The child with meningitis may also have signs of increased intracranial pressure, such as a headache or a bulging fontanelle. Papilledema is uncommon with bacterial meningitis, and when present, other causes should be sought; bacterial meningitis progresses so quickly that papilledema may not have time to develop. Cranial nerve involvement sometimes occurs with bacterial meningitis, and although it is often transient, it can be permanent. The auditory nerve most often is affected, causing deafness or disturbances of vestibular function. Blindness has been reported but is rare. Children may also have paralysis of extraocular or facial nerves.

The degree of CNS derangement observed in children with bacterial meningitis ranges from irritability to coma. As many as 15% of children who have bacterial meningitis are comatose or semicomatose at the time of hospitalization. This circumstance occurs more often with *S pneumoniae* or *N meningitidis* than with Hib. Seizures occur before or within 1 to 2 days after admission in approximately 30% of children. Focal neurologic signs, which are present in approximately 16% of the children, correlate with persistent abnormal neurologic and developmental examinations 1 year after discharge. The distinction between bacterial meningitis and infectious meningoencephalitis

may be difficult to make when the child with coma or seizures first presents.

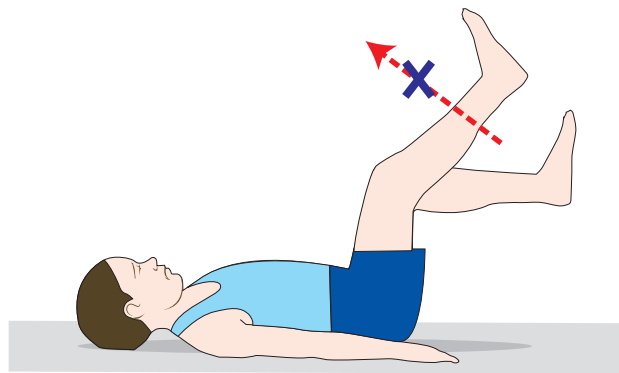
Subdural effusions occur in approximately 50% of children who have bacterial meningitis, but they are seldom clinically significant. Therefore, unless focal neurologic signs or signs of increased intracranial pressure develop, the presence of such effusions need not be sought through the performance of subdural taps or computed tomographic (CT) scans. Infection of subdural effusions is extremely rare.

Arthralgia and myalgia often occur in children who have meningitis, particularly those who have meningococemia. Vasculitis can be seen in children who have any type of bacterial meningitis, but petechiae and purpura are more commonly associated with meningococcal disease. Children who have such rashes should be considered in imminent danger of developing septic shock and should be treated accordingly (see Chapter 366, Meningococemia).

### Laboratory Testing and Findings

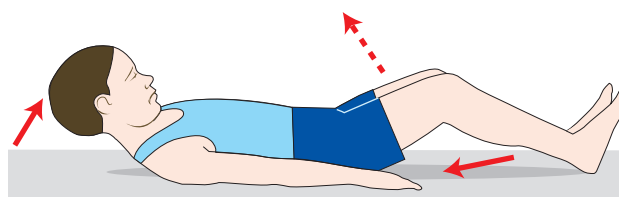
When meningitis is suspected in a child who does not have papilledema, a lumbar puncture should be performed, the opening pressure measured, and the CSF examined immediately. The clinical situation should influence the amount of data required before a





#### Kernig Sign

When the hips are flexed at 90 degrees, attempting to extend the leg at the knee past 135 degrees causes pain and/or extensor spasm.



#### Brudzinski Sign

Flexion of the neck while laying supine causes involuntary hip and knee flexion.

**Figure 289-4** Kernig sign and Brudzinski sign, signs of meningitis at physical examination in addition to nuchal rigidity.

therapeutic decision is made. If the CSF from an ill, febrile child is turbid or purulent, then antimicrobial therapy should be initiated as treatment for bacterial meningitis before further laboratory results are available. In any case, the CSF should be examined as soon as possible. If the nucleated blood cell count of the CSF is not above 6/ $\mu$ L, then the only other tests likely to be useful in diagnosing bacterial meningitis are a Gram stain and a culture. However, most experts suggest that a Gram stain, bacterial culture, cell count, differential cell count, and CSF concentrations of total protein and glucose should be performed on CSF from all samples drawn by a lumbar puncture. If possible, the blood glucose should be measured just before the lumbar puncture is performed so that the ratio of CSF to blood glucose can be determined; measuring the blood glucose level before the lumbar puncture is best because the stress of the procedure can temporarily increase it. If only a small amount of CSF is obtained, then the most important tests to perform are a Gram stain and bacterial culture. Characteristic CSF findings are listed in Table 289-1. A useful review and Internet-accessible video on performing a lumbar puncture is available (see Tools for Practice). Refinements of the reference ranges for CSF opening pressure and chemical and cellular parameters (see Appendix C, Formulas and Reference Range Values)

continue to be published for young children and infants, as some differences from adult ranges are noted.

The CSF should be cultured on chocolate and blood agar plates and in broth. Generally, bacterial cultures will be positive within 2 days if pathogens are present. In some settings, the causative agent may also be identified by latex agglutination reactions, immunochromatographic reactions, or polymerase chain reaction (PCR) amplification of nucleic acids. Rapid diagnostic tests are likely to be most valuable in children who receive a significant amount of antibiotics 24 hours or more before a lumbar puncture, or in developing countries without microbiologic facilities. Blood cultures should be obtained for all children suspected of having bacterial meningitis; blood cultures are positive in 80% to 90% of children who did not previously receive antimicrobial agents and who have meningitis caused by Hib, *S pneumoniae*, or *N meningitidis*.

A common clinical concern is how to distinguish the CSF abnormalities caused by infection from those associated with a traumatic lumbar puncture. Common clinical practice is to use the ratio of red blood cells to WBCs to correct the observed CSF WBC count, either by subtraction or by examination of the ratio of observed to expected cells. Despite the apparently sound theoretical basis for these calculations, in practice, they are generally not helpful to the physician in deciding whether to proceed with antibiotic therapy, and bacterial or viral cultures will yield a more definitive answer relatively quickly.

Two additional common clinical concerns regard the need for a diagnostic lumbar puncture in young children experiencing a stereotypical febrile seizure and the timing of the lumbar puncture, including the need to perform cranial CT scans before the lumbar puncture.

Although seizures in febrile children were reported to be the first manifestation of bacterial meningitis in as many as 20% of children in the pre-conjugate vaccine era, most of the children were also obtunded or comatose at the time of presentation, distinguishing them from children with stereotypical febrile seizures. The large decrease in the incidence of bacterial meningitis in immunized children in the United States, combined with several studies of the nonutility of a lumbar puncture in children with typical febrile seizures in the absence of other symptoms or signs of meningitis have led the American Academy of Pediatrics to revise practice guidelines for neurodiagnostic evaluations in children with febrile seizures. For children 6 to 12 months of age thought to have a simple febrile seizure, a lumbar puncture is considered an optional procedure, and is most important for those with signs and symptoms of meningitis, those pretreated with antibiotics, or incomplete or unknown immunization histories. A lumbar puncture is no longer required for the evaluation of all children with febrile seizures. Conversely, the presence of seizures should not be used to explain abnormalities of the CSF; if found, the diagnosis of meningitis must be considered.

In general, lumbar puncture should be performed whenever the diagnosis of meningitis is known or

suspected. Four reasons for delaying a lumbar puncture exist: (1) clinically important cardiorespiratory compromise, most often observed in the neonate; (2) signs of significantly increased intracranial pressure (eg, retinal changes, altered pupillary responses, focal neurologic signs during the physical examination, or increased blood pressure with associated bradycardia and hyperpnea [Cushing triad]); (3) infection in the skin, soft tissues, or epidural area at the site of the lumbar puncture; or (4) suspicion or history of bleeding disorders (eg, hemophilia, severe thrombocytopenia). In these circumstances, blood cultures should be obtained, and antibiotics should be provided empirically without performing a lumbar puncture. In cases of suspected increased intracranial pressure, arrangements should be made for a neuroimaging study (eg, cranial CT scan with and without contrast enhancement) during or immediately after antibiotic administration, and if the imaging study suggests that it is safe to proceed, then the lumbar puncture may follow. However, performing CT scans routinely before a lumbar puncture is not necessary in children with suspected meningitis, even though all children with meningitis have some degree of increased intracranial pressure by virtue of the disease process.

Herniation of the brain on removal of a small amount of CSF is rare in children with meningitis, especially in infants with open fontanelles. Herniation associated with meningitis has also been observed before a lumbar puncture and in the presence of normal cranial CT scans. Nevertheless, a lumbar puncture should be performed cautiously if significantly increased intracranial pressure is suspected; obtaining CT scans before a lumbar puncture in selected children is reasonable, especially in children or adults with a history of immunosuppression, hydrocephalus, ventricular shunts, or head trauma, as well as in those who have focal neurologic signs or signs of greatly increased intracranial pressure.

If the lumbar puncture could not initially be performed or was contraindicated, then the procedure may be reconsidered after the child is stabilized and contraindications to the procedure are resolved. A lumbar puncture may be performed even 12 to 24 hours after initiating antimicrobial therapy. In this situation, the interpretation of CSF WBC counts and protein and glucose concentrations may still be helpful in discerning the likelihood of true bacterial meningitis.

## Management

### General Care

Antimicrobial therapy, fluid management, and possibly anti-inflammatory adjunctive treatments are crucial for all children who have bacterial meningitis. Even today, controversy remains about mechanisms of action, usefulness, and choice of these interventions.

At the initial examination, children who have meningitis may seem only mildly ill with fever and irritability, or they may be profoundly ill with an altered state of consciousness and hypotension. The severity of illness at the time the child is brought in for care can predict morbidity and should dictate immediate management. Acute bacterial meningitis is always a medical

emergency, and all infants and children who have an altered state of consciousness should be observed closely and the need for intensive care anticipated.

As soon as bacterial meningitis is diagnosed, intravenous access should be secured and appropriate antimicrobial agents (and possibly anti-inflammatory agents) provided. The initial laboratory examination should include CSF examination and culture, blood culture, measurement of serum electrolyte and glucose concentrations, complete blood and platelet count, and measurement of urine specific gravity. If the child has petechiae or purpura or is in shock, then the laboratory tests should include a partial thromboplastin time, prothrombin time, and measurement of fibrinogen- or fibrin-breakdown products. Management of the child who is awake and has stable cardiorespiratory vital signs consists primarily of administering antimicrobial agents and fluids and careful monitoring for changes in level of consciousness, development of seizures, changes in vital signs, and development of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

Other therapies should be considered in more critically ill children (see the discussion of management of septic shock in Chapter 373, Shock). Seizures should be treated with appropriate anticonvulsants. An open airway that provides good oxygenation should be ensured. Children who are in a profound coma or whose level of consciousness deteriorates while receiving therapy should be evaluated for complications such as a cerebral abscess, obstructive hydrocephalus, or high intracranial pressure. A CT scan of the brain with and without contrast is helpful in determining the diagnosis in such cases.

Radiographs may help in identifying suspected bone or joint infection in selected children. CT studies play a role in complicated cases of meningitis and may be helpful for decisions on management later during the course of therapy, as well as, for example, evaluating selected cases of prolonged (primary) or recurrent (secondary) fever. However, CT scans should not be routinely obtained as a result of prolonged or secondary fever because such scans are unlikely to affect clinical management. If high intracranial pressure is a major clinical concern and treatment has been initiated or is anticipated, then a neurosurgeon should be consulted and an intracranial pressure monitoring device placed, although, notably, all children with bacterial meningitis have some increase in intracranial pressure, and monitoring devices are not required for most.

### Fluid Therapy

Traditionally, fluids were restricted to two-thirds of the total daily maintenance amount in children who had bacterial meningitis to minimize brain edema and prevent SIADH, which was reported to occur in 29% to 88% of cases of bacterial meningitis. However, some studies found that plasma antidiuretic hormone concentrations return to normal in children with bacterial meningitis who receive replacement plus maintenance fluids for 24 hours, whereas concentrations remain high in children restricted to two-thirds of maintenance requirements.

How should the physician interpret these contradictory data? Dehydration likely produces an appropriate increase of antidiuretic hormone, but SIADH may still occur in nondehydrated or fluid-replete children. Maintenance fluids are likely necessary to perfuse, oxygenate, and deliver host defenses to the CNS, and although SIADH occurs in bacterial meningitis, no firm evidence has been found that fluid restriction prevents it. Obvious fluid deficits should be rapidly corrected, and serum sodium concentrations should be closely monitored several times during the first 24 hours of therapy, along with measurements of urine specific gravity. If the serum sodium concentration drops below 125 mEq/L, then the test should be repeated as soon as possible. If the serum sodium is still below 125 mEq/L, then fluids should be restricted to keep the vein open until the serum electrolyte concentrations are corrected. Otherwise, for the child with bacterial meningitis, providing routine maintenance fluids (such as 0.45% saline with added potassium and dextrose) at approximately 80% of the maintenance rate after fluid repletion and advancing to full maintenance rates as the serum sodium increases beyond 135 mEq/L seems to be appropriate. The period of fluid restriction likely only needs to be 1 day or less.

### Anti-inflammatory Therapy

The use of glucocorticoids as adjunctive therapy in children who have bacterial meningitis has been studied for decades yet continues to be controversial. Glucocorticoids and other anti-inflammatory compounds produce definite salutary changes in experimental meningitis models that ought to imply better outcomes for children. However, such therapy may also cause gastrointestinal bleeding, decreased penetration of antimicrobial agents into the CSF, and obfuscation of the clinical assessment of children's response to therapy. In addition, there seem to be differences in benefit in studies of adults as opposed to children, and in the industrialized world as opposed to the developing world. At present, it can be said that dexamethasone likely improves the hearing outcomes of children in the industrialized world who have bacterial meningitis caused by Hib, but its usefulness in non-Hib meningitis remains unproven. In addition, dexamethasone does not seem to benefit children or adults with bacterial meningitis in developing nations. In some studies of adults in industrialized countries with meningitis caused by *S pneumoniae*, decreased neurologic morbidity and mortality has been reported. In summary, at present in the United States, dexamethasone should be administered before or within 1 hour of the first dose of antimicrobial agents to children 6 weeks of age or older who have Hib meningitis, and considered for children who have pneumococcal meningitis; it has no role in cases of neonatal meningitis or aseptic meningitis.

### Antimicrobial Therapy

Knowing the causative agent at the time of diagnosis of bacterial meningitis is difficult. Empirical guides to therapy are primarily based on age, which predicts the most likely cause. Adjustments to therapy can be made as conjugate vaccination history and results of the CSF Gram stain and culture are confirmed

(Table 289-5). However, organism-specific points regarding therapy are noted below.

Until the early 1990s, most *S pneumoniae* strains were susceptible to penicillin or ampicillin and the third-generation cephalosporins—ceftriaxone and cefotaxime. Since then, numerous reports have been issued of infections in infants and children caused by resistant strains of pneumococci. Up to 40% of pneumococcal isolates may be resistant to penicillin at some level, and some also are resistant to the third-generation cephalosporins. Therefore, infants and children suspected of having bacterial meningitis caused by pneumococci (ie, gram-positive cocci in pairs seen on a Gram stain of the CSF) should receive vancomycin in addition to either ceftriaxone or cefotaxime. Because dexamethasone can decrease the CSF penetrance (and thus the activity) of vancomycin, some experts advise that either dexamethasone should be omitted altogether or rifampin plus vancomycin plus a third-generation cephalosporin should be used when dexamethasone is provided. As soon as the antimicrobial susceptibility of an isolate is known, vancomycin should be discontinued if the isolate is susceptible to penicillin or if it is nonsusceptible to penicillin but still susceptible to the third-generation cephalosporins. Vancomycin is continued with ceftriaxone or cefotaxime for those isolates found nonsusceptible to both penicillin and the third-generation cephalosporins (and rifampin is added to the combination in some circumstances) (Table 289-4). Consultation with an infectious diseases subspecialist is suggested.

In areas with a low prevalence of penicillin-nonsusceptible pneumococci, especially when examination of the CSF Gram stain shows the absence of gram-positive cocci, providing a third-generation cephalosporin alone (without vancomycin) for empiric therapy is reasonable. Suspected or proven Hib disease may be treated reliably with either ceftriaxone or cefotaxime; ampicillin may be used only if the isolate is known to be susceptible. Disease caused by *N meningitidis* is treated reliably with penicillin G at high doses or alternatively by ampicillin or a third-generation cephalosporin (Table 289-4).

Meningitis caused by *N meningitidis* is usually treated for 7 days, that caused by Hib for 10 days, and that caused by *S pneumoniae* for 10 to 14 days, although a 7-day course of antimicrobial therapy for uncomplicated Hib and *S pneumoniae* meningitis may be effective. Chloramphenicol is now rarely used for therapy in the industrialized world; if an alternative agent beyond ampicillin or third-generation cephalosporins is required, then meropenem may be administered; consultation with an infectious diseases specialist is suggested. Although these 3 organisms cause most cases of bacterial meningitis beyond the neonatal period, other bacteria can cause meningitis. In such cases, antimicrobial therapy must be individualized.

Most therapeutic failures can be related to inadequate therapy with the correct antimicrobial agent, resistant organisms, or a long delay in diagnosis. A repeat lumbar puncture performed after therapy is completed does not reflect the adequacy of therapy or predict the

**Table 289-5** Antimicrobial Therapy of Bacterial Meningitis**PART A. EMPIRICAL THERAPY PENDING CULTURE AND SUSCEPTIBILITY DATA**

AGE	LIKELY PATHOGENS	ANTIMICROBIAL AGENT
0–1 mo	<i>Streptococcus agalactiae</i> , <i>Escherichia coli</i> , <i>Listeria monocytogenes</i>	Ampicillin + cefotaxime or ampicillin + aminoglycoside
1–3 mo	<i>S agalactiae</i> , <i>L monocytogenes</i> , <i>Streptococcus pneumoniae</i> , <i>Neisseria meningitidis</i> , <i>Haemophilus influenzae</i> b	Ampicillin + (cefotaxime or ceftriaxone) <i>plus</i> vancomycin (see text)
3 mo–21 yr	<i>S pneumoniae</i> , <i>N meningitidis</i> ( <i>H influenzae</i> b if not vaccinated)	(Ceftriaxone or cefotaxime) <i>plus</i> vancomycin (see text)

**PART B. SPECIFIC THERAPY**

PATHOGEN	THERAPY
<i>Streptococcus agalactiae</i>	Ampicillin or penicillin G for 14–21 days; first 3 days, add gentamicin; cefotaxime also acceptable
<i>Listeria monocytogenes</i>	Ampicillin for 14–21 days; first 3 days, add gentamicin
<i>Streptococcus pneumoniae</i>	Penicillin MIC $\leq 0.06$ $\mu\text{g/mL}$ and ceftriaxone or cefotaxime MIC $\leq 0.5$ $\mu\text{g/mL}$ : penicillin G or ampicillin for 10–14 days; ceftriaxone or cefotaxime also acceptable Penicillin MIC $\geq 0.12$ $\mu\text{g/mL}$ and ceftriaxone or cefotaxime MIC $\leq 0.5$ $\mu\text{g/mL}$ : ceftriaxone or cefotaxime for 10–14 days Penicillin MIC $\geq 0.12$ $\mu\text{g/mL}$ and ceftriaxone or cefotaxime MIC $\geq 1.0$ $\mu\text{g/mL}$ : (ceftriaxone or cefotaxime) + vancomycin $\pm$ rifampin for 10–14 days
<i>Neisseria meningitidis</i>	Penicillin G for 7 days; alternatives: ampicillin, ceftriaxone, cefotaxime
<i>Haemophilus influenzae</i> b	Ceftriaxone or cefotaxime for 10 days; alternative: ampicillin if isolate is susceptible

**PART C. ANTIMICROBIAL DOSAGE**

AGENT	DOSE (mg/kg/day)		
	AGE 0–7 DAYS	AGE 8–28 DAYS	INFANTS AND CHILDREN
Ampicillin	150–200 divided every 8 hr	200–300 divided every 6 hr	200–300 divided every 6 hr
Cefotaxime	100 divided every 12 hr	200 divided every 8 hr	200–300 divided every 6 hr
Ceftriaxone	Not recommended	80–100 divided every 12–24 hr	80–100 divided every 12–24 hr
Gentamicin	5 divided every 12 hr	7.5 divided every 8 hr	7.5 divided every 8 hr
Penicillin G	100,000–150,000 units divided every 12 hr	150,000–200,000 units divided every 6 hr	300,000–400,000 units divided every 4–6 hr
Rifampin	10 divided every 12 hr	20 divided every 12 hr	20 divided every 12 hr
Vancomycin	20 divided every 12 hr	30 divided every 8 hr	40–60 divided every 6 hr

MIC, minimum inhibitory concentration.

likelihood of recurrence, and such a procedure is usually not indicated. However, a delay in sterilizing the CSF beyond 24 to 36 hours has been associated with adverse outcomes; therefore, another lumbar puncture may be performed at that time. A repeat lumbar puncture at 24 to 48 hours of therapy should be considered if drug-resistant *S pneumoniae* is present, especially if dexamethasone therapy is provided.

Some contacts of patients who have *N meningitidis* or Hib meningitis are at increased risk for the disease and should therefore receive prophylaxis. Prophylactic regimens for those at risk for *N meningitidis* are described in Chapter 366, Meningococcemia. Whether all contacts of children who have Hib disease should receive prophylaxis remains controversial. The American Academy of Pediatrics recommends that rifampin

be provided to all household contacts, including adults, in households that have at least 1 contact younger than 4 years whose immunization status against Hib is incomplete. The definition of complete immunization depends on the age of the individual involved, and that of household contact on how much time has been spent close to the index patient. The index patient should also receive rifampin either during or at the completion of treatment for Hib or meningococcal meningitis, unless ceftriaxone or cefotaxime was used for treatment (ceftriaxone and cefotaxime clear meningococcal and Hib carriage).

**Complications**

Early in the course of bacterial meningitis, increased intracranial pressure, septic shock, disseminated



intravascular coagulation, and even cardiorespiratory arrest may occur. Subdural effusions occasionally cause seizures or focal neurologic deficits; in such cases, the fluid should be removed by subdural taps. Such effusions are rarely infected directly, but subdural empyemas are occasionally reported. Syndrome of inappropriate secretion of antidiuretic hormone can also complicate bacterial meningitis; thus, the child should be monitored carefully for this complication. If it occurs, fluid should be sharply restricted. A brain abscess is extremely rare after bacterial meningitis except in neonates who have meningitis caused by *Citrobacter* or certain *Cronobacter* (formerly *Enterobacter*) species.

### Sequelae

Despite the appropriate use of bactericidal antibiotics, the mortality rate for bacterial meningitis remains at 5% to 10%. Approximately 15% to 25% of survivors have long-term morbidity, including developmental delay and lower educational achievement, seizure disorder, spasticity, and hearing loss.

Predicting long-term sequelae for an individual child is difficult at the time of discharge from the hospital. Some children who are apparently normal are later found to have hearing or learning deficits or a seizure disorder. Conversely, some children expected to have a dismal prognosis based on abnormal neurologic examinations at discharge make remarkable gains. The physician should therefore be guardedly optimistic with the family while remaining sensitive to possible sequelae and observing these children closely for attainment of developmental milestones. Hearing should be tested formally before discharge from the hospital because most sensorineural hearing loss can be detected at this time. The rate of persistent bilateral or unilateral sensorineural hearing loss is 31% after pneumococcal meningitis, 10.5% after meningococcal meningitis, and 6% after Hib meningitis. In young infants, auditory brainstem response or otoacoustic emissions testing is necessary for screening; in older toddlers and children, conditioned response, play, or conventional audiometry may be performed.

Current thinking asserts that much of the hearing loss in meningitis occurs soon after infection. This circumstance may explain why not all studies have shown a reduction of hearing loss by dexamethasone therapy. The timing of other neurologic sequelae is even less certain. Some cases of bacterial meningitis exhibit fulminantly, and the outcome in these cases may be poor no matter how quickly therapy is rendered. In many cases, the exact onset of disease is difficult to pinpoint, and the length of prodromal symptoms before therapy does not correlate well with outcomes.

### Prevention

In 1985 a purified capsular polysaccharide vaccine against Hib was licensed for use in the United States in children older than 2 years (in whom the risk of Hib disease was, albeit, substantially lower than that of the highest-risk group, infants younger than 1 year). Subsequently, several conjugate vaccines were made by coupling the Hib capsular polysaccharide to various

protein carriers to boost immunogenicity in infants. These conjugate vaccines were also more immunogenic in older children with conditions associated with impaired responses to capsular polysaccharide vaccine. As noted in Epidemiologic Features, the widespread use of Hib and pneumococcal conjugate vaccines dramatically reduced the incidence of invasive Hib and pneumococcal infection. Similar changes have been noted in the United Kingdom with meningococcal serogroup C conjugates (see Table 289-3).

One of 3 Hib conjugate vaccines or 1 of 3 Hib conjugate-containing combination vaccine products is routinely provided to US infants beginning at 2 months of age. Pneumococcal conjugate vaccine (13-valent) is recommended for routine universal administration to infants and children younger than 2 years of age, in a similar fashion to Hib conjugate vaccines. The pneumococcal conjugate vaccine is also suggested for high-risk children 2 to 5 years of age, including children who have sickle cell disease, functional or anatomic asplenia, immunosuppression, cancer, chronic renal disease, chronic cardiopulmonary disease, CSF leaks, and diabetes.

At present, 1 of 2 tetravalent meningococcal polysaccharide conjugate vaccines is routinely used for children and adults at higher risk of disease, as well as for young adolescents 11 to 12 years of age (with a booster dose in late adolescence). Meningococcal conjugate vaccines (tetravalent or bivalent) are also used for selected young infants and children at higher risk of disease, and as an adjunct to chemoprophylaxis in outbreak control. Two new meningococcal serogroup B vaccines were licensed for use in the United States in early 2015; recommendations for their use were forthcoming at the time this chapter was prepared (for more detailed information, see Chapter 20, Immunizations; Chapter 315, Pneumonia; and Chapter 366, Meningococcemia.)

### NEONATAL MENINGITIS

Neonatal meningitis merits separate consideration because the incidence is high, the agents that cause it are unique, and it is more often fatal than meningitis in the older child. The incidence of neonatal meningitis varies with the reporting institution, from 0.2 to 1 case per 1,000 live births. The age-specific incidence of bacterial meningitis in the first month of life in the United States between 1978 and 1981 was 366 per 100,000 neonates. Case fatality rates generally range from 5% to 25% in the modern era. In general, mortality is lower for full-term infants than for infants of low birth weight (<2,500 g). Early recognition and treatment are critical because the case fatality rate falls to approximately 5% for neonates who survive the first 24 hours of the disease.

The cause of neonatal meningitis has changed since 1970, and physicians should be alert to the possibility of future shifts. During the 1960s, most cases were caused by gram-negative enteric organisms, primarily *E coli*; gram-positive isolates were likely to be *L monocytogenes*. During the 1970s, group B  $\beta$ -hemolytic streptococci (*S agalactiae*) became prevalent; currently this organism and *E coli* account for 50% to 66% of cases of neonatal meningitis and *L monocytogenes* for

approximately 1% to 5%. Neonatal sepsis and meningitis caused by non-group D  $\alpha$ -hemolytic streptococci and coagulase-negative staphylococci also have been reported. Group B  $\beta$ -hemolytic streptococci can cause sepsis or meningitis (or both) in the first hours of life, and infections in infants younger than 7 days is termed early onset. Late-onset disease—that is, group B  $\beta$ -hemolytic streptococcal infections in infants older than 7 days—is characteristically meningitis rather than sepsis and tends to be associated with capsular serotype III organisms. Antimicrobial prophylaxis of pregnant women found to be carrying group B  $\beta$ -hemolytic streptococci at term, or those with fever, premature labor, or prolonged rupture of membranes, is now performed in the United States, which has led to a decrease in the incidence of early-onset sepsis and meningitis. However, late-onset meningitis rates remain unchanged, reflecting unique differences between these syndromes that remain unclear.

The clinical signs associated with neonatal meningitis are nonspecific and therefore not very helpful. Neonates with meningitis often have apneic episodes or feed poorly, and they can be hyperthermic or hypothermic, irritable or lethargic, and have respiratory distress or diarrhea (or both); only rarely do they have nuchal rigidity. They may exhibit a bulging fontanelle. The neonate has a limited repertoire of clinical responses to disease or insult. Therefore, most sick neonates receive a diagnostic evaluation for sepsis, including a lumbar puncture; antimicrobial agents are initiated pending culture results. The cytology and chemistry of the CSF in neonates have a much broader normal range than those of children in other age groups, especially during the first week of life (Table 289-2); thus, any single test result may not look abnormal. However, infants who have bacterial meningitis rarely have completely normal CSF at examination. During the first 24 hours of life, isolated meningitis without sepsis occurs rarely enough that a lumbar puncture has sometimes been omitted for infants who seem septic on the day of birth. However, this practice may lead to missed cases of both early-onset and late-onset meningitis because as many as 25% of neonates with meningitis have been found to have sterile blood cultures despite positive CSF cultures, and the proportion of such cases might rise as antibiotic prophylaxis is given to mothers and babies in the peripartum period. In general, if possible, any infant thought to have sepsis or meningitis should undergo a lumbar puncture.

### Management of Neonatal Meningitis

#### Antimicrobial Therapy

The principles of antimicrobial therapy for neonates with meningitis are the same as for infants and children, but because the organisms are different, the antimicrobial selection must be adjusted. Based on the most common organisms that cause neonatal meningitis, the ideal antimicrobial agent is effective against *E coli* and other enteric organisms and against group B  $\beta$ -hemolytic streptococci and other gram-positive organisms. Two third-generation cephalosporins—cefotaxime and ceftriaxone—are extremely active against the organisms that usually cause neonatal meningitis, except for

poor activity against *L monocytogenes*. The major difference between these drugs is their pharmacokinetic profile. Ceftriaxone exhibits a much longer serum half-life than cefotaxime. In addition, because ceftriaxone is highly protein bound and can displace unconjugated bilirubin from albumin, it is generally not used in premature infants at risk for kernicterus or in those young infants who have hyperbilirubinemia and for whom no other suitable antimicrobial agent is available with which to treat their infection.

No formal comparison of these newer agents with the historical regimen of ampicillin plus an aminoglycoside such as gentamicin has taken place. However, because the third-generation cephalosporins are safe, are very active against the common pathogens, and enter the CSF relatively well, cefotaxime plus ampicillin (the latter to empirically treat *Listeria*) should be used to treat suspected neonatal meningitis (suspected disease plus abnormal CSF). Some authorities add gentamicin as a third agent if gram-negative enteric meningitis is thought likely. Because some enteric pathogens such as *Pseudomonas aeruginosa* and Enterobacteriaceae readily become resistant to the third-generation cephalosporins, these antibiotics should not be used empirically for all cases of suspected sepsis in neonates (the choice of empiric ampicillin with gentamicin remains appropriate in this situation when the CSF seems normal). Dosages and characteristics of the antimicrobials used most often to treat neonatal meningitis are listed in Table 289-5.

#### Fluid Therapy, Anti-inflammatory Therapy, and Supportive Care

The role of intraventricular antimicrobial therapy remains uncertain and may even be harmful. Other therapeutic considerations (eg, fluid management, close serial monitoring) are the same for neonates as for infants and children who have bacterial meningitis, except that no data support the use of dexamethasone in infants younger than 6 weeks. The head circumference should be measured serially to detect early signs of hydrocephalus. Conflicting data have been reported regarding whether intravenous immunoglobulin is helpful. At present, it does not have a defined role in the therapy of neonatal bacterial meningitis.

#### Prognosis

The complications of neonatal meningitis, which are similar to those seen in older infants but are perhaps more common, include hydrocephalus, deafness, and blindness. The case fatality rate ranges from 5% to 25%. Approximately 65% of survivors of coliform meningitis are normal 3 to 7 years after the illness, approximately 15% to 30% have mild to moderate neurologic sequelae, and 5% to 10% have major sequelae. Approximately 55% of cases of group B  $\beta$ -hemolytic streptococcal meningitis survivors are normal, 25% have mild to moderate sequelae, and 20% have major sequelae (ie, blindness, bilateral sensorineural hearing loss, cerebral palsy, or profound developmental delay).

For unknown reasons, as many as 80% of neonates who have gram-negative enteric meningitis caused by either *Citrobacter* or certain *Cronobacter* (formerly *Enterobacter*) species will develop single or multiple

brain abscesses. This complication is distinctly unusual in meningitis caused by any other organism. Routine follow-up with cranial CT scans is indicated for neonates with meningitis or sepsis caused by *Citrobacter* species or *Cronobacter* (formerly *Enterobacter*) *sakazakii*.

As with older infants and children, all infants recovering from meningitis should have careful audiologic testing and close evaluation for attainment of developmental milestones.

### PARTIALLY TREATED MENINGITIS

Values for WBC counts in CSF, percentage of polymorphonuclear cells, and glucose and protein concentrations in children who have partially treated bacterial meningitis do not greatly differ from those in children who were not previously treated. Even children who received intravenous antibiotics for 44 to 68 hours have CSF findings characteristic of bacterial meningitis. Cultures of CSF from pretreated children with bacterial meningitis often grow Hib, although pneumococci and meningococci grow less often after pretreatment. However, some children who have partially treated bacterial meningitis have CSF findings indistinguishable from the classic findings of aseptic meningitis. Unless clear evidence of a nonbacterial cause exists (eg, identification of viral nucleic acid by PCR or isolation of virus by culture from CSF or blood), antibiotics should be administered to partially treated children for 7 to 10 days at doses appropriate for bacterial meningitis.

### ASEPTIC MENINGITIS

The syndrome of aseptic meningitis consists of a clinical picture of meningitis with CSF pleocytosis and the absence of bacteria on Gram stain or culture. The CSF findings characteristic of aseptic meningitis are shown in Table 289-1. Although aseptic meningitis is usually caused by a virus, treatable causes of this syndrome should be considered in the differential diagnosis. Table 289-4 lists a wide variety of infectious and noninfectious agents and diseases that are associated with aseptic meningitis. Nonpolio enteroviruses cause 85% of cases of aseptic meningitis in the United States, but mumps and polio should be considered in other areas of the world where they are still endemic. A longer duration of symptoms, especially if accompanied by erythema migrans or cranial neuropathies, has been associated with Lyme disease meningitis. West Nile virus infection may cause aseptic meningitis, meningoencephalitis, or acute flaccid paralysis. In general, when encephalitis accompanies aseptic meningitis, the clinical course is more severe, and the chance of sequelae increases (see Chapter 290, Meningoencephalitis).

### Clinical Manifestations

Infants and children who have aseptic meningitis caused by enteroviruses are often acutely febrile, irritable, and lethargic. Their temperature is usually 100.4°F to 105°F (38.0°C to 40.5°C) for 4 to 5 days. Upper respiratory tract symptoms, headache, photophobia, nausea, and vomiting also are commonly present; rashes may be seen as well. In general, a child who has viral meningitis does not seem as critically ill as a child

who has bacterial meningitis and is less likely to have meningeal signs.

The diagnosis of aseptic meningitis is likely when CSF pleocytosis ranges from 10 to 500 cells/ $\mu$ L that are predominantly lymphocytes; the CSF protein is mildly high at 50 to 150 mg/dL; and the CSF glucose concentration is normal. Early in the course of viral meningitis, polymorphonuclear neutrophils can predominate in the CSF. A transition from a predominance of polymorphonuclear neutrophils to lymphocytes usually occurs rapidly, and a repeat lumbar puncture after 8 to 12 hours may show this transition. Tuberculous and fungal meningitis generally have gradual onsets of illness over days to weeks.

Hypoglycorrhachia (low CSF glucose level) rarely occurs with viral meningitis caused by enteroviruses, mumps, herpes simplex, and Eastern equine encephalitis viruses. Hypoglycorrhachia caused by these viruses tends to result in CSF glucose concentrations that equal approximately 30% of the simultaneous blood glucose concentration, whereas bacterial meningitis usually results in CSF glucose concentrations of less than 30% of the blood glucose. The CSF glucose concentration can also be low with tuberculous and fungal meningitis.

Laboratory-confirmed enteroviral meningitis often results in discontinuation of antimicrobial therapy and early discharge from the hospital. For a long time, many physicians were reluctant to obtain specimens for viral culture because they thought that isolating viruses took too long to affect patient management, although enteroviruses may be detected by culture in as little as 4 days. The PCR amplification of viral nucleic acid in CSF has rectified the situation in many hospital laboratories, because PCR is a rapid, sensitive, and specific method of diagnosing meningitis caused by enteroviruses (and herpesviruses, among others). Children with aseptic meningitis should have CSF sent for both bacterial culture and enteroviral PCR, in an attempt to maximize diagnosis and shorten the length of antibiotic therapy in what may be viral meningitis.

### Management

The management of aseptic meningitis is directed mainly to supportive care. No specific anti-enteroviral agents are currently available. Meningoencephalitis caused by herpes simplex or varicella-zoster viruses should be treated with acyclovir. Aseptic meningitis caused by one of the other, less common causes noted in Table 289-4 (eg, Lyme disease) may also require specific therapy.

### Outcome

The outcome of aseptic meningitis relates to both the causative agent and the child's age. Most children with the most common known cause of viral meningitis—enteroviral meningitis—usually recover completely, although rarely some very young infants have been reported to suffer lower intelligence and delayed speech development. In light of these findings, the prognosis for an infant younger than 3 months with aseptic meningitis is more guarded than that of an older child, and the infant's development should be monitored carefully.



## FUNGAL MENINGITIS

Fungal meningitis generally has a more insidious onset than bacterial or viral meningitis, although the nature of clinical manifestations varies with the species of infecting organism. Rare in healthy children, fungal meningitis is most often diagnosed in hosts with some form of immunocompromise (eg, that caused by *Candida albicans* in premature infants or *Cryptococcus neoformans* in older adolescents with advanced HIV infection). However, fungal meningitis from endemic mycoses in the United States, such as *Histoplasma capsulatum* in the Ohio and Mississippi river valleys, *Coccidioides immitis* in Arizona and California, and *Blastomyces dermatitidis* in the upper Midwest and Northeast along the Great Lakes and the St Lawrence river, is seen in both infants and older children. Unusual fungal infections associated with injections of contaminated pharmaceuticals have been reported in adults, but not children, to date. Treatment of fungal meningitis varies according to the organism, and infectious diseases consultation is advised.

## TUBERCULOUS MENINGITIS

Meningitis caused by *Mycobacterium tuberculosis* is the most severe complication of tuberculosis (TB) in infants and children. Most cases occur within the first 5 years of life. In contrast to bacterial meningitis, TB meningitis often has an insidious onset, with nonspecific symptoms for more than 1 week, including fever, vomiting, malaise, poor weight gain or weight loss, and decreased mentation. The CSF profile tends to show a lymphocytic pleocytosis, with a low glucose level and a moderate to markedly high protein level (Table 289-1). The Mantoux skin test was positive in 60% of children with TB meningitis in a large South African study; it is possible that it might be positive more often in areas with fewer nutritional deficits. Tuberculosis of the CNS most often presents as basilar meningitis, but parenchymal tuberculomas and hydrocephalus may also be seen. Treatment of TB meningitis depends in part on the rates of local drug resistance among *M tuberculosis* isolates; for drug-susceptible strains, treatment includes 2 months of isoniazid, rifampin, pyrazinamide, and ethambutol (or ethionamide) once daily, followed by 7 to 10 months of isoniazid and rifampin, either once daily or twice per week, for a total treatment duration of 9 to 12 months. Although evidence for corticosteroid use in TB meningitis in young children is lacking, in older adolescents and adults dexamethasone or prednisone adjunctive treatment for several weeks seems to decrease mortality, although not necessarily morbidity.

### WHEN TO REFER

- All children with bacterial, fungal, or TB meningitis should be treated in consultation with pediatric infectious diseases subspecialists, and pediatric neurologic, critical care, and neurosurgical subspecialists should be available if required.
- Children with viral meningitis in whom unusual features or complications are present (eg, immune

compromise, unexpected severity, slow resolution of illness, possibility of nonviral aseptic meningitis, etc.) should be referred to pediatric infectious diseases and neurology specialists.

- Children with neonatal meningitis should be referred to pediatric infectious diseases, newborn medicine, and neurologic subspecialists.

### WHEN TO ADMIT

All children with suspected or proven meningitis should be hospitalized for evaluation and management.

- Children with bacterial, fungal, or tuberculous meningitis initially hospitalized at the referral hospital should be transferred to a facility experienced in the management of critically ill children, with availability of consultation by pediatric critical care, infectious diseases, neurologic, and neurosurgical subspecialists, which is especially important for newborns with neonatal meningitis. However, treatment must begin at the referral hospital.
- Infants and toddlers with viral meningitis may continue to be hospitalized at the primary care level hospital; transfer to a referral facility may be required for complicated cases (eg, uncertainty in diagnosis, slow resolution, presence of immune compromise, etc.).
- Older children and adolescents with viral meningitis do not always require hospitalization if the CSF evaluation strongly suggests that bacterial disease is not present, provided that adequate hydration and pain control can be undertaken at home and follow-up with the physician can be assured.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Meningitis* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/head-neck-nervous-system/pages/Meningitis.aspx](http://www.healthychildren.org/English/health-issues/conditions/head-neck-nervous-system/pages/Meningitis.aspx))
- *Meningitis* (fact sheets), Centers for Disease Control and Prevention ([www.cdc.gov/meningitis/index.html](http://www.cdc.gov/meningitis/index.html))

### Medical Decision Support

- *Lumbar Puncture* (video), Ellenby MS et al, *New England Journal of Medicine* Vol 355, Issue 13, 2006 ([www.nejm.org/doi/full/10.1056/NEJMvcm054952](http://www.nejm.org/doi/full/10.1056/NEJMvcm054952))
- *Meningitis: Resources for Healthcare Professionals* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/meningitis/clinical-resources.html](http://www.cdc.gov/meningitis/clinical-resources.html))

## AAP POLICY

American Academy of Pediatrics Subcommittee on Febrile Seizures. Febrile seizures: guideline for the neurodiagnostic evaluation of the child with a simple febrile seizure. *Pediatrics*. 2011;127(2):389–394 ([pediatrics.aapublications.org/content/127/2/389](http://pediatrics.aapublications.org/content/127/2/389))

Polin RA; American Academy of Pediatrics Committee on Fetus and Newborn. Management of neonates with



suspected or proven early-onset bacterial sepsis. *Pediatrics*. 2012;129(5):1006–1015 (pediatrics. aapublications.org/content/129/5/1006)

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### SUGGESTED READINGS

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- American Academy of Pediatrics. Meningococcal infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:547–558
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Depending on the extent of the infection, the patient may have signs and symptoms of meningitis, encephalitis, or myelitis. A patient who has meningitis characteristically experiences intense headache, pain on flexion of the neck, and photophobia. Physical findings include fever and meningismus, with positive Kernig and Brudzinski signs (see Chapter 289, Meningitis). In patients with encephalitis, mental status changes such as lethargy, delirium, or hallucinations may be mistakenly attributed to intoxication or psychosis. Signs of myelitis include weakness or sensory loss in the extremities. A central nervous system (CNS) infection should be presumed in any child with fever who has an acute change in mental status or motor function.

## VIRUSES

### Enteroviruses

Enteroviruses are a common cause of aseptic meningitis and encephalitis in infants. Enteroviral infection may be heralded by the development of diarrhea, abdominal pain, or vomiting and occurs most often during the summer (see Chapter 248, Enterovirus and Evolving Infections). Nonpolio enteroviruses include coxsackieviruses A and B and echoviruses. Meningoencephalitis caused by enteroviral infections is typically a mild, self-limited disease. Echovirus infections commonly begin with a petechial rash. Coxsackievirus infections may be heralded by lesions of the palms, soles, and mouth (hand, foot, and mouth disease) (Figure 290-1). An enterovirus may infect a fetus transplacentally.

Cases of polio in the United States now occur primarily in children who are immigrants, in immunodeficient children, and among small communities of unimmunized children. Worldwide cases of polio decreased by more than 99% from 1988 to 2013. Outbreaks of polio persist in developing countries in Asia and Africa because of transmission of wild poliovirus, reinfection of polio-free areas, and outbreaks caused by vaccine-derived polioviruses.

## Chapter 290

# MENINGOENCEPHALITIS

Richard Young, MD, MPH

Infections of the meninges and underlying brain parenchyma can be differentiated into septic and aseptic categories. *Meningitis* caused by bacteria, fungi, and mycobacteria is classified as septic and characterized by fever, altered mental status, and purulent cerebrospinal fluid (CSF). Aseptic meningitis and encephalitis are most often the result of viral infection but less frequently result from infection by parasites, spirochetes, rickettsia, and prions. Encephalitis has also been implicated as a sequelae to immunization, neoplasm, or autoimmune process. Organisms located in the subarachnoid space may spread to the adjacent cortical mantle. When there are signs of both meningeal and cerebrocortical involvement, the term *meningoencephalitis* is appropriate.



**Figure 290-1** Coxsackievirus infections may be heralded by lesions of the palms, soles, and mouth (hand, foot, and mouth disease).

In 2014, a nonpolio enterovirus was associated with infectious encephalomyelitis in children living in Colorado. Symptoms included acute limb weakness and cranial nerve palsies. Magnetic resonance imaging (MRI) disclosed nonenhancing lesions in the gray matter of the spinal cord or brainstem. The CSF revealed a mild to moderate pleocytosis. Of the 6 specimens positive for rhinovirus or enterovirus, 4 were typed as enterovirus D68.

### Herpesvirus

Herpes simplex virus (HSV) encephalitis has a bimodal age distribution, with one-third of cases occurring in childhood. In a study conducted from 1994 through 2005, HSV accounted for 5% of 322 cases of acute encephalitis at the Hospital for Sick Children. In neonates, HSV may produce cutaneous disease, meningoencephalitis, or disseminated disease. Risk factors for neonatal infection include first episode of maternal infection during the third trimester, fetal scalp monitoring, preterm delivery, and maternal age younger than 21 years. Toll-like receptor 3 (TLR3) deficiency may predispose to HSV encephalitis in certain children, some of whom may experience a recurrence of encephalitis. Infection with HSV commonly produces a necrotizing encephalitis, and 50% of untreated cases are fatal. The CSF discloses elevation of both leukocytes (often granulocytes) and erythrocytes. The polymerase chain reaction (PCR) test may be initially negative and subsequently positive in later analyses. Two-thirds of patients who survive have neurologic sequelae, including epilepsy (44%) and cognitive deficits (25%). Mothers of infected infants often have no symptoms of herpes infection during or before gestation, which makes the diagnosis of a neonatal infection more difficult. For more information, see Chapter 266, Herpes Infections.

Most young children are seropositive for human herpesvirus type 6 (HHV-6). Type 6B is associated with the childhood illness, roseola infantum, which causes high fever and morbilliform rash. Infection with HHV-6 may occasionally cause meningoencephalitis in infants and may be acquired perinatally, leading to asymptomatic carriage (often nasal) or persistent neonatal infection. Infection with HHV-6 was the cause of one-third of first febrile seizures evaluated in an emergency department (ED). The CSF of 9 children disclosed no increase in white blood cells and normal glucose and protein; HHV-6 was detected by PCR in approximately 25% of samples.

Nervous system infection with Epstein-Barr virus (EBV) may involve the cortex, cerebellum, spinal cord, or peripheral nerves, resulting in a clinical picture of encephalitis, aseptic meningitis, transverse myelitis, or ascending polyneuropathy. Two-thirds of patients with EBV encephalitis had headache, and 48% developed seizures. The prognosis of EBV encephalitis is generally favorable, although in some patients, the infection may cause death or disability.

### Arboviruses

Arboviral infections caused by *Bunyavirus* species and togavirus are transmitted to humans by arthropods. Arbovirus meningoencephalitis typically occurs during

the summer and early fall. LaCrosse virus, the etiologic agent of California virus encephalitis, remains the most common cause of neuroinvasive disease in children. California virus encephalitis should be suspected in any child in a known endemic region who has signs of fever and cerebrocortical dysfunction. The course of California virus encephalitis is usually mild, with a fatality rate of less than 5%. Western equine encephalitis (WEE), an arboviral disease primarily of infancy, causes a more severe syndrome. Eastern equine encephalitis (EEE) has a predilection for infants and young children. EEE is the most severe of the arboviral diseases and frequently proves fatal. St Louis encephalitis (SLE) may occur in epidemic form in the Midwest and Southeast. Most infections produced by SLE are mild.

Other viral diseases may be transmitted by vectors. The virus that causes Colorado tick fever, a reovirus transmitted by rodent arthropods, produces a dengue-like illness in humans. Tick-borne encephalitis (TBE) is endemic primarily in Europe, the former Soviet Union, and Asia. West Nile virus (WNV) is principally transmitted by *Culex* mosquitoes. West Nile neuroinvasive disease (WNND) occurs most commonly in older adults, with children constituting only 4% of all WNND case subjects reported from 1999 to 2007 (443 cases). Children with WNND often develop signs of meningitis, whereas adults typically manifest signs of encephalitis. Even though cases of intrauterine transmission and possible transmission through breastfeeding have occurred, mothers should continue breastfeeding even in areas with WNV transmission.

Infections with lymphocytic choriomeningitis (LCM) virus, an arenavirus, may be acquired or congenital. Acquired infections may be transmitted directly to humans by infected laboratory rodents or domestic (pet) rodents. LCM may be asymptomatic in one-third of individuals or produce a clinical picture of aseptic meningitis, meningoencephalitis, or transverse myelitis. Congenital infection with LCM may resemble congenital toxoplasmosis or cytomegalovirus (CMV) infection with chorioretinopathy, hydrocephaly, or microcephaly.

### Rabies

Rabies, an encephalitis caused by the neurotropic virus, *Rhabdoviridae*, is transmitted by a bite, scratch, or droplet from an infected wild animal (eg, raccoon, bat) or an unimmunized domestic animal. Rabies has the highest case-fatality rate of any infection and causes an estimated 50,000 deaths worldwide, frequently in children who are bitten by rabid dogs. In the United States, however, rabies infections in children are often attributed to contact with rabid bats. Deaths from rabies has declined from more than 100 deaths per year a century ago to less than 5 per year. Because of the long incubation period of rabies, the exposure may occur overseas, as was the case of a 24-year-old US soldier who presented to an ED in New York with symptoms of right arm pain, vomiting, ataxia, anxiety, and difficulty swallowing. Eight months previously, while deployed to Afghanistan, the soldier was bitten by a feral dog on the right hand. His wound was cleansed, but he had not received rabies postexposure prophylaxis.

Most reported cases of rabies encephalitis have been fatal. Most reported cases of rabies encephalitis have been fatal. A 15-year-old girl who received antiviral therapy while in an induced coma recovered. A shorter latency to symptoms of rabies has been documented after transplantation, as was the case when multiple individuals contracted rabies less than 30 days after tissue was transplanted from a teenager who had unknowingly been bitten by a rabid bat. Clinical symptoms consisted of mental status changes and seizures. MRI disclosed cerebral edema, and pathologic examination of brain tissue disclosed viral inclusions consistent with Negri bodies.

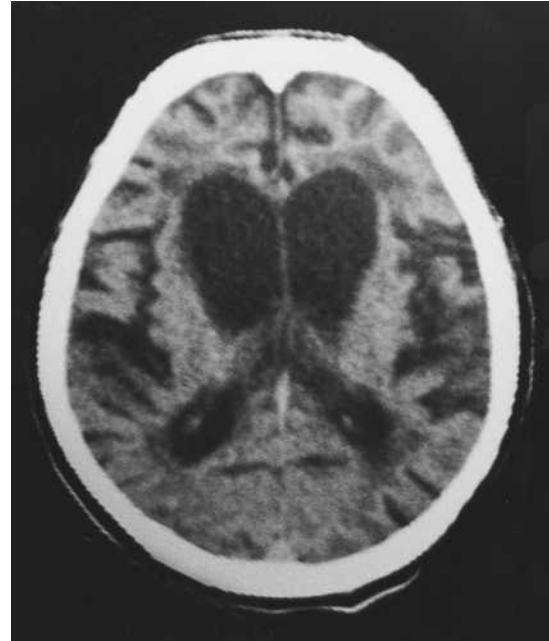
### Viruses Associated With Childhood Exanthems

Although a rare occurrence, childhood viral infections such as rubella, adenovirus, influenza, CMV, rotavirus, and EBV (infectious mononucleosis) can cause meningoencephalitis.

In the prevaccination era, measles was a ubiquitous disease whose spread was facilitated by overcrowding. Records from Ellis Island document more than one-half of deaths at quarantine resulted from measles. Measles viruses cause meningoencephalitis in approximately 1 in 1,000 cases and within 4 to 7 days after onset of the rash. The severity of the neurologic illness (including irritability, drowsiness, and ataxia) does not seem to be related to the intensity of the systemic illness. Endemic transmission of measles ceased in the United States in 2000. Cases of measles nonetheless occur because of immigration (nearly 50% from the Philippines) and outbreaks among unvaccinated persons such as Amish communities in Ohio. There were 173 cases and 5 outbreaks of measles in the first five months of 2015. The CDC, Centers for Disease Control, attribute the multistate outbreak to a visitor to the Disneyland amusement park in California. The measles virus type B3 was identified as the same virus which caused a measles outbreak in the Philippines during 2014.

Mortality in patients with measles meningoencephalitis approximates 10%, and as many as one-half of survivors may have neurologic sequelae. An unusual syndrome of dementia and myoclonic seizures can develop in children 7 to 10 years after measles infection or immunization. This disorder results from a persistent measles infection known as *subacute sclerosing panencephalitis* (SSPE) (Figure 290-2). Data from the US measles epidemic during 1989 to 1991 suggest an incidence of 4 to 11 cases of SSPE per 100,000 cases of measles. Infants and younger children are at higher risk than children older than 5 years. A syndrome of subacute measles encephalitis has also been reported in immunosuppressed individuals. Although encephalitis and aseptic meningitis may occur following immunization with the measles, mumps, and rubella (MMR) vaccine, there is no increase in the incidence of these conditions, suggesting the vaccine was not causal.

Varicella-zoster virus (VZV) is a herpesvirus that causes chickenpox or herpes zoster (shingles) (Figure 290-3). Varicella may cause mild encephalitis or a focal cerebellitis with prominent ataxia. Reactivation of VZV may produce a number of neurologic syndromes,



**Figure 290-2** Subacute sclerosing panencephalitis (SSPE). Marked atrophy of both the cerebral cortex and the deep gray nuclei has occurred in this child, who has long-standing SSPE.



**Figure 290-3** Varicella-zoster virus (VZV) is a herpesvirus that causes chickenpox or herpes zoster (shingles). This child received a VZV vaccination 2 months before eruption of herpes zoster.

including encephalitis, myelitis, stroke, and acute infectious demyelinating polyneuropathy (AIDP, Guillain-Barré syndrome).

Rubella is a mild febrile exanthem of childhood with prominent arthralgia. Infection during the first trimester of pregnancy may result in congenital rubella syndrome. The number of cases has declined from 57,686 in 1969 to 271 in 1999. Rubella in the United States now primarily affects infants born to foreign-born



women. A child affected with rubella in utero may be infectious for 12 months or more.

Mumps meningoencephalitis is a mild illness that generally has a good prognosis. One-half of children with mumps meningoencephalitis are asymptomatic, whereas 15% may exhibit meningismus and headache. Mumps meningoencephalitis may occur without parotitis, before the appearance of parotitis, or after it has resolved.

### Immunizations for Viral Diseases

#### Influenza

Neurologic complications such as seizure or altered mental status have been reported with the novel influenza A (H1N1) virus. The most common complication was simple or complex febrile seizure in 12 of 17 patients. Less frequent neurologic disorders associated with H1N1 infection included encephalopathy, Guillain-Barré syndrome, acute disseminated encephalomyelitis, and transverse myelitis.

#### Rotavirus

Immunization with rotavirus is now recommended by the American Academy of Pediatrics and the Advisory Committee on Immunization Practices. More than 20 cases of meningoencephalitis have been reported with confirmation of rotavirus in the CSF by PCR.

#### Postvaccinal Encephalitis

Postvaccine encephalitis is a rare but serious complication of measles or other live vaccines. Following smallpox vaccine (vaccinia), the attenuated virus may cause encephalitis, with permanent neurologic injury in 25% of those affected. Children younger than 1 year are at greatest risk. Vaccinia virus may be detected in brain or CSF of children with vaccinia meningoencephalitis. Since 1971, routine vaccination was discontinued. Currently, certain laboratory workers and US service members who are being deployed have been inoculated with vaccinia virus. Transmission of vaccinia could occur if a susceptible individual, such as a child with eczema, is in close contact with a recently vaccinated family member.

### Acquired Immunodeficiency Syndrome

Acquired immunodeficiency syndrome (AIDS) is caused by the HIV retrovirus (see Chapter 268, Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome). The syndrome is noteworthy for meningoencephalitis caused by HIV and by CMV, herpesvirus, and *Toxoplasma gondii*. Nervous system involvement in patients infected with the HIV virus also includes development of lymphoma, progressive multifocal leukoencephalopathy associated with JC virus, and infections with *Cryptococcus*, tuberculosis, and *Candida albicans*. Infection with HIV may produce either encephalitis or a progressive encephalopathy in children. Multiple organisms, including viruses, bacteria, fungi, and protozoa, can be recovered from brain tissue of immunosuppressed patients who have AIDS.

### Fungi, Spirochetes, and Parasites

Nonviral causes of meningoencephalitis include infectious (fungi, spirochetes, and parasites) and noninfectious conditions associated with CSF pleocytosis.

Amebic meningoencephalitis may result from swimming in infected freshwater rivers or lakes infected with *Naegleria*. (See Chapter 308, Parasitic Infections.)

In 2012, the incidence of mother-to-child transmission of syphilis (MTCTS, or congenital syphilis) declined to 7.8 cases per 100,000 live births. The rate of MTCTS in infants born to black women was more than 4-fold greater (29.6 cases per 100,000 live births), indicating inadequate prenatal care. MTCTS may result in premature birth or stillbirth. Infected newborns may be asymptomatic or may present with hepatosplenomegaly, petechial rash ("blueberry muffin baby"), rhinorrhea (snuffles), or bony abnormalities.

Neuroborreliosis is a tick-borne spirochetal infection. In addition to headache, neurologic disorders occurring in individuals with neuroborreliosis include facial palsy (8%), radiculopathy (1%), and meningitis-encephalitis (1%). Some children with facial nerve palsy caused by *Borrelia burgdorferi* had CSF pleocytosis (predominantly mononuclear; average number of cells, 191/mcL) or increased CSF protein but lacked meningeal signs. Children with Lyme disease are also at risk for developing transverse myelitis, seizures, pseudotumor, diplopia, headache, and meningismus.

Tick-borne encephalitis include Rocky Mountain spotted fever (RMSF) caused by *Rickettsia rickettsii*. Similar illnesses may be produced by infection with other rickettsial species (eg, spotted fever group *Rickettsia*). RMSF is transmitted by several species of ticks. The initial symptoms are protean, including fever and malaise. The classic petechial rash develops by the fifth day. Children aged 5 to 9 years are at the highest risk for fatal outcome. Pet dogs may concurrently develop RMSF and serve as a vector. Native American children suffer significantly more infections from RMSF than other ethnic groups.

Toxoplasmosis causes cerebral calcifications, microcephaly, and seizures resulting from transplacental infection by the protozoa *T gondii* to the fetus. An estimated 400 to 4,000 cases of congenital toxoplasmosis occur each year, transmitted to humans through ingestion of inadequately cooked meat or ingestion of oocysts from cat feces.

### Prions

The transmissible spongiform encephalopathies include kuru (children of the Fore tribe of New Guinea), bovine spongiform encephalopathy (BSE) (cattle), and Creutzfeldt-Jakob (CJ) disease (humans). Of the 15 cases of CJ disease in individuals younger than 30 years during the time period 1979 to 2006, one-half of the cases contracted the disease through administration of cadaveric growth hormone or dura mater transplants. New-variant CJ disease is a foodborne disorder related to BSE, which is endemic in the United Kingdom. Susceptibility to new-variant CJ disease may be highest in teenagers. Prohibition of beef products in cattle feed has reduced the incidence of both new-variant CJ disease and BSE.

### INCIDENCE

The number of annual viral encephalitis cases in the United States is estimated at 20,000 each year. The pathogens most commonly responsible for viral



encephalitis include enteroviruses, HSV (responsible for 10% of cases), arboviruses (eg, WNV), and rabies virus. Deaths associated with encephalitis were highest in children younger than 1 year and adults older than 65 years in the 20-year period from 1979 to 1998. Viruses reported as producing encephalitis in individuals younger than 25 years in 2012 included WNV, 175; California virus, 60; and EEEE, 4. There were no cases of rabies in those younger than 25 years. Congenital rubella was noted in 3 infants; the mothers of all 3 had been in Africa during their pregnancy. Treponemal infection (congenital syphilis) was reported in 322 infants.

## CLINICAL FEATURES

Most viruses spread through the bloodstream to the choroid plexus and from there to the parenchyma of the cerebrum, brainstem, or spinal cord. Clinical features of cerebral involvement are most commonly seizures and changes in mental status. Rabies travels in a retrograde manner through the peripheral nerves to invade the brainstem, producing cranial neuropathies, such as drooling and choking on liquids (“hydrophobia”). Herpes simplex virus classically infects the temporal lobes, resulting in olfactory seizures (“bad smells”). As the virus spreads from the temporal region, focal or generalized convulsive activity develops.

Poliomyelitis selectively affects the motor neurons, resulting in paralysis of the muscles of respiration (bulbar paralysis) and extremities. Paralysis of the legs can be asymmetrical. Enterovirus D68 is associated with limb weakness and involvement of the spinal gray matter. Varicella-zoster and EBV may infect the cerebellum, producing an acute ataxia. If spinal cord involvement is present, then the patient may have symmetrical limb paralysis, transverse sensory symptoms, and bowel and bladder dysfunction.

Children with aseptic meningitis, in contrast to those with meningoencephalitis, have intense headache, meningismus, and photophobia but may possess a clear sensorium. Ameba, fungi, and the viruses causing EEE, HSV, or rabies may produce cerebral or brainstem dysfunction, intractable seizures, increased intracranial pressure from brain edema, and death.

Ultimately, the course and outcome of meningoencephalitis are related to the virulence of the organism and the host response to the infection. For every 100 individuals excreting poliovirus in their feces, 1 is paralyzed; approximately 5 others have nonspecific sore throat, nausea, vomiting, or flu-like symptoms (abortive poliomyelitis); and 94 are asymptomatic.

## DIFFERENTIAL DIAGNOSIS

The early signs and symptoms associated with viral infection of the nervous system are often protean and include fever, chills, myalgia, and headache. It is frequently challenging for the pediatrician to distinguish “just a cold” from the early stages of meningoencephalitis. Change in mental status is the sine qua non of meningoencephalitis. Nonetheless, change in mental status because of toxins or metabolic derangement must be excluded when considering a diagnosis of meningoencephalitis. Metabolic encephalopathy resulting from hypoglycemia, hyperammonemia, and

Reye syndrome can be diagnosed by appropriate laboratory investigations. When meningoencephalitis is suspected, make certain to exclude the possibility of toxic exposure to lead, alcohol, acetaminophen, or other poisons that could produce encephalopathy.

The clinical course of a brain abscess is usually slower than occurs in meningoencephalitis. Focal findings may be prominent in brain abscess, and a history of sinus infection, middle ear or mastoid infection, or congenital heart disease may be elicited. A myelitic form of viral nervous system infection may be mimicked by a mass lesion or Guillain-Barré syndrome. Differences in seasonal occurrence, clinical course, and outcome allow differentiation of some types of meningoencephalitis.

Demyelinating disease in children may present as a postinfectious inflammation of the brain and spinal cord termed *acute disseminated encephalomyelitis* (ADEM). Varicella and rubella have been implicated as causes of ADEM, but in many cases, no definite virus is identified. CNS demyelinating disease evolves over several days, producing altered mental status, visual loss, paralysis, or seizure. Magnetic resonance imaging may disclose marked signal abnormalities in the subcortical white matter, corpus callosum, cerebellum, brainstem, or spinal cord. Autoantibodies against myelin oligodendrocyte glycoprotein (MOG) may be present in 44% of patients with ADEM but only 2% of patients with multiple sclerosis. Serum aquaporin-4 (AQP4) antibodies can differentiate neuromyelitis optica (NMO), a demyelinating disorder with prominent involvement of the optic nerve and spinal cord.

N-methyl-D-aspartate (NMDA) receptor antibody encephalitis (also termed *anti-NMDA receptor antibody encephalitis*) may produce a syndrome similar to infectious encephalitis with altered sensorium, intractable seizures, movement disorder, MRI abnormalities in the white matter or brainstem, and autonomic dysfunction. One-third of teenage girls with NMDA receptor encephalitis may have ovarian teratomas.

## LABORATORY EVALUATION

Examination of the CSF may be helpful to the diagnosis of meningoencephalitis. However, there may be considerable overlap in the CSF formula that results from viral, bacterial, or fungal infection of the nervous system. In some cases of meningoencephalitis, pleocytosis may be minimal or absent. For example, only 50% of patients positive by PCR for enterovirus infection in CNS had pleocytosis in the CSF. Similarly, the degree of hypoglycorrhachia and protein elevation in CSF varies with type of organism. Every attempt should be made to identify the offending organism to help determine the prognosis and to document potential epidemic outbreaks.

The presence of red blood cells in the CSF may indicate hemorrhagic brain necrosis, commonly seen with herpesvirus infections and EEE. A predominance of mononuclear cells in the CSF is the exception in acute bacterial meningoencephalitis but may be present with syphilis, Lyme disease, listeriosis, or tuberculosis.

Polymerase chain reaction is a powerful tool in identifying enterovirus, mumps virus, CMV, VZV, and other viruses. In adult patients with herpes simplex

encephalitis, PCR of CSF has more than 90% specificity and sensitivity. The reliability of PCR in neonatal HSV may vary according to the assay used in a specific laboratory. A rapid screening test for EBV (Monospot) is available at most hospitals. Brain biopsy is seldom used as a diagnostic tool. Viral culture of CSF has the advantage of detection of viruses not included in the PCR panel, but the disadvantage of being falsely negative. A positive PCR may raise the question of whether presence of viral antigen represents new or prior infection. Comparison of serum and CSF titer may be helpful in this situation.

Brain imaging in children suspected of viral encephalitis is essential. A caveat is that the computed tomographic brain scan, although rapid and widely available, lacks the sensitivity of MRI in discerning edema formation and inflammation. Even MRI may be normal in the early phases of meningoencephalitis. Contrast should be administered to better assess inflammation or cerebral cortical enhancement. Typical MRI findings in meningoencephalitis include scattered or confluent areas of T2-weighted hyperintensities or T1-weighted hypointensities. When the encephalitis produces cerebral edema, MRI may disclose midline shift, ventricular compression, or cerebral cortical effacement. Temporal lobe enhancement or necrosis may be evidence of herpesvirus infection.

An electroencephalogram can be a useful adjunctive test. Infants with HSV often have periodic (2-Hz) lateralized epileptiform discharges in the temporal region.

In summary, MRI with and without contrast is promptly performed in the child with suspected viral meningoencephalitis. The spinal cord should also be imaged if signs of myelitis or radiculitis are present. Samples of CSF and blood are obtained for PCR, cell count and differential, glucose, and protein. Serologic tests should be obtained during the acute and convalescent phases of the disorder. Viral culture of CSF, throat, and stool should also be considered if the PCR is not diagnostic.

## TREATMENT

In a child suspected of having meningoencephalitis, after imaging and laboratory studies have been obtained, treatment with intravenous acyclovir is considered. Acyclovir is indicated for HSV infection, with higher doses (60 mg/kg per day) recommended for neonates. Renal function should be monitored because acyclovir is nephrotoxic. Ganciclovir has been used in treatment of VZV-associated encephalitis, HHV-6, and CMV infection.

Specific treatment of other viral encephalitides remains elusive. In 2004, a 14-year-old girl with rabies responded to the combination of ribavirin, ketamine, and amantadine. However, subsequent treatment of 3 other children with rabies infection was unsuccessful. The management of encephalitis caused by HIV is discussed in Chapter 268, Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome. Corticosteroids are not of proven benefit in treating viral meningoencephalitis and may blunt host defenses.

Encephalitis caused by agents other than viruses are treated appropriately. Rickettsial infection of the

nervous system is treated with doxycycline. *Borrelia* infection should be treated with ceftriaxone, and treponemal infection with penicillin.

Supportive treatment of a patient who has meningoencephalitis includes management of intracranial pressure (see Chapter 364, Increased Intracranial Pressure), respiratory support, treatment of seizures, physical therapy, and maintenance of fluid and electrolyte balance.

Prevention is the most cost-effective method of reducing the morbidity and mortality caused by viral meningoencephalitis. Immunization has reduced, but not eliminated, poliomyelitis, and has made rubella, mumps, and measles meningoencephalitis uncommon. Repeat measles immunizations of older children should reduce the incidence of measles encephalitis and SSPE further.

## PROGNOSIS

The prognosis of meningoencephalitis is related to the virulence of the organism and the age, neurologic status at time of treatment, and immune status of the host. At one extreme, rabies encephalitis is almost always fatal. In contrast, all children with respiratory syncytial virus encephalitis have a full recovery.

The development of antiviral therapy has profoundly affected prognosis in HSV encephalitis. Without antiviral therapy, more than two-thirds of individuals with HSV encephalitis will die, and fewer than 5% regain normal neurologic function. With acyclovir therapy, no deaths were reported from childhood HSV encephalitis, but neurologic sequelae developed in 63% of patients. Infants with HSV-1 encephalitis have better neurologic outcomes than those infected with HSV-2. Developmental scores were significantly higher in infants with neonatal HSV who received oral suppressive therapy with acyclovir for 6 months after their initial intravenous course of antiviral therapy.

In contrast to HSV encephalitis, the prognosis of EBV encephalitis was considerably better: death in 10%, mild neurologic sequelae in 10%, and good neurologic outcome in 80%.

The outcome of arbovirus infections is on a spectrum. Eastern equine encephalitis caused death in one-third of patients, with many of the survivors suffering severe neurologic consequences. In some of the arboviral infections, children are affected more severely than adults. WEE is associated with complete recovery in virtually all adults but causes death in 3% and neurologic sequelae in up to 30% of children. Venezuelan equine encephalitis causes flu-like symptoms in adults, with encephalitis occurring most frequently in children. Similarly, deaths from Japanese encephalitis may be 3-fold greater in children than adults.

A bimodal involvement is seen with RMSF. Children aged 5 to 9 years have the highest risk for death, as do adults older than 70 years.

The neurologic consequences of meningoencephalitis may be lasting. Enterovirus 71 infection of the CNS in children was associated with a nearly 7-fold increase in attention deficit/hyperactivity disorder-related symptoms (20% of children with meningoencephalitis vs 3% of matched control subjects).

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Diseases Spread by Insects* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/from-insects-animals/Pages/Diseases-Spread-by-Insects.aspx](http://www.healthychildren.org/English/health-issues/conditions/from-insects-animals/Pages/Diseases-Spread-by-Insects.aspx))
- *A Parent's Guide to Insect Repellents* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Rabies Information for Kids* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/ncidod/dvrd/kidsrabies](http://www.cdc.gov/ncidod/dvrd/kidsrabies))

### Medical Decision Support

- *Bovine Spongiform Encephalopathy, or Mad Cow Disease* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/prions/bse/index.html](http://www.cdc.gov/prions/bse/index.html))
- *Epstein-Barr Virus and Infectious Mononucleosis* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/epstein-barr/index.html](http://www.cdc.gov/epstein-barr/index.html))
- *HIV/AIDS* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/hiv](http://www.cdc.gov/hiv))
- *Japanese Encephalitis* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/japaneseencephalitis/index.html](http://www.cdc.gov/japaneseencephalitis/index.html))
- *Prion Diseases* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/prions/index.html](http://www.cdc.gov/prions/index.html))
- *Rabies* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/ncidod/dvrd/rabies](http://www.cdc.gov/ncidod/dvrd/rabies))
- *Red Book: 2015 Report of the Committee on Infectious Diseases* (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Rocky Mountain Spotted Fever* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/ncidod/dvrd/rmsf/index.htm](http://www.cdc.gov/ncidod/dvrd/rmsf/index.htm))
- *Tick-borne Encephalitis (TBE)* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/vhf/tbe](http://www.cdc.gov/vhf/tbe))
- *Variant Creutzfeldt-Jakob Disease* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/prions/vcjd/index.html](http://www.cdc.gov/prions/vcjd/index.html))
- *West Nile Virus* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/ncidod/dvbid/westnile/index.htm](http://www.cdc.gov/ncidod/dvbid/westnile/index.htm))

## SUGGESTED READINGS

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## Chapter 291

# METABOLIC DISORDERS BEYOND THE NEWBORN PERIOD

Carol Lynn Greene, MD

## FOUNDATION

### Definition, Epidemiology, Etiology, and Risk Factors

At a conservative estimate, inborn errors of metabolism (IEMs) collectively affect more than 1 per 1,000 individuals. These errors can present at any age and affect any organ system. Many IEMs respond to specific therapies that prevent disability or death, and all are genetic. The failure to suspect and diagnose inborn errors leads to lost opportunities for intervention, resulting in harm to children and families. Appropriately integrating approaches to diagnosing IEMs in pediatric practice yields some of the highest benefits in medicine (Box 291-1). This chapter covers the basic principles and approaches to IEMs, with an emphasis on signs and symptoms for a practical clinical understanding for the primary care physician (PCP) and for nongenetic specialists. In addition, the PCP of the medical home should ensure that families are aware of options for carrier screening because families may be interested in understanding and possibly addressing risks in advance.

Understanding basic principles, presentations, and approaches to IEMs increases the likelihood of prompt

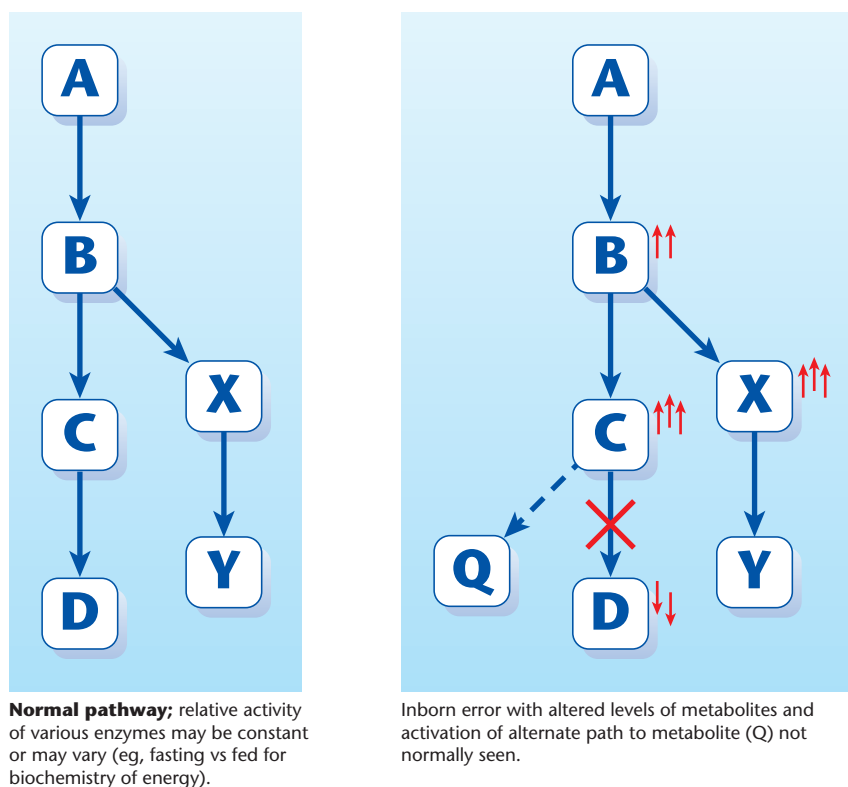
### BOX 291-1 Case 1

A 3-month-old infant is brought to the primary care physician (PCP) with reports of irritability and frequent vomiting. A diagnosis of reflux is made, and treatment measures are somewhat helpful. Weight gain slows over the next few months. At the 9-month visit, the PCP notes inadequate developmental progress. Further evaluation over the next 8 months involves multiple invasive studies, and eventually a combination of urine and blood studies reveals a diagnosis of an inborn error of metabolism. The diagnostic odyssey is over. The condition is autosomal recessive, so the 2-month-old sibling is tested and is also affected.

The diagnosis is methylmalonic acidemia, of a type profoundly responsive to B<sub>12</sub> therapy. The patient responds to treatment that prevents further brain damage. Unfortunately, the patient has permanent brain damage that could have been prevented if the diagnosis had been made at 4 months of age. The affected sibling will benefit from earlier treatment.

If the diagnosis were mitochondrial depletion syndrome (a fatal condition caused by an identifiable mutation in polymerase gamma), prenatal diagnosis would have been available to the family, who must anticipate the early demise of both of their children.





**Figure 291-1** Normal and abnormal metabolic pathway and consequences.

recognition, diagnosis, and appropriate management for patients and their families.

### Defining Inborn Errors of Metabolism: Basic Principles, Types, and Pathophysiology

IEMs are conditions in which a change in gene alters the function of an enzyme or other protein. The change in function causes alterations in a metabolic pathway that leads to clinical consequences. A block in a pathway can lead to the increase of a compound normally present but toxic in excess (eg, ammonia or methylmalonic acid); to inadequate levels of some essential metabolic product (eg, glucose, or adenosine triphosphate for energy); or to production through an alternative pathway of a toxic compound that is not normally present (Figure 291-1).

Some categories of IEMs are identified by the types of molecules involved and some by the organelle into which a certain aspect of metabolism is compartmentalized. Some involve small molecules, and some involve very large molecules. In many categories of IEMs there is more than one kind of pathophysiology. The primary metabolic defects range from simple catalytic failure of an enzyme, failure of post-translational modification of multiple enzymes and other proteins, failure to transport enzyme to appropriate metabolic compartment, failure of production or activation of a cofactor essential for enzyme activity, or complete failure to build a cellular compartment.

Any system of categorization is imperfect. For example, pyruvate carboxylase deficiency is here

categorized as an inborn error of mitochondrial energy metabolism. However, pyruvate carboxylase deficiency may also be part of multiple carboxylase deficiency or biotinidase deficiency. In that case pyruvate carboxylase deficiency is found together with abnormalities of other enzymes that are clearly inborn errors of organic acid metabolism. Other important examples are the disorders of cobalamin ( $B_{12}$ ) metabolism that can cause either altered metabolism of methylmalonic acid (organic acidemia) or homocystine (amino acidopathy), or both, depending on the step in the cobalamin pathway that is altered. Maple syrup urine disease (MSUD) can be classified as an amino acid disorder or organic acidemia depending on the aspect of the biochemistry that is considered. No attempt is made to categorize certain biochemical conditions such as glucose transporter defect (a cause of seizures) and  $\alpha_1$ -antitrypsin deficiency (cause of liver disease in children) that do not fit into any biochemical model of categorization. They are included as appropriate in the recommendations for evaluation of clinical presentation. However, certain biochemical conditions that are traditionally covered elsewhere are not included here, such as the inborn errors of steroid metabolism (eg, congenital adrenal hyperplasia) and the albinisms, although some of the latter conditions are lysosomal disorders and others are abnormalities of metabolism of tyrosine. Table 291-1 provides a practical classification for consideration of pathophysiology and presentation and for use in directing first steps in consideration of the differential diagnosis and evaluation. Inheritance is typically



Table 291-1

## Categories of Inborn Errors of Metabolism With Key Characteristics and Examples

## CATEGORY, DEFINITION, BIOCHEMISTRY, AND GENETICS

## KEY CHARACTERISTICS AND EXAMPLES

**Aminoacidopathies:** Involve abnormal levels of AAs with the amino group still attached; include primary catalytic defects, cofactor defects, transport defects (note that MSUD may be categorized here because AA levels are elevated in blood). Almost all are autosomal recessive.

Usually not acidotic (except MSUD, or with the renal tubular acidosis of tyrosinemia). Typically but not always affect the CNS (eg, PKU, glycine encephalopathy), may affect other organs (eg, liver and renal tubules in tyrosinemia type 1). Episodic, static, or progressive. Homocystinuria may present with stroke or clotting, with or without intellectual disability. Diagnosis with blood AA (PAA or SAA), sometimes UAA, sometimes confirmed by enzyme assay or DNA testing.

*Special presentation:* when the mother has PKU or hyperphenylalaninemia, she may be normal and unaware of diagnosis but have babies with microcephaly and intellectual disability; this has nearly 100% recurrence risk, and adverse outcome is preventable with treatment of mother; diagnosed by blood AA in mother.

**Organic acidemias:** Involve metabolites of AAs after amino group is removed and other compounds with C, H, and O (fatty acids and lactate/energy in separate categories). Essentially all are autosomal recessive.

Usually but not always acidotic, anorexia/vomiting; episodic altered consciousness; may include bone marrow depression or other end-organ failure. Diagnosis with UOAs; blood ACP may be helpful, enzyme assays or DNA testing for confirmation when available.

**Urea cycle defects:** Involve the urea cycle, typically with altered levels of the AAs in the urea cycle. Most are autosomal recessive, but the most common is X-linked.

Altered mental status, decreased appetite or intractable or recurrent emesis including “cyclic vomiting,” migraine, ataxia, and often with protein aversion. Typically not acidotic unless in shock; respiratory alkalosis is common. Diagnosis by blood AA, in some cases confirmed with enzyme assays or DNA testing.

**Fatty acid oxidation and carnitine metabolism disorders:** Involve the oxidation of fatty acids to ketones and the transport of fatty acids into the mitochondria for oxidation. Essentially all are autosomal recessive.

Classic presentation is Reye syndrome or SIDS in an infant or toddler, but more commonly the presentation is excessive irritability or lethargy with ordinary childhood illness or extended fasting. The hallmark is hypoketosis, but some ketones are usually present, and hypoglycemia is only sometimes present. Also may present (especially long-chain fatty acid oxidation and carnitine metabolism) with liver failure, FTT, cardiomyopathy, or rhabdomyolysis; retinopathy and bone marrow failure may occur. Diagnose with ACP, but that may be normal when well, and diagnose some conditions with carnitine levels. Some diagnoses may be confirmed with enzyme assays and/or DNA testing.

**Mitochondrial (energy) metabolism and disorders of lactate and pyruvate:** Include oxidative phosphorylation defects of the mitochondrial respiratory chain, defects of the Krebs cycle and of PDH and pyruvate carboxylase. May occur because of defects of single enzymes, of transport into the mitochondria (of enzymes or substrate), of cofactor synthesis (eg, coenzyme Q), of multiple enzymes because of mutations in mitochondrial DNA (mtDNA) or of mtDNA repair or synthesis. X-linked inheritance (PDH deficiency and some creatine disorders), autosomal dominant inheritance, and maternal inheritance because of mtDNA mutations occur; but most conditions are autosomal recessive.

Any presentation, any age, with variability in biochemical findings and clinical presentation. Examples include dysmorphic features with brain dysgenesis or porencephalic cysts; the normally formed neonate with overwhelming acidosis; Leigh syndrome (an infantile or childhood-onset brainstem neurodegenerative disease); isolated organ failure of heart, liver, kidney, exocrine pancreas, bone marrow, retina, or others; and combinations, eg, Pearson syndrome (bone marrow and exocrine pancreatic failure) or multisystem failure. Other classic pediatric conditions are MELAS, MERRF, and Alpers syndrome (progressive seizures and liver failure). Diagnostic testing depends on presentation; usually begins with blood AA and UOA, lactate and pyruvate, and ACP; but in some cases the first diagnostic test is of DNA sample of blood or biopsy of muscle or liver for histochemistry or enzyme assays. It is well described that enzyme assays or DNA findings can be normal in cases with proven disease.

**Carbohydrate disorders:** Involve metabolism of sugars (with glycogen storage disorders separated out); examples are galactosemia and the disorders of fructose metabolism. Essentially all are autosomal recessive.

Typically presenting with liver disease or hypoglycemia and acidosis, often with renal tubular disease. Cataracts may be seen in galactosemia at presentation in some cases and develop in untreated cases. Diagnosis based on enzyme assay or DNA testing.

Continued

Table 291-1

## Categories of Inborn Errors of Metabolism With Key Characteristics and Examples—cont'd

CATEGORY, DEFINITION, BIOCHEMISTRY, AND GENETICS	KEY CHARACTERISTICS AND EXAMPLES
<b>Glycogen storage disorders:</b> The various disorders of glycogen synthesis and degradation; when glycogen is not normally branched, there are adverse effects on the liver. Most are autosomal recessive, and some are X-linked.	Typically but not always including hepatomegaly, 2 major presentations are seen, with hypoglycemia (eg, glycogen storage disease [GSD] type 1) or with muscle weakness with or without cardiomyopathy and rhabdomyolysis (Pompe disease, McArdle disease). Some conditions lead to liver failure or liver tumors. However, glycogen synthase deficiency is GSD type 0 and presents as ketotic hypoglycemia with a small liver. Diagnosis by histology, enzyme assay, DNA testing for some conditions.
<b>Porphyrias:</b> Disorders of metabolism of the porphyrins in synthesis or degradation of hemo-globins. AIP is autosomal dominant; others are recessive or X-linked.	Most cases present in late childhood or adolescence, with or without skin findings, but some types present in the neonate. CNS is typically spared, but AIP and hepatic coproporphyrin can present with psychotic episodes, recurrent abdominal pain, and peripheral neuropathy, often diagnosed as psychosomatic disease. Diagnosis includes biochemistry, enzyme assay, and DNA testing for some conditions.
<b>Lysosomal storage diseases:</b> Disorders resulting from alteration of function of individual enzymes responsible for breaking down large cell wall molecules (mucopolysaccharides, glycolipids, sphingolipids) within the lysosome, or of import into the lysosome affecting multiple pathways. Most are autosomal recessive, and Hunter syndrome and Fabry disease are X-linked.	Progressive disorders that until recently were untreatable. Some affect the CNS only (Krabbe disease), whereas others also have organomegaly (Tay-Sachs disease), dysmorphic features, and skeletal changes (the mucopolysaccharidoses, except for Sanfilippo syndrome that affects primarily CNS). Cystinosis affects bone by causing renal tubular disease. Hepatosplenomegaly of Gaucher disease leads to preventable anemia and thrombocytopenia. Fabry disease is especially underdiagnosed and untreated; it causes renal failure (typically in early or middle adulthood), cardiomyopathy, stroke, and pain from peripheral neuropathy; enzyme infusion prevents permanent damage. Diagnose by biochemistry (eg, UMPs or oligosaccharides in some), enzyme assay, DNA testing for some conditions, or carrier testing which is available for some conditions.
<b>Peroxisomal disorders:</b> Disorders of individual enzymes in the peroxisome involved in various pathways including very-long-chain fatty acid oxidation and plasmalogen synthesis, or defects of peroxisome development leading to multiple pathway dysfunction.	A wide variety of presentations including the neurodegenerative condition adrenoleukodystrophy or isolated primary adrenal failure. May present as a dysmorphic syndrome; as Zellweger syndrome; with Down syndrome-like facies, hypotonia, and liver and renal cysts; and as progressive neurodegenerative disease. Most have alteration of either very-long-chain fatty acids, plasmalogens, or pipecolic acid, and some have stippled epiphyses on plain film. Diagnose with histology and biochemistry and with DNA testing in some conditions.
<b>Disorders of purines and pyrimidines:</b> Disorders of synthesis or degradation; include disorders of uric acid metabolism. Autosomal recessive or X-linked.	Variable presentation, mostly affecting the CNS or the bone marrow (eg, severe combined immunodeficiency). Include Lesch-Nyhan disease, with self-mutilation; the same enzyme defect in milder cases causes gout. Diagnose with biochemistry; DNA testing in some conditions.
<b>Neurotransmitter disorders (and other conditions evident only on analysis of cerebrospinal fluid):</b> These are conditions in which critical neuroactive molecules are not properly synthesized or metabolized. Include a number of conditions in which cofactor metabolism is the primary problem, including B <sub>6</sub> responsive seizures and disorders of pterin metabolism. Most are autosomal recessive.	By definition, these are conditions that affect function of the central or peripheral nervous system. Typical presentations include seizures, irritability or other altered mental status, and abnormalities of tone and development. Indirect evidence may be present, (eg, low prolactin in blood resulting from low dopamine), or response to pyridoxine trial, but in general collection and handling of spinal fluid need special precautions for diagnosis. Diagnosis with biochemistry of spinal fluid; some can be confirmed with enzyme assay or DNA testing.
<b>Disorders of metals and micronutrients:</b> Conditions that involve altered metabolism of metals, and some micronutrients including iron, copper, and molybdenum; they can involve excess storage or inability to incorporate metal into enzymes for which it is a critical component. Recessive or X-linked and in some forms of hemochromatosis complex with asymptomatic homozygotes and symptomatic heterozygotes.	Disorders of copper include Menkes disease (neonatal seizures with unusual hair) and Wilson disease (progressive CNS or liver disease). Disorders of iron in pediatrics include neonatal hemochromatosis, presenting with liver disease, or rare late childhood presentation of classic hemochromatosis, causing initial nonspecific symptoms resulting in arthritis or single or multiple organ failure (typically liver, heart, or diabetes). This list does not attempt to consider the primary disorders of molybdenum, zinc, and other micronutrients. Diagnose with metal levels, other biochemistry, histology, and histochemistry; DNA testing in some conditions.

Table 291-1

## Categories of Inborn Errors of Metabolism With Key Characteristics and Examples—cont'd

## CATEGORY, DEFINITION, BIOCHEMISTRY, AND GENETICS

## KEY CHARACTERISTICS AND EXAMPLES

**Disorders of connective tissue (collagen, fibrillin, elastin):** Not to be mistaken for the term *connective tissue disorder* meaning autoimmune disorders, these are typically disorders of structural proteins that affect the integrity of the connective tissue of selected or all organs. Recessive, dominant, or X-linked.

Usually considered in general genetics. Abnormal collagen may primarily affect bones causing osteogenesis imperfecta (with or without dental and hearing problems) or may affect joints and skin, with some causing rupture of vessels or hollow organs. Fibrillin mutations cause Marfan syndrome, and elastin mutations cause Williams syndrome. Diagnosis is by clinical evaluation; in some cases confirmed by DNA testing or by biochemistry of the altered molecule in tissue.

**Carbohydrate-deficient glycoprotein disorders:** Disorders that involve multiple biochemical pathways because the primary disorder is a failure of  $\geq 1$  enzymes that attach carbohydrate moieties to proteins (including enzymes) required for correct structure and function of the protein. Most are autosomal recessive.

As a group, there are now more than 30 conditions identified with highly varied presentation, including conditions with dysmorphic features and malformations evident in the neonate, and others that present only much later; the classic “type 1A” has cerebellar hypoplasia. Often with involvement of the CNS and peripheral nervous system, and includes some primary muscular dystrophies. Some have acute episodes of metabolic crisis or organ failure and many have FTT. Diagnosis is by examination of blood for altered pattern of carbohydrates attached to various proteins, many can be confirmed by DNA testing and some by enzyme assay.

**Channelopathies:** Altered transport of ions across cell walls, including especially calcium. The classic disorder of transport, cystic fibrosis, is not typically considered an inborn error of metabolism but does fit the category. Recessive, dominant, or X-linked.

Leaving aside cystic fibrosis, the 2 major presentations of conditions in this category are neurologic (progressive ataxias, seizures, including heritable febrile seizures or progressive seizure disorders) or cardiac arrhythmias (including classic long QT syndrome). Typically without acidosis or altered organ function except for the primary presentation. Diagnosis is clinical, confirmed in some cases by DNA testing.

**Disorders of cholesterol and other sterol metabolism (primarily synthesis):** Alteration in the synthesis of cholesterol and other sterols; pathophysiology may be because of inadequate amounts of an essential metabolite or interference from the abnormal metabolites. Typically autosomal recessive.

Presenting with FTT, neurologic disease, and often with birth defects and skin disease, this category includes a previously well-described autosomal recessive dysmorphic syndrome (Smith-Lemli-Opitz syndrome). These disorders typically include feeding disturbance and hypotonia and may have skin pigment abnormalities. Diagnosis by biochemistry; cholesterol may be low, but measurement of cholesterol alone is not adequate to make or exclude a diagnosis of any of these conditions. Diagnosis depends on demonstration of abnormal patterns of sterols; some may be confirmed with DNA testing.

**Disorders of vitamins and cofactors:** Vitamins and other cofactors must be absorbed and transported across membranes, and many must be metabolized to an active form or synthesized in the human cell. Pathophysiology of these conditions depends on the pathway. Typically autosomal recessive, but X-linked and dominant disease is known.

This category crosses almost all boundaries because cofactors are found in many pathways. Presentation can be systemic or more limited to the nervous system, bone marrow, bones, muscle (including cardiac), or skin. As an example, problems with vitamin B<sub>12</sub> (cobalamin) can alter AA metabolism, organic acid metabolism, or both. An abnormality of vitamin D leads to X-linked rickets, and an abnormality of pterin metabolism leads to autosomal dominant dopa-responsive dystonia, also known to neurologists as Segawa syndrome. Failure to synthesize coenzyme Q10 leads to a particularly reversible disorder of energy metabolism. Diagnosis of a disorder of vitamin or cofactor metabolism is based on measurement of appropriate metabolites and on measurement of levels of specific vitamins or cofactors. In some cases there is functional testing (eg, enzyme assay for biotinidase, and enzyme assay and complementation studies for cobalamin disorders). Often can be confirmed by DNA testing.

AA, amino acids; AIP, acute intermittent porphyria; ACP, acylcarnitine profile; CNS, central nervous system; FTT, failure to thrive; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke; MERRF, myoclonic epilepsy, ragged red fibers; MSUD, maple syrup urine disease; OA, organic acid; PAA, plasma amino acid; PDH, pyruvate dehydrogenase; PKU, phenylketonuria; SAA, serum amino acid; SIDS, sudden infant death syndrome; UAA, urine amino acids; UMPS, urine mucopolysaccharide; UOA, urine organic acids.

autosomal recessive, with some X-linked conditions and with a few autosomal dominant conditions and maternal inheritance for some cases of mitochondrial disease.

### Risk Factors

Any person of any age and in any population could have an IEM. However, certain IEMs are seen with increased frequency in some populations. For example, Tay-Sachs disease is seen with increased frequency in those of Ashkenazi Jewish or Acadian ancestry. Consanguinity is a risk factor for an IEM because most IEMs are autosomal recessive disorders. In addition, it should be appreciated that ordinary childhood illness is a risk factor for the presentation of IEM in an affected but previously healthy child.

## DIAGNOSIS

### Signs and Symptoms: When to Suspect Inborn Errors of Metabolism

IEMs can cause virtually any symptom or sign and can present at any age. These diseases may be static or may cause intermittent or progressive signs and symptoms. They may present commonly with intellectual disability, failure to thrive (FTT), and symptoms of septicemia. Symptoms that should particularly raise suspicion of an IEM are listed in Box 291-2.

The PCP routinely evaluates for IEMs in every healthy child through newborn screening (see Chapter 29, Screening for Genetic-Metabolic Diseases). Newborn screening is designed solely to identify neonates who need evaluation for specific conditions, and a normal newborn screen does not conclusively exclude an IEM. Physicians should maintain a high index of suspicion for an IEM because even expanded newborn screening detects only a fraction of known IEMs.

Another critical point to remember in considering a diagnosis of an IEM is that finding evidence of one condition, such as infection, does not exclude the presence of an IEM. For example, the child with a fatty acid oxidation disorder may present with acute metabolic crisis as a result of an otitis or RSV; the child may be easily diagnosed with otitis or the respiratory syncytial virus, but neither typically causes or should be assumed to explain altered mental status and abnormal liver function. Even documentation of shaken baby syndrome or other nonaccidental trauma does not exclude diagnosis of IEM because infants with underlying medical or developmental problems are at increased risk for abuse; in addition, some IEMs present with signs easily mistaken for nonaccidental trauma, such as the retinal and brain hemorrhages seen in glutaric acidemia type I.

### History and Physical Examination

When taking the history, be sure to ask about tolerance of exercise and of typically mild childhood illnesses. Also ask whether there is any association of symptoms with changes in diet or whether there are any unusual diet cravings or aversions. In addition to noting the presence of any “red flag” symptoms (Table 291-1) be aware that an IEM is more likely when there are problems in more than 1 organ or system,

### BOX 291-2 Symptoms That Raise Suspicion of an Inborn Error of Metabolism

- Altered consciousness, especially recurrent episodes of abnormal mental status out of proportion to physical health (eg, lethargy without hypoxia, shock, or meningitis); this includes altered behavior such as episodic irritability or inattention
- Seizures in the first day of life or intractable seizures
- Ataxia, especially recurrent, and any other movement disorder, especially dystonia
- Exercise intolerance with pain or fatigue that interferes with reasonable activity
- Regression in neurologic function, development or behavior, including regressive autism
- Unusual diet preferences or avoidances, eg, avoidance of protein or of certain sugars, and especially when intermittent or progressive symptoms or signs follow a diet change (eg, from breast milk to formula, or introduction of sugars)
- Odors (maple syrup, “sweaty feet,” “cat’s urine,” “mousy,” rotten fish—each suggests a specific disorder; the fruity smell of ketosis occurs in a number of conditions)
- Recurrent or persistent pain, including headaches, abdominal pain, and extremity pain
- Sun aversion or sensitivity; heat intolerance
- Family history of consanguinity or of a relative with any symptom or sign seen in inborn errors of metabolism; be aware that because most of the conditions are autosomal recessive, waiting for positive family history guarantees you will miss an opportunity to diagnose the index case in most families. Ancestry may be a clue to certain conditions.

even if there seems to be a simple explanation for each of the individual problems.

The physical signs that should particularly raise suspicion of an IEM include those listed in Box 291-3. Measure head circumference even in the older child or adolescent and examine for unusual texture of hair or unusual rashes. Pay careful attention to movement. Pay careful attention to the eyes (assessing for cloudiness or haziness), and consider an ophthalmologic evaluation to assess for the presence of these and other signs, such as retinopathy in the lens, cornea, or retina.

### Differential Diagnosis

An IEM can present with the same features as infection, neglect and nonaccidental trauma, autoimmune disorders, hypoxic ischemic injury, and poisoning. It can present with malformations leading to suspicion of nonmetabolic genetic disorders. IEM presentations overlap with many primary endocrinopathies. The features of IEMs can be thought to be the result of antecedent infection or hypoxia, whether or not there is good evidence for neonatal asphyxia or perinatal infection.



### BOX 291-3 Physical Signs That Raise Suspicion of an Inborn Error of Metabolism

- Unusual tone: Hypertonia in the neonate or hypotonia after 1 year (and certainly after 2 years) of age and mixed tone
- Movement disorders (watch carefully over at least a few minutes to see if the infant can be still for more than seconds)
- Areflexia
- Decreased muscle mass or muscle quality
- Organomegaly
- Microcephaly or macrocephaly
- Odors
- Cataracts and retinopathy
- Coarse features
- Widening of joints, kyphosis, joint contractures
- Coarse or otherwise unusual hair, unusually thick skin, unusual rashes, including sun sensitivity

In particular, if poisoning is suspected, the physician needs to consider an IEM, unless there is absolute evidence of poisoning. When there is convincing evidence for ingestion, such as an empty bottle of medications, or symptoms that perfectly match a specific toxin, such as organophosphate poisoning, it is not necessary to consider an IEM. However, because IEMs are basically a “self-poisoning,” it should otherwise be considered when poison is in the differential diagnosis. An important and instructive case is that of a woman who was tragically and inappropriately imprisoned for the murder of her child by ethylene glycol poisoning; she was released from jail when her second child was found to have the same methylmalonic acidemia that caused the death of her first son.

An IEM can mimic and coexist with child maltreatment. Two important IEMs, Menkes disease and glutaric acidemia type I, present with subdural hematoma or retinal hemorrhages, and many IEMs present with poor feeding and FTT, causing providers to consider medical neglect. However, there is also the risk that some IEMs make maltreatment more likely because of irritability and other symptoms that can make caring for the affected child more challenging.

An IEM can present acutely as a result of an infection. It is incumbent on the physician to consider whether the observed or diagnosed infection is sufficient explanation for *all* of the symptoms and signs with which the patient presents. In particular, recognize that most infections not involving the central nervous system do not cause altered neurologic status; some irritability will be typical with fever, but extreme irritability or lethargy that does not improve with resolution of fever should be a clue to an IEM. An important sign to consider as a clue to an IEM is the presence of acidosis, which should not be expected in a vomiting child unless there is severe diarrhea or poor perfusion.

The first step leading to recognition of an IEM is to include IEMs in the differential diagnosis of the child with diverse presentations. The physician then should consider the differential diagnosis within and among IEMs. The symptoms and signs across the various types of IEMs are overlapping. The specific differential diagnosis of various presentations is considered later under Clinical Scenarios in the section entitled Classification. The list of the various types of IEM in Table 291-1 includes a short synopsis of the typical clinical presentations for each category.

### Diagnostic Approach

The diagnostic approach to a child with a suspected IEM is specific to each presentation and to each condition. Although typically a collaborative effort, the physician in a nongenetics specialty can begin the process using the history—including family history—and the physical examination, followed by judicious use of laboratory studies. The diagnostic approaches are discussed in Clinical Scenarios.

### Laboratory Testing

Basic laboratory testing for an IEM can be accomplished with little added cost for the patient who has acute or chronic neurodevelopmental or health problems by starting with complete blood count (CBC), electrolytes, liver enzymes, and urinalysis in almost all cases, followed by the proper use of blood amino acid levels, urine organic acid (UOA) studies, acylcarnitine profile (ACP), carnitine total and free levels, and properly collected ammonia and lactate levels where appropriate. More specific laboratory testing can be useful.

The laboratory testing for an IEM begins with a proper interpretation of the results of testing, which is commonly done by searching for evidence of an infection and investigating the level of illness by means of CBC, electrolytes, and urinalyses. A short list of results of routine investigations, including laboratory studies that should particularly raise suspicion of an IEM, is given in Box 291-4.

For example, recognition of the inappropriateness of an increased anion gap in a vomiting child can lead to early and appropriate suspicion of an IEM. Attention to the mean corpuscular volume (MCV) may provide an important clue to an IEM as a cause of metabolic acidosis, anemia, or FTT. Judicious addition of some simple studies such as testing of creatine phosphokinase and fractionation of bilirubin can substantially strengthen the initial laboratory contribution to recognition of an IEM.

The physician should consider whether urine ketones are appropriate for the child's medical status. In the nonfasting child with FTT, positive ketones should be a clue to an IEM that produces elevated levels of an organic acid that cross-reacts with the reagent used to measure urine ketones. On the opposite end of the spectrum, absence of or low levels of ketones in the urine of the catabolic child should be recognized as a clue to an IEM that reduces ketone production. For this reason, “normal urinalysis” in a child with history of significantly decreased intake should be a clue to the possibility that the child could have a disorder of fatty acid metabolism.

**BOX 291-4 Common Test Results That Raise Suspicion of an Inborn Error of Metabolism**

- Check electrolytes and renal function; note anion gap
  - Look for acidosis out of proportion to clinical status, especially but not exclusively high anion gap acidosis; remember that renal tubular acidosis can be the result of an inborn error of metabolism (IEM)
  - Alkalosis (suspect hyperammonemia)
  - Low blood urea nitrogen (may indicate inability to make urea via the urea cycle)
- Glucose that is low in a previously healthy child with normal growth is highly suggestive of an IEM
- Check for hyperammonemia in a child with altered mental status (can only be seen if ammonia is measured); caution in sample collection
- Check urinalysis, look for inappropriate pH or ketosis
  - Ketones positive in the neonate or the nonfasting older child can indicate an IEM because the method of testing for “ketones” in urine does not distinguish between  $\beta$ -hydroxybutyrate and other organic acids such as methylmalonic or propionic acids
  - Ketones negative or only minimally increased in the infant or child who has extended fast or hypoglycemia could be because of excess insulin, liver failure, or an IEM that interferes with ketone synthesis
  - pH inappropriate for acid-base status because renal tubular acidosis can be a result of IEM
- Check complete blood count
  - Look for single or multiple failure of bone marrow cell lines
  - Look for macrocytosis (seen in disorders of energy metabolism, B<sub>12</sub> and folate metabolism, and purine-pyrimidine disorders)
- Check liver enzymes for evidence of liver dysfunction
  - Consider whether to fractionate the bilirubin
  - Consider testing prothrombin time and ammonia because they are true measures of liver function, not just liver inflammation
- Look for evidence of pancreatitis
- Consider testing creatine phosphokinase that could be evidence of rhabdomyolysis
- Consider echocardiogram for cardiomyopathy (especially hypertrophic and arrhythmogenic right ventricular dysplasia)
- Look for dysrhythmia in neonate, triphasic waves, or any electroencephalogram described as having abnormal background
- Examine magnetic resonance imaging for white matter disease, including stroke and periventricular leukomalacia in absence of clear history of asphyxia or clot
- Consider magnetic resonance spectroscopy for lactate, creatine, or other appropriate metabolites
- Consider routine radiography in a patient with rickets with normal vitamin D or in a patient with stippled epiphyses or dysostosis multiplex

When an IEM is suspected and the physician is considering specific testing to narrow the differential diagnosis, it is critical to be aware that some test results depend on the status of the patient. Biochemical samples collected while the child is acutely symptomatic may be diagnostic, whereas samples for the same study collected between episodes may be normal in some conditions and some patients. This is especially true for some disorders of organic acids, amino acids, urea cycle, mitochondrial conditions, fatty acid oxidation, and some porphyrias. Therefore diagnostic samples should be collected promptly on presentation of a symptomatic child. Normal results can only exclude a diagnosis if the sample were collected under appropriate circumstances. Artifacts of sample collection are particularly problematic for some tests, most particularly lactate and ammonia (see the accompanying Box 291-5, and for details see Table 291-2). Attention to proper sample collection is critical for interpretable results.

For some IEMs, the informative studies require an analysis of cerebrospinal fluid (CSF) or of tissue, such as muscle, for the measurement of appropriate analytes or for enzyme assay. It is therefore important to consider IEM sufficiently early in the process of evaluation that an appropriate sample can be collected if invasive testing is planned or performed. For example, when a lumbar puncture is considered to evaluate for a possible chronic infection or new-onset afebrile

**BOX 291-5 Focused Testing for Inborn Errors of Metabolism**

- If not already done and if clinically indicated, check for hyperammonemia
- Lactate and pyruvate: Do *not* send child to laboratory or request sample to be collected by phlebotomy because sample collection and handling errors can cause significant problems with interpretation.<sup>a</sup> Lactate and pyruvate should be evaluated, when indicated, under controlled circumstances, ideally in the fasting individual (levels rise with consumption of any sugar, especially fructose), without any struggle (lactate levels rise with muscle activity), and with no tourniquet (lactate levels rise and pyruvate levels fall as pyruvate is converted to lactate in the anaerobic environment)
- Blood amino acids (plasma or serum in accordance with preference of the laboratory that will receive the sample)
- Organic acids
- Acylcarnitine profile
- Carnitine total and free
- Mucopolysaccharides or glycosaminoglycans in urine

<sup>a</sup>Parikh S, Goldstein A, Koenig MK et al. Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. *Genet Med*. 2015;17(9):689–701.

**Table 291-2**      **Specific “Metabolic” Testing**

<p><b>Ammonia</b> Typically green-topped tube (do <i>not</i> use ammonia heparin tube), free flowing and placed on ice and hand-carried to laboratory. However, each institution’s laboratory has specific instructions.</p>	<p>Hyperammonemia is not evident on physical examination. Most accurate if collected without a tourniquet and couriered immediately to laboratory on ice because levels rise in the test tube until the sample is spun. Levels near or above 200 (sometimes 150 <math>\mu\text{mol/L}</math>) cause brain cell dysfunction and may cause cerebral edema; brain damage is universal and typically irreversible after 3 days of ammonia at levels greater than 200 <math>\mu\text{mol/L}</math>. Urea cycle defects may cause levels in the thousands of micromoles per liter. Hyperammonemia is an emergency; dialysis may be needed urgently, and specific drugs are available for “chemical dialysis.” Although ideally collected properly, if an inappropriately collected level is normal, it excludes hyperammonemia as cause of coma; if it is markedly elevated, it is unlikely to be an artifact, and if it is mildly elevated, an immediate repeat sample collected properly should clarify the situation because ammonia does not change rapidly without specific therapy. The level of ammonia will not necessarily distinguish urea cycle defects from organic acidemias, although the latter are more often associated with metabolic acidosis and an elevated anion gap.</p>
<p><b>Lactate (and pyruvate)</b> Ideally special tube that hydrolyzes all protein, free flowing and placed on ice and hand-carried to laboratory. However, each laboratory has specific instructions.</p>	<p>Exquisitely sensitive to conditions of the patient and the sample collection; lactate levels can change in minutes with changes in blood pressure and perfusion and with changes in intravenous glucose. Normal values are available for fasting and resting individuals. Nevertheless, lactate levels are useful in the emergency setting and elevations out of proportion to clinical status may provide clue to a wide variety of IEMs. Lactate-to-pyruvate ratio is altered in some patients with mitochondrial disease, in the same direction as the alteration of the ratio in hypoxia or hypoperfusion. Lactate levels should always be collected and handled properly.</p>
<p><b>Blood AA</b> Typically written PAA for plasma AAs (green top), but some laboratories prefer serum (red or tiger top).</p>	<p>Laboratories that perform the test will have preference for either plasma or serum; however, if your sample is not of the preferred type, contact the biochemical laboratory directly because they will typically be able to analyze the sample. The laboratory also typically is able to perform the test on a sample smaller than that routinely requested for adults. Testing may also be done in some laboratories on filter paper. AA can also be tested in other body fluids, most commonly urine and CSF, but metabolic autopsy testing can be done on vitreous of the eye or on renal papilla. AAs are conserved (reabsorbed) in the kidney so that blood analysis is useful for most conditions, but UAA analysis is key to diagnosis of conditions in which dysfunction of renal absorption of AA is the disorder. Laboratories will provide not only an interpretation but also the specific levels; an intermediary laboratory often will provide only the interpretation. The specific levels are needed to calculate the ratio of alanine to lysine, useful in evaluation of disorders of energy metabolism.</p>
<p><b>OA</b> Typically written UOA for urine OA; typically a random sample</p>	<p>Typically measured in urine because most OAs are toxic compounds that are poorly reabsorbed by the renal tubule, but some laboratories can perform limited testing on blood in anuric patients. Laboratories can typically perform testing on small samples. For acutely ill patients, samples are ideally collected at presentation before any therapies that affect metabolism.</p>
<p><b>ACP</b> Most laboratories request green top for plasma, some prefer serum (red or tiger top), and some can analyze filter paper.</p>	<p>An analysis of markers that indicate what compounds are bound to carnitine. This is <i>not</i> the same as a “carnitine profile.” This is the preferred test for diagnosis of most disorders of fatty acid oxidation and is useful in many organic acidemias. For acutely ill patients, ideally collected at presentation before any therapies that affect metabolism. Often analyzed using the same methods that are used in newborn screening, but normal newborn screen does not substitute for ACP analysis in the symptomatic patient.</p>
<p><b>Carnitine total and free</b> Most laboratories request green top for plasma, some prefer serum (red or tiger top), and some can analyze filter paper.</p>	<p>A measurement of the levels of free carnitine (that which is available for transport of fatty acids into the mitochondria) and of bound carnitine. It is <i>not</i> the same as ACP. It is particularly useful for diagnosis of disorders of carnitine transport and is secondarily abnormal in many fatty acid oxidation disorders, organic acidemias, and some nutritional states.</p>

Continued

**Table 291-2** Specific “Metabolic” Testing—cont’d

Neurotransmitters Typically CSF, <i>requires special handling</i>	Some neurotransmitters can be measured in blood or urine, but certain conditions can only be identified by analysis of CSF. There is a rostrocaudal gradient of neurotransmitter levels in the CSF, and therefore to be interpretable, the laboratory requires that the sample for neurotransmitters be collected in special tubes and that the sample collection begin with the first drop of fluid—before measurement of pressure or collection of fluid for culture (the “special” tubes are also needed to prevent oxidation of some metabolites). CSF analysis for neurotransmitters therefore requires anticipation of collection and collaboration with appropriate specialists and with the local and reference laboratories.
UMPs Spot urine typically requested, first morning sample is preferred but not required.	The test for MPS. In Hurler or Hunter syndrome and other dysmorphic conditions it can help to guide specific choice of enzyme or DNA testing. More controversial is the use of the test for screening patients with nonspecific developmental disability, including autism. However, Sanfilippo syndrome is an MPS that yields no coarse features for the first decade or more, and no skeletal problems; it presents as nonspecific developmental disability and classic autism and is fatal; genetic counseling is indicated for affected families. Ideally, for UMPS testing, send to a laboratory that will fractionate the mucopolysaccharides if the screen is positive, to avoid family stress by requesting follow up sample.
CDG Serum is the sample typically used for screening (red or tiger top).	Evaluation of the level of protein glycosylation is a screening test for CDGs. The extreme complexity and variety of glycosylation of proteins limits the sensitivity of screening, so false-negative results are possible, and false-positive results can occur especially in liver disease. The screening test is nevertheless powerful and can be diagnostic in some cases. The original and more limited test is immunoelectrophoresis of transferrin, with simple N-linked sugars; it is important to distinguish the test for CDG from the test of transferrin glycosylation to monitor alcoholic liver disease. The more powerful screen examines both transferrin and apolipoprotein E, which has O-linked glycosylation. Still more sensitive and specific is tandem mass spectroscopy to examine a broad range of proteins with more varied combinations of carbohydrates.

AA, amino acids; ACP, acylcarnitine profile; CDG, congenital disorders of glycosylation; CSF, cerebrospinal fluid; MPS, mucopolysaccharidosis; OA, organic acid; PAA, plasma amino acid; UAA, urine amino acid; UMPS, urine mucopolysaccharide; UOA, urine organic acid.

seizures of postinfectious etiology, inclusion of non-ketotic hyperglycinemia and glucose transporter in the differential diagnosis would lead to the additional collection of a sample for CSF amino acids. For those conditions, testing also must include the simultaneous collection of blood amino acids and blood glucose to calculate the ratios of glycine and of glucose in CSF and blood. These tests can be included in the evaluation by the astute neurologist with no advance planning, and in some cases, can even be “added on” to the analysis of samples collected for other purposes.

For some special testing, however, advance planning is critical. As an example, analysis of CSF for neurotransmitters requires both special collection starting with the first drop of fluid and immediate transport and freezing at a very low temperature. Advance planning is also needed for tissue biopsies if the sample is to be appropriately handled for biochemical testing. When a liver biopsy does not reveal an infectious cause of liver failure or a muscle biopsy does not reveal a congenital dystrophy as a cause of hypotonia and weakness, mitochondrial disorders then rise to the top of the differential diagnosis. Unless the sample was collected with that possibility in the differential

diagnosis, the sample will not have been collected and handled in a manner that permits appropriate testing.

DNA studies increasingly have the power to confirm specific diagnoses and often to replace invasive studies. Although testing of the whole exome is beginning to be useful, it is most efficient to focus DNA testing to address a specific condition or a panel of disorders. A combination of history, physical examination, and other appropriate studies such as imaging and biochemical testing should be used to select any DNA testing.

DNA testing varies in sensitivity. The sensitivity of the testing depends both on the condition and the methodology used in testing (eg, whether the laboratory tests only for commonly recognized mutations, whether a gene or a panel of genes is sequenced, and whether there is examination for deletions in the gene that would be missed by sequencing). For some conditions and with some methods of testing, the likelihood that DNA testing will identify a condition that is present can be well over 95%. For other conditions the sensitivity of the testing is substantially lower, and in some the specific gene is not identified or testing is not available for some reason. Abnormal results of DNA testing can confirm a diagnosis, especially for



X-linked and autosomal dominant conditions. For autosomal recessive conditions, the finding of 2 different disease-causing mutations is diagnostic if there is evidence that the 2 mutations are not on the same chromosome. Normal results of DNA testing seldom completely exclude a diagnosis but can be used to adjust the providers' ranking of conditions in the differential diagnosis.

Some laboratories and some jurisdictions require patient/parental consent for DNA testing. As with certain other studies (eg, blood typing in a newborn or tissue typing for transplant), it may be possible to find nonpaternity with DNA testing; however, if the patient and not the parents undergoes DNA testing, then nonpaternity could be identified only if a parent has previously been tested. The testing of mitochondrial DNA is a special case in which finding certain types of mutations in the patient provide information about risk for the patient's mother and all maternal relatives to be affected, even if they are symptom free. Specific counseling about that possibility should be done before testing is performed, whether or not the state or the laboratory requires consent with the sample. Sample handling for DNA testing is not particularly difficult, so collection may be simple, but there are special issues in payor approval of these often costly studies. Testing should not be undertaken without considering coverage so that the family and the physician are not exposed to unexpected costs. These issues should all be considered before collecting samples for DNA evaluation, and if the physician is not comfortable providing complete pretest counseling, the assistance of a genetics professional should be sought.

There are special considerations for the biochemical testing of the patient who presents with what may be an IEM and is not expected to survive. In addition to the risk that future offspring to the family may be affected, there is the risk that an already living sibling or other relative could be affected without having yet experienced symptoms. The appropriate use of laboratory testing to make the diagnosis can provide answers to a family and in some instances prevent inappropriate prosecution of family members suspected of abuse or neglect. In addition, using laboratory testing to suspect or confirm a diagnosis of IEM can be life-saving to other family members. Many of the studies listed in Table 291-2 can be performed in the dying child. If the suspicion of an IEM is sufficiently high, the physician should attempt to offer a "metabolic autopsy." This can only be performed if the necessary resources are available through pathology, including immediate (ideally within 1 hour of death) collection and preservation of tissue samples at  $-70^{\circ}$  to  $-80^{\circ}\text{C}$ . These samples could then be used for any enzyme assays that would be indicated by the results of testing of analytes on samples collected either before or at the time of death. The testing of stored samples that might be ordered after the death of the child is not expected to be covered by insurers, and therefore any discussion of the option of "metabolic autopsy" must include the consideration of possible costs. As with most testing in medicine, testing does not guarantee a diagnosis. A lower cost but limited screening option is to send a sample on filter paper to

one of a few laboratories that analyze amino acids and an ACP on autopsy sample. Some laboratories also will accept and bank a sample of DNA for a modest fee, in case the family might require future DNA testing.

### Imaging

Although there is no single imaging test that is specific to the diagnosis of an IEM, imaging is a critical part of the diagnostic evaluation and monitoring in the management of many categories of IEMs. In some cases, the result of imaging is the critical element suggesting a specific diagnosis. An important example is an echocardiogram to identify a cardiomyopathy that should suggest the possibility of disorders of fatty acid oxidation or carnitine, glycogen storage, or disorders of mitochondrial energy metabolism. An echocardiogram is used also in the monitoring of individuals with some of these conditions and of patients with certain organic acidemias and lysosomal storage disorders. Skeletal films and survey in a child with slowing growth who shows dysostosis multiplex of certain lysosomal storage disorders or with the stippling of the epiphyses of certain peroxisomal disorders can narrow the diagnosis to a specific category of IEM. Magnetic resonance imaging (MRI) can show changes in basal ganglial white matter of Leigh disease, suggesting that the child will almost certainly have one of the many disorders of mitochondrial energy metabolism. An MRI can show white matter changes in the occipital region that suggest the peroxisomal disorder adrenal leukodystrophy.

When ordering any imaging, the physician should consider whether special views or studies might be of use. For example, for a skeletal survey, views of the lateral spine are key to identifying dysostosis multiplex. When the imaging testing requires special preparation, for example, sedation for an MRI, it is wise to consider whether additional studies that also require sedation can be done at the same time and, in the case of magnetic resonance spectroscopy (for lactate, creatine, or other metabolites), in the same scanning session.

### Other Diagnostic Procedures

To obtain appropriate samples for examining amino acids, neurotransmitters, and some other analytes, it is sometimes necessary to perform a lumbar puncture to collect CSF. Biopsies may also be key to the diagnosis, including a relatively simple biopsy of the skin (for histology or for culture of fibroblasts for biochemical testing) or of conjunctiva for histology. When histology is useful in the examination of tissue, special stains and electron microscopy are likely to be helpful. Therefore, the pathologist should be specifically included in the discussion of the differential diagnosis to ensure that appropriate sample handling permits the use of the proper strategies in the laboratory. Biopsies of muscle and liver can be especially useful when properly analyzed for histology, histochemistry, and electron microscopy and when properly handled so that enzyme assays and other biochemical testing can be done.

Various functional studies can help in the diagnosis and possibly the monitoring of IEMs. Some examples

include electroencephalography (EEG), which shows nonspecific features that the neurologist reads as suggesting an IEM, or specific findings of hypsarrhythmia suggesting nonketotic hyperglycinemia or, in some older individuals, the triphasic waves that suggest hyperammonemia. Nerve conduction or the electromyogram are abnormal in some IEMs. Some IEMs will affect gastric or intestinal motility.

In some instances, specific physiologic challenges are useful or necessary to establish a clinical diagnosis and to determine appropriate management. These can include challenge by diet, by exercise, by fasting, or with specific medications (eg, allopurinol to test for the most common urea cycle disorder, or glucagon in testing for glycogen storage disease). Challenges can be dangerous, and details of how to perform such testing is well beyond the scope of this chapter. Some challenges can be performed on an outpatient basis, and some should be done only in an intensive care unit with secure vascular access. Challenges to diagnose an IEM should be undertaken in consultation with a specialist in the particular condition. In many cases there may be overlap between the evaluation for endocrine and IEM conditions that can cause a specific presentation, especially when the presentation includes hypoglycemia. The joint development of protocols for evaluation between endocrinology and biochemical specialists is advisable. In particular, if medium-chain acyl-CoA dehydrogenase deficiency (MCADD) is on the differential diagnosis, a child should not undergo fasting until an ACP has shown no evidence of that condition. In addition, providers should be aware that the action of glucagon is to increase lipolysis, and any child with a disorder of fatty acid oxidation will experience worsening symptoms if glucagon is given as part of a challenge.

## CLASSIFICATION

IEMs are classified according to the metabolic pathways (Table 291-1). Some experts classify IEMs according to whether they cause acute toxicity or chronic disease; for the PCP and the nonmetabolic specialist, it may be most appropriate to consider the IEMs, as they are most likely to present. The following clinical scenarios are offered for practical consideration.

### Clinical Scenarios

#### **The Acutely Ill Patient (Shock, Possible Septicemia, Altered Mental Status)**

Inborn errors of the amino acids, organic acids, the urea cycle, fatty acid oxidation, mitochondrial metabolism, and several others may cause severe symptoms with a gradual or sudden onset. When altered mental status is apparent or acid-base status is out of proportion to the physical findings, or when there is a history of prior episodes in which the child has been diagnosed as having dehydration with intercurrent illnesses, suspect an IEM. An IEM should certainly be considered when poisoning is suspected, unless a specific ingestion is known or suspected based on history or characteristic symptoms. Poisons can be created by intrinsic metabolic processes. Finding an infection or nonaccidental trauma does not exclude

an IEM. Be sure to examine ammonia levels and liver functions to avoid missing important clues to a diagnosis. Checking plasma ammonia is especially important in any neonate suspected of sepsis with either gastrointestinal symptoms or altered consciousness, especially because expanded newborn screening does not yet detect all urea cycle defects. Moreover, neonates may become symptomatic even before the results of a newborn screening are available.

When evaluation begins, remove all protein and lipids from the nutritional management and all sugars except glucose. Provide adequate glucose to stop catabolism, which requires a glucose infusion rate (GIR) of 10 mg/kg per minute in the neonate and 6 mg/kg per minute in the older child. The purpose of this GIR is to prevent catabolism and is not driven by blood glucose level. If a patient with an IEM has elevated blood glucose, insulin should be used to move glucose into cells. Because a very small fraction of IEMs worsen with these GIRs, all patients suspected of being in metabolic crisis should receive intravenous glucose initially unless a diagnosis known to require a low (<4 mg/kg per minute) GIR is known. Patients known to require unusually low GIR should carry an emergency letter with instructions. Measure ammonia and consider measuring lactate and pyruvate. Specific diagnostic testing for an IEM in this setting begins with plasma amino acids (PAA), UOA, ACP, and any other studies as indicated by presentation (Table 291-1 and Table 291-2).

#### **Child With Dysmorphic Features and Malformations**

The classic dysmorphic syndromes resulting from IEMs are Smith-Lemli-Opitz syndrome caused by a failure of cholesterol synthesis (classic presentation—small size, feeding disorders, characteristic facial features with cleft soft palate, heart defect, pyloric stenosis, syndactyly of the second and third toes, extra-axial polydactyly, hypospadias) and Zellweger syndrome caused by a failure of biogenesis of peroxisomes (cerebrohepato renal syndrome with characteristic facial features including high forehead and flat face, liver and renal cysts, and extremely low tone). Other conditions involve brain malformations, especially the disorders of mitochondrial energy metabolism and the congenital disorders of glycosylation. Further, many of the mucopolysaccharidoses have characteristic coarse features of face and progressive skeletal dystrophy.

Patients with some chromosomal abnormalities are at increased risk for an IEM. For example, patients with contiguous gene deletions may have only 1 carrier parent for an IEM if the gene is in the deleted region. Patients with uniparental isodisomy are homozygous for all genes on the affected chromosome and are therefore affected with an IEM if the parent providing that chromosome was a carrier. The diagnostic evaluation is guided by the history and physical examination.

#### **Child With Failure to Thrive, With or Without Vomiting**

Most patients with FTT do not have an IEM, but many patients with an IEM present with FTT. The PCP

should consider an IEM particularly if vomiting persists despite reflux management and certainly if there is any alteration in development, neurologic findings, or neurodevelopment. Brain growth and neurodevelopment in children with nutritional FTT are usually preserved unless the malnutrition is severe. Be certain to examine acid-base status and remember that vomiting causes alkalosis, never acidosis, unless the patient is vomiting bile or has developed poor perfusion. Check liver functions and CBC, and examine the MCV to avoid missing clues that further studies should be undertaken for an IEM. Begin an evaluation for an IEM with blood amino acids (PAA or SAA), UOA, ACP, and total and free carnitine.

***Child With Abnormal Neurologic System (Early Hypertonia, Late Hypotonia, Episodic or Progressive Ataxia or Other Movement Disorder, Atypical or Unresponsive Seizures, or Episodic Altered Consciousness)***

Almost any category of IEM can cause abnormal neurologic presentations. Careful attention to the history can yield clues and lead to early diagnosis and treatment. Examine acid-base status and liver function. Assess for macrocytosis and collect blood amino acids (PAA or SAA), UOA, and ACP. Measure blood ammonia in patients with acutely altered mental status or acute ataxia. An ophthalmologic examination for evidence of cataracts or retinopathy may provide clues to a specific IEM. When collecting CSF, examine lactate and amino acids and consider planning in advance for the special handling of samples for measuring neurotransmitters and other metabolites of IEMs. For the evaluation of an IEM as the cause of seizures, collect blood glucose and PAA immediately before a lumbar puncture so that the ratio of CSF to plasma glucose and glycine can be evaluated. When planning an MRI, ask also for magnetic resonance spectroscopy to examine lactate for clues to inborn errors of energy metabolism.

***Child With Intellectual Disability and Autism (Especially With Slowing Development, Developmental Plateau, and Regression)***

Regression should always signal the need for an immediate evaluation for an IEM to identify those who will benefit from therapy and because many conditions that cause regression are IEMs, including some that are both fatal and autosomal recessive. For example, a boy with regression of development may need evaluation for X-linked adrenoleukodystrophy. However, at the initial presentation of a child with mental developmental disability or autism, it is not always clear whether the patient will be stable or improve, or will develop increased problems. History and examination can help to distinguish those in need of more aggressive evaluation, such as those with hypotonia. There are no physical findings that exclude the presence of acidosis, liver disease, or macrocytosis. Therefore, basic studies of electrolytes, liver health, and CBC are appropriate for all children presenting with intellectual disability unless a clear cause of all presentations is known.

The recommendations for the use of more specific studies for an IEM in the absence of regression or other clues on history or examination (such as hypotonia) are variable. The addition of routine testing for IEMs in children with developmental disabilities and an otherwise normal history and examination has undergone few studies and is generally agreed to have low yield. However, testing of blood amino acids and urine mucopolysaccharide is not costly, and the positive effect of making a diagnosis can be extremely high; therefore, many experts typically urge that all patients with an intellectual disability or autism should undergo an evaluation of blood amino acids (for phenylketonuria [PKU] and homocystinuria, which could have been missed on newborn screening; some cases of PKU in particular are indistinguishable from autism) and urine mucopolysaccharides (for Sanfilippo syndrome, which presents without abnormal physical features at onset and may be indistinguishable from classic autism). The most recent recommendations of the American College of Medical Genetics address the issue of metabolic testing in the child with autism spectrum disorder in some detail.

***Child With Single or Multiple Organ Failure***

Renal failure from Fabry disease, liver failure from tyrosinemia, and cardiomyopathy from fatty acid oxidation or Pompe disease are potentially reversible. Other conditions are less responsive to therapy, such as liver or bone marrow failure in children with mitochondrial disease, but awareness of the diagnosis can help with management. For example, it is necessary when possible to avoid valproic acid when treating children with seizures from an IEM. Be aware that an infection may be the trigger leading to the presentation of an IEM and that some IEMs include immune deficiency that can increase the risk for infections. The evaluation for an IEM in a child with single or multiple organ failure typically includes testing for those IEMs known to cause the specific presentation (eg, organic acidopathy as cause of pancreatitis, or tyrosinemia as cause of liver failure) but in general includes the evaluation of blood amino acids, UOAs, ACP, and carnitine (total and free), in addition to any other disease-specific testing.

***Child With Stroke or Clotting Disturbance***

One of the standard presentations of classic homocystinuria resulting from cystathionine  $\alpha$ -synthase deficiency is thrombotic stroke. Up to half the patients with classic homocystinuria and most with variant types are expected to be missed by newborn screening. Although some patients may have marfanoid habitus or a history of developmental disability, many others have no signs or symptoms of an IEM as the cause of stroke. Total homocysteine, blood amino acids, and UOA should be included with studies for other genetic causes of stroke. Also, when evaluating these children consider the possibility that the child has experienced a strokelike episode of MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes) at initial presentation and include Fabry disease and congenital disorders of glycosylation in the differential diagnosis.



## SPECIAL CONSIDERATIONS IN THE BIOCHEMICAL EVALUATION OF INBORN ERRORS OF METABOLISM

Table 291-2 summarizes the routine or common biochemical tests for the primary care or nongenetics pediatric specialist in the evaluation of a child with a suspected IEM. Begin with more general metabolic tests and use additional specific tests as indicated by presentation and results of initial testing. Plans for special studies such as enzyme assays and DNA testing can be developed with the genetics team, but initial testing should typically be initiated before a consultation. A key to suspecting IEMs is understanding the meaning of key results in routine testing. For example, hypoglycemia in a previously healthy toddler or older child with normal growth could be because of acute-onset endocrine disease (eg, from an insulin-secreting tumor). However, these are rare in children, and hypoglycemia from poisoning or an IEM (especially disorders of fatty acid metabolism) is more common than insulin-secreting tumors in a previously healthy toddler. An important IEM that causes hypoglycemia in childhood is MCADD, which affects approximately 1 in 10,000 white children. However, it is equally important for the pediatrician to know that normal glucose levels do not exclude IEM and that patients with MCADD have died with normal glucose levels.

Screening the healthy neonate for an IEM is discussed in Chapter 29, Screening for Genetic-Metabolic Diseases. For the symptomatic patient, an investigation for IEMs begins with a careful examination of routine metabolic studies followed by specific studies. For the patient with a developmental disability who is not acutely ill, examine CBC, electrolytes, and liver function test results because abnormalities in any of these would suggest that further studies are indicated. There is not necessarily any physical finding in patients with macrocytic anemia, renal tubular or metabolic acidosis, or liver dysfunction. For the acutely ill patient, inappropriately low ketosis is also an important clue and can be detected with urinalysis. Acidosis out of proportion to clinical status or the presence of alkalosis should increase the suspicion for an IEM. Be certain to consider an IEM as the cause of findings on imaging. For example, patients with mitochondrial disease may have strokelike episodes, true stroke, or evidence of brain injury in a pattern indistinguishable from hypoxia. They may also have classic presentations that are clearly because of IEM, such as the white matter disease of adrenoleukodystrophy or the basal ganglia injury and extra-axial fluid of classic glutaric acidemia.

Check ammonia level in any patient with acutely altered mental status or acute ataxia and consider ammonia level testing in a neonate with suspected sepsis; Table 291-2 shows cautions to be exercised during collection and handling. In the acutely ill patient or patient with hypotonia consider also testing lactate levels. Be aware that lactate is also sensitive to collection and handling but that unlike ammonia, lactate levels can change in minutes. Lactate can be

normal on a sample collected incorrectly, so it will not be possible to be sure incorrect handling is the cause of elevation. Collecting lactate incorrectly may therefore lead to added testing that could have been avoided if the sample were collected properly (Table 291-2).

Testing for biochemical analytes is guided by clinical presentation. Like testing for toxins, the yield for specific biochemical (analyte) testing varies with the presentation. Biochemical studies of the patient with ammonia level 100 times the upper limit of normal is highly likely to identify a disorder of the urea cycle. Plasma amino acids in a patient with nonspecific developmental disability will have low yield compared with studies such as comparative genome hybridization. However, the total cost of testing the most commonly measured analytes (blood amino acids, UOA, ACP, carnitine total and free, CSF amino acids, and urine mucopolysaccharides) is a very small fraction of the cost of the care of the acutely ill patient or the neurodevelopmentally disabled child; typically that panel of studies can be done for less than the cost of an MRI or comparative genomic hybridization. In addition, patients identified with chromosomal deletions are at higher risk than the general population for IEM. For example, boys with certain deletions of the X chromosome have glycerol kinase deficiency causing recurrent episodes of acidosis and altered mental status, and also have Duchenne muscular dystrophy.

Testing of DNA can assist in the diagnosis of an IEM. As with any DNA testing, be sure that the interpretation (including sensitivity) is discussed with genetic experts if experience in interpreting these test results is lacking. Consider, too, whether the purpose of DNA testing is to guide management of the patient or is to determine whether it will be possible to provide carrier testing to other family members or prenatal testing in the future.

Because most IEMs are autosomal recessive, testing of parents (DNA or enzyme assay) can provide critical help in making or excluding a diagnosis. For example, if galactosemia is suspected in a newborn who has received a transfusion, testing of the mother that demonstrates she is not a carrier will virtually exclude the possibility that galactosemia is the cause of the presentation (paternal uniparental isodisomy from a carrier father could still cause galactosemia, but this is rare). However, DNA testing of family members is not always necessary and can lead to problems. For example, when a child's father has just been diagnosed with hemochromatosis with homozygosity for the common mutation, testing the child and finding the mutation does not add any new information to guide management. Finding no mutation suggests nonpaternity.

A special consideration in testing for IEMs is in the acute setting when the child is dying. When a diagnosis that excludes an IEM is not conclusively established, studies for IEMs could identify living or future relatives at risk and in need of treatment. In addition, studies for IEMs could establish the cause of death and prevent inappropriate prosecution of a parent. Samples for IEM testing should therefore be sent



even if there is no expectation that the patient will respond to efforts at resuscitation. Some samples can be collected after death; however, a full metabolic autopsy requires immediate collection of samples suitable for testing of analytes and enzymes within the first hour after death and requires collaboration of emergency or intensive care unit care providers, pathology and metabolic geneticists, and in some circumstances, permission from a medical examiner.

## MANAGING INBORN ERRORS OF METABOLISM IN PEDIATRIC PRIMARY CARE, ON THE WARDS, IN THE EMERGENCY DEPARTMENT, AND IN THE INTENSIVE CARE UNIT

### Treatment Approach

Many IEMs have specific treatments that can reduce or even prevent disability or death. The first step in managing an IEM in the primary and specialty pediatric practice is making the diagnosis so that appropriate treatment can be offered. The diagnosis can only be made when IEMs are suspected and appropriate testing initiated. The stakes can be high for emergency recognition of IEM, for example, in a child with overwhelming acidosis or a child in a coma that proves to be caused by hyperammonemia. The primary care physician or nongenetics pediatric specialist typically works with a geneticist in management of IEM; however, management is often initiated in the acutely ill patient by excluding potentially harmful dietary components and by providing glucose in amounts sufficient to prevent catabolism. It should be emphasized that patients who have an IEM, when stabilized and in the chronic phase of management, typically are not hospitalized because of the underlying IEM. Rather, a viral illness, fasting, or another disorder will tip the balance and cause a metabolic crisis unless the child is treated promptly. Therefore, pediatricians are on the front lines of management for these children. In addition, the importance of maintaining vaccination schedules as recommended by American Academy of Pediatrics and obtaining annual influenza (killed) vaccinations in both the affected child and family members are simple yet critically important aspects of pediatric care.

### Specific Treatment

Specific management is available for many IEMs, such as the branched chain amino acid–restricted diet for maple syrup urine disease or the provision of cofactor for B<sub>6</sub>-responsive seizures. Some conditions that in the recent past were untreatable and fatal (eg, Pompe disease) can now be treated with enzyme infusions that can reverse some symptoms and prevent further injury. Specific therapy for long-recognized conditions continues to evolve. For example, some individuals with PKU are now recognized to respond to therapy with the cofactor biotin. PKU is also an example of an IEM that requires lifelong therapy. Patients with poor compliance in late childhood and teen years are at risk for developing progressive white matter disease of the brain, and because elevated phenylalanine is a

teratogen, young women with poorly controlled PKU will have offspring with intellectual disabilities and malformations. Other examples of the adverse consequences of poor compliance are liver cancer in those with glycogen storage disease or a stroke in those with homocystinuria.

For other IEMs, the specific current treatment consists solely or primarily of supportive, symptomatic management. Patients and families often wish to participate in experimental therapies, especially for conditions that are fatal and have no proven effective therapy. Anticipatory guidance is critical for managing all IEMs, and genetic counseling is important for families and for the patients themselves when they consider future reproductive risks.

Collaboration is the basis of the specific management for all IEMs, especially for those conditions for which there are risks for metabolic crises requiring emergency management. The metabolic expert should provide—and the family, primary care physician, and other specialists should follow—any relevant instructions both for chronic care and in treating any emergency. In some cases there will be specific adjustment of care if a child is acutely ill, and in all cases—even if the family has made a decision involving limitation of or end-of-life care—it will be appropriate to provide supportive care. Typically in an acute emergency, after the ABCs, the most important part of care for the child with an IEM is the prevention of catabolism. It is critical that the emergency provider distinguishes between concern for catabolism and concern for blood levels of glucose. Except for certain glycogen storage disorders, the pathophysiology of most IEMs that can present with acute crisis is such that blood glucose remains normal until metabolic balance decompensates past a critical point. For example, some children with MCADD have died with normal blood sugar levels. When a patient's metabolic specialist instructs the emergency clinician to administer intravenous glucose at a specific rate, that should be done when the patient is unable to tolerate enteral intake, regardless of the blood glucose level; that child should continue to receive intravenous glucose until enteral intake is appropriately tolerated. The keys to management are understanding the pathophysiology of the condition and the principles of management for each patient and having and using a plan for both chronic and acute care.

### Ongoing Care

#### Follow-up

Management is a collaborative effort with the metabolic specialist or geneticist and any other appropriate medical specialists. For example, management of cystinosis typically requires collaboration with nephrology and ophthalmology specialists, and the management of Pompe disease involves a cardiologist. For many IEMs there is a role for the specifically trained metabolic dietitian or the genetics or metabolic nurse and genetics counselor, working as a team with the geneticist to provide care and support for the pediatric physician and other pediatric specialists. The transition to adult care is an issue for all pediatric patients with chronic disease. In many cases the genetics team will remain constant after the transition to adult care

because the metabolic genetics team typically cares for adults and children.

### **Complications and Prognosis**

The prognosis and complications of IEMs vary with the specific condition. For some IEMs, response to therapy is so predictably excellent that the only “complication” is the need for the affected child to remember that failure to continue therapy is life-threatening, as in the case of biotinidase deficiency. For other conditions, available therapy is limited and complications and eventual death are not preventable.

In some cases in which response to therapy directed at the IEM is expected to be excellent, the child may have already sustained severe neurologic or other injury as a result of the IEM before diagnosis. This is particularly true with some disorders of fatty acid oxidation and some organic acidurias. In these cases the prognosis for the IEM may be excellent, whereas the prognosis for the child may include long-term chronic health and developmental problems. Preventable morbidity from treatable conditions is the justification for newborn screening when it is feasible. The prevention of morbidity and mortality from an IEM is also the reason for considering an IEM even in the dying child or the child with irreversible injury for an opportunity for a better outcome in future offspring or affected siblings.

Complications of many IEMs involve neurologic dysfunction (central and peripheral), cardiomyopathies, liver disease or liver failure, growth failure, intestinal dysfunction, deafness, eye disease including cataracts and retinopathy, muscle disease including rhabdomyolysis, and single or multiple endocrine gland failures; some IEMs cause birth defects. Managing the complications of IEMs can involve multiple medical specialists. The complications of an IEM are also likely to require the attention of various specialists such as speech, occupational, and physical therapists and experts in special devices and education.

An important complication of the IEM is the effect on the family. Even when there is a simple and effective therapy, families are stressed by knowing that a child has a condition that threatens life or health and development. For many conditions a life-saving therapy involves substantial modification of ordinary living, such as with the use of restricted diet that affects family behavior and dynamics. Diagnostic evaluation and therapies can be costly and often inadequately covered by insurance, if covered at all; and there may be need for time-consuming efforts to secure such coverage. As with any child with a chronic disease, there can be substantial time involved in the daily care of a child and effects on other children. There is also the effect on families’ decisions about whether to have other children in the future, and there may be complicated interactions with the broader family both for support for the affected child and for disclosures of genetic risks.

### **Prevention**

There are 3 fundamental kinds of prevention.

First, for the affected individual, the goal is the prevention of the medical and developmental complications

of the IEM, by means of appropriate management. For conditions that can present with metabolic crisis, appropriate management includes especially avoidance of catabolism. In some cases prevention includes avoidance of certain known risks or triggers, including drugs that have adverse effects on relevant pathways, (eg, mitochondrial metabolism, the porphyria pathways, or the synthesis of cholesterol). The use of standard health care and prevention is critical, including use of all relevant vaccines; in almost every case the risk for metabolic crisis from a vaccine is less than the risk if the patient were to contract the condition against which the vaccine protects. For those with conditions that include metabolic crisis as part of the presentation, it is generally recommended to use killed vaccine for the patient and the family members. Although only a few IEMs are associated with immune deficiency, the risks of a live virus-inoculated family member to pass the infection to the affected individual must be considered. Attention to the transition process may help prevent lapses in monitoring and management as the child moves from pediatric to adult care.

Second, the IEMs are by definition genetic, and the recurrence risk within families is therefore significant. In some cases, a living individual is at risk and needs to be offered evaluation and care. In all cases, the family must be offered accurate information about the risk for recurrence. This information should be offered in the context of genetic counseling that assures respect for each individual’s and family’s unique beliefs and values. When there is the possibility of carrier or prenatal testing or other prenatal options, relevant factual information should be offered, along with the opportunity to explore whether and how they will choose to use such opportunities.

Finally, it is incumbent on the physician to offer whatever is possible to mitigate any adverse effects of the IEM and its consequences on the individual’s and family’s function. This includes efforts to secure necessary supportive or habilitative services. The affected individual and family should be offered the option to connect with other affected individuals, families, or support organizations.

### **WHEN TO REFER**

The primary care physician and the emergency medical care provider should refer, or at least discuss the possibility of referral, to an appropriate specialist when there are symptoms and signs that suggest inborn errors of metabolism (IEM) and especially when the newborn, infant, child, or adolescent presents with any of the following:

- Neurodevelopmental abnormalities, especially acute altered mental status and, most especially, recurrent or intermittent symptoms or progression, hypotonia after 1 year of age, or a movement disorder
- Acidosis out of proportion to systemic illness
- Hypoketosis for the state of nutrition and especially hypoglycemia
- Cardiomyopathy, liver failure, failure to thrive, and renal tubular acidosis, which are individually important presentations of IEM and, in

combination with each other or with abnormal neurologic status

- Positive result on newborn screening for an IEM
- Family history of IEM
- IEM suspected for any other reason
- No other cause for the presenting problem that is unequivocally and certainly the primary underlying cause of the presentation

In some cases, especially if the child is critically ill and certainly if there is regression, the referral should be directly to a geneticist who is an expert in IEMs. Children with cardiomyopathy, for example, should be evaluated carefully for a treatable IEM or multisystem IEM that could cause other organ failure, especially before transplantation. When a child is stable, it may be appropriate for the primary care physician to work with another specialist, such as a gastrointestinal or neurology specialist, to consider whether a genetics or metabolic referral is warranted.

### WHEN TO ADMIT

The child with IEM should be admitted if home management is not sufficient to keep the child out of crisis, for example, when the child cannot maintain anabolism. In some cases, a child needs to be admitted for invasive evaluation. Admission is likely to be a joint decision of the PCP, appropriate specialists, and the family.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Genetics Home Reference* (Web site), National Institutes of Health ([ghr.nlm.nih.gov](http://ghr.nlm.nih.gov))

#### Medical Decision Support

- *ACMG ACT Sheets and Confirmatory Algorithms* (e-book), American College of Medical Genetics ([www.ncbi.nlm.nih.gov/books/NBK55832](http://www.ncbi.nlm.nih.gov/books/NBK55832))
- *Clinical Genetics Evaluation in Identifying the Etiology of Autism Spectrum Disorders: 2013 Guideline Revisions* (guideline), American College of Medical Genetics ([www.acmg.net/docs/pp-g-ASD-schaffer-aop-gim201332a.pdf](http://www.acmg.net/docs/pp-g-ASD-schaffer-aop-gim201332a.pdf))
- *Genetics Home Reference* (Web site), National Institutes of Health ([ghr.nlm.nih.gov](http://ghr.nlm.nih.gov))
- *Inborn Errors of Metabolism in the Acutely Ill Child* (chapter with algorithms), *Berman's Pediatric Decision Making*, 5<sup>th</sup> ed ([www.us.elsevierhealth.com/pediatrics/berman-pediatric-decision-making-expert-consult/9780323054058](http://www.us.elsevierhealth.com/pediatrics/berman-pediatric-decision-making-expert-consult/9780323054058))
- *Phenylalanine Hydroxylase Deficiency: Diagnosis and Management Guideline* (guideline), American College of Medical Genetics ([www.acmg.net/docs/Phenylalanine\\_Hydroxylase\\_Deficiency\\_Practice\\_Guideline\\_AOP\\_Jan\\_2013.pdf](http://www.acmg.net/docs/Phenylalanine_Hydroxylase_Deficiency_Practice_Guideline_AOP_Jan_2013.pdf))

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### Chapter 292

## MÜNCHAUSEN SYNDROME BY PROXY: MEDICAL CHILD ABUSE

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Medical child abuse (MCA), more widely known as Münchausen Syndrome by Proxy (MBP), is a rare form of abuse involving the persistent fabrication of physical or mental illness in a child by an adult. MCA now goes by various names, including pediatric condition falsification, factitious disorder by proxy, or fabricated or induced illness. It was first described in 1977 by Meadow, an English pediatrician. The name is derived from Münchausen syndrome, the condition of self-inflicted illness in adults. Compared to other forms of child abuse, MCA has proved to be a form of child maltreatment that is fraught with rather different diagnostic and legal problems. The perpetrator of



MCA, usually the child's mother, often evades the early detection of her noxious ministrations because the symptoms and signs she reports seem plausible and because she seems attentive and concerned. The perpetrator's history often sounds credible to the physician, suggesting a serious illness. Although physicians are educated to critically evaluate the reliability of a historian, pediatricians do not expect that a history is an elaborate lie. Once the diagnosis has been considered, definitive inclusion or exclusion may be problematic. As a consequence, protection of a child and any siblings may also prove difficult. Evaluation of the family, which can help shape therapy and which is useful only when the perpetrator is forthcoming, is often stymied by the mother's refusal to participate or her indignant denial of her role in causing the child's illness. Awareness of MCA also varies significantly among mental health professionals, and the perpetrator may deceive even an experienced therapist.

## DEFINITIONS

MCA occurs when a child undergoes or receives unwarranted medical care. Illness in a child is persistently and secretly simulated, produced, or both by a parent or someone who is *in loco parentis*. This circumstance often results in the parent's repeatedly bringing the child for medical care, and as a result the child undergoes multiple unnecessary medical procedures, both diagnostic and therapeutic. The definition specifically excludes physical abuse only, sexual abuse only, and failure to thrive that is solely the result of nutritional or emotional deprivation. In the context of this syndrome, the term *simulated* means that the caregiver or perpetrator fabricates the child's symptoms. For example, the caregiver may repeatedly report that the child has episodes of stiffening, shaking, or decreased level of consciousness, when, in fact, these episodes never occurred. The term *produced* means that the caregiver or perpetrator secretly interferes with the child's body to produce symptoms or signs in the child. Examples include surreptitious suffocation to cause apnea, or administering unprescribed medicines or substances such as a laxative to produce diarrhea.

The question regarding which diagnostic term should be used is important and has been the topic of much debate. Many questions surround the use of the term MBP. Should a pediatrician or a psychiatrist make the diagnosis of MBP? To whom should the term be applied, the parent or the child? The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*, described the syndrome as a "factitious disorder" that includes 2 components—the child as the victim and the caregiver adult as the perpetrator. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*, uses different diagnostic terminology, including factitious disorder imposed on self and factitious disorder imposed on another. Furthermore, the American Professional Society on the Abuse of Children (APSAC) proposes that physicians use the term *pediatric condition falsification (PCF)* when focusing on the effect on the child, and *factitious disorder by proxy (FDBP)* when focusing on the perpetrator. It is clear from this discussion of

nomenclature that the multiple terms and definitions can be confusing for the physician. The American Academy of Pediatrics (AAP) has published a textbook by Roesler and Jenny that suggests the more inclusive term *medical child abuse (MCA)*. This term clearly indicates that abuse has occurred and allows the physician to focus on the harm sustained by the child as a result of unnecessary medical care. Additionally, it relieves the physician, who is responsible for caring for the child, from the responsibility of describing the psychiatric state or the motivation of the perpetrator.

## DEMOGRAPHICS

Hundreds of cases of MCA have been reported worldwide, although most cases of MCA likely go undiagnosed or unreported in the literature. Most of the literature concerning this form of maltreatment originates in the United Kingdom and the United States. Cases of MCA have also been reported from Canada; Australia; New Zealand; Western, Central, and Eastern Europe; Scandinavia; the Middle East; South America; the Indian subcontinent; Central America; Africa; Sri Lanka; Japan; and Singapore. Clearly, MCA is not a culture-specific disorder, nor is it confined to either a socialized or privatized medical system. In addition, apparently, the perpetration of MCA is not as uncommon as originally thought, although actual incidence is unknown. One study in the United Kingdom estimated the combined annual incidence of MCA by nonaccidental poisoning and nonaccidental suffocation as at least 2.8 per 100,000 in children younger than 1 year. Extrapolation of this data to the United States suggests somewhere between 200 new cases of serious MCA per year to at least 600 new cases per year of suffocation or intentional poisoning. A New Zealand study reported an incidence rate of 2 per 100,000 in children younger than 16 years.

In most cases of MCA, the perpetrator is the biological mother, although fathers, adoptive mothers, other relatives, babysitters, and nurses are occasionally implicated.

Boys and girls are victims almost equally, and no special trend is noted as to birth order. Curiously, however, although several children in a family may be abused sequentially, for more than 1 child to be targeted during the same time period is unusual, except during relatively brief transition periods. Typically, if the original child survives, then the child's medical troubles melt away when another child comes along and develops unusual and inexplicable illness.

Most victims of MCA are infants and toddlers. Presumably, the younger children are more commonly affected than older children because they are preverbal or semiverbal and relatively helpless physically. Although abuse of the children commonly begins in infancy or toddlerhood, a delay in making the correct diagnosis usually occurs. In 2 series, the average time from onset of symptoms and signs to diagnosis was 15 to 22 months, but the time span might be as long as 20 years or never. A rare report describes cessation of MCA not because of medical diagnosis, but rather because the school-aged victim threatened to disclose the caregiver's longstanding, painful, and disfiguring abuse. Older child victims of MCA, whose abuse may



have begun years earlier, may adopt the false symptoms and signs as their own. These children are less likely than young children to have illness produced and are more likely to have falsified reports of symptoms and medical history. Some evidence suggests that these children may go on to develop Münchausen syndrome themselves or some type of personality disorder. A few cases of adult victims of adult perpetrators of MCA have been reported.

In 1 series, 25% of MCA cases involved simulation only, 25% involved production only, and 50% involved both simulation and production of illness. Another, larger series showed that 57% of illness was produced. In 50% to 95% of cases, depending on the meta-analytic series, the perpetrator continued abusing the child in the hospital, often in the most egregious ways, and even in closely monitored settings, such as the pediatric intensive care unit. Short-term morbidity for the children, by definition, is 100%, much of it related to the diagnostic and therapeutic procedures, ordered by the physician. Long-term morbidity, defined as pain, illness, or both that causes permanent disfigurement or impairment, is harder to assess statistically than short-term morbidity. Approximately 8% of survivors of MCA have some kind of long-term morbidity as a result of complications of the attack or, rarely, complications or residua from medical procedures, including surgeries. This figure is probably an underestimate, however, and does not include long-term psychologic morbidity, which may be considerable.

Although assessing the mortality rate from MCA is currently impossible for methodological reasons, an important point to state is that some children die because of an ultimate fatal attack. Series death rates vary from 6% to 33%. In the largest series to date, apnea was the most common repeated symptom that preceded death. Almost all cases were infants and toddlers, and the causes of death notably featured suffocation and poisoning. Other causes of death have been described. Children as old as 8 years have been killed in the context of MCA. Furthermore, siblings of these children tend to die in alarming numbers, often with the misdiagnosis of sudden infant death syndrome (SIDS), and every reason exists to think that they died in a homicidal manner. Child fatality review teams are now common throughout the country and, with the expertise of multidisciplinary teams, are occasionally discovering cases of MCA that had been previously but incorrectly designated as accidental, natural, or undetermined manners of death.

### CLINICAL AND LABORATORY FINDINGS

Although signs, symptoms and laboratory findings in MCA cover an enormous spectrum, the most common serious presentation seems to be apnea. Seizures, feeding problems, bleeding, central nervous system depression, diarrhea, vomiting, fever (with or without sepsis or other localized infection), rash, allergy, and behavioral problems are also reported quite commonly. At no time, however, should any list be considered inclusive, because the understanding of the breadth of presentations of this syndrome is continually expanding. Table 292-1 lists some of the presentations of MCA.

Some child survivors of MCA are developmentally delayed as a result of the damage done by the inflicted illness or as a result of chronic hospitalization, enforced invalidism, or lack of stimulation. Malnutrition may be the result of the chronically inflicted illness, surreptitious withholding of food, or from prolonged emetic or laxative administration. MCA may also present as a *bona fide* chronic disease, when the caregiver has intentionally and surreptitiously withheld treatment to significantly exacerbate the child's illness.

### CONSIDERATION OF MCA IN CASE OF CHILD FATALITY

A significantly positive clinical history of a deceased child would feature 1 or more items listed in Box 292-1. If any of these factors is present, then MCA should be included in the differential diagnosis, along with possible genetic, metabolic, toxicologic, environmental, and other causes of death. These factors are not diagnostic criteria for MCA, but rather historical flags that should spur further investigation and an exhaustive autopsy.

The usefulness of the autopsy by a competent forensic pathologist as an investigative tool for determining cause and manner of death is obviously enhanced when it is performed in the most thorough manner. This would include toxicologic studies. A *routine toxicology study* may be inadequate and includes different tests at different laboratories. The laboratory should be asked to preserve the samples securely because they may be needed later for repeated studies or studies not originally considered. As with all children suspected of having been maltreated, a skeletal survey should be performed to look for fractures. Classic physical abuse injuries have been reported in victims of MCA. Additionally, microbiologic studies may be central to determining whether the child was the victim of inflicted microbial assault.

Homicidal suffocation deaths deserve further comment because they are still too commonly misdiagnosed as SIDS. If any significant history precedes death, then SIDS, by definition, is excluded. The current definition of SIDS is the unexpected death of an infant between 1 month and 1 year that remains unexplained after a *complete* review of the clinical history, death scene investigation, and autopsy. The physician must always be concerned when sudden death occurs in a child who had repeated apnea or acute life-threatening events before death, especially episodes that featured attacks beginning only in the presence of a single caregiver and, when the caregiver called someone to see the infant, the child was hypoxic (ie, cyanotic, gray, gasping, and limp). The physical findings of suffocation more commonly seen in adult victims (head and neck petechiae or bruising [or both], defensive marks) are almost always absent in young children. Intraalveolar hemosiderin found at autopsy may be a marker of past smothering, but this is not definitive.

### PERPETRATORS

What are the characteristics of the perpetrator of MCA? First, an important point to make is that no psychologic test can include or exclude perpetration of MCA. Second, no classic profile exists for a

**Table 292-1**    **Some Clinical Presentations of Medical Child Abuse<sup>a</sup>**

<b>SYSTEM</b>	<b>SYMPTOM, SIGN, LABORATORY FINDING OR DIAGNOSIS</b>
Head, eyes, ears, nose, throat, mouth	Bleeding from ears, nose, throat Conjunctivitis External otitis Hearing or speech impairment Nasal excoriation Nystagmus Otorrhea Parotitis or orbital cellulitis Tooth loss
Respiratory	Apnea or acute life-threatening event Asthma Bleeding from upper respiratory tract Choking or dyspnea Cyanosis (and other color changes, including pallor) Cystic fibrosis Hemoptysis Respiratory arrest Respiratory infection Sleep apnea
Cardiovascular	Bradycardia Cardiomyopathy Cardiopulmonary arrest Hypertension Rhythm abnormalities (including bradycardia, tachycardia, ventricular tachycardia, and others) Shock
Gastrointestinal	Abdominal pain Anorexia Bleeding from nasogastric tube or ileostomy Crohn disease Chronic intestinal pseudo-obstruction Crohn disease Diarrhea Esophageal burns Esophageal perforation Feculent vomiting Feeding problems Gastrointestinal ulceration Hematemesis Hematochezia or melena Hemorrhagic colitis Malabsorption syndromes Polyphagia Pseudomelanosis coli Retrograde intussusception Vomiting (cyclic or otherwise)
Genitourinary	Bacteriuria Hematuria Menorrhagia Nocturia Polydipsia Polyuria or impaired urinary concentrating ability Proteinuria Pyuria Renal failure Urethral stones Urine gravel
Neurologic, musculoskeletal, developmental, psychiatric	Arthralgia Arthritis Ataxia

**Table 292-1**      **Some Clinical Presentations of Medical Child Abuse—cont'd**

SYSTEM	SYMPTOM, SIGN, LABORATORY FINDING OR DIAGNOSIS
	Behavioral or personality disorders (including anxiety, autism-spectrum disorders, panic reactions, rage, disorientation, and others) Cerebral palsy Developmental delay (failure to attain or loss of milestones, or both) Headache Hyperactivity Irritability Learning or attention-deficit disorder Lethargy Morning stiffness Psychotic symptoms Sleep disturbances: prolonged sleep, other sleep problems Seizures Syncope Tourette syndrome Unconsciousness Weakness
Skin	Abscesses Burns Eczema Excoriation Rash
Infectious, immune, allergic	Allergies (to food, drugs, or other substances) Bacteremia (unimicrobial or polymicrobial) Fever Immunodeficiency Osteomyelitis Septic arthritis Sinopulmonary disease Soft-tissue or skin infection Urinary tract infection
Abnormalities of growth Hematologic	Failure to gain weight or weight loss Anemia Bleeding diathesis Bleeding from specific sites (see system) Easy bruising Leukopenia
Metabolic, endocrine, fluid and electrolyte	Acidosis Alkalosis Electrolyte abnormalities Creatine kinase and aldolase increase Cystinosis Dehydration Diabetes Glycosuria
Other	Mitochondrial encephalopathy lactic acidosis and stroke-like (MELAS) syndrome Abuse (sexual, physical, or other) Diaphoresis Fatigue Foreign-body ingestions Hypothermia Pain Peripheral edema Poisonings Premature birth

<sup>a</sup>Including items reportedly observed by mother or actually observed by medical staff.

### BOX 292-1 Review of Clinical History in a Dead Child: Circumstances Suggestive of Medical Child Abuse

- A history of repeated medical visits for unusual, poorly defined, unpredictable, or unresponsive illness, especially apnea and seizures.
  - Symptoms had never been confirmed to be witnessed at their starting moment by anyone other than a single caregiver.
  - A medical evaluation of the child revealed no organic abnormality that might *fully* account for the child's reported illness.
- Ill sibling of decedent, especially if the person was ill or is ill with chronic, poorly defined medical problems.
- Dead sibling of decedent or dead unrelated child in the same home as decedent, especially if any of the following is found:
  - Other child's death was signed out as sudden infant death syndrome (SIDS).
  - Death followed a poorly defined or chronic illness.
  - Cause of death was allegedly an illness that overwhelmingly is nonfatal in childhood.
  - Cause of death was related to poisoning or intoxication.
  - Cause of death was the result of an unusual accident.
  - Death followed a presumed illness that was either unsubstantiated or excluded at autopsy.
  - Explanation for the death was inadequate.
- Mother with chronic, poorly defined medical problems.

perpetrator. The perpetrator of MCA is usually the mother. The perpetrator sometimes has had nursing, medical, or paramedical training, perhaps never completed. The perpetrator may be married, single, or divorced; but, if married, then the relationship with the spouse, although perhaps seemingly satisfactory, is often shallow, with the husband at arm's length from the child's illnesses. In some instances, the spouse endorses the perpetrator's history of the child, even when it is proven definitively to have been untrue. Although the perpetrator was originally described as generally affable with medical and nursing staff, broader experience shows that the perpetrator may have a hostile, difficult, and demanding personality. Some perpetrators, in their roles as champions of their ill children, have had good success at enlisting the admiration of their communities; making useful, powerful, or lucrative contacts; or obtaining benefits consequent on the child's illness, including wish-fulfillment trips. Family medical histories are often unusual and unable to be confirmed.

The personality types, backgrounds, and motivations common to perpetrators of MCA are quite diverse. The perpetrators have been variably diagnosed psychiatrically as normal, depressed, borderline personality disorder, hysterical personality disorder,

narcissistic personality disorder, or various other personality disorders. MCA in the context of postpartum depression has also been reported. Only rarely is the mother deemed to be psychotic or delusional. Some reports cite a history of significant childhood maltreatment in these mothers, including physical and sexual abuse. In the past, the primary motivation has been described as the "use of a sick child as a vehicle to maintain and regulate a relationship with physicians and other medical personnel and later with other people seen as powerful." However, with the new terminology MCA, the motivation of the perpetrator is not the primary concern of the pediatrician.

No evidence whatsoever suggests that perpetrators of MCA are unaware of their actions. On the contrary, the planning and organization involved, the minute attention to secrecy, the fact that the assaults are committed without witnesses, and the carefully woven fabric of lies presented to the physician all suggest great awareness. The perpetration of MCA is volitional, and can be violent. The fact that the violence is encased in duplicity only hides, but does not diminish, its aggression.

### DIAGNOSTIC STRATEGIES

Failure to diagnose MCA means that a fundamentally healthy child and the child's siblings might be killed or irreversibly damaged. Conversely, the failure to exclude MCA may mean that necessary treatment is withheld from an ill child or the child is separated unnecessarily from the family. The single largest impediment to making a diagnosis of MCA is the failure to include it in the differential diagnosis. Once MCA is considered, the difficulty in diagnosis revolves around the dilemma of not wishing to expose the child to any more potential risk and yet needing reasonably definitive proof. This clinical judgment call is best made with the assistance of the multidisciplinary MCA team, which is described in detail later in this chapter. However, *early* involvement of the MCA multidisciplinary team is critical to providing safety for the patient. The diagnostic strategy must maximize diagnostic capability while minimizing risk to the child. When MCA is suspected, confirmation or elimination of the diagnosis may be undertaken through one of several strategies: records review, the search for evidence of illness fabrication, the search for evidence of an explanation other than MCA, and the separation of the child from the suspected perpetrator.

#### Records Review

The first diagnostic strategy is records review. This strategy evolves from the observation that the pivotal facts, although present in the medical record, are often obscured by the sheer volume of information. In other words, the crucial data is there, but is buried. Furthermore, the importance of a comprehensive overview of the child's medical presentation has been repeatedly overshadowed by the immediacy of the crises. Curiously, the more chronic and intractable the child's problem is, the less likely that the problem is given a fresh, comprehensive look. Records review may be the preferred diagnostic strategy because it carries little risk, and may be the only strategy



possible when the child is alive but is unavailable, when the symptoms and signs of fabrication are long gone, or when the child is dead.

For most pediatric patients, a thorough records review is straightforward, with records being relatively brief. However, a substantially different approach to records review is needed when MCA is suspected. This is a consequence of 3 typical features—the record is extensive, the legal implications are broad, and the stakes are high. Records often run to thousands of pages, sometimes from dozens of medical facilities. The physician may be called to testify in civil or criminal proceedings, where the hundreds of medical facts may be minutely tracked and challenged. Reviewers should take note of inconsistencies between the caretaker's history and the observed clinical findings. Furthermore, how do the laboratory results compare with the history given? A computerized system for data entry, storage, organization, and retrieval is often indispensable, and any of several commercially available database-management systems can be adapted for this purpose. While record review is occurring, consider notating pages to reference when talking with the larger MCA multidisciplinary team. The reviewer may also choose to assign page numbers to each page collected in the record so that documents can be found quickly. It may be most helpful to formulate a timeline based on the review, which again helps the multidisciplinary team to navigate a very complex and often confusing medical history.

Because the medical and nursing records are often complicated, using someone (or several people) experienced in both inpatient and outpatient pediatrics to review the records is best. In the process of the records review, compiling a cumulative dated list of factors, such as prescribed medications, operations, consultations, hospitalizations, diagnoses explored, diagnostic tests performed and their results, interventions attempted, and school days missed, is often helpful.

### Search for Evidence of Illness Fabrication

The second diagnostic strategy, the search for evidence of illness fabrication, may include tests such as toxicology studies if poisoning is suspected; blood group typing, subtyping, or DNA typing if contamination with exogenous blood is suspected; or hidden video monitoring if surreptitious suffocation is suspected. To a great extent, the physician must choose, or even design, the test, depending on the fabrication that is suspected. The search for evidence of illness fabrication must be carefully planned and executed. Depending on the situation, this search involves setting up the proper chain of evidence, preserving laboratory specimens, continuous monitoring and recording of video units with plans to intervene immediately and decisively if assault is seen, and establishing precise coordination with law enforcement and social services. The advantage of this diagnostic strategy is that, if positive evidence is uncovered and is reliable, it is more likely to be accepted as definitive, medically and legally. The disadvantage is the risk of continued harm to the child. If the test is negative, then distinguishing among absence of assault, failure to capture the assault, or a false-negative test is often impossible.

One method to search for evidence of illness fabrication is covert video monitoring. Useful clinical data may be accrued with videotaping, although the strategy is somewhat controversial. A video camera may be installed and linked to a monitoring and recording unit in a nearby room. Obviously, this type of system must be in place before the child's admission. Multiple cameras should be considered to take into account the possibility of assault in areas of the room that may not be visible from 1 camera's view. Continuous observation of the videotape by real-time monitoring is essential. As part of the multidisciplinary team, hospital security and the local police department would be aware of the videotaping and available as needed. The topic of diagnostic, covert video monitoring in the hospital has engendered some animated debate, with authors addressing the legal, ethical, and logistic aspects of videotaping. Some authors are concerned with the right to privacy of parents in the hospital, while other authors point out that the parental rights to privacy are abrogated when that parent is thought to be potentially harming the child. One investigator who videotaped mothers smothering their children noted that both children struggled violently until they lost consciousness. Considerable force was used to obstruct their airways, and this force was needed for at least 70 seconds before electroencephalographic changes occurred. Interestingly, in both cases, a soft garment was used to smother the children, and no marks were seen on the lips or around the nose. This reference also includes a description of typical findings on monitor tracings, "which may in the future proved to be pathognomonic for this type (smothering) of apnea." The authors recommend that hospitals collaborate with their legal team to develop a written policy if planning to use covert video monitoring, and, in some jurisdictions, a court order may be necessary.

### Search for an Explanation Other Than Medical Child Abuse

A third diagnostic strategy, the search for an explanation other than MCA, has often been applied extensively by the time MCA is suspected, but not necessarily exhaustively. This approach is best when no opportunity or diagnostic test exists that might capture evidence of commission or when the search for evidence of illness fabrication would expose the child to grave risk. The contending diagnoses on the differential should be those that are subject to definitive inclusion or exclusion. For example, if a child repeatedly presents to the hospital with apnea that begins only in the presence of the mother, then the disorders that might be causing the child's apnea, such as seizures or gastroesophageal reflux, can be definitively included or excluded. Positive test results must be carefully scrutinized to ensure that they are positive neither as a result of maternal contamination or intervention nor as a result of being *overcalled*. Certain gastrointestinal tests seem to be especially vulnerable to this problem, in particular gastrointestinal motility studies and esophageal pH probe studies. Nissen funduplications as well as the installation of central venous catheters are unnecessarily performed with distressing frequency in cases of MCA. Both procedures result in direct-line access

to the child and, therefore, the possibility of further intraluminal assaults on the child with feces, saliva, contaminated water, drugs, salt, air, and other substances. The advantage of this diagnostic strategy is that the gathering of diagnostic evidence does not involve exposing the child to the possibility of another assault. The disadvantage is that it can be time-consuming and expensive and can expose the patient to risks, including various diagnostic procedures or prolonged hospitalization.

### Separation of the Child from the Parent

The fourth diagnostic strategy, the separation of the child from the parent, may be very useful. In certain circumstances, this action carries the most diagnostic weight and is the least onerous. Having a baseline against which to compare the child's subsequent course during separation is important, whether the separation occurs in the hospital or in a foster home. The baseline is the well-documented history of the child's symptoms and signs as provided by the mother. Therefore, the only major change that is made in the child's care during the separation should be the presence of the caregiver. In some instances, the fabrication of illness causes irreversible medical problems. Other times, the fabrication of illness is piled onto an already existing illness. Only reversible conditions of the child can be expected to improve, and these only to the degree and at a rate that is consistent with the condition itself. The advantage of this diagnostic strategy is that it can be definitive without exposing the child to further risk. The disadvantage is that, if MCA is not present, then an ill child has been separated unnecessarily and perhaps harmfully from the mother, and correct diagnosis has been delayed. One way to minimize the possible disadvantages is to have supervised visits with the mother. The supervision must be constant and scrupulous, with no foods, medications, or candy permitted. This strategy may require a court order, as the perpetrator often will not willingly agree to a prolonged separation from the child.

The diagnostic strategies used to detect MCA in its most common presentations are outlined in Table 292-2. These diagnostic strategies will not fit every type of suspected event, and the physician must tailor the diagnostic strategy to the type of perpetration suspected. This effort may involve contacting colleagues in related fields so as to gather information or to seek help. Commonly, various diagnostic strategies must be combined. An excellent example of evaluating seizures by Barber and Davis serves as a useful reference that illustrates a comprehensive approach and can be adapted to many presentations.

## DIFFERENTIAL DIAGNOSIS

While all cases of MCA are different, there are some reemerging themes that are noteworthy and may help the physician attempting to identify MCA. These are listed in Box 292-2. It is critical to emphasize, however, that not all of these case characteristics may be present in a given case of suspected MCA and that many of these characteristics may be present in cases not involving MCA.

As already discussed, a thorough investigation for organic illness must be undertaken. An exhaustive differential diagnosis should be considered and addressed before concluding that indeed MCA is the most likely answer. However, the physician needs to resist putting the child through painful and invasive testing if the likelihood of organic disease is small and MCA seems the more likely diagnosis. Genuine illness and MCA often coexist. The discovery of a real illness in a child does not exclude MCA. The question then becomes, does this illness reasonably explain the severity, extent, and type of the child's symptoms and signs? Often in cases of MCA, the physician may repeatedly comment on the fact that the presentation is unlike anything he or she has ever observed in the past. Occasionally, the distinction between MCA and pathologic physician shopping, or magnification of a child's real but minimal illness for the parent's own psychologic or fiscal gain, may not be clear. For specific cases that seem to fall at the edges of the definition of MCA, one might ask, is this damaging or abusive to the child? Box 292-3 gives the differential diagnosis of persistent presentation.

## DIAGNOSTIC CRITERIA

When MCA is suspected, the strength of the medical findings needed to establish a diagnosis may extend from weak to definitive. Thus, different degrees of diagnostic conviction may be found, not only from case to case, but also within a case, depending on the stage of the assessment. One can, therefore, attempt to categorize the findings as definitive, possible, uncertain, and definitely not MCA. Below are the diagnostic criteria, reprinted and modified from Rosenberg, that must be present, and when taken collectively, are sufficient for diagnosis.

### Definitive Diagnosis

The definitive diagnosis of MCA can be made in by inclusion or exclusion. A diagnosis by inclusion is supported by evidence of commission. For example, if a mother smothers the child who she had previously and repeatedly presented for apnea, and if her act were captured with covert videotaping in the hospital, then the definitive diagnosis of MCA would be by inclusion.

Box 292-4 lists the criteria for the definitive diagnosis by inclusion of MCA.

A diagnosis by exclusion is one in which all other possible explanations for the child's condition have been considered and excluded. For example, if a child who repeatedly presents with apnea while in one person's care that results in observable clinical compromise is observed in the hospital and has no evidence of apnea, and all other possible medical conditions have been investigated and excluded, then the definitive diagnosis of MCA is made by exclusion. Box 292-5 lists the criteria for the definitive diagnosis by exclusion of MCA.

### Possible Diagnosis

A possible diagnosis of MCA is 1 among several likely diagnoses. Box 292-6 lists the criteria for the possible diagnosis of MCA. Medical professionals are legally

Table 292-2

## Symptoms, Methods of Fabricating Illness, and Corresponding Diagnostic Strategies in Medical Child Abuse

PRESENTATION	METHOD OF SIMULATION OR PRODUCTION OR BOTH	METHOD OF DIAGNOSIS
Apnea	Manual suffocation	Video monitoring Implantable ECG recorder Diagnosis by exclusion Patient with pinch marks on nose Witnessed Toxicology of gastric fluid, blood, urine or IV fluid
Seizures	Poisoning: tricyclic antidepressants, hydrocarbons Fabrication Poisoning: phenothiazines, hydrocarbons, sulfonyleurea, tricyclic antidepressants Salt Suffocation or carotid sinus pressure	Diagnosis by exclusion Toxicology of gastric fluid, blood, urine or IV fluid Serum and urine sodium concentrations Witnessed; forensic photographs of pressure points
Diarrhea	Phenolphthalein or other laxative poisoning Salt poisoning	Stool or diaper positive Sodium concentrations of serum, urine or gastric contents; assay of formula
Vomiting	Emetic poisoning Injection of air into gastrostomy tube Fabrication	Urine for drug Video monitoring Hospital observation
CNS depression	Poisoning: diphenoxylate and atropine (Lomotil), insulin, clonidine, barbiturates or narcotics, benzodiazepines, aspirin, diphenhydramine, tricyclic antidepressants, acetaminophen, hydrocarbons, chlordiazepoxide, chloral hydrate, antiepileptics	Toxicology of blood, gastric contents, urine, IV fluid, hair; analysis of insulin type; video monitoring
Bleeding	Rodenticide (warfarin) poisoning Phenolphthalein poisoning Exogenous blood applied	Toxicology Diaper positive Blood group antigen profiling; DNA typing; <sup>51</sup> Cr labeling of erythrocytes Witnessed
Rash	Exsanguination of child Addition of substances (paint, cocoa, dyes) Drug poisoning Scratching	Testing; Washing Assay Diagnosis of exclusion
Fever	Caustics applied/painting skin Contamination with infected material (saliva, feces, dirt) Falsifying temperature Falsifying chart	Assay or wash off Witnessed; type of organism growing from infected sites Careful charting, rechecking (especially rectal temperature or urine for core body temperature) Careful charting; Duplication (ghost record) of temperature chart at nursing station

CNS, central nervous system; ECG, electrocardiographic; IV, intravenous.

From Rosenberg DA. Web of deceit: a literature review of Münchausen syndrome by proxy. *Child Abuse Negl.* 1987;11:547–563, with permission from Elsevier.

mandated to report child abuse to the local authority when they have a reasonable suspicion of it. *Reasonable suspicion* is not a term of art in medicine, but rather roughly translates into the set of diagnostic criteria here noted as a possible diagnosis.

### Inconclusive Determination: Cannot Know

Rather than increasing the weight of medical evidence in support of a diagnosis of MCA, accumulating data may instead diminish its likelihood. Medical criteria for inconclusive findings (that is, for MCA being indeterminate) are, therefore, articulated here. *Cannot know* means that, although the collection of data is complete, the data are insufficient to determine the diagnosis. The investigator can confidently neither

establish nor eliminate MCA as the diagnosis. *Cannot know* differs from possible diagnosis because implicit in a *cannot know* determination is the assertion that all relevant and available strategies for diagnosis have been exhausted. This position is in contrast to a possible diagnosis, in which an expectation of further diagnostic strategy can be found. Box 292-7 lists the criteria for an inconclusive (*cannot know*) determination.

### Definitely Not

*Definitely not* MCA means that the diagnosis can be absolutely eliminated because a wholly credible alternative explanation is at hand. To allow degrees of certainty within this diagnostic option, the physician might want to use some kind of qualifier, for example,

**BOX 292-2 Factors That May Be Present in Cases of Medical Child Abuse**

- Illness is multisystemic, prolonged, unusual, or rare.
- Symptoms and laboratory results are incongruent with patient's presentation.
- Symptoms disappear or diminish when caregiver is absent.
- Caregiver has extensive medical knowledge or background.
- Caregiver encourages medical staff to perform numerous tests and studies.
- Caregiver is not reassured by patient progress or seemingly reassuring results.
- Patient has multiple allergies to foods or medications.
- Patient has poor response to standard therapies (eg, continued report of seizures at home after multiple anticonvulsants).
- Patient unable to tolerate treatment (eg, frequent vomiting, rash, pain).
- Often caregiver's spouse is emotionally or physically absent/distant.
- Family history may include complex medical diagnoses of parent/sibling or diagnoses that are difficult to confirm (pregnancy complications, spontaneous abortion, sudden infant death syndrome [SIDS], etc).
- Caregiver is sometimes admired for overwhelming devotion to patient's care or viewed as the model parent.

**BOX 292-3 Differential Diagnosis of Persistent Presentation**

- Organic illness
- Anxious parent
- Developmentally delayed parent
- Vulnerable child syndrome
- Psychogenic illness
- Medical child abuse
- Münchausen syndrome

*probably not MCA. Probably not MCA* is about the same as saying that, in all likelihood, an alternative explanation is at hand. The fact that diagnostic criteria for the exclusion of MCA are included means that, as with other pediatric disorders, inevitably, more suspected cases than actual cases exist. Recognizing this situation means also recognizing the need for the swiftest and most decisive diagnostic test, but one in which the risk to the child does not seem to be excessive. Extreme care must be taken not to overdiagnose MCA or to be married to the diagnosis in the absence of sufficient evidence. Cases of misdiagnosed MCA are a real tragedy for the family and child. Box 292-8 lists the criteria for excluding the diagnosis of MCA.

**BOX 292-4 Medical Child Abuse: Criteria for a Definitive Diagnosis by Inclusion**

1. Child has been repeatedly presented for medical care.  
AND
2. Test or event is positive for tampering with child or with child's medical situation.  
AND
3. Positivity of test or event is not credibly the result of test error or misinterpretation or of miscommunication or specimen mishandling.  
AND
4. No explanation for the positive test or event other than illness falsification is medically possible.  
AND
5. No findings credibly exclude illness falsification.

From Rosenberg DA. Münchausen syndrome by proxy: medical diagnostic criteria. *Child Abuse Negl.* 2003;27:421–430, with permission from Elsevier.

**BOX 292-5 Medical Child Abuse: Criteria for a Definitive Diagnosis by Exclusion**

1. Child has been repeatedly presented for medical care.  
AND
2. All diagnoses other than illness falsification have been credibly eliminated so that
  - A. If the child is alive, then the competing diagnoses are those that took into account the child's major medical findings, and that account for the entirety of the child's presentation.  
OR
  - B. If the child is alive, then separation of the child from the alleged perpetrator results in resolution of the child's reversible medical problems, in accordance with their degree and speed of reversibility. No variable other than the separation can logically and fully account for the child's improvement.  
OR
  - C. If the child is dead, then autopsy examination does not reveal a cause of death that is credibly accidental, natural, or suicidal.  
AND
3. No findings credibly exclude illness falsification.

From Rosenberg DA. Münchausen syndrome by proxy: medical diagnostic criteria. *Child Abuse Negl.* 2003;27:421–430, with permission from Elsevier.

**INTERVENTION**

A list of treatment directives for all cases in which MCA is suspected is not possible. However, the practicing pediatrician and accompanying multidisciplinary team may find the following considerations useful:

1. **Optimally, the child should be protected while definitive data is collected to either include or**



**BOX 292-6 Medical Child Abuse: Criteria for Possible Diagnosis**

1. Child has been repeatedly presented for medical care.  
AND
2. Test or event is presumptively positive for tampering with child or with child's medical situation. No other explanation is readily apparent. No findings seem to exclude illness falsification.  
OR  
Child has a condition that cannot be fully explained medically, despite a respectable initial evaluation, at least. Cogent hypothesis suggests a faked medical condition. No findings seem to exclude illness falsification.

From Rosenberg DA. Münchausen syndrome by proxy: medical diagnostic criteria. *Child Abuse Negl.* 2003;27:421–430, with permission from Elsevier.

**BOX 292-7 Medical Child Abuse: Criteria for Inconclusive Determination**

1. Child has been repeatedly presented for medical care.  
AND
2. The relevant and available information has been reviewed, the child has been appropriately evaluated, or both.  
AND
3. Physician is left with a differential diagnosis, rather than a single diagnosis.  
AND
4. Conclusively affirming 1 diagnosis is not possible.  
AND
5. It is not possible to conclusively exclude all but 1 diagnosis on the differential diagnosis.

From Rosenberg DA. Münchausen syndrome by proxy: medical diagnostic criteria. *Child Abuse Negl.* 2003;27:421–430, with permission from Elsevier.

**BOX 292-8 Medical Child Abuse: Criteria for Excluding the Diagnosis**

1. Child has been repeatedly presented for medical care.  
AND
2. What had seemed to be possible falsification of illness has been wholly and credibly accounted for in some other way.

From Rosenberg DA. Münchausen syndrome by proxy: medical diagnostic criteria. *Child Abuse Negl.* 2003;27:421–430, with permission from Elsevier.

**exclude the diagnosis.** Professionals must weigh the eventual usefulness of this data against the possibility of a mishap occurring to the child during the data-collection process. When further diagnostic procedures place the child at risk, the protection of the child is always paramount.

2. **A multidisciplinary team should be involved early in the investigation.** The members of the MCA team should include the physician, the bedside and supervising nurses, the hospital social worker, and the subspecialist physicians involved in the patient's care. The bedside nurse and the head nurse often have extensive knowledge of the patient and family from prior hospitalizations. The primary care nurse often becomes responsible for important items such as documentation and chain of evidence of specimens. The county department of social services should also be contacted so that the medical concerns can be clearly explained. Early and clear communication with this team member is critical so that the team member can assist in protecting the child as well as obtain emergency custody if necessary. The hospital attorney, hospital security, risk management, and hospital administrators and public relations personnel need to be involved. If an event results in an arrest, the hospital will almost certainly be contacted by news media. The supervisor of the social workers involved should be included from the start. Police and other law-enforcement personnel should also be involved early. Should an episode of intentional infliction of harm come to light during videotaping, the police generally prefer to have prior knowledge of the case and may want to be prepared with an arrest warrant. Additionally, psychiatrists or psychologists can help to evaluate the caregiver and evaluate the child from a developmental and psychologic perspective, as well as provide support after confrontation of the family with the suspected diagnosis. The mother, who is generally the alleged perpetrator, is at increased risk for suicide after such a confrontation. It is worth stating that the mental health specialist evaluating the caregiver would optimally have experience with MCA cases, because the caregiver is often manipulative and persuasive. The multidisciplinary child-protection team is under no obligation to include the mother's attorney (if she has engaged one) or any other professionals who may divulge either the diagnostic strategies planned or the content of the proceedings to the family.
3. **Medical records should be reviewed in a comprehensive and organized fashion.** The physician should attempt to identify certain patterns, such as intractable vomiting or recurrent apnea, that have never been witnessed by anyone other than the caregiver. The physician should also identify any discrepancies between the caregiver's history and documented laboratory and physical findings.
4. **All medical records of all siblings must be reviewed, including autopsy reports and death certificates.** The process of obtaining these records often requires considerable effort, but they are vital. Neither police summaries nor social work records are sufficient.
5. **The parents' medical, educational, criminal, and work history should be reviewed, if possible.** While other members of the multidisciplinary team, such as law enforcement and CPS investigators, bear much of this responsibility, the treating physician can make recommendations to the

investigators responsible for gathering such information. This is particularly helpful if the parent claims various illnesses or medical education background.

6. **Several methods may be used, singly or in combination, to gain access to records.** In some instances, signed parental consent to obtain the records is possible. Otherwise, the attorneys on the multidisciplinary team may advise canvassing the area with subpoenas or requesting court-ordered discovery of records.
7. **Presentation of the review of records to the multidisciplinary team should include, as briefly as possible, a chronologic review followed by a review of discrepancies, if any.** How does the mother's history compare with the observed clinical findings in the child? How do the laboratory test results compare with the given histories (eg, are drug levels continually subtherapeutic or toxic with a history of absolute compliance)?
8. **Interviewing other family members regarding the child's illness and the mother's veracity can be very helpful.**
9. **Recommending out-of-home placement for the child is prudent.** This measure ensures protection of the child and a diagnostic period of separation to see how the child's health fares. If, up to this point, a mother has only simulated but not produced illness, there is no guarantee that she will not do something more harmful to the child in the future. *Simulators* may become *producers* of illness. Confrontation of the parent with the news of the suspected diagnosis does not, in and of itself, ensure safety for the child. The reader is cautioned in particular about the dangers of placing the child with a family member or friend. This situation is always difficult because, for the child, the easiest transition may be to an aunt or grandmother, but the perpetrator may have access to the child, despite the relative's or the friend's promises to the contrary. This decision places the child at potential dire risk. The perpetrator only rarely admits to MCA; however, curiously, she will more often agree to voluntary services as long as the court is not involved and a dependency petition is not filed. No success with this approach has been reported. Experience has shown that court-ordered intervention is necessary for any hope of successful protection of the child.
10. **If the child is to remain in the hospital for a time, then a medically experienced person must supervise all visits with all family members to ensure that no one is tampering with the child's medical care.** In some instances, the best course of action is to ask the court for a short (ie, 10-day to 2-week) period of hospitalization with only supervised parental visits as a diagnostic trial to determine if the child's symptoms floridly persist. If they do not, then concern about MCA is heightened. If they do, then the court should be asked to vacate the order and turn attention to a fresh look for an organic diagnosis. This approach is useful only if the child's symptoms and signs, if induced, would reasonably be

expected to abate rather quickly in the absence of ongoing assault.

11. **Recommending out-of-home placement of siblings is prudent because they may become the next targets if they remain in the home.** All siblings must at least have court-ordered medical evaluations and review of records.
12. **Once the child is in foster care, the health status of the child must be monitored and documented closely by the same physicians.** Although having the original physician or set of physicians involved in the child's ongoing care is often optimal, this arrangement is sometimes not practical for reasons of geographic circumstances. Continued surveillance is critical and should include ongoing assessment of the child's mental and behavioral health, school functioning, and safety.
13. **Deciding when to send the child home is difficult.** If the diagnosis is indeed MCA, then the same guidelines that apply to other forms of child abuse and neglect should be applied in consideration of when to send the child home. In other words, the perpetrator must acknowledge that she committed these acts, she must have some insight into the reasons for it, and she must provide reasonable assurance that sufficient change has occurred to ensure the safety of the child. Very little information is available on family reunification after psychiatric intervention. In 1 study, family reunification was thought to be feasible in certain cases, but the authors cautioned that long-term follow-up is necessary to monitor the safety of the child and assess whether the perpetrator's mental health has deteriorated. The mental health professional charged with providing the initial assessment and ongoing therapy for the mother should have experience and expertise in MCA. The mother's therapist should discuss with the court and the child-protection team specific issues that concern the safety of the child. If the mother and the psychiatrist insist that all the information is privileged, then the court has no way to determine that the children will be safe at home, and other permanent arrangements must be made for them.
14. **Even if the children are removed permanently and parental rights are terminated, subsequent children born to the mother are at high risk of being targets of MCA.** No formal method is available to keep track of the mother's pregnancies; but every effort must be made to protect future children.

## LEGAL CONSIDERATIONS

Anytime child abuse is suspected, a report to investigating agencies, including CPS and law enforcement, by the concerned physician is mandatory. It is important to emphasize that MCA is no exception. When presenting a case of MCA to the civil or juvenile court, some strategies of presentation may assist in coming to a conclusion. Despite the many hours spent in reviewing records and making an extensive chronologic compilation of the child's medical history, presentation of the information in long, narrative form often

confuses, rather than elucidates, the material. A short summary is often better. The physician may then be asked to clarify or expand on particular events. Graphs and charts that are clearly readable are helpful. For example, a growth chart may show that the child consistently gains weight in the hospital but loses weight at home. A histogram may show the number of apnea episodes that originated in the presence of the mother compared with the number that originated in the presence of the nursing staff. Cases typically involve conflicting medical opinions, and the parents usually have medical experts testify on their behalf. A clear grasp of the medical and epidemiologic evidence and a professional, nonadversarial attitude is always best. Criminal court proceedings undertaken against the perpetrator are still relatively rare, even in homicidal MCA.

In a courtroom or out, physicians are not required to translate the degree of diagnostic conviction into a legal equivalent. Terms such as *probable cause*, *reasonable suspicion*, *preponderance of the evidence*, *clear and convincing evidence*, and *evidence beyond a reasonable doubt* have a specific meaning in the law. If asked whether the evidence conforms to any of these burdens, or if a reasonable degree of medical certainty exists about the diagnosis (a popular question), the medical language that is meaningful to the physician should be used and distilled into lay terms that best embody the physician's meaning.

The physician should be alert to attempted manipulation by lawyers. The physician should not be badgered, flattered, or lulled into changing her opinion. The purpose of the medical witness is to provide a balanced, thorough, and comprehensible interpretation of the medical data. An important point to remember is that practicing attorneys have jobs that are different from those of physicians.

A diagnosis of MCA may have been based, at least in part, on the information that the physician reviewed in records. The physician may be asked if the professional opinion would change given different or additional information, to which the most accurate answer is often that the possibility exists but, absent the information and the time to think it over, the likelihood of that possibility is impossible to determine. It is the court's, not the physician's job to make a final legal determination.

## PHYSICIANS AND MEDICAL CHILD ABUSE

As is well outlined by Donald and Jureidini, the health care system and physician may bear some responsibility for contributing to morbidity in MCA cases. This syndrome has been abstractly characterized as a "dance," in which the physician unknowingly plays a crucial role in perpetuating the illusion of disease. Physicians do not expect a false history. Young physicians are worried by the cautionary tales of missed diagnoses and seasoned physicians are haunted by their own experiences of misdiagnosis. Most physicians want to be thorough while still operating in a very busy primary care practice. What used to be known as *defensive medicine* has now become almost mainstream medicine. Little time exists for pondering.

A well-founded fear of litigation pervades the practice of medicine. It is no longer uncommon for the perpetrator of MCA to make false allegations of malpractice to professional or licensing bodies, or to sue the physician or hospital on a number of pretexts, including defamation of character, malicious reporting, malpractice, wrongful detention of the child, or wrongful death. Additionally, personal vulnerabilities of some physicians may make it difficult for them to say, "I don't know." The interplay between primary care physicians and subspecialists may impede the correct diagnosis. As mentioned previously, a very fragmented system of medical care often develops as more and more subspecialists become involved. Small pieces of the puzzle are held by different physicians, while no one truly has a comprehensive view of the patient's condition. Involving a child abuse physician may be helpful in this situation, to take the responsibility of the MCA diagnosis off the other subspecialists and the primary care physician.

## CONCLUSION

Medical child abuse by any name is a serious form of child abuse. Multiple terms are used when making this diagnosis, however, MCA is the term that the authors of this chapter are recommending because of its ability to clearly define the presence of abuse, while at the same time shifting the focus from the parent or caregiver to the child. A thorough evaluation, although always necessary in child abuse investigations, is critical in evaluating possible MCA. This includes not only a complete history and physical examination, but also a detailed and exhaustive review of the medical record. Care should be taken throughout this process not to expose the child to additional risk or unnecessary tests. A multidisciplinary team is mandatory for proper evaluation and may include individuals who are not typically part of the child protection team, such as attorneys, law enforcement representatives, and mental health specialists. The process of diagnosis is time-consuming and difficult, and requires continued communication among all parties. Involvement of a child abuse specialist, if possible, is helpful. Education of physicians and child protection agencies is paramount so that this diagnosis can be considered and appropriately pursued.

## ACKNOWLEDGMENT

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## SUGGESTED READINGS

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## Chapter 293

# MUSCULAR DYSTROPHY

*Richard T. Moxley III, MD; Emma Ciafaloni, MD*

The muscular dystrophies are a group of slowly progressive, inherited diseases with specific patterns of muscle wasting and weakness. These disorders occur infrequently in childhood; a busy pediatrician may care for only a few patients during a career. However, breakthroughs in molecular biology have provided direct genetic tests for these diseases and have created opportunities to suggest and coordinate family counseling and prenatal testing. The primary care physician plays an important role in facilitating early diagnosis and referral to a neuromuscular specialist, helping with genetic testing, and monitoring patients for the pulmonary, cardiac, and orthopaedic complications of these muscular dystrophies. Duchenne dystrophy is the most common muscular dystrophy in childhood, and major advances have been made in its diagnosis and treatment. For these reasons, this chapter focuses on Duchenne dystrophy, although other muscular dystrophies that occur in childhood are also addressed.

## DUCHENNE DYSTROPHY

### Definition

Duchenne dystrophy is a slowly progressive muscle-wasting disease marked by symptoms that usually develop before age 5 years. Early in its course, Duchenne dystrophy affects the proximal hip and shoulder girdle muscles, as well as the anterior neck and abdominal muscles. The symptoms arise from an absence or extreme deficiency of a large cytoskeletal protein, dystrophin, that attaches to the inner surface of the muscle fiber membrane as a part of a complex of glycoproteins. Dystrophin is also part of the inner membrane structure of smooth and cardiac muscle and of certain cells in the central nervous system, and is found in specialized connective tissues such as the myotendinous junctions. This distribution of dystrophin corresponds closely to tissues that have major clinical manifestations in Duchenne dystrophy, such as cardiomyopathy and autism-like features.

The mechanism by which dystrophin deficiency causes dysfunction in some muscle groups while sparing others is a puzzle. Some experts have speculated that dystrophin protects and strengthens the muscle membrane to withstand the stresses of repeated muscle contractions and that it helps prevent excessive influx of calcium to speed the effective repair of tears in the muscle membrane that occur with vigorous exercise. However, this question still remains: Why do heavily used muscles, such as the extraocular and laryngeal muscles or the gastrocnemius muscles, maintain their strength despite the lack of dystrophin? Some experts speculate that upregulation of another large cytoskeletal protein, such as utrophin, can help maintain muscle function. In mdx mice, overexpression

of utrophin can compensate for the absence of dystrophin, restoring normal function, but no effective upregulation therapy is yet available for clinical use in Duchenne dystrophy. MDX mice are the most popular animal model of Duchenne muscular dystrophy caused by a point mutation in the mouse dystrophin gene with findings not identical to human Duchenne dystrophy. Further research is in progress to clarify the role that such alternative proteins may play in rescuing muscle fibers from destruction in diseases involving dystrophin deficiency. The findings will help in developing new strategies for treatment.

### Genetics

Duchenne dystrophy is an X-linked disease, therefore affecting male newborns only. Female manifesting carriers are very rare. The gene for dystrophin in the *Xp21* region is among the largest known, occupying 1% of the entire X chromosome. It contains 79 exons, and 5 different promoters control production of isoforms that are cell-type specific (eg, muscle, cerebral cortex, Purkinje, glial, Schwann cells). Large deletions occur in approximately 60% to 70% of cases of Duchenne dystrophy and in an even higher percentage of cases of Becker dystrophy (a later-onset X-linked dystrophy also caused by a deficiency of milder dystrophin). In addition to large deletions, duplications occur in about 5% to 10% of patients, and single nucleotide mutations occur in approximately 25% to 35% of patients who have Duchenne dystrophy and 15% of those who have Becker dystrophy. No consistent relationship has been established between clinical severity (Duchenne dystrophy vs the milder Becker dystrophy) and the size of the gene mutation. However, mutations that alter the reading frame (ie, out-of-frame-mutations) result in complete lack of dystrophin and more severe phenotype, while in-frame mutations allow for partial transcription of smaller size dystrophin and a milder phenotype. Deletion of the first muscle exon and the adjoining muscle promoter region seems to produce phenotypes that have either mild muscle involvement or that have mild muscle involvement but severe cardiomyopathy.

### Clinical Presentation and Differential Diagnosis

As outlined in Table 293-1, Duchenne dystrophy typically occurs in patients between 2 and 4 years of age. Parents notice weakness of forward head flexion that persists beyond infancy, accompanied by slowed motor development. Patients demonstrate progressive gluteal and shoulder girdle muscular weakness, leading to a widened stance, lumbar lordosis, forward thrusting of the abdomen, and toe walking. Patients never run normally and usually put their hands on their knees to rise from the floor (Gower's maneuver; Figure 293-1) and to assist in climbing steps. These patients have difficulty keeping up with their peers, a difficulty that becomes more apparent as they enter preschool and kindergarten. The teacher often observes a problem and helps the parents decide to bring



the child to the pediatrician. The child is not just normally clumsy, and poor motivation is not the cause for the child's tendency to fall easily and complain of tiredness and calf cramps. Primary care physicians must be sensitive to the protean nature of these early complaints in Duchenne dystrophy, including toe walking, difficulty with stair climbing, and language delay.

Because many patients with Duchenne dystrophy have mild cognitive deficits and language delay, the child may seem to be intellectually disabled, and the pediatrician may not consider Duchenne dystrophy or ordering a creatine kinase (CK) screen. Because of the gradual development of hip and knee extensor weakness in middle childhood, patients often toe-walk to use the power of the gastrocnemius to help stabilize knee extension. Reliance on the calf muscles during ambulation contributes to the typical hypertrophy of the calf muscles. However, the pattern of walking in these children and the presence of mild cognitive deficits can sometimes lead to the incorrect diagnosis of cerebral palsy, delaying correct diagnosis and effective treatment.

A complete history almost always distinguishes patients who have Duchenne dystrophy from those who have other conditions that cause proximal weakness without sensory findings in childhood. Hypothyroidism usually has more generalized symptoms, as does carnitine deficiency. Blood tests can exclude these 2 conditions from the differential diagnosis. Neither of these conditions causes the high CK levels that occur in Duchenne dystrophy. Variants of spinal muscular atrophy and early-onset cases of limb girdle muscular dystrophies (LGMD) may resemble Duchenne dystrophy. Hypertrophy of the calf muscles may be a feature of Duchenne dystrophy or childhood-onset LGMD. Spinal muscular atrophy produces no increase or only a mild increase in CK. As outlined in Table 293-1 and Figure 293-2, DNA analyses and, only rarely, muscle biopsy are the appropriate diagnostic tests to establish the diagnosis of Duchenne dystrophy. If muscle biopsy is needed, then the findings will help distinguish among many of the autosomal-dominant and autosomal-recessive forms of LGMD that sometimes have a close clinical similarity to Duchenne dystrophy.

Other, more acute conditions such as childhood myasthenia gravis and inflammatory myopathy are not usually confused with Duchenne dystrophy. The more rapid evolution of weakness, along with the presence of ptosis, ophthalmoparesis, and facial weakness distinguish myasthenia gravis from Duchenne dystrophy. The more generalized weakness that occurs in inflammatory myopathy, along with a skin rash, helps separate these patients from those who have Duchenne dystrophy. In rare cases, chronic demyelinating polyneuropathy may be confused with Duchenne dystrophy, but the absence of ankle reflexes, more generalized weakness, a more rapid course, the lack of marked increase of CK, and abnormally slowed nerve conduction identify these patients.

The combination of a complete history and judicious use of the tests outlined in Table 293-1 will establish the diagnosis of Duchenne dystrophy in virtually all cases. In rare cases, a floppy infant will have a markedly increased serum CK level, and physicians will wonder

whether the baby has a variant of Duchenne dystrophy. Newborns or infants who have Duchenne dystrophy also have a marked increase in CK, but they are not floppy. Some other problem must be present as well if a patient with Duchenne dystrophy is floppy. Floppy infants who have high CK levels usually do not have Duchenne dystrophy. If such a patient does not have an infectious, toxic, or metabolic disorder that causes muscle destruction to account for the marked increase of serum CK level, then the child usually has one of the 2 relatively rare childhood muscular dystrophies noted in Table 293-1 and Table 293-2. These diseases are the severe childhood autosomal-recessive forms of congenital muscular dystrophy. The workup and treatment of these disorders are summarized in Table 293-1 and Table 293-2. Certain congenital myopathies may be marked by floppiness, but these infants do not have significantly increased CK levels.

### Evaluation

Once the physician suspects the diagnosis of Duchenne (or Becker) dystrophy, the serum CK should be measured promptly to avoid diagnostic delay. A marked increase (10-fold or more above normal) in a male patient excludes most other disorders and strongly suggests the diagnosis of Duchenne dystrophy. At this point, discussing with the parents the possibility that the child has a muscular dystrophy is appropriate. However, the physician should refer the patient to a neurologist skilled in the care of patients with neuromuscular disease for confirmatory DNA testing. At present, DNA testing for duplication/deletion in the dystrophin gene can confirm the diagnosis in about 60% to 75% of cases. In the remaining patients, DNA sequencing can further identify up to 95% of cases. The remainder of patients with negative DNA testing will need a muscle biopsy for dystrophin western blot to confirm the diagnosis. A detailed discussion of the natural history of Duchenne dystrophy or a discussion of the procedures for screening the mother and other at-risk family members for carrier status at this time is premature and can be postponed. This discussion is best initiated after the neurologic consultation and after specific diagnostic information is available (see Table 293-1 and Figure 293-2). The neuromuscular specialist should take responsibility for the initial description of the course of Duchenne dystrophy and discuss the treatment options. Figure 293-2 provides a flowchart that neurologists typically follow to arrive at a diagnosis of Duchenne dystrophy.

A continuously updated list of laboratories and tests available for the genetic diagnosis of Duchenne muscular dystrophy can be found at GeneTests ([www.genetests.org](http://www.genetests.org)).

### Management Supportive Care

The overall goals in managing children who have Duchenne dystrophy are to maintain ambulation for as long as possible, to optimize the development of the child's cognitive abilities, and to anticipate the occurrence of complications such as excessive weight gain,

**Table 293-1** Symptoms, Genetics, and Diagnostic Tests for Muscular Dystrophies in Childhood

CHARACTERISTIC	DUCHENNE DYSTROPHY	BECKER DYSTROPHY	MYOTONIC DYSTROPHY
Age at onset	Before age 5, typically at 2–4 yr	After age 5; can begin in adult life	Infancy, childhood, or adult life
Initial symptoms	Cannot run or keep up with peers; can take only 1 step at a time	Fatigue or marked thigh weakness; trouble climbing steps; occasional calf or thigh cramps; patients can ambulate beyond age 15 yr	Congenital form—floppy infant, poor suck, weak respiratory effort, talipes; childhood form—bifacial weakness, slurred speech, impaired hearing, intellectual disability
Incidence	1:3,500 of male births	1:35,000 of male births	1:8,000 of all births
Genetics	X-linked recessive/ <i>XP21</i> region of gene for dystrophin	X-linked recessive/ <i>XP21</i> region of gene for dystrophin	Autosomal-dominant chromosome 19
Gene lesion	Mutation in the dystrophin gene	Marked deficiency of dystrophin	Abnormal expansion of CTG trinucleotide repeat in 3' nontranslated region of a gene coding for a serine/threonine kinase
Serum creatine phosphokinase	10× above normal	5–10× above normal	Normal or 2–5× above normal
Electrodiagnostic testing	Normal nerve conductions; myopathic EMG	Normal nerve conductions; mildly myopathic EMG	Normal nerve conductions; myotonic discharges present in children and adults, but often absent in infants (EMG should be performed on the mother)
Muscle biopsy	Active myopathy, absence of dystrophin, severe reduction in dystrophin-associated proteins	Moderately active myopathy, absence or deficiency of dystrophin, reduction in dystrophin-associated proteins	Increased central nuclei atrophy of type I fibers, ringbinden, and subsarcolemma masses
Leukocyte DNA testing	If suspicion is high, perform DNA screening first. If leukocyte DNA testing is negative, perform muscle biopsy. DNA is screened for deletions and duplications (60%–70% have them); if deletion/duplication is found, deletion tests are performed in at-risk family members; if no deletion is found, DNA sequencing for point mutation should be performed	Same as Duchenne dystrophy	If this diagnosis is suspected, a Southern blot analysis is performed to identify an abnormally large expansion of CTG repeats in the gene; if the Southern blot test is normal, a polymerase chain reaction test is done to search for smaller expansion of the repeat; most childhood cases show abnormal CTG repeat enlargements (eg, 500–4,000 repeats), whereas normal alleles have 5–30 repeats

AR-EDMD, autosomal dominant Emery-Dreifuss muscular dystrophy; CMD, congenital muscular dystrophy; CTG, cytosine-thymine-guanine; EDMD, Emery-Dreifuss muscular dystrophy; EMG, electromyography

**FACIOSCAPULOHUMERAL DYSTROPHY**

Rare cases in infancy, occasionally in childhood, usually in adult life  
 Congenital form (rare)—bifacial weakness, sometimes ophthalmoparesis, occasionally floppy, deafness; childhood form (more common)—mild facial weakness and weakness of scapular fixator muscles  
 1:20,000 of all births  
 Autosomal dominant; most cases localize to chromosome 4

Deletion of a variable quantity of 3.3-kb tandem repeats at 4q35 and abnormal methylation of the D4Z4 region

2–5× above normal

Normal nerve conductions; EMG occasionally myopathic, often within normal limits

Nonspecific myopathy; up to 30% have mononuclear inflammation

DNA analysis available to identify the 3.3-kb deletions noted above; should perform before obtaining muscle biopsy if clinical suspicion is high

**CONGENITAL MUSCULAR DYSTROPHIES (CMDs)**

Infancy; before age 2

Floppy infant; joint contractures, spinal rigidity, global developmental delay

1:21,500  
 Autosomal recessive except for 6-deficient CMD, which can be autosomal recessive or dominant; and LMNA-related CMD, which is inherited in an autosomal-dominant manner

Defects of proteins in the basement membrane (laminin alpha-2 [ie, merosin-deficient CMD]); Defects of proteins in the extracellular matrix: collagen VI-deficient CMD (Ulrich CMD); Defects of glycosyltransferase enzymes resulting in abnormal glycosylation of alpha-dystroglycan (Walker-Warburg syndrome; Fukuyama CMD); Defects of proteins of the endoplasmic reticulum: selenoprotein N1 (rigid spine syndrome) Defects of nuclear envelope proteins: lamin A/C and nesprin-1  
 >10× above normal

Normal nerve conductions; electromyography myopathic

Dystrophic changes with adipose and connective tissue replacement, and often prominent inflammatory infiltrates

*LAMA2*; *Col6A1-A2-A3*; *POMT1*; *POMT2*; *FKTN*; *FKRP*; *LARGE*; *POMGNT1*; *SEPN1*; *LMNA*; *SYNE1*

**EMERY-DREIFUSS MUSCULAR DYSTROPHY (EDMD)**

Middle to late childhood

Mild elbow contractures and mild weakness of triceps, biceps, and scapular fixator muscles; occasionally as isolated cardiomyopathy

1:100,000 of all births  
 X-linked recessive form Xq28 and autosomal-dominant form 1q21.3

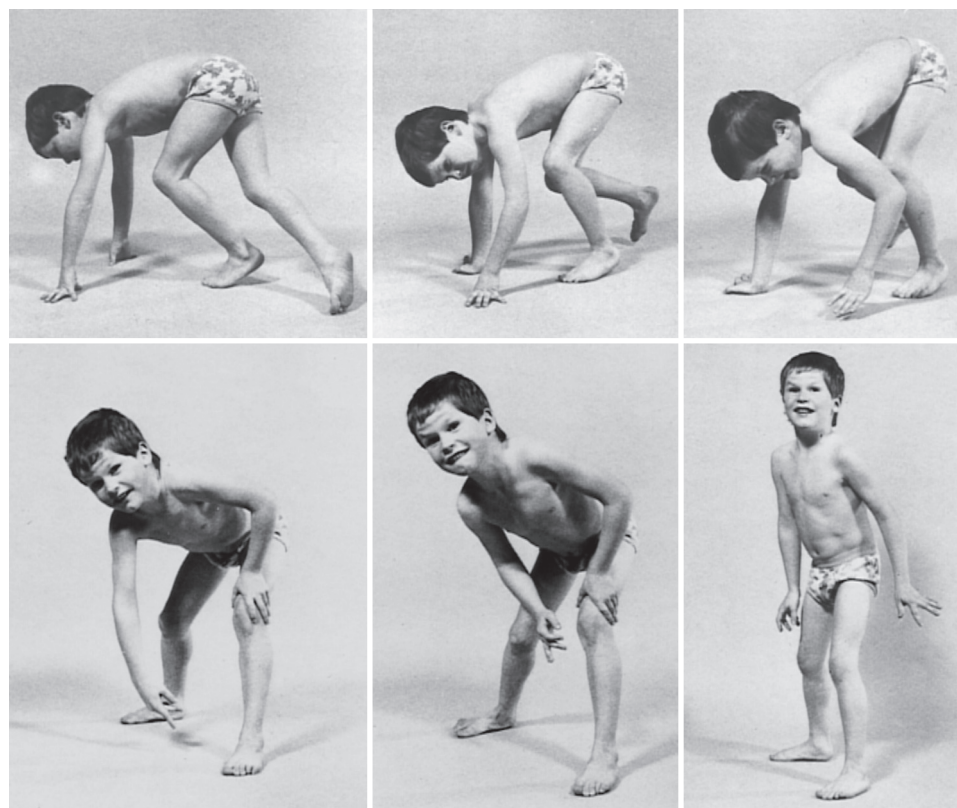
X-linked form involves gene for emerin and dominant form gene for lamin A/C. Emerin and lamin A/C are attached to nuclear membrane. Their functions are not yet known.

5–10× above normal

Normal nerve conductions; EMG often normal in early stages

Mild to moderate active myopathy with occasional atrophic type 1 fibers

Mutations in the *EDMD* gene encoding emerin and *FHL1* gene encoding FHL1 in X-linked EDMD; Mutations in *LMNA* gene encoding lamin A/C for AD-EDMD and AR-EDMD



**Figure 293-1** Boy who has Duchenne muscular dystrophy demonstrating the sequence of maneuvers that constitutes Gowers sign. The child pushes off the floor with all 4 extremities, then prepares to push up by moving the hands along the floor closer to the feet, and finally places the hands on the thighs and pushes up to the erect position. The maneuver is necessary because of the marked weakness of the hip extension. (From Swaiman KF. *Pediatric Neurology: Principles and Practice*. 2nd ed. St Louis, MO: CV Mosby; 1994. Copyright © 1994, Elsevier, with permission.)

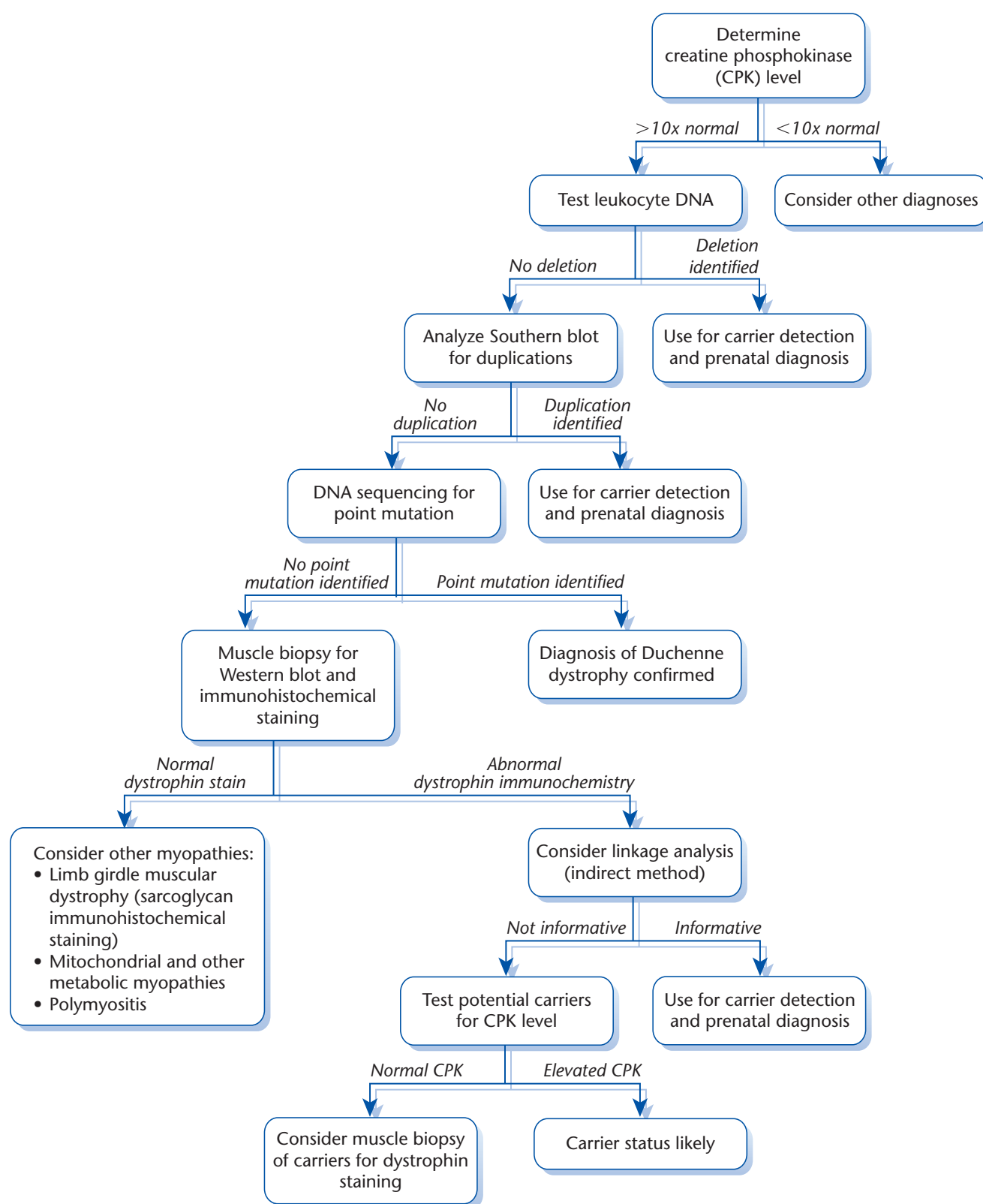
joint contractures (especially of the Achilles tendons), respiratory insufficiency, scoliosis, gastrointestinal hypomotility, and cardiomyopathy. Table 293-2 summarizes the principal problems and treatment options.

The patient and family need to work closely with physicians, schoolteachers, physical educators, and physical and occupational therapists to develop an individualized care plan for the child at each stage of the disease. Early in the illness, the child can usually play with peers in most activities; however, by the first or second grade, some adaptation of physical education requirements becomes necessary. The natural history of Duchenne dystrophy in the absence of treatment with corticosteroids predicts that the child will require a wheelchair for independent mobility between 10 and 12 years of age. Contractures and scoliosis both develop when the child is no longer able to ambulate; they do not appear at a specific age but depend on the child's functional status.

Physical therapy is often consulted at the time of diagnosis or 4 to 6 years of age. Therapy should emphasize range of motion and a home stretching program, particularly for the ankles. Strengthening programs should be avoided as possibly deleterious and the child's energy should be reserved for fun and functional activities. Aquatherapy is ideal if available. Since the use of corticosteroids became the standard

of care, the need for tendon release surgery and spinal stabilization surgery for scoliosis has decreased. Because the Achilles tendon contractures develop after patients can no longer ambulate, surgical lengthening and bracing usually do not affect functional status, and should be reserved for cases where the contractures limit normal positioning and transfers. Although historically tendon lengthening was common, surgical lengthening is now rarely done in ambulatory patients since toe walking is adaptive to maintain walking in the presence of severe proximal muscle weakness. In a Cochrane review of surgery versus controls, controls have better function at 12 months and surgical patients have contracture recurrence at 24 months. Steroids have no direct effect on contracture formation except secondary to maintaining proximal muscle strength. Orthopaedic consultation becomes a particular need in the early nonambulatory stage of Duchenne dystrophy to monitor for the development of scoliosis and tendon contractures that limit sitting ability, because this is when contractures and spinal curvature become prominent. The orthopaedic care, physical therapy, occupational therapy, and neurologic care are often coordinated by the neuromuscular specialist and are typically provided in a clinic financed partly by the Muscular Dystrophy Association (MDA). Scoliosis surgery requires complex





**Figure 293-2** Flowchart outlining diagnostic tests for a boy suspected of having Duchenne muscular dystrophy without a family history of this disorder.

**Table 293-2** Complications and Treatment of Muscular Dystrophies in Childhood

CHARACTERISTIC	DUCHENNE DYSTROPHY	BECKER DYSTROPHY	MYOTONIC DYSTROPHY
Muscle weakness	Treatment with prednisone or deflazacort slows deterioration or stabilizes muscle strength.	No controlled studies of prednisone treatment	No specific therapy; braces for foot drop; children can usually participate in physical education in school.
Respiratory problems	Forced vital capacity is monitored (in later stages, atelectatic pneumonitis is common); colds are treated aggressively; if signs of respiratory failure develop, nasal or oral ventilation should be considered.	Uncommon until late stages; management then as with Duchenne dystrophy	For congenital cases, ventilation is often needed; the prognosis for survival is poor if the patient is ventilator dependent at >4 weeks; other management is as for Duchenne dystrophy.
Cardiac problems	Cardiomyopathy often leads to congestive heart failure in the late stages of the disease; afterload-reducing therapy often helps; patient should be monitored for intracardiac clots.	Severe cardiomyopathy may require cardiac transplant; CHF treatment is the same as for Duchenne dystrophy	Occasionally, tachyarrhythmias or heart block develops in childhood forms, and pacemaker treatment is indicated.
Orthopaedic problems	Achilles tendon contractures respond to stretching in early stages; later, tendon release surgery is sometimes performed; contractures at the hips, knees, elbows, and wrists usually develop after the patient becomes wheelchair limited; scoliosis often develops when patients stop ambulating; spinal stabilization surgery is often unnecessary in patients receiving long-term corticosteroid treatment. Risk vs benefit depends on total medical picture and some patients may experience a slowing in rate of weakness in pulmonary function. The role of spinal stabilization surgery is currently being re-evaluated.	Uncommon; contractures are much less common than in Duchenne dystrophy	Talipes deformity requires treatment with stretching and orthotic support; occasionally, surgery is necessary.
Nervous system problems	Increased incidence of cognitive and behavioral problems; some patients improve with small doses of methylphenidate.	Uncommon	Intellectual disability is common, especially in congenital cases, and special classroom care is needed; hearing deficits are common and may require hearing aids; facial weakness, dysarthria, and hearing problems exaggerate the impression of intellectual disability.
Gastrointestinal problems	Constipation is common, especially late in the disease; careful dietary monitoring, stool softeners, and good water intake (urine specific gravities 1.007–1.010) are usually effective; occasionally, acute gastric dilation occurs; it resolves over 2–3 days with nasogastric tube decompression of the stomach and intravenous hydration.	Uncommon	Spastic colon-type complaints with abdominal pain are common; occasionally, these symptoms improve with antimyotonia therapy with mexiletine; eating small portions at each meal diminishes tendency to aspirate.

FACIOSCAPULOHUMERAL DYSTROPHY	CONGENITAL MUSCULAR DYSTROPHIES	EMERY-DREIFUSS MUSCULAR DYSTROPHY
<p>No specific treatment; patients should avoid lifting with arms fully extended and abducted; braces are sometimes needed.</p> <p>Uncommon</p>	<p>No specific treatment; bracing and physical therapy are useful in some patients.</p> <p>As with Duchenne dystrophy; patients often die of respiratory failure late in childhood or in early teens.</p>	<p>No specific treatment; skeletal muscle weakness is often relatively mild compared with cardiac problems and does not limit function.</p> <p>Mild other than symptoms related to cardiac dysfunction.</p>
<p>Uncommon</p>	<p>Uncommon</p>	<p>Frequent cardiac conduction defects; atrial paralysis, cardiac arrest, and sudden death are common; pacemaker treatment and preventive therapy for cardiac emboli are often necessary.</p>
<p>Occasionally, knee effusion and low back pain develop as a result of weakness; conservative care measures are effective; in late stages, surgery to stabilize the scapula may be performed, but surgery is uncommon.</p>	<p>Contractures develop in 70% of patients by 3 months of age at the ankles, knees, hips, and feet.</p>	<p>Contractures, especially in the elbows and ankles, occur early and respond somewhat to physical therapy; surgical release of Achilles tendon may be necessary; some patients develop a rigid spine syndrome, for which no effective therapy is available.</p>
<p>Uncommon; in rare cases, the infant-onset form of the disease occurs in association with hearing loss, retinal disease, or both.</p>	<p>Intellectual disability common; magnetic resonance imaging of head shows increased signal from white matter on T2-weighted images; occipital agyria; most patients have microcephaly, polymicrogyria, pachygyria, and heterotopias; generalized or focal seizures occur in most patients; anticonvulsant therapy is necessary.</p>	<p>Caused only by stroke from heart block or cardiac emboli.</p>
<p>Uncommon</p>	<p>Uncommon</p>	<p>Uncommon</p>

multidisciplinary decision making. There have been no randomized trials to help define risks versus benefits. Surgery may improve lung function, comfort, and longevity, or it may hasten loss of self-feeding skills and have overall negative effects on quality of life.

Spinal stabilization surgery has become much less common, related in large part to long-term corticosteroid therapy slowing or preventing significant progression of scoliosis during the teenage years. The timing and decision to perform spinal stabilization needs to be individualized to each patient and needs to be coordinated with consultants in orthopaedics, pulmonary medicine, and cardiology as well as with the child's primary care physician and neuromuscular specialist.

Although MDA clinics provide an excellent opportunity to offer multiple services to patients, the role of the primary care physician remains critical. The pediatrician usually provides routine care of upper respiratory infections and routine immunizations, as well as treatment for other common medical problems. In the middle and late nonambulatory stages of Duchenne dystrophy, minor medical problems can provoke major complications. A mild cold may lead to atelectatic pneumonitis and acute respiratory insufficiency. Such a problem, if treated aggressively, is fully reversible. Even chronic constipation can produce respiratory compromise in the later stages of Duchenne dystrophy, because of abdominal distention and upward pressure on the diaphragm. An effective regimen to maintain regular bowel movements becomes important in routine care. Respiratory insufficiency often develops in the late stages of Duchenne dystrophy. Forced vital capacity declines, usually into the range of 600 to 1,000 mL. Management options include nasal ventilation rather than positive pressure ventilation via tracheostomy. Monitoring pulmonary function and screening for nocturnal hypoventilation is essential for proactive use of respiratory aids. Coordination of care with pulmonary medicine consultants and serial monitoring of pulmonary function tests is essential. This monitoring of pulmonary status is necessary to determine the frequency of screening evaluations for nocturnal hypoventilation and initiation of noninvasive nighttime respiratory support with either continuous positive airway ventilation (CPAP) or biphasic positive airway ventilation (BiPAP). The patient is also at risk for obstructive sleep apnea, and a history of snoring should prompt screening for nocturnal hypoventilation even in the absence of significantly decreased pulmonary test results. Noninvasive ventilation requires either nasal, mouth or whole-face masks and close work with respiratory therapy and pulmonary medicine. Invasive tracheostomy and positive pressure ventilation have become uncommon as the noninvasive therapy has received greater use. The use of assistive cough devices (insufflator-exsufflator) is helpful in speeding recovery from episodes of bronchitis and pneumonia. Ventilatory care is usually coordinated among the pediatrician, neuromuscular specialist, pediatric pulmonologist, and patient and family. All have to participate if the treatment plan is

to be effective. Considerable discussion is necessary to educate the patient and family at this stage and to help decide which options are most appropriate. Physicians and nurses who have special training in neuromuscular diseases are often the ones who educate the family, and the roles of the pediatric pulmonologist and pediatrician have to be tailored to each medical care setting.

Periodic consultation with a pulmonologist is important once a child with Duchenne dystrophy is no longer ambulatory. Patients should be monitored for the development of obstructive sleep apnea and nocturnal hypoventilation with periodic polysomnograms. Pulmonary clinic visits typically include measurements of vital capacity, inspiratory and expiratory pressures, and cough peak flow, all of which guide prognosis and expectations regarding the need for ventilatory support and airway clearance assistance during respiratory infections. Pulmonary consultation before and after general anesthesia is an integral part of any elective surgery. This preoperative consultation needs to include training of the patient and the home care providers in the use of assisted coughing techniques and in the use of nasal bilevel positive airway pressure (BiPAP). The use of nasal BiPAP and assisted coughing hastens recovery after general anesthesia and decreases the likelihood of postoperative respiratory complications.

In the late stages of Duchenne dystrophy, patients often develop cardiomyopathy. A chest radiograph reveals a dilated heart, and the cardiac ejection fraction decreases to 10% to 20% of normal. Heart failure is often exacerbated by coexisting respiratory insufficiency. In all of these cases, simultaneous ventilatory support must be considered if the patient and family have decided to pursue a vigorous course of treatment. Heart failure is difficult to manage, and afterload reduction therapy is often more effective than digoxin. An initial trial with an angiotensin-converting enzyme inhibitor, such as lisinopril, is often undertaken. If left-ventricular function worsens, then treatment with beta-blocker therapy, such as carvedilol, is initiated with the goal of keeping the heart rate between 55 and 70 beats per minute. Cardiology consultation needs to guide the care plan. Occasionally, ventricular or atrial clots (or both) are present, and long-term anticoagulant therapy is necessary.

Acute gastric dilation is another infrequent complication in the late stages of Duchenne dystrophy. This condition typically occurs in association with an idiopathic metabolic acidosis and responds rapidly to nasogastric tube decompression of the stomach and intravenous hydration. Caution must be used with intravenous repletion of potassium, because in the late stages of the disease the patient's muscle mass is considerably diminished and is not available to buffer an acute rise in extracellular potassium.

Although the cause of the gastric dilation is unknown, this problem, as well as the chronic intestinal hypomotility (constipation), probably results from the deficiency of dystrophin in the smooth muscle of the gastrointestinal tract. Good hydration, a balanced



dietary intake, and regular bowel habits are the mainstays of treatment for these problems.

Comprehensive care guidelines have been published and provide a useful framework for all practitioners who care for individuals with Duchenne dystrophy.

### **Corticosteroid (Prednisone and Deflazacort) Treatment**

Corticosteroids (prednisone and deflazacort) are the only effective, evidence-based therapy for Duchenne dystrophy. Corticosteroid treatment is the standard of care, and studies indicate that daily prednisone or deflazacort is the most effective short- and long-term treatment to maintain muscle strength and function. The mechanism responsible for the beneficial effect of prednisone is unknown. However, several clues exist about the process involved. The increase in strength begins to develop after only 10 days of treatment and reaches a maximal response after 3 months of therapy. Muscle mass increases 10% after 3 months of prednisone treatment, and the rate of muscle breakdown declines in association with maintenance of a normal rate of muscle protein synthesis. Although azathioprine immunosuppressive therapy has been used, it confers no beneficial effect, which argues against the possibility that an immunosuppressive effect accounts for the improvement in muscle strength with the use of prednisone.

Treatment of Duchenne dystrophy patients with prednisone or deflazacort (not FDA approved in the United States but used in Canada and Europe) is now routine, but it is best carried out and monitored in medical centers experienced with its actions and side effects and with the clinical manifestations and complications of Duchenne dystrophy. Weight gain is an early side effect of corticosteroid therapy. Long-term benefits of corticosteroids are prolonged ambulation, prolonged stabilization of pulmonary function, reduced need for spinal stabilization surgery, and improved quality of life. The most common side effects are excessive weight gain, mood disturbances (more aggressive, more tearful), and cushingoid facial appearance. More serious side effects (compression fractures of the spine, delayed puberty, high blood pressure, gastrointestinal bleeding, severe infections, or diabetes) are uncommon. Some patients have developed small, dot-shaped cataracts; others, as expected, have experienced decreased linear growth, which has probably helped maintain ambulation. One recent multicenter study compared intermittent (10 days “on,” 10 days “off”) to daily prednisolone given for approximately 4 years. The median loss of ambulation was 12 years in intermittent and 14.5 years in daily treatment. Side effects were more apparent with daily treatment. Another prospective trial of treatment comparing prednisone 0.75 mg/kg/d to prednisone 0.75 mg/kg/d (10 days on and 10 days off) and to deflazacort 0.9 mg/kg/d for 30 to 60 months is in progress (see ClinicalTrials.gov, and search using the identifier NCT01603407).

To allow monitoring for the development of side effects, patients are seen every 3 to 6 months, depending

on their clinical picture, to assess weight, blood pressure, pulse, and forced vital capacity checks; for urinalysis; and for assessment of neuromuscular functioning. At each visit, the patient undergoes timed function tests (time needed to travel 30 feet, to arise from supine to standing position, and to climb 4 standard steps) and a muscle strength evaluation (shoulder abductors, elbow flexors and extensors, knee extensors, hip flexors and extensors). These measures help guide the physicians in adjusting the dose of prednisone. The blood count and serum electrolyte levels are measured at 6-month intervals.

With close follow-up, patients have been kept stable or showed only mild progression of muscle weakness for periods exceeding 5 years. Even in the late stages, prednisone seems to maintain respiratory muscle power and has reduced the number of patients who develop respiratory failure.

Current recommendations by the Guideline Development Subcommittee of the American Academy of Neurology concluded that in children with Duchenne muscular dystrophy, prednisone should be offered to improve strength and pulmonary function, improve timed motor function, reduce risk of need for scoliosis surgery and delay the onset of cardiomyopathy.

The discovery of the gene in Duchenne dystrophy and the ability to manufacture small segments of DNA containing the normal gene for dystrophin has raised hopes that direct gene therapy, either by local injection or by viral vector, will prove feasible. Research is in progress. Other advances in research include treatments to *read through* stop codon mutations or to skip certain exons in order to re-establish a reading frame and allow dystrophin transcription (exon skipping) stem cell therapy and treatments to *read through* certain types of mutations. Cost-effective newborn screening with CK is also being studied. This will help identify patients for novel therapeutic treatments prior to onset of clinical symptoms.

### **Other Muscular Dystrophies in Childhood**

Myotonic dystrophy type 1 (DM1), or dystrophica myotonia (Steinert disease), is caused by an abnormal enlargement of a trinucleotide repeat in the third non-translated region of the *DM* gene on chromosome 19. Discovery of the gene has led to the development of gene probes to identify both symptomatic and asymptomatic carriers. Genetic counseling and prenatal testing can now be performed with a high degree of accuracy, an important advance in preventive therapy. Myotonic dystrophy type 2 (DM2) is a disorder similar to but distinct from DM1 and is also a multisystem autosomal-dominant disorder associated with myotonia, weakness, and cataracts. However, DM2 does not occur in infancy or childhood. Complications can occur, particularly in DM1, when patients receive anesthetics and during pregnancy and delivery.

Facioscapulohumeral dystrophy (FSHD) sometimes has onset in childhood. Severe cases that uncommonly occur in infancy and early childhood may result in considerable weakness of facial and bulbar muscles, and affected patients can develop respiratory insufficiency along with generalized weakness. The disease

**Table 293-3** Autosomal-Dominant Forms of Limb Girdle Muscular Dystrophy (LGMD 1A-H)

DISEASE NAME	GENE	CHROMOSOME LOCUS	AGE OF ONSET	CREATINE KINASE	CLINICAL FEATURES	OTHER FEATURES
LGMD1A myotilinopathy	<i>MYOT</i> or <i>TTID</i>	5q31.2	18 and older	Normal to moderately high	Proximal weakness; distal weakness late; ankle contractures	Dysarthria; dysphagia; respiratory insufficiency
LGMD1B	<i>LMNA</i>	1q22	Birth to adulthood	Normal to high	Lower extremity weakness; late upper extremity weakness; contractures as in Emery-Dreifuss muscular dystrophy	Atrioventricular conduction defects; dilated cardiomyopathy
LGMD1C caveolinopathy	<i>CAV3</i>	3p25.3	Any	Moderately to very high	Mild to moderate proximal weakness; cramps after exercise; myalgias	Calf hypertrophy; muscle rippling; hypertrophic cardiomyopathy
LGMD1D desminopathy	<i>DES</i>	2q35	Early adulthood	Normal to moderately high	Mostly lower extremity weakness sparing quadriceps; ambulation preserved	Cardiac conduction defects; dilated cardiomyopathy
LGMD1E	<i>DNAJB6</i>	7q36.3	18–40; late onset in females	Normal to moderately high	Slowly progressive weakness in lower extremities sparing quadriceps	Calf hypertrophy; loss of ambulation 20–30 years from onset
LGMD1F	<i>TNP03</i>	7q32.1–q32.2	Any	Normal to high	Fast progression in early onset cases; facial weakness	Scoliosis; respiratory failure
LGMD1G	<i>HNRPDL</i>	4q21	Adulthood	Normal to very high	Proximal lower extremity weakness	Finger and toe flexion limitation
LGMD1H	?	3p25-p23	Second to fifth decade	Normal to very high	Slowly progressive upper and lower extremity weakness	Calf hypertrophy; muscle atrophy; high serum lactate

is inherited in an autosomal-dominant manner and is caused by a deletion in the number of D4Z4 repeats in the subtelomeric region of chromosome 4q35. DNA testing is available. FSHD type 1 represents approximately 95% of patients and results from a deletion of a key number of repetitive elements on chromosome 4q35. The remaining 5% of FSHD cases are classified as FSHD type 2 and result from a digenic mutation rather than a loss of D4Z4 repeat units. The clinical presentations of FSHD type 1 and FSHD type 2 are indistinguishable.

The infant-onset congenital muscular dystrophies are rare disorders and have already been mentioned in the discussion of the differential diagnosis of Duchenne dystrophy.

Emery-Dreifuss muscular dystrophy is a rare, hereditary disorder, having X-linked, autosomal recessive, and autosomal dominant that are clinically and genetically distinct from, but occasionally confused with, Becker

dystrophy. It can produce severe cardiac complications that require urgent treatment. These cardiac symptoms may prompt medical evaluation before the muscle weakness or contractures occur.

Table 293-3 and Table 293-4 outline the forms of autosomal-dominant and autosomal-recessive forms of LGMD. Some of these disorders can occur during childhood or adolescence and on superficial evaluation, they resemble Duchenne dystrophy. Unlike Duchenne dystrophy, most of the forms of LGMD progress more slowly, and the prognosis differs. The autosomal-dominant forms (LGMD 1A-H) are especially uncommon, as are some of the autosomal-recessive forms (LGMD 2A-V). However, the sarcoglycanopathies (especially LGMD 2I) probably account for more than 10% of patients who have a limb-girdle pattern of muscle weakness and whose muscle biopsy samples stain normally for dystrophin. The sarcoglycans are glycoproteins associated with

dystrophin and other muscle membrane-associated proteins with relationships to specific forms of LGMD, and these different disorders have different causes.

The various forms of LGMD are important to consider in referring children to a neurologist. Simply being aware that a variety of uncommon muscular dystrophies with different prognoses exists will help parents and patients understand that different tests may be necessary to establish a specific diagnosis, a prognosis, and a plan of treatment.

### WHEN TO REFER

Neuromuscular clinic or specialist

- When the diagnosis of Duchenne dystrophy is strongly suspected (ie, symptoms and high creatine kinase levels)
- To facilitate the workup
- Once the diagnosis is confirmed to establish multidisciplinary care

Genetic counselor

- After the diagnosis of Duchenne dystrophy is established
- Offered to family members of patients, especially at-risk carrier women

Cardiologist

- At diagnosis to obtain a baseline cardiologic evaluation
- If any wall motion abnormality is present on echocardiogram, delayed enhancement on cardiac MRI, or suspicion of arrhythmia
- In the late stages of the disease for monitoring of cardiac function and management of cardiomyopathy and heart failure
- Before surgery

Pulmonologist

- To obtain a baseline pulmonary evaluation at time of diagnosis
- In the late nonambulatory stage of the disease to monitor forced vital capacity (FVC), cough pick flow, maximum inspiratory pressure (MIP), and maximum expiratory pressure (MEP) and manage respiratory failure with noninvasive ventilatory support; to discuss tracheostomy
- Before surgery to maximize use of cough assist and BiPAP as necessary

Orthopaedic surgeon

- To obtain a baseline orthopaedic consultation at time of diagnosis
- After the patient with Duchenne dystrophy has lost ability to walk
- For consideration of scoliosis surgery or release of heel cord contractures when the nonambulatory patient shows signs of spinal curvature or progressive heel cord contractures

Physical therapist, occupational therapist, or both

- During the ambulatory stage of Duchenne dystrophy, to develop a heel cord stretching program and an individualized exercise program
- In the late ambulatory stage of Duchenne dystrophy, when the patient may seem to be close to becoming wheelchair limited

- To be fitted with adaptive equipment and night braces
- To evaluate and manage contractures

Dietitian

- During the ambulatory stage of Duchenne dystrophy, particularly in patients receiving corticosteroid treatment
- To help manage weight gain
- To establish a healthy eating pattern for the future

Neuropsychologist

- During the ambulatory and nonambulatory stages of Duchenne dystrophy because these patients are at risk of having emotional, cognitive, and behavioral problems
- In patients with borderline intellectual abilities
- In patients with cognitive or behavioral abnormalities
- In patients and family members who need end-of-life counseling

### WHEN TO ADMIT

- After surgery for 24 hours (or longer, depending on the type of surgery) to monitor cardiac and pulmonary function
- For evaluation and management of pneumonia or respiratory insufficiency, especially in nonambulatory patients with Duchenne dystrophy and in patients with advanced cardiomyopathy with cardiac failure

### TOOLS FOR PRACTICE

#### Community Advocacy and Coordination

- *Building the Legacy: IDEA 2004* (Web page), US Department of Education ([idea.ed.gov](http://idea.ed.gov))
- *Let's Put the Person First, not the Disability!* (fact sheet), Disability Is Natural ([www.disabilityisnatural.com/explore/people-first-language](http://www.disabilityisnatural.com/explore/people-first-language))

#### Engaging Patient and Family

- *All About the IEP* (fact sheet), Center for Parent Information and Resources ([www.parentcenterhub.org/repository/iep](http://www.parentcenterhub.org/repository/iep))
- *Building Your Care Notebook* (Web page), American Academy of Pediatrics ([www.medicalhomeinfo.org/for\\_families/care\\_notebook](http://www.medicalhomeinfo.org/for_families/care_notebook))
- *Emergency Information Form for Children With Special Needs* (template), American Academy of Pediatrics ([www.aap.org/advocacy/blankform.pdf](http://www.aap.org/advocacy/blankform.pdf))
- *Partnering in Self-Management Support: A Toolkit for Clinicians* (Web page), American Academy of Pediatrics ([www.medicalhomeinfo.org/how/care\\_partnership\\_support.aspx#self](http://www.medicalhomeinfo.org/how/care_partnership_support.aspx#self))
- *Pediatric Care Plan* (template), American Academy of Pediatrics ([medicalhomes.aap.org/Documents/PediatricCarePlan.pdf](http://medicalhomes.aap.org/Documents/PediatricCarePlan.pdf))
- *Pediatric Specialists* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/default.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/default.aspx))
- *Transitioning Youth to Adult Care Providers* (booklet), Got Transition ([www.gottransition.org/resourceGet.cfm?id=208](http://www.gottransition.org/resourceGet.cfm?id=208))

**Table 293-4** Autosomal-Recessive Forms of Limb Girdle Muscular Dystrophy (LGMD 2A-V)

DISEASE NAME	GENE AND CHROMOSOME LOCUS	AGE AT ONSET	CREATINE KINASE
LGMD2A Calpainopathy	CAPN3; 15q15	8–15; rarely late	High to very high
LGMD2B Dysferlinopathy	DYSF; 2p13.2	15–25	High to very high
LGMD2C, 2D, 2E, 2F/ Sarcoglyconopathies (SGs)	2C SGCG; 13q12 2D SGCA; 17q21.33 2E SGCB; 4q12 2F SGCD; 5q33	Childhood	High to very high
LGMD2G	TCAP; 17q12	2–15	Moderately high
LGMD2H LGMD2I	TRIM32; 9q33.1 FKRP; 19q13.3	1 <sup>st</sup> –2 <sup>nd</sup> decade	Normal to very high High to very high
LGMD2J	TTN; 2q24.3	2–25	High to very high
LGMD2K LGMD2L	POMT1; 9q34.1 ANOS5; 11p13	First decade Adulthood	Very high Very high
LGMD2M	FKTN; 9q31	Infancy	Very high
LGMD2N	POMT2; 14q24	First decade	Very high
LGMD2O	POMGnT1; 1p34.1	First decade	High
LGMD2P	DAG1; 3p21	Early first decade	Very high
LGMD2Q	PLEC1; 8q24	Early first decade	Very high
LGMD2R	DES; 2q35	Second and third decade	Mildly elevated
LGMD2S	TRAPPC11; 4q35	First decade	High
LGMD2T LGMD2U	GMPPB; 3p21 ISPD; 7p21	First and second decades First, second, or third decade	High High to very high
LGMD2V	GAA; 17q25.3	Wide range first to seventh decade (15–83 yrs)	Moderate to high

**Practice Management and Care Coordination**

- *Care Coordination Toolkit* (booklet), The National Center of Medical Home Initiatives for Children With Special Needs (www.medicalhomeinfo.org/downloads/pdfs/CareCoordinationToolkit06.pdf)
- *Care Delivery Management* (Web page), American Academy of Pediatrics (www.medicalhomeinfo.org/how/care\_delivery)

**AAP POLICY**

American Academy of Pediatrics Council on Children With Disabilities. Care coordination in the medical home: integrating health and related systems of care for children with special health care needs. *Pediatrics*. 2005;116(5):1238–1244 (pediatrics.aappublications.org/content/116/5/1238)

American Academy of Pediatrics Council on Children With Disabilities, Section on Developmental and Behavioral Pediatrics, Bright Futures Steering Committee, Medical Home Initiatives for Children With Special Needs Project Advisory Committee. Identifying infants and young children with developmental disorders in the medical home: an algorithm for developmental surveillance and screening. *Pediatrics*. 2006;118(1):405–420. Reaffirmed August 2014 (pediatrics.aappublications.org/content/118/1/405)

American Academy of Pediatrics Medical Home Initiatives for Children With Special Needs Project Advisory Committee. The medical home. *Pediatrics*. 2002;110(1):184–186. Reaffirmed May 2008 (pediatrics.aappublications.org/content/110/1/184)



CLINICAL FEATURES	OTHER FEATURES	OTHER PHENOTYPES
Mild to severe weakness; difficulty running; calf atrophy Weakness and atrophy of pelvic > shoulder girdle muscles; difficulty running; late upper extremities involvement Severe progression “Duchenne-like”; milder course also possible	Toe walking; early ankle contractures; scoliosis Calf and biceps atrophy; deltoid “bulge”; mean age at loss of ambulation: 45 Calf hypertrophy	NA Miyoshi myopathy; distal myopathy with anterior tibial involvement Dilated cardiomyopathy ( $\delta$ -SG)
Proximal and distal weakness; difficulty running Weakness; flat smile Severe to mild; low forced vital capacity (FVC) in 50% of cases Severe; progressive proximal weakness	Calf hypertrophy; foot drop Wasting Calf and tongue hypertrophy; pectoralis atrophy Distal weakness late in 50% of cases	Dilated cardiomyopathy 1N Myopathy Severe congenital muscular dystrophy Distal myopathy; dilated cardiomyopathy
Mild proximal weakness Pelvic girdle weakness or calf hypertrophy; difficulty walking on tiptoe Rigid spine; viral induced worsening weakness Scapular winging; slow running; motor delay Mild to moderate weakness	Microcephaly; low IQ Asymmetric quadriceps and biceps atrophy Facial and axial weakness Calf hypertrophy Myopia	Walker-Warburg syndrome Occasional Miyoshi-like myopathy Fukuyama congenital muscular dystrophy Walker-Warburg syndrome Muscle-eye-brain type of congenital muscular dystrophy
Mild weakness; muscle hypertrophy Progressive proximal weakness; ptosis; dysphagia; facial weakness	Microcephaly; intellectual deficiency; normal brain imaging Scapular winging; absent deep tendon reflexes	Epidermolysis bullosa simplex with muscular dystrophy; as above with myasthenia
Progressive proximal weakness Slow to moderate progressive weakness	Atrioventricular cardiac conduction defects; no cardiomyopathy Ataxia; intellectual deficiency; hyperkinetic movements	
Occasional proximal weakness pattern Progressive weakness (similar to Duchenne dystrophy); calf and tongue hypertrophy Progressive muscle weakness	Microcephaly; intellectual delay Respiratory insufficiency; cardiac dysfunction Respiratory insufficiency	Walker-Warburg syndrome; cobblestone lissencephaly Pompe disease in early childhood

American Academy of Pediatrics Section on Cardiology and Cardiac Surgery. Cardiovascular health supervision for individuals affected by Duchenne or Becker muscular dystrophy. *Pediatrics*. 2005;116(6):1569–1573. Reaffirmed December 2008 ([pediatrics.aappublications.org/content/116/6/1569](http://pediatrics.aappublications.org/content/116/6/1569))

### SUGGESTED READINGS

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## Chapter 294

### NEPHRITIS

William S. Varade, MD

#### DEFINITION

Nephritis is the general term for noninfectious inflammation of the kidney parenchyma. This inflammation may involve primarily the glomerulus (glomerulonephritis), the tubules and interstitium (tubulointerstitial nephritis), or both. Because glomerulonephritis historically has been the subject of more intense interest, when the term *nephritis* is used, many physicians think only of glomerular lesions.

#### CLINICAL MANIFESTATION

The components of a classic nephritic syndrome are hematuria, proteinuria, the presence of red blood cell casts in the urine, oliguria, hypertension, and uremia. Some or all of these parameters may be evident initially. The finding of hematuria and proteinuria together strongly suggests underlying glomerular inflammation. Hematuria may be microscopic or macroscopic. Proteinuria can range from mild to nephrotic range. Presentation can range from acute, with sudden onset of gross hematuria, edema, and oliguria, to subacute or chronic, with a more protracted course in which symptoms may be lacking and urine abnormalities detected on routine urinalysis are the only findings.

#### INCIDENCE

The true incidence of nephritis in children is difficult to ascertain. Many cases of acute glomerulonephritis may be mild and self-limited and thus go undetected or not lead to biopsy. In a study of 487 children younger than 15 years who underwent renal biopsy, 43% had a diagnosis of glomerulonephritis. Only 8.4% of these had a classic nephritic picture with hematuria, hypertension, oliguria, edema, and reduced glomerular filtration rate. Thus, incomplete nephritic syndrome presentations are more common in children who are ultimately diagnosed with nephritis. Incidence reports of nephritis may be skewed by differing criteria for biopsy in different parts of the world and by differences in the frequency of specific nephritides in different regions.

#### GENERAL EVALUATION OF SUSPECTED NEPHRITIS

Blood pressure should be monitored carefully and frequently in any patient with suspected nephritis, and it should be compared with normal values for gender, age, and height percentiles. Weight should be measured. Significant weight gain compared with values from prior visits might suggest fluid retention. Similarly, poor growth with crossing height percentiles

#### BOX 294-1 Glomerulonephritides With Low Complement Levels

- Acute poststreptococcal glomerulonephritis
- Lupus nephritis
- Membranoproliferative glomerulonephritis
- Nephritis of chronic infection
- Cryoglobulinemia

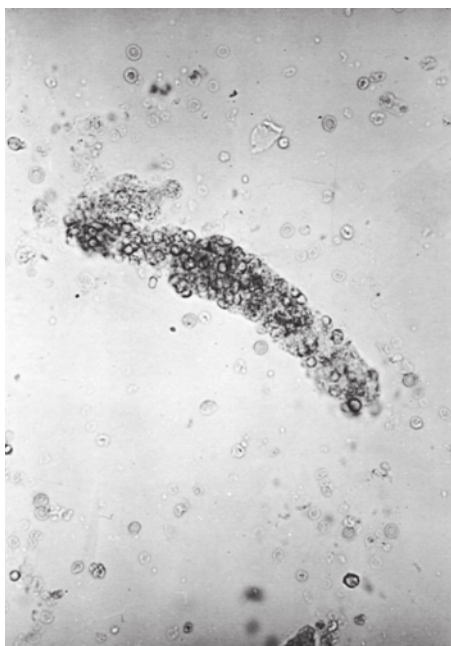
and inappropriate weight gain or loss might suggest a chronic renal disorder. Children with nephritis may have the following findings on physical examination: periorbital or pretibial edema, changes in eye grounds, a uremic odor to the breath, pleural or pericardial friction rubs, ascites, costovertebral angle tenderness, joint swelling or tenderness, and vasculitic rashes.

Laboratory evaluation should include urinalysis with microscopy, serum electrolytes, blood urea nitrogen, creatinine, calcium, phosphorus, albumin, liver enzymes, and complete blood count with platelets. Decreased levels of the third component of complement (C3) and on occasion that of the fourth component (C4) can help narrow the differential diagnosis by distinguishing the hypocomplementemic nephritides from those with normal complement levels (Box 294-1). Antinuclear antibody and antistreptolysin O or other antibodies to streptococcal antigens should be obtained. Anti-double-stranded DNA (anti-dsDNA), antineutrophil cytoplasmic antibodies, and hepatitis B and C serologic tests may be useful in cases of lupus nephritis, Wegener granulomatosis, and microscopic polyangiitis, and in some cases of membranoproliferative glomerulonephritis or membranous nephropathy. Although pyelonephritis can usually be distinguished from glomerulonephritis on clinical grounds, urine culture should be obtained in unclear cases. Imaging studies, in general, are nonspecific and not helpful in evaluating patients with nephritis.

#### ACUTE GLOMERULONEPHRITIS

Acute glomerulonephritis is characterized by the abrupt onset of hematuria, proteinuria, hypertension, and edema. The hematuria is often grossly visible as tea- or cola-colored urine. In some children, however, the hematuria may be microscopic only. Red blood cell casts and dysmorphic red blood cells are present, although several urine samples may have to be examined to demonstrate them (Figure 294-1). White blood cells on microscopy and a positive test for leukocyte esterase are often found but suggest inflammation and not bacterial infection. Acute glomerulonephritis is often the initial presentation of the renal diseases listed in Box 294-2.

This clinical syndrome can have 2 presentations: acute glomerulonephritis with no or mild renal failure and acute glomerulonephritis with rapidly progressive renal failure.



**Figure 294-1** Red blood cell cast (unstained).

**BOX 294-2 Acute Glomerulonephritides That Are Usually Characterized By No or Mild Renal Failure**

**MORE COMMON**

- Acute poststreptococcal glomerulonephritis
- Henoch-Schönlein purpura with nephritis
- Postinfectious (nonstreptococcal) glomerulonephritis
- Interstitial glomerulonephritis
- Radiation nephritis

**LESS COMMON**

- Acute episodes in patients with chronic glomerulonephritis
- Hemolytic-uremic syndrome (milder cases)
- Membranoproliferative glomerulonephritis (some)
- Nephritis of systemic lupus erythematosus (some)

## ACUTE GLOMERULONEPHRITIS WITH NO OR MILD RENAL FAILURE

### Acute Poststreptococcal Glomerulonephritis

Acute poststreptococcal glomerulonephritis (APSGN) is a common form of glomerulonephritis in childhood. The true incidence is unknown because many cases are subclinical. The greatest burden of disease occurs among poor populations in less developed countries. The peak incidence has historically occurred at age 7 years, and it is less common before age 3 years. However, more recently, at least in the developed world, elderly people seem to be more frequently affected.

There is a slight predominance among boys. Sporadic cases of APSGN are most common, although epidemics may occur. Cases of nephritis after streptococcal pharyngotonsillitis are more common in temperate regions, whereas those after streptococcal skin infections are more common in tropical and subtropical climates.

### Etiology

Poststreptococcal glomerulonephritis is the consequence of the host immune response to a nonrenal infection with group A  $\beta$ -hemolytic streptococci (GABHS), although cases associated with group C and G streptococcal infection have been reported as well. Not all GABHS strains are nephritogenic. Nephritogenic strains include types 1, 2, 4, 12, 18, 25, 49, 55, 57, and 60 and possibly some nontypable strains. Types 12 and 49 are the strains most commonly associated with nephritis. The pathogenesis of APSGN remains uncertain. One possibility is that streptococcal proteins are released and lodge in the glomerulus, where they form nephritogenic immune complexes leading to complement activation. Prominent among the candidates for the suspected streptococcal nephritogenic antigen are the nephritis-associated plasmin receptor (NAPlr) and streptococcal pyrogenic exotoxin B (SPEB). These proteins induce an antibody response, can be found in the glomeruli of patients with APSGN, and can activate complement, a form of immune complex-mediated disease. Approximately 15% of patients infected with a nephritogenic strain of streptococci subsequently develop nephritis. The risk for developing nephritis may differ according to site of infection (skin vs throat) and the particular M-type.

### Pathologic Features

The typical glomerular findings are proliferation of mesangial and endothelial cells, as well as the influx of polymorphonuclear leukocytes and mononuclear cells. The glomeruli are larger than normal, and the capillary lumens are compromised by the cellular proliferation within the glomeruli. By immunofluorescence microscopy, granular deposits of immunoglobulin and complement can be seen, corresponding to the subepithelial electron-dense humps seen on electron microscopy. With healing, the increased cellularity and immune deposits become limited to the mesangial region and then gradually resolve.

### Clinical Presentation

Mild and subclinical cases of APSGN are common. Renal involvement characteristically occurs 1 to 4 weeks after an infection caused by the nephritogenic streptococci, with a slightly longer lag time after a pyoderma. Most patients with APSGN exhibit macroscopic hematuria. Patients usually have oliguria and, in rare cases, anuria. Fluid retention leads to edema that is usually periorbital and, rarely, severe. Intravascular overload caused by salt and water retention can lead to signs of congestive heart failure. Approximately 60% to 70% of the patients have hypertension also related to salt and water retention. Patients who have severe hypertension may have symptoms of headache, drowsiness, vomiting, personality and visual changes, and convulsions. Anorexia and pain in the abdomen

or flank are common, although palpation of the abdomen usually does not reveal significant findings. Costovertebral angle tenderness often is present. Although a history of preceding skin or pharyngeal infection supports the diagnosis, such a history cannot be elicited in many cases.

### Laboratory Findings

The urine of children with APSGN usually is tea colored and opaque. The specific gravity is generally increased, and hemoglobin can be detected by dipstick testing. Proteinuria usually parallels the degree of hematuria and rarely reaches the nephrotic range ( $>40$  mg/m<sup>2</sup>/hour or  $>3.5$  g/day in older children and adults). Microscopic examination usually reveals red and white blood cells and granular or cellular casts. Because identifiable erythrocyte casts and dysmorphic erythrocytes may or may not be present, serial urine specimens may need to be examined.

Serum complement levels show a reduction of C3 in 80% of patients with APSGN and, very early in the course, a reduction of C4 in 50%. The erythrocyte sedimentation rate (ESR) is usually elevated. With severe oliguria, azotemia and acidosis may be seen. The plasma volume is usually expanded, causing a decline in serum protein, hemoglobin, and hematocrit levels by dilution. Hemolysis, a shortened erythrocyte half-life, and reduced erythrocyte production may contribute to these hematologic changes. Salt retention with a decreased fractional excretion of sodium is often seen even in the setting of increased intravascular volume.

Evidence of a preceding streptococcal infection can be important to support the diagnosis. The antistreptolysin O titer is elevated in 80% of patients, but increases in titer are less common in patients who have skin infection and in those who receive early treatment with antibiotics. When other streptococcal antibodies (antihyaluronidase, anti-deoxyribonuclease B) are measured, 80% to 90% of patients will have serologic evidence of preceding streptococcal infection. Cultures often are negative for GABHS by the time nephritis develops, particularly if antibiotics were prescribed.

The chest radiograph in patients who have significant fluid retention and hypertension may reveal a large heart with prominent pulmonary vasculature, pulmonary edema, or, in rare cases, pleural effusions. Ultrasound examination is nonspecific, usually revealing bilaterally enlarged echogenic kidneys.

### Course

The acute phase of APSGN will usually resolve after 1 week, heralded by diuresis. Creatinine levels should normalize by 3 to 4 weeks. Gross hematuria resolves within 1 to 3 weeks, although microscopic hematuria may persist for more than 1 year. Proteinuria generally resolves by 3 months but can last more than 1 year. Complement levels should normalize by 8 weeks. The presence of nephrotic-range proteinuria or extensive crescents by biopsy portends a poor prognosis. The failure of complement levels to normalize by 6 to 8 weeks suggests the presence of a form of nephritis other than APSGN, such as membranoproliferative

glomerulonephritis, the nephritis of chronic infection, or lupus nephritis.

### Treatment

Except for rapidly progressive glomerulonephritis (RPGN), which is discussed later, acute poststreptococcal glomerulonephritis most often resolves spontaneously and is not affected by corticosteroids or immunosuppressive agents. Even so, the pediatrician must be aggressive in treating hypertension, electrolyte derangements, uremia, oliguria, and the resulting vascular overload, pulmonary edema, and encephalopathy that may occur in the acute phase of the illness because these can be associated with significant morbidity and mortality.

Although mild hypertension may resolve spontaneously, more severe degrees of hypertension should be controlled with antihypertensive agents that act quickly. Because increased intravascular volume is theorized to be the main determinant of hypertension in acute glomerulonephritis, diuretics are a mainstay of therapy. Control of severe hypertension will often require the use of intravenous sodium nitroprusside, labetalol, nicardipine, or fenoldopam. Oral minoxidil may be effective. Slower acting, less potent antihypertensive drugs are not good initial choices but can be substituted after blood pressure has been acutely stabilized.

Oliguria results from decreased glomerular filtration and salt and water retention. In the absence of evidence of dehydration, administration of fluid boluses will not hasten the resolution of oliguria, and excessive fluid administration will worsen hypertension and fluid overload. The signs of congestive heart failure usually resolve with control of hypertension. Occasionally a patient develops acute kidney injury (AKI) severe enough to require dialysis.

A 10-day course of antibiotics is usually given to eradicate any remaining GABHS and thus prevent the spread of the organism to others. Treatment does not seem to affect the course of nephritis in the patient. Close contacts should be screened for streptococcal infection and treated if present.

Hospitalization for patients who have this disease needs to be determined individually (see When to Admit). Although many children who have mild episodes do well as outpatients, the sudden development of hypertension and oliguria may produce life-threatening symptoms quite rapidly, necessitating hospitalization. After the acute phase the child may be allowed to resume normal activities gradually. Every child should be monitored regularly until the hypertension, electrolyte and creatinine abnormalities, and serum complement values return to normal. To be certain of the diagnosis, a renal biopsy may be indicated for a child whose clinical or laboratory findings are atypical. Any child whose C3 value does not return to normal within 12 weeks should be considered for kidney biopsy.

### Prognosis

Studies have shown that more than 95% of children who have APSGN recover from their illness. Occasionally, patients who have severe involvement, as evidenced by nephrotic-range proteinuria or the presence



of extensive glomerular crescents on biopsy, may have residual damage or even progress to end-stage renal failure. About 7% of children with APSGN have persistent proteinuria, 5% hematuria, 3% hypertension, and 0.9% azotemia. Adults with APSGN tend to fare worse. For most children the critical period is early in the illness when potentially fatal hypertension or fluid overload presents a danger. In general, however, the kidneys have an outstanding recovery potential in this disease. Recurrences of APSGN are rare.

### Postinfectious (Nonstreptococcal) Glomerulonephritis

A variety of bacteria other than streptococci, including fungi, viruses, and parasites, have been associated with acute glomerulonephritis that is not caused by active renal infection. In children, significant renal involvement is unusual in infections caused by common viruses, and those who do have such involvement have no serologic evidence of recent streptococcal infection. In most cases the acute nephritis resolves spontaneously and gradually, and renal function returns completely. However, some infectious agents such as *Staphylococcus aureus*, *Mycoplasma* species, and Gram-negative bacilli can be associated with crescent formation and rapid deterioration of renal function. Treatment of the underlying infection often leads to remission of the nephritis in those with milder renal involvement.

### Henoch-Schönlein Purpura Nephritis

Henoch-Schönlein purpura (HSP) is a small-vessel vasculitis most often affecting children, with a peak incidence between 4 and 6 years of age. It is characterized by palpable purpuric lesions, arthritis, abdominal pain and gastrointestinal bleeding, and nephritis. Not all manifestations need be present at the same time. Renal involvement is the most significant complication of HSP. Its presentation can vary considerably from minimal abnormalities on urinalysis to an aggressive, rapidly progressive glomerulonephritis with nephrotic syndrome and renal failure. The true incidence of renal involvement in HSP is difficult to ascertain and has been reported to range from 20% to 90%, depending on the definition of renal involvement used and whether the report is from a referral center or not. (See Chapter 264, Henoch-Schönlein Purpura.) Most children with HSP have mild renal involvement and experience recovery within 3 to 6 months.

### Rapidly Progressive Glomerulonephritis

RPGN is a variant of acute glomerulonephritis characterized by symptoms of acute nephritis associated with relentless progression to renal failure over weeks or months. Although acute interstitial nephritis stemming from pyelonephritis or hypersensitivity to certain drugs may develop in this way, most cases are the result of glomerular disease. Almost any of the acute or chronic glomerulonephritides may at times exhibit a rapidly progressive course. This group includes rare cases of poststreptococcal glomerulonephritis, indicating the need to monitor renal function and the general clinical course closely

### BOX 294-3 Classification of Acute Glomerulonephritis With Rapidly Progressive Renal Failure

#### IMMUNE COMPLEX

- Postinfectious reaction
  - Streptococcal infection
  - Visceral abscess
  - Other
- Collagen-vascular disease
  - Systemic lupus erythematosus
  - Henoch-Schönlein purpura
  - Mixed cryoglobulinemia
- Primary renal disease
  - IgA nephropathy
  - Membranoproliferative glomerulonephritis
  - Unknown cases (ie, idiopathic)

#### NO IMMUNE DEPOSIT

- Unknown cause
- Vasculitis
  - Microscopic polyangiitis
  - Wegener granulomatosis
  - Hypersensitivity vasculitides
- Hemolytic-uremic syndrome

#### ANTI-GLOMERULAR BASEMENT MEMBRANE ANTIBODY

- With lung hemorrhage (Goodpasture syndrome)
- Without lung hemorrhage
- Complicating membranous nephropathy

Modified from Couser WG. Rapidly progressive glomerulonephritis: classification, pathogenetic mechanisms, and therapy. *Am J Kidney Dis.* 1988;11(6):449-464. Copyright © 1988, Elsevier, with permission.

even in seemingly routine cases. As shown in Box 294-3, RPGN can be classified into 3 categories based on immunopathologic findings as seen in kidney biopsies.

Systemic lupus erythematosus (SLE) not infrequently may result in an acute glomerulonephritis with a rapidly deteriorating course. Of the primary renal disease group, immunoglobulin A (IgA) nephropathy and membranoproliferative glomerulonephritis may result in this presentation as well.

Occasionally, patients who have undiscovered chronic renal failure suffer a sudden deterioration that may be interpreted as acute glomerulonephritis (Box 294-3). Evaluation of these patients often reveals evidence of pre-existing chronic renal failure, such as osteodystrophy or hyperphosphatemia.

Idiopathic RPGN without immune deposits is much less common among children. Etiologies of pauci-immune RPGN include granulomatosis with polyangiitis (formerly Wegener granulomatosis) associated with upper and lower respiratory findings, Churg-Strauss syndrome associated with extravascular granulomas,

hypereosinophilia, asthma and atopic allergies, and microscopic polyangiitis. The presence of antineutrophil cytoplasmic antibodies (ANCAs) in the serum may help distinguish these disorders from each other and from other causes of rapid deterioration of renal function. In particular, antimyeloperoxidase with a perinuclear or P-ANCA pattern of antibody staining is often associated with microscopic polyangiitis, whereas antiproteinase 3 with a cytoplasmic or C-ANCA pattern of antibody staining is often associated with granulomatosis with polyangiitis. Of note, some patients with pauci-immune RPGN test negative for ANCA. Anti-glomerular basement membrane (anti-GBM) antibody-mediated RPGN is even more rare in children.

The hemolytic uremic syndrome (HUS; see Chapter 263, Hemolytic-Uremic Syndrome) is a triad of AKI, hemolytic anemia, and thrombocytopenia, which in children is most frequently related to infection by shigatoxin-producing *Escherichia coli* O157:H7. It is the most common cause of community-acquired AKI in pediatric patients. This entity frequently follows a prodrome of hemorrhagic colitis. Nondiarrheal forms of HUS, including inherited forms leading to abnormal complement regulatory proteins, thrombotic thrombocytopenic purpura, and disseminated intravascular coagulation, are less common but have a poorer prognosis and must be included in the differential diagnosis.

Although the characteristic clinical and laboratory features of a particular RPGN presentation may suggest specific causative factors, a renal biopsy is indicated to make the diagnosis and to determine the extent of the disease.

Treatment of RPGN depends on the particular diagnosis, often determined by kidney biopsy. Methylprednisolone pulses are frequently given initially for fulminant cases of SLE nephritis, membranoproliferative glomerulonephritis, IgA nephropathy, HSP nephritis, granulomatosis with polyangiitis, and polyarteritis nodosa. These pulses are frequently followed by oral or intravenous cyclophosphamide, azathioprine, or methotrexate. Plasmapheresis may be helpful in anti-GBM antibody disease, atypical forms of HUS, thrombotic-thrombocytopenic purpura, and some other resistant forms of RPGN. Typical diarrhea-associated HUS is treated supportively.

## CHRONIC GLOMERULONEPHRITIS

The glomerulonephritides that follow a prolonged, chronic course may be associated with an acute or subacute nephritis or, more insidiously, with only an abnormal urinalysis in an asymptomatic patient. Advanced cases may be discovered during investigation of nonspecific complaints such as anorexia, intermittent vomiting, and malaise that are found to result from undiagnosed chronic renal failure. IgA nephropathy, Alport syndrome, the nephritis of SLE, and membranoproliferative glomerulonephritis commonly follow a chronic course. Non-nephritic causes of chronic kidney failure, such as renal dysplasia and obstructive uropathies with significant unrecognized parenchymal damage, should be considered in the differential diagnosis.

## IgA Nephropathy

IgA nephropathy was first described by Berger and Hinglais in 1969 and has also been called IgA-IgG nephropathy, or Berger disease.

### Etiology

The cause of IgA nephropathy is unknown. Abnormal glycosylation of the hinge region of the IgA antibody molecule has been observed and has been suggested as a possible mechanism of disease. Mesangial IgA deposition and complement activation may play a role in damaging the kidneys. Secondary forms of IgA nephropathy can be seen with inflammatory bowel disease and liver disease.

### Pathologic Features

The sine qua non for the diagnosis of IgA nephropathy is the finding of dominant or codominant IgA staining of the glomerular mesangium by immunofluorescence microscopy. IgG and C3 generally are seen as well. Histologically, a wide variety of glomerular lesions can be seen from essentially normal glomeruli to mesangial hypercellularity with an increase in mesangial matrix or focal segmental proliferative, necrotizing, or sclerosing lesions. IgA nephropathy is difficult to differentiate morphologically from HSP, which has led to speculation that HSP is a form of IgA nephropathy with systemic findings.

### Clinical Presentation

IgA nephropathy typically occurs in the second or third decade of life but can affect all ages. Males are affected more often than females and it seems to occur less frequently in blacks than in whites. Characteristically, children with IgA nephropathy have a sudden onset of painless gross hematuria concomitant with an infection, usually of the respiratory tract, which may be associated with flank pain, although presentation with microscopic hematuria with or without proteinuria seems to be more common in Asia. The gross hematuria usually clears within a few days to a week as the infection resolves. Frequently, gross hematuria recurs with subsequent infections. Microscopic hematuria may persist with or without proteinuria between episodes, or the urine may clear totally. The simultaneous onset of an upper respiratory tract infection with the gross hematuria helps differentiate this disease from APSGN, in which a delay between infection and hematuria is the rule. The absence of a rash, abdominal pain, and arthritis helps differentiate IgA nephropathy from the nephritis of HSP. Approximately 10% of patients with IgA nephropathy may have nephrotic syndrome or AKI at presentation.

### Laboratory Findings

Other than an abnormal urinalysis, laboratory studies at initial presentation and early in the disease, at least in milder cases, are often normal. In particular, hypocomplementemia and serologic evidence of recent streptococcal infection usually are absent. Azotemia, heavy proteinuria, and hypertension, when they do occur, are poor prognostic signs. A renal biopsy may be indicated in patients with renal

insufficiency, nephrotic-range proteinuria, or persistent hematuria and proteinuria to confirm the diagnosis. Evidence of glomerulosclerosis, crescents, or tubulointerstitial fibrosis on biopsy portends a poor prognosis.

### Treatment

Treatment of IgA nephropathy remains controversial. Suggested regimens for patients with poor prognostic indicators include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and long-term, alternate-day prednisone, with or without methylprednisolone pulses. Control of hypertension, as for other renal diseases, is essential.

### Prognosis

Although IgA nephropathy was originally considered to be a benign disorder in children, 10% to 30% of pediatric patients are anticipated to progress to renal failure over the course of several decades. Progression has been related to higher amounts of proteinuria, the presence of hypertension, renal insufficiency at presentation, and the severity of the histologic changes found on the kidney biopsy.

### Thin Basement Membrane Nephropathy

Although not a chronic glomerulonephritis per se, thin basement membrane nephropathy (TBMN; benign familial hematuria) is characterized by persistent hematuria among similarly affected, otherwise healthy family members. As such, it is an important disorder in the differential diagnoses of both IgA nephropathy and Alport syndrome (see previous and following sections) and hypercalciuria. TBMN is a benign condition inherited as a dominant trait. Undoubtedly, many of the early reports included patients who had IgA nephropathy because of the similarities of clinical presentation and because renal biopsy specimens often were not obtained. This condition has also been called *benign recurrent hematuria*.

### Etiology

Mutations in the type IV collagen  $\alpha$ -3 and  $\alpha$ -4 genes have been associated with 40% of TBMN cases. It is unclear whether certain mutations of the type IV collagen  $\alpha$ -5 gene, the cause of most cases of Alport syndrome (discussed in detail later in this chapter), may also give rise to some TBMN cases. The cause of benign familial hematuria thus seems to be heterogeneous.

### Pathologic Features

Light and fluorescence microscopy of renal biopsy specimens are generally normal. Widespread thinning of the GBM is visible by electron microscopy. These pathologic findings may be similar to those seen early in the course of X-linked Alport syndrome in some women. Only the family history lacking progressive renal impairment, deafness, and eye findings distinguishes TBMN from early Alport syndrome.

### Clinical Presentation

Persistent asymptomatic microscopic hematuria in the absence of hearing loss, eye findings, proteinuria, or

progressive renal impairment is the usual presentation. Proteinuria is generally absent, especially in children, but may be present in some adults. Macroscopic hematuria may occur in up to 22% of patients.

### Laboratory Findings

All laboratory test results are usually normal except for the urinalysis, which shows dysmorphic-appearing red blood cells. Demonstrating the presence of hematuria in otherwise asymptomatic family members suggests this diagnosis.

### Course

Most cases are discovered by finding microscopic hematuria on urinalysis during a routine evaluation. The presentation of TBMN may be similar to IgA nephropathy. It was found to be the cause of isolated asymptomatic microscopic hematuria in approximately one-third of adults, whereas IgA nephropathy was responsible for another third of the cases. The hematuria is persistent, but renal failure, deafness, and eye findings do not develop, in contrast to Alport syndrome. No treatment is indicated for TBMN, and the prognosis is generally excellent.

### Alport Syndrome

Alport syndrome, or hereditary nephritis, is an inherited renal disease associated with sensorineural deafness and ocular abnormalities. Alport syndrome is inherited as an X-linked-dominant trait in 80% to 85% of cases. Families with Alport syndrome with autosomal-recessive inheritance (15% of cases) or, very rarely, autosomal-dominant inheritance have also been described. The combination of Alport features and macrothrombocytopenia is known as *Epstein syndrome*. Rarely, X-linked Alport syndrome can also be associated with leiomyomatosis.

### Etiology

X-linked Alport syndrome is caused by a mutation of the gene encoding the  $\alpha$ -5 chain of type IV collagen. Mutations range from point mutations, leading to an amino acid substitution or a premature stop codon, to small or large deletions. The particular type of mutation may influence the severity of the clinical expression of the disease. About 10% to 15% of cases represent new mutations. X-linked Alport syndrome with leiomyomatosis seems to arise from deletions involving the contiguous genes encoding the  $\alpha$ -5 and  $\alpha$ -6 chains of type IV collagen. Autosomal-recessive Alport syndrome has been related to mutations in the genes encoding the  $\alpha$ -3 and  $\alpha$ -4 chains of type IV collagen on chromosome 2. Autosomal-dominant Alport syndrome also has been linked to the region of chromosome 2 containing the genes encoding the  $\alpha$ -3 and  $\alpha$ -4 chains of type IV collagen.

### Pathologic Features

The characteristic findings of Alport syndrome are seen by electron microscopy of renal biopsy specimen. These findings include variations in the thickness of the GBM, with splitting and lamellation of the lamina densa of the GBM, giving it a basket-weave appearance. However, early in the course of the disease the



only ultrastructural abnormality may be diffuse attenuation of the GBM. Thus, in these cases, distinguishing patients with Alport syndrome from those with TBMN may be difficult based on biopsy findings alone. In these indeterminate cases, special stains for the individual type IV collagen chains may prove of value for making the correct diagnosis.

### **Clinical Presentation**

Renal disease is severe and progressive in male patients with X-linked Alport syndrome, with approximately 90% developing end-stage renal failure by age 40 years. Female patients are generally less severely affected, with approximately 12% reaching end-stage renal failure by age 40 years and 30% by age 60 years. Age at the development of renal failure tends to run true within families, although exceptions are well documented. Persistent microscopic hematuria is found early in all affected male patients. Most female patients have intermittent microscopic hematuria. Macroscopic hematuria occurs in up to 70% of male patients and 33% of female patients, often at the time of a respiratory infection. Proteinuria develops in male patients with age and reaches nephrotic range in approximately 30%. Sensorineural hearing loss is progressive, starting with high frequencies, and affects male patients more than female patients. It is not, however, present in all families with Alport syndrome. Eye abnormalities are found in approximately 50% of patients with Alport syndrome. These abnormalities include anterior lenticonus, retinal abnormalities, and corneal ulcerations.

Male and female patients are equally affected in autosomal-recessive Alport syndrome. The course is similar to that of male patients with X-linked Alport syndrome. Approximately two-thirds of patients with the autosomal-recessive form develop hearing loss. Approximately one-half of the carriers of the abnormal gene also have microscopic hematuria (see this chapter's discussion of TBMN).

### **Laboratory Findings**

Laboratory findings reflect the degree of renal impairment and may vary from normal early in the disease to advanced renal failure as the disease progresses. Blood urea nitrogen and creatinine levels become elevated with advancing disease. Serum electrolytes may become abnormal, and hypoalbuminemia may develop in select patients who develop nephrotic syndrome. Serum complement values usually are normal. A renal biopsy may help establish the diagnosis in patients in whom the family history is unclear or in those who have a new mutation.

### **Course**

The disease is progressive in male patients and some female patients with X-linked Alport syndrome, and in patients of both sexes with autosomal-recessive and autosomal-dominant forms of Alport syndrome. Proteinuria is not present initially but usually develops later in the course of the disease. Hearing loss is not present at birth. The course is usually similar for members of an affected family, although variations in the progression have been reported.

### **Treatment**

Treatment is supportive, with medical management of hypertension and the complications of renal insufficiency. Dialysis or transplantation is instituted when medical management is no longer sufficient. Audiologic screening can identify hearing impairment early and allow for the timely implementation of hearing augmentation services. Some studies have shown short-term efficacy of cyclosporine, angiotensin-converting enzyme inhibitors, or receptor blockers to control proteinuria in Alport syndrome, although the impact on renal survival with these therapies remains unclear.

### **Prognosis**

In affected individuals, renal disease and hearing loss are progressive. Families carrying mutations consisting of large deletions or stop codons leading to truncated proteins may be at risk for more severe disease than those with mutations leading to an amino acid substitution. Dialysis and transplantation are offered when end-stage renal failure occurs. About 15% of patients with Alport syndrome receiving a kidney transplant develop anti-GBM antibodies (to previously absent collagen subunits), leading to loss of the transplanted kidney in 3% of these cases.

### **Nephritis of Systemic Lupus Erythematosus**

SLE is an autoimmune disease that affects multiple organ systems and is seen mainly in young women during the childbearing years. Twenty percent of cases, however, involve children. (See Chapter 324, Rheumatologic Diseases, for a full discussion.)

### **Etiology**

The cause of SLE is unknown. Dysregulation of the cellular and humoral branches of the immune system occurs and results in an autoimmune state, with autoantibody production and the deposition of circulating immune complexes or the formation of immune complexes in situ. Complement proteins are activated and lead to damage to the glomeruli. Clearly, however, other factors are involved in disease production as well. Female sex predisposes the patient to the development of SLE. There also seems to be a genetic predisposition, with increased evidence of autoimmune phenomena within these families. Blacks and Asians seem to be disproportionately affected. Some cases are related to inherited deficiencies of early components of the complement cascade.

### **Pathologic Features**

Renal histologic findings vary greatly in patients with lupus nephritis. The revised classification system of renal disease in lupus nephritis by the International Society of Nephrology and the Renal Pathology Society is now widely used for interpreting the renal biopsy findings and guiding therapy in this disease. There are 6 classes of disease. It is important to remember that the renal histology may change over the course of disease. Patients may exhibit resolution, progression, and even change in histology. Classes I and II represent mild disease. Focal proliferative (class III)



and diffuse proliferative (class IV) lesions indicate more severe disease and are found in the kidney biopsies of more than one-half the children with lupus nephritis. Class V lupus nephritis, also called *membranous nephritis*, shares many features with idiopathic membranous nephropathy and portends a guarded prognosis. Depending on the class of lupus nephritis, the physician may observe various degrees and combinations of histologic abnormalities. Immunofluorescence microscopy demonstrates deposition of immunoglobulins and complement components in the mesangium and along the capillary loops. Dense deposits, corresponding to the immune complexes detected by immunofluorescence, are seen by electron microscopy. Cellular proliferation and basement membrane thickening are also seen.

### Clinical Presentation

Children with SLE may present with multisystem symptoms, including fever, neuropsychiatric manifestations (eg, malaise, emotional lability), malar erythema, photosensitivity, Raynaud symptoms, myositis, multiple joint arthritis, pericarditis, or pleuritis. Initial complaints may be vague, and a high index of suspicion is warranted. However, childhood SLE tends to be more severe at presentation than adult-onset SLE. Up to 75% of children will have some evidence of renal involvement on presentation. Renal involvement usually progresses with time in most children with SLE and is an important cause of morbidity and mortality. When present, renal involvement may be characterized by isolated hematuria, hematuria with proteinuria, nephrotic syndrome, hypertension, or rapidly progressive renal failure.

### Laboratory Findings

Antinuclear antibodies (ANAs) are positive in most children with SLE. Anti-dsDNA is positive in many patients with renal involvement as well. Serum complement components are frequently decreased, and similar to ANA and anti-dsDNA, these levels tend to correlate with general disease activity. However, renal progression may not correlate with changes in any of these serologic markers. Evidence of renal disease may be characterized by elevation of serum urea and creatinine levels and decrease in serum albumin levels, the latter in the setting of nephrotic-range proteinuria. Findings on urinalysis vary greatly and range from isolated hematuria to hematuria with proteinuria, to nephrotic-range proteinuria. Pyuria is common and reflects the underlying glomerular inflammation. Red blood cell, white blood cell, and renal tubular epithelial cell casts frequently are seen.

Hematologic abnormalities include Coombs-positive anemia, leukopenia, and thrombocytopenia. Antiphospholipid antibodies are found in as many as 67% of children with SLE and are a risk factor for thrombotic complications.

### Course

The course of SLE varies considerably. Renal manifestations can wax and wane with changes in disease activity, intercurrent illness, and type of therapy. In addition to the risk for morbidity and mortality from

the underlying disease, children with SLE are at risk for complications related to treatment and are at increased risk for infectious complications.

### Treatment

Treatment of lupus nephritis should be tailored according to clinical and pathologic manifestations. A renal biopsy should be performed in any patient with persistent hematuria or significant proteinuria and before therapy is begun. Treatment is divided into induction and maintenance phases. High-dose corticosteroid therapy has been the mainstay of treatment of lupus nephritis, although it is accompanied by considerable morbidity. Pulse methylprednisolone is used for the initial treatment of rapidly progressive lupus glomerulonephritis. Oral or pulse-intravenous cyclophosphamide frequently is recommended for the treatment of class III, class IV, and sometimes class V renal disease. Mycophenolate mofetil has shown promise as a remission-inducing agent substituting for cyclophosphamide, thus preventing the significant side effects, particularly its effects on fertility. This circumstance is especially important for young women of childbearing age, given the prevalence of SLE in this population, although the risk for infertility is higher in males and with oral cyclophosphamide therapy. Azathioprine and mycophenolate mofetil have been used as steroid-sparing agents in the maintenance of treatment. Cyclosporine and tacrolimus have been used to induce remission and in maintaining remission, although there is a high risk for relapse on discontinuation of these agents. B-cell depletion with rituximab and plasma exchange are used in severe and refractory patients. Hydroxychloroquine is used for management of extrarenal manifestations of lupus as well as to maintain remissions. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should be used to control hypertension and decrease proteinuria. Anticoagulation is indicated in children with thrombotic complications of lupus.

The danger of overwhelming sepsis among these immunosuppressed patients is constant. The effectiveness of therapy is indicated by changes in serologic parameters, blood chemistries, urinary protein quantitation, and complement levels. Care of the patient who has SLE is a highly specialized endeavor that requires knowledge of current treatment modalities, the availability of highly specialized tests, and the necessary resources to care for a patient who has a chronic, severe, life-threatening illness for which treatment with steroids often is disfiguring. These patients are managed best by a team trained in dealing with all aspects of this disease.

### Prognosis

Overall survival of children with SLE seems to have improved over the past several decades, with survival rates up to 95% to 100% at 5 years and 94% at 11 years. However, end-stage renal disease developed in 9% at 11 years of follow-up. Patients with diffuse proliferative lesions on biopsy have the poorest renal outcome. In addition, sclerosis on biopsy specimens, hypocomplementemia, decreased renal function, nephrotic

range proteinuria, and persistent hypertension portend a poor renal prognosis.

### Membranoproliferative Glomerulonephritis

The group of disorders classified as membranoproliferative glomerulonephritis (MPGN) have been reconsidered based on reinterpretation of findings seen by immunofluorescence microscopy (IFM) and as new information about the likely pathogenesis of these diseases has been elucidated. A new classification has been proposed that now refers to idiopathic MPGN (those immune complex-mediated diseases, formerly MPGN types I and III, with immunoglobulin present by IFM) and the C3 glomerulopathies, which include dense deposit disease (DDD, formerly MPGN type II) and C3 glomerulonephritis (C3GN, formerly MPGN types I and III, but lacking immunoglobulin staining by IFM). All are chronic inflammatory diseases of the kidney with a poor prognosis.

### Etiology

Based on new understanding regarding factors likely involved in the pathogenesis of MPGN and the C3 glomerulopathies, DDD and C3GN, it has been proposed that these disorders now be classified based on whether the classical or alternative pathways of complement are activated. The finding of both immunoglobulin and complement fragments in glomeruli by IFM suggests that immune complexes activate the classical pathway of complement and cause glomerular inflammation, resulting in the histopathologic pattern of MPGN type I or III. MPGN type I can be idiopathic or secondary to systemic disorders or infectious agents. Among the infectious agents, hepatitis C viral infection is an important cause worldwide. In children, however, the idiopathic form is more common.

In contrast, unregulated activation of the alternative pathway of complement seems to be important in the pathogenesis of the C3 glomerulopathies (C3GN and DDD). Indeed, in many cases of the C3 glomerulopathies, deactivating mutations have been identified in the complement regulatory proteins—factor H, factor I, factor H-related protein 5, and membrane cofactor protein—that normally keep complement-mediated inflammation in check, as well as mutations in complement factors C3 and B, causing them to be resistant to inactivation by the complement regulatory factors. In addition, C3 nephritic factors, autoantibodies directed against and stabilizing the alternative pathway of complement convertases (protein complexes that further activate the complement system) may be present and render the convertases resistant to the regulatory activity of factor H. These abnormalities are expected to lead to ongoing unregulated activation of the alternative pathway of complement, resulting in deposition of complement components without immunoglobulin in the glomeruli, with resulting inflammatory injury.

Depending on the pattern of these deposits shown by electron microscopy, the diagnosis of DDD (deposits in the mesangium and within the glomerular basement membrane) or C3 glomerulonephritis (mesangial, subendothelial, subepithelial, with or without intramembranous deposits) is made.

### Pathologic Features

Classically, 3 types of MPGN have been described based on pathologic appearance and ultrastructural abnormalities of the GBM. MPGN types I, II (DDD), and III patterns account for 44%, 20%, and 36% of cases, respectively. All 3 types have increased mesangial cellularity and matrix with thickening of glomerular capillary walls, duplication of glomerular basement membranes, and deposits within or around the GBM. All show deposition of complement components in the glomeruli as seen by IFM. As mentioned earlier, complement deposition without immunoglobulin staining by IFM allows C3GN to be distinguished from MPGN types I and III. By electron microscopy, type I and C3GN are characterized by subendothelial and mesangial electron-dense deposits. DDD, formerly MPGN type II, has a more variable presentation by pathology, with only 25% of kidney biopsy specimens demonstrating a typical MPGN morphology, others being mesangial, endocapillary, and crescentic glomerulonephritis. All forms of DDD have thickening and deposits within the GBM. In MPGN type III and C3GN with this pathologic pattern, deposits are present most prominently in the subepithelial space but also are observed on the subendothelial side of the GBM, as well as within the GBM.

### Clinical Presentation

The type I pathologic pattern is the most common of the 3. The average age of onset of primary MPGN in children is 10 years. Children with MPGN can present with asymptomatic hematuria and proteinuria detected on routine screening urinalysis, gross hematuria, nephritis, or nephrotic syndrome. Hypertension and decreased renal function may be present, although the presentation may vary according to the histologic subtype.

Patients with acquired partial lipodystrophy often have circulating nephritic factors and low C3 blood levels. Twenty percent develop DDD.

### Laboratory Findings

At presentation, blood urea nitrogen and creatinine values may be elevated, and albumin may be low in severe cases. Anemia is common. Electrolyte disturbances reflect the presence of renal insufficiency. The serum C3 level is depressed in 67% to 75% of patients on presentation. The serum C4 level is also often low in MPGN type I. Nephritic factors are found in 80% of patients with DDD and in up to 50% with C3GN. Liver function studies may be abnormal in cases related to viral hepatitis. Evidence of hepatitis B virus, hepatitis C virus, and HIV infection should be sought. Cryoglobulins may be elevated in cases of hepatitis C infection. Urinalysis most commonly features hematuria and proteinuria. Proteinuria may reach the nephrotic range. Blood lipid levels are often elevated in the presence of heavy proteinuria. Hematuria may be macroscopic. Cellular casts are a common finding. Quantification of urinary protein excretion is helpful for monitoring the course of the disease and can be achieved by 24-hour urine collection or by following the total protein and creatinine levels on spot urine samples. Definitive diagnosis of

MPGN or the C3 glomerulopathies can only be made by kidney biopsy.

### Course and Prognosis

The long-term outcome of MPGN is typically poor, with progressive loss of renal function. Fifty percent of patients reach end-stage renal failure within about 11 years of diagnosis, and 90% do so within 20 years. Clinically, nephrotic-range proteinuria, renal insufficiency, and hypertension predict progression of disease. On renal biopsy, necrosis, sclerosis, and tubulointerstitial fibrosis are poor prognostic indicators. Type I MPGN has a better prognosis than the other 2 types. Progression of secondary forms of MPGN type I may be halted if the underlying cause can be addressed. Outcome data on the subset of patients with C3GN are not yet available. There is a high risk for recurrence after renal transplantation.

Over time, patients with DDD may develop retinal deposits (drusen) seen on ophthalmologic examination. Visual impairment can develop in 10% of patients.

### Treatment

The goal of treatment is to induce a reduction in proteinuria and inflammation and control hypertension. However, treatment is challenging, and the optimal therapy is controversial because rigorous randomized controlled trials are lacking. Therapy with blockers of the renin-angiotensin-aldosterone system with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers to reduce proteinuria and control hypertension should be strongly considered. In children, the most experience reported regarding immunosuppressive treatment of this disorder has been with high-dose, long-term, alternate-day prednisone therapy. Cumulative renal survival of 82% at 10 years and 56% at 20 years have been reported with this therapeutic approach. Some differences in the clinical course and response to treatment may be seen according to the type of MPGN. Other therapies that have shown promise in small groups of patients include cyclophosphamide, mycophenolate mofetil, and calcineurin inhibition with cyclosporine or tacrolimus. These agents have generally been used in combination with corticosteroids. Plasma exchange may be considered in children with documented deficiency of the regulatory protein complement factor H. Anticomplement factor 5 therapy with eculizumab has shown some promise in improving outcomes in some patients with C3 glomerulopathy in small trials.

## INTERSTITIAL NEPHRITIS

Inflammation of the tubules and interstitium of the kidney is an underappreciated cause of AKI. Acute tubulointerstitial nephritis (AIN) has been found in up to 25% of kidney biopsies performed for AKI in adults. The most common presenting signs are unexplained AKI, proteinuria, leukocyturia, and microscopic hematuria. Fever and eosinophilia are seen in only about one-third of patients, and rash in 20%. Although the definitive etiologic agent is often elusive, AIN is most commonly linked to an immune

reaction to drugs, especially antibiotics and nonsteroidal anti-inflammatory drugs. Less common triggers are bacterial, viral, or parasitic infections or systemic autoimmune disorders such as SLE. Idiopathic forms of AIN are associated with anti-tubular basement membrane autoantibodies. Uveitis can be seen with idiopathic AIN and may precede, occur simultaneously with, or follow the onset of renal disease. Prompt ophthalmologic evaluation and treatment are important to preserve vision. Kidney biopsy is needed to confirm the diagnosis of AIN. Interstitial edema with patchy or diffuse cellular infiltrates composed of T lymphocytes, macrophages, eosinophils, and plasma cells are seen on pathologic specimens. Glomeruli are generally normal appearing in AIN, although interstitial inflammation may be seen with primary glomerular diseases, in which case its presence portends a worse prognosis. Irreversible interstitial fibrosis is seen in more severe cases of AIN and may develop within 1 week of disease onset. Treatment consists of eliminating the inciting agent if it can be identified. The role of corticosteroids in the management of AIN is controversial, although some studies suggest that early treatment may shorten the disease process, and in some cases early treatment may improve long-term outcome.

### WHEN TO REFER

- Acute glomerulonephritis with significant complications
- Acute glomerulonephritis that is not following a typical course expected of poststreptococcal glomerulonephritis
- Failure of complement level to normalize within 6 to 8 weeks in suspected acute glomerulonephritis
- Rapidly progressive course
- Glomerulonephritis with the development of nephrotic syndrome
- Persistent hematuria and proteinuria
- Persistent hypertension
- Elevated creatinine level for age
- Family history of renal failure or deafness
- Any chronic glomerulonephritis

### WHEN TO ADMIT

- Severe hypertension
- Renal failure with significant electrolyte disturbances
- Congestive heart failure from volume overload
- Oliguria or anuria
- Rapidly progressive renal failure

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Glomerulonephritis* (fact sheet), MedLine Plus ([www.nlm.nih.gov/medlineplus/ency/article/000484.htm](http://www.nlm.nih.gov/medlineplus/ency/article/000484.htm))
- *Patient & Family Resources* (Web page), National Kidney Foundation ([www.kidney.org/patients/resources](http://www.kidney.org/patients/resources))



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**Chapter 295****NEPHROTIC SYNDROME**

William S. Varade, MD

Nephrotic syndrome (NS) is defined by the clinical findings of heavy proteinuria, hypoalbuminemia, edema (often to the point of frank anasarca), and hyperlipidemia. Many causes of NS exist, and the most likely cause varies by age. NS may be the result of an underlying systemic disease, or it may manifest as a primary idiopathic renal disorder. Examples of causes of primary and secondary NS in children are listed in Box 295-1. The overall outcome depends on the etiology, and ranges from complete remission

**BOX 295-1 Examples of Primary and Secondary Causes of Nephrotic Syndrome in Children**
**PRIMARY NEPHROTIC SYNDROME**

- Minimal change nephrotic syndrome
- Focal segmental glomerulosclerosis
- Diffuse mesangial hypercellularity
- Membranoproliferative glomerulonephritis
- Membranous nephropathy

**SECONDARY NEPHROTIC SYNDROME**

- Inherited diseases (congenital nephrotic syndrome, diffuse mesangial sclerosis, Alport syndrome, nail-patella syndrome, Lowe syndrome)
- Vasculitides (lupus nephritis, Henoch-Schönlein purpura nephritis, Wegener granulomatosis, Goodpasture syndrome)
- Postinfectious (poststreptococcal, HIV, hepatitis B and C, malaria, syphilis, intrauterine infections, other viruses and bacteria)
- Drugs and toxins (nonsteroidal anti-inflammatory drugs, gold)
- Diabetes mellitus (rare in children)

with no long-term sequelae to inexorable progression to end-stage renal failure. Newer treatments offer alternatives for patients with resistant forms of NS or who experience significant side effects from first-line treatments, although such treatments themselves carry the potential for significant morbidity.

**EPIDEMIOLOGIC FEATURES**

The annual incidence and prevalence of idiopathic NS in children are estimated to be 2 and 16 cases per 100,000 children, respectively. The incidence is 10-fold lower in adults. The male-to-female ratio is reported to be 2:1 for children and 1:1 in adolescents and adults. Early studies in the 1960s and 1970s showed that in children with NS from 3 months to 16 years of age, 76% had minimal change nephrotic syndrome (MCNS), 7% had focal segmental glomerulosclerosis (FSGS), 2% to 5% had diffuse mesangial hypercellularity or mesangial proliferation, and 7% had membranoproliferative glomerulonephritis (MPGN). Only 1% of children had membranous nephropathy, which is in contrast to adults with NS, in whom 22% had MCNS, 12% had FSGS, 20% had membranous nephropathy, and 25% had proliferative lesions.

Occurrence of MCNS peaks between 2 and 5 years of age. Eighty-seven percent of children with NS between the ages of 3 months and 6 years have MCNS, and 92% of these will experience remission of their disease when treated with a course of prednisone. However, subsequent studies have suggested a higher incidence of FSGS in children and adults more recently, with FSGS accounting for up to 25% of diagnoses in children who undergo biopsy for NS, although others dispute this. Adolescents are more likely to have a more aggressive cause, such as FSGS, MPGN, or membranous nephropathy, than younger children.

Racial differences are seen in the incidence of underlying histopathologic disorders and prognosis in nephrotic patients. Black and Hispanic adolescents are more likely than white adolescents to have FSGS and to progress to end-stage renal disease. In a predominantly black and Hispanic population of adolescents with NS, 55% had FSGS, 20% had MCNS, and 7% had MPGN.

**EVALUATION****Clinical Presentation**

Typically, children with NS (Figure 295-1) gradually develop edema and an inappropriate weight gain, although cases associated with glomerulonephritis may have a more acute onset, with signs and symptoms of nephritis predominating. The presence of periorbital edema when arising in the morning that resolves during the course of the day is often mistaken for allergy. Clothing may be tight, and socks may leave indentations in the skin of the shins and ankles. The abdomen may be distended, and a fluid wave may be discernible on examination. Breath sounds may be decreased at the lung bases because of accumulation of pleural fluid. Although intravascular volume is low in most children with NS, in



some children, it may be increased. These children may have a gallop on auscultation of the heart, rales over the lung fields, and hepatomegaly. Boys may develop significant scrotal swelling, and girls may develop labial swelling (Figure 295-2). The child or parents may report decreased frequency of urination and the passage of dark, amber-colored, concentrated-appearing urine that seems to foam when voided. Overall, 16% of children with NS have hypertension at presentation. The presence of marked hypertension should suggest the possibility of underlying glomerulonephritis.



**Figure 295-1** A 2-year-old girl with nephrotic syndrome.



**Figure 295-2** Severe labial edema in a 3-year-old girl with nephrotic syndrome.

### Laboratory Evaluation

Laboratory evaluation begins with a urinalysis in the child with edema. This evaluation will demonstrate significant proteinuria in cases of NS. Up to approximately 25% of children who have primary NS will also have 3 to 5 red blood cells per high-power field on urinalysis. The presence of significant microscopic hematuria or gross hematuria suggests that NS might be the result of an underlying nephritic process. The presence of glycosuria in untreated children with NS suggests underlying tubular injury that may be seen with FSGS. Blood urea nitrogen and creatinine values are generally normal or only slightly increased in primary NS. Serum albumin level is low. Mild hyponatremia may be present because of water retention. Total calcium levels are low because of the low serum albumin level, but ionized calcium levels are usually normal. The serum cholesterol level is usually increased. The third component of complement (C3) is generally normal. A lowered level suggests MPGN, poststreptococcal glomerulonephritis, or lupus nephritis. Antinuclear antibody should be tested in older children or those with signs suggestive of systemic lupus erythematosus. Since hepatitis B, hepatitis C, and HIV are associated with certain forms of NS, serology should be determined for these viruses. Chest radiographs will usually show a small cardiac silhouette and, in severe cases, the presence of pleural fluid. Cardiomegaly may be seen in patients with increased intravascular volume.

Urinary protein losses can be quantified with a 24-hour urine collection or estimated with a urine protein-to-creatinine ratio on a first morning urine sample. Nephrotic-range proteinuria is defined as (1) urinary protein excretion on a timed urine collection of more than 3.5 g/day in adults or more than 40 mg/m<sup>2</sup>/hour or 1 g/m<sup>2</sup>/day in children, or (2) a urine protein-to-creatinine ratio (mg/mg) of more than 2 on a random urine sample. Urinary protein quantification is not critical in the management of NS, with heavy proteinuria demonstrated by dipstick determination and with a typical clinical presentation. It is more helpful for monitoring partial response to treatment of children with resistant forms of NS.

Kidney biopsy is recommended for older children who are at higher risk for etiologies of NS other than minimal change disease.

For children with steroid-resistant NS the place of genetic testing for mutations of genes encoding proteins involved in podocyte structure and function (*NPHS1*, *NPHS2*, *PLCE1*), as well as the transcription factor Wilms tumor (WT1), may be considered.

### PATHOPHYSIOLOGIC FEATURES

The glomerular capillary wall acts as a selective filtration barrier composed of the glomerular capillary endothelial cell with its covering glycocalyx, the glomerular basement membrane, and the podocytes of the glomerular visceral epithelial cells. Slit diaphragms connect adjacent podocytes. This filtration barrier normally possesses a net negative electrical charge and behaves functionally as though narrow pores are present. All 3 layers of the glomerular basement membrane seem to contribute to these

characteristics, which serve to prevent the passage of proteins into the urine. In NS, these barriers are variably altered, depending on the severity and nature of the underlying disease process. Examples of alterations in the filtration barrier include the loss of negative charge seen in MCNS, the altered organization of glomerular basement membrane components in Alport and Pierson syndromes, or mutations of genes encoding proteins associated with glomerular podocytes, leading to alterations in podocyte structure and function. The changes in the barriers allow the passage of large quantities of plasma proteins into the urine, which, in turn, may lead to a decrease in the level of proteins in the blood.

Classically, the development of edema has been explained by massive losses of plasma proteins, in particular albumin, in the urine, with the consequent development of hypoalbuminemia, which leads to decreased plasma oncotic pressure and leakage of fluid from the vascular space into the interstitium. The subsequent drop in the circulating blood volume stimulates the renin-angiotensin-aldosterone system, leading to avid sodium retention, and it produces a nonosmotic stimulus for vasopressin secretion and free-water reabsorption. The result of these responses is the development of massive tissue edema with the excretion of a decreased volume of concentrated urine. However, this scenario does not explain the edema formation in all nephrotic patients. Studies have demonstrated that, in patients who experience remission, diuresis often begins as the proteinuria is resolving, but before normalization of plasma albumin levels. In addition, primary sodium retention has been demonstrated with the onset of proteinuria (but before the development of hypoproteinemia) in at least some patients experiencing a relapse of NS. This circumstance would then lead to expansion of vascular volume and the development of edema.

## COMPLICATIONS

### Infection

Morbidity and mortality were high in NS before the introduction of corticosteroid and antibiotic therapy. Infection was the leading cause of death in children. Infectious complications include spontaneous bacterial peritonitis, sepsis, cellulitis, and pneumonia. Streptococcal pneumonia and gram-negative bacteria are responsible for most infections in NS. Predisposing factors for the development of bacterial infections include tissue edema that may facilitate the spread of infection, defective opsonization of invading bacteria caused by loss into the urine of small components of the alternative pathway of complement (complement factor B), and impaired cellular immunity. In addition, the effects of immunosuppressive therapies used in the treatment of NS may increase the susceptibility to infection. Children with recurrent NS should receive 23-valent and heptavalent conjugated pneumococcal vaccination. A role for prophylactic antibiotic therapy has not been established.

### Thromboembolism

Thromboembolic events, such as deep vein thrombosis, pulmonary embolism, renal vein thrombosis,

and dural sinus thrombosis, are well-described complications of NS in children. They are reported to occur less frequently in children than in adults, although the documentation of subclinical pulmonary embolism by radionuclide ventilation-perfusion lung scanning in 28% of children suggests that the true incidence may be underreported. Arterial thrombosis occurs more commonly in children than in adults. Risk factors for development of thromboembolism in children with NS include age 12 years or older at diagnosis and higher degrees of urinary protein loss. Children with thromboembolism are more likely to have secondary as opposed to primary forms of NS. Contributory factors include increased plasma levels of procoagulant factors, urinary loss of inhibitors of coagulation, and thrombocytosis. The predisposition to thrombus formation may be exacerbated by decreased intravascular volume, especially in the face of vigorous forced diuresis.

### Hyperlipidemia

Elevation of plasma lipids in NS has classically been said to result from increased hepatic lipoprotein synthesis caused by generalized increased hepatic protein synthesis in response to a lowered plasma albumin level. The mechanism behind the increase in plasma lipids is probably more complex than this and may involve production of inflammatory cytokines, leading to, or at least associated with, alterations in lipid synthesis, catabolism, and recycling. In severe disease with heavy proteinuria, lipoprotein lipase activity may be decreased, leading to decreased lipolysis and resulting in high triglyceride levels. The return of high cholesterol levels to normal at remission of NS often lags behind the normalization of serum albumin levels. In unremitting NS, increased plasma lipids may contribute to cardiovascular morbidity, and treatment of lipid abnormalities should be considered.

## SPECIFIC HISTOPATHOLOGIC ENTITIES ASSOCIATED WITH PRIMARY NEPHROTIC SYNDROME OF CHILDHOOD

### Minimal Change Nephrotic Syndrome

MCNS, also known as *lipoid nephrosis* and *nil* (nothing in light microscopy) *disease*, is the most common pathologic diagnosis in children with NS; 92% will experience remission with a course of corticosteroids. Hematuria is found in approximately 13% and hypertension is found in 10% to 20% of cases. Relapses are common, but the long-term prognosis is excellent. Relapses tend to become less frequent with age, and the disorder usually resolves around the time of puberty without permanent renal impairment. The diagnosis is assumed in most children because biopsy is generally not performed in those who follow a typical course and who respond to corticosteroid therapy. These children should more correctly be considered to have the clinical diagnosis of steroid-responsive idiopathic NS of childhood, which encompasses a variety of histopathologic diagnoses.

Investigators have proposed that MCNS may be an immune-mediated disease. Evidence supporting this theory includes the response of MCNS to immunosuppressive therapy, an association with allergens, an association with lymphomas, the presence of altered T-lymphocyte function, and the description of various circulating factors, immunomodulatory substances, permeability factors, and lymphokines.

The histopathology of MCNS shows minimal abnormalities by light microscopy. Most pathologists allow for a small amount of mesangial hypercellularity within this classification. Immunofluorescence is negative for immunoglobulin and complement. Electron microscopy shows diffuse fusion of the glomerular epithelial cell foot processes.

### Focal Segmental Glomerulosclerosis

FSGS is found as both an idiopathic and a secondary pathologic diagnosis. Secondary forms are thought to represent a final common pathway to glomerular epithelial cell injury, glomerular adaptation to significant nephron loss with glomerular hypertension or hyperfiltration, inherited abnormalities of the glomerular basement membrane, or severe glomerulonephritis. Disease processes that can be associated with FSGS lesions include diabetic nephropathy, sickle cell disease, HIV nephropathy, and glomerulonephritides such as immunoglobulin A (IgA) nephropathy, MPGN, and lupus nephritis.

Children with idiopathic FSGS tend to be older, and blacks are disproportionately affected. The prognosis of FSGS is more guarded; complete remission is achieved in only one-fourth of children treated with corticosteroids. Many are steroid resistant or dependent from the time of initial treatment, or they become steroid resistant over time. Hematuria may be found in 50% or more, and hypertension in approximately 50% of cases. Up to 50% may progress to end-stage renal disease with time, and a subgroup will progress rapidly within 3 years of presentation. FSGS recurs in up to 40% of patients reaching end-stage renal failure who receive a renal transplant.

Primary FSGS may actually be the manifestation of a systemic disorder. Evidence for this view includes the following: (1) the disease may recur in transplanted kidneys, (2) proteinuria could be induced in animals by infusion of serum from a patient with recurrent FSGS, (3) recurrent FSGS in transplanted kidneys may respond to plasmapheresis, and (4) a circulating factor capable of increasing the permeability of isolated glomeruli to albumin has been demonstrated in the serum of some patients with recurrent FSGS.

The histopathology of FSGS is characterized by the presence of scars affecting portions or segments of some, but not all, glomeruli. Mesangial hypercellularity, tubular atrophy, and interstitial fibrosis are often present. Weak mesangial and segmental deposits of C3 and immunoglobulin M (IgM) can be seen by immunofluorescence, but probably represent nonspecific trapping of these proteins. Electron microscopy may show widespread effacement of foot processes and separation of glomerular epithelial cells from the underlying basement membrane. Different variants of

FSGS have been described that may reflect different stages of disease development, pathogenesis, and prognosis.

### Membranoproliferative Glomerulonephritis

MPGN is a chronic inflammatory disease of the kidney with a poor prognosis. It is discussed in more detail in Chapter 294, Nephritis. The average age at onset of primary MPGN is approximately 9 years. Between 50% and 67% of patients develop NS, and some of these patients may not have significant hematuria. The serum C3 level is low in 67% to 75% of patients.

### Membranous Nephropathy

Membranous nephropathy is a chronic glomerular disease that can also be idiopathic or the result of a systemic disorder. Secondary causes have been reported to be more common in children with membranous nephropathy than in adults. Important causes include hepatitis B and hepatitis C infections, certain drugs, systemic lupus erythematosus, malignancies, and bone marrow and renal transplants. It can affect any age group, but is rare in children and adolescents; it is responsible for only approximately 1% of children with NS. At presentation, up to 75% of children with membranous nephropathy have NS, most have microscopic hematuria, and 37% have hypertension. As many as 40% of children develop gross hematuria. Complement protein levels are usually normal. Spontaneous remissions occur in most patients, but remission may not occur for several years after onset. From 18% to 25% of affected children develop chronic kidney disease. Poor prognostic factors include persistent heavy proteinuria, hypertension, elevated serum creatinine, and significant scarring on biopsy.

By light microscopy, membranous lesions are seen as diffuse thickening of the glomerular capillary walls. Capillary lumens are patent, and little mesangial proliferation is found. Silver-stained biopsy specimens show spikes of basement membrane material projecting on the subepithelial side of the glomerular basement membrane. By electron microscopy, glomerular capillary walls are thickened by subepithelial electron-dense deposits and projections (spikes) of the lamina densa. The extent of these projections with relation to the deposits forms the basis for classifying the stages of membranous nephropathy. Immunofluorescence studies show granular deposits of immunoglobulin G (IgG) and the third component of complement along the glomerular basement membrane.

### Genetic Causes of the Nephrotic Syndrome

Mutations of certain genes, especially those intimately associated with glomerular epithelial podocytes or the glomerular basement membrane, have been implicated in the development of hereditary forms of NS.

*Congenital nephrotic syndrome* refers to NS presenting in the first 3 months of life. Pathologically, it may be a Finnish-type congenital NS diffuse mesangial sclerosis, FSGS, minimal change disease, or membranous nephropathy. Secondary forms may



be caused by congenital infections, heavy metal exposure, or genetic syndromes, among other more uncommon associations. Congenital NS of the Finnish type is an autosomal-recessive disorder caused by mutations in the *NPHS1* gene encoding nephrin, a protein found in the slit diaphragms between adjacent podocytes, or the *NPHS2* gene encoding podocin, a podocyte membrane protein. Less common syndromic forms are caused by mutations in the Wilms tumor suppressor gene (*WT1*), the laminin  $\beta_2$  gene, and others.

Infants are often premature and small for gestational age. The placenta is markedly enlarged, and amniotic levels of  $\alpha$ -fetoprotein are high. Edema often becomes evident within days of birth. Prognosis of congenital NS depends on the underlying cause. It is guarded for congenital NS of the Finnish type with significant morbidity and mortality from complications, particularly malnutrition, infection, and thrombotic events caused by the massive protein losses. Treatment is supportive, but must be aggressive, and it may include intensive nutritional support and nephrectomies to stem the protein losses and maintain the patient on dialysis until kidney transplantation can be performed.

*Diffuse mesangial sclerosis* may be isolated or part of Denys-Drash syndrome, consisting of onset of NS before 2 years of age with rapid progression to end-stage kidney failure, male pseudohermaphroditism, and Wilms tumor. The isolated form is most commonly caused by mutations of the *PLCE1* gene, whereas the Denys-Drash syndrome is associated with mutations of the *WT1* gene. Support until kidney transplantation is required for the renal disease while the risk for or actual presence of Wilms tumor is addressed. Mutations in *WT1* may also be seen in patients with Frasier syndrome, consisting of male pseudohermaphroditism and FSGS.

Nephrin and podocin mutations have also been found in steroid-resistant, autosomal-recessive, and sporadic cases of FSGS in infants and older children, with a rapid progression to renal failure. *PLCE1* and *WT1* mutations may also be associated with some cases of sporadic FSGS. Mutations in the *ACTN4* gene encoding  $\alpha$ -actinin, a podocyte protein that associates with actin filaments of the cytoskeleton and slit diaphragms, results in an autosomal-dominant form of FSGS with onset during early childhood and slow progression to renal failure. Variants of the apolipoprotein L1 (*APOL1*) gene have been associated with increased risk for FSGS and progression to end-stage kidney disease in blacks.

## MANAGEMENT

Nephrotic syndrome occurring in the first 2 years of life should be evaluated and managed with a pediatric nephrologist.

Although a great deal of attention has been paid to the underlying pathologic diagnoses in idiopathic NS occurring in childhood, the clinical response to a course of corticosteroids seems to be as informative in determining long-term outcome as the underlying

histopathology. Initially, 85% of children will respond to a trial of prednisone; 94% will have responded by 4 weeks of initiating therapy. Most corticosteroid-responsive patients have MCNS. However, up to 25% of corticosteroid-resistant patients are found by biopsy to have MCNS, while 5% to 10% of the corticosteroid-responsive patients have FSGS. Biopsy findings do not predict which children who have MCNS will be corticosteroid resistant or which children who have FSGS will be corticosteroid responsive. In general, patients who achieve a remission on steroids, whether they have MCNS or FSGS, do not progress to renal failure if they remain responsive to corticosteroid therapy.

Children between the ages of 1 and 6 years are most likely to have MCNS, as determined by renal biopsy, and respond clinically to a trial of corticosteroids by experiencing remission. Therefore, treating a child in this age range (or even up to age 12 years) who has the new onset of typical, pure NS with a trial of corticosteroids is now customary. Treatment of the initial episode of NS consists of prednisone at 2 mg/kg/day or 60 mg/m<sup>2</sup>/day (maximum, 60 mg/day) for 6 weeks usually given in divided doses, although some studies suggest that it can be given as a single morning dose with a similar rate of response. This treatment is followed by a single dose of 1.5 mg/kg or 40 mg/m<sup>2</sup> (maximum 40 mg/day) for an additional 6 weeks given in the morning on alternate days. The most recent recommendations call for discontinuation of treatment at this point without taper. A relapse is diagnosed if the first morning urine tests 2+ or greater for protein by Albustix or the urine protein-to-creatinine ratio is greater than 2 for 3 consecutive days. Relapses are usually triggered by intercurrent illnesses or allergies, and parents can be taught to use albumin test sticks or sulfosalicylic acid at home to monitor urinary protein excretion. Relapses are treated with prednisone 2 mg/kg/day or 60 mg/m<sup>2</sup>/day until the urine is trace or negative for protein for 3 consecutive days. The prednisone dose then is changed to 1.5 mg/kg or 40 mg/m<sup>2</sup> on alternate days for 4 weeks.

Approximately 25% of children who experience relapse will follow a frequently relapsing course, defined as 2 or more relapses occurring within 6 months of completing an initial course of corticosteroids or 4 or more relapses within a 1-year period. Children who experience relapse while corticosteroids are being tapered, or within 2 weeks of completing a course of corticosteroids, are considered to be corticosteroid dependent. Children who have both frequently relapsing and corticosteroid-dependent NS are more likely to develop corticosteroid toxicity. Second-tier therapies for difficult cases are listed in Box 295-2. Consideration for treatment with these agents should be made in consultation with a pediatric nephrologist. Alkylating agents, either cyclophosphamide or chlorambucil, can induce a prolonged remission in patients with frequently relapsing NS, and some patients with corticosteroid-dependent NS, although with a risk for significant toxicity. Mycophenolate mofetil has also shown some success as a corticosteroid-sparing agent. Cyclosporine or tacrolimus can be used as a corticosteroid-sparing



### **BOX 295-2 Secondary, Tertiary, and Complementary Therapies for Difficult Cases of Nephrotic Syndrome**

- Cyclophosphamide
- Chlorambucil
- Cyclosporine
- Tacrolimus
- Methylprednisolone infusions
- Levamisole
- Mycophenolate mofetil
- Intuximab
- Angiotensin-converting enzyme inhibitors
- Angiotensin-receptor blockers

agent, although relapse after withdrawal of these agents is common. Rituximab, an anti-B cell monoclonal antibody, is being increasingly used for highly recalcitrant cases with some success.

Children whose disease fails to respond to the initial or subsequent courses of corticosteroids have corticosteroid-resistant NS and thus a more guarded prognosis. Many of these children will have focal segmental glomerulosclerosis as the cause of their NS. Consultation with a pediatric nephrologist should be made for consideration of a renal biopsy and more aggressive treatment. Similarly, children who are outside the usual age range for typical idiopathic NS of childhood, who have refractory edema, or who have complicated NS should be referred to a pediatric nephrologist for help with establishing the diagnosis and choosing a treatment plan. Current treatment regimens for corticosteroid-resistant NS are given in Box 295-2 and include high-dose, long-term intravenous methylprednisolone, cyclosporine, or tacrolimus. Cytotoxic agents, such as cyclophosphamide, have not been as successful in the setting of corticosteroid resistance as the other therapies noted previously.

Complications of corticosteroid therapy include the development of cushingoid features, cataract formation, glaucoma, gastritis, peptic ulcer disease, pancreatitis, hypokalemia, hypertension, increased risk for infection, behavioral changes, hyperlipidemia, bone disease, and growth delay if treatment is prolonged. Growth impairment should lead to consideration of use of steroid-sparing agents. Supplemental vitamin D may prevent some bone loss that can occur, especially early in the course of treatment with steroids, although determination of bone mineral density should be considered in those with prolonged exposure to corticosteroids. Use of gastrointestinal prophylaxis with a proton pump inhibitor should be considered when prescribing high doses of corticosteroids. Cytotoxic agents (eg, cyclophosphamide, chlorambucil) can be associated with increased risk for infection, malignancy, and sterility, but usually only with higher doses

than those typically used for NS or after repeated or prolonged courses. Cyclophosphamide can cause hemorrhagic cystitis. Therefore, a large fluid intake and frequent voiding should be encouraged. Chlorambucil therapy has been associated with induction of seizure activity. Cyclosporine and tacrolimus both have nephrotoxic potential and can cause acute and chronic renal injury. Acute renal failure can occur in severely nephrotic patients who are treated with cyclosporine and who have markedly decreased intravascular volume. Mycophenolate mofetil can cause bone marrow suppression and gastrointestinal upset.

Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers can be tried in resistant NS, even in the presence of normotension, to decrease urinary protein excretion. ACE inhibitors act by decreasing glomerular capillary pressure and can cause a reversible increase in serum creatinine and hyperkalemia that must be monitored. High doses of ACE inhibitors may decrease progressive sclerosis.

Salt intake should be restricted in edematous children because of their avid sodium retention. Water intake does not usually need to be restricted, especially if sodium intake is adequately limited, unless significant hyponatremia develops or edema is intractable. Diuretics are used judiciously, given the already reduced intravascular volume in most nephrotic patients and the attendant risk for thromboembolism. Furosemide alone or in combination with a thiazide diuretic is used to treat clinically significant edema. Severe edema interfering with ambulation, compromising respiratory status, or causing tissue breakdown can be treated with intravenous albumin followed by intravenous furosemide if renal function and urine output are fairly well maintained. Patients must be monitored closely during infusion for the development of signs of intravascular overload, such as rales, cardiac gallop, and hepatomegaly. This therapy can also be used in the severely edematous, corticosteroid-resistant nephrotic patient in whom cyclosporine therapy is being considered in an attempt to improve renal perfusion and prevent the precipitation of acute renal failure.

Hospital admission should be considered for children during their first episode of NS, especially if complications are present, for teaching the parents home management and monitoring. Children who have severe edema compromising their ventilatory status, causing cardiovascular congestion, or interfering with ambulation should be admitted for forced diuresis. Infectious complications of NS may require treatment with parenteral antibiotics. Hypertension, renal insufficiency, and electrolyte disturbances may also require hospitalization for stabilization. Children with significant renal insufficiency may require dialysis to manage edema, electrolyte disturbances, and uremia.

The treatment of idiopathic membranous nephropathy is controversial with regard to the choice of agent and the timing of intervention. Investigators have suggested that therapy need not be provided in most patients, given the high rate of spontaneous remission. Patients who have evidence of renal insufficiency, persistent heavy proteinuria, hypertension, or

sclerosis on biopsy should be considered for treatment. Agents that have been used for the treatment of membranous nephropathy include high-dose corticosteroids provided orally or intravenously alone or in combination with cytotoxic agents, mycophenolate mofetil, cyclosporine, and rituximab.

### WHEN TO REFER

- Complicated NS
- Outside the expected age range (<2 years or >10 years of age)
- Accompanied by signs of glomerulonephritis (renal insufficiency, hypertension, hematuria, hypocomplementemia)
- Refractory edema
- Frequently relapsing NS
- Corticosteroid-dependent NS
- Corticosteroid-resistant NS

### WHEN TO ADMIT

- Initial episode for teaching of parents
- Anasarca interfering with ambulation or compromising ventilation
- Pleural effusions or ascites interfering with ventilation
- Signs of volume overload (congestive heart failure)
- Infection (eg, severe cellulitis, peritonitis)
- Significant hypertension
- Significant electrolyte abnormalities
- Compromised renal function

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Childhood Nephrotic Syndrome* (fact sheet), National Kidney Foundation ([www.kidney.org/atoz/content/childns](http://www.kidney.org/atoz/content/childns))
- *Childhood Nephrotic Syndrome* (fact sheet), National Kidney and Urologic Diseases Clearinghouse, National Institutes of Health ([kidney.niddk.nih.gov/kudiseases/pubs/childkidneydiseases/nephrotic\\_syndrome](http://kidney.niddk.nih.gov/kudiseases/pubs/childkidneydiseases/nephrotic_syndrome))

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## Chapter 296

# NEURAL TUBE DEFECTS

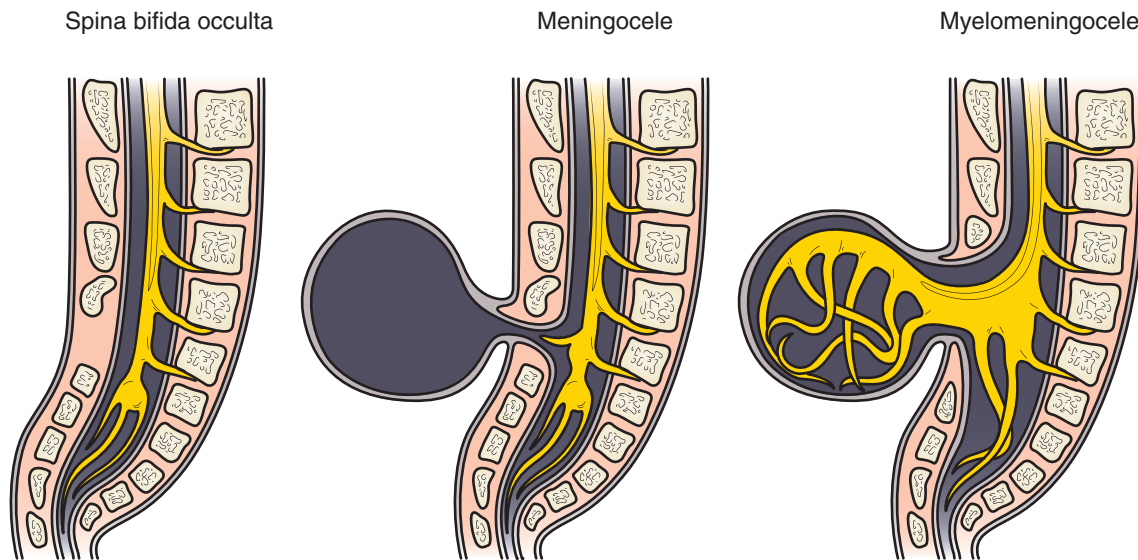
Heidi Castillo, MD

Neural tube defects (NTDs) are a group of congenital anomalies that are the result of failure of the neural tube to close between the third and fourth week of fetal development. Most NTDs can be divided into cranial presentations and spinal presentations. Cranial presentations include anencephaly and encephalocele. The most common spinal presentations include the bony anomaly spina bifida occulta and the combined bony and neural anomalies myelomeningocele, meningocele, myeloschisis, congenital dermal sinus, lipomatous malformations, diastematomyelia, and caudal agenesis. Primary neurulation is the process by which the embryonic notochord and neural plate interact to form the neural tube. This process is complete between 24 and 26 days' gestation. Failure of the neural tube to close during primary neurulation results in anencephaly, encephalocele, and myelomeningocele, the "open" NTDs. Secondary neurulation follows primary neurulation and continues through term gestation. It consists of secondary canalization and retrogressive differentiation of the caudal cell mass that forms at the caudal end of the neural tube. Secondary neurulation is responsible for the formation of the tip of the conus medullaris and filum terminale. Impaired secondary neurulation results in the "closed" NTDs, including diastematomyelia, meningocele, lipomatous malformations, teratomas, dermal sinus tracts, and tethered spinal cord.

In anencephaly, a poorly differentiated brainstem is present, but there is no differentiated supratentorial neural matter. Encephaloceles are characterized by a defect of the skull (usually in the occipital region) that can result in herniation of meninges and brain tissue. These are rare congenital anomalies that are often associated with deformities of the brainstem and skull base along with hydrocephalous.

Spina bifida is a collective term used to describe a group of congenital anomalies of the vertebrae, meninges, and spinal cord (Figure 296-1). Spina bifida occulta refers to incomplete development of the vertebrae, with the spinal cord and overlying skin remaining intact. Spina bifida occulta is the most common type of spina bifida and is seen in up to 15% of the general population. It is most often picked up incidentally on abdominal or spine films. A meningocele is another form of spina bifida in which a cystic sac of cerebral spinal fluid is present into which the meninges protrude; with this type of lesion there is no nerve involvement.

A myelomeningocele is the most severe type of spina bifida. It is characterized by a disruption of the vertebrae with protrusion of both the meninges and spinal cord. A Chiari II malformation is present in most patients with myelomeningocele and is the most common cause of death in infancy. The basic abnormality in Chiari II



**Figure 296-1** Types of spina bifida.

malformation is inadequate development of the fourth ventricle, with a resultant small posterior fossa. This may lead to caudal displacement of the cerebellar tonsils and vermis, caudal medulla, and variably the fourth ventricle into the cervical spinal canal. Patients with Chiari II malformations may also have supratentorial abnormalities, including polymicrogyria, agenesis of the corpus callosum, and aqueductal stenosis, resulting in hydrocephalus. In addition, these patients may have epilepsy, hydrocephalus, and cognitive impairments.

Diastematomyelia is an NTD in which the spinal cord is split along its axis; each hemicord is surrounded by its own dural sac. It is often associated with spina bifida and scoliosis. Lipomatous malformations, the most common of the closed NTDs, occur when excessive lipomatous tissue is within or attached to the spinal cord or the filum terminale. This group of malformations has a variety of presentations that vary in terms of their involvement of the spinal cord. They represent a range of abnormal embryonic development. Included in this group of malformations are lipoma of the filum terminale, lumbosacral lipoma, lipomyelocele, and lipomyelomeningocele. Physical examination with the addition of magnetic resonance imaging (MRI) is key to diagnosing these malformations. Dimples off midline or proximal to the gluteal cleft, abnormal gluteal creases, coarse hair, or hemangiomas are often indicative of a more severe underlying defect and require further investigation.

This chapter will mainly focus on myelomeningocele.

## EPIDEMIOLOGY

It is estimated that the overall prevalence of spina bifida among children and adolescents in the United States is 3.1 cases per 10,000; this represents more than 24,000 children and adolescents living with spina bifida. The overall prevalence of spina bifida is slightly higher among females than males. The prevalence of

NTDs has been shown to vary by race and ethnicity, with the highest rates found among Hispanics and the lowest rates found among blacks and Asians.

Internationally, there is marked geographic variation in the incidence of NTDs. The highest incidence rates worldwide have been observed in the British Isles, where 2 to 3.5 cases of myelomeningocele and anencephaly per 1,000 births have been reported. The lowest incidence rate has been documented in Japan.

Among parents with 1 child with spina bifida or anencephaly, the risk of having a second affected child is approximately 3%. The overall incidence of NTDs has been declining secondary to folic acid supplementation and fortification of food. This decline has also been affected by the choice to terminate pregnancy among those who are prenatally diagnosed.

## ETIOLOGY

Although the exact etiology of NTDs remains unknown, a genetic predisposition does exist. In addition, inadequate intake of folic acid increases the risk of NTDs. As a result of this known link between NTDs and folic acid, periconceptional use of folic acid with a dose of at least 400 mcg per day is universally recommended in all women of child-bearing age. Furthermore, many countries have implemented fortification of grain products with folic acid.

There is an increased risk of NTD among infants of mothers with pregestational diabetes. Maternal use of valproic acid or carbamazepine is also associated with an increased risk of spina bifida.

NTDs can occur as part of malformation syndromes resulting from known chromosomal abnormalities (eg, trisomy 13, 18) and single gene disorders. There is some evidence that suggests, in rare cases, an X-linked autosomal recessive inheritance pattern of certain NTDs. However, most cases are not because of

known chromosomal aberration or to the effects of a mutation in a single genetic locus.

## DIAGNOSIS

### Signs and Symptoms

Many NTDs are diagnosed prior to birth. Screening with maternal serum alpha fetoprotein is most accurate when done between the 16th and 18th week of gestation. Although an elevated value strongly suggests an open NTD (a sensitivity of 75% and a specificity of 97.7%), detection of an open NTD with fetal ultrasound in the hands of a skilled ultrasonographer is highly specific. MRI is obtained at some centers prenatally. It can be used to predict lesion level and to evaluate for intracranial pathology or other structural anomalies.

If not diagnosed antenatally, most open NTDs are apparent upon physical examination. Conversely, closed NTDs may not be apparent at birth. These have variable presentations but often have an associated cutaneous abnormalities including peri-spinal lipomas, hemangiomas or tufts of coarse hair over the defect. Symptoms of a closed NTD that may present later in life can include lower extremity asymmetry, weakness, lower back pain, and bladder or bowel dysfunction. With regard to the Chiari II malformation associated with myelomeningocele, symptoms may occur at any age but most commonly occur in infancy. During this time, disorders of swallowing are the most common clinical manifestations and may include choking on foods and frequent vomiting. Other signs of brainstem dysfunction are repeated aspiration pneumonia, apnea or cyanotic spells, inspiratory stridor, vocal cord paralysis, and a hoarse or high-pitched cry. In older children, signs and symptoms of the Chiari II malformation may include weakness or spasticity of the extremities, headaches caused by hydrocephalus, neck pain, cerebellar dysfunction, oculomotor changes, or scoliosis.

### Diagnostic Approach

A complete neurologic examination is imperative. In particular, head circumference as well as motor and sensory assessments should be detailed upon initial presentation and with subsequent evaluations. It is important to note that the functional motor impairment level does not always correspond to the anatomic level of the lesion as seen on imaging. In addition, the motor function may not be symmetric. Spinal deformity, lower extremity deformity, anal sphincter tone, and urinary stream should also be assessed.

### Laboratory Findings

Urinalysis, urine culture, and serum urea nitrogen and creatinine should be obtained at birth to evaluate renal function. Additionally, these should be repeated routinely, especially for children who have vesicoureteral reflux or any signs or symptoms of a urinary tract infection.

### Imaging

Imaging for central nervous system (CNS) pathology is commenced during the neonatal period and repeated

**Table 296-1** Deep Tendon Reflex Site

DEEP TENDON REFLEX SITE	NERVE ROOT
Biceps	C5-6
Brachioradialis	C5-6
Triceps	C6-7-8
Patellar	L2-3-4
Achilles	S1-2

as necessary for assessment of the secondary conditions associated with spina bifida. Head computed tomography (CT) scan or ultrasound assist in diagnosing and monitoring hydrocephalus. When a ventricular shunt is present and a shunt malfunction is suspected, a CT scan of the head and radiograph of shunt tubing is essential. Cranial MRI can help the evaluation of a Chiari II malformation and may also reveal any defects in cellular migration in the cerebral cortices. An MRI of the spine can help evaluate for the presence of spinal cord tethering or syringomyelia. A baseline MRI of the brain and spine is helpful for comparison in future investigations, especially in the context of progressive neurologic deterioration.

Throughout infancy and early childhood, patients are followed with routine renal and bladder ultrasounds. Voiding cystourethrograms are performed routinely to assess bladder size, shape, and capacity, and to determine if urethral reflux is present. Urodynamic studies assess the function of the bladder and urethra by assessing pressures; these should be obtained regularly to determine if the neurologic lesion has changed or if spinal cord tethering has occurred, and to map the urologic treatment course.

Plain radiographs are important for the clinical evaluation for scoliosis, kyphosis, and dislocation of the hips. Evaluation of the hips should be with ultrasound before 4 to 6 months of age, as radiographs are inaccurate in this age group. Ultrasound evaluation and radiographs should be used to assess any area with pain that may represent a pathologic fracture.

### Classification

Physical examination is the key to classification, because lesion level on imaging may not accurately correlate with functional level. Deep tendon reflexes (Table 296-1) and motor movement evaluation (Table 296-2) can help identify functional level. The motor examination should focus on movements against gravity. A sensory examination, with dermatomal distribution clearly in mind, is also recommended. Often, parents are able to report accurate sensory levels when they may be difficult to elicit on examination. It is important to note any asymmetry and to document the functional level of the lesion accurately. This may allow for future timely detection of progressive neurologic deterioration.

## MANAGEMENT

Management of an individual with an NTD requires a multidisciplinary team approach. Because of the complexity of the secondary conditions associated with



**Table 296-2** Motor Movement Against Gravity and Correlative Nerve Root

MOTOR FUNCTION	NERVE ROOT
Hip flexion	L1-2
Hip adduction	L2-3
Hip abduction	L4-5
Knee extension	L3-4
Knee flexion	L5-S1
Ankle dorsiflexion, foot inversion	L4-5
Foot eversion, great toe dorsiflexion	L5-S1
Ankle plantar flexion	S1-2

NTDs, the team may include neurosurgeons, orthopedic surgeons, urologists, neurologists, physiatrists, developmental pediatricians, nurses, social workers, dietitians, and therapists, with 1 individual acting as the advocate and coordinator of the treatment program. It is also helpful for parents to have contact with a parent support group as early in the process as possible.

### Neurosurgical Management

Investigational multicenter national trials of fetal surgical closure have shown potential benefits in some children. Upon delivery, open NTDs should be immediately covered with a saline-moistened dressing to avoid rupture of the sac or drying of the exposed neural placode. To avoid placing pressure on the defect, the neonate should be maintained and examined in the prone or lateral recumbent position. Meningitic doses of broad spectrum antibiotics should be started promptly. Closure of the defect is usually performed within 72 hours after birth. The surgical repair of the defect involves removing the malformed sac, creating a barrier between the spinal canal and the exterior, and restoring the typical cerebral spinal fluid environment around the spinal cord. Operative mortality during the repair of the primary defect is extremely rare.

After the NTD is surgically closed, the ventricles often enlarge, leading to hydrocephalus; on the other hand, some neonates already have significant hydrocephalus at the time of birth. A ventricular shunt is placed in 80% to 90% of all cases. Timing of shunt placement is straightforward when there is overt clinical and radiologic evidence of hydrocephalus. The rate of shunt revision is high; approximately 40% to 50% of all children with NTDs require a shunt revision in the first year of life and approximately 10% of them every year thereafter. Once the shunt is placed, the goal becomes keeping the shunt functioning optimally. Therefore, each patient should be followed closely for signs and symptoms of shunt malfunction. An alternative to a ventricular shunt is an endoscopic third ventriculostomy, which may be appropriate in certain cases.

A potentially treatable cause of neurologic deterioration in myelomeningocele patients is spinal cord tethering. Following the initial surgical repair, the

terminal spinal cord is commonly imbedded in scar tissue. Tethered cord syndrome is a stretch-induced functional disorder of the spinal cord caused by anchoring of caudal portion of the cord by an inelastic structure. Because essentially all children with repaired myelomeningocele will have a tethered spinal cord, as demonstrated on MRI, the diagnosis of tethered cord syndrome is made on clinical grounds. Evaluation of urologic, motor, and sensory function, as well as symptoms of pain, change in gait, and orthopedic deformity should drive the diagnosis and the treatment of tethered cord syndrome. Untethering is reserved for individuals who have progressive symptoms. The release of a tethered cord may offer improvement or stabilization of neurologic function, urologic dysfunction, and orthopedic deformities. As the cord can re-tether, a multidisciplinary team discussion is important in making decisions to repeat an untethering procedure.

Although the Chiari II malformation is commonly associated with myelomeningoceles, it is only symptomatic enough to require surgical intervention in 15% to 35% of cases.

### Urologic Management

Because the bladder's nerve supply originates from the thoracic, lumbar, and sacral cord, bladder function in children with NTDs is often affected to varying degrees, though level of lesion is not explicitly predictive of bladder function. Regardless of the level of the NTD, all patients should have urinary function monitored. The priority of urologic management is to preserve kidney function and to attain bowel and bladder continence.

Only 10% to 15% of all children with myelomeningoceles are continent of urine; social continence may be achieved by the use of intermittent catheterization. Clean intermittent catheterization successfully eliminates urine from the bladder, mimicking normal voiding; this decreases urinary infection and reduces the effects of hostile bladder pressure on the kidneys. Although clean intermittent catheterization may lead to bacterial colonization of their bladder, it generally does not require antibiotic therapy unless it is symptomatic.

When poor bladder compliance or uninhibited contractions are present, medication, such as an anticholinergic agent, oxybutynin (ditropan), may be started in an attempt to improve bladder compliance and to decrease storage pressure. Urodynamic monitoring of storage pressures and leak point pressure is key to both preservation of renal function and attainment of social urinary continence. Some individuals who are unresponsive to nonsurgical management with anticholinergic medication and catheterization may benefit from operative intervention. These operative procedures are tailored to each individual, but may include vesicotomy, augmentation cystoplasty, catheterisable stoma (Mitrofanoff), slings, or artificial urinary sphincters.

### Bowel Management

Attaining and sustaining bowel continence is a complex issue for individuals with spina bifida. Fecal

incontinence can be socially isolating and, therefore, must be addressed and managed early. In thoracic level spina bifida, there is often difficulty in bearing down, while patients with sacral lesions may have difficulty achieving appropriate stool consistency.

Constipation is common and results from a multitude of factors, including diet, lack of exercise, and mobility, anticholinergic medications, and neurologic dysfunction of the bowel. It can exacerbate bladder function problems and present a risk factor for urinary tract infections. Oral medications can be used to control consistency. Bowel emptying techniques are the cornerstone of stool continence in spina bifida. Goals of a bowel program should include having soft, formed stools on a daily basis. Bowel emptying techniques include behavioral training, rectal stimulation, suppositories, and enemas. Certain patients may benefit from surgical intervention. A cecostomy or a Malone procedure, in which a conduit is created to the proximal colon, may be needed. This stoma is then used for the administration of antegrade colonic enemas.

While bowel management is often time-consuming, it can greatly increase quality of life and encourage social involvement for children with spina bifida.

### Orthopedic Management

A paramount issue for most parents of children with spinal NTDs is the prognosis of ambulation. In the absence of severe developmental delay and hypotonia, ambulation is highly dependent on sensorimotor functional level.

Strong hip flexors, adductors, and quadriceps are needed to ambulate. Independent mobility is likely for almost all cases of low lumbar and sacral lesions. For lesions above L2, independent mobility is unlikely and parents should anticipate wheelchair use. As some children age, their ability to ambulate often declines because of the increased physical effort of walking required by increasing weight and orthopedic deformity. Consequently, a wheelchair may become a more efficient alternative for adolescents and adults.

It is important that an orthopedist be involved in the care of patients with myelomeningocele, as paralysis, muscle imbalance, and spasticity produce orthopedic deformities that often require surgical correction. Spinal deformities in myelomeningocele, such as scoliosis and kyphosis, are exceedingly common. Hip dislocations also frequently occur, but do not always require treatment. Severe foot deformities are seen in up to 80% of children.

For optimal motor function, early involvement of a physical therapist is critical. Range of motion exercises are essential at any age. Goals of physical therapy should include normalization of experiences, improvement of posture for sitting or standing, management of orthotics, and prevention of skin breakdown. Orthotics are commonly used to prevent contractures and promote development of an individual's mobility. They also aid in minimizing energy expenditure to maintain mobility. If feasible, a standing program should be instituted at an early age. Specialized equipment, such as walkers, braces, standers, and parapodiums, may be needed to provide support and promote mobility.

### Developmental and Cognitive Issues

The range of developmental outcomes in individuals with NTDs is extensive. In general, cognitive function is often higher for those with lower lesions and for children who do not experience CNS infections (ventriculitis or meningitis). For individuals without associated hydrocephalus, cognitive function is commensurate with same-age peers.

Most children (80%) with myelomeningocele have intelligence within the normal range, yet they often have specific learning disabilities. Nonverbal learning disorders are associated with hydrocephalus and found more often in children with myelomeningocele with stronger language skills and weaker visual-perceptual and visual-motor skills. Corresponding academic skills include stronger reading decoding and spelling skills and weaker mathematic and reading comprehension skills. In addition, they often have difficulty with attention and executive function, with an increased risk of attention-deficit/hyperactivity disorder. Routine neuropsychologic and psychoeducational evaluations for children with spina bifida ensure that all learning issues are identified.

Referral for an early intervention program and physical therapy are essential during the neonatal period. Given the high incidence of visual-motor and visual-perceptual difficulties associated with hydrocephalus, occupational therapy is also often needed. As children access school services, families should participate in the development of an Individualized Education Plan with school personnel. For adolescents with an NTD receiving special education services, transition plans should begin by age 14 years to specifically address transition to vocational and occupational domains and to assist families in navigating the transition from childhood to adulthood.

It is also important for physicians to remember that families who cope with an NTD are faced with challenges that are very different than those faced by families raising typically developing children. Stressors include the need for continuous interaction with medical care agencies and an increased level of financial stress. Parenting quality and care patterns have an important effect on developmental outcomes in children; specifically, high-quality parental care is linked to higher cognitive abilities and social competence. As family members are likely the main source of support for both physical and psychologic well-being for individuals with spina bifida, physicians should encourage healthy family relationships to support optimal family functioning. Family support groups are often helpful and should be encouraged.

### Dermatologic Issues

Because of impaired sensation caused by spinal cord dysfunction, patients with spina bifida have an increased rate of skin breakdown and pressure sores. Intervention for early signs of inflammation is imperative. Measures to protect insensate skin, such as properly fitted orthotics and shoes, wheelchair push-ups, and time out of the wheelchair, are paramount. As children mature, they should be taught how to check their own skin daily for evidence of pressure sores.

### Latex Allergy

Allergies to latex are more common in this population; reactions can vary from mild to anaphylaxis. Beginning at birth, latex precautions should be in place for patients with myelomeningocele. Latex avoidance in children with spina bifida has been demonstrated to prevent latex sensitization and latex allergy.

### ONGOING CARE

#### Prognosis

There has been a tendency for prenatal counseling to be unduly negative, failing to recognize the heterogeneity of these conditions and the effect of contemporary postnatal medical and surgical management. Prognosis for all NTDs is largely dictated by anatomical site, extent of CNS tissue involvement, and the presence of coexisting conditions. Long-term prognosis for survival is less optimistic if there is an associated syndrome, brain tissue herniation, or repeated CNS infections.

In children with myelomeningocele, prognosis for survival can be improved if shunts function optimally and if kidney function is preserved. In older patients these are the most common, and potentially preventable, causes of death.

#### Prevention

The periconceptional use of daily supplements containing 0.4 mg of folic acid has been shown to prevent 40% to 80% of cases of spina bifida and anencephaly. Counseling provided to women with a previous NTD-affected pregnancy and supplementation with 4.0 mg of folic acid have also been demonstrated to substantially reduce the risk of recurrent NTDs. In addition, countries that have implemented mandatory folic acid food fortification programs have succeeded in significantly reducing the prevalence of NTDs.

### WHEN TO REFER

- Evidence of raised intracranial pressure, such as vomiting or changes in mental status.
- Symptoms of spinal cord tethering.
- Recurrent urinary tract infections.
- Renal calculi or impairment.
- All children 0 to 3 years of age should be referred to an early intervention program.
- Children entering school should be referred to their school district's preschool program to have a formal evaluation of cognitive functioning.
- All patients should be referred to a multidisciplinary clinic where specialists in development, genetics, neurosurgery, nursing, nutrition, orthopedics, orthotics, social work, therapy (occupation and physical), and urology participate or are available.

### TOOLS FOR PRACTICE

#### Medical Decision Support

- *Guidelines for Spina Bifida Health Care Services Throughout the Lifespan* (book), Spina Bifida Association.

### AAP POLICY

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## Chapter 297 NEUROCUTANEOUS SYNDROMES

Dwayne E. Dove, MD; Michael L. Smith, MD

The neurocutaneous disorders consist of a heterogeneous group of conditions in which abnormalities of skin and nervous system predominate. Classically, neurofibromatosis, tuberous sclerosis, and von Hippel-Lindau disease are considered the prototypical neurocutaneous conditions. However, several other genetic or developmental anomaly syndromes share the phenotypic association of cutaneous and neurologic abnormalities, such as Sturge-Weber syndrome, ataxia-telangiectasia, incontinentia pigmenti, hypomelanosis of Ito, and the epidermal nevus syndromes. In addition, many genetic disorders with neurodevelopmental features may exhibit skin lesions, but these myriad conditions are beyond the scope of this chapter. The current discussion focuses on neurofibromatosis, tuberous sclerosis, Sturge-Weber syndrome, von Hippel-Lindau disease, and ataxia-telangiectasia.



NEUROFIBROMATOSIS

Definition

Neurofibromatosis is classically divided into type 1 (NF1) and type 2 (NF2), although these are different conditions with only minimal overlap. Both are autosomal; dominant disorders with high penetrance but variable phenotypic expression. NF1 is more common, occurring in approximately 1 in 3,500, and commonly presents in childhood. The incidence of NF2 is approximately 1 in 25,000, and it usually manifests in the late teens and 20s. No race or gender predilection has been found. Approximately one-half of the cases with each condition represent new mutations. Further recognition of variants has led to expanded classification into 8 subtypes (Table 297-1).

Neurofibromatosis Type 1

NF1, or von Recklinghausen disease, is a complex disorder with neurologic, cutaneous, skeletal, vascular, and endocrinologic abnormalities. A loss-of-function mutation in the neurofibromin tumor suppressor gene is thought to be responsible for most of the clinical features. The characteristic lesion is the neurofibroma,

a proliferation of Schwann cells and fibroblasts, from which the condition derives its name. Neurofibromas are benign tumors that appear in late childhood, grow in response to hormonal changes, proliferate with age, and may compromise local function by mass effect. Small neurofibromas appear as pink to flesh-colored to brown papules with a soft, spongy texture (Figure 297-1). On occasion, gentle downward pressure can cause these lesions to sink through the underlying dermis, creating a dimple (Figure 297-2). Size and number vary greatly. A slight predilection for trunk involvement seems to exist, although neurofibromas can occur anywhere on the body.

A variant of neurofibroma, the plexiform type, can be large and can cause considerable disfigurement. Plexiform neurofibromas (Figure 297-3) are highly variable masses that may have surface hyperpigmentation or may remain flesh colored. Overlying skin may be somewhat thickened and may exhibit increased hair growth. Plexiform neurofibromas often produce soft tissue masses, sometimes feeling soft and spongy in texture, and other times feeling similar to a bag of rope. Plexiform lesions are seen in approximately 50% of patients with NF1.

Table 297-1      Neurofibromatosis Spectrum		
FORMER CLASSIFICATION	CURRENT TERMINOLOGY	CHARACTERISTICS
Type 1	NF1	See text
Type 2	NF2	See text
Type 3 (variant), type 4 (atypical)		Autosomal dominant; not used clinically
Type 5 (segmental)	Segmental NF	Skin lesions all on 1 body segment (eg, leg); somatic mosaicism
Type 6 (CALMs)	Familial CALMs	Only has CALM; must have 2 generations to diagnose
Type 7 (late onset)	Schwannomatosis	Symptoms manifest in the 20s; multiple schwannomas; no vestibular or intradermal schwannomas
Type 8 (not otherwise specified) not used clinically		

CALM, café-au-lait macules; NF, neurofibromatosis.  
Derived from Boyd KP, Korf BR, Theos A. Neurofibromatosis type 1. *J Am Acad Dermatol.* 2009;61:1–14.



Figure 297-1 Cutaneous neurofibromas in neurofibromatosis type 1.



The earliest features are often café-au-lait macules (CALMs), which are tan, oval macules with smooth margins and no surface texture change (Figure 297-4). They remain flat and do not exhibit increased hair growth. They may vary in size and shape, and they may increase in number and size with age.

Axillary or inguinal freckling is seen in almost 90% of NF1 patients, usually developing between 3 and 5 years of age.



**Figure 297-2** Neurofibroma dimpling through underlying dermis.



**Figure 297-3** Plexiform neurofibroma on a breast.



**Figure 297-4** Multiple café-au-lait macules on an infant, with coincidental gray Mongolian spot.

### Diagnosis

NF1 is a highly variable condition, with age-specific expression of its clinical features. Although minor evidence occurs often in infancy with only CALMs, NF1 cannot be diagnosed clinically until 2 or more of the major diagnostic criteria are met (Box 297-1). This feature is particularly important in view of the many other disorders in which CALMs are a presenting feature (Table 297-2).

### Evaluation

The evaluation of patients for possible NF1 depends on age; many of the features develop over time. For example, CALMs are present at birth but will increase in size and number for the first 5 to 7 years. Bowing of the long bones (especially tibia) and cutaneous plexiform neurofibromas typically are visible within the first year of life, whereas axillary (Figure 297-5) and inguinal freckling, optic gliomas, and scoliosis may not be apparent until age 7 years. Cutaneous neurofibromas and iris Lisch nodules usually appear during or after the teenage years.

**HISTORY.** Relevant history should include questions about developmental milestones, including language, social skills, and learning. Emotional and behavioral functioning also needs to be explored, particularly issues regarding self-esteem. Family history is of paramount importance in the initial evaluation of a child with only CALMs because the presence of NF1 in a first-degree relative secures the diagnosis.

**PHYSICAL EXAMINATION.** Initial examination of any child for NF1 should start with a thorough skin survey for CALMs. Six or more CALMs should raise the index of suspicion. Thorough examination of the entire skin surface should also reveal the presence of plexiform neurofibromas. Plexiform neurofibromas may be present at birth or may develop in the first few years of life. Careful attention should also be paid to the long bones of the lower leg because congenital

### BOX 297-1 Diagnostic Criteria for Neurofibromatosis Type 1

NF1 is present when a patient has 2 or more of the following:

- Six or more café-au-lait spots larger than 5 mm in pre-pubertal child and 15 mm after puberty
- Axillary or inguinal freckling
- At least 2 neurofibromas of any type or at least 1 plexiform neurofibroma
- Optic pathway glioma
- At least 2 Lisch nodules of the iris
- Characteristic bony lesion (sphenoid wing dysplasia, or thinning of the cortex of long bones—with or without pseudoarthrosis)
- First-degree relative with NF1

NF1, neurofibromatosis type 1.

Adapted from Yohay K. Neurofibromatosis types 1 and 2. *Neurologist*. 2006;12:86–93; and Tongsgard JH. Clinical manifestations and management of neurofibromatosis type 1. *Semin Pediatr Neurol*. 2006;13:2–7.

**Table 297-2** Differential Diagnosis of Multiple Café-au-Lait Macules

CONDITION	OTHER CLINICAL FEATURES	COMMENT
Normal	—	Up to 25% of normal individuals may have 1–3 CALMs. Up to 40% of people with >6 CALMs and no other symptoms never progress to NF1.
NF1	Axillary freckling, cutaneous NFs, plexiform NFs, Lisch nodules, optic glioma, bony abnormalities, positive family history	Present in 95% of patients with NF1; must have >6 CALMs (>5 mm before puberty; >15 mm after puberty)
NF1-like syndrome	Axillary freckling, multiple CALMs, macrocephaly; no neurofibromas or Lisch nodules	Also called <i>Legius syndrome</i> ; caused by <i>SPRED1</i> mutation; may have learning disability
Hereditary nonpolyposis colon cancer syndrome	Axillary freckling, multiple CALMs, cutaneous neurofibromas; colon cancer at early age	Homozygous form, usually with consanguinity
Watson syndrome	Pulmonic stenosis, ID, axillary freckling	Axillary freckling only in NF1 and Watson syndrome type 1
McCune-Albright syndrome	Polyostotic fibrous bony dysplasia, precocious puberty, hyperthyroid, Cushing syndrome	Usually large-segment CALM with irregular border ( <i>coast of Maine</i> )
Russell-Silver syndrome	Short stature, skeletal asymmetry, abnormal pubertal development	Café-au-lait spots and small achromic macules have been reported, but are not constant features.
Bloom syndrome	Malar facial erythema and telangiectasia; photosensitivity; long, narrow face with prominent nose; short stature; hypogonadism; malignancy risk	Facial photosensitivity with multiple CALMs triggers evaluation.
Tuberous sclerosis	Hypopigmented macules, facial and periungual angiofibromas, seizures, ID, renal and cardiac hamartomas	Hypopigmented macules more common; mixture very concerning for tuberous sclerosis complex.
Noonan syndrome	Hypertelorism, webbed neck, short stature, leg lymphedema, pulmonic stenosis, hypogonadism	CALMs may be seen in 15% of patients with Noonan syndrome.

CALM, café au lait macule; ID, intellectual disability; NF, neurofibromatosis; NF1, neurofibromatosis type 1.

Adapted from Krowchuk DP, Mancini AJ, eds. *Pediatric Dermatology: A Quick Reference Guide*. Elk Grove Village, IL: American Academy of Pediatrics; 2007; and Spitz JL. *Genodermatoses: A Full-Color Clinical Guide to Genetic Skin Disorders*. New York, NY: Williams & Wilkins; 1996.



**Figure 297-5** Axillary freckling in neurofibromatosis type 1.

tibial dysplasia is an early finding in up to 5% of children with NF1. Any curvature or nodularity of the tibia is worrisome, as is any length discrepancy. Head circumference should be monitored at each visit because approximately 50% of children with NF1 have macrocephaly. Thorough developmental evaluation

should be undertaken at each visit and repeated at regular intervals, with attention to language, visual motor skills, and learning in toddlers and preschool-aged children.

Examination of the back for evidence of scoliosis should start by age 2 years because scoliosis appears at an earlier age in NF1, and a severe dystrophic form of kyphoscoliosis can appear between 3 and 5 years of age. Regular blood pressure assessment should also begin by age 2 years. Ophthalmologic evaluation should be obtained annually to age 10 years to assess for the presence of optic pathway glioma. These grade 1 pilocytic astrocytomas, which are present in approximately 15% of children with NF1 younger than 10 years, may produce proptosis, strabismus, papilledema, or vision loss. If the optic chiasm is involved, then hypothalamic extension can produce an endocrinopathy, resulting in precocious or delayed puberty. The development of precocious puberty should prompt evaluation for an optic glioma. Similarly, any rapid increase in linear growth should prompt an investigation for optic pathway glioma with growth hormone excess. Other ocular findings may include congenital ptosis or orbital asymmetry (the latter the result of sphenoid wing dysplasia).

School-aged children should be assessed for limb asymmetry, long bone bowing, scoliosis, and cutaneous neurofibromas. School performance should be addressed, with particular attention to learning disabilities, attention-deficit/hyperactivity disorder (ADHD), executive dysfunction, self-esteem, and socialization.

Teens should be assessed for limb asymmetry, scoliosis, neurofibromas, and hypertension. Ophthalmologic evaluation, including slit-lamp examination, should be obtained to look for iris hamartomas (Lisch nodules). These tan to brown papules usually appear in the teen years, but they have minimal effect other than support of diagnosis. Any complaint of pain, particularly pain associated with focal neurologic deficit or arising from a plexiform tumor, should be thoroughly evaluated by examination and imaging studies. School performance, socialization, and self-esteem issues should be addressed as well.

**LABORATORY EVALUATION.** Routine laboratory testing is unnecessary in NF1 if the diagnosis is firmly established. However, if reason exists to test for gene mutations (in cases of uncertain diagnosis, a child with only CALMs or only 1 criterion), then a complementary series of analyses—including premature truncation test, heteroduplex analysis, and fluorescent in situ hybridization assay—is available clinically. This tiered analysis provides a sensitivity of 95%. Genetic testing may have limited clinical value, with lack of genotype-phenotype correlation except in 2 situations: complete loss of the NF1 gene, which portends more severe disease with severe cognitive impairment, large tumor burden, and higher risk for malignant peripheral nerve sheath tumors; and a known small deletion in exon 17, which confers a milder phenotype without cutaneous neurofibromas.

**IMAGING STUDIES.** Imaging in NF1 should be directed toward evaluation of symptoms. Routine neuroimaging is generally not undertaken. However, head magnetic resonance imaging (MRI) is indicated for evaluation of focal neurologic changes, new-onset seizures, severe headaches, vision changes, proptosis, short stature, rapid change in head circumference, plexiform lesions, severe cognitive deficits, and precocious or delayed puberty. Any evidence of scoliosis or any long bone anomaly should merit plain-film radiography. Scoliosis may also require MRI or computed tomography (CT) to define the extent and help map surgical intervention. MRI is also useful to assess for radiculopathy because neurofibromas have a propensity to develop along or within the spine, often impinging on nerve roots. The development of pain, or any focal neurologic deficit, also warrants a thorough evaluation, including MRI. This evaluation is particularly important if pain develops in a plexiform neurofibroma because pain may herald malignant change. Although MRI is the mainstay of evaluation of plexiform neurofibromas, positron emission tomography (PET) may be of more value in distinguishing benign from malignant lesions. Cranial MRI is indicated to evaluate for possible optic pathway glioma after symptoms have developed. Routine imaging before symptom onset is not indicated. After optic gliomas are diagnosed, MRI should be obtained every 2 years and with any symptom change to age 10 years.

Imaging is also useful in evaluation of cerebrovascular disease and renal artery stenosis.

One unusual finding in NF1 is the presence of unidentified bright objects on T2-weighted sequences of cranial MRI. These lesions, which are present in 60% to 90% of children but only in approximately 30% of adults, are of uncertain significance. Controversial evidence suggests that some learning disabilities seem to correlate with the presence and specific locations of unidentified bright objects.

### Management

Management and health supervision of NF1 should focus on the many organ systems involved, given the wide variability of expression. As a rule, genetic counseling should be provided for all NF1 families because affected individuals have a 50% chance of transmission with each pregnancy.

Neurofibromas present unique management issues of their own. Smaller lesions may become painful or may interfere with activities as a result of location. Plexiform lesions can be disfiguring, especially when they are present on the head or neck. The presence of numerous or large lesions may exert a profound effect on self-esteem and socialization. Surgical excision may be necessary for problematic tumors. Sudden development of pain or focal neurologic deficit in plexiform tumors may represent malignant degeneration. Malignant peripheral nerve sheath tumors (formerly called neurofibrosarcomas) develop in 5% to 13% of patients with NF1, with devastating effect. These aggressive tumors typically arise in the 20s and 30s, are often multicentric, and metastasize quickly. Despite aggressive therapy, they are usually fatal within a year. Other malignant tumors are seen in NF1, with an overall incidence 3% higher than the general population. These tumors include leukemia (especially juvenile myelomonocytic leukemia), rhabdomyosarcoma, pheochromocytoma, gastrointestinal stromal tumors, and carcinoid. The last 3 tumors are predominantly adult-onset tumors.

Optic pathway gliomas develop in 15% to 20% of patients with NF1 at a mean age of 4.2 years. Careful ophthalmologic monitoring for vision change, afferent pupillary defect, or change in funduscopic examination findings should begin in the first year of life and continue annually to age 10 years. Progression of the gliomas beyond age 10 years is rare. Other ocular findings may include congenital ptosis, congenital glaucoma, and pulsating exophthalmos. If optic pathway glioma is present, MRI evaluation should be repeated every 2 years until age 10 years in addition to annual ophthalmologic examinations. Precocious or delayed puberty may be a later clinical sign of optic glioma extending from the chiasm into the hypothalamus and should prompt reevaluation and MRI.

Hormonal surges may affect NF1 and should be discussed with preteens and teens. Oral contraceptives, puberty, and pregnancy are likely to cause increases in both size and number of neurofibromas.

Identification of neurologic and neurodevelopmental issues is of paramount importance in the management of patients with NF1. Headaches occur in 20% of patients;



these are usually migraines that respond well to standard therapy such as amitriptyline or topiramate. Seizures occur in 4% to 10% of patients with NF1 and may include partial or generalized variants or even infantile spasms. Management should be directed toward the specific seizure type (see Chapter 327, Seizure Disorders). Hearing loss, usually unilateral, occurs in approximately 10% of patients with NF1. Learning disabilities are observed in 35% to 65% of children with NF1 compared with less than 20% of the general population. A slight downward shift often occurs in IQ compared with age-matched controls, but the incidence of intellectual disability is only 4% to 8% (approximately twice that of the general population). Learning disabilities are variable, but may include math and reading comprehension problems. In addition, visual perception deficits and delays in both gross- and fine-motor skills are common. Speech and language delays are seen in approximately one-half of these children. ADHD is also common, occurring in approximately one-half of children with NF1. A variety of behavioral problems are seen with increased frequency in NF1 and may include anxiety, depression, social problems, aggression, and unusual behaviors. These issues seem to correlate more with the comorbid diagnosis of ADHD than with academic achievement. Autism spectrum disorders may be seen in up to 14% of children with NF1. Vascular disease is more common in patients with NF1, which may include congenital heart defects, hypertension, occlusive arterial disease, aneurysms, or arteriovenous fistulas. Hypertension in young children may result from renal artery stenosis (1% of patients with NF1). Hypertension in adults may be primary or associated with pheochromocytoma (rarely renal artery stenosis in adults). Workup should include renal angiography in children and urine catecholamine levels in adults.

Bone abnormalities are common in NF1, ranging from skeletal dysplasia to nonossifying fibroma to short stature to kyphoscoliosis. Long bone dysplasia (especially tibia) may be seen during the first year of life and may present as bowing or, rarely, pseudoarthrosis (nodule at the site of a healing pathologic fracture). Pseudoarthrosis occurs in only 3% of children with NF1. Nonossifying fibromas occur in late childhood to the teen years and may lead to pathologic fractures, particularly in the femur, tibia, and humerus. Scoliosis is seen in 10% of children with NF1 and may develop earlier than in the general population. An aggressive dystrophic form may develop between 3 and 7 years of age.

Life expectancy is approximately 10 to 15 years shorter in NF1 compared with the general population, with malignancy and vascular disease as the leading causes of death.

### Neurofibromatosis Type 2

NF2 is a tumor syndrome defined by the presence of bilateral vestibular schwannomas with associated hearing loss. The NF2 gene encodes merlin, or schwannomin, a cytoskeletal protein that may have regulatory and signaling functions. The precise mechanism of tumor formation is uncertain. NF2 is 100% penetrant—patients with the mutation have the disease. However, expressivity is highly variable, with

variable size, number, and location of tumors. In addition to the characteristic vestibular schwannomas that lead to progressive deterioration of hearing, patients with NF2 may develop intracranial or spinal meningiomas; ependymomas; astrocytomas; neurofibromas; schwannomas of the cranial, spinal, and peripheral nerves; and cutaneous schwannomas (the latter with minimal clinical effect). Meningiomas are seen in about 50% of NF2 patients, although the lifetime risk may be as high as 75%. Meningiomas may be the presenting feature, particularly in childhood. Ependymomas and astrocytomas are seen in up to 33% of patients. Peripheral schwannomas may arise from any nerve and may produce pain or sensory or motor dysfunction. Spinal intramedullary tumors, often multiple, are usually ependymomas. Patients with NF2 may also develop peripheral neuropathy that is not related to tumor growth. Seizure disorders are uncommon in NF2. Similarly, cognitive impairment is not a feature of NF2. Ocular findings in NF2 include juvenile posterior subcapsular lens opacities, retinal hamartomas, epiretinal membrane, and cortical wedge opacities. The average age at onset of symptoms is approximately 20 years, with average age at diagnosis of 28 years. Almost all patients develop bilateral vestibular schwannomas by age 30 years. However, 18% of patients show symptoms before age 15 years. NF2 is often underrecognized in children, with ocular or cutaneous findings, or meningioma, presenting in the first few years of life. An increasingly recognized early presentation is mononeuropathy in children, often with persistent facial palsy, squint, or hand or foot drop.

### Evaluation

**HISTORY.** Relevant history for NF2 should include any vision or hearing changes, tinnitus, vertigo, gait disturbances, decreased facial sensation, facial weakness or twitching, hoarseness, dysphagia, or headaches. Family history of NF2 is crucial for diagnosis (Box 297-2).

**PHYSICAL EXAMINATION.** Examination of a patient for NF2 should focus on vision, hearing, and cranial and peripheral nerve function. Younger patients often have headache, tinnitus, cranial nerve symptoms, or skin or spinal tumors before the onset of hearing loss. Eye examination should assess the presence of lens opacities. Cranial nerve examination should specifically address the trigeminal, facial, and auditory nerves. Neurologic examination should assess balance, gait, and deep tendon reflexes. At the skin examination, the physician should note the presence of neurofibromas, CALMs, or cutaneous schwannomas. Cutaneous schwannomas are present in approximately one-half of patients with NF2; they may be subcutaneous nodules or plaques with thickened texture and occasional hair growth, or surface pink to flesh-colored papules (Figure 297-6).

**LABORATORY EVALUATION.** Laboratory testing for possible NF2 should always include formal audiologic testing for sensorineural hearing loss, including a brainstem auditory evoked response. After the diagnosis of NF2 is established, audiometry should be repeated every 6 to 12 months. Molecular genetic testing for the mutations is available on a clinical basis



### BOX 297-2 Diagnostic Criteria for Neurofibromatosis Type 2

#### DEFINITE NF2

- Bilateral vestibular schwannomas
- or
- First-degree relative with NF2
- plus
- Unilateral vestibular schwannomas
- or
- Any 2 of the following: meningioma, schwannoma, glioma, neurofibroma, juvenile posterior subcapsular cataract

#### PROBABLE NF2

- Unilateral vestibular schwannoma
- plus
- Any 2 of the following: meningioma, schwannoma, glioma, neurofibroma, juvenile posterior subcapsular cataract
- or
- Multiple meningiomas
- plus
- Unilateral vestibular schwannoma
- or
- Any 2 of the following: schwannoma, glioma, neurofibroma, juvenile posterior subcapsular cataract

NF2, neurofibromatosis type 2.

Adapted from Yohay K. Neurofibromatosis types 1 and 2. *Neurologist*. 2006;12:86–93; and Neff BA, Welling DB. Current concepts in the evaluation and treatment of neurofibromatosis type II. *Otolaryngol Clin North Am*. 2005;38:671–684.



**Figure 297-6** Multiple schwannomas in neurofibromatosis type 2.

and should be used for relatives at risk. This will allow appropriate long-term screening if needed and might prevent unnecessary expensive testing.

**IMAGING STUDIES.** The most useful imaging modality for assessment of vestibular schwannomas is gadolinium-enhanced MRI with thin cuts through the internal auditory canals. Routine screening MRI of the brain is required for any patient with unilateral vestibular schwannoma, multiple intracranial or spinal

tumors, or a first-degree relative with NF2, or for a child with meningioma. As with audiometric testing, any child at risk for NF2 should have a screening brain MRI annually beginning at age 7 years. Spinal MRI should be considered if any symptoms or neurologic deficits are noted.

#### Management

The most important aspect of management in NF2 is early diagnosis so that surgery to preserve the hearing can be performed. Advanced tumors may prevent the preservation of hearing, leading to the need for either cochlear or auditory brainstem implants or possibly leading to complete deafness. At present, cochlear implants seem to be better than auditory brainstem implants for patients with NF2. After a diagnosis of NF2 is made, the child should be evaluated by ophthalmologic, otolaryngologic, audiologic, and imaging studies. Screening examinations, audiometry, and imaging should then be repeated at least annually starting at age 7 years. Children of a parent with NF2 should have annual ophthalmologic examinations starting in infancy and neurologic and audiometric examinations annually from age 7 years. Most patients with NF2 should be encouraged to learn sign language to prepare for possible future complete hearing loss. Patients with vestibular tumors should also be counseled that problems with balance and underwater disorientation pose drowning risk. Management of the tumors is still primarily surgical. Radiation therapy should be avoided, particularly in children, because of the risk for inducing or accelerating tumor growth.

The prognosis of NF2 is poor, despite the benign nature of the tumors. Location of the tumors often increases morbidity and mortality, with average age at death of 36 years. Survival for patients presenting at age 30 in the past 20 to 30 years was 15 years from diagnosis. Early detection and removal of tumors shows promise for prolonged survival.

#### WHEN TO REFER

##### NF1

- Pediatric ophthalmologic evaluation beginning in the first year
- Neurologic evaluation if seizures are difficult to manage
- Neurodevelopmental testing if evidence of learning disability, ADHD, and speech delay
- Surgical referral for symptomatic neurofibromas, renovascular hypertension

##### NF2

- Hearing loss or tinnitus should prompt referral for audiologic evaluation.
- Headache, gait, or balance concerns should prompt referral to neurology.

#### WHEN TO ADMIT

- Sudden neurologic decline or uncontrollable seizures

## TUBEROUS SCLEROSIS COMPLEX

### Definitions

Tuberous sclerosis complex (TSC), or Bourneville disease, is an autosomal-dominant multisystem disorder characterized by perturbed cellular growth and differentiation in the brain, heart, kidneys, skin, eyes, and other tissues. Although a dominant disorder, approximately 70% of cases arise as spontaneous new mutations. The prevalence of TSC is approximately 1 in 6,000. TSC results from mutations in 1 of 2 genes: *TSC1*, which encodes hamartin, or *TSC2*, which encodes tuberin. Hamartin and tuberin bind together as a heterodimeric protein involved in regulation of cell growth. The intact protein suppresses the protranslational effects of mammalian target of rapamycin. When either hamartin or tuberin is defective, mammalian target of rapamycin starts uncontrolled promotion of protein synthesis and cell growth, leading to tumor formation. Approximately 45% of cases with known mutations are caused by *TSC1*/hamartin mutations, and 55% are caused by *TSC2*/tuberin mutations. Fifteen percent to 20% of patients with TSC have no mutation identified. Determination of the type of mutation (see Laboratory Evaluation) is important for prognosis and may allow more selective emphasis on specific management strategy by mutation type. Patients with *TSC2* mutations are more likely to present with infantile spasms, developmental delay, and angiofibromas and often have more severe disease. Patients with *TSC1* mutations more often present with family history or hypomelanotic macules and may have less severe disease. Patients with no identified mutation are more likely to present with renal angiomyolipomas. Mutations of *TSC1* are more common in familial cases and seem to result in less severe disease.

The classic triad of seizures, intellectual disability, and facial angiofibromas is far from a complete picture of this complex, but highly variable, condition. In fact, only 29% of TSC patients have the complete Vogt triad, and 6% lack all 3 symptoms. Seizures and facial lesions do indeed occur frequently, but intellectual function is often normal or only slightly impaired. Approximately one-half of patients with TSC have normal intelligence, whereas approximately 30% have profound intellectual disability. The hallmark of TSC is the development of hamartomas in the various organ systems involved. An international consensus conference in 1998 developed revised diagnostic criteria for TSC based on newer understanding of the disease and its underlying pathophysiologic features. A summary of these criteria is found in Box 297-3. An important point to note is that TSC has no pathognomonic feature. Because an individual feature may occur as an isolated finding, the primary care physician must consider the diagnosis of TSC only if more than 1 organ system is involved or if different lesion types occur in a single system.

### Central Nervous System Manifestations

Central nervous system (CNS) disease is the most common and often most disabling aspect of TSC. The neurologic features of TSC include seizures, cognitive disability, and behavioral disturbances. Seizures occur in 80% to 90% of patients with TSC.

### BOX 297-3 Diagnostic Criteria for Tuberous Sclerosis Complex

#### MAJOR CRITERIA

- Facial angiofibroma or forehead plaque
- Ungual or subungual fibroma
- More than 3 hypomelanotic macules
- Connective tissue nevus (Shagreen patch)
- Cortical tuber<sup>a</sup>
- Subependymal nodule
- Subependymal giant cell astrocytoma
- Multiple retinal hamartomas
- Cardiac rhabdomyoma
- Renal angiomyolipoma
- Lymphangiomyomatosis

#### MINOR CRITERIA

- Dental enamel pits
- Hamartomatous rectal polyps
- Bone cysts (radiographic evidence sufficient)
- Cerebral white matter migration lines<sup>a</sup>
- Gingival fibromas
- Retinal achromic patch
- Nonrenal hamartomas
- Multiple renal cysts
- Confetti skin lesions

#### DIAGNOSIS

- Definitive: 2 major or 1 major and 2 minor criteria
- Probable: 1 major criterion plus 1 minor criterion
- Possible: 1 major or 2 or more minor criteria

<sup>a</sup>When cortical dysplasia (tuber) and cerebral white matter migration tracks are both present, they count as 1 criterion rather than 2 criteria.

Adapted from Rosser T, Panigrahy A, McClintock W. The diverse clinical manifestations of tuberous sclerosis complex: a review. *Semin Pediatr Neurol.* 2006;13:27–36; Roach ES, Sparagana SP. Diagnosis of tuberous sclerosis complex. *J Child Neurol.* 2004;19:643–649; and Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. *N Engl J Med.* 2006; 355:1345–1356.

All types of seizures except classic absence seizures have been reported in TSC. One of the more common forms is infantile spasms, seen in approximately one-third of infants with TSC. Infantile spasms are the presenting feature in 70% of infants with TSC. A thorough description of the clinical and electroencephalographic findings in infantile spasms is found in Chapter 327, Seizure Disorders. Children with infantile spasms are likely to have intellectual disability.

Seizure onset and severity are also closely associated with severity of cognitive impairment. Early onset of seizures or infantile spasms is associated with poor cognitive outcome. Although most patients with TSC and cognitive disability have epilepsy, many patients with TSC and seizures have normal intellect. However, children with infantile spasms are often cognitively impaired, corresponding to increased cortical hamartoma (tuber) burden in both circumstances. Furthermore, the presence of at least 7 cortical tubers on MRI confers a 5-fold increase in risk for moderate to profound

cognitive impairment, although a few patients with multiple tubers and normal intellect have been reported.

Autism spectrum disorder is also common in TSC, with prevalence estimates ranging from 17% to 68%. Autism spectrum disorder is much more common in children with intellectual disability in TSC (>60%) than among children with TSC and normal cognitive function (6%). Among children with autism spectrum disorder, TSC is found in up to 4%. Almost all children with autism spectrum disorder and TSC have epilepsy. Patients with autism and TSC do not exhibit the male preponderance seen in autism without TSC. Similarly, among children with autism and seizures, TSC is the underlying genetic condition in 14%.

A variety of behavioral abnormalities may be seen in children with TSC, including severe temper tantrums, restlessness, impulsivity, attention deficit with hyperactivity, self-injury, anxiety, and depression. Among children with TSC and a history of infantile spasms and autism, 69% exhibit behaviors disruptive to the family by age 5 years. Anxiety disorder is seen in up to 59%, and depression in 35%, of adults with TSC.

Learning disabilities have been noted frequently in TSC, although no systematic studies are available to date.

The neuropathologic findings responsible for many of the symptoms of TSC include tubers, subependymal nodules, and subependymal giant cell astrocytomas. The cortical tubers are nodular areas of gray and white matter dysplasia, often seen on the apex of a gyrus. Tubers are present in more than 95% of patients with TSC. Tubers have been noted as early as 20 weeks' gestation and are known to persist throughout life. No risk for malignant degeneration exists. Large numbers of tubers are associated with worse overall prognosis (infantile spasms, cognitive impairment, and difficult seizure control). The tubers also function as epileptogenic foci. Subependymal nodules are present in up to 80% of patients with TSC. They arise from the lateral and third ventricle walls and often protrude into the lumen. They can be present before birth and may sometimes be noted on imaging studies during infancy. The presence and number of subependymal nodules do not seem to correlate with severity of neurologic symptoms, in contrast to tubers. Subependymal giant cell astrocytomas, on the other hand, may be symptomatic. They occur in up to 14% of patients with TSC and seem to arise from subependymal nodules. They continue to grow during childhood and may produce focal neurologic deficits or obstructive hydrocephalus.

### Cutaneous Manifestations

Skin findings are the most consistent features of TSC. Hypomelanotic macules (formerly known as *ash leaf spots*) are found in more than 90% of patients with TSC and may be present at birth (Figure 297-7). They are often the earliest sign of TSC. In light-skinned individuals, they may be visible only with a Wood's lamp. They are usually larger than 1 cm and have a characteristic leaf shape—oval with one blunt end and one pointed end. At least 3 lesions must be visible for diagnostic significance. Hypomelanotic macules are



**Figure 297-7** Facial angiofibromas and hypomelanotic macules in tuberous sclerosis complex.

seen most commonly on the trunk, but they may occur anywhere. Fine, stippled hypopigmentation on the extremities is known as *confetti lesions*. When hypomelanotic macules occur on hair-bearing surfaces, associated poliosis (white hair) may be found.

Facial angiofibromas (formerly known as *adenoma sebaceum*) are noted in 70% to 75% of individuals with TSC. These small, discrete, shiny pink to reddish papules develop by approximately age 5 years, but they increase in number and size into the teen or early adult years (see Figure 297-7). Although they are initially distributed over the malar areas, they often spread to chin and nasolabial folds during puberty. Forehead plaques are flesh-colored to erythematous fibrotic plaques on the forehead or frontal scalp in approximately 19% of patients with TSC. They appear later than angiofibromas.

Shagreen patches are connective tissue nevi seen in 20% to 50% of patients with TSC. These patches are flesh-colored, slightly raised, irregularly shaped plaques with prominent follicles and cobblestone texture and are seen most often on the lower back (Figure 297-8). They are usually noted in later childhood.

Ungual and subungual fibromas are firm flesh-colored to red papules that develop beside or beneath the nails. Lesions under the nail may appear as a longitudinal ridge or groove. Toenail involvement is more common. These typically appear during puberty.

### Cardiac Manifestations

Cardiac rhabdomyomas are present in 50% to 70% of infants with TSC, but they usually remain asymptomatic. These tumors, which are often multiple, decrease in size over time. They are often diagnosed on prenatal ultrasound. Cardiac rhabdomyomas are the most common finding in infants diagnosed with TSC in the first week of life. Complications may include heart failure in infancy and various dysrhythmias, including Wolff-Parkinson-White syndrome.

### Ocular Manifestations

Retinal astrocytic hamartomas are seen in 50% to 87% of patients with TSC, although most remain





**Figure 297-8** Shagreen patches have an orange peel texture and often are located over the lumbosacral spine. (From Krowchuk DP, Mancini AJ, eds. *Pediatric Dermatology: A Quick Reference Guide*. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012:461–467.)

asymptomatic. They may be bilateral in up to one-half of patients. Three clinical types include (1) a raised mulberry-like calcified nodule, (2) a flat translucent gray patch, and (3) a transitional lesion with mixed features. Involvement of the macula, enlargement of the hamartoma, vitreous hemorrhage, or retinal detachment may lead to loss of vision. Other ocular findings in TSC may include retinal pigment anomalies, strabismus, cataracts, colobomas, iris depigmentation, and eyelid angiofibromas.

### Renal Manifestations

Renal lesions are the second most common organ system involvement in TSC (after CNS disease), with angiomyolipomas developing in 80% and renal cystic disease in 50% of patients. The prevalence increases with age until adulthood. Angiomyolipomas are found in 55% of 7-year-olds with TSC and 80% of 18-year-olds. Bilateral and multiple tumors are common. Small lesions may remain asymptomatic, but lesions larger than 4 cm pose risks for severe hemorrhage, hypertension, or renal insufficiency. The risk for hemorrhage ranges between 25% and 50%, with 20% to 30% of these patients presenting to emergency departments in shock. The risk for hemorrhage is much higher with aneurysms more than 5 mm in diameter. Renal cysts occur in approximately 17% of children and 47% of adults with TSC. Solitary epithelial cysts are the most common. However, approximately 3% to 5% of patients with TSC will develop polycystic kidney disease as a contiguous gene deletion syndrome because the *TSC2* gene is adjacent to the adult polycystic kidney disease gene *PKD1* on chromosome 16. Polycystic kidney disease may lead to renal insufficiency in late adolescence. Approximately 2% of TSC patients will have severe early-onset polycystic disease. Renal disease may also escalate after acute kidney injury

such as toxic reactions to some anticonvulsants or nonsteroidal anti-inflammatory drugs, or after prolonged seizures. Renal cystic disease is also a significant risk factor for hypertension. Hypertension may also result from the use of adrenocorticotrophic hormone to control infantile spasms. In addition, nephrolithiasis may have increased frequency in TSC because of renal cystic disease, ketogenic diet, and use of drugs such as topiramate. Renal cell carcinoma (RCC) is a less common but potentially severe complication of TSC. Although the lifetime risk for RCC is the same in TSC patients as in the general population, it typically occurs at a much earlier age in TSC patients (average age, 28 years in TSC patients; 52 years in general population). The overall morbidity of renal lesions in TSC is predominantly related to angiomyolipomas.

### Pulmonary Manifestations

Symptomatic lymphangiomyomatosis occurs in 1% to 2% of patients with TSC, almost exclusively in young women. Radiographic evidence of lymphangiomyomatosis may be seen in 26% to 39% of women with TSC. Spontaneous pneumothorax, dyspnea, cough, and hemoptysis are the main clinical findings. This condition is often progressive and is a leading cause of death among women with TSC.

### Vascular Manifestations

Arterial dysplasia is seen most often in renal angiomyolipomas, but it has also been reported with basilar artery and aortic aneurysms.

### Dental Manifestations

Gingival fibromas occur in approximately 50% of adults with TSC. Almost all patients with TSC have dental enamel pits in permanent teeth. The dental pits rarely cause problems, although extensive fibromas may result in malocclusion or abnormal tooth eruption.

### Differential Diagnosis

TSC does not have a pathognomonic lesion; thus, fulfillment of diagnostic criteria is of paramount importance (see Box 297-3). Facial angiofibromas were once considered diagnostic but are now known to occur in multiple endocrine neoplasia syndrome type 1.

### Evaluation

#### History and Physical Examination

In infants, seizures are often the first symptom. Any infant with new-onset seizures should have a detailed history taken, including skin lesions, developmental milestones, and family history. Initial examination should include Wood's lamp examination of the entire skin surface, funduscopic examination for hamartomas, and a thorough neurologic examination. Older children should be screened for seizure disorder, developmental delay, and autism spectrum disorders.

Delay in diagnosis is not uncommon in TSC. Staley and colleagues reviewed records of 243 patients with TSC and found that age at diagnosis ranged from birth to 73 years. Although the average age at diagnosis was 7.5 years, and 81% were diagnosed by age



10 years, 39% of patients were noted to have earlier diagnostic findings. The most commonly missed presenting features were seizures and skin lesions.

### Laboratory Evaluation

Laboratory testing should include an electrocardiogram, especially in infants or children with radiographic evidence of cardiac rhabdomyomas. After criteria are fulfilled for a diagnosis of TSC, molecular testing can be performed to determine the specific mutation. However, 15% to 20% of patients who fulfill TSC diagnostic criteria have no identifiable mutations. Clinical gene testing is available by using combined techniques such as denaturing high-performance liquid chromatography and heteroduplex analysis. Even with combined methods, the mutation detection rate is only 85%.

### Imaging Studies

Imaging studies are valuable for initial evaluation and long-term management of patients with TSC. Initial imaging studies for an infant with TSC include brain studies (MRI or CT), echocardiography, and renal ultrasound. Cortical tubers are best evaluated by MRI. Subependymal nodules may be seen in infancy on MRI as T1-weighted hyperintense nodules. By age 1 year, the subependymal nodules contain calcium and may be visualized with CT scanning. MRI may be useful to identify subependymal giant cell astrocytomas, but radiologic distinction from subependymal nodules is difficult. Renal lesions in older children and adults may be evaluated by ultrasound, CT, MRI, or PET. Chest CT is indicated for all women with TSC to evaluate for possible lymphangiomyomatosis.

### Management

The 2 basic principles of management in TSC are establishment of the correct diagnosis and long-term follow-up for the later manifestations. The treatment of epilepsy in TSC is the same as in other forms of epilepsy (see Chapter 327, Seizure Disorders), with one exception. Infantile spasms in TSC do not respond as well to adrenocorticotrophic hormone as infantile spasms without TSC. The irreversible  $\gamma$ -aminobutyric acid transaminase inhibitor vigabatrin is much more effective, with response rates up to 96% in infants with TSC and infantile spasms. Vigabatrin was approved by the US Food and Drug Administration for infantile spasms in 2009, but concerns remain regarding potential severe ophthalmic toxicity. However, because of the potentially devastating cognitive effect of uncontrolled infantile spasms, vigabatrin may be considered despite its toxicity. With any type of seizures in TSC, better control seems to improve prognosis. Seizures become refractory to treatment in up to 50% of children with TSC.

Neurobehavioral assessment and monitoring are integral to the management of TSC. Routine formal testing should be performed at age-appropriate levels in infancy, preschool, and early school age, and periodically into adulthood to identify cognitive and behavioral issues as early as possible. In addition, any developmental or behavioral regression or new cognitive dysfunction should prompt urgent re-evaluation.

Annual brain MRI is suggested to age 21 years. Annual renal imaging is suggested for monitoring of angiomyolipomas. Serial renal ultrasound is adequate if maximal lesion size is less than 4 cm. Larger renal lesions should be assessed by Doppler, MRI, or magnetic resonance angiography for abnormal vasculature. Screening chest CT for lymphangiomyomatosis is suggested for all women with TSC. Women with lung lesions should have annual pulmonary function tests.

Genetic counseling is mandatory for families and patients with TSC. Because the disorder has autosomal-dominant inheritance, affected individuals have a 50% risk for affected offspring. Germline mutations occur in approximately 2% of patients; thus, seemingly unaffected parents with a single affected child still have approximately a 2% risk for having another affected child.

### WHEN TO REFER

- Ophthalmologic screening: in infancy if TSC is suspected
- Neurologic screening: when seizures are hard to manage or progressive
- Surgery: when symptomatic or progressive renal lesions are larger than 4 cm
- Neurodevelopmental testing: at diagnosis and periodically

### WHEN TO ADMIT

- Sudden neurologic deterioration
- Intractable seizures
- Gross hematuria
- Heart failure or dysrhythmia

## STURGE-WEBER SYNDROME

Sturge-Weber syndrome (SWS), or encephalotrigeminal angiomas, is a rare sporadic disorder characterized by the presence of upper facial port-wine stain (PWS), ipsilateral ocular abnormalities, and ipsilateral leptomeningeal angiomas. Although the syndrome may consist of only 1 or 2 of the triad features, the defining entity is leptomeningeal involvement. SWS has an estimated frequency of approximately 1 in 50,000 live births. It is thought to result from failed regression of the cephalic venous plexus. By the sixth week of embryologic development, a vascular plexus forms around the cephalic part of the neural tube and under the facial skin ectoderm. This plexus usually regresses by the ninth week. In SWS, the plexus persists, with the extent of involvement correlating with the extent of facial and leptomeningeal lesions. No gender predilection has been found. Although a few case reports have suggested familial occurrence, the disorder is thought to result from somatic mosaicism. This concept is supported by discordance between monozygotic twins.

SWS exhibits at birth with an upper facial capillary malformation (PWS), involving the area of skin innervated by the ophthalmic (V1) division of the trigeminal nerve. This area includes the forehead, brow ridge, upper

eyelid, and perhaps the lower eyelid as well. Lower areas of the face (V2 or V3 distributions) may also be involved, but no apparent significant risk for SWS exists in the absence of V1 involvement. Unilateral PWS is the rule, with only 10% to 30% of patients having bilateral PWS. With unilateral facial PWS, the risk for having SWS is approximately 8%, but the risk is much higher if bilateral PWS is present. One of the more useful clinical clues seems to be eyelid involvement, a significant predictor of disease. PWSs are pink to red blanching macules to patches with variable irregularity of the borders (Figure 297-9). They are capillary malformations that remain fixed in location and show no tendency to evolve or involute over time. Growth should be commensurate with the child's growth. With age, the PWS may thicken and darken, becoming somewhat cobbledstoned by adulthood.

Ocular manifestations of SWS may include glaucoma, vascular anomalies of the globe (conjunctiva, episclera, retina, or choroid), buphthalmos, iris heterochromia, retinal detachment, retinal pigment degeneration, cataract, and optic disc coloboma. Glaucoma is the most common ocular problem in SWS, occurring in up to 70% of patients. Glaucoma is usually ipsilateral to the PWS, but it may be bilateral, even if the PWS is unilateral. Although glaucoma may develop from birth to the fifth decade, the median age at onset is 5 years, with 60% developing in infancy to early childhood. Glaucoma developing in infancy, when the globe is more sensitive to increased intraocular pressure, may lead to increased corneal diameter, buphthalmos, or iris heterochromia. Choroidal hemangioma ipsilateral to the PWS is seen in up to 71% of patients with SWS. Choroidal hemangioma is almost always associated with leptomeningeal lesions, making CNS imaging mandatory. Over time, the retinal changes can lead to visual field defects and vision loss.

Neurologic features of SWS may include seizures, focal neurologic deficits, hemiparesis, developmental delay, progressive intellectual disability, or headaches. Seizures are the most common neurologic problem, occurring in 75% to 83% of patients with SWS. Approximately 75% of seizure disorders develop in the first 2 years of life. Partial motor seizures are the most common type (40%), but generalized tonic-clonic,

atonic, and absence seizures may also occur. Infantile spasms may be the presenting seizure type. Seizures tend to worsen with age, becoming more frequent, severe, and complex. Seizures may be provoked by febrile episodes. Status epilepticus may occur in up to one-half of these children. Earlier onset may predict worse outcome, with poor seizure prognosis, more difficult seizure control, and higher risk for cognitive impairment, although this is somewhat controversial. Bilateral leptomeningeal angiomas (7%–26% of patients) has a poor neurologic prognosis. Some patients may develop sudden episodes of weakness, even in the absence of seizures. These episodes are stroke-like and may be transient or may leave permanent hemiplegia. Hemianopsia may develop in up to one-half of SWS patients.

Developmental delays are seen in up to one-half of patients with SWS. Early milestones are often normal, with decline in function noted over time. At least some of the cognitive decline occurs during periods of encephalopathy after prolonged or severe seizures, whereas other patients experience decline in function as a result of recurrent stroke-like episodes. Factors that seem to correlate best with developmental delay and its severity are presence of bilateral cerebral lesions, degree of cerebral atrophy, presence of intractable seizures or multiple seizure types, and possibly early onset of seizures, although the last of these factors remains controversial. In the absence of seizures, cognitive development is normal. Furthermore, 85% of patients with seizure onset after age 4 years have normal intelligence.

Psychological manifestations of SWS may include ADHD, irritability, and social problems. Inattentive and oppositional behaviors may be noted. Approximately 85% of patients with SWS who have intellectual disability exhibit emotional or behavioral problems, including aggressive behavior toward others and self-abuse.

Headache, including migraine, is seen in 30% to 45% of individuals with SWS. The median age at onset is 8 years. Migraines may be associated with visual aura and visual field defects.

### Differential Diagnosis

The differential diagnosis of SWS includes isolated (ie, nonsyndromic) facial PWS and Wyburn-Mason syndrome. Unilateral forehead PWS has no underlying syndrome in 92% of patients. Bilateral PWS, in contrast, has a much higher likelihood of association with SWS. Wyburn-Mason syndrome is a rare disorder consisting of retinal and CNS arteriovenous malformations associated with upper facial PWS. Headaches, seizures, focal neurologic deficits, retinal hemorrhage, and subarachnoid hemorrhage may occur.

### Evaluation

#### History

The earliest manifestation of SWS is the PWS present at birth. Relevant history in a child with facial PWS should include history of seizures, history of eye or vision problems, and any concerns about development. Older children should be asked about headaches, vision changes, episodes of weakness, and school progress.



**Figure 297-9** Port-wine stain in Sturge-Weber syndrome.

### Physical Examination

Examination of any child with facial PWS should include a thorough eye examination. Any difference in sizes of cornea or globe, or any iris heterochromia, may be a clue to early glaucoma. Presence of PWS on eyelids should be noted. Auscultation of the orbits, fontanels, and temples should be performed to detect bruits. Funduscopic examination might reveal the characteristic *ketchup stains* of choroidal angiomas. Tortuous vessels or colobomas should be noted. Neurologic examination should search for focal deficits. Developmental evaluation is important, particularly if the child has a seizure history. Observation of an infant should specifically address the presence of a head turn or early handedness, which are potential clues to visual field cuts.

### Laboratory Evaluation

Routine laboratory testing is not useful in SWS. Evaluation of seizures should include electroencephalography. The typical findings include asymmetry, with background slowing and reduced voltage in the affected hemisphere. The asymmetry becomes more prominent with the progressive cerebral atrophy.

### Imaging Studies

The most sensitive imaging modality to evaluate for leptomeningeal angiomas is gadolinium-enhanced MRI. Leptomeningeal enhancement, with or without cortical atrophy, is the radiologic hallmark of SWS. The leptomeningeal involvement is ipsilateral to the PWS. It may be seen before calcifications develop. Calcification of adjacent gyri may give the classic *tram track* appearance seen on CT and even plain-film radiographs (although the latter rarely are used). Involvement of the parietal and occipital lobes is often noted before frontal or temporal findings. Positron emission tomography and single-photon emission CT may reveal areas of altered metabolism and hypoperfusion. Chronic venous engorgement leading to reduced perfusion is thought to be the mechanism underlying progressive cerebral atrophy in SWS. Choroidal angiomas are best visualized with MRI.

### Management

Infants with facial PWS on the forehead and eyelids should be evaluated for the possibility of SWS. Evaluation should include ophthalmologic examination. If eye findings or any other typical clinical features, such as seizures, are present, then neuroimaging is mandatory. Routine MRI may be performed even in the absence of seizures because prophylactic anticonvulsant therapy may be useful for infants with extensive intracranial disease. Seizure control is the most important aspect of management because seizure activity may further compromise cerebrovascular function and lead to worse neurologic decline. Carbamazepine and oxcarbazepine are useful first-line anticonvulsants for SWS. Valproic acid, topiramate, phenobarbital, phenytoin, and vigabatrin have also been suggested. (For a thorough discussion of anticonvulsant therapy, see Chapter 327, Seizure Disorders.) Refractory seizures in SWS may lead to consideration of seizure surgery.

Hemispherectomy and focal resection have both been found to reduce refractory seizures and improve developmental outcomes. Avoiding fatigue, sleep deprivation, stress, and minor head trauma may help prevent headaches. Glaucoma may be managed medically in most patients with  $\beta$ -adrenergic blockers or carbonic anhydrase inhibitors. Surgical approaches are not usually required. PWS may be treated effectively with pulsed dye laser.

### WHEN TO REFER

- Ophthalmologic evaluation: any infant with forehead and eyelid PWS
- Neurologic evaluation: difficult seizure management

### WHEN TO ADMIT

- Refractory seizures

## VON HIPPEL-LINDAU DISEASE

Von Hippel-Lindau disease (VHL) is an autosomal-dominant multiorgan familial cancer syndrome. Prevalence is estimated at about 1 in 36,000 live births. The disease is inherited in 80% of patients, with the remainder representing new mutations. The disease is more than 90% penetrant by age 65 years. The *VHL* gene is a tumor suppressor gene found on chromosome 3. The normal gene product is part of a protein complex responsible for ubiquitination of hypoxia-inducible factors, leading to their degradation. With functional loss of the VHL protein, these hypoxia-inducible factors trigger transcription of vascular proliferation mediators, including vascular endothelial growth factor, platelet-derived growth factor, transforming growth factor- $\alpha$ , and erythropoietin. These growth factors then lead to unregulated endothelial and vascular proliferation to produce vascular neoplasms. Erythropoietin production may lead to development of polycythemia, including the nontumoral syndrome Chuvash polycythemia, which also is caused by a mutation in the *VHL* gene. The mechanism of nonvascular tumorigenesis remains uncertain. Almost all patients with VHL have germline mutations in the *VHL* gene, as well as secondary somatic mutations (Knudson two-hit hypothesis). VHL is subdivided into 2 major categories that are based on the type of mutation. Type 1 disease mutations are premature termination mutations or deletions, whereas type 2 disease is characterized by missense mutations. Phenotypically, type 1 disease is not associated with significant risk for pheochromocytoma, whereas pheochromocytoma is a predominant tumor in type 2 disease. Further subdivisions are listed in Table 297-3. The diagnosis of VHL is established in a patient who has 1 characteristic tumor and a positive family history, or hemangioblastoma plus 1 other tumor when the family history is negative. The most common tumors in VHL are cerebellar, spinal, and retinal hemangioblastomas. The other associated tumors include renal cysts, RCC, pheochromocytoma, pancreatic cysts or neuroendocrine tumors, endolymphatic sac tumors of the inner



**Table 297-3** Classification of von Hippel-Lindau Disease

SUBTYPE	HEMANGIO-BLASTOMA <sup>a</sup>	RENAL CELL CARCINOMA	PHEOCHROMO-CYTOMA	PANCREATIC CYST OR TUMOR
1	+	+	–	+
2a	+	–	+	–
2b	+	+	+	+
2c	–	–	+	–

+, High risk; –, low risk.

<sup>a</sup>Retinal, central nervous system.

Adapted from Joerger M, Koeberle D, Neumann HP, et al. Von Hippel-Lindau disease: a rare disease important to recognize. *Onkologie*. 2005;28:159–163; and Shuin T, Yamasaki I, Tamura K, et al. Von Hippel-Lindau disease: molecular pathological basis, clinical criteria, genetic testing, clinical features of tumors and treatment. *Jpn J Clin Oncol*. 2006;36:337–343.

ear, and cystadenomas of the epididymis or broad ligament. The major causes of death are RCC and complications from CNS hemangioblastomas.

CNS hemangioblastomas are the most common tumors in VHL (60%–84% of patients). They occur most commonly in the cerebellum (63%), followed by the spinal cord (32%) and brainstem (5%). The mean age at presentation is 33 years, but tumors may develop in childhood (younger than 10 years) through the fourth decade of life. These slow-growing benign tumors produce symptoms largely by mass effect or obstructive hydrocephaly. Cerebellar tumors may present with headache, nausea, vomiting, vertigo, slurred speech, and broad-based gait. Clinical signs may include papilledema, nystagmus, ataxia, and dysmetria. Spinal hemangioblastomas may produce back pain, numbness, pain or weakness in arms or legs, posterior column proprioceptive defects, or incontinence. CNS hemangioblastomas tend to exhibit alternating periods of growth and stability so that low-level chronic symptoms may worsen acutely during a critical growth phase. These tumors or retinal tumors are commonly the first symptomatic lesions of VHL. Although histologically benign, these CNS lesions are a major source of mortality in VHL.

Retinal hemangioblastomas (capillary hemangiomas) develop in more than one-half of patients with VHL. Although most of these patients have solitary tumors, approximately one-third will have multiple lesions, and one-half will have bilateral retinal tumors. Most of these lesions develop in the second to third decades of life, with mean age at diagnosis of 25 years. However, retinal tumors may develop at any time from infancy to the ninth decade. Patients may experience painless loss of visual acuity or visual field defects, although they may remain asymptomatic. Exudation or hemorrhage from the hemangiomas may lead to macular edema or retinal detachment. Secondary changes in the anterior chamber may lead to glaucoma or cataract.

Renal cysts are seen in approximately one-half of patients with VHL. Often multiple and bilateral, they may remain asymptomatic, but are considered premalignant. Stable lesions may not require intervention. RCC develops in 75% of patients with VHL by age 60 years. RCC is seen in patients with type 1 or 2b disease. The typical histologic type is the clear cell type. It usually develops after 20 years of age, although often

earlier than with sporadic renal carcinoma. Lesions are frequently multiple and bilateral. The tumors may be associated with cysts and may have a better 10-year survival than sporadic RCC. However, metastatic RCC is a leading cause of death in patients with VHL. Symptoms may include hematuria, flank pain, or flank mass. By the time symptoms develop, metastases are present in 30% to 50% of patients.

Pheochromocytoma occurs in type 2 disease with a frequency of 10% to 24% and may be the only manifestation of VHL (type 2c). VHL accounts for approximately 20% of all pheochromocytomas. Mean age at presentation is 27 years, but tumors may be present even before age 10 years. In the pediatric age group, pheochromocytoma may be the presenting feature of VHL, with severe hypertension or hypertensive crisis as the most frequent presentation. Pheochromocytoma in VHL differs from sporadic tumors by occurring at an earlier age and by developing multiple, bilateral, and extra-adrenal tumors in VHL. Only 5% of VHL pheochromocytomas are malignant. Clinical features may include hypertension (paroxysmal or sustained), palpitations, sweating, flushing, headache, tachycardia, pallor, and nausea.

Pancreatic cysts or tumors occur in approximately 35% to 77% of patients with VHL in most series, but most are benign. Benign cystadenomas occur in approximately 12% of patients with VHL. Approximately 9% to 17% of patients with VHL will develop neuroendocrine tumors. The latter may be multifocal and may metastasize in 10% to 20%. The mean age at diagnosis of pancreatic lesions is 29 to 38 years, although islet cell tumors may be seen as early as 10 years of age. Most pancreatic lesions are asymptomatic and are found during routine imaging surveillance, but malignant tumors have been reported in up to 50% of VHL patients.

Approximately 10% of patients with VHL will develop endolymphatic sac tumors. These locally invasive papillary cystadenomas arising from the inner ear labyrinth ectoderm may cause deafness, tinnitus, or vertigo. Facial nerve and vocal paralysis may result from progressive tumor growth. The hearing loss is irreversible and presents at an average age of 22 years.

Finally, cystadenomas may develop in the epididymis in men and the uterine broad ligament in women. These are usually asymptomatic.



**Table 297-4** Differential Diagnosis of Retinal Capillary Hemangioma in von Hippel-Lindau Disease

CONDITION	FEATURE	PRESENCE OF RETINAL OR SUBRETINAL EXUDATES
von Hippel-Lindau disease	Orange-red circumscribed tumors Pair of prominent vessels Stellate macular exudates	Yes
Coats disease	Diffuse retinal vascular anomaly	Yes
Wyburn-Mason syndrome	Dilation and tortuosity of retinal arteries and veins, but no intervening hemangioma	No
Retinal cavernous hemangioma	Cluster of small dilated vessels around central vein Lack of prominent feeder vessels	No
Vasoproliferative tumor of the retina	Pink to yellow retinal tumor Lack of dilated feeder vessels Lack of stellate macular exudates	Yes (nonstellate)

Derived from Magee MA, Kroll AJ, Lou PL, et al. Retinal capillary hemangiomas and von Hippel-Lindau disease. *Semin Ophthalmol.* 2006;21:143–150.

### Differential Diagnosis

Central nervous system hemangioblastomas create symptoms by mass effect, as with many other tumors, cysts, and obstructive hydrocephalus. Evaluation of mass effect with neurologic symptoms should reveal the characteristic radiologic findings of hemangioblastomas. The differential diagnosis of retinal capillary hemangiomas is provided in Table 297-4. The differential diagnosis of renal cysts includes the diagnosis of polycystic kidney disease. Pheochromocytoma may occur sporadically or may occur in the setting of VHL, multiple endocrine neoplasia type 2a or 2b with associated medullary thyroid carcinoma, or neurofibromatosis, or with succinate dehydrogenase subunit mutations.

### Evaluation

#### History

The most important historical information is family history because 80% of cases are familial. Other relevant history might include changes in vision; development of neurologic symptoms such as clumsiness, broad-based gait, hearing loss, slurring of speech, pain, numbness or weakness in limbs, or loss of bowel or bladder control after complete toilet training; hematuria or flank pain; heart palpitations, flushing, or sweating spells; or episodic nausea and vomiting.

#### Physical Examination

Physical examination should include regular blood pressure evaluation, thorough eye examination, and thorough neurologic examination with particular attention to cerebellar and spinal functions. Observation of gait, test of balance, deep-tendon reflexes, and test for sensation should be included in the examination.

#### Laboratory Evaluation

Laboratory testing in VHL should begin with molecular testing for the specific mutation in the *VHL* gene because the phenotypic profile and tumor risk are directly related to the types of mutation. Identification of

*VHL* mutation carriers early in life is critical to determine the type of tumor risk and the necessary ongoing surveillance the child will need. It is particularly important to identify those at risk for retinal disease because early detection of intraocular tumors can lead to prompt vision-saving therapy. Subsequent laboratory evaluation for patients with type 2 disease should consist of annual screening for plasma or urine catecholamines and metanephrines beginning at age 10 years. The typical profile in VHL pheochromocytoma is noradrenergic, with norepinephrine elevations representing 98% of these patients.

#### Imaging Studies

Magnetic resonance imaging with gadolinium contrast is the modality of choice for most of the features of VHL. Hemangioblastomas of the cerebellum are usually subpial in location. They may appear as a solid enhancing mass with or without surrounding fluid space or as a more complex tissue or fluid mass. Spinal hemangioblastomas are solid enhancing intramedullary masses frequently associated with a surrounding fluid-filled syrinx that enlarges and displaces the cord. Renal cysts may be found on MRI, ultrasound, or CT. Endolymphatic sac tumors can be detected on MRI or CT imaging. Localization of pheochromocytomas requires use of 2 imaging modalities, often MRI or CT coupled with MIBG or octreotide scintigraphy, PET, or dopamine and deoxyglucose scans.

#### Management

The most important aspect of management in VHL is regular screening for the various tumors. First-degree relatives should also be screened for tumors. After a diagnosis is established, regular imaging and ophthalmologic examinations are indicated. Eye examinations, including dilated funduscopy, should begin by age 6 years and should be repeated annually. Annual cranial and spinal MRI should begin by age 10 to 11 years. Abdominal imaging for kidneys and possible pheochromocytoma should begin by age 15 to 18 years and may consist of ultrasound, CT, or MRI, with MRI

being the best modality for finding all the possible intraabdominal tumors (renal, pheochromocytoma, and pancreatic). Hearing loss or tinnitus should be evaluated by MRI with thin sections through the ear structures, as well as formal audiologic examination. Lifelong surveillance is required, even after excision of tumors, because of both late-onset presentation of new tumors and the risk for late tumor recurrences.

Surgical excision is generally considered the best treatment for most symptomatic VHL tumors. CNS hemangioblastomas that remain stable and asymptomatic may be followed by serial imaging. Proper management for asymptomatic, but radiologically progressive, lesions is a matter of debate. Spinal hemangioblastomas and large or symptomatic intracranial tumors are generally resected. Small retinal lesions are often treated with laser photocoagulation; larger lesions may require cryotherapy, brachytherapy, or vitreoretinal surgery. Screening for eye lesions is of critical importance because the visual prognosis is better when ocular lesions are detected before development of symptoms. Small renal tumors (<3 cm) are often followed by serial imaging. Larger lesions may be addressed by partial nephrectomy. Radical nephrectomy is rarely indicated. Pancreatic tumors larger than 3 cm are generally resected. Almost all metastatic pancreatic tumors have at least 2 of the following features: size larger than 3 cm, mutations in exon 3 of the *VHL* gene, or a tumor doubling time of less than 500 days. Symptomatic pheochromocytomas require excision. Laparoscopic removal of both adrenal and extraadrenal tumors is now favored, with its lower complication rate.

#### WHEN TO REFER

- Ophthalmologic examination: by age 6 years; with any sudden vision change
- Neurologic examination or neurosurgery: on detection of CNS tumors
- General surgery: on detection of intra-abdominal tumors
- Audiology: at diagnosis, or at onset of auditory symptoms

#### WHEN TO ADMIT

- Hypertensive crisis with pheochromocytoma
- Sudden neurologic deterioration

### ATAXIA-TELANGIECTASIA

Ataxia-telangiectasia (A-T), or Louis-Bar syndrome, is an autosomal-recessive progressive neurodegenerative disorder with a frequency of 1 in 40,000 in the United States to 1 in 300,000 in the United Kingdom. Consanguinity is a common finding. The characteristic features are progressive decline in cerebellar function, oculocutaneous telangiectasia, immunodeficiency, susceptibility to cancer, and sensitivity to ionizing radiation. A-T is caused by mutations in the *ATM* (ataxia-telangiectasia, mutated) gene. The ATM protein is a nuclear serine-threonine protein kinase that acts as a regulator of many cellular control pathways. Its primary function seems to be

mobilization of cellular responses to breaks in double-stranded DNA. After a DNA break occurs, *ATM* activates numerous proteins involved in DNA repair, apoptosis, and control of cell cycling. Loss of *ATM* function leads to accumulation of defective DNA and inability to repair or eliminate genetically defective cells. Defective DNA repair explains the sensitivity to ionizing radiation, whereas inability to remove damaged cells has been postulated as a cause of many of the diverse abnormalities in A-T. Similarly, cancer has been linked to genomic instability, helping explain the cancer risks in A-T.

Infants with A-T are normal; they begin to walk at approximately age 12 months. However, by age 2 to 3 years, they develop unsteady gait and staggering. Choreoathetosis begins soon thereafter. Dystonia or choreoathetosis develops in 90% of patients with A-T. By age 10 years, most children require wheelchairs for mobility because they have slow reflexes and tend to fall. Ocular apraxia (difficulty with voluntary eye movement), which may be confused with absence seizures in infants, develops in early childhood. Similarly, dysarthric speech is often present early in childhood but can be difficult to assess.

Telangiectasias (tortuous dilated capillaries) develop several years after the onset of neurologic symptoms. They are found on the bulbar conjunctiva, nasal bridge, ears, neck, knuckles, and both antecubital and popliteal fossae.

Immunodeficiency varies but may be severe in approximately one-third of patients with A-T. Many patients have reduced numbers of T lymphocytes with poor mitogen response. Low serum levels of immunoglobulin (Ig) E (80% of patients), IgG<sub>2</sub> (80%), and IgA (60%) are noted despite normal to high numbers of B cells. In addition, IgM levels vary widely, at times rising enough to create a hyperviscous state. Some patients exhibit poor immune response to pneumococcal polysaccharides. Patients with severe immunodeficiency may develop recurrent sinopulmonary infections. However, opportunistic organisms are not a problem in patients with A-T. Patients with A-T are at higher risk (one-third) for developing cancer. In children, acute lymphoblastic leukemia predominates, followed by other lymphoid tumors such as B-cell non-Hodgkin lymphoma, T-cell lymphoma, and Hodgkin disease. Older children sometimes develop T-prolymphocytic leukemia. Adults tend toward non-lymphoid cancers such as breast, stomach, ovarian, liver, and uterus cancers, melanoma, and basal cell skin cancer. Women who are *ATM* mutation carriers have a 5-fold increase in risk for breast cancer compared with the noncarrier population. Approximately 15% of patients with A-T die from lymphoid malignancies during childhood.

Because of the inability to repair defective DNA, patients with A-T are also susceptible to injury by ionizing radiation and radiomimetic chemotherapeutic drugs. This susceptibility complicates therapy for the various malignancies and poses a life-threatening risk to patients with A-T exposed to these agents.

#### Differential Diagnosis

The differential diagnosis of A-T is provided in Table 297-5.

**Table 297-5** Differential Diagnosis of Ataxia-Telangiectasia

CONDITION	NEUROLOGIC FEATURES	PRESENCE OF TELANGIECTASIA	INCREASED $\alpha$ -FETOPROTEIN	CANCER RISK	IMMUNE DEFICIENCY	SENSITIVITY TO RADIATION
Ataxia-telangiectasia	Early ataxia, oculomotor apraxia, progressive neurologic decline	Yes	Yes	Yes	Yes	Yes
Ataxia-telangiectasia-like disorder ( <i>hMRE11</i> mutation)	Ataxia early	No	No	No	No	Yes
Nijmegen breakage syndrome	Microcephaly, intellectual disability	No	No	Yes	Yes	Yes
Ataxia oculomotor apraxia type 1	Early ataxia, progressive neurologic decline	No	No	No	No	No
Ataxia oculomotor apraxia type 2	Late-onset ataxia	No	Yes	No	No	No

Adapted from Chun HH, Gatti RA. Ataxia-telangiectasia, an evolving phenotype. *DNA Repair (Amst)*. 2004;3:1187–1196; Perlman S, Becker-Catania S, Gatti RA. Ataxia-telangiectasia: diagnosis and treatment. *Semin Pediatr Neurol*. 2003;10:173–182; and Taylor AM, Byrd PJ. Molecular pathology of ataxia telangiectasia. *J Clin Pathol*. 2005;58:1009–1015.

### Evaluation

The earliest manifestation of A-T is the ataxia, beginning as broad-based gait or staggering by age 2 to 3 years. Any other history should focus on additional neurologic symptoms and developmental milestones. Additional history should include the presence of similar neurologic problems or consanguinity in the family.

Examination should focus on neurologic findings, including cerebellar function. Although difficult to assess in young children, voluntary visual tracking of objects will often reveal the early development of oculomotor apraxia. In older children, telangiectasia may be noted on the bulbar conjunctiva and on the skin of the neck, face, ears, and extremity flexures. The examination should include thorough lymph node examination and abdominal evaluation for hepatosplenomegaly.

Laboratory testing in suspected A-T should include serum  $\alpha$ -fetoprotein, which is increased in more than 95% of patients with A-T. Serum  $\alpha$ -fetoprotein increase is only useful beyond age 2 years because some children have persistent mild increases beyond the neonatal period. Karyotyping is rarely normal in A-T, often showing translocations between chromosomes 7 and 14. Quantitative immunoglobulins may show low levels of IgE, IgA, and IgG2. IgM is normal or high. Quantitative T- and B-cell numbers will reveal low levels of T cells, but normal to slightly high levels of B cells. The only radiosensitivity test currently available is the colony survival assay, which uses the patient's transformed lymphocytes. It requires approximately 3 months to complete. Gene testing is not useful unless the family mutation is known because *ATM* is a huge gene with 66 exons and more

than 400 known mutations (none with a frequency of more than 3%). Measurements of the ATM protein from the transformed lymphocyte cell line is also possible (by immunoblotting).

Imaging in A-T is limited. Cranial MRI will reveal gradual cerebellar atrophy, almost always noted by age 10 years. Imaging with radiation should be considered carefully because of these patients' extreme radiosensitivity. Adult female patients and carriers should be screened for breast cancer with regular examinations and ultrasound, but not mammograms.

### Management

The most important aspects of therapy in this degenerative condition are family and patient counseling and support, followed by rehabilitation and assistance with the progressive ataxia. Speech, physical, and occupational therapy should be obtained early to help the child and family with the problems that arise over time. Speech therapy may help with the communication and swallowing difficulties, whereas mobility, safety, and daily living skills can be supported by physical and occupational therapy. Careful monitoring is crucial for the recurrent infection and cancer risks. Recurrent sinopulmonary infections should be treated aggressively, and aspiration should be anticipated. Although ionizing radiation is of concern in these patients, it is imperative to diagnose pulmonary disease early, and chest radiographs deliver relatively little radiation compared with other modalities. Emotional support is crucial, with depression, anger, and isolation occurring frequently.

Life expectancy varies, but survival into the sixth decade is likely. The leading causes of death are malignancy, infection, and pulmonary failure (the latter from combined recurrent infection and recurrent aspiration).

### WHEN TO REFER

- Neurologic examination: on development of ataxia
- Speech therapy: on development of speech or swallowing difficulty
- Physical and occupational therapy: before ataxia becomes severe

### WHEN TO ADMIT

- Severe pulmonary infection, especially if respiratory distress is present
- Severe aspiration event

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Let's Face It* (Web page), ([www.lets-face-it.org.uk](http://www.lets-face-it.org.uk))

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## Chapter 298

# OBESITY AND METABOLIC SYNDROME

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## INTRODUCTION

Childhood obesity has reached epidemic proportions in the United States and worldwide. The US continues to have a high prevalence of obesity with one-third of all adults and one-sixth of all children aged 6 to 19 years classified as obese. The medical complications associated with obesity, including non-insulin dependent diabetes mellitus, hypertension, and dyslipidemia, continue to rise. In the US, total health care expenses for obesity now exceed those for smoking. The cause of this epidemic is multifactorial, including biologic, psychologic, environmental, and social factors. Despite tremendous research efforts, an inadequate understanding of risk factors and protective factors remains. Furthermore, strategies to prevent and treat childhood obesity need to be developed and evaluated. Child health professionals play a crucial role in preventing further escalation of this epidemic and in treating people who are already affected.

## DEFINITIONS

The terms *overweight* and *obese* commonly are used to describe adiposity in the adult population. The currently accepted definitions of overweight and obesity in children and adults are based on body mass index (BMI). Body mass index is weight in kilograms divided by height in meters squared. This calculation has been validated as an approximation of a person's body fat and correlates well with medical complications associated with obesity; BMI is also easily calculated from standard measurements obtained during health care visits. The Centers for Disease Control and Prevention provide age- and sex-specific growth curves for BMI. Electronic medical records allow for routine calculation and plotting of BMI when height and weight data are entered into the record.

In adults, a BMI of 25 or greater is considered overweight, whereas a BMI of 30 or greater is obese. In children, fat mass percent changes throughout development; therefore, BMI percentiles are used to correct for age and gender. Normal BMI trajectories include a decrease in BMI during the preschool years followed by an increase beginning at 5 to 6 years and continuing through adolescence, stabilizing in early adulthood. For children and adolescents, overweight is defined as a BMI at or above the 85th percentile and below the 95th percentile. Obese is defined as a BMI at or above the 95th percentile.

## EPIDEMIOLOGY

Between the 1960s and 2010, the prevalence of obesity dramatically increased worldwide in developed and underdeveloped countries. Only the very poorest geographic areas where food scarcity is widespread, such



as Haiti and sub-Saharan Africa, have yet to be affected. Although worldwide obesity prevalence continues to rise, the prevalence has not been increasing over the last decade in the United States and in several European countries.

The most recent US data from the 2011 to 2012 National Health and Nutrition Examination Survey reveals that 35% of US adults were obese and an additional 34% were overweight. In children and adolescents from 6 to 19 years old, 17% were obese and 15% were overweight. The obese and overweight prevalences in children 2 to 5 years old were 8% and 19%, respectively. In this age group over the last decade, obesity prevalence declined by 43%, suggesting that public health strategies are working. Among infants and toddlers from birth to 2 years old, 8% had weight-for-length percentiles at or above the 95th percentile.

Disparities in obesity prevalence by race, Hispanic origin, and sex remain important. Among non-Hispanic blacks 6 to 19 years old, 23% were obese and 16% were overweight. Similarly, among Hispanic youth 6 to 19 years old, 24% were obese and 18% were overweight. Hispanic boys and non-Hispanic black girls show particular risk, with 44% and 40%, respectively, being overweight or obese. Although adult studies show an inverse relationship between socioeconomic status (SES) and obesity, the relationship between SES and obesity in children is more complicated. Poverty seems to be a risk factor for obesity in non-Hispanic white adolescents; however, no association between SES and obesity has been found in Hispanic youth. Conversely, higher SES is associated with higher rates of overweight and obesity in blacks. Further research is needed to understand the role played by family income in determining nutrition and physical activity patterns.

Childhood obesity is associated with obesity in adulthood. Of children who are obese from 6 to 11 years of age, 50% of girls and 30% of boys are expected to be obese as adults, compared with 18% of nonobese age-matched peers. Obesity during adolescence poses even greater risk with more than 60% of obese adolescents expected to remain obese into adulthood. Obese adults who became obese during childhood are more likely to have severe obesity (BMI >40) than those who become obese during adulthood.

Parental obesity is the most important identified risk factor for developing obesity before young adulthood. For children younger than 3 years, parental weight is a better predictor of adult obesity than the child's actual weight. This effect lessens as children age, with the child's weight becoming an equal predictor at school age and a more important predictor at adolescence. Both overweight and normal-weight children who have one obese parent are at twice the risk for adult obesity compared with children who do not have an overweight parent. Of overweight 10- to 14-year-olds with at least one obese parent, 80% remain obese as adults. Although genetic influences may be important, the rapid rise in obesity over the last 20 years demonstrates that lifestyle and societal influences clearly play a significant role. The fact that children and parents share neighborhood and family

environmental conditions further supports the importance of causal environmental factors. Understanding genetic contributions to childhood obesity will allow more targeted prevention and intervention efforts.

## **PATHOPHYSIOLOGIC FEATURES**

Weight gain is caused by a positive energy imbalance resulting from excessive caloric intake, inadequate energy expenditure, or a combination of the two. Even small surpluses in energy balance over time can have important effects. Estimates suggest that a sustained positive balance of 100 calories per day leads to a weight gain of 10 pounds per year. A common myth is that a slow metabolism causes obesity. However, overweight and normal-weight children do not differ by metabolic rate. Furthermore, overweight adolescents have higher total daily energy expenditures and resting energy expenditures than adolescents who are not overweight. Therefore, overweight children need to eat more to maintain their higher body weight.

Higher prepregnancy maternal BMI is associated with more rapid infant growth and higher risk for later obesity in the infant. Higher birth weight also correlates with later obesity. Sensitive periods of risk for the development of obesity include infancy, adiposity rebound (typically at 5 to 6 years old), and adolescence. Infant BMI is high at birth and increases slightly for the first months of infancy and then declines for 5 to 6 years before gradually increasing toward adult levels. The nadir between 5 and 6 years has been called adiposity rebound. Early adiposity rebound is associated with an increased risk for childhood obesity. During adolescence, a time of significant growth, there are notable changes in fat distribution and body composition that differ by gender. In boys, fat mass decreases by approximately 40%, whereas in girls it increases by approximately 40%. Gender differences in the risk for adult obesity may relate to increasing fat mass during adolescence. Obese and overweight adolescent girls are more likely to remain obese than obese and overweight adolescent boys. Only 20% of overweight girls normalize their weight in adulthood, whereas almost 70% of overweight male adolescents develop normal adult BMI.

The family and food environment are important determinants of obesity. Family environment plays a role in the development of food choices, with many food preferences established by 2 to 3 years old. Food preferences and feeding behaviors relate to the availability of specific foods, role modeling by caregivers, and positive and negative reinforcement of the child's choices. This fact may explain why children of overweight parents are more likely to prefer high-fat foods compared with children of normal-weight parents. Obese children consume less at breakfast and more at dinner than their normal-weight peers. Skipping breakfast is also associated with poorer food choices and increased risk for obesity. Families who eat meals together consume less fried food and carbonated beverages and more fruits and vegetables. Healthy eating in families may come as a package: eating 3 meals a day, preferably together, and choosing nutritional foods.

Eating behaviors and appetite regulation—the response to hunger and satiety—are at least partially conditioned. Overeating can develop in response to environments that interfere with normal regulatory mechanisms, as seen with extremes of parental behavior, including neglect and overinvolvement. Over-protective parents have been shown to use food to comfort their children. Parents who prompt their children to finish what is on their plate may actually impair children's ability to self-regulate appetite and satiety. Overweight children have been found to eat faster and to slow their eating less at the end of meals, suggesting a decreased sensation of satiety. Feeding habits, which may be learned from caregivers early in life, can have a lasting effect on a child's eating habits and preferences.

Food insecurity may also place individuals at higher risk for obesity. Malnutrition during gestation and early infancy are associated with risk for obesity. Possible mechanisms include overeating and excess deposition of fat when adequate food is available. It is also possible that individuals develop increased sensitivity to hunger- and satiety-related hormones and neurotransmitters, resulting in fat deposition in response to early life stress. Further research is needed to determine whether the development of signaling pathways, entrainment of adipocytes, or other factors during the prenatal period and early infancy might explain long-term regulation of adiposity.

The neuroendocrine regulation of ingestive behavior involves the dopamine system, which also modulates learning, motivation and reward, and appetite. Leptin, a hormone that acts on the hypothalamus to regulate hunger and satiety, is secreted by adipocytes. Leptin may be able to reduce the reward value of food because increased leptin signaling decreases food intake. Serum leptin levels correlate with adiposity in both children and adults. Whether increased adiposity results in decreased leptin production or whether primary leptin deficiency is followed by weight gain is unclear. Leptin resistance or deficiency results in an increased food intake in animal models.

## ETIOLOGY

Environmental changes over the last few decades, including urbanization, technologic advances, and easy access to calorie-dense foods, are related to population-level increases in obesity prevalence. Urbanization and urban sprawl have contributed to more sedentary lifestyles because of an increased reliance on motorized transportation. Fewer children walk to school today than they did in the past (Box 298-1). Furthermore, many families perceive their neighborhoods as unsafe and therefore limit their children's outdoor playtime. Even for those whose neighborhoods are considered safe, outdoor playtime has decreased for US children. Technologic advances also have contributed to decreased activity, with children devoting time to television, video games, and computers. Television time of more than 3 hours per day has been associated with a higher average BMI. Screen time displaces more active pursuits and can displace or disrupt sleep. Furthermore, children are the targets of advertising for high-calorie foods and beverages. For these

### BOX 298-1 Activity and Nutrition Changes Over the Last Two Decades

#### ACTIVITY

- Increased screen time (television, video games, computer)
- Decreased physical education in schools
- Decreased walking to school
- Decreased outdoor play time

#### NUTRITION

- Increased sugar-sweetened beverages (including juice)
- Increased fast-food consumption
- Increased fat in school lunches
- Increased portion size
- Decreased family meals

reasons, the American Academy of Pediatrics supports limiting screen time.

Short sleep duration has been associated with increased risk for obesity in children and adults. The biologic mechanisms behind this association are increasingly well understood. Alterations in insulin, leptin, ghrelin, and cortisol result in insulin resistance, sympathetic nervous system activity, hunger, and lower satiety. Sleep-restricted individuals exercise less, eat more, and are likely to consume more calories as fat. Environmental factors that increase risk for short sleep include early school start times for adolescents, caffeine use, and overscheduling related to academics and extracurricular activities. In addition, light from screens (televisions, computer, and other devices) seems to suppress melatonin release, resulting in circadian rhythm disruption.

Obesity can also lead to sleep problems, especially obstructive sleep apnea. Children with snoring, restless sleep, and behavioral problems should be evaluated for possible sleep apnea, using polysomnography. The development of obstructive sleep apnea and disrupted sleep can lead to shorter sleep, which in turn exacerbates obesity.

Dietary habits also changed rapidly after 1960, with larger portion sizes, greater intake of calorie-dense beverages and juice, and increases in consumption of fast-food meals. Servings of sugar-sweetened beverages correlate with risk for obesity. Although the US Department of Agriculture federal school lunch program specifies that no more than 30% of calories may be from fat, many schools provide foods from fast-food contractors, resulting in an availability of high-fat foods. Furthermore, vending machines in schools often provide sugar-sweetened beverages and snack foods (see Box 298-1). Consequently, lunch at school may contain excess calories, with more than 30% of calories from fat.

## MEDICAL COMORBIDITY

Obesity is associated with medical comorbidities in many organ systems. Although some problems are apparent after a relatively short duration of excess

body fat, other complications do not arise for decades. Nonetheless, obesity is responsible for the childhood onset of diseases previously seen only during adulthood, most notably type 2 diabetes mellitus.

Cardiovascular complications of obesity include hypertension and dyslipidemia. Hypertension is defined as a systolic or diastolic blood pressure at or above the 95th percentile for age, sex, and height. Hypertension continues to be underdiagnosed in children, in part because blood pressure norms change with height, age, and gender. Furthermore, technical difficulties, including the use of the wrong-sized blood pressure cuff, can cause errors. The prevalence of diastolic hypertension increases with BMI, and the prevalence of hypertension is 3 times greater in overweight children compared with their normal-weight peers. Disturbances in autonomic function and abnormalities in vasculature may play important mediating roles in the development of hypertension in obese children. As little as 5 to 10 pounds of weight loss can lead to a decrease in blood pressure. (See Chapter 163, High Blood Pressure.) Obesity in adults and children leads to increased concentrations of triglycerides and decreased high-density lipoprotein (HDL) cholesterol. Obese individuals have an increased hepatic production of triglyceride-bearing very low-density lipoprotein (LDL) particles. Hyperlipidemia in youth is a potentially atherogenic condition; therefore family history and fasting lipid levels are recommended for obese children. Intervention is indicated if total cholesterol, LDL cholesterol, or triglycerides are at or above the 95th percentile. Initial treatment begins with dietary measures to reduce calories and dietary cholesterol and recommendations to increase physical activity. Lipid-lowering medication is considered if behavioral modifications are unsuccessful. Obese youth may exhibit impaired glucose tolerance with insulin resistance and postprandial hyperinsulinemia. Impaired glucose tolerance is most common in children with a family history of type 2 diabetes mellitus. Insulin resistance is associated with acanthosis nigricans and menstrual irregularities. Insulin resistance is an independent risk factor for cardiovascular disease through effects on lipid metabolism and vascular changes. The development of type 2 diabetes poses further health risks, including renal, ophthalmologic, and vascular disease.

Metabolic syndrome, also called syndrome X, is a cluster of metabolic abnormalities that lead to cardiovascular disease and increased mortality (Box 298-2). Obesity, insulin resistance or hyperinsulinemia, dyslipidemia, and hypertension are the most commonly noted features. Adults with 3 of the following 5 findings meet criteria for the diagnosis of metabolic syndrome: elevated blood pressure, high triglyceride level, low HDL cholesterol level, high fasting glucose, and central obesity. Data from the National Health and Nutrition Examination Survey (2001 to 2006) estimates an overall prevalence in 12- to 19-year-olds of 8.1% (95% confidence interval [CI], 6.5% to 10.6%). The prevalence of metabolic syndrome may be as high as 30% in obese adolescents (12 to 19 years of age). The risk for metabolic syndrome increases with

### BOX 298-2 Metabolic Syndrome—Clinical Manifestations

#### OBESITY

- Excess body fat
- Increased visceral fat
- Central fat distribution

#### INSULIN RESISTANCE

- Decreased  $\beta$ -cell number
- Elevated fasting insulin levels
- Fasting insulin level  $>15$  mg/dL
- Peak insulin level  $>150$  mg/dL

#### DYSLIPIDEMIA

- Hypertriglyceridemia (very low-density lipoprotein)
- Low high-density lipoprotein
- Increased free fatty acids

#### HYPERTENSION

- Elevated systolic or diastolic blood pressure (or both)

#### GLUCOSE INTOLERANCE OR NON-INSULIN-DEPENDENT DIABETES MELLITUS

- Fasting plasma glucose level  $>126$  mg/dL
- 2-hour plasma glucose level  $>200$  mg/dL (oral glucose tolerance test)

the severity of adiposity (see Box 298-2). Increased odds for metabolic syndrome related to obesity are 66.9 (27.9, 160.4) in obese adolescent boys and 18.9 (6.3, 56.2) in obese adolescent girls. Obese black adolescents have lower risk for metabolic syndrome compared with non-Hispanic white and Hispanic adolescents.

Insulin resistance is thought to play a major role in the pathophysiologic mechanism of metabolic syndrome, with independent effects on lipid metabolism and cardiovascular health. Obese adolescents have higher plasma insulin levels than adolescents who are not obese. Overweight school children are more likely to have elevated total cholesterol, LDL cholesterol, triglycerides, and hyperinsulinemia than normal-weight children. Elevated insulin acts in the liver and in peripheral tissues to increase plasma triglyceride and LDL cholesterol levels. Controlling glucose metabolism reduces cardiovascular risk.

Obesity is associated with a chronic inflammatory state. Adipose tissue itself serves as a secretory organ, releasing peptides and cytokines into the circulation. Adiponectin, an anti-inflammatory peptide, is abundant in lean, insulin-sensitive individuals and is reduced in obese individuals. Low adiponectin levels correlate with a high BMI, and elevated levels of plasma triglycerides and free fatty acids. High adiponectin levels correlate with peripheral insulin sensitivity across age groups. In contrast, proinflammatory peptides, such as tumor necrosis factor- $\alpha$  and interleukin-6 (IL-6), are elevated in obese patients. Interleukin-6 stimulates the liver to produce C-reactive protein

(CRP), a marker of inflammation, and may be the link between obesity, subclinical inflammation, and coronary disease. Obese children have elevated CRP. Furthermore, a linear relationship exists between BMI and CRP and IL-6 levels. These markers have also been shown to correlate with other components of metabolic syndrome in children. Treatment of metabolic syndrome is aimed primarily at weight reduction and treating the component diagnoses: hypertension, diabetes, and hyperlipidemia. Evidence for short- and long-term efficacy of pharmacologic treatment of metabolic syndrome in youth remains sparse. Although studies of oral hypoglycemics (specifically metformin) in adolescents have demonstrated reductions in blood glucose, they have shown little effect on insulin resistance or lipid abnormalities. Although this medication may be helpful as an adjuvant therapy, behavioral and dietary modifications remain first line.

Other associated conditions include polycystic ovarian syndrome (PCOS) and nonalcoholic fatty liver disease (NAFLD) (Table 298-1). Polycystic ovarian syndrome is characterized by oligomenorrhea, insulin resistance, and hyperandrogenemia and may produce hirsutism or acne. Polycystic ovarian syndrome is associated with an increased risk for cardiovascular disease and infertility. Nonalcoholic fatty liver disease, increasingly recognized in obese youth, is most often asymptomatic and is characterized by mildly to moderately

elevated transaminase levels. Because NAFLD may progress to fibrosis and cirrhosis, screening in overweight youth is recommended. See Table 298-1 for conditions associated with obesity.

### MENTAL HEALTH COMORBIDITY

Mental health conditions often coexist with obesity. Nonetheless, the effects of obesity on child and adolescent mental health are still not well understood. During early childhood, body weight is not associated with self-esteem. However, as children approach adolescence, self-esteem is lower in overweight children than in normal-weight peers. Low self-esteem is more likely to be reported in obese 12- to 14-year-old girls compared with nonobese (odds ratio [OR], 3.5; 95% CI, 1.3 to 9.2). They also reported poor school and social functioning (OR, 2.3; 95% CI, 1.2–4.7). Adolescent girls who are concerned about their weight also report more depressive symptoms. Furthermore, depressed adolescents are at increased risk for developing persistent obesity. Otherwise, overweight youth are likely to report physical but not emotional problems, even though some studies show that they may be socially excluded. When caring for overweight and obese children, assessing affect and mental health status is advisable.

Based on a recent, large representative US study of 10- to 17-year-old youths, obese individuals showed increased odds for internalizing problems (adjusted

**Table 298-1** Medical Conditions Associated With Obesity

CONDITION	DISEASE	DESCRIPTION
Cardiovascular	Hypertension Dyslipidemia	SBP >95th percentile for sex, age, and height LDL >130 mmol/L HDL <40 mmol/L Total cholesterol >200 mmol/L Atherosclerosis begins during childhood
	Cardiovascular disease	
Endocrine	Type 2 diabetes mellitus Insulin resistance Polycystic ovarian syndrome	FBG >110 mg/dL Increased serum insulin levels Menstrual irregularities, hirsutism, acne, insulin resistance, hyperandrogenemia
	Metabolic syndrome	Obesity, hypertension, dyslipidemia, insulin resistance
Gastrointestinal	Nonalcoholic fatty liver disease	Increased transaminases; may progress to fibrosis or cirrhosis
	Gallbladder disease	May account for 50% of cases in adolescents
Pulmonary	Obstructive sleep apnea	Snoring, apnea, restless sleep, behavioral problems
Orthopedic	Slipped capital femoral epiphysis	Hip or knee pain, decreased mobility of hip
	Blount disease (tibia vara)	Severe bowing of the tibia
	Osteoarthritis	May present in adolescence
Neurologic	Pseudotumor cerebri	Headaches, vision changes, papilledema
Psychiatric	Anxiety Low self-esteem	Sometimes difficult to assess whether the depression or low self-esteem is the cause of the weight gain or if the weight gain is the cause of the depression
	Depression	
Oncologic	Endometrial cancer	Increased prevalence with adult obesity
	Breast cancer	Increased prevalence with adult obesity
	Colon cancer	Increased prevalence with adult obesity

FBG, Fasting blood glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.



odds ratio [AOR], 1.59, 95% CI, 1.04–2.45), externalizing problems (AOR, 1.33; 95% CI, 1.07–1.65), grade repetition (AOR, 1.57; 95% CI, 1.24–1.99), school problems, and missed school days. In addition, attention-deficit/hyperactivity disorder, conduct disorder, depression, learning disability, developmental delay, bone/joint/muscle problems, asthma, allergies, headaches, and ear infections were all more common in obese children and adolescents.

## COSTS

The current epidemic of obesity poses a significant threat to health care systems already struggling with escalating costs. The US Surgeon General predicted that the costs related to obesity will overtake those of tobacco. Obese adults have higher health care costs compared with normal-weight adults. Excess health care costs for obese individuals are 58% higher than those of smokers. Furthermore, medication expenses are 77% higher for obese individuals compared with those who are not obese. Obesity is associated with having more medical diagnoses and medications, leading to increased medical costs equivalent to 20 years of aging. These figures do not attempt to capture the cost of psychological morbidity.

## DIFFERENTIAL DIAGNOSIS

Primary medical causes of obesity are rare. Endocrine and genetic causes of obesity often cause short stature or cognitive impairment. Children who consume excess calories are likely to experience accelerated linear growth. Therefore, short stature in an overweight child warrants further evaluation. Similarly, syndromes associated with intellectual disability and obesity should be considered in obese children with

developmental delay. Table 298-2 lists endocrine and genetic causes of obesity.

## LABORATORY EVALUATION

Obesity is diagnosed by measuring height and weight and calculating BMI. The rate of obesity identification in pediatric practices is low. Electronic medical record systems with automated plotting of BMI percentiles and prompts for elevated BMI have the potential to improve identification. Brief provider training has also been shown to improve provider identification of BMI and the performance of recommended screening and counseling.

Published guidance for lipid screening by the American Academy of Pediatrics supports fasting lipid screening for children and adolescents whose BMI is at or above the 85th percentile. Lipid screening is also recommended for those with a family history of dyslipidemia, cigarette smokers, and those with diabetes mellitus. In 2011, the National Institute for Heart, Lung and Blood published a recommendation for universal pediatric lipid screening beginning with a nonfasting lipid screen. There is considerable ongoing research, which is expected to result in evidence that will clarify the most effective method for identifying children and adolescents with hyperlipidemia.

The American Diabetes Association recommends a fasting glucose test for children whose BMI is at or above the 85th percentile and for those whose BMI is between the 85th and the 95th percentile if they have a family history of diabetes mellitus or obesity or signs of insulin resistance, including acanthosis nigricans, PCOS, or hirsutism (see Box 298-3). (See Chapter 241, Diabetes Mellitus.) Hemoglobin A1c is sometimes used

**Table 298-2** Endocrine and Genetic Causes of Obesity

DIAGNOSIS	ASSOCIATED SYMPTOM	SIGNS AND SYMPTOMS	TESTING
Hypothyroidism	Short stature	Weight gain, fatigue, constipation, cold intolerance, myxedema	TSH, FT4
Cushing syndrome	Short stature	Central obesity, hirsutism, moon face, plethora, hypertension	Dexamethasone suppression test
Pseudohypoparathyroidism	Short stature	Short metacarpals, subcutaneous calcifications, dysmorphic facies, intellectual disability, hypocalcemia, hyperphosphatemia	Urine cAMP after synthetic PTH infusion
Growth hormone deficiency	Short stature	Fatigue	Evoked GH response, IGF-1
Down syndrome	Short stature	Dysmorphic facies, intellectual disability	Karyotype
Turner syndrome	Short stature	Web neck	Karyotype
Prader-Willi syndrome	Cognitive impairment	Hypogonadism, small hands and feet	FISH <i>15q11</i> microdeletion (70% of cases)
Bardet-Biedl syndrome	Cognitive impairment	Retinitis pigmentosa, renal abnormalities, polydactyly, hypogonadism	<i>BBS1</i> gene
Biemond syndrome	Cognitive impairment	Iris coloboma, hypogonadism, polydactyly	Clinical
Alström syndrome	Cognitive impairment	Retinitis pigmentosa, diabetes mellitus, and hearing loss	<i>ALMS1</i> gene

cAMP, cyclic adenosine monophosphate; FISH, fluorescent in situ hybridization; FT4, free thyroxine; GH, growth hormone; IGF, insulin-like growth factor; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.

to screen children who are unable to comply with fast-ing before the laboratory test. Insulin levels are not currently recommended for evaluating obesity because they can be elevated, low, or normal at the time of pre-sentation of type 2 diabetes.

Baseline liver function tests should be checked for obese children and adolescents. Liver function tests should also be performed before pharmacologic man-agement for type 2 diabetes or surgical intervention for obesity. Other laboratory studies are ordered only as indicated by history or physical examination (Table 298-3; see also Box 298-3).

**BOX 298-3 Criteria for Screening High-Risk Children for Diabetes**

- Overweight (body mass index >85th percentile for age and sex), **AND** any 2 risk factors:
- Family history of type 2 diabetes in a first- or second-degree relative
  - High-risk race or ethnicity (Native American, African American, Latino, Asian American, and Pacific Islander)
  - Signs of insulin resistance or associated conditions:
    - Acanthosis nigricans
    - Hypertension
    - Dyslipidemia
    - Polycystic ovarian syndrome
    - Small for gestational age
  - Maternal history of diabetes or gestational diabetes
- Age to initiate screening:
- 10 years, **OR**
  - Onset of puberty if younger than 10 years
- Frequency: every 3 years
- Preferred screening test: plasma glucose after an 8-hour fast

Adapted from American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37(Suppl 1):S14–80. Copyright © 2014 American Diabetes Association. Reprinted with permission.

**PRIMARY PREVENTION**

Preventing childhood obesity is crucial to public health and requires the concerted efforts of public health of-ficials and multiple government agencies, schools, and health care systems.

Pediatricians and other physicians who care for children have the opportunity to educate families about the importance of healthy nutrition and physical activity from the earliest years. Much confusion exists about good nutrition. Healthful nutrition begins with breastfeeding, which is associated with a lower childhood obesity risk. Exclusive breastfeeding is rec-ommended for 6 months by the World Health Organi-zation along with timely introduction of adequate and safe complementary foods. The American Academy of Pediatrics also recommends introduction of comple-mentary foods at around 6 months. Infants should be provided with a range of flavors so that they become accustomed to the taste of healthy foods, including vegetables (see Chapter 36, Healthy Nutrition: Infants). Consideration of nutrient quality and caloric content is the basis of a healthy diet. Calorie-laden foods with little nutritional value can be offered for occasional treats. Families can begin by planning meals and snacks based on fruits, vegetables, and grains. Healthy diets can include meat and dairy products, supplying fewer calories than fruits, vegetables, and grains. Milk provides important nutrients during childhood, and low-fat milk is recommended for most children after age 2 years. Children should be encouraged to drink water to quench thirst, reserving highly sug-ared beverages for occasional treats. Fruit juice should be consumed in moderation (1 per day, <4 ounces). Fruit and small portions of yogurt, cookies made with oatmeal, occasional puddings made with milk and eggs, and ice cream are satisfying compo-nents of a healthy diet. Using less saturated fat is sug-gested for cardiovascular health. Attention to portion size is important. Children learn food preferences early in life and may also develop habits associated with appetite and satiety.

**Table 298-3 Laboratory Testing as Indicated by Screening Guidelines, History, or Physical Examination**

TEST	INDICATIONS
Thyroid function tests	When symptoms of hypothyroidism are present
Plain-film radiographs	For deformity, hip or knee pain (SCFE or Blount disease)
Head computed tomographic scan, lumbar puncture	Headache, visual changes, papilledema (pseudotumor cerebri)
LH, FSH, total and free testosterone; consider pelvic ultrasound	Menstrual irregularity, acne, hirsutism (PCOS)
Genetic consultation, karyotype	Short stature, dysmorphic features, cognitive impairment
Lipid panel	Ages 2–8 years if family history of dyslipidemia or early cardiovascular disease (<55 years in males, <65 years in females) or if child has diabetes, hyperten-sion, BMI >95th percentile, smokes cigarettes, or has moderate- to high-risk medical condition (ie, renal failure, hypothyroidism, and liver failure). Ages 9–11 years: Universal screening for all children <sup>a</sup> Ages 17–21 years: Universal screening for all children/young adults

BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PCOS, polycystic ovary syndrome; SCFE, slipped capital femoral epiphysis.  
<sup>a</sup>Current recommendation at the time of publication.

Physical activity habits similarly begin early in life. Children whose parents are physically active are more likely to be physically active themselves. Physicians can encourage families to consider planning opportunities for physical activity as a parental responsibility. Children should engage in at least 60 minutes of physical activity on most, preferably all, days of the week. Children who participate in organized sports should be encouraged to be physically active when there are no organized activities. It is unnecessary to rely on organized sports to meet all physical activity recommendations. In addition to aerobic activities, older children and adolescents may benefit from strength training. Overweight children often find this form of physical activity rewarding because strength training does not require aerobic endurance or agility. Overweight children can therefore benefit psychologically and physically from strength training. Increasing physical activity should be accompanied by decreasing sedentary activities. Limiting television and other recreational screen time to less than 2 hours per day is recommended. The American Academy of Pediatrics recommends no television for children younger than 2 years. Parents should strive to be role models for their children for dietary and physical activity habits. Child health professionals can begin to talk to parents about healthy nutrition and activity during the first year of life. These themes can be revisited at annual health care maintenance visits along with BMI monitoring.

Body mass index should be calculated and plotted at each health care maintenance visit. Computerized systems that automatically calculate and plot these percentiles make this feasible. Tracking growth trajectories and explaining these patterns to parents is an essential component of primary prevention. Children with increasing BMI percentiles may be at risk for developing obesity. Health care professionals can help families evaluate nutritional and activity patterns and make adjustments. Child health professionals need to identify parental obesity as a risk factor for the child. Given that early childhood obesity often resolves, optimism is warranted in the early years. By adolescence, nutritional and activity patterns are more difficult to change, and families have less influence. Strategies to engage the parent in preventive efforts are needed. Obesity remains an emotionally charged issue, creating more difficulties for the family and the pediatrician than more purely medical problems.

## INTERVENTION—PREVENTION OF SECONDARY COMORBIDITY

Preventing secondary comorbidity and disability is the principal goal in treating overweight children and adolescents. The primary care physician is faced with the challenge of educating the child and family about lifetime health risks imparted by excess body weight. These risks may seem abstract to the family because they are unlikely to occur for many years. Obesity should be approached as a chronic condition that requires permanent lifestyle change to achieve optimal body weight. Recent work with obese children and their families supports the utility of using the stages of change model for assessment of readiness to change

followed by motivational interviewing (see Chapter 46, Effective Communication Strategies.). Prescribing a treatment plan without engaging the child and family can lead to frustration and feelings of futility, impairing future attempts at weight control. Enhancing the therapeutic relationship can begin with a question to the parent, “Have you ever struggled with your weight?” The answer to this question will reveal a great deal about the family’s perception of body weight as an indicator of health and well-being and the parent’s empathy for the child. Readiness to change can be assessed by asking the child and parent 3 questions:

- How concerned are you about your weight (your child’s weight)?
- Do you think that you can improve your body fitness (your child’s body fitness)?
- Do you think that your family can change eating and physical activity patterns?

If the child is seriously overweight (above the 99th percentile) or has medical complications, referral to a behavioral health specialist may be necessary for the family to progress to a state of readiness to change.

When the child and family are ready to begin a treatment plan, the physician should assist them in setting realistic goals (Box 298-4). Weight maintenance rather than weight loss is usually the first step for growing youth. The objective is to decrease the rate of weight gain and allow the child to achieve a healthier body mass (Box 298-5). Learning healthy eating and activity habits improves the child’s health over time (Box 298-6 and Box 298-7). Focusing on health and healthy behavior changes allows for gradual and long-term change. Fad diets and very low-calorie regimens are not recommended for children because these diets cannot be maintained. Children who possess an acute comorbidity such as sleep apnea may be managed medically (usually in an inpatient treatment program) on a very low-calorie diet. Recommendations for weight maintenance or weight loss are based on the level of overweight, age, and existence of complications (Figure 298-1). Setting goals for weight

### BOX 298-4 Role of the Pediatrician

- Intervene early.
- Assess family’s readiness to change.
- Educate family about medical complications of obesity.
- Involve family and caregivers in the treatment program.
- Aim for permanent dietary and activity change.
- Avoid short-term diets or exercise programs aimed at rapid weight loss.
- Teach family to monitor eating and activity.
- Assist family in making small, gradual changes.
- Encourage and empathize.
- Avoid criticism.
- Refer obese children to a family-based behavioral obesity treatment program.

**BOX 298-5 Parenting Skills for Weight Loss**

- Find reasons to praise child's behavior.
- Set clear guidelines about food.
- Avoid using food as a reward.
- Establish daily family meal, family snack times, and physically active family time.
- Determine what food is offered and when.
- Allow child to decide whether to eat.
- Offer only healthy options.
- Remove temptations (snack food in home).
- Walk instead of drive, take the stairs; decrease television-viewing time.
- Be a role model in diet and physical activity.
- Be consistent.

**BOX 298-6 Dietary Modifications**

- Drink water, sugar-free beverages, or milk with no more than 1% fat.
- Use cooking spray instead of frying.
- Make cut-up fruits and vegetables accessible.
- Limit seconds to fruits and vegetables.
- Serve appropriate portions of meat (size of your palm) and starch (½ cup).
- Review school lunch menu with child to pick healthy options.
- Pack lunch with 4 oz lean meat, whole grain bread, fruit or vegetable, and milk.
- Limit restaurant dining to once per week or less.
- Limit fast food to rarely.
- Eat meals together, and turn off the television while eating.
- Schedule at least 20 minutes for each meal. Eating slowly helps to avoid overeating.
- Eat regular meals. Skipping meals can lead to overeating.
- Remove snack foods, chips, cookies, and desserts from the house.
- Allow occasional treats.
- Make salads with vegetables, not eggs, meat, bacon, or cheese.
- Toss family salad to decrease amount of dressing.

maintenance or weight loss may be based on a child's BMI, age, and complications (see Figure 298-1 and Box 298-4, Box 298-5, Box 298-6, and Box 298-7).

Family-based behavioral treatment programs are evidence-based strategies for treating childhood obesity. These programs involve training the parent in stimulus control and behavioral reinforcement techniques designed to promote child behaviors to facilitate weight loss. In addition, parents are encouraged

**BOX 298-7 Increasing Physical Activity**

- Limit television and video games to no more than 1 to 2 hours per day.
- Engage in active family activities: Ride a bike, walk after dinner, swim, go to zoo or museum.
- Dance to your favorite music.
- Walk with a friend rather than talking on the telephone.
- Walk while you talk on the telephone.
- Engage in team sports.
- Take classes—dance, martial arts, or swimming.
- Strategies for toddlers and preschool-aged children:
  - Engage in outdoor play every day.
  - Engage in active indoor play, soft balls, jumping, or bouncy balls.
  - Buy active toys rather than computer games or videos.

to use an authoritative parenting style and to model healthy behaviors. Involvement in these treatment programs is often associated with weight loss for the parent as well as for the child. For school-aged children, parent-only treatment has been shown to be effective.

To date there is no evidence that pharmacologic agents for weight loss are safe and effective for children. Bariatric surgery may be considered in severely overweight adolescents (BMI >40) with significant medical complications and nearly complete skeletal maturity. Generally it would not be considered without a 6-month trial of dietary and exercise modifications with inadequate improvement. After evaluation by a multidisciplinary team, surgery can be performed by surgeons who are experienced in gastric bypass surgery. A major dilemma in the care of adolescents is how to give informed consent or assent about the consequences of both obesity and the alternative of bariatric surgery. The procedure will change their ability to eat and may have unforeseen long-term consequences. On the other hand, obesity may threaten their lives.

**TOOLS FOR PRACTICE****Community Advocacy and Coordination**

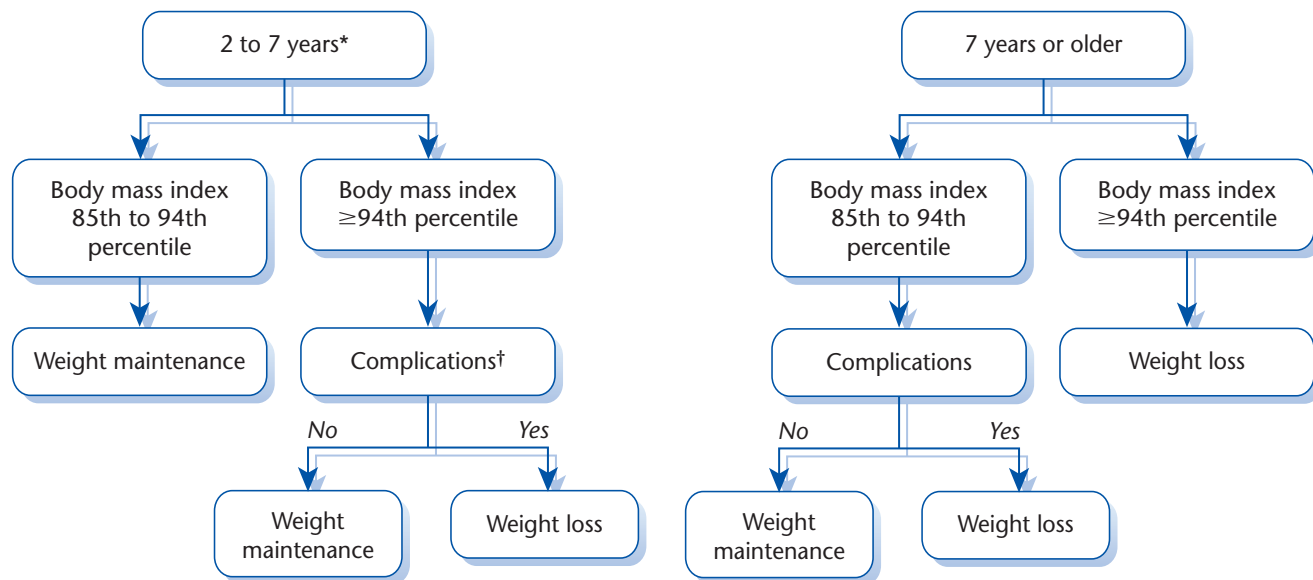
- *State Advocacy Focus: School Physical Education and Activity* (fact sheet), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/state-advocacy/Documents/Obesity.pdf](http://www.aap.org/en-us/advocacy-and-policy/state-advocacy/Documents/Obesity.pdf))

**Engaging Patient and Family**

- About Child & Teen BMI (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/nccdphp/dnpa/bmi/childrens\\_BMI/about\\_childrens\\_BMI.htm](http://www.cdc.gov/nccdphp/dnpa/bmi/childrens_BMI/about_childrens_BMI.htm))
- *BAM! Body and Mind* (Web site), Centers for Disease Control and Prevention ([www.bam.gov](http://www.bam.gov))
- *Encourage Your Child to Be Physically Active* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))



### Recommendations for Weight Goals



**Figure 298-1** Recommendations for weight goals. Asterisk (\*) indicates that children younger than 2 years should be referred to a pediatric obesity center for treatment. Dagger (†) indicates complications such as mild hypertension, dyslipidemias, and insulin resistance. Patients with acute complications, such as pseudotumor cerebri, sleep apnea, obesity hypoventilation syndrome, or orthopedic problems, should be referred to a pediatric obesity center.

- *Feeding Kids Right Isn't Always Easy: Tips for Preventing Food Hassles* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Growing Up Healthy: Fat, Cholesterol, and More* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *The Media and Your Family: Television and Other Screens* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *MyPlate* (Web page), US Department of Agriculture (www.choosemyplate.gov)
- *A Parent's Guide to Childhood Obesity: A Road Map to Health* (book), American Academy of Pediatrics (shop.aap.org)
- *Right From the Start: ABCs of Good Nutrition for Young Children* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Sports and Your Child* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *What's to Eat? Healthy Foods for Hungry Children* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)

#### Medical Decision Support

- *BMI Percentile Calculator for Child and Teen* (interactive tool), Centers for Disease Control and Prevention (nccd.cdc.gov/dnpabmi/Calculator.aspx)
- *Growth Charts* (chart), Centers for Disease Control and Prevention, (www.cdc.gov/growthcharts); also available at AAP bookstore (shop.aap.org)
- *Obesity Prevention in Pediatrics* (online course), American Academy of Pediatrics (pedialink.aap.org)

- *Pediatric Obesity: Prevention, Intervention, and Treatment Strategies for Primary Care*, 2nd ed. (book), American Academy of Pediatrics (shop.aap.org)
- *VERB Campaign* (Web page), Centers for Disease Control and Prevention (www.cdc.gov/youthcampaign/index.htm)

#### Practice Management and Care Coordination

- *Coding Evaluation and Management and Patient Education Services for Obesity* (article), American Academy of Pediatrics, *AAP Coding Newsletter*, Vol 5, Issue 1, 2009 (coding.solutions.aap.org)

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## Chapter 299

# OBSTRUCTIVE UROPATHY AND VESICoureTERAL REFLUX

Hiep T. Nguyen, MD

## OBSTRUCTIVE UROPATHY

Obstructive uropathy is a collective spectrum of biologic changes in the kidney that can result from an impairment of urinary flow at any point in the urinary tract. These changes include proliferation and myofibroblastic transformation of interstitial fibroblasts, expansion of extracellular matrix, loss of renal tubular cells, and decreased numbers of nephrons. They may

have a wide range of effects on the kidney, from sodium wasting, hyperkalemic acidosis, and nephrogenic diabetes insipidus to renal insufficiency or failure. Their effect on renal growth, development, and function depends on the timing, severity, and duration of the urinary obstruction. Obstruction that occurs early during renal development will lead to dysplasia and an arrest of renal development with the persistence of fetal architecture. In contrast, obstruction at the later stages of development may result only in dilatation of the collecting system (ie, hydronephrosis). Complete obstruction, such as from urethral atresia, has more detrimental effects on renal development and function than partial obstruction.

Children with obstructive uropathy usually exhibit urinary tract infections (UTIs). Less common modes of presentation include abdominal mass, hematuria, urinary stone, poor urinary stream, incontinence, failure to thrive, and renal insufficiency or failure. With the advent of routine second-trimester ultrasound (US) screening, most cases of obstructive uropathy are now being detected prenatally. The incidence of prenatal hydronephrosis ranges from 1:100 to 1:500, representing one-half of all abnormalities detected by prenatal US. However, clinical experience has shown that the presence of hydronephrosis does not necessarily indicate the presence of urinary obstruction. The difficulty lies in determining which patients have dilatation that has the potential for compromising renal function. The ability to diagnose clinically important obstruction properly is essential because obstructive uropathy is the leading cause of renal failure in children younger than 2 years and accounts for 17% of the cases of kidney transplants in children.

## DIFFERENTIAL DIAGNOSIS

Obstruction can develop at various locations, resulting in dilatation of the urinary tract (ie, hydronephrosis). The differential diagnosis for hydronephrosis is listed in Box 299-1. Ureteropelvic junction (UPJ) obstruction occurs when an impairment of urine flow occurs from the renal pelvis into the proximal ureter, causing progressive dilatation of the renal pelvis and calyces and potential renal injury. Its anatomic basis is from either an intrinsic or an extrinsic cause. The intrinsic obstruction results from luminal narrowing of the UPJ, with or without kinking, and is usually characterized by excessive connective tissue and decreased smooth muscle content in the ureteral wall (Figure 299-1, A). In contrast, extrinsic obstruction is caused by compression of the ureter by anomalous (eg, lower pole) renal vasculature (Figure 299-1, B). This type of UPJ obstruction is more commonly found in older children and adults. UPJ obstruction is the most common cause of obstructive uropathy in children and is second only to transient, physiologic non-pathologic hydronephrosis as the most common cause of antenatal hydronephrosis (Table 299-1). The incidence of UPJ obstruction is estimated to be 1 in 1,500, with a male-to-female ratio of 2:1. The left side is more commonly affected than the right side (left:right ratio of 1.5:1). Bilateral UPJ obstruction is present in 10% to 40% of cases of neonatal hydronephrosis.

**BOX 299-1 Differential Diagnosis for Hydronephrosis**

- UNILATERAL<sup>a</sup>**
- Ureteropelvic junction obstruction
  - Ureterovesical junction obstruction
  - Ureterocele
  - Ectopic ureter
  - Polycystic kidney disease
  - Extrarenal pelvis
  - Unilateral vesicoureteral reflux
  - Transient physiologic-nonpathologic

- BILATERAL**
- Posterior urethral valves
  - Urethral atresia
  - Prune belly syndrome
  - Megacystis-megaureter syndrome
  - Vesicoureteral reflux
  - Polycystic kidney disease

- UNCOMMON CAUSES**
- Megacalycosis
  - Renal cyst
  - Urachal cyst
  - Ovarian cyst
  - Hydrocolpos
  - Sacrococcygeal teratoma
  - Bowel duplication
  - Duodenal atresia
  - Anterior meningocele

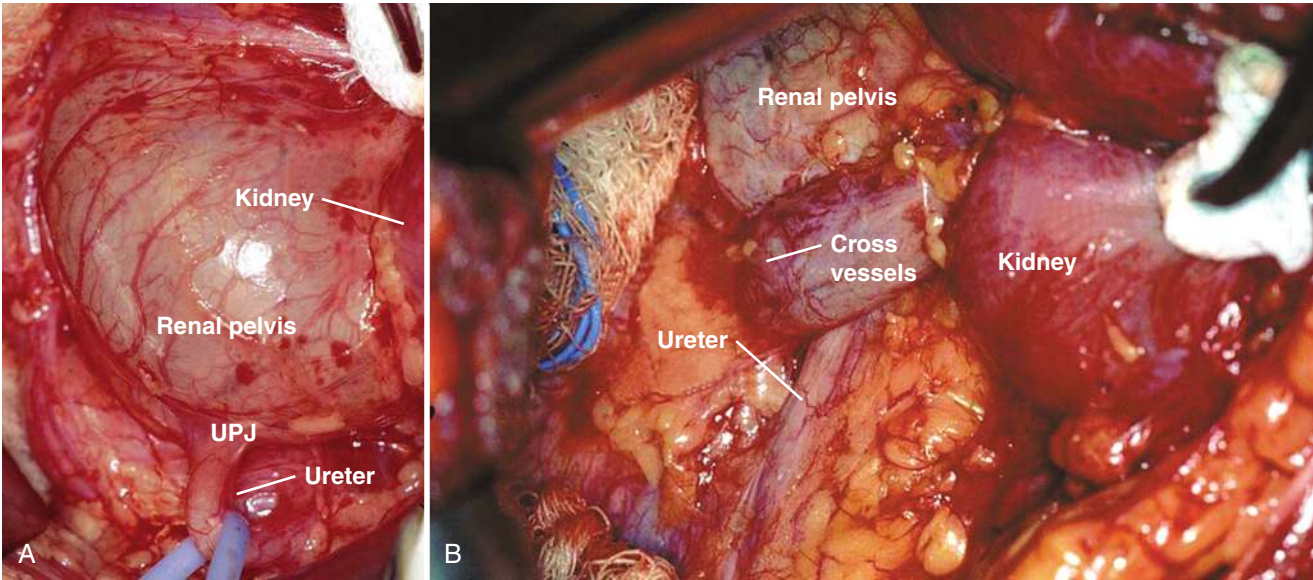
<sup>a</sup>Can also be bilateral

Ureterovesical junction (UVJ) obstruction, also referred to as *obstructed megaureter*, is an impairment of urinary flow from the distal ureter into the bladder, resulting in dilatation of the entire collecting system from the distal ureter to calyces. UVJ obstruction may be primary or secondary. Primary obstruction is caused by a deficiency of smooth muscle in the intravesical ureter, resulting in an adynamic distal segment that impedes normal peristalsis of urine through the ureter (Figure 299-2). Secondary obstruction results from compression of the ureter by a thick bladder wall in pathologic states such as posterior urethral valves (PUV) or neurogenic bladder. Clinically significant UVJ obstruction accounts for approximately 8% of children who had symptoms such as infection, hematuria, or pain and who were found to have hydroureteronephrosis by imaging studies. However, it accounts for 23% of newborns with prenatally diagnosed hydronephrosis and is the third most common

**Table 299-1 Etiology of Prenatal Hydronephrosis**

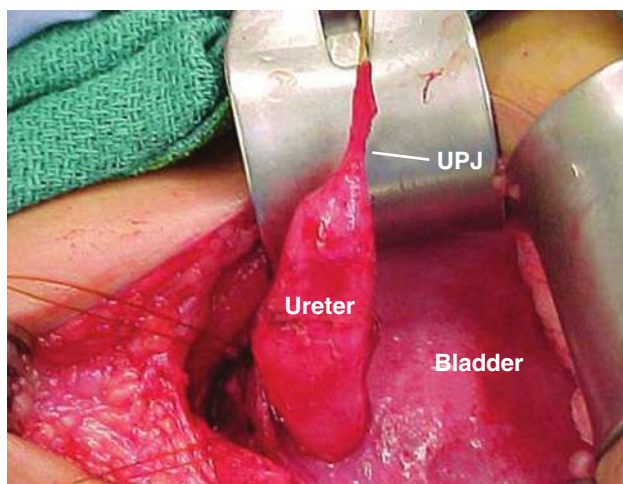
ETIOLOGY	REPORTED INCIDENCE
Transient physiologic-nonpathologic	50%–70%
Ureteropelvic junction obstruction	10%–40%
Vesicoureteral reflux	10%–30%
Ureterovesical junction obstruction	5%–20%
Multicystic dysplastic kidney	2%–5%
Posterior urethral valves	1%–5%
Other*	1%–2%

\*Other causes include ureterocele, ectopic ureter, duplex system, urethral atresia, prune belly, polycystic kidney disease, and renal cysts.



**Figure 299-1** A, Intrinsic ureteropelvic junction obstruction. B, Extrinsic ureteropelvic junction obstruction cause by crossing vessels.



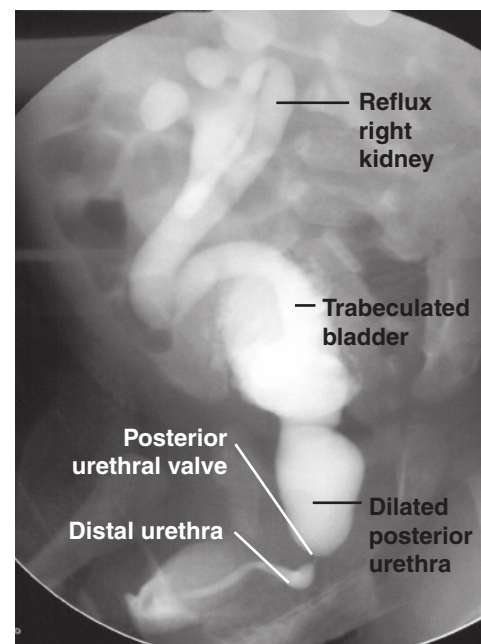


**Figure 299-2** Primary ureterovesical junction obstruction.

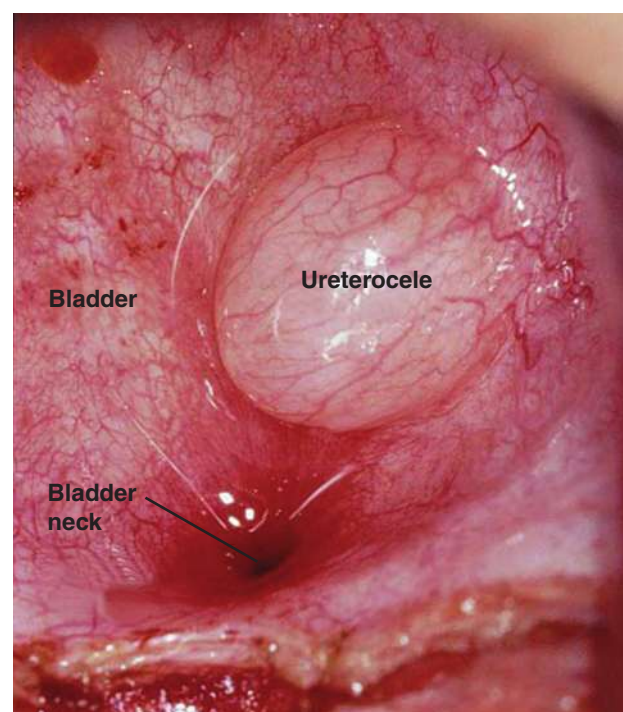
cause of prenatal hydronephrosis, preceded by transient, physiologic nonpathologic hydronephrosis and UPJ obstruction. As with UPJ obstruction, UVJ obstruction is more common in boys and occurs more often on the left side. It occurs bilaterally in 10% of cases, and contralateral renal anomalies (eg, renal agenesis, multicystic dysplastic kidney) are observed in approximately 9% of patients with UVJ obstruction.

Lower urinary tract obstructions are a less common cause of obstructive uropathy. The most common cause of intravesical obstruction is PUVs. One hypothesis suggests that the terminal ends of the wolffian ducts misintegrate and are abnormally integrated into the urethral wall. This action results in obliquely oriented ridges that act as a one-way valve, impeding urine flow from the bladder (Figure 299-3). The incidence of PUV is estimated to be 1 in 5,000 to 1 in 8,000 boys.

Other notable but uncommon causes of obstructive uropathy include ureterocele and ectopic ureter. A ureterocele is a cystic dilatation of the intravesical submucosal ureter, usually associated with a stenotic orifice that impairs urinary flow into the bladder (Figure 299-4). The cause of the ureterocele remains unknown, but investigators hypothesize that it results either from an incomplete breakdown of the ureteral (Chwalla) membrane present at the time of the ureteral bud arising from the mesonephric duct or from a delay in the establishment of the lumen of the ureteral bud. The incidence of ureteroceles is approximately 1 in 500 to 1 in 4,000 children. Ureteroceles are found more commonly in girls (female:male ratio of 7:1) and are bilateral in 10% of cases. In 80% of cases, they are associated with the upper pole ureter of a duplex kidney. An ectopic ureter is one that inserts into an abnormal site (ie, a site other than the bladder trigone), which results from a ureteral bud with an abnormally high origin from the mesonephric duct. In boys, the possible insertion sites for the ectopic ureter are always above the urinary sphincter, whereas, in girls, they can be above or below the sphincter. Consequently, ectopic ureters in boys are often obstructive, whereas those in girls may not be. The incidence of ectopic ureter is approximately 1 in



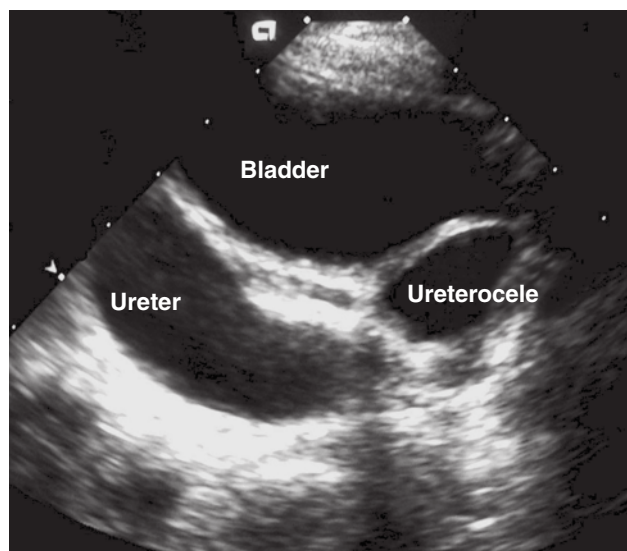
**Figure 299-3** Voiding cystourethrogram demonstrating posterior urethral valves as a cause for bladder outlet obstruction.



**Figure 299-4** Ureterocele.

1,900. Similar to ureteroceles, only 15% of ectopic ureters occur in boys, and in 80% of cases, the ectopic ureter is associated with the upper pole of a duplex kidney. It occurs bilaterally in approximately 10% of cases. Hypoplasia or dysplasia of the associated renal unit is commonly associated with the ectopic ureter.





**Figure 299-5** Ultrasound demonstrating dilated ureter seen behind bladder caused by ureterocele.

## RADIOLOGIC EVALUATION

Before the advent of routine maternal US, children with obstructive uropathy primarily displayed symptoms such as febrile UTI, abdominal mass, pyuria, pain, hematuria, and gastrointestinal symptoms. Less common presenting symptoms included failure to thrive, anemia, sudden onset of hypertension, and renal insufficiency or failure.

A renal and bladder US should be performed first. In children with obstructive uropathy, hydronephrosis is almost always present. However, its presence should not be interpreted as a sign of clinically significant obstruction, because US cannot adequately assess renal function and drainage of the upper urinary tract. Although increased echogenicity and marked parenchymal thinning may portend poor renal function, these findings are not sensitive or specific. Aside from the presence of hydronephrosis, the US may help differentiate the cause of obstructive uropathy. The presence of a dilated ureter on US suggests that the level of obstruction occurs distal to the UPJ, such as from UVJ obstruction, ectopic ureter, ureterocele, or PUV (Figure 299-5). A ureterocele can be visualized as a cystic mass inside the bladder, whereas the presence of a thick wall bladder and a dilated posterior urethra suggests the diagnosis of PUV.

To identify the cause of the obstructive uropathy and to assess renal function accurately, additional imaging studies are often required. A voiding cystourethrogram (VCUG) will identify the presence of vesicoureteral reflux (VUR), a condition that may cause hydronephrosis itself but is found in association with other diagnoses of obstructive uropathy, including UPJ obstruction, ureterocele, and PUV. In addition, a VCUG will help delineate bladder and urethral anomalies such as ureterocele and PUV, respectively. Renal function can be assessed with radionuclide renography.  $^{99m}\text{Tc}$  dimercaptosuccinic acid (DMSA) provides the most accurate assessment of

renal function and the presence of renal scarring.  $^{99m}\text{Tc}$  diethylenetriaminepentaacetic acid (DTPA) and  $^{99m}\text{Tc}$  mercuroacetyltriglycine diuretic renography are less accurate in determining renal function but do provide an assessment of drainage and a quantitative measurement of the degree of obstruction (ie,  $t_{1/2}$ , the time required to achieve 50% clearance of pyelocaliceal activity in the region of interest). However, debate continues about the accuracy of using  $t_{1/2}$  in diagnosing obstruction. Diuretic renography should only be obtained in children at least 2 months of age (because of tubular function maturation) who have moderate or severe hydronephrosis; in these cases, the studies are the most informative. Intravenous pyelogram is an alternative study that can provide assessment of both renal function and anatomy. However, its use in children is limited because of the amount of radiation exposure and the presence of bowel gas, which interferes with the visualization of the urinary tract.

With the advent of routine prenatal US, many children with obstructive uropathy are now detected in utero with hydronephrosis before they develop symptoms. However, not all children with prenatal hydronephrosis have obstructive uropathy; most have transient or physiologic hydronephrosis that often resolves during pregnancy or after birth and do not have any clinical sequelae. Consequently, not all children with prenatal hydronephrosis require extensive radiologic evaluation. If the hydronephrosis persists during pregnancy, then a postnatal US after 48 hours is indicated. In severe cases, such as bilateral moderate to severe hydronephrosis, solitary kidney, oligohydramnios, or giant hydronephrosis, the postnatal US should be done sooner. Because patients with high-grade VUR can have normal US without any hydronephrosis, whether patients with prenatal hydronephrosis should undergo a VCUG regardless the degree of hydronephrosis is a point of debate; the incidence of VUR in children with mild prenatal hydronephrosis was only 4.4% and was 14% in the moderate group. Consequently, a VCUG in patients with mild prenatal hydronephrosis is not needed. However, a VCUG may be indicated if a dilated ureter is seen on US or other clinically significant obstructive uropathies, such as UPJ obstruction or PUV, are suspected. Additional radiographic evaluation with diuretic renography or intravenous pyelogram is limited to specific cases with moderate to severe hydronephrosis, marked parenchymal thinning, or increased echogenicity noted on US. When the degree of prenatal hydronephrosis is not known, a postnatal US should be obtained. The moderate and severe degrees of postnatal hydronephrosis are correlated with increased incidence of obstructive uropathy.

## MANAGEMENT

The goals in the treatment of obstructive uropathy are to preserve renal function and to prevent the development of associated complications such as UTI, pain, and stone formation. Although in some cases the hydronephrosis can spontaneously resolve as the child grows, in other cases it persists, leading to progressive renal compromise. Consequently, the primary

care physician must determine which patients will benefit from surgical intervention and which should be observed, with the expectation that hydronephrosis will resolve without compromising renal function. In many instances, making this determination is difficult, leading to controversies in the management of obstructive uropathy.

In the management of UPJ obstruction, patients with a severely dilated renal pelvis (anteroposterior >2 cm on US), decreased renal function (relative renal function <40%), and marked obstructed pattern on renography ( $t_{1/2}$  >20 minutes) should undergo surgical correction. Surgical correction is accomplished by either removing the stenotic or adynamic UPJ or transposing the ureter anterior to the lower pole-crossing vessels. Other indications for surgery include UTI, renal colic, or pulmonary compromise from giant hydronephrosis. Patients with moderate to severe hydronephrosis, but preserved renal function, may be managed without surgery. The hydronephrosis will resolve in many cases, although it may take several years. In some cases, declining renal function may occur, necessitating surgery. However, in most cases, renal function is recovered after surgery, suggesting that the risk to the obstructed kidney from conservative management is small.

In the management of UVJ obstruction, removal of the distal adynamic segment of the ureter with or without ureteral tapering is indicated in patients with symptoms who seek care for UTI, pain, or nausea and vomiting. In patients who are asymptomatic (ie, diagnosed by evaluation of prenatal hydronephrosis), observation and prophylactic antibiotics have been shown to be safe, allowing for spontaneous regression of the obstruction without a compromise in renal function and minimizing the risk of UTI. Most symptoms will resolve spontaneously. Occasionally, infants with UVJ obstruction diagnosed in the evaluation for prenatal hydronephrosis have greatly decreased renal function at the onset. In these patients, surgical correction is indicated. Although renal function after the procedure is preserved, it is never normalized.

Lower urinary tract obstruction, such as from PUV, usually requires more urgent intervention because both kidneys are at risk. In patients with suspected PUV, catheter drainage is needed until the diagnosis is confirmed and surgical correction can be performed. Stabilization of the patient's pulmonary status (particularly in newborns diagnosed in utero with oligohydramnios), correction of associated metabolic abnormalities, and treatment of UTI should be performed before any surgical intervention. In most patients, endoscopic fulguration of the PUV relieves the bladder outlet obstruction. However, a vesicostomy or alternative treatment, such as ablation with a Fogarty balloon, may be required in very small or premature infants when an endoscopic procedure cannot be performed because of the size of the instruments.

Long-term therapy is directed toward the identification and treatment of associated metabolic abnormalities and bladder dysfunction. After the PUV are treated, the patients may develop postobstructive diuresis with urine output as high as 15 mL/kg/hour; careful attention to the patient's fluid balance is,

therefore, essential after the relief of distal obstruction. Renal insufficiency and failure can occur in up to 50% of patients with PUV. Children with PUV who have a nadir creatinine level of more than 0.8 mg/dL at 1 year of age are at high risk of developing renal insufficiency or failure. Not uncommonly, children with PUV and renal insufficiency lack the ability to concentrate their urine to a specific gravity of more than 1.015, leading to excessive fluid loss. These patients may also develop renal salt wasting and metabolic acidosis with hyperkalemia. In these patients, minor gastrointestinal illness can result in severe dehydration and cardiovascular compromise. In addition to the associated metabolic complications, bladder dysfunction is often associated with PUV despite adequate relief of the obstruction. VUR occurs in approximately 30% to 75% of children with PUV. Antibiotic prophylaxis is indicated in children with PUV and VUR, because improvement in the grade of the reflux occurs with time in most patients. The valve bladder is often poorly compliant and functionally lacks normal sensation. Consequently, many patients with PUV are able to hold large urine volumes at high intravesical pressures. With time, this circumstance can lead to increased upper tract dilatation and pressure and progressive renal compromise. Early treatment of the valve bladder with anticholinergic medications, intermittent catheterization, and nighttime drainage seem to reduce the incidence of bladder and renal dysfunction.

In the management of ureterocele and ectopic ureter, surgical correction is usually needed. As in the management of the other types of obstructive uropathy, urgent surgical correction is indicated in patients who are symptomatic. In children diagnosed during the evaluation for prenatal hydronephrosis, the type and timing of surgical correction are controversial. Long-term follow-up is needed to evaluate renal function and to look for recurrent obstruction. Hypertension and proteinuria can develop in patients with renal insufficiency or dysplasia. Consequently, yearly blood pressure and urinalysis are indicated in all patients with obstructive uropathy.

Fetal intervention for obstructive uropathy is indicated only in specific cases. The goal of fetal intervention is to prevent pulmonary hypoplasia and to preserve renal function. Open fetal surgery, percutaneous vesicoamniotic shunt placement, and fetoscopic surgery have been used with varying success in the treatment of obstructive uropathy such as PUV. Because of the inherent risks of the procedure for the fetus and the mother, fetal intervention should be considered only in cases in which pulmonary or renal dysfunction can be identified and cases in which the treatment of obstructive uropathy will improve pulmonary and renal function. In most cases, obstruction occurs unilaterally; thus, overall renal function and, hence, pulmonary function are normal, and fetal intervention is not indicated. In cases of lower urinary tract obstruction or bilateral obstruction, assessment of renal function should be performed to determine whether fetal intervention is warranted. Serial measurements of urine electrolytes are helpful in assessing fetal renal function. Healthy fetal kidneys produce hypotonic urine,

whereas those that are impaired produce isotonic urine. Consequently, increased urine sodium, chloride, and osmolality suggest the presence of renal damage or dysplasia. Favorable prognosis for good renal function is associated with sodium concentration less than 100 mEq/L, chloride less than 90 mEq/L, osmolality less than 210 mOsm/kg, and  $\beta_2$ -microglobulin less than 508 mmol/L. Analysis of the urine obtained from serial bladder taps at 48- to 72-hour intervals better reflects renal function because the initial sample may be stagnant.

The success of fetal intervention has been variable. Typically, normal amniotic fluid volume is restored, and an associated improvement in lung development is seen. Unfortunately, renal outcome is not significantly improved. A high complication rate is associated with fetal intervention, including premature labor, inadequate drainage or migration of the shunt, perforation of fetal bowel or bladder, chorioamnionitis, iatrogenic gastroschisis, and bleeding. Currently, fetal intervention is primarily reserved for cases in which severe oligohydramnios occurs without associated renal dysplasia, poor renal function, or associated chromosomal anomalies.

## VESICoureTERAL REFLEX

### Definition and Epidemiologic Features

Vesicoureteral reflux occurs when urine in the bladder flows in a retrograde manner into the upper urinary tracts. Under normal conditions, the ureter passes obliquely through the bladder wall with an appropriate submucosal tunnel length and opens onto the trigone of the bladder in a correct location. VUR is prevented by the compression of the intravesical ureter against the bladder wall, which can be accomplished only with the appropriate UVJ anatomy. VUR may result from maldevelopment or delayed maturity of the UVJ (primary reflux) or from distortion of the UVJ by changes in the bladder that are caused by other conditions, such as PUV or neurogenic bladder (secondary reflux). Researchers have long recognized an association between the presence of VUR and renal abnormalities, termed *reflux nephropathy*. The 3 forms of reflux nephropathy are (1) renal scarring associated with intrarenal reflux of infected urine (commonly seen in older children with primary reflux), (2) congenital nephropathy associated with VUR but in the absence of infection (commonly seen in infants with primary reflux), and (3) nephropathy associated with VUR and impairment of urinary flow (commonly seen in children with secondary reflux).

VUR is most often identified after investigation for other urinary tract problems such as UTI and prenatal hydronephrosis or in evaluation of a family history of VUR. The prevalence of VUR in children without any UTI or urologic anomalies is thought to be from 0.4% to 1.8% of the pediatric population. In children with UTI, the prevalence ranges from 30% to 50%, whereas in children with prenatal hydronephrosis, it is approximately 25%. VUR seems to be heritable; 50% to 67% of the children of parents with VUR and 33% to 50% of the siblings of children with VUR will have the

condition. The incidence of VUR is significantly lower in blacks than it is in whites. Similarly, the incidence of VUR is much lower in boys than it is in girls. However, in infants younger than 1 year, the proportions of boys and girls with VUR are more equivalent. In children with UTI, the ratio of girls to boys with VUR is approximately 4:1, whereas, in infants evaluated for prenatal hydronephrosis, the ratio is the reverse.

### Differential Diagnosis

VUR is diagnosed after evaluation for UTI, prenatal hydronephrosis, or family history of reflux. Less common modes of presentation include hypertension, renal insufficiency or failure, or incidental findings of a small or scarred kidney or hydronephrosis observed on radiologic imaging tests such as US, computed tomography, or magnetic resonance imaging. Young children with UTIs often have generalized signs and symptoms such as fever, vomiting, and failure to thrive. Older children may exhibit more specific signs and symptoms for UTI, such as flank pain, dysuria, and gross hematuria. Differentiating between UTI and other causes of sepsis may be difficult, particularly in young infants. Considerable debate exists as to which children with UTI require a VCUG to rule out VUR. The American Academy of Pediatrics (AAP) 2011 Clinical Practice Guideline "Urinary Tract Infection: Clinical Practice Guideline for the Diagnosis and Management of the Initial UTI in Febrile Infants and Children 2 to 24 Months" recommends that the evaluation for VUR is not necessary in children of this age group who presented with a first-time febrile UTI and had a normal US. However, several studies have indicated that the incidence of VUR in young children, especially circumcised boys, who present with a febrile UTI ranges from 30% to 50%. In contrast, older girls with cystitis, nonfebrile UTI, or asymptomatic bacteriuria are less likely to have VUR and consequently do not always require a VCUG for evaluation. Similarly, whether all children with prenatally diagnosed hydronephrosis require a VCUG to rule out reflux is controversial. The incidence of VUR is low in children with mild hydronephrosis detected on prenatal US, but it increases with the moderate and severe grades. Consequently, a VCUG should be performed in children with a history of moderate or severe hydronephrosis observed on prenatal US. Additional indications for a VCUG include findings on prenatal US of a dilated ureter, abnormal bladder wall thickness, renal echogenicity, renal parenchymal thinning, or decreased amniotic fluid volume.

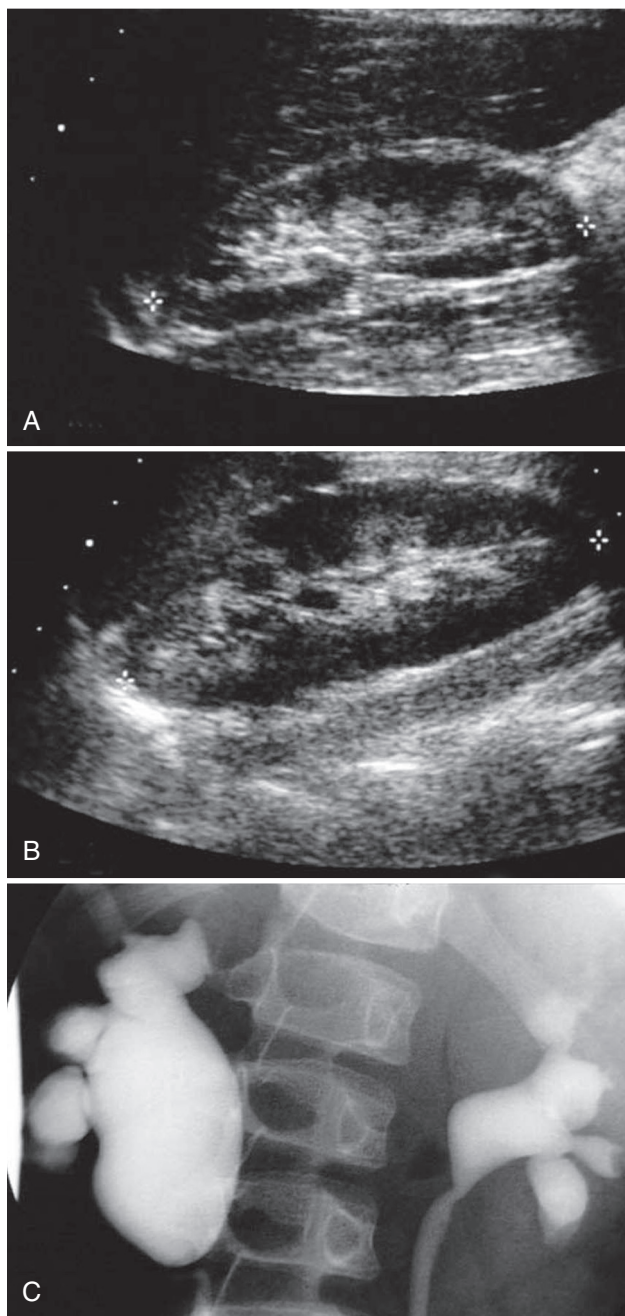
As noted previously, a strong genetic component exists in the development of VUR. Consequently, screening for reflux in families with VUR may be indicated, with the goal of identifying these children early and decreasing their risk of developing long-term complications from VUR. Screening with a radionuclide cystogram (RNC) should be performed in siblings or offspring who are younger than 5 years. They are the ones with the highest likelihood of having VUR and have the greatest risk of developing renal scarring from pyelonephritis. In older siblings or offspring who have never had any UTIs, a screening US would be sufficient. If a history of UTI or hydronephrosis is present, or if evidence of



parenchymal thinning is present on the screening US, then an RNC is indicated.

### Evaluation

In the evaluation for UTI or prenatal hydronephrosis, a US is usually first obtained. However, US cannot confirm the presence or absence of reflux, because severe reflux may be present in the absence of any significant hydronephrosis (Figure 299-6). In children, the VCUG remains the principal method of detecting and quantifying the degree of VUR. A VCUG is

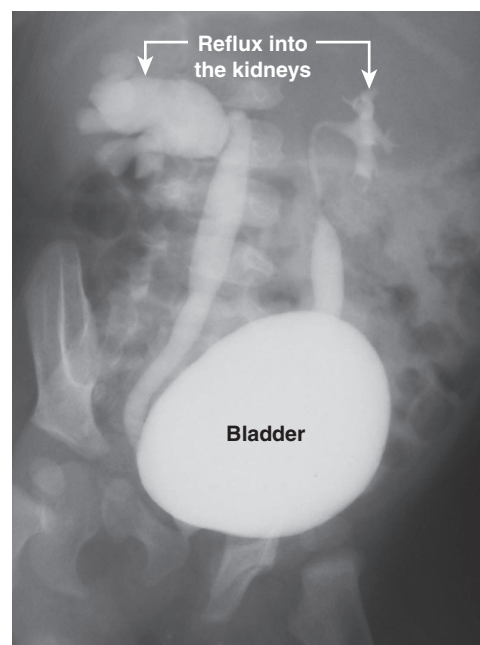


**Figure 299-6** Normal ultrasound of the right and left kidneys despite the presence of high-grade vesicoureteral reflux as seen on voiding cystourethrogram.

performed by placing a urethral catheter into the bladder, instilling a contrast agent, and obtaining images of the bladder and kidneys during filling and voiding. VUR is diagnosed when contrast instilled into the bladder is detected in the ureter or upper urinary tract (Figure 299-7). The degree of VUR is quantified by the International Reflux Study Group classification system (Table 299-2). In addition to detecting and quantifying the degree of VUR, the VCUG also helps identify other bladder and urethral anomalies, such as PUVs, ureterocele, bladder diverticula, and neurogenic bladder, that may cause secondary reflux.

With the conventional fluoroscopic VCUG, images are captured at fixed time points, and episodic reflux might thus be missed. Consequently, especially in infants, a fill-void cycle should be repeated at least once during the test to improve the sensitivity of the VCUG in detecting VUR. An alternative imaging test is the RNC. A radioisotope (eg, DTPA) is placed in the bladder, and the bladder, kidneys and ureters are continuously monitored (Figure 299-8). Because the imaging is continuous, the sensitivity in detecting reflux with an RNC is increased compared to fluoroscopic VCUG. In addition, the use of the RNC exposes the patient to less radiation compared with conventional VCUG. However, the anatomic details (eg, grade of reflux and associated urethra, bladder abnormalities) cannot be resolved well with RNC. Thus, VCUG should be used as the initial study to identify and characterize the reflux; RNC should then be used for follow-up studies. The VCUG should be performed after the infection has resolved and a repeat urine culture is negative. Instrumentation while the infection is still active may lead to sepsis.

Because renal parenchymal abnormalities are found in association with VUR, proper functional imaging



**Figure 299-7** Vesicoureteral reflux seen on voiding cystourethrogram.

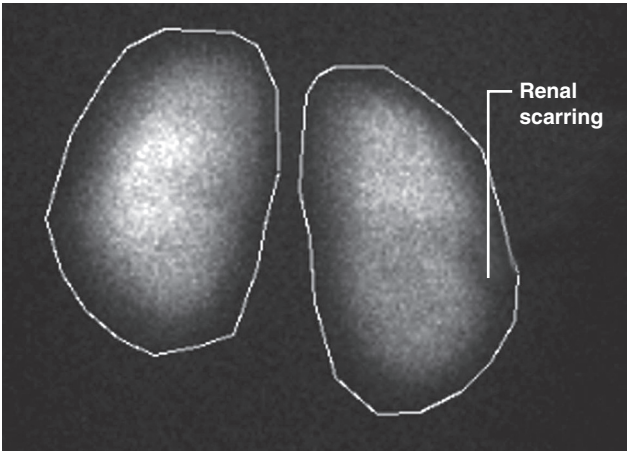


of the kidneys is indicated in patients with reflux. Although US is not invasive or costly, its ability to detect renal abnormalities such as dysplasia and scarring is limited. Renal scanning by DMSA provides an accurate assessment of renal development and permits evaluation for the presence of renal scarring resulting from UTI (Figure 299-9). In the past, intravenous pyelogram has been used to assess renal parenchymal abnormalities. However, it has been replaced by renal scintigraphy as the gold standard because of the increased sensitivity of DMSA scans in detecting renal scarring. Not all children with VUR require imaging with renal scintigraphy. Renal abnormalities such as scarring and dysplasia are more often found in children with at least 1 UTI and in those with higher grades of reflux (grade III and above); therefore, renal scintigraphy is indicated for children with VUR who have at least 1 episode of UTI and those with at least grade III VUR.

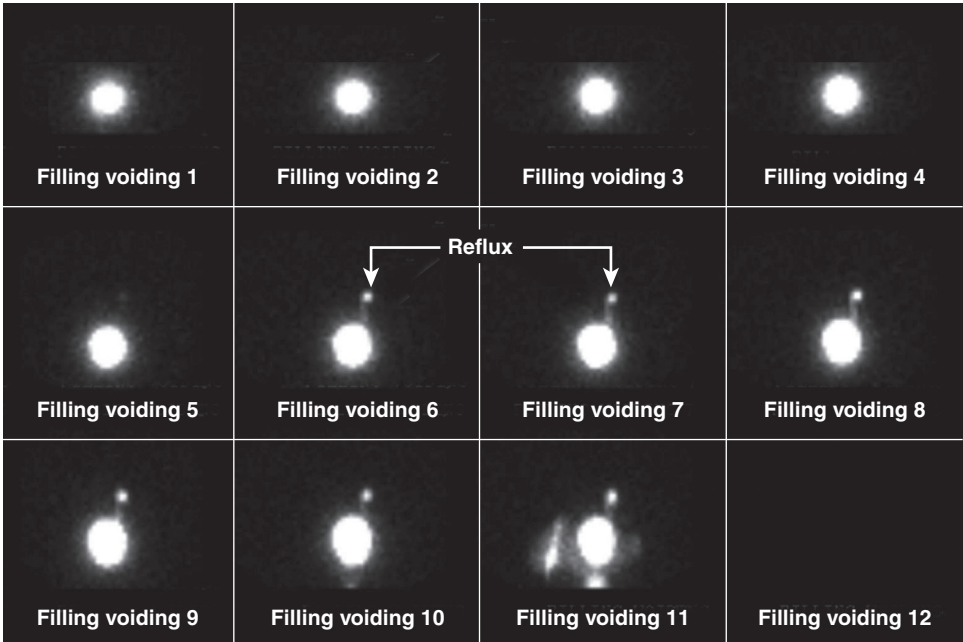
Table 299-2 International Reflux Study Classification System for Vesicoureteral Reflux		
GRADE	REFLUX INTO URETER	REFLUX INTO CALICES
I	Distal segment only	None
II	Without tortuosity	Without distention
III	With minimal tortuosity	With mild distention
IV	With moderate tortuosity	With moderate distention
V	With severe tortuosity	With severe distention

**Management**

In most patients, VUR will resolve spontaneously without requiring surgical intervention. Consequently, medical therapy should be considered, with the goal of preventing the long-term complications associated with VUR, such as renal scarring, hypertension, and renal insufficiency or failure by the prevention of UTI. The use of antibiotic prophylaxis for VUR is controversial. It was generally accepted that the use of chronic low-dose antibiotic prophylaxis can prevent UTI and thus prevent the complications associated with VUR. This is based on past studies in which 21% of children with VUR who did not receive prophylactic



**Figure 299-9** <sup>99m</sup>Tc dimercaptosuccinic acid renal scan demonstrating renal scarring in a patient with vesicoureteral reflux.



**Figure 299-8** Vesicoureteral reflux seen on nuclear cystogram.

antibiotics developed new scars in previously normal kidneys, and 66% developed new scars in previously scarred kidneys. In children with similar grades of reflux, but receiving antibiotic prophylaxis, no progression of renal scars occurred unless a breakthrough UTI was present. More importantly, predicting which children would and would not develop renal scarring was impossible. More recently, a meta-analysis in the AAP UTI Clinical Practice Guideline (2011) suggested that there may be no benefit to using antibiotic prophylaxis for VUR. Data from 6 recent studies did not support the use of antimicrobial prophylaxis to prevent febrile recurrent UTI in infants without VUR or with grade I to IV VUR. However, it should be noted that the studies included in the meta-analysis were from vastly different patient populations. In several of the included studies, most of the patients had low-grade VUR, minimal incidence of renal damage, and variable degree of voiding and bowel dysfunction. Four of the studies included patients much older than 2 years of age who more likely had bladder and bowel dysfunction as a risk factor for UTI rather than VUR. Moreover, the circumcision status, another important risk factor for UTI, was not known in 4 of the studies.

The current suggestions for antibiotic prophylaxis are summarized in Table 299-3 and should be maintained until VUR has resolved spontaneously or after surgical correction. In children older than 7 to 8 years who have persistent low-grade VUR but have not had any recent UTIs, observation while they are no longer receiving antibiotic prophylaxis may be tried because the risk of renal scarring in these children is low. Antibiotic prophylaxis can be used as long as no breakthrough UTIs or compliance issues occur. Length of therapy varies depending on parental preference and the likelihood of reflux resolution. When reflux resolution seems unlikely, stopping the antibiotics and correcting the reflux should be considered. Debate is ongoing about whether to use alternating antibiotic prophylaxis versus monotherapy. Most physicians use monotherapy, and very little evidence has been found in the literature that suggests alternating antibiotic prophylaxis is more effective than monotherapy. In teenagers with reflux, a trial of antibiotic is reasonable; however, their chance of resolution is thought to be somewhat lower. The disadvantages of antibiotic prophylaxis include difficulties in adherence to daily schedule, adverse/allergic reaction to the antibiotics,

and the potential for the emergence of microbial resistance.

The spontaneous resolution rate of VUR depends on several factors, including the grade of the reflux, laterality, gender, and mode of presentation. In general, low-grade VUR is more likely to resolve than high-grade reflux (grades I and II, 70% to 80% resolution rate; grade III, 50%; grades IV and V, <30%). Bilateral high-grade VUR tends to resolve less often than unilateral high-grade VUR. VUR in girls tends to resolve at a slower rate than in boys. High-grade VUR detected after evaluation for prenatal hydronephrosis tends to resolve more quickly than that detected after evaluation for UTIs. In patients with sibling reflux, the rate of resolution is similar to the probands, with grade as the primary determining factor.

Voiding dysfunction can greatly affect the resolution rate of VUR. Voiding abnormalities, such as detrusor instability or detrusor-sphincter dyssynergy, can impede the resolution of reflux, and, in some patients, it can worsen its severity with time. Consequently, in the medical management of reflux, symptoms of dysfunctional voiding, such as urinary urgency and incontinence, must be ascertained, and treatment of dysfunctional voiding with timed voiding, anticholinergic therapy, or both, must be instituted. Similarly, constipation can increase the risk of UTI and delay the resolution of VUR. Aggressive treatment of constipation will help decrease the risk of UTI and improve voiding function.

In some patients, surgical correction for VUR may be required. Recurrent UTI while receiving prophylactic antibiotic therapy is an indication for surgical correction, because protection from renal scarring cannot be adequately achieved with medical management. Additional indications for surgery include lack of compliance with a medical regimen, low probability of spontaneous resolution of reflux (eg, in older children with higher-grade reflux), new renal scar formation while receiving prophylaxis, and anatomic abnormalities such as a paraureteral diverticulum. The overall rate of surgical correction in a general population of children with all grades of VUR ranges from 13% to 20%. The types of surgical correction include transurethral (endoscopic), laparoscopic, and open techniques. The open antireflux procedures have a high success rate (98%), but often require a few days of hospitalization and subsequent recovery time. In contrast, the endoscopic techniques have much lower associated morbidity and shorter recovery time; however, their success rates are not as good as that of open surgery.

In the management of reflux, the goal is not merely to prevent UTIs and to determine whether VUR has resolved. The primary care physician should monitor children for long-term complications such as reflux nephropathy. Approximately 10% of children and 50% of adults with renal scarring will develop hypertension. In addition, estimates suggest that approximately 10% of children with reflux nephropathy will develop end-stage renal disease, and 90% will have diminished glomerular filtration rate. Consequently, blood pressure and urinary protein levels should be measured periodically if renal scarring is present. Women with a

**Table 299-3** Antibiotic Prophylaxis Suggestions

AGE	MEDICATION	DOSAGE
<3 months	Amoxicillin	25 mg/kg once a day
	Cephalexin	25 mg/kg once a day
>3 months	Trimethoprim	2 mg/kg (up to 100 mg) once a day
	Trimethoprim + sulfa	2 mg/kg of the sulfa once a day
	Nitrofurantoin	1–2 mg/kg (up to 100 mg) once a day

history of VUR and in particular with reflux nephropathy should be monitored closely during pregnancy because of the increased rates of pyelonephritis, toxemia, preterm delivery, fetal growth retardation, fetal loss, and decreased maternal renal function.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *What Is a Pediatric Nephrologist?* (fact sheet), American Academy of Pediatrics (patiented.solutions.aap.org)
- *What Is a Pediatric Urologist?* (fact sheet), American Academy of Pediatrics (patiented.solutions.aap.org)

### AAP POLICY

American Academy of Pediatrics Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management. Urinary tract infection: clinical practice guideline for the diagnosis and management of initial UTI in infants and children 2 to 24 months. *Pediatrics*. 2011;128(3):595–610 (pediatrics.aapublications.org/content/128/3/595)

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## Chapter 300 OCULAR TRAUMA

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### INTRODUCTION

Accidental ocular trauma represents a major public health issue. Although only 5% of all eye injuries are serious enough to result in permanent visual loss, trauma accounts for 40% of all cases of monocular blindness in the general population. In addition to the obvious visual consequences, severe trauma in children can also present significant developmental and emotional challenges, especially if a cosmetic defect is present. Amblyopia can develop after injury in

children younger than 8 years, placing an additional physical and psychological burden.

Demographic data from several studies demonstrate that boys are more susceptible to ocular injury than girls, with a ratio of approximately 3:1. Common sources of injury include interactions with other children, sports, motor vehicle crashes, falls, and projectiles. Among sports-related injuries, baseball was most common, followed by basketball, tennis, and hockey. In children who had visual outcome of 20/200 or worse, BB guns, knives, and rocks were commonly implicated. Mandatory eye protection in organized sports such as hockey has significantly reduced eye injuries, but commonsense precautions are not always exercised on the playground or at home. Most severe injuries occur in children with no eye protection, whereas only 5% occur in those who are wearing safety glasses or regular glasses. Pediatricians and eye care providers should actively educate parents and children regarding the importance of eye protection to prevent ocular injuries.

### ANATOMIC CONSIDERATIONS

The orbit is a pear-shaped cavity in the skull that protects the globe from lateral injury. The orbital rim tends to absorb the impact of most blunt injury with large objects such as a ball or fist. The medial wall and orbital floor are thinner and susceptible to fracture, whereas the lateral wall is the thickest and strongest. The orbital roof is also the floor of the anterior cranial fossa; therefore an orbital roof fracture requires neurosurgical evaluation. Any child with an orbital fracture must undergo a careful eye examination to rule out globe injury.

The eyelids protect the globe from debris and direct trauma involving smaller objects. The eyelids are also vital in maintaining a normal smooth tear film over the cornea. Injury to the eyelid, particularly if it involves the lid margin, can result in exposure of the cornea and lead to scarring or infection. Deeper injury to the lids can be associated with globe injury or injury to the levator muscle if the orbital septum has been violated. The lacrimal drainage system starts in the medial aspect of the upper and lower lid at the punctal opening and connects to the lacrimal sac and bony nasolacrimal duct through canaliculi. An eyelid injury medial to the punctal opening frequently results in a canicular laceration, which requires surgical repair.

The globe rests in the orbit, cushioned by orbital fat and suspended by its attachment to extraocular muscles and surrounding elastic tissues. The exposed structures in the interpalpebral fissures are the cornea and conjunctiva, which are frequently involved in eye injuries. The cornea is 0.5 mm thick centrally and 1 mm thick at the periphery. A corneal injury that is limited to the epithelium often resolves without sequelae, whereas an injury that penetrates the epithelial basement membrane into the stroma can result in permanent scarring and vision loss. The bulbar conjunctiva extends from the corneal limbus and covers the sclera. It then forms the cul-de-sac or fornix and reflects over the inner surface of the eyelids as the palpebral conjunctiva. Hemorrhages in the subconjunctival space are usually benign but can hide deeper



injuries to the sclera or extraocular muscles. The sclera covers the posterior four-fifths of the globe and is largely avascular. It is 0.5 mm thick at the equator and 1 mm in thickness posteriorly. The sclera is thinnest (0.3 mm) just behind the insertion of the rectus muscles, making this area a common site for globe rupture after blunt trauma. The iris is the most anterior portion of the uveal tract, the vascular coat of the eye. Trauma can result in bleeding or tears in the iris, especially at its root where it is thinnest. The lens is located just behind the iris and is entirely covered by a capsule. Disruption of the capsule as a result of sharp or blunt trauma can compromise the clarity of the lens, resulting in a traumatic cataract.

The posterior segment of the eye comprises the posterior sclera, choroid, retina, and vitreous. The macula represents the critical central portion of the retina, which is responsible for fine visual acuity. Severe trauma can result in vitreous hemorrhage and retinal edema, retinal tears, and retinal detachment. Injury affecting the macula can result in severe central vision loss, whereas damage to the peripheral retina can be asymptomatic. In general, trauma affecting the posterior segment structures usually carries a worse prognosis for recovery than injury limited to the anterior segment.

## EVALUATION

### History

An accurate and detailed history is helpful in evaluating a patient with ocular trauma because it can suggest the mechanism and nature of injuries. This history can be difficult to obtain in circumstances in which an adult or other reliable observer did not witness the injury, and details obtained from young children may not always be reliable. In such instances, the pediatricians must verify that the physical findings are consistent with the history obtained. Certain historical details are particularly helpful:

1. Does a potential exist of chemical injury? If so, then treatment must be delivered immediately before obtaining a full history and performing an examination to minimize damage from an acid or alkali burn.
2. Has a severe head injury or other nonocular injury occurred that may require attention? Significant head trauma can be associated with globe rupture, traumatic optic neuropathy, cranial nerve palsies, orbital fractures, and cortical visual damage.
3. Is the injury blunt or sharp in nature? A sharp injury is more likely to be penetrating, resulting in a full-thickness laceration through the cornea or sclera. A severe blunt impact can also lead to globe rupture through an inside-out mechanism as a result of globe compression and increased intraocular pressure.
4. Does the possibility exist of a foreign body? A foreign body can be superficial (in the eyelid, cornea, or conjunctiva), intraocular, or intraorbital. An injury associated with flying debris, metallic fragments, projectiles, or any broken object is high risk for a retained foreign body.

After details surrounding the mechanism of injury have been obtained, additional history taking should

focus on prior ocular history (eg, the presence of amblyopia), medical history, medications and allergies, and the date of the last tetanus immunization.

### Physical Examination

A thorough and complete examination ensures proper diagnosis and treatment, particularly when historical details are lacking. If the history is clear and reliable, such as being poked in the eye with a finger, then a more directed examination is possible. An examination can be quite challenging in a child who is in discomfort or who is otherwise uncooperative. If a full-thickness injury through the eyeball is apparent, then further examination is best left to an ophthalmologist. If the index of suspicion for a serious injury or foreign body is high in an uncooperative patient, then examination under sedation or anesthesia is occasionally necessary.

### Vision Testing

The examination should begin with an age-appropriate assessment of vision. Verbal children should have acuity measured with letter charts or, if they cannot name the letters, with letter matching (such as the HOTV chart) or other nonletter testing, such as Allen pictures or tumbling Es. Acuity testing should be performed with proper optical correction, if applicable, and care should be taken to ensure that the normal eye is fully occluded when testing the injured eye. If the child is unable to see the largest target on the chart (usually 20/200 or 20/400), then alternative methods such as their ability to count fingers (recorded as “count fingers at x feet”), perceive hand motion (recorded as “hand motion at x feet”), or perceive light (recorded as “light perception” or “no light perception”) is helpful. Preverbal children are assessed by their ability to *fix and follow* a small object or toy. Once again, each eye should be tested separately. An inability to follow smoothly with 1 eye compared with the other or attempts to look around the occlusion of the normal eye suggest decreased vision in the injured eye.

### External Examination—Ocular Motility

External inspection and observation are helpful to characterize the severity of the injury. Important signs include swelling or bruising of the lids, lacerations of the lids or face, proptosis or enophthalmos, foreign bodies and possible entrance sites, and conjunctival hemorrhage. If a foreign body is likely, then eversion of the upper lid is required to inspect the palpebral conjunctiva properly. An obvious globe laceration with prolapse of intraocular contents might also be visible by inspection alone. If the globe appears intact, then palpation of the orbital rim can be performed to check for fractures of the orbital or facial bones. Ocular motility should be evaluated to ensure full range of motion in all gaze positions. Limited movement can result from orbital hemorrhage or swelling, orbital fractures, cranial nerve palsies, or direct muscle trauma. Diplopia generally results from limited motility, although young children may not verbalize this symptom.

### Pupils

The presence of round and equally reactive pupils greatly reduces (but does not eliminate) the likelihood



of a severe, vision-threatening injury. An irregularity in the size or shape of the pupil can result from blunt trauma with damage to the pupillary sphincter or from a full-thickness laceration of the cornea or sclera. Ideally, the reaction of each pupil to light (direct and consensual) is checked with the child fixating at a distant target. The swinging flashlight test is then performed to check for the presence of an afferent pupillary defect, or Marcus Gunn pupil. This test is performed by alternately shining the light source into each eye. Both pupils should normally stay constricted as a result of the direct and consensual response to light. Paradoxical dilation of the illuminated pupil indicates the presence of an afferent pupillary defect, which results from optic nerve or extensive retinal injury.

### Anterior Segment

An initial assessment of the anterior chamber can be performed simply with a penlight examination or with a direct ophthalmoscope. Conjunctival hemorrhages, corneal or conjunctival lacerations, foreign bodies, anterior chamber depth, and iris and pupillary irregularities can be diagnosed without the aid of the slit lamp. If a slit lamp is available, then a more detailed and accurate examination is possible in a cooperative child. The pediatrician can use the slit lamp to evaluate for smaller conjunctival or corneal lacerations, foreign bodies that might not be visible with a penlight, the presence of red or white blood cells in the anterior chamber, and cataract formation or dislocation of the lens. After penlight or slit-lamp or both types of examination have been completed, fluorescein solution or strips and a cobalt blue filter or lamp should be used to check for abrasions, lacerations, or foreign bodies that might otherwise go undetected.

### Fundus

Detailed fundus examination can be difficult in a child without pupillary dilation. However, the red reflex should be observed, looking for asymmetry. An absence or asymmetry of the red reflex can indicate the presence of vitreous hemorrhage, cataract formation, or hyphema. In addition, other findings such as corneal abrasion or corneal foreign body can also be appreciated as an irregularity or opacity in the red reflex. Although visualization of the optic nerve and macula is possible with the direct ophthalmoscope, the view is generally limited. Any child who is thought to have posterior segment injury or unexplained vision loss should have a dilated fundus examination by an ophthalmologist with the aid of the indirect ophthalmoscope.

## SPECIFIC OCULAR INJURIES

### Eyelid and Lacrimal Injury

Superficial lacerations to the eyelid can be closed with 6-0 nylon sutures, which are removed in 5 to 7 days, or 6-0 plain sutures if the child might be uncooperative for suture removal. A thorough examination of the anterior segment is required to exclude globe injury. Three special categories of eyelid injuries require special attention: lacerations involving the lid margin, lacerations medial to the lacrimal puncta, and deep lacerations of the upper lid, which expose orbital



**Figure 300-1** Full-thickness injury involving the lid margin and lower canaliculus. The laceration is medial to the lacrimal punctum.

fat. Lacerations involving the lid margin should be repaired by an experienced surgeon to ensure that the smooth contour of the lid margin is maintained. Poor closure or reapproximation can result in a notch along the lid margin, leading to both cosmetic and functional consequences. Laceration or injury medial to the punctum carries a high risk for disrupting the lacrimal drainage system, given that the canaliculus is quite superficial just under the surface of the lid margin (Figure 300-1). Failure to recognize and treat a canalicular laceration can result in chronic tearing, particularly if the lower canaliculus is involved. A canalicular injury requires prompt referral and surgical repair with tube placement in the lacrimal drainage system, followed by removal of the tube several months later. Dog bite injuries have an uncanny predilection for involving the lacrimal system. Upper lid lacerations deep enough to expose orbital fat carry the risk for damage to the levator muscle. Surgical exploration is required to repair any involvement of the levator muscle and to close the laceration itself. Failure to recognize levator involvement can result in posttraumatic ptosis, which might require additional surgery.

### Anterior Segment Trauma

#### Chemical Injury

Chemical injuries are acute emergencies and require immediate management to help prevent serious complications. Typically, the caregiver or emergency medical services will have attempted to irrigate the eyes, but it is often difficult to do so sufficiently. When a child reaches the pediatrician's office or emergency care setting after a chemical injury, the history should be limited to the estimated time of injury and nature of the offending agent (eg, household cleaning product).

A helpful first step is to use pH indicator paper to determine the nature and extent of acid or alkali injury. A small strip can be quickly placed in the conjunctival sac; normal pH of the eye is between 6.8 and 7.4. Topical anesthetic should be instilled, and the eye irrigated with up to 2 liters of a pH-neutral solution,

such as buffered saline. A lid speculum may be used to keep the lids open if necessary. Alternatively, an irrigating contact lens can be used. Care must be taken to ensure the flow of saline is adequate; a steady drip is usually not sufficient. When irrigation is completed, pH indicator paper can again be used to determine that the pH of the eye has returned to normal. The conjunctival fornices should be examined to check for any residual chemical agent. If present, then a cotton-tipped applicator may be used to gently remove this precipitate, and the area should be reirrigated.

After irrigation, a more detailed examination should be performed. First, the examiner should note the degree of conjunctival injection. A lack of hyperemia, particularly in the perilimbal area, may be an ominous sign of ischemia. Permanent damage to stem cells located in this area can significantly impair the patient's ability to regenerate corneal epithelial cells. Second, the cornea should be examined for clarity. A hazy or edematous cornea is a sign of serious injury. Finally, the examiner should instill fluorescein to check for corneal abrasions.

Treatment should be tailored to the injury but will often include an antibiotic drop or ointment and artificial lubricants. Corneal abrasions associated with chemical injuries should not be patched so that tears and natural blinking may eliminate any residual chemical. Referral to an ophthalmologist within 24 hours is indicated, particularly with moderate to severe injuries, which can result in permanent vision loss from corneal scarring, corneal vascularization, and other sequelae.

### Thermal Injury

Ocular involvement from thermal injury can be isolated but is often seen in the setting of severe facial burns. Although globe injury is typically mild because of the protective blink reflex, it can be severe if the blink reflex is impaired or if loss of consciousness occurs. As with chemical injuries, immediate irrigation is important, given that it serves to cool the ocular surface. Corneal and conjunctival abrasions are treated with artificial lubricants and topical antibiotics. Severe lid involvement can lead to contracture and cicatricial changes resulting in corneal exposure and ulceration. Initial treatment of lid injury consists of topical antibiotic ointment, and severe injury may require subsequent skin grafting to prevent lid malposition and exposure.

### Subconjunctival Hemorrhages

Significant discoloration is associated with subconjunctival hemorrhages; this condition may be quite alarming to patients and their families (Figure 300-2). When isolated, however, they are harmless and require no treatment. Patients need only be aware that various color changes may occur while the blood is being resorbed and that several days to weeks may elapse before the hemorrhage has completely disappeared.

Surrounding blood can mask tissue laceration. A small, superficial laceration of the conjunctiva often does not require repair, but a thorough ophthalmic examination may be necessary to ensure that no



**Figure 300-2** Subconjunctival hemorrhage after blunt injury.

deeper laceration of the sclera or other trauma to the eye has occurred.

Nontraumatic causes of subconjunctival hemorrhage also exist. Newborns often have small, bilateral hemorrhages, presumably from the pressure of uterine contractions. Severe coughing such as that caused by pertussis or forceful vomiting can cause small hemorrhages. Some forms of viral conjunctivitis can be hemorrhagic and are usually associated with chemosis (edema of the conjunctiva) and symptoms of irritation and mild discharge. Rarely, certain blood dyscrasias such as leukemia can also be associated with subconjunctival hemorrhage, usually bilateral.

### Corneal Abrasion

Corneal abrasions are areas of disruption of the corneal epithelium. The epithelium is laced with numerous fine sensory nerve endings of the first branch of the trigeminal nerve, and abrasions result in extreme pain and sensitivity. Only in rare situations of neurotrophic disease are corneal abrasions relatively asymptomatic. Typically, photophobia and blepharospasm accompany the pain. Associated signs usually include conjunctival injection and mild lid swelling.

Diagnosis of a corneal abrasion may be facilitated by the instillation of a topical anesthetic followed by fluorescein (Figure 300-3). Use of a cobalt blue filter will then easily highlight areas of epithelial loss. Abrasions may be linear or patchy and can be of any size. Care must be taken to open the lids well enough to gain view of the entire cornea. Fine, linear abrasions in the superior cornea, for example, may be easily missed and are often a sign of an associated conjunctival foreign body lodged in the superior tarsal conjunctiva.

Most abrasions heal quickly, particularly in children. Treatment is aimed at keeping the patient comfortable and preventing infection. Typically, an antibiotic ointment or drop is used 2 to 4 times a day until the abrasion has healed. Nonsteroidal anti-inflammatory drops may be used as an adjunct to reduce pain, particularly in older children. The use of a pressure patch is somewhat controversial. When a patch is used, an antibiotic



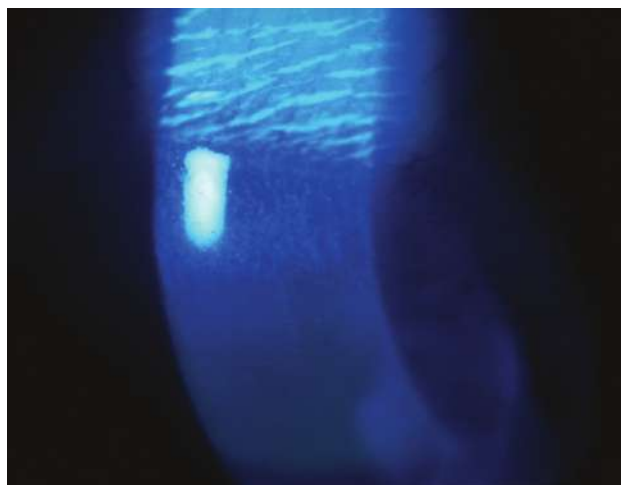
**Figure 300-3** Central corneal abrasion is highlighted with fluorescein dye.

ointment is instilled with soft oval gauze taped over the eye to keep it shut. The patch and antibiotic are then replaced after 24 hours, or the decision is made to discontinue its use. Prolonged patching is discouraged for young children because of the possibility of developing amblyopia or strabismus. The placement of a patch may provide additional patient comfort and may be particularly useful if a child tends to rub the eye excessively. However, no evidence has been found to suggest the abrasion will heal more quickly. Some ophthalmologists think that allowing natural tears, which contain immunoglobulin A, lysozyme, and other anti-infective properties, to stream over the cornea with normal blinking may result in improved healing and decreased risk for infection. Whichever method is used, the patient should be monitored closely, especially within 1 to 2 days, for delayed healing. Delayed healing may suggest the presence of a foreign body, an ulcer, or even a different pathologic process (eg, herpes keratitis).

### Conjunctival and Corneal Foreign Bodies

The sources of most surface, or nonpenetrating, foreign bodies in children are small objects that can be thrown or carried by the wind, such as dirt, sand, gravel, grass, or leaves. In many instances, the foreign body will be readily eliminated from the eye with rubbing and secondary tearing. In some cases, however, medical attention is necessary to help dislodge the foreign material.

Conjunctival foreign bodies typically produce irritation, discomfort, and a mild to moderate amount of conjunctival injection. The lids should be forcefully opened, if necessary, and the bulbar conjunctiva should be directly examined. If this area appears normal, attention is then turned to the tarsal conjunctival surfaces. Eversion of the lower lid can be accomplished readily with gentle inferior traction. Upper lid eversion can be much more difficult, especially if the child is very young or uncooperative. The lashes are grasped and the lid stretched minimally; next, the shaft of a cotton-tipped applicator is placed horizontally along the superior margin of the tarsal plate. The lid is then reflected over the applicator for inspection. After a conjunctival foreign body has been identified, a drop of topical anesthetic should be administered



**Figure 300-4** Fine, linear abrasions of the superior cornea are luminated with fluorescein dye and the use of a cobalt blue filter.



**Figure 300-5** Eversion of the upper lid reveals a small particle resting in the superior tarsal conjunctiva.

and a cotton tip used to remove it gently. If a conjunctival foreign body is not easily identified, then a cotton tip may still be used to sweep the upper and lower conjunctival fornices to ensure that a very small foreign particle has not been missed. Finally, fluorescein should be administered to check for associated corneal abrasions. Multiple, fine vertical abrasions of the superior aspect of the cornea are highly suggestive of a foreign body of the upper tarsal conjunctiva (Figure 300-4 and Figure 300-5).

Corneal foreign bodies usually represent particles that are resting on the surface of the epithelium or have penetrated the epithelium and are embedded in the anterior stroma. The latter types are more common because the normal blink and secondary movement of the tears will usually either expel a nonembedded particle or move it to a conjunctival surface. Again, the lids should be opened to gain full view of the cornea and a light source used to help identify a possible foreign body. A topical anesthetic and cotton-tipped applicator can be used to dislodge



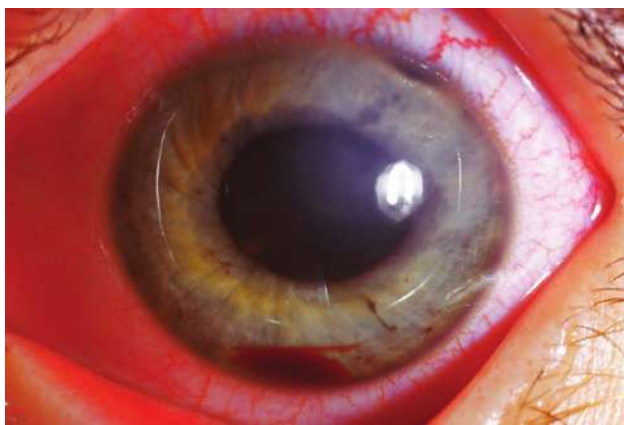
the particle gently, with care taken not to debride a greater area of epithelium in the process. In many instances, however, this method is not successful in removing an embedded object, and referral to an ophthalmologist is necessary. If the child is able to sit at a slit lamp, then the ophthalmologist may be able to use a fine needle, forceps, or burr to remove the foreign body. Younger or uncooperative children will usually require sedation or general anesthesia.

An antibiotic drop or ointment is typically prescribed for a few days after removing a surface foreign body, particularly if the source was organic or if any disturbance occurred in the corneal epithelium. Follow-up care is not necessarily indicated for a simple conjunctival foreign body but is required in cases of corneal involvement.

### Hyphema

The presence of blood in the anterior chamber is termed a *hyphema* (Figure 300-6). In the setting of blunt trauma, blood in this area results when enough force is transmitted to the globe to cause a rupture of the blood vessels located within the iris root and ciliary body. Hyphemas can be of varying severity, from what is labeled as a *microhyphema* (floating red blood cells in the aqueous fluid without layering) to an *8-ball hyphema* (blood filling the entire anterior chamber). Most cases fall in between and are described based on the percentage of the anterior chamber occupied by the layered blood. Hyphemas are readily identified with a light source and good exposure of the anterior segment. After diagnosis, initial management involves placing a protective shield over the eye to avoid the possibility of further injury. Patients should also be instructed to limit their activities until seen by a specialist. Because of their potential vision-threatening complications, all hyphemas, regardless of size, should be referred to an ophthalmologist.

Most ophthalmologists treat hyphemas with a topical steroid drop to reduce the associated inflammation, and a topical cycloplegic agent. A shield is usually continued and bed rest often advised. If the



**Figure 300-6** Small hyphema is associated with an iris root tear at the 2-o'clock position.

hyphema is worrisome and the child is too young to cooperate with restricted activity, then hospitalization may be indicated. This circumstance is of particular importance in the first 2 to 5 days after injury, at which time the clotted blood may begin to resorb and cause a rebleed of injured vessels. In many instances, this rebleed can be more visually devastating than the original injury. Other direct complications of hyphemas include corneal blood staining, glaucoma, and amblyopia. Glaucoma is perhaps the most common of the aforementioned complications. It is often controlled with topical medications but, in certain situations, requires timely surgical evacuation of the hyphema to prevent irreversible optic nerve damage. Patients with sickle cell anemia or trait are at greater risk for having visual compromise from optic neuropathy or central artery occlusion at lower pressures than is the general population and therefore require the surgeon to have a lower threshold for intervention.

### Traumatic Iritis

Iritis, or anterior uveitis, refers to inflammation of the iris and ciliary body. This inflammation can occur in a nontraumatic setting, such as in association with autoimmune disorders; it may also occur in the setting of trauma and will cause the patient to experience blurry vision, pain, and significant photophobia. The eye is usually quite injected, and the pupil may not constrict briskly. If iritis is suspected, then referral to an ophthalmologist is indicated. Floating white blood cells in the anterior chamber are visualized under the high magnification of a slit lamp, confirming the diagnosis. Similar to a hyphema, potential complications include iris synechiae, glaucoma, and cataract formation. Treatment includes a topical steroid and cycloplegic agent if the inflammation is severe.

### Traumatic Mydriasis

A mid-dilated pupil noted on examination of a patient after a blunt, traumatic event can be a result of small ruptures or tears of the iris sphincter muscle. The pupil is therefore unable to constrict normally. The injury may involve only part of the sphincter muscle, giving a slightly irregular appearance to the pupil. Care must be taken to rule out the possibility of a ruptured globe, which can also cause an irregularly shaped pupil.

Often, the ophthalmologist is able to identify free pigment cells released into the anterior chamber. However, unless true associated inflammation (iritis) exists, treatment is usually not indicated.

### Open Globe Injury

An open globe results from a full-thickness injury to the eye wall, involving the cornea or sclera. Most open globe injuries in children are caused by a penetrating injury, but they can also result from severe blunt trauma. Penetrating injuries consist of laceration of the globe with sharp objects such as knives, sticks, pencils, and glass. Severe blunt trauma can cause compression of the globe, leading to elevated intraocular pressure and rupture of the eye wall (ruptured globe). Common sources of blunt trauma include



motor vehicle crashes, fist injuries, and sports injuries (eg, baseball, racquetball). The corneoscleral limbus and the sclera just behind the rectus muscle insertions are the thinnest and most susceptible areas for rupture.

The diagnosis of an open globe is often readily apparent when an anterior laceration with exposed intraocular contents is visible. This can lead to a shallow anterior chamber, irregular pupil, and exposed iris or uveal tissue (Figure 300-7). Other anterior segment findings may include subconjunctival hemorrhage, lowered intraocular pressure, and cataract formation. With blunt trauma or with posterior lacerations, the diagnosis may be more difficult, particularly if extensive subconjunctival hemorrhage obscures visualization of the sclera. External signs may consist of an irregular pupil, a deep anterior chamber, subconjunctival hemorrhage, or conjunctival chemosis. When the diagnosis is not evident from initial inspection with a penlight, further assessment with slit-lamp examination, intraocular pressure measurement, and dilated fundus examination may be required. A low intraocular pressure, vitreous hemorrhage, or retinal detachment can occur secondary to a rupture. Other associated clinical findings in an open globe injury may include vision loss, an afferent pupillary defect, and optic disc edema.

The likelihood of an intraocular foreign body should be considered based on the mechanism of injury. A history involving a BB or pellet gun, broken glass, or metal fragments certainly elevates the risk for an intraocular foreign body, but the possibility must be considered with any penetrating injury. The penetration site may not always be evident, and the presence of hyphema or vitreous hemorrhage may preclude visualization of an intraocular foreign body. A B-scan ultrasound or computed tomography (CT) scan should be obtained in such cases, but magnetic resonance imaging is contraindicated if a metallic foreign body is suspected. Copper and iron are toxic to the retina and require urgent removal, whereas graphite, lead, aluminum, and plastic are better tolerated by the eye.

When an open globe injury (with or without intraocular foreign body) is diagnosed or suspected, a

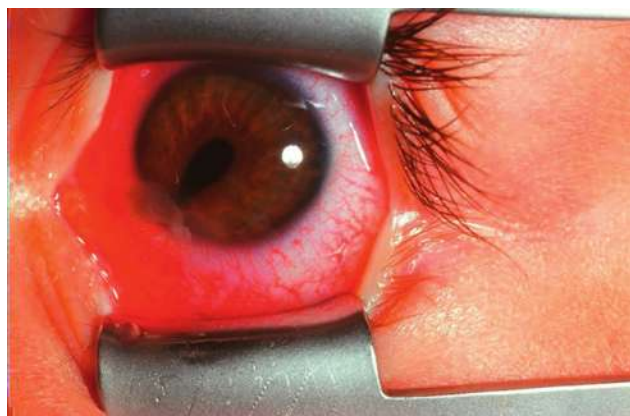
protective shield should be placed over the eye, and further examination should be deferred. The patient should be placed on bed rest with instructions to remain NPO. Urgent ophthalmology consultation is required for surgical repair, with the primary goal to restore the integrity of the eye wall. Surgical exploration of the globe is required in some cases to determine when an open globe injury is present. Additional surgery may be required to manage complications such as traumatic cataract, intraocular hemorrhage, and retinal detachment. The prognosis depends on the severity of the injury, with visual outcomes ranging from 20/20 to NLP (no light perception), whereas enucleation may be required in the most severe cases. In general, injuries that lead to a retinal detachment carry a worse prognosis than those that are limited to the anterior segment. Another serious complication is the development of endophthalmitis, which has been reported to occur in up to 15% of cases after open globe injury.

### Orbital Trauma

Blunt or penetrating trauma may cause severe orbital injury in the absence of an open globe, although diagnosis and management of an open globe take precedence. The most common orbital injuries consist of orbital fractures, retrobulbar hemorrhage, and traumatic optic neuropathy. Evaluation includes assessment of visual acuity, motility, pupils, anterior segment, and intraocular pressure. Obvious proptosis or enophthalmos should also be noted. A marked decrease in vision, presence of an afferent pupillary defect, or elevation of intraocular pressure warrants an urgent ophthalmology consultation.

Orbital fractures typically result from blunt trauma, often with an object such as a fist or a ball. The fracture can occur from increased orbital pressure or from transmission of force from the orbital rim to the orbital walls. The orbital floor is most commonly affected, followed by the medial wall. Involvement of the orbital roof, or the presence of other facial fractures, may require consultation with specialists from neurosurgery or otolaryngology. Common clinical findings with floor fractures include enophthalmos, facial hypesthesia from infraorbital nerve injury, and strabismus from inferior rectus entrapment or cranial nerve injury. A CT scan of the orbits with axial and coronal sections is required to delineate the extent of the fracture. In the absence of globe injury, surgical intervention can be deferred for up to 2 weeks to allow the swelling to subside, although earlier intervention has been reported to improve outcomes. Indications for surgery include the presence of a large defect in the orbital floor, enophthalmos, and tissue entrapment.

Retrobulbar hemorrhage can occur from blunt or penetrating trauma as a result of shearing or laceration of orbital blood vessels. Iatrogenic hemorrhage can occur with peribulbar and retrobulbar injections, typically used to achieve local anesthesia for ocular surgery in adults. Clinical findings consist of rapid-onset proptosis, increased intraocular pressure, limited eye movement, and decreased vision. In the presence of a marked elevation of intraocular pressure or compromised optic nerve function, a lateral canthotomy



**Figure 300-7** Corneal laceration at the 7-o'clock position with exposed intraocular contents, peaked pupil, and shallow anterior chamber.

and cantholysis are required to urgently relieve the retrobulbar pressure on the globe and optic nerve.

Neurologic findings with facial trauma may include cranial nerve palsies and optic neuropathy, typically from blunt trauma involving motor vehicle crashes or sports injuries. A patient with traumatic optic neuropathy may demonstrate decreased vision, an afferent pupillary defect, and decreased color vision. The optic nerve may appear normal or edematous. A CT scan of the orbits may demonstrate a fracture of the optic canal with impingement of the optic nerve or hemorrhage of the optic nerve sheath. Surgical decompression of the optic nerve can be considered in such cases. Standard medical treatment of traumatic optic neuropathy is high-dose intravenous steroids for 1 to 3 days after the injury. However, the efficacy of both surgical and medical interventions remain uncertain.

### Abusive Trauma

Up to 40% of pediatric abuse trauma cases are associated with ocular injuries. Certainly, retinal hemorrhages associated with a shaking injury are of primary concern, but many other signs of eye trauma exist. Direct blunt force can result in multiple injuries, such as lid ecchymosis, orbital fracture, and intraocular hemorrhage. Neurologic injury can result in cranial nerve palsies, which in turn may cause lid and ocular motility abnormalities. Cortical visual impairment may also occur in the setting of severe neurologic damage.

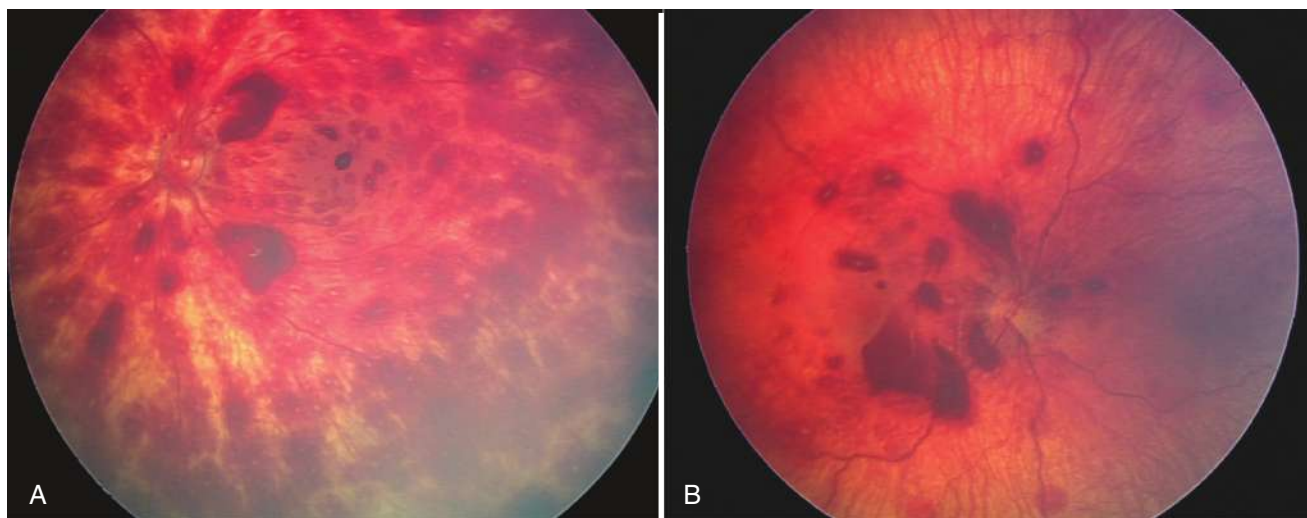
Pediatric sexual abuse can rarely manifest as conjunctivitis caused by *Chlamydia trachomatis* or *Neisseria gonorrhea*. Although these are potential etiologies of neonatal conjunctivitis transmitted by passage through the birth canal, any child outside of the newborn period with a culture positive for these organisms should be suspected as a victim of sexual abuse. *Phthirus pubis* can uncommonly be found on the eyelashes and eyebrows of children and is termed *phthiriasis palpebrarum*. Sexual abuse must also be suspected in these cases,

although some children have been known to become infected from sharing a communal bed with heavily infested adults.

Retinal hemorrhages are a key manifestation of abusive head trauma in children younger than 5 years and are present in up to 85% of cases of abusive head trauma (also known as *shaken baby syndrome*) (Figure 300-8). There is a positive association between the level of neurologic injury (including subdural and subarachnoid hemorrhage) and the severity of retinal hemorrhages.

The hemorrhages are thought to occur secondary to violent, repetitive, acceleration-deceleration maneuvers, causing vitreoretinal traction and subsequent bleeding. This blood can accumulate in 1 or more of several locations, and the presence of multilayered hemorrhages is a key characteristic of nonaccidental trauma. Blood between the retina and underlying choroid is termed *subretinal*; blood in the retina is termed *intraretinal*; blood in front of the inner limiting membrane but behind the vitreous gel is termed *preretinal*. Intrasclear hemorrhage at the optic nerve-globe junction, as well as macular schisis (splitting of the retinal layers) and perimacular folds, are felt to occur predominantly, but not exclusively, in cases of abusive head trauma.

The medicolegal implications of discovering retinal hemorrhages are of course profound, and the determination of whether abuse has occurred should be made after the careful consideration of several factors, including the history, presence of intracranial hemorrhage, fractures, and other signs of abuse. There are multiple other causes of retinal hemorrhages, including (but not limited to) anemia, coagulopathy, leukemia, cytomegalovirus infection, hypertension, and glutaric aciduria. However, many of these can be ruled in or out by the presence of other ocular findings, such as infiltrates in the case of leukemia or exudates in the case of hypertension. Birth trauma can also cause



**Figure 300-8** A, Severe retinal hemorrhages as the result of abusive head trauma. B, Moderate retinal hemorrhages as a result of abusive head trauma. Preretinal hemorrhages, which obscure the retinal vessels, and intraretinal hemorrhages, which are beneath the retinal vessels, are both visualized.

retinal hemorrhages, but these are typically small, few in number, and restricted to the area of the posterior pole. Furthermore, they usually resolve anywhere from 3 days to 6 weeks after birth. Few other etiologies other than abusive head trauma exist for severe, multilayered retinal hemorrhages.

When abuse is suspected, the pediatrician should consult an ophthalmologist within 72 hours of presentation and ideally within 24 hours. If pharmacologic dilation of both pupils is not possible for the sake of neurologic monitoring, then sequential examinations should be performed on each eye. If appropriate equipment is available, retinal photographs should be obtained. The examiner should make sure to document well the number, location, and type of retinal hemorrhages and other pathology seen. Lastly, follow-up care with the ophthalmologist is indicated to help assess long-term vision potential.

### WHEN TO REFER

- Lacerations involving the lid margin, those medial to the lacrimal puncta, and deep lacerations of the upper lid
- Canalicular injury
- Levator muscle injury
- Corneal abrasion
- Removal of corneal foreign bodies
- Hyphema treatment
- Traumatic iritis
- Traumatic mydriasis
- Ruptured globe
- Abusive trauma

### WHEN TO ADMIT

- To treat hyphemas in certain patients
- Ruptured globe
- Abusive trauma

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Eye Safety* (fact sheet), American Association for Pediatric Ophthalmology and Strabismus ([www.aapos.org/terms/conditions/50](http://www.aapos.org/terms/conditions/50))
- *Eye Trauma in Teenagers* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/injuries-emergencies/Pages/Eye-Trauma-in-Teenagers.aspx](http://www.healthychildren.org/English/health-issues/injuries-emergencies/Pages/Eye-Trauma-in-Teenagers.aspx))
- *Ocular Injury* (fact sheet), American Association for Pediatric Ophthalmology and Strabismus ([www.aapos.org/terms/conditions/136](http://www.aapos.org/terms/conditions/136))
- *What Is a Pediatric Ophthalmologist?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/pages/What-is-a-Pediatric-Ophthalmologist.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/pages/What-is-a-Pediatric-Ophthalmologist.aspx))

### AAP POLICY

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## Chapter 301

## OLIGURIA AND ANURIA

Amrish Jain, MD; Tej K. Mattoo, DCH, MD

A decrease in urine output is the most visible sign of acute kidney injury (AKI) in all age groups, particularly younger children. *Oliguria* occurs when the urine output in an infant is less than 0.5 mL/kg per hour for 24 hours or is less than 500 mL/1.73 m<sup>2</sup> per day in older children. *Anuria* is defined as absence of any urine output. An important point to remember is that healthy newborns may have no urine output for 24 hours after birth.

Oliguria is much more common than anuria, and, if not treated appropriately, the patients may become anuric, which may result in serious renal damage that requires specialized care. Oliguria or anuria may be the outcome of a renal response to intravascular circulatory volume depletion or a sudden drop in blood pressure (*prerenal AKI*). Oliguria or anuria may also occur as a result of intrinsic renal damage (*renal AKI*). Rarely, obstruction to the flow of urine (*postrenal AKI*) may result in oliguria or anuria.

### INCIDENCE

The incidence of oliguria or anuria in previously healthy children is not known, particularly oliguria because many such patients have subclinical symptoms or respond promptly to appropriate management, and thus they are not reported in the literature.

In hospitalized patients, oliguric AKI occurs in approximately 10% of newborns in the intensive care unit, 2% to 3% of older children requiring intensive care, and 8% of patients undergoing cardiac surgery. In newborns, the relative incidence of prerenal, renal, and postrenal AKI is 85%, 11%, and 3%, respectively. In older children, the corresponding data extrapolated from studies are 66%, 33%, and less than 1%, respectively.

### ETIOLOGY

The common causes for oliguria, anuria, or AKI in children are best defined in relation to the age of the patient.

Prerenal AKI caused by dehydration is the most common cause of oliguria and anuria in younger children, accounting for 70% of community-acquired cases of AKI and up to 60% of hospital-acquired cases.



Recent literature reveals that the etiology of AKI is changing from predominantly primary renal disease to multifactorial causes. In hospitalized children, nephrotoxic medication is emerging as one of the most common causes of renal AKI. Renal AKI caused by intrinsic renal damage may be further categorized into 4 types: (1) *Acute tubular necrosis* (ATN) occurs as a result of prolonged ischemia or drug- or toxin-mediated renal tubular injury. Oliguria reverses in most cases after repair and regeneration of tubular epithelial cells occurs. (2) *Glomerular lesions* may occur with acute glomerular diseases, including postinfectious glomerulonephritis. (3) *Vascular lesions* may be seen in hemolytic uremic syndrome or vasculitis. (4) *Interstitial lesions* occur in acute interstitial nephritis, mostly as a result of drugs. Although ATN is common in children of all ages, the glomerular and vascular causes of renal AKI are more common in older children.

Postrenal AKI results from a mechanical or functional obstruction to the flow of urine. The obstruction can be in the lower urinary tract, such as the posterior urethral valves, or bilaterally in the upper tract, such as bilateral ureteropelvic junction obstruction, which is rare. Unilateral obstruction can cause AKI in patients with only a single functioning kidney. Postrenal AKI is more common in newborn babies than it is in older infants.

The most common causes of oliguria and anuria in neonates and children are listed in Table 301-1.

### COMORBID CONDITIONS

Although oliguria and anuria are not uncommon in previously healthy children, about two-thirds of such patients have an underlying comorbid condition. These conditions include the following:

- Neurologic conditions, when the patient has a compromised thirst mechanism or is seriously disabled and thus totally dependent on others for nutrition

and hydration, as may be the case in patients with severe cerebral palsy.

- Renal diseases that impair the ability to maximally concentrate the urine, as may occur with salt-losing nephropathy or chronic renal failure.
- Gastrointestinal conditions that cause hypoalbuminemia and decreased intravascular volume as a result of a low oncotic pressure, as in celiac disease or hepatic failure.
- Endocrine diseases such as diabetes insipidus and diabetes mellitus, which are associated with increased hypotonic urine output and osmolar diuresis, respectively.
- Hematologic conditions such as sickle cell disease or trait, which impair urine concentration mechanism, or oncologic emergencies such as tumor lysis syndrome, which causes renal failure, particularly if the patient is not well hydrated.
- Therapy that may predispose the patient to renal failure (eg, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, aminoglycosides, contrast media) because these substances impair renal autoregulation in the presence of mild renal insufficiency or dehydration and may result in oliguria or anuria.

### EVALUATION

#### History

A thorough history and physical examination are important in identifying the cause of oliguria or anuria, which is of particular clinical significance in prerenal and postrenal AKI cases because early diagnosis and prompt treatment often result in quick recovery. A history of vomiting, diarrhea, hemorrhage, sepsis, and decreased oral intake associated with oliguria suggests a prerenal cause. Besides symptoms related to the disease process, such children may exhibit increased

**Table 301-1** Most Common Causes of Oliguria and Anuria

	PRERENAL	RENAL	POSTRENAL
<b>NEONATE</b>	Perinatal asphyxia Respiratory distress syndrome Hemorrhage Sepsis or shock Congenital heart disease Dehydration Drugs (indomethacin, maternal use of ACE inhibitors or NSAIDs)	ATN Exogenous toxins (aminoglycosides, amphotericin B) Endogenous toxins (hemoglobin, myoglobin, uric acid) Congenital kidney diseases Vascular (renal vein thrombosis, renal artery thrombosis)	Posterior urethral valves Meatal stenosis Bilateral ureteral obstruction Neurogenic bladder
<b>CHILDREN</b>	Dehydration Hemorrhage Burns Third-space loss (surgery, trauma, nephrotic syndrome) Renal loss (diabetes mellitus, diabetes insipidus, diuretics) Shock Decreased cardiac output	ATN Glomerulonephritis Exogenous toxins (aminoglycosides, amphotericin B) Endogenous toxins (hemoglobin, myoglobin, uric acid) Vascular (hemolytic uremic syndrome, vasculitis) Interstitial nephritis	Posterior urethral valves Meatal stenosis Bilateral ureteral obstruction Neurogenic bladder Obstructive urinary tract stones or sludge

ATN, acute tubular necrosis; ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs



thirst, palpitations, fatigue, and clinical signs of dehydration, including weight loss. A history of poor urinary stream, dribbling, or enuresis in older children may be the result of urinary tract obstruction. A history of abnormal renal findings during routine antenatal ultrasonography can help diagnose such patients.

A history of gross hematuria or edema strongly suggests intrinsic renal disease. A history of pharyngitis or impetigo a few weeks before the onset of gross hematuria can be the result of postinfectious glomerulonephritis, and bloody diarrhea often precedes hemolytic uremic syndrome. Patients with systemic vasculitis (eg, systemic lupus erythematosus) may have a history of fever, joint pains, and skin rash along with oliguria. A history of recurrent sinusitis or lower respiratory tract infections may suggest Wegener granulomatosis, and hemoptysis may indicate the presence of a pulmonary-renal syndrome, such as Goodpasture syndrome or microscopic polyangiitis. A detailed history of recent or ongoing chronic medications is important to exclude the possibility of interstitial nephritis. In neonates, a history of umbilical artery catheterization favors a diagnosis of renal artery thrombosis. Family history is helpful in diagnosing conditions such as diabetes insipidus and polycystic kidney disease.

### Physical Examination

A comprehensive physical examination is the key to assessing the severity of the disease process and the possible cause of oliguria or anuria. The presence of tachycardia, dry mucous membranes, sunken eyes, orthostatic blood pressure changes, decreased skin turgor, or hypotension indicates hypovolemia, resulting in prerenal oliguria or anuria. A palpable bladder with a weak urine stream or dribbling suggests bladder neck or urethral obstruction. A sacral tuft of hair or myelomeningocele may be associated with neurogenic bladder, which can cause obstructive uropathy with postrenal oliguria or anuria.

Children with intrinsic renal damage are likely to have a circulatory volume overload, and such children may exhibit hypertension, edema, or both. Younger children, particularly infants, may have signs of congestive heart failure, such as hepatomegaly, gallop rhythm, and pulmonary edema. Clinicians need to look closely for specific signs that point to underlying renal disease. These signs may include severe anemia in patients with hemolytic uremic syndrome, a butterfly rash on the face and musculoskeletal involvement in patients with systemic lupus erythematosus, and typical purpuric rash over the buttocks and extensor surface of the lower extremity in Henoch-Schönlein purpura. Abdominal examination may reveal palpable kidney, which may be caused by renal vein thrombosis, polycystic kidney disease, multicystic dysplastic kidney, or hydronephrosis.

### Laboratory Studies

Preexisting risk factors, historical details, and the results of the physical examination will help the physician choose appropriate laboratory tests. Urinalysis is the most important noninvasive diagnostic test. A thorough examination of a freshly voided or bladder-catheterized

urine sample helps distinguish prerenal from renal causes of oliguria or anuria. A normal or near-normal urinalysis, characterized by few cells with little or no casts or proteinuria, is seen in prerenal disease, urinary tract obstruction, and some cases of ATN. A urine sample showing muddy-brown granular casts and epithelial cell casts strongly suggests ATN. The finding of red cell casts is diagnostic of glomerulonephritis, and presence of significant proteinuria indicates glomerular disease.

Urinary indices, including urine sodium, specific gravity, creatinine, and osmolality, are important diagnostic tools for oliguria. The urine sodium concentration is usually above 40 mEq/L in ATN and is below 10 mEq/L in oliguria resulting from intravascular volume depletion. Neonates have decreased ability to conserve sodium, and, as a result, prerenal disease is associated with urine sodium concentration less than 20 to 30 mEq/L. In prerenal oliguria, urine specific gravity is more than 1,020, the ratio of urine to plasma creatinine is more than 40, and the ratio of urinary to plasma osmolality is more than 1.5. In renal causes of oliguria, the ratio of urine to plasma osmolality is less than 1.5, and the ratio of urine to plasma creatinine is less than 20. The effect of variations in urine volume on interpreting these urinary indices is eliminated by calculating fractional excretion of sodium (FENa). A fractional excretion of sodium of less than 1% suggests reabsorption of almost all filtered sodium in response to decreased renal perfusion (prerenal), whereas in ATN the excretion is more than 2%. Newborns and young infants cannot establish a FENa of less than 2%, even in prerenal AKI.

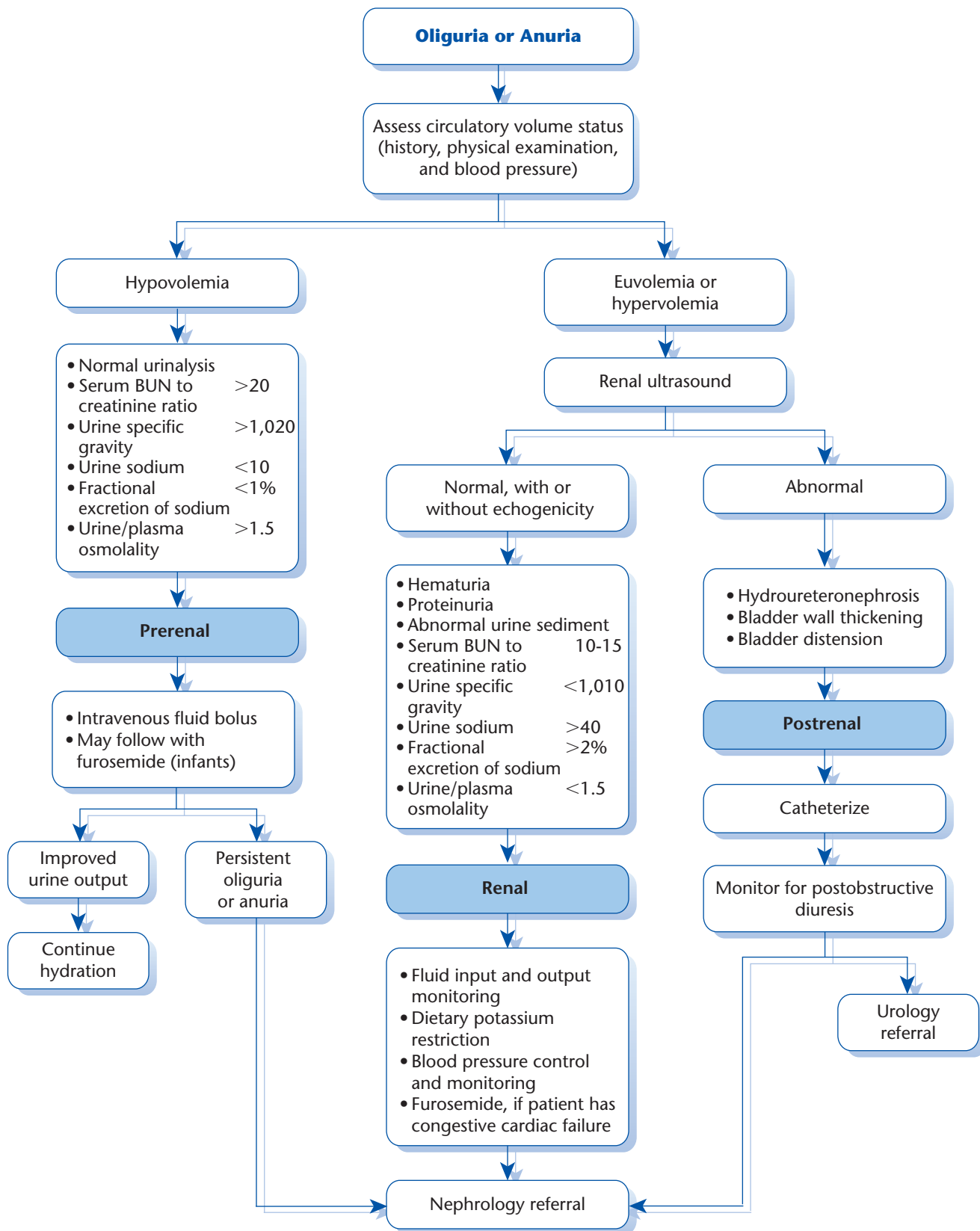
The severity of renal damage or hypoperfusion is also indicated by increased blood urea nitrogen (BUN) and serum creatinine concentrations. In prerenal oliguria, increased BUN is marked, and the ratio of BUN to serum creatinine is more than 20:1, whereas a ratio of 10:1 to 15:1 suggests intrinsic renal damage.

### Imaging Studies

Renal ultrasonography is an important diagnostic tool in patients with oliguria or anuria but is generally not indicated in children with prerenal failure from dehydration who respond promptly to fluid resuscitation. Ultrasonography provides important information regarding kidney size and echogenicity, renal blood flow, collecting system, and urinary bladder. Children with intrinsic causes for oliguria or anuria may have echogenic and slightly enlarged kidneys. An ultrasound examination showing bilateral hydronephrosis or hydroureteronephrosis and bladder wall thickening is consistent with obstruction of the bladder outlet causing postrenal oliguria or anuria. Ultrasonography can also detect congenital renal disorders such as polycystic kidney disease and multicystic dysplastic kidney. Doppler examination of the renal blood flow is helpful in diagnosing renal vascular thrombosis.

## MANAGEMENT

The algorithm for managing patients with oliguria or anuria is shown in Figure 301-1.



**Figure 301-1** Algorithm for management of patients with oliguria or anuria. BUN, blood urea nitrogen.

The key to preventing oliguria or anuria is adequate hydration in at-risk patients. This group may include patients who have just undergone surgery; patients receiving nephrotoxic medications such as amphotericin B, acyclovir, or radiocontrast agent; and patients at risk for developing tumor lysis syndrome or pigment nephropathy caused by hemoglobinuria or myoglobinuria.

The major goal of treatment of prerenal oliguria or anuria is to restore intravascular volume. An estimate of volume status is needed to begin and continue fluid therapy. This amount is assessed by a history and a physical examination that includes assessment of body weight, skin turgor, capillary refill, peripheral edema, and blood pressure. A dehydrated child with oliguria or anuria should receive a fluid bolus of normal saline or Ringer's lactate at 20 mL/kg to restore fluid volume. Depending on the patient's response, another bolus may be needed.

Children with oliguria and volume overload may benefit from furosemide therapy and may require fluid restriction, as well as blood pressure and acid-base monitoring. Children with oliguria that results from obstruction may require urinary catheterization. Relief of obstruction may be followed by postobstructive diuresis and resultant hyponatremia and hypokalemia requiring fluid and electrolyte replacement.

Management of oliguria also includes timely treatment of the underlying etiology: for example, inotropic support in a child with heart failure or shock, appropriate antibiotics in cases of sepsis, and steroids for acute interstitial nephritis and selected cases of glomerulonephritis.

### WHEN TO REFER OR ADMIT

Children should be referred to a nephrologist or admitted to the hospital (or both) if they have any of the following:

- Persistent oliguria or anuria despite an adequate fluid challenge in a dehydrated child
- Persistent oliguria or anuria that continues after removal of the offending nephrotoxins
- Oliguria or anuria associated with swelling, hypertension, gross hematuria, abnormal blood chemistry, and severe systemic signs or symptoms
- Urology referral for oliguria or anuria caused by obstructive uropathy

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## Chapter 302

# OPPOSITIONAL DEFIANT DISORDER

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## CASE REPORT

Keenan, a 9-year-old African American boy, arrives for his annual well-child with his mother. Keenan lives with his mother, stepfather, and older sister (age 12 years). Keenan's mother is tearful when she describes the calls she has been getting from school in the past few months. Keenan sits quietly on a stool in the office looking uncomfortable as his mother talks. His mother reports he was born 6 weeks early after a complicated pregnancy and was intubated in the first 24 hours after his delivery by cesarean section. He remained in the hospital for 2 weeks with some feeding complications. Keenan's mother describes him as a consistently poor sleeper (often waking during the night). He had severe reflux until age 2 years. However, he met all developmental milestones. He has been healthy since his delivery except for a broken arm from a fall off a bike.

Keenan's mother reports he has always been a challenging child. She states, "Nothing is ever easy with him. I am worn out." At home, she is never sure whether he will do what she asks of him. "Some days it seems all he does is argue with us about everything." He often says no when asked to turn off the TV, set the dinner table, or get ready for school or sports practice, and has started to swear at her. Recently he said to his mother, "You think I am a bad kid. You hate me." He frequently blames his sister or the "stupid kids at school" or his "dumb teacher" for anything that doesn't go well.

Until this year it was mostly at home that Keenan was hard to manage. He is now in the fourth grade, and his school is concerned about him. In the past, his teachers often described him as a "handful" or needing to be better at listening but as an enthusiastic member of the class. He is a good athlete and enjoys sports, but now with competitive sports he is often described as being a poor sport and at times rude to his coaches. This year at his midyear report his teachers described him as unpredictable, lacking effort, disruptive and silly, often uncooperative, and just not interested in applying himself. He is academically performing at grade level but "acts up" when asked to complete reading or writing projects.

On physical examination, Keenan is in the 50th percentile for height, weight, and head circumference. His vital signs and vision and hearing screening findings are normal. His tonsils and adenoids seem large. He has no dysmorphic features, and his physical appearance is normal. He is taking no medications. Keenan's mother reports he has a cousin who was expelled for behavioral issues related to attention-deficit/hyperactivity disorder (ADHD) and an aunt

with depression and alcohol addiction. Keenan is well dressed, articulate, and sullen but cooperative in the office, admitting he gets really mad sometimes because other people “can be real jerks.”

## DEFINITION

The case of Keenan demonstrates one of the frequently occurring presentations to pediatric primary care offices: the elementary school child with acting-out behavior of unclear origin. Oppositional defiant disorder (ODD) under the classification of disruptive, impulse control, and conduct disorders, encompasses a broad range of acting-out behavior toward parents or teachers. It is one of the most commonly encountered clinical disorders in children ranging from preschoolers through teenagers.

The pediatrician is usually alerted when problems with compliance, negative and hostile behavior, and other forms of aggression such as verbal threats and physical acts create a significantly problematic disruption in social, academic, or family functioning. According to the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5), the indications of ODD are a pattern of angry or irritable mood, argumentative or defiant behavior, or vindictiveness lasting at least 6 months and exhibited in interactions with someone other than a sibling, leading to poor functioning in school, at home, or in both locations. As seen in the case of Keenan, it is typical that a parent

reports having longstanding struggles with the child that finally become intolerable when school or the community begins to experience the same challenging behavior. The criteria for diagnosing ODD are described in Box 302-1.

## PREVALENCE

A review of epidemiologic studies according to age, gender, socioeconomic status, neighborhood, and urban or rural life estimates that the prevalence of ODD is from 2% to 16% in preschool- and school-aged children. The community prevalence of the disorder is reported as widely ranging, depending on which assessment methods, time frame, definition of diagnosis, and number of participants are used. Prevalence in preschoolers has received particular focus in the past decade because there is increasing evidence that treatments for disruptive behavior disorders (DBDs) identified in early childhood are effective. In one epidemiologic study of preschoolers, a prevalence rate of 6.6% for ODD was noted.

## By Age

Rates of ODD remain relatively constant from age 5 until age 10 years, then begin to decline for both boys and girls. However, if one disregards overlap with conduct disorder (CD), clinically significant levels of oppositionality seem to persist well beyond childhood. According to a large review of the literature on ODD,

### BOX 302-1 DSM-5 Diagnostic Criteria for Oppositional Defiant Disorder

- A. A pattern of angry or irritable mood, argumentative or defiant behavior, or vindictiveness lasting at least 6 months as evidenced by at least 4 symptoms from any of the following categories, and exhibited during interaction with at least 1 individual who is not a sibling.

#### ANGRY OR IRRITABLE MOOD

1. Often loses temper
2. Is often touchy or easily annoyed
3. Is often angry and resentful

#### ARGUMENTATIVE OR DEFIANT BEHAVIOR

4. Often argues with authority figures or, for children and adolescents, with adults
5. Often actively defies or refuses to comply with requests from authority figures or with rules
6. Often deliberately annoys others
7. Often blames others for his or her mistakes or misbehavior

#### VINDICTIVENESS

8. Has been spiteful or vindictive at least twice within the past 6 months

**Note:** The persistence and frequency of these behaviors should be used to distinguish a behavior that is within normal limits from a behavior that is symptomatic. For children younger than 5 years, the behavior

should occur on most days for a period of at least 6 months unless otherwise noted (criterion A8). For individuals 5 years or older, the behavior should occur at least once per week for at least 6 months unless otherwise noted (criterion A8). Although these frequency criteria provide guidance on a minimal level of frequency to define symptoms, other factors should also be considered, such as whether the frequency and intensity of the behaviors are outside a range that is normative for the individual's developmental level, gender, and culture.

- B. The disturbance in behavior is associated with distress in the individual or others in his or her immediate social context (eg, family, peer group, work colleagues), or it has a negative effect on social, educational, occupational, or other important areas of functioning.
- C. The behaviors do not occur exclusively during the course of a psychotic, substance use, depressive, or bipolar disorder. Also, the criteria are not met for disruptive mood dysregulation disorder.

*Specify current severity:*

**Mild:** Symptoms are confined to only 1 setting (eg, at home, at school, at work, with peers).

**Moderate:** Some symptoms are present in at least 2 settings.

**Severe:** Some symptoms are present in 3 or more settings.



no firm conclusion can be reached regarding the prevalence of ODD as a function of age. Thus, rates of ODD across childhood and adolescence indicate the complex developmental trends within the disorder. The diagnosis of ODD is relatively stable over time, but most affected children (approximately 67%) will no longer meet criteria after 3-year follow-up. Earlier age at onset of ODD symptoms conveys a poorer prognosis in terms of progression to CD. Those who have early-onset ODD (before age 8 years) have a threefold increase in CD.

### By Socioeconomic Status

Oppositional defiant disorder, like CD, is more prevalent among children and teens from families of low socioeconomic status. A 2009 study in an urban community sample found ODD to occur in 13.4% of the population of preschoolers. Neighborhoods characterized by high crime rates, social disorganization, and more untreated parental psychopathology also seem connected to higher rates of ODD.

### By Gender

Oppositional defiant disorder is more common in boys than girls, but the data are inconsistent. Gender differences do not emerge until after age 6 years, when boys show more forms of disruptive behavior. There are many more school-aged boys diagnosed with ODD than there are school-aged girls. One hypothesis is that the developmental progression for boys may be toward emergent CD, whereas for girls the trajectory may be toward developing internalizing disorders such as depression. Another explanation for the gender difference is that parents report equal prevalence of ODD in boys and girls, but teachers report significantly more ODD in boys than girls, presumably because acting-out behavior at school draws more attention. By adolescence, the prevalence of ODD in girls and boys is equivalent.

## ETIOLOGY

Etiologic research on ODD tends to be intertwined with research on CD. Most children diagnosed with CD exhibit the behaviors associated with ODD concurrently or at an earlier age. Therefore, to the extent that the behaviors associated with ODD often precede the more serious forms of psychopathology, including not only CD but also adult antisocial personality disorder, the presentation of these behaviors represents an important window of opportunity for prevention efforts. However, the continuity between ODD and CD is not an absolute: approximately two-thirds of children diagnosed with ODD do *not* subsequently develop CD. The behaviors associated with ODD have nonetheless been shown to have potent and negative effects on child–adult and child–peer interactions. Most researchers conclude that there is no single cause or main effects model to explain the complexity of the symptoms that make up ODD. The most widely accepted opinion is that ODD occurs from a complex mix of risk and protective factors found in the biopsychosocial makeup of the individual.

### Biologic Factors

Many authorities think that biology plays an important role in ODD because there is familial clustering of

certain DBDs such as ADHD as well as substance use and mood disorders. Studies of the genetics of ODD have produced mixed results. Recently, researchers have found that mother, father, and teacher reports all point to the influence of additive genetic factors in both boys and girls. ODD appears more in families in which at least 1 parent has a history of a mood disorder, ODD, CD, ADHD, antisocial personality disorder, or a substance-related disorder. In addition, some studies find mothers with depression are more likely to have children with oppositional behavior. It is probable that the joint influence of environment and biology, as in many disorders, plays a role.

Temperamental factors have been implicated in the future development of disruptive behavior. Baseline underarousal has also been found in children with ODD. A compilation of biologic factors such as exposure to toxins, exposure to nicotine in utero, and deficient nutrition all may have effects but are highly inconsistent. Neurobiologic theories have been explored in the etiology of aggression. The role in aggression of neurotransmitters such as serotonin, norepinephrine, and dopamine has been investigated, but no single pathway has been identified as the root cause. ODD is clearly familial, but research has yet to determine what role genetics play.

### Psychological Factors

Some researchers suggest that children with ODD present similarly to children with poor attachment, and that oppositional behavior is a signal to an unresponsive parent. Another line of research has focused on children's deficient social information processing. Aggressive children underuse pertinent social clues, misconstrue hostile intent by peers, and are poor problem solvers. The most prevalent explanation of psychological factors leading to ODD is the coercion or social interactional model. Most representations of this model focus on patterns of parental discipline that contribute to the development of coercive parent–child exchanges.

In addition to the coercion model, more recently alternative conceptualizations of ODD have been proposed. Developmental theorists have long underscored the importance of affective modulation and self-regulation. In keeping with these ideas, an explanation has been proposed that suggests children with ODD suffer from poor self and emotional regulation skills along with various other delays in cognitive areas. Noncompliance is a hallmark behavior in the development of conduct problems. The skill of *compliance*, defined as the capacity to defer or delay one's own goals in response to the imposed goals or standards of an authority figure, can be considered one of many developmental expressions of a young child's evolving capacities in the domains of adaptation, self-regulation, and affective modulation.

## DIAGNOSIS

### Signs and Symptoms

The first symptoms of ODD may be evident during the preschool years and rarely later than adolescence. (Note that diagnosing a preschooler with ODD requires

awareness of what is within normal limits for this young age and what may truly be symptomatic. See Box 302-1.) Onset is typically gradual, occurring over the course of months or years. The negative, hostile behaviors associated with ODD are almost always present in the home and with individuals the child knows well and often occur simultaneously with poor self-esteem, mood lability, and low frustration tolerance.

The diagnosis of ODD can be made most readily from a detailed description of a child's life at home and at school. Currently, there is no biologic marker or specific diagnostic test that reliably identifies ODD in a child or teen.

In clinical practice the greatest challenge is to determine whether there is an underlying medical or psychological condition that could better explain ODD symptoms. All children are defiant at times, especially in early childhood and during adolescence. Determining when parent report, teacher report, direct observation, and the child's own description warrant treatment is dependent on the degree of interference the oppositionality creates within family, school life, and friendships. In making this determination, one area of consideration is the level of punitive discipline at home. Parental physical aggression can be associated with aggressive child behavior. Many studies cite hyperactivity, aggression, and oppositional behavior as all related to elevated levels of punitive discipline and spanking. Thus, children who experience punitive discipline, spanking, and physical aggression show a pattern of increasing severity in the problems they display.

Assessing a child or adolescent with significant hostile or negative behaviors involves more than simply assessing the type, rate, or severity of the child's behavior problems and should involve assessing the many risk factors that can play a role in development of ODD or CD across these pathways. Measures that may be helpful in determining an ODD diagnosis are suggested later in this chapter under Evaluation.

### Differential Diagnosis

Because there are no definitive biologic or imaging markers for ODD, a diagnosis of ODD requires evaluating whether the child meets *DSM-5* criteria (see Box 302-1) and deciding whether any other factors exist that may better explain a child's challenging behavior. The behaviors associated with ODD (temper outbursts, persistent stubbornness, resistance to directions, unwillingness to compromise, unwillingness to give in or negotiate, deliberate annoyance of others, blaming others for one's own mistakes, and verbal and minor physical aggression) can be because of a medical, psychosocial, psychiatric, or neurologic condition. Conditions that may mimic or co-occur with ODD during childhood and adolescence are given in Box 302-2.

Deciding whether these issues are the primary cause of the child's challenging behavior or whether they coexist with ODD is central to treatment. Although mental health physicians, nonphysician clinicians, and educators can assist in identifying mental health and educational disorders, the role of the

primary care physician is crucial in ruling out a medical condition.

There are some noted medical complications that may present with ODD-like symptoms. Many research studies find that obstructive sleep apnea (OSA) is correlated with cognitive challenges. Children who are chronically sleep deprived from OSA may have behavioral, mood, learning, and attention problems that mimic symptoms of ADHD and related learning and disruptive behavior disorders. Alternatively, what might look like a behavioral issue could actually be a sign of hearing loss or even a vision problem. Children who cannot hear or see properly cannot pay attention in class. In addition, medication side effects may explain irritability and oppositionality. Many neurologic disorders can cause learning challenges and disruptive behavior in children as well.

### Coexisting Conditions

ODD is frequently comorbid with other psychiatric disorders and often precedes the development of CD, substance abuse, and severe delinquent behavior. The overlap between ODD and CD warrants careful discussion and may require the assistance of a mental health specialist to determine. The *DSM-5* precludes a diagnosis of ODD in children who meet criteria for CD, so many clinically significant oppositional behaviors are overshadowed by a diagnosis of CD. If the CD exclusion is dropped, data suggest that levels of oppositional behavior severe enough to meet criteria for a disorder persist at essentially the same levels from early childhood to middle adolescence. This suggests that finding a treatment for noncompliance is no less important in older than in younger age groups, even though the noncompliance may be overshadowed by the more severe issues of CD.

There have been continuing debates over the nature of the connection between the angry-irritable mood symptoms and negative, disobedient, and hostile behavior patterns indexed by ODD, and the rule violations and physical aggression more characteristic of CD. Many studies have combined the 2 terms together under DBD, making the significance and role of ODD difficult to understand. Some researchers have asked, Is ODD a precursor to CD or a milder version of essentially the same disorder, or does it embody a somewhat different clinical construct? Three observations have been made. First, if the 2 disorders are assessed independently, each disorder shows quite distinct age profiles. Rates of ODD remain stable from latency through mid-adolescence, whereas rates of CD increase in the teen years. Second, most children with CD also showed high amounts of oppositionality, and this did not change with age. And third, when comorbidity was evaluated with other disorders, both ADHD and anxiety disorders seemed more strongly linked with ODD than with CD symptoms, though depression did not.

Recent research looking at phenotype and causal structure of CD has shown that CD and ODD share half their genetic influences, but their genetic etiologies are distinct in other ways. Unlike most other dimensions of psychopathology, half the genetic influences of CD seem to be unique to CD. In contrast,

**BOX 302-2 Conditions That May Mimic or Co-occur With Oppositional Defiant Disorder (ODD)**

- *Attention-deficit/hyperactivity disorder (ADHD).* This is a common comorbidity. Association of ODD and ADHD confers a poorer prognosis, and children tend to be more aggressive, have more behavior problems that are more persistent, suffer peer rejection at higher levels, and have more significant academic underachievement. See Chapter 168, Inattention and Impulsivity, and Chapter 220, Attention-deficit/Hyperactivity Disorder.
- *Sleep deprivation.* Sleep problems can cause irritability and contribute to outbursts of anger and poor impulse control.
- *Learning problems or disabilities.* Unidentified learning difficulties can contribute to frustration and oppositionality. If disruptive or aggressive behavior is associated with problems of school performance, the child may have a learning disability. See Chapter 172, Learning Difficulty, to explore this possibility.
- *Developmental problems.* Children with overall intellectual or social limitations may experience frustration and poor impulse control, or academically gifted children may find academic placement unstimulating and may exhibit disruptive behavior (persistently annoying and distracting others, refusing to comply with teachers' requests) as a result.
- *Exposure to adverse childhood experiences (ACEs).* Children who have experienced or witnessed trauma, violence, a natural disaster, separation from a parent, parental divorce or separation, parental substance use, neglect, or physical, emotional, or sexual abuse are at high risk for developing emotional difficulties such as adjustment disorder or post-traumatic stress disorder (PTSD) and may manifest outbursts of disruptive or aggressive behavior; this possibility should always be borne in mind because PTSD requires specific trauma-focused interventions. The physician should tactfully explore the possibility that harsh physical or emotional punishment is related to the child's behavior problem or that tensions might escalate to that point. Denial of trauma symptoms does not mean trauma did not occur; questions about ACEs should be repeated as a trusting relationship is established.
- *Bereavement.* Most children will experience the death of a family member or friend sometime in their childhood. Other losses may also trigger grief responses, including separation or divorce of parents, relocation, change of school, deployment of a parent in military service, breakup with a girlfriend or boyfriend, or remarriage of a parent. Such losses are traumatic. They may result in feelings of sadness, despair, insecurity, anger, or anxiety immediately following the loss and, in some instances, more persistent anxiety or mood problems, including PTSD or depression. In some children, such losses trigger aggressive or disruptive behavior. See also Chapter 129, Anxiety, and Chapter 137, Depression.
- *Anxiety.* Many children with disruptive or aggressive behaviors have anxiety. When faced with demands that make them anxious, they use oppositional behavior to manage their anxiety or avoid the expectations that triggered their anxiety. See Chapter 129, Anxiety.
- *Depression or bipolar disorder.* Marked sleep disturbance, disturbed appetite, irritability, low mood, or tearfulness could indicate that a child is depressed. Symptoms of depression rapidly alternating with cycles of agitation may suggest bipolar mood disorder. Common symptoms of pediatric bipolar disorder include explosive or destructive tantrums, dangerous or hypersexual behavior, aggression, irritability, bossiness with adults, driven creativity (sometimes depicting graphic violence), excessive talking, separation anxiety, chronic depression, sleep disturbance, delusions, hallucinations, psychosis, and talk of homicide or suicide.
- *Substance use.* All children exhibiting disruptive or aggressive behavior should be screened for substance use and abuse because drug effects, or withdrawal from drugs, may cause irritability and reduced self-control.
- *Autism spectrum disorders.* Children with this developmental pattern also have problems with social relatedness (eg, poor eye contact, preference for solitary activities), language (often stilted), and range of interest (persistent and intense interest in a particular activity or subject). They often have very rigid expectations for routines or parent promises and become anxious or angry if these expectations are not met.

ODD broadly shares nearly all of its genetic influences with other disorders and has little genetic variance. This finding further supports that CD is a relatively distinct syndrome at both the phenotypic and etiologic levels.

Most children meeting criteria for CD also meet DSM-5 criteria for ADHD and ODD. Importantly, however, only one-third of youth diagnosed with ODD ultimately meet criteria for CD. The most common coexisting condition is ADHD, and the continuity between ODD and ADHD has been well established. Current data show that approximately 65% of children diagnosed with ADHD meet criteria for comorbid ODD and that more than 80% diagnosed with ODD meet criteria for comorbid ADHD. Researchers

have examined the course of ODD in girls with ADHD. At 5-year follow-up (in adolescence), results indicated that ODD at baseline predicted increased risk for ODD and major depression at follow-up, beyond the risk for ADHD alone. The risk for CD was 24% in subjects with ADHD plus ODD versus 10% in subjects with ADHD alone.

The continuity between ODD and mood and anxiety disorders has been increasingly documented. Researchers have shown high rates of ODD in children diagnosed with depression and bipolar disorder. In one study, nearly 70% of children diagnosed with severe depression and 85% of children diagnosed with bipolar disorder were also diagnosed with ODD. In fact, it is children with ODD with comorbid mood

disorders who are at heightened risk for the development of CD. Meaningful rates of anxiety have been found in children with ODD. For example, one study found that more than 60% of youth diagnosed with ODD had comorbid anxiety disorder and 45% of children diagnosed with anxiety disorder had comorbid ODD.

When evaluating severe symptoms of ODD that do not improve with initial psychosocial interventions, or the possibility of comorbid disorders, a child psychiatrist or specialist should be consulted to rule out the possibility of other disorders and assess and monitor potential need for level 2 medications (which include antipsychotics or lithium, described in Chapter 62, Psychotropic Medications in Primary Care Pediatrics). Group 2 medications can be monitored in primary care settings, but because they generally have a more serious safety profile or more complicated monitoring requirements than group 1 medications, they are generally prescribed by specialists, including child psychiatrists, developmental-behavioral pediatricians, specialists in neurodevelopmental disabilities or adolescent medicine, pediatric neurologists, and adult psychiatrists with additional training in adolescent psychiatry.

### Laboratory and Imaging Studies

There are no specific laboratory or imaging studies used to make the diagnosis of ODD. However, besides a thorough psychiatric interview with parents and child, along with diagnostic measures from teachers, it is important to note that visits to the child's pediatrician have occurred regularly and no possible medical complications are identified.

### Evaluation

Children who present with disruptive or aggressive behaviors should be considered carefully if these behaviors are persistent (lasting more than 6 months). If left untreated the child will have an increased risk for school failure, difficulty with the legal system, underemployment, substance abuse, and antisocial personality disorder.

How do you evaluate a child when ODD is a possibility? If ODD is viewed as poor compatibility between child and adult, truly understanding the areas of incompatibility that give rise to oppositional behavior requires an understanding of both the child and adult.

As mentioned previously, often a mental health physician or nonphysician clinician is helpful in making a diagnosis of ODD; however, the primary care physician can rely on the specific guidelines described in this chapter to conduct an initial assessment independently.

An *assessment* can be defined as the identification and understanding of compatibility and incompatibility between a child and given aspects of his or her environment and the contributing factors to these conditions. A variety of assessment elements are considered to be useful. A *situational analysis* provides indispensable information about the child, adult, and environmental details contributing to oppositional moments and the incompatibility that gives rise to

such exchanges. In other words, with whom (mother, father, peer, baseball coach, piano teacher) is the child interacting when the oppositional episodes occur? What are the cognitive demands or expectations precipitating oppositional episodes and how is this understood in terms of compatibility? What are the specific antecedents, triggers, or conditions under which the behavior occurs? A *developmental history* that asks about early temperament, trauma history, attachment history, and family history is informative. A *school history* that asks about the child's academic as well as social-emotional presentation helps to inform the physician about the situational specificity of the behaviors. A *treatment history* including previously implemented medical and nonmedical interventions and their effectiveness is useful. If the belief is that oppositional behavior is resulting from lagging skills on the part of the child and incompatibility in the interaction between adult and child, formal and informal assessment is invaluable in the domains of general cognitive skills, attention and working memory skills, language processing skills, social skills, and problem-solving skills. Some formal assessment measures useful when considering a diagnosis of ODD are listed in Box 302-3. It is important to obtain both parent and teacher ratings of the child to determine behavior in 2 contexts; often a child will seem challenging in one setting, but not the other.

### Importance of Early Diagnosis and Intervention

Early-onset oppositional and aggressive behavior in preschoolers is problematic for parents and a known precursor of more serious and costly antisocial behaviors such as delinquency and substance abuse that may persist into adolescence and adulthood. Young children with disruptive behaviors are at risk for peer rejections, school absences, and academic problems such as underachievement and school dropout.

The underlying reasons for the unique features of ODD development remain unclear. Recent findings suggest that youth oppositionality involves distinct dimensions, each differentially predicting other psychopathology: an irritable dimension predicting depression and generalized anxiety disorder (GAD), a headstrong dimension as a predictor of ADHD and nonaggressive CD, and a hurtful dimension predicting aggressive CD. Researchers point out that referral rates among preschool populations are much lower than prevalence rates of ODD, and therefore primary care physicians need to be alert to opportunities for early detection and interventions for preschoolers especially, because efficacious treatments exist.

## MANAGEMENT

When a pediatrician uses the previously described assessment methods to confirm a possible diagnosis of ODD, a referral to a mental health physician or nonphysician clinician is the next step; however, the most effective treatment model is comanagement in which the pediatrician maintains contact with the mental health specialist and the family throughout the process. The pediatrician has a longer relationship with



**BOX 302-3 Assessment Measures**

- **Connors Rating Scale**
- **SNAP-IV**
- **The Eyberg Child Behavior Inventory (ECBI)**
- **Child Behavior Checklist (CBC)**
- **Pediatric Symptom Checklist (PSC)**
- **The Child Symptom Inventory—Parent**
- **Thinking Skills Inventory** ([www.thinkkids.org](http://www.thinkkids.org))
- **The AAP Task Force on Mental Health** has provided toolkits for helping manage mental health concerns such as ODD ([www2.aap.org/compmpeds/doch/mentalhealth/](http://www2.aap.org/compmpeds/doch/mentalhealth/)).
- **Vanderbilt Assessment Scale: Parent Assessment Scale and Teacher Assessment Scale** (AAP Toolkit) This tool has been developed for children 6 to 12 years of age.
- **Modified Overt Aggression Scale (MOAS)** (AAP Toolkit): This tool was developed for adults but has been used with adolescents.
- **Strengths and Difficulties Questionnaire (SQD)**: also gives indication of ODD.
- **Straight Talk About Psychological Testing for Kids**: This book explains how formal neuropsychological testing can be useful when there is a concern about attention or learning challenges. (Braaten E, Felopulos G. The Guilford Press, 2003.)
- **Bright Futures in Practice: Mental Health** has published an array of tools for the early identification of behavioral problems. This site also breaks down normative behavior by developmental stage, which is helpful to review when determining whether behavior is normative ([www.brightfutures.org/mentalhealth/pdf/bridges/oppositional.pdf](http://www.brightfutures.org/mentalhealth/pdf/bridges/oppositional.pdf)).

See Tools for Practice for where to obtain assessments.

the family and will continue to be involved with the child after the conclusion of work with a mental health specialist; thus, comanagement has significant advantages for treatment adherence and continuity. Contact with the child's school may be led by the mental health physician or nonphysician clinician while collaborating with the pediatrician.

### Best Treatment Approaches

ODD is best addressed from a team approach. For best results the child and family must be engaged in the care. Parents are crucial partners in treatment because they need to implement changes at home. How a parent understands the reasons his or her child is acting in a negative, hostile, maladaptive way has an effect on the choice of an intervention. In addition to parents, teachers spend the most time with a child and need to be involved with understanding and treating a child with ODD. Books and Web sites (listed in Tools for Practice) are good ways to engage and begin to inform parents and teachers about ODD.

Some initial interventions are highlighted by the AAP to try before a more formal treatment: Promote daily positive joint activities between parents and child or teen; encourage parents to focus on prevention such as removing activities or avoiding situations that lead to challenging behaviors; encourage parents to be calm and consistent and create a safety and emergency plan.

If a child needs to be referred for formal treatment, however, a range of treatment options are available. Treatment strategies include behavioral programs for both home and school as well as consideration of medication for comorbid mood disorder, anxiety, or impulsiveness. (See Chapter 62, Psychotropic Medications in Primary Care Pediatrics, and descriptions of medication levels 1, 2, and 3.) Symptoms of disruptive behavior and aggression commonly present

to pediatricians and may require comanagement with a mental health specialist because there is considerable controversy regarding whether medication, targeted at aggression or disruptive behavior only, is an appropriate part of a comprehensive treatment plan. Specifically, the AAP lists the following options under the category of “best support” (indicative of being subjected to rigorous randomized controlled trials): anger control, assertiveness training, cognitive behavioral therapy (CBT), multisystemic therapy (MST), parent management training (PMT), and problem-solving social skills. Although not indicated as “best support” in the AAP guidelines, an additional evidence-based model called *collaborative problem solving* (CPS) is offered.

### Specific Psychosocial Treatment Options

Diverse psychosocial treatments have been applied to children's ODD-related behaviors. The treatments can be classified according to focus on parent, child, or systemic characteristics. Generally, parent training models are designed to improve the coercive interactions between parents and their children. Parent training focuses primarily on a variety of patterns of parental discipline that contribute to the development of oppositional behavior and problematic parent-child exchanges. Skills that are typically taught to parents in such models include positive attending, use of appropriate commands, contingent attention and reinforcement, and use of the time-out procedure. Research has documented the efficacy of these procedures. MST is based on a social-ecological model that treats children by reaching out to multiple layers of the child's social environment including family, neighborhood, peers, and school. CBT for children with ODD targets maladaptive social-cognitive processes and focuses on improving anger control, social skills, and problem-solving skills.

Frequently, aspects of these various approaches are combined into a multifaceted intervention program

that targets both parenting skills and children's social skills. The combined programs have produced reductions in children's conduct problems and aggressive behavior and increases in problem-solving and social cognitive skills. An extensive review by Eyberg and colleagues of treatments for disruptive disorders did not reveal a single best intervention. The study suggests parent training as a first-line approach for younger children and reserves direct skills training approaches for older children.

The 2008 Eyberg Review identified 16 evidence-based psychosocial treatments (EBTs). Seven of these are considered "best support" for ODD on the AAP site and described by Eyberg as "probably efficacious." The final treatment option is collaborative problem solving; although not in the Eyberg review, it offers successful treatment of ODD. (See Box 302-4 and Table 302-1 for descriptions and examples of these treatments.)

### Medication

Effective treatment of ODD entails a multimodal approach in which psychosocial interventions are first line and pharmacotherapy is considered when there are comorbid conditions or initial interventions fail to address symptoms such as severe aggression. There is no single drug or regimen indicated for core symptoms of ODD; when pharmacotherapy is considered, comanagement by pediatricians and caregivers involved in implementing psychosocial interventions is important. A wide variety of medications have been tried in different groups with ODD, often comorbid with ADHD or other conditions. These medications include both level 1 medicines (described in Chapter 62, Psychotropic Medications in Primary Care Pediatrics, as those that would be prescribed and monitored by primary care physicians, including stimulants and  $\alpha$ -adrenergic agonists) as well as level 2 medicines that would be prescribed by a specialist such as a child psychiatrist.

ODD symptoms often improve with appropriate treatment of the comorbid conditions. Because comorbidity is the rule rather than the exception in the assessment and treatment of ODD, physicians must remain vigilant after the initial evaluation in detecting, monitoring, and treating commonly comorbid disorders such as ADHD, anxiety, and tic and mood disorders. The choice of regimen is based not only on the presentation of the child but also on reports from caregivers and teachers that are often discrepant in the severity of symptoms. It is crucial that the baseline behavior is understood as accurately as possible because improvement in symptoms may inappropriately be attributed to medications instead of the stabilization in the child's environment. If ODD is comorbid with ADHD and ameliorated with the regimen within the level 1 drugs, the treatment team may not necessarily need a child psychiatrist for ongoing comanagement because the pediatrician can follow level 1 medications while the psychologist and educators, along with parents, can address the psychosocial interventions.

### Stimulants, Atomoxetine, and $\alpha$ -Adrenergic Agonists

The stimulants methylphenidate and amphetamine are considered first-line treatment of ADHD. Given the

high rate of comorbidity of ADHD and ODD, stimulants (commonly methylphenidate) are considered even when oppositionality and aggression are present (see Chapter 62, Psychotropic Medications in Primary Care Pediatrics, and Chapter 220, Attention-deficit/Hyperactivity Disorder, for more detailed discussion of stimulants and treatment of ADHD). An amphetamine should be considered instead if the initial trial fails to provide adequate improvement in symptoms. This may be a worthwhile consideration because some results have suggested that methylphenidate may not have the same effect on some domains of ADHD in patients who also have ODD.  $\alpha$ -Adrenergic agonists, including clonidine and guanfacine, are second-line treatment for ADHD. They are level 1 medications that may be used initially when ADHD, ODD, and tic disorders are comorbid;  $\alpha$ -adrenergic agonists are also considered if stimulants or atomoxetine, a level 2 medication, are not helpful. Both ADHD and ODD symptoms improve with appropriate treatment of ADHD; therefore, optimization of the ADHD regimen would be the initial step.

When ODD does not improve with initial psychosocial interventions or reflects comorbidity with other disorders not yet identified or properly treated with level 1 medications, a child psychiatrist should be consulted to rule out the possibility of other disorders and to assess and monitor potential need for level 2 medications (including atomoxetine, antipsychotics, mood stabilizers, and certain antidepressants, discussed in Chapter 62, Psychotropic Medications in Primary Care Pediatrics). Stimulants remain first-line treatment of ADHD even when aggressive and disruptive behaviors are present and should be considered before the addition of another agent. Atomoxetine is a potent selective norepinephrine reuptake inhibitor used in the treatment of ADHD. When anxiety and a tic disorder are comorbid with ADHD and ODD, consider a trial of atomoxetine first; if not effective, a stimulant may be used. Atomoxetine was found to be as effective in treating ADHD symptoms regardless of the presence of ODD as a comorbid disorder. However, improvement in ADHD as well as ODD symptoms is achieved at higher doses and over a longer duration than would be required in addressing ADHD not comorbid with ODD. Although atomoxetine is well tolerated, a slower rate of titration is associated with improved tolerability, especially because target doses may need to be higher.

Polypharmacy is not unusual in treating the comorbidities of ODD and requires pediatricians and psychiatrists working in concert with other caregivers to optimize the pharmacologic intervention within a comprehensive treatment program.

### Risks of Not Treating

Treatment with psychotherapy is preferable to treatment with medication in children and teens. However, because it is estimated that up to 60% of patients with ODD go on to develop CD, there is a significant need for early identification and intervention through psychotherapy and if necessary through medication to treat mood, anxiety, or impulsiveness.

**BOX 302-4 Evidence-Based Psychosocial Treatments**

- *Anger control training* is a cognitive behavioral therapy-style treatment for elementary school-aged children based on the social information processing model of anger control. Children meet 1 time a week in groups of 6, usually during the school day. Children discuss vignettes of social encounters with peers and possible social cues and motives of individuals in the vignettes. The focus of the work is learning to increase awareness of feelings and to problem-solve through practice in situations designed to arouse their anger.
- *Group assertiveness training* is based on the verbal response model of assertiveness and was conducted with African American eighth and ninth graders. The group treatments, led by either a peer or counselor, both involve 8 hours of assertiveness training with treatment groups of 6 adolescents meeting twice a week for 4 weeks. This treatment is not widely cited but did meet evidence-based psychosocial treatment standards in Eyberg's 2008 review and was designated by the AAP with "best support."
- *Multisystemic therapy (MIS) (MST)* is an intensive family- and community-based treatment that addresses the externalizing behaviors of youth displaying emotional and behavioral disturbances. It is a therapeutic process that provides on average 50 hours of direct family-based treatment over a 4- to 6-month period. A pragmatic and goal-oriented treatment, MST specifically targets those factors in each youth's social network that are contributing to his or her problematic behavior. Thus, MST interventions are delivered in the natural environment and typically aim to develop youth competence by improving the relationships, interactions, and skills of those who surround the youth, especially family members. MST is provided using a home-based model of services delivery targeting children and adolescents ages 12 to 17 years at high risk of out-of-home placement and their families. Therapists work nontraditional hours and are on call for their families 7 days per week around the clock.
- *PMT (also called parent training or behavior management training)* strategies are well established in helping children with oppositional defiant disorder. A mental health physician helps the parents develop skills that will allow them to parent in a way that is more positive and less frustrating. Treatment sessions include instruction in social learning principles and techniques. The therapist provides an overview of underlying concepts, models the technique, and coaches parents implementing the procedures. Procedures and interaction patterns practiced in the sessions are then used at home. Parents are usually taught how to define, observe, and record behavior at the beginning of treatment because after behaviors (eg, fighting, tantrums) are defined concretely, reinforcement and punishment techniques can be applied. Reinforcement for prosocial and nondeviant behavior is central to treatment.
- *Parent-child interaction therapy (PCIT)* is an evidence-based treatment for families with children 2 to 6 years old. PCIT uses 2 phases of training: child-directed interaction, in which parents are trained in nondirective play skills to alter the quality of parent-child interactions, and parent-directed interaction, which focuses on improving parenting skills by teaching parents to give clear instructions, offer praise for compliance, and administer time-out for noncompliance. During PCIT, therapists actively coach parents while they interact with their children. As a result, parents learn more effective parenting techniques, the quality of the parent-child relationship improves, and problem behaviors decrease. Sessions are 1 time per week for an average of 12 to 16 weeks.
- *Problem-solving skills training (PSST)* is a behavioral treatment designed for children ages 7 to 13 years with disruptive behavior. Children are taught problem-solving strategies and encouraged to generalize these strategies to real-life problems. Therapists use in-session practice to help develop skills, including identifying the problem, generating solutions, weighing pros and cons, making a decision, and evaluating an outcome. Therapists use methods such as token response cost (the child receives tokens for good behavior that can then be cashed in for a prize), corrective feedback, and social reinforcement to develop problem-solving skills gradually. Treatment consists of approximately 25 sessions lasting 40 to 50 minutes, conducted with the child and with occasional parent contact.
- *PSST and PMT*—In this combined format, the 2 types of trainings already described separately are provided individually to children and parents rather than in a group format, and the child and parent components occur concurrently. The content of the 2 approaches is not overlapping, but parents and children are each informed of what the other is learning.
- *Collaborative problem solving (CPS)* is a cognitive behavioral model that posits that chronic and severe externalizing behavior is the product of incompatibility between a child's skills set and the demands placed on him or her by the environment. CPS suggests that lagging cognitive skills interfere with a child's ability to comply with adult expectations. Contrary to conventional approaches that suggest children use their difficult behavior willfully to get or avoid things and prescribe corresponding interventions that focus on increasing motivation, the philosophy of CPS is that challenging children lack the thinking skills required to behave adaptively. Analogous to the contemporary view of children with learning disabilities who are performing below their potential in academic areas, CPS asserts that children who are not successful in complying with behavioral demands have skill deficits in critical areas such as flexibility, social perception, attention and working memory, language processing, or emotion regulation. Thus, in contrast to behavioral approaches, the corresponding intervention focuses on improving these skills rather than increasing the motivation to comply. The Thinking Skills Inventory is used to identify specific skill deficits along with the situations in which these lagging skills cause difficulty meeting adult expectations. A simple framework of 3 options (referred to as plan A, plan B, and plan C) is provided for adults to decide how best to respond to chronic problems and unmet expectations. Interventions are then tailored to assist the child in developing the skills that are lagging. The skill-building process occurs in the context of problem

Continued

**BOX 302-4 Evidence-Based Psychosocial Treatments—cont'd**

solving in a natural setting. CPS is a family therapy designed for ages 4 to 18 years. Primary benefits of the model include a reduction in observed oppositional and defiant behaviors as well as a decrease in related disciplinary and restrictive interventions, including restraints and seclusion. Secondary benefits of

the model have included reduction in adult stress, improvements in adult-child relationships, and decreased staff and patient injuries. Significant reductions in oppositional behaviors have been documented in published research in both family therapy and multifamily groups.

Data from Williams SC, Lochman JE, Phillips NC, et al. Aggressive and nonaggressive boys' physiological and cognitive processes in response to peer provocations. *J Clin Child Adolesc Psychol*. 2003;32(4):568–576; Crick NR, Dodge KA. Social information-processing mechanisms in reactive and proactive aggression. *Child Dev*. 1996;67(3):993–1002; Huey WC, Rank RC. Effects of counselor and peer-led group assertiveness training on black-adolescent aggression. *J Counseling Psychol*. 1984;31:95–98; Henggeler SW. Multisystemic treatment of serious clinical problems. In: Kazdin AE, Weisz JR, eds. *Evidence-Based Psychotherapies for Children and Adolescents*. New York, NY: Guilford; 2003; Burke JD, Loeber R, Birmaher B. Oppositional defiant disorder and conduct disorder: a review of the past 10 years, part II. *J Amer Acad Child Adolesc*. 2002;41(11):1275–1293; Kazdin AE. Child, parent and family dysfunction as predictors of outcome in cognitive-behavioral treatment of antisocial children. *Behav Res Ther*. 1995;33(3):271–281; Kazdin AE. Review: parent training and community-based interventions may benefit children with disruptive behaviour disorders. *Evidence-Based Mental Health*. 2003;6(3):81; Brinkmeyer M, Eyberg SM. Parent-child interaction therapy for oppositional children. In: Kazdin AE, Weisz JR, eds. *Evidence-Based Psychotherapies for Children and Adolescents*. New York, NY: 2003:204–223; Greene RW. The Explosive Child: A New Approach for Understanding and Parenting Easily Frustrated, Chronically Inflexible Children. New York, NY: Harper; 2010; Greene RW, Ablon JS, Goring JC, et al. Effectiveness of collaborative problem solving in affectively dysregulated children with oppositional-defiant disorder: initial findings. *J Consulting Clin Psychol*. 2004;72(6):1157–1164; Bauer NS, Webster-Stratton C. Prevention of behavioral disorders in primary care. *Curr Opin Pediatr*. 2006;18(6):654–660; Johnson M, Ostlund S, Fransson G, et al. Attention-deficit/hyperactivity disorder with oppositional defiant disorder in Swedish children - an open study of collaborative problem solving. *Acta Paediatr*. 2012;101(6):624–630; Ollendick TH. Invited Address: Effective Psychosocial Treatments for Emotional and Behavior Disorders in Youth. Stockholm, Sweden: University of Stockholm; 2011.

**Table 302-1****Effective Treatments for Children With Oppositional Defiant Disorder Mentioned Frequently in the Literature**

INTERVENTION	DESCRIPTION	EXAMPLE
Collaborative problem solving (CPS)	A child's challenging behavior is because of poor flexibility, frustration tolerance, and problem-solving skills. These skills are modeled and taught through a structured process of resolving problems collaboratively with children.	Child chronically refuses to begin homework. Rather than threaten punishment, the parent enlists the child in a proactive conversation aimed at clarifying both adult and child concerns and then together brainstorming potential solutions that are mutually satisfactory.
Parent-child interaction therapy (PCIT)	PCIT uses 2 phases of training: child-directed interaction in which parents are trained in nondirective play skills to alter the quality of parent-child interactions, and parent-directed interactions that focus on improving parenting skills by teaching parents to give clear instructions, praise for compliance, and administer time-out for noncompliance.	Parent sets aside 20 minutes every day to build Legos with child. When child picks up clothes and puts in the laundry, parent is verbally praising. When child refuses to pick up clothes, parent administers time-out.
Parent management training (PMT)	Parents are usually taught how to define, observe, and record behavior at the beginning of treatment because after behaviors (eg, fighting, tantrums) are defined concretely, reinforcement and punishment techniques can be applied. Reinforcement for prosocial and nondeviant behavior is central to treatment.	Child refuses to begin homework. Parent establishes a sticker chart that gives daily points for doing homework, and at the end of the week a prize is earned if the child accrues enough points. If child does homework without being asked, child receives double points and verbal praise.
Multisystemic therapy (MST)	MST interventions typically aim to develop youth competence by improving the relationships, interactions, and skills of those who surround the youth, especially family members. Services are delivered in the natural environment (eg, home, school, community), with the treatment plan being designed in collaboration with family members, and are therefore family driven rather than therapist driven.	Child refuses to obey his nightly curfew. Parent speaks with parents of neighborhood peers and local YMCA director and has a group meeting with child and these community members to discuss the importance of the curfew.



### Emergency Situations

In general, a diagnosis of ODD does not necessitate admission to a medical or psychiatric hospital. Indications for admission include the following:

- Symptoms from any psychiatric conditions related to ODD such as anxiety or depression that make a child unsafe—wishing harm to either self or others
- An adverse reaction or result from a trial of medication
- An accidental injury (resulting from severe dysregulation caused by the child's ODD symptoms) such as losing control and becoming so upset the child falls or harms himself or herself in some way

In severe cases that reflect these criteria, a hospitalization may be helpful in providing diagnostic clarification and, in the case of significant comorbidity, may help optimize the psychopharmacologic regimen in a setting where changes can be closely monitored. Acute changes in mental status as well as new onset of severe aggression should prompt an urgent evaluation and consideration of an admission for both medical and psychiatric assessment.

With complex comorbidities, especially ADHD, anxiety, or mood disorder, a child or teen may need not simply a weekly therapy (discussed earlier) but a more intense treatment such as a day program, residential facility, or inpatient admission. ODD along with depressed mood or suicidal ideation presents an increased risk for self-injury and suicide. Family history of aggression, parenting style, any exposure to drugs or alcohol, imminence of harm to self or others, and the family's ability to contain the child's behavior are included in the risk assessment. Lastly, given the complex nature of the presentation, the pediatrician in conjunction with the mental health physician needs to consider whether aggression is a reaction to an abusive situation, which would prompt a referral to child protective services.

The AAP suggests involving a mental health specialist immediately if indicated by the following circumstances:

- Child is younger than 5 years
- Child's problems do not respond to primary care intervention
- Family is struggling to maintain a calm, consistent, or safe environment—explosions are so severe that safety is a major concern
- Child's behaviors are injurious to other children, themselves, or animals
- Child has comorbid depression
- Child has comorbid anxiety (the combination of shyness, anxiety, and behavior problems is thought to be risky for future behavior problems)
- School problems are interfering with academic success and friendships
- Child or teen is involved with legal authorities

### Role of the School

As outlined in the Evaluation section, receiving teachers' input is crucial in determining a diagnosis and a treatment plan. The mental health physician and the pediatrician must determine which person will be in regular contact with the school. Often this is the mental health physician's role, but the pediatrician as a comanager of the care must be aware of the dynamics

at school as well. A key concern is that problems with schoolwork such as refusal to take tests, forgetting to hand in homework, misplacing books, not participating in class, and being unable to settle down to work may be inappropriately attributed to laziness or lack of motivation by school staff when in fact they may be a result of deficits in crucial thinking skills (see Box 302-5) often related to ODD. Children under law have the right to receive counseling support if their emotional and behavioral challenges are affecting their academic success (see Tools for Practice).

However, unlike academic learning disabilities, it can be difficult for educators to see behavioral challenges as a form of developmental delay or "learning disability." Education of the child, parents, and school staff regarding the inadvertent labeling of oppositionality as willful, manipulative, and intentional is crucial. If adults perceive oppositional behavior as intentional, then the aim of intervention at school will be to use motivational procedures to foster compliance. If school staff perceives the child's oppositionality as the result of lagging skills, the interventions will focus on skill building instead. In addition, not infrequently a child with ODD also has a learning disability and may display challenging and distracting behavior in relation to his or her learning struggles; thus, identifying any learning challenges is essential. If warranted, a child may receive an Individualized Education Plan (IEP) as stipulated by law. If behavior interferes with an individual child's academic performance or the ability of other children in the classroom to learn, then a Functional Behavior Analysis (FBA) and a Behavior Intervention Plan (BIP) are necessary to delineate what behaviors a youth displays, factors that escalate the behavior, and appropriate interventions. Consideration of the best placement of a child (eg, mainstream classroom with or without assistance from an aide, special education setting, private placement) and accommodations can be accessed through an IEP or 504 plan. A 504 plan is a plan developed to make certain that a child who has a disability identified under the law, and who is attending an elementary or secondary school, receives accommodations that will ensure his or her academic success. Sample letters requesting a 504 plan or IEP, as well as additional information on these programs, are available in *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit*, a CD-ROM by the American Academy of Pediatrics (see Tools for Practice).

There is no doubt that students who are defiant or noncompliant can be among the most challenging to teach. They can frequently interrupt instruction, often do poorly academically, and may seem to have little motivation to learn. A compilation of research offers many specific ideas for helping oppositional students in the classroom (see Tools for Practice).

### CASE REPORT RESOLUTION

In the presentation of Keenan at the start of the chapter, his mother stated, "Nothing is ever easy with him." This description of life at home, combined with teacher report of Keenan's struggle to keep friends and comply with requests, is a red flag that a behavior disorder such as ODD be considered. On completing a detailed history

**BOX 302-5 Thinking Skills Inventory****LANGUAGE AND COMMUNICATION SKILLS**

- Understands spoken directions
- Understands and follows conversations
- Expresses concerns, needs, or thoughts in words
- Is able to tell someone what's bothering him or her

**ATTENTION AND WORKING MEMORY SKILLS**

- Stays with tasks requiring sustained attention
- Does things in a logical sequence or set order
- Keeps track of time; correctly assesses how much time a task will take
- Reflects on multiple thoughts or ideas at the same time
- Maintains focus during activities
- Ignores irrelevant noises, people, or other stimuli; tunes things out when necessary
- Considers a range of solutions to a problem

**EMOTION- AND SELF-REGULATION SKILLS**

- Thinks rationally, even when frustrated
- Manages irritability in an age-appropriate way
- Manages anxiety in an age-appropriate way
- Manages disappointment in an age-appropriate way
- Thinks before responding; considers the likely outcomes or consequences of his/her actions
- Can adjust his/her arousal level to meet the demands of a situation (e.g., calming after recess or after getting upset, falling asleep/waking up, staying seated during class or meals, etc.)

**COGNITIVE FLEXIBILITY SKILLS**

- Handles transitions, shifts easily from one task to another

- Is able to see "shades of gray" rather than thinking only in "black-and-white"
- Thinks hypothetically, is able to envision different possibilities
- Handles deviations from rules, routines, and original plans
- Handles unpredictability, ambiguity, uncertainty, and novelty
- Can shift away from an original idea, solution, or plan
- Takes into account situational factors that may mean a change in plans (Example: "If it rains, we may need to cancel.")
- Interprets information accurately/avoids over-generalizing or personalizing (Example: Avoids saying "Everyone's out to get me," "Nobody likes me," "You always blame me," "It's not fair," "I'm stupid," or "Things will never work out for me.")

**SOCIAL THINKING SKILLS**

- Pays attention to verbal and nonverbal social cues
- Accurately interprets nonverbal social cues (like facial expressions and tone of voice)
- Starts conversations with peers, enters groups of peers appropriately
- Seeks attention in appropriate ways
- Understands how his or her behavior affects other people
- Understands how he or she is coming across or being perceived by others
- Empathizes with others, appreciates others' perspectives or points of view

and physical examination of Keenan, you are increasingly convinced that the willful, noncompliant, hostile behavior described by his mother, and now encroaching on his school day, meets criteria for ODD. You are aware, given the high comorbidity of ODD and depression, that his irritability, grouchiness, and comments such as, "You think I am a bad kid" may be symptoms of a depressive disorder. At this point you decide to have the parents and teachers fill out the SNAP-IV rating scale (see Tools for Practice). These measures are available to the public, are useful and supportive documentation of diagnostic criteria, and can be instructive in exploring the possibility of comorbid ADHD, depression, or anxiety. In a brief letter requesting that the teacher fill out the SNAP-IV scale, you also ask for any additional school information, such as grades, written evaluations, or achievement testing results. You also suggest that Keenan's mother write a letter to the school asking for an evaluation of Keenan to rule out any learning disabilities. You elect not to do any imaging or laboratory tests given that Keenan's history and physical examination are not suggestive of a diagnosis that requires that type of information. However, you do make an otolaryngologist referral to rule out OSA because Keenan's mother reports he "wakes frequently

during the night" and you know that poor sleep can be a factor in disruptive behavior. You presume the otolaryngologist will order a radiograph to get a better look at his adenoids.

On the follow-up visit, you have reviewed the teacher and parent results of the SNAP-IV as well as the information the school has sent you about Keenan. You note that on the SNAP-IV Keenan meets criteria for ODD. From his presentation of sullenness and irritability (a subtype of ODD referred to as "dysphoric" or "irritable"), you still cannot rule out a form of depression, but the school narratives and feedback from Keenan's mother indicate this demeanor may be more in relation to Keenan's awareness of how annoyed both his teachers and parents feel with his behavior rather than a biologic depression. Keenan seems relatively happy outside the context of frustrating situations. However, Keenan may have begun to internalize the sense that "I am a bad kid," so you consider referral to a mental health physician to better understand if Keenan meets criteria for depression independently or whether his moodiness is secondary to the frequent conflicts at home and school.

You confirm with his mother and stepfather that Keenan does meet criteria for ODD and review the cause and possible treatment options. In collaboration

with his parents, you design a treatment plan for Keenan. You share your concern about Keenan's mood and advise that you would like to better understand whether it is a chronic state or mostly related to moments of frustration. The mother confirms that testing has been requested at school to rule out learning issues. You mention that depending on those results a neuropsychological battery might be of help as well. The plan includes a referral to a child psychologist to rule out depression and a referral to an individual physician or a local mental health clinic that offers one of the evidence-based treatments for ODD. With the permission of Keenan's mother and stepfather, you draft a follow-up letter to the school explaining the diagnosis and the need for ongoing communication and willingness to try new ways of working with Keenan in school.

After you have referred Keenan to the mental health physician or nonphysician clinician, you clarify your role in comanaging the case. In the next few visits with Keenan you discuss his progress. The psychologist treating Keenan readministers the SNAP-IV to his parents and his teacher and finds that Keenan's hostile, negative behavior has decreased slightly. His mother reports that since trying to reduce areas of conflict, be less rigid about expectations, focus less on being punitive for bad behavior, and offer lots of positive feedback for what Keenan does well, there has been less tension at home (see the discussion of CPS in Box 302-4). Keenan reports feeling that he doesn't think his mother, stepfather, and teachers are "out to get him" anymore but that he still "gets really mad." The psychologist has shared with you that she agrees it is premature to assign a label of depression because much of Keenan's grumpy mood seems connected to his frequent level of conflict with others. The psychoeducational testing reveals moderate dysgraphia, and although he has solid comprehension, reading fluency is quite slow. These 2 findings help to explain why Keenan becomes disruptive and oppositional when asked to do writing or reading assignments—he doesn't have the skill to do them and doesn't know how to understand or communicate this struggle. All Keenan knows is that he hates to read and write. The psychologist has already suggested his parents explore an IEP to get support for both of these areas, and you reiterate the helpfulness of pursuing an IEP. You also review the report from the otolaryngologist who says that although they are enlarged, she does not think Keenan's adenoid or tonsils need to be removed; however, he probably has chronic colds, making breathing hard when he sleeps. A nasal spray is prescribed.

After 4 months following a treatment program, Keenan and his mother should report less conflict at home. His teacher should also feel she better understands why Keenan can be challenging and has new ways to work with him to teach him skills as he navigates his school day. Your role is to continue to comanage Keenan's care with the mental health specialist and to help Keenan and his mother identify Keenan's strengths as well as the challenging situations that need to be resolved so that Keenan has the best support to succeed.

## CONCLUSIONS

Oppositional defiant disorder is a common disorder of childhood and adolescence affecting functioning across multiple areas of a child or teen's life. If left untreated, the symptoms of ODD are likely to become more severe and associated with comorbid depression or anxiety or develop into CD. Diagnosis and treatment are complicated in that there is no clear test or biologic marker, there are high rates of comorbid conditions, and there is a need to coordinate care across multiple settings. There is no one-size-fits-all approach to the treatment of ODD. The treatment for a child whose oppositional behavior is fueled by attention and working memory deficits (see Box 302-5) should differ in meaningful ways from the treatment of a child whose oppositional behavior is fuelled by perfection and obsessiveness and should differ in still other ways for a child for whom language processing is a struggle. Children and teens with ODD can function well at home and at school provided their behavior is recognized not as willful and intentional but as a result of lagging skills. Parents, teachers, and physicians have noted that children whose symptoms are recognized, assessed, understood, and treated at an earlier age will show improved sense of themselves as positive members of their school or family and experience more success. The primary care physician's role is to assure the child and parent that this is not a lifelong disorder and that there are good, helpful interventions that do have excellent outcomes.

## ONGOING CARE

### Follow-up

Oppositional defiant disorder, regardless of the presence of CD, is a highly comorbid condition with the potential for negative outcomes in children and adolescents. Continuing to make sure parents and teachers are working to develop a child's skills rather than becoming more punitive to manage challenging behavior is an ongoing effort.

### Prognosis

There is emerging evidence that psychiatric diagnoses can be reliably ascertained in preschool populations. Approximately half of all children who meet criteria for ODD as preschoolers will have no psychiatric problems by age 8 years. CD symptoms are the most robust predictor of severe and persistent forms of antisocial behavior, but ODD symptoms also predict persistent involvement in the juvenile justice system even when controlling for the co-occurring CD symptoms. ODD and ADHD symptoms independently predicted increases in conduct problems over time as well as the development of internalizing and social problems. Children who meet criteria for ODD are about 4 times more likely to meet criteria for a personality disorder when they grow up than those who do not carry this diagnosis, approximately a 15% chance. By the time preschoolers diagnosed with ODD are 8 years old, only 5% still meet criteria for ODD and nothing else. About 5% to 10% of preschoolers with ODD will eventually meet criteria for ADHD with no signs of ODD. By the time children diagnosed with ODD are at



the end of elementary school, about 25% will have mood or anxiety problems that are disabling. Later in life, ODD can develop into CD, which in turn may develop into passive-aggressive personality disorder or antisocial personality disorder. As is the trend with so many psychiatric disorders, the earlier ODD is diagnosed and the pediatrician helps develop an accurate understanding in the parents of the child's challenges, the more likely the child is to progress developmentally to the point of no longer meeting criteria for ODD.

### Prevention

The best prevention is to urge parents to set developmentally appropriate and realistic expectations with their preschoolers and work to help build their problem-solving, flexibility, and frustration tolerance skills. Accurate and compassionate understanding of developmental problems in these areas can prevent cycles of punitive responses to challenging behavior.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *Building the Legacy: IDEA 2004* (Web page), US Department of Education ([idea.ed.gov](http://idea.ed.gov))
- *School-wide Strategies for Managing Defiance/Non-compliance* (Web page), Intervention Central ([www.interventioncentral.org/behavioral-interventions/challenging-students/school-wide-strategies-managing-defiance-non-compliance](http://www.interventioncentral.org/behavioral-interventions/challenging-students/school-wide-strategies-managing-defiance-non-compliance))
- *Wrightslaw* (Web site) ([www.wrightslaw.com](http://www.wrightslaw.com))

### Engaging Patient and Family

- *All About the IEP* (fact sheet), Center for Parent Information Resources ([www.parentcenterhub.org/repository/iep](http://www.parentcenterhub.org/repository/iep))
- *Child Behavior Disorders* (Web page), US Department of Health and Human Services ([www.nlm.nih.gov/medlineplus/childbehaviordisorders.html](http://www.nlm.nih.gov/medlineplus/childbehaviordisorders.html))
- *Frequently Asked Questions About Section 504 and the Education of Children With Disabilities* (fact sheet), US Department of Education ([www.ed.gov/about/offices/list/ocr/504faq.html](http://www.ed.gov/about/offices/list/ocr/504faq.html))
- *It's My Life Journal Page* (questionnaire), PBS Kids ([pbskids.org/itsmylife/journal/anger\\_journal.html](http://pbskids.org/itsmylife/journal/anger_journal.html))
- *Medication Guides* (Web page), US Food and Drug Administration ([www.fda.gov/Drugs/DrugSafety/ucm085729.htm](http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm))
- *No Child Left Behind: Finding Sources for School Counseling and Mental Health Services* (booklet), American Counseling Association ([www.counseling.org/publicpolicy/pdf/nclb\\_funding\\_sources\\_01-11.pdf](http://www.counseling.org/publicpolicy/pdf/nclb_funding_sources_01-11.pdf))
- *Oppositional and Aggressive Behaviors* (booklet), Bright Futures in Practice: Mental Health - Volume 1. Practice Guide. ([www.brightfutures.org/mentalhealth/pdf/bridges/oppositional.pdf](http://www.brightfutures.org/mentalhealth/pdf/bridges/oppositional.pdf))
- *Straight Talk About Psychological Testing for Kids* (book), Braaten E, Felopulos G; Guilford Press ([www.guilford.com](http://www.guilford.com))

### Medical Decision Support

- *Conners 3<sup>rd</sup> Edition* (assessment), Multi-Health Systems ([www.mhs.com](http://www.mhs.com))

- *Disruptive Behavior and Aggression* (fact sheet), American Academy of Pediatrics, in *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* ([shop.aap.org](http://shop.aap.org))
- *Enhancing Pediatric Mental Health Care: Algorithms for Primary Care* (article), *Pediatrics*, Vol 125, Suppl 3 ([pediatrics.aappublications.org/content/125/Supplement\\_3/S109.pdf](http://pediatrics.aappublications.org/content/125/Supplement_3/S109.pdf))
- *Evidence-Based Child and Adolescent Psychosocial Interventions* (chart), PracticeWise, American Academy of Pediatrics ([www.aap.org/en-us/Documents/CRPsychosocialInterventions.pdf](http://www.aap.org/en-us/Documents/CRPsychosocialInterventions.pdf))
- *Modified Overt Aggression Scale (MOAS)* (scale), University of Washington ([depts.washington.edu/dbpeds/Screening%20Tools/Modified-Overt-Aggression-Scale-MOAS.pdf](http://depts.washington.edu/dbpeds/Screening%20Tools/Modified-Overt-Aggression-Scale-MOAS.pdf))
- *Pediatric Symptom Checklist* (assessment), Bright Futures ([www.brightfutures.org/mentalhealth/pdf/professionals/ped\\_symptom\\_chklst.pdf](http://www.brightfutures.org/mentalhealth/pdf/professionals/ped_symptom_chklst.pdf))
- *Scoring Instructions for NICHQ Vanderbilt Assessment Scales* (fact sheet), American Academy of Pediatrics ([www2.aap.org/sections/dbpeds/pdf/VanderbiltRatingScaleScoringInstructions.pdf](http://www2.aap.org/sections/dbpeds/pdf/VanderbiltRatingScaleScoringInstructions.pdf))
- *Scoring Instructions for the SNAP-IV Rating Scale* (fact sheet), Office of Mental Health ([www.omh.ny.gov/omhweb/ebt/resources/snap\\_instructions.html](http://www.omh.ny.gov/omhweb/ebt/resources/snap_instructions.html))
- *Strengths & Difficulties Questionnaires* (Web site) ([www.sdqinfo.com](http://www.sdqinfo.com))

## AAP POLICY

American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health and Task Force on Mental Health. The future of pediatrics: mental health competencies for pediatric primary care. *Pediatrics*. 2009;124(1):410–421. Reaffirmed August 2013 ([pediatrics.aappublications.org/content/124/1/410](http://pediatrics.aappublications.org/content/124/1/410))

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## Chapter 303 OSTEOCHONDROSES

Donna M. Pacicca, MD

Osteochondroses (categorized by anatomic location in Table 303-1) result from a disturbance of endochondral ossification of growing bones, which may lead to altered growth in the epiphysis or physis. Varying degrees of discomfort, dysfunction, and deformity may occur with osteochondroses. Ossification centers of growing bones often develop irregular mineralization during childhood that is self-limited and often found incidentally on radiographs. The osteochondroses are characterized by symptoms, such as pain and limping, progressive change in the epiphysis, and persistent deformity after resolution.

Apophysitides are also caused by a disturbance of endochondral ossification, but generally are limited to the apophyses and do not cause any potential abnormalities to joint surfaces.

The literature initially describing these entities is old—many of these disorders were described shortly

after radiographs came into clinical use (Box 303-1, 303-2).

### FEMORAL HEAD

Legg-Calve-Perthes refers to a disorder characterized by idiopathic osteonecrosis of the femoral head. The cause is unknown, but it is suspected that the disorder is caused by vascular insult to the femoral head ossification center. Age of onset is generally in early school-age years (4–12), occurring in boys 4 times more frequently than in girls. Most cases are unilateral; in the 10% to 15% of patients with bilateral disease, the hips are usually involved successively.

Children generally present with an intermittent limp, especially after activity. The limp is often associated with hip, thigh, or knee pain. Children may develop loss of internal rotation and abduction because of pain and subsequent deformity. The diagnosis is made on the basis of plain radiographs, which initially may show only height difference, but later show lucency or collapse of the femoral ossific nucleus (Figure 303-1, Figure 303-2). The acute phase of the disease lasts several weeks, with the remodeling phase lasting months to years. In addition to the deformity caused by the collapse of the ossific nucleus, there can be further deformity as a result of abnormal growth of the proximal femoral physis, which may be involved in the disorder as well.

### PROXIMAL TIBIA

Physiologic bowing is common in infants and often persists until 18 months, after which the legs straighten and then progress to a slight degree of knock-knee. Bowing of the legs that persists or progresses beyond 2 years should be evaluated.

**Table 303-1** Osteochondroses

SITE	PEAK AGE AT APPEARANCE (YEARS)
<b>UPPER EXTREMITY</b>	
Humeral head	2–8
Humeral capitulum	4–10
Lower ulna	13–20
Carpal navicular	16–24
Carpal semilunar	16–20
Bilateral entire carpus	10–14
Metacarpal heads	9–15
Basal phalanges	8–14
<b>LOWER EXTREMITY</b>	
Femoral epiphysis	3–12 <sup>a</sup>
Greater trochanter	6–11
Primary patellar center	8–15
Secondary patellar center	8–10
Shaft of tibia	1–5 <sup>b</sup>
	6–12 <sup>c</sup>
Tibial tubercle	10–15
Distal tibial epiphysis	4
Calcaneal epiphysis	3–18
Astragalus	2–8
Tarsal navicular	3–7
Second metatarsal	8–17
Fifth metatarsal	8–16
<b>SPINE AND PELVIS</b>	
Vertebral epiphysis	13–20
Vertebral disk	> 16
Symphysis pubis	12–18
Iliac crest	12–19
Ischial apophysis	13–18
Ischiopubic synchondrosis	12–19

<sup>a</sup> Maximum is 6–8 years.

<sup>b</sup> Form of disease in infants.

<sup>c</sup> Form of disease in adolescents.

### BOX 303-1 Clinically Significant Sites of Osteochondroses

#### LOWER EXTREMITY

- Femoral head (Legg-Calve-Perthes disease)
- Proximal tibial physis (infantile and juvenile Blount disease)
- Tarsal navicular (Köhler disease)
- Metatarsal heads 2, 3, or 4 (Freiberg infraction)

#### UPPER EXTREMITY

- Capitellum (Panner disease)
- Lunate (Kienbock disease)
- Scaphoid

### BOX 303-2 Common Apophysitides

- Tibial tuberosity (Osgood-Schlatter disease)
- Distal pole patella (Sinding-Larsen-Johannson syndrome)
- Calcaneal apophysis (Sever disease)

In Blount disease, normal growth is slowed at the posteromedial proximal tibial physis, resulting in a complex deformity that causes clinical bowing and internal torsion (Figure 303-3). The cause is unknown, but histologic evaluation has shown disruption of the normal architecture of the growth plate, with replacement by fibrous tissue and even bone in very severe cases. The condition was first described by Walter Blount in 1937, and the etiology is still unknown. While there is association with obesity, early walking, and race (Latino or African-American), these are only predisposing factors. Most children with Blount disease that persists or develops beyond age 4 require an osteotomy to correct the bowing. However, earlier treatment often focuses on guided growth to allow for gradual correction of the deformity via a plate or similar device to slow growth on the lateral side of the tibia.



**Figure 303-1** Early presentation of Perthes disease. Note difference in height of epiphysis.

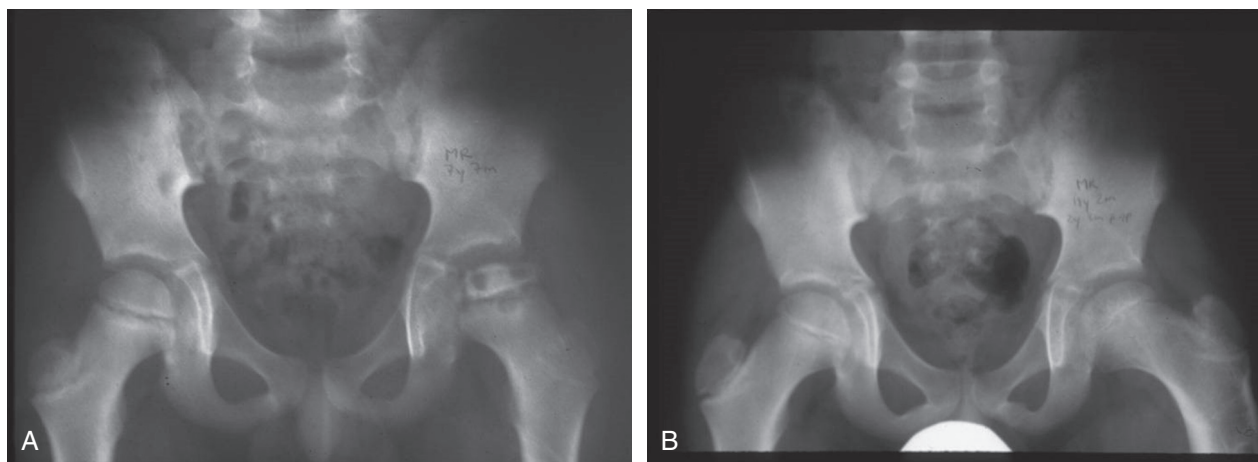
Differential diagnosis includes persistent physiologic varus, vitamin D–deficiency rickets, renal osteodystrophy, vitamin D–resistant (hypophosphatemic) rickets, metaphyseal dysostosis (Schmid, Jansen types), spondyloepiphyseal or metaphyseal epiphyseal dysplasias, thrombocytopenia-absent radius syndrome, focal fibrocartilaginous defect, or proximal tibial physeal injury (eg, infection, fracture, irradiation). There is an adolescent form of Blount’s disease that may present initially with knee pain and progressive varus deformity (Figure 303-4). As with the juvenile form, cause is unknown, but is suspected to be a combination of obesity and possible persistent physiologic varus. Radiographs may demonstrate widening of the medial physis in addition to varus and flexion deformities of the proximal tibia. Treatment is surgical.

### TARSAL NAVICULAR

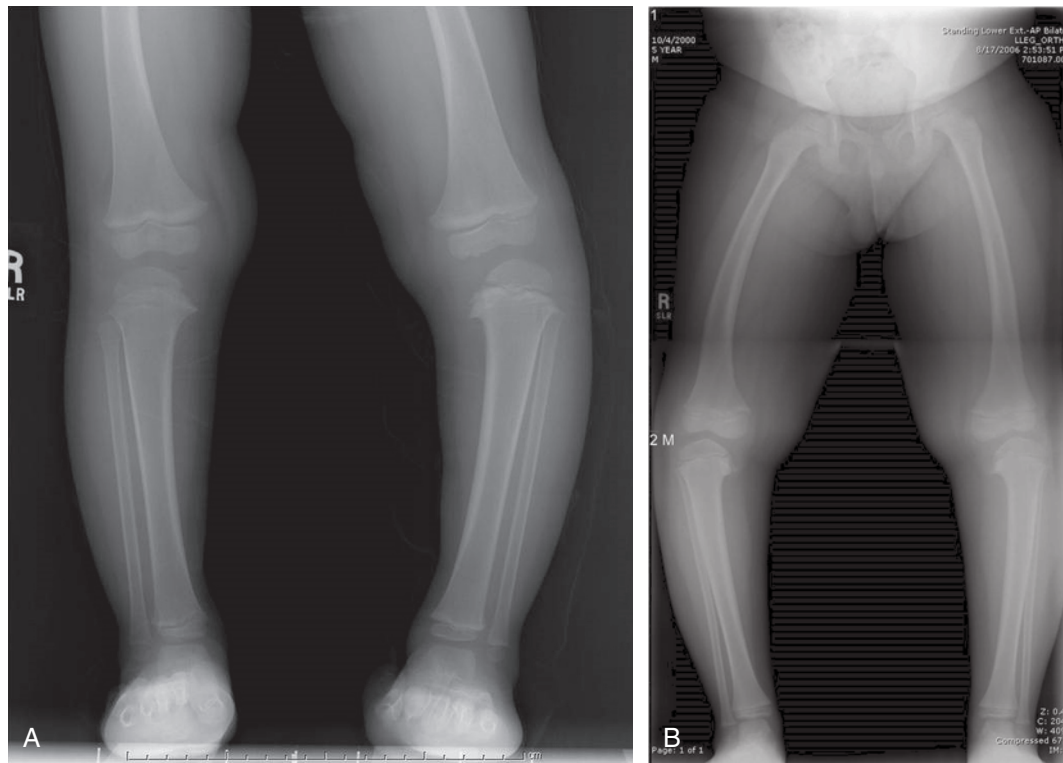
Köhler disease of the tarsal navicular bone results from an interruption of the blood supply to the developing navicular bone, causing necrosis of its ossification center. The disorder is seen primarily in boys between 2 and 9 years of age.

The child often ambulates in equinovarus and complains initially of pain with activity. Palpation of the bone elicits tenderness. Radiographs of the feet show irregularity of the navicular ossification center with collapse, sclerosis, or fragmentation (Figure 303-5). However, these radiographic findings can be seen in asymptomatic children and may represent a normal variant of ossification. The clinical findings are key to making the diagnosis.

The process of revascularization and reconstruction takes from months to years. Initial treatment is symptomatic; use of a cast or walking boot may alleviate pain, and physical therapy may be helpful in the older, more active child. The condition is self-limited, and the ossification center eventually becomes revascularized and completely reconstructed.



**Figure 303-2** (A) Initial presentation of Perthes in a 7-year-old. Note lucencies in femoral head. (B) After surgical intervention and healing of disease, there is still asymmetry in the femoral head.



**Figure 303-3** Juvenile Blount disease. (A) Unilateral. (B) Bilateral.

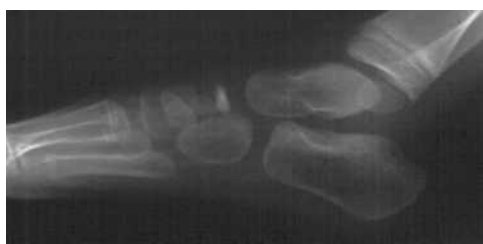


**Figure 303-4** Adolescent Blount disease. (A) Clinical photo. (B) Radiograph.

## METATARSAL HEADS

Freiberg infraction, first described in 1917, is a condition in which a part of the head of a metatarsal bone undergoes osteonecrosis and becomes sufficiently weakened to be susceptible to functional trauma (running, jumping), which may cause compression-related collapse of the metatarsal head. The second metatarsal is most often involved, because it is usually the longest metatarsal; the third metatarsal bone is the next most likely. Girls are affected more often than boys, and onset usually occurs during the adolescent growth spurt.

Affected children generally have pain with ambulation that localizes to the metatarsal head. This is



**Figure 303-5** Typical sclerotic collapsed appearance of tarsal navicular in Köhler disease.

reproducible with palpation. Occasional swelling because of joint effusion may be seen. Children will also complain of painful range of motion of the metatarsophalangeal joint.

Radiographs show sclerosis early in the course of the disease, with collapse and possible arthritic changes occurring later (Figure 303-6).

Initial treatment is with activity modification and protected weight-bearing, as well as orthotics or shoe modifications that can help to off-load the affected metatarsal and limit joint motion. Most children will improve, but for those with persistent symptoms, surgery may be helpful.

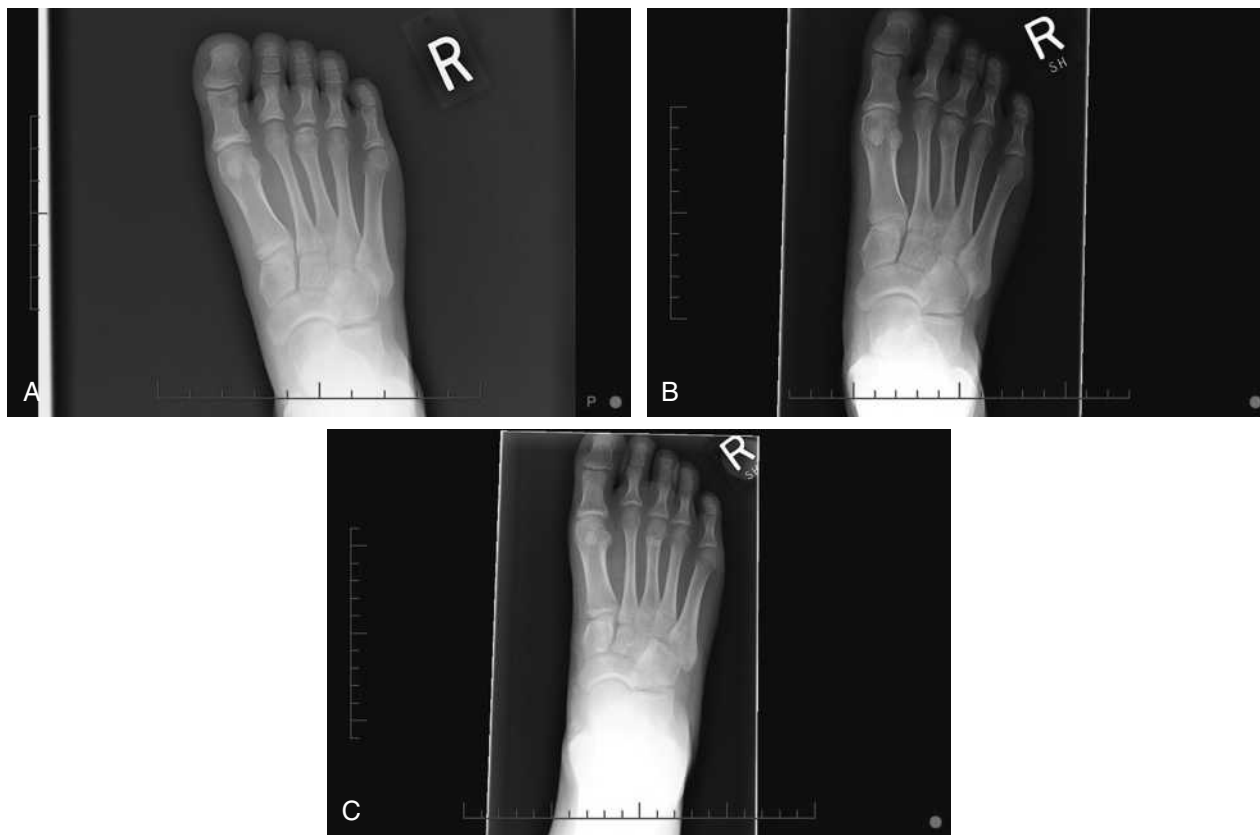
## CAPITELLUM

Panner disease is osteonecrosis of the capitellum. It is seen almost exclusively in boys younger than 10 years of age. There is no association with trauma, but children present with pain and limitation of elbow motion.

Radiographs show fissuring, fragmentation, and lucency involving the entire capitellum (lateral condyle) ossification center. Gradual reossification occurs over months to years.

Treatment is focused on rest with limited casting, and gradual resumption of activity over time.

It is important to distinguish Panner disease from osteochondritis dissecans of the capitellum, which is often associated with trauma or overuse, and has a more focal appearance on radiographs (Figure 303-7).



**Figure 303-6** (A) Initial presentation with lucency. (B) After consolidation, with flattening and deformity of head. (C) After debridement and corrective osteotomy.

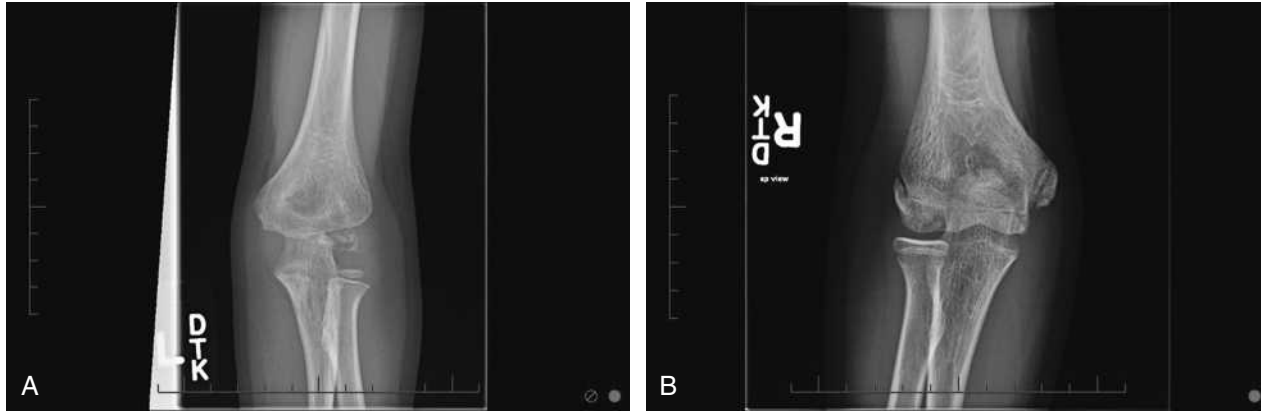


### CARPAL LUNATE

Aseptic necrosis of the lunate bone (Kienbock disease or the newer term, lunatomalacia) is a rare disorder in children. Two forms are described: infantile (up to age 12) and juvenile (13 and up). Cause is unknown. Children note wrist pain, which may be accompanied by swelling. Pain is noted with wrist motion, and in longstanding cases the pain may be present at rest.

Radiographs will show a flattened sclerotic lunate. In the infantile form, the entire lunate is generally involved. In the juvenile form, there may be an elongated palmar horn.

Treatment usually begins with a period of immobilization. Surgery may be indicated in recalcitrant cases or in older children, but there is controversy over the ideal procedure.



**Figure 303-7** (A) Radiographic appearance of Panner disease with total involvement of capitellum. (B) Compared to osteochondral lesion of the capitellum, which is focal.



**Figure 303-8** (A) Typical prominent tibial tubercle of a patient with Osgood-Schlatter disease. This is the area of maximal tenderness. (B) Radiographs that may demonstrate irregular ossification of the tibial tubercle.

## APOPHYSITIDES

Apophysitides are common conditions in late childhood and adolescence that are associated with periods of rapid growth. These are clinical entities, although occasionally there may be associated radiographic changes.

Osgood-Schlatter disease is a clinical disorder that results from an inflammation/stress reaction occurring at the patellar ligament insertion into the epiphysis of the tibial tubercle. Its incidence is higher in boys than in girls, and it generally occurs in ages 10 to 14 years. More than 25% of cases have bilateral involvement. The child complains of pain and tenderness of the tuberosity, which may also be enlarged (Figure 303-8). The radiographic changes vary from no abnormality to irregular ossification of the tibial tubercle; more mature patients may demonstrate a persistent ossicle (Figure 303-8). Radiographs may not relate to the clinical presentation but can rule out other conditions like osteochondritis dissecans. Symptoms commonly include pain during or at the end of activity, and are generally alleviated by rest, ice, and nonsteroidal anti-inflammatory drugs. On examination, children will often have tight quadriceps and weak hamstrings, which may be addressed with physiotherapy. Activity restriction is often helpful initially if children are very symptomatic, followed by physiotherapy and gradual resumption of activity. Osgood-Schlatter disease is generally a self-limited condition. Surgery is rarely indicated, and is generally for a painful ossicle that is refractory to nonoperative intervention.

Sinding-Larsen-Johannson syndrome presents similarly to Osgood-Schlatter disease, but the patient localizes tenderness to the distal pole of the patella.



**Figure 303-9** Area of tenderness localizing to calcaneal apophysis in Sever disease.

Radiographs may show elongation of the distal pole patella, with occasional fragmentation. Again, this is a self-limited condition, but symptoms may resolve more quickly with physiotherapy. Surgical treatment is extremely rare. Neither condition has been shown to predispose children to fracture in these areas.

Sever disease is apophysitis of the calcaneal tuberosity, and commonly affects active children ages 9 to 12 years. While children often complain of pain in the arch or heel, they are not tender over the plantar fascia, but tender at the calcaneal apophysis and Achilles insertion (Figure 303-9). Many of these patients have tight Achilles tendons and respond to a course of physiotherapy and modified activity. While some advocate shoe modifications, inserts, or heel cups, these have not been shown to reliably and completely alleviate symptoms.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *What Is a Pediatric Orthopedic Surgeon?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Orthopedic-Surgeon.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Orthopedic-Surgeon.aspx))

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## Chapter 304 OSTEOMYELITIS

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Osteomyelitis, or infection of the bone, in children is most often the result of hematogenous spread of bacteria to bone. Osteomyelitis can also occur after an open fracture or operative procedure or by direct extension from an adjacent soft-tissue infection. Chronic osteomyelitis can occur if the infection is indolent and the diagnosis is delayed or if treatment does not completely eradicate infection. Acute osteomyelitis should be diagnosed and aggressively treated to decrease the risk of osteomyelitis becoming chronic; chronic infection requires surgical drainage and is more difficult to eradicate than acute cases.

Chronic osteomyelitis can result in lifelong disability related to recurrences and, rarely, to cancer. Regardless of age, osteomyelitis is most often caused by infection with *Staphylococcus aureus*; however, osteomyelitis can be caused by other pathogens in certain age groups or hosts, or the infecting agent can be related to the type of contamination (dirt, water, and other sources). Establishing the diagnosis of osteomyelitis can be difficult, especially when the illness begins insidiously. Physicians who care for children must have a high index of suspicion to avoid missing or delaying the diagnosis.

## DEFINITION OF TERMS

### Acute Osteomyelitis

In children, osteomyelitis caused by hematogenous seeding usually begins in the metaphyses of the long bones, reflecting the rich blood supply in this area throughout childhood. Often, but not always, a history of trauma to the area can be found. Occult transient bacteremia likely seeds a traumatized area more easily than a healthier site.

In infants, osteomyelitis is often accompanied by rapid spread into the adjacent joint, especially the hip. Infection seems to spread quickly across the metaphysis into the epiphysis and then into the adjacent joint. The presence of penetrating vessels that pass through the growth plate to connect the metaphysis with the epiphysis is thought to allow the rapid spread. These vessels are only present in infancy, most commonly before 6 months of age. Infection may also cross the growth plate directly (see Table 334-1 in Chapter 334, Sports Musculoskeletal Injuries, for the components of the growth plate). Infants with signs and symptoms of septic arthritis of the hip must always be evaluated for an accompanying osteomyelitis of the femur. In children older than 1 year of age, infection tends to be held in place by the metaphysis. Infection after infancy is most likely to spread into the diaphysis and down the bone. However, infection of the hip, shoulder, or elbow joints can also be the result of infection breaking out of the cortex located within the joint capsule. Much more rare is infection that begins in the epiphyseal or metaepiphyseal area. *S aureus* is the organism most likely to be responsible for hematogenous osteomyelitis in all age groups. In newborns, other common pathogens include group B streptococcus (*Streptococcus agalactiae*) and gram-negative bacteria such as *Escherichia coli*. Fungal pathogens, especially *Candida* species, occur in infants who have been in the neonatal intensive care unit and who have had vascular lines in place. In older infants and children, *S aureus* followed by the group A *Streptococcus* (*S pyogenes*) are the most common pathogens. Because an effective vaccine has been developed, *Haemophilus influenzae* type b infection has become very rare, but was previously a common pathogen in preschool-age children. *S pneumoniae* occurs mostly in children younger than 2 years, and *Kingella kingae* occurs in young children. Children with hemoglobinopathies are at risk for osteomyelitis, perhaps related to bone infarcts that occur with sickle cell crisis. In this population, *Salmonella* species and *S aureus* are the most

common pathogens. *Salmonella* infections in this population occur at rates much higher than in other children, who only rarely have this pathogen as a cause of osteomyelitis. Organisms that cause a bacteremia can result in an osteomyelitis in the child.

Osteomyelitis following direct invasion of the joint is also most often caused by *S aureus*, but other pathogens and sometimes multiple pathogens can be present. In osteomyelitis, the nearby joint can also be affected with a reactive effusion. In children, trauma is most often the cause, especially after an open fracture, but this circumstance can also occur after orthopedic surgery, especially in the setting of placement of a foreign body such as the insertion of pins or screws into bone. In addition to *S aureus*, coagulase-negative staphylococci, gram-negative organisms, and other unusual organisms can become pathogens. Unusual pathogens reflect the source of contamination. For instance, *Pseudomonas aeruginosa* commonly follows puncture wounds of the foot through a sneaker; *Aeromonas* infections may occur after trauma to bare feet while walking in river water. Multiple pathogens, including anaerobes, may be present, especially if the wound has been contaminated with dirt.

### Chronic Osteomyelitis

Chronic osteomyelitis refers to infection in the bone that has become long-standing (usually months of untreated infection), often related to a delay in the diagnosis or to incomplete eradication of an acute infection. Chronic infection is most often indolent and much harder to cure than acute osteomyelitis. Infection can spread insidiously throughout the diaphysis of the affected bone. This spread can occur even with a staphylococcal species when an infection begins around a foreign body such as a pin to stabilize a bone after orthopedic surgery. Infection in chronic osteomyelitis can track outward to result in a spontaneously draining sinus. A sinus tract that closes can result in more acute symptoms and signs. Chronic osteomyelitis results in bone loss and areas of devascularized bone, which separate and result in the creation of sequestrum or pieces of dead bone in the shaft of the long bones. Once this situation occurs, surgery will be required to treat the infection. A *Brodie abscess* is an abscess with a capsule that can develop in the bone and seems to be the result of walled-off chronic infection, often with no active organisms recoverable when drained.

## DIFFERENTIAL DIAGNOSIS

Osteomyelitis should always be considered in a child who has localized bone pain, especially if fever is present, which may be low grade. Trauma can be confused with bone infection, especially if fever is minimal. In many instances, osteomyelitis does follow a fracture or trauma; thus even in the presence of a fracture, the possibility of osteomyelitis must be considered if fever is present or pain persists after casting. Fever may be minimal and can be overlooked by both parent and physician. Careful examination, seeking focal areas of tenderness, is necessary in the young child who may not be able to describe pain adequately. Hip or femur pain can be confused with intra-abdominal infection,



especially infection in the area of the psoas muscle. An example is a missed appendicitis that can result in a phlegmon in this area, causing a limp that can be confused with osteomyelitis of the femur. Careful abdominal examination is, therefore, necessary in the child who limps, to avoid missing intra-abdominal abnormalities. Back pain and discitis can also be confused with osteomyelitis. The differential diagnosis of a child with back pain must include vertebral body infection, with or without nearby epidural abscess and discitis. Bone pain can also be a presenting symptom of leukemia. An abnormal blood count with anemia, a low white blood count, or thrombocytopenia will often be a clue. Cat-scratch disease can cause osteomyelitis and be confused with lymphoma or other malignancy, but this condition resolves untreated over time. Some bone tumors can cause nonspecific bone pain and lytic bone lesions on radiograph that must also be differentiated from chronic osteomyelitis by biopsy for pathologic abnormalities and by culture of the bone. When fever is not a prominent sign, osteomyelitis is more likely to be confused with a condition not caused by infection. The differential diagnosis of a limp also includes septic arthritis and juvenile idiopathic arthritis. The manifestations of septic arthritis may be similar to those of acute osteomyelitis, and, especially in the infant, these entities may coexist. When septic arthritis is present, the urgency for prompt treatment is acute (see Chapter 328, Septic Arthritis). When erythema over the infected bone is present, distinguishing between cellulitis and osteomyelitis may be difficult. Chronic multifocal osteomyelitis is a recurring inflammatory disease that most often is not associated with infection but can mimic bacterial osteomyelitis. In many cases, it can only be diagnosed over time by observing the pattern of recurring disease, usually with cultures negative for acute infection.

## EVALUATION

### Relevant History

Localized bone pain and fever is the history most typically given in acute osteomyelitis, at times with prior trauma to the area. In infants and young children, the caregiver may have noticed that the child has pain with movement of the affected limb, has stopped using the limb, or has begun to limp. When the infection causes bacteremia, a history of a high fever spike before the onset of pain may be described, or, if ongoing, signs of bacteremia may be present, such as chills and high fever, malaise, and acute illness. In older children, 1 bone is usually involved, whereas in newborns, more than 1 site may be infected with a bacteremia. Nonspecific malaise and poor appetite may occur in the child with chronic osteomyelitis, but only nonspecific complaints of pain may be elicited in the area of the bone. Specific pathogens may have unique histories, such as the child with gastroenteritis and *Salmonella* infection who later has new fever and bone pain, or the child with an open fracture or bone surgery who later develops fever and new pain or drainage at the same site. A child with a fracture, either open or closed, who has new or worsening pain under a cast should have the cast removed and the area evaluated for infection.

The history may be acute, especially if the child is bacteremic, or more subacute or chronic in cases in which the bacteremia has resolved or the pathogen is less virulent. In chronic osteomyelitis, symptoms may have been present for months.

### Physical Examination

Vital signs of the child with osteomyelitis may be normal, especially with chronic infection, or abnormal if the child is bacteremic at presentation. Fever will often be present, even in the absence of a history of fever. Localized pain will almost always be present. Tenderness is often exquisite, but in younger children, only a new limp or absence of movement of an arm or leg may be noted. Other local signs may be associated with inflammation, including swelling, redness, and warmth over the involved bone, which can be confused with cellulitis. Characteristically, the child is reluctant to move the adjacent joint and, when a lower extremity is involved, may refuse to bear weight. In the young infant, the loss of active movement in an extremity may be confused with a neurologic problem. Erythema is often present over the infected bone, in addition to tenderness to palpation or movement. If associated arthritis occurs, then pain on movement of the joint may be prominent.

### Laboratory Testing

The diagnostic evaluation for possible osteomyelitis includes a complete blood cell count and smear review, erythrocyte sedimentation rate, C-reactive protein, blood cultures, and radiographs. However, all of these tests can produce normal findings, especially early in the infection. The white blood cell count can be elevated in acutely ill children with bacteremia, though very low counts occur with sepsis, especially in infants. The presence of anemia, low white blood cell count, or thrombocytopenia in the absence of disseminated intravascular coagulation should raise concern for leukemia or other malignancy. The sedimentation rate may be normal at first but almost always becomes elevated in acute osteomyelitis and often is extremely elevated, differentiating osteomyelitis from other inflammatory processes except autoimmune ones. The C-reactive protein is usually elevated early. These clinical markers are helpful in following the course and response to treatment. The C-reactive protein rises more quickly and normalizes more rapidly than the sedimentation rate, which eventually is most useful in following long-term therapy. Procalcitonin has been studied as a specific marker in differentiating acute osteomyelitis and septic arthritis from viral and noninfectious inflammatory bone and joint infections and may be a useful tool in the future. A blood culture will often identify the pathogen causing the infection, but is not always positive. In chronic osteomyelitis, laboratory markers of inflammation may be normal, making the diagnosis more difficult. In some cases, a TB test by serum interferon may be appropriate, such as in the older child in whom TB is being considered as a cause of infection.

### Imaging

Early in the clinical course, no bony changes are seen radiographically; the earliest detectable signs are



those of blurred soft-tissue planes secondary to edema spreading into fatty tissues. Bone changes are not apparent until at least 7 to 10 days or longer after the onset of symptoms. The first signs consist of nonspecific periosteal reaction. Lytic lesions occur later. Bony radiographs should always be obtained, however, to exclude other pathologic abnormalities such as fracture or a malignant lesion. Although skeletal scintigraphy (technetium bone scan) was recommended in the past for evaluating children with possible osteomyelitis, the advantages of using magnetic resonance imaging (MRI) initially have become clear. MRI provides excellent views of the bony and soft-tissue anatomy, revealing subperiosteal abscesses that require surgical intervention. The use of contrast is helpful with the MRI. The presence of a subperiosteal abscess is diagnostic for an acute osteomyelitis that has broken through the metaphyseal cortex. MRI is also the image of choice when pelvic or spine osteomyelitis is suspected. Very rarely, MRI may be normal at first. Technetium bone scans are sensitive, though less sensitive than MRI, are also less specific, and are often difficult to interpret, with frequent false-negative results. Bone scans are not useful in the neonate because of low bone mineralization. Bone scans provide limited information regarding soft-tissue involvement, subperiosteal space, and bone marrow edema, and the results may be normal in up to 20% of children in the first days of illness. This can occur with MRI, but much less frequently. In addition, malignancy, cellulitis, trauma, and bone infarction can affect the specificity of a bone scan, though 3-stage scans improve sensitivity. Finally, bone scans require large amounts of radiation. However, the bone scan does not ordinarily require sedation or general anesthesia, which frequently are needed for a young child to lie still for an MRI. Bone scans can be useful in cases in which multiple sites of osteomyelitis are suspected.

Ultrasonography can detect a subperiosteal abscess and may be helpful in guiding needle aspiration of an infected bone. The finding of such a collection distinguishes osteomyelitis from cellulitis in an inflamed extremity, but the failure to visualize an abscess does not rule out early osteomyelitis still contained within the bone. Ultrasound also can help evaluate a nearby joint for an effusion that is present with an associated arthritis.

In chronic osteomyelitis, the radiograph will show extensive disease, usually along the diaphysis of the bone, with bone changes that may need to be differentiated from malignancy by history and ultimately by cultures and biopsy.

## MANAGEMENT

A blood culture and a needle aspirate of the site of infection are the most helpful procedures for diagnosing osteomyelitis. Aspiration confirms the diagnosis and can determine the necessity for operative decompaction if frank pus is obtained, may alleviate pain caused by pressure from an abscess, and provides a specimen for pathogen identification by culture and material for immediate Gram stain. Blood cultures are also helpful in identifying the presence of bacteremia

and the cause of the infection, and they are positive in 40% to 50% of cases. If the history and examination fit with the diagnosis and a blood culture is positive, then therapy can be started without a bone aspiration. If response to therapy is prompt, then aspiration may not be required. Needle aspiration of the subperiosteal space and of the metaphysis for culture is indicated to obtain culture identification of the pathogen when blood cultures are pending and whenever a collection of pus exists. When surgery is indicated, it should be prompt and antibiotics should be started as soon as culture material is obtained. In indolent cases and in cases with unusual presentations, aspirating the bone is especially important to obtain the pathogen and to guide therapy. Evaluation for related arthritis also is crucial, given that joint infections can progress rapidly and need adequate drainage to avoid damage to the joint (see Chapter 328, Septic Arthritis). If infection with TB is suggested because of history or setting, then cultures for acid-fast bacteria should be included as well as a tuberculin skin test or IGRA (interferon-gamma release assay) blood test, depending on the age of the child.

Once blood cultures and needle aspiration have been performed, antibiotics should be given empirically and by the intravenous route. After the newborn period, in a previously well child thought to have hematogenous osteomyelitis, a penicillinase-resistant penicillin or first-generation cephalosporin is sufficient, though clindamycin or vancomycin should be considered given the incidence of methicillin-resistant *S aureus* (MRSA) in community-associated infection. In the child who is severely ill or has signs of bacteremia and sepsis, vancomycin should be considered as initial therapy instead of or in addition to a  $\beta$ -lactam. In each case, therapy should be individualized to include other likely pathogens. For example, in the newborn, *S aureus* remains the most common cause, but *S agalactiae*, coagulase negative staphylococcus, gram-negative enterics, and *Candida* species are encountered in neonates in the intensive care unit. Initial therapy in the newborn should always include coverage against gram-negative enterics and might include oxacillin and gentamicin, or vancomycin and ceftazidime or cefepime, when concern for MRSA infection exists or for coagulase-negative staphylococci. Neonates who have been in a neonatal intensive care unit and who have been on antibiotics should be treated most broadly, pending culture results. Fungal coverage is usually not empiric therapy, unless a blood culture or other epidemiologic data suggest the presence of a fungal infection, such as in patients with chronic granulomatous disease. Children with sickle cell hemoglobinopathies who are at special risk for infection with *Salmonella* species in addition to *S aureus* might be treated with cefuroxime or with vancomycin and ceftriaxone or cefotaxime, pending culture results. If a pseudomonal infection is suspected, such as in the child with infection after a puncture wound of the foot, then the initial treatment should be ceftazidime or a carboxypenicillin or acylureidopenicillin combined with an aminoglycoside such as piperacillin-tazobactam and gentamicin or ceftazidime and gentamicin. Piperacillin-tazobactam will also treat *S aureus* while cultures are pending. Chronic

**Table 304-1 Treatment of Osteomyelitis**

CONDITION	THERAPY	COMMENTS
<b>NEWBORN</b>		
Empiric therapy	Nafcillin/oxacillin IV (or vancomycin if MRSA is a concern) AND cefotaxime or gentamicin IV	
Coliform bacteria (eg, <i>Escherichia coli</i> , <i>Klebsiella</i> sp, <i>Enterobacter</i> sp)	For <i>E coli</i> and <i>Klebsiella</i> : cefotaxime OR gentamicin OR ampicillin (if susceptible) For <i>Enterobacter</i> , <i>Serratia</i> , or <i>Citrobacter</i> : ADD gentamicin IV to cefotaxime OR ceftriaxone, OR use cefepime initially	Meropenem for ESBL-producing coliforms Piperacillin/tazobactam or cefepime are alternatives for susceptible bacilli
Gonococcal arthritis and tenosynovitis	Ceftriaxone IV OR cefotaxime IV for 7–10 days	Cefotaxime is preferred for infants with hyperbilirubinemia
<i>S aureus</i>	MSSA: oxacillin/nafcillin IV MRSA: vancomycin IV	Alternative for MSSA: ceftazolin Alternatives for MRSA: linezolid, clindamycin (if susceptible) Addition of rifampin is sometimes attempted if persistently positive cultures
Group B streptococcus <i>Haemophilus influenzae</i>	Ampicillin or penicillin G IV Ampicillin IV, OR cefotaxime IV	
<b>CHILDREN OLDER THAN 30 DAYS</b>		
Infants and children, acute infection (usually <i>S aureus</i> , including MRSA; group A streptococcus; <i>K kingae</i> )	Cefazolin +/- clindamycin or vancomycin depending on how sick the child is at presentation for serious infections For MRSA: clindamycin 30–40 mg/kg/day IV div q8 or vancomycin 60 mg/kg/day IV div Q8, maintaining troughs between 10–15 micrograms/milliliter For MSSA: oxacillin/nafcillin 200 mg/kg/day IV div q6h OR cefazolin 100 mg/kg/day IV div q8h For <i>Kingella</i> : cefazolin 100 mg/kg/day IV div q8h OR ampicillin 150 mg/kg/day IV div q6h, OR ceftriaxone 100 mg/kg/day IV Total therapy (IV plus PO) usually 4–6 wk for MSSA (with end-of-therapy normal ESR, radiograph to document healing) but may be as short as 3 wk for mild infection; may need longer than 4–6 wk for MRSA Follow closely for clinical response to empiric therapy	In children with open fractures secondary to trauma, add ceftazidime for extended aerobic gram-negative bacilli activity <i>Kingella</i> is often resistant to clindamycin and vancomycin For MSSA and <i>Kingella</i> , step-down oral therapy with cephalexin 100 mg/kg/day PO div tid Oral step-down therapy alternatives for MRSA include clindamycin and linezolid with insufficient data to recommend trimethoprim/sulfamethoxazole
Chronic (staphylococcal)	For MSSA: cephalexin 100 mg/kg/day PO div tid OR dicloxacillin caps 75–100 mg/kg/day PO div qid for 3–6 mo or longer For MRSA: clindamycin or linezolid	Surgery to debride sequestrum is usually required for cure For prosthetic joint infection caused by staphylococci, add rifampin Watch for $\beta$ -lactam-associated neutropenia with high-dose, long-term therapy, and linezolid-associated neutropenia/thrombocytopenia with long-term (>2 wk) therapy

div, divided; ESBL, extended spectrum  $\beta$ -lactamase; ESR, erythrocyte sedimentation rate; h, hour; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; PO, by mouth; q, every; qid, 4 times per day; tid, 3 times per day; wk, week.  
From Bradley JS, Nelson JD. *Nelson's Pediatric Antimicrobial Therapy*. 21st ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015.

osteomyelitis must be completely drained and debrided and will require surgical care.

If infection is the result of open wounds, then the setting should guide empiric therapy. Wounds contaminated by dirt require broad coverage of gram negatives and anaerobes, such as piperacillin-tazobactam with an aminoglycoside.

Antibiotics should be adjusted once cultures and sensitivities are available, narrowing the spectrum to cover the pathogen. Clindamycin has good bone penetration and is often used in cases of allergy to  $\beta$ -lactams or to treat MRSA isolates that are sensitive. It has been recommended as empiric therapy if MRSA is suggested, though some isolates may be resistant. The role of the antibiotic linezolid in treating osteomyelitis in children remains to be determined. It should not be used empirically but may be helpful in patients with  $\beta$ -lactam allergies and as a drug that can be used orally to treat a serious infection, though the side effect of thrombocytopenia limits its long-term use. Antibiotics should be continued for 4 to 8 weeks in order to prevent complications, specifically the evolution of infection into chronic osteomyelitis. Clinical response and bloodwork will ultimately guide length of therapy. For specific treatment advice see Table 304-1.

Oral antibiotics can be considered to finish the course of therapy if an oral agent is available that has good bone penetration, has excellent activity against the pathogen, and is palatable, and if the child has a social situation that will guarantee adherence. The switch to oral therapy should not occur before clinical response to intravenous therapy, including absence of fever, return to normal function, and a decrease or normalization of inflammatory markers. Oral antibiotics often require 2 to 3 times the usual dose to achieve adequate bone penetration, making gastrointestinal tolerance of high doses of the antibiotic a requirement. Therapy is sometimes prolonged by several weeks empirically.

An abscess must be drained surgically when detected or suspected. The lack of pus on aspiration should suggest that the site of aspiration may have been inaccurate, or pus may be present but too thick to pass through even a large-bore needle. Care must be taken not to miss infection. A clinical suspicion or failure of the patient to respond to nonoperative therapy is an indication for operative decompression. The risks of unnecessary surgery in the child who has an acute infection are far less than those of necessary surgery not performed. MRI can help locate and define the anatomy of the infection in children failing conservative therapy. Chronic osteomyelitis always requires surgical debridement to remove necrotic bone, and prolonged antimicrobial therapy that typically lasts 3 to 6 months, perhaps less but sometimes longer for complicated cases. As with acute osteomyelitis, much of the treatment for chronic osteomyelitis may be completed with oral antibiotics.

Complications for hematogenous osteomyelitis include deep vein thrombosis (DVT), with increased risk if the child is critically ill at presentation or has a positive blood culture, infection with MRSA, elevated

C-reactive protein, and central venous catheter in place. DVT should be considered if the patient develops pulmonary findings or has persistently positive blood culture. Long-term complications may include pathologic fractures, limb length discrepancy, and avascular necrosis. Risk factors for such complications include a delay in diagnosis greater than 1 week, newborn age, hip joint infection, infection with MRSA, and more than 3-day delay in treatment with appropriate antibiotic(s).

### WHEN TO REFER

The diagnosis of possible osteomyelitis requires thorough evaluation and usually includes consultation with radiology and orthopedic surgery. Discussing the specifics of the case with the radiologist can help focus the radiologic evaluation effectively. Consulting early with the orthopedic surgeon helps expedite aspiration of the bone or open drainage. Infectious disease specialists help organize the evaluation, begin therapy, and follow up with children who are discharged on home intravenous therapy and who have chronic disease.

### WHEN TO ADMIT

Children with acute osteomyelitis require admission to the hospital for rapid evaluation and to begin treatment. The initial evaluation can begin as an outpatient, when the diagnosis of osteomyelitis is not yet established, perhaps with complete blood count, blood culture, and radiograph. However, the physician must follow up closely and consider hospitalization as soon as the diagnosis becomes likely.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Osteomyelitis* (Web page), National Foundation-Kids Health ([www.kidshealth.org/teen/diseases\\_conditions/bones/osteomyelitis.html](http://www.kidshealth.org/teen/diseases_conditions/bones/osteomyelitis.html))

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## Chapter 305

## OTITIS MEDIA AND OTITIS EXTERNA

Tina Q. Tan, MD

## OTITIS MEDIA

Otitis media, an inflammation of the middle ear, is the most common reason that children in the United States receive a prescription for antibiotic therapy. More than 90% of all antibiotic use in the first 2 years of life is attributable to the treatment of otitis media. By the age of 7 years, between 65% and 95% of children will be treated for at least 1 episode of otitis media. Because otitis media is such a prevalent condition, much attention is focused on the consequences and its treatment. Rare suppurative complications, such as intracranial abscess, can be serious. Conductive hearing loss resulting from chronic middle-ear effusions associated with otitis media may contribute to speech and language delay in some children. The overuse of antibiotics to treat otitis media may contribute significantly to the emergence of antibiotic-resistant bacteria. Each year in the United States, billions of dollars are spent on the treatment of otitis media alone. In response to growing concerns about the increasing rates of antibacterial resistance and the escalating costs of antibacterial prescriptions for the treatment of this disease, the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP) published an updated evidence-based clinical practice guideline on the diagnosis and management of acute otitis media in 2013. The major aim of this guideline is to focus attention on the need for the judicious use of antibacterial agents in the treatment of acute otitis media and update the recommendations based on the most current evidence supporting these guidelines. Despite this attention, the management of otitis media remains a source of debate in the medical literature.

## Classification

Otitis media encompasses several clinical entities. *Acute otitis media* (AOM) describes the presence of inflammatory fluid in the middle-ear space accompanied by the acute onset of local findings such as ear pain, otorrhea, or distortion of the tympanic membrane (eg, bulging, erythema, opacity, limited or absence of mobility). Systemic findings such as fever and irritability may also be present. *Otitis media with effusion* (OME), or serous otitis media, describes the presence of inflammatory fluid in the middle-ear space in an asymptomatic child, following an episode of AOM, or in a child with mild upper respiratory tract symptoms, a common reason for examining the ears in the first place. The term *recurrent otitis media* is generally used to refer to 3 or more episodes of AOM in 6 months or 4 episodes in 1 year, with 1 episode in the preceding 6 months. Recurrent otitis media should not be confused with chronic otitis media, which may be used to describe OME

that lasts longer than 3 months or a suppurative middle-ear process that fails to respond to initial antibiotic therapy. Specificity in diagnosis is important because of its significant implications for management.

## Epidemiologic Features

By the age of 1 year, almost two-thirds of children will experience at least 1 episode of AOM. Otitis media is more common in boys and in children of low socioeconomic status. Incidence rates in white and black children are very similar. Several environmental factors increase the risk for developing otitis media, including the winter season, exposure to tobacco smoke, use of a pacifier, and attendance at child care centers, particularly those serving large numbers of children.

In addition, any amount of breastfeeding reduces the incidence of otitis media by 23% and exclusive breastfeeding for more than 3 months reduces it by 50%. The 2013 AOM guidelines also suggest that physicians encourage exclusive breastfeeding for at least 6 months. Interestingly, Xylitol, or birch sugar, was associated with a 25% reduction of AOM among healthy children at child care centers. However, it is not an effective treatment of AOM because it needs to be given 3 to 5 times a day, as well as daily throughout the respiratory illness season. Obviously, children younger than 2 years of age cannot safely use lozenges or chewing gum, the forms in which is most effective.

Children at high risk for developing AOM include those with craniofacial anomalies (eg, cleft palate) that alter the normal air and fluid dynamics of the middle-ear space, those with immunodeficiencies, and those of certain ethnic groups such as Native Americans and Alaskan Natives. A mild hereditary predisposition to develop recurrent otitis media seems to exist, with some of the variation in presentation and incidence explained by genetic factors, whereas familial and individual environmental factors account for the remainder.

## Pathogenesis

Otitis media is an inflammatory process of the upper respiratory tract that usually results from a viral infection. As viruses infect the respiratory mucosa, edema can lead to eustachian tube dysfunction, so that inflammatory fluid and pathogenic respiratory bacteria that reflux into the middle-ear space do not drain normally. This process effectively leads to the formation of an abscess in the middle ear. Otitis media is usually self-limited; as the viral illness resolves, eustachian tube function is restored, and the middle-ear space drains normally. Although acute symptoms generally resolve spontaneously within a few days, middle-ear effusions can persist for weeks after an episode of AOM. In fact, 60% of middle-ear effusions resolve spontaneously within 3 months, whereas 85% resolve spontaneously within 6 months. The persistence of middle-ear effusions (or OME) after an episode of AOM has raised concern about the conductive hearing loss that accompanies these effusions and its effect on speech and language development, especially in younger children. These effusions are sterile and, in the absence of



other acute signs and symptoms, often do not require antibacterial therapy.

In studies of children with AOM, specimens of middle-ear fluid obtained by tympanocentesis are used to clarify the microbiologic mechanism of this disease. These specimens are positive for bacteria approximately 70% of the time: 55% with bacteria only and 15% with bacteria and viruses. The most frequently identified pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae* (increasingly  $\beta$ -lactamase producing), and *Moraxella catarrhalis*. Group A  $\beta$ -hemolytic streptococcus and *Staphylococcus aureus* (including methicillin-resistant strains) are much less common. Rarely, *Mycoplasma pneumoniae* is also detected but not often enough to affect the empirical selection of an antibiotic for treatment of AOM.

*H influenzae* has increasingly become a frequent isolate of middle-ear fluid since the introduction and use of 7-valent pneumococcal conjugate vaccine (PCV7) in 2000. Non-PCV7 serotypes are now just as common. *H influenzae* (nontypeable) is the most likely isolated pathogen causing AOM associated with conjunctivitis. The patterns of isolated pathogens continue to evolve with the continued use of the 13-valent pneumococcal conjugate vaccine that was introduced in 2010. Respiratory viruses such as respiratory syncytial virus (RSV), influenza viruses, and parainfluenza viruses are also recovered often from middle-ear aspirates, either in addition to bacteria or in isolation. Respiratory syncytial virus, in particular, has a tendency to infect the mucosa of the middle ear and probably contributes substantially to the development of otitis media in children.

### Diagnosis

Concern is growing that overdiagnosis of otitis media and liberal use of antibiotics for its treatment contributed to the rapid emergence of antibiotic-resistant bacteria, particularly penicillin-resistant *S pneumoniae*. Therefore, accurate diagnosis is critical to the appropriate management of otitis media. Diagnosis is based on recognition of the characteristic clinical context and physical findings on pneumatic otoscopic examination.

In the classic case of AOM, a young child with a history of a recent upper respiratory tract infection suddenly develops the acute onset of a new fever and ear discomfort. In children old enough to localize pain, the affected ear is often obvious. However, in younger children, discomfort may be more generalized with tugging, rubbing, or holding the ear, and they may exhibit unexplained or excessive crying, irritability, decreased appetite, or changes in their sleep or behavior pattern. Examination may reveal other signs of upper respiratory infection such as rhinorrhea, cough, or conjunctival injection.

The diagnosis of AOM is confirmed using pneumatic otoscopy. To perform this technique, the child must either cooperate or be restrained in a comfortable position that allows the examiner to manipulate the pinna and insert the otoscope into the external auditory canal without difficulty. Cleansing the external auditory canal must be accomplished to free it of obstructions so as to visualize the tympanic membrane;

cerumen or foreign bodies should be removed using a cerumen spoon or gentle irrigation with warm water or suction. The largest speculum that will fit into the external auditory canal at a depth of 1/3-inch to 1/2-inch should be attached to the pneumatic otoscope. This tool permits visualization of the largest possible area with a light source with adequate brightness and ensures a relatively airtight seal for effective insufflation.

Medical school and postgraduate training programs should provide continued education and clinical reinforcement with these techniques for appropriate use of pneumatic otoscopy. The use of training tools and educational resources, combined with Web-based images and video-otoscopes, is invaluable in the evaluation of the middle ear, the diagnosis of AOM, and the distinction between AOM and OME.

Acute otitis media is present when distortion (usually bulging) of the tympanic membrane is noted on direct visualization and when restricted movement of the tympanic membrane, indicative of fluid in the middle ear, is noted with gentle insufflation and exsufflation of air using a squeeze bulb attached to the otoscope. In addition, an air-fluid level behind the tympanic membrane may also be visualized. However, erythema of the tympanic membrane alone is not sufficient to make the diagnosis of otitis media and may be the incidental result of fever or crying. In some cases of AOM, the tympanic membrane may in fact be retracted rather than bulging.

Occasionally, a child with AOM may experience spontaneous rupture of the tympanic membrane, which subsequently leads to marked improvement in ear pain and the presence of otorrhea on examination.

OME may also be an incidental finding on physical examination and is characterized by decreased mobility of the tympanic membrane without the signs of acute inflammation seen in AOM.

In AOM, some experts advocate for making a specific bacteriologic diagnosis by obtaining middle-ear fluid for both culture and sensitivities using the technique of tympanocentesis or carbon dioxide laser-assisted myringotomy. These techniques are often not necessary for the routine diagnosis of AOM but are useful in specific clinical situations in which identification of an organism to guide therapeutic decisions is a high priority. These various situations may include episodes of AOM that do not respond to empirical antibiotic therapy, the child who experiences frequent recurrences of AOM despite what is thought to be appropriate therapy, and the child who is both young and particularly toxic in appearance.

Cultures of other areas of the upper respiratory tract are also useful for research purposes but do not assist in the management of these individual episodes of AOM. Organisms recovered from tympanocentesis or laser-assisted myringotomy specimens are usually also recovered from the nasopharynx, but the presence of an organism on solely a nasopharyngeal culture does not prove that it is present in the middle-ear fluid.

Tympanometry is a technique for documenting tympanic membrane compliance. It can be used to document objectively the presence of fluid in the

middle-ear space but does not add to the information obtained on carefully performed pneumatic otoscopy. Tympanometry measurements can be useful to monitor the course of an episode of OME over time.

## MANAGEMENT OF ACUTE OTITIS MEDIA

Whether an episode of AOM should be treated with antibiotics is a matter of ongoing discussion. The 2013 AAP and AAFP practice guidelines now delineate very specific criteria for which children should receive initial antibiotic therapy and which children should receive initial observation. Recent published studies provide substantial new research on initial management of AOM. The indications on whether to provide initial antibiotic therapy or the safety of observation or delayed antibiotic therapy are also included. Again, these guidelines on initial management assume the physician made an accurate diagnosis of AOM, which, of course, is of paramount importance.

Some of the acute symptoms of AOM, such as fever and ear pain, may resolve more quickly with antibiotic therapy. Early empirical antibiotic therapy may also obviate the need for follow-up office visits to evaluate the patient with otitis media who is not responding to expectant management. However, most episodes of AOM resolve spontaneously. Middle-ear effusions may persist despite effective antibiotic therapy, and rare suppurative complications are generally easily treated with antibiotics and surgical techniques. High-dose amoxicillin is the recommended first-line treatment for most children with AOM. It is used because it is inexpensive, safe, has an acceptable taste, and covers a narrow antimicrobial spectrum. In children with persistent, severe symptoms of AOM and unimproved otologic findings after 48 to 72 hours of amoxicillin therapy, a change to amoxicillin-clavulanate may be indicated. Amoxicillin-clavulanate is also indicated when concurrent purulent conjunctivitis is present. The modest benefits of antibiotic therapy also must be weighed against the negative effect of widespread antibiotic use and its effect on producing antibiotic-resistant species of organisms such as *S pneumoniae*. In some areas of the United States, up to 40% of strains of this organism are resistant to penicillin. Even though the use of PCV7 decreased the amount of antibiotic resistance seen by about 29%, there has been an emergence of a multidrug-resistant 19A strain of pneumococcus that may also cause otitis media. Still, *H influenzae* isolates are susceptible to amoxicillin in 58% to 82% of cases. This represents a significant decrease in  $\beta$ -lactamase-producing *H influenzae* compared with the 2004 AOM guideline.

Although optimal duration of AOM therapy is uncertain, for children younger than 2 years of age and those with severe symptoms, a standard 10-day course is recommended. However, for children between 2 and 5 years of age and with mild or moderate AOM, a 7-day course can be equally as effective. Finally, for children 6 years of age and older with mild to moderate symptoms, a 5- to 7-day course is sufficient.

The new 2013 AOM guidelines stress that the physician should do the following:

1. Prescribe antibiotic therapy for AOM (bilateral or unilateral) in children 6 months and older with severe signs or symptoms (ie, moderate or severe otalgia, otalgia for at least 48 hours, or temperature  $\geq 102.2^{\circ}\text{F}$  [ $\geq 39^{\circ}\text{C}$ ]).
2. Prescribe antibiotic therapy for bilateral AOM in children younger than 24 months without severe signs or symptoms (ie, mild otalgia for at least 48 hours, temperature  $< 102.2^{\circ}\text{F}$  [ $< 39^{\circ}\text{C}$ ]).
3. Either prescribe antibiotic therapy or offer observation with close follow-up based on joint decision making with the parent(s)/caregiver for unilateral AOM in children 6 to 23 months of age without severe signs or symptoms (ie, mild otalgia for at least 48 hours, temperature  $< 102.2^{\circ}\text{F}$  [ $< 39^{\circ}\text{C}$ ]). When observation is used, a mechanism must be in place to ensure follow-up and begin antibiotic therapy if the child worsens or fails to improve within 48 to 72 hours of onset of symptoms.
4. Either prescribe antibiotic therapy or offer observation with close follow-up based on joint decision making with the parent(s)/caregiver for AOM (bilateral or unilateral) in children 24 months or older without severe signs or symptoms (ie, mild otalgia for at least 48 hours, temperature  $< 102.2^{\circ}\text{F}$  [ $< 39^{\circ}\text{C}$ ]). When observation is used, a mechanism must be in place to ensure follow-up and begin antibiotic therapy if the child worsens or fails to improve within 48 to 72 hours of onset of symptoms.

Although there is no proven benefit for the use of antihistamine or decongestant preparations, steroids, acetaminophen, and nonsteroidal anti-inflammatory medications are effective analgesics for mild to moderate pain in the treatment of AOM. Also, topical agents such as Auralgan (antipyrine, benzocaine, and glycerin dehydrated) otic solution can provide additional brief benefit over acetaminophen in children older than 5 years of age.

When initial observation of AOM is warranted based on the above guidelines, it is essential to have an appropriate management strategy consisting of early analgesics, communication, and education about the self-limited nature of AOM in children 2 years and older and, of course, the option of a delayed antibiotic because of potential adverse effects, including diarrhea and diaper dermatitis. A mechanism must be in place to ensure follow-up and begin an antibiotic if the child fails observation.

## FOLLOW-UP AFTER ACUTE OTITIS MEDIA TREATMENT

Most children who respond satisfactorily to treatment of an episode of AOM do not require specific follow-up. As long as a child is asymptomatic, the main reason for follow-up is to document resolution of a middle-ear effusion that may contribute to conductive hearing loss. However, observation for initial management of AOM does not increase suppurative complications if follow-up is provided and delayed antibiotics are then begun for persistent or worsening symptoms. Withholding antibiotics to those who require them, as

detailed in the guidelines, would in fact increase the risk for suppurative complications. After 2 weeks of antibiotic therapy, 60% to 70% of children can have an effusion, whereas after 4 weeks, the percentage decreases to 40%, followed by 10% to 25% after 3 months of appropriate antibiotic therapy. Therefore, follow-up for the otherwise healthy and asymptomatic child should be scheduled no sooner than 6 weeks after diagnosis, if at all. An effusion that persists at 6 weeks does not warrant specific intervention other than perhaps checking for resolution again in 6 more weeks. Further management of an effusion that persists beyond this point is described in the treatment of OME.

In various systematic reviews before 2011 and a meta-analysis, there was a 6% to 14% increase in clinical improvement after antibiotic use, whereas other randomized clinical studies using stringent diagnostic criteria showed a clinical improvement rate between 26% and 35% compared with placebo. A clinically significant benefit of immediate antibiotic therapy is observed for bilateral AOM, *S pneumoniae* infection, or AOM associated with otorrhea. Still, clinicians should reassess the child within 48 to 72 hours to determine whether a change in therapy is needed if the parent(s)/caregiver reports that the child's symptoms are worse or failed to respond to the initial antibiotic treatment.

## MANAGEMENT OF OTITIS MEDIA WITH EFFUSION

Accurate diagnosis of OME is essential before being presented with a different therapeutic challenge than AOM. The goal of therapy for this disorder is to limit any potential long-term detrimental effects on speech and language development that may be caused by conductive hearing loss associated with the presence of a chronic middle-ear effusion. Weak associations have been found between OME and abnormal speech and language development in children younger than 4 years and problems with attention and expressive language delay in older children. However, these associations may be the result of environmental influences that predispose the child to both OME and developmental delays. However, the effects of treating OME on these outcomes, are not well established.

Medical therapies for OME produced largely unsatisfactory results. Although very limited scientific evidence exists, a few experts think that empirical antibiotic therapy either early in the course of OME or later, when the effusion persists for 3 months or more, may hasten resolution of the effusion. Most experts strongly discourage this practice, given the increasing rates of antibacterial resistance being seen. No role exists for steroid medications, antihistamine or decongestant preparations, or tonsillectomy or adenoidectomy in the management of OME. The most effective therapy for OME is the surgical insertion of tympanostomy tubes, which evacuates a middle-ear effusion and restores near-normal hearing, but the effect of this procedure on long-term speech and language outcomes is unclear. A newer technique, laser-assisted myringotomy, may soon replace tympanostomy tube placement for the treatment of OME.

When OME is documented in a child, subsequent follow-up at 3 months is reasonable, assuming acute symptoms did not intervene. If, at 3 months, middle-ear effusions persist and are bilateral, then referral for audiologic testing is indicated. If hearing is normal, then further observation to allow spontaneous resolution is appropriate. If a conductive hearing loss at a threshold of 20 dB or greater is documented at the 3-month follow-up, then consideration should be given to either tympanostomy tube placement or laser-assisted myringotomy to drain the effusions and restore hearing. However, the use of these procedures for OME in otherwise-healthy children with normal hearing is not recommended.

Adenoidectomy is used to manage patients with OME and may be effective in a select group of children. Chronically infected adenoids are thought to serve as a reservoir of pathogenic organisms that leads to tubal edema and malfunction, which may clinically produce persistent OME. The removal of enlarged adenoids has improved effusion resolution. In the otolaryngology literature, adenoidectomy and myringotomy plus ventilation tube insertion is recommended therapy for children with severe ear disease and those undergoing replacement of a second set of ventilation tubes.

## MANAGEMENT OF RECURRENT OTITIS MEDIA

The occurrence of 3 or more episodes of AOM within 6 months or 4 episodes within a year with 1 episode in the preceding 6 months satisfies many experts' definition of recurrent or chronic otitis media. The therapy of recurrent otitis media is also controversial. Past studies showed that long-term administration of prophylactic antibiotics can reduce the incidence of subsequent episodes of AOM in these children; however, the effect is modest at best. Even long-term, low-dose antibiotic use (antibiotic prophylaxis) prevents 1.5 episodes of AOM per year. However, an estimated 5 children would need to be treated for 1 year to prevent 1 episode of otitis media, specifically in children with 6 or more episodes of AOM in the preceding year. Therefore, according to the 2013 AOM guidelines, the use of prophylactic antibiotics is currently not recommended for management of recurrent otitis media. Controlling environmental risk factors such as exposure to tobacco smoke and attendance at large child care centers is a more desirable approach to this problem.

Tympanostomy tube placement or laser-assisted myringotomy should be considered in the management of recurrent otitis media. This approach may be justified when recurrent AOM complicates OME and is accompanied by hearing loss. However, frequent episodes of AOM (without OME) that respond to appropriate antibiotic therapy are not an indication for these procedures. Although AOM does tend to occur less frequently in children who have tympanostomy tubes, this approach is a surgical procedure requiring anesthesia, and the tubes may not remain in place for a sufficient duration to have a measurable effect on the health of a child. Recent literature does suggest that insertion of tympanostomy tubes or



long-term treatment with antibiotics seems to prevent 1 attack of AOM or to keep 1 out of 3 children from developing AOM in the ensuing 6 months.

Use of a conjugated vaccine against *S pneumoniae*, widespread use of the influenza vaccine in healthy children (where many studies show a 30% to 55% efficacy rate in prevention of AOM during the respiratory illness season), and development of an effective vaccine against RSV are all strategies that show promise for preventing future episodes of otitis media.

## CARE OF THE CHILD WITH TYMPANOSTOMY TUBES

Tympanostomy tube placement is the most common surgical procedure performed in children. In fact, all physicians who care for children will encounter tympanostomy tubes in their practice. Examination of the child with tympanostomy tubes should show a patent tube traversing the pars flaccida. Because the tympanic membrane that contains a tympanostomy tube is not intact, its mobility is affected, and pneumatic otoscopy cannot be used as a reliable indicator of the presence of AOM.

Tympanostomy tubes are usually extruded naturally sometime after insertion. Some otolaryngologists recommend actively removing tympanostomy tubes that are in place for 2 or more years to prevent complications such as chronic perforation or tympanosclerosis. If a tympanostomy tube is visualized in the external canal and is no longer seated within the tympanic membrane, then it may be removed carefully with a cerumen spoon under direct visualization.

Occasionally, a granuloma may develop at the site of tympanostomy tube insertion, which can lead to bleeding from the external auditory canal. When this event occurs, these children should be immediately referred to an otolaryngologist for intervention.

Otorrhea is extremely common in children with tympanostomy tubes. Otorrhea associated with other symptoms of upper respiratory infection may indicate the presence of AOM and should be treated accordingly. When otorrhea occurs in isolation, it may respond to topical application of an otic solution containing neomycin, polymyxin B, and hydrocortisone. Otorrhea is no more common in children with tympanostomy tubes who swim or submerge their heads in a bathtub than it is in those who do not engage in these activities. The use of topical antibiotics or earplugs does not reduce the incidence of swimming-related otorrhea. Children with tympanostomy tubes who do not dive to depths of greater than 6 feet nor swim in potentially contaminated water (such as a pond) require no additional special precautions to swim, and the use of earplugs or molds may actually increase drainage from the ears.

## COMPLICATIONS

The most worrisome suppurative complications of otitis media include mastoiditis, intracranial extension of infection, and lateral sinus thrombosis. These complications are rare and occur much less frequently than in the era before routine antibiotic treatment of AOM. Interestingly, the incidence of these complications declined in areas of the world where routine

antibiotic treatment of AOM is less common, suggesting that factors other than early antibiotic treatment may have contributed to this trend.

Recognizing the early signs and symptoms associated with suppurative complications of otitis media is of the utmost importance so that effective medical or surgical therapy can be instituted promptly. These signs and symptoms may include mastoid tenderness, erythema over the mastoid area with swelling and displacement of the pinna, persistent fever associated with chronic tympanic membrane perforation, persistent and severe headache, severe otalgia, retro-orbital pain on the side of the affected ear, vertigo, mental status changes, and nystagmus. Other focal neurologic signs such as facial paralysis, meningismus, and papilledema can also signal intracranial extension of suppurative otitis media.

## OTITIS EXTERNA

Otitis externa (OE) is an inflammatory process that involves the structures of the outer ear, specifically the external auditory canal. It is a common finding in children, especially during the warm-weather months of the year. However, the site of the inflammation is different from otitis media, and the signs and symptoms associated with OE differentiate this condition.

Otitis externa is multifactorial in etiology and often involves an interaction between both host and environmental factors. Some of these factors may include trauma to the external auditory canal, the presence of a foreign body or glandular obstruction, repeated ear cleansing causing loss of the canal's protective coating, prolonged exposure to standing water in the canal that occurs following swimming or bathing (swimmer's ear), high environmental temperature and humidity often leading to increased sweating, and allergy or continued stress. Inflammation may be either focal, at the site of trauma or an infected hair follicle, or diffuse, as is the case with swimmer's ear. When inflammation is focal and associated with infection, the organism most often is *S aureus*, which can ultimately lead to furuncle formation at the site of the inflammation. The most common organism associated with diffuse inflammation is *Pseudomonas aeruginosa*, a hydrophilic bacterial species. Infection is often polymicrobial, and enteric bacilli or fungi are less common causes of OE.

Children with OE complain of ear pain and may also report pain with chewing (owing to the proximity of the temporomandibular joint to the external auditory canal) and difficulty hearing (owing to swelling within the external auditory canal and conductive hearing loss).

Physical examination reveals tenderness with manipulation of the pinna or pressure on the tragus. Insertion of an otoscope into the external auditory canal can also be painful and should be undertaken carefully. Within the canal, focal erythema and swelling may be seen at a site of trauma or folliculitis. If the inflammation is diffuse, then swelling of the entire canal renders a boggy appearance. Edema and the presence of inflammatory debris may subsequently prevent complete visualization of the tympanic membrane, which should seem normal in cases of OE unless coexistent otitis media is also present.



## MANAGEMENT

Diffuse OE usually responds to application of an ototopical antimicrobial-steroid solution containing neomycin, polymyxin B, and hydrocortisone 4 times a day for 7 to 10 days. With the child lying on the unaffected side, 5 drops of this solution are instilled into the affected ear. The child should remain in this position for 5 to 10 minutes after instillation to ensure that the medication comes in contact with the affected skin. Insertion of a cotton wick can help prolong this contact. Moreover, when OE is accompanied by furuncle formation, incision and drainage may be necessary. Otitis externa, on the other hand, can be prevented by keeping the external auditory canal dry and by avoiding vigorous cleaning of the canal that can ultimately lead to superficial trauma.

## MALIGNANT OTITIS EXTERNA

Malignant OE is a complicated form of OE that can develop in immunocompromised children or those with severe malnutrition. It is a necrotizing invasive infection of the external auditory canal, often beginning as minor trauma to the canal, usually caused by *P aeruginosa*, which rapidly spreads to involve the soft tissue, cartilage, nerves, and temporal bone, leading to osteomyelitis of the base of the skull. The pain is severe, and the discharge from the external canal is often copious and malodorous in nature. Children may develop facial paralysis, which is a poor prognostic sign. Diagnosis can often be made by both clinical signs and imaging. Triphasic bone and gallium scintigraphy examinations are often used, but studies suggest that single-photon emission computed tomography images are even more sensitive. Treatment requires administration of intravenous antibiotics and, occasionally, surgical intervention, with close follow-up; erythrocyte sedimentation rate can be used as a good indicator of treatment response. Complications of malignant OE include stenosis of the external auditory canal, auricular cartilage deformity, tympanic membrane necrosis, and sensorineural hearing loss.

## WHEN TO REFER

Patients with recurrent or chronic otitis media or persistent OME (present for at least 3 months) should be referred to an ear, nose, and throat (ENT) specialist for further evaluation. In addition, an infectious diseases consultation should be obtained in children with the following conditions:

- Suppurative complications of otitis media
- Recurrent or chronic episodes of otitis media unresponsive to standard therapy
- Unusual or multiple antibiotic-resistant organisms isolated from middle-ear fluid
- Chronic suppurative otitis media unresponsive to conventional therapy
- Malignant OE

In many of the these conditions mentioned, a multidisciplinary team approach with both ENT and infectious diseases referrals should be used for optimal management of the patient's condition.

## WHEN TO ADMIT

- Children with severe otitis media who are toxic in appearance, children with malignant OE, and children with suppurative complications of otitis media (as briefly described) should be admitted to the hospital. This allows the institution to promptly and effectively administer intravenous antibiotic therapy and further evaluate for possible surgical intervention.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *Get Smart: Know When Antibiotics Work* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/getsmart/community/index.html](http://www.cdc.gov/getsmart/community/index.html))

### Engaging Patient and Family

- *Acute Ear Infections and Your Child* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Ear Infection* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Middle Ear Fluid and Your Child* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

### Medical Decision Support

- *A View Through the Otoscope: Distinguishing Acute Otitis Media From Otitis Media With Effusion* (video), American Academy of Pediatrics ([www2.aap.org/sections/infectdis/video.cfm](http://www2.aap.org/sections/infectdis/video.cfm))

## AAP POLICY

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## Chapter 306

# PANCREATITIS

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## FOUNDATION

### Definition

Pancreatitis in children is a disorder characterized by inflammation of the pancreas in the clinical setting of epigastric abdominal pain. An elevation of pancreatic enzymes (amylase and lipase) in the serum or urine is common. Pancreatitis in children and adolescents is often divided into 2 broad categories: acute and chronic. Acute pancreatitis is a reversible process with complete resolution of the inflammatory reaction and return of normal pancreatic endocrine and exocrine function. Chronic pancreatitis may ultimately result in irreversible changes in glandular histopathology (fibrosis) and pancreatic dysfunction. The incidence of acute pancreatitis is much higher than chronic pancreatitis. The most prevalent causes of acute pancreatitis in children are idiopathic, blunt abdominal injury, pancreaticobiliary disorders, multisystem disease, infection, autoimmune disease, and drug toxicity. Chronic pancreatitis, characterized by a more prolonged and recurrent course, occurs in about 9% of children who present with acute pancreatitis and is often hereditary or results from congenital anomalies of the pancreatic gland or biliary ductal system.

Pancreatitis can also be categorized according to its histopathologic findings. Edematous changes often correlate with mild disease, whereas evidence of hemorrhagic or necrotic changes signifies a more severe process with increased morbidity and mortality or irreversible gland dysfunction. A diagnosis of hemorrhagic or necrotic pancreatitis is an appreciated end product of the inflammatory process and gland destruction. It is primarily based on direct tissue visualization or radiographic imaging and often does not account for the underlying cause of the pancreatic inflammation. Although the prevalence of pancreatitis in children seems to be increasing, much of the literature concerning pancreatic disease remains concentrated in the adult and surgical populations.

### Epidemiology

Although once considered a relatively uncommon diagnosis in children, the prevalence of pediatric pancreatitis has steadily risen over the past several years and now approaches that seen in adults.

Currently, the best estimates suggest that there are 3.6 to 13.2 pediatric cases per 100,000 individuals per year.

Acute pancreatitis seems to account for much of the increase. The diagnosis of idiopathic pancreatitis has risen sharply compared with other known causes of acute pancreatitis. The prevalence of chronic pancreatitis has remained relatively constant, but pancreaticobiliary anomalies are now recognized as the most common cause of recurrent pancreatitis in children. Other causes such as hereditary pancreatitis are recognized more often as well. Factors likely contributing

to the increased prevalence include better physician awareness, increased disease, enhanced imaging techniques, and alterations in referral patterns. Additionally, survival rates for children with complicated systemic diseases have increased, and this population may be at increased risk for developing pancreatitis secondary to ischemic or anoxic injury or underlying inflammatory processes. Despite this increasing prevalence, pancreatitis in children continues to be underdiagnosed. Many children with chronic pancreatitis have been symptomatic for years before a firm diagnosis is made. Thus, the pediatrician faced with a patient who has epigastric abdominal pain should harbor a high index of suspicion for pancreatitis.

### Etiology

Causes of pancreatitis in children differ dramatically from causes in adults. Alcohol and gallstone disease are the most common etiologies in adults, but they are rare causes of pancreatitis in children. Although 16 causes were reported in 1965, up to 80 etiologic considerations have been described in the subsequent years (see Box 306-1). Idiopathic and traumatic causes are the most common, followed by structural and multisystemic causes of pancreatitis. These account for nearly two-thirds of all cases. In most children, pancreatitis is a single event without recurrence. However, in some subpopulations, such as children with cystic fibrosis, those with hereditary pancreatitis, and those with pancreatitis secondary to congenital structural malformations, the pattern of inflammation often develops into one of chronicity.

### Risk Factors

Trauma, structural abnormalities, and multisystemic disease are the most common causes of pancreatic inflammation in children. It is important to determine the cause of pancreatitis so that appropriate preventive, diagnostic, and therapeutic measures can be instituted. Advances in the fields of genetics and DNA sequencing have allowed investigators the ability to identify at-risk populations of children who, because of genetic mutations and variation, are at increased risk for the development of hereditary pancreatitis. Although cystic fibrosis and the *CFTR* mutation are recognized as the most common cause, other identified genetic mutations that have been associated with the development of chronic pancreatitis in children include the *SPINK1* mutation (also known as *PSTI*), mutations in the trypsinogen gene (R122H, R122C, and N29I accounting for most cases), and the *CaSR* mutation. Increasingly, evidence suggests that the likelihood of developing pancreatitis is because of a combination of environmental and genetic factors. Identifying those children who may be more genetically susceptible to developing pancreatitis may assist pediatricians in counseling to avoid known precipitating factors such as alcohol, tobacco, emotional stress, and fatty foods.

The onset of acute pancreatitis is associated with certain medications (most commonly, valproic acid), systemic infections (bacterial and viral), and hypertriglyceridemia. Of particular interest, in view of the growing obesity epidemic, is the association between elevated triglyceride levels and the development of acute pancreatitis. Marked elevations in triglyceride

**BOX 306-1 Conditions Associated With Acute and Chronic Pancreatitis in Childhood****INFECTIONS**

- *Ascaris lumbricoides* (duct obstruction)
- *Campylobacter fetus*
- *Clonorchis sinensis* (duct obstruction)
- Coxsackie B virus
- Cytomegalovirus
- Echovirus
- Enterovirus
- Epstein-Barr virus
- *Escherichia coli*-verotoxinproducing
- Hepatitis A and B
- Human immunodeficiency virus
- Influenza A and B
- Legionnaire disease
- Leptospirosis
- Malaria
- Measles
- Mumps
- *Mycoplasma*
- Rubella
- Rubeola
- Typhoid fever
- Varicella
- *Yersinia*

**TRAUMA**

- Abdominal radiotherapy
- Accidental blunt injury
- Burns
- Child abuse
- Endoscopic retrograde cholangiopancreatography or other ductal imaging using contrast
- Surgical trauma
- Total body cast

**ANATOMIC**

- Absence or anomalous insertion of the common bile duct or pancreatic duct
- Ampullary disease: diverticulum, stenosis
- Annular pancreas
- Anomalous choledochopancreaticoductal junction
- Aplasia of the pancreas
- Biliary tract malformations
- Choledochal cyst
- Choledochoceles
- Cholelithiasis
- Duodenal obstruction (diverticulum, hematoma, tumor, stricture)
- Duodenal ulcer-perforated
- Duplication cyst (duodenum, gastropancreatic, common bile duct)
- Dysplasia of the pancreas

- Gastric trichobezoar
- Heterotopic pancreas
- Hypoplasia of the pancreas
- Pancreas divisum
- Pancreatic pseudocyst
- Sclerosing cholangitis
- Sphincter of Oddi dysfunction
- Tumors of the pancreas

**IDIOPATHIC**

- Up to 25% of cases

**SYSTEMIC/METABOLIC/HEREDITARY**

- Alpha-1-antitrypsin deficiency
- Anorexia nervosa
- Autoimmune diseases
- Brain tumor
- Bulimia
- Collagen vascular diseases
- Congenital partial lipodystrophy
- Crohn disease
- Cystic fibrosis
- Dermatomyositis
- Diabetes mellitus (ketoacidosis)
- Glycogen storage disease types Ia, Ib
- Head trauma
- Hemochromatosis
- Hemolytic-uremic syndrome
- Henoch-Schönlein purpura
- Hereditary pancreatitis
- Hyperalimentation
- Hypercalcemia
- Hyperlipidemia types I, IV, and V
- Hyperparathyroidism
- Hypertriglyceridemia
- Hypothermia
- Inborn errors of metabolism (organic acidemias, cytochrome c oxidase deficiency)
- Juvenile tropical pancreatitis
- Kawasaki disease
- Malnutrition with or without refeeding
- Periarteritis nodosa
- Peritonitis
- Renal failure with uremia
- Reye syndrome
- Sarcoidosis
- Septic shock
- Systemic lupus erythematosus
- Transplantation (bone marrow, heart, kidney, liver, pancreas)
- Ulcerative colitis
- Wilson disease

**BOX 306-2 Conditions Associated With Elevated Serum Amylase****FROM PANCREATIC AMYLASE FRACTION**

- Aortic aneurysm—abdominal
- Appendicitis
- Biliary duct obstruction
- Biliary tract disease
- Choledocholithiasis
- Endoscopic retrograde cholangiopancreatography
- Intestinal infarction, obstruction, or perforation
- Pancreatic duct obstruction
- Pancreatic tumors
- Pancreatitis—acute, chronic
- Perforated peptic ulcer
- Peritonitis
- Pseudocyst

**FROM SALIVARY AMYLASE FRACTION**

- Anorexia nervosa
- Bulimia
- Infection (mumps)
- Lung cancer
- Ovarian tumor/cyst
- Parotitis

- Pneumonia
- Prostate tumors
- Salivary duct obstruction
- Salpingitis
- Trauma

**BOTH (OR UNKNOWN)**

- Alcoholism
- Burns
- Cardiopulmonary bypass
- Cirrhosis
- Cystic fibrosis
- Diabetic ketoacidosis
- Drugs
- Head trauma
- Hepatitis
- Heroin addiction
- Macroamylasemia
- Opiates
- Renal insufficiency
- Renal transplantation
- Ruptured ectopic pregnancy

levels (typically  $>1,000$  mg/dL) seem to be linked to development of acute pancreatitis, and although the mechanism underlying the relationship is ill defined, hypertriglyceridemia occurs in 12% to 38% of adult pancreatitis cases. Although there is insufficient literature describing the relationship between triglyceride elevations and pancreatitis in children, pediatricians should be aware of known associations present in the adult population as they increasingly manage historically adult illnesses now present in children.

**DIAGNOSIS****Signs and Symptoms**

Despite expanding etiologies and increased physician awareness, initial presentation of pancreatitis has changed very little since it was first recognized decades ago. Almost all patients diagnosed with pancreatitis present with upper abdominal pain and tenderness at the onset. The abdominal pain is often mid-epigastric in location or located to either the left or right upper quadrants, with the classic radiation to the back seen in some patients. Concomitant symptoms include nausea, vomiting, low-grade fever, and worsening of pain with eating. Additionally, increased agitation and relief of pain with the child in the antalgic position with hips and knees flexed, sitting in the upright position, or lying on the side can be seen. The age and expressivity level of the child, as with many other diseases, often complicate the initial presentation of pancreatitis, especially in younger children. Many infants and toddlers cannot effectively communicate or quantify the subjective feelings of nausea and abdominal pain. Complicating the clinical picture of a young child with pancreatitis is the finding that many younger children present with a more atypical picture and may

not have the classic abdominal pain, tenderness, or nausea seen in older children and adults. In such cases, a high index of suspicion is required to uncover the diagnosis, especially when there is a history of abdominal trauma, accidental or otherwise.

In cases of severe pancreatitis, symptoms can be particularly impressive. Elevated fevers, signs of shock, jaundice, and pleural effusions can occur. Hemorrhagic or necrotic pancreatitis may present in the setting of bluish discoloration around the umbilicus (Cullen sign) or the flanks (Turner sign). Although rare, hemorrhagic or necrotic pancreatitis often predicts a more severe clinical course, with multisystem inflammatory responses as well as multiorgan dysfunction.

**Differential Diagnosis**

The differential diagnosis for pancreatitis is often quite broad because many times the nonspecific symptoms of abdominal pain, nausea, and vomiting are the only presenting complaints. The diagnosis of pancreatitis is often made only after more common causes of the presenting symptoms have been considered, such as acute gastroenteritis, appendicitis, mesenteric adenitis, and urinary tract infections. However, in the setting of severe pancreatitis with dramatic clinical presentations, it is imperative that the differential diagnoses be expanded to include other etiologies such as perforated viscus, acute peritonitis, biliary tract disease, and intestinal obstruction.

Additionally, laboratory data are often integral in the diagnosis of pancreatitis in children, particularly when elevations in the pancreatic enzymes, amylase and lipase, are appreciated in the serum or urine. Importantly, a multitude of other disease processes can lead to elevations in the pancreatic enzymes



**Table 306-1** Common Laboratory Values in Acute Versus Chronic Pancreatitis

	ACUTE PANCREATITIS	CHRONIC PANCREATITIS
Complete blood count	Leukocytosis with bandemia hemoconcentration	Usually normal
Renal (glucose)	Hyperglycemia, hypocalcemia	May have elevated glucose
Liver function	Elevations in ALT, AST, alkaline phosphatase, total bilirubin	Elevated in patients with concomitant liver disease or bile obstruction
Amylase/lipase	Elevated (generally use 3–6 times the upper limit of normal)	Normal or slight elevation

(particularly amylase), and pediatrician awareness is critical to correctly diagnosing and appropriately directing treatment (Box 306-2).

### Diagnostic Approach

A thorough history and physical examination are crucial to the initial management of a child suspected of having pancreatitis and will help direct additional laboratory and imaging studies. Family history is also important because hereditary pancreatitis is often transmitted as an autosomal dominant trait with incomplete penetrance. However, given the nonspecific qualities of the presentation (abdominal pain, nausea, emesis), laboratory data and radiologic studies are often an integral part of the diagnostic approach.

### Laboratory Findings

Results of laboratory evaluation can greatly assist the pediatrician in the diagnoses of pancreatitis. A complete blood count with differential, renal panel with glucose, liver function studies, and pancreatic enzymes (amylase and lipase) are often obtained in the initial investigation (see Table 306-1). Amylase, an enzyme that breaks down starch to sugar, is the test used most often to confirm acute pancreatitis despite its relatively low sensitivity and specificity (75%–92% and 20%–60%, respectively). Amylase levels reaching 3 times the upper limit of normal are often used as diagnostic cutoffs for pancreatitis. Serum activity begins to increase 2 to 12 hours after pancreatic injury and peaks at 12 to 72 hours. Hyperamylasemia is not diagnostic of pancreatitis and may be secondary to various disease processes in the salivary gland, intraabdominal pathology, or systemic disease. In postmenarchal females, it may herald pregnancy. Laboratories now can separate amylase isoenzymes into pancreatic and salivary fractions so as to assist in differentiating the etiology of the elevated amylase level. However, fractionation is a specialized test, and long turn-around time for results may preclude its usefulness in the acute setting.

In contrast to amylase, serum lipase is almost exclusively derived from the pancreas. It is an enzyme that breaks down dietary fats and converts triglycerides to monoglycerides and free fatty acids and should be obtained in addition to amylase when pancreatitis is suspected. During the course of acute pancreatitis, serum lipase rises by 4 to 8 hours, peaks at 24 to 48 hours, and remains elevated longer than serum amylase.

Despite its high specificity, serum lipase can be elevated in nonpancreatic diseases such as acute cholecystitis, intestinal infarction, perforated peptic ulcer disease, and renal failure.

It is important for the treating pediatrician to be aware that serum levels of these laboratory values are dependent on the chronicity of the inflammatory process and may differ dramatically based on the clinical picture. For example, patients with chronic pancreatitis moving toward glandular insufficiency may experience exacerbations of acute pancreatitis with relatively low serum levels of both amylase and lipase. Indeed, enzymes are often normal even during attacks of pain. Therefore, a normal amylase or lipase level should not exclude the diagnosis in a child with a positive history of pancreatitis.

The gold standard for establishing a diagnosis of chronic pancreatitis is glandular insufficiency. Assessing this involves invasive and direct testing of pancreatic function. Although there are noninvasive tests to assess pancreatic function (decreased serum pancreatic enzymes and fecal assays for fat and pancreatic enzymes), the negative predictive value often limits their interpretation. Additionally, false-positive results may be obtained in the presence of intestinal overgrowth or other mucosal disease. Therefore, true establishment of pancreatic insufficiency often involves oroduodenal or endoscopic intubation, accurate placement of a duodenal catheter, and complete recovery of all duodenal secretions. The difficulty of such testing usually means that their availability is limited to tertiary centers.

Other laboratory abnormalities that may be present in acute pancreatitis include coagulopathy, glucosuria, hypocalcemia, elevated  $\gamma$ -glutamyl transpeptidase, and hyperbilirubinemia.

Recent literature suggests that certain biochemical markers may be useful in predicting the severity and progression of acute pancreatitis, although, being nonspecific, they are not useful in the initial diagnosis. These markers include C-reactive protein (CRP), interleukin-6 (IL-6), and procalcitonin. CRP remains the most useful. Despite its delayed increase, peaking not earlier than 72 hours after the onset of symptoms, it is accurate and widely available. Also helpful is IL-6, which rises in severe pancreatitis in comparison with mild disease as early as the day of admission to the hospital, with peak concentrations on day 3 after the clinical onset of the disease.

Additional markers requiring further investigation include serum amyloid A, trypsinogen activation peptide (TAP), and polymorphonuclear granulocyte (PMN) elastase. Additionally, immunoglobulin G4 elevations may be more specific for autoimmune pancreatitis. Physician awareness of potential biomarker relationships with particular disease etiology is important when directed treatments (such as steroids for autoimmune disease) depend on the underlying causation mechanisms.

Genetic testing may also be indicated in particular patient populations. The most important clinical clue predicting the presence of hereditary pancreatitis is the presence of disease in other family members. Advances in genetics have allowed identification of multiple genetic mutations associated with hereditary pancreatitis. In general, genetic testing can be considered diagnostic or predictive. Diagnostic tests for hereditary pancreatitis are often obtained to determine genetic causes of a patient's pancreatitis, whereas predictive testing occurs in patients without evidence of disease, but who may have relatives with known pancreatitis or genetic susceptibilities to developing pancreatitis. In general, the clinical indications leading to diagnostic testing validate its use, but the role of predictive testing is more controversial.

### Imaging

Along with laboratory data, imaging plays a crucial role in the diagnosis of acute and chronic pancreatitis in children. The most common radiographic studies currently obtained in the evaluation of a child suspected of pancreatitis are ultrasound and computed tomography (CT) owing to their widespread availability, noninvasiveness, and familiarity to physicians. Because ultrasound exposes a child to dramatically less radiation, it is often the initial imaging modality. Smaller patient size with less fatty tissue, along with prominence of the left hepatic lobe, allows ultrasound of the pancreas in children to be more feasible. Furthermore, advances in ultrasound technology, such as high-resolution imaging, color Doppler, and harmonic imaging, have allowed for improved images and better diagnostic capabilities. Findings on ultrasound consistent with pancreatitis include glandular edema, hyperechogenicity, and pancreatic ductal dilation. Pancreatic ducts with diameters greater than 1.5 mm in children between ages 1 and 6 years, greater than 1.9 mm at ages 7 to 12 years, or greater than 2.2 mm at ages 13 to 18 years are significantly associated with the presence of pancreatic inflammation. Additionally, ultrasound is useful in detecting both etiologies and complications associated with pancreatitis such as gallstones, pseudocysts, and splenic vein thrombosis.

CT scans are often obtained as well in the evaluation of pancreatitis, especially if the ultrasound findings are nondiagnostic. However, CT scans do expose children to significant amounts of radiation. Additionally, animal models have shown that CT contrast given early in the course of acute pancreatitis may decrease blood flow to already ischemic areas of the pancreas and may worsen necrosis. Although validation studies have yet to be done in children, physicians should well consider whether the information obtained via the scan is likely to influence the medical management.

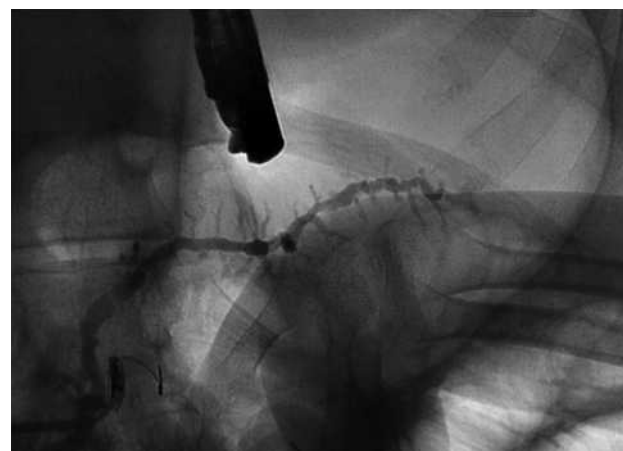
Another imaging modality increasingly used to assess a child with pancreatitis is magnetic resonance cholangiopancreatography (MRCP). MRCP can complement endoscopic retrograde cholangiopancreatography (ERCP) (see Diagnostic Procedures) in more complicated pancreatitis for which additional investigation of ductal anatomy may be needed. The advantages of MRCP over ERCP is that it is noninvasive, does not use radiation, is able to visualize the

pancreatic parenchyma, and can visualize pancreatic ducts as small as 1 mm both proximal and distal to any potential obstructive lesion. Additionally, the polypeptide hormone secretin can be given to patients to increase pancreatic duct signal for improved studies. The limitations to MRCP are that results have been shown to vary based on patient body habitus, patient cooperation and ability to remain still (often requiring sedation), and the medical center's experience with this study. Both an antiquated scanner and misinterpretation of information can limit the value of MRCP.

### Diagnostic Procedures

Endoscopic retrograde cholangiopancreatography is a technique that combines the use of endoscopy and fluoroscopy to diagnose and treat certain problems of the biliary or pancreatic ductal systems. Historically, ERCP has been used in the setting of pancreatitis to better understand an individual's anatomy and help visualize the ductal system (Figure 306-1).

Often ERCP is useful in the diagnoses of pancreatic disease associated with anatomic variations (such as pancreas divisum) or when biliary obstruction is suspected. The main advantage of ERCP over other imaging modalities is the ability to treat an anatomic obstruction at the time of procedure. Examples of therapeutic procedures include sphincterotomies, stone removal, and stent placement in either the biliary or pancreatic ductal system. Additionally, ERCP with glandular drainage has been shown to decrease the frequency of episodes of pancreatitis requiring hospitalization in certain populations, such as those with cystic fibrosis. ERCP seems to be an effective and safe procedure in children, with cannulation rates and visualization of the pancreaticobiliary duct anatomy comparable with those achieved in adults. Complications of ERCP are iatrogenically induced pancreatitis, with up to 11% of procedures developing a clinical picture of pancreatitis. Additionally, asymptomatic hyperamylasemia has been seen in up to 70% of patients after



**Figure 306-1** Endoscopic retrograde cholangiopancreatography image representing irregularity and beading of the pancreatic duct associated with chronic pancreatitis.

the procedure. The recent advances in MRCP have prompted the National Institutes of Health state-of-the-science statement to advise “no role [for ERCP] in the diagnosis of acute pancreatitis except when biliary pancreatitis is suspected.” Consequently, MRCP, with its noninvasiveness and lack of radiation, has the potential to supplant ERCP as an initial diagnostic modality, with the latter reserved as an interventional tool.

Although rare, pancreatic biopsies can be obtained, usually in patients with more chronic clinical courses. Such biopsies provide critical information when a diagnosis such as autoimmune pancreatitis is suspected (characteristic dense lymphoplasmacytic infiltration and fibrosis). Research is needed to better assess the benefits of direct tissue evaluation. Potential benefits are a more specific categorization and stage of chronic pancreatitis, ultimately leading to more targeted and directed therapies.

### Classification

Pancreatitis in children is broadly divided into acute and chronic entities whereby acute pancreatitis is a reversible process without long-term sequelae and chronic pancreatitis is a recurrent disease that ultimately results in changes in histology (fibrosis) and glandular dysfunction—both endocrine and exocrine. Future patients may benefit from a more formal classification system, especially those children diagnosed with chronic pancreatitis, for which a more complete understanding of an individual’s degree of pancreatic dysfunction may help develop more targeted therapies.

## MANAGEMENT

### Treatment Approach

In general, treatment of pancreatitis in children does not differ from that of adults. In children with acute pancreatitis, supportive treatment typically dominates early in the clinical course with fluid hydration, pain control, and “gland rest.” Historically, gland rest consisted of making a patient *nil per os* (NPO) with intravenous fluid support, followed by the slow reintroduction of food as the disease course allowed. When foods are tolerated, carbohydrate-rich foods are introduced first because they place less strain on the inflamed pancreas. If *per os* (PO) intake is not tolerated, total parenteral nutrition (TPN) can be initiated by days 3 to 5 of illness. Although discrepancies in the literature persist, it seems as though intravenous lipids included in the TPN are safe and beneficial, as long as triglyceride levels are monitored closely. However, it is widely accepted that enteral nutrition is preferred over parenteral nutrition. Recent studies in adults have assessed jejunal feeds and have shown good tolerance by most patients with uncomplicated disease. Such therapy allows for gut stimulation while preventing gastric and intestinal phases of pancreatic secretion, therefore preserving gland rest. Although certain complications, such as persistent vomiting or ileus, may prevent placement of a feeding tube and tolerance of jejunal feeds, enteral nutrition should be first-line therapy when possible. Regardless of method, it is imperative that patients with a more severe clinical

course receive some form of nutritional support because of the inherently elevated level of stress and hypercatabolism associated with pancreatitis.

Pain control typically constitutes the remainder of the initial therapy. Morphine is often avoided because of its known effects on the sphincter of Oddi, mainly spasm, and the theorized exacerbation of the patients’ abdominal pain. However, recent evidence does not support opioid avoidance and it is often used clinically. Hydromorphone (Dilaudid) and meperidine are commonly used alternatives to opioids. Meperidine has been shown to lower seizure thresholds in susceptible patients and should be used sparingly in such populations.

After supportive therapies have been implemented, the clinical course often directs additional treatment. As previously noted, although most children with pancreatitis follow a relatively predictable clinical course, certain patients do go on to develop severe complications with the development of shock, systemic inflammatory responses, sepsis, and multiorgan dysfunction. Such patients require escalated medical management, often with antibiotics, aggressive fluid management, respiratory support, and monitoring in intensive care units. The ability to predict which children are at risk for developing such severe clinical courses has been elusive. In the adult population, several prognostic systems have been developed and validated to predict clinical severity. The most widely used are the Ranson criteria, Glasgow Coma Scale, modified Glasgow Coma Scale, and Acute Physiology and Chronic Health Evaluation (APACHE) II score. Despite their clinical utility in adults, these prognostic scoring systems have not been validated in children. Loosely based on the Ranson criteria, recent literature has attempted to develop a prognostic scoring system for children. The scoring system was based on parameters obtained at admission and 48 hours after the onset of illness. Criteria assessed at admission included age younger than 7 years, weight less than 23 kg, white blood cell count higher than 18,500, and lactate dehydrogenase (LDH) level greater than 2,000. The 48-hour criteria were trough calcium less than 8.3 mg/dL, trough albumin less than 2.6 mg/dL, fluid sequestration more than 75 mL/kg per 48 hours, and rise in blood urea nitrogen more than 5 mL/dL. As with the Ranson criteria, patients were given 1 point for each criterion met, with scores assessed at admission and at 48 hours of illness. Ultimately, the authors concluded that children who have a score of zero on admission and during the first hours of illness have the lowest probability of developing severe disease and suggested these patients should be admitted to routine ward beds. Children with scores greater than or equal to 3 on admission should be admitted to the intensive care unit (ICU) for intensive monitoring. Children with intermediate scores need admission and close monitoring with a low threshold for transfer to the ICU if scores increased to 3 parameters or more. Clearly, more research is needed to better refine current systems and develop improved prognostic parameters in children to assist pediatricians in predicting which children are at risk for more severe courses of pancreatitis.



Chronic pancreatitis presents additional challenges to the pediatrician. In the adult population, several treatment options have been proposed, including exogenous pancreatic enzyme supplementation and antioxidant use. Patients with chronic pancreatitis often progress to develop pancreatic exocrine insufficiency, and a growing body of literature suggests that appropriate supplementation of exogenous pancreatic enzymes, although not curative, can assist in achieving symptomatic relief, prevent morbidity and mortality, and improve quality of life. Additionally, oxidative stress has been proposed as a mechanism leading to pancreatic gland destruction in chronic pancreatitis. Antioxidant agents such as selenium are decreased in patients with chronic pancreatitis, and additional research will need to focus on the benefits of antioxidant supplementation as a potential treatment option.

Ultimately, the underlying cause is an important piece of the medical investigation. Although immediate treatments are often similarly focused (eg, pain control, fluid management, gland rest), identifying the causal etiology assists in future therapeutic modalities after the stabilization of the presenting symptoms is achieved.

Finally, because pain control is often a cornerstone of management in pancreatitis, it is critical that physicians recognize patients who exhibit drug-seeking tendencies and address any abusive behaviors, or refer to a specialist who may have more experience in dealing with chronic pain.

## ONGOING CARE

### Follow-up

Children presenting with pancreatitis require follow-up in both the primary and specialty care settings. Given the relative rarity of the disease in children, it is imperative that close monitoring occurs after discharge from the hospital. In most cases, discharge criteria will not necessarily include complete resolution of the presenting symptoms or pancreatic enzyme elevations. In such cases, children should be reassessed for a return to baseline function and activity in the outpatient setting. As previously mentioned, pancreatic enzyme elevations may last for days after an acute pancreatitis attack, and although no universal guidelines direct follow-up care, obtaining repeat labs to confirm continued decreases in amylase and lipase levels may reassure families and physicians that the disease is indeed resolving. In some cases, such as those children whose clinical course was more complicated with documented pancreatic fluid collections (pseudocyst), repeat imaging may be indicated to assess for resolution. Because no specific guidelines have been developed to direct follow-up management, type and frequency of imaging as well as testing should be considered in consultation with a pediatric gastroenterologist. Genetic testing is an emerging modality available to pediatricians to further assess the initial etiologic insult as well as predict potential future episodes of pancreatitis. Because most cases of pancreatitis in children are single events, indications for genetic testing should be based on individual patient factors such as recurrent attacks of pancreatitis

or a strong family history. Again, consultation with a specialist may assist the primary pediatrician in discerning what, if any, tests may be indicated.

Children with chronic pancreatitis or extremely severe acute attacks with pancreatic necrosis may require additional monitoring for development of pancreatic endocrine and exocrine insufficiency. In the chronic setting, repeated episodes of inflammation ultimately result in irreversible gland damage, whereas similar damage can be caused by necrotic changes after an acute attack. Evidence of fat malabsorption or insulin insufficiency may be signs of pancreatic gland dysfunction and prompt additional investigations or treatments.

### Complications

Pancreatitis is associated with several known complications, including anatomic changes to the pancreatic tissue, gastrointestinal and metabolic dysfunction, and systemic complications (see Box 306-3).

Pseudocyst development has been recognized as one of the more common complications of pancreatitis in children, with formation occurring in up to 25% of cases, especially those whose underlying etiology is traumatic. With improved imaging, small pseudocysts are increasingly identified. Most resolve spontaneously, but those that persist and develop a mature capsule must be drained either endoscopically, surgically, or percutaneously with radiographic guidance.

Particular concern should be paid to the relationship between those patients with known hereditary pancreatitis and the development of pancreatic carcinoma. Patients with hereditary pancreatitis have a high risk for developing pancreatic cancer up to several decades after the initial onset of the pancreatitis. Hence, patient counseling and concomitant monitoring are crucial for appropriate management.

In the end, physician awareness of appreciated complications is important in the ultimate recognition and treatment of an individual patient's clinical course.

### Prognosis

In most cases, acute pancreatitis in children is a single event with a relatively predictable course and overall benign outcome. However, severe pancreatitis can have detrimental effects with long-term complications. This wide array of clinical progression is evident in the literature, with morbidity rates ranging from 0% to almost 80%, depending on study size and specific populations assessed. As noted above, prognostic scoring systems have been used in adults for some time and have dramatically improved the management of patients presenting with attacks of pancreatitis. Although such a scoring system has yet to gain complete validation in the pediatric population, increased research continues to contribute to the ability to predict which patients have a greater likelihood of developing severe pancreatitis with its associated complications. Such predictive capabilities would greatly improve the overall management of children with pancreatitis.

Children with chronic pancreatitis are a challenging and emerging population for physicians because ultimate prognosis depends on multiple factors,



**BOX 306-3 Complications of Pancreatitis****PANCREATIC**

- Ascites
- Diabetes mellitus
- Exocrine insufficiency
- Necrotizing pancreatitis
- Pancreatic abscess
- Pancreatic carcinoma
- Pancreatic duct strictures
- Pancreatic calculi
- Pancreatic fibrosis
- Pancreatic fistula
- Pancreatic phlegmon
- Pancreatic pseudocyst

**GASTROINTESTINAL/METABOLIC**

- Biliary obstruction
- Bowel infarction
- Gastritis
- Gastrointestinal fistula
- Hemorrhage
- Hepatic vein thrombosis
- Hepatorenal syndrome
- Hyperglycemia
- Hyperkalemia
- Hypertriglyceridemia
- Hypoalbuminemia
- Hypocalcemia

- Ileus
- Jaundice
- Metabolic acidosis
- Peptic ulcer disease
- Portal vein thrombosis
- Varices—splenic vein

**SYSTEMIC**

- Atelectasis
- Adult respiratory distress syndrome
- Disseminated intravascular coagulation
- Electrocardiographic changes
- Encephalopathy
- Fat emboli
- Fat necrosis
- Hypotension
- Mediastinal abscess
- Pericardial effusion
- Pleural effusion
- Pneumonitis
- Psychosis
- Renal failure
- Renal vessel thrombosis
- Respiratory failure
- Sepsis
- Sudden death
- Thrombosis

including underlying cause, early recognition of increased susceptibility, family and patient education and understanding, and avoidance of exacerbating factors that contribute to recurrent attacks.

**Prevention**

Preventing acute pancreatitis in most cases is difficult because the cause is often unknown. After idiopathic causes, traumatic injury is the leading causes of acute pancreatitis in children. In the acute setting, improved childhood safety measures such as booster seats in cars may help prevent cases of acute pancreatitis. However, other common causes, such as systemic infection and structural abnormalities, are more difficult to prevent. It is therefore important for the pediatrician to maintain a broad differential in children so as not to delay appropriate treatment in a child with pancreatitis.

Preventive measures are increasingly important for patients with chronic pancreatitis. Understanding an individual's exacerbating factors is imperative. However, in children and adolescents with known chronic pancreatitis, universal preventive measures such as avoiding fatty foods, stress, alcohol, and tobacco may assist in decreasing future events and slow the irreversible damage of the pancreatic gland.

**WHEN TO ADMIT**

- All children with suspected acute pancreatitis warrant admission with initiation of supportive therapy and monitoring.
- Younger, smaller children with elevated white blood cell counts or LDH may benefit from direct ICU admission and intensive monitoring.
- Children with chronic pancreatitis present additional challenges and should be admitted based on the severity of the clinical symptoms (ie, intractable vomiting, need for intravenous fluids or nutritional support, inability to tolerate PO pain medications).

**WHEN TO REFER**

- Despite increasing prevalence, pancreatitis is still a relatively uncommon diagnosis in children. All patients diagnosed with pancreatitis would likely benefit from an evaluation by a pediatric gastroenterology specialist.
- More severe cases of pancreatitis with an associated hemorrhagic or necrotic component require surgical consultation for therapeutic peritoneal lavage or pancreatic necrosectomy.

- Patients with pancreatitis and intractable pain may benefit from evaluation by a pain specialist with more experience in dealing with chronic pain disorders.
- Patients with recurrent pancreatitis and a positive family history may benefit from a genetic evaluation by a specialist to determine the utility of additional genetic testing.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *What Is a Pediatric Gastroenterologist?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Gastroenterologist.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Gastroenterologist.aspx))

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## Chapter 307

## PAPULOSQUAMOUS DISEASES

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A number of papulosquamous diseases occur in children. The hallmark of these diseases is the presence of scaly, raised lesions that range in size from small papules (1–3 mm in diameter) to large plaques (>10 cm in diameter). The scale can vary from thin desquamation to thick adherence. Seborrheic dermatitis is included in this category of disease but is described in detail in Chapter 326, Seborrheic Dermatitis.

### PSORIASIS

#### Etiology and Epidemiology

Psoriasis is a chronic inflammatory disease whose cause is a complex interplay of genetic and environmental factors. A number of psoriasis susceptibility loci have been mapped, and the HLA-Cw6 allele in particular is highly associated with the disease. Environmental factors such as streptococcal infection, physical stress, and psychologic stress can precipitate the onset of the

disease. A population-based study found that the annual incidence of psoriasis was approximately 40 per 100,000 individuals younger than 18 years.

#### Clinical Features and Diagnosis

Plaque psoriasis is the most common form of psoriasis in children. The classic lesion is a sharply demarcated, erythematous plaque with overlying silvery scale. The plaques are usually symmetric and occur commonly on the elbows and knees, but may also occur on the scalp, ears, gluteal cleft, and umbilicus. Removal of the scale can produce pinpoint bleeding (Auspitz sign), which is characteristic of psoriasis. Inverse psoriasis affects the intertriginous areas such as the axillae and groin (Figure 307-1) and appears as smooth, erythematous patches, usually without any scale. Small, drop-like papules with a silvery scale, called *guttate psoriasis* (Figure 307-2), commonly occur on the trunk and proximal extremities. Though pustular psoriasis (Figure 307-3) is rare in childhood, it can be seen during the first week of life. It can become generalized with hundreds to thousands of pustules occurring in areas of erythema and scaling, but it may remain localized to only the palms and soles, or in the folds of the neck and inguinal creases. Widespread erythema



**Figure 307-1** Plaque psoriasis on lower abdomen and thigh. Inverse psoriasis with lack of scale in the inguinal region.



**Figure 307-2** Guttate psoriasis triggered by group A streptococcal pharyngitis.

and exfoliation characterize erythrodermic psoriasis. Nail changes are helpful in diagnosis and include pitting (tiny pits on the nail surface), oil spots (yellowish-brown spots signifying separation of the nail from the nail bed), onycholysis (distal separation of the nail from the nail bed), and sometimes destruction of the entire nail. Psoriatic plaques in a linear fashion in areas of skin trauma (Koebner phenomenon) can be useful in diagnosis. Streptococcal disease often triggers the guttate form of the disease. Viral infection, sunburn, and drug eruptions also can precipitate the onset of psoriasis. Arthritis may also occur and can precede or follow the development of skin lesions. The most commonly involved joints are the knee and the small joints of the hands and feet. The diagnosis of psoriasis is usually clinical; however, a skin biopsy can be confirmatory.

### Management

Though no cure for psoriasis exists, effective treatment is available to control the disorder. The natural history of psoriasis includes remissions and exacerbations. The use of medium-potency topical corticosteroids with or without topical vitamin D (calcipotriene) can often control the condition. If new lesions develop with this regimen, high- or super-potency topical corticosteroids may be necessary. Coal tar preparations may be effective, but many patients do not like to use them because of cosmetic issues, including staining of clothes and tar odor. Other treatment modalities include UVB phototherapy, methotrexate, and biologic agents such as etanercept (tumor necrosis factor alpha inhibitor) and ustekinumab (interleukin-12 and interleukin-23 antagonist). Etanercept can be effective in the treatment of moderate to severe plaque psoriasis in children and adolescents. A recent study demonstrated that ustekinumab was more effective than etanercept in individuals 18 and older with moderate to severe plaque psoriasis. A phase 3 trial in adolescents aged 12 to 18 recently concluded. Oral retinoids can be effective in the treatment of generalized pustular psoriasis and erythroderma. Systemic corticosteroids should be avoided in the treatment of psoriasis because they can exacerbate the disease and can cause erythroderma following discontinuation.



**Figure 307-3** Pustular psoriasis with areas of erythema and many pustules.

## PITYRIASIS ROSEA

### Etiology and Epidemiology

The cause of pityriasis rosea is unknown. This common disorder usually occurs in children and adolescents, but infants also may be affected.

### Clinical Features and Diagnosis

In some children, pharyngitis, headache, and malaise may precede the appearance of the skin lesions, but this is not a usual occurrence. Classically, a single, oval, erythematous, scaly lesion (herald patch), usually greater than 1 cm in diameter, develops on the trunk, but may be seen anywhere on the body several days to weeks before the appearance of oval plaques with thin scale in a “Christmas tree” pattern orienting along skin cleavage lines (Figure 307-4). Atypical individual lesions can be vesicular, pustular, or purpuric. Mild pruritus may occur with the generalized eruption, which usually resolves within 4 to 8 weeks, but can take up to 6 months. Recurrences are uncommon. The diagnosis is usually clinical, but a skin biopsy can be confirmatory.

### Management

This is a self-limited disorder and most children do not require any treatment. Pruritus can be managed with emollients or oral antihistamines. Sunlight or UVB phototherapy can hasten the resolution of the lesions. In one study, oral erythromycin was effective in the treatment of pityriasis rosea.



**Figure 307-4** Oval, hyperpigmented plaques following skin cleavage lines in pityriasis rosea.





**Figure 307-5** Hyperpigmented, oval scaly, thin plaques in pityriasis lichenoides chronica.

## PITYRIASIS LICHENOIDES

### Etiology and Epidemiology

Though the cause of this uncommon disorder is unknown, 2 forms have been described: the acute form (pityriasis lichenoides et varioliformis acuta [PLEVA]) and the chronic form (pityriasis lichenoides chronica [PLC]). The usual onset is between 5 and 15 years of age.

### Clinical Features and Diagnosis

The characteristic PLEVA lesions are recurrent crops of erythematous papules and papulovesicles 2 to 4 mm in diameter that often become pustular, hemorrhagic, or necrotic. They occur most commonly on the trunk and extremities and usually spare the scalp, face, palms, and soles. Gradual resolution takes place over weeks to months. Postinflammatory hypopigmentation can occur, especially in darker-skinned children. A rare variant of PLEVA is the ulceronecrotic form in which patients have fever and ulceronecrotic plaques. These children can have extensive painful necrosis of the skin with subsequent secondary infection leading to septicemia.

In PLC, the characteristic lesions are reddish-brown, oval, scaly papules and small, thin plaques that usually occur on the trunk and extremities (Figure 307-5). The lesions may persist for months to several years before resolving without scarring. The diagnosis of PLEVA and PLC is sometimes difficult to make clinically and a skin biopsy can be confirmatory.

### Management

The lesions may resolve without treatment; however, emollients, oral antihistamines, and topical corticosteroids may be used to alleviate pruritus. Oral erythromycin or UVB phototherapy seem to hasten resolution of the lesions. Methotrexate and systemic corticosteroids are often used in cases of the febrile ulceronecrotic form.

## PITYRIASIS RUBRA PILARIS

### Etiology and Epidemiology

The cause of pityriasis rubra pilaris, an uncommon disorder, is unknown. Though most cases are sporadic, some may be familial.



**Figure 307-6** Keratoderma of the sole in pityriasis rubra pilaris.

### Clinical Features and Diagnosis

A combination of types of lesions characterizes this disorder and includes scaly, erythematous macules, reddish-orange keratotic papules, and yellow thickening of the palms and soles (keratoderma) (Figure 307-6).

A clinical classification of 5 types has been proposed: type I (classical type with adult onset) 55% of cases, type II (atypical type with adult onset) 5% of cases, type III (classical type with juvenile onset) 10% of cases, type IV (circumscribed type with juvenile onset) 25% of cases, and type V (atypical type with juvenile onset, usually hereditary) 5% of cases. A sixth, HIV-associated type has been proposed, but this is controversial. Types III and IV usually occur before puberty, while type V is usually present at birth or occurs in the first few years of life.

In type III, macules and papules coalesce into patches and plaques that spread from the head to the trunk and extremities over weeks to months. Unaffected skin or “islands of sparing” can be seen scattered within the erythrodermic skin. In type IV, the usual lesions are erythematous plaques on the elbows and knees. Follicular papules, scaly, widespread erythema as well as scleroderma-like bound-down skin of the palms and soles characterize type V. Keratoderma can occur in each of the types. A skin biopsy is helpful in diagnosis.

### Management

Spontaneous resolution of types III and IV may occur, but type V continues throughout life. With mild forms





**Figure 307-7** Shiny, flat-topped, violaceous, polygonal papules and plaques in lichen planus.

of types III and IV, emollients may relieve skin dryness, while keratolytics (lactic, salicylic, or glycolic acid-based products) may soften and decrease thickening of the skin.

Topical corticosteroids can help to relieve pruritus if present, and topical retinoids can help to smooth the papules, although this is not curative. Complete clearance of type IV PRP with topical tazarotene (retinoid) was recently reported. Oral retinoids are often used for severe type III and type V. A recent report demonstrated near-complete clearance with etanercept in a 16-year-old female with type V.

## LICHEN PLANUS

### Etiology and Epidemiology

Lichen planus is a disorder of unknown cause and is uncommon in children. Most cases are sporadic, although it can occur in families. The age of onset ranges from 1 year through adolescence.

### Clinical Features and Diagnosis

The characteristic lesions are shiny, flat-topped, violaceous, polygonal papules and plaques that vary in diameter from 2 to 15 mm (Figure 307-7). They usually occur in a symmetric fashion on the extremities, but they also may be seen on the scalp, face, genitalia, palms, and soles. Lesions on the buccal mucosa and tongue are less common, but appear as white, pinpoint papules in a lacy pattern (Wickham striae). Rare variations of lichen planus include bullous, linear, hypertrophic, and annular types. Nail involvement is rare in children, but may consist of longitudinal ridging or severe dystrophy. Lesions also may develop in a linear array at the site of skin trauma (Koebner phenomenon). Pruritus can be severe. The diagnosis is clinical; however, a skin biopsy can be obtained if the diagnosis is uncertain.

### Management

Treatment consists of medium- to high-potency topical corticosteroids, which help in the control of the pruritus and resolution of the lesions. Oral antihistamines also are effective in the relief of pruritus. Topical



**Figure 307-8** White, flat-topped papules in lichen nitidus.

corticosteroids in gel or solution form can be effective in relieving pain in oral erosions and ulcerations. Remission often occurs within 6 months. Some cases can take up to 2 years for resolution while oral involvement may take as long as 5 years to resolve. Systemic corticosteroids are useful in children with extensive or unresponsive lesions.

## LICHEN NITIDUS

### Etiology and Epidemiology

Lichen nitidus is a self-limited disorder of unknown cause that occurs primarily in preschool-aged and school-aged children. It is almost always sporadic, but several familial cases have been described.

### Clinical Features and Diagnosis

The characteristic lesions are flesh-colored to white, flat-topped papules 1 to 2 mm in diameter that can occur anywhere on the body, but are usually seen in clusters on the trunk (Figure 307-8). Pruritus may or may not occur. A useful diagnostic finding is the presence of a linear group of papules within an area of skin trauma (Koebner phenomenon). A skin biopsy is diagnostic but rarely necessary.

### Management

The lesions resolve spontaneously over months to years. Because many children are asymptomatic and the lesions resolve spontaneously, no treatment is necessary. Emollients, oral antihistamines, and topical corticosteroids may relieve pruritus.

## LICHEN STRIATUS

The characteristic lesions of lichen striatus are flesh-colored or erythematous papules 1 to 2 mm in diameter which can coalesce into a plaque. They occur most commonly on a single extremity in a linear distribution, following the lines of Blaschko (Figure 307-9), but also may be seen on the abdomen and face. If a lesion extends to a finger or toe, nail dystrophy may occur. The diagnosis is clinical and a skin



**Figure 307-9** Flesh-colored papules in a linear distribution in lichen striatus.

biopsy is rarely necessary. Because the lesions resolve spontaneously, they do not require treatment. Resolution may take months to years, but recurrences are rare.

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## Chapter 308

## PARASITIC INFECTIONS

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### PROTOZOAL INFECTIONS

#### Amebiasis (*Entamoeba histolytica*)

##### Epidemiology

Amebiasis is caused by the protozoan *Entamoeba histolytica*, which also causes amebic liver abscesses and other rare extraintestinal diseases. Worldwide, approximately 40 to 50 million people develop colitis or extraintestinal disease annually, leading to 40,000 deaths. Although amebiasis is a worldwide disease, developing countries have significantly higher prevalence rates. The seroprevalance is as high as 50% in

certain developing areas. This is related to poor hygiene, inadequate water sanitation, and the use of human waste to fertilize crops.

In developed countries such as the United States, amebiasis is mainly seen in migrants from and travelers to endemic countries. Infection with pathogenic *E histolytica* is not a common cause of travelers' diarrhea. Gastrointestinal infection is uncommon in travelers who have spent less than 1 month in endemic areas.

Three species of entamoeba are found: the pathogenic *E histolytica* and 2 nonpathogenic entamoebaes, *Entamoeba dispar* and *Entamoeba moshkovskii*. Therefore, finding the cysts does not indicate invasive disease.

##### Life Cycle and Pathogenesis

*Entamoeba histolytica* has 2 forms: the cysts (the infective forms of the parasite) and the trophozoite. The cysts, when ingested along with contaminated food or drink, release 4 metacystic trophozoites. The ingested cysts, but not trophozoites, can survive the gastric barrier in normal humans. The trophozoites continue to divide via binary fission. The actively motile trophozoites lodge in the submucous layer of the cecum and rectosigmoid, their normal habitat. After a period, trophozoites transform into cysts that are passed in the stool. Trophozoites may be passed in the stool as well, but only the cysts are infective.

Under certain circumstances, the trophozoites invade the bowel wall, producing ulcers and causing destruction and tissue necrosis. The organism then gradually moves from the dead tissue toward healthy tissue. Extraintestinal disease may occur when trophozoites disseminate to other organs through the bloodstream.

##### Clinical Manifestations

All *E dispar* and *E moshkovskii* infections and 90% of *E histolytica* infections are asymptomatic. In general, intestinal amebiasis has a subacute onset, usually over 1 to 3 weeks. Symptoms range from mild diarrhea to severe dysentery, producing abdominal pain, diarrhea, and bloody stools. Nearly 50% of patients experience weight loss. Eight percent to 38% of patients may experience a fever. Fulminant colitis with bowel necrosis leading to perforation and peritonitis occurs rarely but is associated with a mortality rate of more than 40%. Ameboma (a nodular, tumorlike focus of proliferate inflammation in the wall of the colon), toxic megacolon, local perforation, peritonitis, and extraintestinal extension are other rare complications.

Amebic liver abscess is the most common extraintestinal manifestation of amebiasis. The infection occurs by trophozoites ascending the portal venous system. Amebic liver abscess (and other extraintestinal disease) is less common in children than adults. Most patients diagnosed with amebic liver abscess in the United States either will be from a country where amebiasis is endemic or will have a relevant travel history. Pain in the right upper quadrant, fever, anorexia, and fatigue are the symptoms of abscess formation. Concurrent diarrhea is present in less than one-third of patients, though some patients will have had dysentery in the previous few months. Jaundice is

uncommon. For travelers returning from an endemic area, presentation usually occurs within 8 to 20 weeks (median, 12 weeks). In 95% of patients, the presentation will be within 5 months of their return, though a longer lag (sometimes years) has been reported. Extension or rupture into the lung, pleural space, peritoneum, or pericardium may complicate the course of the amebic hepatic abscess.

### Diagnosis

Stool examination is less sensitive than antigen testing and it is considered a poor method for diagnosing intestinal amebiasis. For improved sensitivity, 3 fresh stool samples from separate days should be sent for analysis. However, microscopy cannot differentiate among *E histolytica* and *E dispar* or *E moshkovskii* strains. Other methods have been developed to differentiate among the species and to diagnose the invasive disease.

Serologic testing is useful to differentiate *E histolytica* infections from *E dispar* infections; *E histolytica* infection results in the development of antibodies, whereas *E dispar* infection does not. Because between 10% and 35% of uninfected individuals in endemic areas have antiamebic antibodies related to previous, often undiagnosed infection with *E histolytica*, a negative serology in these populations helps to exclude disease. However, a positive serology is not particularly helpful because it does not distinguish between acute infection and past exposure to the parasite.

In the endemic areas, Agar gel diffusion and counterimmunoprecipitation are more useful than indirect hemagglutination, because specimens usually become negative after 6 to 12 months. However, Agar gel diffusion and counterimmunoprecipitation are less sensitive than the indirect hemagglutination method.

Fecal and serum antigen detection assays have many advantages, including ease and rapidity of the tests, ability to differentiate among strains, greater sensitivity than microscopy, and potential for early diagnosis in the course of infection and in endemic areas where serology is less useful. Fecal antigen assays use monoclonal antibodies to bind to epitopes present on pathogenic *E histolytica* strains but not on nonpathogenic *E dispar* or *E moshkovskii* strains. These assays are now being used commercially to detect *E histolytica* infection using enzyme-linked immunosorbent assay (ELISA), radioimmunoassay, or immunofluorescence.

Diagnosing amebic infection and differentiating among the 3 strains can now be done by detecting parasitic DNA or RNA in feces via probes, but these methods currently are reserved as research tools. Polymerase chain reaction (PCR) techniques can detect *E histolytica* in stool specimens; these are the most sensitive and specific methods, but they are not widely available at present.

Liver amebic abscesses are usually diagnosed based on clinical presentation, recognition of epidemiologic risk factors, serology, and use of noninvasive imaging studies.

### Treatment

The goals of antibiotic therapy for intestinal amebiasis are both to eliminate the invading trophozoites and to prevent the asymptomatic carrier state of the

organism. The treatment for intestinal amebiasis or hepatic amebiasis is metronidazole (35–50 mg/kg/day divided in 3 doses orally for 10 days, maximum 750 mg 3 times daily). This should be followed by an intraluminal agent to target the cyst stage; this could be iodoquinol (30 mg/kg/day divided in 3 doses for 20 days), paromomycin (25–35 mg/kg/day in 3 divided doses for 7 days) or diloxanide furoate (20 mg/kg/day in 3 doses orally for 10 days).

Asymptomatic *E histolytica* infection should be treated with an intraluminal agent because of the potential risk of developing invasive disease and the risk of spread to household members; *E dispar* and *E moshkovskii* infections, however, do not require treatment.

### Amoebic Meningoencephalitis (*Naegleria fowleri*, *Entamoeba histolytica*, and Certain Species of *Acanthamoeba*, *Leptomyxa*, *Gephyramoeba*, and *Balamuthia*)

Knowledge that free-living amoebae are capable of causing human disease dates back to the 1960s. Before that, these amoebae were regarded as harmless soil organisms, or at most, commensals of mammals. Later, however, many amebic organisms were found to cause significant clinical disease in humans. These are *Naegleria*, *Acanthamoeba*, *Balamuthia*, and *Prototheca*.

These free-living amoebae cause 2 distinct clinical presentations: (1) an acute, fulminant disease known as primary amebic meningoencephalitis (PAM), which is caused by *Naegleria fowleri* in previously healthy children and young adults, or (2) granulomatous amoebic encephalitis (GAE) in immunocompromised patients caused by *Acanthamoeba* and *Balamuthia* species, which is usually chronic and slowly progressive.

*Entamoeba histolytica* causes central nervous system (CNS) abscesses that are distinct from CNS lesions caused by meningitis-causing free-living amoebae. Cerebral amebiasis results from hematogenous dissemination. Symptoms are usually of abrupt onset, and rapid progression to death occurs if treatment is delayed. Lesions may be seen on computed tomography (CT) scan as irregular foci without a capsule or surrounding enhancement. Treatment should be very prompt, and should include metronidazole and surgical intervention, if required for decompression.

### Epidemiology

Warm bodies of water such as man-made lakes and ponds, hot springs, and thermally polluted streams, rivers, and healing swimming pool waters are where *Naegleria* may be found. They are not found in seawater. The olfactory neuroepithelium and nasal passage are the ports of entry. Disease typically occurs in previously healthy children and young adults. Affected individuals characteristically have a recent history of water-sports activities in lakes, ponds, or inadequately chlorinated swimming pools. The organism has been isolated from nasal passages and throats of healthy individuals. It is unclear why disease occurs in only a small proportion of exposed individuals. *N fowleri* exists in the environment in 3 forms: trophozoite, which is the invasive form that penetrates the cribriform plate and invades the brain; resistant cyst; and transient flagellate.



Several species of *Acanthamoeba* can cause granulomatous meningoencephalitis disease in humans. *Acanthamoeba* species have a trophozoite and a resistant cyst stage but no flagellate stage, have been identified in soil, various water sources, air conditioners, contact lens fluid, and the noses and throats of healthy individuals. *Acanthamoeba* species are believed to gain access to the brain via the hematogenous route, after entering the human host through the respiratory tract or the skin, and then travel via circulation to the brain. Immunocompromised hosts develop a chronic infection (*Acanthamoeba* encephalitis), and immunocompetent hosts who wear contact lenses may develop *Acanthamoeba* keratitis if exposed to contaminated water.

### Clinical Manifestations

Patients with PAM present similarly to patients with fulminant bacterial meningitis and other meningoencephalitis. The incubation period is usually 2 to 15 days. After that, symptoms start as bifrontal headaches that do not respond to analgesics and fevers ranging from 38°C to 41°C. Alteration in taste or smell and/or rhinitis also may be noted early. Then patients develop emesis, seizures, and lethargy. Physical examination findings include nuchal rigidity, cerebellar ataxia, and dysfunction of the third, fourth, and sixth cranial nerves. Death usually occurs within 3 to 7 days after onset of initial signs and symptoms.

Granulomatous amoebic encephalitis is a disease of immunocompromised and debilitated individuals. These include patients with acquired immunodeficiency syndrome (AIDS), neoplasms, renal transplantation, and liver disease. As the name reflects, this infection is characterized by the host's granulomatous response to the presence of the amoeba. This typically is a chronic and insidious infection that can take weeks to years before it becomes clinically apparent. The symptoms include hemiparesis, personality changes, seizures, neck stiffness, headaches, and fever, and are the result of the single or multiple space-occupying intracranial lesions. In addition to GAE, *Acanthamoeba* is known to cause sinusitis, otitis media, cutaneous lesions, and corneal ulcers.

### Diagnosis

In general, infections caused by the free-living amoebae are difficult to diagnose, and most are recognized on autopsy or necropsy.

In PAM, neuroimaging studies may be normal early in the disease but may show signs of increased intracranial pressure later. Meningeal enhancement of the basilar region is frequently reported. Severe brain edema is a late finding that is indicative of poor outcome. Laboratory studies often reveal increased leukocyte count, hyperglycemia, and glycosuria. Cerebrospinal fluid (CSF) examination shows a pleocytosis with predominance of polymorphonuclear leukocytes, increased CSF protein, and normal or decreased glucose. Routine Gram stain and bacterial culture will be negative. The motile amoebae may be seen on a wet mount of the CSF, preferably unrefrigerated CSF collected within 30 minutes of the evaluation. Performing a culture on non-nutrient agar plated with *Escherichia coli* is a

definitive way to make the diagnosis. Because most cases are fatal, staining with hematoxylin-eosin (H&E) or immunofluorescence study of brain tissue is helpful in confirming a diagnosis of PAM, but this is usually done postmortem. There is little or no antibody response to the presence of the amoebae, because of the short duration of this fatal infection; serologic procedures, therefore, are of little or no help. Polymerase chain reaction (PCR) has been used to detect amoeba DNA in tissue and CSF samples, but the technique is still in its early developmental stages and requires more testing before its reliability can be certified.

In GAE, neuroimaging may reveal space-occupying lesions resembling abscesses, tumors, or hemorrhagic infarction. CSF examination reveals a picture similar to that of aseptic meningitis. Diagnosis is made by finding the amoebae in tissue sections stained with H&E or with indirect immunofluorescence using rabbit anti-amoeba serum samples. Cysts of infecting amoebae can be recognized in corneal scrapings that have been stained with Calcofluor white, a fluorescent stain that binds to polysaccharide polymers in the *Acanthamoeba* cyst wall. *Acanthamoeba* can also be identified by placing biopsy tissue in non-nutrient agar coated with a layer of bacteria. *Acanthamoeba* will emerge from tissue to ingest bacteria and can be identified on agar plates by microscopy.

### Treatment

The mainstay in therapy for PAM is intravenous, or sometimes intrathecal, amphotericin B. One survivor has been described who was treated with intravenous amphotericin, intrathecal amphotericin, oral rifampin, and intravenous and intrathecal miconazole. Even with combined therapy, survival has been the exception.

No optimal antimicrobial therapy exists for the encephalitis caused by *Acanthamoeba*. Multiple drugs have been used in both these infections with varying degrees of success, including amphotericin B, azithromycin, fluconazole, flucytosine, pentamidine isethionate, and sulfa drugs. In vitro, miltefosine and voriconazole are potentially useful drugs for the treatment of free-living amoebic infections, though sensitivities of the various genera, species, and strains differ.

Amoebic keratitis is treatable with 1 or more drugs. Chlorhexidine gluconate (a component of germicidal soaps) and polyhexamethylene biguanide (a disinfectant and swimming pool cleaner) have become the drugs of choice in treating keratitis.

Amoebic CNS infections should be treated at centers where neurologic, neurosurgical, and infectious disease experts are available. Consultation with the US Centers for Disease Control and Prevention (CDC) is advisable.

### Prevention

Natural or artificially warm waters, if they are not properly chlorinated, could harbor *Naegleria amoebae*. Effective chlorine levels are achievable in swimming pools and spas, but less so in the case of lakes and ponds. However, even chlorine levels between 0.5 and 1.5 parts per million are not protective all the time. In general, swimming in warm, stagnant, and possibly fecally contaminated waters should be avoided. Proper chlorination of swimming pools and avoiding diving and



direct introduction of water to the nostrils may help prevent infection. Following proper contact lens care procedures should protect wearers against infection.

### Cryptosporidiosis

*Cryptosporidium* is an intracellular coccidian protozoan parasite that causes gastrointestinal disease among humans as well as different animals including mammals, reptiles, and fish. The organism is 2 to 6  $\mu\text{m}$  in diameter. This protozoan has 10 named species. However, *Cryptosporidium parvum* is the main species that causes disease in humans. *C parvum* is further divided into 2 species: *C hominis* (previously *C parvum* genotype 1), which only infects humans, and *C parvum* (previously *C parvum* genotype 2), which infects both humans and animals.

*Cryptosporidium* is a common parasitic intestinal pathogen in humans. In recent years, it has been increasingly recognized as a cause of diarrhea in healthy individuals as well as severe gastrointestinal disease and life-threatening illness in patients with AIDS.

### Epidemiology

*Cryptosporidium* is seen both sporadically and in outbreaks of diarrheal illness worldwide. Cryptosporidiosis is particularly common in developing countries that have increased crowding and poor sanitation. Patients with underlying cellular and humoral immunodeficiencies are at increased risk for a prolonged and severe clinical course. These include patients with AIDS, organ transplantation, immunosuppressive drugs, immunoglobulin A (Ig) A deficiency and hypogammaglobulinemia.

Cryptosporidiosis is present in 1% to 3% of immunocompetent patients with diarrhea in developed countries compared with 7% to 10% in developing countries. The annual incidence is reported as 3.0 cases per 100,000 persons in the United States and 6.0 per 100,000 persons in Canada. The incidence is higher in children than adults. Reported seroprevalence rates are 25% to 60% in the United States and as high as 65% to 90% in developing countries.

*Cryptosporidium* is transmitted to humans via spread from an infected person (person-to-person contamination) or an infected animal. Because of the risk of autoinfection, ingestion of only 10 to 50 oocysts may cause infection. The infectious dose 50 in healthy persons is 132 oocysts. Extensive outbreaks of cryptosporidiosis have occurred in fecally contaminated environments such as municipal drinking water and swimming pools. The transmission and spread of cryptosporidiosis are facilitated by the resistance of the oocysts to disinfectants, the ineffective removal of oocysts by many filtration systems, and their ability to survive in the environment for months. The oocysts are resistant to chlorine and thus appropriately functioning filtration systems are critical to prevent spread. Most sand filters used in swimming pools are ineffective at oocyst removal. Several outbreaks of cryptosporidiosis have been reported including a large waterborne outbreak in Milwaukee, Wisconsin, in 1993. An estimated 403,000 people developed gastrointestinal symptoms after their drinking water became contaminated. Outbreaks of apple cider contamination with *Cryptosporidium* oocysts have also

been reported. An outbreak of cryptosporidiosis involving 350 people in Illinois at a contaminated waterpark was reported in 2001. Outbreaks involving consumption of contaminated food are less frequent than waterborne outbreaks.

Person-to-person transmission of *Cryptosporidium* can also cause outbreaks at day care centers; rates of 30% to 60% have been reported. Transmission is also common among household members, homosexuals, and health care workers. *Cryptosporidium* can also cause traveler's diarrhea because of contaminated drinking and swimming water. The incubation period for cryptosporidiosis is 2 to 14 days (median, 7 days). Oocyst excretion may continue for 1 week after resolution of symptoms in 73% of infected patients.

### Pathogenesis and Life Cycle

The complete life cycle of *cryptosporidium* requires only 1 host. Humans acquire the infection by ingesting thick-walled oocysts. The oocyst sporulates in the host and is infective immediately after excretion in the stools. Excystation in the gastrointestinal tract occurs in the upper small intestine via the action of proteolytic enzymes and bile salts and causes the release of 4 infectious sporozoites that invade the epithelial cells. The first intracellular stage is the trophozoite, which subsequently undergoes 3 nuclear divisions to form a group of 8 merozoites, which become the first-generation schizont. The merozoites released from the schizont invade other epithelial cells, forming the second-generation schizont composed of only 4 merozoites. The second-generation merozoites invade other epithelial cells and enter the sexual stage, forming microgametocytes and macrogametocytes. Each microgametocyte produces 12 to 16 microgametocytes, whereas each macrogametocyte transforms into 1 macrogametocyte. The 2 sexual stages combine to form the zygote, which later develops into an oocyst, thus completing the life cycle. Oocysts exist in 2 forms: thin- and thick-walled. Thin-walled oocysts sporulate and cause infection in the same person (autoinfection), whereas thick-walled oocysts are excreted in feces and infect new hosts. The infection is generally limited to the superficial parts of the small intestine, but in immunocompromised patients, the infection may spread to involve the biliary tree and pancreas or may disseminate to extraintestinal sites, mainly the respiratory tract.

The mechanism by which *Cryptosporidium* causes diarrhea is not well understood. *Cryptosporidium* causes secretory diarrhea that is associated with malabsorption. No specific toxin associated with *Cryptosporidium* has been identified yet. However, increased proinflammatory cytokine release has been demonstrated during the course of infection. The pathogenesis is probably multifactorial. Loss of vacuolated villous tip epithelium causes a reduction in the absorption area. Reduced lactase activity may cause lactose intolerance and malabsorption. Accumulation of abnormal metabolites in the intestinal lumen may stimulate bacterial overgrowth.

In addition, the host immune response to the infection, both cellular and humoral, may contribute to the inflammatory changes in the gastrointestinal tract.

The T-lymphocyte immune responses are essential to control the infection. Although specific immunoglobulins A, G, and M are produced during the course of illness, they are not associated with clearance of infection, especially in patients with immunodeficiency virus (HIV) infection. However, the production of interferon- $\gamma$  seems to be involved in the clearance of infection.

### Clinical Manifestations

Cryptosporidiosis varies from an asymptomatic infection to severe enteritis and dehydration leading to death. In children, up to 30% of infections may be asymptomatic. The most common manifestation of cryptosporidiosis is acute diarrhea characterized by frequent, watery, foul-smelling nonbloody stools. Diarrhea is commonly associated with malaise, nausea, anorexia, fatigue, abdominal cramps, and weight loss. Fever and vomiting are commonly seen in children who may be misdiagnosed as having viral gastroenteritis. In immunocompetent individuals, including healthy children, the diarrhea is self-limited and resolves spontaneously in 1 to 20 days (mean, 10 days). In the Milwaukee outbreak, the mean maximum number of stools was 19 per day (range, 1–90/d). Thirty percent of affected patients had a recurrence of diarrhea after a 2-day symptom-free period. Occasionally, healthy infants with cryptosporidiosis may develop chronic and persistent diarrhea leading to malnutrition and growth retardation.

In immunocompromised patients, particularly those infected with HIV, cryptosporidiosis frequently takes a severe and protracted course and can lead to significant malnutrition, wasting, dehydration, and death. The disease is particularly severe in those with CD4 counts less than 180/ $\mu$ L. Other clinical manifestations of cryptosporidiosis in patients with AIDS include cholecystitis, cholangitis, hepatitis, pancreatitis, and respiratory tract involvement. The biliary tract is affected in 10% to 30% of HIV-infected patients, and can lead to sclerosing or acalculous cholangitis. Biliary cryptosporidiosis is exclusively seen in patients with AIDS. Symptoms include right upper quadrant pain, fever, nausea, and vomiting with or without diarrhea. Serum alkaline phosphatase and  $\gamma$ -glutamyl transpeptidase are elevated. Radiologic investigations may show dilated intra- and extrahepatic bile ducts as well as a dilated, thick-walled gallbladder. Rarely, pancreatitis may result from involvement of the pancreatic duct.

Respiratory cryptosporidiosis is seen mainly in patients with AIDS. It is not clear if *Cryptosporidium* is a true pathogen or merely colonizes the respiratory tract, because it frequently coexists with other pathogens such as cytomegalovirus, *Mycobacterium* species, and *Pneumocystis jiroveci*. Clinical symptoms include cough, dyspnea, fever, expectoration, and chest pain.

### Diagnosis

Diagnosis of cryptosporidiosis depends on microscopic identification of the oocysts in stool, aspirated fluid, or tissue samples. Routine laboratory examination of stool samples for ova and parasites will not detect *Cryptosporidium*. Thus, the laboratory should be alerted to the potential diagnosis of cryptosporidiosis

to perform specific staining of the samples. Direct fluorescent antibody testing to detect oocysts in stools is considered the best diagnostic test by many laboratories because it provides the highest sensitivity and specificity. A combined direct fluorescent antibody test to detect *Cryptosporidium* oocysts and *Giardia* cysts in stools is available. A modified Kenyon acid-fast stain is used to identify *Cryptosporidium*. The stool samples are usually concentrated using either the sucrose flotation or formalin acetate methods before staining. The oocysts of *Cryptosporidium* are small (4–6  $\mu$ m) and can be missed without careful scanning of slides. At least 3 stool samples should be tested before considering a negative result. Enzyme-linked immunosorbent assay (ELISA) and immunofluorescent staining using monoclonal antibodies can be used to detect oocysts in stool and tissue specimens. Commercial ELISA kits that detect *Cryptosporidium* and *Giardia* antigens in stools are also available.

Serologic testing is available; however, testing is only useful for epidemiologic studies. PCR testing can be performed on stool samples and has been shown to be more sensitive than immunofluorescent and acid-fast staining. PCR is not commercially available but is particularly useful in detecting common source outbreaks by differentiating different *Cryptosporidium* genotypes.

### Treatment

Recovery from cryptosporidiosis depends to a large extent on the immune status of the host. In immunocompetent patients, cryptosporidiosis is a self-limited disease and supportive care, including hydration and nutritional support, may be adequate. Antimicrobial therapy is indicated in patients with severe infection and in immunocompromised hosts. The US Food and Drug Administration (FDA) has approved a 3-day course of nitazoxanide, a nitrothiazole benzamide, for treatment of children of age 1 year and older as well as adults with diarrhea caused by cryptosporidiosis or giardiasis. Paromomycin, a nonabsorbable aminoglycoside, used with or without azithromycin has been used in HIV-infected patients with cryptosporidiosis, but reliable efficacy data are lacking. The most important aspect of cryptosporidiosis treatment in HIV-infected patients is immune reconstitution using highly active antiretroviral therapy. Immune therapy such as oral human immune globulin, hyperimmune bovine colostrum, and bovine transfer factor has demonstrated some benefit.

Diarrhea in cryptosporidiosis is copious and attention to fluid and electrolyte management of affected patients is essential. Chronic diarrhea is frequently associated with malnutrition. Nutritional supplements containing medium-chain triglycerides may be helpful. Because chronic diarrhea may be associated with lactase deficiency in patients with cryptosporidiosis, milk and dairy products should be avoided. Total parenteral nutrition may be needed in HIV-infected patients with chronic diarrhea and weight loss.

### Prevention

The most important preventive measures are good hygiene practices, such as hand washing and appropriate

disposal of infected material. Using an appropriate water filter is another important measure to prevent or control an outbreak. Contact precautions are recommended for diapered and incontinent children. People with cryptosporidiosis should not use public recreational water when they have diarrhea and for at least 2 weeks after symptoms resolve. Although not universally recommended for immunocompromised patients, boiling drinking water for 1 minute is the most reliable method of killing *Cryptosporidium*, particularly in countries with unsafe drinking water. Alternatively, filtration devices that have a particle size rating of 1 to 5  $\mu\text{m}$  are effective in removing *Cryptosporidium* species.

### Toxoplasmosis (*Toxoplasma gondii*)

*Toxoplasma gondii* is an obligate intracellular coccidian parasite that belongs to the class Sporozoa. *Toxoplasma* infects several animal species as well as humans. Members of the cat family are considered definite hosts, whereas humans and mammals are considered intermediate hosts.

#### Epidemiology

*Toxoplasma* infections are distributed worldwide. The highest incidence of infection is in countries in which consumption of raw meat by people is common, such as France, the United States, and other Western countries. Infections are also common in regions with warm, humid climates including tropical areas. The presence of the domestic cat is an important risk factor associated with disease transmission in different parts of the world.

Humans acquire infection by ingesting cysts that are present in raw or undercooked meat or oocysts in material contaminated by cat feces.

Disease outbreaks have occurred following contamination of drinking water supplies. Infection may follow blood transfusion. It may also follow stem cell or solid organ transplantation. Congenital infection is seen after the acquisition of a primary maternal infection during pregnancy. Newborns are most frequently infected when maternal infection is acquired in the third trimester. However, the clinical manifestations of congenital toxoplasmosis are most severe in cases of first-trimester maternal infection during organ development.

#### Life Cycle and Pathogenesis

Cats acquire infection by eating rodents or uncooked kitchen meat that contains *Toxoplasma* cysts. The sexual phase takes place in the intestinal epithelial cells of cats. This is followed by appearance of oocysts in the feces in 3 to 18 days. Shedding of oocysts may persist for approximately 2 to 3 weeks. Shedding is more likely to occur in kittens than older cats. First infection in a cat is associated with shedding of millions of oocysts per day. The oocyst becomes infectious in 1 to 3 days after it sporulates.

The asexual phase occurs in the intermediate hosts, including humans and mammals. Following ingestion, the sporozoites are released in the intestine and become free trophozoites. From there, trophozoites are taken up by macrophages and transported via the

bloodstream to different organs. The most commonly involved organs are the skeletal muscles, brain, cardiac muscle, lymph nodes, eyes, and lungs. They proliferate by budding, and form clusters consisting of vacuoles of macrophages called *pseudocysts*. Because of their rapid proliferation and invasion, they are called *tachyzoites*. After the host immune response becomes established, as occurs in immunocompetent patients, the cysts are formed. The wall of the cyst will form and the organisms within the organisms are no longer actively multiplying. The organisms in these cysts are thus called *bradyzoites*. Morphologically, the tachyzoites and bradyzoites are similar except for the rate of proliferation. Both measure 2 to 6  $\mu\text{m}$ .

Infection in immunocompetent patients is limited and cellular necrosis is controlled. The incubation period is 4 to 21 days. Both cellular and humoral immune responses to *Toxoplasma* develop. However, not all organisms are killed, and cysts may remain in any organ without causing any symptoms or significant damage. Under certain conditions, such as immune dysfunction, or in patients with HIV infection, multiplication of organisms causes the cysts to rupture and release bradyzoites. An inflammatory response is seen, which is characterized by infiltration of lymphocytes, monocytes, and plasma cells and formation of granulomas. This may lead to significant dysfunction in affected organs especially the brain and the eye. It may also lead to disseminated toxoplasmosis.

#### Clinical Manifestations

**CONGENITAL DISEASE.** Congenital toxoplasmosis typically follows a primary infection in the mother during pregnancy. Rarely, the fetus may be infected after *Toxoplasma* is reactivated in immunocompromised mothers, including those with HIV infection. The risk of transmission of *Toxoplasma* infection to the fetus is 15% to 20% if the mother is infected in the first trimester but rises to 60% to 65% if the mother becomes infected in the third trimester. The incidence of congenital toxoplasmosis in the United States is 1 in 1,000 live births. Severely affected fetuses may result in still birth, abortion, or early neonatal death. However, 70% to 90% of congenitally infected infants are asymptomatic. If untreated, a large proportion of asymptomatic infants may develop late-onset sequelae such as choreoretinitis, learning disabilities, and mental retardation months to years later. Clinical manifestations of congenital toxoplasmosis at birth can include hepatosplenomegaly, lymphadenopathy, hydrocephalus, or microcephaly. Clinical signs of meningoencephalitis such as seizures and neurologic deficits may also be present. Other manifestations include choreoretinitis, rash, jaundice, thrombocytopenia, and anemia. Radiologic studies such as ultrasound or computed tomography may show calcifications or dilated ventricles. The calcifications in toxoplasmosis are scattered throughout the brain in contrast to the periventricular calcifications of cytomegalovirus infection.

**ACQUIRED DISEASE.** Most *Toxoplasma* infections acquired after birth are asymptomatic. In symptomatic patients, the most frequent clinical manifestation is cervical lymphadenopathy. Concomitant nonspecific signs and symptoms such as fever, myalgia, and fatigue



may be present. The lymphadenopathy may less frequently present in other regions or may be generalized. In some patients, infectious mononucleosislike manifestations such as sore throat, fever, malaise, adenopathy, splenomegaly, rash, and atypical lymphocytes may be present. Rare complications of primary infection include hepatitis, pneumonitis, myocarditis, pericarditis, and encephalitis.

**DISEASE IN IMMUNODEFICIENT PATIENTS.** Disease in immunocompromised patients including those infected with HIV is more severe than infection in a normal host. Disseminated toxoplasmosis and death may occur. More frequently, these patients develop localized infections in different organs including encephalitis, meningoencephalitis, pneumonitis, myocarditis, pericarditis, and hepatitis. Encephalitis in patients with AIDS usually follows reactivation of chronic disease especially in those with CD4 cell counts less than 100/mL. *Toxoplasma* is the most frequent cause of focal brain lesions in patients with AIDS. Brain involvement can be localized or diffuse. Patients present with fever, headache, deterioration in mental status, seizures, and focal neurologic deficits. Hemiparesis and abnormal speech are the most typical focal findings. Computed tomography scans typically show brain abscesses or ring-enhancing lesions. *Toxoplasma* pneumonitis in patients with AIDS may mimic *P. jiroveci* pneumonia.

**OCULAR DISEASE.** *Toxoplasma* is the most common recognized cause of choreoretinitis in the United States. Isolated ocular toxoplasmosis most frequently follows congenital infection but rarely may follow an acquired infection. Choreoretinitis is bilateral in the congenital form and unilateral in the acquired form of toxoplasmosis. Most affected patients are young adults. Choreoretinitis is not usually the sole manifestation of acquired toxoplasmosis. Nystagmus is a common manifestation of congenital ocular toxoplasmosis. Acute choreoretinitis is characterized by blurred vision, photophobia, and central vision loss secondary to involvement of the macula. Fundoscopy shows yellow-white cottonlike patches with indistinct borders. During the healing stage, black pigment will be seen at the margins. The lesions heal in few weeks to several months. Relapses are frequent and visual loss may occur. Other complications of congenital ocular involvement include choreoretinal scars, microphthalmia, cataract, and retinal detachment.

### Diagnosis

The most definite diagnostic test for toxoplasmosis is isolation of the organism from infected tissue or body fluids either by inoculating into laboratory animals or tissue culture. However, these techniques are not routinely available. Thus, the primary method currently used for diagnosis is based on the detection of specific antibodies and monitoring of the immune response. Recently, molecular methods have been developed, which use PCR for detecting *Toxoplasma* DNA in tissue and fluid samples. Clinical and laboratory data should be carefully correlated during patient evaluation and management.

The most commonly used serologic test is the ELISA. Serum IgG usually becomes positive 4 to

8 weeks after infection and remains positive indefinitely. Paired serum samples should be tested simultaneously 3 weeks apart to document at least a fourfold rise in antibody titers. Serum IgM levels should also be tested simultaneously with IgG. The ELISA IgM tests are more sensitive than the indirect immunofluorescence antibody test. The IgM test may remain positive for 6 months and false-positive results can occur. In newborns and pregnant women, the serum levels of IgA and IgE for *Toxoplasma* also can be tested. These tests become negative sooner than the IgM, thus giving more precise information about the timing of infection. However, anti-*Toxoplasma* IgA and IgE are only available at *Toxoplasma* referral laboratories (Palo Alto Medical Foundation Research Institute, Palo Alto, CA).

IgG avidity testing is used to predict the timing of *Toxoplasma* infection. The presence of these high-avidity antibodies reflects infection at least 3 to 5 months earlier. Testing of high-avidity antibodies is most useful in assessing the risk of transmission of *Toxoplasma* from the mother to the fetus or when only 1 sample is available at the time of decision making. Low-avidity antibodies are, however, unreliable in predicting a recent infection.

Pregnant women should ideally know their serologic status for *Toxoplasma* before conception. If positive, no further testing is needed. However, if the mother was found during pregnancy to have a positive *Toxoplasma* IgG antibody, the serum titers should be repeated for both IgM and IgG after 3 weeks to determine if she has a primary infection. A definitive diagnosis of congenital toxoplasmosis during pregnancy can be made via amniotic fluid sampling. Detecting *Toxoplasma* in amniotic fluid with DNA PCR, tissue culture, or mouse inoculation is considered diagnostic. Similarly, fetal blood sampling to isolate *Toxoplasma* from fetal white blood cells and to test for IgM antibody also may be used. Serial ultrasound examinations can be performed to assess brain ventricular size or other signs of infection.

After delivery, infants should be evaluated for congenital toxoplasmosis if the mother has a primary infection or if she has HIV infection and serology suggestive of past infection. If the diagnosis is suspected, the patient should have a complete clinical evaluation including ophthalmologic, neurologic, and auditory examination. Brain CT should be performed to rule out brain calcification or hydrocephalus. Serum samples should be evaluated for IgG, IgM, IgA, and IgE antibodies for *Toxoplasma*. CSF samples should be analyzed for cells, protein, glucose, *Toxoplasma* antibodies, and *Toxoplasma* PCR. Diagnosis is confirmed serologically by demonstrating a positive IgM or IgA, an IgG titer that is higher in the infant than in the mother, or a persistently positive IgG beyond 1 year of age.

The diagnosis of toxoplasmosis in older children and adults who are immunocompetent relies on the presence of a positive IgM titer or a fourfold rise in IgG titers after 3 weeks. Classic histopathologic findings in tissue samples such as lymph nodes strongly support the diagnosis. Histologic identification of proliferating organisms provides a definite diagnosis.



Similarly, culture-isolated *Toxoplasma* in tissue or body fluid samples or identification of nucleic acid material with DNA PCR is definitive.

In immunocompromised patients, including those with HIV infection, serologic testing may not be reliable. A fourfold rise in titer may not occur in these patients when they acquire a primary infection. Those who have an old infection are diagnosed on the basis of a positive IgG titer. The diagnosis of *Toxoplasma* encephalitis in patients with AIDS relies on characteristic clinical and radiologic findings. Patients with positive *Toxoplasma* IgG titers are treated presumptively. If no response to treatment is seen, identification of *Toxoplasma* in blood or CSF by means of DNA PCR testing may be needed.

Patients with ocular involvement are diagnosed on the basis of classic eye findings and serologic testing. Examination of the vitreous fluid or aqueous humor on DNA PCR may be needed if the retinal lesions are atypical or the patient fails to respond to antimicrobial therapy.

### Treatment

Treatment is not indicated in immunocompetent patients unless clinical symptoms are severe or complications occur. Immunocompromised patients, especially with acute HIV/AIDS infection, should be treated even if they are asymptomatic. Infected pregnant women and neonates, whether symptomatic or not, should also be treated as soon as the diagnosis is established. Patients with chorioretinitis are treated when symptoms are present or progressive.

The recommended treatment in most cases is the combination of pyrimethamine and sulfadiazine. These drugs act on the tachyzoites and the cysts forms are not affected. Thus, lifelong daily maintenance therapy is needed in patients with AIDS. The dose of pyrimethamine in children is 2 mg/kg per day for 3 days then 1 mg/kg per day to a maximum daily dose of 25 mg given for 4 weeks. The dose of sulfadiazine is 85 to 100 mg/kg per day divided every 6 hours for 3 to 6 weeks. Because pyrimethamine is a folic acid antagonist, supplemental leukovorin (folinic acid) is given to prevent bone marrow toxic effects. Pyrimethamine is not given to pregnant women, especially during the first trimester, because of its teratogenic effects. Instead, sulfadiazine alone or spiramycin can be used. However, pyrimethamine and sulfadiazine may be considered for treatment of infections acquired in the third trimester. Patients who are allergic to sulfa drugs can be given a combination of clindamycin and pyrimethamine.

For congenital toxoplasmosis, pyrimethamine and sulfadiazine (with folinic acid supplements) should be continued for a prolonged period, often for 1 year.

Corticosteroids are given in addition to pyrimethamine and sulfadiazine in patients with ocular toxoplasmosis and selected patients with CNS disease.

Prophylactic therapy for toxoplasmosis is given to children with HIV/AIDS with severe immunosuppression and positive *Toxoplasma* IgG antibodies. The drug of choice is trimethoprim-sulfamethoxazole. Alternative therapies are dapsone plus pyrimethamine (with supplemental folinic acid) or atovaquone.

Prophylaxis is also given to prevent recurrence of toxoplasmosis in immunosuppressed patients with prior *Toxoplasma* encephalitis. The recommended regimen is pyrimethamine plus sulfadiazine plus folinic acid. Alternatively, clindamycin plus pyrimethamine plus folinic acid or atovaquone may be used for those who cannot tolerate sulfa drugs.

### Prevention

Preventive measures are aimed at hygienic practices during cat contact and preventing raw meat and shellfish consumption. Pregnant women with negative or unknown serologic status for *Toxoplasma* as well as immunocompromised individuals should avoid contact with cats, cat litter, or soil that has been contaminated by cat feces. Hygienic practices such as using gloves and hand washing should be stressed in such settings. Deep freezing to  $-12^{\circ}\text{C}$  for 24 hours as well as cooking meat, particularly ham and lamb, to an internal temperature of  $65.5^{\circ}\text{C}$  to  $76.6^{\circ}\text{C}$  or until no longer pink will kill cysts. All fruits and vegetables should be washed thoroughly. Ingestion of untreated water, especially in developing countries, should be avoided. Cats may be prevented from acquiring infection by restricting their outdoor activities and feeding them commercially prepared cat food. Because the oocysts are not infective until at least 36 to 48 hours after passage, daily cleaning of cat litter boxes is a simple and effective control measure.

### Malaria (*Plasmodium falciparum*, *P vivax*, *P ovale*, *P malariae*)

#### Epidemiology

Malaria is a global problem and a leading cause of death and illness. The World Health Organization (WHO) report of 2005 estimated that between 350 and 500 million clinical episodes of malaria occur every year, resulting in at least 1 million deaths. Most of the cases and deaths are in sub-Saharan Africa, and most involve children younger than 5 years.

Four species of the plasmodia infect humans: *Plasmodium falciparum*, *P vivax*, *P ovale*, and *P malariae*. They are transmitted from person to person by the bite of the female *Anopheles* mosquito. *P falciparum* causes the most severe disease and it is the predominant malarial parasite in tropical Africa, Southeast Asia, and Oceania. *P vivax*, predominant in Southeast Asia, along with *P falciparum*, causes the most malaria infections worldwide. *P malariae*, the least common type, produces long-lasting infections. *P ovale* is uncommon and found largely in Africa.

#### Life Cycle

The malaria parasites have 2 different life cycles in 2 hosts, the female *anopheles* mosquito and the human. When certain forms of blood-stage parasites ("gametocytes") are picked up by a female *Anopheles* mosquito during a blood meal, they start the sexual stage of life inside the mosquito. This leads to the formation of infective-stage sporozoites which reside in the mosquito's salivary gland and can access the bloodstream of a human when the mosquito feeds again.

In humans, the parasites grow and multiply first in the liver cells (extraerythrocytic stage) and then in the red blood cells (the erythrocytic stage). In the blood, successive broods of parasites grow inside the red cells and destroy them, releasing daughter parasites (“merozoites”) that continue the cycle by invading other red cells. Thus, the mosquito carries the disease from 1 human to another (acting as a “vector”). In contrast to the human host, the mosquito vector does not suffer from the presence of the parasites.

### Pathogenesis

All the typical clinical symptoms and severe disease pathology associated with malaria are caused by the asexual erythrocytic or blood-stage parasites. When the parasite develops in the erythrocyte, numerous known and unknown waste substances such as hemozoin pigment and other toxic factors accumulate in the infected red blood cell. When the infected cells lyse and release invasive merozoites, these waste products are dumped into the bloodstream. The hemozoin and other toxic factors such as glucose phosphate isomerase stimulate macrophages and other cells to produce cytokines and other soluble factors that act to produce fever and rigors and probably influence other severe pathophysiology associated with malaria.

In *P falciparum* infections, consciousness can be impaired by various mechanisms interacting with each other. One of these mechanisms is obstruction of the cerebral microvascular flow by parasites, which induce sequestration of the infected and uninfected erythrocytes. Parasite binding is mediated by a group of variant surface antigens expressed at the red cell surface during development. The best described is *P falciparum* erythrocyte membrane protein-1, which is encoded by a family of approximately 60 variant genes associated with different binding phenotypes. Interleukin 6 and 10, nitric oxide, tumor necrosis factor, and various other inflammatory factors may play a role in the pathogenesis of cerebral malaria.

### Clinical Manifestations

The incubation period in most cases varies from 7 to 30 days. *P falciparum* most frequently is observed to have shorter periods, and *P malariae* has longer periods of incubation. Antimalarial prophylaxis taken by travelers can delay the onset of symptoms by weeks or months. The clinical presentation may also be affected by the malaria species. *P vivax* and *P ovale* are associated with hypnozoite or dormant-stage liver parasites. This liver stage of the disease is only associated with these 2 malaria species and can lead to a relapse months after the infective mosquito bite. Returned travelers should always remind their physicians of any travel in malaria-risk areas during the past 12 months.

Symptoms of malaria occur every second day with the “tertian” parasites (*P falciparum*, *P vivax*, and *P ovale*) and every third day with the “quartan” parasite (*P malariae*). However, these classic patterns are rarely observed; more commonly, the patient presents with a combination of the following symptoms that resemble a flulike illness: fever, chills, sweats, headaches, nausea and vomiting, body aches, and general malaise.

Anemia and an enlarged spleen may be seen on physical examination.

Severe malaria occurs when *P falciparum* infections are complicated by serious organ failures or abnormalities in the patient’s blood or metabolism. The manifestations of severe malaria that could be confused with severe bacterial sepsis include cerebral malaria, abnormal behavior, impaired consciousness, seizures, coma, or other neurologic abnormalities; severe anemia resulting from hemolysis, hemoglobinuria, pulmonary edema, or acute respiratory distress syndrome, which may occur even after the parasite counts have decreased in response to treatment; abnormalities in blood coagulation and thrombocytopenia; cardiovascular collapse; and shock.

Cerebral malaria, as proposed by the WHO, is a clinical syndrome characterized by coma at least 1 hour after termination of a seizure or correction of hypoglycemia, detection of asexual forms of *P falciparum* malaria parasites on peripheral blood smears, and exclusion of other causes of encephalopathy. The main neurologic features are coma, seizures, and brainstem signs. The mortality rate in adults and children is approximately 20%, and most deaths happen within 24 hours of admission, before antimalarial drugs may have had time to work. In African children, a high incidence of neurologic deficits (10.9%) was reported in studies that used similar definitions of cerebral malaria. Some deficits are transient (eg, ataxia), whereas others (eg, hemiparesis) improve over months but may not resolve completely.

Congenital malaria may be seen in infants of infected mothers. Symptoms include fever, severe anemia, and hepatosplenomegaly.

### Diagnosis

Prompt and accurate diagnosis of malaria is part of effective disease management. The most commonly used diagnostic tool is microscopic diagnosis, and more recently, rapid diagnostic tests based on immunochromatographic techniques. Microscopic examination remains the “gold standard” for laboratory confirmation of malaria. Both thick and thin smears are recommended. Thick smears are more sensitive but they cannot be used to differentiate among the different malaria species. Smears should be repeated every 12 to 24 hours for 72 hours if malaria is suspected and the initial smears are negative. Diagnosis of malaria can be difficult in the nonendemic areas because physicians are not familiar with the disease and laboratory technicians inexperienced with malaria may fail to detect parasites when examining blood smears under the microscope. On the other hand, in endemic areas, finding malarial parasites in an individual’s blood specimen could represent solely a carrier state, because these individuals develop enough immunity to protect them from the illness, not from the infection. Other diagnoses should not be overlooked when the parasites are found in such individuals’ blood specimens.

The quantitative buffy coat technique is useful for screening populations for malaria and for detecting asymptomatic carriers to control further transmission of the disease in the community. However, the

diagnosis has to be confirmed with peripheral smears. Serology, using either indirect immunofluorescence or ELISA, does not detect current infection but rather measures past experience, so it may be useful for epidemiologic surveys.

Other new tests include detection of the parasite nucleic acid with PCR, DNA probe, and rapid diagnostic tests using different methods, such as immunochromatography. PCR tests are more sensitive and specific than microscopy but are only available in reference laboratories including some state health departments. Although PCR is typically not readily available, it is very helpful in confirming the infecting species and detecting drug resistance mutations. A new rapid diagnostic test for antigen detection is available in the United States. However, the test cannot confirm the malaria species and may fail to detect low-density *P vivax* infections. In addition, false-positive and -negative test results have been reported with the rapid test and mixed infections may not be detected accurately. Thus, microscopic evaluation should always accompany rapid diagnostic tests to provide additional identification and to quantify the percentage of parasitemia.

### Treatment

**CHEMOTHERAPY.** Malaria must be recognized promptly to treat the patient in time and to prevent complications.

Malaria is a nationally notifiable disease and all cases should be reported to the state health department, which forwards them on to the CDC. Three main factors should be considered when treating malaria: the infecting *Plasmodium* species, the clinical status of the patient, and the drug susceptibility of the infecting parasites as determined by the geographic area in which the infection was acquired. For treatment of *P vivax* and *P ovale*, treatment needs to include drugs that target the liver to minimize the likelihood of recurrence. Patients should be checked for glucose-6-phosphate dehydrogenase deficiency before they are given primaquine. In general, if the diagnosis of malaria is suspected and cannot be confirmed, or if the diagnosis of malaria is confirmed but species determination is not possible, antimalarial treatment effective against *P falciparum* should be selected because all forms of malaria are susceptible to treatment of *P falciparum*. Detailed information about the treatment of malaria is available at the CDC Web site ([www.cdc.gov/malaria/diagnosis\\_treatment](http://www.cdc.gov/malaria/diagnosis_treatment)). The standard drug treatment for uncomplicated (not severe) malaria is summarized in Table 308-1. The treatment of severe malaria should be parenteral with continuous infusion of quinidine gluconate, until the patient can take oral medication and the parasite density is less than 1%. Therapy should be combined with doxycycline, tetracycline, or clindamycin. Patients with severe malaria or cerebral malaria should be monitored closely in the intensive care unit setting; side effects such as hypoglycemia should be monitored also. Consultation with the CDC for the treatment of such severe cases is recommended.

Artemisinin derivatives such as artemether and artesunate are used globally in combination regimens

to treat malaria and could be administered orally, parenterally, or rectally. Oral artemether/lumefantrine is active against chloroquine-resistant *P falciparum* and is approved by the FDA for treatment of acute uncomplicated malaria. Artemether is not approved to treat severe malaria or to prevent infection. Oral artesunate is not available in the United States and only the intravenous formulation is available through the CDC. Intravenous artesunate is typically reserved for patients with severe malaria who cannot tolerate or fail to respond to intravenous quinidine. When used, artesunate should be administered for a minimum of 3 days and given with an oral antimalarial agent such as atovaquone-proguanil, clindamycin, or mefloquine when the patient can tolerate oral intake. Artesunate followed up with mefloquine was associated with a cure rate of greater than 90%.

Finally, a self-treatment course of atovaquone-proguanil can be given to travelers who do not take an antimalarial drug for prophylaxis, are on a less-than-effective regimen, or may be in very remote areas, when they develop fever. Travelers should be advised that self-treatment is not considered a replacement for seeking prompt medical help.

**SUPPORTIVE TREATMENT.** Various supportive measures should be taken to optimize the treatment of patients. These include close monitoring of the fluid and electrolyte status of the patient, treating the convulsions with phenobarbital or diazepam, and vigilance about hypoglycemia, a common complication of severe malaria. Anemia should be corrected with packed red blood cell transfusions. The CDC recommends that exchange transfusion be considered for persons with a parasite density of greater than 10% or severe complications. Gram-negative sepsis must be suspected whenever patients present with shock; appropriate antibiotics should be started after blood cultures are obtained. No added benefits have been shown from using steroids, dextran, heparin, and osmotic diuretics.

### Prevention

Prevention of malaria is achieved through the following methods: preventing *infection* by reducing the population of the anopheles mosquitoes and avoiding bites by parasite-carrying mosquitoes (vector control), or preventing *disease* by using prophylactic antimalarial drugs.

Travelers from nonendemic countries should take precautions against acquiring malaria when they visit a malaria-risk area. These include chemoprophylaxis in addition to following measures to prevent contact with mosquitoes. Detailed guidelines about the chemoprophylaxis of malaria for travelers to endemic areas are available at the CDC Web site ([www.cdc.gov/travel](http://www.cdc.gov/travel)). Table 308-2 summarizes the recommended chemoprophylaxis for travelers. Chemoprophylaxis should begin 1 week before arrival in the area with endemic infection (except doxycycline and atovaquone-proguanil, which should be started 1 to 2 days before arrival), allowing time to develop blood concentrations of the drug and evaluate for adverse reactions. These medications should be continued for 1 week when receiving atovaquone-proguanil and 4 weeks when receiving the

**Table 308-1** Chemotherapy of Uncomplicated Malaria

DRUG	DOSAGE
<b>All <i>Plasmodium</i> species except chloroquine-resistant species<sup>a</sup></b>	
<b>Oral drug of choice:</b> Chloroquine Phosphate	10 mg base/kg (max 600 mg base), then 5 mg base/kg 6 hrs later, then 5 mg base/kg at 24 and 48 hrs
OR	
Hydroxychloroquine	10 mg base/kg (max 620 mg base), then 5 mg base/kg 6 hrs later, then 5 mg base/kg at 24 and 48 hrs
<b><i>P falciparum</i> acquired in areas of chloroquine resistance (if species is not known, assume chloroquine resistance)</b>	
<b>Oral drug of choice:</b> Atovaquone/Proguanil	<5 kg: not indicated 5–8 kg: 2 peds tabs once/day × 3d 9–10 kg: 3 peds tabs once/day × 3d 11–20 kg: 1 adult tab once/day × 3d 21–30 kg: 2 adult tabs once/day × 3d 31–40 kg: 3 adult tabs once/day × 3d >40 kg: 4 adult tabs once/day × 3d
OR	
Artemether/lumefantrine <sup>b</sup>	6 doses over 3 days: 0, 8, 24, 36, 48 and 60 hrs 5–15 kg: 1 tablet/dose ≥15–25: 2 tablets/dose ≥25–35: 3 tablets/dose ≥35: 4 tablets/dose
OR	
Quinine Sulfate	30 mg/kg/day in 3 doses × 3–7d
PLUS	
Doxycycline	4.4 mg/kg/day in 2 doses × 7d
OR	
Quinine Sulfate	30 mg/kg/day in 3 doses × 3–7d
PLUS	
Tetracycline	25 mg/kg/day in 4 doses × 7d
OR	
Quinine sulfate	30 mg/kg/day in 3 doses × 3–7d
PLUS	
Clindamycin	20 mg/kg/day in 3 doses × 7d
<b>Alternatives:</b> Mefloquine	15 mg/kg followed 12 hrs later by 10 mg/kg
<b><i>P vivax</i> acquired in areas of chloroquine resistance (Indonesia or Papua New Guinea)</b>	
<b>Oral drug of choice:</b> Quinine Sulfate	30 mg/kg/day in 3 doses × 3–7d
PLUS	
Doxycycline	4.4 mg/kg/day in 2 doses × 7d
OR	
Quinine Sulfate	30 mg/kg/day in 3 doses × 3–7d
PLUS	
Tetracycline	25 mg/kg/day in 4 doses × 7d
Atovaquone/Proguanil	<5 kg: not indicated 5–8 kg: 2 peds tabs once/day × 3d 9–10 kg: 3 peds tabs once/day × 3d 11–20 kg: 1 adult tab once/day × 3d 21–30 kg: 2 adult tabs once/day × 3d 31–40 kg: 3 adult tabs once/day × 3d >40 kg: 4 adult tabs once/day × 3d
Mefloquine	15 mg/kg followed 12 hrs later by 10 mg/kg



**Table 308-1** Chemotherapy of Uncomplicated Malaria—cont’d

DRUG	DOSAGE
<b>Parenteral drug of choice (severe infection): all <i>Plasmodium</i> species</b>	
Quinidine Gluconate	10 mg/kg loading dose (max 600 mg) in normal saline over 1–2 hrs, followed by continuous infusion of 0.02 mg/kg/min until PO Quinine Sulfate (30 g/kg/day in 3 doses × 7 days) therapy can be started
PLUS either	
Doxycycline	4.4 mg/kg/day in 2 doses × 7d, preferred PO if tolerated
OR	
Tetracycline	25 mg/kg/day in 4 doses × 7d
OR	
Clindamycin	20 mg/kg/day in 3 doses × 7d, preferred PO if tolerated
OR	
Artesunate (followed by one of the following oral agents: atovaquone/ proguanil, clindamycin or mefloquine)	2.4mg/kg/dose IV × 3 days at 0, 12, 24, 48 and 72 hrs (Investigational new drug, contact CDC for information on use)
<b>Prevention of relapses: <i>P vivax</i> and <i>P ovale</i> only</b>	
Primaquine Phosphate	0.6 mg base/kg × 14d

<sup>a</sup>Chloroquine resistant species include *P falciparum* acquired in most areas and *P vivax* acquired in New Guinea and Indonesia, see CDC for detailed map.  
<sup>b</sup>Artemether/lumefantrine tablet: 20mg artemether and 120mg lumefantrine. Take with food or whole milk.  
Modified in part from Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015.

other medications, after departure from the endemic areas. In endemic areas, chemoprophylaxis is used for selected high-risk groups, such as pregnant women and young children.

Vector control aims to decrease contacts between humans and vectors of human disease. Vector control for the prevention of malaria includes insecticide-treated bed nets, indoor residual spraying, and source reduction (larval control). Dichlorodiphenyltrichloroethane (DDT) meets most of the WHO criteria for indoor insecticide. However, resistance to DDT and dieldrin and concern over their environmental impact led to the introduction of other, more expensive insecticides, such as pyrethroids. Pyrethroids are safer to apply than most other insecticides, resistance to them is limited at present, and they are easier to store and transport. Source reduction (larval control) is the method of choice for mosquito control when the breeding sites of the mosquito species are easy to find and treat.

Insecticide-treated bed nets (ITNs) are now an important method for controlling malaria. However, to maintain their efficacy, these nets must be retreated at intervals of 6 to 12 months, more frequently if the nets are washed. House screening to prevent entry of mosquitoes and the use of different repellents such as N,N-diethyl-meta-toluamide (DEET) are other effective methods to prevent contact with mosquitoes.

Developing a vaccine against malaria is difficult because of the inaccessibility of the malarial parasites from an immune attack by replicating inside red blood cells; generally poor immune response to key antigens, compared with the level required for effective

immunity; and high levels of polymorphisms in antigens that are targets of protective responses. According to the Jordan Report, there are 351 vaccines in development, of which 75% of those in phase III trials are attempting to induce full immunity using either recombinant or synthetic subunits.

**Babesiosis**

Babesiosis is a malaria-like illness that is mostly caused by a tick bite. It is a zoonotic disease; the main animal reservoirs are rodents and cattle. More than 100 species of *Babesia* with different animal reservoirs have been identified. However, human disease is mostly caused by the bovine species (*B bovis* and *B divergens*), particularly in Europe, and by the rodent (*B microti*) species in the United States. New emerging species have been identified such as the WA-1 in Washington state and California and the MO-1 in Missouri.

**Epidemiology**

The disease is caused by the bite of the *Ixodes* tick, which also transmits Lyme disease and human granulocytic anaplasmosis. The tick has 3 stages (larva, nymph, adult) and requires a blood meal to mature between stages. Babesiosis disease ends with humans, who get the infection by bite at the nymph stage. Rarely, babesiosis has resulted from blood transfusion. The possibility of perinatal and transplacental transmission has also been considered.

*Babesia* transmission has been found in 2 major geographic areas, with distinct forms of disease:

**Table 308-2** Chemoprophylaxis for Malaria<sup>a</sup>

DRUG	DOSE
<b>Areas with chloroquine-sensitive <i>Plasmodium</i> species</b>	
Chloroquine Phosphate	5 mg/kg base once/week, up to adult dose of 300 mg base
<b>Areas with chloroquine-resistant <i>Plasmodium</i> species</b>	
Atovaquone/Proguanil	5–10 kg: 1–8 tab once/week 11–20 kg: 1 peds tab/day 21–30 kg: 2 peds tabs/day 31–40 kg: 3 peds tab/day >40 kg: 1 adult tab/day
OR	
Mefloquine	11–20 kg: ¼ tab once/week 21–30 kg: ½ tab once/week 31–45 kg: ¾ tab once/week >45 kg: 1 tab once/week
OR	
Doxycycline	2 mg/kg/day, up to 100 mg/day
<b>Alternatives</b>	
Primaquine	0.6 mg/kg base daily
OR	
Chloroquine phosphate PLUS Proguanil	5 mg/kg base once/week, up to 300 mg base 2–6 yrs: 100 mg once/day 7–10 yrs: 150 mg once/day >10 yrs: 200 mg once/day

<sup>a</sup>Chemoprophylaxis should begin 2 weeks before arrival in the area with endemic infection (except doxycycline and atovaquone-proguanil, which should be started 1–2 days before arrival). These medications should be continued, for 1 week when receiving atovaquone-proguanil and 4 weeks when receiving the other medications, after the departure from the endemic areas.

Modified in part from Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015.

Europe and the United States. In Europe, the disease is mostly caused by bovine species, particularly *B divergens*. Patients affected with this species are mostly those who have undergone splenectomy. The disease is transmitted by the tick *Ixodes ricinus*. The disease is typically severe and has high mortality rates. European cases were reported in Yugoslavia, France, Germany, Spain, Sweden, Ireland, Great Britain, and the former Soviet Union.

In the United States, however, most cases are caused by *B microti*. The white-footed mouse is the reservoir of infection. The vector of transmission is the tick *Ixodes scapularis*. The majority of cases occur in the northeastern part of the country as well as the upper midwestern region. This includes islands and coastal areas near Massachusetts, New York, New Jersey, Rhode Island, and Connecticut as well as Wisconsin and Minnesota. Cases have also been reported in other states. Most tick bites go unnoticed and only 10% to 20% of affected individuals recall a tick bite. The majority of cases occur between May and August, the time of nymph abundance and peak outdoor activity. The tick should attach for at least 24 hours to

transmit infection. The majority of infected patients in the United States are immunocompetent. Most infections are asymptomatic. The incubation period is 1 week to several months.

Babesiosis cases have also been reported in other parts of the world including Taiwan, the Canary Islands, Egypt, South Africa, Mexico, and China.

Risk factors for severe disease and mortality caused by babesiosis include age older than 40 years, asplenia, HIV infection, and immunosuppressive therapy including steroids. The disease is particularly overwhelming in patients who have undergone splenectomy.

### Pathogenesis and Life Cycle

The life cycle of *Babesia* is somewhat similar to that of malaria. The parasite multiplies sexually in the vector and asexually in the infected mammal or human. During transmission, humans acquire sporozoites from the salivary gland of the *Ixodes* vector. The sporozoites invade the red blood cells and differentiate into trophozoites, which replicate asexually by budding and release merozoites. This will lead to lysis of red cells and hemolytic anemia. Released merozoites subsequently attack other red blood cells and the cycle goes on. Autoimmune mechanisms may also be implicated in hemolysis as evidenced by a positive Coombs test result in some patients with babesiosis.

In addition to hemolysis, intraerythrocyte multiplication leads to vascular stasis secondary to increased adherence to endothelial cells. This results in ischemic damage in different organs including the liver, spleen, heart, and brain. Hemolysis and vascular injury may also cause renal insufficiency. Increased proinflammatory cytokine release has also been demonstrated in patients. All these may contribute to pulmonary edema and a sepsislike picture may eventually develop.

The spleen plays an essential role in limiting babesiosis by removing deformed erythrocytes. This explains the high levels of parasitemia and severe disease that occur in patients with splenectomy. Both cell-mediated and humoral immunity are demonstrated during infection. However, the cell-mediated immune responses via CD4 cells and interferon- $\gamma$  are known to play a critical role in controlling babesiosis.

### Clinical Manifestations

Most pediatric babesiosis cases are subclinical or mild. In symptomatic patients, the clinical manifestations range from nonspecific symptoms to severe hemolysis. The typical symptoms are characterized by a flulike illness, with gradual onset of malaise, fatigue, and anorexia followed by episodes of fever associated with chills, sweats, myalgia, headache, and vomiting. Less commonly, conjunctival injection, meningismus, altered sensorium, and nonproductive cough may be present. The nonspecific symptoms may cause a delay in diagnosis. Symptoms may last for several weeks or sometimes for months. Patients who are coinfecting with *Borrelia burgdorferi*, the agent of Lyme disease and/or *Anaplasma phagocytophila*, the agent of human granulocytic anaplasmosis, tend to develop more prolonged symptoms. HIV-infected patients have also been reported to have prolonged clinical course.

Infection with *B divergens* is associated with fulminant illness.

Immunodeficient patients and those with splenectomy develop severe infection characterized by hemolytic anemia, jaundice, and dark urine. Severe babesiosis may also occur in post-transfusion cases. Many signs and symptoms are similar to those of malaria. Lactate dehydrogenase levels will be elevated. The hemolysis seen in babesiosis is milder than that of malaria. As a result of hemolysis, renal insufficiency with anurea and azotemia may develop. Other possible complications of babesiosis in this group of patients include hypotension, shock, disseminated intravascular coagulation, heart failure, and acute respiratory distress syndrome.

### Diagnosis

The diagnosis of babesiosis is made by demonstrating the organism in blood smears. Similar to malaria diagnosis, thick and thin smears should be prepared using Wright and Geimsa stains. *Babesia* species may sometimes be difficult to differentiate from *Plasmodium* species. However, the differentiating feature of *Babesia* species include the presence of a cluster of 4 small merozoites called the *tetrads* in red blood cells. Because the red cells tend to be infected repeatedly, multiple parasites may be present in a single cell. The occasional presence of 3 chromatin dots in a single parasite is another differentiating feature. In addition, no pigment is seen in *Babesia* smears; schizonts and gametocytes are also absent.

Serology should be considered when blood smears are nondiagnostic such as in cases with low parasitemia. The most sensitive test is the indirect immunofluorescent assay available in reference laboratories. PCR testing has also become available for the diagnosis of babesiosis. The test is more sensitive than blood smear. It may also be used for monitoring therapy and for epidemiologic surveillance.

### Treatment

The recommended treatment regimens for symptomatic infection are clindamycin plus oral quinine or atovaquone plus azithromycin for 7 to 10 days. Exchange transfusion should be considered for fulminant cases with severe hemolysis and high-grade parasitemia (>10%).

### Prevention

Recommendation for prevention of tickborne infections should be followed. Tick-infested areas should be avoided if at all possible, particularly during the May to September period. Wearing clothing that covers the arms, legs, and other exposed areas and tucking pants into socks or boots should be considered. Tick and insect repellants that contain DEET may be considered, but repeat applications may be needed. Tick-toxic agents such as permethrin may be sprayed on clothes and shoes but not the skin. In addition, people should inspect themselves and the bodies of their children as well as all clothing for ticks after possible exposure. Exposed hairy areas including the scalp and behind the ears should be thoroughly inspected. If a tick is found, it should be grasped with tweezers close to the skin and gently pulled out

straight. Pets should also be inspected every day for ticks; if identified, the ticks should be removed.

## NEMATODE INFECTIONS

### Trichinellosis (*Trichinella spiralis*)

The infection is caused by the roundworm of the genus *Trichinella*. There are 6 species that can infect humans and animals but the most common is *Trichinella spiralis*. In contrast to other parasitic infections, trichinellosis (or trichinosis) is more common in Europe and America than in Asia and Africa.

### Epidemiology

*Trichinella* can infect carnivorous animals, particularly scavengers. Humans acquire infection by eating raw or inadequately cooked meat containing *Trichinella* cysts. Domestic pigs are the most common source of infection in America and Europe. The incidence of trichinellosis has been declining steadily in the United States. This is believed to be a result of new laws governing production and processing of pork, including the feeding of swine; routine slaughterhouse surveillance; and improved public awareness. Undercooked wild game, especially bear, seal, and walrus meat has emerged in recent years as the most common cause of trichinellosis. *T nativa* is the subspecies most frequently associated with arctic sources. Consumption of horse meat has also been associated with trichinellosis. The incubation period is 1 to 2 weeks.

### Life Cycle and Pathogenesis

After the ingestion of infected meat by humans, the larvae are liberated from the cysts in the intestine and mature into adults in epithelial cells. The adult male dies after mating. The fertilized adult female produces embryos at a rate of 1 every 30 minutes during her life span of 4 to 16 weeks. The larvae then enter the bloodstream via the intestinal lymphatics and disseminate to different organs. *Trichinella* larvae survive only in the skeletal muscles and become encysted in 2 to 3 weeks. The most frequently affected muscles are those of the limbs and the diaphragm, followed by the tongue, intercostals, extrinsic muscles of the eye, and laryngeal and paravertebral muscles.

### Clinical Manifestations

Most infections are asymptomatic. The severity of infection correlates with the number of ingested larvae. The infection has 2 stages. The first is the intestinal stage, which begins 24 hours after infection and lasts for 1 to 7 days. During this phase, patients may be asymptomatic or experience gastrointestinal symptoms such as nausea, vomiting, diarrhea, constipation, and abdominal pain. The muscle stage starts after the first week and correlates with dissemination of larvae from the intestine to the bloodstream. The typical symptoms consist of the triad of myalgia, eyelid edema, and eosinophilia. This phase may last 1 to 5 weeks or longer. The myalgias may be prominent and mimic rheumatic pain. Muscle pain, tenderness, swelling, and weakness can occur. The larvae may remain viable in the muscles for years. Calcification may occur after several months and may be detected on radiography. The edema often involves the face, eyelids,



and conjunctiva. Other common associated findings are high and prolonged fever, which is rarely seen in parasitic infections, weakness, and malaise. Other less frequent findings include headache, subconjunctival hemorrhages, retinal hemorrhages, splinter hemorrhages under fingernails, facial flushing, urticarial or macular rashes, hoarseness, dyspnea, and dysphagia. The clinical manifestations of trichinellosis are caused by either larval invasion or host immune response to the parasite.

The most common cause of death in cases of severe trichinellosis is myocarditis with subsequent heart failure and cardiac arrhythmias. Cardiac involvement usually occurs in the second to third week of infection. Severe trichinellosis may also be associated with encephalitis, meningitis, focal neurologic deficits, bronchopneumonia, and nephritis.

### Diagnosis

The diagnosis of trichinellosis should be suspected in patients with a suggestive clinical history, including consumption of inadequately cooked meat, particularly pork, and eosinophilia. The presence of clinical symptoms in other patients who shared the same food makes the diagnosis stronger. Eosinophilia usually appears during the second week of the muscle phase and may be as high as 70%. Muscle enzymes such as creatine kinase and lactate dehydrogenase may be elevated as may be immunoglobulin levels.

Serologic tests are used to make the diagnosis of trichinellosis. Different assays are used including ELISA, indirect immunofluorescence assay, and latex agglutination. ELISA is the most sensitive assay. Serologic tests are only helpful after the second week of infection when antibody titers start to rise. Testing of paired acute and convalescent serum samples is diagnostic. Antibody levels may remain positive for more than 1 year after clinical improvement.

The most definitive diagnostic test is finding larvae microscopically in muscle biopsy. However, this only occurs after the first 2 weeks after ingestion. The number of larvae per gram of muscle has been used as a guide of severity of infection. When tested, specimens should be fresh and compressed between 2 microscope slides or should be digested by artificial gastric juice to increase yield. Suspected infected meat sources may also be tested for larvae. Recently, PCR testing was used to detect *Trichinella*-specific DNA in muscle biopsy specimens. The test was found to be sensitive and specific, but its availability is limited.

### Treatment

Mebendazole and albendazole are recommended for treatment of trichinellosis with comparable efficacy. Mebendazole is given at a dose of 200 to 400 mg 3 times a day for 3 days, then 400 to 500 mg 3 times a day for 10 days. Albendazole may achieve higher tissue levels; the dose is 400 mg twice daily for 10 to 15 days. Both drugs are ineffective for larvae already in the muscles. Coadministration of steroids such as prednisone is indicated in severe cases especially for those with cardiac and CNS involvement. People who have recently ingested *Trichinella*-contaminated meat should be treated with mebendazole or albendazole.

### Prevention

Control can be achieved by thoroughly cooking pork and game meat. Freezing is also effective in killing larvae in meat. The encysted larvae of *Trichinella* are killed by heating to a temperature of 77°C or freezing at –15°C for 3 weeks, which is available via home freezers. Freezing pork meat at –23°C for 10 days is also effective, but *Trichinella* in arctic species may be resistant and may remain viable. Transmission to pigs can be decreased by not feeding them unprocessed garbage and by effective rat control.

### Hookworm Infections (*Ancylostoma duodenale* and *Necator americanus*)

Hookworm infections are widely prevalent in tropical and subtropical regions. Factors that favor spread of hookworm in these regions include warm climate, abundance of rain, soil contaminated with human feces, and people walking barefoot. The 2 most common hookworms are *Ancylostoma duodenale* and *Necator americanus*.

### Epidemiology

The prevalence of hookworm species varies in different geographic areas. *A. duodenale* is prevalent in Mediterranean countries, India, Pakistan, Iran, and the Far East. *N. americanus* is prevalent in North and South America, central Africa, Indonesia, and islands of the South Pacific. Humans are the only reservoir of infection. Hookworm eggs excreted in stool hatch in soil within 1 to 2 days, forming larvae that mature within approximately 1 week into infective larvae. These larvae may persist for weeks or even months in soil if appropriate temperature (23°C–33°C) and conditions such as moisture are found.

Humans acquire infection after percutaneous penetration of larvae. However, *A. duodenale* may also be acquired via the oral route or human milk. As few as 3 larvae are enough to cause infection. From the skin, larvae reach the lungs and then the tracheobronchial tree. Then the larvae are coughed and swallowed, reach the small intestine, and develop into adult worms. Eggs appear in the stools 1 to 3 months after infection.

### Clinical Manifestations

Persistent eosinophilia is a common finding. The symptoms and signs correlate with the stage of infection. The earliest findings result from larval penetration of the skin. Itching, focal eruptions with or without edema or enlargement of adjacent lymph nodes is referred to as “ground itch.” Pulmonary migration is associated with mild respiratory symptoms such as cough. However, in severe cases, Loeffler syndrome may develop.

In the intestinal phase, patients may complain of abdominal pain, nausea, vomiting, increased flatulence, diarrhea, and constipation. However, the main symptoms of hookworm infection are related to iron-deficiency anemia and loss of plasma protein. A single worm of *A. duodenale* sucks 0.01 to 0.04 mL of blood per day, whereas *N. americanus* sucks 0.05 to 0.3 mL of blood per day. Greater blood losses occur around the worm attachment site. Malnutrition and blood loss with iron-deficiency anemia are the most significant



complications of heavy infection in normal hosts. The severity of anemia and malnutrition is higher in children infected with *A duodenale* than in those infected with *N americanus*. Anthelmintic therapy improves nutritional status and hemoglobin levels in these patients.

### Diagnosis

Hookworm infection is diagnosed by identification of eggs in stools. The eggs of *A duodenale* and *N americanus* are morphologically indistinguishable. However, the species can be identified using PCR testing. Adult worms are rarely seen. Larvae are rarely seen in stool samples when the samples are left at room temperature for 24 hours or in patients with constipation. Stool smears are often negative in early stages of infection because of delayed egg excretion. Stool concentration techniques may be needed in patients with mild infection. Repeat stool examinations may also be needed.

### Treatment

Malnutrition and anemia may need correction including iron supplementation. Albendazole, mebendazole, and pyrantel pamoate are the drugs of choice for treating hookworms in children and adults. Albendazole is not approved by the FDA for treatment of hookworm infections. Mebendazole is no longer available in the United States. Albendazole is given at 400 mg once. The dose of mebendazole is 100 mg twice daily for 3 days or 500 mg once; the dose of pyrantel pamoate is 11 mg/kg (maximum 1 g) for 3 days. If given to children younger than 2 years, the doses of mebendazole and albendazole may be reduced by half. Repeat stool examination is recommended 2 weeks after treatment; if positive, retreatment should be considered. A 3-day course of nitazoxanide may be effective in treating hookworms, but no comparative data with albendazole are available.

### Prevention

Proper disposal of human feces is essential. All patients with known infection should be treated to decrease environmental contamination. Individuals at high risk of infection including children and agricultural workers in endemic areas should be screened for the presence of hookworms in stools and appropriately treated.

Education of the population regarding footwear may reduce transmission of hookworm infection.

### Ascariasis (*Ascaris lumbricoides*)

Ascariasis is the most prevalent helminthic infection worldwide. It is estimated that more than 1.4 billion people are infected with ascariasis. It is most common in the tropics and areas of poor sanitation practices, including regions in which human feces are used for fertilization. In the United States, ascariasis is the third most common helminthic infection following hookworm and *Trichuris trichiura* infection. It is caused by *Ascaris lumbricoides*, the largest roundworm that infects humans.

### Epidemiology

The female adult worm measures 22 to 35 cm in length and 3 to 6 mm in diameter and resides in the lumen

of the jejunum and ileum. Females produce 200,000 eggs per day which are excreted in stools. Fertilized eggs become infective in soil 3 to 4 weeks after they are excreted. Human infection occurs by ingesting eggs from contaminated soil. Larvae hatch in the intestine, penetrate the intestinal wall, and migrate to the right heart, lungs, and bronchial tree. From there, the larvae ascend to the pharynx and are subsequently swallowed to mature into adult worms in the small intestine. Female worms begin laying eggs 2 to 3 months after exposure. The lifespan of the parasite is 6 months to 1 year.

### Clinical Manifestations

Most infections are asymptomatic. However, the burden of the disease is high because of the widespread prevalence of disease. Symptoms are caused by either the larval migration or the presence of the adult worm in the small intestine. Clinical features and complications are caused by direct tissue damage, the immune response of the host, obstruction, or malnutrition.

During larval migration, an acute transient pneumonitis known as *Loeffler syndrome* tends to occur 1 to 2 weeks after ingestion of the eggs. This syndrome is often associated with fever, marked eosinophilia, and other symptoms related to hypersensitivity such as urticaria. Nonspecific gastrointestinal symptoms occur in patients with ascariasis such as abdominal discomfort, nausea, vomiting, and diarrhea. Moderate to heavy infections in children may be associated with malnutrition and malabsorption of proteins, lactose, and vitamins. Heavy infection may also lead to acute intestinal obstruction caused by a mass of worms in the bowel lumen. The obstruction most frequently occurs at the ileocecal valve. Most affected patients are young children (1–5 years old). Other intestinal complications in endemic areas include ileocecal intussusception, volvulus, intestinal gangrene, and perforation. Intestinal obstruction is the primary cause of death in ascariasis.

Worm migration into the biliary tree can cause biliary colic, cholecystitis, and ascending cholangitis. Biliary strictures and hepatic abscesses are other less frequent complications. Pancreatitis may also result from migration of the adult worm into the pancreatic duct. Worm migration to the appendix may lead to appendicitis. Migration may occur through body orifices such as the mouth, nose, anus, and lacrimal duct. Worm migration is stimulated by stress factors such as fever, intercurrent illness, diarrhea, spicy foods, and anesthesia. Some anthelmintic agents may also stimulate worm migration.

### Diagnosis

Diagnosis of ascariasis is made by demonstration of characteristic eggs in stools using direct microscopy. Eggs may not appear in the stools until after at least 40 days of infection. Usually 1 stool sample is sufficient to confirm the diagnosis. Sometimes adult worms are passed and provide a clue to the diagnosis. Peripheral eosinophilia occurs during the pulmonary phase of infection. In addition, eosinophils and occasionally *Ascaris* larvae may be demonstrated in sputum samples. Imaging studies may demonstrate worms in

cases of intestinal obstruction as well as in cases of hepatobiliary or pancreatic ascariasis. Serologic testing is not helpful in diagnosis but can be used in epidemiologic studies. Serum IgG antibodies are not protective.

### Treatment

The recommended treatment of symptomatic and asymptomatic infections is albendazole in a single dose (400 mg), mebendazole 100 mg twice daily for 3 days, or ivermectin 200 µg/kg in a single dose. Although data suggest that these drugs are safe, experience with these drugs is limited in children younger than 2 years. Thus, the risk and benefits of treating ascariasis should be considered in this age group. Pyrantel pamoate and nitazoxanide are also effective in treatment of ascariasis. Reexamination of stools after 2 weeks is helpful to assess the effectiveness of the therapy.

Cases with suspected intestinal or biliary obstruction should be managed conservatively with nasogastric suction and intravenous fluid. Piperazine solution (75 mg/kg per day, maximum 3 g/d), which may be given by a nasogastric tube, may relieve obstruction caused by heavy intestinal worm burden. Piperazine paralyzes the worm and prevents migration during passage through the intestine. Piperazine is not available in the United States, and is not approved by the FDA for this indication. Conservative management to alleviate obstruction is followed by anthelmintic therapy with either albendazole, mebendazole, or ivermectin. Nitazoxanide may also be used. Albendazole, ivermectin, and nitazoxanide are not FDA labeled for use in ascariasis. Pyrantel pamoate and piperazine are antagonistic and should not be given together.

Surgery is recommended if medical therapy is not successful at relieving obstruction or in complications such as volvulus peritonitis or perforation. During laparotomy for obstructive cases, the small bowel should be “milked” down to the cecum, avoiding incision of the bowel wall. Endoscopic retrograde cholangiopancreatography is used to extract worms in hepatobiliary cases.

### Prevention

Prevention of reinfection is a challenging problem because of the abundance of *Ascaris* eggs in soil. Sanitary disposal of human feces is essential to prevent soil contamination, particularly near children’s play areas. In some areas, educational programs aimed at stopping the use of human feces as a fertilizer may be needed. In such areas, people should also be educated about proper food washing and cooking.

Mass deworming programs with a single dose of mebendazole or albendazole have been used in some communities in areas in which ascariasis is endemic. School children are the target in most programs. These programs are used every 3 to 4 months and are aimed at treating and preventing morbidity in children as well as decreasing the worm burden in the community. In highly endemic areas where more than 50% of the population is infected, the whole population may be targeted for mass treatment.

## Toxocariasis

### Visceral larva migrans

Toxocariasis is caused by the *Toxocara* species. Visceral larva migrans (VLM), which is also called toxocariasis, is caused by migration of the larvae in the viscera of the host. This syndrome is caused by the dog ascarid, *Toxocara canis* and less frequently by the cat ascarid, *Toxocara cati*. Other nematodes such as *Baylisascaris procyonis*, the common raccoon roundworm, rarely cause VLM. The life cycle of *T canis* and *T cati* in their respective animal species is similar to that of *Ascaris lumbricoides* in humans. Humans are considered unusual hosts for *T canis* and *T cati*. Thus, infection with these parasites causes failure to complete the life cycle or aberrant migration of larvae. Because the parasite fails to mature in humans, it remains alive in the body for months to years.

**EPIDEMIOLOGY.** Humans acquire infection by ingesting soil contaminated with infective eggs of the parasites. The disease is endemic in areas with dogs. The highest number of reported cases of VLM is in the United States. A large number of pets, particularly puppies, are infected and routinely contaminate yards, school playgrounds, and sandboxes. Most affected patients are children 1 to 4 years of age. History of pica is common. The eggs are not immediately infective after shedding by dogs. However, after about 3 weeks in the soil, they can cause infection in humans. Hot, humid regions are associated with persistence of eggs in soil and increased risk of infection. The disease may be found anywhere dogs are present. The highest rates of transmission are in the southern United States, particularly in rural areas. However, infection can also be acquired in urban areas. It has been estimated that 20% of dogs and 98% of puppies are infected.

**PATHOGENESIS AND LIFE CYCLE.** The reservoir of *T canis* infection is the female dog. The disease is reactivated during pregnancy and then transmitted to puppies via the placenta or breast milk. The puppies shed eggs in the surrounding environment. When humans ingest these eggs, the larvae hatch in the intestine and spread via the portal circulation to the liver and then to the systemic circulation. Because the parasite cannot mature, it passes through different organs and tissues before it overwhelms the immune system. The most commonly involved organ is the liver. However, the lungs, heart, kidneys, eye, skeletal muscles, and brain may also be involved. During tissue migration, granulomas are formed and a significant host immune response is demonstrated by peripheral eosinophilia and elevated IgE levels. The manifestations and severity of infection depend on the immune status of the host, the burden of infection, and the site of involvement.

**CLINICAL MANIFESTATION.** Most patients who are mildly infected are asymptomatic. Incidental findings or eosinophilia, hepatomegaly, and history of pica in these patients may prompt a search for the diagnosis of toxocariasis. Symptomatic children with VLM usually present with fever, leukocytosis with eosinophilia, hypergammaglobulinemia, and hepatomegaly. Splenomegaly and lymphadenopathy are other associated findings. Patients may also have allergic manifestations such as urticaria, rhinorrhea, and asthma. Pulmonary

infiltrates may be evident on radiographs. Constitutional symptoms such as anorexia, weakness, failure to gain weight, myalgia, arthralgia, and nocturnal sweats may also be present. Neurologic symptoms include irritability and seizures but are less frequent. Other reported findings include myocarditis, congestive heart failure, pleural effusion, eosinophilic ascitis, and meningoencephalitis.

Ocular involvement usually affects patients older than 4 years of age; when it occurs, usually no other systemic involvement is seen. This suggests that the ocular and visceral forms of oxocariasis are 2 distinct entities. This form of disease, which is seen in older children with no history of pica, is called *ocular larva migrans* (OLM). Patients often have a unilateral solitary posterior retinal lesion. A granulomatous mass or multiple lesions may be seen. Lesions are painless and some are asymptomatic and found incidentally on routine retinal examination. Common symptoms include strabismus, visual impairment, unilateral loss of vision, and leukocoria. Complications of OLM include chronic endophthalmitis, retinal detachment, keratitis, uveitis, iritis, vitreous abscess, optic neuritis, and retinal tracks with larvae. Some cases in the past, such as cases of retinoblastoma, were misdiagnosed and managed as intraocular tumors. Patients with OLM typically do not have other organ-systemic involvement.

**DIAGNOSIS.** A definitive diagnosis of VLM requires demonstration of the larvae in tissue sections, but this is rarely needed. In most cases, the diagnosis is based on clinical findings and serologic testing. In systemic toxocariasis, eosinophilia is a consistent finding. The total white cell count may be as high as 30,000/ $\mu$ L ( $30 \times 10^9$ /L) with up to 80% eosinophils. Other consistent and nonspecific laboratory findings include hypergammaglobulinemia with high IgE levels, sometimes 10 to 15 times the normal levels as well as elevated isohemagglutinins to the A and B blood groups. During the pulmonary phase of involvement, eosinophils may be detected in respiratory secretions. With CNS involvement, CSF specimens may also show eosinophils.

Serologic testing is used to confirm the diagnosis of VLM. ELISA is the most frequently used test and has high sensitivity and specificity. Western blot and immunofluorescence tests have also been used. Serologic tests are often negative in OLM.

**TREATMENT.** Infections in most patients are self limited and require no specific treatment. Treatment is recommended for patients with symptoms and those with systemic form of the disease. The recommended drug for treatment in children is albendazole. The drug has been approved by the FDA but not for this clinical indication. It is given at a dose of 400 mg twice a day for 5 days. Corticosteroids are indicated for cases with severe cardiac and CNS involvement. Ocular involvement is treated with anthelmintic therapy, surgery, steroids, or a combination of these modalities. Diethylcarbazine is another alternative. The drug is not FDA approved but a 3-week course is recommended by the WHO for this indication. The dose is 3 mg/kg twice daily. It is common to start the dose at 1 mg/kg twice daily and then increase gradually to decrease allergic reactions induced by dying larvae.

**PREVENTION.** Underlying causes of pica in children should be corrected. Cat and dog feces should be properly disposed of. Sandboxes that are in use should be covered. Regular anthelmintic therapy for puppies and kittens may prevent secretion of eggs in feces and subsequent potential transmission to toxocariasis.

## CESTODE INFECTIONS

### Taeniasis and Cysticercosis (*Taenia solium* and *Taenia saginata*)

#### Epidemiology

Humans are the only definitive host for 2 *Taenia* species, *Taenia solium* and *Taenia saginata*. Taeniasis is caused by the adult worm of both species whereas cysticercosis is caused by the larval stage of only *T solium* (not *T saginata*). Both species have a worldwide distribution, with a higher prevalence in areas in which undercooked beef or pork are customarily consumed. *T saginata* is found most commonly in some states of the former Soviet Union, the Near East, and Central and Eastern Africa, and is less commonly found in Europe, Southeast Asia, and South America. *T solium* is prevalent in Mexico, Central and South America, Africa, and Southeast Asia, and very rare in Muslim countries. In the United States, human infections are usually found in immigrants from areas with high disease prevalence or travelers who consume undercooked meats in endemic areas. Although most cases of human cysticercosis in the United States have been imported, it has been found that cysticercosis can be acquired from patients or immigrants from endemic areas who have the adult stage of *T solium* infection in the intestine.

#### Life Cycle

Taeniasis is a human infection caused by the adult stage of *T solium* or *T saginata*. Humans acquire infection by ingesting undercooked beef (for *T saginata*) or pork (for *T solium*) that contained cysticerci in the muscle. Inside the human intestine, protoscolices are released from the cysticerci and attach to the intestinal wall with suckers and hooks. The protoscolices become the head of the tapeworm, later develop by forming the proglottids, and mature into an adult tapeworm over a period of 2 months. This maturation occurs inside the human small intestine where the tapeworms can survive for years. As the adult tapeworm develops, mature proglottids are produced and later become gravid. The gravid proglottids that contain egg-filled uterus detach from the tapeworm, migrate to the anus, and are passed in the stool. The eggs inside the gravid proglottids are released in the stool after the proglottids are passed with the feces. In the environment, eggs can survive for days to months. The intermediate hosts, cattle for *T saginata* and pigs for *T solium*, become infected after ingesting vegetation contaminated by eggs or gravid proglottids. The oncosphere hatches inside the animal intestine, invades the intestinal wall, and later migrates through the hematogenous or lymphatic system to the straight muscles. The oncosphere develops into cysticerci in the animal muscle. The cycle completes when humans ingest undercooked meats that contained cysticerci



in the muscle. The cysticerci can survive in the muscle of the animal for years.

Cysticercosis is an infection in humans that occurs when a human becomes infected with the larval stage of *T solium*. Infection occurs after embryonated eggs are ingested by the human. This can occur either by ingesting food contaminated with human feces or autoinfection. In the case of autoinfection, a human becomes infected after ingesting eggs produced by that tapeworm via oral-fecal contamination or possibly from proglottids that are carried backward into the stomach through reverse peristalsis. Inside the human intestine, the oncosphere hatches, penetrates the intestinal wall, and migrates via circulation or lymphatic channels to various tissue sites. Cysticerci may develop in any organ, more commonly the brain, subcutaneous tissue, eye, and liver, resulting in cysticercosis.

### Clinical Manifestations

Taeniasis is often asymptomatic. Patients may experience minimal gastrointestinal tract symptoms such as nausea, diarrhea, and abdominal pain or discomfort. The main symptom usually is the intermittent passage of the proglottids either with the stool or spontaneously. The proglottids may enter the appendix, common bile duct, or pancreatic duct and cause obstruction. A large number of worms can also cause intestinal obstruction.

Cysticercosis can affect humans at any age. Most of the infections occur during the third or fourth decades of life; about 10% of cases occur in children. Cysts can be found anywhere in the body, most commonly in the CNS. Clinical manifestations usually depend on location, stage, and number of cysts as well as the host immune reaction. Symptoms frequently become evident when an inflammatory response develops around a degenerating cyst after a variable period. Cysticercosis in children manifests differently than in adults. The most serious manifestation of cysticercosis is neurocysticercosis or cysticercosis of the CNS. In infants, the initial clinical manifestation of neurocysticercosis is generalized seizure. In most cases, the cysts resolve spontaneously; however, in about one-third of cases, the cyst may remain as a granuloma that later becomes calcified. Children with calcified granuloma in the CNS have a high risk of developing chronic seizures. In adolescents and young adults, neurocysticercosis may remain clinically silent through multiple stages of infection until it becomes a calcified granuloma that eventually serves as foci causing epilepsy, frequently after 25 years of age. Neurocysticercosis in adults manifests differently from that seen in children and generally is asymptomatic. Patients frequently have cysts in more than 1 location. Cysts can be seen in various stages, and some patients may have both active and inactive cysts at the same time. Symptoms, if any, occur mainly because of a mass effect, an inflammatory response, or obstruction of the ventricular system of the brain. The most common form of neurocysticercosis in adults is the active parenchymal cyst. Patients may present with severe headache and focal or generalized seizure. Physical examination findings usually are normal without any neurologic deficit

symptoms. A calcified parenchymal cyst is found less commonly and is usually asymptomatic. However, clinical symptoms such as focal neurologic deficit and seizure may develop as perilesional edema occurs. The other less common forms of neurocysticercosis are subarachnoid cysts, ventricular cysts, and spinal cysticercosis. Patients with subarachnoid cysts may present with visual field defect or cranial nerve palsies as a result of cranial nerve entrapment from meningeal inflammation and irritation. Hydrocephalus or signs and symptoms of increased intracranial pressure are a common manifestation in patients with ventricular cysticercosis. Spinal cysticercosis is rare and is found in only about 1% to 3% of all neurocysticercosis cases. Symptoms depend on the location of the cyst and may not be distinguishable from other spinal cord lesions.

Cysticercal encephalitis is characterized by encephalitis and generalized brain edema occurring as a result of a severe immune response of the human host to massive amount of cysts in the brain parenchyma. Symptoms include fever, headache, vomiting, impaired consciousness, reduced visual acuity, and seizure. This reaction may develop spontaneously or after treatment with medication that leads to degeneration of large numbers of cysts at the same time. Cysticercal encephalitis occurs most commonly in children and young women.

Extraneural cysticercosis typically involves eye, muscle, and subcutaneous tissue. Ocular cysticercosis is found in about 1% to 3% of all cases. Generally, patients are asymptomatic; however, symptoms may become apparent as the cyst degenerates with surrounding inflammatory reaction. In patients with neurocysticercosis, it is recommended that ocular cysticercosis should be excluded before initiating treatment. Patients with subcutaneous or intramuscular cysticercosis usually are asymptomatic. Some patients may notice small palpable nodules that may be inflamed or may experience muscle pain. Subcutaneous and muscular cysticercosis is found more commonly in patients from Asia and Africa than in those from Latin America.

### Diagnosis

Diagnosis of taeniasis is made via microscopic identification of eggs or proglottids in the stool. This may not be possible during the first 3 months of infection before maturation of the adult worm and production of gravid proglottids. Eggs of *T solium* are microscopically indistinguishable from those of *T saginata* or of other tapeworm species, especially the *Echinococcus*. The species can be determined by microscopic examination of the gravid proglottids and scolex, if available.

The definitive diagnosis of cysticercosis is made by demonstration of the cysticercus in the involved tissue. Demonstration of eggs or proglottids in the stool specimen may help support the diagnosis but does not prove the presence of cysticercosis. For neurocysticercosis, CT scan and MRI are the most reliable imaging techniques. MRI has the advantage of better visualization of ocular, ventricular, and subarachnoid cysts. It also clearly demonstrates the degree of edema and inflammation as well as the viability of the cysticercus. The advantage of CT is better detection of a



granuloma or calcification, which can be missed on MRI. Several serologic studies have been developed for the diagnosis of cysticercosis. The serologic test of choice acknowledged by WHO and the Pan American Health Organization for confirming diagnosis of cysticercosis is the CDC immunoblot assay with purified *T solium* antigens. It has 100% specificity and 50% to 97% sensitivity depending on the number and stage of the cysticerci. The enzyme immunoassay (EIA) technique is another serologic study available for the diagnosis of cysticercosis. Compared with the immunoblot, EIA has less sensitivity and specificity. In addition, EIA also can cross-react with other helminthic infections such as echinococcosis and filariasis; hence, the EIA is less preferable than the immunoblot technique. To date, no available serologic test has been developed that can distinguish between active and inactive infection. Both the cysticercosis immunoblot and EIA kit are commercially available in the United States.

### Treatment

Praziquantel is the drug of choice for the treatment of taeniasis caused by both *T solium* and *T saginata*, and is highly effective in eradicating the adult-stage (intestinal stage) tapeworm. Praziquantel is not approved for this indication, but the recommended dose for children is 5 to 10 mg/kg as a single dose.

Niclosamide and nitazoxanide are alternative agents; niclosamide is not available commercially in the United States.

Treatment of cysticercosis is complicated, especially for ocular and neurocysticercosis. The appropriate treatment for a patient depends on location of the cyst, viability of the cyst, the host immune response, and the presence or absence of symptoms. In general, the widely accepted cysticidal agents are albendazole and praziquantel. For neurocysticercosis, treatment is generally not recommended for the asymptomatic patient with a nonviable single parenchymal cyst that is evidently destroyed by the host immune response. In children with viable cysticercus with minimal or no surrounding inflammatory response, a cysticidal agent should be given to prevent further perilesional damage and to reduce the risk of developing chronic seizure. After initiating treatment, patients may develop a treatment reaction as a result of sudden destruction of the cysticerci. This is usually accompanied by an inflammatory reaction of the surrounding tissue. Clinical manifestations include severe headache and vomiting. The treatment reaction can be minimized with a corticosteroid (dexamethazone) 2 to 3 days before treatment initiation and during treatment with a cysticidal agent. The recommended dose for albendazole is 15 mg/kg per day (maximum dose of 800 mg/day) divided into 2 doses for 8 to 30 days. The treatment can be repeated as necessary. Praziquantel is an alternative cysticidal agent. The recommended dose for praziquantel is 50 to 100 mg/kg per day in 3 divided doses for 30 days. In general, albendazole is preferred over praziquantel because of its higher cysticidal activity, less interaction with anticonvulsants, and lower cost. An anticonvulsant agent is usually recommended for patients who present with seizures and patients

with multiple cysts with no history of seizure because of the risk of developing seizure activity after treatment initiation.

For cysticercal encephalitis, the initial goal of treatment is to reduce inflammation and cerebral edema with a corticosteroid or immunosuppressive agent. In these patients, treatment with a cysticidal agent should be deferred because the subsequent inflammatory response may worsen outcome, and in many cases, the cysticerci may resolve with antiinflammatory therapy alone. A small cyst located in the lateral ventricle can be treated effectively with an antihelminthic agent. Insertion of a ventriculoperitoneal shunt is recommended before initiating treatment in patients with hydrocephalus. In a child with a cyst in the fourth ventricle, attached to the middle cerebral artery, or compressing the optic chiasm, surgery is recommended before initiating a cysticidal agent. Children with subarachnoid cysts or a large cyst in the fissures should be treated for at least 30 days.

Surgery is the mainstay of treatment for ocular and spinal cysticercosis with no clearly defined role of anthelmintic therapy. For intraocular subretinal cysts, treatment with albendazole combined with a corticosteroid may be effective, whereas intraocular cysts located in the vitreous chamber should be removed surgically. An ophthalmologic examination should be performed in all cases to rule out intraocular cysts before initiating treatment. Children with symptomatic subcutaneous or muscular lesions should receive an antiinflammatory medication. Surgical excision of a solitary subcutaneous or intramuscular cyst may be considered for patients with persistent symptoms. Children with neurocysticercosis should be monitored with a brain imaging study after completion of treatment.

### Hymenolepiasis (*Hymenolepis nana*)

#### Epidemiology

*Hymenolepis nana* (dwarf tapeworm) is the most common cestode tapeworm infecting humans worldwide. Transmission is associated with poor sanitation and hygiene and usually is acquired by ingestion of food or water contaminated with human or rodent feces. Infections occur most commonly in children because of fecal-oral contamination. The highest disease prevalence is observed among institutionalized school-age children in developing areas of the world. An infection rate of 4% has been reported among school children in the rural southeastern part of the United States.

#### Life Cycle

*H nana* differs from all other cestodes because of its ability to complete its entire life cycle in a single host. The embryonated eggs are passed in the stool of an infected person and become infective immediately. Eggs are ingested by an intermediate arthropod host, and develop into cysticercoids inside the insect. Humans can acquire infection by ingesting embryonated eggs in contaminated food or water, via the hands, or cysticercoids-infected arthropods. In the human small intestine, the oncospheres (hexacanth larvae) are released from the eggs and penetrate into intestinal villus. The oncospheres develop into cysticercoids inside intestinal villus and later migrate back into

intestinal lumen. The cysticercoids evaginate their scoleces, attach themselves to the ileal part of intestinal mucosa, and mature into the adult worm. Eggs are released from the gravid proglottids of the adult worm and passed in the stool. Internal autoinfection can occur when eggs remain in the intestine. The eggs release their oncospheres, which penetrate the intestinal villus and continue the cycle without being passed to the external environment. The adult worms mature within 4 to 6 weeks.

### Clinical Manifestations

Most infections are asymptomatic. Patients with heavy infection may experience abdominal pain, nausea, vomiting, diarrhea, anorexia, weakness, irritability, and headache.

### Diagnosis

Diagnosis is made by the demonstration of eggs in stool specimens. Proglottids are rarely observed in stool. Detection of light infection may require a concentration technique and repeated examination. Peripheral blood eosinophilia may be found.

### Treatment

Although not approved by the FDA for this indication, praziquantel (25 mg/kg as a single dose) is the drug of choice. Close family members, especially siblings, should have their stool specimens examined. Simultaneous treatment of family members may be indicated. Stool examinations should be repeated 2 to 4 weeks after initiating treatment to document cure, especially in patients with heavy worm burden. Nitazoxanide is an alternative treatment option.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Amebiasis: General Information* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/parasites/amebiasis/general-info.html](http://www.cdc.gov/parasites/amebiasis/general-info.html))
- *Ascariasis* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/parasites/ascariasis](http://www.cdc.gov/parasites/ascariasis))
- *Babesiosis* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/parasites/babesiosis](http://www.cdc.gov/parasites/babesiosis))
- *Cryptosporidiosis: General Information* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/parasites/crypto/gen\\_info/index.html](http://www.cdc.gov/parasites/crypto/gen_info/index.html))
- *Cysticercosis* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/parasites/cysticercosis](http://www.cdc.gov/parasites/cysticercosis))
- *Hookworm* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/parasites/hookworm](http://www.cdc.gov/parasites/hookworm))
- *Hymenolepiasis* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/parasites/hymenolepis](http://www.cdc.gov/parasites/hymenolepis))
- *Malaria* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/malaria/index.html](http://www.cdc.gov/malaria/index.html))
- *Taeniasis* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/parasites/taeniasis](http://www.cdc.gov/parasites/taeniasis))
- *Toxocariasis* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/parasites/toxocariasis](http://www.cdc.gov/parasites/toxocariasis))
- *Toxoplasmosis* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/parasites/toxoplasmosis](http://www.cdc.gov/parasites/toxoplasmosis))

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## Chapter 309

# PECTUS EXCAVATUM AND PECTUS CARINATUM

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## PECTUS EXCAVATUM

Pectus excavatum is a syndrome characterized by a concave depression of the sternum. It is the most common congenital chest wall deformity, affecting approximately 1 in 400 live births. Of those affected, 80% are boys. Family history is a risk factor for development of pectus excavatum, with 37% of patients having a first-degree relative with the condition. This congenital defect occurs from excessive growth of the costal cartilage, which displaces the sternum posteriorly. Phenotypically, the appearance resembles a funnel chest. The concavity is often asymmetric, with the right side usually more depressed than the left side, and can range in severity from a mild depression to a profound indentation.

## CLINICAL FEATURES

Pectus excavatum typically becomes problematic as children reach early adolescence, both as a result of embarrassment over the cosmetic appearance of the chest and occasionally of respiratory impairment from the defect. Rapid skeletal growth during this period tends to exaggerate the defect, and can cause a progression from barely noticeable to extremely prominent in the span of a few years. The severity of the defect usually does not increase after the age of 18, by which time most of the skeletal growth has occurred. Although most patients do not exhibit symptoms, some may have decreased exercise tolerance, easy fatigability, and frequent respiratory tract infections from decreased chest excursion and diminished inspirations. Displacement or rotation of the heart because of compression by the chest wall can occasionally lead to chest pain related to the defect, and total lung capacity is decreased.

Pectus excavatum has a known association with many disorders (Box 309-1). Scoliosis is present in approximately 15% of patients, and mitral valve prolapse may be seen up to 30% of the time. Pectus excavatum also has a strong association with Marfan syndrome and represents the most common chest wall abnormality seen in these patients.

Patients with pectus excavatum tend to have rounded shoulders and a protuberant abdomen with a slumped-over appearance, which is referred to as the *pectus posture*. This disfigurement can have serious psychological ramifications. Many patients with pectus excavatum suffer from psychosocial issues including social anxiety, problems with body image, depression, and avoidance of activities that expose the chest.

## EVALUATION

Examination of the child with pectus excavatum should include a thorough history and physical examination, with an attempt to rule out any associated

disorders that may have been previously undiagnosed. Auscultation of the chest may reveal a left displacement of the heartbeat and the click of a valve prolapse. A systolic cardiac murmur is also sometimes appreciated because of the closer proximity of the sternum to the pulmonary artery. Although lung sounds are typically clear, they are often diminished, and pulmonary function tests tend to demonstrate a restrictive pattern. A transthoracic echocardiogram may reveal diminished cardiac output from decreased stroke volume and mitral valve prolapse.

The severity of the defect is measured by the Haller index, which is the computed tomographic scan-measured transthoracic diameter divided by the sternovertebral diameter. An index of more than 3.5 is considered to be a severe defect, but even indices that are less than 2.5 can cause significant cardiopulmonary impairment. Defects with an index of more than 3.2 are usually considered for repair, as this is generally considered the cutoff between mild and moderate pectus excavatum.

## TREATMENT

Some nonoperative measures aimed at decreasing the patient's symptoms exist, but they are generally only minimally effective. Patients can be taught to increase breathing efforts to increase diaphragmatic excursion, allowing for increased oxygen exchange. Improvement in posture, either through conscious efforts to straighten posture or with the help of support vests, can improve air exchange. External braces can help correct posture, but these have been largely associated with only minimal correction of the deformity.

A relatively new alternative to surgery is the vacuum bell. It consists of a bowl-shaped device which fits over the sternal concavity; the air is then removed by the use of a hand pump. The vacuum created lifts the sternum upwards, lessening the severity of the deformity. As this procedure is a recent development, there is currently no information as to whether it is effective in the long term. Nonetheless, some authorities advocate the use of this continuous external vacuum as another alternative to surgical therapy in patients with mild Haller scores who want correction for cosmesis.

Other cosmetic options include the use of bioprosthetics to fill the concavity. Dermal fillers such as polyalkylimide have been used with acceptable cosmetic results. Solid silicone implants have been used for many years as well, and more recently polyethylene implants have been inserted subcutaneously. While these do nothing for the physiologic complications of pectus excavatum, they can significantly alleviate the psychosocial effects and may be considered for patients with mild deformities and no physiologic impairments, or those who are poor surgical candidates.

Surgical repair of pectus excavatum should be performed in patients with cardiopulmonary impairment, pain, or concerns about cosmesis resulting in poor body image. A recent multicenter study has demonstrated that children who underwent corrective surgery for pectus excavatum had significant improvement in lung function and  $\text{VO}_2$  max. Although the best time for repair is uncertain, children ideally

### BOX 309-1 Disorders Associated With Pectus Excavatum

- Asthma
- Bronchial atresia
- Bronchomalacia
- Down syndrome
- Marfan syndrome
- Mitral valve prolapse
- Noonan syndrome
- Osteogenesis imperfecta
- Poland syndrome
- Rett syndrome
- Rickets
- Scoliosis
- Spinal muscular atrophy
- Turner syndrome
- Wolff-Parkinson-White syndrome



should undergo surgical repair between the ages of 12 and 18 years, when they are old enough to understand the nature, consequences, and magnitude of the surgery. This awareness includes the knowledge of the level of pain that might be experienced postoperatively, and the temporary limitation of activity. Although the surgery can be performed when the child is older than 18 years, it should not be delayed too long so as to take advantage of the pliable chest wall of the growing adolescent and effect the greatest change on chest contour.

Two primary methods of surgical repair exist for pectus excavatum. Previously, the standard repair had been the Ravitch technique, introduced by Dr. Ravitch in 1949. Despite its extensive nature, this repair has been associated with good long-term outcomes, although it is now used less often than the Nuss technique except in older patients where the sternum has calcified, when the deformity is complex and asymmetrical, or when the less-invasive Nuss procedure has been unsuccessful. The Nuss repair, developed in 1987, has been associated with equivalent cosmetic results to those from the open Ravitch repair, and the procedure may be more cost-effective because it has a shorter operating time. Both procedures have a bar placed during the procedure. In the Ravitch procedure, the bar is removed after 6 months. In the Nuss repair, the bar remains in place for 2 to 3 years in children to allow for permanent remodeling of the costal cartilage. This process is slower in the older patient because of the decrease in growth; thus, in the Nuss repair in adults, the bar remains for 3 to 5 years. The bar is removed as an outpatient procedure, although some patients elect to keep the bars permanently so as to reduce the risk of pectus excavatum recurrence.

Adequate analgesia is typically the most troublesome problem for either procedure in the postoperative period, although it tends to be slightly more significant in the Nuss repair. Use of an epidural patient-controlled analgesia catheter greatly reduces pain after the procedure. Generally, the epidural catheter is required for several days, representing the main reason the patient remains in the hospital.

Recently, a third surgical option has been approved for testing by the FDA. The magnetic minimover procedure (3MP) uses 2 magnets, 1 inside the chest and the other on a vest worn outside the chest, which create a magnetic force field that applies a controlled sustained force. The goal is to promote movement of the rib cartilage to a more normal position, resulting in a more gradual correction of the chest wall over a period of months using nominal force. Advantages of the procedure over Ravitch or Nuss procedures include significantly improved pain control, decreased length of hospital stay, lack of postoperative activity restrictions, and the ability to perform additional corrections without requiring additional operations. Disadvantages include risk of interference with surrounding implantable devices such as pacemakers if within 6 inches of the device, ineligibility for MRI scanning, and occasionally attracting metal objects in the immediate environment, as well as the fact that this procedure results in

gradual correction over several months versus the relatively immediate results of the more invasive operations. Because the vest must be worn every day for a long period of time, patient adherence is likely to be the most significant difficulty with this approach. Additionally, results are best when used on young children typically younger than 12 years, and the treatment is less effective in older children once a significant amount of cartilage has been replaced with less pliable bone. Moreover, the placement of the magnet requires an incision in the anterior chest, which still leaves a scar, thus minimizing the cosmetic benefit compared to surgical repair. No long-term data exist, since the procedure is currently in testing at the University of California–San Francisco, the University of California–Davis, and Shriners Hospital of Sacramento.

## PROGNOSIS

Long-term outcomes have shown both Ravitch and Nuss types of repair to be effective. Research shows that 97% of patients undergoing the Ravitch procedure express very good or excellent results, with similar satisfaction reported for the Nuss procedure. Symptoms of pain and decreased exercise intolerance that are present before surgery generally improve afterwards. Many asymptomatic patients who have a normal preoperative pulmonary function test and cardiac echo report significant improvement in their exercise tolerance and endurance, although they had not realized they had had any limitations before surgery.

Complications with the Ravitch repair method include impaired chest wall growth with possible constriction of the thorax from inability of the thorax to develop after surgery, abnormal cartilage regrowth and scarring, chest wall defects from failure of cartilage regrowth, pneumothorax, and denervation of the sternum. The most common complication with the Nuss repair method is displacement of the bar, but modifications in the technique and increased surgeon experience have led to low rates of bar migration. Life-threatening complications include cardiac, vascular, and lung injuries, which are rare but are reported in the literature. These typically occur with blind passage of the pectus bar across the chest, and thus this technique should be avoided. No cases of cardiac perforation have occurred with the use of thoracoscopy during the procedure. A large meta-analysis evaluating the differences between the 2 procedures noted no differences with respect to overall complications, length of hospital stay, and time to ambulation. However, the rate of reoperation was higher with the Nuss procedure because of bar migration or persistent deformity. Also, postoperative hemothorax and pneumothorax after the Nuss procedure were higher compared to the Ravitch procedure, as were pain scores while in hospital. The Ravitch procedure showed an increased intraoperative time and a significantly longer period of activity restriction compared to the Nuss procedure, as well as permanent anesthesia over the sternum. No studies showed a significant difference in patient satisfaction.



The advent of a minimally invasive technique to repair pectus excavatum has changed the approach to patients with this deformity. Children who previously lived with psychosocial issues because of poor body image or physical limitations (or both) can now undergo a safe and effective operation with minimal morbidity. The breadth of patients who are referred for surgical repair is likely to widen, and more patients should be able to undergo a secure and dependable elimination of the defect. Results of a multicenter study have demonstrated that the minimally invasive technique is safe and effective in providing functional as well as cosmetic improvement.

## PECTUS CARINATUM

Pectus carinatum is the second most common chest wall abnormality. While excavatum deformities account for approximately 90% of chest wall defects, pectus carinatum comprises less than 5%. It is characterized by a protuberance of the sternum that mimics a pigeon's chest. It is usually a symmetric, midline deformity and is seldom associated with cardiovascular compromise. Most commonly, the open Ravitch repair method for pectus excavatum is performed to correct the deformity. Thoracoscopic techniques are also used to repair this defect. Some investigators have advocated the use of conservative measures, such as external braces applying constant pressure, as an alternative to surgical repair. These have proven to be effective in the treatment of the condition in patients younger than 16 years of age. Similarly to the magnetic vest treatment of pectus excavatum, the most common cause of treatment failure when used in the appropriate age group is lack of adherence. In addition, minimally open variations of the Ravitch repair have been described for both the excavatum and carinatum deformities.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Chest Wall Deformities* (fact sheet), Children's Hospital of Boston ([www.childrenshospital.org/az/Site698/mainpageS698P0.html](http://www.childrenshospital.org/az/Site698/mainpageS698P0.html))

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## Chapter 310

# PERTUSSIS (WHOOING COUGH)

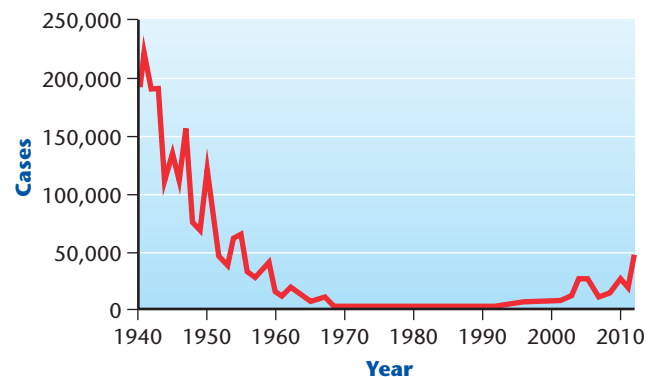
Camilla Sabella, MD

## DEFINITIONS

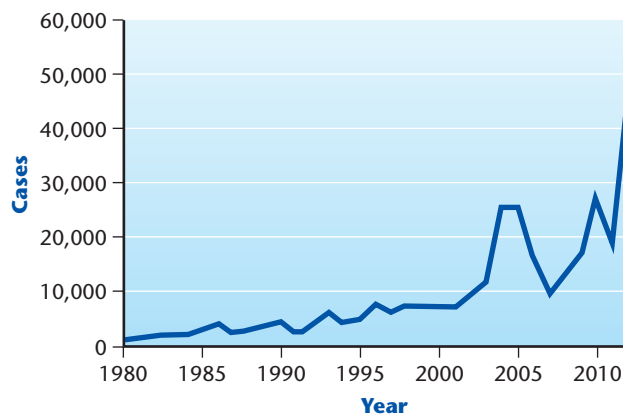
Pertussis (whooping cough) is a highly contagious, bacterial respiratory infection caused by *Bordetella pertussis*, an aerobic gram-negative coccobacillus. The illness is characterized by spasms of intense coughing and a protracted clinical course lasting several weeks. A characteristic severe, paroxysmal cough ending in the inspiratory *whoop* is most often seen in infants and young children, who experience the most severe manifestations of this illness.

## EPIDEMIOLOGIC FEATURES

Worldwide, pertussis is an important killer of children, with an estimated 300,000 pertussis-related deaths annually. Before the availability of whole-cell pertussis vaccines in the late 1940s, pertussis was a major cause of morbidity and mortality in the United States, accounting for almost 300,000 cases and 10,000 deaths annually. Cases significantly decreased after an effective vaccine was introduced—the incidence declined by 99% (compared with the prevaccine era) in the early 1970s, with a record low of 1,010 cases in 1976 (Figure 310-1). However, the incidence of pertussis in the United States has steadily increased since the early 1980s (Figure 310-2). Although the disease is endemic, with all 50 US states reporting cases annually, epidemic peaks occur every 3 to 5 years, and several large outbreaks in North America have been reported in the last several years. These outbreaks have occurred in both highly immunized populations and in infants who had not received 3 doses of the vaccine. In 2004, 25,827 cases were reported in the United States, marking the highest number of cases



**Figure 310-1** Pertussis: United States, 1940–2012. (From Centers for Disease Control and Prevention. Available at: [www.cdc.gov/vaccines/pubs/pinkbook/pert.html](http://www.cdc.gov/vaccines/pubs/pinkbook/pert.html). Accessed September 25, 2015.)



**Figure 310-2** Pertussis: United States, 1980–2012. (From Centers for Disease Control and Prevention. Available at: [www.cdc.gov/vaccines/pubs/pinkbook/pert.html](http://www.cdc.gov/vaccines/pubs/pinkbook/pert.html). Accessed September 25, 2015.)

reported since 1959. In 2010, 27,550 cases and 27 pertussis-related deaths were reported.

During the last several decades, the age distribution of pertussis changed significantly. In the prevaccine era, the peak incidence of disease occurred in children aged 1 to 5 years. With widespread vaccination and by the late 1980s, infants younger than 1 year had the highest age-specific incidence, which declined with increasing age. However, since the early 1990s, a marked increase has occurred in reported cases in children aged 10 years and older. Data from the National Notifiable Diseases Surveillance System reveal that children aged 10 to 19 years comprised 33% of all reported cases between 2001 and 2003, whereas 23% of cases occurred in individuals aged 20 years and older. During the same period, infants younger than 1 year comprised 23% of all cases. From 2004 to 2005, approximately 60% of reported cases were among those 11 years of age and older, but infants younger than 1 year of age continue to have the highest average annual incidence. However, the overall number of pertussis cases is likely underestimated because the infection is often underdiagnosed in adolescents and adults.

*Bordetella pertussis* is a highly contagious organism, as demonstrated by 80% to 90% secondary attack rates among susceptible household contacts. The organism is acquired through direct transmission from close respiratory contact. Most cases in the United States occur between the months of June and October. Although chronic carriage of the organism does not occur, subclinical or mild illness commonly occurs in fully or partially immunized, as well as naturally immune, individuals. This proclivity occurs because immunity wanes within 3 to 5 years of vaccination or natural infection and is often undetectable at 12 years. Thus, neither vaccination nor natural disease provides long-lasting immunity, and adults in this country do not have adequate protection against pertussis. Importantly, adults and adolescents with pertussis serve as important reservoirs for infection and often serve as the index cases for younger infants and children. An

example of this circumstance occurred during the Chicago outbreak of 1993 where mothers served as an important source of pertussis for their infants.

Many studies prove that pertussis is a very common cause of prolonged cough in adolescents and adults, accounting for 12% to 32% of cases of cough lasting 2 weeks or longer. A prospective, US population-based study with active surveillance revealed that 13% of study participants between the ages of 10 and 49 years who visited their community clinic with an acute paroxysmal cough or a persistent cough illness of more than 2 weeks' duration had evidence of an acute pertussis infection. A Canadian study, the largest prospective study examining the rates of pertussis disease in adolescents and adults, demonstrated that 20% of 442 adolescents and adults with cough illness lasting 7 to 56 days' duration were diagnosed with pertussis.

## DIFFERENTIAL DIAGNOSIS

In infants, the differential diagnosis of pertussis includes respiratory viral illnesses, infection with *Chlamydia trachomatis* and with other *Bordetella* species, bacterial pneumonia, foreign body aspiration, and reactive airway disease.

### Adenovirus

Adenovirus can produce a clinical syndrome of prolonged paroxysmal cough, post-tussive emesis, and inspiratory whoop, which can be indistinguishable from pertussis. The presence of associated features commonly found with adenovirus, such as pharyngitis and conjunctivitis, can help distinguish clinically between these entities.

### Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) is a common cause of upper and lower respiratory tract infection in neonates and infants and can occasionally be difficult to distinguish from pertussis. In addition, dual infection with RSV and *B. pertussis* can occur, and apnea is a common complication of both infections. The presence of predominantly lower respiratory tract signs (wheezing), fever, and ongoing symptoms between cough episodes is more suggestive of RSV infection than pertussis.

### *Chlamydia trachomatis*

*Chlamydia trachomatis*, a common cause of afebrile pneumonia in young infants, can mimic pertussis. However, infants with chlamydial infection usually have a staccato rather than paroxysmal cough, lower respiratory tract signs such as tachypnea and rales, and often a history of conjunctivitis in the neonatal period.

### Other *Bordetella* Species

*Bordetella parapertussis* and, rarely, *Bordetella bronchiseptica* are associated with a pertussis-like illness but characteristically cause a less protracted illness.

### Bacterial pneumonia

Bacterial pneumonia caused by *Staphylococcus aureus* and *Streptococcus pneumoniae* is not difficult to distinguish from pertussis based on the clinical manifestations

(high temperature, ill appearance, respiratory distress). However, these agents can secondarily complicate pertussis infection.

The differential diagnosis of pertussis in the older child, adolescent, and adult includes adenoviral infection, infection with *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*, asthma, and upper respiratory tract infection. *M pneumoniae* is a common cause of prolonged cough and may be difficult to distinguish from pertussis. Concurrent outbreaks have been reported. The presence of systemic symptoms, such as headache, sore throat, rales on auscultation of the chest, and a chest radiograph image that characteristically seems worse than the appearance of the child, all favor the diagnosis of *M pneumoniae*.

## EVALUATION

A complete history is by far the most important aspect of the evaluation of the infant or child with possible pertussis. A clinical diagnosis of pertussis can be made based on this history and may be supplemented by information gathered from the physical examination, as well as laboratory and radiographic information. However, because the physical examination is usually normal, the diagnosis may be missed if attention is not paid to the historical description of the coughing paroxysms. Because of the high morbidity and mortality rates associated with neonatal and infant pertussis, any young infant who has a history of cough paroxysms should have these paroxysms witnessed by a medical professional before a disposition is planned.

### Clinical Features in Infants and Children

After a usual incubation period of 7 to 10 days (range, 5–21 days), the catarrhal phase consists of nonspecific upper respiratory tract infection symptoms with rhinorrhea, lacrimation, mild cough, and conjunctival injection. This phase is followed by the paroxysmal stage, which is characterized by an intermittent dry, hacking cough. In this stage, a repetitive series of forceful coughs within a single expiration occur. A sudden, massive inspiratory respiratory effort often occurs at the end of the cough paroxysm, resulting in a high-pitched *whoop*. Between the attacks, the child seems comfortable without apparent distress. The paroxysmal stage in very young infants often lacks the characteristic *whoop* and is characterized by episodes of gagging, gasping, apnea, bradycardia, and cyanosis. Video clips of infants with pertussis can be found at [www.vaccineinformation.org/video/pertussis.asp](http://www.vaccineinformation.org/video/pertussis.asp). The *convalescent* stage is characterized by diminishing severity and frequency of paroxysms. However, patients with pertussis commonly continue experiencing intermittent coughing for weeks to months, which are often exacerbated by subsequent intercurrent respiratory illness.

Physical examination of children with pertussis is usually normal, except that they may have conjunctival hemorrhage and upper body petechial lesions, evidence of the forcefulness of their cough and posttussive emesis. Fever is characteristically absent at all stages and, if present, should immediately suggest

secondary bacterial infection. Leukocytosis caused by absolute lymphocytosis is a common finding in unimmunized infants and children who are in the paroxysmal or late catarrhal stage of pertussis. The degree of lymphocytosis parallels the severity of disease. Chest radiography is commonly normal but may reveal perihilar infiltrates, pneumothorax, or pneumomediastinum.

### Clinical Features in Adolescents and Adults

Pertussis in adolescents and adults does not usually have distinct phases. A persistent (>21 days) cough, which is indistinguishable from other respiratory infections, can be the only symptom. However, a paroxysmal nature to the cough is present in approximately 70% to 99% of infected individuals. Other features include inspiratory whoop, posttussive emesis, choking, and sleep disturbed by cough. Positive predictors of confirmed pertussis infection include a history of prolonged duration of violent cough (median, 43 days), a longer duration of cough illness (median, 56 days), and posttussive emesis. Posttussive emesis is common at all ages and serves as a clue to the diagnosis in older children and adults.

Similar to infants and children, adults with pertussis do not have fever. Unlike in infants, leukocytosis and lymphocytosis are not common in adults and in partially immunized children with pertussis.

### Diagnosis

Definitive diagnosis of pertussis is problematic. Culture and polymerase chain reaction (PCR) testing of nasopharyngeal secretions are insensitive modes of diagnosis, whereas serologic testing is sensitive but impractical.

### Culture

Isolation of the organism by culture remains the diagnostic standard, but, because of the fastidious nature of the organism, is highly dependent on appropriate specimen collection, specimen transport, and isolation technique. Appropriate culture is obtained from the posterior nasopharynx using a calcium alginate or Dacron-tipped (not cotton) swab. The specimen should then be immediately inoculated onto Regan-Lowe medium and incubated for 7 days. A semisolid transport media is available if the specimen cannot be immediately inoculated onto solid media. Even when ideal conditions are met, the sensitivity of culture is suboptimal because cultures are most likely to be positive early in the illness (catarrhal and early paroxysmal phase) in unimmunized children. Culture sensitivity is greatly diminished when obtained late in the illness, in immunized individuals, and in those who received macrolides or sulfonamides.

### Polymerase Chain Reaction Testing

Polymerase chain reaction testing of nasopharyngeal specimens is more widely available and increasingly used to diagnose pertussis. The PCR test is more sensitive than culture, including in individuals who are mildly symptomatic and in those who were treated with macrolides. The sensitivity of PCR when compared with serologic tests that are used for research purposes

is highly dependent on the child's age (60%–70% sensitive in infants and young children but <10% sensitive in older children and adults), which likely reflects past immunization and immune responses. High rates of false-positive results have been reported from some laboratories, and there is no standardized protocol for the *B pertussis* PCR test. Polymerase chain reaction can detect *B paraptussis* as well.

### Direct Fluorescent Antibody Testing

Direct fluorescent antibody testing of nasopharyngeal specimens for pertussis antigens was used in the past but was plagued by poor sensitivity when compared with culture and required experienced laboratories for accurate results. This test is no longer recommended.

### Serologic Testing

Serologic testing for the detection of antibodies to components of *B pertussis* in acute and convalescent samples is the most sensitive mode of diagnosis. These tests have been used extensively in epidemiologic studies and vaccine trials and have enabled an understanding of the role of pertussis in adolescents and adults with prolonged cough illness. However, the results from these tests are difficult to interpret in immunized individuals, cutoff points are not available for diagnostic values, and these tests are not licensed for diagnostic use.

### Complications of Pertussis

Young infants have the highest incidence of morbidity and mortality with 91% of pertussis-related deaths occurring in children younger than 6 months. Secondary bacterial pneumonia is the most common complication, occurring in approximately 5% of all reported cases, and is the cause of most pertussis-related deaths. Infants younger than 6 months have the highest rate of hospitalization (69%), secondary bacterial pneumonia (13%), and seizures (2%). Other important complications include apnea, bradycardia, dehydration, pulmonary hypertension, pneumothorax, central nervous system changes, and retinal hemorrhages. Although complications are much more common in infants, pertussis causes significant morbidity in

adults, including pneumonia, otitis media, sinusitis, rib fracture, pneumothorax, pneumomediastinum, weight loss, and urinary incontinence.

## MANAGEMENT

### Supportive Care

Supportive care continues to be the mainstay of managing pertussis infections. Hospitalization is indicated for most infants younger than 6 months to assess for life-threatening events associated with paroxysms, such as apnea, bradycardia, and hypoxia. Hospitalization also provides continuous cardiopulmonary monitoring, vigilant nasopharynx suctioning, oxygen therapy (if needed), careful attention to feeding and hydration, and monitoring and treating acute complications.

### Antibiotics

A macrolide antibiotic is indicated for proven or suspected pertussis to eliminate the organism from the nasopharynx and thus limit the spread to others. If administered early in the illness, this therapy can reduce the duration and severity of symptoms. However, these agents have little influence on the clinical course of pertussis unless their use is started early in the catarrhal phase of the illness.

The macrolides azithromycin, erythromycin, and clarithromycin are the drugs of choice for treating pertussis infection (Table 310-1). The newer macrolide agents, clarithromycin and azithromycin, are as effective as erythromycin for treating pertussis, are better tolerated, and are associated with fewer and milder adverse effects than erythromycin. Although azithromycin and clarithromycin are not approved by the US Food and Drug Administration for infants younger than 6 months, their use is encouraged based on their *in vitro* effectiveness, demonstrated safety in older infants and children, and more convenient dosing schedule. Although both erythromycin and azithromycin therapy are associated with infantile hypertrophic pyloric stenosis (IHPS), azithromycin is currently the preferred macrolide in infants younger than 1 month because the risk of IHPS is thought to be less. All infants younger than 1 month who receive any macrolide should be monitored for

**Table 310-1**

**Antimicrobial Treatment and Postexposure Prophylaxis for Pertussis by Age Group**

AGE GROUP	RECOMMENDED AGENT
<1 mo	Azithromycin 10 mg/kg/day as single daily dose for 5 days
1–5 mo	Azithromycin 10 mg/kg/day as single daily dose for 5 days, OR erythromycin 40–50 mg/kg/day in 4 divided doses for 14 days, OR clarithromycin 15 mg/kg/day in 2 divided doses for 7 days
Infants ≥6 mo and children	Azithromycin 10 mg/kg/day as single dose on day 1, then 5 mg/kg/day (maximum 500 mg) on days 2–5, OR erythromycin 40–50 mg/kg/day (maximum 2 g/day) in 4 divided doses for 14 days, OR clarithromycin 15 mg/kg/day in 2 divided doses (maximum 1 g/day) for 7 days
Adolescents and adults	Azithromycin 500 mg as single daily dose on day 1, then 250 mg/day on days 2–5, OR erythromycin 2 g/day in 4 divided doses for 14 days, OR clarithromycin 1 g/day in 2 divided doses for 7 days

Adapted from Centers for Disease Control and Prevention. Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis. 2005 CDC guidelines. *MMWR*. 2005;54(RR14):1–16.



IHPS during and for 1 month after completing the course of therapy.

Trimethoprim-sulfamethoxazole (TMP-SMX) is the recommended alternative for children older than 2 months who cannot tolerate macrolides. The dosing regimen for TMP-SMX is:

- 2 months of age or older: TMP, 8 mg/kg/day; SMX, 40 mg/kg/day in 2 doses for 14 days
- Adolescents and adults: TMP, 320 mg/day; SMX, 1,600 mg/day in 2 divided doses for 14 days

The treatment for *B. parapertussis* is the same as for *B. pertussis*.

### Care of Household and Other Close Contacts

Because of the high transmission rate from infected to susceptible individuals and proven efficacy of chemoprophylaxis, a macrolide should be given promptly to all household and close contacts (eg, those in child care) of infected individuals. Chemoprophylaxis significantly reduces but does not eliminate the risk of pertussis. Because immunization may not always prevent infection, chemoprophylaxis should be given to close contacts regardless of age and immunization status. Health care workers who have a definite or likely exposure to pertussis should also receive chemoprophylaxis. The antimicrobial agents that should be used for postexposure prophylaxis are the same as for treatment of pertussis (see Table 310-1). Trimethoprim-sulfamethoxazole is an alternative prophylactic option for children who cannot tolerate macrolides; however, this antibiotic is contraindicated in infants younger than 2 months.

### Prevention

Universal immunization with pertussis vaccines for children younger than 7 years is recommended by the American Academy of Pediatrics (AAP) and is the mainstay of prevention. Vaccination of all children starting in infancy decreased the incidence of pertussis in the United States by more than 97%, compared to the prevaccine era. The currently available acellular vaccines, which are purified subunit vaccines and combination vaccines with diphtheria and tetanus toxoids (diphtheria-tetanus-acellular pertussis [DTaP]), have been shown to be 75% to 90% effective and are well-tolerated. The AAP recommends that a total of 5 doses of pertussis vaccine be administered to every child before school entry, unless contraindicated. The first dose is given at 2 months of age and is followed by 2 subsequent doses at intervals of 2 months. A fourth and fifth dose are recommended at 15 to 18 months of age and at 4 to 6 years of age, respectively. Children between 7 and 10 years of age who have not completed their primary immunization schedule or have an unknown vaccine history should receive a single dose of Tdap.

Despite the successes of universal immunization, reported cases of pertussis in this country are steadily increasing, with resultant significant morbidity and mortality. This increase seems to be because waning immunity occurs after vaccination and natural infection, mild disease is underdiagnosed, and infants who do not complete their primary immunization series remain susceptible to infection.

Because of the role that adolescents and adults play in pertussis transmission, much interest has been

### BOX 310-1 American Academy of Pediatrics Recommendations for Use of Tetanus and Diphtheria Toxoids and Acellular Pertussis (Tdap) Vaccines in Adolescents

- Single dose of Tdap instead of tetanus and diphtheria toxoids (Td) vaccine for booster immunization for adolescents 11 to 18 years of age.
- The preferred age for Tdap immunization is 11 to 12 years.
- Adolescents 11 to 18 years of age who have received Td but not Tdap are encouraged to receive a single dose of Tdap. An interval of 2 years between Td and Tdap immunization is suggested. However, Tdap can be given at shorter intervals in settings of increased risk of pertussis, such as for a close contact with a case, outbreak setting, and close contact with an infant.

Adapted from American Academy of Pediatrics. Pertussis (whooping cough). In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:608–621.

generated in studies evaluating the efficacy and safety of pertussis vaccination in these age groups. Traditionally, pertussis vaccine was not recommended for children aged 7 years and older because of past concerns about the safety of the previously used whole-cell vaccines in this age group. However, adverse reactions to the acellular pertussis vaccines among adolescents and adults are mild, with local swelling and redness most commonly reported. A National Institutes of Health–sponsored prospective multicenter trial, in which 2,781 healthy subjects aged 15 to 65 years were randomized to receive acellular pertussis vaccine or hepatitis A vaccine, found that the acellular pertussis vaccine is safe, immunogenic, and effective in preventing clinical pertussis.

Given the immunogenicity and safety of these vaccines in adolescents and adults, the AAP recommends that adolescents aged 11 to 18 years receive the Tdap vaccine (Box 310-1). It is also reasonable to recommend to parents that they consider getting vaccinated as a means of preventing spread to their children.

### WHEN TO ADMIT

- Strongly consider in any infant younger than 6 months suspected of having pertussis.
- When complications, such as apnea, bacterial pneumonia, bradycardia, or pulmonary hypertension, exist.
- When the infant has an oxygen requirement or when the infection is interfering with feeding.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Pertussis* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/vaccines/vpd-vac/pertussis/fs-parents.html](http://www.cdc.gov/vaccines/vpd-vac/pertussis/fs-parents.html))

- *Vaccine Information Statement: DTaP (Diphtheria, Tetanus, and Pertussis Vaccines): What You Need to Know* (fact sheet), Centers for Disease Control and Prevention ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

### Medical Decision Support

- *Epidemiology and Prevention of Vaccine-Preventable Diseases: Pertussis* (booklet), Centers for Disease Control and Prevention ([www.cdc.gov/vaccines/pubs/pinkbook/downloads/pert.pdf](http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/pert.pdf))
- *Recommended Antimicrobial Agents for the Treatment and Postexposure Prophylaxis of Pertussis* (guideline), Centers for Disease Control and Prevention ([www.cdc.gov/mmwr/preview/mmwrhtml/rr5414a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5414a1.htm))

### SUGGESTED READINGS

- Centers for Disease Control and Prevention. Pertussis—United States, 2001–2003. *MMWR*. 2005;54(50):1283–1286
- Centers for Disease Control and Prevention. Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis. 2005 CDC guidelines. *MMWR*. 2005;54(RR14):1–16
- Heininger U, Klich K, Stehr K, et al. Clinical findings in *Bordetella pertussis* infections: results of a prospective multicenter surveillance study. *Pediatrics*. 1997;100(6):E10
- Langley JM, Halperin SA, Boucher FD, et al. Azithromycin is as effective as and better tolerated than erythromycin estolate for the treatment of pertussis. *Pediatrics*. 2004;114(1):e96–e101
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## Chapter 311

# PHARYNGITIS AND TONSILLITIS

Russell W. Steele, MD

### INTRODUCTION

Acute pharyngitis is one of the more common diagnoses made in pediatric practice, exceeded only by otitis media and viral upper respiratory tract infections. It is also the most common diagnosis requiring treatment with antibiotics in school-aged children.

### DEFINITIONS

The term *pharyngitis* implies inflammation of the throat with or without the presence of exudate; when the tonsils are affected, the terms *tonsillitis*, *tonsillopharyngitis*, and *pharyngotonsillitis* are more commonly used. Pharyngitis may be associated with other inflammatory conditions of the mucous membranes (eg, herpes gingivostomatitis, herpangina, Stevens-Johnson syndrome, Kawasaki disease), or it may be the sole finding in an illness. Generally, a clinical complaint of sore throat indicates some degree of pharyngitis.

### ETIOLOGY

Although pharyngitis is most commonly caused by viral agents, the major management step is to establish whether group A  $\beta$ -hemolytic *Streptococcus* (GABHS) is the responsible pathogen, because the presence of GABHS mandates early antimicrobial therapy within 9 days of onset of symptoms to eradicate this bacterium and thereby prevent acute rheumatic fever. In children younger than 3 years, GABHS is the cause of tonsillopharyngitis in less than 3% of cases, whereas in children older than 3 years, estimates suggest that 15% to 20% of pharyngitis episodes are caused by GABHS. The reason for the low incidence in young children is that their pharyngeal mucosal cells have fewer receptors for GABHS. The cause of pharyngitis varies somewhat depending on the geographic location and season, particularly during recognized outbreaks of GABHS, influenza, respiratory syncytial virus, and mycoplasma. In addition to these causes, many other infectious agents have been associated with pharyngitis (Box 311-1).

### Viruses

Although many primary care physicians associate pharyngitis and tonsillitis with bacterial pathogens, viruses play a major role in the cause of these illnesses. Moreover, when pharyngitis is associated with upper respiratory tract symptoms, such as conjunctivitis, nasal congestion, and rhinorrhea, GABHS and other bacterial agents are highly unlikely causes.

### Adenoviruses

At least 12 different types of adenoviruses have been found to cause pharyngitis in children and adolescents, accounting for up to 23% of cases in some reports. These viruses cause both a nasopharyngitis and a tonsillitis that can be exudative. Outbreaks of a unique clinical illness caused by adenovirus types 3, 7, 2, 4, 7a, 11, and

### BOX 311-1 Causes of Pharyngitis

#### BACTERIA

- *Streptococcus pyogenes*
- *Corynebacterium diphtheriae*
- *Arcanobacterium hemolyticum*
- *Neisseria gonorrhoeae*
- Group C streptococci
- Group G streptococci
- *Chlamydia pneumoniae*
- *Chlamydia trachomatis*
- *Mycoplasma pneumoniae*
- *Yersinia enterocolitica*
- *Francisella tularensis*
- *Coxiella burnetii*

#### VIRUSES

- Epstein-Barr virus
- Adenovirus
- Enteroviruses
- Herpes simplex viruses
- Influenza
- Parainfluenza
- Rhinoviruses
- Coronavirus
- Human metapneumovirus
- Human bocavirus
- Respiratory syncytial virus

14, called pharyngoconjunctival fever because of these consistent features, occur frequently. Affected patients may also have cough, myalgias, and conjunctivitis.

### Enteroviruses

Three prominent members of the enterovirus class of viruses, coxsackieviruses A and B and echovirus, have been shown to cause pharyngitis, often accompanied by respiratory symptoms, commonly in the late summer or early fall. Herpangina is a specific entity caused by various strains of coxsackieviruses A and B, typified by pharyngitis associated with small, shallow, erythematous, ulcerated areas on the soft palate and peritonsillar area.

### Epstein-Barr Virus

Epstein-Barr virus (EBV) is an etiologic agent of infectious mononucleosis that frequently causes a severe exudative pharyngitis with a characteristic white, shaggy membrane on the tonsils and palatal petechiae. In older children, EBV infection is frequently accompanied by fever, adenopathy, malaise, swelling of the eyelids, a generalized rash, and hepatosplenomegaly. EBV is a copathogen of GABHS in 5% to 10% of cases.

### Herpes Simplex Virus

Although most oral colonization and covert infection with herpes simplex virus type 1 is asymptomatic, this virus can cause painful gingivostomatitis and pharyngitis in approximately 1% of infected children. Studies in a college-aged population have also documented that herpes simplex virus types 1 and 2 account for 5.7% of pharyngitis cases.

### Other Viruses

Many other viruses cause pharyngitis, although pharyngitis is usually not the primary manifestation of the illness. These viruses include influenza, parainfluenza, respiratory syncytial virus, human metapneumovirus, human bocavirus, measles, coronavirus, and rhinoviruses.

### Bacteria

One of the main considerations in evaluating a child who has pharyngitis and tonsillitis is to determine whether the cause is bacterial, thus requiring specific antibiotic therapy. GABHS infections are the major bacterial cause, but other organisms should be considered in certain situations.

### *Streptococcus pyogenes*

*Streptococcus pyogenes* causes complete ( $\beta$ ) hemolysis when grown on blood agar and hence has been called  $\beta$ -hemolytic *Streptococcus*. Streptococci have been subdivided into groups based on the C-substance in the cell wall, and most human pathologic disease has been found to be caused by the A group. GABHS was not fully recognized as a frequent cause of pharyngitis with the possibility of subsequent rheumatic fever until the 1940s. Whereas other groups of *Streptococcus* (B, C, F, and G) have been associated at times with pharyngitis, GABHS is by far the most frequent bacterial cause. GABHS can be divided into M and T serotypes, and a certain number of these serotypes have been associated with both the rash of scarlet fever

(GABHS T4) and the development of rheumatic fever (GABHS M3 and M18).

The pharyngitis caused by GABHS characteristically begins after a 2- to 5-day incubation period, usually after exposure to another individual who has the infection. Spread is thought to occur by way of respiratory secretions, although fomites, such as shared silverware or household cats (but not dogs), have occasionally been shown to be vectors. The ingestion of GABHS-contaminated food also has led to outbreaks of pharyngitis. The illness is heralded by sudden onset of fever, sore throat, and dysphagia, often associated with headache and abdominal pain. Examination of the throat reveals an erythematous pharynx and tonsillar area, often with exudate present. Small petechiae (enanthem) are sometimes seen on the uvula and soft palate. Cervical lymph nodes are usually enlarged and tender. These symptoms can last 4 to 5 days, gradually subsiding when no antibiotic therapy is instituted. Penicillin therapy shortens the duration of fever and sore throat by 1 to 1½ days and, if given within 9 days of onset, prevents rheumatic fever.

Key findings include

1. Red throat or tonsils and/or exudative tonsils
2. Swollen and usually tender anterior cervical nodes
3. Fever
4. Scarlet fever rash

### *Neisseria gonorrhoeae*

Pharyngitis in sexually active adolescents or sexually abused children can be caused by *Neisseria gonorrhoeae* acquired from oral sex, and the organism should be sought when appropriate. Exudative tonsillitis is rarely seen with pharyngitis caused by *N gonorrhoeae*.

### *Haemophilus influenzae* Type b

The possible involvement of the *Haemophilus influenzae* type b (Hib) organism in pharyngitis and tonsillitis has been controversial, but evidence suggests that it may contribute to infection in some children, especially those with recurrent tonsillitis. Fine-needle aspiration of tonsils during acute tonsillitis and pathologic specimens from tonsillectomy have documented that as many as 20% of sampled tonsils have Hib infection. However, with Hib immunization of most infants in the United States in recent years, this organism may be less likely to play a role in the pathogenesis of acute tonsillitis and pharyngitis.

### Lemierre Syndrome

This infection caused primarily by the anaerobic bacterium, *Fusobacterium necroforum*, begins as severe tonsillopharyngitis in previously healthy adolescents and young adults. It then progresses to septic thrombophlebitis of the internal or external jugular veins and subsequent severe pulmonary infection. Additional clinical features include fever  $>39^{\circ}\text{C}$  ( $102.2^{\circ}\text{F}$ ), respiratory distress, and unilateral neck swelling or pain.

### *Arcanobacterium hemolyticum*

Approximately 7% of tonsillopharyngitis in adolescents and young adults is caused by *Arcanobacterium*



*hemolyticum*. Physical findings are identical to those seen with GABHS infection, including a scarlatiniform rash present in approximately 20% of cases. The sore throat may persist until patients are treated with erythromycin, azithromycin, or clarithromycin.

### Other Bacteria

A century ago, *Corynebacterium diphtheriae* was a frequent and deadly cause of pharyngitis, with a characteristic gray pseudomembranous exudate over the posterior pharynx and tonsils. Fortunately, *C diphtheriae* now is rare in North America, although it is still being reported in some developing countries. Various reports have been published of other bacteria causing pharyngitis and tonsillitis, including *Actinomyces*, *Chlamydia trachomatis* and *Chlamydia pneumoniae*, *Yersinia enterocolitica*, *Coxiella burnetii*, and *Francisella tularensis* (oropharyngeal tularemia).

### Other Causes

#### *Mycoplasma pneumoniae*

Two types of *Mycoplasma pneumoniae* have been shown to cause pharyngitis, namely *M pneumoniae* and *M hominis*. In children, the former causes a mild pharyngitis, often associated with a laryngotracheitis or progressing to bronchitis or pneumonia. In school-aged children, as much as 5% of pharyngitis may be caused by this organism.

#### Fungi

*Candida* infection is an uncommon cause of pharyngitis in the healthy host but can certainly be seen in immunocompromised patients or those taking steroids. With oral thrush in otherwise healthy children, severe mouth pain can occur, which may be interpreted as a sore throat.

#### Kawasaki Disease

Of unknown cause, Kawasaki disease occurs mostly in preschool-aged children who have pharyngitis associated with erythema and fissuring of the lips as well as palmar and pedal edema and erythema. An association with staphylococcal toxin has been postulated, as have other viral and bacterial etiologies. (See Chapter 280, Kawasaki Disease.)

#### Exposure to Cigarette Smoke

Although smoke itself has not been reported to cause pharyngitis or tonsillitis, a highly significant association has been found between the incidence of tonsillectomy in children and parental smoking. One study found children of smokers also had a much higher frequency of attacks of acute tonsillitis compared with children in a smoke-free environment. Whether this association will be confirmed in other studies remains to be seen, but among children seeking treatment for frequent tonsillitis, a history of parental smoking should be sought. If such a history exists, advising measures to reduce the child's exposure to cigarette smoke would be prudent.

## DIFFERENTIAL DIAGNOSIS

Sore throats are common in children, and almost all children older than 3 years need to be examined to rule out GABHS as the cause. If GABHS is the

documented cause, then antibiotic therapy should be instituted in an effort to prevent rheumatic fever. Unfortunately, multiple studies have shown that streptococcal pharyngitis cannot be distinguished purely on clinical grounds. Streptococcal infections should be considered in children older than 3 years who have pharyngitis, even if no exudate is present. However, pharyngitis associated with nasal, chest, or cold symptoms is much more likely to be a viral illness.

When pharyngitis is atypical, either in its duration or its severity, the physician should suspect infectious mononucleosis or one of the rarer bacterial causes, including those that are sexually transmitted. A peritonsillar abscess or cellulitis (Quinsy) also may cause a sore throat, but thorough examination will reveal swelling extending into the soft palate, with deviation of the uvula and a change in the tonal quality of the voice. Allergies may lead to chronic inflammation of the mucous membranes, which might include the pharynx, but pharyngitis would be infrequent as a sole manifestation. Postnasal drip from a viral respiratory tract infection or allergies has been thought to irritate the posterior pharynx, but this finding is not well documented.

Acute tonsillopharyngitis may progress to a peritonsillar abscess. Researchers have observed that 41% to 70% of peritonsillar abscesses occur in the superior pole. This infection begins with the typical signs and symptoms of pharyngitis such as sore throat, dysphagia, and fever, usually in an older child who often has a history of recurrent tonsillitis. Systemic symptoms such as malaise, poor appetite, and chills appear early, and mild dehydration may develop. These symptoms progress rapidly to more severe pharyngeal symptoms, such as difficulty in swallowing and speaking. The child has a toxic appearance, and trismus almost always occurs. Characteristic signs are a muffled (*hot potato*) voice, trismus, and major leukocytosis. Needle aspiration can be performed only if the abscess is within the superior pole, and the success rate with needle aspiration compares favorably with that of incision and drainage in these types of cases. Computed tomography scanning and intraoral ultrasonography are quite reliable in distinguishing abscesses from cellulitis alone. Initial antimicrobial therapy is clindamycin plus a third-generation cephalosporin such as ceftriaxone, cefotaxime, or ceftazidime. Routine tonsillectomy along with or after medical management is recommended by some experts.

The one entity in the differential diagnosis not to be missed is epiglottitis, which can be life threatening. Generally, the child who has epiglottitis has severe throat pain, rapidly becomes ill, appears to have a toxic condition, and experiences respiratory distress accompanied most often by stridor, although the child may have a croupy cough.

## MANAGEMENT

### Laboratory Procedures

#### Rapid Streptococcal Test and Cultures

The traditional method for determining whether pharyngitis or tonsillitis was caused by a virus or GABHS was to obtain a throat swab and perform a culture. Fortunately, with the availability of rapid



streptococcal tests, this process was made simpler, allowing a result to be obtained in minutes rather than waiting 1 to 2 days. Unfortunately, with the advent of strict federal guidelines for office laboratories, even the use of these rapid tests requires certification. Despite such encumbrances, most clinicians now perform a rapid streptococcal diagnostic test on all patients whose pharyngitis is suggestive of GABHS.

The various rapid streptococcal tests claim differing levels of specificity and sensitivity. They appear to be specific (95%–98%), but their sensitivity can be as low as 70% to 85%; thus, some cases of GABHS are not detected. For this reason, a positive rapid streptococcal test result is sufficient indication to treat the patient; however, if the test result is negative but a high index of suspicion exists that GABHS is the causative agent, then a culture should be sent. If little clinical evidence of pharyngitis or tonsillitis can be found in a child who complains of sore throat, or for those with manifestations highly suggestive of viral infection (coryza, conjunctivitis, cough, hoarseness, herpangina, stomatitis, Sindbis virus), a throat culture is not necessary. The physician also needs to be aware that some individuals are *Streptococcus* carriers, and they may well be found to be positive for *Streptococcus* infection during a viral illness. An asymptomatic *Streptococcus* carrier does not need to be treated, but when symptoms are present, most physicians treat these individuals, given the difficulty of being certain that GABHS is not the cause of the illness. Because performing pre- and post-illness rapid streptococcal tests or cultures on every child who presumably has GABHS pharyngitis is impractical, all those who test positive are treated.

### Serologic Tests

In cases in which EBV infection is suspected, either a heterophile antibody (Mono-spot) or specific EBV antibody test can be ordered. In older children usually a heterophile test is done in the office, and if negative the clinician may then choose to order the more sensitive EBV antibody tests. Tests of specific IgG and IgM levels of antibody to EBV viral capsid antigen (VCA) are available but are usually expensive and slow to produce results, making them less than ideal to determine the cause of an acute pharyngitis (see Chapter 275, Infectious Mononucleosis and Other Epstein-Barr Viral Infections). The EBV-VCA IgM reflects current or recent disease, while the EBV-VCA IgG indicates past infection.

Although serologic tests exist to determine recent streptococcal infections, they are rarely helpful in evaluating for acute pharyngitis. An antistreptolysin-O titer is used more commonly in diagnosing rheumatic fever by documenting a recent exposure to streptolysin with production of antibody.

### White Blood Cell Count

The only real value in performing a white blood cell count is if infectious mononucleosis is suspected. Patients who have an acute EBV infection tend to have relative lymphocytosis, with 10% to 20% atypical lymphocytes. Thus, a white blood cell count may be a helpful diagnostic study, together with a heterophile

or specific EBV antibody test, in a child who has a severe pharyngitis and is culture negative for GABHS.

### Treatment

Pharyngitis caused by viruses generally is treated symptomatically with saline gargles, throat lozenges, and analgesics such as acetaminophen. When GABHS has been documented, either by a positive rapid *Streptococcus* test or by culture, antibiotics are indicated primarily to prevent the subsequent development of rheumatic fever. Various antibiotic regimens have been used for GABHS pharyngitis or tonsillitis, but the standard therapy has been a 10-day oral course of potassium penicillin or amoxicillin given 2 or 3 times a day. Penicillin is given twice a day as 250 mg for children and 500 mg for adolescents and adults, while amoxicillin is given once a day, 50 mg/kg/day. Alternatively, intramuscular benzathine penicillin G may be given as a single injection, although these injections are often painful not only initially but also for a few days afterward. Patients allergic to penicillin may be given azithromycin for 5 days or a cephalosporin for 10 days. Although shorter courses of newer antibiotics have been studied and shown to be effective in eradicating GABHS from the pharynx, their efficacy in preventing rheumatic fever is not clear, although presumed.

Controversy exists over whether to begin antibiotics for presumptive GABHS pharyngitis while waiting for culture results. Because rheumatic fever can be prevented even if treatment is started as late as the ninth day of symptoms, the decision to begin therapy immediately rests with the individual physician, who knows the circumstances of the patient. Early antibiotic treatment will shorten the duration and severity of symptoms by 24 to 36 hours. Patients should be kept out of school and avoid close contact with family and friends for 24 hours, given that numerous studies have shown that they become culture negative after just 24 hours of antibiotic therapy.

Cephalosporins have been shown to be superior to penicillin in eradicating GABHS from the pharynx. In cases of gonococcal pharyngitis, one intramuscular injection of ceftriaxone is recommended. In young children who have this diagnosis, sexual abuse must be investigated. Other possible bacterial causes of pharyngitis are treated with appropriate antibiotics, once the causative organism has been determined (eg, azithromycin for *Arcanobacterium hemolyticum*, or streptomycin or gentamicin for oropharyngeal tularemia).

Parents often raise the question of tonsillectomy after a child has multiple episodes of pharyngitis or tonsillitis. Except in cases of documented recurrent, frequent streptococcal infection or the development of a peritonsillar abscess, tonsillectomy is not indicated in children who have recurrent pharyngitis not thought to be caused by GABHS. (See Chapter 339, Tonsillectomy and Adenoidectomy.)

Although the administration of steroids to decrease pain in acute exudative pharyngitis has been studied in adults and found to provide some benefit, the use of steroids in children is not recommended except in rare situations, such as infectious mononucleosis with imminent airway obstruction.

## COMPLICATIONS

Most cases of pharyngitis present no unusual complications because so many of them are viral and resolve with or without therapy. However, the physician must be aware of the possibility of a peritonsillar or retropharyngeal abscess or cellulitis developing and should re-examine the throat of any patient who is not improving. Other suppurative complications can also develop, such as cervical adenitis, acute otitis media, sinusitis, and pneumonia. In addition, hematogenous spread of a bacterial organism is possible and can result in bacteremia as well as joint, bone, or meningeal infection.

Rheumatic fever (see Chapter 323) is the major complication of streptococcal pharyngitis that can be life threatening, although it occurs some time after the acute throat infection. Although the incidence of rheumatic fever is low in North America, it still occurs and has been seen in increasing numbers at some centers. Although acute glomerulonephritis is possible after streptococcal throat infections, it is much more likely after streptococcal skin infections.

Some evidence has shown an association between GABHS infection and obsessive-compulsive disorders and tic behavior in children. This clinical entity is termed *pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection* (PANDAS). Documentation is largely anecdotal but includes the observation that these children have high concentrations of antibody to streptococcal antigens. Small series have noted improvement in obsessive-compulsive disorder behavior or tics when these children are GABHS positive and treated with penicillin. However, many still question the authenticity of PANDAS.

### WHEN TO REFER

- Suspected peritonsillar abscess
- Suspected retropharyngeal abscess
- Recurrent GABHS (5 episodes in 1 year) for tonsillectomy

### WHEN TO ADMIT

- Toxic appearance (suspected toxic shock syndrome)
- Peritonsillar abscess
- Retropharyngeal abscess
- Acute rheumatic fever

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *The Difference Between a Sore Throat, Strep, and Tonsillitis* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/ear-nose-throat/Pages/The-Difference-Between-a-Sore-Throat-Strep-and-Tonsillitis.aspx](http://www.healthychildren.org/English/health-issues/conditions/ear-nose-throat/Pages/The-Difference-Between-a-Sore-Throat-Strep-and-Tonsillitis.aspx))
- *Sore Throat* (fact sheet) Centers for Disease Control and Prevention ([www.cdc.gov/getsmart/community/for-patients/common-illnesses/sore-throat.html](http://www.cdc.gov/getsmart/community/for-patients/common-illnesses/sore-throat.html))

## SUGGESTED READINGS

Centers for Disease Control and Prevention. *Pharyngitis: Treat Only Proven GAS: Physician Information Sheet*

(*Pediatrics*). Available at: [www.cdc.gov/getsmart/community/materials-references/print-materials/hcp/child-pharyngitis.html](http://www.cdc.gov/getsmart/community/materials-references/print-materials/hcp/child-pharyngitis.html). Accessed September 28, 2015

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## Chapter 312 PHIMOSIS

A. Barbara Oettgen, MD, MPH

Problems and questions related to the foreskin (prepuce) of young boys are relatively common among families in pediatric practices. Understanding the diagnosis and treatment of boys with foreskin problems such as phimosis, paraphimosis, and balanoposthitis is therefore important for physicians caring for children.

## PHIMOSIS

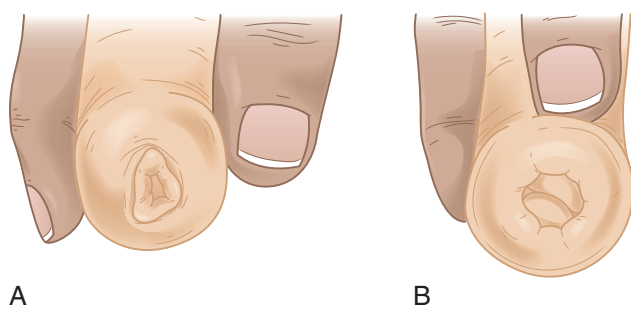
### Definition

Phimosis, or unretractile foreskin, can be both physiologic and pathologic. At birth, most boys have physiologic phimosis—the inner surface of the foreskin is developmentally fused to the glans penis. Over time, desquamation and glanular secretions allow gradual separation of the foreskin. Accumulation of smegma (the epithelial debris generated during desquamation) can sometimes be seen under the foreskin as pearls and requires no intervention. When these accumulations are eventually released, as the foreskin becomes more retractile, they may be mistaken for infection. Distinguishing pathologic phimosis from physiologic phimosis can be difficult because of the lack of clear diagnostic criteria. Probably most of the referrals made to urologists are for boys with physiologic phimosis that will resolve spontaneously over time.

Physiologic phimosis is described as an unretractile foreskin that is supple and unscarred. On attempted retraction, the foreskin lies flat against the penis and is effaced, and the tip opens as a flower (Figure 312-1). Young boys may also exhibit preputial adhesions where part of the foreskin does not completely retract, but no constricting ring is seen—this also is not pathologic and largely resolves on its own. With pathologic phimosis, the margin between the foreskin and the glans is rolled and thickened.

### Incidence

The incidence of true phimosis is probably fairly infrequent. Retractability increases yearly. By 1 year of age, 50% of uncircumcised boys have retractile foreskins, 90% by age 3, 92% by age 6 to 7, and 99% by adolescence. Smith and colleagues reported 1 case per 1,000 boys; a study in France reported a rate of 2.6% and in England 0.9%. These rates were obtained



**Figure 312-1** A, Physiologic phimosis: healthy skin at edge of prepuce. B, Pathologic phimosis: scarred ring at edge of prepuce, holding it open and showing meatus and part of glans.

after looking at pathologic specimens after circumcision. Individuals with evidence of inflammation were counted as true phimosis.

### Etiology

Pathologic phimosis is thought to have a few different causes. It can be the result of a chronic nonspecific inflammatory process or repeated infections that cause scarring and stricture. It can also be caused by forcible premature retraction of the foreskin, causing scarring and adhesions. Balanitis xerotica obliterans (BXO), a chronic dermatitis of unknown cause, histologically resembles lichen sclerosus et atrophicus and causes pathologic phimosis. Severe phimosis can also be a significant complication in boys receiving hematopoietic stem cell transplantation, especially in patients with graft-versus-host disease.

### Management

Treatment of phimosis depends on whether it is thought to be physiologic or pathologic. Watchful waiting will result in resolution of most cases of physiologic phimosis. However, if the child is thought to have pathologic phimosis, then the treatment alternatives include topical steroid cream or surgery.

#### Steroid creams

Multiple studies have investigated the use of topical steroid creams for treatment. A review of the literature in 2001 showed at least 12 studies (2 randomized controlled) in children 1 to 15 years of age. A 4- to 8-week course of therapy was found to be, on average, 85% effective. Since then, there have been a number of studies further confirming the effectiveness of steroid creams of both high and medium potency in children of all ages with varying degrees of phimosis, including those with BXO. High-potency steroid creams, such as 0.05% betamethasone, have been studied the most. However, medium-potency topical steroids (clobetasone butyrate 0.05%, fluticasone propionate 0.05%, and triamcinolone acetonide 0.1%) have also been shown to have similar resolution rates, suggesting that a lower-strength steroid may be an option. The creams are applied to the phimotic ring twice a day for 4 to 8 weeks.

Application of the steroid creams should be accompanied by gentle retraction of the foreskin. To prevent

the incidence of reoccurrence, gentle retraction of the foreskin with cleaning should continue after the steroid cream is discontinued. Steroid creams have even been used in a much younger population (1- to 31-month-old boys) who had urinary tract infections, balanitis, or genitourinary tract anomalies and were found to be successful in relieving phimosis in 92% of children. Steroids are thought to be therapeutic by decreasing any potential inflammation between the foreskin and glans and by thinning the skin, making it more supple.

Topical steroid therapy has multiple advantages over more traditional surgical management—it is less invasive and avoids the risks of surgery (bleeding, deformity, meatal stenosis) and anesthesia. It is much more cost effective, at only 25% the cost of surgery. The prepuce also may deserve preservation for social and cultural reasons, as well as the fact that it is a neurologically complex and erogenous tissue. Finally, medical therapy can prevent severe emotional problems in some boys who undergo circumcision at an older age.

### Surgery

The surgical alternatives for phimosis include dorsal slit surgery or circumcision. The dorsal slit procedure involves making a single slit dorsally in the foreskin, which mostly preserves the prepuce but allows easy retraction of the foreskin. Although the surgery is less involved and preserves the prepuce, the cosmetic result is not as satisfactory as with circumcision and can also be complicated by scarring. Families may choose this option, however, for personal or religious reasons. Circumcision is the much more commonly practiced surgery for phimosis. Beyond the neonatal period, surgery is usually done as an outpatient procedure under general anesthesia. In the postsurgical period, patients should be restricted from rough play or straddling toys for a couple of weeks. In an effort to prevent adhesion to underwear or diaper, petroleum jelly or triple antibiotic ointment should be liberally applied to the newly exposed tip until it is well healed. This will also help decrease the chance of future meatal stenosis. Forced premature retraction of the foreskin is *never* recommended and may lead to significant adhesions and scarring, as well as being painful and traumatic.

### WHEN TO TREAT

Because true phimosis can be a difficult diagnosis to establish, the choice as to which patients should be referred and receive therapy may be unclear. There are some instances for which uniform agreement exists that surgical treatment, in the form of circumcision, should be undertaken. These instances include phimosis that is resistant to steroid therapy and voiding problems. Recurrent balanitis and urinary tract infections may be other indications if topical steroid therapy is unsuccessful. Ballooning of the foreskin during micturition is, by itself, not necessarily a reason for circumcision. Using noninvasive urodynamic studies, no evidence of obstruction could be found in children with physiologic phimosis, even with ballooning of the foreskin.

Given that most cases of phimosis are probably physiologic and will resolve spontaneously over time,



the question remains which children to treat either medically or surgically. Little agreement exists in the literature. Some urologists would question whether true phimosis can exist before age 5 years and, therefore, whether any treatment need be initiated. Others use the age of 3 years as an upper limit and would at least initiate a trial of steroid creams (if no indication for surgery) at that time. Some urologists argue in favor of treating children who are younger (older than 3 years but younger than 5 or 6 years). Their research shows superior adherence with treatment at a younger age because the parents are still able to apply the cream. When older children become responsible for cream application, adherence, and, therefore, success of therapy, decreases. However, other studies have not necessarily shown any preferential success in younger children.

## PARAPHIMOSIS

### Definition

Paraphimosis, unlike phimosis, is a urologic emergency. It occurs when the foreskin is retracted and is not replaced immediately and becomes trapped behind the corona. Paraphimosis may happen during cleaning or during a procedure such as catheterization. The fibrous ring at the base of the corona causes venous congestion, leading to extreme penile pain and swelling of the glans with a collar of swollen foreskin at the coronal sulcus. If no treatment is initiated, then ischemia and necrosis of the glans can result.

### Management

The goal of treatment is to replace the foreskin in its normal position. If the condition is in its early stages, the foreskin may then be replaceable manually without sedation. As the condition progresses, anesthesia in the form of penile block, sedation, or general anesthesia may be required. Gentle persistent pressure is the goal of treatment to decrease edema and allow reduction of the foreskin. In infants and children, allowing an application of 2.5% topical lidocaine to take effect may allow manual reduction to be more successful. Sometimes an incision must be made in the fibrous ring or multiple punctures must be made in the glans to relieve swelling, but such interventions should only be undertaken by a urologist.

## BALANOPOSTHITIS

### Definition

Balanoposthitis is characterized by erythema and edema of the foreskin that produces purulent discharge from the preputial orifice. Occasionally, edema can involve some of the penile shaft as well, and patients may complain of dysuria. The condition usually occurs when the foreskin is wholly or partially retractable. In children, balanitis occurs most often between the ages of 2 and 5 years and is more commonly nonspecific balanitis, caused by poor hygiene, trauma, or irritation from soaps or detergents.

### Management

The treatment for nonspecific balanoposthitis includes local hygienic measures such as sitz baths, gentle

cleaning, and 1% hydrocortisone cream. If irritation does not resolve, then treatment with antimicrobials may be necessary, with the most common causative organisms being *Staphylococcus*, coliforms, *Pseudomonas*, and *Candida*. Another potential cause is *Streptococcus*, which can cause a thin purulent discharge in the preputial-glanular sulcus (but not from the urethra) associated with a red, glistening glans. If there is generalized redness with swelling progressing up the penile shaft or accompanying streaks, there should be a low threshold for hospital admission and IV antibiotics. If taking oral antibiotics, patients should be followed closely to monitor progress and ensure compliance. Sexually transmitted infections (gonorrhea and chlamydia) must also be considered when purulent discharge from the urethra is present, and therefore appropriate diagnostic tests (eg, DNA probes) should be obtained. The presence of sexually transmitted infections in the absence of purulent discharge is extremely unlikely in a prepubertal boy.

Surgical treatment, that is, circumcision, is usually considered only for recurrent episodes of balanoposthitis.

### WHEN TO REFER

Phimosis:

- Obvious or suspected penile deformities
- Failure of topical steroids
- Balanitis xerotica obliterans (BXO)
- Parents desire circumcision
- Association with urinary tract abnormalities/obstructive uropathy

Paraphimosis: failure of manual reduction

Balanoposthitis: recurrent episodes

### WHEN TO ADMIT

Paraphimosis: Failure of manual reduction with vascular compromise of the glans

Balanoposthitis:

- Swelling of the penis with redness and streaking
- Systemic infection or sepsis
- Inability to urinate
- Vascular compromise of the glans

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Circumcision* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/prenatal/decisions-to-make/Pages/Circumcision.aspx](http://www.healthychildren.org/English/ages-stages/prenatal/decisions-to-make/Pages/Circumcision.aspx))
- *Circumcision: Information for Parents* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

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### Chapter 313

## PIERRE ROBIN SEQUENCE

Elizabeth A. Sellars, MD; Robert J. Hopkin, MD

### DEFINITIONS

Pierre Robin syndrome, increasingly known as the Robin sequence or Pierre Robin sequence, comprises the triad of micrognathia, glossoptosis, and obstructive apnea. It is a highly heterogeneous condition. Physicians have used varying sets of criteria to make this diagnosis, which has resulted in widespread confusion. The most appropriate definition is the original description by Pierre Robin, a French stomatologist. In 1923, he described a condition consisting of micrognathia, glossoptosis, and airway compromise. Cleft palate is often associated and has been substituted for respiratory distress. Nevertheless, the initial description from 1923 is the best definition. It is important to have one common definition for families and physicians to communicate to each other appropriately and for future studies of this condition because treatment often involves a multidisciplinary approach that depends on consistent terminology.

Micrognathia is shortening and narrowing of the mandible and chin (Figure 313-1, Figure 313-2, Figure 313-3, and Figure 313-4). Micrognathia often coexists with retrognathia, which is posterior positioning of the lower jaw. These are two distinct entities. Glossoptosis is posterior displacement of the tongue into the pharynx. This may cause airway obstruction, which often affects both breathing and feeding. A cleft palate is often associated with micrognathia and glossoptosis. It can be U-shaped or V-shaped and can involve the soft palate, hard palate, or both.

A point of confusion with Robin sequence is that it is known by many names, including Robin sequence, syndrome, anomalad, and complex. A sequence is a chain of events in which a mechanical disruption or initiating anomaly causes another anomaly or pattern of anomalies. A syndrome is simply a group of abnormalities (often seemingly unrelated) with an initial cause that produces a recognizable pattern.

### ETIOLOGY

In children with Robin sequence, the primary pathology is micrognathia. The initial disruption is interference with normal growth and development of the mandible, which begins to form at 7 weeks' gestation. This leads to posterior displacement of the tongue and interference with the palatal shelves, which close at 11 weeks' gestation. Because of the abnormal mandible,



**Figure 313-1** A newborn with micrognathia and intact palate. Note clinical micrognathia. This patient experienced mild to moderate glossoptosis with airway obstruction that resolved without surgical intervention.



**Figure 313-2** Side view of an infant with micrognathia and glossoptosis but no cleft palate. Note that the degree of micrognathia seen on physical examination often is not predictive of the degree of respiratory or feeding problems.

the tongue stays high and retroposed and impinges against the airway, causing breathing and feeding compromise.

Robin sequence can be an isolated finding or part of another syndrome. Depending on the definition, about 50% of Robin sequence cases are associated with a genetic syndrome or other anomalies. Stickler syndrome is the most common identifiable syndrome associated with Robin sequence and is associated with dysplasia of the orofacial skeletal system. There are at least 50 recognizable syndromes known to be associated with Robin sequence. These include some relatively common conditions, for example, deletion 22q11.2 (velocardiofacial) syndrome and fetal alcohol syndrome (Table 313-1).



**Figure 313-3** Face on view of an infant with micrognathia



**Figure 313-4** Alternate view of newborn with micrognathia.

Table 313-1 Conditions Associated With Robin Sequence	
NAME	DESCRIPTION
Beckwith-Wiedemann syndrome	Macroglossia, risk for tumors, omphalocele, hypotonia, hypoglycemia, overgrowth, hemihypertrophy, visceromegaly
Campomelic dysplasia	Small stature, hypertelorism, congenital limb bowing, clubfoot, intellectual disability, sex reversal
Catel-Manzke syndrome	Abnormal index fingers, hand malformations
CHARGE association	Coloboma of the eye, heart malformation, choanal/esophageal atresia, intellectual disability, short stature, sensorineural hearing loss, abnormal ears
Fetal alcohol syndrome	Low birth weight, growth restriction, congenital heart defect, short palpebral fissures, long smooth philtrum, abnormal cognition, behavioral issues
Fetal hydatoin syndrome	Growth restriction, abnormal cognition, hypoplastic nails
Freeman-Sheldon syndrome	Joint contractures, whistling-shaped mouth, small stature
Microdeletion and duplication syndromes	Dysmorphic features, poor growth, intellectual disability, limb/digit abnormalities.
Moebius sequence	Palsy of sixth and seventh cranial nerves, limb defects
Smith-Lemli-Opitz syndrome	Cholesterol deficiency, intellectual disability, hypotonia, genital hypoplasia, kidney abnormalities, heart abnormalities, polydactyly, contractures
Stickler syndrome	Myopia, detached retina, joint laxity, flat face, marfanoid body
Treacher Collins syndrome	Conductive hearing loss, microtia, facial skeletal defects, colobomas
Velocardiofacial syndrome	Heart defects, developmental delay, hypotonia, hypocalcemia, nasal voice, tapering fingers

EPIDEMIOLOGY

The incidence of Robin sequence is about 1 in 2,000 to 30,000. The true number is not known because of the differing criteria used among physicians and in studies.

DIAGNOSTIC APPROACH

Robin sequence is a clinical diagnosis. There are no universally accepted tests or imaging studies to diagnose micrognathia or retrognathia. However, if a genetic syndrome is suspected related to the micrognathia, testing for the genetic condition may be available. Often, suspicion arises when an infant feeds poorly or cannot maintain his or her oxygen saturation, and closer examination reveals micrognathia. If Robin sequence is suspected, prompt clinical evaluation is

crucial because obstructive apnea can lead to long-term complications. Comprehensive evaluation should be done by any available pediatric otolaryngologist, pulmonologist, speech therapist, anesthesiologist, craniofacial surgeon, and geneticist. Many larger hospitals have a craniofacial team readily available.

The initial evaluation should include a family history focusing on individuals with Robin sequence or cleft palate. This may suggest a genetic cause. For example, family members with high myopia or a detached retina suggest Stickler syndrome. In addition, a prenatal history of maternal teratogen exposure, such as diabetic embryopathy or alcohol consumption while pregnant, is important. A history of oligohydramnios is relevant as constraint on the mandible during fetal development is thought to prevent its normal growth.

Similarly, anything that decreases fetal movement can decrease mandibular growth; therefore, most causes of severe hypotonia that are prenatal in onset can be associated with Robin sequence.

Even if no recognizable syndrome is identified in the infant with Robin sequence, genetic evaluation should be strongly considered. There are hundreds of genetic syndromes associated with micrognathia. It has been reported that about 35% of Robin sequence cases are syndromic. Thus, any child with Robin sequence ideally should be evaluated by a clinical geneticist. Historically, chromosome analysis was the initial screening tool for genetic abnormalities. Recently, advances in genetic testing have discovered chromosomal microdeletions and microduplications linked to multiple congenital anomaly syndromes. These chromosomal abnormalities are identified with a DNA microarray, which has much better sensitivity than chromosome analysis. Deletion 22q11.2 is a common cause of Robin sequence, and fluorescence in situ hybridization (FISH) analysis can identify this syndrome. This technique is not a screening tool because it tests only for the specific disease in question. After the initial examination, a number of genetic tests should be considered with special attention to neurologic findings or malformations unrelated to the micrognathia. If growth and feeding abnormalities persist after airway obstruction has been addressed, genetic testing should also be considered.

Prenatal diagnosis is not always possible, but advances in prenatal imaging and the availability of high-resolution and three-dimensional ultrasound make severe cases of micrognathia identifiable in the fetus. This is useful because these infants may require intubation in the delivery room. Prenatal management should include delivery in a hospital with a neonatal intensive care unit and evaluation by a neonatologist with immediate access to an airway specialist. For extreme cases, it may be desirable to have an otolaryngologist immediately available.

## EVALUATION

An infant identified prenatally with severe micrognathia may need immediate intubation after delivery. Other infants may simply require monitoring for episodes of apnea, decreased oxygenation, and poor feeding. If an infant has no episodes of desaturation and gains weight, no intervention is necessary. However, if an infant has apnea episodes, has oxygen desaturations, cannot feed without desaturation, or fails to gain weight, further evaluation and management is needed.

Obstructive apnea is the most critical problem for an infant with Robin sequence. This may not be an immediate problem but can sometimes become evident later in infancy. At the mildest end of the spectrum, there may be little or no evidence of respiratory difficulty. However, there may be increased caloric expenditure and early fatigue with feeding owing to decreased respiratory reserves. This may result in inadequate weight gain. This relatively mild or subtle presentation is most readily confirmed with a polysomnogram that will demonstrate frequent obstructive events with or without oxygen desaturation.

If apnea spells are suspected, the airway should be examined closely, likely with nasoendoscopy by an

otolaryngologist and bronchoscopy by a pulmonologist. It is important to analyze the position of the tongue and evaluate for any lower airway disease. Unlike laryngomalacia, micrognathia may lead to obstruction with both inspiration and expiration on an endoscopic exam. A polysomnogram or sleep study evaluates apnea spells during sleep in various positions. A barium swallow study with speech evaluation is a better study to evaluate feeding and respiratory dynamics while awake and during feeding. Finally, three-dimensional computed tomography (CT) maps out the bony anatomy, should surgical interventions be needed. This type of CT scan allows the mandible to be viewed from almost any angle. It is important to take any airway compromise seriously because long-term consequences include hypoxia, failure to thrive, dehydration, electrolyte imbalance, cor pulmonale, and death.

Infants with Robin sequence may also have problems with both breastfeeding and bottle feeding, usually secondary to airway obstruction. The suck-swallow-breathe coordination can be very difficult in infants with micrognathia and glossoptosis. Feeding seems to exacerbate limited respiratory reserve. Often, the infant cannot compress the nipple sufficiently. If a cleft palate is also present, feeding is further compromised because suction cannot be generated for feeding. These infants are at increased risk for aspiration of formula or breast milk. Feeding may take so much work that the infant expends more energy than he or she gains, affecting weight gain. If the Robin sequence is part of an associated syndrome, feeding problems and weight gain may be further compromised.

## TREATMENT APPROACH

### Nonsurgical

Treatment algorithms include nonsurgical and surgical interventions. About half of infants with Robin sequence could be managed with nonsurgical interventions. The initial approach to any infant suspected of Robin sequence is to place that infant in a prone position. Gravity will pull the tongue forward, often relieving the glossoptosis and creating an open airway. A polysomnogram should be obtained because pulse oximetry alone is not sensitive enough to detect frequent but brief apneas. If the polysomnogram is normal or mildly abnormal with few apnea spells, positioning and supplemental oxygen through nasal cannula may be the only intervention required. If the polysomnogram demonstrates moderate to severe abnormalities, a nasopharyngeal airway can be placed while further treatments are considered. There are several nonsurgical feeding interventions. Positioning the infant on his or her side or semireclined during feeding can alleviate respiratory distress. If this does not resolve the issue, a skilled speech therapist or occupational therapist should evaluate the infant to optimize feeding technique. Breastfeeding usually requires consultation with a lactation specialist familiar with these issues and almost always results in use of pumping and bottle feeding. Close monitoring of weight gain and apnea spells is essential. Some mothers are able to breastfeed after distraction if they are still lactating and there is no cleft. When a cleft palate is present, a special



bottle should be used with compressibility allowing the milk to be squeezed into the infant's mouth. These bottles include the Haberman Feeder, Pigeon Cleft Palate Nurser, and Mead Johnson Cleft Palate Nurser. Often, an NG tube must be placed for adequate caloric intake, especially during mandibular distraction. Oral feeding often improves significantly after mandibular distraction. In some cases, a G-tube must be considered if intake does not improve after mandibular distraction. A G-tube is also required for infants with severe neurologic deficits and high risk for aspiration.

### Surgical

Surgical interventions for apnea spells depend on the severity and take into account the entire clinical picture. Tracheostomy historically was the primary option for severe, persistent obstruction. It is still performed for many reasons, including airway obstruction, chronic cardiopulmonary disease, and neurologic compromise. Over time, it has been shown that only a small subgroup of infants with respiratory distress due to Robin sequence require intubation or tracheostomy. If the infant has evidence of neurologic impairment, a tracheostomy may be needed to prevent aspiration and other complications. If there is an underlying genetic syndrome with many organ systems involved, such as cardiac and pulmonary, a tracheostomy may be necessary. Finally, a tracheostomy may be necessary if other airway management options have failed.

During the past several years, mandibular distraction osteogenesis has gained favor in many craniofacial centers. Originally, mandibular distraction osteogenesis was done for successful decannulation in older children with tracheostomies using rib bone as grafts. Now, however, this technique is done as a primary treatment to avoid tracheostomy with its associated complications, increased mortality rate, and delayed speech development. Distraction devices can be used on multiple planes of a bone and can be placed internally or externally. Of note, current options are usually not associated with severe scarring.

For Robin sequence, this technique slowly elongates the mandible by bilateral corticotomies (partial fractures) with placement of percutaneous wires and distraction devices. Mandibular distraction relies on the body's ability to lay down new bone when the ends of a bone are separated. After a latency period of 24 to 48 hours, the distractor is turned daily to achieve about 1 to 4 mm of distraction per day. The goal is to bring the base of the tongue forward, relieving the glossop-tosis and apnea. Infants who are otherwise stable can sometimes be taken home after parents are taught to manipulate the distractor device. On average, there are 2 to 4 weeks of active distraction and another 4 to 6 weeks for bone consolidation. During the period of distraction, infants are often fed through a nasogastric (NG) tube. Some facilities allow oral feeding during distraction, but this is not the standard at most places. Importantly, distraction elongates muscle, blood vessels, nerves, and mucosa as well as bone. New techniques for distraction osteogenesis include miniaturized and absorbable distractor plates. Although a large number of children are distracted at a young age (infancy to

3 years old) for reasons illustrated earlier, many patients are distracted at 6 to 7 years old if airway issues permit.

An older technique is tongue-lip adhesion, which sutures the tongue base to the anterior mandible. This method has been abandoned by most surgeons because of the side effects of aspiration, feeding abnormalities, speech delay, and subsequent tongue atrophy and weakness. Less than 15% of pediatric centers report use of this technique.

## SURGICAL COMPLICATIONS

Complications of mandibular distraction osteogenesis are numerous but rare and comparable to the alternative of tracheostomy. These complications can include bone malunion or malalignment requiring repeat distraction. There is potential disturbance of mandibular growth at the temporomandibular joint. The facial nerve can be injured. Tooth loss or damage to underlying tooth buds can occur. More commonly, the skin where the distractor inserts can become infected if not properly cleaned. Tracheostomies carry the risks for dislodgement or occlusion of the tube, buildup of granulation tissue, delayed speech, and recurrent infections—all related to a chronic foreign body in the airway.

## PROGNOSIS

Robin sequence has a broad range of phenotypes associated. With prompt identification of isolated Robin sequence in a neonate who demonstrates respiratory distress, there should be no impact on life span. The immediate management is straightforward, and the initial tools for treating most children (positioning, oxygen, and monitors) are readily available in any hospital with newborn care. Most patients do not require surgical management as neonates. Infants with isolated Robin sequence and those with Stickler syndrome (comprising >50% of cases) should have normal cognition, good growth, and a normal life span. Infants and children with syndromic Robin sequence are at increased risk for long-term morbidity and mortality because of the risks inherent to the specific syndrome. There should be a low threshold for involving a geneticist with any case of Robin sequence to identify these high-risk infants. Furthermore, a team approach should be applied in general for these infants because a single solution cannot be broadly applied, but careful assessment can contribute to appropriate risk stratification and management.

### WHEN TO ADMIT

- Infants with poor weight gain in the first week of life
- Stridor or other respiratory symptoms on examination (or by history)
- Suspicion of other malformations or neurologic abnormalities, requiring further evaluation by specialists

### WHEN TO REFER

- Craniofacial management is expected.
- A surgical intervention or assessment is likely (ie, for airway or feeding).
- Poor feeding or respiratory distress in neonates



## TOOLS FOR PRACTICE

### Engaging Patient and Family

- Pierre Robin Network (Web site), ([www.pierrerobin.org](http://www.pierrerobin.org))

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## Chapter 314

# PINWORM INFESTATIONS

Craig M. Wilson, MD

## ETIOLOGY

Pinworm (*Enterobius vermicularis*) infestation is exceptionally common. When sought carefully, the parasite can be found in at least 30% of children worldwide, and infestation rates may approach 100% in child care centers, boarding schools, and institutions. Good sanitation and advanced socioeconomic status are feeble deterrents to pinworms. Adults are often infested, and finding pinworms in all members of a family is not uncommon. The discovery of *Enterobius* eggs in 10,000-year-old human coprolites from the Hogup and Danger caves in Utah proves that the parasite was no stranger to our ancestors.

*E. vermicularis* is a white, threadlike worm that lives primarily in the cecum and adjacent bowel. The gravid female worm, which is approximately 1 cm long, migrates to the perianal area to deposit up to 10,000 eggs and dies shortly thereafter. Thus, the infestation would be self-limited were it not for reinfestation. Unfortunately, the eggs, which are approximately 50 × 30 μm, oval, flat on 1 side, and thin shelled, become infective in approximately 6 hours. Moreover, *Enterobius* eggs are rather hardy and may survive for weeks in dirt, house dust, clothing, and bed sheets. Survival is enhanced by lower temperature and if inhaled and swallowed. Pets may carry eggs in their fur.

Autoinfestation occurs readily through ingestion of eggs if the host scratches the perianal area or does not wash the hands thoroughly after defecating. Once ingested, the eggs hatch in the upper small intestine, and the worms mature while migrating to the lower ileum and ascending colon. The cycle from ingestion to deposition of eggs is approximately 4 to 6 weeks,

although the adult worms may live up to 13 weeks. The worm burden within an individual may reach the hundreds; but within an infested population, most individuals would be harboring few parasites.

## CLINICAL MANIFESTATIONS

Localized perianal pruritus is the most commonly reported symptom, but one third or more of infestations are asymptomatic. Restlessness and fitful sleep are common complaints, as are secondary excoriation and dermatitis. Migrating pinworms entering the vagina or urinary tract in female patients may lead to genitourinary symptoms. The general lack of abdominal complaints supports the notion of minimal gastrointestinal abnormality with this parasite.

In rare cases, pinworms invade tissue and cause a granulomatous reaction, and granuloma-containing worms have been an incidental finding in the gut, vulva, cervix, fallopian tubes, peritoneum, and bladder. Inflammation associated with the parasite has been found in cases of appendicitis and eosinophilic colitis, suggesting causality with *E. vermicularis*.

## LABORATORY EVALUATION

Diagnosis is dependent on identifying either the adult worms or the eggs. Occasionally, adult pinworms may be noted near the anus, particularly in the morning. Eggs are seldom found in the patient's feces even if concentration techniques are used. The best way to make a diagnosis is to use the cellophane tape technique. When the child awakens in the morning, the adhesive side of a 2-inch strip of clear cellophane tape should be pressed against the perianal skin; this task is most easily done using a tongue depressor (commercially produced kits are available for this purpose). The tape should then be placed on a microscope slide with the adhesive side down and scanned for eggs. The eggs are naturally transparent, and staining with lactophenol cotton blue enhances detection. A single test should detect at least 50% of infestations, 3 tests will detect 90%, and 5 tests will detect virtually 100%.

## PREVENTION AND THERAPY

Elimination of pinworm from patients is extremely difficult. The ubiquity and infectivity of the parasite, the high level of infestation in symptomatic patients, and its persistence in the environment all contribute to the difficulty of eradication. Moreover, vigorous pursuit of a permanent cure may provoke needless turmoil and anxiety in the family. When the diagnosis is confirmed in a patient who has symptoms, the following approach is reasonable.

Both initial treatment of only a confirmed individual patient or therapy for the entire family are reasonable approaches. A single dose of either mebendazole (100 mg for all ages) or albendazole (400 mg for all ages) is extremely effective and has virtually no side effects. Pyrantel pamoate, administered as a single dose of 11 mg/kg (maximum, 1 g), is also effective; a transient headache and abdominal complaints have been reported with this therapy. All of these treatments are effective against the adult worms only, and therefore therapy is usually repeated in 2 weeks to eradicate any emerging parasites.

Other simple, prudent measures can be followed, such as clipping the fingernails (a favorite repository for eggs), washing the hands frequently, and showering daily in the morning. Wearing tight-fitting cotton underpants and applying a bland ointment (eg, petroleum jelly) to the perianal region may limit dispersal of the eggs. The floors in sleeping areas should be cleaned thoroughly, particularly in cases of recurrence. Clothing and bedding should be washed at the time of treatment. The most important aspects of treatment, however, are humility on the part of the physician and reassurance of the family.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Pinworm Infection* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/ncidod/dpd/parasites/pinworm/factsht\\_pinworm.htm](http://www.cdc.gov/ncidod/dpd/parasites/pinworm/factsht_pinworm.htm))

#### Medical Decision Support

- *Enterobius vermicularis*—*Lab Identification* (Web page), Centers for Disease Control and Prevention ([www.dpd.cdc.gov/dpdx/HTML/Enterobiasis.htm](http://www.dpd.cdc.gov/dpdx/HTML/Enterobiasis.htm))

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## Chapter 315 PNEUMONIA†

Michael Light, MD

### INTRODUCTION

Community-acquired pneumonia (CAP) is a common problem worldwide and causes considerable mortality. In North America, the annual incidence is reported to be 34 to 40 cases per 1,000 in children younger than 5 years. The incidence among adolescents is about 7 per 1,000 between 12 and 15 years old. In developing countries, pneumonia is even more common. The mortality rates are high, with 4 million deaths per year, which means pneumonia is the number 1 cause of death in children younger than 5 years in developing countries.

Community-acquired pneumonia is defined as pneumonia that is acquired outside the hospital environment, whereas nosocomial pneumonia is acquired in the hospital environment. The diagnosis of pneumonia is usually made on the basis of signs and symptoms and supported by a radiologic diagnosis. The World Health Organization (WHO) defines pneumonia on the basis of the clinical findings because chest radiology is not readily accessible in many parts of the world.

The agents that cause pneumonia are varied and include bacteria, viruses, fungi, and protozoal organisms. It can also be caused by aspiration and exposure to toxic substances, such as chlorine.

### PATHOLOGY

The pathology of pneumonia is described as either

- Lobar
- Bronchopneumonia
- Interstitial
- Miliary

Lobar pneumonia has 4 stages. The initial stage is congestion, where the alveoli are filled with fibrinous fluid, neutrophils, and bacteria. This stage occurs within 24 hours of infection. The second stage usually occurs on days 2 to 3 and is called red hepatization. The lung reddens and is of the consistency of liver. The alveoli are filled with fibrinous inflammatory exudates with increased numbers of neutrophils and red cells that contribute to the color. The consolidated lobe is airless and evident on chest radiography. The pleura is usually thickened, and a pleural rub may be heard. The next stage is called grey hepatization, where the alveoli are filled with fibrin threads and neutrophils and the red cells are much fewer in number. The lung is still stiff, and the alveolar walls are thickened and fibrosed. The fourth stage is resolution as the inflammatory exudates are resorbed.

Bronchopneumonia is more patchy and, as the name suggests, there is suppurative inflammation of the bronchi and surrounding alveoli. The exudates fill bronchi and bronchioles and affect the adjacent alveoli while the distant alveoli may be free of exudates. The patchy consolidation may affect one or several lobes and is usually bilateral. The lobes more involved include the dependent lung zones and the bases.

Interstitial pneumonia results from inflammation that is within the alveolar wall rather than the alveolar air space. The infiltrate tends to consist of lymphocytes and macrophages, and hyaline membranes may line the alveolar spaces.

An additional category is miliary, which occurs with hematogenous spread to the lung, which leads to multiple discrete lesions often throughout both lungs.

Bacterial pneumonia often follows a viral upper respiratory infection (URI). Lobar pneumonia is most commonly bacterial, including atypical bacteria. Bronchopneumonia may be caused by bacteria, atypical bacteria, or viruses. Interstitial pneumonia may result from measles and *Bordetella pertussis*, as well as non-infectious causes including aspiration. Miliary pulmonary infection is most commonly seen in tuberculosis, histoplasmosis, and coccidioidomycosis. Immunocompromised children are at risk for miliary herpesvirus, cytomegalovirus, or varicella-zoster virus.

### ETIOLOGY

It is difficult to study the etiology of pneumonia because the causes are so diverse, and what is found in one community may not apply to another community. A study of 154 hospitalized children with CAP looking carefully for an infectious cause showed that it was caused by identifiable bacteria in approximately 60% of cases, of which 73% were caused by *Streptococcus*

†This chapter has been adapted and updated from the AAP policy manual *Pediatric Pulmonology*.

*pneumoniae*. A viral cause was found in 45% of cases, of which 23% had concurrent bacterial and viral disease. They also found *Mycoplasma* spp. in 14% and *Chlamydomphila* (*Chlamydia*) *pneumoniae* in 9%.

## CLINICAL FEATURES

The symptoms and signs of pneumonia vary from subtle to highly suspicious. Table 315-1 shows age-related symptoms and signs that suggest the diagnosis of pneumonia. In a pediatric emergency department study in the United States, the finding of respiratory rate alone and clinical impression of tachypnea did not discriminate between those who had radiographic evidence of pneumonia and those who did not, whereas the children who exceeded the WHO respiratory rate thresholds were more likely to have pneumonia. The

most common presentation is cough and fever, which is very nonspecific. The appearance of the child is important; signs of respiratory distress, including retractions and nasal flaring, and abnormal auscultation, will aid the physician in arriving at the diagnosis of pneumonia.

## DIAGNOSIS

The microbiologic diagnosis of pneumonia is difficult to prove in many cases without extensive investigation. The age of the child will suggest the most likely cause, and it is also helpful to be aware of which organisms are in the community at the time. Pneumonia in the pediatric population is most common in infants and toddlers and least common in adolescents.

Box 315-1 lists the more likely causes of pneumonia based on age.

**Table 315-1** Symptoms and Signs of Pneumonia

	≤2 MONTHS	2–12 MONTHS	1–5 YEARS	>5 YEARS
<b>Respiratory rate</b>	≥60/min	≥50/min	≥40/min	≥30/min
<b>WHO threshold</b>				
<b>Symptoms and signs</b>	Cough Poor feeding Apnea Tachypnea Grunting Nasal flaring Retractions	Cough Fever Poor feeding Tachypnea Grunting Rhinorrhea Nasal flaring Retractions	Cough Fever Rhinorrhea Chest pain Tachypnea Retractions	Cough Fever Headache Pleuritic pain Abdominal pain Tachypnea Retractions
<b>Auscultation</b>	Crackles Wheeze	Crackles Wheeze	Crackles Wheeze Pleural rub	Crackles Wheeze Pleural rub

WHO, World Health Organization.

### BOX 315-1 Age-Related Etiology of Pneumonia in the Immunocompetent Child

#### 2 MONTHS AND YOUNGER

- Group B streptococcus (*Streptococcus agalacticae*)
- Pneumococcus (*Streptococcus pneumoniae*)
- *Staphylococcus aureus* (MSSA, MRSA)
- *Listeria monocytogenes*

#### 2–12 MONTHS

- Pneumococcus
- RSV
- Parainfluenza virus
- Influenza virus
- Adenovirus
- Human metapneumovirus
- *Chlamydia trachomatis*
- Pertussis

#### 1–4 YEARS

- Pneumococcus
- Parainfluenza

- Influenza
- Adenovirus
- RSV
- hMPV
- *Mycoplasma pneumoniae*

#### 5–12 YEARS

- *Mycoplasma*
- *Pneumococcus*
- Group A Streptococcus (*Streptococcus pyogenes*)
- Viruses

#### 12 YEARS AND OLDER

- *Mycoplasma*
- *Chlamydomphila pneumoniae*
- *Pneumococcus*
- Group A Streptococcus
- Viruses

hMPV, human metapneumovirus; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; RSV, respiratory syncytial virus.

### Infants to School Age (1 to 4 Years of Age)

After 1 month of age, cough is the most common presentation of pneumonia. A viral upper respiratory illness commonly precedes the pneumonia. If the pneumonia is bacterial a significant fever is usually present, whereas in viral or atypical infections the fever may be low-grade. Generally, though, the height of the fever is a poor indicator of etiology. Most cases of pneumonia are viral, and respiratory syncytial virus (RSV) is the most common pathogen. Although RSV principally causes bronchiolitis, it is also a common cause of pneumonia. In children older than 2 years, RSV does not cause lower respiratory tract infection except in immunocompromised (especially transplant) patients. Respiratory syncytial virus causes significant morbidity and mortality in the elderly. Parainfluenza type 3 occurs year-round, with peaks in the spring, and types 1 and 2 are typically seen in the fall.

### 5 Years of Age to Adolescence

The most common cause of bacterial pneumonia is *S pneumoniae*, but *Mycoplasma* is increasingly being diagnosed as the cause of CAP. Group A *Streptococcus* is also increasingly being diagnosed. Various viruses cause pneumonia, including adenovirus, influenza, parainfluenza, and RSV (in the immunocompromised and transplant patient).

### Laboratory Findings

As previously noted, the diagnosis of pneumonia is clinical and is supported by the radiographic changes if a radiograph is performed. Laboratory investigation is usually of limited value in the outpatient evaluation of a child with pneumonia.

Complete blood cell count may reveal an elevated white count greater than 20,000 cells/ $\mu$ L with pneumococcal pneumonia. Atypical lymphocytes may be found with viral infections, but the finding is nonspecific. It is not considered essential to attempt to find the etiologic agent routinely in children who were previously well. Pneumonia in children does not usually have bacteremia, and blood culture is not routinely required in immunocompetent children unless they are hospitalized.

If the child is critically ill or immunocompromised, blood culture is more likely to be positive. Sputum Gram stain with culture and sensitivity may be considered in the older child. If the child does not respond to initial therapy within 72 hours or if there is a rapid progression of symptoms, further testing may be indicated.

Elevation of C-reactive protein may predict more severe disease, but it does not differentiate bacterial from viral pneumonia.

If the child has a pleural effusion and has not received antibiotics, a pleural tap should be considered. If antibiotics have been given, the yield from pleural tap is low. Polymerase chain reaction (PCR), if available, may be helpful with further etiologic diagnosis.

### Imaging

The standard imaging for diagnosis of pneumonia is a 2-view plain chest radiograph. It is not possible to differentiate between viral and bacterial disease. Lobar

pneumonia, with disease restricted to the involved lobe, is more suspicious for bacterial pneumonia. Perihilar scattered infiltrates, hyperinflation, and hilar adenopathy are more likely in viral pneumonia than in bacterial pneumonia. Round pneumonia, seen in younger children, is likely of bacterial etiology, particularly *S pneumoniae*, but also includes *Staphylococcus aureus* and *Klebsiella* species. Ultrasound is increasingly being used to evaluate pulmonary problems and can assist in evaluation of lobar consolidation and pleural effusion. A computed tomography (CT) scan or ultrasound is indicated if there are complications.

## BACTERIAL CAUSES OF PNEUMONIA

Bacterial pneumonia is an important cause of death if untreated, especially in developing countries. Although most children with bacterial pneumonia improve without sequelae, children with pre-existing conditions may be at increased risk for morbidity, including subsequent infections because of scarring in the lungs. The immune status of the child also affects the risk of mortality and morbidity. Tuberculosis remains an important cause of pneumonia.

### Gram-Positive Organisms

#### *Pneumococcus*

*Streptococcus pneumoniae* was the most common bacterial cause of lower respiratory infection before the institution of the pneumococcal conjugate vaccine, PCV-7, in 2000. Since then, invasive pneumococcal disease was reduced by 80% for children younger than 2 years. This finding may increase because a 13-valent pneumococcal conjugate vaccine (PCV-13) replaced PCV-7 in the routine childhood immunization schedule in 2010. PCV-13 is recommended by the US Food and Drug Administration for use in preventing pneumococcal disease in all infants and young children beginning as young as 6 weeks of age. Surveillance is also indicated for nonvaccine serotypes. Although invasive pneumococcal disease has decreased, complicated pneumonia has increased significantly across the United States, and these cases tend to be from nonvaccine serotypes. Use of PCV-13 coupled with pneumococcal polysaccharide vaccine (PPSV-23) is now recommended by the AAP for children and adults with certain chronic medical conditions or cochlear implants to provide greater protection.

Pneumococci are gram-positive diplococci, which are colonized in the upper respiratory tract of many people. Transmission is by droplet, and the incubation period is short (sometimes 1–3 days). Populations at higher risk for invasive pneumococcal disease (pneumonia, meningitis, and sepsis) are shown in Box 315-2.

Pneumococcal pneumonia may be preceded by a mild URI. Infants may present with a sudden rise in body temperature, possibly a seizure, and diarrhea and vomiting. Cough may be absent, but evidence of respiratory distress includes tachypnea, nasal flaring, and perioral cyanosis. The older child usually presents with fever, chills, dyspnea, and pleuritic chest pain. Older children may have sputum production, and streaks of blood may be apparent in the sputum.

Examination of the chest may not be abnormal in the infant and young child. The older child will usually



### BOX 315-2 Children at Increased Risk for Invasive Pneumococcal Disease

- Children <36 months
- Children with sickle cell disease
- Children with asplenia
- Children with human immunodeficiency virus infection
- Children with cochlear implants
- Children with chronic disease including asthma, immune deficiency (including transplants), cardiac disease, pulmonary disease, renal insufficiency, and diabetes mellitus are at presumed high risk, but the data are insufficient to calculate rates

demonstrate crackles and dullness to percussion with bronchial breathing over the involved lobe. Friction rub is not often elicited. Abdominal pain in the older child is a common symptom, especially if the infiltrate(s) involve the lower lobe of either lung.

Laboratory findings also are not consistent. Although not indicated in the outpatient setting, a white blood cell count over 20,000/ $\mu$ L with the clinical picture of pneumonia is certainly suspicious of pneumococcal disease. The yield from blood culture is low, but the sputum findings of many polymorphonuclear leukocytes with gram-positive diplococci is almost diagnostic. Young age is a barrier to sputum collection. Antigen detection is not considered useful for diagnosis except for pleural fluid.

The chest radiograph in children with pneumococcal pneumonia may initially demonstrate a lobar pattern and then extend beyond the lobar boundaries. It is the most common cause of “round pneumonia” pattern. On occasion, the markings may be patchy or interstitial. The chest radiograph is not consistently able to confirm the diagnosis of a bacterial or viral pneumonia because of the overlap between findings.

**MANAGEMENT.** The clinical course of pneumococcal pneumonia is usually rapid, with response to antibiotics causing reduction of fever within a few hours. In children with CAP proven or suspected to be of bacterial origin who are treated as outpatients, the AAP recommends amoxicillin or amoxicillin-clavulanate. In school-aged children (>5 years), the addition of a macrolide for coverage of atypical organisms is advised. In children ill enough to warrant hospitalization, the use of penicillin, ampicillin, or ceftriaxone and the addition of a macrolide is usually appropriate, and decisions for therapy should take into account local resistance patterns and immunization history. Complications may be systemic, with meningitis, carditis, peritonitis, and septic arthritis resulting from bacteremia. Pulmonary complications include pleural effusion and empyema. Inappropriate secretion of an antidiuretic hormone is common and may significantly reduce serum sodium.

#### Group A Streptococcus

Also known as *Streptococcus pyogenes*, group A  $\beta$ -hemolytic streptococcus is an uncommon cause of

pneumonia. It is important because the clinical course is aggressive and may result in necrotizing pneumonia. The clinical appearance of the child includes fever, chills, lethargy, cough, and dyspnea. The most common radiographic pattern is a patchy bronchopneumonia, but in a minority of cases there is lobar consolidation. Cavitation may occur, as well as pleural effusion with progression to fibrinopurulent empyema.

**MANAGEMENT.** The response to antibiotics tends to be slow, even with sensitive organisms. Complications are common and include pneumothorax, pneumatoceles, bronchiectasis, and bronchopleural fistula. Penicillin remains the treatment of choice, although ampicillin is an alternative.

#### Staphylococcal Pneumonia

*Staphylococcus aureus* was for a long time an uncommon cause of pneumonia in immunocompetent children, but it did occur in infancy. A virulent strain of community-associated methicillin-resistant *S aureus* (MRSA) has emerged and is now associated with life-threatening, complicated pneumonia. *S aureus* also occurs more commonly after influenza infection and other viral URIs. Staphylococci are gram-positive organisms that occur in clusters. Pneumonia results from inhalation of organisms or from bacteremic spread. The clinical picture varies from a mild respiratory infection with fever, cough, and tachypnea to a rapidly progressive illness with dyspnea, cyanosis, and septic shock. The initial radiographic appearance is multiple nodular infiltrates, usually unilateral, which in a few days become cavitory; subsequently, pneumatoceles form. Pneumothorax is common, especially in ventilated infants, and empyema is present in most cases.

The scenario described in the previous paragraph would likely be diagnosed as *S aureus* in an infant, but if the same findings were present in an older child other organisms would be more likely, including *Escherichia coli*, *Pseudomonas*, or *Klebsiella*. These children may be in an intensive care unit or immunocompromised. It is likely that the relative prevalence from *Pneumococcus* to *S aureus* is increasing in older children, and that there are increasing numbers of children with pneumonia caused by MRSA. Schultz and colleagues also compared complications between MRSA and methicillin-sensitive *S aureus* and found similar complication rates.

**MANAGEMENT.** If staphylococcal pneumonia is suspected, the increased prevalence of MRSA requires vancomycin or clindamycin for initial treatment until the sensitivities are known. Physicians should be aware of their local MRSA susceptibilities for these agents.

#### Gram-Negative Organisms

##### *Pseudomonas aeruginosa*

*Pseudomonas* is a gram-negative bacterium that has a predilection to moist environments. It is common to acquire *Pseudomonas*, with colonization in more than 50% of humans, and *Pseudomonas* often causes nosocomial infection. It is an unusual cause of pneumonia in healthy children. Pneumonia caused by *Pseudomonas* is a common complication of children with endotracheal tubes or tracheostomy. It is the dominant

organism in cystic fibrosis (CF). It occurs more often in children with poorly controlled human immunodeficiency virus (HIV) infection, neutropenia, and complement deficiency and those who are immunosuppressed. It is the most common cause of pneumonia in the intensive care environment. It has been reported following exposure in hot tub spas.

Although the typical color of sputum produced in pseudomonal pneumonia is green, this color may be seen with pneumococcal and *Haemophilus* infections. Untreated *Pseudomonas* pneumonia may progress rapidly to necrotizing bronchopneumonia. Pleural effusion is common, and the pneumonia may have a lobar or diffuse bilateral bronchopneumonia radiographic pattern.

**MANAGEMENT.** Treatment of *Pseudomonas* pneumonia should be with 2 antibiotics, usually an aminoglycoside and a  $\beta$ -lactam antibiotic. For children with chronic *Pseudomonas* infection, especially those with CF, there is a major problem with resistance to antibiotics.

### ***Burkholderia cepacia***

*Pseudomonas cepacia* was described initially by Walter Burkholder in 1949 and is now named *Burkholderia cepacia*. It is an important pathogen in CF causing pneumonia and has been reported to cause pneumonia in immunocompromised children, especially those with chronic granulomatous disease (CGD). *B cepacia* does not cause pneumonia in healthy children.

### ***Klebsiella pneumoniae***

*Klebsiella pneumoniae* is a gram-negative rod-shaped bacillus, and clinically the most important member of the *Klebsiella* genus of Enterobacteriaceae.

**CLINICAL FEATURES.** Pneumonia as a result of *K pneumoniae* is typically a nosocomial infection. It may also be community acquired, although it is rare in otherwise healthy children. Pneumonia tends to occur in immunocompromised or debilitated children. It is associated with an acute onset with fever and chills. The cough is productive and yields abundant thick sputum that is typically blood tinged and is known as red currant jelly sputum. *Klebsiella pneumoniae* pneumonia is usually complicated, and abscess formation, cavitation, and empyema are common. Infection is more commonly unilateral, occurring typically in the upper lobes.

**MANAGEMENT.** Hospitalization is indicated, including for CAP, because even with treatment there is significant mortality. Many *Klebsiella* organisms are resistant to multiple antibiotics so, rather than monotherapy, multiple antibiotics are indicated until antibiotic sensitivities are available. Potential choices are wide, including third-generation cephalosporins (eg, cefotaxime or ceftriaxone), carbapenems (eg, meropenem), amino-glycosides, and quinolones. Extended-spectrum  $\beta$ -lactamase- and carbapenemase-resistant strains may occur; thus, the pediatrician should consult with an infectious disease specialist.

### ***Legionella pneumophila***

Legionnaires' disease was first recognized in 1976 at an American Legion convention in Philadelphia. The organism that caused an outbreak of pneumonia was identified as a gram-negative bacillus, *Legionella*

*pneumophila*. While an unusual cause of pneumonia in children, it is important to recognize. It is more common in children who are immunosuppressed, and more than one-third of children in pediatric cases have been younger than 1 year. Transmission occurs by aerosolization and inhalation or aspiration of water containing the organism. It has been linked to contaminated water in hospitals and respiratory therapy equipment, as well as cooling towers; central air conditioning systems; evaporative coolers; hot water systems, including showers and hot tub spas; and ice-making machines. The disease is particularly prevalent in hotels, cruise ships, and hospitals that have outdated cooling systems. The incubation period is 2 to 10 days, and for milder disease, known as Pontiac fever, the incubation period is 1 to 2 days.

**CLINICAL FEATURES.** Legionnaires' disease presents with fever, chills, and cough, which is initially non-productive. Constitutional symptoms include headache, muscle ache, and sometimes ataxia (loss of coordination) and diarrhea or vomiting. The lung examination typically reveals crackles.

A blood test may reveal abnormal hepatic or renal function, and hyponatremia is common. Chest radiograph typically shows unilateral or bilateral bronchopneumonia.

**MANAGEMENT.** Clues to the diagnosis are the constitutional symptoms and the laboratory abnormalities including hyponatremia. Detection of *L pneumophila* serogroup 1 is aided by detecting *Legionella* antigen in the urine.

Azithromycin is the drug of choice for children with suspected or confirmed *Legionella* pneumonia. It is initially recommended by the AAP to give azithromycin intravenously, converting to orally when the child responds. Fluoroquinolones are bactericidal and can be used in adolescents and adults as well as immunocompromised children.

### **Anaerobic Organisms**

The most common anaerobic gram-negative bacilli (AGNB) to cause pneumonia are the pigmented *Prevotella* spp. The *Prevotella* spp. are important components of the bacterial flora of the mouth, nose, and nasopharynx. They are not often cultured because of the difficulty in specimen collection and growth in the microbiology laboratory.

Anaerobic organisms are common contributors to infections such as chronic sinusitis, chronic mastoiditis, chronic otitis media, and retropharyngeal abscess.

Pneumonia caused by anaerobic organisms results from aspiration of upper airway or gastric secretions. Severe gingival disease is a risk factor. Following aspiration there may be progression from pneumonia to necrotizing pneumonia, and AGNB is an important cause of lung abscess. Frequently, AGNB are recovered in culture along with Enterobacteriaceae, *Pseudomonas*, and *S aureus*.

The *Prevotella* are resistant to penicillin and typically susceptible to metronidazole and carbapenems.

### **Atypical Pneumonia**

The term *atypical pneumonia* is applied when the organism that causes the pneumonia does not fit the

category of bacteria or viruses. The agents that cause atypical pneumonia include *Mycoplasma pneumoniae*, *Chlamydia trachomatis*, *Chlamydophila pneumoniae*, and *Chlamydophila psittaci*.

### **Mycoplasma**

*Mycoplasma pneumoniae* is the most common cause of CAP in children older than 5 years, often called “walking pneumonia.” Disease from *M pneumoniae* may occur in children younger than 5 years.

The true incidence is unknown because many cases are treated empirically without confirmation of the diagnosis. There are no geographic limitations, and infection occurs year-round. There may be epidemics every 3 to 7 years, and outbreaks occur in schools and universities.

*Mycoplasma pneumoniae* is called mycoplasma because of the plasticity of the bacterial forms, which resemble fungal elements. Instead of a cell wall there is a cell membrane containing sterols, which are not present in most bacteria or viruses. Unlike viruses they do not require a cell to replicate and can grow in cell-free media, and like bacteria they contain both RNA and DNA.

### **Clinical Features**

*Mycoplasma pneumoniae* infections usually start with a URI with pharyngitis, cough, headache, and myalgias. There may be fever, which is usually lower than 102°F. The cough is initially nonproductive and can be severe and debilitating. Blood streaking of the sputum is not uncommon, and the coughing may cause chest pain that is nonpleuritic. In 5% to 10% of children the URI progresses to bronchitis or pneumonia. Pleural effusion occurs in 5% to 20% of children. Cutaneous manifestations are common and include macular-papular rash and erythema nodosum. Extrapulmonary symptoms are not uncommon and include bullous myringitis, which supports the diagnosis of mycoplasma.

In sickle cell anemia the mycoplasma infection may be severe and is considered an important cause of acute chest syndrome. Mycoplasma infection also can be severe in Down syndrome, especially in those with congenital cardiac disease. Both mycoplasma and chlamydophila cause exacerbations of asthma in children and adolescents.

The physical examination usually reveals oropharyngeal inflammation. The chest examination findings may be relatively benign, with few crackles and rhonchi, at the same time that a chest radiograph shows significant findings of pneumonia. Wheezing may occur, particularly if the child has asthma.

### **Laboratory**

Cold agglutinins are nonspecific (about 75%), and therefore should not be used to confirm the diagnosis. Mycoplasma immunoglobulin (Ig) M and IgG may be useful to confirm the diagnosis, with sensitivity approximately 98% if both are done. Immunoglobulin M may be negative in the first week of illness, and the presence of IgG may be indicative of past infection. The specificity of *M pneumoniae* IgM detection during an outbreak is higher in those persons 19 years of age or older compared with younger individuals. Immunoglobulin G antibody can

persist for months after infection. It is likely that in the future, diagnosis using PCR will be more readily available clinically, which will expedite the results.

### **Imaging**

Infiltrates are more likely to be bilateral than unilateral. There may be lobar, multifocal, or diffuse disease with reticular infiltrates. Pleural effusions are present in about 20% of the images, and hilar adenopathy is seen in 7% to 22%.

### **Management**

The AAP recommends treatment of mycoplasma pneumonia with macrolide antibiotics, although there are now reports of macrolide resistance. Tetracycline is active, in particular doxycycline, and can be used for adolescents, but not for children younger than 8 years. The newer fluoroquinolones are an alternative treatment.

The lack of cell wall predicts that  $\beta$ -lactams are not effective, nor is trimethoprim. Most cases of CAP improve in a matter of days with no residual findings.

### **Chlamydia trachomatis**

*Chlamydia trachomatis* is an important cause of sexually transmitted infection and trachoma. Although uncommon in the United States, trachoma is the most common cause of blindness in the world. *C trachomatis* causes pneumonia, especially in infants. Approximately 5% to 22% of pregnant women have *C trachomatis* of the cervix, and 30% to 50% of these will show culture evidence of infection. The infection in the newborn is conjunctivitis with or without nasopharyngitis, which in some cases results in neonatal pneumonia.

### **Clinical Features**

Most infants with *C trachomatis* pneumonia have a history of conjunctivitis, nasal stuffiness, and cough with tachypnea. The infant with *C trachomatis* pneumonia is characteristically afebrile. The chest examination reveals scattered crackles; wheezing is absent.

### **Imaging**

The chest radiograph typically demonstrates either a lobar or interstitial pattern.

### **Management**

The recommendation to treat infants with *C trachomatis* pneumonia is erythromycin 50 mg/kg/day divided into 4 doses for 14 days. Azithromycin, 20 mg/kg as a single daily dose for 3 days is an alternative.

### **Chlamydophila psittaci**

*Chlamydophila psittaci* causes psittacosis or ornithosis following exposure to infected birds. Ornithosis is the preferred name because it can be caused by any bird, including parrots, chickens, ducks, turkeys, pigeons, and sparrows. It is transmitted from birds to humans by either direct contact or aerosolization. It is much less common since the imposition of quarantine for a period of 30 days for imported birds and the introduction of bird feed laced with antibiotics.

It is quite difficult to diagnose and it is possible that it is more common than appreciated. The most



common disease is a mild pneumonia, but it can produce a more fulminant illness. There is fever without elevation of the pulse, which is usually associated with fever. The clues to the diagnosis include splenomegaly, a blanching erythematous maculopapular rash, signs of hepatitis, disseminated intravascular coagulation, or meningoencephalitis, any of which may be present.

### ***Chlamydophila pneumoniae***

*Chlamydophila pneumoniae* causes a mild pneumonia or bronchitis in older children, adolescents, and adults. Approximately 50% of young adults have serologic evidence of prior infection. *Chlamydophila pneumoniae* is estimated to cause 10% to 20% of CAP. It is transmitted from person to person by respiratory secretion transfer. The incubation period is approximately 3 to 4 weeks.

Initially there is a URI, and many children have no further symptoms. The symptoms can be prolonged, and the presence of hoarseness and headache is helpful in the diagnosis; fever is uncommon. The physical examination reveals crackles, wheezing, and rhonchi. Even with treatment, *C pneumoniae* tends to respond more slowly than mycoplasma, which may also be a clue to the diagnosis. It also tends to recur if therapy is stopped too early. Azithromycin is effective, and doxycycline can be used in older children and adolescents. Mortality of 9.8% has been reported in children with sickle cell disease.

### **Other Causes of Bacterial Pneumonia**

Tularemia, anthrax, and plague are uncommon bacterial syndromes in which pneumonia may be a prominent feature; they should raise the suspicion of bioterrorism.

## **VIRAL CAUSES OF PNEUMONIA**

Viral infections are the most common cause of symptomatic disease in children. The number of respiratory infections per year may be 5 to 10 or even more, with most being URIs. Most cases of pneumonia are diagnosed clinically, but there is an increasing ability to find an etiologic agent as new biotechnology facilitates the diagnosis of viral infections. As noted previously, secondary bacterial infection occurs in one-quarter to one-third of cases of viral pneumonia. Although immunocompromised children are at higher risk for the opportunistic infections, such as cytomegalovirus, varicella-zoster virus, herpes simplex virus (HSV), and measles, they are also at risk of seasonal pneumonias, including RSV, influenza, and parainfluenza virus. The symptoms of viral pneumonia are similar to those of bacterial pneumonia, although there is less chest pain or rigors with viral pneumonia.

### **Respiratory Syncytial Virus**

Respiratory syncytial virus is the most important cause of lower respiratory infection in the first 2 years of life. By 2 years of age, more than 94% of children will have serologic evidence of RSV infection. During the RSV season, RSV will be the cause of more than 90% of infants hospitalized with bronchiolitis. The differentiation between bronchiolitis and pneumonia can be difficult, so the designation of lower respiratory

tract infection caused by RSV may be easier than trying to define whether there is one or both diagnoses. Infants with RSV pneumonia tend to have less wheezing, less hyperinflation, and more crackles.

The clinical scenario is similar to bronchiolitis, with an upper respiratory prodrome followed by worsening cough and increasing respiratory distress. As noted, wheezing tends to be less prominent and there may be crackles on examination. The radiographic appearance of lobar consolidation (especially right upper lobe) or a bronchopneumonia pattern supports the diagnosis of pneumonia.

Most infants with RSV pneumonia recover in a few days, but a small percentage progress to respiratory failure. Infants younger than 2 months and those with significant respiratory distress or apnea should be hospitalized.

### **Influenza Virus**

The influenza virus is a single-stranded RNA virus that is a common cause of pneumonia, especially in the very young and very old. It occurs in epidemic form in the winter months. Children 2 years or younger and chronically ill children are at more risk for serious illness. Pandemics in the last 100 years include the 1918–1919 Spanish pandemic (influenza virus subtype H1), the 1957 pandemic (subtype H2N2), the 1968–1969 pandemic (Hong Kong subtype H3N2), the Russian pandemic in 1977 (subtype H1N1), and the novel influenza A (H1N1) pandemic of 2009–2010. The incubation period is 1 to 5 days following exposure to the virus.

The presentation of influenza is characteristic with high fever, chills, muscle aches, and headache, although young children may have more nonspecific symptoms. The illness starts as a URI with rhinitis, pharyngitis, and initially nonproductive cough. Young children may also have conjunctivitis and gastrointestinal symptoms. Pneumonia is associated with increasing respiratory symptoms and hypoxemia. Secondary bacterial infection may occur following influenza pneumonia.

Positive A or B influenza virus can be determined by immunofluorescence or hemagglutination techniques, although during the 2009–2010 H1N1 pandemic these tests were not very helpful in diagnosis. Polymerase chain reaction has a higher sensitivity and specificity and is now more readily clinically available, especially for hospitalized children and adults.

Symptoms last for several days and are treated with over-the-counter medications. Aspirin is not indicated because of the association with Reye syndrome.

Oseltamivir (Tamiflu) is approved for oral administration in persons older than 1 year with influenza A or B who have been symptomatic for no more than 2 days. Oseltamivir can be given to infants younger than 1 year with reduced dosage. Although vaccination is the preferred approach for prevention, zanamivir and oseltamivir, with specific age considerations, are recommended by the AAP for prophylaxis of influenza infection. Adamantane (amantadine and rimantadine) resistance emerged in the United States during the 2008–2009 influenza season, and by 2009 most influenza A viruses and all influenza B viruses were noted to be resistant to these agents.



### H1N1 Influenza

Following an outbreak of influenza in Mexico in 2009, the WHO raised the pandemic alert to phase 6, implying a global pandemic. The virus that evolved was a combination of swine, avian, and human influenza genes. The epidemiology was different than in previous pandemics because the risk for severe disease and mortality was highest in pregnant women. In addition, the population aged 5 to 59 years was associated with more severe disease than the very young or very old. On August 10, 2010, the WHO declared an end to the 2009 H1N1 pandemic globally, although they and the Centers for Disease Control and Prevention (CDC) warned that the virus is likely to circulate during subsequent influenza seasons. Through the 2015–2016 influenza season, cases of influenza caused by this strain continued to be identified.

### Human Parainfluenza Virus

Human parainfluenza virus (HPIV) has 4 serotypes: HPIV-1, HPIV-2, and HPIV-3 cause croup; HPIV-1 and HPIV-3 cause lower respiratory tract infection, including bronchiolitis, bronchitis, and pneumonia. Outbreaks of HPIV-3 occur during spring and summer. Almost all children have been infected and, as immunity is short lived, repeated infections occur. Human parainfluenza virus is spread via droplet and fomite exposure.

Morbidity and mortality from HPIV lower respiratory tract infection is uncommon in the United States in immunocompetent hosts. It is a significant cause of mortality in both adults and children with primary immunodeficiency as well as those in developing countries, especially following secondary bacterial infection in malnourished children.

### Adenovirus

Adenovirus is an enveloped DNA virus that causes both upper and lower respiratory infection. Most cases are mild, self-limited URIs. The population at risk for severe disease is the immunocompromised, including the post-transplant patient, especially children who received hematopoietic stem cells or solid organ transplants. Treatment is symptomatic. Cidofovir has been used.

### Human Metapneumovirus

Human metapneumovirus was first described in the Netherlands in 2001. It is in the same family as RSV and HPIV (the Paramyxoviridae family). In the pediatric population the infections are similar to RSV, although the illness tends to be milder and the children tend to be older. The symptoms include rhinorrhea, cough, tachypnea, and fever. The signs include retractions, crackles, and wheeze. The clinical manifestations are similar to RSV bronchiolitis, but pneumonia and respiratory failure may occur.

### Coronavirus

Coronavirus made headlines in 2003 when the severe acute respiratory distress syndrome was the cause of life-threatening pneumonia. The virus quickly spread from China to the rest of the world, affecting 8,000 people in 29 countries, and caused 774 deaths. As a

result of intensive infection control measures, the global transmission was halted in 2003. Several coronavirus strains are associated with upper respiratory tract disease and, less frequently, lower respiratory tract infections like bronchiolitis and pneumonia. It is speculated that subsequent variant strains of coronavirus will cause increased cases of pneumonia in the future, especially in infants and immunocompromised individuals.

### Varicella-zoster Virus

Varicella-zoster virus is a herpesvirus that causes chickenpox and has the potential to reactivate as shingles. Risk factors for varicella pneumonia include high-dose steroids (1–2 mg/kg/day for >2 weeks), malignancy (including leukemia), and other immunocompromised states (including HIV). Varicella pneumonia causes significant mortality and is associated with severe invasive group A streptococcal disease. The viremia is treated with acyclovir, and children with varicella pneumonia should be hospitalized.

### Measles Virus

Measles virus is another member of the Paramyxoviridae family. It causes a febrile illness with morbilliform rash; pneumonia can occur. Children who are unvaccinated, malnourished, or immunocompromised are at risk for severe lower respiratory tract infection.

### Cytomegalovirus

Cytomegalovirus (CMV) is a virus in the herpes group. Cytomegalovirus pneumonia is a major cause of pneumonia in immunocompromised children, including those with transplant, HIV infection, and malignancy. The typical scenario is that 2 to 3 months post-transplant there is cough and fever, and severe dyspnea and hypoxia result. The symptoms are non-specific, and the lung involvement is an interstitial pneumonia. The chest radiograph shows bilateral interstitial infiltrates. Pulmonary symptoms may be accompanied by gastrointestinal disease, especially diarrhea and chorioretinitis. Cytomegalovirus pneumonia may also occur in infants younger than 3 months and can be especially severe in premature infants.

Ganciclovir is used as prophylaxis in transplant patients at risk (eg, a seropositive donor and seronegative recipient). It is also beneficial for symptomatic children with pneumonia.

### Herpes Simplex Virus

Herpes simplex virus infection is also seen in immunocompromised and transplant patients. The highest risk group is those patients that are severely neutropenic or lymphopenic. Pneumonia may result from transmission from the upper to the lower airway or as a result of viremia from oral or genital lesions. Treatment is with acyclovir 5 mg/kg every 8 hours intravenously or 400 mg orally 5 times per day.

Herpes simplex virus pneumonia may also rarely occur as a manifestation of HSV disseminated disease in the neonate. Because of the difficulties in making this diagnosis, mortality can be high unless recognized early in the course of the infection. Acyclovir

therapy and infectious diseases consultation is important in such cases.

## FUNGAL CAUSES OF PNEUMONIA

### *Aspergillus*

*Aspergillus* species are common on decaying material everywhere. There are more than 900 species, but *Aspergillus fumigatus* is responsible for about 90% of infections in humans. They are dichotomously branching septate hyphae. The spores or conidia are small, 2 to 3 microns, and easily inhaled into the lower respiratory tract. There are 3 forms of disease associated with aspergillus: invasive aspergillosis, allergic bronchopulmonary aspergillosis, and aspergilloma within a cavity. This section will discuss pneumonia caused by aspergillus. Opportunistic infections result when children are neutropenic or immunocompromised. Both profound (polymorphs  $<100 \mu\text{L}$ ) and prolonged ( $>12$ – $15$  days) neutropenia carry high risk for developing invasive aspergillosis. It is common post-transplant, in children with cancer, and with CGD.

### Clinical Features

Eighty percent to 90% of children with acute invasive aspergillosis will have pulmonary disease. Nonproductive cough with fever, shortness of breath, blood in the sputum, and pleuritic chest pain are the main symptoms. Twenty-five percent of affected children may have minimal physical signs; others may present with hypoxemia. Chronic invasive pulmonary aspergillosis is associated with diabetes mellitus, CGD, and HIV.

### Diagnosis

Hyphae may be evident microscopically, but this does not prove the diagnosis because other fungi may have a similar appearance. Culture of sputum or bronchoalveolar lavage fluid will not provide a definitive diagnosis because it is important to be aware that these specimens may be positive in those who are colonized with aspergillus. Evidence of invasive aspergillosis is supported by the finding of galactomannan (GM) in these fluids; this test has been approved by the US Food and Drug Administration. The negative predictive value of GM is highly specific; however, GM is not positive in 100% of children with pulmonary aspergillosis. The GM test may be falsely positive in children receiving either piperacillin-tazobactam or ampicillin-sulbactam.

### Imaging

Plain chest radiograph of invasive aspergillosis reveals wedge-shaped infiltrates and cavities, and CT may be helpful for the early diagnosis of invasive aspergillosis. The halo sign, which is ground-glass attenuation surrounding a soft tissue nodule, is characteristic, and cavitation may follow.

### Management

Voriconazole has become the treatment of choice for invasive aspergillosis. Rapid institution of treatment is necessary because invasive aspergillosis can be rapidly progressive. Posaconazole or amphotericin B may be considered if there is a possibility of mucor. In

addition, caspofungin has also been approved for treatment of invasive aspergillosis if there is resistance or intolerance to other therapies. Consultation with infectious diseases is indicated.

### *Candida*

*Candida* species, especially *Candida albicans*, are the most common fungal infections to cause disease in humans. Disease caused by *Candida* species includes cutaneous, gastrointestinal, oropharyngeal (thrush), and vulvovaginal candidiasis. The respiratory tract is frequently colonized with *Candida* species and may result in tracheobronchitis or pneumonia. Invasive candidiasis results from host defects and other risk factors, including CGD, diabetes, and immune deficiency states.

*Candida* pneumonia is associated with disseminated candidiasis, and the lungs are rarely the only organ involved. The most common form is multiple lung abscesses as a result of hematologic spread of *Candida*. The physical signs include fever, dyspnea, and evidence of sepsis. The lung examination is variable, from noncontributory to rhonchi, crackles, and wheeze.

Fluconazole is the treatment of choice for the non-neutropenic child, initially intravenous, and with improvement can be switched to oral. If it is unclear whether there are other molds involved, voriconazole may be a better alternative. With more severe infections and in high-risk children, echinocandins, such as caspofungin, may be a better selection, especially if the infection is nonalbicans, such as *Candida glabrata* and *C. krusei*.

### Blastomycosis

*Blastomyces dermatitidis* is a thermal dimorphic fungus, and the conidia (spores) that convert to yeast are infectious to humans. In the United States, the states most likely to be the site of infection are adjacent to the Mississippi and Ohio rivers and the Great Lakes. The conidia are inhaled and deposited in the lungs. Incubation time is variable but averages 4 to 6 weeks.

### Clinical Features

Blastomycosis is rare in children and results from inhalation of spores. About 50% of infected children will be asymptomatic. Those who are symptomatic have flu-like symptoms with fever, chills, night sweats, weight loss, and myalgia. The pulmonary symptoms include cough and chest pain. There is an acute form as well as a chronic form, which may last 2 to 6 months and is associated with weight loss and cough. Either acute or chronic pulmonary blastomycosis has the potential for a more severe course with life-threatening infection, which may disseminate to the skin, central nervous system, and bone.

### Diagnosis

The sputum is full of polymorphonuclear cells and has a high yield for fungal stain; the fungus grows from culture of sputum, tracheal aspirate, bronchoalveolar lavage, cerebrospinal fluid, and urine. Direct identification of the fungus is possible by experienced personnel. Children who do not expectorate sputum may

need bronchoscopy or lung biopsy to confirm the diagnosis.

### Imaging

The chest radiograph shows infiltrates, reticulonodular pattern, and pleural effusion, and in some cases cavitation is evident.

### Management

For moderate to severe disease, amphotericin B should be used until improvement is noted; then the child can switch to itraconazole to complete a 6- to 12-month course of therapy. For mild to moderate disease, itraconazole should be given to complete a 6- to 12-month course of therapy.

### Coccidioidomycosis

*Coccidioides* species are dimorphic fungi endemic in the soil of the southwestern United States, Mexico, and Central and South America. Inhalation of spores, even a single spore, results in an acute pulmonary infection. It is not spread from person to person. There is increased risk when the soil is disrupted, for example by earthquake or farming, particularly when the soil is dry. The incubation period is 10 to 16 days, although the range is 7 to 30 days.

### Clinical Features

The most important part of the history is the story of travel or residence in an endemic area, and the exposure can be as simple as driving through the area. More than half of those infected will be asymptomatic. If there are symptoms the primary infection leads to a flu-like illness. Symptoms include fever, dyspnea, arthritis, and rash. The rash is characteristically erythema multiforme or erythema nodosum. The primary infection may be followed by disseminated coccidioidomycosis, although this is less common in children than in adults. Most children recover even without treatment. Some children have fatigue that lasts for months.

### Diagnosis

Coccidioidal IgM appears within 1 to 3 weeks of onset of symptoms and lasts for 3 to 4 months.

### Imaging

Chest radiograph findings tend to be nonspecific with infiltrates, hilar adenopathy, and small pleural effusions. A small percentage of children have nodules or cavities early on, and 5% to 10% have persistent pulmonary nodules or cavities. The cavities tend to be thin-walled and resolve spontaneously. On occasion the cavities expand. If they are larger than 6 cm they are at risk for rupture and surgery is indicated.

### Management

Most immunocompetent children do not require treatment, but the following are considerations for treatment:

- Continuous fever for longer than 1 month
- Night sweats for longer than 3 weeks
- Weight loss greater than 10%
- Large (>50% of 1 lung) or bilateral pulmonary infiltrates

- Primary infection during infancy
- Primary infection during pregnancy, especially in the third trimester, or immediately postpartum
- Immunosuppression
- Diabetes mellitus or pre-existing cardiopulmonary disease

Treatment of acute pulmonary coccidioidomycosis includes oral azoles, such as fluconazole. During pregnancy amphotericin B is preferred because the azoles may be teratogenic. Although uncommon in children, those with disseminated disease or progressive fibrocavitary disease may require prolonged treatment up to 1 year.

### Histoplasmosis

*Histoplasma capsulatum* is a dimorphic fungus that is endemic in the central United States and other parts of the world that have warm, humid soil and large populations of migratory birds or chickens. It is the most common pulmonary mycosis of humans, and can occur at any age. The geographic distribution is the central United States, specifically the Ohio and Mississippi river valleys, and it is endemic in Central and South America, the Caribbean, Africa, and Asia.

### Clinical Features

The clinical features of histoplasmosis depend on the size of the inoculum, the immune status of the host, and the presence of lung disease. The exposure increases if there is major disturbance of soil, as with construction projects and proximity to chicken coops, especially those with rotten wood. The incubation period is 9 to 17 days, and the acute illness is characterized by flu-like symptoms of fever, chills, muscle aches, nonproductive cough, and chest pain. The acute symptoms may be mild (lasting less than a week) to severe (lasting 2–3 weeks). There are varied clinical manifestations, again differing with the immune status.

Severe acute pulmonary syndrome results from exposure to a large inoculum and starts with an acute flu-like syndrome, with fever, chills, and myalgias. Pulmonary symptoms develop with cough, dyspnea, and hypoxemia. The chest examination includes diffuse fine crackles with possibly a pleural rub. There may be rapid progression to acute respiratory distress syndrome. Some children develop a single pulmonary nodule in the lung parenchyma, which has the appearance of a coin lesion on chest radiograph. It is usually asymptomatic.

Mediastinal obstructive syndrome results from hilar lymphadenopathy, which may be large enough to compress surrounding structures, including the airway, the great vessels, and the esophagus.

### Diagnosis

Rapid enzyme-linked immunoassays for *Histoplasma* antigen in urine, cerebrospinal fluid, and bronchoalveolar lavage fluid along with serology (immunodiffusion or complement fixation), plus cultures or tissue examination and stains are used for diagnosis.

### Management

Acute pulmonary histoplasmosis that is asymptomatic or mild requires no treatment. If the symptoms



are prolonged for more than 4 weeks, oral itraconazole for 6 to 12 weeks is indicated. If there is severe infection, treatment should be initiated with amphotericin B for 1 to 2 weeks followed by a year of itraconazole.

### **Pneumocystis Pneumonia**

*Pneumocystis carinii* pneumonia led to the abbreviation PCP. *Pneumocystis carinii* was originally classified as a trypanosome and later as a protozoan, and now as a unicellular fungus. It was recently renamed *Pneumocystis jiroveci* because *P. carinii* is not found in humans. The accepted abbreviation is still PCP. Pneumocystis pneumonia is the most common opportunistic infection in children with HIV and is common in transplant patients. The routine use of prophylaxis has reduced the prevalence of PCP.

### **Clinical Features**

The symptoms and signs of PCP are nonspecific, so a high index of suspicion is necessary in children who are HIV infected or immunocompromised, especially if they are not taking prophylactic measures. The symptoms are typically shortness of breath, fever, and nonproductive cough, with chills and weight loss. The signs are tachypnea and tachycardia. Auscultation may reveal some crackles, but often there are no adventitious signs. The main finding supportive of the diagnosis is hypoxemia. The typical radiographic appearance is diffuse bilateral infiltrates extending out from the hilum. In the early stages the chest radiograph may be normal; later there may be pneumatoceles. Pleural effusion is uncommon. High-resolution CT may be helpful, as patchy areas of ground-glass appearance are suggestive, particularly in a child with HIV.

Expectorated sputum usually does not yield a satisfactory specimen; induced sputum production with hypertonic saline is the quickest way to make the diagnosis. Bronchoalveolar lavage is the most common procedure performed. The diagnosis is confirmed by various stains, including silver stains, that show the cysts.

The choice of treatment depends on the degree of hypoxemia. The treatment of choice is trimethoprim-sulfamethoxazole (TS), and oral therapy is used for mild cases, although most children will require intravenous treatment at least at first. Intravenous pentamidine is an alternative choice for treatment, especially if there is a reaction to TS. Duration of treatment should be 21 days for children with HIV and 14 days for patients without HIV, and similar durations should be given based on severity of disease (mild vs severe). Those with severe disease may also benefit from the use of corticosteroids.

Chemoprophylaxis against PCP is indicated for children with HIV and those who are immunocompromised, especially transplant patients and those with both primary and acquired immunodeficiency. The standard regimen is 3 consecutive days per week of oral TS. If this is not tolerated, nebulized pentamidine is an alternative. Infectious disease and pulmonary consultation are recommended.

## **MANAGEMENT OF COMMUNITY-ACQUIRED PNEUMONIA**

A sample algorithm for the management of CAP is shown in Figure 315-1. If the clinical impression of pneumonia is high, it is thought that a bacterial etiology is likely, and antibiotics are indicated. The choice of antibiotic will vary depending on age and organisms that are in the community. The "Evidence-Based Care Guideline for Children With Community Acquired Pneumonia (CAP)" from Cincinnati Children's Hospital Medical Center can be reviewed. Additionally, the Infectious Diseases Society of America in conjunction with the Pediatric Infectious Diseases Society published guidelines for the management of CAP in infants and children older than 3 months.

In children from 2 months to 5 years of age the AAP recommends prescribing high-dose amoxicillin 80 to 90 mg/kg/day for 7 days. As previously noted, 17% to 35% of *S pneumoniae* isolates from CAP in the United States are resistant to penicillin G and 15% are resistant to macrolides, which may indicate an alternative when bacterial pneumonia is suspected. However, resistance to penicillin by *S pneumoniae* is a different mechanism from that of *S aureus* and in most otherwise healthy children can be overcome by higher doses of penicillin, ampicillin, or amoxicillin. For hospitalized children with uncomplicated pneumonia, ampicillin, penicillin or, alternatively, a third generation cephalosporin is preferred. Consultation with infectious disease specialists will assist in this decision.

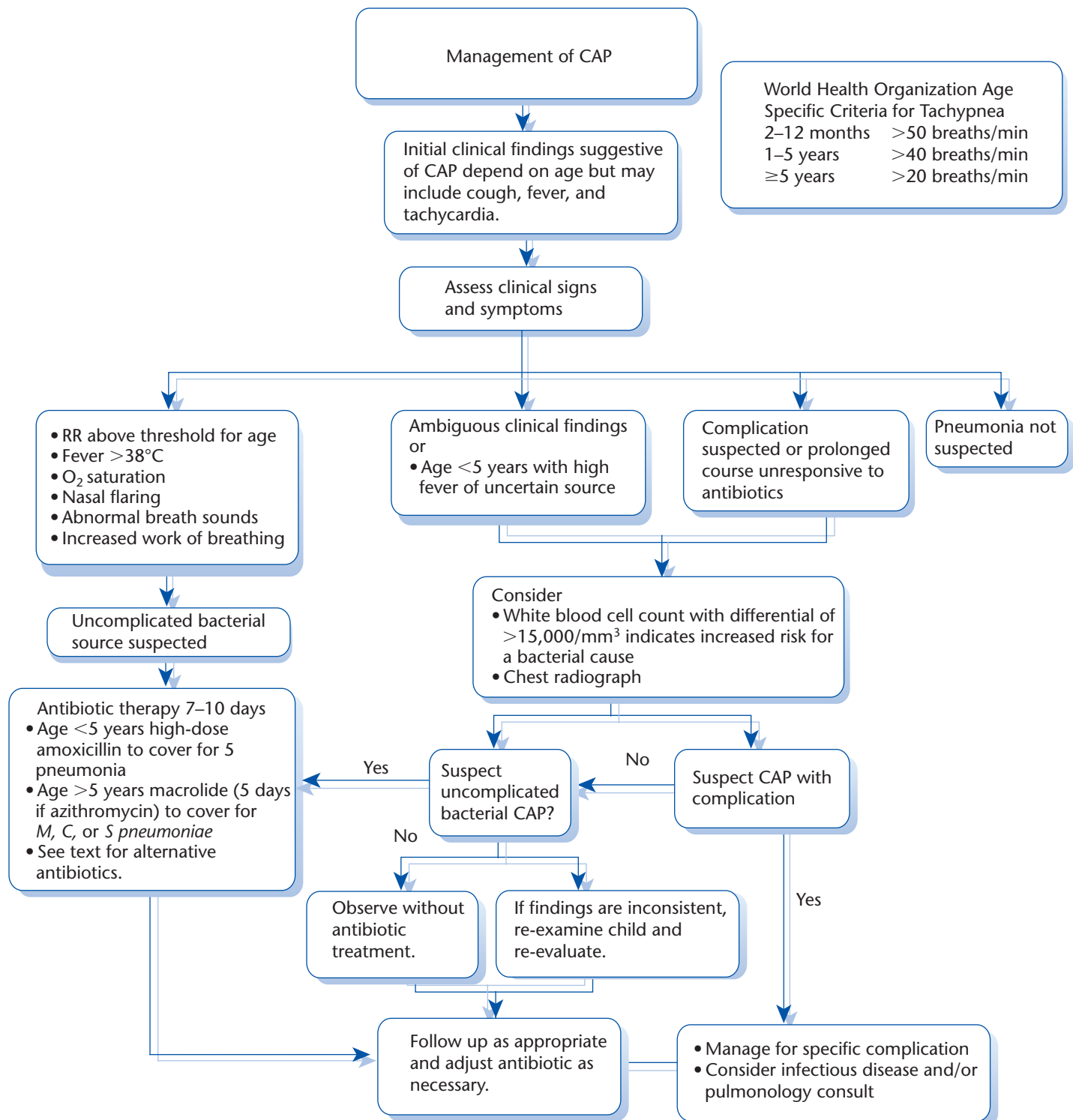
Although mycoplasma infection does occur in children younger than 5 years, a macrolide may not be the best antibiotic choice for empiric treatment at this age, in part because many *S pneumoniae* are now resistant to macrolides or azides. If the child is vomiting or otherwise may be unable to take oral medications, the AAP recommendation is a single initial dose of ceftriaxone prior to attempting oral antibiotics. For children age 5 years and older it is recommended that a macrolide be added to treat CAP in the outpatient setting with either 7 to 14 days of erythromycin or 5 days of azithromycin. Doxycycline for children older than 7 years and levofloxacin alone for older adolescents are alternatives. It is recommended that physicians follow up with children diagnosed with pneumonia within 1 to 3 days.

## **PREVENTION OF PNEUMONIA**

Heptavalent pneumococcal vaccine was recommended in 2000 for children in the United States to reduce the incidence of pneumococcal pneumonia. The original vaccine, which contained 7 serotypes, was highly effective, but two-thirds of the invasive pneumococcal disease was caused by 6 serotypes not included in this vaccine. Subsequently, 13-valent PCV was approved in February 2010 and is recommended for all children from 2 months through 5 years of age.

The CDC recommends that all individuals aged 6 months and older get a seasonal flu vaccine. The seasonal flu vaccine protects against 3 or 4 influenza viruses and varies in composition according to what research indicates will be the most common strains during the upcoming season. Of note, otherwise





**Figure 315-1** Management of community-acquired pneumonia. CAP, community-acquired pneumonia; C, *Chlamydia*; M, *Mycoplasma*; RR, respiratory rate; S, *Streptococcus*.

healthy children aged 2 years and older can also receive either the nasal spray (a live-attenuated influenza vaccine [LAIV]) or the inactivated injectable influenza vaccine (IIV). Children on chronic aspirin therapy should not receive the vaccine because of the

risk of Reye syndrome, and LAIV is not recommended for anyone younger than 2 years of age with chronic health conditions including asthma.

The CDC also recommends that people in contact with certain groups of children get a seasonal flu

vaccine to better protect the child (or children) in their lives from the flu.

The CDC recommends that the following contacts of children receive seasonal influenza vaccination:

- Close contacts of children younger than 5 years (people who live with them), especially those younger than 6 months
- Out-of-home caregivers (nannies, child care providers, etc.) of children younger than 5 years
- People who live with or have other close contact with a child or children of any age with a chronic health problem (asthma, diabetes, etc.)
- All health care workers, to keep from spreading the flu to their patients

Additional considerations are *Haemophilus influenzae* type B vaccine and varicella vaccine.

### WHEN TO REFER

Most children with CAP will not require consultation. If there are complications, such as pleural effusion or prolonged hypoxia, consultation with a pulmonologist may be indicated. If the child has a chronic illness, consultation with the specialist who is involved in their long-term care may be helpful. Consultation with infectious diseases or allergy is indicated when allergies, comorbid conditions, or unresponsiveness to antibiotics are present.

### WHEN TO ADMIT

Children with pneumonia and a chronic illness, for example, if they are immunocompromised, may require hospitalization. If the degree of respiratory distress is significant, if there is hypoxia, or if they seem septic, hospitalization may be required. Currently, validated screening systems do not exist to help predict which children with pneumonia should be hospitalized. Hospitalization is indicated with the following:

- Oxygen saturation consistently less than 90% (definite)
- Suspected sepsis (definite)
- Severe dehydration (definite)
- Inability to drink fluids (possible)
- Moderate or severe respiratory distress (possible)
- Failed outpatient antibiotic treatment (clinical judgment)
- Home circumstance or social situation raises concerns (likely)
- Infants younger than 6 months (unless ideal caretaker)

### AAP POLICY

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## Chapter 316

# POSITIONAL DEFORMATIONAL PLAGIOCEPHALY

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*Plagiocephaly*, a term with a Greek origin, means *oblique head*. It is used to describe any abnormality in the shape of the head, irrespective of its cause. Posterior deformational plagiocephaly (PDP) is a phenomenon in which flattening of the occiput occurs as a result of mechanical factors that affect the malleable growing skull in utero or during early infancy. It is also referred to as *benign positional molding*, *posterior deformational plagiocephaly*, and *occipital deformational plagiocephaly*. In most patients, the head shape improves with changes in head position, and, in some instances, with helmet therapy. Early recognition and intervention is crucial because early intervention improves outcome. If not treated appropriately, quality of life may be affected.

### PATHOGENESIS

During development, genetic makeup and environmental factors determine the shape of the head. Abnormalities in skull shapes may develop prenatally or postnatally during the first 2 years of life. Whether PDP begins prenatally or is an acquired phenomenon remains controversial. Some investigators think that many infants who develop PDP are born with a mild flattening of the occiput that goes unnoticed in the neonatal period and worsens as the infant continues to sleep on the flat side. Because the infant sleeps in the position of comfort (ie, on the flat side), this condition is termed *positional plagiocephaly*.

A deformity present from birth is usually the result of in utero conditions such as small maternal pelvis,

uterine abnormalities, large baby, multiple gestations, and oligohydramnios or polyhydramnios. Controversy exists regarding the reason for development of PDP in these conditions. Some researchers think that the constrictive and restrictive uterine environment leads to conformational changes in the skull, whereas others think that this environment simply causes severe molding and leads to flattening.

Mechanical pressure on the malleable skull caused by static supine positioning leads to the flattening of the occiput in patients with PDP. Therefore, supine sleeping position, congenital torticollis, prolonged periods in car seats and infant carriers, prematurity, and neurologic conditions such as hydrocephalus are often associated with PDP. The correlation between PDP and supine sleeping positioning is explained by the fact that by the time most infants reach 2 months of age, they have slept for almost 700 hours.

Congenital torticollis is a prime example of the static position of the head in which limited neck motion leads to an asymmetrical flattened occiput involving the torticollis side. However, theories suggest that torticollis develops as a result of PDP. Another example of static head position is among premature infants on ventilator support during which the head is kept in 1 position for prolonged periods. Similarly, cephalohematoma can also lead to the development of PDP on the opposite occipital side.

Hydrocephalus is another risk factor for the development of PDP because of the movement of bones and sutures as a result of volume changes in the cranium and because of the limitations imposed by the draining devices and shunts that result in the infant's head being placed in 1 position for prolonged periods.

Another possible mechanism that may promote favoring 1 side of the head and the development of PDP is the position of the baby's crib in relation to the room's major light source. Infants usually spend much time looking toward the source of light in the room when the baby is in the supine position. Therefore, PDP may develop if the crib is kept in the same location (particularly if it is placed in a corner of the room) and the baby is placed in the same position in relation to the light source.

## EPIDEMIOLOGIC FEATURES

Before 1992, when more than 70% of infants were placed in the prone position during sleep, the incidence of PDP was estimated to be 1 in 300 live births. However, after the *Back to Sleep* campaign was initiated by the American Academy of Pediatrics (AAP) in 1992, the incidence of PDP has been on the rise, with a 2013 study showing that the incidence of PDP is as high as 46.6% among infants between 7 and 12 weeks of age.

PDP is more common on the right side than it is on the left side because of the right-sided sleep position preference of most infants. Almost 85% of neonates have left occipital anterior presentation during birth, which causes pressure on the infant's right occiput and left forehead by the mother's pelvis and lumbosacral spine, respectively.

PDP is more common in boys than it is in girls, probably because male infants have larger heads than

female infants and because boys tend to be less flexible than girls. PDP is also common with primiparity, prolonged labor, and assisted delivery.

PDP is most often first noticed by parents and physicians when the infant is 2 to 3 months of age; however, it can be present at birth. The severity of PDP peaks at 4 months and then resolves gradually over time. In two-thirds of the cases, PDP resolves by 2 to 3 years of age. The resolution is observed to be slow in children with limited head rotation and low activity level.

## DIFFERENTIAL DIAGNOSIS

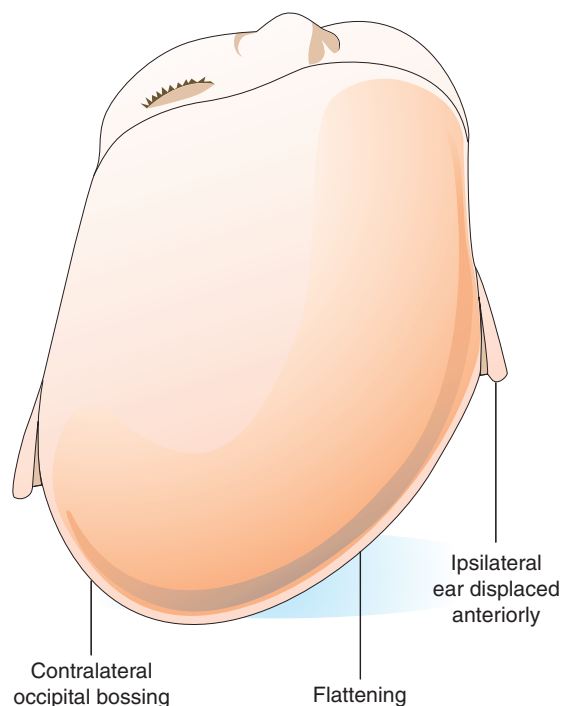
Distinguishing lambdoid synostosis from PDP in infants with flat posterior plagiocephaly is critical, because the management of these 2 conditions is different. Lambdoid synostosis is a rare condition that occurs in approximately 2% of all cases of craniosynostosis. In patients with lambdoid synostosis, the head is trapezoid shaped; in PDP, conversely, the head is shaped as a parallelogram, with significantly greater protrusion of the forehead on the same side of the occipital flattening as compared with lambdoid synostosis. In PDP, the ear on the flattened side is displaced anteriorly, whereas in lambdoid synostosis, it is displaced inferiorly and posteriorly. In lambdoid synostosis, the posterior basal skull is tilted, with the prominence of mastoid process present on the same side. In addition, the facial deformity seen in patients with PDP is absent or minimal in patients with lambdoid synostosis. Rarely, however, clinically differentiating between PDP and lambdoid synostosis may be difficult.

## DIAGNOSIS OF POSTERIOR DEFORMATIONAL PLAGIOCEPHALY

The diagnosis of PDP in infancy is made primarily based on history and physical examination. Imaging studies are not indicated in most situations. If the infant has a normal, rounded head at birth and, after a few weeks or months, develops an occipital flattening, then the most likely diagnosis is PDP.

Infants with PDP exhibit preferential head position (that is, the infant turns the head only to one side). When the head is viewed from above, a frontal prominence on the same side as the occipital flattening may be observed, and the ear on that side is anterior as compared with the other ear (Figure 316-1). Other craniofacial abnormalities that may be observed on the affected side of infants with PDP are prominent mandibular sulcus with mandibular tilt, uplifted lower helix, smaller ear, and unilateral epicanthal fold. Most infants with PDP have 1-sided occipital bald spots.

The presence of torticollis has to be ruled out in every case of flattened occiput because of its greater association with PDP. Therefore, the primary care physician should perform both passive and active head rotations and check for the tightness of the sternocleidomastoid muscle. The eye on the side of torticollis seems to be incompletely open as a result of the vertical displacement of soft tissues of the cheek. In addition, the mothers of infants with torticollis note that they have difficulty feeding the infants from both breasts because the infants have trouble turning their heads.



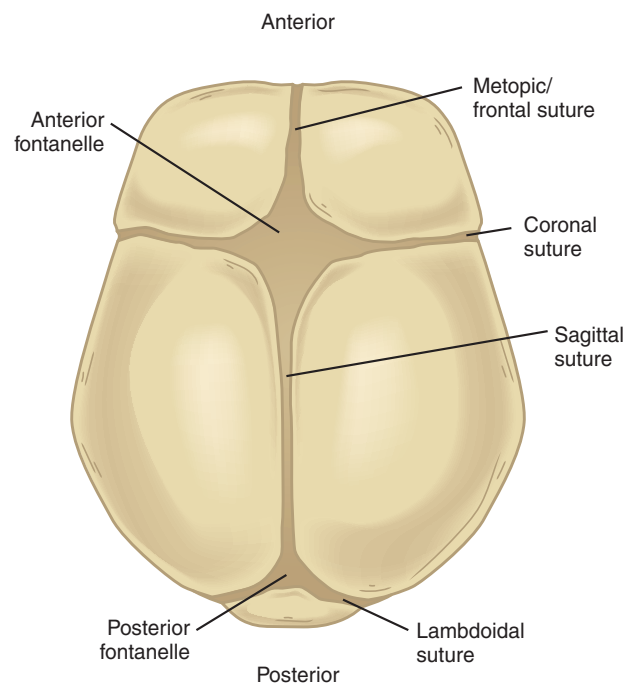
**Figure 316-1** This figure shows typical clinical findings in a scalp of an infant with deformational plagiocephaly, namely flattening of occiput on right side with anterior displacement of ear and frontal bossing on the same side and occipital bossing on the opposite side.

Laboratory or imaging studies are not routinely required to confirm the diagnosis of PDP. In the past, skull radiographs were used to rule out lambdoid suture synostosis (Figure 316-2). However, ultrasound examination of the lambdoid suture has also been shown to be useful in ruling out lambdoid suture synostosis. Computed tomography (CT) scans are sensitive in diagnosing synostotic plagiocephaly. Three-dimensional scans are helpful, but the 2D axial views are actually more sensitive in assessing suture patency because they do not demonstrate the volume averaging that the 3D reconprogram creates.

## PREVENTION

In most infants, PDP can be prevented by alternating the supine head position during sleep and by periodically changing the position of the crib in the room to require the infant to look away from the flattened side to see parents and others in the room or to look at the source of light in the room.

The AAP has recommended a certain amount of prone positioning, or *tummy time*, while the infant is awake and being observed. This positioning may help prevent the development of a flat occiput and may also facilitate development of the upper shoulder girdle strength necessary for timely attainment of certain motor milestones. Theories suggest that prone position prevents PDP by correcting or preventing infants' positional preferences.



**Figure 316-2** This figure shows different sutures of the skull and the positions of anterior and posterior fontanelle.

Parents and health care professionals, such as those working in newborn care units, should be educated on different techniques to reduce the risk for development of PDP in infants. Nursing staff and other caregivers should be encouraged to change the head position of a sick newborn whenever possible. Because most caregivers are right handed, much of the care to the baby is provided from the right side of the bed, and thus the baby is placed facing the right side. Caregivers should be encouraged to provide care from the left side of the crib whenever possible and to reposition the infant from head to foot from time to time.

Infants who are breastfed are less likely to develop PDP because, during breastfeeding, alternate head positioning is promoted. However, during bottle-feeding, babies are often held in the left arm, promoting right occipital flattening. Parents should be advised to use alternate arms during each bottle-feeding.

## TREATMENT

Definitive guidelines for the management of PDP have not been developed. However, early treatment is successful in most cases of mild to moderate PDP. Investigators have observed that treatment started after 12 months does not produce significant benefits. Therefore, treating PDP early and effectively is important because uncorrected or improperly treated PDP can lead to psychosocial developmental sequelae.

The initial management of PDP is the same as the prevention measures, which consist of educating parents about changing the infant's head position often. If the infant is found to have torticollis, then parents should be taught to use neck motion exercises



for the infant. The first exercise is used to stretch the sternocleidomastoid muscle and consists of placing 1 hand on the infant's upper chest and rotating the infant's neck with the other hand so the chin touches the shoulder. The head should be held in this position for 10 seconds. The head is then rotated to the other side and held for an additional 10 seconds. In the second exercise, the infant's head is tilted so that the ear touches the shoulder and is held in that position for 10 seconds. The same process is followed on the other side. This exercise stretches the trapezius muscle. The parents should be asked to perform these neck exercises with every diaper change, with 3 repetitions of each exercise. Estimates suggest that an additional 2 minutes are required for these exercises per diaper change. In most cases, with early implementation of repositioning and neck exercises, considerable response is seen over a 2- to 3-month period. The infant should be referred for physical therapy for stretching exercises if these exercises fail to improve torticollis within 2 to 3 months. If no improvement is evident, or if plagiocephaly worsens after 2 months of repositioning and physical therapy, then the infant should be referred to a pediatric neurosurgeon or a craniofacial surgeon for further management.

Skull-molding helmets have been used for reshaping the affected skull. To achieve the desired response, helmets have to be used in the age range of 4 to 12 months because of the malleability of the young infant's skull during this period. Ideally, therapy is begun at 4 to 6 months of age and may be continued until 12 to 14 months of age. Head growth remains normal during helmet therapy, which works by symmetrically shaping the cranial growth. The use of helmets is more beneficial for patients with severe deformity and in infants with mild to moderate severity who are resistant to position changes and physical therapy.

No consensus exists on the use of helmets in infants with positional plagiocephaly. In some studies, better improvement in the skull shape has been observed in infants treated with helmets as compared with that achieved by repositioning alone. Research has shown that repositioning infants may produce improvement in mild to moderate cases similar to that reported with external orthotic devices. Recently, Dutch researchers used 3D whole-head surface scans to compare 70 infants with deformational plagiocephaly (mean age, 4.8 months) who were treated with helmets (23 hours/day) or active repositioning. Children were matched for initial severity of deformity, and treatment duration was determined by parent and physician satisfaction with outcomes (mean duration, 3 months for helmets and 5 months for repositioning). The helmeted group had significantly greater reductions in asymmetry than the infants who were repositioned (maximum reductions, 4.0% vs 2.5%; mean, 0.9% vs 0.5%). In New Zealand, investigators compared head shape and neurodevelopmental outcomes during infancy and at a mean age of 4 years in 129 children with positional head shape deformities who were treated with repositioning techniques. PDP improved or normalized in 87% of children by age 4 without use of a helmet. Also, concerns about head shape

and parental assessment of development improved. Disagreement also exists on the cost effectiveness of helmets in the treatment of PDP. The AAP states that helmets are beneficial in the treatment of PDP after the position changes and exercise have failed. Helmets used for treating PDP are considered to be class II neurologic devices and are regulated by the US Food and Drug Administration. Information on the approved orthotics can be obtained at [www.fda.gov](http://www.fda.gov).

Although surgery is rarely needed to treat PDP, it may be indicated in severe cases in which infants have been presented late for management, thus missing the window of opportunity for success with repositioning, physical therapy, or helmet therapy. Craniotomy does not provide superior results in comparison with physical or helmet therapy as far as a cosmetic outcome is considered. Surgery is also associated with significant morbidity.

## SEQUELAE

The ipsilateral temporomandibular joint is pushed anteriorly in patients with PDP, and, therefore, the mandible develops asymmetrically. The positional and helmet therapies improve the head shape but not the position of the temporomandibular joint or the asymmetry of the mandible. PDP also causes forehead and facial shifts that may lead to asymmetric positioning of the eyes and cause bilateral astigmatism. Fitting corrective glasses on an asymmetric head is also difficult.

Cognitive and psychomotor development has been observed to be mildly delayed in patients with PDP. Whether these delays can be corrected with therapy or whether they are the cause or the effect of PDP is not known. It has also been suggested that decreased prone positioning may be the main factor associated with mild motor delay. Large prospective short-term outcome studies show motor delays, but long-term outcome studies have inconsistent findings.

### WHEN TO REFER

- After position change and physical therapy have failed to correct PDP
- In severe cases
- When the patient who has PDP is older than 12 months
- When lambdoidal craniosynostosis is a possibility

### WHEN TO ADMIT

- Surgical correction of PDP

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Back to Sleep and Tummy to Play* (handout), American Academy of Pediatrics ([www.healthychildcare.org/pdf/sidstummytime.pdf](http://www.healthychildcare.org/pdf/sidstummytime.pdf))
- *A Parent's Guide to Safe Sleep* (fact sheet), American Academy of Pediatrics ([www.healthychildcare.org/pdf/sidsparentsafesleep.pdf](http://www.healthychildcare.org/pdf/sidsparentsafesleep.pdf))

**Community Advocacy and Coordination**

- *A Child Care Provider's Guide to Safe Sleep* (fact sheet), American Academy of Pediatrics ([www.healthychildcare.org/pdf/sidschildcaresafesleep.pdf](http://www.healthychildcare.org/pdf/sidschildcaresafesleep.pdf))

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**Chapter 317****POST-TRAUMATIC STRESS DISORDER**

Judith A. Cohen, MD; David J. Kolko, PhD

Post-traumatic stress disorder (PTSD) is a psychiatric disorder that some children and adolescents develop in response to experiencing or witnessing traumatic events (eg, child abuse; domestic, community, or school violence; traumatic loss; accidents; fires or natural disasters; terrorism or war; traumatic medical conditions or multiple traumas). More than two-thirds of all children experience trauma exposure, with one-third experiencing multiple traumas. The prevalence of PTSD after such events has been estimated based on studies of various types of stressful events, and thus, not surprisingly, the rates vary considerably by type of event. Other characteristics that are related to prevalence are demographics, family characteristics, and research methods. Among the few nationally representative studies, early studies of adolescents and young adults reported overall lifetime PTSD rates of 9.2%. Many children may not meet full criteria for PTSD but still have clinically important PTSD symptoms.

PTSD is often underrecognized, particularly in young children who have difficulty reporting certain symptoms and in those who have experienced traumas associated with shame, secrecy, or stigma, such as sexual abuse, domestic violence, or bullying. Although reliance on parental reports of the child's symptoms greatly improves diagnosis in young children, parents who are themselves traumatized or who are the perpetrators of the child's traumatic experience may not wish to provide accurate reports of children's trauma exposure or symptoms.

Left untreated, childhood trauma and PTSD are associated with serious and long-lasting negative outcomes, including impairments in learning, memory, and academic performance; increased risk for depression, suicide attempts, and completed suicide in adolescence and adulthood; increased risk for substance abuse, self-injury, and risky sexual behaviors; and impaired physical health and immunity, with increased health care use in adulthood. Early chronic interpersonal trauma (child abuse or family violence that often leads to placement disruption) causes particularly severe problems, often affecting attachment and trust. Children who have significant PTSD symptoms without meeting the strict psychiatric criteria of this disorder often have functional impairment comparable to those with the full disorder. However, these outcomes are not inevitable. Effective treatment is available for children with PTSD symptoms. If these children are identified and treated with effective interventions, then PTSD symptoms can remit relatively quickly and cost-effectively and do not return. The most tested treatment leads to reduction of depressive, anxiety, shame, and behavioral difficulties and improvements in social competence and parenting skills, in addition to remission of PTSD symptoms.

Because many traumatized children do not spontaneously report their traumatic experiences or trauma symptoms, pediatricians and other physicians may be in the best position to identify these children and to influence developmental trajectory positively. For these reasons, pediatricians should be aware of the high prevalence of child trauma exposure and be willing and able to assess children for the presence of PTSD symptoms in the primary care setting. This chapter presents basic information about assessing trauma exposure and PTSD symptoms in children and adolescents in the primary care setting, as well as referral sources for evidence-based PTSD treatments.

**COMPONENTS OF POST-TRAUMATIC STRESS DISORDER**

To receive a diagnosis of PTSD, the child must have experienced a traumatic event that qualifies as a serious traumatic stressor. Although the American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* requires specific criteria for a PTSD-level stressor—that is, that it threatens the child's or significant others' life or physical integrity—a realistic understanding of child development dictates that events that objectively are not threatening to life or physical integrity (eg, disruption of attachment to a primary caregiver) might be perceived in this way by a

young child, particularly if the child fears for the safety of a primary attachment figure, even if this fear is not based in reality. Children's perceptions of threats to their primary caregivers significantly predict the children's PTSD symptoms.

In the new *DSM-5* the 4 core symptom clusters of PTSD are (1) intrusion, (2) avoidance of trauma reminders, (3) negative trauma-related alterations in cognitions and mood, and (4) hyperarousal. To meet full PTSD criteria, children older than 6 years of age must have at least 1 reexperiencing symptom, 1 avoidance symptom, and 2 cognition or mood symptoms and 2 hyperarousal symptoms. Children who are 6 years of age or younger must meet similar symptoms but these are described in developmentally appropriate terms and they must have only 1 intrusion symptom, 1 symptom of avoidance or negative alterations in cognitions, and 2 hyperarousal symptoms. Even if a child does not have enough PTSD symptoms to meet the criteria for a PTSD diagnosis, if the symptoms are of sufficient severity to cause significant distress or functional impairment, then these likely warrant a referral for further evaluation.

Intrusion symptoms occur when upsetting feelings are experienced after memories or reminders of the traumatic event ("trauma reminders") recur. These symptoms may be idiosyncratic and hard for parents and pediatricians to identify. For example, that a child who saw her father shot to death began reliving the shooting in her mind whenever a thunderstorm occurred would not be difficult to understand; the sound of thunder reminded this child of the sound of the gunshots that killed her father. However, many other children's reexperiencing symptoms are less apparent. A child became severely distressed and aggressive after a peer failed to acknowledge his presence in the lunch room. Unknown to the educational staff, this served as a trauma reminder of the child's earlier parental neglect and abandonment. Recognizing these situations as reexperiencing phenomena requires an awareness of the child's traumatic past as well as sensitivity to the wide range of individual trauma reminders. Intrusion symptoms may include the following:

- Recurrent and distressing memories or thoughts of the event, including repetitive play
- Recurrent distressing or frightening dreams, including nonspecific scary dreams in younger children
- Feeling or acting as though the traumatic event is occurring again in the present (flashbacks; rare in younger children)
- Intense psychological distress when reminded of the trauma
- Physiologic reactions to trauma reminders, including upset stomach, headaches, and school refusal

The second PTSD cluster includes avoidance symptoms. Children's trauma reminders are accompanied by strong, upsetting feelings. To escape upsetting feelings when trauma reminders are present in many environments, children may develop avoidance coping strategies. For example, children will try to avoid talking about the traumatic experience or will avoid thinking about it. They will avoid places, people, and situations that serve as trauma reminders. For some children, these avoidant strategies become generalized—that is, they not only

avoid the place where the traumatic event happened but also avoid all similar places. For example, a child who was beaten up on the way to school becomes avoidant of going to school at all. A child who was sexually abused in the bathroom at home is now afraid of all bathrooms and becomes enuretic because the child is unable to use the toilet without becoming overwhelmed with fear. Children who deal with fear through avoidance are reinforcing their fears rather than extinguishing them. These avoidant symptoms include:

- Efforts to avoid thoughts, feelings, or talking about the traumatic event
- Avoiding activities, places, people, or situations that serve as trauma reminders

A new cluster has been included in *DSM-5* which includes negative alterations in trauma-related cognitions (beliefs) and mood. Research shows associations between inaccurate or unhelpful beliefs about trauma experiences (eg, self-blame, believing the world is completely dangerous) and PTSD symptom formation. Negative emotional states (eg, shame, guilt) also are highly predictive of PTSD symptoms. Children older than 6 years must have 2 of the following:

- Inability to remember an important aspect of the trauma
- Persistent and exaggerated negative beliefs or expectations about oneself, others or the world (eg, "I am bad", "No one can be trusted", "the world is completely dangerous")
- Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others
- Persistent negative emotional state (eg, fear, horror, anger, guilt, or shame)
- Markedly diminished interest or participation in significant activities
- Feelings of detachment or estrangement from others
- Persistent inability to experience positive emotions (eg, inability to experience happiness, satisfaction, or loving feelings)

The fourth PTSD cluster includes hyperarousal symptoms that were not present before the traumatic event. In children who have experienced chronic trauma, such as ongoing domestic or community violence or child abuse, assessing the onset of these symptoms or distinguishing them from other syndromes such as attention deficit/hyperactivity disorder may be difficult. A new item included in *DSM-5* is reckless or self-destructive behavior. Increased arousal symptoms include the following:

- Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects
- Reckless or self-destructive behavior
- Hypervigilance
- Exaggerated startle response
- Problems with concentration
- Sleep disturbance (eg, difficulty falling or staying asleep or restless sleep)

To receive a diagnosis of PTSD, a child must have experienced these symptoms for at least 1 month, causing significant clinical distress or functional impairment in social, school, family, health, or another important area of daily living.



## ASSESSING TRAUMA EXPOSURE

Pediatricians who have a favorable relationship with their patients will feel comfortable asking the child directly about possible exposure to a variety of different types of traumas at well-child care appointments. Generally, children and parents should be asked these questions in private, rather than together, because many types of traumas are believed by children or parents to be stigmatizing and shameful or things that should be kept secret within the family. Children may be less likely to disclose such information in the presence of the parent than alone with the pediatrician. Reporting requirements in the case of child maltreatment are discussed elsewhere in this volume, and these guidelines should be followed if the child discloses maltreatment in this context. (See Chapter 367, Physical Abuse and Neglect.) Some general questions designed to elicit information about a child's potential exposure to traumatic events are as follows:

- Has any significant change occurred in the child's life or functioning since the last visit?
- Since the last time the child was seen, has something really scary or upsetting happened to the child or someone in the child's family?
- Has any significant change occurred in the child's behavioral or emotional functioning?
- Has anyone reported or observed any sudden changes in the child's behavior or mood?

The pediatrician is also encouraged to monitor a child's potential exposure to specific traumatic events or experiences. Box 317-1 lists some key domains that should be included in an interview. Self-report instruments are also available for inquiring about trauma exposure. Commonly used exposure instruments include the Traumatic Events Screening Inventory for Children, which can be administered as a self-report instrument, and the UCLA PTSD Index for *DSM-IV*.

## ASSESSING POST-TRAUMATIC STRESS DISORDER SYMPTOMS

When assessing children for the presence of PTSD symptoms, it is common to anchor the symptoms to a specific trauma. However, many children experience multiple traumas, and it is difficult for these children to name a particular trauma as "the worst" or to tie specific symptoms (eg, difficulty sleeping or concentrating) to a particular trauma. It may be best to ask whether the child has any PTSD symptoms related to any traumatic experience. Eliciting PTSD symptoms from traumatized children is a challenging task, particularly when asking about avoidance. Children and parents should ideally be asked about the child's symptoms separately to obtain optimal information. Counting a symptom as present if either the child or the parent reports it (the "OR criterion") significantly improves the rate of accurate diagnosis.

Given all of these requirements, in most pediatric practices, time demands will preclude pediatricians from conducting personal interviews to assess PTSD symptoms. No validated screening instruments are available for *DSM-5* at the time of this writing. The 9-item child self-report Abbreviated UCLA PTSD

### BOX 317-1 Key Domains That Should Be Included in an Interview

- Bad accidents (vehicular, falls, fires)
- Medical trauma, illness, or related procedures (eg, long hospitalization stay, painful procedures)
- Natural disasters (storm, hurricane, blizzard, earthquake, flood, hit by lightning)
- Physical violence (toward child or other, threatened or happened, including bullying)
- Domestic violence (adults fighting, attacking, shooting, stabbing, beating each other up at home)
- Sexual abuse (unwanted touches in private parts, taking pictures, Internet abuse)
- Physical abuse at home (beating, punching, hitting by parent or older sibling)
- Traumatic death (knew or observed someone die—ask about circumstances: was death sudden, shocking, terrifying, gory?)
- Removal from parents or primary caregiver; foster care placement
- Child neglect (eg, caregiver unable to provide for basic needs because of substance abuse or serious mental illness)
- Other scary, frightening events (eg, kidnapping, terrorism)

Index for *DSM-IV* (Figure 317-1) has been used in school settings after disasters such as the September 11, 2001 terrorist attacks with good results and is a reasonable instrument for pediatricians to use in office settings until a *DSM-5* screening tool is available. A score of 20 on the Abbreviated UCLA PTSD Index highly correlates with a diagnosis of PTSD, but because of children's avoidance, underreporting of trauma symptoms, and the general difficulty of eliciting these symptoms, children with scores of 8 or higher also should be referred for evaluation if they have clinically meaningful symptoms or if these are accompanied by functional impairment. If a child with a trauma history is having difficulty getting along with people at school or at home, or if the child has trouble sleeping, eating, or concentrating, then the child should be referred for further mental health evaluation regardless of score on this instrument.

## OTHER TRAUMA-RELATED MENTAL HEALTH PROBLEMS

Childhood traumatic grief (CTG) is another condition that pediatricians should be prepared to recognize and refer for specialized intervention if indicated. CTG occurs in a substantial number of children who lose significant others to death under traumatic (frightening, unexpected) circumstances. Children with CTG get stuck on the traumatic circumstances of the loss and are unable to move through the typical stages of grieving. They may seem less sad than children who are mourning in a more usual fashion because they



1. I get upset, afraid, or sad when something makes me think about what happened.	<b>None</b> <input type="checkbox"/> 0	<b>Little</b> <input type="checkbox"/> 1	<b>Some</b> <input type="checkbox"/> 2	<b>Much</b> <input type="checkbox"/> 3	<b>Most</b> <input type="checkbox"/> 4
2. I have upsetting thoughts or pictures of what happened come into my mind when I do not want them to.	<b>None</b> <input type="checkbox"/> 0	<b>Little</b> <input type="checkbox"/> 1	<b>Some</b> <input type="checkbox"/> 2	<b>Much</b> <input type="checkbox"/> 3	<b>Most</b> <input type="checkbox"/> 4
3. I feel grouchy, or I am easily angered.	<b>None</b> <input type="checkbox"/> 0	<b>Little</b> <input type="checkbox"/> 1	<b>Some</b> <input type="checkbox"/> 2	<b>Much</b> <input type="checkbox"/> 3	<b>Most</b> <input type="checkbox"/> 4
4. I have trouble going to sleep, or I wake up often during the night.	<b>None</b> <input type="checkbox"/> 0	<b>Little</b> <input type="checkbox"/> 1	<b>Some</b> <input type="checkbox"/> 2	<b>Much</b> <input type="checkbox"/> 3	<b>Most</b> <input type="checkbox"/> 4
5. I try not to talk about, think about, or have feelings about what happened.	<b>None</b> <input type="checkbox"/> 0	<b>Little</b> <input type="checkbox"/> 1	<b>Some</b> <input type="checkbox"/> 2	<b>Much</b> <input type="checkbox"/> 3	<b>Most</b> <input type="checkbox"/> 4
6. I have trouble concentrating or paying attention.	<b>None</b> <input type="checkbox"/> 0	<b>Little</b> <input type="checkbox"/> 1	<b>Some</b> <input type="checkbox"/> 2	<b>Much</b> <input type="checkbox"/> 3	<b>Most</b> <input type="checkbox"/> 4
7. I try to stay away from people, places, or things that make me remember what happened.	<b>None</b> <input type="checkbox"/> 0	<b>Little</b> <input type="checkbox"/> 1	<b>Some</b> <input type="checkbox"/> 2	<b>Much</b> <input type="checkbox"/> 3	<b>Most</b> <input type="checkbox"/> 4
8. I have bad dreams, including dreams about what happened.	<b>None</b> <input type="checkbox"/> 0	<b>Little</b> <input type="checkbox"/> 1	<b>Some</b> <input type="checkbox"/> 2	<b>Much</b> <input type="checkbox"/> 3	<b>Most</b> <input type="checkbox"/> 4
9. I feel alone inside and not close to other people.	<b>None</b> <input type="checkbox"/> 0	<b>Little</b> <input type="checkbox"/> 1	<b>Some</b> <input type="checkbox"/> 2	<b>Much</b> <input type="checkbox"/> 3	<b>Most</b> <input type="checkbox"/> 4

**Figure 317-1** Abbreviated UCLA Post-traumatic Stress Disorder Reaction Index for *DSM-IV*. (Derived from Steinberg A, Brymer MJ, Decker KB, et al. University of California PTSD reaction index. *Curr Psychiatr Rep*. 2004;6:96-100.)

develop PTSD symptoms of intrusion, avoidance, cognitive and mood changes or hyperarousal. For example, these children may not talk about the deceased person, or seem detached from current caregivers and friends; or they may become easily angered and irritable when others want to reminisce about the person who is gone. Children who lose primary attachment figures as a result of causes other than death (eg, termination of parental rights because of parental substance abuse or maltreatment) may also develop CTG. The pediatrician can be of help to the child and family by recognizing the signs and presentation of CTG and educating the family about this condition.

Additionally, pediatricians should be aware that PTSD is not the only, or even the most common, outcome in children after trauma exposure. PTSD most typically co-occurs with other difficulties, such as depression, anxiety, and behavioral problems. Consequently, the pediatrician may have to include other assessments or instruments to evaluate these potential comorbidities. In some cases, parents initially identify other clinical concerns that may relate to the child's recent exposure to traumatic events. Children may develop these problems in the apparent absence of PTSD symptoms as well, and substance abuse, self-injury,

problems in relationships, and serious behavior problems (eg, severe aggression, sexual behavior problems) are common sequela of traumatic experiences, particularly child abuse and domestic violence. Current PTSD diagnostic criteria may not best describe the multiple effects trauma has on children, particularly after early complex trauma exposure.

## MAKING REFERRALS TO SPECIALIZED MENTAL HEALTH SERVICES

As noted previously, pediatricians should refer children with scores higher than 8 on the Abbreviated UCLA PTSD Index for specialized mental health evaluation. Pediatricians should be aware that, in addition to PTSD symptoms, additional risk factors exist for developing PTSD and other mental health difficulties after traumatic exposure. These risk factors include female sex; more frequent or intense exposure to the traumatic event; having a preexisting anxiety disorder; lack of parental or other support; parental history of PTSD, anxiety or depression, including parental PTSD related to the index trauma; and past trauma exposure. Genetic factors also are emerging as a significant risk for developing PTSD. Children who have

several of these risk factors may need more prompt mental health referrals or closer pediatrician follow-up (or both) after exposure to traumatic life events. Pediatricians may be particularly well placed to follow-up on such children and to monitor them for the later emergence of mental health difficulties.

Effective treatment is available for children who have significant PTSD symptoms, and with optimal interventions, most children are able to recover in as few as 8 to 12 treatment sessions, although children with more complex presentations may need somewhat longer treatment. (See Tools for Practice at the end of the chapter for resources.) Evidence-based treatments for PTSD in children include Trauma-Focused Cognitive Behavioral Therapy (TF-CBT, [www.musc.edu/tfcbt](http://www.musc.edu/tfcbt)); Child-Parent Psychotherapy, a dyadic treatment for young children (<8 years old) and a primary caregiver; and Cognitive Behavioral Interventions for Trauma in Schools, a group treatment for school settings. Descriptions of additional effective and promising practices for pediatric PTSD are available at the National Child Traumatic Stress Network, ([nctsn.org/resources/topics/treatments-that-work/promising-practices](http://nctsn.org/resources/topics/treatments-that-work/promising-practices)).

Most children are remarkably resilient in the face of trauma and do not go on to develop PTSD. However, many children exposed to trauma may experience clinical or subclinical PTSD, with or without symptoms that interfere with their functioning or cause impairment in other domains such as those described earlier. Improvements in such clinical problems have been reported among physically abused children by using Parent-Child Interaction Therapy, Alternatives for Families: Cognitive-Behavioral Therapy, and Combined Parent-Child Cognitive Behavioral Therapy.

In terms of specific efforts that can be made in the office, the pediatrician is in a unique position to promote an initial response to the child who has experienced traumatic events and who exhibits PTSD symptoms. Opportunities to observe the child during routine physical examinations provide both observational and physical evidence that may be relevant to the identification of traumatic exposure and symptoms. These impressions may be confirmed through parental interview when questions about the child's experiences and the timing of any recent or sudden reactions to these events can be ascertained. The pediatrician may also be in a position to work toward preventing PTSD by noting when children seem to be at risk for traumatic exposure or experiences. Potential high-risk scenarios that may be reported by the family include sudden and frequent moves, major disruptions in caregiving environment or caregiver functioning or status, reports of increased frustration or physical force during child management or disciplinary interactions, exposure to or knowledge of age-inappropriate sexual activities, sudden changes in a child's reactions to a caregiver, exposure to drugs and alcohol, and spending a lot of time with nonbiologically related men. Certainly the pediatrician can offer advice regarding steps that may minimize a child's exposure to high-risk situations and encourage parents to monitor and promote child safety, both in and out of the home.

## SUMMARY

Pediatricians are in a critical position to recognize, respond to, and refer traumatized children. The pediatrician may be the first adult or professional to learn about a child's potential exposure to traumatic events or to obtain evidence consistent with this clinical impression. Consequently, the pediatrician may be an initial responder in terms of understanding and addressing PTSD in children. An understanding of the material described in this chapter may provide the pediatrician with some of the basic tools to assess and treat the traumatized child.

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## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Coping With a Disaster or Traumatic Event* (Web page), Centers for Disease Control and Prevention ([www.bt.cdc.gov/mentalhealth](http://www.bt.cdc.gov/mentalhealth))
- *Mental Health Care: Who's Who* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/healthy-living/emotional-wellness/Pages/Mental-Health-Care-Who%27s-Who.aspx](http://www.healthychildren.org/English/healthy-living/emotional-wellness/Pages/Mental-Health-Care-Who%27s-Who.aspx))
- *Resources for Parents and Caregivers* (Web page), National Child Traumatic Stress Network ([www.nctsn.org/resources/audiences/parents-caregivers](http://www.nctsn.org/resources/audiences/parents-caregivers))
- *Responding to Children's Emotional Needs During Times of Crisis* (fact sheet), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/children-and-disasters/Documents/Responding-to-Childrens-Emotional-Needs.pdf](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/children-and-disasters/Documents/Responding-to-Childrens-Emotional-Needs.pdf))
- *What Is Child Traumatic Stress?* (fact sheet), National Child Traumatic Stress Network ([www.nctsn.org/nctsn\\_assets/pdfs/what\\_is\\_child\\_traumatic\\_stress.pdf](http://www.nctsn.org/nctsn_assets/pdfs/what_is_child_traumatic_stress.pdf))

### Medical Decision Support

- *Pediatric Medical Traumatic Stress Toolkit for Health Care Providers* (toolkit), National Child Traumatic Stress Network ([www.nctsn.org/traumatypes/pediatric-medical-traumatic-stress-toolkitfor-health-care-providers](http://www.nctsn.org/traumatypes/pediatric-medical-traumatic-stress-toolkitfor-health-care-providers))
- *The UCLA PTSD Index for DSM-IV* (Web page), US Department of Veterans Affairs ([www.ptsd.va.gov/PTSD/professional/assessment/child/ucla-ptsd-dsm-iv.asp](http://www.ptsd.va.gov/PTSD/professional/assessment/child/ucla-ptsd-dsm-iv.asp))

## AAP POLICY

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## Chapter 318

# PRADER-WILLI SYNDROME

Eileen Dolan, MD; Susan Wiley, MD

Prader-Willi Syndrome (PWS) is a complex genetic syndrome characterized by extreme hypotonia and failure to thrive during infancy, childhood-onset hyperphagia and obesity, unique behavioral characteristics, and cognitive impairment. Hypogonadism, short stature, small hands and feet, and characteristic facial features are also commonly present in individuals with PWS. Many of the manifestations of PWS seem to be related to insufficient functioning of the hypothalamus. However, the nature of the deficiency has not yet been identified.

In 1956, endocrinologists Prader, Labhart, and Willi first described PWS, and the accuracy of their initial findings later helped to form the diagnostic criteria. Accurate and reliable molecular genetic testing has subsequently been developed and is now widely available. Although the diagnostic criteria continue to help identify appropriate individuals for testing, the gold standard for diagnosing PWS is molecular genetic testing. Because strict clinical criteria are not necessary for diagnosis, suggested new criteria have been developed to prompt DNA testing (see Table 318-1).

PWS has been the subject of many genetic breakthroughs. It was the first known microdeletion syndrome identified by high-resolution chromosome analysis. Through this method, it was discovered that PWS results from a deletion in the proximal long arm of chromosome 15.

PWS was also the first known human genomic imprinting disorder. Genomic imprinting is an

inheritance process in which genes are expressed based on only 1 allele, in a parent-of-origin manner. This differs from most cases of inheritance, whereby gene expression occurs from 2 alleles, 1 inherited from each parent. Genomic imprinting is an epigenetic process, meaning that modifications are made to the structure of the DNA, but the DNA sequence is not changed.

In unaffected individuals, the maternally derived genetic material on the critical region of chromosome 15 is inactivated through the process of hypermethylation. This leaves only the paternal genes to be expressed. PWS results from the loss of the paternally derived genetic material in the 15q11-q13 region. The loss of maternal genes in this same area results in Angelman syndrome.

**EPIDEMIOLOGY**

The prevalence of PWS has been reported to be between 1 in 15,000 and 1 in 30,000 people. This may be an underestimate, however, because diagnosis may be delayed in many individuals. The syndrome occurs in both males and females and in individuals of all races. PWS is the most common known genetic cause of obesity.

The risk for recurrence of PWS varies with the underlying genetic mechanism. In general, the recurrence risk is less than 1%, but it can be significantly elevated in rare cases. As a result, after an individual is diagnosed with PWS, genetic counseling should be offered to the family to determine the risk for recurrence in future pregnancies.

**ETIOLOGY**

PWS results from the loss of the paternally derived genes from the proximal arm of chromosome 15. There are 3 known ways in which this can occur: deletion in the paternally contributed chromosome, maternal uniparental disomy, and an error in the imprinting process.

**Deletion in Paternally Contributed Chromosome**

More than 70% of the cases of PWS result from a deletion of paternal genetic material on chromosome 15, between the bands 15q11 and 15q13. The deletion is

**Table 318-1** Criteria to Prompt DNA Testing for Prader-Willi Syndrome

AGE AT ASSESSMENT	FEATURES SUFFICIENT TO PROMPT DNA TESTING
Birth to 2 yr	Hypotonia with poor suck
2–6 yr	Hypotonia with history of poor suck
	Global developmental delay
6–12 yr	History of hypotonia with poor suck (hypotonia often persists)
	Global developmental delay
13 yr through adulthood	Excessive eating (hyperphagia; obsession with food), with central obesity if uncontrolled
	Cognitive impairment; usually mild intellectual disability
	Excessive eating (hyperphagia; obsession with food), with central obesity if uncontrolled
	Hypothalamic hypogonadism or typical behavior problems (including temper tantrums and obsessive-compulsive features)

From Gunay-Aygun M, Schwartz S, Heeger S, et al. The changing purpose of Prader-Willi syndrome clinical diagnostic criteria and proposed revised criteria. *Pediatrics.* 2001;108(5):e92.

usually sporadic, and the recurrence rate is less than 1%. Recurrence increases in the rare cases of chromosomal translocation in the father. Paternal testing should be offered to rule out chromosomal rearrangement and to determine the recurrence risk.

### Maternal Uniparental Disomy

Prader-Willi syndrome was the first identified syndrome resulting from maternal uniparental disomy (UPD). Maternal UPD accounts for approximately 28% of cases of PWS. In UPD, an individual receives two copies of a chromosome from one parent and no copies from the other parent. This may not be problematic when genes are typically expressed. However, it could lead to the loss of active copies of genes that have undergone genomic imprinting, as in the case of PWS. In this case, both copies of chromosome 15 are inherited from the mother, and the active and imprinted paternal genes are not present.

Recurrence risk is usually less than 1% in maternal UPD. The presence of a Robertsonian translocation in either parent can increase the risk, and parental testing is warranted.

### Error in Imprinting

Less than 2% of cases of PWS result from an error in the imprinting process. The paternally derived genes are present, but they are not expressed because of the imprinting abnormality. Nearly all known cases of family recurrence of PWS originate from an imprinting error. Recurrence rates in this category can be as high as 50% when there is a microdeletion in the imprinting center. Most imprinting defects, however, involve an epigenetic mutation. In this group, the recurrence rate is less than 1%.

Many genes have been identified in the region of the deletion in PWS, but the gene functions and mechanisms of action are still being studied.

## DIAGNOSIS

### Signs and Symptoms

#### Physical Characteristics

Characteristic facial features of PWS are initially subtle and may be difficult to appreciate during infancy. As the child grows, the facial features and body habitus become more evident. The common physical findings include the following:

- Almond-shaped eyes
  - Small-appearing mouth with thin upper lip
  - Down-turned corners of the mouth
  - Narrow bifrontal diameter
  - Small and narrow hands and small feet
  - Hypopigmentation (fair skin, eyes, hair) in about one-third of individuals
  - Genital hypoplasia
  - Centrally distributed obesity
  - Short stature
- (See Figure 318-1)

#### Hypotonia and Feeding Difficulties

The most common presenting sign of PWS in infancy is severe central hypotonia. The consistency of this finding has led to the recommendation that all infants



**Figure 318-1** (A) Facial features and (B) obesity in a male with Prader-Willi syndrome. (From Lyons MJ. *Specific genetic conditions*. In: Saul RA, ed. *Medical Genetics in Pediatric Practice*. Elk Grove Village, IL: American Academy of Pediatrics; 2013:175–234.)

with persistent hypotonia be tested for PWS. The hypotonia is prenatal in onset, resulting in decreased fetal movements, abnormal fetal position, and increased occurrence of cesarean delivery. The infant may seem floppy, have a weak cry, and exhibit decreased arousal. Infants with PWS often have a poor suck, leading to problems with feeding. This, combined with lack of awakening to feed, often results in



failure to thrive. The hypotonia gradually improves with age, but most adults remain mildly hypotonic with decreased muscle bulk and tone.

### **Obesity**

PWS is the leading known genetic cause of obesity. As the central hypotonia of infancy becomes less severe, feeding difficulties resolve, and excessive food intake begins. Between 1 and 6 years of age, children with PWS demonstrate hyperphagia and have an insatiable appetite. Individuals develop obsessive behavior surrounding food, including food-seeking behavior, hoarding, stealing, and eating undesired food, such as garbage, frozen food, or spoiled food.

Individuals with PWS have a decreased need for caloric intake owing to a low metabolic rate and less mean muscle mass. The combination of decreased caloric need, hyperphagia, and lack of satiety makes obesity a problem that is difficult to prevent. Obesity is the major cause of morbidity and mortality in PWS and often leads to secondary conditions, including cardiopulmonary compromise, sleep apnea, type 2 diabetes mellitus, and hypertension.

### **Hypogonadism**

Hypogonadism with genital hypoplasia is present during infancy but may become more apparent as the child grows. In males, this may present as scrotal hypoplasia, cryptorchidism, and a small penis or testes for age. Genital hypoplasia is present but difficult to assess in females.

Hypogonadism becomes more apparent in adolescence because of abnormal and incomplete pubertal development. Precocious puberty is uncommon, but precocious adrenarche has been reported. Females usually exhibit oligomenorrhea or amenorrhea, and males have scant body hair and poor voice change. Adolescents lack the pubertal growth spurt, resulting in short stature. An additional contributor to the short stature is the deficiency of growth hormone and insulin-like growth factor 1.

### **Sleep Disturbance**

Sleep-disordered breathing is a common occurrence in PWS. Obesity contributes to obstructive sleep apnea, but sleep is abnormal even in the absence of obesity. Excessive daytime sleepiness, abnormal circadian rhythm in rapid eye movement sleep, abnormal arousal, and central sleep apnea have all been reported.

### **Musculoskeletal Problems**

Hip dysplasia is seen in about 10% of individuals with PWS. Scoliosis is common and can develop at any time during childhood. Kyphosis also frequently occurs and usually develops in adolescence or early adulthood. Osteoporosis is common in adults with PWS and may be the result of hypotonia, low calcium intake, hypogonadism, and growth hormone deficiency.

### **Developmental Delay or Intellectual Disability**

Early developmental milestones are delayed in children with PWS. The average age of sitting is 12 months and of walking is 24 months. Language milestones are delayed as well, with first words reported from

18 months to as late as 6 years. Articulation difficulties are also common.

Intelligence testing has revealed a range of intelligence from low-normal to severely impaired. Most individuals with PWS function in the range of mild intellectual disability. Relative strengths include visual-spatial skills, reading, expressive vocabulary, and long-term memory. Some individuals display exceptional skills with jigsaw puzzles. Weaknesses are seen in sequential processing and short-term memory.

### **Behavior**

Individuals with PWS have unique behavioral characteristics, including temper tantrums, stubbornness, obsessive-compulsive behaviors, and inflexibility. Behavior difficulties often begin around the age of 3 to 4 years and often are related to the cravings for food. Individuals may be manipulative, lie, steal, and become aggressive in their quest for food. Children are persistent and often clever in obtaining food, so parents need to be diligent to prevent hyperphagia.

Obsessive-compulsive characteristics are common, and individuals are often routine oriented with little tolerance for change. Organizing possessions, insistence in routines, hoarding of food and other objects, skin picking, and repetitive behavior are often seen. Approximately 25% of individuals with PWS have been diagnosed with an autism spectrum disorder. Individuals with maternal UPD have a higher rate of autism diagnoses. About 5% to 10% of individuals with PWS develop psychosis in early adulthood.

### **Additional Findings**

Ophthalmologic findings including strabismus, refractive errors, and hyperopia are often present in PWS. Decreased saliva volume is quite common and leads to dry mouth and a possible increase in dental caries. Saliva often becomes thick and viscous, which may contribute to articulation difficulties. Additional findings, including altered temperature perception, high pain threshold, and high vomiting threshold are commonly present and are thought to be related to abnormalities in hypothalamic functioning.

### **Differential Diagnosis**

The differential diagnosis can vary depending on the age of diagnosis. In infancy, the differential diagnosis includes other disorders that present with hypotonia, feeding difficulties, or failure to thrive, such as spinal muscular atrophy, congenital myotonic dystrophy type 1, Angelman syndrome, botulism, and additional neuromuscular or genetic disorders.

In childhood, the differential diagnosis includes conditions that present with intellectual disability and obesity. Some examples include fragile X syndrome, Bardet-Biedl syndrome, Alstrom syndrome, Cohen syndrome, Börjeson-Forssman-Lehmann syndrome, and Albright hereditary osteodystrophy.

### **Diagnostic Approach**

If PWS is suspected based on the clinical criteria, the diagnosis should be confirmed by genetic testing. The order of testing may vary, depending on previous studies and availability of tests. As a result of rapid advances

in technology, referral to a clinical geneticist may be appropriate and may allow more targeted genetic testing.

DNA methylation is usually the first step in testing because it detects 99% of cases of PWS. If biparental inheritance is identified, PWS is ruled out. If methylation studies detect only maternal alleles, PWS is confirmed. For genetic counseling purposes, it is recommended that testing continue until the specific genetic cause of PWS is known. After PWS is confirmed by methylation studies, fluorescence in situ hybridization, UPD studies, and sequence analysis can then be completed to determine the specific cause (deletion, UPD, or imprinting error).

## MANAGEMENT

A multidisciplinary approach should be used in the management of an individual with PWS. The treatment team often includes medical physicians, psychologists, dietitians, nurses, and therapists, with the primary care pediatrician overseeing and coordinating care. Because of the unique characteristics and complications of the syndrome, subspecialists in genetics, endocrinology, development and behavior, and pulmonology should be part of the care team. Genetic counseling and referral to parental support groups should occur at diagnosis.

### Hypotonia and Feeding

Because of the marked hypotonia and ensuing feeding difficulties, adequate nutrition and growth are the major focus of treatment in infancy. Gavage feeding or the use of a special nipple can compensate for the hypotonia and poor suck. Because infants have a decreased state of arousal, a feeding schedule should be created, and the infant should be woken up to be fed. Fats are necessary for the development of the nervous system and should not be limited in infancy. The infant's height and weight should be plotted on a growth curve monthly to monitor progress. A dietitian is helpful in monitoring adequate caloric intake, with a goal of keeping the infant between the 50th and 75th percentiles on the weight-for-length curve.

### Obesity

The transition to hyperphagia and obesity begins in early childhood, so healthy eating habits should be taught from an early age. No medications have been successful in controlling the appetite of an individual with PWS. As a result, weight should be managed with the combination of a restrictive diet, limited access to food, exercise, and behavioral techniques.

Restrictive diets are often started around preschool, and the child's weight should be frequently assessed to guide further recommendations. Detailed food logs are useful for the family and allow professionals to calculate caloric intake. Individuals with PWS should take a daily multivitamin and calcium and vitamin D supplements to compensate for suboptimal intake resulting from the restrictive diet.

Access to food should be limited, and locks should be placed on the refrigerator, cabinets, and garbage cans. Consistent daily schedules around meals and exercise and the use of positive reinforcement with a

token economy may increase compliance with dietary restrictions. Behavioral techniques are also helpful in initiating and maintaining an exercise program. Thirty to 60 minutes of physical activity is recommended on a daily basis.

### Hypogonadism

Males should be evaluated for cryptorchidism, with a referral for surgical intervention when appropriate. Hormone replacement therapy may be considered in the pubertal years and should be discussed with an endocrinologist. Estrogen replacement in females may be beneficial for bone density.

### Growth Hormone

Growth hormone replacement is approved for use in children with PWS, and stimulation testing is not required. The age for starting growth hormone replacement remains controversial, and it usually begins in early childhood. However, studies have shown benefits with starting replacement therapy at 6 months to 1 year of age. Individuals should be referred to an endocrinologist at the time of diagnosis, and discussions of growth hormone replacement can start early on. Growth hormone replacement has been shown to improve childhood growth, lean body mass, and adult height and may have an effect on overall development when started early.

Cases of sudden respiratory death have been reported in children with PWS while being treated with growth hormone. These individuals had a history of significant obesity and pre-existing respiratory or other contributing complications. The deaths were not clearly related to growth hormone replacement, but great care should be taken when initiating therapy. A sleep study and respiratory evaluation are often recommended, and obstructive sleep apnea should be treated before starting replacement therapy. Individuals should be screened for diabetes, hypothyroidism, and scoliosis (with radiograph) before initiation and during the course of growth hormone replacement.

### Sleep

Sleep studies and ear-nose-throat evaluations should be performed if there are concerns about sleep-disordered breathing to determine an obstructive versus central etiology. This is especially important when considering growth hormone initiation because obstructive sleep apnea increases the risks involved in growth hormone replacement.

### Musculoskeletal

Infants should be evaluated for hip dysplasia and scoliosis, and imaging studies and referrals should be made as appropriate. A physical examination for scoliosis is less accurate in obese individuals. Therefore annual radiographs of the spine should be considered to monitor changes in curvature. Individuals with high body mass index values are at increased risk for developing kyphosis. The management of scoliosis and kyphosis may include bracing or surgery (as in the general population). Individuals should be closely monitored for progression of scoliosis during growth hormone therapy.

### Development and Behavior

An early intervention referral is recommended in infancy because of problems associated with hypotonia, motor delays, and language delays. As children are transitioned into school, an education plan should be developed. Psychoeducational testing is recommended to assess individual strengths and weaknesses. Continued therapy, classroom aides, behavior plans, and supervised lunches should all be discussed with the educational team.

Children with PWS often respond well to structured environments and schedules. Limits should be set and consistently enforced starting at an early age. A specialist in development and behavior can help the family set appropriate limits and construct behavior plans. Early limit setting can help prevent more severe behavior problems in the future.

Children with PWS often respond well to positive reinforcement and the use of a token economy. Skin

picking can be quite difficult to treat, but behavioral strategies should be used, with reinforcement for alternative behaviors. When obsessive traits, tantrums, and food-seeking behaviors continue to be problematic, children and their parents often benefit from behavior counseling. Psychopharmacologic agents may be considered. Children should be referred to a psychiatrist if they exhibit signs of psychosis, such as hallucinations, behavior changes, or disorientation.

### Specialists

Table 318-2 provides guidance about when it is appropriate to refer a child with PWS to a specialist.

## ONGOING CARE

### Routine Medical Care

Clinical screening for scoliosis and kyphosis at routine health care visits is recommended. Radiographs should be ordered as needed.

**Table 318-2** When to Involve Specialists in Management of Children With Prader-Willi Syndrome

SIGN OR SYMPTOM	APPROPRIATE REFERRALS
<b>AT DIAGNOSIS</b>	Genetics Endocrine Early intervention programming, school programming
<b>FEEDING/GASTROINTESTINAL</b>	
Poor feeding/suck (infancy)	Dietitian, speech therapist (feeding support)
Food seeking, hyperphagia (early childhood and beyond)	Specialized behavioral therapy for food seeking
Abdominal pain, vomiting, anorexia	Urgent medical workup, especially for gastric necrosis
<b>ENDOCRINE</b>	
Weight gain	Pediatric endocrinology
Growth hormone deficiency	Surgical referral for cryptorchidism
Glucose intolerance	
Delayed puberty	
Hypogonadism	
<b>VISION</b>	
Strabismus (monitor eye alignment)	Ophthalmologist knowledgeable in pediatric conditions
Failed vision screen	
<b>DENTAL</b>	
At higher risk for caries because of decreased saliva production	Referral to dentist accustomed to working with children with delays Reinforce good dental hygiene
<b>SLEEP</b>	
High risk for sleep disturbances, obstructive and central sleep apnea	Monitor for sleep problems Refer for sleep study as indicated by history and before growth hormone initiation
<b>MUSCULOSKELETAL</b>	
Hip dysplasia	Newborn hip examination with appropriate referrals based on findings
Scoliosis (any age)	Monitor for scoliosis and kyphosis at visits (direct visual inspection and scoliometer); refer for radiographs, orthopedic care as indicated. Imaging recommended before starting growth hormone, and annually in obese individuals
Kyphosis (in adolescence)	
<b>DEVELOPMENT/BEHAVIOR</b>	
Developmental delay, cognitive impairment	Early intervention programming
Language delay	School programming
Food hoarding	Developmental-behavioral pediatrician or psychologist or child psychiatrist
Obsessive-compulsive features	depending on issues and community resources
Skin picking	
Autism spectrum disorder	

Eyes should be evaluated for strabismus (cover/uncover test), with a referral to ophthalmology if visual concerns are indicated.

Individuals with PWS are at a higher risk for dental caries because of decreased saliva. Regular dental visits and good dental hygiene are recommended.

An examination of the skin should be performed at all visits because of picking behavior, possible infection, and bleeding. Keeping nails short and cleaning and covering wounds can help minimize damage.

Individuals should be monitored for known complications of obesity. Blood pressure should be checked regularly, and hypertension should be treated as in the general population. Glycosylated hemoglobin and a lipid profile should be measured annually in adults with obesity. Type 2 diabetes should be treated as in the general population.

Because individuals with PWS have a high pain threshold, all complaints of pain or change in behavior or appetite should be taken seriously. Physicians should thoroughly examine individuals and have a low threshold for imaging studies or further workup.

### Transition Needs

Transition plans should begin in childhood or early adolescence to facilitate a smooth transition to adult services. Issues including vocational training, guardianship, housing, and adult medical providers should be addressed. Individuals with PWS will require a supportive environment throughout their lives.

### Prognosis

Obesity accounts for most cases of morbidity or mortality in PWS. Deaths are often the result of cardiorespiratory failure or complications of sleep apnea (cor pulmonale). There have been reports of deaths from choking because of rapid food consumption. Overeating has resulted in gastric necrosis and rupture, which presented with only mild clinical signs. Individuals with PWS have a high pain tolerance, so minor symptoms, such as abdominal pain, vomiting, or decreased appetite should prompt further workup, often including urgent imaging.

Central adrenal insufficiency (CAI) may be present in individuals with PWS. Some of the sudden deaths in individuals with PWS may be explained by the CAI in times of stress. This should be discussed with the individual's endocrinologist, and individuals may be tested for CAI.

Although PWS remains a complex condition, regular follow-up with the multidisciplinary physician-led team can lead to early intervention or prevention of common complications. Strategies to prevent obesity and the initiation of growth hormone replacement have changed the prognosis for individuals with PWS. Through early identification, diagnosis, and implementation of behavioral strategies, hyperphagia and obesity can be decreased, thereby avoiding the complications of obesity. Increased awareness allows parents and families to seek counseling and support through community groups and professionals. With continued support, quality of life can improve for individuals with PWS and their families.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *Building the Legacy: IDEA 2004* (Web page), US Department of Education ([idea.ed.gov](http://idea.ed.gov))
- *Let's Put the Person First, Not the Disability!* (fact sheet), Disability Is Natural ([www.disabilityisnatural.com/explore/people-first-language](http://www.disabilityisnatural.com/explore/people-first-language))

### Engaging Patient and Family

- *All About the IEP* (fact sheet), Center for Parent Information and Resources ([www.parentcenterhub.org/repository/iep](http://www.parentcenterhub.org/repository/iep))
- *Building Your Care Notebook* (Web page), American Academy of Pediatrics ([medicalhomeinfo.aap.org/tools-resources/Pages/For-Families.aspx](http://medicalhomeinfo.aap.org/tools-resources/Pages/For-Families.aspx))
- *Emergency Information Form for Children With Special Needs* (form), American Academy of Pediatrics ([www.aap.org/advocacy/blankform.pdf](http://www.aap.org/advocacy/blankform.pdf))
- *Pediatric Care Plan* (form), American Academy of Pediatrics ([medicalhomes.aap.org/Documents/PediatricCarePlan.pdf](http://medicalhomes.aap.org/Documents/PediatricCarePlan.pdf))
- *Pediatric Specialists* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/default.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/default.aspx))
- *Transitioning Youth to Adult Care Providers* (booklet), Got Transition ([www.gottransition.org/resource/Get.cfm?id=208](http://www.gottransition.org/resource/Get.cfm?id=208))

### Practice Management and Care Coordination

- *A Toolkit to Improve Care for Pediatric Patients With Genetic Conditions in Primary Care* (e-book), American Academy of Pediatrics ([geneticsinprimarycare.aap.org/YourPractice/Documents/GPCI\\_Toolkit.pdf](http://geneticsinprimarycare.aap.org/YourPractice/Documents/GPCI_Toolkit.pdf))

## AAP POLICY

- American Academy of Pediatrics Committee on Genetics. Health supervision for children with Prader-Willi syndrome. *Pediatrics*. 2011;127(1):195–204 ([pediatrics.aappublications.org/content/127/1/195](http://pediatrics.aappublications.org/content/127/1/195))
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## Chapter 319

# PRESEPTAL AND ORBITAL CELLULITIS

Ellen R. Wald, MD

The pediatrician often has the opportunity to manage the child for whom the chief complaint is a swollen eye. Many of these children have trivial or self-limited disorders, but others can have sight- or life-threatening problems. Noninfectious causes of the swollen eye can often be distinguished from infectious causes by a detailed history of the onset and progression of the eye swelling. Infectious causes of eye swelling are usually acute in presentation. Differentiating between preseptal (common) and orbital (rare) causes of eye swelling is critical to management and can usually be accomplished on the basis of the physical examination.

## NONINFECTIOUS CAUSES OF THE SWOLLEN EYE

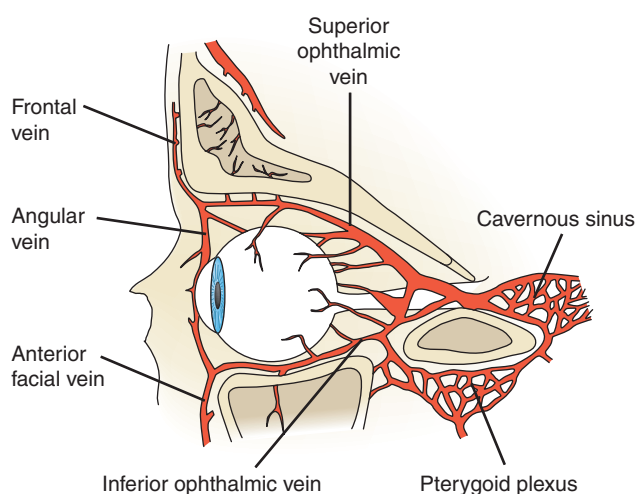
The noninfectious causes of swelling of or around the eye include blunt trauma (leading to the proverbial *black eye*), tumor, local edema, and allergy. In cases of blunt trauma, history provides the key to the diagnosis. Eyelid swelling continues to increase for 48 hours and then resolves over several days. Tumors that characteristically involve the eye include hemangioma of the lid, ocular tumors such as retinoblastoma and choroidal melanoma, and orbital neoplasms such as neuroblastoma, rhabdomyosarcoma, and Langerhans cell histiocytosis. Tumors usually cause a gradual onset of proptosis in the absence of inflammation. An orbital pseudotumor, an autoimmune inflammation of the orbital tissues, exhibits eyelid swelling, red eye, pain, and decreased ocular motility. Hypoproteinemia and congestive heart failure cause eyelid swelling as a result of local edema. Characteristic findings are bilateral, boggy, nontender, nondiscolored, soft-tissue swelling. Allergic inflammation includes angioneurotic edema or contact hypersensitivity. Superficially, these problems can resemble the findings in acute infection. However, the presence of pruritus and the absence of tenderness are helpful distinguishing characteristics of allergic inflammation.

## INFECTIOUS CAUSES OF THE SWOLLEN EYE

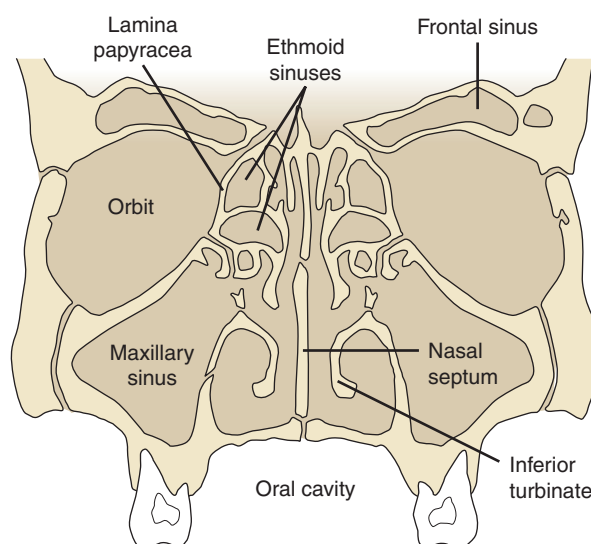
Infections can spread to the eye from contiguous structures. Veins that drain the orbit, the ethmoid and maxillary sinuses, and the skin of the eye and

periorbital tissues (Figure 319-1) constitute an anastomosing and valveless network. This venous system provides opportunities for the spread of an infection from one anatomic site to another and predisposes the child to the involvement of the cavernous sinus, meninges, and brain.

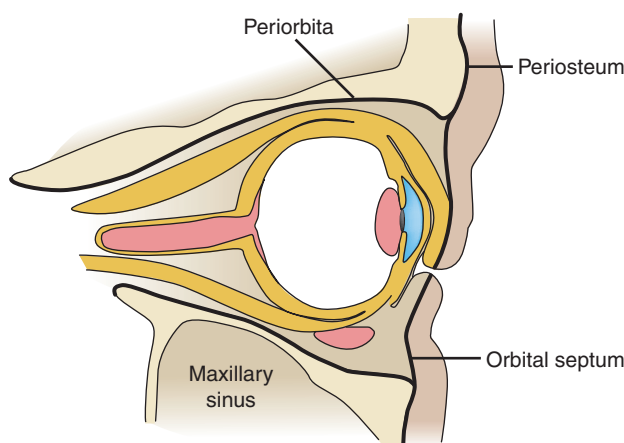
The relationship between the eye and the paranasal sinuses is shown in Figure 319-2. The roof of the orbit is the floor of the frontal sinus, and the floor of the orbit is the roof of the maxillary sinus. The medial wall of the orbit is formed by the frontal maxillary process, the lacrimal bone, the lamina papyracea of the ethmoid bone, and a small part of the sphenoid bone. Infections originating in the mucosa of the paranasal



**Figure 319-1** The valveless venous system of the orbit and its many anastomoses.



**Figure 319-2** The relationship between the eye and the paranasal sinuses is shown schematically. The roof of the orbit, the medial wall, and the floor are shared by the frontal, ethmoid, and maxillary sinuses, respectively.



**Figure 319-3** The orbital septum is a connective tissue extension of the periosteum that is reflected into the upper and lower lid.

sinuses can spread to involve the bone (osteitis with or without subperiosteal abscess) and the intraorbital contents. Orbital infections can occur through natural bony dehiscences in the lamina papyracea of the ethmoid or frontal bones or via foramina through which the ethmoidal arteries pass.

The orbital septum is a connective-tissue extension of the periosteum (or periorbital) that is reflected into the upper and lower eyelids (Figure 319-3). The infection of tissues anterior to the orbital septum is described as a *periorbital* or *preseptal* infection (the terms may be used interchangeably; preseptal will be used throughout the rest of the chapter). The septum provides a nearly impervious barrier to the spread of an infection to the orbit. Although preseptal cellulitis, or periorbital cellulitis, is often considered to be a diagnosis, the term is an inadequate diagnostic label unless accompanied by a modifier that indicates the likely pathogenesis.

Infectious causes of preseptal cellulitis occur in the following 3 settings:

1. Secondary to a localized infection or inflammation of the conjunctiva, eyelids, or adjacent structures (eg, conjunctivitis, hordeolum, acute chalazion, dacryocystitis, dacryoadenitis, impetigo, traumatic bacterial cellulitis)
2. Secondary to hematogenous dissemination of nasopharyngeal pathogens to the periorbital tissue
3. As a manifestation of inflammatory edema in children with acute sinusitis (Box 319-1)

Infections behind the septum that cause eyelid swelling include subperiosteal abscess, orbital abscess, orbital cellulitis, cavernous sinus thrombosis, panophthalmitis, and endophthalmitis. Although all of these entities can be labeled as orbital cellulitis, a systematic approach allows a more specific diagnosis, thereby directing management. Infections intrinsic to the eye (eg, conjunctivitis, keratitis, endophthalmitis) are discussed in Chapter 188, Red Eye/Pink Eye.

### BOX 319-1 Infectious Causes of Preseptal and Orbital Cellulitis

#### PRESEPTAL CELLULITIS

- Localized infection of the eyelid or adjacent structure
- Conjunctivitis
- Hordeolum
- Dacryoadenitis
- Dacryocystitis
- Bacterial cellulitis (trauma)
- Hematogenous dissemination
- Bacteremic periorbital cellulitis
- Acute sinusitis
- Inflammatory edema

#### ORBITAL CELLULITIS (POSTSEPTAL)

- Subperiosteal abscess
- Orbital abscess
- Orbital cellulitis
- Cavernous sinus thrombosis
- Hematogenous dissemination
- Endophthalmitis
- Traumatic inoculation
- Panophthalmitis

## PRESEPTAL INFECTIONS

### Preseptal Cellulitis Infections After Trauma

Occasionally, preseptal cellulitis results from secondary bacterial infection of local skin injury (including lacerations, abrasions, and even insect bites), or with the spread of an infection from a focus of impetigo. The traumatic injury may be extremely modest or completely inapparent. Loosely bound periorbital soft tissues permit impressive swelling to accompany minor infection. The overlying skin can be bright red with subtle textural changes, or intense swelling can lead to shininess (Figure 319-4). Some children have fever, but most are afebrile despite dramatic local findings. The peripheral white blood cell count is variable. In these cases, cellulitis, similar to that on any other cutaneous area, is caused by *Staphylococcus aureus* or *Streptococcus pyogenes*. These are among the most common causes of preseptal cellulitis.

Several other causes of lid cellulitis have been reported; these are much less common but are interesting to consider. Periocular cellulitis and abscess formation have resulted from infection with *Pasteurella multocida* in a healthy child who sustained a cat bite and cat scratch to the eyelid. Ringworm (caused by *Trichophyton* species) is also recognized as a cause of lid infection (leading to preseptal cellulitis) characterized by redness, swelling, and ulceration and vesicle formation. Palpebral myiasis (larval infection) involving the eyelid of a 6-year-old child was reported from the Massachusetts Eye and Ear Infirmary. A small draining fistula through which the larvae were extracted was noted at the site of the erythematous and edematous lid. Several cases of



**Figure 319-4** A 3-year-old boy with rapid onset of left eyelid swelling and erythema after he incurred a small laceration at the lateral margin of the left eye. He had had an upper respiratory tract infection for 10 days. Group A *Streptococcus* was recovered from the wound.

cellulitis of the eyelid caused by *Bacillus anthracis* have been reported from Turkey. The diagnosis was suggested when the erythematous and swollen lid developed an eschar. Scrapings showed the presence of Gram-positive rods, which were confirmed by culture. A primary case of lymphocutaneous *Nocardia brasiliensis* of the eyelid was reported in an adult hunting in England 2 weeks before presentation following a small abrasion on his lower eyelid. In countries where *Mycobacterium tuberculosis* is endemic, this etiology should also be considered in children who present with a swollen lid. Raina and colleagues reported 7 children with tuberculous lesions of their eyelids. In most cases, the presentation was relatively indolent (2 days to 2 months), and fistulas occurred during the course of conventional antibiotic treatment for more typical bacterial disease. The diagnosis was confirmed by a positive tuberculin skin test, the identification of a primary focus of tuberculosis in lung or bone, and the response to antituberculous therapy.

Children with bacterial cellulitis of traumatized areas rarely have bacteremia. A precise bacteriologic diagnosis is made through the culture of the exudate from the wound. If there is no drainage, then a careful attempt at tissue aspiration may be undertaken if it can be done safely (ie, at a distance far enough from the orbit that no damage to the eye can occur). This procedure may be performed on inpatients or outpatients. A tuberculin syringe with a 25-gauge needle can be used for aspiration. Usually, only a minuscule amount of infected material can be aspirated. A small volume of nonbacteriostatic saline (0.2 mL) is drawn into the syringe before the procedure. The saline is not injected into the skin; instead, it is used to expel the small volume of tissue fluid onto chocolate agar for culture. The treatment of preseptal cellulitis likely caused by *S aureus* or *S pyogenes* should be undertaken aggressively because improperly treated infection may lead to cavernous sinus thrombosis. After local cultures are obtained, vancomycin should be initiated (at 15 mg/kg/dose every 6 hours) in communities where methicillin-resistant

*S aureus* (MRSA) is prevalent. If cultures disclose an etiology other than MRSA, intravenous treatment can be tailored to the isolate. Oral therapy can be used to complete a 10-day course of treatment after a substantial improvement in local findings.

### Bacteremic Periorbital Cellulitis

Bacteremia as the pathogenetic mechanism of periorbital cellulitis is very uncommon since the introduction of conjugate vaccines for *Haemophilus influenzae* type b and *Streptococcus pneumoniae* (pneumococcal conjugate vaccine 7 [PCV7] and 13 [PCV13]) in 2000 and 2010, respectively. The child with bacteremic periorbital cellulitis, which is most often seen in infants younger than 18 months, has had a viral upper respiratory infection (URI) for several days. A sudden increase in temperature occurs ( $>102.2^{\circ}\text{F}$  [ $39^{\circ}\text{C}$ ]) accompanied by the acute onset and rapid progression of eyelid swelling. Swelling usually begins in the inner canthus of the upper and lower eyelid and can obscure the eyeball within 12 hours. Periorbital tissues are markedly discolored and usually erythematous, although if the swelling has been rapidly progressive, the area may have a violaceous discoloration. The child's resistance to examination commonly leads to the erroneous impression of tenderness. Retraction or separation of the lids reveals that the globe is normally placed and extraocular eye movements are intact. If retraction of the lids is not possible, then an orbital computed tomography (CT) scan may be necessary. The young age, high fever, and rapid progression of findings differentiate bacteremic preseptal cellulitis from other causes of swelling around the eye (Figure 319-5).

A precise bacteriologic diagnosis is made by the recovery of the organism from blood culture. If tissue aspiration is performed, a culture of the specimen may have a positive result.

The bacteremia usually occurs during the course of a viral URI from a portal of entry in the nasopharynx. This process is akin to the mechanism of most infections caused by *Haemophilus influenzae* type b (Hib) and some infections caused by *S pneumoniae*.

The radiographs of the paranasal sinuses of children with bacteremic periorbital cellulitis are often abnormal. However, the abnormalities almost certainly reflect the viral respiratory syndrome that precedes and probably predisposes the child to the bacteremic event rather than a clinically significant sinusitis. Bacteremic cellulitis rarely arises from the paranasal sinus cavities, as evidenced by the finding that typeable *H influenzae* organisms were almost never recovered from maxillary sinus aspirates and, similarly, were rarely recovered from abscess material in children who had serious local complications of paranasal sinus disease, such as subperiosteal abscess. Although *S pneumoniae* can cause subperiosteal abscesses in children with acute sinusitis, these children are not usually bacteremic.

The treatment for suspected bacteremic periorbital cellulitis requires parenteral therapy. *S pneumoniae* is the most likely cause in a child who has received both the Hib and pneumococcal conjugate vaccine series. Because this infection is usually bacteremic in the age group in whom the meninges are susceptible to inoculation, using an advanced-generation cephalosporin





**Figure 319-5** A 10-month-old with bacteremic periorbital cellulitis due to *Haemophilus influenzae* type b.



**Figure 319-6** A 3-year-old child with inflammatory edema caused by ethmoiditis.

such as ceftriaxone (100 mg/kg/day, divided into 12-hour doses or given once daily) may be prudent. This regimen is appropriate for immunized and nonimmunized children. A lumbar puncture should be performed unless the clinical picture precludes meningitis. Addition of vancomycin (60 mg/kg/day divided into doses every 6 hours) is appropriate if cerebrospinal fluid pleocytosis is present. When the evidence of a local infection has resolved and no meningitis is present, oral antimicrobial therapy is prescribed to complete a 10-day course.

### Preseptal (Periorbital) Cellulitis Caused by Inflammatory Edema of Sinusitis

Several complications of paranasal sinusitis can result in swelling around the eye. The most common and least serious complication is often referred to as *inflammatory edema* or a *sympathetic effusion*. This entity is a form of preseptal cellulitis, although infection is confined to the sinuses.

Typically, a child who is at least 2 years old has had a viral URI for several days when swelling is noted. A history of intermittent early-morning periorbital swelling that resolves after a few hours is often present. On the day of presentation, the eyelid swelling does not typically resolve but progresses gradually (Figure 319-6). Surprisingly, striking degrees of erythema can also be present. Eye pain and tenderness are variable. Eyelids can be very swollen and difficult to evert, requiring the assistance of an ophthalmologist. However, no displacement of the globe or impairment

of extraocular eye movements occurs. Fever, if present, is usually low grade.

The peripheral white blood cell count is unremarkable. Blood culture results are always negative. If a tissue aspiration is performed, culture of the specimen has a negative result. Sinus radiographs show ipsilateral ethmoiditis or pansinusitis. The age of the child, gradual evolution of lid swelling, and modest temperature elevation differentiate inflammatory edema from the uncommon case of bacteremic periorbital cellulitis.

The pathogenesis of sympathetic effusion or inflammatory edema is attributable to the venous drainage of the eyelid and surrounding structures. The inferior and superior ophthalmic veins, which drain the lower lid and upper lid, respectively, pass through or just next to the ethmoid sinus. When the ethmoid sinuses are completely congested, physical impedance of venous drainage occurs, resulting in soft-tissue swelling of the eyelids, maximal at the medial aspect of the lids. In this instance, infection is confined within the paranasal sinuses. The globe is not displaced, and no impairment of the extraocular muscle movements occurs. However, inflammatory edema is part of a continuum, with more serious complications resulting from the spread of infection outside the paranasal sinuses into the orbit. Infection rarely progresses despite the initial optimal management of sympathetic effusions.

The infecting organisms in cases of inflammatory edema are the same as those that cause uncomplicated acute sinusitis (ie, *S pneumoniae*, nontypeable *H influenzae*, *Moraxella catarrhalis*). Antibiotic therapy can





**Figure 319-7** A 12-year-old boy with orbital cellulitis. He had a 5-day history of eye pain and progressive swelling of the eyelids, which were markedly erythematous. When his eyelids were retracted, anterior and lateral displacement of the globe and impairment of upward gaze were noted.

be given orally if, at the time of the first examination, the eyelid swelling is modest, the child does not look toxic, and the parents will adhere to management. Amoxicillin-clavulanate at 90 mg/kg/day in 2 divided doses is preferred to provide the most comprehensive coverage. Otherwise, admission to the hospital and parenteral treatment should be undertaken.

The only source of bacteriologic information is that obtainable by maxillary sinus aspiration, which is usually not performed. Appropriate agents for outpatient therapy have activity against  $\beta$ -lactamase-producing organisms (eg, amoxicillin-potassium clavulanate, cefuroxime axetil, cefpodoxime proxetil). Parenteral agents include ceftriaxone and ampicillin-sulbactam. The latter combination, although not approved for children younger than 12 years, is an attractive choice. Although the use of topically applied intranasal decongestants such as oxymetazoline has not been systematically evaluated, such agents may be helpful during the first 48 hours. After several days, once the affected eye has returned to near normal, an oral antimicrobial agent is substituted to complete a 10- to 14-day course of therapy.

### ORBITAL INFECTIONS

The child or adolescent with true orbital disease secondary to sinusitis usually has a sudden onset of erythema and swelling about the eye after several days of a viral URI (Figure 319-7). Eye pain can precede

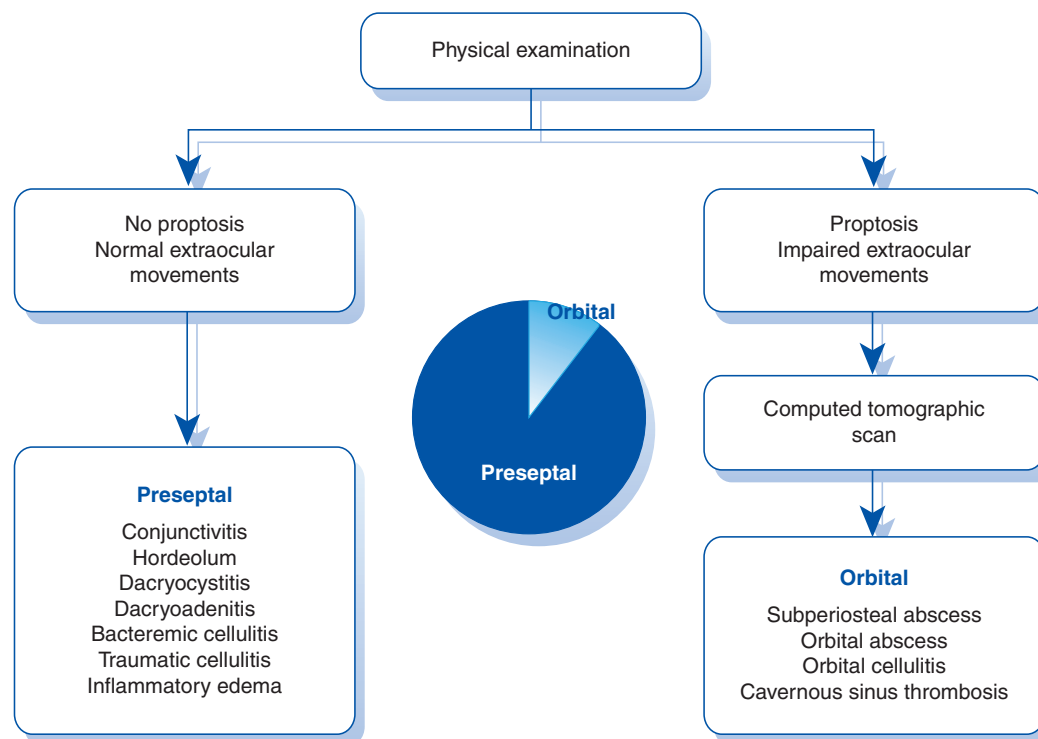


**Figure 319-8** Axial computed tomography scan shows a subperiosteal abscess extending from the right ethmoid sinus.

swelling and is often dramatic. The presence of fever, systemic signs, and toxicity is variable. Orbital infection is suggested by proptosis (with the globe displaced usually anteriorly and downward), impairment of extraocular eye movements (most often upward gaze), chemosis (edema of the bulbar conjunctiva), or, late in the evolution of the infection, loss of visual acuity or decreased pupillary reaction. Fortunately, orbital infection is the least common cause of the swollen eye.

Most orbital infections involve the formation of a subperiosteal abscess that, in young children, results from ethmoiditis and ethmoid osteitis. In the adolescent, subperiosteal abscess can be a complication of frontal sinusitis and osteitis. Orbital cellulitis rarely evolves, without formation of subperiosteal abscess, by direct spread from the ethmoid sinus to the orbit via natural bony dehiscences in the bones that form the medial wall of the orbit.

Imaging studies are usually performed if orbital disease is suspected. They help determine if subperiosteal abscess, orbital abscess, or orbital cellulitis is the cause of the clinical findings (Figure 319-8). In the presence of a large, well-defined abscess, complete ophthalmoplegia or impairment of vision prompts



**Figure 319-9** Algorithm for the differential diagnosis of the swollen eye.

the operative drainage of the paranasal sinuses and the abscess. Several studies have reported on the successful drainage of a subperiosteal abscess via endoscopy. This method, performed through an intranasal approach, has been successful, thereby avoiding an external incision. In many cases, a well-defined abscess is not seen. Instead, inflammatory tissue is observed interposed between the lateral border of the ethmoid sinus and the swollen medial rectus muscle. Usually, children with these symptoms are managed successfully with antimicrobial therapy alone as are children with small orbital abscesses. On occasion, the CT scan can be misleading, suggesting an abscess when inflammatory edema is present; accordingly, the clinical course is the ultimate guide to management.

Empirical antimicrobial therapy should be chosen to provide activity against *S aureus*, *S pyogenes*, *Streptococcus anginosus*, and anaerobic bacteria of the upper respiratory tract (anaerobic cocci, *Bacteroides* species, *Prevotella* species, *Fusobacterium* species, and *Veillonella* species) in addition to the usual pathogens associated with acute sinusitis (ie, *S pneumoniae*, *H influenzae*, and *M catarrhalis*). Appropriate selections include ceftriaxone (100 mg/kg/day given as a single daily dose) or ampicillin-sulbactam (200 mg/kg/day divided into doses every 6 hours) plus vancomycin. Immunocompromised children and diabetic children are at a higher risk of fungal orbital cellulitis (especially *Mucor* species). If surgery is performed, then a Gram stain of material drained from the sinuses or the abscess guides the consideration

of additional drugs or an altered regimen. When the final results of the culture are available, antibiotic therapy may be changed, if appropriate. Intravenous therapy is maintained until the infected eye appears nearly normal. At that time, oral antibiotic therapy can be substituted to complete a 2-week course of treatment.

## SUMMARY

The child with a swollen eye is commonly seen in primary care. Figure 319-9 depicts an approach to diagnosis depending on physical examination. By far, children with preseptal infections are most common.

## WHEN TO REFER

Refer a child with a swollen eye to an ophthalmologist in the following instances:

- When visual acuity is compromised
- When any eyelid swelling occurs in an immunocompromised child or a child with diabetes; referral should be immediate because this situation may require urgent treatment
- If conjunctivitis is the diagnosis and if the clinical findings do not begin to improve after 5 days; this circumstance suggests a diagnosis of either adenovirus or herpes simplex infection
- When a chalazion is large and causes local irritation because incision and drainage of the chalazion may be required
- When dacryoadenitis has not begun to resolve after 5 days

**WHEN TO ADMIT**

Hospitalize a child with a swollen eye in the following instances:

- Diagnosis bacteremic periorbital cellulitis, for parenteral therapy
- Diagnosis of likely bacterial cellulitis is made, for parenteral therapy when the process is extensive, the child is febrile, or the child is younger than 5 years
- Diagnosis is dacryocystitis, for parenteral therapy and consultation with an ophthalmologist
- Oral therapy failed
- Eye is swollen shut and parenteral antibiotics and close observation are required for the management of inflammatory edema (sympathetic effusion)
- Proptosis, impairment of extraocular movements, diminished pupil reaction, or loss of visual acuity occurs; these situations are the herald signs of subperiosteal abscess, orbital abscess, orbital cellulitis, and cavernous sinus thrombosis, and their presence indicates the need for parenteral antibiotics and the likely need for surgical intervention

**TOOLS FOR PRACTICE****Engaging Patient and Family**

- *What Is a Pediatric Ophthalmologist?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Ophthalmologist.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Ophthalmologist.aspx))

**Medical Decision Support**

- *Pediatric Ophthalmology for Primary Care*, 3rd ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *The Physician's Guide to Eye Care*, 4th ed (book), American Academy of Ophthalmology

**AAP POLICY**

American Academy of Pediatrics Committee on Practice and Ambulatory Medicine and Section on Ophthalmology, American Association of Certified Orthoptists, American Association for Pediatric Ophthalmology and Strabismus, American Academy of Ophthalmology. Eye examination in infants, children, and young adults by pediatricians. *Pediatrics*. 2003;111(4):902–907. Reaffirmed May 2007 ([pediatrics.aappublications.org/content/111/4/902](http://pediatrics.aappublications.org/content/111/4/902))

American Academy of Pediatrics Committee on Sports Medicine and Fitness. Protective eyewear for young athletes. *Pediatrics*. 2004;113(3):619–622. Reaffirmed February 2015 ([pediatrics.aappublications.org/content/113/3/619](http://pediatrics.aappublications.org/content/113/3/619))

Wald ER, Applegate KE, Bordley C, et al. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. *Pediatrics*. 2013;132(1):e262–e280 ([pediatrics.aappublications.org/content/132/1/e262](http://pediatrics.aappublications.org/content/132/1/e262))

**SUGGESTED READINGS**

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**Chapter 320**  
**PSORIASIS**

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Psoriasis is a T cell–mediated chronic inflammatory disease that is characterized clinically by well-demarcated, erythematous plaques with an overlying silvery-white scale. Psoriasis affects approximately 2% of the adult population, and 31% to 45% of affected adults noted onset during childhood. While psoriasis can occur as early as infancy, the incidence of pediatric psoriasis increases with age, with an overall annual incidence of 48/100,000 and an estimated prevalence of 0.7% to 1.5%.

Psoriasis is reportedly more common in girls than boys, with a female:male ratio approaching 2:1, although in some studies, no sex predilection was found. Childhood- and adult-onset psoriasis occur more often in the white population compared to the black, Asian, and Native-American populations.

Both genetic and environmental factors play a role in the development of psoriasis. Childhood psoriasis has been associated with a family history of psoriasis in first-degree relatives. The human leukocyte antigen (HLA) Cw6 allele is the strongest genetic link to early-onset psoriasis and guttate psoriasis. Genes involved in IL-23 (*IL-12B*, *IL-23R*, *IL-23A*), Tumor necrosis factor- $\alpha$  (*TNF- $\alpha$* ) (*TNFAIP3*, *TNIP1*) signaling pathways, and TH2 cytokines (*IL4/13*) have also been implicated through large-scale genome-wide association studies. Environmental triggers that likely precipitate or exacerbate childhood psoriasis include streptococcal infections, upper respiratory infections, trauma, and psychological stress.

**CLINICAL VARIANTS OF PSORIASIS**

Psoriasis can occur as one of several types (see summary in Table 320-1). Plaque-type psoriasis is the most common type of psoriasis in both adults and children. Plaque psoriasis usually produces large, erythematous, well-circumscribed plaques covered by the characteristic silvery-white psoriatic scale (Figure 320-1 and Figure 320-2). Presentations vary from solitary lesions to widely distributed plaques. The scalp, elbows, knees, and lumbosacral regions are the most commonly affected areas, often with bilateral symmetry (Figure 320-3, Figure 320-4, and Figure 320-5). The scalp is one of the most frequently involved sites in children and may be misdiagnosed as seborrheic



**Table 320-1** Psoriasis Variants

VARIANT OF PSORIASIS	MORPHOLOGY	DISTRIBUTION
Plaque psoriasis	Large erythematous plaques with overlying silvery-white or grayish scale	Scalp, face, elbows, knees, lumbosacral area, gluteal crease, umbilicus
Inverse psoriasis	Bright-red glazed erythema with minimal to no scale	Diaper area, axillae, groin, postauricular area
Pustular psoriasis	Widespread bright-red erythema studded with 1- to 2-mm pustules; deep-seated 2- to 4-mm pustules in areas of erythema and scaling	Widespread; especially flexural areas, genitals, finger webs, palms, and soles
Erythrodermic psoriasis	Bright-red erythema with massive exfoliation	Widespread



**Figure 320-1** Plaque psoriasis. Large, well-circumscribed plaque covered by silvery-white scale.



**Figure 320-2** Plaque psoriasis on the penis and scrotum.

dermatitis or tinea capitis (Figure 320-6). Facial psoriatic lesions, especially around the eyes, are more common in affected children and may be the only involved site.

Inverse psoriasis—psoriasis that involves intertriginous areas such as the postauricular area, axillae, groin, and the genital and perianal areas—is also common in children. Inverse psoriasis tends to produce a glazed, bright-red erythema, sometimes with fissuring, and the characteristic psoriatic scale is usually



**Figure 320-3** Thin psoriatic plaques on the knees.



**Figure 320-4** Psoriasis involving the gluteal cleft.

absent (Figure 320-7). Psoriatic diaper rash can be the initial presentation of psoriasis in children younger than 2 years and can be difficult to differentiate from other causes of diaper dermatitis.

Guttate psoriasis is more commonly seen in children and adolescents than in adults, and it can be the first manifestation of psoriasis. In guttate psoriasis, the lesions tend to be 2 to 10 mm in size, widespread, and symmetrically distributed. They are round or oval erythematous papules and plaques with a silvery-white scale, often with a predilection for the trunk and proximal extremities (Figure 320-8 and Figure 320-9). Guttate psoriasis can be triggered by





**Figure 320-5** Plaques of linear psoriasis on the shin.



**Figure 320-6** Tinea amiantacea. Scales are thick and strongly adherent, encasing the underlying hair, producing an asbestos-like appearance. This can be a feature of seborrheic or atopic dermatitis but is most commonly associated with psoriasis of the scalp.



**Figure 320-7** Diaper area psoriasis (inverse psoriasis) with bright-red, glazed erythema. Note the absence of the characteristic scale.



**Figure 320-8** Guttate psoriasis. Note the small, droplike plaques.



**Figure 320-9** Guttate psoriasis. Guttate psoriasis has a predilection for the trunk and proximal extremities.



**Figure 320-10** Pustular psoriasis. Pink plaques studded with superficial (subcorneal) pustules.

group A streptococcal infection of the oropharynx and perianal skin, but in some cases an inciting infection is never found.

Childhood pustular psoriasis is rare, but it can be the first manifestation of psoriasis in infants and children. The cause of pustular psoriasis in children is unknown, but several triggers have been implicated, including dental and upper respiratory tract infections, streptococcal infection, withdrawal of systemic corticosteroids, and vaccinations. In addition, experts have postulated that a relationship exists between a history of severe seborrheic dermatitis and the development of pustular psoriasis. Pustular psoriasis can be limited to the palms and soles (palmoplantar pustular psoriasis), but it more commonly occurs as an explosive generalized eruption of pustules on psoriatic plaques or on previously normal skin (generalized pustular psoriasis). These patients develop extensive areas of bright erythema studded with sterile pustules (Figure 320-10), sometimes associated with fever and malaise. The pustules coalesce into lakes, followed by extensive desquamation. Mucous membrane and nail involvement occasionally occurs. Palmoplantar pustular psoriasis and generalized pustular psoriasis tend to follow a chronic, cyclic course, with unexplained exacerbations and remissions, but are generally benign.

Erythrodermic psoriasis is rare in children. It is characterized by diffuse erythema, exfoliation, and decreased ability to regulate body temperature. This type of psoriasis can be complicated by electrolyte imbalances, cardiovascular compromise, and sepsis, and it is considered a dermatologic emergency.



**Figure 320-11** Nail psoriasis. Mild involvement with discoloration, onycholysis, and pitting.

Many children with psoriasis have nail involvement (Figure 320-11). Nail pitting, the most characteristic finding, is best described as multiple, small, irregularly spaced depressions in the nail plate. Other nail findings in psoriasis include discoloration, onycholysis (distal separation of the nail from the nail bed), longitudinal striations, and subungual hyperkeratosis. Evaluation for characteristic nail changes can help in the diagnosis of psoriasis when it is otherwise not apparent.

## COMORBIDITIES

Juvenile psoriatic arthritis (JPsA) is uncommon in children. It can occur with either plaque or guttate psoriasis, and in 80% of individuals, skin lesions precede the onset of psoriatic arthritis. The clinical presentation of JPsA is similar to that seen in juvenile idiopathic arthritis (JIA), and JPsA is thought to be a subset of JIA with specific criteria defined by the International League of Associations for Rheumatology. Individuals must have both arthritis and psoriasis or arthritis with at least 2 associated features (nail pitting or onycholysis, dactylitis, family history of psoriasis in a first-degree relative), and other subsets (eg, systemic JIA, rheumatoid factor–positive disease, enthesitis-related arthritis) must be excluded. Like JIA, JPsA most commonly presents with oligoarticular disease affecting the knees and ankles; however, involvement of the wrists and small joints of the hands (distal interphalangeals) and feet, along with the presence of a bluish discoloration over affected joints, may help distinguish between these entities. Early-onset JPsA (ages 2–3 years) is more often seen in females and is associated with anterior uveitis and antinuclear antibodies positivity, while late-onset JPsA (ages 10–12 years), may present with enthesitis and axial disease and is linked to patients with HLA-B27 haplotype.

An association between cardiovascular disease and psoriasis has been established in adults. Recent evidence also indicates that children with psoriasis have a higher rate of obesity, dyslipidemia, hypertension, and diabetes mellitus compared to their peers. Further studies are needed to determine whether this is a result of chronic systemic inflammation or whether



it is caused by associated risk factors; however, it is important to consider monitoring for metabolic disease in these high-risk children.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for plaque psoriasis includes other papulosquamous disorders such as atopic dermatitis (AD) and pityriasis rubra pilaris (PRP). Compared to the lesions of AD, psoriatic plaques tend to be more clearly demarcated from the surrounding uninvolved skin and are usually less pruritic than AD lesions. In addition, AD lesions lack the characteristic silvery-white scale of psoriasis. Psoriasis generally tends to localize to the extensors, whereas AD preferentially affects flexural areas. However, some children do exhibit a psoriasis-AD overlap.

Juvenile PRP can be the most difficult condition to differentiate from psoriasis. However, in addition to biopsy findings, the classic salmon color of PRP lesions, the focal areas of sparing, and follicular accentuation help clinically distinguish this condition from psoriasis.

Pustular psoriasis may be confused with infectious pustular eruptions, such as disseminated candidiasis or staphylococcal scalded skin syndrome. A skin biopsy, Gram stain, and culture of the contents of several pustules can help differentiate these conditions from pustular psoriasis. Noninfectious pustular eruptions, such as pustular drug eruptions, may also mimic pustular psoriasis. The history of a recently started medication and a skin biopsy can sometimes help differentiate between pustular psoriasis and a pustular drug eruption. While the histopathological distinction between these entities is often challenging, the presence of eosinophils and necrotic keratinocytes suggests a pustular drug eruption, while tortuous blood vessels and psoriasiform epidermal hyperplasia point to the diagnosis of pustular psoriasis.

The differential diagnosis of psoriatic diaper rash and other forms of inverse psoriasis includes seborrheic dermatitis, Langerhans cell histiocytosis, candidal intertrigo, and contact dermatitis.

Scalp psoriasis may be mistaken for tinea capitis or seborrheic dermatitis. Performing a potassium-hydroxide preparation and a fungal culture of the scale is important to rule out tinea capitis, because the treatment for scalp psoriasis (topical corticosteroids) can exacerbate tinea capitis. In contrast to seborrhea, scalp psoriasis is more likely to present with discrete, well-defined, thicker white scaly plaques, lack greasy scale, and extend onto the forehead, posterior neck, and retroauricular areas.

In guttate psoriasis, the differential diagnosis includes pityriasis rosea, tinea corporis, pityriasis lichenoides, and secondary syphilis.

The nail changes seen in psoriasis can also be seen in other conditions. For example, nail pitting can also be seen in alopecia areata, and nail discoloration, onycholysis, and subungual hyperkeratosis are also features of onychomycosis.

Box 320-1 lists issues to address when evaluating a child suspected of having psoriasis. Laboratory tests important in diagnosing psoriasis are summarized in Table 320-2.

BOX 320-1 Issues to Address When Evaluating a Child Suspected of Having Psoriasis

- Family history of psoriasis
- Recent history of streptococcal throat or perianal infection
- Current medications
- Frequency and duration of eruptions
- Tendency for lesions to appear on traumatized skin (eg, sunburned, scratched, tattooed) (Koebner phenomenon)
- Nail changes (eg, nail pitting)
- Behavior of lesions in response to UV light
- Joint pains
- Previous treatment modalities and their efficacy

UV, ultraviolet.

Table 320-2 Laboratory Testing in Diagnosing Psoriasis

LABORATORY TEST	REASON
Bacterial culture of oropharynx and perianal area; antistreptolysin titer	Rule out streptococcal infection, especially in guttate psoriasis; may play a role in pustular psoriasis
Potassium hydroxide preparation of scale	Rule out fungal infection, especially in scalp psoriasis and annular lesions
Skin biopsy	Confirm clinical diagnosis of psoriasis, especially in atypical presentations

MANAGEMENT

One of the most important considerations in the management of psoriasis in children is the psychosocial impact of the disease on the affected child and the child’s family. Psoriasis can adversely effect the quality of life in children, and its effect is comparable to that of other chronic childhood diseases. Furthermore, a psychological disease is diagnosed and treated more often in pediatric patients with psoriasis compared to psoriasis-free controls. Thus, emphasis must be placed on educating the child, siblings, and parents, as well as teachers and classmates, about the nature of psoriasis. Affected families should be provided with information about available psoriasis support groups. In addition, psychological counseling should be sought to equip these children with effective coping skills for this chronic and potentially disfiguring disease.

Another important consideration in the management of psoriasis is the identification and elimination of potential triggers. Streptococcal infection, medications (eg, lithium, beta blockers, interferon, TNF-alpha inhibitors, systemic corticosteroids), stress, and skin

trauma are known triggering or exacerbating factors in psoriasis. Children and their parents must be educated about the so-called Koebner phenomenon, or the development of psoriasis lesions in areas of trauma to the skin such as lacerations, surgical incisions, piercings, tattoos, or sunburns.

### Topical Therapy

The topical agents most commonly used to treat psoriasis in children include topical corticosteroids, calcipotriol, tar preparations, and anthralin. Less commonly used topical therapies include keratolytic agents such as salicylic acid, topical retinoids, and topical calcineurin

inhibitors. Bland emollients, such as petrolatum, are an essential part of the skin care regimen in affected children. Moisturization and application of emollients lessens the dryness and scaling associated with psoriasis and, in some cases, emollients alone may be sufficient to improve mild psoriasis. However, in most children, emollients should be used as adjunctive therapy to anti-inflammatory topical medications. Table 320-3 summarizes treatment for children with psoriasis.

### Topical Corticosteroids

Medium- to high-potency (classes II–IV) corticosteroid ointments are effective as monotherapy in many cases

**Table 320-3** Treatment of Psoriasis in Children

AGENT	USE	SIDE EFFECTS AND COMMENTS	EXAMPLES
<b>TOPICAL AGENTS</b>			
Emollients	Decrease dryness and scaling; useful in mild psoriasis; use as adjunctive therapy in more severe disease	<ul style="list-style-type: none"> <li>No side effects</li> <li>Should not replace medicated topicals in children with significant disease</li> </ul>	<ul style="list-style-type: none"> <li>Petroleum jelly</li> <li>Aquaphor ointment</li> <li>Theraplex emollient</li> </ul>
Topical corticosteroids	First-line therapy for all types of psoriasis; apply twice daily for 1–2 weeks, then 2–3 days per week (eg, weekends) for maintenance	<ul style="list-style-type: none"> <li>Possible cutaneous side effects: atrophy, striae, telangiectasia</li> <li>Possible systemic side effects: hypothalamic-pituitary-adrenal axis suppression, growth impairment, cataracts, glaucoma</li> <li>Avoid use of high-potency preparations on face and intertriginous areas</li> <li>Ointment is the preferred vehicle when treating psoriasis because of occlusive effect and increased potency; useful for dry, scaly lesions</li> <li>Gels readily absorbed; useful in hairy areas, but can cause dryness and irritation</li> <li>Creams rub in well and are aesthetically pleasing; may be less potent than ointment form of same drug</li> <li>Foams, solutions, and oils can be used on the scalp</li> </ul>	<ul style="list-style-type: none"> <li>Class 1 (ultrapotent) <ul style="list-style-type: none"> <li>Clobetasol propionate 0.05%</li> <li>Betamethasone dipropionate 0.05%</li> </ul> </li> <li>Class 2 and 3 (medium to high potency) <ul style="list-style-type: none"> <li>Fluocinonide 0.05%</li> <li>Betamethasone valerate 0.1%</li> <li>Triamcinolone ointment 0.1%</li> </ul> </li> <li>Class 4/5 (medium potency) <ul style="list-style-type: none"> <li>Hydrocortisone valerate 0.2%</li> <li>Mometasone 0.1% cream</li> </ul> </li> <li>Class 6/7 (low potency) <ul style="list-style-type: none"> <li>Hydrocortisone (all concentrations)</li> <li>Desonide 0.05% cream, gel and foam</li> </ul> </li> </ul>
Calcipotriol or calcipotriene	Useful alone in limited disease; useful adjunct to corticosteroids; apply once to twice daily	Irritation	<ul style="list-style-type: none"> <li>Dovonex cream or solution</li> <li>Vectical ointment</li> <li>Calcitrene ointment</li> </ul>
Coal tar preparations	Useful for thicker plaques; apply once to twice daily	<ul style="list-style-type: none"> <li>Irritation, staining, unpleasant odor, folliculitis</li> <li>Increased risk of irritation on face and intertriginous areas</li> </ul>	<ul style="list-style-type: none"> <li>LCD in combination with emollients or corticosteroids</li> <li>Liquid form in bath</li> </ul>
Anthralin	Short-contact therapy; large, thick plaques; apply for 10 minutes, then increase duration as tolerated once daily	Irritation, staining	Dithrocream 1%



**Table 320-3** Treatment of Psoriasis in Children—cont'd

AGENT	USE	SIDE EFFECTS AND COMMENTS	EXAMPLES
Topical calcineurin inhibitors	Useful for lesions on the face, genitals and intertriginous areas; apply twice daily as needed	<ul style="list-style-type: none"> <li>Occasional burning or itching with first few applications</li> <li>FDA black-box warning (theoretical malignancy risk based on oral forms)</li> </ul>	<ul style="list-style-type: none"> <li>Protopic (tacrolimus) ointment 0.03% or 0.1%</li> <li>Elidel (pimecrolimus) cream 1%</li> </ul>
Topical retinoids (tazarotene)	Useful in limited, mild to moderate disease; apply once daily (every night at bedtime)	<ul style="list-style-type: none"> <li>Dryness, local irritation</li> <li>Pregnancy category X (tazarotene)</li> </ul>	Tazorac cream or gel 0.05% or 0.1%
<b>PHOTOTHERAPY</b>			
Psoralens plus UVA	Rarely used in children	Cataracts, skin aging, skin cancer, expensive, inconvenient	Methoxsalen
UVB	Widespread psoriasis	Expensive, inconvenient, skin aging; difficult for younger children	<ul style="list-style-type: none"> <li>Broadband UVB</li> <li>Narrow band UVB (preferred)</li> </ul>
<b>SYSTEMIC AGENTS</b>			
Methotrexate	Recalcitrant widespread psoriasis; erythrodermic psoriasis, pustular psoriasis, psoriatic arthritis	Bone marrow toxicity, nausea, vomiting, fatigue, oral ulcers, hepatotoxicity	—
Cyclosporine	Recalcitrant widespread psoriasis; erythrodermic psoriasis, pustular psoriasis	Renal toxicity, hepatic toxicity, hypertension, hypertrichosis, gingival hyperplasia, immunosuppression	Neoral
Oral retinoids	Erythrodermic psoriasis, pustular psoriasis	<ul style="list-style-type: none"> <li>Cheilitis, xerosis, skin fragility, hypertriglyceridemia, skeletal abnormalities</li> <li>Avoid in adolescent girls (teratogenicity)</li> <li>Injection site reactions</li> <li>Immunosuppression and potential risk of malignancy</li> <li>Live vaccination should be avoided; caution in children with congestive heart failure (anti-TNF-<math>\alpha</math>), multiple sclerosis (anti-TNF-<math>\alpha</math>), tuberculosis risk factors</li> </ul>	Acitretin
Biologic agents (anti-TNF- $\alpha$ and anti-IL-12/23)	Severe generalized, recalcitrant psoriasis in older children; psoriatic arthritis		Etanercept, adalimumab, infliximab, ustekinumab

FDA, Food and Drug Administration; LCD, liquor carbonis detergens; TNF, tumor necrosis factor; UVA, ultraviolet A.

of childhood psoriasis. Ultrapotent (class I) corticosteroid ointments are reserved for unresponsive, thick psoriatic plaques and may be used with occlusion if necessary (eg, plastic wrap placed over topical corticosteroid on an extremity). Continuous twice-daily treatment should not last for more than 2 weeks; after 2 weeks, intermittent application (2–3 days per week) may be used for maintenance therapy. Long-term use of topical corticosteroids can lead to side effects such as striae, atrophy, telangiectasia, tachyphylaxis, and acne. When used over a large body surface area, topical corticosteroids may rarely cause pituitary-adrenal axis suppression and other systemic side effects.

Hydrocortisone 2.5% can be used for facial psoriasis, but this may be ineffective in many children. For lesions on the trunk and extremities, medium- to high-potency corticosteroids tend to be more effective. The continuous use of corticosteroids in the groin or other intertriginous areas should be avoided.

For lesions on the scalp, liquid or foam corticosteroid preparations (eg, clobetasol foam, clobetasol solution, fluocinonide solution) work well, as do corticosteroid, tar, zinc, or salicylic acid shampoos. However, parents should be warned that these products might cause dryness of the hair and scalp. The alcohol base in foam and gel preparations may also cause stinging, especially on excoriated or otherwise irritated lesions.

The nighttime application of oils, such as fluocinolone, or nonsteroid oils, such as olive, mineral, or soybean oil, can be a useful adjunct in treating scalp psoriasis in older children. These preparations can be applied to the scalp at night to loosen adherent scale and then shampooed out in the morning. The addition of low concentrations of salicylic acid (5%–6%) with or without tar (5% liquor carbonis detergens) can be effective in decreasing scale when used for 1 to 2 weeks prior to starting a topical steroid regimen. Some black

patients prefer oilier scalp preparations, such as lotions, ointments, or oils, rather than the foams or gels because the former preparations also lubricate the hair, preventing brittleness and breakage.

### **Calcipotriol (Calcipotriene)**

Calcipotriol is a vitamin-D analog that is safe and effective in treating psoriasis in children. It can be used twice a day as monotherapy in limited disease or as an adjunct to topical corticosteroids in more severe disease. The ointment form is suitable for use on any affected area, but it is more likely to cause burning and irritation on the face or groin. Calcipotriol is also available in a cream and a liquid form for use on the scalp. Calcium homeostasis is not affected by topical calcipotriene in otherwise healthy adults, with the recommended dose of 100 g ointment/week (or approximate equivalent of <50 g ointment/m<sup>2</sup>/week in children). A topical combination preparation of calcipotriene 0.005% and betamethasone dipropionate 0.064% (ointment and suspension) was approved by the US Food and Drug Administration (FDA) for children (12–17 years) for treating psoriasis (maximum 60 g suspension per week).

### **Tar Preparations**

Tar preparations can be used in an emollient base (eg, liquor carbonis detergens 5% in petrolatum) or in combination with topical corticosteroids. However, the undesirable odor and potential for staining make it difficult for children and adolescents to accept.

### **Anthralin**

Short-contact anthralin therapy can be a useful adjunct in treating thick, stubborn plaques. In short-contact therapy, anthralin 1% is applied for 10 minutes, with increasing contact time with subsequent treatments as tolerated. Side effects include local irritation and brownish staining of the skin, bathtubs, and sinks.

### **Topical Calcineurin Inhibitors**

Topical calcineurin inhibitors (tacrolimus and pimecrolimus) are preferred to topical corticosteroids for both facial and intertriginous psoriasis in children. Because the substance does not penetrate thicker plaques well, it is not particularly efficacious in other body sites. The most common adverse effect is burning with initial application, but the topical calcineurin inhibitors are generally well tolerated. Parents must be informed of the FDA black-box warning about a theoretical risk of skin cancer and lymphoma that is associated with oral forms of this medication class. These concerns are being evaluated, and currently there is no statistically significant increase in either adverse event.

### **Topical Retinoids**

The topical retinoid tazarotene can be useful in treating limited (<20% body surface area), mild to moderate psoriasis. It is FDA approved in adults with psoriasis and children with acne (>12 years of age). The most common side effect is local irritation. Tazarotene is a potential teratogen and should be used with caution in adolescent girls.

### **Phototherapy**

In older children, ultraviolet (UV) B (UVB) phototherapy may be used in conjunction with topical or systemic therapy; however, it has been shown to be well tolerated and efficacious in treating psoriasis in children as young as 3 months. The most significant short-term adverse effect associated with UVB is temporary erythema and pruritus. Narrow-band UVB (311–313 nm) can clear plaques with lower amounts of UV light and will typically achieve clearance or near complete clearance over the course of approximately 25 treatments when administered 3 times weekly. The long-term safety of UVB phototherapy in children is still unknown; however, in contrast to psoralen-UVA, the risk of skin cancer from UVB appears to be negligible. As a rule, oral psoralen plus UVA should not be administered in preadolescent children.

Goeckerman therapy is a combination of daily full body crude tar application and daily UVB treatments for 2 to 3 weeks. While this treatment is safe and effective, leading to mean remission of longer than 2 years, there are very few inpatient dermatology centers or day-hospitals in the United States that offer this option.

Excimer (308-nm) laser can be used to deliver high-dose UVB to localized plaques while sparing surrounding normal skin. There is little data regarding its use in children but it is well tolerated and efficacious in adults, requiring fewer treatments than full body UVB, and may be an option for focal disease.

### **Systemic Therapy**

Systemic treatment is indicated for severe forms of psoriasis, such as extensive plaque psoriasis, generalized pustular psoriasis, erythrodermic psoriasis, and psoriatic arthritis. However, because these forms of psoriasis are uncommon in children, clinical experience is limited in the use of systemic agents in treating childhood psoriasis. Methotrexate, oral retinoids, cyclosporine, and biologic agents have all been used in children with varying degrees of success.

### **Methotrexate**

Although methotrexate is extensively used in treating psoriasis in adults and JIA in children, its use in children with pediatric psoriasis is less common, though its efficacy and safety in this population have been demonstrated in short-term use. The side effects of methotrexate include nausea, vomiting, fatigue, oral ulcers, bone marrow toxicity, and hepatic fibrosis, and its use necessitates monitoring the child's complete blood count and liver function tests.

According to the most current guidelines, a liver biopsy after prolonged use is typically unnecessary in low risk children without lab abnormalities; furthermore, in the pediatric population, where alcohol intake and hepatitis are uncommon, clinically significant hepatotoxicity is rare. Methotrexate is administered orally or subcutaneously once weekly (0.3–0.5 mg/kg/week), typically on the weekend to avoid nausea and fatigue during school hours. The use of folic acid to reduce adverse effects, primarily gastrointestinal upset and oral ulcers, is controversial, but folic acid may be given (1 mg/day) without reducing methotrexate efficacy.

### Systemic Retinoids

Systemic retinoids (eg, acitretin, isotretinoin) have been studied in children with keratinization disorders but have not been studied in childhood psoriasis. Children with generalized pustular psoriasis have been treated successfully with acitretin. The most frequently encountered side effects are pruritus, cheilitis, and skin fragility. Chronic use of systemic retinoids has been associated with ossification of interosseous ligaments and tendons, skeletal hyperostosis, and premature epiphyseal closure, leading to concerns that retinoids might affect growth in children.

### Cyclosporine

Cyclosporine is FDA approved for treating severe plaque psoriasis in adults. It is not commonly used in children, primarily because of its immunosuppressive effects and inconsistent efficacy. The adverse effects associated with cyclosporine include hypertension, hypertrichosis, gingival hyperplasia, hyperlipidemia, and nephropathy. Cyclosporine use should be restricted to less than 1 year to limit toxicities.

### Biologic Agents

To date, 4 biologic therapies have been approved for the treatment of moderate to severe plaque psoriasis in adults, including TNF- $\alpha$  inhibitors etanercept (0.8 mg/kg subcutaneous injection weekly), adalimumab (20–40 mg subcutaneous injection every 2 weeks), and infliximab (5 mg/kg intravenously every 8 weeks), along with the IL-12/23 inhibitor ustekinumab (45 mg subcutaneous injection every 12 weeks in adults). While etanercept is approved for treating recalcitrant psoriasis in children younger than 6 years in Europe, it is currently approved only for treating JIA in children older than 2 years in the United States. Etanercept is the only TNF- $\alpha$  modulator that has been studied in a large, randomized, double-blind, phase III trial in children with moderate to severe plaque psoriasis and has demonstrated efficacy in children with few adverse events. The FDA approved adalimumab for the treatment of JIA for children older than 4 years and infliximab for Crohn disease and ulcerative colitis in children older than 6 years; each of these has been successfully used in case reports of children with recalcitrant psoriasis. There is a single case report demonstrating successful use of ustekinumab in an adolescent with psoriasis; further trials are underway in Europe.

Interestingly, anti-TNF- $\alpha$  therapy can induce new-onset psoriasis in children being treated with these drugs for other indications, such as inflammatory arthritis (rheumatoid arthritis/JIA) or inflammatory bowel disease. This paradoxical phenomenon has been demonstrated in children and presents with notable scalp involvement and palmoplantar pustulosis. It is unclear if this is a class effect or if patients can be treated with alternate anti-TNF- $\alpha$  therapies. Prior to initiating biologic therapy, patients should be screened for latent tuberculosis, human immunodeficiency virus (if at risk), and hepatitis. Complete blood count and hepatic function should also be evaluated at baseline and during treatment. In addition to immunosuppression, adverse effects of anti-TNF- $\alpha$  therapy include malignancy, demyelinating disease, and worsening of congestive heart

failure. A thorough discussion of the treatment risks and benefits is required when considering biologic therapy in children.

### WHEN TO REFER

- Unresponsive to first- or second-line therapy
- Widespread disease
- Pustular psoriasis
- Erythrodermic psoriasis
- Worsening joint pains (refer to rheumatologist)

### WHEN TO ADMIT

- Widespread pustular psoriasis
- Erythrodermic psoriasis

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Resources and Tools* (Web page), National Psoriasis Foundation ([www.psoriasis.org/about-psoriasis/resources](http://www.psoriasis.org/about-psoriasis/resources))

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## Chapter 321 PYLORIC STENOSIS

Sushma Reddy, MD; Deepak M. Kamat, MD, PhD

Pyloric stenosis (PS) is among of the most common conditions requiring surgery in infancy. It is characterized by abnormal thickening of the antropyloric muscles. The intervening lumen of the pyloric channel is obstructed, causing progressive vomiting that, in turn, results in dehydration. Management of PS consists of hydration and pyloromyotomy.

### EPIDEMIOLOGICAL FEATURES

PS was recognized as a clinical entity by Hezekiah Beardsley and Harald Hirschsprung in 1887. The incidence of PS ranges from 1 to 3 per 1,000 live births. Early population-based studies reported a rise in the incidence of PS, but more recent reports indicate that the incidence seems to have leveled. Boys are affected 4 times as often as girls. However, the commonly held belief that PS primarily afflicts first-born male infants has not been confirmed. The incidence in white infants exceeds that in black, Native-American, and Asian infants. It is still unclear whether PS is an acquired or congenital entity. The onset of clinical symptoms

between 2 and 8 weeks of life is consistent with an acquired condition, whereas male predilection, familial cases, PS among twins, and an increased frequency of coexisting malformations support a genetic basis for the disease. PS is thought to be associated with the variable transmission of an inheritable trait. Transmission of the PS trait is more often from the mother compared with the father. PS develops in 5% of boys and 2.5% of girls whose fathers had PS and in 19% of boys and 7% of girls whose mothers were affected. Siblings of affected children carry a 30 times greater risk than the general population. Concordance is 0.25 to 0.44 in monozygotic twins and 0.05 to 0.1 in dizygotic twins.

## ETIOLOGY

The mechanism for hypertrophied pyloric muscle and gastric outlet obstruction is not known. It has been speculated that uncoordinated gastric peristalsis and pyloric relaxation may lead to gastric contractions against a closed pylorus, resulting in work hypertrophy of the pyloric muscle. Alterations in gastrin production, changes in breastfeeding practices, and variations in infant milk formulas are among other theories that have been proposed to explain hypertrophy of the pyloric muscle. Impaired neuronal function has been implicated in the development of PS caused by reduction in smooth-muscle vasoactive amines, neurons and nerve fibers, and interstitial *pacemaker* cells of Cajal. Investigators have proposed that deficiency of nitric oxide, a ubiquitous mediator of smooth-muscle relaxation, may be associated with the development of PS, because nitric oxide synthase is selectively depleted in the pyloric muscle of patients with PS. Studies of neuronal nitric oxide synthase gene polymorphisms suggest that this gene represents a susceptibility locus for PS.

Children with prenatal exposure to macrolides or postnatal exposure to systemic erythromycin, particularly within the first 2 weeks of life, have been observed to be at increased risk for developing PS. Postnatal prostaglandins have also been implicated in a case report.

## DIAGNOSIS

### History

Projectile, nonbilious vomiting in a full-term male infant between 3 and 6 weeks of age is a typical history associated with PS. Although the common age of symptom manifestation is 3 to 6 weeks, PS has been reported in newborns and older infants. Initially, an infant vomits a small amount of food immediately after feeding and continues to gain weight. After a few weeks, the vomiting becomes more frequent and projectile and eventually occurs after every feeding. The infant continues to be hungry immediately after vomiting. Infants with PS are usually active and alert, with lethargy ensuing only after significant dehydration. The vomitus is usually nonbilious, but may become coffee-ground with the development of gastritis and bleeding.

### Physical Examination

Physical examination reveals weight loss and dehydration. The enlarged pylorus may be felt as a firm, mobile, ovoid-shaped mass—the so-called olive. If the

infant is relaxed, then the mass can be felt in approximately 80% to 90% of cases. For this examination, the infant's feet should be elevated and the knees placed in the flexed position to relax the abdominal muscles. Two or 3 fingertips are placed in the right upper quadrant, gently advanced into the deeper tissues below the liver edge, and then slowly swept toward the umbilicus. The mass can be felt to roll under the fingertips during this sweeping motion and is usually felt to deep abdominal palpation in a quiet, cooperative infant and is almost never palpable in an agitated, crying infant with a contracted abdominal wall. The mass can be best felt immediately after an episode of projectile emesis, because at this time the pylorus is fully contracted and is at its firmest consistency. If the mass is not felt with the infant in the supine position, then palpation while the infant is lying prone may be successful. A large volume of fluid aspirated from the stomach of a fasting infant who has a history of projectile vomiting strengthens the possibility of PS. Gastric contractions, which move across the upper abdomen from left to right, may be seen in some infants. These contractions are best observed with a bright light directed across the abdomen from the infant's side, with the examiner standing at the foot of the examining table.

Although most infants with PS are otherwise healthy and genetically normal, PS has been reported with a greater frequency in infants with hiatal and inguinal hernias. Associations with malrotation, junctional epidermolysis bullosa, Hirschsprung disease, ovarian cysts, ichthyosis, Smith-Lemli-Opitz syndrome, and deletions of the long arm of chromosome 11 have also been reported.

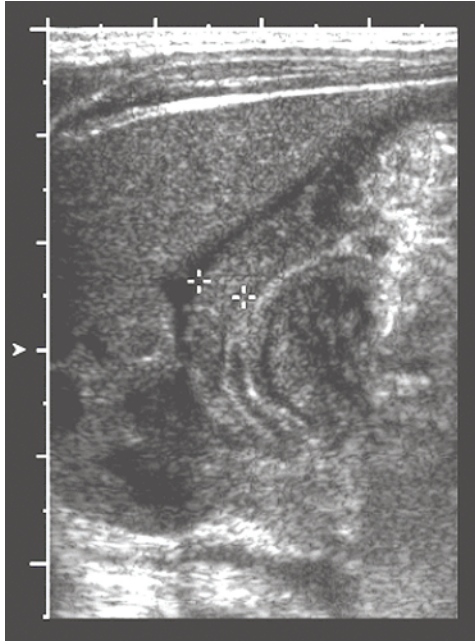
### Laboratory Studies

Persistent vomiting caused by gastric outlet obstruction results in the continuous loss of gastric hydrochloric acid. Dehydration causes an increase in aldosterone production, leading to increased renal excretion of potassium. Loss of hydrochloric acid and potassium results in a hypochloremic, hypokalemic metabolic alkalosis. The depletion of chloride in the blood leads to an exchange of hydrogen and potassium for sodium in the distal tubule, resulting in a paradoxical aciduria. However, a spectrum of electrolyte abnormalities may also be seen. Hypoglycemia may be present and may cause seizures. Unconjugated hyperbilirubinemia is common and correlates with a decrease in hepatic glucuronosyl transferase activity, which resolves after treatment.

### Imaging Studies

With a sensitivity approaching 100%, an ultrasound scan is the most useful modality to confirm the diagnosis when PS is suspected clinically, but the hypertrophied pylorus cannot be palpated. Measurement of pyloric wall thickness, diameter, and pyloric channel length accurately establishes the diagnosis of PS. A pyloric muscle wall thickness of 3.7 mm or greater and a channel length of 17 mm or greater have been shown to have a more than 90% positive predictive value (Figure 321-1). Diagnostic criteria for wall thickness may be reduced to 3 mm in infants younger than



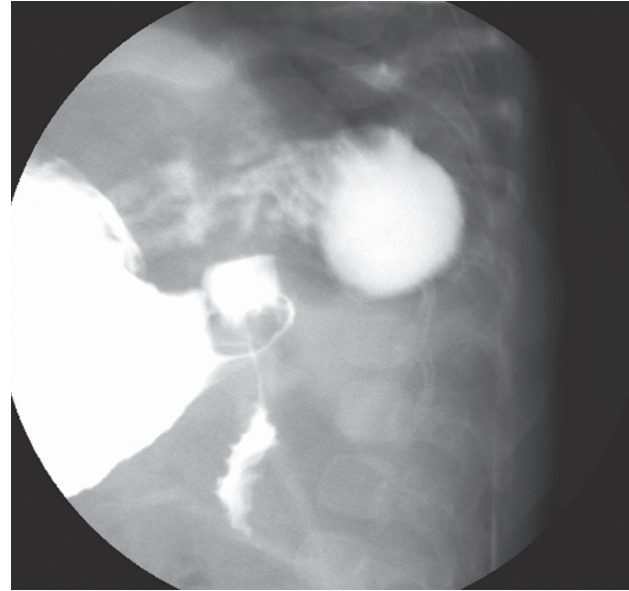


**Figure 321-1** Ultrasound of the abdomen shows abnormal thickening (4.5 mm) of the pyloric wall in a patient with pyloric stenosis.

30 days. An upper gastrointestinal (GI) tract contrast study may be performed in infants in whom the ultrasound is not diagnostic. Characteristic upper GI tract findings in infants with PS include an elongated and narrowed pyloric channel (string sign) with the shoulders of the hypertrophied pylorus bulging into the intestinal lumen (Figure 321-2). The palpation of a mass on physical examination alone should aid in making an accurate diagnosis in most patients. However, increasing reliance is now placed on noninvasive, highly accurate, and relatively inexpensive radiologic tests, such as the ultrasound.

### DIFFERENTIAL DIAGNOSIS

Other causes of gastric outlet obstruction, such as foregut stenosis, gastric duplications, antral webs, pylorospasm, annular pancreas, and malrotation should be considered in the differential diagnosis of an infant with nonbilious emesis. Many of these causes can be excluded by ultrasound and upper GI tract series. When a diagnosis of PS cannot be established in an infant with persistent emesis and normal ultrasound examination and upper GI tract series, the possibilities of a poor feeding regimen, gastroesophageal reflux, sepsis, intracranial disease, renal disorder, or adrenal insufficiency should be considered. Prompt diagnosis and immediate therapy are crucial in an infant with salt-losing congenital adrenal hyperplasia. This condition should be suspected in an infant with abnormal genitalia, hyponatremia, and hyperkalemia. When the workup is inconclusive, reevaluating the infant in a week to 10 days, when the pyloric mass may become palpable or the ultrasound examination or upper GI tract series may become diagnostic, is reasonable.



**Figure 321-2** Upper gastrointestinal study demonstrates a narrowed and elongated pyloric channel with a double-track appearance consistent with pyloric stenosis.

## MANAGEMENT

### Preoperative Management

In the past, infants often had overwhelming malnutrition and electrolyte abnormalities. In the current era of early diagnosis, infants rarely progress to this severe state. The anatomic correction of PS is not a surgical emergency because, although PS is a form of intestinal obstruction, gangrene and intestinal perforation do not occur with this condition. The fluid and electrolyte deficits should be corrected prior to surgical intervention.

Fluid replacement should include deficit correction, daily maintenance fluids, and replacement of ongoing losses. Replacement therapy includes continuous maintenance infusion of 5% dextrose in 0.45 normal saline with the addition of 20 mEq/L potassium chloride once urine output is established in addition to correction of other electrolyte abnormalities. Nasogastric decompression should be performed prior to the induction of anesthesia and surgery.

### Surgical Management

Once the volume and electrolyte status are corrected, the infant is ready for surgery. Ramstedt pyloromyotomy through a right upper quadrant transverse incision has been the traditional treatment for hypertrophic PS. Laparoscopic and circumumbilical approaches have now been introduced as alternative methods to open pyloromyotomy. Meta-analysis data from prospective, randomized controlled trials indicate a benefit of the laparoscopic approach, with lower rates of wound-related complications, decreased time to full feeding, and reduced postoperative length of stay.

### Medical Management

Because surgical myotomy is a reliable and safe procedure, medical therapy alone has been largely discarded during the last several decades. However, medical therapy may be considered an alternative to pyloromyotomy, particularly in children with major concurrent primary disease. Medical therapy with the anticholinergic agent atropine sulfate has been used with success, although the duration of hospital stay was prolonged. Studies comparing predominantly oral atropine sulfate to surgical myotomy have reported similar success rates.

### Postoperative Management

Postoperative vomiting occurs in most infants and will usually subside by the second to fifth feeding. Parental education regarding postoperative vomiting is important before surgery. Infants should be fed full-strength formula or human milk every 3 to 4 hours, starting 6 hours after surgery. In case of emesis, infants can be refed the amount vomited 1 hour later with resumption of the feeding schedule thereafter. This early refeeding has resulted in a reduction in the postoperative hospital stay.

### Discharge Criteria

Infants are usually discharged 24 to 48 hours after surgery. Feeding tolerance must be reassessed before discharge.

## COMPLICATIONS

### Intraoperative and Early Postoperative Complications

Morbidity and mortality from surgical repair have decreased from 50% to less than 1% in the current era. The risk of complications, such as intestinal perforation, hemorrhage, wound dehiscence, and postoperative infection, is negligible.

### Hypoglycemia

Reactive hypoglycemia has been reported in infants who have a wide variety of medical and surgical conditions and may cause respiratory arrest and death. A constant infusion of dextrose results in hyperinsulinemia and can result in severe hypoglycemia if the infusion is suddenly terminated before adequate oral feeding is established. This reaction is particularly likely if liver glycogen stores have been depleted, as has been shown in infants with PS.

### Death

The mortality rate in infants with PS is less than 0.1%. Improvement in anesthetic techniques and monitoring has contributed to these improved results. Delayed diagnosis, inadequate preoperative rehydration, pulmonary aspiration, unrecognized perforation, hypoglycemia, persistent obstruction, hemorrhage, and the presence of other associated congenital anomalies are potential causes of death.

### Late Complications

#### Postoperative Obstruction

Radiographic evaluation is necessary if vomiting persists beyond 5 to 7 days. Excessive vomiting may be

caused by persistent stenosis, gastroesophageal reflux, gastric outlet obstruction, or small-bowel obstruction attributable to adhesions. An upper GI tract contrast series may be helpful, but is also difficult to interpret. Narrowing and elongation of the pyloric channel usually persist for weeks to months after a successful operation, even in infants who have minimal or no postoperative vomiting. Subsequent operation may be indicated in the rare event of persistent pyloric obstruction.

### Long-term Outcome

The long-term outcome for patients treated for PS is excellent. Rapid gastric emptying and duodenogastric reflux have been identified in some patients who had undergone pyloromyotomy 5 to 7 years earlier. However, other studies have shown no differences between previous patients with PS and controls after a long-term follow-up.

### WHEN TO REFER

- All infants with PS should be referred to a surgeon.

### WHEN TO ADMIT

- All infants need to be hospitalized to correct the electrolyte imbalance and for surgery intervention.

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## Chapter 322

# RENAL TUBULAR ACIDOSIS

Ronald Kallen, MD

### DEFINITION

Renal tubular acidosis (RTA) is not a single entity but a collection of complex disorders. RTA is the principal cause of hyperchloremic metabolic acidosis with a normal anion gap in an infant or child ingesting a typical diet who does not have gastroenteritis or chronic kidney disease (anion gap,  $\text{mEq/L} = [\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-])$ ). The term *tubular* means that metabolic acidosis is a consequence of a defect affecting tubular mechanisms for acid excretion. This is in contrast to metabolic acidosis arising from the underexcretion of acid caused by kidney failure or an increase in acid production, as

in diabetic ketoacidosis, lactic acidosis, or total parenteral nutrition, which typically cause an increase in the plasma anion gap. RTA is an impaired capacity of the kidney to excrete the usual daily load of acid arising from metabolism. Renal excretory function, as estimated by creatinine clearance, is relatively intact.

## CLINICAL MANIFESTATIONS

The diagnosis of RTA should be considered in any infant or young child with metabolic acidosis accompanying failure to thrive, recurrent vomiting, short stature, rickets, nephrocalcinosis, hypotonia, muscle weakness, sensorineural hearing loss, recurrent episodes of dehydration, kidney stones, gastroenteritis with incomplete recovery from metabolic acidosis, or a family member already known to have RTA. Failure to thrive during infancy is often the presenting feature of RTA. Growth is a complex process, and the molecular mechanisms of impaired growth in children with RTA are not completely understood. The impaired tubular phosphate reabsorption of Fanconi syndrome (a constellation of proximal tubular transport defects causing glucosuria, aminoaciduria, bicarbonaturia, and phosphaturia) contributes to rickets and short stature. Moreover, the buffering of hydrogen ion ( $H^+$ ) by bone causes the release of calcium ( $Ca^{2+}$ ) and consequent hypercalciuria, which contributes to osteopenia and short stature in certain forms of RTA. Metabolic acidosis inhibits osteoblasts and bone turnover. However, growth impairment is multifactorial and some children with Fanconi syndrome continue to lag in growth despite the correction of metabolic acidosis.

The diagnosis of metabolic acidosis is often based on the measurement of serum bicarbonate by a clinical laboratory autoanalyzer. One report found that the measurement by autoanalyzer tended to falsely estimate a reduction of serum bicarbonate concentration in contrast to estimation by a venous blood gas. RTA is often suspected in infants or young children with failure to thrive and a plasma bicarbonate level below the reference range. However, the monogenic forms of RTA are, in fact, rare disorders and are not found as often as they are suspected.

The serum potassium may be normal, low, or high. RTA associated with episodic hypokalemia may be accompanied by profound muscle weakness and, in rare instances, recurrent paralysis. In the absence of a blood gas analysis confirming acidemia, a venous blood carbon dioxide ( $CO_2$ ) content less than 20 mEq/L in an infant or young child with failure to thrive, in the absence of diarrhea, and accompanied by hyperchloremia and a normal anion gap, should raise suspicion of RTA, especially if the urine pH is 5.5 or higher.

RTA, in association with hyponatremia and hyperkalemia, can also present as an acute life-threatening event in some infants with a profound salt-losing condition and hypovolemia, such as pseudohypoaldosteronism (PHA) type 1 or salt-losing congenital adrenal hyperplasia. However, in these instances the physician is not dealing with “classic” RTA but metabolic acidosis as a secondary accompaniment of impaired mineralocorticoid receptor function or aldosterone deficiency.

RTA may present rarely as isolated “idiopathic” hypercalciuria or by passage of a kidney stone in a

child with incomplete RTA (impaired urinary acidification with normal plasma bicarbonate), which may be accompanied by a family history of nephrolithiasis in association with hypocitraturia. For some children in at-risk families, hypocitraturia may be the only indication of incomplete RTA.

The family history should be explored with questions regarding other affected family members in preceding generations or affected siblings of an individual with suspected RTA. In the instance of an apparent *de novo* occurrence of RTA, consanguinity may play a role. The occurrence of nephrolithiasis in other family members may be significant. A history of a sudden unexplained demise in a neonate suggests the possibility of a salt-losing condition that may be associated with RTA.

## PATHOPHYSIOLOGY

Genetic RTA syndromes in children occur because of mutations of genes encoding ion transporters that play a key role in the kidney's contribution to acid-base homeostasis. These rare conditions are primary monogenic disorders, have an autosomal-recessive mode of inheritance in most instances, and may be associated with ocular defects or hearing impairment. However, the physician is more likely to encounter secondary forms of RTA that result from drugs or acquired tubulointerstitial disease. Other instances of RTA are associated with another primary hereditary disorder, such as cystinosis, or from other causes of Fanconi syndrome. Moreover, a transient form of acquired RTA may occur in very low-birth-weight infants with delayed maturity of renal tubular function. RTA in adults may be associated with autoimmune disease and other conditions not generally encountered in children. These disorders will not be considered further in this chapter. In the evaluation of a child suspected of having RTA, the history should include inquiry about medications.

RTA is a consequence of a mismatch between the usual rate of acid production and the rate of renal acid excretion. The daily production of endogenous acid mainly arises from dietary protein, primarily sulfur-containing amino acids (methionine, cystine) that are not subsequently resynthesized into protein, ultimately yielding the strong mineral acid, sulfuric acid ( $H_2SO_4$ ). The accession of protons ( $H^+$ ) derived from  $H_2SO_4$  into the extracellular fluid is promptly buffered by bicarbonate ( $HCO_3^-$ ). Buffering by the extracellular pool of  $HCO_3^-$  only accounts for approximately one-half of the disposition of an acid load. In more chronic forms of metabolic acidosis, buffering of  $H^+$  by bone mineral is accompanied by the release of  $Ca^{2+}$ , hydroxyl ion ( $OH^-$ ), and phosphate ( $PO_4^{3-}$ ) from the hydroxyapatite crystal surface. During the rapid growth phase of infancy and early childhood, the accretion of calcium, phosphate, and hydroxyl ion into the hydroxyapatite crystal structure of bone also contributes to the endogenous acid load by the release of approximately 1 mEq of  $H^+$  for each milliequivalent of  $Ca^{2+}$  retained in bone.

The rate of endogenous acid production in infants and children, 2 to 3 mEq/kg/day, must be matched, milliequivalent for milliequivalent, by the excretion of  $H^+$  bound to the 2 principal urinary buffers, ammonia ( $NH_3$ ) and monohydrogen phosphate ( $HPO_4^{2-}$ ). Acid



excretion by the kidney is represented by the sum in the urine of  $\text{NH}_4^+$  and  $0.8 \times \text{H}_2\text{PO}_4^-$  (expressed as mEq). The multiplier 0.8 accounts for the 20% of serum phosphate that is in the form of dihydrogen phosphate,  $\text{H}_2\text{PO}_4^-$  at pH 7.40. The major adaptive response to an increasing acid load is an increase in ammonium ( $\text{NH}_4^+$ ) production and excretion in contrast to phosphate, which has a relatively fixed rate of excretion.  $\text{NH}_4^+$  production is regulated and can expand several-fold from baseline in acute metabolic acidosis, such as diabetic ketoacidosis. Metabolic acidosis accompanying newly recognized RTA is generally of intermediate severity and not catastrophic, which is in contrast to the acute metabolic acidosis occurring in some patients with overproduction of acid, as in diabetic ketoacidosis. The essential defect in all forms of RTA is a diminished ability to excrete  $\text{NH}_4^+$  in the face of the usual rate of acid production.

## RENAL MECHANISMS FOR EXCRETION OF ACID

The collection of disorders known as RTA are better understood after discussing the role of the kidney in maintaining acid–base balance. One principal aspect is the segmental topology of the nephron for the absorption and secretion of particular solutes and, in the context of RTA, especially the absorption of filtered sodium bicarbonate and the secretion of  $\text{H}^+$ .

The epithelial cells of the proximal tubule, thick ascending limb (TAL) of the loop of Henle, distal tubule, connecting tubule, and the cortical and medullary segments of the collecting duct are specialized for ion translocation against a gradient and ultimately require the expenditure of energy. These epithelia separate 2 fluid compartments: the lumen of the tubule and the interstitial fluid compartment of the kidney. The epithelial cells are polarized and have a distinct apical membrane facing the lumen and a distinct basolateral membrane interfacing the interstitial fluid compartment (see Figure 322-1). The apical and basolateral membranes meet at the tight-junction complexes between adjacent cells. Each membrane has a unique complement of ion-translocating mechanisms, either transporters anchored to the lipid bilayer of the cell membrane or ion-specific channels. An ion transporter is a membrane-associated protein, with a binding site for the specific ion to be translocated. The rate of translocation is regulated by the cycling of transporters and channels between the membrane and specialized structures in the cytosol. Some transporters perform primary active transport against an electrochemical gradient and have a catalytic site for the hydrolysis of adenosine triphosphate (ATP). The energy released from the high-energy phosphate bond is used to translocate an ion against an electrochemical gradient that would otherwise impede movement of the solute. These channels and transporters affect the distribution of electrical charges on either side of the membrane. If a transported ion is accompanied by an ion with an equivalent but opposite charge, then the transport activity is electroneutral. Other ion transport activities are electrogenic, resulting in an asymmetrical transepithelial distribution of charges. A notable

example of the latter relevant to this discussion of RTA is sodium ( $\text{Na}^+$ ) absorption via the apical epithelial sodium channel (ENaC) of principal cells in the aldosterone-sensitive distal nephron, which generates a lumen-negative potential and is a necessary precondition for  $\text{H}^+$  secretion in the distal nephron.

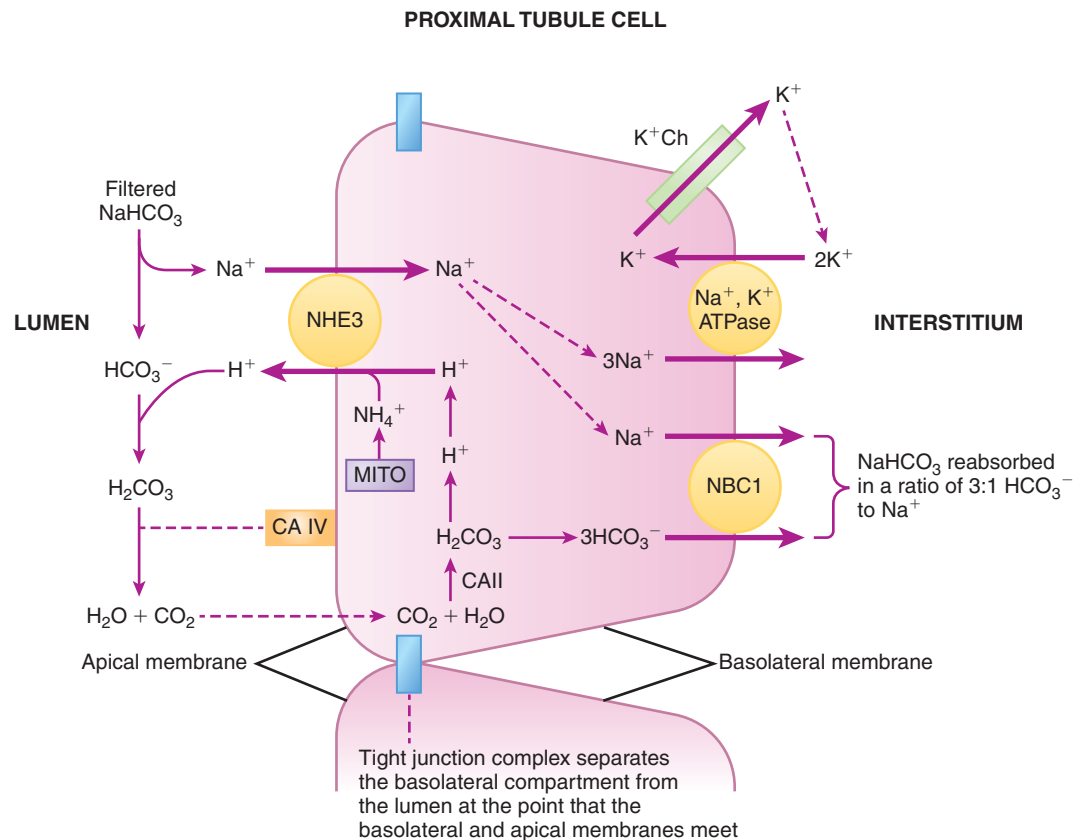
The role of the kidney in maintaining pH homeostasis principally involves 2 discrete processes in the handling of  $\text{HCO}_3^-$ : reclamation and regeneration of  $\text{HCO}_3^-$ . The first, reclamation, absorbs filtered  $\text{HCO}_3^-$  in proximal segments of the nephron, and the second, regeneration in the collecting duct, excretes  $\text{H}^+$  in the form of  $\text{NH}_4^+$  and dihydrogenphosphate ( $\text{H}_2\text{PO}_4^-$ ) and, in the process, generates “new”  $\text{HCO}_3^-$ . The task of reclaiming filtered  $\text{HCO}_3^-$  in the proximal tubule is mediated by  $\text{H}^+$  secretion in exchange for absorbed  $\text{Na}^+$  via the NHE3 exchanger in the lumen-facing membrane (see Figure 322-1). The process of  $\text{HCO}_3^-$  regeneration occurs in more distal segments of the nephron. The bulk of filtered  $\text{HCO}_3^-$ , approximately 80% to 90%, has already been absorbed by the reclamation process in more proximal segments. The remaining filtered  $\text{HCO}_3^-$  is absorbed mainly in the TAL. The task now for the collecting duct is to generate “new”  $\text{HCO}_3^-$ , which serves to replenish the pool of  $\text{HCO}_3^-$  and nonbicarbonate buffers that has had its stock depleted at a rate of 2 to 3 mEq/kg/day as buffer is consumed by  $\text{H}^+$  arising from metabolism. This process of  $\text{HCO}_3^-$  regeneration by the collecting duct is depicted in Figure 322-2, which shows that for every new  $\text{HCO}_3^-$  generated, a  $\text{H}^+$  is also generated *pari passu* by cytosolic carbonic anhydrase II (CA II) and is destined for excretion by an apical proton pump.

## AMMONIUM EXCRETION MECHANISM

All forms of RTA are ultimately caused by the inability of the kidney to maintain plasma  $\text{HCO}_3^-$  concentration at a physiologic level in the face of the usual rate of acid production. The role of the kidney in precisely aligning acid excretion with endogenous acid production is served mainly by  $\text{NH}_4^+$  generation and excretion. The other main urinary buffer,  $\text{H}_2\text{PO}_4^-$ , is a minor actor, because most of the filtered phosphate ( $\text{HPO}_4^-$  and  $\text{H}_2\text{PO}_4^-$ ) is absorbed proximally, and only about 15% to 20% is available for buffering in the collecting duct. The details of the multi-step process of  $\text{NH}_4^+$  excretion are complex. The following description sketches the main features of this process and refers mainly to  $\text{NH}_4^+$  since, in the range of pH between the renal interstitium and of the fluid in the tubular lumen, the equilibrium concentration of  $\text{NH}_3$  and  $\text{NH}_4^+$  is massively shifted in the direction of  $\text{NH}_4^+$  (at pH 7.4, over 98% of the total of  $\text{NH}_4^+$  and  $\text{NH}_3$  is  $\text{NH}_4^+$ ). The former paradigm of the terminal step of  $\text{NH}_4^+$  excretion as a process linked to the passive diffusion of  $\text{NH}_3$  into the lumen of the collecting duct and “trapping” of  $\text{NH}_4^+$  has been superseded by the recognition of a membrane transporter, RhCG, specialized for the translocation of  $\text{NH}_3$  from the medullary interstitium to the lumen of the collecting duct by the type A intercalated cell.

The process of  $\text{NH}_4^+$  excretion can be broken down into 4 steps (see Figure 322-3). First, ammoniogenesis occurs in the proximal tubule. The primary substrate is the amino acid, glutamine, which is transported





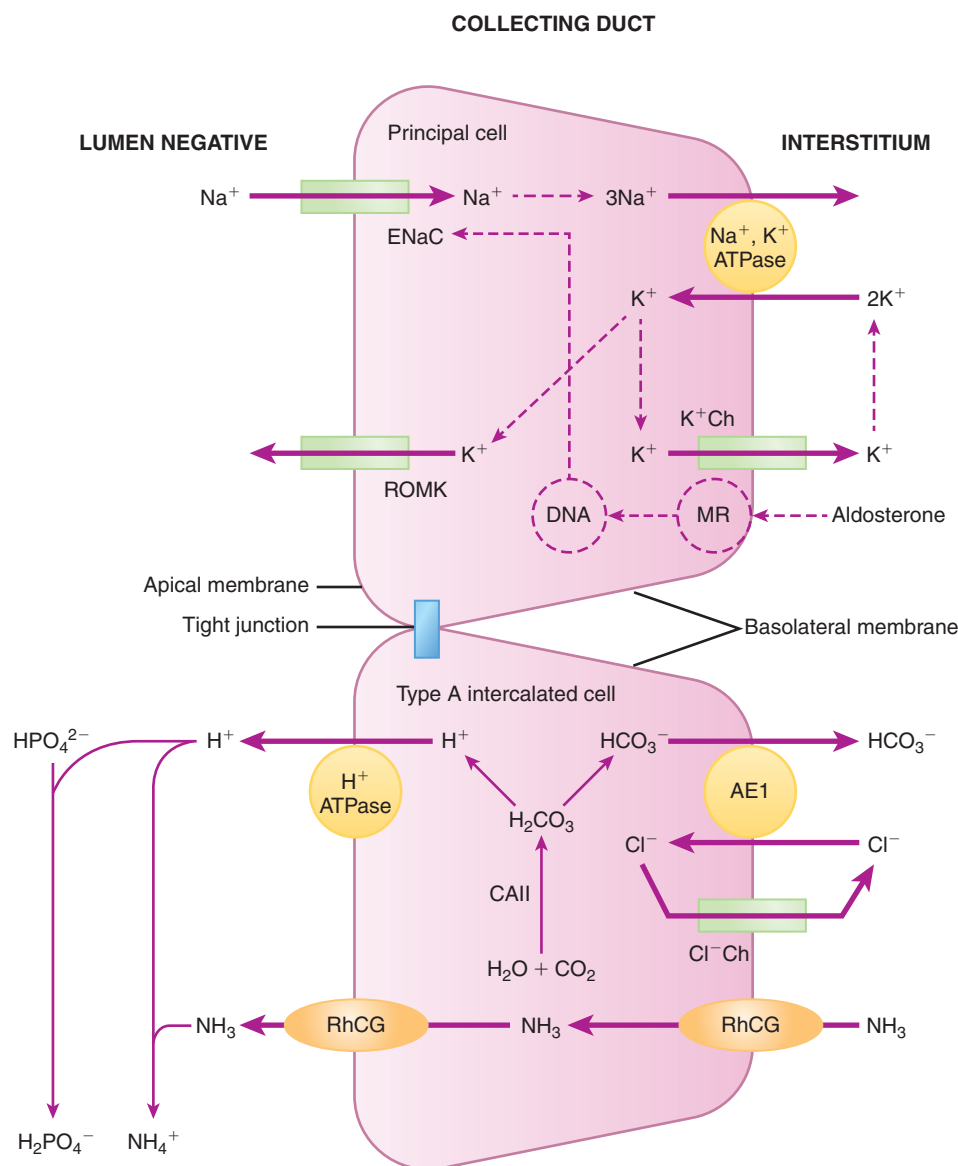
**Figure 322-1** Approximately 80% to 90% of filtered  $\text{HCO}_3^-$  is reabsorbed in the proximal tubule. The basolateral  $\text{Na}^+\text{K}^+$  ATPase maintains transmembrane gradients of  $\text{Na}^+$  and  $\text{K}^+$  that drive the apical  $\text{Na}^+\text{H}^+$  exchanger (NHE3) and the basolateral  $\text{Na}^+\text{HCO}_3^-$  cotransporter (NBC1). The reaction via cytosolic CA II,  $\text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{H}^+ + \text{HCO}_3^-$ , cycles 3 times yielding 3  $\text{HCO}_3^-$  before NBC-1 is able to transport  $\text{HCO}_3^-$  and  $\text{Na}^+$  in a 3:1 ratio. Not depicted in the figure is an apical proton pump ( $\text{H}^+\text{-ATPase}$ ), which is responsible for a smaller proportion of  $\text{H}^+$  secretion and  $\text{HCO}_3^-$  absorption.  $\text{NH}_4^+$  is generated within mitochondria and secreted into the lumen after binding to the  $\text{H}^+$  site of the NHE3 exchanger. The production of  $\text{NH}_4^+$  is inhibited by hyperkalemia. Although not depicted, the apical membrane is arranged as a brush border with many infoldings, which provide a large surface area for bulk absorption of  $\text{Na}^+$  and  $\text{HCO}_3^-$ . CA II, cytosolic carbonic anhydrase II; CA IV, apical membrane carbonic anhydrase IV;  $\text{K}^+\text{Ch}$ , basolateral potassium ion channel; MITO, mitochondrion.

into the mitochondria of cells of the proximal tubule. The oxidative metabolism of 1 glutamine ultimately yields 2 each of  $\text{NH}_4^+$  and  $\text{HCO}_3^-$  in equimolar quantities. This newly formed  $\text{HCO}_3^-$  exits the proximal tubular cell via the basolateral NBC1 cotransporter (in a molar ratio of 1  $\text{Na}^+$  and 3  $\text{HCO}_3^-$ ) and exits the kidney in renal venous blood and becomes part of the extracellular  $\text{HCO}_3^-$  pool that is filtered and reclaimed (see Figure 322-1). This initial step is accomplished by the secretion of  $\text{NH}_4^+$ , in exchange for luminal  $\text{Na}^+$ , by  $\text{NH}_4^+$  occupying the  $\text{H}^+$  binding site on the apical  $\text{Na}^+\text{H}^+$  exchanger (NHE3; see Figure 322-1). Although this initial step has contributed to the restoration of the  $\text{HCO}_3^-$  pool, additional steps in the processing of  $\text{NH}_4^+$  must unfold before acid, in the form of  $\text{NH}_4^+$ , is actually excreted and new  $\text{HCO}_3^-$  is generated.

The second step in  $\text{NH}_4^+$  processing is its absorption in the TAL by occupying the  $\text{K}^+$  site on the apical  $\text{Na}^+\text{K}^+\text{2Cl}^-$  cotransporter (NKCC2; Figure 322-4). The

interstitial accumulation of  $\text{NH}_4^+$  constitutes the third step in the  $\text{NH}_4^+$ -excretion mechanism. The concentration of  $\text{NH}_4^+$  increases at each successively deeper stratum of the medulla, reaching the highest concentration toward the papilla. The mechanism by which  $\text{NH}_4^+$  exits the cells of the TAL is not yet known. Most of the reabsorbed  $\text{NH}_4^+$ , up to 80% of that ultimately excreted, is recycled to the medullary interstitium, where it is available for the fourth step.

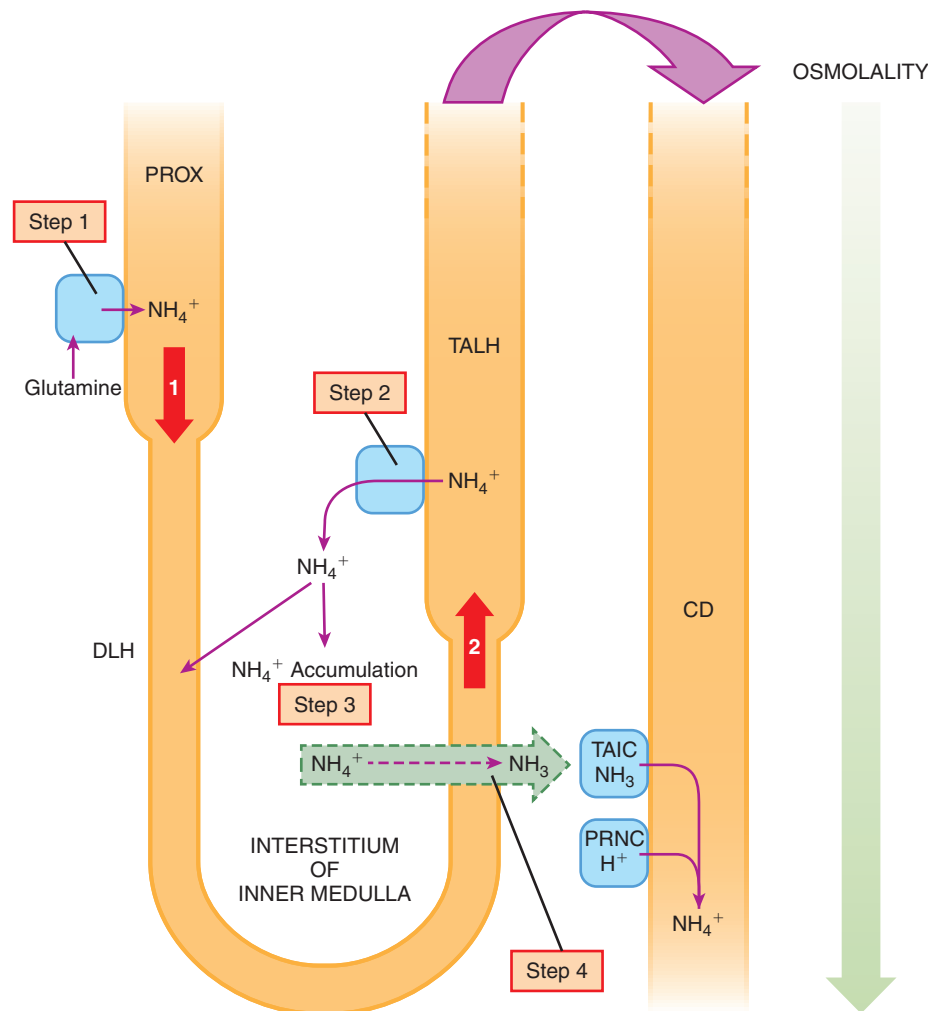
The fourth step in the ammonium excretion mechanism is the transport of  $\text{NH}_4^+$  from the interstitium across the basolateral membrane of the type A intercalated cell of the collecting duct. At this membrane,  $\text{NH}_4^+$  dissociates, yielding  $\text{NH}_3$ , which is transported into the cytosol via the basolateral RhCG transporter, which is thought to function as a “gas channel.” The high concentration of  $\text{NH}_4^+$  in the medullary interstitium “feeds” the  $\text{NH}_3$  transporter, RhCG, in the basolateral membrane. The RhCG transporter is also present in the apical membrane. The intracellular  $\text{NH}_3$  is shuttled to



**Figure 322-2** The epithelium of the collecting duct is a mosaic of Na<sup>+</sup>-absorbing and K<sup>+</sup>-secreting principal cells and H<sup>+</sup>-secreting type A intercalated cells (not depicted in the latter is an apical H<sup>+</sup>,K<sup>+</sup>-exchanger that has a less important role in H<sup>+</sup> secretion than the apical H<sup>+</sup>-ATPase). The lumen-negative transepithelial potential difference is maintained by the aldosterone-stimulated apical epithelial Na<sup>+</sup> channel (ENaC) of the principal cell. The lumen negativity facilitates K<sup>+</sup> secretion by the apical K<sup>+</sup>-channel (ROMK) of the principal cells and H<sup>+</sup> secretion by the type A intercalated cells. A diminution of a lumen-negative electrical gradient is referred to as a *voltage defect*. The apical H<sup>+</sup>-ATPase and the basolateral Cl<sup>-</sup>,HCO<sub>3</sub><sup>-</sup>-exchanger (AE1) of the type A intercalated cell are each affected by loss-of-function mutations causing impaired HCO<sub>3</sub><sup>-</sup> regeneration and RTA. Aldosterone interacts with the mineralocorticoid receptor (MR) of the primary cell, which then translocates to the nucleus and after binding to a promoter region of DNA triggers upregulation of ENaC and Na<sup>+</sup>-K<sup>+</sup>-ATPase. NH<sub>3</sub> pooled in the medullary interstitium undergoes transcellular transport via the basolateral and apical RhCG “gas channels.” Hyperkalemic RTA arises secondary to aldosterone deficiency or unresponsiveness of the mineralocorticoid receptor. The consequent hyperkalemia inhibits NH<sub>4</sub><sup>+</sup> production by the proximal tubule. Principal cell: ENaC, epithelial Na<sup>+</sup> channel; K<sup>+</sup>Ch, basolateral K<sup>+</sup> channel; MR, mineralocorticoid receptor; ROMK, apical K<sup>+</sup> channel. Type A intercalated cell: Cl<sup>-</sup>Ch, basolateral Cl<sup>-</sup> channel; RhCG, basolateral and apical Rhesus C glycoprotein; not depicted, the basolateral Na<sup>+</sup>,K<sup>+</sup>-ATPase transporter.

the apical RhCG transporter for secretion. Once in the lumen, NH<sub>3</sub> is protonated with H<sup>+</sup> secreted by the apical H<sup>+</sup>-ATPase of the type A intercalated cell, driven by the lumen-negative potential created by sodium absorption via the ENaC channel of neighboring principal cells of the collecting duct. As the collecting duct courses from

cortex to the medulla, the most active segment for H<sup>+</sup> secretion is the inner medullary collecting duct. Thus, NH<sub>4</sub><sup>+</sup> excretion is ultimately accomplished by the coordinated action of 4 different cell types in different segments of the nephron: proximal tubule, TAL, and, in the collecting duct segment, the type A intercalated cell and

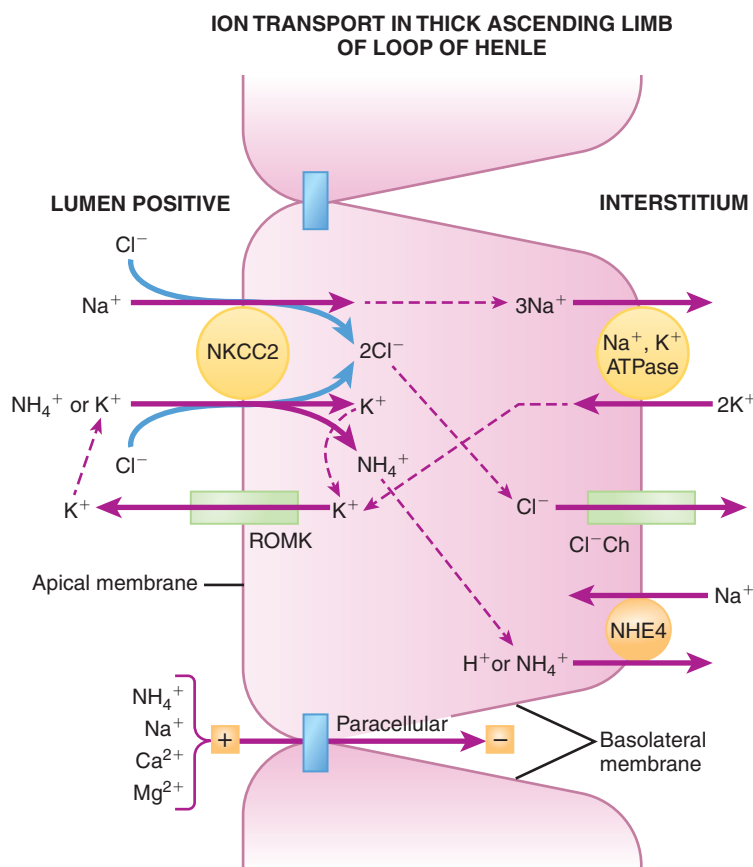


**Figure 322-3** Ammonium excretion is a 4-step process. Step 1 is the generation of ammonium ( $\text{NH}_4^+$ ) from glutamine in the mitochondria of cells of the proximal tubule.  $\text{NH}_4^+$  exits the cell of the proximal tubule after binding to the  $\text{H}^+$  site of the apical  $\text{Na}^+$ ,  $\text{H}^+$  exchanger (NHE3, Figure 322-1). The broad arrow in the figure labeled with the numeral 1 denotes a packet of  $\text{NH}_4^+$  leaving the proximal tubule and entering the descending thin limb of the loop of Henle (DTL). There is further net addition of  $\text{NH}_4^+$  to this packet as the DTL courses through deeper strata of the renal medulla and encounters the high concentration of interstitial  $\text{NH}_4^+$  produced by the reabsorption of  $\text{NH}_4^+$  in the thick ascending limb loop of Henle (TALH) (step 2). The mechanism of transport of interstitial  $\text{NH}_4^+$  into the lumen of the DTL is not known. The broad arrow labeled with the numeral 2 represents a packet of  $\text{NH}_4^+$  arriving at the TALH. Step 2 is the reabsorption of  $\text{NH}_4^+$  in the TALH by binding to the  $\text{K}^+$  site of the apical  $\text{Na}^+$ ,  $\text{K}^+$ ,  $2\text{Cl}^-$  cotransporter (NKCC2, Figure 322-4). Step 3 is the interstitial accumulation of  $\text{NH}_4^+$ . After absorption,  $\text{NH}_4^+$  exits the cells of the TALH by possibly binding to the  $\text{H}^+$  site of a basolateral  $\text{Na}^+$ ,  $\text{H}^+$  exchanger (not depicted in Figure 322-4). The net effect of this recycling of  $\text{NH}_4^+$  is to populate the medullary interstitium with a pool of  $\text{NH}_4^+$ , which “feeds” the uptake of  $\text{NH}_3$  from the interstitium by the type A intercalated cell, TAIC (also see Figure 322-2) via a basolateral RhCG transporter. The cytosolic  $\text{NH}_3$  is then shuttled to the apical RhCG transporter for secretion into the lumen of the medullary collecting duct, CD (also see Figure 322-2). Although not depicted in the above figure, RhCG transporters are also found in principal cells (PRNC) of the CD (also see Figure 322-2). Step 4 is the protonation of  $\text{NH}_3$  and “ion trapping” of  $\text{NH}_4^+$  in the lumen of the collecting duct. As  $\text{NH}_4^+$  (and the  $\text{NH}_3$ , which is in equilibrium with  $\text{NH}_4^+$ ) are removed by excretion, a gradient for continuing transport of  $\text{NH}_3$  from the medullary interstitium is maintained (broad, dotted arrow). The shading of the vertical arrow labeled *osmolality* denotes the increasing concentration of  $\text{NH}_4^+$  and other solutes in successively deeper layers of the medulla. CD, medullary collecting duct; DTL, descending thin limb of loop of Henle; PRNC, principal cell; PROX, proximal tubule; TAIC, type A intercalated cell; TALH, thick ascending limb of loop of Henle.

the principal cell. This is a regulated process, attuned to the demand for acid excretion by upregulation as demand increases. The net effect is that for each  $\text{NH}_4^+$  excreted a new  $\text{HCO}_3^-$  is returned to the extracellular pool. Thus, the  $\text{NH}_4^+$  originally produced by the proximal tubule, which was then reabsorbed in the TAL

to maintain the high interstitial concentration of  $\text{NH}_4^+$ , is now finally out of the body.

In the context of childhood RTA, each of the 4 steps of  $\text{NH}_4^+$  processing is implicated in the pathogenesis of the different forms of RTA. The initial step, proximal ammoniogenesis, is inhibited by hyperkalemia



**Figure 322-4** The thick ascending limb (TAL) is the “recycling center” of the kidney and provides for the pooling of  $\text{NH}_4^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cl}^-$  in the medullary interstitium. It is the site of  $\text{NH}_4^+$  reabsorption by the apical  $\text{Na}^+$ - $\text{K}^+$ - $2\text{Cl}^-$  cotransporter (NKCC2). The lumen-directed  $\text{K}^+$  conductivity of the ROMK channel maintains a lumen-positive electrical gradient.  $\text{NH}_4^+$  binds to the  $\text{K}^+$  site of the transporter. This substitution is possible because both have a similar ionic radius. Recent data suggest that  $\text{NH}_4^+$  exits via a basolateral  $\text{Na}^+$ ,  $\text{H}^+$  exchanger [NHE4] by occupying the  $\text{H}^+$  site. As shown in the figure, a paracellular pathway driven by the lumen-positive electrical gradient adds to pooling of  $\text{NH}_4^+$  in the interstitium. The apical membrane has a low permeability to  $\text{NH}_4^+$ , which facilitates the medullary interstitial accumulation of  $\text{NH}_4^+$ . Cl-Ch, basolateral chloride channel; ROMK, apical  $\text{K}^+$  channel.

occurring in mineralocorticoid deficiency or mineralocorticoid unresponsive states. The second step in the TAL, absorption of  $\text{NH}_4^+$  by the NKCC2 cotransporter, is also impaired by hyperkalemia, because  $\text{K}^+$  in the lumen more effectively competes with  $\text{NH}_4^+$  for the same binding site on the transporter (see Figure 322-4). This impaired transport of  $\text{NH}_4^+$  affects the third step, the accumulation of  $\text{NH}_4^+$  in the medullary interstitium. Another disease process affecting this third step is inflammation and scarring of the inner medulla, distorting the specialized anatomy of the countercurrent multiplier system responsible for the increasing concentration of solutes and  $\text{NH}_4^+$  in the deeper strata of the medulla. Nephrocalcinosis, as a consequence of the treatment of the proximal tubule disorder X-linked hypophosphatemic rickets with vitamin D and phosphate supplement, is a cause of regeneration-defect RTA in some patients. Examples of disorders causing an acquired form of RTA include recurrent pyelonephritis with interstitial fibrosis affecting the renal papillae, obstructive uropathy, medullary sponge kidney, and sickle cell disease. The fourth and final step in  $\text{NH}_4^+$

excretion is also impaired in RTA and is the consequence of 2 different defects; either a  $\text{H}^+$  secretory defect or diminished lumen-negativity (see Figure 322-2). There is no known genetic mutation linked to an impairment of the RhCG translocator protein.

## CLASSIFICATION OF RENAL TUBULAR ACIDOSIS

This chapter introduces a classification of RTA based on the physiology of  $\text{HCO}_3^-$  transport rather than referencing nephron segments (“proximal” versus “distal”). The 2 basic processes of  $\text{HCO}_3^-$  handling described above serve as the basis for this physiologic classification into 2 main types of RTA: a reclamation-defect type and a regeneration-defect type (see Table 322-1). The reclamation-defect type is traditionally referred to as proximal RTA or type 2 RTA. Although the bulk of  $\text{HCO}_3^-$  absorption, 80% to 90%, occurs in the proximal tubule, reclamation is completed in more distal segments, and the term *proximal* RTA is not physiologically correct. Most reclamation-defect RTA disorders



**Table 322-1** Classifications of Renal Tubular Acidosis

PHYSIOLOGIC	CONVENTIONAL
Reclamation defect <ul style="list-style-type: none"> <li>• With Fanconi syndrome</li> <li>• Primary, nonsyndromic</li> </ul>	Type 2, proximal
Regeneration defect <ul style="list-style-type: none"> <li>• Nonhyperkalemic</li> <li>• Hyperkalemic <ul style="list-style-type: none"> <li>■ Acidification intact <ul style="list-style-type: none"> <li>○ Pseudohypoaldosteronism, 1a, 1b, 2</li> </ul> </li> <li>■ Acidification impaired <ul style="list-style-type: none"> <li>○ Medullary tubulointerstitial disease</li> </ul> </li> </ul> </li> </ul>	Type 1, distal  Type 4
Hybrid	Old type 3

in children are also accompanied by other defects localized to the proximal tubule, including impaired absorption of amino acids, glucose, and phosphate (Fanconi syndrome). Regeneration-defect RTA is traditionally referred to as distal RTA or type 1 RTA. The 2 subtypes of regeneration-defect RTA are nonhyperkalemic and hyperkalemic, the latter formerly also referred to as type 4 RTA (see Table 322-1). Another type of RTA has elements of both a reclamation defect and a regeneration defect. In Table 322-1, this is shown as Hybrid or Old type 3.

## TYPES OF RENAL TUBULAR ACIDOSIS

### Reclamation Defect

Reclamation-type RTA (type 2 or proximal RTA; see Table 322-2) is most commonly associated with Fanconi syndrome (aminoaciduria, glucosuria, phosphaturia,  $\text{HCO}_3^-$  wasting, and vitamin D-dependent rickets) of cystinosis. Although the gene defect in cystinosis has been described (OMIM [Online Mendelian Inheritance in Man] 219800, a mutation of *CTNS*, encoding cystinosisin, at locus 17p13), it is not known how the lysosomal accumulation of cystine causes Fanconi syndrome and RTA. One presumption is that the lysosomal accumulation of cystine somehow affects the generation of ATP by the mitochondria of the proximal tubule. Because ATP is the substrate for the basolateral  $\text{Na}^+, \text{K}^+$ -ATPase, which maintains a low intracellular  $\text{Na}^+$  concentration in the face of high transcellular trafficking of  $\text{Na}^+$ , it provides the driving force for  $\text{Na}^+$  absorption (in exchange for  $\text{H}^+$ ) and  $\text{Na}^+$ -coupled absorption of glucose, amino acids, and phosphate.

Urine pH in reclamation-type RTA may be appropriately acidic during acidemia, after the serum  $\text{HCO}_3^-$  in the absence of treatment has declined to approximately 12 to 15 mEq/L. If serum  $\text{HCO}_3^-$  levels are restored to normal during treatment with alkali (sodium or potassium citrate or sodium bicarbonate), then the impaired reclamation of filtered  $\text{HCO}_3^-$  in the proximal tubule results in the flooding of the distal nephron with  $\text{HCO}_3^-$ -rich fluid of alkaline pH. If luminal pH is

relatively alkaline, then  $\text{HPO}_4^{2-}$  and  $\text{NH}_3$  are not effectively protonated because the titration of  $\text{HPO}_4^{2-}$  by secreted  $\text{H}^+$  is mitigated by the reaction of protons with  $\text{HCO}_3^-$  in the lumen. After  $\text{HCO}_3^-$  replacement is stopped, the serum  $\text{HCO}_3^-$  concentration declines to a level that brings the filtered load of  $\text{HCO}_3^-$  into alignment with the proximal tubular capacity for reclamation. The TAL and distal tubule are no longer overwhelmed by a flood of alkaline fluid. Filtered  $\text{HCO}_3^-$  is now effectively reclaimed, and “new”  $\text{HCO}_3^-$  regeneration proceeds in the collecting duct unimpeded by the high luminal pH that existed during  $\text{HCO}_3^-$  wasting. Under this acidemic condition, the urine pH is in the acid range, and net acid excretion, mainly as  $\text{NH}_4^+$ , matches the rate of endogenous acid production such that underexcretion of  $\text{H}^+$  no longer occurs. However, the trade-off is a low plasma  $\text{HCO}_3^-$  and pH and the consequent effects on growth and bone mineral content of acidemia. Replacement of  $\text{HCO}_3^-$  restores plasma pH to normal, but massive  $\text{HCO}_3^-$  wasting ensues, requiring high doses of alkali, which may exceed 10 mEq/kg/day.

A Fanconi syndrome may also be acquired as a consequence of nephrotoxic injury from drugs such as aminoglycosides, valproate, 6-mercaptopurine, cisplatin, ifosfamide, and expired tetracycline. However, rickets or osteomalacia may occur as a consequence of the phosphate-wasting of Fanconi syndrome and impaired conversion by the proximal tubule cell of 25-hydroxy vitamin  $\text{D}_3$  to the biologically active form, 1,25-dihydroxy vitamin  $\text{D}_3$ , as a consequence of acidosis.

Reclamation-defect RTA also occurs in other genetic disorders associated with Fanconi syndrome, including galactosemia, tyrosinemia, Wilson disease, Lowe (oculocerebrorenal) syndrome, Dent tubulopathy of the subtype resulting from *OCRL* mutation, hereditary fructose intolerance, and glycogen storage disease type 1. It also may be acquired as a consequence of nephrotoxic injury that results from drugs such as outdated tetracycline, aminoglycosides, valproate, 6-mercaptopurine, cisplatin, and ifosfamide (see Table 322-2) or heavy metals, such as lead, mercury, or cadmium. Reclamation-defect RTA has also been reported in association with vitamin D deficiency and renal transplantation. Some patients with a syndromic mitochondrial disorder, such as Kearns-Sayre syndrome, may have a reclamation defect.

An autosomal-recessive inheritance of reclamation-type RTA without Fanconi syndrome (OMIM 604278) and associated with intellectual disability and ocular abnormalities (cataracts, corneal opacities, glaucoma, band keratopathy) is the result of a loss-of-function mutation of *SLC4A4* encoding the basolateral  $\text{Na}^+/\text{HCO}_3^-$  (NBC1) cotransporter (see Figure 322-1) of the proximal tubule. The gene has been mapped to locus 4q21 (see Table 322-3). This cotransporter is also found in ocular tissues. This is an exceedingly rare condition.

Isolated nonsyndromic reclamation-defect RTA is very rare. An autosomal-dominant form results from a mutation of *SLC9A3*, encoding the proximal cell apical membrane NHE3 exchanger (not shown in Table 322-3).

**Table 322-2** Drugs Associated With Acquired Renal Tubular Acidosis

RECLAMATION-DEFECT RTA	REGENERATION-DEFECT RTA	HYPERKALEMIC REGENERATION-DEFECT RTA	HYBRID
Acetazolamide Sulfanilimide Topiramate Valproic acid Methotrexate Date-expired tetracyclines 6-mercaptopurine Outdated aminoglycoside Mafenide acetate Cisplatin Antiretroviral	Amiloride Trimethoprim Trimethoprim-sulfamethoxazole Tacrolimus Amphotericin B Lithium Analgesic abuse Vitamin D overdose Foscarnet Methicillin	Spironolactone Eplerenone ACE inhibitor Angiotensin receptor blocker	Acetazolamide Sulfonamide Topiramate

**Table 322-3** Heredofamilial Renal Tubular Acidosis Syndromes

RTA DISORDER	OMIM	MODE OF INHERITANCE	LOCUS	ALLELE	GENE PRODUCT
Primary reclamation defect, ocular abnormalities	604278	AR	4q21	SLC4A4	NBC1
Primary regeneration defect	179800, 109270	AD	17q21-22	SLC4A1	AE1
Primary regeneration defect with deafness	267300	AR	2p13	ATP6V1B1	B1 subunit of H <sup>+</sup> -ATPase
Primary regeneration defect, later-onset hearing impairment	602722	AR	7q33-34	ATP6V0A4	a4 subunit of H <sup>+</sup> -ATPase
<b>SUBTYPES OF REGENERATION DEFECT WITH HYPERKALEMIA</b>					
Hybrid RTA with osteopetrosis	+259730	AR	8q22	CA2	Cytosolic CA II; proximal and distal tubules CA II, osteoclasts
PHA type 1b (systemic)	264350	AR	16p12.2 16p12.2 12p13.31	SCNN1B SCNN1G SCNN1A	Beta subunit of ENaC Gamma subunit of ENaC Alpha subunit of ENaC
PHA type 2 (familial hyperkalemic hypertension, subtypes)					
PHA type 2B	614491	AD	17q21	WNK4	WNK4 Kinase
PHA type 2C	614492	AD	12p13	WNK1	WNK1 Kinase

AD, autosomal dominant; AE1, Cl<sup>-</sup>, HCO<sub>3</sub><sup>-</sup> exchanger; AR, autosomal recessive; ATPase, adenosine triphosphatase; CA, carbonic anhydrase; ENaC, epithelial sodium channel; NBC1, Na<sup>+</sup>, 3HCO<sub>3</sub><sup>-</sup> cotransporter, proximal tubule; OMIM, Online Mendelian Inheritance in Man; PHA, pseudohypoaldosteronism; RTA, renal tubular acidosis.

A reclamation-type RTA may also occur sporadically in infants, often of very low-birth-weight. This entity occurs infrequently. In one report, affected infants were usually boys and most no longer required alkali treatment after the passage of up to 8 years. Treatment with high doses of alkali (10–15 mEq/kg/day) resulted in marked improvement in growth. The serum HCO<sub>3</sub><sup>-</sup> concentration (or threshold) at which HCO<sub>3</sub><sup>-</sup> began to appear in urine ranged between 17.5 and 20 mEq/L, whereas in healthy infants and young children the lower limit of the HCO<sub>3</sub><sup>-</sup> threshold

is a serum concentration of about 22 mEq/L. In addition to failure to thrive, infants with this transient disorder may also experience recurrent vomiting. It may be speculated that this entity results either from a transient insufficiency of the basolateral NBC1 cotransporter or the apical NHE3 exchanger in the proximal tubule.

Reclamation-defect RTA may also occur in association with medications (see Table 322-2). Some of the medications listed in the table are also associated with multiple proximal tubular transport defects (Fanconi syndrome).

The treatment of reclamation-defect RTA with sodium bicarbonate, sodium citrate, or potassium citrate requires large doses to maintain serum  $\text{HCO}_3^-$  in the reference range, and at this level, urinary excretion of  $\text{HCO}_3^-$  approaches 10% to 15% of the filtered load. The dose required to compensate for this high rate of urinary loss, coupled with impaired  $\text{HCO}_3^-$  regeneration (2–3 mEq/kg/day), may approach 10 to 20 mEq/kg/day.

### Nonhyperkalemic Regeneration Defect

Regeneration-defect RTA refers to an impaired ability to generate “new”  $\text{HCO}_3^-$ . It is “new”  $\text{HCO}_3^-$  because reclamation has completely absorbed filtered  $\text{HCO}_3^-$  in nephron segments proximal to the collecting duct. The basic defect in the nonhyperkalemic form is a low rate of  $\text{H}^+$  secretion because of genetic mutations affecting transporters in the collecting duct. In this nephron segment aldosterone-responsive principal cells coexist in a mosaic with type A intercalated cells. Unlike reclamation-defect RTA, the rate of urinary loss of  $\text{HCO}_3^-$  is much lower, generally less than 5% of the filtered load (Table 322-4).

There are 2 forms of regeneration-defect RTA with autosomal-recessive inheritance that are associated with mutations of genes encoding different subunits of the apical proton pump of the type A intercalated cell (see Table 322-3). The proton pump, an  $\text{H}^+$ -ATPase, is a complex multimeric protein assembled from at least 13 subunits. The kidney-specific isoform of  $\text{H}^+$ -ATPase has 2 subunits implicated in autosomal-recessive RTA: the B1 and the a4 subunits. RTA with a defect in the B1 subunit is associated with sensorineural hearing loss (see Table 322-3, OMIM 267300) and is attributed to a mutation of *ATP6V1B1* at locus 2p13.3. The B1 subunit is a component of the catalytic site that hydrolyzes ATP. The sensorineural hearing deficit is evident early in life and may at first manifest as delayed language development. The *ATP6V1B1* gene is also expressed in the cochlea, and presumably the homozygous expression of the mutant alleles accounts for the hearing impairment.

A second form of autosomal-recessive regeneration-defect RTA with mild or later-onset hearing impairment in some individuals (see Table 322-3, OMIM 605239) is the result of a mutation of *ATP6V0A4* at locus 7q33-34, which encodes the a4 subunit of the apical proton pump. This gene is also expressed in the inner ear. The a4 subunit is important for both assembly of the pump and its ATPase activity.

A rare form of regeneration-type RTA has a pattern of autosomal dominant inheritance and is caused by a mutation of *SLC4A1* (OMIM, 179800, 109270, locus, 17q21-22) encoding the basolateral AE1 exchanger (see Table 322-3, Figure 322-2). An autosomal-recessive form consequent to the same mutation has a more severe phenotypic expression.

These rare primary types of RTA are typically associated with impaired growth progress, polyuria, hypercalciuria, nephrocalcinosis, nephrolithiasis, and hypokalemia. Because of impaired concentrating ability, infants are susceptible to the rapid development of severe dehydration in the event of diarrheal illness or protracted vomiting. The tendency to hypovolemia as a consequence of impaired urinary concentrating

ability stimulates aldosterone release, contributing to hypokalemia. Medullary nephrocalcinosis is apparent early in infancy and is readily detected on ultrasound examination as hyperechoic medullary regions. The further accumulation of calcium deposits may lead to chronic kidney disease in later years if acidosis is not adequately treated. Nephrocalcinosis may also interfere with the medullary recycling of  $\text{NH}_4^+$  and contribute to impairment of  $\text{NH}_4^+$  excretion. Nephrocalcinosis is attributed to hypercalciuria (calcium excretion  $>4$  mg/kg/day) and the latter is a consequence of the release of calcium from bone under the stimulus of metabolic acidosis. Enhanced proximal tubular absorption of citrate during acidosis and the consequent diminished rate of citrate excretion contribute to nephrocalcinosis.

Long-standing untreated, or inadequately treated RTA, and consequent buffering of  $\text{H}^+$  by bone mineral, release of calcium from bone, and hypercalciuria may cause decreased bone mineral density and increased risk of fracture. A baseline assessment of bone mineral density and subsequent periodic follow-up should be included in the long-term management plan. The periodic assessment of bone health also includes measurement of vitamin D status (25-hydroxycholecalciferol).

Some infants with primary regeneration-type RTA may also have a transient phase of impaired  $\text{HCO}_3^-$  reclamation and  $\text{HCO}_3^-$  wasting, requiring large doses of alkali. This hybrid type was once referred to as type 3 RTA. The reclamation defect subsides during childhood and the phenotype of regeneration-type RTA emerges. This presumed defect of  $\text{HCO}_3^-$  reclamation has not been characterized and it is not known which transporter in the proximal tubule cell may be affected.

Another variant of regeneration-type RTA is associated with a preserved ability to lower urine pH despite a low absolute rate of  $\text{H}^+$  secretion, resulting in a diminished accumulation of  $\text{CO}_2$  in urine (and a low urinary  $\text{CO}_2$  partial pressure [ $\text{PCO}_2$ ]) during bicarbonate administration. The low urine-to-blood  $\text{PCO}_2$  gradient has been interpreted as a rate-limited defect consequent to a presumed diminished rate of secretion of  $\text{H}^+$  in the collecting duct. However, this entity may simply be a milder expression of a primary secretory defect resulting from partial impairment of the apical  $\text{H}^+$ -ATPase. Nevertheless,  $\text{H}^+$  secretion is sufficient to establish a steep transtubular  $\text{H}^+$  gradient. Consequently, urine pH alone cannot be relied upon for the diagnosis of RTA because individuals with a rate-limited defect will not be identified without assessing the urine-to-blood  $\text{PCO}_2$  gradient (see Table 322-4,  $(\text{U} - \text{B}) \text{PCO}_2$ ).

The obverse of the rate-limited defect is ‘incomplete’ regeneration-type RTA. In this instance, blood acid-base status is normal but urinary acidification is impaired and a minimum urine pH less than 5.5 is not achieved. This condition has been implicated in adults with nephrolithiasis. Kidney stone passage was the first clue to a diminished rate of  $\text{H}^+$  secretion in the collecting duct. A recent report of an affected family with nephrolithiasis, hypocitraturia, and alkaline urine in heterozygotes with a mutation of 1 *ATP6V1B1* allele indicates that the B1 product of the normal allele is a functional component of the  $\text{H}^+$ -ATPase transporter.

Table 322-4  
Comparison of Reclamation Defect–Type Renal Tubular Acidosis and Regeneration Defect–Type Renal Tubular Acidosis

PARAMETER	RECLAMATION DEFECT		REGENERATION DEFECT	
	DURING ACIDEMIA	AFTER TREATMENT OF ACIDEMIA	NON HYPERKALEMIC	HYPERKALEMIC
Urine pH minimum	<5.5	>5.5	>5.5	>5.5
UAG	Negative	Not reliable	Positive	Positive
NH <sub>4</sub> <sup>+</sup> excretion	Decreased	Normal	Decreased	Decreased
Plasma K <sup>+</sup>	Normal or decreased	Normal or decreased	Normal or decreased	Increased
Fractional excretion of HCO <sub>3</sub> <sup>–</sup> as percentage of filtered load	<5	>10–15	<5	<5
(U – B) PCO <sub>2</sub> (mm Hg)	>20	—	<20	>20
Ca <sub>2</sub> <sup>+</sup> excretion	Normal	Normal	Increased	Normal or decreased
Citrate excretion	Normal	Normal	Decreased	Normal
Nephrocalcinosis, nephrolithiasis, or both present	Not present	Not present	Common	Not present
Bone disease	Rickets or osteomalacia	Rickets or osteomalacia	Rickets or osteomalacia	Rickets or osteomalacia
Alkali dose (mEq/kg/day)	10–20	10–20	5–8 (infancy), 3–4 (children)	5–8 (infancy), 3–4 (children)
				Not needed if response to fludrocortisone is adequate

B, blood; RTA, renal tubular acidosis; U, urine; UAG, urinary anion gap; (U – B) PCO<sub>2</sub>, partial pressure of CO<sub>2</sub> gradient between urine and blood.



The authors report that the expression of the normal allele is not negated by the mutant allele and that the milder phenotype of the haplo-insufficient state may explain some cases of calcium nephrolithiasis in individuals with a normal plasma  $\text{HCO}_3^-$  not suspected of having RTA.

Incomplete regeneration-defect RTA has been shown to affect height in boys with posterior urethral valves, normal estimated glomerular filtration rate, and normal acid-base status but impaired urinary acidification after challenge with  $\text{NH}_4\text{Cl}$ . The genetic conditions previously mentioned do not account for all instances of monogenic RTA. There may be up to 20% of primary RTA that has not yet been associated with a specific genetic defect. Moreover, instances of RTA without a known gene defect affecting a transporter may, in fact, be the result of mutations of modifier genes, or genes encoding transcription factors or proteins, involved in the trafficking of transporters to the cell membrane from sites of synthesis within the cell. Moreover, a mutation may not alter the structure or function of a transporter but may affect membrane targeting.

Acquired defects of acidification may occur when the renal medulla of both kidneys has sustained injury or distortion because of diffuse post-pyelonephritic scarring, sickle cell disease, obstructive hydronephrosis, nephrocalcinosis, and medullary sponge kidney.

The nonheritable occurrence of regeneration-defect RTA may also be associated with medications, such as amphotericin B and lithium (see Table 322-2). This may be encountered in medically complex patients receiving chemotherapy for cancer or certain antibiotics as prophylaxis while immunosuppressed.

Hypocitraturia is common in children with a regeneration-defect RTA and contributes to the susceptibility to nephrolithiasis and nephrocalcinosis. Citrate is the predominant urinary organic anion. It acts as an inhibitor of calcium stone formation by chelating ionized calcium as a soluble complex of calcium citrate, thereby lowering the supersaturation index of calcium oxalate or calcium phosphate. Filtered citrate, which exists as the tricarboxylate anion at physiologic pH, is preferentially absorbed as the dicarboxylate anion by an apical  $\text{Na}^+$ -dependent transporter in the proximal tubule. Urinary citrate reflects the proportion of filtered citrate that is not absorbed and is influenced by the state of acid-base balance. Absorption is enhanced by acidosis, which accounts for hypocitraturia in nonhyperkalemic regeneration-type RTA. Hyperkalemia suppresses the apical dicarboxylate transporter, possibly accounting for the normal-to-high urinary citrate and protection against nephrolithiasis in the hyperkalemic form of RTA. Hypokalemia enhances proximal citrate absorption and must be corrected if hypocitraturia is to be prevented or effectively treated. In healthy children between 3 and 15 years, the random urine citrate-to-creatinine ratio ranges between 127 and 300 mg/g creatinine or 75 to 177  $\text{mcmol/mM}$  of creatinine. The lower limit of the reference range of citrate excretion is  $180\text{mg}/1.73\text{m}^2$  in healthy males and  $250\text{mg}/1.73\text{m}^2$  in females based on a recent study of urinary citrate excretion, which showed both age and gender dependence. It is useful to monitor urinary

citrate excretion and the supersaturation indices of calcium oxalate and calcium phosphate in 24-hour urine collections during treatment with citrate to assess its efficacy.

Hypokalemia is common in regeneration-defect RTA and in some patients it may be severe and cause marked muscle weakness. The occurrence of hypokalemia does not seem to depend on a particular genetic subtype, but is more pronounced in autosomal-recessive regeneration-defect RTA. Amiloride, an inhibitor of the principal cell ENaC transporter, has been used to ameliorate the potassium wasting by diminishing the lumen-negative potential in the collecting duct.

### Hyperkalemic Regeneration Defect

There are 2 subtypes of hyperkalemic regeneration-defect RTA listed in Table 322-3. One subtype has an intact ability to acidify urine; the second subtype resembles the classic regeneration-type RTA in its inability to establish a steep  $\text{H}^+$  gradient by lowering urine pH to less than 5.5. In each instance, hyperkalemia suppresses both the production of  $\text{NH}_4^+$  in the proximal tubule and the transport of  $\text{NH}_4^+$  from the lumen of the TAL to the medullary interstitium.

The subtype with intact acidification is associated with rare hereditary conditions, including pseudo-hypoaldosteronism (PHA, type 1a and type 1b). The unresponsiveness of the principal cell of the collecting duct to aldosterone causes diminished lumen negativity that is normally generated by the ENaC channel. As a consequence,  $\text{K}^+$  secretion by the principal cell and  $\text{H}^+$  secretion by the type A intercalated cell are impaired. The diminution of lumen negativity (also referred to as a “voltage defect”) can also occur if there is decreased delivery of  $\text{Na}^+$  from the distal tubule to the collecting duct. The net effect of diminished  $\text{H}^+$  secretion is that accumulation of  $\text{NH}_4^+$  in the lumen of the medullary collecting duct is also diminished. The low rate of  $\text{H}^+$  excretion as  $\text{NH}_4^+$  results in metabolic acidosis, but the proximate causes are diminished lumen negativity, impaired  $\text{K}^+$  secretion, and hyperkalemia. The latter, in turn, suppresses  $\text{NH}_4^+$  generation by the proximal tubule. However, sufficient capacity remains for  $\text{H}^+$  secretion in the inner medullary collecting duct to achieve a urine pH less than 5.5. The impaired lumen negativity limiting  $\text{H}^+$  secretion by the apical proton pump may be partially offset by acidosis-induced upregulation of the apical  $\text{H}^+/\text{K}^+$ -ATPase of the type A intercalated cell (this transporter is not shown in Figure 322-2).

Most primary hyperkalemic RTA is caused by PHA type 1, which includes 2 main subtypes (1a and 1b). The renal-limited, or classic subtype (PHA, type 1a, OMIM 177735, 600983), has autosomal-dominant inheritance of a mutant *MLR* gene at locus 4q31.1, encoding the mineralocorticoid receptor (MR) protein (see Table 322-3). Phenotypic expression is highly variable. A severe salt-losing condition in neonates may result in death. Adults may have normal electrolytes and have an increased plasma aldosterone as the only manifestation of the disorder. Some children have a relatively mild disorder and are readily managed with salt replacement and alkali. In some instances, treatment is not needed beyond childhood, suggesting that

upregulated expression of the nonmutated allele has compensated for the haploinsufficient state by increasing the production of the functional MR protein. Some individuals without a history of affected family members may have a *de novo* mutation. The severe neonatal phenotype of PHA type 1a with salt wasting, hyponatremia, hyperkalemia, vomiting, dehydration, and metabolic acidosis resembles salt-losing congenital adrenal hyperplasia because of hypoaldosteronism consequent to adrenal 21-hydroxylase deficiency, an autosomal-recessive disorder.

The second subtype of PHA type 1 is an autosomal-recessive systemic disorder with multiple target organ defects (PHA type 1b, OMIM 269350) and is a consequence of a mutation affecting any 1 of the 3 genes encoding separate subunits of the ENaC channel protein (see Table 322-3). ENaC is also expressed in the lung, sweat glands, salivary glands, and colon. The concentrations of  $\text{Na}^+$  and  $\text{Cl}^-$  are increased in sweat, and because respiratory symptoms may also be present, this disorder may be confused with cystic fibrosis. The lung ENaC is active in the immediate postnatal period in clearing fluid from the lung, but instances of neonatal respiratory distress syndrome attributable to the systemic subtype of PHA type 1 have not been well documented. This disorder may also present with profound salt-wasting, hypovolemia, and metabolic acidosis, mimicking congenital adrenal hyperplasia. After the electrolyte abnormalities have been treated with salt and alkali, recurrent respiratory infections may dominate the clinical course during infancy. This subtype does not have a spontaneous remission and treatment is lifelong.

Some very low-birth-weight infants with a PHA type 1 phenotype may not actually have a heritable disorder but rather transient insufficiency or hyporesponsiveness of the MR protein to aldosterone. An entity referred to as “early childhood hyperkalemia” may be a consequence of the delayed appearance of MRs, resulting in impaired lumen negativity in the collecting duct. However, it is not associated with the severe sodium wasting and hypovolemia seen in typical neonatal PHA type 1. Plasma renin and aldosterone may be normal or high. This variant seems to be self-limited but, though hyperkalemia persists (serum  $\text{K}^+$  consistently  $>5.5$  mEq/L), it can be treated with furosemide to promote urinary  $\text{K}^+$  loss or with oral administration of a sodium polystyrene sulfonate resin that binds  $\text{K}^+$ . Infant formula can be depleted of  $\text{K}^+$  by adding the resin and then providing the supernatant for oral ingestion.

Another rare form of hyperkalemic regeneration-defect RTA is familial hyperkalemic hypertension, or PHA type 2A (OMIM 145260). This autosomal-dominant condition may not be diagnosed until adolescence or adulthood and is also known as Gordon syndrome or chloride shunt syndrome. Hyperabsorption of  $\text{Na}^+$  and  $\text{Cl}^-$  in the distal tubule by the thiazide-sensitive  $\text{Na}^+, \text{Cl}^-$ -cotransporter (NCCT), results in hypervolemia and low-renin hypertension. The consequent decreased delivery of  $\text{Na}^+$  to the principal cells of the collecting duct limits the ability to generate a lumen-negative potential and diminishes the driving force for  $\text{H}^+$  and  $\text{K}^+$  secretion. Although it typically occurs in adolescents and adults, it may also appear in neonates. This syndrome is known as Spitzer-Weinstein syndrome. A

low dose of a thiazide diuretic is effective treatment of the hypertension and hypervolemia. The increased delivery of  $\text{Na}^+$  to the collecting duct after beginning treatment with a thiazide enables lumen negativity, promoting  $\text{H}^+$  and  $\text{K}^+$  secretion and correcting both the metabolic acidosis and hyperkalemia. This diagnosis should be considered in a family with early-onset hypertension and hyperkalemia. There is genetic heterogeneity of this hyperkalemia-hypertension syndrome, including a mutation of *WNK1* (locus 12p13) or a mutation of *WNK4* (locus 17q21-22, see Table 322-3). The loss-of-function mutations of either of these genes results in upregulation of the activity of the NCCT protein.

Another clinical subtype of hyperkalemic RTA with impaired acidification may be associated with acquired renal parenchymal damage caused by recurrent pyelonephritis, obstructive uropathy, or sickle cell disease. The parenchymal damage may interfere with aldosterone binding to its receptor, as well as the medullary recycling of  $\text{NH}_4^+$ . Acidification by the inner medullary collecting duct may be impaired in these chronic tubulointerstitial nephropathies, and urine pH is generally above 5.5.

Other nonheritable causes of hyperkalemic regeneration-defect RTA are, in rare instances, from medications (see Table 322-2), such as inhibitors of the renin-angiotensin system (angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers). In some instances, RTA is the expected consequence of the pharmacologic action of a medication. For example, amiloride, triamterene, and trimethoprim inhibit the ENaC of the principal cell. The aldosterone antagonists, spironolactone and eplerenone, bind to the MR and indirectly cause impaired lumen negativity by downregulation of the aldosterone-dependent ENaC channel.

Calcineurin inhibitors (cyclosporine or tacrolimus) have been implicated in causing mild metabolic acidosis and hyperkalemia after solid organ transplantation (see Table 322-2). The mechanism seems to be impaired responsiveness of the MR or acquired hypoaldosteronism that results from a hyporeninemic state. This condition responds to fludrocortisone.

A child with edema from nephrotic syndrome or hepatic cirrhosis who is not receiving diuretics may not have sufficient delivery of  $\text{Na}^+$  to the collecting duct to maintain lumen negativity, although this is rare. In essence, this is an acquired form of hyperkalemic regeneration-defect RTA.

### Hybrid

The hybrid type of RTA is rare and was once referred to as type 3 RTA. One well-characterized entity is marble bone disease (Guibaud-Vainsel syndrome), a rare autosomal-recessive disorder, which has elements of both  $\text{HCO}_3^-$  wasting (a reclamation defect) and impaired acidification (a regeneration defect). The cytosolic enzyme, CA II, is present in both the cells of the proximal tubule and the type A intercalated cells of the collecting duct. CA II is also present in osteoclasts. A bi-allelic loss-of-function mutation of *CA2* at locus 8q22 (OMIM +259730) has been identified in children with failure to thrive, osteopetrosis, cerebral calcifications, and mental impairment (see Table 322-3). Most reports

are of children of Arab ethnicity and in many instances there is a history of consanguinity. Osteoclastic resorption of bone is dependent on  $H^+$  secretion at the osteoclast–bone mineral interface. The impairment of osteoclast activity that occurs as a result of a deficiency of CA II causes low bone turnover, osteopetrosis, and an increased susceptibility to fractures. The dose of alkali required to correct the metabolic acidosis is comparable to that for reclamation-defect RTA. Medications inhibiting CA II and CA IV, such as acetazolamide, sulfonamides, or topiramate, are rare nonheritable causes of a hybrid RTA (see Table 322-2). Since cytosolic CA II is expressed widely in the kidney, it is especially susceptible to carbonic anhydrase inhibitors.

### Delayed Maturity

The concept that delayed development of certain discrete tubular functions may account for a self-limited form of RTA is discussed under the presumption that there is a delay in maturation of these functions during infancy. The phenotype, whether reclamation-defect RTA, regeneration-defect RTA, or an RTA with elements of both defects, is variable depending on which function lags in development. This presumption is not yet supported with data as to genetic controls of the maturation program of kidney development.

Some infants with failure to thrive and acidosis are suspected of having RTA and referred for further evaluation. Because the kidney is not an excretory organ during intrauterine life, glomerular filtration rate and tubular functions are low in the immediate newborn period. The postnatal maturation of tubular transport functions is load-driven, but the capacity to augment function in response to the excretory load may lag in some infants. Some very low-birth-weight infants may have a lower renal  $HCO_3^-$  threshold (the plasma concentration at which  $HCO_3^-$  begins to appear in urine), maintaining a steady-state serum  $HCO_3^-$  as low as 17 to 19 mEq/L. As mentioned in the Reclamation Defect section, some infants with recurrent vomiting and failure to thrive seem to have a delay in the development of the reclamation mechanism, which eventually resolves. None of the infants with recurrent vomiting and failure to thrive referenced above had Fanconi syndrome. The presumption is that this reclamation defect is a consequence of a delay in the emergence of a full complement of either NHE3 or NBC1 transporters in the proximal tubule.

In addition to a reclamation defect, some very low-birth-weight infants may also have an impaired ability to conserve  $Na^+$ . This impairment may represent an inability of the distal nephron to respond to aldosterone, perhaps because of a delay in the emergence of an adequate complement of MRs, analogous to the renal subtype of PHA type 1. Moreover, the impaired response to aldosterone may also lead to hyperkalemia and its consequent inhibition of  $NH_4^+$  production in the proximal tubule, which may persist during the first few years of life. The impaired response to aldosterone in infants in the first few months of life may explain the somewhat higher reference range (mean  $\pm$  standard deviation) for plasma  $K^+$ ,  $5.2 \pm 0.8$  mEq/L. A reasonable presumption is that, in addition to an impaired response to aldosterone, delayed

maturation of either the  $H^+$ -ATPase or the AE1 transporter of the type A intercalated cell may produce a transient  $HCO_3^-$  regeneration defect in some infants. Thus, this type of RTA, a consequence of delayed maturity rather than a genetic mutation, is also a hybrid disorder in some infants and has elements of both  $HCO_3^-$  reclamation and regeneration defects. The risk for RTA is further amplified in low-birth-weight infants with nephrocalcinosis as a consequence of furosemide treatment, resulting in impaired accumulation of  $NH_4^+$  in the medullary interstitium. However, not all infants with a low serum  $HCO_3^-$  should be diagnosed as delayed-maturity RTA if they are not acidemic and are gaining weight. These infants may simply have a transiently lowered tubular threshold for  $HCO_3^-$  excretion. In fact, it may be “physiologic” to maintain a somewhat lower steady state concentration of serum  $HCO_3^-$ , since the intake of breast milk or humanized formula is less acidogenic owing to the relatively low protein content.

### Acquired Renal Tubular Acidosis

The genetic forms of RTA are rare. It is more likely that the primary care physician will encounter RTA caused by drugs affecting transporters in certain segments of the nephron. Many drugs have been implicated, but Table 322-2 displays a selected list in relation to the affected mechanism of  $HCO_3^-$  handling. Generally, drug-induced RTA is reversible after cessation of the offending drug unless tubulointerstitial fibrosis has supervened.

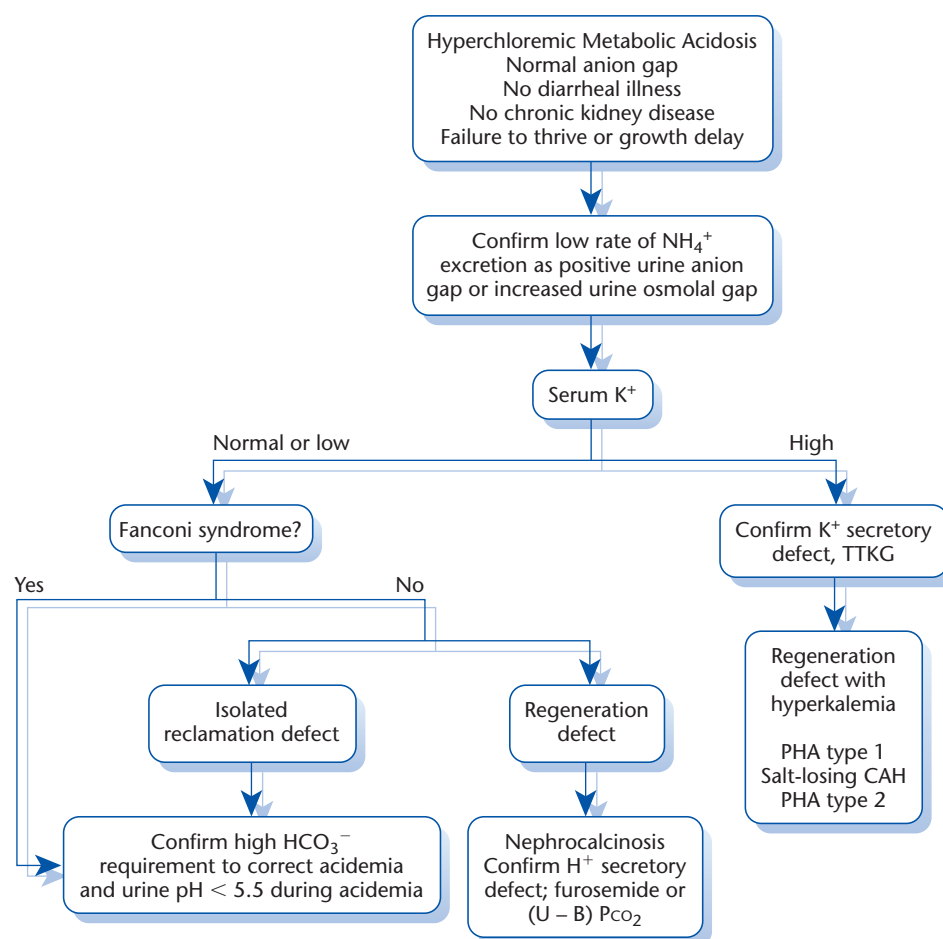
### EVALUATION

The comprehensive evaluation of suspected RTA entails studies with access to a clinical laboratory working in close collaboration with a nephrologist. However, the physician can perform several simple tests. One pathway of decision making for a systematic evaluation is depicted in an algorithm and includes elements of history and physical examination in addition to biochemical findings (see Figure 322-5). The initial presentation of RTA is often that of an infant or young child with failure to thrive. There are many causes of failure to thrive, including disorders that are not primary renal disorders. The initial screening should include an assessment of thyroid function and bone age and other tests appropriate for a possible nonrenal etiology of failure to thrive.

Once it is established that the patient has a renal etiology for hyperchloremic metabolic acidosis, the principal assessment is an estimate of urinary  $NH_4^+$  by measuring  $Na^+$ ,  $K^+$ , and  $Cl^-$  concentration in a random urine specimen and calculating the urinary anion gap (UAG, mEq/L):

$$UAG = [Na^+] + [K^+] - [Cl^-]$$

On a typical diet,  $Cl^-$  is the main anion accompanying urinary  $NH_4^+$ , and the concentration of  $Cl^-$  exceeds the sum of the concentrations of  $Na^+$  and  $K^+$ . Because urinary  $NH_4^+$  is not directly measured, the UAG is a negative quantity or close to zero in healthy individuals. In the instance of regeneration-defect RTA the rate of  $NH_4^+$  excretion is low, and the rate of  $Cl^-$  excretion is accordingly also low and its concentration is usually



**Figure 322-5** This decision tree presumes that nonrenal causes of hyperchloremic metabolic acidosis, such as viral gastroenteritis, have been ruled out. The usual presentation of RTA is either failure to thrive during infancy or growth progress delay in early childhood. This pathway of decision points is intended for the initial evaluation by a primary care provider and is not complete and does not list all the possibilities. After confirming a low rate of  $\text{NH}_4^+$  excretion, the algorithm depicted has two main branch points based on the serum potassium concentration. If the serum  $\text{K}^+$  is low or normal and a Fanconi syndrome is not found, the pathway then branches between either an isolated  $\text{HCO}_3^-$  reclamation defect or a  $\text{HCO}_3^-$  regeneration defect. Monogenic causes of an isolated reclamation defect (if a Fanconi syndrome is excluded) are rare. An isolated reclamation defect is more likely to be encountered as a duration-limited defect in low-birth-weight infants with delayed maturity of tubular function. Beyond this decision point, referral to a pediatric kidney disease specialist is appropriate. If hyperkalemia is found and a  $\text{K}^+$  secretory defect confirmed by TTKG, possibilities include PHA type 1, salt-losing CAH, and PHA type 2 and referral to a pediatric kidney disease specialist or endocrinologist is appropriate. CAH, congenital adrenal hyperplasia; PHA, pseudohypoaldosteronism; RTA, renal tubular acidosis; TTKG, transtubular potassium gradient;  $(U - B) \text{PCO}_2$ , urine minus blood  $\text{PCO}_2$ .

less than the sum  $[\text{Na}^+] + [\text{K}^+]$ , in the formula above. In this instance, the UAG is positive. This estimate is less reliable if urine pH is relatively alkaline, exceeding 6.7, at which  $\text{HCO}_3^-$  becomes a significant component of the unmeasured anions. For example, at a urine pH of 7.0 the concentration of  $\text{HCO}_3^-$  in urine is approximately 10 mEq/L; at a pH of 7.3, it is approximately 20 mEq/L. The UAG is normal in reclamation-defect RTA during the acidemia that ensues after stopping alkali treatment. The UAG estimate in such patients is not reliable during alkali treatment because of massive  $\text{HCO}_3^-$  wasting. The reliability of this estimate is also negatively affected by an increase in other unmeasured anions, such as ketoacid anions or sulfate (the latter may be a consequence of a high protein intake).

Another surrogate measure for urinary  $\text{NH}_4^+$  is the urine osmolal gap (UOG, mOsm/kg; osmolality is expressed as mOsm per kg of water), estimated from urinary constituents as:

$$\text{UOG} = [\text{measured urine Osm}] - (2[\text{Na}_u + \text{K}_u] + [\text{urea}_u] + [\text{glucose}_u])$$

During the first several weeks of life, an infant receiving formula simulating breast milk has a protein intake nearly aligned with the rate of synthesis of new protein, and the “acidogenic drive” is at a low set point. In this setting the mechanism for an adaptive upregulation of  $\text{NH}_4^+$  production has not been fully activated and the urine anion gap may be positive and incorrectly interpreted as consistent with RTA, even in a



normal infant. The concentration of urea in urine ( $[\text{urea}]_u$  as (mM/L) in the above equation), is calculated as  $\text{urea}_u = (\text{urea nitrogen in urine [mg/dL]}/2.8)$ . If glucosuria is not present then  $[\text{glucose}]_u$  is zero. However, if glucosuria is present (Fanconi syndrome) and glucose is reported in units of mg/dL, then  $[\text{glucose}]_u$ , mM/L = (glucose in urine, mg/dL/18). A UOG of more than 100 mOsm/kg suggests that urinary  $\text{NH}_4^+$  excretion is not impaired and that the unmeasured  $\text{NH}_4^+$  is a significant component of the osmolal gap. The actual  $\text{NH}_4^+$  is about one-half of the UOG because the concentrations of  $\text{NH}_4^+$  and  $\text{Cl}^-$  are approximately equal. One caveat is that a child with possible reclamation-defect RTA who has not begun treatment for acidosis will have appropriate excretion of  $\text{NH}_4^+$  and  $\text{Cl}^-$ . This will be reflected in a normal UOG.

If the serum  $\text{K}^+$  is low or normal, then the diagnostic possibilities include either a reclamation-defect RTA or a nonhyperkalemic-regeneration-defect RTA (see algorithm in Figure 322-5). If urine glucose is positive, then further testing is performed to establish the presence of a Fanconi syndrome in association with the reclamation defect. Empiric treatment with a citrate solution may confirm the diagnosis of a reclamation defect if the dose required for correcting the serum  $\text{HCO}_3^-$  approaches 10 to 15 mEq/kg/day, well above the endogenous rate of acid production. However, an increased dose requirement may also occur in some infants with the rare hybrid-type RTA as a transient phenomenon during the first few years of life.

Ammonium chloride challenge to assess the ability to maximally acidify urine is rarely performed in children. As indicated in Table 322-4, the (U – B)  $\text{PCO}_2$  difference may indicate a limitation of acidification if the (U – B)  $\text{PCO}_2$  is less than 20 mmHg, consistent with a defect of the apical  $\text{H}^+$ -ATPase of the type A intercalated cell. This assessment is only applicable for regeneration-defect RTA and should only be performed after treatment with alkali has restored plasma  $\text{HCO}_3^-$  to normal. However, it is best done under the supervision of a nephrologist in collaboration with a laboratory able to process urine collected with minimal exposure to room air to prevent loss of  $\text{CO}_2$ . Acidification may also be assessed by giving a challenge dose of furosemide, 1 or 2 mg/kg, following administration of a priming dose of fludrocortisone (0.1 mg) several hours earlier. Intact acidification is indicated by a urine pH <5.5.

The presence of medullary nephrocalcinosis on ultrasound examination is consistent with the diagnosis of nonhyperkalemic regeneration-defect RTA, because this type is also associated with hypercalciuria and hypocitraturia. In young infants, obtaining a reliable 24-hour urine collection for the estimation of calcium excretion is not possible without an indwelling catheter. One recourse to avoid an indwelling catheter is to collect multiple random “bag” specimens throughout the day for estimation of the urine calcium-to-creatinine ratio. However, this is only a rough approximation of calcium excretion. The norms for calcium-to-creatinine ratio of a random urine specimen vary with age (see Table 322-5).

If the serum  $\text{K}^+$  is high, suggesting the diagnosis of hyperkalemic regeneration-defect RTA, then the

**Table 322-5**

**95th Percentiles for  
Urinary Calcium/  
Creatinine Ratios by Age**

AGE RANGE (yr)	mol/mol	mg/mg
1/12–1	2.2	0.81
1–2	1.5	0.56
2–3	1.4	0.50
3–5	1.1	0.41
5–7	0.8	0.30
7–10	0.7	0.25

From Matos V, van Melle G, Boulat O, et al. Urinary phosphate/creatinine, calcium/creatinine, and magnesium/creatinine ratios in a healthy pediatric population. *J Pediatr*. 1997;131:252–257. Copyright © 1997, Elsevier, with permission.

impaired capacity to secrete  $\text{K}^+$  may be confirmed by the measurement of  $\text{K}^+$  and osmolality in plasma and a random urine specimen obtained at the same time that the blood is sampled. The results are used to calculate the transtubular potassium gradient (TTKG):

$$\frac{[\text{K}^+]_u/[\text{K}^+]_p}{[\text{Osm}]_u/[\text{Osm}]_p}$$

Potassium concentration (mEq/L) and osmolality (mOsm/kg) are measured in both urine and plasma and TTKG calculated according to the above equation. Filtered  $\text{K}^+$  is completely reabsorbed proximal to the collecting duct. Urinary  $\text{K}^+$  is essentially all derived from secretion in the distal nephron. The TTKG is a snapshot of the extent to which secretion of  $\text{K}^+$  in the outer collecting duct has established an aldosterone-driven  $\text{K}^+$  gradient between lumen and plasma, before the tubular fluid is further concentrated in the inner medulla of the collecting duct. The actual transtubular gradient in the collecting duct,  $[\text{K}^+]_u/[\text{K}^+]_p$ , is obscured when urine is further concentrated, and this is accounted for by the ratio,  $[\text{Osm}]_u/[\text{Osm}]_p$ , in the denominator. This assessment is not reliable if urine is dilute and  $[\text{Osm}]_u/[\text{Osm}]_p$  is less than 1. In the setting of hyperkalemia, the TTKG should be at least 8 if the collecting duct is responsive to mineralocorticoid. A value less than 8 suggests either insufficient production of aldosterone or a lack of responsiveness of the MR to aldosterone.

The diagnosis of PHA type 1 is suggested by an increased level of plasma aldosterone (see algorithm in Figure 322-5). If aldosterone and plasma renin are suppressed and blood pressure is increased, the rare familial hyperkalemic hypertension syndrome (PHA type 2) is a possibility. If blood pressure is normal or low and aldosterone is low in a clinical setting of salt-wasting, consideration should include congenital adrenal hyperplasia or if aldosterone is high, then the severe, potentially lethal neonatal presentation of PHA type 1 should be considered. If salt-losing congenital adrenal hyperplasia is suspected, initial testing should include plasma cortisol, aldosterone, and 17-hydroxyprogesterone. The salt-losing tendency is

ameliorated by fludrocortisone in conjunction with cortisol replacement. The metabolic acidosis is usually not severe, and further management of congenital adrenal hyperplasia is best done by a pediatric endocrinologist.

## TREATMENT

The aims of treatment are to correct metabolic acidosis and growth impairment, mitigate nephrocalcinosis or bone mineral loss, and in the instance of a primary  $H^+$  secretory defect (regeneration defect), prevent chronic kidney disease caused by progression of nephrocalcinosis. Appropriate treatment with alkali restores growth to its expected trajectory, but the dose required to sustain growth is 2- to 5-fold greater than the expected rate of endogenous acid production. Alkali in this context refers to sodium bicarbonate or a bicarbonate precursor, such as sodium or potassium citrate.

The mainstay of treatment in most children is a citrate solution. Because hypokalemia and  $K^+$  depletion are characteristic of nonhyperkalemic regeneration-defect RTA, a potassium citrate preparation is optimal. The usual liquid preparation contains 2 mEq/mL of  $K^+$  and 2 mEq/mL of  $HCO_3^-$  precursor as citrate. It also contains citric acid to make it palatable. The solution has a pH of approximately 5 before further dilution. The solution is hyperosmolar and must first be diluted 4- or 5-fold with water or infant formula before oral administration. Citrate is a substrate in the citric acid cycle, and its further oxidative metabolism ultimately yields  $HCO_3^-$  in a molar ratio of 2  $HCO_3^-$  for each citrate transported into a mitochondrion. Potassium citrate is also available for older children as a capsule in 2 dose forms, providing either 5 mEq or 10 mEq of  $K^+$ . Because it is slowly released from a wax matrix, the capsule must be swallowed whole and not opened, chewed, or crushed. It is not suitable for young children.

A combined sodium- and potassium citrate solution provides 1 mEq/mL of  $Na^+$  and  $K^+$  and also requires dilution before administration. However, potassium-containing solutions must be avoided in hyperkalemic forms of RTA. Serum potassium should be monitored, especially if glomerular filtration rate is reduced or if the patient is receiving an angiotensin converting enzyme inhibitor or an angiotensin-receptor blocker.

Sodium citrate solutions (1 mEq/mL) may be used for buffer repletion in the hyperkalemic subtype of regeneration-defect RTA. These solutions provide 1 mEq/mL of  $Na^+$  and thus has a lower osmolality than sodium- and potassium citrate solution (2 mEq/mL) or potassium citrate solution (2 mEq/mL), but it still requires dilution to a lower strength for safety and palatability. Accompanying the multiple transport defects of the Fanconi syndrome, sodium-coupled absorption of filtered citrate by the NDC1 transporter is also decreased. The consequent enhanced urinary citrate excretion provides protection against the development of nephrocalcinosis and nephrolithiasis in reclamation-defect RTA with Fanconi syndrome.

The total daily dose requirement of citrate should be divided into 3 or 4 doses so as to minimize the amplitude of fluctuations of the serum  $HCO_3^-$  level that may occur with less frequent administration. In view of data suggesting that metabolic acidosis inhibits growth hormone secretion, administration of a somewhat larger dose of a citrate solution at bedtime to coincide with the nocturnal peak of growth hormone release has been advocated.

Citrate accomplishes 2 aims of treatment: inhibition of stone formation by complexing ionic calcium in urine and, as a bicarbonate precursor, correction of metabolic acidosis. However, citrate administration can also raise the risk of calcium phosphate stone formation as the urine becomes even more alkaline in individuals with hypercalciuria. This may be monitored by periodic assessment of the supersaturation index of calcium phosphate. This assessment is available at clinical laboratories specializing in kidney stone disease management (see Tools for Practice section). The exact mechanism whereby oral administration of citrate increases urinary citrate is not known. There are data suggesting that a pH sensor in the proximal tubule cell may detect an increase in intracellular pH and downregulates tubular absorption of filtered citrate.

Oral ingestion of  $NaHCO_3$  may also be used, but the rapid buildup of  $CO_2$  in the stomach after ingestion may cause gastric distention. However, this approach may be a preferable means of buffer repletion in infants who refuse citrate solutions. A quarter teaspoon of baking soda powder ( $NaHCO_3$ ) provides 13 mEq each of  $Na^+$  and  $HCO_3^-$  and should be diluted in water or infant formula. Tablets of  $NaHCO_3$  are also available and may be crushed.

Adequate treatment of nonhyperkalemic RTA with citrate should lessen hypercalciuria. However, nephrocalcinosis, once established, is generally not reversible. The aim of treatment is to prevent its further progression to chronic or end-stage kidney disease. Correction of acidosis in patients with regeneration-defect RTA does not ameliorate the hearing impairment associated with the 2 autosomal-recessive forms of proton pump defects (see Table 322-3).

A dietary intake emphasizing meat is acidogenic, thus, a dietician may help with more appropriate meal planning. Intake of fruits and vegetables should be encouraged, because some of these food items are also sources of both potassium and citrate. Orange juice prepared from concentrate is more effective than lemonade as a source of citrate. Lemon or lime juice squeezed from fruit or prepared from concentrate has been shown to provide more citrate, but less potassium, than orange juice or lemonade. Natural lemon juice is more effective than lemonade as a source of citrate.

Growth and serum electrolytes should be monitored periodically. The serum  $HCO_3^-$  should be maintained near the upper limit of the range between 25 and 30 mEq/L (blood should be drawn just before the next dose of alkali). At these levels of  $HCO_3^-$ , osteoclastic bone resorption may be suppressed sufficiently to lower the risk of osteopenia or osteoporosis over the long term.

## ROLE OF THE PRIMARY CARE PHYSICIAN

The RTAs are complex disorders that commonly present as failure to thrive. There are many causes of failure to thrive. An assessment of growth should include previous height and weight data, thyroid function, and bone age. A correct diagnosis of RTA must be made early in life and appropriate treatment initiated to promote growth and mitigate bone mineral loss and nephrocalcinosis. The role of the primary care physician is to be aware of the possibility of RTA and to take some initial steps in the patient's workup, such as calculation of the UAG or UOG. More detailed studies and explanations of this complex disorder to parents are best accomplished by a pediatric kidney disease specialist. Moreover, genetic counseling is needed for parents with a child affected with a monogenic RTA disorder in anticipation of possible future pregnancies. Commercially available gene testing is available for some of the implicated genes (see Tools for Practice section for a link listing laboratories for genetic testing) and is best done in conjunction with genetic counseling. The hereditary forms of RTA are rarely encountered in primary care practice. As discussed above, identified mutations, including the 11 listed in Table 322-3, probably account for only a subset of instances of RTA. There are other candidate genes which may be affected but have not yet been identified. The possibility of a sporadic nongenetic occurrence of RTA, perhaps because of a medication (see Table 322-2), should be considered.

Once a child is established on an effective treatment regimen and is clinically stable with good growth progress, periodic follow-up by the primary care physician may be done in collaboration with a nephrologist.

Most children with RTA, and especially those with nephrocalcinosis, have an impairment of the urinary concentrating mechanism and a consequent obligatory polyuria. A superimposed dehydrating illness such as diarrhea or protracted vomiting can culminate in profound hypovolemia. This susceptibility may warrant prompt hospitalization and fluid administration before signs of severe dehydration emerge. The susceptibility to hypokalemia in children with regeneration-defect RTA calls for regular monitoring of the serum  $K^+$  and, if it is found to be low, an increase in the dose of the potassium-containing citrate solution should be prescribed. If profound hypokalemia exists with a serum  $K^+$  less than 2.5 mEq/L accompanied by muscle weakness, then prompt hospitalization may be needed. A newborn with a salt-losing tendency, such as is common in severely affected infants with type 1 PHA, may not be diagnosed before discharge from the nursery. The emergence of vomiting, feeding difficulty, listlessness, hypotonia, hyperventilation, pallor, and signs of dehydration call for urgent readmission and vigorous volume and sodium repletion. In the absence of virilization, the presence of congenital adrenal hyperplasia in a male infant may not be recognized at birth and an infant may be discharged from the nursery only to develop profound salt wasting and hypovolemic shock 1 to 2 weeks later. Newborn screening in the United States now includes congenital adrenal hyperplasia.

If compliance with the medication regimen or an intercurrent illness interferes with taking medication, then hospitalization may be needed for parenteral administration of fluid and  $HCO_3^-$  for the treatment of severe metabolic acidosis.

A child with nonhyperkalemic regeneration-defect RTA may experience severe pain during passage of a kidney stone and require hospitalization. If the stone is impacted in a ureter, then monitoring for the development of obstructive hydronephrosis and medical pain management will be needed along with urologic consultation.

### WHEN TO REFER

- RTA is suspected by assessment of UAG or UOG or suggested by family history.
- Fanconi syndrome is suspected.

### WHEN TO ADMIT

- Hypovolemia (often caused by an illness accompanied by diarrhea or vomiting)
- Hypokalemia with a serum  $K^+$  less than 2.5 mEq/L, especially if accompanied by muscle weakness
- If adherence to the medication regimen or an intercurrent illness interferes with taking medication, then hospitalization may be needed for parenteral administration of  $HCO_3^-$  for the treatment of severe metabolic acidosis or parenteral potassium administration for severe hypokalemia
- Kidney stone

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Renal Tubule Acidosis* (Web page), National Institutes of Diabetes and Digestive and Kidney Diseases ([niddk.nih.gov/health-information/health-topics/kidney-disease/renal-tubular-acidosis-rta/Pages/facts.aspx](http://niddk.nih.gov/health-information/health-topics/kidney-disease/renal-tubular-acidosis-rta/Pages/facts.aspx))
- *What Is Renal Tubule Acidosis?* (Web page), University of Alberta ([cybernephrology.ualberta.ca/nephkids/rta.htm](http://cybernephrology.ualberta.ca/nephkids/rta.htm))

### Medical Decision Support

- *GeneTests* (Web site), ([genetests.org](http://genetests.org))
- *Genetic Testing Registry* (Web site), National Center for Biotechnology Information ([ncbi.nlm.nih.gov/gtr](http://ncbi.nlm.nih.gov/gtr))
- *Online Mendelian Inheritance in Man* (Web site), Johns Hopkins University ([omim.org](http://omim.org))

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## Chapter 323

# RHEUMATIC FEVER

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## INTRODUCTION

Acute rheumatic fever is a systemic connective tissue disorder that is characterized by polyarthritis, carditis, and chorea, either singly or in combination. The major long-term consequence is the potential for inflammatory cardiac valvar involvement, leading to chronic heart disease. The other manifestations are self-limiting with no late sequelae. Arthritis clears without joint dysfunction or deformity, and chorea leaves no neuromuscular impediment. Preventing recurrent attacks that carry the risk of recrudescence heart involvement and further cardiac damage is the most important concern.

The major goal of pediatric care is preventing an initial attack of rheumatic fever, which can be accomplished by effective treatment of group A  $\beta$ -hemolytic streptococcal (GAS) pharyngitis. A recent American Heart Association Statement has reiterated that penicillin (either oral penicillin V or injectable benzathene penicillin) remains the treatment of choice. GAS resistance to penicillin has not been documented. For patients who are penicillin-allergic, a number of orally administered antibiotic agents are available.

## EPIDEMIOLOGIC FEATURES

### Incidence

An immunologic reaction to GAS infection is the established cause of rheumatic fever. The incidence of rheumatic fever observed in epidemics of streptococcal pharyngitis is approximately 2% to 3%, whereas the attack rate after sporadic streptococcal upper respiratory tract infection is only approximately 0.2% to 0.3%. In patients who have already had one or more attacks of rheumatic fever, however, the recurrence rate of carditis increases to approximately 15% after subsequent streptococcal infection.

### Age

Rheumatic fever is predominantly a disease of school-aged children, with most first occurrences between 5 and 15 years of age. It is uncommon in children younger than 5 years and extremely rare in children younger than 3 years. When occurring in infancy, acute rheumatic fever is usually associated with severe carditis and congestive heart failure. Polyarthritis caused by rheumatic fever is unusual in the preschool-aged group; rheumatoid arthritis and other inflammatory diseases of the joint are more likely diagnoses. Chorea also is uncommon in early childhood; most of the cases occur in children older than 8 years.

### Host Susceptibility

Rheumatic fever has often been called a *social status disease*, and most studies have noted its strong association with poverty. The major social risk factors that

predispose children to rheumatic fever seem to be crowding and lack of medical attention. Crowding increases the likelihood of transmission of the GAS from person to person, and lack of medical care precludes timely treatment of streptococcal pharyngitis, resulting in the later presentation of a child with signs and symptoms of acute rheumatic fever.

The tendency for rheumatic fever to occur in more than one family member has long been recognized. The observation is noted even when family members are not concurrently living in the same household, indicating that environmental influences are probably not solely responsible for the disease. No genetic factors have been clearly established.

Sex predisposition does not exist in the incidence of arthritis or carditis in childhood, although chorea has been noted to be more common in girls. Sex differences exist, however, in the type of valvular lesions that develop with carditis; boys have a higher incidence than girls of aortic regurgitation. In young adults, mitral stenosis is more common in women than in men.

Numerous primary prevention community programs have demonstrated the efficacy of identifying streptococcal infection by performing throat cultures on susceptible children and treating them early. Furthermore, the widespread application of secondary prevention in the form of antistreptococcal prophylaxis programs for patients after their first attack has significantly reduced the recurrence rate and the additive effects of repeated bouts of carditis.

The incidence of acute rheumatic fever has declined in the last 5 decades in the United States and Europe. However, in economically underdeveloped countries, rheumatic fever remains a common illness in childhood. Continued immigration from the Caribbean Islands, South America, and Southeast Asia is also a factor in the prevalence of the disease in the United States. An apparent resurgence of acute rheumatic fever in certain areas of the United States, both urban and suburban, was reported between 1984 and 1988 and again in 1997 and 1998, but no evidence indicates that this trend has continued. Although the disease persists, the annual incidence may be so low, even at large teaching medical centers, that during 3 years of pediatric training, a resident physician may see very few children with acute rheumatic fever.

## DIAGNOSIS

### Jones Criteria

No pathognomonic clinical findings or specific laboratory tests are available to confirm the diagnosis of rheumatic fever; hence the diagnosis must be somewhat arbitrary and empirical. A list of major and minor criteria for the evaluation and diagnosis of rheumatic fever and rheumatic heart disease was published more than 70 years ago by Dr T. Duckett Jones. These guidelines have been accepted as diagnostic criteria throughout the world and have been modified (1955) and revised (1984) by specifically appointed committees of the American Heart Association. A further revision of the Jones criteria was designated in a 1992 update and was reviewed in 2002. The most



recent revision of the Jones criteria was published in 2015. The major highlights include proposing different criteria for medium-risk and high-risk versus low-risk populations, the use of Doppler echocardiography in the diagnosis of silent carditis, and including monoarticular arthritis as a major criterion in moderate-risk and high-risk populations. Low risk is defined as having an incidence of acute rheumatic fever of fewer than 2 per 100,000 school-aged children per year or an all-age prevalence of rheumatic heart disease of 1 or fewer per 1,000 population per year. These guidelines are given in Table 323-1. The 5 major manifestations in order of decreasing frequency are polyarthritis, carditis, chorea, erythema marginatum, and subcutaneous nodules. The 2 major manifestations involving the skin, especially the nodules that were most often seen only after multiple attacks of rheumatic fever, have been extremely uncommon in the United States in recent years.

Poststreptococcal reactive arthritis (PSRA) may complicate the diagnosis of acute rheumatic fever. PSRA refers to patients who have arthritis following GAS pharyngitis without other criteria for rheumatic

fever. It remains unclear whether PSRA is a distinct syndrome, or if antibiotic prophylaxis is required.

Minor manifestations of rheumatic fever include elevated acute phase reactants (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and electrocardiographic (ECG) evidence of prolongation of the PR interval. The clinical observation of fever may be present early in the course of polyarthritis or carditis. Arthralgia is nonspecific and may affect any joint without objective signs of inflammation; it should not be considered a minor manifestation if arthritis is counted as a major manifestation.

Under the current guidelines, the laboratory confirmation of a recent streptococcal infection should be part of the diagnostic evaluation. The absence of evidence of streptococcal infection should make the physician suspicious of the diagnosis of rheumatic fever except in cases in which indolent carditis or chorea are the major manifestations. The tendency to label any low-grade febrile illness with arthralgia for which no obvious cause can be found as rheumatic fever should be avoided.

The Jones criteria should be viewed as a guide to a probable diagnosis of rheumatic fever, but the final diagnosis must remain a clinical judgment. The institution of prophylactic regimens requires prolonged administration of antistreptococcal agents, which places an important responsibility on the physician who diagnoses rheumatic fever. A false diagnosis of acute rheumatic fever results in unnecessary long-term antibiotic prophylaxis and should be avoided. Hospitalizing a child who has arthritis or carditis may be advisable for observation, appropriate documentation of a poststreptococcal illness, and initiation of treatment. Hospitalization also emphasizes to the parents the seriousness of the disease and the importance of prophylaxis to prevent recurrence. Because of the specific association of Sydenham chorea with rheumatic fever, hospitalizing a child who has this manifestation should not be mandatory if abnormal neuromuscular activity is mild and unlikely to cause self-inflicted injury.

Major Clinical Manifestations

The sequence of the manifestations of rheumatic fever is noteworthy: polyarthritis, when it occurs, is usually present before the onset of carditis. Although carditis may be present without preceding joint symptoms, most often the apical systolic murmur of mitral valvulitis occurs within 2 weeks of the onset of arthritis. The diastolic murmur of aortic valvulitis takes longer to appear and may not be heard for 6 to 8 weeks after the joint signs and symptoms appear. Chorea may develop during the convalescent phase of carditis, although a longer latent period usually occurs. Classically, chorea appears as an independent manifestation of rheumatic fever long after the initial streptococcal infection. Most cases begin 2 months after streptococcal infection, with episodes still occurring up to 6 months afterward. Although chorea and carditis may coexist, chorea and polyarthritis rarely appear concurrently, presumably because of the difference in the latent periods.

Polyarthritis

Polyarthritis is the most common initial manifestation of rheumatic fever, and usually involves the large

Table 323-1 Revised Jones Criteria for the Diagnosis of an Initial Episode of Rheumatic Fever	
Evidence of antecedent GAS infections, 2 major manifestations, or 1 major and 2 minor manifestations indicates a high probability of acute rheumatic fever as the diagnosis.	
Low-Risk Populations	Moderate- and High-Risk Populations
MAJOR CRITERIA	
<ul style="list-style-type: none"><li>Carditis<ul style="list-style-type: none"><li>Clinical or subclinical</li></ul></li><li>Arthritis<ul style="list-style-type: none"><li>Polyarthritis only</li></ul></li><li>Chorea</li><li>Erythema marginatum</li><li>Subcutaneous nodules</li></ul>	<ul style="list-style-type: none"><li>Carditis<ul style="list-style-type: none"><li>Clinical or subclinical</li></ul></li><li>Arthritis<ul style="list-style-type: none"><li>Mono or polyarthritis</li><li>Polyarthralgia</li></ul></li><li>Chorea</li><li>Erythema marginatum</li><li>Subcutaneous nodules</li></ul>
MINOR CRITERIA	
Clinical Findings	
<ul style="list-style-type: none"><li>Polyarthralgia</li><li>Fever (≥38.5°C)</li></ul>	<ul style="list-style-type: none"><li>Monoarthralgia</li><li>Fever (&gt;38°C)</li></ul>
Laboratory Findings	
<ul style="list-style-type: none"><li>ESR ≥60 mm/hr</li><li>CRP ≥3.0 mg/L</li><li>Prolonged PR interval</li></ul>	<ul style="list-style-type: none"><li>ESR ≥30 mm/hr</li><li>CRP ≥3.0 mg/L</li><li>Prolonged PR interval</li></ul>
SUPPORTING EVIDENCE OF ANTECEDENT GROUP A STREPTOCOCCAL INFECTIONS	
<ul style="list-style-type: none"><li>Positive throat culture or rapid streptococcal antigen test</li><li>Elevated or rising streptococcal antibody titer</li></ul>	

ARF, acute rheumatic fever; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GAS, group A streptococcal infection. From Gewitz MH, Baltimore RS, Tani LY, et al. Revision of the Jones Criteria for diagnosis of acute rheumatic fever in the era of Doppler echocardiography. A Scientific Statement from the American Heart Association. *Circulation*. 2015;131(20):1806–1818. Copyright © 2015 American Heart Association. Reprinted by permission.

joints of the lower extremities, particularly the ankles or knees. Polyarthritis may result in the complaint of joint pain while walking and is often initially considered to be secondary to trauma. Other large joints (for example, wrists or elbows) become involved in a migratory fashion. An affected joint characteristically is warm and reddened but minimally swollen. Involved joints are exquisitely sensitive to touch and painful on motion. Arthralgias, or aching in the joints without objective signs of inflammation, are suggestive of but not specific for rheumatic fever. The 2015 modification of the Jones Criteria recognizes that only in moderate-risk or high-risk populations, monoarthritis and polyarthralgia may be counted as a major criteria and monoarthralgia may be counted as a minor criteria of rheumatic fever. Fever is almost always present.

### Carditis

The inflammation of cardiac tissue is characteristically expressed as valvulitis, but pancarditis involving the myocardium and pericardium may be present in severe cases. The murmurs audible in rheumatic carditis are the result of mitral or aortic valvulitis, or both, with mitral involvement by far the most common. The auscultatory diagnosis of valvulitis often includes the presence of an apical mid-diastolic murmur. Pericarditis typically is silent, but a friction rub and distant heart sounds may occasionally be noted. Isolated pericarditis without associated auscultatory findings of mitral or aortic involvement, however, is not consistent with the diagnosis of acute rheumatic fever. Although viral inflammation of the heart by coxsackievirus type B or Kawasaki disease may be associated with myocarditis and pericarditis, these entities do not cause clinically evident valvulitis. The recent AHA Revised Jones criteria now also include subclinical carditis, which is defined as the presence of definite Doppler and echocardiographic valvular changes in the absence of clinical auscultatory findings.

Clinical carditis, diagnosed by the presence of valvulitis with characteristic murmurs, may be conveniently designated as mild, moderate, or severe. Such a categorization is useful in the approach to management and to establishing a prognosis for developing rheumatic heart disease. The results of the auscultation of the heart and evaluation of murmurs are influenced by fever and tachycardia; therefore, the patient should be re-examined frequently after the diagnosis of acute rheumatic fever and after the temperature has normalized with aspirin therapy. A changing functional murmur in an anxious or febrile child does not indicate the presence of carditis.

**MILD CARDITIS.** Mild carditis is characteristically defined by the presence of a prominent, high-pitched, apical systolic murmur typical of mitral insufficiency. The heart murmur of mild carditis is usually of grade 2 to 3 (on a scale of 1–6) intensity and occupies all or most of the systole. A mid-diastolic rumble at the apex is not present. The heart size on chest radiograph is usually normal.

**MODERATE CARDITIS.** Moderate carditis is defined as both long systolic and prominent mid-diastolic

apical murmurs, reflecting a greater severity of mitral valvulitis, a basilar diastolic murmur of aortic valvulitis, or a combination of mitral and aortic valvulitis. An aortic diastolic murmur, which is high pitched and decrescendo in character, is usually heard best during end expiration, with the diaphragm of the stethoscope firmly held at the third left intercostal space. A chest radiograph may show mild cardiac enlargement.

**SEVERE CARDITIS.** Severe carditis is defined by the presence of either pericarditis or congestive heart failure in addition to mitral or aortic valvulitis. The quality of the heart sounds may be poor because of either pericardial effusion or low cardiac output. Murmurs may become more intense as cardiac compensation improves. The chest radiograph shows obvious cardiomegaly, and may reveal pulmonary vascular congestion compatible with left-sided heart failure and pulmonary edema; an appearance also may be consistent with what is referred to as *rheumatic pneumonia*.

**SUBCLINICAL CARDITIS.** The 2015 AHA revision of the Jones criteria includes a new category of heart disease in patients who have no clinical evidence of carditis. New recommendations suggest that echocardiography and Doppler testing should be performed in any patient suspected of having rheumatic fever, even in the absence of clinical findings of cardiac disease. Strict echo/Doppler criteria should be followed in order to make the diagnosis of active subclinical carditis, which includes changes in the mitral or aortic valve and documented pathologic mitral or aortic regurgitation. Studies suggest that the prevalence of subclinical carditis in patients with no clinical signs of cardiac involvement is significant. In a meta-analysis of 23 studies, the weighted pooled prevalence of subclinical carditis was 16.8% (95% confidence interval: 11.9%–21.6%). The weighted pooled persistence of carditis 3 to 23 months after diagnosis was 44.7% (95% confidence interval: 19.3%–70.2%) from 11 articles.

**IMAGING.** For the documentation and quantification of pericardial effusion, 2-dimensional echocardiography is invaluable, and it confirms the diagnosis and severity of valvar involvement. The finding of minimal valvular regurgitation by Doppler ultrasound, however, should not constitute the basis of a diagnosis of carditis. Doppler studies in healthy individuals often show a small degree of regurgitation across the mitral valve; trivial aortic valve regurgitation also is described in well children. Strict Doppler and echocardiographic criteria are available in the most recent AHA guidelines to differentiate valvular disease typical of rheumatic carditis from normal variants. The long-term effects of a false diagnosis of acute rheumatic fever with the requirements for chronic antibiotic therapy and potential lifestyle and psychological effects should not be underestimated. There are a number of recent studies using 2-dimensional echocardiography as a screening tool to identify children with a past history of unsuspected rheumatic carditis. It is important to distinguish the use of echocardiography in areas with a high incidence of endemic rheumatic fever from its use in the diagnosis and management of acute rheumatic fever in areas of low incidence.

### Chorea

The clinical picture of Sydenham chorea includes that of poor neuromuscular coordination, sometimes first detected by a change or sloppiness in handwriting. A wide variety of jerky, involuntary movements may occur for 6 to 8 weeks when most cases of chorea are active. Neurologic examination may give evidence of specific deficiencies, particularly in trunk and upper extremity control of movements. A protective environment is recommended while the process is active. Occasionally, mild sedation is indicated, and agents such as valproic acid or prednisone may help in the treatment of more severe movement disorders.

When chorea occurs as an isolated manifestation, the patient is usually afebrile and the sedimentation rate is normal. Because of the long interval after the initiating streptococcal infection, the antistreptolysin O (ASLO) titer is typically normal or only mildly elevated. A murmur of mild mitral insufficiency may be noted.

### Erythema Marginatum

Erythema marginatum is a transient pink rash that has irregular, deeper-colored serpiginous borders that may be seen on the smooth, hairless surfaces of the inner aspect of the upper arms and thighs or trunk. This manifestation, although a specific finding for acute rheumatic fever, has been encountered infrequently in recent decades.

### Subcutaneous Nodules

Subcutaneous nodules are characteristically pea-sized and are usually located on extensor surfaces of fingers, toes, elbows, and other joints and less often on the occiput. They usually reflect a longstanding or smoldering illness after severe carditis; nodules may persist for weeks or months. Subcutaneous nodules are rarely found in children with rheumatic fever in the present era.

### Minor Clinical Manifestations

Among the minor criteria, fever, although almost always present, is nonspecific, as is arthralgia. An elevated acute-phase reactant, such as the ESR, is an invaluable though nonspecific laboratory sign of inflammation in children with acute rheumatic fever. Initial values usually range from 60 to 120 mm/hour. However, in patients with chorea the sedimentation rate is normal because of the long interval beyond the antecedent streptococcal infection. Elevated CRP, although helpful in diagnosing cases with borderline findings, also occurs in a variety of other diseases.

Prolongation of the PR interval (first-degree heart block) on ECG is considered to be a vagal effect and supports the diagnosis of rheumatic fever. It is most commonly noted when polyarthritis is apparent and is not necessarily associated with carditis. The ECG is almost always otherwise normal regardless of cardiac involvement. Although PR interval prolongation is the common manifestation, second- or third-degree heart block occasionally occurs, indicating a further heightening of vagal tone, perhaps more pronounced in the rheumatic state than in other acute illnesses. It is important to note that a first- or second-degree heart block is not a major criterion for carditis, a harbinger

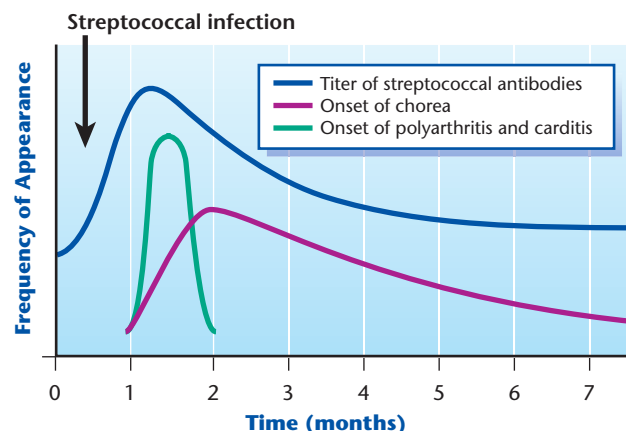
of potential rheumatic heart disease, a threat to progress to complete heart block, nor a cause of symptoms.

The minor criteria have also been modified to differentiate low-risk versus moderate-risk and high-risk populations. Minor criteria in the low-risk group include polyarthralgia, fever higher than 38.5°C (101.3°F) and ESR above 60 mm/hr. In contrast, the moderate-risk and high-risk group minor criteria have been changed to include monoarthralgia, fever above 38°C (100.4°F), and ESR above 30 mm/hr. CRP above 3.0 mg/L and a prolonged PR interval remain the same in both groups.

Streptococcal pharyngitis presumptively precedes an attack of rheumatic fever, even though some patients fail to report such a history. Scarlet fever occasionally is followed by signs of polyarthritis or carditis, but suppurative streptococcal disease, such as a skin infection, is not a precursor of rheumatic fever. Throat cultures may be misleading in the evaluation of patients suspected of having rheumatic fever because the streptococcal infection antedates the common manifestations of polyarthritis and carditis by periods varying from 3 to 8 weeks; only 50% or fewer of patients who have rheumatic fever continue to harbor streptococci during the course of their illness.

The most reliable evidence of a preceding streptococcal infection is obtained by demonstration of an antibody response to one or more of the streptococcal antigens. The most common of these, the ASLO titer, reaches maximal levels 3 to 5 weeks after infection and gradually declines to preinfection levels 6 to 12 months later. The ASLO titer is elevated in approximately 85% of patients who have rheumatic fever; titers are never extremely low. Serologic evidence of an antecedent streptococcal infection rises to 95% if other streptococcal antibody tests (eg, antihyaluronidase, antideoxyribonuclease B, antistreptokinase) are performed.

The temporal relationship between the onset of the common manifestations of rheumatic fever and the antecedent streptococcal infection is illustrated in Figure 323-1. As shown, polyarthritis and carditis



**Figure 323-1** The relationship of the onset of rheumatic manifestations to antecedent streptococcal infection and streptococcal antibody titer (ASLO). (Modified from Stollerman GH. Rheumatic Fever and Streptococcal Infection. New York, NY: Grune & Stratton; 1975.)



usually occur 3 to 5 weeks after infection. The ASLO titer peaks before the onset of the clinical symptoms and then declines gradually. Occasionally, children complain of abdominal pain after a streptococcal infection for which medical or surgical evaluation is sought, and this symptom may occasionally precede signs of joint or cardiac involvement.

## MANAGEMENT

The therapeutic management of acute rheumatic fever includes the use of antistreptococcal antibiotics and anti-inflammatory agents.

### Antistreptococcal Therapy

The eradication of GAS infection (even in the absence of a positive throat culture) by antibiotic treatment is the foremost principle in management of acute rheumatic fever. Antibiotic treatment must always be followed immediately by the institution of a prophylactic program to prevent reinfection (see Recurrence of Rheumatic Fever). Penicillin is the drug of choice prescribed initially in dose and duration to maintain therapeutic blood levels for 10 days. Several treatment schedules, which periodically are revised, are outlined by the American Heart Association. The intramuscular administration of the long-acting repository benzathine penicillin G (Bicillin) is the preferred treatment method at the time of diagnosis, because it ensures therapeutic levels for a sufficient length of time. A single injection of 1.2 million units for children 5 to 15 years of age is recommended. Alternative methods are oral penicillin, 200,000 or 250,000 units (penicillin G or V), given 3 or 4 times a day for a full 10 days; or a combination of oral and intramuscular penicillin.

For patients sensitive to penicillin, erythromycin may be used for antistreptococcal therapy. The sulfonamide drugs, which are bacteriostatic rather than bactericidal, are not effective for streptococcal eradication. They can be used in rheumatic prophylaxis programs to prevent reinfection; however, they are rarely used in the present era.

Following the initial treatment to eradicate streptococci, a program of antibiotic prophylaxis must be instituted. (See Prevention of Recurrence of Rheumatic Fever).

### Anti-inflammatory Therapy

Salicylates are indicated in the presence of acute, painful arthritis during the febrile phase of acute rheumatic fever. The duration of salicylate therapy usually ranges from 4 to 8 weeks. The average initial amount prescribed should be approximately 50 to 75 mg/kg/day given in 4 divided doses, and extremely high doses are not required. Aspirin is used for symptomatic relief only. Aspirin administration is usually associated with a rapid and significant improvement in objective arthritis signs and symptoms and with almost immediate defervescence. Specific blood levels do not need to be reached or maintained if clinical signs have disappeared. No evidence exists that salicylate administration affects the clinical course or later manifestations of cardiac involvement. It should be emphasized that high-dose aspirin may lead to significant side effects, including tinnitus and decreased hearing, gastric

irritation and, hepatotoxicity. Several small studies comparing aspirin and nonsteroidal anti-inflammatory medications have demonstrated similar results in the speed of resolution of arthritis. However, at this time insufficient data exist to routinely recommend the use of nonsteroidal anti-inflammatory agents in the treatment of rheumatic fever.

The administration of steroid hormones, most commonly prednisone, is indicated for severe cardiac involvement characterized by pancarditis with congestive heart failure. When myocarditis seems to be fulminant, steroid therapy has been shown to significantly improve survival; however, as with salicylates, no evidence of long-term palliative effects on chronic rheumatic valvular disease is available. The duration of steroid treatment may be extended to 1 to 3 months in severe cases, with varying schedules of tapering the dose and possibly adding salicylate therapy. As reviewed in a 2012 Cochrane Report, the studies comparing aspirin to steroids in the prevention of long-term cardiac disease have failed to provide evidence of superiority between the 2 methods of treatment.

Additional, specific therapeutic measures to control congestive heart failure may be useful (eg, diuretics, digitalis). Furosemide (Lasix) is used for the management of pulmonary congestion with left-ventricular failure. If digitalis (digoxin) is used, it should be administered cautiously; the threshold for toxicity may be reduced in the presence of inflammatory myocarditis. Withholding digitalis for 1 or 2 days until steroid therapy has begun to suppress the myocarditis may be prudent. Serum potassium levels should be monitored, because steroids and furosemide both decrease body potassium, predisposing the patient to digitalis intoxication. Enalapril is also sometimes used in patients with mitral valve insufficiency.

### Limitation of Activity

The role of bed rest in the treatment of rheumatic fever has been deemphasized in recent years. For children with arthritis, ambulation can be permitted when pain and joint tenderness improve. Patients who have stable, mild cardiac involvement can be allowed to ambulate when they feel well enough. For patients who have more severe carditis, the length of restricted activity is individualized according to the severity of cardiac involvement.

## OUTCOMES OF RHEUMATIC HEART DISEASE

In the months and years that follow an attack of rheumatic fever, the auscultatory findings often change from those heard during the acute episode. The apical systolic murmur of mitral insufficiency heard initially may diminish or even completely disappear. This finding contrasts with the aortic diastolic murmur, which will almost always persist during the follow-up period. An initial diagnosis of carditis does not necessarily imply progression to permanent heart damage. When a child is labeled as having history of acute rheumatic fever, the additional appellation of rheumatic heart disease must be reevaluated continually. Even patients with severe carditis in the acute phase will show



remarkable improvement in the weeks and months after the recuperative period; more than one-half of murmurs of mild or moderate mitral insufficiency will disappear completely. Nevertheless, the ultimate development of rheumatic heart disease after a first attack of rheumatic fever can be correlated with the severity of the acute carditis. In the 10-year follow-up study of treatments begun in 1951, approximately 30% of patients who had mild carditis and 50% of those who had moderate carditis developed chronic rheumatic heart disease (mitral insufficiency or stenosis or aortic regurgitation, or any combination). Nearly 75% of the patients with severe carditis will have residual heart disease.

Most children who develop rheumatic heart disease after a single attack of rheumatic fever have mitral regurgitation. The others either have both mitral and aortic regurgitation or aortic regurgitation alone. Mitral stenosis evolves slowly, usually after repeated episodes of acute rheumatic fever, but it sometimes evolves unexpectedly, many years after initial mild mitral valvulitis, which was perhaps previously undiagnosed. Isolated mitral stenosis is unusual before early adulthood and has become a rare finding in economically developed nations.

An issue that arises in the follow-up of children who have rheumatic heart disease is the amount of physical activity permitted. In general, children who have mild mitral regurgitation with normal heart size should be allowed to engage in all athletic activities, except perhaps for the most strenuous competitive sports. Children who have more severe mitral regurgitation or aortic insufficiency with cardiomegaly should have some restriction of their activities and a continuing appropriate regimen. If symptoms of fatigue or exercise intolerance persist despite medical management, then a full diagnostic evaluation should be performed; if appropriate, surgical intervention with valvuloplasty or valve replacement should be considered.

### Recurrence of Rheumatic Fever

One of the most striking characteristics of rheumatic fever is its tendency to recur. Before the introduction of preventive measures, most patients who had an initial attack of rheumatic fever had one or more recurrences, or what seemed to be a chronic “smoldering” prolongation of a single episode. The recurrence rate is highest during the first 3 years after an initial attack; it diminishes with time after the original episode, and recurrence is rare in adulthood.

The rationale for antibiotic prophylaxis in a patient with known rheumatic fever is protection against recurrence of rheumatic fever through the prevention of GAS infection. To prevent recurrent attacks, continuous antimicrobial prophylaxis should be implemented in all patients who have a history of rheumatic fever, including those who present with chorea. Children who initially had cardiac involvement, but have no evidence of residual heart disease should continue prophylaxis for 10 years or until age 21, whichever is longer. If chronic mitral or aortic valvular disease persists, then prophylaxis should be maintained until

age 40. In children who had no cardiac involvement during the initial attack, prophylaxis can be discontinued after 5 years.

### Prevention of Recurrence of Rheumatic Fever

The most effective method for reducing streptococcal infections and rheumatic fever recurrence is by intramuscular injections of long-acting penicillin (benzathine penicillin G [Bicillin LA], 600,000 units for children weighing 60 lb or less and 1,200,000 units for those weighing more than 60 lb). This preventive regimen is most effective when given every 3 to 4 weeks; with residual cardiac involvement, this approach is recommended for at least a 1- or 2-year period, before initiating oral prophylaxis. An every-3-week regimen is recommended for the first 6 to 12 months. Parenteral therapy is the most effective method of prophylaxis, given that strict adherence to a program of daily oral medication is especially difficult for children and adolescents. Some transient discomfort at the injection site (anterior thigh or buttock) may be relieved by a hot bath on the evening of injection.

Alternative methods of prophylaxis include the oral administration of penicillin V (250 mg twice daily) or sulfadiazine or sulfisoxazole (0.5 g once daily for patients weighing 60 lb or less and 1.0 g once daily for patients more than 60 lb). For the exceptional patient who may be sensitive to both penicillin and sulfisoxazole, daily prophylaxis with another agent may be considered. Successful oral prophylaxis is hard to maintain, and if used, its value and need for compliance should be reinforced constantly by the primary care physician. Because rheumatic fever recurrence is less likely after 2 to 5 years, for patients with chronic rheumatic heart disease, an oral regimen can be substituted for intramuscular penicillin. Oral prophylaxis can be instituted immediately for patients who did not have carditis during the acute attack, because under these circumstances recurrences with carditis are extremely rare.

### Bacterial Endocarditis

Individuals who have a history of rheumatic fever without evidence of significant murmurs on follow-up examination are not susceptible to bacterial endocarditis because they do not have damaged heart valves. Recent guidelines from the AHA report that patients with heart disease are more likely to acquire infective endocarditis from frequent exposure to random bacteremic events associated with daily activities than from bacteremia following dental or surgical procedures. The latest guidelines for preventing infective endocarditis therefore recommend antibiotic prophylaxis for patients with prosthetic cardiac valves, previous infective endocarditis, and certain types of repaired and unrepaired congenital heart diseases. Antibiotic prophylaxis before dental or surgical procedures is no longer recommended for patients with mitral or aortic valve disease following rheumatic fever. However, the maintenance of optimal oral health remains an important aspect of preventive care. The recommendations for preventing recurrent episodes of rheumatic fever have not changed.

### Contraception and Pregnancy

Patients who have severe rheumatic heart disease are at high risk of cardiac complications during pregnancy and delivery. Mitral stenosis has an especially high-risk profile. However, mild rheumatic heart disease is well tolerated during pregnancy. Adolescent girls who have rheumatic heart disease should be counseled in regard to contraceptive methods.

Because of the added cardiovascular burden during pregnancy, thorough obstetrical care should be provided from the first trimester through delivery. Prophylaxis against streptococcal infection should be continued. Psychosocial support may be needed, especially for pregnant teenagers with significant rheumatic heart disease who may face medical complications during pregnancy. If the early termination of a pregnancy is decided upon, therapeutic abortion should be performed in the hospital.

### WHEN TO REFER AND WHEN TO ADMIT

All children with acute rheumatic fever should be hospitalized and referred to a cardiologist for evaluation and management.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Rheumatic Fever* (fact sheet), Office of Rare Diseases Research ([rarediseases.info.nih.gov/gard/5699/disease/resources/1](http://rarediseases.info.nih.gov/gard/5699/disease/resources/1))

#### Medical Decision Support

- *Guidelines for the Diagnosis of Rheumatic Fever* (guideline), *JAMA*, Vol 268, Number 15, 1992
- *Proceedings of the Jones Criteria Workshop* (article), *Circulation*, Vol 106, Issue 19, 2002
- *Treatment of Acute Streptococcal Pharyngitis and Prevention of Rheumatic Fever: A Statement for Health Professionals* (article), *Pediatrics*, Vol 96, Issue 4, 1995

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### Chapter 324

## RHEUMATOLOGIC DISEASES

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### JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis (JIA; previously referred to as *juvenile rheumatoid arthritis* or *juvenile chronic arthritis*) is an uncommon collection of clinical syndromes that share the feature of chronic childhood arthritis. The diagnosis is applied to any child younger than 16 years who has persistent arthritis of 1 or more joints lasting for more than 6 weeks in whom all other diseases have been excluded. JIA is classified further into 7 subtypes, with most patients fitting into systemic-onset, oligoarthritis, or polyarthritis based on the clinical course over the first 6 months of illness.

Although JIA is the most common of the pediatric rheumatic diseases, its true incidence and prevalence are unknown. For all subtypes taken collectively, the peak age at onset is between 2 and 4 years, with a smaller peak later in childhood. Overall, a general female predominance is found, but not in all subtypes. The best estimate of prevalence is approximately 0.5 to 1 case per 1,000 children; thus, approximately 40,000 to 100,000 children in the United States have JIA at any given time.

#### Etiology

The exact cause of JIA is unknown. Data on the frequency of certain subtypes of human leukocyte antigens (HLA) in JIA (eg, HLA-DR5 and -DR8 in younger girls who have oligoarticular JIA, HLA-DR4 in rheumatoid factor [RF]-positive polyarticular JIA, and HLA-B27 in older boys who have enthesitis-related JIA) have led to the concept of a genetic predisposition for the development of an inflammatory arthritis that may be triggered by any of several events, such as trauma, infection, or emotional stress.

Other areas of interesting research include investigations of immunologic abnormalities involving auto-antibodies, cytokines, immunoregulation, and the function of and communication between T and B lymphocytes and antigen-presenting cells. The precise nature of these interactions and how they result in the development of JIA remain to be discovered, but the success of specific cytokine-directed therapy (eg, anti-tumor necrosis factor [TNF], anti-interleukin [IL] 1, anti-IL6 antibodies) supports the central role of these proinflammatory mediators in the clinical manifestations and course of JIA.

#### Rheumatologic Disorders With Arthritis

Juvenile ankylosing spondylitis and the other spondyloarthropathies can present as a subtype of JIA at their onset, especially in an older child who is HLA-B27 positive. Acute rheumatic fever, although long in decline in the United States and other industrialized

nations, has seen a resurgence in the last few decades. Children with acute rheumatic fever can experience both arthralgia and arthritis, classically characterized as migratory. Systemic lupus erythematosus (SLE) has arthritis as one of its major manifestations, but it can be differentiated from JIA by its other systemic features and specific laboratory test abnormalities. As well, children with SLE may have arthralgia without arthritis. Although its sex distribution is equal in younger children, female preponderance is found after puberty. Dermatomyositis is characterized more typically by inflammatory muscle involvement than by arthritis, but children can be affected with joint inflammation and contractures. Scleroderma is occasionally associated with arthritis, but it has classic dermatologic and other manifestations that distinguish it from JIA.

### Clinical Manifestation

Because the diagnosis of JIA is based on clinical findings, the history and physical examination are paramount; no unique or specific diagnostic laboratory tests yet exist. Only by considering all the data on the child's presentation and course is the physician able to diagnose JIA.

The presence of arthritis or inflammation in the joint is an absolute criterion for diagnosing JIA. Arthritis is defined as the presence of intra-articular swelling or effusion or when 2 or more of the following occur: joint pain or tenderness with motion, limitation of joint motion, or increased warmth overlying the joint. Arthralgia (joint pain) is a relatively frequent symptom in children, but true joint inflammation, or arthritis, is much less common. Younger children rarely complain of joint pain but may instead become irritable, stop walking or using an extremity, or regress in their behavior. In fact, a recent retrospective review of presenting complaints at a pediatric rheumatology center found that pain was not a predictor of the diagnosis of juvenile arthritis. Other symptoms include decreased appetite, malaise, inactivity, morning stiffness, nighttime joint pains, and failure to thrive. Features that may also be present in children who have chronic arthritis (varying with the subtype) include fever, rash, lymphadenopathy, hepatosplenomegaly, polyserositis, subcutaneous (rheumatoid) nodules, vasculitis, and growth retardation. The pattern, as well as the number of involved joints, family history, and other factors are important in classifying the disease.

### Systemic-Onset Juvenile Idiopathic Arthritis

Even though the hallmark of systemic-onset JIA (historically referred to as *Still disease*) is its extra-articular manifestations, the eventual presence of arthritis is necessary to confirm the diagnosis. Systemic-onset JIA, which affects approximately 15% of all children who have JIA, is slightly more common among boys than girls and usually begins at an early age, though it has even been recognized in adults (adult-onset *Still disease*). The systemic features may persist for months and occur or recur independently of the arthritis.

Daily intermittent fevers characterize systemic-onset JIA, with rectal temperature reaching as high as

40°C to 41°C (104°F–106°F), most often in the afternoon, and then returning to normal or subnormal levels (known as a *quotidian fever pattern*). An evanescent, salmon-colored rash often accompanies the fevers. The lesions are small macules or papules, frequently with central clearing, and often appear in areas of increased heat (eg, axilla). Mild abrasion of unaffected skin can precipitate the appearance of the rash (Koebner phenomenon).

Polyserositis in the form of pericarditis or pleuritis is common; enlargement of lymph nodes, liver, and spleen may be of sufficient size to suggest the presence of a malignancy. These serosal effusions, however, are rarely symptomatic or clinically significant. Although these children frequently complain of myalgias or arthralgias when they are febrile, they may have few symptoms when the fevers resolve. The arthritis may occur at any time after the onset of disease, and in some patients, it appears only days to weeks after the systemic signs occur. The arthritis tends to be polyarticular, involving both large and small joints, and can be persistent, destructive, and severe.

Laboratory studies reveal a high white blood cell count, with predominance of band forms and polymorphonuclear leukocytes. Most patients are anemic. Thrombocytosis is frequent, as are significant increases of the acute-phase reactants (eg, erythrocyte sedimentation rate [ESR] and C-reactive protein). Rheumatoid factor (RF) and antinuclear antibody (ANA) tests are rarely positive. Serum immunoglobulin and complement levels are usually normal but may be elevated, reflecting the degree of inflammation, and sometimes evidence of a vasculopathy and an intravascular consumption coagulopathy is found. An unusual but severe and potentially fatal complication of systemic-onset JIA is macrophage activation syndrome. This disorder can be rapidly progressive and may be difficult to distinguish from a flare in the underlying disease, but hallmarks are dramatically high ferritin levels (>10,000 ng/mL), paradoxically decreasing ESR accompanied by decreased fibrinogen, increased triglycerides, leucopenia, anemia, thrombocytopenia, and hepatic failure. Definitive diagnosis is based on bone marrow biopsy, and quick therapeutic intervention is necessary.

The clinical course of systemic-onset JIA is extremely variable. Some children have a single systemic episode that lasts weeks to months and have few joint problems; others have multiple systemic episodes before developing the arthritis, which can be oligoarticular, but more commonly is polyarticular in distribution. Poor prognostic signs include the continued presence of systemic features and a platelet count exceeding 600,000/mm<sup>3</sup> 6 months after onset. At least a third of these children will develop severe arthritis.

### Polyarticular Juvenile Idiopathic Arthritis

Approximately 30% to 35% of children who have JIA have the polyarticular type, which can be subdivided into immunoglobulin (Ig) M-RF-positive (approximately 10% of the total) and IgM-RF-negative (approximately 25%) forms. So-called hidden RFs have been found in all subgroups, but their significance remains obscure. Finding a meaningfully positive RF



in a child younger than 7 years is rare. Systemic features in polyarticular JIA are usually mild and include low-grade fever, easy fatigability, and slowing of growth. The growth problems may be local (eg, micrognathia) or generalized and can occur regardless of whether the child receives corticosteroid treatment. Discrepancies between height and weight are seen and can help with diagnosis. For example, children who have polyarticular JIA may be of low weight for height, whereas children who have systemic-onset JIA tend to be average in weight for height. The arthritis is most often chronic and symmetrical, and it involves 5 or more joints. Any joint of the body, including the temporomandibular joint and the cervical spine, can be affected. Nearly all children have wrist involvement, and small joint involvement of the hands and feet is common. Finally, these children may develop a chronic uveitis.

#### ***Rheumatoid Factor–Positive Polyarticular Juvenile Idiopathic Arthritis***

Patients who have IgM-RF–positive polyarticular JIA are most often older than 8 to 10 years, are more likely to be girls than boys, and are similar clinically to patients who have adult rheumatoid arthritis. Severe, rapidly progressive, erosive, crippling arthritis; subcutaneous rheumatoid nodules; and rheumatoid vasculitis can develop, just as in adults. Cyclic citrullinated protein (CCP) is a laboratory study that can be used to assess disease severity and potential for joint destruction. An elevated serum level would serve as a reason to institute early and aggressive therapy.

#### ***Rheumatoid Factor–Negative Polyarticular Juvenile Idiopathic Arthritis***

Children who have IgM-RF–negative polyarticular JIA are usually younger. They often have a better prognosis than those who are IgM-RF positive, and typically these children respond better to therapy and have a lower frequency of severe, early, crippling arthritis than do children who have the IgM-RF–positive form. However, they may develop many significant problems. Because IgM-negative polyarticular arthritis starts earlier, it can lead to deformities and problems as a result of the tendency to develop flexion contractures and, if severe, subluxations at the involved joints. Compared with adults, hand involvement affects the interphalangeal joints more often than the metacarpophalangeal joints. Ulnar deviation of the fingers is much less common in children than in adults, whereas flexion contractures, boutonnière (buttonhole) deformities, and radial deviation of the fingers are seen more frequently. Ulnar deviation and subluxation at the wrist may occur. Arthritis of the apophyseal joints of the cervical spine is common and can lead to rapid and significant limitation of extension and rotation. These children are at the highest risk of developing the local and generalized growth problems mentioned previously.

#### ***Oligoarticular Juvenile Idiopathic Arthritis***

Oligoarticular JIA involves 4 or fewer joints, most often the large joints (eg, knee, ankle, elbow), typically in an asymmetric distribution. The pattern and course of

joint involvement are important in distinguishing this form of JIA from the others, as are the number of joints involved. Systemic features are infrequent and, if present, mild. Fifty percent to 60% of all children who have JIA fall in this oligoarticular subgroup, and they have the best overall prognosis. Oligoarticular JIA can be subdivided further into persistent and extended oligoarticular subtypes.

**PERSISTENT OLIGOARTHRITIS.** Persistent oligoarthritis (5%–10% of all patients who have JIA) occurs typically in girls younger than 6 years of age and involves the large joints. These girls are at higher risk of developing chronic uveitis, particularly when positive for ANA. Despite their obvious arthritis, these children generally function well and only rarely complain of significant pain. Little erosive joint damage typically occurs, even though these patients may have ongoing arthritis for many years. Nonetheless, they are at risk for long-term problems, including leg-length discrepancies (a complication of ongoing asymmetric knee joint involvement) and muscle atrophy. The long bone growth plates around the knee with arthritis can become more active because of the inflammatory-associated hyperemia, resulting in increased length of that leg. Similarly, as a result of changes in the child's biomechanics, decreased quadriceps mass on the affected side is frequently found.

Systemic signs and symptoms, except for uveitis, are few. The chronic anterior uveitis is rarely symptomatic until it has progressed to a severe stage, and it may not occur until years after the onset of the arthritis; it may even occur after the arthritis has resolved. Thus, regular ophthalmologic evaluation, including slit-lamp examinations, should be instituted early and continued indefinitely. Because the risk of uveitis decreases with time and varies by JIA subtype and age at diagnosis, the prescribed intervals between examinations range from 3 to 12 months, eventually lengthening after several years if no uveitis is present (Table 324-1).

Except for ANA positivity, few laboratory abnormalities will be found. When positive, the ANA titer is typically low. Although mild increases in white blood cell count and ESR or a low-grade anemia may be observed, results of all of these tests are often normal. HLA-DR5 gene markers appear to confer increased susceptibility for persistent oligoarthritis, whereas HLA-DR1 and -DR4 are underrepresented in this group.

The course of children with persistent oligoarthritis can be extremely variable. Some children have a single episode; others may have recurrent exacerbations and remissions. Regardless of their individual style, this group has the fewest musculoskeletal complications and more long-term remissions compared with the other JIA subtypes.

**EXTENDED OLIGOARTHRITIS.** Children with the extended oligoarthritis subtype of JIA initially have 4 or fewer joints involved in the first 6 months of their disease. However, at different times after the initial 6 months, they develop arthritis in more joints. This group comprises approximately 20% to 25% of all children with oligoarthritis. It differs from persistent oligoarthritis in several ways. Children with this condition appear to have a different genetic makeup, with a higher frequency of HLA-DR1 and a higher



**Table 324-1****Frequency of Ophthalmologic Examination in Patients With Juvenile Rheumatoid Arthritis**

TYPE	ANA	AGE AT ONSET (Y)	DURATION OF DISEASE (Y)	RISK CATEGORY	EYE EXAMINATION FREQUENCY (MO)
Oligoarthritis or polyarthritis	+	≤6	≤4	High	3
	+	≤6	>4	Moderate	6
	+	≤6	>7	Low	12
	+	>6	≤4	Moderate	6
	+	>6	>4	Low	12
	–	≤6	≤4	Moderate	6
	–	≤6	>4	Low	12
	–	>6	NA	Low	12
Systemic disease (fever, rash)	NA	NA	NA	Low	12

ANA, Antinuclear antibodies; NA, not applicable; +, positive; –, negative.

Recommendations are to continue follow-up through childhood and adolescence.

From Cassidy J, Kivlin J, Lindsley C, et al; American Academy of Pediatrics Section on Rheumatology and Section on Ophthalmology. Ophthalmologic examinations in children with juvenile rheumatoid arthritis. *Pediatrics*. 2006;117:1843–1845.

occurrence of erosive disease. The additionally involved joints are often the wrists, fingers, and other smaller joints. Although chronic uveitis is seen in fewer cases, it still occurs, and these children also need to be monitored closely by ophthalmologists. Although it seems fewer children in this subgroup enter a prolonged remission than do children with persistent oligoarthritis, they also fare better than children with a polyarthritis onset.

### Enthesitis-Related Arthritis

Enthesitis-related arthritis is a newer classification that includes children who previously were classified as late-onset oligoarthritis. This subgroup includes children with arthritis and enthesitis and the presence of at least 2 of the following: sacroiliac joint pain or inflammatory spinal pain (or both); presence of HLA-B27; history of relatives with HLA-B27-associated disease; anterior uveitis usually associated with ocular pain, redness, or photophobia; or onset of arthritis in a boy older than 8 years. Their arthritis is more frequently in the lower extremities, involving the knees and ankles but also occasionally the toes (resulting in so-called *sausage toe*, or dactylitis).

Complaints and findings of enthesitis (ie, inflammation of the attachment of a tendon, ligament, fascia, or capsule to bone) are a hallmark of this group and may predate any joint problems. These children may progress to fulfill the criteria for ankylosing spondylitis, reactive arthritides, or arthritis associated with inflammatory bowel disease. Approximately 10% will develop an acute iritis. In contrast to the chronic uveitis seen in oligoarticular JIA, this is symptomatic, can be treated early, and is usually self-limited. As with oligoarticular JIA, mild to moderate increase in the ESR is common, but infrequently, other laboratory tests are found to be abnormal.

### Psoriatic Arthritis

Psoriatic arthritis is an additional classification subtype of JIA and bears a similarity to enthesitis-related

arthritis in that large joint inflammation, enthesitis, and dactylitis are often found. For this diagnostic label to be used, however, psoriasis must be present in the child or in family members. Thus, a child can have psoriatic arthritis in the absence of skin disease, though a psoriatic rash can appear at some time after the onset of joint disease. A physical finding that can be useful in identifying psoriatic arthritis in the child or adolescent with characteristic musculoskeletal findings, but no skin eruption, is pitting of the fingernails or toenails. Children are placed in the undifferentiated category if they do not meet the criteria for any of the above subtypes or if they meet criteria for more than 1 subtype.

### Differential Diagnosis

Diseases to be considered in the differential diagnosis of JIA are listed in Box 324-1.

The hallmark of JIA is its chronic nature; the best initial strategy is often careful, watchful waiting. Only by meeting the criterion of sustained arthritis (>6 weeks) and excluding other possible diseases can the pediatrician avoid mislabeling other transient entities as JIA. Other conditions that can mimic JIA in its early stages include the various osteochondroses and avascular necrosis syndromes, musculoskeletal trauma, chondromalacia patellae, Osgood-Schlatter disease, slipped femoral capital epiphysis, diskitis, psychogenic arthralgias, and nonspecific musculoskeletal aches and pains. Hemophilia, sickle cell disease, inflammatory bowel disease, collagen disorders (eg, Ehlers-Danlos syndrome, Marfan syndrome), the autoinflammatory diseases (familial Mediterranean fever, TNF- $\alpha$  associated periodic fever syndrome [Tumor necrosis factor receptor-associated periodic syndrome], hyper-IgD syndrome, Muckle-Wells syndrome, neonatal-onset multisystem inflammatory disease [also known as *chronic infantile neurologic, cutaneous, and articular syndrome*], familial cold autoinflammatory syndrome), Wegener granulomatosis, and sarcoidosis may also be associated with arthritis.

**BOX 324-1 Differential Diagnosis of Juvenile Idiopathic Arthritis****RHEUMATIC DISEASE OF CHILDHOOD**

- Autoinflammatory diseases
- Acute rheumatic fever
- Systemic lupus erythematosus
- Juvenile ankylosing spondylitis
- Polymyositis and dermatomyositis
- Vasculitis
- Scleroderma
- Mixed connective-tissue disease/overlap
- Kawasaki disease
- Behçet syndrome
- Wegener granulomatosis
- Postinfectious reactive arthritis
- Reactive arthritis
- Reflex neurovascular dystrophy/reflex sympathetic dystrophy/complex regional pain syndrome type II
- Fibromyalgia syndrome

**INFECTIOUS DISEASES**

- Bacterial arthritis
- Viral or postviral arthritis
- Fungal arthritis
- Osteomyelitis
- Postinfectious reactive arthritis
- Lyme disease

**NEOPLASTIC DISEASES**

- Leukemia
- Lymphoma

- Neuroblastoma
- Primary bone tumors

**NONINFLAMMATORY DISORDERS**

- Trauma
- Avascular necrosis syndromes
- Osteochondroses
- Slipped capital femoral epiphysis
- Diskitis
- Patellofemoral dysfunction (chondromalacia patellae)
- Toxic synovitis of the hip
- Overuse syndromes

**HEMATOLOGIC DISORDERS**

- Sickle cell disease
- Hemophilia

**MISCELLANEOUS**

- Inflammatory bowel disease
- Chronic recurrent multifocal osteomyelitis
- Sarcoidosis
- Collagen (connective tissue) disorders (eg, Ehlers-Danlos syndrome, Marfan syndrome, etc.)
- Growing pains
- Psychogenic arthralgias (conversion reactions)
- Hypermobility syndrome
- Villonodular synovitis
- Foreign-body arthritis

If the child has a single inflamed joint, then bacterial arthritis must be considered. If any question exists as to an intra-articular septic process, then arthrocentesis must be performed to establish the diagnosis. If *Neisseria gonorrhoeae* is the cause of septic arthritis, then the most common time for this is in adolescence, whereas various strains of staphylococci may be found at any age. Emergence of methicillin-resistant *Staphylococcus* has made antibiotic selection in presumed septic arthritis that much more important. Other infectious agents such as fungi, viruses (including parvovirus, rubella, and hepatitis B), and *Mycoplasma* organisms must also be considered as the cause of arthritis. Lyme disease (*Borrelia burgdorferi* infection) is an etiologic consideration for childhood arthritis in a child living in, or who has recently traveled to, an endemic area. Osteomyelitis, involving the bone contiguous to a joint, and reactive arthritis from a gastrointestinal bacterial infection (eg, *Shigella*, *Salmonella*, *Campylobacter*, or *Yersinia* organisms) may also mimic some subgroups of JIA. Neoplasms involving the bone, either primary or metastatic (eg, leukemia, lymphoma, neuroblastoma), can be accompanied by musculoskeletal complaints. Although arthritis is uncommon and usually transient, complaints of pain that are out of proportion to physical findings and

particularly nighttime pain are common and potentially important clues to heed.

Children who have various immunodeficiencies can have arthritis, either related to their primary problem or as a result of infections. Serum sickness and the various vasculitides, including Kawasaki disease (see Chapter 280) and Henoch-Schönlein purpura (see Chapter 264), can produce intermittent arthritis. Finally, several conditions may produce significant arthralgias and myalgias and may mimic an arthropathy. The complaints and disability resulting from hypermobility syndrome and fibromyalgia can be sufficient to make the clinician believe (although incorrectly) that a form of arthritis is present. Reflex sympathetic dystrophy (also known as *complex regional pain syndrome type II*, or grouped with other amplified musculoskeletal pain syndromes) deserves diagnostic consideration in children who have a hot or cold, pale, painful, and exquisitely sensitive (allodynia) extremity that they refuse to move, particularly when a premorbid history of trauma (often minor) is found.

**Management**

Individualizing each child's management in terms of the disease subtype, extent of activity, clinical course

### BOX 324-2 Medications for Juvenile Idiopathic Arthritis

NSAIDs	CORTICOSTEROIDS
<b>FDA-Approved for Use in Children</b>	<ul style="list-style-type: none"> <li>• Cytotoxic and immunosuppressive drugs</li> <li>• Leflunomide</li> <li>• Methotrexate</li> <li>• Azathioprine</li> <li>• Chlorambucil</li> <li>• Cyclophosphamide</li> <li>• Intravenous immunoglobulin</li> <li>• Cyclosporin A</li> <li>• Thalidomide</li> <li>• Lenalidomide</li> </ul>
<ul style="list-style-type: none"> <li>• Salicylates</li> <li>• Indomethacin</li> <li>• Tolmetin sodium</li> <li>• Naproxen</li> <li>• Ibuprofen</li> <li>• Celecoxib</li> <li>• Meloxicam</li> </ul>	
<b>Non-FDA-Approved</b>	<b>BIOLOGIC AGENTS</b>
<ul style="list-style-type: none"> <li>• Diclofenac sodium</li> <li>• Fenoprofen</li> <li>• Flurbiprofen</li> <li>• Ketoprofen</li> <li>• Phenylbutazone</li> <li>• Pirprofen</li> <li>• Piroxicam</li> <li>• Meclofenamate sodium</li> <li>• Sulindac</li> </ul>	<ul style="list-style-type: none"> <li>• Etanercept</li> <li>• Infliximab</li> <li>• Adalimumab</li> <li>• Anakinra</li> <li>• Abatacept</li> <li>• Rituximab</li> <li>• Tocilizumab</li> <li>• Canakinumab</li> </ul>
<b>DMARDs</b>	
<ul style="list-style-type: none"> <li>• Hydroxychloroquine</li> <li>• Sulfasalazine</li> </ul>	

DMARDs, disease-modifying antirheumatic drugs; FDA, US Food and Drug Administration; NSAIDs, nonsteroidal anti-inflammatory drugs.

to date, and family situation is always necessary. Although most physicians are accustomed to considering pharmacologic therapy of primary importance, it is only 1 aspect of the treatment of children who have JIA. A multidisciplinary team approach is the most effective way to meet the needs of a child who has chronic arthritis and his or her family. The goal of therapy is to achieve the highest possible level of physical and psychological function for the child.

Currently available drug therapy (Box 324-2), although not yet curative, can suppress the inflammatory activity in many children who have JIA. The ultimate goal is to have no detectable inflammation. Five major categories of drug therapy are available: nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), corticosteroids, immunosuppressive drugs, and agents that possess immune- and cytokine-modulating effects (also known as *biologic agents*). Significant advances continue to take place, particularly in the biologic arena.

Although salicylates are historically the classic NSAIDs, they are no longer the initial NSAIDs of choice because of concerns regarding the development of Reye syndrome and their short half life, and because other agents have emerged that work well. Although these drugs are essentially equivalent in efficacy and toxicity, individual responses to all NSAIDs vary widely. If a child does not improve while receiving

an NSAID within 4 to 6 weeks, then trying others is reasonable. Naproxen, ibuprofen, indomethacin, and meloxicam are available as liquid preparations that can be administered more easily to younger children and to children who have trouble swallowing pills.

Cyclooxygenase II (COX-2)-selective inhibitors decrease the prostaglandin production that mediates inflammation, but in a gastroprotective manner, thereby reducing the risk of gastric erosion or ulcer formation, or both. However, as a result of cardiovascular safety questions, many of these preparations have been removed from the market by their manufacturers. Celecoxib remains available in the United States, and is now approved for use in children with JIA. Meloxicam is predominantly COX-2 selective and is available in a pill or liquid preparation, as well as in a generic form, thereby decreasing cost.

If a child does not quickly respond to NSAID therapy alone or is in a high-risk category, more aggressive interventions are clearly necessary because JIA is neither a benign condition nor one that children will typically “outgrow.” Moving quickly to DMARDs and/or biologic agents, as well as administering intra-articular corticosteroid injections, appears to achieve the goal of no inflammation with great effectiveness.

Although sulfasalazine has seen something of a resurgence, it should not be administered to any child who is sensitive to sulfa drugs or salicylates, whose renal or hepatic function is impaired, or who has conditions such as glucose-6-phosphate dehydrogenase deficiency. Adverse effects caused by sulfasalazine include rashes, nausea, vomiting, and dyspepsia; in boys, a reversible decrease in sperm count is an adverse effect. Bone marrow depression rarely occurs.

Methotrexate has essentially replaced the other traditional DMARDs—intramuscular and oral gold, D-penicillamine, and hydroxychloroquine—as the primary second-line agent in the treatment of JIA. As a competitive inhibitor of dihydrofolate reductase, it exerts both an anti-inflammatory and an immunosuppressive effect on the arthritis. Its efficacy and its dose-response characteristic have been well established. Subcutaneous administration results in high and consistent blood levels and may provide control of the arthritis if oral dosing is ineffective. Hepatic, bone marrow, gastrointestinal, pulmonary, and teratogenic adverse effects are possible. Laboratory monitoring is recommended every 4 to 8 weeks to detect any liver or hematopoietic adverse effects. The administration of folic (or folinic) acid may mitigate a number of methotrexate’s adverse effects, such as nausea and oral ulcers.

Leflunomide, an immunosuppressive agent that inhibits pyridine synthesis and suppresses TNF- $\alpha$  induced cellular responses, has been shown to have beneficial effects similar to methotrexate. However, leflunomide, too, has possible teratogenic effects; it requires ongoing monitoring and is not US Food and Drug Administration (FDA)-approved for use in the treatment of JIA. Other immunosuppressive agents, including azathioprine, cyclosporine, chlorambucil, cyclophosphamide, intravenous immune globulin, thalidomide, and lenalidomide are occasionally administered in specific patients, but they are not currently the standard.

The last decade has brought with it great advances in the understanding of the inflammatory causes of JIA. TNF- $\alpha$  is a major proinflammatory cytokine in both children and adults with arthritis, psoriasis, and a number of other chronic inflammatory diseases. Three biologic agents are currently available to block the activity of TNF- $\alpha$ : etanercept, infliximab, and adalimumab. Etanercept and adalimumab are approved for use in children with JIA, and all 3 agents have demonstrated dramatic improvements in the condition of children and adults with arthritis. Because each agent is slightly different, a child who has not responded or has had an adverse response to 1 agent may still respond well to another. It is now considered standard therapy to add a TNF- $\alpha$  blocker to the regimen of any child with JIA who has not previously responded to DMARD therapy, as well as when tapering the dose of corticosteroids is not possible without precipitating a flare of the disease. Purified protein derivative (PPD) testing is performed before starting these agents because reactivation of tuberculosis is a risk in the setting of TNF- $\alpha$  inhibition. Other adverse effects include injection site pain or reactions, an increased risk of infections, and a possible increased risk of other autoimmune conditions. Long-term effects of TNF- $\alpha$  suppression are not yet known, but more recent data have raised concern for an increased incidence of lymphoma in those patients who have received etanercept, infliximab, or adalimumab. Nonetheless, since their introduction, this class of agents has dramatically altered both the courses of these diseases and the lives of children and adults with arthritis.

Interleukins 1 and 6 are 2 other proinflammatory cytokines that play a significant role in the treatment of JIA. Systemic-onset JIA is more of an IL-1- or IL-6- (or both) driven condition and often responds better to blocking these cytokines than TNF- $\alpha$ . Anakinra, an IL-1-receptor antagonist, has been found to be effective in the treatment of JIA in many children who have not responded adequately to the TNF- $\alpha$  inhibitors. Anakinra should not be administered in combination with a TNF- $\alpha$  inhibitor or any other biologic agent. Canakinumab is a monoclonal antibody also directed toward IL-1 and is recently approved for treating systemic-onset JIA. IL-6 blockade with tocilizumab is an addition to the treatment armamentarium as well.

Abatacept, a biologic agent recently approved for the treatment of children with JIA, works through a different mechanism. It selectively modulates the CD80/CD86:CD28 costimulatory signal required for full T-cell activation. It has demonstrated efficacy in both children and adults with arthritis who have not responded adequately to TNF- $\alpha$  inhibitors.

Rituximab is a monoclonal antibody directed against the CD20 marker on B lymphocytes. Currently approved for adults who have not responded to TNF- $\alpha$  blockade, its use in the treatment of children is yet to be determined.

In the era of monoclonal antibodies, systemic corticosteroid use in JIA has become much less necessary. However, corticosteroids remain important and effective medications, the use of which should follow these maxims: (1) they should only be administered when other agents have failed or when the child is seriously

ill or has progressive severe chronic anterior uveitis unresponsive to local or other systemic therapy; (2) as small a dose as possible should be administered; and (3) their use should be tapered and discontinued as soon as possible.

Corticosteroids are effective anti-inflammatory agents but do not alter the course of the disease. They can be extremely difficult to discontinue in children who have JIA, and their long-term use is associated with many serious adverse effects, including immunosuppression, osteoporosis, and growth retardation. Small daily doses of prednisone may be effective in treating pain and stiffness; higher doses may be needed to manage systemic features such as pericarditis. High-dose intravenous pulse methylprednisolone therapy can be useful in dire situations, but it is not very effective when used as chronic therapy.

Intra-articular corticosteroids have come to play a larger role in the management of JIA, especially oligo-articular JIA. They can be effective in controlling acute problems associated with 1 or several active joints, but they are usually used in combination with systemic, ongoing therapy. Children who have a painful or swollen joint frequently respond to arthrocentesis and instillation of a long-acting corticosteroid preparation (eg, triamcinolone hexacetonide). This procedure should not be performed more than 3 or 4 times per year, and the physician should be absolutely certain that concomitant infectious arthritis is not the cause of the acute joint problem. Early use of intra-articular corticosteroids may even have the potential to modify the course of JIA.

Despite this progress in treatments, there are still children whose disease has proven unresponsive to all of these and other interventions. In a select group, the use of autologous stem cell transplantation has at times proven to be extraordinarily helpful. The risks are great, but for those children, the benefits can be as well.

Because children with arthritis can experience both acute and chronic pain at various times regardless of treatment, this is an important area that needs to be considered and/or addressed. Not all pain is related to the inflammatory aspects of the arthritis. Therefore, before intervening, it is important to determine whether the pain is from the joint inflammation, joint damage or other mechanical factors, periarticular structures, or other issues. Similarly, not all pain requires intervention with medications because various physical or other techniques can also be effective.

Pharmacologic therapy is not the only aspect of the treatment required by children who have JIA. Physical therapy and occupational therapy are crucial adjuncts to help the child maintain strength and range of motion, to prevent contractures, and to allow the best possible quality of life. All patients should be given a home program of therapy that is reviewed and updated regularly. Heat therapy, such as taking warm baths or using a sleeping bag at night, often helps minimize morning stiffness. Swimming is an excellent exercise; affected children should be encouraged to swim and to participate in as many other activities as possible. Normal play is also a form of physical therapy and occupational therapy.



The orthopedist's contributions to patients whose disease is more extensive range from the application of splints to operative tendon releases and capsulotomies. Some children may require joint resurfacing or joint replacement surgery. Even though most children will not need orthopedic intervention (particularly during childhood), the orthopedist's perspective is an important part of disease management.

In all its forms, JIA is a chronic illness, and none of the current modes of therapy is curative. Furthermore, JIA is one of the few childhood illnesses in which pain is a primary symptom. Therefore, different expectations and attitudes are needed when caring for the patient and family. In addition to an attentive and understanding pediatrician, a family counselor, social worker, and psychologist or similar mental health professional are of particular value in helping the child and family to cope with and adjust to this chronic illness. Patients, siblings, and parents may experience feelings of denial, guilt, and frustration at the time of the diagnosis and throughout the course of the disease. Siblings frequently find it difficult to cope with the special and extensive treatment the affected child may receive.

Periodic depression and anger are frequent problems, especially in the early stages as the child and family realize that many changes may be necessary in their lifestyle and dreams, and again as the child enters adolescence. Despite the frequent disruptive episodes brought on by the disease, families are often able to adapt to their child's chronic illness adequately. Poor maternal function, maternal depression, and social isolation are risk factors for poor psychosocial outcomes. A sense of control and mastery are important positive factors.

Most children who have JIA can do well in school; thus, all efforts should be made to keep them enrolled. Studies of children's school and family adaptations show that children who have JIA and their families develop different, albeit generally normal, styles for coping with this chronic illness. Some school adjustments may be necessary, such as arranging for different transportation or physical education (or both) and allowing the child extra time between classes. Having 2 sets of books, one for school and one for home, reduces the work of carrying the books to and from school. The pediatrician or pediatric rheumatology team may have to advocate on behalf of these children within the school so that they can receive all the school services they require.

Although concentrating on scholastic issues is important, these children will require preparation for adulthood. Independent living and vocational preparation must begin in childhood to reduce any potential barriers and difficulties. Anticipatory guidance on transitional issues should be provided starting in childhood and early adolescence.

Although children whose disease is severe have several obvious problems, the child who has mild disease and a hidden disability also may have problems coping, adapting, and trying to accomplish the unrealistic goals set by a society that does not recognize the disability. Any chronic illness imposes many additional stresses on the entire family. The direct and indirect

financial costs alone create significant burdens for the family of any child with JIA and for society.

### Course and Prognosis

Juvenile idiopathic arthritis is rarely fatal, and in general the long-term prognosis is good, particularly for the oligoarticular subtype. Approximately 60% to 75% of children will experience remission at some point, and for many children it will be permanent. Most children who have JIA will complete school, be gainfully employed, and raise families, just as their siblings and peers will.

Several patterns of disease activity are recognized: persistent active arthritis and destructive arthropathy; active disease, then remission; polycyclic diseases characterized by acute flares of activity followed by temporary remissions; and low-grade continued disease activity with little if any joint destruction.

Oligoarticular (not the extended-type) JIA has the best prognosis, with 40% to 50% of children undergoing complete remission, compared with only 25% to 30% of children who have systemic-onset and polyarticular JIA. Children who have IgM-RF positivity, systemic-onset, and certain extra-articular manifestations (eg, persistent fevers, thrombocytosis, subcutaneous nodules, vasculitis), as well as younger children, usually have a poorer long-term articular outcome. Younger children who have systemic-onset and polyarticular arthritis have a poorer articular prognosis. Children who have oligoarticular arthritis and no chronic anterior uveitis have the best prognosis.

Children should be referred to an ophthalmologist at the time of diagnosis. Most clinical uveitis develops within 4 to 7 years of the diagnosis, but it can occur at any time. Therefore, ophthalmologic examinations should be performed indefinitely. Table 324-1 outlines the frequency of eye examinations recommended by the American Academy of Pediatrics. If a child develops uveitis then the child should be monitored according to the ophthalmologist's directions; uveitis can become the child's most vexing problem.

In summary, increasing awareness of pediatric rheumatic diseases has resulted in earlier diagnosis and treatment of JIA. The rapid advances in understanding the diseases and their therapies, especially the promising biologic agents, are encouraging signs that the number of children disabled by these illnesses will decrease in the future.

### WHEN TO REFER

- Persistent oligo- or polyarticular joint inflammation.
- Spiking fevers and rash, but no obvious infectious cause is present.
- Persistent joint pain, limp, or asymmetric use of an extremity for which no explanation has been found.

### WHEN TO ADMIT

- Systemic-onset JIA with the development of severe chest pain with shortness of breath (suggesting pericarditis with hemodynamic

compromise) or a change in voice quality and difficulty breathing (suggesting cricoarytenoid arthritis).

- Systemic-onset JIA with the development of fevers, organomegaly, liver and/or renal dysfunction, markedly elevated ferritin, decreases in red blood cells, white blood cells, or platelets and paradoxical drop in ESR (suggesting the development of macrophage activation syndrome).
- Chronic arthritis for which the child is receiving corticosteroid therapy, and develops signs of severe infection.
- Chronic arthritis for which the child is receiving NSAIDs, and exhibits acute anemia and melanic stools.
- Longstanding polyarticular arthritis complicated by multiple joint contractures and weakness requiring a period of inpatient rehabilitation (eg, physical and occupational therapy).

## SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus is a chronic multisystem autoimmune disorder that affects blood vessels and connective tissues. Children with SLE tend to have a more severe disease course than patients with adult-onset disease. Classic pediatric SLE is defined by its diagnosis before age 21 years.

### Epidemiology

Twenty percent of all SLE patients are diagnosed in the pediatric age group. Pediatric SLE has an incidence that varies with ethnicity between 6 and 30 per 100,000 children per year. The incidence of SLE is higher among black, Hispanic, and Asian patients compared with white patients. The median age at the onset of childhood SLE is 12 years, and 80% of the patients are girls.

### Pathophysiology

The disease is believed to have been caused by interaction between hormonal and environmental factors in a genetically predisposed individual. Hormonal influences like estrogen play a role in disease activity as seen in pregnant patients. There is a higher female-to-male ratio (7:1) in patients presenting in the periparturient period. Men with Klinefelter syndrome may have a higher incidence of SLE. Environmental factors like ultraviolet light exposure, medications, and infections also play a role.

Ten percent of patients with SLE have an affected first-degree relative, and they are also more likely to have a family member with an autoimmune disease. There is a 25% concordance between monozygotic twins.

A dysregulated immune system involving both the T and B lymphocytes leads to activation of innate immunity and release of inflammatory cytokines. This subsequently leads to aberrant activation of adaptive immunity and production of autoantibody. Recent evidence has implicated interferon- $\alpha$  in the development of SLE.

### Clinical Manifestations

In view of its multisystem involvement, SLE mimics many different diseases. It is important to recognize

the disease pattern when a patient presents with multiple symptoms and signs. The American College of Rheumatology classification criteria are a useful tool for the diagnosis. The initial criteria as outlined in Table 324-2 were published in 1982, followed by a revision in 1997.

Children may manifest nonspecific symptoms like fevers, generalized aches, fatigue, weight loss, anorexia, alopecia, and arthralgias. SLE can affect any organ system. Table 324-3 illustrates the frequency of organ involvement in SLE. Pediatric SLE leads to greater renal and central nervous system (CNS) involvement than does adult SLE.

### Monocutaneous Manifestations

Children may develop any type of skin manifestation (Box 324-3), presenting a diagnostic challenge to the pediatrician. SLE is frequently characterized by the classic malar rash that may have a butterfly appearance. It develops on the malar prominence and crosses the nasal bridge sparing the nasolabial folds. It may involve the chin and forehead. The rash is usually nonpruritic and may be macular to maculopapular with associated scaling. It is photosensitive in more than a third of children and may be the first sign of a systemic flare.

Oral and nasal septal mucosa may have painless ulcers. The oral ulcer is generally present on the hard palate. A careful oral examination is therefore necessary so that this important clinical manifestation is not overlooked.

Nonscarring hair loss is common and is often noted in the temporal region of the scalp. It may be global and severe enough to require immunosuppressive therapy.

Discoid rash is a rare manifestation of pediatric SLE and may occur in 10% of patients. This scarring rash occurs on the forehead and scalp and may mimic a tinea lesion. When this rash occurs in isolation without any other systemic manifestations, it is referred to as discoid lupus erythematosus (DLE). Up to 25% of patients with DLE may have pre-existing SLE. The rate of progression to systemic SLE is higher in pediatric patients—up to 24% to 26%, compared with 5% to 10% among adults.

### Musculoskeletal Involvement

Arthralgias and arthritis are common in SLE with symmetric nonerosive and nondeforming involvement of large and small joints like the knees, ankles, wrists, and fingers. It is characterized by stiffness more than pain. Myalgia and myositis are less common. Myositis may occur in the overlap syndrome that has features common to SLE and other rheumatic diseases. The other skeletal features of SLE may be secondary to the disease process and may include avascular necrosis and osteoporosis. Children may experience generalized pain secondary to poor sleep, fatigue, and deconditioning of muscles.

### Renal Disease

Renal disease contributes largely to morbidity and mortality in children with SLE. Renal involvement occurs in 50% to 75% of children with SLE, and more

**Table 324-2** Classification Criteria for Systemic Lupus Erythematosus

CRITERION	DEFINITION
1. Malar rash	Flat or raised erythema over the malar eminences, spares the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur
3. Photosensitivity	Skin rash following sunlight exposure, by history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless
5. Arthritis	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	Pleuritis—convincing history of pleuritic pain or rub on auscultation or evidence of pleural effusion or Pericarditis—documented on electrocardiogram, echocardiogram, or rub
7. Renal disorder	Persistent proteinuria greater than 0.5 g/d or Cellular casts—may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	Seizures in the absence of offending drugs or metabolic derangements or Psychosis in the absence of offending drugs or metabolic derangements
9. Hematologic disorder	Hemolytic anemia with reticulocytosis or Leukopenia less than 4,000/ $\mu$ L on 2 or more occasions or Lymphopenia less than 1,500/ $\mu$ L on 2 or more occasions or Thrombocytopenia less than 100,000/ $\mu$ L
10. Immunologic disorder	Antibody to native DNA or Antibody to Sm protein or Antiphospholipid antibodies—anticardiolipin antibodies, presence of the lupus anticoagulant, or false-positive result on serologic testing for syphilis
11. Antinuclear antibody	Presence of antinuclear antibody on immunofluorescence or an equivalent assay

From Levy DM, Kamphuis S. Systemic lupus erythematosus in children and adolescents. *Pediatr Clin North Am.* 2012;59(2):345–364, with permission from Elsevier.

**Table 324-3** Common Clinical Features of Childhood Systemic Lupus Erythematosus

CLINICAL FEATURES	PREVALENCE OF INVOLVEMENT
Fever	37%–100%
Lymphadenopathy	13%–45%
Weight loss	21%–32%
Mucocutaneous	60%–90%
Musculoskeletal	60%–90%
Nephritis	48%–78%
Neuropsychiatric disease (NPSLE)	15%–95%
Gastrointestinal	24%–40%
Hematologic	50%–100%
Cardiovascular	25%–60%
Pulmonary	18%–81%

From Levy DM, Kamphuis S. Systemic lupus erythematosus in children and adolescents. *Pediatr Clin North Am.* 2012;59(2):345–364, with permission from Elsevier.

than 90% will develop it in the first 2 years after diagnosis. The common manifestations like proteinuria, hematuria, casts, hypertension, edema, renal insufficiency, and renal failure occur secondary to glomerular involvement. Nephritis occurs secondary to deposition of immune complexes of DNA and anti-dsDNA in the mesangium and subendothelial space, ensuing activation of complement, and influx of inflammatory cells. Severity of nephritis does not correlate with the clinical presentation and hence there should be a low threshold for performing a renal biopsy with histologic, immunofluorescent, and electron micrographic analysis. The histologic diagnosis follows a standard classification devised by the International Society of Nephrology and the Renal Pathology Society. It classifies the renal involvement from class I to VI, and this helps guide treatment and prognostication.

The use of aggressive treatment has lowered the incidence of end-stage renal disease but still continues to be 10% to 20% 10 years from diagnosis.

### BOX 324-3 Common Dermatologic Manifestations of Systemic Lupus Erythematosus

- Rash
  - Malar ("butterfly") rash
  - Annular erythema
  - Discoid lupus erythematosus
  - Maculopapular and/or linear (nonspecific) rash
  - Bullous lupus (rare)
- Photosensitivity
- Alopecia
- Raynaud phenomenon
- Palmar/plantar/perioral erythema
- Livedo reticularis
- Vasculitis
  - Petechiae
  - Palpable purpura (leukocytoclastic vasculitis)
  - Chilblains/nodules
  - Digital ulcers

From Levy DM, Kamphuis S. Systemic lupus erythematosus in children and adolescents. *Pediatr Clin North Am.* 2012;59(2):345–364, with permission from Elsevier.

### Neuropsychiatric Involvement

Nineteen distinct syndromes have been described by the American College of Rheumatology Committee on Nomenclature of neuropsychiatric SLE syndromes (NPSLE), as outlined in Box 324-4. Up to 65% of patients develop NPSLE during the disease course. It is the second leading cause of morbidity and mortality associated with SLE. Headache is the most common manifestation and may be of variable severity in 50% to 95% of children with SLE. Headaches can be a symptomatic manifestation of active SLE. They also may indicate increased intracranial pressure and sinus venous thrombosis. The occurrence of new severe headache in children with SLE should be evaluated immediately because of the possibility of thromboembolic events, especially in children with antiphospholipid antibodies. Children with SLE may have mood disturbances primarily because of their struggles with a challenging disease. Psychosis in SLE is unique for its preserved insight. It can occur in association with acute confusional state and cognitive dysfunction. Visual and auditory hallucinations are known to occur in children with SLE. Cognitive dysfunction can be diagnosed with traditional neuropsychological testing and has been found in 59% of patients.

Generalized seizures are more common than focal and occur in association with other SLE syndromes. They may occur with CNS infection, with hypertension, and as part of posterior reversible encephalopathy. Peripheral nervous involvement is rare in SLE.

### Hematologic Features

Hematologic features may be seen in up to 86% of patients with SLE. Cytopenias are common and may occur in up to 60% of patients. Leukopenia is usually

### BOX 324-4 Neuropsychiatric Syndromes Observed in Systemic Lupus Erythematosus

#### CENTRAL NERVOUS SYSTEM

- Aseptic meningitis
- Cerebrovascular disease
- Demyelinating syndrome
- Headache
- Movement disorder (chorea)
- Myelopathy
- Seizure disorder
- Acute confusional state
- Anxiety disorder
- Cognitive dysfunction
- Mood disorder
- Psychosis

#### PERIPHERAL NERVOUS SYSTEM

- Acute inflammatory demyelinating
- Polyradiculoneuropathy (Guillain-Barré syndrome)
- Autonomic disorder
- Mononeuropathy, single/multiplex
- Myasthenia gravis
- Neuropathy, cranial
- Plexopathy
- Polyneuropathy

From American College of Rheumatology: nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum.* 1999;42:599–608, with permission from John Wiley & Sons, Inc.

caused by lymphopenia, and less frequently by neutropenia. Lymphopenia may be representative of disease activity whereas neutropenia may be a side effect of medications like cyclophosphamide.

Anemia can be caused by antibody-mediated hemolysis or secondary to chronic disease. Hemolytic anemia has been reported in up to 16% of patients, but generally it is mild and rarely requires blood transfusion.

Immune-mediated thrombocytopenia has a wide range of severity in patients with SLE. Up to 50% of patients may have thrombocytopenia at some stage in their disease course, and 30% may have moderate to severe thrombocytopenia. Children and adolescents with idiopathic thrombocytopenic purpura (ITP) should be tested for antinuclear antibodies, and clinicians should be alert to the possibility of subsequent appearance of other clinical features of SLE. Children with ITP who are older than 10 years are more likely to have chronic ITP. Twenty percent to 30% of patients with ITP who are positive for ANA will progress to SLE.

Diffuse lymphadenopathy may be present in up to 20% of patients. Lymph nodes may be enlarged because of inflammatory changes secondary to SLE, macrophage activation syndrome, or infection.

Up to 40% of patients with SLE may have antiphospholipid antibodies like anticardiolipin antibodies and lupus anticoagulant. Lupus anticoagulant confers a high degree of susceptibility to thromboembolic



events. More than half of all patients with a positive anticoagulant response develop thromboembolic events, of which the majority are venous; approximately 10% of patients with SLE will develop a thromboembolic event. The common thromboembolic events are deep venous thrombi, cerebral venous thrombosis, and pulmonary embolus. Arterial thrombi and stroke are rare in children with lupus.

### **Pulmonary Features**

The various pulmonary manifestations of SLE are pleuritis, pleural effusion, pulmonary hemorrhage, pneumonitis, and pulmonary hypertension. Pleuritis is the most common manifestation, with 17% to 30% of patients developing pleuritis and pleural effusion. Pleuritis and effusion may present with sharp pain, especially on inspiration and dyspnea. Dyspnea also may be secondary to restrictive lung disease, and the lung function tests may demonstrate a restricted diffusion capacity. Restrictive lung disease results from the interstitial pneumonitis and interstitial fibrosis caused by long-standing inflammation. Interstitial infiltrates and pleural thickening may be visible on radiographic examination. Subclinical abnormalities detected on lung function studies may not always progress to active clinical lung disease. Pulmonary hemorrhage is a rare manifestation but may be life threatening, and acute dyspnea with falling hemoglobin levels may be the presenting clinical manifestations.

### **Cardiac Features**

Pericarditis, pericardial effusion, myocarditis, bacterial endocarditis, Libman Sacks endocarditis, and premature atherosclerosis are the cardiac manifestations of lupus. Pericarditis with pericardial effusion is the most common cardiac manifestation and is commonly a cause of chest pain in pediatric SLE. An infarct should also be considered in a patient with chest pain, though the risk is low.

Children with SLE are at risk of developing premature atherosclerosis. Factors that contribute to premature atherosclerosis include the inflammatory and immune abnormalities that are intrinsic to SLE, primary dyslipidemias, and the secondary effects of treatments such as corticosteroids.

Valvulitis that is commonly known as *Libman Sacks endocarditis* is a relatively rare manifestation in pediatric SLE. It may predispose to bacterial endocarditis.

Heart blocks are specific to neonatal SLE.

### **Gastrointestinal Features**

Gastrointestinal involvement may occur in 19% of patients, and may present as peritonitis, vasculitis, pancreatitis, and enteritis. Abdominal pain is found to be the most frequent symptom and occurs in 87% of patients with gastrointestinal involvement. It is mainly the result of peritonitis and pancreatitis. Intestinal vasculitis is a rare complication but may lead to intestinal perforation and hence has to be watched for. Abdominal pain may also be related to side effects of corticosteroids and NSAIDs. In the presence of growth failure and abdominal pain, celiac disease should also be considered.

Liver enzymes may be elevated in 25% of patients secondary to medications, active SLE, fatty infiltration, thrombosis, or infection. Testing for autoimmune hepatitis to facilitate treatment should be considered.

### **Vascular Features**

In SLE, any vessel may exhibit active inflammation. Cutaneous, retinal vasculitis, and small-vessel CNS vasculitis are rare. Thrombotic thrombocytopenic purpura is a rare manifestation of SLE and found in 0.8% of patients with SLE. Although Raynaud phenomenon is not caused by a vasculitis and is primarily representative of vasospasm, it occurs in 19% of patients with SLE.

### **Endocrine Features**

Hypothyroidism is very common in SLE. Diabetes mellitus may develop because of obesity and corticosteroid use. Puberty may be delayed in children with SLE.

### **Diagnosis**

Systemic lupus erythematosus is an illness characterized by flares and remissions, and diagnosis may be delayed because of sequential organ involvement and variation in severity. The delay in diagnosis may range from 1 month to 3 years with a median of 4 months. There needs to be a high index of suspicion and recognition of SLE's disease pattern to be able to make a diagnosis. Most children with SLE fulfill 4 or more of the American College of Rheumatology criteria that were developed for use in research studies. Ferraz and colleagues examined the sensitivity and specificity of the criteria in a group of 103 pediatric patients with SLE and 101 pediatric patients with other rheumatic diseases. They found that the most common criteria were positive ANA, arthritis, immunologic disorder, hematologic disorder, malar rash, and photosensitivity. Sensitivity of the criteria was 96% and specificity was 100% in this analysis.

Some children may present solely with renal disease, manifesting as nephrotic syndrome; rarely a child or adolescent may present with renal failure at the onset of disease.

### **Drug-induced Lupus**

The medications most commonly implicated in drug-induced SLE in children include several of the anticonvulsants (eg, phenytoin and carbamazepine), hydralazine, penicillamine, quinidine, isoniazid, and minocycline. Anti-TNF agents like infliximab, etanercept, and adalimumab may also cause drug-induced lupus. The prevalence of drug-induced disease is equal in boys and girls. Chronic use is required for the disease to develop.

Antihistone antibodies are present in 95% of these children, which differentiates drug-induced from classic SLE. Antineutrophil cytoplasmic antibodies may be positive. The treatment involves discontinuing the offending agent. Rarely anti-inflammatories and corticosteroids may be required. The lupus-like disease induced by these medications should resolve within weeks to months after the medication is discontinued. The drug-induced disease can potentially evolve to the classic form of SLE.

**Table 324-4** Differential Diagnosis of Childhood-Onset Systemic Lupus Erythematosus

INFECTION	GENERALIZED (SYSTEMIC SYMPTOMS)
Viral	Cytomegalovirus Epstein-Barr virus Parvovirus B19 Human immunodeficiency virus Human herpesvirus 6
Bacterial	Sepsis ( <i>Streptococcus</i> , <i>Salmonella</i> ) Brucella Leptospira
Other	Q fever ( <i>Coxiella</i> ) Tuberculosis (mycobacterial) Lyme disease (spirochetal) Toxoplasmosis (protozoan)
Malignant	Leukemia Lymphoma Neuroblastoma Langerhans cell histiocytosis
Autoimmune or inflammatory	Antiphospholipid syndrome Juvenile idiopathic arthritis Juvenile dermatomyositis Sjögren syndrome Mixed connective tissue disease Systemic vasculitis Crohn disease Acute rheumatic fever Sarcoidosis Hemolytic uremic syndrome Antiphospholipid syndrome Autoimmune lymphoproliferative syndrome Common variable immunodeficiency Other primary immune deficiencies Hemophagocytic lymphohistiocytosis
Other	Chronic widespread pain syndrome

From Levy DM, Kamphuis S. Systemic lupus erythematosus in children and adolescents. *Pediatr Clin North Am*. 2012;59:345–364, with permission from Elsevier.

### Neonatal Lupus Erythematosus

The common manifestations of neonatal lupus erythematosus are skin rash, cytopenia, and hepatitis. Congenital heart block may be seen in 30% of infants with neonatal lupus erythematosus. All mothers with positive SSA and SSB need close monitoring during pregnancy. Fetal bradycardia may be the first manifestation and can be treated with dexamethasone. The rash is scaly and papular with raised borders in sun-exposed areas. All manifestations resolve in 6 months except for heart block. These neonates are unlikely to develop SLE. About one-third to half of all children with heart block may go on to require a pacemaker within the first 24 months.

### Differential Diagnosis

The other diseases that may share similarities with SLE are represented in Table 324-4. Table 324-5 lists SLE manifestations with isolated organ involvement without generalized features.

**Table 324-5** Isolated or Focal Symptoms That May Indicate an Underlying or Concomitant Diagnosis of Systemic Lupus Erythematosus

ORGAN SYSTEM	CONDITION
Thyroid	Hypothyroidism (Hashimoto)
Gastrointestinal	Autoimmune hepatitis
Cardiovascular	(Autoimmune) chronic pericarditis Noninfective endocarditis
Hematologic	Immune thrombocytopenic purpura (ITP) Autoimmune hemolytic anemia (AIHA) Evans syndrome (ITP plus AIHA)
Neuropsychiatric	Primary psychiatric disorders (eg, major depression, schizophrenia) Primary central nervous system vasculitis
Lymphoid system	Kikuchi-Fujimoto disease

From Levy DM, Kamphuis S. Systemic lupus erythematosus in children and adolescents. *Pediatr Clin North Am*. 2012;59(2):345–364, with permission from Elsevier.

### Laboratory Findings

Laboratory evaluation in the presence of clinical signs and symptoms may aid in confirming the diagnosis of SLE.

A complete blood count needs to be performed to access the hematologic manifestations of SLE. A metabolic panel to evaluate liver and renal function is also necessary. In addition to hepatitis, elevated transaminases may also indicate muscle inflammation. Inflammatory markers like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are adjunct tools. ESR is more indicative of disease activity whereas CRP may be normal except in the presence of active infection, macrophage activation syndrome, or serositis.

Urinalysis is also a very cost-effective test to screen for and monitor renal manifestations of SLE.

### Autoantibodies

Antinuclear antibody is the most common autoantibody, and is present in 99% of patients with SLE. ANA has a high sensitivity (>95%) but low specificity (36%). ANA titers are elevated in 10% of healthy children, and may also be elevated in other rheumatic diseases. Titers of more than or equal to 1:1,080 are highly predictive of SLE. Titers of less than or equal to 1:360, particularly in children younger than 13 years, safely exclude SLE.

Antibodies to double-stranded DNA and extractable nuclear antigens are evaluated in children with elevated ANA titers. Anti-dsDNA antibodies have a high specificity for SLE. This antibody is used for diagnosis and monitoring of disease activity.

Anti-Smith antibody and antiribonucleoprotein (RNP) antibody are ordered together as an extractable nuclear antigen panel. They are highly specific for SLE

and are found in 50% of patients. It is not useful for disease activity monitoring because it remains elevated through the course of the disease. The anti-RNP antibody may indicate the presence of a mixed connective tissue disease whereas the anti-Smith antibody is associated with more severe disease and renal disease.

Other antibodies like anti-Ro (anti-SSA) and anti-La (anti-SSB) are also associated with SLE. Neonates born to mothers with these antibodies are at risk for congenital heart block. Other laboratory test results like low complement levels (C3 and C4) support the diagnosis of SLE. Anti-dsDNA antibody titers and complement levels are very helpful as markers of disease activity as well as for monitoring the disease activity.

### Treatment

The care of the child with SLE requires a multidisciplinary approach and involves primary care, pediatric rheumatology and nephrology, adolescent medicine, psychiatry, psychology, nursing, pain team, physical therapy, and occupational therapy. Pharmacologic treatment is tailored to the disease manifestation. Many immunosuppressant medications used to treat SLE are not approved by the FDA for use in children.

### Nonsteroidal Anti-inflammatory Drugs

These are mainly used for symptomatic treatment of joint pains and serositis.

### Antimalarials

Hydroxychloroquine and chloroquine are used for treatment of mild symptoms and are the key maintenance therapy. Although the mechanism of action is unclear, these drugs may have immunosuppressive, anti-inflammatory, and photo-protective effects. The use of antimalarials has shown a 38% reduction in mortality. They have beneficial effects on the lipid profile by reducing triglycerides, low-density lipoproteins, and very-low-density lipoproteins, and increasing high-density lipoproteins. They help lower the severity of renal disease. They are well tolerated, and the dose should not be increased for weight for obese children because they do not get distributed in the adipose tissue. The common side effects are nausea, vomiting, diarrhea, anorexia, and rarely headaches, dizziness, and elevated liver enzymes. It is important to monitor patients every 6 to 12 months for retinopathy, which is an uncommon but important side effect. The risk of retinal changes is rare at doses lower than 6.5 mg/kg. The risks are higher with liver and renal dysfunction, high cumulative doses, and long duration of therapy. The changes start in the paracentral region of the retina and cause central visual field loss. The other rare side effects are neuromyopathy and cardiotoxicity.

### Corticosteroids

These form the mainstay of therapy when rapid control is required. More than 95% of children require corticosteroids at some stage in their disease. The use of oral versus intravenous corticosteroids differs significantly among different pediatric rheumatology centers. The

dose and duration depend on the organ and disease being treated. Oral corticosteroids are the drugs of choice for SLE-associated skin, serosal, pulmonary, hematologic, renal, and cerebrovascular disease. Corticosteroids are used in combination with immunosuppressive drugs for severe organ involvement. Since the 1970s, the so-called *pulse corticosteroids*, or intravenously administered methylprednisolone at a dose of 10 to 30 mg/kg (max, 1 g), have been used mainly for severe disease exacerbation. Corticosteroids do improve the clinical manifestations of SLE, but the long-term and short-term side effects affect the child's well-being. The long-term use of corticosteroids is associated with fractures related to osteoporosis, avascular necrosis of joints, cataracts, glaucoma, and coronary artery disease.

### Immunosuppressive Agents

Immunosuppressive agents are given to improve outcomes of renal disease and neuropsychiatric SLE. They also act to lower the total cumulative doses of corticosteroids in disease manifestations that flare up with corticosteroid tapering.

- Methotrexate is used for persistent arthritis.
- Azathioprine is used for arthritis, cytopenia, vasculitic rash, and serositis.
- Mycophenolate mofetil (MMF) is used for induction of remission in lupus nephritis, and for maintenance therapy of other organ disease. Hispanic and black children may respond better than white children to MMF.
- Cyclophosphamide, an alkylating chemotherapeutic agent, is used for severe life-threatening involvement like neuropsychiatric manifestations of psychosis and acute confusion. It may be used for lupus nephritis that has responded poorly to MMF.

B cells play a role in generation of autoantibodies in SLE, therefore, anti-B-cell antibody rituximab has also been used for disease with multiorgan involvement that is refractory to corticosteroids and other immunosuppressive therapy. Cyclophosphamide had been used in the past in more than half the patients. Belimumab and anti-B lymphocyte stimulator antibody has been shown to be effective in SLE with mild to moderate symptoms. They have not been studied in children.

### Adjunctive Therapy

For children with nephritis, antihypertensive agents and a low-salt diet may be required. Angiotensin-converting enzyme inhibitors are effective in reducing proteinuria. Lipid-lowering agents are not uniformly prescribed.

For children with neuropsychiatric SLE, psychotropic drugs may be needed, along with anticonvulsants for seizures.

Children with antiphospholipid antibodies or history of thrombi will need anticoagulation with close monitoring.

Patient should consider using contraception based on their individual situation when teratogenic agents are being used. Estrogen-containing agents are acceptable for patients who do not have antiphospholipid antibodies. When there is a risk for thrombosis, progesterone-only alternatives need to be considered.

### Course and Prognosis

Children with SLE have a more severe disease course than adult-onset SLE. Nonwhite race is associated with a worse outcome, but socioeconomic status may be a confounder. Mortality rates have decreased over time, and the current 15-year survival rate is 85%. Mortality in the early years after diagnosis is related to infections, severe lupus exacerbation, and end-stage renal disease. Late mortality is caused by cardiovascular disease. Premature atherosclerosis plays a large role in the increased risk of myocardial infarction in women in their 30s and 40s.

Long-term complications include end-stage renal disease needing dialysis and transplantation. The morbidity in patients with lupus results from a combination of the disease itself and adverse effects of its treatment like osteoporotic fractures, avascular necrosis, and infections. There is an increased risk of malignancy, particularly lymphoma, in these patients.

These children have poor mental and physical functioning. Education is negatively affected, and they eventually require disability support. Health-related quality of life scores are low in these patients.

### Role of the Pediatrician

The pediatrician, along with rheumatologists, plays a key role in the management of children with SLE. The office visit should be used to screen for common complications of the disease and side effects of treatment. Immunizations need to be up to date. Live virus vaccines are contraindicated for patients taking immunosuppressive medications. Children with fever need a careful evaluation for overwhelming sepsis and judicious use of antibiotics.

Families also need help navigating the educational system to establish an Individualized Education Program if the child is adversely affected by the chronic disease. Children's emotional state should be monitored in case psychological help is needed with coping skills.

### Summary

Systemic lupus erythematosus is a lifelong chronic autoimmune disease with unpredictable episodes of flare-ups and remissions. It is more aggressive in children. In view of the unique needs of adolescents, it needs to be managed carefully. Long-term outcome data are being sought, which will help better care for these patients.

#### WHEN TO REFER

- A child with persistent unexplained hemolytic anemia, thrombocytopenia, or neutropenia
- A child with persistent joint pain and other symptoms referred to multiple systems
- A child with malar skin rash
- Any constellation of signs and symptoms where lupus may be suspected

#### WHEN TO ADMIT

- Workup of a child at presentation when the diagnosis is uncertain and the child is sick

- Fever in a child with a diagnosis of SLE on immunosuppressant
- Active disease with poor control of symptoms and failure of outpatient management
- Treatment of an acute disease exacerbation where parenteral medications may be necessary
- Treatment of acute organ involvement leading to renal failure, pulmonary hemorrhage, or cerebrovascular stroke

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *What Is a Pediatric Rheumatologist?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Rheumatologist.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Rheumatologist.aspx))

### AAP POLICY

Cassidy J, Kivlin J, Lindsley C, et al; American Academy of Pediatrics Section on Rheumatology and Section on Ophthalmology. Ophthalmologic examinations in children with juvenile rheumatoid arthritis. *Pediatrics*. 2006;117(5):1843–1845. Reaffirmed October 2012 ([pediatrics.aappublications.org/content/117/5/1843](http://pediatrics.aappublications.org/content/117/5/1843))

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## Chapter 325

# ROCKY MOUNTAIN SPOTTED FEVER

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### INTRODUCTION

Rocky Mountain spotted fever (RMSF), an acute infectious disease caused by *Rickettsia*, is characterized by fever, headache, myalgia, and a distinctive exanthem. The major pathologic lesion, vasculitis, makes RMSF a multisystem disease. Most important, RMSF requires clinical diagnosis and treatment before laboratory confirmation.

RMSF is an infectious disease that produces a vasculitis, giving rise to symptoms in multiple organ systems, including skeletal muscle, brain, lungs, kidneys, adrenal glands, liver, and heart. *Rickettsiae* multiply in endothelial cells and may produce cellular injury by various mechanisms. These mechanisms include cell



wall penetration, disturbance of intracellular metabolism, production of toxic metabolites, and use of metabolites required by the host cell. Necrosis of endothelial cell walls, an increase in vascular permeability, fibrin extravasation, and thrombosis of small blood vessels ensues because of perivascular mononuclear cell infiltration caused by the reproducing organism. Resulting cell damage in multiple locations is responsible for the clinical picture.

## INCIDENCE

The disease was first reported in patients from the Rocky Mountain region. Today, however, the incidence of the disease is greatest east of the Mississippi River, with most cases being reported from the southeastern and south central United States. The reported frequency of the disease in the United States has increased slightly during the last several years from more than 500 cases per year in the 1990s to more than 1,000 cases per year since 2000. This translates to an increase from less than 2 cases per 1 million persons in 2000 to more than 6 cases per 1 million persons in 2010. From 1994 to 2003, 54% of the cases of RMSF reported in the United States were in North Carolina, Tennessee, Oklahoma, South Carolina, and Arkansas. Although the disease occurs predominantly in the United States, it has been reported in other areas in the Western Hemisphere, specifically Canada, Central America, and South America.

## EPIDEMIOLOGIC FEATURES

Ticks serve as a vector for the infectious agent *Rickettsia rickettsii*. Transmission to humans occurs when the tick takes a blood meal or when the abraded skin is contaminated by tick feces or a crushed tick, which may occur when ticks are removed. Usually, tick attachment lasting 12 to 24 hours is needed to transfer the disease to a human host. Two specific ticks serve as major carriers: the wood tick, *Dermacentor andersoni*, is the more important vector in the western United States; the dog tick, *Dermacentor variabilis*, is the usual vector in the eastern United States. Ticks, in turn, acquire the rickettsiae by feeding on infected wild mammals, such as squirrels, opossums, rabbits, dogs, and mice. Infection of laboratory workers has been reported independently of exposure to ticks. The seasonal incidence of RMSF, which occurs primarily in spring, summer, and fall, is in accordance with the activity of ticks. Dog ticks infected with *R. rickettsii* have been found in urban areas, which suggests this tick's ubiquitous nature and places individuals at risk without travel to endemic areas. Additional work has also implicated the brown dog tick, *Rhipicephalus sanguineus*, in causing an outbreak of *R. rickettsii* infection in Arizona in 2002 through 2004.

In adults, occupational or recreational exposure to ticks increases the risk for infection; however, children are the most frequently affected, with two-thirds of cases occurring in children younger than 15 years, and peak ages of infection of 5 to 9 years. Fifteen percent of deaths from RMSF occur in children younger than 10 years. The illness occurs more frequently in boys than girls and more in white people

than people of other races. RMSF can occur at any time of the year, but 90% of cases occur from April to September.

A study by Marshall and colleagues described positive serologic tests for RMSF in 12% of healthy children living in the southeast United States. This finding seems to indicate that many infections may be subclinical.

Exposure to a tick is not elicited in every case. Only 60% of patients with RMSF can recall a specific tick exposure or encounter. The tick bite is painless and leaves no local lesion or regional lymphadenopathy; the clinician should therefore question the patient specifically about prior activities that increase the risk for exposure (eg, removal of a tick from a pet dog, camping or picnicking in a high-risk area). The overall risk to patients, even when in high-risk areas, is low, given that only approximately 1% to 3% of the tick population carries *R. rickettsii* at any given time.

## DIFFERENTIAL DIAGNOSIS

Illnesses to be considered and differentiated from RMSF, especially after the rash appears, include rubeola (measles), meningococcemia, Kawasaki disease, leukemia, typhus, ehrlichiosis, and infectious mononucleosis.

### Meningococcemia

The petechial rash of meningococcemia differs from that of RMSF in its distribution, rapid extension, and coalescence of lesions into larger hemorrhagic, purpuric areas. Prostration develops rapidly if the patient remains untreated and is often apparent on admission to the hospital. Absence of myalgia and an extremely abrupt onset are helpful points in differentiating meningococcemia from RMSF. Although the white blood cell count may be elevated in meningococcemia, the sickest patients are frequently leukopenic. Meningitis with pleocytosis, low glucose levels, and organisms in the cerebrospinal fluid (CSF) also may be present. However, distinguishing between these entities clinically is not often possible; therefore treatment of both diseases in an ill patient is warranted.

### Ehrlichiosis

Ehrlichiosis is a rickettsial disease with clinical similarity to RMSF. Although a rash occurs with less frequency, more than 60% of children with ehrlichiosis have been noted to have rash. The rash, although variable in location and appearance, may be petechial and can be confused with rickettsial exanthems. Early diagnosis and treatment of patients with ehrlichiosis with doxycycline (also the drug of choice for RMSF) reduces morbidity.

### Rubeola

Rubeola (measles) is characterized by a macular rash (infrequently becoming hemorrhagic), which begins on the face and neck and is preceded by an enanthem, and Koplik spots on the buccal mucosa. The coryza and cough in the prodromal stage of illness are not consistent with RMSF. A history of adequate

immunization with rubeola vaccine greatly diminishes this possibility.

### Kawasaki Disease

Kawasaki disease shares many of the features of RMSF: fever, puffy hands and feet, rash, and conjunctival infection. Usually, Kawasaki disease is not considered seriously until after 5 days of fever, and an enlarged cervical node, pharyngeal hyperemia, dry cracked lips, strawberry tongue, and marked irritability tend to suggest the diagnosis. Although patients with Kawasaki disease also have a rash, it typically does not begin peripherally and spread centrally or become petechial in 1 to 2 days. Leukocyte and erythrocyte sedimentation rates are usually elevated significantly. In addition, Kawasaki syndrome usually occurs in the winter and spring months, in contrast to RMSF, which peaks during the summer. Typically, children with Kawasaki disease do not give a history of tick exposures. An elevated platelet count begins during the second week of illness. (See Chapter 280 for a more detailed discussion of Kawasaki disease.)

### Other Illnesses

Other illnesses that produce petechiae must also be mentioned, even though they lack the distinctive distribution of the rash. Patients with leukemia who initially have fever and petechiae would be expected to be anemic and have lymphadenopathy or hepatosplenomegaly. Patients who have infectious mononucleosis, if they have a petechial eruption, usually have lymphadenopathy, hepatosplenomegaly, and a gradual onset. Typhus is a rickettsial infection to be excluded. Murine typhus produces a milder disease, with a rash that is macular and not petechial. Epidemic typhus may produce a petechial rash that typically begins proximally and extends peripherally but does not usually involve the palms or soles; a history of a tick bite is also absent.

## CLINICAL FEATURES

After inoculation with the rickettsiae, the incubation period ranges from 2 to 12 days; the usual period is 5 to 7 days. In general, shorter incubation periods are associated with more serious disease.

In the typical case, the prodromal period lasts 2 to 3 days, with low-grade fever, chills, and muscle aches predominating. Muscle pain is most commonly in the calf region in younger patients. Headache is also an early symptom, and infants and toddlers may express pain from this or myalgias as crying or fussiness. Malaise, anorexia, vomiting, and photophobia also frequently occur. The prodrome is followed by accentuation of symptoms, especially fever, with temperatures often as high as 40°C (104°F) or more. The lowest temperatures, although still elevated, are recorded in the mornings. Lethargy and mental obtundation become prominent. Although the symptoms seen at this stage are not diagnostic, the triad of fever, headache, and myalgia, combined with a history of tick bite or removal within the previous 2 weeks, mandates treatment for RMSF until the diagnosis can be excluded.

Of RMSF symptoms and signs, rash is most distinctive. It usually appears 3 to 5 days after the onset of fever and begins peripherally on the wrists, ankles, hands, and feet. Initially, the lesions are macular, discrete, and erythematous and blanch on pressure. The rash rapidly spreads centrally, involving the arms, legs, axillae, buttocks, trunk, neck, and face. The lesions deepen in color, becoming dusky red, maculopapular, and petechial, but true petechiae may not form until day 6 of illness, and 35% to 60% of patients never develop petechiae. When present, petechial lesions may coalesce and form large ecchymotic areas. In severe cases and when treatment is delayed, these ecchymotic areas may ulcerate, and distal regions (eg, fingers and toes) may become gangrenous in as many as 4% of cases. Furthermore, as many as 15% of patients do not develop rash, or they develop a fine rash that may be difficult to appreciate in patients with darker skin tones. Because the rash does not typically occur until day 4 of the illness (and petechiae may be a much later finding) and some patients never develop a discernible exanthem, the pediatrician must not withhold treatment of a suspected case of RMSF until the rash appears. Tachycardia and an elevated pulse rate are noted early and are proportional to the degree of hyperpyrexia. A sudden increase in pulse rate or a decrease in blood pressure may indicate peripheral circulatory collapse, severe bleeding, or myocardial failure. Photophobia is associated with conjunctival ecchymosis involving both bulbar and palpebral conjunctivae. Retinal hemorrhages also may be seen.

Abdominal pain, vomiting, hepatomegaly, and splenomegaly with generalized abdominal tenderness may occur. Jaundice is not usually seen except in the most critically ill patients, such as those with disseminated intravascular coagulation (DIC). Fever, poor fluid intake from nausea, and vomiting all contribute to a diminished urinary output. Mild azotemia caused by these fluid losses should respond to rehydration.

In addition to the lethargy and obtunded state of consciousness, the patient may exhibit nuchal rigidity as a result of a vasculitic reaction in the meninges. Disorientation and confusion, as well as seizures, may occur. Coma, central deafness, cortical blindness, and sixth nerve palsies are other neurovascular complications that have been reported with RMSF. Vasculitis, hemorrhage from coagulopathy, or secondary metabolic changes caused by circulatory collapse are responsible for these neurologic manifestations. When these symptoms occur early in RMSF, they may mask its diagnosis.

## LABORATORY EVALUATION

The diagnosis of RMSF is made clinically. Treatment should be started before laboratory diagnosis is confirmed because there is significant morbidity and mortality and a confirmed diagnosis is usually only made on the basis of a rise in antibody titer. Available laboratory tests to confirm the presence of *Rickettsia* include a rise in antibody titer detected by immunofluorescence or latex agglutination, polymerase chain reaction testing, immunofluorescence of a skin biopsy,

or isolation of the organism from a clinical specimen. Immunofluorescent staining or polymerase chain reaction testing of the skin biopsy specimen may identify *R. rickettsii* and may provide early proof of RMSF, but these studies are not readily available to most physicians. Appropriate antibiotic therapy started 3 days before biopsy has resulted in negative immunofluorescence. Therefore when appropriate treatment has been initiated before biopsy, clinical criteria justify a full course of antibiotic therapy.

Complement fixation and immunofluorescent antibody studies in serum will identify patients who have RMSF, but results of these tests do not become positive until 7 to 10 days after the onset of illness, or later if antibiotic therapy has begun early. Thus titers should be performed during the acute illness and repeated 3 weeks later. A 4-fold increase in titer in the convalescent sera is diagnostic for infection.

The Weil-Felix reaction, agglutination of *Proteus vulgaris* by the patient's serum, is at best a nonspecific test for RMSF. Again, acute and convalescent serums must be compared, although *Proteus agglutinins* may appear by the end of the first week of illness. Availability of the more specific and sensitive tests makes this test obsolete.

*Rickettsiae* can be isolated from body fluid or tissue specimens when grown in laboratory animals or chick embryos. However, the high rate of disease transmission to laboratory technicians makes such techniques feasible only in laboratories engaged in *Rickettsia*-related research in which all workers are immunized; thus culture identification of *rickettsiae* is not available in most clinical settings.

Blood leukocyte counts and differential counts are usually within normal limits, but neutrophils often predominate. This predominance may help distinguish RMSF from ehrlichiosis, given that most patients with ehrlichiosis have lymphopenic leukopenia. Thrombocytopenia is a complication seen in the later stages of the disease and may be the result of platelet adherence to damaged endothelium.

Up to 20% of patients may have hyponatremia, possibly caused by increased vascular permeability of the kidney to sodium. However, this finding is nonspecific and does not exclude other diagnoses, such as ehrlichiosis. The remainder of the electrolyte profile is usually normal, but hypochloremia is also seen in some patients. Up to 25% of patients will also display increased blood urea nitrogen levels and increased liver enzymes. Abnormalities of prothrombin time, partial thromboplastin time, fibrinogen, and fibrin split products can occur with the development of DIC.

Patients with neurologic manifestations may have normal CSF cell counts, and most have normal CSF glucose and protein levels. However, CSF analysis may reveal neutrophilic or lymphocytic pleocytosis and elevated protein. As with many of the laboratory findings, these are nonspecific and may not help distinguish RMSF from meningococcal disease or ehrlichiosis.

Hematuria and anemia also may occur, but transfusion or renal dialysis is rarely required.

## MANAGEMENT

### Treatment

Treatment should never be withheld or delayed because of absence of rash, lack of exposure to ticks, or the desire to await confirmatory laboratory study results. Furthermore, delaying treatment is not acceptable because the patient is not from an area where RMSF is common or because the pediatrician is uncomfortable using doxycycline in a child younger than 8 years. If a pediatrician strongly suspects RMSF because of the patient's clinical history and physical findings, then therapy should be initiated immediately and can be given concurrently with treatment for meningococemia.

### Pharmacotherapy

#### Doxycycline

The drug of choice for all ages is doxycycline, an antibiotic in the tetracycline class of antibiotics that is given and continued for at least 3 days after clinical improvement and defervescence. The usual length of therapy is 7 to 10 days. Intravenous therapy should be given to all ill patients, who should then be transitioned to oral therapy when their condition has improved. Doxycycline is also effective against ehrlichiosis, which may mimic RMSF. Because doxycycline has a broad therapeutic index, levels do not need to be monitored as required with other RMSF medications, such as chloramphenicol.

#### Tetracycline

Tetracycline has been shown to be effective against RMSF but can lead to increased dental staining compared with doxycycline in children younger than 9 years. For this reason, and because tetracycline is no more effective than doxycycline, tetracycline is less commonly used in children.

#### Chloramphenicol

Chloramphenicol is no longer the drug of choice for RMSF. Data have shown doxycycline may be more effective than chloramphenicol. In addition, the toxic effects of this drug (aplastic anemia) make it an undesirable treatment option. However, chloramphenicol may be given to patients who cannot tolerate doxycycline or tetracycline.

#### Combination Therapy

Initiating treatment for meningococcal disease, as well as RMSF and ehrlichiosis, in an ill patient may be necessary. When this situation arises, doxycycline will provide treatment for both ehrlichiosis and RMSF and can be used in conjunction with an extended-spectrum cephalosporin to treat meningococcal infection.

### Hospitalization

Hospitalization is desirable initially for most patients, both to confirm the diagnosis and to observe the effect of therapy. Therapy should be continued until the patient has improved and has been afebrile for 72 hours, which generally corresponds to a total of 7 to 10 days of therapy.



### Supportive Therapy

Supportive therapy includes maintenance of hydration and nutrition with appropriate intravenous fluids and oral feedings (if tolerated). Management of DIC may include therapeutic maneuvers such as administering fresh-frozen plasma, fresh platelets and packed red blood cells, and vitamin K. Seizures may require the use of anticonvulsant medications.

### PROGNOSIS

Rocky Mountain spotted fever now has a mortality rate of approximately 0.5% to 4% in recognized cases, but patients with RMSF who escaped clinical detection have been identified by serologic evidence, suggesting that the disease may occur in a mild or subclinical form. The importance of abdominal pain mimicking an acute abdominal condition and dominating as an early symptom before the development of a rash must be emphasized. Rocky Mountain spotless fever has also been described. Of great concern is a report suggesting that patients who have *spotless* or *almost spotless* fever have a significantly higher mortality as a result of delayed diagnosis and treatment.

RMSF is a potentially lethal illness, even though younger patients are likely to be less severely affected than older patients. Early diagnosis and prompt therapy lessen disease severity. Under such circumstances, death would be extremely unusual; in most patients, early clinical diagnosis and adequate therapy shorten the duration of illness appreciably. Normal temperatures within the first 3 to 4 days may be expected, and patients recover rapidly from other signs of illness (eg, headache, myalgia, lethargy). Extension of the rash ceases. Recovery from the illness is accompanied by immunity to *R. rickettsii*.

### COMPLICATIONS

Vascular necrosis and thrombosis may result in local gangrene and loss of tissue. Although uncommon, DIC may develop. Patients with this complication have the greatest risk for dying. Myocardial failure may result from myocarditis and arrhythmias. Edema may be generalized as a result of an increase in capillary permeability caused by the vasculitis, of heart failure, of iatrogenic fluid overload, or any combination.

Neurologic complications in addition to the lethargy have already been discussed, but long-term morbidity from these complications, although rare, is still significant. Hematuria and anemia also may occur, but transfusions or renal dialysis are rarely required.

### PREVENTION

N-N-diethyl-M-toluamide (DEET) skin repellents in conjunction with permethrin-containing repellents used on clothes has been shown to be effective against ticks. Systemic reactions to DEET are possible when the repellents contain a high concentration of the chemical. The best preventive measure is avoidance of tick exposure, but when exposure is likely, daily searches for ticks should be performed. For tick-infested areas, twice-daily searches are

advised. Careful inspection at bath time is an excellent way to discover the presence of ticks. They may be removed by gentle traction with forceps or tweezers, but care must be taken not to crush them. The skin should be disinfected both before and after tick exposure to clear it of tick feces that may carry *R. rickettsii*. The tick should never be covered in petroleum jelly, nail polish remover, or alcohol, and no one should attempt to burn the tick to coax it to detach itself. These attempts may lead the tick to defecate or aerosolize infected body fluids. Antimicrobial prophylaxis is not indicated after a tick bite. The chances of a tick carrying the disease, even in an endemic area, are low, and no demonstrable benefit of prophylaxis has been found.

#### WHEN TO REFER

- Uncertain of diagnosis
- Clinical suspicion of disease

#### WHEN TO ADMIT

Most patients need to be hospitalized until they show clinical improvement. Other indications for hospitalization include:

- Hemodynamic instability
- Dehydration
- Need for intensive monitoring
- RMSF with its complications

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *A Parent's Guide to Insect Repellents* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *Stop Ticks* (Web page), Centers for Disease Control and Prevention (www.cdc.gov/features/stopticks)

#### Medical Decision Support

- *Red Book: 2015 Report of the Committee on Infectious Diseases*, 30th ed (book), American Academy of Pediatrics (shop.aap.org)
- *Rocky Mountain Spotted Fever* (Web page), Centers for Disease Control and Prevention (www.cdc.gov/rmsf/info/index.html)

#### Practice Management and Care Coordination

- *Tick-borne Rickettsial Disease Case Report Form* (form), Centers for Disease Control and Prevention (www.cdc.gov/ticks/forms/2010\_tbrd\_crf.pdf)

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## Chapter 326

## SEBORRHEIC DERMATITIS

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Seborrheic dermatitis (SD) is a common, usually asymptomatic dermatosis of unknown cause that is seen primarily in infants but also in adolescents and adults. The incidence in the general population is 2% to 5%. In 50% of affected infants, symptoms begin before 5 weeks of age. Although SD is occasionally seen in infants who are infected with human immunodeficiency virus (HIV), a true increased incidence has not been documented. No evidence suggests a genetic predisposition. Infants with SD may be at an increased risk for developing atopic dermatitis and, less often, psoriasis.

## EVALUATION

Most commonly, SD is characterized as a greasy, scaly dermatitis, less often as psoriasiform SD and rarely as erythrodermic SD. Seborrheic dermatitis in infancy, known as cradle cap, is characterized by diffuse, red, crusted, and yellow scaling plaques on the vertex of the scalp (Figure 326-1). Similar lesions also may be found in the retroauricular creases, the eyebrows, and the nasolabial folds (Figure 326-2). In the axillary and inguinal folds, the neck, and the diaper area, lesions appear as shiny red patches with foul-smelling scales. Posterior lymphadenopathy has been shown to be significantly associated with SD in children with a negative fungal culture. The lesions are usually asymptomatic and distributed symmetrically. The presentation is similar in adolescents. A greasy, scaling, pruritic eruption may be noted on the scalp. Except for lack of inguinal area involvement, the distribution of the lesions is the same as that for infants. Human immunodeficiency virus (HIV)-positive children aged 2 to 5 years may exhibit SD with lesions similar to those seen in adolescents and adults. This circumstance is distinctly unusual in

immunocompetent children and seems to be a manifestation of HIV infection.

Psoriasiform SD, also known as *sebopsoriasis* or *seborrhiasis*, produces features of both SD and psoriasis and may represent a bridge between the 2 conditions. Psoriasiform plaques—annular, red-brown plaques with a silvery scale—may be present among the classic greasy, yellow, scaling lesions of SD. Children may or may not have *pitted* nails, which are seen with classic psoriasis. Erythrodermic SD is rare and causes widespread exfoliative erythroderma. Diffuse desquamation usually begins in the flexures and then spreads.

The child may exhibit signs and symptoms of systemic involvement: fever, chills, lymphadenopathy, peripheral edema, and dehydration. This involvement may also be the presentation of Leiner disease (see Differential Diagnosis).

## ETIOLOGY

The cause of SD remains unknown. In recent years, different pathogenic mechanisms have been proposed. Despite early evidence that *Pityrosporum ovale* may play a role in the evolution of SD, recent data support a causal link between *Malassezia* yeast and SD. Many studies have demonstrated clinical improvement of SD when interventions reduce *Malassezia* counts on the body. Separate research has shown that the use of antifungal agents effectively treats SD. However, no difference has been found in the *Malassezia* carriage rates in children with and without SD. Thus, authorities have proposed that the immunomodulatory factors of the host may influence the manifestation of SD rather than the actual colonization counts. *Malassezia* may serve as the primary trigger in an inflammatory reaction that ultimately results in SD. Studies have revealed an increase in both lymphocyte transformation response and leukocyte migration inhibition. This differing immunogenic host theory may explain the increased prevalence of SD in patients with acquired immunodeficiency syndrome. Other research postulates that SD lesions are induced by the toxin production or lipase activity of *Malassezia*. Seborrheic dermatitis lesions tend to be located on



**Figure 326-1** Cradle cap.



**Figure 326-2** Seborrheic dermatitis in the retroauricular creases, eyebrows, and nasolabial folds.

the scalp, face, eyebrows, and nasolabial, axillary, and inguinal folds. These locations are also areas of highest sebaceous gland concentration. Experts have proposed that an abnormality in the sebaceous gland or an increased sensitivity to circulating maternal or endogenous hormones may result in SD. However, children with SD have normal sebaceous secretion and hormonal levels.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of SD includes atopic dermatitis, psoriasis, dermatophyte infection, diaper dermatitis, and Langerhans cell histiocytosis. Atopic dermatitis is usually distinguished by the presence of extreme pruritus, extensoral distribution in infancy, and flexural distribution in older children (tending to spare the scalp and involve the hands and feet), as well as a family history in 70% of persons affected. Seborrheic dermatitis may also occur concomitantly with atopic dermatitis (see Chapter 219, Atopic Dermatitis). Psoriasis is a common inherited papulosquamous skin disorder characterized by well-demarcated, annular, thick, red-brown, scaling plaques usually present on the trunk, the extensor areas on the arms, knees, elbows, diaper area, and scalp, as well as by nail pitting. Psoriasis usually lacks the specific distribution and greasy component of SD. However, some cases of SD may overlap with psoriasis. Extensive cases of SD become persistent; when the family history of psoriasis is positive, children should be referred to a dermatologist for biopsy and, potentially, long-term follow-up care. Symptoms of dermatophyte infection of the scalp (tinea capitis) may include scaling, pruritus, and redness and usually results in alopecia. In addition, performing a fungal culture by swabbing the affected area vigorously will yield a positive result. Tinea corporis appears as annular, red, scaly plaques with central clearing. Cultures from the skin may be obtained in a similar fashion to the scalp. Potassium hydroxide preparation of scales from body lesions will demonstrate septate hyphae.

Diaper dermatitis, or irritant diaper rash, is characterized by involvement primarily of the convex surfaces by red, scaling plaques; the inguinal folds are spared (Figure 326-3). In candidal diaper dermatitis, similar red, scaling plaques involve the skin folds, but satellite pustules in areas not covered by the diaper may also be found (Figure 326-4). Seborrheic dermatitis in the diaper area involves the skin folds; however, no satellite lesions are found. Langerhans cell histiocytosis refers to Letterer-Siwe disease (diffuse disseminated histiocytosis), Hand-Schüller-Christian disease, and eosinophilic granuloma (chronic multifocal or focal histiocytosis). Letterer-Siwe disease may be confused with SD because its pattern of distribution is similar. However, Letterer-Siwe disease is also characterized by axillary, inguinal, and oral mucosal erosions, purpura and petechiae, and hepatosplenomegaly. A skin biopsy specimen will distinguish the 2 disorders easily and is recommended in cases of SD that are unresponsive to treatment. Erythrodermic SD is an inherited immunologic disorder characterized by generalized SD, persistent diarrhea, failure to thrive, and recurrent



**Figure 326-3** Irritant diaper dermatitis.



**Figure 326-4** Candidal diaper dermatitis.

gram-negative infections. The diagnosis is made by demonstrating deficient yeast opsonic activity in the child's serum. In addition, other immunodeficiencies and metabolic disorders may occur in an erythrodermic SD pattern.

## TREATMENT

Effective treatment for SD may involve a wide range of keratolytic agents, low-potency corticosteroids, and antifungal therapies. Medication choice is tailored to fit the age of the child. A more conservative approach is suggested when treating infantile SD (cradle cap). Applying mineral oil or white petrolatum to the scalp followed by a nonmedicated shampoo is an initial therapy. If the SD is unresponsive to this therapy, then second-line agents include a 1% to 2% salicylic acid in liquid or petrolatum form, followed by a keratolytic shampoo and a topical low-potency corticosteroid (1%–2.5% hydrocortisone or fluocinolone acetonide). Topical antifungals, specifically the azoles, are effective as well. More recently, the use of topical macro-lactam immunomodulators have been successful in treating this inflammatory skin condition. Tacrolimus also has antifungal properties, which contributes to its therapeutic effectiveness.

Therapy for adolescent SD consists of topical corticosteroids and keratolytic shampoos applied to the scalp. In addition, topical and oral ketoconazole may be used in severe cases. Psoriasiform SD of the scalp is treated as described for cradle cap. Psoriasiform lesions on the face and trunk respond to treatment with topical corticosteroid ointments and emollients. If lesions persist into childhood, then a modified Goeckerman regimen consisting of application of a tar preparation followed by outdoor exposure to sunlight and topical corticosteroids is therapeutic. Generalized erythrodermic SD may require systemic corticosteroids and antibiotics to control superinfection in addition to the antiseborrheic therapies already mentioned. Hospitalization for intravenous antibiotic administration may be required.

In treating infantile SD, the initial use of agents to loosen scale (mineral oil), anti-inflammatory low-potency topical steroid, or antifungal agent is preferred because of the potential toxicity of salicylic acid products by absorption through the skin. If this initial regimen does not work, salicylic acid products or petrolatum should be applied for only 10 minutes and then shampooed out carefully, avoiding the face and particularly the eyes because severe contact irritation may occur. The corticosteroid solution should be applied sparingly and left on for several hours. This regimen may be repeated up to twice daily as needed and then tapered. Heavy metal agents such as selenium sulfide should be reserved for teens and adults, especially because coexisting atopic dermatitis can be an issue for infants and these agents can exacerbate underlying atopic dermatitis. Dramatic improvement usually occurs within 1 week. Lesions occurring on the face, intertriginous areas, and diaper area may be treated with a low-potency topical corticosteroid cream (1% hydrocortisone cream) twice a day. A mid-potency corticosteroid such as 0.1% Kenalog cream may be used on the body twice a day. A midpotency or strong halogenated corticosteroid should not be used on the face, intertriginous areas, or diaper area. Topical ketoconazole (Nizoral), which has been used to treat adult SD, has been found to be beneficial in treating infantile SD. Lesions in the diaper and intertriginous areas may become superinfected with *Candida* species and require topical antifungal creams twice a day in addition to a topical corticosteroid.

## PROGNOSIS

The prognosis for infantile SD is usually excellent. Most cases resolve within the first 6 months of life. Adolescent-onset and HIV-related SD may be more persistent; however, they usually respond readily to topical therapy. Infants who have SD may be at an increased risk for developing atopic dermatitis or psoriasis later.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Diaper Rash* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)

## SUGGESTED READINGS

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## Chapter 327

# SEIZURE DISORDERS

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Seizures occur in approximately 1% of all children up to the age of 14 years. The incidence is greatest in the first year of life (approximately 120 cases per 100,000 population) and thereafter the incidence is 40 to 50 cases per 100,000 population until the age of puberty and closer to 10 cases per 100,000 population in the early and mid-teens.

Seizures are caused by abnormal discharges of neurons and may have a wide variety of clinical manifestations. A seizure should be considered a symptom of systemic or central nervous system (CNS) dysfunction. Management consists not only of controlling seizures, but also of diagnosing any potentially treatable underlying condition. Acute conditions associated with seizures include metabolic disturbances, fever, meningitis, encephalitis, and toxic encephalopathy. The terms *seizure disorder* and *epilepsy* are synonymous and are applied to the condition in which a tendency for recurrent, unprovoked seizures exists. Care of children who have epilepsy includes managing the psychosocial effect of epilepsy on the child and family, as well as any associated comorbidities, such as learning disabilities and behavioral problems.

## CLASSIFICATION

Classification of seizures has provided a means to study seizures that have similar pathophysiologic features and to determine which medications are effective for which seizure types. Electroencephalogram (EEG) monitoring aided in the current classification, which is based on characterization of seizure onset and progression. Seizures are either focal or generalized. *Generalized* seizures result from involvement of both cerebral hemispheres simultaneously from the onset of the seizure. Types of generalized seizures include absence, myoclonic, atonic, tonic, clonic, and tonic-clonic seizures. *Focal* seizures, which were called partial seizures in the prior classification, are caused by seizure discharges that begin in 1 hemisphere. Focal seizures are divided further according to the degree of impairment during the seizure and its initial manifestation.



Epilepsy syndromes are also defined in terms of a cluster of signs and symptoms, including seizure type, age of onset, severity, diurnal or nocturnal occurrence, clinical course, associated neurologic dysfunction, inheritance, and EEG findings. Some of the more common generalized epilepsy syndromes include juvenile myoclonic epilepsy, Lennox-Gastaut syndrome, and childhood absence epilepsy. A common focal epilepsy syndrome is benign childhood epilepsy with centrotemporal spikes. Infantile spasms are included in the *epileptic spasms* category because there is inadequate knowledge to make a firm decision regarding whether the spasms should be classified as focal, generalized, or both. As the understanding of the genetics underlying seizure susceptibility and epileptic syndromes evolves, classification will probably change to incorporate that knowledge.

Febrile seizures are considered separately because they are not traditionally diagnosed as a form of epilepsy *unless nonfebrile seizures develop*. Box 327-1 outlines the classification of the various seizure types and some of the epilepsy syndromes.

## Generalized Seizures and Epilepsies

### Generalized Tonic-Clonic Seizures

Generalized tonic-clonic seizures are also known as *grand mal seizures* and consist of motor manifestations and loss of consciousness. The tonic phase is characterized by a sustained contraction of muscles; as a result, the child falls to the ground, usually in opisthotonus. In most instances, extensor posturing

occurs with tonic contraction of the diaphragm and intercostal muscles, which halts respirations and, in turn, produces cyanosis. The tonic phase lasts less than 1 minute and is followed by the clonic phase, which consists of bilateral rhythmic jerking. The jerks may be accompanied by expiratory grunts produced by diaphragmatic contractions against a closed glottis. The frequency of the clonic jerks decreases as the seizure progresses, although the intensity may actually increase. The tongue may be bitten, and bowel and bladder incontinence may occur. The clonic activity usually stops within several minutes. The seizure may be followed by vomiting, confusion, and lethargy, with gradual recovery of consciousness during minutes to hours.

Generalized tonic-clonic seizures may be primary or follow a focal seizure. Primary generalized seizures are usually idiopathic or genetic in origin and are associated with bilaterally synchronous electrical discharges on EEG. Focal seizures may evolve to a bilateral convulsive seizure so rapidly that any suggestion of focal origin by history or EEG is lacking. The EEG may demonstrate a focal discharge that may spread to both hemispheres or may show only bilateral synchronous discharges. The history that is helpful in determining that a seizure is focal in onset is the presence of an aura, head or eye deviation, or focal clonic movement at the onset of the seizure. Neurologic examination may reveal subtle focal signs such as a mild hemiparesis or visual field defect. Complete seizure control is less likely in focal seizures that generalize than in primary generalized seizures.

Effective antiepileptic medications for treating primary generalized tonic-clonic seizures include valproate, lamotrigine, phenobarbital, topiramate, zonisamide, and levetiracetam. Focal seizures that generalize may be effectively treated with these medications, as well as with carbamazepine, oxcarbazepine, and phenytoin.

### Absence Seizures

Absence seizures are generalized, nonconvulsive seizures characterized by interruption of activity, staring, and unresponsiveness; they usually last between 5 and 15 seconds. The episode starts abruptly without warning and ends abruptly with resumption of the child's preictal activity. The child may be unaware that the episode occurred. At times, unresponsiveness is accompanied by eyelid fluttering and upward rotation of the eyes and occasionally by mild clonic movements or automatisms such as lip smacking, grimacing, or swallowing. Seizures may occur more than 100 times per day and may interfere with the child's learning ability. The age of onset is generally between 3 and 8 years; rarely does it occur before 2 years or after 15 years of age. Girls are affected more commonly than boys. The influence of genetic factors in the etiology of absence seizures is suggested by the finding that 15% to 44% of children with absence seizures have first-degree relatives with absence seizures, paroxysmal EEG abnormalities, or both.

The classic finding on the EEG in children who have absence seizures is bilaterally synchronous 3-Hz spike-and-wave discharges. Hyperventilation may be used

### BOX 327-1 Classification of Seizures and Epilepsy Syndromes

#### GENERALIZED SEIZURE TYPES

- Tonic-clonic
- Absence
- Myoclonic
- Clonic
- Tonic
- Atonic

#### GENERALIZED EPILEPSY SYNDROMES

- Lennox-Gastaut syndrome
- Childhood absence epilepsy
- Juvenile myoclonic epilepsy

#### FOCAL SEIZURES TYPES

- Without impairment of consciousness or awareness
- With impairment of consciousness or awareness
- Evolving to a bilateral convulsive seizure

#### FOCAL EPILEPSY SYNDROMES

- Benign childhood epilepsy with centrotemporal spikes
- Epilepsia partialis continua

#### UNKNOWN

- Epileptic spasms



to precipitate the electrical discharge and a clinical seizure. Photoc stimulation during the EEG may also induce the seizure discharge in some children. Generalized tonic-clonic seizures may occur in some children, especially those who have an onset of absence seizures after 8 years of age. The prognosis for remission is good for children with younger age of onset and in whom absence is the sole seizure type, but is less favorable for those who have associated tonic-clonic seizures.

Monotherapy with ethosuximide, valproate, or lamotrigine usually controls absence seizures effectively. Ethosuximide, because of its effectiveness and lower incidence of serious adverse effects, is the drug of choice if the child has only absence seizures. Valproate or lamotrigine are the drugs of choice if associated tonic-clonic seizures exist. Any 2 of these medications may be used together when absence seizures are not completely controlled with 1. Lamotrigine has less deleterious effects on associated problems with attention span than the other 2 drugs. Benzodiazepines also are effective in controlling absence seizures, but their adverse effects on behavior make them second-line therapeutic agents. Phenytoin, phenobarbital, carbamazepine, and oxcarbazepine are usually ineffective for treating absence seizures and may exacerbate them.

### Myoclonic Seizures

Myoclonic seizures are characterized by brief, sudden muscle contractions or jerks that may involve only part of the body or may be generalized. They may occur in clusters, especially when falling asleep or shortly after awakening and, in most instances, no alteration in consciousness is associated with these seizures.

Most drugs that help other primary generalized seizures are helpful for these; however, these may be exacerbated by the medications that are used primarily for focal seizures.

### Clonic Seizures

In clonic seizures, the body part involved contracts and then relaxes, causing a rhythmic jerking. In the contraction phase, the body part or body itself takes on the position caused by the strongest muscles that move that part, which are usually the antigravity muscles—the arm flexors and leg and trunk extensors. If only one side of the body is involved, the body part will be pulled to or activated on that side.

### Tonic Seizures

Tonic seizures are characterized by a sudden sustained contraction of musculature, like the beginning of a tonic-clonic seizure. Sometimes, when these are short, they are hard to distinguish from myoclonic events, which are very short, because the contraction of the muscles involved is not sustained.

### Atonic Seizures

Atonic, or astatic, seizures are also termed *drop attacks*. They are characterized by a sudden decrease in muscle tone, which may result in head nodding or mild leg flexing. More significant decreases in muscle tone may

cause the child to slump to the floor. In most instances, no alteration in consciousness is detectable with these seizures.

Tonic, clonic, myoclonic, and atonic seizures may all be treated by the same medications that are used to treat generalized tonic-clonic seizures.

### Lennox-Gastaut Syndrome

Lennox-Gastaut syndrome is a severe epileptic encephalopathy characterized by focal seizures and a variety of generalized seizures, including tonic, tonic-clonic, and atypical absence seizures, often occurring at a greater frequency than other seizure disorders. Tonic seizures cause sudden, sustained contraction of the muscle groups, at times causing the child to fall. Atypical absence seizures consist of a brief period of staring and immobility. The onset and recovery of atypical absence seizures are less abrupt than those of typical absence seizures. The episodes may be associated with mild tonic motor manifestations, automatisms, or loss of postural tone. Atonic seizures occur and may be preceded by myoclonic jerks. Most of these children begin to have seizures between 3 and 5 years of age; boys are affected slightly more frequently than girls. Many children have neurologic deficits before the onset of Lennox-Gastaut syndrome, including intellectual disability and cerebral palsy, which may be related to hypoxic or other insults to the brain or abnormal brain development. Children may have a history of infantile spasms. The EEG typically shows an irregular, high-voltage, slow (2.5 Hz or slower) spike-wave pattern. The discharges are bilaterally synchronous.

The seizures associated with Lennox-Gastaut syndrome are often very difficult to control. Valproate has been effective in treating the different seizure types and is usually the initial drug of choice. Lamotrigine, topiramate, rufinamide, and felbamate have significantly reduced the frequency of atonic and generalized tonic-clonic seizures. The benzodiazepines, particularly clobazam, have also successfully controlled atonic, myoclonic, and atypical absence seizures. Unfortunately, with increasing doses, the frequency of adverse effects also increases. The development of tolerance is also a problem associated with the use of benzodiazepines. Ethosuximide can help control the atypical absence episodes, and phenytoin can be used for tonic seizures, but sometimes exacerbates the other seizure types involved. The ketogenic diet has been beneficial in seizure control, but because of the nature of the diet, compliance may be a problem. Vagal nerve stimulation has also been beneficial and well tolerated. Some children should be fitted for protective helmets to prevent repeated head injuries with their drop attacks. Generally, the treatment goal is to achieve reasonable seizure control with as few medications as possible to minimize adverse effects. In some instances, the seizures typical of Lennox-Gastaut syndrome occur in otherwise healthy preschool-aged children, associated with normal background and fast polyspike-and-wave changes on EEG. These children have a much better prognosis for seizure control and cognitive development.

### Childhood Absence Epilepsy

Childhood absence epilepsy is the term used for epilepsy that consists only of typical absence seizures with onset before age 8 years. It usually resolves before puberty.

### Juvenile Myoclonic Epilepsy

Juvenile myoclonic epilepsy is a primary generalized epilepsy with an age of onset of 12 to 18 years. It represents 7% of all epilepsy and is characterized by myoclonic jerks that affect mainly the upper extremities and, less commonly, the lower extremities. The jerks usually occur shortly after awakening, and children may complain of clumsiness or difficulty holding objects early in the morning. Approximately 80% of children have generalized tonic-clonic seizures, and 25% have absence seizures in addition to myoclonic seizures. Myoclonic jerks almost always precede the onset of generalized tonic-clonic seizures by months to years. A teenager who has generalized tonic-clonic seizures should be questioned carefully regarding myoclonic jerks. Both the myoclonic jerks and the tonic-clonic seizures may be precipitated by sleep deprivation, stress, alcohol, and hormonal changes. Children remain neurologically normal. Juvenile myoclonic epilepsy is genetic with several different loci identified. The ictal EEG typically shows generalized, symmetrical polyspikes and waves at 4 to 6 Hz. Photoc stimulation precipitates the electrical discharges in some children.

Valproate will control the myoclonic jerks, absence seizures, and generalized tonic-clonic seizures in more than 80% of children, but is often avoided in females of childbearing age. Lamotrigine, topiramate, zonisamide, and levetiracetam are also effective, but phenytoin is not, and carbamazepine and oxcarbazepine may exacerbate the seizures. The rate of seizure recurrence among patients who discontinue therapy during early adulthood is high, but a 25-year follow-up study found that up to 30% may be seizure free or have only morning myoclonic seizures on no medication.

### Focal Seizures

Focal seizures are seizures that originate in a limited area of 1 cerebral hemisphere. The symptoms may be motor, sensory, or cognitive, depending on the location of the neuronal discharge. Motor seizures may be restricted to a part of the body, such as the face or a limb, or they may spread to involve the entire side. They may also spread to the opposite hemisphere, resulting in generalized tonic-clonic seizure activity. Focal tonic-clonic seizure activity may be followed by Todd paralysis, a weakness of the limbs most involved in the seizure. Focal sensory seizures are most often manifested by paresthesias lasting less than 1 to 2 minutes.

Focal seizures may result in impaired consciousness, but, preceding impairment of consciousness, the child may have symptoms that are referred to as the *aura*. Seizure discharges from 1 occipital lobe may cause visual symptoms such as scintillating colored spots or scotoma in the visual field contralateral to the discharge. Seizures with more complex visual hallucinations often progress to altered consciousness.

Auditory seizures are manifested by hearing noises and less commonly by having elaborate, but usually nonverbal, auditory hallucinations such as hearing music. Seizure activity in the olfactory region causes a sensation of an odor, which is usually described as unpleasant. Affective symptoms such as fear or other unpleasant feelings can occur. Anger and rage are extremely rare as seizure manifestations, but may occur during postictal confusion if the child is restrained. *Déjà vu*, the feeling that an experience occurred before, and *jamais vu*, the feeling that a previously experienced sensation is unfamiliar and strange, and a *rising* epigastric sensation are common. Young children have difficulty describing these symptoms and may say only that a “funny feeling” occurred in the head or stomach.

Staring and automatisms, which are involuntary coordinated motor activities, occur when clouding of consciousness occurs. Automatisms include simple phenomena such as chewing, lip smacking, swallowing, and hissing, as well as more complicated activities such as picking at clothes, searching, or ambulating. Automatisms are usually followed by postictal amnesia. The child may become tired and go to sleep.

Focal seizures with impaired consciousness must be distinguished from absence seizures, which are also characterized by staring and unresponsiveness. Episodes of absence seizures have an abrupt onset and termination compared with focal seizures, which have a more gradual onset and termination. Absence seizures last less than 30 seconds and are not associated with postictal confusion. Automatisms can occur if absence episodes are prolonged, but they are often just a continuation of motor activity present before the onset of the seizure.

Focal seizures may evolve into a bilateral or generalized convulsive seizure. When they do, the convulsive or clonic seizure may be asymmetrical. Sometimes focal seizures generalize so quickly that they look like generalized tonic-clonic seizures from the start.

The most frequent EEG finding in focal seizures is an anterior temporal lobe spike discharge, although some children will have spike discharges from other areas. Interictal EEG recordings may be normal. Repeating the EEG increases the likelihood of demonstrating the abnormal discharge. Nasopharyngeal or sphenoidal electrodes rarely add information that is not obtained by scalp recordings that include special temporal placements.

Although focal seizures are caused by focal epileptiform discharges, a focal structural lesion may not be found in most children. Identifiable causes of focal seizures include perinatal insults, head trauma, CNS malformations, encephalitis, and possibly status epilepticus, all of which may be associated with scarring of the temporal lobe. Indolent tumors such as hamartomas and low-grade gliomas can also cause focal seizures and are found in approximately 20% of persons who have intractable focal seizures. Genetic factors play a secondary role in the etiology of focal seizures.

Anticonvulsant drugs used in the treatment of focal seizures include carbamazepine, oxcarbazepine, and valproate. These and most of the newer anticonvulsant medications are used preferentially to phenytoin

and phenobarbital. Carbamazepine and oxcarbazepine are the drugs of choice in children because of their efficacy and relatively mild adverse effects. If seizures are not controlled with carbamazepine, then the addition of acetazolamide may result in improved seizure control. For some children, oxcarbazepine is less sedating. Children who have medically intractable focal seizures should be evaluated at a comprehensive epilepsy center to determine their candidacy for surgical intervention, which results in complete seizure control in up to 90% of children.

### **Benign Childhood Epilepsy With Centrotemporal Spikes**

Benign childhood epilepsy with centrotemporal spikes is also known as *rolandic epilepsy*, *sylvian seizures*, and *centrotemporal epilepsy*. This epilepsy syndrome is a common type of focal motor epilepsy in childhood. The onset is usually between 5 and 8 years of age. Boys are more often affected than girls. Genetic factors play a role in the etiology. The seizures typically occur during sleep, although children may occasionally have episodes during wakefulness. Episodes are characterized by the child awakening with 1 side of the face twitching. The oropharyngeal muscles are also often involved, causing the child to make unintelligible gurgling sounds. The ipsilateral upper extremity may be involved, but only rarely is the lower extremity involved. In rare cases, a seizure episode will become generalized. Consciousness is often retained during the seizure, although the child may not be able to speak. Most seizure episodes last less than 2 minutes. The frequency of seizures is low, with 25% of children having a single-seizure episode and 50% having fewer than 5 episodes. The typical EEG findings are midtemporal or centrotemporal spike discharges occurring unilaterally or independently bilaterally in light sleep and sometimes induced by hyperventilation. Neuroradiologic studies show no abnormalities to correlate with the EEG focus. If a child has infrequent episodes, then no treatment may be needed. If the episodes frighten the child and a decision is made to initiate treatment, then carbamazepine or oxcarbazepine are the drugs of choice, although most anticonvulsants are effective. Some children with rolandic epilepsy are also prone to absence seizures, and carbamazepine and oxcarbazepine may exacerbate the absences. The focal seizures remit when the child is approximately 9 to 12 years of age, but no later than 17 years of age. Remission is long lasting, and no developmental or neurologic impairment is usually associated with these seizures other than some increased incidence of attention deficit or possibly some minor learning difficulties.

### **Epilepsia Partialis Continua**

Epilepsia partialis continua is a rare type of seizure in which twitching is continuous and limited to 1 side of the body. The twitching frequently involves only a few muscles and occurs most often in the hand or foot. Consciousness is preserved, but the seizure activity may weaken the extremity involved. Seizure activity may persist for hours to months. Focal encephalitis and tumor have been associated with this type of

seizure. Most anticonvulsants have some efficacy, but medical control of epilepsia partialis continua is generally difficult to achieve.

### **Unknown Seizures**

#### **Epileptic Spasms**

**INFANTILE SPASMS (WEST SYNDROME).** Infantile spasms are the most common type of “epileptic spasms” and a unique form of epilepsy, with onset during the first year of life. The seizures are characterized by a sudden contraction of neck, trunk, and extremity muscles. The spasms may be flexor, extensor, or mixed flexor-extensor and last only a few seconds each, but they often occur in clusters of up to 100 individual spasms. A typical episode is characterized by dropping of the head along with abduction of the shoulders and flexion of the lower extremities. The infant may cry during or after the spasm. Pallor, flushing, grimacing, laughter, and nystagmus are observed during some episodes. Episodes are common on awakening from sleep, during drowsiness, and with feedings, but are rare during sleep. The peak age of infantile spasm onset is between 3 and 7 months, with an estimated incidence of 0.24 to 0.60 per 1,000 infants. Boys are more likely to be affected than girls.

Infantile spasms are usually divided into symptomatic and cryptogenic groups based on the presence of a predisposing etiologic factor. Included among symptomatic infantile spasms are those associated with abnormal neurologic development before the onset of spasms. Causes include structural abnormalities of the brain, hypoxic-ischemic insults, CNS infections or hemorrhages, and inborn errors of metabolism. Children who have tuberous sclerosis account for up to 25% of patients who have symptomatic infantile spasms. The cryptogenic group are infantile spasms for which no etiologic factor can be found. Cryptogenic infantile spasms tend to start later than the symptomatic spasms.

The EEG pattern associated with infantile spasms is known as *hypsarrhythmia* and is characterized by high-voltage slow waves with irregularly interspersed multifocal spike-and-sharp waves. Hypsarrhythmia may precede the onset of clinical manifestations, or it may occur later or not at all. Over time, the hypsarrhythmia usually evolves into other focal or generalized abnormalities; in some cases, the EEG may normalize.

Infantile spasms are resistant to treatment with most anticonvulsants. The treatment used most commonly in the cryptogenic Adrenocorticotrophic hormone ACTH in a long-acting form is administered as a single daily intramuscular dose of 20 to 40 IU. Adrenocorticotrophic hormone is expensive, and studies of oral corticosteroids suggest that they may be an effective and less expensive alternative. Adverse effects of ACTH and steroids are significant and include Cushing syndrome, hypertension, susceptibility to infections, hyperglycemia, gastrointestinal bleeding, and electrolyte disturbance. In the symptomatic group, alternative anticonvulsants may be tried before ACTH. Vigabatrin is the only anticonvulsant other than ACTH with clear efficacy and is the drug of choice for infantile spasms caused by



tuberous sclerosis. There are reports, but not good evidence, for the benzodiazepines, particularly nitrazepam, topiramate, zonisamide, and valproic acid, sometimes controlling infantile spasms.

The prognosis for infants who have infantile spasms remains grave. The average mortality rate is approximately 20%, with aspiration pneumonia related to severe developmental abnormalities being a common cause of death. Approximately 80% of survivors are intellectually disabled. The spasms usually remit by a few years of age, but 55% to 60% of children subsequently develop other forms of seizures. The prognosis is more favorable for infants whose neurologic development was normal before the onset of the spasms.

### Neonatal Seizures

Seizures are the most common manifestation of neonatal neurologic disease and occur in approximately 0.5% of all newborns. Neonatal seizures may be generalized or focal and are classified using the same criteria as in children. For a long time, seizures have been identified only clinically, but as EEG has become more available to intensive care nurseries, it has been recognized that acute injury of the neonatal brain results in frequent subclinical electrographic seizures that can only be recognized with an EEG. In fact, only 10% or less of electrographic seizures in the neonate may be recognized clinically, particularly after initiating antiseizure medication. Additionally, the traditional antiseizure medications that are available for newborns in parenteral forms (phenobarbital, phenytoin, and lorazepam), and even the newer medication levetiracetam, are not effective in completely controlling these electrographic seizures, which tend to last several days after the injury. Genuine debate exists about whether seizures in the neonate can further the brain damage that caused them, although more recent evidence suggests that seizures worsen neurodevelopmental outcome. Uniformity of opinion is lacking about how aggressive to be in treating subtle neonatal seizures and those which seem to have no clinical correlate, but more recent studies suggest detrimental effects of seizures in neonates. Therefore, most clinicians try to eliminate both electroclinical and electrographic-only seizures, especially when they are the shorter-term seizures related to asphyxia or infection, if that can be done without serious side effects.

The combination of clinical manifestations of neonatal seizures and their likelihood of being associated with simultaneous electrographic seizures has led to revised classifications of seizures in the neonate. The clinical manifestations are classified as follows:

1. Subtle seizures occur in both full-term and premature infants and are often overlooked. These seizures consist of eye deviation, blinking, sucking, swimming movements of the arms, pedaling movements of the legs, and apnea. Electroencephalogram recordings do not always show correlation of electrical seizure discharges with the clinical seizure activity. This finding has raised the possibility that, in some instances, the abnormal movements arise from regions of the brain from which abnormal electrical activity cannot be detected with surface

electrodes or that they may not be seizures. Subtle seizures usually occur in infants who have severe CNS insults.

2. Clonic seizures are either focal or multifocal. Focal clonic seizures are characterized by rhythmic jerking that remains localized and is almost always associated with electrographic seizure discharges from the central part of the opposite hemisphere. Although focal clonic seizures can result from focal CNS lesions such as cerebral infarction, they can also occur with metabolic disturbances. Multifocal clonic seizures are characterized by clonic activity in 1 extremity that migrates randomly and often rapidly from side to side and place to place within the body. The EEG shows multifocal independent areas of electrical discharge. Clonic seizures should be differentiated from benign neonatal sleep myoclonus, which consists of small-amplitude clonic activity that may wax and wane in various parts of the body. The movements of benign neonatal sleep myoclonus occur in healthy term neonates and infants only during sleep and are accompanied by a normal EEG throughout the jerking period. This disorder is self-limited and not associated with later epilepsy.
3. Tonic seizures are focal or generalized. Focal tonic seizures are characterized by sustained posturing of a limb or asymmetrical posturing of the neck and trunk and possibly accompanying subtle seizure activity such as eye deviation. Generalized tonic seizures are characterized by tonic extension of the limbs. Less commonly, the upper extremities are flexed and the lower extremities are extended. They often have no electrographic correlate and may be some kind of brainstem phenomenon rather than seizures. They are usually associated with severe EEG background abnormalities. In premature infants, they may occur at the onset of severe intraventricular bleeding.
4. Myoclonic seizures are flexion jerks of the upper or lower extremities. They may occur singly or in a series of repetitive jerks, and they are sometimes associated with tonic spasms and multifocal seizures. The EEGs in infants with myoclonic seizures are usually abnormal. They may show a burst suppression pattern, although the EEG may not change during the myoclonic event. Infants with myoclonic seizures tend to have severely abnormal dysgenetic brains or metabolic defects. Occasionally, the seizures are cryptogenic. Infants with these seizures may later develop infantile spasms. These myoclonic seizures should be differentiated from benign myoclonic jerks that occur during sleep in neonates and are accompanied by a normal EEG. Jitteriness is a movement in neonates that may be confused with seizure activity. The movement is a tremor that is stimulus sensitive and can be stopped by passively flexing the affected limb. Jitteriness is not associated with ocular phenomena.

Some investigators advocate the identification of neonatal seizures by EEG recording, maintaining that only electrical seizures are true seizures and require treatment. However, this theory remains controversial because identical clinical seizures in the same infant



may, at times, not be associated with electrical seizures. Clearly, however, electrical seizures may not have clinical correlates; hence, EEG recording should be done for all infants at risk for seizures to identify these clinically silent electrical seizures.

When managing neonatal seizures, the physician must rapidly pursue the treatable causes, such as hypoglycemia, electrolyte imbalance, and infection, as well as EEG confirmation of seizure activity to help avoid the pitfall of treating coarse jitteriness or other transient abnormal movements with antiseizure medication. Treating the seizures themselves is urgent if they interfere with vital functions such as maintaining good arterial oxygen saturation. An approach to treating neonatal seizures is outlined in Box 327-2.

The prognosis of neonatal seizures relates to the underlying diseases that caused them. Intellectual disability and cerebral palsy are more common sequelae than seizures. Infants who have seizures related to hypoxic-ischemic encephalopathy, hypoglycemia, or bacterial meningitis have a 50% chance of developing normally; those whose seizures result from late-onset hypocalcemia and primary subarachnoid hemorrhage have a greater than 90% chance of developing normally. The interictal EEG is helpful in determining the prognosis. A normal background EEG pattern is usually associated with a good neurologic outcome; a markedly abnormal background pattern, such as burst suppression or marked suppression of voltage, is associated with a high risk for neurologic sequelae.

### Febrile Seizures

Febrile seizures are seizures that occur in young children who have fever, but no evidence of intracranial infection or acute neurologic illness. Simple febrile seizures are generalized tonic-clonic convulsions that

last less than 15 minutes and do not recur within 24 hours. Complex febrile seizures are less common and are focal or prolonged beyond 15 minutes or recur within 24 hours. Febrile seizures occur in children between 3 months and 5 years of age; the median age of occurrence is 18 to 22 months. Approximately 2% to 5% of children will experience a febrile convulsion; boys are more susceptible than girls. Familial clustering of febrile seizures occurs, and mutations of the *SCN1A* gene have been found in some families.

A febrile seizure may be the first sign that a child is ill. Whether the seizure activity is triggered by the rapid rise of fever or the actual height of the temperature is unknown. Febrile seizures can be triggered by any illness that causes fever, most frequently by otitis media and upper respiratory tract infections. The rate of febrile seizures with shigellosis, salmonellosis, and roseola is high, possibly related to a direct effect the causative organism has on the CNS or to a neurotoxin they produce.

One-third of children who have a febrile seizure will have another seizure with another febrile illness. The younger the child is at the time of the first episode, the greater the risk for recurrence. Approximately 50% of the recurrences occur within 6 months of the initial seizure; 75% occur within 1 year.

Usually, seizure activity stops by the time the child is evaluated. However, if the seizure continues, then lorazepam should be administered (see Chapter 374, Status Epilepticus). The temperature should be brought down by using rectal antipyretics, removing blankets and clothing, and sponging. After seizure activity is controlled, evaluation is directed toward finding the cause of the fever. If the child is younger than 1 year of age, or if the child has not rapidly returned to normal, then a lumbar puncture should be strongly considered to evaluate for meningitis.

### BOX 327-2 An Approach to the Treatment of Neonatal Seizures

- Ensure adequate ventilation and perfusion.
- Make an immediate determination of blood glucose and obtain blood for laboratory testing of glucose, calcium, magnesium, and electrolyte studies.
- Correct any associated metabolic abnormality.
- Hypoglycemia: If glucose level is low (<40 mg/dL), immediately give 10% dextrose intravenously in a dose of 2 mL/kg. Maintain blood glucose levels between 40 and 80 mg/dL by continuous intravenous infusion and monitor the levels in both full-term and premature infants. Try to avoid significant hyperglycemia.
- Hypocalcemia: Correct by administering 5% calcium gluconate solution, 4 mL/kg, intravenously at a rate of 1 mL/min to maintain serum calcium levels above 7 mg/dL while monitoring cardiac rate and rhythm.
- Hypomagnesemia: Correct serum magnesium levels to 1 mmol/L with 50% magnesium sulfate solution, 0.2 mL/kg, intramuscularly.
- Continued seizure activity requires consideration of other etiologies and administration of anticonvulsants.
- Phenobarbital is given in a loading dose of 20 mg/kg intravenously over 10 minutes. Additional doses of 5 or 10 mg/kg can be given, up to a total of 40 mg/kg.
- Fosphenytoin is given intravenously in a loading dose of 20 mg/kg of phenytoin equivalents while monitoring cardiac rhythm.
- Levetiracetam as 20 to 50 mg/kg has been used and is currently being assessed in a multicenter study.
- Lorazepam can be given in doses of 0.1 mg/kg intravenously for persistent seizures. Respiratory status should be monitored.

From Weiner SP, Painter MJ, Geva D, Guthrie RD, Scher MS. Neonatal seizures: electroclinical dissociation. *Pediatr Neurol.* 1991;7(5):363–368; Lawrence R, Inder T. Neonatal status epilepticus. *Semin Pediatr Neurol.* 2010;17(3):163–168; and Maytal J, Novak GP, King KC. Lorazepam in the treatment of refractory neonatal seizures. *J Child Neurol.* 1991;6(4):319–323.

The EEG is generally not helpful in evaluating children who have simple febrile seizures. Electroencephalogram tracings recorded within 1 week of the seizure often show posterior slowing. Paroxysmal activity is seen in the EEGs of 35% to 45% of children who are followed for several years. These EEG abnormalities do not predict recurrence of febrile seizures or the development of epilepsy. In children with focal febrile seizures, an EEG may indicate focal epileptiform abnormalities, which would be associated with an increased chance of recurrence and of epilepsy.

Treatment of febrile seizures includes family education that addresses the benign nature of the seizures, the use of antipyretics, and first aid for seizures. Oral diazepam (0.33 mg/kg body weight administered every 8 hours during febrile illness) reduces the risk for recurrent febrile seizures in that illness, but also sedates the child. No studies have demonstrated that antipyretics reduce the recurrence risk for simple febrile seizures. Administering phenobarbital at the onset of a febrile illness does not prevent seizure activity because therapeutic blood levels are not achieved soon enough. Prophylactic treatment with anticonvulsant agents may be considered if neurologic development is abnormal or if it is a complex febrile seizure. Administering phenobarbital in doses that achieve blood levels of 15 mcg/mL reduces the recurrence of febrile seizures. Valproate also seems to be effective in prophylaxis; phenytoin and carbamazepine do not prevent recurrences. The adverse effects of anticonvulsant therapy must be weighed against the possible benefits. No evidence has been found that prophylactic treatment reduces the risk for subsequent epilepsy.

The risk for subsequent epilepsy in children who have febrile seizures is less than 5%. Factors associated with subsequent development of afebrile focal seizures include focal febrile seizures, prolonged seizures, and repeated episodes of seizures with the same febrile illness. Factors associated with development of afebrile, generalized seizures include more than 3 febrile seizures, a family history of afebrile seizures, and age older than 3 years at the time of the first febrile seizure.

### **Paroxysmal Nonepileptic Events**

Paroxysmal nonepileptic events (PNEs) are also called pseudoseizures, nonepileptic seizures, and sometimes stress seizures. They are a form of conversion reaction and are typically associated with some kind of secondary gain related to sources of stress or anxiety. They must be recognized if inappropriate treatment is to be prevented. They differ from epileptic seizures in several respects. The movements are usually not clonic, but may be quivering or random thrashing. Usually, no incontinence, injury, or tongue biting is associated with PNEs. Episodes may be dramatic, with screaming, shouting, and thrashing of the extremities. Episodes also may vary greatly in the same child. Usually, no postictal period occurs. Paroxysmal nonepileptic events can occur in early childhood, but are more frequent in adolescence, especially in girls. They may occur in children who also have epileptic seizures. A detailed history and observation of an episode may be

all that is needed to diagnose these events. A prolactin level drawn within 10 to 20 minutes of an event may help differentiate it from an epileptic seizure. Usually a prolactin level drawn soon after a PNE remains normal, whereas after a generalized tonic-clonic seizure or a focal seizure with loss of awareness, the level is twice normal or higher. Capturing the event during video EEG monitoring establishes the diagnosis in children in whom the distinction cannot be made clinically because no epileptic discharges occur during the event. Treatment is directed toward the psychosocial issues involved.

## **ETIOLOGY**

### **Neonatal Seizures**

Neonatal seizures have multiple origins; however, only a few causes account for most cases. Determining the cause of neonatal seizures is important because specific treatment may be indicated. The cause of the seizures is also an important factor influencing prognosis. Some of the most common causes of neonatal seizures are described as follows:

1. Hypoxia-ischemia is the most common cause of seizures in both premature and full-term infants. These seizures usually begin within the first 24 hours of life and may be difficult to control for several days. Metabolic disturbances in the infant also may complicate seizure control. Infants with hypoxia-ischemia who are treated with head or body cooling may have seizures after 3 days during rewarming.
2. Intracranial hemorrhage is another cause of seizures in both premature and full-term infants. Intraventricular hemorrhage is seen mainly in premature infants within the first 3 days of life. Generalized tonic seizures may be associated with severe hemorrhage involving the brain parenchyma. Infants who have a primary subarachnoid hemorrhage may not have any clinical symptoms or may develop seizures on the second day of life. These infants often are full term and normal neurologically except for their seizures. Subdural hemorrhage is associated with trauma and may be associated with focal seizure activity.
3. Metabolic disturbances, especially hypoglycemia and hypocalcemia, are also associated with seizures in neonates. Infants who are small for gestational age, post-term infants, and infants of diabetic mothers are at risk for hypoglycemia, and the blood glucose level should be monitored closely. Low-birth-weight infants and infants of diabetic mothers are also at risk for hypocalcemic seizures, which may occur when calcium levels decrease below 7 mg/dL during the first 2 to 3 days of life. In many instances, infants who have hypocalcemia also have a history of hypoxia, which contributes to the risk for seizure. Hypocalcemic seizures that occur later are usually related to a low-calcium and high-phosphate intake in non-breastfed infants. Late hypocalcemic seizures are now rare as a result of the development of formula that has an appropriate ratio of calcium and phosphorus supplementation. Other metabolic disturbances less frequently associated with seizures in neonates include hyponatremia,

hypernatremia, local anesthetic intoxication, pyridoxine deficiency or dependence, and a variety of inborn errors of metabolism, some of which are associated with hyperammonemia and some of which may be ameliorated by dietary restrictions or supplementations. A helpful overview of the inborn errors of metabolism associated with epilepsy and often presenting in infancy was written by Papetti and colleagues.

4. Infection, including bacterial and viral intracranial infections, is an important cause of neonatal seizures. The most common bacterial causes are group B streptococci and *Escherichia coli*. Onset of seizures with meningitis is usually after the first 3 to 4 days of life. Prenatal nonbacterial infections causing neonatal seizures include toxoplasmosis, rubella, herpes simplex virus, coxsackievirus type B, and cytomegalovirus.
5. Malformations of the brain can cause seizures at any time during the newborn period. The malformations associated most commonly with seizures are those that have cortical dysgenesis such as lissencephaly, pachygyria, and polymicrogyria.

### Childhood Seizures

In most children with seizures, if an underlying cause is going to be identifiable, then the child's history or physical examination will provide clues. Whereas in most neonates a cause is identifiable (see section on Neonatal Seizures), in older children and adolescents a cause is identifiable in less than 20%, and if a child has no abnormalities by history or examination at the time of onset of seizures, then a cause is rarely identified. The more abnormal the child's neurodevelopmental status, the more likely a cause will be identified or may already have been determined before the onset of seizures. These causes include brain malformations, genetic disorders, disorders of metabolism, traumatic or previous infectious injury of the brain, and neoplasm. Children with infantile spasms and Lennox-Gastaut syndrome are more likely to have an identifiable cause. Idiopathic generalized epilepsies such as childhood absence epilepsy and juvenile myoclonic epilepsy are more likely to be related to genetic factors.

### Genetic Factors in Childhood Epilepsy

Family histories and twin studies clearly show that genetic factors play a role in some children with epilepsy. Additionally, the fact that some genetic syndromes such as Angelman syndrome and Rett syndrome predispose a child to seizures raises interest in the role of different genes in the susceptibility to seizures. Genes have been identified that govern the formation of the subunits of potassium and sodium channels and of the  $\gamma$ -aminobutyric acid type A and acetylcholine receptors in nerve cell membranes. Aberrations in these genes lead to increased excitability of nerve cell membranes. Benign familial neonatal and infantile convulsions have been linked to potassium channel subunit genes *KCNQ2* and *KCNQ3* and to the *SCN2A* gene, which governs the  $\alpha 2$  subunit of the neuronal sodium channel. Other genes have been identified in a group of familial epilepsies called *generalized*

*epilepsy with febrile seizures plus*. The epilepsies within these families include a range of severity from recurrent febrile seizures to multiple seizure types, including absence, myoclonic, and atonic seizures, and even focal seizures of temporal lobe origin. The most commonly found genetic abnormalities in these families are mutations of the *SCN1A* gene. Even without a family history of epilepsy, especially if a child has seizures combined with dysmorphic features and significant global developmental delay, an underlying genetic abnormality may be found in 25% by targeted gene sequencing panels and a few of these may have specific treatments.

In families with identifiable mutations of 1 gene, the severity of the epilepsy may vary, suggesting that other genes modify the expression of their primary genetic abnormality. Probably a significant number of yet-to-be-identified genes play a direct or indirect role in the excitability of the nerve cell membrane and together define each individual's seizure threshold that is then modified by environmental factors. A helpful overview of the current knowledge of genetic factors in epilepsy was written by Thomas and Berkovic.

## DIFFERENTIAL DIAGNOSIS

The first step in evaluating the child who has a seizure is making the correct diagnosis. Seizures must be differentiated from other paroxysmal disorders in childhood such as syncope, breath-holding spells, staring related to inattention, paroxysmal vertigo, cardiac arrhythmias, and stereotypic behaviors (see Chapter 179, Nonconvulsive Periodic Disorders). Additionally, the type of seizure should be identified to decide what diagnostic tests to pursue and which medication to use when treatment is indicated.

## EVALUATION

### Laboratory Evaluation

Laboratory tests usually performed at the time of the initial seizure include measuring serum electrolytes, calcium, magnesium, and blood glucose. In some cases, the history or examination may indicate that a more extensive laboratory evaluation is required.

### Electroencephalography

The EEG, which measures the physiologic function of the brain, changes throughout childhood, reflecting brain maturation. The EEG is important in evaluating a child who has seizures because it helps define the seizure type. An epileptiform EEG may support the diagnosis of epilepsy, but a normal tracing does not exclude the diagnosis. Other abnormalities, such as slowing and background disorganization, are much less specific. Repeat tracings increase the likelihood of detecting epileptiform discharges in patients who have seizures. Procedures such as hyperventilation, photic stimulation, and sleep should be used when obtaining EEG recordings. Nasopharyngeal and sphenoidal electrodes are now rarely used to detect mesial temporal discharges because they rarely add information to that obtainable by special scalp electrode placements. Video EEG monitoring is useful in correlating clinical symptoms with electrical seizure activity

and may be useful when clinical manifestations are atypical or pseudoseizures are in question. Although the EEG provides electrophysiologic evidence to support the diagnosis of epilepsy, EEG abnormalities must be interpreted in view of the clinical symptoms. Some individuals have epileptiform discharges and other EEG abnormalities without ever having a clinical seizure; anticonvulsant treatment is not indicated for such individuals. The 2 most common epileptiform abnormalities seen in children who have not had a seizure are centrottemporal spikes and 3-Hz spike and wave complexes in drowsiness or light sleep.

### Neuroimaging Studies

Plain radiographs of the skull can detect calcifications that may be seen in some syndromes, but they rarely help in evaluating children who have epilepsy. Computed tomography (CT) and magnetic resonance imaging (MRI) detect structural abnormalities such as changes in myelination, heterotopic gray matter, and low-grade tumors. Magnetic resonance imaging is more sensitive than CT and, therefore, the better study when available. Although it requires sedation in younger children, it is not associated with any risk from irradiation and provides much greater detail. Neuroimaging studies are not warranted in every child who has epilepsy; however, an MRI should be performed in children who have focal neurologic abnormalities on examination or intractable epilepsy. Positron emission tomographic and single-photon emission CT scans are useful in localizing metabolic alterations with seizure activity and seizure foci, but their clinical relevance is only in individuals with intractable epilepsy being evaluated for epilepsy surgery.

### Lumbar Puncture

The cerebrospinal fluid should be examined in children in whom meningitis or encephalitis is suspected. In other children, the lumbar puncture may be helpful in diagnosing disorders of glucose transport or of neurotransmitters.

### Genetic Studies

In some children with unexplained epilepsy, particularly those with other neurodevelopmental or dysmorphic features, it may be important to test for specific genetic disorders. Typically, a geneticist or child neurologist would help with such an evaluation. Several companies offer gene panel testing for the more common genetic causes of epilepsy, and these panels are constantly updated as new genes are identified. (See Genetic Factors in Childhood Epilepsy.) Looking for these disorders will be increasingly important as the gene products are understood and more specific therapies become available.

### Screening for Associated Learning and Behavioral Problems

Children with epilepsy and without global cognitive disability tend to have more learning problems, especially reading problems and attention deficit, than children without epilepsy. Additionally, behavioral problems may be identified in up to 50% of children with epilepsy, and this number may increase with the

added adverse effects of medication and the burden of a chronic disorder. Hence, determining whether these comorbidities exist through history, school records, behavioral checklists, or any combination is essential so that they may also be addressed to improve the overall quality of life of the child with epilepsy.

## MANAGEMENT

### Seizures in Neonates

After clinical seizures are controlled, electrographic seizures may continue and, if frequent or prolonged, may merit further anticonvulsant therapy. In general, seizures related to acute injuries, such as asphyxia, stroke, or acute CNS infections other than herpes, are self-limited and stop after several days, although they may recur months or years later. Although many physicians continue seizure prophylaxis after neonatal seizures for several months or longer, no evidence has been found that continuing treatment past the neonatal period will change the chance of recurrence. Therefore, seizures caused by acute injuries are usually treated short term and, in some nurseries, infants are not sent home on anticonvulsants if their seizures stopped or, if they are, then anticonvulsants are continued for only a few weeks. Because phenobarbital has a long half-life, especially in asphyxiated infants, it will remain at good levels after a full loading dose for several days, and no maintenance therapy may be needed. Seizures related to brain malformations or inborn errors of metabolism may be much more persistent, and the duration of treatment will depend on the infant's clinical course.

### Seizures in Children Beyond the Neonatal Period

The risk for seizure recurrence is important when deciding whether to initiate antiepileptic therapy. Some types of seizures, such as absence, myoclonic, akinetic, and infantile spasms, have a recurrence rate of virtually 100% and usually recur by the time the primary care physician sees the child. These types of seizures require treatment. However, children who have a generalized tonic-clonic or focal seizure have a recurrence risk of approximately 40%. Factors that increase the risk for recurrence include a focal seizure with impaired consciousness, an abnormal neurologic examination, and focal epileptiform abnormalities on the EEG. The best prognosis is in children who have a generalized seizure, normal neurologic examination, and a non-epileptiform EEG. Most children who have a single seizure should be observed for recurrence, but should not be given antiepileptic medication. More than 50% of the recurrences occur within 6 months, up to 69% within 1 year, and 88% within 2 years. If a second seizure occurs, then initiating antiepileptic medication should be considered because approximately 80% of children who have a second seizure will have more.

After the child has recurrent seizures and antiepileptic medication is indicated, the primary care physician is faced with the decision of which medication to prescribe. Diagnosing seizure type correctly is the critical first step in treatment because some seizure



disorders respond to certain medications and may be exacerbated by others. With the increasing understanding of gene aberrations that predispose individuals to epilepsy and the growing field of pharmacogenetics, the hope of being able to choose the best medication at the best dose for a particular individual with epilepsy may soon be realized. Meanwhile, in choosing among potentially effective antiepileptic agents for the specific individual's seizures, the drug that has the least adverse effects should be selected. The medication is given at a dose that will result in a low therapeutic blood level. The dose should be increased until seizures are controlled or adverse effects are prominent. If the initial medication is not fully effective, then a second medication may be added. Consider discontinuing use of the first medication if seizures are fully controlled with the second medication. Striving for monotherapy is important, if possible, given that polytherapy often does not improve seizure control, but may significantly increase toxicity. Closely monitoring for the potential cognitive and behavioral adverse effects of the antiepileptic medications is essential.

When devising an optimal dosing regimen, primary care physicians should consider the pharmacokinetics of the various antiepileptic medications. The dosing frequency is determined by the *half-life*, defined as the time in which the serum level decreases to 50% of the initial value. The dosing interval should be no longer than the half-life of the medication, which means that most antiepileptic agents may be administered twice a day and some only once a day. The efficacy of an antiepileptic medication should be evaluated only after 5 half-lives elapse because this period is required for the medication to reach a steady state. In antiepileptic medications that induce hepatic enzymes (eg, phenobarbital, phenytoin, carbamazepine, oxcarbazepine), the half-life decreases during the first weeks of treatment. If breakthrough seizures occur at times of low (trough) serum drug levels, toxic effects occur at times of peak drug levels, or children require higher antiepileptic medication levels, then the total daily dose should be divided into more frequent doses.

Serum drug levels can guide the dose adjustment of some antiepileptic medications. A baseline level may be obtained when the child has been taking an appropriate dose long enough to have stable levels. Other indications for obtaining levels include verifying compliance, breakthrough seizures, and toxic effects. Levels may also be checked when other medications are added or deleted from the child's regimen. The timing of the sample in relation to the last dose is important for interpreting the levels, especially in drugs with short half-lives.

### Specific Antiepileptic Medications

In the past 25 years, multiple new anticonvulsant drugs were approved for use in the United States. These drugs include felbamate (1993), gabapentin (1994), lamotrigine (1995), topiramate (1996), tiagabine (1997), levetiracetam (1999), oxcarbazepine (2000), zonisamide (2000), pregabalin (2006), lacosamide (2008), rufinamide (2008), vigabatrin (2009), and clobazam (2011). All of these drugs, except rufinamide

and clobazam, were originally tested and approved in the United States as add-on therapy for focal seizures. Most underwent trials with additional seizure types and in younger children after their original approval, and some received additional US Food and Drug Administration (FDA)-approved indications, or evidence exists for wider use than their current FDA-approved indications. Lamotrigine, topiramate, zonisamide, and levetiracetam have demonstrated efficacy in primary generalized seizures. These newer anticonvulsants, except for gabapentin and tiagabine, which have been generally less effective than the others, are more widely used than many of the older agents because of their better side-effect profiles. Pregabalin is approved for adjunctive therapy in individuals older than 18 years of age; data are limited on its use in children.

Table 327-1 outlines commonly used antiepileptic medications and their properties. (Medications used to abort seizures are discussed in Chapter 374, Status Epilepticus.) The reported half-life in some cases takes into account the half-life of active metabolites. Therapeutic blood levels are those reported in children at a steady state whose seizures were controlled or improved with minimal side effects. These levels are not well established for some of the newer anticonvulsants and, in many cases, the reported range in patients who responded to typical doses is large, decreasing the utility of drug monitoring. Because there are varying sensitivities to the side effects of these medications, some individuals will have side effects at levels that others easily tolerate. The most common and more serious side effects are indicated. Most side effects are dose related, but drug rashes, especially Stevens-Johnson syndrome, and hepatic reactions are usually not dose related.

### Acetazolamide

Acetazolamide is an inhibitor of the enzyme carbonic anhydrase. It is an effective adjunctive treatment of several types of seizures, although its antiepileptic properties are not well understood. Acetazolamide can be used in combination with valproic acid for treating absence, myoclonic, and akinetic seizures. Adding acetazolamide to carbamazepine may improve control of focal seizures. Acetazolamide metabolism is not affected significantly by other medications.

### Carbamazepine

Although carbamazepine is one of the older medications, it is still used because it has relatively few effects on cognitive function. It may also affect behavior positively. The most serious adverse effect associated with carbamazepine is aplastic anemia. This effect is extremely rare, occurring at a rate of less than 1 case per 200,000 treatment years. A complete blood cell count should be obtained before carbamazepine therapy is initiated and should be repeated after 2 to 3 weeks. Whether further blood cell counts are useful when the initial counts are normal is unclear, but they should be obtained more readily when the child is ill and are often repeated biannually or annually. Neutropenia as low as 3,000/mm may occur, especially in association with a viral infection, but does not predict

**Table 327-1** Common Antiepileptic Medications

DRUG	INDICATIONS	HALF-LIFE (HR)	USUAL DAILY DOSE (mg/kg)	THERAPEUTIC LEVELS (mcg/mL)	ADVERSE EFFECTS
Acetazolamide	Absence, myoclonic, akinetic, focal	10–12	10–20	10–14	Diuresis, paresthesias, sedation, carbon dioxide retention, rashes
Carbamazepine	Focal, focal evolving to bilateral convulsive	18–55, initially 3–23 on chronic therapy	2–5 initially, 5–25	4–12	Allergic rashes, nausea, diplopia, blurry vision, dizziness, hypersensitivity, hepatitis, aplastic anemia
Clobazam	Lennox-Gastaut syndrome in children $\geq 2$ years of age	12, active metabolites 40	0.1–0.2 initially, 0.6–1.0 maximum	100–300	Sedation/somnolence, increased secretions
Clonazepam	Absence, primary generalized, infantile spasms	20–36	0.01–0.2	0.01–0.07	Sedation, hyperactivity, inattention, aggressiveness, tolerance, ataxia, withdrawal seizures
Ethosuximide	Absence, myoclonic, akinetic	15–68	15–40	40–100	Nausea, abdominal discomfort, hiccups, drowsiness, behavioral problems, dystonias, myelosuppression, drug-induced lupus
Felbamate	Focal (in patients $> 12$ years of age), Lennox-Gastaut syndrome	20 (in monotherapy)	15–45 (maximum 3,600 mg)	30–100	Anorexia, weight loss, nausea, insomnia, headache, fatigue, aplastic anemia
Gabapentin	Focal, focal evolving to bilateral convulsive in patients $> 12$ years of age	5–7	Total daily dose 900–1,800 mg (maximum 3,600 mg)	2–20	Somnolence, dizziness, ataxia, fatigue
Lacosamide	Focal in patients $> 17$ years of age	13	Start 50 mg bid, increase 50 mg every week; top dose is 400 mg daily	5–16	Nausea, vomiting, dizziness, increased PR interval
Lamotrigine	Focal, primary generalized, absence, atypical absence, atonic, myoclonic	7–45	Initially 0.15 if on valproate, 0.6 if on an enzyme-inducing drug, and 0.3 if on both or neither of valproate and an enzyme-inducing drug. Double the dose in 2 weeks and continue slow titration over 2–3 months to target dose	2–14	Rash, including Stevens-Johnson syndrome, vomiting
Levetiracetam	Focal, focal evolving to bilateral convulsive, myoclonic, primary generalized tonic-clonic	6–8	Start at 10–20 mg/kg/day, increase every 2 weeks; top dose 60 mg/kg or 3,000 mg	6–35	Somnolence, irritability, hostility
Oxcarbazepine	Focal, focal evolving to bilateral convulsive	4–9	10–50: start at 10 mg/kg; top dose 2,400 mg divided into 2 daily doses	15–35	Somnolence, nausea, dizziness, rash, hyponatremia

Table 327-1

## Common Antiepileptic Medications—cont'd

DRUG	INDICATIONS	HALF-LIFE (HR)	USUAL DAILY DOSE (mg/kg)	THERAPEUTIC LEVELS (mcg/mL)	ADVERSE EFFECTS
Phenobarbital	Neonatal, febrile, focal, focal evolving to bilateral convulsive, primary generalized, akinetic	36–120	3–5 (<25 kg), 2–3 (25–50 kg), 1–2 (>50 kg)	10–40	Sedation, inattention, hyperactivity, irritability, cognitive impairment, rare hypersensitivity reactions
Phenytoin	Focal, focal evolving to bilateral convulsive, generalized tonic-clonic	7–42 (nonlinear kinetics)	5–7	10–20 (or lower)	Rashes, hirsutism, gingival hyperplasia, coarse features, psychomotor slowing, neuropathy, folate deficiency, myelosuppression, drug-induced lupus
Rufinamide	Lennox-Gastaut syndrome	6–10	Start 10 mg/kg divided into 2 daily doses, increase by 10 mg/kg every other day; top dose of 45 mg/kg or 3,200 mg	15–30	Somnolence, fatigue, dizziness, headache, nausea, shortened QT interval
Tiagabine	Focal	3–9	Start at 0.1 up to 0.25–1.5 (maximum 30 mg)	40–100	Dizziness, somnolence, headache, depression
Topiramate	Focal, primary generalized, tonic, atonic, atypical absence, infantile spasms	20–30	1–9	2–20	Somnolence, anorexia, fatigue, difficulty with concentration, nervousness, kidney stones, oligohidrosis
Valproic acid	Primary generalized, absence, myoclonic, akinetic, febrile, infantile spasms, Lennox-Gastaut syndrome, focal infantile spasms	6–16	10–30, monotherapy, may need more in polytherapy	50–100 (150 if tolerated)	Nausea, tremor, weight gain, hair loss, thrombocytopenia, hepatic failure, pancreatitis
Vigabatrin	Infantile spasms	5.7 in infants to 7.5 in adults	Start 50 mg/kg divided into 2 daily doses, increase by 50 mg/kg per week; top dose of 150 to 200 mg/kg	0.8–36	Visual field loss, irritability
Zonisamide	Focal, primary generalized, infantile spasms	24–60	Start at 1–2 mg/kg and may work up to 10 mg/kg; top adult dose is 600 mg	10–40	Somnolence, dizziness, kidney stones, oligohidrosis

more serious myelosuppression. The dose of carbamazepine may need to be changed during treatment because the drug tends to induce its own metabolic breakdown. Phenobarbital, phenytoin, and clonazepam decrease carbamazepine serum levels.

### **Clobazam**

Clobazam is approved for add-on therapy in Lennox-Gastaut syndrome in children 2 years of age and older. It is converted by subclasses of the cytochrome P-450 enzymes to an active metabolite, desmethylclobazam, which has about half the efficacy, but is present in about 10 times the concentration. Desmethylclobazam and its metabolites are excreted in urine. Although the half-life of clobazam is 12 hours, the half-life of this active metabolite is 40 to 50 hours. It is best to start clobazam at a low dose (5 mg/day in children <30 kg and 10 mg/day in bigger children) and increase it at 1- to 2-week intervals because of the sedation associated with it. The maximum dose suggested for children under 30 kg is 20 mg a day, whereas up to twice that may be used in bigger children. Caution is particularly important when adding it to other sedating medication. The dose should be modified when used with felbamate, selective serotonin reuptake inhibitors, omeprazole, and oxcarbazepine because these drugs may tend to increase its levels and the levels of its active metabolites. Its metabolism and that of its active metabolite are markedly slowed in individuals with deficits in the cytochrome P450 enzyme system. When clobazam is stopped, it requires tapering over several weeks or even months if the child has been taking it for more than a few weeks. It may have less associated tachyphylaxis than other benzodiazepines, and the associated sedation and increased secretions are less than with clonazepam.

### **Clonazepam**

Clonazepam, a benzodiazepine, is not a first-line anti-epileptic medication because of its adverse effects. It causes significant behavioral changes, including hyperactivity, decreased attention span, aggressiveness, and restlessness. It also causes increased secretions, which may be a problem in children with reactive airways or cerebral palsy and associated compromised swallowing mechanisms; it also may lead to swallowing dysfunction in higher levels. Additionally, similar to all of the other benzodiazepines, its efficacy is relatively short term because of tachyphylaxis. Because withdrawal of the drug may cause irritability, myoclonus, and increased seizures, it should be withdrawn slowly. Treatment with clonazepam is usually reserved for myoclonic seizures that are refractory to other medications.

### **Other Benzodiazepines**

Clorazepate is the least sedating of the benzodiazepines and is sometimes used adjunctively for resistant seizures. Diazepam and lorazepam may also be used. However, all of the benzodiazepines are associated with tachyphylaxis and some sedation and withdrawal seizures. Sometimes rotating from one to another helps this class of medications retain its efficacy. Their most significant place in epilepsy is in intermittent use,

as in status epilepticus, for which intravenous lorazepam is the drug of choice (see Chapter 374, Status Epilepticus.) The rectal preparation of diazepam may be administered safely during a prolonged seizure outside the hospital setting. Intranasal or intrabuccal midazolam as 0.2 mg/kg has been shown to act faster than rectal diazepam and is growing in acceptance as an alternative for use outside of the hospital in children with prolonged seizures. These drugs may also be used to stop flurries of seizures in patients predisposed to them or sometimes for nocturnal seizures.

### **Ethosuximide**

Ethosuximide has a limited spectrum of efficacy; it is used mainly for treating absence seizures and some forms of myoclonic seizures. Behavioral disturbances can occur in some children taking ethosuximide, and pancytopenia has been associated with long-term administration. Therefore, periodic blood cell counts may be necessary. Ethosuximide does not interact significantly with other antiepileptic medications.

### **Felbamate**

Felbamate was approved by the FDA in 1993 for treatment of focal seizures in adults and for adjunctive therapy in children who have Lennox-Gastaut syndrome. The most common adverse effects of felbamate are anorexia, weight loss, nausea, insomnia, headache, and fatigue. No serious cardiac effects have been reported. A year after felbamate was approved and widely used because of its lack of associated sedation, more than 20 cases of aplastic anemia among persons taking felbamate were reported. The incidence of, and predisposing factors to, this problem have not been fully determined. Its use decreased significantly after these reports and the associated warning. No cases have been reported in children younger than 13 years of age. A few cases of hepatic toxicity have also been reported. Currently, felbamate should only be used in children whose epilepsy does not respond to other drugs appropriate to the seizure type, and in whom the potential benefits of treatment outweighs the low risk for aplastic anemia. Felbamate interacts with phenytoin, carbamazepine, and valproate; therefore, doses of these medications must be reduced by 25% to 50% when felbamate is added. Felbamate levels are lowered by medications that induce liver enzymes; consequently, felbamate doses may need to be increased.

### **Gabapentin**

Gabapentin is approved as adjunctive therapy for focal seizures and focal seizures evolving to bilateral convulsive seizures in patients 3 years of age and older. Although gabapentin treatment has been shown to significantly reduce seizure frequency among children refractory to conventional anticonvulsants, it has not proved to be as effective an anticonvulsant as most other agents and is currently used more for neuropathic pain than for seizure control. One advantage of gabapentin is that it does not interact with other drugs. Additionally, it has few drug interactions and is 100% excreted renally, offering an advantage to children with liver failure. In add-on trials, the most



common adverse effects were somnolence, dizziness, ataxia, and fatigue.

### **Lacosamide**

Lacosamide is approved as adjunctive therapy of focal seizures in individuals 17 years of age and older. There are no significant interactions with other antiepileptic drugs, but lacosamide may potentiate generalized seizures.

### **Lamotrigine**

Lamotrigine is approved for treatment of focal seizures in individuals older than 16 years of age and as add-on therapy in children 2 years of age and older with Lennox-Gastaut syndrome. Studies in children reveal that lamotrigine reduces the frequency of both focal and generalized seizures. It was particularly effective in patients with absence, atypical absence, and atonic seizures. Its main advantage is its overall alerting effect. The most common adverse effects of lamotrigine are rash and vomiting. The rash is usually maculopapular or morbilliform, but a few cases of Stevens-Johnson syndrome have occurred. Co-medication with valproic acid increases the incidence of rash. Starting a low dose of lamotrigine and slowly increasing the dose throughout 10 to 12 weeks helps minimize the risk for rash. Lamotrigine administration has no effect on the metabolism of other antiepileptic drugs; however, phenobarbital, phenytoin, and carbamazepine decrease the half-life of lamotrigine. Valproic acid increases the half-life of lamotrigine by 2- or 3-fold; therefore, doses of lamotrigine should be lower when given in combination with valproic acid. Recommended starting doses are 0.15 mg/kg when used in combination with valproate, 0.3 mg/kg when used with either both valproate and an enzyme-inducing drug or neither of these, and 0.6 mg/kg when used with an enzyme-inducing drug, but not valproate. The starting dose is doubled after 2 weeks and tripled after another 2 weeks, and then the doses may be increased in larger increments, still taking 2 to 3 months to get to target dose. The range of therapeutic plasma concentrations is wide (1 to  $\geq 14$  mcg/mL), making monitoring of serum levels less useful. Side effects may not be seen with levels as high as 16 to 18 mcg/mL.

### **Levetiracetam**

Levetiracetam is approved as adjunctive therapy for focal seizures in children 4 years of age and older, for myoclonic seizures in children 12 years of age and older, and for primary generalized tonic-clonic seizures in children 6 years of age and older. Adverse effects include somnolence, behavior problems, and nervousness. The irritability that may be associated with levetiracetam can be improved by taking 50 to 100 mg a day of pyridoxine. The lack of significant adverse effects and drug interactions has made levetiracetam an initial choice, especially for primary generalized seizures.

### **Oxcarbazepine**

Oxcarbazepine is approved for initial monotherapy and adjunctive therapy for focal seizures in children

2 years of age and older. It is well tolerated with generally fewer adverse effects and especially less sedation than most other anticonvulsants. Infrequent dose-related adverse effects include somnolence, dizziness, diplopia, nausea, and vomiting. More serious, but infrequent, adverse events include rash and hyponatremia. An advantage over many drugs is its lack of drug interactions. Studies comparing oxcarbazepine with phenytoin and carbamazepine indicated similar efficacy, but lower rates of discontinuation because of adverse effects, and a study comparing it with valproate indicated similar efficacy and rates of discontinuation because of adverse effects. Oxcarbazepine is rapidly becoming a drug of first choice for focal seizures. It has been shown to be well tolerated in infants and young children. Oxcarbazepine is a moderate liver enzyme inducer.

### **Phenobarbital**

Phenobarbital is one of the oldest antiepileptic agents still in use. Because of its long half-life, it has the advantage of requiring dosing only once or twice a day. The dose per kilogram decreases as body weight increases. Failure to decrease the per-kilogram dose levels in older children will result in toxic levels. Because phenobarbital is a relatively safe medication in terms of serious toxic effects, monitoring parameters other than serum levels is not necessary. The major disadvantage of phenobarbital is its effect on behavior and cognitive function, including hyperactivity, irritability, and attention deficits. Because of these side effects, phenobarbital is used mainly in young infants, whereas some of the other drugs are used first in toddlers and school-aged children. Maintaining serum levels at the minimum level for seizure control may help decrease these adverse effects. Phenobarbital administration will lower the serum levels of carbamazepine and valproate. Administering valproate will increase phenobarbital levels; therefore, phenobarbital doses should be decreased by 25% to 50% to prevent toxic effects when prescribed concomitantly with valproate.

### **Phenytoin (Fosphenytoin)**

Phenytoin is also an older antiepileptic medication that was used widely in the past. It is used infrequently now for long-term therapy because alternatives with fewer adverse effects and more steady pharmacokinetics are available. Phenytoin has zero-order kinetics, causing blood levels to vary significantly with small changes in dose. Therefore, changes in dose should be monitored by serum levels, and only small dose changes should be made when serum levels are close to or within the therapeutic range. Phenytoin is commonly used for treating status epilepticus because intravenous administration results in rapid penetration into the CNS. Fosphenytoin is a water-soluble pro-drug of phenytoin with a more neutral pH and less tissue irritation. It can be administered intravenously or intramuscularly, whereas phenytoin may not be used intramuscularly. Although phenytoin is an effective antiepileptic agent in generalized tonic-clonic and focal seizures, its adverse effects limit its use. Cosmetic adverse effects include gingival hypertrophy,

hirsutism, and coarsening of the facial features. Also of concern are its effects on mood and cognitive function, which include depressed mood, slowed psychomotor functioning, and, in a few patients, depressed IQ scores. Other adverse effects include folate-deficiency anemia, cerebellar degeneration, and allergic dermatitis, including Stevens-Johnson syndrome. Valproic acid may lower total serum phenytoin levels, but the free phenytoin level transiently increases and then returns to its original level; thus, no adjustment in dose is necessary. Phenytoin may decrease carbamazepine levels and increase phenobarbital levels. Because it is highly protein bound and, with other protein-bound medications, it is displaced from protein, free levels are sometimes useful, and the therapeutic range for free phenytoin is 1 to 2 mcg/mL.

### Rufinamide

Rufinamide is approved as adjunctive therapy of Lennox-Gastaut syndrome in children 4 years of age and older. Adverse effects include somnolence, dizziness, headache, and nausea. Rufinamide can cause dose-dependent shortened QT interval and is contraindicated in children who have familial short QT interval. It has minimal effects on other antiepileptic drug levels, but can lower carbamazepine and lamotrigine levels and increase phenobarbital and phenytoin levels. Phenytoin, phenobarbital, and carbamazepine all decrease the plasma concentration of rufinamide, and valproate increases its level.

### Tiagabine

Tiagabine is approved for adjunctive therapy of focal seizures in adults and children 12 years of age and older. Its efficacy in generalized seizures is unclear. Adverse effects include dizziness, somnolence, and headache. Tiagabine does not alter the concentrations of other antiepileptic drugs except for a slight decrease in valproate levels. Enzyme inducers such as carbamazepine, phenytoin, and phenobarbital lower tiagabine levels. Tiagabine is used only infrequently for seizure control in children because other anticonvulsants are more effective.

### Topiramate

Topiramate is approved as initial monotherapy for focal seizures and primary generalized tonic-clonic seizures in children 10 years of age and older and for adjunctive therapy in children 2 years of age and older for focal and primary generalized tonic-clonic seizures and for Lennox-Gastaut syndrome. Topiramate has also been effective for treating infantile spasms in some children. The most common adverse effects of topiramate are somnolence, anorexia, fatigue, difficulty with concentration and nervousness, and oligohidrosis. It may be associated with a metabolic acidosis. It also increases the chances of kidney stones and is rarely associated with open-angle glaucoma. Topiramate administration has minimal effects on the metabolism of other antiepileptic drugs. However, concomitant therapy with phenytoin or carbamazepine will lower topiramate levels. Topiramate is also now used for mood disorders and headache prevention.

### Valproic Acid

Valproic acid has a broad spectrum of efficacy and also has the advantage of minimal cognitive adverse effects. Tremor may occur with high serum levels. Other dose-related adverse effects include increased appetite, weight gain, reversible hair loss, nausea and vomiting, and thrombocytopenia. Rarely, fatal hepatotoxicity has been associated with valproic acid. Most cases occur during the first 3 months of treatment. Those at greatest risk for hepatotoxicity are children younger than 2 years of age who receive valproic acid as part of antiepileptic polytherapy. Children younger than 2 years of age and those who develop hyperammonemia without liver failure are generally supplemented with L-carnitine, although this supplementation does not necessarily prevent the serious liver toxic effects. Valproic acid should be administered extremely cautiously to children who have preexisting hepatic dysfunction. Liver function should be monitored in children taking valproic acid, especially those in the high-risk group. Valproic acid raises the level of phenobarbital; therefore, the dose of phenobarbital must be decreased by 25% to 50% if valproic acid is added. Carbamazepine, phenobarbital, and phenytoin decrease valproic acid serum levels.

### Vigabatrin

Vigabatrin is approved as adjunctive therapy in adults with medically refractory focal seizures with impaired consciousness and in children 1 month to 2 years of age with infantile spasms. It may be particularly effective in infantile spasms related to tuberous sclerosis. Its use has been associated with irreversible peripheral visual field loss. There is increased risk in males, with longer length of treatment, and with higher cumulative vigabatrin dose. Another adverse effect is white matter vacuolation and intramyelinic edema. The MRI changes are seen in infants rather than adults and seem to be transient and asymptomatic. The long-term clinical significance of these changes is unknown.

### Zonisamide

Zonisamide is approved as adjunctive therapy in adults with focal seizures. Few studies have evaluated its use in children in the United States. However, in Japan, where it has been available longer, zonisamide is used widely in children with both focal and primary generalized epilepsy and infantile spasms. Adverse effects of zonisamide include somnolence, anorexia, dizziness, kidney stones, oligohidrosis, and rash. An advantage of zonisamide is its half-life of 24 to 60 hours, allowing once-a-day dosing.

## Other Treatments for Seizures

### Ketogenic Diet

In some children, the ketogenic diet has proved to be an effective alternative treatment, with one-half of children with intractable epilepsy showing a 50% decrease in seizure frequency and some being seizure free at 1 year. The benefits of fasting as a treatment for seizures were reported years ago, but the diet was not consistently used. Its popularity has waxed and waned since

its introduction in the 1960s. A multicenter prospective study on the efficacy of the ketogenic diet in children with intractable epilepsy found that 10% of treated children were seizure free at 1 year. A greater than 50% decrease in seizure frequency occurred in an additional 50% of the children. Seizure type, patient age, and EEG abnormalities were not related to outcome.

The exact mechanism by which the diet controls seizures is unknown, although ketone body formation is critical for the diet to be effective. To achieve ketosis, the child is given a high-fat, adequate protein, low-carbohydrate diet, sometimes with calorie restriction. Carbohydrate restriction is so crucial that sometimes medication forms that the child is receiving or may be prescribed must be without any added dextrose, effectively eliminating liquid forms. Dextrose in intravenous fluids should be minimized. The child is usually admitted to the hospital to initiate the diet, which allows monitoring for hypoglycemia and other complications such as intolerance of the high-fat content. Before and during the hospitalization, the dietitian teaches the parents about the diet, giving them sample menus and explaining how to measure foods. The first 24 hours of fasting to initiate the diet is no longer adhered to. Strict adherence to the diet is needed for it to be successful. Complications of the diet include constipation, renal stones, fatigue, and metabolic acidosis. Initiating and monitoring the ketogenic diet requires a multidisciplinary team, including the nutritionist/dietitian, pharmacologist, nurse, social worker, and any others that can help communicate with the school and encourage the family and child to adhere to the diet.

### **Vagal Nerve Stimulation**

Vagal nerve stimulation, a treatment for intractable epilepsy, emerged during the late 1980s and the 1990s. The first vagal nerve stimulation device was implanted into a human in 1988. Several studies report the use of vagal nerve stimulation in children, including children as young as 1 year of age; however, it is approved only in children as young as 4 years of age. Most studies report approximately 50% improvement of seizure frequency in one-half of the children, with a few becoming seizure free. Children selected for vagal nerve stimulation had seizures that were intractable to medical treatment or unacceptable adverse effects from medication. Some children continued to have seizures despite having epilepsy surgery. Positive effects seemed to be maintained over several years of follow-up.

Vagal nerve stimulation is associated with alertness, a benefit to many children with intractable epilepsy who often experience sedation from their anticonvulsant therapy. It may also have antidepressant effects. Adverse effects associated with vagal nerve stimulation are generally uncommon and include infection, hoarseness, neck pain, insomnia, and, occasionally, emergence of behavioral abnormalities, which may be related to increasing alertness. Improvements in language function have been noted in some children.

The vagal nerve stimulation device is surgically implanted subcutaneously in the anterior chest wall, usually just under the clavicle, and stimulates the left

vagus nerve. The mechanism for the antiepileptic effect of vagal nerve stimulation is not known, but changes in cerebrospinal fluid amino acids and activation of the noradrenergic system in the locus coeruleus occur with the stimulation.

### **Psychosocial Issues**

Treating the child with a seizure disorder must also address psychosocial issues. Parents and children may have many fears and need reassurance. The terms *epilepsy* and *seizure disorder* must be explained, and parents need to understand that the diagnosis of epilepsy does not mean that their child is intellectually disabled or has a psychiatric disorder. Guidelines should be given on what to do when a child has a seizure, including positioning on the side and putting nothing in the mouth. Witnessing a seizure can be frightening. Parents may be afraid that the child is going to die and should be told that death from a seizure is rare. Helpful pamphlets are available from the Epilepsy Foundation of America, and some parents appreciate the information available in several books for families of children with epilepsy. The Web sites for the Epilepsy Foundation of America ([www.epilepsyfoundation.org](http://www.epilepsyfoundation.org)) and the American Epilepsy Society ([www.aesnet.org](http://www.aesnet.org)) are also helpful sources of information. Many larger communities have local chapters of the American Epilepsy Society or independent epilepsy associations that provide education and support for individuals and families.

Activities of children with seizures should be restricted as little as possible. A child with a seizure disorder should not swim alone or go bike riding without a helmet. However, these rules apply to all children, whether or not they have epilepsy. Children with epilepsy should take showers rather than baths as soon as they are old enough and should not be allowed to bathe unattended. Contact sports are permissible when epilepsy is controlled. The decision about climbing up to certain heights should be based on how well the child's seizures are controlled. Parents need encouragement to treat the child normally and not be overprotective.

### **Discontinuation of Antiepileptic Therapy**

After seizures are controlled for a period of 2 years, consideration should be given to discontinuing antiepileptic medications. Studies show that approximately 75% of children who were seizure free for longer than 2 years remained seizure free after antiepileptic medications were discontinued. The EEG can be helpful when considering discontinuing antiepileptic medications. In children who have idiopathic epilepsy and a normal EEG, the prognosis for remaining seizure free after discontinuing medications is good, except in juvenile myoclonic epilepsy (discussed earlier). However, if the EEG demonstrates slowing, the risk for seizure recurrence is higher. The risk for recurrence is not increased if medication is tapered over a period as short as 6 weeks versus a longer taper. Long-term follow-up of children after withdrawal of medication has shown that 50% of the recurrences occur within 6 months and 60% to 80% within 2 years.



### Intractable Seizures

When seizures continue despite anticonvulsant therapy, 3 possibilities should be considered before deciding that the child's seizures are intractable to anticonvulsant therapy.

1. Seizures may be occurring at times when the child has lower blood levels of medication because of incomplete compliance or because dosing intervals are too long.
2. The medication may not be appropriate for the child's type of seizures. Primary generalized seizures will often not respond and may even worsen if treated with medications that are indicated for focal seizures (eg, carbamazepine, phenytoin). Any medication may worsen seizures in some individuals, sometimes because of associated drowsiness, but, in many instances, the reason is not understood.
3. The child's repeated events may represent 1 of the non-epileptiform paroxysmal disorders rather than an electrical seizure. Pseudoseizures can be especially difficult to differentiate from seizures because they tend to occur in persons who have epilepsy.

If a child is having epileptic seizures and the seizures continue despite appropriate amounts of the correct medications, then the child has intractable seizures. Approximately 15% of children who have epilepsy have intractable seizures, and approximately 50% of these children may be appropriate candidates for epilepsy surgery. Therefore, children who have intractable seizures should be referred to a center that has a multidisciplinary team of professionals, including epileptologists, specialized neurosurgeons, neurophysiologists, neuropsychologists, neuroradiologists, psychologists, and family therapists. These professionals as a team can best determine the location of the epileptic zone within the child's brain and the potential morbidity from loss of function in that area or adjacent tissue, can perform the surgery, and can treat the secondary effects of the surgery on the child and the family. Although epilepsy surgery can be performed at any age, it is best performed soon after intractability of seizures is established. If a long period of recurrent intractable seizures can be avoided, some of the secondary physiologic and psychosocial effects of growing up with epilepsy may be prevented, and children are more likely to live up to their potential in adult life.

Epilepsy surgery consists either of resecting the epileptic focus, such as a temporal lobectomy, a cortical resection, or a hemispherectomy, or of disconnecting the pathways that may facilitate the spread of epileptic activity within the brain, such as a corpus callosotomy and multiple subpial transections.

The outcome from temporal lobectomies in appropriately chosen children is as good as in adults—65% or more become seizure free, and another 15% are significantly improved; morbidity is minimal. Hemispherectomies in children who have a congenital hemiparesis and resistant seizures originating in the damaged hemisphere result in control of seizures in 75% of cases and often improved function because the normal, opposite hemisphere is no longer being

interrupted by spreading seizure discharges. A few cases of intractable infantile spasms associated with focal brain disturbances may also benefit from lesionectomies or partial or complete hemispherectomies. Corpus callosotomy is a palliative procedure for individuals who do not qualify for a local resection. It can be effective in controlling drop attacks and the resultant injuries in children who have multiple seizure types. Results are best in higher-functioning individuals who have localized CNS dysfunction as opposed to diffuse CNS dysfunction. Multiple subpial transections may be done for children whose epilepsy arises from essential parts of the cortex, which cannot be removed without significant morbidity.

### WHEN TO REFER

- Type of seizure is unclear.
- The need to treat, the choice of medication, or the dose of medication is unclear.
- Seizures are refractory to medication.
- Infantile spasms are suspected—a reason for an urgent consult.

### WHEN TO ADMIT

- Seizures are acutely uncontrolled or prolonged.
- Video EEG monitoring is needed.
- Rapid changes in anticonvulsant doses are needed, resulting in a risk for marked increase in seizures.
- Ketogenic diet is initiated.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Build Your Child's Own Epilepsy Care Notebook* (Web page), Epilepsy Foundation of Florida ([www.efof.org/index.php/family-resources](http://www.efof.org/index.php/family-resources))
- *Epilepsy in Children: Diagnosis & Treatment* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/head-neck-nervous-system/Pages/Epilepsy-in-Children-Diagnosis-Treatment.aspx](http://www.healthychildren.org/English/health-issues/conditions/head-neck-nervous-system/Pages/Epilepsy-in-Children-Diagnosis-Treatment.aspx))
- *Epilepsy in Children: Diagnosis & Treatment (Spanish)* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/Spanish/health-issues/conditions/head-neck-nervous-system/Paginas/Epilepsy-in-Children-Diagnosis-Treatment.aspx](http://www.healthychildren.org/Spanish/health-issues/conditions/head-neck-nervous-system/Paginas/Epilepsy-in-Children-Diagnosis-Treatment.aspx))
- *Febrile Seizures* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/head-neck-nervous-system/Pages/Febrile-Seizures.aspx](http://www.healthychildren.org/English/health-issues/conditions/head-neck-nervous-system/Pages/Febrile-Seizures.aspx))
- *How to Support a Child With Epilepsy: Information for Parents* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/head-neck-nervous-system/Pages/How-to-Support-Child-with-Epilepsy-Information-for-Parents.aspx](http://www.healthychildren.org/English/health-issues/conditions/head-neck-nervous-system/Pages/How-to-Support-Child-with-Epilepsy-Information-for-Parents.aspx))
- *Seizures and Epilepsy in Children* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/head-neck-nervous-system/Pages/Seizures-Convulsions-and-Epilepsy.aspx](http://www.healthychildren.org/English/health-issues/conditions/head-neck-nervous-system/Pages/Seizures-Convulsions-and-Epilepsy.aspx))



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**Chapter 328****SEPTIC ARTHRITIS**

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**DEFINITION OF TERMS**

Pyogenic, or septic, arthritis refers to a bacterial infection of the joint space. Other forms of arthritis include reactive or postinfectious arthritis (an immunologically induced inflammatory response to a distant infection) and the arthritis associated with rheumatologic disorders (eg, juvenile idiopathic arthritis [JIA]). These latter forms of arthritis are aseptically in that no pathogens are found in the joint space or fluid. Pyogenic arthritis most commonly affects young children and infants, but it can occur at any age. Pyogenic arthritis constitutes a clinical emergency because complications of untreated infection include dissolution of

articular cartilage, necrosis of the underlying epiphysis, destruction of the adjacent growth plate, and dislocation of the joint itself. Complications can be minimized by prompt diagnosis and appropriate treatment. A high index of suspicion is necessary to avoid missing a case of septic arthritis.

**PATHOPHYSIOLOGY**

Hematogenous seeding of the synovial membrane is the most common cause of bacterial arthritis in children. Infection also can occur by contiguous spread from an adjoining osteomyelitis or by direct inoculation of bacteria into the joint after a either penetrating wound, intra-articular injection, or joint surgery. (For a more complete discussion, see Chapter 304, Osteomyelitis.) The spread of bacteria from a bone infection into a joint occurs most often in infancy. Transphyseal blood vessels in the very young child allow early spread of bacteria from the metaphysis of the bone across the growth plate to the epiphysis and into the joint cavity. In infants, therefore, infections that begin in the bone often spread quickly into the joint and often manifest as joint symptoms. This manifestation must be considered when evaluating a young child with localized pain, especially involving the femur or hip.

The organism most commonly responsible for septic arthritis across all age groups is *Staphylococcus aureus*. In neonates, Gram-negative organisms, coagulase-negative staphylococci, and *Streptococcus agalactiae* (group B) also cause pyogenic arthritis. In older infants and young children, *Haemophilus influenzae* type b was once a common pathogen, but vaccination against this organism has made it extremely rare as a cause of bacterial infection in children. After *S aureus*, group A *Streptococcus* is the next most common cause of septic arthritis in children older than 5 years. In children younger than 5 years, *Kingella kingae* is an unusual cause of septic arthritis that requires special attention for successful culture. First described in Israel, this organism has been identified with increasing frequency in the United States. Monoarticular gonococcal arthritis can occur after genital infection with *Neisseria gonorrhoeae*. In a sexually active teenager who has monoarticular arthritis of a large joint, evaluation should include gonococcus as a possible cause. Evaluation for genital gonococcal infection and other sexually transmitted infections should be part of the initial evaluation. The organism can be isolated from the joint and genital sites but requires attention to culture technique and prompt plating in the microbiology laboratory on media appropriate for its growth. This infection can follow, and is distinct from, the reactive arthritis involving multiple joints of disseminated gonococcal disease. Gonococcal septic arthritis is a result of hematogenous seeding of the joint and can follow the bacteremia of untreated disseminated gonococcal disease. The bacteremic illness associated with *N gonorrhoeae* causes a reactive (sterile or aseptic) arthritis involving multiple joints and a vesicular rash. Similar to *N gonorrhoeae*, *N meningitidis* also can cause a reactive arthritis. Multiple joints are involved; but unlike with gonococcus, this arthritis occurs after recovery from the acute infection, following treatment of meningitis or meningococcemia with antimicrobial

therapy. This reactive arthritis resolves spontaneously over time and requires only symptomatic therapy.

The consequences of bacterial arthritis can be severe. In addition to the direct destructive effects of the infection, the host's inflammatory response can add to the damage. By raising intra-articular pressure, intra-capsular infection can obstruct blood flow, leading to necrosis of the epiphysis and the underlying growth plate. Finally, an untreated joint infection can result in joint instability through destruction of the ligamentous fibers of the capsule. These factors are of special concern for the hip joint in children.

Considering the possible consequences and, particularly in the young child, the potential for permanent deformity and disability, the need for accurate diagnosis and expeditious treatment of septic arthritis cannot be overstressed.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of pyogenic arthritis includes the other forms of arthritis, reactive and rheumatologic or inflammatory, and, on occasion, leukemia. Reactive and inflammatory arthritis often involve multiple joints, whereas pyogenic arthritis almost always involves a single joint. Transient synovitis, which most often affects the hip in young children, is often preceded by a recent history of upper respiratory infection, pharyngitis, otitis media, or gastroenteritis. Fever is rare in these cases. Legg-Calvé-Perthes disease must be considered when hip pain is involved. Although children with infective arthritis are often very ill from an associated bacteremia, rheumatologic disease is usually more subacute or chronic. A reactive arthritis often follows a prior obvious infection, such as the polyarthritis that can follow meningococcal infections; this history helps guide the diagnosis. The pattern of inflammatory arthritis is sometimes helpful in making the diagnosis, as in the case of the occurrence of multiple and alternating joint involvement in arthritis associated with rheumatic fever. JIA is a diagnosis of exclusion, and can be confused with septic arthritis. When children with JIA have high fever and a single joint is involved, the diagnosis can be more confusing. In many instances, the diagnosis is made only with time when fevers persist, other joints become involved, or the single joint fails to have a pathogen isolated and fails to respond to therapy for a pyogenic infection. The diagnosis of JIA can remain unclear for weeks to months until the course clarifies the chronicity of the disease (see Chapter 324, Rheumatologic Diseases). At times, both JIA and a bacterial infection of the bones and joints can be confused with leukemia. Children with leukemia may present with bone pain, with or without fever. The bone pain of leukemia can cause a limp or other non-specific signs and can be confused with a septic joint, osteomyelitis, or JIA. Examining the bone marrow is often required to confirm the diagnosis. The laboratory tests that support a diagnosis of pyogenic arthritis can help point the evaluation in the proper direction. A child with leukemia may have anemia, low white blood cell count (see Chapter 285, Leukemias), or low platelet count. If not present at first, these signs will occur over time.

Some bacterial pathogens that cause arthritis are more difficult to identify, such as *Mycobacterium tuberculosis* or *Borrelia burgdorferi*. A history of exposure to tuberculosis or the occurrence of infection in the summer in an endemic area for Lyme disease will help direct the evaluation (see Chapter 287, Lyme Disease). These pathogens are identified by special testing, which may be prompted by abnormalities in the fluid aspirates. In both these conditions, the fluid does not grow a common pathogen on routine cultures in spite of fluid analysis that is suggestive of bacterial infection. For example, evaluation of a child for possible tuberculosis includes culturing the joint fluid for *Mycobacterium* on special media, placing a tuberculin skin test, and ordering a chest radiograph to look for signs of primary infection. The child with possible Lyme disease will often have a history of the rash of erythema migrans; serologic testing can help confirm the diagnosis. Knowing the frequency of these unusual pathogens in the pediatrician's area of practice is crucial in guiding the evaluation of a child with presumed bacterial arthritis.

Referred pain from an adjacent joint that is infected can also complicate presentation. At times, septic arthritis causing decreased movement at a joint can be confused with an isolated neuropathy. Additionally, septic arthritis of the shoulder can cause a brachial plexus neuropathy, and septic arthritis of the hip can cause neuropathies of the femoral and sciatic nerves. These diagnoses, occurring without infection, should not be associated with pain or fever.

## EVALUATION

### Clinical History

Signs of acute illness most often accompany the onset of septic arthritis. The onset of fever, malaise, poor appetite, irritability, and localized symptoms and signs is usually acute. In septic arthritis, as in osteomyelitis, the neonate presents a unique challenge because systemic signs may be less apparent. However, localized signs are usually prominent, particularly pain with motion of the involved joint. The failure of a child to move an infected joint should suggest this diagnosis. When septic arthritis is present, passive movement of the affected extremity almost invariably elicits severe pain. Limp may also be a presenting complaint.

### Physical Findings

Swelling, erythema, tenderness, and redness of the skin over the joint are usually present, but are difficult to detect in a deep joint such as the hip. The most characteristic finding is pain with joint motion. When a lower extremity joint is involved, the child usually refuses to bear weight or limps. Manipulation of the hip joint, such as with diaper changes, causes significant pain. This pain is often the first sign to a parent or nurse caring for the child that a problem exists. Limited range of motion of an infected upper extremity joint may result in concerns about a neurologic problem, a *pseudoparalysis*. Although older children and teenagers are usually able to localize pain, the physician should remember that pain can be referred to an unaffected joint. Joints of the lower extremities are the

most common sites of septic arthritis, with the knee the most affected joint. Rarely, and usually with prolonged bacteremia, more than 1 joint can become infected.

Some characteristic signs help suggest the diagnosis. To decrease pain, the child will usually hold an infected joint very still. The joint is held immobile by muscle spasm in a position that maximizes capsular volume, thus minimizing the intra-articular pressure. For the hip, the preferred position is a combination of moderate flexion, abduction, and external rotation; for the knee, gentle flexion; and for the shoulder, adduction against the trunk. For a child to seem entirely well and in no distress is not unusual, so long as the affected joint is allowed to remain undisturbed. If a child holds a joint still and has a fever, then the diagnosis of septic arthritis is assumed.

### Laboratory Testing

Laboratory results can be helpful in supporting the diagnosis of septic arthritis. The erythrocyte sedimentation rate is typically elevated, though it may be normal early in the course of infection. The C-reactive protein is also increased, and it is a more sensitive test during the initial illness because it rises earlier than the sedimentation rate. Both the sedimentation rate and C-reactive protein are useful in following the patient's response to treatment following diagnosis. Blood cultures should always be obtained because most pyogenic arthritis cases in children are of hematogenous origin. Blood cultures are positive in at least 40% of children with septic arthritis. Other testing may include titres for Lyme, *Streptococcus*, and other pathogens. In some cases, a TB test by serum interferon may be appropriate, such as in the older child in whom tuberculosis is being considered as a cause. Procalcitonin has been studied as a specific marker in differentiating acute osteomyelitis and septic arthritis from viral and noninfectious inflammatory bone and joint conditions and may be a useful test in the future.

Joint fluid in pyogenic arthritis is generally cloudy or purulent, with a leukocyte count of more than 50,000 cells/mcL, and has a predominance of polymorphonuclear cells. Although the fluid of JIA can also contain many neutrophils, levels are generally lower than with bacterial infection. Fluid should be sent quickly to the microbiology laboratory for Gram stain and culture. If this is not possible, then inoculating a blood culture bottle is acceptable, but this process may delay identification of pathogens. Though the culture is sometimes negative in cases that seem to be acute bacterial arthritis, the combination of clinical data and fluid characteristics help confirm the diagnosis. Positive joint fluid cultures are encountered in approximately 50% to 60% of cases caused by bacterial infection. A joint effusion with a low white blood cell count and normal glucose suggests that the arthritis may be caused by a sympathetic effusion from an adjacent osteomyelitis, or possibly an aseptic arthritis caused by a reactive arthritis or JIA or other rheumatologic diseases.

### Imaging

Early in the course of septic arthritis, bone changes are unlikely, but soft tissue changes may occur, including swelling and edematous infiltration into fatty tissue

planes. Plain films, however, should be obtained to evaluate for fracture or osteomyelitis if the infection has been present for more than 1 week. Ultrasonography has proved useful in detecting the capsular distention that accompanies septic arthritis of the hip. An experienced radiologist can define the presence of a joint effusion by ultrasound of the joint and, if a joint effusion is present, can assist the operator in accurate needle placement during diagnostic aspiration. Magnetic resonance imaging is sensitive and may be helpful in defining adjacent bony involvement and soft-tissue abscesses, especially in areas of complex anatomy such as the hip, sacroiliac joint, or pelvic bones. However, in clear cases of infection, therapy should not be delayed by waiting for this study to confirm a clinical diagnosis.

### MANAGEMENT

Joint aspiration with a large-bore needle is an important diagnostic maneuver, and an orthopedic surgeon or interventional radiologist skilled in the care of pediatric patients should be consulted to aspirate joints. Fluoroscopy or, possibly, ultrasonography, may be used to confirm entrance into the relatively inaccessible hip and shoulder joints. Failure to obtain pus from a joint that seems clinically to be infected can be caused by the thickness of pus in the joint, and open drainage of the joint may be necessary to confirm the diagnosis and to treat the infection.

Empiric therapy with antimicrobial agents that are appropriate for the likely pathogen should be started urgently after aspiration of the joint. Most infections are caused by *S aureus*; thus, an effective antistaphylococcal antimicrobial is almost always part of the initial treatment. A penicillinase-resistant penicillin, such as nafcillin or oxacillin, or a first-generation cephalosporin is often sufficient, though clindamycin or vancomycin should be considered given the incidence of methicillin-resistant *S aureus* (MRSA) in community-associated infection. In the child who is severely ill or has signs of bacteremia and sepsis, vancomycin should be considered as initial therapy instead of or in addition to a  $\beta$ -lactam.

A first-generation cephalosporin should not be used in a neonate as empiric therapy because of poor cerebrospinal fluid penetration and the concern for a bacteremia seeding the central nervous system. A safer approach would be to start empiric therapy with high doses of a penicillin that is effective for treating *S aureus*, such as oxacillin, combined with an antibiotic to treat gram-negative enterics, such as ceftazidime, cefepime, or an aminoglycoside. Once a pathogen is identified, therapy should be narrowed to treat the specific organism.

Broad coverage is also appropriate for the child who is immunocompromised and the adolescent thought to be abusing an intravenous drug as the cause of a bacteremia. Antibiotics selected empirically for such patients should be effective against *S aureus*, enteric Gram-negative bacilli, and *Pseudomonas*. A broad-spectrum penicillin such as ceftazidime or cefepime and an aminoglycoside with vancomycin might be empiric therapy in these children, pending final joint and blood cultures. The adolescent with possible gonococcal joint infection should be treated for staphylococci and gonococci until the diagnosis is clarified.



In this situation, cefuroxime or ceftriaxone, perhaps with vancomycin, might be selected, depending on the specifics of the case.

Parenteral antibiotic therapy is continued at least until the child is doing well and signs of acute infection have resolved. Oral therapy can be used to finish treatment. This approach is possible when an organism has been identified by blood or joint fluid culture and when an effective oral agent is available. Oral antibiotics can be used only if the child's social situation guarantees reliably that the antibiotics will be given as directed and the antibiotic does not cause a gastrointestinal disturbance that might interfere with absorption or adherence. The organism must be susceptible to the oral antibiotic, and the antibiotic must achieve therapeutic levels in bone and joint. Laboratory tests such as the sedimentation rate and C-reactive protein should be normalizing before switching to an oral agent. Antibiotic therapy should continue for a minimum of 3 to 4 weeks, but treatment should not be discontinued until the clinical response is complete and the markers of inflammation, such as the C-reactive protein level and erythrocyte sedimentation rate, have returned to normal. Treatment will be longer if concurrent osteomyelitis is present, and lengthening therapy is sometimes advisable if most of the course of therapy is oral.

A surgical referral is required because of the necessity to aspirate the joint and, at times, for diagnosis, surgery, and treating the infection. All children with septic arthritis of the hip should be seen emergently by an orthopedic surgeon, because these patients require immediate drainage of the joint. Delay in draining a major joint, such as the hip joint, is associated with poor outcome. Open debridement may be required. Other infected joints less often require open debridement but should also be evaluated for surgical treatment. Repeated aspirations of a joint may be necessary if fluid reaccumulates.

Septic arthritis is an emergent situation and requires consultation among the primary physician, orthopedic surgeon, and radiologist. Treatment is often coordinated by an infectious diseases specialist to aid in selecting an appropriate antibiotic, to monitor response, and to organize and coordinate follow-up after hospital discharge, which may include outpatient home intravenous therapy.

### WHEN TO REFER

Children who are being evaluated for bone or joint infection should be evaluated by an orthopedic surgeon or infectious diseases specialist.

### WHEN TO ADMIT

All children thought to have bacterial infection of a major joint should be hospitalized.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *A to Z: Septic Arthritis* (Web page), KidsHealth From Nemours ([kidshealth.org/parent/dictionary/s/az-septic-arthritis.html](http://kidshealth.org/parent/dictionary/s/az-septic-arthritis.html))

- *Joint Aspiration (Arthrocentesis)* (Web page), KidsHealth From Nemours ([kidshealth.org/parent/system/medical/arthrocentesis.html](http://kidshealth.org/parent/system/medical/arthrocentesis.html))
- *Septic (Infectious) Arthritis* (Web page), Stanford Children's Health, Lucile Packard Children's Hospital ([www.stanfordchildrens.org/en/topic/default?id=septic-infectious-arthritis-90-P01730](http://www.stanfordchildrens.org/en/topic/default?id=septic-infectious-arthritis-90-P01730))

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## Chapter 329

# SEXUAL ABUSE OF CHILDREN

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Although sexual abuse of children has existed for centuries, only in the past 30 years have physicians come to recognize the scope of the problem, including its epidemiologic factors, clinical characteristics, approaches to management, and consequences to children and families.

## DEFINITION AND EPIDEMIOLOGIC FACTORS

Sexual abuse is defined as the involvement of children or adolescents in sexual activities that they do not fully understand, to which they cannot give informed consent, and that violate the social taboos of families or society. This type of abuse includes activities such as the sexual touching of a child's genitals by an adult or adolescent, sexual intercourse between an adult and child, the exposing of children to pornography, or involvement of children in prostitution. Sexual abuse should be distinguished from sexual play or exploration by preschool-aged or young school-aged children or sexual activities between consenting adolescents.

Child protection laws that were passed in the 1960s in each state initially required that cases of suspected physical abuse or neglect be reported, but shortly after were broadened to include children suspected of being sexually abused. Since 1976, national statistics of cases reported to each state's child protection agency have been compiled. The most dramatic increase in reports occurred in the 1980s as a result of increased publicity and increased recognition by



parents and physicians. In the 1990s, substantiated reports of sexual abuse peaked at more than 150,000 cases per year (representing approximately 13% of almost 1.2 million substantiated cases of child maltreatment). Since then, the number has decreased to a total of 61,000 substantiated reports of sexual abuse in 2013, the latest year for which complete data were compiled. These reports represent 9% of all substantiated reports of child maltreatment that year.

In 2013, of all reports made to protective services, approximately 20% were substantiated after investigation. The failure to substantiate an allegation does not necessarily mean that the abuse did not occur, but rather indicates that protective services did not have enough evidence to confirm the allegation.

Approximately 75% of children evaluated for suspected sexual abuse are girls. The age range is from 6 months to 18 years, with a median age of approximately 8 years.

Although such cases represent those reported to child protective services, an alternative approach to estimating the prevalence of the problem has been to interview adults about their childhood experiences of sexual abuse. These studies provide information about lifetime prevalence. A review of 19 studies conducted on community samples in the United States or Canada in the 1980s and early 1990s found that the rates of sexual abuse reported by women were 2% to 62% and by men were 3% to 16%. Finkelhor suggested that a summary statistic for women of 20% would be reasonable. Because only 9 of the studies in Finkelhor's review surveyed men, less certainty existed about a summary statistic for men, but a conservative estimate would be 5% to 10%. A 2009 study that aimed to update Finkelhor's previous work as well as add data from international studies found that these prevalence estimates remain consistent. The prevalence of sexual abuse reported by adults in different studies varies because of the population studied, the response rate, the number and types of questions asked, the definition of sexual abuse, the age used to define childhood, the accuracy of the adults' memories, and the adults' willingness to report past events.

Unlike cases of physical abuse or neglect, which are reported much more commonly in families who are poor and have limited education, cases of sexual abuse occur in families from all social classes and educational backgrounds. Perpetrators of sexual abuse are almost all boys and men, and nearly one-third of them are adolescents. Most children who are sexually abused know the perpetrator, who may be the father, stepfather, another male relative, a family friend, or an adult in the child's community. Since the 1980s, allegations of sexual abuse of children by clergy members in the Catholic church have been made in countries throughout the world, and these have done much to raise awareness about the problem of child sexual abuse. Although female perpetrators are unusual in most clinical series, these rates may be falsely low because of underrecognition. A small number of sexually abused children do not know the perpetrator; these victims are usually older children or adolescents who are victims of forceful sexual assault or rape.

## ETIOLOGY

Although physicians are able to understand how a parent might lose control and physically abuse a child, understanding how an adult can move from close bodily contact and even sensual feelings toward sexually abusing a child is much more difficult. Two prerequisites for sexual abuse to occur include the offender's sexual arousal to children and the willingness to act on this arousal. Studies have attempted to examine adults' sexual attraction to children. For example, 21% of male college students in an anonymous questionnaire indicated that they felt sexual attraction toward children. Some offenders may focus their attention on children of a certain age or gender; others may find themselves aroused only by children in certain circumstances. Factors that influence the offender's willingness to act on the aroused feelings toward the child include a lack of conscience about such behaviors, a lack of empathy for the child, a belief that such sexual behaviors are acceptable and not harmful to the child, poor impulse control, and the use of drugs or alcohol that might further decrease the ability to control behavior. Additional contributors to the likelihood that sexual abuse may occur include the history of the perpetrator (eg, having experienced sexual abuse during childhood), circumstances that allow the perpetrator to have increased contact with the child (eg, a mother hospitalized for a lengthy period), and the particular vulnerabilities of the child (eg, intellectual disability).

Children who are sexually abused are often selected because they seem particularly vulnerable or needy. Such children may initially enjoy and appreciate the attention that they receive from the offender, who may begin by giving the child gifts, attention, and special hugs and touches. These behaviors may progress to special secrets and eventually from nonsexual to sexual activities that lead to sexual intercourse. This process is labeled the child sexual abuse accommodation syndrome, which describes 5 stages that occur in the sexual abuse of children: (1) secrecy; (2) helplessness; (3) entrapment and accommodation; (4) delayed, unconvincing disclosures; and (5) later retraction of the alleged abuse.

## CLINICAL MANIFESTATIONS

Similar to other forms of family violence, sexual abuse of children often occurs in the privacy of a home or in a setting that involves only the abused and the abuser and is seldom witnessed by another person. A child who was sexually abused may have experienced other forms of maltreatment, including physical abuse or neglect, and certainly emotional abuse as well.

A physician's concerns about the possibility of sexual abuse occur because of reports of specific statements made by the child, usually to a parent or other adult, about uncomfortable experiences such as being touched on the genitalia, reports of specific behaviors of the child such as sexualized behaviors with a sibling, symptoms such as encopresis or vaginal discharge or bleeding, or a genital or anal injury noted on physical examination.

Clear statements by the child (or occasionally accidental direct observations of the sexual abuse) are the

best indicators that sexual abuse occurred. Young children are most likely to tell a parent or other close adult caregiver about abuse, but they may lack the necessary vocabulary to describe what happened to them. They may use words that the perpetrator used to encourage their participation (eg, "We played the hugging game") or words that describe their experience of what happened or how it felt but are confusing to the adults (eg, "He stuck a knife in my pee-pee"). Older children are as likely to tell a peer about abuse as they are to tell a parent and may begin by offering a guarded, vague disclosure (eg, "My uncle kisses too hard"). If an adult is told and reacts in a concerned manner with appropriate exploratory questions, then more details may follow. The older child may be embarrassed about what happened, feel partially responsible, experienced pleasurable feelings, or be concerned about the threats that the perpetrator made (eg, "If you tell your mother, I will punch you" or "If you tell, you know they will think you are a liar"). Even after a clear disclosure, once children realize how upsetting the information is to the family, they may retract the statement. Older children also may feel responsible for holding the family together: If the child tells, then the father will go to jail, the house will be sold, and everyone will be angry at the child; on the other hand, if nothing is said, then the sexual abuse will continue, but at least the family will be saved. Some children consciously or unconsciously sacrifice themselves for their family.

Children who were sexually abused may demonstrate a variety of symptoms and behaviors. Some may be relatively asymptomatic and able to function reasonably well in social settings and in school. Many children exhibit nonspecific symptoms such as sleep problems, generalized anxiety, suicidal gestures, or poor school performance, which are seen in response to other childhood stresses as well. A 2008 study of sexually abused girls found high rates of reported genital soreness and dysuria in those who disclosed genital-to-genital contact. Sexualized behaviors, such as excessive masturbation, the use of adult words associated with sexuality, or simulation of sexual intercourse with another child, animal, or doll, are more suggestive of sexual abuse. Other concerning symptoms include vaginal pain, bleeding, discharge, or rectal bleeding. However, even a symptom such as vaginal discharge has a low likelihood of being caused by sexual abuse. Several studies of premenarchal girls who complained of vaginal discharge show that the occurrence of sexual abuse is uncommon (<5%–10% of girls who have this complaint) and that the most common cause is poor hygiene.

Only a small percentage of sexually abused children will have an abnormal genital or anal finding. For example, a study of 2,384 children referred for possible sexual abuse to a tertiary referral center found that only 4% of them had an abnormal examination at the time of evaluation. Acute findings such as genital or anal abrasions may be more likely seen in the emergency department setting. However, the absence of physical findings does not rule out sexual abuse because no injury may have occurred to the genital area, or if an injury did occur, it may have healed without

leaving any physical signs. Even in cases in which the perpetrator is convicted of sexual abuse, having an abnormal examination is unusual for the victim. For example, in a series of 236 child abuse cases in which the perpetrators were convicted, only 23% of the victims' genital examinations were considered suspicious or abnormal in girls, and only 7% of anal examinations were considered so in boys and girls. Even in pregnant adolescents who are examined for suspected sexual abuse, physical findings indicating sexual abuse are unusual. In a case review of 36 pregnant adolescents evaluated for sexual abuse, only 2 of the 36 girls had definitive findings of penetration. The authors of this study suggest 2 possible explanations for this finding: Penetration does not result in visible tissue damage, or acute injuries occur with penetration but heal completely. These studies highlight both the limited role of physical findings in the investigations of sexual abuse and the crucial role of the child's history of the abuse.

During the past several years, research has defined normal and abnormal genital and anal anatomic features in prepubertal children and adolescents. Several studies have described the variations in the anatomic features of the hymen in female newborns and have concluded that the hymen is present in all normally developed newborns. The appearance of the hymen is often thickened early in life because of the effects of maternal estrogen in utero; in preschool-aged and school-aged girls, the hymenal tissue becomes thinner until the effects of estrogen during puberty result in a thickening of the tissue and the development of redundant folds. Studies of normal prepubertal girls have described the shapes of the hymen as crescentic, annular, and fimbriated (or redundant) and have noted the frequency of normal variations, including hymenal mounds, intravaginal ridges, and adhesions of the labia minora. These studies have provided data on the means and ranges of the vertical and horizontal diameters of the hymenal orifice in different age groups, the variations in diameter depending on how the genital examination is performed (eg, separation versus traction of the labia majora), and the width of the posterior hymenal rim.

Children who are sexually abused may have acute injuries of the genitalia, including acute lacerations, abrasions, or hematomas. However, most children who are sexually abused do not disclose until weeks or months after the occurrence of the abuse. In such children, findings that are considered suspicious or suggestive of past abuse include U- or V-shaped clefts (or notches) of the posterior rim (from 3 o'clock to 9 o'clock) of the hymen, which occur in the healing process after an acute laceration, and attenuation or decreased width of the hymenal tissue posteriorly (<1 mm). These findings should persist when the child is examined in the prone, knee-chest position. A study of 192 prepubertal girls between the ages of 3 and 8 years who had a history of penetrating sexual abuse and 200 who denied prior abuse detected few differences in anatomic findings between the abused and nonabused samples. A few specific hymenal findings were evident, however, that were noted in 4 girls in the abused group and not in the comparison group.

These were hymenal deep notches, perforations, or transections, and each was noted in a girl who disclosed penetration. Scarring, such as of the posterior fourchette, is also indicative of previous trauma. Although, in the past, investigators considered an enlarged horizontal diameter of the hymen of greater than 4 mm to be suspicious of previous sexual abuse in prepubertal children, studies of normal children indicate that this demarcation is incorrect and that the size of the opening varies with the child's age and different examination techniques, as well as with the child's state of relaxation. A horizontal diameter of greater than 10 mm may concern a physician about the possibility of sexual abuse but should not be used by itself to make a diagnosis.

Data about normal physical findings in adolescence are limited; 1 study compared 3 groups of female adolescents: (1) those who denied sexual intercourse and used only pads for menses, (2) those who denied sexual intercourse and used tampons, and (3) those who experienced sexual intercourse. Although significant differences were found in the median horizontal diameters of the hymenal orifice in the 3 groups (1.2, 1.5, and 2.5 cm, respectively), overlap certainly existed among the groups. In addition, a striking difference among the groups was that of the sexually active teenagers: 81% had a complete cleft (or V-shaped notch) between the 2-o'clock and 10-o'clock positions on the hymenal border compared with 11% in tampon users and 5% in pad users.

A 2004 study of 85 girls between the ages of 13 and 19 years improved on these data by using a colposcope for magnification and photographic documentation of hymenal morphologic features. In this study, posterior hymenal notches and clefts were more common in girls admitting past intercourse (48%) than in girls who denied intercourse (3%). The 3% of girls who denied intercourse and had posterior hymenal clefts described a painful first experience with tampon insertion. Of note, the mean width of the posterior hymenal tissue was not significantly different between girls who admitted and those who denied past intercourse.

Abnormalities of the male genitalia caused by sexual abuse are unusual. However, acute abrasions, lacerations, or bruises caused by physical abuse can be seen.

Acute anal findings, such as lacerations resulting from anal penetration or injury, have been noted in sexually abused children, but few systematic studies of perianal findings in chronically abused children have been conducted. Worrisome findings include thickening of the rugae, distorted anatomy secondary to scarring, and dilation greater than 2.0 cm (when the child is in the prone, knee-chest position and no stool is visible in the rectal ampulla). In a study of children with documented anal injuries followed from acute injury to healing, 29 of the 31 children healed completely, with scar formation only in the 2 cases requiring acute surgical repair. A study of normal prepubertal children highlighted common normal findings that were noted when the child was examined in the prone, knee-chest position; these included skin tags in the midline, fan-shaped areas in the midline superiorly,

perianal erythema, venous congestion, and anal dilation up to 2.0 cm.

Children who are sexually abused may acquire a sexually transmitted infection (STI). Controversy continues about how children acquire such diseases, in part, because of the social and legal implications and because of the difficulty in believing that a young child's infection is from sexual contact. Approximately 5% of sexually abused children acquire an STI from the perpetrator of the abuse. According to a 2005 clinical report published by the American Academy of Pediatrics, the presence of *Neisseria gonorrhoeae*, syphilis, or *Chlamydia trachomatis* is diagnostic of sexual abuse in prepubertal children in whom perinatal transmission and rare, nonsexual vertical transmission are excluded. The presence of human immunodeficiency virus (HIV) infection in prepubertal children is diagnostic of sexual abuse in those in whom perinatal and transfusion-related acquisition are excluded.

Human papillomavirus (HPV) presents a special case in the evaluation for possible sexual abuse. Condylomata noted in 12- to 24-month-old infants were previously thought to be the result of perinatal transmission. Recent work determined that vertical transmission is either not a common source of HPV infection or not a source of infection at all. Recent epidemiologic data suggest that many preadolescent children acquire HPV from nonsexual horizontal transmission, either by autoinoculation if a child has common skin warts or horizontally from nonabusive contact by a person who has common warts, and that the likelihood of sexual abuse as a possible cause increases with age. History and full medical evaluation are of particular importance in ascertaining the possibility of sexual abuse in a child with HPV.

Pubertal female victims are at risk of pregnancy from sexual abuse. Adolescents who become pregnant from sexual abuse often try to hide the pregnancy and can be extremely reluctant to name the perpetrator. If the perpetrator is a family member, then the psychological consequences for the adolescent and nonoffending family members can be particularly complex and debilitating.

## ASSESSMENT AND DIAGNOSIS

The pediatrician may learn about suspected sexual abuse from concerns raised by parents, direct statements from the child, or abnormalities noted on physical examination or laboratory tests. When sexual abuse is suspected, an important decision point is whether the concerns or suspicions meet the requirement of mandatory reporting to the local child protective service agency. In most states, the requirement to report is based on the level of reasonable suspicion.

When initially evaluating possible sexual abuse, the pediatrician should take 5 important clinical steps. First, a careful decision about how much history to obtain directly from the child should be made. Many locales can provide timely, subspecialty-level evaluation for suspected sexual abuse. When such care is available, only a minimal history or, in some circumstances, no direct history will be necessary because



the child will be interviewed by a specially trained forensic interviewer (with representatives of the police and child protective services observing).

Second, the primary care physician should decide the extent of the physical examination to be performed and whether the collection of laboratory or forensic data is indicated. A brief external examination to rule out acute trauma can be performed with referral for emergency care only in the event that acute trauma is present. If the child has symptoms of an STI, then appropriate laboratory tests should be obtained. If the pediatrician evaluates the child within 72 hours of the last occurrence of sexual abuse, then forensic evidence may need to be collected in an emergency department setting. Parents should be advised to preserve in a paper bag any unwashed clothing or bedding with which a suspected perpetrator may have been in contact for possible forensic evaluation.

Third, careful documentation in the medical record of collected information must be performed.

Fourth, the physician should meet with nonoffending parents (and the child, if old enough) to explain that a report will be made to child protective services and that an investigation will be conducted in the community.

Fifth, and finally, follow-up with the family should be arranged so that the pediatrician can offer ongoing support during the ensuing forensic evaluation.

Many communities have children's advocacy centers (CACs), multidisciplinary teams (MDTs), or both, that provide a rational and coordinated approach to the evaluation of children who may have been sexually abused. Children's advocacy centers provide comprehensive, multidisciplinary assessments of abused children in an environment designed to be both neutral and child friendly. In addition to medical evaluations, Children's advocacy centers may house needed mental health services for children and their families. Multidisciplinary teams members can include representatives from the local police, prosecutors' office, and protective services, and experts in interviewing and examining the child. Multidisciplinary teams meetings provide an opportunity to discuss specific cases resulting in coordinated investigative and treatment efforts for each abused child and a forum for community-wide efforts in prevention and early detection of child sexual abuse. Shared goals of CACs and MDTs are minimizing secondary trauma experienced by the child and family resulting from the investigation and improving case investigations leading to more successful prosecutions.

As part of the evaluation, the subspecialty physicians should consider alternative explanations, including an unintentional injury (or *accident*), a medical problem, or a false allegation. Because evaluations for suspected sexual abuse usually include the child protection and legal systems, care should be taken to provide an unbiased assessment and one that provides documentation that can be reviewed by professionals outside the medical system.

### History

The purpose of the history is to understand what may have happened to the child. This history should

include the events that led to the evaluation, the child's health status and level of development, and the family's strengths and weaknesses. The parents (or guardians) should be asked what the child has said, how the child reacted when telling about the abuse, and whom the child told. Information should be obtained about (1) the child's behaviors, such as changes in behaviors or attitudes toward a specific person or situation, recurrent fears or nightmares, or sexualized behaviors; (2) specific symptoms, such as vaginal bleeding or discharge, dysuria, anal bleeding, constipation, and encopresis; and (3) where the child spends time and who cares for the child. Also to be determined are who the alleged perpetrator is, the relationship with the child, and the amount of time spent with the child. In preparation for interviewing the child, knowing about the child's developmental history is important, for example, whether a language delay is present.

The family history should include information about the parents' physical and mental health, including a history of sexual abuse during childhood; the health and developmental status of the siblings; the presence of family violence, substance abuse, or recent stresses; and the resources and supports available to the family. Understanding how family members view the allegations and how they have reacted is important. Because allegations that arise during a custody fight between parents are often difficult to sort out, the physician should determine whether the parents are separated or divorced, the custody arrangements, the visitation schedule, and any dispute about custody or visitation. Distinguishing whether the allegations of abuse occurred before the separation or divorce, during the process of separation and divorce, or after the divorce was finalized is helpful.

A child who is old enough to be interviewed directly should be asked about what may have happened. Pediatricians should perform minimal interviewing to obtain enough information to warrant a report to child protective authorities. Trained, forensic interviewers can then obtain a full disclosure that can be used as evidence in any legal proceedings stemming from the allegations. The development of forensic interview protocols, such as the National Institute of Child Health and Human Development Protocol for Investigative Interviews of Alleged Sex-Abuse Victims, allow for standardization of techniques, more elicited detail, and minimalization of trauma to the interviewed child. This interview or series of interviews should be conducted with the child alone, if possible. The interviewer should be comfortable and skilled at interviewing young children about the possibility of sexual abuse, use simple questions, and be aware of the child's nonverbal responses and direct statements. Leading questions, such as, "Didn't he touch your pee-pee?" should be avoided, when possible. Nonleading questions are preferable, such as, "Can you tell me what happened?" or "Where did he touch you?" In many instances, however, children are reluctant to talk because of a variety of reasons, including fear and embarrassment; in such cases, questions with forced choice responses, such as, "Was it your mother or father or teacher who did that?" or "Was his pee green or pink or white?" can be helpful.



To help young children during the interview, anatomic drawings or anatomically correct dolls have been used. Considerable controversy has occurred about the sexual nature of the dolls and whether their use suggests to children that they can talk about sex, thus leading to false allegations. However, research indicates that few nonsexually abused children respond in sexual ways with the dolls and that the dolls can be helpful to children in describing what happened. Because of the controversy involving the dolls, most interviewers prefer not to use them. Some older children who have difficulty verbalizing acts of sexual abuse may be able to draw pictures of or write out a description of what occurred.

### Physical Examination

The purposes of the physical examination are to determine the presence or lack of (1) signs of physical abuse or neglect, (2) anogenital injuries that are consistent with or suggestive of sexual abuse, and (3) conditions that need medical treatment. In addition, the examination provides an opportunity for the physician to reassure the child and family about the child's physical condition. In premenarcheal girls, the genital examination is performed best in both the supine and the prone, knee-chest positions; a speculum is seldom used. To visualize the hymen, 2 physical examination maneuvers should be used: (1) labial separation (separating and pulling posteriorly at an angle of 45 degrees) and (2) labial traction (gently pinching the labia and pulling out and toward the examiner). Evaluations conducted in specialty centers rely on the use of a colposcope during the anogenital examination to provide 5- to 30-fold magnification and documentation through photographs or videotape recordings. A study comparing examinations with and without the use of the colposcope indicated that more than 95% of physical findings can be detected without its use. A handheld magnifying lens that provides 2.5- to 3-fold magnification or an otoscope (without a speculum) can provide reasonably good magnification.

### Laboratory Tests

When the child is at risk of acquiring an STI from suspected sexual contact, appropriate tests should be obtained for gonorrhea, herpes simplex, trichomonas, bacterial vaginosis, chlamydia, syphilis, HIV, and hepatitis B and C infections. Historically, cultures for *N gonorrhoeae* and *C trachomatis* were considered the gold standard for diagnosing infection with these organisms. Many medical settings have forgone culture in favor of newer tests, such as nucleic acid amplification tests that detect the presence of the organism's DNA or RNA. A particular advantage of these tests is that they may be run on urine samples as opposed to vaginal or urethral swabs. Data regarding the use of these tests in prepubertal children are scarce, and the prevalence of these infections in children is very low. As nucleic acid amplification tests are increasingly used, their importance both clinically and legally can be expected to increase. Currently, the Centers for Disease Control and Prevention suggest the use of nucleic acid amplification tests for the detection of *N gonorrhoeae* and *C trachomatis* because of the tests'

increased sensitivity over culture. That many medical centers no longer offer culture for *C trachomatis* suggests that newer tests will take on increasing significance in the future. For a child who has a vaginal discharge, additional studies may be performed to test for trichomonal or bacterial vaginosis. Serologic samples may be analyzed for HIV, hepatitis B and C, and syphilis. Although universal screening is recommended for postpubertal children, the decision to screen for these infections in prepubertal children should be guided by the nature of the sexual contact and the signs and symptoms in the child, the presence of another STI, the risk status of the perpetrator, family wishes, and the discretion of the medical provider.

Studies have attempted to determine which children should be tested for STIs. For example, in a review of 2,731 preteens who had vaginal cultures, 84 (3.1%) had gonorrhoeae, and 80 of these had a vaginal discharge. However, no data are available to help determine which children should have cultures taken from all 3 sites: the genitals, throat, and anus. If the child has evidence of 1 STI, conducting a full range of tests for other STIs would then be reasonable.

The collection of forensic evidence is an important component of evaluating victims of sexual assault. When an adolescent is evaluated within 72 hours of an episode of suspected sexual abuse, appropriate forensic information, such as swabs to detect semen, should be collected (see Chapter 371, Rape). However, the DNA and epidemiologic factors of forensic evidence findings in prepubertal victims of sexual abuse suggest that the collection of this evidence has a low yield. A study of forensic evidence findings in 273 prepubertal children in whom abuse was suspected revealed that the likelihood of useful evidence collection 24 hours after an acute assault is extremely low. Swabbing a child's body for evidence is therefore indicated within the 24-hour period immediately after an acute sexual assault. The same study showed that clothing and linens from sexually abused children provided a significantly higher yield of forensic evidence after an acute sexual assault than samples taken directly from the child. These items should be rigorously pursued for analysis in the setting of an acute sexual assault. In pubertal girls, a pregnancy test may be necessary.

### Documentation

Documentation of the evaluation should include direct quotations, when appropriate, from the parents and the child and a clear description of the findings from the physical examination, with sketches, if necessary. In many states, the information is recorded on a specific form for suspected sexual assault. A videotape of the child's interview and videotape or photographs of the examination provide additional detailed information; these should be labeled with the date, child's name, physician's name, and child's medical record number.

### DIFFERENTIAL DIAGNOSIS

Conditions that need to be considered in the differential diagnosis depend on the child's symptoms and physical findings. Some of the physical findings that

can be seen in sexually abused children also are non-specific findings, such as erythema of the vulva or introitus. Bruises to the genital or anal area should raise concern about physical abuse, but if bruising is more widespread, then medical conditions, such as bleeding disorders, need to be considered. Straddle injuries, which can affect the genitalia, are usually witnessed, and thus the history is clear. These types of injuries are usually unilateral or anterior and produce obvious bruising and swelling of the external genitalia; affecting the hymen is unusual for such injuries because of the protection provided by the labia and bones of the pelvis.

An important dermatologic condition that may exhibit genital soreness and subependymal hemorrhages is lichen sclerosus. This condition usually affects the vulva and perianal region and produces an hourglass appearance, with areas of subependymal hemorrhage, decreased pigmentation, and tissue friability. Urethral prolapse can produce vaginal bleeding and dysuria, and the abnormalities noted on physical examination might be considered the result of trauma from sexual abuse. Another condition that may be mistaken for sexual abuse is a streptococcal infection, which can cause marked redness of the perianal region and a vaginal discharge. For children who have a foul-smelling vaginal discharge, a foreign body should be considered in the differential diagnosis.

A critical challenge for the examiner is to identify abnormalities that are caused by trauma from sexual abuse versus normal variations. Studies have shown that physicians do not always agree on their descriptions or interpretations of genital findings. For example, Paradise and colleagues used 7 simulated cases to compare the assessments of 206 US physicians who considered themselves skilled at examining sexually abused children with the assessments of a panel of experts. Not surprisingly, the most experienced physicians were more likely than the less experienced physicians to agree with the ratings of the expert panel. In a related study, the history provided in a simulated case was noted to have an influence on physicians' interpretations of findings: when the history did not suggest sexual abuse, the physicians (especially those who had little experience) were more likely to consider the examination normal. The opposite effect was found as well: when the history suggested sexual abuse, physicians were more likely to consider the same examination as abnormal.

The possibility of a false allegation also should be considered in the differential diagnosis. Although false allegations seem to be uncommon, controversy exists about the accuracy of young children's memory, under what circumstances they can be asked leading questions that result in false reports of what happened, and how relevant these studies are to children's reports of sexual abuse. False allegations should be carefully considered if the child has a serious mental health problem or if the child's statements lack detail about the event, have important inconsistencies, or seem rote in nature. If the child is part of a bitter dispute between the parents (eg, a custody fight), a false allegation, although rare, must also be carefully considered.

## MANAGEMENT AND TREATMENT

Management of children who are suspected of having been sexually abused includes action in 3 domains: (1) providing appropriate medical care, (2) reporting the case to protective services, and (3) ensuring mental health services for the child and family.

Guidelines for the treatment of STIs are highlighted in Chapter 371, Rape. In addition, counseling may be necessary about the implications of certain infections, such as HPV or HIV. Occasionally, surgical repairs of genital or anal injuries are necessary, and adolescents may need counseling about terminating a pregnancy that resulted from sexual abuse. A major purpose of the physical examination is to provide reassurance to children and families that their bodies are physically intact. When abnormalities are noted on the physical examination, reassurance often can be provided by indicating that these likely will heal and be of little functional importance to children.

Physicians who suspect sexual abuse are mandated to report their findings to the state's child protection agency. Because sexual assault is a criminal offense, the local police also participate in the investigations. Issues that need to be considered include the following: to what extent the children should be interviewed further, by whom, and in what setting; where the children should go to ensure their safety; and whether other children in the home need an evaluation.

The period after the child's disclosure can be emotionally upsetting to everyone involved and especially confusing to the child. Repeated interviews of the child (by well-meaning professionals, such as police or a protective service worker) may upset the child, who may be confused about why so many people are asking questions, embarrassed about talking about private parts, and worried about the family's reactions. Family members may blame themselves for allowing the abuse to happen and be furious at the suspected perpetrator. If the abuser is a relative, then the family may be divided, with the child's side believing the child and the abuser's side believing that the abuse could not happen and that the child is lying. If the abuser is in the immediate family, then the psychological issues are even more complicated. For example, a mother may have to decide between siding with and supporting her child or believing that her child lied and supporting her husband. If her husband did sexually abuse their child, then the mother may question her ability to protect her child, her own sexuality, and her ability to choose a partner; at the same time, she may be concerned about how the family will be supported with the father in jail.

The physician can be helpful by maintaining contact with the family, advocating for a reasonable approach by protective services (eg, having the alleged abuser leave the home rather than place the child in foster care), and helping the family to recognize and discuss the various emotional issues that surface.

When a child discloses sexual abuse, a chain of events is set in motion that has immediate and often distressing consequences for the child. What was once a secret for the disclosing child becomes a very public and emotionally charged event. Not only do

children feel guilty for causing this upheaval, but they must also endure potentially terrifying interactions with child protective services and law enforcement. Parents are often overwhelmed by their own reactions to a child's disclosure; intense anger, fear, blame, and helplessness can be very strong and can cause acute distress and significant disturbances in functioning.

Most sexually abused children and their parents need short- or long-term counseling to help come to terms with what happened. Recent work has shown that a cognitive behavioral treatment model that focuses specifically on the sexual abuse of the child and involves both the child and nonoffending parents has achieved measurable improvement in children's functioning in the wake of sexual abuse. Furthermore, the presence or absence of parental support is directly correlated with children's functioning, even as long as a year after disclosure. This finding highlights the importance of involving nonoffending parents, especially those in obvious distress, in counseling.

Because sexual abuse of a child is a criminal offense, the child and family are often involved in the criminal justice system. However, despite this involvement most cases do not actually result in a trial in criminal court for a variety of reasons, including lack of clear evidence that abuse occurred, the young age of the victim, a confession of the perpetrator, or the willingness of the perpetrator to plea bargain for a lighter sentence. In approximately 3% to 5% of cases, a criminal trial is held in which the child actually testifies. Additionally, sexual abuse cases sometimes are tried in family court when allegations of sexual abuse occur as a part of a divorce or custody proceeding or in juvenile court when protective services are concerned about the child's safety in the home.

## PSYCHOSOCIAL CONSEQUENCES

Sexual abuse can have a long-lasting and devastating effect on the development of children, adolescents, and adults. Domains of functioning that can be affected include the survivor's emotional state (eg, depression, anxiety, suicide), sense of self (eg, feeling worthless or powerless, viewing one's self as a victim), and relationships with others (eg, setting poor boundaries, being promiscuous, using inappropriate sexual behaviors, mistrusting others). Important targets for long-term treatment include self-blame for allowing the abuse to happen, the child's sexuality and sexual awareness, poor self-esteem and feelings of powerlessness, and mistrust of adults. For example, school-aged and adolescent boys may be very concerned about their own masculinity and whether, because they were abused by an older boy or a man, they are gay. At the same time, because of changes in the family (eg, the child no longer visits the grandfather), the child has to come to terms with the losses created by the disclosure and the upset and anger in the family.

Teenage girls and young women seem to be at an increased risk for other mental health problems, such as eating disorders, multiple personality disorders, and posttraumatic stress disorders. They are also more likely to become pregnant at a young age.

Men who were sexually abused as children are at increased risk for having mental health or substance abuse problems. They are also more apt to perpetrate sexually coercive acts, including victimizing children sexually.

## PREVENTION

Attempts to prevent sexual abuse have been directed toward developing programs to teach children, usually at school, about *good and bad touches* and what to do if bad touches occur. Children as young as 4 to 6 years are able to learn these concepts and retain them, at least over a short period. In general, evaluations have focused on the children's increased knowledge resulting from participation in a teaching program but have not been able to provide conclusive evidence that such programs actually have resulted in the prevention or earlier recognition of sexual abuse.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Child Sexual Abuse* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

### Medical Decision Support

- *Medical Evaluation of Child Sexual Abuse: A Practical Guide*, 3rd ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Preventing Sexual Violence: An Educational Toolkit on CD-ROM for Health Care Professionals* (CD-ROM), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Treatment of Child Abuse* (book), Johns Hopkins University Press
- *Visual Diagnosis of Child Abuse on CD-ROM*, 3rd ed (CD-ROM), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

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## Chapter 330

# SEXUALLY TRANSMITTED INFECTIONS

Alain Joffe, MD, MPH

Fifteen- to 24-year-olds represent only a quarter of sexually active individuals in the United States, but almost one-half of all sexually transmitted infections (STIs) occur in this age group. Several possible explanations can be given for this observation (see Box 330-1). Rates of sexual activity among adolescents have decreased steadily since 1991, but according to the 2013 Youth Risk Behavior Survey conducted by the Centers for Disease Control and Prevention (CDC), 47% of teenagers have had sexual intercourse and therefore are at risk of acquiring an STI. By virtue of their cognitive developmental level, adolescents often feel invulnerable and underestimate their potential for becoming infected. They may ignore symptoms or think that as long as they (or their sex partners) are free of symptoms, they are neither at risk of being infected nor capable of infecting someone else.

A physiologic basis may be found for adolescent girls being particularly susceptible to infection with a sexually transmitted organism on exposure. The transformation zone of the pubertal cervix, which has a relatively large surface area compared with that of a mature woman, is particularly vulnerable to infection with *Chlamydia trachomatis* and human papillomavirus. Not surprisingly, therefore, current data indicate that adolescent girls and young adult women have higher infection rates with these organisms than any other age group in the United States. Recent age-specific infection rates from the CDC for *C trachomatis* and *Neisseria gonorrhoeae* are shown in Figure 330-1. Rates of infection among 10- to 19-year-olds may actually be higher than indicated because the pool of truly susceptible individuals (those sexually active) is smaller in this age group than in the older groups. For example, only 46% of 9th to 12th graders have had intercourse compared with most adults.

Many studies indicate that consistent and correct use of condoms provides significant protection against STIs, although the degree of protection varies by organism. Adolescents' reported use of condoms at last intercourse increased by more than 30% since 1991, but still 41% did not use a condom the last time they had sex. Furthermore, many teenagers do not use condoms consistently or correctly. In contrast to the protective

### BOX 330-1 Why Adolescents Are at Risk for Sexually Transmitted Infections

- Sense of invulnerability ("It can't happen to me")
- Lack of information ("If I don't feel sick, I can't be sick")
- Inconsistent and improper use of condoms
- Poor communication skills with partners and physicians
- Barriers to care (legal obstacles, concerns about confidentiality)
- Inability to adhere to treatment regimens
- Contextual risk factors (sexual networks with high prevalence of infection, partner concurrency, mating patterns)
- Physiologic changes associated with puberty

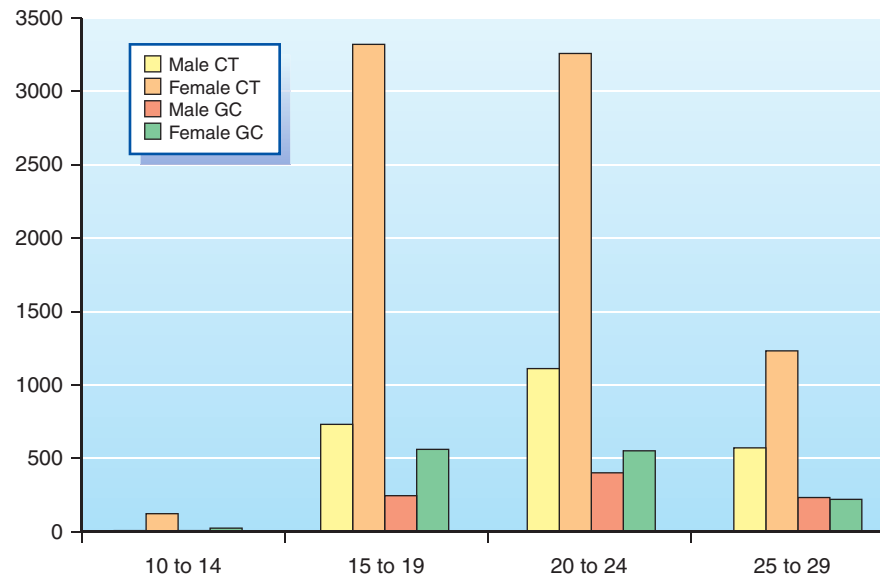
effect of condom use, the relationship between hormonal contraceptive use (such as oral contraceptive pills or depot medroxyprogesterone acetate [DMPA] injections) and risk for STI acquisition is more complex. Use of oral contraceptive pills may increase the risk for chlamydial infection but also decreases the risk for infection with *N gonorrhoeae* and development of symptomatic pelvic inflammatory disease (PID). Women receiving DMPA injections have been shown to be at increased risk for chlamydial infection but decreased risk for gonococcal infection. No data have been collected for other forms of hormonal contraception.

Adolescents often have trouble discussing sexual matters with their partners or their parents and may be reluctant to reveal that they are infected or have been treated. They may postpone a visit to a physician because they are embarrassed, fear a lecture, are concerned about the physician maintaining confidentiality, or lack the money or social skills to access health care. Some physicians hesitate to provide confidential services to an adolescent with a suspected STI because they are uncertain about the adolescent's capacity to consent to treatment without parental involvement. Currently, all 50 states have laws that permit a physician to treat most minors seeking treatment for STIs without parental consent or notification.

Analysis of individual-level risk factors (age, gender, condom use, pubertal status) explains only to a degree the striking differences in STI rates among various racial and ethnic groups. More recent research focuses on contextual risk factors: mating patterns (with whom one has sex and the sexual risk profile of that partner), sexual networks (sex partners drawn from networks with high or low rates of STIs), and partner concurrency (an individual may be unaware that his or her sex partner is having sex with more than 1 individual). Each of these dynamics helps to explain why different racial, ethnic, and socioeconomic groups, each with seemingly similar sexual behaviors, have significantly different rates of infection.

The list of organisms that can be transmitted sexually is extensive. Box 330-2 lists the most common. Gonorrhea, chlamydia, herpes, human papillomavirus,





**Figure 330-1** Rates of infection (per 100,000) with *C trachomatis* (CT) and *N gonorrhoeae* (GC), by age and sex, United States, 2009. (Data from Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2009. Atlanta, GA: US Department of Health and Human Services; 2010.)

### BOX 330-2 Sexually Transmitted Organisms

- *Campylobacter species*
- *C trachomatis*
- Cytomegalovirus
- *Entamoeba histolytica*
- *Giardia lamblia*
- Hepatitis A, B, and C
- Herpes simplex virus types 1 and 2
- Human immunodeficiency virus
- Human papillomavirus
- Molluscum contagiosum (papovavirus)
- *Mycoplasma genitalium*
- *Mycoplasma hominis*
- *N gonorrhoeae*
- *Phthirus pubis* (pubic lice)
- *Salmonella species*
- *Sarcoptes scabiei* (mites)
- *Shigella species*
- *Treponema pallidum*
- *Trichomonas vaginalis*
- *Ureaplasma urealyticum*

and syphilis are discussed in detail in this chapter. Herpes infections are also discussed in Chapter 267, Human Herpesvirus-6 and Human Herpesvirus-7 Infections; Chapter 268, Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome, reviews HIV infection and AIDS. Chapter 205, Vaginal Discharge, provides an overview of organisms

causing vaginal discharge. Information about other STIs should be sought through the index.

An alternative way of conceptualizing the spectrum of health problems attributable to STIs is to focus on symptoms or diseases rather than on specific organisms. More than 1 organism can produce various symptoms, physical findings, or syndromes, and some teenagers may be reluctant to disclose their sexual activity or deny it altogether. A recent study found that approximately 10% of young adults who tested positive for an STI denied having had intercourse in the 12 months prior to the survey. Hence, when an adolescent seeks care for symptoms and clinical findings that might be caused by an STI, the physician must proceed with appropriate diagnostic tests or therapy, even though the history may seem to exclude such a cause. Most sexually active teenagers, however, will be truthful when questioned respectfully without a parent or guardian present and when given appropriate guarantees about confidentiality. Box 330-3 lists a variety of symptoms and syndromes that are often caused by STIs.

Primary care physicians generally concern themselves with the short-term morbidity associated with STIs, but the complications of infection extend into adulthood. Cervical cancer, infertility, ectopic pregnancy, chronic pelvic pain, and AIDS are all long-term sequelae of infections acquired during adolescence and young adulthood. In addition, research has demonstrated that those individuals infected with 1 or more STIs are more likely than those without infection both to acquire HIV infection and to transmit HIV to an uninfected partner. STIs may cause a breakdown of the genital mucosa (providing a portal of entry for HIV) and recruit CD4 cells to the area of infection. However, STI acquisition may be a marker for other

### BOX 330-3 Signs, Symptoms, and Clinical Syndromes Consistent With Sexually Transmitted Infections in Adolescents

#### BOYS

- Dysuria, discharge, urethral itching (urethritis)
- Scrotal pain, swelling (epididymitis)
- Rectal discharge, tenesmus, anorectal pain (proctitis, proctocolitis, colitis)<sup>a</sup>

#### GIRLS

- Mucopurulent cervicitis
- Vaginitis (vaginal discharge)
- Dysuria, urgency, frequency
- Right upper quadrant abdominal pain (perihepatitis)
- Pelvic inflammatory disease (lower abdominal/pelvic pain)
- Bleeding between periods (cervicitis) or a heavier, more prolonged period (pelvic inflammatory disease)

#### BOTH

- Dermatitis<sup>b</sup>
- Genital ulcers (single or multiple)
- Genital warts
- Hepatitis A, B, or C infection
- Lymphadenopathy, especially inguinal or generalized (associated with human immunodeficiency virus infection)
- Persistent pharyngitis
- Septic arthritis

<sup>a</sup>Usually seen in adolescents who practice anal receptive intercourse or oral–anal contact.

<sup>b</sup>Especially generalized papulosquamous (secondary syphilis); papular with central umbilication (molluscum contagiosum); localized pubic itching, or localized itching involving the webs of fingers and the wrists (*Phthirus pubis*, pubic lice; or *Sarcoptes scabiei*, mites); and erythematous macules turning pustular or necrotic, accompanied by tenosynovitis (disseminated gonococcal infection).

unmeasured behavioral characteristics that contribute to the observed link between STI and HIV acquisition and transmission. Hence, while research published in the 1990s suggested that control of STIs could reduce the incidence of HIV infection, more current evidence indicates the effect of STI treatment on HIV incidence rates will also vary as a function of the sexual behaviors and STI prevalence of the population being targeted.

Regardless, the short- and long-term sequelae of STIs underscore the importance of preventing, diagnosing, and treating STIs among adolescents. The increasingly widespread availability and use of nucleic acid amplification tests (NAATs) for the diagnosis of *C trachomatis* and *N gonorrhoeae* infections represent major advances in achieving this goal. These tests are more sensitive than both culture and previous generations of nonculture tests, do not require the recovery of viable organisms, and can be performed on urine specimens or self-obtained vaginal swabs. By eliminating or reducing the need for invasive testing,

NAATs have the potential to expand greatly the number of at-risk youth who are screened. A urine NAAT is the preferred test for detecting chlamydia among males; self-obtained vaginal swabs are the preferred method for chlamydia detection among asymptomatic females, with a sensitivity that exceeds that of urine specimens and that is equal to or better than cervical swabs.

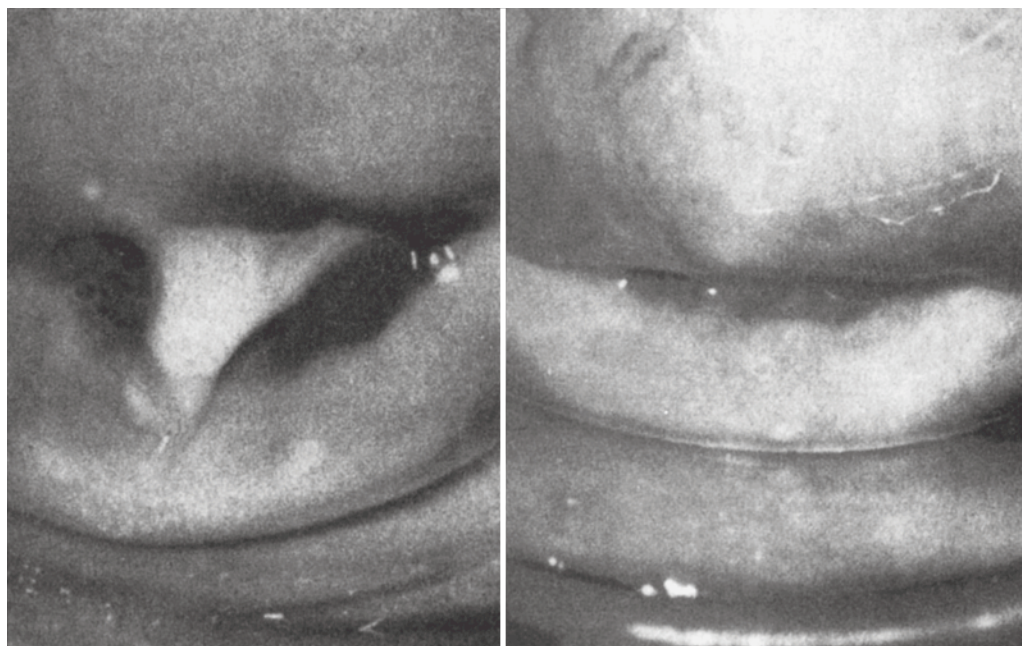
## SPECIFIC AGENTS

### *Chlamydia trachomatis*

The obligate intracellular *Chlamydia* microorganism causes a wide spectrum of disease and is the most common sexually transmitted bacterial organism in the United States. Of greatest importance is its causative role in urethritis and epididymitis in men and cervicitis and PID in women.

*Chlamydia* is thought to cause 35% to 50% of symptomatic nongonococcal urethritis (NGU) among heterosexual men. The organism can also be recovered from men with urethral gonorrhea. Approximately 2% to 10% of asymptomatic adolescent boys will test positive for chlamydia, depending on the population studied. In a recent national study of young adult men ages 18 to 26, a total of 3.7% tested positive for chlamydia (with a range of 1% to 11%, depending on the racial or ethnic group studied). Ninety-five percent reported no symptoms in the 24 hours before urine collection. When symptoms do appear, they generally develop 1 to 3 weeks after infection. Male adolescents may complain only of mild dysuria or itching at the terminal urethra, or they may have a scanty, mucoid discharge that is easily ignored and may disappear without treatment. The best time to examine an adolescent with a suggestive history but no discharge is in the morning, before he has urinated that day. Alternatively, having him strip his urethra may produce some discharge. A profuse, purulent discharge should raise the possibilities of *N gonorrhoeae* coinfection or of its being the single causative agent. Adolescents also may complain of testicular pain, scrotal pain, or both, suggesting that urethral infection has spread to the epididymis.

Because the organism can infect the urethra and the cervix, dysuria can be the primary manifestation of infection. *C trachomatis* infection should therefore be considered in any adolescent girl with symptoms of a urinary tract infection. She may complain of spotting between periods as a result of cervicitis, or if the infection has spread to the upper genital tract, she may complain of low abdominal pain or right upper quadrant pain (Fitz-Hugh–Curtis syndrome). The latter is caused by organisms tracking up the abdominal cavity and causing inflammation of the liver capsule along with adhesions to the diaphragm. Unless a thorough history is obtained, the combination of dysuria and right upper quadrant or right flank pain might lead a physician to the erroneous diagnosis of pyelonephritis. Lower abdominal pain suggests the possibility of PID. Vaginal discharge is more likely to indicate the presence of another infection (see Chapter 205, Vaginal Discharge), although chlamydia may be found incidentally. *C trachomatis* also may infect the Bartholin



**Figure 330-2** Colposcopic photograph showing mucopurulent cervicitis before and 2 weeks after treatment with 500 mg of tetracycline 4 times a day for 7 days. Note disappearance of endocervical exudate after therapy. (From Brunham RC, Paavonen J, Stevens CE, et al. Mucopurulent cervicitis—the ignored counterpart in women of urethritis in men. *N Engl J Med.* 1984;311:1-6. Copyright © 1984 Massachusetts Medical Society. All rights reserved.)

ducts, resulting in an exudative vaginal discharge or an abscess.

Infections in teenage girls are often asymptomatic, just as they are in teenage boys. Rates of infection vary according to region of the country and other factors. At pelvic examination, clues to infection are the presence of mucopurulent discharge from the cervical os (known as *mucopus*; see Figure 330-2), cervical erythema, and friability. Gram stain of cervical tissue will reveal the presence of 10 to 30 polymorphonuclear white blood cells (WBCs) per oil-immersion field. However, many patients lack any symptoms or signs of infection. Given the high prevalence of infection among adolescents and young adults and the serious morbidity associated with untreated disease, every sexually active adolescent and young adult female aged 25 or younger should be screened for chlamydia at least annually; some researchers suggest testing twice a year, especially in areas where the prevalence of infection is high. Screening programs for chlamydia have been shown to reduce the incidence of PID.

The CDC recommends NAAT as the diagnostic assay of choice for the detection of chlamydia infection. A comparison of the sensitivity and specificity of the various diagnostic tests for chlamydia infection can be found at [www.prevent.org/data/files/ncc/research%20brief%201%20std%20testing.pdf](http://www.prevent.org/data/files/ncc/research%20brief%201%20std%20testing.pdf). Box 330-4 lists drugs and dose information for treatment.

As with treatment for any STI, the patient's abstinence from intercourse is imperative until therapy is complete and the patient's partner is notified and treated. Reinfection rates among teenagers treated for chlamydia are lower if the patient knows for certain

that her partner was treated. Another strategy to reduce the burden of reinfection is expedited partner therapy (EPT), in which a physician treats the sex partner(s) of the patient without first requiring a clinical evaluation. EPT has been shown in some studies to reduce the rates of persistent or recurrent gonorrhea and chlamydia infection among heterosexual individuals. Before using EPT, physicians should become familiar with state and local laws governing its use. Short-term complications of chlamydial infection include epididymitis and PID; long-term complications include reactive arthritis and the sequelae of PID. Although infection with chlamydia is not an independent risk factor for the development of cervical dysplasia, it may play some role. An untreated, infected woman can pass the infection to her infant through colonization during birth.

### ***Neisseria gonorrhoeae***

Infection with *N gonorrhoeae* produces a constellation of symptoms similar to that produced by *C trachomatis*. In general, men who are symptomatic with gonococcal infection tend to have more pronounced symptoms (more severe dysuria and a greater amount of and more purulent discharge), and they usually seek health care more quickly than those infected with *C trachomatis*. However, many patients have no symptoms at all. In a recent study of young adult men, the overall prevalence was 0.4%, with a range up to 2.4%; more than 95% were asymptomatic. Among young adult women, the overall rate of infection was 0.4%, (range up to 1.9%); almost 87% were asymptomatic. The gonococcus can cause pharyngitis and proctitis;



**BOX 330-4 Treatment for Sexually Transmitted Infections****CHLAMYDIAL INFECTION IN ADOLESCENTS AND ADULTS****Treatment**

Treatment of infected patients prevents transmission to sex partners, and, for infected pregnant women, treatment usually prevents transmission of *C trachomatis* to infants during birth. Treatment of sex partners helps prevent reinfection of the index patient and infection of other partners.

Coinfection with *C trachomatis* often occurs among patients who have gonococcal infection; therefore, presumptive treatment of such patients for chlamydia is appropriate (see Dual Therapy for Gonococcal and Chlamydial Infections, later in this box). The following recommended treatment regimens and alternative regimens cure infection and usually relieve symptoms.

**Recommended Regimens**

Azithromycin 1 g PO in a single dose OR

Doxycycline 100 mg PO twice daily for 7 days

**Alternative Regimens**

Erythromycin base 500 mg PO 4 times daily for 7 days OR  
Erythromycin ethylsuccinate 800 mg PO 4 times daily for 7 days OR

Levofloxacin 500 mg PO once daily for 7 days OR

Ofloxacin 300 mg PO twice daily for 7 days

A meta-analysis of 12 randomized clinical trials of azithromycin versus doxycycline demonstrated that the 2 treatments were equally efficacious, with cure rates of 97% and 98%, respectively. These investigations were conducted primarily in populations in which follow-up was encouraged, adherence to a 7-day regimen was effective, and culture or enzyme-linked immunoabsorbent assays (rather than nucleic acid amplification tests [NAAT]) were used to determine microbiological outcome. More recent studies have raised concern about the efficacy of azithromycin for rectal *C trachomatis* infection. Although the clinical significance of oropharyngeal *C trachomatis* infection is unclear and routine oropharyngeal screening for *C trachomatis* is not recommended, available evidence suggests oropharyngeal *C trachomatis* can be sexually transmitted to genital sites; therefore, *C trachomatis* detected from an oropharyngeal specimen should be treated with azithromycin or doxycycline.

In populations with erratic health care-seeking behavior, poor compliance with treatment, or unpredictable follow-up, azithromycin may be more cost effective than doxycycline because it offers single-dose, directly observed therapy. Erythromycin might be less efficacious than both azithromycin and doxycycline, mainly because the gastrointestinal side effects frequently discourage patients from complying with this regimen. Levofloxacin and ofloxacin are effective treatment alternatives but are more expensive and offer no advantage with regard to the dose regimen. Other quinolones either are not reliably effective against chlamydial infection or have not been adequately evaluated.

Azithromycin should always be available to treat patients for whom compliance with multiday dosing is questionable. To maximize compliance with recommended therapies, medications for chlamydial infections

should be dispensed on site, and the first dose should be directly observed. To minimize further transmission of infection, patients treated for chlamydia should be instructed to abstain from sexual intercourse for 7 days after single-dose therapy or until completion of a 7-day regimen. Patients should also be instructed to abstain from sexual intercourse until all of their sex partners are treated to minimize the risk for reinfection.

**Follow-up**

Except for pregnant women, patients do not need to be retested for chlamydia after completing treatment with the recommended or alternative regimens unless compliance is in question, symptoms persist, or reinfection is suspected. False-negative results might occur because of small numbers of chlamydial organisms. In addition, NAAT conducted less than 3 weeks after completion of therapy for patients who were treated successfully might yield false-positive results because of the continued presence of nonviable organisms.

Studies have demonstrated high rates of infection among women retested several months after treatment, presumably because of reinfection by an untreated sex partner; infection from a new partner with chlamydia is also possible. Repeat infections confer an increased risk for pelvic inflammatory disease (PID) and other complications. Chlamydia-infected men and women should be retested approximately 3 months after treatment regardless of whether they think their sex partner(s) have been treated. If retesting at 3 months is not possible, physicians should retest whenever persons next seek medical care within the next 12 months following the initial treatment.

**GONOCOCCAL INFECTION IN ADOLESCENTS AND ADULTS****Dual Therapy for Gonococcal and Chlamydial Infections**

Patients infected with *N gonorrhoeae* often are coinfecting with *C trachomatis*; this finding led to the recommendation that patients treated for gonococcal infection also be treated routinely with a regimen effective against uncomplicated genital *C trachomatis* infection. Because most gonococci in the United States are susceptible to doxycycline and azithromycin, routine co-treatment might hinder the development of antimicrobial-resistant *N gonorrhoeae*. Limited data suggest that dual therapy with azithromycin might also enhance the efficacy of oral cephalosporins if used to treat pharyngeal gonococcal infection. Because of the high sensitivity of NAAT for chlamydial infection, patients with a negative chlamydial NAAT result at the time of treatment for gonorrhea do not need to be treated for chlamydia as well. However, if test results for chlamydia are not available or a non-NAAT was negative for chlamydia, then patients should be treated for both chlamydia and gonorrhea.

**Antimicrobial-resistant *N gonorrhoeae***

Gonorrhea treatment is complicated by the ability of this organism to develop resistance to antimicrobial therapies. Quinolone-resistant strains are widespread throughout the United States and the world, and as of 2007 this class of antibiotics is no longer recommended for treatment of gonococcal infection (and associated



**BOX 330-4 Treatment for Sexually Transmitted Infections—cont'd**

conditions such as PID) in the United States. The proportion of isolates in the Centers for Disease Control and Prevention (CDC) Gonococcal Isolate Surveillance Project demonstrating decreased susceptibility to ceftriaxone or cefixime has remained very low. Most treatment failures from use of oral cephalosporins have been reported from Asian countries; hence, physicians should ask patients testing positive for gonorrhea about recent travel to and sexual activity in these countries.

**UNCOMPLICATED GONOCOCCAL INFECTIONS OF THE CERVIX, URETHRA, AND RECTUM****Recommended Regimen**

Ceftriaxone 250 mg IM in a single dose  
PLUS

Azithromycin 1 g orally in a single dose

**Alternative Regimens**

If ceftriaxone is not available:

Cefixime 400 mg orally in a single dose  
PLUS

Azithromycin 1 g PO in a single dose

To maximize compliance with recommended regimens, medications for gonococcal infections should be dispensed on site. Ceftriaxone in a single injection of 250 mg provides sustained, high bactericidal levels in the blood. Extensive clinical experience indicates that ceftriaxone is safe and effective for the treatment of uncomplicated gonorrhea at all anatomic sites, curing 99.2% of uncomplicated urogenital and anorectal and 98.9% of pharyngeal infections in published clinical trials. The 250-mg (rather than the 125-mg) dose of ceftriaxone is now recommended given (1) the increasingly wide geographic distribution of isolates demonstrating decreased susceptibility to cephalosporins *in vitro*, (2) reports of ceftriaxone treatment failures, (3) improved efficacy of ceftriaxone 250 mg to treat pharyngeal infection (which often goes unrecognized), and (4) the utility of having a simple and consistent recommendation for treatment regardless of anatomic site.

The 400-mg oral dose of cefixime does not provide as high nor as sustained a bactericidal level as that provided by the 250-mg dose of ceftriaxone. In published clinical trials, the 400-mg dose cured 97.5% of uncomplicated urogenital and anorectal and 92.3% of pharyngeal gonococcal infections. Although cefixime can be given orally, this advantage is offset by the limited efficacy of cefixime for treating pharyngeal gonococcal infection. Ongoing use of cefixime may hasten the development of resistance to ceftriaxone. The use of ceftriaxone in conjunction with azithromycin may potentially slow the emergence of resistance to cephalosporins. Other single-dose cephalosporin regimens that are safe and highly effective for uncomplicated urogenital and anorectal gonococcal infections include ceftizoxime 500 mg IM, cefoxitin 2 g administered IM with 1 g probenecid administered orally, and cefotaxime 500 mg IM. None of these injectable cephalosporins offers any advantage over ceftriaxone for urogenital infection, and efficacy for pharyngeal infection is less certain. Information about other alternative treatment regimens

for gonococcal infections can be found in the 2015 Sexually Transmitted Diseases Treatment Guidelines, available at [www.cdc.gov/std/tg2015/default.htm](http://www.cdc.gov/std/tg2015/default.htm).

**UNCOMPLICATED GONOCOCCAL INFECTIONS OF THE PHARYNX**

Most gonococcal infections of the pharynx are asymptomatic. Gonococcal infections of the pharynx are more difficult to eradicate than infections at urogenital and anorectal sites. Few antimicrobial regimens, including those involving oral cephalosporins, can reliably cure greater than 90% of gonococcal pharyngeal infections. Physicians should ask about oral sexual exposure; patients who report this sexual behavior should be treated with a regimen that has acceptable activity against pharyngeal infection. Although chlamydial coinfection of the pharynx is unusual, coinfection at genital sites sometimes occurs; therefore, treatment for both gonorrhea and chlamydia is suggested.

**Recommended Regimen**

Ceftriaxone 250 mg IM in a single dose PLUS  
Azithromycin 1 g PO in a single dose

**Follow-up**

Test of cure is not indicated for patients with uncomplicated gonorrhea treated with any of the recommended or alternative regimens. Patients who have symptoms that persist after treatment should be evaluated with culture for *N gonorrhoeae*, and any gonococci isolated should be tested for antimicrobial susceptibility. Persistent urethritis, cervicitis, or proctitis also might be caused by *C trachomatis* or other organisms.

*N gonorrhoeae* infection is prevalent among patients who have been diagnosed with and treated for gonorrhea in the preceding several months. Most of these infections are caused by reinfection rather than treatment failure. Physicians should advise all patients with gonorrhea to be retested 3 months after treatment, and those not seeking retesting within 3 months should be tested when they next seek medical care in the ensuing 12 months.

**DISSEMINATED GONOCOCCAL INFECTION**

DGI results from gonococcal bacteremia. DGI often results in petechial or pustular acral skin lesions, asymmetrical arthralgia, tenosynovitis, or septic arthritis. The infection is complicated occasionally by perihepatitis, and rarely by endocarditis or meningitis. Some strains of *N gonorrhoeae* that cause DGI may cause minimal genital inflammation. No recent studies have been published on the treatment of DGI.

**Treatment**

Hospitalization is recommended for initial therapy, especially for patients who cannot be relied on to comply with treatment, for those in whom the diagnosis is uncertain, and for those who have purulent synovial effusions or other complications. Patients should be examined for clinical evidence of endocarditis and meningitis. Patients treated for DGI should be treated presumptively for concurrent *C trachomatis* infection.

*Continued*

**BOX 330-4 Treatment for Sexually Transmitted Infections—cont'd****Recommended Regimen**

Ceftriaxone 1 g IM or IV every 24 hours PLUS azithromycin 1 g PO in a single dose

**Alternative Regimens**

Cefotaxime 1 g IV every 8 hours OR

Ceftizoxime 1 g IV every 8 hours

PLUS

Azithromycin 1 g PO in a single dose

All regimens should be continued for 24 to 48 hours after improvement begins, at which time therapy may be switched to another oral agent guided by antimicrobial testing to complete at least 1 week of antimicrobial therapy. No treatment failures have been reported with the recommended regimens.

**HUMAN PAPILLOMAVIRUS INFECTION—GENITAL WARTS****Treatment**

The primary goal of treating visible genital warts is the removal of the warts. In most patients, treatment can induce wart-free periods. Left untreated, visible warts may resolve, may remain unchanged, or may increase in size or number. Current evidence indicates that presently available treatments likely reduce, but probably do not eradicate, human papillomavirus (HPV) infectivity. Whether the reduction in HPV viral DNA resulting from treatment affects future transmission remains unclear. No evidence links the presence of genital warts or their treatment with the development of cervical cancer.

**Regimens**

Treatment of genital warts should be guided by the preference of the patient, the available resources, and the experience of the primary care physician. No definitive evidence has been found to suggest that any of the available treatments is superior to other treatments, and no single treatment is ideal for all patients or all warts. Because of the uncertainty regarding the effect of treatment on future transmission of HPV and the possibility of spontaneous resolution, an acceptable alternative for some people is to forego treatment and wait for spontaneous resolution.

Factors that influence selection of treatment include wart size and number, anatomic site of infection, wart morphology, patient preference, cost of treatment, convenience, adverse effects, and physician experience. In general, warts on moist surfaces or in intertriginous areas respond best to topical treatment. The treatment method should be changed if the patient has not improved substantially after a complete course of treatment or if side effects are severe. Most genital warts respond within 3 months of therapy.

The available treatments for visible genital warts are patient-applied therapies (ie, podofilox, imiquimod) and physician-administered therapies (ie, cryotherapy, trichloroacetic acid [TCA], bichloroacetic acid [BCA], interferon, surgery). Having a treatment plan or protocol has been associated with improved clinical outcomes. The response to treatment and its side effects should be evaluated throughout the course of therapy.

Complications rarely occur if treatments for warts are employed properly. Patients should be warned that persistent hypo- or hyperpigmentation is common with ablative modalities. Depressed or hypertrophic scars are rare but can occur, especially if the patient has had insufficient time to heal between treatments. Treatment can result rarely in disabling chronic pain syndromes (eg, vulvodynia or analdynia, hyperesthesia of the treatment site) or, in the case of rectal warts, painful defecation or fistulas. A limited number of case reports of severe systemic effects from podophyllin resin and interferon have been documented.

Patient-applied treatments are preferred by some patients because they can be administered in the privacy of the patient's home. For these treatments to be effective, patients must be able to comply with the treatment regimen and be able to identify and reach all genital warts. Follow-up visits are not required for individuals using patient-applied therapy.

**Recommended Regimens for External Anogenital Warts (i.e., penis, groin, scrotum, vulva, perineum, external anus, and perianus)**

Many persons with external anal warts also have intra-anal warts. Thus, persons with external anal warts might benefit from an inspection of the anal canal by digital exam, standard anoscopy, or high-resolution anoscopy.

**Patient Applied**

**Imiquimod 3.75% or 5% cream:** Patients should apply imiquimod cream once daily at bedtime, 3 times a week for up to 16 weeks. The treatment area should be washed with soap and water 6 to 10 hours after the application. Local inflammatory reactions, including redness, irritation, induration, ulcerations or erosions, and vesicles occur commonly with use of imiquimod, and hypopigmentation has been described. Imiquimod may weaken condoms and vaginal diaphragms. Data from studies of human subjects are limited regarding use of imiquimod in pregnancy, but animal data suggest that this therapy poses low risk.

OR

**Podofilox 0.5% solution or gel:** Patients should apply podofilox solution with a cotton swab, or podofilox gel with a finger, to visible genital warts twice daily for 3 days, followed by 4 days without therapy. This cycle may be repeated as necessary for a total of 4 cycles. The total wart area treated should not exceed 10 cm<sup>2</sup>, and the total volume of podofilox should not exceed 0.5 mL per day. If possible, the primary care physician should apply the initial treatment to demonstrate the proper application technique and identify which warts should be treated. Mild to moderate pain or local irritation might develop after treatment. *The safety of podofilox during pregnancy has not been established.*

OR

**Sinecatechins 15% ointment:** Sinecatechin ointment should be applied 3 times daily (0.5 cm strand of ointment to each wart) using a finger to ensure complete coverage until complete clearance of warts. Treatment should not be continued for longer than 16 weeks. The medication should not be washed off after application, and all sexual activity should be avoided while the

**BOX 330-4 Treatment for Sexually Transmitted Infections—cont'd**

ointment is on the skin. Side effects include erythema, pruritus, burning, pain, ulceration, edema, induration, and vesicular rash. Sinecatechins may weaken condoms and diaphragms. This treatment is not recommended for HIV-positive or immunocompromised individuals or for persons with genital herpes. *The safety of sinecatechins during pregnancy is unknown.*

**Physician Administered****Cryotherapy with liquid nitrogen or cryoprobe:**

Repeat applications every 1 to 2 weeks. Pain after application of the liquid nitrogen, followed by necrosis and even blistering, is common. Local anesthesia (topical or injected) might facilitate treatment if warts are present in many areas or if the area of warts is large.

OR

**Surgical removal either by tangential scissor excision, tangential shave excision, curettage, or electrosurgery**

OR

**Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80% to 90%:** Apply a small amount only to warts and allow to dry (at which time a white frosting develops) before the patient sits or stands up. If pain is intense, the acid can be neutralized with soap or sodium bicarbonate. Powder with talc, sodium bicarbonate (baking soda), or liquid soap to remove unreacted acid if an excess amount is applied. Repeat weekly if necessary.

Because of the shortcomings of available treatments, some physicians employ combination therapy (the simultaneous use of 2 or more modalities on the same wart at the same time). Data are limited regarding the efficacy or risk of complications associated with use of such combinations.

**Alternative Treatments**

Intralesional interferon OR

Photodynamic therapy OR

Topical cidofovir

**Recommended Regimens for Urethral Meatus Warts**

Cryotherapy with liquid nitrogen

OR

Surgical removal

**Recommended Regimens for Cervical Warts**

Cryotherapy with liquid nitrogen

OR

Surgical removal

OR

TCA or BCA 80% to 90% solution

For women who have exophytic cervical warts, high-grade squamous intraepithelial lesions must be excluded before treatment is begun. Management of exophytic cervical warts should include consultation with a specialist.

**Recommended Regimens for Vaginal Warts**

Cryotherapy with liquid nitrogen. The use of a cryoprobe in the vagina is not recommended because of the risk for vaginal perforation and fistula formation.

OR

Surgical removal

OR

TCA or BCA 80% to 90% solution

**Recommended Regimens for Urethral Meatus Warts**

Cryotherapy with liquid nitrogen

OR

Podophyllin 10% to 25% in compound tincture of benzoin. The treatment area must be dry before contact with normal mucosa. Podophyllin can be applied weekly if necessary. *The safety of podophyllin during pregnancy has not been established.* Data are limited on the use of podofilox and imiquimod for the treatment of distal meatal warts.

**Recommended Regimens for Intra-anal Warts**

Cryotherapy with liquid nitrogen

OR

Surgical removal

OR

TCA or BCA 80% to 90%

Intra-anal warts should be managed in consultation with a specialist.

**Genital Herpes Simplex Virus Infection**

Genital herpes is a chronic, lifelong viral infection. Most cases of recurrent genital herpes are caused by herpes simplex virus type 2 (HSV-2). An increasing proportion of anogenital herpetic infections have been attributed to HSV-1 infection, especially young women and men who have sex with men. Most people with HSV-2 infection have not been diagnosed; many of them have mild or unrecognized disease but shed virus intermittently in the genital tract. The majority of genital herpes infections are transmitted by people who do not know they are infected or who are asymptomatic at the time transmission occurs.

Clinical diagnosis of genital herpes is challenging. Recurrences and subclinical shedding are much more common with genital HSV-2 compared to HSV-1 infection. A patient's prognosis and the type of counseling needed depend on whether the infection is caused by HSV-1 or HSV-2. Therefore, the clinical diagnosis should be confirmed by type-specific laboratory testing.

**First Clinical Episode of Genital Herpes**

Many patients with first-episode herpes have mild clinical manifestations but later develop severe or prolonged symptoms. Therefore, patients with initial genital herpes should receive antiviral therapy.

**Recommended Regimens**

Acyclovir 400 mg PO 3 times daily for 7 to 10 days

OR

Acyclovir 200 mg PO 5 times daily for 7 to 10 days

OR

Valacyclovir 1 g PO 2 times daily for 7 to 10 days

Continued

**BOX 330-4 Treatment for Sexually Transmitted Infections—cont'd**

OR

Famciclovir 250 mg PO 3 times daily for 7 to 10 days  
Treatment may be extended if healing is incomplete after 10 days of therapy.

**ESTABLISHED HERPES SIMPLEX VIRUS TYPE 2 INFECTION**

Most patients with symptomatic, first-episode genital HSV-2 infection will have recurrent episodes of genital lesions; recurrences are less frequent after initial genital HSV-1 infection. Intermittent asymptomatic shedding occurs in persons with genital HSV-2 infection, even in those with longstanding or clinically silent infection. Antiviral therapy for recurrent disease can be administered either episodically to ameliorate or shorten the duration of lesions or continuously as suppressive therapy to reduce the frequency of recurrences. Many persons, even those with mild or infrequent outbreaks, benefit from antiviral therapy; therefore, options for treatment should be discussed. Some persons may prefer suppressive therapy, which has the additional advantage of decreasing the risk of genital HSV-2 transmission to susceptible partners.

Daily suppressive therapy reduces the frequency of genital herpes recurrences by 70% to 80% in patients who have frequent recurrences (ie, 6 or more recurrences per year). Treatment is also effective in patients with less frequent recurrences. Safety and efficacy have been documented among patients receiving daily therapy with acyclovir for as long as 6 years and with valacyclovir or famciclovir for 1 year. The frequency of recurrences diminishes over time in many patients, and the patient's psychological adjustment to disease might change. Therefore, periodically (eg, once a year), physicians should discuss the need to continue suppressive therapy with the patient.

Suppressive therapy with valacyclovir 500 mg daily decreases the rate of HSV-2 transmission in discordant, heterosexual couples in which the source partner has a history of genital HSV-2 infection. Suppressive antiviral therapy probably reduces transmission when used by persons who have multiple partners (including men who have sex with men) and by those who are HSV-2 seropositive without a history of genital herpes.

**Recommended Regimens for Daily Suppressive Therapy**

Acyclovir 400 mg PO twice daily OR

Valacyclovir 500 mg once daily OR

Valacyclovir 1 g PO once daily

Famciclovir 250 mg PO twice daily

Valacyclovir 500 mg once daily may be less effective than other valacyclovir or acyclovir dosing regimens in patients who have very frequent recurrences (ie, at least 10 episodes per year).

**Episodic Therapy for Recurrent Genital Herpes**

Effective episodic therapy of recurrent herpes requires initiation of therapy within 1 day of lesion onset or during the prodrome that precedes some outbreaks. The patient should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment as soon as symptoms begin.

**Recommended Regimens**

Acyclovir 400 mg PO 3 times daily for 5 days OR

Acyclovir 800 mg PO twice daily for 5 days OR

Acyclovir 800 mg PO 3 times daily for 2 days OR

Valacyclovir 500 mg PO twice daily for 3 days OR

Valacyclovir 1 g PO once daily for 5 days OR

Famciclovir 125 mg PO twice daily for 5 days OR

Famciclovir 1,000 mg PO twice daily for 1 day OR

Famciclovir 500 mg PO once, followed by 250 mg twice daily for 2 days

**PRIMARY AND SECONDARY SYPHILIS****Treatment**

Parenteral penicillin G is the preferred drug for treatment of all stages of syphilis. The preparation used (ie, benzathine, aqueous procaine, aqueous crystalline), the dose, and the length of treatment all depend on the stage and clinical manifestations of the disease.

**Recommended Regimen for Adults**

Adults who have primary or secondary syphilis should be treated with benzathine penicillin G 2.4 million units IM in a single dose. HIV-infected patients with primary and secondary syphilis should also receive this dose; available data do not suggest that higher doses or use of other antibiotics result in enhanced efficacy.

**Recommended Regimen for Children**

After the newborn period ( $\geq 1$  month), children with syphilis should have a cerebrospinal fluid (CSF) examination to detect asymptomatic neurosyphilis, and birth and maternal medical records should be reviewed to assess whether the child has congenital or acquired syphilis. Children with acquired primary or secondary syphilis should be evaluated for sexual abuse (including consultation with child-protection services) and treated using the following pediatric regimen:

Benzathine penicillin G 50,000 units/kg IM up to the adult dose of 2.4 million units in a single dose. (A child or adolescent weighing  $\geq 48$  kg would receive the adult dose.)

**Other Management Considerations**

All patients who have syphilis should be tested for HIV infection. In geographic areas in which the prevalence of HIV is high, patients who have primary syphilis should be retested for HIV after 3 months if the first HIV test result was negative.

Patients who have syphilis and symptoms or signs suggesting neurologic disease (eg, meningitis or hearing loss) or ophthalmic disease (eg, uveitis, iritis, neuroretinitis, optic neuritis) should be evaluated fully for neurosyphilis and syphilitic eye disease; this evaluation should include CSF analysis and otologic and ocular slit-lamp examinations. Such patients should be treated appropriately according to the results of this evaluation.

Invasion of CSF by *T pallidum* accompanied by CSF abnormalities is common among adults who have primary or secondary syphilis. However, neurosyphilis develops in only a few patients after treatment with the regimens described here. Therefore, unless clinical signs or symptoms of neurologic or ophthalmic involvement are present, lumbar puncture is not recommended for routine evaluation of patients who have primary or secondary syphilis.



**BOX 330-4 Treatment for Sexually Transmitted Infections—cont'd****Follow-up**

Treatment failure can occur with any regimen. However, assessing response to treatment is often difficult, and no definitive criteria for cure or failure have been established. Nontreponemal test titers may decline more slowly for patients who previously had syphilis. Patients should be re-examined clinically and serologically 6 and 12 months after treatment; more frequent evaluation may be prudent if follow-up is uncertain. HIV-infected patients should be evaluated clinically and serologically for treatment failure at 3, 6, 9, 12, and 24 months after therapy.

Patients who have signs or symptoms that persist or recur or who have a sustained fourfold increase in nontreponemal test titer for at least 2 weeks (ie, compared with the maximum or baseline titer at time of treatment) probably failed treatment or were reinfected. These patients should be retreated and reevaluated for HIV infection. Because treatment failure usually cannot be reliably distinguished from reinfection with *T pallidum*, a lumbar puncture also should be performed. HIV-infected patients who meet the criteria for treatment failure (signs or symptoms that persist or recur or persons who have a sustained fourfold increase in nontreponemal test titer) should be managed in the same manner as HIV-negative patients (CSF examination and retreatment as indicated below).

Although failure of nontreponemal test titers to decline fourfold within 6 to 12 months after therapy for primary or secondary syphilis may indicate treatment failure, clinical trial data have demonstrated that at least 15% of patients with early syphilis treated with recommended therapy will not achieve a 2-dilution decline in nontreponemal titer used to define response at 1 year after treatment. Persons whose titers do not decline should be re-evaluated for HIV infection. Optimal management of such patients is unclear. At a minimum, these patients should have additional clinical and serologic follow-up. If additional follow-up cannot be ensured, retreatment is recommended. Because treatment failure might be the result of unrecognized central nervous system infection, many specialists recommend CSF examination in such situations. When patients are retreated, weekly injections of benzathine penicillin G 2.4 million units IM for 3 weeks is recommended, unless CSF examination indicates that neurosyphilis is present.

**LATENT SYPHILIS**

Latent syphilis is defined as syphilis characterized by seroreactivity without other evidence of disease. Patients who have latent syphilis and who acquired syphilis within the preceding year are classified as having early latent syphilis. Patients can be diagnosed as having early latent syphilis if, within the year preceding the evaluation, they had (a) a documented seroconversion or fourfold or greater increase in titer of a nontreponemal test; (b) unequivocal symptoms of primary or secondary syphilis; (c) a sex partner documented to have primary, secondary, or early latent syphilis; or (d) reactive nontreponemal and treponemal tests with the only possible exposure occurring within the previous 12 months. Absent these conditions, an asymptomatic

person is considered to have late latent syphilis or syphilis of unknown duration. Nontreponemal serologic titers are usually higher during early latent syphilis than late latent syphilis. However, early latent syphilis cannot be reliably distinguished from late latent syphilis based solely on nontreponemal titers. All patients with latent syphilis should have thorough examination of all accessible mucosal surfaces (oral cavity, perineum, and vagina in women; perianal area and underneath the foreskin in uncircumcised men) to evaluate for internal mucosal lesions. All patients who have syphilis should be tested for HIV infection.

**Treatment**

Because latent syphilis is not transmitted sexually, the objective of treating patients with this stage of the disease is to prevent complications. Although clinical experience supports the effectiveness of penicillin in achieving this goal, limited evidence is available for guidance in choosing specific regimens.

**Recommended Regimens for Adults**

The following regimens are recommended for penicillin-nonallergic patients who have normal CSF examination (if performed).

Early latent syphilis: benzathine penicillin G 2.4 million units IM in a single dose. This same treatment is recommended for HIV-infected patients.

Late latent syphilis or latent syphilis of unknown duration: benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals. This same treatment regimen is recommended for HIV-infected patients.

**Recommended Regimens for Children**

After the newborn period (1 month of age or older), children with syphilis should have a CSF examination to exclude neurosyphilis. Birth and maternal records should be reviewed to assess whether the child has congenital or acquired syphilis. Older children with acquired latent syphilis should be evaluated as described for adults and treated using the following pediatric regimens. These regimens are for penicillin-nonallergic children with acquired syphilis who have normal CSF examination results.

Early latent syphilis: benzathine penicillin G 50,000 units/kg IM, up to the adult dose of 2.4 million units, in a single dose. (A child or adolescent who weighs  $\geq 48$  kg would receive the adult dose.)

Late latent syphilis or latent syphilis of unknown duration: benzathine penicillin G 50,000 units/kg IM, up to the adult dose of 2.4 million units, administered as 3 doses at 1-week intervals (total 150,000 units/kg up to the adult dose of 7.2 million units).

**Other Treatment Considerations**

Patients (including HIV-infected patients) with late latent syphilis who demonstrate any of the following should have a prompt CSF examination: (a) neurologic (auditory disease, cranial nerve dysfunction, acute or chronic meningitis, stroke, changes in mental status, loss of vibration sense) or ophthalmic signs or symptoms (iritis or uveitis), (b) evidence of active tertiary syphilis (eg, aortitis, gumma), or (c) treatment failure. If a patient misses

*Continued*

**BOX 330-4 Treatment for Sexually Transmitted Infections—cont'd**

a dose of penicillin in a course of weekly therapy for late syphilis, the appropriate course is unclear. Pharmacologic data suggest that if the interval between doses is 10 to 14 days, restarting injections may not be necessary.

**Follow-up**

Quantitative nontreponemal serologic tests should be repeated at 6, 12, and 24 months. A CSF examination should be performed if (a) titers increase fourfold, (b) an initially high titer (at least 1:32) fails to decline at least fourfold (ie, 2 dilutions) within 12 to 24 months, or (c) signs or symptoms attributable to syphilis develop. In such circumstances, even if the CSF examination is negative, retreatment for latent syphilis should be initiated. HIV-infected patients should be evaluated clinically and serologically at 6, 12, 18, and 24 months after therapy. If at any time clinical symptoms develop or nontreponemal test titers rise fourfold, a CSF examination should be performed and treatment administered accordingly. If during 12 to 24 months the nontreponemal test does not decline fourfold, CSF examination should be strongly considered and treatment administered accordingly.

**PELVIC INFLAMMATORY DISEASE**

PID comprises a spectrum of inflammatory disorders of the upper female genital tract, including any combination of endometritis, salpingitis, tubo ovarian abscess, and pelvic peritonitis. Sexually transmitted organisms, especially *N gonorrhoeae* and *C trachomatis*, are implicated in many cases; however, microorganisms that comprise the vaginal flora (eg, anaerobes, *Gardnerella vaginalis*, *Haemophilus influenzae*, enteric Gram-negative rods, and *Streptococcus agalactiae*) also have been associated with PID. In addition, cytomegalovirus (CMV), *Mycoplasma hominis*, *Ureaplasma urealyticum*, and *Mycoplasma genitalium* might be associated with some cases of PID. All women who are diagnosed with acute PID should be tested for *N gonorrhoeae* and *C trachomatis* and screened for HIV infection.

**Treatment**

PID treatment regimens must provide empiric, broad-spectrum coverage of likely pathogens. All regimens should be effective against *N gonorrhoeae* and *C trachomatis*, because negative endocervical screening for these organisms does not preclude upper reproductive tract infection. The need to eradicate anaerobes from women who have PID has not been demonstrated definitively. Anaerobic bacteria have been isolated from the upper reproductive tract of women who have PID, and data from in vitro studies have revealed that anaerobes such as *Bacteroides fragilis* can cause tubal and epithelial destruction. In addition, bacterial vaginosis also is diagnosed in many women who have PID. Until treatment regimens that do not adequately cover these microbes have been shown to prevent sequelae as successfully as the regimens that are effective against these microbes, the use of regimens with anaerobic activity should be considered. Treatment should be initiated as soon as the presumptive diagnosis has been made, because prevention of long-term sequelae is dependent on early administration of appropriate antibiotics. When selecting a treatment regimen, physicians should consider

availability, cost, patient acceptance, and antimicrobial susceptibility.

Evidence is insufficient to recommend the removal of an intrauterine device in women diagnosed with acute PID. However, caution should be exercised if the intrauterine device remains in place and close follow-up is mandatory. Comprehensive observational and controlled studies demonstrate that HIV-infected women with PID have similar symptoms when compared with uninfected controls, except they were more likely to have a tubo-ovarian abscess. Both groups responded equally well to standard parenteral and oral antibiotic regimens. Regardless of the data, whether or not immunodeficient HIV-infected women with PID require more aggressive treatment is uncertain.

**Parenteral Treatment**

For women with mild to moderate PID, parenteral therapy and oral therapy seem to have similar clinical efficacy. Many randomized trials have demonstrated the efficacy of both parenteral and oral regimens. Clinical experience should guide decisions regarding transition to oral therapy, which usually can be initiated within 24 to 48 hours of clinical improvement. At least 24 hours of direct inpatient observation is recommended for patients who have tubo-ovarian abscess.

**Recommended Parenteral Regimens**

Cefotetan 2 g IV every 12 hours

PLUS

Doxycycline 100 mg orally or IV every 12 hours

OR

Cefoxitin 2 g IV every 6 hours PLUS

Doxycycline 100 mg PO or IV every 12 hours

OR

Clindamycin 900 mg IV every 8 hours

PLUS

Gentamicin loading dose IV or IM (2 mg/kg) followed by a maintenance dose (1.5 mg/kg) every 8 hours.

Single daily dosing (3–5 mg/kg) can be substituted.

Because of pain associated with infusion, doxycycline should be administered orally when possible, even when the patient is hospitalized. Oral and IV administration of doxycycline provide similar bioavailability. Although use of a single daily dose of gentamicin has not been evaluated for the treatment of PID, it is efficacious in analogous situations.

Parenteral therapy may be discontinued 24 to 48 hours after a patient improves clinically, but oral therapy with doxycycline (100 mg twice/day) should continue for a total of 14 days. When tubo-ovarian abscess is present, clindamycin or metronidazole with doxycycline can be used for continued therapy rather than doxycycline alone, because this regimen provides more effective anaerobic coverage.

Clinical data are limited regarding the use of other second- or third-generation cephalosporins (eg, ceftizoxime, cefotaxime, ceftriaxone), which also might be effective therapy for PID and might replace cefotetan or cefoxitin. However, they are less active than cefotetan or cefoxitin against anaerobic bacteria.

**BOX 330-4 Treatment for Sexually Transmitted Infections—cont'd**

Parenteral therapy may be discontinued 24 hours after a patient improves clinically; continuing oral therapy should consist of doxycycline 100 mg PO twice daily or clindamycin 450 mg PO 4 times daily to complete a total of 14 days of therapy. When tubo-ovarian abscess is present, clindamycin should be continued rather than doxycycline because clindamycin provides more effective anaerobic coverage.

**Alternative Parenteral Regimens**

Ampicillin/sulbactam 3 g IV every 6 hours PLUS

Doxycycline 100 mg PO or IV every 12 hours

Ampicillin/sulbactam plus doxycycline is effective against *C trachomatis*, *N gonorrhoeae*, and anaerobes in women with tubo-ovarian abscess. One trial demonstrated high short-term clinical cure rates with azithromycin, either as monotherapy for 1 week (500 mg IV for 1 or 2 doses followed by 250 mg PO for 5 to 6 days) or combined with a 12-day course of metronidazole.

**Intramuscular/Oral Treatment**

Intramuscular/oral outpatient therapy can be considered for women with mild-to-moderately severe acute PID, given that the clinical outcomes among women treated with these therapies are similar to those treated with parenteral therapy. Patients who do not respond to IM/oral therapy within 72 hours should be re-evaluated to confirm the diagnosis and should be administered parenteral therapy.

**Recommended Intramuscular/Oral Regimens**

Ceftriaxone 250 mg IM in a single dose

PLUS

Doxycycline 100 mg PO twice daily for 14 days

WITH\* OR WITHOUT

Metronidazole 500 mg PO twice daily for 14 days

OR

Cefoxitin 2 g IM in a single dose and probenecid 1 g PO administered concurrently in a single dose

PLUS

Doxycycline 100 mg PO twice daily for 14 days

WITH\* OR WITHOUT

Metronidazole 500 mg PO twice daily for 14 days

OR

Other parenteral third-generation cephalosporin (eg, ceftizoxime or cefotaxime)

PLUS

Doxycycline 100 mg PO twice daily for 14 days

WITH\* OR WITHOUT

Metronidazole 500 mg PO twice daily for 14 days (\*The recommended third-generation cephalosporins are limited in their anaerobic coverage; therefore, until it is known that extended anaerobic coverage is not important for treatment of acute PID, the addition of metronidazole to these treatment regimens should be considered.)

These regimens provide coverage against frequent etiologic agents of PID, but the optimal choice of a cephalosporin is unclear. Cefoxitin has better anaerobic coverage than ceftriaxone, and in combination with

probenecid and doxycycline has been effective in short-term clinical response in women with PID. Ceftriaxone has better coverage against *N gonorrhoeae*. Metronidazole will also effectively treat bacterial vaginosis, which is often associated with PID.

**Alternative Oral Regimens**

Azithromycin has shown short-term effectiveness in at least one clinical trial (500 mg IV daily for 1–2 doses, followed by 250 mg orally daily for 12–14 days) or in combination with metronidazole; in another study, it was effective when 1 g orally once per week for 2 weeks was used in combination with ceftriaxone 250 mg IM in a single dose. Concomitant use of metronidazole for anaerobic coverage should be considered.

As a result of the emergence of quinolone-resistant *N gonorrhoeae*, regimens that include a quinolone agent are no longer recommended for treatment of PID. If parenteral cephalosporin therapy is not feasible and the community prevalence and individual risk for gonorrhea are low, and follow-up is likely, then use of fluoroquinolones (levofloxacin 500 mg PO once daily or ofloxacin 400 mg PO twice daily or moxifloxacin 400 mg orally once daily for 14 days) with metronidazole (500 mg PO twice daily for 14 days) can be considered. Tests for gonorrhea must be performed before instituting therapy and the patient managed as follows:

- If culture for gonorrhea is positive, treatment should be based on the results of antimicrobial susceptibility.
- If the isolate is determined to be quinolone-resistant *N gonorrhoeae*, or if antimicrobial susceptibility cannot be assessed (if only NAAT testing is available), consultation with an infectious disease specialist is recommended.

**Follow-up**

Patients should demonstrate substantial clinical improvement (defervescence, reduction in direct or rebound abdominal tenderness, reduction in uterine, adnexal, and cervical motion tenderness) within 72 hours of initiation of therapy. Patients who do not improve within 72 hours usually require hospitalization, additional diagnostic tests, and surgical intervention.

Assessment of the antimicrobial regimen and diagnostics (including the consideration of diagnostic laparoscopy for alternative diagnoses) is recommended in women without clinical improvement. Women with documented gonococcal or chlamydial infections have high rates of reinfection within 6 months of treatment. Repeat testing of these women is recommended 3 to 6 months after treatment, regardless of whether their sex partners were treated. All women with acute PID should be offered HIV testing. Male sex partners of women with PID should be examined and treated for gonorrhea and chlamydia if they had sexual contact with the patient during the 60 days preceding the patient's onset of symptoms. If the patient's last sexual intercourse was more than 60 days before onset of symptoms or diagnosis, the most recent partner should be treated.

**Epididymitis**

Empiric therapy is indicated before laboratory test results are available; all patients should therefore receive

*Continued*

**BOX 330-4 Treatment for Sexually Transmitted Infections—cont'd**

ceftriaxone plus doxycycline for the initial treatment of epididymitis. Additional therapy may include a quinolone if acute epididymitis is not caused by gonorrhea (results by a NAAT are negative) or if the infection is most likely caused by enteric organisms. *For men who are at risk for both sexually transmitted and enteric organisms (eg, men who report anal insertive intercourse), ceftriaxone and a fluoroquinolone are recommended.*

**Recommended Regimens**

**For acute epididymitis most likely caused by sexually transmitted chlamydia and gonorrhea:**

Ceftriaxone 250 mg IM in a single dose PLUS

Doxycycline 100 mg PO twice daily for 10 days

**For acute epididymitis most likely caused by sexually transmitted chlamydia and gonorrhea and enteric organisms (men who practice insertive anal sex):**

Ceftriaxone 250 mg IM in a single dose PLUS

Levofloxacin 500 mg PO once daily for 10 days OR

Ofloxacin 300 mg PO twice daily for 10 days

**For acute epididymitis most likely caused by enteric organisms:**

Levofloxacin 500 mg orally once daily for 10 days OR

Ofloxacin 300 mg orally twice a day for 10 days

**Proctitis, Proctocolitis, and Enteritis**

Sexually transmitted gastrointestinal syndromes include proctitis, proctocolitis, and enteritis. Evaluation should include appropriate diagnostic procedures (eg, anoscopy or sigmoidoscopy, stool examination, culture).

Proctitis is inflammation of the rectum (the distal 10 to 12 cm) that can be associated with anorectal pain, tenesmus, or rectal discharge. *N gonorrhoeae*, *C trachomatis* (including lymphogranuloma venereum [LGV] serovars), *T pallidum*, and HSV are the most common sexually transmitted pathogens involved. In patients coinfecting with HIV, herpes proctitis can be especially severe. Proctitis occurs predominantly among persons who participate in receptive anal intercourse.

Proctocolitis is associated with symptoms of proctitis, diarrhea or abdominal cramps (or both), and inflammation of the colonic mucosa extending to 12 cm above the anus. Fecal leukocytes may be detected on stool examination depending on the pathogen. Pathogenic organisms include *Campylobacter* species, *Shigella* species, *Entamoeba histolytica*, and LGV serovars of *C trachomatis*. CMV or other opportunistic agents can be involved in

immunosuppressed HIV-infected patients. Proctocolitis can be acquired by the oral route or by oral–anal contact, depending on the pathogen.

Enteritis usually results in diarrhea and abdominal cramping without signs of proctitis or proctocolitis; it occurs among persons whose sexual practices include oral–anal contact. In otherwise healthy patients, *G lamblia* is most commonly implicated. When outbreaks of gastrointestinal illness occur among social or sexual networks of men who have sex with men, physicians should consider sexual transmission as a mode of spread. Among HIV-infected patients, other infections that usually are not sexually transmitted may occur, including those caused by CMV, *Mycobacterium avium-intracellulare*, *Campylobacter* species, *Shigella* species, *Salmonella* species, *Cryptosporidium*, *Microsporidium*, and *Isospora*. Multiple stool examinations may be necessary to detect *Giardia*, and special stool preparations are required to diagnose cryptosporidiosis and microsporidiosis. Additionally, enteritis can be directly caused by HIV infection. When laboratory diagnostic capabilities are available, treatment should be based on the specific diagnosis.

**Treatment**

Acute proctitis of recent onset among persons who have recently practiced receptive anal intercourse is most often sexually transmitted. Such patients should be examined by anoscopy and should be evaluated for infection with HSV (polymerase chain reaction [PCR] or culture), *N gonorrhoeae* (NAAT or culture), *C trachomatis* (NAAT), and *T pallidum* (dark-field if available and serologic testing). A Gram-stained smear of any anorectal exudate should be examined for polymorphonuclear leukocytes. If the *C trachomatis* test on a rectal swab is positive, a molecular test PCR for LGV should be performed, if possible.

**Recommended Regimen**

Ceftriaxone 250 mg IM PLUS

Doxycycline 100 mg PO twice daily for 7 days

Bloody discharge, perianal ulcers, or mucosal ulcers among men who have sex with men (MSM) with acute proctitis and either a positive rectal chlamydia NAAT or HIV infection should be offered presumptive treatment for LGV (doxycycline 100 mg PO BID for 3 weeks).

Patients with suspected or documented herpes proctitis should be managed in the same manner as those with genital herpes.

Adapted from Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010;59 (No. RR-12):1–109 and Workowski KA, Bolan GA. Sexually transmitted diseases guidelines, 2015. *MMWR Recomm Rep*. 2015;64 (No. RR-3): 1–110. (In some cases, the author has edited the text to condense it.)

adolescent and young adult women may harbor the organism in the rectum even if they do not engage in anal intercourse.

The gonococcus can be grown from urethral or cervical discharge; from swabs of the vagina, cervix, urethra, pharynx, or rectum; and in many instances from urine sediment. In the past, the diagnosis of gonococcal infection rested on culture or on the classic findings of WBCs and gram-negative intracellular

diplococci in Gram stains of discharge or material obtained from a urethral swab. Even under ideal conditions, the organism can be difficult to grow, and physicians relying on culture should be familiar with the yield from the laboratory they use. In men, a typical Gram stain from a urethral discharge is diagnostic. For samples taken from women, sorting out gram-negative organisms that truly are intracellular versus those that may be overlying or near the cells



is more difficult. However, when at least 8 pairs of such diplococci are seen in at least 2 polymorphonuclear leukocytes, the culture will be positive 96% of the time.

As is the case with chlamydia, the CDC recommend use of NAAT for the detection of *N gonorrhoeae*. These tests are more sensitive than culture and have the added advantage of eliminating the need for pelvic examination or swabbing the urethral meatus to obtain specimens; instead, a urine specimen or vaginal swab can be used. Treatment regimens for uncomplicated gonococcal infections are listed in Box 330-4; as a result of increasing gonococcal resistance to fluoroquinolones, the CDC no longer recommends this class of antibiotics for treatment of gonococcal infection. In addition, because of concerns of increasing resistance of *N gonorrhoeae* to cephalosporins and the desire to have a single regimen to treat gonococcal infection at all sites, the CDC currently recommends 250 mg of ceftriaxone administered intramuscularly for treatment of uncomplicated gonococcal infections of the cervix, urethra, rectum, and pharynx. Because of the high likelihood of coinfection with chlamydia, treatment for gonorrhea must also include an effective regimen for *C trachomatis* unless a NAAT for chlamydia is known to be negative.

Gonorrhea also may produce epididymitis and PID. In addition and in contrast to chlamydia, the gonococcal organism has the capacity to become bloodborne and can lead to the so-called arthritis-dermatitis syndrome, or DGI. Approximately 1% to 3% of untreated patients develop DGI. Strains of *N gonorrhoeae* that lead to DGI characteristically tend to cause little in the way of genital symptoms. Typically (although not always), the patient develops fever and may have anorexia, malaise, or both. Skin lesions then appear, generally distributed on the extremities (arms more often than legs). The lesions appear as erythematous macules less than 5 mm in diameter; they become pustular and occasionally hemorrhagic or necrotic (Figure 330-3). They are most often noticed near the small joints of the hands and feet. Accompanying the dermatitis is a tenosynovitis that tends to occur over the extensor and flexor tendons of the hands and feet. During this early phase of the infection, especially if evaluated within 2 to 3 days of onset of symptoms, 25% to 50% of patients will have positive blood cultures.

In general, once the tenosynovitis and dermatitis clear, the patient develops polyarthralgia but usually seeks care only when an oligoarthritis develops. The knee is the joint most commonly infected, followed by the elbow, ankle, and small joints of the hands and feet. Hence, among adolescents, DGI should always be considered in the differential diagnosis of septic arthritis. Aspirates of joint fluid reveal the typical changes of septic arthritis, but joint fluid cultures are usually negative. Meningitis or endocarditis may also be present. Patients with DGI, especially those with arthritis, should be hospitalized—at least initially—for treatment (see Box 330-4).

### Human Papillomavirus (Genital Warts)

Infections with human papillomavirus (HPV) are the most prevalent STI in the United States. Such infections



**Figure 330-3** Disseminated gonococcal infection (DGI). If a gonorrhea infection is allowed to go untreated, the *N gonorrhoeae* can become disseminated throughout the body, forming lesions in extragenital locations. (Courtesy Red Book Online. [redbook.solutions.aap.org](http://redbook.solutions.aap.org))

have always drawn attention because they cause unsightly warts (condylomata acuminata), and because HPV infection represents the most common cause of an abnormal Papanicolaou test (Pap smear screening) among adolescent and young adult women. Current concerns about HPV focus on its role in the development of cervical neoplasia. HPV infection has been associated with more than 90% of cervical dysplasia worldwide.

More than 100 different types of HPV have been identified. The low-risk types 6 and 11 account for 97% of genital wart manifestations (external genital warts). Types 16, 18, 31, and 45 are responsible for approximately 80% of cervical cancers worldwide, with type 16 alone causing 40% to 60% of the disease burden. An individual can be infected with more than 1 type of HPV.

As with other STIs, infection rates among adolescents and young adults are high. The prevalence of cervical HPV infection among adolescents ages 12 to 21 is approximately 51% to 64%. Longitudinal studies of adolescent girls suggest that approximately 45% to 55% become infected over a 3-year period of observation.

Male adolescents constitute a significant reservoir of undetected HPV infection; rates of infection are highest among 20- to 29-year-old males. Few male partners of HPV-positive women have clinical evidence of warts, but when magnification and acetic acid soaks are used to produce the acetowhite changes seen in HPV-infected skin, far more men are found to be infected (see Figure 330-4). Almost all data regarding HPV among men are drawn from those aged 18 and older; little information exists about younger adolescent boys.



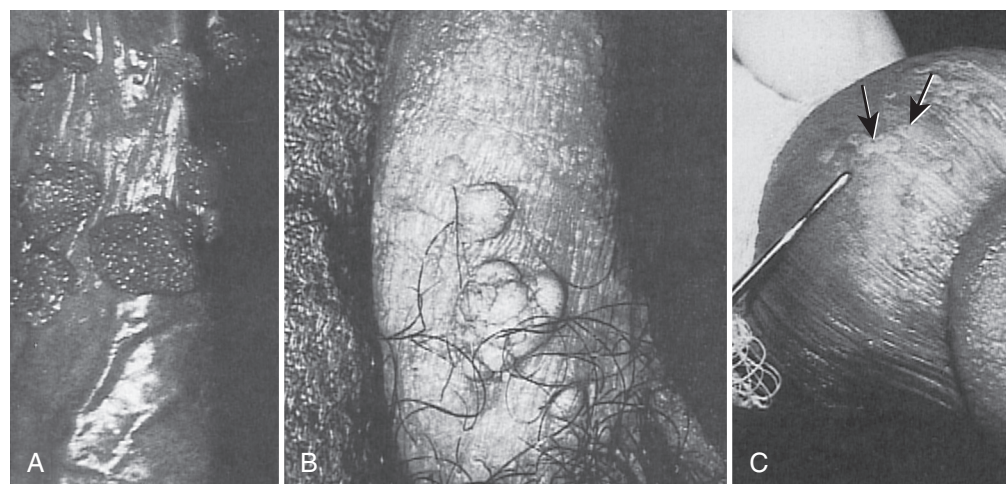
**Figure 330-4** Demonstration of subclinical lesions. **A**, Appearance of penis before application of acetic acid. **B**, Penis after 5-minute application of gauze soaked in 5% acetic acid. Note coalescing sheets (arrows) and discrete dots of acetowhite staining (inset). **C**, Magnified view of apparent subclinical human papillomavirus infection shown in panel B. (From Katelaris PM, Cossart YE, Rose BR, et al. *Human papilloma virus: the untreated male reservoir*. J Urol. 1988;140:300-305. Copyright © 1988, Elsevier, with permission.)

Visible warts usually develop within 6 weeks to 8 months after infection, but the incubation period may be even longer. The typical pedunculated wart with a keratotic and irregular surface is easy to recognize, but warts may also be flat and more difficult to detect. The use of a handheld magnifying glass or even a colposcope is extremely helpful. Among male adolescents, warts are usually seen on the penile shaft, prepuce, frenulum, corona, and glans, but they may also be present on the skin of the scrotum and the anus

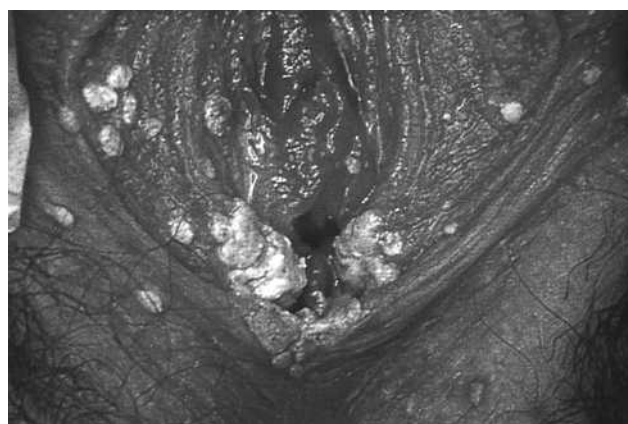
(see Figure 330-5). The presence of anal warts is often associated with anal receptive intercourse, but warts in this location have been described in boys who deny this type of behavior. Occasionally, warts are seen at the urethral opening.

The posterior vaginal introitus, labia minora, and vestibule represent the most common sites of infection among female adolescents (see Figure 330-6); again, however, warts can be seen anywhere on the external or internal genitalia. Perianal warts can be seen even





**Figure 330-5** Morphology of macroscopic warts. **A**, Condylomata demonstrated by preputial retraction. **B**, Verrucous wart at penoscrotal junction. **C**, Small, flat warts (arrows) on distal third of penis. (From Katelaris PM, Cossart YE, Rose BR, et al. *Human papilloma virus: the untreated male reservoir*. J Urol. 1988;140:300–305. Copyright © 1988, Elsevier, with permission.)



**Figure 330-6** Condyloma acuminatum of the vulva appears as a polypoid mass with a keratotic fissured and irregular surface. (From Moscicki AB. *HPV infections: an old STD revisited*. Contemp Pediatr. 1989;6:24. Reprinted by permission.)

in women who have not had anal intercourse. Subclinical disease is most likely to occur on the cervix; the relatively large transformation zone of the maturing adolescent cervix affords a hospitable site of infection for the virus. Extensive disease should raise the possibility of underlying HIV infection.

A comprehensive cervical cytology screening program using the Pap smear to detect premalignant changes in the cervix (cervical intraepithelial neoplasia, usually caused by HPV infection) is a cornerstone of cervical cancer prevention efforts in the United States. However, the natural history of cervical intraepithelial neoplasia is not well understood, and HPV infection, which is widespread in young women, generally is self-limited. These observations, in concert with the knowledge that Pap smear screening in

adolescents can lead to additional unnecessary and expensive diagnostic testing that may be associated with psychologic and physiologic morbidity, have led to changes in Pap smear guidelines. The American Congress of Obstetricians and Gynecologists now recommends that Pap smear screening should not begin until age 21, regardless of the age of first intercourse. This recommendation does not apply to women with HIV infection, who are immunosuppressed, or who have had a previous diagnosis of cervical intraepithelial neoplasia (CIN2 or CIN3), or cancer. HPV DNA testing is also not indicated in women under the age of 21; it may be used in the management of women 21 and older with the diagnosis of atypical squamous cells of undetermined origin (ASCUS) on Pap smear, but repeating the Pap smear in one year is preferable.

A variety of treatments for genital warts exist, including those applied by physicians or by the patient (see Box 330-4); treatment is primarily directed toward symptomatic warts. Physicians who choose to treat genital warts should determine which technique is most suitable to their practice and become familiar with that technique; physicians should be knowledgeable about at least 1 physician-applied and 1 patient-applied regimen. Regardless of which approach is chosen, careful follow-up (initially at 1–2 week intervals) is essential to monitor the results and to prevent regrowth between too-widely-spaced treatment intervals. The benefit of treating subclinical HPV infection in the absence of cervical dysplasia is unclear. Examination and treatment of sex partners is of uncertain benefit.

Because HPV infection is so prevalent, and because it is uncertain whether treatment reduces infectivity, current approaches to the prevention and eradication of HPV infection focus on HPV vaccines. There are now 3 HPV vaccines licensed for use in the United States for the prevention of cervical cancer: the quadrivalent (HPV4) vaccine containing virus-like particles

prepared from the recombinant L1 capsid proteins from HPV types 6, 11, 16, and 18; the bivalent (HPV2) vaccine containing virus-like particles prepared from the recombinant L1 capsid proteins from HPV types 16 and 18; and a 9-valent vaccine that offers protection against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. ACIP recommends routine vaccination of females aged 11 or 12 years with 3 doses of HPV2, HPV4, or HPV9, but the vaccination series can be started beginning at age 9. The schedule for both vaccines is the same: the second dose should be administered 1 to 2 months after the first, and the third dose is administered 6 months after the first. The minimum intervals between doses are as follows: 4 weeks between the first and second doses, 12 weeks between the second and third doses, and 24 weeks between the first and third doses. Doses administered at time intervals shorter than what is recommended should be repeated. Vaccination with any of the 3 vaccines is also recommended for adolescent and young adult women ages 13 to 26 who have not been vaccinated previously or have not received all 3 doses. Women who turn 26 before completing the series can receive the additional doses. The Advisory Committee on Immunization Practices (ACIP) recommends the HPV2, HPV4 and HPV9 vaccines for the prevention of cervical cancer. The HPV4 and HPV9 vaccines are also recommended for the prevention of genital warts.

The US Food and Drug Administration also licensed the use of the HPV4 and HPV9 vaccines in males aged 9 to 26 years. Vaccination of males with HPV4 or HPV9 vaccine is recommended for males aged 13 to 21 years who have not previously been vaccinated or have not received all 3 doses; males aged 22 to 26 years may be vaccinated. HPV vaccination (HPV4 or HPV9) is recommended through age 26 years for men who have sex with men and for individuals with HIV or other immunocompromising conditions. Recent data demonstrate that the HPV4 vaccine prevents infection with HPV-6, 11, 16, and 18 and related external genital lesions in males 16 to 26 years old.

Finally, the US Food and Drug Administration approved the use of the HPV4 and HPV9 vaccines for prevention of anal cancers and associated precancerous lesions caused by the HPV types included in the HPV4/HPV9 vaccines in male and female adolescents and young adults 9 to 26 years old.

### Herpes Genitalis

Herpes simplex viral infections of the male and female genital tract are particularly distressing to patients because of the potential for recurrence after an initial episode, especially if caused by infection with herpes simplex virus (HSV) type 2. HSV-1 and HSV-2 can cause genital tract disease; in recent years, infection with HSV-1 has accounted for an increasing proportion of genital herpes infections. In a recent study at a university health center, just under 80% of culture-positive genital herpes infections among 18- to 24-year-olds were caused by HSV-1. Although genital herpes infections were once thought to be associated with the development of cervical cancer, current evidence indicates that HSV more likely acts as a cofactor. Sero-prevalence surveys indicate that the prevalence of

HSV-2 infection among adolescents aged 14 to 19 years decreased dramatically from the early to the late 1990s, with a smaller but still significant decline for HSV-1.

Infections with the virus can be classified as primary or nonprimary. Primary infection refers to infection with HSV-1 or HSV-2 in an individual without prior antibody to either virus. Nonprimary infection occurs in those with existing antibody to either HSV-1 or HSV-2 who become infected with the other strain. This type of infection, which almost always occurs in individuals who have existing antibody to HSV-1 who then become infected with HSV-2, tends to be less symptomatic. At least 10% of individuals (but probably many more) with a first symptomatic clinical episode of genital herpes have serologic evidence of previous HSV-2 infection.

In primary infection, symptoms usually occur within 2 to 20 days after sexual exposure. The patient experiences burning or itching at the site of inoculation, followed by erythema and the development of discrete vesicles. Initially, the vesicles contain clear fluid, but they rapidly form pustules with an erythematous base. Typically, a patient may have 15 to 30 vesicles, each full of infectious viral particles. Lesions are located on the vulva, cervix, clitoris, or perineum (see Figure 330-7). In male adolescents, they may occur on the penile shaft, glans, or prepuce (see Figure 330-8). Infection also can involve the urethra, leading to dysuria or urinary retention. Vesicles can be seen on the thighs, buttocks, groin, or perianal region as a result of autoinoculation or anal receptive intercourse. Because primary infection represents the first episode of infection with the particular virus type, systemic symptoms such as fever, malaise, and headache are common. Approximately 50% of patients have tender inguinal lymphadenopathy.

After 2 to 4 days, the pustules break open and coalesce to form wet ulcers. This event is usually when patients seek health care. New lesions still may be developing at this point (with a peak at 7–11 days), but within 20 days, all the lesions have crusted over, and the pain and other symptoms have disappeared. The lesions generally heal without scarring.

The diagnosis of herpes genitalis is made most often on clinical grounds. Cell culture and polymerase chain reaction (PCR) testing are the preferred tests for detection of HSV infection. The sensitivity of culture declines as lesions begin to heal and is low for recurrent lesions. PCR assays are more sensitive than culture, but a negative culture or PCR test does not exclude herpes infection. Because recurrence rates for genital HSV-1 and HSV-2 differ significantly, testing should be performed whenever a patient presents with new-onset genital herpes.

After the infection resolves, the virus remains latent in the sacral ganglia and may reactivate at any time. This reactivation is referred to as *recurrent disease*. Recurrences may occur in association with stress, local trauma, fever, or menstruation and tend to be shorter and less symptomatic. Vesicles usually occur near the initial infection site but tend to be fewer in number. Just before the recurrence, the patient may experience burning or itching at the site of infection. Healing takes place within 1 to 2 weeks.

Female adolescents whose only site of recurrence involves the cervix may be unaware of it, although





**Figure 330-7** Genital herpes of the vulva. (From Holmes K, et al, eds. Sexually Transmitted Diseases. 3rd ed. New York: McGraw-Hill; 1999. Reprinted by permission from McGraw-Hill Education.)



**Figure 330-8** In herpes genitalis, the blisters break, leaving tender ulcers that may take 2 to 4 weeks to heal the first time they occur. (Courtesy Red Book Online. [redbook.solutions.aap.org](http://redbook.solutions.aap.org))

they are shedding the virus. Approximately one-third of male adolescents also may have unapparent recurrences but are still infectious. Asymptomatic reactivation is most likely to happen within 6 months after the initial infection. Hence, unless sex partners reveal their history of infection, many exposures can occur without an individual being aware that contact with the virus has been made. Many HSV-seropositive patients who deny a history of genital herpes actually have lesions that they fail to recognize as herpes. Nevertheless, they are capable of infecting their sex partners. A recent study demonstrated that asymptomatic genital shedding of HSV-2 occurred on 26% of days in the first year following the initial episode, on 13% of days in years 1 to 9, and on 9% of days after 10 or more years had elapsed.

In the year after a first documented episode of genital HSV-2 infection, 90% of individuals will

have at least 1 recurrence; approximately one-third will have 6 or more, and one-fifth will have 10 or more. The risk of recurrence depends on many factors. Male adolescents are somewhat more likely to have recurrent disease, as are those whose infection was caused by HSV-2. Once a second episode occurs, the patient is likely to have multiple recurrences.

Development of antiviral drugs such as acyclovir, famciclovir, and valacyclovir has dramatically altered the nature of herpes therapy. These agents greatly reduce the symptoms associated with primary episodes of genital herpes and decrease the duration of virus shedding and the time to resolution of lesions (see Box 330-4). Some patients with recurrent disease may derive benefit from therapy if the medication can be initiated during the prodrome or within 1 day after onset of lesions. Those who have 6 or more recurrences per year have a 75% reduction in recurrences with daily suppressive therapy (see Box 330-4). Patient-initiated administration of a single-day course of famciclovir also shortens the duration of recurrences. Valacyclovir reduces asymptomatic virus shedding and reduces the risk of infection in couples serodiscordant for HSV-2. A successful HSV vaccine has been elusive.

### Syphilis

Rates of primary and secondary syphilis decreased by 90% from 1990 to 2000, reaching a low of 2.1 cases per 100,000 people in 2000. Since then, rates have increased steadily (reaching 6.3 cases per 100,000 people in 2014). Among 15- to 24-year-olds, rates of infection increased between 2005 and 2009 among white, black, and Hispanic males and among white and black females. Since 2000, the largest increase has been among men who have sex with men. Syphilis remains a significant problem in the South and in some urban areas.

The typical chancre of syphilis develops at the site of intimate sexual contact approximately 2 to 3 weeks after exposure to an infected individual. This lesion, which varies in size from a few millimeters to a few centimeters, is painless, has a clean base, and has sharply demarcated, indurated borders. Multiple ulcers may be present. Lymphadenopathy is usually present, often bilaterally. Because the ulcer is painless, its appearance in the vagina or rectum or even in the mouth is likely to go unnoticed. While the ulcer is present, the exudate overlying it is highly infectious. Untreated, the chancre disappears in 3 to 6 weeks.

The rash of secondary syphilis appears 4 to 10 weeks after the chancre appears in the untreated patient. Hence, the rash and the chancre may coexist. Because the spirochetes spread hematogenously from the site of initial infection, constitutional symptoms such as fever, malaise, sore throat, and generalized lymphadenopathy may be present.

The rash is typically papulosquamous but can be macular or pustular. Initially, it involves the trunk and flexor surfaces of the arms but then spreads to the entire body, including the palms, soles, and mucous membranes (see Figure 330-9). Physicians should



**Figure 330-9** A 16-year-old girl with the rash of secondary syphilis. The signs and symptoms of secondary syphilis generally occur 6 to 8 weeks after the primary infection, when primary lesions are healed. (Courtesy Red Book Online. [redbook.solutions.aap.org](http://redbook.solutions.aap.org))

strongly consider screening any sexually active adolescent with a generalized eruption (eg, that seen with pityriasis rosea) for syphilis. Annular papules can appear on the face, and the rash can resemble impetigo or eczema. In some cases, moist, fissured papules or raised, thickened papules (condyloma lata) are seen; both are highly infectious. Finally, loss of scalp or eyebrow hair can be associated with secondary syphilis. The rash disappears spontaneously 3 to 12 weeks after its appearance; at this point, the patient is classified as having latent syphilis.

At the time the chancre is present, a dark-field examination of the nonbloody exudate should be performed by an expert in dark-field microscopy. If performed on 3 successive days, the likelihood of obtaining a positive result from an infected individual is extremely high. If the results of all 3 examinations are negative, then the diagnosis of primary syphilis should be reconsidered. If the dark-field examination is unavailable, then a serologic test for syphilis should be performed. Currently, there are 2 types of serologic tests for syphilis: nontreponemal (Venereal Disease Research Laboratory [VDRL] and RPR) and treponemal (eg, fluorescent treponemal antibody absorbed [FTA-ABS]); some laboratories are now performing initial screening of samples using a treponemal test rather than the traditional method of performing the nontreponemal test first. Using only 1 type of test is insufficient for making the diagnosis, because both tests have limitations. For example, false-positive nontreponemal test results may be obtained in individuals with autoimmune disorders. However, because all the symptoms of syphilis may not be consistently present in everyone infected, most adolescents infected with syphilis will be identified only through routine serologic screening; therefore, testing at-risk youth is important.

Criteria for determining the stage of infection (primary versus secondary syphilis), recommended CDC treatment guidelines for each stage, and guidelines for appropriate follow-up testing are outlined in Box 330-4. All patients with syphilis should be screened for HIV infection.

### ***Mycoplasma genitalium* and *Ureaplasma urealyticum***

The role of *Mycoplasma genitalium* and *Ureaplasma* species in causing disease continues to evolve. *M. genitalium* causes 15% to 20% of nongonococcal urethritis (NGU), 20% to 25% of nonchlamydial NGU, and approximately 30% of persistent or recurrent urethritis. In most settings, infection with *M. genitalium* is more common than with *N. gonorrhoeae* but less common than with *C. trachomatis*. Its role in female reproductive tract disease is less clear. *M. genitalium* can be found in the vagina, cervix, and endometrium, and infections in women are commonly asymptomatic. The organism can be found in 10% to 30% of women with clinical cervicitis, and most studies have found that it is more common in women with cervicitis compared to those without. *M. genitalium* is found in the cervix and/or endometrium of women with PID more often than in women without. It has been detected in 2% to 22% of PID cases, but the frequency with which *M. genitalium*-infected women develop PID is unclear. Overall, evidence suggests that *M. genitalium* can cause PID but this occurs less often than with *C. trachomatis*. The 7-day doxycycline treatment regimen for urethritis is largely ineffective to treat *M. genitalium*. One gram by mouth of azithromycin is effective, but resistance is rapidly emerging. A longer course of azithromycin (500 mg on day 1 followed by 250 mg daily for 4 days) may be marginally more effective, but people who failed the 1 g course generally do not respond to a longer course. Moxifloxacin (400 mg daily for 7, 10, or 14 days) has been successfully used to treat men and women with previous treatment failures, but the drug has not been tested in clinical trials.

*Ureaplasma* species have now been differentiated into *U. urealyticum* (UU) and *U. parvum* (UP). Recent studies suggest that UU (but not UP) causes urethritis, which may explain why previous studies examining the role of *Ureaplasma* species as a cause of urethritis have been conflicting.

## **SYNDROMES ASSOCIATED WITH SEXUALLY TRANSMITTED INFECTIONS**

### **Pelvic Inflammatory Disease**

Pelvic inflammatory disease refers to infection involving the upper genital tract (uterus, fallopian tubes, ovaries, and pelvis) of women; it often occurs as a result of undetected or inadequately treated STIs of the lower genital tract (endocervix). In the short term, PID can lead to such problems as a tubo-ovarian abscess. In the long run, infertility, chronic pelvic pain, and increased risk for ectopic pregnancy are attributable to this condition, even when the acute episode has been managed appropriately. Among all sexually active girls and women, teenagers younger than 19 years are at greatest risk for contracting this disease; the risk is 1:8 for sexually active 15-year-olds and 1:16 for 16-year-olds, but only 1:80 for 24-year-olds. Because a major risk factor for developing PID is a prior episode, adolescent girls who experience this illness early in their reproductive life cycle are at great risk for having further significant problems.



Even though the condition is common, the diagnosis of PID is imprecise. Studies have shown that clinical diagnosis of PID has a positive predictive value for salpingitis of 65% to 90%, with the positive predictive value being higher for adolescents and in clinical settings in which the prevalence of STIs such as chlamydia or gonorrhea is high. Signs and symptoms can be nonspecific, and the only sure method for diagnosis, laparoscopy, is not routinely performed for diagnostic purposes in the United States. Physicians must therefore maintain a high index of suspicion, obtain an extensive history, and perform a thorough physical examination to avoid a misdiagnosis.

When eliciting a history from a patient who has lower abdominal pain, the physician should keep in mind specific factors that place an individual at risk for infection. Failure to use barrier methods of contraception, douching, the presence of a newly inserted intrauterine device, multiple partners, a recent change in partner, or history of other STIs or PID should raise concern. The presence of a new vaginal discharge (or a change in odor, color, or amount), abnormal menstrual bleeding (increased or prolonged; occurring at the wrong time in the cycle), or dyspareunia are all suggestive of PID. Other symptoms include dysuria, dysmenorrhea (usually more severe than normal), nausea, vomiting, diarrhea, fever, and malaise. Except for dysmenorrhea, these symptoms also can be seen in patients who have diseases of the urinary tract (eg, pyelonephritis) or gastrointestinal tract (eg, appendicitis).

Depending on the extent of upper genital tract involvement, physical signs may include pain on movement of the cervix and endometrial or adnexal tenderness, or both. Fever is present in less than 50% of patients who have documented PID. If the infection has spread to involve the capsule of the liver, right upper quadrant tenderness also may be elicited. With extensive infection, signs of peritonitis, particularly rebound tenderness, are present. The palpation of an adnexal mass raises the concern of a coexisting tubo-ovarian abscess. Mucopus visible in the cervical os strongly suggests the presence of infection, but its absence does not rule out the diagnosis. Acute-phase reactants lack the necessary sensitivity and specificity to be helpful in establishing the diagnosis of PID. Although 60% to 80% of patients have an increased WBC count, sedimentation rate, or C-reactive protein, so do 20% to 50% of patients with abdominal pain who do not have PID. Estimates suggest that up to 60% of cases of PID are subclinical.

The CDC's 2015 sexually transmitted disease treatment guidelines recommend that treatment of PID be initiated in sexually active young women if "they are experiencing pelvic or lower abdominal pain, if no cause for the illness other than PID can be identified, and if 1 or more of the following minimum criteria are present on pelvic examination: cervical motion tenderness OR uterine tenderness OR adnexal tenderness." Other supportive criteria for PID are listed in Box 330-5. The physician should take particular note that certain surgical emergency conditions can mimic PID. Hence, the differential diagnosis, as outlined in Box 330-6, should be kept in mind. Because many teenagers at risk for PID are similarly at risk for pregnancy, and

because ectopic pregnancy can mimic PID, a urine or serum pregnancy test should be routinely obtained at the time of evaluation. If an adnexal mass is palpated or suspected, then an ultrasound should be obtained to determine whether a tubo-ovarian abscess is present. Testing for *C trachomatis* and *N gonorrhoeae* should occur routinely.

Treatment is directed toward eradicating the organism responsible for the infection. Unfortunately, the exact nature of the infection is established with great difficulty. Test results obtained from cervical specimens do not necessarily reflect the nature of the endometrial or tubal infection. Many organisms thought to play a role in PID are difficult to grow in culture; thus, studies that do not use state-of-the-art culture techniques may not identify all relevant organisms. Studies that have been performed emphasize the polymicrobial nature of the infection. *N gonorrhoeae*, *C trachomatis*, or both are recovered from approximately 25% to 75% of adolescents and young adults with PID. Facultative and anaerobic bacteria, as well as organisms associated with bacterial vaginosis, have been recovered from various points in the upper genital tract of women who have PID.

As a result of the uncertainty concerning the nature of the infecting organisms, the CDC treatment regimens outlined in Box 330-4 reflect empirical therapy based on the assumption that the infection is polymicrobial. If outpatient therapy is to be attempted, careful follow-up at 48 hours must be ensured, and a mechanism for hospitalizing the patient before that time if symptoms worsen must be in place.

Once therapy is initiated, the patient should improve within 48 to 72 hours. Failure to see improvement should raise concerns about the accuracy of the diagnosis or the presence of complications; reassessment of the initial antimicrobial regimen should also occur. Additional diagnostic testing (eg, diagnostic laparoscopy) should also be considered. Approximately 10% to 20% of patients who have PID develop a tubo-ovarian abscess; 3% to 15% of these abscesses rupture. Depending on the experience of the physician, consultation with a gynecologist should be considered if an abscess is detected or if the patient fails to improve. Consultation with a surgeon is recommended if concern exists that the patient has appendicitis.

If hospitalized (see Box 330-7), the patient may be switched to oral therapy 24 to 48 hours after she demonstrates substantial clinical improvement. Treatment must include a total of 14 days of therapy with doxycycline (or other suitable oral regimens), and follow-up at completion of treatment is essential. The patient should be instructed not to have intercourse until her therapy is completed and her partner is notified and treated. Because an episode of PID is a major risk factor for development of a second episode, the use of barrier methods of contraception must be stressed to the patient.

Even with optimal diagnosis and treatment, the long-term morbidity from a single episode of PID can be significant. Long-term complications include tubal factor infertility, increased risk for ectopic pregnancy, and chronic pelvic pain.

**BOX 330-5 Diagnostic Considerations of Pelvic Inflammatory Disease**

Acute pelvic inflammatory disease (PID) is difficult to diagnose because of the wide variation in the symptoms and signs. Many women with PID have subtle or mild symptoms that do not readily indicate PID. Consequently, delay in diagnosis and effective treatment probably contributes to inflammatory sequelae in the upper reproductive tract. Laparoscopy can be performed to obtain a more accurate diagnosis of salpingitis and a more complete bacteriologic diagnosis. However, in many instances, this diagnostic tool is not readily available for acute cases, and its use is not easy to justify when symptoms are mild or vague. Moreover, laparoscopy will not detect endometritis and may not detect subtle inflammation of the fallopian tubes. Consequently, a diagnosis of PID is usually based on clinical findings.

The clinical diagnosis of acute PID is imprecise. Data indicate that a clinical diagnosis of symptomatic PID has a positive predictive value of 65% to 90% for salpingitis in comparison with laparoscopy. The positive predictive value of a clinical diagnosis of acute PID differs depending on epidemiologic characteristics and the clinical setting, with higher positive predictive value among sexually active young (especially adolescent) women, among patients attending sexually transmitted disease clinics, or in settings in which rates of gonorrhea or chlamydia are high. In all settings, however, no single historical, physical, or laboratory finding is both sensitive and specific for the diagnosis of acute PID (ie, can be used both to detect all cases of PID and to exclude all women without PID). Combinations of diagnostic findings that improve either sensitivity or specificity do so only at the expense of the other. For example, requiring 2 or more findings excludes more women who do not have PID but also reduces the number of women with PID who are identified.

Many episodes of PID go unrecognized. Although some cases are asymptomatic, others are undiagnosed because the patient or the primary care physician fails to recognize the implications of mild or nonspecific symptoms or signs (eg, abnormal bleeding, dyspareunia,

vaginal discharge). Because of the difficulty of diagnosis and the potential for damage to the reproductive health of women, even by apparently mild or subclinical PID, primary care physicians should maintain a low threshold for the diagnosis of PID. The optimal treatment regimen and long-term outcome for women with asymptomatic or subclinical PID are unknown. The following suggestions for diagnosing PID are intended to help primary care physicians recognize when PID should be suspected and when they need to obtain additional information to increase diagnostic certainty. These suggestions are based partially on the fact that diagnosis and management of other common causes of lower abdominal pain (eg, ectopic pregnancy, acute appendicitis, functional pain) are unlikely to be impaired by initiating empiric antimicrobial therapy for PID.

Empiric treatment of PID should be initiated in sexually active young women and others at risk for sexually transmitted diseases if they are experiencing pelvic or lower abdominal pain, if no other cause for the illness other than PID can be identified, and if 1 or more of the following minimal criteria are present on pelvic examination: cervical motion tenderness or uterine tenderness or adnexal tenderness. Requiring that all 3 of the minimal criteria listed previously be present before initiating antibiotic treatment might result in insufficient sensitivity for diagnosing PID.

More elaborate diagnostic evaluation is often needed, because incorrect diagnosis and management might cause unnecessary morbidity. Additional criteria that can be used to enhance the specificity of the minimal criteria and support a diagnosis of PID include the following:

- Oral temperature above 101°F (38.3°C)
- Abnormal cervical or vaginal mucopurulent discharge
- Presence of abundant numbers of white blood cells on saline microscopy of vaginal secretions
- Increased erythrocyte sedimentation rate
- Increased levels of C-reactive protein
- Laboratory documentation of cervical infection with *N gonorrhoeae* or *C trachomatis*

Adapted from Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines 2015. *MMWR Recomm Rep*. 2015;64 (RR-64): 1-134. (In some cases, the author has edited the text to condense it.)

**Perihepatitis (Fitz-Hugh–Curtis Syndrome)**

Perihepatitis associated with gonococcal salpingitis was described in 1920. Subsequently, Fitz-Hugh described a patient who had *violin string* adhesions between the liver and anterior abdominal wall, and Curtis described localized peritonitis of the liver's anterior surface in a woman who had upper abdominal pain and tenderness who was undergoing laparotomy for suspected gallbladder disease. Since then, the fact that *C trachomatis* infections can cause a similar picture has been well documented.

Onset of upper abdominal pain usually follows (but can also precede) the onset of lower abdominal pain. The pain generally occurs on the patient's right side and can radiate to the shoulder. Less than 50% of

patients have mildly increased liver enzyme levels. Treatment for PID also eliminates the perihepatitis.

**Epididymitis**

Epididymitis is characterized by the acute or subacute onset of unilateral scrotal pain; adolescent boys may complain of testicular pain. Preceding symptoms include urethral discharge and dysuria, but these symptoms may be so mild that they are easily ignored. Fever may be present. At physical examination, tenderness may occur on palpation of the epididymis, but the testicle may also be slightly tender. A hydrocele may be present, and the spermatic cord may also be swollen and tender. Urethral discharge may or may not be present at the time of diagnosis.



### BOX 330-6 Differential Diagnosis of Acute Lower Abdominal Pain in Adolescent Girls by Organ System

#### URINARY TRACT

- Cystitis
- Pyelonephritis
- Urethritis
- Other

#### GASTROINTESTINAL TRACT

- Appendicitis
- Constipation
- Diverticulitis
- Gastroenteritis
- Inflammatory bowel disease
- Irritable bowel syndrome
- Other

#### REPRODUCTIVE TRACT

- Acute pelvic inflammatory disease

- Cervicitis
- Dysmenorrhea (primary or secondary)
- Ectopic pregnancy
- Endometriosis
- Endometritis
- Mittelschmerz
- Ovarian cyst (torsion, rupture)
- Pregnancy (intrauterine, ectopic)
- Ruptured follicle
- Septic abortion
- Threatened abortion
- Torsion of adnexa
- Tubo-ovarian abscess

From Shafer M, Sweet RL. Pelvic inflammatory disease in adolescent females. *Pediatr Clin North Am*. 1989;36:513–532. Copyright © 1989, Elsevier, with permission.

Supportive laboratory evidence for the diagnosis of epididymitis includes (1) a positive leukocyte esterase test on a first-catch urine specimen (the first 20 mL of urine voided) or the presence of more than 10 WBCs per high-power field if the first-catch urine specimen is spun down and the sediment examined, or (2) Gram stain of urethral secretions showing more than 5 WBCs per oil-immersion field. If the Gram stain also shows WBCs containing intracellular gram-negative diplococci, *N gonorrhoeae* should be considered the causative agent.

In adolescents, the physician must rule out testicular torsion. Depending on the presentation and laboratory evidence, additional studies (nuclear scan or Doppler flow study) or consultation with a urologist may be necessary.

Among sexually active adolescents, acute epididymitis is most frequently caused by *N gonorrhoeae* or *C trachomatis*. Sexually transmitted enteric organisms (eg, *Escherichia coli* and *Pseudomonas* spp) may be the causative agent in male adolescents who are the insertive partner during anal sex. Patients with epididymitis should be tested for *N gonorrhoeae* and *C trachomatis*.

Most patients can be managed on an outpatient basis. Hospitalization should be considered if the pain is particularly severe (suggesting an alternate diagnosis such as torsion, testicular infarction, or abscess), when patients are febrile, or if noncompliance is of concern.

### BOX 330-7 Suggested Indications for Hospitalization of Patients With Pelvic Inflammatory Disease (PID)

In women with PID of mild or moderate clinical severity, outpatient therapy yields short- and long-term clinical outcomes similar to inpatient therapy. The decision of whether hospitalization is necessary should be based on the judgment of the primary care physician and whether the patient meets any of the following suggested criteria:

- Surgical emergencies such as appendicitis cannot be excluded
- The patient is pregnant
- The patient does not respond clinically to oral antimicrobial therapy
- The patient is unable to follow or tolerate an outpatient oral regimen
- The patient has severe illness, nausea and vomiting, or high fever
- The patient has a tubo-ovarian abscess

No evidence is available to suggest that adolescents benefit from hospitalization for treatment of PID. The decision to hospitalize adolescents with acute PID should be based on the same criteria used for older women. Younger women with mild to moderate PID have similar outcomes with either outpatient or inpatient therapy, and clinical response to outpatient therapy is similar among adolescents and older women.

At least 24 hours of direct inpatient observation is recommended for patients who have tubo-ovarian abscesses.

From Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines 2015. *MMWR Recomm Rep*. 2015;64 (RR-64): 1–134. (Most of the information contained herein is reproduced verbatim from the Treatment Guidelines. In some cases, the author has edited the text to condense it.)

Treatment of epididymitis is outlined in Box 330-4. Adolescents treated as outpatients should be followed up within 48 to 72 hours of initiating treatment. Failure to improve should prompt re-evaluation of the diagnosis and the treatment. The sex partners of adolescents with epididymitis suspected of being or confirmed to be caused by chlamydia or gonorrhea should be evaluated and treated if their contact with the index patient occurred fewer than 60 days before the onset of the patient's symptoms.

#### Enteric Infections

The syndromes of proctitis and proctocolitis are limited mostly to adolescent boys who practice anal receptive intercourse. Symptoms include anorectal pain, tenesmus, constipation, and anal discharge. Those who have proctocolitis or enteritis will have diarrhea. Patients who have proctitis (the distal 10–12 cm of the rectum) should be examined with anoscopy and evaluated for *C trachomatis* (including LGV serovars), *N gonorrhoeae*, herpes simplex, and *T pallidum* infection. Treatment should be with standard doses of ceftriaxone and doxycycline (see Box 330-4).

Patients who have symptoms suggesting proctocolitis (the symptoms of proctitis plus diarrhea or abdominal cramps) should receive more extensive evaluation. Organisms such as *E histolytica*, *Campylobacter* species, the LGV serovars of *C trachomatis*, and *Shigella* species can be sexually transmitted. HIV-infected patients may be infected with opportunistic organisms such as CMV.

Enteritis usually occurs among patients whose sexual behaviors include oral-anal contact. Symptoms are usually limited to abdominal pain and diarrhea; the other symptoms of proctitis and proctocolitis are absent. Among immunocompetent patients, *G lamblia* is the most likely organism; a variety of organisms can cause enteritis in HIV-infected patients.

### Vaginitis

As discussed in Chapter 205, Vaginal Discharge, *T vaginalis*, an important cause of vaginitis among sexually active adolescents, is a sexually transmitted infectious agent. Bacterial vaginosis, which is associated with the overgrowth of *G vaginalis*, displays some characteristics of an STI. Bacterial vaginosis is associated with having multiple sex partners, with having a new sex partner, and with douching. Male sex partners of women who have bacterial vaginosis are more likely to have *G vaginalis* recovered from the urethra than are controls. However, this same organism can be recovered from approximately 15% of women who have never been active sexually. Furthermore, treatment of male partners does not seem to influence recurrence risks for women who are treated for bacterial vaginosis.

Vaginitis in and of itself can be distressing enough. However, current concerns about bacterial vaginosis center on its possible role in the pathogenesis of PID. Nongonococcal, nonchlamydial pathogens associated with PID are recovered more often from the endometrium of women who have bacterial vaginosis than from those who do not. Bacterial vaginosis has been causally related to postpartum endometritis. Thus, treatment of symptomatic women who have bacterial vaginosis is warranted; asymptomatic women who are scheduled to undergo abortion or hysterectomy should also be treated.

### Cervicitis

Cervicitis is characterized by a purulent or mucopurulent discharge from the endocervical os or by significant endocervical bleeding (or both) that is induced when a swab is introduced into the os. It may be detected during a routine pelvic examination even if an adolescent has no genital complaints.

Both *C trachomatis* and *N gonorrhoeae* can cause cervicitis (an association that is stronger in women younger than 25 years), as can *Trichomonas* and HSV, especially HSV-2. *M genitalium*, bacterial vaginosis, and frequent douching may cause cervicitis. However, in most cases of cervicitis, no etiologic agent is identified.

Women with cervicitis should be carefully evaluated for PID and for the presence of trichomonas and bacterial vaginosis; they should also be tested for chlamydia and gonorrhea. Women with cervicitis who are 25 years or younger, who engage in unprotected sex, or who have a new sex partner, a sex partner with

concurrent partners, or a sex partner with an STI should be presumptively treated for *C trachomatis* and *N gonorrhoeae* (see Box 330-4), especially if follow-up is uncertain or if the physician does not have access to NAAT. Sex partners should be identified, evaluated, and treated, depending on the characteristics of the index patient. A follow-up visit should be scheduled to determine if the cervicitis has resolved. According to the 2015 CDC guidelines, “Women with persistent or recurrent cervicitis despite appropriate treatment should be evaluated for possible re-exposure or treatment failure.” Management options for persistent cervicitis are undefined and whether repeat or prolonged antibiotic regimens are effective is not known.

### Urethritis

All adolescent and young adult males with suspected or confirmed urethritis should be tested for gonorrhea and chlamydia and treated according to standard protocols (see Box 330-4). The etiology of urethritis in adolescents who test negative for gonorrhea and chlamydia with NAAT is unclear. *M genitalium* accounts for 15% to 25% of NGU in the United States. *T vaginalis*, HSV, and adenovirus can cause urethritis. NGU can be acquired through oral-penile contact; Epstein-Barr virus (EBV) can also cause urethritis. As discussed previously, the differentiation between *U urelalyticum* (which does seem to be capable of causing urethritis) and *U parvum* (which does not) may help to further clarify the etiology of nongonococcal, nonchlamydial urethritis.

The 2015 CDC guidelines state that adolescents with recurrent and persistent urethritis “should first be evaluated to make certain that they have completed a full treatment course and were not reinfected by an untreated or new sex partner.” Objective evidence of urethritis should be sought before antibiotic treatment is begun. Recent studies show that the most common cause of recurrent or persistent NGU is *M genitalium*. Men initially treated with doxycycline should be treated with 1 g of azithromycin. Those who fail a regimen of azithromycin should be treated with moxifloxacin 400 mg PO for 7 days. *T vaginalis* can cause urethritis. The 2015 CDC guidelines state that in areas where *T vaginalis* is prevalent, men who have sex with women should be treated with 2 g PO of either metronidazole or tinidazole in a single dose.

### Sexual Assault

Comprehensive assessment and management of victims of sexual assault (see also Chapter 371, Rape) should address concerns about possible exposure to STIs, including HIV; what specimens to collect and what diagnostic tests to perform should be individualized. Among female victims of sexual assault, infections with chlamydia, gonorrhea, and trichomonas are those most commonly identified; bacterial vaginosis is also commonly diagnosed. The initial examination of a sexual assault victim can include the following: NAATs for detection of *C trachomatis* and *N gonorrhoeae*; baseline testing for syphilis, hepatitis B, and HIV; and a vaginal wet prep to look for evidence of bacterial vaginosis and to obtain specimens for detection of trichomoniasis.

As follow-up with sexual assault victims is often suboptimal, preventive therapy for STIs should be encouraged. This includes empiric treatment for chlamydia, gonorrhea, and trichomonas (ceftriaxone 250 mg IM plus azithromycin 1 g PO in a single dose plus metronidazole 2 g PO in a single dose or tinidazole 2 g PO in a single dose); HPV vaccination for those who have not received any doses or have failed to complete the series; and hepatitis B vaccination with or without hepatitis B immunoglobulin depending on the vaccination status of the victim and the HBsAg status of the assailant, if known. Emergency contraception should also be offered.

Although the frequency is low, HIV seroconversion has occurred in individuals in whom the only identified risk factor was sexual assault. The nature of the assault, the infection status of the perpetrator, and genital lesions and STIs (clinically apparent or asymptomatic) in the victim all can influence the risk of transmission. If postexposure prophylaxis to prevent HIV infection is being considered, consultation with an HIV specialist is recommended.

Follow-up in 2 to 3 months is recommended to detect repeat or new infections and to monitor the serostatus of the victim if HIV or hepatitis B infection or syphilis is a concern.

### WHEN TO REFER

- If the physician is inexperienced in the diagnosis or management of: PID
  - Disseminated gonococcal arthritis
  - Syphilis (or positive VDRL, RPR or FTA-ABS test)
  - Anogenital warts
  - Genital herpes
  - Abnormal Pap smears
  - Recurrent or persistent urethritis
  - Proctitis, proctocolitis
- If postexposure prophylaxis for HIV infection is being considered in the management of a sexual assault victim
- In the case of sexual assault, survivors should be referred to a designated rape crisis center for evaluation and treatment if one is available

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Bacterial Vaginosis* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/std/BV/STDFact-Bacterial-Vaginosis.htm](http://www.cdc.gov/std/BV/STDFact-Bacterial-Vaginosis.htm))
- *Chlamydia* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/std/Chlamydia/STDFact-Chlamydia.htm](http://www.cdc.gov/std/Chlamydia/STDFact-Chlamydia.htm))
- *Deciding to Wait: Guidelines for Teens* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Genital Herpes* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/std/Herpes/STDFact-Herpes.htm](http://www.cdc.gov/std/Herpes/STDFact-Herpes.htm))
- *Genital HPV Infection* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/std/HPV/STDFact-HPV.htm](http://www.cdc.gov/std/HPV/STDFact-HPV.htm))

- *Go Ask Alice* (Web page), Columbia University ([www.goaskalice.columbia.edu](http://www.goaskalice.columbia.edu))
- *Gonorrhea* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/std/Gonorrhea/STDFact-gonorrhea.htm](http://www.cdc.gov/std/Gonorrhea/STDFact-gonorrhea.htm))
- *Hepatitis B* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/hepatitis/HBV/PDFs/HepBGeneralFactSheet.pdf](http://www.cdc.gov/hepatitis/HBV/PDFs/HepBGeneralFactSheet.pdf))
- *HPV and Men* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/std/HPV/STDFact-HPV-and-men.htm](http://www.cdc.gov/std/HPV/STDFact-HPV-and-men.htm))
- *HPV Vaccine Questions and Answers* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/std/HPV/STDFact-HPV-vaccine.htm](http://www.cdc.gov/std/HPV/STDFact-HPV-vaccine.htm))
- *Making Healthy Decisions About Sex* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Pelvic Inflammatory Disease* (fact sheet) Centers for Disease Control and Prevention ([www.cdc.gov/std/PID/STDFact-PID.htm](http://www.cdc.gov/std/PID/STDFact-PID.htm))
- *Sexually Transmitted Infections Prevention* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/sexually-transmitted/Pages/Sexually-Transmitted-Infections-Prevention.aspx](http://www.healthychildren.org/English/health-issues/conditions/sexually-transmitted/Pages/Sexually-Transmitted-Infections-Prevention.aspx))
- *Syphilis—CDC Fact Sheet*, Centers for Disease Control and Prevention ([www.cdc.gov/std/Syphilis/STDFact-Syphilis.htm](http://www.cdc.gov/std/Syphilis/STDFact-Syphilis.htm))
- *The Pelvic Exam* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Trichomoniasis* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/std/Trichomonas/STDFact-Trichomoniasis.htm](http://www.cdc.gov/std/Trichomonas/STDFact-Trichomoniasis.htm))

#### Medical Decision Support

- *HPV and HPV Vaccine—Information for Healthcare Providers* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/std/HPV/STDFact-HPV-vaccine-hcp.htm](http://www.cdc.gov/std/HPV/STDFact-HPV-vaccine-hcp.htm))
- *Sexually Transmitted Diseases* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/std/default.htm](http://www.cdc.gov/std/default.htm))
- *Sexually Transmitted Diseases 2010 Treatment Guidelines*, Centers for Disease Control and Prevention ([www.cdc.gov/std/treatment](http://www.cdc.gov/std/treatment))
- *Youth Risk Behavior Surveillance System (YRBSS)* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/HealthyYouth/yrbs/index.htm](http://www.cdc.gov/HealthyYouth/yrbs/index.htm))

#### Community Advocacy and Coordination

- *Male Latex Condoms and Sexually Transmitted Diseases* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/nchstp/od/condoms.pdf](http://www.cdc.gov/nchstp/od/condoms.pdf))

### AAP POLICY

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## Chapter 331 SINUSITIS

Tina Q. Tan, MD

Infection of the paranasal sinuses is common in children. Estimates indicate that 5% to 13% of viral upper respiratory tract infections in children are complicated by acute bacterial sinusitis. On average, children develop 5 to 10 upper respiratory tract infections yearly. The distinction between viral infections and acute bacterial sinusitis is based on the persistence and severity of upper respiratory symptoms.

### PATHOPHYSIOLOGY

The paranasal sinuses arise during fetal development as outpouchings beneath the turbinates in the nasopharynx. Only the maxillary and ethmoid sinuses are present at the time of birth. The sinuses continue to

develop and grow until adulthood (Table 331-1). The frontal sinuses develop last, appearing in most individuals after 10 years of age with continuing development through puberty. Growth may be asymmetrical, and some individuals lack one or more sinuses altogether. Various functions have been ascribed to the sinuses, but none of these have been proved. These functions include warming and humidifying inspired air, reducing the weight of the skull, providing thermal insulation to the central nervous system and sensory organs, affecting facial form, and serving as vocal resonators. Recent theories suggest that the sinuses serve as reservoirs for the production and absorption of antigens, allowing for the tolerance of infections until effective specific immunity develops.

The lining of the mucosa of the sinuses is similar to that of the nasopharynx, with pseudostratified, ciliated, columnar epithelium interspersed with goblet cells and submucosal glands. Cilia beat toward the ostium of the sinus to expel mucus and particulate matter into the nasopharynx. The ostia of the maxillary sinuses are located in the upper part of the chamber where cilia must battle gravity to clear secretions. This circumstance probably contributes to the high frequency of infection in these sinuses. Occlusion of the ostia, impairment of ciliary motility, and alterations in the consistency of mucus secretions alone or in combination can predispose the sinuses to infection.

Sinusitis occurs most often after a viral upper respiratory tract infection or as the result of nasal allergy. Inflammation and edema of the respiratory mucosa lead to obstruction of the ostium. Pressure changes in the sinus that result from occlusion or from blowing and sniffing through the nose allow bacteria to invade the normally sterile sinus cavity. Other disorders associated with sinusitis in children are listed in Box 331-1.

Respiratory viruses such as adenoviruses, influenza viruses, parainfluenza viruses, and rhinoviruses contribute to the development of sinusitis. The most common bacterial pathogens associated with acute sinusitis are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. *Staphylococcus aureus* and anaerobes are prevalent in chronic sinusitis, and *Streptococcus pyogenes* (group A *Streptococcus*) may be associated with both acute and chronic disease. Other organisms that may be found in patients with chronic sinusitis and those with altered immunity, particularly in those patients with cystic fibrosis, include gram-negative enteric organisms (eg, *Pseudomonas* species, *Escherichia coli*, *Proteus mirabilis*, *Klebsiella* species, and *Enterobacter* species), fungal pathogens, and anaerobes.

### CLINICAL PRESENTATION AND DIAGNOSIS

Sinusitis is primarily a clinical diagnosis, and differentiating upper respiratory tract infections or allergic rhinitis from acute sinusitis can be difficult in children. Most uncomplicated upper respiratory tract infections improve after 5 to 7 days. Symptoms that persist without improvement for more than 10 days suggest



**Table 331-1 Sinus Development**

SINUS	FIRST APPEARANCE	SIZE (mL)				AGE OF CLINICAL IMPORTANCE
		BIRTH	3 YEARS	10 YEARS	14 YEARS	
Maxillary	3 wk of fetal life	0.13	2.5	10.4	11.6	Birth
Ethmoid	6 mo of fetal life	0.06	0.16	2.4	4.8	Birth
Sphenoid	3 mo of fetal life	0.02	0.68	1.8	2.1	5 yr
Frontal	1 yr of life	—	0.08	1.0	3.6	10–12 yr

Modified from Schaeffer JP. *The Embryology, Development and Anatomy of the Nose, Paranasal Sinuses, Nasolacrimal Passageways and Olfactory Organ in Man*. Philadelphia, PA: Blakiston; 1920.

### BOX 331-1 Disorders Associated With Paranasal Sinusitis

#### ANATOMIC

- Nasal malformations
- Nasal trauma
- Tumors and polyps
- Cleft palate
- Foreign bodies
- Dental infection
- Cyanotic congenital heart disease

#### PHYSIOLOGIC BAROTRAUMA

#### ABNORMALITIES OF LOCAL DEFENSE MECHANISMS

- Allergy
- Cystic fibrosis
- Immotile-cilia syndrome and Kartagener syndrome

#### ABNORMALITIES OF SYSTEMIC DEFENSE MECHANISMS

- Primary immunodeficiency
- Secondary immunodeficiency

From Shurin PA. Etiology and antimicrobial therapy of paranasal sinusitis in children. *Ann Otol Rhinol Laryngol Suppl*. 1981;90(3Pt3):72–74. Reprinted by permission of Annals Publishing Co.

bacterial superinfection, and a diagnosis of acute sinusitis can be made. A similar history persisting for more than 30 days is consistent with both subacute or chronic sinusitis. Regardless of duration, cough, nasal discharge, and nasal congestion are the most common clinical manifestations of acute sinusitis. The cough occurs during the day and is often worse at night or when the child is supine. Nasal discharge may be clear or purulent. Parents of young children may report fetid breath. Headache and facial pain are manifestations of acute sinusitis that are uncommon in children. Painless swelling of the periorbital tissues without erythema, usually in the morning, is an occasional manifestation of sinusitis that may be confused with periorbital cellulitis in its early stage. The diagnosis of acute sinusitis may also be made in a patient with a significant worsening course of signs and symptoms

(worsening or new onset of nasal discharge, nasal congestion, daytime cough, or fever after initial improvement), often beginning on day 6 or 7 of illness after initial signs of improvement from an uncomplicated viral upper respiratory tract infection. A less common presentation of acute sinusitis is an unusually severe upper respiratory tract infection. In most cases of viral upper respiratory infection, fever precedes the onset of watery nasal discharge and is associated with constitutional symptoms. Thickening of nasal secretions occurs later in the course, before resolution. A high fever and purulent discharge that coexist for 3 or more days suggest the diagnosis of acute sinusitis.

On physical examination, the nasal mucosa is usually erythematous and swollen but may be pale and boggy. Mucopurulent material can sometimes be seen in the nose or draining into the nasopharynx. The presence of a foreign body in the nose must be ruled out. Palpation or percussion over the sinuses may elicit tenderness. Periorbital edema and mild discoloration of the skin below the eyelids is occasionally seen.

Routine use of radiographs to confirm the diagnosis of uncomplicated sinusitis is not recommended in young children, but may be useful in children older than 6 years of age when the diagnosis is in question or there is a poor response to treatment. In a patient with clinical signs and symptoms suggestive of acute sinusitis, bacteria are present in a sinus aspirate 75% of the time when maxillary sinus roentgenograms show air-fluid levels, complete opacification, or mucosal thickening of at least 4 to 5 mm. Cysts and polyps also may be seen on sinus roentgenograms.

Computed tomography (CT) imaging of the sinuses with pediatric windows should be reserved for patients who have frequent recurrences or persistent symptoms that are not improving, those who have complicated sinusitis accompanied by orbital or intracranial complications, and those for whom sinus surgery is being contemplated.

Transnasal aspiration of the maxillary sinuses can be performed by an otolaryngologist for diagnostic purposes in specific situations. Nasopharyngeal culture results correlate poorly with sinus culture results. Sinus aspiration and lavage are indicated only in children who fail to respond to conventional antibiotic therapy, in immunosuppressed patients, and in those whose illness is severe or life-threatening.

## COMPLICATIONS

Complications of sinusitis are most often caused by local extension of the disease. Orbital cellulitis is the most common serious complication of sinusitis. The ethmoid sinus is separated from the orbit by the thin lamina papyracea. Erosion of this bone leads to invasion of the orbit by bacterial pathogens. The eyelids appear intensely red and swollen on physical examination. Fever, malaise, and an increased white blood cell count are present. Orbital pain, proptosis, and limitation of eye movement (ophthalmoplegia) help distinguish this condition from preseptal (periorbital) cellulitis, although CT scanning may be needed to differentiate the 2 conditions. Treatment of orbital cellulitis involves parenteral antibiotics; an ophthalmologist and an otolaryngologist should be consulted to determine whether surgical drainage is indicated (see Chapter 319, Preseptal and Orbital Cellulitis). This complication has been reported most often in male adolescents who, in many cases, lack the common symptoms of sinusitis. However, more recent reports have shown a shift in the occurrence of orbital cellulitis toward a younger population, including infants. The reasons for this shift are unclear.

Intracranial infection, most commonly subdural empyema, is the second most common complication of sinusitis. Infection can occur by direct extension through necrotic bone or by bacterial spread through the venous system. The frontal sinuses are involved most often. These sinuses are the last to develop, appearing in most individuals by 10 years of age and continuing to develop during puberty; therefore, the peak age of incidence of this complication is between 10 and 20 years, although it can develop in younger children. Patients have a low-grade fever, malaise, and a frontal headache. Vomiting and a decreased level of consciousness appear as the disease progresses.

If a patient is thought to have an intracranial abscess, then a head CT scan with contrast should be obtained. Lumbar puncture should be avoided until intracranial mass effect has been ruled out. Treatment with high-dose parenteral antibiotics and neurosurgery to drain the abscess and to debride necrotic bone are required. Steroids and hypertonic agents, such as mannitol or glycerol, may be necessary to control intracranial hypertension.

Other, less common complications of sinusitis in children include meningitis, osteomyelitis of the frontal bone (*Pott's puffy tumor*), epidural abscess, and cavernous sinus thrombosis.

## TREATMENT

Treatment of sinusitis in children involves antibiotic therapy, symptomatic relief measures, and drainage, if necessary. Amoxicillin is an appropriate initial choice for treating uncomplicated sinusitis in geographic areas where the prevalence of  $\beta$ -lactamase-producing strains of *H influenzae* and *M catarrhalis* is low. In communities with a high prevalence of nonsusceptible *Streptococcus pneumoniae* (>10%, including intermediate- and high-level resistance attributable to altered penicillin-binding proteins), higher-dose amoxicillin

(80–90 mg/kg/day in 2 divided doses, with a maximum of 2 g per dose) should be considered. Macrolide antibiotics are an option for children allergic to amoxicillin or other  $\beta$ -lactam antibiotics. Broader coverage with amoxicillin plus clavulanate, a carbacephem, a third-generation cephalosporin, or a quinolone should be considered for children who fail to respond to amoxicillin. These alternatives also should be considered for the child who has been treated recently with amoxicillin, has frontal or sphenoid sinusitis, has complicated ethmoid sinusitis, or has very protracted symptoms. Clinical improvement should be expected within 48 hours, and a minimum of 10 days of antibiotic therapy usually is adequate. If symptoms fail to resolve completely within 10 days, then patients should be treated for an additional 7 days beyond the resolution of symptoms.

Decongestants, antihistamines, and saline nose drops have been recommended to help drain the sinuses, but no proof of the efficacy of these agents exists. Intranasal steroids may provide some benefit, particularly in the second week of therapy, but further research is necessary to clarify the value of such treatment.

In unusually severe cases, hospitalization and parenteral antibiotics may be required and otolaryngologic consultation is indicated. Some experts recommend antibiotic prophylaxis for the child who has recurrent sinusitis and no underlying disorder, although no scientific studies support this practice, and it may lead to the rapid development of antibiotic resistance. Surgery may be required in cases of medically recalcitrant severe chronic sinusitis in children.

## Recurrent Sinusitis

Children who have more than 2 to 3 episodes of acute bacterial sinusitis per year should receive evaluation for underlying conditions that can lead to this clinical pattern. The first step is a screening evaluation for allergic rhinitis. If this yields positive results, aggressive environmental controls and medication to reduce allergic inflammation (eg, montelukast, nasal antihistamines, or nasal steroids) should be instituted. If problems persist, the next step is to assess anatomy and to exclude a subtle presentation of chronic infection. A low-radiation limited sinus CT (eg, MiniCAT) can provide a quick, noninvasive, sensitive, and safe evaluation compared to rhinoscopy, plain radiographs, or traditional sinus CT. A positive study can help direct appropriate sinus lavage and define suboptimal sinus ostial anatomy. A poor clinical course despite assessment and treatment of allergic rhinitis and surgical intervention should raise concerns about a humoral immunodeficiency. This is particularly true if the child also has recurrent otitis media, bronchitis, and pneumonia.

Baseline screening evaluation includes quantitative immunoglobulins (IgG, IgA, IgM, IgE), CBC with differential, and CH50. Secondary tests include assessment of response to relevant specific antigens (eg, unconjugated pneumococcal vaccine). Such testing may uncover a child who would benefit from intravenous or subcutaneous gammaglobulin.

## ACKNOWLEDGMENT

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## TOOLS FOR PRACTICE

### Engaging Patients and Family

- *Sinuses, Sinusitis, Rhinosinusitis* (fact sheet), American Academy of Allergy, Asthma, and Immunology ([www.aaaai.org/conditions-and-treatments/conditions-a-to-z-search/sinuses,-sinusitis,-rhinosinusitis.aspx](http://www.aaaai.org/conditions-and-treatments/conditions-a-to-z-search/sinuses,-sinusitis,-rhinosinusitis.aspx))
- *Sinusitis and Your Child* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *What Is a Pediatric Allergist/Immunologist?* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

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Wald ER, Applegate KE, Bordley C, et al. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. *Pediatrics*. 2013;132(1):e262–e280 ([pediatrics.aappublications.org/content/132/1/e262](http://pediatrics.aappublications.org/content/132/1/e262))

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## Chapter 332 SPINA BIFIDA

Amy Houtrow, MD, PhD, MPH

## DEFINITION

Spina bifida is the most common type of neural tube defect. The term *spina bifida* refers to splitting of the vertebral arches. This split may be associated with protrusion of the meningeal sac, which may also include portions of the spinal cord or spinal nerves. When the split of the vertebral arches is isolated, the condition is called *spina bifida occulta*. Nearly one-fourth of the population has abnormalities of the posterior arches that are benign and without symptoms. When the meningeal sac protrudes between the split vertebral arches, the condition is called *meningocele*. When the meningeal sac also contains portions of the spinal cord or spinal nerves, the condition is called *myelomeningocele*. Frequently, physicians use the term *myelomeningocele* interchangeably with the term *spina bifida*. In this chapter, the term *spina bifida* will be used to describe the broad category of

conditions that includes the focus of this chapter: *myelomeningocele*.

## EPIDEMIOLOGY

Myelomeningocele is a complex congenital malformation with an incidence of 0.4 to 0.8 per 1,000 live births. The incidence of myelomeningocele and other neural tube defects is decreasing. Improved prepregnancy nutrition, including folic acid supplementation and fortification, and the establishment of prenatal diagnosis with elective termination have led to the decreasing incidence. The incidence is higher among girls, infants born in households with low socioeconomic status, and families of Hispanic, English, Irish, or Welsh descent. While the incidence is decreasing, the survivability is increasing because of improved medical and surgical care.

## ETIOLOGY AND RISK FACTORS

The etiology of myelomeningocele is unclear. The primary mechanism seems to be the faulty closure of the neural groove in the first 28 days of gestation. By this point in gestation, the neural tube that eventually becomes the spinal cord and vertebral arches is formed. Incomplete closure of the neural tube leads to myelomeningocele or other types of neural tube defects. This primary defect is often associated with the postembryonic development of hindbrain herniation (Chiari II malformation) and hydrocephalus, which can progress during fetal and postfetal development. The proposed mechanism of action is that a decrease in fourth ventricular pressure from cerebral spinal fluid leakage at the myelomeningocele site leads to limited expansion of the posterior fossa, which remains low; then as the hindbrain develops, the posterior fossa cannot accommodate this growth, leading to herniation. The subsequent lack of cerebral spinal fluid flow leads to hydrocephalus. The Chiari II malformation is present in a vast majority of individuals with myelomeningocele, and hydrocephalus is noted in most.

Both genetic and environmental factors influence neural tube closure. For example, abnormalities of the 5,10-methylene tetrahydrofolate reductase enzyme, which is involved in the metabolism of folic acid, predisposes individuals to spina bifida. There are other candidate genes being studied, but in total, the candidate genes only account for a small percentage of spina bifida cases. The current etiologic hypothesis is that spina bifida is the result of an interaction of multiple genes that are modifiable by environmental factors. This explains why only a small percentage of families who have a child with spina bifida have another affected child. However, an affected individual, their siblings, and their parents all have an increased risk for having a baby with spina bifida. The estimated recurrence risk for parents who have a child with spina bifida is 6.3%. Other risk factors include maternal exposure to hyperthermia, ethanol, valproic acid, carbamazepine, and isotretinoin. In addition, mothers with diabetes, obesity, or malnutrition have an increased risk for having a baby with neural tube defects. Myelomeningocele is also sometimes associated with other midline congenital defects and

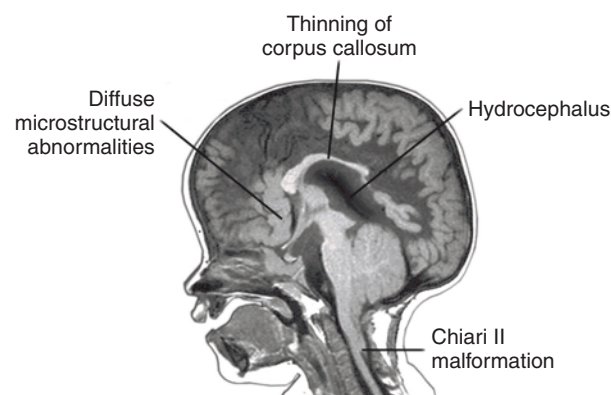


chromosomal aberrations such as cri du chat syndrome and trisomy 13 and 18.

## DIAGNOSIS

Prenatally, the diagnosis of myelomeningocele is suspected when the  $\alpha$ -fetoprotein (AFP) level is high on prenatal triple or quadruple screening. AFP is found in the fetal spinal cord, spinal fluid, and brain. In the presence of an open neural tube defect, the AFP is detectable in the maternal circulation. If the maternal AFP level is high, an ultrasound should be conducted to identify specific abnormalities of the fetal head and spinal column. Cranial findings include a concave shape of the frontal calvarium (the lemon sign) and the posterior convexity of the cerebellum (the banana sign). Some centers also recommend amniocentesis to measure acetylcholinesterase. Mothers may elect not to pursue amniocentesis because of the potential risk for miscarriage. Other centers are also conducting fetal magnetic resonance imaging (MRI) to further delineate the abnormal anatomic findings. The diagnosis of myelomeningocele is formalized after birth. Inspection of the back should be conducted to determine the size and location of the open neural placode defect. Imaging studies of the head and spine should also be conducted. Serial head ultrasounds can be used to monitor the progression of hydrocephalus. A brain and spine MRI can identify the presence and severity of the Chiari II malformation as well as bony and spinal cord abnormalities (Figure 332-1). Neurologic (including an assessment of rectal tone and the anal wink) and orthopedic examinations should be conducted to assess for the functional and anatomic levels as well as spinal and limb deformities. Hip subluxation can be assessed using hip ultrasound, and a plain radiograph can identify spinal deformities such as hemivertebrae, kyphosis, and scoliosis.

Because there are many types of spina bifida and the consequences are variable, it is important to make the correct diagnosis and classification. An infant born with an open lesion or one covered by a thin membrane has either myelomeningocele or meningocele (no nervous tissue in the sac). A child born with a tuft of hair, hemangioma, red birthmark, sinus tract or dimple, or lipoma should be evaluated for occult spinal dysraphism. Children with occult spinal dysraphism are at increased risk for tethered spinal cord, fatty filum, infections, and neurologic deterioration. Infants with spinal dysraphism, meningocele, or myelomeningocele may have additional spinal cord abnormalities such as a split cord (diastematomyelia), a duplicated cord (diplomylia), a flattened malformed cord (myeloschisis), or a hypoplastic cord. MRI will confirm the diagnosis. Some infants with myelomeningocele also have caudal regression (sometimes referred to as sacral agenesis), a syndrome in which the lower portion of the body is underdeveloped. Infants and children with myelomeningocele should be classified based on anatomic level (where the lesion occurred) and motor level (what muscles are innervated well enough to perform muscle contraction for activities).



**Figure 332-1** Cranial magnetic resonance imaging showing abnormalities commonly found in myelomeningocele. (From Liptak GS, Dosa NP. Myelomeningocele. *Pediatr Rev.* 2010;31:443–450.)

## PATHOLOGIC CONSIDERATIONS IN MYELOMENINGOCELE

Four major malformations account for the findings associated with myelomeningocele: soft tissue malformations, vertebral body malformations, spinal cord malformations, and brain malformations. Table 332-1 lists these findings. The percentages of children with myelomeningocele with these findings is unknown (except when noted on the chart) because large epidemiologic studies have not been carried out.

### Soft Tissue Malformations

In myelomeningocele, the soft tissues of the back fail to close, which leaves the spinal cord open to infection and damage. In addition, lipomas or fatty tissue around the distal spinal cord may be present or develop. These may compress or restrict the movement of the spinal cord. Infants born with large soft tissue defects may require rotational muscle flaps and tissue expansions. In these cases, plastic surgeons are often involved in assisting neurosurgeons when performing primary closure of the back after birth.

### Vertebral Malformations

In addition to split vertebral arches, children with myelomeningocele may have absent, partial, fused, or butterfly vertebrae. Infants may be born with kyphotic, lordotic, or scoliotic deformities or may develop them later in life. The higher the spina bifida lesion, the more likely the child is to have kyphosis or scoliosis. Even in the absence of other vertebral abnormalities, children with myelomeningocele can develop neuromuscular scoliosis. Nearly 90% of children with lesions above the sacral level have kyphosis, scoliosis, or both. The consequences of scoliosis or kyphosis can be severe and include pulmonary and cardiac restriction, pain, skin breakdown, and spinal cord damage.

### Spinal Cord Malformations

The effects of myelomeningocele on the spinal cord can be quite extensive. Damage to the spinal cord can



**Table 332-1** Malformations Associated With Myelomeningocele

SOFT TISSUE	VERTEBRAL	SPINAL CORD	BRAIN
Lipoma	Split vertebral arches <sup>a</sup>	Split cord (diastematomyelia)	Chiari II malformation <sup>b</sup> : caudal displacement of the cerebellar tonsils, pons, and medulla (may also include brainstem kinking, aqueductal stenosis or forking, or beaking of the tectum)
Fatty filum terminale	Absent vertebrae Fused vertebrae Butterfly vertebrae Wedge vertebrae Scoliosis Kyphosis	Flattened malformed cord (myeloschisis) Hypoplastic cord Duplicate cord (diplomyelia) Low-lying conus Hydromyelia	Polymicrogyria Heterotopia Dysgenesis or agenesis of the corpus callosum Hydrocephalus <sup>c</sup>

<sup>a</sup>Split vertebral arches are necessary for diagnosis.<sup>b</sup>Chiari II malformation is almost always present.<sup>c</sup>Hydrocephalus is identified in 80% to 90% of cases.

lead to motor and sensory dysfunction. The loss of sensation can occur after predicted dermatomal patterns seen in spinal cord injury, but frequently individuals with myelomeningocele report spotty sensation that does not necessarily correspond to their motor or anatomic level. The loss of sensation puts the individual with myelomeningocele at risk for skin breakdown, burns, abrasions, and limited awareness of occult fractures. The loss of motor function from damage to the spinal cord or spinal nerves can lead to decreased movement in utero, which is associated with deformities seen at birth such as clubfeet and dislocated hips.

Motor function in infancy and childhood affects the child's attainment of developmental milestones. Most obvious is the delay or limited attainment of gross motor skills, but limitations in mobility in infancy have also been associated with poor development of visual perceptual skills. Ambulation is clearly affected by motor level, but other factors, including motivation, medical management, cognition, age, and obesity, also affect mobility. A major predictor of community and household ambulation is quadriceps strength. Although there are no hard and fast rules, having a sacral-level lesion is predictive of community ambulation, whereas children with lower lumbar lesions often successfully ambulate in the community but are more likely to use a wheelchair part-time. Children with high lumbar lesions tend to use a wheelchair primarily but may do some household or short-distance ambulation. Children with thoracic lesions tend to exclusively use wheelchairs for mobility. Therapeutic and bracing interventions can improve ambulation for most children with myelomeningocele.

Because the spinal cord and nerves supply the innervation to the intestines, the urinary system, and the reproductive system, virtually all individuals with myelomeningocele experience dysfunction in these areas. Individuals with myelomeningocele tend to have neurogenic bowel characterized by constipation and fecal incontinence. Constipation is the result of slow transit and delayed or incomplete expulsion of stool. Hindgut control by the enteric nervous system is modulated by

central connections from the sympathetic and parasympathetic nerves. In lower motor neuron bowel dysfunction, there is no spinal cord-mediated reflex peristalsis, which leads to a "relaxed" colon with slow propulsion. Incontinence is common because the external anal sphincter is denervated. In upper motor neuron bowel dysfunction, individuals experience constipation with fecal retention because their anal sphincter is spastic. Most children with myelomeningocele have lower motor neuron bowel dysfunction.

In addition to neurogenic bowel, nearly all children with myelomeningocele have neurogenic bladder, also referred to as neurogenic voiding dysfunction. The bladder has 2 main functions: storing urine produced by the kidneys and emptying the urine after the bladder is full. Bladder dysfunction is classified as either a failure to store urine or a failure to empty it. Storage failure is caused by a hypotonic bladder outlet or a spastic bladder. Emptying failure is caused by a spastic outlet or a hypotonic bladder. There can also be discoordination between bladder wall and bladder neck activities. The combination of a spastic bladder and a spastic outlet, which represents a dyssynergy between bladder contraction and relaxation of the external urinary sphincter, is a serious concern because of the likelihood of reflux and hydronephrosis, which can lead to permanent kidney damage.

Sexual functioning is neurologically complex, involving the autonomic and somatic nervous systems, and is frequently impaired in both men and women with myelomeningocele. Erectile dysfunction is common, and among those who can achieve erection, many have impaired ejaculation and decreased fertility. One study found that only 35% of men with myelomeningocele reported successful sexual intercourse. Women also experience difficulty with sexual functioning related to decreased sensation and lubrication, but they tend to have normal fertility. Many women with myelomeningocele can achieve orgasm.

### Brain Malformations

The most common brain malformation in myelomeningocele is the Chiari II malformation, in which the

brainstem and part of the cerebellum are displaced downward. Most have this malformation, although many children do not have symptoms associated with it. The symptoms, if present, relate to brainstem and proximal spinal cord compression and can include difficulty swallowing, choking, hoarseness, central apnea, disordered breathing, opisthotonos, and even sudden death. Many children with myelomeningocele also have cranial nerve abnormalities that lead to problems such as strabismus. The presence or development of hydrocephalus is extremely common. It is caused by abnormal cerebral spinal fluid flow pattern, which leads to enlargement of the ventricular system and pressure on the surrounding brain tissue. Up to a quarter of infants born with myelomeningocele have evidence of hydrocephalus before or at the time of birth. After primary closure of the back, most infants develop some amount of ventriculomegaly, but not all of these children require ventriculoperitoneal shunting for hydrocephalus. Additional clinical features of hydrocephalus include a bulging fontanel, crossing growth chart curve trajectories for head circumference, cranial nerve dysfunction such as sixth nerve palsy, sunsetting eyes (paralysis of upward gaze), vomiting, headache, irritability, and lethargy. These signs and symptoms are also indicators of possible shunt malfunction in children with ventriculoperitoneal shunts and require immediate evaluation. When shunt failure occurs, progression of symptoms can lead to loss of consciousness, papilledema, abnormal pupillary responses, and deterioration to death.

Children with myelomeningocele can have a host of other intracranial abnormalities, including partial dysgenesis of the corpus callosum, cortical dysplasias, abnormal cortical thickening in frontal regions and reduced thickness in posterior regions, reduced cerebellar size, and limbic track anomalies. Seizures are common among individuals with myelomeningocele and occur more frequently among children with higher lesion levels, shunts, and supratentorial brain abnormalities. Intellectual impairment is also more frequent among children with higher-level lesions and brain malformations compared with other children with myelomeningocele. Nearly three-fourths of children with myelomeningocele have IQ scores within the normal range. Children without hydrocephalus tend to have higher IQs and better executive functioning and memory. The cognitive phenotype of myelomeningocele is characterized by relative strengths, usually in language skills, and weaknesses, usually in visual-perceptual and mathematic skills. For example, many children with myelomeningocele are noted to have a “cocktail personality” with strong verbal fluency. In the classroom, neurocognitive problems can manifest as inattention and distractibility, poor task completion, disorganization, poor problem-solving skills, poor memory and comprehension, and emotional lability.

## MANAGEMENT

### Treatment Approach

The overall goals of treatment are to maximize health, well-being, and independence and to minimize disability.

The Institute of Medicine has defined health in childhood as “the extent to which children are able or enabled to a) develop and realize their potential, b) satisfy their needs, and c) develop the capacities that allow them to interact with their biological, physical, and social environments.” When thinking about health from this perspective for children with myelomeningocele, a helpful framework is the International Classification of Functioning, Disability, and Health. In this framework, health conditions interact with personal and environmental factors to affect functioning. Medical interventions, social supports, and community services can substantially influence the experience of disability for children with myelomeningocele. Achieving the aforementioned goals of maximizing health and minimizing disability for children with myelomeningocele requires diligent surveillance, careful and thoughtful interventions, and a strong interdisciplinary team. Because of the complex nature of myelomeningocele, children benefit from a team of health care providers offering coordinated comprehensive care in conjunction with the primary care medical home and community-based supports.

### Specific Treatments

Closure of the myelomeningocele lesions is of primary concern. Closure should be performed by an experienced pediatric neurosurgeon in a tertiary care setting with a neonatal intensive care unit familiar with the management of myelomeningocele. Some centers are now offering fetal repair of myelomeningocele. A recent multicentered trial compared fetal repair (before 26 weeks’ gestation) versus standard postnatal repair and found improved motor function at 1 year of age and reduced need for shunting in the fetal repair group. Currently, only a few very specialized centers with maternal-fetal treatment programs specializing in multidisciplinary fetal surgery are fully capable of performing this procedure and providing ongoing care to mothers and fetuses. Although limited information is available on the long-term effects of fetal repair, more centers are offering the procedure, and it is expected to become more common. Another advance in fetal intervention is endoscopic closure, which may improve neurologic functioning but is also associated with high risks to the fetus. Clinical trials are necessary to determine the appropriateness of this intervention.

Despite the recent advances in fetal intervention, most infants undergo standard postnatal repair after elective cesarean delivery. These infants should be stabilized with their lesions protected. Antibiotics are given to reduce the risk for central nervous system infection. An infant born outside of a tertiary care center should be transferred for ongoing management after being stabilized and receiving antibiotics. Primary closure should occur within 72 hours of birth. The wound requires careful monitoring and protection with the infant lying prone or on its side. Monitoring for progression of hydrocephalus is necessary and accomplished through serial head ultrasounds and head circumference measurements and by paying close attention to the symptoms associated with hydrocephalus. Because many more infants are

discharged from the hospital without a shunt but with evidence of ventriculomegaly or hydrocephalus, ongoing monitoring for worsening hydrocephalus is necessary on an outpatient basis. In recent years, neurosurgeons have been advocating for watchful waiting because of the high shunt complication rate. Because there is no consensus on shunting criteria, reported shunt rates vary substantially by center from 50% to 95%. Although the standard management for hydrocephalus is shunt placement, some neurosurgeons are managing hydrocephalus with third ventriculostomies and choroid plexus cauterization. Success with this technique is variable. Therefore, third ventriculostomies are not considered part of the standard of care. Hydrocephalus symptoms requiring urgent shunt placement include rapidly increasing head circumference, stridor, new or worsening swallowing dysfunction, and central apnea.

Neonates should also be evaluated for clubfeet and may require casting or splinting before discharge. Hip ultrasounds should be conducted to determine hip positioning and the need for a Pavloc harness. A renal and bladder ultrasound should be conducted along with voiding cystourethrogramurodynamic studies to assess the anatomy and function of the voiding system. Vesicoureteral reflux can occur in newborns and, if left untreated, lead to kidney damage in infancy. Neonates with a hostile bladder or reflux should be started on a clean intermittent catheterization (CIC) program. Additionally, many centers take a proactive approach to bladder management by initiating CIC for all neonates. Other centers recommend watchful waiting before initiating CIC, but this puts the child at risk for irreversible renal changes as a result of late intervention and may be more difficult for children and families to accept as part of their daily routine. Before discharge home for the first time, neonates should be assessed for safe swallowing, and a physical therapist should be consulted to teach the family a home program that involves stretching, positioning, and splint management (if they were prescribed). The infant should be referred to early intervention services and other community programs. Families should be supported as they adjust to the responsibilities of caring for a child with multiple medical issues.

## ONGOING CARE

### Follow-up

Ideally, all children with myelomeningocele should receive their primary care in a medical home along with coordinated care in an interdisciplinary spina bifida clinic that includes pediatric rehabilitation medicine and/or developmental pediatrics, neurosurgery, orthopedic surgery, urology, social work, nursing, physical and occupational therapies, and nutrition, with ready access to neuroradiology services; plastic surgery; pulmonary, endocrinology, neuropsychological testing; cognitive and speech therapy; and dysphagia therapy. Many children may live far away from a coordinated interdisciplinary clinic, requiring the pediatrician to take a more hands-on approach. Additionally, many interdisciplinary clinics do not have the

full complement of providers listed previously and refer to some subspecialists on an as-needed basis.

### Functioning and Development

One of the ongoing goals of care is minimizing disability or, more positively framed, maximizing function. This is achieved through aggressive medical management, the prevention of secondary conditions and complications, and attention to the developmental needs of the child in the context of the family and community. It should be expected that children with myelomeningocele will be delayed in their attainment of some developmental milestones and that certain milestones may never be achieved in some circumstances. It is important to work toward developmentally appropriate skills and make accommodations to maximize function despite existing limitations. Therapeutic goals should be discussed with the family and the treating therapists, and progress toward these goals should be monitored with an eye toward functional independence. Many children with myelomeningocele require adaptive equipment, such as lower extremity braces and mobility devices to help them achieve independent mobility. An orthotist familiar with pediatric bracing should be involved and work closely with the physical therapist and pediatric physiatrist to determine the best bracing options for each child.

When considering the developmental skills of a child, it is helpful to consider them by domain (self-care, mobility, cognition, and social skill development). Children develop self-care skills as they age. These skills are referred to as activities of daily living (ADLs) and include feeding, grooming, bathing, dressing, toileting, and bowel and bladder management. By age 7 years, typically developing children should be independent with these skills. Older children also learn instrumental ADLs (IADLs), such as being able to prepare meals, go shopping, and perform housekeeping tasks. The child with myelomeningocele may have difficulties with ADLs and IADLs because of neurologic or cognitive impairments, limited access to adaptive equipment and therapies, or lack of encouragement to learn independent skills in the home environment.

As described previously, impairments in mobility are extremely common among children with myelomeningocele. The neurologic motor level of the lesion is a strong predictor, but other factors certainly influence mobility. For most families, ambulation is a clear goal, but for some children, wheelchair mobility will offer more independence. Cognition, communication, and social skill development are also influenced by several factors, some of which are amenable to intervention. Children with myelomeningocele who exhibit difficulty in academic settings benefit from focused classroom adaptations as part of their individualized education programs. Some children may need extensive neuropsychological testing to elucidate specific neurocognitive deficits. In addition, some children need behavioral therapy or counseling to optimize social functioning. Generally speaking, children with myelomeningocele with hydrocephalus and higher lesion levels are at risk for not achieving independence in their day-to-day lives, owing to the more extensive nature of their impairments. These children

often require more adaptations and assistance to achieve optimal functioning.

As children with myelomeningocele age, they face the same developmental and social challenges that all children face. Despite the universal nature of growing up, children with myelomeningocele face special challenges. These challenges are physical and social in nature. Many children with myelomeningocele experience barriers to independent functioning and full participation in society. It is important to note that children with myelomeningocele have higher than typical rates of depression and anxiety. The pediatrician should be proactive in helping to address barriers to participation and should screen patients with myelomeningocele for mental health concerns. In addition, the pediatrician should be attentive to family functioning. Families of children with myelomeningocele can experience substantial social and financial effects and may benefit from referrals to supportive services.

### Neurologic

As detailed previously, children with myelomeningocele have alterations to their brains and spinal cords that are associated with a host of consequences. The neurologic follow-up for children with myelomeningocele should be ongoing. As early as possible, a neurologic level should be assigned. Many children have spotty sensation and varying degrees of motor control, which make assigning a level challenging. Nonetheless, documentation of neurologic function is essential because children can experience decrements in neurologic functioning related to complications such as tethered cord, hydrocephalus, worsening of the Chiari malformation, and syringomyelia. Routine monitoring of neurologic function can help identify developing problems and provides a baseline for comparison when new symptoms emerge.

Monitoring for hydrocephalus in infancy requires routine measurements of head circumference, assessing the fontanel for fullness, and obtaining serial head ultrasounds. In situations in which the infant's head is growing out of proportion with weight and length or is crossing percentiles on the growth curve chart, the neurosurgeon should be actively involved and the child monitored for acute symptoms of hydrocephalus. The decision to shunt hydrocephalus is usually made in infancy, although children can have progressive hydrocephalus. If concerns for hydrocephalus exist after infancy, computed tomography (CT) or rapid-sequence MRI should be ordered to assess the size of the ventricles. Symptomatic hydrocephalus is an indication for urgent evaluation by a neurosurgeon for cerebrospinal fluid diversion. Similarly, children with shunted hydrocephalus may develop shunt malfunctions or infections and require urgent intervention by neurosurgery to prevent clinical deterioration. If the clinical case is suspicious for shunt malfunction, a shunt series and CT or rapid-sequence MRI should be ordered. Pediatricians should also look out for the development of symptoms from the Chiari malformation. The infant or child with a symptomatic Chiari malformation may experience respiratory problems, swallowing difficulties, and cranial

nerve dysfunction. Use of MRI is necessary to characterize the Chiari malformation. A child with new-onset Chiari malformation symptoms should be evaluated for worsening hydrocephalus and syringomyelia. Management of hydrocephalus is important before performing a Chiari malformation decompression.

As described previously, in addition to the Chiari malformation, children with myelomeningocele can have other intracranial abnormalities that can significantly affect functioning. Because children with myelomeningocele are at increased risk for seizures, pediatricians should make sure to elicit any concerns about seizures. If seizures are suspected, a neurologist should be consulted for a workup that includes neuroimaging and electroencephalogram evaluations.

Essentially all children with myelomeningocele have evidence of spinal cord tethering on neuroimaging, but most do not develop symptoms. About 25% of children aged 2 to 8 years develop tethered cord symptoms. Urologic symptoms include changes in bladder habits, repeated urinary tract infections, upper tract dilation, and vesicoureteral reflux. Children also usually present with other neurologic symptoms such as worsening weakness, changes in lower extremity tone, or worsening foot deformities. Children with symptomatic tethered cords should be sent for imaging and then referred to neurosurgery for management. Although the untethering procedure is relatively straightforward, many children have retethering because of the formation of scar tissue and their pre-existing anatomic abnormalities. Therefore, most neurosurgeons proceed with caution when considering a second untethering.

Ongoing monitoring and management of neurogenic bowel and bladder are necessary throughout the life course. The level of intervention needed for each child varies greatly, but all children with neurogenic bladder need to be monitored because of the possibility of kidney damage from vesicoureteral reflux. The urologist will recommend a schedule for routine renal and bladder ultrasounds as well as voiding cystourethrograms. It should be noted that the presence of spontaneous voiding does not indicate normal bladder activity. As mentioned earlier, not all individuals are placed on CIC in infancy. However, the status of the bladder may change over time, requiring the use of CIC to maintain a low-pressure bladder and prevent kidney damage. The use of CIC also helps children with neurogenic bladders achieve social continence. By the age of 5 years, children are capable of learning how to perform their own catheterizations. In addition to the use of CIC, many children are placed on medication to assist with urine storage. This helps protect the renal system and can help children stay dry in between catheterizations.

The 2 main issues children with myelomeningocele face with respect to neurogenic bowel are constipation and incontinence. Most children have slower fecal transit times, which can lead to constipation. A diet rich in fiber is helpful in the management of constipation, but many children require promotility agents to improve transit times. In addition to constipation, children with a lower motor neuron colon have frequent fecal incontinence. For these children, manual



removal of stool on a regular basis can help with incontinence. For children with upper motor neuron colons, assistance with stool output is often required for successful evacuation. A suppository or enema, with digital stimulation near the internal anal sphincter, helps bring the stool into the rectum for evacuation. Some children can have successful bowel movements with the use of digital stimulation alone and do not need a rectal medication as part of their bowel program. In general, to achieve fecal continence and manage constipation, children should have bowel routines that include a regular diet rich in fiber, medications for motility if needed, and a plan for regular evacuation of stool. Children who are unable to achieve continence with their bowel program may be considered for surgery to create a conduit from the abdominal wall to the colon for the use of an antegrade colonic enema. Because surgery is not without risks, the child's bowel program should be optimized before surgery is considered.

### **Orthopedic**

The orthopedic issues are either lower extremity or spinal in nature. In the neonatal period, as described previously, infants may require management for congenitally dislocated hips and foot deformities. As children age, they may require additional orthopedic interventions. Notably, however, the management of the subluxed hip has changed substantially over the past decades because of the limited utility of surgical intervention. More important to a successful gait are the prevention of hip flexion contractures and the use of bracing and therapeutic interventions to maximize strength and function. Children may also need interventions for management of abnormal rotational forces and ongoing foot deformities. Although the Ponseti method may be effective for clubfeet in infancy, many children with myelomeningocele have relapse after initial management and may require soft tissue releases and, in the more severe cases, bony surgical interventions. With or without surgical intervention, most children with myelomeningocele require orthotics for maintenance of foot positioning and to assist with gait optimization. Most children with myelomeningocele do not have spasticity but are at risk for the development of contractures at the hips, knees, and ankles. A proactive approach that focuses on maintaining range of motion is important. In some cases, orthopedic release of contractures is warranted.

Most children with myelomeningocele develop spinal curvatures (scoliosis or kyphosis or both) as they age. Some infants are born with substantial curvatures at birth that progress during childhood. The development of spinal curvatures is correlated with the presence of congenital vertebral abnormalities such as hemivertebrae or wedge vertebrae, higher lesion level, higher neurologic motor level, syringomyelia, and tethered cord. Rapidly progressive curves should prompt the medical care team to consider neuroimaging for syringomyelia or tethered cord. In these cases, neurologic function may be deteriorating, and neurosurgical intervention may be warranted before orthopedic intervention. Goals for management of spinal curvatures include preventing the progression of the

deformity, achieving a solid fusion with a level pelvis for improved sitting tolerance, and maximizing functional independence. The indications for operative intervention are not clearcut, but in general, if the scoliotic curvature is rapidly progressing and conservative management is ineffective, surgery is warranted. For many surgeons, the presence of scoliosis greater than 50 degrees is an indication for surgery. In recent years, orthopedic surgeons have started using grow rods or the vertebral expandable prosthetic titanium rib procedure to address scoliosis but preserve growth. Anticipatory guidance before surgery is important because children undergoing operative intervention for either scoliosis or kyphosis are at risk for a host of complications, including infection, skin breakdown, loss of functional skills, loss of sensation or motor control, and pseudarthrosis. Immediately after surgery, many children are prescribed activity restrictions that can necessitate more assistance with transfers, self-care, and mobility. Also, children may need changes to their seating systems and other equipment. In the immediate postoperative period, consultations with physical and occupational therapy can assist in planning adaptations and training parents in biomechanically safe techniques for transfers and assisting with care. Plans should be made to address missed school and returning to school with activity restrictions. After restrictions are lifted, children should engage in a therapeutic program that focuses on restoration and improvement of function.

### **Skin**

Special attention to the skin covering the insensate areas of the body is essential throughout the individual's life. Parents of children with myelomeningocele should be taught about the risks for skin breakdown and how to prevent it. When children are old enough, they should be taught to do regular skin checks and pressure relief exercises if they use a wheelchair or stay in one position for an extended period of time. Just 2 hours of immobility can restrict blood flow enough to cause skin breakdown. The National Pressure Ulcer Advisory Panel classifies skin breakdown into 4 stages. Stage 1 is characterized by intact skin with nonblanching erythema. In stage 2 breakdown, the skin is open and the dermis is damaged or the area is covered by a blister. Stage 3 breakdown involves the subcutaneous tissues, and stage 4 extends down to muscle, bone, or tendons. The best management for skin breakdown is prevention because healing can be prolonged and the treatment can limit the individual's activities. The first and most important tenet of treatment is eliminating the cause of the breakdown and relieving the pressure on the wound. Debridement of dead tissue may be necessary, in addition to keeping the wound clean and protected from possible infections. Depending on the severity and location of the wound, a plastic surgeon may need to be consulted for surgical management.

### **Respiratory**

Disordered breathing is frequently under-reported and under-recognized by health care professionals. Especially in the very young child with myelomeningocele,

central respiratory dysfunction is of concern. Because of hydrocephalus and the Chiari II malformation, infants and young children can experience vocal cord paralysis and central hypoventilation. In severe cases, infants and young children may present with stridor, increased work of breathing, and apneic episodes. These patients need urgent intervention, usually consisting of placing a shunt or replacing the malfunctioning shunt and considering Chiari malformation decompression. In older children, respiratory problems may also be a sign of shunt malfunction. Children with myelomeningocele may also have restrictive lung disease from poor chest wall compliance, which worsens with progressive scoliosis. Sleep-exacerbated respiratory dysfunction may be identified on sleep study after identification of symptoms such as daytime fatigue, attention difficulties, frequent awakening during the night, or snoring with or without respiratory pauses. Children with severe respiratory dysfunction may require a tracheostomy and assistive ventilation if other interventions are not successful.

### Endocrine

Children with myelomeningocele are at risk for a host of endocrine abnormalities. An impressive percentage of children with myelomeningocele are overweight or obese. The risk for obesity is increased for nonambulatory children with higher lesion levels. Prevention of obesity is an important goal. Anticipatory guidance about aerobic exercise and healthy eating should be a part of every health maintenance visit. Some children may require adaptations to allow them to participate in physical activity that adequately raises their heart rate for aerobic exercise. Children with myelomeningocele are also at risk for early-onset type 2 diabetes and should be screened appropriately. Precocious puberty is more common in girls with myelomeningocele because hydrocephalus can disrupt the hypothalamus. If early pubertal development is noted, laboratory studies should be performed and the child referred to an endocrinologist. Some children with myelomeningocele also have growth hormone deficiency, which can contribute to short stature. In addition, nonambulatory children with myelomeningocele are at risk for decreased bone density resulting from decreased weight bearing. Children may be monitored with bone density testing if treatment would be initiated. Pathologic fractures are unfortunately relatively common in this population. Because children with myelomeningocele may be insensate, they may not know that they have a fracture. New deformities, swelling, and warmth in a limb should prompt an investigation for an occult fracture. In the face of a pathologic fracture, interventions for low bone density should be considered.

### Latex Allergies

All children with myelomeningocele are considered latex sensitive, and about 50% develop latex allergies. Latex should be avoided by all children with myelomeningocele. This means that certain toys, household objects, and medical equipment should be avoided. Parents should be provided a list of items to avoid and the children educated as they mature. If a latex allergy

is suspected, allergy testing should be performed and an epinephrine autoinjector (EpiPen) prescribed. There is also some cross-reactivity with bananas, kiwi, and avocado, so these fruits should be avoided in the latex-allergic child.

## COMPLICATIONS

Myelomeningocele should be considered a nonprogressive condition with multisystem involvement requiring vigilant monitoring and management. Changes to the child's functioning warrant investigation. In many cases, the pediatrician will need to engage a surgical or medical subspecialist in the workup and management. Some complications are urgent and life threatening, including shunt malfunctions and infections and symptomatic Chiari malformations. Some complications are not urgent but life threatening, including progressive pulmonary compromise from scoliosis and renal failure. Still other complications may be urgent but not life threatening, including tethered cord or a syrinx in the thoracolumbar spine.

## PROGNOSIS

The survival rate for children with myelomeningocele has drastically improved in the past 50 years. Routine use of shunting for hydrocephalus has markedly improved long-term survival, as has routine CIC. Despite recent improvements, the risk for death in individuals aged 5 to 40 years with myelomeningocele is 10-fold higher than the general population, and most of these deaths are unexpected. Just as there have been improvements in survival, there have been improvements in functional outcomes. Nonetheless, individuals with myelomeningocele frequently experience substantial disability. Prognosticating disability is challenging because it is multifactorial. Initial severity, medical complications, personal and family preferences, and social factors all contribute to the experience of disability. Many parents ask if their child with myelomeningocele will walk. The answer to this question is almost always yes with a lot of caveats. Except for children with very high lesions, the motivated child can walk. For children with high lumbar and lower thoracic lesions, walking may require extensive bracing, the use of an assistive device, intense physical therapy, and high energy expenditure, but it can often be achieved. For the child with a mid-lumbar lesion, walking is often achieved with bracing and crutches. The child with low lumbar or sacral lesions may not require any assistive device to ambulate successfully.

## PREVENTION

At this time there is no way to completely prevent myelomeningocele, but folic acid supplementation has been effective in decreasing the risk for myelomeningocele. The American Academy of Pediatrics and the Centers for Disease Control and Prevention recommend that all women of childbearing age receive 0.4 mg of folic acid daily. Women with neural tube defects or first-degree relatives with neural tube defects should take 4 mg of folic acid daily.

### WHEN TO REFER

- If meningocele is discovered prenatally, the mother should be referred to high-risk obstetrics and to a tertiary medical center that specializes in the care of infants with congenital malformations.
- If meningocele is diagnosed prenatally before 25 weeks, and the mother is interested in pursuing fetal repair, the mother should be referred to quaternary medical center with a multidisciplinary team specializing in fetal surgery.
- Infants born with meningocele should be referred to a tertiary medical center that specializes in the care of these infants.
- All infants born with meningocele should be monitored during childhood by a multidisciplinary team that includes experts in pediatric rehabilitation child development, neurosurgery, orthopedics, urology, neuropsychology, orthotics, social work, nursing, and physical and occupational therapies.
- Referral to an early intervention program should be accomplished early on.
- Parents of a child with meningocele who are considering subsequent pregnancies should be referred to genetic counseling.
- Individuals with meningocele who are considering having children should be referred to genetic counseling, and young women with meningocele considering pregnancy should be referred to high-risk obstetrics.

### WHEN TO ADMIT

- The child is acutely ill and cannot be managed at home.
- There is concern for sepsis or shunt infection.
- The child requires surgical intervention.

### TOOLS FOR PRACTICE

#### Community Advocacy and Coordination

- *Building the Legacy: IDEA 2004* (Web page), US Department of Education ([idea.ed.gov](http://idea.ed.gov))
- *Let's Put the Person First, Not the Disability!* (fact sheet), Disability Is Natural ([www.disabilityisnatural.com/explore/people-first-language](http://www.disabilityisnatural.com/explore/people-first-language))

#### Engaging Patient and Family

- *All About the IEP* (fact sheet), Center for Parent Information and Resources ([www.parentcenterhub.org/repository/iep](http://www.parentcenterhub.org/repository/iep))
- *Emergency Information Form for Children with Special Needs* (form), American Academy of Pediatrics ([www.aap.org/advocacy/blankform.pdf](http://www.aap.org/advocacy/blankform.pdf))
- *Pediatric Care Plan* (booklet), American Academy of Pediatrics ([medicalhomes.aap.org/Documents/PediatricCarePlan.pdf](http://medicalhomes.aap.org/Documents/PediatricCarePlan.pdf))
- *Pediatric Specialists* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/default.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/default.aspx))

- *Spina Bifida* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/developmental-disabilities/Pages/Spina-Bifida.aspx](http://www.healthychildren.org/English/health-issues/conditions/developmental-disabilities/Pages/Spina-Bifida.aspx))
- *Transitioning Youth to Adult Care Providers* (booklet), Got Transition ([www.gottransition.org/resourceGet.cfm?id=208](http://www.gottransition.org/resourceGet.cfm?id=208))

#### Practice Management and Care Coordination

- *Care Delivery Management* (Web page), American Academy of Pediatrics ([www.medicalhomeinfo.org/how/care\\_delivery](http://www.medicalhomeinfo.org/how/care_delivery))

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### Chapter 333

## SPINAL DEFORMITIES

John T. Anderson, MD

### SPINAL CORD AND VERTEBRAL EMBRYONIC DEVELOPMENT

Genetic abnormalities and teratogen exposure occurring during the embryonic period can adversely affect normal differentiation of the musculoskeletal system, resulting in malformations of the extremities or the spine. Formation of the defined spinal column occurs from the fourth through the sixth week of gestation. Somatic mesodermal tissue surrounding the notochord differentiates into a less cellular and dense upper portion and a more dense and cellular lower portion, which cleave together. The intervertebral disc



develops at the site of the cleavage. The notochord, which is contained within the newly joined primitive vertebral bodies, degenerates, and specific portions at the site of cleavage become the nucleus pulposus of the intervertebral disc. The neural arches and ribs develop from the more dense portions of the somite, and the vertebral body develops from the less dense portions.

Chondrification begins in the primitive mesodermal vertebrae during the sixth week of pregnancy and progresses rapidly to form cartilaginous models of the vertebral body by the end of the first trimester. Ossification of the cartilaginous models begins during the second trimester. The ossification of each side of the neural arch and of the body at each level proceeds separately. In the neonate, the ossified vertebral body and neural arches at each level are clearly visible radiographically, separated by the neurocentral synchondroses. The neural arches posteriorly are also separated by a cartilaginous synchondrosis. The ossification centers of the neural arches and body coalesce during the first 3 to 7 years of postnatal development, whereas the synchondroses of the neural arches close at approximately 3 years of age.

The first and second cervical segments are distinct from the remainder of the spinal column. The first cervical vertebra lacks the physical form characteristic of other vertebrae, having instead only a narrow anterior arch. This arch is not ossified at birth or during the neonatal period but is most often visible by 1 year of age.

Errors in the embryologic sequence of the spine cause several congenital defects of the spinal column and spinal cord. These errors range in severity from isolated hemivertebrae to complex errors of vertebral formation and segmentation associated with defects of the neural tube or spinal cord. When such errors result in asymmetrical vertebral formation or produce asymmetrical vertebral growth potential, structural spinal curves such as congenital scoliosis or kyphosis develop.

Malformations of the head and neck, especially the internal and external auditory apparatuses, maxillae, and mandibles, occur frequently in children with high thoracic and cervical curves. The association of a short neck, low posterior hairline, and restriction in neck motion caused by the congenital fusion of cervical vertebrae represents Klippel-Feil syndrome. Renal anomalies, the congenital elevation of the scapulae (ie, Sprengel deformity), impaired hearing, and congenital heart disease are common associated anomalies in affected patients. The VATER syndrome (vertebral defects, imperforate anus, tracheoesophageal fistula, and radial and renal dysplasia) and the VACTERL complex (see later discussion) underscore the complex nature of the relationships between the rapidly evolving organ systems and the musculoskeletal system during the first trimester of pregnancy.

## SPINE ABNORMALITIES

### Postural

Back pain in children is, occasionally, a sign of an underlying disorder. Postural abnormalities may or

may not indicate an underlying spine disorder. The challenge to the physician is to determine whether the child's posture or pain is caused by an underlying musculoskeletal disorder or is merely a habit that alters—exaggerates, increases, or decreases—the normal spinal alignment. The cervical and lumbar spine are normally lordotic, and the thoracic spine is kyphotic. These sagittal plane curves (as viewed from the side) determine a person's sagittal balance. When viewed from the front, or coronal plane, the spine should be straight, with the head balanced over the pelvis. Abnormal curvatures and protrusions merit careful investigation. If either condition is excessive, progressive, or painful, then concern is appropriate. Scoliosis, a side-to-side curve, is always abnormal. A classification of spinal deformities is provided in Box 333-1.

### Congenital Malformations

When a newborn is held prone in the examiner's palm, the infant's spine falls into slight flexion, allowing detection of meningocele, scoliosis, or hyperkyphosis. An underlying spinal dysraphism may be indicated by a hair tuft, dimple, discoloration, or palpable spina bifida lamina defect (see Chapter 332, Spina Bifida).

### Congenital Scoliosis

Congenital scoliosis is caused by abnormal in utero vertebral development. These anomalies are caused by failure of formation or failure of segmentation (Figure 333-1 and Figure 333-2). The anomalous vertebrae lead to asymmetrical spinal growth that manifests as scoliosis. Congenital spinal anomalies are sometimes related to cardiac or urologic abnormalities that develop during the same period. Therefore, it is recommended that these children receive a renal ultrasound and, if clinically indicated, a cardiac evaluation. Overall, this disorder shows progression in 75% of cases, although this can vary greatly depending on the type of anomaly present. Children with a unilateral unsegmented bar and a contralateral hemivertebra (up to 10 degrees/year progression) have the poorest prognosis, followed by unilateral unsegmented bar (5 degrees/year), 2 unilateral fully segmented hemivertebrae (3 degrees/year), and unilateral fully segmented hemivertebra (1–2 degrees/year). The least severe progression is seen with block (bilateral nonsegmented bar) and wedge vertebrae.

The management of congenital scoliosis requires frequent clinical and radiographic follow-up to detect progression. Referral to a spine specialist is recommended. As is the case for most spinal deformities in children, the risk for progression is highest during periods of accelerated growth. This occurs during the first 2 years of life and during the adolescent growth spurt. When the deformity is located near the middle of the spine, the segments of the spine above and below often attempt to compensate by curving in opposite directions. The result is a balanced spine. Treatment may be unnecessary. When, however, the anomalous vertebra is at the base of the spine (low lumbar or lumbosacral), progression will lead to continued oblique growth of the lumbar



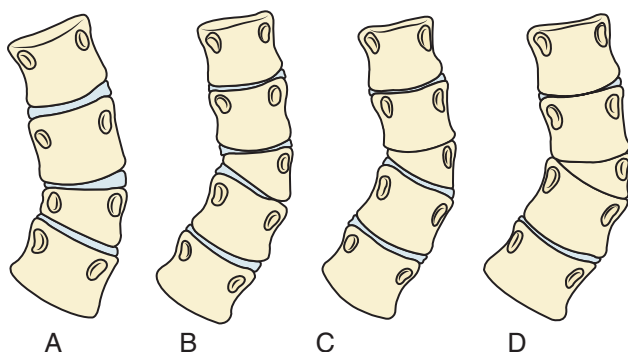
**BOX 333-1 Classification of Spinal Deformity**

- |   |   |
|---|---|
| <ul style="list-style-type: none"> <li>A. Idiopathic               <ul style="list-style-type: none"> <li>1. Infantile</li> <li>2. Juvenile</li> <li>3. Adolescent</li> </ul> </li> <li>B. Neuromuscular               <ul style="list-style-type: none"> <li>1. Neuropathic                   <ul style="list-style-type: none"> <li>a. Upper motor neuron lesions                       <ul style="list-style-type: none"> <li>(1) Cerebral palsy</li> <li>(2) Spinocerebellar degeneration</li> <li>(3) Syringomyelia</li> <li>(4) Spinal cord tumor</li> <li>(5) Spinal cord trauma</li> </ul> </li> <li>b. Lower motor neuron lesion                       <ul style="list-style-type: none"> <li>(1) Poliomyelitis</li> <li>(2) Other viral myelitis</li> <li>(3) Trauma</li> <li>(4) Spinal muscular atrophy</li> <li>(5) Meningomyelocele (paralytic)</li> </ul> </li> <li>c. Dysautonomia (Riley-Day syndrome)</li> </ul> </li> <li>2. Myopathic                   <ul style="list-style-type: none"> <li>a. Arthrogryposis</li> <li>b. Muscular dystrophy</li> <li>c. Fiber-type disproportion</li> <li>d. Congenital hypotonia</li> <li>e. Myotonia dystrophica</li> </ul> </li> </ul> </li> <li>C. Congenital               <ul style="list-style-type: none"> <li>1. Congenital scoliosis                   <ul style="list-style-type: none"> <li>a. Failure of formation                       <ul style="list-style-type: none"> <li>(1) Wedge</li> <li>(2) Hemivertebra</li> </ul> </li> <li>b. Failure of segmentation                       <ul style="list-style-type: none"> <li>(1) Unilateral bar</li> <li>(2) Bilateral bar</li> </ul> </li> </ul> </li> <li>2. Congenital kyphosis                   <ul style="list-style-type: none"> <li>a. Failure of formation</li> <li>b. Failure of segmentation</li> <li>c. Mixed</li> </ul> </li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>3. Congenital lordosis</li> <li>4. Associated with neural tissue defect               <ul style="list-style-type: none"> <li>a. Meningomyelocele</li> <li>b. Meningocele</li> <li>c. Spinal dysraphism (diastematomyelia)</li> </ul> </li> <li>D. Neurofibromatosis</li> <li>E. Mesenchymal               <ul style="list-style-type: none"> <li>1. Marfan syndrome</li> <li>2. Ehlers-Danlos syndrome</li> </ul> </li> <li>F. Traumatic               <ul style="list-style-type: none"> <li>1. Fracture or dislocation</li> <li>2. After irradiation</li> <li>3. After laminectomy</li> </ul> </li> <li>G. Soft tissue contractures               <ul style="list-style-type: none"> <li>1. After thoracoplasty</li> <li>2. Burns</li> </ul> </li> <li>H. Osteochondrodystrophies               <ul style="list-style-type: none"> <li>1. Achondroplasias</li> <li>2. Spondyloepiphyseal dysplasia</li> <li>3. Diastrophic dwarfism</li> <li>4. Mucopolysaccharidosis</li> </ul> </li> <li>I. Scheuermann disease</li> <li>J. Infection</li> <li>K. Tumor</li> <li>L. Rheumatoid disease</li> <li>M. Metabolic               <ul style="list-style-type: none"> <li>1. Rickets</li> <li>2. Juvenile osteoporosis</li> <li>3. Osteogenesis imperfecta</li> </ul> </li> <li>N. Lumbosacral anomalies</li> <li>O. Hysterical</li> <li>P. Functional               <ul style="list-style-type: none"> <li>1. Postural</li> <li>2. Secondary to short limb</li> <li>3. Secondary to pain</li> </ul> </li> </ul> |
|---|---|

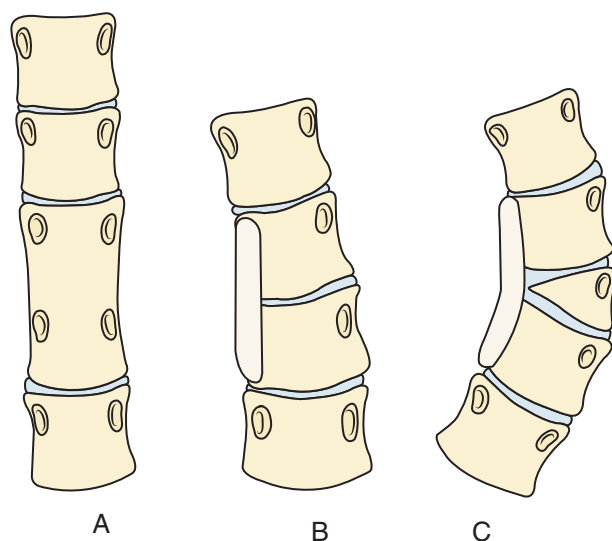
spine that causes marked truncal imbalance. Many surgeons now advocate excision of the anomalous vertebra and a short segment fusion to prevent progression. Congenital scoliosis affecting the upper thoracic spine or cervicothoracic junction is very common, but, fortunately, does not typically cause large curves. However, it can elevate the shoulder on the convex side of the curve and cause an oblique take off of the cervical base, which results in head tilt. Obviously, this can be a significant cosmetic concern for the child. For progressive deformities, the treatment can involve many different strategies, depending on the type of anomaly (isolated or diffuse), the location of the deformity, the age of the child, and the degree of deformity. Current emphasis

has been placed on treatment methods that avoid early and/or extensive spinal fusion in the hope of affording these often very young children the opportunity to gain additional chest wall growth and pulmonary development.

A certain subset of patients with congenital scoliosis can develop deformities that lead to a condition termed *thoracic insufficiency syndrome*. This is defined as the inability of the thorax to support respiration or lung growth. The classic description is a patient with congenital scoliosis and fused or absent ribs on the concave side of the deformed spine. The deformity can inhibit chest wall growth and thus lung development. This may ultimately lead to restrictive lung disease and eventual cardiopulmonary



**Figure 333-1** Congenital scoliosis. Failure of formation: A, wedge vertebra; B, fully segmented hemivertebra; C, partially segmented hemivertebra; D, unsegmented hemivertebra.

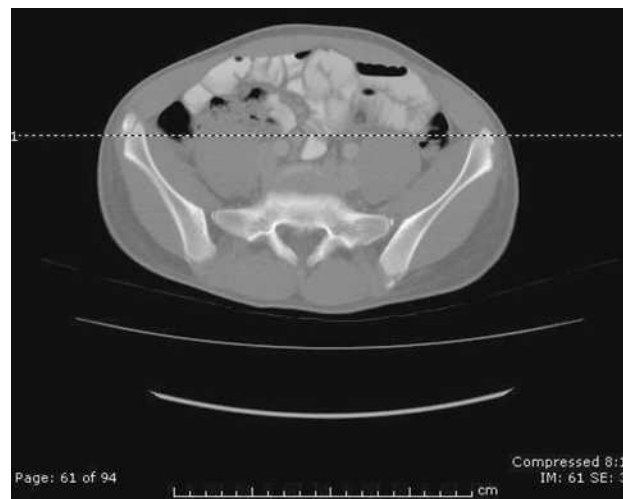


**Figure 333-2** Congenital scoliosis. Failure of segmentation: A, block vertebra; B, unilateral bar; C, unilateral bar with contralateral hemivertebra.

failure. Therefore, referral to a pulmonologist is often indicated to optimize pulmonary health. The vertical expandable prosthetic titanium rib (VEPTR) was developed to treat this particular disorder. The device can be anchored to the ribs, spine, and/or pelvis to simultaneously expand the chest wall and control the spine deformity. The device is traditionally lengthened every 6 months. The use of this device has gained in popularity as an alternative to early spinal fusion that halts chest wall development and thus additional lung growth. It can also be used to treat congenital chest wall deformities secondary to conditions such as Jeune syndrome and Jarcho-Levin syndrome.

### **Congenital Kyphosis**

Similar to congenital scoliosis, congenital kyphosis is caused by either a failure of segmentation or failure of formation. The anomaly typically occurs at the



**Figure 333-3** Axial computed tomography image of spina bifida occulta of S1.

anterior aspect of the spine. This causes asymmetrical growth, with more growth occurring posteriorly. Thus, with time, a sagittal plane deformity (as viewed from the side) develops that can cause hyperkyphosis of the thoracic spine and loss of lordosis in the lumbar spine. The more severe deformities are usually recognized in the neonate, and they rapidly progress thereafter. The less obvious deformities may not appear until several years later. After progression begins, it does not cease until the end of growth. The most important factor regarding congenital kyphosis is the possibility that a progressive deformity in the thoracic spine can result in paraplegia. This potential outcome is usually associated with failure of the formation of the vertebral body. Congenital kyphosis, for the most part, is a surgical problem. This can take on many forms depending on the degree of deformity, the child's age, and his or her neurologic status. Severe degrees of kyphosis can lead to restrictive lung disease and respiratory symptoms such as dyspnea.

### **Spina Bifida**

*Spina bifida* is a rather nonspecific term often used to describe children with myelomeningocele. This should not be confused with spina bifida occulta, which is usually an incidental radiographic finding in an otherwise normal child. Spina bifida occulta is an incomplete formation of the posterior neural arch, usually at L5 or S1 (Figure 333-3). It generally does not involve the underlying neural elements and has no effect on the child's health. However, this should not be ignored if the area has an overlying sinus, lipomatous lesion, or hemangioma, indicating a possible underlying dysraphism.

Both meningocele and myelomeningocele involve a failure of posterior neural arch formation of the dural layers and of the overlying skin. Thus meninges (meningocele) or meninges and neural elements (myelomeningocele) are exposed. Both conditions usually warrant early surgical closure to prevent

central nervous system infection. Because meningocele does not involve the neural elements, these children are generally not prone to bowel, bladder, and lower extremity paralysis, whereas this is usually the case for children with myelomeningocele. These children are at high risk for hydrocephalus and Arnold-Chiari II malformation, most of them requiring ventriculoperitoneal shunt insertion shortly after defect closure. Although the exact etiology of Arnold-Chiari II malformation is debatable, it is generally thought to be secondary to progressive caudal migration of the hindbrain, resulting from the low-pressure gradient caused by the open myelomeningocele. This leads to impaired cerebrospinal fluid dynamics and, ultimately, hydrocephalus. These children are also at risk for other central nervous system-related problems, such as hydromyelia, diastematomyelia, and tethering of the spinal cord.

Myelomeningocele is a severe disorder affecting many different systems, requiring a multidisciplinary team model to coordinate a child's care and optimize a his or her health. Spinal care is often complicated by many factors: allergy to latex; lack of protective sensation; increased risk of postoperative wound infections; major joint contractures; and poor soft tissue coverage over the spine.

Spinal deformity is common in myelomeningocele. It is present in up to 70% of children. With thoracic-level paralysis, the incidence is as high as 94%. Therefore, all children should be periodically screened. It can present in many different forms, including idiopathic-type curves, long-sweeping curves typical of neuromuscular disease, congenital scoliosis or kyphosis related to vertebral anomalies, and severe lumbar level kyphosis. Children should be assessed for how the deformity is affecting their life. Treatment should be individualized to the child. It may be wise to delay treatment as long as possible in ambulatory children because surgical treatment may affect their ability to ambulate efficiently. On the other hand, a nonambulatory child who is having problems maintaining proper wheelchair sitting balance, resulting from a large curve causing pelvic obliquity and severe trunk shift, may be better suited for more expedient surgical care—particularly if the child is not able to use his or her hands because they must be used to support the trunk. In general, it is appropriate to attempt bracing in mild curves (25 to 45 degrees) in a skeletally immature child. This may slow the rate of progression. Children with curves that progress beyond 45 degrees can be considered for surgical treatment; but, again, the child's individual needs must be considered when making this decision. As with scoliosis related to other etiologies, it is desirable, when possible, to delay definitive fusion in a child with substantial growth remaining to allow for ample chest wall maturity to occur.

Lumbar kyphosis is a very difficult deformity to manage in this patient population. It can present very early and create problems with defect closure and skin integrity. It is more common in lower thoracic and upper lumbar levels of paralysis. In the event of skin breakdown over the prominence, an attempt should be made to modify the child's activities and seating

supports to remove pressure from the area. With progressive deformities, surgical treatment is often the only alternative. This usually involves removing a portion of the spine (kyphectomy) and performing an instrumented spinal fusion. The assistance of a plastic surgeon may be necessary for soft tissue management and wound closure.

### **Larsen Syndrome**

Larsen syndrome is an autosomal-dominant osteochondrodysplasia. Recently, Larsen syndrome was shown to be caused by missense mutations or small in-frame deletions in the *FLNB* gene. These children have very marked orthopedic-related problems, including multiple dislocated joints, clubfeet, cervical kyphosis, and scoliosis. It is imperative that the cervical spine is evaluated early in this patient population. Cervical kyphosis and anterior-posterior dissociation can threaten the spinal cord. Furthermore, the presence of either needs to be recognized to avoid catastrophic events during intubation for other required surgical procedures.

Cervical kyphosis should be surgically treated if the spinal cord is under compression. This should be evaluated by magnetic resonance imaging (MRI). If cord compression is evident by imaging or physical examination findings, then posterior spinal fusion should be performed. Continued anterior spinal growth may correct the deformity with time.

Anterior-posterior dissociation can also be present in children with cervical kyphosis. This entails a lack of continuity between the anterior and posterior aspects of the vertebra through multiple wide pars interarticularis defects. This is best seen on computed tomography (CT). Simple posterior fusion will not adequately address this particular problem. Therefore, a long anterior-posterior fusion will be necessary. The abnormal portion of the spine must be fused to more normal areas.

Scoliosis is reported in 25% to 70% of children with Larsen syndrome. Onset is usually in the juvenile age group. Treatment is similar to juvenile idiopathic scoliosis. However, bracing must be recommended with caution because the chest wall plasticity associated with these children can be problematic. The pressure induced by the brace may cause chest wall deformities.

### **Goldenhar Syndrome—Ocular-Auriculo-Vertebral Spectrum**

Abnormalities in Goldenhar syndrome include a variety of ocular, auriculo, and vertebral anomalies, and thus was appropriately renamed *ocular-auriculo-vertebral spectrum* (OAVS). However, of note, the terms *Goldenhar syndrome* and *OAVS* are used interchangeably to describe this myriad of congenital anomalies.

The incidence of OAVS is rare; the prevalence is estimated to be approximately 1 in 45,000 live births. Male infants are affected more often than female infants, and the right side of the face or body (or both) is generally more commonly and severely affected than the left. OAVS has wide phenotypic variation, and, at present, no clear standard for diagnosis exists.

However, authorities generally agree that the spectrum includes 2 or more of the following abnormalities: ear malformations (including microtia and accessory tragi), low-set ears, hemifacial microsomia (including micrognathia), coloboma, and vertebral anomalies (fused or cervical hemivertebrae). Of these abnormalities, multiple accessory tragi in a preauricular-mandibular distribution is one of the more constant findings and is an important diagnostic clue to recognizing the syndrome. Multiple malformations, including congenital heart, brain, and renal disease, have been seen in small numbers of children with OAVS.

Abnormalities of the spine are present in up to 60% of this patient population. Congenital malformations as seen in children with congenital scoliosis are common. Therefore, children identified as having this syndrome should be routinely screened for spinal anomalies.

#### **Morquio Syndrome (Mucopolysaccharidosis Type IV)—Odontoid Dysplasia With Atlantoaxial Subluxation**

Mucopolysaccharidosis type IV (A and B) is also known as *Morquio syndrome*. This disorder consists of 2 forms with similar clinical findings and autosomal recessive inheritance. Mucopolysaccharidosis type IV-A results from mutations in the gene-encoding galactosamine-6-sulfatase, located at 16q24.3. Mucopolysaccharidosis type IV-B (a milder variant) is caused by  $\beta$ -galactosidase deficiency. The clinical features result from accumulation of keratin sulfate and chondroitin-6-sulfate. In both forms, mental symptoms are absent or only mildly present, a feature that distinguishes it from the other mucopolysaccharidoses. These children seem “normal” at birth but will present at 12 to 18 months of age with an “abnormal” appearance. The musculoskeletal findings may include joint laxity, short stature, pectus carinatum, genu valgum, pes planus, and enlarged joints. Corneal clouding is present in 50% of cases. These individuals often stand with their hips and knees flexed and their head thrust forward on a shortened neck.

Individuals with Morquio syndrome often present to the orthopedist with thoracolumbar kyphosis. Radiographically, they have flattened vertebrae with an anterior beak in the thoracolumbar spine (Figure 333-4). This may resolve with growth but may become progressive and eventually require surgical neural element decompression and spinal fusion.

The spinal manifestation most concerning in this population is atlantoaxial instability secondary to odontoid hypoplasia. This can cause upper cervical cord compression. These children present with difficulty walking. It is important not to ascribe this to their lower extremity problems. The potential for this problem should be evaluated before intubation for other surgical procedures with flexion-extension cervical spine radiographs. This is a surgical problem that, when present, needs to be addressed quickly. Morquio syndrome is also associated with pulmonary complications such as obstructive sleep apnea and restrictive lung disease. Therefore, referral to a pulmonologist is often indicated.



**Figure 333-4** Lateral radiograph of a child with Morquio syndrome. Note wedging of vertebrae with anterior beaking.

#### **VACTERL Complex**

VACTERL complex refers to anomalies of the vertebrae, atresias in the gastrointestinal tract, congenital cardiac lesions, tracheoesophageal defects, renal and distal urinary tract anomalies, and rib and limb lesions. The categorical breakdown of anomalies in a large series were as follows: vertebral (25%), anal, esophageal (or other gastrointestinal) atresia (15%), cardiac (33%), tracheoesophageal fistula (95%), urinary (renal dysplasia, urethral valves) (17%), and skeletal (16%). The overall incidence of infants born with 3 or more components of this spectrum is estimated to be 1 in 25,000 live births.

#### **Treatment Advances**

Several groups have reported exciting advances in spinal surgery techniques to correct deformities. Research concerning the successful implementation of growing rods has revived this technique as a viable option for preserving near-normal growth of the spine in both congenital and acquired disorders.

New techniques were also recently described, including vertebral body stapling that produces asymmetrical and corrective growth of the concavity of a deformity. This ultimately may prove to be a useful technique to treat children with scoliosis that continues to progress despite brace wear.



## Acquired Abnormalities

### Scoliosis

Acquired scoliosis can present in many different forms. It is very important that the treating physician make the correct diagnosis because treatment options vary depending on the etiology. The most common form of acquired scoliosis is idiopathic in nature. Although much has been done to elucidate the genetics contributing to this form of scoliosis, little is still known of its etiology. Traditionally, this form of scoliosis was classified as infantile (0 to 3 years), juvenile (4 to 10 years), and adolescent (>10 years). More recently, the term *early-onset scoliosis* has been used to classify children with the onset of deformity before age 5 years. Adolescent idiopathic scoliosis is the more common variety of the 3 and is the most common form of acquired scoliosis.

Acquired scoliosis can also occur in children with certain genetic and neuromuscular diseases. The treating physician must recognize when a child is at risk and appropriately screen for progression. Referral to a pulmonologist is recommended if there are concerns for restrictive lung disease.

Children particularly prone to developing progressive scoliosis are those with static encephalopathy, especially those with spastic quadriplegia. These children commonly develop large thoracolumbar or lumbar scoliosis that can affect their sitting balance (Figure 333-5). This type of spinal deformity can also cause marked pelvic obliquity. Unfortunately, little is known of the natural history of scoliosis in this patient population. The available literature is conflicting. It seems that these curves do tend to progress if they exceed 40 to 50 degrees before skeletal maturity. Treatment options vary depending on the overall health of the child, degree of truncal deformity, effect the spinal deformity has on the child's ability to function, and expectations of the caregivers. The effect of bracing on this type of scoliosis is controversial. However, at times it can be a useful modality to improve the child's sitting balance. Wheelchair modification can also be an effective measure. For curves that are progressive and causing functional limitations, particularly issues with wheelchair sitting, spinal fusion and instrumentation are sometimes necessary. These usually involve fusion to the sacrum with fixation to the pelvis to control pelvic obliquity. This is an extensive operation with significant risks, but with reports of very high caregiver satisfaction. Surgical intervention is sometimes warranted when scoliosis is causing severe restrictive lung disease.

### Infantile Idiopathic Scoliosis

Infantile idiopathic scoliosis presents before the age of 3 years. Most patients are boys with convex left curves. Females with convex right curves have a worse prognosis. It should only be diagnosed after all other etiologies are excluded. This type of scoliosis resolves spontaneously in most children. There are radiographic criteria to predict curve progression. For those that progress, the disease can significantly reduce life expectancy because of cardiopulmonary compromise. These curves can become quite large at a very young age. Treatment is difficult because of the



**Figure 333-5** Neuromuscular scoliosis with pelvic obliquity.

young age of the children. Early spinal fusion should be avoided to allow for continued chest wall and lung development. There are few data to suggest that bracing effects the natural history of the disease. More recently, serial casting has gained momentum as a means of controlling the deformity. There have been some reports of deformity resolution. If resolution is not accomplished or the deformity continues to progress, then surgical options that do not involve a formal fusion of the spine should be considered. Children with curves greater than 20 degrees should have total-spine MRI to rule out an underlying dysraphism.

### Juvenile Idiopathic Scoliosis

Juvenile idiopathic scoliosis is typically defined as scoliosis that presents in the 4- to 9-year age group. It presents during a time of relatively slow spinal growth. These curves can behave as either infantile or adolescent in nature. Up to the age of 6 years, the girl-to-boy ratio is equal and convex left curves are common. After the age of 6 years, girls are predominately affected and convex right curves are more common. Similar to children with infantile idiopathic scoliosis, those affected in this age group can rapidly progress and develop cardiopulmonary compromise. A recent study reported that children with curves

30 degrees or greater at the onset of puberty have a 100% chance of requiring surgery. Treatment is dependent on the age of the patient and the degree of progression. For curves exceeding 20 to 25 degrees, bracing can be instituted. It can also be attempted for larger curves in hopes of slowing progression to allow time for chest wall development. In a skeletally immature child, curves greater than 40 degrees can be considered for surgical treatment. Because of the young age of these children, recent emphasis has been placed on nonfusion instrumentation (growing rods) that controls the deformity but still allows growth. This allows the surgeon and child to postpone a definitive spinal fusion and instrumentation until the child achieves adequate chest wall and pulmonary development.

As with children with infantile idiopathic scoliosis, these children should have a total spine MRI to rule out an underlying spinal dysraphism.

### Adolescent Idiopathic Scoliosis

Adolescent idiopathic scoliosis (AIS) is the most common type of idiopathic scoliosis. It is defined as a lateral curvature of the spine of more than 10 degrees with vertebral rotation on a standing radiograph. Typically, the deformity is discovered when truncal asymmetry is noted. Adam's forward bend test is commonly used to assess the rib or flank prominence created by the scoliosis (Figure 333-6). A scoliometer measurement can be made of the angle of trunk rotation (ATR). A 7-degree ATR is often cited as the magnitude at which to initiate referral. The efficacy of school screening remains a controversial and debated topic.

It is critical that the treating physician rule out other etiologies because AIS is a diagnosis of exclusion. One should look for the presence of abnormal cutaneous findings, asymmetry of shoulder height and scapular prominence, waist line asymmetry, and iliac crest height discrepancy, which indicates a leg-length discrepancy. The child's feet should be assessed for asymmetry or deformity. For example, a child with a



**Figure 333-6** Adam's forward bend test.

unilateral high-arched foot (cavus foot) or a cavus foot with clawed toes may have an underlying neural axis abnormality (eg, syringomyelia) or nervous system disease (eg, Charcot-Marie-Tooth disease). The child should have a complete neurologic examination.

Patients with back pain should be questioned carefully to ascertain whether the pain is a serious problem or simply fatigue related. Certainly, children having pain that limits their ability to perform activities of daily living or engage in their usual activities should raise concern. Furthermore, pain that is associated with unexplained weight loss, malaise, night pain, fevers and chills, or neurologic complaints should be thoroughly evaluated.

Standard screening radiographs include upright posteroanterior and lateral views that include the cervical spine and pelvis. These should be obtained on 36-inch cassettes. The lateral radiograph should be taken with the elbows flexed in front of the child and hands positioned beneath the chin. The arms should not be flexed forward as is standard for a chest radiograph. Curves are measured with the Cobb measurement (Figure 333-7). Advanced imaging such as MRI or CT are appropriate in certain cases when an underlying neural axis or structural abnormality is suggested by the history, physical examination, or radiographs. Radiographic findings suggestive of an underlying



**Figure 333-7** Cobb angle measurement.

neural axis abnormality are convex left thoracic curves, double thoracic curves, triple curves, long right thoracic curves with an end vertebra (the last vertebra contributing to the Cobb measurement) caudal to T12, and curves with a high or low apex. These findings are even more concerning in boys. Additionally, thoracic curves that have normal kyphosis or hyperkyphosis on the lateral radiograph should raise suspicion of an underlying neural axis abnormality because thoracic scoliosis is normally a hypokyphosing or lordosing deformity.

It is thought that AIS is likely a genetically linked disorder, but the genetics of the disease have not been fully elucidated to date. Adolescent idiopathic scoliosis typically progresses during times of rapid growth, such as the adolescent growth spurt when children are at their peak height velocity (PHV). Therefore, it is important to determine where the children are in their development. For girls, the onset of menses is an important landmark, as is the development of axillary hair in boys. Both typically occur about 6 months before the PHV. Radiographically, it is useful to assess whether the triradiate cartilage is open or closed and the Risser sign (Figure 333-8). Typically, closure of the triradiate cartilage occurs after PHV; in boys, however, closure may signal the start of PHV. Immature children with a Risser grade of 0 or 1 and with curves exceeding 20 degrees have an approximately 70% chance of progression. A bone age radiograph (posteroanterior left hand radiograph) is often useful because a child's chronologic age and skeletal age can differ. A lateral radiograph of the elbow can also be useful in determining whether children have achieved their PHV (Figure 333-9).

The natural history of scoliosis depends on the degree of deformity, location of the curve, and skeletal maturity of the child. As for curve patterns, thoracic curves and double curves are most likely to progress in immature individuals. After skeletal maturity, thoracic curves greater than 50 degrees tend to progress at a rate of about 1 degree per year. Thoracolumbar

and lumbar curves may progress into adulthood even when below 50 degrees in magnitude. In general, curves less than 30 degrees at skeletal maturity tend not to progress. The effect scoliosis has on overall health is not well documented. Respiratory failure has been documented in adults with scoliosis greater than 110 degrees. However, according to a recent long-term follow-up study of 117 children with untreated scoliosis, most children reported good general health. They reported more back pain, but this did not seem to affect their ability to work or perform activities of daily living. Children with curves greater than 80 degrees tended to experience shortness of breath with activities more often, but this did not reach statistical significance.

Treatment of AIS depends on the age of the child and the curve magnitude. In general, brace treatment is initiated in skeletally immature children (Risser grades 0–2) with curves in the range of 30 to 45 degrees or with curves that progressed more than 5 degrees after presenting at 25 to 30 degrees. Individuals who have a Risser grade of 0 and a curve of 25 degrees or greater should be considered for bracing. The use of bracing seems to be supported by the current literature.



**Figure 333-8** Risser sign. The iliac crest apophysis ossifies, radiographically, from lateral to medial. Risser V equals skeletal maturity.



**Figure 333-9** Lateral elbow radiography in a 10-year-old girl. Note the present of two olecranon ossification centers, indicating that she is at peak height velocity.



For children who continue to progress beyond 50 degrees in the thoracic spine and perhaps 40 to 45 degrees in the thoracolumbar or lumbar spine, surgical treatment can be considered. The goal of the operation is to balance the trunk, while fusing the fewest levels possible, and obtaining a solid fusion to prevent progression. Many different approaches can be used, each having pros and cons, but most children undergo a posterior spinal fusion and instrumentation.

### Kyphosis

An excessive amount of thoracic kyphosis can occur for many reasons, including, but not limited to, spinal tumors, radiation, trauma, infection, or surgery (eg, after laminectomy). The most common cause of acquired kyphosis is an osteochondrosis known as Scheuermann disease (see Chapter 303, Osteochondroses), which occurs in 5% of the population. Scheuermann disease, by definition, involves wedging of 3 contiguous vertebrae more than 5 degrees (Figure 333-10). Alternatively, glucocorticoid-induced osteoporosis, caused either by supraphysiologic

levels of endogenous glucocorticoids (Cushing disease) or by exogenously administered glucocorticoids, can provoke kyphosis. Excess glucocorticoids often act to suppress bone formation and increase bone resorption, leading to trabecular bone loss, vertebral body collapse, and pathologic fractures and resulting in an increased propensity to kyphotic spinal malalignment. The most common site is in the lower thoracic vertebrae, but this condition can occur in any site in the vertebral column. The initial event is bulging of the intervertebral discs in the direction of contiguous vertebral bodies, which exerts pressure against the cartilage plates covering the bodies, causing thinning of the plates. This event interferes with endochondral bone formation on the growth surface of the plates, causing gaps that are the basis for the herniation of the disc into the bodies, isolating the apophyseal ossification center from the vertebral body. The disc space narrows, more so anteriorly, causing increased pressure on the anterior portions of contiguous vertebral bodies and impeding their longitudinal growth anteriorly, resulting in attendant kyphosis.

In children with Scheuermann disease, an aching pain aggravated by physical exertion is present in the affected part of the vertebral column, typically the thoracic or thoracolumbar spine. The affected area may be tender to palpation. Having the child assume a stooping position often causes the pain to increase. In many instances, the pain is so minor that the child first complains of pain caused by *poor posture*, and then the kyphosis is noted. Radiographs reveal a narrowing of the anterior disc space and defects on the surfaces of adjacent vertebrae at sites where the disc tissue penetrated the bodies. The prolapsed disc tissue, in time, becomes walled off by osseous tissue, forming a bulbous mass of extruded tissue appearing as an area of lucency in the affected body (Schmorl nodule). In some children, the condition can progress to cause severe deformity and dysfunction.

Treatment depends on the cause of the hyperkyphosis. Obviously, in cases of hyperkyphosis caused by medically related problems, the underlying source of the problem must be addressed. When spinal stability is compromised secondary to previous operation, tumor treatment, infection treatment, or trauma, the spine will need to be surgically stabilized. For children with maintained spinal stability and acceptable balance, casting or bracing may assist with pain management until the underlying problem is adequately addressed.

In children with Scheuermann disease who have adequate growth remaining, bracing may be useful. A physical therapy regimen focusing on spinal extensor and abdominal wall strengthening is reasonable and should be attempted for at least 6 months before entertaining any thought of surgical treatment. The indications for the surgical treatment of Scheuermann disease are limited. The natural history is generally benign. For children with kyphosis exceeding 70 degrees who have recalcitrant pain and a self-perceived unacceptable appearance, surgical treatment may be warranted. This typically involves an instrumented fusion procedure.



**Figure 333-10** Lateral radiograph of a child with Scheuermann kyphosis. Note wedging of the apical vertebra and end-plate irregularities or Schmorl nodes (superior aspect of T12).



### Back Pain

Although scoliosis and kyphosis can be painful, they are usually painless postural deformities. The pediatrician should be aware of several painful disorders related to spinal deformity (see Chapter 131, Back Pain).

### Spondylolysis and Spondylolisthesis

Spondylolysis is a defect in the continuity of the pars interarticularis, which is a strut of bone that connects the superior and inferior articular processes of a vertebra. In children and adolescents, it usually involves either L4 or L5 (Figure 333-11). In certain children, it may lead to forward slippage (listhesis) of the vertebral body, known as *spondylolisthesis*. The horizontal slippage usually involves the L5 vertebral body moving anteriorly in relationship to S1. However, this deformity can occur anywhere in the vertebral column. Both spondylolysis and spondylolisthesis can cause back pain. The pain may radiate to the buttocks, but true radicular symptoms are rare. The pain is usually activity related, worse when upright than when seated or supine. Because spondylolysis is fairly common in young athletes with low back pain, primary care physicians need to have a high index of suspicion with this group of children.

Trauma, causing disruption of the pars interarticularis, is thought to be the cause of spondylolysis in a genetically susceptible host. Gymnasts and other athletes (football front lineman) who repeatedly hyperextend the spine have a higher incidence of spondylolysis than the

general population. In adolescence and adulthood, the incidence is estimated at 6%. Current research emphasizes the role of spinopelvic balance in the pathogenesis and treatment of spondylolisthesis. Spondylolisthesis can progress in certain children, especially during times of accelerated growth; therefore, periodic follow-up is indicated in children 10 years of age or younger.

The physical examination may reveal tenderness in the lower back. The child may have tight hamstrings and, in the case of a high-grade slip (>50%), may assume a posture of leaning forward, with the hips and knees flexed. Usually, children experience pain with trunk extension.

The diagnosis is usually suggested by the history and physical examination findings and confirmed with radiographs. At times, advanced imaging is necessary. For example, single-photon emission tomography scan is useful when the diagnosis is suspected but radiographs are normal. A CT scan is useful for gaining a better assessment of bony detail, and an MRI is useful when neurologic symptoms are present.

In the absence of symptoms, spondylolysis or spondylolisthesis with less than a 50% listhesis requires no treatment. If a child has significant low back pain, then activity modification, physical therapy, and a brace may be used in an effort to ameliorate the symptoms. For those with recalcitrant pain or pain associated with slips of greater than 50%, surgical stabilization may be necessary. In cases of spondylolysis, in an otherwise normal spine, an attempt can be made to perform a pars interarticularis repair, treating the defect like a fracture and avoiding a formal spinal fusion. Theoretically, this is a motion-preserving procedure. For those with spondylolisthesis, particularly listhesis greater than 50%, surgical stabilization is most often accomplished by an instrumented spinal fusion. Whether the listhesis should be reduced or whether the surgery is performed anteriorly, posteriorly, or by a combined approach remains a topic of considerable debate.

### Infections of the Spine

*Pyogenic spondylitis* is a term used to describe both diskitis and vertebral osteomyelitis. Both entities may represent different spectrums of the same process. This is a common cause of back pain in children younger than 8 years. Because the disc is relatively avascular, the infection most likely starts in the vertebral end plates and then involves the disc. With time, the vertebral body becomes involved. These children may present with abdominal pain, back pain, limp, or refusal to walk. The differential diagnosis is broad. At times, these children may seem ill. Typically, they try to avoid flexion of the spine and have a very hard time picking objects up off the floor. They typically flex through their knees and avoid flexing the trunk. Inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate are commonly elevated.

The radiograph of a child with pyogenic spondylitis reveals disc space narrowing and end-plate irregularities. Magnetic resonance imaging further delineates the extent of disease and reveals any abscesses (Figure 333-12, Figure 333-13).



**Figure 333-11** Spondylolysis of L4.



**Figure 333-12** Lateral radiograph of a child with L3-4 diskitis.

Treatment is generally nonsurgical. Infectious disease consultation may be appropriate. Antibiotic treatment targeted for *Staphylococcus aureus* is usually curative. An orthosis may be used to treat pain. For those who do not respond, an image-guided percutaneous biopsy can be performed.

It is important to keep atypical infections in mind when evaluating children with spinal infections. Tuberculosis of the spine (Pott disease) typically affects the vertebral body to a greater extent and can spread subligamentously (beneath the anterior longitudinal ligament). As with pyogenic spondylitis, treatment is generally medical in nature.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Backpack Safety* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/safety-prevention/at-play/Pages/Backpack-Safety.aspx](http://www.healthychildren.org/English/safety-prevention/at-play/Pages/Backpack-Safety.aspx))
- *Lower Back Pain in Athletes* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/injuries-emergencies/sports-injuries/Pages/Lower-Back-Pain-in-Athletes.aspx](http://www.healthychildren.org/English/health-issues/injuries-emergencies/sports-injuries/Pages/Lower-Back-Pain-in-Athletes.aspx))
- *Spina Bifida* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/developmental-disabilities/Pages/Spina-Bifida.aspx](http://www.healthychildren.org/English/health-issues/conditions/developmental-disabilities/Pages/Spina-Bifida.aspx))



**Figure 333-13** Sagittal magnetic resonance imaging of same child with L3-4 diskitis.

### AAP POLICY

American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health and Task Force on Pain in Infants, Children, and Adolescents. The assessment and management of acute pain in infants, children, and adolescents. *Pediatrics*. 2001;108(3):793–797 ([pediatrics.aappublications.org/content/108/3/793](http://pediatrics.aappublications.org/content/108/3/793))

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**Chapter 334****SPORTS MUSCULOSKELETAL INJURIES***Nirupama Kannikeswaran, MBBS; Srinivasan Suresh, MD, MBA*

Sport injuries result from acute trauma or repetitive stress associated with athletic activities. Thirty to 35 million children ages 5 to 18 years participate in organized sports in the United States. Many athletes now train in sports year round and frequently play several sports at a time. Organized sports account for only approximately one-third of sports injuries, with the remainder occurring in physical education classes and recreational sports. A study based on the national emergency medicine data set (2008) estimated that approximately 432,609 emergency department (ED) visits were made by 13- to 19-year-old children who experienced sports-related injuries, with total charges close to \$447.4 million and a mean total per-visit charge of \$1,205. The most frequently occurring injuries were superficial injury or contusion ( $n = 118,250$  ED visits); sprains and strains ( $n = 105,476$ ); fracture of the upper limb ( $n = 63,151$ ); open wounds of the head, neck, and trunk ( $n = 46,176$ ); and intracranial injury ( $n = 30,726$ ). The incidence of traumatic brain injury in children ages 5 to 14 years increased by 40% from 498.8 to 888.7 per 100,000 visits from 2001 to 2010.

Wrestling and football have the highest significant injury rates per participant in high school, followed by softball, gymnastics, track and field, and soccer. Tennis and swimming produce the fewest injuries. Frequency of injury, however, is not always the best measure of a sport's risk. The trampoline, for example, accounts for a disproportionately large number of injuries that cause paralysis. Although younger athletes appear to be at greater risk for injury because of lack of experience, injury rates are actually higher in older athletes because of increased speed, strength, size, and competitive motivation. Indeed, injury rates are higher in older high school students than among junior high and younger participants.

This chapter discusses some issues regarding sports participation such as drug use, overuse syndromes, and acute trauma-related injuries. It also discusses the common problem of anterior knee pain in young athletes. Sports medicine is a discipline in itself. This chapter can serve only as an introduction to some of the more common problems. Sports medicine texts should be consulted for more information on treatment and exercises for rehabilitation.

Most sports injuries are predictable and often preventable. Estimates suggest that nearly two thirds of all injuries might be reduced by improvements in conditioning, equipment, compliance with rules, coaching and supervision, rehabilitation of existing injuries, and efforts to prevent reinjury.

Many schools use certified athletic trainers for the prevention of and rehabilitation from sports injuries. These programs should be encouraged and supported. Inexperienced coaches with high expectations

of young athletes and a poor understanding of training may contribute to injury.

Participation in organized sports provides an opportunity for young people to increase their physical activity and develop physical and social skills. However, when the demands and expectations of organized sports exceed the maturation and readiness of the participant, the positive aspects of participation can be negated. The nature of parental or adult involvement can also influence the degree to which participation in organized sports is a positive experience for children of all ages. The American Academy of Pediatrics (AAP) offers recommendations on how primary care physicians can help determine a child's readiness to participate, how risks can be minimized, and how child-oriented goals can be maximized. The AAP also provides information for primary care physicians on sports participation for children and adolescents with medical conditions.

**DRUG USE IN ATHLETES**

Athletes frequently use drugs and nutritional supplements that they believe will give them a competitive advantage or improve their strength or appearance. The AAP and the American College of Sports Medicine have issued policy statements condemning the use of these supplements.

Despite this warning, use of drugs and stimulants is exceedingly common. Anabolic steroid use has been reported to be as high as 5% to 11% among high school boys and 2.5% among high school girls.

Anabolic steroid use is most common among football players and track participants. Clues to excessive use include jaundice, increased acne, behavioral changes (aggressiveness, irritability, marked mood swings), gynecomastia, and testicular atrophy. Women may develop hirsutism and deepening of voice. Liver enzymes may be elevated, and lipid profile may be adversely affected. Although controversy exists, anabolic steroids do appear to increase muscle mass and decrease catabolism of muscle in some situations. Anabolic steroid withdrawal may cause side effects such as mood changes, irritability, hot flashes, nausea, myalgia, malaise, tachycardia, and hypertension. Little information is available on long-term effects.

The Anabolic Steroids Control Act of 1990 made most anabolic steroids schedule-3 controlled substances (abuse of the drug may lead to moderate or low physical dependence or high psychological dependence). Illicit distribution is a felony. However, androstenedione, often mentioned in the media as a drug used by major league baseball players is still available without a prescription. Unlike most androgen supplements, creatine supplements can be obtained legally at many gyms and health food stores. Though they are not banned in professional sports or in the Olympic games, some supplements are found to contain small doses of stimulants that may cause athletes to test positive for banned substances. Creatine is converted to phosphocreatine in muscle with the help of the enzyme creatine kinase. Phosphocreatine is believed to serve as a reservoir for the depletion of the high-energy phosphate adenosine triphosphate



(ATP). The idea behind the supplements is that excess phosphocreatine will lead to a higher rate of ATP re-synthesis during exertion and delay the fatigue that results from activities requiring short bursts of high-intensity muscle contraction. Little evidence exists that creatine is helpful in endurance sports. Some athletes argue that it helps them train more vigorously by reducing the time to recover from exertion.

Creatine supplements appear to increase serum creatinine levels, which is not an indication of renal dysfunction but a reflection of an increased creatinine load. Long-term effects of such supplements are unknown. The American College of Sports Medicine recommends against creatine supplementation in athletes younger than 18 years old.

## INJURIES TO BONE AND SOFT TISSUES

Injuries related to sports participation fall into the general categories of overuse syndromes that develop over time and acute traumatic injuries.

### Overuse Syndromes

Overuse injuries are characterized by injury to bone, cartilage, or soft tissue caused by repetitive submaximal physical stress. In contrast to an acute fracture or soft-tissue injury, the tissue breakdown in overuse injuries occurs gradually. This phenomenon of hard- and soft-tissue breakdown is a normal, daily occurrence. The body continually remodels these tissues so that they recuperate fully. Overuse injuries happen when the chronic repetitive stress overwhelms the normal reparative processes without sufficient recovery time.

In young athletes, the frequency with which these problems occur has grown tremendously over the last several decades. Box 334-1 lists factors that contribute to overuse injuries in young athletes.

An increasing proportion of youths are becoming involved in competitive sports. More young athletes are training harder and longer than before as competition intensifies. Many athletes now train year round for participation in a sport, whereas others participate in several sports each year, even playing several sports at a time. Time off is not usually considered a

priority. Inexperienced coaches may have unrealistic expectations of young athletes. All these factors contribute to the growing number of training errors that often underlie these conditions.

Prevention of overuse syndromes involves the education of young athletes, their parents, their coaches, and the entire health care team, from trainers to physicians. Understanding these principles is crucial to returning an athlete to sports successfully after experiencing one of these overuse conditions. Failure to change the underlying problem often simply results in reinjury.

### Stress Fracture

Stress fracture of bone is conceptually the simplest overuse syndrome of the musculoskeletal system. When there is an imbalance between bone resorption and formation, repetitive loading of the bone leads to microfracture that eventually progresses to a stress fracture. Stress fracture commonly occurs with long-distance running. Hard running surfaces, poor footwear, overtraining, and female athlete triad (amenorrhea, disordered eating, and osteoporosis) are some of the risk factors associated with stress fractures. Nearly 50% of stress fractures occur in the tibia. Other commonly reported sites are the metatarsals, fibula, navicular bone, and lumbar spine. The usual presenting symptom is pain during or soon after activity and eventually progresses to pain at rest. Plain radiographs have a low sensitivity for diagnosing stress fractures, and can be normal for up to the first 3 weeks with symptoms. A bone scan has a high sensitivity, but low specificity. Magnetic resonance imaging (MRI) is the diagnostic modality of choice. Avoiding painful activities is crucial until healing occurs. The athlete can typically return to the sport after being pain free for 1 month.

### Metaphyseal and Diaphyseal Stress Injuries

The athlete may experience gradual onset of symptoms of metaphyseal and diaphyseal stress injuries. Eventually, pain may preclude running. In some circumstances, the weakened bone may fail completely and result in a complete or displaced fracture. Although most of these injuries occur in later adolescence (ages 16–19 years), some do occur at younger ages. Typically, the distribution of male and female patients is equal. Metaphyseal and diaphyseal stress fractures in young athletes most commonly involve the fibula, metatarsals, tibia, femur, and ulna, but virtually any bone can be affected. Stress fractures of the metatarsals (typically the second or third) and the distal fibula rarely have complications other than pain and temporary disability. Fractures of the tibia, humerus, and forearm rarely displace, but they have the potential to do so. Stress fractures of the hip are rare but have the highest potential for morbidity; displaced femoral neck fractures can disrupt the blood supply to the femoral head and lead to avascular necrosis and arthritis.

A bone scan may detect an early stress fracture of the metaphysis or diaphysis (see Table 334-1). The bone scan findings, however, must be correlated to the clinical symptoms. As many as 50% of adolescents

#### BOX 334-1 Factors Contributing to Overuse Injuries in Young Athletes

- Training errors
- Increased recreational time
- Increased intensity and duration of competition
- Increasing standards of competition
- Inadequate preseason conditioning
- Suboptimal facilities and equipment
- Overly enthusiastic coaches and parents
- Participation in multiple sports
- Lengthy seasons



with stress fractures will show multiple areas of stress response on bone scan, many of which do not correlate to areas of symptoms. For stress fractures, MRI may be the most sensitive study.

Most diaphyseal and metaphyseal stress fractures are managed by rest. Crutches are often necessary. Occasionally, casts and immobilization are needed. Healing time ranges from 4 to 12 weeks. A well-designed plan of alternative training, gradual resumption of participation in sports, and monitoring for recurrent symptoms is necessary. Stress fractures occasionally require surgical intervention.

### Apophyseal Conditions Osgood-Schlatter Disease

In 1903, Osgood and Schlatter separately described a disorder of the proximal tibial apophysis that commonly affects young athletes but may affect other active youngsters who are not involved in formal, organized sports. The tubercle of the proximal tibia is the insertion site of the patellar tendon. The quadriceps is the strongest muscle group in the body, and the tensions it generates through the patellar tendon are enormous. Stresses applied at the interface between the tendon and the apophysis create a disruption of the normal transition from the ossified and unossified tubercle into the tendon. This condition commonly occurs with impact and decelerating activities such as running, jumping, and cutting. Patients are typically 10 to 15 years of age at the time of onset of this disorder.

Boys are more commonly affected than girls; however, female gymnasts are particularly prone to this problem. Approximately 15% of teenage boys and 10% of teenage girls have complained of pain at their tibial tubercle at some point. Bilaterality is high, though its reported incidence varies considerably. The average youngster with symptomatic Osgood-Schlatter disease has significant pain, tenderness, and swelling of the tubercle on the presenting side and usually has some degree of findings on the contralateral side as well. Many of these patients have a history of heel pain compatible with Sever disease (calcaneal apophysitis). As many as 20% to 30% have siblings who also have had apophysitis. Signs and symptoms of intra-articular problems of the knee joint itself are absent. A lateral radiograph of the knee can help confirm the diagnosis by showing irregularity of the tibial tubercle and rule

out a tumor or infection, which can mimic Osgood-Schlatter disease.

In most patients, Osgood-Schlatter disease will run its course with time. Symptoms can last for 1 to 4 years. In approximately 3% of patients, a persistent ossicle will form that can remain symptomatic and may ultimately require surgical excision. Fracture of the tibial tubercle has been reported in patients with Osgood-Schlatter disease; its incidence is not known, but it appears to be low. Thus, remaining active in sports is possible.

The symptoms are often relieved with topical application of an ice pack to the area, intermittent use of oral nonsteroidal anti-inflammatory drugs (NSAIDs), application of a compression band over the area, activity modifications as indicated by the symptoms, and hamstring stretching. Casts are not routinely used because immobilization may weaken ligament insertions. However, brief periods of rigid immobilization may be necessary for acute exacerbations.

### Sinding-Larsen-Johansson Disease

Sinding-Larsen-Johansson (SLJ) disease affects the inferior pole of the patella and typically occurs as a result of the same stresses that lead to Osgood-Schlatter disease. Although an apophysis is not present at the inferior pole of the patella, a transition of the patellar ligament fibers occurs as they join the bone. In response to chronic repetitive stresses, the patellar periosteum can create a bony reaction, which is a classic finding of SLJ disease. Repetitive, eccentric, and decelerative loading of the extensor mechanism of the knee such as running, jumping, and kicking sports exacerbate symptoms.

Affected children are typically 10 to 13 years of age. They complain of well-localized pain at the inferior pole of the patella. As with patients with Osgood-Schlatter disease, they have no signs or symptoms of internal derangement of the knee joint itself. On physical examination, they exhibit point tenderness at the inferior edge of the patella, and typically have no other abnormal findings. A lateral radiograph of the knee may demonstrate irregular ossification at the inferior pole of the patella. Some physicians mistake this finding for a fracture.

Pain in the same area without radiographic change is often caused by patellar tendonitis or jumper's knee. This phase is an early stage of SLJ disease. With

**Table 334-1**      **Parts of the Growth Plate of a Long Bone**

NAME	ROOT ORIGIN	DEFINITION
Physis	—	Specialized area of growth cartilage occurring at both ends of major long bones or at 1 end of the smaller tubular bones, such as metatarsals and phalanges
Epiphysis	Epi- (on)	Secondary ossification center interposed between the physis and joint articulation
Metaphysis	Meta- (next to)	Flared transition from the primary spongiosa of the physis to the dense tubular bone of the diaphysis
Diaphysis	Dia- (in between)	Dense cortical and tubular bone comprising the shaft
Apophysis	Apo- (arising from)	Specialized growth cartilage area to accommodate insertion of a major tendon

advanced skeletal maturity, the periosteal reaction is usually not seen.

This entity is self-limited and typically lasts 3 to 12 months. Similar to Osgood-Schlatter disease, treatment with ice, NSAIDs, and activity modification may be helpful. Immobilization and surgery are rarely necessary. Rupture of the patellar tendon or a sleeve fracture (avulsion of the inferior pole of the patella with attached cartilage) is not a well-recognized complication of this disorder. In general, athletes may participate in sports as tolerated.

### **Calcaneal Apophysitis**

Calcaneal apophysitis, or Sever disease, occurs at the apophyseal insertion of the Achilles tendon into the calcaneus. The patient is typically 9 to 14 years of age, with a substantial peak occurring at 10 and 11 years of age. Most (60%–80%) cases are bilateral. This is usually seen in impact sports that involve running and in sports in which cleats are worn.

Athletes may complain of heel, ankle, or foot pain. On physical examination, however, the discomfort is typically well localized at the region of the calcaneal apophysis. It is typically medial or posterior, although occasionally the tenderness may be on the lateral side. Rarely does the tenderness occur distal near the origin of the plantar fascia. No swelling, warmth, or limitation of motion should be present. Occasionally, because of concurrent tendonitis, some tenderness can occur along the course of the Achilles tendon itself. Pain is reproducible with medial and lateral compression of the heel (“the squeeze test”). No classic radiographic change of calcaneal apophysitis is seen. Significant irregularity of the ossifying calcaneal apophysis is a normal finding at this age and should not be confused with evidence of a fracture.

Radiographs of the heels can be obtained to rule out other osseous processes, such as tumor or infection. In bilateral cases, radiographs are only necessary if some atypical component of the history and physical examination exists, which raises concern about some other diagnosis.

Treatment focuses primarily on symptom management. This condition almost always resolves with time, and complications are extremely rare. Shoe inserts that provide padding beneath the heel can be helpful. The material must be resilient enough so that it does not collapse. Typically, a 3/8-inch silicone or felt pad works best. Ice, NSAIDs, and activity modification may be indicated based on severity of symptoms. Casts or controlled ankle motion walkers (removable rigid walking splint) are occasionally necessary for severe cases. Surgery is not indicated.

**LITTLE LEAGUE ELBOW.** Little League elbow is seen in young throwing athletes, especially pitchers, and is caused by traction of the medial structures of the elbow during the acceleration phase of pitching. The term is used to describe a group of injuries of the elbow, including apophysitis and fragmentation of the medial epicondyle, and osteochondritis dissecans of the radial head and capitellum. Patients usually present with medial elbow pain and have localized tenderness of the medial epicondyle. These athletes

should refrain from throwing until symptoms resolve. Specific therapy includes muscle strengthening and pitch training. Activity modification and adherence to league regulations that limit the number of pitches are beneficial.

## **Repetitive Physeal Injuries**

### **Little League Shoulder**

Little League shoulder, or physiolysis of the proximal humerus, is a widening of the proximal humeral physeal plate. It occurs almost exclusively in Little League baseball players. It typically affects pitchers, but occasionally, players who do a lot of throwing from other positions can develop Little League shoulder. Usually the patient is a 12- to 15-year-old boy who complains of pain in the shoulder related to overhead throwing. The key consideration in the differential diagnosis is internal impingement, which presents in younger, overhead athletes. This refers to a constellation of conditions that include rotator cuff tears, labral tears, biceps tendonitis, anterior instability, and scapular dysfunction, which result from the performance of repetitive actions at the limits of arc of motion under extreme loading conditions. This results in pathologic changes at the point of contact of the humeral head with the undersurface of the rotator cuff in the gleno-humeral joint resulting in labral and rotator cuff injury. Many of the signs and symptoms are the same. Another differential diagnostic consideration is impending pathological fracture from a simple bone cyst in the upper humerus.

Radiographic widening of the proximal humeral physis on the affected side confirms the diagnosis of Little League shoulder. The essence of treatment is rest. Complications are uncommon. If the symptoms are minimal, then the young baseball player can often be allowed to bat and play in an infield position that involves minimal throwing. Clinical and radiographic resolution can take up to 6 months. A carefully planned resumption of pitching can then begin, but monitoring for recurrence of symptoms is necessary.

### **Physeal Widening of the Distal Radius**

Physeal stress injury of the distal radius occurs almost exclusively in young female gymnasts (“gymnast’s wrist”). These injuries usually cause progressive pain in the wrists. Most often the pain is bilateral, but it may be more prominent on 1 side. On physical examination, point tenderness is often present, and a prominence may be noted on the dorsum of the distal radial physis. Differential diagnoses include carpal laxity with dorsal wrist capsular impingement, posterior interosseous neuroma, and avascular necrosis of the lunate. Anteroposterior and lateral radiographs should demonstrate the physeal widening. Comparison films of the other side are almost always obtained, though both sides may be involved. Typically, some asymmetry is noted.

Premature closure of the distal radial physis has been described, resulting in relative overgrowth of the ulna at the wrist. This closure causes asymmetric loading of the carpal bones, which can lead to chronic wrist disability. The goal of treatment is resolution of symptoms and normalization of the radiographs,

which usually takes 3 months or longer. Once the athlete returns to gymnastics, clinical and radiographic monitoring are required.

### Epiphyseal Overuse Conditions

The best example of a repetitive stress-related injury of the epiphyses occurs at the capitellum (the lateral condyle of the distal humerus where it articulates with the radius). These injuries are typically classified as osteochondroses rather than stress fractures. In osteochondroses, a segment of epiphyseal bone and overlying articular cartilage becomes loose.

### Osteochondritis Dissecans of the Capitellum

Although the term *osteochondritis dissecans* implies an inflammatory process, there is no histologic evidence. Osteochondritis dissecans is clearly a repetitive stress phenomenon, and it occurs most commonly in baseball pitchers. As the ball is released during the pitching motion, a valgus movement occurs at the elbow. Tension occurs on the medial side of the elbow, and compressive forces are created across the radial capitellar articulation. The capitellum has an end-arterial blood supply, which may be partially responsible for its susceptibility to avascular necrosis from these chronic repetitive compression forces.

Any pitching style that releases the ball lateral to the body's midsagittal plane accentuates the valgus moment at the elbow. Therefore side-arm pitches and many curve-ball techniques can increase the compression loads across the lateral side of the elbow.

Patients typically experience aching pain in the lateral side of the elbow. With time, they can lose range of motion. Osteochondral fragments can displace acutely, resulting in a loose body sensation, a locked elbow, significant synovitis, and pain. Plain film radiographs often demonstrate a lesion of the capitellum. Either a sclerotic region or radiolucency may be present. Tangential views may be necessary to visualize the lesion. Occasionally, computed tomography scanning or MRI or both are helpful.

Unlike most overuse syndromes in young athletes, the sequelae of this condition are not always benign. Osteochondritis of the capitellum can result in permanent arthrosis of the elbow joint.

Junior baseball programs typically have rules limiting the frequency and duration that youngsters can pitch. Typically, this limit is 3 innings per game and up to 6 innings per week. Young athletes, parents, and coaches need to be educated about this condition so that excessive pitching does not occur at other times. The American Sports Medicine Institute has published recommendations to prevent injuries in youth baseball players.

Cases of osteochondritis dissecans of the capitellum occasionally heal with prolonged rest. However, surgery is indicated for locked elbow, symptomatic loose bodies, and persistent pain and limitation of movements after a period of nonoperative treatment.

### Overuse Syndrome of Soft Tissues

#### Tendonitis

Tendonitis is seen with less frequency in young athletes compared with their adult counterparts because the apophysis (site of attachment of the tendon to

bone) is weaker than the tendon itself and more likely to get injured. Tendonitis is divided into 3 stages based on the progression of the disease. These stages are (1) from inflammation of the paratenon (the fatty or synovial tissue between a tendon and its sheath), (2) through inflammation of the tendon itself, and (3) into degenerative change of the tendon that ultimately results in rupture. Typically in young athletes, only the earliest inflammatory stage is seen.

The most common tendonitis in young athletes is that of the Achilles tendon, seen usually in dancers, gymnasts, and figure skaters. Symptoms are typically located 2 to 6 cm above the insertion of the Achilles tendon into the calcaneus. Some lack of flexibility in the gastrocnemius muscle group may be found on physical examination. Other sites include the rotator cuff in throwing athletes and swimmers, and the ilio-psoas in dancers.

The diagnosis is typically made clinically. Radiographs and MRIs are rarely indicated. The treatment in young athletes is entirely nonoperative. If analysis of lower extremity mechanics during gait suggests a hyperpronation pattern, then custom foot orthoses can help control this hyperpronation. Ice, stretching, and NSAIDs are also used. Training modifications and heel lifts can be helpful as well. Immobilization is rarely necessary.

#### Internal Impingement

The rotator cuff is a convergence of the tendons of the subscapularis, supraspinatus, infraspinatus, and teres minor muscles. These tendons extend laterally from the scapula over the humeral head. Together, they function to help stabilize the humeral head in the glenoid fossa of the scapula. A particularly important function of the rotator cuff is preventing the upper humerus from impinging on the superior glenoid and undersurface of the rotator cuff. The supraspinatus muscle is most important for this function.

Many factors contribute to rotator cuff tendonitis. In young athletes, inherent laxity of the glenohumeral capsule (ligament complex) is likely to be a significant factor. Sporting activities that stress the shoulder joint with the arm extended overhead are particularly prone to precipitate symptoms. Some typical activities include overhead throwing in baseball, swimming, tennis serves, and gymnastics. Once a shoulder becomes irritated, a reflex arc inhibits the firing of the rotator cuff muscles. This precipitates further dysfunction of the shoulder muscle and leads to impingement of the humeral head beneath the acromion. With time, a well-established bursitis and tendonitis develop. Typically, the patient complains of pain with overhead activities. In many instances, the athlete will complain of the arm becoming heavy or tired or feeling dead. Full-thickness rotator cuff tears are almost never seen in children younger than 18 years.

The neck and shoulder should be thoroughly examined, assessing for range-of-motion limitation, muscle atrophy, and focal tenderness in the subacromion region, both anteriorly and laterally. Tenderness may occur along the course of the biceps tendon as well. Bringing the shoulder fully overhead may produce pain; this finding is referred to as a *positive impingement test*.

**Table 334-2**     **Severity Grading of Sprains**

GRADE	DESCRIPTION	CLINICAL PRESENTATION	TYPICAL RECUPERATION TIME
I (mild)	Stretching of the ligament with minimal microscopic injury	Mild swelling, limp	0–2 wk
II (minor)	Partial disruption of the ligament	Modest swelling, diffuse tenderness, difficulty bearing weight	1–4 wk
III (severe)	Complete disruption of the ligament	Extensive swelling and bleeding, instability, and disability	4–12 wk

The supraspinatus strength should be tested, and glenohumeral laxity should be assessed as well. Plain film radiographs are not diagnostic of rotator cuff tendonitis but are often obtained to rule out other bony abnormalities. An MRI can be diagnostic for rotator cuff tendonitis but is often not necessary. The diagnosis can usually be made clinically.

### Acute Trauma

Acute injuries include sprains, muscle tears, and fractures. Sprains are injuries to ligaments, and they typically are graded from mild to severe (see Table 334-2).

The fundamental principles of treatment for many musculoskeletal injuries go by the acronym RICE (rest, ice, compression, and elevation). Rest is especially important for the first 24 to 72 hours after a significant injury. For lower-extremity injuries, crutches should be used to avoid bearing weight. Randomized studies have demonstrated that athletes can return to full activity faster if cryotherapy is begun immediately after the injury. Ice may be applied for 20 minutes every 2 to 4 waking hours. A wet cloth can be used between the ice and skin to decrease the chance of cold injury. Many trainers advise continuing the use of ice until the swelling disappears completely. Compression may be applied with an elastic bandage. The goal of elevation is to place the injured extremity above the level of the heart to aid in reducing edema.

### Ankle Sprains

Ankle sprains are the most common musculoskeletal injury in sports and account for 28% of all sports-related injuries. Approximately 97% involve the lateral ankle ligaments. Rarely, the syndesmosis (high ankle sprain) and medial ligaments are involved. The typical mechanism of injury involves inversion and external rotation of the foot, which results in a sequential tearing of the anterior talofibular ligament, calcaneal fibular ligament, and finally, the posterior talofibular ligament.

The presence of bony tenderness should be determined, particularly over the distal fibula, the anterolateral tibia, the medial malleolus, the base of the fifth metatarsal, or the proximal fibula. In the skeletally immature athlete, the bone is usually weaker than the ligaments; thus lateral ankle injuries often result in physeal fractures of the distal fibula. Sometimes, separating focal tenderness over the physis from diffuse tenderness of the lateral ankle ligaments can initially be difficult. Percussing with the tip of the finger can

often separate tenderness at the proximal physis from tenderness around the ligaments.

Stress tests such as anterior drawer and talar tilt can be performed to confirm the diagnosis and grade injury severity. Anterior drawer test is performed by using a brisk motion to pull the heel forward with the ankle relaxed in 10-degree plantar flexion, and stabilizing the distal lower leg with the nondominant hand. The test result is positive if more anterior displacement is noted compared with the uninjured side. Talar tilt test assesses the calcaneal fibular ligament. It is performed using a brisk motion to invert the calcaneus and the talus on the fibula, with the ankle in neutral or slight dorsiflexion and stabilizing the distal lower leg with the nondominant hand. The test result is considered positive if there is more inversion compared with the uninjured ankle.

The distal fibular physis is weaker than the surrounding ligament; therefore, all skeletally immature athletes need radiographs of the ankle to rule out fibular fracture. As simple as the injury may sound, the treatment options for ankle sprains are complicated. Treatment modalities vary widely and are chosen based on the severity of the injury (see Table 334-2), the demands of the athlete, and the experience of the treating health care team.

If the injury does not appear severe, then RICE principles can be applied and the ankle periodically reevaluated. At reevaluation, if the pain is minimal and the ankle is stable, the athlete should then be observed in functional tasks such as running, cutting, and twisting. If these tasks are performed well without significant pain, then the individual may return to competition. Ideally, the ankle should be taped or splinted to lessen the risk of reinjury, and a preventive physical therapy program should be considered.

For ankle sprains of moderate grade, many other options come into play. For the less-serious athlete, an expectant approach can be used, including crutches, elastic bandage wrap, and gradual progression of weight bearing, with the athlete returning to sports only after symptoms resolve. Occasionally a cast or controlled ankle motion walker is helpful. For the serious athlete with moderate-grade sprains, referral to a physical therapist is often helpful. Range of motion is begun early, and strengthening is emphasized. As the ankle becomes comfortable, a proprioception training phase of rehabilitation begins. In all cases, functional criteria for return to sports, prevention of reinjury, and reassessment of progress are key components.



Severe-grade sprains should be managed by someone with advanced skills in dealing with musculoskeletal problems. A period of immobilization to reduce bleeding and swelling is often helpful. Assessment for chronic laxity and tarsal coalitions should be made. The risk of reinjury after an initial ankle sprain is 5 times higher and 20% to 40% of athletes experience chronic ankle instability. Return to sports averages 8 days for grade I, 15 days for grade II, and 28 days for grade III lateral ankle sprains.

Persistent anterolateral ankle pain can occur after even mild ankle sprains. In many instances, this ankle pain is caused by an area of fibrosis or synovial hypertrophy in the anterior lateral corner of the joint. The differential diagnosis should include chondral and osteochondral injuries at the dome of the talus, chronic laxity of the ankle or subtalar joints (or both), and tarsal coalition. If symptoms persist, then referral to an orthopedist or sports medicine specialist is indicated.

### **Collateral Ligament Injuries of the Knee**

Injuries to the medial and lateral collateral ligaments occur rarely in skeletally immature individuals, because ligaments are stronger than the growth plates. Physeal injuries should always be suspected in children with open growth plates. The collateral ligaments of the knee originate from the epiphyses of the femur and insert into the epiphyses of the tibia and fibula, with 1 exception. The distal portion of the superficial medial collateral ligament inserts over a broad area of the proximal tibial metaphysis. The mechanism is a valgus stress and/or external rotation of the tibia on a fixed foot, and often occurs in contact sports. The player reports sharp medial knee pain, immediate swelling, and inability to bear weight. Physical examination reveals severe limitation of range of motion.

Plain film radiographs may not be diagnostic. Stress radiographs or an MRI are usually needed to make this diagnosis. Concurrent injury to the cruciate ligaments, menisci, and articular surfaces need to be considered as well.

Most collateral ligament injuries heal satisfactorily. Initially, the principles of RICE are used. Depending on the severity of the injury, the knee is mobilized as the swelling and tenderness diminish. As range of motion returns, strength should be assessed. A physical therapist or athletic trainer can be helpful in designing an adequate rehabilitation program. For moderate- and severe-grade sprains, the use of a dual, upright, hinged, functional knee orthosis should be considered.

### **Anterior Cruciate Ligament Injuries**

As adolescents become skeletally mature, the incidence of anterior cruciate ligament (ACL) injuries rises rapidly. While ACL injuries can occur from direct contact of the lower extremity of an athlete with another player or an object, about 70% of these injuries occur without any contact mechanism (noncontact). Such noncontact ACL injuries occur with evasive maneuvers that involve some form of deceleration, change of direction, or landing. Four factors: hormonal, anatomic, environmental, and neuromuscular,

particularly predispose female athletes to noncontact ACL injuries.

Overall incidence of ACL injuries is about 1 in 100 high school-aged athletes, with girls 2 to 8 times more likely to sustain these injuries. The increased incidence in girls is thought to be the result of the effect of estrogen on ACL laxity, genu valgum, shape of the intercondylar notch, hyperextensible knees, and poor neuromuscular control of knee motion during athletic tasks such as landing and cutting. These injuries are commonly seen in sports that involve cutting and twisting such as soccer, basketball, gymnastics, and football.

In classic cases, athletes describe an acute pop and pain in the knee after a rotational injury on a fixed foot. They often fall to the ground and experience moderate to severe pain. The knee typically swells within the first few hours because of the development of a hemarthrosis with significant limitation in range of movements. Occasionally the tenderness is not marked, and athletes will attempt to return to their sporting competition, only to discover that the knee is not stable, which may worsen the injury. A high index of suspicion should be maintained for ACL injury and it must be ruled out before the young athlete with a knee injury returns to practice or competition.

The most sensitive physical examination component is the Lachman examination, which is performed with the patient lying supine; the knee is gently flexed to approximately 30 degrees. The patient must be able to relax the quadriceps and hamstrings enough to allow the examiner to attempt to slide the proximal tibia anteriorly. Although the amount of movement of the tibia has some importance, the key factor is the endpoint. If the test is negative (ie, the ligament is intact), then a distinct endpoint or cessation of forward movement should be felt. This endpoint should feel similar to holding the 2 ends of a short piece of rope and quickly pulling the ends apart until the movement suddenly stops.

This test may however be falsely negative soon after the injury when the knee is painful and swollen. The size of the patient's leg, the ability of the patient to relax, and the size of the examiner's hands are factors that contribute to successful performance of the test. If doubt exists, then the knee should be reevaluated later or the patient referred to an orthopedist.

Radiography should be performed in a skeletally immature athlete to rule out a tibial eminence fracture that can mimic an ACL injury. Radiographs may also reveal a "Segond fracture" (avulsion fracture of the lateral aspect of proximal tibia) which is pathognomonic of an intra-articular injury. Arthroscopy or MRI is often required for a definitive diagnosis of an ACL injury.

Initial treatment for an ACL injury consists of RICE and bearing weight as tolerated. Aspiration of the joint may be helpful in relieving pain in athletes with a large hemarthrosis. A comprehensive rehabilitation program including weight-bearing and range of motion exercises should be initiated early. The rehabilitation program should include an assessment of and remedy for biomechanical predisposition to ACL injury. Specific exercises that encourage balance, coordination, and reaction will help to sharpen the

responses in the surrounding structures, thus minimizing the effect of the lost ligament. Left without the stability of the ACL, most knees in young, active adolescents eventually become symptomatically unstable, and reinjury will occur. For the very young athlete, a brace, physical therapy, and activity modification is probably the best approach to managing ACL injuries. In older and less-active patients, nonoperative management of these injuries plays a role; however, most ACL injuries in young athletes should be reconstructed. In contrast to the collateral ligaments of the knee, the healing potential of the ACL is limited because of its susceptible vascular supply. As a result, most injuries to the ACL do not heal well, and primary surgical repairs (as opposed to reconstructive surgery) are not effective.

Return to sports varies from 6 to 12 weeks for those treated nonoperatively to 6 to 8 months for those who undergo surgical reconstruction.

### **Meniscal Tears**

The meniscal cartilages have several important functions within the knee joint. These functions include providing mechanical shock absorption between the weight-bearing articular cartilages of the femur and tibia, enhancing the distribution of synovial fluid, which provides nourishment to the superficial portion of the articular cartilage, and enhancing the stability of the articulation between the tibia and femur. Loss of the meniscal cartilages has little detectable effect on the knee joint initially. However, over the ensuing decades, particularly after 20 years, the rate of degenerative joint disease rises significantly. As a result, all reasonable efforts should be made to protect, preserve, and repair menisci of younger patients.

In youths 10 years of age and younger, most meniscal tears are related to discoid menisci. These menisci are congenitally abnormal, and are almost always on the lateral side of the joint. Discoid menisci are thicker than normal menisci, less mobile, and much more prone to tear.

A discoid variant, the Wrisberg type, has thick margins and is usually not attached to the capsule posteriorly. These patients exhibit a classic finding of a snapping knee. As the knee actively extends, it suddenly shifts and pops as the thick, mobile discoid meniscus shifts between the weight-bearing surfaces of the tibia and femur.

For patients older than 10 years, the incidence of tearing of normal menisci rises. Most commonly, this tearing occurs in association with significant ligament injury, such as a tear of the ACL. Rarely do normal menisci in teenagers tear without a substantial injury. As a result, meniscal tears are not typically at the top of the list of differential diagnoses of a young athlete with gradual onset of nonspecific knee pain. Meniscal tears usually occur when the knee is twisted during weight bearing. The player reports a popping sensation, a feeling of the knee “giving out,” and “locking of the knee” with inability to fully extend the knee.

Meniscal tears are assessed with the McMurray and Apley compression tests. The former is performed with the patient supine, by flexing the knee and applying valgus stress on the lateral aspect of the knee. Then the

knee is flexed and extended while alternately internally and externally rotating the tibia. A ‘click’ indicates a positive test result. The Apley test is performed with the patient prone and the knee flexed to 90 degrees. Pressure is applied to the heel while the tibia is rotated. Presence of pain with this maneuver indicates a positive test.

If a meniscal tear is suspected, then an MRI or referral to an orthopedic surgeon is indicated. Some studies suggest that MRI may not be as sensitive and specific for meniscal tears in children as in adults, and hence, judicious use of MRI is recommended.

The pattern and location of the tear determine whether the meniscus may heal on its own or will require arthroscopic partial removal or repair. The principles of treatment are to preserve as much of a normal functioning rim of meniscal cartilage as possible while alleviating the mechanical snapping that ultimately leads to degenerative changes of the articular surfaces. Symptomatic discoid lateral menisci require surgical intervention.

### **Quadriceps Contusion**

Minor contusions of the quadriceps muscle are common events in contact sports such as football, soccer, and lacrosse. However, significant hematomas can develop within the quadriceps, which can be quite disabling. More extensive hematomas have a propensity to rebleed. Myositis ossificans traumatica (heterotopic ossification of the muscle) may develop, which can also be disabling.

The key finding for separating minor hematomas from major ones is limitation of knee flexion when tested 12 to 24 hours after injury (mild >90 degrees; moderate, 45–90 degrees; severe, <45 degrees). Occasionally, differentiating a large quadriceps hematoma from a malignant tumor of the thigh becomes challenging, such as Ewing sarcoma and osteosarcoma, both of which have a propensity to occur in teenagers and which may bleed internally themselves.

Initial treatment of quadriceps hematoma involves RICE and crutches. As pain and swelling diminish, active knee flexion exercises are begun. Full return of motion is the minimal requirement for return to contact sports, at which time a padded guard should be used. Monitoring for reinjury is essential. Return to sports averages 13 days for mild contusions, 19 days for moderate contusions, and 21 days for severe contusions.

### **Avulsion Fractures of the Pelvis**

Six major apophyses are present on each side of the pelvis. These apophyses include the iliac crest, the anterior-superior iliac spine, the anterior-inferior iliac spine, the lesser trochanter, the greater trochanter, and the ischial apophysis. Each of these areas is prone to develop an apophysitis, and, except for the greater trochanter, avulsion fractures also are fairly common.

An avulsion fracture typically causes acute onset of pain during a sudden athletic motion. Examples include an explosive start for a sprint, an extreme pike maneuver (hips flexed and knees extended) in gymnastics, or a combination twisting movement and direct blow to the iliac crest. A complete history will

sometimes reveal mild antecedent symptoms consistent with a preexisting apophysitis.

Findings include focal tenderness to palpation over the affected apophysis and pain with resisted strength testing of the corresponding muscle insertion or origin. The diagnosis can often be confirmed with plain film radiography. Special oblique views and occasionally a computed tomographic scan or an MRI are helpful.

Most of these avulsions do not cause significant displacement; almost all heal with time and rest. Typically, crutches and rest are suggested for the first few weeks. Stretching may inhibit healing and should be avoided until the site is pain free. Complete healing typically takes 6 weeks to several months. The athlete should gradually return to activity and be monitored for recurrence of symptoms.

### Muscle Strains

Injuries to muscle tendon units almost always occur at the musculotendinous junction. These are caused by a sudden forceful change in the length of the muscle-tendon unit, resulting in a stretch or tear of the muscle fibers. Similar to sprains, muscle tendon injuries vary in severity from mild to severe, depending on the degree of injury to the muscle and range of motion. Mild injuries heal fairly rapidly, whereas severe strains can lead to large areas of scar tissue that are prone to reinjury.

The diagnosis of muscle strain has several pitfalls. Muscle strains are not as common in young athletes as they are in older athletes. The diagnosis of a strain is too often applied to a musculoskeletal malady for which the true diagnosis is not obvious to the examiner. Particularly around the hip and thigh area, the examiner should be careful not to miss a slipped capital femoral epiphysis, an avulsion fracture, an infection, or a tumor as causes of pain.

The most common muscle strain in teenage athletes is of the hamstring. This strain causes pain at the junction of the middle and distal thirds of the posterior thigh. More proximal hamstring tenderness should raise suspicion of an occult injury to the ischial apophysis.

The treatment principles for hamstring strain initially involve RICE and crutches. Reduction of tenderness can take days to weeks, depending on the initial severity of the injury. Once comfortable, a gradual stretching and strengthening program is initiated. The athlete can return to activities as tolerated and be monitored for recurrent symptoms. Reinjury is likely in 12% to 31% of hamstring strains. Return to play ranges from 2 to 3 days for mild strains to 3 to 12 weeks for severe strains.

### Dislocations

The most common dislocations of young athletes include patella, shoulder (glenohumeral joint), elbow, and fingers. With severe trauma, dislocations and fracture dislocations can occur in virtually any joint, and musculoskeletal specialists generally manage these injuries.

**PATELLAR DISLOCATION.** A common musculoskeletal dislocation in young athletes involves the patella. Patellar dislocation should not be labeled as knee dislocation, which denotes displacement of the

articulation between the tibia and femur. The latter is a high-energy injury and has a high associated morbidity including, occasionally, loss of limb. By contrast, patellar dislocation is often the result of a trivial injury. Many individuals are predisposed to dislocation of the patella as a result of genetic variability in their knee extensor mechanism. Variations leading to easy dislocation include a shallow sulcus in the distal femur, lateral translation of the insertion of the patellar tendon into the tibia, relative underdevelopment of the vastus medialis muscle, and tightness of the lateral retinaculum.

The incidence is estimated at approximately 43 children per 100,000 and is similar in both sexes. Almost all patellae dislocate to the lateral side. The history of injury can vary from a minor twisting episode to a significant direct blow to the knee. Occasionally the athlete will report having seen a medial prominence, but this is typically because the medial femoral condyle is exposed by the displaced patella.

A patellar apprehension test, wherein the athlete expresses fear that the patella may dislocate as the examiner applies gentle laterally directed pressure, is almost always positive. Ninety percent of patellar dislocations resolve spontaneously. Manipulative reduction can often be achieved relatively easily. Procedural sedation and gentle extension of the knee will result in the reduction of the laterally located patella.

Unless the patellar dislocation or subluxation is a trivial event that incites little pain in the joint, radiographs should be obtained to assess for osteochondral fragments. These loose pieces typically arise from the lateral femoral condyle or the patella.

After a significant patellar dislocation, the knee is immobilized, and the principles of RICE are used. As the pain and swelling subside, a rehabilitation program is initiated that emphasizes strengthening of the quadriceps muscles, particularly the vastus medialis. The hamstrings are stretched and a lower extremity rehabilitation program is undertaken. A patellar-stabilizing knee sleeve is used during the initial phases of return to activity.

Most patellar dislocations can be successfully managed with a single therapeutic program. Recurrent patellar instability, particularly in those with a familial history, may require reconstruction.

**SHOULDER DISLOCATION.** As with the patella, dislocations of the shoulder joint can occur from relatively minor trauma in predisposed individuals or as a result of major trauma in the average person. Approximately 90% of the dislocations are anterior. Posterior dislocations tend to occur with seizures or trauma. The most common mechanism of injury is a forceful abduction/external rotation with or without an associated fall. The patient typically holds the affected arm in a cradle position, and there is loss of shoulder contour.

Reduction can occur spontaneously; however, fixed dislocations can be difficult to reduce. These dislocations may require transportation to an emergency care facility. Reduction may require expertise, local anesthesia, sedation, and occasionally, general anesthesia. Unless the episode is minor, radiographs are generally obtained to confirm reduction and rule out an associated fracture.

Traditionally, shoulder dislocations have been treated with 3 weeks of immobilization, followed by a rigorous physical therapy program. The therapy should be directed at strengthening the rotator cuff muscles. The principle is to strengthen these dynamic stabilizers of the joint to help compensate for laxity of the shoulder joint capsule. Recurrent instability despite a therapy program is generally an indication for surgical stabilization.

### Anterior Knee Pain

The most common knee complaint of adolescents is that of anterior knee pain. This ubiquitous symptom can arise from a wide variety of disorders. In many cases, a specific diagnosis such as Osgood-Schlatter disease, SLJ disease, patellar tendonitis, or patellar instability can be made. In some instances, a degree of psychological overlay to the symptoms can be found, which can make management challenging.

Some of the more common causes of anterior knee pain have been discussed previously, and 2 additional entities—chondromalacia patella and patellofemoral pain syndrome—are discussed here. A wide variety of less common disorders not discussed in detail here can cause anterior knee pain. These disorders include quadriceps tendonitis, bipartite patella, osteochondritis dissecans of the femur or patella, iliotibial band tendonitis, popliteus tendonitis, and prepatellar bursitis. Osteomyelitis, septic arthritis, inflammatory arthritis, and tumors should always be kept in mind.

### Chondromalacia Patella

The term *chondromalacia patella* refers to softening of the articular surface of the patella, which can occur in mild to severe grades, ranging from edema of the cartilage to complete ulceration of the articular surface. This term had previously been misapplied to virtually any case of anterior knee pain. The diagnosis should be reserved for specific instances of symptomatic articular change of the surface of the patella.

In mild cases, the pain from chondromalacia patella will abate with intermittent use of NSAIDs, a quadriceps-strengthening program, and judicious activity modification. Although a therapy program can be helpful, the patient must have a clear understanding that the goal is to reduce symptoms. Completely eliminating symptoms may not be possible. Occasionally, surgical intervention to alter the patella's articular surface is indicated.

### Patellofemoral Pain Syndrome

The typical patient with patellofemoral pain syndrome is a teenage girl older than 12 years who complains of a diffuse pain over the anterior surface of her knee. Predisposing biomechanical factors, including femoral anteversion, external tibial torsion, pronating gait, and increased valgus alignment at the knees, may be present. In some cases, the syndrome may result from training errors. Sudden increase in mileage, running on hard surfaces, poor preseason conditioning, and inadequate footwear may be contributing factors. Although the cause of this problem is not clear, investigators believe that an abnormality of the tracking of the patella is responsible. Abnormal stresses in the

patellofemoral articulation or the surrounding soft tissues are probably responsible. Typically the long-term history of this presentation is benign, though the symptoms can be troublesome.

The typical onset is insidious and without a specific history of trauma. Usually, no signs of erythema, warmth, induration, or effusion is noted. Occasionally, patients describe the knee having become slightly puffy. Typically, mechanical complaints of catching or locking are absent. Popping may be present, and is usually painful. On physical examination, tenderness is often present along the medial and lateral sides of the patellofemoral articulation. Mild discomfort may be felt over the anterior portion of the joint line, but typically no tenderness occurs over the middle or posterior portion of the tibial femoral articulation. The joint is stable with full range of motion and no crepitation. The knee is stable. Plain film radiographs are usually negative. Further diagnostic evaluation is not indicated.

The most important role of the physician in this case is to rule out other serious or more specifically treatable disorders. For patients with significant flexible flat feet, foot orthoses such as arch supports may reduce pronation at the foot and thereby diminish torsional stresses applied at the knee. Stretching and strengthening the quadriceps muscles often reduces anterior knee pain. The principles are to strengthen the vastus medialis and improve patellar tracking. Occasionally, taping or supportive knee sleeves will provide relief. The intermittent and judicious use of NSAIDs may help as well. In some cases, adjustment of expectations and activities is necessary. Psychological concerns need to be considered as well. In refractory cases, referral to a musculoskeletal specialist may become appropriate.

## WINTER SPORTS INJURIES

Millions of people ski, snowboard, and sled each year in the United States. These cold weather activities result in many injuries each year. Various winter sports have distinct injury characteristics (see Table 334-3).

In general, children are more likely to experience upper extremity injuries, and lower extremity injuries are more frequent in adolescents and adults. Children younger than 10 years incur more fractures and

**Table 334-3**

### Injuries Associated With Winter Sports

SPORT	INJURY
Downhill snow skiing	Knee contusions, anterior cruciate ligament sprains, spiral fracture of tibia
Cross-country snow skiing	Medial collateral ligament sprain, acute ankle inversion strain, acromioclavicular joint separation, skier's toe, hypothermia
Snowboarding	Wrist, ankle, and knee injuries
Snowmobiling	Multisystem trauma with head injury
Sledding	Head and face, extremity, abdominal injuries



catastrophic injuries (head injuries) with individual recreational activities than they do with organized winter sports.

## CONCUSSION

The American Academy of Neurology defines concussion as a clinical syndrome of disturbance of brain function typically affecting memory and orientation, which may involve loss of consciousness caused by an impact or jolt to the head. About 1.4 million ED visits are made annually for traumatic brain injury, of which 75% to 90% are the result of concussions. However, this is likely to be underreported because the majority of athletes who sustain a mild traumatic brain injury do not seek medical care or attention. Among high school sports, football and ice hockey have the highest rate of concussion, followed by soccer, wrestling, basketball, field hockey, baseball, softball, and volleyball. The concussion rate is higher among men than women for all sports combined because of higher participation in sports by men. The age of the athlete or level of competition does not affect the rate of concussion. Use of head gear has been shown to have a protective effect against concussion.

The disturbance of brain function in concussion is secondary to changes in brain metabolism rather than structural damage as seen in severe brain injuries. Symptoms of concussion can manifest soon after injury or may be delayed for several hours. Signs and symptoms of concussion typically fall into 4 categories:

1. Physical: Headache, nausea, vomiting, ataxia, visual problems, photophobia and phonophobia, numbness/tingling, dazed, or stunned
2. Cognitive: Feeling slowed down and mentally “foggy,” difficulty concentrating, memory disturbances, confusion about recent events, slow response to questions
3. Emotional: Irritability, sadness, nervousness
4. Sleep: Drowsiness, sleeping more or less than usual, trouble falling asleep

Symptoms of concussion generally last for 72 hours and most of the symptoms resolve within 7 to 10 days. Recovery may be prolonged in some children and adolescents who have persistent concussive symptoms (see section on postconcussive syndrome). Athletes who exhibit worsening of symptoms such as persistent or worsening headache, persistent vomiting, altered mental status, irritability, and focal neurologic signs should be referred to the ED for evaluation.

Medical evaluation is recommended and mandated before participation in organized sports. The central goal of such preparticipation evaluation is prevention of concussion and prompt recognition and reporting of concussive injuries. It is to be reiterated that loss of consciousness is not the only symptom of an athlete having suffered a concussion. The history elicited should include number of previous concussions, severity of concussions, and time of recovery from previous concussions. In an injured athlete, after ensuring that airway breathing and circulation are adequate, acute management includes an assessment

of severity of concussion. Although a number of tools are available for this assessment, the Standardized Assessment of Concussion is well-validated, can be performed at the sidelines in 5 minutes, and has normative data for high school athletes.

Pediatric athletes need help from their parents and coaches to monitor their recovery from a concussion. Adequate sleep and limited physical and cognitive exertion have been shown to facilitate quicker recovery. Symptomatic students may require accommodations with school work until their cognitive functioning improves.

Return to play after a concussion has been the subject of much study and controversy, but most experts agree that an athlete can return to play when:

1. No signs or symptoms of any kind are apparent at rest or during exertion
2. Neurologic examination is normal
3. Neuroimaging, if performed, is unremarkable

## POSTCONCUSSIVE SYNDROME

Postconcussion syndrome (PCS) is defined as persistence of a cluster of cognitive, physical, sleep, and emotional problems beyond the usual period of recovery after a concussion. The presence of at least 3 symptoms 3 months after injury is required to meet the diagnostic criteria for PCS. PCS includes a number of disparate symptoms, such as headache, dizziness, fatigue, irritability, difficulty in concentration and performing mental tasks, memory impairment, insomnia, and reduced tolerance to stress, emotional excitement, or alcohol. Risk factors for persistent symptoms include adolescent age, loss of consciousness, posttraumatic amnesia, initial symptom of headache, high levels of initial symptoms, and a history of prior concussion. Symptomatic pharmacologic and rehabilitative interventions have been prescribed for PCS but the efficacy of such interventions is not known. Exercise, especially noncontact aerobic exercise, may be beneficial and have a positive impact on recovery from PCS provided the athlete avoids impact during the period of vulnerability for repeat injury.

### WHEN TO REFER

- When the diagnosis of the musculoskeletal injury is uncertain
- When injuries involve the growth plate in which future growth may be compromised
- When the patient is not responding to initial treatment
- When uncertainty exists in the safety of the young athlete to return to a competitive sports environment
- When an ACL tear or meniscal tear is suspected

### WHEN TO ADMIT

- Fractures requiring open reduction
- Fractures associated with neuro or vascular injury
- True knee dislocation

- Traumatic brain injury in conjunction with internal organ injuries

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Steroids: Play Safe, Play Fair* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)
- *What Is a Pediatric Sports Medicine Specialist?* (fact sheet), American Academy of Pediatrics (healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Sports-Medicine-Specialist.aspx)

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## Chapter 335 STOMATITIS

Linda S. Nield, MD

Stomatitis, or inflammation of the oral mucosa, is characterized by multiple ulcerations inside the mouth. Frequently painful, this condition may lead to decreased oral intake and dehydration.

### ETIOLOGY

Stomatitis can be a disease entity unto itself, such as recurrent aphthous stomatitis (RAS), or it may be a symptom of an underlying condition. Infection, trauma, irritant exposure, medical interventions, and systemic disorders are the major causes of oral inflammation.

#### Recurrent Aphthous Stomatitis

RAS is a benign condition characterized by painful oral ulcers that recur at irregular intervals. In otherwise healthy individuals, most cases are idiopathic. Although the exact cause of RAS is not known, stress, genetics, hormonal and immunologic influences, trauma, and smoking are suggested triggers for this common condition.

#### Infection

Viruses, bacteria, and fungi can inflame the oral mucosa. Some viral causes include herpes simplex, varicella-zoster, various subtypes of coxsackievirus, rubeola, Epstein-Barr virus, and HIV. Several coxsackieviruses cause an acute febrile illness associated with the development of lesions in the posterior oropharynx known as herpangina. Coxsackie A16 is the most common cause of hand-foot-mouth disease (HFMD), but other enteroviral subtypes have been implicated as causative agents.

*Borrelia vincentii* and *Fusobacterium dentium* are bacterial causes of oral inflammation known as *necrotizing ulcerative gingivitis*. Syphilis, gonorrhea, and tuberculosis can also lead to oral inflammation.

Fungal infections rarely occur in the immunocompetent child except for *Candida* spp. mucositis in the first several months of life. Histoplasmosis can develop in otherwise healthy children and produce mucosal ulceration along with other systemic manifestations.

#### Irritants

Exposure to a large array of external irritants can lead to stomatitis. The irritant may directly traumatize the mucosal surface (irritant contact stomatitis) or incite an allergic delayed-type hypersensitivity reaction (allergic contact stomatitis).

Trauma secondary to biting one's own mucosa or exposure to friction from dental appliances will cause irritant contact stomatitis. A rare condition known as *Riga-Fede disease* is characterized by the formation of ulcerative lesions of the lower lip, lingual frenulum, and ventral tongue secondary to repeated rubbing of the teeth against these mucosal surfaces. The age of onset of Riga-Fede disease is 6 to 8 months and coincides with the age of primary tooth eruption.

Exposure to excessive heat, cold, and acidic or basic substances can irritate the mouth. Smokeless tobacco is another mucosal irritant that has been found to lead to oral lesions in older school-aged children.

The most common causes of allergic contact stomatitis include preservatives and oral flavorings such as cinnamon, menthol, and peppermint. Metals, such as nickel found in dental instruments, may also elicit an oral allergic reaction.

### Iatrogenic Causes

Stomatitis may arise from medical interventions. Chemotherapy agents and radiation are the most notorious iatrogenic causes of mucosal breakdown. These treatments disrupt the mucosal barrier of the mouth, allowing ulceration, desquamation, and secondary infection by both acquired and endogenous flora. Infrequently, medications such as cyclooxygenase-2 inhibitors, non-steroidal antiinflammatory agents, and sertraline (an antidepressant) lead to oral dryness and the development of aphthous stomatitis. The misuse of commercial mouthwash with high alcohol content can also cause oral mucosal ulceration.

### SYSTEMIC DISORDERS

Although typically a benign, self-limited process, stomatitis may be one of the presenting symptoms of a serious, systemic illness such as Behçet syndrome, inflammatory bowel disease, gluten-sensitive enteropathy, diabetes mellitus, systemic lupus erythematosus, scleroderma, dermatomyositis, and granulomatosis with polyangiitis (Wegener). Stomatitis is also caused by periodic fever accompanied by aphthous stomatitis, pharyngitis, and (cervical) adenopathy (PFAPA syndrome), as well as cyclic neutropenia. Nutritional deficiencies of iron, vitamins B<sub>12</sub> and B<sub>6</sub>, folate, and zinc can also cause oral mucosal breakdown. Some dermatologic disorders associated with oral lesions include pemphigus, erythema multiforme, Stevens-Johnson syndrome, erosive lichen planus, and epidermolysis bullosa.

### EPIDEMIOLOGIC FACTORS

Because of the many diverse causes of stomatitis, a large number of children suffer from stomatitis at some time in childhood. RAS is the most common form of painful oral ulcers, and Kleinman and colleagues found that 37% of surveyed school-aged children reported a history of suffering from RAS. The peak age of onset of RAS is in the second decade of life, and bouts may recur throughout adulthood.

Viruses are the most common infectious cause of stomatitis. In the Kleinman study, 33% of the 5- to 17-year-old participants reported a history of recurrent herpes labialis. Herpangina and HFMD are also quite frequently experienced by young children. Outbreaks of acute stomatitis caused by herpangina are most likely to occur in the summer and early fall; HFMD is most likely to occur in the spring and summer. Bacteria and fungi infrequently cause stomatitis in otherwise healthy children, except for *Candida* spp. infection, in the first several months of life. The presence of syphilis and gonorrhea pharyngitis in a young child is rare and suggests sexual abuse and warrants a thorough child abuse investigation.

The number of children who suffer from stomatitis caused by irritants is not known; however, the use of orthodontic devices is quite prevalent, and oral flavorings and preservatives are ubiquitous in many commercial products. Oral inflammation secondary to medications is likely to occur only in the select group of children who use the offending agents.

Stomatitis as the only presenting feature of one of the systemic disorders does occur, but it is rare. About 15% of patients with aphthous ulcers and other symptoms will have a systemic disorder. PFAPA syndrome is a relatively newly described entity, with multiple case series reported in the medical literature.

### DIFFERENTIAL DIAGNOSIS

The differential diagnosis of stomatitis in children consists of the entities listed in Box 335-1.

### CLINICAL MANIFESTATIONS

Each of the conditions associated with stomatitis will display unique clinical features. The history of presentation of the oral lesions will provide the clues for the possible diagnosis. The time of year, the presence of local outbreaks, and the accompanying systemic symptoms should be noted. The physical examination will determine the location of the lesions and the presence of failure to thrive, fever, lymphadenopathy, organomegaly, and dermatologic and joint abnormalities.

#### BOX 335-1 Differential Diagnosis of Stomatitis

##### RAS: Infection

- Viruses: herpes simplex type 1, varicella-zoster, coxsackievirus and other enteroviruses, rubeola, Epstein-Barr virus, HIV
- Bacteria: *Borrelia vincentii*, *Fusobacterium dentium*, syphilis, gonorrhea, tuberculosis
- Fungi: *Candida*, *Histoplasmosis*

##### Irritant contact stomatitis

##### Allergic contact stomatitis

##### Iatrogenically induced stomatitis

##### Systemic disorders:

- Behçet syndrome
- Inflammatory bowel disease
- Celiac disease
- Diabetes mellitus
- Systemic lupus erythematosus
- Scleroderma
- Dermatomyositis
- Granulomatosis with polyangiitis (Wegener)
- PFAPA syndrome
- Cyclic neutropenia
- Nutritional deficiencies
- Dermatologic disorders

HIV, human immunodeficiency virus; PFAPA, periodic fever accompanied by aphthous stomatitis, pharyngitis, and (cervical) adenopathy; RAS, recurrent aphthous stomatitis.



The recurrence of 1 or more painful ulcers on the buccal, labial, and lingual surfaces, as well as on the floor of the mouth, characterizes RAS. The oral lesions will be the only physical examination finding. Three clinically distinct types of RAS have been described. Small, round craters, smaller than 5 mm in diameter and surrounded by an erythematous halo, typify the minor variety that heals in 1 to 2 weeks. The major variety may last 6 weeks and is characterized by lesions larger than 5 mm that often scar. The herpetiform variety is named as such not because herpesvirus is the etiologic agent but because of its herpes-like appearance of multiple, small clusters of pinpoint lesions that resolve in 1 week to 10 days. The child with RAS is otherwise healthy.

The primary infection with herpes simplex virus type 1 is associated with systemic signs and symptoms of fever, malaise, sore throat, and cervical adenopathy. Vesicles can develop anywhere on the oral mucosa but most typically in the anterior oropharynx on the lips, tongue, and buccal mucosa (Figure 335-1). The gingiva may be swollen and erythematous. The perioral area may also display vesicles and small ulcers that coalesce and continue to appear for the next week. Anorexia as a result of the oral pain may produce dehydration that is severe enough to warrant hospitalization. Children in the first few years of life are most likely to experience a primary infection, and recurrences vary in number. The recurrences are less severe than the initial bouts and are not usually associated with systemic symptoms. Spontaneous resolution occurs in 1 week to 10 days.

Herpangina is characterized by ulcers surrounded by erythematous halos located in the posterior oropharynx (Figure 335-2). Spontaneous resolution occurs in 3 to 5 days. In HFMD, along with lesions of the posterior oropharynx, blanching red macules or vesicles appear on the palms, soles, and buttocks. Erythematous halos may also surround the macules. Spontaneous resolution occurs within a week. Systemic

symptoms of fever, malaise, dysphagia, and anorexia accompany these coxsackievirus infections, which can lead to dehydration in children with either herpangina or HFMD.

The bacterial condition necrotizing ulcerative gingivitis is characterized by painful, erythematous, and friable gingiva. Foul breath accompanies the necrotic tissue that accumulates as a pseudomembrane over the gingival surface. Fever, malaise, anorexia, and dehydration may also be part of its clinical presentation.

Candidal mucositis produces white, curdlike patches on many of the surfaces of the oral mucosa. If scraped, then a white patch can be removed, unveiling ulceration at the base. Diaper dermatitis may also be present.

Contact stomatitis can present in 4 general ways: (1) red lesions with general mouth erythema, (2) white lesions and leukoplakia, (3) erosions and ulcerations, or (4) no obvious lesions accompanied by mouth pain and burning. Location of the lesions in close proximity to dental appliances, for example, will provide the clue that the etiology may be irritant contact stomatitis. The manifestation of stomatitis in the multitude of potential underlying multisystem diseases will vary depending on the diagnosis. Immunocompromised patients may experience more frequent and severe episodes of oral ulceration that take longer to resolve. The appearance of the individual aphthae in stomatitis secondary to a benign or self-limited condition may be indistinguishable from those associated with a serious underlying systemic disease. Therefore, the search for other symptoms and physical examination findings are important to help determine the appropriate etiology.

Ulcerations may occur in other body parts as well, such as in the genitals and gastrointestinal tract in Behçet syndrome. Gastrointestinal symptoms, fever, weight loss, joint and ocular abnormalities, and rash are some constitutional complaints that the child with an underlying disease may experience.

PFAPA syndrome is characterized by recurrent fevers every 4 to 6 weeks with onset in the first 6 years



**Figure 335-1** Herpes simplex stomatitis is a primary infection of the anterior oral mucous membranes. Tongue lesions also are common with primary herpes simplex virus infections.



**Figure 335-2** Herpangina (coxsackievirus) lesions on the posterior palate of a young male adult. Coxsackievirus lesions are usually found in the posterior aspect of the oropharynx and may progress rapidly to painful ulceration.



of life. Along with the symptoms described in its name, PFAPA syndrome may also cause general malaise, anorexia, headache, abdominal pain, and arthralgias that typically resolve within 1 week. The child has complete resolution of symptoms between the recurrences.

## LABORATORY EVALUATION

In most cases of stomatitis, laboratory evaluation is not helpful in the diagnosis or management of the patients. Monitoring serum electrolytes in patients with severe dehydration is prudent during the rehydration process. In the case of a child with stomatitis of uncertain etiology or oral lesions that persist for longer than 2 weeks, a further evaluation should be undertaken while the pain-relieving and hydrating measures continue. If frequently recurring or persistent oral aphthae are present, along with genital lesions or other systemic findings, an initial evaluation for an underlying cause may then include laboratory studies of complete blood count, erythrocyte sedimentation rate, and serum levels of iron, folate, vitamin B<sub>12</sub>, and zinc. Depending on the history, screening for anti-nuclear antibodies, HIV, and celiac disease may be necessary. Establishing the definitive diagnosis and appropriate treatment may require the expertise of an allergist-immunologist, rheumatologist, dermatologist, gastroenterologist, ophthalmologist, oral surgeon, or otolaryngologist, depending on the clinical scenario. A biopsy of an oral lesion may be needed, especially if the child chews tobacco and has a persistent, nonhealing ulcer.

## MANAGEMENT

### Uncomplicated Cases

Relieving pain and preventing dehydration are the goals of treatment for the child with RAS or stomatitis caused by an acute infectious process or for a child with contact stomatitis. By maximizing pain relief, the child will be able to remain hydrated and consume a soft diet. Systemic ibuprofen, acetaminophen, or opiates may help with the pain, but more relief may be obtained from the application of soothing, topical substances. In a cooperative child, the topical substances may be administered by allowing the child to swish and then spit or, alternatively, by painting the substance on the sores with a cotton-tipped swab. The many topical agents that have been studied minimally for safety and efficacy include saline rinses, diphenhydramine–aluminum hydroxide with magnesium hydroxide–viscous lidocaine compounded in various combinations, benzocaine, kaolin, and pectin. Most of these agents, if used too aggressively, can lead to overdose and adverse side effects. The topical anesthetic preparations, in particular, must be used cautiously because of the risk for aspiration, loss of protective airway reflexes, and systemic toxicity (such as methemoglobinemia) caused by absorption through the inflamed oral mucosa.

Antimicrobials are of limited value, except in the instance of necrotizing ulcerative gingivitis, in which case chlorhexidine mouth rinses and systemic antibiotics such as penicillin may be required. Oral acyclovir is of limited therapeutic benefit in the otherwise

healthy child with herpes stomatitis, and topical acyclovir is ineffective.

### Complicated Cases

An immunocompromised child or one with stomatitis secondary to cancer treatment should receive topical and systemic analgesics and be monitored for secondary infection. Topical sucralfate and capsaicin have been found to relieve the pain of chemotherapy or radiation-induced mucositis and are not routinely used for children with benign, self-limited conditions. However, these agents may be an option for an otherwise healthy child with persistent pain despite aggressive use of the standard medications. On a case-by-case basis, topical corticosteroids, local anesthetics, topical tacrolimus, and systemic medications (colchicine, dapsone, thalidomide) may be used to treat the oral symptoms in these complicated patients; however, these medications are not typically prescribed in general pediatric practice. PFAPA syndrome typically responds well to a short course of oral steroids (1–2 mg/kg/day for 5 days) if prescribed at the onset of symptoms.

## PREVENTION

Most causes of stomatitis cannot be prevented. In general, along with avoidance of tobacco products and any possible irritants, good oral hygiene should be promoted to reduce the risk for dental caries and gingivitis. Exposure to the proposed triggers for RAS should be lessened. Based on adult studies, continuous oral acyclovir is a therapeutic option for preventing recurrences in a child with frequent herpetic flares. Children with cancer may benefit from a preventive protocol that includes frequent plaque biofilm removal and teeth brushing, chlorhexidine or saline rinses, and nystatin.

### WHEN TO REFER

If the underlying cause of the stomatitis is uncertain, or if oral lesions persist for longer than 2 weeks, then referral to an oral surgeon or otolaryngologist should be considered for definitive diagnosis. Biopsy of a lesion may be necessary, especially for a child who uses smokeless tobacco.

A child with stomatitis plus multiple symptoms and abnormal physical examination findings may require the expertise of an allergist-immunologist, rheumatologist, dermatologist, gastroenterologist, or ophthalmologist to establish the definitive diagnosis and administer appropriate treatment.

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## Chapter 336

## SUBSTANCE USE DISORDERS

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## INTRODUCTION

Most adolescents in the United States have used a substance—most commonly alcohol, marijuana, or tobacco—by the 12th grade. All psychoactive substance use during adolescence presents a health risk because even occasional use of substances is associated with a high risk of acute health consequences. For most adolescents who use substances with peers and without related problems or interference with domains of functioning, such as school and home life, the pediatrician can address their substance use in the medical home. Chapter 198, Substance Use: Initial Approach in Primary Care, describes the pediatrician's role in caring for children whose use does not rise to the level of a "disorder" and in identifying those who need the care of the substance abuse specialty system—many of whom have a substance use disorder (SUD).

Only about 10% of youth with SUDs receive care in the specialty system. By default, the primary care setting is often the site of initial care, requiring the pediatrician to be knowledgeable in the basics of treatment as well as referral.

This chapter introduces the new classification system for SUDs, summarizes the types of specialty services available for children with SUDs, provides information about commonly used substances, and recommends a role for pediatricians in supporting families and providing a medical home for children who receive substance abuse specialty care.

## CLASSIFICATION OF SUBSTANCE USE DISORDERS

In May 2013, the American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) was released and included new terms and criteria. The terms "substance abuse" and "substance dependence" were replaced by *substance use disorder, mild, moderate, or severe*. The new diagnostic classification is based on the number of criteria that are met: 2 to 3 constitute a mild disorder, 4 to 5 moderate, and 6 or more severe. Meeting criteria for a mild or moderate SUD indicates that use is particularly hazardous or that an individual has begun to have problems associated with use. Meeting criteria for severe SUD, sometimes referred to as addiction, suggests that an individual has lost control over substance use, has cravings for use, and has a compulsion to use. Addiction is a chronic, neurologic condition associated with changes in the brain's reward center. Effective treatments, including medication and psychosocial support, are available. Addiction is treatable, but not curable, and so requires long-term treatment.

## SPECIALTY TREATMENT OF YOUTH WITH SUBSTANCE USE DISORDERS

A variety of evidence-based and evidence-informed psychosocial interventions are available for the treatment of SUDs in youth. Ideally, children referred for care in the substance use disorder specialty system have access to the safest and most effective treatments. Examples include cognitive behavioral therapy, community reinforcement therapy, and family therapy. Treatment should occur in adolescent settings and with licensed providers, although it is possible that adults may be treated in the same facility. Youth who use substances often have co-occurring mental health disorders; they require referral for mental health services, ideally delivered by a physician qualified to address both substance use and mental health needs. Many youth benefit from additional services such as individual counseling, school evaluation, neuropsychological evaluation, vocational services, or family counseling. The pediatrician may contact the local Bureau of Substance Abuse Services to find community resources.

Table 336-1 summarizes the types of referral options for substance abuse treatment, and Table 336-2 provides a description of the kinds of substance use treatment available.

## COMANAGEMENT OF YOUTH WITH SUBSTANCE USE DISORDERS

Referral of a youth to the SUD (or mental health) specialty system should not end the pediatrician's involvement with the youth. An SUD is a special health care need, and affected youths, like those with attention-deficit/hyperactivity disorder (ADHD) or asthma, continue to benefit from the services of a medical home in addition to subspecialty medical care. The pediatrician and specialist can reach agreement on respective roles in the youth's care and establish a mechanism for communicating progress. The pediatrician can support the youth by encouraging his or her positive view of treatment; monitoring progress in care; observing for co-occurring disorders; and coordinating care provided by parents, school, the medical home, and specialists. Resources available to help physicians in these roles are provided in Tools for Practice at the end of this chapter.

The pediatrician has an important role in supporting parents of youth with an SUD, as well as the youths themselves. The following are common issues that may arise and suggestions for how to manage them.

1. *Does a parent or other family member have an active SUD?* Explore this individual's readiness to seek and accept care. Advise parents that seeking an evaluation for their own substance use is excellent role modeling and emotionally supportive for their children. However, not all parents are receptive to such advice. The youth is the patient; his or her safety and well-being remain the priority. For his or her own well-being, suggest the youth attend a community-based support group like Alateen ([www.al-anon.alateen.org](http://www.al-anon.alateen.org)) and consider involving child protective services if the youth is at acute risk.

**Table 336-1** Referral Options for Substance Use Disorders

TYPE OF TREATMENT	CHARACTERISTICS
Outpatient treatment	<ul style="list-style-type: none"> <li>Includes community and school resources, 12-step groups, peer-support groups, and individual counseling and medication-assisted treatment in general medical settings</li> <li>May be used for youth who are motivated to change behaviors or whose caregivers and family feel that it will benefit them</li> </ul>
Partial or day hospital	<ul style="list-style-type: none"> <li>May also be used as a transition from more intensive treatment settings</li> <li>May be considered for youth who need more intensive structure and support to break the cycle of substance use</li> </ul>
Residential treatment	<ul style="list-style-type: none"> <li>May also be used as a transition from more intensive treatments</li> <li>Relatively long term (30–90 days)</li> <li>For youth who are unlikely to be able to stop drug or alcohol use if they remain in their home environment</li> </ul>
Inpatient treatment	<ul style="list-style-type: none"> <li>For those with a history of treatment failures in less restrictive settings</li> <li>Relatively short term (days to weeks)</li> <li>For youth in need of immediate stabilization because of safety concerns</li> <li>For those who have serious psychiatric disorders or symptoms (eg, suicidal, homicidal, psychotic, acutely dangerous behaviors) co-occurring with substance use disorders</li> </ul>

Derived from American Academy of Pediatrics Committee on Substance Abuse. Substance use screening, brief intervention, and referral to treatment for pediatricians. *Pediatrics*. 2011;128(5):e1330–e1340.

2. *Is the parent enabling the adolescent's use of substances?* Being the parent of a youth with an SUD can cause a great deal of strain on the family unit. Parents often struggle with setting appropriate limits around substance use. Pediatricians can guide parents in setting firm limits and consequences for use.
3. *Does the parent feel responsible?* Provide reassurance that the parent is not at fault. Adolescents commonly experiment with substances; as a result of a complex combination of risk factors, environment, and genetics, some will develop an SUD. Helping the parent realize that focusing on the present and supporting treatment for their child is the most important action he or she can take can help relieve the responsibility he or she may feel. In addition, some communities have groups for parents that can provide an important source of support.
4. *Does the parent understand that SUDs are brain diseases and not simply bad behavior?* Although SUDs and addiction are considered chronic medical conditions, stigma is associated with diagnosis. Explain SUDs in the framework of a medical model to help reduce the stigma and increase understanding.

## ACCURATE INFORMATION ABOUT SUBSTANCE USE

### Alcohol

Short- and long-term health effects are associated with alcohol use in adolescents. Common problems include unintentional accidents and injuries and unwanted sexual contact. "Blackouts" or periods of anterograde amnesia—episodes during which an individual walks and talks but has no subsequent memory—commonly occur with heavy drinking and place individuals at risk. Alcohol use during adolescence is associated with reduced hippocampus volume and

difficulties with memory and learning. Early initiation of alcohol use is also associated with developing an alcohol use disorder later in life. Adolescents with a family history of alcohol use disorders are at particularly high risk.

Adolescents who have experienced 1 or more negative consequences associated with alcohol use may be receptive to quitting or reducing alcohol use. Counseling should focus on the highest-risk behaviors, and all adolescents who agree to reduce alcohol use should be offered a follow-up appointment.

Symptoms of alcohol withdrawal in adolescents are rare, though adolescents who frequently binge drink may develop withdrawal syndromes of varying severity. The most common symptoms associated with alcohol withdrawal are nausea, vomiting, insomnia, autonomic hyperactivity, and confusion. Any adolescent with a history of daily heavy drinking should be observed for signs of withdrawal in an inpatient setting, because alcohol withdrawal can be life threatening.

### Marijuana

Marijuana refers to the dried leaves, flowers, stems, and seeds from the hemp plant, *Cannabis sativa*. The psychoactive component is delta-9-tetrahydrocannabinol, commonly known as THC. Marijuana is an addictive substance. Similar to other drugs with addictive potential such as heroin and nicotine, use of THC causes a release of dopamine in the brain's reward pathway in the nucleus accumbens, and long-term administration alters the limbic system in the brain. As with alcohol and other psychoactive substances, increased risk of addiction is associated with younger onset of use.

Since 2008, in the context of the national debate over marijuana policy, the perceived risk of harm of marijuana use has been decreasing and the rate of marijuana use by adolescents has been increasing.

**Table 336-2** Descriptions of Substance Use Treatment

<b>OUTPATIENT</b>	
Group therapy	A mainstay of substance abuse treatment for adolescents with SUDs. It is a particularly attractive option because it is cost-effective and takes advantage of the developmental preference for congregating with peers. However, group therapy has not been extensively evaluated as a therapeutic modality in this age group, and existing research has produced mixed results.
Family therapy	The best validated approach for treating adolescent substance abuse. A number of modalities have demonstrated effectiveness. Family counseling typically targets domains that figure prominently in the etiology of SUDs in adolescents: family conflict, communication, parental monitoring, discipline, child abuse/neglect, and parental SUDs.
Intensive outpatient program	Serves as an intermediate level of care for patients who have needs that are too complex for outpatient treatment but do not require inpatient services. These programs allow people to continue with their daily routine and practice newly acquired recovery skills both at home and at work. Intensive outpatient programs generally comprise a combination of supportive group therapy, educational groups, family therapy, individual therapy, relapse prevention and life skills, 12-step recovery, case management, and aftercare planning. The programs range from 2–3 hours/day, 2–5 days/week, and last 1–3 months. These programs are appealing because they provide a plethora of services in a relatively short period of time.
Partial hospital program	A short-term, comprehensive outpatient program in affiliation with a hospital that is designed to provide support and treatment for patients with SUDs. The services offered at these programs are more concentrated and intensive than regular outpatient treatment; they are structured throughout the entire day and offer medical monitoring in addition to individual and group therapy. Participants typically attend sessions for 7 or 8 hours/day, at least 5 days/week, for 1–3 weeks. As with intensive outpatient programs, patients return home in the evenings and have a chance to practice newly acquired recovery skills.
<b>INPATIENT/RESIDENTIAL</b>	
Detoxification	Refers to the medical management of symptoms of withdrawal. Medically supervised detoxification is indicated for any adolescent who is at risk of withdrawing from alcohol or benzodiazepines and might also be helpful for adolescents withdrawing from opioids, cocaine, or other substances. Detoxification may be an important first step but is not considered definitive treatment. Patients who are discharged from a detoxification program should then begin either an outpatient or residential substance abuse treatment program.
Acute residential treatment	A short-term (days to weeks) residential placement designed to stabilize patients in crisis, often before entering a longer-term residential treatment program. Acute residential treatment programs typically target adolescents with co-occurring mental health disorders.
Residential treatment	Highly structured live-in environments that provide therapy for those with severe substance abuse, mental illness, or behavioral problems that require 24-hour care. The goal of residential treatment is to promote the achievement and subsequent maintenance of long-term abstinence and equip each patient with both the social and coping skills necessary for a successful transition back into society. Residential programs are classified as short term (<30 days) or long term (≥30 days). Residential programs generally comprise individual and group-therapy sessions plus medical, psychological, clinical, nutritional, and educational components. Residential facilities aim to simulate real living environments with added structure and routine to prepare patients with the framework necessary for their lives to continue drug- and alcohol-free after completion of the program.
Therapeutic boarding school	Educational institutions that provide constant supervision for their students by a professional staff. These schools offer a highly structured environment with set times for all activities; smaller, more specialized classes; and social and emotional support. In addition to the regular services offered at traditional boarding schools, therapeutic schools also provide individual and group therapy for adolescents with mental health disorders or SUDs.

SUD, substance use disorder

Adapted from American Academy of Pediatrics Committee on Substance Abuse. Substance use screening, brief intervention, and referral to treatment for pediatricians. *Pediatrics*. 2011;128(5):e1330–1340.



Currently, 6.5% of high school seniors use marijuana daily. Unfortunately, the known harms of marijuana use in adolescents are often understated or completely neglected in policy debate. Heavy marijuana use in adolescence has been associated with increased mood, anxiety, and thought disorders and decreasing IQ scores over time. Imaging studies have demonstrated morphologic changes consistent with these findings. Physicians must be prepared to have conversations with adolescents about use as more states legalize marijuana for medical purposes and either decriminalize or legalize recreational use. Counseling should include a discussion of the known medical, psychological, and cognitive side effects and a clear statement that there is no known benefit to children or adolescents.

In addition to euphoria, marijuana use results in a loss of critical judgment, distortions in time perception, impairment of tracking (the ability to follow a moving object accurately), and poor performance on *divided-attention* tasks, such as driving. Other behavioral effects include impaired short-term memory, interference with learning, and difficulty with oral communication, all of which can affect school performance adversely. Occasionally, a pediatrician will encounter a child who has an acute adverse reaction to marijuana characterized by a toxic psychosis with depression or panic. Both the symptoms and the treatment of these reactions are similar to those for hallucinogen abuse. Prolonged (and possibly permanent) personality changes have been reported in long-term marijuana users. An example of a change is an amotivational syndrome, marked by lethargy and a lack of goal-directed activity. Physiologic effects do occur with marijuana use but are generally less acutely dangerous than those caused by other substances. Respiratory effects with prolonged exposure include bronchodilation with acute inhalation and subsequent chronic intermittent bronchoconstriction. Thus, adolescents who have asthma may experience either relief or exacerbation of symptoms. Allergic reactions to marijuana do occur and may cause asthmatic attacks. Furthermore, chronic marijuana use has been found to cause exercise-induced dyspnea and chronic cough that may be mistaken for new-onset asthma in an adolescent. Cardiovascular effects include both tachycardia and a transient low-grade elevation of systolic and diastolic blood pressure. Marijuana has been reported to have numerous effects on the endocrine system in boys and men who have histories of prolonged and frequent use, including depression of testosterone levels in the blood, diminished sperm counts, impaired sexual function, and gynecomastia. The associated clinical problems of impotence and infertility are expected to respond to abstinence from marijuana.

Marijuana withdrawal is more subtle than withdrawal from other substances and is therefore often overlooked. This is in part because marijuana's lipophilia ensures a slow physiologic taper even among individuals who quit "cold turkey." Marijuana produces pharmacologic tolerance after several days of regular use, and a clinical withdrawal syndrome begins within 24 to 48 hours of discontinuing the drug. Withdrawal

symptoms peak in intensity by the fourth day and gradually resolve by 10 to 14 days. The withdrawal symptoms from marijuana include anxiety, restlessness, and sleeplessness.

Use of synthetic cannabinoids, such as "spice" or "K-2," is common: 11% of 12th graders reported use in 2012 despite the US Drug Enforcement Agency's scheduling of the related chemicals in 2011. These substances are similar to THC and bind to the human CB1 receptor. They are synthesized chemically, dissolved in solvent, and sprayed on the leaves of a variety of plants so that they can be smoked like marijuana. As with other cannabinoids, binding at the CB1 receptor in the central nervous system results in euphoria, time distortion, intensification of sensory experiences, altered state of consciousness, impaired short-term memory, and increased reaction times. Also as with marijuana, use is associated with anxiety, hallucinations, paranoia, increased heart rate, and confusion, and can also be associated with myocardial ischemia and kidney failure.

### Other Drugs of Abuse

#### *Ecstasy/Molly*

The substance known as 3,4-methylenedioxymethamphetamine (MDMA, ecstasy, Molly) has recently gained attention because of a series of deaths in individuals who were not known to have SUDs. The resurgence of MDMA under the name Molly has been primarily among young adults; prevalence of past-year use of MDMA among 12th graders has decreased from its peak 9.2% in 2001 to 4% in 2013. Signs of MDMA toxicity include sympathetic overactivity, disturbed behavior, and hyperthermia. Serious complications such as delirium, seizures, and coma are more common when MDMA is used in combination with other substances, especially other stimulants. Rhabdomyolysis and acute renal failure have been reported with MDMA use by individuals who use the drug in the setting of prolonged physical activity such as all-night dance parties or "raves." All of these effects are potentiated by alcohol, benzodiazepines, and other drugs.

#### *Prescription Opioids and Heroin*

The use of opioids other than heroin by 12th graders peaked in 2004 at 9.5% and has continued to decrease to 7.1% in 2013. Use of heroin peaked in 2000 and has recently plateaued to 0.6% annual prevalence. Although not as common as alcohol and marijuana use, the risk of opioid misuse is high because of the high risk for addiction and associated complications, including fatal overdose and transition to injection drug use. For adolescents with suspected opioid use disorders, referral to specialty care—which may be either outpatient or residential—is key, because there is effective pharmacologic treatment available with buprenorphine-naloxone, a partial opioid agonist approved for adolescents 16 years and older. As with other conditions, adolescents with opioid use disorders should be treated in the least restrictive environment. Most adolescents with opioid use disorders are candidates for medication-assisted treatment in the outpatient setting. Few pediatricians have waived to prescribe buprenorphine to date, leaving a treatment gap.

Opioid withdrawal results in flu-like symptoms, including vomiting/diarrhea, myalgia, nasal congestion, and joint pain. These symptoms can be very unpleasant but generally are not life threatening in otherwise healthy adolescents. Medical detoxification programs can help to ease the discomfort associated with withdrawal, but should not be considered stand-alone treatment. Patients who have successfully completed detoxification should be referred to ongoing treatment.

### Prescription Stimulants

In adolescents with ADHD, stimulants can provide effective treatment; however amphetamines are also commonly misused by adolescents. An adolescent may misuse his or her own medication or take a friend's prescription. Misuse can be driven by a desire to get high and also to enhance academic achievement. Amphetamine use peaked at 10.9% in 12<sup>th</sup> graders in 2002. Since then, annual prevalence has fluctuated with an increase in 2013 to 8.7%. Children and adolescents with ADHD are at increased likelihood of developing an SUD; treatment for ADHD may lower this risk.

### SUMMARY

While substance use is common among adolescents and often does not rise to the level of a disorder, some adolescents do develop SUDs and require specialty treatment. These services may take place in outpatient, partial or day-hospital, residential, or inpatient settings and may incorporate a variety of evidence-based approaches, depending on the needs of the child. Pediatricians continue to play important roles in the care of children served by the SUD specialty system.

### TOOLS FOR PRACTICE

#### Community Advocacy and Coordination

- *Julius B. Richmond Center of Excellence* (Web site), American Academy of Pediatrics ([www.aap.org/richmondcenter](http://www.aap.org/richmondcenter))

#### Engaging Patient and Family

- *Become an EX* (Web site), American Legacy Foundation ([www.becomeanex.org](http://www.becomeanex.org))
- *Campaign for Tobacco-Free Kids* (Web site), ([www.tobaccofreekids.org](http://www.tobaccofreekids.org))
- *Contract for Life* (Web page), Students Against Destructive Decisions ([www.sadd.org/contract.htm](http://www.sadd.org/contract.htm))
- *Drug Strategies Treatment Guide* (Web site), Drug-Strategies.org ([www.drugstrategies.org/youths](http://www.drugstrategies.org/youths))
- *National Institute on Drug Abuse* (Web site), ([www.drugabuse.gov](http://www.drugabuse.gov))
- *National Youth Anti-Drug Media Campaign* (Web Site), Office of National Drug Control Policy ([www.abovetheinfluence.com](http://www.abovetheinfluence.com))
- *NIDA for Teens* (Web site), National Institute on Drug Abuse ([teens.drugabuse.gov](http://teens.drugabuse.gov))
- *The Partnership at Drugfree.org* (Web site), ([www.drugfree.org](http://www.drugfree.org))
- *Smokefree.gov* (Web site), US Department of Health and Human Services ([www.smokefree.gov](http://www.smokefree.gov))

### Medical Decision Support

- *Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide* (book), National Institute of Alcohol Abuse and Alcoholism, American Academy of Pediatrics ([www.niaaa.nih.gov/Publications/EducationTrainingMaterials/Pages/YouthGuide.aspx](http://www.niaaa.nih.gov/Publications/EducationTrainingMaterials/Pages/YouthGuide.aspx))
- *CRAFFT* (screen), Center for Adolescent Substance Abuse Research ([www.ceasar-boston.org/CRAFFT/index.php](http://www.ceasar-boston.org/CRAFFT/index.php))

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**Chapter 337****SUDDEN UNEXPECTED  
INFANT DEATH***Rachel Y. Moon, MD***DEFINITION AND DIAGNOSIS**

Sudden unexpected infant death (SUID); also sometimes referred to as sudden unexpected death in infancy, or SUDI) refers to all causes of death during infancy that occur suddenly and unexpectedly. Sudden infant death syndrome (SIDS), accidental injuries (including suffocation, strangulation, and entrapment), and undetermined causes of death comprise most SUID deaths; most of these deaths occur while the infant is sleeping. Undetermined deaths are those for which a cause of death cannot be definitively ascertained; for instance, the autopsy findings are consistent with SIDS, but the sleep circumstances suggest that suffocation is a possibility.

SIDS is defined as “the sudden death of an infant under 1 year of age, which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history.” It is a diagnosis of exclusion.

**INCIDENCE**

In the United States, SIDS and other SUIDs account for approximately 4,000 deaths annually; approximately half of these can be attributed to SIDS. Since 1992, when the American Academy of Pediatrics (AAP) recommended that infants be placed in a non-prone position for sleep as a strategy to reduce the risk for SIDS, the rate of prone sleeping has decreased from 70% to 13.5% in 2010, and the rate of SIDS has decreased from 1.2 deaths per 1,000 live births to .42 deaths per 1,000 live births in 2012. Similar decreases in SIDS have been experienced in other countries that have initiated similar educational campaigns. However, this decline in SIDS has occurred concurrently with an increase in the incidence of other causes of SUID, primarily accidental suffocation and strangulation in bed and undetermined causes of death. In fact, since 1984, infant deaths caused by accidental suffocation and strangulation in bed have quadrupled. Most of these deaths occur on either an adult bed or a couch. Some of the increase in the incidence of non-SIDS causes of SUID is likely because of a diagnostic shift. Largely because of more extensive and detailed death investigation protocols for infants, deaths that would have been attributed to SIDS a decade ago may now be ascribed to asphyxia or suffocation, or be undetermined by medical examiners and coroners. This is the case particularly when the infant is found in an unsafe sleep environment (adult bed, couch, cushioned chairs, soft bedding) or is bed sharing with an adult or another child. According to one examination of US mortality data, more than 90% of the drop in SIDS rates between 1999 and 2001 may be attributable

to a concurrent increase in the rates of non-SIDS causes of SUID.

Some racial disparities are seen in SIDS and SUID. In black infants, the rate of SIDS was 2 times that of white infants in 2012. Black infants are also 2.5 times and 2.8 times more likely than white infants to die from accidental suffocation and strangulation in bed or an undetermined cause of death, respectively. These disparities may be partially attributed to differences in sleep practices. African Americans are twice as likely to place their infants prone for sleep and to bed share with their infants; both of these practices are associated with increased risk for SIDS or other forms of SUID.

The occurrence of SIDS is rare in the first month of life, peaks between 2 and 3 months of age, and then decreases thereafter. Approximately 90% of SIDS deaths occur in the first 6 months of life. Similarly, deaths caused by accidental suffocation and strangulation in bed and undetermined deaths are more likely in young infants, with most occurring between 1 and 4 months of age.

Although SIDS is rare in infants during the first month of life, there is growing recognition of the increased vulnerability of apparently healthy newborn infants to SUID and apparent life-threatening events during the first week of life. This condition, referred to as sudden unexpected postnatal collapse (SUPC), is reported to occur in 2.6 to 38 of 100,000 live births. Infants appear to be most vulnerable during the first 12 to 24 hours of life. Contributing factors among infants without an underlying etiology include prone positioning of an infant on the mother's chest during skin-to-skin care, airway obstruction during breastfeeding, and maternal primiparity (inexperience) and/or maternal fatigue/sedation. (See Chapter 217, Apparent Life-Threatening Events, for additional discussion.)

**ETIOLOGY**

SIDS likely represents a variety of causes of death. However, the leading hypothesis regarding the etiology of SIDS is that certain infants, for reasons still unknown, have a maldevelopment or delay in maturation of the brainstem neural network that is responsible for arousal and the physiologic responses to life-threatening challenges during sleep. Postmortem examination of the brainstem of a series of infants who had died of SIDS, using quantitative techniques, have demonstrated deficits in serotonin receptors throughout the ventral medulla compared with age-matched controls who had died from some other well-defined cause. Authorities think that these brainstem regions are involved with arousal, chemosensitivity, respiratory drive, thermoregulation, and blood pressure responses. In addition, polymorphisms in the promoter region of serotonin transporter protein genes (5-HTT) have been associated with SIDS in several studies. When the physiologic stability of such infants becomes compromised during sleep, they may not arouse sufficiently to avoid the fatal noxious insult or condition. The rebreathing theory proposes that if the regular circulation of air around an infant's mouth



and nose becomes partially obstructed during sleep, exhaled CO<sub>2</sub> is more likely to be trapped around an infant's face. If the infant does not arouse and move to amend the situation, the resultant hypercarbia and hypoxia lead to SIDS. Investigators have argued that prone sleep position, soft sleeping surfaces, soft bedding, and covering of the head increase the likelihood of rebreathing.

## DIFFERENTIAL DIAGNOSIS

When an infant dies suddenly and unexpectedly, a full investigation, including complete autopsy, death scene investigation, and review of the clinical history, should be undertaken to determine cause of death. Illnesses that should be considered in the differential diagnosis include sepsis, pneumonia, myocarditis, cardiomyopathy, congenital heart defect, arrhythmia, prolonged QT syndrome, trauma (accidental or nonaccidental), suffocation, strangulation, entrapment, SIDS, adrenal hypoplasia, and inherited metabolic disorders such as fatty acid oxidation disorders.

Most SIDS cases have no evidence suggesting parental psychiatric disease or neglect of the infant. However, much media attention has been given to a few cases of Münchausen syndrome by proxy causing apparent life-threatening events and of multiple cases of SIDS within a family later determined to be multiple homicides. The proportion of SIDS deaths attributable to homicide is probably less than 10%. A family in which an infant has previously died of SIDS has a 2% to 6% risk for a second SIDS death.

Suffocation, either accidental or nonaccidental, is difficult to distinguish on autopsy from SIDS. Indeed, since 1999, some deaths that would previously have been classified as SIDS are now being classified as suffocation. Therefore, the death scene investigation has become a crucial component in the determination of cause of death, and the Centers for Disease Control and Prevention have introduced a standardized protocol for investigating all sudden and unexpected infant deaths. When an infant death occurs in an environment where the infant's respiratory efforts have been compromised, such as may be seen when the infant was sleeping with soft bedding (pillows, blankets) or on a soft surface (couches, armchairs, some adult beds), suffocation is more likely than SIDS to be considered as the cause of death. When there are factors in the death scene investigation and/or review of the infant's clinical history that make it difficult to declare a cause of death with a degree of certainty, the cause of death may be declared as undetermined.

## EPIDEMIOLOGIC CONSIDERATIONS

The following characteristics have consistently been identified as independent risk factors for SIDS and SUID: prone or side sleep position, sleeping on a soft surface, maternal smoking during pregnancy, overheating, late or no prenatal care, young maternal age, preterm birth or low birth weight (or both), male gender, and African American or American Indian/Alaska Native origin.

Prone or side sleep position can increase the risk for rebreathing, and the prone position places infants at high risk for SIDS/SUID. Sleeping prone may create

fatal levels of hypercarbia in infants with an underlying vulnerability, such as an arousal defect. The side sleep position is inherently unstable, and a large proportion of infants placed on the side will roll to prone, which confers an exceptionally high risk for SIDS. Secondary caregivers (grandparents, babysitters, pediatricians, relatives) are more likely to place infants prone, which also increases the risk for SIDS, particularly if the infant is unaccustomed to the prone position.

Soft bedding, such as pillows, quilts, comforters, and sheepskins, and soft sleep surfaces, such as waterbeds, sofas, and soft mattresses, increase the potential for rebreathing and significantly increase the risk for SIDS and suffocation, when either placed under the infant or loose in the infant's sleep area. Crib bumper pads also increase a baby's risk for suffocation, entrapment, and strangulation. A strong interaction has been found between prone sleep position and soft bedding surface; these 2 factors together increase the risk for SIDS 21-fold. In addition, soft and loose bedding have been associated with accidental suffocation deaths. Soft surfaces have also been implicated in infant deaths occurring on adult beds.

Aside from sleep position, smoke exposure is the largest contributing risk factor for SIDS. Maternal smoking during pregnancy is a major risk factor; postnatal exposure to tobacco smoke is a separate risk factor, although separating this variable from prenatal maternal smoking is difficult. There is a dose-dependent relationship between tobacco smoke exposure and SIDS risk.

An increased risk for SIDS has been associated with increased layers of clothing or blankets on the infant and warmer room temperatures. Head covering during sleep also increases SIDS risk. Infants who sleep prone are at higher risk for overheating than supine sleeping infants. It is yet unclear whether overheating and head covering are independent factors or merely a reflection of the use of more clothing, quilts, and other potentially asphyxiating objects in the sleeping environment during cold weather.

Infants born preterm or who are low birth weight are at increased risk for SIDS, and the risk increases with decreasing gestational age or birth weight. The increased risk cannot be explained by a greater likelihood of apnea of prematurity among preterm SIDS victims while they are in the hospital after birth. Whether other complications of prematurity can explain the increased risk is unclear. The association of sleep position and SIDS is equally strong for infants born preterm as for those born at term. Strategies designed to reduce risk in full-term infants should also be applied to infants born preterm after they are no longer in an intensive care setting.

Physiologic and behavioral studies demonstrate that bed sharing between an infant and adult facilitates breastfeeding and enhances maternal-infant bonding. However, bed sharing may increase the risk for rebreathing and exposure to tobacco smoke (a known risk factor for SIDS), and epidemiologic studies have shown that it can be hazardous. In addition, bed sharing increases the risk for accidental suffocation and entrapment. The risk for sudden unexpected death during bed sharing is particularly high when



multiple people share the bed, when the infant is younger than 11 weeks, and when bed sharing occurs for the whole night. The risk for death also increases substantially when the infant is placed on excessively soft surfaces, such as waterbeds, sofas, and armchairs; when soft bedding accessories such as pillows or comforters are used; or when the parent is overtired or has consumed alcohol and/or medications that alter arousal. Bed sharing is particularly hazardous when one or both parents are smokers or if the infant is younger than 11 weeks, regardless of smoke exposure. Room sharing without bed sharing is associated with a reduced risk for SIDS. Notably, breastfeeding in bed has not been shown to carry a risk if the baby is returned to the crib after the feeding. Because breastfeeding has many benefits, including a reduced risk for SIDS, parents should be encouraged to bring the infant into bed for breastfeeding and for bonding. However, the baby should be returned to the crib or bassinet when the parent is ready for sleep.

More recent studies have demonstrated that breastfeeding offers protection against SIDS. Possible protective mechanisms include lower arousal thresholds, decreased infections, and immune system benefits. Exclusive breastfeeding and breastfeeding for longer duration offer the most protection, but any breastfeeding is also more protective against SIDS than no breastfeeding.

Pacifiers, by a yet unidentified mechanism, seem to reduce the risk for SIDS when used at sleep time. Case-control studies demonstrate a strong protective effect. However, because early pacifier use may interfere with establishment of good breastfeeding practices, pacifiers should not be offered for the first few weeks of life to breastfed infants until breastfeeding has been well established. In addition, practices that promote breastfeeding should be encouraged in delivery hospitals, and continued breastfeeding support for the parents should be offered.

## RISK REDUCTION

For many years, apnea was thought to be the predecessor of SIDS, and home apnea monitors were used in an effort to prevent SIDS. However, although they may be useful in some infants who have had an apparent life-threatening event, no evidence has been found that home monitors are effective in reducing the risk for SIDS when no event has occurred in a particular infant.

SIDS and SUID risk reduction has centered on eliminating risk factors that have been shown epidemiologically to be associated with these deaths. The AAP has made the following recommendations for SIDS risk reduction:

- Infants should be placed in a supine position for every sleep. Side sleeping is not as safe as supine sleeping and is not advised.
- A firm sleep surface, such as a firm crib mattress covered by a well-fitted sheet, should be used.
- Soft materials or objects such as pillows, quilts, comforters, sheepskins, and stuffed toys should not be placed under or near the sleeping infant. Loose bedding, such as blankets and sheets, should be avoided.

- Smoking during pregnancy or in the infant's environment should be avoided.
- A separate but proximate sleeping environment is recommended; the infant should sleep in the same room, in a crib or bassinet, close to the parent's bed.
- Offering a pacifier at nap time and bedtime should be considered. The pacifier does not need to be reinserted after the infant falls asleep and should not be forced if the infant refuses it. Pacifiers with attached strings or elastic should not be used for sleeping infants. Introduction of the pacifier should be delayed in breastfeeding infants until 1 month of age to ensure that breastfeeding is fully established.
- Overheating and head covering during sleep should be avoided.
- Commercial devices marketed to reduce the risk for SIDS should not be used.
- Home monitors should not be used as a strategy to reduce the risk for SIDS.

## Supine Sleeping and Plagiocephaly

With the increased rate of supine sleeping, the incidence of plagiocephaly without synostosis has increased. Infants with plagiocephaly are more likely not to have had the head position altered when placed for sleep, more likely to spend little awake time in the prone position (tummy time) and less likely to have been held in the upright position while awake. Development of positional plagiocephaly can be avoided by altering the supine head position during sleep; encouraging upright cuddle time; avoiding excessive time in car seats, infant carriers, and bouncers, all of which place pressure on the occiput; and encouraging tummy time when the infant is awake and observed. Awake tummy time will also enhance upper-body motor development. For more information on plagiocephaly, see Chapter 316, Positional Deformational Plagiocephaly.

## Supine Sleeping and Gastroesophageal Reflux

A perception exists that sleeping supine may increase the risk for gastroesophageal reflux, choking, and aspiration, and this is a common reason for parents and physicians to place infants prone for sleep. However, evidence indicates that infants who vomit are at greater risk for choking when they are prone. Indeed, the incidence of aspiration or complaints of vomiting has not increased with increased supine sleeping. Infants with gastroesophageal reflux should be placed for sleep in the supine position, with the rare exception of infants for whom the risk for death from gastroesophageal reflux is greater than the risk for SIDS, specifically infants with upper airway disorders for whom airway protective mechanisms are impaired. Elevating the head of the infant's crib while the infant is supine is not effective in reducing gastroesophageal reflux and may result in the infant sliding to the foot of the crib into a position that may compromise respirations; therefore, it is not recommended.

## MANAGEMENT AND SUPPORT

The loss of an infant to SIDS or SUID is devastating for the family, friends, and physicians. If there is lack of certainty as to how the infant died, this can add an additional and difficult element to the grief process.

The physician can play an active role by ensuring that an autopsy is performed in all cases of sudden unexpected death, discussing the results of the autopsy with the parents, and providing emotional support to the entire family, including age-appropriate support for surviving siblings. The family should be directed to local counseling and support groups.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Safe Sleep and Your Baby: How Parents Can Reduce the Risk of SIDS and Suffocation* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

#### Community Advocacy and Coordination

- *Reducing the Risk of Sudden Infant Death Syndrome* (booklet), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

### AAP POLICY

American Academy of Pediatrics Task Force on Infant Sleep Position and Sudden Infant Death Syndrome. Changing concepts of sudden infant death syndrome: implications for infant sleeping environment and sleep position. *Pediatrics*. 2000;105:650–656 ([pediatrics.aappublications.org/content/105/3/650](http://pediatrics.aappublications.org/content/105/3/650))

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## Chapter 338

## TOBACCO AND NICOTINE USE

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### PREVALENCE OF TOBACCO AND NICOTINE USE

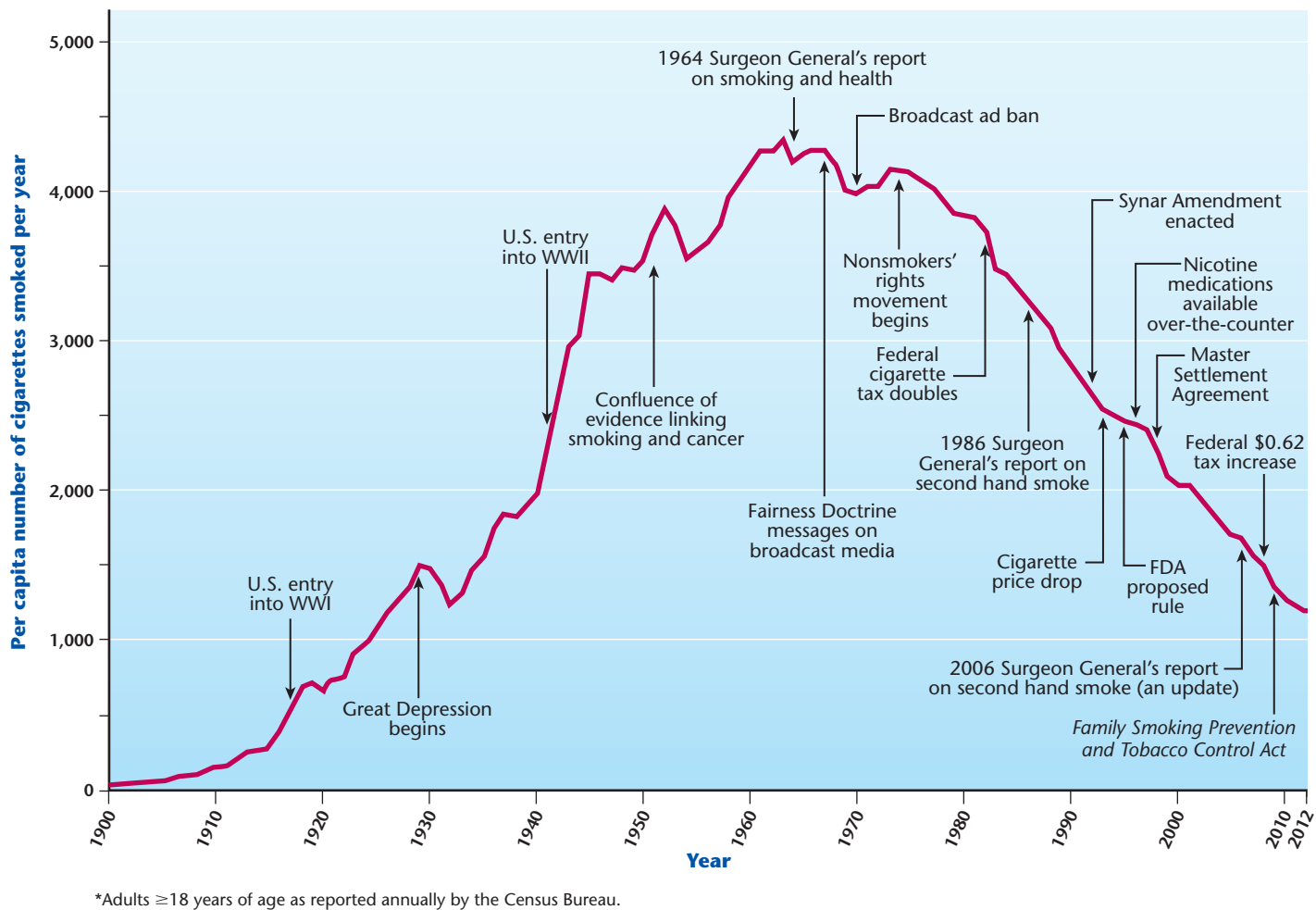
Tobacco use remains the leading cause of preventable morbidity and mortality in the United States. Cigarette

smoking, the most common form of tobacco use among US adults, leads to more than 480,000 premature deaths annually and has led to the premature death of more than 20 million people since 1964. Combusted tobacco products (including cigarettes, cigars, cigarillos, hookahs (waterpipe), bidi, kretek, pipes, and roll-your-own) clearly have more substantial health risks than noncombusted products, leading to deaths from cancers, cardiovascular diseases, stroke, diabetes mellitus, and respiratory diseases such as asthma, emphysema, and chronic obstructive pulmonary disease. Noncombusted products such as smokeless tobacco (dip, chew) and snus are not without harm, however, leading to dental issues as well as death from head and neck cancers. While the prevalence of cigarette smoking among US adults reached a low of 17.8% in 2013, 25.2% of adults reported current use (in the past 30 days) of any tobacco product. This reflects an increase in noncigarette products such as cigars and electronic cigarettes (e-cigarettes). Among youth, current use of any tobacco product by high school students in 2014 was 24.6%, which was very similar to the rate in 2013 (22.9%). Although cigarette use among high school students declined from 12.7% in 2013 to 9.2% in 2014, the prevalence of e-cigarette and hookah use increased significantly. From 2011 to 2014, current e-cigarette use among high school students increased from 1.5% to 13.4%, and hookah use from 4.1% to 9.4%. Figure 338-1 plots historic US adult cigarette use in the context of major health events.

Although flavors other than menthol are prohibited in cigarettes, such restrictions are not applied to other tobacco products. Approximately 70% of current high school tobacco users report using flavored products. There are substantial disparities in tobacco use between groups based on socioeconomic status, education, race/ethnicity, region of the country, and other demographics—men; those with lower educational attainment; those who live in poverty; those who identify as lesbian, gay, bisexual, and transgender; and Native American/Alaskan Natives have higher tobacco use. No form of tobacco use is safe, particularly for youth. Tobacco has been marketed extensively to attract users, and cigarettes in particular have been very carefully engineered to deliver nicotine quickly and efficiently to the brain to reinforce addiction. Cigarettes deliver a chemical cocktail of some 7,000 compounds that lead to disease and death, but it is the nicotine and its chemical relatives that lead to their ongoing use.

### HEALTH EFFECTS AND ADDICTION POTENTIAL OF NICOTINE

Nicotine is a psychoactive drug well known for its high level of toxicity, as well as the ease with which dependence occurs. Nicotine has complex pharmacodynamics: at low doses, it acts as a neurostimulant in the reward pathways, stimulating memory and alertness, improving mood, and decreasing appetite. At high doses, nicotine can cause nausea, vomiting, abdominal pain, headache, dizziness, and seizures; in very high doses, nicotine can be lethal. There are receptors for nicotine throughout the body, allowing



**Figure 338-1** Adult per capita cigarette consumption and major smoking and health events, United States, 1900–2012. (Adapted from *Fifty years of change 1964–2014*. In: US Department of Health and Human Services. *The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General*. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.)

nicotine to have broad physiologic effects including suspected effects on the immune system. Repeated exposure to nicotine leads to tolerance, which results in higher nicotine needs to avoid withdrawal. Insufficient nicotine in someone who is dependent leads to craving and withdrawal symptoms of irritability, anxiety, restlessness, difficulty concentrating, and anhedonia/depression. The addictive potential of nicotine products is known to vary by the delivery of the nicotine: faster delivery, more rapid rate of absorption, and the attainment of higher concentrations of nicotine all increase the potential for addiction. Nicotine exposure does not have a specific threshold to predict addiction. However, the nicotine source appears to make a difference, with tobacco-delivered nicotine substantially more addictive than pure nicotine. The basis of nicotine addiction is reinforcement of behavior that restores nicotine and makes the user feel pleasure and avoid unpleasant withdrawal. Nicotine addiction among those most heavily affected requires frequent dosing to limit withdrawal symptoms: a 2-pack per

day smoker will have 40 “doses” of nicotine per day, or at approximately 21 minute intervals (if averaged over typical waking hours). Smokers have been shown to report “needing” a cigarette even with intermittent cigarette smoking. Smokers also progress through a characteristic process of nicotine addiction that is characterized by stages: wanting, craving, and needing a cigarette.

The adolescent brain seems uniquely susceptible to nicotine addiction, with symptoms of dependence appearing within days to weeks of intermittent tobacco use and well before daily smoking. Nearly all adult smokers initiated smoking before the age of 20 years, and tobacco use at a younger age predicts greater levels of dependence and difficulty quitting. Animal studies have demonstrated that nicotine exposure during the adolescent period has long-standing effects on the brain, including cell damage that leads to both immediate and persistent behavior changes. These effects are not found with nicotine exposure to the adult. The weight of evidence suggests that nicotine exposure

modifies the developing adolescent brain and has long-term effects into adulthood. Although the evidence showing that cigarette use during adolescence leads to addiction is well established, whether use of noncombustible tobacco products such as e-cigarettes might encourage initiation or transition to combustible tobacco smoking by young people is not yet known. Two early studies assessing combusted tobacco initiation among e-cigarette users found a prospective association between e-cigarette use and subsequent combusted tobacco. A number of studies demonstrate dual use of combusted and noncombusted tobacco products, but provide insufficient data on whether noncombusted tobacco use precedes combusted tobacco use. It has been shown, however, that nicotine replacement therapies have low potential for dependence because of differences in absorption.

Regular users develop habits associated with nicotine use that also become connected with the rewarding feelings of nicotine use, creating cues for use. Known as *operant conditioning*, smokers become cued to want a cigarette after a meal, or with coffee, or in certain locations, for example. These habits of tobacco use are particularly reinforcing, making tobacco use difficult to overcome.

## TOBACCO USE IN ADOLESCENCE AND YOUNG ADULTHOOD

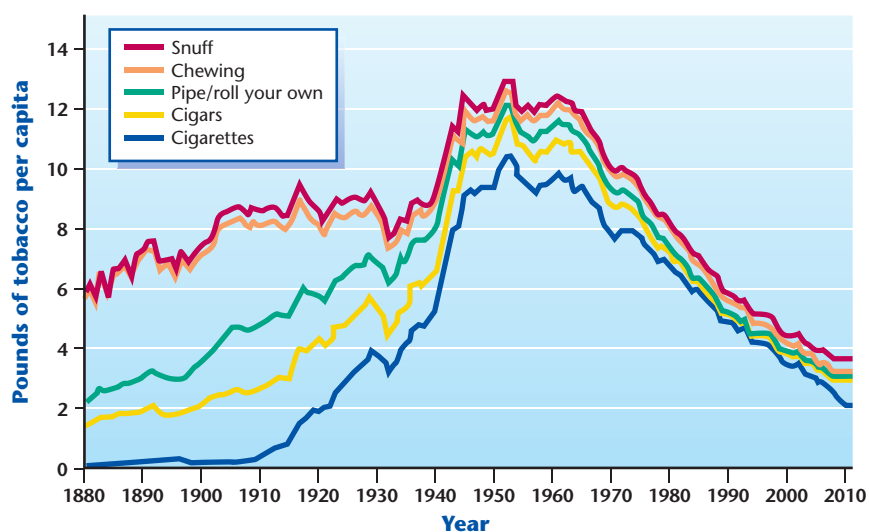
Most young people do not intentionally make the decision to start using tobacco, yet the decision can have significant, lifelong effects. Tobacco use has been aggressively marketed through traditional advertising as well as entertainment media, which has been found to be causally related to adolescent tobacco use. Each day, more than 2,800 US adolescents aged 12 to 17 years try smoking for the first time, with 10.9% of students reporting trying their first cigarette before age 13 years. The likelihood of

subsequent nicotine dependence and addiction is high, and symptoms of addiction appear soon after onset of smoking in some adolescents. While daily smoking in adolescents lags 2 to 3 years behind initiation, roughly 700 adolescents transition to daily smoking each day, and more than 60% of teen smokers still smoke 5 years later. Although most of what is known about youth tobacco use involves cigarettes, a substantial proportion of tobacco use now occurs with tobacco products other than cigarettes, and many youths now use multiple products. Recent data show that nearly 50% of all high school students currently using tobacco use multiple tobacco products concurrently, and some 36% of all current tobacco users do not smoke cigarettes at all. Many youth do not identify themselves as smokers, with occasional, light, or intermediate smoking being common; few youth expect to have difficulty with cessation.

Adolescents underestimate how addictive nicotine is and believe it will be easy to quit; however, relatively few adolescent daily users are successful at quitting. The difficulty that tobacco users face in quitting underscores the importance of prevention. Prevention has become far more complex in recent years with the introduction of new tobacco products to the market such as snus, dissolvables, and e-cigarettes, and the expansion of the flavored “little cigar” and cigarillo market as alternatives to traditional cigarettes. Based on the increase in use of these products as described later in this chapter, these products are expected to be more appealing and may be perceived as less harmful.

### Cigars, Little Filtered Cigars, and Cigarillos

Cigar smoking predates cigarette smoking by hundreds of years and was more popular until the early 1900s (see Figure 338-2). At present, cigars are not regulated by the US Food and Drug Administration



**Figure 338-2** Per capita consumption of different forms of tobacco, 1880–2011. (Adapted from *Patterns of tobacco use among US youth, young adults, and adults*. In: US Department of Health and Human Services. The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.)



(FDA); however, their use continues to be prevalent among young people and is of significant concern because they currently bypass many of the laws on cigarettes with regard to sales, taxation, and flavors. In contrast to cigarettes, cigars are wrapped in tobacco leaf (rather than paper) and the tobacco differs slightly. While adult users may puff on premium cigars and not inhale them, there is no specific instruction for cigar use; little filtered cigars are in most ways indistinguishable from cigarettes other than color and flavor. At present, cigars are the fourth most common type of tobacco used by youth (behind e-cigarettes, hookah, and cigarettes). In 2014, 8.2% of high school students reported using cigars/cigarillos/little cigars in the past month. An assessment by Monitoring the Future in 2013 found that approximately 20% of high school seniors had used cigars in the past 12 months. Cigars of all types can be sold in characterizing flavors, in packs of small quantity, and are taxed differently, so that they are less expensive than cigarettes. The low price and flavors of these products increase their appeal to youth. Cigar users are at risk for the same health effects as cigarette users.

### Other Combusted Tobacco Products

Waterpipes (hookah) have also recently gained in popularity in the United States, particularly in group social settings and with the advent of “Hookah Bars.” Past-year prevalence of hookah use among 12th graders in 2013 was 21.4%, and past month-use among high school students was 9.4% in 2014. Although many users perceive that smoke inhaled from a hookah is safer than cigarette smoke, studies show that the hookah produces concentrations of carbon monoxide, nicotine, tar, and metals at levels similar to or higher than those produced by cigarettes. Communicable disease risks are significant, given the shared mouthpiece, and herpes outbreaks have been reported from hookah use. In spite of these actual health risks, the misperception of safety and the appeal of social use have attracted non-cigarette users to hookah, and there is the attendant concern that these users will progress to other forms of tobacco and nicotine addiction. Given the popularity of these products, particularly among college students, it is important that physicians ask adolescent patients about them specifically.

### Noncombusted Tobacco Products

Smokeless tobacco, including “dip” and “chew,” has been a common form of tobacco use that was exceeded by combusted tobacco only with the invention of the automated cigarette machine in the early 1900s. The use of smokeless tobacco among youth remains relatively low, but those who use smokeless tobacco use it frequently: it is the tobacco product that has the highest likelihood of daily (or almost-daily) use among high school students. Smokeless products in particular have “starter” class versions that are milder in nicotine content and flavor. Users often progress to a higher nicotine product as their addiction develops. Many users of such products also smoke combusted tobacco products.

The contribution of newer noncombusted products such as electronic nicotine delivery systems (also

known as e-cigarettes or ENDS), snus, and dissolvables to the emergence of tobacco addiction in youth is not yet known, because these products are recent entries to the US market.

### E-cigarettes

E-cigarettes are a category of products that deliver varying amounts of inhaled nicotine and flavoring through a battery-powered device that heats and vaporizes cartridges or tanks filled with solution (see Figure 338-3). Introduced in the United States in 2007, these products are marketed widely on the internet, at point-of-sale outlets, in print and radio media, and on US television as alternatives to cigarette use. Unlike traditional cigarettes, e-cigarettes come in an expansive variety of tobacco, fruit, and food flavors. Given the relatively recent introduction of these devices to the market and rapid evolution of their technology, it is yet to be determined whether they play a role in recruiting new tobacco users or in replacing combusted cigarettes, ceasing tobacco use, or reducing harm. The potential for these devices to introduce non-tobacco users to nicotine addiction or to perpetuate smoking among smokers who would otherwise have quit is of particular concern. Their use among young people is growing: in just 1 year (from 2011 to 2012), the ever and current use of e-cigarettes doubled among US middle- and high school students, and current use then tripled between 2013 and 2014. This



**Figure 338-3** E-cigarette examples and comparators, from top: Refillable tank “pen” system; traditional combusted tobacco cigarette; “cigalike” store-branded disposable e-cigarette; Vuse, a rechargeable cartridge-based e-cigarette; Krave disposable e-cigarette; e-hookah pen; refillable vape pen; e-cigar; another refillable vape pen; and modifiable voltage refillable vaporizer. Note the variations in size and appearance among the 4 refillable tank devices shown.

meteoric rise of e-cigarettes among youth is concerning for various reasons. The e-cigarettes themselves are not without risk, and as previously noted, there is a concern that e-cigarette users will begin using combusted tobacco. While by far most of those who try e-cigarettes have also smoked cigarettes, a proportion of high school ever-users of e-cigarettes have never tried a traditional cigarette. Initiation of e-cigarettes is noted in studies to be directly related to perceptions: young adults who believed that e-cigarettes can help people quit smoking and that e-cigarettes are less harmful than cigarettes were more likely to try e-cigarettes. With tobacco companies now selling e-cigarettes, including Vuse by R.J. Reynolds, MarkTen by NuMark (a subsidiary of Altria), as well as the older Blu e-cig now owned by Lorillard, there is a significant amount of marketing of, and media attention to, e-cigarettes.

E-cigarettes vary dramatically depending on whether they are a disposable or rechargeable cartridge system versus a refillable tank system, and whether the end user can modify the voltage of the device. The nicotine concentration in e-juice solutions ranges vastly from 0 to 100 mg of nicotine in a single milliliter of solution. Producers of this e-juice buy concentrated nicotine and dilute it with propylene glycol or vegetable glycerin to deliver the intended strength, and then add flavor. The creation of this e-juice is at present completely unregulated, and may be done by the end consumer. No standards exist for production, safety, or labeling, and these products have been found to be markedly variable. The availability of tantalizing and delicious-smelling flavors such as “Grape Freeze,” “Simply Mango,” “Death by Chocolate,” “Sour Skittles,” and “Bubblegum Jungle” make these products particularly attractive to youth. Introduction of nicotine to adolescents through the use of e-cigarettes is highly worrisome if these youth become nicotine addicted. As noted, however, the trajectories from e-cigarette initiators are not yet known, and e-cigarette use remains a deeply divisive topic within tobacco control. Many scientists think that e-cigarettes represent a harm-reduction strategy that has substantial promise. Others think that e-cigarettes have intrinsic risks, including the potential to recruit new tobacco users and maintain dual use, and therefore that e-cigarettes represent a net negative to public health. This creates confused messaging arising from public health authorities. The “safest” state is the use of zero tobacco products, including e-cigarettes. Given that vapor, even with low nicotine, contains ultrafine particles with respiratory risks, youth should be warned that “vaping,” even without nicotine, is not a safe experience.

### **Snus and Dissolvables**

Snus and dissolvables have been suggested as safer alternatives to traditional cigarettes and a potential way to decrease the harm caused by combusted tobacco. Adolescents use these forms of tobacco less than cigarettes. Available 2013 data on past-year prevalence among 12th graders is 7.7% for snus and for 1.9% for dissolvable tobacco. Snus is a smokeless tobacco product that does not require the user to spit,

unlike dip or chew. With slogans like “When you can’t smoke, snus,” this tobacco product is marketed specifically as one that can be used in places where smoking is not allowed, and is often cobranded with cigarettes (Marlboro and Camel, for example). The Tobacco Products Scientific Advisory Committee determined that the weight of evidence points to the fact that if an individual were to replace cigarette smoking entirely with snus, the latter would be less harmful than cigarettes. Indeed, those who promote snus as a policy to reduce harm look to Sweden, where snus use is high but smoking prevalence is low. However, some of the product being sold in the United States is qualitatively different from that sold in Sweden, and it appears that more US snus users are engaged in dual use; thus, snus may serve to maintain dependence among smokers who might otherwise have quit.

Dissolvable tobacco products are another new class of smokeless, spitless, finely milled tobacco that dissolves in the mouth until the fine powder is swallowed. Similar to snus, these products have been marketed as tobacco that can be used in places where smoking is prohibited, and are cobranded with traditional cigarettes. Dissolvables are available in mint, wintergreen, cinnamon, and citrus flavors, and are of similar size to candy. While uptake among adolescents has been low to date, ongoing monitoring is warranted, particularly with regard to dual and multiple use.

### **TOXICITY AND POISONING POTENTIAL**

Given the tolerance that occurs with regular nicotine, a wide range of doses have been shown to lead to acute toxicity. Most cases of acute toxicity have been found with accidental ingestion of tobacco or nicotine-containing solutions, or with dermal absorption such as green tobacco sickness. The estimated lethal dose of nicotine is 1 to 13 mg/kg of body weight, with toxicity at lower levels among the nicotine naïve, such as children. Most toxic exposures in youth result in complete recovery; however, there is significant new poisoning potential from nicotine refill solutions for e-cigarettes. E-liquid is a likely candidate for ingestion by young children because it is colorful, candy-flavored, and scented, and often sold without child-proof packaging. Given that nicotine is rapidly dermally absorbed, e-liquid can be dangerous even if it merely comes into contact with the skin. E-liquids are sold in highly concentrated form, with common concentrations containing upwards of 36 mg of nicotine per milliliter of e-liquid. At this concentration, a small 15-mL eye-dropper-sized bottle of e-liquid would contain 540 mg of nicotine. Given the estimated lethal dose range of nicotine, even a single teaspoon of e-liquid at this concentration could kill a small child, and a smaller dose could make a child ill. From the standpoint of risk to young children, it is the flavors and smell that make liquid nicotine refill solutions a prime candidate for accidental ingestion and resultant toxicity. The Centers for Disease Control and Prevention reported that in the month of February 2014 alone, poison control centers received 215 calls related to e-cigarette exposures, many of these in young children. In December 2014, the first child death in the United States from nicotine refill solution was reported.

The Child Nicotine Poisoning Prevention Act of 2015, which would mandate the Consumer Product Safety Commission to require childproof packaging on liquid nicotine, was passed by Congress in January of 2016.

## TOBACCO DEPENDENCE TREATMENT

Although most youth tobacco users want to quit, few seek assistance to do so, and many attempt to quit on their own. Unsurprisingly, most attempts at cessation are unsuccessful, and relapse is frequent. Tobacco cessation is possible, however, as evidenced by the fact that the United States has more former smokers than current smokers. The approach to tobacco cessation is largely the same for adult and adolescent tobacco users, but with a greater emphasis on counseling for adolescents because the evidence for efficacy of pharmacotherapy for this group is insufficient. The Public Health Service (PHS) Clinical Practice Guideline recommends the “5 A’s” model of care (Ask, Advise, Assess, Assist, Arrange follow-up) (see Box 338-1), which has been shown to improve tobacco cessation rates in adults. The first step is to **ASK** about and document all tobacco use at every clinical encounter (including well, ill, and specialty visits). All family members of all ages also should be asked about second-hand smoke exposure, and all families should be advised to make their homes and cars smoke-free. As noted, many youth use both cigarette and noncigarette tobacco products concurrently, so they should be asked about all forms of tobacco use. For all tobacco users, **ADVISE** cessation in a clear, strong manner, personalizing the risks of tobacco use and the benefits of quitting and expressing confidence in the tobacco user’s ability to quit. Regardless of whether the tobacco user is a patient or the parent of a patient, advice should be routinely offered on quitting, helping, and referring all tobacco users. The physician should also **ASSESS** the level of nicotine addiction, reasons for wanting to quit, confidence in ability to quit, and readiness to quit or begin tobacco dependence treatment. In the **ASSIST** step, the physician should initiate treatment, tailoring support to the tobacco user’s readiness to quit and severity of addiction.

Many resources are available to physicians, including self-help materials, referral to statewide or national quitlines (which can provide free telephone counseling to assist tobacco users with cessation), smartphone applications, text support programs, and local community cessation resources. As noted, pharmacotherapy for adolescent tobacco cessation is not recommended by the PHS 2008 guideline because of insufficient evidence of effectiveness. Pharmacotherapy has been demonstrated to be effective in adults, however, and is known to be a safer alternative to tobacco use. Tobacco users should be offered tobacco-cessation medications to assist their quit plan whenever appropriate. These cessation medications include over-the-counter nicotine replacement products (NRT), such as the patch, gum, and lozenge; prescription nicotine inhalers and nasal sprays; bupropion; and varenicline. Details regarding prescription recommendations are available in the PHS Clinical Practice Guideline, but a simple approach would be for a tobacco user to replace each cigarette with a single

### BOX 338-1 The 5 A’s

- Ask
  - Obtain a tobacco use and exposure history from all patients and families
  - Ask about current and past tobacco use and second hand smoke exposure
- Advise
  - Look for “teachable moments”
  - Personalize health risks
    - Use clear, strong, personalized messages: “Smoking is bad for you (and your child). Would you like to quit?” “How can I help you?”
- Assess
  - Determine if the patient is willing to make a behavior change
  - Establish whether he or she is willing to try to quit tobacco use at this time
- Assist
  - Provide information about tobacco use cessation to all tobacco users
  - Strongly urge smoke-free (and tobacco-free) homes
  - Help patients set realistic and specific goals
    - “Quit” date
    - “Smoke-free home” date
  - Help your patient prepare
    - Get support
    - Anticipate challenges
    - Practice problem-solving
    - Provide information about pharmacotherapy and patient resources
    - Provide supplemental materials: Refer to telephone quit lines: 1-800-QUIT NOW
- Arrange Follow Up
  - Plan to follow up on any behavioral commitments
    - Schedule follow-up in person or by telephone soon after important dates, such as quit date or anniversary
- The 6th A – Anticipate
  - Discuss tobacco use with preteens and teens during health supervision visits
    - Include tobacco use with discussions of alcohol, substances of abuse, and sexual activity
- For the Unwilling/Not Ready
  - Discuss the “5 R’s”: Relevance, Risks, Rewards, Roadblocks, and Repetition

lozenge or piece of NRT gum. The strength and frequency of NRT should match the severity of addiction/withdrawal symptoms. As most tobacco users are very familiar with the feeling of using too much tobacco, most tobacco users learn to titrate their NRT dosing just as they learned to titrate their tobacco use. Pediatricians who choose not to prescribe pharmacotherapies should make referrals to cessation services and recommend that parents discuss pharmacotherapies with their health care providers or purchase over-the-counter



products. The final step is to **ARRANGE** follow-up to increase adherence to recommendations.

Motivational interviewing techniques to encourage behavior change should be used throughout all discussions with tobacco users (see Chapter 31, Applying Behavior Change Science; and Chapter 46, Effective Communication Strategies). Encouraging tobacco users to question their own tobacco use and come up with reasons and ways to quit has been shown to be an effective way to motivate change.

## CONCLUSION

Tobacco use remains a preventable and treatable cause of substantial morbidity and mortality in the United States and throughout the world. Pediatricians are well positioned to interact with tobacco users and assist in motivating them to improve their health by quitting tobacco completely. Only with ongoing prevention and treatment strategies will tobacco use be surmounted, and pediatricians and other physicians must be part of this process.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- Julius B. Richmond Center of Excellence (Web site), American Academy of Pediatrics ([www2.aap.org/richmondcenter](http://www2.aap.org/richmondcenter))

## AAP POLICY

- American Academy of Pediatrics Section on Tobacco Control. Clinical practice policy to protect children from tobacco, nicotine, and tobacco smoke. *Pediatrics*. 2015;136(5):1008–1017 ([pediatrics.aappublications.org/content/136/5/1008](http://pediatrics.aappublications.org/content/136/5/1008))
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## Chapter 339

# TONSILLECTOMY AND ADENOIDECTOMY

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## INTRODUCTION

Tonsillectomy and adenoidectomy (T/A) are two of the most common surgical procedures performed on children worldwide. Guidelines based on current research define the workup and clinical indications for T/A, and procedural recommendations define best practice. This chapter informs the practicing physician on key issues related to this important and sometimes controversial topic.

## INDICATIONS AND CONTRAINDICATIONS FOR TONSILLECTOMY AND ADENOIDECTOMY

### Obstructive Sleep Apnea Syndrome

Obstructive sleep apnea syndrome (OSAS) is a “disorder of breathing during sleep characterized by prolonged partial upper airway obstruction or intermittent complete obstruction (obstructive apnea) that disrupts normal ventilation during sleep and normal sleep patterns.”

Sleep-disordered breathing (SDB) is defined as “abnormalities of respiratory pattern or adequacy of ventilation during sleep, which includes snoring, mouth breathing, and pauses in breathing”. Sleep-disordered breathing encompasses a wide spectrum of disorders, from snoring to OSAS.

The American Academy of Pediatrics (AAP) and the American Academy of Otolaryngology (AAO) guidelines concur that if a child has symptoms of SDB with significant OSAS on polysomnography (PSG) and adenotonsillar hypertrophy, they should undergo T/A as long as there are no contraindications. However, no evidence specifies the degree of abnormality noted on PSG required for T/A to be indicated. Most reference works define an abnormal PSG to be an apnea-hypopnea index (AHI) greater than 1 or a pulse oximetry below 92%. In practice, an AHI of 5 defines OSAS severe enough for surgery for most otolaryngologists. However, a T/A may be indicated for a symptomatic child with a lower AHI, because specific parameters have not yet been defined by current evidence. More confusing, there are children who have symptoms of SDB but do not have PSG-documented sleep apnea who benefit from T/A. It seems that PSG results do not always correlate with clinical symptoms either pre- or postoperatively. Although PSG is the gold standard for assessment of OSAS, it is an imperfect gold standard.

Finally, although tonsillar size is not always correlated with PSG results, enlargement is considered a requirement for T/A by both the AAP and AAO.



Significant hypertrophy is diagnosed when the tonsils fill more than 50% of the transverse tonsillar space. When a child presents with an abnormal PSG but has no hypertrophy on the visual examination of the pharynx, lateral neck films may provide additional information regarding tonsillar obstruction below the oropharynx or adenoidal obstruction in the nasopharynx.

### Polysomnography

Polysomnography is the gold standard for assessing children who may have OSAS. The AAP guidelines on OSAS recommend that all children and adolescents be screened for snoring. If snoring is present, then further analysis via directed history and physical examination should take place (see Box 339-1).

#### BOX 339-1 Indications for Polysomnography

##### AMERICAN ACADEMY OF PEDIATRICS GUIDELINES

###### *Snoring history plus any of the following:*

- History is positive for:
  - SDB
  - Frequent snoring (>3 nights/week)
  - Labored breathing during sleep
  - Gasps/snorting noises/observed episodes of apnea during sleep
  - Sleep enuresis
  - Sleeping in a sitting position or with the neck hyperextended
  - Cyanosis
  - Headaches on awakening
  - Daytime sleepiness
  - ADHD symptoms
  - Learning problems
- Physical examination reveals:
  - Tonsillar hypertrophy
  - Under or overweight
  - Adenoidal facies
  - Micrognathia/retrognathia
  - High arched palate
  - Failure to thrive
  - Hypertension

##### AMERICAN ACADEMY OF OTOLARYNGOLOGY GUIDELINES

- Obesity
- Down syndrome
- Craniofacial abnormalities
- Neuromuscular disorders
- Sickle cell disease or mucopolysaccharidoses
- Uncertainty between physical findings and history

SDB, symptoms of sleep disordered breathing.

Note: this guideline is not intended to restrict PSG only to these indications, but rather to define where PSG should be performed before a T/A.

Approximately 10% of children have nighttime snoring, but only one-third of these have OSAS found on PSG. Therefore, infrequent snoring alone is not a criterion for referral for PSG testing. At least one finding in addition to frequent snoring (defined as being present >3 nights/week) is needed and may include a history of labored breathing during sleep, gasping/snorting noises, observed apnea, nocturnal enuresis, sleeping in a sitting position or with the neck hyperextended, cyanosis, headaches on awakening, daytime sleepiness, attention deficit/hyperactivity disorder symptoms, or learning problems. Other findings on physical examination might include: tonsillar hypertrophy, under- or overweight, adenoidal facies, micrognathia, retrognathia, high arched palate, failure to thrive, or hypertension. If frequent snoring plus one of these other criteria are found, then PSG should be performed. Another option is to refer the patient to a sleep specialist or otolaryngologist for a more extensive evaluation. Also per the AAP guidelines, if PSG is not available, then alternative diagnostic tests such as video recording, nocturnal oximetry, daytime nap PSG, or ambulatory PSG may be ordered.

The American Academy of Sleep Medicine, similar to the AAP, recommends PSG any time there is a concern about symptoms that could indicate OSAS.

In contrast with the AAP, the AAO has more selective recommendations pertaining to PSG before T/A (see Box 339-1). The AAO recommends PSG for children suspected of OSAS who are obese or who have Down syndrome, craniofacial abnormalities, neuromuscular disorders, sickle cell disease, or mucopolysaccharidoses. The AAO guideline, which was written as a quality improvement document for head and neck surgeons, also recommends PSG when there is uncertainty between physical findings and the history. The AAO guideline states that there is not enough evidence to recommend portable monitoring devices. Furthermore, the AAO does not recommend PSG for all children who are being considered for T/A, but rather for those with the clinical presentations listed above.

In clinical practice, fewer than 10% of children and adolescents who undergo T/A undergo preoperative PSG. Thus, children who have none of the risk factors listed in the AAO guidelines but who have significant symptoms of SDB and tonsillar hypertrophy will likely undergo T/A without PSG if referred to an otolaryngologist directly. The AAP guidelines support a direct referral in this situation.

Polysomnography is also used to help identify children with more severe OSAS who need to be monitored in an inpatient setting after T/A, because most T/A surgeries are performed as outpatient procedures (see Inpatient versus Outpatient Setting).

Children who have severe OSAS on preoperative PSG may need repeat postoperative PSG if symptoms remain to determine the need for further management with continuous positive airway pressure (CPAP) or other modalities.

In summary, although PSG seems to be a useful clinical tool in evaluating the child or adolescent with SDB as noted above, opinions differ as to when PSG is necessary.

### Medical Options

The AAP supports the option to prescribe topical intranasal corticosteroids when OSAS is mild or when T/A is contraindicated. Also, recent evidence demonstrates a benefit from montelukast for nonobese children with mild OSAS (AHI <10). In this study, the AHI decreased by greater than 50% in 65.2% of children after medication was used for 12 weeks.

### Prognosis

Polysomnography and parental questionnaires assessing sleep disturbance, growth, breathing problems, emotional problems, hyperactivity, school problems, enuresis, aggression, swallowing disorders, speech problems, parental anxiety, activity limitations, and somatization behaviors show significant resolution of these symptoms after T/A. Also, there are reports of significant improvements in quality of life. Nonobese children with SDB who undergo T/A can expect a resolution of symptoms 70% to 80% of the time. However, in a meta-analysis of obese patients, a resolution of SDB occurred in only 10% to 25% of patients. Thus, obese children and those with neuromuscular weakness, craniofacial anomalies, severe preoperative OSAS, family history of sleep apnea, and African American ethnicity are less likely to have a complete resolution of sleep abnormalities after T/A and may warrant PSG postoperatively.

The Childhood Adenotonsillectomy Trial investigators published a recent, well-designed, randomized controlled study that demonstrated no difference in executive function or attention for those undergoing T/A as measured by the Developmental Neuropsychological Assessment test administered 6 to 7 months postoperatively. However, there was improvement in the T/A group in the Connors' rating scales (both teacher and parent), the Epworth Sleepiness Scale, and 2 quality-of-life measures. On PSG, there was significantly greater improvement in AHI score, oxygen desaturation index, hypercapnia and arousal index in the T/A group. Finally, reversal of obstructive sleep apnea was more common in the T/A group (79% vs 46%;  $p < 0.001$ ). Of note in this study, obese children improved in many of the parameters with T/A. Thus, despite finding no difference in attention and executive function, there were many improvements in other parameters for those undergoing T/A for OSAS symptoms.

Treatment with CPAP is indicated for children who do not respond to T/A. Also, weight loss, montelukast, and perhaps nasal steroids may be important adjunctive treatments.

### Recurrent Tonsillitis

Many children with recurrent tonsillitis are referred for T/A. The criteria for recommending this surgery have been a subject of significant controversy in the medical literature. The AAO Guideline on Tonsillectomy in Children recommends watchful waiting for children who do not meet the stringent Pittsburgh criteria (Box 339-2). Physicians may refer children for T/A if these criteria are met.

### BOX 339-2 Tonsillectomy and Adenoidectomy for Recurrent Tonsillitis (Pittsburgh Criteria)

#### DOCUMENTATION REQUIRED:

1. Frequency criteria:
  - 7 episodes in the past year
  - 5 episodes per year for the past 2 years
  - 3 episodes per year for the past 3 years
2. Sore throat plus 1 of the following clinical features:
  - Temperature  $>101^{\circ}\text{F}$  ( $38.3^{\circ}\text{C}$ ) OR
  - Cervical lymphadenopathy ( $>2$  cm) OR
  - Tonsillar exudate OR
  - Positive test for Group A  $\beta$ -hemolytic streptococci
3. PLUS antibiotics for proven or possible streptococcal infection

If not documented, physician should observe patient closely to determine if above clinical pattern is continuing prospectively.

Baugh RF, Archer SM, Mitchell RB, et al.; American Academy of Otolaryngology—Head and Neck Surgery Foundation. Clinical practice guideline: tonsillectomy in children. *Otolaryngol Head Neck Surg.* 2011; 144(1 Suppl):S1–S30; and Paradise JL, Bluestone CD, Bachman RZ, et al. Efficacy of tonsillectomy for recurrent throat infection in severely affected children. Results of parallel randomized and nonrandomized clinical trials. *N Engl J Med.* 1984;310(11):674–683.

The Pittsburgh criteria are derived from a study by Paradise on children severely affected by recurrent pharyngitis. The criteria include at least 7 episodes in 1 year, 5 episodes in 2 successive years, or 3 episodes per year in 3 years. Each episode should have documentation of sore throat plus one or more of the following 4 criteria: temperature greater than  $101^{\circ}\text{F}$  ( $38.3^{\circ}\text{C}$ ), cervical lymphadenopathy, tonsillar exudate, or positive culture for group A  $\beta$ -hemolytic streptococci. Additionally, the criteria include the child having been prescribed antibiotics in a conventional dosage for proved or suspected streptococcal episodes (see Box 339-2).

The children in the Paradise study who met these criteria and who underwent T/A had consistently lower throat infection rates than the observation group, especially in relation to episodes rated moderate or severe. After 1 year, the surgical group had a 14-fold reduction in throat infection episodes rated as moderate or severe; after 2 years, a 6-fold reduction occurred. In addition, sore throat days and sore throat-associated school absences were reported more often for individuals who were treated nonsurgically. Despite the better outcomes in the surgical group, rates of having more than 1 moderate or severe infection in the control group in the subsequent follow-up years were relatively low (year 1: 26%; year 2: 24%; and year 3: 5%). Therefore, the conclusion might be made that this low rate of infection in subsequent years favors observation over surgical intervention. A 14% complication rate occurred in the

surgical group, all of which were judged to be self-limited and readily managed.

Additional research by Paradise and Bluestone analyzed the issue of T/A for children with less severe criteria than those reported from their original study. Using a randomized controlled trial, they found statistically significant, but not clinically significant, differences between the surgical group and controls and reported that moderate inclusion criteria did not justify the risks of surgery, including morbidity (7.9% complication rates) and cost. Van Staaïj and colleagues, who proposed a wait-and-see approach for persons who do not meet the stringent Pittsburgh criteria, supported this concept. In this study, a 4% complication rate was noted, with 1% requiring repeat surgery for hemorrhage and 2.6% having severe nausea or dehydration, which were thought to outweigh the minimal reductions in the frequency of tonsillitis. Because of the cost and complications associated with surgery, most experts recommend presenting surgery as an option (not recommendation) only for children with recurrent pharyngitis who meet the stringent Pittsburgh criteria.

More recent studies, including a Cochrane systematic review, revealed minimal benefit during the first postoperative year of 1.4 fewer sore throat episodes in the surgical group vs. control group that was negated by the one sore throat incurred by those with the surgical procedure.

Two additional systematic reviews both showed just modest improvement in those who had T/A. One study showed 43% fewer sore throat episodes in the first year; the number needed to treat to reduce sore throat by 1 per month was 11. In another review of 13 randomized trials, the T/A group had 1.2 fewer sore throat episodes and 2.8 fewer missed school days per person-year. In each of these studies, the control group also showed significant improvement in tonsillitis episodes.

In developing the most recent AAO guideline that provided a step-by-step logical analysis of the above literature, the panel felt there was not a preponderance of benefit over harm for T/A even for children meeting strict Pittsburgh criteria. Therefore, T/A is stated to be an option that physicians “may recommend” for those meeting the Pittsburgh criteria. Therefore, there is a role for shared decision-making with caregivers. Weighing the risk of complications compared to modest benefits of T/A, watchful waiting remains a reasonable alternative even for children who meet the Pittsburgh criteria.

The AAO guideline for T/A recommends assessing for modifying factors in children with recurrent throat infection who do not meet the Pittsburgh criteria. (see Box 339-3). These conditions include multiple antibiotic allergies making treatment of recurrence difficult and recurrent pharyngitis associated with peritonsillar abscess or PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and adenitis). The presence of these circumstances might lower the threshold for recommending T/A.

### Other Indications

Tonsillectomy is indicated in cases of suspected malignancy where there is asymmetric tonsillar hypertrophy

### BOX 339-3 Modifying Factors for Tonsillectomy in Patients Not Meeting Pittsburgh Criteria

- Multiple antibiotic allergies making treatment of recurrence difficult
- Recurrent pharyngitis associated with peritonsillar abscess
- PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and adenitis)

Derived from Baugh RF, Archer SM, Mitchell RB, et al.; American Academy of Otolaryngology—Head and Neck Surgery Foundation. Clinical practice guideline: tonsillectomy in children. *Otolaryngol Head Neck Surg.* 2011; 144(1 Suppl):S1–S30.

in the setting of lymphadenopathy larger than 3 cm, splenomegaly, fever, or sweats.

Other reported indications that lack evidence include T/A to treat pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, chronic tonsillitis, muffled speech, halitosis, malocclusion, or group A  $\beta$ -hemolytic carrier state. The theoretical benefits of surgery for these conditions, for which there is scant evidence, do not justify the risk of T/A.

Adenoidectomy without tonsillectomy has not been studied as well as T/A. Indications may include chronic otitis media with effusion if pressure-equalization tubes have to be reinserted. This is especially the case in children older than 4 years of age, in whom adenoidectomy seems to be effective in decreasing the rate of pressure-equalization tube reinsertion. Other indications include significant nasal obstruction, recurrent sinusitis, and chronic adenoiditis.

### Contraindications

Relative contraindications for T/A include uncontrolled bleeding disorders and medical conditions causing the child to be unstable for anesthesia. Special consideration should be given for children with submucosal cleft palate who are at risk for velopharyngeal insufficiency after T/A. Physicians should evaluate for the presence of a bifid uvula or a notched hard palate as clues to making this diagnosis preoperatively.

## PERIOPERATIVE MEDICATION

### Steroids

The AAO guideline strongly recommend one intraoperative dose of intravenous dexamethasone to children undergoing T/A (dose 0.0625–1 mg/kg—total dose range 8–25 mg). This was demonstrated in a Cochrane review to reduce postoperative nausea and vomiting (relative risk 0.54; 0.42–0.69) with 4 being the number needed to treat. Also, steroid treatment resulted in less postoperative throat pain and earlier return of oral intake. There were no significant negative consequences of steroid use. This Cochrane review also showed that postoperative hemorrhages were not increased with steroid use.



## Antibiotics

The AAO guideline make a strong recommendation against the use of antibiotics in the perioperative period. This recommendation was based on a Cochrane review of studies that showed no significant benefit.

## Analgesia

The adequate management of pain is important in children who underwent T/A. Generally, pain lasts a week or more and can lead to poor oral intake and dehydration. The AAO recommends ensuring adequate hydration as an important measure after T/A in addition to medications to reduce pain. There was no superiority of around-the-clock over as-needed medication administration except in one study that used hydrocodone.

Concerns about the safety of opioids have caused many surgeons to avoid their use in children younger than 6 years or those with other risk factors for OSAS. Recommended pain management for these children includes acetaminophen (total daily dose of 15 mg/kg/dose up to 5 times per day, maximum dose 4,000 mg/day); ibuprofen (5–10 mg/kg/dose up to 4 times per day, maximum dose of 40 mg/kg/day); and oral corticosteroids in a single dose postoperatively. Of note, no increase in postoperative bleeding was noted with nonsteroidal anti-inflammatory drugs except in the case of ketorolac, where post-T/A hemorrhage rates of 4.4% to 18% have been reported.

The use of narcotics, especially codeine, has received increased scrutiny with recent reports of deaths after T/A in children given codeine. This prompted a US Food and Drug Administration Drug Safety Communication stating that codeine should not be used for pain following T/A. When codeine is ingested, it is converted to morphine in the liver by cytochrome CYP-2D6. Certain children are ultrarapid metabolizers, which can lead to higher than expected levels of morphine and result in respiratory depression. Best practice is to avoid codeine analgesia.

Noncodeine opiates such as oxycodone are still being used in clinical practice in children who undergo T/A. It is unresolved how safe this practice is, because children with significant OSAS were excluded from studies of analgesia after T/A. One study demonstrated that those with OSAS and a preoperative oxygen saturation nadir below 85% had heightened sensitivity to opioid therapy. Recently, a survey of anesthesiologists conducted by the Society for Pediatric Anesthesia examining deaths or serious adverse events after T/A found significantly higher rates of death from apnea among those at risk for OSAS based on risk factors/symptoms. Many of these children received opiate analgesia post-operatively. Most children undergoing T/A do not have a preoperative PSG, and therefore the physician may not know the degree of OSAS in the child. Based on their review of the literature and the survey results, the authors conclude that opiates are responsible for deaths after T/A, with special concern in high-risk children. A normal dose may be too high for the OSAS patient. Therefore, the authors recommended a 50% reduction in opiate dosing for those in the higher risk categories for postoperative apnea.

Oxycodone is an example of a noncodeine opioid that may be considered for pain after T/A. Oxycodone has a more favorable clinical profile than codeine, fewer side effects, more effective analgesia, and less concern with CYP-2D6 metabolism. While oxycodone provides analgesia without metabolism, a small amount of the drug is metabolized via the CYP-2D6 pathway into noroxycodone and oxymorphone. Noroxycodone has weaker analgesic activity compared to oxycodone; oxymorphone is active, but only a small amount (<15%) of the parent drug is converted to this metabolite. Oxycodone is a Schedule II drug. This should be taken into consideration for prescribing, as the prescription must be provided to the pharmacy on paper and cannot be phoned in for dispensing. One advantage of this product is the availability of a tablet and liquid formulation. The liquid can be used to measure small doses for children that do not need a whole tablet for their dose or cannot swallow a tablet.

Hydrocodone, also an opioid agonist, is metabolized by CYP-2D6 into hydromorphone and norhydrocodone. Hydromorphone is a major active metabolite from the CYP-2D6 pathway that can have anywhere from a 33- to 100-fold increase in binding affinity for  $\mu$ -opioid receptors over hydrocodone. Norhydrocodone is metabolized primarily by the CYP-3A4 pathway, and has lesser activity. Hydrocodone is a Schedule III drug. Prescriptions can be written or called in to a pharmacy for dispensing. It is unavailable as a liquid by itself, however, does have a liquid preparation in combination with acetaminophen. When the combination product is prescribed, parents must be counseled not to give regular acetaminophen along with the combination product.

In summary, more research is needed to determine the risk involved in the use of noncodeine opiates, especially in those cases where the degree of OSA was not determined preoperatively. Current practice is to use noncodeine opiates when acetaminophen or ibuprofen are not controlling pain. The dosage should be reduced for those at risk for apnea. (see Box 339-4) Finally, parents should be instructed to be sure to dose medications accurately, especially by using a syringe for liquid medications. Also, excessive acetaminophen dosage should be avoided when using hydrocodone/acetaminophen combinations.

## PROCEDURES

Over the years, various techniques have been used to remove tonsils and adenoids. Techniques have evolved more recently with the goal of decreasing intraoperative blood loss, minimizing postoperative pain, and decreasing postoperative complications.

Cold dissection with a scalpel, surgical scissors, guillotine, or snare has been the traditional method of removing the tonsil by separating the capsule from the superior pharyngeal constrictor muscle and gaining hemostasis with suture ligation. The adenoids have traditionally been removed with curettage. Electrocautery was later added as a tool to achieve hemostasis in the nasopharynx and tonsillar fossa. Although still deemed a safe technique, it can be associated with considerable blood loss.



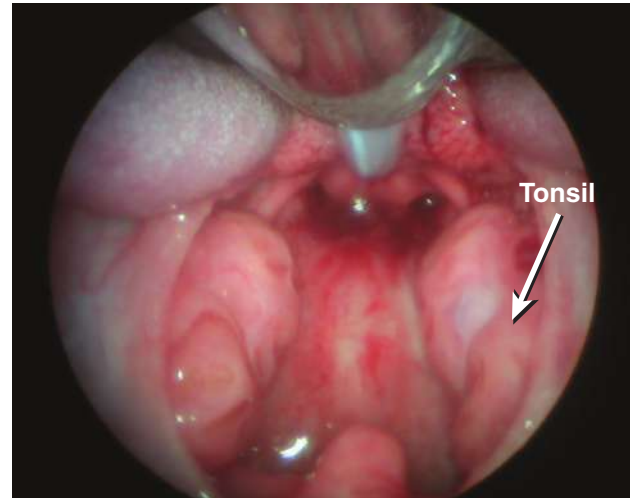
**BOX 339-4 Usual Doses for Analgesia**

- Acetaminophen
  - 15 mg/kg/dose (maximum dose of 75 mg/kg/day, in  $\leq 5$  divided doses/day with 4,000 mg/day)
- Ibuprofen
  - 5–10 mg/kg/dose up to 4 times/day (maximum dose of 40 mg/kg/day); administer with food if GI upset occurs
- Opioids
  - Note: for opioid analgesia, consider reducing dose by 33% to 50% for patients at risk for or documented to have OSAS.
  - Oxycodone
    - Patient weight  $< 50$  kg, over 6 months old: Oral: Initial dose: 0.1–0.2 mg/kg/dose every 4–6 hours as needed; for severe pain, some experts have recommended an initial dose of 0.2 mg/kg/dose; usual maximum dose range: 5–10 mg
    - Patient weight  $\geq 50$  kg: Oral: Initial dose: 5–10 mg every 4–6 hours as needed; for severe pain, an initial dose of 10 mg may be used; usual maximum dose: 20 mg/dose
  - Hydrocodone and acetaminophen (Norco):
    - Patient weight  $< 50$  kg: Oral: Usual initial dose: hydrocodone 0.1–0.2 mg/kg/dose every 4–6 hours
    - Patient weight  $\geq 50$  kg: Oral: Usual initial dose: hydrocodone 5–10 mg every 4–6 hours
    - Note: opioid-naïve patients—limited data available in infants and children  $< 2$  years; use caution. Also, the maximum daily dose of acetaminophen should be limited to  $\leq 75$  mg/kg/day in  $\leq 5$  divided doses; should not exceed 4,000 mg/day

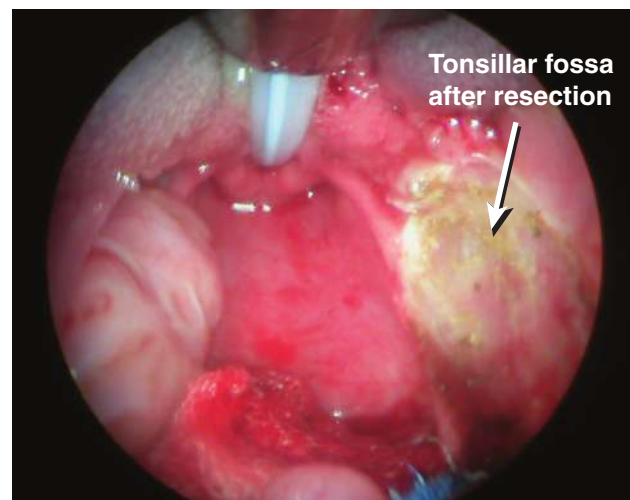
GI, gastrointestinal; OSAS, obstructive sleep apnea syndrome.

Monopolar electrocautery was then introduced as a technique to vaporize adenoid tissue and dissect the tonsils from the fossae. Monopolar electrocautery is currently the most popular technique because it can be performed rapidly with little or no blood loss with equipment that is relatively inexpensive and widely available (Figure 339-1 and Figure 339-2). Electric energy generating temperatures of 400°C to 600°C has the ability to coagulate blood vessels and achieve hemostasis during the dissection. Electrocautery reduces the intraoperative blood loss and the risk of immediate postoperative hemorrhage, but may increase the risk of secondary hemorrhage and postoperative pain when compared with cold dissection, because of the thermal injury to the underlying constrictor muscle. Although rare, airway fire and other fire-related injuries are potential risks of using electrocautery in an oxygen-rich environment.

Surgical lasers have been used in T/A for the last few decades. The oropharynx is easily accessible with laser handpieces used in either illumination (thermo-coagulation) or contact (vaporization) modes. The potential advantages to using lasers include less superior pharyngeal constrictor muscle injury and less



**Figure 339-1** Operative field prepared for electrocautery tonsillectomy.



**Figure 339-2** Tonsil completely removed from the pharyngeal constrictor. (Courtesy of Louis Petcu MD MS.)

pain when compared with the more popular electrocautery technique. In certain cases, electrocautery may be required as an adjunct to achieve hemostasis. Special equipment and precautions must be used by the operating room staff to avoid injury by reflected or misdirected laser light and to avoid airway fire.

Other techniques evolved more recently that allow tonsil removal with less potential for thermal injury to the surrounding tissue. One of these includes the harmonic scalpel, which uses ultrasonic energy to cut and coagulate at a temperature less than 100°C. Another technique includes the coblation device, which uses bipolar radiofrequency energy to ablate and coagulate soft tissue by generating a high-energy plasma field. The ionized plasma field is generated by radiofrequency current that passes through a normal saline medium, working at a much lower temperature of

40°C to 70°C. The Peak plasma blade (Medtronic) uses short bursts of radiofrequency via a highly insulated cutting electrode. The pulsed waveforms deliver less energy, allowing this instrument to work with a temperature range of 40°C to 170°C. A disadvantage of the newer technology is the cost of the disposable hand-pieces that are used with each of these units.

Extracapsular T/A involves the traditional method of removing the tonsils by separating the tonsillar capsule from the surrounding muscles. An alternative method includes using instruments to remove 90% to 95% of the tonsil medial to the tonsillar capsule. This technique intentionally leaves the tonsillar capsule to cover the superior constrictor muscle as a physiologic bandage to minimize swallowing difficulty postoperatively. The procedure may be performed with any of the powered instrumentation as described above or with a microdebrider. This intracapsular technique may be used as an alternative for management of younger patients with obstructed breathing, but may not be appropriate for patients with recurrent infections.

## INPATIENT VS OUTPATIENT SETTING

The decision of whether to perform T/A in the inpatient or outpatient setting hinges on the presence of risk factors as noted in the AAP, AAO, and American Society of Anesthesiologists (ASA) guidelines. Note that there is not a consensus as to what PSG indications require inpatient monitoring. (see Box 339-5).

The AAO guideline cites the ASA guideline, which defines severe OSA as an AHI score greater than 10. The ASA uses a scoring system that includes a combination of severity of OSAS, invasiveness of surgery, and requirement for opioids to determine the need for inpatient monitoring. Of note, using this scoring tool, lower AHI scores may warrant inpatient admission. The AAP uses an AHI score of 24 or higher for inpatient monitoring or where the lowest oxygen saturation is less than 80% or partial pressure of carbon dioxide ( $P_{CO_2}$ ) of 60 or higher on preoperative PSG. These children may also warrant more caution when using narcotic pain medications postoperatively. There are additional criteria recommended by the AAP, the AAO, and the ASA when deciding whether to admit to an inpatient setting postoperatively (see Analgesia).

## COMPLICATIONS

Life-threatening complications in T/A and adenoidectomy are rare and generally involve catastrophic hemorrhagic and respiratory complications. Mortality rates after T/A are difficult to estimate because death is a very rare outcome of this procedure. Most of the studies date back to the 1960s and 1970s. The estimated mortality rate in England was 1:10,000 (1945 to 1965), 1:10,000 (1957 to 1961), 1:16,000 (1961 to 1969), and 1:35,000 (1970s). More recent studies estimate ranges from 1:33,921 (2003–2004), 1:27,000 to 1:100,000.

This improvement in mortality can likely be attributed to improved anesthesia, monitoring equipment, medications, and preparation for hemorrhagic consequences. As anesthetic and surgical techniques and medications continue to evolve and improve, this mortality rate will likely be further reduced.

### BOX 339-5 Potential Indications for Inpatient T/A

- <3 years
- Score of  $\geq 5$  on the Scoring System for Perioperative Risk, found in the ASA Practice Guidelines for the Perioperative Management of Patients With Obstructive Sleep Apnea.
- Severe OSAS on polysomnography (AHI  $\geq 24$  in the AAP guidelines vs  $>10$  in the ASA, AAO guidelines; significant hypercapnia (peak  $P_{CO_2} \geq 60$  mm Hg))
- Lowest oxygen saturation  $<80\%$  (either on preoperative polysomnography or during observation in the recovery room postoperatively)
- Cardiac complications of OSAS
- Failure to thrive
- Obesity
- Craniofacial anomalies
- Neuromuscular disorders
- Current or recent respiratory infection
- Significant asthma
- African American race (4-fold increased risk of OSAS)
- Down syndrome
- Mucopolysaccharidosis and other serious metabolic disorders
- Sickle cell disease
- Central apnea

AAO, American Academy of Otolaryngology; AAP, American Academy of Pediatrics; AHI, apnea-hypopnea index; ASA, American Society of Anesthesiologists;  $P_{CO_2}$ , partial pressure of carbon dioxide; OSAS, obstructive sleep apnea syndrome.

Recent reviews of causes of mortality by the AAO T/A guidelines indicate bleeding as cause in one-third of cases, with other causes being aspiration, cardiopulmonary failure, electrolyte imbalance, or anesthetic complications. Another study demonstrated airway compromise as the major cause of death in malpractice claims. One study based on a survey of anesthesiologists found that a larger proportion of deaths were because of apnea among those who were at high risk for obstructive sleep apnea. Those who were at low risk for OSAS had a higher proportion of death from hemorrhage.

A relatively common complication of T/A and adenoidectomy is minor postoperative bleeding, which is thought to occur at a frequency of 1% to 2% of all cases in the United States. Postoperative hemorrhage can be divided into 2 groups. The immediate postoperative hemorrhage occurs within 24 hours of the T/A or adenoidectomy and is generally thought to be related to surgical technique. The second form of post-tonsillectomy bleeding occurs without identifiable cause and is delayed; it occurs approximately 1 to 2 weeks after surgery.

Postoperative airway obstruction occurs mainly in the child younger than 3 years. In most cases, this complication is caused by edema of the palate, tongue, or lateral pharynx. High-risk patients (Box 339-5) should be identified preoperatively and observed closely in the postoperative period.

**Table 339-1** Post-T/A Complications

COMPLICATION	ONSET	PRESENTATION	TREATMENT
Immediate hemorrhage	0–24 hr	Oral bleeding Hemoptysis Hematemesis	Exploration and ligation of blood vessel
Delayed hemorrhage	5–14 days	Oral bleeding Hemoptysis Hematemesis	Ice pack to neck and iced liquids Elevation of head and neck AgNO <sub>3</sub> cautery Blood vessel ligation Coagulopathy work-up
Immediate airway compromise	Extubation—2 hr	Cyanosis Stridor	Rule out upper airway obstruction/aspiration Rule out laryngospasm Rule out pulmonary edema
Delayed airway compromise	2–24 hr	Shortness of breath Stridor	Intravenous or oral steroid Nasopharyngeal airway
Dehydration	1–6 days	Lethargy Tachycardia Anuria/oliguria	Intravenous rehydration Pain control, hydration Parent education

Occasionally, children with severe OSAS will exhibit postoperative, postobstructive pulmonary edema or central apnea. Other rare complications of T/A include Grisel syndrome (atlantoaxial subluxation—more common in Down syndrome), Lemierre syndrome (parapharyngeal infection with internal jugular vein thrombosis), and posttonsillectomy taste distortion.

Table 339-1 provides a summary of common post-T/A complications.

## SUMMARY

The main indications for T/A are children who have:

1. A combination of SDB or obstructive sleep apnea documented on overnight polysomnography, and tonsillar hypertrophy on physical exam (Best option)
2. Recurrent tonsillitis meeting the Pittsburgh criteria (Option) or if criteria are not met, considering modifying factors that would support T/A (Best option) such as multiple antibiotic allergies, recurrent peritonsillar abscess or PFAPA.
3. Suspected malignancy

In the diagnosis of OSAS, the AAP recommends wide usage of PSG for children who snore and have at least one other symptom or physical finding that supports the diagnosis of OSAS. The AAO, however, recommends PSG only for children who have symptoms of SDB if they are high risk or in cases where there is uncertainty of clinical findings as to whether OSAS is present. In practice, the presence of SDB plus significant tonsillar hypertrophy in nonobese, low-risk children may suffice for T/A without requiring PSG.

Regarding the surgery, a single dose of dexamethasone is strongly recommended intraoperatively, antibiotics are not recommended, and pain control is recommended. Special caution about the use of opioid analgesia should be applied to treating postoperative pain, especially for children who are at risk for or found to have OSAS who undergo T/A in outpatient centers. Specifically, codeine should not be used.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Sleep Apnea and Your Child* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Tonsils and the Adenoid* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *What Is a Pediatric Otolaryngologist?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Otolaryngologist.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Otolaryngologist.aspx))

### Medical Decision Support

- *Polysomnography for Sleep-disordered Breathing Prior to Tonsillectomy in Children* (guideline), *Otolaryngology—Head and Neck Surgery*, Vol 145, Supplement 1, 2011
- *Practice Parameters for the Respiratory Indications for Polysomnography in Children* (guideline), *Sleep*, Vol 34, Issue 3, 2011
- *Tonsillectomy in Children* (guideline), *Otolaryngology—Head and Neck Surgery*, Vol 144, Supplement 1, 2011

## AAP POLICY

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## Chapter 340

# TOXIC SHOCK SYNDROME

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Toxic shock syndrome (TSS) is a disease mainly caused by *Staphylococcus aureus* and *Streptococcus pyogenes*. Staphylococcal TSS can be divided into 2 categories based on the causal association of infection: menstrual and nonmenstrual. Menstrual TSS usually occurs a few days after initiation to a few days after completion of menstruation and is associated with tampon usage in women colonized vaginally by superantigen-producing *S aureus*. A public health campaign on proper tampon use resulted in a shift from menstrual cases to predominantly nonmenstrual cases. Nonmenstrual TSS occurs as a complication of *S aureus* infections after surgical procedures, burns, or influenza pneumonia. Population-based active surveillance for staphylococcal TSS conducted in the Minneapolis-St. Paul area from 2000 to 2006 showed no increase in incidence during that time.

Staphylococcal TSS may occur when a patient who lacks protective antibodies against staphylococcal toxins becomes colonized or infected with toxin-producing *S aureus*. Staphylococcal TSS is likely under-recognized in children because of a common misconception that a foreign body is required for the illness to develop. The overall case fatality rate is from 2% to 5%, which is lower than the reported fatality rates of streptococcal TSS. Mortality is increased significantly—by up to 50%—if adult respiratory distress syndrome or refractory hypotension is apparent. Moreover, nonmenstrual TSS seems to carry a worse prognosis than menstrual TSS, probably because of the delay in diagnosis and the more serious nature of the primary infection.

*Streptococcus pyogenes*, also known as group A  $\beta$ -hemolytic *Streptococcus* (GAS), can cause severe invasive diseases including necrotizing fasciitis, necrotizing myositis, bacteremia, and sepsis; all of which may lead to streptococcal TSS, which is characterized

by vascular collapse, hypotension, and multiorgan failure. Beginning in the 1980s, reports began to shift in the epidemiology of GAS disease toward the occurrence of more severe clinical illness. Subsequent reports indicated the emergence of a toxic shock-like syndrome caused by GAS. Patients with streptococcal TSS have epidemiologic features that distinguish them from patients with other invasive GAS infections, including younger age, alcohol abuse, and fewer underlying illnesses. Published incidence rates of severe invasive GAS infections have ranged from 1.5 to 7.0 cases per 100,000 population annually. Outbreaks of severe invasive GAS infections have occurred in some closed environments, such as military bases, nursing homes, and hospitals. In children, varicella is the most important risk factor associated with invasive GAS infections, including streptococcal TSS. A population-based surveillance study in the United States indicated a high fatality rate associated with invasive GAS infections, with rates of 22% for necrotizing fasciitis and 45% for streptococcal TSS. Although the overall fatality rate of invasive GAS diseases is lower in children (5%–10%) than in adults (30%–80%), the case fatality rate associated with streptococcal TSS remains high in children and adults.

## ETIOLOGY AND PATHOGENESIS

Toxic shock syndrome is a superantigen-mediated disease. Superantigens are potent immunostimulators that are able to simultaneously bind to the major histocompatibility complex class 2 molecules and the T-cell receptor. This binding results in the activation of a large number of T cells that express specific V- $\beta$  subsets of the T-cell repertoire and leads to increased secretion of large quantities of specific cytokines, such as tumor necrosis factor  $\alpha$  and interleukin 1 $\beta$  and T-cell mediators such as interleukin 2 and interferon  $\gamma$ . Unrestrained release of these cytokines may activate the complement, coagulation, and fibrinolytic cascades, resulting in the hypotension, tissue injury, and multiorgan failure characteristic of TSS. A specific staphylococcal exotoxin (SE) known as TSS toxin type 1 (TSST-1) and SEs A, B, C, D, E, and H are a family of superantigens associated with staphylococcal TSS. TSST-1 is responsible for 75% of cases, and SEs are responsible for the remainder. TSST-1 is found in over 90% of menstrual staphylococcal TSS cases and approximately 50% of nonmenstrual cases. Various SEs are found in the other 50% of nonmenstrual cases. Approximately 20% of all clinical isolates of *S aureus* produce TSST-1, which is regulated by a gene known as *agr*. All strains of *S aureus* possessing the *agr* gene produce TSST-1, but the amount of toxin produced varies by strain. Physical and chemical factors are known to influence the production of TSST-1. These factors include pH (toxin production increases between pH 6 and 8), oxygen concentration (toxin production increases at lower oxygen levels), concentration of carbon dioxide (toxin production increases with rising carbon dioxide levels), and concentration of divalent cations (especially magnesium). The absence of antibodies to TSST-1 is a major risk factor for the development of staphylococcal TSS, and it explains why not all patients exposed to virulent



*S aureus* strains develop TSS. The prevalence of antibodies against TSST-1 is over 90% in adults, but is lower in children. A failure to generate anti-TSST-1 antibodies after an episode of TSS predisposes a person to recurrent TSS episodes. Similar to TSST-1, SEs also are potent mediators of cytokine production and release; they behave in a manner similar to TSST-1 in producing clinically comparable TSS disease.

The pathogenic mechanisms responsible for invasive GAS infections have yet to be completely defined. Skin and mucous membranes, often at the site of minimal or inapparent local trauma, are common portals of entry of GAS. The opened lesion of chickenpox has been identified as a risk factor for acquiring invasive GAS diseases, including streptococcal TSS, in otherwise healthy children. Severe invasive GAS infections, however, rarely occur after an episode of acute GAS pharyngitis. The major human host defense against invasive GAS infection is that of phagocytosis and killing by polymorphonuclear leukocytes. Thus, a critical somatic GAS virulence factor is an antiphagocytic surface constituent known as M protein. M protein forms an elongated structure on the bacterial surface and exerts its antiphagocytic effect by interfering with opsonization via the alternate complement pathway. In addition, M protein is shed from the bacterial surface and forms a complex with fibrinogen. The M protein–fibrinogen complexes bind to integrins on the surface of polymorphonuclear leukocytes, activating these cells to adhere to endothelium and degranulate, releasing a wide variety of hydrolytic enzymes and producing a respiratory burst. The resulting damage to the underlying endothelium leads to vascular leakage and hypercoagulability, which in turn cause the hypotension, disseminated intravascular coagulation, and organ damage that are characteristic of TSS. Strains of GAS isolated from patients with TSS are not of a single M type, but M1 and M3 infections have been commonly associated with invasive diseases and streptococcal TSS.

Most cases of streptococcal TSS are caused by GAS strains that produce bacterial superantigens known as the streptococcal pyrogenic exotoxins (Spe). Their structures are similar to each other and to the structures of staphylococcal superantigens. The probable direct importance of streptococcal pyrogenic exotoxins, particularly exotoxin A (SpeA), in the development of streptococcal TSS is emphasized by the total inability of patients' sera to neutralize the lymphocyte mitogenic properties of SpeA, the known biologic property of SpeA as a superantigen. Among the streptococcal pyrogenic exotoxins, SpeA is the most potent inducer of massive T-cell proliferation and interferon  $\gamma$  and tumor necrosis factor  $\beta$  production. In addition, there is evidence that the host immunogenetics, specifically human leukocyte antigen class II allelic variation, contribute to differences in the severity of invasive GAS infections, including streptococcal TSS, through the ability to regulate immunomodulator responses triggered by streptococcal superantigens. Patients with severe GAS disease have significantly lower serum levels of protective antibodies against M protein and superantigens compared with serum samples from noninvasive cases. These findings provide evidence

that a lack of protective humoral immunity against GAS virulence factors contributes to susceptibility to invasive infection.

## EVALUATION

### Clinical Presentation

#### *Staphylococcal Toxic Shock Syndrome*

Staphylococcal TSS presents with an abrupt onset of fever, chills, and severe gastrointestinal symptoms consisting of abdominal cramps; nausea; vomiting; and profuse, watery, nonbloody diarrhea. Occasionally, a prodrome consisting of low-grade fever, malaise, myalgia, or vomiting occurs in the week preceding the acute illness. Many children may also complain of a headache, myalgia, and a sore throat. At this stage of the illness, an incorrect diagnosis of acute viral gastroenteritis may be suspected. However, over the next 24 to 72 hours, a diffuse, blanching, macular erythroderma (sunburn-like) or scarlatiniform rash may appear. The rash may be faint or evanescent. The rash is not pruritic but is occasionally petechial. Patients demonstrate bilateral conjunctival hyperemia without discharge and may complain of photophobia. Oropharyngeal involvement includes a strawberry tongue or buccal ulcerations. Among adolescents, vaginal erythema with minimal clear watery discharge may be present in association with menstruation.

The case definition of staphylococcal TSS by the Centers for Disease Control and Prevention (CDC) is shown in Box 340-1.

Within 24 to 72 hours of onset, most patients with staphylococcal TSS experience orthostatic dizziness or syncope or both because of orthostatic hypotension. These symptoms can occur abruptly and may precede the development of hypovolemic shock. The peak of illness occurs on the second or third day and involves multiple organ systems. Central nervous system dysfunction may consist of headache, confusion, disorientation, hallucinations, or complaints of paresthesias of the hands and feet. Some patients have a stiff, tender neck. If a lumbar puncture is performed, cerebrospinal fluid is usually normal, although some patients may have up to 100 white blood cells/mm<sup>3</sup>, 50% of which may be polymorphonuclear cells. Abdominal musculature tenderness, absent or hypoactive bowel sounds, and radiologic evidence of a nonobstructive ileus are common. Common renal symptoms include azotemia, oliguria, and a diminished creatinine clearance; complete renal shutdown is rare. Exquisite muscle tenderness and severe myalgias are common. Arthralgias and joint effusions may be seen. Nonpitting edema over the wrists and ankles and synovitis of the small joints of the hands and feet have been reported. Patients may experience adult-type respiratory distress syndrome (shock lung). Hematologic involvement includes a progressive normochromic normocytic anemia, thrombocytopenia, and leukocytosis. Arrhythmias or prolonged shock may lead to eventual myocardial failure. Convalescence is characterized by a desquamation of the palms and soles within 1 to 2 weeks after the onset of illness. Some patients also experience hair and nail loss. Fatigue and weakness for as long as 3 months may occur in the recovery phase.

### BOX 340-1 Case Definition for Staphylococcal Toxic Shock Syndrome

- Fever: temperature:  $\geq 102.0^{\circ}\text{F}$  ( $38.9^{\circ}\text{C}$ )
- Rash: diffuse macular erythroderma; desquamation of palms and soles 1 to 2 weeks after onset of illness
- Hypotension: systolic blood pressure 90 mm Hg for adults or below fifth percentile by age for children under 16 years; orthostatic drop in diastolic blood pressure  $\geq 15$  mm Hg from lying to sitting, or orthostatic syncope
- Multisystem involvement—3 or more of the following:
  - Gastrointestinal: vomiting or diarrhea at onset of illness
  - Muscular: severe myalgia or creatinine phosphokinase level at least twice the upper limit of normal for laboratory
  - Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
  - Renal: blood urea nitrogen or creatinine at least twice the upper limit of normal for laboratory or urinary sediment with pyuria ( $>5$  white cells per high-power field) in the absence of urinary tract infection
  - Hepatic: total bilirubin, serum glutamic oxaloacetic transaminase, or serum glutamic pyruvate transaminase at least twice the upper limit of normal for laboratory
  - Hematologic: platelet count  $\leq 100,000/\text{mm}^3$
  - Central nervous system: disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent
- Negative results on the following tests, if obtained:
  - Blood, throat, cerebrospinal fluid cultures; blood culture may be positive for *S aureus*
  - Antibody titer: Rocky Mountain spotted fever, leptospirosis, and rubeola

Adapted from Wharton M, Chorba TL, Vogt RL, Morse DL, Buehler JW. Case definitions for public health surveillance. *MMWR Recomm Rep*. 1990;39(Rr-13):1–43.

### Streptococcal Toxic Shock Syndrome

Streptococcal TSS is characterized by fever, rapid-onset hypotension, rapidly accelerated renal failure, and multisystem organ involvement, similar to staphylococcal TSS. Pharyngitis and local soft-tissue infection (eg, cellulitis, abscess, myositis, necrotizing fasciitis) associated with sudden severe pain is common with TSS. Pain, the most common initial symptom of streptococcal TSS, usually involves an extremity, but it may mimic peritonitis, pelvic inflammatory disease, or acute chest syndrome. Twenty percent of patients may have preceding influenza-like syndrome characterized by fever, chills, myalgia, nausea, vomiting, and diarrhea. Fever is the most common early sign, although hypothermia may be present in patients with shock. A diffuse scarlatina-like erythema occurs in only 10% of patients. Confusion is present in 55% of patients, and in some, coma or combativeness may occur.

### BOX 340-2 Streptococcal Toxic Shock Syndrome (*Streptococcus pyogenes*) 2010 Case Definition<sup>a</sup>

- Hypotension defined by a systolic blood pressure  $\leq 90$  mm Hg for adults or less than the fifth percentile by age for children aged younger than 16 years.
- Multi-organ involvement characterized by 2 or more of the following:
  - Renal impairment: creatinine  $\geq 2$  mg/dL ( $\geq 177$   $\mu\text{mol/L}$ ) for adults or greater than or equal to twice the upper limit of normal for age. In patients with pre-existing renal disease, a greater than twofold elevation over the baseline level.
  - Coagulopathy: platelets  $\leq 100,000/\text{mm}^3$  ( $\leq 100 \times 10^6/\text{L}$ ) or disseminated intravascular coagulation, defined by prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products.
  - Liver involvement: alanine aminotransferase, aspartate aminotransferase, or total bilirubin levels greater than or equal to twice the upper limit of normal for the patient's age. In patients with pre-existing liver disease, a greater than twofold increase over the baseline level.
  - Acute respiratory distress syndrome: defined by acute onset of diffuse pulmonary infiltrates and hypoxemia in the absence of cardiac failure or by evidence of diffuse capillary leak manifested by acute onset of generalized edema, or pleural or peritoneal effusions with hypoalbuminemia.
  - A generalized erythematous macular rash that may desquamate.
  - Soft-tissue necrosis, including necrotizing fasciitis or myositis, or gangrene.

<sup>a</sup>Clinical manifestations do not need to be detected within the first 48 hours of hospitalization or illness, as specified in the 1996 case definition. The specification of the 48 hour time constraint was for purposes of assessing whether the case was considered nosocomial, not whether it was a case or not.

From Centers for Disease Control and Prevention. Streptococcal toxic shock syndrome (STSS) (*Streptococcus pyogenes*) 2010 case definition. Available at: [wwwn.cdc.gov/nndss/conditions/streptococcal-toxic-shock-syndrome/case-definition/2010](http://wwwn.cdc.gov/nndss/conditions/streptococcal-toxic-shock-syndrome/case-definition/2010). Accessed February 3, 2016.

The case definition for streptococcal TSS is shown in Box 340-2.

Soft-tissue swelling and erythema is present in 80% of patients with streptococcal TSS, and up to 70% can progress to necrotizing fasciitis or myositis and will require surgical debridement, fasciotomy, or amputation. Necrotizing fasciitis is a life-threatening soft-tissue infection primarily involving the superficial fascia with a relative sparing of the skin and muscles, both of which may be infected secondarily. The patient may have a history of soft-tissue injury from an animal or insect bite, blunt or penetrating trauma, surgical wounds, or subcutaneous injections of insulin or illicit drugs. Streptococcal TSS may occur after varicella infection; 15% to 30% of invasive GAS diseases were reported to be associated with varicella. In some instances, an inconsequential scratch or abrasion may be implicated. Most patients have an

erythematous, tender, swollen area that resembles cellulitis with disproportionately severe pain at the site of involvement. An ominous sign of necrotizing fasciitis is the progression of soft-tissue swelling to the formation of vesicles, then bullae, which seem violaceous or hemorrhagic. The line of demarcation becomes sharply defined, and the dead skin begins to separate at the margins or breaks in the center, revealing an extensive necrosis of the subcutaneous tissue. The presence of crepitus on physical examination or soft-tissue air by plain-film radiograph, which is pathognomonic for necrotizing soft-tissue infections, is seen in only one-third and one-half of cases, respectively.

Severe pain, swelling, erythema, and fever may be the early signs of myositis. Pain is often out of proportion to the clinical findings, possibly related to muscle compartment syndrome, which may develop rapidly. Both necrotizing fasciitis and myositis are difficult to diagnose; therefore, clinical acumen and suspicion are important. Some patients with streptococcal TSS may have both necrotizing fasciitis and myositis. Emergent surgical exploration should be performed to establish and distinguish GAS infection from other soft-tissue infections. Nearly one-half of patients with streptococcal TSS may have normal blood pressure at the time of admission but soon develop hypotension. The presence of hypotension is a significant risk factor for death.

Renal dysfunction, which may occur before or after hypotension, progresses or persists in all patients for 48 to 72 hours in spite of treatment, and many patients require dialysis. In patients who survive, serum creatinine values return to normal within 4 to 6 weeks. Acute respiratory distress syndrome occurs in one-half of the cases and generally develops after the onset of hypotension. Profuse watery diarrhea, vomiting, abdominal pain, generalized erythroderma, conjunctival injection, and severe myalgias that are commonly present with staphylococcal TSS are present but less common with streptococcal TSS. Streptococcal TSS also may be associated with invasive GAS infections, such as pneumonia, meningitis, peritonitis, osteomyelitis, bacteremia, or septic arthritis. However, streptococcal TSS may occur without a readily identifiable focus of infection in 21% of cases. Recurrent episodes have not been reported for streptococcal TSS.

### Laboratory Evaluation

No single laboratory test confirms the diagnosis of TSS. Initial laboratory findings often include mild leukocytosis, but the mean percentage of immature neutrophils can reach 40% to 50%. Leukopenia has occasionally been observed in children with TSS. Progressive anemia and thrombocytopenia are often observed. Thrombocytopenia may be accompanied by the prolongation of prothrombin time and partial thromboplastin time and the appearance of increased fibrin split products. However, serious bleeding during the acute phase or thrombosis secondary to rebound thrombocytosis during recovery is uncommon. Most patients have hypoproteinemia and hypoalbuminemia, probably as a result of increased capillary



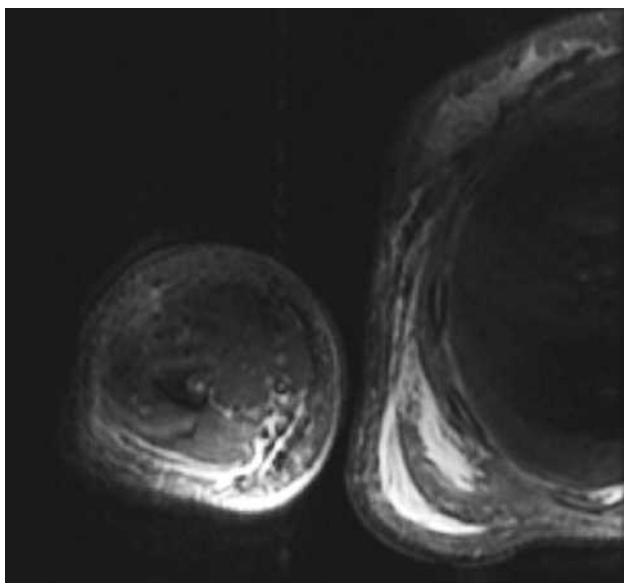
**Figure 340-1** A plain radiograph of an adolescent with necrotizing fasciitis reveals soft tissue air in the perineal region and the left abdominal wall (Courtesy of Shipra Gupta, MD, Children's Hospital of Michigan).

permeability caused by exotoxin-mediated vascular cell membrane change. A significant number of patients also experience lactic acidosis from inadequate tissue perfusion. Hyponatremia, hypokalemia, hypocalcemia, hypophosphatemia, and hyperglycemia are also noted. Renal involvement is indicated by the presence of hemoglobinuria and by rising serum creatinine values. Renal impairment precedes hypotension in 40% to 50% of patients. The serum creatinine kinase level is useful in detecting deeper soft-tissue infections; when the level is increased, a good correlation exists with necrotizing fasciitis or myositis. Hepatic enzyme and bilirubin levels are typically elevated initially but tend to revert to normal in convalescence. Blood cultures are generally negative for staphylococcal TSS, whereas blood cultures are positive for GAS in 60% of streptococcal TSS cases; however, the presence or absence of GAS bacteremia does not affect the mortality. Subcutaneous fluid may be aspirated from the affected limb for Gram stain and culture. All tissues obtained at the time of initial surgical debridement should be subjected to Gram staining and to culturing for aerobic and anaerobic microorganisms. Rapid antigen detection tests for GAS have not been approved for any specimen besides pharyngeal swab specimens; however, GAS may be identified from necrotic tissue with a rapid antigen test. In children with necrotizing soft-tissue infections, GAS is identified as a single organism in only 25% of cases; the remaining cases are polymicrobial.

### Imaging Studies

The use of imaging studies depends on clinical presentations. Such studies are more useful in the diagnosis of streptococcal TSS. The presence of soft-tissue air at the affected area may be observed in plain films (Figure 340-1). Computed tomography and magnetic resonance imaging also aid in the diagnosis of necrotizing fasciitis and myositis and in the delineation of the extent of infection. Features that indicate necrotizing fasciitis by computed





**Figure 340-2** Magnetic resonance imaging of a shoulder of a child with toxic shock syndrome shows significant enhancement of soft tissue and muscles with fluid tracking along the fascia (Courtesy of Shipra Gupta, MD, Children's Hospital of Michigan).

tomography or magnetic resonance imaging include deep fascial thickening and enhancement and the presence of fluid and gas in the fascial planes (Figure 340-2). The typical radiologic findings of myositis are of a general homogenous enlargement of the muscle, with low attenuation values and edema or the presence of intramuscular gas. It should be emphasized that imaging studies are only adjuncts in the evaluations of patients with TSS and necrotizing soft-tissue infections, and they should not be relied on to exclude the diagnosis or to delay surgical interventions. The diagnosis of invasive infection, including TSS, is still based primarily on clinical assessment.

## TREATMENT

The main treatment of a child with TSS includes hemodynamic stabilization, therapeutic support for multiorgan failure, and specific antibiotic therapy. A thorough search for possible sites of infections is mandatory to eliminate any preformed toxin and to prevent the synthesis of new toxins. Vaginal examination and removal of a tampon or other foreign body are mandatory. Surgical wounds should be considered as possible reservoirs of infection, even if no superficial signs of local infection are present. Infected wounds should be debrided, and any packing should be removed. Abscesses need to be drained and irrigated. Prompt and aggressive surgical exploration, fasciotomy, and debridement of suspected infection are mandatory. Culture specimens from all possible sites should be obtained. Surgical exploration and incisional biopsy, particularly in streptococcal TSS, provide both definitive diagnosis and treatment. Survival is possible with early surgical debridement, re-exploration at 24 to 36 hours, and intensive supportive

care. The extent of debridement is determined not only by the radiographic findings, but also by physical findings at the time of surgery.

Because TSS caused by *S aureus* and GAS is difficult to distinguish clinically, children suspected of having TSS should receive empiric, broad-spectrum antibiotic therapy with activities against both pathogens. The most commonly advocated antibiotic regimen includes the combination of expanded-spectrum penicillin or cephalosporins and clindamycin. As multidrug-resistant *S aureus* (MRSA) has emerged as an important pathogen in children, empiric antibiotic therapy that is effective against this pathogen should be considered. However, a recent study indicated a low prevalence of MRSA in TSS cases. The antibiotic regimen should be changed once the causative organism is identified. Antimicrobial therapy should be continued for at least 10 to 14 days to eradicate the organism and prevent recurrences. The total duration should also be based on the clinical improvement and the usual duration established for the underlying focus of infection.

Several pathophysiologic rationales support the use of combination antibiotic therapy of  $\beta$ -lactam and clindamycin for TSS. In patients with staphylococcal TSS, clindamycin has been shown to reduce TSST-1 production, whereas  $\beta$ -lactam antibiotics, including nafcillin and first-generation cephalosporins, increase TSST-1 in culture, probably by lysis or increased cell membrane permeability. Thus, the use of clindamycin in combination with a  $\beta$ -lactamase-resistant antistaphylococcal agent results in a potentially beneficial effect by decreasing the synthesis of TSST-1. In the setting of streptococcal TSS, penicillin is less efficacious in overwhelming GAS infections when large numbers of organisms are present (the so-called *Eagle effect*). Large inocula of GAS reach the stationary growth phase quickly, and penicillin is less efficacious against slowly growing organisms. Certain penicillin-binding proteins are not expressed by GAS during the stationary phase. The loss of penicillin-binding proteins may be responsible for the inocula effects observed and may account for the failure of  $\beta$ -lactam to control severe GAS infection. Conversely, the inhibitory effects of protein synthesis in clindamycin are independent of the inoculum size or the stage of bacterial growth. In addition, clindamycin suppresses the synthesis of bacterial toxins including the superantigens, facilitates phagocytosis of GAS by inhibiting M protein synthesis, has a postantimicrobial effect, and suppresses the synthesis of penicillin-binding proteins that, in addition to being targets for  $\beta$ -lactam, are also enzymes involved in cell-wall synthesis and degradation. Research has shown that clindamycin suppresses lipopolysaccharide-induced monocyte synthesis of tumor necrosis factor  $\alpha$ . The efficacy of the drug may thus also be related to its ability to modulate the immune response. A retrospective study demonstrated a favorable outcome among children with invasive GAS infections being treated with the combination of  $\beta$ -lactam and clindamycin. Clindamycin should not be used alone, because strains of *S aureus* or GAS with clindamycin resistance have been reported.

Intravenous immunoglobulin (IVIG) may be considered in children with TSS unresponsive to all other



therapeutic measures above. IVIG has been shown to reduce the morbidity and mortality of staphylococcal and streptococcal TSS, although most evidence was from streptococcal TSS. High levels of antibodies to TSST-1, streptococcal superantigens, and M proteins have been found in IVIG preparations. The usual dose of IVIG is 400 mg/kg over a period of 4 to 8 hours as a single dose. Staphylococcal superantigens are not inhibited as efficiently as streptococcal superantigens by IVIG, so a higher dose of IVIG may be required for therapy of staphylococcal TSS to achieve protective titers and clinical efficacy. The use of high-dose corticosteroids has sometimes been advocated as possibly beneficial in the treatment of shock syndromes. However, such therapy should not be administered routinely to patients with TSS, because it may result in a shorter time to defervescence and clinical stability while making no difference in overall risk of mortality. An association between the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and the development of TSS has been reported; this is likely because NSAIDs enhance the production of tumor necrosis factor. NSAIDs can impair granulocyte function and may mask signs of disease progression by relieving pain, reducing swelling, and suppressing fever, thus contributing to a delay in diagnosis.

Hyperbaric oxygen, a form of medical treatment in which the patient is enclosed in a chamber and breathes 100% oxygen at a pressure greater than 1 atmosphere absolute, has gained acceptance for treatment of a variety of medical conditions. Although a physiologic rationale can be found for the use of hyperbaric oxygen therapy in the treatment of necrotizing fasciitis, the results of clinical studies have been inconsistent. Some studies have shown that such therapy can improve patient survival and decrease the number of debridements required to achieve wound control, whereas others have shown no benefit.

## PREVENTION

### Staphylococcal Toxic Shock Syndrome

Primary prevention for menstrual staphylococcal TSS is achieved by encouraging limited use of high-absorbency tampons and educating the general public about the proper use of tampons and the importance of early recognition of TSS. If symptoms of TSS occur, tampons should be removed and prompt medical attention should be sought. Since as many as 30% of women who had menstrual TSS relapse during subsequent menstruation, tampon use in these women should be discontinued. Nonmenstrual staphylococcal TSS can be prevented by proper infection-control practices in surgical procedures and burn wound care. Vaccination against influenza should prevent influenza-associated staphylococcal pneumonia, an important cause of staphylococcal TSS.

### Streptococcal Toxic Shock Syndrome

Opportunities for preventing streptococcal TSS are few. Because of the association between invasive GAS infections, including TSS and varicella infection, in healthy children, routine childhood immunization against varicella is recommended by the AAP. Children who receive the varicella vaccine are less likely to

be hospitalized for varicella-related invasive GAS infections. A relationship between the use of NSAIDs and necrotizing fasciitis has been reported. Evidence suggests that NSAIDs can impair granulocytic function and enhance production of cytokines. Although some physicians have suggested that NSAIDs should not be used to treat children with varicella, a causal relationship between NSAID use and severe invasive GAS infections has not been established. Nosocomial GAS infections should be prevented by improving infection-control practices for surgical and obstetric procedures and for placement and care of intravascular devices.

GAS can easily spread through the household. In many of these clusters, additional family members, usually children, are identified with pharyngitis or with carriage of the same strain of GAS that caused the invasive disease. The relative risk of invasive GAS infections among household contacts of patients with invasive GAS infections are 19 to 200 times the baseline risk in the general population. Secondary cases of invasive GAS infections, including STSS within the same household, have been reported. Although the risk of subsequent invasive GAS disease among household contacts is higher than the risk among the general population, such infections are rare. No studies have evaluated the effectiveness of chemoprophylaxis in preventing invasive GAS disease among household contacts of patients with invasive GAS infections; thus, routine chemoprophylaxis among household contacts is not warranted. Health care providers should inform members of the household about the clinical manifestations of pharyngeal and invasive GAS infections and emphasize the importance of seeking immediate medical attention if they develop such symptoms, particularly within 30 days after the diagnosis is made in the index case. Routine use of cultures to identify household contacts who are colonized with GAS is not suggested.

Because of the high mortality rate associated with invasive GAS infections in persons older than 65 years and those with underlying illnesses or other host factors, chemoprophylaxis to prevent secondary cases may be offered to household members aged 65 years or older and those with human immunodeficiency virus infection, concurrent varicella infection, diabetes mellitus, cancer, chronic cardiac or pulmonary diseases, injection drug use, alcoholism, known immunodeficiency disorder, or corticosteroid use. Because the source of GAS in households is not necessarily the person with invasive infection, physicians who elect to prescribe chemoprophylaxis for an elderly or high-risk household member should prescribe chemoprophylaxis for all members in that household. If available, antibiotic susceptibility data should be used to select the most appropriate chemoprophylactic agent. Everyone who receives chemoprophylaxis should watch for signs and symptoms of invasive GAS disease for 30 days after the diagnosis of invasive disease in the index case. The chemoprophylactic regimens are as follows:

1. A single dose of benzathine penicillin G (600,000 units intramuscularly for persons weighing <27 kg or 1,200,000 units intramuscularly for persons weighing  $\geq$ 27 kg) and oral rifampin 20 mg/kg/day

(maximum daily dose, 600 mg) in 2 divided doses for 4 days

2. Clindamycin 20 mg/kg/day (maximum daily dose, 900 mg) in 3 divided doses for 10 days
3. Azithromycin 12 mg/kg/day (maximum daily dose, 500 mg) once a day for 5 days. It should be noted that a significant proportion of GAS strains have been reported as being resistant to macrolides, including azithromycin.

There is limited evidence that first- and second-generation cephalosporins are effective in eradicating the pharyngeal colonization of GAS, and these agents could be considered for patients who are allergic to penicillin whose allergic reactions are not anaphylactic. Rifampin is not recommended for pregnant women because of its teratogenic effect.

Enhanced surveillance by infection control personnel should be implemented after identifying a case of postpartum or postsurgical invasive GAS infection. All GAS isolates from suspected cases should be stored and compared by serotyping or molecular techniques. The occurrence of 2 or more cases of invasive GAS infection by the same GAS type within a 6-month period suggests that a health care worker might be the source of the cluster; therefore, it is strongly recommended that health care workers who are epidemiologically linked to the case patients be screened by obtaining cultures from throat, anus, vagina, and skin lesions. One of the 3 prophylactic regimens mentioned above can be prescribed to health care workers who are colonized with GAS. Follow-up culture should be performed 7 to 10 days after the completion of therapy.

### WHEN TO REFER

All children with TSS should be managed by a multidisciplinary team of pediatric critical care specialists, pediatric infectious diseases specialists, and pediatric surgeons.

### WHEN TO ADMIT

All children with TSS should be admitted.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Toxic Shock Syndrome* (fact sheet), US National Library of Medicine ([www.nlm.nih.gov/medlineplus/ency/article/000653.htm](http://www.nlm.nih.gov/medlineplus/ency/article/000653.htm))
- *Toxic Shock Syndrome* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/infections/Pages/Toxic-Shock-Syndrome.aspx](http://www.healthychildren.org/English/health-issues/conditions/infections/Pages/Toxic-Shock-Syndrome.aspx))

## AAP POLICY

Infectious Diseases Society of America. The treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. AAP endorsed. *Pediatrics*. 2011; 127(3):598 ([pediatrics.aappublications.org/content/127/3/598](http://pediatrics.aappublications.org/content/127/3/598))

## SUGGESTED READINGS

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## Chapter 341 TUBERCULOSIS

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Tuberculosis (TB) is a serious disease caused by *Mycobacterium tuberculosis* complex. TB disproportionately affects young children as a result of their increased risk for progression to disease when infected by *M tuberculosis* and the increased likelihood of disseminated disease. In the United States, children who are at the highest risk for TB are children of color, children born in countries with a high prevalence of TB or into families from these countries, children who live with or in contact with adults who are at risk for TB, and children younger than 4 years of age.

## DEFINITIONS

### Tuberculosis

Tuberculosis is caused by infection with an organism of the *M tuberculosis* complex, which includes *M tuberculosis* and *Mycobacterium bovis*, and is distinguished from latent TB infection (LTBI). Common clinical presentations of TB include pneumonia, pleuritis, intrathoracic or peripheral lymphadenopathy, meningitis, disseminated TB, and bone and joint disease. In the United States, children diagnosed with TB disease are often asymptomatic but have radiographic evidence of disease such as an infiltrate or intrathoracic adenopathy. Asymptomatic presentations of TB disease are treated with multidrug therapy because they will progress in many children if not treated. Table 341-1 provides epidemiologic data for TB in children. Among the 460 US children 0 to 14 years of age with TB in 2014, 262 were younger than 5 years, 198 were ages 5 to 14 years; 41% were Hispanic, and 23% were black. A total of 22% of TB cases in children occurred in the foreign born with Mexico being the leading country of birth. From 1993 to 2014, TB case rates declined from 2.9 to 0.8 cases per 100,000 children. Forty percent of the cases reported were from California, Texas, and New York.

### Latent Tuberculosis Infection

Latent infection with *M tuberculosis* complex occurs when the organism is in a metabolically slower state and replicating slowly within granulomata in the lung

or other tissues. The patient usually has a positive tuberculin skin test (TST) result or a positive interferon- $\gamma$  (IFN- $\gamma$ ) release assay (IGRA) blood test result but no clinical or radiographic evidence of TB disease (although evidence of healed disease such as calcified nodes may be present). Patients should be treated with isoniazid (isonicotinylhydrazine [INH]) monotherapy daily for 9 months, unless they have a medical contraindication (including infection with a known INH-resistant strain). Because LTBI is not a reportable condition in most states, the number of children who have LTBI can only be estimated.

**Table 341-1** Tuberculosis (TB) Among Children, United States, 2014

GROUP	TB CASE RATE PER 100,000 CHILDREN
Children ages 0–14 yr	0.8
Children <5 yr	1.3
Hispanic or Latino	2.1
Asian	5.0
Black or African American	2.1
White	0.3

From Centers for Disease Control and Prevention, Division of Tuberculosis Elimination. *Reported Tuberculosis in the United States, 2014*. Atlanta, Ga: US Department of Health and Human Services, Centers for Disease Control and Prevention; October 2014. Available at: [www.cdc.gov/tb/statistics/reports/2014/default.htm](http://www.cdc.gov/tb/statistics/reports/2014/default.htm).

### Tuberculosis Exposure

A person exposed to TB is one who has spent time in close proximity to a potentially contagious patient with pulmonary TB disease. The exposed individual may or may not be infected. Because young children can progress rapidly to TB once infected, they should be quickly evaluated and receive prophylactic treatment if found to be exposed to an individual with TB.

### DIFFERENTIAL DIAGNOSIS

TB symptoms mimic many different diseases. Because TB is uncommon in the United States among most populations, the pediatrician must maintain a high index of suspicion for TB, especially among children who fit the epidemiologic profile and who have risk factors for infection and disease. The differential diagnosis for TST results is outlined in Box 341-1. The differential diagnosis for forms of TB disease is provided in Box 341-2.

### Testing for Tuberculosis Infection

The American Academy of Pediatrics (AAP) does not recommend universal testing for TB. Assessment at the first visit and annually thereafter for TB risk factors and testing of children with defined risk factors is the standard of care. Testing asymptomatic children without known risk factors for TB is no longer performed. The TST and IGRA are used to diagnose LTBI and support the diagnosis of TB disease. Because of the poor sensitivity and specificity of the TST in low-incidence populations, it is given only to children identified as having increased risks for TB exposure or

### BOX 341-1 Differential Diagnosis for Tuberculin Skin Test Results

#### TRULY POSITIVE

- Caused by infection with *M tuberculosis* complex

#### FALSELY POSITIVE

- Cross-reaction with nontuberculous mycobacteria, such as *M avium* complex and *Mycobacterium scrofulaceum*. These reactions are often, but not always, smaller than those caused by *M tuberculosis*.
- Cross-reaction with a recent or multiple vaccinations with BCG. In general, the public health strategy in the United States is to discount the history of BCG vaccination when deciding to administer or interpret the TST. If a patient has received only a single BCG vaccination in the newborn period and a year has elapsed since the last BCG, then a positive TST reaction resulting from BCG is unlikely.
- Allergic-type reactions. These reactions peak within 24 hours of TST placement and should resolve within 48–72 hours. Induration that peaks >24 hours after TST placement is caused by a delayed-type hypersensitivity, the mechanism of a true positive TST reaction.

- Irritation from a circular bandage or tape
- Injection with a substance other than PPD
- Incorrect interpretation of reaction

#### FALSELY NEGATIVE

- Recent infection with *M tuberculosis* (delayed-type hypersensitivity reaction takes 2–8 weeks after infection to develop)
- Infants age <6 months
- Improper storage of the PPD skin test material (eg, not refrigerated, prolonged storage in syringe)
- Improper placement (eg, subcutaneous placement, pressure by gauze or a bandage leading to the absorption of PPD solution)
- Vaccination with a live virus vaccine within the previous 6 weeks
- Generalized or specific anergy associated with extensive or disseminated TB or as seen in immunocompromised patients, especially those infected with HIV
- Incorrect interpretation of reaction

BCG, bacille Calmette-Guérin; PPD, purified protein derivative; TB, tuberculosis; TST, tuberculin skin test.

From Centers for Disease Control and Prevention. Guidelines for the investigation of contacts of persons with infectious tuberculosis: recommendations from the National Tuberculosis Controllers Association and CDC. *MMWR Morb Mortal Wkly Rep*. 2005;54(RR-15):1–37; American Academy of Pediatrics. Tuberculosis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:805–831.

### BOX 341-2 Differential Diagnosis for Forms of Tuberculosis Disease

#### PULMONARY INFILTRATE

- Community-acquired pneumonia (ie, bacterial pneumonia, including lung abscess and necrotizing pneumonia; viral pneumonia)
- Atelectasis caused by reactive airways disease or other processes
- Other granulomatous diseases (eg, coccidioidomycosis, histoplasmosis)
- Anatomic, foreign body, and structural disorders

#### INTRATHORACIC LYMPHADENOPATHY

- Infections caused by fungus, virus, or bacteria
- Nontuberculous mycobacterial infections
- Malignancies
- Round pneumonia
- Other granulomatous diseases (eg, coccidioidomycosis, histoplasmosis)

#### SUBACUTE PERIPHERAL ADENOPATHY

- Nontuberculous mycobacteria
- Cat-scratch disease
- Toxoplasmosis
- Partially treated pyogenic infection

#### MENINGITIS

- Viral, bacterial, fungal, and chemical meningitis

disease. A TST or IGRA should be undertaken only for children who have clinical disease that raises concern for TB, children at high risk for progression to TB disease, and children who have new risk factors for TB exposure since their last test. Most children with US-born parents never require a TST or IGRA.

In the United States, the only recommended TST is intradermal instillation of 5 TU (0.1 mL) purified protein derivative (PPD) by the Mantoux method. The skin test should be administered and interpreted by a trained health care professional. The definition of a positive TST result depends on risk factors for infection and the likelihood of TB disease. Box 341-3 lists the breakpoints used to interpret TB skin test results in children.

In areas with low TB rates, most positive TST reactions are in fact falsely positive. (See Box 341-1 for details.) If a child is found to have a positive TST or IGRA result, the evaluation includes a chest radiograph, focused history, and physical examination. A 2-view chest radiograph (frontal and lateral views) is particularly helpful in differentiating intrathoracic lymphadenopathy from other hilar structures. National guidelines suggest obtaining 2-view radiographs on all children when resources permit. If resources are limited, children older than 6 years can be screened with 1-view chest radiographs.

Targeted testing is the strategy of testing only children who are at high risk for contracting infection with *M tuberculosis* or developing TB disease once infected. This strategy results in fewer unnecessary

### BOX 341-3 Breakpoints for Interpretation of Tuberculin Skin Test Results

A  $\geq 5$ -mm induration is interpreted as positive in the following circumstances:

- Child is a recent contact of a person with TB or suspected TB disease
- Child is immunosuppressed (receiving immunosuppressive therapy) or immunocompromised, including HIV infection
- Radiograph or clinical evidence suggests TB disease
- Calcified granuloma on chest radiograph are consistent with prior TB infection

A  $\geq 10$ -mm induration is interpreted as positive in the following circumstances:

- Child is  $<4$  years of age
- Child has medical conditions (eg, lymphoma, Hodgkin disease, diabetes mellitus, chronic renal failure, malnutrition)
- Child or parent was born in a country with a high prevalence of TB
- Child has frequent exposure to high-risk adults (HIV infected, homeless, residents of nursing homes, institutionalized, incarcerated, users of illicit drugs, migrant farm workers)
- Child has traveled to a high-prevalence country

A  $\geq 15$ -mm induration is interpreted as positive in the following circumstance:

- Child is  $\geq 4$  years of age and has no risk factors

TB, tuberculosis.

Adapted from American Academy of Pediatrics. Tuberculosis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:805–831.

tests and avoids evaluation and treatment of children with false positive test results. At each well-child visit, the child should be screened with a risk-factor questionnaire. The child should undergo testing only if a new risk factor has been identified since the last test. Foreign birth, foreign travel, and close contact with individuals with a positive TST or IGRA result or TB disease predict increased risk for LTBI. Individual questionnaires should be modified based on local risks. A sample questionnaire is provided in Box 341-4, and the general strategy for targeted TB testing is outlined in Figure 341-1.

Prior bacille Calmette-Guérin (BCG) vaccination sometimes causes a small, transient TST reaction as a result of cross-reactivity among antigens. The effect of BCG vaccination on TST reaction is an ongoing challenge for pediatricians. The Centers for Disease Control and Prevention and the AAP advise pediatricians to discount the history of BCG vaccination when interpreting the TST. The following factors decrease the likelihood that the skin test reaction is caused by BCG:

- TST reaction (induration)  $>10$  mm
- Previous receipt of a single rather than multiple BCG vaccines
- BCG given in the first month of life



**BOX 341-4 Tuberculosis Risk Assessment Questionnaire**

Name: \_\_\_\_\_ DOB: \_\_\_\_\_

Last test:

TST date: \_\_\_\_\_ Results: \_\_\_\_\_ mm induration OR \_\_\_\_\_ not read by health care professional

IGRA date: \_\_\_\_\_ Results: \_\_\_\_\_

If positive TST or IGRA result in the past, chest radiograph date and result: \_\_\_\_\_

1. Was your child born outside the United States? \_\_\_\_\_ Yes \_\_\_\_\_ No  
Country: \_\_\_\_\_
2. Since the last TST or IGRA, has your child traveled outside the United States? \_\_\_\_\_ Yes \_\_\_\_\_ No  
Country or countries visited: \_\_\_\_\_  
Dates of travel and how long did the child travel? \_\_\_\_\_  
Where did the child stay (hotel, family, resort)? \_\_\_\_\_
3. Since the last TST or IGRA, has your child been exposed to anyone with TB disease? \_\_\_\_\_ Yes \_\_\_\_\_ No  
Name of the person's disease: \_\_\_\_\_  
Did the person have a positive TST or IGRA result with normal chest radiograph taking 1 medicine or no treatment OR TB disease taking many pills and different kinds of medicine?  
Name of person: \_\_\_\_\_ DOB: \_\_\_\_\_  
Where is the person being treated? \_\_\_\_\_
4. Since the child's last skin test, has your child had close contact with a person who has a positive TST result? \_\_\_\_\_ Yes \_\_\_\_\_ No  
Nature of the person's disease: \_\_\_\_\_  
Did the person have a positive TST result with normal chest radiograph taking medicine or no treatment OR TB disease taking many pills and different kinds of medicine?  
Name of person: \_\_\_\_\_ DOB: \_\_\_\_\_  
Where is the person being treated? \_\_\_\_\_

Optional questions depending on local epidemiology:

Since the last TST or IGRA, has your child consumed unpasteurized milk or cheese (from Mexico or Central America)? \_\_\_\_\_ Yes \_\_\_\_\_ No

Since the last TST or IGRA, has your child been around people in jail, people who were homeless or in shelters, people who have HIV or use illegal drugs? \_\_\_\_\_ Yes \_\_\_\_\_ No

Since the last TST or IGRA, has your child lived with a new person who was born or traveled outside the US? \_\_\_\_\_ Yes \_\_\_\_\_ No

INSTRUCTIONS FOR PROVIDERS: Test only children who have a new risk factor since their last TST or IGRA.

If the child has previously had a positive TST or IGRA result, then do not administer another test.

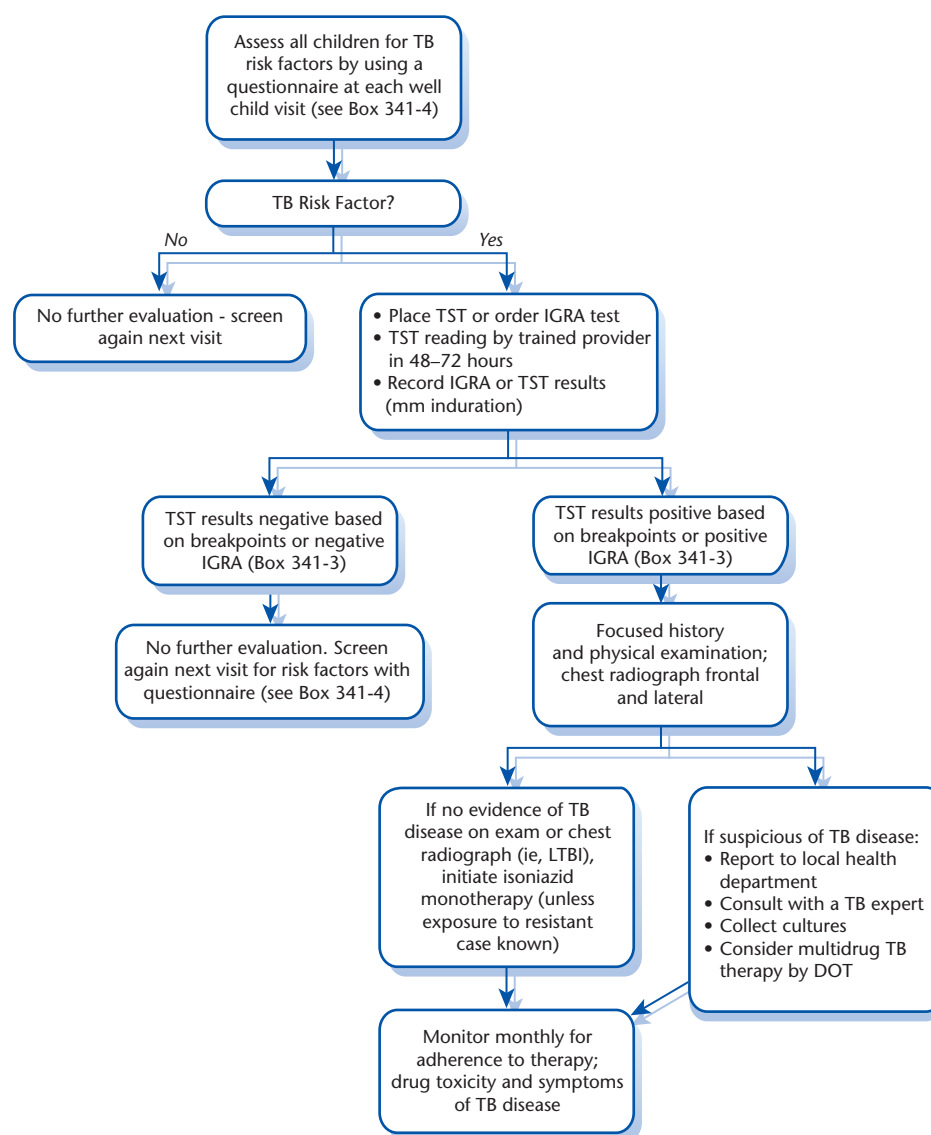
Significant travel is considered travel to a country with a high prevalence of TB (eg, in Africa, Asia, Latin American, and Eastern Europe) for >1 week AND had a substantial contact with indigenous people from such countries (did not stay in a resort).

Adapted from Pediatric Tuberculosis Collaborative Group. Targeted tuberculin skin testing and treatment of latent tuberculosis infection in children and adolescents. *Pediatrics*. 2004;114:1175–1201.

- A long period since the BCG dose
- Receipt of no other recent TST

The IGRA tests are *in vitro* diagnostic tests for detecting either IFN- $\gamma$  production directly when a patient's whole blood is incubated with antigens that are fairly specific to *M tuberculosis* complex and controls, or by enumerating sensitized T cells that release IFN- $\gamma$  in the vicinity of the T cells. The detection of IFN- $\gamma$  or sensitized T cells indicates a response by the patient's lymphocytes and probable infection with *M tuberculosis*. During the past several years, many IGRA studies have

been done or are underway supporting their use in children and adolescents. As with TSTs, IGRAs cannot distinguish between LTBI and TB disease. A negative result from these tests cannot exclude the possibility of TB disease. A number of studies demonstrate that IGRAs perform well in most children 3 years of age or older. The sensitivity of these blood tests is comparable to that of TSTs for detecting *M tuberculosis* infection in older children who have culture-confirmed tuberculosis. The specificity of IGRAs is higher than that for TSTs because the antigens used are not found in BCG or most



**Figure 341-1** General strategy for targeted tuberculosis testing. DOT, directly observed therapy; IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection; TST, tuberculin skin test.

nontuberculous mycobacteria (eg, are not found in *M avium* complex). The correct interpretation of a negative IGRA test result in a child with a positive TST result is difficult because of the absence of longitudinal studies to determine the prognostic value of the IGRAs (especially when the TST result is positive).

Neither an IGRA nor the TST can be considered a “gold standard” for diagnosis of LTBI. Current AAP recommendations for use of IGRAs in children are as follows:

- Children with a positive result from an IGRA should be considered infected with *M tuberculosis* complex. A negative IGRA result cannot necessarily be interpreted as absence of infection.
- For immunocompetent children 5 years of age and older, IGRAs can be used in place of a TST to diagnose cases of LTBI or as an adjunct in diagnosing

cases of tuberculosis disease and likely will yield fewer false-positive test results.

- The 2015 AAP *Red Book* endorses use of IGRA tests in children as young as 3 years of age in the following circumstances:
  - Children with a negative TST, but high clinical suspicion for TB disease and/or high risk for infection, progression, or poor outcome
  - Children with a positive TST, but who are healthy with low risk for TB infection, when additional information is required to ensure adherence to LTBI treatment or the child is suspected of having nontuberculous mycobacterial disease
- Because of their higher specificity and lack of cross-reaction with BCG, IGRAs are the preferred test for children 5 years or older who have received BCG vaccine. If a TST already has been performed in

these children and is reactive, a negative IGRA is evidence against the diagnosis of LTBI but does not exclude infection.

- Negative IGRA results should be interpreted with caution in children younger than 3 years and in immunocompromised children of any age because of a relative lack of published data about test sensitivity among these groups.
- Indeterminate IGRA results, most often owing to a low mitogen response or improper handling, do not exclude *M tuberculosis* infection and should not be used to make clinical decisions. Consideration should be given to repeating the IGRA or performing a TST.

## MANAGEMENT

### Tuberculosis Exposure

A child exposed to an adult or adolescent with potentially contagious TB requires prompt and thorough evaluation to determine whether the child already has evidence of LTBI or TB disease. All exposed individuals should undergo a symptom review, testing with either a TST or an IGRA, and a focused history and physical examination. These evaluations should be coordinated with the local health department. Children younger than 5 years of age and all immunocompromised individuals with significant exposure should receive *window prophylaxis* after TB disease has been ruled out by a normal chest radiograph and negative physical examination. Window prophylaxis is the practice of treatment with INH until a repeat TST or IGRA is given 8 to 10 weeks after their last exposure (Figure 341-2) is performed and the result is negative.

### Latent Tuberculosis Infection

Management of LTBI is reasonably easy after TB disease is eliminated as a possibility. INH monotherapy should be initiated unless strong evidence exists of INH drug resistance in the source case (not merely LTBI acquisition in an area with a high level of INH resistance). Dosing is 270 daily doses (twice or three times a week administered by directly observed therapy [DOT]) within a 12-month period. Table 341-2 lists INH doses by weight. When a prolonged break occurs after a short initial treatment period, then therapy should be restarted, but short lapses are tolerated, especially if the regimen is well underway. If interruption of therapy is greater than 2 months, then the child should be reevaluated for possible TB disease before restarting INH. Vitamin B<sub>6</sub> (pyridoxine) supplementation is indicated only for exclusively breastfed infants, children and adolescents on milk- and meat-deficient diets, children who experience paresthesias while receiving isoniazid therapy, those with symptomatic HIV infection, and pregnant adolescents.

INH is available as 100-mg and 300-mg scored tablets and as a liquid suspended in sorbitol. The liquid formulation causes cramping and diarrhea in more than one-half of children because of its osmotic load. As an alternative, the tablet can be crushed and mixed with or layered into a strong-flavored semisoft food in a spoon. INH should be prescribed in monthly

allocations, with clinic visits scheduled for periodic (monthly or bimonthly) face-to-face monitoring for drug toxicity. INH-related transient increase of transaminases has been noted in children, with the effects increasing with increasing age; however, INH rarely causes clinical hepatotoxicity in children. Routine monitoring of liver transaminases is not indicated for asymptomatic children who do not have underlying liver disease and who are not receiving other hepatotoxic drugs. Families should be thoroughly educated about recognizing symptoms of hepatotoxicity (eg, anorexia, malaise, abdominal pain, vomiting) and instructed when to stop therapy and return to the clinic for assessment and possible laboratory testing. Lack of association with other viral symptoms and lack of improvement after a few days should suggest the possibility of hepatotoxicity rather than an intercurrent illness.

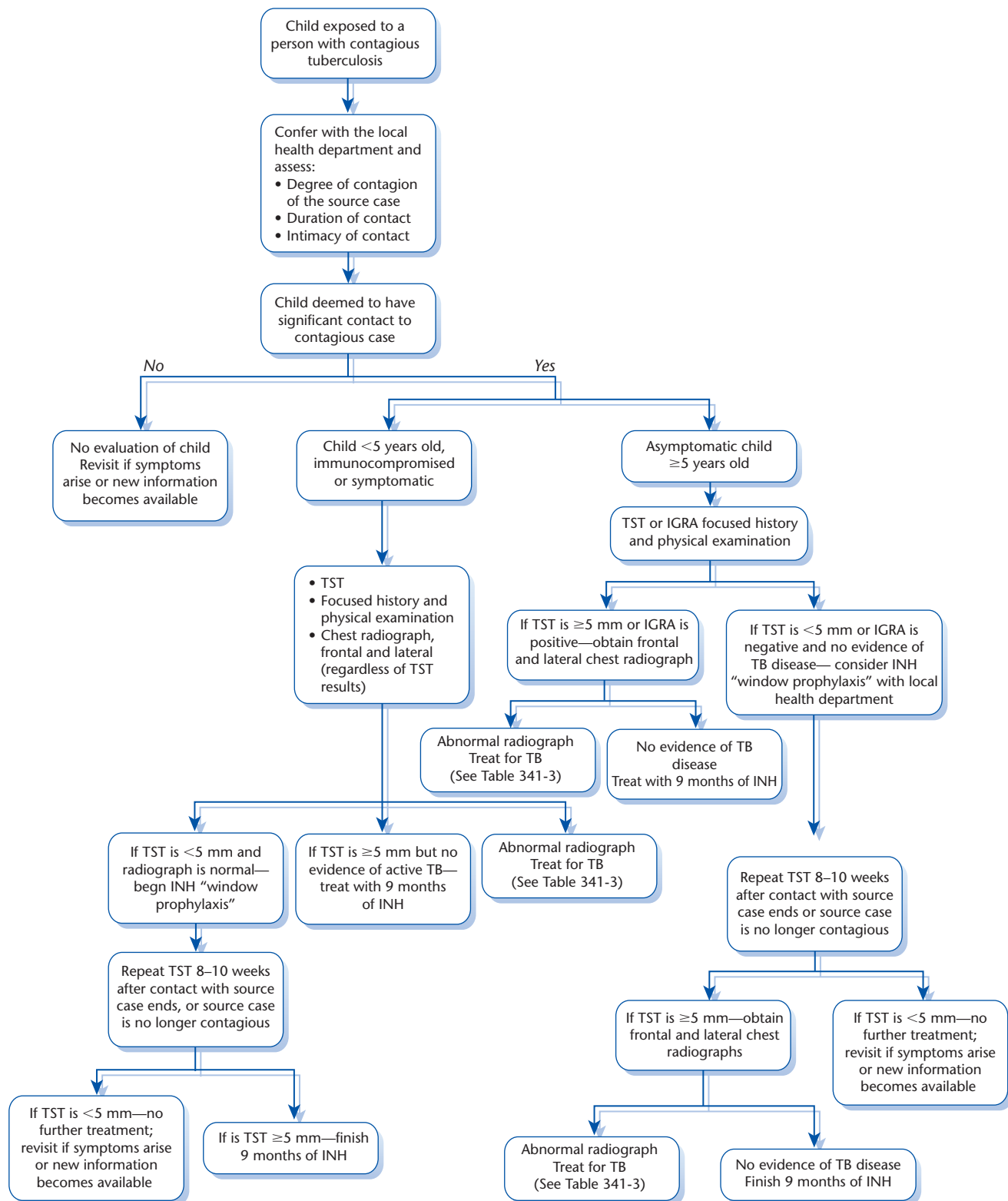
Caregivers should be asked about the child's adherence to therapy and results of testing with TSTs or IGRAs of family members and other contacts. Figure 341-3 shows an example of a flow sheet for monitoring LTBI treatment. Every effort should be made to promote and facilitate adherence through enablers such as walk-in visits for refills (nurse visits) or school-based dosing or monthly monitoring. Incentives such as stickers, prizes, and end-of-treatment rewards can also be used to promote adherence (eg, see [www.maine.gov/dhhs/mecdc/infectious-disease/epi/tuberculosis/treasure-chest.shtml](http://www.maine.gov/dhhs/mecdc/infectious-disease/epi/tuberculosis/treasure-chest.shtml)). Children receiving antiepileptic drugs (particularly phenytoin and carbamazepine) should be monitored closely because INH affects the drug levels of some of these medications.

After completing the 270 doses of INH for LTBI, the family should be provided with a card or letter documenting completion of therapy and reminded that the child should not undergo tuberculin testing in the future. An end-of-completion radiograph is not necessary.

Rifampin (10–20 mg/kg) given for 120 daily doses is occasionally used as an alternative for a patient who is intolerant to INH or is known to be infected by an INH-resistant TB strain. Most side effects of INH can be overcome with adjustments of timing or symptomatic management. Rifampin may accelerate the metabolism or have other interactions with several important classes of drugs, including anticonvulsants, antiarrhythmics, antifungals, barbiturates, beta blockers, calcium channel blockers, antibiotics, corticosteroids, oral contraceptives, oral hypoglycemics, and drugs used to treat HIV infection. Adjusting the dose of these drugs may be necessary if they are given concurrently with rifampin. Providers caring for children and adolescents receiving antiretroviral therapy should consult updates on drug interactions.

A newer LTBI regimen has undergone limited trials in young children, but was well studied in older children and adults. Once weekly INH and rifapentine by DOT for 12 doses is effective in preventing progression to TB disease. It is generally used for children 12 years and older, but has been used in younger children down to the age of 2 years.

Treatment of children infected by persons having multidrug-resistant TB (resistance to both INH and rifampin) should be done in consultation with a pediatric tuberculosis specialist.



**Figure 341-2** Evaluation of a child exposed to a person with contagious tuberculosis. *IGRA*, interferon-gamma release assay; *INH*, isoniazid; *TST*, tuberculin skin test.



**Table 341-2** Isoniazid Daily Dosing

CHILD'S WEIGHT		DAILY DOSE (10–15 MG/KG/DAY) <sup>a</sup>		
KILOGRAMS	POUNDS	MILLIGRAMS	100-MG TABLETS	300-MG TABLETS
3–5	6.6–11	50	½	0
5–7.5	11–16.4	75	¾	OR ¼
7.5–10	16.5–22	100	1	0
10–15	22–33	150	0	½
15–20	33–44	200	2	0
>20	>44	300	0	1

<sup>a</sup>Maximum dose, 300 mg.

## EVALUATION

### History

Evaluation is intended to discern TB disease from LTBI, as well as to identify a possible source of infection, risks for drug resistance, and underlying medical conditions that might increase the risk for TB or complicate TB treatment (Figure 341-4).

In the United States, approximately one-half of children diagnosed with TB disease either have no symptoms or their symptoms have been developing so subtly and insidiously that their parents have not noticed. Common symptoms include weight loss or failure to gain weight, anorexia, fever, and cough, as well as decreased energy, playfulness, or activity. Other symptoms may be noted for patients with extrapulmonary TB: lymph node enlargement, headache, personality changes, focal neurologic changes, or musculoskeletal pain. TB can produce fulminant or indolent symptoms, but symptoms are typically more chronic when caused by TB than when caused by bacterial or viral infections. Cough is often noted for weeks rather than days; lymph node swelling develops over weeks, with gradual and modest changes in the overlying skin. Occasionally, symptoms such as cough and fever are actually improving at the time of diagnosis.

The history should include information that would suggest an alternative diagnosis, such as reactive airways disease, bacterial or viral pneumonia, pyogenic lymphadenitis, or viral meningitis. Pertinent medical history includes previous TST or IGRA results, previous TB treatment, and results of any previous chest radiographs. The medical history should also include factors that would complicate TB therapy, including underlying liver disease and use of potentially hepatotoxic drugs. Patients infected with HIV or who have another immunocompromising condition are more likely than others to have TB and are more likely than others to have an atypical or extrapulmonary presentation of TB.

Close contact to a contagious person results in a significant proportion of household contacts becoming infected. If the family knows of a TB exposure, then the history should include the name, address, and date of birth of the patient with TB, as well as the jurisdiction of treatment, susceptibility data, and treatment details.

If the family does not know anyone with TB disease, then family members should be asked whether they have close contact with an adolescent or adult with

chronic cough, fever, or unexplained weight loss or if they have household contact with an individual with a positive TST or IGRA result (especially a newly positive result). Because almost two-thirds of adult patients with TB disease are born outside the United States (primarily in Latin America, Asia, Africa, and Eastern Europe), contacts including visitors and caregivers from these areas should be solicited. Children who were born in an area with a high incidence of TB or who have traveled to these areas are at increased risk for TB and LTBI. Family members should be asked where children were born, where they have traveled, how long they stayed, and with whom they stayed when traveling in TB-endemic areas.

Ingestion of foreign unpasteurized milk and milk products, such as Mexican-style soft cheeses (queso fresco), raises the possibility of infection with *M bovis* (although *M bovis* has a propensity to cause peripheral and intraabdominal lymphadenitis, it can cause any TB manifestation, including pneumonia).

Finally, if several family members have positive TST or IGRA results, then the likelihood that the child's disease is TB increases. The pediatrician should perform a TST or IGRA on any family member who has not recently undergone such a test (and has never had a positive result in the past). To prevent possible continued transmission of TB, chest radiographs of adults with a previous or newly positive TST or IGRA result or suspicious TB-like symptoms should be obtained in conjunction with the local health department.

### Physical Examination

The focused physical examination should emphasize vital signs, growth parameters, conjunctival examination, neck flexion, lymph node palpation, auscultation of heart and lungs, abdomen and flank palpation, spine and bone palpation, brief skin examination, and neurologic examination (depending on concerns for TB of the central nervous system). Children diagnosed as having LTBI will have no examination abnormalities that suggest TB disease. Even children with pulmonary TB may have no findings at physical examination. The findings on chest radiograph are often more useful than those found by physical examination.

### Laboratory Evaluation

Routine testing for children suspected of having TB includes HIV serologic testing and mycobacterial

### TUBERCULOSIS MANAGEMENT RECORD

Name: \_\_\_\_\_ Parent name: \_\_\_\_\_  
 DOB: \_\_\_\_\_ Parent telephone: (\_\_\_\_) \_\_\_\_\_  
 Language spoken by parent: \_\_\_\_\_

**VISIT DATE:** \_\_\_\_\_  
**PATIENT WEIGHT:** \_\_\_\_\_


*Prescribe 1 bottle of 30 doses each visit. When 9 bottles (270 doses) are consumed, therapy is complete.*

**MEDICATION:**

Isoniazid (IHN) dose in milligrams: \_\_\_\_\_

Bottle number: \_\_\_\_\_

Date on current bottle: \_\_\_\_\_

Number of pills in bottle: \_\_\_\_\_


*Recalculate dose if weight increases significantly (10-15 mg/kg/dose)*

**DRUG SCREEN (yes or no answers):**

Taking medications regularly? \_\_\_\_\_

Fatigue? \_\_\_\_\_

Loss of appetite? \_\_\_\_\_

Rash or itching? \_\_\_\_\_

Nausea or vomiting? \_\_\_\_\_

Tingling of fingers or toes? \_\_\_\_\_

Color change in skin or eyes? \_\_\_\_\_

Tender abdomen? \_\_\_\_\_

See progress note? \_\_\_\_\_


*Remind the family during each visit to stop medication and call if concerning side effects (3 days of anorexia or malaise that does not improve)*

**FOLLOW-UP:**

Tuberculosis education: \_\_\_\_\_

Return appointment: \_\_\_\_\_

Provider's initials: \_\_\_\_\_

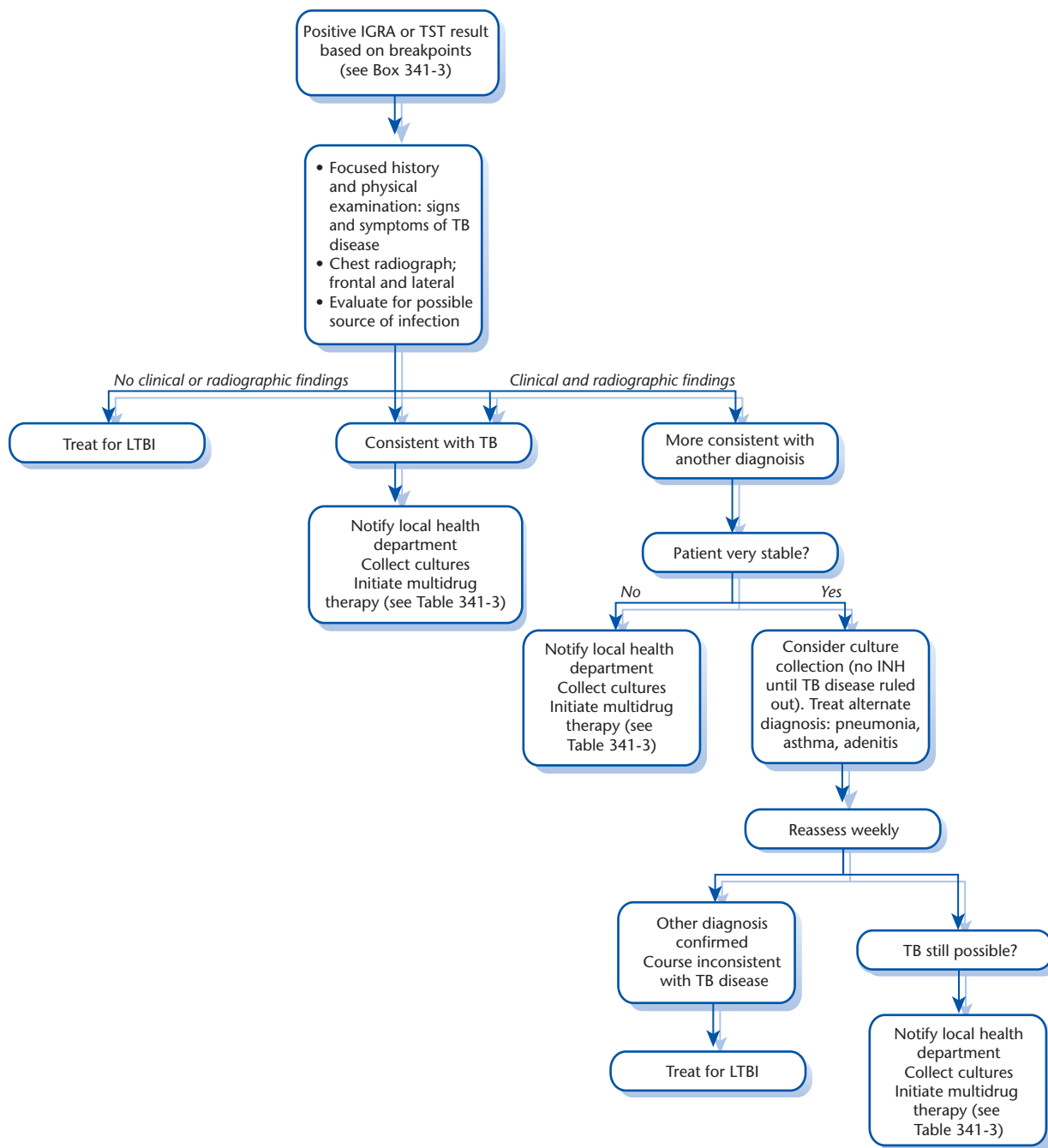

Pharmacy name: \_\_\_\_\_ Pharmacy telephone: (\_\_\_\_) \_\_\_\_\_  
 Prescription number: \_\_\_\_\_

**Figure 341-3** Tuberculosis medication flow sheet.

cultures. Sputum specimens are challenging to collect from young children, but they can be collected by gastric aspiration (Box 341-5), induction, or bronchoalveolar lavage. Gastric aspirates are typically collected on 3 consecutive mornings after an overnight fast. Historically, yields are between 30% and 50%, with the highest yields being in the youngest infants and from the initial sample collected. If the child is not otherwise ill

enough to require inpatient management, then gastric aspirates can be collected in the outpatient setting.

In older children, sputum induction with hypertonic saline should be attempted; inducing sputum in infants is difficult. Bronchoalveolar lavage is used primarily when diagnostic possibilities other than TB are being strongly considered. Yield for bronchoalveolar lavage in culturing *M tuberculosis* in children is



**Figure 341-4** Evaluation of a child with a positive TST or IGRA result. *IGRA*, interferon-gamma release assay; *LTBI*, Latent tuberculosis infection; *TST*, tuberculin skin test.

between 10% and 21%, and yields are generally less than that for gastric lavage in children.

Guided by the physical examination and clinical scenario, other specimens may be collected, including cerebrospinal fluid (CSF). CSF culture has a 50% to 75% yield in diagnosis of TB meningitis. Acid-fast bacillus (AFB) smear has an even lower yield, but it can be improved by centrifugation of large volumes of CSF. The use of the polymerase chain reaction technique has been disappointing, but it may play a role as an adjunct diagnostic method. AFB smear and culture

of other tissues should be undertaken as indicated for lymph node tissue, abscess drainage, bone or synovial fluid, urine, blood, bone marrow, or other tissue. Specimens for AFB smear and culture should be submitted in a sterile cup (rather than on a swab) and without formalin preservative.

Regardless of the culture collection method or specimen being collected, culture for *M tuberculosis* in children has suboptimal yields. Families should understand that AFB smears are not usually positive from specimens from children, that cultures must be incubated for

several weeks before any results are available, and that cultures have less than 50% yield in most situations. Specimens are collected so that if cultures are positive and yield susceptibility data, then the treatment regimen can be optimized. In most cases, the diagnosis of TB in a child is a clinical diagnosis, influenced by the probability of exposure to a person with infectious TB, TST or IGRA results, clinical symptoms and signs, and results of imaging tests. Although none of these elements is diagnostic for TB disease, the experienced TB physician weighs all these factors along with the risk to the child of not treating TB when considering whether to begin treatment. Unless an alternative diagnosis is established, most often, once TB therapy is begun, the course should be completed.

Other laboratory evaluations should be considered based on individual circumstances. Patients who have TB and HIV coinfection, severe TB disease, symptoms or signs of hepatitis, or known underlying liver disease or those who are receiving other hepatotoxic medications should have liver transaminase levels measured.

### Imaging Studies

Any child whose TST or IGRA result is positive or who is suspected of having pulmonary or extrapulmonary TB should have a chest radiograph performed. For the best-quality radiograph, the child should be in full inspiration and should not be rotated. Guidelines suggest obtaining 2-view radiographs on all children when resources permit. If resources are limited, children older than 6 years can be screened with 1-view

chest radiographs. The lateral view is particularly helpful in distinguishing other central shadows from intrathoracic lymph nodes, which are spherical and can often be seen on both views. Ideally the films should be interpreted by a physician or radiologist experienced in pediatric TB. Computed tomography is not indicated in the evaluation of an asymptomatic child with a normal chest radiograph and a positive TST or IGRA result. A computed tomography scan can be helpful when the radiograph is equivocal and when looking for other causes of lung disease is necessary.

Findings on chest radiographs of children with TB are variable. Enlarged intrathoracic lymph nodes and infiltrate are the most common abnormalities. Intrathoracic adenopathy is often seen in children and is reported to be present in up to 85% of children younger than 3 years. Hilar, mediastinal, paratracheal, and subcarinal nodes may be seen and are most often found on the right side. Isolated adenopathy should be considered as possible TB disease. Figure 341-5 shows the radiograph of a child with typical intrathoracic adenopathy caused by TB.

An infiltrate may be seen in any lung field and is seen in multiple lobes in one-fourth of children. Parenchymal disease may be caused by several processes. A larger consolidation may be associated with advancement of the infection—the so-called progressive primary process—or it may be caused by atelectasis or collapse and consolidation that results from lymph node obstruction. Lymph node obstruction can also cause air trapping behind the node with resultant wheezing and hyperinflation. Older children, especially

### BOX 341-5 Gastric Aspirate Procedure for Culture of *Mycobacterium tuberculosis*

- Health care workers present during gastric aspirate procedures of a patient with suspected or confirmed infectious TB disease should wear at least a N-95 disposable respirator.
- Collect all supplies and have everything ready: N-95 respirators, papoose board or sheet, No. 10 French or larger nasogastric or suction tube, 30-mL syringe with appropriate connector for tube; pen; sterile water; specimen cup or laboratory-prepared tube containing bicarbonate for bedside neutralization; requisition and label; helper.
- Child should not take anything by mouth for at least 6 hours before the procedure.
- Immobilize the child with a sheet with or without a papoose board.
- Measure the distance from the nose to the stomach.
- Insert a No. 10 French (or larger) nasogastric tube through the nose into the stomach.
- Puff in the child's face as the tube enters the throat to elicit a swallow reflex.
- Gently aspirate the tube with an appropriately fitted 30- to 60-mL syringe.
- If no significant yield, then advance and withdraw the tube slightly while aspirating.
- If yield is still less than 5 to 10 mL, then place any collected mucus into a container.
- Check tube position by auscultating the stomach while pushing air from the syringe into tube.
- Instill 20 mL of sterile water into the stomach and quickly aspirate again.
- If yield is less than 5 to 10 mL, then roll the child on the side, advance the tube, aspirating continuously to find the pool of mucus in the stomach.
- As tube is withdrawn, continuously aspirate the syringe.
- Place any yield, including any spontaneously vomited emesis, in the specimen container.
- Label the specimen and order AFB smear and culture.
- Promptly transport the specimen to the laboratory for processing (tell the laboratory if the specimen has already been neutralized).

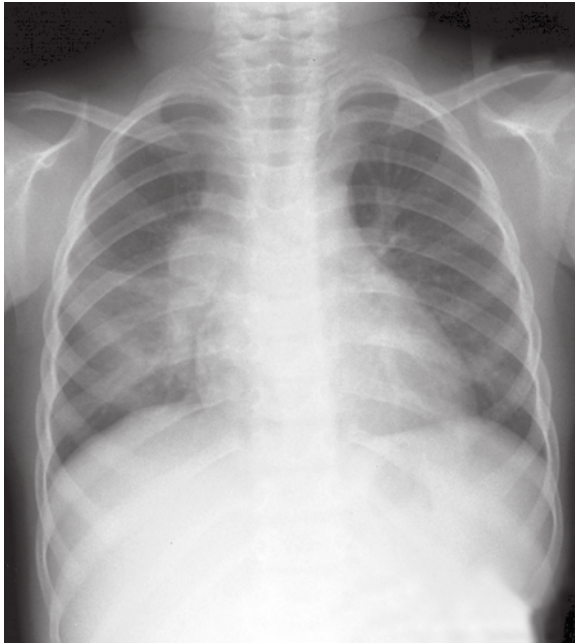
AFB, Acid-fast bacillus; TB, tuberculosis.

From Curry International Tuberculosis Center. Pediatric Tuberculosis: A Guide to the Gastric Aspirate Procedure. Available at: [www.currytbcenter.ucsf.edu/topics-interest/pediatric-tb](http://www.currytbcenter.ucsf.edu/topics-interest/pediatric-tb). Accessed February 3, 2016. Reprinted by permission.



adolescents, may have radiographic findings that are consistent with adult reactivation (postprimary) TB, including upper lobe disease with fibronodular infiltrates, volume loss, hilar retraction, and cavities.

Infection is sometimes spread to other parenchymal locations after erosion of a lymph node with spilling of infectious material (bronchogenic spread). This situation can cause a segmental lesion when the material is



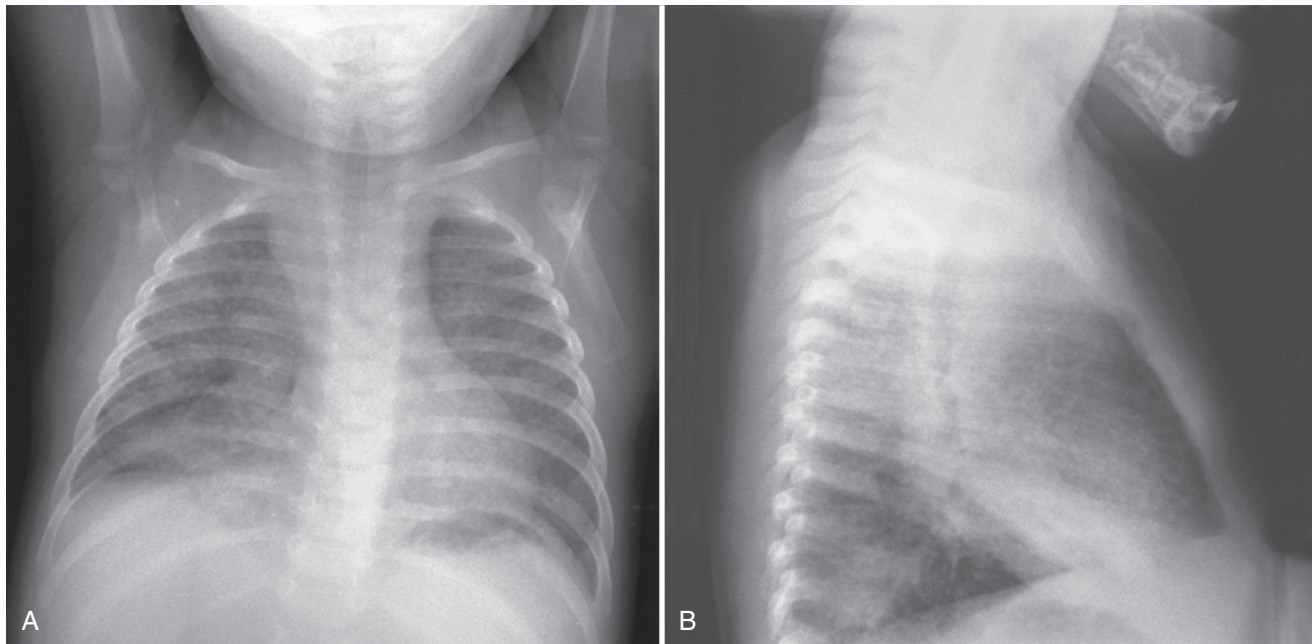
**Figure 341-5** Chest radiograph of a child with enlarged intrathoracic lymph nodes.

limited to 1 bronchus, or it may result in diffuse bronchopneumonia when the organism spreads throughout the lung.

Distribution of *M tuberculosis* through hematogenous dissemination that causes disease to the lung and other organs is termed *disseminated disease*, although the term *miliary disease* was formerly used because of the small, round, millet-like appearance of the diffuse lesions. Figure 341-6 shows the radiograph of an infant with disseminated TB. Primary bacillema occurs during the initial process of the proximal lymph nodes draining into the thoracic duct. The infection may also be disseminated secondarily if a necrotizing lymph node or air space focus erodes into a blood vessel. These disseminated processes do not always appear radiographically in the classic disseminated pattern. Larger, patchy, reticulonodular lesions may be present and difficult to distinguish from other diffuse lung infections.

Pleural effusion and empyema are less common in children with TB compared with adults. Isolated, small, dense nodules with calcification, nonenlarged calcified lymph nodes, and isolated pleural thickening are considered signs of healed *M tuberculosis* infection and are not considered to be TB disease. Peribronchial cuffing or thickening is commonly associated with reactive airway disease and viral infection and, in isolation, is not consistent with TB.

The pediatrician should obtain a chest radiograph 2 months after therapy for TB disease has begun, whenever clinically indicated, and again when therapy has ended. Radiographic abnormalities in children with TB resolve slowly, and enlargement of lymph nodes may persist for a long period. The chest radiograph is not normal in more than one-half of children at the end of therapy. However, these children continue to



**Figure 341-6** Chest radiograph of infant with disseminated tuberculosis.

improve gradually. The radiograph at the completion of therapy should be greatly improved compared with the original radiograph, which will serve as a baseline for monitoring future changes. The chest radiograph need not be repeated for children receiving or completing LTBI treatment unless they develop symptoms compatible with TB disease.

### Treatment of Tuberculosis Disease

In all states, Puerto Rico, and US territories, physicians are legally mandated to report persons suspected of having or confirmed to have TB to the local health department. Reporting is an important public health function because the health department assumes responsibility for collaboration in case management, provides direct observation therapy (DOT), and tests exposed contacts.

Children with TB disease should be managed in a dedicated TB clinic or by the most experienced pediatric TB physician available. In areas where this treatment is not feasible, close and ongoing consultation with an experienced physician should be sought.

Children with clinical or radiographic evidence of TB disease, regardless of the TST or IGRA result, should be evaluated immediately, as outlined in Figure 341-4. Specimens for AFB smear and culture should be collected. TB disease is difficult to diagnose definitively in children because culture confirmation is often lacking or can be delayed for several weeks. Children who have a positive TST or IGRA result, who have known exposure to TB or risk factors for TB exposure, who have radiographic changes consistent with TB, or who have relatively few symptoms compared with their radiographic changes are more likely to have TB as opposed to alternative diagnoses such as community-acquired pneumonia or reactive airway disease.

Table 341-3 shows treatment regimens for TB disease in children. A 4-drug empirical regimen (INH, rifampin, pyrazinamide, and ethambutol) is indicated for most children suspected of having TB disease (most experts would initiate just 3 drugs for children exposed to an adult with drug-susceptible disease). After 2 months of treatment, a repeat chest radiograph should be performed. For children from whom sputum can be obtained, follow-up sputum should be obtained to document culture conversion. If the patient has been adherent to therapy, is clinically well, has an improving or at least stable radiograph, and there is no reason to suspect drug resistance, the regimen can then be changed to 2 drugs (INH and rifampin) to complete a 6-month course. Select children and adolescents may require extension of treatment to a 9-month course. Twice- or thrice-weekly dosing by DOT can be used after the 2-month induction phase of daily treatment if the child is tolerating the regimen well and has shown considerable clinical improvement. The number of doses actually observed should be counted when considering whether a patient has completed therapy. Patients receiving daily doses for the first 2 months will typically receive 40 observed doses (Monday through Friday for approximately 8 weeks) followed by 36 twice-weekly or 54 thrice-weekly doses in the following 18 weeks.

Treatment of INH-mono-resistant TB disease requires at least 6 months of rifampin, pyrazinamide, and ethambutol. Treatment of drug-resistant TB should be performed in consultation with an expert in this area.

The most important element of TB therapy is the actual ingestion of the drugs. Children are difficult to dose with TB drugs, given that the formulations are not particularly child friendly. See dosing suggestions in the previous section on Latent Tuberculosis Infection. The parents and public health staff should be warned that they might have to endure a several-week period of trial and error. Patients should be monitored monthly during therapy. Routine laboratory evaluation need not be performed unless the patient has symptoms of toxicity or underlying liver disease or unless the patient is taking other medications, which might interfere with the TB drugs or cause similar toxicities.

An end-of-therapy chest radiograph should be obtained. Many children do not have a normal radiograph at the end of therapy, but significant improvement is expected.

Corticosteroids have been shown to be beneficial in central nervous system disease, particularly stage 2 and 3 (altered mental status). Some physicians would use steroids for any child with symptomatic TB meningitis. Steroids are also often used for TB pericarditis. Two reports support the use of steroids in children with symptomatic airways compression caused by lymphatic disease. Prednisone is generally used at a dose of 1 to 2 mg/kg/day given for 4 to 8 weeks and then tapered over several weeks.

## CONCLUSION

TB is a focal problem in the United States, disproportionately affecting immigrant and minority populations. TB risk assessments at well-child and other visits have replaced universal screening of children by TST. Only children who have a new risk for TB exposure since the last TST or IGRA or who have features suggestive of TB disease should undergo the TST or IGRA. All children diagnosed as having LTBI should be treated and closely monitored for adherence and toxicity. Providers should develop or modify systems to remove barriers to completion of therapy, including walk-in nurse visits, minimal paperwork, easy chart forms, and incentives. Many children with TB in the United States are asymptomatic at the time of diagnosis. TB disease in children is diagnosed clinically and radiographically, often without culture confirmation. Experienced TB physicians are best qualified to manage TB disease, but ongoing consultation should be sought when local resources are limited.

Prevention of TB includes identification of children at risk for exposure to TB, aggressive evaluation of children exposed to potentially contagious adolescents and adults with TB (young children are generally not contagious), treatment of LTBI, and prompt treatment of contagious TB patients.

*The authors thank Phil LoBue, MD and Michael Iademarco, MD, MPH, Centers for Disease Control and Prevention, for their input on this chapter.*

**Table 341-3** Treatment Regimens for Tuberculosis in Children<sup>a</sup>

TB MANIFESTATION	MINIMAL DURATION OF THERAPY	INITIAL REGIMEN	FOLLOW-UP REGIMEN	COMMENTS
Pulmonary TB	6 mo	Isoniazid, rifampin, pyrazinamide, and ethambutol daily for 2 mo	<ul style="list-style-type: none"> <li>Stop ethambutol as soon as the patient or reliable source case isolate is found to be drug susceptible</li> <li>Document a follow-up chest radiograph 2 mo into therapy</li> <li>If the isolate is sensitive, the patient is clinically well, and the radiograph is improving or stable, then change to isoniazid and rifampin at 2 mo to complete a 6-mo course; twice- or three-times weekly therapy can be provided by directly observed therapy</li> <li>Document chest radiograph at end of treatment—often not quite normal</li> </ul>	<ul style="list-style-type: none"> <li>Some experts initiate 3-drug therapy with isoniazid, rifampin and pyrazinamide only when the risk of drug resistance is low</li> <li>If a cavitary lesion was present on the chest radiograph and sputum culture is still positive after 2 mo of treatment, then the total treatment should be extended to 9 rather than 6 mo</li> </ul>
Extrapulmonary (meningitis, bone or joint, disseminated)	9–12 mo	Same as pulmonary disease	<ul style="list-style-type: none"> <li>7–10 mo of isoniazid and rifampin, either daily or twice a week by directly observed therapy</li> </ul>	<ul style="list-style-type: none"> <li>Some physicians use an injectable drug (eg, amikacin, kanamycin) for initial treatment of disseminated or meningeal disease. Strongly consider corticosteroid therapy for some types of extrapulmonary disease (eg, meningitis, pericarditis)</li> </ul>
Other extrapulmonary (cervical adenopathy)	Same as pulmonary disease	Same as pulmonary disease	<ul style="list-style-type: none"> <li>Same as pulmonary disease except no need to follow chest radiographs if initially normal</li> </ul>	<ul style="list-style-type: none"> <li>Same as pulmonary disease</li> </ul>

TB, tuberculosis.

<sup>a</sup>Directly observed therapy by a trained health care worker is the standard of care for all children with TB.

*The findings and conclusions in this chapter are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention, Agency for Toxic Substances and Disease Registry.*

### WHEN TO REFER

- All patients suspected of having TB disease should be reported to the local health department according to state statute (eg, within 1 working day).
- In many jurisdictions, young children with LTBI should be reported to the local health department, according to local regulations.

- Ideally, an experienced pediatric TB physician should manage children with TB disease. If local resources are not available, then close and ongoing consultation with a pediatric TB expert should be established.
- Any patient whom you suspect has multidrug-resistant TB should be treated by a pediatric TB expert or with ongoing and close consultation

### WHEN TO ADMIT

- Children should be admitted to the hospital for culture collection if local resources are not available for outpatient culture collection.
- Few children require admission to the hospital based on clinical severity of TB disease. Patients



with increased work of breathing, meningitis, or complicating simultaneous conditions or patients who require diagnostic evaluation should be admitted.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Pediatric Tuberculosis: An Online Presentation* (Web page), Curry International Tuberculosis Center ([www.currytbcenter.ucsf.edu/topics-interest/pediatric-tb](http://www.currytbcenter.ucsf.edu/topics-interest/pediatric-tb))
- *Tuberculosis* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/Tuberculosis.aspx](http://www.healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/Tuberculosis.aspx))
- *Tuberculosis* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/tb/pubs/tbfactsheets/tb.htm](http://www.cdc.gov/tb/pubs/tbfactsheets/tb.htm))

#### Medical Decision Support

- *Core Curriculum on Tuberculosis: What the Clinician Should Know* (manual), Centers for Disease Control and Prevention ([www.cdc.gov/tb/education/core-curr/index.htm](http://www.cdc.gov/tb/education/core-curr/index.htm))
- *Find TB Resources* (Web site), Centers for Disease Control and Prevention ([www.findtbresources.org/index.aspx](http://www.findtbresources.org/index.aspx))
- *Red Book: 2015 Report of the Committee on Infectious Diseases*, 30th ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Tuberculosis* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/tb/pubs/tbfactsheets/tb.htm](http://www.cdc.gov/tb/pubs/tbfactsheets/tb.htm))
- *Tuberculosis: Guidelines by Topic* (Web page), Centers for Disease Control and Prevention and the National Prevention Information Network ([www.cdc.gov/tb/publications/guidelines/default.htm](http://www.cdc.gov/tb/publications/guidelines/default.htm))

### AAP POLICY

American Academy of Pediatrics Council on Community Pediatrics. Providing care for immigrant, migrant, and border children. *Pediatrics*. 2013;131(6):e2028–e2034 ([pediatrics.aappublications.org/content/115/4/1095](http://pediatrics.aappublications.org/content/115/4/1095))

American Academy of Pediatrics. Tuberculosis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:805–831

### SUGGESTED READINGS

- Centers for Disease Control and Prevention. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent mycobacterium tuberculosis infection. *MMWR Morb Mortal Wkly Rep*. 2011; 60(48):1650–1653
- Cruz AT, Starke JR, Lobato MN. Old and new approaches to diagnosing and treating latent tuberculosis in children in low-incidence countries *Curr Opin Pediatr* 2014;26:106–113
- Starke JR; American Academy of Pediatrics Committee on Infectious Diseases. Interferon- $\gamma$  release assays for diagnosis of tuberculosis infection and disease in children. *Pediatrics*; 2014;134(6):e1763–e1773

### Chapter 342

## TURNER SYNDROME AND NOONAN SYNDROME

Jonathan C. Howell, MD, PhD; Philippe Backeljauw, MD

### TURNER SYNDROME

#### Definition and Etiology

Turner syndrome (TS) describes a phenotype of girls with short stature, gonadal failure, and varying degrees of skeletal, cardiovascular, renal, endocrine, lymphatic, and neurodevelopmental abnormalities; it is genetically characterized by an abnormal or missing X chromosome. It was first described as a syndrome of sexual infantilism, cubitus valgus, and webbing of the neck by Henry Turner in 1938. All individuals with TS have a female phenotype; males are not given this diagnosis. Turner syndrome is caused by loss of all or part of one of the X chromosomes. Some children have structural abnormalities of the X chromosome, such as deletions of a portion of the short arm, a ring X chromosome, or an X isochromosome. These individuals can be clinically indistinguishable from the classic (45,X) TS patient. Some female children with TS (5% to 6%) have karyotypes including Y chromosome material, such as in 45,X/46,XY mosaicism.

#### Epidemiology and Risk Factors

Turner syndrome occurs in approximately 1 in 2,000 live female births. With about 2 million live female births in the United States annually, this translates to 800 females born with TS every year. Approximately 3% of all females conceived have TS, but nearly 99% of all TS conceptions do not survive beyond 28 weeks of gestation. Risk factors for TS include faulty chromosome distribution, such as nondisjunction during paternal meiosis, or postfertilization mitotic errors leading to TS mosaicism (eg, 45,X/46,XX). In rare cases, familial TS is transmitted by a carrier of a balanced translocation.

#### Diagnosis

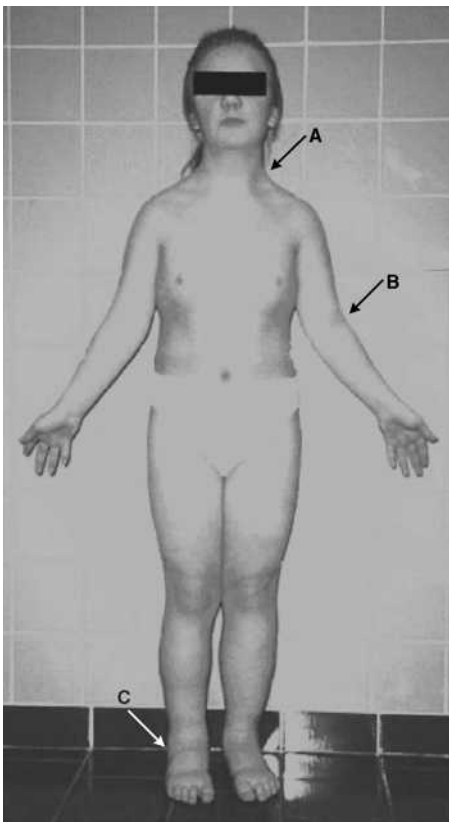
##### Signs and Symptoms

Owing to the haploinsufficiency of several genes encoded on the X chromosome, the presentation can be heterogeneous. See Figure 342-1 and Table 342-1 for the characteristic features of TS.

#### Differential Diagnosis

The differential diagnosis of TS must include Noonan syndrome (NS), and a karyotype will reveal no sex chromosome abnormalities in NS patients. Additionally, NS is often associated with right-sided heart abnormalities, whereas TS heart defects are typically left-sided. Additionally, in the differential diagnosis for TS is any disorder causing growth failure or short stature in females: hypothyroidism, growth hormone deficiency, skeletal dysplasia, short stature associated with chronic illness, and normal short stature variants. Although primary ovarian failure is quite common in girls





**Figure 342-1** Photo of patient with Turner syndrome. The arrows point to some of the classical features: (A) short webbed neck; (B) cubitus valgus; (C) lymphedema. (From Gawlik A, Malecka-Tendera E. Hormonal therapy in a patient with a delayed diagnosis of Turner syndrome. *Nat Clinical Pract Endocrinol & Metab.* 2008;4(3):173–177. Reprinted with permission from Nature Publishing Group.)

with TS, those presenting with delayed puberty and amenorrhea must be distinguished from those with any other cause of ovarian failure (long-term survivors of childhood neoplasia, autoimmune ovarian disease).

**Diagnostic Approach**

For the diagnosis of TS, karyotyping with a minimum of 30 cells in metaphase will identify at least 10% mosaicism with 95% confidence. Testing for the presence of Y chromosome material should be done by fluorescent in situ hybridization in any child with chromosome material of unknown origin. The diagnosis of TS is often made late (late childhood and beyond), and cytogenetic analysis should be considered for all females with unexplained short stature, pubertal delay, or any constellation of other clinical findings of TS. Turner syndrome is increasingly diagnosed prenatally through amniocentesis or chorionic villus sampling. If a karyotype was obtained in utero, it should be repeated following birth. Features suggestive of TS found on fetal ultrasonography include polyhydramnios, edema, and increased nuchal fluid. Fetal echocardiography is indicated at 18 to 20 weeks of gestation if TS is suspected.

Table 342-1 Characteristic Features of Turner Syndrome	
AREA	FEATURE
Cardiovascular	Coarctation of the aorta Bicuspid aortic valve Aortic root dilation/dissection Hypertension
Craniofacial	Epicanthal folds Excess nuchal skin Webbed neck Low posterior hairline
Dermatologic	Pigmented nevi
Endocrine	Hypothyroidism
Genitourinary	Gonadal dysgenesis—leads to delayed/absent puberty Streak ovaries (most infertile) Renal malformations (horseshoe kidneys most common)
Growth	Short stature
Musculoskeletal	Lymphedema of hands and feet at birth Deep-set hyperconvex nails Short fourth metacarpals Cubitus valgus Broad chest with wide-spaced nipples Scoliosis
Neurodevelopment	Learning difficulties (typically normal intelligence)
Ophthalmologic	Strabismus
Otolaryngologic	Hearing loss

From Lyons MJ. Specific genetic conditions. In: Saul RA, ed. *Medical Genetics in Pediatric Practice*. Elk Grove Village, IL: American Academy of Pediatrics; 2013.

**Laboratory Evaluation and Imaging**

Anticipatory monitoring is highly recommended during the lifetime of children with TS (see Table 342-2 for a screening schedule). Females with TS are encouraged to regularly see an endocrinologist to address their growth, pubertal delay, and bone health. Further specialty involvement comes from a cardiologist if cardiac anomalies are present, a nephrologist if renal disease is apparent on ultrasonography, and an ear, nose, and throat specialist with an audiologist to address recurrent otitis and hearing loss. If learning, processing, and attention difficulties are suspected, evaluation by a developmental pediatrician, a psychologist, or other mental health providers is recommended.

**Management**  
**Growth and Endocrine Issues**

Short stature in TS is related to short stature homeobox (*SHOX*) gene deficiency resulting from the loss of all or part of the X chromosome. Growth charts are available for use in the clinical setting (Figure 342-2). Infants often have some degree of intrauterine growth restriction, and postnatal growth lags behind that of other children. Feeding difficulties can negatively affect nutrition and weight gain. There is delayed

**Table 342-2** Screening and Monitoring for Turner Syndrome

AGE	SCREENING AT DIAGNOSIS	ONGOING MONITORING
All patients	Cardiology consultation (Figure 342-2) Renal ultrasonography Audiology evaluation Examination for scoliosis/kyphosis Discussion of aspects of TS Support group referral Evaluation of progress of growth and pubertal development	Cardiology follow-up and evaluation as indicated Annual blood pressure check Re-evaluation by ENT/audiology physician every 1–5 years Growth evaluation
Age 0–4 years	Hip examination for congenital hip dislocation Pediatric ophthalmology examination (age >1 year)	Social skills evaluation at age 4–5 years
Age 4–10 years	Thyroid function testing ( $T_4$ , TSH) Celiac screen (tTG Ab) Educational/psychosocial assessment Orthodontic evaluation (age >7 years)	Liver/thyroid screening yearly Celiac screen every 2–5 years Yearly education/social progress evaluation Dental/orthodontic evaluation as needed
Age >10 years	Thyroid function testing ( $T_4$ , TSH) Celiac screen (tTG Ab) Educational/psychosocial assessment Ovarian function evaluation Begin estrogen replacement when appropriate Liver function testing, fasting blood glucose, CBC, renal function testing Bone mineral density (age >18 years)	Fasting lipids/blood glucose yearly Liver/thyroid screening yearly Celiac screen if clinically indicated Evaluation of pubertal development and psychosocial development at age-appropriate times

Ab, antibody; CBC, complete blood count; ENT, ear, nose, and throat;  $T_4$ , thyroxine; TS, Turner syndrome; TSH, thyroid-stimulating hormone; tTG, tissue transglutaminase.

Adapted from Loscalzo ML. Turner Syndrome. *Pediatr Rev.* 2008;29(7):219–222; and Bondy CA. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. *J Clin Endocrinol Metab.* 2007;92(1):10–25.

childhood growth and lack of a pubertal growth spurt in most girls with TS. Treatment with recombinant human growth hormone (GH) has been approved for TS patients since 1996, and GH therapy should be considered as soon as growth failure is confirmed.

In a randomized, controlled trial of GH in girls with TS initiated before the age of 4 years, significant improvement in height standard deviation (SD) scores compared with matched controls was shown, and GH restored height into the normal range in 93% of patients by the age of 6 years. Additional studies have shown variable increases in final adult height relative to pretreatment projected height, depending on the type of study considered (range between 5.1 and 17.2 cm, with a mean of 7.0 cm). Children with earlier age at GH initiation and longer duration of GH therapy demonstrated the most benefit. Other advantages of early GH treatment initiation include improvement in peer group integration and the ability to provide age-appropriate estrogen replacement.

In those with a relatively late diagnosis of TS (ie, about 8 to 10 years of age), oxandrolone, a nonaromatizable anabolic steroid with weak androgen effect, given for up to 4 years, may be considered as adjuvant therapy for growth promotion. Although it results in height gain improvement in many girls, this addition of oxandrolone to GH therapy may yield only modest augmentation in height gain in some children. It is also often accompanied by a deceleration in breast development.

Individuals with TS are prone to develop autoimmune conditions. Autoantibodies are present in nearly

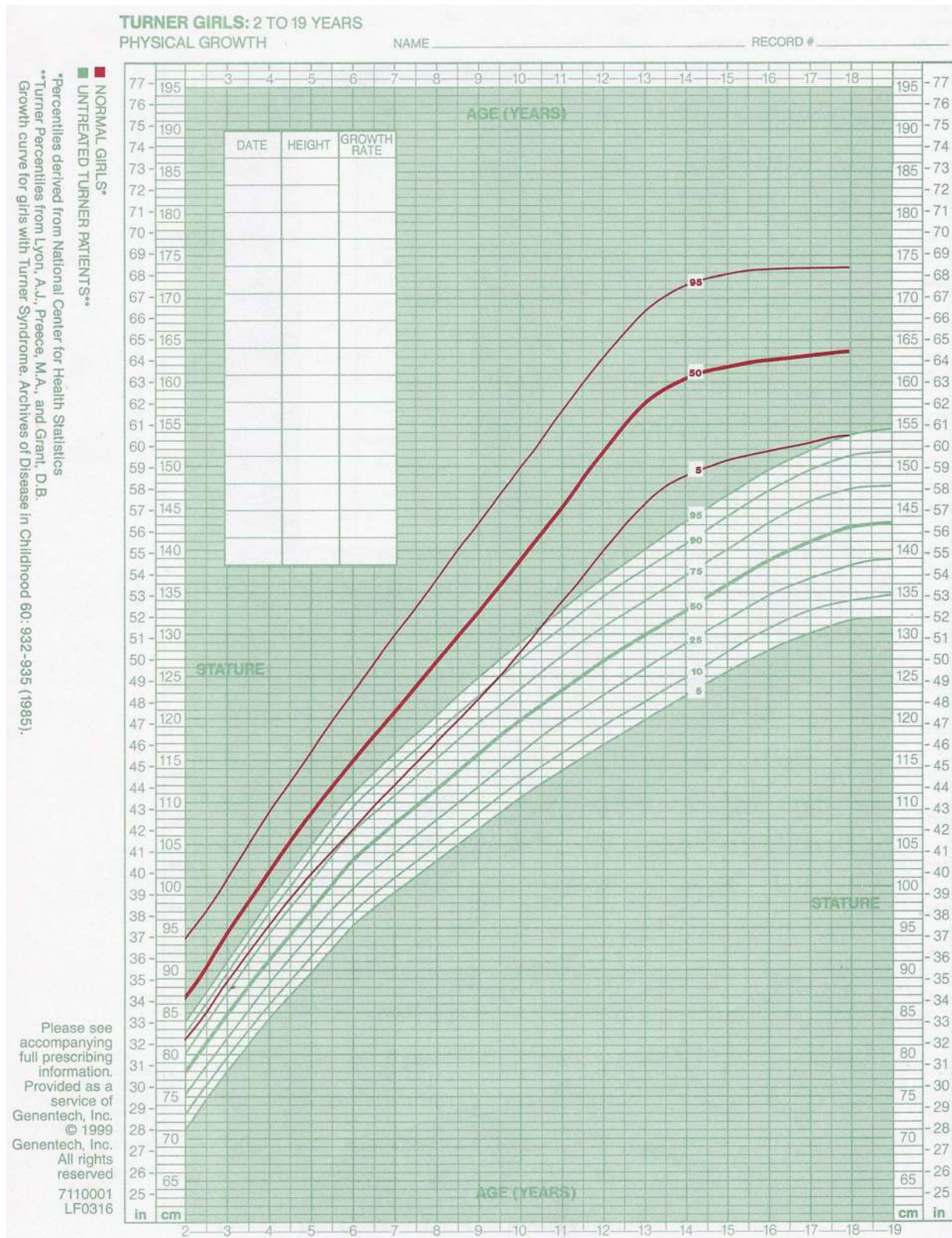
60% of female TS patients, and 18% of those have more than 1 organ targeted. Annual screening of thyroid function is recommended. Treatment of hypothyroidism because of autoimmune thyroiditis is usually at typical doses used to treat hypothyroidism, and regular follow-up with an endocrinologist is required. The incidence of celiac disease among TS patients is 6%. Screening for tissue transglutaminase should occur by age 4 and every 2 to 5 years thereafter.

### Cardiovascular Issues

If cardiovascular anomalies are found on initial screening, individuals with TS should have further evaluation by a pediatric cardiologist (Figure 342-3). Hypertension warrants periodic evaluation for aortic dilation, increasingly being done by cardiac magnetic resonance imaging. Obesity is a common feature of TS that can complicate treatment for hypertension and result in negative effects on cardiac health. Baseline measurement of fasting glucose, insulin, lipids, and liver enzymes are helpful from age 10 years on, with follow-up testing at 1- to 2-year intervals and as needed.

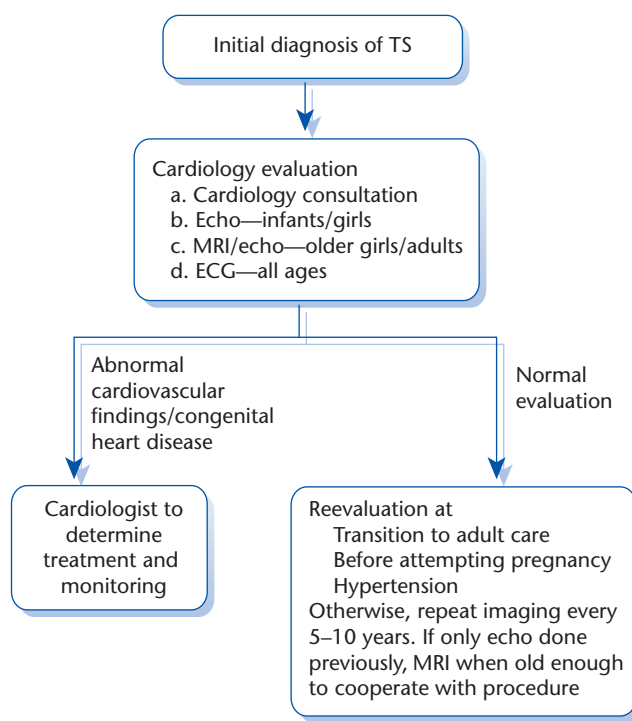
### Renal and Genitourinary Issues

Renal malformations in TS children are relatively common, although not always with clinical implication. Horseshoe kidney, ectopy, and malrotation are typical structural abnormalities. Children with renal defects are more likely to have hypertension. A renal ultrasound should be obtained at diagnosis, and consultation by a pediatric nephrologist is recommended if the findings are abnormal.



**Figure 342-2** Turner syndrome-specific stature chart overlaid with percentiles of normal children aged 2–19 years. (Data originally adapted from Lyon AJ, Preece MA, Grant DB. Growth curve for girls with Turner syndrome. Arch Dis Childhood. 1985;60(10):932–935.)





**Figure 342-3** Recommendations for cardiac evaluation of TS patients. ECG, electrocardiogram; MRI, magnetic resonance imaging; TS, Turner syndrome. (Adapted from Loscalzo ML. Turner syndrome. *Pediatr Rev.* 2008;29(7):219-227.)

### Pubertal Delay and Hypogonadism

Because of gonadal dysfunction, up to 30% of TS patients have some degree of spontaneous puberty. Follicle-stimulating hormone (FSH) concentrations are increased in the first 1 to 2 years of life, followed by a gradual decline in mid to late childhood. In females with mosaic TS, FSH can be indistinguishable from that of healthy females. Estrogen therapy is used to induce the development of the secondary sexual characteristics, followed by progestin cycling. The exact timing of pubertal induction is still the subject of ongoing study. Current recommendations are to consider treatment between the ages of 12 and 13 years if no spontaneous puberty has occurred. Timely treatment with estrogen can promote bone health and improve psychological outcomes of adolescent girls. Many forms of estrogen are available, including oral, transdermal, and injectable. Physiologic low-dose replacement is preferable, with a gradual increase in dosing every 4-6 months, and this is best achieved with transdermally applied estradiol preparations. Progesterone is withheld until 18 to 24 months after estrogen initiation, or when breakthrough menstruation occurs.

### Vision and Hearing

Individuals with TS can have a variety of eye problems because of structural eye abnormalities (downward sloping palpebral fissures, ptosis, and epicanthal folds). Strabismus and hyperopia have been reported in up to 30% of patients. Initial ophthalmologic evaluation is recommended between 1 and 2 years of life.

The pediatrician should maintain a high level of suspicion for otitis media. Light otoscopy and pneumatic tympanometry are useful throughout childhood. Current recommendations also include ENT and audiology evaluation every 1 to 5 years. If hearing loss or chronic ear infections are present, yearly audiology examinations should take place, and referral to an audiologist is recommended. For those without documented hearing loss or chronic otitis, similar examinations can take place every 2 to 3 years.

### Neurologic, Cognitive, and Behavior Issues

For most TS children, intelligence is typical. However, it is common to score lower on assessments of nonverbal learning and demonstrate reduced speed in mental processing, or to have deficits in executive function. Careful attention should be paid if school performance begins to decline. Families should be encouraged to request educational accommodations, such as extra time to complete homework or examinations. Poor social skills and challenges in executive functioning can often lead to and be exacerbated by social isolation. Questionnaires provided to adolescents with TS have shed light on social anxieties related to delayed puberty and questions surrounding fertility. It is important to be honest when discussing fertility with patients and their families. Alternative means of motherhood, such as adoption, should be explored. Psychosexual and vocational counseling may require input from psychologists, educators, and school counselors.

### Orthodontics and Skin Issues

Dental malocclusion, articulation defects, micrognathia, and crowded teeth are common in TS children because of a narrow maxilla and small mandible. Orthodontic evaluation is begun by 7 years of age.

Generalized lymphedema with excessive nuchal skin, easy bruising, and hyperpigmentation can be seen in individuals with TS. The risk for melanoma is not increased over the general population, but TS children often develop multiple nevi. They are also more likely to have keloid scarring. Lymphatic accumulation in TS can be associated with fetal hydrops, pleural effusions, lymphangiectasis, and anomalous lymphatic vessels. Although the neonatal lymphedema improves over time, the management of persistent lymphedema can be difficult, and follow-up with a specialized center is recommended.

## NOONAN SYNDROME

### Definition and Etiology

Although children with NS can have a similar phenotype to TS, with short stature, neck webbing, and gonadal failure (in males), the etiology is completely different, and individuals with NS have normal 46,XX or 46,XY karyotypes. Slightly more than half of children with NS have a dominant-negative mutation in the *PTPN11* gene, which encodes the nonreceptor protein tyrosine phosphatase signaling molecule, SHP-2. This mutation leads to disruption of intracellular signaling of several growth factors, cytokines, and hormones. Other less common mutations in genes





**Figure 342-4** Broad neck, wide-spaced nipples, and facial features in a female with Noonan syndrome. (From Lyons MJ. *Specific genetic conditions*. In: Saul RA, ed. *Medical Genetics in Pediatric Practice*. Elk Grove Village, IL: American Academy of Pediatrics; 2013:175–234.)

encoding signaling molecules have also been identified (*KRAS*, *RAF1*, *SOS1*, *BRAF*, *SHOC2*, *NRAS*, and *MEK1*). Characterization of the NS phenotype occurred in the late 1960s by Jacqueline Noonan. In addition to distinct facial features, children with NS often have cardiac, endocrine, skeletal, neurologic, and hematologic abnormalities.

**Epidemiology and Risk Factors**

The incidence of NS is reportedly between 1 in 1,000 and 1 in 2,500 live births. Transmission of NS is thought to be autosomal dominant, with many cases arising spontaneously. Moreover, a wide variability in the presentation of NS is indicative that the phenotypic features of NS can be caused by a variety of molecular etiologies.

**Diagnosis**

**Signs and Symptoms**

The variable genetic background of NS leads to a wide range of features. See Figure 342-4 and Table 342-3.

**Differential Diagnosis**

Although TS should be considered in the differential diagnosis for females with NS, several other syndromes have overlapping phenotypes with NS. These include Cardio-facio-cutaneous syndrome, Costello syndrome, Neurofibromatosis type 1, and LEOPARD syndrome (multiple lentigines, electrocardiogram conduction abnormalities, ocular hypertelorism, pulmonic stenosis,

Table 342-3	Characteristic Features of Noonan Syndrome
AREA	FEATURE
Cardiovascular	Pulmonic stenosis Hypertrophic cardiomyopathy Lymphatic abnormalities
Craniofacial	Low-set ears Posteriorly rotated ears Fleshy helices Hypertelorism Downward-slanting palpebral fissures Epicanthal folds Ptosis Thick eyelids Broad, webbed neck
Genitourinary	Cryptorchidism in males Renal abnormalities
Growth	Short stature
Hematology	Coagulation defects
Musculoskeletal	Superior pectus carinatum with inferior pectus excavatum Low-set nipples
Neurodevelopment	Developmental delay Mild intellectual disability (may be present in one-third of cases)
Ophthalmologic	Strabismus
Otolaryngologic	Hearing loss

From Lyons MJ. *Specific genetic conditions*. In: Saul RA, ed. *Medical Genetics in Pediatric Practice*. Elk Grove Village, IL: American Academy of Pediatrics; 2013.

abnormal genitalia, retardation of growth, and deafness). Syndromes with distinct facial dysmorphology, cardiac defects, and short stature (Williams and Aarskog syndromes) may be difficult to differentiate from NS.

**Diagnostic Approach**

DNA sequencing, liquid chromatography, and oligonucleotide microarray testing are available to detect the gene mutations associated with NS. If NS is clinically suspected, initial screening for a *PTPN11* mutation is recommended. When *PTPN11* mutations are absent, other mutations can be investigated (Table 342-4). The availability of the Noonan Spectrum Panel performed by next-generation gene sequencing allows for a comprehensive analysis of potentially pathologic variants that may offer definitive diagnosis. However, the lack of a detectable genetic mutation does not rule out a diagnosis of NS in patients for whom there is a strong clinical suspicion, and, in total, the frequency of gene mutations among children with NS is only approximately 60%. Prenatal diagnosis can be achieved through amniocentesis or chorionic villus sampling, and findings such as polyhydramnios, edema, and increased nuchal fluid on fetal ultrasonography, can suggest NS. If NS is suspected during prenatal evaluation, fetal echocardiography is also indicated. Several clinically based scoring systems are in place to help diagnose NS (see Table 342-5).

### Laboratory Evaluation and Imaging

A similar multidisciplinary approach has been advocated for NS as previously described for TS. A pediatric genetics consultation and follow-up are recommended at diagnosis. Because negative genetic testing cannot always rule out an NS diagnosis, a decision about whether to obtain genetic testing relies in part on family preference and the presence or absence of additional features associated with NS (see Table 342-4).

### Management

Management and interval comorbidity screening recommendations are summarized in Table 342-6.

### Growth and Endocrine Issues

The GH-secretory dynamics in NS reflect the existing genetic heterogeneity, and both GH sufficiency and deficiency have been reported. Insulin-like growth factor-I is often lower in *PTPN11* mutation-positive NS patients, which may point to some degree of GH resistance when associated with normal GH secretion. Although birth length is typically preserved, birth weight is often low, and consultation by a gastroenterologist should be obtained in children

who have failure to thrive. Growth spurts for both boys and girls can be delayed because of delayed puberty, and mean NS adult height only reaches the lower limits of normal late in the second decade of life. Recent data suggest that height standard deviation (SD) scores and growth kinetics can vary depending on the exact genetic mutation encountered in the RAS/MAPK pathway. Specific length, stature, weight, and growth velocity charts for NS are available for clinical use (Figure 342-5).

Growth hormone therapy has been approved for use in NS children and should be initiated in consultation with a pediatric endocrinologist when growth failure is evident. Although most studies to date involve small numbers of children, data on adult height achieved with GH therapy suggest there is significant improvement in height SD scores and mean overall height gain (between 9.5 and 13 cm for boys and 9.0 and 9.8 cm for girls). Furthermore, as in TS, earlier treatment and longer duration seem to have the most effect. Children with *PTPN11* mutations may respond less favorably to GH therapy than those without such mutations.

### Cardiovascular Issues

Cardiovascular defects are common in NS and typically involve right-sided malformations. In severe pulmonary valve dysplasia (a subset of pulmonary valve stenosis), a valvectomy or pulmonary homograft is required in childhood. Less severe forms of stenosis can be treated with balloon angioplasty. Hypertrophic obstructive cardiomyopathy can resolve spontaneously in some NS children, or become rapidly progressive. Management includes beta blocker medications and surgical myomectomy to reduce outflow obstruction. Regardless of ultimate cardiac diagnosis, lifetime follow-up by a cardiologist is needed.

### Renal and Genitourinary Issues

Renal anomalies have been reported in 10% to 11% of children with NS and include solitary kidney, renal pelvic dilation, and duplicated collecting system; as in TS, they often are clinically insignificant. Consultation by a pediatric nephrologist is helpful if hypertension is noted. Fertility does not seem to be affected in females with NS. In males, if cryptorchidism is present, prompt

**Table 342-4** Indications for Genetic Testing in Noonan Syndrome

CLINICAL PRESENTATION	GENETIC TESTING CONSIDERED
Initial presentation of NS phenotype <i>If PTPN11 gene testing is negative:</i>	<i>PTPN11</i>
No developmental delays or normal stature	<i>SOS1</i>
Hypertrophic obstructive cardiomyopathy	<i>RAF1</i>
Significant developmental delays	<i>KRAS</i>
Sparse, thin, slow-growing hair	<i>SHOC2</i>

NS, Noonan syndrome.

Adapted from Romano, AA, Allanson JE, Dahlgren J, et al. Noonan syndrome: clinical features, diagnosis, and management guidelines. *Pediatrics*. 2010;126(4):746–759.

**Table 342-5** Scoring System for Noonan Syndrome<sup>a</sup>

FEATURE	A = MAJOR	B = MINOR
1. Facial	Typical face dysmorphism	Suggestive face dysmorphism
2. Cardiac	Pulmonary valve stenosis, HOCM and/or ECG typical of NS	Other defects
3. Height	<3rd percentile	<10th percentile
4. Chest wall	Pectus carinatum/excavatum	Broad thorax
5. Family history	First-degree relative with definite NS	First-degree relative with suggestive NS
6. Other	Intellectual disability, cryptorchidism, and lymphatic dysplasia	Intellectual disability, cryptorchidism, or lymphatic dysplasia

<sup>a</sup>Definitive Noonan syndrome: 1 “A” plus 1 other major sign or 2 minor signs; 1 “B” plus 2 major signs or 3 minor signs.

ECG, electrocardiogram; HOCM, hypertrophic obstructive cardiomyopathy; NS, Noonan syndrome.

Adapted from van der Burgt I. Noonan syndrome. *Orphanet J Rare Dis*. 2007;2:1–6. © 2007 van der Burgt; licensee BioMed Central Ltd. Available at: [http://ojrd.biomedcentral.com/articles/10.1186/1750-1172-2-4#CR2\\_55](http://ojrd.biomedcentral.com/articles/10.1186/1750-1172-2-4#CR2_55). Accessed February 9, 2016.

evaluation by a urologist and orchiopexy before 1 year of age are recommended.

### Pubertal Delay/Hypogonadism

Puberty is often delayed in both boys and girls with NS and is accompanied by a decreased growth spurt. Mean age in boys for onset of puberty is between 13.5 and 14.5 years, and in girls, it is between 13 and 14 years. In some instances, puberty may then progress with rapid tempo (<2 years). Induction of puberty with appropriate sex hormone replacement can be accomplished in boys at 14 years of age and girls at 13 years.

### Vision and Hearing

Similar to TS patients, NS children can have frequent otitis media. Examination, not only with light otoscopy but also with pneumatic tympanometry, is useful until at least 7 years of age. If hearing loss is identified or ear infections persist, yearly hearing examinations and referral to an audiologist are recommended. For those without documented hearing loss or chronic otitis, screening audiology is done every 2 to 3 years.

### Neurologic, Cognitive, and Behavior Issues

The neurologic and behavioral aspects of NS are less well understood and quite variable. Learning disabilities, peripheral neuropathy, and seizures are all increased in NS children compared with nonsyndromic children. Although brain structural malformations are relatively uncommon, Arnold-Chiari type I malformations and hydrocephalus are known to occur at low frequencies. A generalized motor delay is present in most. Body image problems and poor self-esteem, depression, and feelings of social inadequacy have all been noted in adolescents and adults with NS. Psychiatric or psychological intervention is recommended for NS children who have poor coping skills, self-injurious behavior, or severe attention deficit/hyperactivity disorder.

### Hematologic, Orthodontic, and Skin Issues

Individuals with NS are at higher risk than the general population for bleeding disorders, and a number of coagulation-factor anomalies have been described: thrombocytopenia, platelet dysfunction, and deficiencies in factors VIII, XI, or XII. Evaluation by a

**Table 342-6** Screening and Monitoring for Noonan Syndrome

CLINICAL SPECIALTY ISSUE	RECOMMENDATIONS
Cardiovascular	Evaluation by cardiologist at time of diagnosis, including echocardiogram and electrocardiogram Regular follow-up if defect present Interval follow-up every 5 years if no defect present
Growth and endocrine	Weight and height measurements regularly by primary physician Evaluation by an endocrinologist if growth deceleration, height $\leq 2$ SD, or delayed puberty Thyroid testing if goiter present
Renal and genitourinary	Renal ultrasonography at time of diagnosis Consider antibiotic prophylaxis with hydronephrosis or recurrent urinary tract infection Orchiopexy performed by age of 1 year if cryptorchidism present
Gastrointestinal	Evaluation by gastroenterologist for feeding difficulties or persistent vomiting
Hematology	Screening CBC with differential, PT, and aPTT at diagnosis and after 6–12 months of age If bleeding, first obtain CBC, PT, and aPTT; then evaluate specific clotting factor activity in consult with hematologist Preoperative evaluation for all surgeries by hematologist
Cognitive and behavioral	Developmental screen annually Complete neuropsychiatric testing if abnormal Evaluations by physical therapist, occupational therapist, and speech therapist if delayed, with earliest intervention possible Individual education plans updated yearly with schools Evaluation by neurologist if seizures suspected Brain and upper spine MRI with any neurologic problem Consider MRI angiogram if sudden focal findings
Eye and ear	Detailed eye examination at diagnosis Eye reevaluation as indicated if problems or at least every 2 years thereafter Hearing testing in infancy and/or at diagnosis with regular testing in childhood
Orthopedic	Annual examination of chest and back, radiography if abnormal
Orthodontic	Dental referral between 1 and 2 years of age Careful oral examination at each visit
Lymphatic	Referral to specialty lymphedema clinic if possible For more information, contact National Lymphedema Network ( <a href="http://www.lymphnet.org">www.lymphnet.org</a> )

aPTT, activated partial thromboplastin time; CBC, complete blood count; MRI, magnetic resonance imaging; PT, prothrombin time; SD, standard deviation.  
Derived from Romano AA, Allanson JE, Dahlgren J, et al. Noonan syndrome: clinical features, diagnosis, and management guidelines. *Pediatrics*. 2010;126:746–759; and Lee BH, Kim JM, Jin HY, et al. Spectrum of mutations in Noonan syndrome and their correlation with phenotypes. *J Pediatr*. 2011;159:1029–1035.





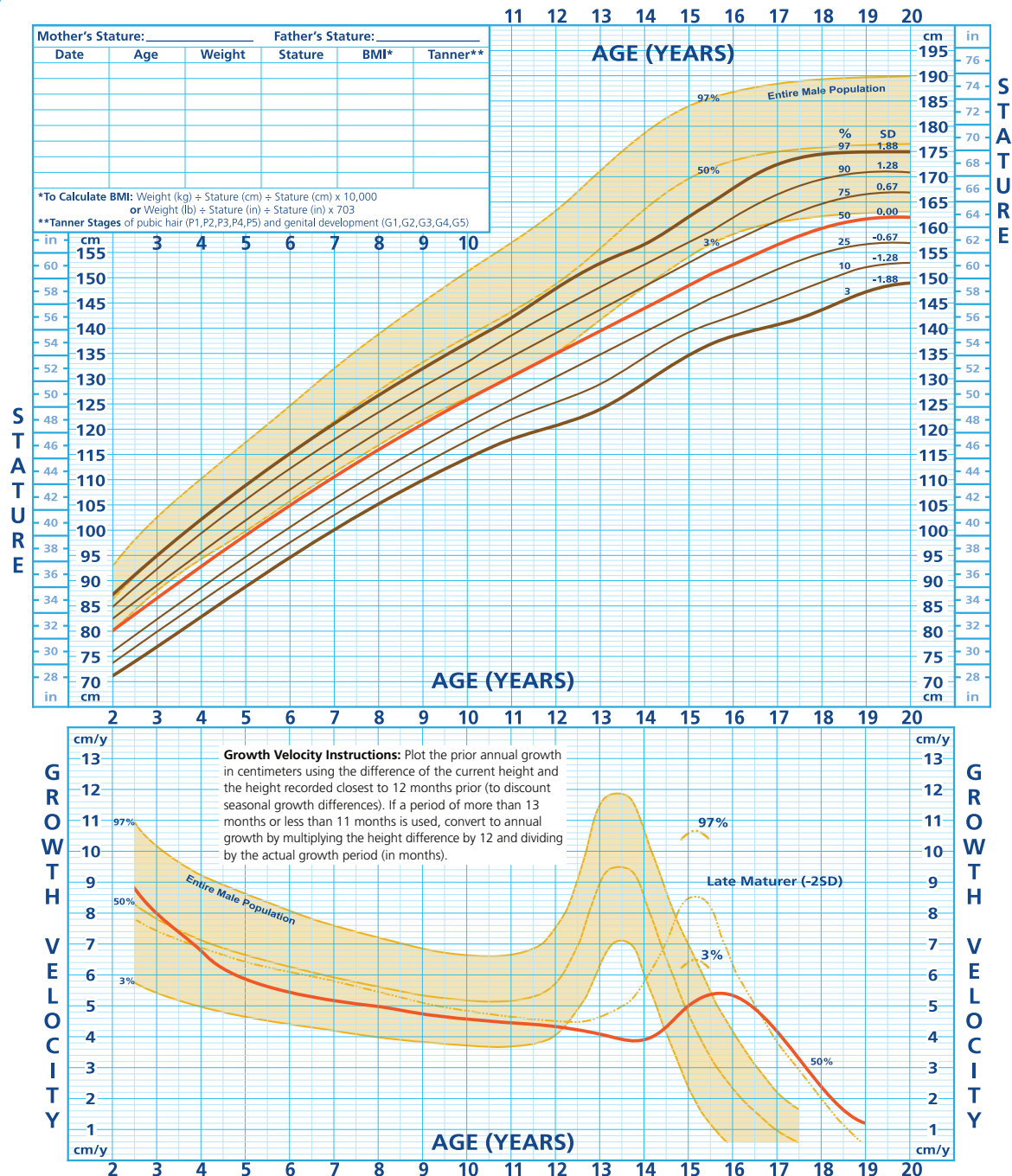
# NOONAN IN BOYS

## 2 to 20 Years

### Stature and Growth Velocity for Age<sup>a,b</sup>

Name: \_\_\_\_\_

DOB: \_\_\_\_\_ ID: \_\_\_\_\_



\*Chart and curve selection by Susan Rose, MD, Cincinnati Children's Hospital, University of Cincinnati.  
 †No weight for age data have been published in children with Noonan syndrome.

**Charts created with data from:** Ranke, et al. *Eur J Pediatr*. 1988;148(3):220-227. Tanner, et al. *J Pediatr*. 1985;107(3):317-329. Usher, et al. *J Pediatr*. 1969;74(6):901-910. Witt, et al. *Clin Genet*. 1986;30:150-153.

Plot points taken from data available at:  
<http://www.cdc.gov/nchs/data/nhanes/growthcharts/stage.txt>.



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**Figure 342-5, cont'd.**

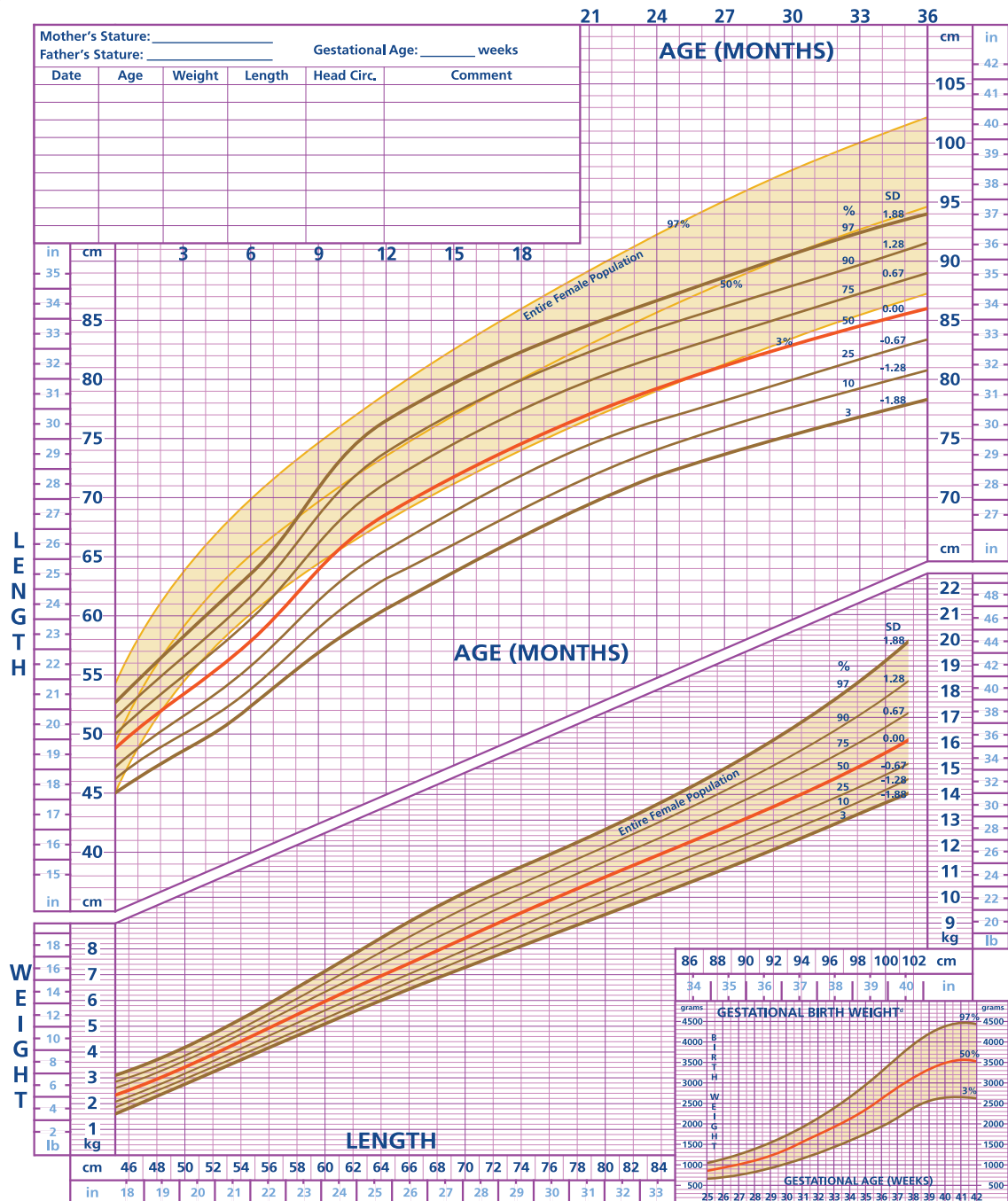
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# NOONAN IN GIRLS

Birth to 36 Months  
Length and Weight for Age<sup>a-c</sup>

Name: \_\_\_\_\_

DOB: \_\_\_\_\_ ID: \_\_\_\_\_



\*There is no evidence of deviation from normality for weight-length ratios in children with Noonan syndrome.  
No weight for age data have been published in children with Noonan syndrome.  
Chart and curve selection by Susan Rose, MD, Cincinnati Children's Hospital, University of Cincinnati.  
Gestational birth weight data for patients with Noonan syndrome do not differ from those of the normal population.

Charts created with data from: Panke, et al. Eur J Pediatr. 1988;148(3):220-227.  
Lyoner, et al. J Pediatr. 1989;114(6):901-910.  
Witt, et al. Clin Genet. 1980;30:130-133.

Plot points taken from data available at:  
<http://www.cdc.gov/nchs/data/nhanes/growthcharts/boys/lengthinf.xls> and  
<http://www.cdc.gov/nchs/data/nhanes/growthcharts/boys/weightinf.xls>



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Figure 342-5, cont'd.

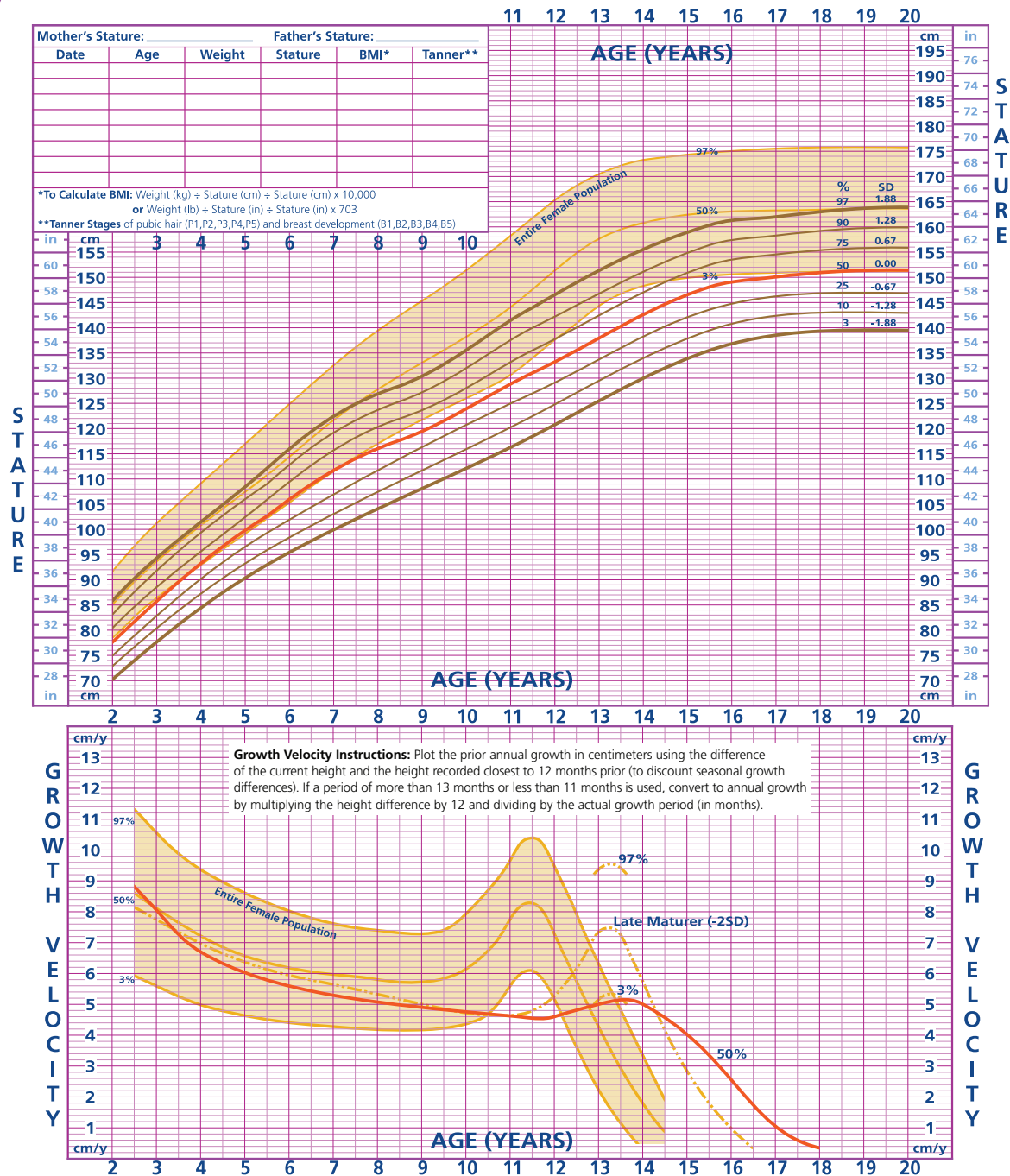
# NOONAN IN GIRLS

## 2 to 20 Years

### Stature and Growth Velocity for Age<sup>a,b</sup>

Name: \_\_\_\_\_

DOB: \_\_\_\_\_ ID: \_\_\_\_\_



\*Chart and curve selection by Susan Rose, MD, Cincinnati Children's Hospital, University of Cincinnati.  
 †No weight for age data have been published in children with Noonan syndrome.

**Charts created with data from:** Ranke, et al. *Eur J Pediatr*. 1988;148(3): 220-227. Tanner, et al. *J Pediatr*. 1985;107(3): 317-329. Usher, et al. *J Pediatr*. 1969;74(6):901-910. Witt, et al. *Clin Genet*. 1986;30:150-153.

Plot points taken from data available at:  
<http://www.cdc.gov/nczhs/data/nhanes/growthcharts/stage.txt>.



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**Figure 342-5, cont'd.**

hematologist is recommended if easy bruising, epistaxis, or menorrhagia is present.

Dental malocclusion, articulation defects, micrognathia, and crowded teeth are all features of NS. Orthodontic evaluation is recommended by 7 years of age.

Lymphedema, excessive nuchal skin, easy bruising, and hyperpigmentation can occur in NS. Lymphatic accumulation in NS can involve fetal hydrops, pleural effusion, lymphangiectasia, and anomalous lymphatic vessels. Management of these can be difficult, and follow-up with a lymphedema center is helpful.

## CLINICAL SIMILARITIES AND TRANSITION TO THE ADULT CLINIC

Although there is some overlap in the clinical features of TS and NS, each represents a distinct diagnosis with a specific genetic etiology (see Table 342-7). Because of the varied manifestations affecting multiple organ systems in both syndromes, children are typically followed by primary care physicians in conjunction with several subspecialty physicians.

Recent attention has been paid to the lack of coordinated transition of TS and NS children from pediatric to adult care physicians, especially because multiple subspecialists are involved from an early age. It is important for the primary care pediatrician to educate young adults with TS or NS about key potential medical and psychosocial issues and empower them to proactively pursue care as they mature. Suggestions include providing children and their families with a medical “passport” documenting medical and surgical history, ongoing medications, advised annual or biannual testing, target weight and blood pressure, and data on prior cardiac evaluation and recommendations. This should be done in succinct and secular language. The use of a transition coordinator to facilitate movement of data and appointments to adult clinics has been shown to be highly effective in some

countries. Furthermore, use of social media, telephone calls, and interactive Web sites can make the transition process more attractive for these children, who are often in the midst of many life changes. For young adults with NS, especially, it is appropriate to undergo genetic counseling given the autosomal dominant inheritance pattern. Because the spectrum of the NS phenotype varies broadly, it may be worthwhile to screen the parents of children with NS for genetic mutations to assess the risk for recurrence.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *Building the Legacy: IDEA 2004* (Web page), US Department of Education. ([idea.ed.gov](http://idea.ed.gov))
- *Let's Put the Person First, Not the Disability!* (fact sheet), Disability Is Natural ([www.disabilityisnatural.com/explore/people-first-language](http://www.disabilityisnatural.com/explore/people-first-language))

### Engaging Patient and Family

- *All About the IEP* (fact sheet), Center for Parent Information and Resources ([www.parentcenterhub.org/repository/iep](http://www.parentcenterhub.org/repository/iep))
- *Building Your Care Notebook* (Web page), American Academy of Pediatrics ([medicalhomeinfo.aap.org/tools-resources/Pages/For-Families.aspx](http://medicalhomeinfo.aap.org/tools-resources/Pages/For-Families.aspx))
- *Emergency Information Form for Children With Special Needs* (form), American Academy of Pediatrics ([www.aap.org/advocacy/blankform.pdf](http://www.aap.org/advocacy/blankform.pdf))
- *Pediatric Specialists* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/default.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/default.aspx))
- *Protecting Students With Disabilities: Frequently Asked Questions About Section 504 and the Education of Children with Disability* (fact sheet), US Department of Education ([www.ed.gov/about/offices/list/ocr/504faq.html](http://www.ed.gov/about/offices/list/ocr/504faq.html))
- *Transitioning Youth to Adult Care Providers* (booklet), Got Transition ([www.gottransition.org/resourceGet.cfm?id=208](http://www.gottransition.org/resourceGet.cfm?id=208))
- *Turner Syndrome Introduction* (Web site), The MAGIC Foundation ([www.magicfoundation.org/www/docs/114/turner-syndrome](http://www.magicfoundation.org/www/docs/114/turner-syndrome))

### Practice Management and Care Coordination

- *A Toolkit to Improve Care for Pediatric Patients With Genetic Conditions in Primary Care* (e-book), Genetics in Primary Care Institute ([geneticsinprimarycare.aap.org/YourPractice/Documents/GPCI\\_Toolkit.pdf](http://geneticsinprimarycare.aap.org/YourPractice/Documents/GPCI_Toolkit.pdf))

## SUGGESTED READINGS

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- Roberts AE, Allanson JE, Tartaglia M, Gelb BD. Noonan syndrome. *Lancet* 2013;381(9863):333–342
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**Table 342-7** Phenotypic Overlap of Turner and Noonan Syndromes

SIMILARITIES	DIFFERENCES
<ul style="list-style-type: none"> <li>• Short stature (most)</li> <li>• Pubertal delay (most TS, some NS)</li> <li>• Eyelid ptosis</li> <li>• Increased inter-nipple distance</li> <li>• Webbed neck</li> <li>• Kidney malformations</li> <li>• Chronic otitis media</li> </ul>	<p>Genetic etiology</p> <ul style="list-style-type: none"> <li>• TS: Loss of X chromosome material</li> <li>• NS: Mutation in <i>PTPN11</i> (or other genes)</li> </ul> <p>Cardiac anomalies</p> <ul style="list-style-type: none"> <li>• TS: Left-sided</li> <li>• NS: Right-sided</li> </ul> <p>Neurobehavioral</p> <ul style="list-style-type: none"> <li>• TS: Nonverbal learning deficits</li> <li>• NS: Global developmental delay, seizures</li> </ul> <p>Gonadal dysgenesis in most TS girls</p> <p>Normal fertility in NS girls</p>

NS, Noonan syndrome; TS, Turner syndrome.



## Chapter 343

## UMBILICAL ANOMALIES

Robert W. Marion, MD; Joy Samanich, MD

*"[The umbilicus] is all that remains of the stem that bound us to the parental stalk. It is a reminder that we have been plucked and must sooner or later die. It might be said that when the stem is severed, we cease to live in any true sense. We may be ornamental like roses or useful like cabbages but only for a little while. Our dissolution has begun."*

—THOMAS STEPHEN CULLEN, 1916

Despite its essential role in the survival of the fetus during prenatal life, the umbilicus, the external vestige of the umbilical cord, is frequently ignored or overlooked by the pediatric primary care physician. However, aberrations in either the formation or the position of this structure can offer helpful clues to underlying disease in the young child. Major congenital anomalies of the ventral abdominal wall, such as omphalocele, gastroschisis, and exstrophy of the bladder and cloaca, are described in detail elsewhere. This chapter deals with minor anomalies in configuration, placement, and formation of the umbilicus. In addition to the conditions described here, the umbilicus can be the site of both tumors (either vascular or teratomatous neoplasms) and infections (omphalitis).

To understand the causes and significance of anomalies of the umbilicus, a review of some basic fundamentals of the embryologic development of the umbilical cord is necessary.

### EMBRYOLOGIC DEVELOPMENT OF THE UMBILICAL CORD

Appearing within the first 6 weeks of gestation, the umbilical cord is derived from the fusion of 3 separate embryonic structures: (1) the primitive or primary yolk sac, which contains the allantois and a portion of the vitelline duct, transient structures that ultimately form

the central portion of the embryonic gut, the urinary bladder, the urachus, and the umbilical blood vessels (usually 2 arteries and 1 vein); (2) the secondary yolk sac, composed of the remainder of the vitelline duct; and (3) the mesenchyme of the connecting body stalk of the embryo, the tissue that produces Wharton jelly, which is the packing substance that holds the cord together. After fusion is complete, these unified structures become covered by the amnion and are ultimately surrounded by amniotic fluid.

Many of these embryonic structures that form the umbilical cord are present for only brief periods during embryogenesis. After the seventh week of gestation, the vitelline duct regresses and is ultimately completely resorbed. Similarly the allantois, which is contiguous with the urinary bladder, degenerates, forming a fibrous cord called the *urachus*, which connects the apex of the bladder with the umbilicus. Anomalies may result when these structures fail to undergo normal regression, causing them to persist into postnatal life.

### ANOMALIES

#### Abnormalities of Position and Morphology

Anatomically, the level of the umbilicus is usually at the top of the iliac crest ventral to the third or fourth lumbar vertebra. Variations in the position of the umbilicus can result from abnormalities in the way in which the abdominal wall itself has formed and, as such, may be a clue to the diagnosis of specific dysmorphic syndromes. For example, as described in Table 343-1, the umbilicus has been noted to be low set in achondroplasia (in which disproportionate growth of the trunk accounts for the aberration in position), in bladder and cloacal exstrophy, and in association with various anomalies of the urinary tract. Higher than normal placement of the umbilicus occurs in Robinow syndrome, a condition also known as *fetal face syndrome* because of the striking ocular hypertelorism and macrocephaly that occurs in affected individuals.

Variations in the appearance of the umbilicus, as well as abnormal location, can suggest the presence of a syndrome. In Aarskog-Scott syndrome, also known as *faciogenital dysplasia*, a disorder that combines abnormalities of the face (ocular hypertelorism, small nose with anteversion of the nares, minor anomalies of the ears), digits (mild soft-tissue webbing with clinobrachydactyly of the fifth fingers), and genitalia (*shawl*

Table 343-1

Conditions Associated With Abnormalities in Position or Morphology of the Umbilicus

DISORDER	ABNORMALITY IN POSITION	ABNORMALITY IN MORPHOLOGY
Aarskog-Scott syndrome	—	Prominent, protruding, pouting
Achondroplasia	Low placement	—
Bladder exstrophy	Low placement	—
Cloacal exstrophy	Low placement	—
Cornelia de Lange syndrome	—	Hypoplasia
Rieger syndrome	—	Prominent, broad, redundant periumbilical skin
Robinow syndrome	High placement	Broad, scar is poorly epithelialized

scrotum, cryptorchidism), the umbilicus is prominent and appears pouting and protuberant. In Robinow syndrome, previously described, the umbilical scar is broad and poorly epithelized. Hypoplasia of the umbilicus occurs in Cornelia de Lange syndrome, a disorder combining growth and developmental retardation with a characteristic facial appearance and multiple congenital anomalies. Finally, in Rieger syndrome, which combines iris dysplasia and other ophthalmologic malformations with hypodontia (absence of the upper incisors), failure of involution of the periumbilical skin occurs, leading to a protruding umbilicus.

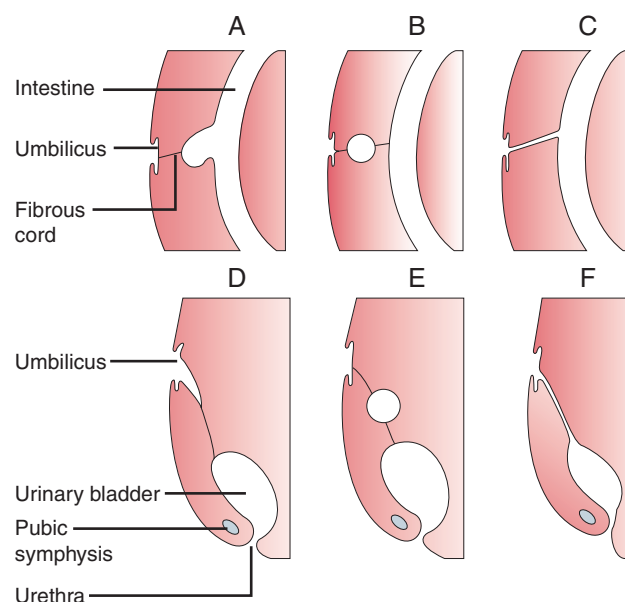
### Embryonic Umbilical Remnants

As previously noted, the umbilical cord is formed of the vitelline duct, which connects the yolk sac to the midgut; the allantois, which ultimately degenerates into the urachus, a structure that forms a connection between the apex of the urinary bladder and the umbilicus; and the umbilical blood vessels. Persistence of these structures can lead to the presence of anomalies within the newborn; unfortunately, there are usually no external indicators of the persistence of these structures, making diagnosis impossible before symptoms and signs occur.

Failure of the closure and total regression of the vitelline duct by the seventh week of gestation may lead to the presence of Meckel diverticulum (an outpouching of the gut without attachment to the anterior abdominal wall), a vitelline cyst or enterocystoma (a connection between the midgut and umbilicus without communication with either structure), an enteric or vitelline fistula (formed from a communicating connection between the midgut and the umbilicus), or a urachal sinus, cyst, or fistula (resulting from a connection between the bladder and the urachus) (Figure 343-1). In a child, the presence of these anomalies may be signaled by the presence of signs of infection and of a lower midline abdominal mass (caused by infection of a vitelline cyst); the discharge of feces and urine, which can lead to an erosive dermatitis (from enteric and urachal fistulas); and urinary tract infections (also resulting from urachal fistulas). Furthermore, the persistence of a fibrous band of tissue attached to the gut, the result of incomplete involution, may serve as the lead point for a volvulus or the cause of intestinal obstruction.

Of all these anomalies, Meckel diverticula clearly are the most common. Present in 2.5% of newborns in the United States, they are a well-known cause of clandestine lower intestinal bleeding in children and adults. The bleeding results from the presence of ectopic gastric mucosa within the diverticulum, which is prone to ulceration and hemorrhage. Additionally, given that these diverticula, which can occur anywhere from the ileocecal valve to a point 3 feet or more proximal to the valve, resemble a supernumerary vermiform appendix, their presence may be signaled by symptoms and signs of acute appendicitis.

Embryonic umbilical remnants that are lined with gastric mucosa can be detected by gastrointestinal radionuclide scans using technetium-99m ( $^{99m}\text{Tc}$ ) pertechnetate. Sonography or computed tomography is helpful in delineating vitelline cysts that, after onset of



**Figure 343-1** Embryonic umbilical remnants. **A**, Meckel diverticulum. **B**, Enterocystoma. **C**, Enteric (vitelline) fistula. **D**, Urachal sinus. **E**, Urachal cyst. **F**, Urachal fistula.

infection, exhibit as abdominal masses. The presence of a urachal fistula can best be documented by noting the presence of methylene blue dye in the urine after the dye has been instilled at the umbilicus. Surgical excision and repair is the treatment of all internal umbilical cord remnants that are symptomatic.

### Vascular Abnormalities of the Umbilical Cord

Derived from the primitive or primary yolk sac, the blood vessels are the most important structures present in the umbilical cord. Although usually consisting of 2 arteries and 1 vein, variations on this pattern are well known, occurring in 0.7% of all births. By far the most common variation is the presence of only 2 vessels in the cord, consisting of 1 vein and 1 artery. In 25% to 50% of cases, this arrangement is associated with various additional anomalies, including malformations of the central nervous system, genitourinary tract, spine, and extremities.

The pattern of anomalies seen in infants with aberrant cord vessels often depends on which vessels are present and which are missing. Blackburn and Cooley describe 3 separate patterns. In the first pattern, the single umbilical artery is of allantoic origin; this pattern is associated with growth restriction, anomalies of the central nervous system such as anencephaly and spina bifida, and abnormalities of the lower genitourinary tract. In the second pattern, the single artery is of vitelline origin; associated anomalies include sirenomelia, sacral agenesis, reduction defects of the lower extremities, anal atresia (features of the VACTERL [vertebral, anal atresia, cardiac, trachea, esophageal, renal, and limb defects] association), and trisomy 18. Infants with the third pattern have cords that have 3 vessels, including a single umbilical artery (of either allantoic or vitelline origin), a left umbilical vein, and

a persistent and aberrant right umbilical vein; such a pattern has been described in some children with Noonan syndrome and 47,XXY karyotype.

### Umbilical Hernia

The predisposition to develop an umbilical hernia occurs during the second trimester after the midgut, which has until then been developing extra-abdominally, returns to the abdominal cavity. Failure to form the normal fascial reinforcements that keep the midgut in place leads to a weakness in the abdominal wall.

Umbilical hernias are so common that they should be considered a variation of normal. The incidence varies with race and age. Evans found that at 6 weeks of age, 32% of black infants had umbilical hernias, whereas only 4% of white babies did. At 1 year, the prevalence decreased to 12% and 2%, respectively. Low-birth-weight babies are also at markedly increased risk. No gender predilection has been noted: boys and girls are equally affected.

In most affected individuals, umbilical hernias are associated with no medical sequelae. One study revealed that incarceration, strangulation, rupture, or skin breakdown occurred in less than 5% of 590 children. Other studies have revealed even lower rates of complication. Furthermore, in most cases, the hernia will close spontaneously without any medical intervention. Thus, the major indication for surgical treatment of the condition is cosmetic. As such, surgery should only be considered in carefully selected individuals.

Although most umbilical hernias occur as isolated findings in otherwise healthy children, they can also be associated with a variety of known conditions, many of which feature increased abdominal girth or hypotonia. As shown in Box 343-1, these conditions include the common autosomal trisomies, the mucopolysaccharidoses and other inborn errors of metabolism that are associated with organomegaly, and various dysmorphic syndromes such as Beckwith-Wiedemann syndrome.

### Umbilical Granulomas

At birth, the normal umbilical cord contains only the umbilical vessels surrounded by the protective Wharton jelly. Within the first 2 weeks after birth, the umbilical stump normally dries and separates from the abdomen; the region is completely covered by skin in 3 to 4 weeks. Delayed healing with the accumulation of excessive amounts of granulation tissue produces an umbilical granuloma, which is a small, reddened mass. The lesion may be associated with infection at its base or with a foreign body such as talcum, but it recedes rapidly after repeated topical applications of silver nitrate. Persistence of a granulomatous-seeming lesion after treatment, the presence of erosive dermatitis at the site, or the egression of gas, feces, or urine from it should suggest the persistence of one of the embryonic remnants described previously.

### Umbilical Polyps

Although polyps may superficially resemble umbilical granulomas, those at the umbilicus actually represent external remnants of the umbilical cord. They may be

## BOX 343-1 Some Conditions Associated With Umbilical Hernias

### CHROMOSOMAL ANOMALIES

- Trisomy 18
- Trisomy 21
- Deletion 9p
- Duplication 3q

### METABOLIC DISORDERS

- Hypothyroidism
- Mucopolidosis III (pseudo-Hurler syndrome)
- Type 1 (Hurler syndrome)
- Type 2 (hunter syndrome)
- Type 4 (Morquio syndrome)
- Type 6 (Maroteaux-Lamy syndrome)

### DYSMORPHIC SYNDROMES

- Aarskog syndrome
- Beckwith-Wiedemann syndrome
- Fetal hydantoin syndrome
- Marfan syndrome
- Opitz syndrome
- Weaver syndrome

sinuses of the vitelline duct or the urachus. Often larger in size than granulomas, umbilical polyps are bright red and do not respond to treatment with silver nitrate. Diagnosis depends on histologic examination, and treatment is surgical excision.

### Umbilical Separation

The umbilical cord normally separates and sloughs within the first 2 weeks of life. A delay in this process beyond 2 to 3 weeks of life may indicate an underlying abnormality. It is known that granulocyte influx and phagocytosis are important in the process of cord separation. In the event of delayed separation, 2 diagnostic considerations should be leukocyte adhesion deficiency (LAD) and urachal anomaly. LAD is a rare disorder of defective neutrophil function, often associated with omphalitis in infancy and with high morbidity and mortality. Urachal anomalies, such as urachal cyst (described previously), may also present with delayed umbilical separation.

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## Chapter 344

# URINARY TRACT INFECTIONS

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### INCIDENCE

Urinary tract infections (UTIs) are common in children. Approximately 2% of boys and 8% of girls experience at least 1 UTI episode by 10 years of age. Among febrile children of both genders, between 0 and 24 months of age the pooled prevalence of UTI is 7% (95% confidence interval [CI], 5.5%–8.4%).

The susceptibility to a UTI depends on a child's age and gender, with the highest incidence in children younger than 1 year. Boys constitute the majority of infants 6 months of age or younger with a UTI, and UTIs occurring beyond 6 months are most commonly seen in girls. Approximately 30% of children younger than 12 months are affected by recurrent infections

after their first UTI. The recurrence rate depends on the degree of vesicoureteral reflux (VUR); recurrences are more common in children with a higher (grade 3–5) degree of VUR. Most recurrences (85%) occur within 6 months after the primary episode of UTI.

Studies have shown that gender is not associated with risk for recurrence of UTI. In school-aged children, symptomatic UTIs are 5 times more common in girls than boys. Febrile UTIs (pyelonephritis) are more common in children younger than 12 months, whereas the most common presentation for UTI in older children is cystitis. Table 344-1 shows the common causative organisms and incidences of UTI for various age groups. The symptoms of cystitis and pyelonephritis in infants can be nonspecific and therefore difficult to recognize, which may partly explain the higher proportion of severe UTIs in the younger age groups.

### ETIOLOGY

#### Community-Acquired Infections

*Escherichia coli*, occurring naturally in the feces, is responsible for more than 75% of community acquired

**Table 344-1** Common Pathogens and Incidence of Urinary Tract Infection in Different Age Groups

AGE	GENDER	INCIDENCE (%)	COMMON ORGANISM	SYSTEMIC/PYELONEPHRITIS/CYSTITIS/ASYMPTOMATIC BACTERIURIA (%)
0–1 y	Female Male	0.4–1 0.2–0.7	<i>E coli</i> <i>Proteus mirabilis</i> <i>Klebsiella</i> <i>Enterococcus</i> <i>Staphylococcus</i>	4–9/70/30/2.5
1–5 y	Female Male	0.9–1.4 0.1–0.2	<i>E coli</i> <i>Proteus mirabilis</i> <i>Staphylococcus</i>	1–5/60/40/1.5
>6 y	Female Male	0.7–2.3 0.04–0.2	<i>E coli</i> <i>Staphylococcus</i> Sexually transmitted organisms in adolescents	0–4/40/60/0.5–1.0
Cumulative incidence, 0–6 y	Female Male	6.6 1.8	—	—
<b>SPECIAL SCENARIOS</b>				
Myelomeningocele, Spina bifida	—	100%	<i>E coli</i> <i>Pseudomonas aeruginosa</i> <i>Klebsiella</i> <i>Staphylococcus</i> <i>Enterococcus</i> <i>E coli</i>	Asymptomatic bacteriuria 90%
Obstructive uropathy	—	—	<i>E coli</i> <i>E coli</i> <i>Candida albicans</i> <i>Pseudomonas aeruginosa</i> <i>Enterococcus</i> <i>Staphylococcus</i> <i>Klebsiella</i>	—
Immunocompromised patients/those in intensive care units	—	10%–20%/1%		—



UTI cases (see Table 344-1). In neonates, UTIs caused by group B *Streptococcus* are more common, which perhaps reflects the colonization status of the mothers.

Other commonly occurring pathogens are *Klebsiella*, *Proteus*, *Enterococcus*, and coagulase-negative *Staphylococcus*, with each accounting for approximately 3% to 5% of cases. Genotypic analysis of pathogens causing second-time UTIs has shown that 65% of the recurrences are caused by the same pathogen that caused the first episode of UTI. The same bacteria were also found in the feces of patients, suggesting that the colon is a reservoir of uropathogenic bacteria. The prevalence of anatomic abnormalities of the urinary tract is significantly higher among patients with “complicated” UTIs, including those caused by non-*E coli* bacteria or those caused by nonvirulent *E coli* strains. Researchers have speculated that an anatomic or functional abnormality can enhance the invasion of bacteria with low virulence into the urinary tract.

### Non-Community-Acquired and Unusual Infections

Organisms such as *Neisseria gonorrhoeae* and *Chlamydia trachomatis* should be considered as possible causes of UTIs in sexually active adolescents. These organisms most commonly cause lower tract (urethritis) infection. Multidrug-resistant *E coli* strains and non-*E coli* pathogens, including *Candida*, are the most common pathogens causing nosocomial infections. Most of these infections are associated with urinary tract instrumentation or catheterization, which makes critically ill children especially prone to UTI. Fungal infections are significant in patients with compromised immune systems or diabetes. Fungal overgrowth, however, may complicate antibiotic treatment of immunologically normal children with abnormal urinary tract emptying or those with indwelling urinary catheters. Symptomatic viral uropathogens are relatively uncommon except for adenovirus infections in patients with acute hemorrhagic cystitis. Several viruses, including adenovirus, polyomavirus, and cytomegalovirus, can also cause UTI and hemorrhagic cystitis in immunocompromised patients, especially those undergoing solid organ or bone marrow transplantation. Although protozoan infections of the urinary tract, especially schistosomiasis, are important in many parts of the world, they remain uncommon in the United States. Urinary infections with *Mycobacterium tuberculosis* occur rarely in secondary tuberculosis but should be considered when sterile pyuria is found in a suspected clinical setting.

### Pathogenesis

Generally, a UTI occurs when bacteria adhere to the uroepithelium and induce an inflammatory response. Situations that result in urinary stasis, such as obstructive uropathy, voiding abnormality, or constipation, predispose a child to the development of a UTI. Asymptomatic bacteriuria (ABU) is a condition with bacterial growth in urine culture but without symptoms or signs typical for UTI. ABU is generally detected on routine urine screening. Antimicrobial treatment is contraindicated; in fact, treatment may hasten the

development of a symptomatic UTI. Treatment usually includes management of the underlying voiding abnormality. The pathogenesis of UTI is, in most cases, considered to be by ascending route. The invasion of uropathogens may be restricted to the distal part of the urinary tract, causing urethritis or cystitis (ie, lower UTI), or they may reach the upper urinary tract, causing ureteritis and pyelitis or pyelonephritis (or both) (ie, upper UTI). The probability and level of UTI depends on the virulence factors of the bacteria and on the defense mechanisms of the host. Rarely, UTIs in infants are hematogenous (eg, associated with sepsis) rather than ascending in origin.

Bowel and bladder dysfunction (BBD) is known to be a significant risk factor for UTI and recurrent infections. Although detrusor instability is often associated with BBD, infrequent voiding along with large postvoid residual urines are the main causes of recurrent UTI in this group. Children with BBD have a form of rectal and urethral sphincteric dyssynergia resulting in holding both urine and stool. Hence, they are typically constipated and have recurrent UTIs. This can be most reliably identified by a toileting diary and questionnaire. BBD can be treated using cathartics and biofeedback therapy in older toilet-trained children.

### Bacterial Virulence Factors

The uropathogenicity of bacteria depends on the presence of virulence genes, which determine their adhesive capacity and ability to cause tissue damage by toxin production. The expression of these genes varies among different strains. Bacterial adhesion depends on the presence of fimbriae or pili on the surface of the pathogen. Adhesins, which are situated at the tips of the bacterial fimbriae, recognize specific receptors on uroepithelial cells and enable adhesion to these cells. Bacterial toxins also have an important role in inducing inflammation and tissue damage in the host. These factors influence the severity of symptoms, such as fever or dysuria, and the long-term effects of UTI (renal cell damage and scarring). Several *E coli*-derived toxins have been recognized, but their exact role in UTIs remains unclear.

### Host Defense

Local and systemic host defense mechanisms are relatively effective in preventing UTI. Uroepithelium forms a physical barrier against microorganisms. In addition to providing a passive shield, uroepithelium produces antimicrobial proteins and responds to bacterial invasion by activating the immune cascade. Under physiologic conditions, overgrowth of uropathogenic bacteria at the periurethral area is controlled by colonization of low-virulence bacterial strains that are considered to be normal flora. Disturbances in normal periurethral flora can allow enrichment of pathogenic bacteria, leading to their spread into the urinary tract. Most bacteria entering the urinary tract are eliminated by the wash effect of urine flow. Adherence of remaining bacteria is decreased by antibodies (immunoglobulin A) and Tamm-Horsfall protein. Pathogens that survive this first line of defense can later adhere to the urothelium. These

organisms then face the next level of defense mechanism, which is a set of proteins called *defensins*. However, the exact mechanism by which defensins kill the microorganisms is unclear. Once the pathogens cross the mucosal barrier, they may be cleared by the systemic immune defense mechanisms. Local production of inflammatory chemokines and cytokines represents an important defense mechanism of the uroepithelium during acute infection. Abnormalities in any of the defense layers can predispose a person to develop UTI. Frequent bladder emptying, especially relevant in infants, is another important defense mechanism against the development of UTI. Acidic pH and high urine osmolality and urea may also impede the growth of bacteria.

The role of circumcision in preventing UTIs has also been debated. The intact foreskin has been implicated in the cause of UTIs in boys younger than 1 year. Circumcision reduces the risk for UTI. Newborn circumcision has been reported to result in an almost 10-fold decrease in the incidence of UTI during the first year of life. The possible benefits of circumcision can be explained partly by better penile hygiene compared with uncircumcised boys. No clear recommendation about circumcision is currently available; however, it can be considered in boys with recurrent UTIs.

A consensus seems to be emerging that the health benefits of newborn male circumcision outweigh the risks, but the benefits are not great enough to recommend universal newborn circumcision. Therefore, the final decision should be left to parents to make in the context of their religious and cultural beliefs. (See Chapter 89, The Circumcision Decision.)

## EVALUATION

### History

The clinical presentation of a UTI depends on the age of the child, virulence of underlying pathogen, and inflammatory response of the host. Dysuria, frequency, urgency, and lower back pain are the symptoms most often associated with UTIs. However, in young children, especially in infants, the symptoms of UTI are variable and nonspecific. Fever is an important sign in infants and children younger than 2 years. Even a bacteremic UTI can be clinically indistinguishable from other types of infection in very young children. This ambiguity may sometimes lead physicians to think of alternate possibilities, causing a delay in diagnosis and appropriate treatment.

In children older than 5 years, the classic symptoms of a UTI—urgency, frequency, and dysuria—are often present. Children younger than 4 years may not reliably be able to localize pain or report their precise symptoms, although some parents can detect symptoms suggestive of UTI in these children. By age 4 years, a child's capability to report specific symptoms such as abdominal pain or dysuria improves. A UTI should always be considered as a possible cause of unexplained fever and should always be included in the sepsis workup of seriously ill infants and younger children. With some caveats, fever can be used as a rough estimate of the level of UTI. A body temperature less than 38°C (100.4°F) suggests cystitis, whereas a

fever of 38.5°C (101.3°F) or more most often is associated with an upper UTI. In newborns, however, normal body temperature does not exclude the possibility of upper UTI, and the newborn with a UTI may occasionally be hypothermic. Fever can be an inconsistent finding and exists in only approximately 10% to 40% of UTI cases in children younger than 2 years. In these cases, other symptoms such as vomiting, irritability, abnormal crying, lethargy, failure to thrive, and feeding problems should be considered as indications for a urine screening.

### Physical Examination

The physical findings of a child with a UTI vary depending on the severity of the infection and the age of the patient. Especially in infants, the findings are nonspecific and are rarely suggestive of a definitive diagnosis. In addition to fever, other findings suggestive of septicemia, including irritability, abnormal crying, peripheral cyanosis or hypothermia, and prolonged capillary filling time, can be seen in young infants. Tenderness on palpation of the abdomen in the suprapubic region can be found in those with cystitis, whereas costovertebral angle tenderness is elicited in older children with pyelonephritis. However, the absence of these findings does not rule out the possibility of a UTI.

An examination of the urethral meatus should be included in the physical examination of every child with a suspected UTI. In some cases, dysuria can be caused by local inflammation or irritation of the external genitalia. The external genitalia in girls should be examined carefully, given that labial adhesions are often associated with UTIs.

### Laboratory Testing

A correct diagnosis is crucial for the successful treatment and follow-up of a child with a UTI. An incorrect diagnosis of UTI may lead to missing a potentially harmful urinary tract abnormality or to unnecessary studies, costs, and stress. A UTI must be always confirmed by an adequate urine collection for urinalysis and culture.

### Urine Collection

Adequate urine collection is essential for a correct diagnosis. All samples should be collected and stored to prevent contamination and then analyzed carefully. If a febrile child with a suspected UTI cannot provide a clean-catch urine, the urine specimen should be obtained through catheterization or suprapubic aspiration before antimicrobial treatment is started. The diagnosis of a UTI cannot be established reliably through the culture of urine collected in a bag. Sample collection at home is discouraged because of the high risk of contamination. The urine samples should be kept at 39.2°F (4°C) unless a culture is performed less than 1 hour after voiding.

Before micturition, the periurethral area and surrounding skin should be washed and dried properly. When the urine sample is obtained through bladder catheterization or voiding, the first few drops should be allowed to fall outside the sterile container, because they may be contaminated by bacteria in the

### BOX 344-1 Guidelines for Suprapubic Percutaneous Aspiration of Urine

- Indications
  - Verification of urinary tract infection in newborns and infants
  - Sepsis workup in critically ill children
- Equipment
  - 21- to 25-gauge needle
  - 5- to 10-mL syringe
  - lidocaine/prilocaine cream
  - Sterile gloves
  - Portable ultrasonography equipment
- Technique
  - Ensure that there is urine in the bladder, optimally with an ultrasound. Alternatively, careful observation that the child has not voided for at least 45–60 minutes should occur.
  - Put a small amount of lidocaine/prilocaine cream on a circle area (~3 cm) approximately 2–3 cm above symphysis midline; wait about 30 minutes.
  - Set child in a supine position.
  - Clean the patient's skin with antiseptic solution.
  - Insert needle percutaneously at approximately 1 finger's breadth above the symphysis pubis.
  - Advance slowly with continuous suction; usually urine is obtained at the depth of 2–3 cm
- Complications
  - Generally safe and reliable with an experienced operator
  - Occasionally transient hematuria (2%–3%)
  - Intestinal puncture not harmful

distal urethra. The cultures of urine samples collected via bag applied to the perineum have a very high false-positive rate. They are valid only when they yield negative results. In incontinent children, a urine bag or absorbent pad are avoided because of the high risk of contamination. Urine contamination rates are similar for bag and pad (75% of positive cultures) and are significantly higher than for clean-catch urine, catheterization, or suprapubic aspiration. Positive culture results from a urine bag or urine pad sample should always be verified by catheterization or suprapubic aspiration (see Box 344-1 and Box 344-2). A negative culture result from a urine specimen collected by bag or pad does exclude UTI. For toilet-trained children and adolescents, the midstream urine sample is preferred for culture. If the child is critically ill, then suprapubic aspiration or catheterization is preferred in all age groups.

#### Urine Culture

The diagnosis of UTI is confirmed by the growth of a single pathogen on urinary culture and significant pyuria on urinalysis. The bacteria level that is considered significant depends on the method used for urine

### BOX 344-2 Steps for Transurethral Bladder Catheterization

- Restrain the child in the supine and frog leg position, because this position permits adequate stabilization of the pelvis and complete visualization of the external genitalia.
  - Cleanse the anterior urethra thoroughly with povidone-iodine solution.
  - Apply a sterile lubricant jelly to the end of an appropriately sized catheter
- Following are the urinary catheter sizes recommended by age:
- 5 French for children younger than 6 months;
  - 8 French for those between 6 months and adolescence
  - 10 French for adolescents
  - If a topical anesthetic is used, it should be applied 2–3 minutes before the procedure is performed. However, the efficacy of using topical lidocaine to reduce pain during urethral catheterization in children remains uncertain.

#### BOYS

- In uncircumcised boys, retract the foreskin of the glans gently to permit complete visualization of the urethral meatus
- Straighten the urethra by using the nondominant hand to hold the penis perpendicular to the lower abdomen and apply gentle traction.
- Insert the catheter with the dominant hand until urine returns.
- Advance the catheter and continue to palpate it along the posterior aspect of the penis. Maintain traction on the penis, while applying gentle pressure with the catheter. The catheter should never be forced.
- Reduce the foreskin to its normal position so that a paraphimosis does not develop in uncircumcised boys.

#### GIRLS

- The urethra may be difficult to visualize in girls, and an assistant often is needed to retract the labia majora. Have the assistant lift the labia majora anteriorly, laterally, and cephalad. Swab the area from front to back; this may help push this tissue out of the way and permit the povidone-iodine solution to pool in the meatus, thus making identification easier.
- Insert the catheter into the urethral meatus until urine returns.
- Discard the first few drops of urine obtained to prevent contamination of the urine with urethral organisms or cells. This will help decrease the false-positive results on urinalysis for white blood cell counts and bacteria detection.

collection. For voided samples (clean-catch urine, urine bag, and absorbent pad), a bacterial count of 100,000 or more colony-forming units (CFU)/mL is considered significant. Bag and absorbent pad cultures are not accurate and must be confirmed as stated earlier. The new American Academy of Pediatrics (AAP) UTI guidelines indicate that counts greater than 50,000 CFU/mL are diagnostic for UTI. The

contamination risk for catheterization and suprapubic aspirate is considerably lower than for a clean-catch specimen, and therefore any bacterial growth in suprapubic aspirate or a bacterial count of 50,000/mL or more in a catheter sample is indicative of a UTI. Urine cultures showing growth of more than 1 pathogen should be considered as contamination, and a repeat sample is required before starting any treatment.

### Urinalysis

The results of a urine culture are not generally available on the same day that the sample is collected, which may cause a delay in diagnosis. A urinalysis showing leukocyturia can support the diagnosis of UTI. However, a urinalysis is not sufficient by itself to diagnose a UTI, because leukocytes may be present in the urine (pyuria) for several reasons besides UTI.

Pyuria is defined as 10 or more leukocytes/mcL in an uncentrifuged urinary specimen. A count of less than 10 leukocytes/mcL is almost invariably associated with a sterile urine culture, whereas a count of 10 or more leukocytes/mcL is found in 90% of patients with bacterial growth of 50,000 or more CFU/mL. A high urinary leukocyte count is very sensitive (about 95%) but not specific for the presence of a UTI. A UTI can also be an important cause of microscopic hematuria. However, the presence of red blood cells in urine does not have diagnostic or prognostic value. The leukocyte esterase test has a sensitivity of about 83% when used in the context of a clinically suspected UTI. Some studies have reported a lower sensitivity, because the results of leukocyte esterase tests were related to culture without the exclusion of children with ABU. Either a positive leukocyte esterase or a positive nitrate is highly suggestive of a UTI, with a sensitivity of 93% and a specificity of 72%. The combination of leukocyte esterase test and a positive nitrite test does not improve sensitivity (78.7%) but increases the specificity (98.3%). A combination of cell counts and a Gram stain has more sensitivity (87.7%) and specificity (99.2%) when assessing the risk for a UTI. Combining the leukocyte esterase test plus a nitrite test or urine microscopy significantly increases the sensitivity (99.8%). A nitrite test is usually positive if the bacterial counts are high enough (>100,000 CFU/mL). However, there are several reasons why a urinary nitrite test may be negative in the presence of a UTI. First, the chemical reaction (conversion of nitrates to nitrites) requires that urine be present in the bladder for at least 4 hours. In addition, not all organisms convert nitrate to nitrite. Overall, only about 50% of UTIs will feature a positive urine nitrite test.

### Determining the Location of a Urinary Tract Infection

The reliable differentiation of an upper UTI from a lower UTI can be difficult; however, several investigations or findings can help make this distinction. Only 55% to 85% of children with a febrile UTI have changes on radionuclide studies, such as 99m technetium dimercaptosuccinic acid (DMSA) scan, which has been suggested to be the gold standard for diagnosing pyelonephritis. In addition, infants may have an

afebrile bacteremic UTI. However, a fever of 38.5°C (101.3°F) or higher, increased levels of C-reactive protein ( $\geq 40$  mg/L), and leukocytosis should suggest pyelonephritis. Several biomarkers are currently being evaluated as possible indicators for an upper UTI. Procalcitonin is one such marker and has recently been proposed as a possible indicator for pyelonephritis. Increased serum procalcitonin levels have been shown to correlate significantly with renal parenchymal involvement in children with febrile UTI. This method, however, is not currently routinely available or used in the diagnostic testing of UTI. No correlation between the level of UTI and serum electrolyte and creatinine concentrations has been reported. However, these serum electrolytes and creatinine parameters should be measured in febrile infants or children with associated symptoms such as vomiting or diarrhea to assess the level of hydration or other attendant complications.

## IMAGING STUDIES

Children with UTIs are more often found to have anatomic abnormalities in the kidneys or in the urinary tract, such as obstructive disorders and VUR. The highest risks for significant urinary tract abnormalities are in children younger than 1 year and in children with non-*E coli* UTI versus those with *E coli*-associated UTI. Imaging studies of the urinary tract are no longer recommended for all children with a first-time UTI but should be focused on high-risk patients. The imaging studies for UTI include renal and bladder ultrasonography (RBUS), voiding cystourethrography (VCUG), and DMSA scan.

A summary of indications for various imaging studies for children with a suspected UTI is found in Box 344-3. The AAP recommends that infants 2 to 24 months of age with first-time febrile UTI should be studied by means of RBUS. The timing of RBUS can

### BOX 344-3 Indications for Imaging Studies in Children

#### ULTRASONOGRAPHY

- First-time febrile UTI and age 2–24 months (AAP guideline)
- Atypical UTI, all ages (NICE guideline)
- Recurrent UTI, all ages (NICE guideline)

#### VOIDING CYSTOURETHROGRAM

- First-time febrile UTI, abnormal RBUS, complex clinical circumstances and age 2–24 months (AAP guideline)
- Atypical UTI and age <6 months (NICE guideline)
- Recurrent UTI and age <6 months (NICE guideline)

#### DMSA SCAN

- Atypical UTI and age <3 years (NICE guideline)
- Recurrent UTI, all ages (NICE guideline)

DMSA, dimercaptosuccinic acid; NICE, National Institute for Health and Clinical Excellence; RBUS, renal and bladder ultrasound; UTI, urinary tract infection; VUR, vesicoureteral reflux.



be decided based on clinical situation. If fast clinical improvement is achieved, the RBUS can be delayed until full recovery; however, if there is no clear response to treatment within 48 hours, acute RBUS should be performed. This helps in identifying complications such as renal and perirenal abscesses and pyonephrosis. In children 2 to 24 months old, VCUG is indicated when RBUS reveals hydronephrosis, scarring, or other findings suggesting high-grade VUR or obstruction of the urinary tract. When indicated, the VCUG can be done within a week of diagnosis. There are currently no AAP recommendations about imaging studies after UTI in older children and in infants and children with afebrile UTI. Because the probability of imaging studies to reveal factors predisposing the patient to renal damage is relatively low in children older than 2 years and in children with uncomplicated UTI, the indications for imaging studies are therefore scarce. These factors could be recurrent UTI, non-*E coli* infection, or a positive family history. The present recommendations may change when the results of ongoing multicenter studies in the United States and other countries are available.

### Renal and Bladder Ultrasound

The RBUS is the least invasive and most widely available imaging modality that can be performed during the acute phase of a UTI. It can detect dilated collecting system, thinning of kidney parenchyma, the size of the kidneys, and the thickness and size of the urinary bladder. However, ultrasonography may not be able to detect VUR or smaller renal scars. The reliability of ultrasonography is highly dependent on the experience of the radiologist. The need for ultrasonography after UTI has been questioned. It has been suggested that ultrasonography results may have little or no influence on the treatment of children with UTI because of routine prenatal ultrasonography. The widespread use of maternal-fetal ultrasonography in industrialized countries has possibly lessened the need for ultrasonography later in childhood. However, several studies have shown that a significant kidney or urinary tract abnormality may be missed in spite of a prenatal RBUS in 5% to 6% of the children with a first-time febrile UTI and that abnormal RBUS predicts risk for renal scarring. These findings suggest that the RBUS will probably continue to play a major role as a primary imaging study after first-time febrile UTI in children.

### Voiding Cystourethrography

VCUG is traditionally used to diagnose VUR, which predisposes patients to pyelonephritis and recurrent infections and may be associated with renal scarring. VUR is graded from I to V (Box 344-4). The incidence of VUR is highest in children younger than 2 years. A VCUG can be performed using either radiopaque medium or radiolabeled nuclides. A contrast voiding cystography is usually preferred in boys because it is more reliable than other methods in detecting urethral valves, and it allows more exact grading of reflux. Cystography requires catheterization, which is relatively invasive and stressful, especially in older children. Cystography exposes children to radiation, and it is

relatively laborious and costly. Moreover, evidence suggests that a low-grade VUR (grade < 3) itself is not a significant risk factor for renal damage and that antimicrobial prophylaxis is not effective in preventing renal damage in children with VUR. For these reasons, the use of cystography has dramatically decreased in recent years. According to the current AAP recommendation, VCUG should not be performed on a routine basis after a first febrile UTI. It should be performed in children 2 to 24 months old if RBUS shows evidence of hydronephrosis, scarring, or other findings that would suggest either high-grade VUR or obstructive uropathy. The National Institute for Health and Clinical Excellence (NICE) guideline from the United Kingdom has restricted cystography only to children less than 6 months old with atypical UTI (dilation on ultrasound, poor urine flow, non-*E coli* infection, family history of VUR). A VCUG should, however, be considered in children presenting with complex clinical circumstances. VUR spontaneously resolves in a high proportion of children, especially in those with grades I–II VUR; hence, isotope voiding cystography is recommended every 1 to 3 years until resolution of VUR is documented. VCUG should be considered if there is a positive family history of VUR, if the urinary tract dilation is detected prenatally, or there is a history of complicated or recurrent pyelonephritis.

### Dimercaptosuccinic Acid Scan

One of the most reliable methods to differentiate pyelonephritis from lower UTI is a DMSA scan. DMSA is a radionuclide that is taken up by renal tubular cells and provides information on functional anatomy as well as scarring of renal parenchyma. It is more often abnormal in patients with documented reflux than in children without VUR. Based on these results, some authors, including the authors of the NICE clinical guideline, suggest that the DMSA scan should be performed 4 to 6 weeks following the first-time UTI in all children younger than 3 years with atypical UTI or recurrent UTIs and in children older than 3 years with recurrent UTIs. Recurrent UTI has been defined as 2 or more episodes of upper UTI, or 1 episode of upper UTI plus 1 or more episodes of lower UTI, or 3 or more episodes of lower UTI. This approach has likely reduced the number of VCUGs performed by

#### BOX 344-4 International Classification of Vesicoureteral Reflux

- Grade I: involves only ureters
- Grade II: involves ureters and intrarenal collecting systems
- Grade III: mild ureteral and pelvic dilatation; no or slight obliteration of caliceal fornices
- Grade IV: moderate ureteral and pelvic dilatation; clear obliteration of caliceal fornices
- Grade V: gross dilation of ureters and renal pelvis and calyces

approximately 50% without adding any major risk for the patient. The AAP guideline does not recommend a routine DMSA scan after the first UTI in children.

## TREATMENT

The cornerstones of the successful treatment of a UTI are early recognition and early, appropriate treatment. Before initiating treatment, adequate samples of urine should be collected for culture and for determining the antibiotic sensitivities of the organisms. If the patient has sepsis or dehydration, then adequate rehydration should coincide with antibiotic therapy. The route of antibiotic administration (oral or parenteral) depends on the age and clinical condition of the patient (Figure 344-1).

### Pyelonephritis

Infants younger than 1 year are usually hospitalized and treated with parenteral antibiotics followed by oral antibiotic therapy for a total of 14 days. However, oral antibiotics (for patients who can tolerate them) are as effective as parenteral antibiotics even in young children with a febrile UTI. Hence, if the child with a UTI does not seem to have sepsis and is able to tolerate oral medications, initial treatment with an oral antibiotic might possibly be appropriate. However, follow-up is essential to ensure complete recovery. Infants younger than 2 months should be hospitalized in all instances.

### Cystitis

Assuming adequate liquid intake and an ability to tolerate antibiotics, oral therapy alone is usually adequate to treat cystitis. The first-line therapy for outpatient treatment of a UTI usually consists of amoxicillin plus clauvalunnic acid, cephalosporin, or trimethoprim-sulfamethoxazole (TMP-SMX). It is important to know the sensitivity patterns of common UTI-causing organisms in a given geographical area in order to select the most effective initial agent before sensitivity results are available from urine culture. The suggested dosing is shown in Table 344-2; 5 days of treatment with appropriate antibiotics is adequate for children younger than 2 years who are afebrile and have uncomplicated cystitis.

### Asymptomatic Bacteriuria

Studies involving infants and schoolgirls have shown that untreated ABU does not increase the risk for pyelonephritis or renal damage. In fact, children treated with antibiotics for ABU can have a higher incidence of pyelonephritis than untreated children. Researchers have suggested that pathogens causing ABU have low virulence, which may protect against an overgrowth of uropathogenic bacteria. Current recommendations are that it should not be treated with antibiotics. Children who undergo intermittent catheterization or those with neurologic bladder dysfunction frequently have ABU, but are asymptomatic and often do not have leukocyturia.

### Prophylaxis

Prophylactic antibiotics are no longer recommended for all children after their first UTI. The efficacy of prophylactic antibiotics has been questioned based on recent reports showing that use of low-dose

antimicrobial treatment does not necessarily reduce the number of recurrent infections or protect against renal scarring. On the contrary, the prolonged use of antimicrobials may lead to development of bacterial resistance. Prophylaxis should be considered for children with an increased risk of UTI; that is, children with higher grades of VUR (grades III–V), especially with bowel and bladder dysfunction or obstructive uropathy and previous history of UTI or recurrent UTIs (3 febrile UTIs/6 months or 4 total UTIs/year). The most common prophylactic regimen is of cotrimoxazole (TMP-SMX [2 mg of TMP and 10 mg of SMX/kg/day]) or nitrofurantoin (1–2 mg/kg/day) as a single daily bedtime dose. The duration of prophylaxis depends on the indication. In children with VUR, especially older children, the prophylaxis is usually continued until reflux has resolved or has been surgically corrected and the child has been free of symptoms and bacteriuria for at least 1 year.

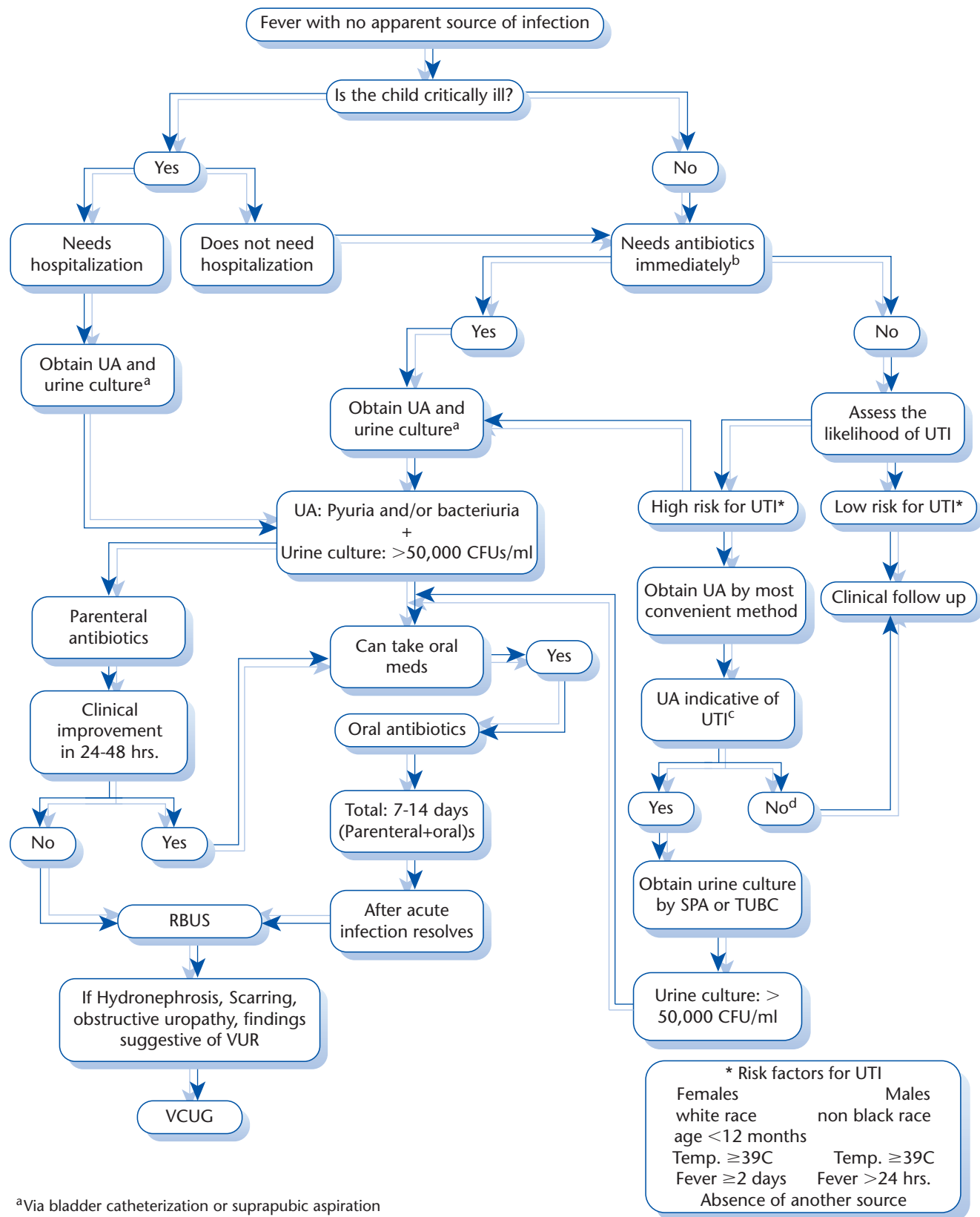
### Supplemental Therapy

Constipation and encopresis are known to be risk factors for UTI and should be especially anticipated in children with recurrent UTI. Treatment of these problems by behavioral and dietary modification or medication is important to prevent recurrent UTIs. Besides constipation, the role of circumcision in preventing UTI has also been studied. Although the relative risk of UTI in uncircumcised male infants compared with circumcised male infants is increased from 4-fold to as much as 10-fold during the first year after birth, the absolute risk of developing a UTI in an uncircumcised male infant is low (at most, approximately 1%). Currently, the health benefits are not great enough to recommend routine neonatal circumcision.

## COMPLICATIONS—RENAL SCARRING

Isotope uptake studies (DMSA scans) have shown that the renal parenchyma is affected in approximately 55% to 75% of children with a febrile UTI. Approximately 15% to 40% of these children will develop permanent renal parenchymal damage; that is, renal scarring. In a recent meta-analysis of 33 published studies, of all children with an initial episode of UTI, 57% had changes consistent with acute pyelonephritis on the acute-phase DMSA renal scan and 15% had evidence of renal scarring on the follow-up DMSA scan. VUR is a major determinant of the development of renal scars. Children with VUR were significantly more likely to develop pyelonephritis (relative risk [RR], 1.5 [95% CI, 1.1–1.9]) and renal scarring (RR, 2.6 [95% CI, 1.7–3.9]) compared with children with no VUR. Children with VUR grades III or higher were twice as likely as children with lower grades of VUR to develop scarring.

In some cases, renal disease may be congenital rather than acquired and therefore not dependent on UTI. In an analysis of 1,221 children with a first-time UTI, the incidence of permanent renal damage was 86% in boys and 30% in girls. The mean age of boys at the time of a UTI was significantly lower compared with girls, and VUR was present in 67% of the boys and in only 19% of the girls. Infants (mean age, 4 months) with high-grade VUR without a UTI have been shown to have fewer scars than patients with VUR



**Figure 344-1** Diagnosis and Management of the Initial UTI in Febrile Infants and Children of age 2 to 24 Months

**Table 344-2****Antibiotics for Treatment and Prophylaxis in Children With Urinary Tract Infection**

DRUG	TREATMENT REGIMEN	PROPHYLAXIS REGIMEN
<b>PARENTERAL THERAPY</b>		
Ampicillin	100 mg/kg/d divided every 6 h	—
Amikacin	15–22.5 mg/kg/d divided every 8 h	—
Ampicillin-sulbactam	100–200 mg/kg/d ampicillin divided every 6 h	—
Cefepime	100–150 mg/kg/d divided every 8 h	—
Cefotaxime	100–150 mg/kg/d divided every 8 h	—
Ceftazidime	100–150 mg/kg/d divided every 8 h	—
Gentamicin	5–7.5 mg/kg/d divided every 8 h	—
TMP-SMX	8–12 mg/kg/d TMP with 40–60 mg/kg/d SMX divided every 12 h	—
<b>ENTERAL THERAPY</b>		
Amoxicillin	30–40 mg/kg/d divided every 12 h	10–15 mg/kg once daily at bedtime
Amoxicillin-clavulanate	30 mg/kg/d divided every 12 h	25 mg/kg once daily at bedtime
Cefixime	8–16 mg/kg/d once daily or divided every 12 h	—
Cephalexin	40–50 mg/kg/d divided every 6–8 h	12–15 mg/kg once daily at bedtime
Cefpodoxime	10 mg/kg/d divided every 12 h	—
Methenamine mandelate	40–50 mg/kg/d divided every 8–12 h	—
Nitrofurantoin	5–7 mg/kg/d divided every 6 h	1–2 mg/kg once daily at bedtime
Sulfisoxazole	150 mg/kg/d divided every 6 h	50 mg/kg once daily at bedtime
TMP-SMX	6–12 mg/kg/d TMP with 10 mg/kg SMX once daily at bedtime	2 mg/kg TMP with 30–60 mg/kg SMX divided every 8–12 h

TMP-SMX, Trimethoprim-sulfamethoxazole.

Adapted from American Academy of Pediatrics Subcommittee on Urinary Tract Infection and Steering Committee on Quality Improvement and Management. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics*. 2011;128:595–610.

and a history of UTI. In children with high-grade VUR, UTI, and renal damage, determining the exact contribution of congenital factors, reflux, and infection to renal dysfunction may be difficult. The risk factors for renal parenchymal damage include gross VUR, young age at the time of first infection, delayed initiation of treatment, and recurrent infections.

### LONG-TERM EFFECTS OF URINARY TRACT INFECTION

A UTI is generally considered an infectious disease with a very good prognosis. If no renal abnormalities are found in imaging studies performed after a first childhood UTI, it appears unlikely that subsequent childhood UTIs will cause chronic kidney disease later in life. Although most children with UTIs have no long-term consequences, several sequelae can be associated with UTIs. A small risk exists of permanent renal damage, which may increase the risk of hypertension and ultimately cause varying degrees of renal failure. A UTI may also increase the risk of pre-eclampsia during pregnancy. The risk for end-stage kidney disease, however, is relatively small in children with UTI without structural anomalies. According to the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) ([www.naprtcs.org](http://www.naprtcs.org)), which collects data on pediatric patients with renal failure in the United States, pyelonephritis (without known structural disease) or interstitial nephritis accounts for renal failure in only 1.8% of all patients who require renal transplantation. The respective numbers

for obstructive uropathy, renal hypoplasia or dysplasia, and reflux nephropathy are 16.1%, 16%, and 5.2%, indicating that anatomic abnormality with or without UTI is a more important threat to kidney function than the UTI itself. Hypertension remains an uncommon and important long-term complication of childhood UTI, but its incidence may be lowered by careful attention to risk factors and early treatment. Bacteriuria and symptomatic UTI are significantly more common in pregnant women with a history of childhood UTI. A UTI may also contribute to increased risk for pre-eclampsia (hypertension and proteinuria) and may be harmful for the fetus and cause premature labor.

#### WHEN TO REFER

- Abnormal findings on imaging
- VUR
- Frequently relapsing UTIs
- Suspicion of voiding dysfunction
- Renal insufficiency (elevated creatinine)
- Hypertension

#### WHEN TO ADMIT

- Suspected urosepsis
- Infant younger than 3 months with UTI
- Suspected UTI in dehydrated patient or patient unable to retain oral fluids
- Patient whose symptoms worsen or do not improve despite oral treatment



## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Care of the Uncircumcised Penis* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Urinary Tract Infections in Children* (Web page), National Institute of Diabetes and Digestive and Kidney Diseases ([kidney.niddk.nih.gov/KUDiseases/pubs/utichildren/index.aspx](http://kidney.niddk.nih.gov/KUDiseases/pubs/utichildren/index.aspx))
- *Urinary Tract Infections in Young Children* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

## AAP POLICY

American Academy of Pediatrics Subcommittee on Urinary Tract Infection and Steering Committee on Quality Improvement and Management. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics*. 2011;128:595–610 ([pediatrics.aappublications.org/content/128/3/595](http://pediatrics.aappublications.org/content/128/3/595))

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## SUGGESTED READINGS

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## Chapter 345 VERRUCAE (WARTS)

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## VERRUCAE (WARTS)

Verrucae (warts) are virally induced tumors of the skin. They are a frequent cause of physician office visits. Cutaneous warts affect up to 10% of children between 2 and 12 years of age and rank among the top 3 dermatoses in this age group, with no gender

predilection. Genital warts are uncommon in children before puberty but represent one of the most common sexually transmitted infections in adolescents and adults.

### Etiology

The wart virus is a human papillomavirus (HPV) that infects epidermal cells and causes focal epidermal proliferation, expressed clinically as a verrucous papule.

More than 100 types of HPV have been characterized, and the number continues to grow. Specific types have been associated with specific warts. For example, HPV types 1 (HPV-1), 2, and 4 are found in plantar warts; HPV-2 and HPV-7 in common warts; HPV-3 and HPV-10 in flat warts; HPV types 1, 6, and 11 in benign genital warts; HPV types 6, 7, 11, 16, and 32 in laryngeal papillomas; and HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 in genital warts that have malignant potential (eg, cervical carcinoma). Thus, HPV typing holds promise in helping identify premalignant warts, as well as sources of the transmission of warts.

### Epidemiologic Features

The wart virus is presumably inoculated into the skin from some external source, but usually neither the source nor event of inoculation is elicitable. Frogs and toads have been unfairly incriminated as carriers. However, asking about and searching for warts on other areas of the body is reasonable; for example, patients who have warts on their lips often have them on their fingers. Given that warts are transmissible, other family members may also have them.

In young infants, warts (including those in laryngeal and genital locations) are assumed to have been acquired from the mother's vaginal tract during delivery. Genital warts in children can raise the question of sexual abuse. No clear age exists below which sexual abuse is not a concern; however, several recent studies of anogenital warts in children found no evidence of sexual abuse in most of the subjects younger than 3 years. Based on HPV typing, anogenital HPV infection in most infants seems to be acquired either by nonsexual transmission or perinatally. In fact, a study demonstrating a high incidence of HPV-2 in anogenital warts in prepubertal children suggested that innocent autoinoculation or heteroinoculation from cutaneous warts may be a common means of acquisition. Evidence also exists pointing to the possibility of in utero transmission of HPV, although the exact mechanism (hematogenous, infected semen at fertilization, ascending maternal infection) is unclear. A complete social history and thorough physical examination may be helpful in determining the need for evaluation for possible sexual abuse.

Patients who have systemic defects in cell-mediated immunity are more susceptible to warts, which are often recalcitrant to treatment. In addition, because cellular immune responses in the skin are impaired with atopic dermatitis, these patients, too, have more difficulty with warts and other viral infections of the skin.

### Prevention

Gardasil, a vaccine for HPV types 6, 11, 16, and 18, which together cause 70% of cervical cancers and

90% of genital warts, was approved by the US Food and Drug Administration (FDA) in June 2006 for use in female patients 9 to 26 years of age. In October 2009, it was then approved for use in male patients 9 to 26 years of age to prevent genital warts resulting from HPV types 6 and 11. It is administered 3 times over a 6-month period. The question about whether it should become mandatory or remain voluntary is currently being addressed at the state level.

### Clinical Findings

#### Physical Findings

The clinical appearance of warts varies, depending on the type and location. The common wart, or *verruca vulgaris*, is easily recognized as a superficial, light-colored papule that has a coarse, roughened surface. Warts are often studded with black specks, which many patients call *seeds*, but which are actually small, superficial dermal capillaries. Warts are sometimes found in linear array, presumably as a result of autoinoculation through scratching. Not all warts appear as verrucous papules. Variants include flat (planar) warts, plantar warts, periungual warts, and anogenital warts.

#### Laboratory Findings

Warts are almost always diagnosed clinically. If doubt exists, then a skin biopsy can provide histologic confirmation.

#### Differential Diagnosis

The distinctive clinical appearance of the common wart usually presents no problem in diagnosis. Although epidermal nevi, which are hamartomas, may be confused with warts, they are usually softer, more pigmented, more persistent, and much less common. Flat (planar) warts appear as small, flesh-colored papules (Figure 345-1). When located on the face, flat warts are often confused with the closed comedones (whiteheads) seen in acne. On very close inspection, however, flat warts are seen to have sharp borders and a finely verrucous surface, whereas closed comedones are smooth, dome-shaped lesions.



**Figure 345-1** Flat warts. Flat warts may be confused with comedones.

Plantar warts are so named because they appear on the plantar surface of the foot (Figure 345-2). They are often confused with calluses and corns, although corns are much less common in children than are warts. Large plantar warts are often composed of confluent smaller warts, which form a mosaic wart surrounded by satellite lesions. Additionally, plantar warts differ from corns by having a verrucous surface that interrupts skin markings and are often punctuated with black specks. In some cases, the 2 entities can only be distinguished by paring down the surface; wart tissue still has a roughened texture, whereas a corn is smooth. A corn also becomes smaller in diameter as it is pared; a wart does not.

Periungual warts that occur around the nail fold should not pose diagnostic difficulty. Warts under the free edge of the nail, however, can cause the nail plate to separate from the nail bed and may be confused with a fungal infection. On close inspection, the verrucous nature of the wart usually can be appreciated.

Anogenital warts (*condylomata acuminata*) are sometimes, but not always, acquired by sexual contact. They can usually be easily identified as verrucous papules (Figure 345-3), but they are sometimes small or flat and, therefore, more difficult to see. In this situation, the acetowhitening technique can aid in the diagnosis. A compress containing 5% acetic acid is applied for several minutes to the suspected area, which is then reexamined, ideally under magnification. With this technique, warty tissue turns white and thus is visualized more easily.

Genital warts may be confused with the less common *condylomata lata*, skin lesions found in secondary syphilis. In general, *condylomata acuminata* are drier and usually more verrucous than *condylomata lata*, which are flat and moist. If doubt exists, then a serologic test for syphilis can confirm the diagnosis.

### Psychosocial Considerations

Among school children, warts are often a focus for teasing and insensitive remarks. Consequently, when children ask that their warts be treated, they usually



**Figure 345-2** A mosaic plantar wart with a roughened surface punctuated with black specks.

do so because of social pressure. Successful therapy gives patients the opportunity to feel better about themselves and their appearance.

### Management

Over the years, a wide variety of treatments have been recommended, including some interesting unproven approaches, such as applying banana peels or slices of raw potato, which probably seem to work because most warts eventually regress spontaneously. One prospective study of untreated common warts in children showed that two-thirds of the warts underwent spontaneous regression within 2 years. This finding must be kept in mind when physicians credit their treatment for a successful result. Nonetheless, when a patient requests treatment of a wart, physicians are usually inclined to oblige. However, because a specific antiviral medication for warts has not yet been developed, physicians still rely on nonspecific destructive techniques as therapy; the following techniques are used most often.

### Cryotherapy

Tissue is frozen by applying liquid nitrogen ( $-195^{\circ}\text{C}$ ) to the wart either with a swab or through a canister delivery system. The freeze should extend beyond the wart to include a 1- to 2-mm rim of normal skin. To destroy affected tissue more effectively, the wart may be refrozen after the initial thaw. The patient must be advised that the frozen area will be sore for several days, a blister may form, and several weeks are usually needed for the wart to turn dark and drop off. Cryotherapy is a frequently used office therapy for common warts. For small warts, a single treatment is often successful, but large warts frequently need to be refrozen approximately every 3 weeks. Scars may result, but are uncommon. The skin may also become

hypopigmented. When freezing warts on the fingers, care must be taken to avoid freezing too deeply because underlying structures such as digital nerves can be damaged. Over-the-counter freezing treatments are now available, but these products may not be as effective as liquid nitrogen.

### Keratolytic (Acid) Therapy

Acid therapy is slower and involves more patient participation than freezing, but it is less immediately painful and is least likely to cause scarring. A variety of acids are available for treating warts. Salicylic acid is available as a solution in 26% (Durasal) and 27.5% (Virasal) concentrations. A convenient outpatient medication incorporates 17% salicylic acid in a polyacrylic or flexible collodion vehicle (Occlusal-HP, Duo-film). The vehicle dries rapidly to prevent spread of the acid onto surrounding skin. The patient is instructed to apply the medication to the wart at bedtime and to cover the area with thick tape. Superficial necrotic tissue should be pared daily, with either a pumice stone or, for thick palmar or plantar warts, a callus grater. The latter warts often require a stronger acid, such as a 40% salicylic acid plaster. These products can be bought over the counter (Mediplast and Duofilm patches), but patients need instruction in application. A piece of plaster is cut to match the size of the wart, and its adhesive, medicated side is applied to the wart and held in place with tape. The plaster is changed every 24 hours and the macerated wart pared daily, as previously described.

Flat warts are often treated successfully with topical adapalene (Differin), tretinoin (Retin-A), or imiquimod (Aldara, Zyclara; see later discussion), applied nightly to the entire affected area. In this situation, these products probably act as *peeling* agents. Painful irritation may occur, necessitating less frequent use.

These home acid therapies usually require at least 1 month of continuous use to be effective. If no progress has been made after several months, then other treatments should be considered. For deeply seeded warts, paring followed by a combination of acid and cryotherapy usually provides successful treatment. Caustic acids such as trichloroacetic acid at concentrations of 30% to 100% are reserved for office treatment of palmar or plantar warts. These acids must be carefully applied because they can cause destruction of normal tissue as well. Cantharidin is a protein phosphatase inhibitor produced by the Spanish fly, *Lytta vesicatoria*. It penetrates the epidermis and causes acantholysis, resulting in vesiculation and destruction of infected keratinocytes. Cantharidin can be used for almost all nongenital warts. Reapplication may be required at 1- to 3-week intervals. It has the advantage of being painless when initially applied and causes little risk for scarring. Occasionally, a ring wart will develop at the edge of the treated site.

All of these treatments are nonspecific, and none are foolproof. In some instances, different modalities are used in sequence. Although warts commonly regress spontaneously, the time required for this varies considerably. In some patients, therapy may only serve to appease the patient while nature takes its course. In other patients, the destructive techniques may initiate an



**Figure 345-3** Condylomata acuminata appear as skin-colored papules and plaques.



inflammatory reaction, exposing the wart viral antigen to the body's immune system, which finally rejects the wart. This reaction may explain the occasionally observed phenomenon that by treating the mother wart, the baby wart goes away. In any event, whenever warts are treated, the pediatrician must consider the risk-benefit ratio of therapy. Accordingly, surgical excision is usually discouraged, and radiotherapy is contraindicated.

### Immunotherapy

Imiquimod cream (in 5% [Aldara] or 3.75% [Zyclara] concentrations) is an immunomodulator that augments cellular immunity by inducing a variety of cytokines. It can be self-administered daily or every other day and should be left on overnight. Controlled, multicenter trials have evaluated its role in treating genital warts, but trials will soon be underway for common warts as well. In addition, some smaller studies and case reports are already suggesting its potential as an alternative treatment, either alone or in combination with other modalities, such as cryotherapy and salicylic acid. Imiquimod's mechanism of action may also make it especially useful in treating nongenital warts in immunosuppressed patients.

Sensitization to squaric acid is another therapeutic option. It is available as squaric acid dibutylester in acetone (SADBE) in concentrations of 0.5% and 1% for home use, and 2% for office use. The solution is first applied in the office to a small area (usually the inner arm), usually causing no reaction, or occasional mild redness. Then 2 weeks later, it can be applied at home with a cotton-tipped applicator to the lesions. It can be applied 3 times a week, then gradually increased by 1 night a week on a weekly basis as tolerated. Usually improvement is seen by 3 weeks and clearance by 7 weeks. Complete clearance rates range from 58% with home use, to 68% with in-office use, to 86.2% with in-office application after 70% salicylic acid in petrolatum use at home before therapy. This treatment is absolutely contraindicated in vitiligo because it can exacerbate the associated depigmentation.

Intralesional therapy involving sensitization to antigens, such as *Candida*, mumps, or *Trichophyton*, is another technique used by dermatologists when topical therapies fail. Studies have demonstrated response rates ranging from 54% to 87% in treated warts and 34% to 78% in untreated, distant warts.

### Electrodesiccation and Laser Therapy

Electrodesiccation of a wart can be preceded or followed by curettage. One advantage of this technique is that the patient leaves the office without visible evidence of the wart, although the cure rate is probably no higher than with cryotherapy. The disadvantages are that (1) the procedure requires local anesthesia, and (2) scarring is more likely. The carbon dioxide laser can be used to destroy large or refractory warts, but the risk for scarring is significant. The pulsed dye laser, which destroys the vascular component of the wart, may become another alternative, with less risk for scarring. It is used for some recalcitrant warts, particularly in palmar, plantar, periungual, and anogenital areas.

### Other Treatments

A recent study showed that duct tape occlusion therapy was significantly more effective than cryotherapy in treating nongenital warts.

The efficacy of oral cimetidine in the treatment of warts is still controversial. It may be useful in the treatment of flat warts. Use of oral cimetidine in other types of warts is under investigation.

Zinc can function as an immunomodulator, and its deficiency causes lymphopenia. Two studies in zinc-deficient patients with warts suggest that oral zinc sulfate may be an effective, inexpensive, and painless therapeutic alternative. Additional controlled studies in nondeficient patients are needed to confirm its therapeutic efficacy.

Phototherapy uses topical photosensitizing agents, most commonly 5-aminolevulinic acid (ALA), followed by exposure to light, which causes accumulated porphyrins to unleash a photooxidation cascade that destroys treated cells. In randomized controlled trials investigating it for recalcitrant palmar and plantar warts, cure rates ranged from 56% to 75%. It also demonstrated 94.4% clearance of facial warts in one study.

### Treatment of Genital Warts

Although condylomata in children are usually asymptomatic, they may be treated to curtail their spread and allay parental concerns. Some forms of therapy may be painful, and recurrence rates may be as high as 50%. Weighing the risks versus the benefits is wise before treating genital warts in children.

Two therapeutic options for condyloma have been approved by the FDA in adults, and case reports with children have shown promise—imiquimod (described previously) and podophyllotoxin. Podophyllin is derived from the mayapple plant and is available in 10% to 25% solutions in alcohol or benzoin. It is exclusively for office use. Podophyllin is painless when applied but can be toxic if used over large areas. It must be washed off within 6 to 8 hours of application. Podophyllin is also marketed as purified 0.5% podophyllotoxin (Condylox) solution or gel. Podophyllotoxin has also been shown to be effective in case reports involving children and infants. It is available for home use but can be very irritating for some patients.

A third therapeutic option, sinecatechins, has been approved by the FDA for adults, but its use in children has not yet been reported in the literature. Sinecatechins is a partially purified fraction of the water extract of green tea leaves from *Camellia sinensis* (L.) O Kuntze and is a mixture of catechins and other green tea components; it is thought to have antioxidant, antiviral, and antitumour activity against warts. It is marketed as an ointment (Veregen) that should be applied 3 times a day for up to 16 weeks. Other options for treatment of condylomata include cryotherapy, lasers, caustic acids, and cimetidine.

### Complications

The major complications of warts are those caused by overzealous therapy, resulting in short-term discomfort or scarring. The annoyance of the presence of a wart, which is usually temporary, must be balanced



against the inconvenience of a scar, which is usually lifelong, may be unsightly, and is sometimes tender, particularly if present on a pressure-bearing surface such as the sole of the foot.

### Prognosis

Most warts eventually involute spontaneously, probably through immunologic rejection. Because the time required for involution varies greatly, predicting when it might occur for an individual patient is impossible. The goal of therapy, then, is to shorten the time required for the wart to disappear. The therapies outlined in this chapter result in clearing in most cases; but patients who have resistant, persistent warts will continue to be plagued by them. More specific therapy is needed for these patients especially, and these patients may benefit from an evaluation by a dermatologist.

## MOLLUSCUM CONTAGIOSUM

Since the eradication of smallpox, molluscum contagiosum is the only poxvirus infection that specifically affects humans. Similar to warts, molluscum lesions are virally induced tumors of the skin. In children, molluscum contagiosum is a common, benign, self-limited process.

### Etiology

Molluscum contagiosum is caused by molluscum contagiosum virus (MCV), a large double-stranded DNA virus of the *Molluscipoxvirus* genus. Four subtypes of the virus have been identified. Although most cases of infection are caused by the first subtype, MCV-1, the subtypes are clinically indistinguishable.

### Epidemiologic Features

In the United States, fewer than 5% of children demonstrate MCV infection, with approximately 80% of cases occurring in children younger than 8 years. Gender distribution is equal. It is spread by contact, through skin-to-skin contact (eg, certain sports, sexual activity), fomites (eg, sponges, towels, beauty parlors, heated public pools and baths), or autoinoculation. Of note, patients with impaired cell-mediated immunity have increased incidence and severity. Examples include HIV-positive patients (although incidence has been somewhat controlled with the success of highly active antiretroviral therapy [HAART]), patients with atopic dermatitis, and patients receiving immunosuppressants.

### Physical Findings

The lesions of molluscum contagiosum are discrete, dome-shaped, umbilicated, waxy papules, and their color can be skin colored, pink, or white. Their translucence may cause them to resemble vesicles. The lesions may also resemble milia or skin tags. Their diameter usually does not exceed 5 mm, although they can sometimes be as wide as 15 mm (ie, giant molluscum). Lesions may occur anywhere on the body, although the most common locations are the axilla, sides of the trunk, lower abdomen, thighs, and face. Although genital molluscum contagiosum in young children do not necessarily indicate sexual abuse, it should be considered.

### Laboratory Findings

Molluscum contagiosum is usually diagnosed clinically. If the diagnosis is unclear, then a skin biopsy can confirm it.

### Differential Diagnosis

The diagnosis of molluscum contagiosum is generally straightforward. However, it may occasionally be mistaken for verrucae, varicella, folliculitis, furunculitis, milia, juvenile xanthogranuloma, spitz nevi, and skin tags.

### Management

#### Active Nonintervention

Some lesions resolve spontaneously within a few weeks, although the average lesion takes 2 to 3 years to clear, with some lesions taking up to 5 years. For most active children, avoiding situations that promote spread and proliferation is sufficient. Behaviors to avoid include excoriating lesions, walking barefoot in public places, and sharing personal items such as towels and sponges. However, if lesions are numerous or persistent, or if new lesions continue to appear, then therapeutic intervention can be helpful. In the case of periocular molluscum contagiosum, the risk for iatrogenic injury justifies active nonintervention unless symptomatic conjunctivitis is present, when surgical removal under general anesthesia is merited.

#### Tretinoin

The ability of topical tretinoin to induce local inflammation has also been helpful in treating molluscum contagiosum, although controlled trials are needed to confirm its efficacy. It can be applied daily for 2 to 3 months, and it can be used safely on the face and other sensitive areas. Side effects are usually mild and include site irritation, dryness, and photosensitivity; thus, patients should be advised to wear sunscreen and limit sun exposure while using tretinoin.

#### Duct Tape

Duct tape can be used for recalcitrant molluscum contagiosum. It can be cut to the size of each lesion and applied (and reapplied if needed) until all lesions have cleared. Duct tape is an attractive treatment option because it is affordable, available over the counter, nondestructive, and painless (or minimally painful), and it can be used at home, reducing the need for office visits. Controlled studies comparing it with conventional treatments are needed to further establish its efficacy.

#### Cantharidin

Cantharidin, a vesiculating agent derived from the Spanish fly, is a helpful in-office treatment for molluscum contagiosum lesions. Although it has not been approved by the FDA, cantharidin has been recommended by the FDA's Pharmacy Compounding Advisory Committee for inclusion as a compounded medication to be used in physicians' offices since 1998. Local pharmacies may compound the 0.7% solution, or it can be obtained in compounded form by several American and Canadian manufacturers. Cantharidin is administered in the office using the blunt wooden end of a cotton-tipped swab and applied sparingly to the lesions. It should be rinsed

off with liberal amounts of water in 4 to 6 hours, or sooner if the patient complains of pain or if vesiculation occurs. Cantharidin may be reapplied in 2 to 4 weeks. In a recent study involving 300 children with molluscum contagiosum treated with cantharidin, 90% had clearance of their lesions after an average of 2 treatment visits, and an additional 8% had improvement of their lesions. The most common side effects were related to site irritation. Experts have suggested that occlusion with translucent tape 5 minutes after cantharidin application can enhance clearance of persistent lesions; the tape can be removed when blistering or soreness develops. On rare occasions, patients may have an exaggerated response with large blister formation. Some experts recommend that every patient have a test dose of the agent to a few lesions and wait up to a week to assess the response before proceeding to treat extensive areas. Some patients never get blisters—just irritation and erythema. Because cantharidin can cause hyperpigmentation or hypopigmentation, it is not recommended for use on facial lesions.

### **Podophyllin**

Podophyllin 25% solution acts as a keratolytic. It is applied in the office sparingly to lesions and should be washed off within the first 6 hours of treatment to minimize site irritation. Podophyllin can be reapplied weekly for up to 4 weeks. Controlled studies are needed to establish its efficacy in comparison to other treatment modalities.

### **Cryotherapy**

A light freeze with liquid nitrogen can be helpful in treating older children with a small number of large lesions. Treatment may need to be repeated in 2 to 4 weeks.

### **Curettage or Needle Extraction**

Curettage or needle extraction done with local anesthesia is an older technique that may be used for larger lesions that do not respond to topical treatments, but are best reserved for older children who can better tolerate these procedures.

### **Pulsed Dye Laser**

Although very effective and generally well tolerated, the use of pulsed dye laser is limited by its high cost, the need for special equipment, and the risk for transient hyperpigmentation. Pulsed dye laser remains a third-line treatment for recalcitrant lesions.

### **Other Treatments**

Trichloroacetic acid (TCA) solution in 20% to 35% concentration is another destructive treatment technique. Unlike cantharidin, it does not cause significant irritation or dyspigmentation, making it ideal for facial lesions. Using the pointed edge of a cotton-tipped applicator, it is repeatedly applied to the center of a lesion until a white frost appears. It can induce a mild stinging sensation but is otherwise well tolerated.

Intralesional immunotherapy with *Candida* antigen is another technique performed by dermatologists

for lesions resistant to topical therapy. Studies have demonstrated complete clearance rates of about 55% and partial clearance rates ranging from 28% to 38%.

Cimetidine is an histamine-2 antihistamine that is thought to stimulate the cell-mediated immune response and remains an adjunctive therapy. Controlled studies are needed to verify its efficacy.

In patients with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), MCV lesions do not usually resolve until CD4<sup>+</sup> lymphocyte counts remain consistently above 200 cells/mm<sup>3</sup>. Since the introduction of HAART, there are significantly fewer cases of AIDS-related MCV. If lesions are resistant to HAART, cidofovir is an option. Cidofovir is a nucleotide analog of deoxycytidine monophosphate with activity against MCV. Although both systemic and topical forms are effective against MCV, topical cidofovir is preferable because it does not have the nephrotoxicity seen in its systemic form. Topical cidofovir 1% or 3% should be combined with a vehicle containing propylene glycol and applied once a day, 5 days a week, for 8 weeks. For maximal efficacy on nonfacial lesions, it should be applied under occlusion for at least 12 hours. Side effects include superficial scars, post-inflammatory hypopigmentation and hyperpigmentation, and varioliform scars after large lesions. No systemic adverse effects have been reported.

Many homeopathic remedies, such as Natrum Sulphuricum, sulfur, Natrum Muriaticum, and thuja ointment and cream, have been advertised for the treatment of MCV, but no controlled studies have been published in the Western medical literature to confirm their safety and efficacy.

### **Complications**

Molluscum contagiosum virus infection is considered a benign condition. During resolution, mild erythema and irritation can occur as part of the local cellular immune response. These signs should not be confused with those of bacterial superinfection, which can occur secondary to excoriation and resulting impetiginization. If significant tenderness, crusting, or purulent drainage occurs, then treatment with topical or oral antibiotics is warranted.

Atopic individuals frequently develop patches of eczema (molluscum dermatitis) in the area of the lesions, presumed to be a result of their immune response to the virus or repeated excoriation of the lesions.

### **Prognosis**

Although most healthy children do not experience recurrences of MCV infection, extensive molluscum infections can occur in immunocompromised individuals, especially patients with HIV or AIDS.

### **WHEN TO REFER**

- Warts or molluscum contagiosum in the perineal or perianal area in a child
- Unresponsive/persistent or extensive warts or molluscum contagiosum

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *What Is a Pediatric Dermatologist?* (fact sheet), American Academy of Pediatrics ([healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Dermatologist.aspx](http://healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Dermatologist.aspx))

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## Chapter 346

# VITAMIN D INADEQUACY

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## OVERVIEW

Vitamin D and its active metabolites (primarily D<sub>3</sub>), in addition to calcium and bone metabolism, have been shown to mediate effects on cellular metabolism in almost every organ system in the body, including a role in upregulating innate immune and downregulating autoimmune functions. While evidence continues to mount from epidemiologic studies regarding vitamin D's role in long-latency diseases such as cancers, and autoimmune and other inflammatory diseases, there is much controversy surrounding what constitutes vitamin D sufficiency and insufficiency, and what is an adequate intake throughout the life span. The data are insufficient for a determination of what is an optimal vitamin D concentration within the various compartments of the body although, emerging evidence suggests that what once was thought adequate—the amount of vitamin D necessary to prevent rickets, whether derived from the sun, diet, or supplement—is not enough to optimize immune function. How then can a physician determine if a growing child is receiving adequate vitamin D? Does the source of vitamin D matter—is sunlight-derived vitamin D superior to that from dietary sources? What about toxicity? For some of these questions, there are answers; for others, the answers change as our understanding of the cellular and molecular functions of vitamin D improves.

## WHAT IS VITAMIN D?

Vitamin D is a hormone that is either synthesized by the skin (vitamin D<sub>3</sub> or cholecalciferol) or derived from the diet (found in fish, eggs, animal organs such as

liver, or plants). Vitamin D synthesis by the skin accounts for more than 90% of the vitamin D stores in most people. Vitamin D obtained from foods or as a supplement is absorbed from the small intestine into the bloodstream and carried to the liver, where it is converted to 25(OH)D. Within the body, vitamin D synthesized from the skin seems interchangeable with that obtained from the diet. The half-life of vitamin D is 12 to 24 hours and that of the active form of the hormone, 1,25(OH)<sub>2</sub>D is 4 to 6 hours. In comparison, the half-life of 25(OH)D is approximately 3 weeks, which makes it the best indicator of vitamin D status.

Whereas excessive exposure to sunlight does not further increase vitamin D production to cause toxicity, the same is not true for intestinal absorption of the dietary vitamin D. With ongoing sunlight exposure, previtamin D<sub>3</sub> is degraded into inert products with no effects on calcium metabolism. With oral vitamin D, there is the potential for toxicity, because vitamin D is a fat-soluble compound and is stored in the liver and fat. There are numerous cases of vitamin D toxicity described when individuals received thousands to hundreds of thousands IU of vitamin D per day. The Institute of Medicine (IOM) states in a recent report that in infants younger than 6 months old, up to 1,000 IU/day and in those aged 6 to 12 months 1,500 IU/day vitamin D are safe. In adults, that level is 4,000 IU/day. More recent studies suggest that for adults, the upper limit of safety is higher than 4,000 IU/day. The upper limit of safety for older children and adolescents remains unclear.

## VITAMIN D INADEQUACY: DIFFERENTIATING VITAMIN D DEFICIENCY FROM INSUFFICIENCY

There is excellent evidence that a total circulating 25(OH)D level greater than 10 ng/mL (25 nmol/L) will prevent rickets, but recent global review indicates that the threshold of serum 25(OH)D for developing rickets may be higher. If the goal, for example, is to achieve a circulating 25(OH)D concentration that is associated with optimal immune function, then that goal is unclear. The needs of the growing child are even less clear. There is mounting evidence that better health outcomes, particularly in adults, are associated with 25(OH)D levels greater than 20 ng/mL (>50 nmol/L) and still better outcomes at levels greater than 32 ng/mL (80 nmol/L); whether or not the same holds true across the life span remains uncertain. No evidence to date suggests that when compared to adults, children have different metabolic pathways or thresholds for deficiency. Indicators of overt disease such as rickets or osteomalacia are seen in both adults and children at serum 25(OH)D levels below 10 to 12 ng/mL (25–30 nmol/L). Across the lifespan, parathyroid hormone (PTH) levels seem to increase when circulating 25(OH)D concentrations fall below 20 ng/mL (50 nmol/L). With children, an increase in alkaline phosphatase (ALP) also accompanies worsening vitamin D deficiency. The American Academy of Pediatrics (AAP) considers serum 25(OH)D less than 20 ng/mL (50 nmol/L) as insufficiency, and IOM considers values below 12 ng/mL (30 nmol/L) associated with rickets as deficiency.



### BOX 346-1 Causes of Vitamin D Deficiency and Insufficiency

- The substrate supply is limited or has become limited by an ongoing lack of sunlight exposure
- A diminished dietary supply of vitamin D (particularly in exclusively breastfed infant)
- Enhanced metabolic processing of 25(OH)D to more biologically inert vitamin D moieties
- Malabsorption of dietary vitamin D

## ETIOLOGY AND INCIDENCE OF VITAMIN D DEFICIENCY AND INSUFFICIENCY

The causes of vitamin D deficiency and insufficiency are listed in Box 346-1. There is a seasonal variation in the presentation of the disease—the risk is greater in late winter and early spring than summer or fall. Those who have darker pigmentation are at greatest risk because their melanocytes filter the very UVB necessary for the conversion of 7-dehydrocholesterol to vitamin D<sub>3</sub> in the skin. It is also known that those who have higher body mass indices are at greater risk of vitamin D deficiency. Others at risk for vitamin D deficiency include those with fat malabsorption, most notably children with cystic fibrosis; they cannot absorb vitamin D well from the gut, because it is fat-soluble. Children who take antiepilepsy medications such as phenobarbital and phenytoin, which can increase the liver's P450 conversion of 25(OH)D to inactive compounds, can lower serum 25(OH)D concentrations and reduce calcium absorption.

The 2001–2006 NHANES provides the most recent data on the vitamin D nutritional status of 4,558 US children aged 1 to 11 years. Overall, 1% of the children had serum 25(OH)D levels below 10 ng/mL (<25 nmol/L), 18% had levels below 20 ng/mL (<50 nmol/L) and 95% had levels below 30 ng/mL (<75 nmol/L). The prevalence of vitamin D deficiency and insufficiency is higher in non-Hispanic black and Hispanic than non-Hispanic white children. In a recent study in South Carolina involving pregnant women, more than 75% of African American women, 50% of Hispanic women, and 12% of Caucasian women were vitamin D deficient as defined by circulating 25(OH)D concentrations below 20 ng/mL (50 nmol/L). If the mother is deficient, her developing fetus—who derives vitamin D stores from the mother—is deficient. Neonatal 25(OH)D concentrations in the blood are 0.6 to 0.7 that of the mother, so vitamin D must be supplied soon after birth. In a study of neonates and their mothers in the Netherlands, Dijkstra and colleagues reported a significant difference in the prevalence of vitamin D deficiency [25(OH)D <10 ng/mL (<25 nmol/L)] between newborns of mothers with either dark skin or concealing clothing (risk group) or light skin (control group) (63.3% vs 15.8%;  $p < 0.001$ ). The situation becomes more complicated if the newborn is breastfeeding, because most newborns have little direct sunlight exposure and depend solely on the

lactating mother for their vitamin D. If the lactating mother is deficient in vitamin D, then her breast milk is deficient, with diminished vitamin D ingested by her breastfeeding infant.

## WHAT OCCURS DURING VITAMIN D DEFICIENCY?

When 25(OH)D is less than 20 ng/mL (50 nmol/L), net intestinal calcium absorption is decreased to 10% to 15%, and there is a decrease in the total maximal reabsorption of phosphate. Low ionized calcium levels stimulate PTH secretion, which leads to an increase in calcium reabsorption in renal tubules and an increase in 1 $\alpha$ -hydroxylase activity that has a direct effect on 1,25(OH)<sub>2</sub>D synthesis. Increased PTH leads to renal tubular reabsorption of calcium at the expense of phosphorus, which is lost in the urine. Sustained decreased levels of phosphorus initially and then accompanied by calcium loss lead to a decrease in the calcium and phosphorus product necessary for ongoing bone mineralization resulting in decreased bone mineralization. At the cellular level, low phosphorus levels are associated with failure or delay of osteoid calcification, referred to as osteopenia in mature bones or rickets in immature bones (see section on vitamin D deficiency rickets).

The effect of vitamin D deficiency on other systems besides bone and calcium are just beginning to be understood. The association of respiratory infections in those children with rickets well described by scientists at the turn of the 20th century went largely unnoticed until more recent laboratory molecular techniques allowed experiments to be performed that linked vitamin D with both innate and adaptive immune function. These findings in the laboratory, together with a plethora of epidemiologic studies, suggest that vitamin D plays a significant role in maintaining health not only in the short term (eg, reducing the risk of acute respiratory infections) but also in the long term, with such long-latency diseases as diabetes, multiple sclerosis, and certain cancers. Childhood diabetes has been associated with the lack of vitamin D supplementation, but again, the optimal blood concentration of 25(OH)D remains uncertain. Future research is needed to determine if these effects are through the direct effects of vitamin D and its metabolites, or through a cascade of events initiated or circumvented by vitamin D.

## CLINICAL FEATURES OF VITAMIN D DEFICIENCY RICKETS

The clinical presentation of overt vitamin D deficiency is variable and depends on the duration and age at presentation. Although rare, profound maternal vitamin D deficiency during pregnancy could result in congenital rickets. Newborns present with respiratory distress, muscle weakness, wide anterior fontanel, craniotabes, intrauterine growth restriction and hypocalcemia, and in some cases, hypocalcemic seizures. Overt vitamin D deficiency in infancy has skeletal and nonskeletal clinical presentations.



**Table 346-1** Common Clinical Features of Rickets in the United States (1986–2003)

FEATURES	NUMBER OF PATIENTS ASSESSED	% WITH ABNORMAL FINDINGS
Skeletal deformities	147	74
Poor growth	142	60
• Length for age (<5th percentile)	91	44
• Weight for age (<5th percentile)		
Delayed motor development	64	14
Hypocalcemic seizures	121	12
Radiologic evidence of rickets	159	98

Adapted from Weisberg P, Scanlon KS, Li R, Cogswell ME. Nutritional rickets among children in the United States: review of cases reported between 1986 and 2003. *Am J Clin Nutr*. 2004;80(6 suppl):1697S–1705S.

Hypocalcemia is the typical nonskeletal presentation in early infancy. There are reported cases of seizures and tetany (both of which typically occur in association with hypocalcemia) in early infancy and adolescence, which are periods of increased growth velocity. With rapid growth, the increased demand for calcium cannot be met in a timely fashion, and the patient may present with hypocalcemia even before bone demineralization or rickets secondary to profound vitamin D deficiency is observed.

In later infancy and early childhood, the most common presentations are skeletal abnormalities, delayed motor development, suboptimal physical growth, and muscle weakness and myalgias. In 166 cases of rickets reported in the United States between 1986 and 2003, the most common features were skeletal abnormalities, suboptimal growth, and radiographic changes of rickets (see Table 346-1). The skeletal abnormalities associated with rickets typically include widening of the wrists and the ankles, bow legs (genu varum), abnormal gait, prominence of costochondral junctions (rachitic rosary), and skull abnormalities such as delayed closure of fontanels, craniotabes, and frontal bossing. Rarely, dilated cardiomyopathy with heart failure may be associated with hypocalcemia, and the infants usually respond to vitamin D and calcium therapy.

Children with vitamin D deficiency are reported to be at increased risk of acute lower respiratory tract infections (ALRTIs). A case control study from Ethiopia found a 13-fold higher incidence of rickets among children with pneumonia than among the controls. In another case control study from India, severe ALRTI is 11 times more common in infants with 25(OH)D levels below 10 ng/mL (<25 nmol/L) than those with levels above 10 ng/mL (25 nmol/L). An observational study from Canada found that children with vitamin D deficiency [defined as serum 25(OH)D <20 ng/mL (<50 nmol/L)] were 8 times more likely to require pediatric intensive care than general ward admission. Such aspects of the disease are consistent with vitamin D's putative role in maintaining innate and adaptive immune functions. The clinical presentations and features by age at presentation are summarized in Box 346-2.

Rickets is often diagnosed by radiologic and laboratory findings. The radiologic features include irregular bone mineralization, cortical thinning of

### BOX 346-2 Clinical Presentations of Vitamin D Deficiency by Age at Presentation

#### AT BIRTH

- Intrauterine growth restriction
- Hypocalcemia
- Congenital rickets
- Neonatal seizures resulting from hypocalcemia

#### EARLY INFANCY

- Hypocalcemia
- Hypocalcemic seizures or tetany
- Craniotabes

#### LATE INFANCY AND CHILDHOOD

- Delayed physical growth (short stature)
- Delayed gross motor development
- Inability to bear weight on legs or walk
- Waddling gait
- Muscle weakness
- Frontal bossing
- Delayed closure of fontanelle
- Swelling of wrists, ankles, or knees
- Rachitic rosary (enlargement of costochondral junctions)
- Bowing of lower legs
- "Pigeon chest" deformity
- Rarely, stridor, cardiomyopathy, and fracture
- Increased risk of acute lower respiratory tract infection

long bones, metaphyseal widening, fraying and cupping, and underdevelopment of the epiphysis. The typical radiologic changes in rickets are shown in Figure 346-1.

Common laboratory findings in vitamin D deficiency rickets are hypophosphatemia, varying degrees of hypocalcemia, elevated serum ALP and PTH levels. Other biochemical abnormalities include generalized aminoaciduria and reduced urinary calcium excretion. The diagnosis of vitamin D deficiency rickets is confirmed by measuring serum 25(OH)D concentration. Although there is no absolute threshold

level of 25(OH)D for development of vitamin D deficient rickets, the serum 25(OH)D level is usually below 20 ng/mL (50 nmol/L) and values below 12 ng/mL (30 nmol/L) are very common. In a recent study from the United States of 47 cases of rickets with documented serum 25(OH)D levels, 37 (79%) had levels lower than 20 ng/mL (50 nmol/L) and 30% of these were lower than 5 ng/mL (12.5 nmol/L). In another recent study of 38 cases of rickets from the United Arab Emirates, 35 (92%) had serum 25(OH)D levels lower than 10 ng/mL (25 nmol/L).

### DIFFERENTIAL DIAGNOSIS

In addition to vitamin D deficiency rickets, physicians should be alert to other causes of childhood rickets, including phosphate deficiency caused by abnormal phosphate metabolism, calcium deficiency, 1 $\alpha$ -hydroxylation defect (type 1 vitamin D-dependent rickets), impaired biological response to 1,25-dihydroxy vitamin D (vitamin D-resistant rickets), renal tubular acidosis, and renal osteodystrophy. The clinical features of these various conditions are similar, but the medical history,



**Figure 346-1** Untreated vitamin D deficiency rickets. The figure demonstrates widening of the epiphyseal plate, underdevelopment of the epiphysis, splaying, irregularity (fraying), and cupping of the metaphysis.

biochemical changes, and clinical response to vitamin D supplementation are helpful to distinguish among them. These cases would require specialist referrals. The biochemical parameters: serum calcium (Ca), phosphorous (P), PTH, 25(OH)D, 1,25(OH)<sub>2</sub>D, and urinary calcium in the different forms of rickets are summarized in Table 346-2.

### TREATMENT AND PREVENTION

#### When to Check Levels

Pediatricians should be aware that vitamin D insufficiency and deficiency are common in children. This justifies a low threshold for diagnosing vitamin D deficiency, especially in winter months and in those at high risk, which includes rapid growth, dark-skinned breastfed infants without vitamin D supplementation, children on chronic anticonvulsant therapy, and children with chronic disorders associated with malabsorption, such as cystic fibrosis and inflammatory bowel disease. Furthermore, a study from the United Arab Emirates suggests that maternal vitamin D deficiency is more common in infants with rickets than in those without rickets and additionally suggests that maternal vitamin D deficiency should prompt suspicion of subclinical vitamin D deficiency in the infant. The suspicion of vitamin D deficiency should be confirmed by measurement of serum 25(OH)D. Measurement of serum 25(OH)D levels is also indicated when a child presents with clinical manifestations of rickets. In cases of unexplained fractures in children, it is imperative to check serum Ca, P, ALP, and 25(OH)D levels to rule out organic causes as the etiology of the fracture(s).

#### Treatment

Vitamin D and calcium therapy is necessary for infants and children who manifest clinical features of hypocalcemia as a result of vitamin D deficiency or who present with rickets and have serum 25(OH)D levels that are in the deficient range. In active rickets, vitamin D supplementation in a total cumulative dose of 200,000 to 600,000 IU is required to replenish vitamin D stores. Three different dosing regimens advocated are as follows:

1. Daily oral administration of 2,000 to 5,000 IU vitamin D for 2 to 3 months to normalize the 25(OH)D levels and replenish vitamin D stores;

**Table 346-2** Biochemical Findings in Different Forms of Rickets

TYPE OF RICKETS	CA	P	PTH	25(OH)D	1,25 (OH) <sub>2</sub> D	URINARY CA
Vitamin D deficiency	LOW/NRML	LOW	HIGH	VLOW	LOW/NRML	LOW
Calcium deficiency	LOW	LOW	HIGH	NRML	HIGH	LOW
Hypophosphatemia	NRML	LOW	NRML	NRML	LOW/NRML	NRML
Vitamin D metabolism defect	LOW	LOW	HIGH	NRML	LOW	LOW
• Type 1 vitamin D dependent						
Vitamin D receptor defect	LOW	LOW	HIGH	NRML/HIGH	VHIGH	LOW
• Vitamin D resistant						
Renal osteodystrophy	LOW	HIGH	HIGH	LOW	LOW	LOW

NRML, normal range; VHIGH, markedly increased; VLOW, markedly decreased.

- 2. Weekly 50,000 IU vitamin D for 8 weeks or until the serum 25(OH)D level is normalized;
- 3. Single or divided dose of 200,000 to 400,000 IU vitamin D (Stoss therapy) has been suggested when lack of compliance is a concern. Close monitoring is required with this regimen in view of the concern for hypercalcemia.

Serum calcium, phosphorous, and ALP should be monitored in the first month. Serum 25(OH)D levels should be monitored during the first 3 months and at 3-month intervals with calcium, phosphorous, and ALP to achieve a normal calcium level and serum 25(OH)D above 20 ng/mL (50 nmol/L). After the serum calcium and vitamin D levels have returned to normal, the vitamin D intake will be reduced to a minimum of 400 IU daily as a maintenance dose with adequate calcium intake.

Hypocalcemia should also be treated with calcium supplements. Treatment of symptomatic hypocalcemia consists of administering a 10% calcium gluconate solution at 10 to 20 mg of elemental calcium per kilogram intravenously slowly over 5 to 10 minutes. This is sufficient to treat symptomatic hypocalcemia, but repeated doses may be necessary. Oral calcium supplements should be continued until serum calcium levels return to normal.

A biochemical monitoring plan during treatment of vitamin D deficiency rickets includes serum Ca, P, ALP (at 1 month); serum Ca, P, ALP and 25(OH)D (at 3 months); and serum 25(OH)D levels at 6 months and at 1 year. A radiological evaluation should be repeated at 3 months and after 1 year to monitor healing. Skeletal abnormalities usually take much longer than biochemical abnormalities to return to normal.

Prevention of Vitamin D Deficiency

Given the growing knowledge about the effects of vitamin D not only on bone mineral metabolism, but

also on immune function and in preventing various kinds of cancer and autoimmune diseases, a low threshold for avoiding vitamin D insufficiency in infants and children is recommended. Infants who are at high risk of vitamin D insufficiency, particularly breast-fed infants or formula-fed infants whose vitamin D intake is less than 400 IU daily, should be given adequate vitamin D supplementation to ensure vitamin D sufficiency. The American Academy of Pediatrics (AAP) recommends that physicians caring for children should ensure that infants and children achieve a minimum of 400 IU of vitamin D intake daily (note that the Recent IOM report suggests a 600 IU RDA) either through vitamin D supplements or from food fortification. Higher doses of vitamin D supplements may be required in other high-risk infants—including those with fat malabsorption and those on anticonvulsant medications—to ensure vitamin D sufficiency.

VITAMIN D PREPARATIONS AVAILABLE FOR INFANTS AND CHILDREN

During the past decade, there has been an increase in the types of vitamin D supplements available to the physician and to the public. The most widely used form of vitamin D supplementation in children continues to be as part of a multivitamin preparation, which typically contains 400 IU per mL, either as a liquid preparation or in the form of a chewable vitamin. Vitamin D-only preparations are now available, some of which are summarized in Table 346-3, adapted from the 2008 AAP statement.

The main concern when dosing any vitamin or medication is the correct dispensing of the vitamin or drug. The US Food and Drug Administration issued a warning regarding the use of vitamin D-only preparations and the potential for overdosing.

The IOM 2010 report deemed 1,000 IU per day as the upper limit of safety for infants 0 to 6 months old,

Table 346-3 Vitamin D Preparations Available for Infants and Children	
PREPARATION	DOSAGE
Baby Ddrops The Ddrops Company Toronto, Canada (distributed in United States through Carlson Labs)	1 drop gives 400 IU Coconut and palm oil preparation Also comes in 2,000 IU/drop preparation 5-year shelf life
Bio-D-Mulsion Biotics Research Laboratory Rosenberg, Texas	1 drop gives 400 IU Corn oil preparation Also comes in 2,000 IU/drop preparation <sup>a</sup> 1-year shelf life
Just D Sunlight Vitamins, Inc.	1 mL gives 400 IU Corn oil preparation
Carlson Laboratories Arlington Heights, IL	1 gel cap gives 400 IU
Multivitamin preparations polyvitamins A, D, and C vitamin preparations	1 mL gives 400 IU

<sup>a</sup>Single-drop preparation may be better tolerated in patients with oral aversion issues, but proper instruction regarding administration of these drops must be given to the parents or care provider, given the increased risk of toxicity, incorrect dosing, or accidental ingestion. Adapted from Wagner CL, Greer FR. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics*. 2008;122(5):1142–1152.

1,500 IU per day for infants 6 to 12 months old, 2,500 IU for toddlers 1 to 3 years old, 3,000 IU for children 4 to 8 years old, and 4,000 IU for all patients older than 8 years. Gordon and colleagues reported no safety issues in a small cohort of infants and young children ( $n = 35$ ) diagnosed with vitamin D deficiency who were at risk for osteopenia and rickets supplemented with either 2,000 IU/day vitamin D<sub>2</sub>, 2,000 IU/day vitamin D<sub>3</sub>, or 50,000 IU/week vitamin D<sub>2</sub>.

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### TOOLS FOR PRACTICE

#### Medical Decision Support

- *Position Statement on Vitamin D* (guideline), American Academy of Dermatology ([www.aad.org/forms/policies/Uploads/PS/AAD\\_PS\\_Vitamin\\_D.pdf](http://www.aad.org/forms/policies/Uploads/PS/AAD_PS_Vitamin_D.pdf))

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### AAP POLICY

Wagner CL, Greer FR; American Academy of Pediatrics Section on Breastfeeding, Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics*. 2008;122(5):1142–1152 ([pediatrics.aappublications.org/content/122/5/1142](http://pediatrics.aappublications.org/content/122/5/1142))

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### SUGGESTED READINGS

- Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96:1911–1930
- Institute of Medicine. *Dietary reference intakes for calcium and Vitamin D*. The National Academies Press: Washington, DC; 2011
- Misra M, Pacaud D, Petryk A, et al. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. *Pediatrics*. 2008;122:398–417
- Wagner CL, Greer FR. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics*. 2008;122(5):1142–1152





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## PART 8

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# Critical Situations

- 347 Acute Surgical Abdomen
- 348 Airway Obstruction
- 349 Altered Mental Status
- 350 Anaphylaxis
- 351 Appendicitis
- 352 Croup (Acute Laryngotracheobronchitis)
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- 354 Diabetic Ketoacidosis
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## Chapter 347

# ACUTE SURGICAL ABDOMEN

Michael D. Klein, MD

Although some abdominal pain can be evaluated in a measured way, the acute abdomen may require immediate surgical intervention. Three major diagnoses that are the most common and the most likely to cause complications if treatment is delayed must be considered. These are malrotation and midgut volvulus, which usually presents in the newborn period; intussusception, which occurs most often in children between the ages of 2 months and 2 years; and appendicitis, which is most common in children older than 5 years. Other causes of abdominal pain, some requiring immediate surgical intervention, are highlighted in Box 347-1.

### APPROACH TO THE CHILD WITH ACUTE ABDOMINAL PAIN

#### History

A complete history is important in evaluating all patients with abdominal pain. Emphasis should be placed on eliciting the nature, location, radiation, and timing of the pain and whether it is associated with physical activity or eating. Attention to symptoms of peritonitis, such as pain with cough, bumps during a car ride, or jumping, can be helpful. Most patients with an acute surgical problem will have anorexia and will usually have nausea and vomiting. Generally, their bowel habits are unchanged, or they will have constipation. Diarrhea is unusual in diseases requiring urgent operation. The pain usually precedes vomiting. Systemic symptoms such as headache and myalgia are seldom present. Pharyngitis, however, does not rule out a surgical problem. The physician must ask specifically about genitourinary tract symptoms, other illnesses, and prior operations.

#### Physical Examination

The physical examination of the abdomen is crucial. Inspection can reveal distension or a mass. Palpation should begin by gently stroking all abdominal quadrants while looking at the patient's face. With peritonitis, cutaneous hyperesthesia is often present, which can be determined by narrowing of the outer canthus of the eye (wincing). The physician should next gently percuss the entire abdomen; pain on percussion is termed rebound and indicates peritonitis, which can be localized or general. Other tests for rebound, such as pushing in on the abdomen and then suddenly letting go, are very painful and unnecessary. Gentle palpation and percussion will provide sufficient information. Percussion can also indicate gaseous distension of the intestine by the resonant note of tympany. The next step in the abdominal examination is to palpate the abdomen quadrant by quadrant, again while looking at the patient's face. The physician should

make several passes of each quadrant, with each pass being deeper, looking for a mass, tenderness, and guarding. Guarding is a specific and important sign. When the examiner pushes on a quadrant of the abdomen over the rectus muscle and it pushes back, this is known as *guarding*. Guarding cannot occur voluntarily; it indicates localized peritonitis and, most often, the need for an operation. If both the right and the left rectus push back, then this is known as *rigidity*. Rigidity indicates generalized peritonitis, but in contrast to guarding in which a single rectus muscle tenses, rigidity can be performed voluntarily.

Auscultation of the abdomen seldom offers useful information. While it is often taught that there are no bowel sounds with an ileus and high-pitched hyperactive bowel sounds are heard with obstruction, there are no data to support this distinction. The rectal examination is useful if the physician suspects a pelvic abscess or gynecologic etiologies, or if stool is needed for guaiac to screen for intussusception, but these events are unusual. The physician should assess structures or organs superior and inferior to the abdomen, because pneumonia, inguinal hernia, and testicular torsion can cause abdominal pain.

#### Evaluation

##### Laboratory Tests

Laboratory tests are helpful when the history and physical examination are not conclusive. Patients with anemia can have one of many medical conditions, such as sickle cell anemia, Henoch-Schönlein purpura, and lead toxicity. An elevated white blood cell (WBC) count is revealing. In acute appendicitis without perforation, the count is elevated from 9,000 to 14,000/mm<sup>3</sup>. If the bowel is perforated or gangrenous, or if an intra-abdominal abscess exists, then the WBC count will exceed 12,000/mm<sup>3</sup>. The urinalysis can also be revealing. A high specific gravity indicates hypovolemia. Ketones in the urine indicate significant anorexia and emesis. WBCs and bacteria in a catheterized specimen indicate a urinary tract infection. Red blood cells indicate trauma or stone. Casts may indicate glomerulonephritis that can be associated with primary peritonitis. Most patients with intussusception will have a positive stool guaiac test result.

##### Imaging

Imaging studies can also aid in diagnosis. Plain-film radiographs of the abdomen can show bowel obstruction (distended loops of bowel, air-fluid levels, absence of colonic gas), localized ileus, free air in the abdomen, scoliosis, or the impression of a mass. The chest radiograph may show free air under the diaphragm or pneumonia. Ultrasound is useful in assessing acute abdominal pain, especially in ovarian disease, but can also suggest appendicitis, intussusception, and even malrotation with midgut volvulus (reversal of the normal relationship between the superior mesenteric artery and the superior mesenteric vein). Computed tomography (CT) scan is useful in diagnosing appendicitis in patients who are obese, have sickle cell anemia, or are immunocompromised (transplant patients and those being treated for malignancy).

**BOX 347-1 Causes of Abdominal Pain in Children**

- Peritoneum—inflammatory
  - A. Bacterial
  - B. Primary
  - C. Secondary
  - D. Perforated viscus<sup>a</sup>
  - E. Stomach, duodenum<sup>a</sup>
  - F. Appendix<sup>a</sup>
  - G. Foreign body<sup>a</sup>
- Hollow intestinal organs—inflammatory
  - A. Appendicitis<sup>a,b</sup>
  - B. Cholecystitis<sup>a</sup>
  - C. Gastroenteritis<sup>b</sup>
  - D. Regional enteritis<sup>b</sup>
  - E. Meckel diverticulitis<sup>a</sup>
  - F. Colitis—ulcerative, Crohn, bacterial, amebic<sup>b</sup>
  - G. Typhlitis
- Hollow intestinal organs—noninflammatory
  - A. Intussusception<sup>a</sup>
  - B. Malrotation and midgut volvulus<sup>a</sup>
  - C. Intestinal obstruction<sup>a,b</sup>
  - D. Inguinal hernia<sup>a</sup>
  - E. Biliary colic<sup>a</sup>
  - F. Peptic ulcer
  - G. Constipation<sup>b</sup>
  - H. Cystic fibrosis
- Enteric infections (gastroenteritis)
  - A. *Shigella*
  - B. *Salmonella*
  - C. *Campylobacter*
  - D. *Clostridium difficile*
  - E. Viral gastroenteritis<sup>b</sup>
- Unusual infections
  - A. Malaria
  - B. Tuberculosis of the spine
  - C. Osteomyelitis
  - D. Psoas abscess
  - E. Helminthic infestation
- Solid viscera
  - A. Acute hepatosplenomegaly
  - B. Abscess of spleen or liver
  - C. Pancreatitis
  - D. Hepatitis
  - E. Fitzhugh-Curtis syndrome
  - F. Mesenteric lymphadenitis
  - G. Torsion of:
    - 1. Testicle<sup>a</sup>
    - 2. Scrotal appendages<sup>a</sup>
    - 3. Omentum<sup>a</sup>
    - 4. Spleen<sup>a</sup>
  - H. Appendix epiploica<sup>a</sup>
- Gynecologic<sup>b</sup>
  - A. Salpingitis
  - B. Mittelschmerz
  - C. Ovarian cyst (usually ruptured)
  - D. Menstrual pain
  - E. Threatened abortion
  - F. Ectopic gestation<sup>a</sup>
  - G. Ovarian torsion<sup>a</sup>
  - H. Pelvic inflammatory disease
    - I. Endometritis
    - J. Endometriosis
- Urinary tract<sup>b</sup>
  - A. Pyelonephritis
  - B. Hydronephrosis
  - C. Calculi<sup>a</sup>
  - D. Cystitis
- Trauma<sup>b</sup>
  - A. Rectus muscle tear
  - B. Hematoma
  - C. Solid-organ injury<sup>a</sup>
  - D. Hollow-organ injury<sup>a</sup>
- Trauma to a previously unsuspected mass
  - A. Hydronephrosis
  - B. Wilms tumor<sup>a</sup>
- Medical diseases
  - A. Pneumonia
  - B. Sickle cell anemia<sup>b</sup>
  - C. Henoch-Schönlein purpura
  - D. Streptococcal pharyngitis
  - E. Lead poisoning
  - F. Green-apple bellyache
  - G. Hemolytic-uremic syndrome
  - H. Diabetic ketoacidosis<sup>b</sup>
    - I. Porphyria
    - J. Hyperlipidemia
  - K. Rheumatic fever
  - L. Epilepsy
  - M. Migraine
  - N. Hemophilia
  - O. Herpes zoster
  - P. Lupus erythematosus
- Immunosuppressed
  - A. Ischemic colitis
  - B. Typhlitis
  - C. Primary peritonitis
- Nonorganic—chronic
  - A. Recurrent
  - B. Psychogenic
  - C. Functional
  - D. Psychophysiologic

<sup>a</sup>The most common causes of abdominal pain.<sup>b</sup>Diagnoses considered acute surgical problems.



### Observation

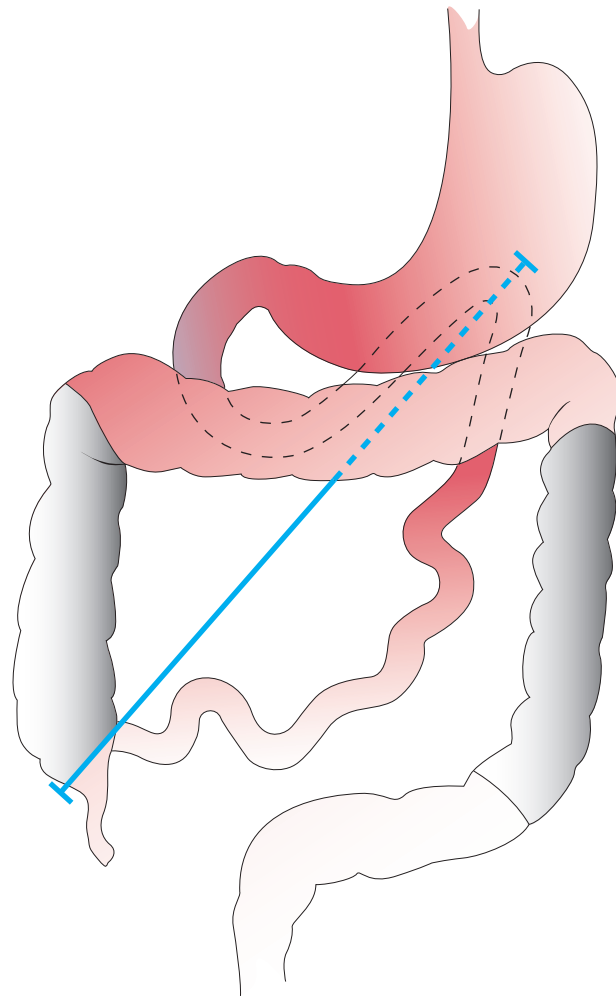
In most cases of acute surgical abdomen, an operation is emergent. When considering malrotation and midgut volvulus or intussusception, immediate surgical intervention can prevent intestinal necrosis. When considering appendicitis, however, observation is a useful diagnostic aid. If a diagnosis of appendicitis cannot be made with history, physical examination, complete blood count, urinalysis, and plain films, then a period of 6 to 12 hours of observation with serial examination and a repeat WBC count may be diagnostic. Patients with appendicitis generally worsen; those without appendicitis usually improve. If observation for 6 to 12 hours does not clarify the diagnosis, then an ultrasound or a CT scan is indicated. In performing the CT scan, the patient must have a good enteric preparation with contrast, or the contrast should be instilled rectally so that it can reach the cecum. Intravenous contrast is also important because it makes the presence of inflammation much clearer.

## THREE COMMON CAUSES OF ACUTE ABDOMINAL PAIN IN CHILDREN REQUIRING URGENT INTERVENTION

### Malrotation and Midgut Volvulus

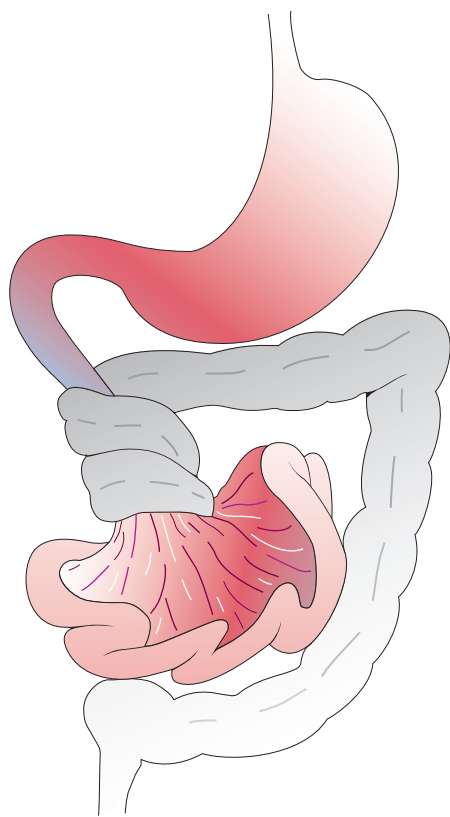
At 5 to 6 weeks of gestation, the elongating midgut pushes out into the umbilical coelom. When it returns to the abdominal cavity at 10 to 12 weeks of gestation, it rotates and fixes to the posterior abdominal wall. The duodenum returns first and is mainly retroperitoneal. It courses behind the mesenteric vessels and enters the peritoneal cavity at the duodenojejunal junction, just to the left of L2, the ligament of Treitz. The colon enters the abdomen last and rotates so that the ileocecal region is in the right lower quadrant. The right and left colon are fixed to the posterior abdominal wall by avascular attachments. Thus, the small bowel mesentery is normally fixed along a line from the ligament of Treitz in the left upper quadrant just to the left of L2 to the right lower quadrant at the right sacroiliac joint (Figure 347-1). This long fixation prevents the lengthy mass of small bowel from rotating with the superior mesenteric artery and vein as a center. This rotation, twisting, or volvulus would obstruct blood flow to the intestine and cause gangrene (Figure 347-2). If an anomaly of rotation is present, or if this long fixation does not occur, then volvulus can occur. In such anomalies of rotation and fixation (usually termed *malrotation* or *nonrotation*) the avascular adhesion of the cecum still seems to occur, although, in this case, the cecum is usually in the midabdomen and the adhesive bands (now called Ladd bands) cross the duodenum to the right upper quadrant (Figure 347-3). This obstruction of the duodenum in malrotation causes bilious emesis. The possibility of volvulus in malrotation requires urgent intervention.

Malrotation and midgut volvulus usually develop in the newborn period but can occur at any age. The characteristic symptom is bilious emesis. The occurrence of this symptom should provoke urgent gastrointestinal (GI) contrast studies. Approximately one-third of all children who have bilious emesis will



**Figure 347-1** Normal rotation and fixation of the intestine. The small-bowel mesentery is fixed to the duodenojejunal junction just to the left of L2 to the ileocecal junction at the sacroiliac joint. This arrangement prevents twisting or volvulus.

require operative intervention (although not always for malrotation and midgut volvulus). Any child with bilious emesis who has abdominal pain or tenderness should have either an operation or a contrast examination. An upper GI series to assess for the position of the ligament of Treitz is the surest way to determine malrotation. Normally, the ligament of Treitz should be at the level of the pylorus and just to the left of the midline, with the second portion of the duodenum coursing posteriorly on a lateral view. If the imager is not experienced, then a barium enema can help find the position of the cecum, which is normally below the iliac crest and to the right of the midline (although it can occasionally be in this position in malrotation). Once the diagnosis has been made in a patient with symptoms, an operation is urgently required to untwist the bowel and to perform a Ladd procedure. If the diagnosis of malrotation is serendipitous and symptoms are not present, then a Ladd procedure should be performed to decrease the likelihood of volvulus. In this procedure the Ladd bands are lysed,

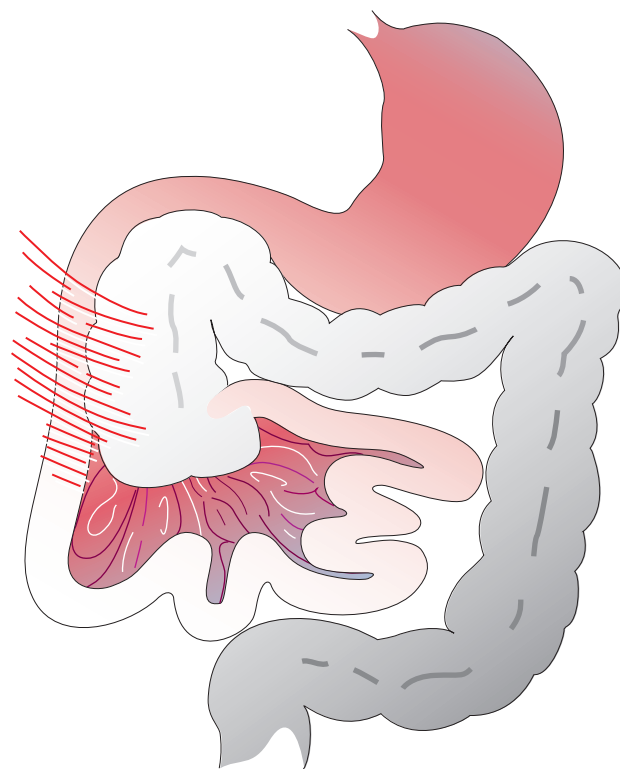


**Figure 347-2** Malrotation with midgut volvulus. The small-bowel mesentery has no attachment, and, with the peristaltic motion of the intestine, the entire small bowel can twist around the axis of the superior mesenteric artery.

and the duodenum and colon are separated in an attempt to create a broad mesentery. The appendix is removed, because it will not usually be in the right lower quadrant and thus will complicate any future diagnosis of appendicitis. Hopefully some adhesions will be created to help decrease the chance of volvulus postoperatively.

### Intussusception

Intussusception occurs most commonly when the terminal ileum telescopes into the right colon. This circumstance causes not only bowel obstruction but also ischemia, because the mesenteric vessels are dragged along with the ileum. Intussusception is most likely caused by hypertrophic ileal lymphatic tissue, which acts as a lead point that is *consumed* by the more distal bowel. Other conditions associated with intussusception include Meckel diverticulum, polyps, tumors, hematoma, and vascular malformations. Most children exhibit intermittent colicky abdominal pain, although some children will be lethargic. They seem well between bouts of pain (approximately 20 minutes). Physical examination reveals a mass in the epigastrium and a feeling of emptiness in the right lower quadrant (signe de Dance). Tenderness and guarding are present as ischemia progresses. Stool is usually guaiac positive, and a *currant jelly* bloody stool may be



**Figure 347-3** Malrotation with Ladd bands. No attachment of the small-bowel mesentery to the posterior abdominal wall is seen. The avascular adhesions that would normally perform this task instead extend across the duodenum, causing an obstruction.

passed. Diagnosis is made most rapidly by ultrasound or contrast enema. Reduction of the intussusception often can be made by contrast enema using barium, nonionic contrast, or air. When contrast enema reduction fails, an operation is necessary. During the operation, the physician can usually reduce the intussusception, or a resection and anastomosis can be performed. The appendix is also removed. Recurrence occurs in 5% of cases, usually within 72 hours of the original disease. Treatment is the same as that in the initial occurrence. See Chapter 257, Gastrointestinal Obstruction, for more information.

### Appendicitis

Appendicitis (see Chapter 351, Appendicitis) is probably caused by obstruction of the lumen by feces or hypertrophic lymphatic tissue that allows stasis and bacterial multiplication to occur in the closed space. Early symptoms of appendicitis are diffuse or periumbilical abdominal pain followed by anorexia, nausea, vomiting, and localization of the pain to the right lower quadrant. Physical examination reveals a fever of up to 38.6°C (101.5°F), right lower quadrant tenderness, and guarding. The WBC count is usually elevated to 9,000 to 14,000/mm<sup>3</sup>. Symptoms usually progress over 36 hours until perforation occurs; usually diffuse peritonitis follows. After perforation, the tenderness is

no longer localized and the guarding becomes rigidity. The temperature rises above 38.6°C, and the WBC count exceeds 14,000/mm<sup>3</sup>. Abdominal radiographs may reveal scoliosis to the right, an ileus pattern, and a fecalith early on. In perforated appendicitis, the impression of a right lower quadrant soft-tissue mass may be present, as well as a gas pattern of bowel obstruction, with multiple loops of bowel with air-fluid levels. In female patients, an ultrasound can be helpful to evaluate the possibility of ovarian or tubal disease, and some experts think this evaluation is helpful in male patients to identify appendicitis. Most surgeons currently prefer an abdominal CT scan with intravenous contrast and with contrast of the GI tract in which the contrast has reached the colon when the diagnosis cannot be made clinically. Once the diagnosis of appendicitis has been made, an operation is indicated. This procedure is performed either laparoscopically or by laparotomy, whether perforation has occurred or not. Laparoscopy is especially useful when the diagnosis remains in doubt, because the entire abdomen and pelvis usually can be well visualized; it also can reduce the morbidity associated with the large incision needed in obese patients. Once the diagnosis has been made, administering analgesics and antibiotics is reasonable.

If a patient reports symptoms lasting longer than 72 hours, then the physician should consider a perforated appendicitis with abscess or phlegmon. This diagnosis is usually made by visualizing abscess or phlegmon on a CT scan. These patients can be treated with broad-spectrum intravenous antibiotics. If an abscess is present, this may be drained percutaneously. If their symptoms resolve in 2 to 3 days, these patients can then be discharged home on antibiotics. Some physicians ask patients to return in 6 to 8 weeks for interval appendectomy, which can be done laparoscopically. Little morbidity exists to an elective laparoscopic appendectomy, even after perforation. Most patients will eat on the evening of the operation and be discharged the next day. Immediate operation for a delayed presentation of perforated appendicitis can result in a very large incision and a long, complicated hospital course.

## DIFFERENTIAL DIAGNOSIS

Secondary bacterial peritonitis is usually caused by appendicitis, but it can be the result of any hollow-organ perforation. Other organs that can rupture and lead to peritonitis are the spleen and kidney, although the peritonitis and pain from these ruptured organs are likely caused by the irritation from blood and urine in the peritoneal cavity.

The second most common organ to perforate is the jejunum, as a result of blunt abdominal trauma. A radiograph of the patient's upright abdomen may not show free air, and a CT scan may show only a small amount of fluid. Persistent abdominal tenderness after blunt abdominal trauma may be the only sign of a perforated jejunum. A seat belt mark is often associated with internal injuries such as intestinal perforation. In children, a history of trauma causing such a rupture may not be obvious (a fall or wrestling match) and may be difficult to elicit, particularly if the child is injured while playing in an unsafe area and is

reluctant to admit this activity to the parents. Injury to the spleen or kidney may be related to a previously undiagnosed enlarged kidney (hydronephrosis, Wilms tumor) or spleen (mononucleosis). A perforated ulcer is rare in children and is characterized by free air on abdominal and chest radiographs. Meckel diverticulitis is less common than bleeding from a Meckel diverticulum. The signs, symptoms, and other findings are not especially different from those of appendicitis. Most foreign bodies, including open safety pins, will pass through a child's GI tract without event, but perforation can occur.

Bowel obstruction usually causes bilious emesis and abdominal pain. The abdomen is distended (unless it is a high small-bowel obstruction), and a radiograph of the upright abdomen shows distended loops of bowel with air-fluid levels and no gas in the colon or rectum. The most common cause of bowel obstruction is adhesions resulting from a previous operation; incarcerated hernia and congenital bands are other causes.

Ectopic gestation can be diagnosed with a pregnancy test or an ultrasound. Ultrasound is also important to identify gynecologic conditions such as ovarian torsion. The consideration of pelvic inflammatory disease indicates a pelvic examination, which may reveal discharge from the cervical os or cervical motion tenderness. Pain originating from testicular disease is often referred to the abdomen. Diagnosis can usually be made on physical examination. (See Chapter 190, Scrotal Swelling and Pain.)

Right upper quadrant symptoms and signs suggest gallbladder disease that can be confirmed by ultrasound or CCK-HIDA scan. Pancreatitis in children will usually have an underlying cause. Ultrasound and pancreatic enzyme levels will often confirm pancreatitis. Torsion of the spleen or the omentum is an uncommon cause of abdominal pain that can be diagnosed by ultrasound. Torsion of an epiploic appendage (the fat hanging off the colon) is only diagnosed at laparotomy or laparoscopy.

Although the GI mucosa does not have touch sensation, the bowel is acutely sensitive to distension, which is why constipation can cause abdominal pain. When cystic fibrosis is responsible for abdominal pain, even in older children, it is usually because of the distal intestinal obstruction syndrome (DIOS; formerly called meconium ileus equivalent).

In immunocompromised patients, right lower quadrant pain and tenderness usually indicates typhlitis (neutropenic enterocolitis) and not appendicitis. The inflammatory mass can be seen on CT scan and can be monitored with ultrasound. Treatment is generally nonoperative with broad-spectrum antibiotics. Recently, several studies of nonoperative (antibiotic only) management have been published. Even in selected patients, this appears to be only 70% effective, and long-term follow-up is not available.

Most medical diagnoses of abdominal pain can be ruled out by their lack of tenderness or guarding on physical examination. Patients with sickle cell anemia often have abdominal pain. They also usually have WBC counts of approximately 14,000 to 16,000/mm<sup>3</sup>, so this test is not helpful. If the physician is not sure of

**Table 347-1** Most Common Diagnoses in Boys With a Chief Complaint of Abdominal Pain by Age

<2 yr (n = 56)		2-5 yr (n = 128)		5-12 yr (n = 230)		>12 yr (n = 86)	
DIAGNOSIS	FREQUENCY (%)	DIAGNOSIS	FREQUENCY (%)	DIAGNOSIS	FREQUENCY (%)	DIAGNOSIS	FREQUENCY (%)
Abdominal pain of unknown etiology	30 (60)	Abdominal pain of unknown etiology	59 (46)	Abdominal pain of unknown etiology	117 (51)	Abdominal pain of unknown etiology	33 (38)
Constipation	9 (18)	Constipation	21 (16)	Constipation	27 (12)	Appendicitis	14 (16)
Infection	4 (8)	Infection	13 (10)	Appendicitis	24 (10)	Constipation	7 (8)
Bowel obstruction	2 (4)	Gastroenteritis	13 (10)	Gastroenteritis	14 (6)	Gastritis, esophagitis	5 (6)
Dental	1 (2)	Hematologic	4 (3)	Gastritis, esophagitis	14 (6)	Infection	4 (5)
Gastritis, esophagitis	1 (2)	Gastritis, esophagitis	4 (3)	Infection	10 (4)	Diabetes	2 (2)
Crohn disease	1 (2)	Bowel obstruction	4 (3)	Hematologic	5 (2)	Hematologic	2 (2)
Abdominal trauma	1 (2)	Appendicitis	3 (2)	Cancer	2 (1)	Cancer	2 (2)

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**Table 347-2** Most Common Diagnoses in Girls With a Chief Complaint of Abdominal Pain by Age

<2 yr (n = 25)		2-5 yr (n = 94)		5-12 yr (n = 248)		>12 yr (n = 150)	
DIAGNOSIS	FREQUENCY (%)	DIAGNOSIS	FREQUENCY (%)	DIAGNOSIS	FREQUENCY (%)	DIAGNOSIS	FREQUENCY (%)
Abdominal pain of unknown etiology	11 (44)	Abdominal pain of unknown etiology	53 (56)	Abdominal pain of unknown etiology	126 (51)	Abdominal pain of unknown etiology	59 (39)
Constipation	6 (24)	Gastroenteritis	9 (10)	Constipation	42 (17)	Genital, pregnancy	14 (10)
Gastroenteritis	2 (8)	Infection	6 (6)	Gastritis, esophagitis	17 (7)	Pelvic inflammatory disease	14 (10)
Infection	1 (4)	Constipation	6 (6)	Gastroenteritis	17 (7)	Urinary	10 (7)
Hematologic	1 (4)	Urinary	5 (5)	Appendicitis	12 (5)	Constipation	10 (7)
Malabsorption	1 (4)	Bowel obstruction	4 (4)	Urinary	8 (3)	Gastritis, esophagitis	9 (6)
		Gastritis, esophagitis	3 (3)	Infection	5 (2)	Appendicitis	6 (4)
		Appendicitis	3 (3)	Hematologic	4 (2)	Gastroenteritis	5 (3)

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the diagnosis even after CT scan, then treatment for sickle cell crisis, even including transfusion, is best. If the pain resolves, then the diagnosis was not appendicitis. If the pain does not resolve, then the patient needs to go to the operating room.

## ROLE OF THE PRIMARY CARE PHYSICIAN

The primary care physician must be able to recognize which patients with abdominal pain have an acute surgical abdomen. In brief, indicators of a possible acute surgical abdomen include the following:

- Pain lasting more than 1 hour that is severe enough to require analgesics
  - Bilious emesis
  - Acute abdominal pain lasting more than 6 hours
  - Obstipation
  - Localized abdominal tenderness
  - Guarding
  - Rebound
  - Guaiac-positive stools, melena, or hematochezia
- Indicators of nonsurgical problems include the following:
- Diarrhea
  - Symptoms of systemic illness: headache, sore throat, and myalgia
  - Emesis preceding pain
  - High fever very early in the illness
  - No abdominal tenderness

Ordering a complete blood count with differential and urinalysis is reasonable for the primary care physician when abdominal pain is the chief complaint. Examination by a pediatric surgeon before any other tests, including imaging studies, are ordered is in the patient's best interest. Certainly, when appendicitis is suspected, the diagnosis can often be made without resorting to imaging studies. When malrotation is in question, an upper GI series is the best test. However, if the patient already has signs of peritonitis and abnormal signs on plain-film radiograph, then prompt operation might be a better course. When intussusception is being considered, a diagnostic ultrasound or contrast enema is indicated unless signs of obstruction, peritonitis, or necrotic bowel are present, which should prompt immediate operation. When appendicitis is a possibility, the first imaging studies should be radiographs of the chest and abdomen. If the diagnosis is not clear, then an ultrasound followed by CT if necessary is the next step. The subtleties of the individual case might alter these judgments; involving the surgeon early will allow a more prompt and accurate diagnosis.

All patients with an acute surgical abdomen have volume depletion. Administering intravenous hydration at 150% of the maintenance requirement with appropriate solutions is reasonable unless there are signs of dehydration requiring more aggressive rehydration. Broad-spectrum antibiotics (ampicillin, gentamicin, and metronidazole) and analgesics (morphine) are also of benefit, but should probably be started only after consultation with the surgeon. If a patient is vomiting or has marked abdominal distension, then a nasogastric tube should be placed.

Certainly, any patient with abdominal pain as any part of their chief complaint should not have any food or drink until a diagnosis and disposition are decided.

## IMPROVING DIAGNOSTIC ABILITY

Making a diagnosis is certainly the most difficult task in medicine. Knowledge of the prevalence of a disease can aid the differential diagnosis (Table 347-1 and Table 347-2).

This information allows emergency department personnel or the primary care physician to evaluate the child with abdominal pain in an efficient and accurate manner. The physician should consider common conditions first while evaluating a child with abdominal pain. Once these possibilities are exhausted, which will be rarely, the physician can look for more esoteric diseases.

## TOOLS FOR PRACTICE

### Medical Decision Support

- *Abdominal Pain Clinical Practice Guideline* (guideline), Royal Children's Hospital Melbourne ([www.rch.org.au/clinicalguide/cpg.cfm?doc\\_id=5036](http://www.rch.org.au/clinicalguide/cpg.cfm?doc_id=5036))
- *Infants and Children: Acute Management of Abdominal Pain* (guideline), Ministry of Health, New South Wales ([www0.health.nsw.gov.au/policies/pdf/2013/pdf/PD2013\\_053.pdf](http://www0.health.nsw.gov.au/policies/pdf/2013/pdf/PD2013_053.pdf))

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## Chapter 348 AIRWAY OBSTRUCTION

Carol Conrad, MD; David N. Cornfield, MD

Respiratory distress is common in children. An airway obstruction can be precipitated acutely by infections, trauma, inhalational injury, a mass lesion, or foreign-body aspiration. In addition, an acute illness can significantly worsen an obstruction caused by either a chronic process or an anatomic abnormality. An acute upper airway obstruction presents an immediate threat to life. If the airway obstruction is relieved quickly, then rapid clinical improvement can occur. An

acute airway obstruction can occur throughout the respiratory tract. A knowledge of developmental respiratory physiology and anatomy, combined with historical information, can help determine the anatomic site of the obstruction. Definitive treatment and relief of the obstruction is critical to prevent hypoxic-ischemic injury.

An airway obstruction and the adverse effects of hypoventilation result either from blockage of the airway from aspiration of a foreign object, from mucus plugging, when the inner diameter of the airway is reduced (as occurs with mucosal edema in the case of acute laryngotracheobronchitis), or with constriction of the peribronchiolar muscles (as occurs with status asthmaticus).

Alternatively, the airway can be compressed from an external mass, such as a mediastinal tumor. The onset can seem to occur quite rapidly, even with a slowly growing tumor. A patient with a chronic airway obstruction, such as a prematurely born infant, can experience an acute airway obstruction caused by an acute viral infection, such as respiratory syncytial virus bronchiolitis.

Infants have a greater incidence of respiratory compromise than older children because they have a smaller airway diameter and exponentially increased airway resistance. In addition, the connective tissue in infants has incompletely hardened cartilaginous structures (malacia). This is the case for the cartilaginous structures such as the larynx (epiglottis, aryepiglottic folds, arytenoid cartilage, tracheal cartilage), the trachea, bronchi, bronchioles, and the chest wall itself. As a result, any increase in airway obstruction results in relatively higher airflows, thereby increasing the dynamic obstruction caused by relatively flexible airway structures. In infants younger than 1 year, collateral lower airway circulation in the alveoli and the bronchioles, the pores of Kohn, and the canals of Lambert are absent, predisposing the infant to atelectasis. The narrowest portion of the airway in the infant and child is the cricoid ring, unless an infant is born with congenital airway anomalies such as tracheal stenosis or bronchomalacia. In the older child and adolescent, the narrowest portion of the airway is the vocal cord aperture.

## INITIAL ASSESSMENT

To determine whether a child requires emergent intervention, consideration should focus on upper airway patency, the degree of respiratory effort, and the effectiveness of respiratory function. A complete upper airway obstruction or respiratory failure demands immediate intervention. The child should be kept calm and comfortable. Anxiety and crying can substantially increase dynamic airway obstruction and the work of breathing in young children. Simple observation of the child, without a detailed examination, is an invaluable tool. By determining the respiratory rate, whether the child is using accessory muscles, has retractions, recognizes parents, can speak, or can suck on a bottle or pacifier, the physician can match the appropriate level of support to the condition of the child.

## HISTORY

Contingent on the degree of acuity, historical information can be obtained before initiating therapy. Historical information can establish a cause for the respiratory disease. An acute onset, particularly in the absence of fever, prompts concern about an aspirated foreign body. Conversely, if a child has had respiratory problems before the acute process, then a dynamic obstruction caused by underlying laryngomalacia, subglottic stenosis, or malacia of the trachea or bronchus may be worsened by superimposed infection or reactive airway disease.

The pulmonary history should elicit information regarding the duration of the problem and factors that either worsen or improve the signs or symptoms. Historical information regarding the prenatal and neonatal periods can guide diagnosis and treatment. A history of decreased fetal motion may indicate a neuromuscular disorder that can lead to alveolar hypoventilation and restrictive chest wall disease. A history of oligohydramnios can indicate the presence of pulmonary hypoplasia. A knowledge of whether resuscitation efforts were required in the perinatal period and for what reason is helpful. The gestational age at birth and whether the infant required intubation, mechanical ventilation, or supplemental oxygen can provide information regarding the presence of either upper or lower respiratory tract disease. The quality of a child's cry can provide information regarding vocal cord function and tracheal patency. A history of cyanosis in the absence of cardiac anomalies may prompt concern over respiratory disease. A prior history of wheezing or cough responsive to bronchodilator therapy could indicate asthma. Often, children with recurrent episodes of cough have associated gastroesophageal reflux disease (GERD). Immune compromise may be suspected in children with prior episodes of pneumonia.

## PHYSICAL EXAMINATION

The initial evaluation should include careful observation. Observation of the child and of the quality and timing of the respiratory pattern is important. Close attention to the child's work of breathing, level of consciousness, and degree of interaction can be particularly instructive. Attention to whether accessory muscles are being used, the relative ratio of inspiration to expiration, and movement of the head and neck with respirations provide important clinical information. By approaching the child from a distance and observing the child in the relative comfort of parental arms, an assessment can be made without biasing the examination by introducing fear and anxiety. Careful attention to the facial expressions of the child can provide further insight into the clinical presentation. The child with incipient respiratory collapse may demonstrate furrowed eyebrows, may be unable to regard and to focus on the examiner, and may seem fatigued and anxious. The child may demonstrate nasal flaring and may be pale and diaphoretic. Cyanosis may be present, but this is a late finding in children who do not have a previous history of cyanotic heart disease.

**Table 348-1** Sounds Produced From the Lower Airway

SOUND (ATS)	FREQUENTLY USED SYNONYM	ACOUSTIC CHARACTERISTICS	LIKELY LOCATION OF FLUID, MUCUS, OR OBSTRUCTION
<b>Crackle</b>	—	Usually inspiratory sound	—
Coarse	Rhonchi	Loud, low in pitch	Large- or medium-sized bronchi
Fine	Rale	Softer and shorter in duration, higher in pitch	Alveoli or small bronchioles
<b>Wheeze</b>	—	Usually expiratory sound	—
High pitched		Long, musical	Small airways, typical of asthma
Low pitched		Loud, long, sonorous	Large airways, such as bronchi or trachea, such as in tracheo- or bronchomalacia

ATS, American Thoracic Society.

From Pasterkamp H, Kraman S, Wodicka G, et al. Respiratory sounds: advances beyond the stethoscope. A state of the art review. *Am J Respir Crit Care Med*. 1997;156:974–987. Reprinted by permission of the American Thoracic Society.

Abnormal breath sounds and physical examination findings are either more prominent on the inspiratory or the expiratory phase of breathing depending on the site of disease. In the presence of complete upper airway obstruction, no effective air movement is present. In such an emergency situation, the child would be unable to cough audibly, speak, or produce any sound. Audible phonation or breath sounds indicate airway patency, though partial obstruction may be present. Partial extrathoracic upper airway obstruction results in stridulous respirations with increased obstruction to airflow on inspiration relative to expiration. Retractions and nasal flaring with diminished air movement or worsening hypoxemia (poor color and decreased mental status) portend impending respiratory failure.

Children with respiratory failure have inadequate oxygenation, ventilation, or both. Children in extremis look ashen, obtunded, lethargic, or extremely anxious. Central cyanosis may be present. Chest wall movement may be diminished because of weak or inefficient breaths, thereby decreasing any signs of respiratory distress. Extreme tachypnea can precede hypopnea. Given that respiratory insufficiency leads to respiratory failure, as children develop overt failure, the pattern of respirations becomes irregular. In the presence of a tenuous airway, avoiding components of the examination that will increase the child's anxiety is prudent. Comprehensive airway evaluation ought to be deferred pending the presence of critical care personnel and access to equipment that will allow for definitive airway management if necessary.

For the chest examination, the physician should observe the breathing pattern and respiratory effort. Removing the child's shirt allows observation of the accessory muscles of respiration and how they are used. Children with obstructive disease (cystic fibrosis and asthma) may have a prolonged expiratory phase and a hyperinflated thorax that may be clinically evident as an increase in anteroposterior diameter. A normal inspiratory/expiratory ratio is 1:2. In the presence of small airway obstruction, the ratio is 1:3 or 1:4. Children with restrictive lung disease breathe rapidly and with smaller tidal volumes. The physician should

inspect the chest wall for symmetry, pectus deformity, and the size of the thorax. Retractions are more clinically apparent in younger children than in adolescents and adults, owing to the relatively high compliance of the chest wall. Retractions are evident in the lower part of the thorax as the rib cage is pulled inward with diaphragmatic contraction on inspiration. Head bobbing results from the use of the suprasternal accessory muscles of respiration and is a sign of increased airway resistance. The degree of respiratory effort required is directly proportional to the degree of obstruction. Percussion of the thorax can reveal localized air trapping, hyperresonance, or lobar consolidation or dullness.

When auscultating breath sounds, the physician should listen for crackles, wheezing, or stridor. The physician should also determine whether the sounds occur on inspiration, on expiration, or throughout the respiratory cycle. The distribution, pitch, and quality of sounds can differentiate between upper and lower airway pathology. Table 348-1 describes the types of sounds that can be appreciated in various forms of disease as described by the American Thoracic Society and the American College of Chest Physicians. Causes of intra- and extrathoracic obstructing lesions of the upper airway are detailed in Table 348-2. A lesion in the extrathoracic trachea increases airflow resistance primarily during inspiration and is characterized by stridor. Obstruction in the intrathoracic trachea results in an increase in airflow resistance during expiration and is clinically characterized by wheezing. A lesion may be *fixed* or *variable*. If airflow limitation does not vary during the respiratory cycle, then the lesion is fixed. Noise that occurs on both inspiration and expiration suggests a fixed stenosis of the airway.

In a child or infant, the dynamics of the lesion can be assessed for the change in character of the stridor by making the child breathe more forcefully. By making the child inspire with high inspiratory flow, a dynamic compression (an acute airway narrowing) will develop below an extrathoracic lesion and above an intrathoracic lesion. Variable lesions are those that can be distended or compressed during the phases of

**Table 348-2** Localize the Source of the Noise

LESION	NOISE	
	INTRATHORACIC LOCATION	EXTRATHORACIC LOCATION
<b>Fixed</b> Tracheal stenosis Double aortic arch anomaly Cricoid ring	Noise occurs on inspiration and expiration	Noise occurs on inspiration and expiration
<b>Variable</b> Foreign body aspiration Laryngomalacia	Wheeze predominates on expiration	Stridor dominates on inspiration

**Table 348-3** Causes of Stridor and Guide for Diagnostic Evaluation

CONDITION	DIAGNOSTIC STUDIES
<b>STRIDOR—ACUTE</b> Laryngotracheobronchitis Epiglottitis Spasmodic croup Foreign-body aspiration	Anteroposterior neck radiograph, history Lateral neck or direct visualization in an operating room with a qualified surgeon History Inspiratory and expiratory films, right and left lateral decubitus films, fluoroscopy, barium esophogram, rigid bronchoscopy
Retropharyngeal abscess Trauma Allergic reactions Peritonsillar abscess	Lateral neck radiograph or CT of the neck History, radiographs or CT of the neck/chest History History and physical examination of oropharynx, lateral neck radiograph or CT of the neck
Angioneurotic edema	History, C1 esterase level
<b>STRIDOR—CHRONIC</b> Choanal atresia Laryngomalacia Subglottic stenosis Laryngeal cysts, webs, hemangiomas Vocal cord dysfunction Laryngotracheoesophageal clefts Retained foreign body Epiglottic cysts Laryngeal papilloma	Inability to pass a nasogastric tube History, fluoroscopy, flexible bronchoscopy History, pulmonary function test, flexible bronchoscopy Flexible bronchoscopy Flexible bronchoscopy, history Suspension laryngoscopy Rigid bronchoscopy, chest radiographs Flexible bronchoscopy Flexible bronchoscopy

CT, computed tomography.

respiration. An extrathoracic variable obstruction (laryngomalacia) worsens on inspiration and improves during expiration, given that positive intraluminal pressures will distend this portion of the airway during exhalation but will compress the airway during a forceful inhalation. A variable intrathoracic obstruction is primarily appreciated on expiration, given that the airway is dilated on inspiration by the negative intrathoracic pressure but compressed during forceful exhalation.

## DIFFERENTIAL DIAGNOSIS

The causes of airways obstruction differ at various developmental stages. A summary of the causes of stridor in children is found in Table 348-3. Determining the correct pathological cause of the obstruction entails consideration of the child's age.

## NEONATES

### Laryngomalacia

Infants have more compliant chest walls and soft tissue, breathe faster, and have smaller-caliber airways than older children. These factors combine to increase the likelihood that infants will have respiratory difficulty. The most common cause of stridor in an infant is laryngomalacia. The onset is typically within the first 2 weeks of life. The stridor is positional, with greater severity when the infant is lying supine and diminished severity with prone positioning. Stimuli that increase the rate of airflow on inspiration, such as crying, feeding, or an upper respiratory tract infection, worsen the dynamic inspiratory obstruction associated with laryngomalacia. The symptoms come from immature cartilaginous structures of the larynx. The condition can aggravate underlying gastroesophageal reflux.



Moreover, the relatively more negative intrathoracic pressure that is necessary to bypass the dynamic and intermittently obstructive upper airway can result in microaspiration. Generally, laryngomalacia worsens in the first several months of life and resolves by the end of the first year.

In severe cases of laryngomalacia with constitutional symptoms of failure to thrive or an evolving chest wall deformity, epiglottoplasty with or without tracheostomy may be necessary. Respiratory distress, thoracic deformities (caused by severe and chronic retractions), failure to thrive, and hypoxia may occur in severe cases. Generally, diagnosis can be achieved with a complete history and physical examination. Definitive diagnosis, often unnecessary, can be made with flexible laryngoscopy. Endoscopically, the epiglottis folds over the larynx on inspiration as the arytenoid cartilages move to the midline on inspiration. Infants with laryngomalacia often have feeding problems and may exhibit coughing or choking when they feed as their first symptom. Stridor often worsens with minor respiratory tract infections. Through continuous noninvasive monitoring, studies have demonstrated that infants who have laryngomalacia are more likely than age-matched controls to have transient, albeit nonlife-threatening, episodes of hypoxemia and hypercapnia. As their disorder improves over time, these infants rarely require an artificial airway.

### Vocal Cord Paralysis

Unilateral or bilateral vocal cord paralysis may occur in otherwise healthy newborns and has been associated with birth trauma. A neonate with a shoulder dystocia, forceps delivery, or vacuum extraction is more likely to have unilateral vocal cord paralysis than a neonate experiencing an atraumatic delivery. Trauma associated with airway instrumentation can cause vocal cord paralysis as well. Infants intubated in the delivery room or those who have undergone mechanical ventilation may also have injury to the vocal cords as a result of airway instrumentation. The diagnosis is best made by flexible laryngoscopy while the baby is breathing spontaneously. If the endoscopic evaluation is performed during positive pressure ventilation, discerning vocal cord paralysis is difficult. However, performing the examination through a laryngeal mask allows for positive pressure ventilation noninvasively and can provide excellent visualization of the vocal cords. In the spontaneously breathing child with vocal cord paralysis, the true cord or cords move passively to the midline with inspiration. Unilateral cord paralysis caused by stretching of the recurrent laryngeal nerve often requires no specific therapy and resolves over time. However, surgical transection of the recurrent laryngeal nerve that might occur during surgical correction of congenital heart anomalies will result in permanent paralysis. Bilateral cord paralysis is associated with chronic aspiration and hypoxemia. In the presence of bilateral paralysis, a tracheotomy may be necessary.

To determine the feasibility of feeding the infant, a video swallowing study is essential. In some cases, infants can protect the airway by consuming highly

textured, thickened food, but they are unable to do so if thin food is consumed.

Vocal cord paralysis may also result from elevated intracranial pressure, a congenital Arnold-Chiari malformation, or from an intracranial mass as a result of nerve compression. In the presence of bilateral cord paralysis, determining the underlying cause is particularly important. In an otherwise healthy child whose vocal cord paralysis is thought to be caused by birth trauma, improvement over time is the rule.

Data indicate that vocal cord paralysis, either unilateral or bilateral, is a relatively common complication of congenital heart disease surgery. In the presence of a patent ductus arteriosus, the recurrent laryngeal nerve can be compressed, resulting in unilateral vocal cord paralysis. In the course of repairing congenital heart disease, injury to the recurrent laryngeal nerve often occurs, leading to vocal cord paralysis. Continuation on the lesion, the incidence may be approximately 10%.

### Extrinsic Compression of the Trachea

Compression of the trachea can lead to stridor. Potential causes of airway compression include thyroglossal duct cyst, ectopic thyroid tissue, esophageal duplication cyst, lymphoma, cardiac anomaly, or vascular anomaly. The optimal diagnostic and therapeutic approach depends on the condition of the child and the rate of progression of the symptoms. Clearly, a relatively asymptomatic patient with gradual onset can be evaluated at a less urgent pace than an acutely ill child with rapidly progressive illness.

### Craniofacial Anomalies

Congenital craniofacial anomalies can place newborns and older children at risk for chronic and severe obstructions of the upper airway. An obstruction of the upper airway can occur because of micrognathia (Pierre Robin sequence and Treacher Collins syndrome), macroglossia (Beckwith-Wiedemann syndrome), small mid-face or small oropharyngeal space (achondroplasia), and adenotonsillar hypertrophy (Down syndrome). Macroglossia can develop in children with lipid or glycogen storage disorders; this anomaly is rarely present at birth and develops slowly. Apnea studies that monitor nasal and oral airflow, chest wall movement, and pulse oximetry or a full polysomnogram can grade the level of severity of hypoventilation and hypoxemia in these children. Some infants require treatment with noninvasive or invasive (via tracheostomy) mechanical ventilation before reconstructive surgery can be performed.

### Tracheomalacia

Tracheomalacia is a congenital disorder of the trachea characterized by respiratory distress and wheezing. Typically, symptoms appear before the infant is 2 months old. The predisposing risk factors include a previous history of intubation, prematurity, and gastroesophageal reflux. Tracheomalacia results from incompletely formed cartilaginous rings. Normally, the cartilaginous component of the trachea comprises approximately two-thirds of the airway

circumference, with the membranous trachea comprising the remainder of the tracheal circumference. In tracheomalacia, the proportion of membranous to cartilaginous trachea is increased, resulting in poorly supported tracheal structures. Depending on the position of the diminished cartilaginous structure in the airway, the dynamic obstruction to airflow may be more apparent in inspiration or expiration. If the tracheomalacia is particularly severe, both phases of respiration may be affected. Tracheomalacia can be either primary or secondary. The primary form is characterized by relatively decreased cartilage in the tracheal rings. Secondary tracheomalacia results from extrinsic compression of the trachea. Causes of extrinsic compression might include an anomalous vascular structure, mediastinal tumor, lymphadenopathy, or enlargement of the left atrium.

The child with moderate or severe tracheomalacia exhibits chronic wheezing that is often diagnosed as asthma. Many premature infants have some component of tracheo- or bronchomalacia. In children with tracheomalacia, treatment with  $\beta$ -agonists may relax the tracheal smooth muscle in the membranous trachea and increase the flaccidity of the tracheal tone, thereby worsening airflow obstruction. The use of medications that increase tracheal airway smooth-muscle cell tone (eg, ipratropium bromide, bethanechol) can improve airflow.

## CHILDREN BEYOND THE NEONATAL PERIOD

### Acquired Infectious Causes of Airways Obstruction

Croup (laryngotracheobronchitis) is the most common cause of upper respiratory obstruction in childhood, with peak incidence in the second year of life (range: 6 months to 3 years). (See Chapter 352, Croup [Acute Laryngotracheobronchitis]), for more information.) Admission rates for croup in children seen in outpatient settings range from 1.5% to 31% of cases seen; these figures vary widely, depending on hospital admission practices and the severity of the disease in the population being assessed. Croup occurs most commonly in late fall and early winter. Croup is caused by inflammation and edema of the mucosal and submucosal tissues of the subglottic space. The swollen mucosa expands into the airway lumen and narrows the trachea.

Most children with croup have an uncomplicated course and are managed without formal medical care. Only a small percentage of children who require urgent care require hospitalization. Croup is diagnosed clinically and causes a barking cough, hoarse voice, high-pitched inspiratory stridor, and fever. The clinical presentation follows a prodrome of mild fever and upper respiratory tract infection symptoms lasting several days. Croup severity is generally worse at night compared to daytime. Mild croup is characterized by an intermittent barking cough, stridor only with agitation, mild tachypnea, and tachycardia. A child with mild croup is minimally distressed, well hydrated, and has a normal mental status. Moderate croup produces audible stridor at rest, worsening stridor with

agitation, a barking cough, and increased work of breathing (retractions, tachypnea, tachycardia). A child with moderate croup may be fussy but is alert, interactive, and comforted by parents. Hypoxia is atypical in mild or moderate croup. Laboratory tests are nondiagnostic. Radiographic studies of the neck are confirmatory but do not alter management and are not necessary in most cases. Classically, the trachea looks narrowed in the subglottic space in a characteristic steeple-like appearance on anteroposterior chest/airway radiographs.

### Peritonsillar Abscess and Retropharyngeal Abscess

Peritonsillar and retropharyngeal abscesses are common infections that occur in childhood and can be life threatening. A retropharyngeal abscess occurs most commonly in children between the ages of 2 and 4 years. A retropharyngeal abscess may extrinsically compress structures in the upper airway. Prominent presenting complaints are usually neck pain, fever, and sore throat rather than acute, severe airway obstruction. The symptoms caused by a retropharyngeal abscess relate to the pressure and inflammation produced by the abscess on either the airway or the upper digestive tract and pharynx. The patient may have intense dysphagia, drooling, and odynophagia, or some element of respiratory distress from edema and inflammation of the airway (stridor, tachypnea, or both) may be present. An unwillingness to move the neck because of discomfort is often a prominent presenting feature and should lead to consideration of retropharyngeal abscess if the child is febrile and irritable. Usually, extension of the neck is affected more than flexion. This circumstance causes the patient to hold the neck stiffly or have torticollis.

A peritonsillar abscess is the most common deep-neck infection in children and adolescents, accounting for at least 50% of cases. A peritonsillar abscess generally occurs in later childhood and adolescence, although it can occur at any age. (See Chapter 311, Pharyngitis and Tonsillitis.) The sudden onset of severe respiratory distress is rare. The infection is usually in the superior pole of the tonsil, where a defined collection of pus is located between the tonsillar capsule, the superior constrictor, and the palatopharyngeus muscle. The typical clinical presentation of peritonsillar abscess is a severe sore throat, fever, and a *hot-potato* muffled voice. Drooling may be present. Trismus is common; patients will often have swelling of the neck and complain of neck pain. The discomfort associated with the peritonsillar abscess creates fatigue and irritability in the patient.

### Bacterial Tracheitis

Bacterial tracheitis has been termed membranous croup, bacterial croup, and pseudomembranous croup. Although the incidence is low, bacterial tracheitis is a serious illness. It generally affects children between 4 and 8 years of age. The pathogenesis of bacterial tracheitis remains controversial. Bacterial tracheitis often occurs as a secondary bacterial infection complicating a preexisting viral infection, including adenovirus, influenza A, and influenza B. Bacteria

gain access to the trachea epithelium after a viral infection that compromises epithelial integrity. A tracheal epithelial inflammation occurs, and thick mucopurulent secretions accrue. Although *Staphylococcus aureus* formerly was the primary causative organism, more recently the predominant organisms are *Moraxella catarrhalis*, Streptococcal species, and oral anaerobes. The incidence of bacterial tracheitis caused by *Haemophilus influenzae* is decreasing because of the routine practice of *Haemophilus influenzae* b (Hib) childhood vaccinations in most areas of the United States.

Bacterial tracheitis can be distinguished from croup by the child's age and the degree of toxicity (Table 348-4). Children commonly experience a viral prodrome of fever, barking cough, and stridor. In contrast to croup, in bacterial tracheitis, symptoms worsen over time. To evaluate the child, lateral and anteroposterior radiographs of the neck and chest may be helpful. Findings on plain-film radiographs include subglottic narrowing, a ragged edge to the usually smooth tracheal air column, and a hazy density within the tracheal lumen. The epiglottis and supraglottic structures seem normal on neck films. In the event of respiratory collapse or an inability to mobilize secretions effectively, mechanical ventilation is necessary. Careful attention to the suctioning and mobilization of secretions is essential. Occlusion of the endotracheal tube has been reported as a common cause of death in intubated and mechanically ventilated children with bacterial tracheitis. For this reason, some otolaryngologists have advocated for expectant placement of tracheotomy tubes in children with bacterial tracheitis, because tracheostomy canulas can be rapidly and safely replaced in the event of

obstruction with tenacious secretions. Antibiotics and supportive care are essential for full recovery. Complications associated with bacterial tracheitis include toxic shock syndrome, septic shock, postintubation pulmonary edema, acute respiratory distress syndrome, and subglottic stenosis.

### Epiglottitis

Acute epiglottitis is a potentially life-threatening infection of the supraglottic structures, and can lead to a sudden, fatal airway obstruction if treatment is delayed. Classically, the disease does not involve the subglottic or tracheal mucosa. If treatment is delayed in young children, the condition may rapidly progress to a complete airway obstruction with cardiorespiratory arrest.

Acute epiglottitis was initially described as a disease of adults, but events occurred that led to an epidemiologic shift in the 1960s and it became primarily a pediatric disease, with an incidence of 1 per 100,000 children by 1993. Before the introduction of the Hib vaccine, invasive disease from *H influenzae* occurred at a rate of 116 per 100,000 children in 1986, and this was the organism most often cultured in children with epiglottitis. After the introduction of the conjugate vaccine against *H influenzae* type b in 1985, the incidence of invasive disease from *H influenzae* decreased dramatically, and was accompanied by a dramatic decline in the incidence of acute epiglottitis in children.

As the frequency of Hib disease decreased, the infectious etiology of epiglottitis shifted toward other causative organisms. In this era, in which vaccination for many Streptococcal serotypes has been introduced into the routine vaccination schedules

**Table 348-4**

**Comparison of Epiglottitis, Laryngotracheobronchitis, Spasmodic Croup, and Bacterial Tracheitis**

FACTOR	EPIGLOTTITIS	VIRAL CROUP	SPASMODIC CROUP	BACTERIAL TRACHEITIS
Age (yr)	2–6	0.6–2	0.5–3	4–8
Cause	<i>Haemophilus influenzae</i> type b	Parainfluenza 1,2,3	Gastroesophageal reflux, asthma	<i>Staphylococcus aureus</i> , <i>Haemophilus influenzae</i> type b
Season	All year	Late spring, late fall	All year	All year
Clinical presentation	Child sitting Toxic Drooling Dysphagia Muffled voice	Child lying down Nontoxic Barking cough Hoarseness	Nontoxic Barking cough Hoarseness	Toxic Barking cough
Onset prodrome	Rapid, over a few hours	Variable; few hours to 4 days	Sudden	Variable; few hours to 5 days
Stridor	Less common	Common	Very common	Common
Fever	High	Low-grade	Afebrile	High
Chest retractions	Less common	Common	Common	Common
Lateral neck film	Swollen epiglottis	Subglottic narrowing	None	Pseudomembrane
Progression	Rapid	Usually slow	Rapid	Usually slow
Recurrence	Rare	Common	Very common	Rare

recommended by the Centers for Disease Control and Prevention and the American Academy of Pediatrics, most cases are thought to be caused by other bacteria, such as *S aureus*, *M catarrhalis*, *Pseudomonas* species, *Candida albicans*, *Klebsiella pneumonia*, *Pasturella multocida*, and *Neisseria* species. Bacterial superinfection of viral infections is also common, particularly with herpes simplex, parainfluenzae, varicella-zoster, and Epstein-Barr.

Epiglottitis occurs throughout the year, but mainly during the 6-month period from December to May. It previously occurred equally in males and females with a slight male predominance between the ages of 2 and 6 years of age, though more recently, the epidemiology shifted again toward significantly older patients.

The onset of epiglottitis is usually abrupt, preceded by a minor upper respiratory infection in some cases. The onset is characterized by high fever, toxic appearance, and sore throat that progresses over a few hours to dysphagia, drooling, and respiratory distress. The patient seems anxious and irritable. Stridor is a late finding. Breathing becomes noisy, and the voice and cry are muffled as swelling of the aryepiglottic folds and supralaryngeal mucosa swells and obstructs the glottic inlet. The patient tends to sit forward in the "sniffing position" with the neck hyperextended in order to increase airway patency. Complete airway obstruction may occur at any time without any preceding deterioration in clinical signs.

A very high index of suspicion must be maintained, and epiglottitis should be considered in every child with apparent acute upper airway obstruction who has a high fever and sore throat, and especially when those signs developed over a few hours. A lateral neck radiograph can be helpful, though should only be attempted if the patient is stable and the diagnosis is in doubt, since the condition can progress rapidly. Therapeutic trials of inhaled medicines such as corticosteroids or racemic epinephrine should not be initiated, as time is wasted, and the child may become more irritated upon manipulation, leading to complete obstruction of the airway. Additionally, direct visualization of the epiglottis should not be undertaken until the child is undergoing tracheal intubation.

Most fatalities occur within the first few hours after the patient has arrived at the hospital. All deaths result from complete airway obstruction. Once the diagnosis is made, there should be no delay in establishing an artificial airway. If there is time, the child should be intubated in the operating room under general anesthesia by personnel who can perform emergency tracheostomy if intubation fails. Corticosteroids and epinephrine have been used in the past. However, there is no good proof that these medications are helpful in cases of epiglottitis.

Between 10% and 25% of cases may be managed by observation; these are normally older children with larger airways, although mortality is higher in this group historically. The normal treatment algorithm is as follows:

1. Avoid disturbance until an airway is secured. Allow the child to sit up and stay in his parent's arms so as to avoid agitation.
2. Give 100% oxygen by blow-by administration.

3. Perform a radiologic study of the lateral neck, only if the child seems stable and has no stridor.

4. Intubate in the operating room.

5. Sedate (after intubating).

6. Intravenous antibiotics may effectively control inflammation and rid infection from the body.

A pediatric ear, nose, and throat surgeon should be contacted immediately, and should be the only physician to try to visualize the airway. The medical and surgical team should be ready to emergently place an endotracheal tube, and also be ready for emergent tracheotomy. It is best for the surgeons to visualize the airway when in the operating room. All children who are suspected of having bacterial epiglottitis should be admitted to the hospital for IV antibiotic treatment and intensive care monitoring. Antibiotics are prescribed to treat the most common types of bacteria. Blood cultures are usually obtained for the potential verification of an organism. Generally, amoxicillin/clavulanic acid or ceftriaxone are extremely effective.

### Laryngeal Papillomatosis

Respiratory papillomatosis is a disease caused by infection of the airway by human papilloma virus (HPV). The lesion is benign but can transform to a malignant lesion, particularly in the lung parenchyma. More commonly, HPV is life threatening if the aggressive growth and rapid proliferation of the papilloma lesions in the airway cause airway obstruction. HPV infection in children is most commonly acquired as the neonate passes through the birth canal. HPV-6 and -11 are the most common subtypes in this population, as is true for genital HPV infection in women.

In most instances, children with HPV infection of the larynx exhibit hoarseness, though advanced cases can have stridor and respiratory distress. Most commonly, it occurs on the vocal cords but can infect the trachea and even the bronchi. In children, HPV infection of the larynx is usually diagnosed at age 2 to 4 years. The growth of the papilloma will be more aggressive the earlier it occurs. Treatment is generally focused on removing the obstructing lesions with laser ablation of the root of the papilloma to prevent regrowth. Often, repeated ablations are necessary as lesions regrow at sites of ablation. Vaccine trials and adjuvant therapies using antivirals such as  $\alpha$ -interferon injected into the lesion are being evaluated as therapeutic alternatives. A case report published in 2011 discusses the sustained remission in a 5-year old child with recurrent HPV infection of the larynx after treatment with the quadrivalent HPV vaccine. Clinical trials with bivalent and quadrivalent vaccines have demonstrated greater than 95% efficacy in preventing infection in HPV-naïve recipients. Data regarding transvaginal infection rates are not yet published. When there is a clinical need to instrument the airway, great care must be taken to avoid introducing infection by inoculating the more distal components of the airway with viral particles.

### VASCULAR ANOMALIES

Stridor or dysphagia can be a manifestation of extrinsic compression of the airway or esophagus by an anomalous vascular structure. The anomalies result



from abnormal persistence or regression of embryonic structures. The most common anomaly—aberrant right subclavian artery—produces minimal symptoms. In many cases the only clinical manifestation is dysphagia caused by compression on the esophagus. A barium swallow can yield diagnostic information. In the presence of a severe obstruction, infants can be quite ill. Poor feeding may lead to failure to thrive. Wheezing and stridor may be consistently present and exacerbated by feeding. In the most profound cases, cyanosis and apnea may occur.

In the presence of a right-sided aortic arch, a child may experience vascular impingement on the airway as a result of a double aortic arch, wherein the aortic arches encircle the esophagus and trachea. The disease results when resorption of the fourth embryonic aortic arch is incomplete. The problem may cause stridor or wheezing. The right and left arches compress the right and left sides of the trachea and the esophagus. The right arch indents the esophagus posteriorly. Division of one of the arches, usually the smaller posterior, opens the constricting ring and is curative.

In the context of right-sided arches, a residual patent ductus arteriosus or ligamentum arteriosum can form a complete ring around the airway. A division of the ductus or ligamentum is curative. Occasionally, a carotid or innominate artery compresses the anterior margin of the trachea. This compression may show on radiographs of the tracheal air column or on a tracheogram, but the esophagram is normal. If needed, the compressing artery can be displaced anteriorly at surgery.

Although not a vascular ring, the anomalous left pulmonary artery also causes an airway obstruction. The left pulmonary artery arises from the right pulmonary artery and passes between the esophagus and trachea, compressing the trachea and the right main bronchus. This lesion causes compression on the anterior edge of the esophagus. A collapse or hyperinflation of part of the right lung may occur. Diagnosis is made by a combination of esophagrams, bronchoscopy, computed tomographic angiography, or magnetic resonance imaging. The surgical reattachment of the left pulmonary artery to the main pulmonary artery relieves the obstruction, but residual tracheomalacia may be present.

## ACQUIRED, NONINFECTIOUS CAUSES OF AIRWAYS OBSTRUCTION

### Vocal Cord Dysfunction

Vocal cord dysfunction (VCD) is characterized by the inappropriate adduction of the vocal cords during inspiration. Typically, vocal cord dysfunction causes a sudden onset of labored breathing with inspiratory stridor. The sound is often erroneously characterized as wheezing. For some patients, the symptoms are precipitated by physical activity. The inappropriate adduction during inspiration may result in severe airflow limitation characterized by profound, high-pitched stridor and dyspnea. The acute onset and severity of symptoms in some children with VCD have resulted in intervention with endotracheal intubation

or tracheotomy for severe upper airway obstruction. Diagnosis entails flexible laryngoscopy during an acute exacerbation. Subsequent to the definitive diagnosis, patient education, speech therapy, and biofeedback have produced favorable results. Techniques taught by a speech therapist who is familiar with this disorder result in the ability of patients to control vocal cord movement in the event that symptoms recur. Techniques focus on training the extrinsic laryngeal muscles. In the short term, this treatment course is associated with high rates of success.

The diagnosis of VCD is often complicated by an initial diagnosis of asthma. Current data indicate that VCD is often a self-limiting disorder. Most patients have no long-term sequelae once the diagnosis has been established. For some patients, only high-level exercise can precipitate the VCD. For such patients, insight-driven biofeedback is difficult to use. Data suggest that the use of ipratropium bromide may be a safe and effective measure for treating exercise-induced VCD.

### Anaphylaxis

Anaphylaxis and anaphylactoid reactions may be severe and life threatening when edema involves the retropharynx or larynx. The increasing incidence of food allergies correlates with more anaphylactic reactions. The onset of symptoms is usually sudden. Presenting signs and symptoms can include urticaria and facial edema. Treatment must be initiated immediately. Initial therapy should include the intramuscular injection of epinephrine. Patients at risk for an anaphylactic reaction should always have immediate access to portable epinephrine devices that can be used in an ambulatory setting (home or school) when the first signs of anaphylaxis are noted. Even if the device is effective, the patient should be transported to a local emergency room for monitoring as the effects of initial treatment wane and to ensure that the late phase of the allergic response does not compromise the child. After the initial treatment with epinephrine, systemic corticosteroids should be provided to mitigate any biphasic or prolonged effect of the allergic response.

### Foreign-Body Aspiration

Foreign-body aspiration (FBA) is a common and potentially life-threatening event. The number of emergency room visits for FBA in 2001 exceeded 17,000. Less than 1% of these events resulted in death, though the estimated number of deaths per year caused by foreign body aspiration ranged between 22 deaths per year average between 1972 and 1992 to 160 deaths in 2000 in the United States. Most of these events occur in children younger than 3 years, and the peak incidence occurs between 1 and 2 years of age. The most commonly aspirated objects are peanuts and other types of nuts and seeds, food particles, hardware, and pieces of toys. Balloons are the most common object involved in fatal FBA, but aspiration of small marbles and balls results in considerable morbidity and mortality. Foreign bodies that lodge in the back of the mouth/throat and above the vocal cord can cause complete obstruction and death. Most foreign bodies that are aspirated are found in the major bronchi and

do not entirely block the airway; laryngeal and tracheal foreign bodies are less common. The right lung was involved in 60% of cases, the left lung in 23% of cases, the trachea or carina in 13%, and the larynx in 3%. Bilateral FBA occurred in 2% of cases.

The presentation of FBA depends on whether the event was witnessed, the age of the child, the type of object aspirated, the amount of time that has elapsed since the event, and the anatomic location of the object. A presentation and diagnosis within 24 hours of aspiration occurs in approximately 50% to 75% of cases. Children who have signs of severe respiratory distress, such as cyanosis, stridor, or wheeze, and altered mental status have to be evaluated and treated immediately with a rigid bronchoscopic removal of the foreign body. More commonly, the situation is less emergent. The examination may reveal localized wheezing, cough, and diminished breath sounds, but these are not universally present. A history of choking or a sudden onset of coughing, dyspnea, or cyanosis may be present in a previously healthy child. The choking phase occurs immediately after the episode but tends to resolve quickly because of tachyphylaxis of cough receptors in the lower airways. The lack of ongoing symptoms should not be construed as a sign of resolution, given that a delay in diagnosis may result in chronic infection of the lung parenchyma distal to the foreign body. Children may have fever and other signs of pneumonia.

Plain-film radiographs may or may not be helpful in establishing the diagnosis of FBA. If the child is able to cooperate, then chest radiographs obtained in the exhalation phase can demonstrate asymmetric gas trapping. Given that most inhaled objects are not radiopaque, direct radiographic evidence of their presence is absent. Other radiographic signs can include focal segmental or entire lung hyperinflation, atelectasis, mediastinal shift, and pneumonia. Hyperexpansion of the lung distal to an obstruction is exaggerated on expiratory views because of ball-valve obstruction. In young children for whom expiratory views may be difficult to obtain, a substitute can be obtained using 2 lateral decubitus views. The lower side is the “expiratory” view.

The most sensitive and specific method is that of direct visualization by bronchoscopy. If the index of suspicion is high, then an otorhinolaryngologist or general surgeon should be consulted. In children, a rigid bronchoscopy is the preferred mode of visualization and airway instrumentation, because the rigid bronchoscopy provides control of the airway throughout the removal process. If the index of suspicion is lower, flexible bronchoscopy by the pulmonologist is merited for diagnostic purposes. Lodged nasal foreign bodies should be removed quickly, particularly corrosive objects such as nickel batteries. (See Chapter 251, Foreign Bodies of the Ear, Nose, Airway, and Esophagus.)

### SUGGESTED READINGS

- Khariwala SS, Lee WT, Koltai PJ. Laryngotracheal consequences of pediatric cardiac surgery. *Arch Otolaryngol Head Neck Surg.* 2005;131:336–339
- Sigillito RJ, DeBlieux PM. Evaluation and initial management of the patient in respiratory distress. *Emerg Med Clin North Am.* 2003;21:239–258

## Chapter 349

# ALTERED MENTAL STATUS

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Many disease processes act directly or indirectly on the central nervous system (CNS) to cause an alteration in the level of consciousness. Although in severe cases the child seems unresponsive, the initial changes in mental status are often subtle. These changes are recognized by assessing the child’s actions and responses to external and internal stimuli in what is collectively known as *behavior*. Behavior is a combination of a variety of observations, including appearance, level of alertness, speech, affect, mood, thought, and judgment. These actions are child and age specific. For example, apprehension, avoidance, and crankiness may be normal responses of a toddler to a physician’s physical examination, whereas a similar response by an adolescent may be abnormal. Although major changes in behavior are readily apparent, subtle changes are often best appreciated by parents and caregivers.

## DEFINITION OF TERMS

Consciousness is the awareness of self and the environment. Alteration of the level of consciousness usually begins with becoming unaware of self, followed by reduced awareness of the environment, and finally an inability to be aroused. A child who is in a coma is unresponsive to all stimuli, including pain. Although consciousness and coma represent the extremes of mental status, many intermediate levels of consciousness exist. Although specific definitions are given to each stage of consciousness, a progression of symptoms is not an all-or-nothing phenomenon. Rather, a continuum of the levels of consciousness may exist.

Confusion is a state in which a person’s responses are slowed and cognitive abilities are impaired, usually accompanied by some disorientation. Infants and toddlers may exhibit irritability as a sign of confusion. Delirium is a succession of confused and unconnected ideas. Children with delirium are often aggressive, agitated, and combative, with episodes of somnolence and withdrawal. Lethargy is a state of profound slumber in which the child has limited movement and speech. The lethargic child can be awakened with moderate stimuli but then returns to a state of slumber. In stupor, the child seems unresponsive and can be aroused only by repeated, vigorous stimuli. In the vegetative state, the child has lost all cognitive neurologic function, communication, and awareness but may retain some noncognitive functions (eg, eye opening) and a sleep–wake cycle. In coma, the child is totally unresponsive, and the eyes remain closed.

## ETIOLOGY

An altered level of consciousness in children has many causes. The mnemonic AEIOU TIPS is helpful when considering the major categories of illness or injury (see Table 349-1). Although these disorders can occur

**Table 349-1** Mnemonic for Altered Mental Status (AEIOU TIPS)

A	Alcohol, abuse
E	Epilepsy, encephalopathy, electrolyte abnormalities, endocrine
I	Insulin, intussusception, inadequate fluid, ingestion
O	Overdose, oxygen deficiency, occult trauma, obstructed ventriculoperitoneal shunt
U	Uremia
T	Trauma, temperature abnormality, tumor
I	Infection
P	Poisonings, psychiatric, postictal
S	Shock, stroke, space-occupying lesion (intracranial)

**BOX 349-1 Common Causes of Altered Mental Status by Age****INFANT**

- Infection
- Complication of congenital malformation (cardiac or CNS)
- Metabolic
- Inborn error of metabolism
- Seizure
- Nonaccidental trauma/abuse
- Ingestion

**CHILD**

- Infection
- Seizure
- Toxin
- Trauma
- Metabolic
- Nonaccidental trauma/abuse
- Intussusception
- Ingestion

**ADOLESCENT**

- Toxin
- Trauma
- Infection
- Psychiatric
- Seizure
- Ingestion

at any age, certain conditions are more prevalent at certain ages (see Box 349-1). Nontraumatic coma has a bimodal distribution and is most common in infants and toddlers, with a smaller peak in adolescence. Infection of the brain, meninges, or both is the most common cause of altered level of consciousness, accounting for more than one-third of nontraumatic cases. Exposure to or ingestion of toxic substances is the next most common cause. Many medications are brightly colored and taste similar to candy, resulting in accidental ingestion, especially in toddlers. Ingestion by adolescents is often intentional and typically involves over-the-counter medications or psychotropic drugs, such as antidepressants. Commonly ingested

**BOX 349-2 Commonly Ingested Agents That Cause Altered Mental Status**

- Amphetamines
- Anticholinergics
- Anticonvulsants
- Barbiturates
- Benzodiazepines
- Camphor
- Clonidine
- Cocaine
- Dextromethorphan
- Ethanol
- Haloperidol
- Narcotics
- Phenothiazines
- Salicylates
- Selective serotonin reuptake inhibitors
- Tricyclic antidepressants

agents that cause an altered level of consciousness are listed in Box 349-2. Congenital heart and brain malformations typically present in the first few months after birth, but complications from surgical correction of such problems—for example, ventriculoperitoneal shunt obstruction—may occur at any age.

Inborn errors of metabolism, including urea cycle defects, organic acidemias, and specific disorders of amino acid metabolism, typically occur in infancy. Diabetic ketoacidosis is the most common metabolic disorder that can present with an alteration of consciousness. It can occur at any age but is more common in adolescence. An acute confusional state can be seen in autoimmune disease, especially systemic lupus erythematosus. Thrombotic thrombocytopenic purpura is a rare hematologic disorder that can present with confusion and may be associated with systemic lupus erythematosus. Prolonged seizures, anticonvulsive therapy, and the postictal state can alter the level of consciousness at any age.

Although the overall incidence of traumatic and nontraumatic coma is similar, the rate of traumatic injury tends to increase throughout childhood. Head trauma can cause intracerebral, epidural, or subdural bleeding, as well as contusions and diffuse axonal

### BOX 349-3 Differential Diagnosis of Altered Level of Consciousness

#### STRUCTURAL CAUSES

- Cerebral vascular accident
- Cerebral vein thrombosis
- Hydrocephalus
- Intracerebral tumor
- Subdural empyema
- Trauma (intracranial bleeding, diffuse cerebral swelling, shaken baby syndrome)

#### MEDICAL CAUSES (TOXIC-INFECTIOUS-METABOLIC)

- Anoxia
- Autoimmune (systemic lupus erythematosus)
- Diabetic ketoacidosis
- Electrolyte abnormality
- Encephalopathy
- Hematologic (thrombotic thrombocytopenic purpura)
- Hypoglycemia
- Hypothermia or hyperthermia
- Inborn errors of metabolism
- Infection (sepsis)
- Ingestion
- Intussusception
- Meningitis and encephalitis
- Postictal state
- Psychogenic
- Toxin
- Uremia (hemolytic uremic syndrome)

injury. These conditions can lead to cerebral dysfunction, by either primary neuronal damage or the effects of cerebral herniation with brainstem compression. Child abuse should always be considered in any infant with an altered level of consciousness.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of a child with altered mental status can be divided into structural (anatomic) causes and medical (toxic, infectious, metabolic) causes (see Box 349-3). This framework is useful in the context of the pathophysiologic factors of maintaining a state of consciousness. Normal mental status requires the combination of thought content (ie, cognition, affect) and a state of arousal. The content is controlled by the cerebral hemispheres, whereas the state of arousal is controlled by the ascending reticular activating system (ARAS). The ARAS, also known as the sleep center, is a core brainstem structure that courses from the medulla to the thalamus. As part of the normal cycling of behavior, consciousness moves from the awake state to drowsiness to sleep. At any time during this transition, sensory impulses may reach the ARAS, leading to an increased awareness and a more awake state. These sensory impulses may be external, such as noise, touch, or smell, or they may be internal, such as headache or abdominal pain.

To maintain a normal level of consciousness, functioning cerebral hemispheres and a functioning ARAS must be present. Defects in either of these components will cause an alteration in mental status. Thus altered mental status can result from depression of both cerebral hemispheres, a localized abnormality of the sleep center, or a global central nervous dysfunction in which both the cerebral cortex and the ARAS are affected. In general, structural causes, such as an epidural hematoma, a cerebral vascular accident, or an intracranial tumor, produce dysfunction in the region of the ARAS. Medical causes, such as meningitis, hypoglycemia, or ingestion of a toxic substance, generally cause dysfunction of both cerebral hemispheres.

The differentiation of structural and medical causes therefore rests on the ability to assess the function of the ARAS. The ARAS is located in the vicinity of several brainstem reflexes, the most important of which is the pupillary light reflex. Pupil size is a balance of parasympathetic and sympathetic inputs. For example, lesions in the midbrain affect the parasympathetic and sympathetic fibers equally, resulting in pupils that are fixed at midsize. Lesions of the pons preferentially affect the descending sympathetic fibers and result in fixed, pinpoint pupils. Importantly, the pupillary reflex is relatively resistant to metabolic insult. Thus preservation of the pupillary response to light, even if sluggish, is one of the most important ways to differentiate structural from medical cause of altered mental status. The cranial nerves that control reflex eye movements and maintain conjugate gaze are also located in the vicinity of the ARAS. Therefore, asymmetrical eye movements, such as a fixed gaze or an inability to abduct an eye, suggest dysfunction in the region of the ARAS, which is often caused by structural problems.

Structural lesions compress or destroy areas of the brainstem and are often characterized by unequal or unreactive pupils, as well as focal neurologic findings. Medical causes produce dysfunction in both cerebral hemispheres but result in preserved pupillary reflexes and nonfocal neurologic findings. Structural causes sometimes occur without focality, such as acute bilateral cerebrovascular disease or early acute hydrocephalus. Similarly, some medical causes, such as hypoglycemia, hypercalcemia, uremia, and a postictal state with Todd paralysis, may be accompanied by focal neurologic findings.

## EVALUATION

Regardless of the underlying cause, patients with an acute change in mental status may exhibit a reduced awareness of self, may have a reduced awareness of the environment, may be agitated with periods of heightened mental activity, or may be unable to be aroused. A complete history and thorough physical examination are crucial in identifying the underlying cause and managing these patients appropriately.

## HISTORY

The history of the manifesting event is often the part of the clinical evaluation with the greatest diagnostic value. Specific detail should be obtained concerning the circumstances of the onset of the neurologic symptoms, including events and actions directly preceding the



change in mental status. Associated symptoms may include weakness, headache, vomiting, dizziness, diplopia, and seizure-like activity. If the alteration in consciousness occurred abruptly, then the physician should consider intracranial hemorrhage, seizure, sudden cardiac arrhythmia, trauma, or ingestion of a toxic substance. A more gradual change in mental status may suggest infection, metabolic abnormality, or a slowly growing intracranial mass. If the altered mental status is preceded by headache (especially on waking), double vision, or nausea and vomiting, then increased intracranial pressure should be suspected. Vomiting and decreased oral intake, especially if accompanied by bloody stool, is seen with intussusception.

A history of trauma is important because it directs the differential diagnosis toward a structural lesion such as an epidural hematoma or cerebral contusion. However, the possibility of nonaccidental trauma, especially if the caregiver's history is inconsistent with the clinical findings, should not be excluded.

Ingestion of toxic substances is a common cause of altered mental status in toddlers and adolescents. In the young child, the history of an accidental exposure is often obtained from the child's caregiver. However, sometimes the ingestion is not witnessed; thus a detailed list of potential poisons to which the child may have access, including prescription and nonprescription medications, should be obtained. It is important to specifically ask about use of alternative and herbal remedies. For example, imported camphor products have been identified as a source of seizures in children in certain ethnic populations that use it as a natural remedy. The adolescent may admit to an intentional overdose, but the history is often obscure or unobtainable. In these cases, interviews with accompanying friends and family members are essential.

The medical history may include an underlying disorder that predisposes the child to a condition that results in altered mental status. A child with diabetes may have ketoacidosis or hypoglycemia. Children with a metabolic disorder or with hepatic or renal failure may develop encephalopathy. An adolescent with systemic lupus erythematosus may have cerebritis.

## PHYSICAL EXAMINATION

A thorough physical examination not only may lead to a probable diagnosis but also may provide a baseline with which future examinations can be compared so as to assess the improvement or deterioration of the child's clinical status. The level of consciousness can be determined by the child's appearance, interactivity, consolability, speech, cry, and gaze. Care must be taken, especially for young children and those with chronic illness, to ascertain the child's baseline state of functioning and responsiveness.

Vital signs are particularly important. Hyperthermia may be present with infection, heatstroke, or certain toxins (eg, cocaine, anticholinergics, phencyclidine). Hypothermia occurs with exposure to cold or with alcohol overdose. Hypertension, bradycardia, and irregular respirations (the Cushing triad) are signs of impending cerebral herniation but only appear late in the course of increasing intracranial pressure. Abnormalities in heart rate and blood pressure

can also occur with fever, pain, arrhythmias, hypovolemia, myocardial injury, and status epilepticus. Abnormal respirations can be seen with pain, hypoxia, acidosis, intoxication, and brainstem lesions. In some cases, the respiratory pattern may be a clue to the level of neurologic dysfunction. Posthyperventilation apnea—a short apnea after deep breathing—occurs with lesions in the cerebral hemispheres. As dysfunction moves rostrally from the midbrain to the medulla, the respiratory pattern progresses from Cheyne-Stokes breathing (crescendo-decrescendo hyperpnea followed by apnea) to central neurogenic hyperventilation (sustained, rapid, deep breathing). Finally, irregular, sporadic, apneustic respiration occurs with low brainstem dysfunction.

The mouth and throat should be examined for signs of airway obstruction causing hypoxia. A budging fontanel and nuchal rigidity are signs of meningitis or meningeal irritation from an intracranial mass. The skin examination can be helpful in identifying hypoxia, anemia, jaundice, carbon monoxide and other poisonings, trauma, and certain infections. Adolescents who are pretending to be unresponsive usually resist opening their eyes, and they avoid hitting themselves when their hand is raised and then allowed to drop to their face. Furthermore, when feigning coma, the eyes close quickly and deliberately after being held open by the examiner, as opposed to true coma, during which the eyes close slowly.

The neurologic examination should be directed at determining whether the underlying diagnosis is of structural or medical origin. The pupillary reflex and extraocular movements may provide essential clues. In pathologic states confined to the cerebral hemispheres, the pupils function normally, unless this state results in herniation. At the level of the diencephalon (thalamus and hypothalamus), pupils are miotic but react to light. With midbrain involvement, pupils may be midposition, irregular, or widely dilated; light reflexes may be absent if oculomotor nerves are involved. Bilateral fixed and dilated pupils indicate massive CNS dysfunction. A unilateral dilated pupil is a common early sign of uncal herniation. Extraocular muscle positions should be noted at rest (deviation may mean seizure activity or structural lesions); spontaneous abnormal eye movements should be identified, and ocular responses to vestibular stimulation should be tested. As with pupillary response, extraocular movements will vary with the level of the lesion. In general, asymmetry is seen with midbrain and upper pons involvement, and lack of extraocular movements is present with lower pons and medullary involvement. Negative doll's eyes—a condition in which the eyes seem painted on the face because the eyes remain stationary with respect to head movement—is seen in comatose patients with a low brainstem lesion.

Not all abnormal pupillary response is because of increased intracranial pressure. Mydriasis can be seen in Horner syndrome and in exposure to certain toxic substances, including anticholinergics, amphetamines, cocaine, and tricyclic antidepressants. Miosis may be caused by cold exposure, opiates, ethanol, barbiturates, cholinergic agents such as organophosphates, and clonidine.

When assessing motor function in patients with an altered mental status, spontaneous movements should be evaluated for signs of hemiparesis that may suggest a structural lesion or uncal herniation. Tone should be assessed for flaccidity and responses to painful stimuli. Patients who are unresponsive may have depressed brainstem function, and those who have increased tone may have diffuse cortical injury. Posturing is a bad sign, and the type of posturing aids in determining the extent of the injury. Decorticate posturing occurs when the patient flexes the arms, wrists, and hands, and adducts the upper extremities while internally rotating and plantar-flexing the lower extremities. This form of posturing occurs as a result of diffuse damage to the cerebral cortex, white matter, and basal ganglia. Decerebrate posturing is when the patient exhibits marked opisthotonus with extended arms and hands, which is usually the result of extensive damage involving the midbrain.

## LABORATORY EVALUATION

In the setting of altered mental status, laboratory testing should focus first on determining life-threatening metabolic derangements and then determination of the underlying cause. Rapid bedside glucose determination can identify hypoglycemia within minutes of clinical evaluation. In addition to being a common cause of altered mental status, hypoglycemia also accompanies many other underlying causes, such as diabetes, metabolic disorders, and sepsis. Calcium and sodium abnormalities can be identified on a serum chemistry panel. Serum bicarbonate and arterial blood gas levels may show acidemia, either as a direct result of an underlying metabolic disorder or as a result of abnormal respiratory effort. Hemoglobin levels can help determine whether anemia is present, and the white blood cell count may be high if the altered mental status results from an infection. Thrombocytopenia is associated with hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. Serum ammonia is an important screening test for many inborn errors of metabolism, although mild hyperammonemia can be a nonspecific finding in children. Other testing to be performed in suspected metabolic abnormalities or when the diagnosis is unsure after initial testing include urine porphyrins, ketone bodies, plasma free fatty acids, carnitine, creatine kinase, lactate, pyruvate, serum amino acids, and urine organic acids.

If ingestion of a toxic substance is considered, then directed drug levels (eg, phenytoin, salicylates) might pinpoint a diagnosis. A qualitative urine toxicology screening can identify a variety of commonly ingested agents, but its usefulness is limited because of the delay until the results become available. Measurement of serum osmolality may be helpful if poisoning with methanol, ethylene glycol, or isopropanol is suspected. Serum co-oximetry is needed for determining carbon monoxide level. If the child is febrile, and infection is a possibility, then blood and urine should be tested for bacterial and viral pathogens. If infection of the cerebrospinal fluid (CSF) is suspected, consider urgent evaluation of the CSF after a mass lesion has been excluded.

Abnormalities on an electrocardiogram (ECG) may be seen in cardiac causes such as myocarditis or

dysrhythmias. However, a normal ECG finding does not rule out these disorders. In addition, many serious drug overdoses have ECG findings. Tricyclic antidepressants cause sodium channel blockage, resulting in primary conduction delays and prolongation of the QRS interval. Ischemic changes on the ECG are seen with cocaine overdose. Neuroleptic overdose (eg, phenothiazines, thioridazine, haloperidol, chlorpromazine) causes QT prolongation.

## Imaging Studies

Although the history and physical examination may provide clues to the underlying diagnosis, neuroimaging of the brain is the fastest, most reliable test to differentiate structural from medical causes of altered mental status. The decision of whether to obtain a computed tomography (CT) scan or a magnetic resonance imaging (MRI) study depends on a variety of factors, including the clinical situation, the stability of the patient, and the availability of the test. MRI uses no ionizing radiation and therefore poses reduced risk to the developing brain of the child. In addition, MRI provides more detail of the soft tissues and better imaging of the brain parenchyma, cerebellum, and brainstem than CT. Therefore, rapid MRI is the preferred imaging modality for the clinically stable child. However, in the setting of an acute change in mental status, a CT scan is usually a readily available, rapid screening test that can identify acute intracranial bleeding, masses, or contusions in emergency situations.

## MANAGEMENT

Management of a child with altered mental status is similar to any emergency condition. The primary objective is to stabilize the child's clinical status and correct any acute life-threatening conditions. Once stabilized, the child should be transported to an acute care facility for additional evaluation and management.

Initial management begins with the ABCs—airway, breathing, and circulation. If the airway is obstructed, which is usually identified by the presence of stridor or an abnormal breathing pattern, then immediate maneuvers to open the airway either by manual positioning or artificial methods (oral airway or endotracheal intubation) should be performed. Oxygen should be routinely administered. Patients with a Glasgow Coma Scale of 8 or less or with respiratory failure should undergo endotracheal intubation. Because many of the causes of an altered mental status require intravenous (IV) fluid or medication, a peripheral IV catheter should be placed. Immediate bedside blood glucose levels should be determined because hypoglycemia is readily identified and easily corrected with administration of IV dextrose. Additional blood tests to help determine the underlying cause should be performed. Empirical administration of naloxone should be considered if the underlying cause is unknown. Naloxone can reverse the depressive cardiorespiratory effects of narcotic ingestion, but it may also be helpful in ingestions of clonidine, dextromethorphan, valproic acid, and captopril. A fluid bolus with normal saline should be administered if signs exist of poor perfusion or hypotension. Acid-base and electrolyte abnormalities, if present, should be corrected.

If the patient has a history of trauma, or if the suspected cause is structural, then intracranial pressure may be high. To control the intracranial pressure, the head should be elevated to 30 degrees and placed in a midline position. Hyperventilation can be a temporizing measure to reduce intracranial pressure. Every effort should be made to stabilize the child as soon as possible and obtain an emergent, rapid MRI or CT scan, as well as a consultation with a neurosurgeon. Obstructive hydrocephalus resulting from an intracranial mass lesion or obstructed ventriculoperitoneal shunt may need to be relieved emergently with a ventriculoperitoneal shunt tap or ventriculostomy.

If a medical cause is suspected, then additional laboratory and radiologic testing may help determine whether the cause is infectious, metabolic, or toxicologic. Fever may indicate an infectious origin, and the child should be provided with IV antibiotics after a blood culture is obtained. If meningitis with altered mental status is suspected, then a lumbar puncture can be performed to help confirm this diagnosis, usually after neuroimaging to rule out increased intracranial pressure. It should be performed if the patient is stable and does not have focal neurologic signs. However, if the child is clinically unstable, then the lumbar puncture should be deferred but without delay in administration of empirical IV antibiotics. If herpes encephalitis is a concern, then empirical acyclovir should be provided. A positive stool guaiac test raises the concern of intussusception, which can be diagnosed by plain-film radiography or ultrasonography and reduced by an air-contrast enema. ECG can identify cardiac dysrhythmias or conduction abnormalities. If unexplained bruising exists, then child abuse should be considered.

When a clear cause cannot be identified, ingestion of a toxic substance should be suspected. Family members should be questioned about the availability of any medication. If possible, the bottle of the medication should be checked and the remaining pills counted to estimate the maximal amount ingested. For some ingestions, antidotes are available. Specialists at the local poison control center can assist in the management of a suspected overdose. Many children will require a dose of activated charcoal, which binds the toxin and limits intestinal absorption.

After stabilization and initial management, the patient should be observed in a monitored setting until mental status improves.

### WHEN TO ADMIT

- Any child with altered mental status

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## Chapter 350 ANAPHYLAXIS

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### DEFINITION OF TERMS

Anaphylaxis is a systemic allergic reaction that occurs suddenly after contact with an inciting substance and has been defined as “a serious allergic reaction that is rapid in onset and may cause death.” However, anaphylaxis may also be mild and self-limited. Anaphylaxis is a syndrome that has been classically defined as involving 2 or more organ systems. However, it is now accepted that anaphylaxis can be diagnosed when hypotension alone occurs following exposure to a known or likely allergen. Single organ involvement of the upper airway (larynx, oropharynx, or tongue) is not considered to be anaphylaxis. Severe allergic reactions mediated by IgE have been classically referred to as anaphylaxis while clinically similar events not attributable to IgE were historically referred to as anaphylactoid. The term *anaphylactoid* has been dropped because the clinical syndromes are often indistinguishable and the treatment recommendations are the same regardless of the etiology and pathophysiology. Box 350-1 shows the clinical criteria for anaphylaxis.

### ETIOLOGY

Anaphylactic reactions are mediated through antigen-induced, IgE-mediated mast cell and basophil degranulation. Most of these reactions are induced by foods or medications. Non-IgE-mediated reactions are often the result of direct mast cell degranulation (eg, radiocontrast media or opioids). Some cases of exercise-induced anaphylaxis are also thought to be secondary to direct mast cell degranulation. In anaphylactic reactions to nonsteroidal anti-inflammatory agents, most cases seem to be caused by an inhibition of the cyclooxygenase pathway. Exercise, certain medications (eg, nonsteroidal anti-inflammatory drugs), anesthesia, and alcohol may increase the severity of the response to the allergen. The final common pathway for all of these reactions is mast cell and usually basophil degranulation. When mast cells or basophils are activated, several well-characterized mediators are released (eg, histamine and tryptase). Histamine may account for most of the signs and symptoms. Nevertheless, antihistamines alone cannot prevent or reverse all anaphylactic symptoms. Other mediators such as leukotrienes and platelet activating factor probably contribute to the pathophysiology and symptoms of anaphylactic reactions. Recent work suggests that platelet activating factor is associated with the severity of anaphylactic reactions. Animal studies suggest that nitric oxide production may contribute to the cardiovascular manifestations of the anaphylaxis. Nitric oxide increases the activity of guanyl cyclase, which produces cyclic GMP, which in turn causes vasodilation. Methylene blue is an inhibitor of guanyl cyclase and nitric oxide synthase. Treatment with methylene blue has reversed refractory hypotension in several patients.

**BOX 350-1 Criteria for Anaphylaxis**

Anaphylaxis is highly likely when any 1 of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin or mucosal tissue (eg, generalized hives, pruritus or flushing, swollen lips, tongue, or uvula) AND AT LEAST 1 OF THE FOLLOWING:
  - A. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
  - B. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotension [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly (minutes to several hours) after exposure to a likely allergen:
  - A. Involvement of the skin or mucosal tissue (eg, generalized hives; pruritus or flushing; swollen lips, tongue, or uvula)
  - B. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
  - C. Reduced BP or associated symptoms (eg, hypotension [collapse], syncope, incontinence)
  - D. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen (minutes to several hours)
  - A. Infants and children: low systolic BP (age specific) or  $>30\%$  decrease in systolic BP. Low systolic BP for children is defined as  $<70$  mm Hg from 1 month to 1 year,  $<70$  mm Hg +  $[2 \times \text{age}]$  from 1 to 10 years and  $<90$  mm Hg from 11 to 17 years.
  - B. Adults: systolic BP of  $<90$  mm Hg or  $>30\%$  decrease from that person's baseline.

BP, blood pressure; PEF, peak expiratory flow.

From Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117(2):391–397, with permission from Elsevier.

**EPIDEMIOLOGY**

The incidence of anaphylaxis varies by study but is generally reported as less than 1% and anywhere from 0.04% to 0.4% (40 to 400/100,000/year). It is thought that the incidence is higher than reported because of under-reporting and under-recognition of the syndrome. There is no racial predisposition. In childhood, boys are more likely to suffer from anaphylaxis than girls, and in adult life, women are more likely than men. Atopy is a predisposing factor for food-induced anaphylaxis. Reactions to injected agents tend to be more severe and more rapid than for ingested agents. Risk factors associated with death from anaphylaxis include extremes of age, concomitant cardiac disease, asthma, delay of epinephrine administration, and season of the year.

**SIGNS AND SYMPTOMS**

Ninety percent or more of patients experiencing anaphylactic reactions will report skin manifestations of urticaria, facial swelling (angioedema), pruritus, or

**BOX 350-2 Clinical Signs and Symptoms of Anaphylaxis****CUTANEOUS/SUBCUTANEOUS/MUCOSAL TISSUE**

- Flushing, pruritus, hives (urticaria), angioedema, morbilliform rash, pilor erection
- Pruritus of lips, tongue, and palate; edema of lips, tongue, and uvula
- Periorbital pruritus, erythema, and edema; conjunctival erythema; tearing

**RESPIRATORY**

- **Laryngeal:** pruritus and tightness in the throat; dysphagia; dysphonia and hoarseness; dry staccato cough; stridor
- Sensation of pruritus in the external auditory canals
- **Lung:** shortness of breath, dyspnea, chest tightness, deep cough, and wheezing/bronchospasm (decreased peak expiratory flow)
- **Nose:** pruritus, congestion, rhinorrhea, sneezing

**CARDIOVASCULAR**

- Hypotension
- Feeling of faintness (near-syncope), syncope, altered mental status
- Chest pain, dysrhythmia

**GASTROINTESTINAL**

- Nausea, crampy abdominal pain, vomiting (stringy mucus), diarrhea

**OTHER**

- Urinary urgency, aura of doom, uterine contractions in women

From Sampson HA, Muñoz-Furlong A, Bock SA, et al. Symposium on the definition and management of anaphylaxis: summary report. *J Allergy Clin Immunol*. 2005;115(3):584–591, with permission from Elsevier.

flushing. Difficulty breathing (shortness of breath, chest tightness, or wheezing) is the second most common complaint. Lightheadedness or weakness and palpitations are often reported. Gastrointestinal symptoms such as diarrhea and vomiting may occur. Headache may also be present. Some patients report a sense of impending doom accompanying the onset of anaphylaxis. Although most patients experiencing anaphylaxis develop skin manifestations, the absence of this cutaneous involvement does not rule out anaphylaxis. The onset of symptoms may be related to the route of administration and the rapidity of the systemic absorption of the inciting agent. (See Box 350-2.)

**DIFFERENTIAL DIAGNOSIS****Vasodepressor/Vasovagal Reactions**

Hypotension, pallor, weakness, nausea, and bradycardia are common features of this syndrome, which often occurs after an emotional stressor. Loss of consciousness may also occur. Lack of skin and airway manifestations usually seen in anaphylactic reactions and prompt recovery upon assuming a recumbent position help to differentiate the syndromes. Since



bradycardia occurs in 5% of patients with anaphylaxis, even in the absence of the use of  $\beta$ -adrenergic blockers, it alone does not differentiate anaphylaxis from vasovagal reactions. It is important to remember that anaphylaxis may present with only cardiovascular and no cutaneous signs or symptoms, especially in the context of the administration of a known allergen.

### Panic Attacks

Palpitations, flushing, shortness of breath, and GI symptoms are common with panic attacks. If they are accompanied by vocal cord dysfunction and stridor they may mimic anaphylaxis. Even if these latter symptoms are not accompanied by upper airway involvement, such as stridor, anaphylaxis must be excluded. Patients with panic attacks are unlikely to have wheezing, mucocutaneous manifestations, or hypotension. A comprehensive psychosocial history, physical examination, and a period of monitored observation will help differentiate a panic attack from anaphylaxis.

### Mastocytosis and Mast Cell Activation Syndrome

Anaphylaxis may occur in patients with systemic mastocytosis and mast cell activation syndromes, because these mast cell lesions bind IgE and release histamine and other mast cell mediators. Urticaria pigmentosa, the most typical skin lesions of mastocytosis, may suggest the diagnosis. If the lesions are primarily internal, a higher level of suspicion will be necessary to make the diagnosis. Tests, including total serum tryptase, urinary histamine metabolites, and genetic testing for mastocytosis, may be necessary to diagnose mastocytosis in patients with anaphylaxis. Serum/plasma concentrations of total tryptase are acutely elevated in patients with anaphylaxis, while total tryptase is increased in patients with mastocytosis even when they are not acutely ill.

### Hypoglycemia

Flushing can occur with hypoglycemia, mimicking an early allergic skin reaction. This may be associated with tachycardia, anxiety, diaphoresis, and lightheadedness.

## EVALUATION

### Relevant History

Food-induced anaphylaxis is more common in children than in adults. A history of recent food ingestion should always be sought. Most anaphylactic reactions to foods occur in the first 2 hours after eating, with most occurring within the first 30 minutes. There are reports of reactions beginning up to several hours later. Gastrointestinal symptoms such as nausea, vomiting, crampy abdominal pain, and diarrhea are more likely in patients with food-induced anaphylaxis. Peanuts, tree nuts, fish, and shellfish account for most anaphylactic reactions to foods, with peanut being the most common (up to 62% of cases). These foods usually are responsible for lifelong allergies in affected persons, and children are not likely to “outgrow” these reactions. Milk, soy, egg, and wheat also are responsible for severe allergic reactions in infants and toddlers, but unlike reactions to peanuts, tree nuts, fish, and shellfish, most children become tolerant to milk and soy in particular, and to eggs in some but not all cases. In some patients with severe food allergy,

inhalation of the offending antigen is sufficient to lead to a reaction in a sensitized individual. Some with apparent idiopathic anaphylaxis may actually be reacting to inhalation of pollen to which they are exquisitely sensitive.

Injected venoms from *Hymenoptera* insect sting (ie, bees, yellow jackets, hornets, wasps, fire ants) can cause anaphylaxis in sensitized individuals. From 0.5% to 3.0% of the population experiences a systemic reaction after *Hymenoptera* stings. History of exposure to particular insects may be important later if venom injection immunotherapy is to be considered. In the case of bee sting it is important to remove the stinger early to avoid further venom injection. Identification of the wound or stinger helps identify the species. Bees (and very rarely yellow jackets) leave a stinger in the skin while other *Hymenoptera* do not.

Medications are another common cause of anaphylactic reactions. Penicillin is the most common cause. Aspirin and other nonsteroidal anti-inflammatory agents may also induce reactions. Drugs that are administered intravenously or intramuscularly are absorbed more rapidly and are associated with more severe reactions. Anaphylactic reactions occurring in hospitalized patients are most commonly caused by medications, latex, and, rarely, anesthetics. Latex allergy has become less common.

Exercise-induced anaphylaxis usually occurs in teenagers and young adults. It may occur unpredictably and is often difficult to diagnose. There may be a prodrome of flushing and abdominal pain followed by collapse during exercise. Some cases of exercise-induced anaphylaxis occur only after ingestion of foods that cross-react with pollens (eg, melons/ragweed or apples/birch). The combination of exercise with food ingestion seems to be necessary for the event in this subgroup. Some also have exercised-induced anaphylaxis after ingestion of any food combined with exercise. This variability may make exercised-induced anaphylaxis difficult to diagnose. Exercise-induced anaphylaxis may follow episodes of exercise-induced urticaria.

Exercise, certain medications (eg, nonsteroidal anti-inflammatory drugs), anesthesia, and alcohol may affect the severity of the response to allergen.

### Physical Examination

#### Respiratory

Bronchospasm with wheezing is common. Edema of the airway may cause stridor or hoarseness. Cyanosis may occur. Upper respiratory findings include nasal congestion, rhinorrhea, sneezing, and lingual and pharyngeal edema.

#### Skin

Urticaria, angioedema, or flushing is evident in approximately 90% of cases.

#### Cardiovascular

Tachycardia is a common finding resulting from the adrenergic response to decreased intravascular volume or histamine activity through the H<sub>2</sub> receptor. Hypotension may then occur and be followed by anaphylactic shock. Postural hypotension may precede frank hypotension.

### Ocular

Tearing, conjunctival erythema, and edema (chemosis) may be present.

### Laboratory Testing

The history and clinical assessment are far more important in the initial evaluation of anaphylaxis than laboratory testing. Histamine, which mediates many of the symptoms in anaphylaxis, has a very short half-life. Histamine plasma concentrations peak within 5 to 60 minutes after an anaphylactic event, so histamine is not a reliable or useful marker in most instances. However, histamine metabolites in the urine may be clinically useful in the diagnosis of systemic mastocytosis. Specific IgE (skin prick tests for specific allergens or serum antigen specific IgE tests) may be useful to help determine the cause of the reaction. These tests may not be valid at the time of presentation because the specific IgE may no longer be present in the skin or serum. It may have been consumed in the allergic reaction. For this reason, testing for specific IgE may not reliably be done for up to 6 weeks after the incident. If there is uncertainty as to whether the reaction is anaphylaxis and the incident has occurred within the last 1 to 2 hours, serum tryptase may be useful in establishing the diagnosis. It may remain elevated in the blood for up to 6 hours after the event. Serum tryptase concentrations that are 135% increased from a patient's baseline level at 2 to 5 hours after exposure suggest the diagnosis of anaphylaxis even if the absolute value is below the upper limit of normal. The baseline level should be determined more than 3 days after the event and more than 1 day after resolution of symptoms. Tryptase is measurable up to several days later in serum samples that have been refrigerated. This allows for determination of tryptase after the fact from samples that were obtained for other laboratory studies. Pulse oximetry or arterial blood gas determinations may be appropriate in patients with cyanosis or respiratory compromise.

### Imaging

Imaging is not an important modality in evaluating anaphylaxis.

### Management

**Epinephrine** injected in the lateral thigh muscle is the most important initial treatment for anaphylaxis. Epinephrine should be administered while the assessment is being made. The dose for children is 0.01 mg/kg of a 1:1,000 solution (0.01 mL/kg up to a maximum of 0.5 mL) intramuscularly, preferably in the outer thigh. The dose may be repeated as needed every 5 minutes. It may be necessary to administer epinephrine as a 1:10,000 solution intravenously in the event of severe hypotension with peripheral vasoconstriction resulting from severely decreased intravascular volume. A common factor associated with fatal anaphylaxis is delay in epinephrine administration.

**Fluid replacement** may be necessary if hypotension from increased vascular permeability is present. Children should receive up to 30 mL/kg of crystalloid solution in the first hour to treat hypotension, although additional IV fluids, usually in boluses of 20 mL/kg,

may be necessary to treat anaphylactic shock. Adults often require 1 to 2 liters over the first hour.

The airway should be secured, and respiratory rate, blood pressure, and pulse rate should be obtained and monitored. The patient should be placed in the supine position with feet elevated if the blood pressure is decreased. A compromise regarding the recumbent position may have to be made to allow adequate air exchange if the patient is wheezing. Oxygen should be administered.

Although not widely appreciated as a treatment adjunct, a tourniquet that is applied on an extremity proximal to a *Hymenoptera* sting or medication injection will slow systemic absorption of antigen and anaphylactic mediators. This is especially valuable when medication is not immediately available.

### Intravenous Vasopressors

In severe refractory hypotension (failure to maintain systolic blood pressure above 90 mm Hg), continuous intravenous infusions of dopamine, norepinephrine, or epinephrine may be required. Vasopressin may also be used in patients who do not respond to epinephrine or these other pressors. The vasopressin infusion may be started at 0.0003 UI/kg/min.

In cases in which the patient is on a beta blocker (more common in adults than children) the patient may be refractory to standard therapy and have relapsing symptoms or hypotension and bradycardia that have not responded to treatment. These patients are at increased risk for death from anaphylaxis. Glucagon is recommended when the patient has been on a beta blocker, and should be considered in cases of anaphylaxis with refractory hypotension even without a clear history of  $\beta$ -blockade. The recommended dosing of glucagon is 1 to 5 mg (20–30 mcg/kg, maximum dose 1 mg in children), administered intravenously over 5 minutes and followed by an infusion (5–15 mcg/min) titrated to clinical response.

Methylene blue, which is used to treat methemoglobinemia, has been successfully used to treat patients with severe anaphylactic hypotension. The dose is a 1.5 to 2 mg/kg bolus of 4% methylene blue. Then a 1- to 2-hour continuous infusion of 1.5 mg/kg diluted in 5% dextrose in water is administered.

### Nebulized $\beta_2$ Agonists

Inhaled albuterol may be used for wheezing that is not responsive to parenteral epinephrine.

### Antihistamines

H<sub>1</sub> antihistamines have a slower onset of action than epinephrine, have little effect on blood pressure (unless combined with an H<sub>2</sub> antagonist), and should be considered a second-line treatment for anaphylaxis.

H<sub>1</sub> antihistamines are often given to relieve pruritus, urticaria, and angioedema. It is very important, however, to remember that these drugs are not effective for treating life-threatening symptoms. They do not replace epinephrine. H<sub>1</sub> antihistamines are often used mistakenly as the primary treatment for anaphylaxis. First-generation H<sub>1</sub> antihistamines commonly cause drowsiness and may impair the patient's ability to relate the progress or resolution of his or her symptoms.

The intravenous administration of the combination of an H<sub>1</sub> antihistamine (eg, diphenhydramine 25–50 mg) with the H<sub>2</sub> blocker cimetidine (300–400 mg intravenously by piggyback infusion) has been demonstrated to block both the cardiac and peripheral vascular effects of histamine. Ranitidine may also be used.

### Corticosteroids

The use of adrenal corticosteroids (eg, methylprednisolone) is recommended based on their efficacy in asthma and their beneficial effect in decreasing vascular permeability. The data, however, do not indicate that use of corticosteroids prevents biphasic reactions. Patients with biphasic reactions often experience the recurrence of their initial signs and symptoms several hours following their apparent resolution.

If given, the dosing of intravenous corticosteroids should be equivalent to 1.0 to 2.0 mg/kg per dose of methylprednisolone every 6 hours. Oral administration of prednisone at 1.0 mg/kg, up to 50 mg, might be sufficient for milder attacks. Box 350-3 provides further details on recommended drugs and dosages for management of anaphylaxis in children.

### Discharge

Patients having had anaphylaxis should be discharged with an epinephrine autoinjector. They must be taught

how and when to use the device and must understand that it should be available at home, school, work, or anywhere the patient travels. The patient needs to understand that the devices have expiration dates and should be renewed.

A referral to a board-certified allergist is recommended to identify the etiology of the reaction and to provide education on avoidance of subsequent reactions. This is particularly important for reactions to food, insect stings, and medication. A “medic alert” bracelet should be prescribed. Venom injection immunotherapy is indicated for treatment of moderate to severe *Hymenoptera* sting anaphylaxis. In cases of exercise-induced anaphylaxis, patients should be advised never to exercise or swim alone.

### Clinical Course

Anaphylaxis may be uniphasic, biphasic, or protracted. Biphasic reactions occur in 4% to 20% of patients with anaphylaxis. Patients with biphasic reactions often experience the recurrence of their initial signs and symptoms several hours following their apparent resolution. This biphasic response usually occurs within 8 hours of the initial reaction, but can occur up to 72 hours later.

## BOX 350-3 Drugs and Dosages

**Epinephrine** (aqueous) 1:1,000 concentration: 0.01 mg/kg, maximum dose 0.5 mg (0.5 mL)

### For hypotension refractory to epinephrine

- Vasopressin started at 0.0003 U/kg/min
- Levarterenol 0.5–1.0 mcg/min, titrated to maintain blood pressure
- Dobutamine 2–20 mcg/kg/min, titrated to maintain blood pressure

### For β-Blockade

- Glucagon 20–30 mcg/kg, maximum dose 1 mg in children intravenously over 5 minutes, then 5–15 mcg/min titrated to clinical response vs 50 micrograms/kg intravenous loading dose, followed by a continuous infusion of 1–15 mcg/hr, titrated to patient vs 50–150 mcg/kg bolus over 1 minute, then 1–5 mg/hr

### For shock

- Methylene blue, 4%: 1.5–2 mg/kg bolus, then a 1–2 hour continuous infusion of 1.5 mg/kg diluted in 5% D<sub>5</sub>W

### Antihistamines: use H<sub>1</sub> together with H<sub>2</sub> blocker

- Diphenhydramine 1–1.5 mg/kg, maximum dose 75 mg

### H<sub>2</sub> receptor blockers

- Ranitidine 1–2 mg/kg, maximum dose 150 mg
- Cimetidine 20–40 mg/kg/day divided q6hr IV/IM/PO
- Neonates (<28 days old): 5–20 mg/kg/day divided q8–12hr IV/IM/PO
- Infants: 10–20 mg/kg/day divided q6–12hr IV/IM/PO

### Adrenal corticosteroids

- Methylprednisolone 1–2 mg/kg up to 125 mg
- Prednisone 1–2 mg/kg up to 75 mg

IM, intramuscular; IV, intravenous; PO, by mouth.

### WHEN TO REFER

All patients with anaphylaxis and anaphylactoid reactions should be referred to an allergist for identification of the responsible agent and for patient education.

### WHEN TO ADMIT

A reasonable length of time to consider observing the postanaphylactic patient is 4 to 6 hours for patients with mild to moderate anaphylaxis. Prolonged observation times (8–24 hours) or hospital admission are appropriate for patients with severe reactions (hypoxemia, airway edema, or shock) or refractory symptoms. More caution should be used in patients with a history of asthma or wheezing.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Anaphylaxis* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/injuries-emergencies/Pages/Anaphylaxis.aspx](http://www.healthychildren.org/English/health-issues/injuries-emergencies/Pages/Anaphylaxis.aspx))
- *Anaphylaxis* (Web page), American Academy of Allergy, Asthma, and Immunology ([www.aaaai.org/patients/resources/easy\\_reader/anaphylaxis.pdf](http://www.aaaai.org/patients/resources/easy_reader/anaphylaxis.pdf))
- *Food Allergy* (Web page), American Academy of Allergy, Asthma, and Immunology ([www.aaaai.org/patients/gallery/foodallergy.asp](http://www.aaaai.org/patients/gallery/foodallergy.asp))
- *Food Allergy Research & Education* (Web site), ([www.foodallergy.org](http://www.foodallergy.org))
- *Students With Chronic Health Conditions* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *What You Should Know About Food Allergy* (fact sheet), American Academy of Allergy, Asthma, and Immunology ([www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Libraries/Food-Allergy.pdf](http://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Libraries/Food-Allergy.pdf))



**Medical Decision Support**

- *Pediatric Nutrition Handbook* (book), American Academy of Pediatrics (shop.aap.org)

**Community Advocacy and Coordination**

- *Food Allergy Action Plan* (form), Food Allergy Organization (www.foodallergy.org)
- *School Tools: Allergy & Asthma Resources for Professionals* (Web page), American Academy of Allergy, Asthma, and Immunology (www.aaaai.org/conditions-and-treatments/library/school-tools.aspx)

**AAP POLICY**

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## Chapter 351

# APPENDICITIS

R. Scott Strahlman, MD

Abdominal pain is a common chief complaint in the pediatric population. The pediatric primary care physician is crucial in the initial evaluation, diagnosis, and management of abdominal pain and is often the first person to suspect appendicitis. Although appendicitis is a surgical emergency, a physician's high index of suspicion can be the driving force that leads to an appropriate, timely appendectomy. Prompt diagnosis and preoperative management help reduce the high morbidity associated with a perforated appendix.

**DEFINITIONS**

Appendicitis is an inflammation of the vermiform appendix, a small appendage arising from the cecum. Vermiform means *worm shaped* and accurately describes the appearance of this structure. Appendicitis is the most common cause of an acute surgical abdomen in childhood. Although the exact incidence is unknown, appendicitis is rare in early childhood and more common after age 10 years. Boys and girls are affected equally before puberty, but after age 15 years, twice as many boys are affected as girls. An increased incidence in the spring and autumn months has also been observed. In addition, appendicitis is more common in children who have a family history of appendicitis. Whether this tendency is genetic or diet related is unclear; the risk for appendicitis may be reduced with a high-fiber diet.

**ETIOLOGY AND PATHOPHYSIOLOGY**

Appendicitis is always initiated by obstruction of the appendiceal lumen, usually by a fecalith or by lymphoid hyperplasia. In rare cases, a parasite, tumor, or foreign body may obstruct the lumen. inspissated secretions of cystic fibrosis may also obstruct the appendiceal lumen (thus, although rare, the initial presentation of cystic fibrosis may be appendicitis). As secretions accumulate within the obstructed appendix, it becomes distended, and the appendiceal wall stretches. Continued distention causes ischemia and inflammation of the appendix, leading to irritation of the adjacent somatic peritoneum.

Clinically, the initial distention of the appendix produces a dull, steady periumbilical pain. After 4 to 6 hours, this pain often shifts to the right lower quadrant as local peritoneal inflammation develops. Without surgical intervention, the appendix will eventually rupture, causing peritonitis. The incidence of rupture increases dramatically 24 to 36 hours after the onset of abdominal pain. Organisms cultured from the peritoneal cavity after perforation include both aerobic and anaerobic bacteria. The most common aerobic bacteria are *Escherichia coli*, *Staphylococcus aureus*, and *Enterococcus* spp. organisms. Common anaerobes include *Bacteroides* and *Clostridium* spp.

**EVALUATION****History**

A thorough history is invaluable in differentiating appendicitis from other disorders; an important component of this history is pain. The onset of symptoms is often heralded by a dull, steady periumbilical pain. The pain is thought to be caused by acute appendicitis if it awakens the patient from sleep. Anorexia is a consistent, but not invariable, finding. One or 2 episodes of vomiting may follow; however, these episodes essentially never precede the pain. After 4 to 6 hours, the pain commonly migrates to the right lower quadrant. Given the many variations in the location of the appendix, however, the location of abdominal pain may vary. Bowel habits usually do not change. Although the child may have a low-grade fever, the temperature is rarely above 37.9°C



(100.3°F) before perforation. Even if the clinical picture suggests appendicitis but does not convince the physician that appendicitis is the problem, referral for surgical evaluation would be best. Because an appendix rarely perforates within 24 hours of the onset of pain, a period of observation can safely differentiate a potential surgical condition from a non-surgical one. It is important, however, to be aware that perforation of the appendix may be associated with an initial lessening in the pain, only to be followed by a worsening of symptoms within a few hours.

### Physical Examination

As always, a gentle, nonthreatening approach is most effective during the physical examination. The physician should assess for peritoneal signs such as pain on walking or coughing. If the patient can jump up on the examining table, then the patient does not usually have appendicitis. Patients may be most comfortable lying supine with their legs flexed. Abdominal tenderness is always present and is often greatest at the McBurney point (two-thirds of the distance on a direct line from the umbilicus to the anterosuperior iliac spine). Rebound tenderness of the abdomen, especially referred to the right lower quadrant, is common, as is hyperesthesia of the skin overlying the painful area. (In infants, tenderness is present diffusely over the abdomen because they are rarely seen before perforation.) Pain in the right lower quadrant may be accentuated when the inflamed appendix is located retroceally by (1) placing the patient in the left decubitus position and extending the right leg at the hip, thereby placing tension on the right psoas muscle, the origins of which underlie the appendix (psoas sign); and (2) placing the patient supine and internally rotating the flexed right hip, thereby extending the right internal obturator muscle, the origins of which also underlie the appendix (obturator sign). When the inflamed appendix is located anteriorly, pain in the right lower quadrant may be accentuated when the child is asked to sit up from the supine position while pressure is placed against the forehead. Bowel sounds may be diminished or hyperactive. A rectal examination will often facilitate making the diagnosis by revealing right-sided tenderness. Examination of the lungs is important to rule out a right lower lobe pneumonia that may generate referred pain to the right lower quadrant of the abdomen. A pelvic examination is indicated for any adolescent girl who has abdominal pain to rule out gynecologic conditions.

### Laboratory Testing

The only essential laboratory studies are a blood count and urinalysis. Appendicitis, without perforation, has a characteristic blood count; the white blood cell count is most often in the range of 10,000 to 20,000/mcL, with a slight increase in the number of neutrophils, particularly young forms. The blood count may help rule out viral infection and other processes that do not increase the white blood cell count. The erythrocyte sedimentation rate is usually normal and, if elevated, may suggest such alternative diagnoses as inflammatory bowel disease. Urinalysis is performed to rule out urinary tract infection or diabetic ketoacidosis as a cause of

the abdominal pain. Some hospitals are using the laboratory markers of a white blood cell count above 12,000/mcL and a C-reactive protein above 3 mg/dL to indicate possible appendicitis.

### Imaging

If the diagnosis is in doubt, then imaging studies can provide important information. Abdominal radiographs are occasionally helpful. Radiographic features that suggest appendicitis include a calcified appendicolith or an air-filled appendix, although the absence of abnormalities does not rule out the diagnosis. Recently, ultrasonography and computed tomography have been used to establish the diagnosis in equivocal cases. In 1 study, the selective use of computed tomography and ultrasound decreased the incidence of perforated appendicitis from 35.4% to 15.5% and decreased the rate of removing a normal appendix (a negative appendectomy) from 14.7% to 4.1%. When available, consultation with a pediatric surgeon may minimize the need for imaging studies while maintaining low rates of perforation and negative appendectomy.

Some physicians use clinical decision rules to aid in the diagnosis of appendicitis and to avoid overuse of imaging studies. A white blood cell count of greater than 10,000/mcL and the presence of rebound abdominal tenderness are highly suggestive of appendicitis and warrant a prompt surgical evaluation without the need for imaging studies. A white blood cell count of less than 6,750/mcL with the absence of nausea and of right lower quadrant tenderness are highly associated with the absence of appendicitis. Careful observation without imaging studies can be considered in such cases.

The typical progression of signs and symptoms in appendicitis may be summarized as follows: periumbilical abdominal pain followed by nausea, vomiting, and localization of the pain to the right lower quadrant. Low-grade fever, direct tenderness to palpation in the right lower quadrant and indirect tenderness referred to the right lower quadrant, right-sided tenderness on rectal examination, and a mild leukocytosis often accompany these symptoms.

### DIFFERENTIAL DIAGNOSIS

The differential diagnosis of appendicitis, which is the same as the differential diagnosis of acute abdominal pain, is extensive (Box 351-1). Gastroenteritis can be differentiated from appendicitis based on a generally benign abdominal examination in the former condition. Vomiting and diarrhea usually occur before the onset of pain, not afterward, as is the case in appendicitis. Constipation can often seem to be appendicitis; however, this pain is usually diffuse, not localized to the right lower quadrant, and the patient often has a history of constipation. An abdominal flat-plate radiograph can help in the diagnosis, and a small Fleet enema is often both diagnostic and therapeutic.

The typical progression of signs and symptoms in appendicitis is probably the most helpful in differentiating it from other diagnoses—periumbilical abdominal pain followed by nausea, vomiting, and localization of the pain to the right lower quadrant. Low-grade fever, direct tenderness to palpation in

**BOX 351-1 Differential Diagnosis of Appendicitis**

<b>COMMON CONDITIONS</b>	Ruptured ectopic pregnancy
Gastroenteritis	Dysmenorrhea
Constipation	Mittelschmerz
<b>MEDICAL PROBLEMS</b>	Ruptured corpus luteum cyst
Urinary tract infection	<b>UNUSUAL CONDITIONS</b>
Diabetic ketoacidosis	Henoch-Schönlein purpura
Sickle cell crisis	Hemolytic uremic syndrome
Right lower lobe pneumonia	Rocky Mountain spotted fever
Primary peritonitis	<b>SURGICAL EMERGENCIES</b>
Inflammatory bowel disease	Meckel diverticulitis
<b>GYNECOLOGIC PROBLEMS</b>	Intestinal adhesions
Pelvic inflammatory disease	Intussusception
Ovarian torsion	Necrotizing enterocolitis

the right lower quadrant and indirect tenderness referred to the right lower quadrant, right-sided tenderness on rectal examination, and a mild leukocytosis often accompany these symptoms.

An appropriate initial evaluation can rule out the following nonsurgical conditions in a patient who has abdominal pain: urinary tract infection, diabetic ketoacidosis, sickle cell crisis, right lower lobe pneumonia with referred pain, nephrotic syndrome with primary peritonitis, and inflammatory bowel disease. Gynecologic disorders can be ruled out based on the history, a pelvic examination, and appropriate diagnostic studies; pelvic inflammatory disease, ovarian torsion, ectopic pregnancy, dysmenorrhea, and Mittelschmerz can all mimic appendicitis.

Unusual conditions such as Henoch-Schönlein purpura and hemolytic uremic syndrome may be indistinguishable from appendicitis. Even Rocky Mountain spotted fever can mimic appendicitis. Surgical emergencies that mimic appendicitis (see Box 351-1) can be ruled out only in the operating room.

### APPENDICITIS IN INFANTS

Appendicitis in the first 2 years of life is rare, accounting for fewer than 2% of all childhood cases. The morbidity is high, however, and the incidence of perforation approaches 100%. Therefore, appendicitis must be considered in any infant thought to have abdominal pain. The presenting symptoms consist of vomiting and fever, and the baby may appear to be colicky. Physical examination shows abdominal distention with diffuse tenderness. Abdominal radiographs can be diagnostically helpful in a neonate by showing an appendicolith, free peritoneal fluid, bowel wall edema, or, rarely, free air. With a high index of suspicion, surgery must be performed immediately to prevent or manage perforation, with its high morbidity.

### MANAGEMENT

Once the diagnosis is made, referral for surgery should be made immediately. Nothing is given by mouth, and a nasogastric tube is inserted and placed on low suction if the child is vomiting. Intravenous hydration is started, and fever may be controlled with acetaminophen given by rectum. Broad-spectrum antibiotics (eg, ampicillin, gentamicin, and clindamycin or a cephalosporin) are administered intravenously before surgery. Antibiotics have been shown to reduce morbidity, even in nonperforated cases. An appendectomy is performed as soon as the patient's condition has been stabilized. Laparoscopic appendectomy is being performed at most institutions.

For patients who have symptoms for 5 days or longer and a palpable mass consistent with an appendiceal abscess, many surgeons initially prefer nonsurgical management. The patient is treated with broad-spectrum antibiotics for 14 days (initiated in the hospital and completed at home) if the child's clinical condition allows and, barring interim complications, returns in 6 to 8 weeks for an elective appendectomy. This approach lowers the incidence of diffuse peritonitis and the associated complications precipitated by surgical manipulation during the acute inflammatory stages of the disease.

### PROGNOSIS

For uncomplicated appendicitis treated with prompt surgical intervention, the mortality rate is less than 1%, and long-term morbidity is primarily the risk for adhesive small bowel obstruction. The average hospital stay is about 2 days. Although a ruptured appendix increases the risk for mortality (with most of the increase occurring in infants or in older children with delayed diagnosis who develop sepsis), perforation significantly extends the average hospital stay. Complications that increase morbidity include peritonitis, postoperative abscesses, and prolonged ileus. Perforation also significantly increases the risk for postoperative adhesive small bowel obstruction. In women, although infertility was thought to be a possible long-term complication of a ruptured appendix, recent studies have shown this not to be the case.

The incidence of perforated appendicitis exceeds 30%, a disconcertingly high figure, despite increasing use of radiographic imaging. A higher index of suspicion on the part of families and pediatricians may lead to earlier diagnosis of the condition and reduce the incidence of appendiceal perforation and its morbid complications.

#### WHEN TO REFER

- Refer to surgery immediately whenever appendicitis is suspected.

#### WHEN TO ADMIT

- Hospitalize for inpatient observation if the diagnosis cannot be excluded and for appendectomy if the diagnosis of appendicitis is made.

## TOOLS FOR PRACTICE

### Medical Decision Support

- *Cope's Early Diagnosis of the Acute Abdomen* (book), Oxford University Press

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## Chapter 352

# CROUP (ACUTE LARYNGOTRACHEOBRONCHITIS)

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## DEFINITION

Viral croup (acute laryngotracheobronchitis) is an age-specific viral syndrome characterized by acute laryngeal and subglottic swelling, resulting in hoarseness, cough, respiratory distress, and inspiratory stridor. Inflammation at the subglottic area is apt to cause marked airflow obstruction because the anatomy of the cricoid and thyroid cartilage make this area the narrowest and the least distensible part of the larynx. Inflammation, however, commonly affects the conducting airways at all levels.

This syndrome, recognized and respected by physicians for centuries, inherited its name, croup, from the Anglo-Saxon word *kropan*, or from an old Scottish word *roup*, which meant to cry out in a hoarse voice. *Spasmodic croup* is a term sometimes used to denote afebrile episodes of croup that may be recurrent. Airway hyperreactivity resulting from allergens may play a role in predisposing some children to repetitive bouts of croup. In the past, diphtheria was commonly referred to as *membranous croup*, which, until the twentieth century, was considered the cause of most croup cases. Occasionally, *membranous croup* is still used for croup-like cases caused by bacteria.

## ETIOLOGY AND EPIDEMIOLOGY

### Viral Agents

A variety of agents may be associated with croup. The parainfluenza viruses are identified most often as causing this disease, especially parainfluenza virus type 1. In an 11-year study of croup in a private practice in Chapel Hill, North Carolina, the parainfluenza viruses constituted 75% of viral isolates obtained from children who had croup, and 65% of the parainfluenza viral isolates were parainfluenza virus type 1. Among 144 children presenting with inspiratory stridor to emergency departments in Helsinki, the parainfluenza viruses accounted for 42% of the cases, and parainfluenza virus 1 was the single most often identified agent (31%).

However, among hospitalized children, a recent multicenter population-based study showed that parainfluenza viruses 1 and 2 were almost equal in frequency.

Influenza viruses A and B and respiratory syncytial virus (RSV) are usually the next most often identified agents. Influenza virus, especially influenza A virus, has been associated with croup that is more severe than the usual cases associated with the more common parainfluenza viruses. With the increasing use of molecular diagnostic techniques, such as reverse transcriptase polymerase chain reaction (RT-PCR), many more viruses have been detected in children with croup. Rhinoviruses, enteroviruses, and bocaviruses have been detected in approximately 10% of children presenting with croup, and adenovirus, human metapneumoviruses, *M pneumoniae*, and human coronaviruses have been detected occasionally, in 1% to 2% of specimens from croup cases. However, 1 type of human coronavirus, NL63, seems to cause infection that often manifests as croup. A large prospective German study identified human coronavirus NL63 in 5% of children younger than 3 years, and it was strongly associated with croup. This agent was more often identified during the winter than at other times of the year and among ambulatory children more than among hospitalized children.

Many of these agents have been identified as coinfections, which leads to diagnostic confusion. Rhinoviruses are detected concurrently with another virus especially often. Two-thirds of the specimens with rhinoviruses obtained from children presenting with croup to Finnish emergency departments had another respiratory agent concurrently identified by RT-PCR.

In the United States, measles was once a major cause of croup cases, which were often severe. Measles should still be considered in inadequately immunized populations.

Although the number of croup-related visits to emergency departments has increased in recent years, the number of hospital admissions from croup has been declining since the 1990s. This decline is most likely explained by the wider use of therapeutic modalities, primarily corticosteroids and nebulized epinephrine, which may be administered in the outpatient setting.

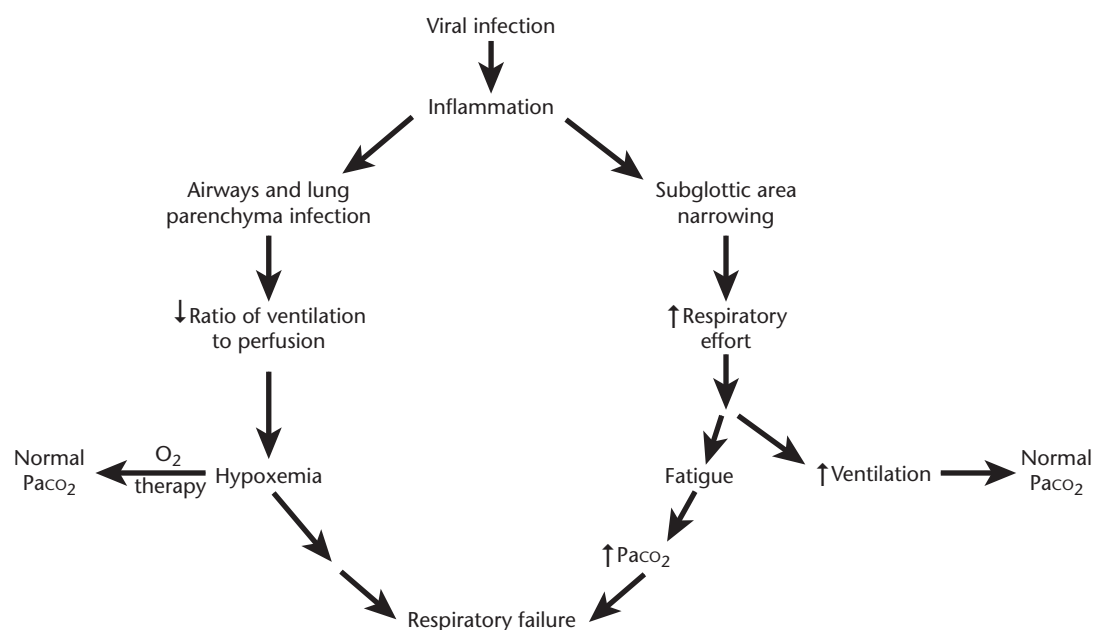
### Seasonal Occurrence

The singular seasonal patterns of croup cases correlate closely with activity of the major viral agents causing the syndrome, predominantly the parainfluenza viruses (Table 352-1). Parainfluenza virus type 1, the most common cause of croup, has the distinctive pattern of producing epidemics of croup and other associated respiratory illnesses every other year in the autumn. In a long-term surveillance program conducted in Monroe County surrounding Rochester, New York, the parainfluenza viruses constituted approximately 17% of all the viral isolates obtained from outpatients in private practices and for 67% of the isolates from children who had croup. Smaller peaks of croup are associated with outbreaks of parainfluenza virus types 2 and 3, influenza, and RSV. Although the proportion of RSV infections that are exhibited as croup is relatively small (approximately 5%), RSV is associated with up to 11% of all croup cases.

<sup>†</sup>Deceased

**Table 352-1** Agents and Seasonal Patterns of Viral Croup in the United States

AGENT	SEASONAL PATTERN
<b>MOST COMMON</b>	
Parainfluenza type 1	Biennial epidemics in the fall
Parainfluenza type 2	Variable fall outbreaks, commonly biennial concurrent with parainfluenza type 1 outbreaks
Parainfluenza type 3	Annual spring outbreaks, extending into summer and early fall
<b>LESS COMMON</b>	
Influenza A	Epidemic, winter
Influenza B	Epidemic, winter
Respiratory syncytial virus (RSV)	Epidemic, winter and spring
Human metapneumovirus	Winter and spring
Adenoviruses	All year
Picornaviruses	Fall, spring–summer
Coronaviruses	Winter and spring



**Figure 352-1** Physiologic abnormalities in viral croup. Viral infection of the subglottic area produces inflammation and obstruction, resulting in an initial decrease in the child's tidal volume. To maintain an adequate alveolar ventilation, the child increases the respiratory rate. With greater degrees of obstruction, however, the work of breathing may increase such that the child can no longer compensate by the increased respiratory effort. The ensuing decrease in tidal volume and respiratory rate may then result in hypercapnia and secondary hypoxemia.

### Host Factors Affecting Croup

Epidemiologic observations indicate that both the predilection for acquiring croup and for developing more severe illness are related to certain characteristics of the affected child. Boys seem more susceptible to developing croup than girls. Among both hospitalized and ambulatory croup cases, the ratio of boys to girls is approximately 2:1. Furthermore, although essentially all children acquire infection with the common respiratory viruses, such as the parainfluenza viruses and RSV, only a minority will manifest primary infection as croup. Also, some children will have multiple episodes of croup caused by different viruses.

Most striking is the affect of age on the occurrence and manifestations of croup. Croup occurs primarily in children between 3 months and 3 years of age and accounts for approximately 10% to 15% of respiratory

tract disease in children. The peak incidence of croup occurs between 6 and 24 months of age among both ambulatory and hospitalized cases. The age predilection of viral croup can be explained partly by the anatomic features of the airway of young children. Their small airways are particularly prone to obstruction from inflammation of the lining membranes. The subglottic trachea of a young child is relatively smaller and also more pliable than that of an older individual. The narrowing that occurs with inspiratory effort, therefore, may be exaggerated in a young child with croup. In addition, obstruction above the subglottic area, which occurs with nasal congestion, increases the collapsing force, and an increased respiratory rate associated with crying or anxiety may compromise the child's ventilation further (Figure 352-1).



Other host factors (eg, genetic and immunologic mechanisms), as yet poorly defined, are likely to contribute to the development and severity of croup. Atopy or hyperreactivity of the airways has been suggested in some studies as playing a role in the development of spasmodic and recurrent croup by the higher incidence of a family history of allergy and positive skin tests for allergens in such children. However, other studies have failed to show children with a single episode compared to those with recurrent episodes to be significantly different in their or their family's history of atopy.

The role in croup of genetic and anatomic host factors is suggested by the prospective Tucson studies of lower respiratory tract disease. Children were enrolled at birth and monitored through 13 years of age with periodic pulmonary function tests and markers of atopy. Children who had croup associated with wheezing had significantly lower levels of indices of intrapulmonary airway function as infants, before any lower respiratory tract illness, and an increased risk of persistent wheezing in later life. In contrast, premorbid inspiratory resistance was significantly higher among children who subsequently developed croup without wheezing compared with those who developed croup with wheezing or who never developed croup.

## DIFFERENTIAL DIAGNOSIS

Many entities may cause stridor and mimic viral croup (Box 352-1) with an important differentiating factor being the relatively acute onset of croup. However, most important and urgent to consider in the differential diagnosis are the 2 bacterial causes of stridor: bacterial tracheitis and epiglottitis. Although these entities currently are uncommon, they may be fatal without immediate therapy. Since the conjugated *Haemophilus influenzae* type b vaccines were licensed and incorporated into the routine immunization schedule of young children, epiglottitis has become rare in the United States. The differentiating features of epiglottitis are the fast and unrelenting course, accompanied by drooling and anxiety; and often the child is sitting and leaning forward. In most instances, the coryza, barking cough, and laryngitis characteristic of viral croup are not present with epiglottitis. Instead, the child's voice may be muffled.

Bacterial tracheitis is the second emergent entity that must be differentiated from viral croup. Bacterial tracheitis is a relatively uncommon infection that may affect children of any age and sometimes occurs after an episode of viral croup. The onset is acute with respiratory stridor, high fever, and copious, purulent secretions. As with epiglottitis, the child seems toxic, and the respiratory obstruction rapidly progresses, often necessitating tracheal intubation. The pathogens most often involved are *Staphylococcus aureus* and group A  $\beta$ -hemolytic streptococci. The diagnosis may be confirmed by direct laryngoscopy, which shows the purulent secretions and inflammation in the subglottic area, and sometimes by a lateral neck radiograph, which may reveal an area of subglottic narrowing with a shaggy membrane.

Infection of the deep neck spaces, including peritonsillar and retropharyngeal abscesses, may occasionally

### BOX 352-1 Differential Diagnosis of Acute Viral Laryngotracheobronchitis

#### INFECTIOUS CAUSES OF STRIDOR

- Epiglottitis
- Bacterial tracheitis
- Human papillomavirus (acquired perinatally)
- Retropharyngeal and parapharyngeal abscess

#### NONINFECTIOUS CAUSES OF STRIDOR

- Foreign body aspiration
- Vocal cord paralysis
- Angioneurotic edema of upper airway
- Hypocalcemic tetany
- Congenital malformations of upper airway
- Laryngotracheal malacia, web, cleft
- Vascular ring
- Tracheal stenosis
- Hemangioma, cyst of larynx or trachea
- Cystic hygroma
- Trauma

have features similar to those of viral croup and especially should be considered in a child with a history of a penetrating pharyngeal injury, such as that caused by a fish bone. Peritonsillar and retropharyngeal abscesses are commonly preceded by a mild pharyngitis and are more gradual in onset than croup. The child may be febrile with complaints of a sore throat and have difficulty in swallowing. Stridor usually is not present until the disease has markedly progressed. Important differential findings include a muffled voice, rather than a hoarse voice, the head held in a position allowing extension of the neck, the child resisting oropharyngeal examination, and progressive drooling and visible asymmetry to the wall of the posterior oropharynx. Diphtheria, which immunization fortunately has made rare, may be excluded by a history of adequate immunizations and by the absence of the characteristic gray pharyngeal or laryngeal diphtheritic membrane.

Multiple noninfectious entities can cause stridor, most of which (eg, congenital malformations, trauma) can be differentiated by obtaining a thorough history. An aspirated foreign body, among the more common causes of stridor, is abrupt in onset with respiratory distress; the lack of preceding respiratory symptoms, fever, and a history of previous choking on food or foreign body suggest this diagnosis. Acute edema of the upper respiratory tract caused by an allergic reaction may cause abrupt swelling and severe respiratory distress with stridor. The history of the circumstances of the abrupt onset, the lack of previous respiratory signs, and the concurrent onset of other manifestations of an allergic reaction, such as swollen lips and tongue and urticaria, are helpful in the differentiation from viral croup. (See Box 352-1.)

## EVALUATION

### History

The history is integral both in making the diagnosis of viral croup, as noted previously, and in assessing the severity of the illness on which the management depends. The child's prodromal signs, the characteristics of the onset of the illness, and the course of the development of the respiratory signs should be carefully obtained. A child with an atypical onset, with a rapidly progressive illness, with a history of recurrent episodes of illness with respiratory distress, or with an underlying condition may be at an increased risk for developing severe disease.

The typical history of a child with viral croup includes the child having had signs of an upper respiratory tract infection for 1 to 2 days. However, some children with few prior respiratory signs will awaken at night with the acute onset of spasms of cough, respiratory distress, and inspiratory stridor. This period is then followed by a characteristic cough, which may be spasmodic, with a deep brassy or harsh barking quality. This cough has been likened to a seal's bark and a brass bell. In 1836, Ley described the stridor as "the crowing of a cock, the yelping of a fox, the barking of a dog, the braying of an ass, or a ringing sound, as if the voice came from a brazen tube." Laryngitis with a raspy-sounding voice may also develop. Fever is commonly present, particularly with influenza and parainfluenza viral infections, and may reach 39.4°C to 40°C (103°F–104°F).

### Manifestations and Course of Croup

The pathophysiology of the development of croup in a young child explains the clinical manifestations, the course of illness, and potential complications (Figure 352-1). The virus initially infects the upper respiratory tract and produces congestion of the nasal passages and nasopharynx. The larynx, trachea, and often the bronchi, especially during primary infection, subsequently become involved. The 3 hallmark signs of croup—hoarseness, cough, and stridor, are produced primarily from the inflammation and obstruction of the larynx and trachea (Figure 352-1).

The stridor results from obstruction to airflow during both inspiration and expiration, but is most marked during inspiration. Because the subglottic region is outside the pleural cavity, the negative pressures generated on inspiration tend to narrow the passage further, similar to sucking on a partially occluded straw. Even minimal inflammation of the membranes lining the narrow passages of the larynx and glottis causes a considerable degree of obstruction, because resistance to airflow is inversely related to the fourth power of the radius of the airway. With subglottic obstruction, the child's tidal volume may decline, but may be compensated for by an increased respiratory rate. However, if the obstruction worsens and the child tires from the increased work of breathing, hypercarbia, hypoxemia, and respiratory failure can ensue (Figure 352-1).

### Physical Examination

On physical examination, therefore, the child's distress is most evident during inspiration. Each inspiratory

effort is marked audibly by the stridulous sound and is accentuated visibly by the retractions of the accessory muscles of the chest wall. The suprasternal, supraclavicular, and particularly the substernal retractions are characteristic of the inspiratory obstruction. Furthermore, distress may be marked by asynchronous movements of the chest wall and abdomen.

The respiratory rate is increased, but usually is not more than 50 breaths/min. This is in contrast to bronchiolitis, in which the picture of respiratory distress may be accompanied by respirations of 80 to 90 breaths/min. Auscultation of the chest reveals a prolonged inspiration, which may be accompanied by coarse crackles. Wheezes and rhonchi may also be heard on expiration. With more severe obstruction, the breath sounds may be diminished.

### Course of Illness

A varying intensity of the respiratory distress is characteristic of croup. The child may seem severely compromised and an hour later seem improved, only to worsen over the next hour. In some children, the symptoms seem to abate on waking in the morning but may worsen again as the day progresses. The signs of croup may extend over 3 to 4 or more days when untreated, but with dexamethasone therapy the respiratory stridor and distress usually are diminished within hours. The other signs associated with viral infection, such as nasal congestion and cough, may last longer.

In a few children, the respiratory distress may be unremitting or recurrent and associated with significant pneumonitis and hypoxemia leading to rapid, but shallow respirations, which indicate the child is fatiguing (Figure 352-1).

### Laboratory Testing

Croup is usually diagnosed based on the characteristic clinical findings and a compatible history. Laboratory testing is usually not necessary for most outpatients and may upset the child, causing an increased respiratory effort, which will augment the subglottic narrowing and obstruction to airflow. Laboratory evaluation should be limited to those tests necessary for management of a more severely ill child, such as tests needed for assessment of dehydration and oxygenation. The white blood cell count and differential usually are not helpful. The total white blood cell count may be normal or low from the viral infection. However, a mild shift to the left with an increased number of neutrophils and band forms may also occur in more distressed and hypoxemic children.

Multiple laboratory assays are available to determine the specific viral agent, including viral isolation, rapid antigen detection techniques such as immunofluorescence assays and enzyme immunoassays, and methods to detect viral RNA, as by RT-PCR. In most cases, however, specific diagnosis of the viral agent is not necessary and is not available in the time required for initial management decisions. In some instances, determination of the specific viral cause may be helpful in determining infection control procedures or when antiviral therapy, such as for influenza or RSV, is being considered.



**Figure 352-2** Radiograph of the posteroanterior neck of a child with viral croup, showing narrowing in the subglottic area.

### Imaging

Imaging is not usually necessary in diagnosing or managing children with viral croup. In some cases that are atypical or apt to be confused with other syndromes characterized by stridor, the differential diagnosis of croup may be aided by a lateral inspiratory and expiratory radiograph or by a posteroanterior radiograph of the neck (Figure 352-2). The air shadow of the larynx is seen to narrow, resembling an hourglass or a steeple, in the subglottic region as a result of the characteristic inflammation in this area. An inspiratory lateral view may also show distension of the hypopharynx. However, the variable sensitivity and specificity of neck radiographs for diagnosing viral croup make their value questionable.

## MANAGEMENT

The first phase of management is to evaluate which children may be cared for at home and which require hospitalization. Severity is often difficult to determine in this fluctuating disease, and no clinical signs are consistently prognostic of a complicated course. Clinical scoring systems, such as the Westley croup score, have been used to aid in the decision as to which children should be hospitalized. Toxic appearance, dehydration, and fatigue are indications for hospitalization. These are primarily based on such clinical findings as the degree of stridor, chest wall retractions, cyanosis, and the level of consciousness or fatigue (Table 352-2).

### Supportive Care

Supportive care is of prime importance for children with croup, whether they are outpatients or hospitalized. The child should be made comfortable to

avoid unnecessary anxiety and fatigue. Crying and anxiety tend to make the young child take rapid, short breaths, which aggravate the narrowing of the airway and the metabolic need for gas exchange. Fluids should be encouraged, and antipyretics may be given for fever and to diminish the associated increased respiratory rate and fluid requirements. Despite a multitude of cures passed down from generation to generation, few other home therapies have proved beneficial. Because of croup's fluctuating nature, several unverified therapeutic modalities may seem to work.

### Humidified Air

Humidified air from vaporizers, home-devised mist tents, and teakettles to showers have commonly been tried. The water particles that these devices produce, nevertheless, are generally too large to reach the lower respiratory tract, and are primarily helpful in humidifying the anterior nares and oropharynx. Furthermore, devices that use hot water and steam pose the potential hazard of accidental burns. Studies in children evaluating the efficacy of humidified air in treating croup are few and involve small numbers of patients, and no beneficial effects of mist have been proven.

### Nebulized Epinephrine

For children with severe croup, nebulized epinephrine, racemic or L-epinephrine, may be added to dexamethasone (Table 352-2). Epinephrine causes diminished subglottic swelling via its stimulus of  $\alpha$ - and  $\beta$ -adrenergic receptors, decreasing blood flow and swelling in the upper respiratory tract. The arterial oxygen saturation is not affected by the administration of epinephrine, and the amelioration of the clinical signs is transient. Thus, the child should be observed for at least 2 hours.

### Corticosteroid Therapy

Beyond supportive care, the major advance and mainstay in the management of both ambulatory and hospitalized children with viral croup is the use of dexamethasone (Table 352-2). Multiple well-designed trials have shown that 1 dose of dexamethasone orally or intramuscularly when necessary has resulted in significant clinical improvement within 24 hours, decreased hospitalization, fewer follow-up visits, and less need for additional medications. Although, in mild croup, many physicians prescribe dexamethasone for such children, the primary benefit supported by the evidence for mild croup is a modest 1-day reduction in the duration of illness. Some physicians and parents may not think that the potential risks of systemic steroids, even a single dose, are worth this magnitude of benefit.

### Antibiotic Therapy

Because croup is of viral etiology, antibiotics are rarely indicated. Secondary or concurrent bacterial infection is unusual, and antibiotics should be reserved for such documented cases.

**Table 352-2** Evaluation and Management of Children With Croup

	CROUP SEVERITY (WESTLEY SCORE)		
	MILD ( $\leq 2$ )	MODERATE (3–7)	SEVERE ( $\geq 8$ )
	Barking cough, hoarseness. No stridor, no or minimal chest wall retractions <i>at rest</i> , but may have them with crying or increased activity	Stridor and chest wall retractions <i>at rest</i> . No agitation	Stridor, sternal retractions <i>at rest</i> , accompanied by agitation or fatigue
<b>THERAPY</b>			
Decongestants, cough suppressants, antibiotics	Not recommended	Not recommended	Not recommended
Humidification	Not proven beneficial	Not effective	Not effective
Corticosteroids	Consider Dexamethasone (0.6 mg/kg, 1 dose PO)	Dexamethasone (0.6 mg/kg, 1 dose PO or IM)	Dexamethasone (0.6 mg/kg, 1 dose PO or IM)
Nebulized epinephrine	Not recommended	Consider nebulized racemic epinephrine (2.25%, 0.5 mL in 2.5 mL saline or L-epinephrine (1:1,000 dilution in 5 mL of saline)	Nebulized racemic epinephrine (2.25%, 0.5 mL in 2.5 mL of saline or L-epinephrine (1:1,000 dilution in 5 mL of saline)
<b>DISPOSITION</b>	Discharge home	Discharge to home if no stridor, no retractions at rest. If no improvement in 4 hours, consider hospitalization.	Observe for 2 hours. Good response: no recurrence, no stridor, no retractions at rest—discharge to home possible. Poor response: stridor, retractions at rest after 2 epinephrine doses—hospitalize

IM, intramuscular; PO, by mouth.

### WHEN TO REFER

- Child has a wheezing condition predisposing to more severe croup
- Child has a history of recurrent episodes of croup
- Episode of croup occurs during the neonatal period
- Symptoms progress despite supportive care at home

### WHEN TO ADMIT

- Child seems toxic, lethargic, in respiratory distress, or dehydrated
- Onset of illness was sudden with rapid progression of symptoms
- Signs of respiratory distress are unresponsive to outpatient drug therapy

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Common Childhood Infections* (handout), American Academy of Pediatrics (shop.aap.org)
- *Croup Treatment* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/Croup.aspx](http://www.healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/Croup.aspx))

- *Croup and Your Young Child* (audio), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/Croup-and-Your-Young-Child.aspx](http://www.healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/Croup-and-Your-Young-Child.aspx))
- *Croup and Your Young Child* (handout), American Academy of Pediatrics (shop.aap.org)

#### Medical Decision Support

- *Clinical Practice: Croup* (article), *N Engl J Med*, Vol 358, Issue 4, 2008
- *Guideline for the Diagnosis and Management of Croup. 2008 Update* (fact sheet), Alberta Clinical Practice Guideline Working Group ([www.topalbertadoctors.org/download/252/croup\\_guideline.pdf](http://www.topalbertadoctors.org/download/252/croup_guideline.pdf))
- *Human Parainfluenza Viruses (Common Cold and Croup)* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/parainfluenza/index.html](http://www.cdc.gov/parainfluenza/index.html))
- *National Respiratory and Enteric Virus Surveillance System (NREVSS)* (database), Centers for Disease Control and Prevention ([www.cdc.gov/surveillance/nrevss](http://www.cdc.gov/surveillance/nrevss))
- *What Is the Westley Croup Score?* (Web page), PediatricEducation.org ([www.pediatriceducation.org/2012/12/03/what-is-the-westley-croup-score](http://www.pediatriceducation.org/2012/12/03/what-is-the-westley-croup-score))



### SUGGESTED READINGS

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## Chapter 353 DEHYDRATION

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The terms *volume depletion* or *hypovolemia* (a condition in which extracellular fluid is lost) and *dehydration* (a condition in which pure water loss occurs) are used interchangeably. The most common cause of dehydration is diarrheal illness, which results in 2.5 million deaths annually worldwide. Gastroenteritis causes more than 200,000 hospital admissions and more than 1.5 million outpatient visits every year in the United States. Although not a leading cause of death in the United States, gastroenteritis and related disorders result in a substantial amount of morbidity and generate significant health care costs.

### ETIOLOGY

Dehydration in infants and children is overwhelmingly the result of infectious processes. Of these processes, viral agents are of primary importance in the industrialized countries. Rotavirus and the Norwalk agent account for most cases of viral gastroenteritis in children. Some other causes of gastroenteritis are listed in Table 353-1.

Noninfectious causes of dehydration in children include agents that produce osmotic diarrhea, such as laxatives or cathartics that contain high concentrations of sugars; obstructive processes in the gastrointestinal tract; and, occasionally, vomiting as a sign of elevated intracranial pressure. Although each of these conditions occurs only rarely, they should be borne in mind when evaluating the child who is dehydrated and has a history that is not typical for infectious gastroenteritis. Finally, nondiarrheal causes of water and electrolyte loss can also result in severe dehydration. Losses can occur through the skin, respiratory system (ie, increase in insensible losses), or renal conditions. Losses that occur through the skin because of fever are usually in the range of a 10% to 15% rise in insensible losses for each 1°C rise in temperature above 38°C. A few

**Table 353-1**

### Causes of Pediatric Gastroenteritis

TYPE OF ORGANISM	COMMON	UNCOMMON
Viral	Rotavirus Norwalk Enteric adenovirus	Calicivirus Astrovirus
Bacterial	<i>Salmonella</i> <i>Shigella</i> <i>Campylobacter jejuni</i>	<i>Yersinia enterocolitica</i> <i>Vibrio cholerae</i> <i>Escherichia coli</i> <i>Clostridium difficile</i>
Parasitic	<i>Giardia lamblia</i>	<i>Entamoeba histolytica</i> <i>Cryptosporidium</i>

### BOX 353-1 Nondiarrheal Causes of Dehydration

#### WATER DEFICIT

- Nephrogenic diabetes insipidus
- Central diabetes insipidus

#### INCREASED INSENSIBLE LOSSES

- Premature infants
- Radiant warmers
- Phototherapy

#### INADEQUATE INTAKE OF WATER

- Ineffective breastfeeding
- Child abuse

#### WATER AND SODIUM DEFICITS

- Burns
- Excessive sweating
- Renal losses
- Diuretic use or abuse
- Diabetes mellitus
- Chronic renal disease, obstructive uropathy
- Cystic fibrosis, cystinosis, and other causes of the renal Fanconi syndrome

#### MISCELLANEOUS

- Surgical drains and third spacing

common causes of nondiarrheal dehydration are listed in Box 353-1.

### PATHOPHYSIOLOGIC MECHANISM OF DEHYDRATION IN GASTROENTERITIS

Children are at an increased risk for hypovolemia and dehydration because of the following:

1. Gastroenteritis is more common in children than in adults.

2. Very young children have higher surface-area-to-volume ratios than adults; thus, they have a proportionally higher rate of insensible losses, which can be accentuated in disease states.
3. Infants are less able to concentrate urine than are older toddlers and children.
4. Young children are often unable to communicate or actively seek fluids to replenish their losses.

To make the best-informed decisions about appropriate treatment of dehydration, primary care physicians should understand the basic principles underlying dehydrating diarrhea and the mechanisms by which rehydration occurs.

Regardless of which pathogen is involved, diarrhea and fluid loss ultimately result when intestinal fluid secretion exceeds the rate of absorption. In the case of viral agents and cytopathic bacteria, such as *Shigella*, *Salmonella*, *Campylobacter*, and enteropathogenic strains of *Escherichia coli*, fluid absorption is diminished because absorptive cells at the intestinal villus tip are destroyed. However, secretory processes that occur at the level of intestinal crypt cells remain unimpaired. On the other hand, toxin-producing bacterial pathogens such as *Vibrio cholerae*, toxigenic *E coli*, and some strains of *Shigella* cause significant increases in fluid secretion from crypt cells by deranging modulation of ion channels in the crypt cell membranes. Intestinal absorptive function is normal in such cases but does not keep pace with secretion, and diarrhea results.

Substantial fluid loss from the intestines or other sites depletes intravascular volume, resulting in end-organ hypoperfusion and poor nutrient and oxygen delivery; ultimately, tissue acidosis develops. Elevated aldosterone levels resulting from hypovolemia lead to renal potassium loss. Eventually, circulatory collapse and shock occur; irreversible organ damage and death may follow. The chain of events can be interrupted by very rapid repletion of fluids to restore circulating volume, reverse acidosis, and improve perfusion and end-organ function.

## EVALUATION

All children with dehydration should be systematically evaluated with the following 5-point assessment:

1. What is the magnitude of volume deficit?
2. Is osmolar imbalance present?
3. Is acid-base disturbance present?
4. Is abnormality in potassium metabolism present?
5. Is the renal function impaired?

The 5-point assessment can be evaluated by a combination of clinical and laboratory techniques as detailed in Table 353-2.

### Physical Examination

During the initial evaluation of a child with dehydration, physicians must determine and document the degree of dehydration. Volume depletion is most objectively measured as a change in weight from baseline. Ideally, the pre-illness weight should be used to determine the exact proportion of weight loss that is attributable to the fluid deficit. Given that the pre-illness weight is often unavailable, physicians should use pulse rate, blood pressure, urine output, skin turgor, and other signs (Table 353-3) to categorize the

**Table 353-2**

### Five-Point Assessment of Dehydration

POINT OF ASSESSMENT	METHOD
Volume deficit	History and physical examination
Osmolar disturbance	Serum sodium and serum osmolality measurement
Acid-base disturbance	Blood pH, PCO <sub>2</sub> , and serum bicarbonate measurement
Potassium	Serum potassium
Renal function	Blood urea nitrogen, creatinine, urine specific gravity

PCO<sub>2</sub>, partial pressure of carbon dioxide.

child as having mild (3%–5% volume loss), moderate (6%–9% volume loss), or severe dehydration (≥10% volume loss).

### Laboratory Evaluation

Laboratory testing is used to determine the clinical condition of the child and the origin of dehydration. Many children with mild or moderate dehydration do not need any laboratory tests. The minimal amount of testing in patients with moderate to severe dehydration is measurement of serum electrolytes, including sodium, potassium, chlorides, and bicarbonates, along with blood urea nitrogen, serum creatinine, urine specific gravity, and serum glucose (by the finger-prick method at the bedside). Laboratory testing is less useful in assessing the degree of volume depletion. A review of the literature and a prospective study found that only serum bicarbonate (<17 mEq/L) differentiated a child with moderate or severe hypovolemia from one with mild hypovolemia. Serum sodium measurements are useful in categorizing the child as having isotonic or hyponatremic (150 mEq/L) dehydration. The signs of dehydration (see Table 353-3) will be delayed if the patient has hypernatremic dehydration (ie, higher relative loss of free water as compared with loss of sodium), because the increased serum sodium causes an osmotically driven fluid shift from the intracellular compartment to the extracellular compartment. Similarly, the signs of dehydration are present earlier if the child has hyponatremic dehydration. Serum potassium levels may be falsely elevated (acidosis causes a shift from the intracellular compartment) or low (caused by losses in the gastrointestinal tract). Urine osmolality and specific gravity will be high (often exceeding 450 mOsm/kg), but may be low if the patient has lost renal concentrating ability (in patients with osmotic diuresis or diabetes insipidus). Stool diagnostic studies similarly should be used sparingly. Bacterial cultures certainly should be obtained in ill-seeming children, those with fever (≥38°C in infants younger than 3 months and ≥39°C in children older than 3 months), those who have bloody or mucoid stools, or those in whom a travel or

**Table 353-3** Degree of Dehydration

PARAMETER	DEGREE OF DEHYDRATION		
	MILD	MODERATE	SEVERE
Weight loss (%)—infants	5	10	15
Weight loss (%)—children	3	6	>9
Skin color	Pale	Gray	Mottled
Skin turgor	May be normal	Decreased	Tenting
Mucous membranes	Slightly dry	Dry	Dry, parched, collapse of sublingual veins
Eyes	Normal	Decreased tears	Sunken, absence of tears
Central nervous system	Alert but thirsty	Irritable	Lethargic, grunting, coma
Pulse	Normal and strong	Rapid and slightly weak	Significantly tachycardic and very weak to not palpable
Capillary refill	Normal (<2 sec)	2–4 sec	>4 sec
Blood pressure	No change	Orthostatic decrease	Shock
Urine	Normal to mildly reduced	Significantly reduced	Anuria
Volume of deficit—infants	50 mL/kg	60 mL/kg	150 mL/kg
Volume of deficit—children	30 mL/kg	100 mL/kg	>90 mL/kg

exposure history is suggestive of enteric pathogens. Most children will not meet these criteria, and routine stool cultures should be discouraged. Similarly, little additional diagnostic or therapeutic guidance is provided by detection of the rotavirus antigen in stool samples, and such studies rarely should be performed.

## TREATMENT

### Principles of Fluid Therapy

In children, dividing fluid therapy into replacement therapy (corrects deficit) and maintenance therapy (replaces ongoing losses, including insensible losses) is useful. Details of maintenance therapy are provided in Chapter 58, Fluids, Electrolytes, and Acid-Base Composition. Replacement therapy is based on 2 steps.

1. First-fluid (emergent) phase: This phase restores moderately or severely compromised effective circulating volume and prevents tissue damage. This phase is typically begun with a 20-mL/kg fluid bolus with isotonic saline (0.9 normal saline [NS]) or lactated Ringer solution over 1 to 2 hours. Fluid boluses should be repeated until signs of shock begin to disappear. Although some advantages can be found for using colloid solutions (albumin or hetastarch, namely that the colloid solutions remain for a longer time in the intravascular space and have a lower risk of developing pulmonary edema caused by dilutional hypoalbuminemia), many clinical trials have failed to demonstrate these theoretical benefits.
2. Second-fluid phase: This phase essentially replaces the body's fluid and electrolyte loss and can be in the form of parenteral intravenous fluids or oral replacement as oral rehydration therapy (ORT).

Physicians should recognize that, in mild to moderate cases of dehydration, this phase will often suffice and the physician may not have to resort to the first-fluid or emergent phase. Administration of ORT is discussed later in this chapter. Intravenous fluids are often indicated if the child is unable to undergo ORT because of altered mental status or persistent vomiting, or has severe electrolyte abnormalities. The type of intravenous fluids used depends on the serum sodium levels (ie, whether the child has isonatremia, hyponatremia, or hypernatremia). Most cases of dehydration in children are associated with isonatremia and can be managed over a few hours in an ambulatory setting (either the physician's office or the observation unit in an emergency department). Table 353-4 provides details about the estimated water and electrolyte deficits associated with moderate-to-severe dehydration.

### Controversies Regarding Optimal Fluid Management in Dehydration

Although rapid reexpansion of the extracellular fluid volume with 0.9% saline followed by ORT has become the gold standard therapy in infants with moderate-to-severe dehydration, few physicians are actually using this therapeutic regimen. Tables 353-5, 353-6, and 353-7 provide examples of a child who is 10% dehydrated with isonatremic, hyponatremic, and hypernatremic dehydration.

Normal saline or 0.9 NS solution has 154 mEq/L of sodium, and half normal saline or 0.45 NS has 77 mEq/L of sodium. Similarly, 0.25 NS has 38 mEq/L of sodium. Physicians should be aware of these sodium concentrations in intravenous fluids while calculating replacement of maintenance and ongoing losses

**Table 353-4** Estimated Fluid and Electrolyte Deficits in Moderate-to-Severe Dehydration

TYPE OF DEHYDRATION	WATER (mL/Kg)	SODIUM (mEq/kg)	POTASSIUM (mEq/kg)	CHLORIDE AND BICARBONATE (mEq/kg)
Isonatremic	100–150	8–10	8–10	16–20
Hyponatremic	50–100	10–14	10–14	20–28
Hypernatremic	120–180	2–5	2–5	4–10

**Table 353-5** Intravenous Fluids for a 5-kg Child With 10% Dehydration and Normal Serum Sodium

	WATER	SODIUM	POTASSIUM
Maintenance <sup>a</sup> Deficit <sup>b</sup>	5 kg × 100 mL/kg per day = 500 mL Weight × % dehydration	3 mEq/100 mL = 15 mEq Sodium in ECF × proportion of fluid loss from ECF × deficit (mL)	2 mEq/100 mL = 10 mEq Potassium in ICF × propor- tion of fluid loss from ECF × deficit (mL)
	5 kg × 0.1 = 0.5 g (500 mL)	135 mEq/L × 0.6 × 500 mL = 40 mEq	150 mEq/L × 0.4 × 500 mL = 30 mEq
Ongoing losses	Replace mL-for-mL	Add sodium in proportion to expected fluid loss (stool, gastric contents, etc)	Add potassium in proportion to expected fluid loss (stool, gastric contents, etc)
Total	1,000 mL	55 mEq	40 mEq

ECF, extracellular fluid; ICF, intracellular fluid.

<sup>a</sup>After the initial bolus, maintenance fluids are administered over 24 hours; one-half the deficit is given over 8 hours and the remainder over 24 hours.<sup>b</sup>The water and sodium content in the initial bolus of normal saline does not count toward either maintenance or replacement of ongoing losses or deficit therapy.**Table 353-6** Intravenous Fluids for a 5-kg Child With 10% Dehydration and Hyponatremia (Serum Sodium = 128 mEq/L)

	WATER	SODIUM	POTASSIUM
Maintenance <sup>a</sup> Deficit <sup>b</sup>	5 kg × 100 cc/kg/d = 500 mL Weight × % dehydration	3 mEq/100 mL = 15 mEq Sodium in ECF × proportion of fluid loss from ECF × deficit (mL) PLUS (desired sodium – observed sodium) × weight × sodium in ECF	2 mEq/100 mL = 10 mEq Potassium in ICF × propor- tion of fluid loss from ECF × deficit (mL)
	5 kg × 0.1 = 0.5 g (500 mL)	135 mEq/L × 0.6 × 500 mL = 40 mEq PLUS (135 mEq/L – 128 mEq/L) × 5 × 0.6 = 21 mEq	150 mEq/L × 0.4 × 500 mL = 30 mEq
Ongoing losses	Replace mL-for-mL	Add sodium in proportion to expected fluid loss (stool, gastric contents, etc)	Add potassium in proportion to expected fluid loss (stool, gastric contents, etc)
Total	1,000 mL	76 mEq	40 mEq

ECF, extracellular fluid; ICF, intracellular fluid.

<sup>a</sup>After the initial bolus, maintenance fluids are administered over 24 hours; one-half the deficit is given over 8 hours and the remainder over 24 hours.<sup>b</sup>The water and sodium content in the initial bolus of normal saline does not count toward either maintenance or replacement of ongoing losses or deficit therapy.



**Table 353-7** Intravenous Fluids for a 5-kg Child With 10% Dehydration and Hypernatremic Dehydration (Serum Sodium = 160 mEq/L)

	WATER	SODIUM	POTASSIUM
Maintenance	5 kg × 100 mL/kg/d = 500 mL	3 mEq/100 mL = 15 mEq	2 mEq/100 mL = 10 mEq
Deficit	Weight × % dehydration  5 kg × 0.1 = 0.5 g (500 mL)	Free water deficit = ([observed sodium – desired sodium] weight × 4 mL/kg); thus, free water deficit = (160 – 145) × 5 kg × 4 mL/kg = 300 mL Sodium in ECF × proportion of fluid loss from ECF × (total deficit – free water deficit) 135 mEq/1,000 mL × 0.6 × (500 – 300 mL) = 16 mEq/L	Potassium in ICF × propor- tion of fluid loss from ECF × deficit (mL); thus, free water deficit = (160 – 145) × 5 kg × 4 mL/kg = 300 mL 150 mEq/L × 0.4 × (500 – 300 mL) = 12 mEq
Ongoing losses	Replace mL-for-mL	Add sodium in proportion to expected fluid loss (stool, gastric contents, etc)	Add potassium in proportion to expected fluid loss (stool, gastric contents, etc)
Total	1,000 mL	31 mEq	22 mEq

ECF, extracellular fluid; ICF, intracellular fluid.

of fluids and electrolytes. In general, in the presence of otherwise normally functioning kidneys, most patients will do well with 0.45 NS or 0.9 NS when it is used as replacement solution.

### Oral Rehydration

Fluid absorption can be promoted by the enteral administration of properly designed fluids, even in the face of ongoing losses. In healthy adults, more than 6,500 mL per day of fluids, including both ingested liquids and intestinal secretions, are introduced into the intestinal tract and reduced to form a stool output of less than 100 mL per day. Oral rehydration exploits a normal cellular process known as cotransport, in which absorption of a molecule of an organic substrate promotes the absorption of an ion of sodium from the small intestine. With enhanced absorption of sodium, water, in turn, is absorbed rapidly into the circulation. Intravascular fluid volume can be restored in this fashion rapidly and reliably.

A fluid that is designed to promote water and electrolyte absorption through the cotransport system in the gut is referred to as an *oral rehydration solution* (ORS). A physiologically appropriate ORS contains 70 to 90 mEq/L sodium and not more than 25 g/L of glucose. In addition, an ORS typically contains 20 mEq/L of potassium and 30 mEq/L of base in the form of citrate. Almost all juices, soft drinks, and punches contain much higher concentrations of sugars and almost no sodium, making them inappropriate for use as ORSs. In fact, the higher sugar concentrations in these fluids may exacerbate diarrhea by presenting a large osmotic load within the intestinal lumen.

An ORS can be used to restore both fluid and electrolyte balance in children who have a wide range of initial serum sodium values. By the end of the rehydration

period, both hypernatremia and hyponatremia generally have resolved.

## MANAGEMENT

Most dehydrated children can be rehydrated successfully without resorting to parenteral (intravenous or intraosseous) therapy. The combined use of an ORS and an appropriate regimen of refeeding is referred to as *oral rehydration therapy* (ORT). The number of deaths worldwide that are attributable to diarrhea in children younger than 5 years fell from 4.6 million to 1.5 million per year from 1980 to 2000 concomitant with the increased use of ORT. In addition, ORT has been found to have a low failure rate (4%) and to lead to reduced hospital stays and fewer adverse events, and was less expensive than intravenous therapy.

### Intravenous Rehydration

Patients who have severe dehydration (shock) should receive initial rehydration fluids parenterally via either the intravenous or, when line placement proves difficult, the intraosseous route. Patients treated parenterally should be given rapid boluses of 0.9% sodium chloride in initial volumes of 20 mL/kg for not more than 20 minutes. In especially severe cases, it is not unusual for patients to require 60 to 100 mL/kg before the restoration of circulating volume is apparent. Enteral fluid therapy may begin immediately by either the mouth or a nasogastric tube, provided that the patient is conscious and airway protective reflexes are intact. It is important to note that there may be an increased incidence of iatrogenic hyponatremia with the use of hypotonic solutions in the maintenance phase of intravenous hydration. This has led some experts to recommend using 0.9 NS as maintenance fluid after the initial bolus therapy.

**Table 353-8** Solutions Commonly Used in Children Who Have Diarrhea

SOLUTION	GLUCOSE/PHENOL (g/L)	SODIUM (mEq/L)	BASE (mEq/L; CITRATE OR BICARBONATE)	POTASSIUM (mEq/L)	OSMOLALITY (mmol/L)
<b>PHYSIOLOGICALLY APPROPRIATE SOLUTIONS</b>					
Pedialyte	25	45	30	20	270
Ricelyte	30 <sup>a</sup>	50	30	25	200
Rehydralyte	25	75	30	20	310
WHO and UNICEF oral replacement solution	20	90	30	20	310
<b>PHYSIOLOGICALLY INAPPROPRIATE SOLUTIONS</b>					
Cola	700	2	13	0.1	750
Apple juice	690	3	0	32	730
Gatorade	255	20	3	3	330

UNICEF, United Nations International Children's Emergency Fund; WHO, World Health Organization.

<sup>a</sup>Rice syrup solids.

### Oral Rehydration

In the conscious child who has mild or moderate dehydration, fluid replacement always should be initiated orally. Successful ORT depends on proper fluid selection and skilled administration. Simply instructing parents to purchase and feed a child an ORS is unlikely to result in success and satisfaction.

### Types of Oral Rehydration Solutions

In the industrialized world, ORSs are most widely available commercially as premixed liquids. These solutions contain sodium levels varying from 50 to 70 mEq/L. For the mildly dehydrated child, any of these solutions is appropriate. For more significantly dehydrated infants and children, a solution containing 70 to 90 mEq/L of sodium should be chosen. Packets of oral rehydration salts for preparation of a solution containing 90 mEq/L of sodium are available for mixing with 1 L of water to provide an inexpensive and reliable alternative. These packets always should be distributed with a 1-L bottle to promote proper mixing. Juices, punches, and other soft drinks are inappropriate solutions for children who have diarrhea because of the high osmotic load they introduce into the intestines. Table 353-8 lists the most commonly available solutions and their compositions. Information on juices and soft drinks is provided for comparison. The World Health Organization (WHO) formula (2002) contains 13.5 g/L of carbohydrates, 75 mEq/L of sodium, 20 mEq/L of potassium, and 30 mEq/L of bicarbonate base, and has an osmolarity of 245 mOsm/kg of water. The desired properties for an ORS as recommended by WHO and the United Nations International Children's Emergency Fund (UNICEF) for global use include the following:

1. Total osmolality between 200 and 310 mmol/L
2. Equimolar concentrations of glucose and sodium
3. Glucose concentration not in excess of 20 g/L (111 mmol/L)
4. Sodium concentration between 60 and 90 mEq/L
5. Potassium concentration between 15 and 25 mEq/L

6. Citrate concentration between 8 and 12 mmol/L

7. Chloride concentration between 50 and 80 mEq/L

Although homemade sugar-salt solutions can be prepared to produce an appropriate ORS, the risk of incorrect mixing is high. Such homemade solutions should not be used when commercial solutions are available.

### Administration of Oral Replacement Therapy

In general, ORT can be started in the office or emergency department immediately after assessment excludes acute abdominal processes (eg, appendicitis, volvulus, intussusception, pyloric stenosis) and extraintestinal causes of fluid losses (eg, intracranial hypertension caused by tumor, meningitis, or hydrocephalus, all of which may induce volume loss as a result of vomiting). Ideally, the goal is to replace the entire fluid deficit in the first 4 to 6 hours (Table 353-9).

### Rehydration Phase

Fluids are best administered initially by a parent who is instructed to place the fluids into the child's mouth (via a needleless syringe), 1 teaspoon (5 mL) per minute for infants, 10 mL/min for toddlers, and 15 mL/min for older children. This amount, at a steady rate of administration, provides 300, 600, and 900 mL/h, respectively, which generally replaces the calculated deficit within a 4- to 6-hour period. Frequent reassessment of the child and encouragement of the parent are crucial during this rehydration period. The rehydration phase should be completed in the office, clinic, or emergency department before the child is sent home. In general, vomiting is not a contraindication to ORT. Even when vomiting occurs, steady fluid replacement is continued orally. Children usually do not discharge their entire stomach contents when they vomit. As dehydration and tissue acidosis are corrected, the frequency and severity of vomiting are generally reduced. However, children who only have vomiting (without diarrhea) warrant especially careful evaluation for conditions other than gastroenteritis, such as appendicitis, intussusception, volvulus, or pyloric stenosis, depending on age.

**Table 353-9** Fluid Therapy for Dehydration

DEGREE OF DEHYDRATION <sup>a</sup>	SIGNS	REHYDRATION PHASE (FIRST 4HR; REPEAT UNTIL NO SIGNS OF DEHYDRATION REMAIN)	MAINTENANCE PHASE <sup>c</sup> (UNTIL ILLNESS RESOLVES)
Mild (3%–5%)	Slightly dry mucous membranes, increased thirst	ORS 60 mL/kg <sup>b</sup>	Breastfeeding, undiluted lactose-free formula, half-strength cow milk, or lactose-containing formula
Moderate (6%–9%)	Sunken eyes, sunken fontanelle, loss of skin turgor, dry mucous membranes, decreased urine output	ORS 80 mL/kg	Same as above
Severe (>10%)	Signs of moderate dehydration plus 1 or more of the following: rapid thready pulse, hypotension, cyanosis, rapid breathing, delayed capillary refill, markedly reduced or absent urine output, lethargy, coma	Intravenous or intraosseous isotonic fluids (0.9% saline or lactated Ringer solution), 20 mL/kg over 1 h; repeat until pulse and state of consciousness return to normal, then 50–100 mL/kg of ORS based on remaining degree of dehydration <sup>d</sup>	Same as above

ORS, oral rehydration solution.

<sup>a</sup>Percent of total body weight lost.

<sup>b</sup>If no signs of dehydration are present, the rehydration phase may be omitted. Proceed with maintenance therapy and replacement of ongoing losses.

<sup>c</sup>While parenteral access is being sought, nasogastric infusion of ORS may be administered at 30 mL/kg/hr, provided airway protective reflexes remain intact.

<sup>d</sup>In addition to the rehydration amounts shown, replace ongoing stool losses and vomitus with ORS, 10 mL/kg for each diarrheal stool and 5 mL/kg for each episode of vomitus.

### Maintenance Phase

At the end of 4 hours, the state of hydration should be reassessed by using the original clinical criteria. If detectable dehydration remains, then the rehydration phase should be repeated based on the remaining calculated volume deficit. If rehydration has been completed, then the maintenance phase is begun. In this phase, the parent is instructed to continue to administer an ORS in ad libitum quantities, but to alternate this fluid intake with human milk, formula, or other appropriate feedings. Regular feedings should not be withheld once rehydration is complete. Strong evidence suggests that both the volume and the duration of diarrhea are reduced when children are fed immediately after rehydration.

### Children Treated in Emergency Departments

The subpopulation of children who seek treatment at emergency departments may represent a distinct group of patients. These children have often seen a primary care physician earlier in the illness, and the physicians may have attempted to rehydrate the children orally. Although use of ORT in the emergency department should be strongly encouraged and should always be attempted in the mildly and moderately dehydrated child, physicians should realize that ORT in these children will likely fail. Therefore, intravenous treatment probably will be required, especially in the older (school-age) child in whom vomiting is the most prominent feature. Such children are often simply too exhausted to continue with efforts to drink. A brief trial of ORT followed, if necessary, by a brief course of intravenous

fluids and subsequent reintroduction of liquids and solids is a reasonable approach in such children.

### Management of Children With Acute Renal Failure

For fluid management in children with acute renal failure, physicians need to obtain additional testing, such as serum blood urea nitrogen, serum creatinine, urinary electrolytes, and urinary creatinine to assess the status of kidney function and determine whether renal failure is largely caused by severe hypovolemia (prerenal azotemia) or secondary to renal damage. Apart from the aforementioned tests, the fractional excretion of sodium (FENa) is one way of differentiating prerenal disease (a reduction in glomerular filtration rate caused solely by decreased renal perfusion) from acute tubular necrosis (ATN), the 2 most common causes of acute kidney injury. FENa is calculated by dividing the product of urinary sodium and serum creatinine by the product of serum sodium and urinary creatinine, expressed as a fraction. In general, a FENa value below 1% indicates prerenal disease whereas a value above 2% usually indicates ATN. Although there are some exceptions to this rule, the FENa is generally more accurate than the urine sodium concentration in differentiating prerenal disease from ATN because it directly measures sodium handling.

Children with acute renal failure should be categorized as hypovolemic, euvolemic, or hypervolemic, and fluid replacement should be adjusted based on this

categorization. This should be in conjunction with ongoing assessment of serum electrolytes and measures of renal function (blood urea nitrogen and serum creatinine) and acid-base status. In general, vigorous fluid management is recommended in hypovolemic patients to prevent patients in prerenal azotemia from progressing to ATN, and should include normal saline bolus along with replacement of ongoing losses and provision of maintenance fluids. In euvoletic children, ongoing fluid losses (insensible fluid [300–500 mL/m<sup>2</sup> per day], urine, and gastrointestinal losses) need to be balanced with administered fluids. Patients who are hypervolemic (ie, have signs of fluid overload) will require either fluid removal with a trial dose of furosemide to convert the oliguric renal failure to nonoliguric state or fluid restriction. Furthermore, it is important to restrict or even avoid potassium- and phosphorous-containing fluids in anuric or oliguric patients. Sodium should be replaced at 2 to 3 mEq/kg per day to ameliorate fluid accumulation and hypertension.

## COMPLICATIONS

Complications of inadequately treated dehydration may be severe, ultimately including full-blown shock and multiorgan dysfunction syndrome, with end-organ damage to the kidneys, liver, and brain, culminating in death. In practice, such extreme consequences may be prevented readily by early and aggressive fluid therapy, using the oral or, occasionally, the intravenous or intraosseous routes. As a rule, risking overhydration is far better than being exceptionally cautious with fluid administration. On rare occasions, aggressive oral hydration has resulted in mild overhydration, with some transient periorbital puffiness and a 2% to 3% weight gain. These findings are generally self-limited and of no clinical consequence.

Hypokalemia, which results from the losses of total body potassium as a consequence of the increased aldosterone activity in the kidney, is a common occurrence in severe dehydration. As sodium is avidly retained, potassium is lost in the urine. Hypokalemia can result in ileus, which may impair fluid and electrolyte absorption from the intestines. An ORS generally contains 20 mEq/L potassium chloride; such a solution is capable of restoring potassium balance.

## PROGNOSIS

Although diarrheal dehydration is the leading cause of death among children globally, when appropriately treated, it carries an excellent prognosis. Rapid restoration of circulating volume coupled with proper dietary management results in maintenance of hydration and earlier resolution of diarrheal symptoms. Parents should be warned, however, that even with ideal therapy, typical episodes of gastroenteritis last 3 to 7 days. Parents and pediatricians should be reassured about the child's state of good hydration. The physician should reinforce the idea that the diarrheal illness itself is of little consequence as long as hydration is maintained and feeding reintroduced in a timely fashion.

## SUMMARY

Dehydration resulting from gastroenteritis is a common condition generally managed by ORT on an outpatient

basis. Little laboratory evaluation is necessary. Parenteral therapy is reserved for severe or unusual cases. Regardless of the route of delivery, fluid should be administered rapidly and with the intent to restore the entire fluid deficit in 4 to 6 hours. Proper dietary management is essential to minimize the severity and duration of symptoms.

## WHEN TO ADMIT

- The child has a persistently abnormal mental status, persistently abnormal electrolyte levels, or chronic diarrhea (>14 days' duration).
- The child has other medical problems, such as short gut syndrome and inflammatory bowel disease.
- The child's hydration status cannot be restored or maintained after a 6-hour outpatient treatment period.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Diarrhea and Dehydration* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Exercise-Related Heat Illness* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/injuries-emergencies/sports-injuries/Pages/Exercise-Related-Heat-Illness.aspx](http://www.healthychildren.org/English/health-issues/injuries-emergencies/sports-injuries/Pages/Exercise-Related-Heat-Illness.aspx))
- *Nutritional Needs for Young Athletes* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/ages-stages/gradeschool/nutrition/Pages/Nutritional-Needs-for-Young-Athletes.aspx](http://www.healthychildren.org/English/ages-stages/gradeschool/nutrition/Pages/Nutritional-Needs-for-Young-Athletes.aspx))
- *Rotavirus* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Treating Dehydration with Electrolyte Solution* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/abdominal/Pages/Treating-Dehydration-with-Electrolyte-Solution.aspx](http://www.healthychildren.org/English/health-issues/conditions/abdominal/Pages/Treating-Dehydration-with-Electrolyte-Solution.aspx))
- *Treating Vomiting* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/abdominal/Pages/Treating-Vomiting.aspx](http://www.healthychildren.org/English/health-issues/conditions/abdominal/Pages/Treating-Vomiting.aspx))

### Medical Decision Support

- *Diarrhea and Vomiting Caused by Gastroenteritis. Diagnosis, Assessment and Management in Children Younger Than 5 Years*, (guideline), National Institute for Health and Clinical Excellence; 2009 ([www.nice.org.uk/nicemedia/pdf/CG84FullGuideline.pdf](http://www.nice.org.uk/nicemedia/pdf/CG84FullGuideline.pdf))
- *European Society for Paediatric Gastroenterology, Hepatology and Nutrition/European Society for Paediatric Infectious Diseases Evidence-based Guidelines for the Management of Acute Gastroenteritis in Children in Europe: Executive Summary*, (article), *Journal of Pediatric Gastroenterology and Nutrition*, Vol 46, Issue 5, 2008
- *The ESPGHAN/ESPID Guidelines for the Management of Acute Gastroenteritis in Children in Europe*, (article), *Journal of Pediatric Gastroenterology and Nutrition*, Vol 46, Suppl 2, 2008



### AAP POLICY

American Academy of Pediatrics Council on Sports Medicine and Fitness, Council on School Health. Climatic heat stress and exercising children and adolescents. *Pediatrics*. 2011;128(3):e741–e747. Reaffirmed February 2015 (pediatrics.aappublications.org/content/128/3/e741)

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## Chapter 354 DIABETIC KETOACIDOSIS

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Diabetic ketoacidosis (DKA) is the metabolic consequence of absolute insulin deficiency, or its ineffectiveness in the presence of counterregulatory hormones (cortisol, growth hormone, glucagon, etc) during stressful situations such as major illnesses or surgery. This condition represents a medical emergency that requires meticulous attention to optimize outcomes. The biochemical hallmarks of this disorder are hyperglycemia and acidosis. Historically, DKA has been associated with type 1 diabetes (T1D); however, clearly patients with type 2 diabetes (T2D) may develop DKA. Hispanic and African-American youth with T2D seem to be more prone to developing DKA than other populations. With the increasing incidence of both T1D and T2D, early recognition and appropriate intervention are imperative to prevent the significant morbidity and mortality associated with DKA.

DKA is often present at the time of initial diagnosis in patients with T1D. The risk of developing DKA at the onset of diabetes has been associated with factors such as younger age, lower socioeconomic status, and the absence of family history of a parent or a sibling with diabetes. Most children with newly diagnosed T1D who have DKA will have symptoms consistent with the diagnosis, including polyuria, fatigue, and weight loss.

Despite improvement in the understanding of diabetes and methods for its treatment, recurrent DKA remains a significant problem. Box 354-1 lists several factors associated with an increased risk of DKA in patients with established diabetes. Teens, patients with high HbA1c values, and patients with high reported daily insulin doses have been reported to have an increased incidence of DKA. A high risk of DKA

### BOX 354-1 Risk Factors for Diabetic Ketoacidosis in Patients With Established Type 1 Diabetes

- Poor glycemic control (higher HbA1c)
- Previous episode of DKA
- Coexisting psychiatric disorders
- Lower socioeconomic status (underinsured/lack of access to medical care)
- Adolescent age (especially girls 13–19 years of age)
- Patients with high reported insulin requirements

has also been reported in children who were underinsured or diagnosed as having a coexisting psychiatric disorder. The presence of previous episodes of DKA also confers a particularly high risk of recurrence. Several investigators have reported that only a few patients account for a significant proportion of DKA cases.

### DEFINITION

DKA results from a lack of insulin effect, which leads to decreased peripheral glucose utilization despite continued hepatic glucose production. Counterregulatory hormones including glucagon, catecholamines, and cortisol may have elevated levels and contribute to the hyperglycemia. Fat stores are broken down in the absence of adequate insulin action, which leads to ketone body formation and subsequent metabolic acidosis. Criteria for the biochemical diagnosis of DKA were proposed in a consensus statement from the European Society for Pediatric Endocrinology and the Pediatric Endocrine Society (ESPE/PES) and in the International Society of Pediatric and Adolescence Diabetes 2009 consensus guidelines. The biochemical requirements include a blood glucose level greater than 200 mg/dL and metabolic acidosis with a venous pH less than 7.3 or bicarbonate level less than 15 mmol/L. In the context of uncontrolled diabetes, an elevated serum  $\beta$ -hydroxybutyrate ( $>3.0$  mmol/L) is another helpful diagnostic tool. These findings are associated with ketonemia and ketonuria. Although these criteria identify most patients, a glucose concentration of less than 200 mg/dL does not always rule out the possibility of DKA, especially in young, partially treated children and children who are fasting or have consumed only a small amount of carbohydrates.

### DIFFERENTIAL DIAGNOSIS

In the early stages, signs and symptoms of DKA can be nonspecific and may be misdiagnosed as gastroenteritis or reactive airway disease exacerbation. When the biochemical criteria listed previously are applied to define DKA, the diagnosis is usually straightforward. During the initial assessment of a patient with DKA, the precipitating factors associated with the episode should be identified. Many factors have been described to precipitate an episode of DKA (Box 354-2). In young adults with diabetes, myocardial infarction

**BOX 354-2 Factors Associated With Diabetic Ketoacidosis in Children and Adolescents**

Omission of insulin  
Insulin pump failure or disconnection  
Illness  
Trauma  
Surgery  
Alcohol  
Medications  
Depression

and stroke should also be considered. The omission of insulin is the most common cause of DKA in children and young adults with established diabetes mellitus. Insulin doses are sometimes not given during illness, especially if the patient is not eating. Failure to recognize the ongoing need for insulin (and sometimes increased requirements) during illness is a common mistake that is best addressed by providing adequate education to the patient and family. In addition to missed or inadequate insulin dosing, illness and trauma may contribute to the occurrence of DKA. Continuous infusion pump failure or disconnection should be considered in every patient on a pump presenting with DKA. Primary care physicians should also consider the relative contribution of other illnesses to the metabolic acidosis. Lactic acidosis as a result of sepsis or poor perfusion may coexist with DKA, and its cause should be treated concurrently.

**EVALUATION****Relevant History**

Most patients with T2D have a family history of diabetes. In contrast, a relatively small percentage of patients with T1D have another family member with the disease. The symptoms a patient with DKA reports vary and are consistent with the degree of metabolic disturbance. As insulin deficiency progresses and blood glucose levels rise, the renal threshold for glucose reabsorption in the proximal tubule is surpassed ( $\approx 180$  mg/dL). An osmotic diuresis ensues, leading to symptoms of polyuria and polydipsia. With excess renal water loss, obligate losses of sodium, potassium, and phosphorus also occur. The osmotic diuresis can lead to enuresis in previously continent children. Weight loss caused by dehydration and the loss of calories in the urine is often reported but difficult to quantify unless a recent accurate weight is available. If the child has limited access to fluids or is vomiting, dehydration can be severe. Fatigue is a common symptom that may be evident even before significant dehydration and acidosis. Polyphagia may be evident early in the disease but is typically replaced with a loss of appetite as ketosis and metabolic acidosis worsen. Patients who develop moderate to severe ketoacidosis often experience abdominal pain and vomiting, which contribute to the dehydration, thereby reducing the

glomerular filtration rate and thus impairing the clearance of glucose and ketones. The state of metabolic acidosis results in alveolar hyperventilation (Kussmaul breathing pattern). Families may notice a fruit odor of acetone on the patient's breath.

The early recognition of DKA in infants and young children can be particularly challenging. Infants and young children are not able to verbalize their symptoms. In addition, an infant's inability to access fluids freely may mask the polyuria. Increased urine production may also be difficult to judge based on how wet infants' diapers are or how frequently the diapers need to be changed. Parents are less likely to recognize symptoms of hyperglycemia and DKA in children younger than 2 years. This circumstance may lead to a delay in the diagnosis of diabetes and partially explain why more children in this age group experience DKA at the time of the initial diagnosis compared with older children.

**Physical Examination**

Similar to historical clues that should prompt consideration of the diagnosis of DKA, physical findings are commensurate with the degree of metabolic disturbance. Despite many patients having moderate to severe dehydration at the time of diagnosis, few become hypotensive. If a patient is in shock, a coexisting illness should be considered.

**Dehydration**

True dehydration (intracellular and extracellular fluid loss) rather than simple hypovolemia (intravascular fluid loss) is the rule. As the intravascular osmolality increases as a result of hyperglycemia, water shifts from the intracellular space into the vascular space. This process results in an osmotic diuresis, leading to profound water and electrolyte loss if the cycle remains uninterrupted. Clinically assessing the degree of dehydration is an important part of assessing a child with DKA because over- or underestimating the degree of dehydration may affect the child's outcomes. Assessing the degree of dehydration can be difficult because of the extravascular and intravascular components of dehydration in DKA, but weight loss, tachycardia, delayed capillary refill time, and reduced skin turgor may be useful signs. Most children with moderate to severe DKA are considered to be 5% to 10% dehydrated.

**Acid Load**

As expected in a child with metabolic acidosis, compensatory respiratory mechanisms attempt to correct the excess acid load. This correction is accomplished by increasing the minute ventilation, which may be evident as rapid, deep respirations (Kussmaul breathing).  $\beta$ -hydroxybutyrate, acetoacetic acid, and acetone are produced in excess in children with DKA. Although acetone does not contribute to the acid load, as it is exhaled, a fruity breath odor may be detected.

**Neurologic Signs**

When DKA goes untreated and becomes severe, neurologic signs may become prominent. Confusion and an altered sensorium may be observed. Seizures and

**Table 354-1**  
**Estimate of Fluid and Electrolyte Deficits in Children With Diabetic Ketoacidosis**

FLUID OR ELECTROLYTE	EXTENT OF LOSS PER KG BODY WEIGHT
Water	60–100 mL/kg
Sodium	6 mEq/kg (range 5–13)
Potassium	5 mEq/kg (range 4–6)
Chloride	4 mEq/kg (range 3–9)
Phosphate	3 mEq/kg (range 2–5)

Modified from Schwenk WF 2nd, Haymond MW. Treatment of diabetic ketoacidosis in children and young adults. *Prim Care*. 1983;10(4):663–676. Copyright © 1983, Elsevier, with permission.

coma may also occur as a complication of DKA. Although cerebral edema typically has been reported after the initiation of therapy, cases have been described where edema has been present before therapeutic intervention. Cerebral edema should be considered in all children with DKA who exhibit signs or symptoms of neurologic compromise regardless of whether treatment has been initiated.

### Laboratory Findings

As previously mentioned, hyperglycemia (glucose >200 mg/dL) and acidosis (pH <7.3 or bicarbonate <15 mmol/L) are the defining biochemical characteristics of DKA. The presence of ketosis is important to document to confirm that DKA is the cause of a child's acidosis. In addition to these findings, several other biochemical features of DKA are consistent with the diagnosis. Electrolyte depletion is a prominent feature of DKA that requires close attention and meticulous treatment (Table 354-1).

### Sodium

Sodium concentrations are commonly low at the initial evaluation. Hyponatremia during DKA is the result of the combined effect of renal sodium losses and dilutional effects. As dehydration from the osmotic diuresis ensues, sodium is lost in excess through the kidney. In addition, hyperglycemia and the elevation of other osmotically active solutes (blood urea nitrogen [BUN] and ketone bodies) provide a gradient between the intracellular and extracellular spaces such that water is drawn into the extracellular space, resulting in a dilutional effect and exhibiting as a low serum concentration. The most commonly used correction factor for hyponatremia has been to add 1.6 mEq/L to the measured sodium concentration for every 100 mg/dL of glucose over the normal range. A study in children with DKA showed a decline of approximately 1.6 to 1.8 mmol/L in sodium concentration per 100 mg/dL increase in serum glucose level. Studies in adults have reported different findings for sodium correction, ranging from a decline of 1.35 to 2 mmol/L per 100 mg/dL to 2.4 to 4 mmol/L per 100 mg/dL. Pseudohyponatremia may also be seen in

patients with significant elevations in plasma lipid concentrations. Insulin is a stimulator of lipoprotein lipase, which is necessary for the clearance of triglycerides from the blood. DKA is a state of inadequate insulin, and hyperlipidemia is not an uncommon finding. Sodium is primarily a part of the aqueous fraction of blood, and when the lipid fraction is significantly elevated, the result is apparent hyponatremia (pseudohyponatremia). Because some laboratory methods take this into account when measuring sodium, such as direct potentiometry using an ion-selective electrode, primary care physicians need to know the method used by the laboratory to determine if pseudohyponatremia is contributing to this biochemical abnormality. Accurate assessment of the sodium concentration is necessary to determine appropriate fluid management. It is important to note that a lower than expected rate of rise in sodium concentration during the treatment of DKA has been associated with a higher risk of cerebral edema.

### Potassium

Potassium is primarily an intracellular electrolyte that becomes depleted in children with DKA. In a state of metabolic acidosis, excess hydrogen ions are exchanged for intracellular potassium, which is then excreted through the kidneys. Additional potassium may be lost through the gastrointestinal tract if vomiting occurs. Because of the multiple factors influencing potassium in a patient with DKA, serum potassium levels may vary at presentation and during treatment. However, even if the initial serum potassium concentration is elevated, DKA represents a state of total body potassium depletion as intracellular stores are reduced. At the initial evaluation, potassium levels are typically normal or elevated. When treatment with insulin is begun, potassium shifts to the intracellular compartment, resulting in a decrease in the measured potassium concentration. The resulting profound hyperkalemia or hypokalemia may lead to cardiac arrhythmias, and this electrolyte must be monitored closely and replaced appropriately.

### Phosphorus

Phosphorus is another predominantly intracellular electrolyte that becomes depleted during DKA. The mechanism is similar to that of potassium with the primary loss occurring through the kidneys. Children with DKA may have profound hypophosphatemia that may only become apparent during therapy.

### Other Laboratory Components

An assessment of renal function and dehydration should be performed, including the measurement of BUN and creatinine. These values are typically elevated in a pattern consistent with a prerenal state. Insulin and C-peptide concentrations are generally low in children with newly diagnosed T1D. In the context of uncontrolled diabetes, an elevated serum  $\beta$ -hydroxybutyrate (>3.0 mmol/L) is another helpful diagnostic tool. Although antibody levels against islet cell antigens and insulin are often elevated at the time of diagnosis, they are not useful in the diagnosis or management of DKA. The principles of managing DKA are the same regardless of diabetes type.

## MANAGEMENT

The management of DKA should be focused on correcting the metabolic disturbances while preventing potential complications. The major complications that arise during the treatment of DKA include cerebral edema and hypoglycemia. An increased risk of venous thrombosis has also been associated with DKA, especially in children with a central venous catheter. The effective treatment of DKA includes insulin administration and fluid and electrolyte replacement. Many algorithms have been proposed to assist the physician in the management of DKA. The following principles have been used successfully. However, it must be stressed that no single protocol is appropriate for all children. Specific therapy must be designed according to the clinical circumstances and coexisting diseases, such as infection, which should be treated concomitantly.

### Assessment and Disposition

The initial assessment of a child with DKA should include an estimation of the severity of disease (Table 354-2). The child's cardiovascular and respiratory status should be evaluated and addressed immediately if compromise is present. Signs of neurologic dysfunction should prompt evaluation for cerebral edema, which can be present before any therapeutic intervention. The laboratory assessment should include measurement of the child's blood glucose, pH, bicarbonate, serum  $\beta$ -hydroxybutyrate or urine ketones, and electrolyte (sodium, potassium, chloride, phosphorus, and calcium) levels. A coexisting illness often contributes to the precipitation of DKA; additional studies including cultures (blood, urine, and cerebral spinal fluid) should be obtained when clinically indicated. Urine should also be assessed for glucose and ketones.

Children with mild DKA may not exhibit any clinical findings of dehydration. In many children with established diabetes, mild ketosis can be managed in the outpatient setting if they are able to maintain oral intake. As a part of chronic diabetes care, children and families should be educated on treatment strategies for mild ketosis. Written education materials and access to a physician experienced in the management of children with diabetes may prevent some emergency department visits and hospitalizations. For children with moderate to severe DKA, admission to a pediatric intensive care unit or general pediatric ward is

indicated. Familiarity with the level of care available within a particular institution is essential for the proper placement of the child. Most children with severe DKA require a level of care offered only in an intensive care setting. However, some hospitals are equipped to manage moderate ketoacidosis on a general pediatric ward.

### Fluid Replacement

Children with moderate to severe DKA are generally considered to be between 5% and 10% dehydrated, with calculations based ideally on the child's presenting weight. Ten to 20 mL/kg intravenous fluids are suggested for initial fluid replacement. The American Diabetes Association (ADA) consensus statement and ESPE/PES recommend isotonic solutions such as lactated Ringer's solution or 0.9% saline, which are commonly used for the treatment of dehydration or hypovolemia from any cause. Additional fluid resuscitation may be required in some patients, but caution must be used, especially for children with signs or symptoms suggestive of cerebral edema. Aggressive fluid resuscitation to manage hemodynamic instability is rarely required even for children with severe DKA. In this setting, other causes of hypotension such as sepsis should be considered. The goal of initial fluid resuscitation is not to replace the entire fluid deficit; rehydration should take place over the subsequent 48 hours. In adults and children with DKA, less aggressive rates of fluid replacement have been associated with more rapid correction of the acidosis. A gradual rehydration strategy may reduce the risk of cerebral edema compared with more aggressive fluid administration. Fluid therapy (even before insulin) will result in a reduction of the blood glucose concentration. This reduction is partially the result of a dilutional effect, as well as an improved glomerular filtration rate and increased renal clearance of glucose.

After the initial fluid bolus, the content of the intravenous fluid should be changed to address additional electrolyte abnormalities that may be present and to prevent hyperchloremic metabolic acidosis that may occur if isotonic saline solutions are continued. The ADA and ESPE/PES guidelines suggest that rehydration should take place over at least 48 hours and that the rate of fluid administration should rarely exceed 1.5 to 2 times maintenance fluids requirements. This should be accomplished using a lower tonicity fluid such as 0.45% saline unless the development of cerebral

**Table 354-2** Assessment of the Severity of Diabetic Ketoacidosis

	MILD	MODERATE	SEVERE
Sensorium	Alert	Drowsy, lethargic	Obtundation, coma
Hyperpnea	Absent	Mild	Severe
Hydration	No dehydration	Mild to moderate (3%–5%)	Severe (>5%)
Plasma bicarbonate	>16–18 mEq/L	>10 mEq/L	<10 mEq/L
Anion gap	18–20 mEq/L	<20–25 mEq/L	>25 mEq/L

Modified from Schwenk WF 2nd, Haymond MW. Treatment of diabetic ketoacidosis in children and young adults. *Prim Care*. 1983;10(4):663–676. Copyright © 1983, Elsevier, with permission.



edema requires higher tonicity fluid. The ESPE/LWPES also recommends that urinary losses not be added to the calculated fluid requirement. Because total body stores of potassium are invariably depleted, potassium should be added to the intravenous solution when the potassium concentration is normal or low and urine flow has been established. If the initial potassium concentration is low, potassium should be replaced before initiating insulin therapy to prevent potentially life threatening hypokalemia. When the child transitions to oral intake, after the correction of the acidosis, intravenous fluids should be reduced or discontinued accordingly.

### Insulin Therapy

#### Delivery

Insulin is essential to correct the metabolic disturbances present in children with DKA. Intravenous insulin therapy *should be initiated after starting fluid replacement therapy*. The early administration of insulin is associated with an increased risk of cerebral edema. Intravenous regular insulin is the preferred route of administration. Subcutaneous and intramuscular insulin have been used successfully in the treatment of DKA. However, these modes of insulin delivery should only be used when intravenous access is not possible, especially in severely dehydrated children in whom insulin absorption may be impaired because of poor circulatory status. Intravenous insulin can be titrated frequently if necessary because of its short half-life.

#### Dosing

An initial infusion rate of 0.1 unit/kg/hour of intravenous regular insulin is generally an effective dose. The insulin infusion acts to decrease gluconeogenesis, decrease lipolysis and ketogenesis, and increase peripheral glucose utilization. The blood glucose concentration should not be used alone to determine when to discontinue or decrease the rate of insulin infusion. Ketosis and metabolic acidosis will not correct without adequate insulin administration. The metabolic acidosis often corrects many hours after euglycemia has been restored. For this reason, a constant insulin infusion rate should be used, and glucose should be added to the intravenous fluids when the blood glucose level falls below 250 to 300 mg/dL. An infusion of 5% dextrose may be sufficient for many children. However, higher rates of dextrose infusion may be required to prevent hypoglycemia while the ketoacidosis is resolving. The rate of insulin infusion may need to be increased in some children if the ketoacidosis does not improve or worsens. In this circumstance, additional causes of acidosis or coexisting illnesses should be considered and treated appropriately. In some cases, such as in the very young, the rate of insulin infusion may need to be reduced to 0.05 unit/kg/hour to avoid hypoglycemia. When using a lower rate of insulin infusion, it is important to confirm continued improvement in ketosis.

#### Monitoring

Monitoring the patient's response to therapy frequently is imperative to assess when a change in treatment is required. Such monitoring should include

hourly glucose determinations. Electrolytes, bicarbonate, ketones, and pH should be measured every 2 to 4 hours to ensure correction of the metabolic disturbances. More frequent monitoring is suggested (every 2 hours) with severe DKA and less frequent monitoring (every 4 hours) when improvement in the ketoacidosis has been established. It is also important to perform periodic neurologic exams and monitor the child's neurologic status while managing DKA, particularly in children who are at high risk for developing cerebral edema or those with altered mental status or neurologic findings before or during the initial treatment of DKA.

### Electrolytes

#### Sodium

Sodium concentrations are often low because of the reasons previously mentioned. The isotonic solutions suggested for initial fluid management are intended to increase the intravascular volume and improve the glomerular filtration rate. Sodium depletion is also addressed with this therapy. After the initial fluid administration, the deficit should be replaced with a solution that has a tonicity between 0.45% and 0.9%. A solution of 0.45% saline is often used to prevent excessive sodium and chloride delivery. Excessive isotonic sodium chloride may result in hyperchloremic metabolic acidosis. On the other hand, some authors have suggested that the failure of an increase in the sodium concentration with therapy may be associated with a higher risk of developing cerebral edema. Therefore, sodium concentrations should be monitored closely.

#### Potassium

Potassium concentrations may be elevated, normal, or low before the initiation of therapy in children with DKA. The concentration likely depends on several factors, including the severity and duration of DKA and the presence of gastrointestinal losses caused by vomiting. In children with significantly elevated potassium concentrations, an electrocardiogram should be obtained to check for the presence of a T wave abnormality that occurs in the context of hyperkalemia. An EKG should also be checked if there are delays in obtaining the first electrolyte measurements. With the initiation of insulin therapy, potassium concentrations invariably decline and may become normal or low. Insulin facilitates the intracellular transport of potassium, and the correction of acidosis also results in the exchange of intracellular hydrogen for extracellular potassium, leading to further reductions in potassium concentrations. Adding 20 mEq/L potassium acetate and 20 mEq/L potassium phosphate to 0.45% saline works well in most patients. This combination of salts prevents excess chloride while replacing not only potassium, but also phosphorus, which is often depleted. This solution is a safe and effective means to prevent profound hypokalemia. Potassium should be replaced after the initial isotonic fluid bolus has been given, the serum potassium concentration becomes normal or low, and urine output is established. Potassium levels should be monitored closely and therapy adjusted according to the individual child's needs. If the initial potassium concentration is low, potassium should be

replaced before initiating insulin therapy to prevent potentially life threatening hypokalemia.

### Phosphorus

Phosphate depletion occurs as a result of many of the same mechanisms as potassium depletion. Phosphate concentrations may also be variable before the initiation of therapy. Hypophosphatemia may become profound as intracellular phosphate transport from the extracellular space is facilitated by insulin. Phosphate replacement in the treatment of children with DKA has not been shown to provide clinically important improvements in outcome or to eliminate significant complications. However, the possibility exists of a decrease in oxygen delivery to tissues caused by a shift of the oxyhemoglobin dissociation curve to the left. The addition of potassium phosphate to the rehydration solution is safe and effective at maintaining a normal or near-normal phosphate concentration. If phosphate therapy is used, then serum calcium concentrations should be monitored, because hypocalcemia may occur.

### Bicarbonate

A recent systematic review concluded that the current evidence does not support the use of bicarbonate in the emergent treatment of DKA, especially in children. However, the studies on which the evidence was based were retrospective studies because of the lack of randomized trials in children. In addition, there were no studies on patients with severe profound DKA (pH < 6.9). The current recommendation based on the consensus statement from the ESPE/PES and the International Society of Pediatric and Adolescent Diabetes 2009 advises cautiously administering bicarbonate in cases of profound acidosis, as insulin administration and correction of the underlying metabolic abnormalities is the safest and most effective way to restore bicarbonate levels. Use of bicarbonate in children with DKA may not be appropriate for several reasons. The ketoacidosis can be completely corrected by the administration of intravenous fluids and insulin. Treatment with bicarbonate results in additional sodium administration that may not be required. Paradoxical central nervous system acidosis that may occur as a result of bicarbonate treatment is a potential concern. Bicarbonate therapy has also been associated with an increased risk of cerebral edema. Despite these concerns, some children with cardiovascular dysfunction caused by severe acidosis or hyperkalemia (or both) may benefit from cautious alkali administration.

### Converting to Subcutaneous Insulin

Converting to subcutaneous insulin should be considered when the serum bicarbonate level is greater than 16 to 18 mmol/L (or pH is greater than 7.3) and the child is able to begin oral intake. If DKA has occurred in a child with a previous diagnosis of diabetes, the home insulin regimen may serve as a guide in choosing initial subcutaneous insulin doses and the type of program to use (split-mixed vs multiple daily injection vs continuous subcutaneous insulin infusion). For children with newly diagnosed diabetes, 0.5 to

1.0 units/kg/day in divided doses is appropriate. Frequently, adjustments to the initial doses are necessary depending on the child's meal plan, level of activity, and pubertal status. Children with and without diabetes have increased insulin requirements during puberty compared with prepubertal children. Additional details regarding subcutaneous insulin therapy are discussed in Chapter 241, Diabetes Mellitus.

### COMPLICATIONS: CEREBRAL EDEMA

The reported mortality rate in children with DKA is low (<0.5%). Most of these deaths have been in those who developed clinically apparent cerebral edema. The incidence of clinically apparent cerebral edema in children has been estimated to be approximately 1%. Some, but not all, studies suggest that the incidence of subclinical cerebral edema is higher when using imaging criteria to diagnose the condition. In adults, coexisting conditions such as myocardial infarction contribute to a larger percentage of the mortality associated with DKA.

Although cerebral edema is a rare complication of DKA, the consequences are severe. Several studies in children have reported a mortality rate of approximately 20% to 25% for those who developed cerebral edema. A significant proportion of those who survive have permanent neurologic consequences. The symptoms of cerebral edema attributed to increased intracranial pressure include a decreased level of consciousness, elevated blood pressure, and bradycardia. Nonspecific symptoms such as headache may also be present, and a high index of suspicion should be maintained to identify this potentially fatal condition early. If these clinical findings are encountered at any time during the treatment of DKA, prompt assessment, including imaging of the head, should be undertaken.

The precise etiology of cerebral edema is not clear; however, several potential risk factors have been identified (Box 354-3). Few data are available to establish optimal therapy for cerebral edema associated with DKA. If cerebral edema occurs, the ESPE/PES consensus statement recommends that the rate of fluid administration be reduced. Intravenous mannitol may be given and repeated after 2 hours if clinically indicated. Case reports of improvement in cerebral edema with this therapy have been published. However, a randomized clinical trial with a small number

#### BOX 354-3 Risk Factors for Cerebral Edema

- Lower partial pressure of arterial carbon dioxide at presentation
- Severity of dehydration (higher initial BUN)
- Smaller rise in serum sodium during treatment
- More severe acidosis at presentation
- New-onset diabetes
- Treatment with bicarbonate
- Younger age
- Longer duration of symptoms before presentation
- Insulin administration in the first hour of fluid treatment

of children found that the rate of fluid infusion did not change the MRI measures of cerebral edema in children with DKA. Hypertonic saline has also been suggested as an alternative to the use of mannitol in the treatment of children with cerebral edema. If intubation is required, then hyperventilation should be avoided, because this has been associated with worse outcomes. Frequent neurologic examinations should be performed in children with DKA in an attempt to identify and intervene early. Because cerebral edema can be present before therapy for DKA, prevention of DKA may be the only effective strategy to prevent this potentially devastating complication.

## PREVENTION

In children with established T1D, ketoacidosis is largely preventable with proper attention to glycemic control, especially during times of illness. Most children develop DKA because of the omission of insulin, which may occur for a variety of reasons, including financial constraints or a lack of knowledge regarding proper management during illness. This finding emphasizes the importance of ongoing diabetes education for the children and their families to help them understand the factors that lead to DKA in an effort to prevent its occurrence.

Few prospective studies have been performed with the goal of preventing DKA in children with newly diagnosed diabetes. There were 2 large studies (in Italy and Australia) that investigated the effects of raising public awareness regarding diabetes and found significantly fewer episodes of DKA at the time of diagnosis in the studies' regions compared with surrounding communities (64% reduction in the rate of DKA in the Australian study). Raising public awareness of the symptoms of diabetes may be a cost-effective way to prevent this potentially fatal illness.

In children with established diabetes, the cause of DKA cited most often is the omission of insulin, which is a preventable problem. Effective education should be a part of any comprehensive diabetes program and has the potential to decrease the rates of recurrent DKA. Clinical experience and a review of the literature indicate that a small percentage of patients with diabetes account for a disproportionate number of episodes of DKA. Interventions targeted at this high-risk population seems appropriate. For further information, see Chapter 241, Diabetes Mellitus.

### WHEN TO REFER

- When facilities to provide frequent patient assessment (clinical and laboratory) are not available
- When a physician experienced in the diagnosis and treatment of DKA is not available

### WHEN TO ADMIT

- Patients with moderate to severe DKA
- Patients with dehydration or those who are unable to maintain adequate oral intake
- Most patients with newly diagnosed diabetes regardless of the severity of ketoacidosis

## SUGGESTED READINGS

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## Chapter 355

# DISSEMINATED INTRAVASCULAR COAGULATION

Steven W. Pipe, MD; Anjali A. Sharathkumar, MBBS, MD, MS

## DEFINITION

Disseminated intravascular coagulation (DIC) is a pathologic syndrome that arises from a heterogeneous group of medical disorders. It is characterized by simultaneous activation of both clotting and fibrinolysis. This action leads to widespread intravascular deposition of fibrin with resultant thrombotic end-organ complications and consumption of platelets and coagulation proteins, resulting in severe bleeding. DIC is always a secondary phenomenon and not a disease entity in its own right. The clinical expression of DIC varies and may be displayed by laboratory abnormalities alone or in combination with hemorrhagic and thrombotic complications. Because of the variable clinical manifestations and heterogeneity of primary disorders associated with the development of DIC, this entity has been recognized under various different names, including *consumptive coagulopathy*, *hemorrhagic syndrome*, *defibrination syndrome*, or *consumptive thrombohemorrhagic disorder*.

## INCIDENCE

Given that DIC often occurs in combination with sepsis, trauma, and systemic inflammatory syndrome, the precise incidence of this condition is difficult to assess. The frequency of DIC in hospitalized children is approximately 0.4% to 1%. The incidence of DIC according to the underlying disease process is not known. Infection is the most common etiologic factor, contributing to DIC in almost 95% of children; multiorgan dysfunction occurs in almost 85% of children. Associated comorbidities, such as the underlying disease, multiorgan dysfunction, and respiratory failure, determine the outcome of DIC.

## PATHOGENESIS

### Physiologic Features of Hemostasis

Improved understanding of molecular mechanisms involved in the physiologic features of hemostasis has



led to better understanding of the pathogenesis of DIC. In healthy individuals, physiologic hemostasis is tightly controlled as a balance of forces promoting and impeding coagulation and fibrinolysis. Normally, in response to injury, coagulation is limited to the site of vascular injury. After such injury, platelets adhere to the exposed collagen mediated by the von Willebrand factor, which activates platelets. A signaling cascade within activated platelets causes release of platelet granule contents and facilitates thrombin generation on their surface. As a result of platelet activation and thrombin formation, platelets aggregate, leading to a primary hemostatic plug. Simultaneously, the extrinsic pathway of coagulation is activated. Tissue factor (TF), up regulated on endothelial cells adjacent to the vascular injury and present on monocytes, forms a complex with circulating factor VII, resulting in the activation of factor VII and the formation of a TF–factor VII/VIIIa complex. This complex then activates factors IX and X on the negatively charged phospholipid surface of platelets. Factor Xa, in turn, converts prothrombin to thrombin, the major procoagulant. Thrombin generation is greatly amplified through activation of a feedback loop (intrinsic pathway) through activation of factor XI, which, in turn, activates more factor IX. Thrombin also activates the coagulation cofactors, factor VIII and factor V. Activated factors VIII (VIIIa) and V (Va) increase the efficiency of factor Xa and thrombin generation, respectively, by several orders of magnitude. Once thrombin is generated, it converts soluble fibrinogen to insoluble fibrin. Fibrin monomers polymerize, and adjacent fibrin monomers are cross-linked between their respective D domains by factor XIIIa. The insoluble, cross-linked fibrin enmeshes the platelet plug, forming a secondary hemostatic plug.

This process is kept in check by anticoagulant and fibrinolytic pathways. TF pathway inhibitor (TFPI) is an endogenous anticoagulant protein that binds to and inactivates the TF–factor VIIa complex and factor Xa. Thrombin is quickly inactivated by antithrombin (AT) by forming thrombin-AT (TAT) complexes that are rapidly cleared from plasma. Thrombin also binds to thrombomodulin (TM) on the endothelial surface, abrogating its procoagulant activity. Thrombin-TM complexes, in turn, activate protein C, which, in the presence of its cofactor, protein S, proteolytically inactivates factors VIIIa and Va, dampening further thrombin generation. Fibrinolysis is promoted by thrombin-induced tissue-type plasminogen activator release from endothelial cells, generating plasmin. Plasmin will degrade both soluble fibrinogen and insoluble fibrin. The resultant fragments can be measured as fibrinogen-fibrin degradation products (FDPs). When plasmin cleaves cross-linked fibrin, it liberates a soluble D-dimer. Plasmin generation is also regulated through inhibition by plasminogen activator inhibitor type 1. As shown in Figure 355-1, thrombin generation plays a crucial role in interconnecting all of these pathways.

### Primary Events of Disseminated Intravascular Coagulation

In DIC, the normal physiologic feature of coagulation is disturbed by the simultaneous action of 4 mechanisms:

increased thrombin generation, suppressed physiologic anticoagulant pathways, activation and subsequent impairment of fibrinolysis, and activation of the inflammatory pathway. Figure 355-2 illustrates the primary events involved in DIC. During an inciting event such as sepsis, monocytes and endothelial cells are injured by toxic substances that are elaborated during the disease process. They generate TF, which activates the coagulation cascade (see Figure 355-1). Continuous activation of coagulation leads to an unregulated and explosive generation of thrombin, which, in turn, depletes clotting factors and platelets and activates the fibrinolytic system. Activation of clotting leads to generalized fibrin deposition and microthrombi formation. These microthrombi deposit in various organs, leading to tissue ischemia and multiorgan failure. Deposition of fibrin in microvasculature also leads to mechanical fragmentation of erythrocytes, causing microangiopathic hemolytic anemia (Figure 355-3; see also Figure 355-1). Impaired function of the physiologic anticoagulant pathways can amplify thrombin generation and contribute to fibrin formation. Plasma levels of AT are reduced in patients with sepsis, and the activated protein C system may be significantly depressed through consumption and down regulation of TM expression on the endothelium. An initial hyperfibrinolytic response causes clot lysis, contributing to cutaneous hemorrhages and bleeding into the internal organs. Subsequently, however, increases in the plasma levels of plasminogen activator inhibitor type 1 (PAI-1) can suppress fibrinolytic activity. Finally, stimulation of endothelial cells to synthesize proinflammatory cytokines can promote further coagulation activation. This is accompanied by vasodilatation and loss of tight junctions between endothelial cells, leading to capillary leak and shock. Thus, the overall clinical manifestation of DIC depends on simultaneous activation of the inflammatory cascade, coagulation cascade, and involvement of endothelial microvasculature.

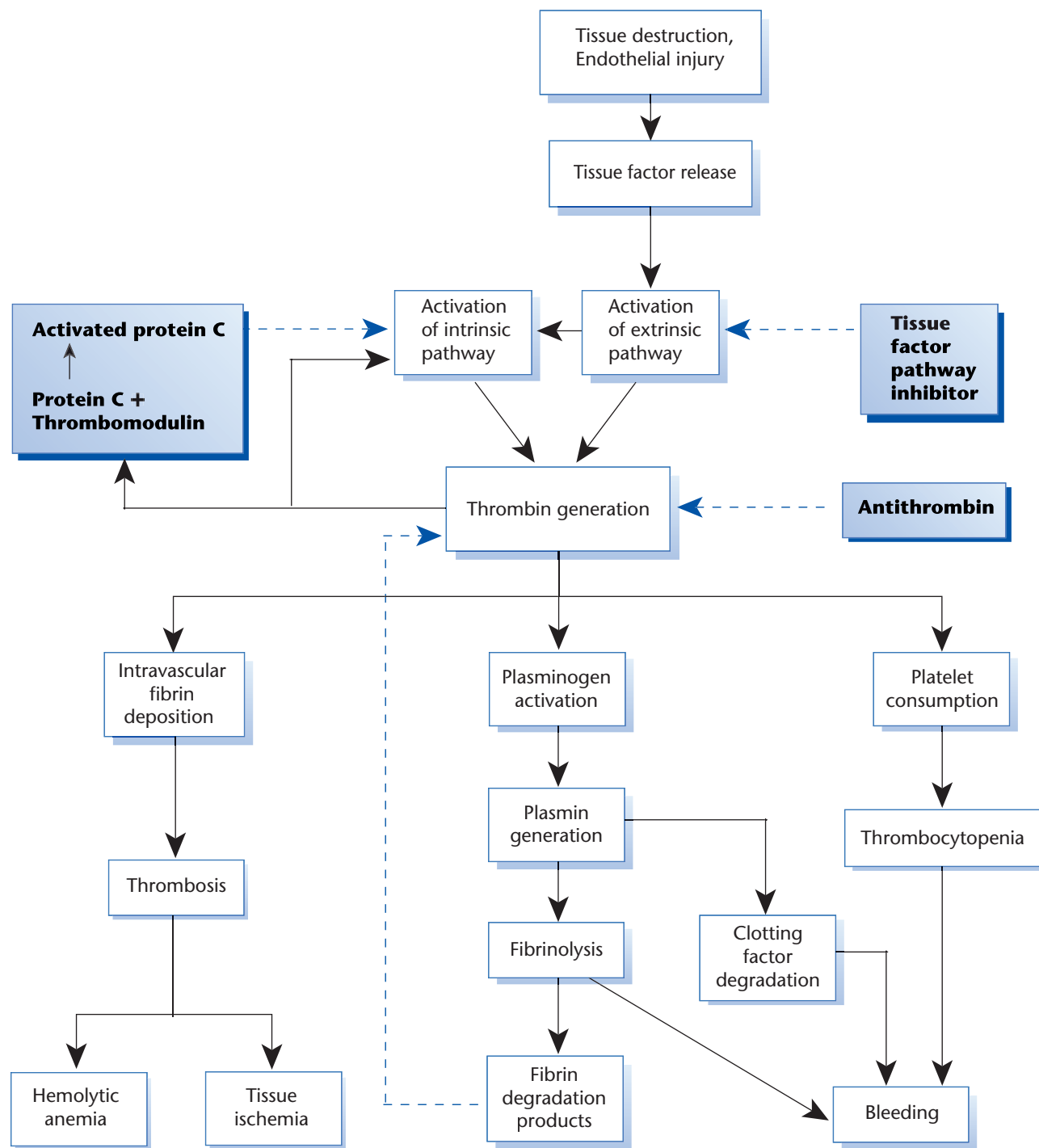
## DIFFERENTIAL DIAGNOSIS

The clinical manifestations and laboratory abnormalities of several conditions may mimic or may be indistinguishable from DIC, yet may require unique diagnostic evaluations and management. Commonly encountered systemic diseases that present with clinical features of DIC are discussed in the following text.

### Fulminant Hepatic Failure

Synthesis of coagulation proteins (factors II, V, VII, IX, X, and fibrinogen) and inhibitors of coagulation (AT III, protein C, and protein S) is affected in hepatocellular failure. Associated hypersplenism contributes to thrombocytopenia. Bleeding manifestations predominate. The main treatment strategy is supportive care and blood component therapy to provide deficient coagulant proteins until the underlying disease is treated.





Blue color indicates inhibitors of coagulation

**Figure 355-1** Pathophysiological mechanism of disseminated intravascular coagulation.

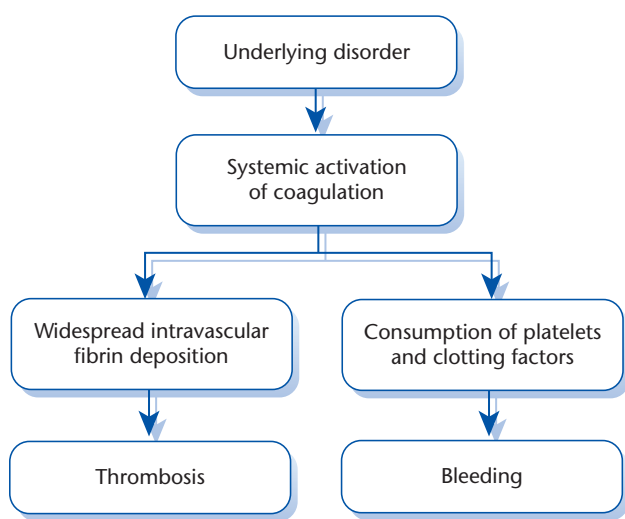
### HELLP Syndrome

HELLP (hemolysis, elevated liver function tests, and low platelets) syndrome is commonly associated with pregnancy. Clinical and laboratory features are similar to DIC, but hypertension is relatively common in HELLP syndrome. In severe cases, the treatment is to

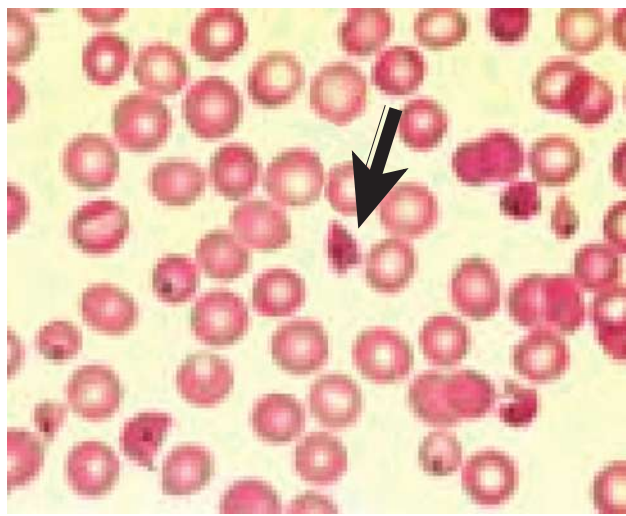
promptly deliver the fetus and placenta along with supportive care.

### Chronic Disseminated Intravascular Coagulation

Chronic DIC, also known as *Trousseau syndrome*, occurs rarely in children. Chronic DIC is commonly



**Figure 355-2** Primary events in disseminated intravascular coagulation.



**Figure 355-3** Blood smear of a patient with disseminated intravascular coagulation showing schistocytes (arrow).

associated with malignancies such as mucinous adenocarcinomas, ovarian cancer, and pancreatic tumors. It exhibits as migratory thrombophlebitis, arterial and venous thrombosis, hemorrhagic diathesis, and laboratory values consistent with DIC. The mainstay of treatment is long-term anticoagulation with heparin therapy until the underlying condition is resolved.

### Massive Transfusion

Massive transfusion has been defined as the replacement of more than 1 blood volume in 24 hours or the replacement of 50% of the total blood volume within 3 hours. For example, considering the blood volume of a 30-kg child to be roughly 2,400 mL, such a transfusion would require approximately 8 units of blood products over 24 hours or 4 units over 3 hours. Hemostatic failure can result from dilution of clotting factors or acquired

platelet dysfunction. Hemostatic tests typically show prolongation of the prothrombin time (PT) and partial thromboplastin time (PTT), reduced fibrinogen, and thrombocytopenia. Clinical bleeding associated with hemostatic failure can be managed first with prompt transfusion with cryoprecipitate and fresh frozen plasma (FFP). However, platelet transfusion may be required if bleeding persists. Recent randomized, placebo-controlled, double-blind trials have suggested a benefit of recombinant factor VIIa in the management of excessive perioperative bleeding.

### Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) is considered a primary disorder in which platelet-rich thrombi form within the microvasculature, leading to tissue ischemia. TTP is caused by congenital (Upshaw-Schulman syndrome) or acquired deficiency of a von Willebrand factor-cleaving protease (ADAMTS13). Patients can exhibit fever, thrombocytopenia, microangiopathic hemolytic anemia, renal failure, and neurologic signs. Screening coagulation tests (PT, PTT) and FDPs are usually normal. Treatment is plasmapheresis and supplementation of ADAMTS13 protease through FFP infusion.

### Hemolytic Uremic Syndrome

Hemolytic uremic syndrome (HUS), the triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal insufficiency, is clinically similar to TTP and is often confused with DIC. HUS occurs in children younger than 3 years. Most cases are caused by Shiga toxin-producing strains of *Escherichia coli*, most often the O157:H7 subtype. Acute mortality in HUS is 3% to 5%, mostly from central nervous system involvement, cardiac failure, or multiorgan failure. Laboratory findings in HUS include microangiopathic hemolytic anemia, with a hemoglobin level of less than 10 g/dL and a negative direct antiglobulin (Coombs) test. HUS is a clinical diagnosis; the presence of schistocytes and helmet cells on the blood smear suggests mechanical trauma. Typical findings accompanying hemolysis include increased indirect bilirubin, decreased haptoglobin, and increased lactate dehydrogenase values. Thrombocytopenia (platelet count  $<100 \times 10^3/\mu\text{L}$ ) is usually present and can be severe ( $<20 \times 10^3/\mu\text{L}$ ). Screening coagulation test (PT, PTT) results are normal. Urinalysis shows hematuria and proteinuria. Blood urea nitrogen and creatinine concentrations are elevated, and the albumin concentration may be decreased from protein loss in the gastrointestinal tract. Management is primarily supportive, and includes renal replacement therapy.

### EVALUATION

Disseminated intravascular coagulation is a clinical diagnosis based on the evaluation of laboratory results in a patient with a clinical condition known to be associated with DIC (Box 355-1).

### Relevant History and Physical Examination Findings

Clinical manifestations of DIC include bleeding, thrombosis, or both. However, in general, bleeding manifestations predominate. Bleeding is typically

**BOX 355-1 Causes of Disseminated Intravascular Coagulation in Children****SEPSIS OR SEVERE INFECTION**

- Bacterial (eg, methicillin-resistant *Staphylococcus aureus*, streptococci)
- Viral (eg, HIV, cytomegalovirus, varicella, hepatitis viruses)
- Fungal (eg, *Histoplasma*)
- Parasitic (eg, malaria)

**TRAUMA**

- Polytrauma
- Neurotrauma
- Fat embolism

**ORGAN FAILURE**

- Severe pancreatitis
- Liver cell failure

**MALIGNANCY**

- Acute promyelocytic leukemia
- Lymphoproliferative disorders
- Hemophagocytic lymphohistiocytosis
- Solid tumors

**OBSTETRICAL CALAMITIES**

- Dead fetus syndrome
- Abruptio placentae
- Amniotic fluid embolism

**VASCULAR ABNORMALITIES**

- Kasabach-Merritt syndrome
- Large vascular aneurysms

**IMMUNOLOGIC CONDITIONS**

- Systemic lupus erythematosus
- Autoimmune hemolytic anemia
- Crohn disease
- Ulcerative colitis
- Transfusion reactions
- Transplant rejection

**MISCELLANEOUS**

- Snake bites
- Recreational drugs
- Poisoning
- Burns
- Massive transfusions

acute and occurs from multiple sites. Bleeding from venipuncture sites and intravascular access sites, such as intra-arterial lines or surgical wounds, is an important early indication of DIC. Mucocutaneous bleeding, such as petechiae, purpura, epistaxis, gum bleeding, bleeding after tracheal suctioning, gastrointestinal bleeding, and hematuria, is commonly observed. In more advanced cases, internal bleeding in vital organs such as the brain, lung, heart, and organs of the gastrointestinal system may constitute a medical emergency, with patients experiencing raised intracranial pressure, brain herniation, respiratory compromise, or shock. Generalized microvascular thrombosis may produce purpura fulminans, peripheral acrocyanosis, and pregangrenous changes in digits, genitalia, and nose. Microvascular thrombosis in various organs further contributes to multi-organ failure and hemodynamic instability. DIC in neonates carries some unique considerations as discussed in Chapter 103, The Newborn With Hematologic Abnormalities.

A practical approach to categorize and understand many clinical presentations of DIC is by rate of progression (acute or chronic), extent (localized or systemic), and chief clinical manifestations (thrombotic or hemorrhagic, with or without progressive organ dysfunction). The International Society of Thrombosis and Haemostasis (ISTH) Subcommittee of the Scientific and Standardization Committee (SSC) recommended classifying DIC into 2 broad categories: overt or decompensated DIC, and non overt or stable hemostatic function, based on a scoring system. This scoring system is currently widely

used in adult patients. Details of this scoring system are described in the Clinical Monitoring section.

**Laboratory Testing**

The role of laboratory tests in DIC is to show evidence of a consumptive coagulopathy with activation of the fibrinolytic cascade. A complete blood cell count may show moderate-to-severe thrombocytopenia with or without anemia. Thrombocytopenia is present in approximately 50% of patients and suggests consumption of platelets, whereas anemia might be caused by bleeding or mechanical destruction of red blood cells. Presence of fragmented red blood cells (schistocytes) on blood smear confirms the diagnosis of microvascular angiopathy (see Figure 355-3). Screening tests for the extrinsic and intrinsic coagulation cascade, such as the PT and PTT, respectively, are prolonged in 50% to 60% of patients, reflecting consumption of many coagulation proteins, including prothrombin; factors V, VII, and VIII; and fibrinogen. FDPs and D-dimers are both increased in concentration in most patients with DIC, suggesting activation of the fibrinolytic process.

The most sensitive tests for diagnosis of DIC are markers of endogenous thrombin generation: prothrombin fragment 1.2 and TAT complexes. Prothrombin fragment 1.2 is released when thrombin is generated from prothrombin. TAT complexes are generated by binding of thrombin with its inhibitor AT.

In practice, although the standard assays are relatively rapid and simple to perform, changes in these test results do not always occur at the same time, and

### BOX 355-2 Treatment of Disseminated Intravascular Coagulation

- Aggressive treatment of the underlying cause
- Obtaining reliable venous access and considering central venous access
- Possible multiorgan support required
  - Ventilatory support
  - Circulatory resuscitation or inotropic agents
  - Hemodialysis
- Blood product support if evidence of active bleeding
  - Platelets if less than  $50 \times 10^9/L$
  - Fresh frozen plasma if clotting times prolonged (dose: 15 mL/kg)
  - Cryoprecipitate to keep fibrinogen more than 100 mg/dL (dose: 1–1.5 bags/10 kg)
  - Packed red blood cell transfusion (dose: 10 mL/kg)
  - Recombinant factor VIIa for intractable bleeding or volume overload (dose: 75 mcg/kg every 2 hours)
  - Recombinant human activated protein C in desperate situations with severe sepsis and multiple organ failure, provided platelet count is more than  $50 \times 10^9/L$  (dose: 24 mcg/kg per hour for 24–72 hours)

laboratory values change rapidly based on the patient's clinical status, which may create confusion in patient management. These changes also make the diagnosis of DIC at an early stage particularly difficult.

## MANAGEMENT

Most children with DIC will either already be in the intensive care unit because of their underlying disease or require admission because of the disease complications that can occur. The fundamental principle of DIC treatment is the specific and vigorous treatment of the underlying disorder. In some cases, DIC will completely resolve within hours after resolution of the underlying condition (eg, in cases of DIC induced by placental abruption or intrauterine fetal demise). However, in other cases, supportive measures are required to control the DIC until the underlying condition is resolved (eg, the use of all-trans-retinoic acid and chemotherapy for the treatment of acute promyelocytic leukemia and DIC). Recent insights into mechanisms that contribute to DIC have been helpful in developing new preventive, supportive, and therapeutic management strategies. However, therapeutic decisions remain controversial and need to be individualized according to the underlying basis for the DIC and severity of the clinical symptoms. Consultation with a hematologist (if available) is advisable for management of DIC. Box 355-2 lists the key components of DIC management.

### Clinical Monitoring

The underlying condition, the DIC itself, and response to therapy can rapidly change the clinical manifestations of the disease in children. Therefore, frequent

clinical monitoring along with monitoring of PT, PTT, fibrinogen, and platelet counts may be needed several times per day. Monitoring of other biomarkers of DIC, including D-dimer, prothrombin 1+2, TAT, and FDP levels once every day is usually enough.

The ISTH Subcommittee of the Scientific and Standardization Committee (SSC) on DIC has recommended the use of a scoring system for overt DIC. The ISTH criteria incorporate a 5-step diagnostic algorithm to calculate a DIC score, using simple laboratory tests that are available in almost all hospital laboratories (see Figure 355-4). The presence of an underlying disorder known to be associated with DIC is a prerequisite for the use of the algorithm. For overt DIC, a cumulative score of 5 or more from prolonged PT, reduced platelets and fibrinogen, and elevated fibrin-related markers (eg, D-dimer or FDP) was proposed. A total score of 5 or more is considered compatible with DIC. The sensitivity and specificity of this scoring system are more than 90%. Recent observations have suggested that scoring for rates of change in the PT, platelet count, and D-dimer levels can help identify non overt DIC in the early stages. Although this scoring system is applicable at bedside, it has not yet been validated in the pediatric population. Texas Children's Hospital has modified the ISTH DIC scoring system for clinical use. This system recommends daily monitoring of coagulation parameters to improve the sensitivity of the scoring system. Widespread use of its clinical application is limited at this point, because this scoring system is not validated in large clinical studies.

## Treatment Modalities

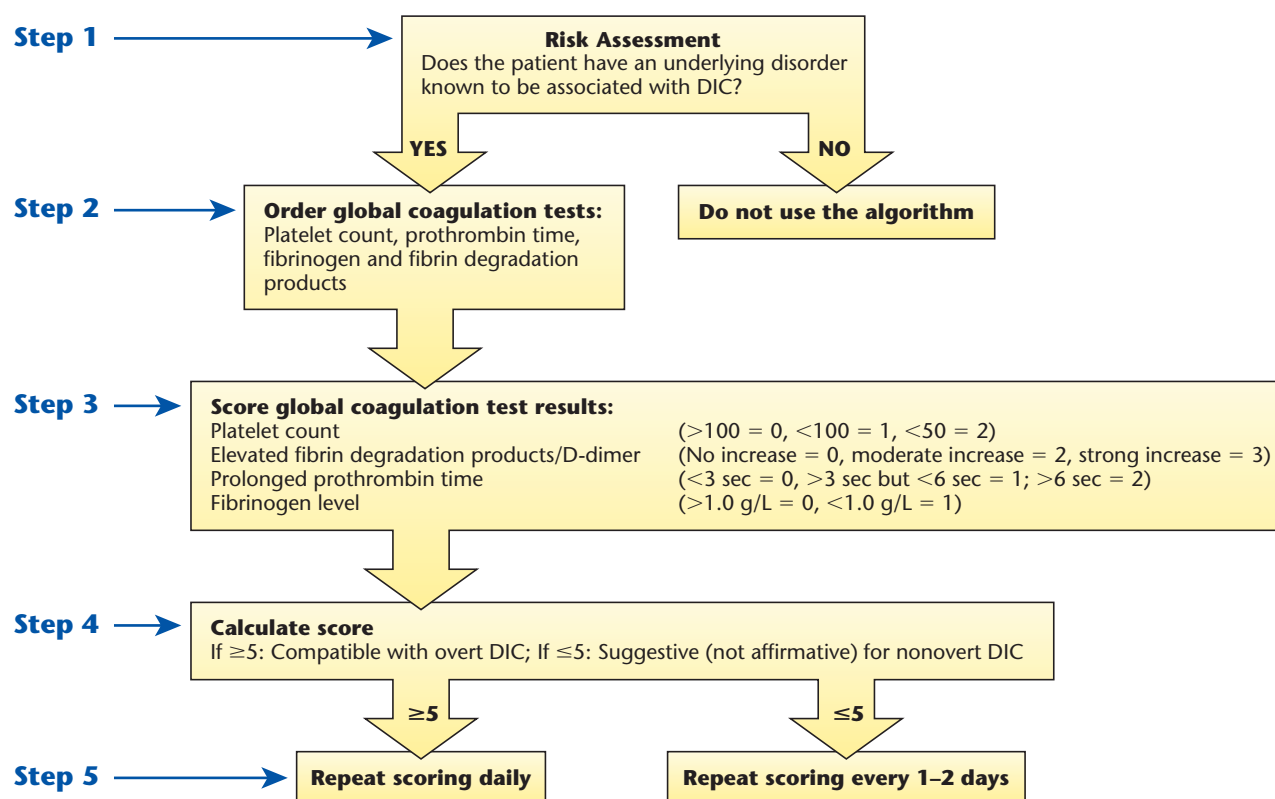
### Blood Component Therapy

Low levels of platelets and coagulation factors may increase the risk of bleeding. Thus, treatment with FFP, fibrinogen, cryoprecipitate, or platelets seems to be a rational therapy for patients with bleeding or those who are at risk for bleeding with significant depletion of these hemostatic factors. However, blood component therapy should not be instituted based on laboratory results alone; it is indicated only in patients with active bleeding, those who require an invasive procedure, or those who are otherwise at risk for bleeding complications. Using large volumes of plasma may be necessary to correct the coagulation defect.

### Anticoagulants

Use of heparin or other anticoagulants seems reasonable to inhibit thrombin generation, considering the central role played by thrombin in DIC. Experimental studies and case reports have shown that heparin can at least partly inhibit the activation of coagulation in sepsis and other causes of DIC. However, a beneficial effect of heparin on clinically important outcome events in patients with DIC has never been demonstrated in controlled clinical trials. In addition, the safety of heparin treatment is debatable in patients who have DIC and who are prone to bleeding. Hence, using heparin is not a standard of care in overt cases of DIC. Heparin is generally contraindicated in children with overt or suspected bleeding within vital





**Figure 355-4** International Society of Thrombosis and Haemostasis (ISTH) scoring system for overt disseminated intravascular coagulopathy. DIC, disseminated intravascular coagulation. (Based on Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M; Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost*. 2001;86(5):1327–1330.)

organs such as the central nervous system, or bleeding within closed cavities like the abdomen. However, therapeutic doses of heparin are indicated in patients with clinically overt thromboembolism, chronic DIC, or extensive fibrin deposition, as seen in purpura fulminans or acral ischemia, as long as there is no ongoing major bleeding.

### Restoration of Natural Anticoagulant Pathways

Another therapeutic option that seems appealing is to restore natural coagulation inhibitors such as protein C, protein S, AT, and TFPI inhibitors to physiologic levels. Use of FFP as a source of AT, protein C, and protein S is not practical because of the short plasma half-life of these proteins, specifically proteins C and S, and issues related to volume overload.

Protein C concentrates and AT III concentrates have been used in adults and in a few pediatric trials of DIC in general or meningococemia-associated DIC in particular. Although the double-blind, placebo-controlled, phase III trial of recombinant human activated protein C worldwide evaluation in severe sepsis (known as the PROWESS trial) was successful, showing a significant decrease in mortality when compared with the placebo group in an adult population, those results could not be replicated in children. A large-scale randomized

clinical trial in children with sepsis recruited 477 children (ages 28 days to 17 years) but showed no benefit of activated protein C concentrates. The subanalyses showed that the safety profile of recombinant activated protein C concentrates was unacceptable in infants younger than 60 days because of increased incidence of intracranial bleeding. Bleeding is the only recognized adverse effect with this therapy. Maintaining platelet counts above  $30 \times 10^9/L$  is prudent during this therapy. The dose of recombinant activated protein C is 24 mcg/kg per hour.

Clinical trials of AT III concentrates in adult population have failed to show clear benefit in sepsis populations. Although there are reports about the safety and efficacy of AT concentrates in children, there is hesitancy to use them in clinical practice because of discouraging results from adult studies.

Similar to protein C and AT concentrates, recombinant TFPI and soluble TM concentrates are being evaluated in phase II/III clinical studies in adult populations. Early reports are inconclusive about their efficacy, and more work needs to be done before performing clinical trials in pediatric population.

### Other Agents

Recently, recombinant factor VIIa (rFVIIa) has become an attractive option for controlling bleeding in various

scenarios. In situations in which volume overload is an issue or bleeding persists despite adequate blood component support, use of rFVIIa (75 mcg/kg every 2 hours) has been shown to be effective. High doses of rFVIIa (270 mcg/kg every 2–4 hours) have been shown to inhibit fibrinolysis in patients with severe hemophilia A with inhibitors. Because of the thrombogenic potential of this product, it should be used with caution in children with DIC.

## CONCLUSION

Disseminated intravascular coagulation has been associated with unacceptably high mortality. New information about the pathophysiologic features and treatment of DIC promises new hope of an improved prognosis for this disorder. Understanding the relationship between inflammation and coagulation has led to a conceptual shift in the treatment strategy for DIC. Coordinated clinical efforts are required to study the safety and efficacy of newer agents in the treatment of DIC.

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## Chapter 356

# DROWNING AND NEAR DROWNING (SUBMERSION INJURIES)

Lorry R. Frankel, MD

*Drowning* and *near drowning* refer to submersion accidents. *Drowning* is defined as death caused by suffocation within 24 hours after submersion in a liquid medium. *Near drowning* refers to an event whereby a person has survived this initial time period through resuscitative efforts. *Submersion injury* is now the term more commonly used for drowning and near drowning. Drowning remains an important cause of accidental death among children and adolescents, ranking second to motor vehicle accidents as the leading cause of accidental death in this age group. There are over 4,000 pediatric deaths each year attributed to submersion injuries.

Submersion injuries are among the most tragic and catastrophic accidents that can occur to children. Within a matter of minutes, a perfectly healthy child may die from submersion or may be left with severe neurologic injury. Although the mortality rates for submersion injuries have declined, survivors may endure neurologic injuries ranging from a permanent vegetative state to motor and cognitive disabilities.

The most important determinant in the patient's outcome is the patient status following resuscitative measures at the scene of submersion. Patients who are conscious at arrival at a hospital have an excellent chance of intact survival. Pulmonary injury can be managed successfully with newer innovative approaches to mechanical ventilation. Persons with the worst prognoses are those who continue to require resuscitation in the emergency department (ED). This remains true regardless of the age of the patient, duration of submersion, pH at the time of care, or body temperature. The best predictor of outcome is return of normal neurologic function within 24 to 72 hours. It has been well documented that people who do not have a return of cognitive function within 72 hours of the hypoxic episode either do not survive or do so in a persistent vegetative state. Other poor prognostic findings include the continuation of cardiopulmonary resuscitation (CPR) beyond 25 minutes; fixed, dilated pupils; seizures; flaccidity; a Glasgow coma score of less than 5; and decreased cerebral blood flow.

Cold-water submersions that produce severe hypothermia may influence the outcome, but not all victims of hypothermic submersion escape serious neurologic sequelae.

## EPIDEMIOLOGIC CONSIDERATIONS

In the United States, approximately 1,400 drowning deaths occur each year in children younger than 19 years. The groups most at risk include children younger than 5 and boys between the ages of 5 and 19 years. Among those younger than 5, the drowning rate is higher for white children than for black children. The overall outcome for submersion injuries seems to be bimodal, with children either dying or being discharged home. A few children are either discharged home with skilled nursing care or discharged to a long-term or chronic care facility.

The circumstances that surround submersion injuries vary by age and geographic region. Bathtub submersion injuries are more common in children younger than 1 year of age who are left in the care of an older sibling or who are without adult supervision. Child abuse should be suspected when bathtub submersion events occur. Bathtub submersion injuries may be associated with scald burns from hot water. Toddlers are more likely than older children to experience submersion injuries in family swimming pools, hot tubs, or on top of pools by falling into a puddle of water on top of the pool cover. Older children and adolescents may experience submersion injuries during a diving accident. Adolescent and adult drowning incidents are often associated with drinking alcohol or using drugs, which may impair judgment and increase risk-taking behaviors. Portable above-ground pools represent another significant problem in residential settings

for children younger than 5 years. Many incidents occur in the child's own yard and usually in the summer months.

Not all submersion injuries are fatal. However, the morbidity may not be inconsequential. For every submersion injury that results in a death within 24 hours, approximately 4 hospital admissions and 14 ED visits occur. Despite efforts to educate children about pool safety, submersion injuries continue to occur. Community education and mandatory barriers around private pools have resulted in a reduction in the number of submersion injuries.

### **PATHOPHYSIOLOGICAL FEATURES OF SUBMERSION INJURIES**

Asphyxia, anoxia, hypothermia, and reperfusion injuries are the hallmarks of submersion injuries. The child initially panics, then holds his or her breath and loses consciousness. During this period, the child may lose cough and gag reflexes and then aspirate large amounts of water. This action produces anoxia, resulting in decreased oxygen delivery to the tissues. The child's heart rhythm becomes abnormal, with evidence of fibrillation and finally asystole. In addition, the child's core temperature begins to drop. Theoretically the type of fluid aspirated affects the circulatory volume and electrolyte balance. Fresh water is hypotonic and is rapidly absorbed across the alveoli, which may result in increased blood volume, hemodilution, a reduction in serum electrolytes, and hemolysis. On the other hand, a submersion injury in salt water may result in hemoconcentration, decreased blood volume, and an elevation in serum electrolytes.

For blood volume to be seriously altered, the patient must aspirate at least 11 mL of fluid per kilogram of body weight; at least twice this amount must be aspirated to result in marked electrolyte changes. However, most children aspirate less than 4 mL/kg of fluid, which means that, practically speaking, little clinical relevance exists to the type of water in which the child is submerged. Most patients who experience near drowning are intravascularly hypovolemic as a result of capillary leak from asphyxia. The effects on the body may be on a single system or multiple systems. In addition to hypovolemia, patients who experience near drowning may experience serious injury to other organ systems, including pulmonary injury with surfactant washout and aspiration of gastric contents or contaminated water contents, central nervous system (CNS) injury resulting from anoxic or ischemic events, myocardial injury, renal impairment, injury to the gut mucosa, and liver function abnormalities.

#### **Pulmonary Effects**

Usually the lungs are the most seriously affected organs. The decrease in the functional residual capacity of the lungs results in hypoxia and hypercarbia. The lung injury may progress from either aspiration pneumonia or simple pulmonary edema with alterations in surfactant to the acute lung injury commonly referred to as *acute respiratory distress syndrome*. The child may have apnea or agonal respirations or may have difficulty with airway protection. Understanding these

changes enables the astute pediatrician to act appropriately to prevent further hypoxic or anoxic injury.

If spontaneous respirations are present, then the pediatrician should first administer oxygen to the child. If the child does not possess the capability to protect the airway, then the airway must be intubated with an endotracheal tube of the appropriate size. Initial ventilatory settings will require enough tidal volume (6–10 mL/kg) or inspiratory pressure to allow for adequate rising of the chest wall. Higher tidal volumes may be associated with ventilator-induced lung injury. Positive end-expiratory pressure (4–8 cm H<sub>2</sub>O) must be used to help alveolar distension. An age-appropriate respiratory rate and a fraction of inspired oxygen of 1.0 should be provided. The child should undergo chest radiography to evaluate the degree of lung injury and to make certain that the endotracheal tube is placed correctly.

#### **Hemodynamic Effects**

The cardiovascular system may be seriously affected as a result of the period of anoxia. Myocardial contractility may be greatly reduced, and the patient may require inotropic support in the form of dopamine, epinephrine, or dobutamine. The goal is to hydrate the child adequately with 20 to 40 mL/kg of isotonic crystalloid or colloid. If the hemodynamic response is suboptimal, inotropes should be added. To accomplish this task safely and effectively, a central venous catheter and an arterial line should be inserted. A double-lumen catheter should be used for the central venous access. The distal port should be used to transduce the central venous pressure (CVP) and the proximal port used to infuse inotropes. The line may be inserted into any one of several vessels (subclavian, internal jugular, external jugular, or femoral).

The child will require continuous monitoring of vital signs and CVP. CVP monitoring enables the physician to better understand the child's volume status, which helps guide fluid administration. An arterial line enables continuous monitoring of the mean arterial pressure, which should be kept in the correct range for age. If the patient continues to struggle with high CVPs and poor cardiac output, then the physician should consider placing a pulmonary artery catheter to measure the wedge pressure, which is a reflection of the true CVP. Cardiovascular instability, hypotensive shock, and metabolic acidosis may persist. Therefore, the physician must understand that hypovolemia and decreased myocardial function may result from the asphyxial component of submersion injuries. The cardiogenic component may be related to hypoxic injury, dysrhythmia, or metabolic acidosis. In addition, pulmonary vascular resistance may be increased as a result of pulmonary vasoconstriction and the release of various inflammatory mediators. This increased resistance affects right-sided heart function and further decreases left-sided heart performance. This additive effect results in decreased left-sided filling pressures and a further decrease in oxygen delivery to an already compromised periphery, which further potentiates the metabolic acidosis seen with submersion injuries. If cardiovascular instability continues, then the physician must consider sepsis or further myocardial dysfunction.

### Effects on the Central Nervous System

Profound CNS dysfunction is the ultimate complication of submersion injuries. The duration of hypoxia and hypotension determines the severity of the neurologic injury seen after serious submersion events. As the neurons are deprived of oxygen, the patient loses consciousness. After this stage, blood flow to the CNS may be increased, resulting in a reperfusion injury, followed by a marked decrease in cerebral blood flow. Thus, the pediatrician may see severe CNS injury even after the restoration of cardiac output, normalization of blood pressure, and adequate oxygenation.

Given that intensive care unit techniques have advanced to improve cardiac output and innovations in mechanical ventilation have resulted in the restoration of a favorable acid–base status and oxygenation, the degree of CNS injury remains the major determinant of survival and neurologic morbidity in patients with asystole who are resuscitated and then transferred to a pediatric intensive care unit (PICU). The exact mechanism of CNS injury is complex and includes increased intracranial pressure, vasogenic changes in autoregulation and cytotoxic cerebral edema, and the accumulation of various metabolites and oxygen free radicals. Although hypothermia from the submersion injury may have some protective effects on the CNS, the child's outcome after submersion injuries will be determined within the first 24 to 72 hours.

### Multisystem Organ Effects

In addition to the pulmonary, hemodynamic, and CNS effects, other organ systems in the body may be adversely affected. These organ systems include the gastrointestinal system, the liver, kidney, and hematopoietic systems with disseminated intravascular coagulation. One of the other ominous signs is discharge from the rectum of material sloughed from the intestinal mucosa mixed with blood. This discharge is commonly associated with severe hypoxic-ischemic injury after the perfusion to the gastrointestinal tract becomes severely reduced, followed by gut necrosis. In addition, severe hypoxic-ischemic injuries may result in coagulopathy, renal failure, and predisposition to infection.

### Other Effects

Hypothermia is among the physiologic changes that occurs most commonly in association with submersion injuries. Children submerged in cold water (<41°F [5°C]) have had astonishing outcomes. The period of submersion hypothermia may protect the CNS. Severe hypothermia results in a decrease in energy use and thus decreases the metabolic rate of the brain. For each 1°C reduction in core temperature, the cerebral metabolic rate is reduced by 6% to 7%. Severe hypothermia may result in cardiac dysrhythmia, loss of consciousness, and a predisposition to infection.

During a submersion incident, the diving reflex may provide some form of protection. This well-known reflex, which is present in diving mammals such as seals, allows oxygen to be conserved. The diving reflex enables these animals to be submerged for 15 or 20 minutes. The reflex results in a marked reduction of blood flow to tissues that are more resistant to hypoxia while

preserving blood flow to more sensitive organs such as the brain and heart. However, the role of the diving reflex in submersion in children is uncertain.

In addition to hypothermia and the diving reflex, other preexisting associated conditions may be relevant in submersion injuries. Children with underlying seizure disorders, occult cardiomyopathy, or alterations in the myocardial conduction system may be predisposed to submersion injuries.

## APPROACH TO SUBMERSION INJURY

The approach to a child who has experienced significant submersion injury has been standardized and involves a minimum of 4 phases: initial lay person rescue at the scene, emergency medical team or paramedic response, stabilization in the ED, and care in the PICU.

### Initial Lay Person Rescue

The initial lay person rescue at the scene consists of identifying the problem and activating the local emergency medical services, removing the child from the water, and clearing the airway and performing CPR for a child who meets guidelines for initiating CPR until the emergency medical team arrives. Effective CPR at the scene is one of the major determinants of success in submersion injuries. The lay rescuer should note the time that CPR was initiated. If possible, an estimation of length of time of submersion should be noted, as should the temperature of the water.

### Emergency Medical Team or Paramedic Response

At the scene, determining the extent of the CNS injury is often initially difficult. Therefore, every effort is made to resuscitate the child to restore cardiac output, oxygenation, and acid–base status. The best approach is to ignore the down time that the child may have had during this initial resuscitative phase. Assessing the patency of the airway is critical, as is clearing the airway of any debris before attempting to ventilate the patient either with a bag-mask device or through intubation in the field. Efforts should be made to protect the airway from the aspiration of stomach contents and the lungs from aggressive positive pressure ventilation, which may produce overdistention of the lungs and possibly barotrauma.

Once a palpable pulse has been established and adequate chest wall rise is observed, the child should be transported to the closest ED that can deal with children. The child's vital signs, including temperature, should be assessed, and the child's cardiorespiratory status should be monitored, which includes continuous electrocardiographic monitoring, recording of oxygen saturation, and, if possible, intermittent recording of blood pressure. Most children in submersion incidents do *not* need spinal motion restriction. It is also important for the child to be dried and warmed.

### Stabilization in the Emergency Department

On arrival in the ED, for further stabilization and evaluation the child should be placed in a room large enough to provide space for the many interventions that will be required: a careful examination, which



includes a survey to ascertain whether any other traumatic injuries exist that are associated with the submersion event (eg, head injury, thoracoabdominal injury); further stabilization of the patient, which includes the use of equipment needed for vascular access, gastric decompression, and bladder catheterization; and provision of appropriate respiratory support. In addition, the child should be dried and warmed to a core temperature greater than 95°F (35°C).

For children who are spontaneously moving and breathing, close observation and monitoring are required to ensure that response to the submersion injury is not delayed. Children who are well saturated in room air and who have age-appropriate responses and a normal Glasgow coma score may be discharged after 4 to 8 hours; however, those with abnormal findings on chest radiograph, who require significant amounts of oxygen, or who have abnormal sensorium need to be admitted to the hospital. They may also require imaging studies while in the ED to make certain that the internal organs are not adversely affected (eg, CT scan of the head to rule out a concomitant CNS hemorrhage). It had been common practice that all patients be admitted for a period of observation for delayed onset of pulmonary edema. There seems to be a movement for short-term observation and discharge from the ED if the child has returned to his/her pre-submersion state, has no respiratory issues, and is neurologically intact.

Patients who were intubated in the field require thorough evaluation in the ED before being extubated. At most institutions, these children will probably remain intubated and mechanically ventilated. The patient then requires transfer to the closest PICU. The stomach must be decompressed with a nasogastric tube, a bladder catheter must be placed to measure urine output, and appropriate vascular access lines must be inserted. If the patient was not intubated in the field but now has poor oxygenation, displays signs that indicate increased work of breathing, or has a high oxygen requirement, then positive pressure ventilation is indicated. The child should then be intubated with an appropriately sized endotracheal tube. The patient should be placed on the appropriate ventilator setting for the underlying condition. Patients who are intubated and mechanically ventilated may need sedatives and paralytics to facilitate effective management. Obviously, if possible the neurologic status of the patient should be documented before the administration of paralytics.

To facilitate intubation, the physicians may administer a paralytic and an analgesic-amnesic agent. The patient's neurologic status is continuously monitored and documented before transfer to the PICU. In addition, if indicated, the physician may wish to order a CT scan to evaluate the brain and to determine whether an associated traumatic head injury has occurred. The spine should also be evaluated and cleared. In those who have an altered mental status it may not be possible to clear the spine and thus precautions to protect the spine must be continued in the PICU. All lines and tubes must be stabilized to make certain that the patient cannot dislodge any of the lines or the endotracheal tube.

Efforts should be made to restore vascular volume with an isotonic solution (10–20 mL/kg). The patient should be warmed to treat existing hypothermia and prevent further hypothermia, which can be associated with abnormal cardiac rhythms. Antibiotic treatment may be initiated if the patient aspirated contaminated water or if pulmonary infection is suspected. Before transfer to the PICU, radiographic studies must be performed to confirm the placement of the endotracheal tube, vascular access catheters, and contour of the lungs. Patients should also be assessed to ensure that no pneumothorax or other evidence of air leak exists.

### Care in the Pediatric Intensive Care Unit

On the child's arrival into the PICU, the physician closely monitors all vital signs, including oxygen saturation, end-tidal carbon dioxide (either inline with the ventilator, or with a nasal cannula-based capnometry device).

All PICU efforts are aimed at minimizing any injury that resulted from the submersion event itself, because the primary injury—the hypoxic-ischemic event—cannot currently be treated. PICU efforts are now directed to supportive care of the patient and trying to minimize secondary or further neurologic injury.

If the patient is intubated, an arterial line should be placed, and if the child requires cardiovascular support with inotropes, then a central venous catheter should be placed. Further management is aimed at restoring cardiac output, minimizing injury to the brain, and preventing catastrophic complications. Neurointensive care support is often required; however, aggressive management of intracranial hypertension with osmotic agents, hypothermia, hyperventilation, steroids, or barbiturate-induced coma has not proved to be of much benefit. In fact, these interventions may increase the risk for nosocomial infections, pulmonary insufficiency, and cardiac dysfunction.

The approach taken in the PICU varies from institution to institution, but the major goal is always to restore the child, if possible, to the previous state of health by preventing further injury to the brain. Efforts should be made to assess the degree of neurologic injury over the first 24 to 48 hours. Electroencephalographic monitoring may help with the recognition of electrical seizures. Seizure activity should be treated quickly and aggressively. Monitoring intracranial pressure has not proved to be of benefit for these patients. Patients should only receive sedation if it is clinically indicated. The severity of the encephalopathy is the main determinant of outcome.

When possible, nutritional support is provided either in the form of enteral nutrition if the intestinal tract can tolerate feeds or parenteral nutrition once the patient's fluid and electrolytes issues have resolved. Normalization of blood gases by various ventilatory strategies (to ensure adequate oxygenation and acid-base status) is preferred to hyperventilation. The appropriate support of the cardiovascular system with inotropes as needed to maintain an adequate blood pressure is required to maintain blood flow to vital organs. Minimizing the development of stress ulcers in the gastric mucosa is vitally important;

thus, agents may be used to maintain a gastric pH of greater than 5. This can be accomplished with either proton pump inhibitors or H<sub>2</sub> blockers. The appropriate use of antibiotics to treat suspected or proven infections is often necessary, because submersion victims are susceptible to bacterial infections that result from aspiration of water. Bacterial infections also may result from complications of mechanical ventilation or vascular access attempts. Therefore, initiating empiric antibiotic treatment may be reasonable.

A periodic review of blood tests for changes in hematocrit level, coagulation profile, or white blood cell count is also important. A review of liver and renal function studies helps the pediatrician ascertain whether other organs have been injured. Unusual forms of ventilatory support may include the use of high-frequency ventilation for acute pulmonary injury, inhaled nitric oxide for severe hypoxia-induced respiratory failure, and extracorporeal oxygenation. Extracorporeal oxygenation, which may be used for rewarming, theoretically allows the lungs to rest, helping to prevent barotraumas associated with high airway pressures.

### When Neurologic Function Is Likely to Be Impaired

When a child has experienced a serious submersion injury and remains comatose 72 hours after the incident despite interventions, the child will not likely recover full neurologic function. This fact must be explained to the child's parents within 12 to 24 hours after the child's admission to the PICU. A multidisciplinary meeting (neurologists, primary care physician, PICU nurses, and a social worker assigned to the case) should be held with the family to explain in great detail the potential outcomes of children who have experienced a serious submersion injury and who are still comatose. Palliative care may be incorporated in the care plan, as palliative care skill sets may be very helpful for the pediatricians in the ICU, staff, and the family. Clearly, once it has been determined that severe neurologic sequelae have occurred, the family needs to be made aware of the various options now available for the ongoing care of the child. It may be helpful for the families to understand what long-term care needs may require, such as tracheostomy, gastrostomy and possibly placement in a subacute care facility if one exists. Families should also be informed that appropriate care may not require such interventions, and that natural death can be allowed to occur by limiting further interventions and providing more comfort care measures.

At this initial meeting, depending on the child's clinical condition, the full spectrum of outcomes should be presented in an open and forthright manner: the child may regain much, but not all, of previous neurologic function; the child may experience less severe neurologic sequelae; or the child may remain in a vegetative state or experience brain death.

During the next 48 to 72 hours, if the patient does not return to appropriate neurologic functioning, then the family is presented with this information again so that the difficult process of deciding what to do next

can begin. The parents need to make informed decisions about aggressive approaches to care. Once the determination has been made that the child's chances for meaningful survival are remote, the family may be presented with information about the potential need for technology-based ongoing support; long-term mechanical ventilation, tracheostomy, gastrostomy feeds, and fundoplication. In addition, the parents may consider placing the child in a long-term or chronic care facility or nursing the child at home. It may be beneficial for the family to visit a long-term care facility before making decisions regarding further life-prolonging interventions.

A pediatric palliative care consultation helps the parents make these complex decisions. Family members must participate in decisions about further aggressive care or decisions to limit or withdraw care based on the potential for poor outcome. This participation empowers the parents to decide to limit aggressive interventions that will not change the ultimate outcome. A natural death may result from withdrawing life support. If the parents choose this route, they must be prepared to deal with an extubation that results in the child's death. In such instances, if possible, a *do-not-resuscitate* order should be obtained.

Some parents may wish to attempt extubation with the idea that if the child does not succeed with breathing without mechanical ventilation, then the child will be reintubated, thereby providing the parents with more time to come to a consensus about what to do next. Nonetheless, once the medical team has established that the most likely neurologic outcome for the child is the potential for severe encephalopathy or a persistent vegetative state, some parents request that the child be extubated, not reintubated, and permitted to die naturally. A *do-not-resuscitate* order on record ensures that no further heroic efforts will be undertaken to save the child.

An open, honest policy enables parents to participate in decisions that will profoundly affect them for years to come. The health care team should provide resources to the family as needed: support for sustaining the child in a long-term care facility should be provided to the family, or after a child's death, the palliative care team or another specialist may provide bereavement support for the family. (See Chapter 67, Palliative, End-of-Life, and Bereavement Care.)

## PREVENTION

The overall effect of submersion injury prevention and pool safety cannot be overstated. The efforts of the American Academy of Pediatrics and communities have resulted in a reduction in serious submersion injuries by advocating standards for pool safety. During routine office visits, primary care physicians need to educate families about pool safety.

A swimming pool in the yard can be dangerous for children. If possible, swimming pools should not be built until the children in the household are older than 5 years. If a pool is already in place, then safety measures should be undertaken to prevent drowning. Box 356-1 provides tips on how to protect children from drowning.

### BOX 356-1 How to Protect Children From Drowning

- Never leave your children alone in or near the pool, even for a moment.
- Put up a fence to separate your house from the pool. Most young children who drown in pools wander out of the house and fall into the pool. Install a fence at least 4 feet high around all 4 sides of the pool. This fence will completely separate the pool from the house and play area of the yard. Use gates that auto-close and auto-latch, with latches higher than your children's reach.
- Consider the use of a safety cover. A power safety cover that meets the standards of the American Society for Testing and Materials adds to the protection of your children but should not be used in place of the fence between your house and the pool. Even fencing around your pool and using a power safety cover will not prevent all drownings.
- Keep rescue equipment (eg, a shepherd's hook, life preserver) and a telephone by the pool.
- Do not let your child use air-filled swimming aids because they are not a substitute for approved life vests and can be dangerous.
- Know CPR. Anyone watching young children around a pool should learn CPR and be able to rescue a child if needed. Stay within an arm's length of your child.
- Remove all toys from the pool after use so children are not tempted to reach for them.
- After the children are finished swimming, secure the pool so they cannot get back into it.
- Teaching your child how to swim does not mean that your child is safe in water.

Derived from American Academy of Pediatrics. *A Parent's Guide to Water Safety*. <http://patiented.solutions.aap.org>

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Home Water Hazards for Young Children* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/safety-prevention/at-home/Pages/Home-Water-Hazards-for-Young-Children.aspx](http://www.healthychildren.org/English/safety-prevention/at-home/Pages/Home-Water-Hazards-for-Young-Children.aspx))
- *Swimming Pool Safety* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/safety-prevention/at-play/Pages/Swimming-Pool-Safety.aspx](http://www.healthychildren.org/English/safety-prevention/at-play/Pages/Swimming-Pool-Safety.aspx))
- *Water-Related Injuries* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/HomeandRecreationalSafety/Water-Safety/index.html](http://www.cdc.gov/HomeandRecreationalSafety/Water-Safety/index.html))
- *Water Safety for Older Children* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/safety-prevention/at-play/Pages/Water-Safety-for-Older-Children.aspx](http://www.healthychildren.org/English/safety-prevention/at-play/Pages/Water-Safety-for-Older-Children.aspx))

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## Chapter 357 DRUG OVERDOSE

Angela Lumba-Brown, MD

### FOUNDATION

#### Definition

*Pediatric drug overdose* refers to the intentional or accidental ingestion of a drug not medically recommended or the intentional or accidental ingestion of a drug in quantities larger than medically recommended for that child.

#### Epidemiology

Pediatric drug overdose is a serious public health problem that can have fatal consequences. Calls to the Poison Control Center about medication ingestion in children increased by 10% from 2002 to 2006. More than 70,000 children younger than 18 years are treated for accidental or intentional drug overdoses in US emergency departments (EDs) annually. Eighty-one percent of ED visits for drug overdose involve children younger than 6 years. Fatalities in this age group are most often caused by overdose of analgesics, followed by antihistamines, and then sedative-hypnotic-antipsychotic drugs. At all ages, analgesics are the most common pediatric poisoning in general (68%), surpassing poisoning from household product ingestion.

#### Etiology

Pediatric drug overdose can be separated into 2 categories—intentional and accidental. Intentional overdoses occur when the patient ingests medications

with the intent to self-harm, for recreational drug misuse, or as a symptom of a substance use disorder.

Misuse, defined as the nonmedical use of a drug, is the main cause of medication overdose in children aged 13 to 19 years. The 2011 National Survey on Drug Use and Health reported that 2.8% of 12- to 17-year-olds reported nonmedical use of prescription drugs within the past month.

Accidental drug overdoses occur as a result of therapeutic errors or inadvertent ingestion. The Poison Prevention Packaging Act of 1970 mandated child-resistant packaging for hazardous products and prescription drugs. Subsequently, the Consumer Product Safety Commission reported a reduction of 1.4 deaths per 1 million children younger than 5 years. Despite this improvement, children younger than 5 years continue to have the highest incidence of accidental drug overdose.

Fourteen percent of ED visits occur because of medication errors and misuse. Most ED presentations for pediatric drug overdose (82.2%) occur as a result of unsupervised ingestions.

### Risk Factors

The risk factors for pediatric drug overdose are multifactorial.

In the United States, 82% of adults and 56% of children take at least 1 medication at home. Frequency of use and storage of medications at home increase the

potential for drug overdose. Further risk factors are discussed in Box 357-1.

## DIAGNOSIS

### Signs and Symptoms

Manifestations of overdose may affect any organ system and are related to the type of drug ingested. Identifying signs and symptoms representative of a specific toxidrome aids in the diagnosis of drug overdose, especially if the ingestion was unwitnessed.

Common general overdose symptoms include nausea and vomiting, abdominal pain, diarrhea, skin flushing, diaphoresis, abnormal respiratory patterns, temperature abnormalities, visual disturbances, pupil irregularities, paresthesia, agitation, lethargy, irritability, and altered mental status.

Complications of drug overdose include seizures, further mental status changes, hemodynamic instability, hypoglycemia, cardiac arrhythmia, and death.

### Differential Diagnosis

The differential diagnosis of drug overdose is broad; see Box 357-2.

### Diagnostic Approach

Diagnostic approach to the pediatric patient with a possible drug overdose begins with the rapid identification of the critically ill patient by assessing the airway, breathing, circulation, and disability. Full vital signs, including blood pressure, are obtained as soon as possible in a child with a possible drug overdose to aid in determining respiratory and hemodynamic compromise. A complete physical examination follows and can be concurrent with history taking. Patients with drug overdose may have pupillary abnormalities or other abnormal eye movements; abnormal odors that

### BOX 357-1 Risk Factors for Pediatric Drug Overdose

- **Age:** Toddlers and young children may ingest medications in play or with the assumption of a drug being food or candy.<sup>a</sup> Adolescents may purposefully ingest drugs for recreational or self-harm purposes.
- **Availability:** Child-resistant packaging has made accidental pediatric drug overdose more technically challenging. However, the presence of medications in the household and within a child's reach is a risk factor for ingestion.
- **Decreased or inadequate supervision:** Unintentional ingestions in young children often occur when they are unsupervised.<sup>b</sup>
- **Unclear medication dosage or directions:** Often, children's medications are liquid formulations requiring measurement and administration by parents, allowing for medication error.
- **Previous self-harm attempt:** Teens and adolescents who have previously attempted drug ingestion as a suicidal attempt or gesture are at risk for repeat attempt.<sup>c</sup>
- **Drug abuse:** Teens and adolescents who abuse drugs are at risk for drug overdose.

<sup>a</sup>Schillie SF, Shehab N, Thomas KE, Budnitz DS. Medication overdoses leading to emergency department visits among children. *Am J Prev Med.* 2009;37(3):181-187.

<sup>b</sup>Bryant S, Singer J. Management of toxic exposure in children. *Emerg Med Clin North Am.* 2003;21(1):101-119.

<sup>c</sup>Reid WH. Prognosis after suicide attempt: standard of care and the consequences of not meeting it. *J Psychiatr Pract.* 2009;15(2):141-144.

### BOX 357-2 Differential Diagnosis of Drug Overdose

- Meningitis and encephalitis
- Seizure
- Metabolic derangements like hypothermia and hyponatremia
- Diabetes with hypoglycemia and hyperglycemia
- Endocrinologic emergencies, such as thyroid and adrenal dysfunction
- Trauma
- Pneumonia
- Cardiac arrhythmia
- Sepsis
- Gastroenteritis
- Envenomation
- Dehydration
- Other poisonings
- Psychiatric conditions



are characteristic of a specific ingestion, such as the smell of wintergreen in a patient who has a salicylate overdose; neurologic abnormalities, such as change in tone or clonus; and skin changes, such as absent perspiration or flushing. The physical examination also includes an evaluation of mental status and current cognition to assess for altered mental status, lethargy, and cognitive derangements. The physician should place the patient in a position of comfort with the airway maximized; be ready to perform cardiopulmonary resuscitation if necessary; and obtain the patient's weight, height, and age.

The history of ingestion begins with the patient and caregiver interview to determine the name, quantity, and dosage of the medication ingested. (See Figure 357-1). If the amount is unknown, the physician can count the number of pills or tablets in the bottle and determine how many were originally in the bottle, if it is available. If the drug ingestion is unknown, caregivers can provide information

regarding medications in the home and medications potentially brought into the home by visitors.

Past medical history, including history of recent illness, may contribute to the clinical picture of the patient with an overdose and raise concern for compounded symptoms. For example, a beta-blocker overdose in an asthmatic patient may have more serious consequences. Other important points in the patient's history include recent medication use and chronic medication use that may represent an overdose or that may affect metabolism of the overdose. The patient's last oral intake and allergies may change management planning.

Physicians must identify the circumstances of exposure and intent and discuss any previous history of self-harm, suicide attempts, or drug use. If the ingestion is a suspected or confirmed attempt for self-harm or suicide, the patient will require constant observation.

Patients who present within the first hour of ingesting a life-threatening amount of a known or suspected

### INITIAL PEDIATRIC INTAKE FORM FOR SUSPECTED DRUG INGESTION

American Association of Poison Control Centers 1-800-222-1222

Date/Time of call: \_\_\_\_\_

#### **Patient Information**

Patient name: \_\_\_\_\_

Age: \_\_\_\_\_ Weight : \_\_\_\_\_ Kg Height: \_\_\_\_\_

Time of patient arrival: \_\_\_\_\_

#### **Suspected Drug(s) Ingestion**

Name(s) \_\_\_\_\_

Formulated: (circle one)      Tablets      Capsules      Liquid  
Topical

Dosage of formulated: \_\_\_\_\_ x Amount ingested: \_\_\_\_\_

= Total drug ingested: \_\_\_\_\_ circle:      mcg      mg      ml

Time of ingestion: \_\_\_\_\_

#### **Patient History**

Past medical history: \_\_\_\_\_

Allergies: \_\_\_\_\_ Current medications: \_\_\_\_\_

Last oral intake: \_\_\_\_\_

#### **Initial Patient Examination**

Vital Signs: (circle)      alert      playful      crying      sleepy/listless      unconscious

Temp: \_\_\_\_\_ RR: \_\_\_\_\_ HR: \_\_\_\_\_ BP: \_\_\_\_\_ O<sub>2</sub> sat: \_\_\_\_\_

**Figure 357-1** Initial pediatric intake form for suspected drug ingestion.

**Table 357-1** Lethal Pediatric Drug Overdoses: “One Pill Can Kill”

DRUG	MANIFESTATIONS	MANAGEMENT CONSIDERATIONS
Beta blockers	Hypotension	Glucagon Fluid resuscitation Vasopressors
Calcium channel blockers	Hypotension	Calcium replacement Insulin and glucose Fluid resuscitation Vasopressors
Camphor	Central nervous system excitation/ seizures Respiratory depression	Airway control Activated charcoal Benzodiazepines for seizures
Quinine derivatives, including cardiac glycosides and antimalarials	Cardiac dysrhythmia and prolonged QRS duration and/or prolonged QT interval Neurotoxicity and seizures Cinchonism Hypokalemia	Sodium bicarbonate Potassium replacement
Clonidine Oxymetazoline	Bradycardia Hypotension Respiratory depression Miosis	Atropine Consider naloxone Supportive care Vasopressors
Opioids/narcotics	Central nervous system depression Respiratory failure	Naloxone; likely to need repeat doses or continuous infusion resulting from short half-life
Oral hypoglycemic (eg, sulfonylureas)	Hypoglycemia	Glucose Glucagon Inpatient monitoring
Salicylates	Metabolic derangement	Activated charcoal Sodium bicarbonate Possible hemodialysis
Tricyclic antidepressants (eg, imipramine, desipramine, amitriptyline)	Cardiac dysrhythmia with QRS widening Anticholinergic symptoms Hypotension	Airway control Activated charcoal Benzodiazepines for seizures Cardiac monitoring

drug may require immediate administration of activated charcoal. See Table 357-1 for a list of drugs that can be lethal in children.

### Laboratory Findings

The laboratory evaluation of a child with a suspected drug overdose includes the tests listed in Table 357-2. Many drugs can cause cardiac arrhythmias, such as widened QRS or prolonged QT intervals. The physician should obtain a 12-lead electrocardiogram in cases of such drugs and in cases of hemodynamic instability.

### Imaging

Abdominal radiographs may identify radiopaque medications, such as chloral hydrate, iron-containing preparations, calcium carbonate, iodinated compounds, acetazolamide, busulfan, and potassium preparations. Antihistamines, phenothiazines, and tricyclic antidepressants exhibit varying radiopacity. Factors like the size of the patient, concentration of enteric

coating of the pill, air density, and layering in the gastrointestinal tract affect visibility on plain radiograph.

In the obtunded patient, head computed tomography can rule out other causes of altered mental status.

A chest radiograph should be obtained if there is concern for aspiration of the drug or aspiration pneumonia. A chest radiograph may also be obtained to confirm the placement of nasogastric tubes, central lines, and endotracheal tubes.

## MANAGEMENT

### Treatment Approach

The caregiver of a child with suspected toxic ingestion should immediately consult with the local Poison Control Center at 800-222-1222.

The obtunded or hemodynamically unstable patient requires immediate intravenous (IV) access and application of supplemental oxygen via non-rebreather face mask. The physician should begin fluid resuscitation in hemodynamically unstable patients with 20 mL/kg of

**Table 357-2** Laboratory Evaluation of a Child With Suspected Drug Overdose

TEST	FACILITY	PURPOSE
Serum glucose	Rapid Bedside	Hypoglycemia may be caused by many drug ingestions, such as oral hypoglycemic agents, beta blockers, insulin, salicylates, and quinine Hyperglycemia may be caused by beta agonists and calcium channel blockers
Urine pregnancy	Within 1 hr	Qualitative identification of pregnancy in an adolescent
Urine drug screen	Within 6 hr	Qualitative standard testing of amphetamine, barbiturates, benzodiazepines, cocaine, marijuana, opiates, phencyclidine May be useful in children in whom diagnosis is uncertain
Venous blood gas	Within 30 min	Assesses acid-base status and ventilation Increased anion gap metabolic acidosis suggests salicylate, ethylene glycol, and methanol overdose
Basic metabolic panel	Within 1 hr	Reports electrolyte levels and evaluate for renal function Allows calculation of anion gap ( $\text{Na} - [\text{Cl} + \text{HCO}_3]$ ) Hyperkalemia may occur with overdose of cardiac glycosides Hypokalemia may occur with overdose of beta agonists
Urinalysis	Within 6 hr	Assesses specific gravity and presence of myoglobin to suggest rhabdomyolysis Calcium oxalate crystals may suggest ethylene glycol ingestion
Ethanol breathalyzer	Rapid	Allows for rapid assessment of the breath alcohol content
Serum ethanol level	Within 6 hr	Quantitative evaluation of blood alcohol content
Osmolar gap	Within 6 hr	Elevated osmolar gap may occur in alcohol poisonings
Quantitative serum acetaminophen	Within 6 hr	Assesses for toxic levels Should be screened for in any intentional poisonings
Quantitative serum salicylate	Within 6 hr	Assesses for toxic levels Should be screened for in any intentional poisonings
Liver function tests	Within 1 hr	Evaluation of baseline status if acetaminophen ingestion is suspected
Coagulation panel	Within 6 hr	Evaluation of baseline status in acetaminophen and salicylate ingestions

crystalloid fluid and obtain a bedside blood glucose measurement. The physician should consider naloxone administration empirically in the patient with miosis and altered mental status if other causes are not apparent. Children suspected of having a drug overdose who are actively seizing should be treated with benzodiazepines while other reasons for seizure, such as hypoglycemia, hyponatremia, or isoniazid ingestion, are evaluated. Immediate endotracheal intubation is required in the obtunded patient who is unable to maintain her airway, displays ineffective oxygenation, lacks a gag reflex, or declines rapidly.

### Activated Charcoal

Activated charcoal should not be used in the home, but it has a role in decontamination following life-threatening, acute pediatric drug overdose in the ED setting. Activated charcoal reduces drug absorption and enhances elimination. It may be effective if given within 1 hour of ingestion at a dose of 1 g/kg up to

50 g per dose, although it can be beneficial up to 4 hours after ingestion. Complications of activated charcoal administration, especially multi-dose activated charcoal or charcoal-cathartic combinations, are nausea, vomiting, aspiration, possible pulmonary aspiration, constipation, hypovolemia, hypernatremia, and hypermagnesemia. Multiple doses of activated charcoal should be considered after life-threatening ingestions of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. Some slow-release medications, metals, and electrolytes are not bound by activated charcoal.

Cathartics alone have no role in the management of the drug-overdosed patient, and they should not be used with multidose administration of activated charcoal.

### Sodium Polystyrene Sulfonate

Sodium polystyrene sulfonate is a salt that acts as a cation binder. It is an effective therapy in lithium

overdoses and for hyperkalemia. Complications are hypokalemia and constipation.

### **Whole Bowel Irrigation**

Whole bowel irrigation is used to increase the gastrointestinal transit time of a drug and thereby decrease its absorption and in cases of life-threatening ingestion of select agents in the acute setting—this occurs generally within the first 60 minutes. Whole bowel irrigation may be useful in life-threatening ingestions of sustained-release preparations, enteric-coated pills, and very large ingestions including drug packets. A polyethylene glycol electrolyte solution is administered at a rate of 500 mL/hour in children aged 9 months to 6 years, 1,000 mL/hour in children aged 6 to 12 years, and 1,500 to 2,000 mL/hour in adolescents and adults, often by nasogastric tube. Whole bowel irrigation used after administration of activated charcoal decreases its efficacy of binding. Use is contraindicated in the child with an unstable airway or hemodynamic status, active seizures, or concern for bowel obstruction.

### **Syrup of Ipecac**

Home use of syrup of ipecac in ingestions has not been shown to improve patient outcome or reduce resource use. The American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists do not recommend its use in the ED.

### **Gastric Lavage**

Studies have not shown a benefit of gastric lavage compared with activated charcoal administration. There are potential adverse effects of gastric lavage, such as gastrointestinal perforation, pulmonary aspiration, and pneumonia. Additionally, pediatric-sized gastric tubes may not be large enough to remove pills.

### **Supportive Care**

For the most part, management of pediatric drug overdose is exclusively supportive. Patients in respiratory distress should be placed on oxygen via a non-rebreather face mask to titrate oxygen saturations to greater than 93%. Patients with altered mental status or without gag reflex should be intubated and ventilated. A trial of naloxone (0.1 mg/kg IV) may be helpful in these patients.

Hypotension should be treated with bolus infusions of crystalloid fluid. For refractory hypotension, vasopressors, such as norepinephrine, should be initiated. Bradyarrhythmias should be treated with atropine.

Conversely, hypertension may be a manifestation of overdose. In this case, if hypertension is suspected to be because of agitation, benzodiazepines may be employed. In hypertensive crisis, phentolamine or nitroprusside may be used. The exclusive administration of beta blockers should not be used because of the risk for subsequent alpha blockade and worsening clinical status.

Physicians should immediately evaluate for hypoglycemia and treat with oral or IV dextrose, if indicated. The starting glucose dosage is 2.5 mL/kg of dextrose 10% via peripheral IV. If the patient cannot

tolerate oral medication and IV access is not readily available, subcutaneous glucagon may be administered at 0.03 mg/kg up to a maximum of 1 mg.

### **Specific Antidotes**

Several drugs have known antidotes and are listed in Table 357-3.

## **ONGOING CARE**

### **Follow-up**

In patients without symptoms, 6 hours of ED observation for signs of drug overdose, such as hypotension, cardiac arrhythmia, or seizures, is generally sufficient in most cases of suspected pediatric drug ingestion. However, if an extended-release medication is a suspected ingestant, such as a hypoglycemic agent, the patient should be admitted for monitoring overnight. Additionally, it is important to note that a drug's calculated half-life is based on therapeutic dosing and cannot be readily applied in the scenario of overdose.

All patients who intentionally overdose for either recreational purposes or in suicide attempt require evaluation by a trained social worker. Those with suicidal intent also require psychiatric assessment and inpatient admission until deemed psychiatrically stable.

If a caregiver is suspected to have intentionally given a drug to the child or caused the child's overdose, or if inadequate supervision is suspected, Child Protective Services must be notified. All states have laws mandating that physicians and other medical personnel report suspected child abuse and neglect.

### **Complications**

The complications of pediatric drug overdose depend on the medication ingested. Prolonged hypoglycemia caused by ingestion of oral hypoglycemic agents or resulting from induced metabolic derangements can cause brain injury, coma, and death. Hypoxemia caused by the depressed respiratory drive in opioid- or clonidine-overdosed patients can cause brain injury and death. Overdoses causing prolonged seizures like antihistamines, cyclic antidepressants, or isoniazid may result in rhabdomyolysis and renal dysfunction or failure. Acetaminophen poisoning can cause hepatitis and liver failure.

### **Prognosis**

Three-fourths of calls to the Poison Control Center are managed over the telephone and do not result in direct treatment by a health care professional. Most children with drug overdose return to their baseline health status within 24 hours.

In 2010, only 11% to 12% of children younger than 13 years who were reported to the Poison Control Center for toxic ingestion were admitted to the hospital. Meanwhile, 48% of teens aged 13 to 19 years reported for toxic ingestion were admitted for hospital management. There are 4 times as many hospital admissions for teens as for young children because most teen overdoses are intentional.

In 2010, there were 91 pediatric fatalities due to toxic ingestion reported by the American Association of Poison Control Centers National Poison Data System. Forty-six of these fatalities were in 13- to 19-year-old



**Table 357-3** Drug Ingestions and Their Specific Antidotes

DRUG	TREATMENT	DOSAGE
Acetaminophen	N-acetylcysteine	Oral: 140 mg/kg/dose PO, then 70 mg/kg/dose every 4 hr PO x 17 doses. IV: 150 mg/kg IV over 1 hr, then 50 mg/kg over 4 hr, then 100 mg/kg IV over 16 hr.
Anticholinergics	Physostigmine	0.02 mg/kg IV infusion to be administered no faster than 0.5 mg/min, to repeat every 10 min as needed with a maximum total dose of 2 mg. Not for use in patients with widened QRS.
Beta blockers	Glucagon	0.15 mg/kg initially over 1 min followed by repeat dose, if necessary, and continuous infusion at 0.1 mg/kg/hr.
Benzodiazepines	Flumazenil	0.01 mg/kg IV every 1 min for 1–5 doses (maximum dose, 0.2 mg/dose).
Calcium channel blockers	Calcium Insulin	Calcium gluconate: 100 mg/kg IV. Calcium chloride via central venous line: 20 mg/kg IV. Repeat doses as needed. Insulin: 1 U/kg IV with a glucose infusion.
Cardiac glycosides	Digoxin-specific antibody (Fab) fragments Atropine, in symptomatic bradycardia	Digibind: 5–10 vials via slow IV push for children. Atropine: 0.02 mg/kg IV.
Ethylene glycol and methanol	Ethanol Fomepizole	Loading dose: 10 mg/kg IV or PO, followed by maintenance dose 1 to 2 mL/kg/hr IV or PO. 15 mg/kg IV bolus, then 10 mg/kg IV every 12 hr for 4 doses; after these, increase dose back to 15 mg/kg.
Iron	Deferoxamine	15 mg/kg/hr IV for 8 hr.
Narcotics/opioids	Naloxone	0.1 mg/kg IV (maximum, 2 mg) per dose, may be repeated every 3 min for effect, with a maximum cumulative dose of 10 mg.
Oral hypoglycemic agents	Glucose Glucagon Octreotide	2.5–5 mL/kg dextrose 10% IV. 2–4 mL/kg dextrose 25% IV. 1–2 mL/kg dextrose 50% IV via central line. 0.03 mg/kg up to a maximum of 1 mg. Consult Poison Control Center.
Tricyclic antidepressants (eg, imipramine, desipramine, amitriptyline)	Sodium bicarbonate	1–2 mEq/kg IV bolus for widened QRS; may repeat to maintain effect.

IV, intravenous; PO, by mouth.

children with intentional exposures. Twenty-six fatalities occurred in children 5 years of age and younger.

### Prevention

Strategies to prevent pediatric drug overdose are categorized as engineering, educational, and enforcing.

- *Engineering* involves modifying the drug or how it is accessed. The Poison Prevention Packaging Act of 1970 mandated childproof containers on all

prescription medications, resulting in an estimated reduction in the child mortality rate from accidental drug overdose by 45% between 1974 and 1992.

- *Education* of caregivers by their pediatricians and dispensing pharmacists regarding the dangers of drug overdose may modify behaviors of medication storage and therapeutic errors. Adolescent and teen counseling by parents, pediatricians, school health counselors, public service announcements,

and outreach programs may help to prevent drug misuse and overdose. Pediatric patients who have intentionally overdosed on a medication require psychiatric assessment.

- **Enforcement** refers to upholding drug dosing, packaging, and administration regulations. Therapeutic errors by health care workers may be enforced by hospital policy and legal measures.

### WHEN TO REFER

To a Poison Control Center or toxicologist

- Ingestion of any known or unidentified drug
- Suspicion of a toxic ingestion

To the emergency department

- Suspicion of a toxic ingestion
- Concern for potential decompensation
- Monitored observation required
- Acute ingestion that would benefit from activated charcoal administration or whole bowel irrigation
- Hemodynamic instability
- Altered mental status
- Concern for child abuse or intent for self-harm/suicidal intent

### WHEN TO ADMIT

- Concern for potential decompensation
- Prolonged monitored observation required
- Worsening medical status
- Hemodynamic instability
- Hypoxemia
- Hypoglycemia
- Significant metabolic acidosis or electrolyte derangement
- Protracted vomiting
- Cardiac dysrhythmia
- Altered mental status
- Respiratory distress
- Inability to tolerate oral intake
- Concern for self-harm/suicidal intent

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *American Association of Poison Control Centers* (Web site) ([www.1-800-222-1222.info/poisonhelp.asp](http://www.1-800-222-1222.info/poisonhelp.asp))

### AAP POLICY

Sullivan JE, Farrar HC, American Academy of Pediatrics Section on Clinical Pharmacology and Therapeutics and Committee on Drugs. Fever and antipyretic use in children. *Pediatrics*. 2011;127(3):580–587 ([pediatrics.aappublications.org/content/127/3/580](http://pediatrics.aappublications.org/content/127/3/580))

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## Chapter 358 ENVENOMATIONS

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Envenomations present unique problems in children. An amount of venom injected that may not be enough to cause morbidity in an adult may be disastrous for a child. Venoms are complex chemical mixtures designed for either defending or hunting. Animal venoms used for immobilizing prey may also have predigestive effects to aid the hunter.

Various venom delivery systems exist. Most systems of clinical relevance consist of specially evolved exocrine gland mechanisms to make and store venom and a sophisticated delivery apparatus. Snake fangs resemble hypodermic needles, and the Hymenoptera stinging device is similar to a blood sampling stylet. *Envenomation* is the injection of venom through the bite or sting of venomous creatures. *Bites* refer to the injection through structures associated with the mouth and are primarily evolved for handling prey, whereas *stings* are delivered through a posterior structure (stinger) and are primarily defensive. Pediatricians, primary care physicians, and emergency medicine physicians often manage patients with complaints of envenomation. Concerns about allergic reactions, mostly from insects, result in referrals to allergy and immunology specialists. See Box 350-3 in Chapter 350, Anaphylaxis, for drugs and dosages for the management of anaphylaxis.

### EPIDEMIOLOGIC FEATURES

In 2013, the American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS) reported 2,188,013 human exposures, with 56,378 resulting from bites or stings (see Table 358-1 for a partial breakdown). Of the 1,218 deaths reported, 4 (0.33%) were from bites and stings, and 1 involved a child younger than 6 years. Although bites and envenomations ranked number 14 of the top 25 substance categories most frequently involved in human exposures for all age groups reported in NPDS, they did not make the top 25 in children younger than 6 years.

**Table 358-1** National Poison Data System: 2013 Envenomation Exposures in the United States

ANIMAL	TOTAL	CHILDREN AGES 0–5 YEARS
Ants, fire ants	1,014	311
Hymenoptera	5,248	862
Scorpions	18,270	1,670
Total snakes	6,425	339
Crotalines	3,877	167
Coral	73	1
Total spiders	8,664	853
Brown recluse spiders	1,326	95
Black widow spiders	1,866	152

Excerpted from Mowry JB, Spyker DA, Cantilena LR, et al. 2013 Annual Report of the American Association of Poison Control Centers' National Poisoning Data System (NPDS): 31st Annual Report. *Clin Toxicol*. 2014;52:1032–1283.

Although most cases are minor, serious local and systemic injury can result. Consequently, the primary care physician must be aware of local venomous species and be able to recognize and treat the injuries caused by them. In North America, venomous species include arthropods, specifically Hymenoptera (bees, wasps, hornets, and ants), arachnids (spiders and scorpions), and snakes (pit vipers and coral snakes).

## HYMENOPTERA

In the United States, Hymenoptera are the largest order of insects known and are responsible for most insect stings. Hymenoptera include the family Apidae (honeybees), family Bombidae (bumblebees), superfamily Vespidae, and superfamily Formicidae (harvester ants and native and imported fire ants). Vespids consist of *Vespula* species (yellow jackets) and *Polistes fuscatus* (hornets and wasps). All Hymenoptera possess a posterior stinger.

Hymenoptera stings can cause local or systemic reactions. Reactions may be a direct effect of the venom, or they may occur through an IgE-mediated allergic reaction. Anaphylaxis from various origins results in approximately 400,000 visits to emergency departments annually. Hypersensitivity has been reported to occur in 0.05% to 5% of the population. This prevalence is second only to drug-induced (penicillin) anaphylaxis.

Large local cutaneous reactions to stings occur in approximately 2.3% to 18.6% of the general population. A history of systemic allergic reactions documented in medical records occurs in 0.8% of children. Biphasic anaphylactic reactions, characterized by return of symptoms 1 to 10 hours after the initial symptom resolution, may occur in up to 20% of patients. There are reports of returning symptoms being delayed up to 72 hours. Systemic allergic sequelae can occur at any age, often after numerous uncomplicated stings. Though evidence suggests that most children do outgrow systemic allergic responses to insect

stings, 1 in 5 individuals stung up to 32 years after the original reaction still elicit an allergic reaction. Death by honeybee or wasp envenomation is rare. In the United States, 40 to 100 people suffer fatal envenomation caused by bee, wasp, or ant stings annually. IgE-mediated type-1 anaphylaxis, although uncommon, is usually responsible for related deaths. Massive envenomations involving hundreds of stings may also result in death.

## Winged Hymenoptera

### Characteristics and Distribution

Winged Hymenoptera are found in most areas of the United States. Honeybees usually nest in hollow trees and crevices, whereas bumblebees prefer nesting underground. Wasp nests can often be found under roofs and eaves, hornets prefer to nest in the branches of trees, and yellow jackets tend to build their nests in the ground.

Most social bees and wasps sting primarily in defense of their nest or while in search of food. Yellow jacket wasps are common near exposed food and garbage, resulting in stings not associated with nest protection. Yellow jackets have also been implicated in frequent stings in late summer and early fall associated with *yellow jacket delirium*, a poorly understood seasonal behavior characterized by aggressiveness toward objects that are not threatening or provocative. If disturbed, any wasp or bee will sting in self-defense. Mass envenomations occur when a human is perceived to be intruding or threatening the colony. Honeybee colonies consist of approximately 40,000 workers, with Africanized honeybees having slightly smaller colonies. In contrast, yellow jackets and hornets maintain colonies of several hundred to a few thousand insects.

The sting apparatus, or *aculeus*, of wasps (vespids) and honeybees resembles a stylet with 2 shafts. The shafts, propelled by muscular attachments, alternately slide back and forth, like a saw, pulling the sting deep into the flesh. Barbs located in the tips of the stylet help anchor the aculeus. Venom is then pumped down a central channel into the wound. Unlike the aculeus of the honeybee, the vespids sting stylet is wider than the stylet shaft barbs, and the dorsal stylet surface is smooth, decreasing the likelihood that the sting will remain in the victim. The insect with the barbed stinger dies within hours to days after stinging because the stinger remains anchored in the skin of the victim, thereby eviscerating the insect. However, because vespids can withdraw their stingers, they are able to sting multiple times. When the stinging apparatus detaches from the insect and remains in the victim's skin, the muscles surrounding the venom sac contract and can pump venom into the flesh for an additional 30 to 60 seconds.

Much attention has been garnered by Africanized honeybees, commonly referred to as *killer bees*, which are now found in southern Texas, Arizona, and California. The original colonies of these bees were imported to South America to breed with European varieties in an attempt to increase honey production. However, the ensuing generations of bees retained the ferocity of the African bees. The bees are not more

individually dangerous than European bees. Their venom is similarly potent, and similar amounts are delivered per sting. However, their aggressive “swarm-and-attack” nature can result in massive envenomation because of the sheer number of stings delivered in an attack.

Venoms of the winged Hymenoptera contain many protein components that account for the reactions that have been observed. Phospholipids A<sub>2</sub>, hyaluronidase, histamine, apamin, melittin, mast cell degranulating peptide, acid phosphatase, norepinephrine, dopamine, and allergen C are the main constituents of honeybee venom. Mast cell degranulating protein causes cell breakdown and histamine release. Bumblebee venom contains acid phosphatase, tryptic amidase, and melittin. Melittin is the main pain-inducing compound, and it causes membrane integrity alteration. The major vespid allergens are antigen 5 and hyaluronidase, but they also contain histamine, kinins, serotonin, phospholipase A<sub>1</sub> and B, and mastoparans. Cross-reactivity between the apid and the vespid venoms is limited, but a marked cross-reactivity exists between the different vespid venoms.

The most common areas to be stung are the head, neck, feet, and hands. Stinging is most common during the summer months, and children are often affected. Most patients cannot reliably identify the insect that stung them. Bees and wasps are strongly attracted to dark colors. Therefore eyes, mouth, and nostrils may be selectively targeted. Although stings to the eye are uncommon, when they occur, the cornea is the most common site.

### Physical Examination

**LOCAL.** Both nonallergic and allergic local reactions may occur after a sting. The nonallergic reaction is a non IgE-mediated, direct result of envenomation through mast cell degranulation and histamine release, resulting in the production of a wheal-and-flare response. This response produces erythema, swelling, pain, and itching. These signs and symptoms usually subside in a few hours but may last for several days or exhibit a biphasic reaction where symptoms resolve fully, yet reappear several hours after initial resolution. Localized cutaneous reactions occur in 80% of individuals and are often the sole finding in children following a sting.

Allergic local reactions occur in approximately 17% of people stung by winged Hymenoptera. They consist of erythema and local edema more than 10 cm in diameter; they often persist for 48 to 72 hours, and they may become indurated for a period of up to 5 days. Some patients may experience headache, nausea, or malaise with these reactions.

As mentioned previously, a stinger may sometimes be found at the sting site, which usually indicates a honeybee sting or, in some cases, a yellow jacket sting. Skin and soft-tissue necrosis in the weeks after a Hymenoptera sting have also been reported.

Corneal stings may result in local damage through toxic and immunologic reactions. Stingers retained in the eye may cause corneal edema and ulceration, with striate and toxic keratopathy. Immunologic reactions can result in extensive inflammation and uveitis.

Inflammatory glaucoma may occur as a result of severe uveitis. Severe neuro-ophthalmic complications such as optic neuritis, loss of vision, and cataracts have also been reported.

**SYSTEMIC.** The more common systemic manifestations of an allergic reaction to Hymenoptera stings include urticaria, angioedema, wheezing, shortness of breath, stridor, nausea, vomiting, diarrhea, abdominal pain, malaise, dizziness, and anaphylaxis. Systemic reactions are typically caused by an immunologically induced mast cell or basophil mediator release from an IgE-mediated response. This reaction generally develops within minutes after a sting. Dysphagia, dysarthria, hoarseness, weakness, and confusion also have been described. Effects on the hematologic system include hemolysis with associated hemoglobinuria and hemoglobinemia, thrombocytopenia, and disseminated intravascular coagulation. Respiratory and cardiovascular complications are observed in adults more often than in children. Fatal anaphylaxis is rare, especially in children. However, the sheer number of exposures makes Hymenoptera envenomation the second-leading cause of anaphylactic reactions after penicillin exposure, and it accounts for more deaths in the United States than any other envenomation.

The risk of developing a systemic reaction seems to be increased in the patient with a history of multiple stings or after being stung within a few weeks after a previous sting. The risk is also increased in patients who have a history of anaphylaxis. Their risk of anaphylaxis with subsequent stings is 35% to 60%. The pattern of reaction, however, is difficult to predict. Atopic patients do not seem to be at greater risk of developing systemic complications, but the severity of their symptoms may be greater than in nonatopic individuals. A history of a large local reaction does not reliably predict progression to systemic complications. The risk of subsequent anaphylaxis after a large local reaction is approximately 5% to 10%.

Systemic reactions may also be caused by the direct action of bee venom. In rare cases, serum sickness, vasculitis, encephalopathy, neuritis, and renal disease with or without rhabdomyolysis have been observed. Renal failure or death may occur when 20 to 200 wasp stings or 150 to 1,000 or more honeybee stings have been inflicted. The human 50% lethal dose for honeybee stings has been estimated to be between 500 and 1,200 stings. However, recovery has been reported in children involving incidents of 200 to 1,000 or more honeybee stings. Children are considered to be at high risk because of their failure to perceive the risk, and they are less apt to be able to escape while being stung. The presence of Africanized bees may result in multiple stings resulting in high doses of venom, in turn resulting in hemolysis, thrombocytopenia, rhabdomyolysis (skeletal and myocardial), and acute tubular necrosis. Systemic damage may develop within 24 hours, although delayed onset (2–6 days) has been reported.

### Differential Diagnosis

The differential diagnosis of the local reaction includes other arthropod envenomations, puncture wounds with reactive erythema or cellulitis, or simple cellulitis. The differential diagnosis of systemic reactions includes any



other cause of allergic reaction, reactive airway disease, or infectious processes. Other causes of stridor, wheezing, and allergic reaction should be considered if a sting site cannot be identified.

### Laboratory Studies

No specific laboratory test is useful in the acute management of Hymenoptera stings.

### Management

Insect sting sites should be inspected for the presence of a stinger. Honeybee stingers remain present and will further embed themselves and continue to pump venom after separation from the bee. The venom sac is emptied within 2 minutes of entering the skin; therefore, quick removal of the stinger is imperative. Traditional teaching advocates the removal of the stinger by scraping it with a hard-edged object, such as a credit card, to prevent pressure on the venom sac. Such pressure would theoretically result in an increase in envenomation. However, experimental data show that removal of the stinger with the fingers does not increase envenomation. Rapid removal of the stinger by any means is most effective in minimizing envenomation. Removal of bee stingers that have been embedded for more than 1 minute will not reduce envenomation because most of the venom empties from detached honeybee stingers within 10 to 20 seconds.

Nonallergic local reactions require symptomatic treatment, including cool compresses (ice should not be placed directly on the skin), elevation, and local wound care. No further evaluation is necessary. If local itching is bothersome, then an oral histamine-1 ( $H_1$ ) antagonist such as diphenhydramine may help. Local allergic reactions require care similar to that provided for nonallergic reactions. For very large cutaneous reactions, prednisone (0.5–2 mg/kg/day given in 1–4 doses for 3–5 days) may be useful.

The acute management of a corneal bee sting is aimed at preventing a secondary infection and includes broad-spectrum topical antibiotics, reducing inflammation with topical corticosteroids, treating anterior uveitis, early detection and treatment of inflammatory glaucoma, and providing pain relief. Surgical removal of the embedded stinger is controversial. Pulse corticosteroids may prevent permanent loss of vision.

Mild systemic allergic reactions may be treated with diphenhydramine or another  $H_1$  antihistamine, supportive care, and observation. Epinephrine is the mainstay of therapy for severe systemic allergic reactions, along with  $H_1$  and  $H_2$  antagonists, corticosteroids, and intensive supportive care. A 0.01-mL/kg dose of 1:1,000 aqueous epinephrine solution is injected subcutaneously. The original dose should not exceed 0.3 mL, but it may be repeated in 15 minutes. Susceptible individuals should carry epinephrine self-administered kits when they go outdoors. After a kit is used, medical help should be sought, because the effect of the drug is short lasting. Elevating lower extremities to optimize venous return may be helpful. Severe systemic reactions from direct toxic effects of massive envenomation require intensive supportive care, therapy similar to that for anaphylactic reactions, and careful monitoring for rhabdomyolysis,

thrombocytopenia, cardiac arrhythmias, and renal failure. Dialysis may be required.

Children with systemic reactions who respond completely to therapy in the emergency department should be observed for 6 to 8 hours after the sting because of the possibility of a delayed anaphylactic episode. The mechanism of this delayed complication is not well understood. Children with severe symptoms, including airway, cardiovascular, or pulmonary compromise, or persistent symptoms may benefit from a short course of corticosteroids.

At the time of discharge after a systemic reaction, all patients should be given a prescription for a self-administered epinephrine kit. The patient or caretaker should be instructed in its proper use before discharge from the emergency department. They also should be encouraged to wear a Medic Alert bracelet identifying them as being allergic to insect stings. Patients should be taught how to prevent further stings (see Box 358-1).

The perception that children generally outgrow Hymenoptera sting allergies is not always accurate. Research has found that the long-term risk of a systemic allergic reaction to a sting among patients who do not receive venom immunotherapy is far higher in those with a history of moderate to severe reactions than in those with strictly mild (cutaneous) systemic reactions.

Children who experience extracutaneous systemic reactions should be referred to an allergist for risk analysis and possible venom immunotherapy. Various immunotherapy regimens exist; consequently, susceptible patients may be effectively protected within hours to days, although typical regimens take weeks to months. The immediate access to aqueous epinephrine and a thorough understanding of its administration remain important aspects of care for children undergoing immunotherapy until maintenance doses are reached.

### Fire Ants

#### Characteristics

Approximately 20 species of ants comprise the genus *Solenopsis* (commonly known as fire ants) in the United

#### BOX 358-1 How to Avoid Insect Stings

- Do not disturb nests or hives—have someone else remove them.
- Do not wear perfume, cologne, scented sunscreens, or hairspray when outdoors.
- Use footwear when outside.
- Avoid picnic areas, garbage sites, orchards, fields of clover, and flowerbeds.
- Be extra careful when gardening, and cover the hands and body.
- Avoid trips outdoors if medical help is not readily available or until maintenance immunotherapy is established.
- Do not wear brightly colored clothes or jewelry.
- Install screens on windows and doors to prevent insects from entering the home.

States. Of these, 2 imported species have the most clinical importance: *Solenopsis invicta* and *Solenopsis richteri*. Three common species of native fire ant, *Solenopsis xyloni*, *Solenopsis geminata*, and *Solenopsis aurea*, are less aggressive, have limited geographic range, and have largely been displaced by the imported species.

*S. invicta* is red, 3 mm to 4 mm in length, and native to northern Argentina, Paraguay, and western Brazil. These ants arrived in Mobile, Alabama in the late 1930s and spread aggressively throughout the Southeast from Texas to Virginia, and into California. *S. invicta* is expected to spread north along the West Coast and may reach the Canadian border eventually, displacing native species as it spreads. In infested areas, imported fire ants can make up 90% of the ant population.

*S. richteri* is black, slightly larger than *S. invicta*, and is native to Argentina and Uruguay. *S. richteri*'s importation to southern Alabama preceded *S. invicta* by approximately 20 years, and *S. invicta* has largely displaced *S. richteri*. Currently, *S. richteri* is found only in northeastern Mississippi and northwestern Alabama.

Significant changes in the characteristics of imported fire ants have occurred in the United States. *S. invicta* and *S. richteri* have formed hybrid species with a greater tolerance to cold, which will likely increase their geographic distribution. The spread of fire ants is largely passive, commonly through soil or plant matter.

Imported fire ants are extremely aggressive, which results in a high frequency of envenomation among humans in endemic areas. The literature suggests a 20% to 30% annual attack rate in endemic areas, although rates as high as 58% have been reported. Children are especially vulnerable. The highest sting rate (close to 50%) occurs in persons younger than 20 years. Trespassing into the fire ants' territory or disturbing a nest will incite aggressive, swarming behavior, often resulting in multiple stings. Cases of ants attacking victims indoors are not uncommon. Heavy rains seem to increase this occurrence, although increasingly the ants are noted to nest in human-made structures.

Fire ants bite the skin of their victims with their mandibles, then they arch their bodies to inject venom through a lancet-shaped stinger located at the distal end of their abdomen. If undisturbed, they will continue to sting the victim repeatedly in a circular pattern, using their mandibles as a pivot; venom is injected with each sting.

Fire ant venom differs from bee and wasp venom in that it is mostly composed of alkaloid piperidine hemolytic factors and contains very little protein. However, this protein moiety is responsible for the IgE-mediated allergic reactions sometimes encountered with fire ant stings. Antigenic similarity exists between these proteins and bee and wasp venoms. The alkaloid portion is thought to be responsible for releasing histamine, leading to the common local dermal reactions; it also has some neurotoxic properties.

Fire ant envenomations are becoming an increasingly important public health concern in the United States, resulting in fatalities caused by fire ant-induced anaphylaxis.

### Physical Examination: Signs and Symptoms

**LOCAL.** Stings from imported fire ants often occur on children's ankles and feet in the summer. Stings tend to be multiple and cause immediate local burning and itching. Soon after, the area becomes erythematous and raised. This reaction usually subsides after 30 to 60 minutes. The classic pathognomonic finding of small, sterile pustules (see Figure 358-1) develops between 4 and 24 hours after the sting and is more common with stings of imported fire ants. Pustules may occur in rings or lines consistent with stinging behavior patterns. Pustules usually resolve over 3 to 10 days. Some patients develop a large local reaction similar to that of other Hymenoptera stings. An initial wheal-and-flare reaction evolves into an erythematous, pruritic, warm, indurated area around the sting site. Large local reactions may progress for 48 hours and may not subside for 7 days. The pathophysiologic mechanism of large local reactions is not clear, and they may be confused with cellulitis.

Secondary bacterial infections from excoriation and open erosions are common after fire ant stings. These infections are usually minor and localized. However, sepsis may result from superinfected lesions.

**SYSTEMIC.** Systemic allergic reactions occur in up to 16% of patients treated for fire ant stings, with serious reactions, including anaphylaxis, occurring in up to 2%. Systemic allergic reactions are similar to those associated with other insects and include bronchospasm, angioedema, urticaria, pruritus, laryngeal edema, hypotension, and anaphylaxis. Seizures, mononeuritis, Guillain-Barré syndrome, serum sickness, nephritic syndrome, and worsening of preexisting cardiopulmonary disease have also occurred. The venoms of native and imported fire ants are highly cross-reactive, and phospholipase components of fire ant venom have been shown to be cross-reactive with vespid venom phospholipases. The direct systemic toxic effects of fire ant venom are not well understood. No deaths have been attributed to date to fire ant venom toxicity.



**Figure 358-1** Fire ant stings on adult hand. (From eXtension. Fire ants stings can be serious. Available at: <http://articles.extension.org/pages/69336/fire-ants-stings-can-be-serious#VbaKoPIUJ1A>. Accessed February 9, 2016.)

### Laboratory Studies

The diagnosis of fire ant stings is clinical; no confirmatory laboratory test has been developed.

### Management

Mild local reactions are treated conservatively with cool compresses, oral antihistamines, and wound care. Large local reactions may require oral antihistamines and systemic corticosteroids, and they must be carefully examined to differentiate them from cellulitis. The absence of lymphadenopathy and lymphangitis supports the diagnosis of large localized reaction. Systemic allergic reactions are treated similarly to those from any cause. Epinephrine is the mainstay of therapy, coupled with H<sub>1</sub> antagonists and systemic corticosteroids for symptomatic relief and vigorous supportive care as appropriate. Patients who have experienced severe allergic reactions to stings should be referred to an allergist or immunologist for venom immunotherapy assessment.

### Harvester Ants

Harvester ants (genus *Pogonomyrmex*) belong to the Hymenoptera order, subfamily Myrmicinae, which includes the genus *Solenopsis* (fire ants). More than 20 native species inhabit the United States, but only 3 have been associated with anaphylaxis: *Pogonomyrmex barbatus*, *Pogonomyrmex rugosus*, and *Pogonomyrmex maricopa*. Harvester ants occupy a wide geographic area and are found in the southern and western United States and in Mexico.

Similar to fire ants, harvester ants attach to the skin with their mandibles and envenomate their victim through a sting. Their venom differs from fire ant venom in that it contains a much larger fraction of protein constituents; in this regard, it is more similar to other Hymenoptera venoms.

Unlike imported fire ants, harvester ants do not leave characteristic skin lesions. Their sting resembles that of other insects and may be associated with allergic reactions. Treatment of *Pogonomyrmex* stings is the same as that for other Hymenoptera stings.

## ARACHNIDS

The class Arachnida, which includes spiders, belongs to the phylum Arthropoda. In addition to spiders, other members of Arthropoda include Crustacea (shrimp and crab), Myriapoda (centipedes and millipedes), Chelicerata (a subphylum of Arachnida; spiders and scorpions), and Uniramia (Insecta; bees and flies). Members of Arachnida are distinguished from Insecta by the fact that they have 2 main body regions (cephalothorax and trunk) and Insecta have 3 (head, thorax, and abdomen). Arachnids have 4 pairs of legs to insects' 3, and arachnids are always wingless and lack antennae.

The 2 arachnid orders that will be discussed here are Araneae (spiders) and Scorpionidae (scorpions). Although creatures from both of these orders can inflict envenomations that result in significant morbidity, fatalities are rare. The AAPCC 2013 Annual Report of the NPDS reports no fatalities as a result of spider envenomation. However, poison centers are not consulted for every envenomation, so fatalities

(not reported) from spider envenomation may have occurred.

### Spiders

The order Araneae, which includes all spiders, covers a diverse group numbering 105 families with approximately 40,000 species worldwide. In North America, the spiders most commonly involved in human exposures are *Loxosceles* species (brown recluse spider, also known as the violin spider or fiddleback spider), *Latrodectus* species (black widow spider), and tarantulas. All tarantulas are in the family Theraphosidae. Tarantulas are composed of 13 subfamilies, with multiple genera and species. All spider venom probably evolved for paralyzing prey—insects, other arthropods, or small vertebrates.

Approximately 50 spider species are of medical importance. Most are venomous and can sometimes cause serious injury. The differential diagnosis includes other arthropod bites, skin infections, and injury caused by chemical and physical agents.

Eradicating brown recluse spiders, black widow spiders, and tarantulas is not possible. Most spiders are not aggressive and only bite in self-defense when humans invade their territory or when the spider becomes lost in items such as bedclothes. Tarantulas, which are sometimes kept as pets, pose a risk to the unsuspecting child. Prevention is therefore mostly focused on caution in areas inhabited by spiders. A clean house greatly decreases the risk of spider bite. Refer to the National Pesticide Information Center ([npic.orst.edu/pest/spiders.html](http://npic.orst.edu/pest/spiders.html)) for suggestions on controlling spiders habitating inside and outside the home. Wearing long-sleeved shirts and gloves when outside gardening or wearing long pants tucked into socks when hiking are good preventive measures. While professional extermination may help temporarily, it is not effective for long-term spider control. Insect repellants that contain meta-N, N-diethyltoluamide (DEET) or picaridin may offer some protection.

### *Loxosceles* (Brown Recluse Spider)

**CHARACTERISTICS AND DISTRIBUTION.** In the United States, 11 *Loxosceles* species have been identified. *Loxosceles* are usually found in the Southeast and Southwest United States. Although they have been suspected of traveling in baggage or cargo to other areas, the spider has only rarely been verified outside its normal habitat. In the United States, the brown recluse spider, *Loxosceles reclusa*, is usually responsible for most envenomations. Its natural habitat includes the states of southeastern Nebraska, Kansas, Oklahoma, Texas, Louisiana, Arkansas, Missouri, Kentucky, Tennessee, Mississippi, Alabama, northern Georgia, and southern areas of Ohio, Indiana, Illinois, and Iowa. *Loxosceles* species are not found in Canada. Other *Loxosceles* species include *arizonica*, *deserta*, *devia*, and *rufescens*. Brown recluse envenomations have been shown to exhibit a seasonal correlation, with more bites occurring during the months of April through October. These spiders are hearty and live in dry areas such as woodpiles, rodent burrows, vacant buildings, attics, or closets. They



are reclusive, nocturnal, and nonaggressive unless disturbed. Their web is irregular and common in appearance. Other non *Loxosceles* species spiders that have been reported to cause necrosis ("necrotic arachnidism") include hobo spiders (*Tegenaria agrestis*) from the northwestern United States, yellow sac spiders (cheiracanthium species), and wolf spiders (Lycosidae family) found worldwide.

It should be noted that patients presenting with necrotic arachnidism outside of endemic areas for brown recluse spiders probably were not bitten by a brown recluse spider but were instead bitten by another spider whose venom results in similar clinical manifestations.

The body of the brown recluse spider is oval (10 to 15 mm long, 4 mm wide) and light fawn to dark chocolate in color. The leg span is approximately 25 mm. The eye pattern easily distinguishes them from other spiders. *Loxosceles* differ from other US spiders in that they have 6 eyes arranged in pairs—1 anterior and 2 lateral—instead of 8 eyes. The other often-quoted physical feature, which gives rise to the names *violin spider* or *fiddleback spider*, is a violin-shaped marking on the dorsal side of its cephalothorax, with the violin's neck pointing toward the abdomen. Although this pigmented area is seen on adult spiders, it is not always found on some species in the West and on young spiders.

Bites are usually the result of accidental contact, such as looking through boxes or woodpiles, or contact with linens or clothing in which the spider has become trapped.

#### **PHYSICAL EXAMINATION: SIGNS AND SYMPTOMS.**

**Local.** The bite itself does not cause much discomfort and may go unnoticed. Sometimes a minor stinging or burning sensation may be felt at the site. Erythema, pruritus, pain, and edema typically develop within 2 to 8 hours. These symptoms may be followed in the next 24 to 48 hours by the appearance of a blue-gray halo surrounding the erythematous center. Vesicles or bullae containing serous or hemorrhagic fluid soon follow.

Local ischemia and necrosis result in the formation of a black eschar within 7 to 10 days of the bite. This necrotic area may expand slowly in diameter for weeks, especially in fatty areas that have delicate blood supplies such as the abdomen, buttocks, and thighs. The eschar is shed after 2 to 5 weeks and an ulcer remains that may take weeks to months to heal.

**Systemic.** Systemic manifestations of the bite, called "loxoscelism," are less common than cutaneous manifestations. The most common symptoms are fever, chills, and malaise. Symptoms usually occur within 24 hours of the bite and also may include nausea, vomiting, diarrhea, arthralgia, urticaria or maculopapular rash, hemolytic anemia, disseminated intravascular coagulation, jaundice, renal failure, transverse myelitis, seizures, and shock. Systemic loxoscelism may cause potentially life-threatening complications, especially in children.

**DIFFERENTIAL DIAGNOSIS.** In the absence of a definitive history of spider bites, other diagnostic possibilities must be considered, such as emboli, thrombi, focal vasculitis, envenomation by other insects

or reptiles, fat herniation with infarction, pressure sore, pyoderma gangrenosum, poison oak or ivy, cutaneous manifestation of gonorrhea or herpes simplex, diabetic ulcer, purpura fulminans, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome, or abusive or self-inflicted trauma. Cutaneous anthrax has also been misdiagnosed as *Loxosceles* envenomation.

Other species of spiders have been implicated in the formation of necrotic skin lesions similar to those caused by *Loxosceles*. These are *Argiope* (orb weaver spider), *Chiracanthium* (sac spider), *Lycosa* (wolf spider), *Phidippus* (jumping spider), and *Tegenaria agrestis*. Because other spiders can produce a necrotizing skin lesion, the temptation to diagnose all necrotizing skin lesions as *Loxosceles* bites should be avoided. Positive identification of the spider is important not only for the correct diagnosis, but also to understand better the true clinical course of *Loxosceles* envenomation.

**LABORATORY STUDIES.** No current clinical laboratory study can confirm the presence of arachnid venom-related necrosis. Several research tests, including enzyme-linked immunosorbent assay and passive hemagglutination inhibition test, have been studied, but no such test is in clinical use. Complete blood counts, coagulation profiles, electrolytes, and renal function should be monitored in systemic illness.

**MANAGEMENT.** Management is controversial because the unpredictable natural course of the wounds makes prospective trials difficult. Serial observations, cleansing, cool compresses, splinting of the affected extremity, and tetanus prophylaxis are commonly suggested measures. Symptomatic relief with antipruritics and analgesics may be useful in some cases. Patients with exclusively local findings likely do not need hospital admission. Patients (especially children) with systemic symptoms should be admitted and monitored for signs of hemolysis.

Different therapies have been proposed, including systemic corticosteroids, antibiotics, antihistamines, colchicine, dapsone, electric shock, hyperbaric oxygen, metronidazole, and surgical excision and skin graft. None of these therapies is of proven efficacy for *Loxosceles* envenomation. Although the most suitable therapy in children is unclear, general agreement exists on delaying any surgical repair of skin defects until the necrotic demarcation is discrete and no further spread occurs. This period is approximately 8 weeks.

#### ***Latrodectus (Black Widow Spider)***

**CHARACTERISTICS.** Although both male and female black widow spiders have venom, only the female spider has fangs powerful enough to bite through skin and envenomate humans. Black widow spiders are among the largest spiders in the world, with a leg span of 40 mm and a body of 1.5 cm. The mature female spider is black, with a red or orange hourglass-shaped marking on the ventral surface. The immature female spider may be red, brown, or cream in color, and the hourglass marking may be cream colored or even incomplete.

The web, usually built close to the ground in dimly lit, moist areas, is distinguishable by its irregular pattern. It may be found in barns, outhouses, lumber



piles, and sheds where insects are plentiful. Bites are usually a result of the spider being disturbed and acting in self-defense.

While black widow spider envenomation remains a significant health problem in the US, there are no cases of death resulting from envenomation by the widow species in the US.

**DISTRIBUTION.** *Latrodectus* spiders are found in both temperate and tropical climates throughout the world. There are 5 species found in the United States; Alaska is the only state that does not have this genus. The most common spiders implicated in bites are *Latrodectus mactans*, *Latrodectus variolus*, and *Latrodectus hesperus*. Envenomations by any of these species result in the same clinical syndrome.

**PHYSICAL EXAMINATION: SIGNS AND SYMPTOMS.**

**Local.** A bite may go unnoticed or may be experienced as a pinprick or burning sensation. Two small puncture lesions may be visible. Within 30 minutes, pain develops at the site and in the regional lymph nodes. Central pallor at the bite site with surrounding erythema has been described. Unlike the bite of *Loxosceles*, the black widow bite does not usually induce an impressive inflammatory response. An unusual reaction may include compartment syndrome, which may improve after antivenin administration.

**Systemic.** The onset of systemic symptoms, known as “latrodectism,” is often sudden, with crampy, skeletal muscle pains in the legs, abdomen, back, and chest and associated autonomic dysfunction. The most common systemic signs and symptoms are generalized abdominal pain or back pain, local or extremity pain, hypertension, both systemic and local diaphoresis, and isolated abdominal or chest pains. Nausea and vomiting and tachycardia may also be present. Restlessness, salivation, bronchorrhea, priapism, urinary retention, periorbital edema, tremor, and convulsions may also be seen. Abdominal rigidity may mimic peritoneal irritation. Respiratory paralysis, heart failure, and myocarditis have been reported. In children, symptoms include abdominal pain, hypertension, muscle complaints, target-shaped skin lesions, and irritability or agitation. Treatment may alleviate symptoms.

Patients who do not receive antivenin may experience protracted symptoms lasting for several days to a week. Symptoms can include fatigue, weakness, paresthesias, generalized aches, diaphoresis, headache, sleeplessness, excessive sweating, impotence, mental status changes, and transient hemiparesis.

The primary protein component of *Latrodectus* venom is  $\alpha$ -latrotoxin. This protein binds to motor end plate receptors, causing increased synaptic concentration of catecholamines. This excess catecholamine results in characteristic muscle cramps, hypertension, nausea, vomiting, weakness, tremors, and malaise.

Historically, it was posited that black widow spider venom could cause spontaneous abortion or preterm labor in a pregnant patient. This belief has not been documented in modern times. Black widow envenomation in pregnant women is a rare occurrence, and short-term outcomes seem favorable.

**LABORATORY STUDIES.** No specific laboratory test helps establish a diagnosis. Leukocytosis and

hyperglycemia are common. Creatine phosphokinase may be increased as a result of increased muscle activity. Serum calcium levels are normal.

**DIFFERENTIAL DIAGNOSIS.** The causes of acute abdominal pain should be part of the differential diagnosis. Of interest is the close resemblance of the autonomic hyperactivity seen after black widow spider bites and those seen in organophosphate poisoning. The pain can also mimic myocardial infarction.

**MANAGEMENT.** While latrodectism can be severe, in the United States, most symptomatic black widow envenomations reported to the NPDS have minor sequelae, and most symptoms resolve after proper analgesia. Most black widow spider bites require only cool compresses, elevation of the affected extremity, tetanus update (if needed), and analgesics. In more severe cases, the administration of oxygen, cardiac monitoring, and intravenous access are suggested.

Muscle cramps may be relieved with opioids and muscle relaxants. Diazepam, methocarbamol, and calcium gluconate have been used with varying results. The efficacy of 10% calcium gluconate has been questioned. Retrospective analyses of the literature failed to find any significant relief in pain following administration of calcium gluconate, and for this reason calcium is not recommended. Patients who do not receive antivenin gradually improve over the next 12 to 48 hours, and some patients may experience protracted symptoms.

*Latrodectus* antivenin of equine origin is available and neutralizes venom from all related species. Because of the concern for fatal anaphylaxis, patients should be tested for horse serum hypersensitivity before it is administered. It should be considered in cases of severe envenomation when the patient shows evidence of respiratory distress, marked hypertension, and cardiovascular compromise. *Latrodectus* antivenin should also be considered in pregnant women and for protracted symptoms that do not respond to analgesics and muscle relaxants. The response is usually dramatic after antivenin infusion. The administration of antivenin may decrease the length of the hospital stay and prevent lingering neurologic complications.

Unfortunately, there is limited inventory of this antivenin and there are limitations on distribution. For safety and supply issues, alternative antivenin pursuits have led to the creation of highly purified equine F(ab')<sub>2</sub> antibody preparation (Analatro), commercially available in Mexico and being studied in trials in the United States. A randomized, placebo-controlled, double-blind, clinical trial was conducted in 12 academic emergency departments in patients older than 10 years who experienced moderate to severe pain following a suspected black widow spider envenomation. Although the overall reduction in pain was similar for antivenin- and placebo-treated subjects, antivenom reduced pain more rapidly than placebo. No significant adverse events occurred in either group. At the time of press, Analatro is not yet approved for general distribution and use.

**Tarantulas (Mygalomorphs)**

**CHARACTERISTICS.** Tarantulas, more appropriately called *mygalomorphs*, are considered primitive forms

of true spiders. In the United States, the species spends most of the daytime hours in burrows, emerging to hunt at night. They are docile, and bites are unusual. Body size varies; they can reach up to 10 cm in diameter. These spiders possess large fangs that point straight down and require them to lean back on their hind legs to bite—a characteristic defensive posture. More than 30 species of tarantulas are found in the tropical and subtropical desert areas of the southwestern United States. Some North American and foreign species are kept as pets. Children who keep tarantulas as pets should be instructed on identifying defensive behavior.

**PHYSICAL EXAMINATION: SIGNS AND SYMPTOMS.**

Most bites are no more severe than a bee sting and occasionally result in local erythema, swelling, and pain. Nausea and vomiting may occur from the bite. Some genera (*Lasiadora*, *Grammostola*, *Acanthoscurria*, and *Brachypelma*) are capable of releasing urticaria-producing hairs from their abdomen by rubbing their hind legs on the area. This event can result in local histamine release with mild pruritus. However, the itching can last for weeks. The hairs may cause itching in eyes or airways and cause considerable discomfort. Hairs embedded within the cornea may cause chronic keratitis and retinitis.

**MANAGEMENT.** Local wound care and a tetanus update are all that is needed in most cases; antihistamines and oral analgesics may be helpful. Adhesive tape or irrigation with saline solution may be used to remove the urticaria-producing hairs from the skin. Steroids may be indicated for significant ophthalmological complications from the hairs of a tarantula.

## Scorpions

### Characteristics

*Centruroides exilicauda*, formerly *Centruroides sculpturatus*, or the bark scorpion, is the only medically relevant species of scorpion in the United States. Envenomation may be life threatening, especially in infants and children. The bark scorpion's habitat is Arizona and adjacent states in the southwestern United States. Scorpions are found in Arizona and parts of southern California, Nevada, New Mexico, and Texas. *C. exilicauda*, which is considered a climbing scorpion, can be sighted on trees, fence posts, and rocks and in cracks and trash piles. It measures 1.3 to 7.5 cm in length and envenomates its victim with a stinger located at the tip of its tail. The venom is a potent neurotoxin that activates neuronal sodium channels and results in excessive firing of the affected neurons, including both adrenergic and parasympathetic systems. Patients may exhibit both adrenergic and cholinergic symptoms.

Stings usually result from accidental contact with a scorpion trapped in linen or clothing or during outdoor play. Not all stings result in clinical evidence of envenomation. Although most stings take place in scorpion-endemic areas, scorpions can be accidentally transported to other areas by travelers.

### Physical Examination: Signs and Symptoms

**LOCAL.** Pain always occurs at the sting site with or without paresthesias, especially with species other

than *Centruroides*. In mild envenomations, pain may be the only symptom. Infants may exhibit this symptom as unexplained or prolonged crying. Local erythema and swelling may surround a small puncture wound, but the sting site is often unidentifiable. Paresthesias and pruritus are also frequent.

**SYSTEMIC.** Systemic manifestations of *Centruroides* scorpion envenomation can be dramatic, usually develop within 60 minutes of the sting, and persist for days. They tend to be more common in children younger than 10 years. Cardiovascular findings include tachycardia or bradycardia. Children may experience central nervous system dysfunction, a finding that is rare in adults. Severe hypertension may be present in one-third to two-thirds of the victims. Hypertension is sometimes associated with acute hypertensive encephalopathy. Heart failure and acute lung injury may also be seen. An ischemic electrocardiographic pattern may be present. Hypertension may not respond to medical management.

Echocardiographic, scintigraphic, and hemodynamic evaluations reveal hypodynamic ventricular motion with decreased systolic performance. Pulmonary edema is a common feature and is likely because of decreased ventricular performance in the setting of increased venous return, arterial hypertension, kinin-induced increased permeability of the pulmonary vasculature, and impaired left-ventricular filling caused by tachycardia. Electrocardiographic changes are common and include nonspecific ST-T changes or ST elevation or depression consistent with myocardial infarction.

Pathologic cardiac specimens show evidence of ischemia and direct toxicity. The primary mechanism of cardiovascular toxicity is thought to be the result of excessive stimulation of the autonomic nervous system, with the sympathetic influence generally being greater than the parasympathetic. Cardiac effects may also be mediated by electrolyte changes, in particular a relative hyperkalemia.

Neurologic toxicity in the form of cranial nerve abnormalities includes blurred vision, tongue fasciculations, nystagmus, and characteristic opsoclonus-like roving eye movements. Bulbar muscle dysfunction including dysarthria, stridor, pharyngeal spasm, and dysphagia may also be present.

Excessive cholinergic stimulation results in sweating and vomiting. Profound sialorrhea may be evident because of increased cholinergic transmission and difficulty swallowing secretions.

Skeletal muscle findings include twitching or jerking of the extremities, which in some cases may be severe enough to be mistaken for seizure activity. Rhabdomyolysis may result from this event. Nystagmus may be present. Seizures and agitation may also occur.

In pregnant patients following scorpion envenomation, the limited available literature suggests that adverse outcomes are largely related to venom effects to the mother rather than to the fetus in utero.

### Differential Diagnosis

Two factors make establishing the correct diagnosis difficult. The first is that the sting site may not be

identifiable; the second is that the child may not be able to communicate the history of a sting clearly. Seizure disorders, latrotoxicity, intra-abdominal catastrophes, phenothiazine or cholinergic (organophosphate) poisoning, and allergic reactions are some of the differential diagnostic possibilities. Some children have been misdiagnosed as having asthma in the presence of wheezing and respiratory distress. In infants presenting with unexplained crying and restlessness, the differential is further broadened and well discussed elsewhere in the pediatric literature. The characteristic eye movements (if present) in high-grade scorpion envenomation can distinguish this diagnosis from others.

On rare occasion, in *C sculpturatus*-endemic areas, envenomation should be included in the differential when methamphetamine intoxication is being considered.

The progression of symptoms is not predictable; the progression to serious symptoms usually occurs in less than 5 hours, if at all. Numbness, tingling, and pain may persist for 2 weeks. The duration of symptoms has been found to be inversely related to the age of the patient.

Laboratory Studies

Scorpion envenomation is a clinical determination. No confirmatory laboratory test exists. Leukocytosis, cerebrospinal fluid pleocytosis, and increased creatine phosphokinase have been reported.

Management

The treatment of scorpion envenomation is primarily supportive, with the use of cold compresses, tetanus prophylaxis, and analgesics for mild to moderate envenomation. Severe cases require aggressive supportive therapy, which may include endotracheal intubation for airway protection or hyperthermia, benzodiazepines for the treatment of seizures or agitation, and narcotic analgesics for pain control. Although various adjunctive therapies have been tried, no clear standard therapy has been developed. Antihypertensives, including calcium-channel blockers, hydralazine, prazosin, and captopril, have all been used. At present, afterload reducers such as angiotensin-converting enzyme inhibitors, calcium-channel blockers, or prazosin are front-line therapeutic agents for hypertension. Concern about reflex tachycardia has led some physicians to favor prazosin and captopril. The use of diuretics for pulmonary edema is controversial. Atropine

may be used with caution if cholinergic symptoms become severe. Atropine may improve hypersecretion, obviating more aggressive therapy. Treatment should be guided by thorough hemodynamic monitoring. Neither corticosteroid therapy nor systemic antibiotics are routinely recommended.

Before 2011, scorpion antivenin was not widely available. A horse serum-derived whole immunoglobulin preparation used to be available in Arizona in limited supply; however, manufacture of this product ceased. Because of its minimally refined nature and high protein dose, there was a high rate of hypersensitivity and serum sickness. In 2011, Anascorp, *Centruroides* (Scorpion) Immune F(ab')<sub>2</sub> (Equine) Injection was approved after priority review as an orphan drug in the United States by the US Food and Drug Administration (FDA) (see 3-vial dosing guidelines in Table 358-2). The effectiveness of Anascorp was based on results from a randomized, double-blind, placebo-controlled trial of 15 children with neurologic findings consistent with scorpion envenomation. These signs resolved within 4 hours of treatment in the 8 subjects who received Anascorp, but in only 1 of the 7 subjects who received the placebo. Anascorp also reduced the need for concomitant sedation with midazolam and reduced the levels of circulating unbound venom. The safety of equine F(ab')<sub>2</sub> antivenin was evaluated prospectively during development of the product for a biological license application through the US FDA, in 1,534 patients aged 0.1 to 90.5 years who received antivenin. The antivenin was well tolerated. Only 3 patients had acute reactions to antivenin infusion, and 8 had rashes suggestive of Type 3 immune reactions. No patient developed the full syndrome of serum sickness. Two women were treated for envenomation during their first trimester of pregnancy; one of these women suffered spontaneous abortion.

Routine use of the new antivenin is not indicated for every scorpion-envenomated patient because of the risk of reactions and high cost considerations. Prompt supportive care is the mainstay of therapy. After implementing symptomatic and supportive care, patients who have persistent signs of severe envenomation or neurotoxicity should be strongly considered for antivenin therapy.

SNAKES

There are over 2,500 species of venomous snakes in the world; approximately 30 species are known to

Table 358-2 Anascorp Dosing		
Initial Dose	3 vials	<ul style="list-style-type: none"><li>• Reconstitute each vial with 5 mL of sterile normal saline.</li><li>• Combine and further dilute to a total of 50 mL.</li><li>• Infuse intravenously over 10 minutes.</li></ul>
Additional Dose(s)	As needed	<ul style="list-style-type: none"><li>• Administer 1 vial at a time at 30–60 minute intervals.</li><li>• Dilute to a total of 50 mL with sterile normal saline.</li><li>• Infuse intravenously over 10 minutes.</li></ul>

From Anascorp package insert. [http://www.anascorp-us.com/resources/Package\\_Insert.pdf](http://www.anascorp-us.com/resources/Package_Insert.pdf). Accessed February 9, 2016. Reprinted with permission from Rare Diseases Therapeutics, Inc.

exist in North America. In 2013, the AAPCC NPDS recorded more than 6,000 total snake envenomations (339 in children younger than 5 years), with more than half belonging to the Crotalinae family. All 3 of the deaths reported from snake envenomations were caused by Crotalid bites. The venomous snakes of North America can be divided into 2 families: Viperidae (subfamily Crotalinae) and Elapidae. The Crotalinae includes genera *Crotalus* (rattlesnakes), *Agkistrodon* (water moccasins or cottonmouths and copperheads), and *Sistrurus* (pygmy rattlesnakes and Massasauga rattlesnakes). As a group, these snakes are known as *pit vipers* because of a heat-sensitive pit found behind and below their nostrils. Snakes use this organ to locate the victim of a strike. The Elapidae family includes coral snakes and the nonindigenous cobras and mambas.

### Epidemiologic Features

#### Type of Snake

Envenomations by snakes in North America are overwhelmingly caused by indigenous Crotalinae; Elapidae constitute less than 2% of envenomations. Nonindigenous snakes in North American zoos or kept as exotic house pets are responsible for only a small percentage of envenomations. All sea snakes are venomous, but fortunately, none inhabit the coastal waters of North America.

#### Host Factors

The typical snakebite victim is a young adult white male between 17 and 27 years of age who is bitten while handling or playing with a snake. Many of those bitten have a blood alcohol level of more than 0.1%. Fewer than one-half of rattlesnake bites occur before an encounter with a snake was recognized or while the person was attempting to move away from the snake. Most bites in the United States occur in the southwestern states.

#### Body Area

Most bites are inflicted on the upper extremity, including fingers, hand, and arm. Other, less commonly affected sites are leg or foot and torso. Given the high percentage of bites experienced while the snake was intentionally being handled, these sites are less surprising than reports of snakebites to the tongue and the glans penis.

#### Mortality

The number of deaths from snakebite in the United States ranges from 0 to 14 per year. Most snakebite deaths are associated with the absence of medical care, bites to the face or throat, errors in medical management, or the presence of an underlying medical condition. Children are at increased risk for serious sequelae because of their lower body mass and the relatively high venom dose per kilogram of body weight compared with adults.

#### Prevention

Historically, Native Americans used numerous plants, animal tissues, oils, and excrement to prevent snakebites. Box 358-2 provides current practical suggestions for preventing snakebites that are based on the epidemiologic

### BOX 358-2 Snakebite Prevention

1. Differentiating poisonous from nonpoisonous snakes is impossible without years of experience. Therefore, children should not approach, disturb, play with, capture, or kill any snake. These practices are dangerous for both the human and the snake.
2. Children should not put their hands or feet in places they cannot see. Children should not put their hands or feet anywhere without first looking.
3. Snakes often can be found under rocks, boulders, fallen trees, fences, rubbish piles, and boats that have been left on shore for several hours; in tall grass and heavy underbrush; or sunning themselves on logs, boulders, trees, walls, or cliffs. Extra caution should be used in these areas.
4. The striking distance of a snake is roughly half its length. Children should be taught to keep a safe distance from snakes.
5. The striking reflex remains intact for up to an hour after the snake has died. Dead snakes or snake parts should not be handled directly for this reason.
6. Rattlesnakes are nocturnal feeders and therefore are active after dark. Never gather firewood after dark. Campsites should be set up on open ground, never near wood, rubbish piles, swampy areas, or the entrance of a cave.
7. Children should wear boots when walking in areas endemic for snakes.
8. Children should not be allowed to walk alone in an area endemic for snakes.
9. Children should not be allowed to swim in waters known to be infested with snakes.
10. Once bitten, everyone present should get away from the snake as quickly as possible. The benefit of identifying the snake is small in comparison to the risk of additional bites.

mechanism of these injuries and the medical community's understanding of snake behavior.

### Characteristics

Some key characteristics can help distinguish between venomous and nonvenomous snakes; however, overlap and exceptions create difficulty in distinguishing the difference (see Table 358-3). Crotalinae are characterized by a heat-sensing pit on either side of the head between the eye and the nostril. This apparatus is used to locate and estimate the size of prey and predators. The snake can estimate a venom dose in accordance with the size of the prey that is to be immobilized, killed, and digested.

Crotaline snakes have highly mobile, retractable, hollow fangs that function similarly to a hypodermic needle. They usually penetrate to subcutaneous tissue, but large snakes can reach a depth of 8 to 19 mm. The speed of a pit viper's strike has been clocked at 8 feet per second, and the animal can reach distances of approximately one-half of its body length. Consequently, larger snakes may penetrate dermal or subcutaneous structures and deposit venom into the muscle. Venom



**Table 358-3** Characteristics of Venomous Versus Nonvenomous Snakes<sup>a</sup>

CHARACTERISTIC	VENOMOUS SNAKE	NONVENOMOUS SNAKE
Triangular head shape	+	+/-
Elliptical pupils	+	+/- <sup>b</sup>
Single row of subcaudal scales	+/- <sup>c</sup>	+/-
Presence of fangs	+	+/-
Pit sensor	+	-
Rattle	+/-	-

<sup>a</sup>+ indicates present; -, absent.<sup>b</sup>Some North American boas have cat's-eye pupils.<sup>c</sup>Coral snakes have a double row of scales.

is generally absorbed through the lymphatic system, although rare cases of intra-arterial and intravenous deposition of venom have been reported. For an envenomation to take place, the pit viper must be venomous at the time of the strike, penetrate the skin, and inject venom during penetration. Approximately 20% to 25% of pit viper bites are *dry*, meaning they do not result in envenomation.

Crotaline venom is a complex mixture of biologically active proteins and peptides capable of damaging vascular endothelial cells, leading to increased permeability to plasma and erythrocytes into the extravascular space, which can ultimately result in hypotension and shock. This process may also occur in the lungs, myocardium, kidneys, peritoneum, and central nervous system. Other enzymes specific to pit viper venom include proteolytic enzymes, hyaluronidase, thrombin-like enzymes, phospholipase-A<sub>2</sub>, L-amino acid oxidase, collagenase, RNase, DNase, and arginine ester hydrolase. Venom is spread throughout the body as a result of the action of hyaluronidase and its integrity-reducing effect on connective tissue.

Pit viper venoms, which are derived from the salivary glands, are designed to immobilize and digest prey. Prominent effects include direct tissue injury resulting from enzymatic degradation. Local inflammatory responses are exaggerated by metalloproteinases, which cleave pro-tumor necrosis factor alpha (TNF-α), releasing activated TNF-α. Myotoxin-α acts to increase intracellular calcium in skeletal muscle, resulting in prolonged contraction and necrosis. The presence of systemic myotoxin-α and phospholipase-A<sub>2</sub> is thought to be the cause of myonecrosis and rhabdomyolysis. Phospholipids A<sub>2</sub> also increase permeability of red blood cell membranes, changing their morphology and potentially causing hemolysis. One of the byproducts of the enzymatic action of phospholipase-A<sub>2</sub> is lysolecithin, which can damage mast cell membranes and cause histamine release.

A coagulopathy caused by fibrinolysis and thrombin-like peptide actions may result in isolated defibrination. Thrombocytopenia occurs as a result of platelet aggregation at sites of tissue injury and from a direct effect of venom on individual platelets, particularly rattlesnake venom. Given that thrombocytopenia and defibrination both occur independently, the physician must distinguish between these processes occurring

### BOX 358-3 Indigenous Locations for North American Pit Vipers

#### SOUTHEAST

- Cottonmouths and copperheads<sup>a</sup>
- Eastern diamondback (*Crotalus adamanteus*)
- Timber (*Crotalus horridus*)
- Southeastern pygmy rattlesnakes (*Sistrurus miliarius barbouri*)

#### MIDWEST

- Cottonmouths and copperheads<sup>a</sup>
- Eastern diamondback (*Crotalus adamanteus*)
- Timber (*Crotalus horridus*)
- Prairie (*Crotalus viridis*)

#### NORTHEAST

- Cottonmouths and copperheads<sup>a</sup>
- Eastern diamondback (*Crotalus adamanteus*)
- Timber (*Crotalus horridus*)
- Eastern Massasauga rattlesnakes (*Sistrurus catenatus*)

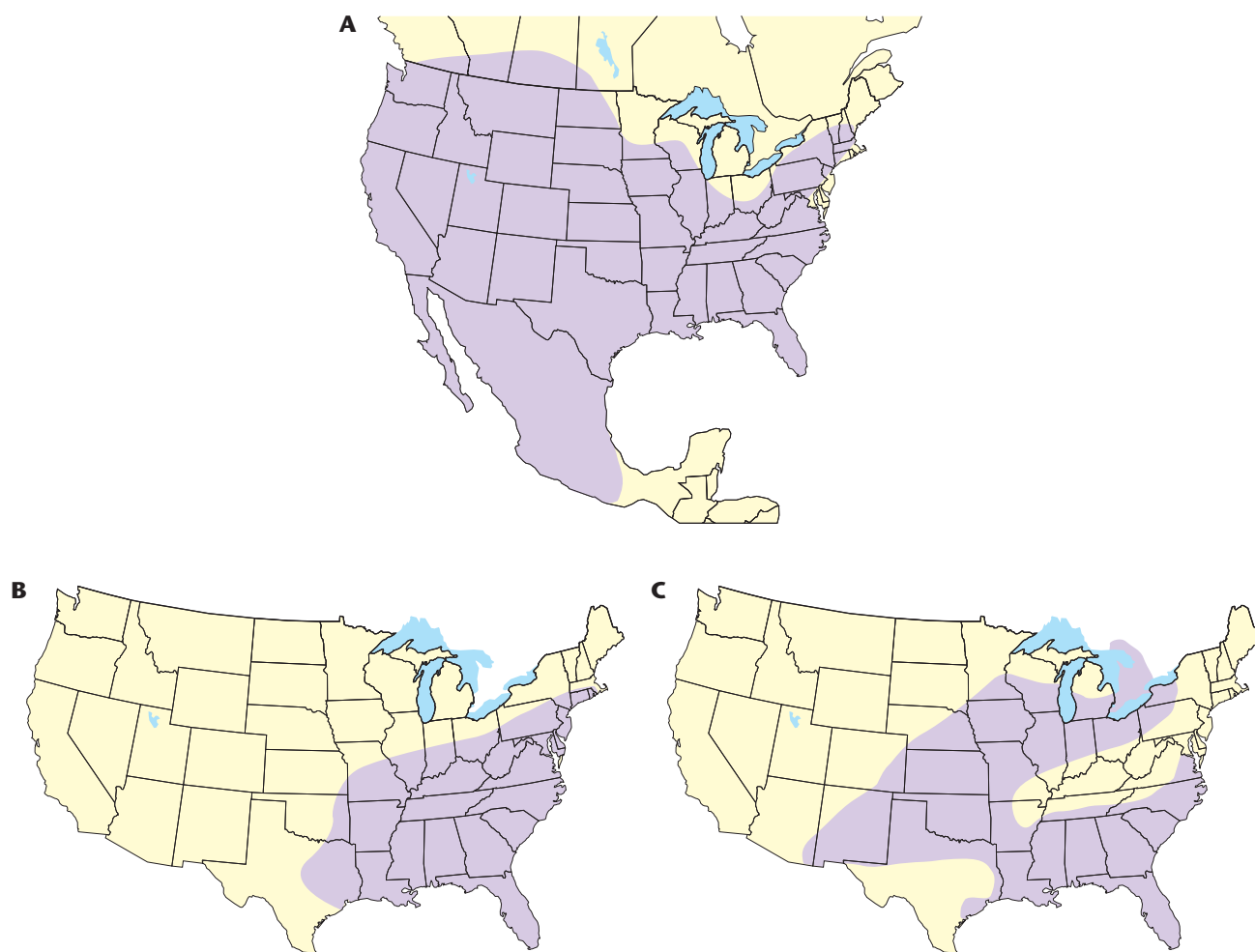
#### NORTHWEST

- Great Basin (*Crotalus viridis lutosus*)
- Northern Pacific (*Crotalus viridis oregonus*)

#### SOUTHWEST

- Western diamondback (*Crotalus atrox*)
- Sidewinder (*Crotalus cerastes*)
- Rock (*Crotalus lepidus*)
- Speckled (*Crotalus mitchellii*)
- Black-tailed (*Crotalus molossus*)
- Twin-spotted (*Crotalus pricei*)
- Red diamond (*Crotalus ruber*)
- Mojave (*Crotalus scutulatus*)
- Tiger (*Crotalus tigris*)
- Prairie (*Crotalus viridis*)
- Grand Canyon (*Crotalus viridis abyssus*)
- Southern Pacific (*Crotalus viridis helleri*)
- Great Basin (*Crotalus viridis lutosus*)
- Ridge-nosed (*Crotalus willardi*)

<sup>a</sup>Agkistrodon speciesDerived from Russell FE. *Snake Venom Poisoning*. Great Neck, NY: Scholium International, Inc; 1983.



**Figure 358-2** Distribution of Crotalinae in North America. (A) *Crotalus*, (B) *Agkistrodon*, and (C) *Sistrurus*. (From Quan D. North American poisonous bites and stings. Crit Care Clin. 2012;28:633–659, with permission from Elsevier.)

simultaneously and true disseminated intravascular coagulation, which may also occur. Neurotoxins are also present in varying degrees, notably in the Mojave and timber rattlesnakes, and can produce weakness and paralysis, as well as myokymia, which appears as involuntary wormlike muscle movements under the skin. The cause of crotaline-induced neurotoxicity remains under study.

The notion that juvenile rattlesnakes are more dangerous than adult snakes is a misconception. The venom of some juvenile rattlesnakes may be slightly more toxic, but larger rattlesnakes are capable of delivering more venom in a single bite. Additionally, venom composition seems to change as the rattlesnake matures. Specifically, phospholipase- $A_2$  activity decreases with the snake's age, but proteolytic activity increases. The clinical relevance of these differences is uncertain.

### Distribution

Native venomous snakes have been identified in all states except Alaska, Hawaii, and Maine.

Box 358-3 lists the indigenous locations for North American pit vipers. See also Figure 358-2.

### First Aid

Commonly accepted guidelines for snakebite first aid are summarized in Box 358-4. Other forms of first aid are controversial (see treatments in number 7 in the table) and are discussed here because the physician may see patients who are less damaged by the snake than by the field treatment of well-meaning but untrained (and possibly inebriated) attendants.

### Identification

The helpfulness of identifying the type of snake is controversial. Snake parts should never be handled directly because the bite reflex in recently killed or decapitated snakes can remain intact, rendering them capable of biting even when they are dead. Snakebite victims should be rushed to medical attention, and the rescue party should not expose themselves to risk while trying to find and identify the snake. If medically necessary, a herpetologist from a zoo or aquarium may be able to help with positive identification.

### Cryotherapy

Cryotherapy is a form of snakebite treatment that is theorized to constrict blood flow, thus diminishing

### BOX 358-4 First Aid for Snakebites (Pre-Hospital care)

1. Don't waste significant time trying to identify the snake. If possible and you are able to keep yourself and others safe and out of the snake's striking range, take a photo of the snake to capture approximate size and characteristics.
2. Move the patient as little as possible.
3. Mark the victim's skin with an indelible pen to indicate the area of swelling and the time. Repeat this every 15 minutes.
4. Remove rings, watches, and constrictive clothing.
5. Immobilize the affected limb by splinting as if for a fracture, and keep the limb below the level of the heart if possible.
6. Regardless of early symptoms, transport the victim to the nearest medical facility at a safe speed.
7. Avoid the use of ice (tissue damage), tourniquet/pressure bandages, aspirin (anticoagulation), alcohol or sedative drugs (vasodilation), or stimulants such as caffeine (acceleration of venom absorption).
8. Do not use any extraction devices or have anyone attempt to suck out the venom. This will prevent further damage to tissue as well as preventing a second exposure (caregiver) to the venom.
9. As soon as possible, start basic life support, including volume expansion and Trendelenburg position for patients with hypotension.

systemic venom absorption and inactivating the venom enzymes and proteins. Freezing does not inactivate snake venom. Cases of limb ischemia have been reported from cryotherapy. Cryotherapy should not be used to treat snake envenomation.

#### Incision and Suction

Incision at the bite site and suction has shown mixed results in clinical and laboratory trials. Complications of incision and suction include damage to underlying neurovascular structures, increased rate of wound infection, and further tissue damage. Given that no clear benefit has been demonstrated, incision and suction should not be performed.

#### Constricting Bands

Constricting bands that impede blood flow should not be used. Only loose-fitting bands placed in an effort to reduce lymphatic flow have been advocated, but these have not been shown to be of clear benefit. Thus, constricting bands of either type should not be used. Although the routine use of an extractor device for care in the field is not advocated, patients who have an extractor or suction device in place should not remove it until they arrive at a health care facility.

#### Immobilization

Splinting of the affected extremity and placing it in a position below the level of the heart should be performed without delaying transport to a medical

facility. Patients should be kept as calm as possible during transport because agitation hastens venom distribution.

#### In-Hospital Care

Information elicited in the medical history of known envenomations includes the size and species of the snake, the circumstances of the bite (eg, through clothing, alcohol related), the number of bites and body area affected, first-aid methods used, time of bite and transport time, previous snakebite history, allergy to horse- or sheep-derived products (eg, drugs, food, animal products), and tetanus immunization status. The patient's coexisting medical conditions, with special attention paid to the cardiovascular, pulmonary, and neurologic systems, should be factored into the clinical management of the exposure. Snakebites from exotic (nonindigenous) species, which usually occur in zoo employees or in those illegally keeping the snake as a house pet, also occur, and physicians must address this issue as part of the history-gathering process. The clinical presentation and medical management of an exotic bite may differ from bites of North American poisonous snakes.

#### Physical Examination: Signs and Symptoms

##### Local

Local signs and symptoms usually include the presence of 1 or more fang marks, pain, edema, ecchymosis, and erythema from 15 minutes to 4 hours after the bite. The notion that copperhead envenomations are generally benign as compared with other pit viper envenomations is not true. Although ecchymosis and swelling are considered to be less common after copperhead bites, significant local injury after copperhead envenomation has been reported. Pain is present in more than 90% of envenomations, although an exception is the Mojave rattlesnake, the bites of which inflict little or no pain. Fang marks typically have ragged edges, but these edges may be obscured as a result of trauma experienced during the flight from the snake or trauma resulting from first-aid attempts. Because of the presence of hemorrhagic toxins in pit viper venom, blood may ooze from the puncture sites, and hemorrhagic bullae may develop. Muscle necrosis also may become apparent. Lymphangitis and lymphadenopathy with tender regional lymph nodes and warmth in the injured body part may occur as a result of the lymphatic spread of venom components.

##### Systemic

Typical systemic findings may include malaise, weakness, lightheadedness, diaphoresis, visual disturbances, nausea, vomiting, syncope, myokymia, perioral paresthesias, and a metallic or minty taste. More severe systemic effects include altered sensorium, acute respiratory distress syndrome, respiratory depression, hemodynamic instability leading to circulatory collapse, and renal failure. A consumptive coagulopathy is often present in serious envenomations characterized by hemolysis, an unmeasurable international normalized ratio (INR) and activated partial thromboplastin time, hypofibrinogenemia, the presence of fibrin degradation products, thrombocytopenia, and generalized

hemorrhage. When combined with defibrination, venom-induced thrombocytopenia may appear as, or be a contributing factor to, disseminated intravascular coagulation. The Mojave rattlesnake may cause more neurotoxicity, specifically myokymia, than other rattlesnakes.

### Laboratory Studies

Laboratory studies have been found to be of only minor assistance when the severity of rattlesnake envenomation is being assessed. Laboratory studies may be useful early in the course of treatment, however, in determining whether an envenomation has actually occurred. Studies should include a metabolic panel, creatinine kinase, a complete blood count with differential, red blood cell morphology (to assess for spherocytosis), INR and prothrombin time, plasma thromboplastin time, fibrinogen levels, fibrin-split products, and platelet count. If these studies reveal any abnormalities, or if the patient has clinical symptoms, then envenomation must be assumed, and an analysis of electrolytes, urinalysis, blood urea nitrogen, and a blood type and cross-match should be performed. Patients may require further testing as the clinical situation dictates.

### Disposition

After a pit viper envenomation, a patient should be observed in the emergency department for a minimum of 8 hours. The absence of symptoms, systemic findings, or laboratory abnormalities after 8 to 12 hours of observation suggests a “dry bite” in which no venom was released following envenomation. Patients who remain asymptomatic and whose coagulation study results are normal may then be discharged with instructions to return if symptoms develop. Not all patients require treatment with antivenin; many envenomations resolve completely with adequate symptomatic and supportive care. Symptomatic patients and all patients treated with antivenin should be admitted, preferably to an intensive care unit.

### Local Therapy

Local wound care includes gentle irrigation, nonconstrictive immobilization, elevation of the bitten extremity, and close observation for a minimum of 8 to 12 hours to evaluate for the onset or progression of symptoms and thus determine whether antivenin is indicated. Circumferential measurements at several points along the affected limb should be performed at baseline and regularly repeated to monitor the progression of swelling. Intercompartmental pressures should only be measured in cases when the patient's symptoms are consistent with compartment syndrome. The snakebite extremity may seem nearly identical to an extremity with a compartment syndrome. In cases of suspected compartment syndrome, the clinical diagnosis requires objective evidence of increases in compartment pressure to more than 30 mm Hg. Fasciotomy has not been shown to be of benefit, may lengthen the hospitalization, and cause significant long-term morbidity. No evidence exists for the use of excisional therapy, and its use is discouraged. Digital dermatomy may be indicated on clinical grounds.

### Shock

Patients may have a marked decrease in intravascular volume as a result of hemorrhage, third-space fluid loss, vomiting, and diaphoresis. Crystalloid replacement should begin immediately in envenomated patients. In the case of hypotension caused by extravascular fluid shifts or hemorrhage, antivenin therapy should be considered.

### Fluid and Electrolyte Abnormalities

Extensive third-space fluid loss may cause fluid and electrolyte imbalances. Electrolyte and urine output monitoring with fluid and electrolyte replacement with crystalloid is essential.

### Hematologic Complications

The treatment of thrombocytopenia and anemia (caused by hemolysis) may require multiple transfusions. Transfusions of fresh-frozen plasma and cryoprecipitate may be required in severely envenomated patients. Therapy with blood products is rarely effective, however, in the absence of antivenin therapy. Treatment with coagulation factors may actually worsen the coagulopathy by adding more substrate for unneutralized venom, thus increasing the levels of degradation products, which are also anticoagulants. Thrombocytopenia often corrects with antivenin therapy alone, and clotting factor levels rarely improve when blood products are provided without antivenin. Disseminated intravascular coagulopathy caused by snakebite does not respond to heparin; antivenin is the treatment of choice.

### Use of Antivenin

The sole antivenin used from 1954 to 2000 in the United States to treat pit viper envenomations was antivenin (*Crotalidae*) polyvalent (ACP). It was produced by injecting horses with venom from *Crotalus adamanteus*, *Crotalus atrox*, *Crotalus durissus terrificus*, and *Bothrops atrox*. A high incidence of serum sickness and serious allergic reaction was associated with its use. Skin testing was necessary before administration of antivenin. After December 2000, crotaline polyvalent immune Fab (ovine) antivenin (CroFab, BTG International Inc, West Conshohocken, PA) was released. CroFab has replaced the horse serum-based antivenin ACP as the drug of choice for crotaline envenomations, and ACP is no longer manufactured. CroFab is a purified ovine polyvalent Fab immunoglobulin fragment product produced by immunizing sheep with venoms of 4 crotaline snakes: *C. adamanteus* (eastern diamondback), *C. atrox* (western diamondback), *Crotalus scutulatus* (Mojave rattlesnake), and *Agkistrodon piscivorus* (cottonmouth). The newest US antivenin for the treatment of snake envenomations received FDA approval in May, 2015. Anavip (*Crotalidae* Immune F(ab')<sub>2</sub> (Equine), a *Crotalinae* equine immune F(ab')<sub>2</sub> antivenin indicated for the management of adult and pediatric patients with North American rattlesnake envenomations, was developed by joint efforts of Rare Disease Therapeutics, Inc. and Instituto Bioclon, S.A. De C.V. However, it has not yet been released and is not available for distribution.



Categorizing envenomations based on their severity is not required when considering antivenin therapy. The early indication for “mild to moderate” envenomation has since been expanded to include severe envenomation. As a result, the indications for CroFab therapy are simply the treatment of patients with North American crotaline envenomations. The manufacturer of CroFab has developed a treatment algorithm that may be useful in guiding the physician when treating a victim of crotaline envenomation ([www.crofab.com/documents/CroFab-Treatment\\_Algorithm.pdf](http://www.crofab.com/documents/CroFab-Treatment_Algorithm.pdf)). The administration of CroFab within 6 hours is advised to prevent clinical deterioration and the occurrence of systemic coagulation abnormalities. However, the delayed use of CroFab has been reported with successful correction of significant toxicity incurred after crotaline envenomation.

Antivenin use should proceed simultaneously with supportive therapy (see Box 358-5). CroFab is administered with the goal of achieving *initial control*, which is defined as the reversal or marked attenuation of all effects of venom. This process encompasses 3 general areas: coagulation abnormalities, systemic effects, and local effects (progression of swelling). Box 358-5 outlines the dosing. If *initial control* is not achieved, then the loading dose of 4 to 6 vials should be repeated until the envenomation syndrome is halted. Once initial control has been established, the manufacturer recommends maintenance doses of 2 vials every 6 hours for 3 doses. However, the decision to omit maintenance doses based on the patient’s clinical status, the type of snake, or consultation with a poison center or toxicologist, should be made on a case-by-case basis. Epinephrine, corticosteroids, antihistamines, and airway maintenance equipment should be provided at the bedside. Volume depletion should be aggressively treated before initiating antivenin therapy because of the risk of rapid vasodilatation and third-space fluid loss associated with anaphylaxis. Anaphylaxis associated with antivenin therapy should be treated in the standard fashion.

Preliminary dosing recommendations for Anavip [Crotalidae Immune F(ab')<sub>2</sub> (Equine)] suggest an initial dose of 10 vials, followed by an additional 10 vials as needed to achieve initial control, with a final 4 vials for re-emergence of symptoms as indicated.

Fab antivenin (AV) therapy is associated with clinical improvement in severe crotaline snake envenomations. Based on the results of a multicenter observational case series study of patients who received FabAV at 17 US hospitals from 2002 to 2004, immediate hypersensitivity and serum sickness rates may be less than described in the FabAV prescribing information.

The use of CroFab in children is loosely defined. Children with crotaline envenomations may be more likely to experience serious effects as a result of the larger ratio of venom to serum volume. Any child with a crotaline envenomation that meets the criteria for antivenin therapy should receive the same dosing regimen as adults. Weight-based (ie, per-kilogram) dosing is not appropriate for antivenin neutralization because the dose should reflect venom load, not patient size.

### BOX 358-5 Steps in Using Antivenin

- 1. Prepare to manage anaphylaxis.** An anaphylactic reaction to CroFab is uncommon but has been reported.<sup>a-c</sup> All patients receiving antivenin should be monitored and 2 sites for intravenous access should be considered—1 for the antivenin and 1 for emergency drugs and fluids. Intravenous epinephrine, diphenhydramine, and plasma expanders, as well as cardiorespiratory support, must be readily available.
- 2. Testing for sensitivity—NOT required.** Unlike the previous horse serum–based antivenin, skin testing is not needed for the administration of CroFab. Pretreatment with epinephrine, H<sub>1</sub>- and H<sub>2</sub>-receptor antagonists, or corticosteroids is not routinely recommended unless the patient has a history of hypersensitivity.
- 3. Start the infusion.<sup>d</sup> The dosing is based on estimated venom injected; no dosing adjustment is required for children.** Each vial of CroFab is reconstituted with 18 mL of 0.9% saline. After reconstitution, the entire dose (4–6 vials) is diluted in 250 mL of 0.9% sodium chloride and mixed by swirling gently. Use reconstituted and diluted product within 4 hours. This dose should be infused intravenously over 60 minutes with careful observation for allergic or anaphylactoid reactions.
- 4. Repeat infusion.<sup>d</sup> If initial control is not achieved,** the loading dose of 4 to 6 vials of CroFab should be repeated until initial control of the envenomation syndrome has been achieved. After initial control has been achieved, additional 2-vial doses of CroFab every 6 hours for 3 doses is recommended. Additional 2-vial doses may be necessary, as guided by the patient’s clinical status and consultation with a physician experienced in treating snakebite envenomations or a regional poison control center.

<sup>a</sup>Holstege CP, Wu J, Baer AB. Immediate hypersensitivity reaction associated with the rapid infusion of Crotalidae polyvalent immune Fab (ovine). *Ann Emerg Med.* 2002;39:677–679.

<sup>b</sup>Dart RC, McNally J. Efficacy, safety, and use of snake antivenoms in the United States. *Ann Emerg Med.* 2001;37:181–188.

<sup>c</sup>Dart RC, Seifert SA, Carroll L, et al. Affinity-purified, mixed monospecific crotalid antivenom ovine Fab for the treatment of crotalid venom poisoning. *Ann Emerg Med.* 1997;30:33–39.

<sup>d</sup>CroFab [package insert]. West Conshohocken, PA: BTG International Inc; 2012.

CroFab use in children ages 14 months to 13 years has been found to be safe and effective.

### Recurrence Phenomena

*Recurrence phenomena* are described as worsening status caused by the return of the venom effect after it has been successfully abated with antivenin. *Local recurrence* indicates the return of swelling after initial control is achieved, and *coagulopathic recurrence* describes the return of thrombocytopenia or hypofibrinogenemia after initial control is achieved. Recurrent coagulopathy has been reported after the use of both ACP and CroFab. With CroFab, the cause of recurrence is probably the clearance of unbound antivenin faster than the absorption and clearance of some venom components. Such may not be the case with

coagulopathic recurrence. All CroFab recipients should be reevaluated at least once during the 5 days after antivenin treatment. The decision to administer additional antivenin in patients who develop delayed coagulopathy must be made on a case-by-case basis. Recent studies indicate that the F(ab')<sub>2</sub> product (Anavip) may be superior at preventing delayed or recurrent coagulation defects versus CroFab, but larger and additional studies are necessary for statistical confirmation of this finding.

An isolated hematologic abnormality after envenomation poses a low risk for significant bleeding, whereas *multicompartment coagulopathies* (critically abnormal INR, activated partial thromboplastin time, fibrinogen, platelets) may represent a risk for bleeding and may warrant additional antivenin consideration. Conservative management for this scenario may be adequate; however, physicians should consult with a clinician experienced in treating crotaline envenomations or with a regional poison control center.

### Antivenin Use in Copperhead Bites

Envenomations by copperheads are not considered to be as serious as rattlesnake or cottonmouth bites. However, clinically significant local effects may occur, suggesting that these bites should be cautiously managed. Furthermore, a retrospective 26-year analysis of annual rates of medical outcomes following copperhead envenomation actually showed significantly *decreased* rates of bites resulting in none or minor effects, with a significant *increase* in rates with moderate outcomes. Those with major outcomes did not significantly change. The victims of copperhead envenomations treated with CroFab had a marked improvement in local tissue effects, but clinical failures and recurrence of local effects also occurred. The use of CroFab in copperhead bites has been shown to halt local tissue effect; however, more data are needed to define the role of CroFab for treatment of copperhead envenomation. The suggested dosing of CroFab in treating a copperhead envenomation is a single loading dose. Additional maintenance doses after initial control did not reduce the incidence of recurrent swelling in one study. After administering the loading dose, the patient should be monitored for progressive swelling, coagulopathy development, and systemic effects. The need for additional antivenin should be evaluated on a case-by-case basis, and a poison control center consultation is advised.

### Prevention and Treatment of Serum Sickness

Delayed reactions to antivenin are thought to be the result of serum sickness-like reactions attributable to immune complexes as a result of an immune response against antivenin proteins. *Serum sickness* is a type-3 hypersensitivity reaction that may occur 7 to 21 days after completion of treatment. Many patients develop serum sickness sometime within 4 weeks after treatment with antivenin, but only a few require hospitalization for this complication. Oral corticosteroids (prednisone) should be prescribed at the first signs (usually urticaria and pruritus) and should be continued for 24 hours after all symptoms have subsided.

The corticosteroid should then be tapered over 72 hours. If necessary, diphenhydramine or hydroxyzine may be added to control pruritus.

### Additional Therapeutic Measures

#### Pain Control

Analgesics should not be overlooked in the management of snakebites. Adequate pain control allows rehabilitation to begin as early as possible to prevent contractures. However, opioid analgesics should be used cautiously if the venom is known to have neurotoxicity (eg, Mojave rattlesnake). Nonsteroidal anti-inflammatory agents should also be used with caution, especially in patients with evidence of coagulopathy.

#### Infection Control

Although snakes have been found to carry a wide variety of bacteria in their mouths (histotoxic *Clostridia*, *Bacteroides*, and many gram-positive and gram-negative aerobes), infection is rare in the absence of severe necrosis, and good wound care is usually sufficient to prevent secondary infections. Systemic and local changes produced by envenomation and the subsequent vascular damage may be difficult to differentiate from infections. If an infection is suspected by clinical or microbiologic evidence, then antibiotic therapy should be instituted. Antibiotic prophylaxis is not currently suggested.

#### Corticosteroids

Corticosteroids should not be used to reduce the inflammation caused by pit viper envenomations. They are not considered a standard of care, and they should not be routinely administered to snakebite victims. However, their use is efficacious in patients who develop serum sickness after antivenin administration.

#### Tetanus Prophylaxis

*Clostridium tetani* are not part of the mouth flora of snakes. Updating the patient's tetanus immunization is the only necessary intervention.

#### Follow-Up Care

The preservation of joint mobility and muscle strength is a goal after pit viper envenomation. Patients who experience full-thickness tissue damage may require referral to a surgeon. Pain control may be needed in the weeks after discharge. If the patient received antivenin therapy, then serum sickness should be discussed and the patient taught how to monitor for this syndrome. Physical or occupational therapy may also be needed to encourage the joint mobilization of the affected extremity. Patients who develop coagulopathy during hospitalization should have follow-up coagulation studies performed on an outpatient basis following discharge.

### CORAL SNAKES

Coral snakes are the members of the Elapidae family that are indigenous to North America. Although their venom can cause a life-threatening paralysis, coral snakes tend to be small, secretive, and mild-mannered unless provoked. Few bites are reported, and death is rare.

### Characteristics

The Eastern coral snake is often mistaken for the non-venomous scarlet king snake because of similar colorful bands encircling the body. The mnemonic *red to yellow, kill a fellow; red to black, venom lack; head of black, step back, Jack!* refers to the color patterns of these snakes. In the United States, all that needs to be remembered is that the coral snakes have black heads (snouts). The poisonous black-snouted snake has broad red and black bands separated by narrow yellow ones; the non-poisonous variety's snout is red, and its broad red bands are separated by narrow yellow ones bounded on each side by black. Despite these distinctions, many people bitten by coral snakes thought they were handling a harmless scarlet king snake.

Unlike pit vipers, coral snakes lack facial pits, are diurnal, and have fixed fangs and nearly round pupils. Their bites may produce superficial scratches or definite fang marks. Their retroverted teeth gnaw or chew on their prey, which makes coral snakes difficult to shake off. Because they must stay attached long enough for their venom to be deposited around their teeth, 50% of coral snake bites are dry. Elapidae venom is primarily neurotoxic; systemic neurologic symptoms are the rule, and local tissue injury is uncommon. Elapidae venom causes paresthesias and paralysis by inhibiting acetylcholine receptors at the neuronal synapse.

### Distribution

Three types of coral snakes are found in the United States: the Eastern coral snake (*Micrurus fulvius*), the Texas coral snake (*Micrurus fulvius tenere*), and the Arizona or Sonoran coral snake (*Micruroides euryxanthus*). Their distribution is shown in Figure 358-3. The bite of the Sonoran coral snake produces no more than local pain and a small amount of nausea.

### Venom Characteristics

*Micrurus* and *Micruroides* venoms have minimal proteolytic activity but contain hyaluronidase and some

phospholipase-A<sub>2</sub>. The venom contains a neurotoxic compound that blocks acetylcholine binding sites at the neuromuscular junction. Despite the relatively simple composition of coral snake venom, its potency should not be underestimated.

### First Aid

Cryotherapy, incision and suction (including the Sawyer extractor), and constricting bands should not be used in any snakebites, including coral snake bites. The Australian pressure mobilization technique has been used, which involves wrapping the entire bitten extremity with a crepe bandage, elastic bandage, or article of clothing as tightly as possible, then splinting it. This approach is different than first aid for pit viper envenomations because, in this setting, differences in venom characteristics mean that local necrosis is not expected.

### Physical Examination: Signs and Symptoms

#### Local

Erythema and local pain from a coral snake bite are transient or absent. Although most patients have evident fang marks, envenomations have been reported that were not associated with apparent fang marks on close examination.

#### Systemic

Systemic manifestations may be delayed for 12 hours and may appear suddenly. They may include bulbar paralysis with ptosis, dysphagia, dysarthria, excessive salivation, paresthesias, euphoria or apprehension, drowsiness, dizziness, weakness, confusion, nausea, vomiting, diaphoresis, muscle tenderness or fasciculations, tremors, altered sensorium, drowsiness, and ophthalmoplegias that cause visual disturbances. These manifestations may be followed by seizures, respiratory paralysis, and pulmonary hemorrhage. Often unclear is which findings are the result of the venom itself and which are the result of hypoxia.

### Laboratory Studies

Coral snake bites do not mandate routine laboratory screening. Transcutaneous pulse oximetry, arterial blood gases, or both, should be assessed if respiratory insufficiency is suspected.

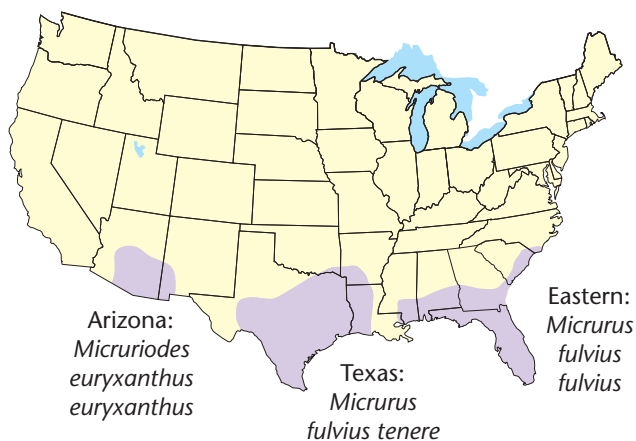
### Supportive Therapy

Elective intubation before impending respiratory paralysis tends to prevent aspiration pneumonia. Elective intubation should be performed if any signs of bulbar paralysis develop. The patient should receive cardiac and pulse oximetry monitoring (if not intubated), and intravenous access should be established.

All victims of potential coral snake envenomation should be admitted to an intensive care unit for close monitoring for a minimum of 12 hours, because the effects of envenomation may develop precipitously hours after a bite and are not easily reversed once they occur.

### Use of Antivenin

Historically, antivenin effective against Eastern and Texas coral snake venom (*M. fulvius*), produced by Pfizer, Inc./Wyeth Pharmaceuticals, was used if a



**Figure 358-3** Coral snake distribution in North America. (From Quan D. North American poisonous bites and stings. Crit Care Clin. 2012;28:633–659, with permission from Elsevier.)



patient had been bitten by a coral snake (positively identified) or if any signs or symptoms of envenomation developed. These guidelines were based on the judgment that the risks of intravenous hyperimmune horse serum are offset by the potential prevention of respiratory paralysis, which may occur if therapy is not immediately administered. At the time of this chapter revision, Pfizer/Wyeth Pharmaceuticals, who is the sole producer of coral snake antivenin, will no longer manufacture it. *When present stocks are depleted, there will be no FDA-approved antidote for coral snake envenomation.* Currently, hospital pharmacists can order replacement supplies of North American Coral Snake Antivenin (*Micrurus fulvius*), Lot #4030024 by calling Customer Service at 1-800-666-7248. Though this lot is labeled with an expiration date of February, 2007, the FDA again extended the expiration date from April 30, 2015 to April 30, 2016.

Additionally, there is a trial in Florida currently underway evaluating a novel antivenin, INA2013. Contact the Florida Poison Information Center-Tampa at 813-844-7044 for more information about this clinical trial.

If antivenin is available and the decision to administer it is made, skin testing may be performed but yields many false-negative findings and is of little benefit in making therapeutic decisions. Three to 5 vials of antivenin are mixed in 250 to 500 mL of normal saline, and 1 to 2 mL is given intravenously over 3 to 5 minutes. The medical team must be prepared for anaphylaxis and have necessary drugs and equipment at bedside. If the patient does not exhibit any signs of an allergic reaction, then the remainder of the solution is infused slowly as tolerated. An additional 3 to 5 vials of antivenin-saline mixture may need to be infused if the patient's signs and symptoms do not abate or worsen. Rarely are more than 10 vials of antivenin required for victims of coral snake envenomations.

### Additional Therapeutic Measures

Prophylaxis for infection and tetanus are the same as for pit viper bites. Additional measures may become necessary if aspiration pneumonia develops. Patients should be aware that muscular weakness may persist for 3 to 6 weeks.

## NONINDIGENOUS SNAKES

The variety of imported snakes is too great to detail in this text. If a bite from an exotic species is suspected, then the suggested approach includes local wound care, supportive care, and consultation with experts at a regional poison control center.

### WHEN TO REFER

- Hymenoptera: systemic reactions to be evaluated for immunotherapy
- Arachnids
  - *Loxosceles*: surgical intervention necessary for wound care
  - *Latrodectus*: before administration of antivenin therapy
- Snakes
  - *Tarantulas*: hairs in eyes that are not easily removed
  - *Scorpions*: considered use of antivenin
  - *Pit vipers*
    - Considered use of antivenin
    - Surgical intervention necessary for wound care
  - *Coral snakes*: anticipated need for airway control or intensive care unit monitoring

### WHEN TO ADMIT

- Hymenoptera: severe systemic allergic reactions or severe systemic reactions caused by massive envenomation
- Arachnids
  - *Loxosceles*
    - Secondary infection requiring intravenous antibiotics
    - Inability to provide adequate wound care at home
    - Presence of systemic symptoms, as severe hemolysis can occur quickly
  - *Latrodectus*
    - Severe systemic symptoms
    - After use of antivenin
  - *Tarantulas*
    - Significant comorbidity
    - Inability to tolerate oral fluids
  - *Scorpions*
    - Cardiac or neurologic toxicity
    - Severe systemic signs or symptoms
- Snakes
  - *Pit vipers*: symptomatic envenomation
  - *Coral snakes*: chance of envenomation

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Bee or Yellow Jacket Sting* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/tips-tools/Symptom-Checker/Pages/Bee-or-Yellow-Jacket-Sting.aspx](http://www.healthychildren.org/English/tips-tools/Symptom-Checker/Pages/Bee-or-Yellow-Jacket-Sting.aspx))
- *Insect Bites* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/tips-tools/Symptom-Checker/Pages/Insect-Bites.aspx](http://www.healthychildren.org/English/tips-tools/Symptom-Checker/Pages/Insect-Bites.aspx))
- *Your Poison Center Brochure* (Web page), American Association of Poison Control Centers ([www.aapcc.org/prevention](http://www.aapcc.org/prevention))

### Medical Decision Support

- *2013 Annual Report of the American Association of Poison Control Centers' National Poisoning and Exposure Database* (article), American Association of Poison Control Centers ([aapcc.s3.amazonaws.com/pdfs/annual\\_reports/2013\\_NPDS\\_Annual\\_Report.pdf](http://aapcc.s3.amazonaws.com/pdfs/annual_reports/2013_NPDS_Annual_Report.pdf))
- *Health Care Providers* (fact sheet), American Association of Poison Control Centers ([www.aapcc.org/prevention/health-care-providers](http://www.aapcc.org/prevention/health-care-providers))
- *Moccasin Envenomation* (Web page), Medscape ([emedicine.medscape.com/article/771329-overview](http://emedicine.medscape.com/article/771329-overview))
- *Snakes of Arizona* (Web page), Reptiles of Arizona ([www.reptilesfaz.org/snakes.html](http://www.reptilesfaz.org/snakes.html))



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## Chapter 359

# ESOPHAGEAL CAUSTIC INJURY

Robert L. Ricca, MD; George T. Drugas, MD

Caustic injury of the esophagus is a major, although preventable, pediatric public health concern. Despite an increasing public awareness and prevention strategies, unintentional and intentional ingestion of agents remains a significant cause of morbidity and mortality in this country. Corrosive esophageal injuries continue to occur in the United States in spite of federal legislation mandating preventive packaging and labeling, injury prevention programs designed for children and parents, and laws restricting the potency and availability of caustic substances. Most exposures still occur in young children. Over 35% of all toxic ingestions occurred in children younger than 3 years and nearly 50% occurred in children younger than 6 years in 2013. Household cleaning agents are still among the top 5 substances ingested by children, comprising 7.6% of ingestions by patients in 2013 (down from 9.7% in 2003). In children younger than 5 years, these agents account for 10.4% of all toxic agents ingested.

Boys continue to comprise most patients younger than 13 years. In children over 13 years, when intentional ingestion becomes more prevalent, there is a preponderance of girls. Despite this seemingly large number of exposures, less than 9% of all fatalities from human ingestion occurred in the pediatric (<19 years) population in 2013. Twenty percent of caustic ingestions result in some form of esophageal injury, and, although death from caustic ingestion is rare (3.2% of all pediatric deaths from ingestion in 2010 due to household cleaning agents), the morbidity can be devastating. Medical treatment for corrosive esophageal injury is reasonably well established, but best surgical management remains debatable and can entail rather complex procedures with significant

long-term functional, cosmetic, and psychological sequelae. A concerning development in the changing spectrum of esophageal ingestion injury is the increase in household use and ingestion of lithium battery cells. There has been a 6.7-fold increase in the percentage of button battery ingestions with major or fatal outcomes from 1985 to 2009, according to the National Poison Data System.

### PATHOPHYSIOLOGIC FEATURES

The extent of injury after a caustic ingestion depends on the type of agent (acid versus alkaline), whether the substance was liquid or solid, the concentration, the volume ingested, and the duration of contact between the substance and the mucosal lining. Additionally, agents with a pH under 2 or over 12 are extremely corrosive. Solid or powder substances adhere to the oropharynx, maximally burning focally with sparing of the esophagus. Liquids rapidly reach the esophagus and stomach, causing greatest damage to these more distal sites. Alkaline substances are more available than acidic substances in Western countries and are involved in most corrosive ingestions. Household bleaches, drain cleaners, automatic dishwasher detergents, anhydrous Benedict's reagent tablets, and denture cleaning tablets are common alkaline household products. Common household acids are toilet bowl cleaners, rust removers, battery fluids, and swimming pool cleaners (Table 359-1).

Ingestion of liquid laundry detergents and dishwasher solutions found in the home usually results in mild esophageal injury that heals without complication. Special consideration should be given to the recent availability of alternative packaging of detergent in pod packets. These packets potentially result in more extensive injury because of higher concentration of detergent despite the smaller volume. Household bleaches have rarely been associated with severe esophageal injury because of their low concentration of sodium hypochlorite. Strong alkalis cause liquefaction necrosis that allows penetration of the corrosive agent transmurally through the esophagus and into adjacent mediastinal tissues. Heat production and small-vessel thrombosis resulting from the reaction compound the initial damage. The ensuing inflammatory reaction can result in gangrene, perforation, mediastinitis, fibrosis, or severe contracture of the esophagus. Lye (sodium hydroxide) is the lay term for the alkaline agent found in most cleaning substances. Liquid lye is the most common cause of esophageal caustic injury and is associated with the greatest morbidity. Lye is odorless, tasteless, and viscous; these characteristics allow it to be easily ingested by children and in massive volumes by suicidal teens and adults. Lye's high viscosity retards transit through the esophagus, making it particularly injurious; tissue injury is rapid in the first few minutes but can persist for hours. Solid alkalis, such as anhydrous Benedict's reagent tablets and batteries, tend to lodge during transit, resulting in focal burns, pressure necrosis, and subsequent perforations at their point of impaction.

Lesions caused by lye injury occur in 3 phases. The acute *necrotic* phase usually lasts 24 to 96 hours after ingestion. An intense inflammatory reaction surrounds

**Table 359-1 Household Agents Causing Caustic Exposures**

CHEMICAL	PRODUCT
<b>ACIDIC</b>	
Hydrochloric acid	Swimming pool cleaners, toilet bowl cleaners, metal cleaners
Hydrofluoric acid	Rust removers
Sulfuric acid	Automotive batteries, drain cleaners
<b>ALKALINE</b>	
Ammonia	Toilet bowl cleaners, hair dyes, floor strippers, glass cleaners
Sodium hydroxide	Anhydrous Benedict's reagent tablets, detergents, laundry powders, paint removers, drain cleaners, button batteries, oven cleaners
Sodium borates, carbonates, phosphates	Detergents, electric dishwasher detergents, water softeners
Sodium hypochlorite	Bleaches, household cleaners, mildew remover

nonviable tissue. During the second *ulceration and granulation* phase 3 to 5 days after injury, superficial necrotic tissue sloughs and is replaced by an ulcerated and inflamed granulation bed. The healing tissue lacks collagen deposition and has very little tensile strength. Although perforation can occur at any point during the first 2 weeks after injury, during this phase (lasting 10–12 days), the esophagus is most vulnerable. The third phase of *scarring and cicatrization* begins during the third week after injury. In this period, contracture of the wound may lead to stricture formation and alteration of lower esophageal sphincter pressure, leading to gastroesophageal reflux.

Batteries can cause injury to the esophagus through multiple mechanisms. Aside from pressure necrosis, batteries can contain mercuric oxide or disperse electrical charge at the negative pole, causing mucosal burn as well as injury to adjacent structures. Additionally, caustic injury may occur from leakage of alkaline material (hydroxide). The most injurious tend to be lithium hydroxide batteries and larger cell batteries over 20 mm in diameter. Even spent cells have sufficient residual voltage and capacitance to generate an external current, produce hydroxide, and cause disastrous outcomes. Rapid identification through radiographic imaging and immediate removal is recommended to mitigate injury. Short exposure time has been shown to still produce severe injury. Exposures of 2 to 3 hours have resulted in major morbidity, including stricture, vocal cord paralysis, requirement for tracheostomy, tracheoesophageal fistula, or potentially life-threatening hemorrhage through aortoesophageal fistula.

Strong acids, unlike alkalis, have an offensive odor and bitter taste that usually results in rapid expectoration after accidental ingestion. Because acids exhibit rapid esophageal transit, they were previously thought to cause more damage to the stomach or intestine; however, recent studies have revealed that acids also cause extensive esophageal injury. Acids cause coagulation necrosis, resulting in superficial eschar formation, which may, in part, limit penetration into deeper tissues. However, a recent retrospective review of more than 200 children with caustic ingestion saw no differences in the incidence of stricture formation after acid or alkali ingestion. Acids and alkalis alike

can induce pylorospasm, resulting in pooling of the caustic agent in the gastric antrum, with extensive damage to this area.

## DIAGNOSIS AND INITIAL MANAGEMENT

After caustic ingestion, symptoms can consist of searing or burning pain of the mouth and lips, drooling or hypersalivation, and difficulty with swallowing. Worth emphasizing is that the absence of pain does not exclude significant injury. Epiglottic or vocal cord edema may result in stridor, dysphonia, or aphonia. Substernal or back pain usually results from esophageal disruption and mediastinitis. Acute epigastric pain may indicate gastric perforation. The presence of fever is strongly correlated with significant esophageal injury. The primary care physician must recognize that the absence of oral burns does not exclude an esophageal burn injury and that 20% to 45% of patients with esophageal burns have no evidence of oral burns. Conversely, oropharyngeal damage does not reliably indicate esophageal involvement; 70% of persons with oropharyngeal injuries do not have esophageal lesions. Bleeding can occur and results from mucosal sloughing, with persistent ooze from the exposed submucosa or muscularis. Life-threatening hematemesis from the development of an aortoesophageal fistula is, however, a rare event. Tracheoesophageal fistula is another rare complication seen with injury to the anterior wall of the esophagus. No single symptom, sign, or combination has been found to predict accurately the degree of esophageal injury after corrosive ingestion.

Every attempt should be made to identify the agent ingested. In the case of young children, parents are usually aware of the offending agent and often bring the container to the emergency department. With suicidal intent, the caustic agent may be unknown. Stridor or aphonia indicate laryngoepiglottic injury and may require urgent orotracheal intubation for airway protection. Occasionally, severe laryngeal destruction necessitates emergency cricothyroidotomy or tracheostomy. Adequate vascular access should be obtained to allow for correction of hypovolemia or hypotension. A chest radiograph may identify concomitant



**Figure 359-1** Esophageal caustic injury from battery ingestion.

aspiration, subcutaneous cervical emphysema, or pneumomediastinum corroborating perforation. A lateral chest radiograph is essential to help distinguish a coin from a battery, the latter prompting emergent endoscopic retrieval. Additional information can be obtained by determining the narrow portion of the battery, which corresponds to the negative charge and adjacent area of necrosis. This can assist with localization of the injury during subsequent endoscopic evaluation. Gastric lavage and emetics should be avoided because of the risk of re-exposing the esophagus to the ingested corrosive agent and because of the threat of aspiration. Any attempt to neutralize an ingested caustic agent poses an additional danger because the resultant exothermic reaction often exacerbates the primary burn injury. Activated charcoal is ineffective and obscures visualization with endoscopy, and is therefore not recommended. Gastric lavage is contraindicated because it may result in propagation of injury beyond the level of the pylorus. Placement of a nasogastric tube should be deferred because of risk of esophageal perforation.

Only after the patient is stabilized should the airway and gastrointestinal tract be inspected. The initial examination should include laryngoscopy. Evidence of a supraglottic or epiglottic burn indicates a risk for airway obstruction and requires endotracheal intubation. Presence of a third-degree burn to the hypopharynx precludes advancement of the endoscope beyond that level. Once the upper airway integrity is confirmed, endoscopy should be performed, even in the absence of oropharyngeal burns, to establish the extent of injury (see Figure 359-1). More than 50% of patients of caustic ingestion will have no evidence of damage to the oropharynx or proximal gastrointestinal tract. A thorough examination, however,

### BOX 359-1 Grading of Caustic Esophageal Burns

- Grade 0: normal
- Grade I: mucosal hyperemia and edema
- Grade IIa: mucosal hemorrhage, exudate, superficial ulceration, sloughing, and pseudomembrane formation
- Grade IIb: IIa plus deep discrete or circumferential ulcerations
- Grade IIIa: deep ulcerations and necrosis, massive hemorrhage, obliteration of the lumen, charring, and perforation
- Grade IIIb: extensive necrosis

Modified from Zargar SA, Kochhar R, Mehta S, et al. *Gastrointest Endosc.* 1991;37(2):165–169. Copyright © 1991, Elsevier, with permission.

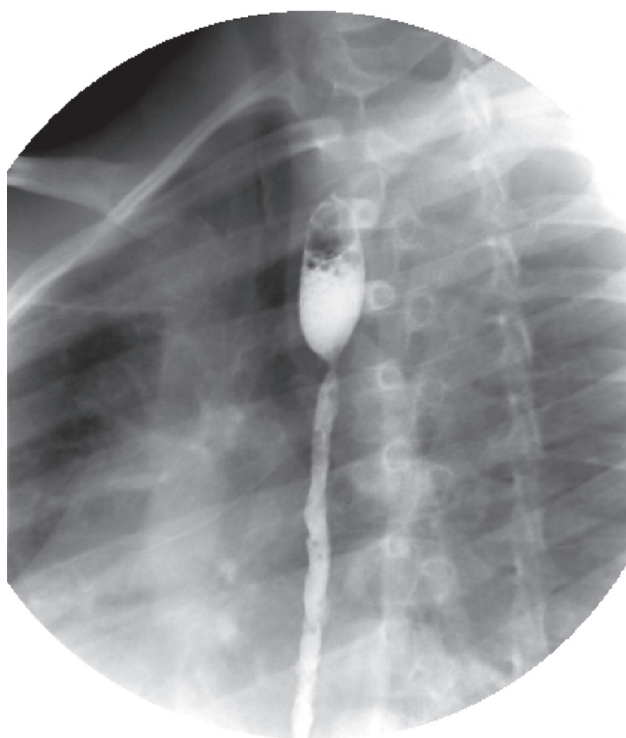
is warranted, because many will have extensive esophageal damage in the absence of oropharyngeal lesions. Flexible, rather than rigid, esophagoscopy is preferred to minimize the risk of iatrogenic perforation. Most endoscopists, fearing perforation, will advance the scope only to the level at which maximal injury is encountered; others advocate full examination of the stomach and, if possible, the duodenum. The degree of injury can be graded similarly to that of thermal skin burns and holds similar prognostic implications (Box 359-1). Accurate assessment by an experienced endoscopist can guide therapy for severe injury and avoid unnecessary treatment for patients with mild or no injury. Endoscopy only allows examination of superficial mucosa, which makes differentiating between grade-IIb and grade-III lesions difficult. Circumferential burns limit full visualization with endoscopy, and contrast radiography may be required for identification of grade-III injuries. Contrast radiography uses water-soluble contrast followed by thin barium (Figure 359-2). Batteries should be removed from the esophagus emergently, typically by endoscopy, preferably within 2 hours of ingestion. Endoscopy will additionally allow further identification of the negative pole relative to the surface of the esophagus. Batteries that have passed into the stomach, unless ingested with a magnet, can be allowed to pass with expectant management.

### MEDICAL MANAGEMENT

Therapy for a caustic injury to the esophagus depends on the grade assigned at endoscopy. Children with no injury or grade-I injuries are usually admitted and observed for 24 to 48 hours. Children with more severe injuries are admitted to the pediatric intensive care unit for monitoring and management. As with any patient, close attention to the ABCs (airway, breathing, and circulation) is of paramount importance. Aside from the risk for perforation, nasogastric tube placement is not indicated routinely because it may be associated with subsequent stricture formation.

Initially, patients with more severe or extensive injuries may ingest nothing orally and require proper





**Figure 359-2** Esophagram demonstrating long-segment esophageal stricture after lye ingestion in a 2-year-old girl.

fluid resuscitation, nutritional support through total parenteral nutrition, and pain management. After disruption of the mucosal barrier by caustic ingestion, bacterial translocation and secondary bacterial invasion are likely events. This rationale is offered for early institution of prophylactic antibiotic therapy; however, controlled trials do not support antibiotic use, and therefore most experts no longer advocate empirical therapy. Vigilance for mediastinitis or systemic infection must be maintained and appropriate antimicrobials reserved for any evidence of local or systemic infection. For grade-II and grade-III injuries, parenteral nutrition is begun and oral feedings are withheld until the dysphagia of the initial phase has regressed and no evidence exists of clinical or radiographic deterioration.

Proton pump inhibitors should be prescribed, because loss of lower esophageal sphincter tone occurs secondary to corrosive esophageal injury, and acid reflux can exacerbate the underlying injury and accelerate stricture formation. The use of steroids to limit fibrosis after caustic injury has debatable efficacy in humans. Most studies demonstrate a lack of proven benefit, and the potential side effects of steroids argue against routine use. Strictures after grade-I and grade-IIa injuries are rare, and follow-up contrast esophagography is unnecessary. After grade-IIb and grade-III injuries, a barium esophagram for the early detection of stricture development is performed 2 to 4 weeks later. Multiple animal studies with a variety of agents (heparin, epidermal growth factor, caffeic acid phenethyl ester) have

demonstrated varying degrees of success in ameliorating stricture formation, but none of these agents have been studied in humans.

## SURGICAL INTERVENTIONS

Initial therapy begins with endoscopy, which can rapidly ascertain the extent of injury as well as the possible need for immediate surgical therapy, including esophagectomy. If immediate surgical management is not needed and medical management is required, then repeat endoscopy is used for those patients at an increased risk for developing stricture (higher-grade injuries) or those patients whose symptoms arouse concern for stricture development. Initial treatment of esophageal stricture following caustic ingestion is through repeat endoscopy and subsequent dilation of the stricture. While initial studies looking at esophageal dilation did not show promising results, more recent studies have been more optimistic. Primary treatment with esophageal dilation offers a satisfactory outcome for most otherwise healthy children with grade-IIa injuries. However, repeated dilation is rarely successful for the most severe corrosive strictures, and early surgical resection is associated with a better outcome. Esophageal dilation to prevent adhesion formation in the injured segment, intraluminal stenting, and prolonged esophageal rest (maintenance of nothing-by-mouth status; total parenteral nutrition) have all been proposed for prophylaxis against stricture formation, but none has demonstrated a proven benefit. Because the risk of perforation is highest in the first weeks after injury, most experts advocate waiting 6 weeks before initiating dilation therapy. Dilation can be accomplished by 2 methods—passing graded bougies over endoscopically or radiographically placed guide wires (pulsion dilation), or using endoscopically or radiographically controlled balloon dilation (radial dilation). Dilation with bougies passed endoscopically is difficult with tortuous or complicated strictures and warrants fluoroscopic guidance. Dilation is typically performed every other week with the goal of dilating the stricture to 18 mm, which is the required diameter for normal swallowing. Typically, 3 or more dilations are required to achieve this goal. Early or aggressive dilation may result in further injury to the esophagus. The reported incidence of rupture resulting from dilation ranges from 17% to 32%. Esophageal rupture is a potentially fatal complication of dilation and warrants immediate surgical repair. In addition to the risk of perforation, serial dilations are also complicated by dysphagia between treatments, which may precipitate pulmonary aspiration. An adequate lumen is usually attained within 6 months to 1 year, with progressively longer intervals between dilations. Consider esophageal replacement if dilation is ineffective beyond 1 year.

Esophageal stenting may be used alone or in combination with dilation to treat esophageal stricture. A recent study looking at 79 children using a custom-made stent in addition to acid blockade and steroids showed promise in preventing stricture formation. Seventy of the 79 children treated were able to be managed with stenting alone, thereby avoiding further surgical therapy. Many of



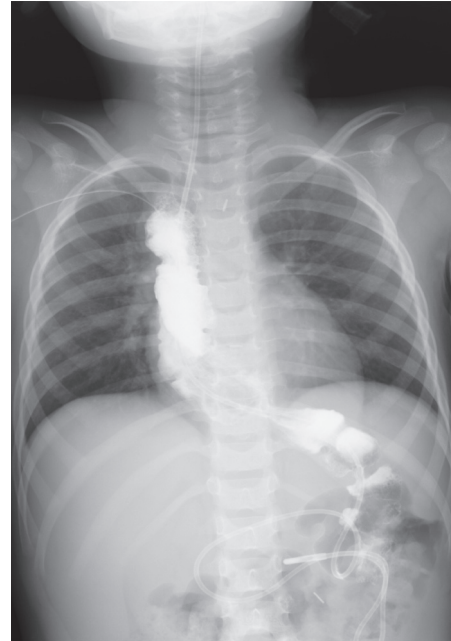
these children still required esophageal dilation following stent removal but were able to avoid the morbidity and mortality of major esophageal surgery. A second, smaller study looked at the use of available nitinol stents in 8 children with esophageal stricture. Short, 6-month follow-up revealed improvement in dysphagia scores and tolerance of oral feedings, and only 2 children required further esophageal dilation. Severe complications, including stent migration and erosion of the stent, have been reported in the literature. Further improvements in stent design and deployability continue to make this an attractive alternative in the armamentarium of surgical management.

For children who present with severe caustic injuries, early surgical intervention is vital and can be lifesaving. Full and immediate resection of devitalized tissue is necessary to prevent expansion of the corrosive injury. Delay in diagnosis of an esophageal perforation can be fatal, and a high index of suspicion in grade-II and grade-III injuries must be maintained. The presence of peritonitis, pneumoperitoneum, or clinical deterioration, as evidenced by refractory acidosis, neurologic decline, or coagulopathy, requires immediate surgical intervention. Complete surgical exposure of the foregut—esophagus, stomach, and duodenum—is necessary to assess the extent of the damage and allow for possible resection. Full-thickness injury to the stomach or duodenum invariably predicts severe esophageal injury and is an indication for complete esophagogastrectomy. Full-thickness circumferential injury to the esophagus carries 20% mortality, mandating surgical resection. Conservative management, including later esophageal dilation, may be considered for short segments of full-thickness esophageal mucosal damage. If any question persists after the initial exploration, then a second-look operation (often within 24 hours) is required.

Surgical management is required for the most severe corrosive injuries and for intractable esophageal strictures. The surgical options include bypass with placement of an esophageal substitute or resection, or both, or esophagoplasty (Figure 359-3). Bypass with complete esophageal resection is the preferred approach, because retained proximal esophagus may distend and form a mucocele or abscess; distal esophagus may develop reflux esophagitis, ulceration, and hemorrhage; and retained esophagus carries increased risk for malignant transformation. Resection, however, is not without risk; the extensive dissection necessary to remove the damaged esophagus can result in significant morbidity. Colonic interposition, gastric advancement, gastric tube esophagoplasty, and jejunal interposition are accepted procedures to replace the injured esophagus. Esophagoplasty with a colonic patch over less extensive but persistent strictures has also been used in the management of focal strictures. Decisions regarding surgical management are based on patient age, general health, severity and extent of stricture, and risk of long-term complications.

## DELAYED COMPLICATIONS

Long-term complications of corrosive ingestions include stricture formation (see Medical Management),



**Figure 359-3** Colonic interposition in a child 6 months after esophageal injury. This is the same child in Figure 359-1.

gastric outlet obstruction, and esophageal carcinoma. Not surprisingly, the long-term morbidity after corrosive esophageal ingestion correlates with the grade of injury. Gastric outlet obstruction occurs in approximately 9% of corrosive ingestions and is characterized by early satiety and weight loss. The obstruction can occur years after the initial injury and follows acid or alkaline ingestions with equal frequency. The treatment of gastric outlet obstruction is surgical, and balloon dilation of the pylorus, pyloroplasty, and Billroth I reconstruction are all effective. The type of operation performed depends on findings at laparotomy and surgeon preference.

For patients in whom the native esophagus is retained, the risk of post-corrosive esophageal carcinoma is estimated to be 1,000- to 3,000-fold higher than the incidence for esophageal cancer in the general population, and up to 3% of patients with esophageal carcinoma have a history of corrosive ingestion. These squamous cell carcinomas usually originate in the mid-esophagus. Local dissemination occurs infrequently, so the potential for curative resection is slightly improved over primary esophageal malignancies. The interval between burn injury and the development of carcinoma ranges from 10 to 70 years, with a mean of 50 years. Long-term follow-up of children who have grade-II and grade-III burns is warranted, regardless of their symptoms. Esophagography and surveillance esophagoscopy should be performed one or two times per year.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Button Battery Injuries in Children: A Growing Risk* (fact sheet), American Academy of Pediatrics ([www.aap.org](http://www.aap.org)).

healthychildren.org/English/safety-prevention/at-home/Pages/Button-Battery-Injuries-in-Children-A-Growing-Risk.aspx)

- *Protect Your Child From Poison* (handout), American Academy of Pediatrics (patiented.solutions.aap.org)

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## Chapter 360 HEAD INJURIES

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Traumatic brain injury (TBI) is the leading cause of death and disability in children. It is estimated that half a million children in the United States experience TBI annually, and TBI accounts for 435,000 emergency department (ED) visits, 60,000 hospitalizations, and 7,400 deaths each year. The financial burden in terms of medical costs and lost productivity has been estimated at \$100 billion per year.

The epidemiology of TBI varies with gender (boys are twice as likely as girls to suffer from TBI) and age. In infants and school-aged children, the major mechanisms of injury include falls from height and from standing, whereas assault, sports injuries, and motor vehicle collisions account for most TBIs in adolescents. For all ages combined, falls are the most common cause of head trauma, but vehicular collisions are the leading cause of TBI that results in serious injury. In most vehicular collisions, the child is a pedestrian. Most children who are hit by a vehicle and have TBI are not supervised by an adult at the time of the accident.

### PATHOPHYSIOLOGIC FEATURES

The brain is covered by 3 layers of meningeal tissue (pia mater, arachnoid mater, and dura mater), followed by the skull bones (calvarium) and scalp, which has a strong layer of tissue (galea aponeurotica). The brain does not adhere to the skull and is able to move freely within it, cushioned to some extent by the cerebrospinal fluid in which it bathes. *Primary brain injury* refers to the neural injury caused by the traumatic insult and presents in the form of contusions, intracranial bleeding, fractures, or diffuse axonal injuries. *Secondary brain injury* refers to the subsequent injury to the neural tissue after a trauma has occurred. It has

numerous causes, including hypoxia, hypoperfusion, excitotoxic damage, free radical damage, or metabolic derangements. Sometimes the damage caused by secondary brain injury is more devastating than that from the primary insult. The most important cause of secondary brain injury is brain ischemia resulting from inadequate cerebral blood flow. Adequate cerebral blood flow depends on the cerebral perfusion pressure, which is the difference between mean arterial pressure and intracranial pressure (ICP). Normally the cerebral perfusion pressure fluctuates inside a narrow range, the result of cerebral autoregulation. However, when this control mechanism is lost because of brain injury and secondary brain tissue damage, an increase in intracranial volume (mainly the result of intracranial hemorrhage or cerebral edema) will lead to a disproportionate increase in ICP. This increase further accentuates neuronal damage by reducing cerebral blood flow. An increase in ICP may lead to cerebral herniation syndromes. These syndromes are characterized by worsening of sensorium, pupillary changes, widening pulse pressure, and the Cushing triad, which includes hypertension, bradycardia, and irregular respirations.

### TYPES OF TRAUMATIC BRAIN INJURY

#### Concussion

*Concussion* or *mild TBI* is defined as brain injury caused by a biomechanical force resulting in alterations in neurologic function. The typical spectrum of symptoms involves changes in memory and orientation and may include loss of consciousness. It is estimated that annually, 3.8 million people suffer from concussions related to sports or recreational activities. This figure is likely a conservative estimate because the number of children participating in organized sports has increased from 40 million in 2000 to 60 million in 2008.

Sports-related concussion is a relatively frequent injury in the United States and occurs commonly in athletes who play American football, ice hockey, soccer, basketball, baseball, and softball. The diagnosis of concussion comprises a constellation of symptoms including physical (headache, nausea), cognitive (feeling mentally “foggy” or slowed down), emotional (irritability, sadness), and sleep (drowsiness, sleeping more/less than usual) changes. On-field evaluation of players with suspected concussions is critical and should be performed by a physician or other licensed clinician. A number of sideline assessment tools are available, such as the Sports Concussion Assessment Tool V.3 (SCAT3), to aid in identification of mild TBI, but the evidence to identify the best diagnostic measures is insufficient. Routine imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is not currently recommended. Those who have been determined to have concussion should be serially monitored on the sideline and not be allowed to return to play on the day of injury; they should have prompt follow-up with their primary physician.

#### Skull Fractures

Skull fractures occur in approximately 2 per 1,000 infants and 0.5 to 1 per 1,000 older children and adolescents. The most common bone to fracture is the parietal

bone. Most fractures can be diagnosed with plain-film radiography or CT with bone windows. Linear skull fractures often require no intervention, although most pediatricians would admit these children for a period of observation. Depressed skull fractures are often associated with underlying brain abnormalities and may require surgical interventions. Basilar skull fractures are often associated with cerebrospinal fluid leakage and cranial nerve damage. These fractures require pediatric neurosurgical intervention and should ideally be managed at tertiary care pediatric trauma centers.

### Parenchymal Injuries

*Cerebral contusions* are bruises of the cerebral cortex that can occur as a result of direct injury (coup injury) or at the opposite point where the relatively mobile brain strikes the bone on the other side (contrecoup injury). Clinical manifestations vary, but patients often exhibit some alteration in consciousness, focal seizures, or focal neurologic findings (eg, cortical blindness in cases of occipital lobe injury). Most cases are diagnosed with CT, and management depends on the extent of injury. Patients may need to be observed with ICP monitoring, and some may require craniotomy for drainage of intracerebral hematomas.

### Diffuse Axonal Injury

*Diffuse axonal injury* is often seen after an acceleration-deceleration or rotational mechanism (commonly called *whiplash*); the damage is at the gray matter–white matter junction. Most children experience changes in sensorium, and some studies have reported that about 82% develop coma. Although some changes with diffuse axonal injury may be seen on CT,

MRI is often diagnostic. Most patients with diffuse axonal injury will need hospitalization along with monitoring of ICP in the intensive care unit.

### Intracranial Hematoma

Although hematomas can occur anywhere in the intracranial space, the 2 most common types are epidural and subdural (Table 360-1).

### INITIAL CARE

Most physicians have little trouble identifying patients who require intensive care at a regional medical center. More difficult is deciding whether to admit the less severely injured child to the hospital for observation. Decisions regarding the hospitalization of less severely injured patients must be made on a case-by-case basis.

The improved prognosis for survival and neurologic recovery after a severe head injury in a child compared with an adult dictates that the physician providing emergency care make every effort to adequately and appropriately resuscitate the child who has a severe head injury. The basic ABCs of resuscitation (airway, breathing, and circulation) should be addressed first. Maintaining normal oxygenation is imperative, as was aptly stated by Haldane in 1919: “Anoxia not only stops the machine but wrecks the machinery.” In addition, ischemia, increased ICP, and uncontrolled seizures may cause further brain injury. The correction of hypotension, hypothermia, hypocapnia, and acidosis is imperative in reducing overall mortality and length of stay in the intensive care unit.

Patients with severe TBI often require assisted ventilation to maintain ICP and benefit from rapid sequence induction for airway management. In the

**Table 360-1** Differences Between Epidural and Subdural Hematomas

CHARACTERISTIC	EPIDURAL HEMATOMA	SUBDURAL HEMATOMA
Mechanism	Direct trauma leads to bleeding from the middle meningeal artery or shearing of epidural veins.	Shaking (acceleration-deceleration) injury leading to tearing of bridging veins in the subdural space. In young children, this may result from child abuse.
Clinical manifestations	Lucid interval—symptom-free interval between time of injury and time of manifestation can be seen in <50% of cases. Patients run the gamut from asymptomatic to those who exhibit focal seizures and coma.	Lucid interval unlikely. Many children exhibit coma, seizures, or evidence of chronic changes (tense anterior fontanel, macrocephaly).
Investigations	CT is diagnostic for a lenticular lesion, which is often seen without an overlying fracture.	CT scans reveal blood collection as a hyperdense crescentic collection along the cerebral hemisphere. In cases of child abuse, hemorrhage of different ages can be seen with changes suggestive of hydrocephalus.
Management	Most small bleeds resolve with supportive therapy; however, if clinically indicated, treatment may involve a craniotomy with drainage of hematoma and repair of the ruptured blood vessel.	Management will vary depending on extent of bleeding, and in some cases ICP monitoring with expectant observation may be the only therapy; intracranial evacuation of blood clot may be the therapy of choice for some cases.
Prognosis	Excellent after initial insult is adequately treated.	Poor with high mortality and high morbidity (sequelae).

CT, Computed tomography; ICP, intracranial pressure.



severely injured patient, the airway requires intubation to ensure adequate ventilation and reduce the chance of developing increased ICP. Close attention to blood pressure is necessary because sedatives may cause hypotension. In the past, prolonged hyperventilation was suggested for patients with acute severe head injury. Although hyperventilation constricts intracranial blood vessels and lowers ICP, concerns exist that it may decrease cerebral perfusion. Meticulous attention must be paid to carbon dioxide pressure in the arterial blood to prevent hypercapnia at all costs, and can be accomplished through the use of end-tidal capnography. Mild hyperventilation to maintain partial pressure of carbon dioxide at 30 to 35 mm Hg is recommended and may be useful in an emergency situation in which the patient's condition deteriorates acutely because of increased ICP.

### History

When taking a history, the possibility of abuse must be kept in mind. Abuse should be considered when families deny any trauma or when they provide a history of minor trauma and the child has life-threatening, severe, or multiorgan injury. For example, children rarely experience a serious injury when they fall out of bed, so such a history, when given as the cause of severe injury, may be an indication of child abuse. Loss of consciousness, seizures, amnesia for the circumstances surrounding the injury, and focal neurologic deficits are indicators of more severe head trauma. Vomiting and headache are common symptoms after head trauma, and their presence, if not persistent or severe, is not particularly ominous or suggestive of a specific pathologic finding. Persistent clouding of consciousness is the most reliable sign of a significant brain injury. In addition, the duration of posttraumatic amnesia, defined as an inability to generate new memories after head injury, correlates positively with the severity of the injury.

### Physical Examination

Examination of the patient should begin with assessment of mental status and assignment of a Glasgow Coma Scale (GCS) score. Neurologic examination should proceed with assessment of the cranial nerves. Particular attention needs to be given to pupillary responses and symmetry, funduscopic examination (to rule out papilledema or hemorrhage), eye movements (to assess for dysconjugate gaze), asymmetries of facial sensation or movement, tongue movement, and gag reflex. As a sensory screening examination, symmetrical responses to pain in all 4 limbs should be determined. Symmetry of muscle tone and movement and of the deep tendon reflexes and plantar responses needs to be determined, as should the alert, cooperative child's ability to manipulate small objects. The child's gait and posture also need to be assessed. The general physical examination should focus on the presence of injury to other body systems and on seeking evidence of physical neglect or abuse.

### Neurologic Evaluation

A more detailed neurologic examination should be performed only when adequacy of the airway, breathing, and circulation are ensured. The GCS, or

a modified GCS for children and infants, can be used to evaluate mental status and is valuable in assessing level of consciousness and in following the child's progress (Table 360-2). The scale is based on the patient's response in 3 areas: motor response, verbal response, and eye-opening response. Severe head injury may be defined as that resulting in a GCS score of less than 9, whereas moderate head injury is associated with a score of 9 to 12. A score of 13 to 15 indicates a mild head injury.

Motor response is evaluated by noting symmetry of tone, movement, and reflexes. Cranial nerve examination may reveal signs of focal injury to the brainstem. Pupil size, symmetry, and reactivity should be noted carefully, and the fundus should be examined for signs of papilledema. Retinal hemorrhages suggest the possibility of abusive head trauma. Pontine and midbrain function may be assessed by examining oculovestibular reflexes. In the unconscious child, the head should be rotated briskly from side to side after making certain that the cervical spine has not been injured. Normally, when the head moves to the right, the eyes move to the left, and vice versa. Loss of these reflex eye movements in a comatose patient suggests an injury to the midbrain or pons. Alternatively, if the tympanic membranes are intact, then ice-water caloric responses should be elicited. With the child's head elevated to 30 degrees, 120 mL of ice water is infused alternately into each ear canal. The eyes should turn toward the irrigated ear. If they do not, then a brainstem injury is likely. The quality and symmetry of the grimace evoked by painful stimulation of the face should be observed. Next, the corneal reflex should be tested, and failure to react by blinking is consistent with pontine injury or deep coma. All the tests should be performed, even if 1 of them is positive. Function is evaluated by assessing the child's gag reflex and tongue movement. The child's craniospinal axis should be examined in concert with the neurologic assessment for signs of trauma. Swelling and bony depression of the skull suggest an underlying fracture. Ecchymoses behind the ear (the Battle sign) or around the orbits (raccoon sign), cerebrospinal fluid rhinorrhea, otorrhea, or hemotympanum suggest a basilar skull fracture. Basilar fractures or scalp lacerations overlying fractures are important to detect because they serve as portals of entry for bacteria into the subarachnoid space and may cause meningitis. Because of the risk for meningitis with any of the prior clinical findings, serial neurologic examinations are critical to provide ongoing monitoring.

### Imaging Studies

The following 5 clinical findings identify 99% of all children with TBI documented with CT and 100% of those who require neurosurgery: abnormal mental status, clinical signs of skull fracture, scalp hematoma, history of headache, and vomiting. A clinical decision rule excludes TBI that needs neurosurgical intervention (negative predictive value of 100%) when none of these 5 clinical variables is present. Use of this rule will reduce unnecessary exposure to CT radiation by 25%. Although CT is the diagnostic test of choice for evaluating children with head trauma, this procedure has disadvantages, including exposure to radiation,



**Table 360-2** Glasgow Coma Scale<sup>a</sup>

EYE-OPENING RESPONSE			
SCORE	>1 Y	≤1 Y	
4	Spontaneous	Spontaneous	
3	To verbal command	To shout	
2	To pain	To pain	
1	None	None	
MOTOR RESPONSE			
SCORE	>1 Y	≤1 Y	
6	Obeys commands	Spontaneous response	
5	Localizes pain	Localizes pain	
4	Withdraws from pain	Withdraws from pain	
3	Displays abnormal flexion to pain (decorticate rigidity)	Displays abnormal flexion to pain (decorticate rigidity)	
2	Displays abnormal extension to pain (decerebrate rigidity)	Displays abnormal extension to pain (decerebrate rigidity)	
1	None	None	
VERBAL RESPONSE			
SCORE	>5 Y	2–5 Y	0–23 MO
5	Is oriented and converses	Uses appropriate words and phrases	Babbles, coos appropriately
4	Conversation is confused	Use inappropriate words	Cries but is consolable
3	Words are inappropriate	Cries or screams persistently to pain	Cries or screams persistently to pain
2	Sounds are incomprehensible	Grunts or moans to pain	Grunts or moans to pain
1	None	None	None

<sup>a</sup>The Glasgow Coma Scale score is the sum of best eye-opening, motor, and verbal responses. Scores range from 3 to 15. Derived from Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet*. 1974;2:81–84.

transport of the child away from supervision in the ED, the frequent need for pharmacologic sedation, additional health care costs, and increased time for completing the ED evaluation. Therefore, cranial CT scans should be used selectively in the ED evaluation of children with minor blunt head trauma.

A landmark prospective study conducted on children with minor head injury helped to reduce the use of unnecessary CT scans in children. Kuppermann and colleagues enrolled 42,412 patients younger than 18 years presenting within 24 hours of head trauma with GCS scores of 14 or 15. They aimed to identify children at very low risk for clinically important TBI, for whom CT might be unnecessary. They identified clinical criteria or a prediction rule for children younger than 2 years—normal mental status, no scalp hematoma except frontal, no loss of consciousness or a loss of consciousness for less than 5 seconds, nonsevere injury mechanism, no palpable skull fracture, and acting normally according to the parents. The criteria for children aged 2 years and older were normal mental status, no loss of consciousness, no vomiting, nonsevere injury mechanism, no signs of basilar skull fracture, and no severe headache. Using these criteria, which can easily be done in the clinical setting, most patients not requiring a CT scan could be identified.

In children who have a known severe head injury or are found unconscious after a sports-related

injury, coexisting cervical spine damage should be assumed until proved otherwise. Clinically significant cervical spine injury is rare in children, occurring in about 1% to 2% after blunt trauma. However, if there is a high index of suspicion, the neck should not be moved until imaging studies are completed. Appropriate immobilization requires placing the head and neck in normal anatomic alignment, which will vary depending on the age of the child. Younger children have proportionally larger heads, resulting in cervical flexion in the supine position and requiring elevation of the body to achieve correct positioning. Adult data recommend CT of the cervical spine as the imaging modality of choice, yet because of the concern for ionizing radiation in children, plain radiographs are still the initial imaging modality of choice. CT is reserved for more diagnostic certainty or if the physician is sufficiently concerned. Plain films should include cross-table lateral, anteroposterior, and odontoid views.

### Secondary Brain Damage

After TBI has been detected and the patient resuscitated, the subsequent management is directed at preventing secondary insults. The most important causes of secondary brain damage are hypoxia, systemic hypotension, and raised ICP (intracranial hypertension). To the degree possible, these situations must be

prevented. Vital signs should be frequently assessed to ensure adequacy of circulation. Shock leads to further brain injury despite adequate airway management and oxygenation. Vigorous fluid therapy to restore adequate circulating blood volume and sufficient cerebral perfusion is essential. Isotonic solutions or blood products should be administered because hypotonic solutions may promote movement of free water into damaged brain tissue, increasing the potential for cerebral edema. Some authorities have even argued for the use of hypertonic solutions in acute severe brain trauma, but this approach is not widely used. If the child is in shock, then a source of bleeding should be sought. Patients rarely sequester sufficient blood volume in the head to produce shock (notable exceptions include the infant with an expansible skull and the presence of a large subgaleal hematoma). Additional measures directed at reducing secondary brain injury include elevating the patient's head 30 degrees and keeping it in a midline position to maximize venous outflow from the cranial vault.

Intracranial pressure should be monitored and lowered if necessary. Placement of an intracranial ventricular catheter is the most accurate and reliable method for monitoring ICP. Intracranial hypertension is defined as a sustained ICP of more than 20 mm Hg. The Cushing triad is an ominous sign that implies increased ICP. This response and unilateral pupillary dilation (a sign of impending catastrophic temporal lobe herniation) should prompt administration of hyperosmolar therapy (preferably hypertonic saline, also mannitol) as a temporizing measure before obtaining an emergent CT scan. Reduction of cerebral metabolism by initiating barbiturate coma may improve outcomes and should be considered when pediatric neurosurgeons and pediatric intensive care units are available. The role of therapeutic hypothermia in the treatment of children with severe TBI is still unclear. Corticosteroids do not improve outcome when used in the acute phase management of TBI.

Antipyretics should be administered if the child has a fever. Hyperthermia may increase cerebral metabolic demands, further taxing delivery of nutrients to the injured brain. Similarly, seizures greatly increase the metabolic demands of the brain and should be treated promptly with intravenous diazepam or lorazepam, followed by intravenous phenytoin or levetiracetam. The latter should not be provided if the child is pharmacologically paralyzed because it results in an inability to detect seizure activity. Intravenous phenytoin is also advisable before transfer to another medical center. It may be difficult to see clinical seizures in children who are in the intensive care unit because of multiple factors, including altered mental status and the use of sedatives and paralytics. For this particular group of children, it may be beneficial to use continuous video-electroencephalography to avoid missing both clinical and subclinical seizure activity.

## TREATMENT

The acute care of patients presenting with TBI depends on the level of severity. The low-risk category

includes children younger than 2 years who have a GCS of 15, no signs of altered consciousness, no scalp hematoma except for frontal, and no significant mechanism of injury. These patients do not require imaging and typically only need monitoring in the ED and discharge home with a reliable caretaker. The same holds true for children older than 2 years who have a GCS of 15, no altered mental status, no signs of basilar skull fracture, no history of vomiting or headache, and no significant mechanism of injury.

Intermediate-risk children who are younger than 2 years have nonfrontal scalp hematoma, loss of consciousness for more than 5 seconds, caretakers concerned about current behavior, or high-force mechanism of injury. For patients in this risk category older than 2 years, the characteristics include history of loss of consciousness, history of emesis, severe headache, or significant mechanism of injury. Cases in this category can be managed in 1 of 2 ways: with a 4- to 5-hour period of observation and re-evaluation or with a head CT scan.

High-risk patients of any age have any of the following characteristics: GCS score of 14 or less, depressed mental status, focal neurologic findings, signs of depressed or basilar skull fracture, seizure, irritability, acute skull fracture, and bulging fontanel. All high-risk patients require a cranial CT scan.

Further management for high-risk cases may include endotracheal intubation with avoidance of hypoxemia, hypercarbia, hypotension, and hyperthermia. It is crucial to closely monitor the neurologic examination, heart rate, and blood pressure to observe for signs of impending herniation. When there is a concern for herniation, osmotic agents are typically used to reduce brain tissue edema; the agents of choice include mannitol and hypertonic saline.

## DISCHARGE HOME

Children with mild head injury who promptly recover their neurologic function, who are not suspected of being abused, and who have reliable caregivers can be discharged home with appropriate instructions. Children with normal neurologic examination findings and negative CT scans rarely have neurologic deterioration after discharge from the ED. Parents are often instructed to observe the child carefully for at least 24 hours, but they are not required to periodically awaken the child from sleep. Caregivers should return immediately to the ED if the child cannot be awakened, demonstrates decreasing mental status while awake, or develops seizures, focal weakness, increasing headache, progressive instability, or vomiting to the point of dehydration. Linear skull fractures do not require admission to the hospital if the child is asymptomatic, but they do require close observation because the force required to fracture a child's skull is significant. A reliable observer at home is required. Physicians are required to report any suspected cases of child abuse, and those children who have suffered abusive head trauma may require hospital admission for protective placement.

After hospital or ED discharge, the family should contact their pediatrician the following day and schedule an office follow-up at 1 to 2 weeks. The child's

recovery can be reviewed and further anticipatory guidance provided to the family regarding relevant neurologic sequelae of the child's head injury. Children should have between 1 and 3 days of complete cognitive rest, which includes abstaining from school, homework, cell phones, computers, video games, and television. Before returning to school, the child should be completely asymptomatic and able to perform basic academic skills without worsening symptoms. Time at school and workload should be gradually increased as tolerated with the coordination of the school teachers, counselors, and physicians. For athletes, a return-to-play protocol has been recommended by a consensus statement from the Fourth International Conference on Concussion in Sport. It is a 6-step approach with the child spending at least 24 hours in each step. It progresses from no activity to light exercise, then sport-specific exercise, then non-contact training, then full-contact practice, and finally return to play. Children younger than 2 years who have diastatic fractures (fractures that involve normal suture lines) should be evaluated again in 6 to 8 weeks to check for a *growing fracture*. These enlarging fractures occur as a result of leptomeningeal cyst formation, and they frequently require neurosurgical closure.

## PROGNOSIS

Children who experienced mild head trauma (GCS score of 13–15) are indistinguishable from their peers 1 year after their injuries. Despite this fact, significant neurologic dysfunction may be seen in the period immediately after the child's injury and may persist for weeks to months. Most children with mild TBI will have complete recovery from symptoms within 7 to 10 days; however, about 10% may have ongoing symptoms beyond 2 weeks. Those with persistent symptoms may be encompassed under the clinical criteria of postconcussion syndrome. The definition according to the World Health Organization *International Classification of Diseases*, 10th edition includes 3 or more of the following: fatigue, sleep disturbance, headache, dizziness, irritability, affective disturbance, apathy, or personality change. Most postconcussive symptoms resolve on their own after 1 month with adherence to the treatment recommendations stated in the 2012 Consensus Statement on Concussion in Sport with regard to return to school and play. However, in children who continue to have deficits, studies have found neurocognitive rehabilitation to improve neuropsychological testing scores and cognitive function. For those with vestibular disturbances such as dizziness and impaired gait, vestibular rehabilitation has been shown to be efficacious.

Children who have moderate head injury (GCS score of 9–12) and severe head injury (GCS score of 3–8) may suffer from multiple physical, cognitive, and psychological disabilities. However, prognosis is generally more favorable for head-injured children than adults. For example, children with an initial GCS score of 6 or higher have an 80% chance of achieving functional independence. Intellectual recovery continues for as long as 2 years after head injury in children; thus, long-term rehabilitative services are needed. Formal psychological assessment for staging school

re-entry and for ongoing adjustment of the child's academic curriculum should be performed.

Five percent of patients will experience seizures within the first week after their head injury. The occurrence of these early-onset seizures does not accurately predict the development of later posttraumatic epilepsy. The risk for subsequently developing epilepsy is significantly increased if seizures are present beyond the first week after head injury, particularly when severe head trauma, intraparenchymal hematoma, or depressed skull fracture occurs. With these risk factors, approximately one-third of patients will develop posttraumatic epilepsy. Electroencephalographic studies do not accurately predict its subsequent development. The use of prophylactic anticonvulsant medications does not appear to reduce the risk for its occurrence. These medications are generally not used in mild brain injury. They are indicated for children who have had severe brain injury to prevent increased ICP caused by the seizures.

## PATIENT EDUCATION

Education on preventing head injury events is an essential role for the physician. Anticipatory guidance on appropriate supervision of children, high-risk activities, and use of protective equipment such as car seats for infants and helmets for older children while biking, skateboarding, skiing, snowboarding, and snowmobiling can dramatically reduce the morbidity and mortality that result from head injury.

### WHEN TO REFER

- Deteriorating mental status
- Coma or persistent alteration in mental status
- Glasgow Coma Scale score of less than 12
- Subdural, epidural, or intraparenchymal hematoma
- Focal abnormalities on neurologic examination
- Seizures after the first week or recurrent seizures
- Shock
- Signs of Cushing triad (bradycardia, hypertension, irregular respirations)
- Suspicion of child abuse (refer to appropriate local governmental agency)
- Cervical spine injury
- Basilar skull fracture
- Depressed skull fracture
- Increasingly severe headaches
- Facial laceration or suspicion of significant trauma at other locations
- If symptoms persist beyond 2 weeks or a student athlete has multiple sports-related concussions

### WHEN TO ADMIT

- Persistent alteration in mental state
- Focal neurologic deficits
- Seizures
- Persistent vomiting that precludes adequate hydration
- Severe headache
- Suspicion of abuse

- Unreliable caregivers or observers at home
- Any injury requiring neurosurgical intervention
- CT scan indicating intracranial bleeding or brain injury

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Bicycle Helmets: What Every Parent Should Know* (fact sheet), American Academy of Pediatrics (www.healthychildren.org/English/safety-prevention/at-play/Pages/Bicycle-Helmets-What-Every-Parent-Should-Know.aspx)
- *Head Injury* (fact sheet), American Academy of Pediatrics (healthychildren.org/English/health-issues/injuries-emergencies/Pages/Head-Injury.aspx)
- *Skiing and Snowboarding* (fact sheet) (www.healthychildren.org/English/healthy-living/sports/Pages/Skiing-and-Snowboarding.aspx)
- *What Is a Child Neurologist?* (fact sheet), American Academy of Pediatrics (www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Child-Neurologist.aspx)

### Medical Decision Support

- *Consensus Statement on Concussion in Sport: The 4th International Conference on Concussion in Sport Held in Zurich, November 2012* (article), *J Sci Med Sport*, Vol 16, Issue 3, 2013
- *Heads Up: Brain Injury in Your Practice—A Tool Kit for Physicians* (toolkit), Centers for Disease Control and Prevention (www.cdc.gov/ncipc/tbi/Physicians\_Tool\_Kit)

### Community Advocacy and Coordination

- *Heads Up* (Web page), Centers for Disease Control and Prevention (www.cdc.gov/headsup)
- *National Federation of State High School Associations* (Web site), (www.nfhs.org)

## AAP POLICY

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## Chapter 361

# HEART FAILURE

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Heart failure (HF) is a common outcome of many conditions affecting the heart in children. It results from a broad spectrum of diseases that include primary and secondary cardiomyopathies, myocarditis, valvular and congenital heart defects, and coronary artery disease. Heart failure can also occur as a secondary result of chronic diseases of noncardiac origin, such as renal failure and diabetes.

For many decades, HF has been perceived as a progressive and consistently fatal condition. In the recent past, pharmacologic treatment only consisted of anti-congestive therapy with digoxin and diuretics. Now, HF is seen no longer as a “pump failure” but rather as a more complex condition resulting from changes at the molecular, cellular, interstitial, structural, and functional levels that negatively reshape and remodel the heart. This improved understanding has led to a broader range of medical and surgical therapies for HF in patients of all ages.

Heart failure can occur in infants or children of any age, but up to 90% of cases arise during infancy from a variety of congenital conditions. This chapter reviews the pathophysiologic mechanisms of HF, especially as they relate to differences in age at presentation. The signs and symptoms of HF are discussed, as are specific causes and associated findings. In many children, HF results in a chronic, smoldering, and initially compensated course that may not be recognized early. Finally, the chapter presents various medical and surgical treatments for specific conditions. Understanding the causes and associations of pediatric HF and being able to recognize its signs and symptoms will help with early diagnosis, which may in turn improve the clinical outcomes for these challenging patients.

## PATHOPHYSIOLOGIC FEATURES

Left ventricular force differs at each developmental stage. In general, the contractile efficiency is greater in neonates than in fetuses and is similarly better in adults than in neonates. Thus for a particular left ventricular preload, cardiac output or stroke volume rises progressively from the fetal to the neonatal and through to the adult stages of life. Although the mechanisms of this relationship are not clear, the properties



of contractile proteins, ion channels, and cell surface receptors are expressed differently at each developmental stage. For example, the sodium-potassium pump is an ion channel largely responsible for maintaining the resting sodium gradient along the sarcolemmal membrane. Although of uncertain functional consequence, this channel has been shown to be less active in the immature myocardium. Additionally, developmental changes have been documented in terms of catecholamine receptor expression and second messenger system function. Thyroid hormone, cortisol, and catecholamine release surrounding birth lead to a transient increase of myocardial contractility. Catecholamine responsiveness is thereafter reduced, increasing again as sympathetic innervation subsequently matures. Animal studies suggest that neonates operate closer to their maximal inotropic potential than do adults, and neonatal hearts seem to have less diastolic compliance (they are “stiffer”) and therefore are more sensitive to preload variation than a normal adult heart (Table 361-1).

Heart failure is most often characterized by a decrease in cardiac output. Low cardiac output leads to the activation of several major neurohormonal compensatory systems. The renin-angiotensin-aldosterone system (RAAS) is activated as a result of decreased renal perfusion. This decrease in perfusion has several physiologic effects, including systemic vasoconstriction that increases systemic vascular resistance, which raises the blood pressure toward normal. Aldosterone release leads to salt and water retention, thereby expanding the circulating blood volume. Heart failure also leads to central activation of the vasopressin system, which promotes a further increase in circulating blood volume through renal water retention. This excess intravascular volume contributes directly to the symptoms of congestive HF.

Importantly, low cardiac output produces marked sympathetic activation that increases serum levels of circulating catecholamines. This acute baroreceptor mechanism restores blood pressure by producing systemic vasoconstriction and increasing myocardial contractility. These responses may have short-term advantages, but long-term catecholamine exposure is clearly harmful to the failing heart. Chronic sympathetic activation adversely affects the heart through a broad series of both intuitive and surprisingly interdependent mechanisms. For example, myocyte apoptosis (programmed cell death) occurs with prolonged catecholamine elevation. Peripheral vasoconstriction further raises systemic vascular resistance, increasing myocardial workload and enabling ventricular remodeling and hypertrophy. Sympathetic input augments the RAAS response, again increasing systemic vascular resistance and volume expansion. Progressive cardiac remodeling with fibrosis often develops, which is thought to increase myocyte automaticity and the risk for arrhythmia. As contractility and stroke volume fall, faster heart rates are required to maintain cardiac output. This resulting tachycardia increases myocardial oxygen demand in a failing organ that may be reaching the limits of its oxygen delivery capacity. Thus, nearly all compensatory mechanisms are designed to maintain stroke volume and cardiac output but lead to increased cardiac demand that hasten progressive HF.

Little is known about differences in the RAAS response to cardiac insult at different stages of development. There is evidence that in normal subjects, RAAS activity is increased in infancy and childhood compared with adults. Plasma renin activity and renin concentration are more elevated in infancy than adulthood and tend to decrease with age; plasma aldosterone also is elevated in infancy, and its level decreases

**Table 361-1** Major Differences Between Neonatal and Mature Hearts

CHARACTERISTIC	NEONATAL	MATURE
<b>PHYSIOLOGIC</b>		
Contractility	Limited	Normal
Heart rate dependence	High	Low
Contractile reserve	Low	High
Afterload tolerance	Low	Higher
Preload tolerance	Limited	Better
Ventricular interdependence	Significant	Less
<b>CALCIUM ION CYCLING</b>		
Predominant site of calcium ion flux	Sarcolemma	Sarcoplasmic reticulum
Dependence on normal ionized $\text{Ca}^{2+}$	High	Lower
Circulating catecholamines	High	Lower
Adrenergic receptors	Downregulation, insensitive $\beta_2$ , $\alpha_1$ predominant	Normal, $\beta_1$
Predominant innervation	Parasympathetic predominates; sympathetic incomplete	Complete
Cytoskeleton	Higher water content	Lower water content
Cellular elements	Incomplete sarcoplasmic reticulum, disorganized myofibrils	Mature sarcoplasmic reticulum, organized myofibrils

Adapted from Altman C, Kung G. Clinical recognition of heart failure in children. In: Chang AC, Towbin JA, eds. *Heart Failure in Children and Young Adults: From Molecular Mechanisms to Medical and Surgical Strategies*. Philadelphia, PA: Saunders Elsevier; 2006. Used with permission.

over the first 4 years of life. Angiotensin-converting enzyme (ACE) inhibitor can reverse cardiac remodeling in children, similar to in adults. In a prospective study of 24 children aged 0.3 to 16 years with volume overload secondary to aortic mitral regurgitation, Mori showed that long-term use of ACE inhibitors is effective in reducing left ventricular volume and hypertrophy compared with controls.

## **SIGNS AND SYMPTOMS OF CONGESTIVE HEART FAILURE**

Heart failure in children occurs most frequently in the very young. A thorough clinical history often provides clues to the presence and causes of HF.

### **Feeding**

Feeding is exercise activity for an infant. Heart failure impairs tissue oxygen delivery and alters lung function through pulmonary edema and airway obstruction. When HF progresses and lung function deteriorates, infants typically become tachypneic as their work of breathing increases. Tachypnea increases caloric expenditures while limiting the ability to feed effectively. For these reasons, a detailed history of feeding and growth is essential when screening an infant for heart disease. The average 6-week-old child consumes roughly 3 to 4 ounces of formula per feeding and nutritively sucks no longer than 20 minutes per feeding. A lower intake or a much longer feeding time may be of concern. Similarly, infants tend to gain 10 to 30 g/day and consume more than 90 kcal/kg/day.

Children with HF often have greater nutritional needs because of increased metabolic demands and may require 150 kcal/kg/day to gain adequate weight. Infants with HF often feed only in short, interrupted periods, and feedings may be associated with tachypnea and diaphoresis. Parents and caregivers will report that the infant feeds all day long, yet the total intake remains low, and the associated weight gain is poor. In older children, chronic HF results in malnutrition. Weight is usually the initial anthropometric measurement to be affected, followed by delays in the normal development of height and eventually head circumference. Evaluating growth velocity is critical to understanding the true nutritional effect of HF.

### **Activity Level**

Children with new-onset HF usually become either less active or more irritable and anxious.

### **Tachycardia**

Resting heart rates are low in normal infants and children but may be persistently and abnormally high in children with HF.

### **Tachypnea**

Sleeping respiration rates are typically low in healthy infants and children but may be higher in children with HF.

### **Rales**

Rales are less likely to be found in infants and young children with HF than in older children. In a young child,

rales may suggest active pulmonary disease. In advanced HF, bronchial edema can result in airway obstruction and “cardiac wheezing,” which is most common in younger infants. Chest radiographs in infants with HF show classic signs of overinflation and air trapping.

### **Jugular Venous Distention**

Although jugular venous distention may be seen in many older children with HF, it is less frequent in infants and young children, probably because observing their jugular veins is difficult and right-sided filling pressures may be lower than those often seen in adults.

### **Hepatomegaly**

The liver is frequently enlarged in infants and children with HF. Measuring the total liver span by percussion is more useful diagnostically than determining how far the liver edge extends below the right costal margin. The left lobe of the liver is often enlarged in infants and young children who have HF, and thus a palpable liver edge that crosses the midline suggests HF.

### **Gallops**

A third heart sound ( $S_3$ , an early diastolic, low-pitched sound corresponding to the rhythm of “Kentucky,” where the “ky” is the third sound) is common and normal in healthy children. An  $S_3$  can be heard in patients with HF and therefore may also be a pathologic gallop. In contrast, an  $S_4$  gallop (the sound corresponding to the rhythm of the first syllable of “Tennessee”) is always pathologic but is less common in pediatric HF. The  $S_4$  gallop is thought to be generated by the decreased compliance of a dilated, failing ventricle.

### **Pulses and Perfusion**

As discussed previously, HF is often associated with decreased cardiac output and peripheral vasoconstriction (a high “SVR” state). This peripheral vasoconstriction occurs through a variety of mechanisms (eg, increased catecholamine levels, renin-angiotensin system response), resulting in cool and pale extremities with decreased (“thready”) distal pulses. In some cases, the infant may be overtly mottled or cyanotic. The character of the pulses in the arms and legs should also always be compared because reduced or delayed pulses in the leg may indicate coarctation of the aorta, an interrupted aortic arch, or a similar condition requiring prompt treatment.

### **Arrhythmias and Sudden Death**

Arrhythmias may be both a cause and effect of HF in children and young adults. Ventricular dysfunction resulting from dilated cardiomyopathy may be associated with high-grade ectopy, which may increase the risk for death in association with HF. Similarly, unexplained syncope or palpitations in children may be the signs of an undiagnosed cardiomyopathy. Syncope, in particular, may predict sudden death in some children and may prompt interventions such as the placement of an automatic implanted cardiac defibrillator.

### **Heart Failure Scoring Systems**

Accurate patient-specific or population-based discussions of HF require standard terms and classifications.

Furthermore, because heart disease and HF are common in adults, discussions of adult HF are used, to some extent, toward the care of children. However, congenital heart disease and HF, comparative to large adult populations, remain relatively rare conditions in children. In adults, the New York Heart Association classification is widely used to indicate functional limitations resulting from HF. Unfortunately, this classification system is not particularly useful in infants and children because developmental stages greatly affect physical activities and exercise capabilities across age groups.

The Ross classification (Table 361-2) and the Ross scoring system (Table 361-3) are similar to the New York Heart Association classification and are validated for grading pediatric HF (Table 361-4). Both the New York and the Ross systems describe only functional status, without regard to the cause or the course of disease progression. Adult treatment guidelines published by the American College of Cardiology (ACC) and the American Heart Association (AHA) use the New York Heart Association classification but add another stage of disease to better indicate severity and to guide intervention. In 2004, the International Society for Heart and Lung Transplantation used these classifications, interpreted by expert pediatricians, as models when creating their practice guidelines for managing HF in children. These practice guidelines do differ substantially from those for adults, often as a result of the lack of pediatric-specific evidence. The guidelines also propose an HF staging system for infants and children that is also modeled after the adult systems and that uses the age-specific findings from the Ross classification (Table 361-5).

## LEADING CAUSES OF CONGESTIVE HEART FAILURE AT DIFFERENT AGES

The age at onset of HF in children, especially in infants, is an important initial clue about the cause of disease. Structural congenital disease tends to present

early in life, whereas progressive diseases, such as dilated cardiomyopathy, usually present in older children. The transition from fetal to postnatal circulation requires precise steps, any of which may be compromised and lead to HF. Some examples of age-related presentations are described below.

### Prenatal Period

Fetal cardiomyopathy and HF can result in hydrops fetalis and fetal demise. Fetal heart disease is now commonly identified in developed nations where routine prenatal ultrasound examinations are regularly performed. The causes of fetal HF are diverse and can arise from maternal (placental, rheumatologic), fetal (anatomic, arrhythmic), and infectious (viral) sources. Viruses affecting the fetus are generally the same as those found postnatally (eg, parvovirus, enteroviruses, adenovirus). Prolonged supraventricular tachycardia

**Table 361-2** Ross Classification of Heart Failure in Infants and Young Children

CLASS	DESCRIPTION
I	No physical limitations or symptoms, essentially normal and healthy seeming
II	Mild tachypnea or diaphoresis with feeding in infants Dyspnea on exertion in older children No growth failure
III	Marked tachypnea or diaphoresis with feeding or exertion Prolonged feeding times Growth failure from congestive HF
IV	Symptoms at rest with tachypnea, chest retractions, grunting, or diaphoresis

HF, heart failure.

**Table 361-3** Ross Scoring System of Heart Failure in Infants

CHARACTERISTIC	0 POINTS	1 POINT	2 POINTS
Volume per feed, oz	>3.5	2.5 to 3.5	<2.5
Time per feed, min	<40	>40	...
Respiratory rate, breaths/min	<50	50–60	>60
Heart rate, beats/min	<160/min	160–170/min	>170/min
Respiratory pattern	Normal	Abnormal	...
Peripheral perfusion	Normal	Decreased	...
S <sub>3</sub> or diastolic rumble	Absent	Present	...
Liver edge from costal margin, cm	<2	2 to 3	>3
Interpretation: The severity of congestive heart failure			
Totals			
No CHF	0–2 points	—	—
Mild CHF	3–6 points	—	—
Moderate CHF	7–9 points	—	—
Severe CHF	10–12 points	—	—

CHF, Congestive heart failure; S<sub>3</sub>, third heart sound.

From Ross RD. Grading the severity of congestive heart failure in infants. *Pediatr Cardiol*. 1992;13:72–75. Reprinted with permission from Springer.

is often not well tolerated by fetuses and may require maternally administered antiarrhythmic therapy. Such fetuses should be closely monitored and managed with a multidisciplinary team consisting of a perinatologist, cardiologist, and neonatologist. Maternal drug toxicity, efficacy, and the effect of premature delivery need to be considered in treatment decisions. Pediatric cardiologists with expertise in fetal development are invaluable for directing the fetal and postnatal care of these infants.

**Delivery Room or the Immediate Presentation of Compromised Cardiovascular Status**

**Persistent Pulmonary Hypertension**

Severe pulmonary hypertension may develop in infants aspirating meconium or experiencing acidosis from a complicated delivery. High pulmonary pressures result in right-to-left blood flow across a patent ductus arteriosus and a condition known as *persistent pulmonary hypertension* or *persistent fetal circulation*. If severe, this condition can lead to right ventricular failure and low cardiac output in conjunction with possibly severe overlying hypoxic lung disease.

Many therapies for neonates with persistent pulmonary hypertension are directed to improving right ventricular cardiac output and reducing the severity of hemodynamic compromise. Fluid administration, inotropic use, ventilator adjustments to reduce pulmonary

vascular resistance, and extracorporeal circulatory support (extracorporeal membrane oxygenation, or ECMO) are standard hemodynamic interventions often required to treat this challenging disease. Septic shock should always be considered in the differential diagnosis of a sick neonate and typically requires evaluating and treating with antibiotics any infant presenting with this level of life-threatening disease.

**Hematologic Abnormalities and Neonatal Heart Failure**

Acute or chronic anemia can compromise the hemodynamic status in newborns. Conversely, polycythemia, as seen in infants of diabetic mothers, can lead to hyperviscosity, sludging, and HF. Treatment of these conditions is determined by the severity of the infant's clinical condition and the specific context of care. Severe anemia can result in hydrops fetalis with high-output HF or acute cardiogenic shock, depending on the time course and duration of blood loss. Acute blood loss, from abruptio placenta, for example, can be managed with aggressive volume resuscitation and red cell transfusion. On the other hand, a chronic anemia, such as that caused by Rh sensitization, may be associated with some degree of volume expansion and physiologic compensation. In this case, the infant will have a chronic volume overload. In this setting, red cell replacement needs to be monitored carefully to avoid acute volume overload and progressive HF-associated pulmonary edema. Patients with severe anemia may benefit from double-volume exchange transfusions, particularly if antibodies may need to be removed. In other cases, a more gradual transfusion, coupled with diuretic administration and careful monitoring, may be appropriate.

**Electrolyte and Metabolic Causes of Cardiac Compromise**

Electrolyte abnormalities can lead to early hemodynamic compromise. Neonates are exquisitely sensitive to hypoglycemia and hypocalcemia. The neonatal myocardium uses glucose for energy metabolism, and

Table 361-4 New York Heart Association Functional Classification of Heart Failure	
CLASS	DESCRIPTION
I	No limitations to normal exertion
II	Symptoms on ordinary exertion
III	Symptoms with less than ordinary exertion
IV	Symptoms at rest

Table 361-5 The International Society for Heart and Lung Transplantation Proposed Heart Failure Staging for Infants and Children	
STAGE	INTERPRETATION
A	Patients with increased risk for HF but who have normal cardiac function and no evidence of cardiac chamber volume overload. Some sources of increased risk: previous exposure to cardiotoxic agents; family history of heritable cardiomyopathy; univentricular heart; and congenitally corrected transposition of the great arteries.
B	Patients with abnormal cardiac morphology or function, with no past or present symptoms of HF. Examples: aortic insufficiency with left ventricular enlargement; history of anthracycline exposure with decreased left ventricular systolic function.
C	Patients with underlying structural or functional heart diseases and past or present symptoms of HF.
D	Patients with end-stage HF requiring continuous infusion of inotropic agents, mechanical circulatory support, cardiac transplantation, or hospice care.

HF, Heart failure.  
Adapted from Rosenthal D, Chrisant MR, Edens E, et al. International Society for Heart and Lung Transplantation: practice guidelines for the management of heart failure in children. *J Heart Lung Transplant*. 2004;23:1313–1333. Copyright © 2004, Elsevier, with permission.



episodes of hypoglycemia can lead to hemodynamic collapse. Neonates generally have limited fat and energy stores, compared with older children. A newborn with low blood sugar and signs of poor perfusion will often improve when blood sugar levels return to normal. Similarly, hypocalcemia is another metabolic cause of hypotension and hemodynamic collapse on the first day of life. Current thinking is that neonates generally do not have fully developed and efficiently regulated intramyocardial calcium stores (the sarcoplasmic reticulum complex) and therefore depend greatly on serum ionized calcium to maintain normal myocardial contractility. Restoring normal calcium levels can reduce signs or symptoms of hypotension and low cardiac output. Hypoglycemia and hypocalcemia often occur together in infants of diabetic mothers.

### Arrhythmias

Heart rate abnormalities may also lead to HF in the fetus, newborn, or older child. In general, supraventricular arrhythmias are well tolerated, at least in the short term. Most older children will sense palpitations and will immediately seek attention at the onset of sustained tachycardia. In neonates and infants unable to verbalize such concerns, tachycardia may persist to the point of ventricular compromise. Supraventricular arrhythmias in neonates, which are often re-entrant rhythms through an accessory bypass tract, occur at rates of 250 to 300 beats per minute. At such high pulse rates, cardiac output is low as a result of incomplete diastolic relaxation, abnormal coronary perfusion, and eventual ventricular dysfunction. As such, tachycardia-associated cardiomyopathy may begin after a period of unrecognized, sustained tachycardia. In this case, sinus rhythm should be restored immediately through vagal maneuvers, medications (adenosine intravenously), or electrical cardioversion. Infants are then generally treated with either oral beta blockers or digoxin for long-term rhythm control.

Bradycardia can also cause acute or chronic HF in any age group. In general, symptomatic HF is seen in association with heart rates less than 60 beats per minute in infants and less than 40 beats per minute in older children and adults. Fetal and neonatal complete heart block is classically associated with maternal lupus erythematosus that often requires pacemaker placement. Direct myocardial injury beyond the conduction system has also been associated with neonatal lupus syndrome, perhaps as a direct cause of a progressive dilated cardiomyopathy.

### Heart Failure in the Neonate

Congenital heart disease in infants is often diagnosed in the first few days after birth. Several classic presentations should be kept in mind. For example, severe respiratory distress with progressive pulmonary edema and a small heart (indicated by the radiographic image of a “snowman in a snowstorm”) develops early in infants with obstructed total anomalous pulmonary venous connections. This relatively rare lesion must be identified early because surgery is the only effective intervention. Echocardiography can confirm the diagnosis.

A wide variety of congenital heart diseases present in the first several days of life. Symptoms occurring during this period warrant a high suspicion of a closing ductus arteriosus that may have been physiologically beneficial. These benefits depend on the anatomy involved. In right-sided obstructive lesions, such as pulmonary atresia, severe tetralogy of Fallot, or tricuspid atresia, the ductus initially is a source of pulmonary blood flow. With ductal closure, infants become progressively cyanotic and progressively symptomatic. In transposition of the great arteries, ductal flow increases pulmonary blood flow, increasing left atrial pulmonary venous return and beneficial atrial intracirculatory mixing. Again, in some infants, ductal closure will precipitate acute cyanosis, which may be severe and lead to acute hypoxic symptoms. In left-sided obstructive lesions, such as hypoplastic left heart syndrome, critical aortic stenosis, or critical coarctation of the aorta, infants depend on ductal blood flow to provide a source of systemic blood flow. Infants with these lesions become critically ill when the ductus closes from inadequate systemic perfusion. Prostaglandin E<sub>1</sub> infusion maintains ductal patency and is life-saving in these situations. Prostaglandin infusion is now routine and allows unhurried surgical planning for most cyanotic duct-dependent congenital heart defects.

The ductus closes in most children after 3 or 4 days of life. However, in some lesions, such as coarctation of the aorta, ductal patency can be prolonged. In fact, severe or critical coarctation of the aorta commonly presents 1 to 2 weeks after birth and is often accompanied by ventricular dysfunction or signs of poor renal and intestinal perfusion (eg, absent femoral pulses, acidosis, elevated blood urea nitrogen-to-creatinine ratio). Prostaglandin treatment at this age is usually effective, at least for partially reopening the ductus and restoring flow to the lower circulation. Surgery is then indicated when the infant has recovered from any acute organ dysfunction, typically within a few days after an acute presentation.

### Heart Failure in the First 3 Months of Life

Left-to-right shunts commonly lead to pulmonary overcirculation as pulmonary vascular resistance falls toward normal adult values at 4 to 8 weeks of age. Infants with large ventricular septal defects are the quintessential example of this overcirculation. As pulmonary vascular resistance falls, so does right ventricular pressure. This reduction in pressure allows a progressively larger volume of left ventricular blood to cross the ventricular-septal defect and enter the pulmonary circulation, essentially stealing systemic cardiac output from the left ventricle.

Falling systemic cardiac output activates several acute and chronic compensatory mechanisms. Activated carotid and aortic arch baroreceptors increase catecholamine release. Catecholamines produce tachycardia and increase inotropy and peripheral vasoconstriction. The rise in systemic vascular resistance is favorable in that blood pressure increases toward normal but is unfavorable because the rise increases again the volume of ventricular-level shunting. Loss of renal blood flow from ventricular shunting

activates the RAAS. Through angiotensin II-mediated vasoconstriction, systemic vascular resistance increases further, thereby re-exacerbating the volume of the intracardiac shunt. Aldosterone effects lead to volume expansion by way of salt and water retention. The final result is an infant who has high catecholamine levels, tachycardia, constricted peripheral vasculature and cool extremities, and pulmonary edema caused by volume overload. These pathophysiologic conditions occur in all low-cardiac output states, and their reduction explains the mechanistic benefits of anti-HF drugs (diuretics, ACE inhibitors,  $\beta$ -adrenergic blockade, antialdosterone agents). Other examples of common left-to-right shunts include atrial-septal defects, complete atrioventricular canal defects, and patent ductus arteriosus.

From the above discussion, it should be clear that the timing of presentation often suggests the cause of the infant's HF. Most of these lesions can be surgically corrected in early infancy, returning the patient's physiologic state back to normal.

### Heart Failure in Months 6 to 12 of Life

In the second 6 months of life, metabolic, genetic, infectious, and inflammatory cardiomyopathies become more common because most children with congenital disease have already been identified. Children with metabolic or genetic cardiomyopathy tend to be perceived as asymptomatic with only mild, clinically unrecognized disease early in the course of their illness. Disease typically becomes evident during evaluation for a presumed or supervening, often viral, illness. Symptoms, such as anorexia and vomiting or respiratory distress and hypoxia, should prompt a more thorough evaluation to identify any underlying cardiac disease. Glycogen storage diseases, hypertrophic cardiomyopathies, and infectious and inflammatory diseases, such as HIV infection and Kawasaki disease, are but a few of the diverse causes of cardiac dysfunction in this age group.

### Heart Failure in Years 1 to 18 of Life

Heart failure in children older than 1 year occurs most commonly with comorbid severe or chronic illnesses. For example, a child treated for cancer is at risk for HF during and after treatment with anthracycline-containing chemotherapy or radiation to the chest. This risk for HF persists lifelong as a result of the inherent cardiotoxicity and myocyte loss induced during cancer treatment. The leading indications for pediatric heart transplantation, after failed medical management of HF, are congenital heart disease and cardiomyopathy. Dilated cardiomyopathy is the leading cause of progressive HF and cardiac transplantation during childhood and adolescence. When examined systematically, dilated cardiomyopathy is most commonly an idiopathic disease resulting from unknown insults in two-thirds of cases. Although commonly implicated, only about 16% of dilated cardiomyopathy occurs as a result of a viral myocarditis. Many viruses have been implicated in the development of acute viral myocarditis, including the enteroviruses, adenoviruses, and seasonal influenza. Although rare, acute toxic ingestions, malignant hypertension, malnutrition and

eating disorders, and hypothyroidism have all been associated with acute and subacute cardiac failure. Careful patient histories can help guide appropriate etiologic studies.

## THERAPY FOR CONGESTIVE HEART FAILURE IN CHILDREN

### Pharmacotherapy

Pharmacologic therapy for chronic pediatric HF is based mainly on precedent and extrapolation from the vast data on adults. Given the relatively low incidence of HF in children, pediatric-specific, evidence-based data to inform treatment are limited. Historically, treatment has consisted mainly of anticongestive therapy with diuretics and digoxin. The AHA and the American College of Cardiology (ACC) nearly universally recommend ACE inhibitors and  $\beta$ -adrenergic antagonists as the mainstays of treatment for adults. Aldosterone antagonists have also been recently added as standard interventions for most stage C HF patients. Standard adult practice guidelines recommend titrating diuretics to achieve euvolemia. Digoxin is recommended to treat symptoms, but its use has not improved survival.

Unfortunately, the rationale for using these drugs to treat pediatric HF is limited by the paucity of trials in children. No large, randomized trials of ACE inhibitors for treating pediatric HF have been conducted, and the results of other studies remain controversial, mainly because of small sample sizes. One study showed the beneficial effect of enalapril on systolic function and left ventricular size and mass in children with doxorubicin-induced cardiomyopathy over 6 years of treatment. However, all left ventricular characteristics deteriorated to baseline cardiac function from 6 to 10 years on treatment. Conversely, a 10-week, randomized, double-blind, placebo-controlled crossover trial in 18 patients after a Fontan procedure showed that enalapril did not improve cardiac index or exercise duration.

Data on beta blockers for treating pediatric HF are similarly limited. Several early studies showed that carvedilol (a nonselective beta blocker) improved symptoms and function in children with HF. Conversely, the one randomized, multicenter study of children with ventricular dysfunction treated with carvedilol found no benefits. This study did, however, find that systolic function and functional class tended to improve in the subset of children with cardiomyopathy. Over 4 years, this study enrolled 161 patients with symptomatic HF secondary to systemic ventricular dysfunction with dilated cardiomyopathy or congenital heart disease. Patients were randomly assigned to receive low-dose carvedilol, high-dose carvedilol, or placebo for 8 months. The primary outcome was a composite of several HF outcomes. Although the results were mainly negative, adverse events were less than expected, suggesting that the trial may have been underpowered. As a result of the foregoing, consensus guidelines for managing pediatric HF incorporate experience, opinion, and data from adults and children.

Angiotensin-converting enzyme inhibitors, beta blockers, aldosterone antagonists, and even diuretics

target maladaptive compensatory responses in HF to lessen the long-term cardiac work load. The rarity of children with HF means that a pediatric cardiologist should generally direct their care.

Acute or decompensated HF is typically treated in the intensive care unit. In AHA and ACC staging, patients with severe symptomatic HF at rest have decompensated, stage D, disease. Heart failure in this stage is not expected to resolve with the routine use of oral medications and requires more aggressive interventions. Short-term symptomatic relief can often be provided by intravenous inotropic agents (eg, milrinone, dobutamine, epinephrine). These agents are for short-term use only, however, because long-term administration of any of them reduces survival. Children with acute decompensation typically receive temporary inotropic support in an attempt to return them to oral medications. Should this attempt fail, then more invasive therapy, such as mechanical circulatory support or heart transplantation, is considered for some patients. In others, comfort care with palliative inotropic infusions or hospice is appropriate.

### Arrhythmias

In addition to pharmacotherapy for treating the specific symptoms of HF in children, arrhythmias must always be managed. Arrhythmias are a major cause of morbidity and mortality in these children, especially in the later stages of disease. Short-term treatment with intravenous antiarrhythmic agents and cardioversion or defibrillation should be considered for all hemodynamically unstable children. Long-term suppressive therapy or radiofrequency ablation of appropriate conditions may be required to treat chronic arrhythmias. In adults with HF and ischemic or dilated cardiomyopathy, implantable cardiac defibrillators have greatly improved survival. Data in children with HF are limited, and no clear guidelines for placing implantable cardiac defibrillators or for cardiac resynchronization therapy are available for these children. The guidelines currently in use are part of the general recommendations for device-based therapy published in 2008. Pediatric experience in these areas is growing, and in general, the indications for placing cardiac defibrillators in children are similar to those for adults.

### Nutritional Management

The classic problem of failure to thrive remains a major challenge in caring for children with HF. Weight gain and linear growth in children with congenital heart disease are often delayed. Poor growth seems to be an overall marker for poor outcomes after either medical or surgical interventions. Treating failure to thrive is generally approached systematically, beginning with basic patient and parental counseling to optimize feeding and to increase caloric intake.

Breastfeeding is less stressful than bottle feeding for infants and should be promoted when possible. The decision to breastfeed or bottle feed should be made on an individual basis by consensus among parents, the primary care physician, and other health care professionals familiar with the needs of the infant. Gastrostomy placement and parenteral feeding should be considered for severely malnourished infants, in

part because after placement, the infant will not incur the energy costs of feeding.

Most congenital heart defects can be corrected or palliated surgically, often in the neonatal period. Early anatomic correction is aimed at alleviating the condition that led to HF in the first place, thereby preventing or alleviating chronic malnutrition. Despite great surgical advances, cardiac surgery in underweight infants still shows increased surgical risk. The risk and benefits of a specific intervention must be considered if an infant continues to fail to thrive after trying all other aggressive feeding and nutrition measures. Surgery may be necessary and advisable, even if the infant is not at an ideal weight. Other nutritional considerations common in children with HF include electrolyte abnormalities associated with diuretic use and balancing fluid intake in situations of HF-associated volume overload.

### Biomarkers

Cardiac myocytes and interstitium are affected by changes at the molecular, cellular, structural, and functional levels by a complex interaction of enzymes, hormones, and other biologic markers of cardiac stress, myocyte injury, or malfunction. Biomarkers are becoming more important for their ability to inform the diagnosis, prognosis, and management of HF. Brain natriuretic peptide (BNP) and its inactive form, N-terminal pro-brain natriuretic peptide (NT-proBNP), have been studied extensively in adults with HF. Studies in children are still in an early phase of development and are limited by small samples. In children and adolescents, BNP level has determined the presence of cardiac disease in acute care settings and may indicate the presence of left ventricular volume and pressure overload from shunting. Price et al found that in children with HF, a BNP level greater than 300 pg/mL was highly sensitive and specific for predicting morbidity and mortality. In a retrospective study of 36 children with dilated cardiomyopathy, Rusconi et al found that increases in NT-proBNP were associated with echocardiographic indices of advancing HF. An NT-proBNP level greater than 1,000 pg/mL was 95% sensitive and 80% specific in identifying children with constant or intermittently severe (functional class III or IV) symptoms.

In a study of 19 patients with HF secondary to both dilated cardiomyopathy and congenital heart disease, Ratnasamy et al found that levels of plasma NT-proBNP, hsCRP (high-sensitivity C-reactive protein), TNF- $\alpha$  (tumor necrosis factor- $\alpha$ ), and sTNF-RII (TNF- $\alpha$  receptor II) were associated with functional class and echocardiographic indices of left ventricular function. As in the above study, NT-proBNP and hsCRP levels were significantly higher in patients with more severe HF symptoms and discriminated between stages of HF. Similarly, TNF- $\alpha$  levels correlated with markers of declining left ventricular function.

The association of natriuretic peptide with functional status and echocardiographic indices of left ventricular dysfunction in children with HF and its ability to predict outcome may be useful in diagnosing and managing HF. Natriuretic peptide levels may provide an objective assessment of the severity of HF in



these challenging patients, who are undergoing developmental and hormonal changes. Brain natriuretic peptide levels may contribute to an early diagnosis, particularly in high-risk patients, allowing earlier medical interventions with the hope of preventing and reversing some of the remodeling processes that characterize HF.

The specific roles and potential uses of individual molecular biomarkers need further study. These biomarkers arise from several classes of molecules, including inflammatory molecules, neurohormones, products of myocyte injury, oxidative stress, and markers of extracellular matrix remodeling. Currently only natriuretic peptide levels (BNP and NT-proBNP), hsCRP (a biomarker of generalized inflammation) and cardiac troponin T or I (biomarkers of myocyte injury) are used routinely in children with heart failure, although as biomarker research advances new biomarkers may be added to clinical evaluations in the future. Eventually, specific biomarker panels may provide objective data to inform comprehensive risk assessment, guide medication choices, and monitor the efficacy and titration of ongoing medical and surgical interventions.

### Cardiac Transplantation

Surgical correction of congenital cardiac defects is central to the modern management of cardiac failure in infants and children. Most congenital defects are amenable to surgical repair or palliation, and most surgeries can be performed during infancy. However, residual lesions and cardiac dysfunction may occur or progress after repair. In cases of progressive cardiac dysfunction, cardiac transplantation is effective, is fairly widespread, and has a 1-year survival rate greater than 90% and a median survival time ranging from 11 years for adolescents to 18 years for infants. After transplantation, overall survival and quality of life are excellent for most patients. More than 90% of children report no activity limitation 5 and 10 years after transplantation.

Cardiac transplantation should be considered when expected survival is less than 2 years, the patient's quality of life is unacceptably poor, or there are no other surgical options. The risk for death in children waiting for cardiac transplantation is at least 17%, so early referral to a HF or transplantation center is essential. A thorough pretransplantation evaluation is required to assess the potential for long-term complications, determine the cause of cardiac disease, and identify any contraindications to transplantation, including certain metabolic or genetic disorders. The patient should be on the highest tolerable dosages of the appropriate medications, and pretransplantation nutritional status should be maintained to prevent cachexia and to optimize both presurgical and postsurgical outcomes.

### Mechanical Circulatory Support

Mechanical circulatory support is most commonly provided with ECMO. This technology extends cardiopulmonary bypass from the operating room into the intensive care unit to provide circulatory support for long periods. Its judicious use has contributed to

improved outcomes in a variety of critical diseases over the past several decades. As a result, many physicians can skillfully apply ECMO and manage patients on it. For patients with acute or chronic progressive disease or decompensated HF, ECMO can provide full cardiopulmonary function. This and other forms of mechanical circulatory support can also be used temporarily to support patients through periods of reversible illness, such as acute myocarditis, uncontrolled arrhythmia, or even an episode of myocardial rejection after cardiac transplantation. Mechanical support is also indicated as a bridge to cardiac transplantation. The advantages of ECMO are that it is familiar, can be deployed relatively quickly, and can provide pulmonary support to patients with concurrent respiratory disease. Its disadvantages are its relatively short duration of use and the associated complications, including hemorrhage, infection, and potential neurologic impairment.

Several types of ventricular assist devices (VADs) can provide mechanical cardiac support in the absence of primary lung disease. This technology consists of a variety of pneumatic pumps or rotary impeller devices that can provide an increased duration of circulatory support, mainly in adult populations. Experience, technologic advancements, and miniaturization have expanded VAD use, such that it is now a standard of care in cardiac transplantation centers when treating ventricular failure in children. Ventricular support is generally preferred to ECMO as a bridge to cardiac transplantation because it is safer and has better neurologic and transplant outcomes. Whereas ECMO can generally be used for days to weeks, VADs are more typically used from weeks to months. Regardless of the system, mechanical circulatory support requires great expertise, institutional commitment, and expense. Mechanical support has become a standard and essential component of care in intensive care units before transplantation, and its use will likely increase as the technology is refined.

### SUMMARY

Heart failure can occur at any age in infants and children. Epidemiologic data confirm that HF is most common during the first year of life. Although it can be acute and fulminant, HF is most often a chronic, smoldering process that causes substantial morbidity and mortality. Early recognition of the signs and symptoms of HF may allow treatment that can reduce morbidity and improve the child's quality of life (Box 361-1). Medical and surgical therapies are often life-saving, after the underlying condition is identified. The causes of HF vary with the age of the child at the time of diagnosis. Congenital defects dominate in younger patients, whereas chronic disease and underlying illnesses are more common in older patients. Primary care physicians should strive to make an early diagnosis, to address growth and nutritional concerns, and to institute cause-specific treatment under the direction of a pediatric cardiologist. Medical and technologic advances promise new surgical and therapeutic options for treating heart disease in all ages. Coming developments in preventing and managing pediatric heart disease will likely take the



### BOX 361-1 Highlights From International Society for Heart and Lung Transplantation Recommendations for Managing Pediatric Heart Failure<sup>a</sup>

1. The underlying cause of new-onset ventricular dysfunction (HF stages B, C, and D) should be diligently sought in all patients. In selected patients, the search may include metabolic and genetic considerations. Invasive techniques, including myocardial biopsy, may also be considered in selected cases. In infants, coronary artery anomalies and other anatomic causes of HF need to be ruled out.
2. First-degree relatives of patients with new-onset ventricular dysfunction caused by dilated cardiomyopathy (HF stages B, C, and D), should be screened for the presence of similar disease.
3. Fluid retention associated with ventricular dysfunction (HF stage C) should be treated with diuretics to achieve euvolemia, using clinical criteria of fluid status and cardiac output (daily weight, respiratory status, monitoring hepatomegaly, monitoring perfusion, renal parameters).
4. Digoxin should be given to patients with ventricular dysfunction and symptoms of stage C HF to relieve symptoms. Lower doses of digoxin are preferred for this purpose.
5. For treating moderate or severe left ventricular dysfunction, with or without symptoms (HF stages B and C), ACE inhibitors should be routinely used unless contraindicated. These medications should be started at low doses and titrated up to the maximal tolerated safe dose. Higher dosages of ACE inhibitors may require reducing the dose of diuretics.
6. In all cases of HF associated with structural heart disease (HF stages B, C, and D), surgical repair should be considered because long-term results may be better than those from medical management alone.
7. Clinical management of diastolic dysfunction should address symptoms and the underlying cause, if known. Management should include a careful search for pericardial disease and coronary insufficiency with attendant myocardial ischemia. Systemic hypertension, if present, should be aggressively treated.
8. Fluid management to control symptoms remains a cornerstone in treating symptomatic diastolic dysfunction (HF stage C). Diuretics can help control symptoms but must be used cautiously because cardiac output depends on increased filling pressures. Renal function should be followed closely to determine optimal doses. Restricting sodium and fluid intake may help control symptoms.
9. Atrial arrhythmias can occur in patients with diastolic dysfunction caused by atrial enlargement. However, atrial contribution to ventricular filling is particularly important for these patients (HF stages B and C). Therefore, if possible, sinus rhythm should be maintained with antiarrhythmic therapy and pacemakers.
10. Patients with diastolic dysfunction refractory to medical or surgical management should be evaluated for heart transplantation because the risk for pulmonary hypertension and sudden death is high (HF stage C).
11. Mechanical cardiac support should be considered in patients without structural congenital heart disease, who present with acute low cardiac output, or who have intractable arrhythmias during a presumably temporary condition that is refractory to medical therapy (HF stage D), such as myocarditis, septic shock, or acute rejection after heart transplantation.
12. Mechanical cardiac support should be considered in patients with or without structural congenital heart disease who have acute decompensation of end-stage HF, primarily as a bridge to heart transplantation (HF stage D).
13. In patients with marked arrhythmias and HF associated with structural heart disease (HF stages B, C, and D), surgical repair of uncorrected or residual defects should be considered because such repairs are likely to be essential for controlling arrhythmias.
14. In patients with marked arrhythmias and HF associated with structural heart disease (HF stages B, C, and D), medical treatment for HF should be optimized, and aggravating factors, such as electrolyte abnormalities, should be corrected because these actions are key to controlling arrhythmias.
15. In patients with marked arrhythmias and HF associated with structural heart disease (HF stages B, C, and D), maintaining atrioventricular synchrony is critically important to optimize hemodynamics, and intra-atrial arrhythmias should be managed to restore sinus rhythm, rather than solely to control ventricular rate.

ACE, Angiotensin-converting enzyme; HF, heart failure.

<sup>a</sup>All recommendations are class I recommendations, meaning that a given therapy is generally accepted as being useful and effective.

Adapted from Rosenthal D, Chrisant MR, Edens E, et al. International Society for Heart and Lung Transplantation: practice guidelines for the management of heart failure in children. *J Heart Lung Transplant*. 2004;23:1313–1333.

form of age- and disease-specific treatments. We look forward to the day when molecular defects can be corrected, injured heart muscles can be repaired, and congenital defects can be prevented.

### AAP POLICY

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### SUGGESTED READINGS

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## Chapter 362

# HYPERTENSIVE EMERGENCIES

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Acute hypertensive emergencies are relatively infrequent in the pediatric population. However, their full clinical manifestations represent potential life-threatening events, demanding prompt identification and carefully implemented therapeutic intervention. The increasing array of potent oral and parenteral antihypertensive agents, as well as the widespread availability of dialysis, has resulted in marked reductions of morbidity and mortality associated with hypertensive crises. With the development of databases and the US Food and Drug Administration (FDA) Modernization Act in place (including endeavors such as the Best Pharmaceuticals for Children Act), studies for the evaluation and management of hypertension in children will be forthcoming.

Hypertensive crisis is classified into urgency and emergency. *Hypertensive emergency* is distinguished from *hypertensive urgency* by the presence of acute end-organ dysfunction discovered in the history, physical examination, or laboratory studies, and not from the child's blood pressure (BP). The division into these 2 categories determines where treatment should be administered: in the emergency department (ED), intensive care unit (ICU), or routine hospital unit. Classifying the hypertensive episode as *urgent* or *emergent* governs the approach to treatment. Although hypertensive urgencies develop over days to weeks, hypertensive emergencies may develop over hours.

*Malignant hypertension* is characterized by marked increases in systolic BP, diastolic BP, or both (eg,  $\geq 160$  mm Hg systolic and  $\geq 105$  mm Hg diastolic for children younger than 10 years;  $\geq 170$  mm Hg systolic and  $\geq 110$  mm Hg diastolic for children older than 10 years) and is often associated with spasm and tortuosity of the retinal arteries, papilledema, and hemorrhages and exudates on fundoscopic examination. Hypertensive encephalopathy (an example of hypertensive emergency), often seen in malignant hypertension, consists of a combination of signs and symptoms that may include nausea, vomiting, headaches, altered mental status, visual disturbances, seizures, and stroke.

## EVALUATION

As part of the initial physical assessment, all children evaluated for hypertension must have their BP measured in both upper extremities and in at least 1 lower extremity. When faced with newly diagnosed hypertension in the

child, the physician should determine: (1) Is the hypertension primary or secondary? (2) Does evidence exist of target organ injury? (3) Do associated risk factors exist?

## History

A brief but thorough history should be obtained with the goal of classifying the severity of the hypertension. Some key features in the history would be the duration and onset of hypertension, degree of adherence with any drug therapy, and possibility of renal disease. Therefore physicians should be alert to any history of urinary tract infections, failure to thrive, hematuria, edema, or umbilical artery catheterization. Physicians should also inquire about any history of joint pain, palpitations, weight loss, flushing, weakness, drug ingestion, headaches (including characterization), nausea, and vomiting and should ask about a family history of renal disease or hypertension.

## Physical Examination

With severe hypertension, this evaluation should progress only after the ABCs (airway, breathing, and circulation) of resuscitation have been accomplished. BP should be recorded several times. Improper cuff size can affect the diagnosis; thus taking BP with the properly sized cuff is important. By convention, an appropriate cuff size is one with an inflatable bladder width that is at least 40% of the arm circumference at a point midway between the olecranon and the acromion. For such a cuff to be the optimal size for an arm, the cuff bladder length should cover 80% to 100% of the circumference of the arm. BP measurements tend to be overestimated when a cuff is too small and underestimated when a cuff is too big. If a cuff is too small, then the next largest cuff should be used, even if it seems large.

A focused physical examination should immediately be performed, with a focus on checking for any evidence of neurologic dysfunction. Funduscopy should be performed to assess for hemorrhage, papilledema, or infarcts. Hepatomegaly, rales on chest auscultation, and edema suggest congestive heart failure. Any discrepancy in the upper and lower extremity BP measurements should be noted because this may indicate coarctation of aorta. Presence of an abdominal bruit suggests a renovascular cause of hypertension.

## Laboratory Evaluation

The laboratory and radiologic workup can then be divided into 3 categories: tests for diagnosis of primary or secondary hypertension, tests for target organ injury, and tests for associated risk factors (Box 362-1).

## MANAGEMENT

### Hypertensive Emergency

In children with hypertensive emergency, vascular access should be established immediately, and the patient should undergo cardiac and continuous BP monitoring, preferably by an intra-arterial catheter. Urine output should be monitored from the outset. Any serious complications must be managed simultaneously with the hypertension (eg, anticonvulsants should be administered to a patient experiencing seizures, along with hypertensive medications).

**BOX 362-1 Laboratory Tests for Hypertension****TESTS FOR DIAGNOSIS OF PRIMARY OR SECONDARY HYPERTENSION****Laboratory**

- Urinalysis
- Urine culture
- Urinary catecholamines
- Complete blood count with platelet count and blood smear
- Serum electrolytes, calcium, phosphorus
- Serum blood urea nitrogen, creatinine
- Serum C3 complement, antistreptolysin O titer, antinuclear antibody
- Plasma renin

**Radiology**

- Chest radiograph
- Intravenous pyelogram

- Voiding cystourethrogram
- Cardiac catheterization
- Renal ultrasound
- Renal scan
- Renal arteriogram

**Other**

- Electrocardiogram

**Tests for Target Organ Injury**

- Urinalysis
- Chest radiograph
- Electrocardiogram

**Tests for Associated Risk Factors**

- Serum lipid profile (eg, lipoprotein electrophoresis)
- Serum uric acid

Several medications are available for hypertensive emergencies (see Table 362-1). The drugs chosen depend on several factors, such as the child's clinical condition, the presumed cause, whether a change occurred in cardiac output or total peripheral resistance, and whether end-organ involvement is present. The goal is to lower the BP promptly but gradually because a sudden decrease in BP can lead to neurologic complications, such as intracranial bleeding. Hypertensive emergencies should be treated by an intravenous antihypertensive drug that produces a controlled reduction in the BP, with the aim of decreasing the pressure by 25% or less over the first 8 hours, then gradually normalizing the BP over 24 to 48 hours. Each of the most commonly used medications has advantages and disadvantages, and each clinical situation requires its own mode of management. However, some helpful general guidelines exist.

Labetalol is an  $\alpha_1$ - and nonselective  $\beta$ -adrenergic blocker. It has been reported to be effective in the management of severe hypertension that results from pheochromocytoma and coarctation of the aorta. Because dosing is independent of renal function, it is a reasonable alternative in the treatment of hypertensive crises in patients with end-stage renal disease.

Nicardipine is an excellent drug for use in emergencies because it can be administered as an easily prepared and titrated infusion.

Therapy with sodium nitroprusside, an arteriolar and venous vasodilator, is frequently effective. This drug works by reducing peripheral resistance and cardiac filling pressure. BP decreases with minimal change in cardiac output, and hence reflex tachycardia does not occur. The drug is administered by constant infusion, and the effects, which are seen quickly, last only as long as the infusion is continued. Use requires close observation, and therefore sodium nitroprusside may be inappropriate in the ED. Other disadvantages are that the drug requires 10 minutes

to prepare, is photosensitive, and is associated with a potential for cyanide accumulation.

Hydralazine is an arteriolar vasodilator that is not as potent as nitroprusside. However, it has an excellent safety profile. The half-life is short (3–7 hours); thus frequent dosing is required. Reflex tachycardia frequently occurs, necessitating the introduction of a beta blocker.

Esmolol is a selective  $\beta_1$  blocker that has been used in the treatment of postoperative hypertension following congenital heart disease repair. Experience with esmolol use outside of the postoperative setting is limited.

Phentolamine is a pure  $\alpha$ -adrenergic blocker used almost exclusively for the treatment of catecholamine crisis, as seen in patients with pheochromocytoma or in patients who ingested sympathomimetic agents such as cocaine. The effect is immediate. Phentolamine carries a high risk for hypotension after the primary lesion (eg, pheochromocytoma) is excised.

Nifedipine, a calcium channel blocker, reduces peripheral vascular resistance and does not affect cardiac output. It can be administered sublingually, but biting the capsule and swallowing its contents achieves blood levels more rapidly than administration by the sublingual route. Use depends on the patient's state of consciousness. Nifedipine is contraindicated in the presence of intracerebral bleeding.

Newer agents include fenoldopam and clevidipine. Fenoldopam reduces mean arterial pressure by vasodilation. Clevidipine is an ultra-short-acting dihydropyridine calcium channel antagonist that causes less tachycardia than nitroprusside. These properties make it a valuable drug in the management of hypertensive emergency in the ED.

Diazoxide, an arteriolar vasodilator, is no longer recommended for routine use.

**Hypertensive Urgency**

Patients with hypertensive urgency may not require hospitalization if the therapy in the ED is successful

**Table 362-1****Most Commonly Used Antihypertensive Agents for the Treatment of Hypertensive Urgencies and Emergencies in Children<sup>a,b</sup>**

DRUG	CLASS	ROUTE	DOSE	ONSET OF ACTION	DURATION OF ACTION
Labetalol	$\alpha_1$ , $\beta$ Blocker	IV	Bolus dosing: 0.2–1 mg/kg (max 40 mg/dose) Infusion: 0.25–3 mg/kg/hr IV	5–10 min	2–4 hr
Nicardipine	Calcium channel blocker	IV	1–3 mcg/kg/min	2–5 min	30–60 min
Sodium nitroprusside <sup>c</sup>	Direct vasodilator	IV	0.5–8 mcg/kg/min	Seconds	During infusion only
Hydralazine <sup>c</sup>	Direct vasodilator	IV/IM	0.1–0.6 mg/kg/dose (max 20 mg)	10–30 min	4–12 hr
Esmolol	$\beta_1$ Blocker	IV	Bolus 100–500 mcg over 1 min; 25–100 mcg/kg/min; can increase to 500 mcg/kg/min	Seconds	10–20 min
Phentolamine <sup>c</sup>	$\alpha$ Blocker	IV	0.1–0.2 mg/kg/dose; not to exceed 5 mg/dose (0.05–0.1 mg/kg/dose for treatment of hypertension during surgery)	Seconds	15–30 min
Fenoldopam <sup>c</sup>	Dopamine receptor agonist	IV	0.2–1.2 mcg/kg/min	5–15 min	1–4 hr
Nifedipine	Calcium channel blocker	Sublingual	0.1–0.25 mg/kg/dose (max 10 mg)	20–30 min	6 hr
Isradipine	Calcium channel blocker	PO	0.05–0.1 mg/kg/dose (max 5 mg)	30 min–2 hr	12 hr
Clonidine <sup>c</sup>	$\alpha_2$ -Receptor agonist	PO	0.05–0.3 mg	15–30 min	6–8 hr
Minoxidil <sup>c</sup>	Direct vasodilator	PO	0.1–0.2 mg/kg/dose (max 10 mg)	Within 1 hr	8–12 hr

ICP, intracranial pressure; IM, intramuscular; IV, intravenous; MAP, mean arterial pressure; PO, by mouth.

<sup>a</sup>Because several of these medications have not been extensively tested in children, existing pharmacokinetic data are frequently based on studies in adults.

<sup>b</sup>Dosing recommendations vary by source.

<sup>c</sup>Indicates drugs with US Food and Drug Administration–approved pediatric labeling for use in hypertension.

and if follow-up is adequate. In many instances, oral antihypertensive agents are sufficient, although parenteral therapy is sometimes indicated. Generally, one-third of the total planned BP reduction should be done during the first 6 hours, another third during the next 24 to 36 hours, and the final third during the next 24 to 96 hours or even longer. A 4- to 6-hour period of observation after the administration of the antihypertensive agent is recommended in the ED to identify any untoward effects of the medication. Patients should be discharged with the same medications that were used in the ED to treat the hypertension.

Results of pediatric studies of amlodipine, felodipine, isradipine, intravenous nicardipine, and nitrendipine have been published. Enalapril, an angiotensin-converting enzyme inhibitor, is commonly used as an antihypertensive agent in children. The maximal serum concentration occurs approximately 1 hour after administration, and that of its metabolite, enalaprilat, peaks 4 to 6 hours after the first dose and 3 to 4 hours after multiple doses. Amlodipine is a safe and effective antihypertensive drug in children with chronic renal disease. When administered in the ICU, intravenous

nicardipine is safe and effective in lowering the BP in children with severe hypertension.

### Malignant Hypertension

The urgency of prompt treatment of malignant hypertension is attested to by the fact that one-third of severely hypertensive children develop neurologic abnormalities that may be sudden in onset and leave permanent neurologic deficits. These abnormalities include cortical blindness, infarction of the optic nerve, and hemiplegias. Patients with malignant hypertension are usually admitted to an ICU for continuous cardiac monitoring and frequent assessment of neurologic status and urine output. An intravenous line is placed to permit administration of fluids and medications. Patients typically have altered BP autoregulation, and overzealous reduction of BP to reference range levels may result in organ hypoperfusion.

The initial goal of therapy is to reduce the mean arterial pressure by approximately 25% over the first 24 hours. An intra-arterial line is helpful for continuous titration of BP. Sodium and volume depletion may be severe, and volume expansion with isotonic sodium



chloride must be considered. No trials have been performed that compare the efficacy of various agents in the treatment of malignant hypertension in children. Drugs are chosen based on their rapidity of action, ease of use, special situations, and convention.

## PROGNOSIS

The immediate prognosis of the child who has symptoms resulting from a hypertensive emergency depends on the rapidity of recognition of the problem and achievement of appropriate BP reduction thereafter. Although the initial neurologic and visual disturbances may improve or resolve with time, risks remain for residual abnormalities such as seizure disorders, cranial nerve palsies, hemiplegia, and blindness. Renal function often deteriorates acutely in patients who have chronic renal disease after a hypertensive emergency or urgency. With sustained BP control, renal function may improve over a period of weeks or longer.

The long-term prognosis also depends on the underlying cause, as well as the effective management of the malignant hypertension. Some causes, such as acute poststreptococcal glomerulonephritis, may resolve on their own. Others, such as isolated vascular abnormalities, are amenable to correction. In other settings, such as hypertension associated with chronic glomerulonephritis, the condition may be controlled by continued antihypertensive therapy, although failure to adhere to medication regimens remains a problem. The development of end-organ damage (eg, hypertensive cardiomyopathy, stroke) is directly related to the adequacy of long-term BP control.

## CONCLUSION

Hypertensive emergencies in symptomatic children should be treated without delay to avoid further damage to vital organs. When treating children with hypertensive emergencies, BP should be brought down by no more than 25% within the first few hours. A pathogenesis for hypertension may be evident in individual cases, and management decisions must be made based on the cause of the hypertension.

### WHEN TO REFER

- Consultation with a pediatric nephrologist should be undertaken for diagnostic evaluation of the cause of the hypertension and short- and long-term management suggestions.
- Consultation with a pediatric cardiologist or pediatric neurologist should be undertaken if end-organ cardiac or central nervous system injury is suspected or if a question exists of the relationship between end-organ dysfunction and hypertension.

### WHEN TO ADMIT

- All hypertensive emergencies
- Most cases of hypertensive urgencies

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *High Blood Pressure in Children* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/conditions/heart/Pages/High-Blood-Pressure-in-Children.aspx](http://www.healthychildren.org/English/health-issues/conditions/heart/Pages/High-Blood-Pressure-in-Children.aspx))

## AAP POLICY

National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114(2/52):555–576. AAP endorsed. ([pediatrics.aappublications.org/content/114/Supplement\\_2/555](http://pediatrics.aappublications.org/content/114/Supplement_2/555))

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## Chapter 363 HYPOGLYCEMIA

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## INTRODUCTION

Any acutely ill child should be evaluated for hypoglycemia, especially when the history reveals diminished oral intake. Diagnosing hypoglycemia promptly is essential because low blood glucose levels that persist or recur may have catastrophic effects on the brain, particularly in infants. Accordingly, the primary care physician must recognize the clinical symptoms associated with hypoglycemia, document the low blood glucose level, and treat appropriately with glucose. Delineating the cause of the hypoglycemia is necessary to initiate effective continuing treatment.

## DEFINITIONS

A child who has a serum or plasma glucose concentration less than 40 mg/dL or a whole blood glucose concentration less than 35 mg/dL should be investigated and treated for hypoglycemia; those who have plasma glucose concentrations between 40 and 50 mg/dL should be followed carefully. On the basis of observational data and expert opinion, the World Health Organization (WHO) currently provides different definitions for different specific clinical categories: newborns and infants with “signs of illness” (<45 mg/dL), healthy term or preterm newborns “feeding well” (<19.8 mg/dL), and

infants and children with severe malnutrition (54 mg/dL). If hypoglycemia is suspected, then the blood glucose level may be approximated quickly at the bedside using a visual test strip or glucose meter and later confirmed by an appropriate chemical laboratory test. Although these thresholds have been commonly quoted and used, the level of plasma glucose that is safe is uncertain, and some authorities advocate a therapeutic goal of maintaining a plasma glucose level above 60 mg/dL in both neonates and older children to prevent permanent brain damage.

## CLINICAL MANIFESTATIONS

The clinical findings in hypoglycemia are those caused mainly by cerebral dysfunction and adrenergic discharge. Incoordination of eye movements, strabismus, excessive irritability, motor incoordination, and convulsions may occur after 1 month of age. In the older child, pallor, tachycardia, sweating, limpness, inattention, staring, listlessness, hunger, abdominal pain, ataxia, stupor, coma, and convulsions are frequent findings. Episodes of hypoglycemia may be present at any age without obvious clinical manifestations.

## ETIOLOGY

The blood glucose level is the final balance between the sum of hepatic glucose production and dietary intake minus peripheral glucose use. An adequate fasting blood glucose concentration depends on sufficient amounts of endogenous nonglucose precursors (eg, alanine, lactate, glycerol), effective hepatic enzyme pathways for gluconeogenesis and glycogenolysis, and normal hormonal activities (insulin, growth hormone [GH], cortisol, glucagon, and epinephrine) for the mobilization of substrates and the regulation of these processes.

## INCIDENCE

The overall incidence of symptomatic hypoglycemia in newborns varies from 1.3 to 3 per 1,000 live births. Early feeding decreases the incidence of hypoglycemia. Prematurity, hypothermia, hypoxia, maternal diabetes, maternal glucose infusion in labor, and intrauterine growth restriction increase the incidence of hypoglycemia.

## DIFFERENTIAL DIAGNOSIS

Metabolic acidosis, ketonemia, or hepatomegaly in association with hypoglycemia strongly suggests the presence of an inborn error of metabolism of carbohydrate, amino acid, or organic acid. Hypotonia and hyperammonemia may also be present in infants who have defects in organic acid and amino acid metabolism. The presence of non-glucose-reducing substances in the urine may indicate galactosemia or hereditary fructose intolerance (HFI). Nonketotic hypoglycemia in patients who have hepatomegaly, with or without metabolic acidosis, suggests 3-hydroxy-3-methylglutaric aciduria, glutaric aciduria type II, systemic carnitine deficiency, carnitine palmityl transferase deficiency, or long- and medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiencies. In contrast, hepatomegaly, ketonuria, and metabolic acidosis are usually absent in patients with hypoglycemia accompanied by hyperinsulinism. The findings of ketonuria and hypoglycemia without hepatomegaly

among small and underweight boys older than 1 year suggest ketotic hypoglycemia, although ketosis may be present in some hypoglycemic patients who have hypopituitarism and adrenocorticotrophic hormone (ACTH) unresponsiveness.

## Hyperinsulinism

Hyperinsulinism may be caused by any of several abnormalities of the  $\beta$  cell (Box 363-1) and is the most common cause of persistent or recurrent hypoglycemia in the first year of life. In Beckwith-Wiedemann syndrome (omphalocele, macroglossia, and gigantism), hypoglycemia occurs in many of the affected infants and resolves at several months of age. Some of these infants also have hemihypertrophy. An increased incidence of adrenal, liver, and kidney (Wilms) tumors occurs in these patients. More commonly, hyperinsulinism is transient and associated with infants of diabetic mothers.

Most children who have hypoglycemia caused by persistent hyperinsulinism (previously called *nesidioblastosis*, *islet cell dysplasia*, or *congenital hyperinsulinism*) have symptoms beginning during the first year of life. The understanding of the genetic basis of this condition has advanced enormously in the past several years. Pancreatic  $\beta$ -cell insulin secretion is regulated through a multistep signaling pathway. Glucose, amino acids, and other fuels are metabolized in the  $\beta$  cells, raising the ratio of adenosine triphosphatase to adenosine diphosphate. This action, in turn, activates a plasma protein, the sulfonylurea receptor (SUR), to close a potassium channel ( $K_{ATP}$ ), depolarizing the membrane and leading to an influx of calcium and release of insulin. The rate-limiting step in glucose metabolism is the enzyme glucokinase. The most severe form of congenital hyperinsulinism has been found to be caused by a recessive mutation in the  $K_{ATP}$ . Other forms of congenital hyperinsulinism are caused by mutations in the SUR, potassium pore, glucokinase, and other steps of the signaling path. Congenital hyperinsulinism seems to occur in association with either focal or diffuse abnormalities of the  $\beta$  cells.

Pancreatic islet cell adenomas are uncommon in children. Although hypoglycemia caused by varying histologic types of insulinoma may have its onset in the newborn period, symptoms begin after the age of 4 years in 85% of patients.

## Inborn Errors of Metabolism

### Carbohydrate Enzyme Defects

Several enzymatic defects of carbohydrate metabolism result in deficiencies of hepatic glucose formation and release. Glucose-6-phosphatase deficiency is the most common deficiency, and the symptoms are more severe than those in other glycogen storage disease (GSD) types (see Box 363-1). Patients who have GSD types 1a and 1b have growth restriction, cherubic facies, a protuberant abdomen, a large smooth liver, enlarged kidneys, normal intelligence, fasting hypoglycemia of only a few hours' duration, ketosis, lactic acidemia, hyperlipidemia, hyperuricemia, and bleeding diathesis. In type 1b, the patients also have neutropenia and an increased frequency of infections. Among infants and young children, poor food intake during an

**BOX 363-1 Causes of Hypoglycemia in Childhood<sup>a</sup>****HYPERINSULINISM**

- Islet cell dysplasia (functional  $\beta$ -cell secretory disorder)
- Islet cell adenoma
- Adenomatosis
- Beckwith-Wiedemann syndrome

**HEREDITARY DEFECTS IN CARBOHYDRATE METABOLISM**

- Glycogen storage diseases
- Glucose-6-phosphatase deficiency types Ia and Ib
- Amylo-1,6-glucosidase deficiency type III
- Defects of liver phosphorylase enzyme system

**ENZYME DEFICIENCIES OF GLUCONEOGENESIS**

- Fructose-1,6-diphosphatase
- Phosphoenolpyruvate carboxykinase
- Pyruvate carboxylase

**OTHER ENZYME DEFECTS**

- Galactose-1-phosphate uridyltransferase (galactosemia)
- Fructose-1-phosphate aldolase (hereditary fructose intolerance)
- Glycogen synthetase

**HEREDITARY DEFECTS IN AMINO ACID AND ORGANIC ACID METABOLISM**

- Maple syrup urine disease
- Propionic acidemia
- Methylmalonic aciduria
- Tyrosinosis
- 3-Hydroxy-3-methylglutaric aciduria
- Glutaric aciduria type II

**HEREDITARY DEFECTS IN FAT METABOLISM**

- Systemic carnitine deficiency
- Carnitine palmitoyl transferase deficiency
- Long- and medium-chain acyl-coenzyme A dehydrogenase deficiencies

**HORMONE DEFICIENCIES**

- Congenital hypopituitarism or hypothalamic abnormality

- Growth hormone
- Cortisol
- Adrenocorticotrophic hormone (ACTH)
- ACTH unresponsiveness
- Glucagon
- Thyroid hormone
- Catecholamine

**KETOTIC HYPOGLYCEMIA**

- Nonpancreatic tumors
- Mesenchymal tumors
- Epithelial tumors
- Hepatoma
- Adrenocortical carcinoma
- Wilms tumor
- Neuroblastoma

**POISONING OR TOXINS**

- Salicylate
- Alcohol
- Propranolol
- Oral hypoglycemic agents (eg, sulfonylureas)
- Insulin
- Unripe ackees (hypoglycin) (Jamaican vomiting sickness)
- Pentamidine
- Quinolones (eg, gatifloxacin when used in various infections<sup>b</sup>)
- Quinine (acute malaria and cerebral malaria)

**LIVER DISEASE**

- Hepatitis, cirrhosis
- Reye syndrome

**OTHER CAUSES**

- Malnutrition
- Malabsorption
- Chronic diarrhea
- Cyanotic congenital heart disease
- Postsurgery

<sup>a</sup>Data from Cornblath MD, Schwartz R. *Disorders of Carbohydrate Metabolism in Infancy*. 2nd ed. Philadelphia, PA: WB Saunders; 1976; Kogut MD. Hypoglycemia: pathogenesis, diagnosis, and treatment. In: Gluck L, ed. *Current Problems in Pediatrics*. Chicago, IL: Mosby; 1974; Kogut MD. Neonatal hypoglycemia: a new look. In: Moss AJ, ed. *Pediatrics Update: Review for Physicians*. New York, NY: Elsevier; 1980.

<sup>b</sup>Murad MH, Coto-Yglesias F, Wang AT, et al. Clinical review: drug-induced hypoglycemia: a systematic review. *J Clin Endocrinol Metab*. 2009;94(3):741–745.

illness may result in severe lactic acidosis and hypoglycemia. Death may result if hypoglycemia and lactic acidemia are not treated adequately and promptly with intravenous glucose and sodium bicarbonate.

**Reye Syndrome**

Because children who have an inborn error of metabolism may exhibit a Reye syndrome–like illness, the primary care physician must be alert to the possibility

of an underlying metabolic defect, particularly in young children or in a child who has a recurrence of Reye syndrome–like symptoms.

**Galactosemia**

Galactosemia in a lactose-fed infant is characterized by failure to thrive, jaundice, vomiting, susceptibility to infection, hepatomegaly, edema, ascites, a tendency to bleed, cataracts, proteinuria, aminoaciduria, and

**Table 363-1** Hypoglycemia in Infancy and Childhood

	<b>INBORN METABOLIC ERRORS OF CARBOHYDRATE AND AMINO ACIDS</b>	<b>HORMONE DEFICIENCY</b>	<b>HYPERINSULINISM</b>
Family history	+	Variable	Variable
Hypoglycemia			
Fasting	GSD, fructose-1,6-diphosphatase deficiency	+	+
After lactose	Galactosemia	—	—
After sucrose	Hereditary fructose intolerance	—	—
After protein	Amino acids, organic acids	—	Variable
Hepatomegaly	+	Variable	—
Ketosis	+	Variable	—
Acidosis	+	—	—
Tests	Glucose, glucagon, galactose, fructose tolerance tests; amino acids, gas chromatography	Blood growth hormone, cortisol; stimulation tests	Random blood glucose and immunoreactive insulin; leucine tolerance test
Liver biopsy (enzymes)	Diagnostic for carbohydrate errors (not for galactosemia; use red blood cells)	Not indicated	Not indicated
White blood cells, fibroblasts (enzymes)	Amino acids, organic acids	—	—
Treatment	Specific	Specific	Diazoxide; somatostatin analog; partial excision of the pancreas

+, Present; —, absent.

GSD, Glycogen storage diseases, types I, III, and defects of liver phosphorylase enzyme system.

Data from Cornblath MD, Schwartz R. *Disorders of Carbohydrate Metabolism in Infancy*. 2nd ed. Philadelphia, PA: WB Saunders; 1976; Kogut MD. Hypoglycemia: pathogenesis, diagnosis and treatment. In: Gluck L, ed. *Current Problems in Pediatrics*. Chicago, IL: Mosby; 1974; Kogut MD. Neonatal hypoglycemia: a new look. In: Moss AJ, ed. *Pediatrics Update: Review for Physicians*. New York, NY: Elsevier; 1980.

galactosuria. Intellectual disability, progressive liver failure, and death may occur unless galactose-containing feedings are eliminated. Symptomatic hypoglycemia is not a common finding and is reversed quickly by intravenous glucose.

### **Hereditary Fructose Intolerance**

Clinical manifestations of hereditary fructose intolerance (HFI) develop only after fructose ingestion and include vomiting, profound hypoglycemia, and convulsions. Continued ingestion of fructose is associated with failure to thrive, prolonged vomiting, jaundice, hepatosplenomegaly, hemorrhage, abnormal liver function, fructosuria, defects in proximal renal tubular function (including proteinuria, glucosuria, and aminoaciduria), and, in some cases, hepatic failure and death.

### **Fructose-1,6-Diphosphatase Deficiency**

Patients who have fructose-1,6-diphosphatase (FD-Pase) deficiency may have episodic hyperventilation, fasting hypoglycemia, lactic acidosis, ketosis, hyperuricemia, and hepatomegaly. Refusal to eat and vomiting, often associated with febrile illness, precipitate the attacks. The disorder is life threatening in neonates and in young children. In contrast to those who have HFI, these patients do not vomit after fructose intake and do not develop an aversion to sweets.

### **Amino Acid and Organic Acid Metabolic Defects**

Hypoglycemia has been noted in a variety of inborn errors of amino acid and organic acid metabolism (see Box 363-1). Although symptoms usually begin in the neonatal period, they may occur later. The infants tend to improve when protein feedings are discontinued and glucose is administered intravenously. Occasionally, peritoneal dialysis or exchange transfusion may be life-saving. Amino acid analysis and gas chromatography of blood and urine are often helpful in detecting these inborn errors (Table 363-1). Diagnosis and treatment of a specific disorder depend on detection of its characteristic metabolites in blood and urine and on assays of specific enzyme activities in skin fibroblasts or white blood cells.

The most common defect of fatty acid oxidation is medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. This condition may exhibit as nonketotic hypoglycemia (similar to Reye syndrome), an acute life-threatening event, or even sudden death. In fact, an association has been made between infants with known MCAD deficiency and a history of a sibling dying of sudden infant death syndrome. Initial screening for defects of fatty acid oxidation is best performed with analysis of urine organic acids, plasma acylcarnitine profile, and measurement of serum carnitine.



### Hormonal Deficiencies

Growth hormone deficiency, cortisol deficiency, or combined hormonal deficiencies may cause hypoglycemia.

#### Hypopituitarism

Congenital hypopituitarism, caused by either a hypothalamic abnormality or aplasia of the anterior pituitary gland, is associated with severe hypoglycemia during the first few days of life. Occasionally, however, hypoglycemia may first appear later in infancy or childhood. A few patients may have midline deformities, including hypotelorism, abnormality of the frontonasal process, and cleft lip or palate. Septo-optic dysplasia (optic nerve hypoplasia and absence of the septum pellucidum) is present in some patients and may be accompanied by nystagmus. Some male patients who have congenital hypopituitarism may have a small penis (microphallus) or genitalia, and children with hypopituitarism are often overweight. Measurement of height and weight is essential for the evaluation of a child in whom GH deficiency is suspected because these children have significant growth restriction, which may begin within the first 1 to 2 years of life.

#### Cortisol Deficiency

Deficient cortisol production may be caused by Addison disease, congenital adrenal hyperplasia, adrenocorticotrophic hormone (ACTH) deficiency, or ACTH unresponsiveness. Patients who have ACTH unresponsiveness and Addison disease may have abnormal pigmentation.

### Ketotic Hypoglycemia

Although the pathogenesis of hypoglycemia in ketotic hypoglycemia has not been defined, the evidence suggests that it represents an exaggeration of the starvation state. During hypoglycemia, blood insulin levels are appropriately low; blood alanine levels also may be low; GH, glucagon, cortisol,  $\beta$ -hydroxybutyrate, and free fatty acid levels in the blood are elevated; urinary ketones are present; and blood glucose levels fail to rise after the administration of glucagon.

Ketotic hypoglycemia is the most common cause of hypoglycemia after 1 year of age. Symptoms mimicking those noted in ketotic hypoglycemia have occurred in children who have GH deficiency, ACTH unresponsiveness, FDPase deficiency, glycogen synthetase deficiency, and Reye syndrome. Before a child is classified as having ketotic hypoglycemia, therefore, a thorough laboratory investigation must be conducted to consider these and other diseases.

The combination of ketonuria, hypoglycemia, and central nervous system symptoms, which may vary from unresponsiveness, pallor, and vomiting to coma and convulsions and which often occur in the early morning hours in association with an upper respiratory tract infection or prolonged fast, is typical of ketotic hypoglycemia for which no cause is known. The onset is between 9 months and 5.5 years of age, with a peak incidence at 2 years. Hypoglycemic episodes occur at intervals of a few months to a year or more; they then decrease in frequency and tend to disappear, usually by 7 to 8 years of age.

### EVALUATION

Hypoglycemia reflects the failure of 1 or more factors that regulate the concentration of glucose in the blood (see Box 363-1). Clinical clues enable the physician to plan a logical approach to the diagnostic evaluation of a patient who has hypoglycemia. The age at onset of hypoglycemia is important. The inborn errors of carbohydrate, amino acid, organic acid metabolism, and hormonal deficiencies become apparent during the first 2 years of life. Hyperinsulinism has 2 peak times of onset: during the first year of life and after the age of 3 years. Ketotic hypoglycemia is the most likely cause of hypoglycemia with onset after 1 year of age. In toddlers, hypoglycemia may result from ingestion of alcohol, aspirin, and other drugs (see Box 363-1). Hypoglycemia is rare after the age of 5 years.

#### History

A history of other affected family members or the occurrence of unexplained infant deaths among close relatives suggests the possibility of an inherited metabolic disorder. Some disorders associated with hormonal deficiencies and hyperinsulinism also may be familial. The physician should inquire about the frequency of hypoglycemic episodes, the possibility of drug ingestion, and the malicious administration of drugs. The temporal relationship of symptoms to food intake is important in assessing for hypoglycemia. In hereditary defects of amino acid and organic acid metabolism, hypoglycemic symptoms may occur shortly after the ingestion of protein. Symptoms that occur after the ingestion of lactose suggest galactosemia; those that occur after sucrose ingestion suggest HFI. In contrast, fasting hypoglycemia is characteristic of ketotic hypoglycemia, hormonal deficiencies, hyperinsulinism, GSD, and FDPase deficiency (see Table 363-1).

#### Laboratory Evaluation

At the time hypoglycemia is suspected in a child, a diagnostic blood sample for glucose, insulin, GH, cortisol, ketone bodies, lactic acid, and amino acids must be obtained, generally before the low blood glucose level has been corrected. These measurements provide important information concerning cause. Unnecessary blood sampling can be minimized by using a bedside glucose meter to decide if the patient is truly hypoglycemic during a symptomatic episode. If available blood volume is a limiting factor, then judgment must be used in ranking the importance of these tests, with measurement of the blood glucose and insulin levels receiving priority. Urinary ketones, as well as specific tests for urinary glucose and non-glucose-reducing substances, should also be determined. If ketones are present, then the urine should be tested further for presence of amino acids and organic acids. For diagnostic purposes, the administration of glucagon can be useful; a robust glycemic response to glucagon strongly suggests hyperinsulinism.

### Diagnostic Evaluation for Specific Disorders

#### Hyperinsulinism

Hyperinsulinism in infants and older children is usually characterized by fasting hypoglycemia, even if of only a

few hours' duration, and low fasting plasma levels of  $\beta$ -hydroxybutyrate and free fatty acids. Frequent random simultaneous measurements of blood glucose and insulin levels, particularly before feeding and as hypoglycemia occurs, help identify patients who have hyperinsulinism (see Table 363-1). The diagnosis depends on detecting inappropriate insulin secretion by demonstrating insulin levels disproportionately high relative to blood glucose values, particularly during hypoglycemia. A high rate of glucose infusion ( $>12$  mg/kg/min) is often necessary to maintain euglycemia. Leucine or tolbutamide challenges are not helpful in delineating the specific cause of hyperinsulinism.

In any child who has intermittent attacks of non-ketotic hypoglycemia, the physician should always investigate the possibility of malicious or self-administration of insulin or oral sulfonylurea drugs. Measurement of C-peptide, insulin, and insulin antibodies in blood may identify the patient who has an exogenous source of insulin. In contrast to patients who have endogenous hyperinsulinism, C-peptide levels are suppressed; insulin antibodies may be present in patients to whom insulin has been administered. In children who have received oral hypoglycemic agents, plasma insulin and C-peptide levels may be misleading; however, the drug may be detected in the child's blood or urine.

### Inborn Errors of Metabolism

A suggested outline for the investigation of hypoglycemia caused by inborn errors of carbohydrate

metabolism is provided in Table 363-1 and Table 363-2. These studies should be performed in a pediatric metabolic center but only when the child's condition is stable and the blood glucose level is normal. Judgment must be exercised in choosing the proper diagnostic test to delineate the underlying abnormality. The presence of specific hepatic enzyme deficiencies may be determined by the use of other tolerance tests (see Table 363-2). The tolerance tests are performed after a variable period of fasting and only with a primary care physician in attendance, who must be prepared to interrupt the test by administering intravenous glucose should symptoms and signs of hypoglycemia occur or should a low blood glucose level be detected. Definitive diagnosis of any of the inherited disorders of carbohydrate metabolism (see Box 363-1) except galactosemia depends on assay of specific hepatic enzyme activities (see Table 363-2). Galactosemia, on the other hand, may be detected by the absence of galactose-1-phosphate uridylyltransferase activity in red blood cells; thus liver biopsy is unnecessary for its definitive diagnosis.

### Hormone Deficiencies

Laboratory studies should include determination of GH and cortisol in the blood, particularly when the child has hypoglycemia (see Table 363-1). Hypoglycemia is an excellent stimulus for GH and cortisol secretions; therefore low values of either hormone in the presence of hypoglycemia raise suspicion of deficiencies of these hormones and the need for further studies. In patients

Table 363-2

Differential Diagnosis of Hepatic Enzyme Defects

BLOOD VALUES	GSD-I	GSD-III	GSD, PHOSPHORY-LASE ENZYME SYSTEM	FDPase	HFI
<b>FASTING</b>					
Glucose	↓	↓ or N	↓ or N	↓	N
Lactic acid	↑	N	N	↑	N
<b>AFTER GLUCOSE<sup>A</sup></b>					
Glucose	↑	↑	↑	↑	↑
Lactic acid	↓	↑	↑	↓	↔
<b>AFTER GLUCAGON<sup>A</sup></b>					
Glucose	↔	↑ <sup>b</sup>	↑ or ↔	↑ or ↔ <sup>c</sup>	↑ <sup>d</sup>
Lactic acid	↑	↔	↔	↑ or ↓	↔
<b>AFTER GALACTOSE<sup>A</sup></b>					
Glucose	↔	↑	↑	↑	↑
Lactic acid	↑	↑	↑	↔	↔
<b>AFTER FRUCTOSE<sup>A</sup></b>					
Glucose	↔	↑	↑	↓	↓
Lactic acid	↑	↑	↑	↑	↑

FDPase, Fructose-1,6-diphosphatase; GSD, glycogen storage diseases; HFI, hereditary fructose intolerance.

↑, increased; ↓, decreased; ↔, no change; N, normal.

<sup>A</sup>Tolerance tests done after variable fasting period.

<sup>B</sup>Two hours after feeding.

<sup>C</sup>Variable; dependent on duration of fast.

<sup>D</sup>No increase in glucose at time of fructose-induced hypoglycemia.

who have suspected hypopituitarism or GH deficiency, magnetic resonance imaging and computed tomography of the brain may be of diagnostic help. Correction of hypoglycemia by intravenous administration of glucose makes up the treatment of acute episodes. Specific treatment depends on identifying the underlying hormonal deficiency. However, if GH or cortisol deficiency is suspected on clinical grounds, then empirical replacement therapy should be started while awaiting test results. Patients should be encouraged to avoid prolonged fasting.

## MANAGEMENT

Healthy, full-term infants are functionally and metabolically programmed to make the transition from their intrauterine-dependent environment to their extrauterine existence without the need for metabolic monitoring. Full-term infants are equipped with homeostatic mechanisms that preserve adequate energy substrate to the brain and other vital organs. Thus routine newborn screening for blood glucose concentration is not necessary. Glucose water supplement should not be given to breastfeeding newborn infants unless a medical indication exists. However, many healthy infants and young children, in contrast to adults, cannot maintain normoglycemia during a 24-hour fast. The glycogen stores of healthy infants are sufficient only to meet glucose requirements for 8 to 12 hours in the absence of caloric intake; therefore after 24 to 36 hours of fasting, the young child depends totally on gluconeogenesis for glucose production. Because of relatively lower protein and fat stores, fasting infants and young children may not be able to supply sufficient substrates for adequate glucose production. Hence the primary care physician caring for a child requiring surgery or other procedures accompanied by fasting must prevent hypoglycemia by ensuring that extended fasting is avoided, by administering parenteral glucose before and after surgery, and by monitoring the patient's blood glucose level.

### Immediate Management

After appropriate laboratory tests are sent, hypoglycemia should be corrected by administering 2 to 4 mL/kg of 10% to 25% glucose intravenously. Intravenous fluids containing appropriate electrolytes and glucose should be given at a rate sufficient to maintain plasma or serum glucose levels above 50 to 60 mg/dL. A common mistake is to think that the hypoglycemia resolved after the initial bolus and failing to follow up with sufficiently frequent blood glucose monitoring to determine the adequacy of the continuous glucose infusion. The blood glucose level should be monitored initially every 30 to 60 minutes at the bedside until stable, then every 2 to 4 hours, and the rate of glucose administered should be adjusted accordingly. Overcorrection with subsequent hyperglycemia may complicate fluid management by causing an osmotic diuresis. In term healthy neonates, biochemical "hypoglycemia" is treated with early frequent sucking and skin-to-skin contact (kangaroo care). This was found effective in maintaining body temperature and safe blood glucose levels with no need for supplemental feeds.

Significant hypoglycemia should be evaluated on an inpatient basis to allow for close monitoring. During transport to the hospital, personnel experienced in intravenous techniques and rapid bedside blood glucose determinations must ensure that adequate amounts of glucose are infused continuously. The previously obtained diagnostic blood samples should be sent with the patient to the hospital, preferably on ice. The child who has hypoglycemia should be under the combined care of a pediatric specialist and primary care physician.

### Hyperinsulinism

Patients with hyperinsulinism require a higher rate of glucose infusion ( $>12$  to  $14$  mg/kg/min) to maintain a normal blood glucose level compared with other conditions causing hypoglycemia. The further management depends on the age at onset of the condition.

### Diazoxide

An infant's response to diazoxide is of great diagnostic and therapeutic value in hyperinsulinism. Diazoxide raises blood glucose levels primarily by suppressing pancreatic insulin secretion. In patients in whom diazoxide results in restoration of normal glucose levels, use of the drug is continued, and the patients are assessed periodically until approximately 5 to 7 years of age. Some patients remain euglycemic without medication by this age. The knowledge that many of these patients harbor genetic defects supports the concept that although clinical improvement may occur with increasing age, abnormalities of glucose regulation remain. Because hyperglycemia, ketosis, and hyperosmolar nonketotic coma can occur with diazoxide therapy, the parents should be instructed to monitor urinary glucose and ketones.

Diazoxide acts by inhibiting the  $\beta$ -cell SUR. Although it is effective in many children, hyperinsulinism caused by SUR mutations may not respond to this drug. If hypoglycemia associated with hyperinsulinism persists or recurs despite diazoxide therapy, then octreotide, a long-acting analog of somatostatin, may be used. Tachyphylaxis has prevented its long-term use in all but a small number of severely affected children.

### Surgery

Congenital hyperinsulinism of infancy (CHI) is characterized by inappropriate insulin secretion resulting in persistent hypoglycemia, which can lead to irreversible severe neurologic damage in the infant. Most patients with CHI respond to medical therapy. Surgery is needed if medical therapy fails. Surgical strategies vary, depending on whether the disease is focal or diffuse. Near-total pancreatectomy is the procedure of choice for diffuse CHI, whereas a localized resection is curative in focal CHI. Open surgery is the traditional approach to pancreatic resection. However, laparoscopy is increasingly used, particularly in localized resection for focal disease.

### Carbohydrate Enzyme Defects

In treating carbohydrate enzyme defects, a significant advance has been the introduction of continuous nocturnal glucose-containing gastric feedings. To maintain

normal blood glucose levels during the day, frequent feedings, at least every 3 to 4 hours, are essential. Foods rich in fructose and galactose should be avoided. The daily oral administration of an uncooked cornstarch suspension has been beneficial in older children but not as effective in infants in maintaining normoglycemia and attaining adequate metabolic control.

### Galactosemia

When the diagnosis of galactosemia is suspected, the patient should be given a galactose-free diet immediately. This diet should be maintained carefully while the primary care physician awaits the results of erythrocyte enzyme studies and should be continued if the diagnosis is confirmed. Long-term management consists of avoidance of lactose- and galactose-containing foods.

### Hereditary Fructose Intolerance

The acute episodes of hypoglycemia are reversed promptly by the intravenous administration of glucose. Long-term treatment consists of strict elimination of dietary fructose and of fructose in cough syrups and other drugs.

### Fructose-1,6-Diphosphatase Deficiency

Treatment of acute attacks of FDPase deficiency consists of correcting the hypoglycemia and acidosis by intravenous infusion of glucose and sodium bicarbonate. Long-term management should emphasize the avoidance of fasting and the provision of a fructose-free, high-carbohydrate diet.

### Ketotic Hypoglycemia

In patients with ketotic hypoglycemia, the primary care physician should document hypoglycemic blood glucose levels at the time of symptoms by obtaining a diagnostic blood sample. After the child has had several days to recover from the acute episode and is eating well, the administration of a provocative low-calorie, high-fat ketogenic diet has been useful in establishing the diagnosis if a blood sample is unobtainable. The child must be observed carefully for hypoglycemia during the test period.

The acute hypoglycemic attacks are reversed by the intravenous administration of glucose; glucagon usually has no effect. Because the attacks occur infrequently, long-term drug therapy is not indicated. A liberal carbohydrate diet, including a bedtime snack, should be followed. Prolonged overnight fasting, particularly during weekends or holidays and periods of illness, should be avoided. The parents should be encouraged to test their child's urine for ketones during illness or periods of fasting. Carbohydrate-containing foods, given promptly when acetonuria develops, are usually successful in aborting attacks.

### WHEN TO ADMIT

- Any child with documented hypoglycemia not caused by insulin therapy should be hospitalized for careful monitoring and diagnostic testing. These patients need to be referred to an endocrinologist.

- If hypoglycemia is diagnosed in an infant younger than 3 months, then surgical intervention may be necessary. Surgical exploration is usually performed in severely affected neonates who are unresponsive to glucose and somatostatin therapy.

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## Chapter 364

# INCREASED INTRACRANIAL PRESSURE

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Elevated intracranial pressure (ICP) is a potentially life-threatening neurologic or neurosurgical emergency. Rapidly identifying and managing the cause can prevent serious morbidity and possible mortality. Elevated ICP has many causes, and symptoms can be acute, subacute, or chronic.

### PATHOPHYSIOLOGIC CONSIDERATIONS

The skull in older children and adults is closed and rigid and filled with 3 compartments—the brain (80%–90% of the volume), circulating cerebrospinal fluid (CSF; 5%–10% of the volume), and circulating blood (remainder of the volume). The Monro-Kellie doctrine dictates the pathophysiologic relationship of these compartments when altered. Based on this dictum that the relative volume is fixed, small increases in any of these compartments will result in a compensatory decrease in the others. ICP rises if the increase exceeds normal compensatory mechanisms. Also affecting this variable is the brain's compliance (stiffness), which is altered in various disease states. Changes in brain compliance dampen compensatory mechanisms because the brain accounts for most of the intracranial volume.

Normal ICP in older children and adults is usually 7 to 15 mm Hg in the recumbent position, and is lower in young children. ICP is pulsatile and varies around a baseline; variation results from cardiac and respiratory activity. Transient increases of up to 50 mm Hg or higher normally occur with actions that increase intrathoracic pressure or that impede venous return, such as coughing, sneezing, and straining. However, ICP returns rapidly to baseline when these actions are discontinued.

Under normal conditions, blood flow to the brain is autoregulated, maintaining a constant perfusion level



over a range of blood pressures. A disruption in autoregulation makes blood flow pressure passive, which, in turn, can lead to significant changes in cerebral perfusion with any change in blood pressure. The cerebral perfusion pressure (CPP) is the mean arterial pressure minus the ICP. CPP falls when ICP increases, leading to further cerebral compromise, ischemia, swelling, and further increases in ICP. This cycle may persist and ultimately cause death if not treated.

## ETIOLOGY

Many factors can cause increased ICP in children, which can be classified as shown in Box 364-1. Depending on the cause, intracranial hypertension can be chronic (as with pseudotumor cerebri) or acute (as with head trauma resulting in cerebral edema or intracerebral hemorrhage). Common causes of increased ICP in children include head trauma, infection, hydrocephalus, and mass lesions.

In idiopathic intracranial hypertension (pseudotumor cerebri), the mechanism is less clear, but, based on experimental data, is thought to be derived from 2 primary mechanisms—vasogenic extracellular brain edema and delayed reabsorption through the arachnoid villa. Idiopathic intracranial hypertension may be compounded by secondary exacerbation of intracranial venous sinus compression that results in further reduction of flow across the arachnoid villi. This condition predominantly affects young, obese women of childbearing age. Among young women of childbearing age, risk factors include the following:

1. Medications (vitamin A in infants, isotretinoin [Accutane], corticosteroids, all-trans-retinoic acid for treatment of promyelocytic leukemia, levothyroxine, tetracycline, trimethoprim-sulfamethoxazole, cimetidine, nalidixic acid, nitrofurantoin, recombinant growth hormone)
2. Endocrinopathies (recent weight gain, menstrual irregularity, adrenal insufficiency, Cushing disease, hypoparathyroidism, hypothyroidism, and excessive thyroxine replacement)
3. Chronic renal failure
4. Systemic lupus erythematosus

## SIGNS AND SYMPTOMS

Signs and symptoms of both acute and chronic increased ICP are presented in Box 364-2. Many of these are the same between the acute and chronic forms, demonstrating their somewhat nonspecific nature. The temporal pace of development differs between the 2 forms. Acute signs of rapidly increasing ICP result from displaced neuronal tissue through the several dural openings, with subsequent compression and ischemic changes to the cerebral structures. For example, with uncus herniation in association with supratentorial masses, the uncus is displaced through the tentorial opening, leading to compression of the ipsilateral third nerve and displacement of the peduncles and brainstem laterally (Figure 364-1). Clinically, the patient is comatose and has an ipsilateral pupillary dilation (third nerve palsy) and ipsilateral hemiparesis, which suggests a falsely localizing lesion in the contralateral hemisphere. The pupil reliably

### BOX 364-1 Causes of Increased Intracranial Pressure in Children

#### HEAD TRAUMA

- Cerebral edema
- Intracerebral hemorrhage
- Extracerebral hemorrhage (subdural, epidural)

#### VASCULAR CAUSES

- Arterial or venous infarctions
- Intracerebral hemorrhage
- Dural sinus thrombosis
- Subarachnoid hemorrhage
- Vascular anomalies (vein of Galen malformation, arteriovenous malformations)

#### NEOPLASTIC CAUSES

- Primary brain tumors
- Metastatic (intracerebral, meningeal infiltration)
- Hydrocephalus (congenital or acquired, communicating or noncommunicating)
- Pseudotumor cerebri (benign intracranial hypertension)
- Central nervous system infections
- Meningitis (bacterial, fungal, mycobacterial)
- Encephalitis (focal or diffuse)
- Abscess

#### METABOLIC CAUSES

- Inborn errors of metabolism (hyperammonemia)
- Hepatic encephalopathy
- Diabetic ketoacidosis
- Renal failure
- Reye syndrome
- Status epilepticus
- Hypoxic-ischemic encephalopathy
- Fluid-electrolyte abnormalities (hyponatremia, hypernatremia)

#### STRUCTURAL CAUSES

- Craniosynostosis

localizes the side of the lesion. Downward herniation of the cerebellar tonsils through the foramen magnum leads to compression and vascular compromise of the lower brainstem structures (medulla) (see Figure 364-1). Patients are comatose and exhibit decorticate or decerebrate rigidity and autonomic (respiratory and circulatory) changes. The symptoms of a widened pulse pressure, bradycardia, and deep, slow respiration are classically referred to as the *Cushing triad*. Clinically, this triad is rarely seen.

## DIAGNOSIS

The key to managing increased ICP is rapidly recognizing intracranial hypertension in a patient. As with

### BOX 364-2 Symptoms and Signs of Acute and Chronic Increased Intracranial Pressure in Children

#### INFANTS

##### Acute

- Irritability
- Poor feeding or emesis
- Split sutures (especially lambdoidal)
- Bulging fontanelle
- Altered mental status
- Seizures
- Parinaud sign (upgaze paresis)

##### Chronic

- Irritability
- Poor feeding or emesis
- Increased head circumference
- Bulging fontanelle
- Split sutures (especially lambdoidal)
- Apparent developmental arrest or regression
- Parinaud sign (upgaze paresis)

#### CHILDREN

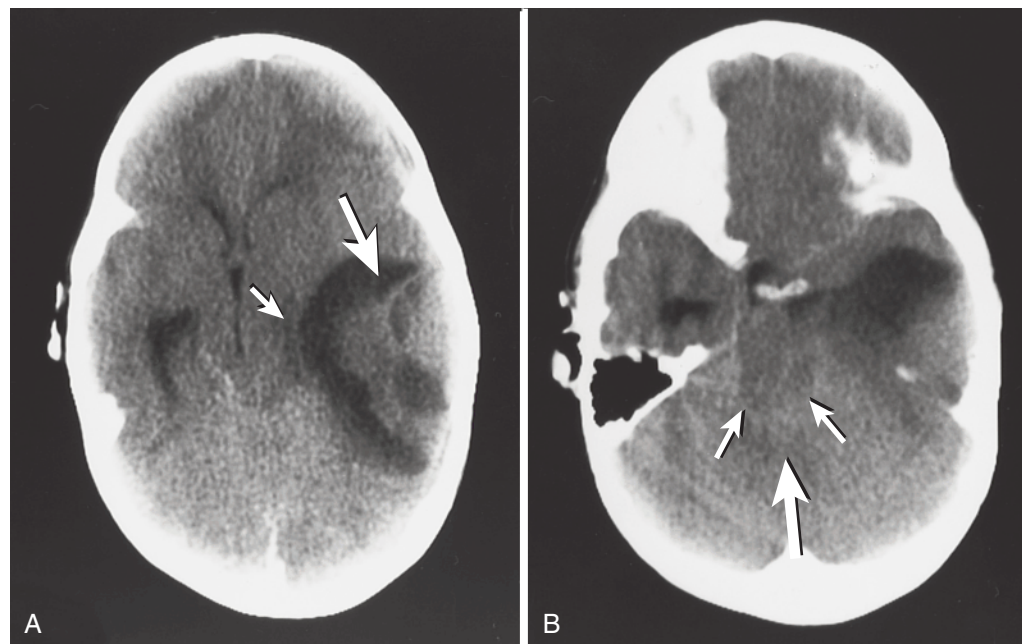
##### Acute

- Severe, acute headache
- Seizures

- Emesis
- Rapidly deteriorating mental status
- Decerebrate or decorticate posture
- Focal neurologic deficits
- Papilledema
- Pupillary abnormalities
- Autonomic dysfunction (Cushing triad)

##### Chronic

- Chronic, progressive headache
- Seizures
- Early morning emesis
- Change in school performance
- Altered mental status
- Cranial neuropathy (eg, sixth cranial nerve palsy)
- Focal neurologic deficits
- Papilledema
- Visual changes

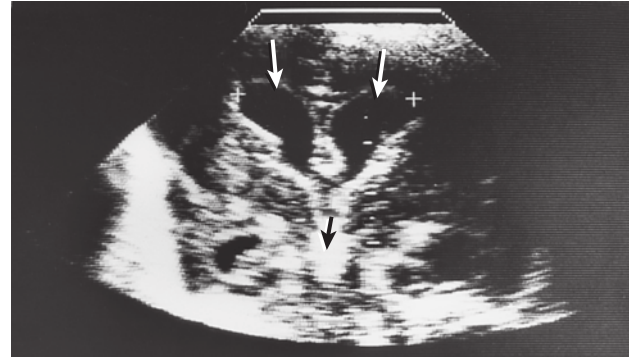


**Figure 364-1** Two sections from a computed tomography scan of a 5-year-old girl who is comatose and has increased intracranial pressure. **A**, Large, cystic left temporal lobe mass (*large arrow*) causing left uncus herniation (*small arrow*) with loss of perimesencephalic cistern and midline shift. **B**, A lower cut demonstrating loss of the fourth ventricle (*large arrow*) and a quadrigeminal cistern (*small arrows*), suggesting downward (tonsillar) herniation.

any individual with neurologic complaints, the history and physical and neurologic examinations are the most important aspects of the initial diagnostic evaluation. These examinations provide the physician with information on the pace of the illness, which allows the physician to discern the need for urgent versus emergent management. If a rapidly evolving process (eg, impending herniation) is evident, then stabilizing the patient is essential before proceeding to definitive diagnosis and therapy.

Performing a lumbar puncture (LP) provides an opportunity to evaluate the ICP by inserting a spinal needle into the thecal sac, attaching a manometer, and measuring the CSF column height while the patient is in the lateral decubitus position with legs extended. CSF opening pressures obtained during LP in this fashion correlate with ICP. It is important to note that instant measures of CSF pressure in a fluid column may be misleading because of its dynamic nature; measurement should, therefore, be averaged over 30 minutes. Opening pressures may also be influenced by age, body mass index (BMI), and depth of sedation. Normal opening CSF pressures range from 12 to 28 cm of water. However, if a mass lesion is suspected, then withdrawing lumbar CSF may create a pressure gradient intracranially and precipitate a herniation syndrome; therefore, neuroimaging is generally recommended before an LP. The lone exception is in children suspected of having meningitis, in which case neuroimaging before an LP may unnecessarily delay antibiotic treatment. If meningitis is a serious consideration and a computed tomography (CT) scan is still desired, then antibiotic therapy should not be delayed pending completion of the CT scan and, in turn, the LP. A spinal fluid analysis should always include glucose and protein measurement and a total and differential cell count. Depending on the clinical situation, other studies can be obtained, including microbial cultures (bacterial, fungal, viral, mycobacterial), special stains, and cytology.

CT or magnetic resonance imaging (MRI) can provide essential information in diagnosing and managing patients with increased ICP. Although MRI provides better anatomic differentiation than CT, it is often unavailable in the emergency setting; therefore, CT is performed more often than MRI. If a mass lesion is suspected, then neuroimaging (regardless of modality) should include contrast enhancement. Both modalities are effective in evaluating the cause of intracranial hypertension and are performed primarily to determine the presence of a mass lesion. The only exception is in the patient suspected of having a subarachnoid hemorrhage, when CT followed by LP remains the mainstay of initial diagnosis. It is important to note that children with severe traumatic brain injury (TBI) may not demonstrate radiologic signs on CT to indicate intracranial hypertension. Finally, ultrasonography is a reasonable alternative to CT or MRI in infants suspected of having aqueductal stenosis (Figure 364-2). Other neuroimaging studies, such as angiography, rarely play a role in the initial diagnostic management of intracranial hypertension.



**Figure 364-2** A coronal head ultrasound of a baby born at 30 weeks' gestation with a history of an intraventricular hemorrhage with increasing head circumference. Prominent dilated lateral ventricles (*white arrows*) and a clot-filled third ventricle (*black arrow*) are demonstrated.

## MANAGEMENT

Rapidly recognizing and stabilizing the patient suspected of having acutely increased ICP is essential in preventing greater morbidity and mortality. The goal of early management is to lower ICP without compromising cerebral perfusion and to identify the cause so that definitive therapy can be provided, whether medical or neurosurgical. Management is usually directed toward definitive therapy for patients with chronically elevated ICP.

As in any emergency, the first step in management is to assess the airway, breathing, and circulation (the ABCs). Also useful is to obtain a fingerstick glucose and, in the case of trauma, to expose the patient completely so as to identify injuries. The following initial steps should be taken when acute increased ICP is suspected:

1. Stabilize the airway. In most instances, this step requires rapid, controlled intubation, taking care to minimize any patient Valsalva maneuvers, which increase ICP further, albeit transiently.
2. Obtain intravenous (IV) access. Use only isotonic solutions, minimizing fluids initially unless circulatory compromise is evident.
3. Measure the vital signs and assess the neurologic state rapidly and frequently.
4. Position the head at 30 degrees and maintain a midline position in the event an injury to the cervical spine exists.
5. Maintain adequate intravascular volume and blood pressure.
6. Maintain adequate oxygenation.

Following these initial maneuvers, further interventions should be attempted based on the patient's clinical situation. The pediatric section of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies issued evidence-based practice guidelines for the acute medical management of severe TBI in infants, children, and adolescents that provide specific recommendations as they relate to acute intracranial hypertension.



treatment. These guidelines were adapted from previously published guidelines for adult TBI treatment. Based on these guidelines, further interventions to consider for treating intracranial hypertension are discussed in the following sections.

### Monitoring Intracranial Pressure and Removing Cerebrospinal Fluid

There is growing evidence for the benefit of monitoring ICP despite the lack of Level I evidence, especially in severe TBI. Maintaining normal ICP allows for the maintenance of adequate CPP, oxygenation, and metabolic substrate delivery while preventing cerebral herniation. ICP- and CPP-targeted protocols and therapies have improved outcomes. ICP monitoring and control of intracranial hypertension have become standards of care in adult patients with severe TBI treated at many hospitals with neurocritical care facilities and are recommended by the Brain Trauma Foundation. However, its implementation and use in the pediatric population is quite sporadic. The guidelines in the pediatric population support ICP monitoring and recommend treatment goals to keep ICP under 20 mm Hg and maintain CPP above 40 mm Hg.

Numerous invasive devices are available to assess ICP, including intraventricular catheters that allow CSF drainage, therefore reducing ICP. This is the most accurate and cost-effective method of monitoring ICP. The disadvantage is the higher risk of infection, seizures, and hemorrhage compared with other available devices. A fiberoptic catheter tip pressure transducer or strain gauge device placed within the brain parenchyma provides an effective way to continuously monitor ICP with minimal morbidity. Intraparenchymal catheters that measure brain tissue oxygenation ( $\text{PbO}_2$ ) and oxygen delivery ( $\text{DO}_2$ ) and microdialysis catheters that allow for measurement of substrates such as pyruvate and lactate enable monitoring for brain ischemia and can be used in conjunction with ICP monitoring. Jugular bulb indwelling catheters enable measurement of cerebral venous oxygenation. Transcutaneous, transcranial near-infrared spectroscopy can assess ICP and cerebral perfusion indirectly and noninvasively.

In severe TBI, standard ICP and CPP monitoring often do not reflect true  $\text{DO}_2$ . The combination of ICP and  $\text{PbO}_2$  monitoring using  $\text{PbO}_2$ -directed critical care is associated with improved outcomes. High ICP correlates with decreased cerebral  $\text{DO}_2$ . Monitoring ICP and  $\text{PbO}_2$  allows early recognition of low oxygen delivery states, hence enabling appropriate therapeutic intervention.

### Hyperventilation

Cerebral blood flow is exquisitely sensitive to carbon dioxide levels. Low carbon dioxide levels lead to cerebral vasoconstriction, whereas elevated levels lead to dilation. Early hyperventilation (HV) of the patient with increased ICP leads to a decrease in cerebral blood volume and a decrease in ICP. This method is the most rapid and effective way to lower ICP acutely. This effect is transient; therefore, other methods must be employed to maintain normal or near-normal ICP. Current recommendations support short periods of

hyperventilation ( $\text{PaCO}_2$  30–35 mm Hg) as therapeutically useful.

Further decreases can lead to a significant decrease in cerebral blood flow, producing ischemia and further increasing ICP. Failure to respond to HV is often a poor prognostic sign. Evidence suggests that the alkalizing effect of HV, and, therefore, lowered ICP, can be minimized through IV buffers, such as tris hydroxymethyl aminomethane.

HV, although long a mainstay in the treatment of increased ICP, was recently called into question as possibly causing more harm than good. HV induces a more pronounced change in cerebral blood flow than in cerebral blood volume, which can lead to a reduction in oxygen pressure despite the beneficial affect on CPP and ICP. One study found that aggressive HV had worse outcomes for patients with early, severe head trauma than those who were normocapnic. Although HV is the most rapid method for lowering ICP acutely, aggressive HV is not beneficial for the chronic treatment of increased ICP. The recent guidelines suggest considering aggressive HV ( $\text{PaCO}_2 < 30$  mm Hg) for refractory intracranial hypertension for brief periods while monitoring for brain ischemia, including brain tissue  $\text{O}_2$  ( $\text{PbO}_2$ ), cerebral blood flow, or jugular venous oxygen saturation. Mild HV ( $\text{PaCO}_2$  30–35 mm Hg) may be considered for longer periods for intracranial hypertension refractory to other modes of treatment.

### Osmotic Agents and Diuretics

Intravenous osmotic agents (mannitol and glycerol) do not permeate the blood–brain barrier and, therefore, draw fluid from the intracellular brain compartment to the vascular space, thereby reducing ICP and allowing increased cerebral perfusion. Traditionally, mannitol is favored over glycerol; however, one study found that although mannitol decreased ICP, it did not improve cerebral oxygen pressure. Mannitol is given rapidly in an initial IV bolus of 0.5 to 1 g/kg. Following this administration, additional boluses ranging from 0.25 to 0.5 g/kg should be given every 2 to 5 hours, depending on the patient's status. Response to IV mannitol is rapid and usually occurs within 10 to 20 minutes. Serum osmolarity should be maintained in the 295- to 320-mOsm/L range. Mannitol is excreted renally, so it cannot be given in the setting of renal failure because it can provoke potentially life-threatening pulmonary edema. Glycerol acts in a similar fashion to mannitol, but has lost favor because of its potential for creating a reversed osmotic gradient and a rebound increase in intracranial pressure, intravascular hemolysis, and other side effects.

Loop diuretics such as furosemide reduce ICP by provoking a diuresis of water and electrolytes, thereby establishing a gradient between the intravascular compartment and the brain. Diuretics must be used cautiously in patients with TBI and subarachnoid hemorrhage because volume depletion can worsen the outcome. Diuretics are often used in combination with osmotic diuretics, but are seldom used alone. Care must be taken when using any of the aforementioned agents to maintain intravascular volume and adequate blood pressure. Electrolytes must be monitored carefully.



### Hypertonic Saline

The use of hypertonic saline for treatment of increased ICP has become much more popular because of a number of small trials demonstrating its efficacy and safety. It is administered in various concentrations and volumes of 3% to 23.4% hypertonic saline via IV. IV boluses can reduce ICP and augment CPP for several hours. Hypertonic saline creates an osmotic gradient and draws water from the intracellular and extracellular spaces into the intravascular compartment. It can be given quickly and requires lower fluid volumes than osmotic agents. Central venous access is required for administration, although the first dose may be given peripherally in emergent situations. No immediate concern exists for volume depletion, as can occur with mannitol. The potential side effects include hyperosmolar central pontine myelinolysis, congestive heart failure, subdural hematomas, and, rarely, coagulopathy. The trauma guidelines provide recommendations for the continuous infusion of 3% saline between 0.1 and 1.0 mL/kg/hour administered on a sliding scale with the minimal dose needed to maintain ICP under 20 mm Hg. Alternatively, periodic infusions of 23.4% NaCl can be administered as 30-mL boluses over 15 to 30 minutes in the manner of mannitol for ICP spikes greater than 20 mm Hg and have been shown to be as effective and possibly safer than mannitol. Serum osmolarity should be maintained below 360 mOsm/L when using hypertonic saline as the only hyperosmolar therapy to control brain edema.

### Neuromuscular Blockade

Using agents such as pancuronium and vecuronium can effectively decrease ICP by preventing maneuvers that increase intrathoracic pressure, such as coughing, straining, or *bucking* the ventilator. The physician must remember that these agents do not provide analgesia or sedation; therefore they should be used in conjunction with analgesic agents and short-acting sedatives. Succinylcholine should be avoided for its potential for transiently raising intracranial pressure.

### Temperature Control

Hyperthermia leads to greater cerebral metabolism; therefore, measures should be taken to prevent body temperature elevation. This process generally includes judicious use of antipyretics, cooling blankets, and antibiotics if infection is suspected. Conversely, hypothermia decreases cerebral metabolism and may be advantageous in managing elevated ICP, as long as shivering is prevented and efforts are made to maintain full cardiorespiratory function. Although the guidelines provide Level II and Level III recommendations for the use of moderate hypothermia (32°C–33°C) in early severe TBI to reduce intracranial hypertension, a recent major trial of hypothermia in pediatric TBI was stopped because of futility. Body temperature should be maintained between 36°C and 37°C (96.8°F and 98.6°F).

### Seizure Control

Seizure activity, whether clinical or subclinical, places excessive metabolic demand on already compromised

brain tissue. Treatment with antiepileptic drugs is necessary for any patient who is having or is suspected of having seizures, especially if neuromuscular blocking agents are to be used. In general, diazepam (0.1 mg/kg/dose IV) or lorazepam (0.05–0.1 mg/kg/dose IV) is to be used in treating acute seizures. For more prolonged therapy, phenytoin, fosphenytoin (a water-soluble prodrug of phenytoin), or phenobarbital can be used. Phenytoin and fosphenytoin have the distinct advantage of not depressing mental status. Phenytoin needs to be given slowly (50 mg/min). Although fosphenytoin can be given more rapidly (150 mg/min), it is water soluble and, therefore, can also be given intramuscularly. Levetiracetam has gained considerable popularity for its favorable side-effect profile and has consequently become the preferred first-line agent in seizure prophylaxis in many centers. A recent phase II Levetiracetam trial for children with acute head injury at risk for post-traumatic epilepsy showed both safety and efficacy. If possible, the cause of seizure activity (eg, fever, drug toxicity, hypoglycemia, electrolyte abnormalities) should be identified and treated.

### Corticosteroids

Corticosteroids are not currently recommended in managing acutely elevated ICP associated with head trauma, intracerebral hemorrhage, and ischemic stroke per the guidelines for management of pediatric severe TBI. Several controlled studies involving the use of glucocorticoids in head injury did not find any change in outcome or benefit for controlling increased ICP. However, they do have clear utility in managing edema associated with brain tumors and refractory pseudotumor cerebri. Their mechanism of action is unknown, but hypotheses include stabilizing the blood-brain barrier, enhancing brain energy supplies, decreasing tumor growth, reducing CSF production, and stabilizing cellular membranes. Dexamethasone is generally used.

### Glycemic Control

Hyperglycemia after head injury is associated with a poorer outcome than that for patients who are normoglycemic. Many centers now remove glucose from IV fluids and aggressively treat hyperglycemia. However, there is also evidence that intensive insulin therapy significantly increases the risk of hypoglycemia that may also adversely affect neurologic outcomes. Hence, it is suggested that intermediate glycemic goals may be the most appropriate approach.

### High-Dose Barbiturates

Treating refractory increased ICP with high doses of barbiturates can sometimes be effective. These agents act to decrease cerebral blood flow and metabolism. Pentobarbital is given for prolonged therapy; in general, an IV loading dose of 3 to 10 mg/kg is given followed by a maintenance infusion of 1 to 2 mg/kg/hour. The dose should be titrated based on the electroencephalogram with a goal of obtaining a burst-suppression pattern. This therapy should be maintained for 24 hours or more and then tapered. Side effects are common and include myocardial suppression and hypotension, often requiring pressors. Which groups of refractory increased ICP patients benefit from this therapy has

not yet been determined. Etomidate has also been demonstrated to effectively reduce ICP in severe TBI while increasing CPP. However, it is also associated with adrenal suppression. Pentobarbital should be used only when all other medical and surgical therapies have failed.

### Surgical Decompression

Obviously, removing large intracranial masses causing acutely increased ICP can be lifesaving. Surgery may also play a role in decreasing ICP in select patients with large intracerebral hemorrhages by removing the clot, in trauma patients with massive edema and contusion, or in patients who have a large cerebral infarction through craniectomy or decompression of the edematous mass. In the latter 2 instances, surgery is performed after all other measures have failed and increased ICP becomes refractory, but it should be considered before the ICP critically impairs the CPP.

The trauma guidelines recommend considering decompressive craniectomy to treat severe TBI and medically refractory intracranial hypertension, particularly when a potentially recoverable brain injury occurs. Although mortality in children with severe TBI remains high, craniotomy has been shown to be effective in reducing ICP and can be associated with favorable outcomes in surviving patients.

In pseudotumor cerebri, management is based on symptoms (intractable headache) or when signs of papilledema or visual loss are detected. Imaging studies are recommended to screen for mass lesions or hydrocephalus, although most have normal scans. CT of the head may show small, slit ventricles. MRI of the brain with gadolinium enhancement is the preferred modality for its sensitivity in screening for other conditions. Magnetic resonance venography is recommended for patients with suspected dural venous sinus thrombosis and may show extraluminal narrowing of the transverse sinus that may be a typical feature of pseudotumor cerebri. LP is recommended to document opening CSF pressure and may be used therapeutically to decrease ICP by draining CSF. Medical management includes the use of carbonic anhydrase inhibitors (acetazolamide) to decrease CSF production. Digoxin has also been suggested as a comparable alternative with the same effect, but lesser side effects. Patients with severe symptoms or visual loss, or failing standard medical therapy, may also benefit from a short course of high-dose corticosteroids (prednisone).

Patients with pseudotumor cerebri failing medical therapy or those experiencing progressive visual loss may be considered for surgical treatment that includes CSF shunting procedures (ventriculoperitoneal, ventriculoatrial, or lumboperitoneal shunt) or optic nerve sheath fenestration.

### Future Trends

In the future, cerebral protectants, such as free radical scavengers, excitotoxic amino acid antagonists, laze-roids, and *N*-methyl-D-aspartate receptor antagonists, may be part of the cocktail in the initial emergent management of acutely increased ICP.

## OUTCOME

Increased ICP is a major complication that affects morbidity and, possibly, ultimate outcome in at least 50% of children who have severe head injuries and in children who are comatose from other cerebral insults (eg, hypoxia, infections, metabolic disorders). It is still uncertain which variables—ICP, CPP, or initial Glasgow coma scale score (see Table 360-2 in Chapter 360, Head Injuries)—are helpful in predicting prognosis. Emerging studies are exploring various biomarkers in CSF and blood that may predict outcomes in brain injury. Regardless, significant morbidity remains for children with increased ICP. Clearly, in select children with mass lesions or treatable metabolic disorders, early identification and treatment before a catastrophic increase in ICP occurs will improve outcome. Evidence has shown marked reduction in mortality and decreased rate of intracranial hypertension when the guidelines for management of severe TBI are adhered to.

With respect to neurologically stable patients who exhibit evidence of chronically increased ICP, management is directed toward definitive therapy; that is, evacuating the chronic subdural hematoma, appropriate tumor management (corticosteroids, surgery or radiation plus chemotherapy or both), and treatment with acetazolamide, loop diuretics, steroids, or a lumbar drain in patients who have more benign causes of intracranial hypertension.

### WHEN TO REFER

- Macrocephaly or accelerating head growth (*crossing percentiles*)
- Chronic unremitting headache or new onset of severe headache
- Mild papilledema
- Visual abnormalities (field cuts, diplopia)
- Developmental arrest or regression

### WHEN TO ADMIT

- Bulging fontanel
- Altered mental status
- Prolonged seizures
- New focal neurologic deficits
- Moderate to severe papilledema
- Cushing triad (widened pulse pressure; bradycardia; and deep, slow respirations)

## SUGGESTED READINGS

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## Chapter 365

# ACUTE KIDNEY INJURY

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## DEFINITION OF TERMS

Acute kidney injury (AKI) is a syndrome of sudden diminution or cessation of kidney function. The term AKI has been adopted to replace the previous clinical nomenclature of acute renal failure (ARF), because it focuses attention on early recognition of kidney insult and interventions to prevent or mitigate the effects of significant renal failure. Until 2004, more than 30 AKI/ARF definitions existed in the published literature. However, in the past 10 years, standardized, multi-dimensional, graded AKI diagnostic criteria have been developed and validated to demonstrate increasing morbidity and mortality in patients with increasing AKI severity. These criteria include the RIFLE criteria (risk, injury, failure, loss and end-stage kidney disease), the Acute Kidney Injury Network (AKIN) criteria, and the pediatric modified RIFLE (pRIFLE) criteria. Each classification system uses increasing relative changes in serum creatinine ( $S_{Cr}$ ) concentration and increasing duration of oliguria in its definition. In 2012, the Kidney Disease Improving Global Outcomes (KDIGO) AKI consensus work group harmonized the above criteria (see Table 365-1). The KDIGO criteria should be considered the standard

AKI diagnostic system, because each of its components has been validated in both pediatric and adult patient populations. It is important to understand that AKI will be fulfilled by the criteria, in most instances prior to the classic metabolic derangements previously associated with ARF, including hyperkalemia, acidosis, uremia, and fluid overload. Nonetheless, clinical decision making is still often guided by the relative volume of urine produced by a patient with AKI.

- **Nonoliguric state:** Sufficient urine volume to allow for administration of necessary fluids, nutrition, blood products, and medication without resulting volume overload
- **Oligoanuric state:** Insufficient urine volume to allow for administration of necessary fluids, nutrition, blood products, and medication without resulting volume overload

## EPIDEMIOLOGIC FEATURES

The causes of AKI in children have changed from primary kidney diseases to secondary effects of other systemic illnesses or their treatment. In studies of acutely ill hospitalized patients, the most common causes of AKI in children are congenital heart disease, sepsis, and nephrotoxic medicines.

The 3- to 5-year patient survival of an AKI episode is 57%; approximately 60% of patients demonstrate evidence of chronic kidney injury. Routine evaluation of all pediatric AKI survivors for evidence of chronic kidney disease, hypertension, and microalbuminuria may help prevent the long-term sequelae of AKI.

## ETIOLOGY

The classification of AKI should focus on determining the cause and site of kidney insult (Table 365-2). Factors leading to diminished kidney function are often grouped according to pre-renal, renal (parenchymal), postrenal, or a combination of these mechanisms. However, the recent discovery and validation of novel urinary AKI biomarkers, which provide information regarding the mechanism for particular causes of AKI, have led to a

**Table 365-1** Kidney Disease Improving Global Outcomes Acute Kidney Injury Staging Criteria

KDIGO STAGE	SERUM CREATININE	URINE OUTPUT
1	1.5–1.9 times baseline OR ≥0.3 mg/dL increase	<0.5 mL/kg/hr for 6–12 hr
2	2.0–2.9 times baseline	<0.5 mL/kg/hr for ≥12 hr
3	3.0 times baseline OR increase to ≥4.0 mg/dL OR initiation of renal replacement therapy OR In patients <18 years, decrease in eGFR to <35 mL/min/1.73m <sup>2</sup>	<0.3 mL/kg/hr for ≥24 hr OR Anuria for ≥12 hr

eGFR, estimated glomerular filtration rate.

From Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group - KDIGO clinical practice guideline for acute kidney injury. *Kidney Int*. 2012; suppl(2):1–138. Reprinted with permission.

movement away from these previous groupings to the concept and terms of functional and structural AKI.

Functional (prerenal) causes are those that diminish kidney perfusion without producing actual parenchymal injury. In children, hypovolemia is the most common clinical situation in which diminished kidney function occurs, and it usually results from dehydration associated with acute gastrointestinal losses. Hypovolemia may also occur in shock as the result of hemorrhage, burns, sepsis, or trauma. Less-common causes of functional AKI are those that diminish renal blood flow in the absence of hypovolemia, such as congestive heart failure, kidney vascular obstruction from thrombosis or embolism, nephrotic syndrome, liver failure, or increased kidney vascular resistance occasionally after anesthesia or surgery. Although  $S_{Cr}$  increase and oliguria can both occur in functional AKI, normal compensatory kidney tubular function usually persists, characterized by high urinary osmolality and low urinary sodium concentrations as the result of kidney water and sodium conservation.

AKI from intrinsic structural injury may result from glomerular, tubular, or interstitial disorders. AKI from glomerular injury results most commonly from any of the glomerulonephritides or the microangiopathy of the hemolytic-uremic syndrome. Tubular injury is often the result of prolonged ischemia or exposure to a variety of nephrotoxins. Renal ischemia may be seen in hypotensive episodes, severe dehydration, sudden hemorrhage, or sepsis. Tubular toxins may be endogenous (eg, hemoglobin, myoglobin) or exogenous (eg, medications such as aminoglycoside antibiotics), and various chemicals (eg, carbon tetrachloride, diethylene glycol, heavy metals) may cause acute parenchymal kidney failure. Drugs can also produce acute kidney failure by

inducing a hypersensitivity reaction (drug-induced interstitial nephritis). Diffuse pyelonephritis also may result in AKI, particularly in infants. Kidney cortical necrosis associated with infection, hemorrhage, or dehydration can produce significant irreversible injury to both glomeruli and tubules.

Post-renal AKI results from obstruction to the urinary flow, either from internal causes (eg, stones, anatomical obstruction from urethral or ureteral stenosis) or external compression (eg, masses, abdominal compartment syndrome).

## EVALUATION

### Relevant History

The processes contributing to kidney functional impairment can often be identified from the patient's history. Reduction in urine production is not necessary for fulfillment of the AKI definition, because kidney failure occurs not only in anuric states, but also in patients with oliguric or nonoliguric states. Some kidney insults, such as various glomerulonephritides and hemolytic-uremic syndrome, are often associated with oligoanuric AKI; others, such as aminoglycoside toxicity, will more often cause nonoliguric kidney failure. Determining the type of insult provides the physician with insights into the possible manifestations of kidney failure, the probable duration of AKI, and the overall prognosis. The history often helps distinguish between an episode of AKI in an otherwise healthy child and the acute deterioration of kidney function in a child who has preexisting, undiagnosed, chronic kidney disease. History of urinary abnormalities, fatigue, pallor, slowed linear growth, poor school performance, and anorexia extending over a period would lead the physician to suspect the latter.

**Table 365-2**

**Clinical Tests to Differentiate Functional From Structural Oliguric Acute Kidney Injury**

TEST	FUNCTIONAL AKI	STRUCTURAL AKI	DISCRIMINATION
<b>SODIUM CONSERVATION</b>			
Urine sodium concentration ( $U_{Na}$ )	<20 mEq/L	>40 mEq/L	Poor
Fractional excretion of sodium ( $FE_{Na}$ ); $FE_{Na} = (U_{Na} \times S_{Cr}) / (S_{Na} \times U_{Cr}) \times 100$	<1	>1	Good
Fractional excretion of urea ( $FE_{urea} = (U_{UN} \times S_{Cr}) / (BUN \times U_{Cr}) \times 100$ )	<35	$\geq 35$	Good for patients on diuretics
<b>WATER CONSERVATION</b>			
Urine osmolality ( $U_{osm}$ )	>500 mOsm/L	<350 mOsm/L	Poor
Urine-serum osmolality ratio ( $U_{osm}/S_{osm}$ )	>2	<1.1	Fair
Response to diagnostic challenge with intravenous mannitol and furosemide	Urine flow increase	No change	Good

AKI, acute kidney injury; BUN, blood urea nitrogen; Cr, creatinine; Na, sodium; S, serum; U, Urine; UN, urea nitrogen.

Children with nonoliguric acute tubular necrosis can have fractional excretion of sodium less than 1%. The  $FE_{Na}$  test is only helpful for oliguric AKI in patients not receiving loop diuretics. The threshold for  $FE_{Na}$  in neonates is 3% and not 1%.



Acute kidney injury may be heralded by seizures. Seizures can be precipitated by hypocalcemia, hypertensive encephalopathy, uremia, and water intoxication. It is not unusual for a child to first have a sudden onset of seizures and other signs of central nervous system dysfunction, only to be found to have AKI.

### Physical Findings

Many children with AKI will have markedly diminished urine output. Complete anuria is unusual and leads to consideration of a catastrophic renovascular event or urinary obstruction. In the child who has anuria or oliguria, fluid retention can produce edema, water intoxication, vascular overload with congestive heart failure, pulmonary edema, hypertension, or any combination of these. In many instances, the fluid overload is iatrogenic, resulting from attempts to increase urinary output by increasing fluid intake. Early detection of fluid retention is determined best by short-term weight gain on serial measurements and carefully recorded intakes and outputs, with appropriate allowances for insensible fluid losses. In contrast, nonoliguric AKI may be clinically covert; it is usually suspected only after laboratory tests reveal an elevation in  $S_{Cr}$  or an electrolyte imbalance.

In the intensive care unit (ICU), where daily weight assessment is often not feasible, relative percent fluid overload (%FO) can be calculated with the following formula:

$$\%FO = [(Fluid\ intake\ (liters) - Fluid\ output\ (liters))/ICU\ admit\ weight\ (kg)] \times 100\%$$

Relative %FO has been shown in multiple pediatric ICU studies to be independently associated with

mortality and prolonged ventilator support. It is important to note that measured intake and output were used for these studies and insensible losses were considered to be negligible.

### Laboratory Findings

The biochemical disturbances that contribute to clinical findings in AKI are complex and interrelated. Inherent to the diagnosis of severe AKI is the accumulation of nitrogenous waste products, characterized by a rise in blood urea nitrogen and  $S_{Cr}$ . If hypotonic fluids have been used in excess to hydrate the patient, then dilutional hyponatremia and anemia may affect central nervous system and cardiac function adversely.

Hyperkalemia is often the result of injudicious potassium administration or inadequate renal potassium excretion. (Table 365-3 lists treatment options.) Hyperkalemia is a potentially life-threatening complication of AKI and can be especially severe in disease states associated with cellular damage and the consequent release of intracellular potassium (hemolysis, burns, trauma, and infections). Hyperkalemia produces a state of increased neuromuscular excitability, including a vulnerability to cardiac arrhythmias. Unfortunately, hyperkalemia produces no consistent physical signs; diagnosis depends on the measurement of serum potassium and, if indicated, assessment of the electrocardiogram for evidence of altered cardiac electrical activity.

In AKI, metabolic acidosis develops as the result of the kidney's failure to excrete hydrogen ions and reabsorb bicarbonate. Furthermore, any state associated with increased catabolism, such as shock, fever, poor caloric intake, or extensive tissue damage, may

**Table 365-3** Treatment of Hyperkalemia in Pediatric Patients

AGENT	DOSE	EFFECT	REMARKS
Calcium gluconate (10%)	50 mg/kg IV over 2–4 min	Rapid but transient	Monitor electrocardiogram for bradycardia during injection; may be repeated but <i>not likely</i> to be effective.
Sodium bicarbonate (8.4%) Glucose (50%)	1–2 mEq/kg IV by slow push 0.5–1 g/kg IV by slow push	Rapid but transient Within 1–2 hr	Repetition <i>not</i> recommended. Attempt to increase blood glucose to 250 mg/dL; may be maintained by infusion of 30% glucose at rate equal to insensible fluid loss.
Insulin (regular)	0.1 units/kg IV	Rapid	Give <i>only</i> with hypertonic glucose infusion (30%).
Sodium polystyrene sulfonate (Kayexalate)	1 g/kg PO or PR	3–6 hr	Side effects: gastric irritation (nausea and vomiting), diarrhea, or fecal impaction; PO more effective than PR; enemas should be retained >60 min—removed by cleansing enema; may cause <i>hypokalemia</i> : use cautiously in patients who tolerate sodium loads poorly; also chelates $Ca^{+}$ and $Mg^{+}$ . The FDA has placed a warning for the medication with respect to the potential for intestinal necrosis. <sup>a</sup>

$Ca^{+}$ , Calcium ion; IV, intravenous;  $Mg^{+}$ , magnesium ion; PO, orally; PR, rectally.

<sup>a</sup>Full warning available at [www.fda.gov/Safety/MedWatch/SafetyInformation/ucm186845.htm](http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm186845.htm).

accentuate the degree of acidosis as a result of increased production of organic and inorganic acid radicals. The acidosis promotes further hyperkalemia resulting from movement of intracellular potassium into the extracellular space as the body attempts to accommodate the higher hydrogen ion concentration. Respiratory compensation for an underlying metabolic acidosis may cause low carbon dioxide pressure, resulting from tachypnea or Kussmaul breathing.

Failure of phosphate excretion can lead to hyperphosphatemia. The hypocalcemia associated with hyperphosphatemia may exhibit clinically as tremors, tetany, or seizures.

## MANAGEMENT

Acute kidney injury management should begin before consulting with a nephrologist and before initiating renal replacement therapy. Maintenance of adequate urine volumes and prevention and treatment of metabolic derangements comprise the goals of therapy in children with AKI. Preservation or restoration of renal perfusion with appropriate fluid resuscitation and inotropic agents is essential and is the first measure to maintain urine output in critically ill patients.

*Goal-directed fluid therapy* is a term that represents the use of physiologic endpoints such as heart rate, central venous pressure, and mean arterial pressure to guide initiation and termination of fluid resuscitation of patients in shock. Goal-directed fluid therapy leads to better survival in adults with shock. Adult patients who receive early goal-directed fluid therapy in the emergency department (ED) receive more fluid in the ED, but receive less fluid and have better survival in the ICU compared with patients who receive standard therapy. Although fluid resuscitation in critically ill children is essential to treat acute hypovolemic and septic shock state, the concept that worsening fluid overload is associated with worse outcomes in critically ill pediatric patients who require renal replacement therapy has been the focus of recent pediatric study. Both single-center data and a multicenter effort, the Prospective Pediatric Continuous Renal Replacement Therapy Registry Group (known as the ppCRRT Registry) demonstrate that worsening fluid overload in patients receiving continuous renal replacement therapy (CRRT) is an independent risk factor for mortality, as assessed by the pediatric risk of mortality score, irrespective of the severity of illness. These data, coupled with the predilection for early multiorgan system failure and death in critically ill children, argue for early and aggressive initiation of renal replacement therapy. Earlier initiation at lesser fluid overload degrees may allow for more expeditious optimal nutrition and blood product provision without further fluid or waste product accumulation, and may prevent the worsening volume overload and, in particular, pulmonary edema. Because most pediatric drug dosing is based on ICU admission weight, worsening fluid overload might increase the volume of distribution of inotropes, antimicrobials, and chemotherapeutic agents, thereby resulting in underdosing.

Medication dosing should be altered for specific drugs that are primarily eliminated by the kidneys; drug

dose or interval (or both) may need to be altered based on the level of kidney dysfunction. In addition, drug concentrations can be wholly or partially reduced by dialysis in patients who receive either intermittent or continuous renal replacement therapy. Factors associated with enhanced dialytic elimination include low volume of distribution and low protein binding.

Well-designed prospective randomized studies of adult patients at risk for acute tubular necrosis have called into question the utility of intravenous furosemide or renal-dose dopamine in preventing oliguria. Other recent studies support the use of fenoldopam, a dopamine  $\alpha$ 1-agonist, to prevent AKI in certain critically ill adult populations. To date, no large prospective, controlled study has been conducted with respect to the optimal pharmacologic management of pediatric AKI.

### WHEN TO REFER

- For guidance on diagnostic evaluation
- Management of complex fluid, mineral, electrolyte, and blood pressure abnormalities
- Evaluation of dialysis options and preparation for and implementation of dialysis or CRRT treatment
- Disease-specific management

### WHEN TO ADMIT

- When AKI is unexplained, rapidly progressive, or oliguric or anuric
- In the presence of severe or potentially dangerous fluid or metabolic abnormalities (eg, hyperkalemia, hypocalcemia, acidosis, clinical fluid overload, dehydration)
- For renal biopsy

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *What Is a Pediatric Nephrologist?* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Nephrologist.aspx](http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Nephrologist.aspx))

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## Chapter 366

## MENINGOCOCCEMIA

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## DEFINITION OF TERMS

Meningococcemia is a classic example of fulminant bacterial sepsis and is the most dreaded consequence of infection with *Neisseria meningitidis*. Although occult or chronic meningococcemia is detected occasionally, patients with the severe form of the disease can progress from a state of good health to death in hours, regardless of whether meningitis is present.

## EPIDEMIOLOGY AND ETIOLOGY

*Neisseria meningitidis* is an aerobic gram-negative coccus that appears typically in pairs (diplococci) with the adjacent sides flattened. The organism is enclosed by a cell envelope containing outer membrane proteins and lipopolysaccharide (endotoxin) and by a polysaccharide capsule. Thirteen serogroups have been identified based on the antigenic structure of the capsular polysaccharide. Six of these serogroups are responsible for most human disease: serogroups A, B, C, Y, W-135, and X. Additionally, multilocus sequence typing (MLST), a procedure for sequencing housekeeping genes of *N meningitidis*, has led to the recognition of sequence types (STs) used in epidemiologic investigations.

*N meningitidis* is found only in the human nasopharynx and is spread via respiratory droplets or contact with secretions. Invasive meningococcal disease is an uncommon event, with most individuals colonized only intermittently with the organism. In nonepidemic conditions, about 5% to 30% of the population is colonized, with the peak age of colonization in adolescence. Closed populations, such as military recruits, can have rates as high as 80%, and carriage rates are even higher in household contacts of infected patients. Colonization with both pathogenic and nonpathogenic *Neisseria* spp., in addition to other gram-negative organisms that have structurally similar carbohydrate antigens, induces the development of natural immunity to *N meningitidis*.

Nonetheless, *N meningitidis* causes both epidemic and endemic disease worldwide, with fluctuations in the incidence of disease usually varying over 5- to 8-year cycles. Despite these fluctuations, *N meningitidis* remains a leading cause of meningitis and sepsis in children and young adults. Between 1998 and 2007, 1525 cases of meningococcal disease occurred annually in the United States, with an overall incidence of 0.53 cases per 100,000 people. The highest incidence of disease is consistently found in infants, with an attack rate of 5.38 cases per 100,000 population. From 20% to 25% of all cases of meningococcal disease occur in children younger than 2 years, when passively acquired maternal antibody concentrations have reached their nadir and a substantial number of children have not yet acquired

protective antibodies after colonization. A second, smaller peak of disease is found in adolescents and young adults 14 to 24 years of age, with rates of 0.78 cases per 100,000 population.

Risk factors associated with the development of invasive disease in adolescence include male gender, symptoms of an upper respiratory tract infection, marijuana use, and attendance at night clubs. Polymorphisms in genes involved in host response also appear to confer an increased susceptibility to disease with *N meningitidis*. These genes include factor H, a complement regulator, interleukin-1 receptor antagonist (IL-1RA), surfactant protein A, and carcinoembryonic antigen cell adhesion molecules. Pathogen factors that have been associated with virulence include the polysaccharide capsule, the repertoire of adhesin molecules used by the organism, and the regulation of bacterial metabolism, with invasive disease linked to only a subset of highly virulent strains.

The serogroup distribution of *N meningitidis* causing invasive disease varies across regions. From 1998 to 2007, serogroups B and C were each identified in about 30% of cases of meningococcal disease in the United States, with serogroup Y accounting for 35% of isolates. Despite the relative equality in the overall number of cases caused by each of these 3 serogroups, 52% of disease caused by serogroup C occurred in persons between 2 and 24 years of age, whereas almost half of disease caused by group B occurred in children younger than 9 years of age, making serogroup B meningococci more of a threat to the younger age groups. Serogroup Y disease has been found to be associated with older age groups and the clinical syndrome of pneumonia. The occurrence of meningococcal infection also varies with the seasons. Winter and spring constitute the peak time of disease in the United States. Several older studies have shown an association between meningococcal disease and influenza and other viral respiratory infections, although the exact nature of this interaction is not clear.

Fifty percent of cases of invasive meningococcal disease are associated with meningitis; about 35% are classified as bacteremia, 9% pneumonia, and 2% arthritis. The overall mortality rate for meningococcal disease is 5% to 15%. Patients with meningitis tend to have lower case fatality rates than those with bacteremia or pneumonia. Subgroups of patients, such as those who have fulminant meningococcemia, can have fatality rates as high as 50% to 80% despite aggressive therapy.

## CLINICAL MANIFESTATIONS AND DIFFERENTIAL DIAGNOSIS

The classic signs of invasive meningococcal disease are hemorrhagic rash, meningism, and impaired consciousness (Figure 366-1). Fever and rash are consistent findings noted in about 70% of patients. Unfortunately, fever and rash are not specific to meningococcemia and have been described in many other infectious and noninfectious diseases (Box 366-1). In a study of more than 200 children in an emergency department with a non-blanching rash, 11% were found to have meningococcal disease. Children with meningococcemia were more likely to be judged ill by the investigators and to have a

body temperature of 38.5°C or higher, a purpuric rash, and a capillary refill time of more than 2 seconds. A similar study found that 15% of children with fever and hemorrhagic rash had documented invasive meningococcal disease. After a full evaluation, 45% of the children did not have a specific diagnosis identified, and presumably most had self-limited viral illnesses. Poor general condition, the presence of nuchal rigidity, more than 2-mm maximal diameter of skin hemorrhages, and a generalized distribution of the rash were highly associated with a diagnosis of invasive meningococcal disease. These 2 studies also confirmed the absence of meningococcal disease in children with petechial



**Figure 366-1** A 4-year-old white girl with acute meningococemia without meningitis. Note the nearly uniform distribution of petechiae over the trunk and extremities.

rashes confined to the area of distribution of the superior vena cava (above the nipple line).

Not only are fever and rash not specific for meningococcal disease, but in fact, the rash may be a late finding in the evolution of the clinical syndrome. Other common symptoms and signs include irritability or lethargy in slightly more than 50% of patients, vomiting in about 35% of children, and shock in 42%. Less frequent symptoms include delirium, headache, coryza, diarrhea, myalgia, and hypothermia. Because of the nonspecific nature of many of these symptoms, early recognition of a child with meningococcal disease is challenging, and physicians must maintain a high index of suspicion. The median time between onset of symptoms and hospitalization for pediatric patients is between 13 and 22 hours. The first specific signs noted by caretakers include abnormal color (pallor or mottling), leg pain, and cold hands and feet. These symptoms develop within the first 12 hours of illness and are present in more than one-third of the cases; hemorrhagic rash, neck stiffness, and confusion may develop in the second 12 hours of illness.

Once a rash has developed, the type and duration provide important information about the course and prognosis of the disease. Early in the infection, a tender, pink, maculopapular rash similar to that seen in rubella, secondary syphilis, or disseminated gonorrhea can appear on any part of the skin. The rash often fades rapidly with treatment, and patients who have this type of manifestation are less likely to have a fulminant course. A generalized petechial rash, most prominent on the distal extremities, including the palms and soles,

### BOX 366-1 Causal Agents and Illnesses in Which Petechiae or Purpura Occurs

Viruses	<i>Neisseria gonorrhoeae</i>
Varicella-zoster virus	<i>Neisseria meningitides</i>
Cytomegalovirus (congenital infection)	<i>Moraxella catarrhalis</i>
Variolavirus	<i>Haemophilus influenzae</i>
Coxsackieviruses	<i>Streptobacillus moniliformis</i> (rat-bite fever)
Echoviruses	<i>Pseudomonas aeruginosa</i> (erythema gangrenosa)
Colorado tick fever virus	<i>Yersinia pestis</i> (plague)
Rubella virus	<i>Bartonella henselae</i> (cat-scratch disease)
Measles virus	<i>Treponema pallidum</i> (congenital syphilis)
Alpha viruses (ie, Ross River fever)	<i>Borrelia species</i> (relapsing fever)
Lassa virus	<i>Trichinella spiralis</i> (trichinosis)
Marburg viruses	<i>Toxoplasma gondii</i> (congenital toxoplasmosis)
Nonviral Agents	Miscellaneous
<i>Rickettsia typhi</i> (murine typhus)	Henoch-Schönlein purpura
<i>Rickettsia prowazekii</i> (epidemic typhus)	Immune thrombocytopenic purpura
<i>Rickettsia rickettsii</i> (Rocky Mountain spotted fever)	Kawasaki disease
<i>Ehrlichia canis</i>	Serum sickness
<i>Mycoplasma pneumoniae</i>	Poisons
<i>Streptococcus pyogenes</i> (scarlet fever)	Erythema multiforme
<i>Streptococcus pneumoniae</i>	Erythema nodosum
Enterococcal and viridans group streptococci (endocarditis)	Systemic lupus erythematosus

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usually is associated with meningococcal disease (Figure 366-2). Initially, the lesions are discrete, 1 to 2 mm in diameter, and found in clusters where clothing puts pressure on the skin. This rash must be differentiated from that seen with Rocky Mountain spotted fever, rat-bite fever, bacterial endocarditis, and *Enterovirus* spp. infections. Scrapings of petechial lesions reveal the organism about 70% of the time.

The most ominous manifestation of meningococcal disease is an ecchymotic or purpuric rash, with a centrifugal distribution usually present in cases of fulminant meningococcemia (Figure 366-3). Meningococcemia is the most common infectious cause of purpura. Patients with purpura fulminans have a 20% to 50% mortality rate. The case fatality rate also is significantly higher in patients who have petechiae for 12 hours or less. Therefore, a febrile child who has purpura or petechiae that have been present for fewer than 12 hours should be managed as a medical emergency. The differential diagnosis of illness with petechial or purpuric exanthems includes Rocky Mountain spotted fever, plague, measles, septicemia with other bacteria, and Henoch-Schönlein purpura (see Box 366-1 for a full list).

## EVALUATION

### History

The early recognition of meningococcemia is an important determinant of survival. Most children with

invasive meningococcal disease have an illness with symptoms and signs lasting only a few hours to a day. About 25% may report a recent respiratory illness, but in general, the children have no significant medical history. Patients often describe the acute onset of fever, nausea, vomiting, irritability or lethargy, and rash. Other symptoms include myalgia, leg pain, cold hands and feet, neck pain or stiffness, sore throat, diarrhea, headache, and abnormal skin color (Table 366-1).

### Physical Examination

The physical examination of a child or adolescent with suspected meningococcemia should be performed expeditiously and with close attention to the vital signs and skin findings. A maculopapular rash may precede the more classic generalized petechiae. Petechiae are often clustered, 1 to 2 mm in size, and more prominent on the distal extremities, including the palms and soles. Purpura may also be present with the petechiae. In addition to the skin findings, the adequacy of respiration, the central and peripheral circulation, and mental status need to be evaluated to determine the presence of shock. Because of the rapid evolution of meningococcemia, frequent reassessments are warranted.

### Laboratory Testing

An infant or child with signs and symptoms of invasive meningococcal disease should be evaluated immediately with aggressive monitoring and treatment as soon as the diagnosis is reasonably thought to be present; the use of early antibiotics is associated with a decreased risk for death in some studies. If the patient is being transported to a pediatric intensive care unit, blood should be drawn, antibiotics given, and intravascular access secured beforehand. The patient should be attended during transport by a physician prepared to treat shock and respiratory failure because the disease may worsen when endotoxin is liberated after antibiotic therapy. Initial laboratory tests should include a blood culture or polymerase chain reaction (PCR) test to identify the organism, a



**Figure 366-2** Meningococcemia showing striking involvement of the extremities with relative sparing of the skin of the child's body surface.



**Figure 366-3** Ecchymotic or purpuric rash is the most significant manifestation of meningococcal disease. Note the centrifugal distribution in this child with fulminant meningococcemia.

**Table 366-1****Cumulative Proportion of Children Developing Clinical Features During the Course of Meningococcal Disease**

	<b>FATAL CASES (n=103)</b>	<b>NONFATAL CASES (n=345)</b>	<b>OVERALL (95% CONFIDENCE INTERVAL [CI])</b>	<b>MEDIAN HOUR OF ONSET</b>
<b>EARLY SYMPTOMS</b>				
Leg pain	22.3%	38%	36.7% (28-47)	7
Thirst	41.7%	40.6%	40.7% (31-50)	8
Diarrhea	54.4%	44.6%	45.2% (36-56)	9
Abnormal skin color	73.8%	53.9%	55.1% (45-65)	10
Breathing difficulty	75.7%	58.0%	59.1% (50-69)	11
Cold hands and feet	81.6%	75.7%	76.1% (67-85)	12
<b>CLASSIC SYMPTOMS</b>				
Hemorrhagic rash	94.2%	88.4%	88.8% (82-95)	13
Neck pain or stiffness	94.2%	91.6%	91.8% (86-97)	13
Photophobia	94.2%	92.5%	92.6% (87-97)	15
Bulging fontanel	94.2%	93.0%	93.1% (88-98)	15
<b>LATE SYMPTOMS</b>				
Confusion or delirium	94.2%	95.1%	95.0% (90-99)	16
Seizure	96.1%	95.4%	95.4% (91-99)	17
Unconsciousness	97.1%	95.9%	96.0% (92-99)	22

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complete blood count and differential, a partial thromboplastin time, a prothrombin time, measurement of fibrin breakdown products, and serum chemistries. If the patient is stable when first evaluated, a lumbar puncture should be performed to examine the cerebral spinal fluid for organisms, obtain cultures, and assess the prognosis more accurately. If the patient is not stable on initial assessment, the lumbar puncture should be deferred until a later time. Antibiotic therapy should never be withheld while waiting to obtain cerebrospinal fluid.

### Management

The recommended antibiotic regimen for treatment of meningococemia is aqueous penicillin G 250,000 to 300,000 units/kg of body weight per day in 4 to 6 divided doses (maximum of 12 million U/day). Although a small percentage of meningococcal isolates with intermediate susceptibility to penicillin have been identified in North America, no resistance to penicillin or ceftriaxone has been reported. Ceftriaxone, cefotaxime, and chloramphenicol are alternative antibiotics recommended for patients who have a serious allergy to penicillin (anaphylaxis). Antibiotic therapy generally is continued for 5 afebrile days or 7 days total. Rifampin is prescribed at the end of the course of penicillin to eliminate carriage of the organism from the nasopharynx (see below). Rifampin is not necessary if the patient has been treated with a third-generation cephalosporin because these agents are effective in eliminating carriage.

In addition to antibiotic therapy, patients with meningococemia often require aggressive supportive therapy in an intensive care setting, with invasive

monitoring of hemodynamic, neurologic, and respiratory function. Mechanical ventilation often is necessary to treat respiratory failure. Maintenance of optimal plasma expansion with intravenous fluids is the first step in stabilizing the circulatory system. Large amounts of fluid may be needed because of the capillary leak associated with endotoxic shock. Additionally, transfusions with platelets and fresh-frozen plasma may be necessary to correct the coagulopathy associated with meningococemia. Myocardial dysfunction precedes shock in meningococcal sepsis; therefore, the use of inotropic agents is recommended.

Supportive measures for severe purpura include treatments aimed at relieving the ischemic complications associated with vasculitis. Continuous epidural anesthesia may help in improving perfusion of the lower extremities and preventing gangrenous necrosis. The mechanism of action is thought to be vasodilation of partially occluded vessels through sympathetic blockade. If no evidence of coagulopathy exists, then an anesthesiologist can perform this type of regional block with an indwelling catheter in the caudal space. The topical administration of nitroglycerin can be useful in restoring blood flow to limited areas of skin and superficial tissues without notable adverse effects.

Other ancillary treatments include plasmapheresis, whole blood exchange, extracorporeal membrane oxygenation, and continuous venovenous hemodiafiltration. The bacterial load in whole blood measured by PCR is significantly associated with mortality, the need for dialysis or skin grafting, and limb or digit loss in meningococcal disease. The bacterial load is correlated with levels of endotoxin, and several studies have shown a link between plasma levels of endotoxin

**Table 366-2** Glasgow Meningococcal Septicemia Prognostic Score

POINTS	SCORE
Blood pressure <75 mm Hg systolic, age <4 yr and <85 mm Hg systolic, age >4 yr	3
Skin to rectal temperature difference >3°C	3
Modified Glasgow Coma Scale score <8 or deterioration of at least 3 points in 1 hr	3
Clinical deterioration in hour before scoring	2
Absence of meningitis	2
Extending purpuric rash or widespread ecchymoses	1
Base deficit (capillary or arterial) >8.0	1
Maximal score	15

A score of at least 9 has a sensitivity of 100%, a specificity of 95%, a positive predictive value of 73.7%, and a negative predictive value of 100% in predicting mortality.

Modified from Sinclair JF, Skeoch CH, Hallworth D. Prognosis of meningococcal septicaemia. *Lancet*. 1987;2(8549):38, with permission from Elsevier.

or tumor necrosis factor and multiorgan failure or disease severity, making the previously listed strategies theoretically attractive. The use of high-dose steroids in children who have meningococcal disease remains controversial.

Numerous investigators have attempted to predict the outcome for individual patients who have meningococcal disease based on laboratory and clinical data. In 1966, Stiehm and Damrosch developed a prognostic score whereby patients who had three or more symptoms (the presence of petechiae for fewer than 12 hours before admission, shock, the absence of meningitis, normal or low white blood cell counts, or normal or low erythrocyte sedimentation rates) had fatality rates of 85% or greater when the score was validated. The Glasgow Meningococcal Septicemia Prognostic Score was developed in 1987 (Table 366-2) and is designed for rapid bedside assessment without the need for multiple laboratory tests. Points are assigned for shock, a skin-to-rectal temperature differential of greater than 3°C, a pediatric-modified coma scale score of less than 8, absence of meningismus, an extending purpuric rash, deterioration in the hour before scoring, and a base deficit greater than 8. A score of 10 or greater has a positive predictive value of 87.5% and a negative predictive value of 100%. Although multiple scoring systems have been developed for invasive meningococcal disease, the Glasgow Meningococcal Septicemia Prognostic Score continues to perform well in clinical studies compared with other methods. In general, these scoring systems are used to determine which patients might benefit from more aggressive or experimental therapies and to help evaluate the usefulness of newer treatments.

## COMPLICATIONS

About half of children who survive meningococcal disease recover completely; 15% to 57% of patients, however, develop a complication of infection that may be categorized broadly as suppurative, neurologic, ischemic, or allergic. The suppurative complications include subdural effusions, subdural empyema, and acute suppurative arthritis. Suppurative complications occur in about 9% of children. Deafness occurs in 2% to 6% with significant numbers of adolescents reporting hearing or speech problems after recovering

from meningococcal disease (12% and 13%, respectively). Other neurologic sequelae noted by adolescent survivors include vertigo in 17% and seizures in 2%. Adolescents also report more subtle long-term consequences of meningococcal disease, including a decreased quality of life, increased depression and fatigue, decreased educational achievement, and decreased social support compared with matched controls up to 3 years after their disease.

The percentage of survivors who have ischemic complications such as gangrenous necrosis of the skin or extremities requiring skin grafting or amputation varies from 3% to 20%. Arthritis and pericarditis are also common sequelae of meningococcal infection, reported in 4% to 10% of pediatric cases. These complications are thought to be caused by an allergic phenomenon with immune complex deposition rather than a direct invasion of the heart or joints by the organism. Allergic arthritis and pericarditis are late in onset and more common in adults than in children. The symptoms usually are self-limited, and specific therapy is generally not required; however, drainage of pericardial or joint fluid occasionally is necessary.

Although not a true complication, complement deficiency has been reported in about 15% of adolescents and children who have meningococcal infection and is a known risk factor for the development of disease. These patients are at high risk for recurrent episodes of invasive infection. Based on this information, screening for complement deficiencies with a total hemolytic complement assay should be considered in any pediatric patient who has meningococemia.

## DISEASE CONTROL AND PREVENTION

Antimicrobial chemoprophylaxis is an integral component in the control of invasive meningococcal disease. Household, child care, and preschool contacts of patients who have invasive disease have a rate of infection about 100 to 800 times that of the general population. In addition, 50% of secondary cases occur within 5 days of the index case and 70% within 1 week. Rifampin is highly effective in eliminating carriage of the meningococcus from the nasopharynx. The American Academy of Pediatrics recommends that all household, child care, or preschool contacts or anyone directly exposed to a

patient's secretions be given chemoprophylaxis within 24 hours of recognizing the primary case. The most commonly used drug for children is rifampin at a dose of 10 mg/kg per dose (maximal adult dose is 600 mg) every 12 hours for 2 days for children older than 1 month of age and 5 mg/kg per dose every 12 hours for 2 days for infants younger than 1 month of age (Table 366-3).

Alternative agents that have been proved effective in chemoprophylaxis include ceftriaxone, ciprofloxacin, and azithromycin. Although ceftriaxone is not recommended for widespread chemoprophylactic use, a single 250-mg intramuscular dose has the advantage of being safe for pregnant women. Ciprofloxacin is not approved for children or pregnant women for the prevention of meningococcal disease, but it can be used in older adolescents and adults as a single oral 500-mg dose. However, resistance of *N meningitidis* to ciprofloxacin has been reported in the United States at low levels. Despite this finding, ciprofloxacin remains a useful drug for chemoprophylaxis in areas with only a single episode of resistance.

Vaccination is an additional cornerstone of meningococcal disease prevention. Two quadrivalent meningococcal polysaccharide-protein conjugate vaccines are licensed for use in individuals from 11 to 55 years of age, MCV4 and MenACWY-CRM. Routine immunization with a conjugate vaccine is recommended for

all children aged 11 to 18 years and for those aged 2 to 55 years with an increased risk for meningococcal disease. Both vaccines contain purified capsular polysaccharide of serogroups A, C, Y, and W-135 conjugated to a protein carrier. The conjugated protein elicits a T-cell-dependent antibody response and induces immunologic memory. In a trial comparing meningococcal polysaccharide vaccine with MCV4, among more than 800 children aged 11 to 18 years who received conjugate vaccine, 82% to 97% of children achieved 4-fold or greater increases in serum bactericidal antibody titers, and 98.6% to 99.8% achieved protective levels to all 4 serogroups. The newer MenACWY-CRM vaccine is also highly immunogenic, inducing higher bactericidal antibody titers to the 4 serogroups compared with MCV4 in subjects from 11 to 18 years of age. Additionally, MenACWY-CRM vaccine has been shown to elicit protective levels of bactericidal antibody following infant immunization, suggesting that this vaccine may be useful in the first year of life. Adverse reactions to both conjugate vaccines are mild and infrequent and are usually limited to local reactions and fever.

Unfortunately, no vaccine is currently available in the United States for protection from group B meningococcal disease. The group B capsule is not strongly immunogenic in humans and has been found to share cross-reacting antigens with human neural tissue.

**Table 366-3**

### Recommended Chemoprophylaxis Regimens for High-Risk Contacts and People with Invasive Meningococcal Disease

AGE OF INFANTS, CHILDREN, AND ADULTS	DOSE	DURATION	EFFICACY (%)	CAUTIONS
<b>RIFAMPIN<sup>a</sup></b>				
<1 mo	5 mg/kg, orally, every 12 hr	2 days		
≥1 mo	10 mg/kg (maximum 600 mg), orally, every 12 hr	2 days	90-95	Can interfere with efficacy of oral contraceptives and some seizure and anticoagulant medications; can stain soft contact lenses
<b>CEFTRIAXONE</b>				
<15 yr	125 mg, intramuscularly	Single dose	90-95	To decrease pain at injection site, dilute with 1% lidocaine
≥15 yr	250 mg, intramuscularly	Single dose	90-95	To decrease pain at injection site, dilute with 1% lidocaine
<b>CIPROFLOXACIN<sup>a,b</sup></b>				
≥1 mo	20 mg/kg (maximum 500 mg), orally	Single dose	90-95	
<b>AZITHROMYCIN</b>	10 mg/kg (maximum 500 mg)	Single dose	90	Not recommended routinely; equivalent to rifampin for eradication of <i>Neisseria meningitidis</i> from nasopharynx in one study

<sup>a</sup>Not recommended for use in pregnant women.

<sup>b</sup>Use only if fluoroquinolone-resistant strains of *N meningitidis* have not been identified in the community.

From American Academy of Pediatrics. Meningococcal infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL; American Academy of Pediatrics; 2015: 547-558.



Attempts to create broadly protective vaccine by using outer membrane proteins continue.

### WHEN TO REFER

All patients with suspected invasive meningococcal disease should be discussed with both Critical Care and Infectious Disease specialists.

### WHEN TO ADMIT

All patients with suspected invasive meningococcal disease should be admitted to the hospital for full evaluation and treatment.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Five Facts about Meningococcal Disease and Prevention* (Web page), National Meningitis Association ([www.nmaus.org/disease-prevention-information/five-facts-about-meningococcal-disease-and-prevention](http://www.nmaus.org/disease-prevention-information/five-facts-about-meningococcal-disease-and-prevention))
- *Meningococcal Disease—Information for Teens and College Students* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Meningococcal Disease* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/meningococcal/index.html](http://www.cdc.gov/meningococcal/index.html))
- *Meningococcal Vaccine* (fact sheet), Vaccine Education Center Children's Hospital of Philadelphia ([www.chop.edu/centers-programs/vaccine-education-center/vaccine-details/meningococcal-vaccine#.Vfwym5dTc8A](http://www.chop.edu/centers-programs/vaccine-education-center/vaccine-details/meningococcal-vaccine#.Vfwym5dTc8A))
- *Vaccine Information Statement: Meningococcal Vaccine* (fact sheet), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

### Medical Decision Support

- *National Foundation for Infectious Diseases* (Web site), ([www.nfid.org/default.aspx](http://www.nfid.org/default.aspx))

## AAP POLICY

American Academy of Pediatrics Committee on Infectious Diseases. Recommended childhood and adolescent immunization schedule—United States, 2015. *Pediatrics*. 2015;135(2):396–397 ([pediatrics.aappublications.org/content/135/2/396](http://pediatrics.aappublications.org/content/135/2/396))

American Academy of Pediatrics Committee on Infectious Diseases. Updated recommendations on the use of meningococcal vaccines. *Pediatrics*. 2014;134(2):400–403 ([pediatrics.aappublications.org/content/134/2/400](http://pediatrics.aappublications.org/content/134/2/400))

## SUGGESTED READINGS

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Wu HM, Harcourt BH, Hatcher CP, et al. Emergence of ciprofloxacin-resistant *Neisseria meningitidis* in North America. *N Engl J Med*. 2009;360:886–892

## Chapter 367

# PHYSICAL ABUSE AND NEGLECT

Howard Dubowitz, MD, MS; Martin A. Finkel, DO

The abuse and neglect (maltreatment) of children are pervasive problems, with short- and long-term physical and mental health and social consequences. Primary care physicians have an important role in helping address this problem. In addition to their responsibility to identify maltreated children and help ensure their protection and health, primary care physicians can also play vital roles related to prevention, treatment, and advocacy.

## DEFINITIONS

*Abuse* is generally defined as acts of commission, and *neglect* as acts of omission. To guide the states, the federal government defines child abuse as “any recent act or failure to act on the part of a parent or caretaker, which results in death, serious physical or emotional harm, sexual abuse or exploitation, or an act or failure to act which presents an imminent risk of serious harm.” Children may be in situations without an imminent risk for serious harm, although there may be risk for such harm in the months or years ahead. Most state laws include potential harm, and any interest in preventing abuse or neglect requires intervening when potential harm is a concern.

Predicting potential harm, however, is inherently difficult. Two aspects should be considered. One is the likelihood of harm; the other is the severity. In general, even a small likelihood of serious harm is worrisome, such as leaving an infant alone in a bathtub. Conversely, a greater likelihood of minor harm is often construed as less concerning. The history may be helpful. For example, a child with severe asthma may be at substantial risk for returning to the intensive care unit if she does not adhere to the treatment plan.

## Physical Abuse

Physical abuse includes beating, slapping, shaking, scalding, and biting that may injure any part of the body. Given that corporal punishment is widely accepted in the United States, what is the threshold for considering spanking or hitting as abusive? One approach is to consider any injury beyond transient redness lasting more than 24 hours as abuse. If parents do spank a child, it should be limited to the buttocks, over clothing, and should never involve the head and neck. When parents use objects other than a hand, the potential for serious harm increases. Acts of serious violence (eg, throwing an object at a child, slapping an

infant's face) should also be seen as abusive even if no injury ensues; significant risk for harm exists.

It can be argued that all physical punishment should be construed as abusive, given the substantial evidence on its short- and long-term potential harm. One review of more than 300 original articles on corporal punishment found many associations with problems in childhood (eg, aggression and delinquent and antisocial behavior) as well as in adulthood (eg, aggression, criminal and antisocial behavior, mental health problems, and abuse of one's own child and spouse).

### Child Neglect

Child neglect refers to parental or caregiver omissions in care regarding health care, education, supervision, protection from hazards in the environment, physical needs (eg, clothing, food), and emotional support that result in actual or potential harm. An alternative view to focusing on caregiver omissions in care is to instead consider the basic needs of children (eg, adequate food, clothing, shelter, health care, education, nurturance); neglect occurs when a basic need is not adequately met and results in actual or potential harm, whatever the reasons. Several state laws exclude neglect when it is thought to be primarily a result of poverty. Although state laws generally include potential harm, child protective services (CPS) often gets involved only after actual harm has occurred.

### Psychological Maltreatment

*Psychological maltreatment* and *emotional maltreatment* are interchangeable terms that reflect acts both of commission and omission that impair children's well-being and can be evidenced by emotional distress and maladaptive behaviors. Psychologically abusive behaviors by caregivers include spurning, terrorizing, isolating, exploiting or corrupting, and denying mental health, medical, or emotional care. Such caregiver behaviors may be extremely harmful, resulting in depression, anxiety, estrangement, poor self-esteem, and lack of empathy. There are, however, few or no physical indicators, and CPS generally does not become

involved unless the maltreatment is accompanied by other forms of abuse. Primary care physicians suspecting psychological maltreatment have a role in engaging CPS and facilitating an appropriate mental health assessment, which is essential to understanding a child's experience and accessing appropriate treatment. All forms of abuse and neglect should be presumed to have an associated adverse psychological effect. For example, long after bruises fade and fractures heal, emotional scars may endure.

### Sexual Abuse

Please refer to Chapter 329, Sexual Abuse of Children.

## INCIDENCE

In 2012, 3.4 million reports were made to CPS at a rate of 46 per 1,000 children. Two million (62%) of these reports were considered appropriate for investigation. The highest rate of maltreatment, 21.9 per 1,000, was for children aged 0 to 1 years. Boys accounted for 49% of victims. The rate for black children was almost twice that for white children (20.4 vs 11.0 per 1,000). This rate is likely caused, in part, by professional bias in reporting low-income and minority families for maltreatment. Professionals accounted for 59% of all reports investigated by CPS. Just 18% of investigations were substantiated. Seventy-three percent involved neglect, 18% physical abuse, 9% sexual abuse, 5% emotional abuse, and 3% medical neglect. Reported cases reflect only the tip of the iceberg; child abuse and neglect usually occur behind closed doors and are often not detected.

In 2012, 1,593 children died from abuse and neglect, a national rate of 2.2 per 100,000 children. Nearly three-fourths (70%) of fatalities were in children younger than 3 years. Boys had a higher fatality rate than girls, 2.5 versus 1.9 per 100,000. Four-fifths of child fatalities were caused by one or both parents.

## ETIOLOGY

Child maltreatment seldom has a single cause; rather, multiple and interacting risk factors usually exist at 4 levels, shown in Table 367-1. For example, a single

**Table 367-1** Major Risk Factors for Physical Abuse and Neglect

CHILD	PARENT	FAMILY	COMMUNITY/SOCIETY
Prematurity	Young/teenage	Intimate partner (domestic) violence	Violent neighborhood
"Difficult" temperament	Depression and other mental health problems	Single parent, uninvolved father	Limited access to child care
Chronic illness	Substance abuse	Poverty	Few services that support parents, families
Emotional and behavioral problems	Poor impulse control and anger management skills	Unemployment	Limited government "safety net"
Developmental disability	History of abuse as a child	Nonbiologically related adult living in the home	
Physical disability	Lack of social support		
Multiple gestation	Single parent		
	Limited knowledge of child development and unreasonable expectations		

parent with a severely asthmatic child, living in a dangerous neighborhood and with few supports, may be at relatively high risk for neglect or abuse. Although poverty and its associated burdens contribute to child maltreatment, children in middle- and high-income families can also be abused and neglected. Pediatricians need to guard against possible biases leading to overdiagnosing maltreatment in low-income families and missing the problem in high-income families.

### Protective Factors

In medicine, the orientation is to identify the pathology or problems. There are, however, invariably also positive or protective factors that help buffer the effect of risk factors. These may be internal to the family, such as a parent's wish for the child to be healthy. They may be external, such as a caring pediatrician or community program. It is valuable to identify and build on protective factors. For example, saying to the parent who has not filled a prescription for his or her severely asthmatic child, if appropriate—"I can see how much you love your daughter, and you don't want her back in this ICU. What can we do to keep her healthy?"—is more likely to be effective than calling attention to what the parent has failed to do for the child. In such ways, protective factors are useful for intervening effectively.

### PREVENTION

In general, medical responses to child maltreatment have been after the fact; preventing the problem is clearly preferable. Primary care physicians can help in several ways. An ongoing relationship in primary care offers opportunities to develop trust and knowledge of a family's circumstances. Astute observation of parent-child interactions can also reveal useful information. Pediatricians generally have excellent rapport with parents and children, and they are seen as authorities on many issues affecting children's health and development. This offers a remarkable entry to understand the child's environment and to intervene.

Naturally, there are limits to what can be achieved in the pediatrician's office, making it necessary to be well informed of community resources. There are well-studied programs such as Nurse-Family Partnership, Triple P, and Circle of Security that support families and can help prevent child abuse and neglect.

### Education and Anticipatory Guidance

Educating parents and children regarding medical conditions helps ensure implementation of the treatment plan and to prevent neglect; older children can increasingly share responsibility for their own care. Possible barriers, such as concerns about a medication's side effects or inability to pay for treatment, should be addressed. Practical strategies such as providing written care plans can help. In addition, anticipatory guidance helps with the challenges of childrearing, diminishing the risk for maltreatment. Interventions that educate parents of newborns about how to approach infant crying and the risks of shaking may help prevent abusive head trauma.

### Screening

Another approach is for pediatricians to identify and help address common risk factors for child maltreatment, such as parental depression, substance abuse, harsh punishment, and intimate partner violence. This fits well within the social history and with the recognition that these problems jeopardize children's health, development, and safety. By providing more comprehensive care, pediatricians can strengthen families, support parents, promote children's well-being, and help prevent abuse and neglect. Regular checkups—focused on prevention—offer excellent opportunities to play this role.

The Safe Environment for Every Kid (SEEK) model has been evaluated in 2 randomized controlled trials showing reduced child maltreatment and harsh punishment. Core components of the model include the SEEK training available online, use of the SEEK Parent Questionnaire to identify targeted problems, parent handouts, and ideally access to a mental health professional. Alternatively, pediatricians can briefly assess and initially manage problems, with office staff facilitating referrals to community resources.

Information obtained directly from children or youth is also important, especially given that separate interviews with teens have become the norm. Sample questions include the following:

- "How do you get along with your parents?"
- "If you're really upset about something, who do you talk to?"
- "Is anyone giving you a hard time at home?" If yes, "how so?"
- "Most kids get punished sometimes. How do you get punished?"
- "Are you sometimes hungry, and there's no food at home?"
- "What do you wish could be different at home?"

### Responding to a Positive Screen

As with the SEEK model, any concerns raised by youth require a brief assessment, initial management, and possible referral for further evaluation or treatment. More frequent office visits can be scheduled to offer support and counseling while monitoring the situation. Other key family members (eg, fathers) might be invited to participate, thereby encouraging informal support. Practices might arrange parent groups through which problems and solutions are shared. Primary care physicians also need to recognize their limitations and when other professional intervention is indicated, making knowledge of community resources essential.

Finally, many of the problems underpinning child maltreatment require policies and programs to enhance families' abilities to care for their children. Examples include improving access to health care including mental health and dental care; extending food benefit programs such as the Women, Infants, and Children (WIC) Nutrition Program and the Supplemental Nutrition Assistance Program (SNAP); and improving access to community family support centers. Primary care physicians can be effective advocates for such policies and programs.



## EVALUATION

Pediatricians are accustomed to consulting with subspecialists; pediatric experts in child maltreatment (child abuse pediatricians, or CAPs) should be viewed this way. Pediatricians should identify a local specialist in child maltreatment with whom they can consult. When the pediatrician's concern meets jurisdictional or agency criteria for suspected maltreatment, there is a statutory requirement to refer to CPS. The threshold for reporting is a *reason to believe* standard rather than certainty. If uncertain about whether a situation meets the threshold to report, the pediatrician can call CPS, share concerns, and seek advice. CPS may have information on past or current involvement. Their investigation can add helpful information on the home and family situation.

No single discipline has all the information about what a child might have experienced—hence the need for working in an interdisciplinary manner. The primary care pediatrician cannot typically directly access an interdisciplinary team, but the information he or she provides to CPS can be of great value to the team. Interdisciplinary practice provides the optimal approach to the complex problem of child maltreatment. Pediatricians focus on the medical piece of the puzzle; colleagues from mental health, CPS, law enforcement, and schools can add important perspectives and information. Interdisciplinary evaluation is optimal not only for determining whether maltreatment has occurred but also for clarifying the needs of the child and family. For example, law enforcement officers or CPS workers who have visited the home may provide useful information on the circumstances surrounding an injury (eg, the temperature of the hot water thought to have caused a child's burn) and insight into the functioning of a family. Ultimately the collective insight of several professionals is generally required to substantiate abuse, and this collaboration results in shared decision-making and liability in these complex cases.

Hearing about or seeing the results of child abuse can create a visceral response, and pediatricians need to modulate their feelings and maintain objectivity. It is best to avoid being accusatory or confrontational. Being a concerned, helping professional with a mandate to protect children will best serve the child's and the family's interests. Pediatricians can cautiously empathize, "What you've told me sounds really tough!" Most maltreated children are not removed from their caregivers. Maintaining a constructive relationship with the child's parents, without compromising the statutory requirement to report suspected maltreatment, is best.

### Obtaining a History About an Injury

The physical findings may be nonspecific, making the history especially important. A history that does not reasonably explain an injury is key to determining abuse. Caregivers may state that they did not witness the incident, which may be true. Primary care physicians generally think that parents provide an accurate history. Unfortunately, when abuse occurs, there may be deliberate or unconscious motives for not disclosing what happened. Therefore primary care physicians

need to assess carefully the likelihood that the history adequately explains the findings.

Physicians confronted with a child's injury need to decide whether the history reasonably explains the injury. This requires understanding the clinical aspects of trauma and the context in which maltreatment occurs. Carefully considering alternative explanations for the injury is essential. A thorough history is needed, which includes comprehensive psychosocial information, a thorough physical examination, and appropriate laboratory and radiologic studies.

Whenever possible, primary care physicians should obtain separate histories from each of the child's caregivers and from the child. Children can frequently explain how their injuries occurred if approached in a manner that is empathetic and nonjudgmental. Even young children can explain circumstances that lead to an injury. Children and caregivers may be reluctant to be truthful because of unrealistic fears regarding the consequences.

If a child has experienced physical discipline, open-ended questions inviting a narrative might help illuminate a child's experience. Examples include the following:

- "Can you tell me everything about what happened?"
- "Can you tell me what you want to happen?"
- "Are you a perfect child?" In response they may say yes or not always. Then ask: "What does (insert name) do when you're not perfect?" If they respond, "Puts me in time out," then ask, "If time out doesn't work, what happens next?" Children will generally explain what happened.
- "Grown-ups put kids in time out sometimes. If you could put a grown-up in time out, would you do it? What for?"

Yes-or-no questions do not enable the child to provide contextual details that better describe the experience. Encouraging children to express their feelings provides insight into the psychological effect of what occurred. Asking children what they want to happen after they describe physical punishment helps empower children. Most children respond that they just want the hitting to stop.

Leading and suggestive questions should be avoided. Examples include "I heard your dad hit you, right?" or "Did someone hit you there?"

Pediatricians are hampered by not witnessing the scene where an injury occurred. Thus they may need information collected by CPS and law enforcement professionals regarding the circumstances surrounding the injury.

### Physical Examination

Just as great care is needed when obtaining a history, the physical examination must be comprehensive and meticulous, with clear and detailed documentation. Whenever possible, injuries should be photographed, appropriately identifying the child, using a measuring scale providing a permanent and objective record, and enabling second opinions.

### Cutaneous Manifestations of Abuse

#### Bruises

Bruises are the most common manifestation of physical abuse. Primary care physicians often face the



dilemma of whether the bruise was caused by noninflicted (accidental) trauma. Bruising in preambulatory children is rare (2.2%) and should raise concern for abuse. “Cruising” (18%) and walking children (52%) often experience bruises. Noninflicted bruises are characteristically anterior and over bony prominences, such as shins and forehead, usually resulting from falls. Well-padded areas such as the buttocks, cheeks, and thighs are less likely to bruise during most activities, as are the neck, ears, and genitalia. Bruises of these areas suggest abuse. Some bruises carry the imprint of the implement used. For example, circumferential marks around the wrists, ankles, and neck may result from squeezing, grabbing, or ligatures.

Physicians may be asked to age a bruise to identify the likely perpetrator, corroborate the explanation for injuries, or confirm that injuries occurred at different times. However, precisely dating bruises is very difficult. Many factors determine the color of a bruise, including the depth of the injury, location, force employed, vascularity of the tissues, time since the injury, skin color, and ambient lighting. Previously published tables on dating bruises should be ignored.

Although bruises are the most common manifestation of physical abuse, there may be an underlying medical explanation, such as blood dyscrasias or connective tissue disorders. The family or child’s history or examination usually provides clues to these conditions. Henoch-Schönlein purpura, the most common vasculitis in young children, may be confused with abuse. If an underlying bleeding disorder is suspected, then a platelet count, prothrombin time, international normalized ratio (the ratio of a patient’s prothrombin time to a normal [control] sample, raised to the power of the International Sensitivity Index [ISI]), and partial thromboplastin time should be obtained. However, the pattern and location of bruises caused by abuse are usually different from those resulting from a coagulopathy. The presence of a medical disorder does not preclude possible abuse. Birthmarks and Mongolian spots can be confused with bruises; however, these skin markings are not tender and do not rapidly change color or size.

Cultural practices need to be considered in the differential diagnosis. Cao Gio, commonly known as *coining*, is a Southeast Asian folkloric therapy. A coin or other hard object is vigorously rubbed on the skin in a linear fashion, causing petechiae or purpura. Cupping is another approach popular in the Middle East. A heated glass is applied to the skin, often on the back. As it cools, a vacuum results, leading to perfectly circular bruises. The context is important, and such circumstances should not be considered abusive.

### Bites

Bites have a characteristic pattern of 1 or 2 opposing arches with multiple bruises. They can be inflicted by an adult, another child, an animal, or the patient. Bites by a child (younger than approximately 8 years with primary teeth) typically have a distance of less than 2.5 cm between the canines—often the most prominent bruises. Animal bites vary and usually have narrower arches than human bites and are often deep. Self-inflicted bites are on accessible areas, particularly the

hands. Adult bites raise concern for abuse. Multiple bites by another child suggest inadequate supervision and neglect. If there is a question as to whether the bruise represents a bite and whose bite it might be, it is important to photograph the bite with either an American Board of Forensic Odontology ruler if available or a known-sized object such as a coin. A photograph obtained in either way helps a forensic odontologist identify the source.

### Burns

Childhood burns may be caused by abuse (Box 367-1). More commonly, burns involve inadequate supervision or neglect, such as when a young child topples something on the stove. Scalding burns may be from immersion or splash. Immersion burns, when a child is forcibly held in hot water, have clear delineation between the burned and the healthy skin. The depth of the burn may be uniform and may have a sock or glove distribution. In many instances, no splash marks are evident, as might be expected if a child inadvertently encountered hot water. Symmetrical burns are especially suggestive of abuse, as are burns of the buttocks and perineum. A splash burn may be the result of abuse but more commonly results from accidental contact with a hot liquid. Caustic substances such as household cleaning solutions, pool chemicals, battery fluid, bleach, and drain cleaners are examples of substances that can burn on contact. Laxatives containing Senna or sorbitol can result in perianal blisters and skin breakdown in children in diapers.

Burns from hot objects such as curling irons, radiators, steam irons, metal grids, hot knives, and cigarettes have shapes that reflect the object. A child is likely to try to escape from a hot object; thus burns that are extensive and deep reflect more than fleeting contact and are suggestive of abuse. Other causes of inflicted abusive burns can involve hair dryers, microwave ovens, and stun guns.

Neglect frequently contributes to childhood burns. Children home alone may be burned in house fires. A parent compromised by prescription or nonprescription drugs or alcohol may be unable to effectively intervene if a fire develops. Children explore their environment; for example, unattended pots on the stove with projecting handles present a hazard. Liquids cool as they flow downward so that the burn is

#### BOX 367-1 Characteristics of Burns Suggestive of Abuse

- History that does not adequately explain the burn
- Burn reflecting shape of an object
- Multiple burn sites
- Deep or extensive burn
- Extremities on both sides burned, such as a glove or sock pattern
- Clear, regular edge, uniform depth, no splash marks
- Other history or examination findings suggestive of abuse

most severe and broad superiorly. If the child is wearing a diaper or clothing, hot water may soak into the fabric and cause burns worse than otherwise might be expected, with patterns that follow the child's clothing. Children may stick objects into an electrical outlet, perhaps causing internal (eg, cardiac) injury and a burn where the current exits the body. Burns may occur from electric water heaters being set much higher than the recommended 120 degrees.

Several conditions may mimic abusive burns, such as brushing against a hot radiator, car seat burns, hemangiomas, and folk remedies such as moxibustion. Impetigo may resemble cigarette burns. Cigarette burns are usually 7 to 10 mm in diameter, whereas impetigo has lesions of varying sizes. Noninflicted cigarette burns are usually oval and superficial.

Concluding whether a burn was inflicted depends on the history, burn pattern, and the child's capabilities. A delay in seeking health care may be the result of the burn initially appearing minor, before blistering or becoming infected. This circumstance may represent reasonable behavior albeit an unfortunate momentary lapse in supervision and should not be automatically deemed neglectful. A home visit to investigate the scene where the child was burned is necessary to clarify the circumstances surrounding the burn (eg, testing the water temperature). Severe burns can lead to lifelong scarring and serious psychosocial sequelae. Prevention is key, such as setting hot water cylinders at 120°F.

### Skeletal Trauma

Any bone can be fractured as a result of abuse; however, fractures strongly suggestive of abuse are classic metaphyseal lesions (ie, corner fractures at ends of long bones), posterior rib fractures, and fractures of the scapula, sternum, and spinous processes, especially in young children. These fractures all require more force than would be expected from a minor fall or routine handling and activities. Few fractures are pathognomonic of abuse, however, and all must be considered in light of the history. It is always necessary to assess whether the history plausibly explains the fracture. For example, a history that a child walked comfortably with a displaced femoral fracture is unlikely to be truthful.

The history begins with a careful family history to probe possible underlying genetic bone conditions, such as osteogenesis imperfecta. Questions should cover multiple or frequent fractures, hearing difficulties, unusual flexibility, and teeth abnormalities. These should also be asked with regard to the child. A detailed history is needed regarding the presenting injury: whether the fall was witnessed, by whom, how the child fell, from what height, onto what surface, whether there were objects in the way (eg, toy truck on the floor), how the child behaved after the fall, what the parents did, the psychosocial circumstances, and any any past history of trauma.

Multiple fractures, especially if at different stages of healing, are suspicious for abuse. The possibility of an increased susceptibility to fractures caused by an underlying bone condition needs to be considered. These conditions include osteopenia of prematurity,

osteogenesis imperfecta, metabolic and nutritional disorders (eg, scurvy, rickets), renal osteodystrophy, osteomyelitis, congenital syphilis, and neoplasia. The presence of a bone disorder, however, does not exclude the possibility of abuse.

Subperiosteal new bone formation is a nonspecific finding and can be seen in infectious and metabolic disorders or may result from trauma and thus may suggest abuse. In young infants, new bone formation may be a normal physiologic finding and is usually bilateral, symmetrical, and less than 2 mm wide.

Rib fractures in young children rarely present clinically. They are mostly diagnosed on chest radiographs obtained for another reason. Both rib and sternal fractures rarely result from cardiopulmonary resuscitation, even when performed by untrained adults. Rib fractures are likely caused by excessive compression of a young child's thorax. They are very rarely caused by birth trauma; 1 study of nearly 35,000 infants found no such injuries. Sternal fractures are mostly seen after car crashes; without such a history, they likely indicate the child was stomped on. Clavicular, femoral, supracondylar humeral, and distal extremity fractures in children older than 2 years are most likely not inflicted, unless they are multiple or accompanied by other signs of abuse. With increasing mobility and running, toddlers can fall with enough rotational force to cause a spiral, femoral fracture, meaning such fractures are not specific to abuse. Fractures of long bones, spiral and otherwise, in nonambulatory infants, however, are highly suggestive of abuse. In addition, abuse is a concern when there are other injuries including bruising, other than from high-energy impacts such as a motor vehicle crash.

Skull fractures are the most common type of fracture in children younger than 2 years, most commonly resulting from short falls from 3 to 6 feet. Of note, only 1% to 2% of children experiencing such falls fracture their skulls, usually a simple linear fracture of the parietal bone, associated with hitting a hard object such as the floor or table corner. Complex, depressed, bilateral, or basilar skull fractures require greater biomechanical forces; without a plausible history, they are suspicious for abuse.

### Radiologic Studies

A skeletal survey should be routine in children younger than 2 years with a fracture, especially if a possibility of abuse exists. When fractures are identified or concerns persist despite no findings on a skeletal survey, follow-up surveys 2 weeks later have been found to identify new previously missed occult fractures. In children between 2 and 5 years of age, the usefulness of a skeletal survey depends on the specific circumstances. *Babygrams* (1 or 2 radiographs of the entire body) do not provide adequate visualization of the entire skeleton and should be avoided. If the survey is negative but concern for an occult injury remains, a radionuclide bone scan should be performed. A scan will be generally positive for fracture within 24 to 48 hours after an injury and will remain positive throughout the stage of callous formation. Standards for a skeletal survey and other forms of imaging have been developed by the American College of Radiology.

### Timing of Injury

In corroborating the history and the injury, the age of the fracture can be crudely estimated. Soft tissue swelling generally subsides in 2 to 21 days. Periosteal new bone can be seen as early as 4 days after injury but up to 21 days later. Loss of definition of the fracture line occurs between 10 and 21 days. A soft callus on a long bone can first be observed 10 days after an injury. A hard callus is evident between 14 and 90 days. The child's age, the type of bone, and the nature of the fracture influence the healing process. The remodeling of bone can continue until epiphyseal closure. These time frames are shorter in infancy and longer when the child has poor nutritional status or a chronic underlying disease. Fractures of flat bones such as the skull do not form a callus and cannot be aged.

## Central Nervous System

### Epidemiology

The rate of inflicted head trauma has been estimated at between 16 and 34 per 100,000 infants per year. Risk factors include male infants and socioeconomic and other stressors, but not race or ethnicity. Of all inflicted injuries, those to the central nervous system result in the most significant morbidity and mortality. Long labeled "shaken baby syndrome," the recommended term is now *abusive head trauma* (AHT). This reflects our understanding that often both shaking and direct trauma are involved.

### Mechanism

Infants, with their poor neck muscle tone and relatively large heads, are most vulnerable to AHT. Shaking is considered to exert severe, repetitive, and often rotational forces injuring the brain as it moves within the skull. This may cause acute concussion, diffuse traumatic axonal injury, nonfocal acute subdural bleed, contusions, and brain lacerations. Direct contact injury may result from punching, slapping, or striking the child's head against a hard surface. Injuries include bruising, lacerations, abrasions, and soft tissue swelling of the head or face, subgaleal bleeds or cephalohematomas, skull fractures, and associated intracranial pathology related to skull deformation. It is estimated that the forces involved far exceed those occurring during normal activities and play, such as gently tossing an infant into the air and catching him or her.

### History

As with abuse in general, there is seldom a forthright account when AHT is involved. Instead, common histories include finding the previously healthy baby suddenly unresponsive or not breathing, a choking episode while feeding, a minor bump against a hard surface, or a short fall off a sofa or changing table. Multiple studies have demonstrated that such falls rarely result in skull fractures and very rarely cause significant intracranial pathology. Such histories do not plausibly explain the clinical picture of an infant with severe neurologic symptoms.

### Clinical Presentation

The clinical picture can range from mild vague symptoms to coma or respiratory arrest to death. Lucid

periods after severe head injuries are rarely seen with witnessed trauma (eg, motor vehicle crashes). Most infants lose consciousness at the time of injury; even those who remain lucid are still symptomatic. Children with less severe injuries may initially have mild symptoms, such as vomiting or irritability, before symptoms become worse.

There is naturally a spectrum of severity, and "minor" AHT may cause no overt signs or symptoms or a subtle presentation that may be missed. Subtle findings include unexplained lethargy, vomiting without fever or diarrhea, and inconsolable crying. One study of children younger than 3 years with AHT found that one-third had previously had medical encounters in which the possibility of AHT should have been considered but was missed; 28% suffered subsequent AHT. Factors associated with missed instances were normal respiration, no seizures, no facial or soft tissue injuries, and a white family with 2 caregivers.

As with fractures, the history should include a detailed account of whether any trauma was witnessed, by whom, whether and how the child fell, from what height, onto what surface, whether there were objects in the way, how the child behaved after the fall, what the parents did, the psychosocial circumstances and any past history of trauma. With multiple caregivers, obtaining separate histories is recommended. An investigation by law enforcement of the site where the injury allegedly occurred is valuable.

The physical examination may show cutaneous or other injuries, or no external sign of trauma. Bruises from attempted strangulation may be visible on the neck. In contrast, choking or suffocation may result in asphyxia and hypoxic brain injury, often with no or minimal external signs. A very thorough examination is critical. For example, there may be injuries inside the mouth or blood behind the tympanic membrane. A careful neurologic examination is needed, including coma scores. Associated cutaneous, visceral, or skeletal findings suggestive of abuse, in the absence of readily verifiable major noninflicted trauma, add to the likelihood that the head trauma was abusive.

Further evaluation including a pediatric ophthalmologic examination, laboratory testing, and radiologic studies may reveal occult trauma. Subdural hematomas, retinal hemorrhages, and diffuse axonal injury, although not exclusively caused by AHT, should always raise the question of AHT.

Subdural hematomas are commonly present, caused by shearing of the bridging veins. Subarachnoid bleeds are less common, and intraparenchymal hemorrhages are rare in AHT.

Retinal hemorrhages are a key marker of AHT. Whenever AHT is considered, a dilated indirect ophthalmologic examination by a pediatric ophthalmologist should be performed. If possible, photographic documentation should be obtained. Although retinal hemorrhages are found in other conditions, hemorrhages that are bilateral and extensive, involve multiple layers, and extend to the periphery—beyond the neonatal period and in the absence of a known medical cause—are most often caused by AHT. Severe noninflicted head trauma rarely results in retinal hemorrhages; when this does occur, the hemorrhages



tend to be few in number and confined to the posterior pole. The indirect trauma, most commonly caused by repeated acceleration-deceleration from shaking, seems responsible for extensive retinal and vitreous hemorrhages. It is not possible to estimate when the injury occurred based on the appearance of retinal hemorrhages.

Other causes of retinal hemorrhages include coagulopathy, leukemia, retinal diseases, carbon monoxide poisoning, and metabolic disorders such as glutaric aciduria. Birth-related retinal hemorrhages are very common, but superficial (*flame*) and deeper intraretinal (*dot* or *blot*) hemorrhages resolve by 1 and 6 weeks, respectively. A severe accidental life-threatening direct crush injury to the head can rarely cause an extensive hemorrhagic retinopathy. Cardiopulmonary resuscitation rarely, if ever, causes retinal hemorrhage in infants and young children, and, if so, there may be very few hemorrhages near the optic nerve. Hemoglobinopathies, diabetes mellitus, routine play, minor accidental head trauma, and vaccinations do not seem to cause retinal hemorrhage in infants. Almost all of the medical causes of retinal hemorrhage are readily diagnosed based on history, eye examination, full physical examination, and, when indicated, laboratory testing.

Another ocular finding that points strongly to abuse is traumatic retinoschisis. The retinal layers are sheared apart as a result of traction from the repeatedly accelerating-decelerating vitreous gel to which it is firmly attached. Blood accumulates between the layers. Direct trauma to the orbital region may result in corneal abrasions, subconjunctival hemorrhages, hyphema, globe rupture, and periorbital edema or ecchymosis. The postmortem examination may demonstrate posterior orbital hemorrhage and intraorbital optic nerve injury, helping differentiate noninflicted head injury from AHT.

In summary, the diagnosis of AHT is made by a careful integration of the history, examination findings, ophthalmologic consultation, and results of laboratory and radiologic studies (see Box 367-2). Alternative explanations need to be thoroughly probed.

### Orofacial Injuries

Injuries to the head, neck, and oral cavity may be seen in physically abused children. Soft tissue injuries to the upper lip or the frenulum and palate are seen in forced feeding of an infant but can also occur when a toddler trips, especially with a hard object in the child's mouth. The forceful introduction of hot or caustic liquid into a child's mouth may result in intraoral mucosal injury. Intraoral injuries represent 11% of "sentinel injuries"—relatively minor injuries that may predict more serious ones. Noninflicted trauma to the forehead, lower lip, chin, and nose is common in toddlers and is generally accompanied by a history of an accidental fall. Dentists can identify orofacial and intraoral injuries such as frenulum tears, palatal trauma, and fractured teeth. Their consultation should be considered in children with head trauma.

Blunt trauma to the ear may produce subperichondrial hematoma and intracranial injury resulting from rotational acceleration of the head. Accidental injuries of the ear are rare. A slap to the face may leave a hand

### BOX 367-2 Evaluation of Children With Possible Abusive Head Trauma

1. As with the rest of medicine, a differential diagnosis needs to be developed and plausible explanations fully probed.
2. Obtain head computed tomography (CT) scan (unenhanced).
3. Consider magnetic resonance imaging (MRI) of the head to help clarify extra-axial fluid, determine timing of injuries, assess parenchymal injury, and identify vascular anomalies. MRIs should be with T1- and T2-weighted images, different susceptibility-weighted sequences, and FLAIR sequences.
4. Consider magnetic resonance angiography and venography if a vascular anomaly is suspected.
5. A skeletal survey should be routine.
6. Check complete blood count and platelets.
7. Check liver and pancreatic enzymes. In addition, consider CT scans of the abdomen and thorax to help identify occult thoracic and abdominal injuries.
8. Consider obtaining additional laboratory tests that assist in identifying metabolic diseases such as glutaric aciduria type 1 or conditions such as osteogenesis imperfecta. These conditions are rare, but they should be obtained depending on the clinical circumstances.
9. Consultation with a child abuse pediatrician is recommended.

Derived from Kemp AM. Abusive head trauma: recognition and the essential investigation. *Arch Dis Child Educ Pract Ed.* 2011;96(6):202–208.

imprint, but even more importantly may cause injuries within the head and neck. Any blow to the head can also have significant psychological consequences.

Long-term dental neglect may result in multiple dental caries, abscess formation and risk for septicemia, eating difficulties, chronic pain, and periodontal infection.

### Abdominal Trauma

Abdominal trauma accounts for significant morbidity and mortality in abused children. Young children are especially vulnerable because of their relatively large abdomens and lax abdominal musculature. Hollow organs can be ruptured by a blow or kick. Solid organs such as the pancreas, which can be compressed against the spine when the abdomen is struck, can be injured. Indeed, any of the abdominal organs may be injured because of abuse. Intra-abdominal bleeding may result from trauma to an organ or shearing of the vascular supply. Children may have cardiovascular failure or an acute abdomen, often after a delay in care. Bilious vomiting in a young child without fever or peritoneal irritation suggests a duodenal hematoma, usually a result of abuse and acute in onset.

The manifestations of abdominal trauma are often subtle, even with severe injuries. Subclinical injuries can be identified by elevated liver and pancreatic enzymes reflecting injury not evident on imaging or examination. Bruising of the abdominal wall is



### BOX 367-3 Manifestations of Possible Neglect

Neglect may manifest in many ways. Most commonly, pediatricians encounter the following:

- *Unmet physical needs* (eg, nonadherence to treatment, delay in seeking health care, inadequate food or clothing)
- *Inadequate supervision* (eg, recurring injuries or ingestions, exposure to environmental hazards—in and out of the home, poor hygiene and sanitation)
- *Inattention to cognitive needs* (eg, little stimulation at home, not attending to child's learning or special educational needs)
- *Inadequate attention to emotional needs* (eg, not showing affection, not being supportive at times of need, not enabling mental health care for serious problems)

unusual, and symptoms may evolve slowly. Delayed perforation may occur days after the injury, and bowel strictures or a pancreatic pseudocyst may occur weeks or months later.

Primary care physicians should consider screening for occult abdominal trauma when other evidence of physical abuse exists. Screening should include urinalysis for blood and liver and pancreatic enzyme levels. An abdominal ultrasound should also be considered, although computed tomography is preferable for detecting trauma to solid organs. Children with abdominal injuries resulting from abuse may also have fractures and head injuries; these too should be considered. Noninflicted mechanisms may apply, such as a bicycle handlebar injury, but caution is needed in accepting unlikely explanations.

### Child Neglect

Neglect is the most prevalent form of child maltreatment, with potentially severe and long-lasting sequelae. Physicians may encounter several manifestations of possible neglect (Box 367-3). Initial questions to ask oneself include, "Is this neglect?" and "Have the circumstances harmed the child, or jeopardized the child's health and safety?" For example, adherence to treatment may be suboptimal without clearly impairing a child's health, or it may be life threatening. Inadequacies in the care children receive fall along a continuum, requiring a range of responses tailored to the individual situation.

Pediatricians need to be familiar with their state laws defining child abuse and neglect and the mandatory reporting requirements. For example, most states include the risk for serious harm in their neglect definition. A complementary approach is to focus on children's basic needs; when 1 or more of these needs (eg, adequate food, health care, education) is inadequately met and results in actual or potential harm, the child experiences neglect.

There are advantages to using a child-centered definition of neglect, rather than simply focusing on

parental omissions in care. It fits well with a pediatric mandate to promote children's health, development, and safety. Focusing on the child offers a more constructive way to engage parents, most of whom share an interest in their children's well-being. This approach also encourages consideration of other possible contributors to the neglect, not just a parent's behavior. For example, the physician may not have clearly explained the asthma treatment regimen. Adopting a broader view should lead to consideration of other strategies to help the family take good care of their child.

In most instances, multiple and interacting factors contribute to neglect. For example, consider a young single mother living in a rough neighborhood with her 2 children; one has asthma and the other attention deficit/hyperactivity disorder. She has few supports and faces eviction at the end of the month. Given this highly stressful situation, it is no mystery that she may struggle to cope and filling a prescription may not be a priority.

With this understanding, it is necessary to comprehensively probe what may be underpinning the neglect, recognizing that neglect is really the symptom. The assessment includes understanding possible risk factors—at the levels of child, parent, family, and community. The system of health care should also be examined. Do barriers to health care exist? Does a problematic relationship exist between the pediatrician and the parent or child? Poor adherence to treatment may be the result of not understanding the treatment plan or being worried about a medication's side effects. The pediatrician needs to be cautious not to assume that parents are responsible when a child's medical course is problematic. This may not reflect poor adherence to treatment; the disease may be inherently difficult to control (eg, "brittle diabetes"). In addition to probing for risk factors, strengths and resources (protective factors) should also be assessed; these factors are often crucial to intervening effectively. A parent's interest in keeping a child out of the hospital, for example, may motivate adherence to treatment, as may a child's interest in playing sports. A pediatrician's concern can also be a protective factor, helping to counter the family's challenges.

Pediatricians may encounter other forms of neglect. For example, a child may have inadequate clothing, or the family may be homeless—conditions that can affect children's health. Children may not be enrolled in school. A child's learning may be problematic and the school's response inadequate. A broad view of health and an interest in children's health and development require attention to such facets of their environment. Neglect is a heterogeneous phenomenon that calls for varied responses to address the specific circumstances. Some key principles are outlined later in this chapter.

### OUTCOMES OF CHILD MALTREATMENT

Child maltreatment often has significant short- and long-term medical, mental health, cognitive, and social sequelae. Physically abused children are at risk for behavioral and learning problems, including conduct disorders, aggressive behaviors, decreased cognitive functioning, and poor academic performance. There

may also be internalizing disorders, such as depression, perhaps associated with suicidality and suicide attempts. Neglect is similarly associated with many potential problems. It is apparent that a wide array of health, cognitive, and social problems may relate to physical abuse or neglect. In probing these problems, the possibility of maltreatment needs to be considered. At the same time, none of these problems is specific to abuse or neglect, limiting their usefulness in diagnosing maltreatment.

At the time of an evaluation, a maltreated child may seem to be functioning well. There remains the risk for problems emerging months or years later, and parents and pediatricians need to carefully monitor these children. Even in situations in which all appears satisfactory, a mental health evaluation and possible treatment may help address a child's troubled thoughts and feelings and prevent later problems. Child maltreatment increases the risk for several health risk behaviors and physical and mental health problems in adulthood. Maltreated children are also at risk for becoming maltreating parents. Increasingly, research is showing neurobiologic effects of child maltreatment on the developing brain, with potentially lifelong consequences.

Some children seem to be resilient and may not exhibit sequelae of maltreatment, perhaps owing to protective factors or interventions. The benefits of intervention have been found in even the most severely neglected children, such as those from Romanian orphanages, who were adopted—the earlier the better. Children who were adopted before 6 months of age fared better than those adopted at an older age.

## REPORTING, DOCUMENTATION, AND LEGAL ISSUES

### Reporting

State laws mandate that all physicians report *suspected* child abuse or neglect to the designated public agency. Some states penalize mandated reporters who fail to do so. All reporting statutes supersede any ethical duty to protect confidentiality. As long as the report of suspected abuse or neglect is made in good faith, physicians are immune from both civil and criminal liability. Whether the level of suspicion meets the threshold for reporting is sometimes a judgment call. Pediatricians need not be certain that maltreatment has occurred to make a report; reasonable suspicion is adequate, although *reasonable* is not defined in most regulations. If concerned that a child may have been maltreated, even if uncertain, it is generally necessary to report the concerns to CPS, which in turn decides whether to investigate. A report to CPS may also uncover possible past or current family involvement with the agency. Alternatively an interdisciplinary child protection team or a primary care physician with expertise in this field can provide useful guidance. If in doubt, a call to CPS is recommended.

The decision to report child maltreatment is never easy. Parental response to informing a family that a report will be made may evoke considerable anger or an understanding that reporting provides an opportunity to secure help. In great part the parental

response will depend on how the information is conveyed by the pediatrician and supported by CPS. A recommended approach is to convey one's concern for the child, which is hopefully a concern shared by parents. The basis for the concern should be explained forthrightly but kindly, without being accusatory. Framing the report positively is important to clarifying what happened and to providing helpful services. Some prefer to present the report as a legal obligation, perhaps helping parents accept the physician's role.

It is also useful to explain to parents and children what will likely ensue (eg, a visit from a CPS worker and sometimes a police officer) and what is unlikely. Parents may be anxious about the involvement of CPS, fearing that they might lose their child. Primary care physicians can cautiously reassure parents that CPS is responsible for helping children and families and that, in most instances, children remain with their parents. Even when CPS does not accept a report or when a report is not substantiated, they may offer voluntary supportive services such as food, shelter, homemaker services, and child care. State laws concerning confidentiality and reporting responsibility in suspected child abuse and neglect cases vary; primary care physicians need to know their state's laws, which are available on the Child Welfare Information Gateway Web site at [www.childwelfare.gov](http://www.childwelfare.gov) (state statute search) or by contacting the local CPS agency.

### Documentation

Clear documentation is crucial to the admissibility of all forms of evidence. Verbal and photographic documentation preserves evidence for future reference. The medical history is the verbal evidence; thus it is important to document the concerning circumstances, which may be as important as any physical evidence. Written documentation should include both the key questions asked and the verbatim responses, in quotation marks. This practice enables careful evaluation of the evidence. A clear and comprehensive record may obviate the need to testify. Whenever possible, physical evidence should be documented photographically with an accompanying measuring scale or known size object such as a dime.

### Legal Issues

Whenever a primary care physician is involved in a case of possible abuse or neglect, there is the potential for legal involvement even though few cases are tried in court. Most cases are not criminally prosecuted because of the difficulty of proving who was responsible, or not tried because many cases are plea bargained. Neglect is rarely considered a criminal offense and is seldom prosecuted. Therefore the likelihood of having to testify is generally small. In cases involving custody matters there is an increased likelihood of civil litigation.

Pediatricians who do not specialize in child abuse may testify to provide *facts* about the case, but not be allowed to provide an *expert* opinion regarding the interpretation of those facts. An expert witness is allowed by the court to *opine*, and the jury decides how to weigh the testimony. The medical evidence is 1 piece of the puzzle.

Primary care physicians provide their opinion in their capacity as the treating physician, who obtains the medical history for the purpose of diagnosis and treatment. The medical history may also be admissible in criminal court proceedings as an exception to hearsay rules of evidence. A requirement for admissibility of these out-of-court statements obtained during the history taking is that the patient understands that they are being examined for diagnosis and treatment. A simple explanation of this circumstance and documentation in the medical record help ensure admissibility of a child's statements as an exception to hearsay. This initial history may be crucial to understanding a child's experience. As cases proceed, children may recant their initial statements regarding abuse because of either direct threats or fears of consequences.

### Preparing for Court Testimony

Primary care physicians may be called to testify before a grand jury, juvenile court, or family court or in criminal proceedings. The rules guiding testimony in these various proceedings differ and span the spectrum from relatively informal to highly structured environment of criminal testimony.

The legal system is an adversarial system that can be intimidating. It is common practice for one side to undermine the credibility of witnesses supporting the opposing view. One is well advised to remain calm and not take an attack personally. Preparation with the attorney who issued the subpoena should clarify what can and cannot be said in court.

The grand jury in many states is a preliminary step to indictment. It is an opportunity for the prosecution alone to present its case. A grand jury indictment implies that sufficient evidence exists to justify a trial, and it determines what charges will be filed. If the case proceeds to trial, most primary care physicians who testify do so to describe the medical history and examination findings. A fact witness should not be asked to render an opinion regarding the likelihood of abuse. The court may, however, determine that the primary care physician can testify as an expert, thus allowing an opinion. In some cases, another expert in child maltreatment will be brought by the opposing side to interpret the findings for the court.

A subpoena is often the first notice of the need for involvement in the legal system. Subpoenas are either *subpoena ad testificandum* or *subpoena duces tecum*—the first for actual testimony and the second for supplying records. Different subpoenas may be generated on behalf of the state, the child, and the defendant. When a subpoena is received, the person issuing the subpoena should be asked to clarify what is being requested and to prepare for the legal proceeding. Prosecutors and the court generally try to accommodate primary care physicians' time constraints and schedules.

After a testimony is scheduled, meeting with the attorney who issued the subpoena provides an opportunity to discuss the strengths and weaknesses of the case and review potential questions. It is useful to consider questions that may be posed by the opposing side. If a particular question lacks clarity, it is appropriate to ask for clarification or repetition. Testimony

should educate the jury and judge and thus be presented with a calm and respectful demeanor using plain English that can be easily understood. If technical language is used, terms need to be carefully explained. If asked questions that cannot be answered, one can say, "I don't know."

Regarding testimony, the acronym HELP is helpful: honesty, even-handedness, limits of expertise, and preparation. Adhering to the HELP principles, the physician can effectively assist the court in understanding the evidence.

In the pretrial process of discovery, both the prosecutor and the defense attorney have an opportunity to learn what evidence the other possesses. The defense attorney may contact the examining physician directly to discuss the case as part of discovery. The physician is not legally obligated to comply unless the request is accompanied by a subpoena. Any information a primary care physician has should be considered privileged and confidential and should be disclosed only when the client or legal guardian consents or a subpoena requires such disclosure. In general, state laws grant CPS access to parts of medical records pertaining to a maltreatment report.

An important point to remember is that in criminal trials the defense is responsible for representing the accused; the interests of the child are secondary. Providing a balanced, objective, and defensible opinion is the responsibility of the fact and expert witnesses. This opinion should be the same whether testifying at the request of the prosecution or of the defense. The best way to prepare for testifying in court is to practice good medicine. The child's interests may be represented by an appointed "guardian ad litem" whose responsibility is to act as a fact finder for the court to assist the court in making determinations that serve the best interest of the child in court proceedings.

### TREATMENT

Treatment should address the specific problems contributing to a child's maltreatment and its consequences. Primary care physicians are naturally responsible for helping address any medical problem. Approaching problems of neglect should begin with less intrusive interventions. For example, if an infant's failure to thrive is the result of an error in mixing the formula, parent education and perhaps a visiting nurse should be the initial strategy. At the same time, ensuring a child's safety is paramount. Therefore severe failure to thrive requires hospitalization, and if the contributing factors are particularly serious (eg, a psychotic mother), out-of-home placement may be needed. Thus in neglect situations in which less intrusive efforts have not succeeded or in which the circumstances are moderate or more severe, a report to CPS should be made. CPS can conduct a home assessment that provides valuable insights to develop a fuller picture of the family situation. Physicians can be a valuable liaison between the family and public agencies, and they should make every effort to remain involved after reporting to CPS. Families are typically under great stress after a report, and the involvement of different professionals and agencies can be confusing. With frequent office visits offering support and

guidance, primary care doctors can play an important role in monitoring how a child and family are doing after a report.

In families in which maltreatment occurs, the parents may need to be nurtured before they are able to nurture their children. The parents, even if suspected as perpetrators, remain “patients” of the pediatrician and should be presumed innocent for the purpose of delivery of care to the family unless CPS or the judicial system temporarily or permanently limits their parental rights. Therefore a comprehensive assessment of the child, parents, and family is important to guide appropriate interventions. The use of informal supports such as family members, neighbors, and friends (eg, inviting the father to an office visit) should be encouraged. Families also may need other professional interventions (eg, drug treatment, mental health services); primary care physicians can help with referrals.

The importance of addressing concrete needs should not be overlooked. Accessing nutrition programs, obtaining health insurance, enrolling children in preschool programs, and helping with housing can make a valuable difference. The problems contributing to child maltreatment often require long-term professional support and monitoring; few quick fixes are available.

Although abuse and neglect may lead to physical disability and sometimes death, lasting psychological harm is a major concern. To ensure long-term positive outcomes, children and caregivers benefit especially from evidence-based mental health care. Before receiving a specific form of therapy the child should undergo a pretreatment assessment to determine the effect of the maltreatment and serve as a baseline to assess improvement. Examples of evidence-based mental health treatment modalities are trauma-focused cognitive behavioral therapy, parent-child interaction therapy, and combined parent-child cognitive behavioral therapy. The US DHHS National Registry of Evidence-based Programs and Practices is a resource for finding effective treatment approaches. ([nrepp.samhsa.gov](http://nrepp.samhsa.gov)). The National Child Traumatic Stress Network is also an excellent resource for helping children recover from trauma ([www.nctsn.net](http://www.nctsn.net)).

## ADVOCACY AND PREVENTION

The primary care physician is well positioned to understand the factors that contributed to the child’s maltreatment. Advocating for the best interest of the child and family involves identifying and addressing risk factors and must be done at the levels of individuals, family, and community. At the individual level, an example of advocating on behalf of a child is explaining to a parent that an active toddler is behaving normally and not intentionally challenging the parent. Learning about a parent’s response to a child’s difficult behavior also offers an opportunity to educate the parent regarding appropriate responses. Encouraging a mother to seek help dealing with a violent spouse, saying, “You and your life are very important,” asking about substance abuse and smoking, and assisting parents to seek health insurance for their children are all forms of advocacy.

Physicians advocate on behalf of families when they try to enhance the functioning of families. Encouraging

the involvement of fathers in child care, strengthening ties with extended family, and, in some instances, facilitating family therapy are examples of advocacy. Remaining involved after a report to CPS and helping ensure that appropriate services are provided are other examples.

In the community, physicians can be influential advocates for resources for children and families. These resources may include parenting programs, services for victims of domestic violence and their children, and recreational facilities. Physicians have many opportunities to share their knowledge of children’s physical, developmental, and emotional needs. They can participate on local multidisciplinary child death review teams or as advisors to organizations concerned with child abuse. Engaging in such activities provides opportunities to better understand the issues concerning child maltreatment and to help build safe and nurturing environments for children.

Finally, physicians can play an important role in advocating for policies and programs at the local, state, and national levels that will benefit children and families. Advocacy is needed for community-wide maltreatment prevention efforts at the primary, secondary, and tertiary levels. Primary care physicians can share their knowledge on the health and welfare of children and families with CPS colleagues. This contribution can lead to system changes that are responsive to the needs of children and families. Such efforts may include involvement with state officials along with outreach to legislators and organizations involved in child advocacy. The American Academy of Pediatrics has an office in Washington, DC that is engaged in legislative advocacy on a range of important child health issues and conducts annual training in legislative advocacy. Child maltreatment is a complex problem that has no easy solutions. Through partnerships with colleagues in child protection, mental health, education, and law enforcement, primary care physicians can make a valuable difference in the lives of many children and families. Beyond preventing abuse and neglect, they can promote children’s health, development, and safety in many ways.

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## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Child Physical Abuse* (fact sheet), American Academy of Pediatrics ([pediatriccare.solutions.aap.org](http://pediatriccare.solutions.aap.org))
- *Child Maltreatment: Prevention Strategies* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/ncipc/factsheets/cmprevention.htm](http://www.cdc.gov/ncipc/factsheets/cmprevention.htm))
- *Prevent Shaken Baby Syndrome* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

### Medical Decision Support

- *Child Abuse: Medical Diagnosis and Management*, 3rd ed (book), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))
- *Child Maltreatment: Fact Sheet* (fact sheet), Centers for Disease Control and Prevention ([www.cdc.gov/ncipc/factsheets/cmfacts.htm](http://www.cdc.gov/ncipc/factsheets/cmfacts.htm))



- *Practicing Safety: To Promote Healthy and Safe Child Development* (Web page), American Academy of Pediatrics ([www2.aap.org/sections/scan/practicing-safety/index.htm](http://www2.aap.org/sections/scan/practicing-safety/index.htm))
- *Visual Diagnosis of Child Abuse*, 4th ed (digital resource), American Academy of Pediatrics ([shop.aap.org](http://shop.aap.org))

### Community Advocacy and Coordination

- *Child Welfare Information Directory* (Web page), Child Welfare Information Gateway ([www.childwelfare.gov](http://www.childwelfare.gov))
- *State Statutes* (interactive tool), Child Welfare Information Gateway ([www.childwelfare.gov/topics/systemwide/laws-policies/state](http://www.childwelfare.gov/topics/systemwide/laws-policies/state))

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## Chapter 368

# PNEUMOTHORAX AND PNEUMOMEDIASTINUM

C. Michelle Zebrack, MD; Susan L. Bratton, MD, MPH

Pneumothorax and pneumomediastinum are uncommon events in healthy children. A pneumothorax is a collection of air in the potential space between the parietal and visceral layers of the pleura. Pneumothoraces are typically classified as spontaneous, traumatic, or iatrogenic. Pneumomediastinum is a condition in which air is present in the mediastinum. The 3 main causes of pneumomediastinum are (1) alveolar rupture; (2) perforation or rupture of the esophagus, trachea, or main bronchi; and (3) dissection of air from the neck or the abdomen. Failure to recognize and properly manage pneumothorax or pneumomediastinum can have serious consequences.

## PNEUMOTHORAX

### Spontaneous Pneumothorax

Spontaneous pneumothoraces occur in the absence of antecedent thoracic trauma and are further subdivided into primary or secondary spontaneous pneumothorax. Primary spontaneous pneumothorax affects patients who do not have *clinically apparent* lung abnormality or an underlying condition known to promote pneumothorax. Secondary spontaneous pneumothorax occurs in the setting of underlying pulmonary disease such as pneumonia, asthma, or cystic fibrosis.

Little is known about the true incidence of spontaneous pneumothorax in children; however, it is infrequent and usually related to underlying lung disease.

### Primary Spontaneous Pneumothorax

Although primary spontaneous pneumothorax is said to occur without a precipitating event or underlying lung disease, patients initially diagnosed with primary spontaneous pneumothorax frequently (76%–100%) have unrecognized lung disease, usually subpleural bullae. The incidence of primary spontaneous pneumothorax in children is not reported, but 1 study documents only 58 children with primary spontaneous pneumothorax in a 20-year period. In adults, the estimated incidence is between 7.4 and 18 cases per 100,000 population per year among men and between 1.2 and 6 cases per 100,000 population per year among women. The typical patient is a tall, thin, male patient between the ages of 10 and 30 years. Smoking increases the risk for primary spontaneous pneumothorax 9-fold among women and 22-fold among men.

### Secondary Spontaneous Pneumothorax

Secondary spontaneous pneumothorax occurs in patients with lung disease. Pediatric incidence related specifically to secondary spontaneous pneumothorax has not been reported, but the adult estimated incidence is 6.3 cases per 100,000 population per year among men and 2 cases per 100,000 population per year among women. Pneumothorax is a known complication of asthma, and, by some estimates, tension pneumothorax is present in almost 30% of patients who die suddenly from asthma. Nearly 3.5% of all patients with cystic fibrosis will experience a pneumothorax, and subsequent pneumothoraces are common. The risk for spontaneous pneumothorax is also increased in various inherited disorders, such as  $\alpha_1$ -antitrypsin deficiency, Marfan syndrome, and Ehlers-Danlos syndrome. Some familial cases without evidence of connective tissue disease do occur. Spontaneous pneumothorax is a well-recognized complication of acquired immunodeficiency syndrome (AIDS) in pediatric patients and is associated with *Pneumocystis carinii* pneumonia. Catamenial pneumothorax, a condition related to endometriosis with diaphragmatic hernia, should be considered in female patients with spontaneous pneumothorax temporally related to menstruation.

### Other Precipitating Factors

Foreign-body ingestion must be considered in any child with an unexplained pneumothorax, particularly children aged 6 months to 6 years. Exposure to loud music has been reported as a precipitating factor in patients with spontaneous pneumothorax. Spontaneous pneumothorax is associated with illicit drug use and may result from attempted jugular or subclavian vessel injection (mainlining), cavitating septic thromboemboli, forceful exhalation of crack smoke into another individual's respiratory tract (shotgunning), or deep inhalation and Valsalva maneuvers while smoking marijuana. Emesis and coughing, both Valsalva maneuvers, can also cause spontaneous pneumothorax.

### Traumatic Pneumothorax

When a child has a traumatic pneumothorax, the physician must recognize that chest trauma is often an indicator of multisystem injury (eg, life-threatening head injury, abdominal injury). Trauma to the chest is classified as blunt or penetrating. The leading causes of blunt thoracic trauma are vehicle–pedestrian injuries and motor-vehicle crashes. Falls and child abuse are also causes of blunt traumatic pneumothorax. The leading causes of penetrating thoracic trauma are gunshot and stab wounds. In 1 report of children with blunt trauma, 38% had an associated pneumothorax, hemothorax, or both. In children with penetrating thoracic trauma, 64% had an associated pneumothorax, hemothorax, or both.

### Iatrogenic Pneumothorax

Iatrogenic pneumothoraces are caused by diagnostic or therapeutic interventions, including transthoracic-needle aspiration, central venous catheter insertion, thoracentesis, and barotrauma or volutrauma related to mechanical ventilation. Rates of pneumothorax caused by mechanical ventilation have fallen in all

age groups because of improved modes of mechanical ventilation with better patient synchrony and lower tidal-volume strategies that limit delivered airway pressure. Use of surfactant has also been credited with substantial decreases in pneumothorax rates for preterm neonates (30%–65%). The observed rate of iatrogenic pneumothorax in the hospitalized pediatric population was recently reported as 0.06 per 1000 discharges. Some reports note an incidence of iatrogenic pneumothorax that exceeds that of spontaneous pneumothorax.

### Neonatal Pneumothorax

The incidence of neonatal pneumothorax depends on gestational age, birth weight, and the presence of lung disease. Spontaneous pneumothorax is present in 1% to 2% of live births, and most are term infants. Of affected infants, about one-half have symptoms. A history of delivery-room resuscitation efforts or infant aspiration of meconium or blood often exists. Pneumothoraces are common in critically ill ventilated neonates, and the incidence increases with prematurity. Pneumothorax in an infant with the neonatal respiratory distress syndrome is associated with mortality rates exceeding 60% in some studies. Familial cases of spontaneous pneumothorax in neonates have also been described.

### PNEUMOMEDIASTINUM

Pneumomediastinum is uncommon in the pediatric population and is usually self-limited. Although no apparent consensus exists regarding classification of pneumomediastinum, the term *spontaneous pneumomediastinum* is used frequently in the medical literature and is applied to younger patients who have no obvious precipitating event. The incidence of spontaneous pneumomediastinum detected by screening symptomatic infants was 25 of 10,000 live births. The incidence of spontaneous pneumomediastinum in the noninfant pediatric population is not known. The most common etiology of spontaneous pneumomediastinum in pediatric patients is bronchospasm related to respiratory tract infection. Because healthy young people do not often have severe symptoms or physical examination findings, spontaneous pneumomediastinum may go undetected, and the actual incidence is thus difficult to ascertain.

Pneumomediastinum is seen in a variety of clinical circumstances; it is often associated with exaggerated Valsalva maneuvers during cough, emesis, hiccupping, heavy lifting, straining at stool, illicit drug inhalation, and sports activities. Pneumomediastinum has been noted in situations in which external pressure changes occur, such as scuba diving and air travel. Marked decreases in interstitial pressure such as that seen with hyperpnea from diabetic ketoacidosis can also cause pneumomediastinum. Asthma is a well-recognized risk factor. Pneumomediastinum is associated with barotrauma or volutrauma secondary to mechanical ventilation or manual resuscitative ventilation. The physician must consider the possibility of foreign body as a cause of pneumomediastinum, especially in children younger than 6 years. Spontaneous esophageal perforation (Boerhaave syndrome) and

mediastinitis must be considered in the differential diagnosis.

Pneumomediastinum can be secondary to trauma and has been reported in child abuse and other blunt thoracic trauma such as motor-vehicle crashes. Isolated facial trauma has also been reported as a cause. Tracheobronchial and esophageal rupture can also cause pneumomediastinum. Care must be taken to evaluate for penetrating injury because air can enter the mediastinum from penetrating neck or chest wall injury.

### EVALUATION OF PNEUMOTHORAX

#### History

Patients often note abrupt ipsilateral pleuritic chest pain with or without acute dyspnea. Pleuritic pain may be more prevalent in primary than in secondary spontaneous pneumothorax. Dyspnea is typically quite severe in patients with secondary spontaneous pneumothorax because they have decreased cardiopulmonary reserve at baseline. Symptoms associated with primary spontaneous pneumothorax often resolve within 24 hours, even if untreated. This feature contrasts with the progressive course of secondary spontaneous pneumothorax. Respiratory symptoms might be vague in young children, and parents may note sudden dyspnea and irritability.

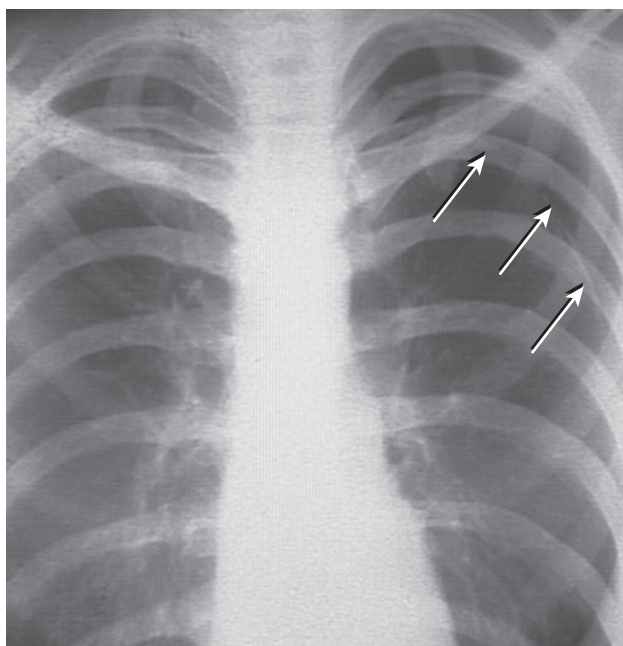
#### Physical Examination

The physical examination findings in primary spontaneous pneumothorax are variable and depend on the pneumothorax size and patient age. A patient with a pneumothorax occupying less than 15% of the hemithorax may have a normal physical examination. Most commonly, vital signs demonstrate tachycardia and tachypnea. Hypoxemia caused by a small primary spontaneous pneumothorax is uncommon in older children because most will have adequate alveolar reserve to preserve oxygenation. However, smaller children are often hypoxemic. Because the underlying lung function is normal, hypercarbia does not typically develop in patients with primary spontaneous pneumothorax. In contrast, patients with secondary spontaneous pneumothorax often have hypoxemia and hypercarbia, and as the size of the pneumothorax increases, characteristic signs such as diminished or absent breath sounds, hyperresonance to percussion on the involved side, and chest asymmetry may be noted.

Neonates may have severe respiratory distress with marked tachypnea, grunting, retractions, and cyanosis. In infants with respiratory distress syndrome or other underlying lung disease, pneumothorax can be rapidly life-threatening. Such infants may demonstrate cardiorespiratory instability and progress to cardiac arrest. Detection of pneumothorax by physical examination in infants can be difficult because of the small thorax size; however, a shift of the apical heart impulse away from the side of the pneumothorax has been reported to be a reliable sign.

Iatrogenic pneumothorax should be suspected in any patient who becomes more dyspneic after a medical or surgical procedure known to be associated





**Figure 368-1** Pneumothorax. A white visceral pleural line is separated from the parietal pleura by radiolucent air. (Used with permission from Richard Wiggins, MD.)

with the development of a pneumothorax. Iatrogenic pneumothorax should also be suspected in any patient treated with positive pressure ventilation who experiences a sudden clinical deterioration or demonstrates an unexplained increase in peak and plateau pressures or decreased tidal volume.

No matter the pneumothorax classification, hypotension, profound hypoxemia, or tracheal deviation in the setting of diminished breath sounds heralds *tension* pneumothorax, which is life threatening and requires immediate attention. Intervention for tension pneumothorax should not be delayed for radiologic imaging to confirm the diagnosis.

### Laboratory Testing

Pneumothorax diagnosis is routinely made by chest radiograph, preferably with the patient in an upright position. The main radiologic feature of a pneumothorax is a white visceral pleural line, separated from the parietal pleura by an avascular collection of gas (Figure 368-1). In many instances, no pulmonary vessels are visible beyond the visceral pleural edge. In films in which the patient is upright, the accumulation of gas occurs primarily in an apicolateral location. In supine views, more pleural gas is needed for definitive diagnosis of a pneumothorax. The pleural gas accumulates in a subpulmonic location, outlining the anterior pleural reflection, the costophrenic sulcus (the so-called deep sulcus sign), and the anterolateral border of the mediastinum.

A computed tomography (CT) scan can detect pneumothoraces that do not appear on radiograph (occult pneumothoraces) but is often not practical in the initial workup. Portable ultrasound devices may

play a role in the future, but application of thoracic ultrasound for pneumothorax in children has yet to be established. In young infants, neonatal pneumothorax must be differentiated from congenital lobar emphysema, which can appear as an expanded radiolucent pulmonary segment. A CT scan may be required to make this differentiation, which is important because the treatment for congenital lobar emphysema is lobectomy. Aspiration or chest tube placement in a patient with congenital lobar emphysema is associated with substantial risk for mortality.

In trauma patients, the presence of a large pneumothorax with persistent air leak into the pleural space despite tube thoracostomy is an indication for fiberoptic bronchoscopy to assess the possibility of a bronchial tear. Physicians must also rule out traumatic rupture of the esophagus because the mortality rate approaches 100% if surgical treatment is not prompt.

## EVALUATION OF PNEUMOMEDIASTINUM

### History and Physical Findings

Patients with pneumomediastinum may complain of chest pain, cough, and dyspnea, as well as dysphonia, dysphagia, or neck pain. The examination will often reveal subcutaneous cervical emphysema with crepitance. Less commonly, Hamman sign (a mediastinal crunching sound synchronized with systole) may be heard.

### Laboratory Testing

Pneumomediastinum is recognized by air outlining mediastinal structures such as the thymus (sail sign) or the superior surface of the diaphragm (continuous-diaphragm sign). Pneumomediastinum is usually bilateral and does not move with decubitus positioning, which helps differentiate it from anteromedial pneumothorax (Figure 368-2). However, pneumothorax may also be present.

## MANAGEMENT OF PNEUMOTHORAX

### Primary Spontaneous Pneumothorax

#### Management of Small Primary Spontaneous Pneumothorax in Adolescents and Young Adults

Although guidelines for the management of spontaneous pneumothorax in adult patients have been published by both the British Thoracic Society and the American College of Chest Physicians, no similar guidelines exist for treatment of infants and small children. The British and American adult guidelines distinguish between small and large primary spontaneous pneumothorax in the recommended treatment pathways. Small pneumothoraces are defined as less than 15% to 20% of the chest volume.

These guidelines estimate loss of lung volume by the distance from the lung apex to the ipsilateral thoracic cupola at the parietal surface on a standard upright radiograph. This method is, however, a poor way of quantifying pneumothorax volume, usually underestimating it. The British Thoracic Society defines *small* as





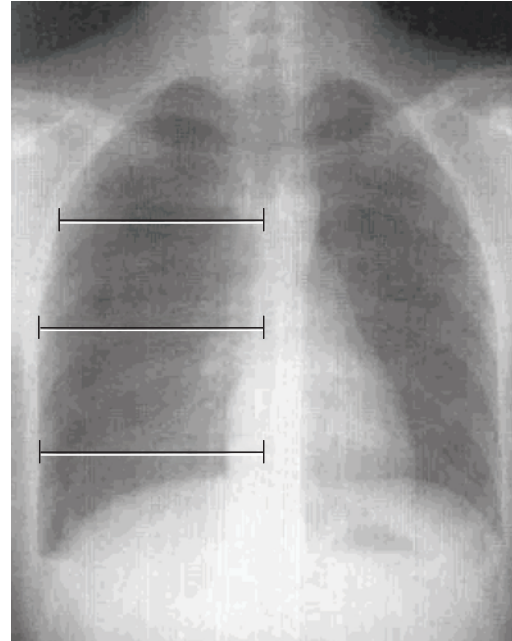
**Figure 368-2** Pneumomediastinum. The mediastinal structures, usually invisible, are outlined, particularly the medial side of the descending aorta.

a rim less than 2 cm, whereas the American College of Chest Physicians define *small* as a rim less than 3 cm. This simple linear measurement is of little use for infants and small children but can be applied in adolescents and young adults. Another way to estimate the size of a pneumothorax is to realize that the volume of the lung approximates the ratio of the lung diameter to the hemithorax cubed. The physician can measure the ratio of length of the lung to the hemithorax at several rib levels and apply the following formula:

$$\text{Estimated size of pneumothorax (\%)} = (1 - L^3/H^3) \times 100,$$

where H = diameter of the hemithorax, and L = diameter of the *collapsed* lung (Figure 368-3).

Using this formula, a pneumothorax smaller than 15% would be considered small. If the pneumothorax size is small, and if the severity of acute symptoms is mild with unlabored breathing, and if room air saturations are greater than 90%, then supplemental oxygen and observation in the emergency department (ED) for 3 to 6 hours, followed by a repeat chest radiograph to exclude progression of the pneumothorax, is recommended for adolescents and young adults. Patients must have careful instructions to return for worsening shortness of breath and have a follow-up in 12 hours to 2 days with a planned chest radiograph to document improvement. Breathless patients should undergo intervention, regardless of pneumothorax size. All patients should be referred to a lung specialist for follow-up care because they have recurrent risk for spontaneous pneumothorax. Smoking is a risk factor for primary spontaneous pneumothorax recurrence, and smoking cessation should be encouraged. Supplemental oxygen is administered to all pneumothorax patients because it increases the pleural air reabsorption



**Figure 368-3** Measurements estimating volume of pneumothorax. (Reprinted from Shaw KS, Prasil P, Nguyen LT, Laberge J-M. *Pediatric spontaneous pneumothorax*. *Semin Pediatr Surg*. 2003;12[1]:55–61, with permission from Elsevier.)

rate 3- to 4-fold above the baseline of 1.25% per day and is recommended to hasten resolution. A 15% pneumothorax is expected to resolve in about 12 days without oxygen therapy.

### Management of Small Primary Spontaneous Pneumothorax in Children

Children with small primary spontaneous pneumothorax are typically admitted for observation. However, based on the adult guidelines, older children and adolescents with asymptomatic small primary spontaneous pneumothorax who have been observed in the ED for 3 to 6 hours can be discharged to home with close follow-up as recommended for adult patients. Any patient with breathlessness should be admitted and should undergo intervention to remove the air. Although simple needle aspiration has been advocated by experts in the United Kingdom, such is not standard practice in the United States.

### Management of Moderate to Large Primary Spontaneous Pneumothorax in Adolescents and Young Adults

The British Guidelines recommend simple aspiration as the first-line treatment for all symptomatic primary spontaneous pneumothoraces and for all with greater than 2 cm rim of air on chest radiograph (large); however, the US guidelines do not generally endorse attempts at simple aspiration over placement of a chest drain. Recent publications regarding primary spontaneous pneumothorax in adults show

that aspiration is successful in more than 50% of cases but is more likely to fail if the pneumothorax is larger than 40%. A randomized study of 50 adult participants showed that aspiration was immediately successful in 59% of adults compared with immediate resolution of the pneumothorax in 64% of patients treated with a chest drain. Of note, 48% of the patients who had simple aspiration were discharged from the ED compared with none of the patients treated with chest tube placement. Success at 1 week did not differ between groups (93% vs 85%), and recurrence of spontaneous pneumothorax within 1 year was also similar (26% vs 27%). A meta-analysis of 3 randomized studies showed significantly shorter length of hospital stay with simple aspiration and equivalent success at 1 week compared with chest tube drainage. No difference in recurrence of pneumothorax was noted for 1 year after the initial spontaneous pneumothorax between treatment groups.

In the British Guidelines, patients who have successful aspiration of a primary pneumothorax may be observed in the ED for similar follow-up. The American College of Chest Physicians recommends placement of a chest drain for symptomatic or any large (>3 cm rim) primary spontaneous pneumothorax. Patients are then managed with either a Heimlich valve (one-way valve) or a chest tube to water seal or suction.

### **Management of Large Primary Spontaneous Pneumothorax in Children**

Simple aspiration versus chest tube placement for children with large pneumothorax is based on experience of the treating physician. However, published pediatric series suggest that hospital admission with placement of a pleural catheter or chest tube is usual practice.

### **Spontaneous Secondary Pneumothorax in Young Adults and Children**

Guidelines recommend hospital admission for patients with spontaneous secondary pneumothorax for treatment of the underlying condition and symptomatic treatment of the pneumothorax, if needed. Small pneumothoraces can be treated with oxygen therapy and observed, whereas large pneumothoraces are drained either by aspiration or by chest tube placement.

### **Traumatic Pneumothorax**

If a tension pneumothorax is suspected, then emergency needle aspiration of the second intercostal space in the midclavicular line is required. If the patient improves with needle aspiration, then a chest drain should immediately be placed on that side. However, a substantial number of pneumothoraces are not seen on initial chest radiographs but are found on subsequent imaging (CT or ultrasound) of the chest. Placement of a larger-caliber chest drain for symptomatic or large pneumothorax among trauma victims is customary treatment because many patients require positive pressure ventilation and may have an accompanying hemothorax. Small

asymptomatic pneumothorax may be observed if the patient is not receiving positive pressure and radiographic evaluation does not reveal chest multitrauma.

### **Iatrogenic Pneumothorax**

Treatment of iatrogenic pneumothorax should be tailored to the patient's clinical circumstance. Patients receiving positive pressure ventilation are at risk for extension of the pneumothorax and generally require chest tube placement. Patients who are not on mechanical support who have a small pneumothorax and limited symptoms can receive supportive care with close observation.

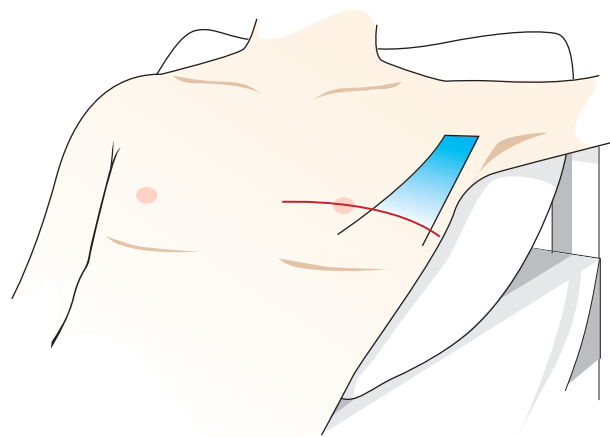
### **Chest Tube Insertion and Management**

#### **Planning**

Before inserting a chest tube, a predrainage risk assessment is appropriate. Risk for hemorrhage should be corrected when possible; however, routine platelet count and bleeding times are recommended only for patients with known risk factors. When possible, the physician should obtain informed consent and provide sedation with standard monitoring. Risks include bleeding, infection, failure of pneumothorax resolution, laceration of the lung, and extrathoracic placement with potential injury of abdominal organs. In 1 report, 3% of tubes were placed in an extrathoracic position, and 6% were placed in the lung parenchyma.

#### **Positioning**

The preferred position for chest drain insertion is supine with the ipsilateral arm above the patient's head to expose the axilla. Alternative positions are for the patient to sit upright leaning over an adjacent table with a pillow or in a lateral decubitus position. The triangle in Figure 368-4 illustrates the safe area that is bordered by the lateral margin of pectoralis major muscle, the anterior margin of the latissimus dorsi muscle, the line superior to the horizontal level



**Figure 368-4** Diagram to illustrate the safe triangle.

of the nipple, and an apex below the axilla. This supine position minimizes risk to underlying structures such as the internal mammary arteries, breast tissue, and solid organs. A more posterior position is chosen if the pneumothorax is loculated and posterior. However, loculated collections are most safely approached under fluoroscopic guidance. Although a more posterior position is safe, the chest tube is uncomfortable for the patient to lie on after insertion and is at risk for kinking. The second intercostal space in the midclavicular line may be chosen for apical pneumothorax; however, this position is uncomfortable and may leave a visible scar. A survey of house officers showed that about one-half did not know the recommended anatomic landmarks for safe chest tube insertion.

### Thoracostomy Tube Size Selection

Smaller tubes are recommended for aspirating air and are more comfortable than larger tubes, which are recommended for draining blood or a large air leak. Age-based sizes for thoracostomy tubes recommended for trauma victims by the American Heart Association are shown in Table 368-1. These tubes are relatively large based on the patient size and are intended to drain blood if needed. The Adult Guidelines for pneumothorax management recommend relatively smaller tubes for draining air. The British Guidelines recommend a 10- to 14-French tube for the management of pneumothorax in adults, whereas the American College of Chest Physicians recommends initial management with a 16- to 22-French tube in patients not at risk for large air leaks. Roberts and colleagues reported use of 7- and 8.5-French percutaneous pigtail catheters (polyurethane) in children, with resolution of pneumothorax in 75% of cases. In that study, the pigtail catheters drained serous fluid well (96% success) but were less effective for draining blood (81%) and ineffective for draining pus (0%). The catheters are much more pliant and can be kinked by the chest wall in obese patients; the tubing connection also can be kinked.

### Insertion Techniques

Small-bore chest tubes are usually inserted with the aid of a needle and guidewire using a modified Seldinger technique. Blunt dissection is not needed because a dilator is used. Blunt dissection of the subcutaneous tissue and muscle into the pleural cavity is performed for insertion of medium and large chest drains. A finger-sized opening allows exploration to ensure that no underlying organs will be damaged by

tube insertion; creation of the track prevents excessive force. Once the tube is past the chest wall, it is directed apically to drain air and basally to drain fluid. The chest tube is then sutured in place. If an incision has been made, then 1 stitch is placed to assist with wound closure after tube removal, and 1 stitch is placed to secure the drain. A chest radiograph is obtained after insertion to check placement and resolution of the pneumothorax.

### Management of Chest Drain

The chest tube is connected to a closed system with a water seal device. If the lung fails to expand quickly, then continuous suction delivered through a measured column of water is applied and remains until the lung has completely re-expanded. The closed system allows detection of air bubbles through the water chamber, suggesting continued visceral pleural air leak. However, an air leak may be caused by a leak in the system; the chest tube air holes are outside the chest, or the chest tubing connections are not airtight.

The chest tube should remain in place as long as persistent air leak is present. Surgical referral is recommended if air leak persists for longer than 4 to 7 days in patients without preexisting lung disease, and earlier referral is recommended if the lung fails to expand or in patients with a large air leak and underlying lung disease. Chest tubes are removed in a staged manner after a pneumothorax is resolved. Suction is discontinued, and the chest tube is placed on water seal. Opinions differ regarding the appropriate length of time for a water seal trial, ranging from 3 to 24 hours. After a trial on water seal, a chest radiograph is obtained to rule out recurrence. The chest tube may then be removed. Clamping of a chest tube should never be done unless the physician is expert in chest tube management and the patient has constant nursing supervision.

### Risk for Recurrence

Children with primary spontaneous pneumothorax have a 17% to 54% risk for recurrence, with a greatest risk for recurrence within 1 year. Some experts recommend CT imaging to detect pleural blebs after initial pneumothorax to help determine risk for recurrence. However, at this point, surgical treatment is generally limited to children with recurrent pneumothorax. Surgery usually involves repair of the air leak and adherence of the visceral pleura to the parietal pleura (pleurodesis). Surgical approach through a mini-thoracotomy or video-assisted thoracoscopic surgery (VATS) is based on surgeon's preference; however, VATS is associated with less postoperative pain and shorter hospital length of stay.

**Table 368-1** Age-Based Sizes for Thoracostomy Tubes

AGE (WEIGHT IN KG)	CHEST TUBE SIZE (FRENCH)
Newborns (2-5 kg)	8-12
<1 yr (5-11 kg)	14-20
Children 1-8 yr (12-30 kg)	20-28
Children >8 yr (>30 kg)	29-36

## MANAGEMENT OF PNEUMOMEDIASTINUM

Initial therapy for pneumomediastinum is directed at the underlying disease process. Because mediastinal air decompresses into the cervical fascia and rarely causes tamponade, observation is standard management. Efforts to lower intrathoracic pressures or tidal volume among patients receiving mechanical ventilation may decrease continued air

leakage. If signs of tamponade occur, then placement of a mediastinal tube using echocardiographic guidance should be done by a specialist with skills in this procedure. Because of the high prevalence of asthma-related pneumomediastinum, children for whom the underlying cause of pneumomediastinum is unknown should undergo diagnostic pulmonary function tests after the acute episode.

### WHEN TO REFER

- Infants and children with primary or secondary spontaneous pneumothorax or spontaneous pneumomediastinum should be referred to either a hospital or an ED for evaluation and management. All children with spontaneous pneumothorax should be referred to a lung specialist for follow-up because of the risk for recurrent pneumothorax.
- Infants and children with traumatic pneumothorax should be referred to a trauma center for evaluation and management.
- Infants and children with iatrogenic pneumothorax should be cared for by physicians with expertise in chest drain insertion and management.
- Infants and children with pneumomediastinum and signs of cardiac tamponade should be evaluated by a cardiologist or surgeon able to place a mediastinal drain.

### WHEN TO ADMIT

- Children with asymptomatic small primary spontaneous pneumothorax who have been observed for 6 hours in the ED and who have reliable transportation and social circumstances can be considered for discharge from the ED with follow-up within 24 hours in the ED.
- Children with symptomatic pneumothorax of any size should be admitted to a hospital for observation or management.
- All infants with pneumomediastinum or pneumothorax should be admitted to a hospital.
- Any trauma victim with pneumothorax or pneumomediastinum should be admitted to a trauma center for evaluation and management.

## TOOLS FOR PRACTICE

### Medical Decision Support

- *Pneumothorax Volume (%)* (calculator), ChestX-ray.com ([www.chestx-ray.com/index.php/calculators/pneumothorax-volume](http://www.chestx-ray.com/index.php/calculators/pneumothorax-volume))

## SUGGESTED READINGS

- Baumann MH, Strange C, Heffner JE, et al. Management of spontaneous pneumothorax: an American College of Chest Physicians Delphi consensus statement. *Chest*. 2001;119(2):590–602
- Henry M, Arnold T, Harvey J. BTS guidelines for the management of spontaneous pneumothorax. *Thorax*. 2003;58(suppl 2):ii39–ii52
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## Chapter 369 POISONING

Jeffrey S. Fine, MD

Injuries are a leading cause of pediatric morbidity and mortality, and poisoning is one important mechanism of injury. As a result, physicians who provide primary care to children have been at the forefront in promoting the field of medical toxicology, particularly in the area of poison prevention. This chapter reviews the epidemiologic considerations of pediatric poisoning and provides more specific information on some important poisonings.

### EPIDEMIOLOGIC FEATURES

The ingestion of potentially toxic substances is a common pediatric problem. More than 2 million ingestions are reported each year to the American Association of Poison Control Centers (AAPCC); approximately 65% are exposures that involve children and adolescents up to 19 years of age. Children younger than 6 years account for approximately 80% of these childhood and teenage exposures and, as a result, for more than 50% of all reported childhood, adolescent, and adult exposures. Males account for approximately 55% of childhood exposures and 45% of the adolescent reports.

Childhood exposures most frequently occur in children between 1 and 3 years of age. In young children, ingestions result from the natural curiosity, increasing mobility and dexterity, and oral exploration typically displayed by toddlers. Although a young child may find a pill and purposefully put it in his or her mouth, the resulting toxicity, if it occurs, is “unintentional,” and the typical exploratory childhood ingestion is generally referred to as an unintentional exposure.

Several characteristics differentiate typical childhood exposures from adolescent and adult exposures: they are unintentional; only one agent is involved; the agents are frequently nontoxic; the amount ingested is small; and toddlers are brought in for evaluation soon after the ingestion is discovered.

Certain behavioral characteristics increase the risk for ingestion, such as hyperactivity, impulsive risk-taking behavior, rebelliousness, and negativistic attitude. In addition, social isolation, poor parenting skills, and maternal depression have been identified as family variables that predispose young children to unintentional poisonings. Unintentional exposures occur at times of family disorganization, with deviations from normal routines (eg, household moving, spring cleaning, vacation, holidays) and during times of family stress (eg, sickness, death, divorce). Repeat exposures may occur in as many as 10% to 40% of childhood poisoning victims.

Most childhood exposures occur in the child's own home. One common site of exposure in the home is the kitchen, where cleaning and polishing products are often stored underneath the sink or in easily accessible lower cabinet shelves. Improper storage of solvents and cleaning agents in drinking glasses, cups,



and beverage bottles contributes to the risk for unintentional exposures. Medications are sometimes stored in the refrigerator or left out on the kitchen table. In the bedroom, medications are left out on the dresser or on the bedside table. Medications and cosmetics are typically kept in the bathroom, another common site for unintentional exposures. The grandparents' home is another setting where unintentional exposures may occur. Grandparents often have cardiovascular or psychotropic medications at home and may not be as vigilant as parents in "child-proofing" their home. Grandparents' medications may not be in child-resistant containers.

Poisoning is unusual in children younger than 6 months. It may result from a medication error, intentional administration of a medication by a parent or sibling, or passive exposure to a psychoactive substance—for example, exposure to the smoke of crack cocaine or to methamphetamine being manufactured in a clandestine home laboratory. Child abuse and neglect should be part of the differential diagnosis of all cases of childhood poisoning, particularly when

the child is younger than 1 year. Children who ingest poisons may also be at risk for other types of injuries.

Unintentional ingestion is unusual after age 5 years. For school-aged children, poisoning may be a reflection of intrafamilial stress or suicidal intent. For older children and adolescents, xenobiotic exposure is usually intentional; the resulting toxicity may be unintentional. These exposures may be the result of a suicide attempt or gesture or the result of the recreational use of psychoactive substances. Adolescents are also at risk for repeat exposures.

Table 369-1 lists the AAPCC categories of agents to which children and adolescents are frequently exposed. Most pediatric exposures are to common plants and products found around the house and to pharmaceutical products. Pharmaceutical agents account for most fatalities. Table 369-2 lists the categories of agents responsible for poisoning fatalities. A comparison with Table 369-1 demonstrates that most exposures do not cause significant toxicity. Most childhood poisoning fatalities are caused by analgesic agents, carbon monoxide, hydrocarbons, cleaning agents, and cough and cold preparations. In contrast, most adolescent fatalities are caused by analgesic agents, drugs of abuse, and psychiatric medications. Childhood hydrocarbon deaths are

**Table 369-1** Top Poison Exposure Categories\*

CATEGORY	PERCENTAGE OF ALL REPORTED EXPOSURES
<b>AGE &lt;6 YR</b>	
Cosmetics and personal care products	14
Cleaning substances	10
Analgesics	9
Topical preparation	7
Vitamins	4
Cough, cold, and antihistamine preparations	4
Insecticides, pesticides, rodenticides	3
Antihistamines	3
Plants	3
Gastrointestinal preparation	3
Other	40
<b>AGE 6–19 YR</b>	
Analgesics	12
Cosmetics and personal care products	6
Cough, cold, and antihistamine preparations	5
Cleaning substances	5
Antihistamines	4
Sedative-hypnotic medications	4
Stimulants and street drugs	4
Antidepressants	3
Insecticides, pesticides, rodenticides	3
Antimicrobials	2
Plants	2
Other	52

\*Does not include envenomations, bites, stings, foreign bodies, or food-related exposures.

Data taken from American Association of Poison Control Centers Web site. <http://www.aapcc.org>. Accessed February 11, 2016.

**Table 369-2** Top Fatal Poisoning Categories

CATEGORY	PERCENTAGE OF ALL REPORTED FATALITIES
<b>AGE &lt;6 YR</b>	
Analgesic agents	22
Carbon monoxide	17
Hydrocarbons	11
Cleaning agents and chemicals	6
Cough, cold, and antihistamine preparations	6
Alcohol	5
Cardiovascular agents	4
Antidepressants and antipsychotics	4
Insecticides, pesticides, rodenticides	3
Stimulant and street drugs	3
<b>AGE 13–19 YR</b>	
Analgesic agents	41
Stimulants and street drugs	13
Antidepressants, antipsychotics	12
Alcohol	5
Carbon monoxide	5
Cardiovascular agents	4
Hydrocarbons	7
Cough, cold, and antihistamine preparations	3
Cleaning agents and chemicals	1
Insecticides, pesticides, rodenticides	1

Data taken from American Association of Poison Control Centers Web site. <http://www.aapcc.org>. Accessed February 11, 2016.

related to unintentional exposures with aspiration leading to acute lung injury, whereas adolescent hydrocarbon fatalities are typically related to intentional inhalant abuse with unintentional asphyxiation.

Poison-related mortality is low overall; poisoning deaths represent 3% of annual childhood and adolescent deaths from unintentional injury. For children younger than 6 years, the AAPCC reported an average of 24 deaths per year from 1983 to 2013.

These deaths represent only 4% of the poisoning fatalities for all age groups and a 94% decrease from a high of 456 in 1959. Factors contributing to this decline include pediatric anticipatory guidance, preventive measures that include child-resistant closures and unit-dose packaging, and improved medical care.

Childhood exposures have changed in recent years. Aspirin overdoses, once a leading cause of death in children, are now rare. This change may be related to packaging changes and to the decreased antipyretic and analgesic use of aspirin at home because of its previous association with Reye syndrome. Some agents, such as kerosene or lye, which remain a significant risk in other countries, are rare causes of poison-related mortality in the United States.

Iron poisoning was also formerly a leading cause of poison-related mortality; but now, childhood iron poisoning is rare. This reduction may be the result of changes in packaging. In 1997 the US Food and Drug Administration (FDA) issued a regulation to package products with 30 mg or more of elemental iron per tablet in unit-dose packages such as blister packs. In 2003 this rule was overturned when it was legally determined that the FDA did not have the statutory authority to regulate a medication for the purpose of poison prevention.

## PREVENTION

Every child is at risk for a potentially toxic exposure; thus effective prevention strategies are directed toward the environment of all children and require parental cooperation. Primary care physicians must educate parents and caregivers in the importance of safe storage practices for household products and prescription medications, as well as the use of child-resistant closures, the only preventive measure of proven efficacy. The American Academy of Pediatrics (AAP) recommends anticipatory guidance about poisoning prevention beginning with the 6-month well-child visit. Educational materials are available from the AAP as part of the Injury Prevention Program. All parents should be given the telephone number of Poison Help (1-800-222-1222), which connects callers to a regional poison control center, and should be advised to keep the number posted by the telephone and programmed into mobile phones for immediate use if necessary.

With respect to prevention, a caretaker's primary responsibilities include selecting appropriate products for storage within the home, selecting an appropriate place to store these products, and practicing prompt disposal of old, unused, and unnecessary medications and potentially toxic materials. Toxic substances (medications, psychoactive substances, alcohol, household chemicals, and products) must be inaccessible to children and

stored in locked cabinets or boxes. These agents should be kept in their original containers so that they are not mistaken for food, beverages, or nontoxic products. If toxic substances are no longer being used, then they should be safely discarded according to the pharmaceutical manufacturer's recommendations or returned to the pharmacy where "take-back" programs are available. Guidance regarding the appropriate disposal of chemicals and other potentially hazardous household products is available from the US Environmental Protection Agency (EPA) and various local and state governmental agencies.

Parents should be advised to exercise particular care with agents that can be fatal to a toddler in small doses (see Box 369-1). They should also be cautioned about a few agents to which children are infrequently exposed but which cause severe toxicity, such as acetonitrile (artificial fingernail remover), ammonium fluoride (wheel cleaner or rust-removal agent), and selenious acid (gun-bluing compound).

Preventing errors in the administration of therapeutic medications is another area where caregivers play an important role. It is critical to ensure that the right patient gets the right medication in the right dose at the right time by the right route. It is recommended that medications be prescribed and dispensed in metric doses only (eg, mg or mL) and that patient-specific dose labeling be indicated on clearly labeled liquid medication devices at the time medications are dispensed. With regard to the home administration of prescribed or over-the-counter liquid medications, it is important to use metric-only dosing devices such as a graduated spoon or cup; other devices such as teaspoons or droppers are not accurate and can lead to unintentional underdose or overdose resulting from measuring errors.

### BOX 369-1 Agents With Significant Toxicity in Toddlers After a Small Dose

- Antihistamines
- Benzocaine
- $\beta$ -Adrenergic antagonists (sustained release)
- Calcium channel antagonists (sustained release)
- Camphor
- Clonidine
- Diphenoxylate-atropine (Lomotil)
- Ethylene glycol
- Methanol
- Methylsalicylate (oil of wintergreen)
- Opioids (methadone, codeine, oxycodone)
- Phenothiazine
- Quinine, chloroquine
- Sulfonylurea antidiabetic agents
- Theophylline
- Tricyclic antidepressants

## PRINCIPLES OF MANAGEMENT

### General Considerations

Primary care physicians should be familiar with the signs, symptoms, and management of common acute ingestions. Recent toxicology textbooks are an important part of an office library. Micromedex, a commercial poison information software package, is available in many emergency treatment facilities and in many medical libraries. Access to much of this material is available online.

Primary care physicians should be familiar with community resources that can provide information or practical help with acute poisonings. Pharmacists can provide information about medications when the name of the medication or the amount dispensed does not appear on the label. Manufacturers can help identify the chemicals in a commercial product. Local or regional emergency care facilities should be identified that can accept patients for urgent evaluation and care.

Poison control centers provide comprehensive information on poison management and other toxic exposures and can usually help organize a referral to an appropriate treatment facility. Guidance for management of acute poisonings, prevention of poisonings, and assessment of poison hazards is available 24 hours a day from the Poison Help Line of the AAPCC at 1-800-222-1222. In addition to guidance in managing acute poisonings, the Poison Help Line can provide information regarding questions such as how to clean up a broken CFL bulb or whether to worry about chemicals in plastic bottles. A list of regional poison centers can be found at the Web site of the AAPCC ([www.aapcc.org](http://www.aapcc.org)).

### Telephone Calls

Telephone triage is an important first step in managing potentially toxic exposures. Many exposures can be managed over the telephone, although home therapy of serious poisonings is limited. The physician should determine the name and type of agent, the quantity involved, the weight of the child, and the presence or absence of symptoms (see Box 369-2). The relative risk for toxicity can then be estimated. Alternatively, symptoms alone may indicate toxicity, despite the fact that, by history, neither the agent nor the dose would have predicted it. In the case of non-toxic exposures, reassurance is appropriate.

#### **BOX 369-2** Important Historical Questions Regarding a Possible Toxic Exposure

- What was the substance?
- What was the specific name of the product?
- What was the formulation of the substance?
- How much of the substance was involved?
- How much does the child weigh?

Prompt decontamination may reduce subsequent symptoms and the need for further treatment. Skin and eyes may be washed in the home or office, if appropriate.

When the history of the exposure or the reported signs and symptoms suggest an acute toxicity, the patient should be expeditiously transferred to an emergency care facility, ideally one with pediatric and toxicologic expertise and experience.

Although many calls can be initially managed by primary care practitioners, especially in the case of nontoxic exposures, all calls regarding potentially toxic exposures should be referred to trained poison information specialists at local and regional poison control centers.

Poisoning and injury prevention should be discussed with parents within a few days of a poison exposure call. Experience suggests that addressing prevention at the time of the initial call is less effective than doing so later. The recent exposure may focus the mind of the parents, providing a valuable opportunity to impart advice on poison prevention.

### Approach to the Symptomatic Patient

When no specific history of a toxic exposure can be found, the diagnosis of poisoning can be challenging. The signs and symptoms of poisoning can mimic those of many acute illnesses; therefore the possibility of toxic exposure should be considered in the differential diagnosis. The rapid onset of central nervous system (CNS), gastrointestinal (GI), or respiratory symptoms should alert the physician to ask about possible exposures to medications, gases, or fumes (eg, carbon monoxide) or to other potentially harmful substances around the home. The physician should always consider the possibility of poisoning when faced with a puzzling situation in which the diagnosis is unclear. Any patient with a possible or confirmed exposure to a toxic substance should be managed in consultation with poison specialists available through a local or regional poison control center and additionally, for emergency and admitted patients, hospital-based toxicology consultants when available.

Some xenobiotics such as opioids or anticholinergic agents produce a typical constellation of signs and symptoms known as a *toxidrome*, or toxic syndrome (see Box 369-3). When present, these toxidromes may suggest a likely agent.

This chapter focuses on the medical management of acute poisonings. For many patients, this phase of care represents only the beginning of a complete multidisciplinary evaluation. A patient with unresolved toxicity will generally require admission to an observation or inpatient unit for ongoing medical care. After toxic manifestations are resolved or the risk for toxic effects is past, many patients require consultation with mental health services for an evaluation of the need for psychiatric admission.

## THERAPEUTIC MODALITIES

The important principles of the management of acute poisonings are (1) resuscitation—attention to the ABCs (airway, breathing, and circulation) and D (disability—altered mental status and seizures), (2) decontamination,

**BOX 369-3 Toxidromes****SYMPATHOMIMETIC**

Agitation  
Diaphoresis  
Fever  
Mydriasis  
Tachycardia

**ANTICHOLINERGIC**

Blind as a bat—mydriasis  
Dry as a bone—dry skin  
Hot as Hades—fever  
Red as a beet—red  
Mad as a hatter—central nervous system stimulation  
Decreased gastrointestinal motility—decreased bowel sounds  
Urinary retention—full bladder

**OPIOID**

Respiratory depression  
Miosis  
Coma  
Bradycardia

**CHOLINERGIC**

**D**efecation  
**U**rination  
**M**iosis, muscle fasciculations, muscle weakness  
**B**ronchorrhea, bradycardia, bronchospasm  
**E**mesis  
**L**acrimation  
**S**alivation

(3) administration of specific antidotes, (4) enhanced elimination, and (5) supportive care. Although management will typically follow this sequence, in certain cases, priorities will differ. For example, in a chemical terrorism event, decontamination may need to precede any medical intervention, even resuscitation. After an opioid overdose with respiratory arrest, administration of naloxone, an opioid antidote, is part of resuscitation.

**Resuscitation**

Some poisons cause toxicity that requires immediate attention. Such effects include airway obstruction, difficulty breathing, dysrhythmias, hypotension, and seizures. Specific details of the resuscitation of the poisoned patient are beyond the scope of this chapter; however, resuscitation generally proceeds according to the recommendations of the American Heart Association within the Pediatric Advanced Life Support (PALS) and the Advanced Cardiac Life Support (ACLS) programs.

Patients with airway obstruction or respiratory failure require urgent airway management and may require assisted ventilation or endotracheal intubation. Patients with respiratory depression should receive an empirical trial of naloxone. This agent is both diagnostic and therapeutic for opioid intoxication and may preclude the need for intubation.

An escalating dosing scheme allows administration of sufficient naloxone to reverse respiratory depression without precipitating withdrawal in a person chronically exposed to opioids (see Table 369-3). For patients with a prolonged opioid effect that outlasts the effect of a single reversing dose, naloxone can be administered as a continuous infusion. Naloxone-induced withdrawal in an opioid-dependent patient can cause profound hypertension and tachycardia that may be associated with cardiac dysrhythmias and pulmonary edema. Although naloxone administration may precipitate seizures as part of the withdrawal

syndrome in newborns born to opioid-dependent mothers, seizures are not a typical part of the withdrawal syndrome in patients outside of the newborn period who are chronically exposed to opioids.

The clinical toxicity of clonidine (a presynaptic  $\alpha_2$  agonist) with altered mental status and respiratory depression resemble the opioid toxidrome. Some cases of respiratory depression associated with clonidine poisoning have also responded to treatment with naloxone; however, clonidine and certain opioids may require higher doses of naloxone before a treatment effect is seen. A failure to respond to naloxone does not rule out clonidine intoxication.

Hypotension should be treated with a saline bolus and infusion. Hypotension unresponsive to fluid alone may require the use of a vasopressor. Although the use of dopamine is common, it acts indirectly by releasing epinephrine and norepinephrine, which are stored within the nerve terminal. When these stores are depleted, a direct-acting agent such as norepinephrine may be useful.

Patients experiencing cardiovascular toxicity from certain agents such as clonidine, beta blockers (BBs), calcium channel blockers (CCBs), tricyclic antidepressant agents, cocaine, and type 1 antidysrhythmic agents (eg, quinidine) may benefit from antidotal therapy (see Table 369-3).

Many xenobiotics cause altered mental status, and several antidotes may be appropriately administered during the resuscitation phase. Although the primary reason for administering naloxone is to reverse respiratory depression, patients who have coma related to opioid intoxication may wake up after the administration of naloxone.

All patients with an altered mental status should be evaluated for hypoglycemia at the bedside by a glucose oxidase test strip. Hypoglycemia should be promptly treated with dextrose (see Table 369-3). However, there is little risk associated with empirically administering a large dose of glucose to a child or adolescent with



Table 369-3

Antidote Table<sup>a</sup>

SUBSTANCE	ANTIDOTE	DOSE	COMMENTS
Acetaminophen	N-acetylcysteine	IV: 150 mg/kg over 1 hr, then 50 mg/kg over 4 hr, then 100 mg/kg over 16 hr. (Maximal weight for calculation: 100 kg)	AE: vomiting (PO); anaphylactoid reaction (IV). IV protocol requires large volumes of free water, which may cause hyponatremia and seizures in children.
Anticholinergic agents (eg, atropine)	Physostigmine	P: 0.02 mg/kg (max: 0.5 mg) IV slowly over 5 min A: 1–2 mg IV slowly over 5 min	May repeat dose after 10–15 min AE: cholinergic symptoms occur with excessive dosing.
Benzodiazepines	Flumazenil	P: 0.01 mg/kg IV slowly every min (max: 0.2 mg/dose, max: 1 mg total dose) A: 0.1–0.2 mg IV slowly every min (max: 1 mg)	Titrate to effect or maximal dose. May not reverse respiratory depression. If positive response is of short duration, may be administered as a continuous infusion AE: withdrawal symptoms in dependent or chronic use; seizures or dysrhythmias in cyclic antidepressant overdose
β-Adrenergic antagonists (BB)	Glucagon	P: 0.05 mg/kg IV over 1–2 minutes A: 0.05 mg/kg IV over 1–2 minutes	If positive response is of short duration, may be administered as a continuous infusion AE: vomiting, hyperglycemia, hypocalcemia
	Insulin and dextrose	Insulin 0.5 U/kg/hr IV with dextrose 1 g/kg/hr	AE: hypoglycemia or hyperglycemia, hypokalemia
	Intralipid 20% emulsion <sup>48</sup>	1.5 mL/kg bolus; 0.25 mL/kg/min for 30–60 min	Bolus can be repeated 1–2 times for persistent asystole. Infusion rate can be increased if the BP declines.
Carbon monoxide	Oxygen (100%)	100% oxygen by nonrebreather	Treat until normal CO level or until hyperbaric oxygen initiated.
	Oxygen (hyperbaric)	100% oxygen at 2–3 atmosphere for 20 min	AE: pneumothorax, perforated tympanic membrane.
Calcium channel blockers	Calcium chloride (10%)	P: 20 mg/kg (0.2 mL/kg) IV slowly, via central line A: 1–2 g (10–20 mL) IV slowly	May use glucagon, insulin and dextrose, and intralipid rescue as adjunctive treatment in CCB as in BB toxicity AE: hypercalcemia, phlebitis, nausea, vomiting, flushing, confusion, angina
	Calcium gluconate (10%)	P: 60 mg/kg (0.6 mL/kg) A: 3–6 g (30–60 mL) IV	
	Insulin and dextrose	Insulin 0.5 U/kg/hr IV with dextrose 1 g/kg/hr	
	Intralipid 20% emulsion <sup>48</sup>	1.5 mL/kg bolus; 0.25 mL/kg/min for 30–60 min	
Cyanide	Hydroxocobalamin	P: 70 mg/kg IV (max: 5 g IV) A: 5 g IV	May repeat x 1
Digoxin	Digoxin-specific antibody fragments	For known ingested dose: number of vials = mg ingested × 1.5 For known SDC (ng/mL): number of vials = SDC × weight (kg)/100 For unknown SDC or dose acute overdose: 10–20 vials For chronic overdose: P: 2 vials; A: 5 vials	Each 40-mg vial binds 0.6 mg digoxin. AE: hypokalemia, worsening CHF
Ethylene glycol and methanol	Fomepizole (4-methylpyrazole)	15 mg/kg over 30 min IV, then 10 mg/kg/dose every 12 hr × 4 doses, then 15 mg/kg/dose every 12 hr	Continue therapy until serum methanol or ethylene glycol level <20 mg/dL. Increase dose during dialysis. AE: headache, nausea, dizziness, bradycardia, eosinophilia, transient increase of liver enzyme levels
Heparin	Protamine sulfate	Use 1 mg protamine for every 100 units of heparin to be neutralized.	AE: hypotension, bradycardia, hemorrhage. Use with caution with known fish allergy.

Continued

**Table 369-3** Antidote Table<sup>a</sup>—cont'd

SUBSTANCE	ANTIDOTE	DOSE	COMMENTS
Iron	Deferoxamine	5–15 mg/kg/hr IV (max: 6 g/24 hr)	Titrate dose slowly to avoid hypotension. Continue therapy until <i>vin rose</i> urine color clears, symptoms clinically resolve, or maximal dose attained. Deferoxamine challenge no longer suggested AE: flushing, hypotension, acute respiratory distress syndrome
Isoniazid (INH)	Pyridoxine (vitamin B <sub>6</sub> )	Known INH dose: 1 g per g of INH ingested IV slowly Unknown INH dose: 5 g IV over 10 min	Administer 1 g every 2–3 min. AE: CNS toxicity—headache, seizure, peripheral neurotoxicity
Lead	Succimer (DMSA)	10 mg/kg/dose PO every 8 hr × 5 days, then 10 mg/kg/dose twice daily × 14 days	AE: rash, neutropenia, increased LFTs, GI upset
	Dimercaprol (BAL)	75 mg/m <sup>2</sup> /dose IM every 4 hr (max: 450 mg/m <sup>2</sup> /dose/24 hr)	Pretreatment with diphenhydramine suggested. Contraindicated with peanut allergy, hepatic insufficiency. AE: G6PD hemolytic crisis, nausea, vomiting, histamine release
	CaNa <sub>2</sub> EDTA	1–1.5 g/m <sup>2</sup> /day continuous IV infusion × 5 days	In cases of encephalopathy, administer after dimercaprol to prevent increased CNS lead levels. AE: phlebitis
Methanol Methemoglobinemia	See Ethylene glycol Methylene blue (1%)	1–2 mg/kg IV over 5 min	Repeat doses as needed. AE: dyspnea, chest pain, and hemolysis
Opioids	Naloxone	Full reversalN: 0.1 mg/kg IV/IM IV/IM/IO/SCP: <5 yr old or <20 kg: 0.1 mg/kg IV/IM/IO/SC/ET≥5 yr old or ≥20 kg: 2 mg IV/IM/IO/SC/ETPartial reversal: A: 0.04–0.08 mg IV/IM/IO/SC/ET Continuous infusion:P: 0.0025–0.01 mg/kg/hr	ET route not recommended for newborns. Do not administer naloxone to a newborn whose mother is suspected of chronic opioid use because of the risk for seizures with acute withdrawal. In general, full reversal is indicated for an opioid-naïve patient with an unintended acute opioid exposure. Higher doses may be required for certain agents or for high-dose exposures. Partial reversal at approximately 1/10 the full reversal dose is indicated for patients with chronic opioid exposure and acute respiratory depression that may be related to opioid exposure. The goal in this type of patient is to reverse respiratory depression without inducing acute withdrawal. For infants and children, 1–15 mcg/kg may reverse the respiratory depression associated with therapeutic opioid use. Doses may be repeated as needed to maintain opiate reversal. If a positive response is of short duration, repeat bolus dosing or continuous infusion may be required. Patients should be observed continuously for recurrence of respiratory depression and other opioid effects for at least 2 hr after the last dose of naloxone. AE: opioid withdrawal (piloerection, agitation, vomiting hypertension, tachycardia), pulmonary edema, seizures (in neonate)

**Table 369-3** Antidote Table<sup>a</sup>—cont'd

SUBSTANCE	ANTIDOTE	DOSE	COMMENTS
Cholinergic agents (eg, malathion)	Atropine	P: 0.02 mg/kg IV initial dose (min: 0.1 mg) A: 0.5–1 mg IV initial dose	Double dose every 3–5 min. Titrate to reduced bronchorrhea or improved oxygen saturation. May require total doses 5 or 10 times the initial dose or higher. AE: anticholinergic toxicity
	Pralidoxime	P: 25–50 mg/kg over 30–60 min, then 20 mg/kg/hr A: 1–2 g IV over 15–30 min, then 0.5 g/hr	Pralidoxime should be administered in addition to atropine. Continue therapy for 24–72 hr.
Oral antidiabetic agents	Octreotide	P: 1–2 mcg/kg SC/IV every 6–12 hr A: 50–100 mcg SC/IV, then 50 mcg every 12 hr	Continue therapy until euglycemic. May require several days of therapy. AE: bradycardia, dysrhythmias, GI upset, hyperglycemia
	Dextrose	Neonatal: 0.2 g/kg IV (use D <sub>10</sub> W, 2 mL/kg) P: 0.5–1 g/kg IV (use D <sub>25</sub> W, 2–4 mL/kg) A: 25 to 50 g IV (use D <sub>50</sub> W)	AE: hyperglycemia, extravasation may cause local tissue reaction. Patients able to release insulin in response to glucose administration may develop recurrent hypoglycemia.
Tricyclic antidepressants	Sodium bicarbonate	1–2 mEq/kg IV bolus, then titrate to pH ~7.5 with additional doses or with continuous infusion	AE: volume overload, hypernatremia, metabolic alkalosis
Warfarin	Vitamin K	P: 1–5 mg SC/IM/IV/PO, every 6–8 hr PRN A: 10 mg SC/IM/IV/PO, every 6–8 hr PRN	Much larger doses may be required. Continue therapy until INR within normal limits.

<sup>a</sup>Pediatric (P) and adult (A) doses are the same unless specifically noted.

A, Adult; AE, adverse effects; BB,  $\beta$ -adrenergic blocker; CCB, calcium channel blocker; CHF, congestive heart failure; CNS, central nervous system; CO, carbon monoxide; D<sub>10</sub>W, 10% dextrose and water; ET, endotracheally; G6PD, glucose-6-phosphate dehydrogenase; GI, gastrointestinal; Hb, hemoglobin; IM, intramuscular; INR, international normalized ratio of prothrombin time; IO, intraocular; IV, intravenous; LFT, liver function tests; max, maximum; min, minimum; N, neonate; P, pediatric; PO, oral; PRN, as needed; SC, subcutaneous; SDC, serum digoxin concentration.

altered mental status, and many physicians opt to administer glucose without specific bedside testing. If a patient is intoxicated with an antidiabetic agent that has a long half-life (eg, glipizide), then a continuous intravenous dextrose infusion or the administration of octreotide may be required (see Table 369-3).

The empirical use of the benzodiazepine antagonist flumazenil to treat CNS depression after an overdose of an unknown agent is controversial. Flumazenil administration is appropriate in the setting of a known acute benzodiazepine exposure associated with significant CNS or respiratory depression. Flumazenil may precipitate withdrawal seizures in the patient with benzodiazepine dependence, and it may induce dysrhythmias or seizures in patients exposed to tricyclic antidepressant agents. If the duration of the antagonistic effect of flumazenil is shorter than that of the xenobiotic, then repeat doses or a continuous intravenous infusion of flumazenil may be required (see Table 369-3).

Intoxication or poisoning is only one cause of altered mental status. Other important causes are trauma and CNS infection. Trauma is especially important to consider because intoxication is common before trauma. When the cause of altered mental status is unclear, cranial computed tomographic imaging should be

considered. In addition, a lumbar puncture should also be considered in cases of altered mental status, especially in the presence of fever.

Many xenobiotics cause seizures and require urgent intervention. Benzodiazepines are the preferred agents for the initial treatment of most xenobiotic-induced seizures. However, seizures related to isoniazid or the *Gyromitra* species of mushrooms (false morel) should be treated with pyridoxine (vitamin B<sub>6</sub>); seizures related to hypoglycemia should be treated with dextrose (see Table 369-3). Withdrawal from sedative-hypnotic agents such as ethanol or benzodiazepines also cause seizures and is being seen more commonly in adolescents and young adults.

Agitation is a common manifestation of altered mental status and places the patient at risk for injury, hyperthermia, and rhabdomyolysis. Evaluating a highly agitated patient is difficult. Benzodiazepines are the preferred sedative agents, and the dose should be titrated to effect. Extremely agitated patients may require high doses of benzodiazepines to achieve sedation. When multiple doses of the same or different sedative-hypnotic agents are administered over a short period of time, sedation may be associated with respiratory depression and the patient may require endotracheal intubation and ventilatory support.

## Decontamination

Decontamination is considered in 2 large categories: surface decontamination of the skin and eyes and GI decontamination. Because most exposures in children are ingestions, GI decontamination is most commonly considered. In an era when chemical terrorism is a serious concern, however, the issues related to surface decontamination take on added importance.

*Skin exposures* require thorough washing with soap followed by copious rinsing. Eye exposures also require copious irrigation with water or saline. For certain agents such as organophosphate (OP) pesticides or nerve agents, in which significant dermal absorption occurs, decontamination must occur before other interventions, even resuscitation, can proceed. Clothing must be removed and secured. Health care workers involved in the decontamination process must be appropriately protected with gowns and gloves; some exposures require using complete personal protective equipment. If the patient is not appropriately decontaminated, then health care workers are at risk for toxicity from secondary exposure. The prehospital approach to managing chemical incidents includes decontamination at the site of the incident, although decontamination facilities are also found at many health care facilities. Detailed information on decontamination techniques can be found at the Web site of the Centers for Disease Control and Prevention ([http://emergency.cdc.gov/planning/personal\\_cleaningfacts.asp](http://emergency.cdc.gov/planning/personal_cleaningfacts.asp)).

*GI decontamination* refers to any procedure that removes a xenobiotic or reduces absorption from the GI tract and currently includes the use of activated charcoal and whole bowel irrigation (WBI). Syrup of ipecac, gastric lavage, and cathartic agents such as magnesium citrate and sorbitol are *not recommended* as part of the general management of poisoned patients.

Activated charcoal adsorbs most large molecules such as acetaminophen, aspirin, and phenobarbital and can prevent the absorption of these xenobiotics from the GI tract if administered within a short time after ingestion. Activated charcoal does not adsorb small molecules or ions such as lithium or iron. The most common side effects related to activated charcoal administration are vomiting and aspiration. If the patient has a depressed level of consciousness, then the airway must be protected. The use of activated charcoal is contraindicated with GI tract obstruction or perforation. Activated charcoal should not be administered after acid or alkali exposures, especially when endoscopy is planned, because the charcoal will obscure the endoscopist's view of the esophagus and stomach.

The use of activated charcoal may be beneficial in selected cases. The most significant adverse effect of activated charcoal administration is aspiration, and there are some reports of fatal charcoal aspiration. Therefore the risk for activated charcoal aspiration and the discomfort of oral or nasogastric administration may outweigh the benefit in many cases.

WBI involves flushing the entire GI tract with an iso-osmotic electrolyte solution, polyethylene glycol, a procedure frequently used to prepare the bowel for surgery or colonoscopy. In this procedure, large volumes (liters) of polyethylene glycol are infused until

the effluent turns clear, at which point the GI tract is presumed to be empty. WBI is not generally associated with fluid and electrolyte abnormalities, but patients sometimes experience GI discomfort and bloating. WBI may be particularly helpful for agents that cannot be adsorbed to activated charcoal, such as iron or lithium, and for extended-release medications.

## Enhanced Elimination

*Ion trapping*, particularly urinary alkalization, is a method to enhance xenobiotic clearance and is most often used for salicylate poisoning. At physiologic pH levels, salicylate is a weak acid; but in acidosis, salicylate exists mostly in the un-ionized state and can freely traverse cell membranes. When sodium bicarbonate is administered, the bicarbonate ion is excreted in the urine. In alkaline urine, salicylate exists in the ionized state and cannot be reabsorbed across the renal tubule; the salicylate ion has been trapped in the urine. The net effect is to create a concentration gradient that moves salicylate from the CNS into the urine.

Ion trapping may also enhance the elimination of phenobarbital, chlorpropamide, and myoglobin. Theoretically, the elimination of weak bases such as phenylcyclidine and amphetamines should be enhanced in acidic urine. However, urinary acidification has greater risk than benefit and is not used therapeutically.

Hemodialysis provides definitive therapy for a limited number of agents, including ethylene glycol, lithium, methanol, and salicylate. In the past, charcoal hemoperfusion was recommended for theophylline and sometimes for carbamazepine poisonings. However, specialized charcoal cartridges are not generally available, and these poisonings are currently being treated with new high-efficiency, high-flux hemodialysis techniques.

## Supportive Care

Supportive care continues the management outlined in the previous section on Resuscitation, with ongoing attention paid to cardiorespiratory and neurologic status.

Laboratory testing should be directed to the diagnosis of particular xenobiotics or to medical management. A few screening tests are generally appropriate, however, especially for adolescent patients. An electrocardiogram (ECG) can be a useful screening test for agents with characteristic ECG findings such as tricyclic antidepressants or digoxin. Pregnancy testing should be part of the evaluation of adolescent females because suicidal adolescents often have an acute stressor such as pregnancy that precipitates xenobiotic exposure. Because acetaminophen is widely available, because most patients are asymptomatic after acetaminophen ingestion, and because a window exists for antidotal therapy, acetaminophen levels should be assessed after any questionable or suicidal ingestion.

Antidotes are available for many different agents (see Table 369-3). Some of these antidotes are administered empirically during resuscitation or when the history or a toxidrome points strongly to a particular agent. Other antidotes are administered later during the period of supportive care when a specific xenobiotic has been identified.



## SPECIFIC AGENTS

### Analgesics

#### Acetaminophen

Acetaminophen is one of the most commonly used antipyretic and analgesic agents in the United States. It is available in many dosage forms and is formulated in combination with other medications such as opioids, diphenhydramine, dextromethorphan, and pseudoephedrine. Acetaminophen-containing products lead to approximately 7% of all childhood exposures, 4% of all adolescent exposures, and 12% of all childhood and adolescent poisoning fatalities. At therapeutic doses, acetaminophen is remarkably safe. Toxicity occurs after overdose or therapeutic error. Therapeutic dosing errors result from confusion related to the multitude of formulations and strengths and account for many of the childhood fatalities. To reduce the number of medication errors, the FDA currently recommends a single formulation of 160 mg/5 mL (32 mg/mL). Further, the FDA recommends that all dosing for liquid medications be made in milliliters only and that the medication delivery instrument, either syringe or cup, be graduated in milliliters only. In addition, the FDA has recommended that health care professionals discontinue prescribing and dispensing prescription combination products that contain more than 325 milligrams of acetaminophen per tablet, capsule, or other dose unit.

More than 90% of a therapeutic dose of acetaminophen is metabolized by the liver to nontoxic sulfate and glucuronide conjugates. The remainder is metabolized to a toxic intermediate, *N*-acetyl-*p*-benzoquinoneimine (NAPQI), which is conjugated with glutathione to form a nontoxic metabolite. In an overdose, metabolic pathways are saturated, larger quantities of NAPQI are generated, and glutathione stores are depleted. Unconjugated NAPQI causes hepatic necrosis. Young children have relatively larger livers and relatively greater stores of glutathione, which may explain the apparent lower incidence of serious acetaminophen toxicity in children.

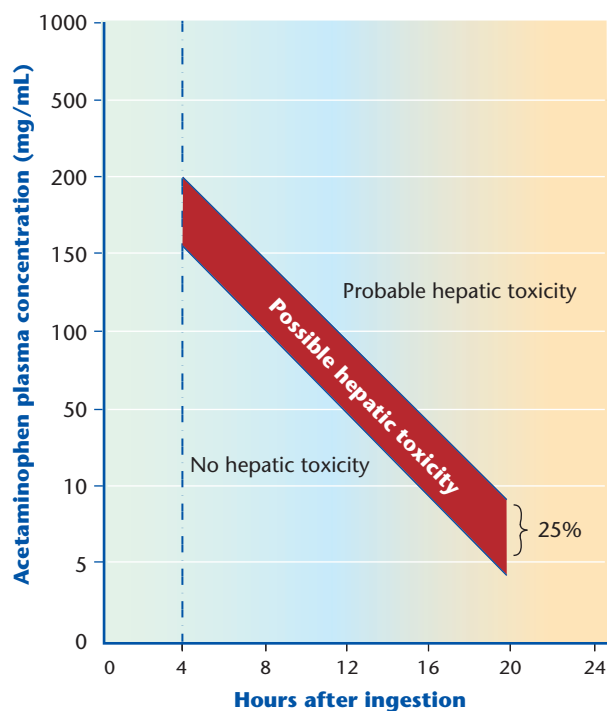
After an overdose, patients are usually asymptomatic for the first 24 hours, although they may have some mild GI distress. Clinical hepatitis develops over the next 2 days and may progress to fulminant hepatic failure. Although patients may recover spontaneously, liver transplantation may be necessary in severe cases.

Poison control centers refer patients to the emergency department for evaluation after a single acute ingestion when the ingested dose is unknown; the child is younger than 6 years and the ingested dose is at least 200 mg/kg; or the patient is older than 6 years and the ingested dose is at least 10 g or 200 mg/kg, whichever is lower. GI decontamination with activated charcoal is appropriate. When an otherwise healthy patient takes a single acute overdose of *immediate-release* acetaminophen, the only test necessary is an acetaminophen level performed on samples drawn 4 hours after the exposure. Levels drawn before 4 hours will not reliably predict the need for antidotal therapy. Following a single acute ingestion of an *extended* or *slow-release* preparation, a second level is recommended 4 to 6 hours after the initial 4-hour level (see

below). Additional laboratory testing may be indicated in certain circumstances, such as a case of a mixed overdose, a case of repeat supratherapeutic dosing, when a patient seeks care late, or when an underlying chronic disease is present.

*N*-acetylcysteine (NAC), the specific antidote for acetaminophen overdose, replenishes glutathione (see Table 369-3). The decision to initiate NAC therapy requires using the Rumack-Matthew nomogram (see Figure 369-1). If the level on a sample drawn between 4 and 24 hours after a single acute ingestion is above the *possible toxicity* line (eg, 150 mcg/mL at 4 hours), then the patient should receive NAC. Because the nomogram was developed following single acute ingestions, the applicability of the nomogram to ingestions of extended- or sustained-release formulations or to repeat ingestions of supratherapeutic doses is unclear. In the case of extended-release preparations, if the first or second level (as described previously) is above the treatment line, NAC should be initiated. There is some evidence to suggest that patients whose second level “crossed the line” and had a delayed peak acetaminophen level had massive overdoses or took combination products with agents that can slow GI motility such as diphenhydramine.

Intravenous NAC was approved for use in the United States in 2004 and is the preferred formulation. The incidence of adverse reactions to intravenous NAC administration, primarily anaphylactoid reactions, may be as high as 20%. These side effects are not completely mitigated by lowering the infusion rate, but they are usually amenable to therapy, after



**Figure 369-1** Rumack-Matthew nomogram for deciding whether to use *N*-acetylcysteine (NAC) as an antidote in treating acetaminophen overdose.

which treatment can be restarted. The incidence of these reactions may be increased in patients with lower acetaminophen levels.

Intravenous NAC is reconstituted in 5% dextrose in water and administered according to a complex regimen that delivers a large volume of free water to the patient. As a result, there is a report of a child who developed hyponatremia and seizures while receiving NAC. Intravenous NAC should be administered in consultation with a toxicologist familiar with its use.

The rate of hepatotoxicity is approximately 5% if NAC is administered within 8 to 10 hours of the time of ingestion; after 12 hours, efficacy may be reduced. Therefore, if a patient arrives 4 hours or more after an ingestion and a level will not be available within the 8-hour window, if the patient used an *extended-release* product and a second level is required, or if the patient presents with clinical or laboratory evidence of hepatotoxicity, then NAC should be administered empirically pending the results. Although the efficacy of NAC is reduced after 8 hours, it should still be administered, even to patients who seek care later than 8 hours after the time of ingestion.

Patients in fulminant hepatic failure may require liver transplantation. The King's College Criteria (see Box 369-4) identify patients at increased risk for mortality who should be considered for liver transplantation. Consultation with a transplant team should be initiated early in the course of managing a patient with hepatotoxicity. Spontaneous recovery is not associated with long-term clinical or pathologic sequelae.

If a patient's initial 4-hour acetaminophen level following a single acute overdose of *immediate-release* acetaminophen is below the possible toxicity line of the nomogram, then the patient does not need further medical evaluation. If both a patient's initial 4-hour acetaminophen level and second level drawn 4 to 6 hours later following a single acute overdose of *extended-release* acetaminophen are below the possible toxicity line of the nomogram, then the patient is unlikely to require further medical evaluation. Decisions regarding patients with the ingestion of multiple substances, acetaminophen combination products, *extended-release* products, or repeat supratherapeutic doses should be made with additional consultation of a medical toxicologist.

### Salicylates

Salicylate formulations comprise one of the oldest and most commonly used classes of analgesic and antipyretic medicines and are available in many formulations, including standard, enteric-coated,

extended-release, and chewable tablets. Salicylates are formulated together with opioids and over-the-counter cold remedies, and they can be found in antidiarrheal agents, herbal medications, and analgesic ointments.

Patients ingesting more than 150 mg/kg are at risk for toxicity and generally require direct evaluation. Methyl salicylate is a liquid formulation used as a topical analgesic (oil of wintergreen); a 100% solution contains 1.5 g/mL, and even a single teaspoon of this formulation presents a significant risk for toxicity in a toddler.

Salicylates stimulate the chemoreceptor trigger zone to cause nausea and vomiting and the respiratory center of the medulla to cause hyperpnea and respiratory alkalosis. Salicylates are weak acids that uncouple oxidative phosphorylation and cause a positive anion gap metabolic acidosis. Thus patients may have a respiratory alkalosis, a metabolic acidosis, or a mixed acid-base disturbance. Children usually exhibit acidosis.

Sick patients demonstrate an increased anion gap metabolic acidosis, altered mental status, and hypovolemic shock. Other acute effects include seizures, coma, hyperthermia, hypoglycemia, hypokalemia, and sometimes noncardiogenic pulmonary edema. A laboratory evaluation requires assessment of serum electrolytes, blood gases, and a serum salicylate level. With acute intoxication, mild symptoms are typically seen with salicylate levels as low as 30 mg/dL, although severe toxicity is typically found with levels of 80 to 100 mg/dL. Repeat salicylate levels are indicated for patients with clinical toxicity, with elevated salicylate levels, or in special situations in which the onset of toxicity may be delayed, such as the ingestion of enteric-coated preparations, the possible presence of bezoars, or a history of ingestion of a large dose. Levels should be repeated until there is clear evidence of nonexposure or only low-dose exposure without clinical toxicity or there is a clear trend of decreasing levels associated with clinical improvement. Patients with significant toxicity also need to undergo the repeated measurement of electrolytes and pH.

Ferric chloride can be used as a quick bedside test to confirm exposure to salicylates. Urine that contains salicylate turns purple or brown when 1 or 2 drops of 1% ferric chloride are added to 1 mL of urine. This qualitative test is positive after taking even 1 aspirin tablet; thus proof of salicylism still requires a salicylate level.

The Done nomogram was formerly used to assess the risk for clinical toxicity based on the salicylate level, but its use has fallen out of favor as a clinical tool because it did not predict outcome. Salicylate toxicity is likely with elevated salicylate levels, but toxicity does not specifically correlate with salicylate levels; hence decisions regarding therapy are based on the clinical evidence of toxicity.

Although patients can be quite sick, the need for intubation is unusual, and hypoventilation after intubation may worsen acidosis. Fluid resuscitation is critical, and patients may require treatment for hypoglycemia. Several doses of activated charcoal are useful to prevent the absorption of ingested salicylate and may interrupt salicylate's enterohepatic circulation. Rarely, salicylate tablets form a conglomeration in the

#### BOX 369-4 King's College Criteria

1. Arterial pH <7.3 or lactate >3 mmol/L  
or
2. All of the following
  - a. Creatinine >3.3 mg/dL
  - b. PT >100 sec
  - c. Grade III or IV encephalopathy

stomach that requires surgical removal. In the case of methyl-salicylate, patients may require skin decontamination to prevent ongoing dermal absorption.

The first intervention to enhance salicylate elimination is to alkalinize the urine as described in the previous section on Enhanced Elimination. Optimal elimination occurs when the urine pH is greater than 8. Any patient with clinical evidence of salicylate toxicity is a candidate for alkalization unless administering large volumes of fluid is contraindicated.

Hemodialysis is used to eliminate salicylate and to correct acidosis. Indications for hemodialysis include persistent CNS toxicity; severe, worsening, or intractable acidosis; extremely high salicylate levels (usually >100 mg/dL); or any condition that precludes the administration of a high-volume bicarbonate infusion, such as pulmonary edema, renal insufficiency, or congestive heart failure.

Any patient with evidence of toxicity requires hospital admission for further evaluation and management. If there is no clinical evidence of toxicity after 6 to 8 hours of observation, salicylate levels at that time do not suggest significant exposure, and there is a low risk for delayed absorption as from a bezoar, then the development of subsequent toxicity is unlikely.

## Antidepressants

### Tricyclic Antidepressants

The classic tricyclic antidepressants such as imipramine or amitriptyline have largely been replaced by selective serotonin reuptake inhibitors (SSRIs) as first-line agents in the treatment of depression. Nonetheless, tricyclic antidepressants are still used to augment SSRIs and to treat conditions such as insomnia or neuropathic pain. Tricyclic antidepressant overdose is a leading cause of poisoning morbidity and mortality and ingestion of only 1 or 2 pills may be toxic in a toddler.

Tricyclic antidepressants affect many neurotransmitters and have a myriad of effects. They inhibit norepinephrine and serotonin reuptake from the nerve synapse.  $\alpha_1$ -Adrenergic blockade leads to hypotension. Sodium-channel blockade impairs depolarization throughout the myocardium, leading to prolonged QRS and QT intervals on ECG, right bundle branch block, and wide, complex dysrhythmias.  $\gamma$ -Aminobutyric acid (GABA) receptor inhibition lowers the seizure threshold; brief generalized seizures occur 1 to 2 hours after ingestion. Anticholinergic effects also contribute to delirium, coma, and seizures. The risk for seizures and ventricular dysrhythmias is increased with a QRS duration of more than 100 msec, R-wave amplitude in aVR more than 3 mm, and R/S ratio in aVR more than 0.7.

Because of the high risk for coma, seizures, and dysrhythmias in patients with a tricyclic antidepressant overdose, the benefit of gastric lavage may not outweigh the risk and should only be performed when adequate airway protection is ensured. Reversal agents such as flumazenil and physostigmine are contraindicated in the setting of known or possible tricyclic antidepressant overdose.

The initial management of patients with significant cardiovascular or CNS toxicity follows the principles

outlined in the previous section on Resuscitation. The specific therapy for tricyclic antidepressant-related wide complex ventricular dysrhythmias and hypotension is sodium bicarbonate administration to raise the serum pH to approximately 7.5. A more alkaline pH lowers the concentration of free xenobiotic by stimulating protein binding; the increased serum sodium overcomes the sodium channel blockade. The adverse effects of bicarbonate infusion include volume overload, hyponatremia, and severe metabolic alkalosis.

For refractory hypotension, direct-acting pressors such as norepinephrine are preferred. Extracorporeal cardiovascular support may also be required in appropriate cases.

There are a number of case reports in both adults and children of the successful use of intravenous lipid emulsion therapy to treat cyclic antidepressant toxicity.

Adjunctive therapy for ventricular dysrhythmia includes lidocaine and magnesium. Classes IA, IC, and III antidysrhythmics are likely to exacerbate cyclic antidepressant toxicity.

Benzodiazepines are the preferred treatment for seizures. Barbiturates and propofol may be considered as adjuncts for seizures refractory to benzodiazepines. Phenytoin should not be used because it blocks sodium channels and exacerbates tricyclic antidepressant cardiotoxicity in animal models.

Symptoms of toxicity appear within 6 hours of ingestion. Patients who remain asymptomatic throughout this observation period are unlikely to develop toxicity. Medical admission will be required for patients with signs of cardiovascular or neurologic toxicity.

### Selective Serotonin Reuptake Inhibitors

SSRIs such as fluoxetine, sertraline, and paroxetine are first-line agents for the treatment of depression and anxiety. They increase the synaptic serotonin concentration with little sodium channel, adrenergic, cholinergic, or GABA effect. SSRIs have decreased toxicity in overdose compared with the classic tricyclic antidepressants. The primary adverse effects of SSRIs result from excessive serotonergic stimulation.

*Serotonin syndrome*, a rare but potentially lethal condition, includes altered mental status, agitation, myoclonus, hyperreflexia, diaphoresis, tremor, diarrhea, and incoordination. If untreated, patients may develop lactic acidosis, rhabdomyolysis with renal failure, hepatic dysfunction, disseminated intravascular coagulation, and acute respiratory distress syndrome. Serotonin syndrome most commonly results from therapy with a combination of serotonergic agents or the combination of an SSRI with a monoamine oxidase inhibitor.

The main focus of therapy of serotonin syndrome is to decrease muscle rigidity and its sequelae, myoglobinuria, and renal failure. Initial therapy for muscle relaxation is with benzodiazepines. Adjunctive therapy may be provided with cyproheptadine, a histamine and serotonin antagonist. Severe hyperthermia should be treated with aggressive cooling. If muscle rigidity is severe and unresponsive to conventional measures, then the patient may require endotracheal intubation with neuromuscular blockade maintained after the patient is intubated.



After acute overdose and following a short period of observation, asymptomatic patients do not require medical admission. Patients with symptoms of serotonin syndrome should be admitted to the hospital for further evaluation and management.

### Antihistamines

Antihistamines are commonly available prescription and over-the-counter allergy medications, antinausea medications, and sleep aids. They are available in both short- and long-acting formulations and are found in combination with other medications such as acetaminophen.

Antihistamines are broadly categorized as  $H_1$ -receptor and  $H_2$ -receptor antagonists. First-generation  $H_1$  antagonists (eg, diphenhydramine) typically cause sedation and CNS depression. Second-generation  $H_1$  antagonists (eg, loratadine) generally have less sedation than the first-generation agents; however, several agents in this class (eg, terfenadine) were withdrawn from the US market because of the high risk for torsades de pointes.  $H_2$ -receptor antagonists such as ranitidine and cimetidine primarily act in the GI tract.

Antihistamine toxicity is marked by either CNS depression with somnolence or coma or by CNS excitation with tremor, hyperactivity, hallucinations, or seizures. Peripherally, antihistamines cause an anticholinergic toxidrome (see Box 369-3). The association of fever and altered mental status may be confused with meningitis or encephalitis.

Most patients with antihistamine toxicity do well with supportive care alone. The administration of activated charcoal is appropriate if it can be administered safely. For large ingestions or for ingestions of sustained-release formulations, WBI may be useful although there are few supportive data. Significant agitation or seizures should be treated with benzodiazepines, as described in the previous section on Resuscitation.

Physostigmine, a carbamate with cholinergic properties, is an antidote for patients with anticholinergic toxicity and is appropriate for use in a pure antihistamine overdose with moderate to severe symptoms (see Table 369-3). The reversal of anticholinergic symptoms after the use of physostigmine is diagnostic, however, because of physostigmine's short half-life, the duration of effect may be shorter than the duration of toxicity. Continued observation after therapy is indicated, and repeat dosing of physostigmine may be necessary.

The adverse effects of physostigmine include seizures, ventricular dysrhythmias, and asystole. Therefore, physostigmine is contraindicated for patients with evidence of cardiotoxicity or for treatment of overdoses of cardiotoxic agents such as tricyclic antidepressants, which may also exhibit anticholinergic effects. Physostigmine therapy should not be administered as nonspecific therapy in patients with coma or agitation of unknown cause.

Patients who remain asymptomatic after 4 to 6 hours of observation generally do not need further medical evaluation. However, symptoms may sometimes be delayed after a large ingestion, and patients may require a longer period of observation.

### Carbon Monoxide

Carbon monoxide (CO), an odorless, colorless, tasteless, and nonirritating gas, is a byproduct of hydrocarbon combustion and is the leading cause of poisoning deaths in the United States. Vehicular exhaust is one of the most common sources of exposure, and children have even been exposed in the back of pickup trucks. House fires are another significant source of unintentional exposure to CO and, in some cases, cyanide. CO exposure also occurs with the use of poorly vented kerosene space heaters, charcoal grills, camping stoves, and gas generators. The paint-stripping agent methylene chloride is converted to CO in vivo and may occasionally cause toxicity. The prevention of CO poisoning involves educating people about the safe use of space heaters and other small CO-generating devices in closed spaces and encouraging the use of CO detectors and smoke detectors in the home and workplace.

The toxic effects of CO poisoning are the result of a variety of mechanisms. CO binds to hemoglobin with a much greater affinity than oxygen and blocks the binding of oxygen. The binding of CO also leads to structural changes in the hemoglobin molecule that decrease the oxygen-carrying capacity and the tissue delivery of oxygen and that shift the hemoglobin-oxygen dissociation curve to the left. CO also binds to myoglobin and impairs oxygen delivery to the heart. The binding of CO to cytochrome oxidase may impair the use of energy that is generated from oxidative phosphorylation. Finally, CO leads to increased nitric oxide production and free radical formation, which causes lipid peroxidation, damage to myelin, and neurotoxicity.

Symptoms of mild CO poisoning can be nonspecific. Headache is the most common symptom. Malaise, nausea, and dizziness may accompany the headache and mimic a nonspecific viral syndrome. Severe disease produces CNS toxicity (altered mental status, seizure, syncope, and coma) and cardiac toxicity (dysrhythmias and myocardial ischemia). Significant toxicity is often associated with metabolic acidosis and increased lactate levels. Cherry-red skin, although frequently mentioned, is rarely seen. Higher carboxyhemoglobin (CO-Hb) levels are associated with more severe disease, but no correlation exists between a particular symptom and a particular level. Children develop symptoms at lower CO-Hb levels than adults.

CO causes lesions in the deep white matter and damage to the thalamus, basal ganglia, hippocampus, and globus pallidus. Neurocognitive deficits, personality changes, focal neurologic symptoms, and movement disorders may be delayed for 2 weeks after exposure. Although children can experience delayed effects, adults have a higher risk, particularly if a loss of consciousness occurs during the early phase of the exposure. Again, these delayed symptoms do not correlate well with the presenting level of CO.

When a pregnant woman is exposed to CO, the fetus is at particular risk. In animal models, peak fetal CO-Hb levels are approximately 10% to 15% higher than and peak later than maternal levels. Brain damage and fetal death have been reported, generally after severe maternal CO exposures.



The best measure of CO exposure is the CO-Hb level. Normal CO-Hb levels are 1% to 2%; smokers may have levels of 5% to 10%. Fetal hemoglobin may be assayed as CO-Hb, and infants may have a CO-Hb of approximately 3%. Standard pulse oximeters cannot differentiate CO-Hb from oxyhemoglobin. Blood gas CO oximetry is necessary to obtain accurate measurements of CO-Hb and methemoglobin. Although levels do not specifically correlate with symptoms, high levels indicate significant exposure. Blood CO-Hb levels fall rapidly after exposure is discontinued, however, postexposure levels may not accurately reflect the maximal exposure in high-demand tissues such as the brain and heart.

Seriously poisoned patients will have impaired CNS and cardiovascular function. Standard PALS and ACLS protocols should be initiated. All exposed patients should initially receive 100% oxygen until an accurate assessment of exposure can be determined or a CO-Hb level can be measured, or both. A pH and blood lactate level should be obtained concurrently because lactate seems to correlate to some extent with the severity of disease and may also suggest exposure to cyanide, which may be produced during a house fire.

The half-life of CO-Hb in a patient breathing room air is 4 to 8 hours but decreases to 1 hour while breathing 100% oxygen and to 15 to 30 minutes when hyperbaric oxygen is administered. Thus, hyperbaric oxygen therapy increases the concentration of dissolved oxygen to displace CO from binding sites on hemoglobin, myoglobin, and cytochrome oxidase; improves the delivery of oxygen to tissues; and reduces lipid peroxidation. Limited data suggest that hyperbaric oxygen therapy reduces the incidence of delayed neurologic and neuropsychiatric effects, particularly if administered within 6 hours, although data are conflicting and specific indications for therapy have not been well defined. Data suggest that hyperbaric therapy is safe for pregnant women and may benefit the fetus. Hyperbaric chambers can be located through the Undersea and Hyperbaric Medicine Web site ([www.uhms.org](http://www.uhms.org)).

Although the use of hyperbaric oxygen for the treatment of severe CO poisoning remains controversial, many experts support its use. Specific indications for hyperbaric therapy have not been clearly defined. Potential candidates include patients with significant CNS, cardiovascular, or neuropsychiatric symptoms; persistent metabolic acidosis; ECG changes or clinical symptoms that do not respond to standard 100% oxygen therapy; CO-Hb level exceeding 25%; or, in pregnant women or children, a CO-Hb level exceeding 20%. Decisions regarding the potential utility for any particular patient should be made in consultation with a medical toxicologist or a hyperbaric specialist.

In general, symptomatic patients require hospitalization for further evaluation and management. Patients with relatively low CO-Hb levels and mild symptoms, especially when symptoms resolve after a short course of oxygen therapy, do not require hospitalization. Identifying and ameliorating the source of CO is imperative; identifying other potentially exposed persons who may require evaluation is also important.

## Cardiovascular Medications

Although childhood poisoning with cardiovascular agents is unusual, even small doses may cause serious toxicity. Four classes of cardiovascular agents are reviewed here: cardiac glycosides, calcium channel antagonists (CCBs),  $\beta$ -adrenergic antagonists (BBs), and  $\alpha_2$ -adrenergic agonists.

### Cardiac Glycosides

Cardiac glycosides include digoxin, digitalis, and related compounds found in plants such as oleander and foxglove and in some toad venoms (bufotoxin). Bufotoxins have become popular as hallucinogens and aphrodisiacs, and their use has resulted in death.

The cardiac glycosides inhibit myocyte sodium-potassium adenosine triphosphatase pumps and increase the concentration of intracellular sodium and calcium during systole. Cardiac glycosides increase inotropy and automaticity, shorten repolarization intervals, and decrease conduction through the sinoatrial and atrioventricular (AV) nodes. The result is to increase the force and velocity of myocardial contractions.

Symptoms associated with acute overdose are typically nausea, vomiting, headache, weakness, confusion, changes in vision, palpitations, and dizziness. A severe acute overdose leads to hyperkalemia, bradycardia, hypotension, and dysrhythmia. Hypercalcemia, hypokalemia, hyperkalemia, or hypomagnesemia can exacerbate cardiac toxicity. A chronic overdose is often characterized by nausea and vomiting, psychiatric disturbances, drowsiness, headache, and hallucinations.

A serum digoxin level drawn 4 to 6 hours after ingestion assists in management. Levels above the therapeutic range may be associated with toxicity; higher levels are generally associated with a higher risk for and more serious toxicity. Children may tolerate high digoxin levels with less clinical toxicity. The laboratory assays used to measure digoxin cross-react incompletely with plant- and toad-derived digoxin-like substances; thus an increased digoxin level may at least indicate exposure to one of these substances. Specific digitoxin levels are sometimes available.

Activated charcoal and steroid-binding resins such as cholestyramine adsorb cardiac glycosides in the GI tract and may interrupt their enterohepatic circulation. Hyperkalemia should be aggressively treated with bicarbonate, insulin, and glucose. Calcium administration is contraindicated for the treatment of hyperkalemia in this setting because it can exacerbate glycoside toxicity, but magnesium sulfate should be used in patients with hypomagnesemia. Kayexalate can also be administered.

Significant toxicity is treated with digoxin-specific antibody antigen-binding fragments (Fab) (see Table 369-3). In the acute setting, Fab therapy is used to treat significant dysrhythmia, serum digoxin levels of more than 15 ng/mL at any time or more than 10 ng/mL 6 hours after ingestion, a serum potassium level of more than 5 mEq/L, hypotension, second- or third-degree heart block, or a digoxin dose of more than 10 mg in a teenager or adult or more than 4 mg in a child. The administration of Fab causes a marked increase in the measured serum digoxin

level; therefore, post-treatment levels do not reliably indicate a response to therapy.

Adjunctive therapy includes atropine for bradycardia and phenytoin and lidocaine for ventricular dysrhythmias. Cardioversion should be avoided because the ensuing sympathetic discharge can be fatal. Classes Ia, Ic, II, and IV antidysrhythmics are contraindicated because they decrease AV conduction and worsen bradycardia and other dysrhythmias.

### **$\beta$ 1-Adrenergic Antagonists and Calcium Channel Antagonists**

$\beta$ -Adrenergic antagonist medications (BBs) such as propranolol, atenolol, and metoprolol are commonly prescribed for the treatment of hypertension, angina, dysrhythmias, and headache.  $\beta_1$ -Receptor blockade results in decreased myocardial contractility and conduction;  $\beta_2$ -receptor blockade increases smooth muscle tone (bronchospasm) and peripheral vascular tone (hypertension).

After an oral overdose of BBs, symptoms begin within 2 hours; sustained-release formulations may result in delayed onset. Cardiovascular manifestations include hypotension, bradycardia, wide QRS and PR intervals on ECG, bundle branch block, and ventricular dysrhythmias such as ventricular tachycardia and torsades de pointes. CNS depression ranging from drowsiness to coma and seizures can also occur. Bronchospasm may occur in patients with a history of asthma. Metabolic effects include hyperkalemia and hypoglycemia.

Calcium channel antagonists (CCBs) such as verapamil, diltiazem, and nifedipine are used to treat hypertension, angina, and cardiac arrhythmias and are available in both immediate-release and long-acting formulations.

Calcium channels are found in the sinoatrial and AV nodes, the myocardium, and vascular smooth muscle. CCBs block the influx of calcium into myocytes and reduce contractility and conduction; smooth muscle relaxation also occurs. CCBs cause sinus bradycardia, hypotension, AV block, CNS depression, hyperglycemia, and lactic acidosis.

CCB and BB overdoses are clinically similar. For both BB and CCB ingestions, activated charcoal can be administered. WBI should be considered for ingestions of sustained-release preparations. Glucagon is considered a specific antidote for significant hypotension and bradycardia associated with BB overdose, but it may also be useful for CCB ingestions. Glucagon increases cyclic adenosine monophosphate (cAMP) activity, leading to positive inotropy. High-dose insulin and glucose are another therapeutic option; insulin may increase myocardial glucose use or alter myocardial calcium handling. There are case reports of the successful use of intravenous lipid emulsion for both BB and CCB poisoning. Calcium chloride may be useful after CCB or BB overdose. There may be a role for phosphodiesterase inhibitors such as milrinone, which also inhibit the breakdown of cAMP, in select cases.

Table 369-3 provides additional information on glucagon, insulin, intralipid emulsion therapy, and calcium.

In both CCB and BB overdose, adjunctive therapy for severe refractory bradycardia includes atropine,

epinephrine, isoproterenol, and cardiac pacing. Patients may require therapy for hyperglycemia, hyperkalemia, or seizures.

All symptomatic patients with a history of a BB or CCB overdose should be admitted to an intensive care unit. Patients with exposure to a sustained-release preparation should be admitted for observation. Patients who remain asymptomatic for at least 6 hours after exposure to an immediate-release product may be discharged.

### **$\alpha_2$ -Adrenergic Agonists (Clonidine)**

Clonidine is used to treat hypertension and other disorders such as attention deficit/hyperactivity disorder and nicotine withdrawal. Oral and patch formulations are both available. Even 1 or 2 clonidine pills may cause toxicity in a toddler. The patches contain high doses of clonidine to ensure transdermal delivery, and they are a particular problem when ingested by children.

Clonidine stimulates central  $\alpha_2$ -adrenergic receptors and can modulate opiate receptors. At therapeutic doses, clonidine primarily affects  $\alpha_2$  receptors, but at high doses, both  $\alpha_1$  and  $\alpha_2$  receptors can be stimulated.

Toxic symptoms begin within 1 hour of ingestion and can last up to 24 hours. Clonidine toxicity mimics opioid toxicity, with altered mental status, coma, respiratory depression, and miosis. Hypotension and bradycardia may develop, and dysrhythmias such as first- and second-degree AV block may also occur.

Naloxone should be administered in cases of respiratory depression; high doses may be required (see Table 369-3). Naloxone may also be useful in cases of CNS depression or hypotension. When naloxone is effective but clonidine toxicity outlasts naloxone's effect, a continuous infusion of naloxone is indicated. Decontamination with activated charcoal is appropriate, and WBI may be indicated for children who have ingested clonidine patches. Atropine may have modest effects on bradycardia, and fluids and pressors are indicated for hypotension.

Patients may be discharged if they are asymptomatic 4 hours after ingestion. All symptomatic patients should be admitted to the hospital.

### **Caustic Ingestions**

Caustic agents are broadly categorized as *acids* and *alkalis*. Common sources of acid in the home include toilet bowl cleaners, rust removal products, and automotive battery liquids. Common alkaline-containing products include drain cleaners, bleaches, ammonia-containing cleaners, oven cleaners, dishwasher detergents, and hair relaxers. Serious caustic exposures are unusual in childhood, but these agents have the potential to cause significant injury with even small exposures.

Acids injure tissue by coagulation necrosis. Even though the resulting eschar might theoretically limit the initial depth of injury, esophageal, gastric, or intestinal injuries frequently occur. Significant exposures may cause metabolic acidosis or acute renal failure.

Alkali ingestions injure tissue rapidly by liquefaction necrosis. Within minutes, tissue edema develops in the oropharynx and esophagus, potentially leading to airway obstruction. Over several weeks, scar tissue

from full-thickness burns in the esophagus may progress to form strictures.

Caustic ingestions produce dysphagia, odynophagia, drooling, stridor, hoarseness, abdominal pain, nausea, and vomiting. GI hemorrhage and perforation may occur. A tissue eschar may sometimes mask findings despite a significant acid ingestion.

A gastric lavage is generally contraindicated after caustic ingestions because of the risk for esophageal or gastric perforation. In the case of large-volume acid ingestions, nasogastric suction performed within 30 minutes of exposure may prevent the passage of acid into the small intestine. Activated charcoal adsorbs caustic chemicals poorly and may interfere with endoscopy and is therefore not recommended. Plain-film radiographs of the chest and abdomen are helpful to assess pneumomediastinum, pneumoperitoneum, and aspiration pneumonitis. Esophagoscopy defines the extent of injury and should be performed in symptomatic patients.

Almost all significant caustic exposures require admission for endoscopy. If any suspicion of perforation exists, then a surgical consultation should be obtained and broad-spectrum antibiotics should be administered. The neutralization of acids and bases should be avoided because of the excessive heat this generates and the risk for emesis. A repeat esophagram will be required 3 to 4 weeks after caustic ingestion to check for strictures.

### Hydrocarbons

Hydrocarbons are organic compounds that have significant toxicity. They are broadly categorized into 3 classes: aliphatics (kerosene, gasoline, mineral seal oil, solvent, paint thinners), aromatics (industrial solvents such as benzene and toluene), and terpenes (turpentine and pine oils). Hydrocarbon aspiration after unintentional exposure to such household products is a leading cause of poison-related death in young children.

Pulmonary toxicity results from chemical pneumonitis after aspiration. Local or diffuse infiltrates, pleural effusions, and pneumatoceles may develop. Lipoid pneumonitis may result from aspirating hydrocarbons with high viscosity, such as petroleum jelly.

Most patients will experience some coughing after hydrocarbon exposure, but cough does not by itself indicate pulmonary toxicity. Significant exposures cause gasping, choking, gagging, and vomiting that begins within 30 minutes, and patients may develop cough, tachypnea, rales, rhonchi, wheeze, and diminished breath sounds. In the most severe cases, acute lung injury, hemorrhagic pulmonary edema, and respiratory failure may occur with long-term respiratory dysfunction. Respiratory effects may progress over the first 24 hours and resolve over the ensuing 2 to 5 days. Associated acute symptoms may include CNS depression and fever.

Contaminated clothing should be disposed of properly, and the skin should be washed with soap and water to limit continuing exposure to hydrocarbon vapors. GI decontamination plays only a limited role; toxicity is related more to pulmonary exposure than to GI absorption. Most patients experience nausea and

vomiting after hydrocarbon exposure and do not require further gastric emptying. Gastric emptying is contraindicated after most hydrocarbon ingestions because the risk for aspiration increases with any gastric-emptying procedure.

Symptomatic patients have radiographic evidence of aspiration as early as 30 minutes after exposure. Asymptomatic patients occasionally develop radiographic changes, but the importance of these changes is unclear.

The management of pulmonary toxicity includes supplemental oxygen, humidified air, and intravenous fluids. Nebulized  $\beta_2$ -receptor agonists may be useful. Severely ill patients may require continuous positive airway pressure, mechanical ventilation with positive end-expiratory pressure, or extracorporeal membrane oxygenation. Corticosteroids are not beneficial in hydrocarbon ingestions. Leukocytosis and fever are associated with hydrocarbon aspiration and, at least early in the course, do not signify infection.

Patients with persistent respiratory symptoms should be hospitalized. Patients who are asymptomatic or whose initial symptoms have resolved and whose radiographic findings are normal should be observed for 6 hours. If a patient remains asymptomatic after 4 to 6 hours of observation, then the patient generally does not need further medical evaluation.

### Iron

Despite consumer product safety improvements, iron poisoning remains a problem for toddlers. Prenatal vitamins typically contain 62 mg of elemental iron per tablet and can resemble candies such as M&Ms or Good & Plenty, making them appealing to children. Most significant toxicity is related to ingestion of adult iron tablets, not children's liquid or chewable vitamin preparations.

Iron is a GI irritant that causes abdominal pain, nausea, vomiting, and diarrhea. Severe poisoning causes mucosal ulceration and hemorrhagic necrosis, leading to hematemesis, melena, or hematochezia. GI fluid losses lead to hypovolemic shock and contribute to positive anion gap metabolic acidosis. Absorbed iron leads to the production of free radicals, with adverse effects on cellular metabolism, which exacerbate the acidosis. The combination of the shock state and iron's direct toxic effects contributes to progressive myocardial dysfunction and acute hepatic injury. As hepatocellular damage progresses, coagulation is disrupted, further exacerbating the GI hemorrhage. In rare cases, corrosive injury to the GI tract leads to gastric outlet obstruction weeks after the ingestion.

In general, the higher the dose of iron ingested, the greater the likelihood of toxicity (see Table 369-4). Poison control centers typically refer patients for evaluation if the ingested dose of elemental iron is more than 20 mg/kg. Similarly, the higher the serum iron level, the greater the likelihood of resultant toxicity (see Table 369-4). A peak serum iron level is best measured 4 to 6 hours after ingestion.

GI symptoms alone do not necessarily predict severe toxicity but do confirm exposure. Because GI distress is a marker of exposure, asymptomatic patients do not require gastric emptying. Patients experiencing toxicity



**Table 369-4**  
**Iron Toxicity Based on Dose and Serum Iron Level**

INGESTED DOSE <sup>a</sup>	EXPECTED TOXICITY
<20	None or minor
20–40	Mild to moderate
40–60	Moderate to severe
>60	Severe
Serum iron level (mg/dL)	Expected toxicity
<300	None or minor
300–500	Mild to moderate
>500	Severe

<sup>a</sup>Ingested dose of elemental iron (mg/kg).

vomit spontaneously, and in these cases, no additional benefit exists to gastric emptying.

Nonetheless, a limited role for gastric decontamination exists after a significant ingestion or when a large number of pills are radiologically evident in the stomach or GI tract. WBI may be effective in removing these pills. In rare cases, surgery may be necessary to remove the iron pills.

Radiographs detect residual iron pills in less than 3% of all ingestions. However, the absence of pills on radiographs does not exclude a toxic overdose. In particular, chewable and liquid iron formulations do not appear on abdominal radiographs, but they do not account for most toxic exposures.

Although significant iron poisoning is associated with both an increased serum glucose and an increased white blood cell count, normal values do not rule out significant exposure. A total iron-binding capacity greater than the serum iron level was once thought to be protective in poisoning; however, the total iron-binding capacity is factitiously increased in the setting of iron poisoning. Deferoxamine also interferes with the accurate measurement of total iron-binding capacity.

In addition to the initial GI symptoms, patients with significant poisoning are in shock with a positive anion gap metabolic acidosis. These patients are very ill and need immediate and vigorous resuscitation. Although a serum iron level might be useful because the optimal time to draw the level would be 4 to 6 hours after exposure and because results may be delayed, decisions regarding treatment will usually have to be made on clinical grounds alone.

Chelation therapy with deferoxamine should be considered for any symptomatic child who is in shock, has an altered mental status, or is experiencing protracted vomiting or GI bleeding (see Table 369-3). Serum iron levels exceeding 500 mcg/dL or abdominal radiographs suggesting a serious ingestion may also be an indication for chelation. Desferrioxamine, the deferoxamine-iron chelate, is excreted in the urine and imparts a dark brown or *vin rose* color to the urine. This color change is only a qualitative measure of desferrioxamine and is an unreliable marker of iron elimination. Chelation therapy

should continue until the child is clinically improved and the metabolic acidosis is resolved, but a duration of therapy greater than 24 hours may present an increased risk for toxicity.

Patients who remain asymptomatic without treatment for 6 hours after ingestion generally do not need further medical evaluation.

### Isoniazid

Isoniazid (isonicotinyl hydrazine [INH]) is a medication primarily used for the prophylaxis and treatment of tuberculosis. It can cause hepatic toxicity, peripheral neuropathy, and optic neuritis even at therapeutic doses. INH doses of more than 30 mg/kg are likely to cause acute toxicity. Effects occur within 2 hours of ingestion. Patients initially experience nausea, vomiting, slurred speech, dizziness, tachycardia, urinary retention, and hyper-reflexia or hyporeflexia. Significant toxicity causes an anion gap metabolic acidosis, coma, and refractory seizures. INH inhibits the effects of vitamin B<sub>6</sub> (pyridoxine), an essential cofactor for the synthesis of GABA, an inhibitory neurotransmitter. Seizures occur as a result of decreased GABA activity.

If an asymptomatic patient seeks care soon after a significant exposure, then activated charcoal may be provided. To prevent seizures, prophylactic pyridoxine should be administered to patients who seek care within 2 hours of ingestion.

Seizure therapy can begin with benzodiazepines; phenytoin is not useful in treating INH-related seizures. Definitive seizure therapy requires administration of pyridoxine, the specific antidote for INH toxicity (see Table 369-3). If intravenous pyridoxine is unavailable, then crushed tablets can be given by nasogastric tube. Hemodialysis may be considered for patients with massive toxic ingestions.

Patients who remain asymptomatic for 6 hours generally do not need further medical evaluation.

### Lead Poisoning

Public health efforts during the past 2 decades have dramatically reduced environmental lead exposure by limiting its concentration in automotive gasoline and paints. Nonetheless, lead poisoning remains a significant public health concern. In 2012 the Centers for Disease Control and Prevention (CDC) recommended a new reference blood lead level (BLL) of 5 mcg/dL based on the 97.5th percentile of the BLL distribution among children 1 to 5 years old in the United States. The CDC estimates that approximately 450,000 children in the United States have BLLs higher than this reference value.

In this regard the prevention of any lead exposure, even before conception, is the primary goal as opposed to screening for and treatment of elevated blood levels.

The principal childhood source of lead is from deteriorating paint in houses built and painted before 1978. Although pica may result in oral lead exposure, more children are exposed to aerosolized lead paint flakes or contaminated dust inside the home or in the soil. Other sources of lead include lead-based plumbing, ceramics, or imported goods in lead-soldered



cans. Folk remedies for colic advocated by some Chinese, South Asian, and Hispanic cultures may also result in lead exposure. Prenatal exposure to lead is another source for concern.

Gastrointestinal absorption of ingested lead is facilitated by deficiencies in essential trace elements such as iron, calcium, and zinc, which compete for the same absorption sites. Absorbed lead is bound to erythrocytes and distributed into relatively labile soft tissue storage sites such as the liver and brain and into more stable reservoirs such as bone. Although the inhalation of lead fumes occurs in occupational exposures among adults, in children, aerosolized lead particles are inhaled, coughed up, and swallowed.

Lead inhibits heme biosynthetic enzymes, producing a hypochromic, microcytic anemia. Lead also interferes with vitamin D biosynthesis, impairing calcium metabolism. Chronic lead poisoning can produce a reversible but progressive lead nephropathy with a Fanconi-like syndrome of glycosuria, aminoaciduria, and phosphaturia. As lead accumulates in the CNS, it compromises the capillary endothelium, causing cerebral edema and increased intracranial pressure. Irreversible neuronal damage and alterations in neurotransmitter function can also cause more subtle neurocognitive disabilities.

The initial clinical manifestations of chronic lead poisoning are subtle; most children with a history of lead exposure and absorption are asymptomatic. Pallor, hearing impairment, constipation, and behavioral disturbances may be the first signs of chronic lead poisoning, but a loss of developmental milestones and declines in school performance are sometimes seen. A threshold no-effect level for lead has not been defined, and decreased IQ has been observed in children with whole blood lead (BPb) levels less than 10 mcg/dL.

Encephalopathy is one of the more dramatic clinical manifestations of lead toxicity. Children with BPb levels that exceed 70 mcg/dL may experience coma, intractable seizures, or even death. Patients with BPb less than 70 mcg/dL may exhibit ataxia, incoordination, lethargy, or irritability. Subacute encephalopathy may cause anorexia, intermittent abdominal pain, nausea, vomiting, or constipation. Peripheral neuropathy is uncommon in children, but wrist and foot drops may occasionally occur with sickle cell disease.

In all cases of suspected lead poisoning, any sources of lead exposure should be identified and abated, and parents should be counseled regarding optimal nutrition. Most children with lead exposure are asymptomatic, but many are hospitalized to remove them from further exposure. Symptomatic children are also hospitalized to remove them from the source of lead and to administer chelation therapy. If abdominal radiography finds radiopaque material, then WBI with polyethylene glycol should be initiated.

Chelation therapy is reserved for symptomatic children or those with modest to severe lead burdens (BLL >45 mcg/dL); blood lead levels less than 45 mcg/dL represent excessive exposure to lead but do not require chelation therapy. Three lead chelating agents are available in the United States: dimercaprol (also known as British anti-lewisite [BAL]), CaNa<sub>2</sub>EDTA,

and succimer (dimercaptosuccinic acid [DMSA]) (see Table 369-3). A fourth agent, D-penicillamine, is not approved by the FDA, but its use may be necessary in the unusual event of adverse reactions to both DMSA and CaNa<sub>2</sub>EDTA. CaNa<sub>2</sub>EDTA (*calcium* disodium EDTA) used for lead chelation must not be confused with Na<sub>2</sub>EDTA (disodium EDTA), which can cause severe hypocalcemia.

Asymptomatic children with BPb between 45 and 70 mcg/dL are chelated with oral succimer; intravenous CaNa<sub>2</sub>EDTA is also an option. Children with BPb more than 70 mcg/dL are chelated in the hospital with intramuscular BAL and intravenous CaNa<sub>2</sub>EDTA. Encephalopathy is treated with the same 2-medication regimen but for a longer course. After initial chelation therapy, the decision to repeat treatment depends on symptoms and subsequent BPb levels.

### Organophosphates Pesticides

Organophosphate (OP) agents such as parathion or malathion are highly toxic compounds that are found in a variety of pesticides. Ingestion of the agent directly or of contaminated fruit is the most common route of exposure in children, although these agents are highly lipophilic and are well absorbed through the skin, eyes, and lungs. Assistance in identifying individual agents can be obtained from the US National Pesticide Telecommunications Network at 800-858-7378 or npic.orst.edu.

OPs bind to and inactivate acetylcholinesterase; acetylcholine accumulates in nerve terminals of the autonomic nervous system and CNS and at the neuromuscular junction. This bond, which is initially reversible, becomes permanent after a 24- to 48-hour period. After inactivation is permanent, new acetylcholinesterase must be synthesized.

Acute OP poisoning causes cholinergic symptoms (see Box 369-3). CNS symptoms are often the presenting symptoms in younger children. The diagnosis of OP poisoning is made when a patient has a confirmed exposure or a history of a suspected exposure and consistent physical findings. The hydrocarbon carrier may produce an odor of garlic. Symptoms occur within several hours but may be delayed for several days with the more fat-soluble compounds.

The poisoned patient has pinpoint pupils, vomiting, changes in mental status, and copious secretions. Untreated, the combination of bronchial hypersecretion, bronchial constriction, and the failure of respiratory musculature leads to respiratory failure, which may be complicated by coma and convulsions. Atypical presentations can occur in children. For example, a child might have only mydriasis and tachycardia. Other clinical sequelae that have been reported in children include hyperglycemia, metabolic acidosis, and prolongation of the QT interval with subsequent torsades de pointes.

The *intermediate syndrome*, uncommon in children, describes delayed toxicity that occurs after the resolution of initial cholinergic symptoms. Symptoms include proximal muscle weakness, cranial nerve deficits, and hyporeflexia. These symptoms are present 1 to 3 days after the cholinergic crisis, are not

responsive to atropine, and require supportive care for several weeks. An increased risk for the intermediate syndrome seems to exist with the more lipophilic agents, which may not have been accessible to antidote and which are released from fat-storage sites into the circulation. Delayed polyneuropathy, ataxia, neuropsychiatric symptoms, peripheral neuropathy, and spasticity have also been reported up to 3 weeks after exposure. Most of these cases improve with time and do not cause permanent disability.

Although serum levels of both butyrylcholinesterase (pseudocholinesterase) and red blood cell cholinesterase (true cholinesterase) can be measured, red blood cell cholinesterase is a more sensitive measure of OP toxicity. However, red blood cell cholinesterase testing is not available in most hospital laboratories. Treating a patient for a suspected OP poisoning should not wait for laboratory confirmation.

When a patient seeks care for a suspected or confirmed OP exposure, decontamination should follow the principles outlined earlier in this chapter. Rescuers and health care workers are at risk for exposure if a patient has not been appropriately decontaminated. Contaminated clothing must be safely discarded. For ocular exposures, the eyes should be copiously irrigated. After ingestions, activated charcoal can be administered.

The immediate life-threatening problem is bronchorrhea (copious airway secretions). A patient in severe respiratory distress should be intubated, and atropine should be administered (see Table 369-3). Succinylcholine should not be used for rapid-sequence intubation because it requires the inactivated cholinesterase for its metabolism. The goal of therapy is to dry the airway secretions with atropine. High-dose, continuous infusions of atropine may be required. Tachycardia, which may be related to atropine administration but which may also be related to hypoxia, is not a contraindication to the use of higher doses of atropine.

The OP-acetylcholinesterase enzyme complex ages over time, leading to irreversible inactivation of the enzyme. 2-Pralidoxime, also known as 2-PAM, can hydrolyze the bond and reactivate the cholinesterase when administered before complete aging. Because this agent does not cross the blood-brain barrier, the reversal of neurologic symptoms requires atropine. Pralidoxime's efficacy varies with the different OP compounds, but it should be administered in all cases of severe toxicity.

All patients with OP toxicity require admission. The time to full recovery depends on the agent and can range from a few hours to several weeks.

### Nerve Agents

Organophosphate compounds that were too toxic to be used as pesticides were developed as nerve agents in the 1940s. Sarin, soma, tabun, and VX are all agents with very rapid rates of permanent cholinesterase inactivation, leading to the rapid onset of severe cholinergic symptoms. These agents can be dispersed through a blast or can be aerosolized. Sarin, soma, and tabun are volatile liquids with easily inhaled fumes. VX is less volatile than the others and is more

likely to be absorbed through the skin. The volatile fumes of sarin, soma, and tabun are quickly dispersed in the air and degrade within several hours. Patients exposed to these agents are not at further risk after they are removed from the site of exposure. VX is more persistent in the environment and may present a risk for ongoing exposure. Overall, these agents are more dense than air and are concentrated near the ground; thus children may have an increased exposure risk. More information on OPs and nerve agents with potential for use as chemical weapons can be found at [www.bt.cdc.gov/agent/nerve](http://www.bt.cdc.gov/agent/nerve).

The treatment for these agents is the same as that outlined for OP insecticides previously. In June 2003, the FDA approved an atropine autoinjector for children that is available for prehospital use.

### Plants

Plant exposures are common in children because plants are easy to reach in the home and environment. More than 750 toxins have been identified in more than 100 plant species. Plants do not require labeling for potential toxins as is done for pharmaceuticals and household products, and no federal regulations exist on sales of plants or herbs.

Exposure to plants occurs by contact with the skin or eyes or by ingestion. Although plant exposures are common, only a very few patients seek medical attention, and even fewer require intervention. For example, common plants such as the dandelion pose little hazard. The most common plants that result in clinical sequelae are peace lily, holly, philodendron, poinsettia, pokeweed, poison ivy, rubber tree, and nightshade (see Table 369-5).

Prevention of plant exposures occurs through education. Parents must learn the names of the plants they purchase, be familiar with plants that are toxic, and keep them safely away from children.

### Substance Abuse

The high prevalence of ethanol and substance use among adolescents despite educational efforts makes it an important issue for parents and health care providers alike. Ethanol and marijuana are the substances most commonly used by adolescents in the United States followed by prescription drug abuse (see Table 369-6). Use of most other substances have shown some decline over recent years. The recognition of substance use is a challenging but necessary skill of any pediatrician. The primary outpatient management of substance use and abuse is beyond the scope of this chapter.

### Marijuana

Marijuana is made from the dried leaves of the plant *Cannabis sativa*. Extracts of the *Cannabis* plant are available as hashish (dried resin) and hash oil (liquid extract). These various forms can be smoked or eaten. Medical marijuana is available in pill form (Dronabinol).

The active component in marijuana is tetrahydrocannabinol (THC), a lipophilic and psychoactive compound that easily crosses the blood-brain barrier. When inhaled, the onset of action is 10 to 30 seconds, and the effects last from 1 to 4 hours. Ingestion results

**Table 369-5**      **Toxic Plants**

PLANT	TOXIN OR TOXIC PART	TOXICITY AND TREATMENT
<b>HOUSEPLANTS AND CULTIVATED FLOWERS</b>		
Aloe	Latex contains anthraquinones	Oral irritation, nausea, vomiting, diarrhea
Anemone	Protoanemonin aglycone	Irritation of mucous membranes and GI
Autumn crocus, glory lily	Colchicine	GI, respiratory, renal, CNS toxicity
Christmas pepper	Capsicum	Strong irritant, stinging or burning of mucous membranes
Chrysanthemum	Sesquiterpene, lactones, pyrethrins	Skin reactions
Iris	Resin-like podophyllotoxin	Gastroenteritis
Jerusalem cherry	Solanine alkaloids	GI, CNS depression
Lily of the valley, foxglove, oleander	Cardiac glycosides	Irritation of mucous membranes, CV toxicity
Monkshood, larkspur	Alkaloid aconitine	Restlessness, salivation, irregular heartbeat Rx: gastric decontamination
Narcissus, amaryllis, daffodil	Alkaloid lycorine	Vomiting and diarrhea
Philodendron, caladium, dumb cane, elephant ear, peace lily, pothos	Oxalates	Irritation of buccal mucosa, edema, gastroenteritis, hypocalcemia Rx: rinse mouth with milk; administer calcium
Snow on the mountain	Unknown acrid principle in milky sap	Irritation of mucous membranes and GI
<b>WILDFLOWERS AND WEEDS</b>		
Buttercup, morning glory	Protoanemonin; seeds contain lysergic acid monoethylamide	GI irritation, CNS stimulation, hallucinations
Deadly or black or climbing nightshade, jimson weed, henbane	Atropine, solanine, and related glycoalkaloids	Anticholinergic Rx: physostigmine
Death camas	Veratrum alkaloids	Nausea, vomiting, hypotension, bradycardia, syncope, paresthesia, weakness Rx: atropine
Green or false hellebore	Veratrum alkaloids	GI irritation, respiratory, CV depression Rx: atropine
Horse nettle	Solanine alkaloid	GI, CNS depression
Jack-in-the-pulpit, wild calla, skunk cabbage	Calcium oxalate crystals	Irritation and burning of mouth Rx: rinse with milk and magnesium hydroxide
May apple	Podophylloresin	May produce peripheral neuropathy, vomiting, colic, diarrhea, drowsiness, impaired vision
Poison hemlock	Alkaloid coniine	Salivation, nausea, vomiting, diarrhea, sensory disturbances, seizure, coma; death from respiratory paralysis
Poison ivy, oak, sumac, wood	Urushiol	Rhus dermatitis—red, itchy, and clear blisters that exude serum; if ingested, causes severe mucosal irritation Rx: topical or oral corticosteroids
Pokeweed	Podophyllotoxins	Vomiting, sweating, colic, diarrhea, CNS depression
Rosary pea	Abrin	Burning sensation of mouth and throat, delayed GI, depression of vasomotor center, CV collapse
Spurges	Unknown acid principle	Severe mucosal irritation
Water hemlock	Cicutoxin	Generalized seizures Rx: symptomatic to prevent or control seizures
White snakeroot	Tremetol, may be in milk of poisoned cow	Weakness, vomiting, tremor, and death
<b>CULTIVATED FLOWERS AND CROPS</b>		
Castor bean	Ricin, must be chewed to release	Burning sensation of mouth and throat, delayed GI, depression of vasomotor center, hepatic, hemolysis, convulsions, and death

Continued

**Table 369-5** Toxic Plants—cont'd

PLANT	TOXIN OR TOXIC PART	TOXICITY AND TREATMENT
Potato, tomato	Foliage and sprouts contain solanine alkaloids	GI irritation, headache, CNS depression, dermatitis
Rhubarb	Leaves contain oxalate crystals and soluble oxalates	Irritation of mucosa, hypocalcemia with seizures Rx: rinse mouth with milk, replace calcium
Tobacco	Nicotine	Salivation, gastroenteritis, seizures
<b>TREES AND WOODY SHRUBS</b>		
Black locust	Toxalbumin	Anorexia, weakness, GI, dilated pupils, irregular and weak pulse
Cherry, apple, peach, apricot, choke cherry	Leaves, pits, or seeds contain glycosides hydrolyzed to hydrocyanic acid on chewing	Dyspnea, paralysis, convulsions, coma, and death Rx: cyanide antidote kit
Daphne	Glycoside in which the aglycone is dihydroxycoumarin	Burning and irritation to the skin and GI tract, bloody diarrhea, stupor, weakness, and convulsions
English holly	Ilexanthin and ilex acid	Vomiting and diarrhea
Mistletoe	Berries contain lectins, phoratoxin, viscotoxin, polysaccharides	Gastroenteritis and CV collapse
Mountain laurel, rhododendrons	Grayanotoxin	Local and GI irritation, respiratory and CV depression Rx: atropine
Yew	Alkaloid taxine	Vomiting, colic, hypotension, respiratory depression

CNS, Central nervous system; CV, cardiovascular; GI, gastrointestinal; Rx, treatment.

Adapted from Rodgers GC, Matyunas NJ. *Handbook of Common Poisonings in Children*. 3rd ed. Elk Grove, IL: American Academy of Pediatrics; 1994.

**Table 369-6** Substance Use by High School Students

SUBSTANCE	EVER USED (%)	CURRENT USE (%) <sup>a</sup>	FIRST USE BEFORE AGE 13 YEARS (%) <sup>a</sup>
Ethanol	66	35	19
Marijuana	41	23	9
Prescription medication	18		
Inhalants	9		
Hallucinogen	7		
Ecstasy	7		
Cocaine	6		
Methamphetamine	3		
Steroids	3		
Heroin	2		
Been offered, gave, or sold illicit substance at school	22		

<sup>a</sup>Current and first use reported only for ethanol and marijuana. Data from Centers for Disease Control and Prevention (CDC): Youth risk behavior surveillance—United States, 2013. *MMWR Morb Mortal Wkly Rep Surveill Summ*. 2014;63:1–172.

in slower onset of action (30 to 60 minutes) and more prolonged effects. THC stimulates cannabinoid receptors, activates the mesolimbic dopaminergic pathway (the reward pathway), and increases turnover in the GABA pathway. THC metabolites accumulate in adipose tissue and can be detected by urine toxicologic screens up to 1 month after use.

The clinical effects of marijuana include euphoria, impaired motor coordination and speech, impaired short-term memory, paranoia, and agitation. In rare circumstances, patients may experience hallucinations, delusions, and psychosis. Other effects include dry mouth, conjunctival injection, tachycardia, and urinary retention. Compared with other hallucinogens, the



effects of marijuana are usually mild and self-limited and require minimal medical intervention.

### Hallucinogens

Hallucinogens are substances that principally alter perception, thought, and mood. This section examines 3 common hallucinogens: lysergic acid diethylamide (LSD), phencyclidine (or phenylcyclohexylpiperidine, [PCP]), and ketamine.

**LYSERGIC ACID DIETHYLAMIDE.** LSD was first synthesized in 1938 from ergot alkaloids extracted from the plant *Claviceps purpurea*. In the 1950s, LSD was used to facilitate psychotherapy, and by the 1960s, it had become a popular recreational drug. LSD is available in several forms, including liquid-impregnated blotter paper, microdots, tiny tablets, windowpane gelatin squares, liquid, powder, and tablets. LSD is usually ingested and has rapid GI absorption.

LSD's psychedellic effects include existential experiences, intensified perceptions, hallucinations, and paranoia. Clinical signs of LSD intoxication include tachycardia, palpitations, blurred vision, tremors, incoordination, and mydriasis. These effects are most intense in the early part of the intoxication. LSD users may experience flashbacks during which an individual re-experiences aspects of the acute intoxication. These episodes are typically short lived and self-limited but may provoke anxiety.

**PHENCYCLIDINE AND KETAMINE.** PCP was commercially available in the 1950s as an anesthetic and re-emerged as a recreational drug in the 1960s. PCP can be used orally or intravenously, smoked, or inhaled. Ketamine is a derivative of PCP and is used medically as a dissociative anesthetic. Ketamine is also a popular recreational agent because of its short duration, low cost, and hallucinatory effects. Recreational ketamine is typically diverted from medical, dental, and veterinary sources and is administered orally, intramuscularly, and intravenously.

PCP blocks the N-methyl-D-aspartic acid receptor to produce its dissociative and psychotic effects. PCP also produces sympathomimetic effects by blocking the reuptake of dopamine and norepinephrine. The clinical effects of PCP can last up to 48 hours after a large dose is ingested. Ketamine is pharmacologically similar to PCP but differs with respect to pharmacokinetics. Intoxication will typically last for approximately 8 hours after oral exposure and 90 to 120 minutes after intramuscular or nasal exposure.

PCP and ketamine cause a dissociative psychotic reaction manifesting as changes in body image and feelings of spiritual separation from the body. Users may have difficulty seeing themselves as separate from their environment. PCP users may experience dangerous or violent behavior, and the emotional state created by PCP is frequently unpleasant. Physical signs of PCP and ketamine intoxication include nystagmus, ataxia, sensory impairment, catatonia, tachycardia, hypertension, and increased secretions. Ketamine intoxication is usually less severe and shorter lived than PCP intoxication. Both ketamine and PCP also have sympathomimetic effects.

Supportive care in a quiet environment with minimal loud or noxious stimuli is usually all that is needed, although verbal and physical contact with friends or family members may be helpful. When agitated, patients should be sedated with appropriate doses of benzodiazepines. Prolonged or severe psychosis will require psychiatric evaluation.

### Stimulants

Cocaine, amphetamine, and related compounds are the most commonly used stimulants. All the stimulants have sympathomimetic effects.

Cocaine is a short-acting stimulant with local anesthetic properties. It is extracted from the leaves of the *Erythroxylum coca* plant. Cocaine can be insufflated (snorted), smoked, or injected. Crack is a purified alkaloid form of cocaine that vaporizes instead of burning, allowing it to be smoked. *Freebasing* describes a technique of heating a cocaine solution until it vaporizes and then inhaling the fumes.

When smoked or used intravenously, cocaine effects begin almost immediately and peak within several minutes. With nasal use, effects begin in a few minutes and peak after 30 minutes. Cocaine is rapidly metabolized to benzoylecgonine and ecgonine methyl ester. These inactive metabolites have a half-life of 4 to 6 hours and can be detected in a urine drug screen up to 48 hours after single use and longer after chronic use. Cocaine interferes with the reuptake of adrenergic neurotransmitters and causes CNS stimulation, vasoconstriction, and blockade of fast sodium channels in axons and in myocardial tissue.

$\alpha$ -Methylphenylethylamine and its derivatives are generically referred to as *amphetamines*. Although amphetamines have been used to treat narcolepsy, asthma, and obesity, their primary current medical indication is for treatment of attention-deficit/hyperactivity disorder (eg, methylphenidate). Methylene-dioxymethamphetamine (MDMA) is an amphetamine derivative commonly known as *ecstasy*, a popular club drug that is used at raves and rock concerts. MDMA stimulates feelings of enhanced emotion and arousal, and hallucinations can occur at high doses.

Amphetamines stimulate the release of dopamine and norepinephrine to cause altered perception, stereotypical and psychotic behaviors, and locomotor stimulation. MDMA stimulates serotonin release and inhibits serotonin synthesis and reuptake. Acute ingestion causes a functional increase in the serotonin concentration; with chronic use, however, serotonin stores are depleted.

The clinical effects associated with these agents are related to stimulation of the CNS and cardiovascular system. Severe effects include seizures and intracranial hemorrhage. The cardiac toxicity of stimulants can cause tachycardia, hypertension, myocardial ischemia, and dysrhythmias. The specific sequelae of cocaine use include endocarditis, pneumothorax, and tactile hallucinations. Amphetamines have been reported to cause choreoathetoid movements and compulsive behaviors. MDMA can cause hyponatremia resulting from the intake of large volumes of water combined with the release of alcohol dehydrogenase.

The treatment of stimulant intoxication requires good supportive care. Benzodiazepine sedation is the most effective treatment for agitation, chest pain, hypertension, hyperthermia, and seizures. Rhabdomyolysis is a common complication of stimulant use and may require aggressive intravenous hydration, urinary alkalization, and rarely hemodialysis. Hyperthermia requires aggressive cooling.

Patients who respond appropriately to sedation and remain asymptomatic for a 4- to 6-hour period of observation generally do not need further medical evaluation.

Cocaine-associated chest pain is an issue of concern. Although most cocaine-related chest pain is short lived and benign, approximately 6% of patients will have an acute myocardial infarction. Most cases occur in the absence of underlying heart disease and can occur in adolescents. The management of myocardial ischemia and dysrhythmias may require the use of benzodiazepines, nitroglycerin, phentolamine, aspirin, morphine, and CCBs. Wide-complex tachycardias associated with cocaine may respond to the use of bicarbonate.

If patients display any persistent signs of cardiac involvement (eg, chest pain, ECG changes, abnormal cardiac enzymes), then they should be admitted to a chest pain observation unit. If patients have normal levels of troponin I, no new ischemic ECG changes, and no cardiovascular complications during a 12-hour observation period, then they generally do not need further medical evaluation.

### Novel Psychoactive Agents

Several psychoactive agents have become more popular during the 1990s and early 2000s. As a group, these agents are often referred to together as “novel” or “new” psychoactive agents (NPS). They are sometimes referred to as “designer drugs” because the chemical structures are often chosen or modified to circumvent legal regulations and changes in the US Drug Enforcement Agency (DEA) scheduling of specific agents. The true chemical constituents of any particular street product can change; when the DEA moves a specific agent to Schedule I status, illicit drug producers try to create a derivative product that is sufficiently different so as to remain unscheduled and that may still technically be legal. Another method of trying to circumvent regulations is to market these substances as bath salts, potpourri, or plant food “not for human consumption.” In this regard, a particular agent may not be scheduled and is marketed as a “legal high.” Although these “novel” agents are structurally diverse, they mimic the stimulant drugs in many of their effects. Polysubstance use is common among users; these novel substances are often used along with one or more other psychoactive substances or alcohol.

**SYNTHETIC CANNABINOID AGONISTS (“K2,” “SPICE”).** Synthetic cannabinoid agonists (SCAs) are not closely structurally related to THC, the active component in marijuana, but they do stimulate both the CB1 and CB2 cannabinoid receptors and were developed specifically to study cannabinoid receptor physiology. Because of their cannabinomimetic activity SCAs have been referred to as “synthetic marijuana.” Sometimes the research-grade chemicals are added to

or sprayed onto mixtures of other plant materials, and these combinations may be referred to as “herbal marijuana alternatives.” The products are typically sold as incense or potpourri and labeled “not for human consumption.” K2 and Spice were specific product names, but the SCA group overall is colloquially referred to as K2 or Spice. Again, the constituents of any particular product are not necessarily specific and are subject to change.

The plant components are typically rolled into cigarettes and smoked like marijuana. Because there are a large number of different compounds within the SCA group, because testing for the specific agents is not generally available, and because the possible toxicity of the other components is largely unknown, attribution of particular clinical effects to specific agents is difficult. In only a small number of cases have the specific agents been identified. Nonetheless, the clinical effects of these agents are becoming better known through the publication of more case reports and case series and have been reviewed. The predominant effects are tachycardia, diaphoresis, dry mouth, and conjunctival injection. More significant effects include agitation, anxiety, paranoia, delusions, psychosis, and suicide. Rhabdomyolysis, respiratory failure, renal failure, myocardial infarction, and death have also been reported. There are no specific antidotes, and treatment is generally supportive and follows the recommendations for the stimulants as described previously.

### SYNTHETIC CATHINONES (“BATH SALTS”).

Cathinone is a naturally occurring amphetamine analog found in the Khat plant (*Catha edulis*). The plant is native to parts of the Middle East and Africa; local populations chew the leaves of the plant for the stimulant effect. Synthetic cathinones are referred to colloquially as “bath salts,” a term that was meant to mask their use as psychoactive agents and circumvent drug regulations. Among the multiple synthetic analogs, the 3 most common derivatives are mephedrone, methylenedioxypyrovalerone (MDPV), and methylone. The antidepressant bupropion is the only synthetic cathinone used medically.

Pharmacologically, the cathinones interact with the transporters of the monoamine neurotransmitters dopamine, norepinephrine, and serotonin, and individual agents will either increase or decrease transmitter concentrations in the synaptic cleft. Overall, the effects of the synthetic cathinones are sympathomimetic. Users report increased energy, empathy, and libido. Adverse effects include nausea, vomiting, headache, hyperthermia, agitation, seizures, and psychosis. Chest pain and palpitations are often the reason for emergency evaluation. Hyponatremia similar to that seen with MDMA has also been reported in several cases. There are no specific antidotes, and treatment is generally supportive and follows the recommendations for the stimulants as described previously.

### 2C-PHENYLETHYLAMINE COMPOUNDS (“NBOME”).

This group of agents includes phenylethylamine derivatives of the 2C class of hallucinogens. The most commonly reported agent is 25C-NBOMe [2-(4-chloro-2,5-dimethoxyphenyl)-N-(2-methoxymethyl)ethanamine]; iodinated and brominated derivatives

are also in circulation. Pharmacologically, this agent is a 5-HT<sub>2A</sub> partial agonist. These agents are used for their hallucinogenic effects and are often sold as or substituted for what a user thinks is LSD. They are typically sold on blotter paper and taken orally or used sublingually. Overall these agents are considered significantly more toxic than LSD.

The desired psychedelic effects include a whole body tingling sensation, euphoria, and auditory and visual hallucinations. Adverse effects include generalized shaking, bruxism, nausea, vomiting, headaches, agitation, tachycardia, hypertension, hyperthermia, agitation, seizures, rhabdomyolysis, and acute lung and kidney injury. Fatalities have been reported related to the use of NBOMe products, particularly 25I-NBOMe. The relative contribution of sympathomimetic versus serotonergic toxicity is unknown, but both are probably contributory. There are no specific antidotes, and treatment is generally supportive and follows the recommendations for the stimulants as described previously. Whether there is a therapeutic role for the use of cyproheptadine, a 5-HT<sub>2A</sub> antagonist, is unknown.

### Inhalants

The inhalation of volatile hydrocarbons such as glue, spray paint, or gasoline is a common form of adolescent substance abuse. Typically, patients will *sniff* (inhale directly), *huff* (soak a rag and inhale from it), or *bag* (squirt or spray hydrocarbon in a bag and inhale from the bag or place the bag over the head). The acute presentation and management of inhalant intoxication differs from the hydrocarbon aspiration syndrome described previously. The primary acute effect of hydrocarbon *inhalation* is altered mental status. At high doses, inhalation may cause significant CNS depression, coma, and respiratory depression. Alternatively, when a person covers the head with a bag, the individual may pass out and become asphyxiated.

Halogenated hydrocarbons such as typewriter correction fluid (trichloroethane) or freon are cardiotoxic; these agents sensitize the heart to catecholamines and can cause malignant dysrhythmias. *Sudden sniffing death* occurs when a patient has been using these agents, experiences a catecholamine surge (eg, when running away from police), and develops sudden ventricular fibrillation.

### Sedative-Hypnotic Agents

Sedative-hypnotic agents encompass a diverse group of agents, including benzodiazepines, barbiturates, ethanol, and  $\gamma$ -hydroxybutyrate (GHB).

Benzodiazepines such as diazepam or alprazolam are commonly prescribed anxiolytic agents. Flunitrazepam (Rohypnol, or *roofies*) is an illicit benzodiazepine common in drug-facilitated sexual assault (date rape); its anxiolytic effects are also used to soften the coming-down phase after cocaine or heroin use. Barbiturates such as phenobarbital, thiopental, or pentobarbital are commonly used sedative, anesthetic, or anticonvulsant agents.

Benzodiazepine and barbiturate effects are mediated by GABA, the predominant inhibitory neurotransmitter

in the brain. Enhanced GABA activity leads to increased sedation. Subtle variations in the GABA receptor allow for the variable physiologic effects of these agents (sedation, hypnosis, anxiolysis, amnesia, and muscle relaxation), and at least 2 types of benzodiazepine receptors have been identified.

Ethanol (ethyl alcohol) is commonly used by teens and preteens and is a contributing factor to injuries related to motor vehicle collisions, homicide, fire, drowning, and suicide attempts. At high doses, ethanol intoxication progresses to CNS depression, with coma and death resulting from respiratory suppression. Ethanol is frequently ingested with other drugs. Ethanol's inhibitory effects are the result of enhanced GABA transmission and inhibition of NMDA glutamate receptors.

GHB was introduced as an anesthetic agent and gained popularity with body builders as a reputed facilitator of growth hormone release. In the late 1980s, its illicit use as a sedative agent and for drug-facilitated sexual assault became more common. Sodium oxybate, a prescription form of GHB, is a Schedule III medication prescribed for narcolepsy and other sleep disorders.

GHB is available in either pill or powder form. It crosses the blood-brain barrier and acts on GHB-specific receptors, the function of which are poorly understood but which may involve dopaminergic pathways. GHB receptor activation may cause agitation or sedation, vomiting, bradycardia, hypotension, coma, and seizures.

Sedative-hypnotic agents are usually identified on urine drug screens. Barbiturates may be detected up to 4 days after ingestion, although phenobarbital may be detected in urine up to 4 weeks after ingestion. Benzodiazepines can be detected from 1 to 30 days after ingestion, depending on the individual agent. Blood alcohol concentrations are routinely available. Standard urine drug assays do not screen for GHB.

The hallmark of sedative-hypnotic intoxication is CNS depression with or without respiratory depression. Respiratory depression can be seen with barbiturate intoxication but is unusual after benzodiazepine intoxication alone. Any combination of agents, including ethanol, increases the risk for respiratory depression. Most sedated patients do well with supportive care. Significant CNS and respiratory depression may require urgent endotracheal intubation to ventilate the patient and to protect the patient from aspiration. Medical interventions should be focused on xenobiotic-specific side effects.

Administration of flumazenil, a specific benzodiazepine antagonist (see Table 369-3), is appropriate in the setting of a known benzodiazepine exposure associated with significant CNS depression, respiratory depression, or both. The empirical use of flumazenil to treat respiratory or CNS depression after an overdose with an unknown agent is not suggested. Flumazenil should not be administered to patients with possible chronic benzodiazepine use because of the high risk for inducing withdrawal or after possible TCA exposure because of the possible risk for inducing dysrhythmias.

Patients with suspected sedative-hypnotic intoxication should be admitted to monitor their respiratory and neurologic status. Patients with barbiturate or benzodiazepine intoxication may require a prolonged hospitalization as a result of the prolonged duration of effect. Patients with uncomplicated ethanol ingestion can usually be observed and discharged after observation in an emergency department setting. GHB and flunitrazepam usually have short durations of action and can typically be managed in the emergency department.

### Opioids

Opioid medications such as morphine, meperidine, codeine, hydrocodone, and oxycodone are commonly used analgesic agents. Heroin is primarily used for its psychoactive effects; methadone is prescribed to treat heroin addiction but is also used to treat chronic pain. Different formulations of these agents are available for oral, intravenous, intramuscular, and subcutaneous administration. Many of these agents can also be insufflated or smoked. Intravenous administration (morphine, meperidine, and heroin) leads to rapid onset of effect and carries the highest risk for adverse effects. All opioids bind to specific opioid receptors; Mu (OP<sub>3</sub>) receptors mediate analgesia, euphoria, and respiratory depression.

Several opioid medications are typically found around the home and are commonly abused, including hydrocodone, oxycodone, and dextromethorphan. A liquid formulation of methadone is frequently prescribed, even to adults. This liquid methadone formulation represents a particular hazard for young children in the home who may be unintentionally exposed.

Oxycodone and hydrocodone are opioid medications commonly prescribed for acute and chronic pain control. Wide-scale prescribing and overprescribing have led to the increased availability and recreational use of these agents. Particularly for adolescents these agents are available around the home and therefore do not require illicit purchase. "Pharming" is a term used to describe the recreational use of prescription medications such as oxycodone or hydrocodone. Recently, efforts to restrict the sale and diversion of prescription opioids have actually led to a resurgence in the use of heroin, even among adolescents.

Dextromethorphan is of special interest to pediatric health care providers because it is an over-the-counter product that has significant abuse potential. It is a well known constituent of a number of cough and cold preparations. As the dextro isomer of the codeine analog levorphanol, it is structurally an opioid, although at therapeutic doses it only has activity at the sigma opioid receptor. It is metabolized to dextrophan, an NMDA receptor antagonist, which gives it some dissociative effects similar to ketamine. It also has some peripheral catecholamine reuptake inhibition, which leads to increased sympathomimetic effects. Users can experience CNS stimulant effects such as hallucinations and euphoria or CNS depressant effects such as a decreased level of consciousness, slurred speech, and memory impairment. Other adverse effects include tachycardia, hypertension, respiratory depression, prolonged QT syndrome, seizures, nausea, and vomiting. Occasional deaths have been reported.

The management of opioid intoxication is based on the history of the exposure and the presence of clinical symptoms. The classic opioid toxidrome includes respiratory depression, CNS depression, and miosis (see Box 369-3). A heroin overdose is also associated with pulmonary edema, which is rarely seen with an overdose of other opioids but may be related to withdrawal. Patients with respiratory or CNS depression related to known or presumed opioid intoxication should receive naloxone as described in the previous section on Resuscitation (see Table 369-3). The most recent advance has been to make naloxone available for bystander administration in the hope that early administration by a family member or friend may prevent an inadvertent opioid death. Opioid metabolites are excreted in the urine and can be detected on a urine drug screen up to 4 days after acute use and longer after chronic use.

Patients who are awake and alert after opioid use do not require further medical evaluation. Patients whose status is reversed by a single dose of naloxone should be observed for at least several hours in case of a recurrence of symptoms. Patients with significant opioid symptoms who have received high or multiple doses or a continuous infusion of naloxone require hospitalization.

### Toxic Alcohols

#### Methanol and Ethylene Glycol

Methanol is found in many commercial products, including antifreeze, windshield washing fluid or de-icer, and picnic stove fuel. Ethylene glycol has a sweet taste and is found in antifreeze, inks, pesticides, adhesives, cosmetics, and paints. The metabolites of methanol and ethylene glycol are toxic. Methanol is initially metabolized to formaldehyde via alcohol dehydrogenase and then to formic acid by aldehyde dehydrogenase. Although absorption of methanol after ingestion is rapid, metabolism and symptoms can sometimes be delayed up to 24 hours. Ethylene glycol is metabolized to glycoaldehyde and then to glycolic acid, glyoxylate, and oxalic acid. Oxalic acid can chelate calcium, and calcium oxalate crystals can precipitate within renal tubules.

Methanol intoxication causes nausea, headache, decreased vision with mydriasis, and weakness. Without treatment, these symptoms may progress to blindness, coma, and death. Ethylene glycol intoxication produces neurologic symptoms ranging from drunkenness to coma followed by tachypnea and pulmonary edema. Ethylene glycol toxicity may cause hypocalcemia and acute renal failure with precipitated oxalate crystals.

Both methanol and ethylene glycol cause an increase in serum osmolality and a positive anion gap acidosis. Increased osmolality is related to the concentration of the parent compound in the serum and is present early in the course of intoxication, whereas an elevated anion gap results from the metabolism of the parent compound and therefore occurs later. Thus the osmolal gap, the difference between the calculated and the measured serum osmolality, decreases while the anion gap increases. An increased osmolal gap suggests intoxication with these alcohols but is neither



sensitive or specific. Methanol and ethylene glycol do not cause lactic acidosis or ketonuria.

Antifreeze often contains fluorescein as an additive to help mechanics locate radiator leaks; thus a Wood's lamp examination of the urine for fluorescence is sometimes suggested to help identify the presence of ethylene glycol. However, this test lacks sensitivity.

Because these agents have rapid absorption from the GI tract, gastric decontamination is not generally useful.

For both of these alcohols the toxic cascade begins when the parent compound is metabolized via aldehyde dehydrogenase. Both fomepizole (4-methylpyrazole) and ethanol competitively inhibit alcohol dehydrogenase and prevent the formation of toxic metabolites (see Table 369-3). Because of adverse effects related to the administration of parenteral ethanol, fomepizole is the preferred antidote. It is important to note that if the patient ingested ethanol in addition to methanol or ethylene glycol, the onset of toxicity may be delayed. Folate and folinic acid enhance the metabolism of formic acid and can be used as adjunctive therapy for methanol poisoning. Thiamine and pyridoxine shunt ethylene glycol metabolism toward less toxic metabolites and are adjunctive therapy for ethylene glycol poisoning. Maintaining the pH near normal with sodium bicarbonate will reduce the availability of and enhance the elimination of some of the toxic metabolites.

For patients who are clinically asymptomatic and in whom acidosis has not yet developed or in patients with mild symptoms or acidosis, fomepizole therapy alone is often adequate. In cases with very high levels of the parent compound or metabolites or with severe acidosis, hemodialysis may still be indicated.

### Isopropyl Alcohol (Isopropanol)

Isopropanol is found in common household products such as rubbing alcohol. In some instances, isopropanol is ingested intentionally as a substitute for ethanol. Unmetabolized isopropanol causes clinical toxicity; as little as 20 mL can cause symptoms. It is metabolized to acetone, which is nontoxic and is excreted by the kidneys and the lungs.

GI toxicity causes nausea and vomiting and can progress to hemorrhagic gastritis. CNS findings include ataxia, muscle weakness, areflexia, lethargy, and coma. Patients who ingest isopropanol can develop myocardial depression with tachycardia and hypotension, renal tubular acidosis, and tracheobronchitis. Patients with isopropanol intoxication have increased serum osmolality and ketonuria but do not have metabolic acidosis.

The clinical presentation of patients with isopropanol ingestion is not usually severe and is rarely fatal. These patients require supportive care and symptomatic therapy. In severe cases, hemodialysis may be necessary for persistent hypotension, plasma levels exceeding 400 mg/dL, prolonged coma, or underlying renal or hepatic disease that limits the metabolism and excretion of isopropanol.

Any patient with suspected or confirmed significant toxic alcohol ingestion and any symptomatic patient should be hospitalized. Patients who have no symptoms

and who are treated early have an excellent prognosis. However, patients with seizures, coma, or pH less than 7.20 have a poor prognosis. Patients who are asymptomatic should be observed for 4 to 6 hours. If they remain asymptomatic, they may be discharged or transferred for further psychosocial evaluation as needed.

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## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Childhood Lead Poisoning Prevention Program* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/nceh/lead/about/program.htm](http://www.cdc.gov/nceh/lead/about/program.htm))
- *Lead Is a Poison* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Poison Help Line* (hotline), American Association of Poison Control Centers (1-800-222-1222; [www.aapcc.org](http://www.aapcc.org))
- *Protect your Child from Poison* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Tips for Poison Prevention and Treatment* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/news/Pages/Tips-for-Poison-Prevention-and-Treatment.aspx](http://www.healthychildren.org/English/news/Pages/Tips-for-Poison-Prevention-and-Treatment.aspx))

### Medical Decision Support

- *The Agency for Toxic Substances and Disease Registry (ATSDR)* (Web page), ([www.atsdr.cdc.gov](http://www.atsdr.cdc.gov))
- *Carbon Monoxide Poisoning* (Web page), Centers for Disease Control and Prevention ([www.cdc.gov/co](http://www.cdc.gov/co))
- *Chemical Agents: Facts About Personal Cleaning and Disposal of Contaminated Clothing* (fact sheet), Centers for Disease Control and Prevention ([emergency.cdc.gov/planning/personalcleaningfacts.asp](http://emergency.cdc.gov/planning/personalcleaningfacts.asp))
- *Chemical Emergencies* (Web page), Centers for Disease Control and Prevention ([www.bt.cdc.gov/chemical](http://www.bt.cdc.gov/chemical))
- *Medical Management Guidelines for Chemical Agents* (Web page), Centers for Disease Control and Prevention ([emergency.cdc.gov/chemical/mmg.asp](http://emergency.cdc.gov/chemical/mmg.asp))

## AAP POLICY

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## SUGGESTED READINGS

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### Chapter 370

## PSYCHIATRIC EMERGENCIES: SUICIDALITY, AGITATION, PSYCHOSIS, AND DISASTER EXPOSURE

Heather J. Walter, MD, MPH; David R. DeMaso, MD

Pediatricians increasingly face psychiatric emergencies in their daily work. Pediatric physicians are being asked to assess levels of risk in crisis situations and determine if immediate intervention is indicated, and to have systems in place to ensure that mental health evaluations will be completed. This chapter provides a solid foundation for understanding psychiatric emergencies in general, and evidence-based approaches to 4 specific emergency situations—suicidality, acute agitation, acute psychosis, and disaster exposure.

### NATURE AND SCOPE OF PSYCHIATRIC EMERGENCIES

The number of visits for psychiatric problems by children and adolescents to both pediatric primary care and emergency department settings has increased dramatically; such visits now account for up to 25% to 50% of primary care and 5% of emergency department visits. Compared to other pediatric emergency department visits, psychiatric visits are longer, more frequently triaged to urgent evaluation, and more likely result in patient admission or transfer.

Several factors contribute to the apparent increase in psychiatric emergencies. Among these is the high prevalence of youth risk behaviors likely to result in emergency psychiatric evaluation (see Box 370-1). Another factor is the unavailability of mental health services at both ends of the treatment spectrum. Community and outpatient mental health services and inpatient psychiatric beds and lengths of stay have been steadily eroded by dwindling funds and efforts at cost containment by the government and the private sector. Available services are further constrained by the extreme shortage of mental health professionals across disciplines, including child and adolescent psychiatry,

### BOX 370-1 Prevalence of Youth Risk Factors in Psychiatric Emergencies

- 24.7% of students had been in a physical fight 1 or more times
- 5.2% of students carried a weapon on school property
- 6.9% of students had been threatened or injured with a weapon on school property
- 19.6% of students had been bullied on school property
- 7.1% of students were afraid to go to school because of safety concerns
- 17.0% of students had seriously considered attempting suicide
- 8.0% of students had attempted suicide
- 20.8% of students had had 5 or more drinks of alcohol in a row
- 2.2% to 66.2% of students (depending upon the substance) had used potentially intoxicating substances

From *Youth Risk Behavioral Surveillance—United States 2013* ([www.cdc.gov/mmwr/pdf/ss/ss6304.pdf](http://www.cdc.gov/mmwr/pdf/ss/ss6304.pdf))

child psychology, and child-trained clinical social work and mental health counseling, and by a shortage of training in evidenced-based approaches to treatment. As a result, untreated or undertreated children accumulate across the spectrum of care, and predictable crises occur.

The judgment of what constitutes a psychiatric emergency derives from a number of sources, including the perceptions of a caregiver, teacher, public safety officer, primary care physician (PCP), or of the child himself. Rarely does an emergency occur without warning. Almost invariably, the acute event has been preceded by a long period of instability on the part of the child and impaired relationships within the family or community. Indeed, the cause of the emergency may be as likely to involve a change in the ability of individuals in the child's environment to manage the child's distress as to involve a change in the child's pre-existing psychopathology. Accordingly, a child in crisis represents a family and community in crisis.

Adolescents account for a substantial majority of psychiatric emergencies in youths. Data suggest a preponderance of females among emergency visits, perhaps because girls in crisis are more often perceived to have a psychiatric problem, while boys are perceived to have a delinquency problem. Although varying by community, most emergency visits are for suicidal threats or behavior, followed by assaultive, destructive, or otherwise violent behavior. Additional common presenting psychiatric emergencies are anxiety states (often combined with physical complaints or school refusal) and acute mental status changes including intoxication, psychosis, and delirium.

### GENERAL EMERGENCY PSYCHIATRIC ASSESSMENT CONSIDERATIONS

Child psychiatric emergencies are characterized by severe symptoms, functional impairment, significant distress, and a sense of danger and urgency. Because

a child's mental health is highly dependent on the functioning of the family, school, and community in which she lives, any disturbance in the functioning of these systems has the potential to precipitate a crisis. It is, therefore, critical to answer the questions, *Who is concerned about the child?* and *Why now?*

Whether information is obtained in a clinic visit or in a caretaker telephone call, the PCP needs to determine if the problem is sufficiently severe to require emergency assessment. Threats of harm to self or others, severe out-of-control behavior, and acute mental status changes such as psychosis or delirium all require immediate evaluation. Overwhelming caregiver distress, acute change in overall functioning, or significant symptom exacerbation are examples of circumstances warranting urgent (within 48–72 hours), but not necessarily immediate, evaluation. When immediate evaluation is indicated, physicians must have a system in place to obtain an emergency assessment; Figure 370-1 presents an algorithm for accessing this level of care.

## ELEMENTS OF EMERGENCY PSYCHIATRIC ASSESSMENT

The critical elements of an emergency psychiatric assessment are outlined in Box 370-2. Although the requirement to obtain consent for assessment and treatment is generally waived in emergency situations, reasonable attempts should be made to obtain and document consent from the child's legal guardian. State laws vary with regard to the age at which a minor may self-consent to mental health assessment and treatment. Before beginning an assessment, the limits of confidentiality should be reviewed with the youth and his caregivers. Confidentiality of the youth's disclosures to the physician should not be maintained in circumstances in which the youth presents a danger to herself or others. All professionals are required by federal law to report suspected abuse or neglect. The federal Child Abuse Prevention and Treatment Act sets forth broad guidelines for defining child abuse and neglect; states vary regarding whether there must be knowledge of abuse or merely suspicion of abuse to initiate a report. A searchable database of state statutes is available online through the Child Welfare Information Gateway ([www.childwelfare.gov/topics/systemwide/laws-policies/state](http://www.childwelfare.gov/topics/systemwide/laws-policies/state)). Although consent from the child's guardian or older youth may be a prerequisite for exchanging clinical information with collateral informants, the identification of the situation as emergent can supersede confidentiality protections.

The physical setting for the emergency assessment should reflect the severity of the presenting problem. Some presentations (eg, suicidality, assaultiveness, dangerous unmanageable behavior, and acute mental status changes) generally require the full spectrum of evaluative and stabilization services available in the hospital emergency department setting. Other, less urgent presentations may be suitable for assessment in less restrictive settings. In situations where there is imminent risk of substantial harm, the setting should be secluded from other patients and safeguarded by removing any potentially dangerous personal

possessions, clothing, furniture, medical equipment, and medications. Assistance should be readily available in the event of escalating unmanageability.

Obtaining a full and accurate diagnostic picture requires gathering information from diverse sources, including (as relevant) the family; school staff; prior and current treatment providers; representatives from social services, child welfare, and juvenile justice agencies; and public safety officers. At a minimum, the assessment should include an interview of the child and any accompanying adults. If the caregivers are not present, every effort must be made to contact them for inclusion in the assessment.

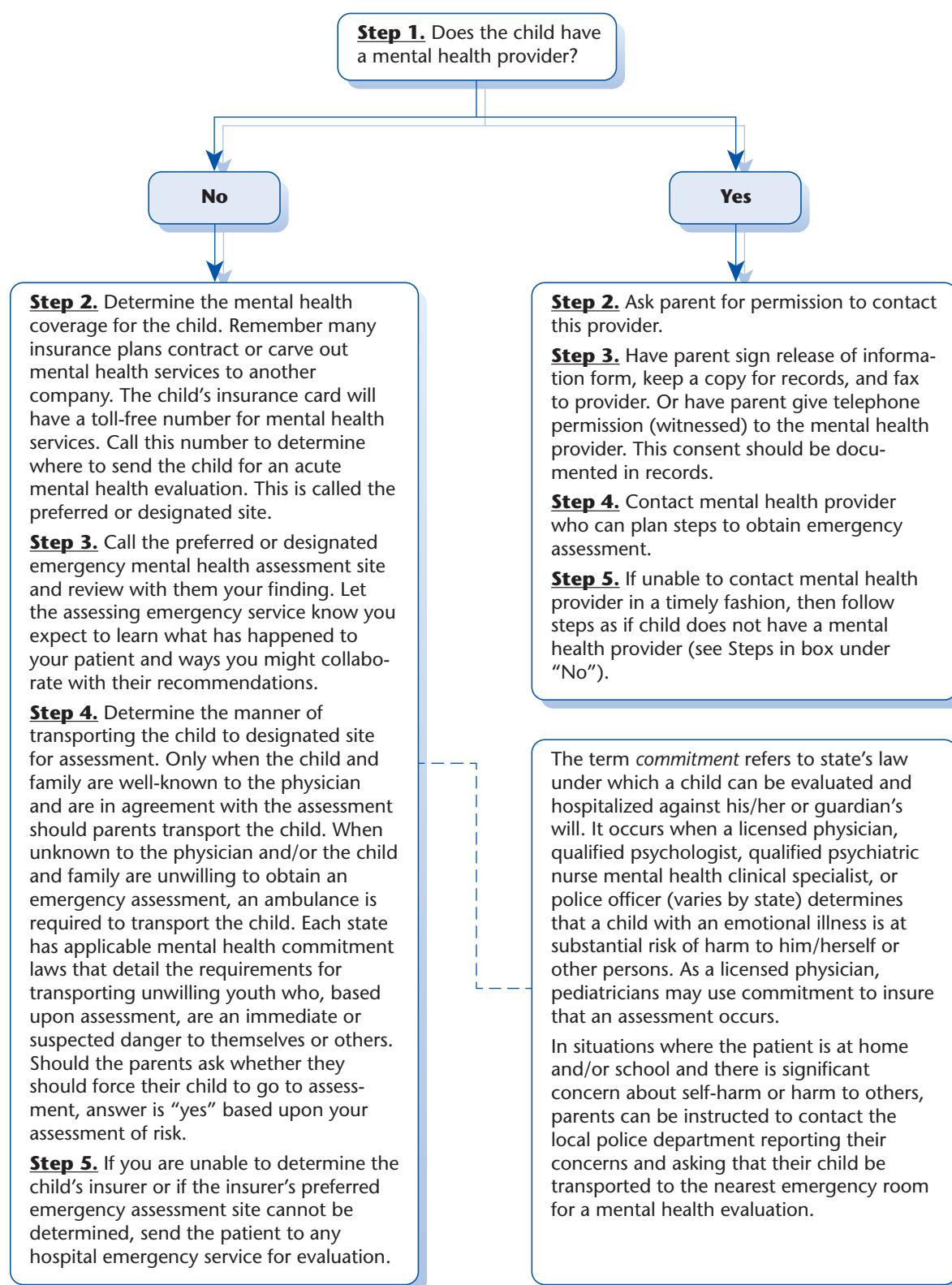
Informants may differ in their access to relevant information. Caregivers or school staff may be quick to report the child's disruptive, aggressive behavior or angry mood, but may be less aware of the child's sadness, worries, or fears. Caregivers may be unaware of how discord within the family system or other traumatic exposure can precipitate a mental health crisis in the child. The interviewer should be aware that vague or sketchy responses to queries, either from the caregivers or the child, or minimization of clear problems can signal a child or family secret, such as physical or sexual abuse, domestic violence, illegal activity, or parental impairment.

In contrast to a routine mental health assessment, in which several sessions may be required to reach a comfort level with the interviewer, an emergency assessment requires that the interviewer gather salient information expeditiously, thereby precluding systematic relationship building. Nonetheless, the interviewer must make every effort to put the child at ease. A useful strategy is to emphasize an interest in the child's perspective of the events leading to the crisis.

The emergency assessment includes a careful physical examination and laboratory tests when indicated by history and physical signs or symptoms, including evidence of a physical illness, prescribed medication use, or substance use that may cause altered mental status.

A key outcome of the emergency assessment is achieving consensus between the caregiver or other referring party and the child on the nature of the presenting problem, its precipitants, and realistic solutions to the problem. Lack of consensus bodes poorly for the success of crisis intervention and disposition plans. Conversely, caregivers/referral sources and children who are able to recognize recurrent patterns and their role in those patterns may be more likely to successfully transition from emergency intervention to treatment, and eventually to health. Caregivers reassuming the care of children after emergency assessment must be capable of adhering to, safeguarding, and monitoring disposition recommendations.

Disposition of the child requires 2 primary decisions—*Does the child present imminent and substantial danger to himself or others?* and *What is the most appropriate level of care?* Empirically derived risk factors for inpatient level of care include suicidal or aggressive presentation, increasing age, presentation during the school year, and substance use by the child or a family member. Disposition decision making is complicated by the constraints of the mental health care delivery



**Figure 370-1** Algorithm for accessing an emergency assessment. Source: (From Children's Hospital Boston, Blue Cross Blue Shield of Massachusetts. Rapid Mental Health Triage for Children and Adolescents: A Practical Guide for Clinicians. 2007.)



### BOX 370-2 Elements of an Emergency Psychiatric Assessment

- Obtain each informant's account of the crisis from his or her point of view.
- Develop a working alliance with the patient and other involved parties around assessment and disposition.
- Obtain a focused history of the child, including present illness, stressors, psychiatric treatment, and medical, school, developmental, social, and family elements.
- Perform a mental status examination, with close attention to suicidal or homicidal ideation and other mental status abnormalities (eg, hallucinations, delusions, thought disorder, disorientation or confusion, rage, humiliation, anxiety, hopelessness, agitation, impulsivity, impaired communication or cognition, impaired judgment or insight).
- Assess the characteristics of the family relevant to crisis intervention and disposition planning, including the presence of firearms in the home.
- Perform a focused medical assessment as indicated by history and physical signs or symptoms.
- Develop a differential diagnosis, including a formulation of predisposing and precipitating factors.
- Arrive at a judgment of probable danger to self or others.
- Develop and implement a crisis intervention plan.
- Plan and implement an appropriate disposition.
- Communicate assessment findings to relevant parties.

Derived in part from King RA. Practice parameters for the psychiatric assessment of children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 1995;34(10):1386-1402.

and reimbursement systems. In general, there has been a decline in available psychiatry inpatient beds and fewer days of inpatient care for children and adolescents. When children needing a higher level of care are discharged to community or outpatient settings (where there is often a long wait to first visit and between subsequent visits), the stage is set for recurrent crisis presentations.

### SPECIFIC EMERGENT PRESENTATIONS

#### Suicidality

##### Presentation

Suicidality presents on a dimensional spectrum ranging from thoughts about causing intentional self-injury or death (suicidal ideation) to acts that cause intentional self-injury (suicide attempt) or death (completed suicide). The intent to harm oneself, which may be explicit and strong or ambiguous and vague, is the defining characteristic of suicidal behavior, complicated by variations in the construct of intentionality from early childhood to late adolescence. Suicide is rare before puberty. Teenage/young adult American Indian/Alaska Native and non-Hispanic white males have the highest rates of suicide completions, and teenage Hispanic females have the highest rates of suicide attempts. Firearms and ingestion are the most commonly used methods of completing suicide for males and females, respectively. Ingestion is the most commonly used method of attempting suicide. Attempters who have made prior suicide attempts, who used a method other than ingestion, and who still want to die are at increased risk of completed suicide. Table 370-1 outlines several important risk factors for youth suicide.

**Table 370-1** Risk Factors for Youth Suicide

RISK FACTORS	COMMENT
Prior history of a suicide attempt	Increases the risk of suicide nearly 90-fold; strongest predictor.
Psychiatric disorder	~90% of youths who complete suicide have a psychiatric disorder at the time of death, most commonly mood disorders, including major depression and bipolar disorder, followed by substance abuse disorders.
Multiple psychiatric disorders	>70% have multiple psychiatric disorders.
Comorbid mood and substance use disorders	Increase risk of completed suicide nearly 20-fold.
Lack of psychiatric treatment	Large proportion of youths completing suicide had not received treatment.
Personality characteristics	Such as mood instability, impulsiveness, perfectionism, aggression, odd thinking, introversion.
Neurotransmitter dysregulation	Especially serotonergic systems.
Neuroendocrine dysregulation	Especially the hypothalamic-pituitary-adrenal axis.
Disordered sleep architecture	Chronobiological studies suggest a role.
High rates of cumulative stressors	Such as family losses, family discord and dysfunction, parental incapacity, physical or sexual abuse, sexual orientation, immigrant status, living outside the home, not working or attending school, having academic difficulties, bullying, early physical insults (pre-, peri-, postnatal), chronic medical illness.
Social maladjustment	Such as poor interpersonal relationships with family, teachers, or counselors resulting in lack available empathic adults who could offer guidance and support.
Cognitive distortions	Perceived inadequacies, catastrophic thinking, hopelessness. Hopeless feelings in particular impair the youth's ability to manage strong feelings, solve problems, and cope with adversity.

### Evaluation

Assessment of suicidal ideation should be a part of every presentation of a child in crisis, especially those with depressed mood, substance use, or altered mental status. All suicidal ideation and attempts should be taken seriously and require a thorough assessment to evaluate the youth's current state of mind, underlying psychiatric conditions, and ongoing risk of harm. Gathering information from multiple sources and by varied culturally and developmentally sensitive techniques is essential in evaluating suicidal risk factors.

Suicidal ideation can be assessed by a series of questions such as those in Box 370-3. A number of self-report instruments can be helpful in screening for suicidal ideation (see Box 370-4); however, they tend to be oversensitive and underspecific. Using 2 scales with different foci simultaneously (eg, the Suicidal Ideation Questionnaire and the Child-Adolescent Suicidal Potential Index) may provide better coverage of key predictive constructs. All positive results on a screening instrument must be followed by a thorough assessment.

The assessment of suicidal attempts should include a detailed exploration of the hours immediately preceding

the attempt to identify precipitants, as well as the circumstances of the attempt itself to identify intent and potential lethality. A series of relevant topics to address is listed in Box 370-5. Developmental considerations should guide the interview. Thus, young children are susceptible to accidental suicide through imitation or suggestion. Preadolescents may have difficulty with the construct of intentionality. In adolescents, lethality is not necessarily related to the severity of the attempt; youths with serious intent, for example, may think that a small number of over-the-counter analgesic pills can be lethal.

Acute changes in mental status (eg, intoxication, agitation, psychosis, disorientation) increase the risk of suicidality and require physical examination to rule out a medical etiology for the change. Physical examination may provide evidence of physical or sexual abuse, prior suicide attempts, or other self-harm, or a physical illness that could cause altered mental status. Laboratory studies should be considered when suggested by the physical findings (eg, urine toxicology screen or a pregnancy test).

### Management

The assessment of suicidality culminates in answers to 2 basic questions—*Is the patient at current risk for attempted or completed suicide?* and *Are the patient and family able to adhere to recommendations regarding supervision, safeguarding, and follow-up care?* Management should be embedded within the pediatric medical home, where the PCP is informed and aware of the management plan. Follow-up visits in the pediatric setting support mental health management.

Psychiatric hospitalization is indicated when the youth actively voices suicidal intent. Intent can be explicitly stated (“I want to die”) or implied (“I can’t see

#### BOX 370-3 Questions to Elicit Suicidal Ideation/Behavior

- Did you ever feel so sad or upset that you wished you were not alive or wanted to die?
- Have you ever thought that you or your family would be better off if you were dead?
- Did you ever do something that you knew was so dangerous that you could get hurt or killed by doing it?
- Have you ever thought about killing yourself?
- Did you ever try to kill yourself?
- Did you ever try to kill yourself, and not tell anyone?
- Did you ever make a plan to kill yourself? If so, what was the plan?

#### BOX 370-4 Selected Screening Instruments for Suicidality

##### Suicide Behaviors Questionnaire-Revised (SBQ-R)

4 items for adolescents

[measures.earlyadolescence.org/measures/view/25](http://measures.earlyadolescence.org/measures/view/25)

##### Suicidal Ideation Questionnaire (SIQ) and Suicidal Ideation Questionnaire–Junior (SIQ-Jr)

30 items for ages 13–18 years (SIQ for grades 10–12 & SIQ-Jr for grades 7–9)

[www4.parinc.com/Products/Product.aspx?ProductID=SIQ](http://www4.parinc.com/Products/Product.aspx?ProductID=SIQ)

##### Child Adolescent Suicidal Potential Index (CASPI)

30 items for ages 6–18 years

[books.google.com/books?id=-r309ILpxTkC&pg=PA95](http://books.google.com/books?id=-r309ILpxTkC&pg=PA95)

#### BOX 370-5 Topics to Explore for a Suicide Attempt

- Why was the method chosen?
- What were the expectations from the attempt (did the patient think the attempt was going to kill him)?
- How reversible was the attempt?
- Did the circumstances permit the patient to change her mind about the attempt?
- Does the patient demonstrate ambivalence about living?
- How strong was the patient's intent to die?
- Was there evidence of premeditation, including preparations and precautions against discovery?
- Did the patient tell anyone about the attempt, particularly responsible caretakers?
- What did the patient do immediately after the attempt?
- Did the patient seek help or simply disregard the danger of the attempt?
- Did the patient acknowledge the attempt or try to hide or deny the attempt?
- Is the patient relieved or disappointed that he survived the attempt?

any reason to go on living"). These youths typically have frequent thoughts about suicide that occur over long periods of time. They describe specific plans that are not only well conceived and potentially lethal, but also feasible in their environment. Concern is heightened if the youth has known risk factors for suicidality (especially a previous attempt, untreated depression, or substance use), or if the youth is aware of another youth (with whom he can identify) or a family member who has completed suicide. Medical hospitalization may follow a suicide attempt, and when the youth is medically stable, but remains potentially dangerous, a transfer to a psychiatric facility should be arranged.

Hospitalization also is indicated in the context of altered mental status, a history of psychiatric disorder unsuccessfully treated in outpatient or day-hospital settings, active substance use, and caregiver incapacity. Caregivers of suicidal youths must believe that their relationship with their child is sufficiently close that their child will disclose suicidal thoughts should they occur in the future. Caregivers must be able to supervise the child closely during the acute phase of assessment and treatment, to safeguard the home by removing access to potentially lethal methods of suicide (eg, firearms, prescribed and over-the-counter medications), and to adhere to all follow-up assessment and treatment recommendations.

The primary goal of hospitalization is to keep the child safe from self-harm. Other goals are to clarify psychiatric diagnoses and develop a comprehensive treatment plan with individual, family, and environmental (eg, school and community) interventions. Pharmacotherapy may be initiated in the presence of moderate to severe psychopathology. Youths typically remain hospitalized until active intent to die has abated, and a safe and secure discharge plan to which caregivers can adhere is in place.

A referral for psychiatric outpatient follow-up may be appropriate if the youth has suicidal ideation without intent or plan; has an intact mental status; has few to no other risk factors for suicidality; is willing and able to participate in outpatient treatment; and has caregivers able to provide emotional support, supervision, safeguarding, and adherence to follow-up. Other considerations are systems related, including the availability of urgent outpatient appointments, qualified

mental health providers, and evidence-based treatment modalities.

PCPs should be aware that the rate of completed psychiatric outpatient referrals is known to be very poor. Moreover, approximately one-third of referred youths attend only 1 or 2 sessions, and one-quarter appear only 3 or 4 times. Several factors influence likelihood of follow through, including a history of previous hospitalization, severe symptoms of psychiatric disorders, and the lethality of the attempt. PCPs can help educate the patient and family about the causes and treatment of suicidality, and the risks of failing to treat. The likelihood of a completed referral also can be increased by making sure that the family secures a specific appointment day and time at the time of the emergency psychiatric assessment.

The goals of psychiatric outpatient treatment are to successfully treat the underlying psychiatric disorders and to prevent further suicidality. Optimal treatment will consist of evidence-based approaches, including individual psychotherapy and pharmacotherapy, family therapy, and group therapy. Although no specific treatment modalities have been shown in rigorous studies to prevent suicidality, several psychotherapies have been shown to be promising, including dialectical behavioral therapy and cognitive behavioral therapy–suicide prevention (see Table 370-2).

If the psychiatric disorder underlying suicidality is depression, antidepressant medication can be considered as part of a comprehensive treatment plan. In a pilot study among adolescent suicide attempters with depression, combination treatment (antidepressant medication and cognitive behavioral therapy) resulted in improvements in depressive symptoms similar to those demonstrated in other studies among nonsuicidal depressed adolescents. Physicians must be aware of the association between antidepressant medications and suicidal thoughts, and the need to closely monitor patients who are prescribed these medications.

### Acute Agitation Presentation

Acute agitation encompasses a psychological state (feeling of inner tension or arousal) as well as a motoric state (pacing, hand wringing, fidgeting). It can occur in the context of a number of psychiatric,

**Table 370-2** Psychotherapies for Suicidality

PSYCHOTHERAPY TYPE	DESCRIPTION
Dialectical behavioral therapy	Designed for individuals with deficits in emotional regulation; focus is both on mindfulness and acceptance (derived from Asian philosophy) and on skills building (derived from cognitive behavioral therapy). Uses 4 skills modules to address emotion regulation, interpersonal effectiveness, mindfulness, and distress tolerance.
Cognitive behavioral therapy–suicide prevention	Designed for youths who have made a suicide attempt; detailed chain analysis identifies proximal risk factors (eg, emotional, cognitive, behavioral, and family) active just before and after the attempt. These factors include deficits in the youth's ability to regulate emotions, resolve problems, tolerate distress, and address negative thoughts such as worthlessness or hopelessness. A core feature of the treatment is the development of an individualized case conceptualization that identifies problem areas to be targeted and specific interventions to be used during periods of acute emotional distress.

general medical, and substance-induced conditions, as outlined in Box 370-6. The critical first step is to determine whether the acute agitation is because of a general medical condition, substance- or medication-induced condition, or primary psychiatric disorder.

Acute agitation in a general medical or substance/medication-induced condition is characterized by disturbances in consciousness (reduced clarity of awareness of environment) and changes in cognition over a short period of time. Consistent with the diagnosis of delirium, this type of agitation is often accompanied by cognitive changes (eg, memory deficit, disorientation, inattention, language disturbance), mood changes (eg, irritability), and perceptual disturbances (eg, acute illusions, hallucinations, or delusions). In contrast, agitation in primary psychiatric disorders generally is not accompanied by the acute disturbances in consciousness or cognition. Agitation in autism spectrum disorder can be associated with underlying physical illnesses that cannot be readily communicated by the patient to others, or to environmental changes that unsettle the needed consistent daily routines.

### **BOX 370-6 Disorders Commonly Associated With Agitation**

#### **General Medical Conditions**

- Delirium related to direct effect of physical illness
- Acute drug intoxication

#### **Psychiatric Disorders**

- **Neurodevelopmental disorders**
  - Intellectual disability
  - Autism spectrum disorder
  - Attention-deficit/hyperactivity disorder
- **Disruptive, impulse control, and conduct disorders**
  - Oppositional defiant disorder
  - Intermittent explosive disorder
  - Conduct disorder
- **Anxiety disorders**
  - Separation anxiety disorder
  - Panic disorder
  - Generalized anxiety disorder
- **Depressive and bipolar**
  - Major depressive disorder
  - Bipolar disorder
  - Disruptive mood dysregulation disorder
- **Obsessive-compulsive disorder**
- **Trauma- and stressor-related disorders**
  - Post-traumatic stress disorder
  - Acute stress disorder
- **Psychotic disorders**
  - Schizophrenia
  - Other psychotic disorders
- **Substance-related disorders**
  - Intoxication or withdrawal states

**Parent-child relational problem**  
**Abuse and neglect**

### **Evaluation**

An acutely agitated child must be thoroughly assessed for underlying medical, medication, or substance use causes using physical examination and laboratory and imaging tests as indicated (Box 370-7). This process must be completed before assuming a psychiatric cause for a patient's agitation. In the case of suspected delirium, serial assessments are required because of the fluctuating nature of the disorder. Various instruments are used to diagnose delirium and assess symptom severity. Among the most widely used instruments for youths is the Delirium Rating Scale, which has versions for younger and older children. Table 370-3 outlines the differential diagnosis of pediatric delirium using the mnemonic "I WATCH DEATH."

### **Management**

For all cases of agitation, the most effective treatment addresses the underlying cause. In the interim, the physician treats the acute agitation to ease the distress of the patient and family, reduce the potential for unintentional harm, and improve the medical outcome (if relevant). Box 370-8 outlines nonpharmacologic approaches for the physician facing a child or adolescent with acute agitation. If these initial interventions are ineffective, physicians should consider the use of pharmacologic interventions or seclusion or restraint if necessary to prevent harm to self or others. States vary in their regulations on the use of emergency pharmacologic interventions and seclusion or restraint for out-of-control behavior. Box 370-9 presents considerations for the assessment of children for emergency medication treatment, and Box 370-10 presents national guidelines for the use of seclusion and restraint.

Special treatment considerations pertain to the child with delirium. Environmental intervention is particularly important. Frequent and repeated reassurance

### **BOX 370-7 Selected Tests to Be Considered for the Medical Evaluation of Agitation**

#### **HEMATOLOGY**

Complete blood count

#### **CHEMISTRY**

Electrolytes, glucose, blood urea nitrogen, creatinine, total protein, liver function tests, calcium, magnesium, phosphorus, thyroid function tests, kidney function tests

#### **OTHER LABORATORY**

Pregnancy, heavy metals, B<sub>12</sub>, folate, lupus prep, antinuclear antibodies, urine porphyrins, ammonia, erythrocyte sedimentation rate, human immunodeficiency virus, urine toxicology screen, serum drug levels, arterial blood gases, electrocardiogram

#### **IMAGING**

Chest radiograph, computed tomography, magnetic resonance imaging, echocardiography, endoscopy

#### **OTHER**

Electroencephalogram, electrocardiogram, lumbar puncture



**Table 370-3****Differential Diagnosis of Pediatric Delirium: The “I WATCH DEATH” Mnemonic**

<b>Infection</b>	Encephalitis, <sup>a</sup> meningitis, <sup>a</sup> syphilis, human immunodeficiency virus, or sepsis <sup>a</sup>
<b>Withdrawal</b>	Alcohol, barbiturates, or sedative-hypnotics <sup>a</sup>
<b>Acute metabolic</b>	Acidosis, alkalosis, electrolyte disturbance, <sup>a</sup> hepatic failure, or renal failure
<b>Trauma</b>	Closed-head injury, <sup>a</sup> heatstroke, postoperative, <sup>a</sup> or severe burns <sup>a</sup>
<b>Central nervous system pathology</b>	Abscess, hemorrhage, hydrocephalus, subdural hematoma, infection, <sup>a</sup> seizures, <sup>a</sup> stroke, tumors, metastases, or vasculitis <sup>a</sup>
<b>Hypoxia</b>	Anemia, carbon monoxide poisoning, hypotension, pulmonary failure, or cardiac failure
<b>Deficiencies</b>	Vitamin B <sub>12</sub> , folate, niacin, or thiamine
<b>Endocrinopathies</b>	Hyper/hypoandrenocorticism, hyper/hypoglycemia, myxedema, or hyperparathyroidism
<b>Acute vascular</b>	Hypertensive encephalopathy, stroke, arrhythmia, or shock <sup>a</sup>
<b>Toxins or drugs</b>	Medications, <sup>a</sup> illicit drugs, pesticides, or solvents
<b>Heavy metals</b>	Lead, manganese, or mercury <sup>a</sup>

<sup>a</sup>More commonly seen in pediatric delirium.

From Wise MG, Brandt G. Delirium. In: *The American Psychiatric Press Textbook of Neuropsychiatry*. 2nd ed. Hales RE, Yudofsky SC, eds. Washington, DC: American Psychiatric Press; 1992:302. Copyright © 1992, American Psychiatric Press, Inc. Used with permission.

**BOX 370-8 Nonpharmacologic Approaches to the Child or Adolescent with Acute Agitation****EDUCATE**

- Explain to the patient and caretaker your understanding of the cause of the acute agitation and that it is a time-limited consequence of an underlying disorder.
- Because of interference with cognitive ability, explanations or statements to the patient should be short, succinct, and focused (eg, “You must calm down . . . we will be giving you medicine to help you stay safe...you can have the medicine by mouth or by injection”).
- Outline the needed intervention, which may include physical and medication restraints. Explain that this is an emergency situation that will require intervention to protect the patient as well as others.
- If possible, obtain consent from the caretaker regarding the intervention plan.

**CALMING INTERVENTIONS**

- If you are feeling alarmed, this is an indication that patient is “out of control.”
- Do not take anger personally, but do take into consideration your own safety.
- Clearly introduce yourself to patient.
- Use simplified language, soft voice, and slow movements.
- Explain what will happen in the outpatient setting, the emergency department, or the medical/surgical floor.
- Reassure the patient that you are there to keep him safe.
- Have someone familiar provide frequent, repeated reassurance and reorientation to help decrease fear and confusion.
- Do not leave the patient alone; instead, the patient should remain in the company of a family member or clinical staff.
- Tell the patient how you plan to honor her reasonable requests.
- Understand the patient’s goal, and link cooperation to the goal.
- Offer food or drink.
- Reduce environmental stimulation (eg, reduce lighting and number of people).
- Remove access to breakable objects or equipment.
- Find things for the patient to control.
- If appropriate, offer distracting toys or sensory modalities.
- Limiting staff changes and involving relatives in care often eliminates the need for medication.
- If the patient does not respond to verbal reassurance, it may be necessary to provide a “show of force” to convey a message to the patient that external control will be placed on his behavior to protect him as well as others. Hospital security staff or police in the community can effectively deter acting-out behaviors simply by being visible in sufficient numbers.

### BOX 370-9 Considerations in Assessment of Children for Emergency Medication Treatment

1. Benefits of treatment and risks of withholding treatment.
2. Benefits and potential risks of proposed medication.
3. Route of medication administration: Is oral administration possible? If not, does the patient have alternative routes already in place such as intravenous access or a gastric tube, or would the medication have to be administered rectally or intramuscularly and potentially be more traumatic?
4. Necessity of physical restraint to administer medication.
5. Patient age: A mature minor may be able to consent to treatment. Efforts should be made to document that the physician has communicated with the patient before giving the medication. The younger the child, the less input she will have regarding treatment.
6. Level of anxiety: A mild panic attack episode characterized by hyperventilation and tremors may not require any immediate intervention, whereas a severe attack associated with acute agitation (eg, pulling out intravenous or nasogastric tubes or removing an oxygen mask) constitutes a higher level of urgency.
7. Level of agitation: A mild episode characterized by restlessness may not require any immediate intervention, whereas severe agitation associated with significant threat of harm to others would constitute a higher level of urgency.

From Ibeziako P, Bourne R, Shaw RJ, DeMaso DR. Legal and forensic issues. In: Shaw RJ, DeMaso DR, eds. *Textbook of Pediatric Psychosomatic Medicine: Mental Health Consultation with Physically Ill Children*. Washington, DC: American Psychiatric Press, Inc; 2010:47–62. Copyright © 2010, American Psychiatric Press. Used with permission.

and reorientation by someone familiar helps to decrease fear and confusion. Limiting staff changes, providing a safe and uncluttered environment, but with orienting objects (eg, clocks, calendars, pictures of family and home, familiar objects from home), minimizing excess ambient noise, and providing good day lighting and low night lighting all facilitate orientation. If pharmacologic interventions are needed to maintain safety, antipsychotic medications can be very beneficial for the agitated patient with perceptual disturbances, sleep-wake cycle abnormalities, and behavioral dyscontrol. Haloperidol has been favored because it has few metabolites, a safe parenteral form, few anticholinergic and hypotensive side effects, and relatively less sedation than other agents. The intravenous route should be considered if rapid acute control of agitation is required. Care should be taken to monitor anticholinergic (eg, acute dystonia) and cardiac (eg, prolongation of the QTc interval) side effects.

Agitation derived from causes other than delirium can be treated with medication according to guidelines presented in Table 370-4 and Box 370-11.

### Acute Psychosis

#### Presentation

Psychotic symptoms include delusions, hallucinations, disorganized thinking (as manifested in disorganized

### BOX 370-10 Guidelines for the Use of Seclusion and Restraint for Children and Adolescents

1. Restraint or seclusion must only be used when it can be clinically justified or when warranted by patient behavior that threatens the physical safety of the patient, staff, or others.
2. A physician or clinical psychologist, or other authorized licensed practitioner (physician) primarily responsible for the patient's ongoing care orders the use of restraint or seclusion in a manner consistent with hospital policy.
3. The physician is consulted as soon as possible if he or she did not order the restraint or seclusion.
4. The physician primarily responsible for the patient's ongoing care conducts an in-person evaluation of the patient within 1 hour of initiation.
5. The in-person evaluation by the physician includes an evaluation of the patient's immediate situation, the patient's reaction to the intervention, the patient's medical and behavioral condition, and the need to continue or terminate the restraint or seclusion.
6. Orders are time limited and may be renewed within 2 hours for children and adolescents aged 9–17 years, and within 1 hour for children under age 9 years, for a maximum of 24 consecutive hours.
7. At least every 24 hours, the physician must evaluate the patient before writing a new order for restraint or seclusion.
8. Patients in seclusion or restraint must be continuously monitored.
9. Seclusion and restraint must be documented in the patient's medical record in a manner consistent with hospital policy.

Adapted with permission from 2016 *Comprehensive Accreditation Manual for Hospitals*. Oakbrook Terrace, IL: Joint Commission Resources; 2015.

speech), disorganized behavior, and “negative” symptoms (eg, diminished emotional expressiveness, decreased motivation). Hallucinations can be auditory, visual, tactile, olfactory, or gustatory, and occur in the absence of identifiable external stimuli.

#### Evaluation

New-onset psychotic psychiatric disorders are uncommon before adolescence; psychotic symptoms occur more commonly in the context of an underlying medical illness or substance-related conditions. The differential diagnosis of medical causes of acute psychosis is broad (Box 370-12). As with the evaluation of acute agitation, a thorough history and physical examination are crucial investigatory tools, and laboratory and radiologic workup can narrow the differential (see Box 370-7).

If a medical cause for acute psychosis can be ruled out, psychiatric etiologies can be considered. The differential diagnosis comprises a broad range of psychiatric disorders, including diagnoses in which hallucinations are not the hallmark feature but may be viewed as associated symptoms (eg, post-traumatic

Table 370-4

## Psychotropic Medication Management of Acute Agitation in Children and Adolescents

## MEDICATION CONSIDERATIONS FOR MILD AGITATION

- Mild agitation can be defined as excessive worries or fears that respond to calming interventions; physician feels in control; patient agrees to take medication.

PARAMETER	CHILD (8–12 YEARS)	ADOLESCENT (≥13 YEARS)
Preferred agent(s)	Lorazepam <b>or</b> standing antipsychotic <sup>a</sup>	Lorazepam <b>or</b> standing antipsychotic <sup>a</sup>
Administration route	By mouth	By mouth
Initial dosing	Lorazepam 0.5–1 mg	Lorazepam 1–2 mg
Initial endpoint	Calm/cooperative	Calm/cooperative
Assessment frequency	q15min until calm	q15min until calm
Redosing frequency	Lorazepam q2hrs	Lorazepam q2hr
Time to maximum plasma concentration	Lorazepam 2 hr	Lorazepam 2 hr

## MEDICATION CONSIDERATIONS FOR MODERATE AGITATION

- Moderate agitation can be defined as verbal aggression; patient does not respond to interventions; physician feels worried; patient agrees to take medication.

PARAMETER	CHILD (8–12 YEARS)	ADOLESCENT (≥13 YEARS)
Preferred agent(s)	Risperidone <sup>c</sup> <b>or</b> haloperidol <sup>d</sup>	Risperidone <sup>c</sup> <b>or</b> haloperidol <sup>d</sup>
Administration route	By mouth	By mouth
Initial dosing	Risperidone 0.25–0.5 mg <b>or</b> haloperidol 2 mg	Risperidone 0.5–1 mg <b>or</b> haloperidol 5 mg
Initial endpoint	Calm/cooperative	Calm/cooperative
Assessment frequency	q15min until calm	q15min until calm
Redosing frequency	Haloperidol q4–8hr Risperidone q12hr	Haloperidol q4–8hr Risperidone q12hr
Time to maximum plasma concentration	Haloperidol 2–4 hr Risperidone 1 hr	Haloperidol 2–4 hr Risperidone 1 hr

## MEDICATION CONSIDERATIONS FOR SEVERE AGITATION

- Severe agitation can be defined as physical aggression or destruction of property; explosive situation; physician feels alarmed; patient refuses medication.

PARAMETER	CHILD (8–12 YEARS)	ADOLESCENT (≥13 YEARS)
Preferred agent(s)	Haloperidol <sup>f</sup> alone <b>or</b> haloperidol <b>and</b> lorazepam together <sup>g</sup>	Haloperidol <sup>f</sup> alone <b>or</b> haloperidol <sup>f</sup> <b>and</b> lorazepam together <sup>g</sup>
Administration route	Intramuscular	Intramuscular
Initial dosing	Haloperidol 2 mg <b>or</b> haloperidol 2 mg and lorazepam 0.5–1 mg	Haloperidol 5 mg <b>or</b> haloperidol 5 mg and lorazepam 1–2 mg
Initial endpoint	Calm/cooperative	Calm/cooperative
Assessment frequency	q15min until calm	q15min until calm
Dosing frequency	Haloperidol q4–8hr	Haloperidol q4–8hr
Time to maximum plasma concentration	Haloperidol: 30 min; lorazepam: 10 min	Haloperidol: 30 min; lorazepam: 10 min

## IF NO ORAL OR INTRAMUSCULAR ACCESS—MEDICATION CONSIDERATIONS

- Patients can present with agitated states in the pediatric hospital setting where there is *no access by mouth and intramuscular is contraindicated* (eg, muscle wasting). In these situations, acute control is required given the endangering nature of the agitation (eg, pulling tubes).

Continued

**Table 370-4 Psychotropic Medication Management of Acute Agitation in Children and Adolescents—cont'd**

PARAMETER	CHILD (8–12 YEARS)	ADOLESCENT (≥13 YEARS)
Preferred agent(s)	Haloperidol <sup>h</sup>	Haloperidol <sup>h</sup>
Administration route	Intravenous	Intravenous
Initial dosing	Haloperidol 0.5–1 mg	Haloperidol 1–2.5 mg
Initial endpoint	Calm/cooperative	Calm/cooperative
Assessment frequency	q5–10min until calm	q5–10min until calm
Dosing frequency	q30min when necessary	q60min when necessary
Time to maximum plasma concentration	10 min	10 min

<sup>a</sup>If already on a standing antipsychotic, consider an additional ¼ to ½ of the usual dose.

<sup>b</sup>Consider clonidine 0.05–0.1 mg for patients with standing clonidine or a diagnosis of attention-deficit/hyperactivity disorder, autism spectrum disorder, or disruptive behavior disorders.

<sup>c</sup>For Risperidone, if no response after 30 min, repeat ½ original dose; if no response after 60 min, may give lorazepam (child 0.5–1 mg; adolescent 1–2 mg).

<sup>d</sup>For haloperidol, if no response after 30 min, repeat ½ original dose; if no response after 60 min, may give Diphenhydramine (child 25 mg; adolescent 50 mg). Diphenhydramine also may be given with the initial dose of haloperidol to prevent acute dystonia.

<sup>e</sup>Risperidone is available in liquid formula; haloperidol is available in a liquid concentrate.

<sup>f</sup>For haloperidol, if no response after 30 min, repeat ½ original dose; if no response after 60 min, may give diphenhydramine (child 25 mg; adolescent 50 mg). Diphenhydramine also may be given with the initial dose of haloperidol to prevent acute dystonia.

<sup>g</sup>The combination of haloperidol and lorazepam can be considered when there is *imminent risk of substantial harm to self or others*.

<sup>h</sup>Monitor for prolongation of the QT interval and cardiac arrhythmias.

From *The Patient Care Manual*. Children's Hospital Boston. 2014.

### BOX 370-11 Medication Monitoring Requirements and Administration Considerations

#### MONITORING REQUIREMENTS

- Vital signs and blood pressure along with observation for the development of extrapyramidal side effects (eg, akathisia, dystonic reactions) and respiratory depression.
- Intravenous haloperidol only: ideally, assess QTc at baseline and periodically after administration. Avoid use in patients with known QTc prolongation.

#### ADMINISTRATION CONSIDERATIONS

- Both first-generation (typical) and second-generation (atypical) neuroleptics have evidence supporting their utilization for acute agitation. To date, neither type has been proven superior to the other. Each medication has its own individual side effects, which should be considered for each patient. These medication guidelines are only for acute situations.
- Medication can be given in an emergency situation without parental (or legal guardian) consent when there is danger to self or others.
- Show of force (eg, security or other personnel) when administering medication can be helpful, if medication is resisted by patient.
- Prepare both by mouth and intramuscular formulations so that either can be given.
- Use a time frame (eg, you have 5 minutes to take this medication by mouth; otherwise, we will need to give you the medication as a shot).
- Half-life of diphenhydramine is potentially much shorter (2–9 hours) than that of antipsychotics (haloperidol 12–36 hours, risperidone 24 hours), so if acute dystonia is treated with diphenhydramine, a dose of benzotropine or additional dose of diphenhydramine should be considered within a few hours.

stress disorder [PTSD], nonpsychotic mood disorders, and disruptive behavior disorders); diagnoses that are defined by psychotic features (eg, brief psychotic disorder, schizophrenia, major depression or bipolar disorder with psychotic features); and at-risk clinical states (poor reality testing).

In children with nonpsychotic hallucinations, the symptom cluster of psychosis (delusions, disorganized thoughts and behavior, negative symptoms) is absent. Nonpsychotic hallucinations commonly occur in the context of severe traumatic stress, developmental delays or disorders, social and emotional deprivation, caregivers whose own psychopathology promotes a breakdown in the child's sense of reality, cultural beliefs in mysticism, unresolved mourning, and normal development ("magical thinking").

#### Management

The underlying condition will determine the type of treatment needed. Nonpsychotic hallucinations suggest the need for disorder-specific psychotherapy (eg, trauma-focused cognitive behavioral therapy for PTSD, parent management training for behavior disorders) and perhaps adjunctive medication (eg, an antidepressant for depression or anxiety, or a brief course of antipsychotic medication). Psychotic hallucinations may be an indication for antipsychotic medication. Hallucinations from intoxication or physical illness typically resolve in parallel with the underlying condition.

#### Disaster Exposure Presentation

A disaster is a sudden and severe ecological and psychosocial disruption that greatly exceeds the coping capacity of the community. Children may experience a spectrum of psychological effects across the disaster timeline that vary according to developmental stage (Box 370-13). Transient moderate psychological distress



**BOX 370-12 Differential Diagnosis of Medical Causes of Acute Psychosis****Drugs (prescribed and illicit)****Trauma****Organ failure**

- Cardiopulmonary
- Hypertensive encephalopathy
- Renal azotemia
- Hepatic encephalopathy

**Electrolyte abnormalities****Neurologic**

- Stroke
- Lupus cerebritis
- Multiple sclerosis
- Seizures
- Huntington disease/chorea

**Endocrine**

- Diabetic ketoacidosis
- Addison disease
- Cushing disease
- Thyroid disease
- Pituitary disease

**Hematologic****Paraneoplastic****Acute intermittent porphyria****Structural**

- Chronic subdural hematoma
- Intracranial aneurysm/angioma
- Normal pressure hydrocephalus
- Cerebral neoplasm
- Cerebral abscess

**Toxins**

- Plants
- Carbon monoxide
- Heavy metals, industrial toxins

**Infections**

- Sepsis
- Acquired immunodeficiency syndrome encephalopathy
- Pneumonia
- Meningitis, encephalitis
- Rocky Mountain spotted fever
- Legionnaire disease
- Lyme disease
- Acute rheumatic fever

**Vitamin deficiencies****Anoxia/hypoxia**

may be a normative reaction to traumatic exposure. More severe symptoms in the first month may qualify for a diagnosis of acute stress disorder; symptoms persisting longer than 1 month may qualify for a diagnosis of PTSD.

**BOX 370-13 General Trauma Reactions in Children and Adolescents****YOUNGER CHILDREN**

- Clinging and dependent behaviors
- Phobic reactions
- Sleep and appetite disturbances
- Nightmares
- Loss of bladder and bowel control
- Temper tantrums
- Hyperactivity

**OLDER CHILDREN**

- Reenacting the trauma through play
- Sleep and appetite disturbances
- Somatic complaints
- Concentration difficulties
- Irritability
- Hyperactivity
- Decline in school performance

**ADOLESCENTS**

- Hyperarousal
- Avoidance
- Numbing
- Anxiety, including panic
- Depressed mood
- Social withdrawal
- Suicidal ideation and behavior
- Flight into pseudoindpendence
- Belligerence
- Risky behaviors (sex, drugs, violence)
- Interpersonal conflict

**Risk Factors**

A number of factors can mediate the effect of disaster exposure on youths. These include the specific nature of the traumatic exposure (eg, type of disaster, intensity, duration, physical proximity, injury, loss of loved ones, loss of possessions, exposure to media coverage); individual factors (eg, age and developmental stage, gender, pre-existing academic function, pre-morbid psychiatric or medical illnesses, post-trauma exposure or grief experiences, adaptive coping skills, resilience, positive emotions); family factors (eg, good parent-child relationships, parental harmony, positive family ambience, extended family support, cultural identification); and community factors (eg, secondary stressors, traumatic reminders, social support, and school and religious affiliations).

Most individuals who experience life-threatening events manifest symptoms immediately. However, only around one-third tend to manifest enduring symptomatology after the first month. Female gender, previous trauma exposure, multiple traumas, greater exposure to the index trauma, presence of a pre-existing psychiatric disorder (particularly an anxiety

### **BOX 370-14 Selected Screening Instruments to Assess Traumatic Exposure**

#### **THE CHILD PTSD SYMPTOM SCALE (CPSS)**

26 items for ages 8–18 years

[www.ptsd.va.gov/professional/assessment/child/cpss.asp](http://www.ptsd.va.gov/professional/assessment/child/cpss.asp)

#### **THE UCLA CHILD/ADOLESCENT REACTION INDEX FOR DSM-5**

Semi-structured interview assessing PTSD diagnostic criteria for school-aged children and adolescents

[www.ptsd.va.gov/professional/assessment/child/ucla\\_child\\_reaction\\_dsm-5.asp](http://www.ptsd.va.gov/professional/assessment/child/ucla_child_reaction_dsm-5.asp)

disorder), parental psychopathology, and lack of social support are risk factors for a child developing PTSD after trauma exposure. Conversely, parental support, lower levels of parental PTSD, and resolution of other parental trauma-related symptoms have been found to predict lower levels of PTSD symptoms in children. Increased television viewing of disaster-related events, delayed evacuation, extreme panic symptoms, or having felt that one's own or a family member's life was in danger have each been found to be independently and significantly associated with the development of PTSD. Untreated PTSD is associated with significant morbidity. Despite some studies showing "natural recovery," other studies have shown that PTSD symptoms in children can persist over many years, affecting function in multiple domains.

#### **Assessment**

Psychological screening of disaster survivors facilitates intervention by identifying those with the greatest need. The appropriate timing of screening remains in debate because of the nearly ubiquitous distress that accompanies disasters. Screening is often conducted in school settings using instruments to assess trauma exposure as well as internalizing and externalizing reactions to the exposure. Examples of such instruments are presented in Box 370-14. A limitation of standardized screening is the wide variety of emotional and behavioral responses to trauma exhibited by children.

For children with clinically significant symptoms, formal clinical assessment should ensue, including a personal interview with the child and caregivers supplemented by information from other sources. The parent interview should clarify the nature, severity, and duration of the child's and family's disaster exposure and experience; identify the inventory of current stressors; examine the spectrum of symptoms in the child; document the child's psychiatric, developmental, school, and family history; and enumerate important contextual mediators. Children should be asked directly about their experience of and reactions to traumatic exposure. In most instances, children are able to recount their experience in words or to use nonverbal means (eg, play, drawing) to relate what occurred. It is important that the interviewer provide

the child with the opportunity to describe his experiences in whatever medium he chooses, and support the child by explaining emotional reactions, cognitive distortions, and maladaptive behaviors.

The diagnosis of both acute stress disorder and PTSD require exposure to actual or threatened death, serious injury, or sexual violation in one of the following ways: directly experiencing the event; witnessing, in person, the event as it occurred to others; learning that the event (which must be violent or accidental) occurred to a close family member or close friend; and, in the context of work eg, first responders, experiencing repeated or extreme exposure to aversive details of the event. If the trauma exposure criterion has been satisfied, diagnosis requires meeting the specified number of symptoms for the disorder, along with duration, distress, and impairment criteria. In acute stress disorder, the disturbance persists for at least 3 days to 1 month; for PTSD, the disturbance persists for more than 1 month. A diagnosis of PTSD requires 1 or more symptoms of intrusion (eg, recurrent, distressing memories or dreams; dissociative reactions; physiologic reactions to internal or external cues related to the event); 1 or more symptoms of avoidance (eg, of distressing memories or external reminders of the event); 2 or more symptoms of negative cognition or mood (eg, inability to remember an important aspect of the event, persistent negative emotional state, diminished interest in significant activities); and 2 or more symptoms of hyperarousal (eg, irritable, reckless, or self-destructive behavior; hypervigilance; sleep disturbance). A separate set of symptom clusters (not presented) pertains to children younger than age 6 years. The major differences in the PTSD criteria for very young children include the requirement for only 1 or more avoidance or negative cognition/mood symptom, the elimination of symptoms requiring reflective cognitive ability, and the expression of intrusion symptoms in play rather than verbally.

#### **Treatment**

Recovery from a disaster occurs across several distinct phases. In the impact phase (immediate aftermath), efforts focus on restoring children's and families' sense of safety and security (eg, provision of basic needs including food, water, and shelter). In the short-term adaptation phase (first 3 months), efforts focus on limiting the youth's ongoing exposure to the trauma and decreasing negative psychological reactions to the trauma. In both of these phases, interventions may be provided in a broad range of venues (eg, emergency shelters, family assistance centers, medical and pediatric health care settings, schools, community agencies) by a broad range of personnel (eg, trained volunteers, PCPs, school and community agency personnel). In the medium- to long-term recovery phase (3 months or longer), efforts focus on facilitating controlled re-exposure to the traumatic event, emotional and cognitive reparative reprocessing of the event in a safe setting, and the development of coping skills. These interventions typically are provided in mental health settings.

Psychological first aid is the primary intervention used during the impact phase of a disaster. Several organizations, including the National Child Traumatic

Stress Network (NCTSN), the National Center for Post-traumatic Stress Disorder (NCPTSD), and the American Red Cross, have developed modular approaches to psychological first aid for use by mental health responders in diverse settings under diverse conditions. Psychological first aid focuses on establishing contact, reducing physiologic hyperarousal, offering and mobilizing support and psychosocial assistance, providing accurate and timely information about disaster reactions and available resources, and conducting ongoing assessments of functional status with triage and referral as indicated.

Beyond psychological first aid, specific clinical approaches in the aftermath of a disaster include family outreach and psychoeducation as well as anxiety reduction. Caregivers often underestimate the suffering of their children; thus, family outreach is an important first step in the recovery process. Once contact is established, psychoeducation is employed to normalize disaster reactions, correct distortions and misperceptions, enhance the child's sense of control, encourage use of family and social supports, promote adaptive coping, and assess risk and protective factors. Specific psychoeducational advice that can be given to parents of children of different ages is presented in Box 370-15. Several organizations, including the American Academy of Child & Adolescent Psychiatry ([www.aacap.org](http://www.aacap.org)), the American Red Cross ([www.redcross.org/services/disaster](http://www.redcross.org/services/disaster)), FEMA ([www.fema.gov](http://www.fema.gov)), the National Association of School Psychologists ([www.nasponline.org/resources](http://www.nasponline.org/resources)), and the NCTSN ([www.nctsn.org/nctsn](http://www.nctsn.org/nctsn)) publish psychoeducational fact sheets and other useful information about coping with disaster events.

The management of anxiety, which dominates the clinical presentation in the aftermath of a disaster, is an essential aspect of the therapeutic response. Recent data have suggested that panic symptoms in the immediate aftermath of trauma exposure are predictive of the development of PTSD. Maintaining routines to the extent possible should help allay anxiety. Specific anxiety reduction techniques include relaxation strategies such as deep breathing and muscle relaxation, and cognitive behavioral strategies such as positive self-talk, problem solving, and scheduling enjoyable activities.

Trauma-focused cognitive behavioral therapy (TF-CBT) has received the most empirical support for the clinical treatment of PTSD. In TF-CBT, the clinician teaches stress management skills in preparation for the exposure-based interventions that are aimed at providing mastery over trauma reminders. The usual components of TF-CBT are presented in Box 370-16.

Evidence derived from one study suggests that intervening early after a traumatic event with brief caregiver-and-child dyadic therapy can significantly reduce trauma-related symptoms. Early intervention focuses on education about normalizing the child's symptoms in the context of trauma; teaching relaxation techniques to address anxiety; and teaching coping strategies to address intrusive thoughts (eg, guided imagery, thought stopping, distraction techniques).

## CONCLUDING COMMENTS

In the face of increasingly frequent psychiatric emergencies, such as those outlined in this chapter, it can

### BOX 370-15 Psychoeducation Guidelines for Caregivers

#### INFANTS AND TODDLERS

- Provide reassurance.
- Return to normal activities as soon as possible.
- Provide soothing activities.
- Avoid unnecessary separation from caregivers.
- Maintain calm among caregivers.
- Avoid television exposure.

#### PRESCHOOL CHILDREN

- Provide reassurance.
- Return to normal activities as soon as possible.
- Provide explanations using simple language.
- Expect and tolerate regressed behavior.
- Expect and tolerate repetitive play about the event.
- Avoid media exposure.
- Censor adult conversations about the trauma.
- Give honest answers (OK to say, "I don't know.").

#### SCHOOL-AGED CHILDREN

- Maintain routines.
- Expect and tolerate repetitive play and retelling of the event.
- Give the child control over choices.
- Provide clear and honest answers.
- Allow the child to discuss the event at her own pace.
- Check with school and other caregivers to assess the child's functioning.
- Limit media exposure.

#### ADOLESCENTS

- Be flexible around routines.
- Discuss family, work, school changes.
- Reassure and normalize strong emotions.
- Try to delay any major changes.
- Encourage involvement in enjoyable activities.
- Provide access for conversations, but do not push.
- Limit media exposure.

prove useful for PCPs to establish collaborative partnerships with mental health clinicians. These partnerships can provide physicians with consultative, educational, and case-management services that are important to ongoing patient care. Such partnerships are crucial to having a responsive pediatric medical home wherein the physical and emotional needs of children and their families are fully addressed.

## TOOLS FOR PRACTICE

### Engaging Patient and Family

- *Coping With a Disaster or Traumatic Event* (Web page), Centers for Disease Control and Prevention ([www.bt.cdc.gov/mentalhealth](http://www.bt.cdc.gov/mentalhealth))
- *Mental Health Care: Who's Who* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org](http://www.healthychildren.org))

### BOX 370-16 Components of Trauma-Focused Cognitive Behavioral Therapy

- Psychoeducation
  - Educating the child and parent about the nature of the traumatic event and expected trauma reactions.
- Parenting skills
  - Use of effective parenting interventions (contingency management).
- Relaxation skills
  - Focused breathing, progressive muscle relaxation, positive imagery.
- Affective modulation skills
  - Identification of feelings, use of positive self-talk and thought interruption, enhancing safety, problem solving, and social skills; recognizing and self-regulating negative affective states.
- Cognitive coping and processing
  - Recognizing relations between thoughts, feelings, and behaviors; changing inaccurate and unhelpful thoughts.
- Trauma narrative
  - Creating a narrative of the child's experience of the trauma; correcting cognitive distortions; placing the experience in the context of the child's whole life.
- In vivo mastery of trauma reminders
  - Graduated exposure to feared trauma-related stimuli.
- Conjoint child–caregiver sessions
  - Child shares trauma narrative with caregiver; other family issues are addressed.
- Enhancing future safety and development
  - Prevention of future trauma; return to normal developmental trajectory.

org/English/healthy-living/emotional-wellness/Pages/Mental-Health-Care-Who%27s-Who.aspx)

- *Responding to Children's Emotional Needs During Times of Crisis* (fact sheet), American Academy of Pediatrics ([www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/children-and-disasters/Documents/Responding-to-Childrens-Emotional-Needs.pdf](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/children-and-disasters/Documents/Responding-to-Childrens-Emotional-Needs.pdf))
- *What Is Child Traumatic Stress?* (fact sheet), National Child Traumatic Stress Network ([www.nctsn.net/org/nctsn\\_assets/pdfs/what\\_is\\_child\\_traumatic\\_stress.pdf](http://www.nctsn.net/org/nctsn_assets/pdfs/what_is_child_traumatic_stress.pdf))

#### Medical Decision Support

- *Child-Adolescent Suicidal Potential Index (CASPI): A Screen for Risk for Early Onset Suicidal Behavior* (article), *Psychological Assessment*, Vol 12, Issue 3, 2000
- *The Child PTSD Symptom Scale (CPSS)* (assessment scale), US Department of Veterans Affairs ([www.ptsd.va.gov/PTSD/professional/assessment/child/cpss.asp](http://www.ptsd.va.gov/PTSD/professional/assessment/child/cpss.asp))
- *The CRAFFT Screening Tool* (questionnaire), Center for Adolescent Substance Abuse Research ([www.ceasar-boston.org/CRAFFT/index.php](http://www.ceasar-boston.org/CRAFFT/index.php))

- *Enhancing Pediatric Mental Health Care: Algorithms for Primary Care* (article), *Pediatrics*, Vol 125, Suppl 3, 2010 ([pediatrics.aappublications.org/content/125/Supplement\\_3/S109.pdf](http://pediatrics.aappublications.org/content/125/Supplement_3/S109.pdf))
- *Evidence-Based Child and Adolescent Psychosocial Interventions* (chart), PracticeWise, American Academy of Pediatrics ([www.aap.org/en-us/Documents/CRPsychosocialInterventions.pdf](http://www.aap.org/en-us/Documents/CRPsychosocialInterventions.pdf))
- *Pediatric Medical Traumatic Stress Toolkit for Health Care Providers* (toolkit), National Child Traumatic Stress Network ([www.nctsn.net/org/traumatypes/pediatric-medical-traumatic-stress-toolkitfor-health-care-providers](http://www.nctsn.net/org/traumatypes/pediatric-medical-traumatic-stress-toolkitfor-health-care-providers))
- *Suicide Behaviors Questionnaire-Revised (SBQ-R)* (questionnaire), Substance Abuse and Mental Health Services Administration ([www.integration.samhsa.gov/images/res/SBQ.pdf](http://www.integration.samhsa.gov/images/res/SBQ.pdf))
- *Suicidal Ideation Questionnaire (SIQ) and Suicidal Ideation Questionnaire-Junior (SIQ-Jr)* (booklet), PAR Inc. ([www4.parinc.com/Products/Product.aspx?ProductID=SIQ](http://www4.parinc.com/Products/Product.aspx?ProductID=SIQ))
- *The UCLA PTSD Index for DSM-IV* (Web page), US Department of Veterans Affairs ([www.ptsd.va.gov/PTSD/professional/assessment/child/ucla-ptsd-dsm-iv.asp](http://www.ptsd.va.gov/PTSD/professional/assessment/child/ucla-ptsd-dsm-iv.asp))

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## Chapter 371 RAPE

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Rape is a legal definition, not a medical diagnosis; every state has statutory definitions of sexual assault and rape. Physicians should be familiar with the statutes in their local jurisdictions. (See Tools for Practice: Community Advocacy and Coordination at the end of this chapter.)

In general, *rape* refers to sexual intercourse with force or the threat of force or without a person's consent. Sexual intercourse may include penile-oral, penile-vaginal, or penile-anal penetration. The threat may be an overt physical threat, a verbal threat, or an implicit threat as a result of age and power differentials between sexual partners. In 2012, The Uniform Crimes Report implemented a new definition of rape: "The penetration,



no matter how slight, of the vagina or anus with any body part or object, or oral penetration by a sex organ of another person, without the consent of the victim.” Rape can occur at all ages; however, this chapter focuses on adolescent survivors of rape. Rape entails an assault acted out sexually, rather than a sexual act per se. Not only is rape an unchosen act for the victim, but it also causes unchosen health risks. In this chapter, information is provided on rape, not chronic sexual abuse, such as incest.

## INCIDENCE

Exact statistics on the incidence and prevalence of adolescent rape are not available because many survivors never report the crime. Estimates of unreported rape range from 40% to 90%. Between 40% and 60% of all rape survivors are younger than 18 years, and most are adolescents.

Although national rates of rape have decreased, female adolescents aged 12 to 19 years remain the group at greatest risk. Female adolescents aged 16 to 19 years are 4 times more likely to be sexually assaulted than women in all other age groups. Worldwide, estimates indicate that between one-third and two-thirds of rape victims are 15 years of age and younger. Although most rape victims are women, 5% to 10% are men. Ninety percent of adolescent rape victims are assaulted by someone they know, and more than 50% of these cases occur on a date. Survivors of prior sexual abuse are at particular risk for subsequent assault. Adolescents who engage in high-risk behaviors, such as running away and using drugs and alcohol, are at an increased risk for rape. Approximately one-half of all reported rapes in the United States eventually lead to arrests; approximately two-thirds of those arrested are prosecuted, and approximately one-half of those prosecuted are found guilty. In other words, for every 100 reported rapes, only 16 of the perpetrators are convicted.

## TYPES OF RAPES

Types of rape vary considerably based on the relationship of the victim to the assailant. The various types of rapes raise different issues that are crucial to consider when providing care for the adolescent survivor. Psychosocial sequelae of rape often vary according to the type of rape involved.

### Known Assailant

In most reported pediatric rape cases, the injured child knows the assailant, who may be a parent, a stepparent, an adult relative or friend of the family, a neighbor, an acquaintance, or a classmate. This relationship may cause conflicting family or social loyalties. In these cases, the rape is less likely to be reported. Furthermore, rape survivors who know their assailants are prone to self-doubt and self-blame, and when they do report the rape, their reports may be received with skepticism and disbelief, even by the professionals to whom they turn for help.

### Stranger Rape

An estimated 15% to 55% of reported rapes are committed by individuals who are not known by the person

who is assaulted. Stranger rape is more likely to entail threats or use of violence and fear of immediate danger, and it is associated with a higher incidence of reporting the rape and of subsequent conviction of the assailant. Stranger rape is most likely to occur in areas of poverty and in high-crime districts where walking and playing outside pose risks of danger.

### Date Rape

Estimates of the incidence of date rape vary. However, in a survey of middle and high school students, nearly 20% of the girls and more than 10% of the boys reported a history of unwanted sexual activity on dates. Surveys of college students indicate that approximately 25% of female students and 6% of male students report a history of sexual assault that meets the definition of rape while on a date. Almost none of the college students in these surveys reported the sexual assault to authorities. Particularly in cases of young female adolescents (ages 10 to 15 years) and older men, questions of statutory rape arise, along with questions of consent, refusal skills, and exploitation.

Of the various types of rape, date rape is the least likely to be reported. Of particular concern is the fact that the incidence of date rape seems highly correlated with one or both parties engaging in drinking alcohol or using other drugs before the rape. As would be expected, date rapes are more likely to occur on weekends between 10 pm and 1 am, in automobiles, or at the home of the assailant.

Date rape may not be reported if the rape was facilitated by the administration of pharmaceuticals, including  $\gamma$ -hydroxybutyric acid (GHB), flunitrazepam (Rohypnol), and ketamine hydrochloride (Ketamine), known as *date rape drugs*, given that these medications cause anterograde amnesia.

Trust, self-blame, and vulnerability are important long-term issues for survivors of date rape, as in any other form of rape. The female date rape survivor may not trust her judgment concerning men, and she may blame herself for the rape, erroneously believing that she did not resist clearly or did not resist convincingly enough. She may be ashamed that she ended up in a situation that resulted in rape. These thoughts of guilt may be reinforced by the response and degree of support provided by parents, guardians, and friends. Parents' and friends' understanding and support are significant prognostic factors for recovery. The tendency for survivors to have reservations about reporting date rape is easy to understand. Unfortunately, such secrecy also applies to discussing the incident in general, making catharsis, as well as verbal and emotional support from others, difficult to obtain.

### Gang Rape

Gang rape typically involves a group of young men raping a solitary female. This type of rape may be associated with ritualistic behavior, or sexualized rites of passage. Issues of sexualized rites of passage apply both to stereotypical adolescent gangs and to college fraternities. Survivors of college campus gang rapes are more likely to not report to police.

## Male Rape

In this discussion, *male rape* refers to same-sex rape. Although sporadic reports have surfaced of male rape by women, data are limited. The area of male rape remains understudied and is far less understood than female rape. Specific subgroups of young men are at particular risk for sexual abuse: those in institutionalized settings (such as the criminal justice system), street youth (who may engage in survival sex), young male homosexuals (who may be runaways), and youth who have a parental history of physical or sexual abuse (parents who were abused themselves may become abusers as adults). The occurrence of male rape in institutionalized settings is often attributed to displaced heterosexual behavior or undifferentiated sexual orientation, along with aggressive dominance of a weaker partner. Male rape outside institutions often occurs through coercion by an individual perceived as an authority figure.

Although male rape survivors are more likely than their female counterparts to sustain physical trauma, the treatment of males should parallel that described for women. Issues of loss of control are particularly relevant for the male rape survivor, along with subsequent symptoms of depression, anxiety, sleep disturbances, and suicidal ideation. Conflicted sexual identity is common among male rape survivors, whether they are homosexual or not. Males are often controlled by entrapment, intimidation, physical force, or any combination. The intimidation is accomplished by threats of physical harm, by brandishing a weapon, or both. They frequently perceive the rape as a life-threatening event (a perception that may result in long-term psychological problems). Because of the pervasive reluctance of boys and men to report rape, the preclusion of social support and intervention is a particularly challenging issue.

## MALE PERPETRATORS

Just as female adolescents constitute a large proportion of reported rape assaults, male adolescents make up a large proportion of convicted rape assailants; males under age 18 were arrested for 14.4% of all forcible rapes in 2009 and 17.2% of all sex offenses in 2009.

Perpetrators tend to fall into 1 of 3 clusters: those for whom anger is the primary dynamic; those for whom power or conquest is the central issue; and the sadistic person, for whom anger and control are, in and of themselves, erotic. For the anger-driven rapist, the act tends to be impulsive, with the intent of hurting, humiliating, and degrading the target of the assault. Physical brutality is common. Rape functions as the outlet for anger, essentially by using sex as a weapon. The power-oriented rapist is more likely to engage in premeditated, obsessive, or stalking behavior, in which the rape essentially compensates for social and sexual incompetence or inadequacy. Aggression for the power-oriented rapist is less likely to be violent than a means of dominating his prey. Both anger- and power-driven rapists have serious deficits in social skills and the inability to interpret and respond to social cues from others. For the sadistic rapist, eroticism and violence are enmeshed; victims are typically subjected to premeditated, deliberate

acts of cruelty and dehumanization. The sadistic perpetrator finds gratification in inflicting pain and powerlessness.

Although some rapists are sexually dysfunctional at the time of the rape, most rapists are sexually active with available, consensual partners outside the rape. Perpetrators usually seem ordinary by most standards; most do not have symptoms of major psychiatric illnesses such as psychoses, nor does a preponderance exist of intellectual disability. However, other conditions such as antisocial, schizoid, paranoid, and narcissistic personality disorders are noted more commonly among convicted rapists than in the general population.

The use of alcohol and drugs has been associated with the occurrence of rape. Ironically, alcohol intoxication sometimes seems to have the effect of both diminishing a perpetrator's sense of responsibility and increasing a survivor's perceived culpability. Specifically, the perpetrator's act of rape is *excused* because he was drinking and not responsible for his actions, whereas victim intoxication is consistently coupled with the process of *unfounding*, or disproving, rape charges.

## RESPONSE TO RAPE

### Immediate Response to Rape by the Survivor

Immediate responses to rape vary considerably, ranging from distraught histrionics to near-mute withdrawal. Most survivors have intense levels of fear and anxiety. Varying levels of cognitive disorganization, shock, and disbelief also characterize this postrape acute phase. As occurs in any crisis, many adolescents regress to previous stages of development. An adolescent rape survivor who was previously self-assured and appropriately independent may become clinging and dependent on the parent or health professional.

### Immediate Response by the Family

Unlike other crime victims, the survivor of rape rarely contacts the police immediately. Typically, the first contact is with an intermediary such as a friend or family member. This individual's response is crucial in the ensuing medical and legal processes; but most family and friends need guidance to know how best to be supportive. The disclosure of rape is usually traumatic for the family as well as the survivor. Parents may blame themselves inappropriately for the rape. In other instances, parental activities (eg, neglect) may have contributed to the rape. In either scenario, the issues are highly sensitive and need to be addressed with skill and compassion.

Familial responses to a child's rape range from denial and disbelief to shame and outrage. No guarantee exists that a family is prepared to respond appropriately to a raped child's needs at this time. In some cases, a mother's financial dependence on a perpetrator may confound reactions. During the initial evaluation session, health care professionals must therefore spend some time with the family members and friends of the survivor to determine their own psychological response and their ability to be supportive.

## LEGAL ISSUES

All states have laws that require physicians to report cases involving violent assault, including rape. To report statutory rape, the physician should be familiar with the state's laws regarding report of sexual abuse and the legal age of consent. Statutory rape is defined as sexual activity of an adult with an adolescent under the age of legal consent. Reporting concerns include the possibility that reporting statutory rape can cause barriers for adolescents to obtain appropriate medical care. Physicians have expressed the desire to use their clinical judgment in reporting cases of sexual activity that fall within the definition of statutory rape. Some states require parental notification of a minor's sexual assault, and in those states, this statute overrides issues of confidentiality.

Most states permit a minor to receive treatment for sexual assault without parental consent. All physicians must be familiar with local statutes. Physicians should seek additional guidance from their legal counsel or from their state attorney general's office.

Consent for treatment of rape is different from consent for collection of evidence. An adolescent patient above the legal age of consent has the ability to consent to a medical evaluation and treatment and refuse collection of forensic evidence, or the adolescent may consent to both. Many survivors are reluctant to give permission because they fear social isolation and possible retribution by the perpetrator. Those who decide not to report the rape to law enforcement should be informed that if they want to pursue possible prosecution in the future, then the evidence must be collected at this time. Therefore, the physician must ask the adolescent patient for permission to complete a full evidentiary examination and to release the evidence to the police. Cases of child sexual abuse in which state law requires reporting to a child welfare agency, law enforcement, or both are an exception; such cases do not require consent from patient or family to report.

From a medical-legal perspective, physicians must realize that their responsibility is limited to the documentation of evidence. Determining whether a rape really occurred is not the physician's role; this determination is a court decision. The physician will be of most help by providing appropriate nonjudgmental support for the patient, being thorough in the evaluation, and keeping accurate medical records.

## MEDICAL EVALUATION

Rape is a serious medical and psychological emergency for both the survivor and the family. The purpose of the initial evaluation is 4-fold: treatment of injury and infection, prevention of pregnancy, collection of evidence, and psychological assessment with referral for follow-up counseling.

### General Concepts

Many metropolitan areas have treatment centers with trained interdisciplinary teams available for adolescent and child survivors of rape; these treatment centers are ideal sites for an initial evaluation and are usually staffed with an interdisciplinary care team, most frequently consisting of a physician, nurse, and

social worker. An interdisciplinary approach is beneficial for several reasons, including the ability to provide support to the child and family simultaneously and to serve as a resource for future services. For various reasons, most pediatric rape survivors do not use such specialized facilities, and they may receive medical evaluations at emergency departments or private medical offices. To minimize the physical and psychological trauma of the evaluation, eliminate the need for repeat evaluations, and maximize the probability of collecting forensic evidence, the most skilled professional available should perform the initial evaluation. The gender of the examiner is less important than the individual's comfort with adolescents and children, skill at conducting the examination, and level of compassion.

The rape evaluation can be long and tedious, but it should never be rushed. Although the youngster is coping with personal outrage and physical and psychological pain, the patient is expected to tolerate and cooperate with uncomfortable procedures that may feel similar to the acts of intrusion and aggression experienced previously. The approach to the evaluation should be calm, gentle, and private. Rape protocols, if available, are helpful and will serve to minimize the chance for error or omission in the evidence-collection process. Most jurisdictions have printed standardized forms for the evidence-procurement process; these forms are available in each state's *forensic evidence kit*. Before the examination, the physician should become familiar with these forms.

The physician should avoid making inappropriate assumptions based on the patient's psychological state. Many survivors are in a state of shock or denial immediately after the event. How a patient responds in the emergency department varies and depends on numerous factors, including developmental maturity. Seeming physically mature but functioning cognitively at the level of a preadolescent is not uncommon. Therefore the patient's psychological state should not alter the physician's approach to care. Furthermore, the physician should not attempt to minimize the patient's sense of personal guilt, shame, and anxiety by offering reassurance immediately. Taking a few minutes to empathize with and acknowledge the patient's feelings before proceeding with the evaluation helps both the patient and the physician. Particularly in cases in which acute trauma may compromise coping skills, the establishment of the patient's safety is crucial. The physician should never leave the patient alone, if at all possible.

Taking whatever time is necessary at the beginning of the examination to explain the process and allow for questions is always prudent, particularly for rape survivors who have not had a previous sexual relationship or a prior gynecologic examination. Some may also be fearful of anticipated pain and discomfort. Whenever possible, the physician should allow the patient some control over the proceedings; the patient should set the pace of the examination. The physician should be careful to inform the patient in advance of what tasks must be accomplished. Whenever applicable, making reference to prior experience with other rape survivors of a similar age may help establish that



the patient is not the only child or adolescent to whom this ordeal has happened; it also establishes that the physician is not shocked at such circumstances and has some practical knowledge with which to anticipate concerns. The patient should be the one who signals when to begin the procedure. If he or she becomes visibly agitated with the proceedings, then the physician should stop and allow the patient to regain composure before continuing with the examination. At no point should a physician continue the examination against the child or adolescent's will.

After obtaining consent from the patient, the physician should obtain a detailed and relevant history, followed by a thorough general physical examination and a gentle but complete pelvic examination. A female nurse or assistant must be present during this process; for some young adolescents, having a parent present during the examination is helpful if the parent is reassuring, rather than openly distraught, during the procedure. Some aspects of the evaluation will change depending on the temporal proximity of the evaluation to the alleged event. The following guidelines are recommended for evaluations conducted within 72 hours of the assault. Modifications are necessary if the evaluation is conducted after this time. In some centers the interdisciplinary team obtains the history simultaneously and together so that it does not have to be repeated unnecessarily.

### History

History taking necessarily entails asking some very personal and potentially awkward questions. The patient should be assured of privacy and offered respectful compassion. The history should include the time, date, and location of both the event and the examination. Recalling the event may be emotionally traumatic for the patient; thus, beginning with a relevant, but relatively neutral, medical history is sometimes useful. Such information as general medical history, physical and behavioral symptoms, and a thorough menstrual history—including the age of menarche; the date of the last menstrual period; the frequency of menses; sexual activity if relevant; previous pregnancies, miscarriages, and abortions; and the use of contraceptives and feminine hygiene products—is important. Additional history should include parental response to disclosure, fear of parental reaction and risk for running away, and fully exploring past and current suicidal ideation.

Next, the event itself should be the focus. Questions should be asked calmly and with sensitivity and patience. The patient's own words should be recorded whenever possible. The medical chart is a legal document and will be subjected to the same scrutiny as any other form of evidence. Only the historical facts, without embellishment or interpretation, should be recorded.

The patient should be asked about the use of intoxicating substances before or during the event, as well as whether any loss of consciousness that may have occurred. The physician needs to ask whether weapons or restraints were used during the assault. The patient should be asked to describe in detail the location of the event, the appearance of the perpetrator,

the type of sexual contact and the positions used, the use of force (by both parties), the removal of clothing and the manner in which it was removed, and what measures, if any, the patient took to cleanse or relieve herself or himself (eg, bathing, douching, changing clothes, urinating, defecating). Whether the assailant used a condom or any other means of contraception should be determined. Finally, the physician should ask about the presence of clinical symptoms in the musculoskeletal, gastrointestinal, and genitourinary system.

### Physical Examination

A detailed history and physical examination, as well as specimens for forensic and laboratory evaluation, should be obtained for all rape survivors who consent to complete an examination. Particular focus should be placed on the evaluation of the oral cavity, the genitals, and the anus.

Although a complete physical examination from head to toe is warranted, 40% to 60% of sexual assault survivors will have no visible physical injuries. Inspection of the entire body may provide the corroborative evidence necessary to convict the perpetrator, and follow-up examinations may reveal emerging bruising or injuries in areas initially noted to have tenderness or swelling but no visible bruising on the initial examination.

The patient's physical appearance and emotional state and the condition of the patient's clothing should be noted. If the patient is still wearing the same clothing as at the time of the event, then its condition should be noted and each piece saved in a separate, labeled bag. Applying a fluorescent lamp to the clothing and skin may illuminate the presence of dried semen. Semen fluoresces best at wavelengths of 420 and 450 nm, when viewed through orange goggles. A Wood lamp emits light at only 360-nm wavelength. Therefore specialized alternate light sources that emit wavelengths at 420 and 450 nm, such as a Bluemaxx, should be used. Although this type of lamp will improve the detection of dried semen, many other substances will fluoresce as well; thus, confirmation of semen cannot be made with this method. These specimens should be marked for later analysis for the presence of seminal vesicle-specific antigen. Next, a topical survey of the body, documenting any evidence of recent trauma or bruising, should be done. Photographs may be useful during subsequent litigation. Use of a diagram to indicate locations of visible injuries can be helpful. The physician should use the fluorescent lamp to identify any fluorescent areas on the skin and obtain swabs of these areas.

Particular attention should be given to the examination of the head and neck. Compression injuries of the neck are fairly common if force is used. This type of injury may lead to obstruction of venous return from the head, causing the development of neck bruising or petechial hemorrhages in the eyelids and conjunctiva. The inner surface of the lips may have tiny abrasions resulting from forced pressure applied to the mouth by the perpetrator to prevent screaming. Common injuries to the mouth include torn frenula and palate petechiae.



The breasts may show bite marks or bruises. The physician should swab all bite marks to collect genetic markers (ABO group) and photo-document these injuries because the bite impression may be matched to a potential perpetrator. Tanner staging to determine the level of sexual maturation (breasts and pubic hair in female patients, genitalia and pubic hair in male patients) should also be performed.

### Genital Examination

#### Female Patient

After the initial physical examination, the patient can be draped and placed in the lithotomy position. If the patient seems too anxious and a speculum examination is not required to investigate for a source of undiagnosed internal bleeding, then the supine frog-leg position may be a suitable alternative. A speculum examination is not necessary for younger adolescents or children unless active vaginal bleeding is present, which is a rare occurrence. In these rare instances of active vaginal bleeding, performing the pelvic examination with the patient under sedation or under general anesthesia may be necessary.

The pelvic examination should begin with inspection of the thighs and perineum for evidence of trauma, bruising, semen, or blood. Appropriate forensic evidence should be taken at this time (Box 371-1). General inspection of the external genitalia should be performed, with documentation of any erythema, edema, ecchymosis, or abrasions noted.

In some cultures, an intact hymen is important as an indicator of virginity, and the patient and parents will be concerned with its structural integrity. An intact hymen does not rule out the diagnosis of rape. Acute injuries to the hymen such as bruising, petechiae, or acute transactions should be documented by describing any active bleeding and the location, as though a face of a clock were superimposed over the hymen (eg, acute swelling and transaction of hymen with active bleeding at 8-o'clock position). The entire rim of the hymen must be visualized; proper labial traction

along with a saline-moistened cotton swab rolled around the edges of the hymen is necessary. The use of a light source or the application of aqueous toluidine blue (1%) to the posterior fourchette may help locate and identify acute tears. Many experts use colposcopy, which provides a light source, magnification, and photo-documentation of the examination. Colposcopy or photo-documentation with a camera is essential in providing documentation of the examination, and images can later be evaluated by expert review.

Older female adolescents should be able to undergo a speculum examination of the internal genitals, which will allow a clear view of the vaginal walls, fornices, and cervix. Appropriate specimens for culture and forensics should be obtained (see Box 371-1).

#### Male Patient

The testes, epididymis, vas deferens, penile shaft, foreskin, and glans penis should be examined thoroughly for the presence of infection or trauma.

### Anal Examination

A history of sodomy in either males or females indicates the need to conduct a thorough anal inspection. The physician should document any erythema, ecchymosis, abrasions, or rectal bleeding noted. Aqueous toluidine blue (1%) may be applied to help visualize acute microtrauma to the perianal area.

### Summarizing the Examination

When the physical examination is complete, the patient should be given ample time to dress and regain composure before discussing any findings. Most patients will benefit from knowing that their genital anatomy is normal. Several studies have demonstrated that more than 90% of anogenital examinations performed after rape are normal. It is also important to discuss physical findings, treatment options, and plans for follow-up.

### Forensic and Laboratory Information

The recovery of laboratory and forensic data is probably the most controversial aspect of the evaluation, especially when recovery of semen and sperm is involved; nonetheless, the finding of male ejaculate is neither predictive nor essential for criminal conviction. In one study, physical evidence of rape was found in only 23% of all the cases that resulted in felony convictions. Forensic evidence identified in younger children is more often obtained from the clothing, bed linens, or both. There are on-going developments in forensics science for the laboratory analysis of semen.

### Sexually Transmitted Infection

Most patients are concerned about the risk for acquiring a sexually transmitted infection (STI) as a result of the rape. This risk is related directly to the health status of the assailant and the victim, the site of the assault, and the infectivity of the disease in question. Overall, the risk for contracting an STI from a single encounter is small. Repeat assaults or assaults by more than a single assailant increase the risk for infection. Many adolescents, however, also engage in high-risk behaviors that put them at increased risk for

#### BOX 371-1 Recommended Procedures for Collecting Forensic Data

- Forensic evidence kit: complete forms for authorization and release of evidence, history, and physical examination. Individual envelopes will be completed if indicated by the history provided.
- Additional tests:
  - Pregnancy test
  - Syphilis screening
  - HIV test
  - Cultures for gonorrhea (oral, urethral, vaginal, and anal)
  - Cultures for *Chlamydia* (urethral, vaginal, and anal)
  - Wet mount for detection of *Trichomonas* and spermatozoa

While culture is the gold standard, there are some institutions that use NAAT testing for Gonorrhea, Chlamydia, and Trichomonas

having a preexisting STI. Additionally, as many as 50% of sexual assault survivors do not return for follow-up appointments. The Centers for Disease Control and Prevention recommend using prophylactic antibiotics for treating potential sexually acquired infections (see Chapter 330, Sexually Transmitted Infections). A prophylactic hepatitis B vaccination against possible exposure is recommended.

Regardless of the antibiotics given, the physician must emphasize to the patient that the incubation period for STIs varies and that an infection may not be detected or may be missed or treated inadequately at the time of the evaluation examination. Therefore, although baseline studies should be obtained at the initial evaluation, medical follow-up is absolutely crucial. After 2 weeks the patient should be re-examined for the presence of an STI. Serial testing for syphilis, human papillomavirus, and HIV infection should be performed after the assault in most cases.

### Pregnancy

The occurrence of pregnancy after rape is strongly influenced by whether a female patient is in the fertile interval of her menstrual cycle, as well as by the possible sexual dysfunction of the assailant (eg, failure to maintain an erection or to ejaculate). Many adolescents, however, have irregular menstrual cycles; therefore, the occurrence of ovulation for any particular cycle may be in question. If the assault occurred within 5 days of the evaluation, then emergency contraception (see the discussion of postcoital *morning after* contraception in Chapter 123, Contraception and Abortion) should be offered to the patient after a negative pregnancy test has ruled out the presence of an already existing pregnancy. Two types of emergency contraceptive medications are available. The first type contains only progestin. Plan B is a progestin-only emergency contraceptive that reduces the risk for pregnancy by 89%. Because Plan B contains only progestin, it has fewer side effects of nausea or vomiting. The second type contains both progestin and estrogen. Most brands of the daily oral contraception pill contain both progestin and estrogen and reduce the risk for pregnancy by 75%. When medication containing both progestin and estrogen is used, antiemetics should be offered because of the frequent side effects of nausea and vomiting. The occurrence of pregnancy after unprotected exposure should be strongly suspected when menses does not occur within 4 weeks of the rape, at which point the patient should return for a repeat evaluation.

### PSYCHOLOGICAL ASSESSMENT

The psychosocial and emotional implications of rape in children and adolescents are complex. This circumstance is tempered further by the young person's stage of development and the family's response to the rape. For example, young adolescents who are just beginning to grapple with their own sexuality may believe that they deserved to be raped because of having begun to experience sexual urges. A female child who sees her mother respond with tearful distress to the news that her child was raped may feel guilt not

just because of the rape but also because of the emotional trauma inflicted on the mother.

How the youngster copes with the rape is also related to how society responds to survivors of rape. Unlike most crimes, the crime of rape is often blamed on the victim rather than on the perpetrator, particularly in adolescents. Following no other crime are the victim's prior reputation, appearance, and behavior subject to such scrutiny as in rape. Running away, sexual activity, and even hitchhiking are used as justification for the rape, placing further blame on an already troubled young person. Physicians must avoid compounding such punitive dynamics.

### Follow-up Care

After the initial evaluation is complete, arrangements should be made for follow-up care, not only for the medical issues discussed previously, but also to assess the victim's ability to cope with the rape and to accept counseling concerning the rape. All rape survivors and their families should be seen as soon as possible after the rape by a mental health professional who is trained to work with adolescents and who is knowledgeable about the emotional sequelae to rape.

### Short- and Long-Term Psychological Sequelae

Multiple factors will determine how a child or adolescent responds to the rape; these factors include level of social support, coping styles and strengths, and developmental variables and cognitive functions. How any given individual will respond to rape cannot be predicted. However, children and adolescents who have been raped experience a variety of both short-term and long-term consequences. In addition, sexually traumatized children have been noted to have higher levels of precocious sexualization than non-traumatized children. Confusion may exist about what is normal adult sexual behavior, sometimes leading to inappropriate sexual acting-out behaviors. Some children experience developmental arrests at the time of the trauma; such arrests are not necessarily readily apparent. Although child and adolescent studies are still too scarce to be considered definitive, apparently the earlier and more traumatic the rape is, the greater the chance is of developmental and functional impairment.

Behavioral concerns frequently associated with adolescent rape sequelae include school phobias, generalized fearfulness and withdrawal, and, especially in adolescents, the onset of truancy. Suicidal ideations are not uncommon, with increased lifetime risks for major depression and suicide attempts being associated with women in the aftermath of rape. For male rape survivors the existing research is less clear; however, male sexual trauma in childhood may be associated with sexually abusive behavior toward other boys during adolescence. Obviously, although not all children and adolescents who have been raped will have psychiatric sequelae, all of those who have been raped should be assessed and monitored for serious sequelae. Particularly in cases in which sexual acting out follows a rape, careful clinical attention to issues such as posttraumatic stress disorder and depression

is required. Self medication with various substances is an ongoing clinical hazard after rape and deserves consideration as a *red flag* for physicians working with at-risk patients.

## SUMMARY

Rape is an act of violence that involves a disparity of power between the perpetrator and the victim. Because of its sexual context, rape is easily misinterpreted as erotic or sexual behavior, which it is not.

Adolescents who have been raped should have sensitive and thorough evaluations and follow-up assessments. From the time of initial disclosure through eventual legal outcome, many developmental, familial, and social variables can shape the experience for young survivors and their families. Long-term adjustment following rape varies considerably, with both developmental and familial factors having considerable effect.

## TOOLS FOR PRACTICE

### Community Advocacy and Coordination

- *Center for Adolescent Health & Law* (Web site), (cahl.org)
- *State Laws on Reporting Child Abuse and Neglect* (Web site), US Department of Health & Human Services (www.childwelfare.gov/responding/reporting)

### Medical Decision Support

- *2015 Sexually Transmitted Disease Treatment Guidelines* (Web page), Centers for Disease Control and Prevention (www.cdc.gov/std/tg2015/tg-2015-print.pdf)
- *Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States*. (article), Centers for Disease Control and Prevention (www.cdc.gov/mmwr/PDF/rr/rr5402.pdf)
- *A National Protocol for Sexual Assault Medical Forensic Examinations: Adults/Adolescents*, 2nd ed (e-book), National Criminal Justice Reference Service (www.ncjrs.gov/pdffiles1/ovw/241903.pdf)
- *Visual Diagnosis of Child Abuse* 4th ed (digital resource), American Academy of Pediatrics (shop.aap.org)

## AAP POLICY

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## Chapter 372

# SEVERE ACUTE ASTHMA (STATUS ASTHMATICUS)

Alan R. Schroeder, MD; David N. Cornfield, MD

Asthma is a major cause of morbidity and mortality in children. Asthma exacerbations impose a significant strain on health care systems and can compromise the quality of life of patients and their families. Asthma death rates in US children increased progressively between 1980 and 1999, with the highest mortality rates in blacks. In recent years, asthma death rates have been relatively stable, and overall hospital admissions actually decreased by 50% from 1992 to 2006. Severe acute asthma (*status asthmaticus*) generally refers to an acute exacerbation that does not respond to initial doses of nebulized bronchodilating agents, thereby placing the asthmatic patient at risk for respiratory failure.

Risk factors for near-fatal and fatal asthma differ across studies and between pediatric and adult populations. The risk for fatal or near-fatal asthma is greater in patients with more long-standing disease and in patients with more severe disease. Signs of increased asthma severity include multiple hospitalizations, prior intubations, and previous attacks with severe, unexpected, and rapid deterioration. Many studies have demonstrated associations between  $\beta$ -agonist use and death or near death, likely representing an epidemiologic phenomenon whereby  $\beta$ -agonist use is a marker for more severe asthma. A putative link also exists between the use of long-acting  $\beta$ -agonists and significant adverse events. The association between significant adverse events and  $\beta$ -agonist exposure underscores the importance of familiarity with a patient's medical regimen when treating an asthma exacerbation. Abrupt cessation of inhaled corticosteroids may further increase risk for death.



Overall, most asthma deaths (80%–85%) occur in patients with severe and poorly controlled asthma with progressive deterioration characterized by histologic evidence of extensive mucous plugging and eosinophilic inflammation. These patients tend to respond slowly to treatment. More optimal chronic anti-inflammatory therapy may assist in preventing the death of these patients. A smaller proportion of deaths occur in patients who have acute deterioration (eg, sudden asphyxic asthma), in whom mucous plugging is substantially reduced and the inflammatory cells are neutrophils. These attacks are less preventable given their acute onset; however, if appropriately treated, they usually demonstrate faster response to treatment.

## CLINICAL MANIFESTATIONS

Asthma exacerbations are most frequently triggered by viral infections in children. Other common triggers include aeroallergens (animal dander, dust mites, molds, and pollens), cockroaches, tobacco smoke, pollutants, cold or dry air, exercise, and laughter.

The hallmark of asthma is cough and wheezing, although wheezing may not be evident if air entry is limited. Patients in status asthmaticus may complain of shortness of breath or chest tightness and demonstrate signs of increased work of breathing, including tachypnea, accessory muscle use, nasal flaring, head bobbing, and grunting. Patients may have difficulty speaking or completing short sentences in one breath. Patients are often anxious and, in severe cases, may have altered mental status or lethargy. Signs of impending respiratory failure include cyanosis, decreased breath sounds, altered level of consciousness, diaphoresis, and inability to speak more than a few words or phrases with a single breath.

Physical examination should include a complete set of vital signs, including pulse oximetry. Patients in status asthmaticus often have tachycardia, tachypnea, hypoxemia, and pulsus paradoxus, defined as an accentuation of the physiologic drop in systolic blood pressure by greater than 10 mm Hg during inspiration. Close attention should be paid to the level of consciousness, hydration status, and peripheral perfusion. The eyes, ears, nose, and throat should be examined to assess for a possible source of infection that may have triggered the asthma. The nares should be inspected for polyps and signs of allergic rhinitis. A heart examination is necessary to rule out a cardiac cause of wheezing. During the abdominal examination, hepatomegaly may be noted if the lungs are hyperinflated.

The chest should be directly inspected to assess the work of breathing, to assess for the presence of chest wall deformities, and to observe whether chest movement is bilaterally symmetrical. Auscultation should be performed to evaluate air entry (depth and symmetry), determine inspiration-to-expiration ratio, and detect wheezing or rales. Spirometry is helpful in older children and should be performed serially to follow the disease trajectory, but is of little value in the context of an acute exacerbation. Comparison of peak expiratory flow rates to baseline values or to normal values based on age and height can be helpful in assessing the severity of an acute exacerbation.

Chest radiographs are often ordered but rarely add meaningfully to the diagnosis and management of severe asthma exacerbations. Findings may include bilateral hyperinflation, an area of opacification, and, rarely, pneumothorax or pneumomediastinum. The history and physical examination should guide the decision to obtain a radiograph. Indications include asymmetry or focal abnormality on auscultation, endotracheal intubation, and a suspicion of foreign body aspiration, in which case unilateral hyperinflation may be present. Pulse oximetry and arterial, venous, or capillary blood gas analysis can provide additional assessment of the adequacy of ventilation and oxygenation, although needle sticks may increase anxiety and distress in a borderline patient. Hypoxemia and respiratory alkalosis are present initially, but the pressure of carbon dioxide in the blood will slowly start to increase as airway obstruction increases. Historically, a finding of carbon dioxide retention has been considered as an indication for endotracheal intubation and mechanical ventilation. However, more recent reviews advocate basing escalation of therapy and intubation decisions on clinical parameters, such as altered mental status or hemodynamic instability, rather than blood gas results alone.

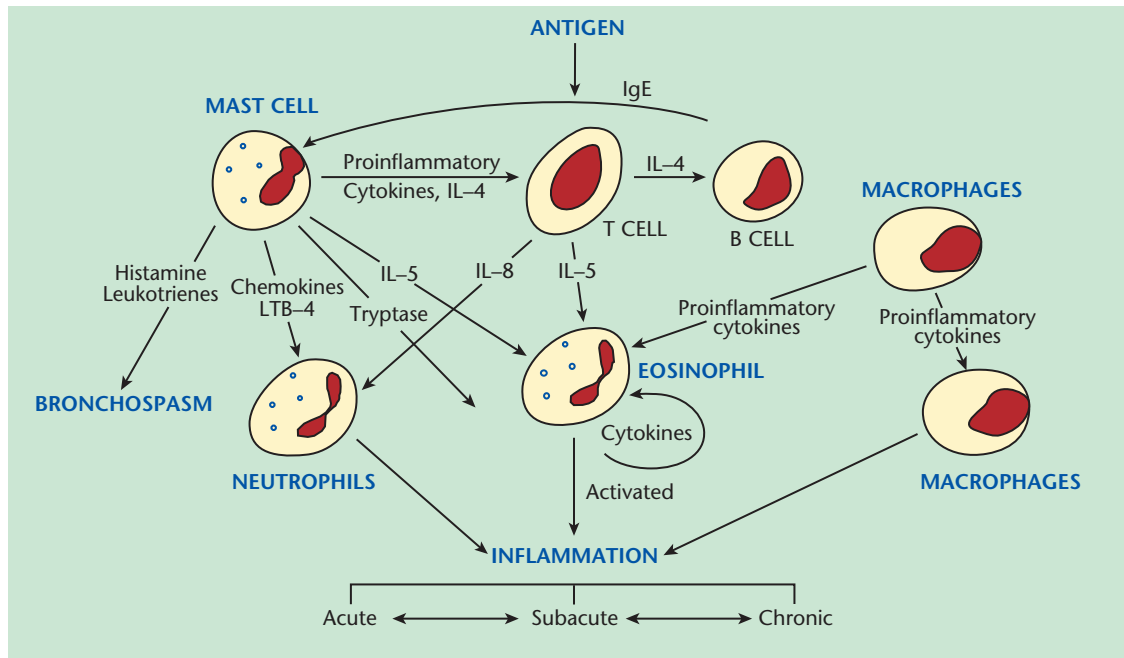
Patients with severe acute asthma may have some degree of metabolic acidosis caused by either compensatory renal bicarbonate loss (as compensation for respiratory alkalosis if the exacerbation has been long-standing) or lactate accumulation.

The source of lactic acidosis is unclear, but it may be the result of a combination of high-dose parenteral  $\beta$ -agonist use, anaerobic metabolism from overused respiratory muscles, or tissue hypoxia. The presence of lactic acidosis is an ominous sign, but is rare in children with status asthmaticus, and there is generally no reason to obtain lactate levels in asthmatic patients.

## PATHOPHYSIOLOGIC CONSIDERATIONS

Asthma is an inflammatory condition characterized by widespread, variable obstruction of the lower airways. The airflow limitation results from inflammation of the lower airways, mucosal edema, epithelial sloughing, mucous plugs, and bronchospasm. The inflammation is a complex response that includes eosinophils, mast cells, T lymphocytes, macrophages, neutrophils, and epithelial cells. The primary event is generally activation of mast cells in response to local irritation, which leads to mast cell degranulation and promotes activation of T lymphocytes (Figure 372-1). Multiple proinflammatory mediators are released, including histamine, leukotrienes, platelet-activating factor, and several helper T-cell type 2 cytokines. These cytokines augment immunoglobulin E production by B lymphocytes, thereby increasing leukotriene release from mast cells. Ultimately, this inflammatory environment is rich in leukotrienes, prostaglandins, nitric oxide, and platelet-activating factor, causing overproduction of mucus and epithelial cell destruction. The loss of epithelial cells exposes nerve endings, rendering the airway even more hyperirritable in response to environmental triggers. Epithelial damage is correlated with the severity of airway reactivity.





**Figure 372-1** Cellular mechanisms involved in airway inflammation. (From National Asthma Education and Prevention Program. Guidelines for the Diagnosis and Management of Asthma, Expert Panel Report 2. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services; 1997. NIH Publication 97-4051.)

Airway caliber and mucus secretion are regulated by the autonomic nervous system. Bronchial nerve ganglia receive direct vagal innervation, but they are also modulated by circulating catecholamines. Vagal parasympathetic stimulation leads to the release of postganglionic acetylcholine, causing bronchoconstriction, and mucus secretion.  $\beta$  receptors are found on airway smooth muscle, epithelium, and mucous glands, as well as on various inflammatory cells. Stimulation of  $\beta$  receptors causes cyclic adenosine monophosphate activation of protein kinase A, which, in smooth muscle, leads to muscle relaxation and bronchodilation. Polymorphisms in the  $\beta_2$ -adrenergic receptor have been described in children and may explain some ethnic differences in asthma severity and response to bronchodilators.

Airway obstruction compromises inspiratory and expiratory gas flow, leading to ventilation-perfusion mismatch. Distal lung segments become hyperinflated as alveoli empty incompletely. In the respiratory cycle, inspiration begins before exhalation is complete. This process of dynamic hyperinflation creates large end-expiratory lung volumes, which may be evident on clinical or chest radiographic examination. Hyperinflation worsens ventilation as large residual volumes create difficulty in generating effective tidal volumes. As obstruction worsens, hyperinflation can lead to ventilation-perfusion mismatch and hypoxemia. If airway obstruction is not relieved, then muscle fatigue can further compromise ventilation, resulting in hypercarbia and, ultimately, respiratory failure.

The severe obstruction that characterizes status asthmaticus can diminish venous return to the right atrium, thereby decreasing cardiac output. Pulmonary

vascular resistance can be increased by hypoxia, acidosis, and hyperinflation, further increasing the workload of the right ventricle. Spontaneously breathing patients in status asthmaticus generate large negative intrapleural pressures, with inspiratory pressures as low as  $-35$  cm  $H_2O$ . Negative pleural pressure increases left-ventricular oxygen demand and work by increasing left-ventricular transmural pressure. Furthermore, the generous negative intrapleural pressure creates a gradient for fluid movement from capillaries to alveoli, leading to a decrease in cardiac output and a potential for pulmonary edema. Increasing negative pleural pressure can also increase left ventricular afterload, which can have an untoward effect on cardiac output. Pulsus paradoxus occurs when systemic cardiac output drops markedly during inspiration, resulting primarily from increased capacitance of the pulmonary vasculature and resulting in decreased left-ventricular preload.

## MANAGEMENT

### Supportive Care

Any child in status asthmaticus should be hospitalized in a monitored bed. Indications for pediatric intensive care unit (PICU) admission vary across hospitals and may depend on hospital policies and staffing issues. Any child requiring positive-pressure ventilation (PPV), sedation, or continuous intravenous bronchodilator infusions should be monitored in a PICU.

Although significant hypoxemia is rare outside of severe asthma, administration of supplemental oxygen can address hypoxemia and may ease work of breathing. Oxygen can be delivered by nasal cannula,

but, in cases of significant hypoxemia, oxygen can be delivered more efficiently by a non-rebreather or partial non-rebreather face mask. According to National Institutes of Health guidelines, the target oxygen saturation should be more than 90% in most patients.

Most asthma exacerbations are caused by viral infections or noninfectious triggers. Antibiotics should, therefore, not be provided for acute asthma exacerbations except as needed for cases in which a strong suspicion of bacterial pneumonia exists (eg, fever and purulent sputum, chest radiograph demonstrating focal infiltrate). However, it warrants reiteration that many chest radiographs in asthmatic patients demonstrate opacifications because of nonbacterial causes, usually atelectasis, and thus should be avoided in most cases.

Patients are often dehydrated as a result of poor oral intake and increased insensible losses from the respiratory tract. The effects of dehydration on preload, coupled with the cardiopulmonary interactions present in severe asthma and the effect of multiple medications on systemic vascular resistance, highlight the importance of paying very close attention to fluid status and hemodynamics. Rehydration is necessary to maintain euvolemia and cardiac output, but overhydration can lead to pulmonary edema. Urine output and electrolytes should be monitored closely, given that the syndrome of inappropriate antidiuretic hormone may occur in severe asthma.

Patients with respiratory failure or impending failure should be intubated and mechanically ventilated. However, patients with severe asthma should receive prompt and aggressive therapy as soon as possible to avoid endotracheal intubation because manipulation of the airway may exacerbate bronchospasm. Furthermore, PPV, even noninvasive ventilation, increases the risk for pneumothorax and may result in untoward hemodynamic sequelae. Noninvasive PPV prevents the risks inherent in intubation and may be considered as an alternative to intubation and mechanical ventilation. Bilevel positive airway pressure has been used successfully for children in the emergency department with status asthmaticus and, in some cases, may obviate the need for admission to a PICU.

In the event of a clinical decision that respiratory failure is imminent and intubation is necessary, great care must be exercised in the course of induction and intubation. Induction medications that minimize the effects on the patient's cardiovascular status should be chosen. Intravenous access should be established before intubation because administration of analgesic and sedative agents can cause vasodilation, leading to profound hypotension. If a patient is intubated and mechanically ventilated, then sedation should be used.

Neuromuscular blockade may be necessary to minimize peak inspiratory pressures on the ventilator, although neuromuscular blockade may potentiate subsequent muscle weakness. In nonintubated patients, use of sedative-hypnotic agents should be undertaken with caution because such agents can further compromise the respiratory effort. If sedation is used, then objective criteria to assess respiratory status, such as blood gases, should be monitored even more closely than usual. Because of its

bronchodilatory effects, ketamine is the sedative agent of choice, and it has been used successfully in nonintubated and intubated children. However, prolonged ketamine infusions have not been adequately studied.

### Bronchodilators

$\beta_2$ -agonists are the mainstay of bronchodilator pharmacotherapy for severe asthma, and they are most often provided in the inhaled form. These drugs stimulate  $\beta_2$  receptors in airway smooth muscle, leading to smooth muscle relaxation and subsequent bronchodilation. Inhaled albuterol can be given by a metered-dose inhaler with a spacer chamber or by nebulization. Studies comparing the efficacy of the 2 methods of delivery for acute asthma show no significant difference, although patients receiving albuterol by metered-dose inhaler or spacer seem to have a shorter length of stay in the emergency department than patients using nebulization. For severe exacerbations, however, nebulization is generally the preferred route, and continuous nebulization seems to be better than intermittent doses, even when the same cumulative dose is used. The standard dose of continuous albuterol is 5 to 20 mg/hour, although doses as high as 40 to 150 mg/hour have been reported.

The standard formulation of albuterol is a 50/50 mixture of the (R)- and (S)-enantiomer forms of the drug. (R)-albuterol (levalbuterol) is the active form of the drug that leads to bronchodilation, whereas (S)-albuterol has a longer half-life and may contribute to side effects. In 1999, the US Food and Drug Administration approved the use of levalbuterol for asthma. Studies comparing levalbuterol with the racemic form have demonstrated similar clinical efficacy with the 2 preparations, although the cost of levalbuterol is 10-fold greater than that of generic albuterol. For hospitalized patients, continuous nebulized levalbuterol offers no benefit over continuous nebulized racemic albuterol. Thus, there is no reason to use levalbuterol, given its cost, over albuterol. Use of long-acting  $\beta$ -agonists in the treatment of acute asthma is not indicated. Common side effects of inhaled  $\beta$ -agonists include tachycardia, tremulousness, headache, hypokalemia, and nausea and vomiting.

Other  $\beta$ -agonists include epinephrine and terbutaline, which can be given by aerosolized, subcutaneous, or intravenous routes. Epinephrine, although sometimes used subcutaneously, is rarely used by the intravenous route because of its lack of  $\beta_2$  selectivity and the resulting dangerous side-effect profile. Terbutaline is often provided subcutaneously during a severe exacerbation when intravenous access is not readily available. The usual dose is 0.01 mg/kg given subcutaneously every 20 minutes in 3 doses, as necessary. In the PICU, terbutaline can be administered as bolus of 2 to 10 mcg/kg followed by a continuous infusion, with a dose range of 0.4 to 10 mcg/kg per minute. It is generally well tolerated, although it may cause a decrease in diastolic blood pressure. Given in a protocol-based fashion as an adjunct to aerosolized bronchodilators, terbutaline has been shown to reduce length of stay in both the PICU and the hospital. Recent randomized trials, however, failed to show any significant benefit

of terbutaline over placebo in patients already on continuous albuterol, or of terbutaline over aminophylline, which is substantially cheaper.

Anticholinergics are often used as adjuncts to  $\beta$ -agonists in managing status asthmaticus. These agents produce bronchodilation by blocking the effects of acetylcholine-induced bronchoconstriction, and they may have some effect on thinning or reducing secretions. The prototypical anticholinergic drug is ipratropium bromide, which is similar to atropine but has the advantage of not inhibiting ciliary beat frequency and mucociliary clearance. When given as an adjunct to albuterol and corticosteroids, ipratropium has been demonstrated to reduce hospitalization rates of asthmatic children and adults seen in the emergency department for asthma exacerbations. Ipratropium produces minimal systemic side effects, although inadvertent spread of the aerosolized drug to the eyes may cause unilateral or bilateral mydriasis, which can be alarming in a critically ill patient. There is no evidence to support ongoing use of ipratropium beyond the initial emergency department setting.

Whether magnesium sulfate plays a meaningful role in the management of the patient with severe asthma remains unclear. Magnesium exerts its bronchodilatory effects through inhibition of calcium entry into smooth muscle cells. A recent meta-analysis demonstrated that intravenous magnesium sulfate improves pulmonary function and modestly decreases the rate of hospitalization in children seeking emergency care, although, in adults with asthma, a meta-analysis of intravenous magnesium sulfate use demonstrated that a reduction in hospitalization rates occurred only with severe asthma. Intravenous magnesium sulfate is usually given over 20 to 30 minutes at reported doses of 25, 40, and 75 mg/kg, to a maximum dose of 2 g. A dose of 75 mg/kg does not produce any added benefit, and therefore dosages in this range are unnecessary. Adverse effects include flushing, nausea, and hypotension. Serious toxicities such as cardiac arrhythmias, muscle weakness, and respiratory depression are rare. Further research is needed to guide dosing recommendations and the necessity of following magnesium levels.

### Corticosteroids

Corticosteroids are indicated for any moderate to severe asthma attack and should be administered as soon as possible. The anti-inflammatory properties of corticosteroids include reduction in the number and activation of inflammatory cells, inhibition of the vascular leak induced by proinflammatory mediators, restoration of disrupted epithelium, normalization of ciliated cell:goblet cell ratio, decrease in mucus secretion, and downregulation of proinflammatory cytokine production and release. Corticosteroids also increase  $\beta$ -adrenergic receptor density on bronchial smooth muscle cells, thereby increasing  $\beta$ -agonist efficacy.

In the acute setting, corticosteroids can be administered by oral, intravenous, or intramuscular route. Although the bioavailability of oral and intravenous corticosteroids is similar, intravenous administration is preferred in status asthmaticus to ensure rapid entry

into the bloodstream and decrease the risk for aspiration. Inhaled corticosteroids, which are a mainstay of chronic asthma therapy, reduce hospitalizations in acute asthma compared with placebo, but are less efficacious than systemic corticosteroids. Commonly prescribed oral corticosteroids include dexamethasone, prednisone, and prednisolone.

Intravenous corticosteroids include methylprednisolone, hydrocortisone, and dexamethasone. For severe acute asthma, methylprednisolone is administered most often, generally given intravenously at a dose of 2 to 4 mg/kg per day divided every 6 to 12 hours, with a maximum daily dose of 60 mg. Adverse effects of corticosteroid therapy usually occur only after prolonged administration (ie, >3 weeks). In the short term, hyperglycemia, hypertension, leukocytosis, and mood and appetite changes may be encountered. A varicella vaccination and exposure history should be taken before corticosteroid therapy is initiated because of the rare but serious risk for disseminated varicella.

### Methylxanthines

Methylxanthines used in asthma include theophylline and its water-soluble salt analog, aminophylline. The primary effect of theophylline lies in phosphodiesterase inhibition, which reduces the degradation of cyclic adenosine monophosphate, resulting in dilation of airway smooth muscle. Theophylline also strengthens diaphragmatic contractility and increases respiratory drive. Although there is no longer a role for theophylline in outpatient, chronic asthma, the addition of intravenous aminophylline to  $\beta_2$ -agonists and corticosteroids in children with severe asthma improves lung function within 6 hours of treatment. However, it does not lead to any apparent reduction in symptoms or length of hospital stay and is associated with a significantly increased risk for vomiting. Because of the narrow therapeutic window of theophylline (10–20 mcg/dL), levels should be closely monitored, and use of this agent should be reserved for patients with severe asthma whose disease is not responding to maximal conventional therapy.

### Helium-Oxygen Mixtures

Helium-oxygen (heliox) mixture was used for treating upper and lower airway obstruction as early as 1935, and its use in asthma increased in the 1980s when asthma deaths began to rise. Helium gas is less dense than air and, therefore, facilitates laminar gas flow, decreases turbulent flow, and thereby reduces work, leading to easier breathing in patients with high airway resistance. Heliox is used most frequently in children with upper airway obstruction, but a randomized trial demonstrated that heliox decreased work of breathing, diminished pulsus paradoxus, and may have prevented intubation in children hospitalized with asthmaticus. Another trial demonstrated improvement in pulmonary index scores and quicker discharge from the emergency department when children were given albuterol nebulized with heliox as opposed to albuterol with oxygen alone. However, several other studies have demonstrated no benefit from heliox in the emergency department or PICU setting.

**BOX 372-1 A Stepwise Approach to the Management of Status Asthmaticus**

**Step 1:** Supportive care and prompt inhaled  $\beta$ -agonists and anticholinergics plus systemic corticosteroids

**Step 2:** Intravenous magnesium sulfate and/or intravenous aminophylline

**Step 3:** Sedation and noninvasive or invasive ventilation. Inhaled anesthetics, bronchoscopy, and extracorporeal life support may be needed for the most severe cases

There is little evidence to support the use of heliox in the context of severe acute asthma. Furthermore, any theoretical benefit of heliox is lost if less than 60% helium is in the mixture. Thus heliox may not be tolerated in patients with significant hypoxemia.

**Other Therapeutic Strategies**

A stepwise approach to management of status asthmaticus is recommended (Box 372-1). In severe, refractory cases of status asthmaticus, the use of inhalational anesthetics has been reported in the context of case reports and case series, but no randomized trials have been reported. The mechanism of action remains unknown but may involve inhibition of baseline vagal tone. In children, halothane and isoflurane have been described most extensively, and ventilation improved in most patients. However, the need for scavenging systems may pose a barrier to routine use of inhalational anesthetics outside of the operating room. Bronchoscopy with lavage and instillation of mucolytic agents is another treatment modality that has been used in severe cases in which extensive mucous plugging, bronchial casts, or both are suspected. Given the potential that bronchoscopy might worsen respiratory status, great caution should be exercised before undertaking the procedure in the context of status asthmaticus. Finally, extracorporeal life support has been used in both adults and children with life-threatening status asthmaticus, and it may be lifesaving in its ability to ameliorate severe hypoxemia, hypercarbia, or cardiovascular collapse.

**TOOLS FOR PRACTICE****Medical Decision Support**

- *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma* (guideline) National Heart, Lung, and Blood Institute ([www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm](http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm))

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**Chapter 373  
SHOCK**

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The primary care pediatrician can influence the outcome of a child who presents in shock. Promptly recognizing and treating shock and following consensus guidelines and algorithms can dramatically reduce mortality and morbidity associated with shock regardless of the cause. Prompt recognition and management of shock minimizes mortality and morbidity, even if transfer to a tertiary care facility is eventually required. Simple principles of fluid and vasopressor therapy are effective regardless of the cause. The physician should be confident in treating the hemodynamic abnormalities first and establishing the cause later.

**EPIDEMIOLOGIC FACTORS**

Shock, especially septic shock and hypovolemic shock caused by diarrhea or blood loss, remains a common cause of pediatric morbidity and mortality. Severe sepsis is among the most common causes of death in infants and children in the world. In the United States, 10% of pediatric patients hospitalized for severe sepsis die during their hospitalization. Children who survive their hospitalization for severe sepsis remain at an increased risk for morbidity and mortality. Diarrhea leading to dehydration severe enough to produce shock is no longer a common cause of death in the United States, but remains a world health problem. The cost to treat shock is substantial. In a 2005 report, the national annual cost of caring for children with severe sepsis alone is estimated at \$2.3 billion.

**CLINICAL DIAGNOSIS**

Prompt recognition and early treatment can dramatically change the outcomes for pediatric patients in shock. A high index of suspicion helps identify shock in the early stages. Shock can be considered a progressive process of compensated, decompensated, and irreversible states. The diagnosis may be made in the early, compensated state by easily detectable clinical signs: tachycardia, decreased capillary refill, and altered mental status. The presence of hyperthermia or hypothermia, altered mental status, and altered perfusion (brisk in warm shock [vasodilated] or delayed in cold shock [vasoconstricted]) confirms the diagnosis of shock. Mental status is a remarkably sensitive indicator of cerebral perfusion, allowing for the



assessment of the degree of illness and response to therapy. The presence of coma or neurologic compromise implies significant brain hypoperfusion. Restoration of neurologic well-being must be a primary goal of therapy. Urine output is an additional measure of end-organ perfusion reflecting blood volume and perfusion to the kidneys. An unexplained metabolic acidosis (defined as a base deficit of  $>3.0$  mEq/L) or an increased arterial lactate (2 times the upper limit of normal) in a patient with cardiovascular symptoms confirms inadequate end-organ perfusion. Pulse rate is a reasonable proxy of cardiac output, and capillary refill is a reliable indicator of end-organ perfusion. In fact, capillary refill  $<2$  seconds is a reliable marker for therapeutic end point.

In compensated shock, all of these indicators of end-organ perfusion may be decreased, but the blood pressure (BP) will still be adequate. In the decompensated phase of shock, hypotension occurs as the child's compensatory mechanisms are exhausted. Hypotension and tachycardia are the hallmarks of severe shock in a decompensating patient. Restoration of BP and reduction of heart rate are indicators of therapeutic success. Ranges of heart rate and BP by age group can be found in Appendix C, Formulas and Reference Range Values.

Decompensated shock can quickly lead to organ failure and, ultimately, the child can enter a phase of refractory shock, which carries an increased risk of morbidity and mortality. Children with refractory shock are not responsive to aggressive volume resuscitation, catecholamines, steroids, vasopressin, or other inotropic agents.

In practice, the diagnosis of septic shock in children is confirmed with the use of simple physical assessments—mental status, pulse rate and quality, capillary refill, BP, and urine output. The phase of shock is defined by the response to treatment.

## DIAGNOSIS OF SHOCK: HISTORY

After the patient is stabilized, an accurate history may help choose additional treatments and guide appropriate referral. Infants younger than 6 weeks of age who are in shock merit special attention and a broader differential diagnosis should be considered than in older infants or children. Shock in a newborn requires attention to both acquired and congenital conditions listed in Box 373-1.

Shock in toddlers usually has a determinable, apparent cause. The physician should be aware of the propensities that are unique to this age group, especially poisonings, ingestions of medications, inhaling and swallowing of foreign bodies, trauma resulting from falls, playground and household accidents, and child abuse. The adolescent may not be forthright in volunteering an accurate history. The risk-taking behavior of the teenage years should be taken into consideration when considering the differential diagnosis in this age group. Individuals who are available to give a history may not report experimentation with drugs and alcohol. Antipsychotic medications can cause cardiovascular collapse and arrhythmias. Ingestion of antihypertensive agents and opiates in the home should also be considered in the differential diagnosis of an adolescent in shock.

### BOX 373-1 Causes of Shock in Infants

#### Cardiac

- Hypoplastic left heart syndrome
- Coarctation of the aorta
- Myocarditis
- Arrhythmia

#### Infectious

- Bacterial meningitis
- Urinary tract sepsis
- Herpes (meningitis and sepsis)
- Streptococcal sepsis

#### Metabolic

- Hypoglycemia
- Inborn errors of metabolism

#### Traumatic

- Child abuse
- Occult central nervous system hemorrhage

#### Surgical

- Bowel obstruction

#### Occult blood loss

Infants in shock present unique diagnostic challenges. Algorithmic approaches to shock diagnosis developed for children and adults may not be appropriate.

Derived from Perkin RM, Levin DL. Shock in the pediatric patient. part I. *J Pediatr*. 1982;101(3):163–169; Perkin RM, Levin DL. Shock in the pediatric patient. part II. therapy. *J Pediatr*. 1982;101(3):319–332.

In all age groups, history of travel may lead to further clues. In a child with recent exposure to pets and who has diarrhea, the possibility of *Salmonella* infection must be considered. Recent ingestion of meat and early onset of central nervous system symptoms with bloody diarrhea imply hemolytic uremic syndrome. Exposure to organophosphates should be sought if weakness is part of the presentation.

Additionally, family history is important. In a study of Danish families, the risk of death was increased 5-fold in children whose parent had died with a severe infection before the age of 50.

## CLINICAL PHYSIOLOGIC MECHANISM OF SHOCK

The underlying mechanism resulting in both symptoms and complications from shock is the inadequate delivery of oxygen to meet the metabolic demands of the body. In all shock states, oxygen delivery and blood flow to vital organs is decreased and cellular oxygen needs are increased. The signs, symptoms, and sequelae of shock are the result of inadequate perfusion of oxygen to the tissues. Delivery of oxygen to tissues is the product of the oxygen content in the blood and the cardiac output. Oxygen content depends on the percentage of hemoglobin saturated with oxygen and the dissolved amount of oxygen in the blood. Cardiac output is the product of heart rate and stroke volume, which is expressed in liters of blood flow per minute. Stroke volume is dependent on contractility (inotropy), preload (venous return to the

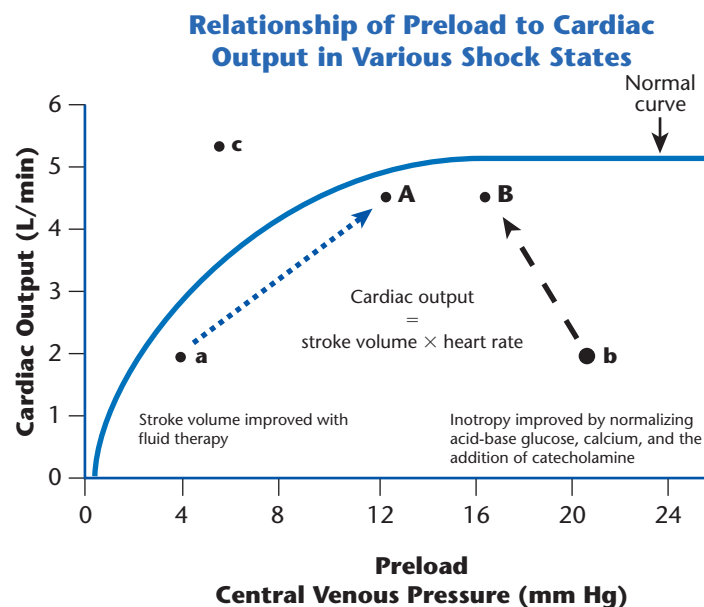
right heart) and afterload (arterial vascular resistance). Contractility of the myocardium is depressed by acidosis, hypoglycemia, and hypocalcemia. Epinephrine and other catecholamines act as inotropic agents, increasing contractility. Preload is the vascular volume presented to the heart during diastole, which stretches cardiac muscle, to enable optimal contraction during systole. Clinically, the central venous pressure and left atrial pressure represent preload to right and left ventricles, respectively. A patient with hypovolemia is said to have a low preload, and if blood volume is restored, then preload increases and stroke volume is increased (Figure 373-1, point a). Afterload represents the force the heart must pump against to move blood forward and is measured as systemic vascular resistance.

Children with shock may exhibit symptoms of hyperdynamic, vasodilated shock (see Figure 373-1, point c). Physiologically, cardiac output is high, peripheral vasculature is vasodilated, venous return (preload) to the heart is diminished, and systemic vascular resistance is low. On physical examination, the

patient has brisk capillary refill, is warm to the touch, and has bounding pulses, tachycardia, and a hyperdynamic precordium. Symptoms result not from low cardiac output, but rather from maldistribution of blood flow. Patients with this presentation of shock are considered to be in *warm shock*.

*Cold shock* is the opposite of *warm shock* in that children present with increased capillary refill (>2 seconds), cold extremities, and decreased pulses. *Cold shock* results from low cardiac output, constricted peripheral vasculature, decreased preload, and high systemic vascular resistance.

Heart rate is a valuable clinical sign both for diagnosis and treatment of shock in children. Infants cannot increase stroke volume as readily as adults can and rely on an increase in heart rate as a compensatory mechanism to increase blood flow to vital organs. Thus, an infant in shock whose heart rate is 2 standard deviations above normal is attempting to increase cardiac output. The return of pulse rate and BP to normal values is a valuable indicator of therapeutic success.



**Figure 373-1** The interaction of adequate volume status (preload or central venous pressure [CVP]) and contractility (cardiac output). Note the plateau in cardiac output relative to central venous filling pressure. As cardiac output reaches its maximum (in this example, at a central venous pressure of 10–12), further increase in CVP does not improve cardiac output. **Point a** represents the situation in hypovolemic shock. Here cardiac output is low, as is the CVP. The arrow indicates that as fluid administration increases preload, there is an improvement in cardiac output to **Point A**. **Point b** is a patient with a high preload (venous congestion), who would most likely have congestive signs on examination—rales, hepatomegaly, edema, and distended neck veins, with low cardiac output causing poor perfusion. This could be secondary to primary cardiogenic shock, as in myocarditis or after an ischemic event, or with myocardial dysfunction in late stages of septic shock. Evidence of poor perfusion would be obvious on examination—cold, clammy skin, prolonged capillary refill, and thready rapid peripheral pulses. The restoration of acid-base balance, glucose, calcium and magnesium levels to normal, and the addition of inotropic agents can dramatically improve function. The line from point **b** to point **B** demonstrates an improvement in output with a reduction in filling pressure. (It should be noted that, in infants, resting cardiac output is near maximum, and infants rely on increasing heart rate, whereas adults increase cardiac output by mechanisms intended to increase stroke volume.) **Point c** represents a patient who is vasodilated, with hyperdynamic cardiac output and relatively low cardiac preload. This would occur in distributive forms of shock—anaphylaxis and septic shock. This state would be reflected in the physical examination by presence of rapid capillary refill, bounding cardiac pulses, and a hyperdynamic precordium with tachycardia. (See text.)

## CLASSIFICATION OF SHOCK

The immediate goal of treatment of a patient in shock is to restore adequate tissue perfusion, and treatment should be guided by the physiologic manifestations of shock (ie, cold shock or warm shock). The physician must also determine the cause of shock, because without addressing the cause of shock, restoration of adequate tissue perfusion, if possible, will be short-lived. To assist the physician in identifying its cause, shock can be classified by the mechanisms leading to inadequate tissue perfusion—hypovolemic, cardiogenic, and distributive. Again, the pediatrician should recall that, despite complexities of cause, the early stages of shock are easy to recognize, and the treatments are straightforward.

### Hypovolemic Shock

Shock from loss of blood volume is the most common form of shock in children. Loss of fluid leads to low intravascular volume, which, in turn, decreases preload to the heart. When such losses occur over days, patients can compensate by retaining fluid and concentrating urine. Large volumes of fluid loss that occur acutely (over a few hours) lead to decompensation, represented by diminished mental status, tachycardia, oliguria, and hypotension. Two types of blood volume losses can lead to shock—hemorrhagic and nonhemorrhagic. Hemorrhagic volume loss is seen most commonly in patients following surgery or trauma, but is also commonly seen in children with gastrointestinal

bleeding. Nonhemorrhagic shock is seen in children with diarrhea, vomiting, excessive urinary losses, third spacing of intravascular fluid (peritonitis, edema), and burns.

Physical signs in hypovolemic shock occur as a result of decreased venous return to the heart, which leads to diminished cardiac output. Catecholamines are released, producing the hallmark vasoconstriction in skin, muscle, and splanchnic blood vessels. The renin-angiotensin system is activated, promoting the retention of salt and water. Fluid resuscitation restores preload, increasing cardiac output and leading to improved tissue perfusion and resolution of symptoms. Physical signs in nonhemorrhagic patients can be helpful to estimate the percentage of body fluid losses (Table 373-1).

In hemorrhagic shock, physical findings correlate to the amount of blood loss (see Table 373-2).

### Cardiogenic Shock

Cardiac shock can be caused by mechanical obstruction or muscle (pump) failure. The heart can fail as a mechanical pump from a variety of causes Box 373-2.

Patients with cardiac failure have low cardiac output because of decreased contractility and low stroke volume. The most common causes of obstructive cardiogenic shock involve narrowing of the left ventricular outflow tract Box 373-3.

Rarely, obstruction of forward flow of blood through the heart can be caused by rapid expansion of fluid in the pericardium or pleural spaces, leading to tamponade physiology. In addition to the signs and symptoms of shock discussed earlier, patients with cardiogenic shock usually exhibit distended neck veins from increased jugular venous pressure, along with evidence of venous congestion (hepatomegaly).

**Table 373-1**

#### Physical Signs in Dehydration

PERCENTAGE OF DEHYDRATION	PHYSICAL SIGNS
5% (mild)	Dry skin, mild tachycardia, concentrated urine
10% (moderate)	Lethargy, poor perfusion
15% (severe)	Obtundation, tachycardia, hypotension, very poor perfusion to skin

**Table 373-2**

#### Physical and Vital Signs in Hemorrhagic Shock

BLOOD VOLUME LOST (%)	SIGNS
<15%	Minimal tachycardia, normal respiratory rate, blood pressure, and capillary refill
15%–30%	Tachycardia, tachypnea, decreased pulse pressure, normal systolic pressure, prolonged capillary refill, anxiety
30%–40%	Hypotension, decreased urine output, mental status changes
>40%	Hypotension, loss of consciousness

#### BOX 373-2 Pump Failure

- Arrhythmia
- Hypoplastic left heart syndrome
- Decreased contractility acquired in sepsis syndrome or shock from any cause
- Myocardiopathy
- Myocarditis
- Anomalous coronary artery
- Cardiac contusion
- Storage disease—glycogen storage disease

#### BOX 373-3 Causes of Obstructive Cardiogenic Shock

- Tamponade (air, blood, or effusion)
- Coarctation of the aorta
- Aortic valve stenosis or atresia
- Hypoplastic left heart syndrome

### Septic Shock

Septic shock is the most common and certainly best studied cause of shock the primary care pediatrician will encounter. The causes of bacterial septic shock have changed since vaccination against *Haemophilus influenzae* type b was instituted in 1988. If sepsis in the immunocompromised patient is excluded, staphylococci and streptococci are the most commonly encountered bacterial causes of sepsis. Patients with infections caused by *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida* species, and *Streptococcus pyogenes* have higher mortality rates compared to patients with infections caused by coagulase-negative *Staphylococcus* and *Acinetobacter* species.

Children and adults exhibit developmental differences in the hemodynamic response to sepsis. In adults, mortality is caused by a vasopressor and volume resistant state characterized as vasomotor paralysis. Myocardial dysfunction is common in adults, but cardiac output is maintained by tachycardia and ventricular dilatation.

In pediatric septic shock, low cardiac output, not vasodilatation, is associated with mortality. In children, oxygen delivery is the major determinant of oxygen consumption, and survival correlates with the restoration of adequate cardiac output and oxygen delivery.

A large number of children with septic shock have absolute or relative adrenal insufficiency. This state results from inadequate adrenal corticosteroid release despite a very stressful condition. Infants and children at risk include those with septic shock and purpura, those with known or suggested adrenal abnormalities, and children who have received a therapeutic course of steroids in the 6 months before the onset of sepsis. In patients whose shock state is refractory to volume, dopamine or dobutamine, and the addition of epinephrine or norepinephrine (catecholamine-resistant shock), empirically initiating stress-dose steroids would be reasonable for those at risk for adrenal insufficiency.

Those children who remain in shock despite aggressive fluid resuscitation, cortisol supplementation, the addition of 2 catecholamine drugs, and normalization of acid-base, glucose, and calcium homeostasis are characterized to be in refractory shock; aggressive therapies, including extracorporeal life support, should be considered.

### Distributive Shock

Distributive shock disorders result from a dysfunction of vasomotor control resulting in maldistribution of blood flow and oxygen to tissue. Anaphylaxis and spinal cord injury are the 2 types most likely to be encountered in primary care. Cardiac output may be normal or increased. These patients lose sympathetic control of the vascular system, which reduces peripheral vascular tone resulting in pooling of blood in the periphery, which, in turn, leads to decreased venous return to the heart.

In anaphylactic shock, the inciting agent should be removed if possible. These patients uniformly respond well to volume administration, epinephrine infusion, antihistamines that include an H<sub>2</sub>-receptor blocker, and steroid therapy.

### TREATMENT

Three basic principles that should guide the therapy of a patient in shock are prompt recognition of a patient in shock, rapid restoration of systemic and regional perfusion to prevent ongoing shock and cellular injury, and correction of the cause of shock.

The most important predictor of outcome is appropriate resuscitation and reversal of shock within 75 minutes of recognition. Han and colleagues documented increased survival and decreased morbidity in a group of infants and children in shock treated by community physicians. Children treated following the American College of Critical Care Medicine *Pediatric Advanced Life Support* (ACCM-PALS) practice parameters for hemodynamic support of pediatric patients had improved survival compared to children who did not receive treatment following the guidelines (see Appendix A, Pediatric Cardiopulmonary Resuscitation).

The guidelines for diagnosis, care, and treatment of infants and children are based on a time line from recognition of shock and are the patient's response to each therapy. Key features of the guidelines include:

5 minutes:

- Recognize decreased mental status and poor perfusion. Secure the airway and provide bag-mask ventilation (ie, bag-mask the patient). Start to establish venous access upon recognition of shock. Peripheral intravenous or intraosseous access is appropriate for initial resuscitation. Provide intravenous fluid (20 mL/kg) once venous access is established.
- Begin monitoring the child (see monitoring guidance in Box 373-4).

15 minutes:

- Administer intravenous fluids within the first 15 minutes. The volume of each fluid bolus should be 20 mL/kg and should be administered in less than 5 minutes. Fluid needs can exceed 60 mL/kg of body weight.
- Begin broad-spectrum antibiotics as soon as possible.

#### BOX 373-4 Monitoring the Child in Shock in the Primary Care Setting

- Capillary refill
- Documentation of mental status
- Pulse oximetry
- Continuous electrocardiogram
- Blood pressure (cuff)
- Temperature
- Urine output
- Glucose and ionized calcium level
- Serum hemoglobin or hematocrit
- Hepatomegaly is a reliable indicator of volume overload and cardiac compromise

#### Successful resuscitation is recognized by

- Return of pulse rate to normal
- Improvement in mental status
- Return of capillary refill
- Improvement in acid-base status



- 30 minutes (15 minutes after fluid therapy begins):
- For children who do not immediately respond to fluid administration (15 minutes from beginning of fluid therapy) as indicated by improved end-organ perfusion, peripheral low-dose dopamine or epinephrine should be initiated through a second peripheral intravenous or intraosseous catheter until a central venous line is placed. Administration of vasopressors should not be delayed pending placement of the central venous line.
  - Children who do not respond to dopamine infusion up to 10 mcg/kg/min and fluid resuscitation (at least 60 mL/kg) have dopamine–fluid refractory shock. Institute infusion of epinephrine (0.05–0.3 mcg/kg/min) for cold shock or norepinephrine (0.05–0.3 mcg/kg/min) for warm shock. Glucose, serum hemoglobin or hematocrit, acid-base homeostasis, and ionized calcium should be monitored and restored to normal values.
- 60 minutes:
- Children who do not respond to fluid and an infusion of 2 catecholamine agents within 60 minutes have catecholamine-resistant shock, and adrenal insufficiency should be considered.
  - Refer to a tertiary care pediatric intensive care unit if children do not respond to fluid administration and to dopamine and epinephrine or norepinephrine infusions. These children require diagnostic evaluation for cardiac function and will require central venous access, echocardiography, and mixed venous oxygen saturation monitoring.

Treatment of shock, especially in primary care settings, is based on restoring adequate circulating blood volume, thereby achieving adequate delivery of glucose and oxygen to all tissues. Drugs and fluids for the treatment of shock are listed in Table 373-3. Monitoring and documenting the patient's response to each intervention is essential. Patients who develop organ failure have a markedly worse prognosis in shock. Specific definitions of organ failure are listed in Box 373-5.

Early volume resuscitation and vasopressor therapy are always indicated in the treatment of shock. Low-dose vasopressors may be initiated peripherally and should not be delayed until central venous access is established. Hepatomegaly is a reliable clinical indicator of volume overload. In children who develop hepatomegaly, but remain hemodynamically unstable, cardiac or renal failure must be considered.

Physicians should remember that fluid requirements in shock may exceed 60 mL/kg, and a common error is to give too little fluid too slowly. Rather than fearing fluid overload and thus undertreating the vast majority of patients, the physician should gauge the patient's response to fluid administration. Assessment of the patient's vital signs, mental status, and urine output should take place after each rapid 20 mL/kg fluid bolus. No conclusive data are found in the literature proving superiority of one fluid over another. Commonly used solutions are normal saline, lactated Ringer solution, or 5% albumin. The volume of the bolus should be 20 mL/kg of body weight.

Central venous access should be established in fluid/dopamine refractory patients once they are stabilized. Patients who remain tachycardic with poor capillary refill and inadequate urine output (<0.5 mL/kg/hr) after 60 mL/kg of fluid and the addition of 2 vasopressors are in catecholamine-resistant shock. Patients in this decompensated state will require referral to a tertiary pediatric intensive care unit for further diagnosis and treatment.

All patients in shock should immediately be given 100% oxygen. The oxygen saturations should be monitored continuously with a pulse oximeter. However, physicians need to appreciate that normal oxygen saturation on a pulse oximeter does not imply adequate oxygen tissue delivery. Because normal oxygen saturation does not reflect adequate oxygen content, the hemoglobin (the carrying vehicle for oxygen) should be measured and oxygen content should be determined. Blood transfusions may be necessary to ensure adequate oxygen delivery. If the circulation is compromised and cardiac output falls, then oxygen delivery to tissues will be compromised. The outcome for children in shock is dependent on adequate oxygen delivery and adequate oxygen delivery is associated with improved survival.

Oxygen delivery is the product of oxygen content and cardiac output. Oxygen content =  $1.36 \times$  the percentage of saturation  $\times$  hemoglobin (in grams) and is expressed as milliliters of oxygen per 100 mL of blood. In healthy children, oxygen consumption is 25% of oxygen delivery. In shock states, oxygen consumption may increase simultaneously with inadequate cardiac output, leading to inadequate tissue oxygenation. If lung disease is present or hypoventilation occurs, then hemoglobin is

**Table 373-3** Drugs and Fluids Used in the Treatment of Shock in Children and Infants

MEDICATIONS AND FLUIDS FOR TREATMENT OF SHOCK	DOSES
<b>FLUIDS</b>	
Normal saline	20–80 mL/kg
Albumin 5%	20–80 mL/kg
<b>MEDICATIONS</b>	
Dopamine	5–20 mcg/kg/min
Epinephrine	0.01–0.2 mcg/kg/min
Norepinephrine	0.01–0.2 mcg/kg/min
Dobutamine	5–20 mcg/kg/min
Milrinone	0.3–0.7 mcg/kg/min
Hydrocortisone (vasopressor resistant)	2 mg/kg/dose
Vasopressin	0.0003 units/kg/min to 0.01 units/kg/min
Calcium chloride (10%)	20 mg/kg

**BOX 373-5 Definitions of Organ Failure for Pediatric Patients in Septic Shock****CARDIOVASCULAR DYSFUNCTION**

Despite administration of isotonic intravenous fluid bolus  $\geq 40$  mL/kg in 1 hr,

- Decrease in blood pressure (BP) levels (hypotension): 2 standard deviations below normal for age

OR

- Need for vasoactive drug to maintain BP in normal range (dopamine  $> 5$  mcg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose)

OR

- 2 of the following:

Unexplained metabolic acidosis: Base deficit  $> 5.0$  mEq/L

Increased arterial lactate:  $> 2$  times upper limit of normal

Oliguria: Urine output:  $< 1$  cc/kg/hr

Prolonged capillary refill:  $> 5$  sec

Core to peripheral temperature gap:  $> 3^{\circ}\text{C}$

**RESPIRATORY**

- $\text{PAO}_2/\text{FIO}_2$ :  $< 300$  in absence of cyanotic heart disease or pre-existing lung disease

OR

- $\text{PaCO}_2$ :  $> 65$  torr or 20 mm Hg over baseline  $\text{PaCO}_2$

OR

- Proven need or  $> 50\%$   $\text{FIO}_2$  to maintain saturation  $\geq 92\%$

OR

- Need for nonelective invasive or noninvasive mechanical ventilation

**NEUROLOGIC**

- Glasgow Coma Score:  $\leq 11$

OR

- Acute change in mental status with a decrease in Glasgow Coma Score of  $\geq 3$  points from abnormal baseline

**HEMATOLOGIC**

- Platelet count:  $< 100/\text{mL}$  or a decline of 50% in platelet count from highest value recorded over the last 3 days (for patients with chronic hematologic disease or cancer)

OR

- International normalized ratio:  $> 2$

**RENAL**

- Serum creatinine:  $\geq 2$  times upper limit of normal for age, or 2-fold increase in baseline creatinine level

**HEPATIC**

- Total bilirubin:  $\geq 4$  mg/dL (not applicable for newborn)

OR

- Alanine aminotransferase (ALT): 2 times upper limit of normal for age

Each additional organ failure increases the risk of death.

From Goldstein B, Giroir B, Randolph A, et al. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6:2–8. Reprinted with permission from Lippincott Williams & Wilkins.

desaturated and oxygen delivery is compromised further. Initiation of mechanical ventilation may be necessary, both to decrease oxygen consumption by supporting the work of breathing and to optimize oxygen delivery.

Arterial lactic acidosis (normal is  $< 2$  mmol/L) or an increasing base deficit ( $> 3$  mEq) document inadequate perfusion. The effects of restoring the pH to over 7.25 are important: myocardial contractility is enhanced, sensitivity to catecholamines is improved, and potassium is returned to the intracellular space. Sodium bicarbonate (2 mEq/kg) may be required to improve

blood pH to over 7.25 and serum bicarbonate levels to more than 15 mEq/dL. Any remaining base deficit may be corrected by using the following guide:  $0.3 \times \text{body weight in kilograms} \times \text{base deficit} = \text{milliequivalents of sodium bicarbonate}$ .

Other metabolic derangements should also be corrected in children in shock, especially low levels of glucose and calcium. Children consume glucose at a faster rate than do adolescents and adults. In infants and toddlers, glucose levels should be considered a vital sign, and blood glucose needs to be added to

maintain adequate blood glucose levels. Glucose replacement is crucial, especially in very young patients. Glucose should be maintained at over 60 mg/dL. Hypocalcemia is also common in children with shock. Total calcium measurements do not correlate with measurements of the biologically important ionized calcium. Restoring ionized calcium to normal levels improves myocardial contractility, especially in neonates and infants.

### Vasopressor Drugs

Catecholamines do not replace adequate, aggressive, and early fluid administration as the initial treatment for shock. Dopamine, norepinephrine, epinephrine, and dobutamine are the drugs of choice in the early treatment of shock. Most cases of shock encountered in primary care are likely to require only fluid resuscitation. A vasoactive drug should be infused continuously with a calibrated infusion pump, and continuous heart rate and BP monitoring are required.

The physiologic effects of catecholamines are based on their relative effects on the  $\alpha$ - or  $\beta$ -adrenergic receptor. The  $\alpha$ -receptor produces vasoconstriction and, when stimulated, increases BP.  $\beta$ -agonists have 2 receptor sites:  $\beta$ -1 receptors stimulate heart rate and cardiac muscle contractility;  $\beta$ -2 receptors are present in bronchial and arteriole smooth muscles, and these muscles relax when stimulated. Dopamine has primarily  $\alpha$ -adrenergic and  $\beta$ -1 adrenergic effects. Epinephrine has predominantly  $\beta$ -1 adrenergic effects, and norepinephrine has predominantly  $\alpha$ -adrenergic effects.

Dopamine is the initial drug of choice and is administered at doses of 5 to 10 mcg/kg/min and titrated to effect. The  $\alpha$ -adrenergic effects predominate with vasoconstriction and reduced peripheral perfusion. Patients who do not respond to fluid resuscitation of 60 mL/kg and 10 mcg/kg/min of dopamine are in a state referred to as dopamine–fluid resistant shock and require addition of epinephrine (cold shock) or norepinephrine (warm shock).

Children who are thought to have low cardiac output may benefit from dobutamine. Dobutamine differs from dopamine because of its enhanced inotropic effect with less chronotropic effect than dopamine; it also has less effect on systemic vascular resistance. In some circumstances, especially shock after hypoxemic-ischemic injury, epinephrine or dobutamine may be preferred because dopamine may precipitate tachyarrhythmias and increase myocardial oxygen consumption.

Hydrocortisone is indicated in limited circumstances. Children with anaphylaxis, those with known or suggested adrenal abnormalities, and children who have received a therapeutic course of steroids for chronic illness in the 6 months before the onset of shock will require stress-dose steroids at 1 to 2 mg/kg of hydrocortisone. Children in refractory septic shock are, by definition, unresponsive to volume resuscitation, the addition of 2 catecholamine drugs, and normalization of acid-base, glucose, and calcium homeostasis; they may respond to hydrocortisone.

In select situations, and in tertiary care settings only, the use of vasodilator drugs (nitroprusside, milrinone, nitroglycerin) may be beneficial in reducing afterload when high peripheral vascular resistance and low cardiac output is encountered. This therapy optimizes

### BOX 373-6 Sample Case Report

A 3-year-old child exhibits a lung contusion and splenic hematoma. The hemoglobin is 10, heart rate is 180 beats per minute, systolic blood pressure is 80 mm Hg, and arterial saturation of oxygen by pulse oximetry is 90%. On examination, the patient is difficult to rouse, tachycardic, and has capillary refill >4 seconds. Evidence is ample that the patient's cardiac output is compromised because heart rate is elevated, perfusion is inadequate, and mental status is depressed.

The patient's oxygen content is  $(1.36 \times \text{serum hemoglobin} \times \text{arterial saturation})$  or  $1.36 \times 10 \times 0.90 = 12.3$  mL of oxygen/100 mL blood, whereas normal oxygen content is  $1.36 \times 13 \times 100 = 17.68$  mL oxygen/100 mL blood. Transfusion of red blood cells to reach a hemoglobin count of 13 thus increases oxygen content of the patient's arterial blood nearly 50% (from 12.3 to 17.8 mL/100 mL blood).

myocardial contractility and improves cardiac output, but requires sophisticated monitoring, including pulmonary arterial oximetry, cardiac output measurement, and pulmonary vascular pressure catheters.

Vasopressin is an endogenous hormone that works on the pituitary gland to release adrenocorticotrophic hormone (ACTH) and acts as an antidiuretic by its direct effect on renal tubules. Currently, its use is limited to tertiary care centers and is indicated for warm shock with low BP. Extracorporeal membrane oxygenation (ECMO) is considered for children in refractory septic shock in tertiary institutions. (See Table 373-3.)

### SEQUELAE OF SHOCK

Several organ systems may be affected by shock (see Box 373-5). A common form of hypoxemic respiratory failure known as acute respiratory distress syndrome occurs 24 to 48 hours after presentation of shock. The child becomes dyspneic and hypoxemic, with a P/F (partial pressure of oxygen/fraction of inspired oxygen) ratio of less than 200. Physical examination reveals rales and tachypnea; a chest radiograph reveals diffuse pulmonary infiltrates. The interstitial edema that develops seems to be caused by a capillary leak syndrome. This complication is life-threatening, and the patient should be referred to a tertiary intensive care unit. Mechanical ventilation and positive end-expiratory pressure, high-frequency oscillatory ventilation, or extracorporeal membrane oxygenation support may be required.

Myocardial depression is commonly encountered in septic shock. Inadequate perfusion, increased work, and distension of cardiac muscle in the presence of inflammatory mediators affect contractility and may lead to decrease in cardiac output.

Renal failure, especially acute tubular necrosis, is common. A serum creatinine more than twice normal for age is diagnostic. Renal failure is suggested when the urine output is under 0.5 mL/kg/hr, despite adequate restoration of blood volume.

Unrecognized renal failure will increase the mortality resulting from shock. Serum levels of drugs in the blood become uncertain. Doses of antibiotics, sedatives, and analgesics must be monitored carefully, following blood

levels in serum whenever possible. Fluid therapy must be titrated carefully to insensible fluid loss replacement; otherwise congestive heart failure will result. Anuria or oliguria complicating shock requires referral or consultation with a nephrologist or intensivist.

The central nervous system is most susceptible to inadequate oxygen delivery. A child may suffer significant neurologic impairment, although other organs are spared. Early central nervous system signs of shock include delirium, irritability, confusion, and coma. Signs of increased intracranial pressure are usually delayed 24 to 72 hours after a hypoxemic-ischemic insult. A Glasgow coma score of less than 11 or a decrease of 3 points from baseline are diagnostic of central nervous system compromise.

Liver function may become impaired as a result of inadequate perfusion. Bilirubin levels of more than 4 mg/dL and alanine aminotransferase levels greater than twice normal are diagnostic of hepatic failure. Clotting factors may be diminished. In septic shock, liver perfusion may be adequate, but bacteria or toxins may damage hepatic cells. Liver failure is usually transient.

Immune dysfunction can also occur following shock, leading to a state of immunoparalysis. Pediatric patients identified as immunoparalyzed are at increased risk for development of nosocomial infections.

## SUMMARY

Shock in the pediatric setting is a relatively common emergency. The diagnosis of shock is clinical, based on mental status, tachycardia, and peripheral perfusion. Early treatment does not require sophisticated monitors, central venous catheters, or invasive monitoring. Community caregivers can make a significant difference in the outcome of children in shock by recognizing shock early and following established guidelines for the early treatment of shock.

## SUGGESTED READINGS

- Brierley J, Carcillo JA, Choong K, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med.* 2009;37:666–688
- Dellinger R, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med.* 2013;41:580–637
- Mtaweh H, et al. Advances in monitoring and management of shock. *Pediatr Clin North Am.* 2013;60:641–654

## Chapter 374 STATUS EPILEPTICUS

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*Status epilepticus* is defined by the World Health Organization as “a condition characterized by an epileptic seizure that is sufficiently prolonged or repeated at sufficiently brief intervals as to produce an unvarying and enduring epileptic condition.” In 1993 the International

League Against Epilepsy further defined status epilepticus as any seizure that continues for 30 minutes or intermittent seizures lasting 30 minutes or longer in which the person does not regain consciousness between the episodes. Data have suggested that earlier treatment decreases the likelihood that status epilepticus will become refractory. It is now widely accepted that, if available, treatment for status should begin if a seizure has not stopped within 5 minutes.

Status epilepticus can be classified in terms of the type of seizure. *Generalized convulsive status epilepticus* is the most common and easily recognized type in children. The seizure activity usually is tonic-clonic or clonic and is less often tonic or myoclonic. In *focal motor status epilepticus*, also known as *epilepsia partialis continua*, focal seizure activity is prolonged and restricted to one side of the body without loss of consciousness. *Nonconvulsive status epilepticus* includes absence status and complex partial status and exhibits as a confused, drowsy, or obtunded state in which the patient may seem to move in slow motion or may be motionless, resulting from continuing or repetitive generalized or focal discharges (see Chapter 327, Seizure Disorders).

## INCIDENCE

The incidence of status epilepticus in patients who have epilepsy ranges from 4% to 16%. Its frequency is highest in the younger age groups. Up to 70% of children with epilepsy beginning before the age of 1 year experience status epilepticus. Infants and children also are far more likely than adults to have status epilepticus as the manifestation of their first seizure: roughly 10% of children with seizures have initial presentation as status epilepticus. Status epilepticus accounts for 5% of all febrile seizures in children.

## ETIOLOGY

In approximately 32% of cases, status epilepticus is provoked solely by fever. Remote symptomatic status epilepticus occurs in patients with a history of a central nervous system abnormality known to be associated with increased risk for seizure. This group accounts for another 18% of cases of status in children; many of these affected patients have cerebral palsy or intellectual disability. Another 29% are cryptogenic—presumed to be related to an underlying factor, but the factor has not been identified. Acute symptomatic status epilepticus accounts for another 17% of cases and is an expression of an encephalopathy or brain injury occurring within a week of status. Causes in this group include central nervous system or meningeal infection, electrolyte disturbance, low levels of antiepileptic drugs, and drug ingestion. Approximately 4% of cases of status are idiopathic. The cause in a small percentage of cases is a progressive encephalopathy such as in neurodegenerative diseases. It is important to determine the cause of status epilepticus through history, physical examination, laboratory investigations, neuroimaging, and electroencephalography (EEG) in order to guide treatment.

## HISTORY

A history should be obtained from an accompanying family member and should include any history of



previous seizures, chronic and recent medication use, intercurrent illness, head trauma, how an infant's formula is mixed, medications available in the home, and details of the onset of status epilepticus. Family history of seizures and previous history of signs or symptoms of underlying neurologic disorder are also important.

### PHYSICAL EXAMINATION

At physical examination, vital signs, fever, and any evidence of head trauma, increased intracranial pressure, or infection should be noted. Additionally, the examiner should look carefully for any evidence of asymmetry in cranial nerves, muscle bulk and tone, movement, and deep tendon reflexes.

### LABORATORY EVALUATION

A rapid bedside blood glucose level should be obtained immediately, and if the glucose level is less than 60 mg/dL, give 2.5 mL/kg of 10% dextrose as a bolus followed by infusion of 5 to 8 mg/kg/minute in infants and 3 to 5 mg/kg/minute in older children. Blood samples should be drawn to assess levels of electrolytes, glucose, blood urea nitrogen, and calcium; complete blood count; and possibly liver and renal function. If the patient was previously treated for seizures, levels of the prescribed anticonvulsant medication should be determined. If the cause of status is not obvious on initial history and examination, a urine sample should be assessed for drugs of abuse, and a blood sample should be taken for assessing levels of medications available in the home that may be associated with seizures, especially bupropion hydrochloride. Blood cultures and evaluation of cerebrospinal fluid may be indicated in febrile status epilepticus but are rarely helpful in afebrile status.

### ELECTROENCEPHALOGRAPHY

Baseline EEG, after treatment, is important for all children presenting in status epilepticus as their first seizure but is rarely useful in children with a history of seizures and previous EEG. Continuous EEG monitoring is important in children with status epilepticus if they have not returned to their baseline within 30 minutes of the cessation of visible signs of status. Up to 25% of children with convulsive status epilepticus have nonconvulsive status epilepticus persisting after cessation of the convulsion, and the incidence increases to 45% if the convulsive status epilepticus was refractory to initial treatment.

### Imaging Studies

Neuroimaging is important in all children who present in status epilepticus as their first seizure unless a previous neuroimaging study has defined a brain lesion and no new insults are expected. Head magnetic resonance imaging (MRI) is preferable because of the lack of radiation to the child and the detail MRI provides for small lesions and white matter changes. Head computed tomography (CT) is often more readily available and typically does not require sedation. CT is a good study to assess for the possibility of intracranial bleeding. Studies indicate that 13% to 32% of

children presenting with status epilepticus as their first seizure show abnormalities on neuroimaging.

### TREATMENT

The objective in treating convulsive status epilepticus is to prevent mortality and morbidity by maintaining vital functions, identifying and correcting any precipitating factors, and controlling seizure activity. Box 374-1 outlines a plan for treatment. Most episodes of status epilepticus are controlled by 1 or more of the drugs named in Box 374-1.

Nonconvulsive status epilepticus and epilepsy partialis continua require prompt treatment, but slightly less urgency exists because these seizures do not alter the body's homeostatic mechanisms to the degree that convulsive status epilepticus does. Convulsive status epilepticus is considered a medical emergency because it is life threatening and is sometimes followed by severe neurologic sequelae. The longer convulsive status epilepticus continues or the higher the fever associated with it, the more resistant it is to therapy and the greater the incidences of mortality and morbidity. Studies have shown that continued seizure activity for more than 60 minutes results in permanent cell damage, even in ventilated animals whose metabolic parameters are kept in the normal range. Neurologic sequelae from status epilepticus include intellectual impairment and motor dysfunction.

If the history or physical examination suggests a central nervous system infection, then antibiotics should be administered immediately and a lumbar puncture performed as soon as seizure activity has been controlled and the presence of significantly increased intracranial pressure has been excluded because of the risk for herniation. Because neurologic sequelae of status epilepticus can result from precipitating factors such as hypoxia, hypotension, and acidosis, immediate attention should be given to the respiratory and cardiovascular status of the child. If the patient is febrile, then priority is given to reducing body temperature because of the synergy between fever and status epilepticus in producing brain damage.

After seizure activity is controlled, management should be directed toward preventing recurrence of seizures, including maintenance anticonvulsant therapy. The appropriate duration of therapy after an initial episode of idiopathic status epilepticus is not clear. For a child who has had generalized convulsive status epilepticus, consideration should be given to prescribing nasal/buccal midazolam or rectal diazepam gel to be administered by caregivers at home for seizures lasting longer than 5 minutes. Epilepsy occurs in one-third of children after an initial presentation of status epilepticus. Status epilepticus recurs in 15% to 20% of children; the recurrence is about 4% in idiopathic or febrile status and up to 88% in symptomatic status.

### OUTCOME

Over the past 25 years, morbidity and mortality from status epilepticus have declined, probably because of the availability of benzodiazepines, better access to medical care, and more aggressive treatment by emergency medical technicians. In children with idiopathic or febrile status epilepticus, less than 5% develop new

**BOX 374-1 Treatment of Status Epilepticus**

- Assess and support cardiopulmonary function by making sure that the airway is clear and the patient is in a good position for airway patency and avoiding aspiration—generally on the left side. Air exchange in the lungs during vigorous tonic-clonic status occurs because of recurrent rib cage and diaphragmatic contraction rather than actual breathing, or a patient may be breathing on top of the seizure movements. It may be helpful to increase the percentage of oxygen in the air that is being exchanged by applying a mask with oxygen. Assess blood pressure and pulse and consider applying electrocardiogram leads. Provide respiratory support and cardiac stimulation (cardiopulmonary resuscitation) as necessary.
- Establish an intravenous or intraosseous access and obtain blood samples for bedside glucose determination, electrolytes, blood urea nitrogen, calcium, complete blood count, and anticonvulsant medication levels. If the rapid glucose determination is less than 60 mg/dL, give 2.5 mL/kg of 10% dextrose as a bolus followed by infusion of 5 to 8 mg/kg/minute in infants and 3 to 5 mg/kg/minute in older children. Blood glucose should be reassessed at frequent intervals until stable in the normal range, and significant hyperglycemia should be avoided.
- As the first 2 steps are being implemented, a member of the emergency team should obtain a history while another does a physical examination.
- If the patient is febrile, especially with fever above 102°F, attention should be given to aggressively cooling the child with rectal antipyretics and mechanically with ice, wet towels, or a cooling blanket. This is important because it is harder to stop status in a febrile patient, and the combination of status and fever doubly increases the metabolic needs of the brain compared with either alone. Therefore, with the combination of prolonged fever and status epilepticus, brain damage is more likely.
- Administer anticonvulsant drugs in the following order until seizure activity is controlled:
  - Lorazepam should be the initial anticonvulsant administered intravenously at a dose of 0.1 mg/kg (maximum 4 mg) over 2 minutes; a dose of 0.05 to 0.1 mg/kg may be repeated every 5 minutes as necessary up to a maximum of 0.5 mg/kg, but not over 10 mg total. Lorazepam has a 6- to 8-hour duration of effect. Therefore, unlike diazepam, another anticonvulsant need not be administered right away if the status epilepticus has stopped.
  - If lorazepam is not available, then diazepam should be administered intravenously at a dose of 0.1 to 0.2 mg/kg (maximum 10 mg) by pushing one-half the dose over 1 minute and the remainder at 1 mg/minute. A dose of 0.1 mg/kg may be repeated in 5 minutes if necessary. Because of diazepam's short duration of anticonvulsant effect, another anticonvulsant such as fosphenytoin must be administered immediately, even if the status epilepticus has stopped.
  - If intravenous access is not available, the patient should be given 0.2 to 0.3 mg/kg (up to 10 mg) of intranasal or intrabuccal midazolam, using the more concentrated solution of 5 mg/mL for better absorption. Rectal diazepam gel at 0.3 to 0.5 mg/kg may also be used as an alternative. Intranasal/intrabuccal midazolam acts a little faster and is easier to administer than rectal diazepam. It is helpful to split the intranasal/intrabuccal dose between the 2 nostrils or cheeks for better absorption.
- If the patient is known to be receiving phenytoin on a chronic basis, then 5 to 8 mg/kg phenytoin equivalents of fosphenytoin should be administered as the initial anticonvulsant. Fosphenytoin is the water-soluble prodrug of phenytoin with a more neutral pH value. If fosphenytoin is not available, intravenous phenytoin may be used carefully as one-fourth of the 15- to 20-mg/kg dose administered during the first 2 minutes, and the remaining at a rate of 1 mg/kg/minute (maximal rate of 50 mg/minute).
- If status epilepticus continues and the patient is not receiving phenytoin, then administer fosphenytoin as 20 mg/kg of phenytoin equivalents to a total maximum dose of 1,000 mg. Intravenous fosphenytoin may be administered at 3 mg/kg/minute (maximal rate of 150 mg/minute). Monitor the heart rate and slow the rate of fosphenytoin infusion if bradycardia occurs. Intravenous fosphenytoin is superior to intravenous phenytoin because it will not cause vein and skin sclerosis if extravasated from the small veins of children. If intravenous access is not available, the loading dose of fosphenytoin—not phenytoin—may be given intramuscularly. If seizure activity continues despite a full loading dose of fosphenytoin, then correction of presumed underlying acidosis with sodium bicarbonate (0.25 to 0.5 mEq/kg) may be indicated.
- If status epilepticus continues, then 1 of the following 3 drugs may be given intravenously. If the attempted medication is not effective, then another may be tried.
  - Phenobarbital is given in a dose of 20 mg/kg up to a total of 800 mg. Administer this amount over 15 minutes, monitoring respirations and blood pressure, especially if the patient has been treated with a benzodiazepine.
  - Levetiracetam may be given in a dose of 30 to 50 mg/kg over 5 to 15 minutes. Its side effects include sedation but less respiratory suppression than phenobarbital.
  - Valproic acid is administered as 25 mg/kg over 8 to 10 minutes. Valproate is not a good choice in a patient with liver dysfunction but has the advantage of less sedation and lack of respiratory depression.
- Generally by the time a third intravenous drug has been given, especially if phenobarbital has been added to full doses of lorazepam, the patient will require intubation, particularly before further treatment such as midazolam or pentobarbital infusion is given. If a muscle relaxant is used for intubation, it must be short acting, and treatment of the status should continue even though the convulsive

**BOX 374-1 Treatment of Status Epilepticus—cont'd**

movements are not seen clinically. Continuous EEG monitoring is strongly indicated if muscle relaxant therapy persists or the patient has not returned to baseline within 30 minutes of the end of convulsive status epilepticus. If seizure activity of unknown cause persists, 100 mg of pyridoxine (vitamin B<sub>6</sub>) may be given to treat the rare patient with pyridoxine dependency or insufficiency, preferably with an EEG running to help assess its effect.

- If seizure activity still persists, it is considered to be refractory status epilepticus, and it is important to consult a neurologist and/or intensivist to determine the need for other anticonvulsants, general anesthesia, or induction of pentobarbital, diazepam, midazolam, or propofol coma. A neurologist will be needed to pursue continuous EEG monitoring.

neurologic dysfunction. Mortality in children attributable to status epilepticus is 2% to 6%, with most deaths caused by the illness that precipitated the seizure. Morbidity (epilepsy, cognitive deterioration, behavioral problems, motor syndromes including spasticity, extrapyramidal syndromes, and cerebellar syndromes) is reported in up to 15% of children, is often related to the cause of the status, and is more common in younger children.

**WHEN TO REFER**

- When seizure activity cannot be controlled
- After seizure activity is controlled, if a history of previous afebrile seizures is present and a physician with experience in prescribing maintenance anticonvulsant medication is not available
- If the patient does not return to baseline within 30 minutes of the cessation of motor status and continuous EEG monitoring is not available

**WHEN TO ADMIT**

- Always for a child whose status epilepticus was not quickly controlled
- Always for a child who is unresponsive after status epilepticus, or not back to baseline in 30 minutes
- For any child who may have acute symptomatic status

**AAP POLICY**

American Academy of Neurology, Child Neurology Society. Diagnostic assessments of the child with status epilepticus (AAP endorsed). *Pediatrics*. 2007;119(2):404 ([pediatrics.aappublications.org/content/119/2/404](http://pediatrics.aappublications.org/content/119/2/404))

**SUGGESTED READINGS**

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- Riviello J, Ashwal S, Hirtz D, et al. Practice parameter: diagnostic assessment of the child with status epilepticus (an evidence-based review). Report of the Quality Standards of the Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2006;67(9):1542–1550

## Chapter 375

# THERMAL INJURIES

Robert L. Sheridan, MD

Burns are common, with nearly 100,000 children per year treated for burns in emergency rooms. Most pediatricians need to deal with burns periodically. Expectations for the functional and aesthetic quality of burn outcomes have become very high. In recent years, survival has improved significantly for children with serious burns. The long-term outcome for children, even with severe burns, is generally good when they participate in a burn aftercare program. Coincident with increasing survival and improving outcome quality has been the evolution of the burn center paradigm, in which all aspects of necessary care are coordinated in a single program.

**EPIDEMIOLOGIC FEATURES**

Approximately 70% of pediatric burns are caused by hot liquid. In older children and young working adults, flame, electrical, and chemical injuries become more common. Approximately 20% of burns in young children involve abuse or neglect. Organized burn prevention efforts have met with mixed success when based on public education, but legislation has been more effective than these efforts. Examples include factory settings of hot-water heaters, fire-safe cigarettes, and flammability standards for children's bedclothes.

**CLINICAL PRESENTATION AND EVALUATION**

Despite a broad spectrum of burn injury severity, from a practical perspective, the number of burn-injured children can be divided into 2 categories: those reasonably managed in the outpatient setting and those requiring inpatient or burn center care. This decision is based on an evaluation of the child and of the wound.

**Evaluating the Burn Patient**

An evaluation of the child should precede an evaluation of the wound, especially if the burn is large or

physiologically threatening. Patient evaluation is organized into a primary and a secondary survey, following the guidelines of the American College of Surgeons Committee on Trauma and the Advanced Burn Life Support Course of the American Burn Association.

As in trauma, the primary survey begins with an assessment and control, if necessary, of the airway. Deep burns of the face and neck can result in progressive airway edema. Rarely, a child will aspirate hot liquids, resulting in very severe upper airway edema and mandating urgent intubation.

A burn-specific secondary survey evaluates issues uniquely associated with burn injury (Box 375-1). This process may take just a few seconds in a child with a small burn, but it can be much more time consuming if the injury is large. In children with small injuries, essentials include a detailed determination of the mechanism of injury, a screen for associated trauma, consideration of the possibility of abuse, and a detailed assessment of the burn wound. Delayed presentation for care, confusing and conflicting stories, sharply demarcated margins, immersion patterns, and contact injuries are physical findings worrisome for abuse or neglect. All such children should be admitted for evaluation (Figure 375-1).

### Evaluating the Burn Wound

After the patient has been evaluated, the burn wound should be examined for size, extent, depth, and circumferential components. Decisions regarding outpatient care, hospitalization, or transfer will generally be made based on this information.

Burn extent is best estimated using a chart based on the Lund-Browder diagram that compensates for the changes in body proportions with age (Figure 375-2). An alternative is a modified *rule of nines*, in which the head and neck area is given 18% (instead of the adult 9%), each lower extremity is given 15% (instead of the adult 18%), each upper extremity is given 10% (instead of the adult 9%), and the anterior and posterior torso are each given 16% (instead of the adult 18%). For scattered or irregular burns, the entire palmar surface of the patient's hand represents approximately 1% of the body surface over all ages.

Burn depth is classified as first, second, third, or fourth degree. First-degree burns are red, dry, and painful and are often deeper than they appear, sloughing the next day. Second-degree burns are red, wet, and very painful (Figure 375-3, A). Enormous variability exists in their depth, ability to heal, and propensity to hypertrophic scar formation. Third-degree burns are leathery, dry, insensate, and waxy (Figure 375-3, B). Fourth-degree burns involve underlying subcutaneous tissue, tendon, or bone (Figure 375-3, C).

Nearly or completely circumferential burns should be identified for special monitoring and possible escharotomy. If across the torso, such wounds will interfere with ventilation. When they involve an extremity, limb-threatening ischemia may occur during resuscitation. This complication usually becomes an issue 12 to 24 hours after injury. These procedures can be performed with coagulating electrocautery. They can be

frightening and painful, and anesthesia or sedation is generally required in children. The physician should avoid damaging uninjured skin or superficial neurovascular structures.

### Selection for Outpatient Versus Inpatient Care

Most burns can be successfully managed in the outpatient setting. However, poorly provided outpatient burn care can be frustrating and painful for patients and providers. The key is careful patient selection and a detailed care plan. Several issues should be considered when making this decision (Box 375-2).

## MANAGEMENT

### Outpatient Burns

Many correct answers exist to the question, "How should outpatient burn wounds be treated?" However, certain characteristics are universal. The wound should be kept clean and inspected regularly for infection. Accumulated exudate and topical medications should be periodically cleansed. The small superficial burns managed in the outpatient setting present a low risk for infection; therefore, clean rather than sterile technique is reasonable. If topical agents rather than membrane dressings are used, then wounds may be cleansed with lukewarm tap water and a bland soap. Soaking adherent dressings before removal will decrease the pain associated with daily wound care. The wound is gently cleansed with a gauze or clean washcloth, inspected for any sign of infection, patted dry with a clean towel, and redressed. Instructing the patient and family to return promptly if they notice erythema, swelling, increased tenderness, lymphangitis, odor, or drainage is important so that infectious complications can be addressed early. The frequency of wound cleansing and dressing change is debated, but most small burns are adequately managed with a daily cleansing and dressing change. In some cases, a membrane dressing, designed not to be changed daily, is applied when early surgery is clearly not needed and early infection has not occurred. Pain and anxiety can be an issue for many children. Some of these children benefit from an oral narcotic given 30 to 60 minutes before a planned dressing change. Especially if dressings are occlusive, pain in between dressing changes tends to be modest for most children.

Increasing pain and anxiety associated with dressing changes, inability to keep scheduled follow-up appointments, delayed healing, signs of infection, or a wound that seems deeper than appreciated at the time of the initial examination should prompt early return and specialty evaluation. Wounds selected for outpatient management are usually fairly superficial and heal within 2 weeks. Patients with mid and deep dermal injuries may have a more problematic component, with resulting scarring that may benefit from specialty evaluation. Finally, wounds of the face, ears, hands, genitals, and feet have a functional and cosmetic importance out of proportion to their wound size. In some cases, early specialty evaluation may be prudent because initial care can have an effect on long-term outcome.



**BOX 375-1 Burn-Specific Secondary Survey****HISTORY**

- Mechanism of injury.
- Closed space exposure and extrication time.
- Delay in seeking attention.
- Fluid and pain medication given during transport.
- Prior illnesses and allergies.
- Prior child protective services involvement.

**HEAD, EARS, EYES, NOSE, AND THROAT**

- Early examination of the globes for corneal burns.
- Tonometry for intraocular hypertension if deep facial burns.
- Check for intraocular hypertension if extreme periorbital swelling or very deep periorbital burns are noted. Patient may need lateral canthotomy orbital decompression.
- Progressive hoarseness, perioral and intraoral burns, and carbonaceous material may signify inhalation injury.
- Consider hot liquid aspiration.
- Continuously assess endotracheal tube security.

**NECK**

- Radiographic evaluation if indicated by injury mechanism.
- Rare need for neck escharotomy.

**CARDIAC SYSTEM**

- Cardiac monitoring after significant electrical injury.

**PULMONARY SYSTEM**

- Chest escharotomy indicated if near circumferential torso burn and difficulty with ventilation.
- Inhalation injury can be associated with airway obstruction and bronchospasm initially.

**VASCULAR SYSTEM**

- Perfusion of burned extremities should be closely monitored.
- Escharotomy is indicated for decreasing perfusion.
- Fasciotomy is indicated after electrical or deep thermal injury when flow is compromised.
- Compartment pressures can be followed in equivocal extremities.
- Worrisome extremities should be decompressed based on serial examination.

**ABDOMEN**

- Nasogastric tubes are often indicated, especially before air transport.
- Inappropriate volume requirement may be a sign of an occult intra-abdominal injury.
- Torso escharotomy may be required to facilitate ventilation.
- Ulcer prophylaxis is indicated in all patients with serious burns.

- Consider abdominal compartment syndrome in very large burns or delayed resuscitation.

**GENITOURINARY SYSTEM**

- Catheterization is appropriate in those who require a fluid resuscitation.
- Ensure that the foreskin is reduced over the bladder catheter.

**NEUROLOGIC SYSTEM**

- Level of consciousness is often reduced during the hours after injury.
- Computed tomographic scanning is useful to exclude head injury if mechanism appropriate.

**EXTREMITIES**

- Monitor perfusion if near circumferential burns or electrical injury is present.
- Limbs at risk for decreased perfusion should be dressed so that they can be easily reexamined.

**WOUNDS**

- Evaluate wounds for size, depth, and circumferential components.
- Wounds are often underestimated in depth and size initially.

**ELECTRICAL FACTORS**

- Consider monitoring cardiac rhythm for high (>1,000) or intermediate (>220) volt exposures.
- Neurologic and ocular examination is important.
- Extremities should be serially evaluated for intracompartmental edema.
- Bladder catheters are useful in high-voltage exposures to document clearing of pigment.

**CHEMICAL FACTORS**

- Irrigate wounds with tap water for at least 30 minutes.
- Irrigate eyes with isotonic crystalloid solution.
- Blepharospasm may require ocular anesthetic.
- Hydrofluoric acid may be complicated by life-threatening hypocalcemia.

**TAR**

- Cool with tap water irrigation and remove later with a lipophilic solvent.

**LABORATORY AND RADIOGRAPHY DATA**

- Evaluate blood gas when inhalation injury is present.
- Normal carboxyhemoglobin does not eliminate significant exposure.
- Baseline hemoglobin and electrolytes can be helpful later.
- Perform a urinalysis for occult blood in patients with deep thermal or electrical injuries.
- Perform radiographic evaluation as needed for mechanism of injury.



**Figure 375-1** Some burn patterns are worrisome for abuse or neglect. This photograph illustrates popliteal flexor sparing, which may indicate abuse or neglect.

Intervals between discharge and first clinic follow-up and between subsequent follow-up visits will vary depending on the depth and location of the burn, surgery needed, and competence and comfort of the home-care providers. In general, a first follow-up a week after initial discharge is reasonable, rapidly increasing the duration of time between visits to 6 months, depending on patient progress.

### Wound Medications and Membranes

The proliferation of wound medications and membranes is increasingly confusing. Thankfully, most superficial wounds heal well under any of these products. Wound medications and membranes provide 3 benefits: (1) pain control, (2) prevention of wound desiccation, and (3) reduction of wound colonization.

A wide variety of topical wound medications are available, ranging from aqueous solutions to antibiotic-containing ointments and debriding enzymes. Most topical agents in outpatient use have a viscous carrier that prevents wound desiccation and a more or less broad antibacterial spectrum that reduces wound colonization. A gauze wrap minimizes soiling of clothing and protects the wound from trauma. Superficial burns are commonly treated with a clear, viscous, antibacterial ointment containing low concentrations of various antibiotics. Wounds around the eyes can be treated with topical ophthalmic antibiotic ointments. Silver sulfadiazine is commonly used for deeper injuries because it is painless on application and has a broad spectrum of antibacterial activity. Significant ear burns should be treated with mafenide acetate because it is the only agent that will penetrate the relatively avascular cartilage.

Wound membranes play an increasing role in outpatient burn programs. They provide transient physiologic wound closure while the underlying wound heals (Box 375-3). Physiologic closure implies a degree of protection from mechanical trauma, vapor transmission characteristics similar to skin, and a physical barrier to bacteria. The major benefit of wound membranes is that when successful, they minimize wound

manipulations. These membranes help create a moist wound environment with a low bacterial density and are generally intended for use on selected clean superficial wounds and donor sites. Occlusive synthetic membranes must be used with caution if wounds are not completely clean and superficial because submembrane infection can occur, deepening underlying wounds and causing systemic infection and toxicity. Membrane dressings are generally applied over a clean wound, without intervening topical medications. When used, these products are often applied after a period of care with a topical medication that allows the wound to be inspected and a clear determination made that the wound is superficial and will likely heal.

### Inpatient Burns

Inpatient burn care is resource intensive. A system of burn center verification has evolved to ensure that children requiring such care receive coordinated efforts by experienced providers. An increasing body of data supports the efficacy of this approach. Transfer to a burn center should be considered for patients meeting American Burn Association referral criteria (Box 375-4). Care of severe burns can be divided into 4 phases: initial evaluation and resuscitation; initial excision and biologic closure; definitive wound closure; and rehabilitation and reconstruction. Significant critical care needs often exist during the first 3 phases of care.

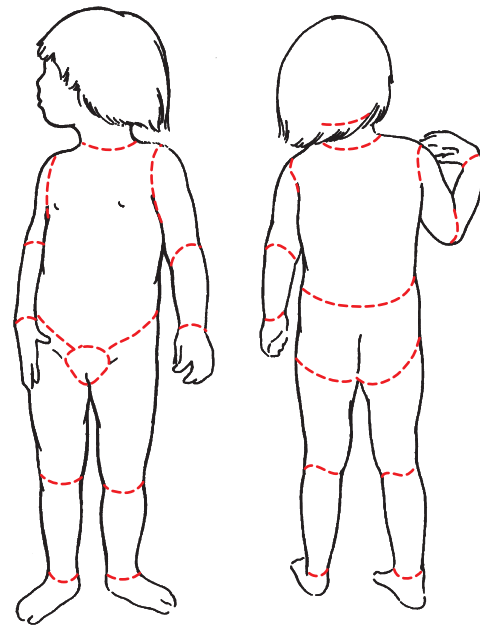
Priorities during the initial evaluation and resuscitation phase are to document the entire extent of the injury, including nonburn trauma, and to address the physiologic changes that accompany burns. This phase occupies the first 24 to 72 hours after injury. These needs will vary with the mechanism of injury, extent of burn, and child's social and medical history. If burns involve more than approximately 15% of the body surface, then a poorly understood syndrome of reduced capillary integrity is seen, necessitating a fluid resuscitation. This complication typically abates after about 24 hours. Any one of several burn formulas may be used to initiate resuscitation, but all should be carefully titrated to individual patient needs. One commonly cited formula is listed in Box 375-5.

In the initial excision and biologic closure phase, large full-thickness injuries are identified and excised, ideally within the first few days of injury, to avoid otherwise inevitable local and systemic sepsis, and systemic inflammation. Resulting wounds are closed with autograft or, in some circumstances, temporary wound membranes. This strategy changes the natural history of the injury from inevitable sepsis and inflammation to a more controlled wound closure situation.

In the definitive wound closure phase, which varies in duration with wound size and complexity, temporary wound membranes are replaced with autologous tissue, and small complex wounds, such as those on the hands and face, are addressed. In very large burns, this process may take many weeks. Intensive care is often a prominent part of the first 3 phases of care. Verified burn programs have embedded critical care units. Proper attention to pain and anxiety management is essential in all phases of care.

Burn Estimate: Age Versus Area

	Birth– 1 yr	1–4 yr	5–9 yr	10–14 yr	15 yr	2°	3°	Total
Head	19	17	13	11	9			
Neck	2	2	2	2	2			
Anterior trunk	13	13	13	13	13			
Posterior trunk	13	13	13	13	13			
Right buttock	2½	2½	2½	2½	2½			
Left buttock	2½	2½	2½	2½	2½			
Genitalia	1	1	1	1	1			
Right upper arm	4	4	4	4	4			
Left upper arm	4	4	4	4	4			
Right lower arm	3	3	3	3	3			
Left lower arm	3	3	3	3	3			
Right hand	2½	2½	2½	2½	2½			
Left hand	2½	2½	2½	2½	2½			
Right thigh	5½	6½	8	8½	9			
Left thigh	5½	6½	8	8½	9			
Right Leg	5	5	5½	6	6½			
Left Leg	5	5	5½	6	6½			
Right foot	3½	3½	3½	3½	3½			
Left foot	3½	3½	3½	3½	3½			
					<b>Total</b>			



**Figure 375-2** Burn chart for estimating the extent of injury. Numbers equal the percentage of total body surface.



**Figure 375-3** A, Second-degree burns are red, wet, and very painful. Enormous variability exists in their depth, ability to heal, and propensity to hypertrophic scar formation. B, Third-degree burns are leathery, dry, insensate, and waxy. This wound demonstrates peripheral second-degree component with central third-degree areas. C, Fourth-degree burns involve underlying subcutaneous tissue, tendon, or bone.

**BOX 375-2 Requirements for Outpatient Burn Management**

- Clear airway—has no need for airway monitoring.
- Wound size should be generally less than 10% (fluid resuscitation not needed).
- Child must be able to take in adequate fluid by mouth.
- No significant burns occur to the face, ears, hands, genitals, or feet.
- Family must have the resources to support an outpatient care plan.
- Adult caregiver should be able to stay at home with the child.
- Adult who is able to perform wound cleansing, inspection, and dressing changes should be available.
- Child must have transportation and access to clinic follow-up.
- Family must have transportation for clinic and emergency visits.
- No suspicion of abuse or neglect is noted.
- No clearly full-thickness areas that will require surgery are found.

**BOX 375-3 Partial Listing of Some Commonly Used Wound Membranes—Selected Characteristics**

- Porcine Xenograft (Brennan Medical, St Paul, MN): adheres to coagulum, excellent pain control
- Biobrane (Dow-Hickham, Sugar Land, TX): bilaminate, fibrovascular in growth into inner layer
- Acticoat (Westhaim Biomedical, Saskatchewan, Canada): nonadherent dressing that delivers silver
- Aquacel-Ag (Convatec, Princeton, NJ): absorptive hydrofiber that delivers silver
- Mepilex Ag (Mölnlycke Health Care, Gothenburg, Sweden): absorptive silver-releasing dressing
- Various semipermeable membranes: provide vapor and bacterial barrier
- Various hydrocolloid dressings: provide vapor and bacterial barrier; absorb exudate
- Various impregnated gauzes: provide barrier while allowing drainage

**BOX 375-4 American Burn Association Burn Center Referral Criteria**

- Second- and third-degree burns over more than 10% of total body surface area (TBSA) in patients younger than 10 years or older than 50 years
- Second- and third-degree burns over more than 20% of TBSA in patients aged 10 to 50 years
- Second- and third-degree burns that involve the face, hands, feet, genitalia, perineum, and major joints
- Third-degree burns over more than 5% of TBSA in any age group
- Electrical burns, including lightning injury
- Chemical burns
- Inhalation injury
- Burn injury in patients with preexisting medical disorders that might complicate management, prolong recovery, or affect mortality
- Any patients with burns and concomitant trauma (eg, fractures) in which the burn injury poses the greatest risk of morbidity or mortality. (In such cases, if the trauma poses the greater immediate risk, then the patient may be treated initially in a trauma center until stable before being transferred to a burn center. Physician judgment will be necessary and should be in concert with the regional medical control plan and triage protocols.)
- Hospitals without qualified personnel or equipment for the care of children should transfer patients with burns to a burn center with these capabilities
- Burn injury in patients who will require special social or emotional or long-term rehabilitative support, including cases involving suspected child abuse or substance abuse

Adapted with permission from American Burn Association. *Advanced Burn Life Support Course: Provider Manual*. Chicago, IL: American Burn Association; 2011: 25-26.

The final phase of care, rehabilitation and reconstruction, is of the longest duration. This phase begins as soon as the child is able to participate and lasts well past discharge, again depending on wound size and complexity. This process requires initially ranging and splinting and progresses through strength and endurance training. Long-term scar management and emotional support must be a part of this plan. As children

grow and scars contract, burn reconstruction procedures become important. A long-term follow-up plan is an essential part of discharge.

**Complications**

In the outpatient setting, patient selection should ensure that major complications are few. The most common issues that arise are wound sepsis, excessive pain



**BOX 375-5 Consensus Resuscitation Formula****FIRST 24 HOURS****Adults and Children Weighing More Than 20 kg**

- Lactated Ringer solution: 2–4 mL/kg per percentage of total body surface area (TBSA) burned per 24 hours (first half in first 8 hours)
- Colloid: In many children, particularly those with small injuries, no colloid is advised in the first 24 hours. However, colloid, generally as 5% albumin solution, is increasingly used early in resuscitation of patients with large burn injuries. This is program specific and should ideally be discussed with the unit to whom the child with a large injury will be referred. The author routinely replaces a maintenance rate of lactated Ringer solution with a similar volume of 5% albumin solution in children with burns over 30% BSA during the first 24 hours of resuscitation.

**Children Weighing Less Than 20 kg**

- Lactated Ringer solution: 2–3 mL/kg per percentage of TBSA burned per 24 hours (first half in first 8 hours)
- Lactated Ringer solution with 5% dextrose: Maintenance rate (approximately 4 mL/kg/hr for the first 10 kg, 2 mL/kg/hr for the next 10 kg, and 1 mL/kg/hr for weight over 20 kg)
- Colloid: In most circumstances, none; however, many physicians initiate colloid infusions in children with large burns. The author routinely replaces a maintenance rate of lactated Ringer solution with a similar volume of 5% albumin solution in children with burns over 30% BSA during the first 24 hours of resuscitation.

**SECOND 24 HOURS—ALL PATIENTS**

- Crystalloid: To maintain urine output. If silver nitrate is used, then sodium leeching will mandate continued isotonic crystalloid. If other topical is used, then free-water requirement is significant. Serum sodium should be monitored closely. Nutritional support should begin, ideally by the enteral route.
- Colloid (5% albumin in Ringer's lactate solution):
  - 0%–30% burn: none
  - 30%–50% burn: 0.3 mL/kg per percentage of TBSA burned per 24 hours
  - 50%–70% burn: 0.4 mL/kg per percentage of TBSA burned per 24 hours
  - 70%–100% burn: 0.5 mL/kg per percentage of TBSA burned per 24 hours
  - Colloid, generally as 5% albumin solution, is increasingly used early in resuscitation of children with large burn injuries.

From Sheridan RL. Comprehensive management of burns. *Curr Probl Surg*. 2001;38(9):641–756. Copyright © 2001, Elsevier, with permission.

and anxiety, and underestimation of burn depth. The most common wound infection in this setting is streptococcal cellulitis, which initially produces surrounding erythema that progresses to lymphangitis and systemic toxicity (Figure 375-4). Children with cellulitis often need admission for antibiotics, observation, and, sometimes, surgery. In some situations, adequate pain and anxiety management is difficult in the outpatient setting, especially around dressing changes. This problem can be addressed with judicious medication and, in some instances, carefully monitored membrane dressings. Some children will require admission for pain management. For burn depth to be underestimated initially is common, with areas of full-thickness injury not appreciated for several days. These children may require admission for surgery.

As burn severity increases, the local injury is accompanied by an increasing degree of systemic derangement. An initial phase of reduced perfusion and metabolic rate, which lasts 24 to 48 hours, is followed by a phase of protein catabolism and a hyperdynamic circulation, lasting until well after wound closure. Management of this physiologic process is an essential part of inpatient burn care. Children with large burns are susceptible to a host of other complications related to sepsis and organ failures. Careful monitoring and early intervention are essential to successful outcomes.



**Figure 375-4** The most common infectious complication in the outpatient setting is streptococcal cellulitis, as demonstrated here. Note blanching by examiner's fingers, suggesting surrounding erythema.

**LONG-TERM CARE**

Burn wounds and grafts typically develop some degree of hypertrophy. This process involves a gradual increase in vascularity and collagen deposition in the

months after healing. Some wounds will demonstrate significant contracture formation, with important functional and aesthetic consequences. Many children will have bothersome pruritus. A long-term follow-up plan consisting of scar management strategies, rehabilitation, reconstructive surgery, and emotional support will facilitate optimal outcomes. This care is best provided in a multidisciplinary burn clinic, ideally part of a comprehensive burn program. With such supports in place, the long-term outcome for children is surprisingly good. When managed in a comprehensive follow-up program, even patients who have suffered devastating burns may become happy and productive adults.

### TOOLS FOR PRACTICE

#### Engaging Patient and Family

- *Fire Safety* (Web page), American Academy of Pediatrics ([www.healthychildren.org/English/safety-prevention/all-around/Pages/Fire-Safety.aspx](http://www.healthychildren.org/English/safety-prevention/all-around/Pages/Fire-Safety.aspx))
- *Keep Your Family Safe: Fire Safety and Burn Prevention at Home* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Protect Your Home Against Fire...Planning Saves Lives* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))
- *Treating and Preventing Burns* (fact sheet), American Academy of Pediatrics ([www.healthychildren.org/English/health-issues/injuries-emergencies/Pages/Treating-and-Preventing-Burns.aspx](http://www.healthychildren.org/English/health-issues/injuries-emergencies/Pages/Treating-and-Preventing-Burns.aspx))

#### Medical Decision Support

- *Advanced Burn Life Support Course* (online course), American Burn Association ([www.ameriburn.org/ablsnow.php](http://www.ameriburn.org/ablsnow.php))
- *TIPP The Injury Prevention Program* (handout), American Academy of Pediatrics ([patiented.solutions.aap.org](http://patiented.solutions.aap.org))

### AAP POLICY

- American Academy of Pediatrics Committee on Injury and Poison Prevention. Fireworks-related injuries to children. *Pediatrics*. 2001;108(1):190–191. Reaffirmed October 2011 ([pediatrics.aappublications.org/content/108/1/190](http://pediatrics.aappublications.org/content/108/1/190))
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# Appendices

## Appendix A

### PEDIATRIC CARDIOPULMONARY RESUSCITATION

Élise W. van der Jagt, MD, MPH

#### HISTORY

An estimated 23,440 infants younger than 1 year old and 18,888 children between 1 and 19 years old died in the United States during 2012 from various causes. The mortality rate is clearly biphasic, with most deaths occurring in the first year of life and then again in the 15- to 19-year age group. Deaths of infants younger than 1 year are the result primarily of congenital malformations (20%) and conditions relating to prematurity and very low birth weight (18%). However, 7% of deaths are the result of sudden infant death syndrome, and 5% are caused by unintentional injuries. In children older than 1 year, injuries are the leading cause of death.

Although children also die from acute cardiac disease, including dysrhythmias and congenital heart disease, the major causes of death are substantially different from the causes of adult cardiac arrest, in which acute myocardial ischemia secondary to coronary artery disease is the predominant cause. Such myocardial ischemia often results in an acute dysrhythmia, usually ventricular fibrillation or ventricular tachycardia, and cardiac arrest. Unless children suffer a traumatic death, reasons for cardiopulmonary arrest are more commonly related to respiratory failure, infection, shock, and metabolic and neurologic events. Nevertheless, up to 17% of children with out-of-hospital cardiac arrest have ventricular fibrillation, similar to the 5% recently described for pediatric in-hospital arrests. Thus, many of the efforts in improving outcome for adults with cardiac arrest are also applicable to pediatric patients.

Outcomes from pediatric cardiopulmonary arrest are generally poor. Survival to hospital discharge from out-of-hospital arrest is less than 10%, with even fewer having intact neurologic function. Children who have sustained a cardiac arrest from a submersion injury have somewhat better outcomes, at 23% survival to hospital discharge and 6% with intact neurologic survival. However, based on the most recent data from the American Heart Association (AHA) “Get With the Guidelines: Resuscitation” (formerly called the National Registry of Cardiopulmonary Resuscitation), a registry of adult and pediatric in-hospital arrests, overall risk-adjusted survival in pediatric patients is 43%, a threefold increase in survival between 2000 and 2009. Asystole/pulseless electrical activity is the most common initial cardiac arrest rhythm (85%). Based on several studies, the outcomes

of pediatric respiratory arrest alone are better, with a survival of 75%; however, a 25% mortality rate is still highly significant.

Given that the outcomes of respiratory and cardiac arrest are poor, a proactive approach is best:

1. Identify children who are at risk for respiratory and cardiac arrest.
2. Institute treatments that prevent deterioration of the at-risk child.
3. If respiratory or cardiac arrest occurs, treat the child expeditiously and effectively using evidence-based therapies.

Until the mid-1980s, training was focused primarily on the third step of this approach, the treatment of pediatric patients who were in cardiac arrest. Currently the preventive approach outlined in steps 1 and 2 is also recognized as having significant importance. Moreover, the AHA has emphasized the importance of a community and serial approach to the significant problem of cardiopulmonary arrests by advocating for a concept called the Chain of Survival. Each link is integrally related to the next, and only if all the links are accomplished will it be less likely that death and disability will occur from cardiac arrest. Because the major causes of pediatric cardiopulmonary arrest are not cardiac in origin, but are from injuries, sudden infant death syndrome, respiratory failure, sepsis, neurologic diseases, and other illnesses, a separate Pediatric Chain of Survival has been developed for the management of pediatric critical illness and injury. It consists of prevention; early cardiopulmonary resuscitation (CPR); prompt access to the emergency response system; rapid pediatric advanced life support; and integrated post-cardiac arrest care.

#### ASSESSMENT

Given the paramount importance of recognizing children who are critically ill or injured before they deteriorate into respiratory or cardiac arrest, a rapid systematic assessment is required, with due attention paid to possible respiratory and circulatory compromise. This process requires a rapid performance of those parts of the physical examination that pertain especially to the respiratory, circulatory (including cardiac and vascular systems), and neurologic systems. The neurologic system is especially important in that failures of either or both respiratory and circulatory systems will have an effect on neurologic function. The AHA and the American Academy of Pediatrics (AAP) have jointly developed an excellent systematic approach, which is included in their Pediatric Advanced Life Support Course training materials, accessible via the AHA Web site ([www.heart.org](http://www.heart.org)).

The components of this rapid, systematic evaluation include an initial impression, a primary assessment using an A-B-C-D-E approach to rule out immediate, life-threatening problems, a secondary assessment

that includes both a history and a more detailed head-to-toe physical examination, and a tertiary assessment using bedside monitoring and laboratory and radiologic diagnostic tests (Table A-1).

### Initial Impression

The *initial impression* is a quick look at the child, focusing on level of consciousness, general appearance, work of breathing (including its absence or only gasping, abnormal airway sounds, and retractions), and color (may be altered by either or both respiratory and circulatory problems). A quick decision is made on whether this child might be in respiratory failure, circulatory failure, or both, including full cardiopulmonary arrest, and immediate management is begun, such as calling for help, immediate provision of CPR if

necessary (after a pulse check), providing oxygen, and obtaining a monitor.

### Primary Assessment

The child is examined in a systematic fashion using an **A** (airway), **B** (breathing), **C** (circulation), **D** (disability), and **E** (exposure) approach.

**A: Airway**—the examiner quickly determines whether the airway is patent with air able to flow into and out of the chest, whether it is maintainable with minimal head or jaw positioning or with an insertion of an oropharyngeal or nasopharyngeal airway, or whether the child needs establishment of a laryngeal mask airway (LMA), invasive airway, such as an endotracheal tube (ET) or cricothyroidotomy.

**B: Breathing**—respiratory rate, work of breathing, and lung sounds are determined by visual inspection and auscultation of the chest at the apices and in the peripheral lung fields (lung bases posteriorly and in axillae). The purpose is to determine the presence of life-threatening problems such as apnea, respiratory failure with inadequate oxygenation and ventilation, pneumothorax, hemothorax, severe wheezing, or rales from congestive heart failure or pneumonia. Normal respiratory rates are shown in Table A-2.

**C: Circulation**—heart rate, blood pressure (BP), peripheral and proximal pulses, capillary refill, distal extremity temperature, and distal extremity color should all be noted.

Changes in heart rate reflect changes in cardiac output the most quickly, but unfortunately these changes are nonspecific. Children have a wide range of normal heart rates, and rates are highly dependent on activity (see Table A-1). For neonates, the typical sleeping heart rate should be no greater than 160 beats per minute (bpm). By age 2 years, heart rates are usually between 75 and 160 bpm, with a mean of approximately 130 bpm; from 2 to 10 years of age, the sleeping heart rate should be no greater than approximately 90 bpm; and over age 10, even the non-sleeping heart rate should be no more than 100 bpm. Heart rates above a certain level are highly associated with a primary cardiac dysrhythmia. Heart rates that are above 220 bpm for infants, 180 bpm

Table A-1	Pediatric Assessment
LEVEL	AREAS OF ASSESSMENT
<i>Initial impression</i>	Level of consciousness/general appearance, work of breathing, color
<i>Primary assessment</i>	<b>A</b> irway, <b>B</b> reathing, <b>C</b> irculation, <b>D</b> isability, <b>E</b> xposure
<i>Secondary assessment</i>	<b>SAMPLE:</b> <b>S</b> igns and symptoms <b>A</b> llergies <b>M</b> edications <b>P</b> ast history <b>L</b> ast meal <b>E</b> vents Physical assessment (head to toe)
<i>Tertiary assessment</i>	Bedside and laboratory tests Oximetry or capnography Imaging or echocardiography Invasive arterial and venous pressure monitoring

Derived from *Pediatric Advanced Life Support: Provider Manual*. Dallas, TX: American Heart Association; 2011.

Table A-2	Normal Ranges of Body Surface Area, Weight, and Vital Signs for Infants, Children, and Adults				
AGE	BODY SURFACE AREA (m <sup>2</sup> )	WEIGHT (kg)	PULSE RATE <sup>a</sup> /MIN	SYSTOLIC BLOOD PRESSURE <sup>b</sup> (mm HG)	RESPIRATORY RATE <sup>c</sup> /MIN
Newborn	0.19	3.5	90–200	60	30–60
1 mo	0.30	4.0	90–180	65	30–60
6 mo	0.38	7.0	90–180	70	24–30
1–2 yr	0.50–0.55	10–12	70–140	72–74	20–24
3–5 yr	0.54–0.68	15–20	60–120	76–80	16–22
6–9 yr	0.68–0.85	20–28	60–120	82–88	14–20
10–12 yr	1.00–1.07	30–38	60–110	90	12–20
12–14 yr	1.07–1.22	38–48	50–100	90	12–20
15–16 yr	1.30–1.60	53–58	50–100	90	12–18
Adult	1.40–1.70	60–70	50–100	90	12–18

<sup>a</sup>Pulse rate range includes sound sleep and vigorous crying.

<sup>b</sup>Systolic blood pressure less than fifth percentile.

<sup>c</sup>Respiratory rate above 60 or below 10 respirations/minute is abnormal at any age.



for children up to age 8, and over 160 bpm for older children are suggestive of a primary dysrhythmia such as supraventricular or ventricular tachycardia. Sinus tachycardia from volume depletion is typically at a lower rate. When a sinus tachycardia fails to compensate adequately for tissue oxygen needs, eventually hypoxia, acidosis, and ultimately bradycardia develop. Bradycardia is present when the heart rate is below 60 bpm and, in a distressed child, is always a sign of impending cardiac arrest.

Blood pressure is the product of cardiac output multiplied by the peripheral vascular resistance. It should be measured early to detect decompensated hypotensive shock. Hypotension is a late and serious finding in patients who are in shock. A useful way to remember the minimally acceptable systolic BP is

- If younger than 1 month of age, systolic BP above 60 mm Hg
- From 1 month to 1 year, systolic BP above 70 mm Hg
- From 1 to 10 years, systolic BP above  $70 + (2 \times \text{the age in years})$  mm Hg
- Older than 10 years, systolic BP above 90 mm Hg

These parameters have been derived from the lowest fifth percentile of office BPs in normal children taken from cross-sectional data sets. An infant or child whose BP is below these parameters should be considered hypotensive.

Palpating the peripheral pulses (a reflection of peripheral perfusion) allows the examiner to estimate the stroke volume, heart rate, and, indirectly, the cardiac output. The stroke volume is the volume of blood pumped out of the heart with each heartbeat. The cardiac output is the volume of blood pumped by the heart every minute (heart rate multiplied by stroke volume). Organ perfusion is determined by the cardiac output and the peripheral vascular resistance. Peripheral pulses that can be palpated are the radial, brachial, dorsalis pedis, and posterior tibial arteries. Central pulses are the carotid, axillary, and femoral pulses. Attention should be given to the quality of the pulse, especially whether it is bounding (consistent with low systemic vascular resistance) or narrow/thin (narrow pulse pressure and a high systemic vascular resistance). Decreased distal pulses are consistent with circulatory compromise.

When circulatory compromise occurs, the skin loses its perfusion first, because blood is shunted to more important organ systems. Skin perfusion is assessed by determining capillary refill time (ie, the time required for normal skin color to return after blanching pressure is applied); this interval should be 2 seconds or less (or less than the time required to say “capillary refill”). When testing for capillary refill, the extremity used should be kept at the level of the heart. Poor perfusion also can be identified by mottled skin color, especially distally (acrocyanosis), and cool hands and feet, with an often noticeable line of demarcation between warm skin proximally and cool skin distally.

Once these circulatory physical parameters have been assessed, a determination can be made as to whether the patient either has no circulatory compromise, is in early compensated shock (normotensive circulatory failure), or is in late decompensated shock (hypotensive circulatory failure).

**D: Disability**—a quick neurologic examination is performed by evaluating the level of consciousness (AVPU: Alert, responds to Voice, responds to Pain, Unresponsive), pupillary response to light, motor response to discomfort, and muscle tone. Both respiratory and circulatory failure can result in blunting of mental status because of hypoxia or poor oxygen delivery. However, a primary neurologic problem should also be excluded, particularly given that many critically ill children have sustained a head injury, have seizures, or have an infectious neurologic disease such as meningitis.

**E: Exposure**—attention must be given to the core temperature of the child because both elevated and low temperatures may alter other physiologic parameters. In addition, a thorough inspection of the child's skin is necessary to ensure that areas of bleeding, rashes, and signs of trauma are not missed.

No more than about 60 seconds is needed to perform the primary assessment and determine whether the child is stable, has respiratory distress only, has respiratory failure, has compensated or decompensated shock, or has combined cardiopulmonary failure. This last physiologic state is usually present when a child exhibits agonal breathing, cyanosis, and bradycardia. Usually this state will have been identified already during the general assessment described previously.

The necessity for instituting urgent treatment is dictated by the results of the initial impression and primary assessment. Monitoring should be initiated with at least a continuous pulse oximeter and frequent BP checks, but often there is benefit from continuous electrocardiographic (ECG) monitoring as well. A high concentration of oxygen (non-rebreather will give approximately 90% to 100% fraction of inspired oxygen [ $\text{Fio}_2$ ]) should be provided to all children with respiratory and circulatory problems. If significant respiratory distress is present, the child may be in respiratory failure, and assisted ventilation with a bag-mask device should be provided with progression toward ET intubation as needed. Any form of shock that is related to volume depletion, whether because of extrinsic losses of water, loss of blood, or a redistribution of intravascular volume such as that seen in septic or anaphylactic shock should be treated with intravenous (IV) (or intraosseous [IO] if necessary) administration of 20 mL/kg of normal saline or Ringer's lactate given within approximately 5 to 10 minutes (often requiring a 3-way stopcock and syringe to draw rapidly from a bag of fluid and manually push it into the patient's IV or IO line). The need for further boluses is determined by response in heart rate (tachycardia would be expected to decrease) and restoration of normal vital signs. Dysrhythmias should be treated with antiarrhythmic maneuvers (eg, facial ice for supraventricular tachycardia [SVT]) or medications, as described later and in the dysrhythmia algorithms.

### Secondary Assessment

The secondary assessment consists of performing a focused history and a complete physical examination.

A focused history can be remembered with the mnemonic **SAMPLE**:

- Signs and symptoms
- Allergies

**Medications****Past history****Last meal****Events**

Although all of the items in the SAMPLE mnemonic are important, special attention should be given to the last time food or drink was ingested. If the child requires assisted ventilation by bag or needs to have an ET tube inserted, emesis of stomach contents may occur, especially if the time interval from the last meal is short (<6 hours). Use of a Sellick maneuver (anterior cricoid pressure directed posteriorly during bagging or intubation) may decrease the likelihood of emesis by occluding the esophagus and decreasing the chance of introducing air/oxygen into the stomach. It should only be attempted in an unconscious patient, and, in small children, anterior cricoid pressure may occlude the compliant trachea. The physician should ensure the immediate availability of large-bore suction (pediatric and adult size Yankauer suction) to remove vomitus or secretions and to prevent aspiration.

The past history is important because it may reveal medical problems that are related to the current condition of the child or that should be taken into consideration when management is instituted.

A focused head-to-toe standard physical examination will provide a more fine-tuned constellation of clinical clues to the physiologic state of the child. In this examination, important areas to include are the head, the fontanelles in infants (flat or sunken vs full or bulging), ears, eyes (especially pupillary reaction), nose, mouth, teeth and pharynx, neck (supple or stiff), more detailed lung and heart sounds, abdominal examination (especially assessing for tenderness), organomegaly (such as an increase in liver or spleen size), bowel sounds and distention, extremities (evidence of injury), color change, skin (evidence of bleeding and rashes), and neurologic examination assessing for mental status, movement, deep-tendon reflexes, cranial nerves, and muscle tone.

**Tertiary Assessment**

The tertiary assessment is performed by using non-historical or direct physical examination techniques. This assessment includes diagnostic modalities such as pulse oximetry and capnography, bedside tests such as finger-stick blood glucose, laboratory and imaging tests, and invasive monitoring. Some of these tests might be performed simultaneously with the earlier parts of the assessment. Once the rapid preliminary clinical assessment has been performed to determine the most likely physiologic state of the child, appropriate laboratory tests should be ordered to define further the child's physiologic state and treatments necessary, and to assist in determining etiology. In a critically ill child, the important tests that should be considered include an arterial blood gas level; a chest radiograph; electrolyte (sodium, potassium, chloride, bicarbonate, calcium, magnesium) levels; blood urea nitrogen levels; glucose level; lactate level; a complete blood count (hematocrit, white blood cells with differential, platelets); a urine analysis; and cultures of blood, urine, and spinal fluid as appropriate.

Although the time needed to obtain these results can be lengthy, the information obtained will be useful in determining the severity of the illness and the further management required. Meanwhile, ongoing advanced life support should be given as indicated by the clinical examination and revised as laboratory and radiologic tests return.

**DIAGNOSIS OF PHYSIOLOGIC STATE****Respiratory Distress, Failure, or Arrest**

The principal functions of the respiratory system are to introduce oxygen into the blood and to remove carbon dioxide. Failure of the respiratory system results in significant compromise to cellular metabolism, changing aerobic to anaerobic metabolism with the accumulation of lactic acid, and an increase in carbon dioxide, resulting in a respiratory acidosis. The initial physiologic responses to failure of oxygenation and ventilation are usually an increase in respiratory rate with efforts to improve air entry, and an increase in heart rate to improve oxygen delivery to the tissues. However, in young children these responses may be blunted, and bradycardia from hypoxia is common. The presence of central (oral or perioral) pallor and cyanosis is an indicator of significant hypoxemia and should be treated rapidly with administration of 90% to 100% oxygen via a non-rebreather mask with oxygen reservoir while the remainder of the respiratory examination is completed. Bradypnea (slow respiratory rate) can indicate fatigue and failure of the brainstem to respond to normal stimuli for breathing; tachypnea can suggest either a need to maintain minute ventilation because of a smaller tidal volume (minute ventilation = tidal volume  $\times$  rate/minute) or because of an increase in metabolic rate and carbon dioxide production. Any respiratory rate over 60 breaths per minute or under 10 breaths per minute is abnormal at any age and might suggest respiratory distress, respiratory failure, or both. If respiratory compromise is untreated, it may rapidly and unexpectedly progress to respiratory failure and respiratory arrest.

*Respiratory distress* is defined as an increase in the work of breathing, typically characterized by an increase in the use of the main muscles used for breathing, as well as the use of muscles that typically do not contribute much to breathing (accessory muscles). Thus, the examiner might see retractions (intercostal, subcostal, sternal, substernal, sternocleidomastoid) and nasal flaring and head bobbing, hear a grunting sound on exhalation (to increase pressure in the airways to keep alveoli open), and notice an accentuation of abdominal breathing for children who have weak intercostal muscles.

Sounds heard during inhalation and exhalation may give an excellent clue to the etiology of the respiratory abnormalities. Stertor suggests nasopharyngeal obstruction; stridor suggests upper airway obstruction (usually in epiglottic/glottic and tracheal areas); wheezing suggests obstruction in the middle airways (eg, asthma, bronchiolitis); and inspiratory rales suggest lung parenchymal disease or alveolar fluid from pulmonary edema or congestive heart failure.

Asymmetric or diminished lung sounds might reflect the presence of atelectasis, pneumonia, a pleural effusion, or a pneumothorax.

*Respiratory failure* is defined as inadequate oxygenation, inadequate ventilation, or both. Although failure to oxygenate is now easily diagnosed by pulse oximetry, the diagnosis of respiratory failure still may be difficult to make purely on clinical grounds. Nasal capnography is a more recent advance that may be helpful in assessing the adequacy of ventilation even in the presence of adequate oxygenation. Generally, the greater the respiratory distress, the greater the likelihood of impending or existing respiratory failure. An arterial blood gas assessment will provide objective information about the adequacy of oxygenation and ability to remove carbon dioxide. A normal arterial pressure of oxygen ( $\text{Po}_2$ ) is usually 90 to 100 mm Hg (unless the child has congenital heart disease and part of the blood remains deoxygenated because it bypasses the lung as a result of intracardiac or extracardiac shunting, usually resulting in  $\text{Po}_2$  levels in the 35 to 45 range (oxygen saturation levels of 65% to 80%); a normal arterial pressure of carbon dioxide ( $\text{PCO}_2$ ) is between 38 and 42 mm Hg, and a normal pH is between 7.38 and 7.42. The  $\text{PCO}_2$  and pH are related such that a change in  $\text{PCO}_2$  of 10 mm Hg usually results in a pH change of 0.08. If the pH is normal in the presence of an elevated  $\text{PCO}_2$ , chronic rather than acute respiratory failure may be present because there has been time for the kidneys to absorb bicarbonate as a metabolic compensation.

If respiratory failure is present and no improvement is seen with oxygen administration or head positioning for optimal air entry, the examiner should initiate assisted ventilation with a bag-mask device and proceed with ET intubation.

*Respiratory arrest* is the cessation of any breathing efforts, with complete failure of ventilation and oxygenation. Failure of tissue oxygenation because of desaturated hemoglobin leads to anaerobic metabolism and a metabolic acidosis. Failure of carbon dioxide removal caused by a lack of air exchange results in an accumulation of carbon dioxide and respiratory acidosis. This combination of severe hypoxia and respiratory acidosis can lead rapidly to cardiopulmonary failure and cardiac arrest, sometimes called *asphyxial arrest*. Frequent brief apneic episodes, especially in infants, can be a harbinger of full respiratory arrest. Agonal respirations also suggest respiratory arrest and are not normal efforts at respiration; they are also known to occur in the presence of cardiac arrest, including ventricular fibrillation.

### Circulatory Failure or Compromise (Shock)

Circulatory failure or shock is a clinical state characterized by failure of the cardiovascular system to perfuse vital organs adequately, resulting in inadequate oxygen and substrate delivery to meet the metabolic needs of the tissues and inadequate removal of waste metabolites. This state results in anaerobic metabolism and accumulation of acids. In shock, the blood contains an adequate amount of oxygen, but it is

delivered poorly. In respiratory failure, the blood is delivered adequately to the body tissues, but the blood delivered is deficient in oxygen. Both conditions can lead to tissue hypoxia, anaerobic metabolism, acidosis, and cardiopulmonary arrest.

Shock (inadequate perfusion) may occur with a normal, increased, or decreased cardiac output and BP. In compensated shock, the cardiac output may be high or low, but the BP is normal. In decompensated or hypotensive shock, the BP is low and the child is at imminent risk of deteriorating into full cardiac arrest.

Shock may be classified by cause as hypovolemic, cardiogenic, distributive, or obstructive. Hypovolemic and distributive shock are the most common types of shock in children and are characterized by an inadequate preload in the ventricles and thus an inadequate stroke volume. Because preload is determined primarily by the volume of blood in the ventricle, any condition that decreases this amount will result in decreased output. Dehydration, blood loss, dilation of the peripheral vasculature with peripheral pooling or redistribution of blood volume, and increased permeability of capillaries with water lost may all result in a diminished amount of blood reaching the heart and thus a diminished preload. Cardiogenic shock results from an intrinsic inability of the heart to pump out an adequate amount of blood, even when the amount of preload is sufficient. Examples are myocarditis, cardiomyopathies, rhythm disturbances that interfere with cardiac output, and a heart that has been compromised during cardiac arrest or cardiopulmonary bypass. Obstructive shock is caused by failure of blood to enter or exit the heart because of some sort of obstruction. Examples are cardiac tamponade (the atria are collapsed because of impingement by fluid in the pericardial sac), tension pneumothorax (obstruction of venous return to the heart), obstructed valves such as critical aortic stenosis, or massive pulmonary embolus.

As described previously, to determine the presence and severity of compromise or shock, the examiner should thoroughly evaluate the heart rate, BP, peripheral and central pulses, and skin perfusion (capillary refill and distal extremity color and temperature). In addition, the level of consciousness and ongoing urinary output can be helpful in determining the severity of circulatory failure.

Any time a lack of sufficient oxygen delivery to the brain exists, abnormal central nervous system examination findings may occur. Because oxygen delivery depends on the amount of oxygenated hemoglobin in the blood and the cardiac output, failure of cardiac output will diminish the amount of oxygen delivered. Irritability, agitation, clouding of sensorium, and eventually lack of responsiveness are all clinical symptoms consistent with poor perfusion of the brain with concomitant poor oxygen delivery.

Similarly, the failure of normal urine production may be secondary to inadequate perfusion of the kidneys. The normal urinary output is 1 to 2 mL/kg/hr and depends on normal blood flow to the kidneys. Although this measure is unavailable during the initial evaluation, ongoing assessment of the volume of urine



produced over time is a valuable indicator of the adequacy of kidney perfusion.

### Cardiopulmonary Failure or Cardiac Arrest

Cardiopulmonary failure is a failure of both the respiratory and circulatory systems. Progression of cardiopulmonary failure leads to agonal or gasping respirations, bradycardia, cyanosis, and ultimately cardiac arrest. A patient in cardiac arrest is entirely unresponsive, does not move, and does not make sounds, although agonal gasps may be present (not to be confused with respiratory effort). Most pediatric patients who develop cardiac arrest usually progress to it via cardiopulmonary failure and lack of oxygen delivery. Such arrests are called *asphyxial arrests*. However, up to 19% of out-of-hospital pediatric cardiac arrests occur suddenly from a cardiac arrhythmia, such as ventricular fibrillation. These episodes are primary cardiac arrests. In both types of arrests, the heart can no longer eject an adequate amount of blood either to the lungs for oxygenation or to the systemic circulation for distribution of oxygen and other nutrients. If no intervention occurs within 5 to 10 minutes, the child will either die or survive with serious neurologic and other sequelae.

## RESUSCITATION MANAGEMENT

### General Overview

A considerable amount of resuscitation research from the last 20 years has demonstrated that the more quickly a person in cardiopulmonary arrest is provided with basic CPR and defibrillation when indicated, the better the outcomes are. For this reason, the AHA recommends immediate bystander CPR and the use of an electrical device for defibrillation (when indicated) within 3 to 5 minutes of the cardiac arrest. Although this information is taken primarily from adult studies, if children are given the same speed and type of treatment, they will likely have similar outcomes. Moreover, the most recent resuscitation science demonstrates that immediate and proper BLS, particularly chest compressions at an appropriate rate and depth, without interruption and allowing for adequate chest recoil, is foundational to all CPR. Furthermore, resuscitation science of the last 5 to 10 years now supports the concept that chest compressions should be done first, before initiation of ventilation. Studies on bystander-initiated hands-only CPR in adults with out-of-hospital witnessed arrests have shown that the addition of ventilations does not improve survival and may also discourage bystander CPR. Although ventilation remains an essential part of pediatric CPR and improving survival, there has been international consensus since 2010 that instead of CPR being *initiated* with airway opening, ventilation, and then circulation/compressions (A-B-C approach), it should be initiated with immediate chest compressions after a pulse check for no longer than 10 seconds, followed by airway opening and administration of ventilations (C-A-B approach). Effectively, this delays the onset of ventilations only minimally (<18 seconds) and allows for rapid onset of cardiac compressions.

Given the critical importance of basic life support in improving survival from cardiac arrest, this appendix will emphasize BLS, providing the pediatrician with some familiarity with this important skill. Nevertheless, because this knowledge is insufficient to enable the physician to perform this psychomotor skill, all professionals who provide care to pediatric patients should undergo formal training in basic CPR (BLS) and refresh these skills at least every 2 years and preferably more frequently.

Added to the need for this basic CPR training is the need to be able to use automated external defibrillators (AEDs). These electrical devices enable even trained lay providers to give a defibrillatory shock to patients in cardiac arrest when necessary. Placement of AEDs in locations such as airports, casinos, public buildings, and, most recently, schools has contributed greatly to the survival of many people in sudden cardiac arrest, including children.

Care providers such as pediatricians, who might encounter seriously ill or injured children in their practice setting, should also be trained in the principles and skills of pediatric advanced life support. Such training includes proper recognition of seriously ill patients, the proper interventions for preventing a child from developing respiratory or cardiopulmonary arrest, and the skills necessary to provide full resuscitation if arrest ensues. The AHA, in conjunction with the AAP, has developed excellent and comprehensive pediatric advanced life support courses, which are available in AHA training centers around the world.

Finally, given the importance of early BLS and electricity in out-of-hospital pediatric arrest, these skills must be integrated into a community-wide emergency response plan that deals with children. Because children spend so much time in the school system, schools especially should have an emergency response plan in place, coordinated with the local emergency medical system, and with medical direction from pediatricians or family practitioners.

### Specific Recommendations

In 2015, an international group of resuscitation experts reviewed the world literature on CPR for the fourth time (the initial international review was in 2000) and developed a global consensus and conclusions on what types of resuscitation treatments have been shown to be effective in neonates, children, and adults (2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations, available at [www.circ.ahajournals.org/content/132/16\\_suppl\\_1.toc](http://www.circ.ahajournals.org/content/132/16_suppl_1.toc)).

Subsequently, similar to other resuscitation groups around the world, the AHA published formal practice guidelines based on these scientific recommendations and incorporated them into their courses. These practice guidelines were also published in the journal of the AHA, *Circulation*, available at [circ.ahajournals.org/content/132/18\\_suppl\\_2.toc](http://circ.ahajournals.org/content/132/18_suppl_2.toc).

The recommendations also emphasize the importance of following guidelines established by the US Occupational Safety and Health Administration (OSHA) to prevent transmitting disease from the victim to the rescuer, and they advocate the use of gloves and mechanical



ventilation equipment, including resuscitative masks, that divert expired air away from the rescuer.

### Basic Life Support

The AHA algorithm for pediatric BLS by health care providers is depicted in Figure A-1 and outlines the steps to be taken in providing pediatric basic CPR. Note that use of a mobile device to summon help is included. In addition, Table A-3 describes the BLS maneuvers and how they may differ among adults, children, and infants.

#### Step 1: Determining the Presence of Cardiac or Respiratory Arrest

If the child is unresponsive, the rescuer should shout for help and activate the Emergency Response System by mobile device (cell phone) if possible, requesting a defibrillator (either an AED or a manual defibrillator). Next, the rescuer should quickly check for breathing (gaspings is not considered breathing) with simultaneous checking for a pulse for no longer than 10 seconds. If there is no breathing but the pulse is definitely present, rescue breathing should be started at a rate of between 12 and 20 per minute. If both breathing and pulse are absent, the patient should be considered to be in cardiac arrest and chest compressions begun immediately. If nobody else is present, and if the length of time the child might have been in cardiac arrest or respiratory arrest is unknown, the rescuer should perform basic CPR for about 2 minutes before calling 911 (*phone FAST*). If the child is witnessed to have a sudden, unexpected cardiac arrest, ventricular fibrillation or ventricular tachycardia is highly likely, and obtaining a device that can defibrillate the child as quickly as possible is of paramount importance. Even before basic CPR is begun and if only a single provider is present, an immediate call to 911 or an equivalent emergency response system should be made to obtain the device and those who are trained in its use (*phone FIRST*).

#### Step 2: Checking the Pulse

For children older than 1 year, the carotid artery just lateral to the trachea or the femoral artery just below the inguinal ligament midway between the anterior iliac spine and the pubic tubercle should be palpated; for children younger than 1 year, the brachial artery in the upper medial arm should be palpated. Pulse checks are not recommended for the lay provider because they are often misinterpreted, resulting in withholding of cardiac compressions when they are indicated.

#### Step 3: Cardiac Compressions

Cardiac compressions should be started as soon as it is determined that there is no pulse (ventilations should not be initiated until 15–30 compressions have been given). For a child older than approximately 1 year, the heel of one hand should be placed on the lower sternum (avoiding the xiphoid process). The heel of the other hand may be placed over the first so as to have sufficient strength to compress the chest to approximately one-third to one-half of its anterior-posterior diameter. The child must be placed on a firm surface (backboard if the child is in a bed) so that the

ability to compress the chest adequately is not compromised. Compressions should be performed at a rate of at least 100, but no more than 120, compressions per minute, with attention paid not only to the depth of compression, but also to the adequacy of chest recoil after each compression. The heel of the hand should virtually come off the chest after each compression so that the chest can re-expand fully and the heart can fill with blood. The adequacy of chest compressions may be determined by ensuring that a femoral pulse can be felt with each compression; if the child has an arterial line, the intra-arterial pressure generated by each compression can be seen directly. The basic premise is to *push hard and push fast*. However, if compressions are performed too quickly, time may be inadequate for recoil of the chest, with failure of the heart to refill with blood because of inadequate venous return (which occurs during the recoil phase).

In infants, the optimal technique for chest compressions is to place both thumbs immediately below a line drawn between the 2 nipples (nipple or intermammary line) and encircle the chest with the palms and fingers of the hand, so that the fingers overlie the back. Compressing or squeezing the chest in this manner has been shown to result in better cardiac output than the long-taught 2-finger method, in which the third and fourth fingers are used to compress the anterior chest in the same location. The latter technique can be used if there is only 1 rescuer; however, with 2 rescuers, the chest encircling technique should be used.

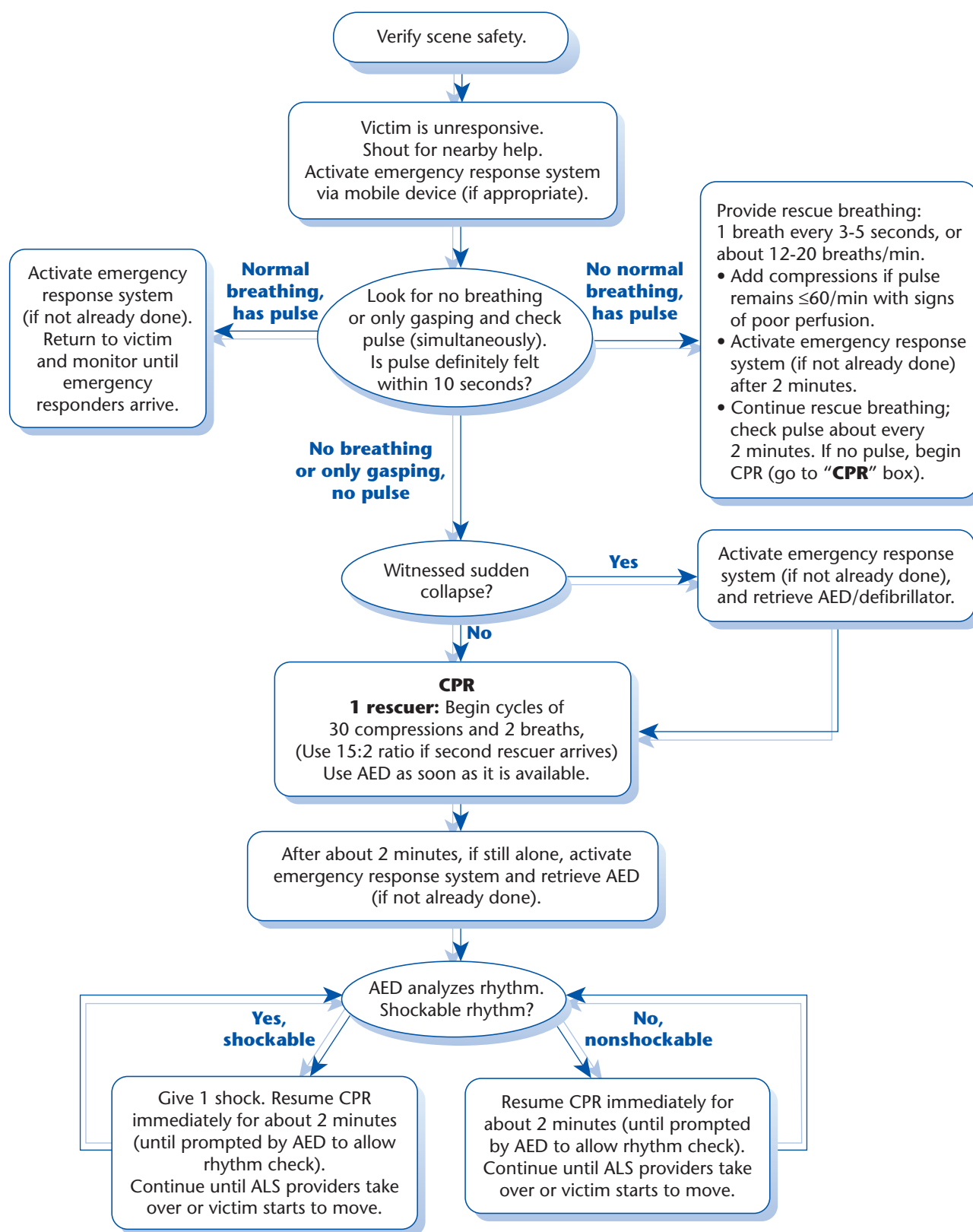
Compression of the chest is performed to enhance cardiac output, including coronary artery flow, either by direct cardiac compression (infants) or via a thoracic pump mechanism (blood flows out of the chest, heart, or aorta during compression and into the chest and heart during recoil). Therefore, attention to both the compression and recoil phases is important.

Since it is critically important for compressions to be done optimally (adequate depth, adequate rate, and adequate recoil) and with as little interruption as possible (goal: 80% of CPR time should be devoted to compressions), sensing devices interposed between the rescuer's hands and the chest wall are now available with integration of information about the depth, rate, and recoil into the monitor with visual and auditory feedback to the rescuer about compression adequacy.

In intubated patients in cardiac arrest, it is strongly recommended by the AHA that a capnograph be attached to the ET tube to measure end-tidal  $\text{PCO}_2$ . If it is less than 10 to 15 mm Hg, cardiac compressions should be done deeper, faster, and with better chest recoil, with a goal of 20 mm Hg. A sudden increase to a normal  $\text{PCO}_2$  indicates return of spontaneous circulation; CPR should be stopped and a rhythm check done.

#### Step 4: Opening the Airway and Initiating Ventilation

Once 30 compressions (single rescuer) or 15 compressions (2 rescuers) have been performed, the airway should be opened by tilting the head back slightly by pushing on the forehead with one hand and pulling



**Figure A-1** BLS health care provider pediatric cardiac arrest algorithm for the single rescuer—2015 update. (From American Heart Association. 2015 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 11: basic life support and cardiopulmonary resuscitation quality. *Circulation*. 2015;132:S519–S525. © 2015 American Heart Association, Inc. Reprinted with permission.)

**Table A-3** Summary of High-Quality CPR Components for BLS Providers

COMPONENT	ADULTS AND ADOLESCENTS	CHILDREN (AGE 1 YEAR TO PUBERTY)	INFANTS (AGE LESS THAN 1 YEAR, EXCLUDING NEWBORNS)
Scene safety	Make sure the environment is safe for rescuers and victim		
Recognition of cardiac arrest	Check for responsiveness No breathing or only gasping (ie, no normal breathing) No definite pulse felt within 10 seconds (Breathing and pulse check can be performed simultaneously in less than 10 seconds)		
Activation of emergency response system	If you are alone with no mobile phone, leave the victim to activate the emergency response system and get the AED before beginning CPR Otherwise, send someone and begin CPR immediately; use the AED as soon as it is available	<b>Witnessed collapse</b> Follow steps for adults and adolescents on the left <b>Unwitnessed collapse</b> Give 2 minutes of CPR Leave the victim to activate the emergency response system and get the AED Return to the child or infant and resume CPR; use the AED as soon as it is available	
Compression-ventilation ratio <i>without advanced airway</i>	<b>1 or 2 rescuers</b> 30:2	<b>1 rescuer</b> 30:2 <b>2 or more rescuers</b> 15:2	
Compression-ventilation ratio <i>with advanced airway</i>	Continuous compressions at a rate of 100–120/min Give 1 breath every 6 seconds (10 breaths/min)		
Compression rate	100–120/min		
Compression depth	At least 2 inches (5 cm) <sup>a</sup>	At least one-third AP diameter of chest About 2 inches (5 cm)	At least one-third AP diameter of chest About 1½ inches (4 cm)
Hand placement	2 hands on the lower half of the breastbone (sternum)	2 hands or 1 hand (optional for very small child) on the lower half of the breastbone (sternum)	<b>1 rescuer</b> 2 fingers in the center of the chest, just below the nipple line <b>2 or more rescuers</b> 2 thumb-encircling hands in the center of the chest, just below the nipple line
Chest recoil	Allow full recoil of chest after each compression; do not lean on the chest after each compression		
Minimizing interruptions	Limit interruptions in chest compressions to less than 10 seconds		

<sup>a</sup>Compression depth should be no more than 2.4 inches (6 cm).

AED, automated external defibrillator; AP, anteroposterior; BLS, basic life support; CPR, cardiopulmonary resuscitation.

From American Heart Association. *Web-based integrated 2010 & 2015 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 5: adult basic life support and cardiopulmonary resuscitation quality*. Reprinted with permission. © 2015 American Heart Association, Inc.

the chin or mandible forward with the other hand (head tilt/chin lift maneuver). In all trauma patients, or if the head tilt/chin lift maneuver is unsuccessful in patients without trauma, a jaw thrust should be performed instead by placing the index and third fingers of both hands under the angle of the mandible and pushing anteriorly or upward. (The neck should be kept in a neutral position if the child is a trauma victim.) If the jaw thrust is unsuccessful in trauma patients and the airway is still not open, a head tilt/chin

lift maneuver may be performed carefully, but only sufficiently to allow air entry with ventilation. In an infant, no hyperextension of the neck should occur, given that this action may collapse the very compliant airway or trachea. Instead, the infant's head position should be neutral and placed in the sniffing position.

Mouth-to-mouth or bag-mask ventilation must be instituted by giving two 1-second breaths, each just effective enough to make the chest rise. With an infant, the rescuer should give mouth-to-mouth

ventilation by covering the mouth and nose of the infant with the rescuer's own mouth; in the older child, the rescuer pinches the nose and seals the patient's mouth with the rescuer's own mouth. The rescuer delivers puffs of air given over 1 second, breaking the mouth seal after each puff to allow the patient to exhale. The breath should be just sufficient to cause the chest to rise, given that excess ventilation volume and time may interfere with venous return. Using this volume of air and puffs prevents gastric distention in the patient and should still allow air to enter the lungs freely. The most common reason for inadequate air entry is improper head positioning resulting in a partially obstructed upper airway; it should be readjusted and mouth-to-mouth breathing repeated.

If a pocket mask or a ventilation bag (with 100% oxygen) with mask is used, the mask must fit properly over the nose and mouth with a tight seal so that no leakage of air (and thus an inability to provide an adequate breath) occurs.

Anterior cricoid pressure (using 1 fingertip in infants or the thumb and index finger in children to put pressure on the anterior trachea just below the cricothyroid membrane) is *no longer recommended* in the 2015 AHA guidelines. During basic CPR as a standard maneuver to occlude the proximal esophagus and prevent entry of air into the stomach. However, it may be considered if there is inadequate air entry and to help visualize the glottis in infants and young children during ET intubation.

If the chest still does not rise even after proper positioning to open the airway and attempts at ventilation, a foreign body lodged in the upper airway should be suspected. The rescuer should perform a Heimlich maneuver (abdominal thrusts) in children over 1 year of age, or back blows alternating with chest thrusts in infants. In children older than 1 year, the child is positioned supine, and the rescuer performs rapid and short upward pushes (abdominal thrusts) with the heel of the hand in the central upper part of the child's abdomen (below the xiphoid process but above the umbilicus) until the object is expelled. The examiner should inspect the mouth every 5 to 10 abdominal thrusts to see if a foreign body can be manually removed. Blind finger sweeps should not be performed because the risk of pushing an object down further is increased. If the patient remains unresponsive, CPR should be resumed. In children less than 1 year (infant), the infant is straddled over the rescuer's forearm, the head positioned lower than the trunk, and the jaw held open by the rescuer's fingers, and up to 5 back blows with the heel of the hand are delivered between the shoulder blades. If this action does not remove the foreign body, the infant should be turned over so that the head, neck, and back are well supported on the rescuer's forearm. Up to 5 chest thrusts similar to cardiac compressions, but deeper, should be given. Alternate 5 back blows with 5 chest thrusts until the foreign body is expelled (the mouth is inspected periodically). If no response occurs, basic CPR is continued.

In children who have a tracheostomy and who are not breathing or are unresponsive, ensuring a patent airway is essential. Attempts to provide breath via

mouth-to-tracheostomy or bag-to-tracheostomy should be initiated. If no chest rise ensues, the tracheostomy may be obstructed or dislodged. Immediate tracheal suctioning should be performed. However, if tracheal suctioning cannot be accomplished rapidly, the tracheostomy should be removed, a small roll should be placed under the shoulders (if available), and either a fresh tracheostomy should be inserted or a breath given by sealing the mouth over the stoma and blowing into it. If no chest rise is observed, the stoma should be occluded and breaths provided via the nose or mouth.

**COMPRESSION/VENTILATION RATIO.** Given that current science has shown that continuous and effective cardiac compressions with minimal interruptions are necessary to maintain coronary blood flow to the myocardium, a compression/ventilation ratio of 30 compressions to 2 ventilations should be used for single-rescuer CPR for all ages except neonates who remain hospitalized after birth in neonatal intensive care units. Although this ratio is to be maintained for single- and 2-rescuer CPR in adults and children who have reached puberty, as well as for lay providers who are performing CPR in all age groups, a ratio of 15 compressions to 2 ventilations is recommended when 2 health care providers are providing basic CPR to a prepubertal child (approximately 12 years of age or younger), including infants.

Because maintaining adequate chest compressions for a long time period is difficult for an individual, compressors should be changed approximately every 2 minutes.

Although these ratios should be maintained in an infant or child who does not have a definitive airway, once an ET tube is in place, continuous compressions should be maintained at a rate of between 100 and 120 compressions per minute and ventilations at a rate of 10 ventilations per minute (1 every 6 seconds) without an effort to coordinate them.

### Step 5: Defibrillation/AED Use

Defibrillation of a shockable rhythm should occur within 3 minutes of the event for best results. Thus, if the defibrillator or AED has arrived, pads should be placed immediately on the patient and an analysis of the rhythm should be performed. If a shock is advised by the AED or if the manual defibrillator shows a shockable rhythm (ventricular fibrillation or ventricular tachycardia), a single shock should be delivered and CPR should be resumed immediately for another 2 minutes before another rhythm check is undertaken. If there is only a single rescuer, after 2 minutes of CPR the rescuer should try to alert the emergency response system and attempt to get a defibrillator.

### Step 6: Rhythm Checks

A rhythm check should be done after every 2 minutes of CPR to determine if there is a shockable rhythm or if a perfusing rhythm has returned. If there is a perfusing rhythm, a pulse check should be done before continuing with CPR.

### Automated External Defibrillation

Although most cardiac arrests in children are from noncardiac causes, a substantial number of children



with out-of-hospital cardiac arrest (15%–20%) are known to have sudden onset of ventricular fibrillation or ventricular tachycardia. These children have a variety of conditions, including prolonged QT interval or other channelopathies, hypertrophic cardiomyopathy, myocarditis, repaired congenital heart defects with postsurgical dysrhythmias, toxic ingestions, and *commotio cordis*. The last of these conditions is a sudden episode of ventricular fibrillation or ventricular tachycardia resulting from a sharp blow to the chest, such as might occur in baseball, lacrosse, hockey, or other sports during which flying objects might impinge on the chest. Because these sports are played in many high schools around the country, attention has been increasingly focused on ways to treat ventricular fibrillation arrests in children within the 3 minutes recommended by the AHA. As demonstrated in adult studies and seen in many individual patients, including children and adolescents, the best outcomes from sudden cardiac arrest occur when bystander CPR is initiated immediately coupled with early defibrillation, preferably within 3 minutes of cardiac arrest. Given that this combination has been shown to result in 50% to 60% or better survival from sudden cardiac arrest (usual survival is <5%) in adults, widespread availability of both bystander CPR training and AEDs has been strongly encouraged. In fact, as the use of AEDs has become more widespread and available, training in the use of these devices has been added to many of the basic CPR courses taught to laypersons. Given the increased recognition that children also experience cardiac arrest from ventricular fibrillation, efforts have been initiated to develop AEDs that are safe to use in children. In addition, because sudden episodes of ventricular fibrillation in adolescents are known to happen in schools, especially during athletic activities, making AEDs available in schools has been advocated. New York State took the lead in this effort by passing a law in 2001 requiring AED devices to be available in all schools with more than 500 students, giving specific instructions as to their location and quantity, and the need to have them available at all school sports events.

An AED device is a portable system consisting of chest pads, a cable, a biphasic current-generating device using (generally) a fixed voltage, a computer that can sense and analyze ECG rhythms, and a voice generator for providing appropriate instructions to the operator. Audible instructions to the operator are simple and sequential, including a sequence such as “Attach pads”; “Insert connector”; “Analyzing rhythm. Do not touch the patient”; “Shock advised [or not advised]”; “Charging”; “Press the orange button”; “Shock delivered”; and “If necessary, start CPR.” Although previously AEDs were programmed to deliver 3 shocks in succession, they have been reprogrammed to reflect the AHA guidelines that only 1 defibrillation shock should be given each time.

Although AEDs have a fixed voltage of between 120 and 200 joules (much more than the 2–4 joules/kg recommended for children), they can be used safely in children and even infants with some adaptations. Based on the 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency

Cardiovascular Care Science with Treatment Recommendations, the AHA has made the following recommendations:

1. For patients from 1 to 8 years old (up to 25 kg), an AED that is equipped with pediatric cables (containing a resistor limiting the shock to 50 joules), and that shows both a high degree of specificity (100%) for recognizing normal rhythms and sensitivity for diagnosing shockable rhythms, should be used if at all possible. If these features are not available, an AED with adult cables may be used (gives 150–200 joules).
2. For patients weighing 25 kg or more (over 8 years of age), a standard AED should be used.
3. For infants, there is now sufficient scientific evidence to recommend a pediatric-capable AED and, if this is not available, use of a standard AED.

Although not well tested as to improving outcomes, a significant number of hospitals and medical centers are beginning to place AEDs on general inpatient units (including children’s units), lobbies, and cafeterias, among other locations, as it becomes clearer that trained nonphysician staff can use these devices effectively and respond more quickly than conventional hospital code teams led by physicians.

### Advanced Life Support

When pediatric BLS measures, such as CPR, are ineffective in resuscitating and stabilizing affected infants and children, advanced life support should be initiated immediately using the most current AHA guidelines. Advanced life support includes improved airway access and management, administration of oxygen, vascular access, administration of fluids and electrolytes, and drug therapy. To implement these measures, the physician must be familiar with the ranges of weight and vital signs for children (see Table A-2) and the guidelines for use of resuscitation equipment of various sizes according to the patient’s age and weight (Table A-4). Use of a length-based pediatric emergency tape to determine appropriate drug doses and equipment based on size has been validated and is useful for children, particularly those weighing less than 25 kg. The child’s approximate weight is determined by measuring the child’s recumbent length.

### Respiratory Management

The purpose of respiratory management is to provide and maintain adequate oxygenation and ventilation to meet the body’s metabolic requirements.

**OXYGEN ADMINISTRATION.** The correction of tissue hypoxia is fundamental to the management of all critical illness and injury and also to resuscitation. Tissue oxygenation depends on adequate oxygen delivery into the alveolar spaces of the lungs, ability to bind to hemoglobin as blood circulates through the alveolar capillaries, an adequate amount of hemoglobin in the blood, an adequate cardiac output, and ability to release oxygen from hemoglobin to the tissues. Thus, even if an airway with appropriate ventilation exists, a sufficient supply of oxygen must still be available to bind to hemoglobin, particularly when tissue oxygen demands are significant. Normally,

Table A-4 Pediatric Resuscitation Equipment Sizes

AGE	WEIGHT (KG)	ETT INT DIAM (mm)	LARYNGOSCOPE BLADE (NO.)	ETT SUCTION CATHETER (FRENCH)	ETT DISTANCE FROM		CHEST TUBE (FRENCH)	VENOUS CATHETER (GAUGE)	FOLEY CATHETER NASOGASTRIC TUBE (FRENCH)
					MIDTRACHEA TO TEETH (cm)				
Newborn, premature	<1	2.5	0	5 or 6	8		10–1	22–24	5
Newborn, full-term	3	3.0 ± cuff <sup>a</sup>	1	6	10		12–18	22–24	6
6 mos	7	3.5 ± cuff	1	8	12		14–20	22–24	8
1 yr	10	4.0 ± cuff	1	8	12		14–24	20–22	10
18 mos	11	4.0 ± cuff	1	8	14		14–24	20–22	10
3 yrs	14	4.5 ± cuff	2	8	16		18–26	20–22	10
5 yrs	18	5.0 ± cuff	2–3	10	16		20–32	20–22	10–12
8 yrs	25	6.0 cuff	3	10	18		28–34	20–22	12
10 yrs	34	6.5 cuff	3	10	18		30–38	18–20	12
12 yrs	38	6.5–7 cuff	3	10	20		34–38	18–20	12–14
16 yrs	55	7.5–8 cuff	3	12	22		34–38	18–20	12–14
Adult		8–8.5 cuff	3	12	22		34–38	18–20	12–14

Cuff, cuffed endotracheal tube; ETT, Endotracheal tube

<sup>a</sup>If cuffed tube is used, decrease size by 0.5 mm.

when a person breathes room air (21%  $\text{FiO}_2$ ), the  $\text{PO}_2$  is approximately 100 mm Hg. Mouth-to-mouth breathing delivers only 16%  $\text{FiO}_2$  and results in an intra-alveolar oxygen tension ( $\text{PO}_2$ ) of only 64 mm Hg. Given a higher oxygen demand in critical illness, oxygen is indicated in any situation in which a significantly inadequate amount of oxygen is bound to hemoglobin (oxygen saturation less than approximately 90%–91%), tissue hypoxia is suspected even in the presence of a high oxygen saturation (eg, if there is poor cardiac output or severe anemia), or respiratory distress is significant.

Oxygen can be administered by blow-by nasal cannula (up to 50%–60%  $\text{FiO}_2$ ), face tent, partial rebreather mask (up to 70%  $\text{FiO}_2$ ), non-rebreather mask (90%–100%  $\text{FiO}_2$ ), or a Venturi mask with fixed concentrations of oxygen based on flow. If the child has any possibility of a serious illness or injury or is being resuscitated from a respiratory or cardiac arrest, 100% oxygen should be provided by either a non-rebreather mask (making sure the reservoir bag is at least partially full); with a free-flowing oxygen anesthesia bag with mask fitting snugly over the child's nose or mouth; or with positive-pressure breaths, if necessary, with a self-inflating bag and 10- to 15-L/min flow of 100% oxygen and a reservoir (most do not deliver oxygen spontaneously unless the bag is compressed). Although for acute management and a short time period, nonhumidified, cold oxygen is adequate, for longer-term oxygen administration, the oxygen should be humidified and preferably warmed to room temperature. If assisted ventilation is necessary to provide oxygen and the child is breathing, the breaths should be synchronized with the child's so that the risk of gastric inflation is reduced. When a self-inflating bag is used, the pop-off valve should be occluded, because the pressures needed to ventilate the lungs may exceed the valve's limit (usually set at approximately 45 cm  $\text{H}_2\text{O}$  pressure).

**AIRWAY ADJUNCTS.** For children who have inadequate air entry into the chest despite head tilt/chin lift or jaw thrust maneuver, airway adjuncts may be helpful. Nasopharyngeal and oropharyngeal airways can stent open the upper nasopharynx or oropharynx; an ET tube can provide an unobstructed airway directly from the nose or mouth into the trachea, and a laryngeal mask airway device, placed into the hypopharynx or upper esophagus, can effectively direct oxygen through the glottis without it going into the esophagus (the inflated cuff obstructs the upper esophagus).

**OROPHARYNGEAL AND NASOPHARYNGEAL AIRWAYS.** An oropharyngeal airway may be used in an unconscious patient to prevent the tongue from occluding the pharynx. It should not be used in conscious patients, because significant gagging and vomiting may occur. When placed next to the child's mandible, a proper-sized oropharyngeal airway should extend from the anterior gums or incisors (flange) to the angle of the jaw (tip). Insertion is accomplished by depressing the tongue with a tongue depressor and inserting the airway into the mouth or pharynx in the position of function. If the airway is too large, it may impinge on the epiglottis and close the airway or injure it; if the airway is too small, it may push the tongue back into the oropharynx and occlude it.

If the patient is semiconscious, or if placing an oropharyngeal airway is impossible (eg, during grand mal status epilepticus), a nasopharyngeal airway may be inserted. The proper length of a nasopharyngeal airway is determined by measuring the length from the tip of the nose to the tragus of the ear, and the width is similar to the width of the nares. Care must be taken during insertion because hypertrophied adenoidal tissue is common in young children and can bleed when traumatized. Because obstruction of nasopharyngeal airways with mucus and blood can occur, periodic suctioning with a flexible suction catheter should be performed to maintain patency.

**SUCTIONING.** Suctioning of the oropharynx should be accomplished quickly and with a large-bore suction device. Yankauer or tonsil suction devices are rigid but available in both adult and pediatric sizes. They are designed to suction vomitus and other large secretions out of the posterior pharynx quickly. Large (14 French) flexible suction catheters can be used in infants to accomplish this function, but flexible suction catheters are intended primarily for nasopharyngeal and ET suctioning. Generally, suctioning should be performed for no longer than 5 to 10 seconds because vagal-induced bradycardia from stimulating the posterior pharynx may occur and oxygen may be removed by suctioning via the ET tube. Continuous monitoring of the heart rate during suctioning in a critically ill patient is useful for early recognition of bradycardia.

**Endotracheal Intubation of Airway.** Although ET intubation is critically important in a child who is in respiratory failure (inadequate ventilation or oxygenation), it is less urgent in a child who can be easily oxygenated and ventilated either on his own with supplemental oxygen, by bag-mask ventilation, or by noninvasive ventilation (eg, Bilevel Positive Airway Pressure [BiPap]). Particularly in a child who is in cardiac arrest, persistent and uninterrupted (no more than 10 seconds) cardiac compressions are more important than ET intubation (compressions have to be interrupted while intubation proceeds) as long as ventilation and oxygenation remain adequate. In addition, although resuscitation medications (lidocaine, epinephrine, atropine, naloxone) can be given through the ET tube if no other route is available, resuscitation medications by intravascular or IO routes are preferable. Medications given down the ET tube are variably absorbed, and there is little scientific evidence to indicate proper dosing. However, if a child cannot be oxygenated adequately despite high concentrations of oxygen, ET intubation should be considered early.

ET intubation should be accomplished by the available person with the most intubation expertise. The procedure should be preceded by oxygenation with 100%  $\text{FiO}_2$ , either by non-rebreather mask or by assisted ventilation with a bag-mask device delivering 100%  $\text{FiO}_2$ . If the patient is awake, sedation and muscle relaxants should be administered by persons properly qualified to perform this task to enable safe and efficient intubation. Of note, etomidate is an excellent drug for sedating a child who needs to have an ET tube placed, because it causes little hemodynamic instability. However, it should *not* be used if there is a possibility that the child has sepsis, because even a single dose can

significantly depress adrenal function, resulting in hypotension and hypocortisolism for 24 to 48 hours. If the child is in cardiac arrest, medications are not necessary.

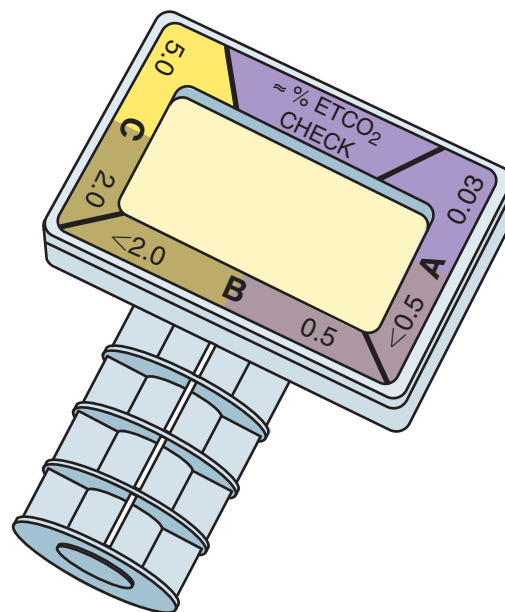
Before intubation, the operator should put on gloves, a mask, and preferably goggles to prevent self-contamination with secretions. Equipment at the bedside should include a working and proper-sized bag-mask device; oropharyngeal suction equipment (Yankauer); ET suction catheters to suction out the ET tube; a working and proper-sized laryngoscope blade; proper-sized ET tubes, including cuffed tubes; a stylet; an end-tidal PCO<sub>2</sub> detector or capnometer or capnograph; and tape or benzoin. For the potentially difficult airway, ancillary equipment should be considered, such as laryngeal mask airway devices, a videolaryngoscope, ET bougies, and a needle cricothyrotomy setup.

The ET tube should be translucent, of uniform diameter (not tapering), and equipped with a standard 15-mm adapter; preferably the tube should have distance markers and an opening on its side wall (Murphy tube, not in neonates), as well as at its end. Cuffed ET tubes may be used at all ages, but a cuffed tube size that is 0.5 to 1 mm less than an orotracheal tube for young children should be considered. An air leak with an uncuffed ET tube should be present when a breath is given at 20 cm H<sub>2</sub>O pressure; if it is not, the tube is too large and should be replaced with a smaller tube. Although the proper-sized tube should be determined by checking a size-based chart or tape, the proper-sized *uncuffed* ET tube may also be determined by its internal diameter as follows: term neonate: 3.0 mm; 6-month-old: 3.5 mm; 1-year-old: 4.0 mm; 1- to 12-year-old: [(age in years ÷ 4) + 4] mm. The depth of the ET tube is determined by multiplying the size of the tube by 3 and having this number at the gum line/teeth. If a *cuffed* ET tube is used, the size of the tube is determined as follows: up to 1 year: 3.0 mm; 1 to 2 years: 3.5 mm; after 2 years: [(age in years ÷ 4) + 3.5] mm. Cuffed ET tubes may be used in children younger than 8 to 10 years who are in a hospital setting, because they have been shown to be as effective and safe as uncuffed ET tubes (class 1). Whether such is the case in an out-of-hospital setting is unknown.

Straight-blade laryngoscopes to visualize the larynx are preferred in children, given that the larynx is quite anterior and the glottis may not be seen unless the epiglottis is lifted. Before laryngoscopy is begun, the examiner should check the equipment and the light source. Attempts at ET intubation should not exceed 30 seconds, and the heart rate and oxygenation should be monitored during the procedure. Bradycardia below 80 bpm in a neonate or 60 bpm in a child mandates interruption of the procedure and administration of 100% oxygen by face mask and bag. The ET tube should be passed into the trachea to a length that places the distance marker at the level of the vocal cords.

Once intubation has been established, the ET tube should be held securely in position, an end-tidal PCO<sub>2</sub> detector (Figure A-2) attached, and the patient ventilated with a bag (100% oxygen).

The ET tube position is confirmed by observing symmetrical movements of the chest, auscultating the apical and axillary lung fields to detect bilateral breath



**Figure A-2** End-tidal CO<sub>2</sub> detector.

sounds, auscultating over the stomach to ensure that air entry sounds are absent, demonstrating persistent evidence of carbon dioxide exhalation (color change) after 6 breaths. A colorimetric end-tidal PCO<sub>2</sub> detector is not reliable in the presence of cardiac arrest (insufficient PCO<sub>2</sub> delivered to the lungs) and should not be used as the primary way to confirm proper placement of the ET tube. Visual inspection of the vocal cords for evidence that the ET tube is in the proper location will be more helpful in this situation. However, during a cardiac arrest, a capnograph should be attached to the ET tube for a continuous objective readout of exhaled PCO<sub>2</sub>. This will allow for better assessment of the adequacy of cardiac compressions.

Asymmetrical right-sided breath sounds usually indicate intubation of the right main bronchus. When this occurs, the tube should be withdrawn until breath sounds are heard bilaterally; the ET tube should then be withdrawn another 1 to 2 cm (depending on the size of the patient; an infant has a very short trachea) to ensure a midtracheal position, keeping in mind the optimal depth of the tube by the measurement at the gums (3 times the width of the ET tube). The final position of the ET tube must be confirmed by chest radiograph.

A properly placed tube, but inadequate chest expansion, may indicate that the tube is too small or that a large laryngeal air leak is present (detected by auscultating the anterior neck), the *pop-off* valve on the ventilator bag is not disabled so that air escapes when the preset pressure is reached, the bag-valve device leaks, or the breath administered is too small.

The position of the tube should be verified by noting the distance marked on the tube at the gums; it should be secured to the patient's face with benzoin and tape. Its position should be assessed frequently by observing



chest wall expansion, listening for bilateral breath sounds, and noting improvement of color and perfusion, obtaining blood gas values, and checking pulse oximeter readings.

Esophageal detector devices may be used for confirmation of appropriate ET tube placement in children who weigh at least 20 kg and who have a perfusing rhythm. However, given that no information about the efficacy of these devices in children who are in cardiac arrest is available, they are not recommended for use in this situation.

Once an infant or child in cardiac arrest has had an ET tube placed, 1-second ventilations should be given no faster than 8 to 12 breaths per minute. Excessive ventilation may be detrimental to outcome from cardiac arrest because positive-pressure ventilation interferes with the venous return necessary for refilling of the heart during the recoil phase of compressions. Once spontaneous circulation has been re-established, the rate of ventilations should be 12 to 20 breaths per minute for all ages.

Drugs may be administered through the ET tube while vascular access is sought. These drugs are lidocaine, epinephrine, atropine, and naloxone (LEAN). Double to triple the usual IV dose (diluted in 1 to 2 mL of 0.9% saline or followed by a 5-mL normal-saline flush) is administered through a catheter that has been passed beyond the ET tube as deeply as possible into the tracheobronchial tree. The dose of epinephrine, however, should be 10 times the IV dose (0.1 mg/kg using a 1:1,000 solution), except in neonates, where it may be 0.05 to 1 mg/kg. After the drug has been instilled, at least 5 manual positive-pressure breaths should be given to distribute the medication throughout the lung fields.

Even after an ET tube has been placed successfully, sudden problems can occur with the airway with inadequate oxygenation and ventilation. An easy way to evaluate the cause of the problem is to use the mnemonic DOPE: Displacement, Obstruction, Pneumothorax, and Equipment. The gas delivery system (if the child is being mechanically ventilated) should be disconnected, and the patient should receive manual ventilation by means of a resuscitation bag and use of 100% oxygen. Auscultation should be used to determine the tube's position and patency. Decreased resistance to inflation occurs when the ET tube has been misplaced into the esophagus, with a gurgling sound often present. Corroboration of tracheal placement of the ET tube can be accomplished with an end-tidal PCO<sub>2</sub> detector in a nonarrested patient. If the tube has slipped down one of the main bronchi (usually the right), no or diminished breath sounds on the opposite side will be heard. If obstruction is the problem, poor breath sounds, a lack of chest movement, and increased resistance to inflation are observed. The ET tube can be either kinked or obstructed. If obstructed, 1 to 3 mL of saline should be instilled, bagging should be attempted to irrigate the tube and break up mucous plugs, and then suctioning of the ET tube should be performed for 5 to 10 seconds. After suctioning, the breath sounds, airway resistance, and adequacy of chest movements should be re-evaluated. If proper positioning and adequate manual ventilation of the ET

tube are ensured and no asymmetric breath sounds are heard, problems with equipment, including the oxygen source, should be considered. If ventilation cannot be re-established with chest rise and improved oxygenation, the ET tube should be removed, the child should be ventilated with 100% oxygen, and a new ET tube should be inserted. If the child has asymmetric breath sounds, a pneumothorax may be present on the side without breath sounds, and urgent needle thoracentesis needs to be considered. A needle catheter is placed in the second intercostal space in the midclavicular line on the side without breath sounds, and the catheter is aspirated with a syringe. Aspiration of air suggests a pneumothorax, and plans for chest tube insertion should be initiated immediately.

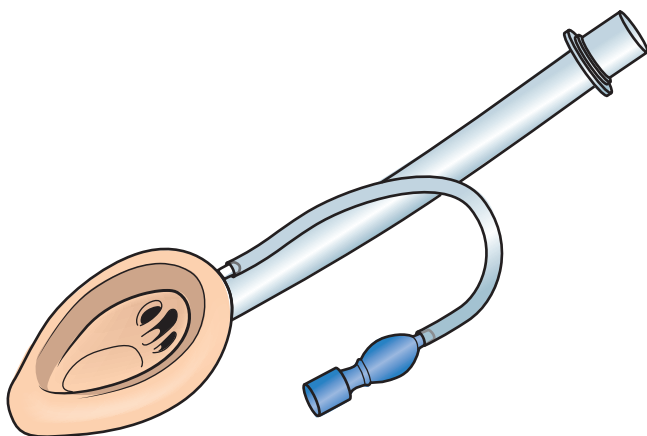
**CRICOTHYROTOMY.** If ET intubation is not an option or cannot be accomplished, and if no air entry is attained after airway positioning and ventilation, a needle cricothyrotomy may be attempted. A roll is placed underneath the shoulder, and the head is hyperextended so that the larynx is brought anteriorly. A large-bore needle catheter (14–16 gauge) is placed with its bevel caudally directed, midline, just below the thyroid cartilage in the cricothyroid membrane. A syringe is attached, and while the needle-catheter is advanced, continuous aspiration is performed. Entrance into the trachea is indicated by aspirating air, and the catheter should be advanced, similar to cannulating a blood vessel. Either the adapter from a small ET tube can be attached directly to the catheter hub or the barrel of a 3-mL syringe can be attached, with an oxygen tube under high pressure inserted into the barrel. By providing a continuous inflow of oxygen through the catheter, oxygen can be supplied for a short time period (<20 minutes). Ventilation cannot occur through this type of setup, and a surgical tracheostomy should be performed as soon as possible.

In patients younger than 8 years, airway obstruction may occur at the cricoid ring, the narrowest portion of the larynx in this age group. Because the ring is located below the cricothyroid membrane, cricothyrotomy may not be effective in establishing an airway.

**LARYNGEAL MASK AIRWAY DEVICE.** A laryngeal mask airway device (Figure A-3) is placed blindly into the hypopharynx or upper esophagus so that air or oxygen can be directed anteriorly into the glottis, but will not enter the stomach. These airway devices are available in different sizes, are suitable even for neonates, and may be useful for children who require an artificial airway for short-term management or who are difficult to intubate (eg, children with mandibular hypoplasia). Children seem to have a higher incidence of complications with these devices than adults, and only trained providers should insert them. In addition, they have not been tested for safety or efficacy in a prehospital (emergency medical system) setting or in patients in cardiac arrest (class IIb).

### Circulatory Management

The basic purpose of circulatory management is to maintain sufficient cardiac output to deliver appropriate amounts of oxygen and other nutrients to the



**Figure A-3** Laryngeal mask airway.

tissues, especially to the vital organs—the heart, the brain, the kidneys, and the splanchnic bed.

Cardiac output and perfusion depend on an adequate amount of preload (end diastolic volumes of the heart), good cardiac contractility and heart rate, and appropriate afterload (the resistance against which the heart has to eject its blood). All circulatory management is directed toward optimizing each of these factors, starting with preload, then addressing cardiac contractility or rate, and finally manipulating afterload.

**VASCULAR ACCESS.** Given that circulatory management in a critically ill patient involves the use of both fluids and medications, venous access should be established as quickly as possible. Antecubital veins—the lesser saphenous vein just above the medial malleolus and external jugular veins—are excellent veins to attempt if more peripheral hand and foot veins are not palpable. Scalp veins are generally not recommended, because insertion into them often will interfere with airway management, and even external jugular veins may complicate simultaneous airway management. In patients who are in cardiac arrest or decompensated shock, or who require rapid initiation of infusion of fluids or medications, an IO line should be used if vascular access cannot be established after approximately 90 seconds. The IO space is a plexus of noncollapsible veins in continuity with the central venous circulation. Any type of fluid or medication may be infused through an IO line, including blood products, calcium, and glucose. Most providers will find placing an IO device faster and easier than cannulating a central vein, even when such a vein is accessible (eg, the femoral vein).

IO access may be obtained in patients of all ages, including newborns in the delivery room and adults. The most common site selected is the flat part of the proximal tibia, a few centimeters below the tibial tuberosity, but other sites for IO infusion include the distal tibia just above the middle malleolus, the distal part of the femur just above the patella, the anterior iliac crest, and, in older children, the proximal humerus. A line should not be placed in a fractured bone or in a bone in which an attempt at an IO line

has already been made. (If a hole exists into the bone from the previous attempt, fluid from a new line in that bone will leak out into the soft tissues.) The typical IO needle is 15 gauge in caliber, although in infants even 18- to 21-gauge spinal needles have been used. The needle should have a trocar or stylet within, so that bone fragments do not occlude the needle during placement. Battery-powered drills with preset needle depth are now available to allow for easier insertion.

Because resistance to flow via the IO route may be high, infusions may require pressure bags, pumps, or manual infusion by syringe. In addition, IO lines should be carefully secured, because they are easily dislodged. Constant assessment of the soft tissues at the site of the IO infusion device should also occur, given that dislodgement can result in significant extravasation. IO lines are only for short-term use and should be removed within 6 hours if at all possible to avoid a complicating bone infection.

**FLUIDS.** Most children who are in shock will have a deficit in intravascular volume because of lack of fluid from water losses (eg, diarrhea or excess urine output), from inadequate fluid intake, or from blood loss. Given the deficit in intravascular volume, these children will have a diminished preload and decreased cardiac output (stroke volume multiplied by heart rate/min). Rapid infusion of a 20-mL/kg bolus of fluid within 10 minutes with re-evaluation during and immediately after infusion will quickly determine whether lack of intravascular volume is the problem. In a child who shows signs of circulatory compromise with tachycardia, prolonged capillary refill, and decreased peripheral pulses, a response to such a rapid infusion with a decrease in heart rate and improved pulses and capillary refill suggests that preload was not adequate and now has improved. Further boluses of fluid may be warranted depending on the degree of improvement found. A child who is in hypovolemic shock often requires 40 to 60 mL/kg of fluid in the first hour of resuscitation and, occasionally, up to 100 to 200 mL/kg in the first few hours. A 3-way stopcock attached to a 20-mL or 60-mL syringe may be useful in pushing fluids with the aid of the syringe. Fluid resuscitation should be monitored by reassessing perfusion frequently. Fluid overload is detected by auscultating the chest for signs of pulmonary edema, palpating hepatomegaly, and noting the size of the heart on a chest radiograph. In hypovolemia, the heart is normal or small in size; in cardiogenic shock or fluid overload, it is usually enlarged.

The types of fluids available for volume expansion include the following:

1. Crystalloids—lactated Ringer's or 0.9% saline. Lactated Ringer's is often preferred because it contains less chloride than normal saline (134 mEq/L vs 154 mEq/L) and thus does not aggravate acidosis. Because only approximately one-third to one-fourth of crystalloids remain in the vascular space, approximately 3 to 4 times the deficit is required to restore plasma volume in the event of blood loss.
2. Colloids—albumin, fresh-frozen plasma, human plasma protein fraction. Colloids are never the fluids of first choice and should be used only for

specific indications or after at least 2 to 3 crystalloid boluses have been given without persistent effect. A 20-mL/kg dose of 5% albumin, a 4-mL/kg (1 g/kg) dose of 25% albumin, or a 20-mL/kg dose of fresh-frozen plasma may be used while assessing the perfusion in the patient continuously.

3. Packed red blood cells (10 mL/kg) should be given to a patient who is suspected of having significant or ongoing blood loss if 2 to 3 boluses of crystalloid do not improve perfusion persistently. If the child is a trauma victim, surgical consultation is mandatory, because expeditious evaluation for occult blood losses may be necessary (eg, exploratory laparotomy). Infusion pumps or mini-drip chambers should generally be used for infusion therapy. However, infusion pumps typically cannot infuse fluids more quickly than 1,000 mL/hr. If the goal is to give a 20-mL/kg bolus of normal saline to a 20-kg patient over 10 minutes, a rate of 2,400 mL/hr would be required. In such a case, a better approach would be to place a 3-way stopcock in the IV or IO line and manually infuse fluids in 60-mL aliquots, refilling the syringe repeatedly from the main saline supply bag. In addition, giving this amount of fluid using 2 or 3 IV or IO lines simultaneously should also be a consideration.

Dextrose is not administered in the initial resuscitative fluids unless hypoglycemia exists. In many critically ill children, the endogenous catecholamines are elevated, resulting in an increase in blood glucose. Hyperglycemia may induce an osmotic diuresis with more intravascular volume loss, and the hyperglycemia may also exacerbate neurologic injury.

**INOTROPIC AND VASOACTIVE DRUGS.** Even after preload has been corrected, the disease process causing circulatory compromise may affect contractility significantly, either from infectious agents or from metabolic factors. In these instances, providing inotropic support may be lifesaving. A variety of agents can provide inotropic support, along with concomitant effects on heart rate and on the peripheral circulation. The effects will vary from patient to patient and from drug to drug.

**DOPAMINE.** Dopamine is an endogenous catecholamine that is an immediate precursor of norepinephrine. At low doses (2–5 mcg/kg/min), it binds to dopamine receptors in splanchnic, coronary, and renal vascular beds, causing predominantly vasodilation and increased contractility with relatively little effect on heart rate and BP. At higher doses (6–12 mcg/kg/min),  $\beta_1$ -adrenergic effects (inotropic, chronotropic, and dromotropic) and  $\alpha$ -adrenergic effects (arterial and venous vasoconstriction) predominate, resulting in increased cardiac output and BP. At doses above 12 mcg/kg/min, vasoconstrictive effects dominate. The indications for use of dopamine at this dose are hypotension or poor peripheral perfusion in the presence of a stable rhythm and with adequate vascular volume.

A reasonable starting dose of dopamine for a patient in nonhypotensive shock is 5 to 10 mcg/kg/min. Infusion rates above 20 mcg/kg/min are not useful, because the effect is predominantly vasoconstrictive and because more selective drugs are available to use for this indication; if more inotropic effect is needed, epinephrine is probably a better choice than dopamine

because it is more potent, and dobutamine might be an alternative because it does not result in as much tachycardia as dopamine and has some afterload-reducing properties. In moderate to high doses, dopamine causes tachycardia (which increases myocardial oxygen demands), hypertension, arrhythmias, and, in some instances, extremity ischemia. At usual doses, dopamine should be given in a central vein, if possible; low doses (2–4 mcg/kg/min) may be given peripherally as long as careful monitoring of the extremity is undertaken to prevent infiltration and possible ischemic necrosis.

**DOBUTAMINE.** Dobutamine is a synthetic catecholamine with selective  $\beta_1$ -adrenergic action and a mild peripheral  $\beta_2$ -adrenergic effect (vasodilation), resulting in increased cardiac contractility, a mild increase in heart rate (but not as much as with dopamine), and decreased afterload (systemic resistance); this combination may significantly improve cardiac output. Dobutamine is most commonly used in patients with cardiogenic shock caused by myocarditis or cardiomyopathy or in children post-cardiac arrest. These patients usually have an adequate or excessive preload but have decreased contractility. Dobutamine provides improved contractility without as much tachycardia as is seen with dopamine or epinephrine. In children with a low preload, such as those with septic shock or anaphylaxis, the peripheral vasodilating effect of dobutamine may result in hypotension. Typical dosing starts at 2 to 5 mcg/kg/min and may be increased to 20 mcg/kg/min as tolerated. Dobutamine may be given peripherally because it has no significant vasoconstrictive effects.

**EPINEPHRINE.** Epinephrine is a catecholamine that is produced by the adrenal gland, but is also available for exogenous administration. It has dose-dependent effects— $\alpha$ -adrenergic (peripheral vasoconstrictive),  $\beta_1$ -adrenergic (inotropic, chronotropic, dromotropic), and  $\beta_2$ -adrenergic (vasodilatory). An epinephrine infusion is the treatment of choice for patients with marked circulatory instability and hypotension, given that it is potent and has superb inotropic effects and some vasoconstrictive effects in higher doses. The starting dose is 0.05 to 0.1 mcg/kg/min and may be increased up to 1 mcg/kg/min, with the dose titrated to reach the desired effect. In addition to its inotropic effect, lower doses under 0.1 mcg/kg/min usually result in peripheral vasodilation with a decrease in afterload. This circumstance may significantly improve cardiac output as long as preload is adequate. Higher infusion rates than 1 mcg/kg/min may be necessary in asystole. Epinephrine should be administered through a central line if at all possible, because at doses higher than approximately 0.1 mcg/kg/min, vasoconstrictive ( $\alpha$ -adrenergic) effects may be pronounced. The adverse effects of epinephrine infusion are tachycardia, arrhythmias, hypertension, hyperglycemia, and, at doses exceeding 0.5 mcg/kg/min, profound vasoconstriction that may compromise skin and extremity blood flow. Although epinephrine may reduce renal blood flow in high doses because of vasoconstriction, its inotropic effect improves renal blood flow by increasing cardiac output and tissue perfusion.



**NOREPINEPHRINE.** Norepinephrine, a catecholamine, is the neurotransmitter of the adrenergic nervous system and is noted primarily for its prominent vasoconstrictive ( $\alpha$ -adrenergic) effect, although it also has some moderate inotropic effect without the increase in heart rate so commonly seen with epinephrine. Infusion of norepinephrine is particularly useful in patients with shock in whom systemic vascular resistance needs to be increased rapidly (eg, warm septic shock, anaphylaxis, spinal shock). Infusions may be started at 0.1 mcg/kg/min and can be increased to 2 to 3 mcg/kg/min. Pronounced peripheral vasoconstriction may occur with a decrease in peripheral pulses and an increase in lactate, even though BP will be maintained. Its effect may be noted not only by an increase in BP, but also by an increase in diastolic BP, with a resulting narrow pulse pressure. Infusion should always be accomplished in a central line if at all possible because of its pronounced vasoconstrictive effects and significant risk of tissue ischemic necrosis, especially if it infiltrates.

**MILRINONE.** Milrinone is a phosphodiesterase inhibitor that has both inotropic effects, without an increase in heart rate, and vasodilator effects, resulting in afterload reduction. Over the last 10 years, experience with this class of drugs (which also includes inamrinone, an older drug of the same class) has been increasing for patients who have circulatory failure, especially from a primary cardiac etiology. Given milrinone's peripheral vasodilating effects, the patient should have sufficient preload (intravascular volume) so that hypotension does not result when it is started. The half-life of milrinone is also relatively long (4–6 hours); thus, its effects linger after it is stopped. For this reason, milrinone generally should not be used in the first few hours of stabilizing a patient, given that the physiologic state of the child may not be clear and may change quickly. Because no vasoconstrictive effects are associated with it, milrinone may be infused peripherally, aiming for a dose range of 0.25 to 0.75 mcg/kg/min. Although a loading dose should be considered for attaining rapid therapeutic blood levels, this amount may increase the risk of hypotension. Milrinone generally should not be considered as the drug of choice in forms of distributive shock, because a great deal of vasodilation is already present with low preload. However, in patients whose circulatory compromise is caused by cardiomyopathy, myocarditis, or poor cardiac function after cardiac arrest, this drug is excellent because it is not associated with the increased cardiac work caused by tachycardia. This drug has shown excellent results in pediatric patients who have undergone cardiopulmonary bypass for repair of a congenital heart defect and who have post-bypass circulatory compromise.

**SEPTIC SHOCK.** Septic shock contains elements of distributive, cardiogenic, and hypovolemic shock. Although infection with bacteria, viruses, and fungi is most commonly associated with septic shock, the constellation of signs, symptoms, and abnormalities in the physiologic mechanism of infectious septic shock may also be seen with noninfectious conditions (eg, severe hemorrhage, hypothermia). A cascade of cytokines and other inflammatory mediators are released, resulting in a systemic inflammatory

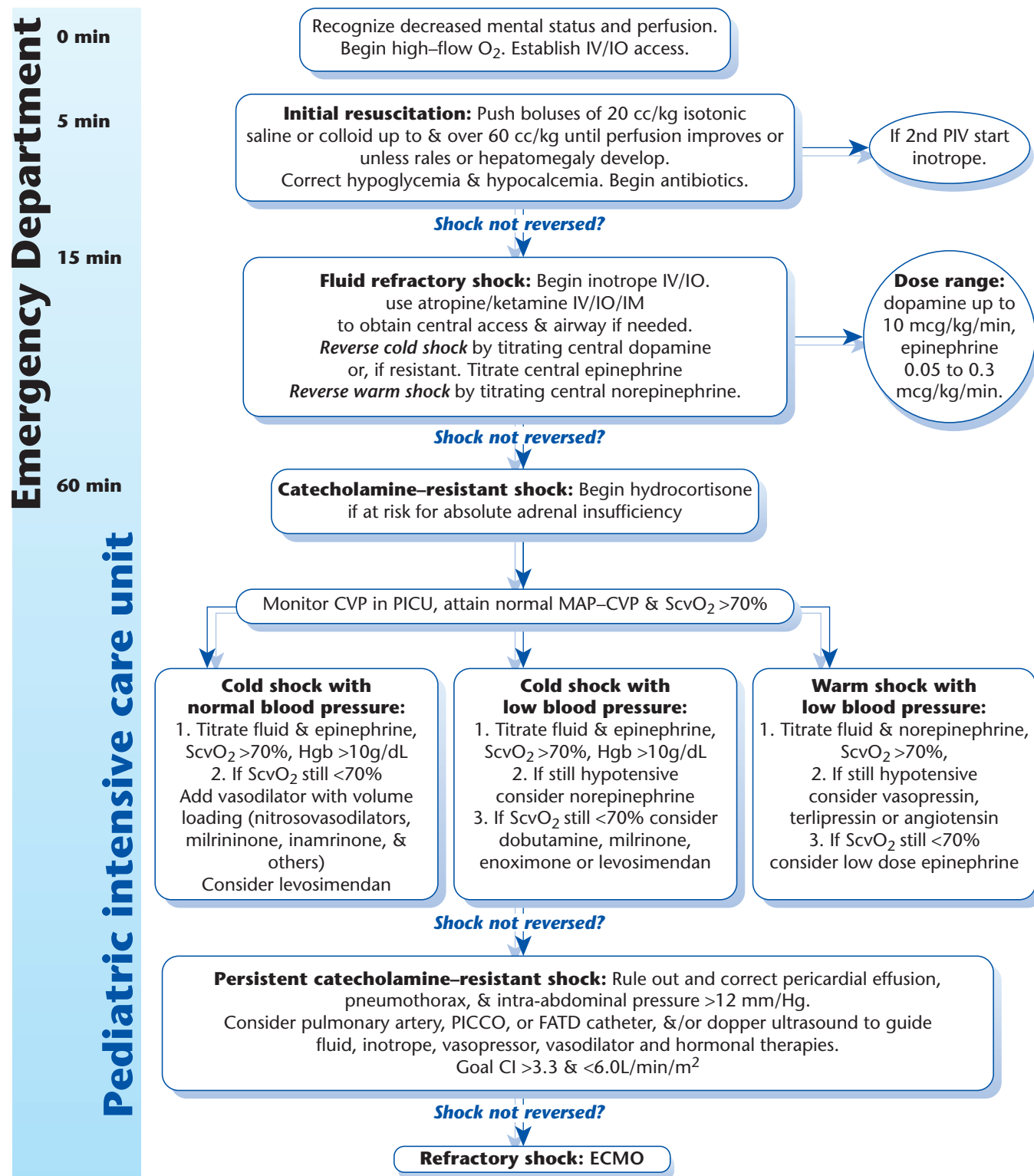
response syndrome (SIRS) reflected in metabolic, hemodynamic, respiratory, coagulation, and cellular disturbances. The result is a change in objective clinical and laboratory parameters, specifically temperature (fever or hypothermia), heart rate, respiratory rate, capillary refill, blood pressure, neurologic dysfunction, white blood cell count, coagulation tests, and both liver and renal function tests. If severe, this inflammatory response can lead to severe sepsis/septic shock.

With the recognition that rapid treatment of severe sepsis/septic shock is critical to improving survival, increasing attention has been given to defining sepsis and septic shock and developing guidance for their management. To this end, the international Surviving Sepsis campaign ([www.survivingsepsis.org/GUIDELINES/Pages/default.aspx](http://www.survivingsepsis.org/GUIDELINES/Pages/default.aspx)) has sought to promulgate management guidelines developed by a consensus of experts in the field.

A prominent feature of severe SIRS is that, in some patients, it can produce deceptively excellent perfusion with brisk (flash) capillary refill, bounding peripheral pulses, and pink, well-perfused skin (warm septic shock). Patients are usually febrile and may even have significant hypotension, but these are associated with excellent peripheral perfusion and a very high cardiac output. A major redistribution of blood occurs to the peripheral tissues, including skin and muscle, and low systemic vascular resistance results from the release of many cytokines. Nevertheless, although the patient initially seems quite well, the cardiac output is insufficient to meet the demands of the body, lactic acidosis occurs, and, over a brief period, peripheral vasoconstriction occurs with cool and poorly perfused extremities. Another complicating aspect of recognizing pediatric septic shock, and one that differentiates it from adult septic shock, is that BP may be normal and lactic acidosis may not be present.

Early recognition of septic shock is essential in improving morbidity and mortality. Very early and rapid fluid resuscitation seems to be key, with meticulous ongoing assessment to maintain cardiac output with both fluids and appropriate inotropic or vasoactive drug support. Because the adequacy of cardiac output can be deceiving, central venous oxygen saturation measurements can be helpful. These saturations reflect the adequacy of oxygen delivery to the tissues (determined by cardiac output, the amount of hemoglobin in the blood, oxygen saturation, and oxygen consumption by the tissues). Low central venous oxygen saturation (<70%) may indicate inadequate cardiac output and the need to improve it either by improving preload (intravascular volume) and cardiac contractility or by altering afterload. In addition, if the hematocrit is below 30%, transfusion of packed red cells should be considered to increase the oxygen-carrying capacity of the blood. Because relative adrenal insufficiency may also be present, steroids should be considered if response to fluids and vasoactive drugs is lacking. A full discussion of this complicated process is beyond the scope of this appendix, but an algorithm for the initial management of septic shock is shown in Figure A-4. See also Chapter 373, Shock.





**Figure A-4** Algorithm for time-sensitive, goal-directed stepwise management of hemodynamic support in infants and children. Proceed to next step if shock persists. (1) First-hour goals—Restore and maintain heart rate thresholds, capillary refill  $\leq 2$  sec, and normal blood pressure in the first hour/emergency department. Support oxygenation and ventilation as appropriate. (2) Subsequent intensive care unit goals—If shock is not reversed, intervene to restore and maintain normal perfusion pressure (mean arterial pressure [MAP]-central venous pressure [CVP]) for age, central venous O<sub>2</sub> saturation >70%, and CI >3.3, <6.0 L/min/m<sup>2</sup> in pediatric intensive care unit (PICU). CI, cardiac index; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; FATD, femoral arterial thermodilution; Hgb, hemoglobin; IM, intramuscular; IO, intraosseous; IV, intravenous; PICCO, pulse contour cardiac output. (From Brierley J, et al. *Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine*. Crit Care Med. 2009;37:666–688. Reprinted with permission.)

**Table A-5** Normal Ranges of Electrocardiographic Parameters

AGE (YR)	HEART RATE (BPM)	PR INTERVAL (SEC)	QRS COMPLEX (SEC)
<1	90–180	0.07–0.16	0.03–0.08
1–3	70–140	0.08–0.16	0.03–0.08
4–10	60–120	0.09–0.17	0.04–0.08
>10	55–110	0.09–0.20	0.04–0.10

Modified from Garson A. *Electrocardiogram in Infants and Children: A Systematic Approach*. Philadelphia, PA: Lea & Febiger; 1983.

### Rhythm Disturbance Management

Although less common than in adult patients, cardiac rhythm disturbances in children are not rare and may result in significant morbidity and mortality. Given that bradycardias, tachycardias, and rhythms that result in no cardiac contractions (collapse rhythms) may also cause a significant drop in cardiac output, they should be recognized and managed expeditiously. Some arrhythmias occur suddenly without warning, with immediate cardiac compromise or arrest (eg, ventricular fibrillation, pulseless ventricular tachycardia); others occur more gradually secondary to hypoxia and metabolic problems. Some are associated with genetic syndromes (long QT syndrome, accessory tracts such as Wolff-Parkinson-White syndrome, channelopathies); others are the result of injury (*commotio cordis*), drug toxicity (beta-blocker overdose), congenital heart disease (including postoperative), or infectious etiologies (myocarditis).

Emergency management should be focused on initiating treatment only for rhythms that compromise cardiac output significantly or might deteriorate into a lethal rhythm. Emergency therapies include oxygen, medications, basic CPR (if indicated), and electrical therapy. Electrical therapy includes defibrillation, the delivery of a random (unsynchronized) electrical shock to the myocardium to eliminate all electrical activity (by depolarization) and allow for a return of sinus rhythm; and cardioversion, the delivery of an electrical shock synchronized with the ventricular R wave to stop rhythms generated from either atrial or ventricular ectopic foci and allow for the resumption of a sinus rhythm.

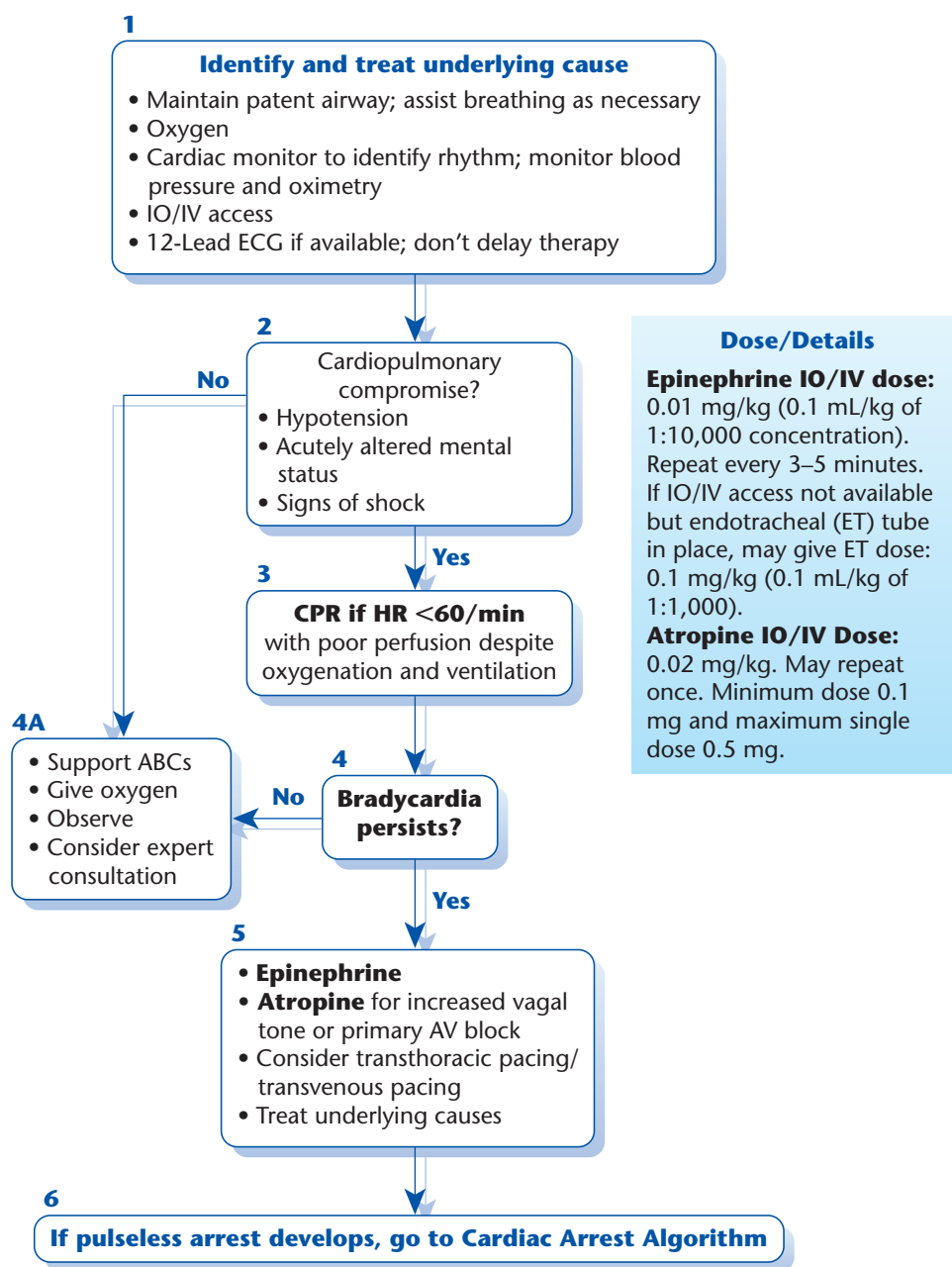
Appropriate therapies can be given only if at least some basic rhythm disturbances can be identified. Fortunately, a sophisticated knowledge of complex rhythms is unnecessary, and a noncardiologist can easily learn how to assess and provide the proper care for the common pediatric rhythm disturbances using the methods first described by the AHA in its first Pediatric Advanced Life Support Course in 1988 and continued in subsequent editions. This method, which divides rhythm disturbances into 3 major groups and uses group-specific algorithms for decision making, is outlined here. Other arrhythmias may need evaluation and treatment but do not usually constitute an emergency.

The 3 major rhythm groups are the bradycardias, the tachycardias, and the collapse rhythms. The last group includes any rhythm that does not have a discernible central pulse (ie, no recognizable cardiac output). Given that the grouping of the rhythms is

largely based on heart rate, knowing the ranges of normal in infants and children is important. In addition, a normal ECG must be recognized as consisting of a P-wave (atrial depolarization), followed by a QRS complex (ventricular depolarization and Q, R, and S waves), and then a T wave (reflecting ventricular repolarization). Table A-5 shows the normal ranges for heart rates and includes the normal PR and QRS complex intervals at various ages; although all of these values are important in interpretation of ECGs, the interval that is most important to assess is the length of the QRS complex. A QRS complex longer than 0.08 second in a child younger than 10 years (>0.10 second in the adolescent and adult) is consistent with one that originates in the ventricle (ventricular beat) or possibly originates from the atrium with some aberrant pathway. The length of this interval becomes important in differentiating an SVT from a ventricular tachycardia.

**BRADYARRHYTHMIAS.** Bradycardia below 60 bpm in infants and children is usually associated with poor perfusion (weak peripheral pulses, prolonged capillary refill, cool distal extremities with peripheral cyanosis) and requires emergency treatment even if the BP is normal. Figure A-5 shows the 2015 AHA recommended treatment algorithm. Given that hypoxia is a common cause of bradycardia, 100% oxygen should be given immediately and cardiac compressions instituted if bradycardia with poor perfusion continues. Because young children are especially dependent on their heart rate for maintaining cardiac output (they cannot increase stroke volume very readily), cardiac compressions at a rate between 100 and 120 compressions per minute begins to restore cardiac output immediately. Epinephrine in a dose of 0.01 mg/kg IV or IO should then be given, because epinephrine increases both heart rate and stroke volume. If no IV or IO access is possible and an ET tube is in place, epinephrine 0.1 mg/kg may be given as a 1:1,000 solution followed by 3 to 5 mL of normal saline and bagged in with 5 manual breaths.

Although epinephrine is generally the drug of choice in significant bradycardia, atropine may be considered first if excess vagal tone or atrioventricular (AV) block is present or if epinephrine is ineffective. Atropine competes with acetylcholine, the neurotransmitter of the parasympathetic nervous system, which includes the vagus nerve, thereby accelerating sinus and atrial pacemaker discharges and AV conduction. The dose of atropine is 0.02 mg/kg IV or IO (maximum of 0.5 mg). If no IV or IO line is in place and the child



**Figure A-5** Pediatric bradycardia with a pulse and poor perfusion algorithm. (From American Heart Association. Web-based integrated 2010 & 2015 guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 12: pediatric advanced life support. Reprinted with permission. © 2015 American Heart Association, Inc.)

is intubated, atropine in a dose 2 to 3 times the IV or IO dose can be given down the ET tube and followed by a normal saline flush. Atropine effects remain for 2 to 4 hours and may affect the pupillary response, making an accurate neurologic examination more difficult. However, a single dose of atropine is unlikely to result in full atropinization and elimination of pupillary responses.

If no response to these measures occurs, consideration should be given to increasing the heart rate by external pacing. Many defibrillator or monitor devices

now have multifunction pads for electrical therapy, allowing the same pads that are used for monitoring and defibrillation to be used for external pacing. Pacing should be initiated with 10 milliamperes (mA) and increased until a wide QRS complex follows the pacing spike (capture). Rate can be separately controlled and should start at 100. If the QRS complex occurs at 10 mA, the current can be decreased until it is at the lowest current that can generate a complex.

**TACHYARRHYTHMIAS.** By far, the most common cause of tachycardia in infants and children is a sinus

tachycardia induced by activity, fever, anemia, shock, and other reasons in which a need exists for increased cardiac output. In these patients, the primary problem is noncardiac, and the tachycardia is secondary and compensatory so that adequate cardiac output is maintained to serve the needs of the body. As the primary problem is treated (eg, fluids in hypovolemic shock, acetaminophen in a febrile child), the heart rate will decrease. However, in tachycardias that are truly dysrhythmic, tachycardia is the primary problem, often resulting in inadequate cardiac output and circulatory failure. If the heart rate is too rapid, filling time is inadequate, and thus the volume ejected with each beat is inadequate. Figure A-6 provides a treatment algorithm.

Tachycardias may be divided into those that originate from the supraventricular areas (atria, AV node) and those that originate from the ventricle. If the tachycardia originates from the ventricle, the QRS will be wide; if from above the ventricle, it will be narrow. A primary, intrinsic SVT should be considered if the heart rate in infants is over 220 bpm and in children is over 180 bpm. If any tachycardia is present and a wide QRS complex is observed, a ventricular tachycardia should be considered.

In SVT, P waves are difficult to find, the QRS complex is narrow in 98% of cases, and the rate is usually regular with an abrupt onset. If the patient is hemodynamically stable, vagal maneuvers may be tried (eg, applying an ice bag to the face suddenly, being careful to avoid obstructing the nose and mouth or having an older child exhale against an occluded straw). These maneuvers are often successful. If vagal maneuvers are unsuccessful, adenosine should be administered intravenously. Adenosine is an endogenous nucleoside that causes a temporary block through the AV node; it is very effective, and side effects are minimal because its half-life is only 10 seconds. However, because of its short half-life and the need to get the drug into the central circulation as soon as possible, adenosine in a dose of 0.1 mg/kg should be given by rapid IV or IO bolus immediately and followed by a 5- to 10-mL normal saline flush (this is usually a 2-person procedure using a 3-way stopcock). If unsuccessful, the dose may be doubled up to 12 mg (or even quadrupled if being given by IO infusion).

If the patient has significant hemodynamic instability and no IV line is in place to give adenosine rapidly, or if adenosine is unsuccessful, immediate *synchronized* cardioversion (0.5–1 J/kg) should be attempted. If SVT persists, the cardioversion dose should be increased to 2 J/kg. If it still persists, the diagnosis should be re-evaluated and a cardiologist consulted. Amiodarone at 5 mg/kg over 20 to 60 minutes should be considered. Verapamil should *not* be used to treat SVT in infants or children because cardiovascular collapse has been reported following its use in infants.

Ventricular tachycardia is characterized by wide QRS complexes, absence of P waves, and T waves that are opposite in polarity to the QRS complex. To be defined as ventricular tachycardia, at least 3 of these complexes in a row should be observed. Although patients may have sustained ventricular tachycardia for a short time without hemodynamic instability,

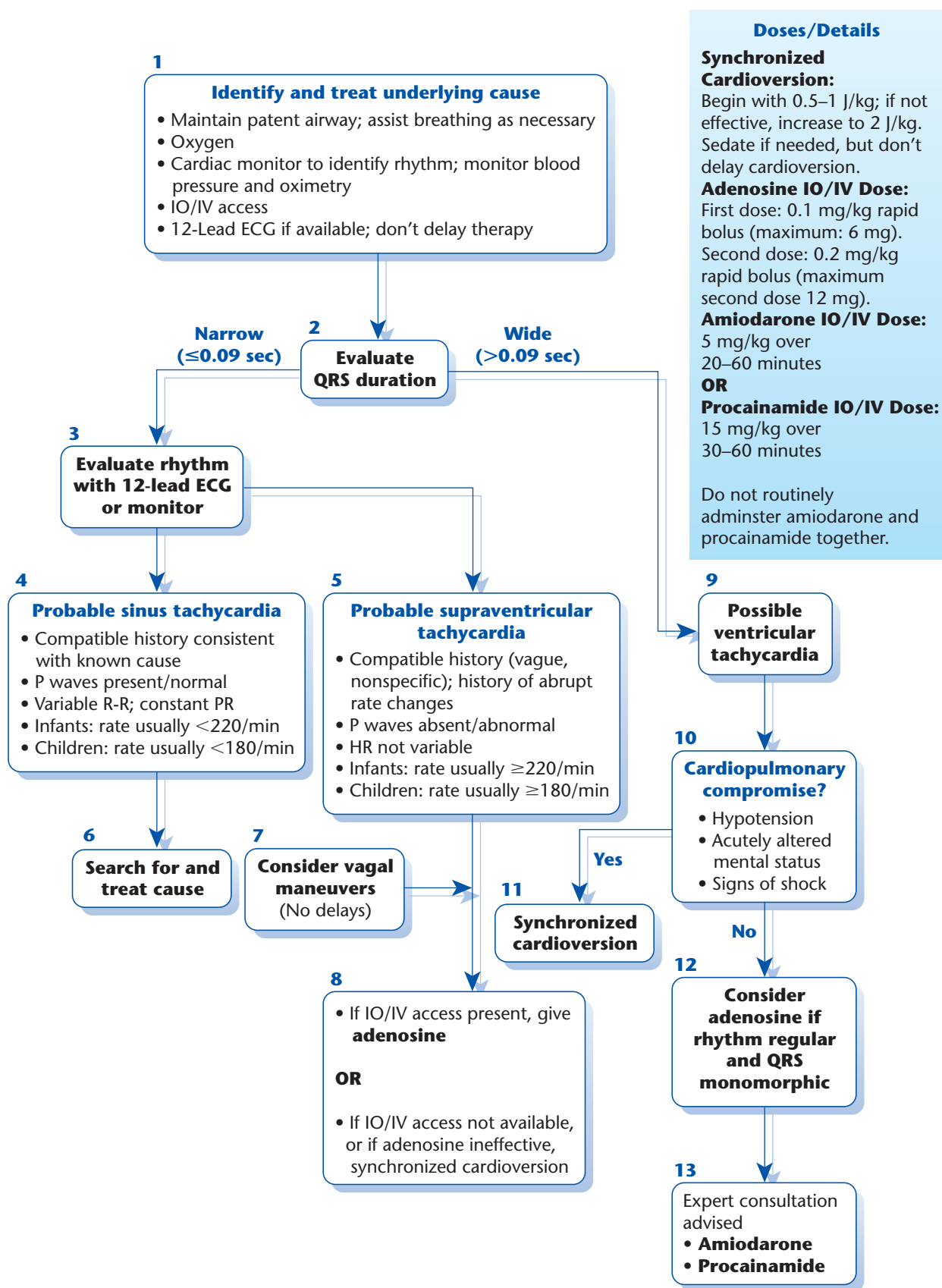
treatment should be instituted especially quickly because ventricular tachycardia with poor perfusion may rapidly degenerate into ventricular fibrillation.

If perfusion is poor, *synchronized* cardioversion (0.5–1 J/kg) should be attempted immediately. If it can be performed without delay, and if the rhythm is more likely to be aberrantly conducted supraventricular beats, adenosine may be given. Ventricular tachycardia will not be altered by adenosine. If no response to the first attempt at cardioversion is observed, the dose may be doubled (2 J/kg). If ventricular tachycardia recurs or no response to the second shock is observed, an infusion of amiodarone should be considered at 5 mg/kg IV or IO over 20 to 60 minutes (or 1 mg/kg every 10 minutes). A subsequent shock can be attempted once this circumstance has occurred. A pediatric cardiologist or pediatric intensive care physician (or both) should be consulted early in the management of ventricular tachycardia.

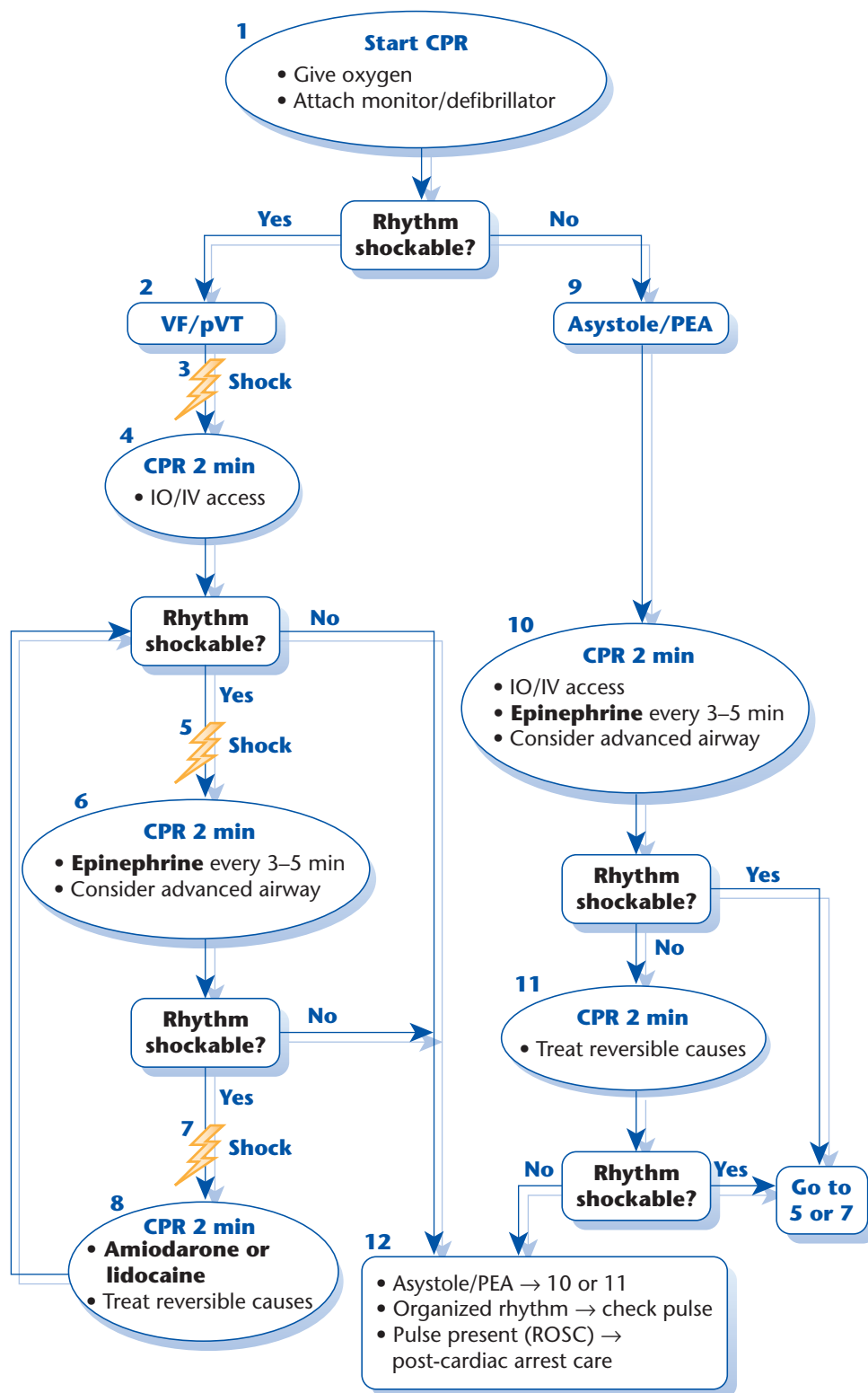
**COLLAPSE RHYTHMS OR CARDIAC ARREST.** None of the collapse rhythms—*asystole*, pulseless electrical activity, ventricular fibrillation, or pulseless ventricular tachycardia—produce sufficient cardiac output to generate a central pulse. Immediate basic CPR, as described previously, is necessary, with emphasis on chest compressions that are fast (at least 100 compressions/minute), have good compression depth (one-third to one-half the chest), and have complete recoil. Rapid connection of the patient to a monitor is imperative because the presence of ventricular fibrillation or ventricular tachycardia requires defibrillation as soon as possible, with best outcomes occurring if it is accomplished quickly (within 3 minutes). With each minute that passes, mortality increases by 10%. Figure A-7 provides a treatment algorithm for a pulseless arrest.

**ASYSTOLE AND PULSELESS ELECTRICAL ACTIVITY.** Asystole is the absence of any cardiac electrical activity and is characterized by the absence of any waveforms on the ECG. Pulseless electrical activity is any electrical activity, except for ventricular fibrillation and ventricular tachycardia, that has no central pulses associated with it. AHA Guidelines state the treatment of both is identical and consists of basic CPR, oxygenation, and the administration of epinephrine 0.01 mg/kg IV or IO (or 0.1 mg/kg by ET tube) every 3 to 5 minutes. CPR should be resumed immediately after epinephrine is given (to circulate the epinephrine and maintain coronary artery perfusion pressure) and continued for 2 minutes of CPR (5 cycles of 30:2 CPR for a single rescuer for the adult or 10 cycles of 15:2 CPR for 2 health rescuers for the child) before the rhythm is checked. If no response to this treatment is observed, possible reasons should be considered and treatment instituted. Considerations are outlined in Figure A-7 under 6 Hs (*hypovolemia*, *hypoxia*, *hydrogen ion*, *hyper- or hypokalemia*, *hypoglycemia*, and *hypothermia*) and 5 Ts (*toxins*, *tamponade-cardiac*, *tension pneumothorax*, *thrombosis-pulmonary or coronary*, and *trauma*). Many drugs that have been used in the past are no longer routinely recommended by AHA in pulseless arrest, especially intravascular or IO high-dose epinephrine (0.1 mg/kg), atropine, and calcium. High-dose epinephrine, in particular, is not recommended by AHA as a standard





**Figure A-6** Pediatric tachycardia with pulse and poor perfusion algorithm. ECG, electrocardiogram; HR, heart rate; IM, intramuscular; IO, intraosseous; IV, intravenous. (From American Heart Association. Web-based integrated 2010 & 2015 guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 12: pediatric advanced life support. Reprinted with permission. © 2015 American Heart Association, Inc.)



**Figure A-7** Pediatric Advanced Life Support cardiac arrest algorithm. CPR, cardiopulmonary resuscitation; IO, intraosseous; IV, intravenous; ROSC, return of spontaneous circulation; PEA, pulseless electrical activity; pVT, pulseless ventricular tachycardia; VF, ventricular fibrillation. (From American Heart Association. 2015 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 12: pediatric advanced life support. Circulation. 2015;132:S526–S542. Reprinted with permission. © 2015 American Heart Association, Inc.)

## Doses/Details

### CPR Quality

- Push hard ( $\geq \frac{1}{3}$  of antero-posterior diameter of chest) and fast (100–120/min) and allow complete chest recoil
- Minimize interruptions in compressions
- Avoid excessive ventilation
- Rotate compressor every 2 minutes or sooner if fatigued
- If no advanced airway, 15:2 compression-ventilation ratio. If advanced airway, 8–10 breaths per minute with continuous chest compressions

### Shock Energy for Defibrillation

First shock 2 J/kg, second shock 4 J/kg, subsequent shocks  $\geq 4$  J/kg, maximum 10 J/kg or adult dose.

### Drug Therapy

#### • Epinephrine IO/IV Dose:

0.01 mg/kg (0.1 mL/kg of 1:10,000 concentration). Repeat every 3–5 minutes. If no IO/IV access, may give endotracheal dose: 0.1 mg/kg (0.1 mL/kg of 1:1,000 concentration).

#### • Amiodarone IO/IV Dose:

5 mg/kg bolus during cardiac arrest. May repeat up to 2 times for refractory VF/pulseless VT.

#### • Lidocaine IO/IV dose:

Initial: 1 mg/kg loading dose  
Maintenance: 20–50 mcg/kg per minute infusion (repeat bolus dose if infusion initiated >15 minutes after initial bolus therapy)

### Advanced Airway

- Endotracheal intubation or supraglottic advanced airway
- Waveform capnography or capnometry to confirm and monitor ET tube placement
- Once advanced airway in place give 1 breath every 6 seconds (10 breaths per minute) with continuous chest compressions

### Return of Spontaneous Circulation (ROSC)

- Pulse and blood pressure
- Spontaneous arterial pressure waves with intra-arterial monitoring

### Reversible Causes

- Hypovolemia
- Hypoxia
- Hydrogen ion (acidosis)
- Hypoglycemia
- Hypo-/hyperkalemia
- Hypothermia
- Tension pneumothorax
- Tamponade, cardiac
- Toxins
- Thrombosis, pulmonary
- Thrombosis, coronary

medication in cardiac arrest because no consistent evidence has been found that it is effective and because some evidence suggests that it actually decreases survival, particularly in asphyxial arrest. High-dose epinephrine may be considered in special circumstances, such as beta-blocker overdose. Although sodium bicarbonate should not be used routinely, in prolonged arrest (more than 10 minutes) or with evidence of significant metabolic acidosis it may be used recognizing that it may result in an increase in intracellular acidosis. Recent evidence suggests that calcium is not appropriate unless there is documented or very high likelihood of hypocalcemia, hypermagnesemia, hypocalcemia, or calcium channel blocker overdose.

**VENTRICULAR FIBRILLATION OR PULSELESS VENTRICULAR TACHYCARDIA.** AHA guidelines recommend that defibrillation (unsynchronized shock) must occur as soon as possible, using appropriately sized pads or paddles (pediatric paddles are used for children weighing less than 10 kg), conducting gel as appropriate, and proper voltage (2 J/kg as a starting dose). Because most defibrillators are now biphasic with a success rate of 90% after 1 shock, AHA recommends only 1 shock. After the single shock, CPR is resumed immediately without checking the rhythm and continued for 2 full minutes. The reason for resuming CPR immediately is that, after defibrillation occurs, asystole or pulseless mechanical activity is usually present, both still requiring cardiac compressions. After the 2 minutes of CPR, the rhythm is rechecked, and if ventricular fibrillation or pulseless ventricular tachycardia is still present, a shock of 4 J/kg is delivered (compressions should be continued until the defibrillator is fully charged). CPR is resumed immediately and a dose of epinephrine (0.01 mg/kg up to 1 mg) is given via IV or IO line. After 2 minutes of CPR, another rhythm check is performed, and if ventricular fibrillation or ventricular tachycardia is still present, a 4 to 10 J/kg shock (up to the adult dose) is given with immediate resumption of CPR. Amiodarone at 5 mg/kg IV or IO push is then given. Alternately, lidocaine may be used if amiodarone is not available. Epinephrine is continued every 3 to 5 minutes, but AHA does not recommend vasopressin in children because no scientific evidence has been found to support its use in children, and only some mixed evidence in adults has been found. If no response occurs, the 6 Hs and 5 Ts should be reviewed to see if any other management is indicated (eg, a fluid bolus of 20 mL/kg to ensure adequate intravascular volume, checking blood glucose level to ensure the absence of hypoglycemia). If the rhythm suggests Torsades de pointes (a variant of ventricular tachycardia), magnesium at 25 to 50 mg/kg IV push should be given.

The sequence for managing ventricular fibrillation or pulseless ventricular tachycardia is very fast paced, requires thorough planning so that medications are given on time, and is dependent both on persistent, uninterrupted CPR and proper defibrillation. A team with assigned roles led by a capable team leader is invaluable in the rendering of optimal and timely management.

**CARDIAC ARREST MEDICATIONS.** Medications used in situations of cardiac arrest are listed and discussed in Table A-6.

**AMIODARONE.** Amiodarone is a class III antiarrhythmic that inhibits  $\alpha$ - and  $\beta$ -adrenergic receptors, slows the sinus rate, and prolongs the effective refractory period. In adults, it has been shown to be an excellent drug for the management of pulseless ventricular tachycardia and ventricular fibrillation at an IV or IO push dose of 5 mg/kg. In children, amiodarone is also useful in SVT and ventricular tachycardia with pulses. In the latter settings, 5 mg/kg IV or IO should be given over 20 to 60 minutes, thus over an appreciably longer time period than in the patient with cardiac arrest. Side effects include hypotension and prolongation of the PR and QT intervals. Although amiodarone has a fairly rapid onset of action (within 30 minutes), its terminal elimination half-life is extremely long (days to weeks). Caution should be used in neonates and young infants, because amiodarone preparations contain benzyl alcohol, which is associated with gasping syndrome and death in this age group.

**BICARBONATE (SODIUM).** Intravenous or IO administration of sodium bicarbonate (a base) can correct severe and ongoing metabolic acidosis. Although bicarbonate was previously used routinely during advanced CPR, some significant adverse effects should be considered. Bicarbonate shifts the oxygen dissociation curve to the left and thus reduces the delivery of oxygen to the tissues; shifts the potassium intracellularly, lowering its serum level and increasing the risk of arrhythmias; reduces plasma-ionized calcium and increases risk of arrhythmias; lowers the ventricular fibrillation threshold; increases the risk of hypernatremia and water overload; increases the risk of hyperosmolality with risk of cerebral bleeding; and may produce paradoxical cerebrospinal fluid and intracellular acidosis. Given these adverse effects, bicarbonate should be used cautiously and generally only if the acidemia is severe (pH <7.20) and not improving. Severe acidosis may depress cardiac contractility and result in poor cardiac output. Because the administration of bicarbonate increases  $P_{CO_2}$  by its combination with hydrogen ion ( $H^+ + HCO_3^- \rightleftharpoons H_2CO_3 \rightleftharpoons H_2O + CO_2$ ), satisfactory ventilation must be established before administering it.

Because the acidemia that results from a metabolic acidosis can be corrected by inducing a respiratory alkalosis (decreased  $P_{CO_2}$ ), the following relationships, known as golden rules, are useful to know:

Rule 1: An acute change in  $P_{CO_2}$  of 10 torr is associated with an increase or decrease of 0.08 units in the pH.

Rule 2: A pH change of 0.15 units is associated with a change in bicarbonate of 10 mEq/L from its 20-mEq/L baseline.

Rule 3: The dose of bicarbonate (mEq) required to correct the metabolic acidosis *fully* is the base deficit (mEq/L  $\times$  patient's weight [kg]  $\times$  0.3). Usually, only one-half this amount is administered and then the acid-base status is reassessed. This amount translates into a bicarbonate dose of 1 mEq/kg.

Other indications for bicarbonate infusion include hyperkalemia and tricyclic antidepressant (sodium-channel blocker) overdose.

**Table A-6 Medications for Pediatric Resuscitation**

MEDICATION	DOSE	REMARKS
Adenosine	0.1 mg/kg (max: 6 mg) Second dose: 0.2 mg/kg (max: 12 mg)	Monitor ECG. Rapid IV or IO bolus with flush.
Amiodarone	5 mg/kg IV or IO; may repeat twice up to 15 mg/kg Max single dose: 300 mg	Monitor ECG and blood pressure; adjust administration rate to urgency (IV push during cardiac arrest, more slowly—over 20–60 minutes with perfusing rhythm). Expert consultation strongly recommended prior to use when patient has a perfusing rhythm. Use caution when administering with other drugs that prolong QT (obtain expert consultation).
Atropine	0.02 mg/kg IV or IO 0.04–0.06 mg/kg ET <sup>a</sup> Repeat once if needed Max single dose: 0.5 mg	Higher doses may be used with organophosphate poisoning.
Calcium chloride (10%)	20 mg/kg IV or IO (0.2 mL/kg) Max single dose: 2 g	Administer slowly.
Epinephrine	0.01 mg/kg (0.1 mL/kg 1:10,000) IV/IO 0.1 mg/kg (0.1 mL/kg 1:1,000) ET <sup>a</sup> Max dose: 1 mg IV/IO; 2.5 mg ET	May repeat every 3–5 minutes.
Glucose	0.5–1 g/kg IV or IO	Newborn: 5–10 mL/kg D <sub>10</sub> W Infants and Children: 2–4 mL/kg D <sub>25</sub> W Adolescents: 1–2 mL/kg D <sub>50</sub> W
Lidocaine	Bolus: 1 mg/kg IV or IO Infusion: 20–50 mcg/kg/min	
Magnesium sulfate	25–50 mg/kg IV or IO over 10–20 minutes, faster in torsades de pointes Max dose: 2 g	
Naloxone	Full reversal: <5 yr or ≤20 kg: 0.1 mg/kg IV, IO, or ET <sup>a</sup> ≥5 yr or >20 kg: 2 mg IV, IO, or ET <sup>a</sup>	Use lower dose to reverse respiratory depression associated with therapeutic opioid use (1–5 mcg/kg titrate to effect).
Procainamide	15 mg/kg IV or IO Adult dose: 20 mg/min IV infusion to total maximum dose of 17 mg/kg	Monitor ECG and blood pressure. Administer slowly—over 30–60 minutes. Use caution when administering with other drugs that prolong QT (obtain expert consultation).
Sodium bicarbonate	1 mEq/kg per dose IV or IO slowly	After adequate ventilation

BP, blood pressure; ECG, electrocardiogram; ET, endotracheal tube; IO, intraosseous; IV, intravenous.

<sup>a</sup>Flush with 5 mL of normal saline and follow with 5 ventilations.

From American Heart Association. *Web-based integrated 2010 & 2015 guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 12: pediatric advanced life support.* Reprinted with permission. © 2015 American Heart Association, Inc.

Given that the osmolality of the standard sodium bicarbonate preparation is very high (1 mEq/mL, 8.4%) and neonates, especially premature ones, are at risk for having central nervous system bleeding when high osmolar substances are infused, they should receive more dilute bicarbonate at a concentration of 0.5 mEq/mL (4.2%).

#### **CALCIUM CHLORIDE OR CALCIUM GLUCONATE.**

Calcium has a positive inotropic effect on the heart, but calcium entry into cell cytoplasm is also the final common pathway in cell death. These 2 paradoxical effects require judicious use of calcium, and its use is no longer routinely recommended in cardiac arrest protocols. Nevertheless, indications do exist for calcium administration—documented hypocalcemia,

hyperkalemia, hypermagnesemia, and calcium-channel blocker overdose. Calcium chloride is the salt preferred in emergency hypocalcemia because it delivers ionized calcium directly into the bloodstream. It should be given centrally if at all possible because it may cause severe arterial vasoconstriction, even when no discernible infiltrate is present. Calcium gluconate is better tolerated peripherally, but it requires first-pass metabolism in the liver before calcium ion is released. The dose of calcium gluconate (60 mg/kg) is 3 times the dose used for calcium chloride (20 mg/kg). Calcium should always be injected slowly, concurrent with ECG and BP monitoring, because bradycardia and hypotension may occur.



**EPINEPHRINE.** (See previous discussion under Circulatory Management.) Epinephrine is an endogenous catecholamine that can affect the adrenergic nervous system by stimulating  $\alpha$ -adrenergic (vasoconstricting),  $\beta_1$ -adrenergic (cardiac), and  $\beta_2$ -adrenergic (vasodilating) receptors. In doses used for CPR (0.01 mg/kg IV or IO), it has predominantly strong  $\alpha$ -adrenergic effects.  $\alpha$ -Receptor stimulation results in vasoconstriction, thereby increasing systemic vascular resistance, increased coronary artery perfusion pressure, and increased oxygen delivery to the myocardium. Because of this effect, epinephrine is indicated in asystole, pulseless electrical activity, pulseless ventricular tachycardia, and ventricular fibrillation. Epinephrine's  $\beta$ -adrenergic effects result in increased cardiac inotropy, (increased contractility), chronotropy (increased rate), and dromotropy (increased intracardiac conduction). These effects are very useful in managing unstable bradyarrhythmias, hypotensive shock, and anaphylaxis, and during the postresuscitation phase when the heart needs assistance in contractility and stroke volume. High-dose epinephrine (0.1 mg/kg) should be given only down the ET tube during cardiac arrest when no other means is possible to give standard dose epinephrine (0.01 mg/kg) or IV when beta-blocker overdose has occurred with an inability to increase the heart rate.

**GLUCOSE.** Small infants and chronically ill children have limited glycogen stores, and hypoglycemia may develop quickly. Glucose is a major metabolic substrate for the neonatal myocardium. A rapid blood glucose test should be obtained, and if hypoglycemia exists, glucose should be administered. In children older than 1 month, dextrose as a D<sub>25</sub>W solution (dilution of D<sub>50</sub>W 1:1 with sterile water) should be used in a dose of 2 to 4 mL/kg. In infants younger than 1 month, a D<sub>10</sub>W solution (dilution of D<sub>50</sub>W 1:4 with sterile water) in a dose of 8 to 10 mL/kg is preferred. In the older child, the usual adult dose of D<sub>50</sub>W solution at 1 to 2 mL/kg up to 50 mL (25 g) is given. Sufficient amounts should be given to keep the blood glucose level above 100 mg/dL. The diluted dextrose is important because repeated hyperosmolar doses have been associated with intracranial hemorrhage in premature infants.

**LIDOCAINE.** Lidocaine is a class IB antiarrhythmic and, in usual doses, has no effect on myocardial contractility, BP, or cardiac conduction. Its action reduces ventricular automaticity, raises the ventricular fibrillation threshold, and inhibits the formation of re-entry circuits that lead to ventricular tachycardia and ventricular fibrillation. It may be considered as an alternative to amiodarone.

To ensure adequate plasma concentrations, a bolus of 1 mg/kg should be given. If the child is in shock or has liver disease, beginning doses of 1 mg/kg/hr (15–20 mcg/kg/min) should be used to prevent toxicity from impaired lidocaine clearance. The dose for an adolescent is a 50- to 100-mg bolus followed by infusion of 1 to 4 mg/min. The antiarrhythmic effect occurs at a serum concentration of 1 to 5 mcg/mL. Concentrations above 6 mcg/mL may cause seizures, and those above 10 mcg/mL may cause myocardial depression. The physician should be prepared to treat bradycardia and hypotension. Lidocaine is

contraindicated in severe heart block and should not be given in idioventricular rhythms. Widening of the QRS complex by more than 0.02 seconds or significant ventricular slowing suggests cardiac toxicity.

Procainamide can be used for ventricular tachycardia with pulses or atrial flutter as long as there is a pulse, but it generally should NOT be used for ventricular fibrillation or ventricular tachycardia without pulses. It is a negative inotrope and can result in significant hypotension as well as prolongation of the QT interval. It should be used only with expert consultation. Concomitant use with amiodarone should be avoided.

## POSTRESUSCITATION MANAGEMENT

Once initial, urgent therapies have been provided for the critically ill infant or child, further stabilization, a method for performing frequent assessments, and a plan for safe and efficient transfer to a place where definitive care can be rendered need to be addressed. Early consultation with a pediatric tertiary care center is strongly recommended, especially if the infant or child is in a facility without pediatric tertiary care expertise. Ongoing close monitoring and treatment are imperative, because rapid deterioration may again occur unless proper care is rendered. For children who have had a respiratory or cardiac arrest, such definitive care involves transfer to a pediatric intensive care unit where multidisciplinary pediatric critical care expertise is available.

### Important Considerations

#### Monitoring

Ongoing cardiopulmonary monitoring with frequent nurse/physician assessments of the patient are imperative after a cardiopulmonary arrest so that early interventions can be made as necessary.

**RESPIRATORY ASSESSMENTS.** Respiratory assessments should include adequacy of airway; respiratory rate, depth, and effort; and pulse oximetry. An arterial blood gas assessment should be obtained if any questions exist about adequacy of ventilation or oxygenation. Results can then be correlated with the clinical examination. In addition to pulse oximetry, capnography (end-tidal Pco<sub>2</sub>) should be encouraged for intubated patients, and is recommended if they are to be transported within or to another facility.

**CARDIOVASCULAR ASSESSMENTS.** Cardiovascular assessments should include heart rate, continuous ECG, BP assessment by either frequent cuff pressures or arterial line, peripheral and central pulses, capillary refill, and urine output. Placing the child on a continuous ECG or respiratory monitor is most efficient, with noninvasive BP readings taken at regular intervals. If the child has unstable BPs, an arterial line should be inserted as soon as possible. A bladder catheter should be placed for ongoing monitoring of urine production (adequate urine output suggests adequate perfusion to the kidneys). Although usually not feasible in the initial stages of treatment, central venous pressure monitoring should be considered early on because it can be very helpful in monitoring the adequacy of preload. In addition, by having a central line in place, blood samples can be drawn from the central circulation to measure systemic

venous oxygen saturations ( $SvO_2$ ), and medications that require central vein infusion can be given as necessary. Desirable central venous oxygen saturations are at or above 70%. If these values are below this level in the setting of normal arterial oxygen saturations, the cardiac output may be insufficient and need to be corrected.

**NEUROLOGIC ASSESSMENTS.** Neurologic examinations should be performed frequently and include level of consciousness (use the AVPU scale or the Glasgow Coma Scale to assess responsiveness), pupillary responses, any evidence of increased intracranial pressure (decreased responsiveness, nonreactive or unequal pupils, abnormal respirations including hyperventilation and irregular respiration, Cushing's triad of bradycardia, hypertension and abnormal breathing), and seizures. Seizures occur frequently after cardiac arrest. This evaluation is especially important for patients who, in addition to the cardiac arrest, have also sustained a head injury, have a primary neurologic problem such as status epilepticus or meningitis, or have significant elevations in  $PCO_2$  or significant hypoxia.

**TRAINED PERSONNEL.** Although technical monitoring is necessary, staff trained to perform acceptable physical assessments and interpret data from monitors are essential. Early deterioration in a patient may be subtle, and an experienced health care provider can often note this event. Critically ill or injured patients who are not yet stabilized should never be left alone to depend exclusively on mechanical monitors.

### General Management

**RESPIRATORY.** The child should receive 100% oxygen (preferably humidified and at body temperature) until lower levels are clearly acceptable with maintenance of oxygen saturation in the 95% to 99% range. Careful attention to the level of oxygenation is especially important for patients who have had a cardiac arrest, because excess oxygen may result in the generation of injurious free oxygen radicals in brain tissue. Although the optimal oxygen level post arrest is not known, keeping oxygen at physiologic  $PO_2$  levels of 90 to 100 ( $O_2$  saturation 94%–99%) is recommended by the AHA. If the child has not had a cardiopulmonary arrest, but concerns exist about her ability to maintain adequate oxygenation and ventilation during transport to definitive care, the child should be intubated and placed on mechanical ventilation. A chest radiograph should be obtained to ensure that the ET tube is in the right position (midtrachea), and the tube should be well secured with tape. Initial settings for the ventilators are as follows:  $F_{IO_2}$ , 1.00; positive end-expiratory pressure (PEEP), 5; pressure support, 8 (if available); tidal volume, 8 to 10 mL/kg; peak inspiratory pressure (inspiratory + PEEP), 20 to 30 cm  $H_2O$ ; inspiratory time, 0.5 second for infants and 1 second for older patients, and a rate of approximately 20 inspirations per minute. There should be a discernible, but not excessive, chest rise with each breath. Further adjustments should be made based on arterial blood gas levels. A nasogastric or orogastric tube should be placed after intubation so that gastric air can be removed intermittently manually or by low intermittent suction.

**CARDIOVASCULAR.** Thorough assessment and ongoing management of preload (intravascular volume), contractility, and afterload is necessary in every critically ill child because rapid deterioration may occur again. This effort requires the placement of at least 2 well-secured functional venous lines. If fluid boluses are required, they should be given in 20 mL/kg aliquots over approximately 10 minutes. Assessment of heart rate and pulses during and after a bolus (rate should decrease, pulses increase) will provide immediate feedback regarding the appropriateness of this therapy. If blood is required (eg, in trauma patients), it should be given in 10 mL/kg of packed red blood cells. Inotropic support may also be necessary.

Once adequate preload has been established and the child or infant needs inotropic support, dopamine or dobutamine can be used for the child with nonhypotensive shock, and epinephrine or norepinephrine for children who are hypotensive. For the child who has had a cardiac arrest, improving contractility without excessive tachycardia is important, because the latter results in significantly increased oxygen requirement. Because dobutamine will typically result in less tachycardia than dopamine, it might be a better drug to use post arrest. Although milrinone or amrinone are excellent drugs to use after a child has had cardiac arrest (neither results in tachycardia, but both have inotropic and afterload-reducing effects), they may require the expertise of a pediatric critical care physician.

**NEUROLOGIC.** Hyperventilation, hyperglycemia, hypoglycemia, and fever should all be avoided because they may result in less-than-optimal outcomes. Unless used for acute rescue (signs of impending cerebral herniation), hyperventilation has no benefit and may significantly impair neurologic outcomes. Hyperventilation results in a drop of  $PCO_2$  with resultant cerebral artery vasoconstriction and ischemia, especially in specific areas in which circulatory compromise has occurred. In addition, each time a breath is given, cardiac output is jeopardized (positive-pressure breath decreases venous return and subsequent cardiac output), including cerebral blood flow.

Hyperglycemia has been associated with unfavorable neurologic outcomes in adult patients with stroke and an increase in mortality for adults with critical illness. Maintaining good glycemic control in critically ill medical and surgical adult patients has been demonstrated to improve morbidity and mortality. There are no published studies in children, but it may be that hyperglycemia is also not useful in pediatric patients. However, hypoglycemia is a significant risk factor in young children particularly and should be prevented. Thus, glycemic control is becoming more important in the management of critically ill patients, and the patient is probably served best by maintaining normoglycemia.

Fever results in increased metabolic activity of the brain with worse outcomes noted post-cardiac arrest in both animals and humans. For this reason, fever should be assiduously prevented. Based on an international, prospective, randomized pediatric study (Therapeutic Hypothermia After Pediatric Cardiac Arrest—THAPCA study), the 2015 AHA Resuscitation Guidelines

recommend continuous temperature measurement for the first 5 days after arrest with goal temperature either normothermic (36–37.5° C) for these 5 days, or a combination of 2 days of mild hypothermia (32–34° C) followed by 3 days of normothermia. Similar targeted temperature strategies have also been recommended for adults with aggressive assessment and control of any fever.

Postischemic and recurrent seizures secondary to metabolic abnormalities (hypoglycemia or hypocalcemia) may occur and should be treated aggressively. IV lorazepam (0.05–0.1 mg/kg) is often effective and may be followed by IV phenytoin (20 mg/kg) (or fosphenytoin in young patients or in patients with cardiovascular instability) for additional control. Children who have had an intracranial bleed may be at higher risk for seizures and are often treated with phenytoin prophylactically. Although it may not be possible to fully implement these therapies until the child is admitted to the pediatric critical care unit, they often need to be initiated while arrangements are being made for transport to such a facility.

**RENAL.** The goal for urine output should be between 1 and 2 mL/kg/hr. Because the adequacy of urine output is an indirect measurement of the adequacy of cardiac output, a bladder catheter is recommended whenever concern exists about a child's hemodynamic state. Low urine output may require an adjustment of preload by infusing a fluid bolus or an adjustment of vasoactive drugs to improve cardiac contractility. It is essential to use the urine output in conjunction with other assessments of the cardiovascular system, such as heart rate, pulses, BP, and capillary refill, because urine output may be low for other reasons.

**INFECTIOUS.** After providing the initial management of a critically ill patient, including the patient who has suffered a respiratory or cardiac arrest, early treatment for suspected infectious disease should occur. After suitable cultures are taken (usually at least a blood and urine culture), broad-spectrum antibiotics should be started to cover the most likely causes. Ceftriaxone at 50 mg/kg IV or intramuscularly for possible sepsis or 100 mg/kg for possible meningitis is an excellent choice for patients who are older than 6 weeks; for those younger than 6 weeks, ampicillin plus gentamicin or cefotaxime should be used so that infections from the perinatal period are covered. If herpes encephalitis is a possibility, acyclovir should also be started.

If bacterial sepsis is present and antibiotics are given, significant hemodynamic instability may occur within an hour of antibiotic administration. As bacteria die, a significant release of inflammatory mediators will occur, resulting in vasodilation, an increase in capillary permeability, third-spacing, depression of myocardial function, and concomitant hypotension. Additional boluses of fluid may be required to maintain preload, and continuous monitoring of hemodynamics is essential, particularly if the patient is to be transported to another facility.

**HEMATOLOGIC.** As part of the initial assessment (tertiary assessment), it is important to make sure that the child has a sufficient number of red blood cells to transport oxygen and a sufficient number of white blood cells to fight infection. Severe anemia may significantly interfere with oxygen carrying capacity

and require correction. Moreover, ongoing blood losses may occur that are occult, particularly in trauma victims. Additional laboratory studies that should be obtained in addition to hematocrit and hemoglobin include platelets, prothrombin time, partial thromboplastin time, and international normalized ratio. Coagulation disturbances are extremely common in critically ill patients and may require early correction if the child is bleeding. It is best to discuss the need for correction of these parameters with a tertiary care center before providing therapy, because transfusions themselves may result in complications.

**METABOLIC.** In the postresuscitation phase of a critically ill child or a child who has had a cardiac arrest, several minerals require correction to optimize cardiac function. These minerals include calcium, potassium, phosphate, and magnesium. Restoration of all 4 of these ions to normal levels will allow for best cardiac muscle function and reduce the likelihood of an arrhythmia mediated by a deficiency in one of these minerals. If replacement is necessary, infusion over an hour is the norm, with continuous ECG monitoring for any arrhythmias and concomitant frequent BP checks. Severe acidosis (pH <7.20–7.25; base deficit of –6 or more), especially in a recently arrested patient, should probably be corrected by the administration of sodium bicarbonate at 1 mEq/kg. Hyperglycemia should also be prevented, with blood glucose levels kept below 150 mg/dL. Hyperglycemia may result in glycosuria with an osmotic diuresis and a decrease in intravascular volume or preload with subsequent worsening of cardiac output.

### Interfacility Transport

Agreements, protocols for specific clinical situations, and general protocols for transport to the regional pediatric tertiary or quaternary care center should be prepared in advance by key stakeholders. Input from primary care physicians (pediatricians, family practitioners), community hospitals or emergency rooms, regional pediatric hospitals (especially pediatric emergency medicine and critical care physicians), out-of-hospital emergency medical service providers, and insurance companies is crucial to this effort. Developing a general system of pediatric emergency transport in an area helps ensure that children will likely reach definitive care faster and more safely, and will receive the best care possible. In planning such a system, consideration should be given to the types of expertise (physicians, nurses, laboratory, radiology, inpatient beds) present in each local facility or region, the geography (including terrain, weather factors, and distance from regional pediatric centers), the availability and expertise of out-of-hospital or pre-hospital care providers, the transport modes available (ground vs air), and the mechanisms necessary for effective and efficient communication. An important point to note is that the sending facility is responsible for ensuring that both the transport and the facility to whom the child is transported are appropriate.

Even though a general system of pediatric transport care may be in place, each pediatric patient who requires transfer should be assessed thoroughly to



determine the child's specific needs. Decisions must be made regarding the speed of transport to a pediatric tertiary care facility, the makeup of the team that is to transport the child, the need for a pediatric specialty transport team, and the mode of transport (air vs ground; weather considerations). The expertise and comfort level of the providers who gave initial care should also be assessed along with their ability to provide care in the interim until the transport team takes over. Because of the complexity of these decisions, a pediatric transport expert from the regional center must be consulted to give recommendations about the preparation and method of transport. In many regional pediatric centers, formal pediatric transport programs are in place to assist in this transfer process, with experienced teams led by trained pediatric transport nurses overseeing the transports and coordinating the process under the supervision of pediatric intensivists or pediatric emergency medicine physicians.

To ensure that decisions about the transport can be made as easily as possible, the referring physician should provide the following information to the consulting or receiving facility:

1. The referring hospital's name and location and the referring physician's name and telephone number
2. The child's name, age, and weight and the parents' names, address, telephone number, and insurance carrier
3. A history of the present illness and significant elements of the past history, including medications and any allergies
4. The current clinical status, including the level of consciousness, heart rate, presence and adequacy of peripheral pulses, capillary refill time, respiratory rate, air entry status, respiratory effort, skin color, body temperature, and BP
5. Results of diagnostic tests—laboratory, radiologic, ECG or echocardiographic; copies should be made of radiographs so that the receiving hospital can re-review, or the radiographs should be made electronically available
6. All medications and fluids administered, including dosages and times given
7. Number of IV or IO and central lines, including their infusion rates
8. Size of ET tube, cuffed or uncuffed, tip location on chest radiograph, and ventilator settings
9. Availability and condition of parents or primary care physician for providing consent for treatment

If a pediatric specialty team is unavailable for the transport, arrangements must be made to manage any problems that might occur during the transport, including clearly defining the person or persons who will be responsible, particularly which physician is accepting responsibility.

Communication should occur at multiple levels during the transport process. In addition to communication between referring and receiving physicians, communication should be established among nursing staff at both institutions, social workers (when available), and administrative personnel to deal with such factors as insurance and the admission process.

The Section on Transport Medicine of the AAP has published comprehensive guidelines for air and ground transport of critically ill pediatric patients.

## FINAL CONSIDERATIONS

### Family Presence During Resuscitation

It has become increasingly common for families to be present during pediatric resuscitation and invasive procedures. Families who have been present during a resuscitation have usually expressed how much it meant to them to be near to their loved one, even when the child did not survive, and how much they appreciated what the resuscitation team was trying to do. Although having the family present during such a stressful time may be difficult for some caregivers, it is now recognized that there is significant value to this presence. However, because many aspects of care might be confusing and frightening to the family during the resuscitation, a person must be designated to attend to the family and be able to explain what is happening.

Similarly, it is now recognized that not only is the family presence important during a resuscitation of a child, but there are many peri-resuscitation issues that need to be addressed. Appropriate communication with the family both during and after the resuscitation is critically important. Discussion of organ donation, autopsy, medicolegal issues, and appropriate follow-up with the child's primary care physician and/or specialists who have been involved with the care previously are all important. It is best that written protocols are established so that none of these aspects of care around the time of resuscitation are missed. The AAP, along with the American College of Emergency Physicians and the Emergency Nurses Association, have developed a policy statement that addresses many of these issues.

### Brain Death and Organ Donation

With aggressive attention to identifying children who are at risk for developing respiratory or cardiac arrest, instituting management to prevent further deterioration, and optimizing respiratory and cardiac arrest management when they do occur, the hope is that outcomes are better. Nevertheless, children continue to experience cardiac arrest with severe neurologic morbidity and mortality. Unfortunately, predicting accurately during a resuscitation which children will ultimately not survive and when to terminate resuscitation efforts is impossible. Longer efforts should probably be made for children who have primary hypothermia (eg, falling into freezing water) and who have ventricular fibrillation with rapid bystander CPR and quick defibrillation.

One of the most difficult situations after a cardiac arrest is when a child who is resuscitated from the initial cardiac arrest progresses to brain death over the next 24 to 48 hours. This is the time when great expertise is needed to help the family understand the concepts of brain death and its implications. Formal and strict criteria have been developed for pediatric patients and should be meticulously applied. Moreover, because many families would like to donate the



child's organs, a thorough and complete brain death assessment should be performed by the medical team while professional certified organ procurement staff (as determined by the US Code of Federal Regulations, 42 CFR 482.45 governing organ, tissue, and eye procurement) assist in ensuring the best donating outcomes for the family once brain death has been determined (the time of brain death is the same as the time of pronouncing the child dead).

In the event that the child cannot be declared brain dead, donation of organs may still be accomplished by removing the organs immediately (within minutes of cardiac death in the operating room) after withdrawing support in a hopeless situation. This type of patient is classified as *donation after cardiac death* (DCD), and specific protocols should be available for this method of donating organs. Although initially done primarily in adult patients who died, this is now increasingly common in pediatrics where families wish to have some good come out of their child's death.

### Do-Not-Resuscitate Orders

The purpose of basic and advanced life support is to prevent sudden, unexpected, and unwanted death. However, these therapies may not be indicated when a child has a terminal, irreversible illness in which death is not unexpected, when resuscitation is likely to result in a poor neurologic outcome, or when these efforts are likely to be futile. Whenever a decision to forego CPR is made after thorough discussion with the family, a do-not-resuscitate order should be written on the patient's order sheet and the physician should explain in a progress note both the rationale for the decision and the names of those who participated in making the decision. In addition, the order and the note should be very clear regarding what aspects of resuscitation should not be performed. For example, in some cases, the decision will have been to proceed with intubation in the event of respiratory arrest, but not in the event of cardiac arrest; or for

basic CPR for a limited time period with constant communication during the procedure; for others, neither intubation or basic CPR would be considered appropriate. Very careful communication and recommendations should be made by physicians who are responsible for these discussions. The relatively new discipline of palliative care can be very helpful in developing these discussions and clarifying the goals of treatment, including not performing CPR.

For children who have a high risk of cardiopulmonary arrest because of chronic or congenital underlying disease, discussions about resuscitation are best held in an anticipatory way so that there are no hasty decisions required in the event of an arrest. Once a decision has been made about the extent of resuscitation, it is very important that the documentation is available quickly so that these decisions can be honored. This is especially important in schools, child care centers, chronic care facilities, and other settings where an acute arrest can occur and both the staff and emergency medical service providers need to be aware of the decisions that have been made. In many states, such as New York, Maryland, and Pennsylvania, there is a universal Medical Orders for Life Sustaining Treatment (MOLST) form that is signed by physicians.

### SUMMARY

Since the introduction of the technique of basic CPR in the 1960s, many advances have been made in the management of children in respiratory and cardiac arrest. With ongoing research in this area, and with due attention to strategies that would prevent arrests from occurring in the first place, the incidence will likely decrease, and outcomes will improve. However, this circumstance will occur only if cardiac and respiratory arrests are seen as a public health problem that requires universal education and training in prevention, recognition, and basic treatment.



## Appendix B OUTPATIENT PROCEDURES

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Physicians who perform procedures in children need to be competent in basic procedures as well as the management of the sedated child, a core competency of which is airway management. This appendix addresses patient preparation, sedation and analgesia, sample collection for diagnostic and therapeutic purposes, vascular access for medication and fluid administration, airway management skills, and circumcision.

### PATIENT PREPARATION

The first step in any procedure is to communicate the reason for the procedure to the parents and child. By establishing a clear understanding among parents and child of what is to be done, a physician gains their confidence and facilitates proper care. Honest and accurate descriptions of the steps involved in the procedure allow the parents and child to control some aspects of the procedure (eg, when to start, from which arm to draw blood) and will also instill a greater trust in the physician. Procedures that the physician may consider routine and ordinary have great significance to the parents and child, so all procedures require explanation.

The parents and the patient should be informed about the indications for each procedure, the information that is to be gained from it, the risks of performing (or not performing) the procedures, and any complications that may arise because of the procedure. Parents should be given information about the degree and duration of discomfort and inconvenience their child will experience because of the procedure. Reassurance that the physician understands the child and the child's perceptions must be conveyed to the parents.

The spectrum of ages and ranges of development in children requires an adaptive approach by the physician. Parent and child perceptions and fears will require a calm, empathetic, and reassuring approach. The toddler's fear of pain, of being handled by strangers, and of separation from the parents must be considered. In older children, describing the procedure to them in a developmentally appropriate manner is important. In the older or socially mature child, a contract of cooperation can be established (eg, "You can help by holding very still").

Whether the parents will be in attendance during the procedure should be ascertained before any preparation of the child. Not every parent will want to be present; therefore, participation should be voluntary.

### MONITORING

Safe and efficient performance of a procedure requires monitoring the patient. Some procedures will require sedation for full cooperation of the patient, which necessitates specific monitoring. Monitoring

during sedation should be treated as if the child were undergoing general anesthesia. The American Academy of Pediatrics (AAP) has developed standards of care for monitoring and managing patients before, during, and after procedures. Box B-1 lists monitoring devices and equipment needed for procedures.

Oxygen saturation, heart rate, and respiratory rate must be monitored because children are particularly vulnerable to hypoxemia. The child's respiratory rate, effort, and airway-protective reflexes must be continuously observed.

The presence of an assistant whose only responsibility is to monitor the stability of the patient during the procedure is important for patient safety. This second caregiver's only responsibility should be to monitor the respiratory and hemodynamic status of the sedated child.

### SEDATION AND ANALGESIA FOR PROCEDURES

Sedation may be required for therapeutic as well as diagnostic procedures. The AAP has set the following goals during sedation and analgesia for procedures.

#### Goals for Sedation and Analgesia in Children

The physician who administers sedation must have a complete understanding of the risks, the medications used, and the criteria a patient must meet to discontinue close monitoring. Physicians and caregivers who administer sedation must be both competent and credentialed in airway management. The physician must be comfortable identifying and treating complications, including cardiorespiratory depression, airway obstruction, and emesis in all patients. Patients requiring sedation who have chronic diseases, especially patients who have neuromuscular, pulmonary, cardiac, or renal disease, are at risk for adverse events. Box B-2 lists goals for sedation and analgesia.

#### Assessing Risk

Physicians must identify factors that may place a child at risk for poor outcomes with sedation. The child's medical history, including chronic illness, problems with sedation or anesthesia, allergies to medications, and current signs or symptoms of illness must be fully

#### BOX B-1 Monitoring Devices and Equipment for Procedures

- Pulse oximeter
- Blood pressure cuff
- Cardiorespiratory monitor
- Resuscitation equipment, including resuscitation bag and mask
- Intubation equipment
- Airway suctioning equipment
- Flow sheet for documentation
- Oxygen source and delivery services
- Equipment for intravenous access

investigated. Appropriate fasting times before sedation are given in Table B-1.

The most common complication of sedation is loss of respiratory drive and the ability to protect the airway, leading to hypoxemia. However, the adequacy of a child's airway, and, therefore, the child's risk for airway compromise during sedation, can be estimated.

A physician trained in advanced airway management should be consulted if the child has a potential risk for a difficult airway. Best practices, as characterized in standardized protocols and national guidelines for sedation, reduce the risk of adverse events.

### Medications for Sedation and Analgesia

The type and amount of medication used for sedation will depend on the procedure, the degree of analgesia required, and the experience of the physician in charge of sedation. Some procedures (eg, diagnostic imaging) may require sedation and no analgesia. Other procedures may require only local analgesia and no sedation. Combinations of medications may be required to achieve the desired duration of sedation and analgesia. Because each situation is different, physicians should be familiar with the mechanisms, indications, interactions, contraindications, and side effects of a variety of medications used for sedation and analgesia. Commonly used medications are discussed briefly in this section; thorough reviews are available.

Topical anesthetic creams (eutectic mixture of local anesthetics [EMLA and ELA-MAX]) can provide local analgesia and may be useful as an adjunct to other agents. These creams are applied to the local site and covered with an occlusive patch for anywhere between 45 and 60 minutes for EMLA and 20 to 30 minutes for

ELA-MAX prior to the procedure. Cost and time should be considered when these agents are used. In some children, these creams can reduce the anxiety associated with certain procedures.

Local anesthesia can be produced by infiltration of the skin with lidocaine (1% solution, 10 mg/mL). Systemic effects of local lidocaine are rare, but may have serious consequences that include hypotension, seizures, and respiratory arrest. The maximum dose of locally infiltrated lidocaine is 5 mg/kg (0.5 mL/kg of a 1% solution).

A burning, stinging sensation accompanies infiltration of lidocaine as a result of its low pH. This may be minimized by using lidocaine buffered 10:1 by volume with sodium bicarbonate (1 mEq/mL). Slow injection of the buffered lidocaine also reduces the stinging sensation.

The most commonly used agent for sedation in children is midazolam. It is water soluble and has a rapid onset (1–5 minutes) and a short duration of action (45–60 minutes). It produces good anxiolytic effect and retrograde amnesia. The initial dose of midazolam is 0.05 to 0.1 mg/kg intravenously or 0.5 to 0.75 mg/kg orally. The intravenous (IV) dose may be titrated to effect with a maximum dose of 0.6 mg/kg. Hypotension and respiratory depression (especially when given with opioids) are the most common side effects. The side effects of midazolam, as with any of the benzodiazepines, may be reversed with flumazenil (0.005–0.02 mg/kg intravenously).

Fentanyl is a short-acting opioid that does not cause histamine release, making it an effective analgesic in children. As with all opioids, respiratory depression is the most common side effect; it may be reversed with naloxone (0.1 mg/kg/dose, maximum 2 mg/dose; may repeat every 2 minutes). If naloxone is used to reverse the side effects of opioids, repeated doses may be necessary because its effects are transient. If moderate to severe pain is anticipated, a combination of fentanyl and midazolam may be used. Again, the dose of each should be reduced by one-half if the patient has cardiac, respiratory, hepatic, or renal organ failure.

More potent drugs are available for procedures that will cause intense pain. Ketamine and propofol should be used only by physicians skilled in deep sedation management and experienced in the use of these agents. General anesthesia is a reasonable consideration. Consultation with an anesthesiologist or pediatric intensivist may be helpful.

### BOX B-2 Goals for Sedation and Analgesia

- Guard the patient's safety and welfare
- Minimize physical discomfort or pain
- Minimize negative psychological responses to treatment by providing analgesia and maximize the potential for amnesia
- Control behavior
- Return the patient to a state in which safe discharge, as determined by recognized criteria, is appropriate

**Table B-1** Fasting Guidance for Children Undergoing Sedation<sup>a</sup>

AGE	DURATION OF FASTING FOR MILK AND SOLIDS	DURATION OF FASTING FOR CLEAR LIQUIDS
0–5 mo	4 hr	2 hr
6–36 mo	6 hr	2 hr
>36 mo	8 hr	2 hr

<sup>a</sup>Guidance is for elective sedations. In situations in which emergent sedation is required and the patient does not meet the fasting requirement, the physician must weigh the risk of aspiration against the benefit of the sedation. Securing the airway to help prevent aspiration should always be considered in these situations.



### Discharge Criteria

Approximately 12% of children sedated for a procedure experience a serious adverse event, mainly hypoxemia. Most complications will occur during the procedure itself, but monitoring is necessary after the procedure. All patients should be monitored for a minimum of 30 minutes from the last dose of medication and should meet the criteria developed by the AAP before monitoring is discontinued. Box B-3 lists discharge criteria for children who have been sedated.

#### BOX B-3 Discharge Criteria for Children Who Have Been Sedated

- Cardiovascular function and airway patency are satisfactory and stable
- Patient can be easily aroused, and protective reflexes are intact
- Patient can talk (if age appropriate)
- Patient can sit up unaided (if age appropriate)
- For a very young patient or a child incapable of the usually expected responses, the presedation level of responsiveness or a level as close as possible to the normal level for that child should be achieved
- State of hydration is adequate

### SAMPLE COLLECTION

#### Blood

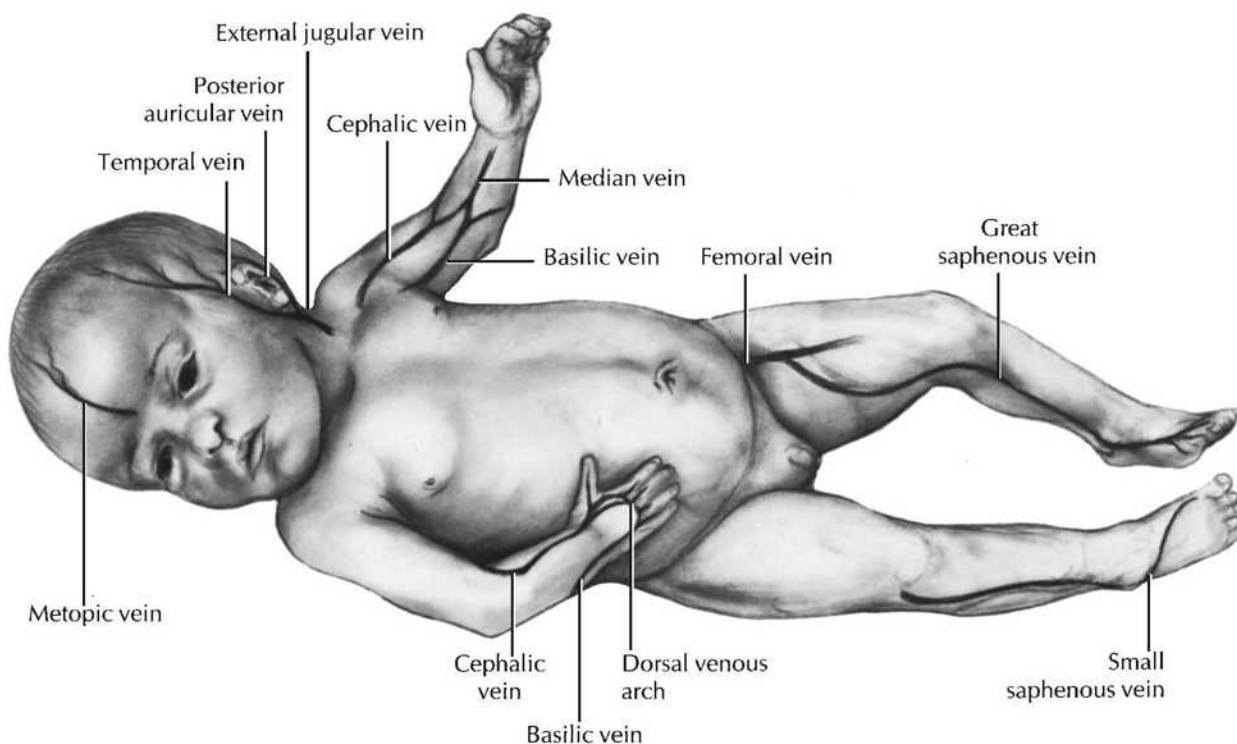
##### Capillary Puncture

Blood samples may be obtained from the capillary bed of a finger, toe, or heel. After the skin is warmed and prepared with alcohol, a firm stab wound is made with a lancet in the ventrolateral aspect of the distal phalanx, avoiding the pad and joint, or the posterior edge of the heel pad. Frequent wiping may be needed to prevent clotting and to obtain free flow without squeezing. Local pressure applied with dry gauze will stop the bleeding after the sample has been obtained.

##### Venipuncture

Figure B-1 illustrates the location of superficial veins commonly used to obtain blood samples. The largest superficial veins are those of the cervical and femoral areas, although these veins should be avoided for routine blood sampling.

For venipuncture of an extremity, the limb is restrained and the skin is prepared with alcohol. A tourniquet is applied to the extremity above the point of planned venous puncture tightly enough to produce venous stasis and vein distention, yet loosely enough to allow arterial perfusion. A 20- or 22-gauge needle or butterfly needle attached to a syringe may be used. The vein is stabilized by traction on the overlying skin along the longitudinal axis of the vein. The skin is pierced with the needle bevel up. The needle tip is then advanced subcutaneously and the vein is entered with a short jab to prevent its rolling away. Negative pressure



**Figure B-1** Superficial veins accessible for blood sampling and intravenous device placement.

in the syringe is used to withdraw the amount of blood needed. After the blood is obtained, the tourniquet is released, the needle removed, dry gauze applied with pressure to the site, and the extremity elevated for 1 or 2 minutes to prevent bleeding at the puncture site.

### Arterial Puncture

Assessment of the arterial blood gasses is essential in monitoring and diagnosing a variety of cardiopulmonary diseases. The radial artery is the preferred site for arterial puncture. It is in a consistent anatomic position and is well fixed by surrounding connective tissue. Arterial punctures may be complicated by arterial laceration, spasm, or hematoma.

The wrist is supported in a position of supination and slight dorsiflexion. The artery may be located at the wrist by feeling for the point of maximum pulsation. In newborns, it is usually found along the first flexor crease, at one-sixth of the width of the wrist measured from its radial edge (Figure B-2).

The size of the needle used varies with the patient's age (25-gauge for newborns and infants to 22-gauge for older children and adolescents). Care must be taken to avoid compressing the artery during restraint. The syringe is held as a pencil or dart would be held, and the needle is introduced into the artery at approximately a 45-degree angle. A flash of blood spurting into the syringe indicates a successful puncture. Gentle aspiration is required when a syringe is used. Many individuals find that performing the procedure with a butterfly needle is easier, especially in infants. Once collected, the sample should be sealed and any air bubbles removed, and then the sample should be placed on ice and sent to the laboratory for analysis.

### Cerebrospinal Fluid

The need to perform a lumbar puncture to rule out meningitis and other central nervous system infections must be weighed against the dangers inherent in performing a lumbar puncture in the presence of

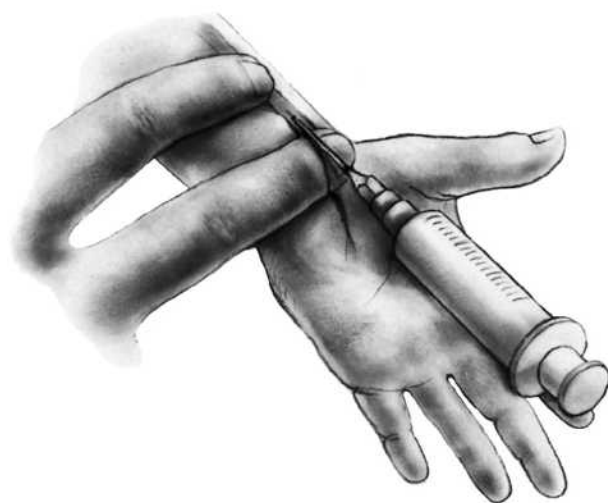
increased intracranial pressure. Increased intracranial pressure is a contraindication to lumbar puncture. Its presence dictates immediate neurosurgical consultation if collection of cerebrospinal fluid (CSF) is judged clinically necessary. Coagulopathy and thrombocytopenia are relative contraindications to lumbar puncture. If meningitis is suspected, antimicrobial therapy should be initiated promptly.

The position of the patient during lumbar puncture varies. Some physicians prefer infants to be held upright, whereas others prefer the lateral recumbent position (Figure B-3). Local or topical anesthetic (or both together) will assist in ensuring a painless procedure. Reassurance and clear communication with the older child is as important as the local anesthetic.

The preferred site is the L3-L4 interspace. It is located by determining the site at which an imaginary line drawn between the superior edge of the right and left iliac crests crosses the spine. The interspace above and below the L3-L4 space may also be used. The skin is prepared with appropriate antiseptic, and the site is draped. The person performing the procedure wears sterile gloves and a mask.

Care must be taken so that the needle enters the intervertebral space in the sagittal plane. This target requires several different perspectives of the proposed line of entry. A way to achieve this with a child in the lateral recumbent position is to make sure the line drawn between the superior edge of the right and left posterior iliac crests is perpendicular to the examination table. For a child in the upright sitting position, this line should be parallel with the surface of the examination table. The spinal needle is then advanced perpendicular to this line into the L3-L4 interspace aimed toward the umbilicus.

Once the skin is penetrated, the needle is advanced slowly in the sagittal plane. Although a distinct pop may be felt in older patients when the dura is pierced, such is not the case in infants. When the physician suspects that the spinal canal has been entered, the



**Figure B-2** Radial artery puncture. The position of the radial artery is determined by palpation.



**Figure B-3** Positioning an infant or a toddler for a lumbar puncture.

stylet is removed and the needle gently rotated to maximize the flow of CSF through the needle. If no flow is obtained, the stylet is reinserted and the needle is advanced further or is withdrawn and redirected. Care must be taken to avoid a so-called *bloody tap*, or *traumatic tap*, caused by pushing the needle into the venous plexus along the anterior wall of the spinal canal. A syringe should never be used to enhance the aspiration of CSF.

A stopcock and manometer are attached to the spinal needle to measure the opening and closing pressure. One milliliter of fluid is collected in each of 4 sterile test tubes to be used for bacteriologic, chemical, and cytologic determinations. In the case of a traumatic tap, the red cells in the first and fourth tubes should be counted. A traumatic tap usually results in fewer red cells in the latter tube. Blood from a central nervous system hemorrhage will have the same number of red blood cells in both samples. Once the fluid is collected, the stylet is replaced and the needle withdrawn. Direct pressure is applied to the puncture site.

## Urine

### Urethral Catheterization

To collect a sterile specimen of urine from a child who cannot produce a midstream, clean-catch, voided specimen, or to monitor urine output continuously, a catheter is inserted into the bladder through the urethra. The child is placed supine in a frog-leg position and prepared with sterile technique, including drapes, gloves, and skin cleansing. A small (8 French) straight or indwelling catheter should be used for a child; a No. 5 feeding tube may be used for an infant. The catheter or tube should be coated with sterile lubricating jelly. For a girl, the labia majora and minora are widely separated and the urethral meatus is identified, cleaned, and entered with the catheter. For a boy, the penis is held at a right angle to the abdomen while the catheter is placed in the urethra and advanced until urine is obtained. If the catheter is to remain in place, the balloon should be filled with sterile saline or water and connected to a closed, sterile collection system.

The catheter should not be forced at any time during the procedure. Damaging the urethra in both boys and girls is possible if the catheter is forced against resistance. Extreme care must be exercised in children with coagulopathy. Strict adherence to sterile technique will reduce infectious complications.

### Percutaneous Suprapubic Bladder Aspiration

A suprapubic bladder aspiration can be performed to obtain a sterile urine specimen. To ensure that there is adequate urine in the bladder, this procedure should not be attempted if the child has voided in the previous hour. An assistant holds the child in the supine frog-leg position while the operator percusses the bladder above the symphysis pubis and cleans the skin. To prevent urination during the procedure, the urethra should be compressed by pressure through the rectum of a girl or by direct pressure to the penis of a boy. The abdominal wall is entered in the midline 1 to 2 cm above the symphysis pubis with a 22-gauge, 1-inch needle attached to a syringe (Figure B-4). The needle

should be directed slightly cephalad and negative pressure maintained in the syringe as it is advanced.

The procedure may be repeated once if no urine is obtained with the first attempt. If the repeat attempt is unsuccessful, an hour should be allowed to elapse before trying again. When urine is obtained, the needle is withdrawn and the entry site is covered with a dry dressing. Complications include transient hematuria and, rarely, perforation of the bowel.

## Middle-Ear Fluid

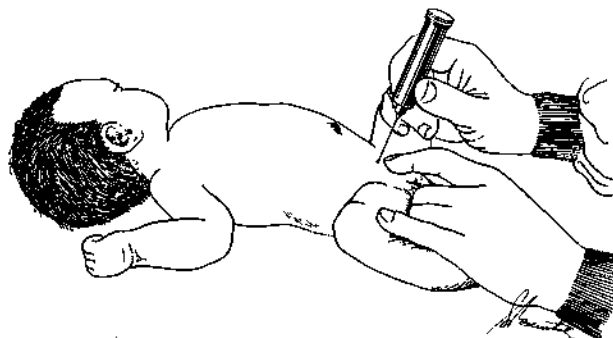
Tympanocentesis is most often performed to obtain cultures of middle-ear fluid. It may be particularly important for identification of persistent or refractory infection in the immunocompromised child. Tympanocentesis is contraindicated if the child has a bleeding disorder.

The child should be appropriately restrained by the assistant, who should hold the child's head absolutely immobile. The otic canal is cleansed with alcohol, and topical anesthetic should be placed in the canal. After cleansing and before the puncture, specimens should be taken from the ear canal and cultured to identify contaminating organisms.

The tympanic membrane is visualized through the open-ended otoscope. A 3.5-inch, 20- or 22-gauge spinal needle with a double bend (Z-shaped) allows clear visualization of the tip and the membrane. The needle puncture is made in the posterior inferior quadrant of the tympanic membrane. Gentle negative pressure is applied to withdraw middle-ear fluid. If no aspirate is observed, the needle can be flushed with nonbacteriostatic sterile saline into culture media.

## Pleural Fluid and Air

Pleural fluid can be analyzed for diagnostic purposes. In patients with large effusions, fluid removal may improve gas exchange. The same technique can also be used for the emergency relief of a tension pneumothorax. The site is determined by radiograph and by findings at physical examination. Ultrasound examination may help to determine the location of an effusion. When fluid is removed from the bases of the lungs, care must be taken to avoid damaging abdominal viscera. Anteroposterior, side up-side down, and lateral radiographs may aid in



**Figure B-4** Bladder tap for suprapubic aspiration of urine. The index finger of the opposite hand locates the symphysis pubis.



the determination of position and suggest the presence of loculated fluid.

The complications of thoracentesis include pneumothorax, hemothorax, and introduction of infection. Laceration of the abdominal viscera through the diaphragm can be avoided by appropriate selection of the puncture site. Removal of large amounts of fluid can result in hemodynamic compromise. Re-expansion pulmonary edema is a rare complication of fluid removal, but should be suspected in patients who develop tachypnea and hypoxemia after a pleurocentesis.

The positioning of the child depends on whether the anterior or posterior aspect of the chest is to be entered. The older child should be seated and leaning forward, either against the back of a chair or leaning on a bedside table. An infant or small toddler may be held in a hugging position against an assistant's chest.

The sites used for drainage of a pleural effusion or aspiration of free air include the anterior, middle, or posterior axillary line in the fourth, fifth, or sixth intercostal space. Other sites may be selected as dictated by the location of loculated collections of fluid. These sites may be selected with ultrasound guidance. A skilled radiologist can perform a computed tomography-assisted aspiration in difficult cases.

A wide area is prepared with an appropriate antiseptic, and with a 25-gauge needle, local anesthetic is infiltrated over the body of the rib just below the intended puncture site. The needle is inserted into the skin overlying the rib and then moved over the surface of the rib upward to the interspace while gentle aspiration is alternated with infiltration of the anesthetic solution so that the subcutaneous tissues and the pleura are anesthetized. The intercostal blood vessels and nerves lie along the inferior margin of each rib and can, therefore, be avoided by this approach.

Materials are simple—an 18- or 22-gauge plastic over-the-needle catheter, a sterile 50-mL syringe, a 3-way stopcock, and an appropriate sample container. The needle and catheter are advanced along the previously described tract, with gentle suction applied to the syringe. When the pleura are entered, the plastic cannula is threaded over the needle and advanced into the pleural space. A 3-way stopcock is attached to the catheter, and fluid is aspirated and placed in appropriate containers for Gram stain and culture. Pleural fluid may also be examined for white blood cells and differential counts, pH, protein, glucose, lactate dehydrogenase, and cell cytology as appropriate.

An alternative to needle thoracostomy for drainage of effusions is placement of a pigtail catheter or chest tube by use of a modified Seldinger technique. This method has the benefits of being easy and safe. A kit is available that contains the catheter, dilator, introducer needle, guidewire, and an adaptor that connects the catheter to large-bore rubber tubing for continuous suctioning. This system can remain in place as an indwelling catheter if needed for continual drainage of fluid or air collections. This is a relatively painful procedure, so appropriate sedation and analgesia may be required.

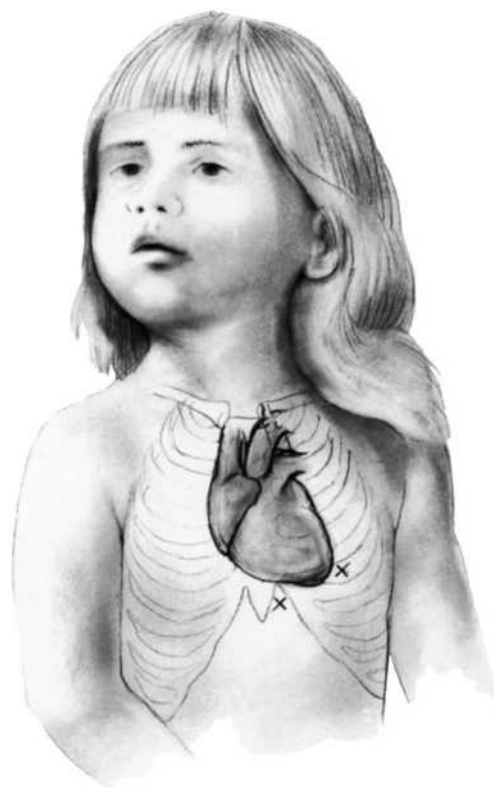
The tube is inserted by first advancing the needle over the superior margin of a rib, usually T4 to T6, in the midline or anterior axillary line, into the pleural

space. Immediately after entering the pleural space, a guidewire is advanced through the needle into the pleural cavity. A small stab wound, 2 to 4 mm in diameter, is made at the site where the guidewire enters the skin. A hard polyurethane dilator is advanced over the wire. This dilator enlarges the tract to facilitate passage of the pigtail catheter. With the wire position fixed, the dilator is withdrawn. The catheter is threaded over the wire and advanced into the pleural space; then the wire is withdrawn. The catheter is attached to the large-bore tubing and placed on the appropriate suction device. The pressure in the suction device should be set at 15 to 20 cm H<sub>2</sub>O. Chest radiographs document the position of the catheter. The catheter is secured to the chest with a small adhesive dressing or simply sutured in place.

### Pericardial Fluid and Air

Pericardiocentesis is a high-risk procedure, but it can be lifesaving. The dangers of this procedure must be weighed against the urgency of diagnosing a pericardial effusion or an unchecked cardiac tamponade. In nonurgent situations, consultation with a cardiologist or intensivist is suggested. Complications of the procedure include myocardial injury, laceration of a coronary artery, cardiac arrhythmia, and infection. The internal mammary arteries are within 2.5 cm of the sternal border and may also be damaged.

The alternate points of entry into the chest are illustrated in Figure B-5. The preferred site is at the left



**Figure B-5** Two sites for aspiration of fluid or air from the pericardial sac.



chondroxiphoid angle. Whenever possible, fluoroscopy or echocardiography should be used for guidance.

The patient should be supine at approximately a 30-degree angle and carefully restrained with appropriate cardiorespiratory monitoring. Appropriate sedation and analgesia will be needed. A wide area is prepared with antiseptic. The entry site is infiltrated with lidocaine. A 50-mL syringe is connected to a 3-way stopcock and an 18-gauge needle. The needle is directed inward and medially when the intercostals approach is used. When the chondroxiphoid approach is used, the needle is aimed upward and posteriorly. Gentle negative pressure should be applied to the syringe as the needle is advanced. The fluid should be aspirated slowly. The needle is withdrawn, and a simple sterile dressing is applied over the puncture site.

A modified Seldinger technique may be used to place a pigtail catheter for long-term drainage of a pericardial effusion.

### Vascular Access

#### Emergency Intravenous Access and Protocol

The small size of the child, the stress of the situation, and venous collapse make insertion of a peripheral IV device difficult in the critically ill child. A protocol approach to the problem of establishing venous access has been suggested. In a series of pediatric resuscitations, more than 10 minutes was required to establish venous access, and, in 6% of the subjects, no access could be established. Best-practice guidelines suggest that in the treatment of shock, attempts at peripheral vein insertion should be limited to 90 seconds, and then an intraosseous device should be placed.

Current recommendations and standards of care guidelines for shock and cardiorespiratory arrest mandate the early use of the intraosseous needle in emergent situations. Undue time should not be spent on attempts at placing peripheral or central venous lines when no other vascular access is present. All physicians who treat children should familiarize themselves with this technique.

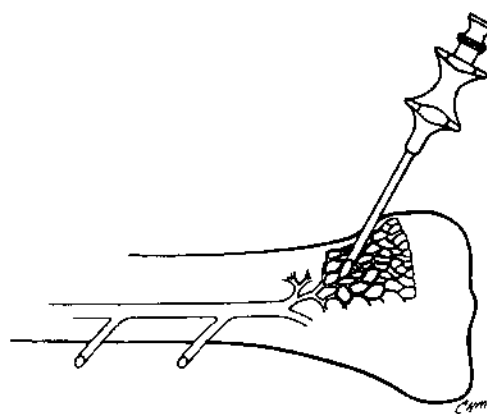
#### Intraosseous Infusions

Intraosseous infusion is a procedure that should be familiar to all who provide care to children. It can be used in the care of a critically ill child younger than 6 years whenever a delay in establishing venous access might compromise the patient. Treatment should not be delayed while waiting for central access. The ability to place an intraosseous needle allows even a technically inexperienced person to gain immediate access to the intramedullary venous system, which is continuous with the venous circulation. Crystalloid and colloid for fluid resuscitation, blood, plasma, catecholamines (eg, epinephrine, dopamine), glucose, calcium, and sodium bicarbonate can all be administered by the intraosseous route. Intraosseous needles manufactured specifically for this purpose should always be available.

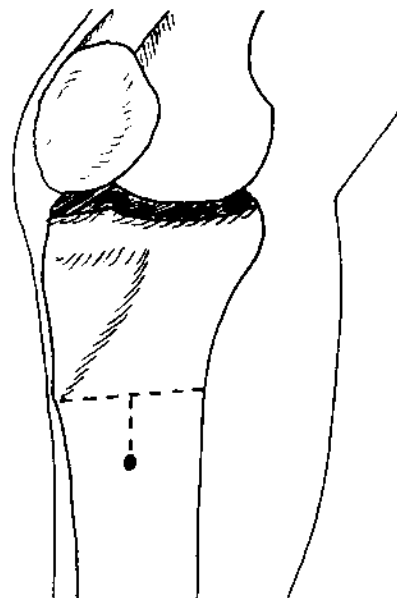
The preferred sites are the anterior medial surface of the proximal tibia and the medial surface of the distal tibia proximal to the medial malleolus (Figure B-6, Figure B-7, Figure B-8). The iliac crest, sternum, and femur are alternative sites. The epiphysis must be avoided when the proximal tibia is used. The cortex in

the midshaft of the tibia is difficult to penetrate, although it is sometimes used in emergencies. In a child older than 6 years, the thick cortex at the proximal and distal tibia prevents use of these sites.

The site is aseptically prepared. The needle is advanced perpendicular to the bone, with firm pressure in a rotary motion. Entry to the marrow cavity is detected by decreasing resistance. Aspiration with a syringe should produce blood and marrow. To clear the needle, it should be flushed with 3 to 5 mL of sterile saline in a sterile syringe. Resuscitative medications



**Figure B-6** Intraosseous needle in position in the medullary sinusoids. Marrow aspiration documents correct placement. (From Spivey WH. *Intraosseous infusions*. J Pediatr. 1987;111:639–643. Reprinted with permission.)



**Figure B-7** Insertion of intraosseous needle at the proximal tibia. The tibial tuberosity and the medial border of the tibia are palpated. The needle is inserted halfway between these 2 points and 1–2 cm distal, pointing in a caudal direction away from the joint space. (From Spivey WH. *Intraosseous infusions*. J Pediatr. 1987;111:639–643. Reprinted with permission.)

should be flushed with 3 to 5 mL of saline. The device is then connected to standard IV tubing. The flow rate should be steady, and the site must be frequently monitored for extravasation. If the needle dislodges or fluid extravasates, the opposite leg should be used. Compartment syndrome has been described when fluid extravasates into soft tissue of the leg. This complication can be limited by changing the site if evidence exists of edema or vascular compromise.

### Percutaneous Intravenous Infusions

The location of accessible superficial veins suitable for percutaneous IV infusions is demonstrated in Figure B-1. All physicians who care for children should be adept at gaining percutaneous intravascular access. Early fluid resuscitation decreases mortality in critically ill children. The veins of the extremities and scalp are commonly used; the latter have no valves and can be punctured in either direction. Skin preparation should be especially meticulous when scalp veins are used because they communicate with the dural sinuses through emissary veins.

The child is positioned and immobilized. A tourniquet is applied above the vein to be infused, and the

skin is cleaned with alcohol. A 20- to 24-gauge percutaneous needle catheter is used to pierce the skin. The vein is then punctured, and when blood is seen in the hub of the needle, it is stabilized and the catheter sleeve advanced into the vein. When the vein is entered, the tourniquet is removed and blood flow is tested. Saline is then injected through the catheter to check for extravasation.

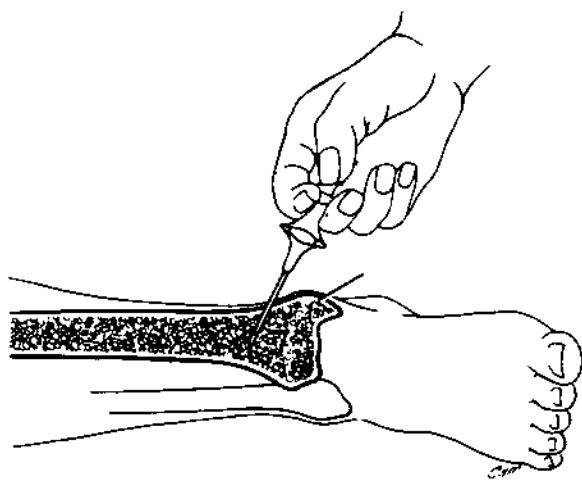
### Heparin Lock

An IV catheter may be converted to a heparin lock for intermittent administration of medications. Heparin in normal saline solution is used to flush and fill the catheter and tubing. A concentration of 10 U/mL of heparin prevents clotting within the catheter without affecting the patient. Prolonged use of any indwelling device carries the risk of local and disseminated infection.

### Peripherally Inserted Central Venous Catheters

Peripherally inserted central catheters (PICCs) can be inserted in larger peripheral veins and provide a safe route for long-term alimentation, antibiotics, medication, and hypertonic fluid therapy that are more appropriately delivered to the central circulation. The Centers for Disease Control and Prevention recommend the use of these catheters as an alternative to surgically placed or traditional central venous catheters for long-term use. Data suggest that the use of PICC lines may reduce infectious and thrombotic complications. These catheters are composed of biologically inert silicone or polyurethane. Specialized PICC lines have been designed to be used with rapidly infusing contrast systems used for computed tomography scans. In many institutions, they are placed by nurses with special training.

Complications are similar to other types of central catheters, but are rare, reported to occur in 3% to 10% of centrally placed catheters. Expected duration of use is nearly 2 weeks. Catheters with tips placed in a non-central location seem to have a higher rate of complications (most commonly thrombosis). PICC catheters are commonly placed in the large veins in the antecubital fossa or the basilic vein of the upper arm. In neonates and young infants, smaller PICC lines can be inserted in the saphenous vein or in scalp veins. They are available in numerous sizes and with multiple lumens for children of various ages (Table B-2).



**Figure B-8** Insertion of the intraosseous needle in distal tibia. The needle is inserted at the junction of the malleolus and the tibial shaft. The tip is aimed away from the joint space. (From Spivey WH. *Intraosseous infusions*. J Pediatr. 1987;111:639–643. Reprinted with permission.)

**Table B-2** Venous Catheter Sizes

AGE	PICC	FEMORAL VEIN CATHETER	SUBCLAVIAN VEIN CATHETER	INTERNAL JUGULAR CATHETER
Newborn	24-gauge	3 F	3 F	3 F
3–12 months	3 F	4 F	4 F	4 F
1–4 years	4 F	4 or 5 F	4 or 5 F	4 or 5 F
4–8 years	5 F	5 F	5 F	5 F
Adolescent	6 F	7 F	7 F	7 F

F, French

PICC lines are longer than other central catheters and are, therefore, more useful for long-term delivery of medications and other therapies than for rapid fluid resuscitation.

PICC line placement is similar to other central catheter placement and uses the modified Seldinger technique as described previously. The catheter must be cut to the appropriate length to reach the central circulation. The thin stiffening guidewire within the catheter must be pulled back to the desired length prior to cutting the catheter. The vein to be cannulated may be identified by palpation or with the use of ultrasound guidance. A tourniquet is used to increase the size of the peripheral vein. The vein is accessed with either the introducer needle or a standard peripheral IV. A wire is passed through either the introducer needle or peripheral IV. The introducer needle or peripheral IV is removed while leaving the wire in place. Unlike with other central catheters, a peel-away dilator is then introduced over the wire after nicking the skin. Some peel-away dilators are designed to be placed using standard peripheral IV insertion technique without a wire. Once the dilator is in place, the wire and inner cannula are removed. The trimmed catheter is inserted into the peel-away dilator, which is peeled away as the catheter is advanced to its desired position.

### Central Venous Catheters

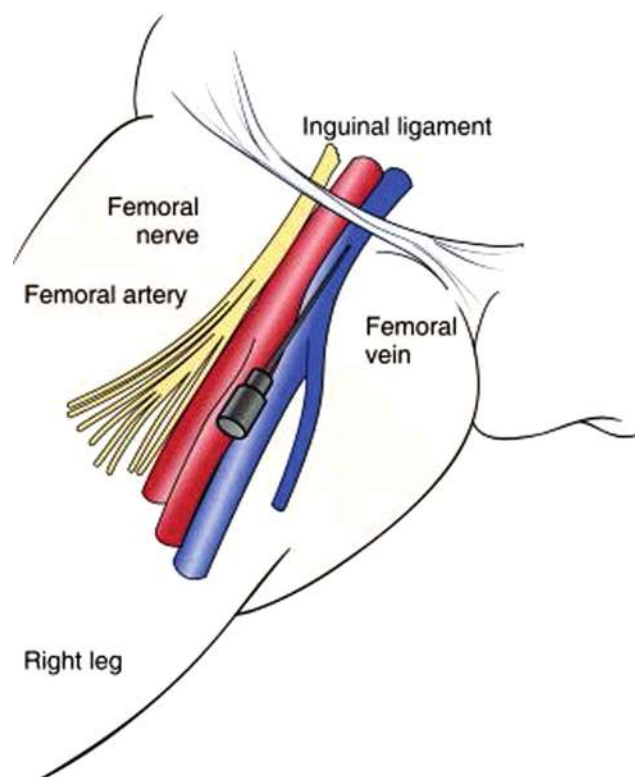
In general, central venous catheters are used in critically ill children. These catheters may be necessary for fluid administration, maintenance of cardiac output and blood pressure by direct infusions of vasoactive drugs, and central venous pressure and venous oxygen saturation monitoring. A central venous catheter is not immediately required for resuscitation. In this situation, an intraosseous device is recommended. However, in advanced stages of shock therapy, central venous pressure and central venous oxygen saturation measurements are invaluable in evaluating and choosing treatment options.

Complications of central venous cannulation include bleeding, infection, inadequate venous drainage, thrombus formation, and inadvertent penetration of viscera or a vessel wall. The incidence of inadvertent penetration of viscera or other vessels has been reduced by the use of ultrasound by experienced physicians. These complications must be weighed against the benefits of obtaining secure, large-bore venous access, the need to determine the central venous pressure, and the need to measure oxygen saturation. The incidence of catheter-related infections has been reduced with the introduction of catheters impregnated with antimicrobial drugs. Deep-vein thrombosis is a frequent complication of indwelling central vascular catheters. The risk of occurrence of a deep-vein thrombosis is related to young age and the presence of cancer. The peak timing of detection is within 4 days of insertion. If swelling is detected in an extremity in a child with a central vein catheter, deep-vein thrombosis should be suspected, and ultrasonography should be performed. Catheters manufactured with heparin bonding have been reported to reduce thrombosis and infection.

### Femoral Vein Catheter Placement

The femoral vein is a safe, easily accessible vessel for cannulation with a single- or multiple-lumen catheter. With reasonable care, it can be used for relatively long-term access as well, although the longer the catheter is in place, the higher the risk is for a bloodstream infection. Thrombosis is a potential complication. The consistent anatomy of the area and proximity to the femoral arterial pulse allow the vessel to be easily located, because it lies 1 to 2 cm medial to the artery and 2 to 4 cm below the inguinal ligament (Figure B-9). It is usually easy to visualize by bedside ultrasound, even in obese or hypotensive patients. Most bedside ultrasound devices have a Doppler function that makes it easier to distinguish between the femoral vein and femoral artery. The vein will be larger, compressible, and less pulsatile. When the femoral artery pulse cannot be located because of obesity or hypotension, the femoral artery can be easily confused with the vein and inadvertently catheterized. A transcutaneous Doppler or bedside ultrasound can facilitate placement.

The patient should be supine, and the groin should be widely prepared with an appropriate antiseptic



**Figure B-9** Approach to the femoral vein. The patient is flat and supine, with the thigh slightly abducted and externally rotated. The introducer needle enters the skin 2 to 3 cm distal to the inguinal ligament and 0.5 to 1 cm medial to the pulse of the femoral artery. (From Schexnayder SM, Storm EA, Stroud MH, et al. *Pediatric vascular access and centeses*. In: Fuhrman BP, Zimmerman JJ, Carcillo JA, et al, eds. *Pediatric Critical Care*. 4th ed. Philadelphia, PA: Elsevier Saunders; 2011:154. Reprinted with permission.)



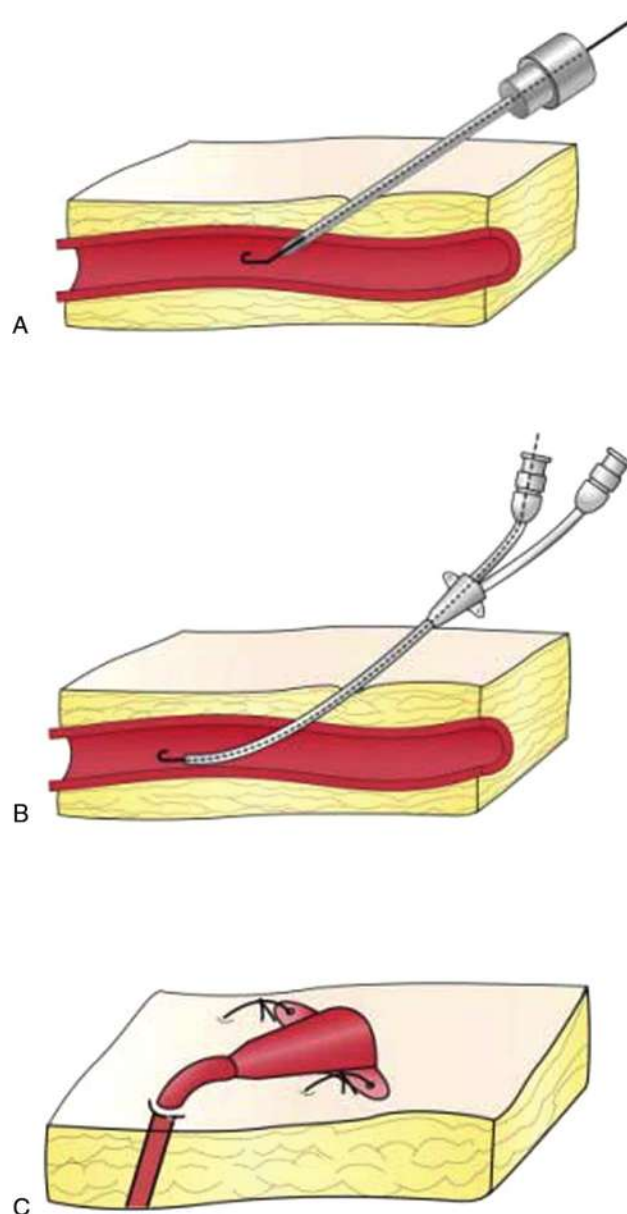
agent. For infants, a towel roll under the hips can facilitate access to the vein. Sterile technique, including gloves, gowns, and masks, and a sterile sleeve for the ultrasound probe are important for preventing infections. The femoral artery is palpated 2 to 4 cm below the inguinal ligament; the vein is 1 to 2 cm medial to the artery. The skin and immediate subcutaneous tissues are infiltrated with 1% lidocaine.

The operator must be familiar with the use of the modified Seldinger technique for percutaneous placement of a catheter over a guidewire, which is placed through an introducer needle (Figure B-10). Manufacturer-supplied kits containing an introducer needle, dilator, guidewire, and catheter are available. The appropriate-sized catheter has an outer diameter of 3F to 4F for patients under 1 year of age, 5F to 6F for children 1 to 7 years old, and 7F for children 8 years or older. A syringe that contains 2 to 3 mL of heparinized saline is attached to the introducer needle. The needle is introduced at a 30- to 45-degree angle from horizontal and aimed at the umbilicus. Care should be taken to avoid advancing the needle beyond the inguinal ligament because the peritoneum, bowel, and bladder can be perforated. Its tip should be visualized on the ultrasound image and can be followed into the vessel. The needle tip can often be seen indenting the vessel wall substantially, and it is not uncommon to get blood flow or needle visualization in the lumen of the vessel until the needle is gently pulled back. With continuous, gentle aspiration, the needle is advanced into the vein. When good blood return is documented, the syringe is removed. The guidewire is then advanced into the vein. Resistance to the passage of the wire should be minimal (if resistance is encountered, the needle and wire must be removed simultaneously to prevent shearing the wire off in the patient's vein). The needle is then withdrawn, leaving the wire in place. An incision, 2 to 4 mm deep, is made with a scalpel at the point where the guidewire enters the skin. A dilator is threaded over the wire and passed through the skin and subcutaneous tissue and into the vessel. It is then withdrawn, leaving the wire in place. The catheter is threaded over the wire. Care must be taken to ensure that at least 1 to 2 cm of the guidewire extends from the proximal end of the catheter before it is threaded into the vein; otherwise, the wire can be lost in the vessel. The physician, being careful to avoid changing the position of the wire, slowly advances the catheter over the wire to the desired distance, and then removes the wire. The catheter is then sutured in place. The position should be verified by radiography. Each lumen in the catheter should flush and aspirate easily.

### Subclavian Vein Catheter Placement

The subclavian vein is readily accessible. Risks include pneumothorax or accidental penetration of the subclavian artery, hematoma formation, hemorrhage, and thrombosis. The risk of this procedure must be balanced with the skill of the physician and the benefit to the patient.

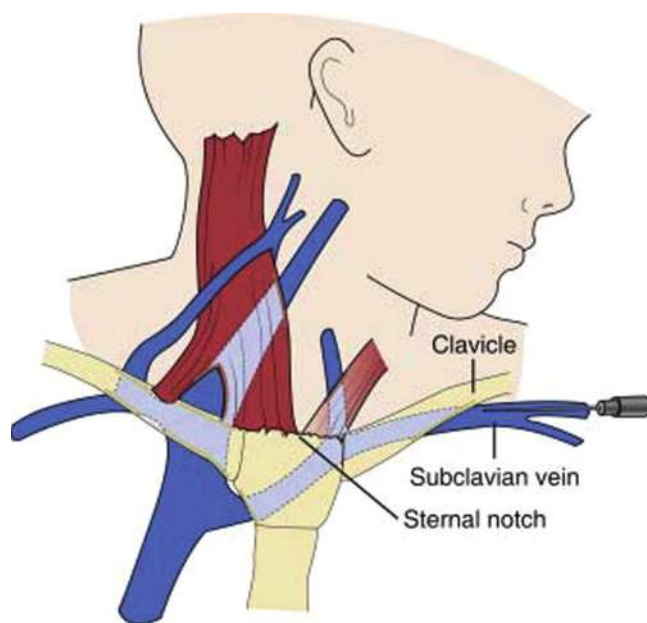
Catheterization kits containing an introducer needle, dilator, guidewire, and catheter are available.



**Figure B-10** A, Guidewire is placed through the introducer needle into the lumen of the vein. B, Catheter is advanced into the vein lumen along the guidewire. C, Hub of the catheter is secured to the skin with suture. (From Schexnayder SM, Storm EA, Stroud MH, et al. *Pediatric vascular access and centeses*. In: Fuhrman BP, Zimmerman JJ, Carcillo JA, et al, eds. *Pediatric Critical Care*. 4th ed. Philadelphia, PA: Elsevier Saunders; 2011:152. Reprinted with permission.)

The appropriate-sized catheter has an outer diameter of 3F for infants, 4F for toddlers, 5F for children aged 4 to 12 years, and 7F for adolescents. The right subclavian vein is preferred over the left because of its more direct entry to the superior vena cava, and because the risk is reduced of pneumothorax (the right lung lies lower in the thorax than the left) and injury to the thoracic duct, which lies in the left hemithorax.





**Figure B-11** Approach to the subclavian vein. The patient is supine, in slight Trendelenburg position, with a small roll along the spine between the shoulders. The needle enters the skin at the junction of the lateral and middle thirds of the clavicle and is directed toward the sternal notch in the horizontal plane. (From Schexnayder SM, Storm EA, Stroud MH, et al. *Pediatric vascular access and centeses*. In: Fuhrman BP, Zimmerman JJ, Carcillo JA, et al, eds. *Pediatric Critical Care*. 4th ed. Philadelphia, PA: Elsevier Saunders; 2011:154. Reprinted with permission.)

The patient is restrained and placed in the Trendelenburg position. The child's face is turned 90 degrees away from the intended puncture site. A 3-inch towel roll is placed along the long axis of the thoracic spine between the shoulder blades. The area overlying the puncture site is cleansed widely, and drapes are used to provide an aseptic field. Masks, gloves, and gowns are used. The infraclavicular approach is simpler for most physicians to learn (Figure B-11). The vein lies approximately parallel to the proximal third of the clavicle. The subclavian artery runs posterior to the vein beneath the anterior scalene muscle. The skin overlying the puncture site and intended tract is infiltrated with 1% lidocaine.

The introducer needle is placed just medial to the midclavicular line 2 to 3 cm below the inferior border of the clavicle. The needle is aimed toward the mid-sternal notch and is advanced to the inferior border of the medial position of the clavicle. A syringe containing a few milliliters of saline is attached to the introducer needle, and negative pressure is applied to the barrel of the syringe; the needle is advanced deep to the clavicle on a course nearly parallel to its medial portion. Small cephalad adjustments of the target point (approximately 0.25-cm increments) can be made if the vein is not entered immediately.

When the vein has been entered, as evidenced by blood entering the syringe, the hub of the introducer

needle should be held securely in place and the syringe removed. Caution must be exercised because air may be introduced into the vein as the patient increases the negative pleural pressure when initiating a breath. Therefore, the proximal orifice of the needle must be temporarily occluded by placing a finger over the opening.

The flexible, spring-loaded end of the guidewire is inserted into the introducer needle and advanced through the bore of the needle into the subclavian vein and subsequently into the superior vena cava. A minimum of 3 cm of wire is passed beyond the estimated tip of the needle. A cardiac arrhythmia may signal that the guidewire has been passed too far into the right ventricle, in which case it should be drawn back. The proximal end of the wire should be held securely as the introducer needle is removed.

The catheter is flushed with heparin solution and advanced over the guidewire after the skin and subcutaneous tissues have been stretched with the dilator. Once the catheter is in the desired position, the wire is removed. The proximal end of the catheter is attached to the central venous pressure monitoring or IV fluid administration system. The catheter is sutured into place and covered with a sterile dressing.

Placement should be verified by radiography. The typical a, c, and v wave of a central venous catheter should be present. The catheter should flush and aspirate blood with ease. The tip of the catheter should be in the distal third of the superior vena cava, above the junction with the right atrium.

### **Umbilical Vessel Catheter Placement**

Catheterization of the umbilical vein is useful in newborns for emergency correction of acidosis, hypoglycemia, and hypotension and for the measurement of central venous pressure. The complications of umbilical vein catheterization include sepsis and micro-embolization from catheter-induced thrombosis. An umbilical venous catheter can be easily misplaced into a branch of the portal venous system, and injecting hyperosmolar solutions that contain substances such as glucose or sodium bicarbonate can lead to portal-vein thrombosis and hepatic necrosis. Umbilical vein catheters have also been implicated in cases of necrotizing enterocolitis and spontaneous perforation of the bowel.

Manufactured kits are available, and the catheter size is based on the patient's weight: a 3.5F catheter should be used for infants weighing less than 1,500 g and a 5F catheter for those weighing more than 1,500 g. The small premature infant is susceptible to chilling during the procedure; thus, a radiant warmer should be used. Special attention to aseptic technique—surgical scrubbing of the operator's hands, antiseptic preparation of the baby's abdomen and umbilical cord, and maintenance of a sterile field—is essential. The physician should be gloved, masked, and gowned.

The catheter is measured to determine the length of insertion by measuring the distance from the infant's shoulder to the umbilicus by the conversion method shown in Figure B-12. This length ideally places the catheter at the junction of the inferior vena cava and

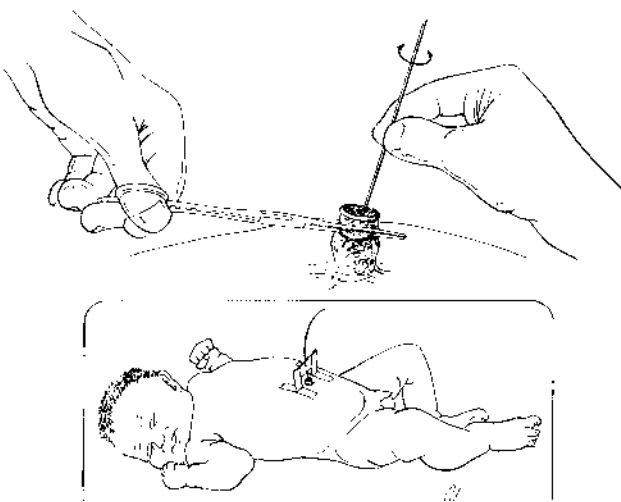
the right atrium. Care must be taken to avoid covering the infant's chest in such a manner that apnea or malfunction of the heat probes or monitor leads will go undetected.

An assistant provides gentle traction to the cord stump while the physician transects the cord with a scalpel 1 to 1.5 cm above the skin. Gauze sponges should be available for tamponade to control oozing of blood from the umbilical vein; the amount of oozing is usually insignificant. The cord stump is inspected to locate the thin-walled umbilical arteries. The catheter is attached to a 3-way stopcock and a syringe containing heparinized saline solution. The catheter is flushed with the heparin solution. Minimal traction on the superior edge of the cord stump may be helpful in locating the orifice of the umbilical vein; this is gently dilated with pickup forceps or a small probe, and the catheter is inserted the predetermined distance. Resistance is occasionally met at the level of the abdominal wall or at the level of the ductus venosus. Gentle pressure and partial withdrawal and rotation of the catheter usually overcomes this resistance; force should not be used. The position of the catheter should be verified by radiograph except under emergency circumstances.

Care must be taken to avoid iatrogenic blood loss through accidental dislodgement of the catheter, which can be prevented by making a purse-string suture around the umbilical stump and carefully taping the catheter to the abdominal wall. A bridge made of adhesive tape (Figure B-12) and supplemented with a purse-string suture or umbilical tape will secure the catheter.

### Airway Management

Hypoxemia is a common and preventable complication of sedation and a frequent consequence of illness



**Figure B-12** Umbilical vessel cannulation. The hemostat is used to grasp the edge of the cord stump, which is then rolled toward the operator. A probe may be used to dilate the orifice of the vessel. The inset demonstrates a bridge of adhesive tape to fix the catheter in position.

in children. All health care providers involved in the care of children should master basic techniques of airway management. Basic airway maintenance skills, including jaw-thrust maneuvers, placement of nasal or oral airway, and bag-mask ventilation, are essential for all providers of health care to children. In rescue scenarios, bag-mask ventilation has been demonstrated to be as effective as intubation in influencing morbidity and mortality. Pediatric Advanced Life Support (PALS) courses and provider manuals are excellent sources for a more thorough review.

### Oral Airway Placement

Oral airway placement may be required in deeply sedated patients who have intact respiratory drive, but who have lost control of the upper airway. Oral airways should not be placed in conscious and semi-conscious patients because their placement may induce vomiting and aspiration of gastric content. If a child has an intact gag reflex, a nasopharyngeal tube is a better choice.

Size is crucial, given that misplacement will exacerbate, not relieve, airway obstruction. The appropriate size is estimated by holding the airway next to the patient's face. With the flange of the airway at the lips of the child, the distal end should end at or just distal to the angle of mandible. Airway management tackle boxes and emergency carts should be stocked with an array of sizes for all age groups. The airways range in size from 4 to 10 cm in length. For this and all airway support techniques, including intubation and mask ventilation, position of the head and neck is crucial. The head and neck should be in the so-called *flower-sniffing* position except in neonates and infants, whose large occiputs necessitate the use of a shoulder roll. A thin pillow or folded towel under the occiput usually aids in positioning. A tongue depressor holds the tongue at the floor of the mouth when placing the airway. The position of the head and neck must be maintained after the airway is placed.

### Nasopharyngeal Airway Placement

Nasopharyngeal airways are useful when airway obstruction is caused by lack of tone in the upper pharynx. These airways can be used in conscious children and are available as specially manufactured soft tubes. An endotracheal tube can be shortened at the bedside and used as a substitute. The standard diameter fitting of the endotracheal tube must be firmly replaced if the tube is shortened. These can be placed in a child with a gag reflex. If the child exhibits no gag reflex, the oral airway is preferred.

The diameter should be chosen to prevent blanching of the alae nasae, which indicates compromised blood flow. The length is chosen by estimating the distance from the nostril to the tragus of the ear. Lubrication will ease passage. Care must be taken to avoid lacerating mucosa or the adenoids. If the device is too long, coughing, laryngospasm, and vagal-induced bradycardia may result. These devices have a narrow internal diameter, and therefore patency is difficult to maintain; in addition, they may become obstructed with secretions, blood, and vomitus.

### Bag-Mask Ventilation

Bag-mask ventilation is an essential skill for physicians who care for children. In addition to being the best rescue technique, it is an essential component of airway management. Proper use of this technique preserves patient safety until personnel skilled at intubation are available. Tracheal intubation may not be advisable outside the hospital setting. PALS provides a thorough learning experience. Practice with patient simulators and mannequins can reinforce skill in the technique.

An appropriate-sized mask reaches from the bridge of the nose to just below the lower lip. The self-inflating bag should be large enough to provide an adequate tidal breath for the child; such bags are sized for infants, children, or adults. They can be used without an oxygen source, but in most rescue situations they are used in conjunction with an oxygen source.

There are 2 types of self-inflating bags available—with and without an oxygen reservoir. The distinction between the types is important. In a bag with an oxygen reservoir, the concentration of oxygen in the bag is 100%, and, with compression, 100% oxygen is delivered to the patient. In a bag without an oxygen reservoir, the bag is reinflated with a mixture of room air and 100% oxygen; therefore, less than 100% oxygen is delivered to the patient, generally 30% to 80%, depending on the oxygen flow rate chosen. A flow rate of 10 to 15 L/min is required to maintain adequate volume in the bag.

In the so-called E-C rescuer technique for hand and finger placement, which is taught in PALS provider courses and which is easily mastered, the third, fourth, and fifth fingers form an inverted capital letter E; this supports and lifts the mandible while the thumb and forefinger form a C around the mask (Figure B-13).



**Figure B-13** E-C technique for single-rescuer bag and mask ventilation. The thumb and index finger form a letter C at the base of the face mask, and the other 3 fingers form the letter E, lifting the jaw and sealing the mask to the face while avoiding compression of the neck, which would obstruct the airway. (From American Heart Association. Web-based integrated 2010 & 2015 American Heart Association guidelines for cardiopulmonary resuscitation and cardiovascular care. Part 11: pediatric basic life support and cardiopulmonary resuscitation quality. Reprinted with permission. © 2015 American Heart Association, Inc.)

To maintain airway patency, the child should be placed supine with the head in a neutral position. After connecting the mask to the bag, the flow of oxygen should be confirmed. The mask is placed on the face of the child so that it covers both the nose and mouth. The index finger and thumb should be opposed encircling the base of the mask. The third, fourth, and fifth fingers of the same hand should be placed along the angle of the jaw. The jaw should be brought up into the mask, creating a tight seal. Care must be taken to ensure that no leaks exist around the mask and that the chest rises adequately. Positioning of the head and neck and the use of an oral airway may be helpful if an appropriate seal and breath cannot be achieved.

The 2-handed technique is better than the single-rescuer method and should be used whenever possible. A rescuer uses both hands to seal the mouth and face to the mask and position the head and neck while the second rescuer uses both hands to compress the bag.

### Endotracheal Intubation

The key to success in endotracheal intubation is approaching the procedure calmly and deliberately, with a much-practiced technique and properly prepared and available equipment. Reliably predicting patients who cannot be intubated or patients in whom the intubation will be difficult is possible. For such patients, a clear documentation of the existence of a potentially difficult airway should be conspicuously placed in the record. Skilled personnel should be alerted and a care pathway chosen should an airway emergency arise. Sample critical airway management pathways have been described. Complications of intubation are seen in Box B-4.

Protection of the airway and adequate oxygenation guarantee safe and successful intubation of the airway. Medications undoubtedly improve patient safety. Atropine administered before intubation minimizes the side effects of vagal stimulation (bradycardia) and may be considered as a preintubation medication. The use of neuromuscular blockade to reduce muscle tone and respiratory effort is usually indicated. Patients must have an adequate peripheral IV line in place.

Emesis and subsequent aspiration are hazards encountered in emergency intubations. Before any airway manipulation, a source of suction and a supply of suction catheters should be readily available. The Sellick maneuver may help prevent aspiration. Downward

### BOX B-4 Complications of Intubation

- Hypoxemia and hypercarbia
- Aspiration of gastric content, oral content, or both
- Damage to teeth or gums
- Esophageal intubation
- Intubation of a mainstem bronchus



### BOX B-5 Equipment Required for Intubation

- Laryngoscope handle (checked to be in working order just before beginning intubation)
- Laryngoscope blades (sizes 00, 0, 1, 2, and 3)
- Suction source and suction catheters
- Endotracheal tubes (one size larger and one size smaller than those deemed appropriate by age)
- Oxygen supply
- Bag and mask for ventilation
- Tape and adhesive solution
- Expired carbon dioxide detector
- Nasogastric tube

pressure exerted on the cricoid cartilage effectively closes the esophagus and can prevent passive regurgitation and aspiration of oral or gastric material.

When possible, preoxygenation of the patient (3 minutes of breathing 100% oxygen) reduces hypoxemia and increases time for placement. Oxygen saturation, pulse rate, and blood pressure must be monitored during the attempt.

Sedation with a fast-acting agent must be given before neuromuscular blockade. Agents for this purpose include fentanyl, etomidate, and midazolam. Fentanyl is preferred if the patient exhibits evidence of hemodynamic instability, but may not provide anxiolysis or amnesia. Etomidate may precipitate an adrenal crisis and should be used by caregivers with experience in management of complications of intubation and sedation.

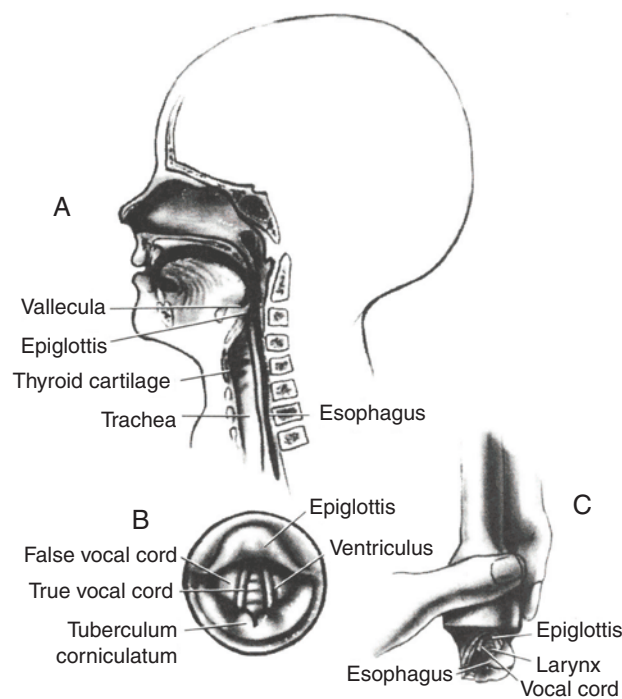
Vecuronium (0.1 mg/kg), rocuronium (0.3 mg/kg), and succinylcholine (1 to 2 mg/kg) all have the advantage of onset within 60 seconds. Succinylcholine has the added advantage of being rapidly metabolized, but its use is contraindicated in patients with hyperkalemia, burn injuries, and neuromuscular disease.

### TECHNIQUE OF INTUBATION

The equipment required for intubation is listed in Box B-5. Guidelines for laryngoscopy blade type and size, endotracheal tube size, depth of placement, and suction catheter diameter are provided in Table A-4, found in Appendix A, Pediatric Cardiopulmonary Resuscitation.

Perhaps the most important key to success of intubation is positioning the patient. The patient should be placed on a firm surface with the head extended. The neck is extended only slightly and the jaw pulled forward only slightly. To visualize the glottic opening correctly, and to prevent undue manipulation of the head and neck, the oral, pharyngeal, and tracheal axes must be in correct alignment.

The nose and mouth should be carefully suctioned. When possible, the child should be preoxygenated with 100% oxygen for 3 minutes. Care must be taken to prevent damage to teeth, gums, and lip with the blade. Loose deciduous teeth should be removed.



**Figure B-14** Laryngoscopy. Laryngeal structures in sagittal section (A), and as seen with the laryngoscope (B and C).

Figure B-14 illustrates the relationship of the laryngoscope blade to the epiglottis and vocal cords. After the equipment has been checked, the laryngoscope is held in the left hand. Appropriate medications are provided, and the laryngoscope blade is introduced into the mouth to the right of the tongue so that the tongue will be deflected to the left. The tip of the blade is inserted to the vallecula. The handle of the laryngoscope is tilted slightly backward and upward toward the operator. Care must be taken to avoid using the teeth or the alveolar ridge as a fulcrum. The vocal cords should be in full view. The endotracheal tube can be advanced along the right side of the child's mouth, inserted between the cords into the trachea, and advanced further to a position below the level of the vocal cords. The endotracheal tube should be positioned midway between the vocal cords and the carina. A carbon dioxide detection device and chest radiograph should be used to ensure appropriate placement. The size of the endotracheal tube, position of the tip of the tube in the trachea, and distance of insertion from the child's lip must be documented in the patient record.

### Confirmation of Placement of the Endotracheal Tube

Placement of the tube must be confirmed and documented. No single method is completely reliable. Box B-6 includes elements useful in confirmation of placement.

In a child with a perfusing rhythm, expired carbon dioxide is the most reliable method for verification of tube placement in the trachea. After 6 rescue breaths, the presence of yellow color change confirms placement



### BOX B-6 Confirmation of Correct Placement of Endotracheal Tube

- Symmetric chest rise
- Auscultation of air entry
- Water vapor in the tube
- Presence of exhaled carbon dioxide (in a child with a perfusing rhythm)
- Chest radiograph
- Direct laryngoscopy

### BOX B-7 Troubleshooting Patient Instability After Intubation

- Endotracheal tube too small
- Inadequate tidal volume
- Inadequate positive end-expiratory pressure
- Leak in the bag tube connections
- Pop-off valve leak
- Follow the DOPE mnemonic: **d**isplacement of endotracheal tube, **o**bstruction of endotracheal tube, **p**neumothorax, **e**quipment failure.

in the trachea. Exhaled carbon dioxide detection is not reliable in cardiac arrest. In patients with cardiac arrest, a positive color change predicts accurate placement. However, when pulmonary blood flow is absent, the absence of color change does not confirm esophageal misplacement. In a patient with cardiac arrest, placement should be confirmed by direct laryngoscopy and radiograph.

Caregivers should be mindful of conditions in which a false-negative result can occur. In some situations, an expired capnometer may produce false-negative results. In patients with severe asthma and pulmonary edema, the color change may be impaired. In patients who have received endotracheal epinephrine or who have aspirated gastric contents, the results are suspect. Again, in these situations, direct laryngoscopy is the best practice to confirm tracheal placement.

A slight air leak is to be expected with a tube of appropriate size. Small-cuffed endotracheal tubes are available and may be safely used in children who require high airway pressures during mechanical ventilation. An audible leak should be detected with bag insufflation at a pressure of 20 cm H<sub>2</sub>O.

If there is difficulty with adequate ventilation after intubation, a systematic approach will help identify the cause and solution (Box B-7).

### Postintubation Care

The intubated infant or child requires exacting nursing care. The patient needs monitoring of vital signs and frequent physical examinations to ascertain the

### BOX B-8 Safe Method for Suctioning

- The endotracheal tube is disconnected from the ventilator
- Normal saline (0.25–0.5 mL) is instilled into the tube
- The child receives ventilation for 60 seconds
- The head is turned to one side
- A sterile, end-hole catheter is passed a premeasured 1–2 cm beyond the distal orifice of the tracheal tube
- Suction is applied after the catheter has been pulled back 1 cm
- Suction is applied as the catheter is withdrawn over a 5-second interval
- The endotracheal tube is reconnected to the ventilator
- The head is turned to the opposite side and the procedure is repeated

adequacy of ventilation. Pneumothorax, tube obstruction, and dislodgement of the tube must be anticipated in the care of these children. Adequate sedation is mandatory.

Head and neck position alters the position of the tip of the endotracheal tube. In general, the tip of the tube follows the position of the chin. This factor should be borne in mind when radiographs are used to document the tube position in the trachea.

Suctioning the airway reduces tidal volume and available oxygen; it also predisposes the child to apnea and bradycardia. The physician and nurse should jointly decide how often suctioning should be performed; once an hour is a reasonable initial schedule. Box B-8 provides a safe method for suctioning.

## CIRCUMCISION

### Contraindications

The neonate should first be screened for any potential contraindications including coagulation, urologic, or general medical disorders.

### Coagulopathies

First, if any concerns exist, a pediatric hematologist should be consulted before proceeding with the circumcision. When obtaining consent from the parents, the examiner should ask about any history of bleeding disorders. If the family knows the specific diagnosis, the examiner should screen for that with the appropriate test (ie, factor VIII for hemophilia A, factor IX for hemophilia B, etc). If a family history of easy bruising or excessive bleeding with surgical procedures or trauma exists, screening coagulation tests should be conducted before proceeding. These tests include a complete blood count and platelet count, partial thromboplastin time (PTT), prothrombin time (PT), and thrombin time (TT). If any abnormalities are found, the circumcision should be deferred and a pediatric hematologist should be consulted to assist with diagnosis and further management. A family history of anemia is not a contraindication to circumcision.

### ***Urologic and Structural Contraindications***

**AMBIGUOUS GENITALIA.** In the presence of ambiguous genitalia, including phallus abnormalities or bilateral absent testicles, the circumcision should be deferred to urology and the sex of the baby confirmed by karyotype. The child should be evaluated for any possible virilizing syndrome, such as congenital adrenal hyperplasia.

**URINARY OBSTRUCTION.** The child should urinate before the circumcision is performed. If doubt exists as to the presence of urinary obstruction, circumcision should be deferred, and a pediatric urologist should be consulted.

**INADEQUATE SIZE AND MICROPENIS.** The penis should be at least 2 cm in length and of an adequate width to accommodate the smallest equipment available for the procedure.

**BURIED PENIS AND INCONSPICUOUS PENIS.** If an illusion of excessive foreskin is observed caused by the penis being covered by the surrounding suprapubic fat pad, the circumcision should be deferred until a later date when the penis is more exposed. If adequate exposure of the penis is not possible, too much foreskin may be removed, causing adhesions between the phallus and the surrounding skin during the healing process.

**EPISPADIAS, HYPOSPADIAS, AND MEGAMEATUS.** In these situations, the circumcision should be deferred and the patient referred to pediatric urology for cosmetic repair.

**SCROTAL WEBBING AND CHORDAE.** If webbing exists between the ventral phallus and scrotum, the circumcision should be deferred and the patient referred to pediatric urology for cosmetic repair, because this procedure may affect the ability for adequate erections in the future.

**PENILE TORSION.** The ventral raphae, which begins in the scrotum and proceeds onto the phallus, contains a vascular bundle that would make a circumcision more technically difficult because of increased risk of bleeding if more than a 90-degree rotation exists. For this reason and the possible need for cosmetic repair in the future, these patients should be referred to a pediatric urologist.

### ***Other Contraindications***

Relative contraindications would include respiratory distress, difficulty breathing, difficulty feeding, congestive heart failure, renal failure, and fever.

### ***Rate of Complications***

Complications that include bleeding, infection, accidental injury to the penis or surrounding structures, and an undesired cosmetic result occur in 1% of newborns receiving circumcisions. The risk of excessive bleeding occurs in 1 in 1,000 cases despite appropriate screening for bleeding disorders.

### ***Circumcision Procedures***

There are 3 options available for the circumcision procedure, with no studies showing any as superior to the others—the Gomco clamp, the Mogen clamp, and the PlastiBell.

### **BOX B-9 Sterile Equipment**

- 1% lidocaine without epinephrine
- Betadine swabs
- Sterile gloves
- 3 straight hemostats
- 1 narrow blunt probe
- 1 ten-blade scalpel
- 1 pair of scissors
- 4 × 4 gauze

Besides the specific equipment associated with each approach, other sterile equipment listed in Box B-9 should be available.

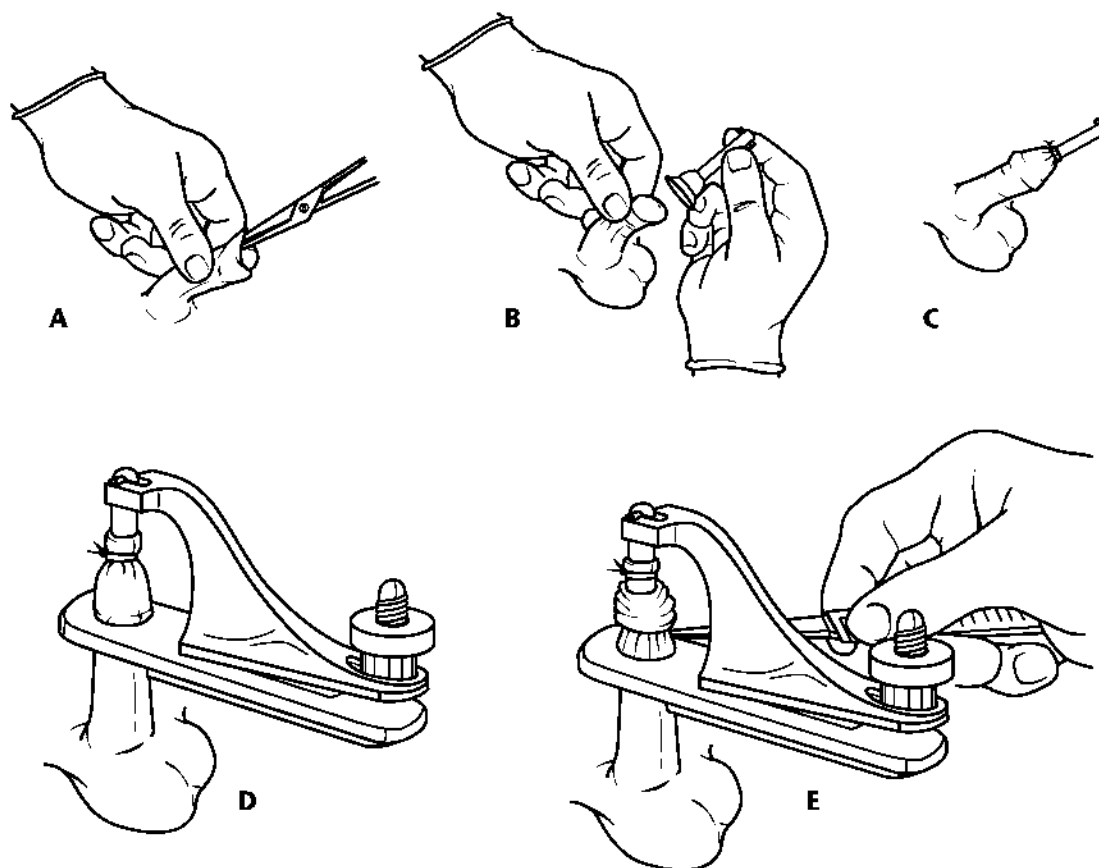
Procedural analgesia should be provided. The child should first be restrained with his legs immobilized and local anesthesia administered. A penile block should be performed by injecting 0.4 cc of 1% lidocaine without epinephrine targeting the dorsal penile nerves at base of the penis. The injection should be made at the dorsal aspect of the penis, parallel and just to the right and left of the phallus. An alternate block is circumferential, injecting 0.2 to 0.4 mL of 1% lidocaine without epinephrine each time to raise 3 to 4 wheals around the circumference of the penis. Additional analgesia can be offered using a pacifier dipped in a sucrose solution.

The penis should then be prepped and draped in a sterile fashion before proceeding with one of the 3 circumcision approaches.

### ***Gomco Clamp***

Three sizes of Gomco clamp bells are available, increasing based on the diameter of the glans (1.1, 1.3, and 1.6). All 3 sizes should be on hand in case a different size is found to be needed during the procedure. Each clamp should be checked, especially the seal, to maximize the possibility of obtaining hemostasis.

1. Using 2 hemostats, free up the end of the foreskin from the glans (Figure B-15, A), clamp the foreskin at the left lateral and right lateral edges, and stretch it, being cautious to clamp only the foreskin and not the glans.
2. Insert the third hemostat, running it under the foreskin to prevent accidentally inserting it into the urethra. Perform a gross blunt dissection around the glans to separate it from the synechia by opening the hemostat, avoiding the ventral frenulum because of the vascular structures it contains.
3. Repeat this process with the narrow probe, breaking down any adhesions.
4. Apply a hemostat to the dorsal foreskin, taking care to avoid going past the distal end of the glans. Close the hemostat for 5 seconds to obtain hemostasis.
5. Using scissors, make a dorsal slit through this crushed area with the scissors angled up to avoid cutting the glans.



**Figure B-15** The Gomco clamp method.

6. Retract the foreskin past the glans.
7. Run the narrow probe along the corona to break any adhesions that exist between the corona and the foreskin. Again, use caution around the frenulum, because this is the most common area of bleeding.
8. Reduce the foreskin.
9. Put the bell over the glans (Figure B-15, B), choosing a size that is able to get past the slit cut in the foreskin and covering the glans while not going beyond it. Err on the smaller size when choosing the bell to decrease the risk of removing excessive foreskin.
10. Clamp the 2 foreskin flaps together with a hemostat to make sure they are symmetric. Remove the 2 hemostats that were previously attached to each flap (Figure B-15, C).
11. Assemble the base of the Gomco clamp.
12. Use another hemostat to reach through the other side of the hole of the Gomco base, and secure both flaps of the foreskin at the site of the first hemostat.
13. Remove the bottom hemostat to allow the bell to be pulled through the hole in the base.
14. Pull the foreskin up with 1 hemostat to make it symmetric on top of the bell. Be sure that a symmetric amount of skin and the complete dorsal slit is through the other side of the Gomco clamp. Looking from the side of the Gomco clamp apparatus, make sure that there is no tension on the scrotum, which would suggest that too much foreskin is being removed, or that wrinkling is excessive, which would suggest that not enough foreskin is being removed (Figure B-15, D).
15. Tighten the clamp with the thumb stabilizing the top of the unit, the first finger on the shaft, and the third finger on top of the clamp. Do not torse the penis. Begin a timer to keep the clamp on for a total of 5 minutes to maximize hemostasis.
16. Incise the foreskin around the bell and discard it appropriately (Figure B-15, E). Scrape any remaining particles of foreskin to prevent the formation of inclusion cysts.
17. After 5 minutes, remove the clamp. Apply downward pressure on the foreskin and rock the bell away, breaking the skin-mucosal seal.
18. Dress the patient with lubricating jelly and cloth diaper within a disposable diaper to provide a pressure dressing, which is kept on for 2 hours. During that time, wound checks are performed regularly to check for bleeding. Acetaminophen should be offered for pain relief.

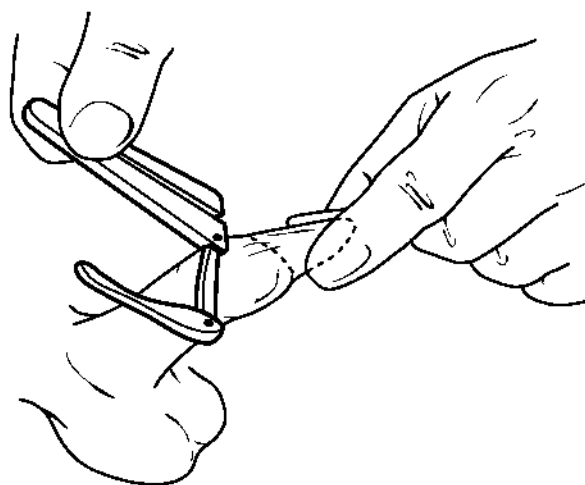
19. Bleeding is the most common complication. Any bleeding that might occur is usually controlled by direct pressure or with topical thrombin or epinephrine-soaked gauze. Very rarely, a suture may be needed for intractable bleeding.

### Mogen Clamp

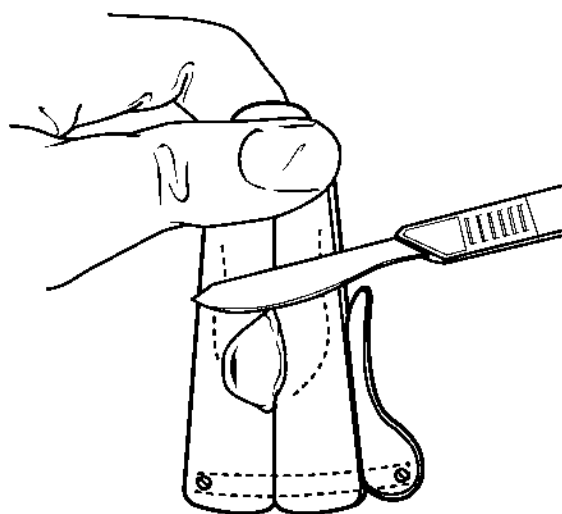
1. Using 2 hemostats, free up the end of the foreskin from the glans, clamp the foreskin at the left lateral and right lateral edges, and stretch it, being cautious to clamp only the foreskin and not the glans.
2. Insert the third hemostat, running it under the foreskin to avoid accidentally inserting it into the urethra. Perform a gross blunt dissection around the glans to separate it from the synechia by opening the hemostat, avoiding the ventral frenulum because of the vascular structures it contains.
3. Repeat this process with the narrow probe, breaking down any adhesions.
4. Using a hemostat, elevate the foreskin in an upward and outward direction, which will retract the glans toward the scrotum, decreasing the risk of accidental injury.
5. Position the Mogen clamp around the foreskin with the grooved surface facing the glans and lift upwards (Figure B-16)
6. Close the clamp and keep it closed for 5 minutes to ensure hemostasis.
7. While the clamp is closed, using a scalpel, incise the foreskin distal to the clamp (Figure B-17).
8. After 5 minutes, remove the clamp.
9. Dress the patient with lubricating jelly and cloth diaper within a disposable diaper to provide a pressure dressing, which is kept on for 5 hours. During that time, wound checks are performed regularly to check for bleeding. Acetaminophen should be offered for pain relief.
10. Bleeding is the most common complication. Any bleeding that may occur is usually controlled by direct pressure or with topical thrombin or epinephrine-soaked gauze. Very rarely, a suture may be needed for intractable bleeding.

### PlastiBell

1. Using 2 hemostats, free up the end of the foreskin from the glans (see Figure B-18), clamp the foreskin at the left lateral and right lateral edges and stretch it, being cautious to clamp only the foreskin and not the glans.
2. Insert the third hemostat, running it under the foreskin to avoid accidentally inserting it into the urethra. Perform a gross blunt dissection around the glans to separate it from the synechia by opening the hemostat, avoiding the ventral frenulum because of the vascular structures it contains.
3. Repeat this process with the narrow probe, breaking down any adhesions.
4. Apply a hemostat to the dorsal foreskin, taking care to avoid going past the distal end of the glans. Close the hemostat for 5 seconds to obtain hemostasis.
5. Using a scissors, make a dorsal slit through this crushed area with the scissors angled up to prevent cutting the glans.
6. Retract the foreskin past the glans.
7. Run the narrow probe along the corona to break any adhesions that exist between the corona and the foreskin. Again, use caution around the frenulum because this is the most common area of bleeding.
8. A PlastiBell of appropriate size is placed around the glans, and the foreskin is reduced over it (Figure B-18).
9. A ligature is placed in the ridge of the bell and tightened as much as possible around the foreskin.
10. After keeping the ligature in place for 2 minutes to allow for hemostasis, the foreskin is sliced off distal to the PlastiBell using a scalpel.
11. The handle of the bell is then removed.



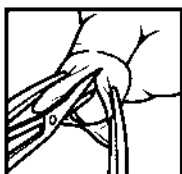
**Figure B-16** Positioning the Mogen clamp. Position the Mogen clamp around the foreskin with the grooved surface facing the glans and lift upwards.



**Figure B-17** Incising with the Mogen clamp. While the clamp is closed, using a scalpel, incise the foreskin distal to the clamp.

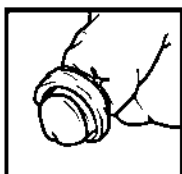
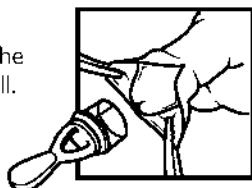


### The PlastiBell® Circumcision Method



1. An incision is made on the top of the foreskin after separating the foreskin from the glans. To minimize bleeding, the foreskin is previously crushed with a hemostat among the line of the incision for one minute.

2. A PlastiBell of the appropriate size is placed over the glans and the foreskin is pulled over the PlastiBell.



3. A ligature is tied around the foreskin over the tying groove in the PlastiBell. Foreskin beyond the ligature is trimmed away. The handle of the bell is snapped off, leaving the bell in place. The bell falls off 5–10 days later.

**Figure B-18** The PlastiBell method. (*Plastibell is a Registered Trademark of Briggs Medical Service Company. Reprinted with permission.*)

12. The remaining foreskin will become necrotic and separate with the PlastiBell in 5 to 10 days. Occasionally, edema will trap the bell on the shaft of the penis and the bell will need to be removed with a guide and ring cutter.

### Care of the Circumcision After the Procedure

After the procedure, parents should be advised that the glans of the penis will look swollen and bright red in color. Within 1 to 2 days, they will see a decrease in the swelling and a yellow covering over the glans, which is a part of the normal healing process.

After the initial 2-hour period using the cloth diaper (for the Gomco and Mogen clamp procedures), standard diapers may be used. The parents should be advised to use approximately 1 teaspoon of petroleum jelly on the front of the diaper with every diaper change until the coloration of the penis returns to normal, which can take between 4 and 14 days. For the first 2 to 3 days, the entire penis can be cleaned by pouring warm water over it. Afterward, if necessary, mild soap may be used.

Infant acetaminophen can be used as directed for pain relief.

### When to Contact a Physician

- Signs of infection are observed, including fever, increased swelling and redness of the penis, and greenish-yellow discharge.
- Active bleeding occurs from the penis. (Observing some blood spots on the baby's diaper for the first 1 to 2 days is normal.)
- The baby does not urinate once within 24 hours after the circumcision.
- Signs of paraphimosis are observed, including edema, tenderness, and erythema of the glans or foreskin.



## Appendix C

FORMULAS AND REFERENCE  
RANGE VALUES

Lamia Soghier, MD

## CONVERSION FORMULAS

## HEIGHT (LENGTH)

1 mm = 0.04 in	1 in = 2.54 cm
1 cm = 0.4 in	1 m = 39.37 in

## WEIGHT

60 mg = 1 g	1 L = 1.06 qt
28.35 g = 1 oz	1 fl oz = 29.57 mL
453.6 g = 1 lb	1 tbsp = 15 mL
1,000 g = 1 kg	1 tsp = 5 mL
1 kg = 2.2046 lb	

## MILLIGRAM–MILLIEQUIVALENT CONVERSIONS

$\text{mEq/L} = \text{mg/L} \times \text{valence/atomic weight}$   
 $\text{Equivalent weight} = \text{atomic weight/valence}$   
 $\text{mg/L} = \text{mEq/L} \times \text{atomic weight/valence}$

## MILLIGRAM–MILLIMOLE CONVERSIONS

$\text{mmol/L} = \text{mg/L} \div \text{molecular weight}$

## MILLIOSMOLS

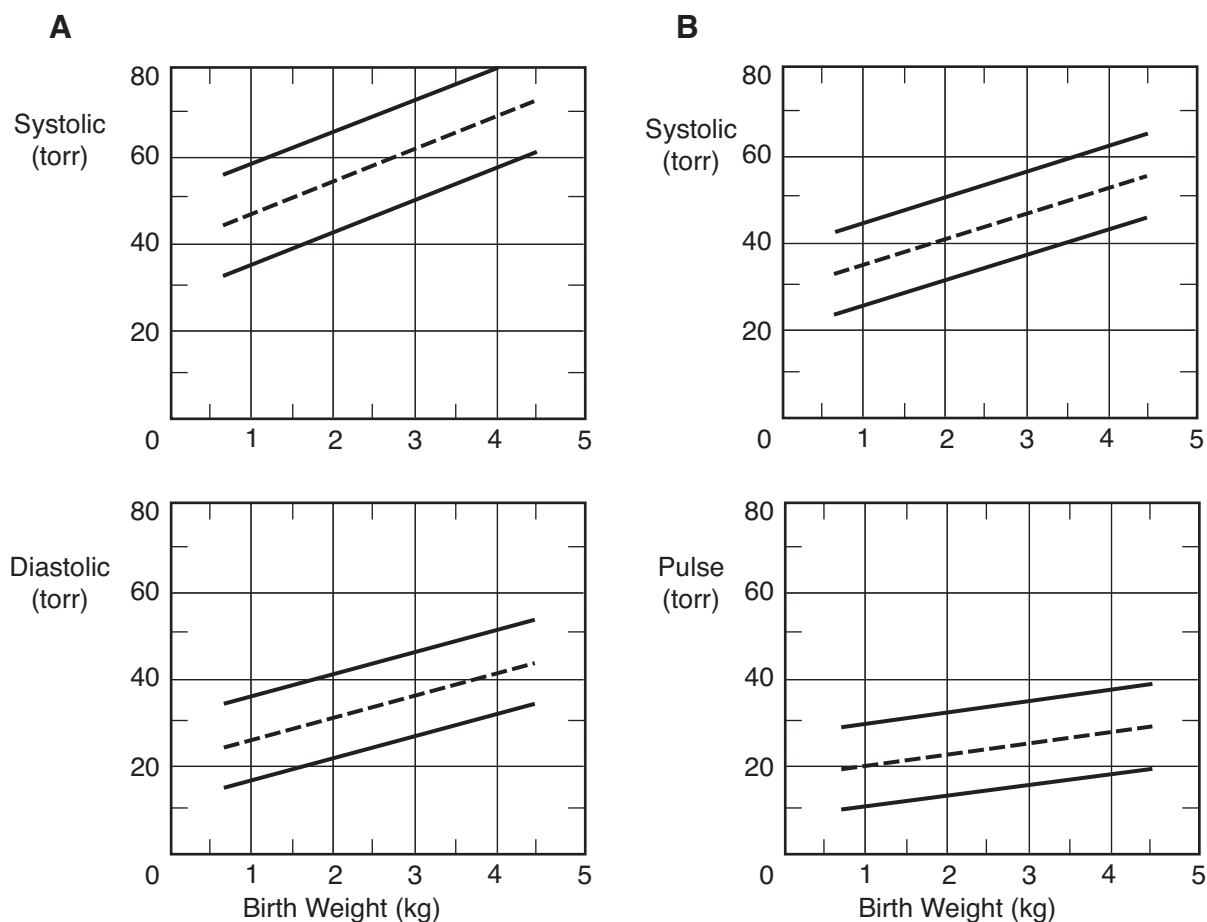
The milliequivalent (mEq) is roughly equivalent to the milliosmol (mOsm), the unit of measure of osmotic pressure or tonicity. One osmole (Osm) is the amount of a substance that dissociates in solution to form one mole (mol) of osmotically active particles.

## HEART RATE

## Average Heart Rate for Infants and Children at Rest

AGE	HEART RATE AT REST (BEATS/MIN)
Birth–1 mo	100–180
1–12 mo	100–180
1–3 y	70–110
4–6 y	70–110
7–12 y	70–110
13–19 y	55–90

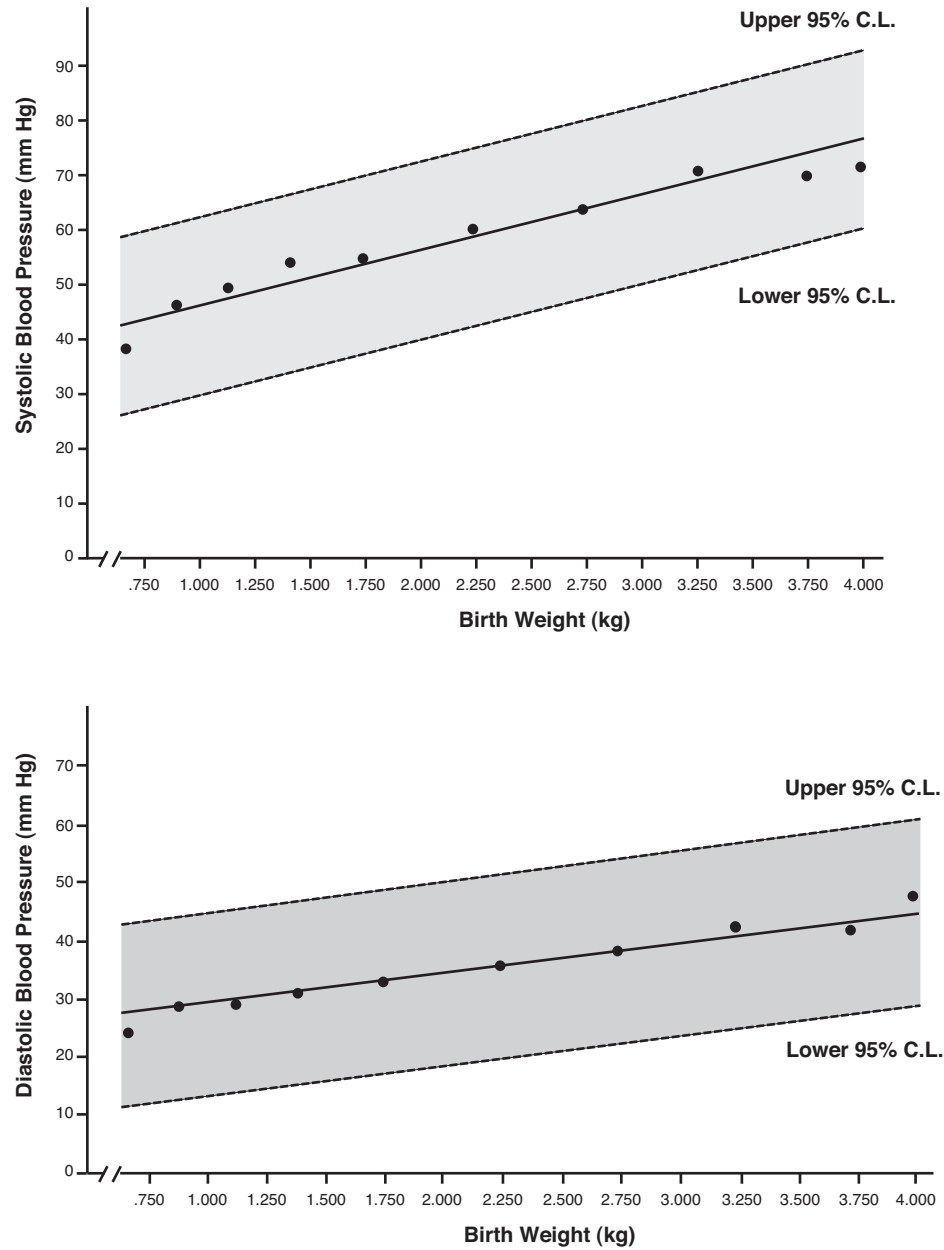
Adapted from Monaghan A. Detecting and managing deterioration in children. *Paediatric Nursing*. 2005;17:32–35.

**BLOOD PRESSURE****Blood Pressure Nomograms***Blood Pressure Nomograms for Healthy Term Infants During the First 12 Hours of Life*

**A,** Linear regressions (broken lines) and 95% confidence limits (solid lines) of systolic (top) and diastolic (bottom) aortic blood pressures on birth weight in 61 healthy term newborns during the first 12 hours after birth. For systolic pressure,  $y = 7.13x + 40.45$ ;  $r = 0.79$ . For diastolic pressure,  $y = 4.81x + 22.18$ ;  $r = 0.71$ . For both,  $n = 413$  and  $p < .001$ . **B,** Linear regressions (broken lines) and 95% confidence limits (solid lines) of mean pressure (top) and pulse pressure (systolic-diastolic pressure amplitude) (bottom) on birth weight in 61 healthy term newborns during the first 12 hours after birth. For mean pressure,  $y = 5.16x + 29.80$ ;  $n = 443$ ;  $r = 0.80$ . For pulse pressure,  $y = 2.31x + 18.27$ ;  $n = 413$ ;  $r = 0.45$ . For both,  $p < .001$ . (From Versmold HT, Kitterman JA, Phibbs RH, Gregory GA, Tooley WH. Aortic blood pressure during the first 12 hours of life in infants with birth weight 610 to 4,220 grams. *Pediatrics*. 1981;67(5):607–613.)

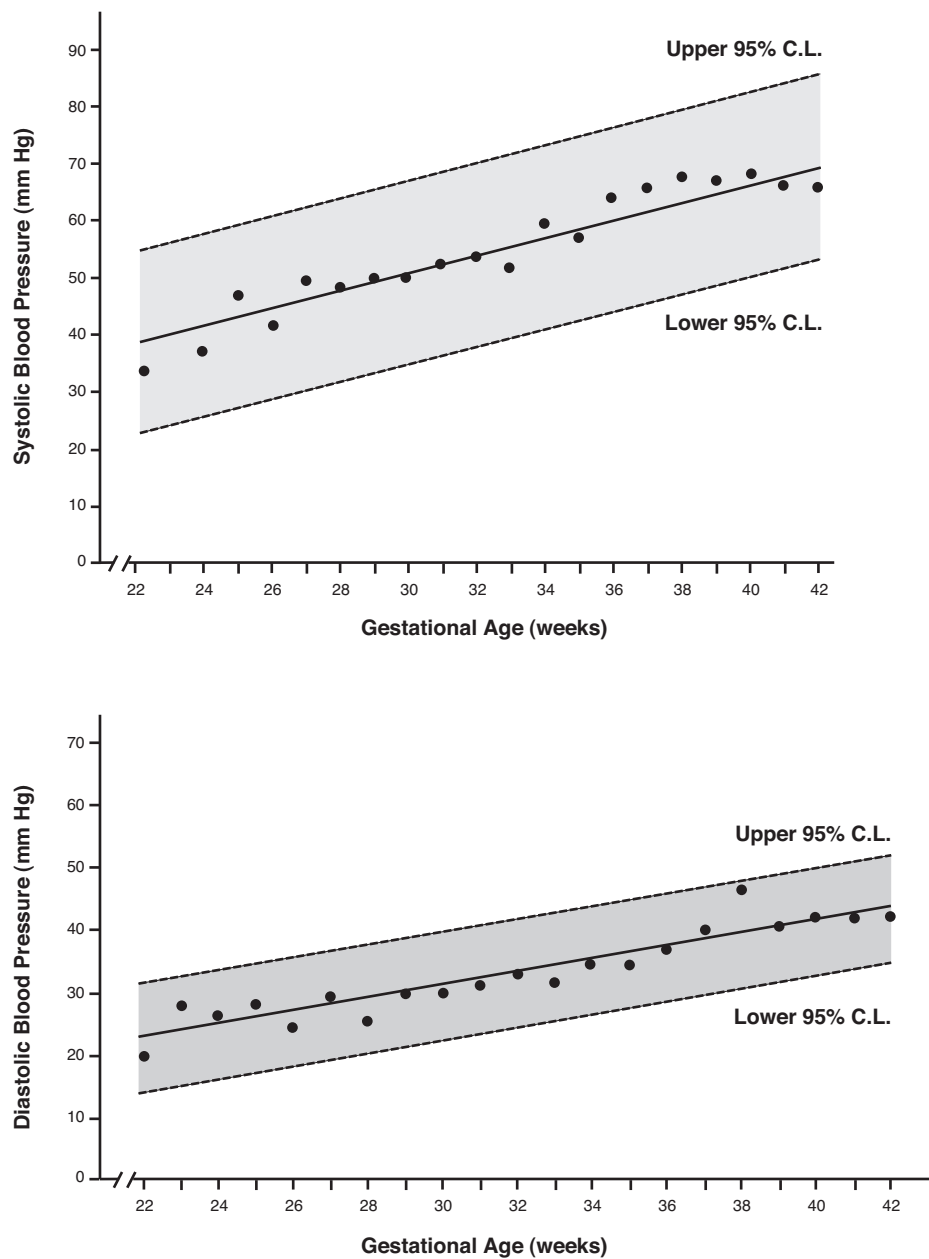


**Blood Pressure Nomograms for Preterm and Full-term Neonates During the First Day of Life  
(According to Birth Weight)**



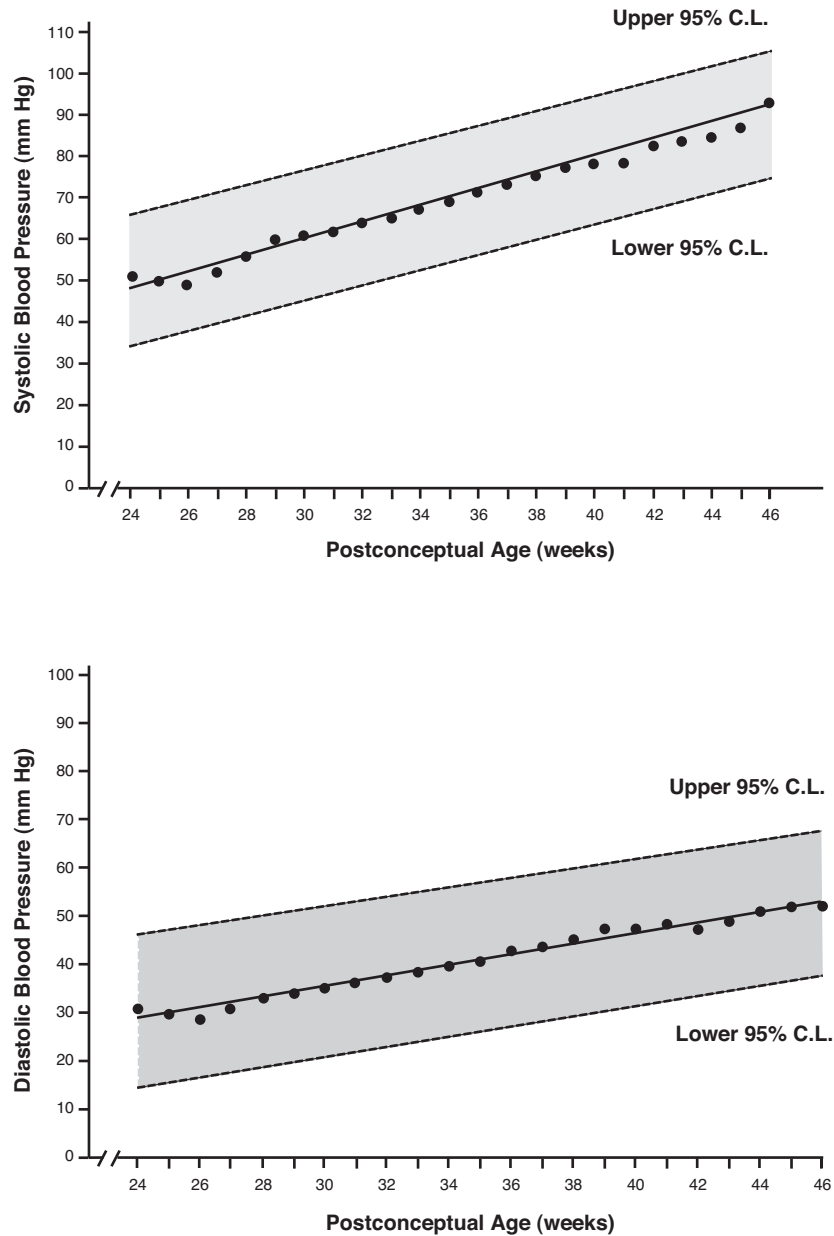
Linear regression of mean systolic and diastolic blood pressures by birth weight on day 1 of life, with 95% confidence limits (CLs) (upper and lower dashed lines). (From Zubrow AB, Hulman S, Kushner H, Falkner B. Determinants of blood pressure in infants admitted to neonatal intensive care units: a prospective multicenter study. Philadelphia Neonatal Blood Pressure Study Group. J Perinatol. 1995;15(6):470–479. Reproduced with permission. Copyright © 1995 Nature Publishing Group.)

**Blood Pressure Nomograms for Preterm and Full-term Neonates During the First Day of Life  
(According to Gestational Age)**



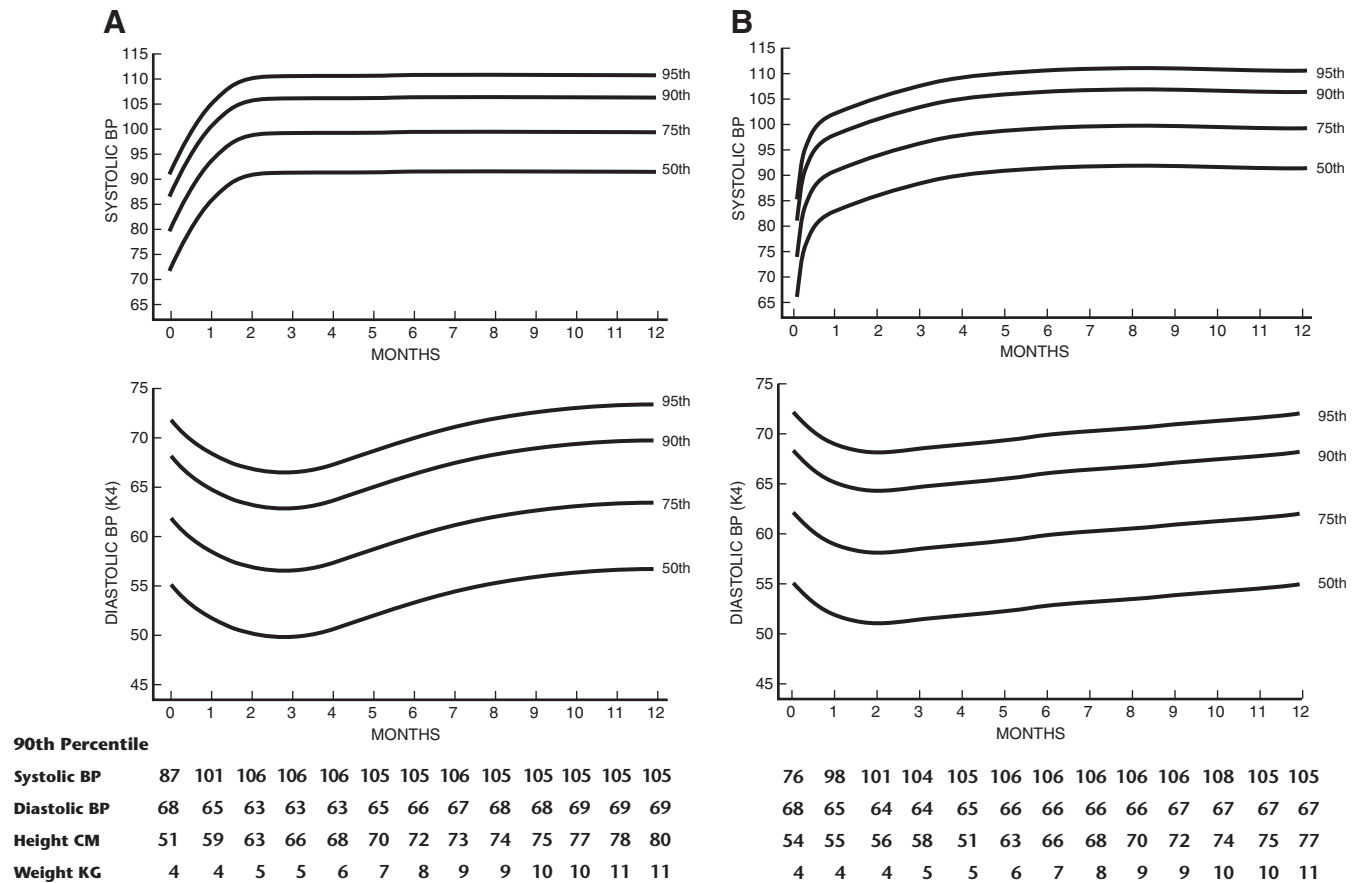
Linear regression of mean systolic and diastolic blood pressures by gestational age on day 1 of life, with 95% confidence limits (CLs) (upper and lower dashed lines). (From Zubrow AB, Hulman S, Kushner H, Falkner B. Determinants of blood pressure in infants admitted to neonatal intensive care units: a prospective multicenter study. Philadelphia Neonatal Blood Pressure Study Group. *J Perinatol.* 1995;15(6):470-479. Reproduced with permission. Copyright © 1995 Nature Publishing Group.)

### Blood Pressure Nomograms for Preterm and Full-term Neonates During the First Few Weeks of Life



Linear regression of mean systolic and diastolic blood pressures by postconceptual age in weeks, with 95% confidence limits (upper and lower dashed lines). (From Zubrow AB, Hulman S, Kushner H, et al. *Determinants of blood pressure in infants admitted to neonatal intensive care units: a prospective multicenter study*. Philadelphia Neonatal Blood Pressure Study Group. *J Perinatol*. 1995;15(6):470–479. Reproduced with permission. Copyright © 1995 Nature Publishing Group.)

### Blood Pressure Nomograms for Children Younger than 1 Year



**A**, Age-specific percentiles of blood pressure (BP) measurements in boys—birth to 12 months of age; Korotkoff phase IV (K4) used for diastolic BP. **B**, Age-specific percentiles of blood pressure (BP) measurements in girls—birth to 12 months of age; Korotkoff phase IV (K4) used for diastolic BP. (From Task Force on Blood Pressure Control in Children. Report of the Second Task Force on Blood Pressure Control in Children—1987. *Pediatrics*. 1987;79(1):1–25.)



**Blood Pressure Levels for Boys by Age and Height Percentile**

		SYSTOLIC BP (mmHg)							DIASTOLIC BP (mmHg)						
		← PERCENTILE OF HEIGHT →							← PERCENTILE OF HEIGHT →						
AGE (YEAR)	BP PERCENTILE	5TH	10TH	25TH	50TH	75TH	90TH	95TH	5TH	10TH	25TH	50TH	75TH	90TH	95TH
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91

Continued

Blood Pressure Levels for Boys by Age and Height Percentile—cont'd

		SYSTOLIC BP (mmHg)							DIASTOLIC BP (mmHg)						
		← PERCENTILE OF HEIGHT →							← PERCENTILE OF HEIGHT →						
BP AGE PERCENTILE (YEAR)	TILE	5TH	10TH	25TH	50TH	75TH	90TH	95TH	5TH	10TH	25TH	50TH	75TH	90TH	95TH
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP, blood pressure.  
Note: The 90th percentile is 1.28 SD, the 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

**Blood Pressure Levels for Girls by Age and Height Percentile**

		SYSTOLIC BP (mm Hg)							DIASTOLIC BP (mm Hg)						
		← PERCENTILE OF HEIGHT →							← PERCENTILE OF HEIGHT →						
BP AGE PERCENTILE (YEAR)	TILE	5TH	10TH	25TH	50TH	75TH	90TH	95TH	5TH	10TH	25TH	50TH	75TH	90TH	95TH
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91

Continued

**Blood Pressure Levels for Girls by Age and Height Percentile—cont'd**

		SYSTOLIC BP (mm Hg)							DIASTOLIC BP (mm Hg)						
		← PERCENTILE OF HEIGHT →							← PERCENTILE OF HEIGHT →						
BP AGE PERCENTILE (YEAR)	TILE	5TH	10TH	25TH	50TH	75TH	90TH	95TH	5TH	10TH	25TH	50TH	75TH	90TH	95TH
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

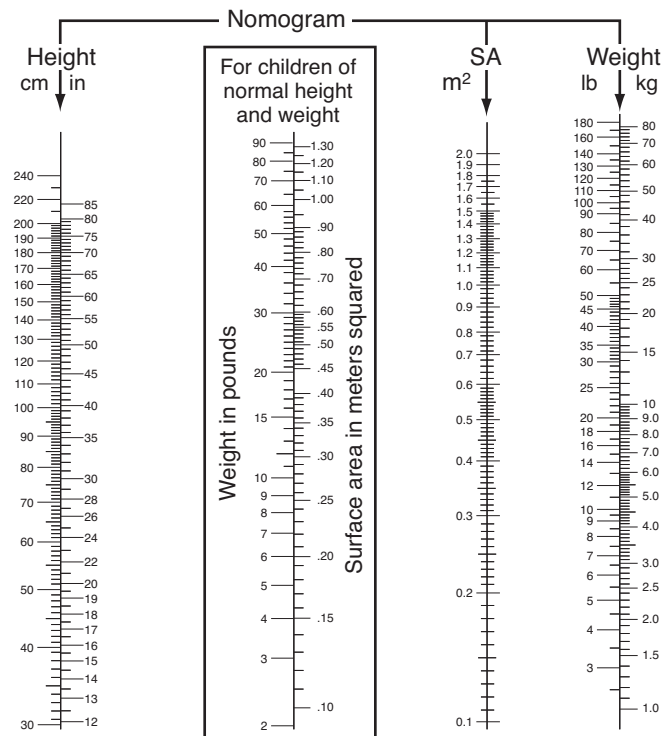
BP, blood pressure.

Note: The 90th percentile is 1.28 SD, the 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.



## DETERMINING BODY SURFACE AREA

Based on the nomogram, a straight line joining the patient's height and weight will intersect the center column at the calculated body surface area (BSA). For children of normal height and weight, the child's weight in pounds is used, then the examiner reads across to the corresponding BSA in meters squared. Alternatively, Mosteller's formula can be used.



Alternative (Mosteller's formula)

$$\text{Surface area (m}^2\text{)} = \sqrt{\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3600}}$$

Nomogram and equation to determine body surface area.  
(From Engorn B, Flerlage J, eds. *The Harriet Lane Handbook*. 20th ed. Philadelphia, PA: Elsevier Saunders; 2015. Reproduced with permission. Copyright © 2015 Elsevier.)

## BONE AGE

### Sontag Method

The Sontag method is used to evaluate the skeletal development of children between 1 and 60 months of age:

1. Radiographs are taken of all epiphyseal centers on the left side of the body: shoulder, elbow, wrist and hand, hip, knee (anteroposterior [AP] views before 24 months of age, lateral views after 24 months), and ankle and foot (AP views before 48 months of age, lateral views after 48 months).
2. All ossification centers in the left half of the body are counted. A center is counted as soon as it casts any shadow on the roentgenogram.
3. The number of ossification centers is compared with normal values for the patient's age. (For normal values, see Sontag and colleagues' article "Rate of Appearance of Ossification Centers From Birth to the Age of Five Years" in the November 1939 issue of *American Journal of Diseases of Children*.)

### Gruelich and Pyle Method

The Gruelich and Pyle method is used to evaluate the skeletal development of girls 5 to 18 years old and of boys 5 to 19 years old:

1. A radiograph is taken of the left hand and wrist.
2. Calculation of the skeletal development is based on the order of appearance and maturation of the epiphyseal centers. (For normal values, see Gruelich and Pyle's *Radiographic Atlas of Skeletal Development of the Hand and Wrist*, 2nd ed. [Stanford University Press, Stanford, CA].)

## REFERENCE RANGE VALUES

## Cerebrospinal Fluid

COMPONENT	PRETERM NEWBORN	FULL TERM 1–7 DAYS	FULL TERM 8–30 DAYS	1–3 MONTHS	4 MONTHS– 16 YEARS	ADULT
<b>Note: Entries listed in alphabetical order.</b>						
Color	Clear or xantho-chromic	Clear or xantho-chromic	Clear or xantho-chromic	Clear	Clear	Clear
Red blood cells (/mCL)	—	3–23 (0–1,070)	—	—	—	—
White blood cells (/mCL)	<22–28	<30	<12	<6	<1	<5
Polymorphonuclear cells (/mCL)	<20%–60%	<38%–60%	<10%	None (36%–71%)	None (26%–35%)	None
Lymphocytes (/mCL)	—	0–20 (if <24 h) 0–4 (if 7 days)	≤11	≤5	≤5	60%–70%
Monocytes (/mCL)	—	<4 (50%–99%)	≤4 (50%–99%)	<4 (33%–67%)	<4 (44%–90%)	30%–50%
Protein (mg/dL), mean ± SD (95th percentile)	65–150	79 ± 23 (132)	68 ± 20 (100)	58 ± 17 (89) up to 42 days; 53 ± 17 (83) up to 56 days; 5–45 after 56 days	5–45	5–45
Glucose (mg/dL)	24–63 (1.3–3.5 mmol/L)	>50 (>2.77 mmol/L)	>50% in serum ≥38 (2.1 mmol/L)	≥45 (≥2.5 mmol/L)	45–72 (2.5–4.0 mmol/L), 60% in serum	2.2–4.7 mmol/L
CSF glucose/blood glucose	0.55–1.05	≥0.6	≥0.6	≥0.6	≥0.6	—
Lactate (mmol/L)	5–30 (approx 10% serum value)	<3.1 (if >2 days)	<3.1	<3.1	<2.4 (if 1–12 y)	—
Opening pressure (mm H <sub>2</sub> O) in lateral recumbent position	—	8–11	<28	<28	<28	50–180
CSF volume (mL)	—	—	—	—	60–100	100–160
Fluctuation with respiration	—	0.5–1.0	0.5–1.0	0.5–1.0	0.5–1.0	0.5–1.0

CSF, Cerebral spinal fluid; SD, standard deviation.

Calculating the ratio of red blood cells (RBCs) to white blood cells (WBCs) in CSF

General rule: For every 500 RBCs in CSF, it is acceptable to have 1 WBC.

Normal ratio of RBCs to WBCs in peripheral blood is 1,000 RBCs: 1–2 WBCs × 10<sup>6</sup>/L.

$$\text{Number of WBCs introduced into the CSF per L} = \frac{(\text{WBC}_{[\text{peripheral}]} \times \text{RBC}_{[\text{CSF}]})}{\text{RBC}_{(\text{peripheral})}} \times 10^6/\text{L}$$

Compare this number with the actual number of WBCs in the CSF.

1,000 × 10<sup>6</sup>/L RBCs in CSF raises CSF protein by approximately 0.015 g/L.

Note: correction factors should not be used to reassure that meningitis is unlikely.

**REFERENCE RANGE VALUES—(CONT'D)****Clinical Chemistry**

	CONVENTIONAL UNITS	SI UNITS
<b>ALANINE AMINOTRANSFERASE (ALT)</b> (Major sources: Liver, skeletal muscle, and myocardium)		
Infant <12 mo	13–45 U/L	13–45 U/L
1–3 yr	5–45 U/L	5–45 U/L
4–6 yr	10–25 U/L	10–25 U/L
7–9 yr	10–35 U/L	10–35 U/L
10–11 yr		
Female	10–30 U/L	10–30 U/L
Male	10–35 U/L	10–35 U/L
12–13 yr		
Female	10–30 U/L	10–30 U/L
Male	10–55 U/L	10–55 U/L
14–15 yr		
Female	5–30 U/L	5–30 U/L
Male	10–45 U/L	10–45 U/L
>16 yr		
Female	5–35 U/L	5–35 U/L
Male	10–40 U/L	10–40 U/L
<b>ALBUMIN</b> (See Proteins)		
<b>ALDOLASE</b> (Major sources: Skeletal muscle and myocardium)		
10–24 mo	3.4–11.8 U/L	3.4–11.8 U/L
2–16 yr	1.2–8.8 U/L	1.2–8.8 U/L
Adult	1.7–4.9 U/L	1.7–4.9 U/L
<b>ALKALINE PHOSPHATASE</b> (Major sources: Liver, bone, intestinal mucosa, and kidney)		
Infant	150–420 U/L	150–420 U/L
2–10 yr	100–320 U/L	100–320 U/L
Adolescent male	100–390 U/L	100–390 U/L
Adolescent female	100–320 U/L	100–320 U/L
Adult	30–120 U/L	30–120 U/L
<b>AMMONIA</b> (Heparinized venous specimen on ice analyzed within 30 min)		
Newborn	90–150 mcg/dL	64–107 mcmol/L
0–2 wk	79–129 mcg/dL	56–92 mcmol/L
Infant/child	29–70 mcg/dL	21–50 mcmol/L
Adult	15–45 mcg/dL	11–32 mcmol/L
<b>AMYLASE</b> (Major sources: Pancreas, salivary glands, and ovaries)		
0–14 days	3–10 U/L	3–10 U/L
15 days–13 wk	2–22 U/L	2–22 U/L
13 wk–1 yr	3–50 U/L	3–50 U/L
>1 yr	25–101 U/L	25–101 U/L
<b>ANTINUCLEAR ANTIBODY (ANA) IMMUNOFLUORESCENCE ASSAY (IFA)</b>		
Negative	<1:40	
Patterns with clinical correlation:		
Centromere: CREST		
Nucleolar: Scleroderma		
Homogeneous: Systemic lupus erythematosus (SLE)		

Continued

	CONVENTIONAL UNITS	SI UNITS
<b>ANTISTREPTOLYSIN O TITER</b>		
(Fourfold rise in paired serial specimens is significant.)		
Newborn	Similar to mother's value	
6–24 mo	≤50 Todd units/mL	
2–4 yr	≤160 Todd units/mL	
≥5 yr	≤330 Todd units/mL	
<b>ASPARTATE AMINOTRANSFERASE (AST)</b>		
(Major sources: Liver, skeletal muscle, kidney, myocardium, and erythrocytes)		
0–10 days	47–150 U/L	47–150 U/L
10 days–24 mo	9–80 U/L	9–80 U/L
>24 mo		
Female	13–35 U/L	13–35 U/L
Male	15–40 U/L	15–40 U/L
<b>BICARBONATE</b>		
Newborn	17–24 mEq/L	17–24 mmol/L
Infant	19–24 mEq/L	19–24 mmol/L
2 mo–2 yr	16–24 mEq/L	16–24 mmol/L
>2 yr	22–26 mEq/L	22–26 mmol/L
<b>BILIRUBIN (TOTAL)</b>		
Cord:		
Term and preterm	<2 mg/dL	<34 mcmmol/L
0–1 days:		
Term and preterm	<8 mg/dL	<137 mcmmol/L
1–2 days:		
Preterm	<12 mg/dL	<205 mcmmol/L
Term	<11.5 mg/dL	<197 mcmmol/L
3–5 days:		
Preterm	<16 mg/dL	<274 mcmmol/L
Term	<12 mg/dL	<205 mcmmol/L
Older infant:		
Preterm	<2 mg/dL	<34 mcmmol/L
Term	<1.2 mg/dL	<21 mcmmol/L
Adult	<1.5 mg/dL	<20.5 mcmmol/L
<b>BILIRUBIN (CONJUGATED)</b>		
Neonate	<0.6 mg/dL	<10 mcmmol/L
Infants/children	<0.2 mg/dL	<3.4 mcmmol/L

	pH	Pao <sub>2</sub> (mm Hg)	Paco <sub>2</sub> (mm Hg)	HCO <sub>3</sub> <sup>-</sup> (mEq/L)
<b>BLOOD GAS, ARTERIAL (BREATHING ROOM AIR)</b>				
Cord blood	7.28 ± 0.05	18.0 ± 6.2	49.2 ± 8.4	14–22
Newborn (birth)	7.11–7.36	8–24	27–40	13–22
5–10 min	7.09–7.30	33–75	27–40	13–22
30 min	7.21–7.38	31–85	27–40	13–22
60 min	7.26–7.49	55–80	27–40	13–22
1 day	7.29–7.45	54–95	27–40	13–22
Child/adult	7.35–7.45	83–108	32–48	20–28

**NOTE:** Venous blood gases can be used to assess acid-base status, not oxygenation. Pco<sub>2</sub> averages 6–8 mm Hg higher than Paco<sub>2</sub>, and pH is slightly lower. Peripheral venous samples are strongly affected by the local circulatory and metabolic environment. Capillary blood gases correlate best with arterial pH and moderately well with Paco<sub>2</sub>.



	CONVENTIONAL UNITS	SI UNITS
<b>C-REACTIVE PROTEIN</b>	0–0.5 mg/dL	
<b>CALCIUM (TOTAL)</b>		
Premature neonate	6.2–11 mg/dL	1.55–2.75 mmol/L
0–10 days	7.6–10.4 mg/dL	1.9–2.6 mmol/L
10 days–24 mo	9–11 mg/dL	2.25–2.75 mmol/L
24 mo–12 yr	8.8–10.8 mg/dL	2.2–2.7 mmol/L
12–18 yr	8.4–10.2 mg/dL	2.1–2.55 mmol/L
<b>CALCIUM (IONIZED)</b>		
0–1 mo	3.9–6.0 mg/dL	1.0–1.5 mmol/L
1–6 mo	3.7–5.9 mg/dL	0.95–1.5 mmol/L
1–18 yr	4.9–5.5 mg/dL	1.22–1.37 mmol/L
Adult	4.75–5.3 mg/dL	1.18–1.32 mmol/L
<b>CARBON DIOXIDE (CO<sub>2</sub> CONTENT)</b> (See Blood Gas, Arterial)		
<b>CARBON MONOXIDE (CARBOXYHEMOGLOBIN)</b>		
Nonsmoker	0.5%–1.5% of total hemoglobin	
Smoker	4%–9% of total hemoglobin	
Toxic	20%–50% of total hemoglobin	
Lethal	>50% of total hemoglobin	
<b>CHLORIDE (SERUM)</b>		
0–6 mo	97–108 mEq/L	97–108 mmol/L
6–12 mo	97–106 mEq/L	97–106 mmol/L
Child/adult	97–107 mEq/L	97–107 mmol/L
<b>CHOLESTEROL</b> (See Lipids)		
<b>CREATINE KINASE (CREATINE PHOSPHOKINASE)</b> (Major sources: Myocardium, skeletal muscle, smooth muscle, and brain)		
Newborn	145–1,578 U/L	145–1,578 U/L
>6 wk–adult male	20–200 U/L	20–200 U/L
>6 wk–adult female	20–180 U/L	20–180 U/L
<b>CREATININE (SERUM) (Enzymatic)</b>		
Cord	0.6–1.2 mg/dL	53–106 mcmmol/L
Newborn	0.3–1.0 mg/dL	27–88 mcmmol/L
Infant	0.2–0.4 mg/dL	18–35 mcmmol/L
Child	0.3–0.7 mg/dL	27–62 mcmmol/L
Adolescent	0.5–1.0 mg/dL	44–88 mcmmol/L
Adult male	0.9–1.3 mg/dL	80–115 mcmmol/L
Adult female	0.6–1.1 mg/dL	53–97 mcmmol/L
<b>ERYTHROCYTE SEDIMENTATION RATE (ESR)</b>		
Child	0–10 mm/hr	
Adult male	0–15 mm/hr	
Adult female	0–20 mm/hr	
<b>FERRITIN</b>		
Newborn	25–200 ng/mL	56–450 pmol/L
1 mo	200–600 ng/mL	450–1350 pmol/L
2–5 mo	50–200 ng/mL	112–450 pmol/L
6 mo–15 yr	7–140 ng/mL	16–315 pmol/L
Adult male	20–250 ng/mL	45–562 pmol/L
Adult female	10–120 ng/mL	22–270 pmol/L
<b>FOLATE (SERUM)</b>		
Newborn	16–72 ng/mL	16–72 nmol/L
Child	4–20 ng/mL	4–20 nmol/L
Adult	10–63 ng/mL	10–63 nmol/L
<b>FOLATE (RBC)</b>		
Newborn	150–200 ng/mL	340–453 nmol/L
Infant	74–995 ng/mL	168–2254 nmol/L
2–16 yr	>160 ng/mL	>362 nmol/L
>16 yr	140–628 ng/mL	317–1422 nmol/L
<b>GALACTOSE</b>		
Newborn	0–20 mg/dL	0–1.11 mmol/L
Older child	<5 mg/dL	<0.28 mmol/L

Continued

	CONVENTIONAL UNITS	SI UNITS
<b>GAMMA-GLUTAMYL TRANSFERASE (GGT)</b> (Major sources: Liver [biliary tree] and kidney)		
Cord	37–193 U/L	37–193 U/L
0–1 mo	13–147 U/L	13–147 U/L
1–2 mo	12–123 U/L	12–123 U/L
2–4 mo	8–90 U/L	8–90 U/L
4 mo–10 yr	5–32 U/L	5–32 U/L
10–15 yr	5–24 U/L	5–24 U/L
Adult male	11–49 U/L	11–49 U/L
Adult female	7–32 U/L	7–32 U/L
<b>GLUCOSE (SERUM)</b>		
Preterm	20–60 mg/dL	1.1–3.3 mmol/L
Newborn, <1 day	40–60 mg/dL	2.2–3.3 mmol/L
Newborn, >1 day	50–90 mg/dL	2.8–5.0 mmol/L
Child	60–100 mg/dL	3.3–5.5 mmol/L
>16 yr	70–105 mg/dL	3.9–5.8 mmol/L
<b>HAPTOGLOBIN</b>		
Newborn	5–48 mg/dL	50–480 mg/L
>30 days	26–185 mg/dL	260–1850 mg/L
<b>HEMOGLOBIN A<sub>1c</sub></b>		
Normal	4.5%–5.6%	
At risk for diabetes	5.7%–6.4%	
Diabetes mellitus	≥6.5%	
<b>HEMOGLOBIN F, % TOTAL HEMOGLOBIN (MEAN [SD])</b>		
1 day	77.0 (7.3)	
5 days	76.8 (5.8)	
3 wk	70.0 (7.3)	
6–9 wk	52.9 (11)	
3–4 mo	23.2 (16)	
6 mo	4.7 (2.2)	
8–11 mo	1.6 (1.0)	
Adult	<2.0	
<b>IRON</b>		
Newborn	100–250 mcg/dL	17.9–44.8 mcmmol/L
Infant	40–100 mcg/dL	7.2–17.9 mcmmol/L
Child	50–120 mcg/dL	9.0–21.5 mcmmol/L
Adult male	65–175 mcg/dL	11.6–31.3 mcmmol/L
Adult female	50–170 mcg/dL	9.0–30.4 mcmmol/L
<b>LACTATE</b>		
Capillary blood:		
0–90 days	9–32 mg/dL	1.1–3.5 mmol/L
3–24 mo	9–30 mg/dL	1.0–3.3 mmol/L
2–18 yr	9–22 mg/dL	1.0–2.4 mmol/L
Venous	4.5–19.8 mg/dL	0.5–2.2 mmol/L
Arterial	4.5–14.4 mg/dL	0.5–1.6 mmol/L
<b>LACTATE DEHYDROGENASE (AT 37°C)</b> (Major sources: Myocardium, liver, skeletal muscle, erythrocytes, platelets, and lymph nodes)		
0–4 days	290–775 U/L	290–775 U/L
4–10 days	545–2000 U/L	545–2000 U/L
10 days–24 mo	180–430 U/L	180–430 U/L
24 mo–12 yr	110–295 U/L	110–295 U/L
>12 yr	100–190 U/L	100–190 U/L
<b>LEAD</b>		
Child	<10 mcg/dL	<0.48 mcmmol/L
<b>LIPASE</b>		
0–30 days	6–55 U/L	6–55 U/L
1–6 mo	4–29 U/L	4–29 U/L
6–12 mo	4–23 U/L	4–23 U/L
>1 yr	3–32 U/L	3–32 U/L

	CHOLESTEROL (mg/dL)			LDL (mg/dL)		HDL (mg/dL)	
	DESIRABLE	BORDERLINE	HIGH	NEAR/ ABOVE OPTIMAL	OPTIMAL	BORDERLINE	HIGH DESIRABLE
<b>LIPIDS</b>							
Child/ adolescent	<170	170–199	>200	<110		110–129	>130
Adult	<200	200–239	<240	<100	100–129	130–159	>160
							40–60

	CONVENTIONAL UNITS	SI UNITS
<b>MAGNESIUM</b>	1.6–2.4 mg/dL	0.63–1.05 mmol/L
<b>METHEMOGLOBIN</b>	0.78% ( $\pm 0.37\%$ ) of total hemoglobin	
<b>OSMOLALITY</b>	275–295 mOsm/kg (neonates as low as 266)	275–295 mmol/kg
<b>PHENYLALANINE</b>		
Preterm	2.0–7.5 mg/dL	121–454 mcmol/L
Newborn	1.2–3.4 mg/dL	73–206 mcmol/L
Adult	0.8–1.8 mg/dL	48–109 mcmol/L
<b>PHOSPHORUS</b>		
0–9 days	4.5–9.0 mg/dL	1.45–2.91 mmol/L
10 days–24 mo	4.0–6.5 mg/dL	1.29–2.10 mmol/L
3–9 yr	3.2–5.8 mg/dL	1.03–1.87 mmol/L
10–15 yr	3.3–5.4 mg/dL	1.07–1.74 mmol/L
>15 yr	2.4–4.4 mg/dL	0.78–1.42 mmol/L
<b>PORCELAIN</b>	9.0–24.11 mg/dL	9.0–28.13 mmol/L
<b>POTASSIUM</b>		
Preterm	3.0–6.0 mEq/L	3.0–6.0 mmol/L
Newborn	3.7–5.9 mEq/L	3.7–5.9 mmol/L
Infant	4.1–5.3 mEq/L	4.1–5.3 mmol/L
Child	3.4–4.7 mEq/L	3.4–4.7 mmol/L
Adult	3.5–5.1 mEq/L	3.5–5.1 mmol/L
<b>PREALBUMIN</b>		
Newborn	7–39 mg/dL	
1–6 mo	8–34 mg/dL	
6 mo–4 yr	12–36 mg/dL	
4–6 yr	12–30 mg/dL	
6–19 yr	12–42 mg/dL	

AGE	TOTAL PROTEIN	ALBUMIN	$\alpha$ -1	$\alpha$ -2	$\beta$	$\gamma$
<b>PROTEIN ELECTROPHORESIS (G/DL)</b>						
Cord	4.8–8.0					
Premature	3.6–6.0					
Newborn	4.6–7.0					
0–15 day	4.4–7.6	3.0–3.9	0.1–0.3	0.3–0.6	0.4–0.6	0.7–1.4
15 day–1 yr	5.1–7.3	2.2–4.8	0.1–0.3	0.5–0.9	0.5–0.9	0.5–1.3
1–2 yr	5.6–7.5	3.6–5.2	0.1–0.4	0.5–1.2	0.5–1.1	0.5–1.7
3–16 yr	6.0–8.0	3.6–5.2	0.1–0.4	0.5–1.2	0.5–1.1	0.5–1.7
$\geq 16$ yr	6.0–8.3	3.9–5.1	0.2–0.4	0.4–0.8	0.5–1.0	0.6–1.2

Continued

	CONVENTIONAL UNITS	SI UNITS
<b>PYRUVATE</b>	0.7–1.32 mg/dL	0.08–0.15 mmol/L
<b>RHEUMATOID FACTOR</b>	<30 U/mL	
<b>SODIUM</b>		
<1 yr	130–145 mEq/L	130–145 mmol/L
>1 yr	135–147 mEq/L	135–147 mmol/L
<b>TOTAL IRON-BINDING CAPACITY (TIBC)</b>		
Infant	100–400 mcg/dL	17.9–71.6 mcmol/L
Adult	250–425 mcg/dL	44.8–76.1 mcmol/L
<b>TOTAL PROTEIN</b> (See Proteins)		
<b>TRANSAMINASE (SGOT)</b> (See Aspartate aminotransferase [AST])		
<b>TRANSAMINASE (SGPT)</b> (See Alanine aminotransferase [ALT])		
<b>TRANSFERRIN</b>		
Newborn	130–275 mg/dL	1.30–2.75 g/L
3 mo–16 yr	203–360 mg/dL	2.03–3.6 g/L
Adult	215–380 mg/dL	2.15–3.8 g/L

	CONVENTIONAL UNITS (mg/dL)	SI UNITS (mmol/L)
<b>TOTAL TRIGLYCERIDE</b>		
	Male	Female
0–7 days	21–182	28–166
8–30 days	30–184	30–165
31–90 days	40–175	35–282
91–180 days	45–291	50–355
181–365 days	45–501	36–431
1–3 yr	27–125	27–125
4–6 yr	32–116	32–116
7–9 yr	28–129	28–129
10–19 yr	24–145	37–140
	Male	Female
	0.24–2.06	0.32–1.88
	0.34–2.08	0.34–1.86
	0.45–1.98	0.40–3.19
	0.51–3.29	0.57–4.01
	0.51–5.66	0.41–4.87
	0.31–1.41	0.31–1.41
	0.36–1.31	0.36–1.31
	0.32–1.46	0.32–1.46
	0.27–1.64	0.42–1.58

	CONVENTIONAL UNITS	SI UNITS
<b>TROPONIN-I</b>		
0–30 days	<4.8 mcg/L	
31–90 days	<0.4 mcg/L	
3–6 mo	<0.3 mcg/L	
7–12 mo	<0.2 mcg/L	
1–18 yr	<0.1 mcg/L	
<b>UREA NITROGEN</b>		
Premature (<1 wk)	3–25 mg/dL	1.1–8.9 mmol/L
Newborn	2–19 mg/dL	0.7–6.7 mmol/L
Infant/child	5–18 mg/dL	1.8–6.4 mmol/L
Adult	6–20 mg/dL	2.1–7.1 mmol/L
<b>URIC ACID</b>		
0–30 days	1.0–4.6 mg/dL	0.059–0.271 mmol/L
1–12 mo	1.1–5.6 mg/dL	0.065–0.33 mmol/L
1–5 yr	1.7–5.8 mg/dL	0.1–0.35 mmol/L
6–11 yr	2.2–6.6 mg/dL	0.13–0.39 mmol/L
Male 12–19 yr	3.0–7.7 mg/dL	0.18–0.46 mmol/L
Female 12–19 yr	2.7–5.7 mg/dL	0.16–0.34 mmol/L
<b>VITAMIN A (RETINOL)</b>		
Preterm	13–46 mcg/dL	0.46–1.61 mcmol/L
Full term	18–50 mcg/dL	0.63–1.75 mcmol/L
1–6 yr	20–43 mcg/dL	0.7–1.5 mcmol/L
7–12 yr	20–49 mcg/dL	0.9–1.7 mcmol/L
13–19 yr	26–72 mcg/dL	0.9–2.5 mcmol/L



	CONVENTIONAL UNITS	SI UNITS
VITAMIN B <sub>1</sub> (THIAMINE)	4.5–10.3 mcg/dL	106–242 mcmol/L
VITAMIN B <sub>2</sub> (RIBOFLAVIN)	4–24 mcg/dL	106–638 nmol/L
VITAMIN B <sub>12</sub> (COBALAMIN)		
Newborn	160–1300 pg/mL	118–959 pmol/L
Child/adult	200–835 pg/mL	148–616 pmol/L
VITAMIN C (ASCORBIC ACID)	0.4–2.0 mg/dL	23–114 mcmol/L
VITAMIN D <sub>3</sub> (1,25-DIHYDROXY-VITAMIN D)	16–65 pg/mL	42–169 pmol/L
VITAMIN E		
Preterm	0.5–3.5 mg/L	1–8 mcmol/L
Full term	1.0–3.5 mg/L	2–8 mcmol/L
1–12 yr	3.0–9.0 mg/L	7–21 mcmol/L
13–19 yr	6.0–10.0 mg/L	14–23 mcmol/L
ZINC	70–120 mcg/dL	10.7–18.4 mmol/L

CREST, Calcinosis/Raynaud syndrome/Esophageal dysmotility/Sclerodactyly/Telangectasis

From Engorn B, Flerlage J. Blood chemistries and body fluids. In: Engorn B, Flerlage J, eds. *The Harriet Lane Handbook*. 20th ed. Philadelphia, PA: Elsevier Saunders; 2015:621–633. Reproduced with permission. Copyright © 2015 Elsevier.

**Newborn Clinical Chemistry****Descriptive Statistics of Measured Variables in Samples Obtained From Cord and Venous Blood at 2 to 4 Hours of Life**

	CORD BLOOD			2- TO 4-HOUR BLOOD			P VALUE
	MEAN $\pm$ SD	RANGE OF VALUES	95% CI	MEAN $\pm$ SD	RANGE OF VALUES	95% CI	
pH	7.35 $\pm$ 0.05	7.19–7.42	7.25–7.45	7.36 $\pm$ 0.04	7.27–7.45	7.28–7.44	NS
Pco <sub>2</sub>	40 $\pm$ 6	24.5–56.7	28–52	43 $\pm$ 7	30–65	29–57	0.034
Hct (%)	48 $\pm$ 5	37–60	38–58	57 $\pm$ 5	42–67	47–67	<0.001
Hgb (g/L)	1.65 $\pm$ 0.16	1.29–2.06	1.33–1.97	1.90 $\pm$ 0.22	0.88–2.3	1.46–2.34	<0.001
Na <sup>+</sup> (mmol/L)	138 $\pm$ 3	129–144	132–144	137 $\pm$ 3	130–142	131–143	NS
K <sup>+</sup> (mmol/L)	5.3 $\pm$ 1.3	3.4–9.9	2.7–7.9	5.2 $\pm$ 0.5	4.4–6.4	4.2–6.2	NS
Cl <sup>−</sup> (mmol/L)	107 $\pm$ 4	100–121	99–115	111 $\pm$ 5	105–125	101–121	0.002
ICa (mmol/L)	1.15 $\pm$ 0.35	0.21–1.5	0.4–1.85	1.13 $\pm$ 0.08	0.9–1.3	0.97–1.29	NS
IMg (mmol/L)	0.28 $\pm$ 0.06	0.09–0.39	0.12–0.4	0.30 $\pm$ 0.05	0.23–0.46	0.2–0.4	0.0005
Glucose (mmol/L)	4.16 $\pm$ 1.05	0.16–6.66	2.05–6.27	3.50 $\pm$ 0.67	5.11–16.10	2.16–4.82	—
Glucose (mg/dL)	75 $\pm$ 19	2.9–120	37–113	63 $\pm$ 12	29–92	39–87	0.0005
Lactate (mmol/L)	4.6 $\pm$ 1.9	1.1–9.6	0.8–8.4	3.9 $\pm$ 1.5	1.6–9.8	0.9–6.9	0.033
BUN (mmol/L)	2.14 $\pm$ 0.61	1.07–3.57	0.93–3.36	2.53 $\pm$ 0.71	1.43–4.28	1.11–3.96	—
BUN (mg/dL)	6.0 $\pm$ 1.7	3.0–10.0	2.6–9.4	7.1 $\pm$ 2.0	4–12	3.1–11.1	0.0029

BUN, blood urea nitrogen; CI, confidence interval; Hct, hematocrit; Hgb, hemoglobin; ICa, ionized calcium; IMg, ionized magnesium; Pco<sub>2</sub>, partial pressure of carbon dioxide.

From Dollberg S, Bauer R, Lubetzky R, Mimouni FB. A reappraisal of neonatal blood chemistry reference ranges using the Nova M electrodes. *Am J Perinatol*. 2001;18(8):433–440. Reproduced with permission. © Georg Thieme Verlag KG.

**Hematology**  
*Hematologic Values*

AGE	HEMOGLOBIN (g/dL, %) MEAN (–2 SD)	HEMATOCRIT (%) MEAN (–2 SD)	MEAN CELL VOLUME (fL) MEAN (–2 SD)	MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION		RETICU- LOCYTES (%)	WBC ( $\times 10^3/\text{mL}$ ) MEAN ( $\pm 2$ SD)	PLATELETS ( $10^3/\text{mL}$ ) MEAN ( $\pm 2$ SD)
				TRATION (g/dL RBC) MEAN (–2 SD)	TRATION (g/dL RBC) MEAN (–2 SD)			
26–30 wk, gestation <sup>a</sup>	13.4 (11)	41.5 (34.9)	118.2 (106.7)	37.9 (30.6)			4.4 (2.7)	254 (180–327)
28 wk	14.5	45	120	31		5–10		275
32 wk	15.0	47	118	32		3–10		290
Term (cord) <sup>b</sup>	16.5 (13.5)	51 (42)	108 (98)	33 (30)		3–7	18.1 (9–30) <sup>c</sup>	290
1–3 d	18.5 (14.5)	56 (45)	108 (95)	33 (29)		1.8–4.6	18.9 (9.4–34)	192
2 wk	16.6 (13.4)	53 (41)	105 (88)	31.4 (28.1)			11.4 (5–20)	252
1 mo	13.9 (10.7)	44 (33)	101 (91)	31.8 (28.1)		0.1–1.7	10.8 (4–19.5)	
2 mo	11.2 (9.4)	35 (28)	95 (84)	31.8 (28.3)				
6 mo	12.6 (11.1)	36 (31)	76 (68)	35 (32.7)		0.7–2.3	11.9 (6–17.5)	(150–350)
6 mo–2 y	12.0 (10.5)	36 (33)	78 (70)	33 (30)			10.6 (6–17)	
2–6 y	12.5 (11.5)	37 (34)	81 (75)	34 (31)		0.5–1.0	8.5 (5–15.5)	(150–350)
6–12 y	13.5 (11.5)	40 (35)	86 (77)	34 (31)		0.5–1.0	8.1 (4.5–13.5)	(150–350)
<b>12–18 Y</b>								
Male	14.5 (13)	43 (36)	88 (78)	34 (31)		0.5–1.0	7.8 (4.5–13.5)	(150–350)
Female	14.0 (12)	41 (37)	90 (78)	34 (31)		0.5–1.0	7.8 (4.5–13.5)	(150–350)
<b>ADULT</b>								
Male	15.5 (13.5)	47 (41)	90 (80)	34 (31)		0.8–2.5	7.4 (4.5–11)	(150–350)
Female	14.0 (12)	41 (36)	90 (80)	34 (31)		0.8–4.1	7.4 (4.5–11)	(150–350)

<sup>a</sup>Values are from fetal samplings.

<sup>b</sup>In newborns younger than 1 month, capillary hemoglobin exceeds venous hemoglobin: 1 hour of age—by 3.6 grams; 5 days of age—by 2.2 grams; 3 weeks of age—by 1.1 gram.

<sup>c</sup>Mean (95% confidence limits).

Adapted from Gajjar R, Jalazo E. Hematology. In: Engorn B, Flerlage J, eds. *The Harriet Lane Handbook*. 20th ed. Philadelphia, PA: Elsevier Saunders; 2015:305–333. Reproduced with permission. Copyright © 2015 Elsevier.

## Lymphocyte Subset Counts in Peripheral Blood

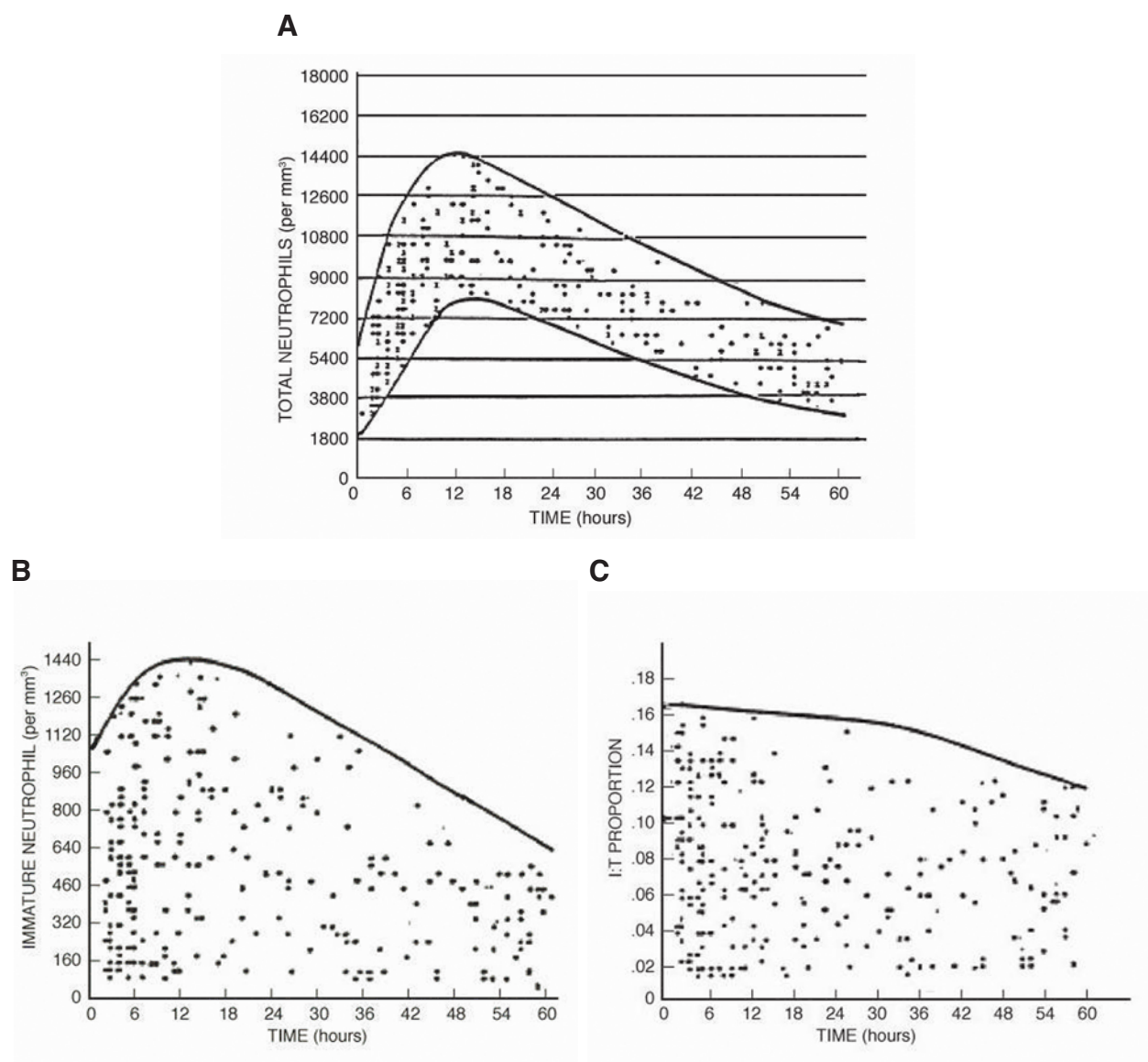
SUBSET	N	0-3 MONTHS	3-6 MONTHS	6-12 MONTHS	1-2 YEARS	2-6 YEARS	6-12 YEARS	12-18 YEARS
White blood cells	800	10.60 (7.20-18.00)	9.20 (6.70-14.00)	9.10 (6.40-13.00)	8.80 (6.40-12.00)	7.10 (5.20-11.00)	6.50 (4.40-9.50)	6.00 (4.40-8.10)
Lymphocytes	800	5.40 (3.40-7.60)	6.30 (3.90-9.00)	5.90 (3.40-9.00)	5.50 (3.60-8.90)	3.60 (2.30-5.40)	2.70 (1.90-3.70)	2.20 (1.40-3.30)
3	699	3.68 (2.50-5.50)	3.93 (2.50-5.60)	3.93 (1.90-5.90)	3.55 (2.10-6.20)	2.39 (1.40-3.70)	1.82 (1.20-2.60)	1.48 (1.00-2.20)
19	699	0.73 (0.30-2.00)	1.55 (0.43-3.00)	1.52 (0.61-2.60)	1.31 (0.72-2.60)	0.75 (0.39-1.40)	0.48 (0.27-0.86)	0.30 (0.11-0.57)
16/56	770	0.42 (0.17-1.10)	0.42 (0.17-0.83)	0.40 (0.16-0.95)	0.36 (0.18-0.92)	0.30 (0.13-0.72)	0.23 (0.10-0.48)	0.19 (0.07-0.48)
4	699	2.61 (1.60-4.00)	2.85 (1.80-4.00)	2.67 (1.40-4.30)	2.16 (1.30-3.40)	1.38 (0.70-2.20)	0.98 (0.65-1.50)	0.84 (0.53-1.30)
8	699	0.98 (0.56-1.70)	1.05 (0.59-1.60)	1.04 (0.50-1.70)	1.04 (0.62-2.00)	0.84 (0.49-1.30)	0.68 (0.37-1.10)	0.53 (0.33-0.92)
4/45RA/62L	694	2.25 (1.20-3.60)	2.23 (1.30-3.60)	2.10 (1.10-3.60)	1.64 (0.95-2.80)	0.96 (0.42-1.50)	0.56 (0.31-1.00)	0.39 (0.21-0.75)
8/45RA/62L	696	0.73 (0.38-1.30)	0.74 (0.45-1.20)	0.70 (0.33-1.20)	0.76 (0.40-1.40)	0.54 (0.26-0.85)	0.41 (0.20-0.65)	0.30 (0.17-0.56)
4/45RA	694	2.27 (1.20-3.70)	2.32 (1.30-3.70)	2.21 (1.10-3.70)	1.65 (1.00-2.90)	0.98 (0.43-1.50)	0.57 (0.32-1.00)	0.40 (0.23-0.77)
8/45RA	696	0.87 (0.45-1.50)	0.91 (0.55-1.40)	0.87 (0.48-1.50)	0.94 (0.49-1.70)	0.67 (0.38-1.10)	0.54 (0.31-0.90)	0.40 (0.24-0.71)
4/DR/38	694	0.08 (0.03-0.18)	0.11 (0.05-0.26)	0.10 (0.04-0.22)	0.10 (0.05-0.25)	0.06 (0.03-0.14)	0.04 (0.02-0.08)	0.03 (0.01-0.06)
8/DR/38	697	0.05 (0.02-0.16)	0.07 (0.03-0.17)	0.09 (0.04-0.27)	0.15 (0.05-0.54)	0.11 (0.05-0.34)	0.06 (0.03-0.18)	0.04 (0.02-0.13)
4/DR	694	0.10 (0.04-0.18)	0.15 (0.06-0.28)	0.12 (0.05-0.26)	0.13 (0.07-0.28)	0.09 (0.05-0.18)	0.07 (0.04-0.12)	0.06 (0.03-0.10)
8/DR	697	0.05 (0.02-0.16)	0.08 (0.03-0.17)	0.09 (0.04-0.29)	0.18 (0.06-0.60)	0.14 (0.07-0.42)	0.09 (0.04-0.27)	0.07 (0.03-0.18)
4/38	694	2.54 (0.16-3.90)	2.77 (1.60-4.00)	2.55 (1.20-4.10)	2.02 (1.20-3.30)	1.21 (0.59-2.00)	0.75 (0.48-1.20)	0.57 (0.33-1.00)
8/38	697	0.93 (0.55-1.60)	0.94 (0.53-1.50)	0.93 (0.45-1.60)	0.95 (0.57-1.90)	0.67 (0.39-1.10)	0.48 (0.24-0.74)	0.31 (0.16-0.70)
4/28	695	2.56 (1.60-3.80)	2.65 (1.60-4.00)	2.58 (1.20-4.20)	2.12 (1.30-3.40)	1.33 (0.69-2.00)	0.94 (0.63-1.50)	0.79 (0.49-1.20)
8/28	696	0.71 (0.35-1.30)	0.73 (0.35-1.20)	0.67 (0.28-1.10)	0.72 (0.40-1.30)	0.50 (0.28-0.87)	0.40 (0.21-0.70)	0.29 (0.16-0.52)
4/95	695	0.29 (0.16-0.58)	0.41 (0.23-0.62)	0.51 (0.29-0.82)	0.50 (0.27-0.91)	0.42 (0.27-0.65)	0.36 (0.25-0.62)	0.40 (0.25-0.66)
8/95	696	0.12 (0.05-0.31)	0.16 (0.06-0.39)	0.22 (0.08-0.66)	0.34 (0.10-0.85)	0.30 (0.11-0.58)	0.25 (0.08-0.53)	0.21 (0.08-0.45)



SUBSET	N	0-3 MONTHS	3-6 MONTHS	6-12 MONTHS	1-2 YEARS	2-6 YEARS	6-12 YEARS	12-18 YEARS
3/4/45RO	644	0.32 (0.06-0.90)	0.33 (0.12-0.63)	0.34 (0.16-0.80)	0.40 (0.21-0.85)	0.36 (0.22-0.66)	0.35 (0.23-0.63)	0.38 (0.24-0.70)
3/4 <sup>-</sup> /45RO	644	0.10 (0.03-0.33)	0.12 (0.03-0.29)	0.12 (0.04-0.33)	0.23 (0.06-0.57)	0.19 (0.09-0.44)	0.21 (0.07-0.39)	0.16 (0.06-0.31)
3/45RO	644	0.48 (0.09-1.20)	0.46 (0.15-0.86)	0.47 (0.22-1.10)	0.65 (0.30-1.30)	0.57 (0.33-1.00)	0.59 (0.32-0.95)	0.56 (0.34-0.97)
3 <sup>-</sup> /19/38	655	0.60 (0.12-2.00)	1.20 (0.00-2.80)	1.29 (0.02-2.20)	1.04 (0.00-2.20)	0.56 (0.01-1.20)	0.28 (0.00-0.67)	0.03 (0.00-0.35)
3 <sup>-</sup> /19	655	0.62 (0.12-2.10)	1.26 (0.00-2.80)	1.33 (0.02-2.30)	1.10 (0.00-2.30)	0.67 (0.02-1.40)	0.34 (0.00-0.74)	0.04 (0.00-0.39)

Note: Values are presented as medians (10th and 90th percentiles). Subset counts (numbers of cells per microliter  $\times 10^{-3}$ ) were obtained by multiplying subset percentages times anchor marker percentages (ie, CD3CD4 or CD3CD8) of total CD45 lymphocyte population times the absolute lymphocyte count (white blood cells  $\times$  lymphocyte percentage).  
 From Shearer WT, Rosenblatt HM, Gelman RS, et al; Pediatric AIDS Clinical Trials Group. Lymphocyte subsets in healthy children from birth through 18 years of age: the Pediatric AIDS Clinical Trials Group P1009 study. *J Allergy Clin Immunol*. 2003;112(5):973-980. Reproduced with permission. Copyright © 2003 Elsevier.

## Neutrophil Count Reference Ranges for Term Neonates



**A**, Solid lines represent the upper and lower boundaries of total neutrophil count for this full-term population. Dots represent individual data, and numbers represent number of values at the same point. **B** and **C**, Immature neutrophil count and I:T proportion: reference range in the first 60 hours of life for term neonates. (Reprinted from Manroe BL, Weinberg AG, Rosenfeld CR, et al. *The neonatal blood count in health and disease. I. Reference values for neutrophilic cells.* J Pediatr. 1979;95[1]:89, with permission from Elsevier.)

**Thyroid Function Tests****Reference Ranges in Very Low-Birth-Weight Infants**

SCREENING T4 LEVELS BY BIRTH WEIGHT AND POSTNATAL AGE (mcg/dL)			
POSTNATAL DAYS	VLBW ( $<1,500$ g)	LBW ( $<2,500$ g)	TERM
1–3	$7.9 \pm 3.3$	$11.4 \pm 2.5$	$12 \pm 1.9$
4–6	$6.5 \pm 2.9$	$9.9 \pm 2.5$	$11 \pm 2.5$
7–10	$6.3 \pm 3.0$	$9.5 \pm 2.3$	
11–14	$5.7 \pm 2.8$	$9.2 \pm 2.1$	
15–18	$7.0 \pm 2.5$	$9.1 \pm 2.3$	
29–56	$7.8 \pm 2.5$	$9.3 \pm 3.3$	

LBW, low birth weight; T4, thyroxine; VLBW, very low birth weight. Data expressed as  $\pm$  SD.

From Frank JE, Faix JE, Hermos RJ, et al. Thyroid function in very low birth weight infants: effects on neonatal hypothyroidism screening. *J Pediatr*. 1996;128(4):548. Reproduced with permission. Copyright © 1996 Elsevier.

**Reference Ranges for Preterm Infants**

GESTATIONAL AGE	FREE T4 (ng/dL)	THYROID-STIMULATING HORMONE (mcU/dL)
25–27 wk	0.6–2.2	0.2–30.3
28–30 wk	0.6–3.4	0.2–20.6
31–33 wk	1.0–3.8	0.7–27.9
34–36 wk	1.2–4.4	1.2–21.6
Term 37–42 wk	2.0–5.3	1.0–39
PCA	CONCENTRATIONS AFTER THE FIRST WEEK OF LIFE <sup>a</sup>	
Preterm 28–40 wk	0.8–2.6	0.8–12.0
Term 42–60 wk	0.9–2.3	1.7–9.1

PCA, postconceptional age (gestational age + postnatal age); T4, thyroxine.

<sup>a</sup>Clark SJ, Deming DD, Emery JR, Adams LM, Carlton EI, Nelson JC. Reference ranges for thyroid function tests in premature infants beyond the first week of life. *J Perinatol*. 2001;21(8):531–536.

Modified from Adams LM, Emery JR, Clark SJ, et al. Reference ranges for newer thyroid function tests in premature infants. *J Pediatr*. 1995;126(1):122. Reproduced with permission. Copyright © 1995 Elsevier.

**Reference Ranges for Infants, Children, and Adults**

AGE	THYROXINE (mcg/dL)	FREE THYROXINE (ng/dL)	TRIODO- THYRONINE (ng/dL)	FREE TRIODO- THYRONINE (ng/dL)	THYROXINE- BINDING GLOBULIN (mg/dL)	THYROID- STIMULATING HORMONE (mcU/dL)
Cord blood	6.6–17.5	1.03–1.73	14–86	0.09–0.36	0.7–4.7	$<2.5$ –17.4
1–3 d	11.0–21.5	0.6–2.0 (1–10 d)	100–380	0.17–0.57 <sup>a</sup>		$<2.5$ –13.3
1–4 wk	8.2–16.6	0.7–1.7 ( $>10$ days)	99–310	0.17–0.65 <sup>a</sup>	0.5–4.5	0.6–10.0
1–12 mo	7.2–15.6	0.8–1.8 (5–24 mo) <sup>b</sup>	102–264	0.24–0.65 <sup>a</sup>	1.6–3.6	0.6–6.3
1–5 y	7.3–15	1.0–2.1 (2–7 y) <sup>b</sup>	105–269	0.29–0.8 <sup>a</sup>	1.3–2.8	0.6–6.3
6–10 y	6.4–13.3	0.8–1.9 (8–20 y) <sup>b</sup>	94–241	0.34–0.72 <sup>a</sup>	1.4–2.6	
11–15 y	5.6–11.7	0.59–2.45 <sup>c</sup>	83–213	0.37–0.7 <sup>a</sup>	1.4–2.6	0.6–6.3
16–20 y	4.2–11.8	0.54–2.23 <sup>c</sup>	80–210	0.42–0.68 (16–18 y) <sup>a</sup>	1.4–2.6	0.2–7.6
21–45 y	4.3–12.5	0.9–2.5	70–204		1.2–2.4	0.2–7.6

<sup>a</sup>Soldin SJ, Morales A, Albalos F, Albalos F, Lenherr S, Rifai N. Pediatric reference ranges on the Abbott Imx for FSH, LH, prolactin, TSH, T4, T3, free T4, free T3, T-uptake, IgE and ferritin. *Clin Biochem*. 1995;28(6):603–606.

<sup>b</sup>Nelson JC, Clark SJ, Borut DL, Tomei RT, Carlton EI. Age-related changes in serum free thyroxine during childhood and adolescence. *J Pediatr*. 1993;123(6):899–905.

<sup>c</sup>Zurakowski D, DiCanzio J, Majzoub JA. Pediatric reference intervals for serum thyroxine, triiodothyronine, thyrotropin and free thyroxine. *Clin Chem*. 1999;45(7):1087–1091.

**Coagulation Tests****Healthy Full-term Infant During the First 6 Months of Life**

TESTS	DAY 1 (n)	DAY 5 (n)	DAY 30 (n)	DAY 90 (n)	DAY 180 (n)	ADULT (n)
PT (s)	13.0 ± 1.43 (61) <sup>a</sup>	12.4 ± 1.46 (77) <sup>a, b</sup>	11.8 ± 1.25 (67) <sup>a, b</sup>	11.9 ± 1.15 (62) <sup>a</sup>	12.3 ± 0.79 (47) <sup>a</sup>	12.4 ± 0.78 (29)
aPTT (s)	42.9 ± 5.80 (61)	42.6 ± 8.62 (76)	40.4 ± 7.42 (67)	37.1 ± 6.52 (62) <sup>a</sup>	35.5 ± 3.71 (47) <sup>a</sup>	33.5 ± 3.44 (29)
TCT (s)	23.5 ± 2.38 (58) <sup>a</sup>	23.1 ± 3.07 (64) <sup>b</sup>	24.3 ± 2.44 (53) <sup>a</sup>	25.1 ± 2.32 (52) <sup>a</sup>	25.5 ± 2.86 (41) <sup>a</sup>	25.0 ± 2.66 (19)
Fibrinogen (g/L)	2.83 ± 0.58 (61) <sup>a</sup>	3.12 ± 0.75 (77) <sup>a</sup>	2.70 ± 0.54 (67) <sup>a</sup>	2.43 ± 0.68 (60) <sup>a, b</sup>	2.51 ± 0.68 (47) <sup>a, b</sup>	2.78 ± 0.61 (29)
II (U/mL)	0.48 ± 0.11 (61)	0.63 ± 0.15 (76)	0.68 ± 0.17 (67)	0.75 ± 0.15 (62)	0.88 ± 0.14 (47)	1.08 ± 0.19 (29)
V (U/mL)	0.72 ± 0.18 (61)	0.95 ± 0.25 (76)	0.98 ± 0.18 (67)	0.90 ± 0.21 (62)	0.91 ± 0.18 (47)	1.06 ± 0.22 (29)
VII (U/mL)	0.66 ± 0.19 (60)	0.89 ± 0.27 (75)	0.90 ± 0.24 (67)	0.91 ± 0.26 (62)	0.87 ± 0.20 (47)	1.05 ± 0.19 (29)
VIII (U/mL)	1.00 ± 0.39 (60) <sup>a, b</sup>	0.88 ± 0.33 (75) <sup>a, b</sup>	0.91 ± 0.33 (67) <sup>a, b</sup>	0.79 ± 0.23 (62) <sup>a, b</sup>	0.73 ± 0.18 (47) <sup>b</sup>	0.99 ± 0.25 (29)
vWF (U/mL)	1.53 ± 0.67 (40) <sup>b</sup>	1.40 ± 0.57 (43) <sup>b</sup>	1.28 ± 0.59 (40) <sup>b</sup>	1.18 ± 0.44 (40) <sup>b</sup>	1.07 ± 0.45 (46) <sup>b</sup>	0.92 ± 0.33 (29) <sup>b</sup>
IX (U/mL)	0.53 ± 0.19 (59)	0.53 ± 0.19 (75)	0.51 ± 0.15 (67)	0.67 ± 0.23 (62)	0.86 ± 0.25 (47)	1.09 ± 0.27 (29)
X (U/mL)	0.40 ± 0.14 (60)	0.49 ± 0.15 (76)	0.59 ± 0.14 (67)	0.71 ± 0.18 (62)	0.78 ± 0.20 (47)	1.06 ± 0.23 (29)
XI (U/mL)	0.38 ± 0.14 (60)	0.55 ± 0.16 (74)	0.53 ± 0.13 (67)	0.69 ± 0.14 (62)	0.86 ± 0.24 (47)	0.97 ± 0.15 (29)
XII (U/mL)	0.53 ± 0.20 (60)	0.47 ± 0.18 (75)	0.49 ± 0.16 (67)	0.67 ± 0.21 (62)	0.77 ± 0.19 (47)	1.08 ± 0.28 (29)
PK (U/mL)	0.37 ± 0.16 (45) <sup>b</sup>	0.48 ± 0.14 (51)	0.57 ± 0.17 (48)	0.73 ± 0.16 (46)	0.86 ± 0.15 (43)	1.12 ± 0.25 (29)
HMWK (U/mL)	0.54 ± 0.24 (47)	0.74 ± 0.28 (63)	0.77 ± 0.22 (50) <sup>a</sup>	0.82 ± 0.32 (46) <sup>a</sup>	0.82 ± 0.23 (48) <sup>a</sup>	0.92 ± 0.22 (29)
XIIIa (U/mL)	0.79 ± 0.26 (44)	0.94 ± 0.25 (49) <sup>a</sup>	0.93 ± 0.27 (44) <sup>a</sup>	1.04 ± 0.34 (44) <sup>a</sup>	1.04 ± 0.29 (41) <sup>a</sup>	1.05 ± 0.25 (29) <sup>b</sup>
XIIIb (U/mL)	0.76 ± 0.23 (44)	1.06 ± 0.37 (47) <sup>a</sup>	1.11 ± 0.36 (45) <sup>a</sup>	1.16 ± 0.34 (44) <sup>a</sup>	1.10 ± 0.30 (41) <sup>a</sup>	0.97 ± 0.20 (29)
Plasminogen (CTA, U/mL)	1.95 ± 0.35 (44)	2.17 ± 0.38 (60)	1.98 ± 0.36 (52)	2.48 ± 0.37 (44)	3.01 ± 0.40 (47)	3.36 ± 0.44 (29)

Note: All factors except fibrinogen and plasminogen are expressed as units per milliliter, where pooled plasma contains 1.0 U/mL. Plasminogen units are those recommended by the Committee on Thrombolytic Agents (CTA). All values are expressed as mean ± 1 SD.

aPTT, activated partial thromboplastin time; HMWK, high molecular-weight kininogen; PK, prekallikrein; PT, prothrombin time; TCT, thrombin clotting time; vWF, von Willebrand factor.

<sup>a</sup>Values that do not differ statistically from the adult values.

<sup>b</sup>These measurements are skewed because of a disproportionate number of high values. The lower limit that excludes the lower 2.5th percentile of the population has been given in the respective figures. The lower limit for factor VIII was 0.50 U/mL at all time points for the infant.

From Andrew M, Paes B, Milner R, et al. Development of the human coagulation system in the full-term infant. *Blood*. 1987;70(1):165. Copyright © 1987 American Society of Hematology. Reprinted with permission.



**Inhibition of Coagulation in the Healthy Full-term Infant During the First 6 Months of Life**

INHIBITORS	DAY 1 (n)	DAY 5 (n)	DAY 30 (n)	DAY 90 (n)	DAY 180 (n)	ADULT (n)
AT-III	0.63 ± 0.12 (58)	0.67 ± 0.13 (74)	0.78 ± 0.15 (66)	0.97 ± 0.12 (60) <sup>a</sup>	1.04 ± 0.10 (56) <sup>a</sup>	1.05 ± 0.13 (28)
a2-M	1.39 ± 0.22 (54)	1.48 ± 0.25 (73)	1.50 ± 0.22 (61)	1.76 ± 0.25 (55)	1.91 ± 0.21 (55)	0.86 ± 0.17 (29)
a2-AP	0.85 ± 0.15 (55)	1.00 ± 0.15 (75) <sup>a</sup>	1.00 ± 0.12 (62) <sup>a</sup>	1.08 ± 0.16 (55) <sup>a</sup>	1.11 ± 0.14 (53) <sup>a</sup>	1.02 ± 0.17 (29)
C1E-INH	0.72 ± 0.18 (59)	0.90 ± 0.15 (76) <sup>a</sup>	0.89 ± 0.21 (63)	1.15 ± 0.22 (55)	1.41 ± 0.26 (55)	1.01 ± 0.15 (29)
a3-AT	0.93 ± 0.22 (57) <sup>a</sup>	0.89 ± 0.20 (75) <sup>a</sup>	0.62 ± 0.13 (61)	0.72 ± 0.15 (56)	0.77 ± 0.15 (55)	0.93 ± 0.19 (29)
HCII	0.43 ± 0.25 (56)	0.48 ± 0.24 (72)	0.47 ± 0.20 (58)	0.72 ± 0.37 (58)	1.20 ± 0.35 (55)	0.96 ± 0.15 (29)
Protein C	0.35 ± 0.09 (41)	0.42 ± 0.11 (44)	0.43 ± 0.11 (43)	0.54 ± 0.13 (44)	0.59 ± 0.11 (52)	0.96 ± 0.16 (28)
Protein S	0.36 ± 0.12 (40)	0.50 ± 0.14 (48)	0.63 ± 0.15 (41)	0.86 ± 0.16 (46) <sup>a</sup>	0.87 ± 0.16 (49) <sup>a</sup>	0.92 ± 0.16 (29)

Note: All values are expressed in units per milliliter as the mean ±1 SD.

<sup>a</sup>Values that do not differ statistically from the adult values.

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**1994 Revised Pediatric HIV Classification System****Immunologic Categories Based on Age-Specific CD4+ T-Lymphocyte Counts and Percentage of Total Lymphocytes**

IMMUNOLOGIC CATEGORY	AGE OF CHILD					
	<12 MO		1–5 YR		6–12 YR	
	mCL	(%)	mCL	(%)	mCL	(%)
1: No evidence of suppression	≥1,500	(≥25)	≥1,000	(≥25)	≥500	(≥25)
2: Evidence of moderate suppression	750–1,499	(15–24)	500–999	(15–24)	200–499	(15–24)
3: Severe suppression	<750	(<15)	<500	(<15)	<200	(<15)

From Centers for Disease Control and Prevention. 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age; official authorized addenda: human immunodeficiency virus infection codes and official guidelines for coding and reporting ICD-9-CM. *MMWR*. 1994;43(RR-12):1–10.

## FORMULAS

### Preparation of Infant Formulas for Standard and Soy Formulas

FORMULA TYPE	CALORIC CONCENTRATION (kcal/oz)	AMOUNT OF FORMULA	WATER (oz)
Liquid concentrates (40 kcal/oz)	20	13 oz	13
	24	13 oz	8.5
	27	13 oz	6.3
	30	13 oz	4.3
Powder (44 kcal/scoop)	20	1 scoop	2
	24	3 scoops	5
	27	3 scoops	4.25
	30	3 scoops	4

<sup>a</sup>Does not apply to Enfamcare, Neocate Infant, Neosure; Enfamil AR should not be concentrated greater than 24 kcal/oz. Use a packed measure for Nutramigen LIPIL and Pregestimil LIPIL and unpacked powder for all others.  
Adapted from Koldobskiy M, Thompson J. Nutrition and growth. In: Engorn B, Flerlage J, eds. *The Harriet Lane Handbook*. 20th ed. Philadelphia, PA: Elsevier Saunders; 2015:485–522. Reproduced with permission. Copyright © 2015 Elsevier.

### Common Caloric Supplements<sup>a</sup>

COMPONENT	CALORIES
Protein	Beneprotein (powder)
	ProSource Protein Powder
	Complete Amino Acid Mix
	Liquid Protein Fortifier
Carbohydrate	Polycose
	SolCarb
Fat	MCT oil <sup>b</sup>
	Vegetable oil
	Microlipid
	Liquigen (emulsified MCT)
Fat and Carbohydrate	Duocal

MCT, medium-chain triglyceride.

<sup>a</sup>Use these caloric supplements when you want to increase protein or when you have reached the maximum concentration tolerated and wish to further increase caloric density.

<sup>b</sup>MCT oil is unnecessary unless there is fat malabsorption.

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## Enteral Formulas, Including Their Main Nutrient Components

	Kcal/ oz	PRO- TEIN (g)	FAT (g)	CARBS (g)	Na (mEq)	K (mEq)	Ca (mg)	P (mg)	Fe (mg)	OSMO- LALITY
<b>A. INFANT FORMULAS</b>										
<b>HUMAN MILK</b>										
Term	20	11	39	72	8	14	279	143	0.3	286
Preterm	20	14	39	66	11	15	248	128	1.2	290
<b>HUMAN MILK AND FORTIFIERS ANALYSIS</b>										
Enfamil HMF Liquid + Preterm Human Milk (5 mL + 25 mL breastmilk)	24	32	48	65	20	20	1,100	640	15	322
Similac HMF + Preterm Human Milk (1 pkt/25 mL)	24	23	41	82	17	30	1,381	777	4.6	N/A
<b>PRETERM FORMULAS</b>										
Enfamil Enfacare	22	21	39	77	11	20	890	490	13.3	260
Enfamil Premature 20	20	20	34	74	17	17	1,100	553	3.4	240
Enfamil Premature 24 High Protein	24	28	41	85	20	21	1,340	670	15	300
Enfamil Premature 30	30	30	52	112	26	28	1,670	840	18	300
Gerber Good Start Premature 20	20	20	35	71	16	21	1,110	570	12	229
Gerber Good Start Premature 24 High Protein	24	29	42	78	19	25	1,310	680	14	299
Gerber Good Start Premature 30	30	30	53	107	24	31	1,660	860	18	341
Gerber Good Start Nourish	22	21	38	76	12	20	880	470	13	275
Similac Neosure	22	21	41	75	11	27	781	461	13.4	250
Similac Special Care 20	20	20	37	70	13	22	1,217	676	12.2	235
Similac Special Care 24 High Protein	24	27	44	81	15	27	1,461	811	14.6	280
Similac Special Care 30	30	30	67	78	19	34	1,826	1,014	18.3	325
<b>COW MILK-BASED FORMULAS</b>										
Enfamil Infant	20	14	36	74	8	19	520	287	12	300
Enfamil Newborn	20	14	36	73	8	19	520	287	12	300
Enfamil A.R.	20	17	34	74	12	19	520	353	12	230 (240 <sup>a</sup> )
Enfamil LactoFree	20	14	36	73	9	19	547	307	12	200
Enfagrow Toddler Transitions	20	18	36	70	10	23	1,300	867	13.4	270
Evap. Milk (13 oz + 19 oz water + 30 mL corn syrup)	20	27	31	72	21	32	1,066	832	0.8	N/A
Organic Milk-Based Infant Formula	20	15	36	71	7	15	420	280	12	294
Parent's Choice Premium Infant Formula	20	14	36	72	8	19	520	287	12	295
Similac Advance	20	14	37	76	7	18	528	284	12	310
Similac Go and Grow Milk-Based Formula	20	14	37	72	7	18	1,014	548	13.5	300
Similac Sensitive	20	14	37	72	9	19	568	379	12.2	200

<sup>a</sup>Liquid formulation.

Continued

	Kcal/ oz	PRO- TEIN (g)	FAT (g)	CARBS (g)	Na (mEq)	K (mEq)	Ca (mg)	P (mg)	Fe (mg)	OSMO- LALITY
<b>A. INFANTS, Continued</b>										
<b>COW MILK-BASED FORMULAS, Continued</b>										
Similac Advance Organic	20	14	37	71	7	18	528	284	12.2	225
Similac PM 60/40	20	15	38	69	7	14	379	189	4.7	280
Similac for Spitup	20	14	37	72	9	19	568	379	12.2	180
<b>SOY-BASED</b>										
America's Store Brand Soy (also w/ARA/DHA)	20	17	36	68	11	21	700	460	12	164
Enfamil Prosobee	20	17	36	71	11	21	700	460	12	170
Enfagrow Soy Next Step	20	22	30	79	11	21	1,300	867	13.3	230
Gerber Good Start Soy	20	17	34	75	12	20	704	422	12.1	180
Gerber Good Start 2 Soy	20	19	34	73	12	20	1,273	710	13.4	175
Similac Soy Isomil	20	17	37	70	13	19	710	507	12.2	200
Similac for Diarrhea	20	18	37	68	13	19	710	507	12.2	240
Similac Go and Grow Soy-Based Formula	20	17	37	70	13	19	1,014	676	13.5	200
<b>CASEIN, EXTENSIVELY HYDROLYZED</b>										
Alimentum	20	19	37	69	13	20	710	507	12.2	370
Nutramigen	20	19	36	69	14	19	627	347	12	300 (320 <sup>a</sup> )
Nutramigen with Enflora LGG	20	19	36	69	14	19	627	347	12	300
Pregestimil	20	19	38	69	14	19	640	350	12.2	250
<b>WHEY, PARTIALLY HYDROLYZED</b>										
Gerber Good Start Gentle	20	15	34	78	8	19	449	255	10.1	250
Gerber Good Start Protect	20	15	34	75	8	19	449	255	10.1	250
Gerber Good Start 2 Gentle	20	15	34	78	8	19	1,273	710	13.4	180
Gerber Good Start 2 Protect	20	15	34	75	8	19	1,273	710	13.4	180
Gerber Good Start Soothe	20	15	34	75	8	19	480	270	10	195
<b>WHEY AND CASEIN, PARTIALLY HYDROLYZED</b>										
Enfamil Gentlease	20	15	36	72	10	19	547	307	12	230
<b>AMINO ACID-BASED</b>										
Elecare Infant	20	20	32	72	13	26	780	568	10	350
Neocate Infant	20	21	30	78	11	27	830	624	12.4	375
PurAmino	20	19	36	69	14	19	627	347	12	350
<b>SPECIALIZED</b>										
3232A	20	19	28	89	13	19	627	420	12.5	250
RCF	20	20	36	68	13	19	710	507	12.2	168
Enfaport	30	35	54	102	13	29	940	520	18	280
<b>B. TODDLER AND YOUNG CHILD 1–10 YEARS</b>										
<b>COW MILK-BASED FORMULAS</b>										
Boost Kid Essentials	30	30	38	135	24	30	1,181	886	14	550/600/570
Boost Kid Essentials 1.5 (w/fiber)	45	42	75	165	30	33	1,300	990	14	390 (405)
Carnation Instant Breakfast Essentials	24	43	16	105	24	27	1,539	1,539	13.8	N/A
Compleat Pediatric	30	38	39	132	33	42	1,440	1,000	14	380
Cow's Milk, 2%	15	35	20	50	22	41	1,258	979	0.5	N/A
Cow's Milk, whole	19	34	34	48	22	40	1,226	956	0.5	285



	Kcal/ oz	PRO- TEIN (g)	FAT (g)	CARBS (g)	Na (mEq)	K (mEq)	Ca (mg)	P (mg)	Fe (mg)	OSMO- LALITY
<b>B. TODDLER AND YOUNG CHILD 1–10 YEARS, Continued</b>										
<b>COW MILK–BASED FORMULAS, Continued</b>										
KetoCal 3:1	30	22	97	10	18	35	1,140	801	16	180
KetoCal 4:1	43	30	144	6	26	55	1,600	1,300	22	197
Monogen	30	27	28	163	21	22	617	480	10.1	370
Nutren Junior (also w/fiber)	30	30	50	110	20	34	1,000	800	14	350
Pediasure Enteral (also w/fiber)	30	30	40	133	17	34	972	845	14	335 (345)
Pediasure 1.5 (also w/fiber)	45	59	67	160 (165)	17	42	1,476	1,054	11	370 (390)
Pediasure Sidekicks	19	30	21	89	17	42	1,055	844	11	420
Pediasure Sidekicks, Clear	18	30	0	120	8	4	175	750	9	325
Pediasure Vanilla	30	30	38	131	17	34	972	845	14	480
Pediasure with Fiber, Vanilla	30	30	38	135	17	34	972	845	14	480
Portagen	30	32	44	104	22	29	850	642	17	350
<b>SOY-BASED</b>										
Bright Beginnings Soy Pediatric Drink	30	30	50	109	17	40	970	800	14	350
<b>SEMI-ELEMENTAL, HYDROLYZED</b>										
Peptamen Junior Fiber	30	30	39	137	20	34	1,000	800	14	390
Peptamen Junior with Prebio	30	30	39	137	20	34	1,000	800	14	365
Peptamen Junior, unflavored (w/fiber, vanilla flavored)	30	30	39	138	20	34	1,000	800	14	260 (390)
Peptamen Junior 1.5	45	45	68	180	30	51	1,652	1,352	20.8	450
Pediasure Peptide (also flavored)	30	30	41	134	31	35	1,060	844	14	250 (390)
Pediasure Peptide 1.5	45	45	61	201	47	52	1,580	1,265	21	450
<b>SOY AND PORK, HYDROLYZED</b>										
Pepdite Junior, Unflavored	30	31	50	106	18	35	1,130	940	14	430
<b>AMINO ACID–BASED</b>										
Elecare Jr, Unflavored and Vanilla	30	31	49	109	20	39	1,172	852	15	560
EO28 Splash	30	25	35	146	9	24	620	620	7.7	820
Neocate Junior Flavored	30	35	47	110	19	36	1,200	738	16	690
Neocate Junior Unflavored	30	33	50	104	18	35	1,130	697	15	590
Vivonex Pediatric	24	24	24	130	17	31	970	800	10	360
<b>C. OLDER CHILDREN AND ADULT STANDARD FORMULAS</b>										
<b>COW MILK–BASED FORMULAS</b>										
Boost	30	40	17	171	24	43	1,250	1,250	19	625
Boost Glucose Control	32	59	50	84	48	29	1,160	928	15	400
Boost High Protein	30	63	25	138	31	41	1,459	1,250	19	650
Boost Plus	45	59	59	188	31	41	1,459	1,250	19	670
Compleat	32	48	40	128	43	44	760	760	14	340
Ensure Clear	30	35	0	215	8	0	0	0	9	700
Ensure Immune Health	32	38	25	177	37	40	1,266	1,055	19	620
Ensure Plus	45	55	212	47	41	45	1,266	1,266	19	680
Glucerna 1.0 Cal	30	42	54	96	41	40	705	705	13	355
Jevity 1 Cal	32	44	35	155	40	40	910	760	14	300
Jevity 1.2 Cal	36	56	39	169	59	47	1,200	1,200	18	450

Continued

	Kcal/ oz	PRO- TEIN (g)	FAT (g)	CARBS (g)	Na (mEq)	K (mEq)	Ca (mg)	P (mg)	Fe (mg)	OSMO- LALITY
<b>C. OLDER CHILDREN AND ADULT STANDARD FORMULAS, Continued</b>										
<b>COW MILK-BASED FORMULAS, Continued</b>										
Jevity 1.5 Cal	45	64	50	216	61	55	1,200	1,200	18	525
Nepro	54	81	96	167	46	27	1,060	700	19	585
Novasource Renal	60	74	100	200	39	21	1,300	650	18	700/960
Nutren 1.0, vanilla (w/fiber)	30	40	38	127	38	32	668	668	12	370 (410)
Nutren 1.5, unflavored	45	60	68	169	51	48	1,000	1,000	18	430
Nutren 2.0	60	80	104	196	57	49	1,340	1,340	24	745
Optimental	30	51	28	139	49	44	1,055	1,055	13	585
Osmolite 1 Cal	32	44	35	144	40	40	760	760	14	300
Osmolite 1.2 Cal	36	56	39	158	58	46	1,200	1,200	18	360
Osmolite 1.5 Cal	45	63	49	204	61	46	1,000	1,000	18	525
Promote (w/fiber)	30	63	26	130	44	51	1,200	1,200	18	340 (380)
Pulmocare	45	63	93	106	57	50	1,060	1,060	19	475
Renalcal	60	35	83	291	0	0	0	0	0	600
Replete, unflavored	30	63	34	113	39	39	1,000	1,000	18	300/350
Resource 2.0	60	84	88	217	35	39	1,042	1,042	18.8	790
Resource Breeze	32	38	0	230	15	1	42	633	11	750
Suplena	54	45	96	205	35	29	1,055	717	19	600
TwoCal HN	60	84	91	219	64	63	1,050	1,050	19	725
<b>SOY-BASED</b>										
Fibersource HN	36	53	39	160	52	51	1,000	1,000	17	490
Isosource 1.5 CAL	45	68	65	170	56	58	1,070	1,070	19	650/585
Isosource HN	36	53	39	160	48	49	1,200	1,200	15	490
<b>SEMI-ELEMENTAL HYDROLYZED</b>										
Peptamen, unflavored	30	40	39	127	25	39	800	700	18	270
Peptamen with Prebio	30	40	39	127	25	39	800	700	18	300
Peptamen 1.5, unflavored	45	68	56	188	45	48	1,000	1,000	27	550
Peptamen AF	36	76	55	107	35	41	800	800	14.4	390
Peptamen Bariatric	30	93	38	78	29	34	670	670	12	345
Perative	39	67	37	180	45	44	870	870	16	460
Pivot 1.5	45	94	51	172	61	51	1,000	1,000	18	595
Vital 1.0 Cal	30	40	38	130	46	36	705	705	13	390
Vital HN	30	42	11	185	25	36	667	667	12	500
<b>AMINO ACID-BASED</b>										
Tolerex	30	21	1.5	230	20	30	560	560	10	550
Vivonex RTF	30	50	12	175	29	31	670	670	12	630
Vivonex Plus	30	45	7	190	27	27	560	560	10	650
Vivonex T.E.N.	30	38	3	210	26	24	500	500	9	630

Ca, calcium; Fe, iron; K, potassium; Na, sodium; P, phosphorous

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